Navigating Gout Care in Complex and Older Adult Populations

by

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Table of Abbreviations and Terms

Abbreviation	Name
A2RB	Angiotensin-II receptor blocker
ACEI	Angiotensin-converting enzyme inhibitor
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
ADR	Adverse drug reaction
AE	Adverse event
AHS	Allopurinol hypersensitivity syndrome
AI	Artificial intelligence
BBB	Blood Brain Barrier
BIS	Berlin Initiative Study
BMQ	Beliefs about Medicines Questionnaire
CAGCD	Central Adelaide Gout Clinic Database and Biobank
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COX	Cyclooxygenase
CQR	Compliance Questionnaire Rheumatology
CrCl	Creatinine clearance
CYP	Cytochrome
DDD	Drug-drug interaction
DECT	Dual-energy computed tomography
DHA	Docosahexaenoic acid
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
FACT	Febuxostat versus Allopurinol Controlled Trial
FAS	Full Age Study
GFR	Glomerular filtration rate
GIS	Gout Impact Scale

GP	General practitioner
IL-1	Interleukin-1
IVIVE	In vitro-in vivo extrapolation
MARS-5	Medication Adherence Report Scale (5-item version)
MEMS	Medication Event Monitoring Systems
ML	Machine learning
MMAS-8	Morisky 8-item questionnaire
MSU	Monosodium urate
ND	Nasoduodenal
NG	Nasogastric
NJ	Nasojejunal
NLP	Natural Language Processing
NMA	Network meta-analysis
NSAID	Non-steroidal anti-inflammatory drug
PBPK	Physiological-based pharmacokinetic modeling and simulation
P-gp	P-glycoprotein
PPI	Proton pump inhibitor
RCT	Randomised controlled trial
RR	Risk ratio
SD	Standard deviation
SF-36	Short Form (36) Health Survey
SIMS	Satisfaction with Information about Medicines Scale
SR	Systematic review
SU	Serum urate
TIQ	Tophus Impact Questionnaire
ULT	Urate lowering therapy
US	Ultrasound

Abstract

Gout is the most common form of inflammatory arthritis and is increasing in prevalence worldwide, in part due to an ageing population and rising rates of multimorbidity. Gout is characterised by flares, which place a substantial physical and psychological burden on individuals due to their severe, unpredictable, and recurrent nature. Long-term urate lowering therapy (ULT) is the mainstay of gout management. ULT lowers serum urate (SU) concentrations with the aim of preventing flares and ultimately mitigating chronic complications. However, managing gout, particularly flare prevention, is complex, especially in older adults and those with multimorbidity.

The initiation of ULT has been associated with a transient increase in flare rate, which is thought to be related to the speed and extent of SU reduction. However, it remains unclear whether this flare risk differs between ULT dosing strategies and specific ULT drugs. To reduce this flare risk, clinical guidelines recommend concurrent flare prophylaxis during ULT initiation, typically for up to six months. However, prophylactic medications such as colchicine, non-steroidal anti-inflammatory drugs, and corticosteroids are not without risk, particularly in older adults, due to potential adverse events, drug-drug and drug-disease interactions, and contraindications. Furthermore, evidence to guide the optimal duration, safety, and efficacy of flare prophylaxis remains limited. Another key challenge in gout management is poor adherence to ULT, contributing to inadequate long-term disease control and recurrent flares. Thus, the overarching objective of this thesis was to explore the challenges of gout management, with a focus on complex patients, adherence to ULT, flare risk during treatment initiation, and the role of prophylaxis in preventing flares.

This thesis is structured as follows: **Chapter 1** presents a comprehensive literature review of gout, with a particular focus on allopurinol, gout flare prophylaxis, and the management of gout in older adults with multimorbidity and polypharmacy. **Chapter 2** builds on this by reviewing age-related physiological changes affecting drug disposition and their relevance to gout medications, alongside the impact of geriatric syndromes on disease management. **Chapter 3** presents a cross-sectional study that explores both intentional and unintentional non-adherence to allopurinol using three different adherence measures. It also investigates social, patient, clinical and treatment related factors that may influence these adherence behaviours. **Chapter 4** is a systematic

review with network meta-analysis that aims to understand the impact of ULT drug and dosing strategy on ULT-induced flares, as well as the benefits, harms and optimal duration of flare prophylaxis. **Chapter 5** is a prospective observational cohort study of individuals with more clinically challenging gout presentations, providing real-world insights into flare patterns, quality of life, treatment outcomes and flare risk factors. This thesis concludes with a discussion of the primary findings, and emphasises the need for more individualised approaches to gout management. Key recommendations for future research and clinical practice are also discussed. This thesis is submitted as a Thesis Containing Published Research in accordance with Appendix AB-58 AD2: Content and Form of the Research Degree Thesis.

Publications Arising from Candidature

Paper 1: Maher D, Ailabouni N, Mangoni AA, Wiese MD, Reeve E. Alterations in drug disposition in older adults: a focus on geriatric syndromes. Expert Opinion on Drug Metabolism & Toxicology. 2021;17(1):41-52.

Paper 2: Maher D, Reeve E, Hopkins A, Tan JM, Tantiongco M, Ailabouni N, Woodman R, Stamp L, Bursill D, Proudman S, & Wiese M. Comparative Risk of Gout Flares When Initiating or Escalating Various Urate-Lowering Therapy: A Systematic Review With Network Meta-Analysis. Arthritis care & research (2010). 2024;76(6):871-81.

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Presentations Arising from Candidature

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Maher D, Reeve E, Hopkins A, Tan JM, Tantiongco M, Ailabouni N, Woodman R, Stamp L, Bursill D, Proudman S, & Wiese M. Preventing urate-lowering therapy

induced gout flares: a systematic review and network meta-analysis. Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists Garth McQueen Prize Session [Oral and Poster award sessions]. Australasian Pharmaceutical Science Association and Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists Joint Conference, 29-2 December 2022: Perth, Australia.

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Awards and Recognition Arising from Thesis

Paper 2 was mentioned by four news outlets and was the Top 6 most widely viewed article in Arthritis Care & Research for 2024, https://wiley.altmetric.com/details/159168330.

Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists Garth McQueen Prize. Awarded in 2022 for the best oral communication by a Higher Degree student member of ASCEPT. In recognition of this award, I was invited by the ASCEPT Executive Board to attend Science Meets Parliament 2023, a valuable event offering the opportunity to engage directly with policymakers and fellow researchers.

Online article featured in the MOD. It's Complicated Exhibit. 'When treatment is tricky… Words by Sarah Keenihan', 2021, https://mod.org.au/2021/02/09/when-treatment-is-tricky/

Vice Chancellor and President's Scholarship. Awarded in 2019. This prestigious scholarship acknowledges and supports the University's outstanding PhD candidates.

Declaration

I declare that:

This thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.

Dorsa Maher



9th September 2025

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1 Literature Review

Chapter overview

This chapter reviews the literature on gout, covering its epidemiology, pathophysiology, and diagnosis. It examines key treatment strategies, including flare treatment, urate-lowering therapies (ULTs) (with a focus on allopurinol), and flare prophylaxis, along with adherence challenges and other management considerations. This chapter also highlights the complex factors affecting treatment, such as ageing, comorbidities, and polypharmacy. It describes the aim of this thesis and outlines the structure of the subsequent chapters.

Epidemiology, signs and symptoms

Gout is the most common form of inflammatory arthritis, affecting 1.6–6.8% of the Australian population (1). It is more prevalent in men and the incidence increases with age and post menopause in women (1, 2). Gout prevalence is rising, likely due to the ageing population and increase in associated metabolic co-morbidities (3, 4).

Gout is caused by the formation and subsequent deposition of monosodium urate (MSU) crystals in the joints and soft tissues of susceptible individuals, which develop in the presence of sustained elevation of serum urate (SU) (5). Individuals with gout typically first present with an intense acute inflammatory pain in a lower limb joint, such as the first metatarsophalangeal joint (known as podagra), knee, foot, or ankle (6). This is known as a 'gout flare' and is caused by a complex interaction between MSU crystals and the immune system (7). Other features include warmth, swelling and erythema in the affected joint (8). Flares typically occur in a single joint but occasionally they can be oligoarticular (2-4 joints), or polyarticular (≥5 joints) (9), which usually occurs in long-standing or sub-optimally managed gout (5). Similarly, while lower limb involvement is more typical, as the MSU crystal burden increases, flares may be observed in the upper extremities such as fingers, wrists, and elbows (5). While uncommon, flares can also occur in the spine (10).

Although self-limiting and generally lasting 7-14 days, gout flares typically cause immense pain, have considerable impact on quality of life and can reoccur frequently (11-14). Individuals with gout have described the pain associated with flares as an intense throbbing or burning pain (14), which typically reaches peak intensity within 12 hours (6). During a flare, the associated pain usually renders even the simplest of tasks such as self-care, walking, social activities and the ability to work unfeasible (14). Beyond physical functioning, the unpredictability of flares can generate fear and harm emotional and psychological wellbeing (11, 15, 16).

Gout is a chronic disease and therefore between flares (called the intercritical gout phase) the underlying disease pathology continues. If untreated, gout can progress to more severe disease including the development of tophi, chronic gouty arthritis, joint erosion and permanent disability (17). Sub-optimal management can also accelerate this decline, exacerbating disease progression and reducing quality of life (18). In Australia, an estimated $230.8 million was spent on the treatment and management of gout in

2020-21 (19) and estimates in the United States exceed $6 billion annually (data from 2013) (20). By 2050, the global prevalence of gout is forecast to rise by over 70% compared to 2020, due to an ageing population and increasing life expectancy (21). It is thus important to focus on optimising management to not only improve the quality of life for people with gout, but with the overall economic burden set to rise, to minimise the associated health care costs and rate of hospitalisation (19, 20).

Risk factors and comorbid conditions

Sustained elevation of plasma urate concentrations (hyperuricaemia) is the strongest risk factor for the development of gout and this relationship is concentration dependent (22). Hyperuricaemia is caused by excessive dietary purine intake, endogenous urate overproduction or most commonly via underexcretion (approximately 70% of urate is eliminated by the kidneys and 30% via the gastrointestinal tract) (23). Dietary risk factors for incident gout increase the concentration of SU and include purine rich meat and seafood, drinks high in fructose and alcoholic beverages (24). However, dietary modification alone only has a modest urate lowering effect, which is generally insufficient to achieve target SU concentrations (25). Urate overproduction can occur in some high cell turnover conditions such as myeloproliferative disorders and psoriasis (26). Non-modifiable risk factors for gout include advancing age (2), male sex, and ethnicity (e.g. Taiwanese indigenous peoples and Maori peoples (1)). Differences in gender may relate to the potential uricosuric effects of oestrogen (27), particularly on the ABCG2 and SLC2A9 urate transporters, which mediate the excretion of uric acid (28). Genome-wide association studies have highlighted that underlying genetics affects the risk of hyperuricemia and gout, with over 350 independent urate-associated genetic loci identified thus far (29, 30). Studies report that the identified genetic loci explain between 7.7% (31) and 8.36% (30) of age-and sex-adjusted variance in SU concentrations.

Gout is also associated with metabolic co-morbidities including cardiovascular disease, hypertension, hyperlipidaemia, obesity, diabetes mellitus and chronic kidney disease (CKD), some of which, such as obesity and CKD, are known to directly contribute to hyperuricemia (26). Given the high risk of cardiovascular disease (32) and mortality (33, 34) in the gout population, several gout management guidelines actively promote healthy lifestyle habits, weight loss and the management and optimisation of metabolic

co-morbidities (35, 36). Many of the medications used to manage these co-morbidities can also elevate SU by varying mechanisms (37). Diuretics (both loop and thiazide used for hypertension and heart failure) increase SU by 6–21% (37) in a dose dependent manner. The high cardiovascular risk in this population often necessitates the use of low-dose aspirin, which reduces the secretion of uric acid and increase its reabsorption in the kidneys leading to elevated SU (38). Ciclosporin, an immunosuppressant used in organ transplants, also has a profound effect on urate clearance and can accelerate the development of gout in the transplant population (37).

Risk factors for gout flares are not fully established, although several factors have been identified as contributing to flare risk. Higher SU concentrations are associated with an increased frequency of flares and a shorter time interval between them (39). A cohort study focused on comorbidities found alcohol consumption, CKD, obesity, hypertension and ischaemic heart disease to be major flare risk factors (40). Other factors linked to gout flares include baseline crystal deposits (41-43), co-morbidity clusters (44), ferritin levels (45), and omega-3 fatty acids (46). However, further research is needed to more accurately understand who might experience a gout flare and when.

Pathophysiology

Uric acid is the end-product of human purine metabolism (**Figure 1**). Biologically, urate acts as an antioxidant and has roles in the innate immune response (47). Hyperuricemia is typically defined as a SU concentration above 0.36 mmol/L (48) and is a necessary factor for the development of gout. However, only around one third of people with hyperuricaemia will go on to develop gout, indicating that other genetic and/or environmental factors are involved (49). Gout occurs when there is formation and deposition of MSU crystals in the joints, bones, or soft tissues, and there is typically an inflammatory response, either acute or chronic, to the presence of those crystals. These are discussed briefly below:

1. Hyperuricemia

The kidneys play a pivotal role in regulating SU, with various transporters involved in the process of urate secretion and reabsorption from the proximal tubal (50). Similar processes occur in the intestinal tract (51). Reduced urate clearance via altered urate transport in the kidneys and intestinal tract is the predominant factor in the pathogenesis of hyperuricemia and gout (29). Genome-wide association studies have identified single

nucleotide polymorphisms in various renal and intestinal urate transporters, resulting in direct effects on urate concentration (29, 31). Other risk factors for hyperuricemia and gout have been discussed in the previous section ('Risk factors and comorbid conditions').

2. Monosodium urate crystallisation

For MSU crystals to form, the SU concentration must first exceed the solubility threshold to reach supersaturation. Following this, nucleation is required to cluster together the dispersed molecules and form distinct crystal nuclei, which then allows for rapid crystal growth (52). The in vitro solubility threshold of urate is 0.42 mmol/L at pH 7.4 and 37 °C (53). Physiological, this threshold may be lower due to cooler temperatures in the extremities and a high concentration of sodium ions in the synovial fluid and around the joints, which reduces urate solubility (52). Other factors that promote urate crystallisation include slightly basic conditions (pH 7-9) and specific components of the cartilage or synovial fluid such as uric acid binding antibodies and collagen (52).

3. Acute inflammatory response

Up to a quarter of individuals with hyperuricemia have MSU crystal deposition but do not have gout (54). In individuals with gout, there is an innate immune response to the MSU crystals in the synovial fluid. This response is primarily driven by the activation of the NLRP3 inflammasome via Toll-like receptor activation and phagocytosis of MSU crystals by macrophages (55). NLRP3 inflammasome activation involves a two-signal initiation system to avoid unregulated activation. The first signal stimulates nuclear factor kB signalling and synthesis of inflammasome components and pro-IL-1B (56). The presence of MSU crystals is the second activation signal, causing the formation of an active inflammasome complex (57). This active complex converts pro-IL-1B and pro-IL-18 into mature forms, leading to a downstream signalling cascade. This cascade involves proinflammatory cytokines and chemokines which result in the recruitment of innate immune cells, interferon production and enhanced cytolytic activity of natural killer cells and T cells at the MSU crystals (55). Factors that can trigger the first signal include free fatty acids, lipopolysaccharides, gut microbiota and other microbiological factors (29). In most individuals, this acute inflammatory response is self-limiting, meaning that despite the continued presence of the MSU crystals, the gout flare will resolve (5). This resolution is mediated by various anti-inflammatory factors and by

neutrophil extracellular traps in which neutrophils release their DNA into the extracellular matrix causing degradation of proinflammatory mediators (58).

4. Chronic inflammatory response

When there is a chronic inflammatory response to the MSU crystals, tophi, chronic gouty arthritis, and structural joint damage can develop. This is generally referred to as advanced gout. Tophi can be described as chronic granulomatous inflammatory tissue around the MSU crystals (59) and can lead to infection, chronic pain and joint deformity (60). Tophaceous gout has a significant impact on quality of life (60) and has been associated with an increased risk of mortality (61) and rapid decline in renal function (62).

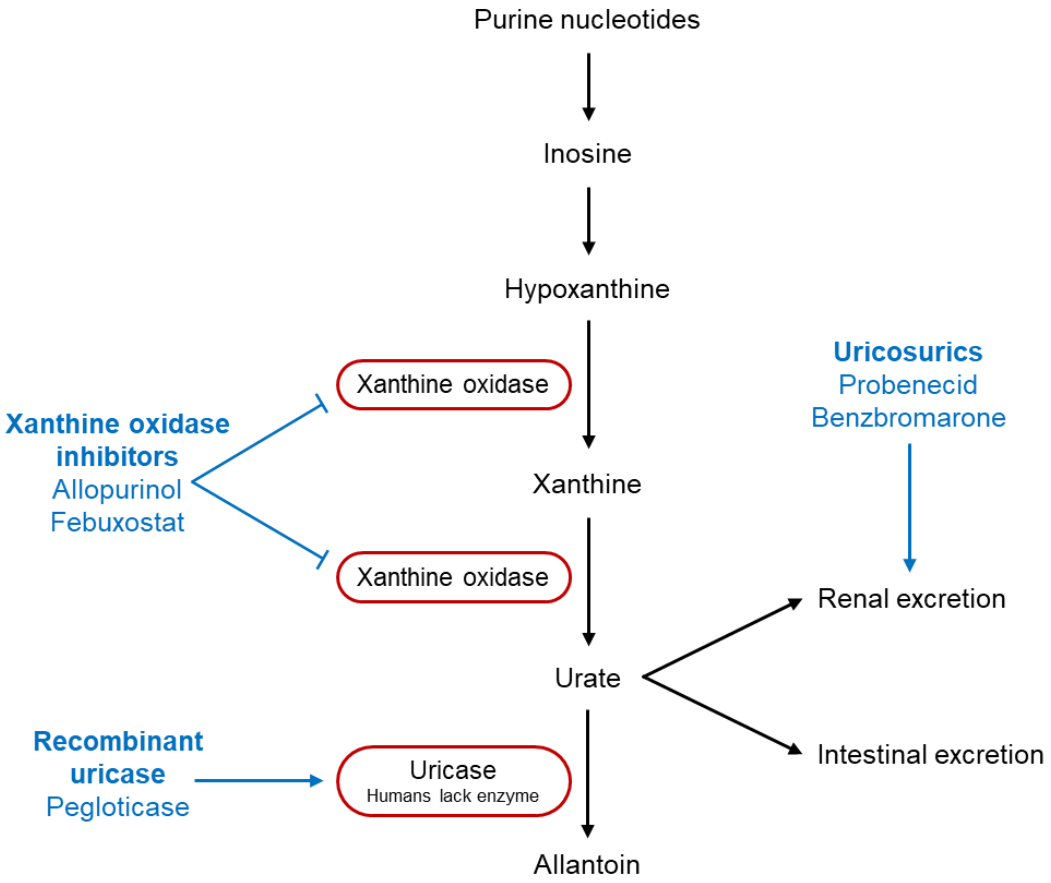


Figure 1. Purine metabolism pathway and site of action of different urate lowering therapies. Adapted from Stamp et al, 2024 (63) and Yip et al, 2023 (64).

Diagnosis

The gold standard for the diagnosis of gout is polarising light microscopy of MSU crystals obtained from a synovial fluid aspirate or material aspirated from tophi (65). This is particularly important in long standing gout which may present more atypically. Imaging studies (66), clinical history, examination and laboratory investigations may aid in diagnosis when aspiration is not feasible, and the presentation is a typical manifestation of gout (67). Hyperuricemia alone is insufficient to diagnose gout and relying on hyperuricaemia, alongside swollen or tender joints, may lead to the misdiagnosis of other forms of arthritis, such as calcium pyrophosphate crystal deposition disease, rheumatoid arthritis or psoriatic arthritis (68). During a gout flare, SU concentrations may drop which can also contribute to misdiagnosis (69). In research, the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria is most often used to classify gout (70) (**Table 1**).

Table 1. Simplified version of the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for Gout (70)

Entry Criterion	≥ 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	If **yes**, continue
Sufficient Criterion	Presence of MSU crystals in a symptomatic joint or bursa or tophus	If **yes**, can classify as gout without applying criteria below
Criteria (if Sufficient Criterion not met)	**Description**	**Score**
Clinical features		
Joint involvement during flare	Ankle or midfoot involvement	1
	MTP1 involvement	2
Characteristics of flare: 1. Erythema overlying joint 2. Can't bear touch or pressure to joint 3. Difficult to walk or use joint	One characteristic	1
	Two characteristics	2
	Three characteristics	3
Time-course of flare (presence of ≥2): 1. Time to maximal pain <24 hours 2. Symptom resolution ≤14 days 3. Complete resolution between flares	One typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus	Present	4
Laboratory tests		
Serum urate	Categories include: <0.24, 0.24-<0.36, 0.36-<0.48, 0.48-<0.60 and ≥0.60 mmol/L	Range from -4 to 4
Synovial fluid analysis of symptomatic joint	Not done	0
	MSU crystal negative	-2
Imaging		

Imaging evidence of urate deposition in joint via ultra-sound or DECT	Present	4
Imaging evidence of gout-related joint damage via x-ray	Present	4
Total score		**≥8 = classify as gout**

NOTE: This table provides a modified and highly simplified summary of the 2015 ACR/EULAR Classification Criteria for Gout. Key details and scoring specifics are omitted, and this table should not be used for diagnosing or assessing gout. For the complete and detailed criteria, please refer to the original source (70). DECT = Dual-energy CT, MSU = monosodium urate, MTP1 = first metatarsophalangeal joint.

Treatment strategies

There are four key pharmacotherapeutic principles in the management of gout: (i) rapid treatment of gout flares; (ii) long-term ULT to achieve target SU; (iii) gout flare prophylaxis to prevent flares when initiating ULT; and (iv) assessment and management of comorbid conditions (71).

1. Flare treatment

From the perspective of those with gout, the appropriate prevention and treatment of flares is a fundamental concern (11). Effective management of flares leads to more rapid and complete resolution of joint pain and inflammation. Oral treatment options include colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. The choice of therapy usually depends on the individual's comorbidities and concomitant medications, the side effect profile and the individuals previous experience (efficacy and/or adverse effects) with the drug (71).

Colchicine reduces inflammation by inhibiting microtubule polymerisation in neutrophils and monocytes, which blocks key inflammatory pathways (72). It is effective in managing acute gout flares (73), although gastrointestinal side effects such as diarrhea and nausea are common, especially at higher doses (72). Colchicine is typically administered as an initial single dose of 1 to 1.2 mg, followed by 0.5 to 0.6 mg one hour later (maximum dose of 1.5 to 1.8 mg in 24 hours) (73, 74). If the flare continues, colchicine can be reduced to 0.5 to 0.6 mg once or twice daily until 24-48 hours after the resolution of the flare (74). Dose adjustments are often required in individuals with renal or hepatic impairment, such as older adults (72). Co-administration with P-glycoprotein or CYP3A4 inhibitors reduces colchicine clearance (75), which increases the risk of myelosuppression and fatal pancytopenia, particularly

with chronic use (76). Additionally, concurrent use of statins or fibrates can increase the risk of myotoxicity (77). As it has a narrow therapeutic index, colchicine's use is limited by these potential drug-drug interactions and alterations in drug clearance (76).

NSAIDs reduce inflammation by inhibiting cyclooxygenase (COX) enzymes, which decreases the synthesis of prostaglandins (78). All NSAIDs appear to be similarly effective for gout (79), however aspirin is not used for treatment or prevention of flares as it can increase uric acid retention, potentially worsening gout (38). Commonly used NSAIDs include naproxen, ibuprofen, and indomethacin and are typically used for the duration of the flare (74). NSAIDs are generally effective and well-tolerated in patients without contraindications, such as renal impairment, peptic ulcer disease or cardiovascular risk factors (80). However, prolonged or high-dose use may lead to adverse effects such as gastrointestinal bleeding, renal dysfunction, and cardiovascular events (81), thus limiting their suitability, especially in older individuals and/or those with significant comorbidities.

Corticosteroids reduce inflammation by inhibiting multiple pathways involved in the immune response (82). Prednisolone is commonly used for systemic treatment, while intra-articular injections may be used for localised joint involvement in one or two joints (83). Systemic corticosteroids are typically used for the duration of the flare and tapered over days to weeks to reduce the risk of rebound flares, depending on factors such as flare severity, duration, and the number of joints involved (74). Although effective, corticosteroids can exacerbate conditions such as diabetes, hypertension, and cardiovascular disease (84), which are prevalent in the gout population. Short-term use is also associated with side effects such as insomnia, hyperglycaemia, oedema, and weight gain (84).

Interleukin-1 (IL-1) Inhibitors such as anakinra, canakinumab, and rilonacept are alternative treatment options for acute gout flares, especially when conventional therapies are ineffective or contraindicated (85). These biological agents inhibit the effects of IL-1, a key cytokine that drives inflammation in gout (55). While effective, these treatments are not currently registered for this indication in Australia and are associated with higher costs than conventional therapies and carry an increased risk of infections (86). Consequently, their use is typically restricted to specific cases where conventional treatments have failed (85).

2. Urate-lowering therapy

The long-term management of gout involves lowering and maintaining the SU below target concentrations to inhibit the formation of new MSU crystal deposits and to allow present ones to dissolve, thereby preventing both flares and the chronic complications of gout (87). The current recommended SU treatment target is <0.36 mmol/L, but in patients with a greater disease burden, <0.30 mmol/L is recommended to allow for faster MSU crystal dissolution (88). All rheumatology societies now recommend using a treat-to-target SU approach (88, 89), with extensive evidence that reaching the SU target improves long-term clinical outcomes (90, 91). A treat-to-target approach involves gradually lowering SU concentrations to a specific target, through stepwise adjustments in ULT, the medications used to achieve and maintain SU levels. As gout is a chronic crystal deposition disease, some guidelines suggest considering ULT in all patients with confirmed gout (35, 92). Additionally, studies have indicated potential cardiovascular and renal benefits of ULT treatment (particularly xanthine oxidase inhibitors) in gout (93, 94). Some guidelines argue against life-long therapy after a single or infrequent flare as the burden of treatment may outweigh the risks associated with gout (36). However, most agree that ULT should be commenced in people with a history of recurrent flares (≥2 per year) or in anyone with tophi, urate arthropathy, CKD and/or urate urolithiasis (35, 92, 95).

In Australia, two classes of ULT are available: xanthine oxidase inhibitors (i.e. allopurinol and febuxostat) which reduce urate synthesis and uricosurics (i.e. probenecid) which increases the renal excretion of urate. Allopurinol is first-line because of its efficacy, tolerability, low cost and once daily dosing. Febuxostat is an alternative xanthine oxidase inhibitor, however safety warnings of increased cardiac and all-cause mortality in 2018 (96) led to reductions in its use (97). While new evidence suggests there may in fact be no increased risk (98), in light of conflicting data, most guidelines still recommend febuxostat as a second line option for people in which allopurinol is contraindicated or intolerable (35, 99). Febuxostat may also be preferable in certain ethnic groups at higher risk of severe cutaneous reactions with allopurinol, such as those more likely to carry the *HLA-B*5801* allele, as discussed later in this chapter. Probenecid, a uricosuric, increases the renal excretion of uric acid and may be used as second-line monotherapy, particularly in individuals with a high cardiovascular risk, or added to ULT if monotherapy is insufficient. However, its use is limited by

reduced efficacy in people with poor renal function (creatinine clearance <50 ml/min) and it is contraindicated in people with previous urolithiasis, both of which commonly occur in gout (100). Benzbromarone is a second line uricosuric, but it is not registered in Australia and is only available through the Special Access Scheme, which allows certain health practitioners to access unapproved therapeutic goods for an individual patient on a case-by-case basis (101). It is associated with severe hepatotoxicity and requires regular monitoring (101). Newer ULT options for use in severe, treatment-refractory gout include pegloticase, a recombinant form of the uricase enzyme (102), although it has not been approved for use in Australia.

While ULT is effective and the treat-to-target approach is well-established, achieving target urate levels remains challenging for many patients. Furthermore, allopurinol is under-utilised (103), under-dosed (104) and poorly adhered to (105). Contributing to this is likely the significant changes to allopurinol dosing strategies over the last decade which affect allopurinol initiation, up-titration and maintenance dosing and are discussed in detail in the following sections.

2.1 Allopurinol

After oral absorption, allopurinol is rapidly and almost entirely converted to the active metabolite oxypurinol, which is thought to have the main therapeutic effect (104). Allopurinol and oxypurinol are structural analogues of hypoxanthine and xanthine (respectively) (53). They act by competitively inhibiting the xanthine oxidase enzyme, thereby preventing the development of uric acid (**Figure 1**). Oxypurinol is primarily cleared by the kidneys and has a half-life of 18-30 hours in individuals with normal renal function (53).

Allopurinol is generally well tolerated but carries the risk of developing the rare but potentially fatal allopurinol hypersensitivity syndrome (AHS; approximate incidence 0.1% (106)). AHS most commonly develops shortly after allopurinol initiation with over 90% of cases occurring within the first 9 weeks of exposure (106). It is characterised by cutaneous reactions (ranging from mild to fatal), fever, renal failure, hepatic dysfunction and blood dyscrasias. Carriage of the *HLA-B*5801* allele significantly increases the risk. Carriage of this allele is more prevalent in people of Han Chinese, Korean and Thai ethnicity (8–20%) compared to Caucasians (<5%) (107). Genetic testing is recommended in high-risk populations so that allopurinol use can be

avoided in those who carry the allele. Hande et al. identified high allopurinol dose, concomitant diuretic use and poor renal function as other risk factors for AHS (108). As these factors increase exposure to oxypurinol, it was presumed that heightened oxypurinol exposure increased AHS risk. Creatinine clearance (CrCl) based maintenance dose restrictions were thus implemented whereby 300 mg daily was the maximum recommended dose for people with CrCl <100 ml/min (108). However, these dosing guidelines resulted in less than 20% of people on allopurinol achieving SU targets (109, 110). Since then, conscientious efforts by Stamp et al. have identified that a high allopurinol initiation dose, but not the maintenance dose, is the major risk factor for the development of AHS (111). A maximum dose of 1.5 mg of allopurinol per unit of estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) has been proposed as a safe initiation dose (111). Thus, many guidelines recommend that allopurinol be commenced at 100 mg daily in patients with normal renal function and 50 mg daily is recommended in those with CKD (35, 36, 92, 95), although the degree of CKD that justifies a dose reduction is often unspecified.

Despite advances in knowledge about the optimal initiation dosing of allopurinol, maintenance dosing has been contentious, particularly in those with renal impairment. Studies whereby allopurinol was gradually increased beyond 300 mg daily to achieve target SU concentrations have shown no increased risk of AHS (112). However, no dose escalation study has, nor is likely to ever be sufficiently powered to detect a difference in the rate of AHS (107). Thus, a very small minority of guidelines still state that allopurinol maintenance dose should be restricted by CrCl (35). Regardless of the maximum dose, allopurinol should be up-titrated slowly to reduce the risk of AHS. Up-titration schedules vary, but guidelines generally suggest an escalation of 50–100 mg daily every 2- to 4-weeks until the SU target or maximum recommended dose is reached (88). Dose escalation studies have highlighted that the allopurinol maintenance dose required to achieve target SU concentrations varies greatly between individuals (63). Regression models have linked this variability to pre-treatment SU concentrations, with higher pre-treatment levels correlating with larger allopurinol dose requirements (104). Population pharmacokinetic-pharmacodynamic models have found the variability in allopurinol dose requirements between individuals to be explained by differences in baseline SU concentrations, renal function, total body weight and ethnicity (113). Additionally, a loss-of-function polymorphism in the *ABCG2* urate transporter has been

associated with a poor response to allopurinol (114). Failure to achieve and maintain SU targets is a commonly encountered problem, with patients consequently more likely to experience recurrent flares, tophi, and chronic gouty arthritis.

2.2 Adherence

Another major barrier to effective gout management is the low rates of adherence to ULT, with medication adherence in gout rated as one of lowest among chronic conditions (115). Various factors have been associated with this poor adherence, such as a limited disease understanding by some patients and healthcare providers (116), the asymptomatic periods between flares that may lead patients to perceive ULT as unnecessary (117), concerns about medication side effects (118), or a perceived lack of effectiveness of ULT (117). Strategies to address these challenges have been explored (119), including nurse- or pharmacist-led services (120), behavioural and educational interventions (121), and the development of self-management apps that encourage patient engagement and accountability in their care (122). In more complex cohorts, the presence of multiple comorbidities, polypharmacy, and the complexity of treatment regimens can further hinder adherence (123). Additionally, different adherence measures may provide diverse insights into adherence behaviours such as intentional versus unintentional non-adherence (124). Exploring adherence in specific patient populations, such as those with severe or difficult-to-manage gout, may offer valuable insights to inform tailored strategies for improvement.

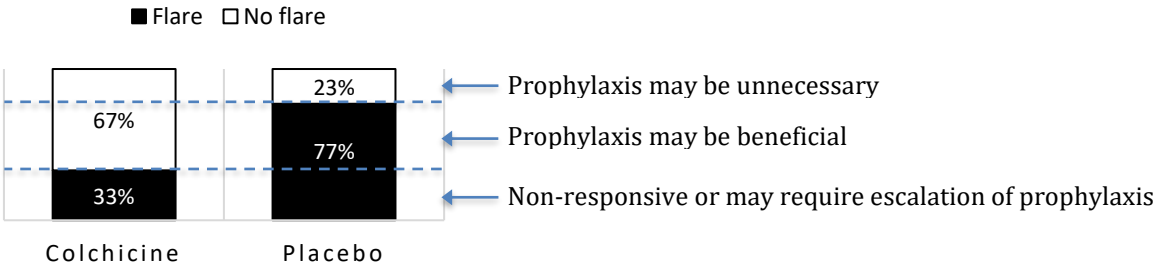
3. Flare prophylaxis

The initiation of ULT may precipitate a transient rise in gout flares, particularly during the first 6 months (99). While the exact mechanism of this rise in flares remains poorly understood, it has been proposed that a rapid decrease in SU concentration results in alteration of the chemical and/or physical state of existing MSU crystals (125). As SU concentrations fall, superficial crystals begin to dissolve, exposing an unprotected surface. Contact with this surface activates and increases expression of inflammatory cytokines, triggering flares. Favouring this theory is a post-hoc analysis of two ULT clinical trials, concluding that during weeks 9 to 12 after initiating ULT, lower post-baseline SU concentrations were associated with a higher incidence of gout flares ($P < 0.001$) (126). This trend reversed by weeks 49 to 52, with lower SU concentrations correlating with a reduced flare rate ($P = 0.002$).

To minimise this rise in flares, contemporary guidelines recommend the concurrent use of 'gout flare prophylaxis' when initiating ULT. Prophylaxis is generally recommended for a minimum of 6-months, with an even longer duration in people with a history of tophi or recurrent flares (127). Prophylactic options include low-dose colchicine, NSAIDs or corticosteroids. These medications are also used in the treatment of acute flares, albeit at higher doses and for significantly shorter durations. Despite integration into routine practice, the evidence supporting the use of prophylaxis is limited. Colchicine is recommended as first-line and is the only medication with randomised controlled trial (RCT) data supporting its prophylactic efficacy where reducing gout flares was the primary trial outcome (128-130). NSAIDs are used as first- or second-line and information supporting their safety and efficacy as prophylaxis has primarily been obtained from three large RCTs comparing febuxostat to allopurinol as ULT (131-133). Participants in these trials received either colchicine or naproxen for 8-weeks (131, 132) or 6-months (133) as prophylaxis whilst initiating the randomised study drug (allopurinol or febuxostat). Using a post-hoc analysis, 6-months of prophylaxis was deemed to be more effective than 8-weeks, with no apparent increase in adverse events (134). Corticosteroids are recommended as last-line and should only be used in people who are intolerant, contraindicated or refractory to colchicine and/or NSAIDs (135). There is however no RCT evidence on the use of corticosteroids as gout flare prophylaxis (92), although their use and side effect profile are well established in many other inflammatory conditions.

With limited high-quality evidence investigating the efficacy of these medications in preventing flares during ULT initiation, it is difficult to establish their true benefit. The two primary RCTs comparing prophylactic colchicine to placebo in patients commencing ULT both demonstrated lower flare rates in the colchicine arm, although the studies were small, with fewer than 22 participants per arm completing each trial (128, 129). Between 16% and 27% of participants withdrew or were lost to follow up, and those with severe renal impairment were excluded. The first RCT (128), published in 1974, only included men, did not report participant demographics, and excluded participants who failed to achieve or maintain SU concentrations, demonstrating potential bias and limited applicability to typical gout patients. Thus, extrapolating these findings from a small group of individuals to the vast population requires caution. Furthermore, given the advancements in gout management since this trial, caution is

also needed when interpreting these findings in the context of current practice. In the second RCT (129), published in 2004, although flare rates were statistically lower in the colchicine arm (33% versus 77% for placebo, over 6-months, P = 0.008), the absolute reduction was 1.5 fewer flares on average per person during the first 3-months and 1 fewer flare during months 3–6. Compared to the additional costs, monitoring, pill burden, side effects and potential for drug-disease or drug-drug interactions, the overall benefit is less apparent. Another important consideration is that the risk of flares varies between individuals. Hence, although some will benefit from prophylaxis, others will continue to flare despite receiving it, and some may not require prophylaxis at all. Thus, the current approach of administering prophylaxis to all patients may result in inefficient, prolonged or unnecessary drug use. This is illustrated by comparing the proportion of participants that flared whilst receiving colchicine in the aforementioned study with those administered placebo (**Figure 2**) (129). Almost 1 in 4 individuals (23%) who received placebo did not flare and were therefore at risk of unnecessary



prophylactic drug exposure. A third (33%), continued to flare despite receiving prophylaxis, signifying potential non-responders or individuals requiring escalation of therapy. Thus, less than half (44%) of individuals administered prophylaxis appeared to benefit.

Figure 2. Visual representation of the proportion of participants that had ≥1 flare (over the 6-month study period) in the prophylaxis arm versus placebo arm after initiating allopurinol therapy for gout (129).

The risk of unnecessary prophylactic drug exposure is significant given the complexity and multi-morbidity often encountered in this patient population, combined with the well-known toxicities and potential for drug-disease and drug-drug interactions with these prophylactic medications. Severe and potential lethal colchicine toxicity can occur if doses are not adjusted for renal impairment or if drug-drug interactions are not identified and doses modified accordingly (135). Studies have reported inappropriate

prescribing of colchicine to be as high as 73.8%, with some patients given colchicine prophylaxis without any ULT and others where prophylaxis was continued beyond clinically necessary (136).

There are also many well-known risks associated with NSAID use (100), including increased risk of bleeding, peptic ulcers, cardiovascular events, worsening heart failure and renal impairment. In the studies used to support the use of NSAIDs as flare prophylaxis (134), multiple safety measures were implemented which may not be routinely followed in everyday practice. For instance, participants with a CrCl <50 ml/min were prohibited from receiving naproxen. However, data from a gout registry indicates that nearly half of all gout patients have CKD, and NSAIDs were administered to 14% of patients with stage 3 (CrCl 30–59 ml/min) and 4% with stage 4 (CrCl 15–29 ml/min) CKD (125). This highlights a potential gap between clinical trial protocols and real-world practice, particularly for higher-risk patients. Additionally, in the 6-month RCT (133), participants on naproxen were co-administered a proton pump inhibitor (PPI) for gastrointestinal protection. Although concomitant PPI use is recommended by some guidelines, whether it is co-prescribed and appropriately deprescribed in clinical practice is unknown. Long term oral corticosteroids can also increase the risk of peptic ulcers and worsen heart failure, and they are also associated with impaired glycaemic control, hypertension, immunosuppression, psychiatric effects, sleep disturbance, glaucoma, osteoporosis, weight gain, impaired wound healing, muscle wasting and skin atrophy (100).

With limited studies investigating flare risk factors, particularly during the initiation of ULT, and minimal data on the real-world use and safety of prophylaxis, improving the use of prophylaxis remains both a challenge and unique opportunity to improve patient outcomes. Recent research on start-low, go-slow treat-to-target dosing strategies for ULT has shown promise in reducing the need for prophylaxis. For example, trials examining stepwise dose escalation with febuxostat have shown that this approach is as effective as standard-dose febuxostat plus colchicine (137, 138). Understanding how different ULT dosing strategies influence flare risk could improve the use of prophylaxis and enhance long-term patient outcomes. Additionally, rapid reductions in SU may also have broader implications, with studies linking such reductions to poorer health outcomes and an increased risk of cardiovascular events (139). Therefore, optimising ULT dosing strategies, along with a better understanding of the benefit,

safety and optimal duration of current prophylactic drugs could be key to improving gout management.

4. Other management

Due to the high prevalence of cardiovascular comorbidities in gout, it is important to screen individuals with gout for associated metabolic co-morbidities and cardiovascular risk factors. These cardiovascular comorbidities can complicate gout management and increase the risk of adverse health outcomes (35, 140). Managing these co-existing conditions also reduces the broader risk of cardiovascular events, enhancing overall patient health and quality of life. Careful consideration should be given to medication selection, as treatments for comorbidities may affect gout management, and vice versa (71). For example, angiotensin-II receptor blockers such as losartan may lower SU whereas antihypertensives such as thiazide diuretics may increase SU (141, 142). In addition to pharmacological management, lifestyle modifications such as weight loss, regular physical activity, and dietary adjustments such as reducing purine-rich foods, alcohol intake, and sugar-sweetened drinks can help reduce SU concentrations and improve cardiovascular health (35).

Complex factors and optimising therapy

As previously highlighted, real-world management of gout is complex due to various factors. These include evolving approaches to ULT dosing, poor medication adherence, the potential for increased flares when initiating ULT, and an ageing population with more comorbidities and polypharmacy, which complicate standard therapeutic approaches. Suboptimal management can lead to severe disease progression, marked by recurrent flares, painful joint deformities, and heightened disability, all of which diminish quality of life (17). Conversely, individuals with complicating factors, such as high disease burden, organ dysfunction, polypharmacy, comorbidities, and geriatric syndromes (143) are inherently more challenging to treat, which may result in suboptimal gout control (144).

Individuals with severe or multifaceted presentations of gout often require specialised management by a rheumatologist to enable the provision of tailored treatment strategies. In these complex cohorts, optimising therapy is particularly challenging, especially in managing and preventing flares during the initiation or escalation of ULT. A deeper understanding of the real-world management of individuals with complex gout and their

flare patterns may help identify important factors for personalising therapy and improving outcomes. Additionally, recognising the factors that may contribute to complex gout can support early identification and timely intervention, which can enhance long-term care in this population.

Therefore, the overarching objective of this thesis was to investigate the challenges of gout management in complex patients and explore potential strategies to personalise the use of ULT and flare prophylactic treatments.

Primary research questions

This thesis aimed to investigate the following primary research questions:

1. What is the impact of age-related physiological changes on drug disposition, particularly in older adults with geriatric syndromes, to understand implications for personalising medication safety and effectiveness.

2. What is the real-world adherence rate to allopurinol among complex patients when using multiple adherence measures, and what are the factors that may influence individualised adherence strategies within this population.

3A. What are the risks of gout flares associated with ULT initiation or escalation, and what is the influence of different ULT regimens on flare risk.

3B. What is the efficacy and safety of prophylactic treatments in preventing flares during ULT initiation and escalation and what is the optimal duration of prophylaxis use.

4A. What are the clinical characteristics and flare patterns among complex gout patients, and are there any age-related differences to support age-specific management approaches.

4B. What is the impact of factors such as age, tophaceous gout, use of prophylaxis, and omega-3 index on flare frequency and management needs, and can these be used to guide individualised treatment planning in complex gout patients.

Thesis Outline

Chapter	Chapter Title and Publication Status
1	Literature review
2	Alterations in drug disposition in older adults: a focus on geriatric syndromes. ***Published.***
3	Investigating adherence to allopurinol in patients with gout using three approaches.
4	Comparative risk of gout flares when initiating or escalating various urate-lowering therapy: a systematic review with network meta-analysis. ***Published.***
5	Characterising gout in complex populations: exploring age-related differences and flare patterns
6	General discussion and conclusion

2 Alterations in drug disposition in older adults: a focus on geriatric syndromes

Chapter overview

The literature review in this thesis (**Chapter 1**) highlights the complexities of medication management in gout, particularly in complex older adults with polypharmacy and multiple comorbidities. This chapter presents a review on alterations in drug disposition associated with aging and geriatric syndromes (**Paper 1**). While **Paper 1** is not specific to people with gout, changes in drug disposition are highly relevant to gout management in older adults. To align this chapter with the broader context of this thesis, additional text (i.e., beyond what is included in the published manuscript) specific to gout has been added at the end of this chapter. In brief, gout predominantly affects older populations, who often present with multiple comorbidities and age-related physiological changes that may influence the efficacy and safety of gout therapies. Understanding these changes is important to enable the safe and effective use of urate-lowering therapies (ULTs) and prophylactic treatments, particularly in the presence of polypharmacy and common geriatric syndromes such as frailty, falls and cognitive decline. By highlighting key pharmacokinetic and pharmacodynamic considerations in older adults, this chapter provides a foundation for addressing the complexities of gout treatment in this vulnerable population discussed in **Chapter 5**.

Citation details

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Additional information

The statement of authorship for the research presented in this chapter is available in **Appendix 4**.

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REVIEW

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Alterations in drug disposition in older adults: a focus on geriatric syndromes

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ABSTRACT

Introduction: Age-associated physiological changes can alter the disposition of drugs, however, pathophysiological changes associated with geriatric syndromes in older adults may lead to even greater heterogeneity in pharmacokinetics. Geriatric syndromes are common health problems in older adults which have multifactorial causes and do not fit into distinct organ-based disease categories. With older adults being the greatest users of medications, understanding both age- and geriatric syndrome-related changes is important clinically to ensure safe and effective medication use.

Areas covered: This review provides an overview of current evidence regarding pharmacokinetic alterations that occur with aging and in common geriatric syndromes, including frailty, sarcopenia, dementia, polypharmacy and enteral feeding. The evidence is presented according to the four primary pharmacokinetic processes (Absorption, Distribution, Metabolism and Excretion).

Expert opinion: There is some evidence to inform our understanding of the impact of chronological aging and various geriatric syndromes on drug disposition. However, many areas require more research, including drug induced inhibition and induction of cytochrome P450 enzymes and the clinical utility of emerging methods for estimating renal function. There is a need to develop tools to predict alterations in drug disposition in subgroups of older adults, particularly where the currently available clinical information is sparse.

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Advancing age; aging; dementia; drug disposition; enteral feeding; frailty; geriatric syndromes; pharmacokinetics; polypharmacy; sarcopenia

1. Introduction

Worldwide, the number and proportion of older adults continues to rise. By 2050, it is predicted that one in six people will be aged 65 years or older and the number of people aged 80 years or older, known as the oldest-old, will triple to 426 million [1]. With aging, the prevalence of chronic medical conditions increases, leading to multimorbidity and subsequent polypharmacy [2]. Polypharmacy, commonly defined as the use of five or more regular medications [3], is associated with a significant increase in the risk of experiencing drug-drug interactions (DDIs), drug-disease interactions, adverse drug reactions and other subsequent negative effects. These include increased healthcare expenditure, falls, cognitive impairment and mortality [4]. Despite being the greatest users of medications, older adults are often excluded from clinical trials due to complex pathophysiology, altered organ function, polypharmacy or simply older age [5–7]. This under-representation is particularly problematic as age-related physiological changes can significantly alter the pharmacokinetics and pharmacodynamics of numerous drugs, placing older adults at a greater risk of adverse outcomes. These physiological changes are caused by the cumulative effects of various forms of molecular and cellular damage, resulting in a gradual decline in various body functions and hence, a reduced ability to adapt to environmental exposures [8]. There is a large degree of interindividual variability in the aging process which increases with advancing age. Even within an individual, age-related changes are not consistent, therefore some biochemical processes or organ functions may be compromised whilst others remain fully functional [9]. Biological aging, also known as physiological aging, is therefore more accurate than chronological age at describing the aging process [10].

In addition to multiple medical conditions, older adults also commonly experience geriatric syndromes. Geriatric syndromes refer to common health problems that result from multifactorial causes; they do not necessarily fit into distinct organ-based disease categories [11]. Examples of geriatric syndromes include sarcopenia (a progressive and generalized skeletal muscle disorder), cognitive syndromes, falls and frailty. Often, other conditions such as polypharmacy and the need for enteral feeding are also considered geriatric syndromes due to their common occurrence in older adults and multifactorial causes. Geriatric syndromes are associated with increased hospitalization, health care expenditure, morbidity and mortality [12]. They can be challenging to identify and manage, as the presenting complaint may not necessarily represent the underlying pathological cause, such as delirium (acute confusion) occurring as a consequence of a urinary tract infection. Also, geriatric syndromes are often multifactorial and co-occur with one another. For example, falls are more likely to occur in the presence of polypharmacy and sarcopenia [11].

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Article highlights

- The pharmacokinetics of drugs may be significantly different in older adults when compared to younger adults. Within the older patient population, drug pharmacokinetics might further differ according to the presence or absence of geriatric syndromes.
- Changes to oral drug absorption are unlikely to be clinically significant with ageing, although the evidence to support this is inconclusive. However, depending on the placement (pre or post pyloric), drugs administered via enteral feeding tubes may have significantly altered bioavailability.
- Significant changes in body weight, body composition (i.e. muscle mass and fat mass) and protein binding can occur with advanced age and in some geriatric syndromes including frailty and sarcopenia. Such changes can alter the volume of distribution of drugs.
- Drug clearance via hepatic metabolism and renal excretion is the most clinically significant pharmacokinetic parameter to guide drug dosing in older adults.
- In older adults there is reduced phase I metabolism in the liver due to reduced liver size, blood flow and oxygen supply. In frailty there may also be reduced phase II metabolism. Polypharmacy increases the risk of drug-drug interactions via hepatic enzymes.
- Older adults generally have reduced renal drug clearance compared to younger adults. Renal impairment is common in frail older adults due to their reduced capacity to recover post injury. Drug-drug interactions can also occur in the kidneys, affecting the clearance of drugs.
- This box summarizes key points contained in the article.

With a multitude of possible alterations occurring in diverse organ systems (Table 1.), the combined effects of these changes on drug disposition is of high clinical importance to ensure safe and effective medication use in older adults. The aim of this review is to provide an overview of the possible clinically relevant pharmacokinetic changes that occur with both aging and common geriatric syndromes. Specifically, we will outline and discuss the changes according to the four primary pharmacokinetic processes (Absorption, Distribution, Metabolism and Excretion).

2. Chronological age-related changes in drug disposition

Drug disposition describes the movement of a drug into, through and out of the body, whereas pharmacodynamics refers to the biochemical and physiologic response of the body to a drug. The disposition of a drug is mathematically expressed using pharmacokinetics. In this review, however, the terms drug disposition and pharmacokinetics are used interchangeably. Age-related changes in physiology have been found to alter the pharmacokinetics of many drugs depending on both drug-specific and patient-specific characteristics [13]. These characteristics include the physiochemical properties of the drug, its hepatic extraction ratio, the

Table 1. Key changes that may affect drug disposition in older adults.

Determinant	Definition and Physiological/Pathophysiological Characteristics	Potential Alterations Important in Pharmacokinetics
Chronological age	• Associated with an increased prevalence of chronic medical conditions, multimorbidity and polypharmacy • Geriatric syndromes are common in older adults	• Limited available evidence on age-related changes in drug disposition, particularly for the oldest old (people aged 80 years or older) • Drug metabolism and excretion are the most likely to have clinically significant changes in older adults
Frailty	• Compromised ability to response to external stressors and decreased physiologic reserve • Associated with unspecified inflammation, weight loss, and reduced albumin concentrations, muscle strength and adiposity	• May result in reduced phase II drug metabolism and renal clearance
Sarcopenia	• Low muscle strength and low muscle volume and/or quality • Includes the sub-type sarcopenic obesity in which there is both low muscle mass and increased adiposity	• Limited evidence available on the effects of sarcopenia on drug disposition
Dementia	• Progressive reduction in cognitive and physical function and behavior • Associated with weight loss and reduced albumin concentrations	• May result in increased permeability and reduced P-glycoprotein activity of the blood brain barrier
Polypharmacy	• Term used to denote the concurrent use of multiple medications (most commonly defined as five or more medications)	• Increases the risk of both drug-drug and drug-disease interactions • Can affect all aspects of drug disposition including absorption, distribution, metabolism and excretion
Enteral feeding	• Involves the placement of an enteral feeding tube as an alternative method to administer nutrition and drugs	• Significant alterations in drug absorption may occur depending on the physiochemical properties of the drug and whether a pre-pyloric or post-pyloric tube is inserted • Multiple factors should be taken into consideration before using the enteral route for drug administration

elimination pathway and the organ function, concomitant medications, and disease states of the patient [8]. Alterations to any of the four primary pharmacokinetic processes may affect clinicians' choice of drug, dose, dosage form, frequency, route of administration and the duration of treatment. Considering each of those factors, is important to achieve a safe and effective medication regimen in older adults.

2.1. Absorption

Absorption refers to the process in which a drug proceeds from the site of administration into the systemic circulation. For oral drugs, absorption commonly occurs in the small intestine via passive diffusion or active transport. The fraction of the drug dose that enters the systemic circulation unchanged (i.e. avoiding first pass metabolism) is known as the bioavailability [14]. After oral ingestion, drugs may undergo partial or full dissolution in the stomach. In older adults, this process may be affected by reduced gastric acid production [15,16] and further impeded by commonly encountered medications such as proton pump inhibitors (or other medications that increase gastric pH) [16,17]. Higher gastric pH may increase the absorption of weakly acidic drugs due to increased dissolution, or more commonly, reduce absorption of weakly basic drugs due to decreased dissolution. Elevated pH may also cause early dissolution of enteric coated delayed-release dosage forms (e.g. enteric coated sulfasalazine), which may cause drug degradation and hence reduced therapeutic effect [16,17].

Older adults may also experience delayed gastric emptying and decreased gastrointestinal motility due to reduced intestinal blood flow and gastric mucosal atrophy [18,19], although the evidence to support this is inconsistent and its relationship with drug absorption is unclear. There does not appear to be altered drug absorption via passive diffusion across the gastrointestinal epithelium with aging. However, a reduction in carrier-mediated transport has been shown to compromise the absorption of actively transported nutrients including iron, calcium and vitamin B12 [20].

Age-related changes in the function and expression of p-glycoprotein (P-gp), the main intestinal efflux transporter, and mucosal enzyme activity in the intestine remains largely unclear. The effects of aging on the liver (discussed below) may reduce first-pass metabolism, thereby increasing the amount of drug that enters the systemic circulation unchanged. This may be clinically significant for drugs with extensive first-pass metabolism and a narrow therapeutic index, or for prodrugs (which require metabolic conversion to the active form) [21]. Overall however, the clinical significance of the effects of increased chronological age on oral drug absorption are inconclusive. Absorption is not limited to the oral route and occurs after drug administration to other extravascular sites including intramuscular, intradermal, subcutaneous and pulmonary. However, limited evidence exists regarding age-related changes on non-oral drug absorption.

2.2. Distribution

In the distribution phase, the volume of distribution refers to the theoretical volume a drug would distribute into, if its concentration corresponded to the measured blood, serum, or plasma concentration. Therefore, larger volumes of distribution indicate an increased distribution of the drug within compartments other than the circulating blood. The volume of distribution is largely dependent on the extent of tissue and plasma protein binding. Older adults on average have a relative reduction in total body water (20%) and lean muscle mass (30%) and a relative increase in body fat (30%) [22]. These variations in body composition may increase the volume of distribution for highly lipophilic drugs such as diazepam, resulting in the prolongation of their elimination half-life, potentially leading to accumulation and toxicity. In contrast, the volume of distribution for highly hydrophilic drugs (e.g. digoxin, theophylline and cimetidine) may decrease, resulting in higher plasma concentrations shortly after administration [21]. This is particularly important for highly hydrophilic drugs such as digoxin that are administered as a loading dose, whereby loading dose reductions are often recommended in older adults to avoid toxicity. However, the lipophilicity of a drug should not be used as a sole factor to predict the direction or magnitude of change in volume of distribution as in some cases the change can be unpredictable, particularly in obese populations [23].

A reduction in albumin, one of the two-primary drug-binding proteins, is commonly observed in older adults. In contrast, alpha 1-acid glycoprotein concentrations often increase with older age, but this is likely due to concomitant disease states such as acute illness or chronic inflammatory diseases including cancer, rather than chronological aging alone [24]. Changes to plasma binding proteins may theoretically affect the unbound portion of highly protein-bound drugs. For most drugs however, this change in unbound fraction is unlikely to alter unbound drug concentration due to the equilibrium that occurs through drug elimination. While changes to plasma protein binding are unlikely to be of clinical importance, caution must be taken when interpreting therapeutic drug concentrations as they typically concern total drug concentrations. This is because the unbound concentration is likely to be more closely correlated to the 'drug effect' in comparison to the total drug concentration [25].

2.3. Metabolism

Metabolism is the process by which a drug is converted from one chemical form to another, often to a more water-soluble form to facilitate elimination via the kidneys. Although metabolism most commonly occurs in the liver, the gastrointestinal wall, lungs, blood and kidneys also possess metabolic capacity [26]. In the liver, the rate of drug metabolism depends on the rate of hepatic blood flow, drug transfer into the hepatocytes and the metabolic

capacity of intracellular enzymes. Hepatically cleared drugs are broadly classified as having a high or low hepatic extraction ratio. The metabolism of drugs with a high hepatic extraction ratio (flow-limited) is largely dependent upon the rate of hepatic blood flow. In contrast, for drugs with a low hepatic extraction ratio (capacity-limited), metabolism is largely dependent upon intracellular enzyme activity and the unbound drug fraction. The liver undergoes various changes with advancing age including reduced hepatic blood flow (40–60%), liver mass (20–40%) and oxygen supply (required as a co-substrate in cytochrome pathways) to the hepatocytes [27]. These changes can result in reduced phase I metabolism, such as oxidation via cytochrome (CYP) P450 enzymes, reduction and hydrolysis [28]. Consequently, flow-limited drugs such as morphine, propranolol and verapamil are most likely to be affected and may have reduced metabolism and increased risk of toxicity [27]. Some capacity-limited drugs may also have reduced clearance in older adults, particularly drugs such as theophylline that have a high fraction unbound [29]. Reduced hepatic clearance is not thought to be due to a reduction in the expression or function of the CYP450 enzymes, but rather a result of the aforementioned changes to liver size, blood flow, drug transfer and reduced oxygen supply [30,31]. By contrast, phase II metabolism appears to be largely preserved in healthy older adults [28].

2.4. Excretion

The final phase in the drug disposition cycle is excretion, whereby the drug or metabolite is removed from the body, predominately through the urine, but this could also occur via the bile, feces or exhalation. After age thirty, renal function begins to decline, and from age forty, there is a decline of approximately 1% per year [32]. This decline is related to structural and functional changes in the kidney, including a reduction in the number of functioning glomeruli and increased nephrosclerosis, resulting in decreased renal blood flow and permeability, alterations to cortical and medullary volume and impaired tubular function (both secretion and re-absorption) [33,34]. This may be further exacerbated by co-morbid conditions commonly experienced in older adults such as hypertension, diabetes mellitus and cardiovascular disease, or by the medications used to manage these conditions [8]. As renal function diminishes, the elimination of renally cleared drugs or their metabolites decreases, with consequential prolongation of drug half-life and increased plasma concentration [35]. This is particularly important for narrow therapeutic index and/or nephrotoxic drugs such as lithium, gentamicin and digoxin [21]. There is also some evidence to suggest that chronic kidney disease (CKD), which is more common in older adults, can reduce the clearance of non-renally cleared drugs via reduced activity of specific phase I and phase II drug metabolizing enzymes [36–38].

3. Frailty

Frailty is a biological syndrome that is characterized by the compromised ability to respond to external stressors and decreased physiologic reserve. Frail individuals have cumulative impairment in the function of multiple organs and systems, resulting in increased vulnerability and a reduced ability to recover after an acute event (such as an infection) [39–41]. Frailty is also characterized by unspecified systemic inflammation, indicating either a contributory role of inflammation to the development of frailty or a shared pathway [27,42,43]. The concept of frailty was introduced, in part, to address the limitations of chronological age as a marker for underlying biological age with the aim of being able to identify those who are at increased risk of morbidity and mortality [41]. Frailty is highly correlated with chronological age, as such this section aims to highlight the changes observed in frail older adults, compared to healthy older adults. Based on the definition of frailty, changes in pharmacokinetics are likely to be exaggerated in people living with frailty compared to non-frail age matched people [41].

Changes in absorption with frailty are largely unknown. Increased bioavailability of oxybutynin has been observed in frail versus robust older adults, possibly due to increased absorption or reduced first pass metabolism [44]. Changes in the microbiota of the gastrointestinal track may impact absorption; reduced lactobacilli and increased *Enterobacteriaceae* has been observed in people with high frailty scores [45], but the clinical implications for absorption of medications has been largely undetermined.

Frailty is often characterized phenotypically through weight loss, reduced muscle strength and adiposity [46,47] (changes in pharmacokinetics with sarcopenia are presented separately). This altered body composition could theoretically impact the distribution of hydrophilic and hydrophobic drugs. However, Hilmer and colleagues found no changes in the volume of distribution of gentamicin (a hydrophilic drug) in frail older adults [48]. In addition to changes in body composition, albumin concentration is reduced by a further 5% in frail compared to healthy older adults [42,49,50]. Additionally, while alpha 1-acid glycoprotein is thought to be unchanged with aging, it is increased in a number of chronic inflammatory diseases indicating that it may also be increased in frail older adults [51,52]. These changes in plasma drug-binding proteins are likely only clinically relevant for drugs that are highly protein bound and are either primarily cleared by the kidneys or have a high hepatic extraction ratio [53].

Inflammation associated with frailty or other states of increased inflammation (such as cancer and auto-immune diseases) may lead to down regulation of drug metabolizing enzyme expression [54], as increases in inflammatory markers have been associated with reductions in the activity of phase I metabolism through CYP enzymes and esterases [55,56]. However, a study of HIV medications (efavirenz and atazanavir/ritonavir) which all undergo metabolism via CYP450 enzymes found no difference in clearance with frailty [57]. Phase II metabolism may also be reduced in frailty. Wynne

and colleagues found reduced clearance of paracetamol (through glucuronidation) and metoclopramide (via glucuronidation and sulfation) in frail but not robust older adults [58–60].

Frail older adults generally have reduced renal function and there is a resultant reduced clearance of renally cleared medications [48,61]. As impaired ability to recover homeostasis is a hallmark of frailty, this observation of reduced renal function is likely due to reduced ability to recover from previous renal injury (due to medications or otherwise) [48,61,62].

Overall, individuals living with frailty likely have physiological changes that result in altered drug disposition, including reduced hepatic and renal drug clearance. This could lead to increased medication exposure, increasing the risk of toxicity and adverse drug events. However, studies demonstrating a clear cause-effect relationship between the proposed pharmacokinetic changes and adverse clinical outcomes are still lacking or inconclusive [63,64]. Frailty has been associated with an increased risk of medication-induced harm such as adverse drug reactions [65–-65–68]. This increase in harm may be due to the pharmacokinetic changes described here, due to vulnerability to the adverse effects conferred through their state of frailty (i.e. pharmacodynamic changes), or a combination of both.

4. Sarcopenia

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality [69]. It is considered probable in the presence of low muscle strength and is confirmed if low muscle volume or quality is also present. If low physical performance is additionally present, then sarcopenia is considered severe [69]. A limitation of this criteria is that different cut-points have been applied clinically, and some measures are population and device specific, limiting the ability to develop standardized definitions. An increasingly recognized sub-type of sarcopenia is sarcopenic obesity, which occurs in individuals who have both low muscle mass and increased adiposity [70], and as such have reduced muscle mass despite increased body mass index. Due to this variability in clinical diagnosis and definitions, determining how sarcopenia alters drug disposition and the clinical implications of this can be difficult.

Based on pharmacokinetic principles, distribution of drugs is likely to be altered in older adults with sarcopenia. Specifically, drugs that are preferentially distributed to skeletal muscle are likely to have a lower volume of distribution in sarcopenic vs non-sarcopenic individuals. Assuming that overall drug clearance is unchanged, this will not alter the average steady state drug concentration. However, the lower volume of distribution will result in higher peaks and lower trough drug concentrations, which may potentially increase the likelihood of an individual experiencing adverse drug reactions.

Unfortunately, the results of clinical trials to determine the association between sarcopenia and the pharmacokinetics of medications are not yet available. In a small trial of 25 patients who received chemotherapy agents (5-fluorouracil and oxaliplatin) with or without bevacizumab for colorectal cancer, no association between skeletal muscle mass and total exposure to 5-fluorouracil was identified [71]. Drug trials in various cancers have demonstrated an association between sarcopenia and dose related drug toxicities, necessitating treatment delays and dose reductions [72]. Numerous other outcomes have been associated with sarcopenia, including post-operative survival, morbidity and drug treatment (cancer specific survival and cancer remission) related outcomes [72]. Some, but not all of these may be explained by altered drug pharmacokinetics. Since the underlying causative factors of sarcopenia are numerous and its pathophysiology is complex, whether adverse treatment outcomes are due to direct effects on drug pharmacokinetics (and/or pharmacodynamics), or if it is a surrogate for other effects remains to be determined [70]. Furthermore, all cases of sarcopenia are unlikely to have an equivalent effect (if any) on the pharmacokinetics of a medication, meaning high interindividual variability. Evidently, further research is warranted to address these important issues.

5. Dementia

Dementia is the term used to describe a progressive syndrome characterized by reductions in cognitive and physical function and behavior. There are different types of dementia with different underlying etiology, the most common being Alzheimer's disease [73]. There is limited direct evidence of the pharmacokinetic changes that may be observed with dementia and specific changes may depend on the type of dementia. Dementia is highly correlated with aging and frailty. Therefore, when caring for a person living with dementia, age-related changes presented in the previous sections, particularly chronological aging and frailty, should be considered [52].

It is currently unclear whether there are specific changes to absorption in people with dementia. Studies in mouse models of Alzheimer's disease have found reduced intestinal permeability and alterations in intestinal expression of certain drug transporters, resulting in reduced oral absorption of certain drugs (e.g. valsartan and digoxin) [74,75]. A human clinical study that investigated the pharmacokinetics of delta-9-tetrahydrocannabinol found no difference to time to peak concentration in people with versus without dementia [76], while a study with rivastigmine found increased oral absorption in people with dementia, but with a delay to peak concentrations [77]. Therefore, further research is currently required.

Regarding distribution, weight loss is common in people with dementia, particularly in the advanced phases of the disease, which may affect the distribution of medications [78]. Additionally, a 10% reduction in albumin has been observed in people with dementia compared to age-matched controls, but changes in alpha 1-acid glycoprotein are unclear [79–82]. Perhaps the most studied pharmacokinetic process in people with dementia is the distribution of medications into the brain. This is influenced both by the integrity of the Blood Brain Barrier (BBB) (which functions as a protective barrier, limiting movement of certain molecules while still allowing oxygen and carbon dioxide exchange) and the activity of P-gp at the BBB (which facilitates removal of molecules from the brain). Studies indicate that there is

increased permeability of the BBB in people with dementia compared to age-matched controls without dementia [83,84]. Studies also suggest that P-gp activity at the BBB may be impaired in people with dementia [85,86]. Taken together, these changes in BBB permeability and reduced P-gp activity likely result in increased access of drugs into the brain. This is supported by clinical studies which have found increased susceptibility of people with dementia to neurological adverse drug effects [52,87].

Both increases and decreases of CYP enzyme expression have been found in mouse models of Alzheimer's disease [75]. Additionally, mouse studies have found alterations in drug transporters in the kidneys which could lead to alterations in renal drug excretion [88]. The clinical implications of these potential alterations in humans have not, to our knowledge, been investigated. However, renal impairment is common in people with dementia [89,90].

Overall, there is evidence that there may be physiological alterations which impact drug disposition, but the clinical relevance of these, outside of changes associated with aging and frailty, are unknown [52]. More research is required, particularly into alterations in drug transporters (e.g. in the intestine, liver, kidney, and brain) with a focus on the potential clinical relevance of observed changes. For example, while P-gp changes have been found in a mouse model [75], a clinical study found no difference in the concentration of digoxin (a P-gp probe) in people with compared to those without dementia [91].

6. Polypharmacy

Polypharmacy is the term used to denote the concurrent use of multiple medications. This has various definitions in the literature, the most common of which is the concomitant use or prescription of five or more medications [3]. In older adults, polypharmacy is prevalent in various healthcare settings worldwide [92]. Clinically, potential negative consequences of polypharmacy in older adults are well established. These include adverse drug reactions and adverse drug events such as falls/fractures, hospitalization and even mortality [93,94]. A novel mouse model of polypharmacy has shown that even short-term exposure to more medications can cause adverse geriatric outcomes [95]. This was evident as impairment in mobility, balance and strength in old male mice.

The potential for polypharmacy to impact pharmacokinetics is due to the increased risk of DDIs; that is, the pharmacokinetic profile of one drug is impacted by the co-administration of another drug(s), including where an adverse drug reaction of one drug impacts the pharmacokinetics of another. Pharmacokinetic DDIs can potentially alter drug concentrations via alterations in absorption, distribution, metabolism and excretion. Medications such as proton pump inhibitors and histamine-2 receptor antagonists can reduce the acidity of the stomach, which can lead to reduced absorption of weakly basic drugs (e.g. ketoconazole) [52,96] and increased absorption of weakly acidic drugs (e.g. levodopa) [21]. Other medications commonly prescribed in older adults such as anticholinergics or opioids may delay gastric emptying and reduce gastrointestinal motility, however the consequences of this on the absorption of other drugs are varying and generally not considered significant [97].

DDIs can in principle impact the distribution of drugs. Certain drugs can lead to alterations in body composition through adverse drug reactions such as nausea, vomiting and alterations in appetite, which can lead to malnutrition and sarcopenia. Some drug interactions can result in drug displacement from plasma binding proteins thus increasing the unbound fraction of the displaced drug. As previously discussed, changes to protein binding are generally not clinically significant with the exception of interpreting serum concentrations or if the elimination of the displaced drug is also inhibited by the interacting drug [98]. The latter scenario can cause elevated drug concentrations and subsequent toxicity, such as in the example of warfarin and phenylbutazone [99].

Many drug interactions occur via the CYP450 enzyme system in the liver [52]. This can either be via induction of enzymes which enhance drug metabolism, or via inhibition of enzymes which reduce drug clearance. An example of such an interaction is the co-administration of ketoconazole, an anti-fungal (potent CYP3A4 inhibitor) with donepezil, an anti-dementia medication [52,100]. This can lead to increases in donepezil concentrations, contributing to increased risk of older adults experiencing adverse drug events and consequent hospitalization [100]. Whether the magnitude of the inhibition and induction of the CYP enzymes are affected by aging and the subsequent impact this has on DDIs requires further investigation.

Finally, many medications, as well as combinations of medications, can adversely affect renal function. For example, the so called 'triple whammy' (angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-II receptor blocker (A2RB) plus diuretic and non-steroidal anti-inflammatory drug (NSAID)) [101]. In this DDI, inhibition of prostaglandin-mediated afferent glomerular tone by NSAIDs (prevents dilation) and angiotensin-mediated efferent control by ACEI/A2RBs (prevents constriction), blocks the autoregulatory response of the glomerulus. This results in significantly lower trans-glomerular hydrostatic pressure, and combined with the hypovolaemic effect of diuretics and reduced blood pressure from ACEI/A2RBs, the subsequent decrease in glomerular filtration rate (GFR) can predispose vulnerable individuals, particularly older adults, to renal failure [102].

The interplay of causation between aging and geriatric syndromes with polypharmacy is complex. Age-related pharmacokinetic changes increase the risk of polypharmacy-related harms [93,103]. That is, the changes described above can lead to increased concentrations of medications, increasing older adults' risk of developing type-A dose-related adverse drug reactions [21,103]. Polypharmacy may also increase the risk of certain geriatric syndromes such as frailty, which can, in turn alter pharmacokinetics. While research has shown that geriatric syndromes (falls, frailty, delirium) are associated with poorer health outcomes in

older adults, little is known regarding the clinical consequences of drug exposure in an older adult with an established geriatric syndrome [104]. To provide evidence for safer prescribing in older adults, further research is needed to better understand this association in the context of age-related pharmacokinetic changes.

7. Enteral feeding

When oral intake is inadequate or not possible in some patients, such as those suffering from swallowing difficulties (i.e. dysphagia) after a stroke [105], the placement of an enteral feeding tube is an alternative method for necessary nutrition and drug administration [106]. This is recognized as a fundamental aspect of medical/surgical care [107]. This is particularly relevant for those who are frail and/or living with sarcopenia or advanced dementia as the temporary or permanent use of enteral tubes is common in this patient population [108]. Various enteral feeding tubes are available. These are classified according to the site of insertion (e.g. nasal, oral, percutaneous) and the location of the distal tip of the feeding tube (e.g. stomach (nasogastric; NG), duodenum (nasoduodenal; ND), jejunum (nasojejunal; NJ)) [106]. The risks and benefits associated with the preference between pre-pyloric (NG) and post-pyloric (ND and NJ) tubes is controversial and beyond the scope of this review [107].

Drug absorption and bioavailability will differ substantially depending on whether a pre-pyloric or post-pyloric tubes is inserted [107]. Alterations to drug absorption is correlated with possible toxicity from increased absorption or suboptimal dosing/treatment failure from reduced absorption. Where a post-pyloric tube is used, the drug will bypass the stomach. While some oral medications are absorbed from the small intestine, the stomach is the primary target for drug absorption and drug activation for most other drugs. Therefore, ambiguity exists as to whether some medications can in fact be absorbed if directly deposited into the intestine [109]. This is particularly relevant for drugs that require the acidic condition of the stomach for optimal absorption (e.g. antifungals such as ketoconazole, iron supplements) [110].

A recent review examined the impact of enteral drug administration on the metabolism and bioavailability of commonly prescribed immunosuppressive drugs, which typically have a narrow therapeutic index. Adequate immunosuppression is important to achieve in patients with solid organ transplants, cancer patients and autoimmune diseases [111]. Ensuring immunosuppression can be additionally challenging if these patients require enteral nutrition for extended periods of time, especially when limited data exist on safe and effective alternative drug formulations/options. For example, an effective therapy option for patients suffering from Crohn's disease involves receiving exclusive enteral nutrition for up to 8-weeks [112]. These patients are commonly prescribed azathioprine, an immunosuppressant with significant adverse drug effects (e.g. hepatotoxicity, bone marrow suppression) [113]. When administered into the jejunum (via a NJ tube), azathioprine's absorption can increase by 68%-129%, increasing the patient's risk of developing potentially life threatening adverse drug reactions [107]. Therapeutic drug monitoring of azathioprine may assist with efficacy and safety monitoring during enteral drug administration.

While the enteral route is effective for delivering nutrition, clinicians must take into consideration a number of other factors before using this route for drug administration. Examples of these include suitability of crushing medications, availability of liquid formulations/injectables instead of tablets, determining compatibility between drug and feeding formulas, considering physiochemical incompatibilities between tube material with drugs and prevention of tube-clogging [109,114]. Therapeutic drug monitoring should be utilized where possible to ensure appropriate drug concentrations are achieved when oral medications are administered enterally.

8. Conclusion

In conclusion, both aging and geriatric syndromes may alter drug disposition. This can impact the benefits and safety of medications in older adults. Thus, prescribing medications (drug selection, dosing, frequency, duration, and monitoring) to older adults can be challenging. It is important to understand the physiochemical properties of the drug and consider the most clinically relevant physiological and pathophysiological alterations that may occur. However, identifying these alterations may be difficult given the large degree of inter-individual variability observed in older adults. Furthermore, it is important to consider the complex interplay between different geriatric syndromes and their individual and combined effects on drug disposition. However, overall, when considering prescribing medications, the most clinically significant alterations are those that affect drug clearance via hepatic metabolism and renal excretion. In general, chronological aging is associated with reduced drug clearance, which may lead to drug accumulation and toxicity. Therefore, when prescribing new medications to older adults, clinicians should consider the potential for altered drug clearance as well as any other relevant clinical factors including concomitant medications and comorbidities. Fundamental to managing medications in older adults will be to monitor clinical response (both benefits and adverse drug reactions) and to regularly review the dose and appropriateness of a medication, as drug disposition is likely to change within an individual over time.

9. Expert opinion

The aging process and development of geriatric syndromes is complex and so too is the impact on drug pharmacokinetics. An interdependence exists between geriatric syndromes in which one could affect the other and vice versa. For example, polypharmacy could increase the risk of frailty and frailty could in turn increase the likelihood of negative harms associated with polypharmacy. These include falls, cognitive and physical

function decline. This can further worsen frailty, with serious consequences including increased hospitalization, morbidity and mortality. A vicious cycle could also develop where age-related pharmacokinetic changes could contribute to the development of geriatric syndromes. This further alters drug pharmacokinetics, worsening geriatric syndromes. With a limited reserve to tolerate additional stressors, stopping or limiting the progressive nature of this vicious cycle is difficult to achieve. Therefore, it is paramount to integrate knowledge of the complexity and consequential impact of geriatric syndromes on the four discussed primary pharmacokinetic processes in clinical decisions related to medication choices.

Hepatic metabolism influences bioavailability (via first-pass metabolism) and hepatic drug clearance. As outlined in this review, phase I metabolism via the CYP450 enzymes can be affected by the aging process. However, it is concerning that little knowledge is available on the effect of aging on the drug-induced inhibition and induction of the CYP450 enzymes, particularly considering the rising prevalence of polypharmacy. Differences in enzyme inhibition and induction could place older adults at an increased risk of drug toxicity or potential inefficacy. In clinical practice, some drugs may be dose reduced in anticipation of the inhibition of its clearance by another drug (e.g. halving the dose of digoxin when used with amiodarone [115]). However, if inhibition of CYP enzymes is affected by aging and/or geriatric syndromes, this dose reduction may be inappropriate. Improved knowledge in this area could enable dose adjustments in anticipation of alterations in enzyme induction and inhibition. Overall, this lack of information highlights the importance of integrating therapeutic drug monitoring when feasible to guide drug dosing and effect. Therapeutic drug monitoring can also be useful to determine if a lack of therapeutic response may be a result of poor medication adherence [116]. Poor medication adherence is commonly encountered in older adults with polypharmacy and/or complex medication regimens [117]. Estimating renal function in older adults can be challenging. Certain disease states such as frailty, sarcopenia or malnutrition can lead to the overestimation of GFR when using serum creatinine or serum creatinine-based equations. It is therefore paramount that appropriate renal function estimators are used to inform dose adjustments to minimize the risk of toxicity caused by drugs that are predominantly renally cleared. Additionally, integrated warnings in electronic renal function estimators could be a useful tool to assist with identifying patients for which results should be interpreted with caution. Preliminary findings from a recent multicentre observational study found similar estimates of GFR between the Berlin Initiative Study (BIS) [118] and Full Age Study (FAS) [119] equations, both of which were specifically designed to estimate GFR in older adults [120]. However, there was a significant discrepancy between BIS or FAS compared to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [121] equation. Compared to the gold standard of renal inulin clearance, Selistre *et al.* found no superiority in diagnostic performance between BIS, FAS and CKD-EPI [122]. Therefore, although designed for and externally validated in older adults [122,123], the clinical use of BIS and FAS in guiding drug dosage adjustments in renal impairment requires further examination. It is important to emphasize that many commercially available medications have renal dosing recommendations based on either serum creatinine or a specific renal function estimator such as creatinine clearance (CrCl) calculated using the Cockcroft-Gault equation [124]. Dosing recommendations may not be interchangeable between the different renal function estimators. This is particularly important for drugs that have a defined cutoff for a dose adjustment (e.g. apixaban may require dose reduction in atrial fibrillation if the serum creatinine is greater than 133 micromol/L) or if a contraindication to the drug exists (e.g. empagliflozin may be contraindicated if CrCl is less than 45 mL/min) [115]. Many guidelines/recommendations outlining dose adjustments do not include information on the specific renal function estimator used to formulate such recommendations. Improved clinical trial reporting and additional measures of external validation of new renal measures (i.e. independent researchers accessing participant level data) may help to improve transparency.

In the foreseeable future, we are likely to see an increased number of older adults living with multi-morbidity and relatedly, polypharmacy and geriatric syndromes. The pharmaceutical industry should therefore strongly reconsider the stringent trial criteria that limits the inclusion predominately to younger adults or 'healthy' older adults. Ideally, regulatory processes should be in place to ensure that, where appropriate, pharmaceutical companies include complex older adults with multi-morbidity and geriatric syndromes in clinical drug trials. Realistically, however, it may be challenging to include such a complex cohort when considering the practical implications and ethical responsibilities of conducting randomized controlled trials. Additionally, assessing the pharmacokinetics of each new drug in every disease and/or drug combination may not be feasible. A potential method to address this challenge could be to consider combining in vitro-in vivo extrapolation (IVIVE) with physiological-based pharmacokinetic modeling and simulation (PBPK). This type of modeling does not rely on 'rich' data (many observations or subjects). Hence, when 'sparse' data exists (few observations or subjects), using such a model to predict the appropriateness of a medication could help overcome the lack of available clinical data. Primarily, such a model would extrapolate data collected from an individual-level to the population-level, accounting for inter- and intra-individual variability. These models could be used to predict drug exposure in different populations by identifying clinical factors or patient characteristics that may alter drug disposition. It is important that the pharmacokinetic guidance produced from such models is combined with clinically relevant pharmacodynamic outcomes, such as drug benefit and harm. Additionally, it may be possible to use these models to predict when a medication may no longer be necessary. For example, over time the development of further geriatric syndromes such as dementia or frailty could render a medication once appropriate to become inappropriate. In such instances, the model could assist clinicians in

determining when continuation or deprescribing (reducing or stopping a medication) is appropriate. To note, there is very little data available on age-associated changes in people aged greater than 80, therefore caution should be exercised when using model-based predictions in populations outside of those used to inform the model. Again, improved clinical trial transparency could assist in developing a comprehensive database summarizing the relevant anatomical, physiological and biological parameters in older adults to help inform these IVIVE-PBPK models. For this to be achievable, studies need to report relevant covariates such as markers for frailty and body composition, which is not routinely done. Perhaps, a greater incentive for drug companies is required to ensure this data is reported. Model based approaches also present an opportunity for close collaboration between pharmaceutical industry, academia and research organizations, and clinicians to promote the quality use of medicines.

Overall, there is still limited clear information on the changes in drug disposition which can be expected in older adults with geriatric syndromes. Therefore, it is necessary to closely monitor the efficacy and potential harms of medication use, both when initiating medications and overtime as the individual ages and may experience new medical conditions, other medications and geriatric syndromes.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. World Health Organization. World report on ageing and health. Geneva, Switzerland: World Health Organization; 2015.
2. Moore KL, Patel K, John Boscardin W, et al. Medication burden attributable to chronic comorbid conditions in the very old and vulnerable. PLoS One. 2018;13(4):e0196109.
3. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol. 2012;65(9):989–995.
4. Davies LE, Spiers G, Kingston A, et al. Adverse outcomes of polypharmacy in older people: systematic review of reviews. J Am Med Dir Assoc. 2020;21(2):181–187.
5. Ruiter R, Burggraaf J, Rissmann R. Under-representation of elderly in clinical trials: an analysis of the initial approval documents in the food and drug administration database. Br J Clin Pharmacol. 2019;85(4):838–844.
6. Fialova D, Laffon B, Marinkovic V, et al. Medication use in older patients and age-blind approach: narrative literature review (insufficient evidence on the efficacy and safety of drugs in older age, frequent use of PIMs and polypharmacy, and underuse of highly beneficial nonpharmacological strategies). Eur J Clin Pharmacol. 2019;75(4):451–466.
7. Chetty M, Johnson TN, Polak S, et al. Physiologically based pharmacokinetic modelling to guide drug delivery in older people. Adv Drug Deliv Rev. 2018;135:85–96.
8. Reeve E, Wiese MD, Mangoni AA. Alterations in drug disposition in older adults. Expert Opin Drug Metab Toxicol. 2015;11(4):491–508.
   • **Narrative review on pharmacokinetic alterations with ageing**
9. Hartmanshenn C, Scherholz M, Androulakis IP. Physiologically-based pharmacokinetic models: approaches for enabling personalized medicine. J Pharmacokinet Pharmacodyn. 2016;43(5):481–504.
10. Hamczyk MR, Nevado RM, Barettino A, et al. Biological Versus Chronological Aging JACC Focus Seminar. J Am Coll Cardiol. 2020;75(8):919–930.
11. Magnuson A, Sattar S, Nightingale G, et al. A practical guide to geriatric syndromes in older adults with cancer: a focus on falls, cognition, polypharmacy, and depression. Am. 2019;39:e96–e109.
12. Inouye SK, Studenski S, Tinetti ME, et al. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55(5):780–791.
13. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev. 2009;41(2):67–76.
14. Drenth-van Maanen AC, Wilting I, Jansen PAF. Prescribing medicines to older people-How to consider the impact of ageing on human organ and body functions. Br J Clin Pharmacol. 2019;19:19.
15. Soenen S, Rayner CK, Jones KL, et al. The ageing gastrointestinal tract. Curr Opin Clin Nutr Metab Care. 2016;19(1):12–18.
16. Abuhelwa AY, Williams DB, Upton RN, et al. Food, gastrointestinal pH, and models of oral drug absorption. Eur J Pharm Biopharm. 2017;112:234–248.
17. Patel D, Bertz R, Ren S, et al. Review of gastric acid-reducing agent-mediated drug-drug interactions with orally administered medications. Clin Pharmacokinet. 2020;59(4):447–462.
18. Dumic I, Nordin T, Jecmenica M, et al. Gastrointestinal tract disorders in older age. Can J Gastroenterol Hepatol. 2019;2019:6757524.
19. Merchant HA, Liu F, Orlu Gul M, et al. Age-mediated changes in the gastrointestinal tract. Int J Pharm. 2016;512(2):382–395.
20. Russell RM. Changes in gastrointestinal function attributed to aging. Am J Clin Nutr. 1992;55(6Suppl):1203S–7S.
21. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6–14.
22. Thurmann PA. Pharmacodynamics and pharmacokinetics in older adults. Curr Opin Anaesthesiol. 2020;33(1):109–113.
23. Jain R, Chung S, Jain L, et al. Implications of obesity for drug therapy: limitations and challenges. Clin Pharmacol Ther. 2011;90(1):77–89.
24. Grandison MK, Boudinot FD. Age-related changes in protein binding of drugs - Implications for therapy. Clin Pharmacokinet. 2000;38(3):271–290.
25. Dasgupta A. Usefulness of monitoring free (unbound) concentrations of therapeutic drugs in patient management. Clin Chim Acta. 2007;377(1–2):1–13.
26. Krishna DR, Klotz U. Extrahepatic metabolism of drugs in humans. Clin Pharmacokinet. 1994;26(2):144–160.
27. Tan JL, Eastment JG, Poudel A, et al. Age-related changes in hepatic function: an update on implications for drug therapy. Drugs Aging. 2015;32(12):999–1008.
   •• **A comprehensive review of age-related changes in hepatic function**

28. Stader F, Siccardi M, Battegay M, et al. Repository describing an aging population to inform physiologically based pharmacokinetic models considering anatomical, physiological, and biological age-dependent changes. Clin Pharmacokinet. 2019;58(4):483–501.
• **The development of a population-based database describing an ageing population**
29. Butler JM, Begg EJ. Free drug metabolic clearance in elderly people. Clin Pharmacokinet. 2008;47(5):297–321.
30. Waring RH, Harris RM, Mitchell SC. Drug metabolism in the elderly: A multifactorial problem? Maturitas. 2017;100:27–32.
31. Polasek TM, Patel F, Jensen BP, et al. Predicted metabolic drug clearance with increasing adult age. Br J Clin Pharmacol. 2013;75(4):1019–1028.
• **A study using IVIVE-PBPK modelling and simulation to predict metabolic drug clearance in older adults**
32. Cohen E, Nardi Y, Krause I, et al. A longitudinal assessment of the natural rate of decline in renal function with age. J Nephrol. 2014;27(6):635–641.
33. Bolignano D, Mattace-Raso F, Sijbrands EJG, et al. The aging kidney revisited: A systematic review. Ageing Res Rev. 2014;14:65–80.
34. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. Adv Chronic Kidney Dis. 2016;23(1):19–28.
35. Pea F. Pharmacokinetics and drug metabolism of antibiotics in the elderly. Expert Opin Drug Metab Toxicol. 2018;14(10):1087–1100.
36. Yoshida K, Sun B, Zhang L, et al. Systematic and quantitative assessment of the effect of chronic kidney disease on CYP2D6 and CYP3A4/5. Clin Pharmacol Ther. 2016;100(1):75–87.
37. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. Expert Opin Drug Metab Toxicol. 2008;4(8):1065–1074.
38. Tan ML, Yoshida K, Zhao P, et al. Effect of Chronic kidney disease on nonrenal elimination pathways: a systematic assessment of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and OATP. Clin Pharmacol Ther. 2018;103(5):854–867.
39. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people: Europe PMC funders; 2013.
40. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol Ser A. 2007;62(7):722–727.
41. Hilmer SN, Wu H, Zhang M. Biology of frailty: implications for clinical pharmacology and drug therapy in frail older people. Mech Ageing Dev. 2019;181:22–28.
42. Hubbard RE, O'Mahony MS, Savva GM, et al. Inflammation and frailty measures in older people. J Cell Mol Med. 2009;13(9b):3103–3109.
43. Chang SS, Weiss CO, Xue QL, et al. Association between inflammatory-related disease burden and frailty: results from the women's health and aging studies (WHAS) I and II. Arch Gerontol Geriatr. 2012;54:9–15.
44. Hughes K, Lang J, Lazare R, et al. Measurement of oxybutynin and its N-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. Xenobiotica. 1992;22(7):859–869.
45. Van Tongeren SP, Slaets JPJ, Harmsen HJM, et al. Fecal microbiota composition and frailty. Appl Environ Microbiol. 2005;71:6438–6442.
46. Marzetti E, Calvani R, Tosato M, et al. Sarcopenia: an overview. Aging Clin Exp Res. 2017;29(1):11–17.
47. Buch A, Carmeli E, Boker LK, et al. Muscle function and fat content in relation to sarcopenia, obesity and frailty of old age—an overview. Exp Gerontol. 2016;76:25–32.
48. Hilmer SN, Tran K, Rubie P, et al. Gentamicin pharmacokinetics in old age and frailty. Br J Clin Pharmacol. 2011;71:224–231.
49. Le Couteur DG, Blyth FM, Creasey HM, et al. The association of alanine transaminase with aging, frailty, and mortality. J Gerontol A Biol Sci Med Sci. 2010;65:712–717.
50. Hubbard RE, O'Mahony MS, Calver BL, et al. Nutrition, inflammation, and leptin levels in aging and frailty. J Am Geriatr Soc. 2008;56:279–284.
51. Israili ZH, Dayton PG. HUMAN ALPHA-1-GLYCOPROTEIN AND ITS INTERACTIONS WITH DRUGS †,‡. Drug Metab Rev. 2001;33:161–235.
52. Reeve E, Trenaman SC, Rockwood K, et al. Pharmacokinetic and pharmacodynamic alterations in older people with dementia. Expert Opin Drug Metab Toxicol. 2017;13(6):651–668.
•• **A narrative review on pharmacokinetic and pharmacodynamic alterations in people with dementia**
53. Roberts J, Pea F, Lipman J. The clinical relevance of plasma protein binding changes. Clin Pharmacokinet. 2013;52:1–8.
54. Morgan E. Impact of infectious and inflammatory disease on cytochrome P450–mediated drug metabolism and pharmacokinetics. Clin Pharmacol Ther. 2009;85(4):434–438.
55. Hubbard RE, O'Mahony MS, Calver BL, et al. Plasma esterases and inflammation in ageing and frailty. Eur J Clin Pharmacol. 2008;64:895–900.
56. Abou-Hatab K, O'Mahony MS, Patel S, et al. Relationship between age and plasma esterases. Age Ageing. 2001;30:41–45.
57. Dumond J, Chen J, Cottrell M, et al. Population pharmacokinetics modeling of unbound Efavirenz, Atazanavir, and Ritonavir in HIV-infected subjects with aging biomarkers. CPT Pharmacometrics Syst Pharmacol. 2017;6(2):128–135.
58. Wynne H. Drug metabolism and ageing. J Br Menopause Soc. 2005;11:51–56.
59. Wynne H, Cope LH, Herd B, et al. The association of age and frailty with paracetamol conjugation in man. Age Ageing. 1990;19:419–424.
60. Wynne HA, Yelland C, Cope LH, et al. The association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. Age Ageing. 1993;22:354–360.
61. Johnston C, Hilmer SN, McLachlan AJ, et al. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. Eur J Clin Pharmacol. 2014;70:549–555.
62. Shlipak MG, Stehman-Breen C, Fried LF, et al. The presence of frailty in elderly persons with chronic renal insufficiency. Am J Kidney Dis. 2004;43:861–867.
63. Kane AE, Mitchell SJ, Mach J, et al. Acetaminophen hepatotoxicity in mice: effect of age, frailty and exposure type. Exp Gerontol. 2016;73:95–106.
64. Mitchell SJ, Hilmer SN, Murnion BP, et al. Hepatotoxicity of therapeutic short-course paracetamol in hospital inpatients: impact of ageing and frailty. J Clin Pharm Ther. 2011;36:327–335.
65. Cullinan S, O'Mahony D, O'Sullivan D, et al. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age Ageing. 2016;45:115–120.
66. Herr M, Robine J-M, Pinot J, et al. Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. Pharmacoepidemiol Drug Saf. 2015;24:637–646.
67. Bonaga B, Sánchez-Jurado PM, Martínez-Reig M, et al. Frailty, polypharmacy, and health outcomes in older adults: the frailty and dependence in albacete study. J Am Med Dir Assoc. 2018;19:46–52.
68. Porter B, Arthur A, Savva GM. How do potentially inappropriate medications and polypharmacy affect mortality in frail and non-frail cognitively impaired older adults? A cohort study. BMJ Open. 2019;9:5.
69. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age and Ageing. 2019;48:16–31.
70. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393(10191):2636–2646.

• **A recent comprehensive review of sarcopenia.**
71. Williams GR, Deal AM, Shachar SS, et al. The impact of skeletal muscle on the pharmacokinetics and toxicity of 5-fluorouracil in colorectal cancer. Cancer Chemother Pharmacol. 2018;81(2):413–417.
72. Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N. Sarcopenia in patients with colorectal cancer: A comprehensive review. World J Clin Cases. 2020;8(7):1188–1202.
73. Association As. Alzheimer's disease facts and figures. Alzheimer's Dementia. 2015;2015(11):332–384.
74. Jin L, Pan Y, Tran NLL, et al. Intestinal permeability and oral absorption of selected drugs are reduced in a mouse model of familial Alzheimer's disease. Mol Pharm. 2020;17(5):1527–1537.
75. Pan Y, Omori K, Ali I, et al. Altered expression of small intestinal drug transporters and hepatic metabolic enzymes in a mouse model of familial Alzheimer's disease. Mol Pharm. 2018;15 (9):4073–4083.
76. Ahmed AIA, Van Den Elsen GAH, Colbers A, et al. Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia. Psychopharmacology (Berl). 2015;232:2587–2595.
77. Polinsky RJ. Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of alzheimer's disease. Clin Ther. 1998;20(4):634–647.
78. Gillette Guyonnet SAVKG, Alix E, Andrieu S, et al. International Academy on Nutrition and Aging Expert Group. IANA (International Academy on Nutrition and Aging) expert group: weight loss and Alzheimer's disease. J Nutr Health Aging. 2007;11:38–48.
79. Maes M, DeVos N, Wauters A, et al. Inflammatory markers in younger vs elderly normal volunteers and in patients with Alzheimer's disease. J Psychiatr Res. 1999;33:397–405.
80. Duarte P, Duarte M, Pelichek A, et al. Cardiovascular risk factors and inflammatory activity among centenarians with and without dementia. Aging Clin Exp Res. 2017 Jun;29(3):411–417.
81. Zhang R, Barker L, Pinchev D, et al. Mining biomarkers in human sera using proteomic tools. Proteomics. 2004;4:244–256.
82. German DC, Gurnani P, Nandi A, et al. Serum biomarkers for Alzheimer's disease: proteomic discovery. Biomed Pharmacothe. 2007;61:383–389.
83. Blood-brain barrier: ageing and microvascular disease - systematic review and meta-analysis; 2009.
84. Janelidze S, Hertze J, Nägga K, et al. Increased blood-brain barrier permeability is associated with dementia and diabetes but not amyloid pathology or APOE genotype. Neurobiol Aging. 2017;51:104–112.
85. van Assema DME, Lubberink M, Bauer M, et al. Blood-brain barrier P-glycoprotein function in Alzheimer's disease. Brain. 2012;135:181–189.
86. Deo AK, Borson S, Link JM, et al. Activity of P-glycoprotein, a β-amyloid transporter at the blood-brain barrier, is compromised in patients with mild Alzheimer disease. J Nucl Med. 2014;55:1106–1111.
87. Mehta DC, Short JL, Hilmer SN, et al. Drug access to the central nervous system in Alzheimer's disease: preclinical and clinical insights. Pharm Res. 2015;32:819–839.
88. Pan Y, Omori K, Ali I, et al. Increased expression of renal drug transporters in a mouse model of familial Alzheimer's disease. J Pharm Sci. 2019;108(7):2484–2489.
89. Schubert CC, Boustani M, Callahan CM, et al. Comorbidity profile of dementia patients in primary care: are they sicker? J Am Geriatr Soc. 2006;54:104–109.
90. Zuliani G, Galvani M, Sioulis F, et al. Discharge diagnosis and comorbidity profile in hospitalized older patients with dementia. Int J Geriatr Psychiatry. 2012;27:313–320.
91. Ali I, Guidone D, Nicolazzo JA, et al. Impact of reduced P-glycoprotein function on digoxin concentrations in patients with dementia. Br J Clin Pharmacol. 2019;85(10):2351–2359.
92. Jyrkkä J, Enlund H, Korhonen MJ, et al. Patterns of drug use and factors associated with polypharmacy and excessive polypharmacy in elderly persons: results of the Kuopio 75+ study: a cross-sectional analysis. Drugs Aging. 2009;26(6):493–503.
93. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. Clin Pharmacol Ther. 2009;85(1):86–88.
94. Thomsen LA, Winterstein AG, Søndergaard B, et al. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother. 2007;41 (9):1411–1426.
95. Huizer-Pajkos A, Kane AE, Howlett SE, et al. Adverse geriatric outcomes secondary to polypharmacy in a mouse model: the influence of aging. J Gerontol A Biol Sci Med Sci. 2016;71 (5):571–577.
96. Hurwitz A, Brady DA, Schaal SE, et al. Gastric acidity in older adults. JAMA. 1997;278(8):659–662.
97. Soenen S, Rayner CK, Horowitz M, et al. Gastric Emptying in the Elderly. Clin Geriatr Med. 2015;31(3):339–353.
98. Bohnert T, Gan LS. Plasma protein binding: from discovery to development. J Pharm Sci. 2013;102(9):2953–2994.
99. Rolan PE. Plasma-protein binding displacement interactions - why are they still regarded as clinically important. Br J Clin Pharmacol. 1994;37(2):125–128.
100. Pasqualetti G, Tognini S, Calsolaro V, et al. Potential drug-drug interactions in Alzheimer patients with behavioral symptoms. Clin Interv Aging. 2015;10:1457–1466.
• **A review of clinically important drug-drug interactions in people with dementia**
101. Loboz KK, Shenfield GM. Drug combinations and impaired renal function - the 'triple whammy'. Br J Clin Pharmacol. 2005;59(2):239–243.
102. Thomas MC. Diuretics, ACE inhibitors and NSAIDs - the triple whammy. Med J Aust. 2000;172(4):184–185.
103. Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. Fundam Clin Pharmacol. 2007;21 (3):217–230.
104. Gnjidic D, Hilmer SN, Le Couteur DG. High-risk prescribing in older people: more harm than good? Aging Health. 2012;8(4):325–327.
105. Singh S, Hamdy S. Dysphagia in stroke patients. Postgrad Med J. 2006;82(968):383–391.
106. Williams NT. Medication administration through enteral feeding tubes. Am J Health Syst Pharm. 2008;65(24):2347–2357.
107. Jabbar A, McClave SA. Pre-pyloric versus post-pyloric feeding. Clin Nutr. 2005;24(5):719–726.
108. Mundi MS, Patel J, McClave SA, et al. Current perspective for tube feeding in the elderly: from identifying malnutrition to providing of enteral nutrition. Clin Interv Aging. 2018;13:1353–1364.
109. Zhu LL, Zhou Q. Therapeutic concerns when oral medications are administered nasogastrically. J Clin Pharm Ther. 2013;38(4):272–276.
110. Magnuson BL, Clifford TM, Hoskins LA, et al. Enteral nutrition and drug administration, interactions, and complications. Nutr Clin Pract. 2005;20(6):618–624.
111. Silva RME, Portela RDP, Da Costa IFR, et al. Immunosuppressives and enteral feeding tubes: an integrative review. J Clin Pharm Ther. 2020;45(3):408–418.
112. Adamji M, Day AS. An overview of the role of exclusive enteral nutrition for complicated Crohn's disease. Intest Res. 2019;17(2):171–176.
113. Pearson D, May G, Fick GH, et al. Azathioprine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2000;(2): CD000067.
114. Sacks GS. Drug-nutrient considerations in patients receiving parenteral and enteral nutrition. Pract Gastroenterol. 2004;28(7):39–49.
115. Australian Medicines H. Australian medicines handbook: AMH. Adelaide, South Australia: AMH; 2020.

116. Koren G, Nordon G, Radinsky K, et al. Clinical pharmacology of old age. Expert Rev Clin Pharmacol. 2019;12(8):749–755.
117. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57–65.
118. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med. 2012;157(7):471–U54.
119. Pottel H, Hoste L, Dubourg L, et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant. 2016;31(5):798–806.
120. Corsonello A, Roller-Wirnsberger R, Wirnsberger G, et al. Clinical implications of estimating glomerular filtration rate with three different equations among older people. Preliminary results of the project "screening for chronic kidney disease among older people across Europe (SCOPE)". J Clin Med. 2020;9(2):17.
121. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612.
122. Selistre LD, Rech DL, de Souza V, et al. Diagnostic performance of creatinine-based equations for estimating glomerular filtration rate in adults 65 years and older. JAMA Intern Med. 2019;179(6):796–804.
• **A review of the diagnostic performance of different equations for estimating renal function in older adults**
123. Alshaer IM, Kilbride HS, Stevens PE, et al. External validation of the Berlin equations for estimation of GFR in the elderly. Am J Kidney Dis. 2014;63(5):862–865.
124. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

Impact of age-associated physiological changes in older adults with gout

The management of gout in older adults is significantly influenced by age-related changes in drug disposition, comorbidities, and polypharmacy. While reduced renal function is common with ageing, gout itself is associated with chronic kidney disease (CKD), and the kidneys play a key role in serum urate (SU) excretion (2). Allopurinol's active metabolite, oxypurinol, is renally cleared and can accumulate in individuals with impaired renal function, increasing the risk of toxicity and allopurinol hypersensitivity syndrome (145). Consequently, a lower starting dose is often required (107). However, because reduced renal function also decreases SU clearance, up-titration to standard maintenance doses of allopurinol may be needed to achieve target SU concentrations (113). Similarly, the metabolism of febuxostat may be affected by both renal and hepatic impairment, often necessitating a lower maximum dose (146). Uricosuric drugs, such as probenecid, require adequate kidney function to be effective, and they are thus often unsuitable for older adults (147).

Gout flare management and prevention presents unique challenges in older adults due to the potential for drug-drug and drug-disease interactions. Many precautions and contraindications to the use of these medications, namely colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, have been discussed in **Chapter 1.** As individuals age, they develop more co-morbidities and are often prescribed additional medications, increasing the likelihood of polypharmacy (148). Two commonly used drug classes in older adults, angiotensin-converting enzyme inhibitors /angiotensin-II receptor blockers and loop diuretics, are frequently prescribed for hypertension, cardiovascular prevention, and heart failure, all of which are common in gout (2, 149). When combined with an NSAID, this combination can precipitate acute kidney injury, a phenomenon known as the 'triple whammy'(150), which is associated with significant morbidity and mortality (151). NSAIDs also have significant cardiovascular risks such as increased risk of myocardial infarction and gastrointestinal bleeding, and are therefore often contraindicated in older adults (81).

Drug interactions extend beyond kidney function. Verapamil and diltiazem, commonly used for cardiovascular disease, inhibit CYP3A4 and p-glycoprotein (verapamil only), reducing colchicine clearance and increasing the risk of toxicity in an already high-risk population (75). Statins and fibrates, widely prescribed in older adults, increase the risk of colchicine-induced myopathy (77), which may be exacerbated further by conditions

such as frailty and sarcopenia, where muscle mass is already diminished (152). Corticosteroid-induced muscle weakness, osteoporosis, and frailty can also increase the risk and consequences of falls, particularly when gout flares affect mobility. Long-term corticosteroids can also contribute to sarcopenia, diabetes, hypertension, glaucoma, peptic ulcer disease and heart failure (84), but may be the only option for flare prophylaxis in complex individuals with significant renal or hepatic impairment (147). Additionally, the gastrointestinal systems of older adults are more vulnerable to damage, increasing the risk of ulcers and bleeding with long-term corticosteroid and NSAID use. NSAIDs are often co-prescribed with proton pump inhibitors (92), increasing the risk of adverse drug reactions and drug-drug interactions. Out of the three currently available flare prophylactic drug options in Australia (colchicine, NSAIDs, and corticosteroids), all have contraindications or safety concerns related to conditions and medications commonly observed in older adults.

Cognitive decline and dementia introduce additional challenges in gout management. Patients with impaired cognition may struggle with complex medication regimens, increasing the risk of missed doses or inappropriate administration (153). This is particularly relevant for allopurinol, which requires slow up-titration in renal impairment, sometimes from a starting dose as low as 50 mg twice a week in patients with severe CKD (estimated glomerular filtration rate of <15 ml/min/1.73m^2) (111). While dose administration aids can help with maintenance therapy, medications used for acute flare treatment are not suitable for dose administration aids. Colchicine dosing for acute flares is particularly intricate, requiring a single dose followed by another an hour later, and subsequent doses need to be spaced appropriately to avoid toxicity (154). Patients already on colchicine prophylaxis must pause their daily dose during flare treatment, adding another layer of complexity (154). Corticosteroids, often used for both prophylaxis and flare treatment, may require gradual tapering to minimise the risk of rebound flares and adverse effects, which can be difficult to manage, particularly in those with cognitive impairment (74). The variety of NSAIDs available also increases the risk of unintentional duplication with over-the-counter products, increasing toxicity risks (155). While carers, including both non-paid family members and paid carers and nurses, would likely be involved in supporting safe medication use, effective flare management still relies on the person with cognitive impairment being able to express

the symptoms they are experiencing. This could lead to delays in flare management and more significant flare burden if assistance is required to initiate treatment.

Physical limitations also play a role. Vision impairment can make it difficult to read prescription labels or consumer information leaflets. Colchicine's child-resistant packaging, designed to prevent overdose (156), may pose challenges for older adults with reduced dexterity, increasing the risk of delayed or missed doses. Swallowing difficulties, which are common in older adults, may further impact adherence, particularly with larger urate-lowering therapy (ULT) tablets such as allopurinol and febuxostat (depending on the brand) (157, 158).

These complexities must be carefully considered when developing treatment plans for older adults. A thorough understanding of age-related changes to physiology and drug disposition, as well as the mechanisms behind drug-drug and drug-disease interactions may help to identify and minimise medication-related harm in this population. Regular medication reviews and deprescribing where appropriate, such as discontinuing unnecessary gout flare prophylaxis, can help reduce the burden of polypharmacy and its associated risks.

3 Investigating adherence to allopurinol in patients with gout using three approaches

Chapter overview

The previous chapter (**Chapter 2**) identified age-related changes to pharmacokinetics and pharmacodynamics that should be considered when managing gout in older and/or complex individuals. As highlighted in the previous section, this population may have characteristics that limit adherence to medications such as complex medication regimens and polypharmacy. During the ethics approval phase for **Chapter 4**, the onset of the COVID-19 pandemic lockdowns in April 2020 introduced significant limitations to participant recruitment, both in terms of participant numbers and delays to initial recruitment. The urate crystal arthritis clinic was temporarily paused, and appointments were moved to telehealth, making it difficult to start participant recruitment. To account for these delays, we collaborated with colleagues to develop this current chapter (**Chapter 3**), using raw data provided by their research team. The collaborating research team (AM, KW, RD, SS) was responsible for the original data collection and the methods of data collection. However, all writing, subsequent methods, data cleaning, analysis, interpretation, and development of this chapter was performed specifically for this thesis. The aim of this chapter, a cross-sectional study, is to explore adherence to allopurinol, the most widely used ULT for gout. Adherence was assessed using three different adherence tools, each with its own strengths and weaknesses. Additionally, the analysis explores clinical and social factors that may influence this adherence, aiming to identify potentially modifiable and non-modifiable factors associated with non-adherence behaviours. Gaining a better understanding of why individuals do or do not take their gout medications can help inform the development of tailored management strategies.

Additional information

The statement of authorship for the research presented in this chapter is available in **Appendix 4**. In addition to the development of the initial project and data collection, which was performed by AM, KW, RD and SS, SS provided advice on data analysis and write up. ER and MW provided advice on data analysis and write up. I was responsible for all data cleaning, analysis, interpretation and writing.

Abstract

Objectives. To determine the rate of adherence to allopurinol in individuals with gout using three measures of adherence and investigate the correlation between those adherence measures. Additionally, to explore clinical and social factors that influence adherence to allopurinol.

Methods. An investigator led, paper-based survey was administered between November 2006 and March 2008 to consenting adult hospital inpatients with gout who had received allopurinol for at least seven days. The 22-item survey included questions on gout history, management, disease and treatment understanding and medication adherence. Adherence was assessed using three measures: self-report, a developed modified 3-item Compliance Questionnaire Rheumatology (CQR), and the Beliefs About Medicines Disease Specific Questionnaire (BMQ-Specific) for allopurinol. Correlation between adherence measures was examined using Spearman's rank-order correlation, and factors influencing adherence were explored using non-parametric univariate analyses.

Results. A total of 122 participants were included, with a mean age of 71.5 years. The majority (79.5%) were male, and 60% had been on allopurinol for less than 10-years. Adherence to allopurinol was inconsistent across measures: 69% self-reported as adherent, 29% met the typical CQR adherence threshold (>80%), and the mean BMQ-Specific necessity-minus-concerns differential (difference between the necessity and concerns sub-scale scores) for allopurinol was 4.4 (standard deviation 4.8), indicating that most participants perceived that the necessity of allopurinol outweighed their concerns. Correlations between the adherence tools were variable. Greater adherence was associated with a greater number of concomitant medications, experiencing no flares or more than five flares in the previous two years, longer allopurinol use (>30 years), type 2 diabetes mellitus and chronic kidney disease. Conversely, adherence was lower in those with 4-5 flares in the previous two years, allopurinol use of 0-5 or 11-20 years, and hyperlipidaemia.

Conclusion. Improving adherence behaviours in gout remains complex. While further validation is needed for tools like the 3-item CQR, implementing multiple, short, user-friendly adherence assessment methods could improve adherence monitoring in both research and clinical settings. Identifying, understanding, and ultimately addressing

barriers to adherence are key components in improving outcomes for individuals with gout.

Significance and Innovations

- Adherence to allopurinol in gout remains poor, although the exact rate of adherence can vary depending on the adherence tool used and whether it captures intentional and/or unintentional adherence behaviours.
- This study has identified various clinical and social factors that may influence adherence to allopurinol, which may help to guide further research in this area.
- Combining multiple adherence measures may offer a more comprehensive understanding of patient medication-taking behaviour, which could enhance adherence monitoring in both clinical practice and research.

Introduction

Gout is the most common form of inflammatory arthritis in men and is characterised by episodes of painful acute flares (159). Gout occurs when there is deposition of monosodium urate (MSU) crystals in joints and soft tissues (160). Poorly controlled gout is associated with high morbidity (161), reduced health-related quality of life (162) and increased mortality (161). If left untreated or treated sub-optimally, tophi (visible MSU crystals in joints), joint erosion and permanent disability can develop (5).

The long-term management of gout involves the use of urate-lowering therapy (ULT) to lower and maintain serum urate concentrations below 0.36 mmol/L, thereby promoting dissolution of MSU crystals and preventing formation of new MSU crystals (35, 92, 99). Despite the availability of well-tolerated, cheap, and effective ULT, gout management remains sub-optimal. Only 24% of gout patients attain target serum urate concentrations (121). A major barrier to the management of gout is low medication adherence (163), particularly to allopurinol, the first-line and most commonly used ULT worldwide (35).

Medication adherence refers to the extent to which an individual's medication taking behaviour corresponds with the agreed recommendations from their health care provider (124). In general, adherence in gout is lower than many other chronic conditions (115). A systematic review and meta-analysis of 24 studies found that about half of gout patients were non-adherent to their ULT (164). Factors associated with adherence to ULT vary between studies (164), with the exception of older age (165-167) and multiple co-morbidities (166, 167) which are consistently associated with higher ULT adherence.

Reported rates of adherence to allopurinol in the literature range between 17% and 78% (165, 168-175). This variability is likely due to differences in study design and study population, but also the tools and definitions used to assess adherence (176). Most studies investigating adherence to allopurinol have used a retrospective, administrative or prescription claims design (171-173, 175) or Medication Event Monitoring Systems (MEMS) (164). While useful in research, the accessibility and application of these methods is limited in practice.

Self-report is the simplest method to measure adherence, however individuals may overestimate adherence, either intentionally for social desirability or due to recall bias

(177, 178). Validated questionnaires, such as the 19-item Compliance Questionnaire Rheumatology (179), can reduce this bias (178). Adherence behaviours can also be examined indirectly by understanding an individual's attitudes and beliefs towards their medicines (180). A multi-method approach has been recommended to accurately measure adherence (181, 182), however few studies have implemented this approach when measuring allopurinol adherence in gout.

This study aimed to: (i) prospectively determine the rate of adherence to allopurinol in individuals with gout using three measures of adherence; (ii) investigate the correlation between the three adherence measures; and (iii) explore clinical and social factors that may influence adherence to allopurinol.

Methods

Study design and study population

This cross-sectional study recruited individuals with gout who were admitted to a tertiary teaching hospital in Sydney, Australia. The primary aim of this study was to obtain relevant clinical data, including drug concentrations, to develop a population pharmacokinetic model to describe the plasma drug concentration-time profile of oxypurinol, the active metabolite of allopurinol (183). This manuscript describes an *a priori* secondary aim to explore allopurinol adherence in individuals with gout.

Electronic and paper medication charts of all hospital inpatients admitted between November 2006 to March 2008 were screened for eligibility. Participants were included if they were: (i) aged 18 years or older; (ii) had a documented history of hyperuricemia and/or gout; (iii) were prescribed allopurinol for the treatment of hyperuricemia and/or gout; and (iv) had received allopurinol for at least seven days. Individuals that were unable to complete the survey due to cognitive impairment were excluded. For this *a priori* secondary analysis, participants with a history of hyperuricemia without gout were excluded. All participants provided written, informed consent. Ethics approval was obtained from the Human Research Ethics Committee of St Vincent's Hospital, Sydney (Approval H06-107).

Data collection

Participants completed an investigator administered survey consisting of 22 open-ended and multiple-choice questions assessing their gout history, management, disease and

treatment understanding and medication adherence. The survey included a modified version of the Compliance Questionnaire Rheumatology (CQR) (179). Participants also completed two versions of the Belief About Medicines Disease Specific Questionnaire (BMQ-Specific) (180); one considering allopurinol only and the other for all their prescription medication(s). Clinical data was collected based on the World Health Organisation guidance (184) and included: (i) social- and economic-factors such as age and sex; (ii) health system/health care team-related factors such as history of treatment by a rheumatologist; (iii) therapy-related factors such as allopurinol dose and duration; (iv) condition-related factors such as duration of gout or presence of palpable tophi; and (v) patient-related factors such as co-morbidities. Laboratory investigations included serum urate.

Outcome measures

Adherence was examined using three measures: (i) self-report; (ii) a modified CQR; and (iii) the BMQ-Specific for allopurinol.

For self-reported adherence, participants were asked if they ever forget to take a dose of their allopurinol and if so, were prompted to estimate how many doses they missed per month. Responses were categorised as: (i) adherent (less than one dose missed per month); (ii) mostly adherent (one dose missed per month); and (iii) possibly non-adherent (greater than one dose missed per month).

The CQR is a 19-item questionnaire developed to predict medication adherence specifically in rheumatic diseases and is sensitive in detecting low adherence (179). Items are assessed on a 4-point Likert scale, ranging from strongly agree (4-points) to strongly disagree (1-point). Scores are computed and corrected to produce a final score ranging from 0 to 100, with 0 indicating complete non-adherence and 100 indicating perfect adherence (185). An arbitrary score of >80% has also been used in the literature to define adherence (185). To reduce the length of the survey, only 4-items that had previously demonstrated a high predictive value relative to the full 19-item CQR (185) were included in the survey. Pilot testing (n=5) on the 4-item CQR was conducted prior to implementation to assess question comprehension. Based on participant feedback, the original questions were re-worded to improve clarity and understanding for the gout population (**Table 1**).

Table 1. The original and modified wording of the 4-items used from the Compliance Questionnaire Rheumatology (CQR) (179)

Item	Original wording	Modified wording
3	I definitely don't dare to miss my anti-gout medications.	I would never miss taking my gout medicine.
5	My medicines are always stored in the same place, and that's why I don't forget them.	My gout medicine is always stored in the same place, so I never forget to take it.
7	The most important reason to take my anti-gout medicines is that I can still do what I want to do.	I take my gout medication because it helps me to live life normally.
12*#	If you can't stand the medicines, you might say: "throw it away, no matter what".	If a medicine has any side effects, then you should stop taking it.

* This item is negatively worded, thus individual Likert scores were reversed when computing the final and corrected CQR scores
#This item was removed when calculating the final and corrected CQR score to improve internal consistency

The BMQ-Specific consists of two 5-item sub-scales assessing patient's beliefs on the necessity of their prescribed medications and their concerns about the risks associated with them (180). Each item was assessed on a 5-point Likert scale, ranging from strongly agree (5-points) to strongly disagree (1-point). Scores from each 5-item sub-scale were summed to provide an overall sub-scale score ranging from 5 to 25 for medication 'necessity' and medication 'concerns'. A 'necessity-concerns differential' was calculated by comparing the difference between the necessity and concerns sub-scale scores, with the final score ranging from -20 (highest medication concerns beliefs) to +20 (highest medication necessity beliefs). Studies have found higher medication necessity to be strongly correlated with medication adherence (186). To assess the BMQ-Specific for allopurinol, the word 'medication' was replaced with 'allopurinol' for all 10-items. BMQ-Specific scores for allopurinol were compared to all of the participants medications by subtracting the BMQ-Specific necessity-concerns differential for all medications from the BMQ-Specific necessity-concerns differential for allopurinol. A positive difference indicated a higher medication necessity belief for allopurinol and a negative difference indicated a higher medication concerns belief for allopurinol compared to all of the participants medications.

Statistical analysis

Descriptive statistics were used to describe the study population. Imputation for missing data was not performed and incomplete questionnaires were excluded from analysis. The internal consistency of the modified 4-item CQR and the BMQ-Specific for allopurinol were assessed using Cronbach's alpha. The removal of a specific item from the modified 4-item CQR improved the internal consistency to moderate (187) (raw alpha change from 0.45 to 0.64). Thus, the final analysis was performed using a modified 3-item CQR (**Table 1**). All analyses for the 3-item CQR were performed using corrected CQR scores as a continuous rather than discrete measure of adherence. The adherence measures were compared using Spearman's rank-order correlation. To assess the level of agreement between self-reported adherence and the CQR, self-reported adherence was grouped into 'adherent' (less than one dose missed per month) and 'mostly adherent or possibly non-adherent' (one or more doses missed per month). A "cut off" point on the CQR score (0-100 scale) to discriminate between 'adherent' and 'mostly adherent or possibly non-adherent' was determined using a receiver operating characteristic (ROC) curve with a maximise metric to ensure maximal sensitivity.

Associations between allopurinol adherence and participant characteristics were explored using each adherence measure. Categorical variables (e.g. gender, comorbidities, presence of palpable tophi) were assessed using Wilcoxon-Mann-Whitney test (two groups) and Kruskal-Wallis test (three or more groups). Clinical variables in continuous scales such as age and allopurinol dose were assessed using Spearman's rank-order correlation. Each variable was tested for normality. A correlation coefficient ≥0.30 was considered relevant (188) and a P-value of <0.05 was considered statistically significant. Statistical analysis was performed using R statistical software package v4.1.0.

Results

Baseline characteristics

Of the 8860 patients screened, 228 (2.6%) fulfilled the inclusion criteria. In total, 131 consented to the study and 122 were included in the final analysis. Of the nine participants excluded from the analysis, one withdrew consent, three had hyperuricemia without gout and five did not complete the questionnaires (**Figure 1**).

Participants were on average 71.5 (standard deviation (SD) 11.7) years old and 79.5% were male (**Table 2**). Almost 60% of participants had been living with gout for more than 10 years and 15.6% had palpable tophi. Approximately 40% of participants had been taking allopurinol for greater than 10 years, with most participants prescribed either 300 mg (48.4%) or 100 mg (35.2%) per day. In the preceding two years, almost half (45.9%) had experienced no gout flares, while 13.9% had experienced more than five. The mean serum urate concentration was 0.35 mmol/L (SD 0.11, range 0.14-0.81) and 69 (57.5%) participants had subtherapeutic serum urate concentrations (≥0.36 mmol/L (35)). The most common concomitant medications were angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers (54.9%), statins (54.1%), and diuretics (52.5%) (**Table 3**). Metabolic co-morbidities (cardiovascular disease, hypertension, hypercholesteremia and type 2 diabetes) were highly prevalent and almost a third of participants had documented chronic renal failure.

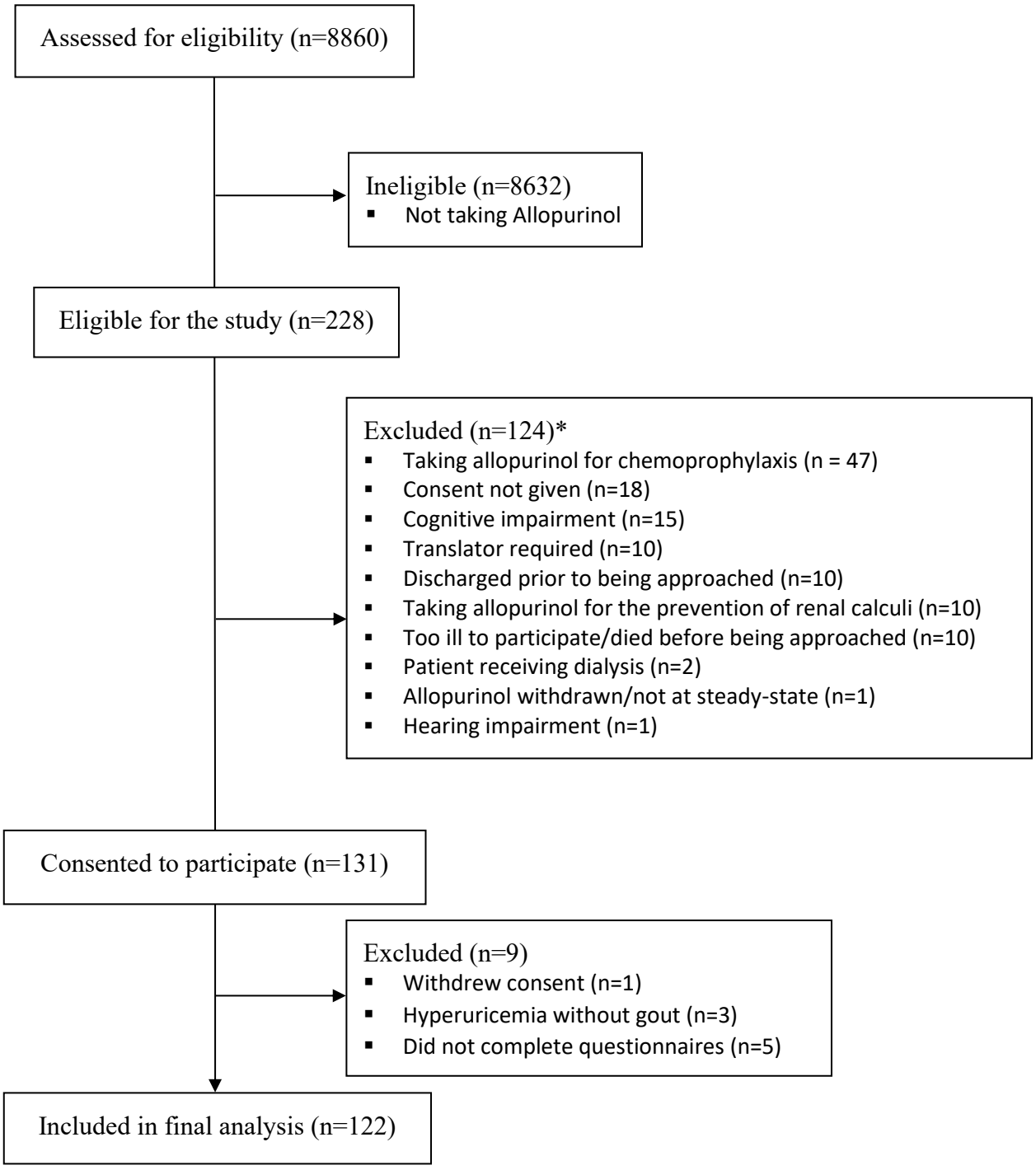


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram

NOTE: * Individuals may be counted in more than one category

Table 2. Summary of clinical characteristics and results of the Spearman's rank-order correlation tests performed between each variable and adherence to allopurinol measured using the three adherence measures. Adherence measures included self-reported adherence, the modified corrected 3-item compliance questionnaire rheumatology (CQR), and the belief about medicines disease specific questionnaire (BMQ-Specific) necessity-concerns differential for allopurinol.

Clinical characteristic		Analysis					
Variable	**Participants (N = 122)**	**Self-reported adherence (n=121)**		**Modified 3-item CQR (n= 117)**		**BMQ-Specific for allopurinol (n= 92)**	
Social and economic factors		r value	p value	r value	p value	r value	p value
Mean age, years (SD)	71.5 (11.7)	0.10	0.29	0.09	0.32	0.07	0.49
Sex, n (%)		-	0.92	-	0.90	-	0.05
Male	97 (79.5)						
Female	25 (20.5)						
Mean body mass index, kg/m^2 (SD)	28.3 (5.4)	-0.07	0.44	-0.11	0.25	-0.06	0.54
Mean socio-economic status, rank (SD)	68.0 (27.1)	-0.01	0.93	0.12	0.21	0.01	0.99
Smoking status, n (%)		-	0.90	-	0.23	-	0.38
Current	6 (4.9)						
Non-smoker/ex-smoker	115 (94.3)						
Missing	1 (0.8)						
Mean alcohol intake, standard drinks/day (SD)	3.0 (3.4)	-0.12	0.20	-0.08	0.42	0.13	0.25
Disease-related factors		r value	p value	r value	p value	r value	p value
Duration of gout (years), n (%)		-	0.60	-	0.60	-	0.34
0-10	47 (38.5)						
11-20	29 (23.8)						
21-30	17 (13.9)						
31-40	14 (11.5)						
>40	12 (9.8)						
Cannot recall	3 (2.5)						
Gout flare frequency in the preceding year prior to commencing allopurinol, n (%)		-	0.95	-	0.39	-	0.63
0	7 (5.7)						
1	26 (21.3)						
2	14 (11.5)						
3-4	17 (13.9)						
5-6	4 (3.3)						
>6	14 (11.5)						
Cannot recall	40 (32.8)						
Gout flare frequency in the preceding two years, n (%)		-	**0.02**	-	**0.04**	-	0.20
0	56 (45.9)						
1	13 (10.7)						

2-3	22 (18.0)						
4-5	8 (6.6)						
>5	17 (13.9)						
Cannot recall	6 (4.9)						
Recency of last gout flare (months), n (%)							
<1	17 (13.9)						
1-5	13 (10.7)	-	0.60	-	0.49	-	0.83
6-12	17 (13.9)						
>12	45 (36.9)						
Cannot recall	30 (24.6)						
Presence (or history) of palpable tophi, n (%)	19 (15.6)	-	0.29	-	0.92	-	0.72
Mean serum urate concentration, mmol/L (SD)	0.35 (0.11)	0.02	0.81	-0.12	0.21	0.03	0.78
Impact of gout on day-to-day living, n (%)							
'Not at all'	40 (32.8)						
'Only a little'	39 (32.0)						
'Moderately'	29 (23.8)	-	0.11	-	0.14	-	0.36
'Very much'	12 (9.8)						
Missing	2 (1.6)						
Therapy-related factors		r value	p value	r value	p value	r value	p value
Allopurinol duration (years), n (%)							
0-5	48 (39.3)						
6-10	23 (18.9)						
11-20	18 (14.8)	-	0.66	-	0.90	-	**0.03**
21-30	14 (11.5)						
>30	14 (11.5)						
Cannot recall	5 (4.1)						
Allopurinol dose (mg), mode (range)	300 (50-300)	-0.16	0.08	0.07	0.45	0.08	0.46
History of side effects from allopurinol, n (%)	3 (2.5)	-	0.92	-	0.87	-	0.15
Currently taking any gout flare prophylaxis medications[a], n (%)	30 (24.6)	-	0.99	-	0.51	-	0.97
Health-system / healthcare team factors		r value	p value	r value	p value	r value	p value
History of management by a rheumatologist, n (%)							
Yes	22 (18.0)	-	0.37	-	0.24	-	0.47
No	55 (45.1)						
Missing	45 (36.9)						
Patient-related factors		r value	p value	r value	p value	r value	p value
Mean number of concomitant medications, number (SD)	9.1 (3.3)	0.18	**0.04**	0.14	0.14	0.12	0.27
Comorbidities, n (%)							
Obesity[b]	38 (31.1)	-	0.84	-	0.44	-	0.32
Hypertension	77 (63.1)	-	0.12	-	0.60	-	0.89
Hyperlipidaemia	49 (40.2)	-	**0.01**	-	0.84	-	0.10

Cardiovascular disease	89 (73.0)	-	0.75	-	0.28	-	0.42
Coronary artery disease	57 (46.7)	-	0.98	-	0.71	-	0.52
Congestive heart failure	22 (18.0)	-	0.33	-	0.51	-	0.99
Heart transplant	5 (4.1)	-	0.13	-	0.71	-	0.50
Arrythmia	42 (34.4)	-	0.07	-	0.26	-	0.87
Cerebral vascular disease	9 (7.4)	-	0.95	-	0.72	-	0.88
Type 2 diabetes mellitus	31 (25.4)	-	**0.04**	-	0.48	-	0.80
Chronic renal failure[c]	27 (22.1)	-	**0.01**	-	0.15	-	0.97
Renal caliculi	9 (7.4)	-	0.77	-	0.78	-	0.32

[a]Gout flare prophylaxis medications were defined as colchicine, non-steroidal anti-inflammatory drugs and/or prednisolone
[b]Obesity defined as a body mass index ≥30 kg/m^2
[c]Renal disease defined as meeting criteria for Australian refined diagnosis-related groups classification system
NOTE: Missing data or "cannot recall" responses were excluded from statistical analysis

Table 3. Summary of allopurinol dosing history, gout flare prophylaxis medications and other concomitant medications

Medication Details	Participants (N = 122)
Allopurinol dose (mg/day), n (%)	
50	5 (4.1)
100	43 (35.2)
150	6 (4.9)
200	9 (7.4)
300	59 (48.4)
Concomitant gout flare prophylactic medications, n (%)	
Prednisolone	16 (13.1)
Colchicine	9 (7.4)
Colchicine and Prednisolone	3 (2.5)
Non-steroidal anti-inflammatory drugs	2 (1.6)
Concurrent medications, n (%)	
ACEI or A2RB	67 (54.9)
Statin	66 (54.1)
Diuretic	64 (52.5)
Beta-blocker	48 (39.3)
Aspirin	41 (33.6)
Calcium channel blocker	25 (20.5)
Other	121 (99.2)

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor. A2RB, angiotensin-II receptor blocker

Rates of adherence and beliefs about medicines

Based on the self-reported adherence question (n=121, as one participant commenced allopurinol during the current admission), 83 (68.6%) participants were categorised as adherent to allopurinol, 22 (18.2%) as mostly adherent and 16 (13.2%) as possibly non-adherent (**Figure 2A**).

The median corrected 3-item CQR score (n=117) was 66.7% (interquartile range (IQR) 66.7%-88.9%) (**Figure 2B**) and 29% of participants had a corrected CQR score of >80.

In total 75% (92/122) of participants completed the BMQ-Specific for allopurinol. The median (IQR) necessity and concerns subscales were 16.0 (14.0-19.0) and 12.0 (10.0-13.3), respectively. Each subscale demonstrated acceptable internal consistency with a Cronbach's raw alpha of 0.79 (necessity subscale) and 0.77 (concerns subscale). The correlation between each subscale was negligible (r=0.07, P=0.49), indicating acceptable independence. The necessity-concerns differential was normally distributed with a minimum score of -8 and a maximum of 19 (mean 4.4, SD 4.8; **Figure 2C**).

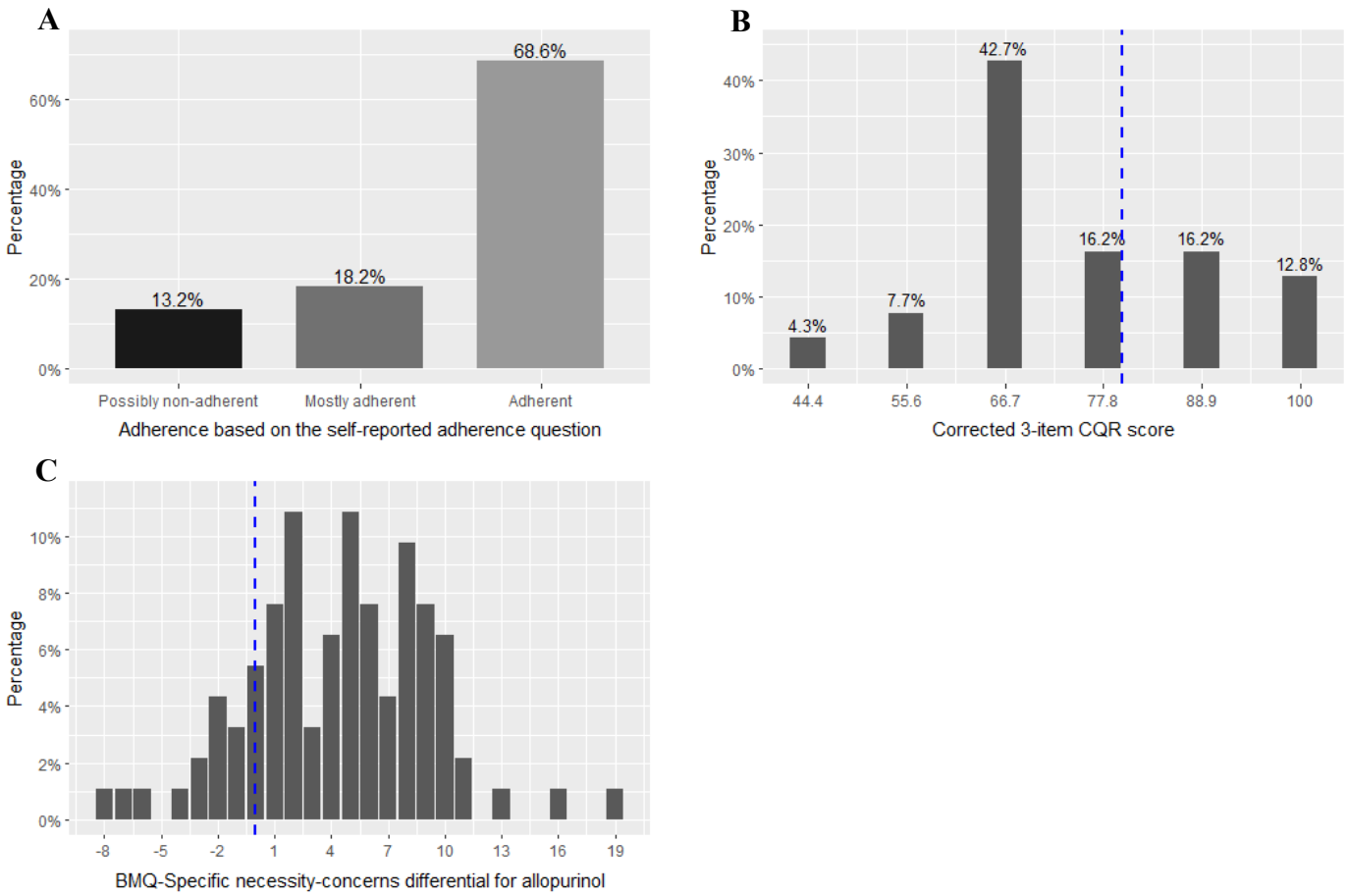


Figure 2. Reported adherence to allopurinol in people with gout using three adherence measures. **(A)** self-reported adherence question (n=121); **(B)** corrected modified 3-item compliance questionnaire rheumatology (CQR) scores (possible range: 0 to 100) (n=117), with a blue dashed line at a score of 80, commonly used as cutoff for adherence (>80) and non-adherence (≤80); and **(C)** the belief about medicines disease specific questionnaire (BMQ-Specific) necessity-concerns differential for allopurinol (possible range: -20 to 20) (n=92), with a blue dashed line at 0, representing an equal balance between necessity belief and concerns belief for allopurinol.

Correlation and level of agreement between adherence measures

The self-reported adherence question was statically correlated with the 3-item CQR (r=0.35, P<0.001) (**Figure 3A**) and the BMQ-Specific for allopurinol (r=0.23, P=0.03) (**Figure 3B**). However, as the correlation coefficient with BMQ-Specific was <0.30, it was not considered to be a relevant association. There was no correlation between the 3-item CQR and the BMQ-Specific for allopurinol (r=0.10, P=0.37) (**Figure 3C**).

A score of 66.7% on the corrected 3-item CQR was identified as the optimal "cut off" point to categorise participants who self-reported as 'adherent' versus 'mostly adherent or possibly non-adherent' (sensitivity 0.99, specificity 0.36, accuracy 79.3%) (**Figure 4**).

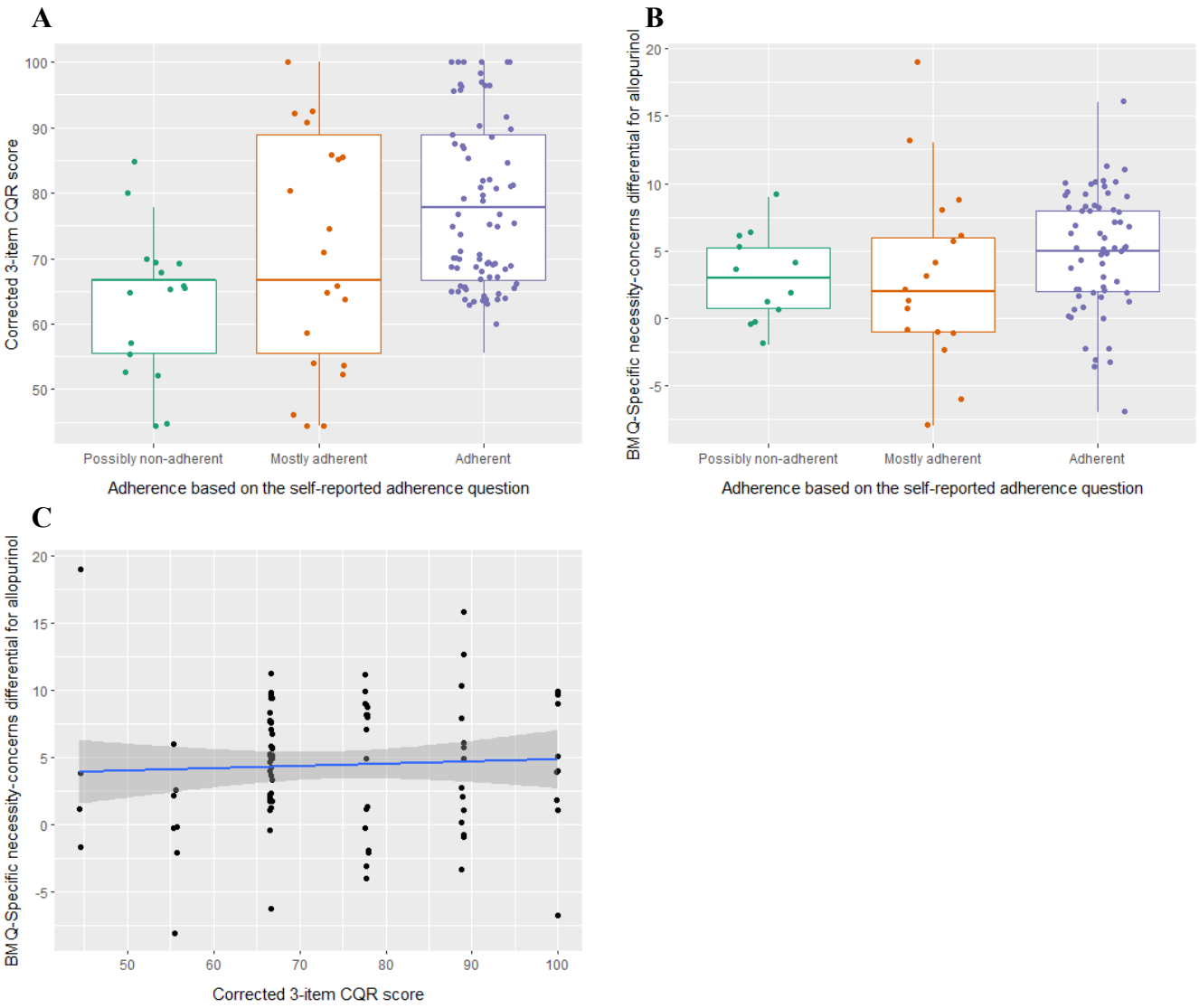


Figure 3. Correlation between allopurinol adherence measures. **(A)** self-reported and corrected 3-item compliance questionnaire rheumatology (CQR) (r=0.349, P<0.001); **(B)** self-reported and the belief about medicines disease specific questionnaire (BMQ-Specific) necessity-concerns differential for allopurinol (r=0.228, P=0.0290); and **(C)** corrected 3-item CQR and BMQ-Specific necessity-concerns differential for allopurinol (r=0.0959, P=0.368).

CQR: compliance questionnaire rheumatology; BMQ-Specific: belief about medicines disease specific questionnaire

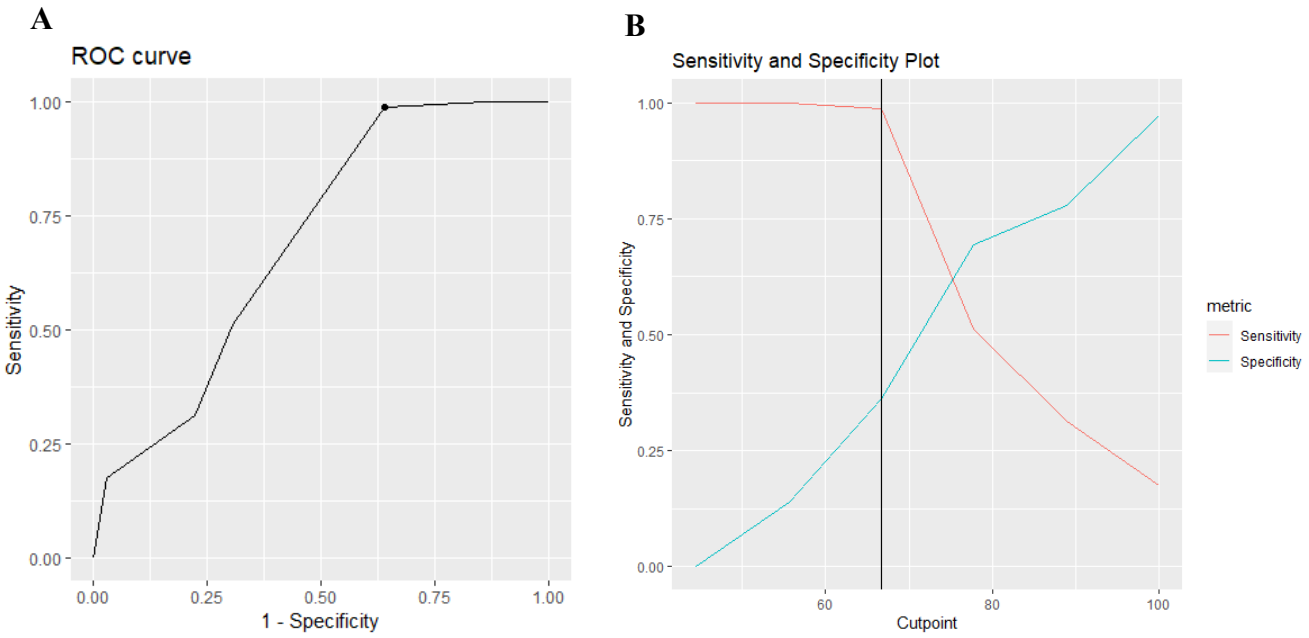


Figure 4. Receiver operating characteristic (ROC) analysis and cutpoint determination for the 3-Item compliance questionnaire rheumatology (CQR). **(A)** Area under the ROC curve for the 3-item CQR (modelled as the modified corrected 3-item CQR score versus the dichotomised self-reported adherence question). The model has a sensitivity of 0.988, specificity of 0.361 and area under the curve of 0.694. **(B)** Sensitivity and specificity plot for the cutpoint on the 3-item CQR with a maximised sensitivity metric. The cutpoint is 66.7, with an accuracy of 79.3%.

BMQ-Specific for allopurinol compared to all medicines

All participants who completed the BMQ-Specific for allopurinol also completed one for all their medications in general, except one participant who was solely taking allopurinol. The two BMQ-Specific questionnaires were correlated (r=0.49, P<0.001). Most participants (85.7%) had a lower or equal necessity-concerns differential for allopurinol compared to all their medications (**Figure 5**). The median difference in the necessity-concerns differential between allopurinol and all medications was -4 (IQR -6 to -1). This difference in the necessity-concerns differential did not correlate with adherence to allopurinol using either self-reported adherence (r=0.09, P=0.39) or the 3-item CQR (r=-0.12, P=0.26).

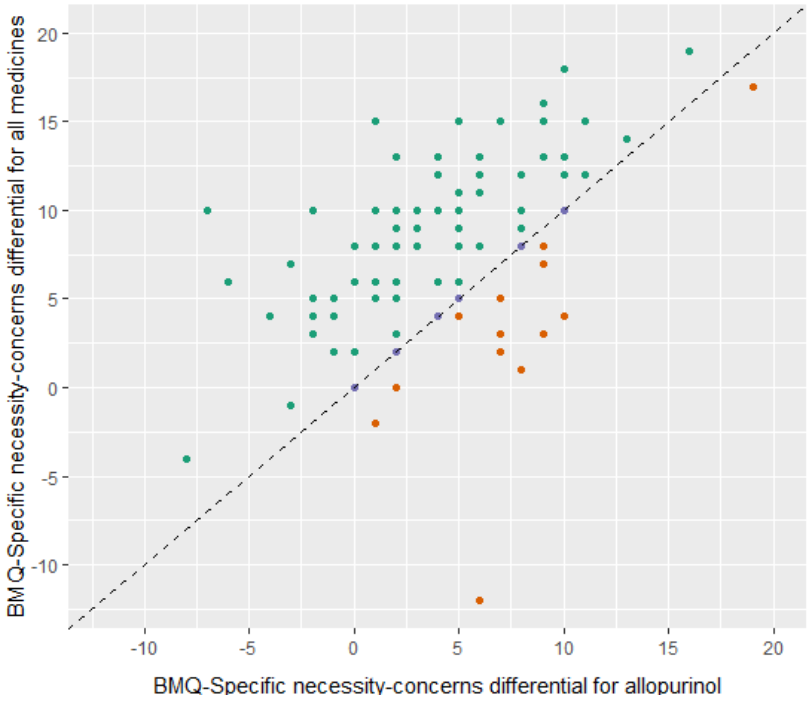


Figure 5. Belief about medicines disease specific questionnaire (BMQ-Specific) necessity-concerns differential for allopurinol versus the BMQ-Specific necessity-concerns differential for concomitant medications (P<0.001 r=0.488). The purple points on the line indicate an identical necessity-concerns differential, the green points indicate participants who had a lower necessity-concerns differential for their allopurinol compared to their concomitant medications and the orange points indicate participants who had a higher necessity-concerns differential for their allopurinol compared to their concomitant medications.

Factors influencing adherence

A higher number of medications (r=0.18, P=0.04) and a diagnosis of type 2 diabetes mellitus (P=0.04) and chronic renal failure (P<0.01) were associated with greater self-reported adherence and hyperlipidaemia (P=0.01) was associated with lower self-reported adherence (**Table 2**). Participants with 4-5 gout flares in the past 2-years had lower self-reported adherence (P=0.02) and lower CQR scores (P=0.04) compared to the zero and greater than five flare groups (**Table 2** and **Figure 6**). Participants who had been taking allopurinol for greater than 30 years had a higher BMQ-Specific necessity-concerns differential for allopurinol (P=0.03) compared to the 0-5 and 11-20 year groups (**Table 2**). This was driven by differences in the necessity scores rather than the concerns scores. No other significant associations were found between any of the three adherence measures and participant clinical characteristics, including serum urate level.

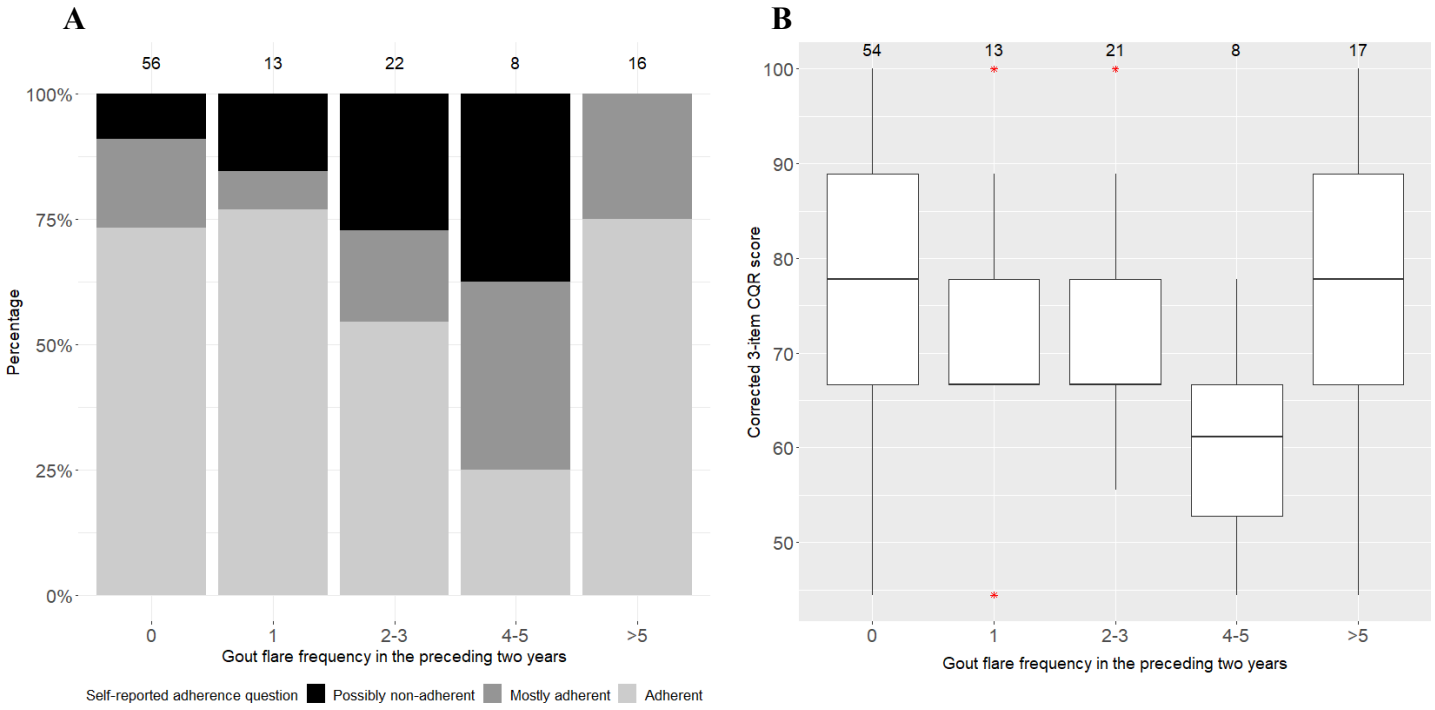


Figure 6. Gout flare frequency in the preceding two years and its association with self-reported adherence and 3-item compliance questionnaire rheumatology (CQR) score. **(A)** Gout flare frequency in the preceding two years, grouped by allopurinol adherence categories based on the self-reported adherence question. **(B)** Corrected 3-item (CQR) score grouped by gout flare frequency in the preceding two years.

NOTE: The number of participants in each gout flare frequency group is displayed at the top of each figure.

Discussion

This study investigated adherence to allopurinol in patients with gout using a multifaceted approach. A greater number of concomitant medications, zero or more than five flares in the previous 2-years, allopurinol treatment duration of more than 30 years, type 2 diabetes mellitus and chronic kidney disease were associated with greater adherence. In contrast, adherence was lower in participants with 4-5 flares in the previous 2-years, allopurinol treatment duration of 0-5 or 11-20 years and hyperlipidaemia. While the correlation between the tools used to measure adherence varied, each tool provided a different insight into the medication taking behaviour of individuals with gout.

Self-reported adherence to ULT has been measured using various methods in the literature (189-191). Using our method, 69% of participants self-reported being adherent to allopurinol. This is consistent with previous studies using a similar approach

(190) or the Morisky 8-item questionnaire (MMAS-8) (191) (78.5% and 61.9%. respectively). In contrast, only 29% of participants would be considered adherent to allopurinol using a typical CQR score of >80%. While the 19-item CQR has been validated for use in gout against MEMS (179, 185), few studies (192) have utilised it to measure adherence to ULT. This underutilisation might reflect the long survey length of the 19-item CQR compared to other adherence measures. We reduced the length of the CQR to increase survey participation and in lieu of using a discrete CQR score for analysis, we assessed the CQR as a continuous measure to increase reliability and power (181). Similarly, a reduced 5-item CQR has been validated for use in patients taking disease-modifying antirheumatic drugs for rheumatoid arthritis (193). While we found self-reported adherence and the 3-item CQR to be positively correlated, the low specificity and moderate accuracy of agreement suggests a complementary rather than interchangeable use of these tools. However, an important limitation is that both tools require further evaluation before they should be used in routine clinical practice, given that the 3-item CQR is not yet validated and the number of missed doses per month to define self-reported adherence was pragmatic and not necessarily clinically based.

The BMQ-Specific for allopurinol questionnaire had minimal to no correlation with self-reported adherence or adherence as determined by the CQR, respectively. In contrast, previous studies report higher adherence to ULT, measured by the MMAS-8 (194), in participants with a greater BMQ necessity-concerns differential (195). Similarly, a study of adherence to disease-modifying antirheumatic drugs in individuals with rheumatoid arthritis (196) found a lower BMQ necessity-concerns differential correlated with non-adherence as measured by the CQR but not the Medication Adherence Report Scale (197). The variations observed between studies might reflect the different components of non-adherence behaviour measured by specific instruments (124). Self-report and CQR are reflective of intentional and/or unintentional non-adherence. Unintentional non-adherence occurs due to factors such as forgetfulness, problems accessing prescriptions, or confusion with complex medication regimens (124). Intentional non-adherence is when an individual consciously decides not to take a medication as prescribed (177), and is best measured by exploring an individual's beliefs towards their medicines (198).

Consistent with beliefs towards ULT observed in the literature (195, 199), most participants believed the necessity of allopurinol outweighed concerns. Additionally, a

longer treatment duration was associated with a greater belief in allopurinol necessity, similar to observations of adherence in rheumatoid arthritis (186). Interestingly, beliefs about allopurinol alone scored lower overall on the necessity-concerns differential compared to the participants beliefs towards all their prescription medications. This unique observation suggests that most participants believe their concomitant medications are more necessary than their ULT. This is perhaps unsurprising given a large proportion of the concomitant medications in this study were used for the treatment or prevention of cardiovascular related diseases. Although gout is a disease with significant morbidity and mortality (161), disease perceptions in gout remain stigmatised and misperceived (116, 200). Qualitative studies have highlighted low disease priority, lack of knowledge, and disease stigma as some of the barriers to medication adherence in chronic conditions (123). Recent interventions have focused on education and behavioural strategies to modify individuals beliefs and improve adherence to ULT (120). Studies suggest facilitating a greater motivation to adhere to therapy can be as simple as improving the patients understanding of how allopurinol works and why it is required long-term (117).

We identified a range of factors that were associated with adherence to allopurinol. One of these factors was a non-linear relationship between the number of gout flares in the preceding two years as was identified by two adherence measures. A possible explanation for this U-shaped trend is that adherence to allopurinol will result in a lower MSU crystal load, leading to flare reductions. Paradoxically, individuals with a higher number of flares might also regularly take their allopurinol to try and reduce their disease activity. Both fewer (201) and greater (174) flares have been associated with adherence in the literature, however, our U-shaped observation requires further validation given the small participant numbers within the groups. Additionally, we did not observe any association between serum urate and adherence to ULT (202). This might reflect limitations in our data, which was collected between 2006-2008, when allopurinol was dosed based on creatine clearance rather than to serum urate target, resulting in a high failure rate to achieve target serum urate concentrations (109). Additionally, we were unable to use plasma oxypurinol concentrations as a measure of direct adherence (203), as our study was performed in the inpatient setting where administration of medications was supervised by nursing staff. Hence, oxypurinol

concentrations may not have reflected the individual's medication taking behaviour at home.

Strategies to improve medication adherence include identifying and targeting at-risk patient populations, for example those with poor health literacy or complex medication regimens (123). However, which factors are predictors of low adherence to ULT is unclear. For example, select comorbidities or polypharmacy, may be associated with greater adherence in some studies and in contrast, lower adherence in others or no association at all. Similar to many previous studies we identified greater adherence in those with type 2 diabetes mellitus (165, 170, 173), and yet we did not observe the commonly reported association with hypertension (165, 170, 173). These inconsistencies between studies might reflect the different approaches and tools used to measure medication adherence and thus different measures of adherence behaviour. This further supports the rationale that multiple and varied approaches provide the most comprehensive assessment of adherence.

There are several limitations to this study, many of which have already been discussed throughout. Firstly, while factors potentially associated with allopurinol adherence were explored using univariate analysis, the p-values were not corrected for multiple testing, increasing the risk of false positives. In addition, multivariate analysis was not performed, and therefore potential correlations in the data have not been accounted for. Secondly, self-reported adherence was assessed using a one-month recall period. This timeframe was chosen to capture the participants' medication taking behaviours at home rather than in hospital, but this may have increased the risk of recall bias. The very low number of reported missed doses per month also necessitated the use of pragmatic adherence categories, rather than the more typical threshold of ≥80% proportion of days covered to define adherence (204). In our study, applying the 80% threshold would likely have overestimated adherence, reflecting potential limitations of self-report and highlighting the value of using multiple measures of adherence. Thirdly, although the BMQ was included to explore participants beliefs towards allopurinol, it should be noted that the BMQ is not a direct measure of adherence. Rather, it provides insights into the psychological drivers that may influence adherence behaviours and has been widely used and validated in the literature. Finally, although nearly two decades have elapsed since the data for this study was collected, the adherence rates and associated factors observed are broadly consistent with more recent literature. Concerningly, this

suggests that adherence to allopurinol has not substantially improved over time and continues to require targeted strategies for improvement.

Conclusion

Measuring and improving adherence to allopurinol in gout remains a challenging issue. Having validated, easy to use, short adherence assessment tools may help to measure adherence both in research and in clinical practice. The assessment of allopurinol adherence and associated factors varied between the three adherence tools used in our study, two of which require further validation. Using multiple complimentary measures is therefore likely the most comprehensive approach for assessing adherence. Further research should also investigate our findings of lower medication necessity beliefs for allopurinol compared to an individual's other medications, with the aim to further understand exactly why and how individuals prioritise their medications. These research priorities are particularly important to explore using contemporary data, in which allopurinol is dosed to target serum urate concentrations rather than creatinine clearance-based dosing, as was the case in this study.

4 Comparative risk of gout flares when initiating or escalating various urate-lowering therapy: a systematic review with network meta-analysis

Chapter overview

The previous chapter (**Chapter 3**) assessed adherence to the most widely used ULT for gout, allopurinol. Within this chapter, gout flares were identified as a key factor that may influence adherence to allopurinol. **Chapter 1** highlighted the unpredictability of flares, particularly when starting or escalating treatment, and the limited information available on the efficacy, safety and duration of gout flare prophylaxis. This, combined with complexities of the available gout flare prophylaxis drugs described in **Chapter 2** led to the need for **Chapter 4**, a systematic review and network meta-analysis comparing the risk of gout flares associated with the initiation or escalation of various ULTs (**Paper 2**). The analysis explores the influence of different ULT drugs and dosing strategies, as well as the benefit, harms, and potential optimal duration of gout flare prophylaxis. Following publication of **Paper 2**, a Letter to the Editor was submitted to the journal based on our paper, titled 'Gout flare prophylaxis trials: comment on the article by Maher et al' (205). This letter highlighted canakinumab, an interleukin-1 inhibitor, and its potential role in preventing ULT-induced gout flares. We were subsequently invited to write a reply, in which we further discussed the role of canakinumab along with other newer gout flare prophylaxis drugs. This reply has been included in this thesis as **Paper 3**.

Citation details

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Maher D, Reeve E, Wiese M. Reply to: "Gout flare prophylaxis trials". Arthritis care & research (2010). 2025.

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Additional information

The supplementary material for **Paper 2** is presented in **Appendix 1** of this thesis.

The statement of authorships for the research presented in this chapter are available in **Appendix 4**.

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Comparative Risk of Gout Flares When Initiating or Escalating Various Urate-Lowering Therapy: A Systematic Review With Network Meta-Analysis

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Objective. We systematically examined comparative gout flare risk after initiation or escalation of different urate-lowering therapies (ULTs), comparative flare risk with and without concomitant flare prophylaxis, adverse event rates associated with flare prophylaxis, and optimal duration of flare prophylaxis.

Methods. We searched the Medline, Embase, Web of Science, and Cochrane databases and clinical trial registries from inception to November 2021 for trials investigating adults with gout initiating or escalating ULT. We performed random effects network meta-analyses and calculated risk ratios (RRs) between treatments. Bias was assessed using the revised Cochrane risk-of-bias tool.

Results. We identified 3,775 records, of which 29 publications (27 trials) were included. When compared to placebo plus prophylaxis, the RR of flares ranged from 1.08 (95% confidence interval [CI] 0.87–1.33) for febuxostat 40 mg plus prophylaxis to RR 2.65 [95% CI 1.58–4.45] for febuxostat 80 mg plus lesinurad 400 mg plus prophylaxis. Compared to ULT alone, the RR of flares was lower for ULT plus rilonacept 160 mg (RR 0.35 [95% CI 0.25–0.50]), ULT plus rilonacept 80 mg (RR 0.43 [95% CI 0.31–0.60]) and ULT plus colchicine (RR 0.50 [95% CI 0.35–0.72]). There was limited evidence for other flare prophylaxis and on prophylaxis harms and optimal duration. Primarily because of missing outcome data and bias in the selection of reported results, 71.4% and 63.4% of studies were assessed as high risk of bias for flares and adverse events, respectively.

Conclusion. The RR of flares when introducing ULT varies depending on ULT drug and dosing strategies. There were limited data on ULT escalation. Flare prophylaxis with colchicine and rilonacept reduces flare incidence. More research is required on the harms and optimal duration of prophylaxis.

INTRODUCTION

Gout is the most common form of inflammatory arthritis, with a prevalence ranging from approximately 0.1% to 10% worldwide.[1] It is caused by the formation and subsequent deposition of monosodium urate crystals in the joints and soft tissues of susceptible individuals, which form in the presence of elevated serum urate (SU).[2] Through a complex cascade, the interaction between monosodium urate crystals and the immune system results in an acute inflammatory response, known as a "gout flare." Although self-limiting, flares cause immense pain, have considerable impact on quality of life, and can reoccur frequently.[3]

Preliminary findings of this research have been presented as an oral presentation at the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) 2022 8th Annual Research Symposium, the Australasian Pharmaceutical Science Association – Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (APSA-ASCEPT) 2022 Joint Conference, and the Australian Rheumatology Association (ARA) 2023 Annual Scientific Meeting.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (http://onlinelibrary.wiley.com/doi/10.1002/acr.25309).

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SIGNIFICANCE & INNOVATIONS

- The risk of gout flares when introducing urate-lowering therapy varies approximately three-fold depending on the treatment strategy used.
- Less intensive urate-lowering therapy and the use of flare prophylaxis is associated with fewer gout flares.
- The optimal duration and efficacy of nonsteroidal anti-inflammatory drugs and corticosteroids as flare prophylaxis is unclear.

High or prolonged monosodium urate crystal burden can also result in tophi, chronic gouty arthritis, gouty bone erosion, and permanent disability.[2]

The cornerstone of long-term gout management is urate-lowering therapy (ULT), which reduces SU concentrations, thus facilitating crystal dissolution.[2] However, initiation of ULT may precipitate a transient increase in the number of flares.[2] Although the exact mechanism remains poorly understood, this increase in flares is thought to be caused by a rapid decrease in SU concentrations resulting in crystal mobilization and an enhanced inflammatory response.[4] If poorly managed, adherence to ULT may be compromised, with people with gout potentially attributing these flares to ineffectiveness of ULT.[5] Because of the relatively unpredictable nature of flares when introducing ULT, several treatment guidelines recommend that "gout flare prophylaxis" with low-dose colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids be considered in all patients starting ULT to minimize flare risk.[6,7]

A systematic review published in 2014 found no direct evidence to support the prophylactic use of low-dose NSAIDs or corticosteroids when initiating ULT,[8] but a subsequent review from 2016 reported indirect evidence to support NSAID use.[9] This review references a post hoc analysis of three large randomized controlled trials (RCTs) of the ULT medications febuxostat and allopurinol.[7,9] There is little consensus on the optimal duration of prophylaxis, with guideline recommendations including at least 8 weeks,[10] 3 to 6 months,[6] or 6 months from commencing ULT,[11,12] or until the target SU concentration has been attained.[13]

In recent years, gradual ULT dose-escalation strategies without prophylaxis have demonstrated comparable flare rates to standard-dose ULT with prophylaxis and may therefore mitigate the need for prophylaxis.[14] Avoidance of unnecessary therapy is important given the complexity and multimorbidity often encountered in the gout population and the well-known toxicities and potential drug-disease and drug-drug interactions of the available prophylactic medications.[15] A systematic examination of the comparative flare rates following the initiation or escalation of ULT, with and without prophylaxis, at various ULT and/or prophylaxis starting doses and dosing schedules may enable more informed decision-making, particularly for those who may be intolerant or have contraindications to prophylactic therapy or for individuals whose only prophylactic option is corticosteroids. We therefore aimed to systematically examine the (1) comparative flare risk after initiation or escalation of different ULTs, (2) comparative flare risk with and without concomitant flare prophylaxis, (3) adverse event (AE) rates associated with flare prophylaxis, and (4) optimal duration of flare prophylaxis.

MATERIALS AND METHODS

Study design. This study follows the Preferred Reporting Items for Systematic Review and Meta-Analyses statement[16] and the Preferred Reporting Items for Systematic Review and Meta-Analyses for network meta-analysis (NMA) extension statement[17] (Supplementary Tables 1 and 2). The protocol was preregistered in PROSPERO (CRD42020178479).

Search strategy and selection criteria. The Ovid Medline, Embase, Web of Science, and Cochrane Library and Cochrane Central Register of Controlled Trials databases were searched from inception to November 10, 2021. Searches were supplemented with manual searches for published and unpublished studies using reference lists of key articles and international trial registers (the Australian New Zealand Clinical Trials Register, ClinicalTrials.gov, and the European Union Clinical Trials Register). Searches included terms relating to gout, ULT, and flare prophylaxis (including specific ULT and prophylaxis drug names and classes) (Supplementary Exhibit 1). Duplicate records were removed with EndNote version 20 (Clarivate Analytics). Teams of paired investigators (DM, JMT, MT, and NA) independently used Covidence (Veritas Health Innovation) to screen titles and abstracts, review full-text studies, and extract data on trial design, characteristics of the trial population, intervention, and outcomes (Supplementary Methods). Discrepancies were resolved by discussion or through consensus with a senior reviewer (ER). Study authors were contacted when necessary to determine study eligibility or to supplement incomplete, missing, or unclear data.

Eligibility criteria. Articles were included if they were RCTs or prospective controlled (nonrandomized) clinical trials, included adults (aged ≥18 years) with confirmed gout either initiating ULT or escalating subtherapeutic ULT, and reported on the frequency of (1) flares or (2) flare prophylaxis-related AEs. Trials with or without concurrent administration of prophylaxis (colchicine, NSAIDs, corticosteroids, or inteleukin-1 inhibitors [canakinumab or rilonacept]) were included. To best inform clinical practice, we included only approved ULTs (ie, allopurinol, febuxostat, probenecid, benzbromarone, sulfinpyrazone, rasburicase, pegloticase, topiroxostat, and lesinurad or verinurad [with allopurinol or febuxostat]). Articles were excluded if they investigated flare treatment (ie, intentionally recruited participants currently experiencing a flare) rather than prophylaxis, did not report outcomes

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separately for the different ULT arms, were not published in English, or were conference abstracts. A full list of the inclusion/exclusion criteria and protocol amendments are available in the Supplementary Methods.

Outcomes and statistical analysis. The primary outcomes were flare rates and prophylaxis-related AE frequencies. The secondary outcomes were flare severity, pain scores, flare duration, and health-related quality of life. For statistical analysis, flare rates were measured as the proportion of participants who had one or more flares using data over the longest available time period from time zero (see Supplementary Table 3 for clarifications). Prophylaxis AEs were measured by the total number of participants who withdrew because of AEs, had any AE (total AEs), had serious AEs, or had treatment-related AEs.

We performed a NMA, which combined both direct and indirect sources of evidence across a network of studies to enable the comparison of three or more interventions within a single analysis. To ensure network validity, studies included in the network must, on average, be similar in all key characteristics that may influence the relative effects.[18] Separate NMA models were used to evaluate the (1) flare risk following initiation or escalation of different ULT drugs and/or doses (referred to as the "ULT-based flare network"), (2) flare risk following ULT initiation or escalation with different prophylaxis drugs and/or doses ("prophylaxis-based flare network"), and (3) risk of AEs with different prophylaxis drugs and/or doses (separate analyses were conducted for each category of AE, ie, the "prophylaxis-based AE networks").

To be eligible for the NMA of prophylaxis AEs, trials had to report AEs separately for each prophylactic drug and/or dose compared to a different prophylactic drug and/or dose and/or to no prophylaxis/placebo with the same or similar ULT use between groups. Trials that failed to report flares or prophylaxis-related AEs within the aforementioned format were considered part of the review and included narratively.

Using inverse-variance random effects NMA models, risk ratios (RRs) with 95% confidence intervals (CIs) of flares and AEs were estimated for each pairwise comparison. When a trial had an arm with zero events, it was included via 0.5 event continuity correction.[19] Trials reporting zero events in all arms were excluded from the respective NMA. Heterogeneity in random effect distributions were assessed via t^2 and I^2 statistics.[20] Equal heterogeneity was assumed across all comparisons, and correlations induced by multi-arm trials were considered. Inconsistencies between direct and indirect comparisons were evaluated both statistically and visually, including via the design-by-treatment test and back-calculation method for pairwise comparisons.[21] The transitivity assumption for indirect comparisons was evaluated via inspection of the distribution of key characteristics (ie, potential effect modifiers) across trials.[18] Network diagrams were used to graphically depict the structure of network interventions. NMA estimates (based on direct and indirect evidence) were presented via forest plots and league tables displaying the relative effects between interventions with associated uncertainty. RR < 1 corresponded to beneficial effects for the first intervention relative to the comparator. Direct evidence–only estimates were also presented within league tables. P-scores (range 0 to 1) were used to rank interventions by taking the precision of frequentist point estimates into account.[22] Interventions with larger *P*-score were considered more beneficial. [Correction was added on 27 March 2024, after first online publication: '*P* values' has been corrected to "*P*-score" in this version.] Comparison-adjusted funnel plots and the Egger's test was used to assess publication bias. For outcomes in which NMA was not possible, findings were presented descriptively. Analyses were performed using the "netmeta" package (2.1-0) in R (version 4.1.2).

Risk-of-bias assessment and data availability statement. Included studies were critically appraised by two independent reviewers (DM and JMT) using the revised Cochrane risk-of-bias tool for randomized trials,[23] with discrepancies resolved by consensus. Risk of bias was assessed separately for the co-primary outcomes of flares and AEs related to prophylaxis. The statistical analysis plan and dataset for this systematic review and NMA can be available from the corresponding author on reasonable request. No individual level data are included in this manuscript. All data are aggregated data from clinical trials.

RESULTS

Trial characteristics. Of 3,775 screened publications, 29 publications reporting on 27 RCTs were included (Figure 1). No eligible prospective controlled (nonrandomized) trials were identified. A detailed description of treatment groups and characteristics for each trial are presented in Supplementary Table 4 and Supplementary Exhibit 2. Briefly, there were 19 trials that randomized ULT,[7,24–43] 7 that randomized prophylaxis,[44–50] and 1 that randomized both (Figure 1).[51] Three trials escalated existing ULT (either by dose escalation[37] or by the addition of lesinurad[24,35]). Seventeen trials used fixed ULT dosing,[24–27,29,30,32,34–36,38,39,41–43,47,50] 8 trials gradually increased (up-titrated) ULT dosage,[28,33,37,40,44,46,48,51] and 2 did not report ULT dose.[45,49] Trials were predominately based in North America or China, >90% of participants were male, and the mean age was approximately 50 years.

Risk-of-bias assessment. Quality assessment indicated that the overall risk of bias was low for 4 (14%) of 28 and 2 (18%) of 11 eligible publications presenting flare and prophylaxis-related AE data, respectively (Supplementary Figures 1–4). This was driven by 61% and 45% of publications being determined to have high risk or some concerns toward bias because of missing outcome data, and 64% and 73% of publications were determined as having a high risk or some concerns toward bias in the selection of the reported results (flare- and prophylaxis-related AE data, respectively).

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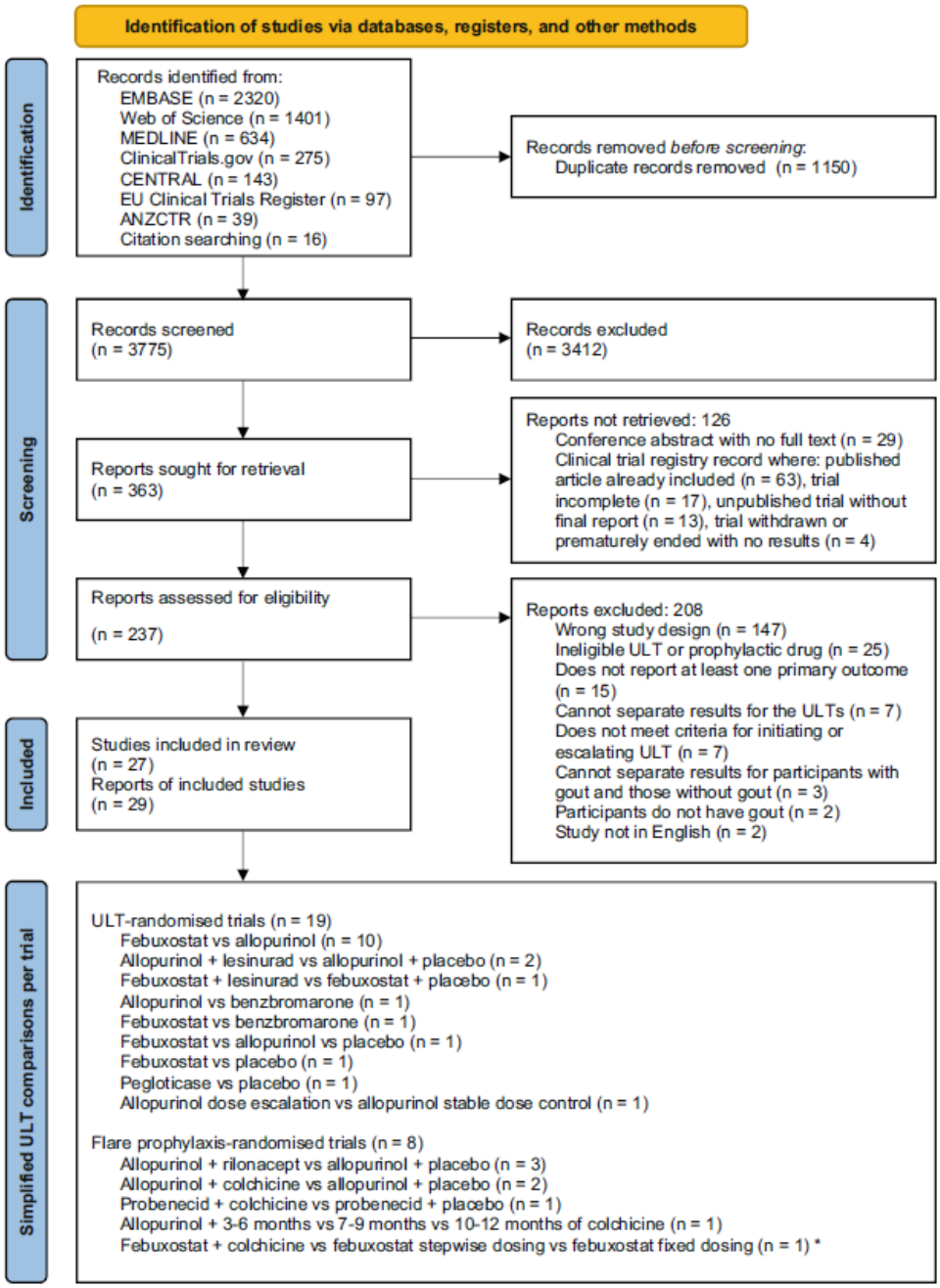


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. *Considered a flare prophylaxis-randomized trial rather than a ULT-randomized trial. ANZCTR, Australian New Zealand Clinical Trials Register; CENTRAL, Cochrane Library and Cochrane Central Register of Controlled Trials; ULT, urate-lowering therapy.

NMA and ULT-based flare network. Figure 2 shows the network of eligible comparison for the co-primary outcomes (see Supplementary Table 8, Supplementary Exhibits 5–9, and Supplementary Figures 5–25 for full NMA results). Thirteen trials involving 7,816 participants were included within two disconnected ULT-based flare networks[25–28,33,34,36,41,42,44,46,48,51] (Figure 2A), all of which were ULT initiation trials. Flare results are summarized per trial in Supplementary Table 3, pairwise comparisons are presented in Figure 3, and forest plots of direct comparisons are presented in Figure 4A and B. For subnetwork 1, compared to placebo plus any prophylaxis, the RR (95% CI) of flares ranged from 1.08 (0.87–1.33) for febuxostat 40 mg plus any prophylaxis to 2.65 (1.58–4.45) for febuxostat 80 mg plus lesinurad 400 mg plus any prophylaxis (Figure 4A). Flare rates for febuxostat 40 mg plus any prophylaxis, allopurinol approximately 300 mg plus any

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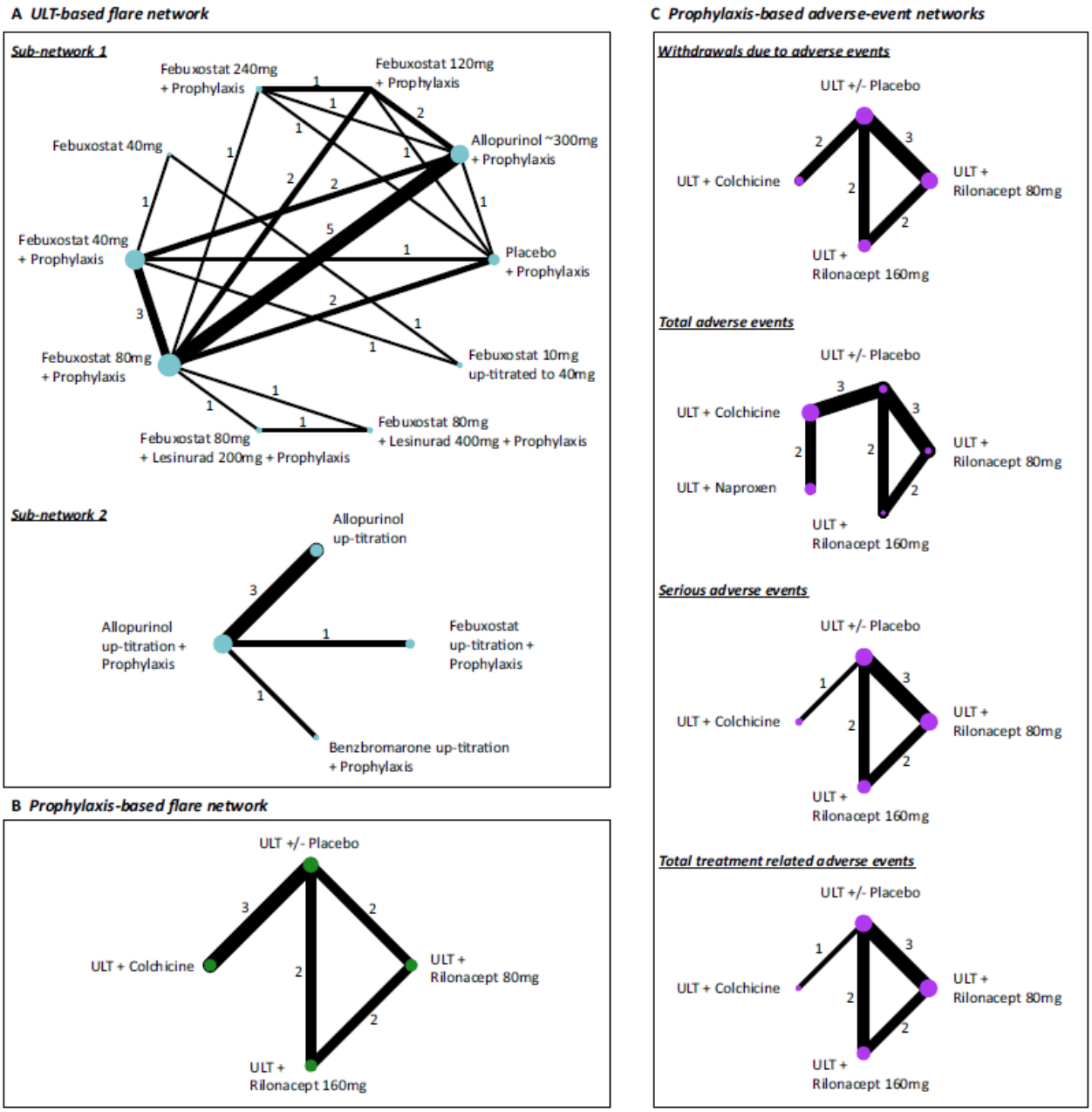


Figure 2. Network meta-analysis diagram for gout flares (A and B) and flare prophylaxis-related adverse events (C). Each intervention is represented by a colored circle. The size of the circles is proportional to the number of randomly assigned participants within each network. Randomized comparisons between the interventions are shown by the lines and numbers between the circles. The width of the lines is proportional to the number of trials within each network or subnetwork. In (A) the ULT-based flare network, nodes represent different ULT drug, dose (either fixed or up-titrated), and flare prophylaxis combinations (prophylactic options were aggregated). In (B) the prophylaxis-based flare network and the (C) prophylaxis-based adverse event networks, nodes represent different prophylactic drug and/or dose combinations (ie, different ULT options were aggregated). Because of variability across trials, all colchicine doses were aggregated. Fourteen trials were ineligible for inclusion in (A) the ULT-based flare network because 8 did not report data in a suitable format for analysis,[29,30,35,40,43,45,47,50] 4 had no common comparator arm to connect to the network,[24,32,37,39] 1 did not report the ULT dose or dosing schedule,[49] and 1 was excluded because of violations of the transitivity assumption.[38] Twenty-two trials were ineligible for inclusion in (B) the prophylaxis-based flare network because 13 did not report flares separately for each prophylactic drug used in the trial,[24–28,30,33–38,40] 6 had no comparator group,[29,32,39,41–43] and 3 did not report data in a suitable format for analysis.[45,47,50] Seventeen trials were ineligible for inclusion in (C) the prophylaxis-based adverse event networks because 9 did not report on flare prophylaxis-related adverse events,[28–30,33,34,37,38,41,42] 5 reported limited data that were not suitable for analysis,[24,27,35,40,45] and 3 did not use flare prophylaxis.[32,39,43] ULT, urate-lowering therapy. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25309/abstract.

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A + P	**0·61 [0·50-0·75]**	**0·50 [0·38-0·66]**	-	1·02 [0·79-1·32]	0·88 [0·76-1·03]	-	-	-	1·15 [0·77-1·72]	NA	NA	NA	NA
0·61 [0·51-0·73]	F120mg + P	**0·78 [0·61-0·99]**	-	-	**1·43 [1·18-1·72]**	-	-	-	**1·79 [1·23-2·60]**	NA	NA	NA	NA
0·50 [0·39-0·63]	0·81 [0·65-1·02]	F240mg + P	-	-	**1·65 [1·26-2·15]**	-	-	-	**2·30 [1·57-3·37]**	NA	NA	NA	NA
0·55 [0·31-0·99]	0·90 [0·50-1·63]	1·10 [0·60-2·04]	F40mg	**1·90 [1·09-3·31]**	-	-	-	**1·73 [1·01-2·96]**	-	NA	NA	NA	NA
1·05 [0·87-1·26]	**1·71 [1·38-2·11]**	**2·10 [1·62-2·72]**	**1·90 [1·09-3·31]**	F40mg + P	0·84 [0·72-0·97]	-	-	0·91 [0·51-1·61]	1·06 [0·83-1·35]	NA	NA	NA	NA
0·88 [0·75-1·02]	**1·43 [1·21-1·69]**	**1·76 [1·40-2·21]**	1·59 [0·90-2·82]	**0·84 [0·73-0·97]**	F80mg + P	0·68 [0·41-1·15]	**0·49 [0·30-0·79]**	-	**1·32 [1·08-1·62]**	NA	NA	NA	NA
0·60 [0·35-1·03]	0·98 [0·56-1·69]	1·20 [0·68-2·13]	1·09 [0·50-2·37]	**0·57 [0·33-0·98]**	0·68 [0·41-1·15]	F80mg + L200mg + P	0·71 [0·47-1·07]	-	-	NA	NA	NA	NA
0·43 [0·26-0·70]	0·70 [0·42-1·16]	0·86 [0·50-1·46]	0·77 [0·37-1·64]	**0·41 [0·25-0·67]**	**0·49 [0·30-0·79]**	0·71 [0·47-1·07]	F80mg + L400mg + P	-	-	NA	NA	NA	NA
0·95 [0·52-1·73]	1·55 [0·85-2·85]	**1·91 [1·02-3·57]**	**1·73 [1·01-2·96]**	0·91 [0·51-1·61]	1·09 [0·60-1·96]	1·59 [0·72-3·49]	**2·23 [1·04-4·76]**	F up-titration	-	NA	NA	NA	NA
1·13 [0·90-1·42]	**1·84 [1·45-2·34]**	**2·27 [1·71-2·99]**	**2·05 [1·13-3·72]**	1·08 [0·87-1·33]	**1·29 [1·06-1·57]**	**1·88 [1·08-3·29]**	**2·65 [1·58-4·45]**	1·19 [0·65-2·18]	Placebo + P	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	A up-titration + P	0·28 [0·01-6·55]	1·50 [0·71-3·17]	**0·40 [0·31-0·51]**
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0·28 [0·01-6·55]	B up-titration + P	-	-
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1·50 [0·71-3·17]	5·38 [0·21-138·10]	F up-titration + P	-
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**0·40 [0·31-0·51]**	1·43 [0·06-33·88]	**0·27 [0·12-0·58]**	A up-titration

Figure 3. League table: ULT-based flare network. Network meta-analysis results are presented in the lower left diagonal and direct evidence–only estimates in the upper right diagonal. The risk ratios, with 95% confidence intervals, represent the relative difference in the proportions for one or more gout flares. A risk ratio <1 favors the column-defining intervention. Interventions from ULT-based flare subnetwork 1 are shown in blue, and interventions from ULT-based flare subnetwork 2 are shown in gray. The results with significant difference are bold. A, allopurinol; A + P, allopurinol ~300 mg + prophylaxis; B, benzbromarone; F, febuxostat; F up-titration, febuxostat 10 mg up-titrated to 40 mg; L, lesinurad; NA, not applicable; P, prophylaxis. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25309/abstract.

prophylaxis and febuxostat up-titration to 40 mg were not statistically different to placebo plus any prophylaxis (Figure 4A). For subnetwork 2, compared to allopurinol up-titration without any prophylaxis, the RR (95% CI) of flares was 0.27 (0.12–0.58) for febuxostat up-titration plus any prophylaxis, 0.40 (0.31–0.51) for allopurinol up-titration plus any prophylaxis, and 1.43 (0.06–33.88) for benzbromarone up-titration plus any prophylaxis (Figure 4B).

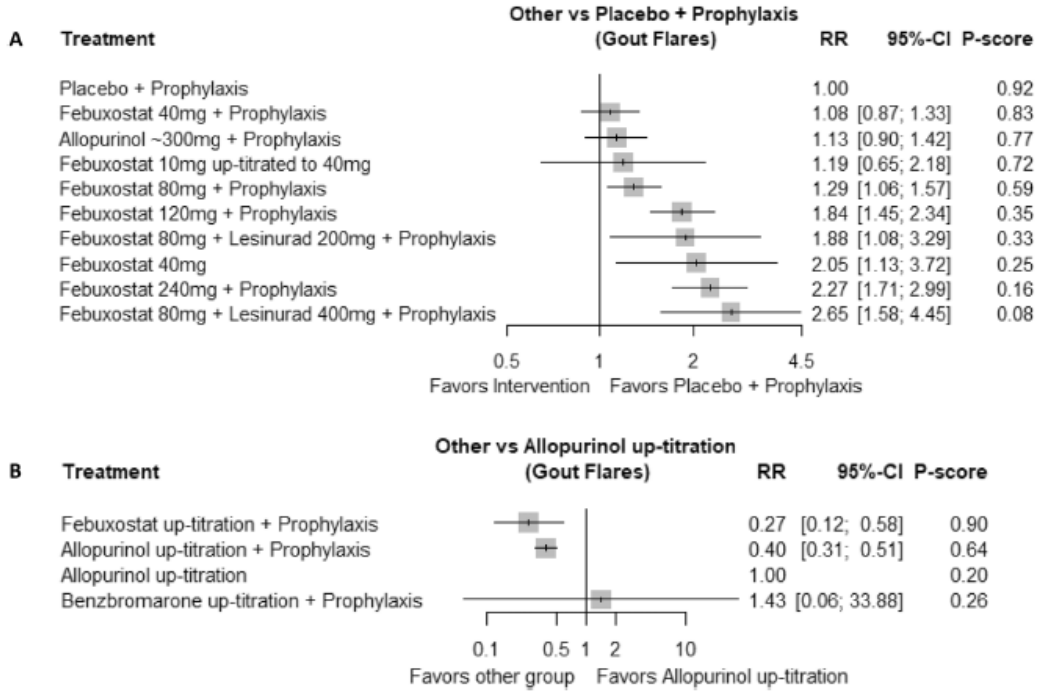


Figure 4. Forest plot of direct comparisons for gout flares by urate-lowering therapy. In (A), urate-lowering therapy drugs and doses (± flare prophylaxis) are compared with placebo plus flare prophylaxis (urate-lowering therapy–based flare subnetwork 1). In (B), urate-lowering therapy up-titration by drugs plus flare prophylaxis are compared with allopurinol up-titration (urate-lowering therapy–based flare subnetwork 2). CI, confidence interval; RR, risk ratio.

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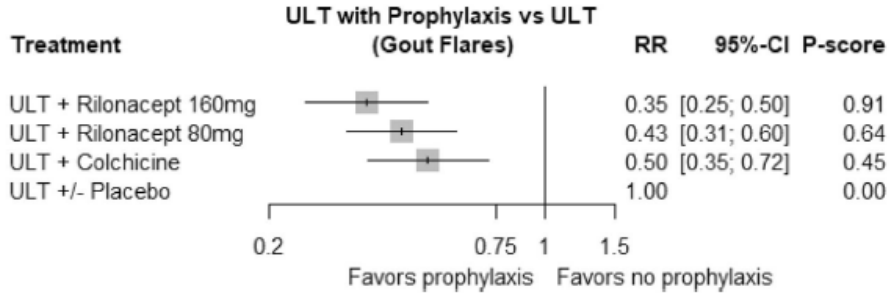


Figure 5. Forest plot of direct comparisons for gout flares by flare prophylaxis. ULT plus different flare prophylaxis drugs (± doses) are compared with ULT (± placebo). CI, confidence interval; RR, risk ratio; ULT, urate-lowering therapy.

Prophylaxis-based flare network. Five trials involving 758 participants were included in the prophylaxis-based flare network (Figure 2B), all of which were RCTs of prophylaxis.[44,46,48,49,51] All but one study[51] included a placebo arm. A forest plot of direct comparisons and a league table of pairwise comparisons are presented in Figures 5 and 6, respectively. ULT plus prophylaxis had a lower RR of flares compared to ULT without any prophylaxis, with the RR (95% CI) ranging from 0.35 (0.25–0.50) for rilonacept 160 mg to 0.43 (0.31–0.60) for rilonacept 80 mg and 0.50 (0.35–0.72) for colchicine (Figure 5). There was no significant difference in the RR of flares between the different prophylactic treatments.

Prophylaxis-based AE networks. Seven trials[44,46–51] and one post hoc analysis[7] of three trials[25,26,36] were included within the prophylaxis-based AE networks (Figure 2C). AE results are summarized per trial in Supplementary Table 5, and pairwise comparisons are presented in Figure 6. Compared to ULT without prophylaxis, the respective NMA did not identify any statistically significant differences in withdrawals caused by AEs, total AEs, or serious AEs with prophylaxis, and no statistically significant difference was observed between the different prophylactic drugs.

ULT + naproxen	NA NA 0·89 [0·78-1·02] NA NA	NA NA - NA NA	NA NA - NA NA	NA NA - NA NA
NA NA 0·89 [0·78-1·02] NA NA	**ULT + colchicine**	- - - - -	- - - - -	**0·50 [0·35-0·72]** 1·45 [0·22-9·58] 1·02 [0·74-1·40] 3·00 [0·13-71·53] 1·69 [0·61-4·69]
NA NA 0·88 [0·59-1·31] NA NA	1·43 [0·87-2·35] 2·42 [0·23-25·33] 0·99 [0·68-1·43] 3·89 [0·14-108·71] 0·57 [0·16-2·02]	**ULT + rilonacept 160mg**	0·82 [0·53-1·26] 0·51 [0·12-2·13] 0·98 [0·80-1·20] 0·74 [0·26-2·10] 1·18 [0·58-2·39]	**0·35 [0·25-0·50]** 0·76 [0·17-3·40] 1·05 [0·85-1·28] 0·84 [0·29-2·44] **3·51 [1·53-8·04]**
NA NA 0·87 [0·60-1·28] NA NA	1·16 [0·72-1·88] 1·32 [0·16-11·00] 0·98 [0·69-1·40] 3·11 [0·12-81·26] 0·74 [0·22-2·48]	0·82 [0·53-1·26] 0·55 [0·14-2·12] 0·99 [0·82-1·20] 0·80 [0·29-2·17] 1·30 [0·66-2·56]	**ULT + rilonacept 80mg**	**0·43 [0·31-0·60]** 1·05 [0·40-2·77] 1·04 [0·89-1·22] 0·96 [0·45-2·07] **2·28 [1·18-4·40]**
NA NA 0·91 [0·64-1·28] NA NA	**0·50 [0·35-0·72]** 1·45 [0·22-9·58] 1·02 [0·74-1·40] 3·00 [0·13-71·53] 1·69 [0·61-4·69]	**0·35 [0·25-0·50]** 0·60 [0·15-2·43] 1·03 [0·85-1·25] 0·77 [0·28-2·13] **2·99 [1·40-6·38]**	**0·43 [0·31-0·60]** 1·10 [0·42-2·88] 1·04 [0·89-1·22] 0·96 [0·45-2·08] **2·29 [1·19-4·43]**	**ULT ± placebo**

Gout flare | Withdrawal due to AE | Total AE | Serious AE | Total treatment-related AE

Figure 6. League table: prophylaxis-based flare network and prophylaxis-based adverse-event networks. Network meta-analysis results are presented in the lower-left diagonal and direct evidence only estimates in the upper-right diagonal. The risk ratios, with 95% confidence intervals represent the relative difference in the proportions for (1) one or more gout flares (shown in green), (2) withdrawals because of AEs (shown in white), (3) total AEs (shown in light blue), (4) serious AEs (shown in medium blue), and (5) total treatment-related AEs (shown in dark blue). A risk ratio below 1 favors the column-defining intervention. The results with significant difference are bold. Colchicine doses varied between 0.5 mg and 0.6 mg once or twice daily. Naproxen was dosed at 250 mg twice a day. AE, adverse event, NA, not applicable; ULT, urate-lowering therapy. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25309/abstract.

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ULT with rilonacept 160 mg (RR 2.99 [95% CI 1.40–6.38]) or 80 mg (RR 2.29 [95% CI 1.19–4.43]) but not colchicine (RR 1.69 [95% CI 0.61–4.69]) was associated with a higher risk of treatment-related AEs compared to ULT without prophylaxis. There was no statistically significant difference in treatment-related AEs between these prophylactic options.

Duration of flare prophylaxis. Four trials reported flare rates during and immediately after cessation of prophylaxis.[24,26,48,51] Schumacher et al[48] reported an increase in flares in the four weeks after rilonacept was ceased at week 16; however, this was comparable with placebo cessation. Yamanaka et al[51] randomized participants to three arms, one of which included fixed-dose febuxostat (40 mg) with colchicine for 12 weeks followed by fixed-dose febuxostat alone. Although the statistical significance was not reported, this arm reported a greater mean number of flares per participant in weeks 13 to 24 compared with the first 12 weeks in which colchicine was administered (1.53 vs 1.33 flares, respectively). Although the Febuxostat versus Allopurinol Controlled Trial (FACT)[26] reported an increased rate of flares in all arms in the 4 weeks after cessation of prophylaxis at week eight, no significant increase in flares was observed in a lesinurad escalation trial in which prophylaxis was ceased at month five.[24]

Diminishing flare rates over a 12-month study period were reported in the other lesinurad trials[27,35] in which prophylaxis was also ceased at month five. Two trials[25,41] that continued prophylaxis throughout reported relatively high flare rates during the first 8 weeks. Karimzadeh et al[45] was the only trial to investigate the optimal duration of prophylaxis, with participants randomized to either 3 to 6, 7 to 9, or 10 to 12 months of colchicine while initiating allopurinol. Flares were lowest with 10 to 12 months of prophylaxis, although the authors concluded that 7 to 9 months was as efficacious but more cost effective. This trial was at high risk of bias across multiple domains.

Other results. There were insufficient data to perform the prespecified subgroup analyses of flare risk categorized by the definition of a flare, participants who achieved the SU target of <0.36 mmol/L, participants with tophaceous gout, and ULT treatment–naive versus treatment-established participants. Secondary outcomes and detailed sub-group analyses information are presented in Supplementary Tables 6 and 7, and Supplementary Exhibits 3 and 4.

Large heterogeneity was only detected in the prophylaxis-based total treatment-related AEs NMA; however, this was not statistically significant (I^2 = 61.8% [95% CI 0.0%–87.2%]). There was no clear evidence of global or local inconsistency (Supplementary Exhibits 7 and 8). Treatment rankings based on the *P*-score for each NMA are presented in Supplementary Exhibit 9. [Correction was added on 27 March 2024, after first online publication: '*P* values' has been corrected to "*P*-score" in this version.] We found no evidence of publication bias (Supplementary Figures 19–25).

DISCUSSION

This systematic review represents the most comprehensive data synthesis regarding the relative risk of gout flares when initiating or escalating ULT. It is the first NMA investigating the relative risk of gout flares with different ULT drugs, ULT dosing schedules and prophylaxis, and AEs with prophylaxis. Fourteen trials were included in the NMA of flares with 26 direct and 31 indirect comparisons, and the results of 10 trials were included in the NMA of AEs related to prophylaxis with 17 direct and 11 indirect comparisons. The data were too limited to make definite conclusions about optimal ULT drug and/or dosing strategies, but higher fixed doses of febuxostat and febuxostat in combination with lesinurad were generally associated with greater flare risk. Prophylaxis with either colchicine or rilonacept significantly reduced the incidence of flares, and the safety of prophylaxis was generally comparable to placebo or no prophylaxis. There was insufficient evidence regarding gradual up-titration strategies, NSAIDs and corticosteroids as prophylaxis, and the optimal duration of prophylaxis.

A dose-response relationship has been established between ULT and reductions in SU concentrations.[52,53] However, high ULT starting doses have greater flare risks. In clinical practice, ULT dosing has shifted away from commencing at fixed standard/high-dose regimens (eg, allopurinol 300 mg daily) toward approaches that start low and up-titrate gradually until the target SU is reached.[6,11,12] This shift in dosing was implemented to reduce the risk of the rare but potentially life-threatening allopurinol hypersensitivity syndrome.[54] It was then subsequently observed that this dosing strategy may reduce the risk of gout flares at ULT initiation.[54] Only one gradual versus fixed ULT dosing trial was included within the NMAs.[51] Although this trial demonstrated fewer flares with a step-wise dose increase, it should not be inferred that all gradual up-titrations cause fewer flares, as febuxostat was up-titrated to a low dose (40 mg daily) rather than to a specific SU target as is generally recommended.[12] Because they could not be connected to the network, we were unable to conclude whether flare risks differ for individuals re-initiating ULT or escalating subtherapeutic ULT compared to ULT-naive individuals. With a high proportion of the gout population either underdosed[55] or poorly adherent to ULT,[56] a greater understanding of flare risk during treatment escalation or re-initiation will inform prophylaxis recommendations in these populations.

In concordance with previous systematic reviews,[8,9,15,57] we found that colchicine and rilonacept (an interleukin-1 inhibitor) were beneficial in reducing flares when initiating ULT. Additionally, our study was the first to directly compare colchicine and rilonacept and identify that they have similar effects with regards to flare suppression. Incomplete reporting of flares stratified by the prophylactic therapy received impeded the ability to assess NSAIDs and corticosteroids. Despite these therapies being recommended in guidelines, we highlight a significant gap in evidence

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that could be filled either by RCTs or a re-analysis of individual patient data from previous RCTs of ULT that included nonrandomized NSAIDs and/or corticosteroids. Furthermore, there is emerging evidence of an association between a recent gout flare and increased risk of myocardial infarction and stroke,[58] making it essential to determine the most effective and safe regimen to prevent gout flares.

We found no increase in the risk of total or serious AEs or withdrawals because of AEs with the addition of prophylaxis or between different prophylactic drugs, but there were significant limitations in the available data. Very few studies analyzed AEs associated with prophylaxis separately from ULT AEs, and most were post hoc analyses, which may introduce bias. Furthermore, methods to capture and report AEs were generally inconsistent,[59] and many trials implemented safety measures that may not occur in routine practice, such as co-prescribing proton pump inhibitors. People with gout commonly experience comorbidities[55] and are therefore at a greater risk of AEs from prophylactic medications, but people with significant comorbidities are generally excluded from clinical trials.[60] Avoiding unnecessary or prolonged prophylactic drug exposure is important given the risks of prophylaxis drugs combined with the additional medication costs, monitoring, and pill burden.

The optimal duration of prophylaxis remains contentious and guidelines provide conflicting recommendations.[61] This is unsurprising given that only one study in our review, which was judged to have a high risk of bias, investigated different durations of prophylactic treatment.[45] Indirect inferences from other trials were again limited by trial reporting, wherein few trials reported flare rates for both the period during and immediately after prophylactic cessation. Identifying clinical characteristics that may alter an individual's susceptibility to gout flares when initiating or escalating ULT may be a useful approach to tailoring prophylactic use, and although research in this area is expanding, more adequately powered clinical trials to solidify the associations are required.[62–66] Additionally, established risk factors for flares, such as the presence of tophi, require quantifiable measurement by dual-energy computed tomography[67] or ultrasonography[68] to accurately assess the risk, and access to these in practice may be limited.

Our literature search was comprehensive and included unpublished data. Although we cannot rule out the possibility that some unpublished data were not identified, our comparison-adjusted funnel plots were not suggestive of small study effects or publication bias. In comparison to previous systematic reviews,[8,15] we allowed for the inclusion of RCTs with nonrandomized prophylaxis. Another strength was our NMA design, which facilitated analysis according to ULT and/or prophylaxis by drug and/or dose.

Our study had some limitations. The risk of bias for both primary outcomes was assessed as high for most publications. For flare data, this was primarily the result of unbalanced withdrawals caused by flares. This is unlikely to affect our results because those who withdrew because of flares would, for most studies, still be captured within our primary flare outcome. The data and comparisons within our NMA were also heavily limited by trial reporting.[69] Some trials did not report data in a suitable format for analysis, whereas others reported data over selected timeframes. Many of our networks had single-standing nodes that were connected to only one other node, which increased the number of network estimates based solely on indirect evidence. There was also a disproportionality high number of trials with fixed ULT dosing compared to the newer, gradual up-titrated dosing. Lastly, because of our strict inclusion/exclusion criteria, not all available therapies were included within our review, primarily because of inapplicable study designs or trials with no suitable comparator. Additionally, some drugs included have since been discontinued (eg, lesinurad) or are not licensed for use in gout (eg, rilonacept). Nevertheless, the range of medications in our review reflects contemporary therapies for gout.[70]

In conclusion, high fixed doses of ULT were associated with a greater risk of flares. However, because most treatment guidelines have shifted to a gradual ULT up-titration approach, coupled with the reductions in flare risk noted with prophylaxis, there should be a greater emphasis on the need for future studies to compare gradual up-titration approaches against the prophylactic therapies currently used in clinical practice (ie, colchicine, NSAIDs, and/or corticosteroids) and to define the optimal duration of prophylaxis. Emphasis should be placed on ensuring more consistent and comprehensive trial reporting of flares as well as prespecification and thorough reporting of prophylaxis-related AEs in future clinical trials.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Maher, Reeve, Hopkins, Woodman, Stamp, Bursill, Proudman, Wiese.

Acquisition of data. Maher, Reeve, Tan, Tantiongco, Ailabouni, Wiese.

Analysis and interpretation of data. Maher, Reeve, Hopkins, Woodman, Wiese.

REFERENCES

1. Proudman C, Lester SE, Gonzalez-Chica DA, et al. Gout, flares, and allopurinol use: a population-based study. Arthritis Res Ther 2019; 21(1):132.

21514658, 2024, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25309 by National Health And Medical Research Council, Wiley Online Library on [18/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

2. Dalbeth N, Choi HK, Joosten LAB, et al. Gout. Nat Rev Dis Primers 2019;5(1):69.
3. Tatlock S, Rudell K, Panter C, et al. What outcomes are important for gout patients? In-depth qualitative research into the gout patient experience to determine optimal endpoints for evaluating therapeutic interventions. Patient 2017;10(1):65–79.
4. Schlesinger N, Etzel CJ, Greenberg J, et al. Gout prophylaxis evaluated according to the 2012 American College of Rheumatology guidelines: analysis from the CORRONA Gout Registry. J Rheumatol 2016;43(5):924–930.
5. Nasser-Ghodsi N, Harrold LR. Overcoming adherence issues and other barriers to optimal care in gout. Curr Opin Rheumatol 2015; 27(2):134–138.
6. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken) 2020;72(6):744–760.
7. Wortmann RL, Macdonald PA, Hunt B, et al. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clin Ther 2010;32(14):2386–2397.
8. Seth R, Kydd AS, Falzon L, et al. Preventing attacks of acute gout when introducing urate-lowering therapy: a systematic literature review. J Rheumatol Suppl 2014;92:42–47.
9. Shekelle PG, Newberry SJ, FitzGerald JD, et al. Management of gout: a systematic review in support of an American College of Physicians clinical practice guideline. Ann Intern Med 2016;166(1):37–51.
10. Qaseem A, Harris RP, Forciea MA, et al; Clinical Guidelines Committee of the American College of Physicians. Management of acute and recurrent gout: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2017;166(1):58–68.
11. Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology guideline for the management of gout. Rheumatology (Oxford) 2017; 56(7):1056–1059.
12. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76(1):29–42.
13. Graf SW, Whittle SL, Wechalekar MD, et al. Australian and New Zealand recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion in the 3e Initiative. Int J Rheum Dis 2015;18(3):341–351.
14. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis 2013;72(6):826–830.
15. Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. Rheumatology (Oxford) 2014; 53(11):1920–1926.
16. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4(1):1.
17. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162(11):777–784.
18. Chaimani A, Caldwell DM, Li T, et al. Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al, eds. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. The Cochrane Collaboration; 2019:285–320.
19. Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.3. The Cochrane Collaboration; 2022.
20. Harrer M, Cuijpers P, Furukawa TA, et al. Doing Meta-Analysis With R: A Hands-On Guide. 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021.
21. Higgins JPT, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Syn Meth 2012;3(2):98–110.
22. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol 2015;15(1):58.
23. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
24. Bardin T, Keenan RT, Khanna PP, et al. Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). Ann Rheum Dis 2017;76(5):811–820.
25. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther 2010;12(2):R63.
26. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005;353(23):2450–2461.
27. Dalbeth N, Jones G, Terkeltaub R, et al. Lesinurad, a selective uric acid reabsorption inhibitor, in combination with febuxostat in patients with tophaceous gout: findings of a phase III clinical trial. Arthritis Rheumatol 2017;69(9):1903–1913.
28. Desideri G, Rajzer M, Gerritsen M, et al. Effects of intensive urate lowering therapy with febuxostat in comparison with allopurinol on pulse wave velocity in patients with gout and increased cardiovascular risk: the FORWARD study. Eur Heart J Cardiovasc Pharmacother 2021; 8(3):236–242.
29. Hao G, Duan W, Sun J, et al. Effects of febuxostat on serum cytokines IL-1, IL-4, IL-6, IL-8, TNF-alpha and COX-2. Exp Ther Med 2019; 17(1):812–816.
30. Huang X, Du H, Gu J, et al. An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia. Int J Rheum Dis 2014;17(6):679–686.
31. Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients >=65 years of age. BMC Geriatr 2012;12:11.
32. Liang N, Sun MS, Sun RX, et al. Baseline urate level and renal function predict outcomes of urate-lowering therapy using low doses of febuxostat and benzbromarone: a prospective, randomized controlled study in a Chinese primary gout cohort. Arthritis Res Ther 2019;21(1):9.
33. Reinders MK, Haagsma C, Jansen T, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in patients with gout. Ann Rheum Dis 2009;68(6):892–897.
34. Saag KG, Becker MA, Whelton A, et al. Efficacy and safety of febuxostat extended and immediate release in patients with gout and renal impairment: a phase III placebo-controlled study. Arthritis Rheumatol 2019;71(1):143–153.
35. Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad combined with allopurinol: a randomized, double-blind, placebo-controlled study in gout patients with an inadequate response to standard-of-care allopurinol (a US-based study). Arthritis Rheumatol 2017;69(1):203–212.
36. Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59(11): 1540–1548.
37. Stamp LK, Chapman PT, Barclay ML, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Ann Rheum Dis 2017;76(9): 1522–1528.

21514658, 2024, 6, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/acr.25309 by National Health And Medical Research Council, Wiley Online Library on [18/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

38. Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment two randomized controlled trials. JAMA 2011;306(7):711–720.
39. Wang S. The efficacy of febuxostat and allopurinol in the treatment of gout with hyperuricemia. Pak J Pharm Sci 2018;31(4):1623–1627.
40. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018; 378(13):1200–1210.
41. Xu S, Liu X, Ming J, et al. A phase 3, multicenter, randomized, allopurinol-controlled study assessing the safety and efficacy of oral febuxostat in Chinese gout patients with hyperuricemia. Int J Rheum Dis 2015;18(6):669–678.
42. Yu KH, Lai JH, Hsu PN, et al. Safety and efficacy of oral febuxostat for treatment of HLA-B5801-negative gout: a randomized, open-label, multicentre, allopurinol-controlled study. Scand J Rheumatol 2016; 45(4):304–311.
43. Zhang Z, Zhang X, Sun Y, et al. New urate depositions on dual-energy computed tomography in gouty arthritis during urate-lowering therapy. Rheumatol Int 2017;37(8):1365–1372.
44. Borstad GC, Bryant LR, Abel MP, et al. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004;31(12):2429–2432.
45. Karimzadeh H, Nazari J, Mottaghi P, et al. Different duration of colchicine for preventing recurrence of gouty arthritis. J Res Med Sci 2006; 11(2):104–107.
46. Mitha E, Ralph Schumacher H, Fouche L, et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology (Oxford) 2013;52(7):1285–1292.
47. Paulus HE, Schlosstein LH, Godfrey RG, et al. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis Rheum 1974;17(5):609–614.
48. Schumacher HR Jr, Evans RR, Saag KG, et al. Rilonacept (interleukin-1 trap) for prevention of gout flares during initiation of uric acid-lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. Arthritis Care Res (Hoboken) 2012;64(10):1462–1470.
49. Efficacy and safety of colchicine for the prevention of gout flares during the initiation of allopurinol. ClinicalTrials.gov identifier: NCT01451645. Updated May 12, 2014. Accessed July 13, 2022. https://clinicaltrials.gov/study/NCT01451645
50. Study of the safety and efficacy of long-term rilonacept treatment for the prevention of gout flares (UPSURGE). ClinicalTrials.gov identifier: NCT01459796. Updated July 18, 2017. Accessed July 13, 2022. https://clinicaltrials.gov/study/NCT01459796
51. Yamanaka H, Tamaki S, Ide Y, et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. Ann Rheum Dis 2018;77(2):270–276.
52. Li S, Yang HX, Guo YA, et al. Comparative efficacy and safety of urate-lowering therapy for the treatment of hyperuricemia: a systematic review and network meta-analysis. Sci Rep 2016;6:33082.
53. Fan M, Liu J, Zhao B, et al. Comparison of efficacy and safety of urate-lowering therapies for hyperuricemic patients with gout: a meta-analysis of randomized, controlled trials. Clin Rheumatol 2021;40(2): 683–692.
54. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum 2012;64(8):2529–2536.
55. Narang RK, Dalbeth N. Management of complex gout in clinical practice: update on therapeutic approaches. Best Pract Res Clin Rheumatol 2018;32(6):813–834.
56. Scheepers L, van Onna M, Stehouwer CDA, et al. Medication adherence among patients with gout: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;47(5):689–702.
57. National Institute for Health and Clinical Excellence. Gout: diagnosis and management. Published June 9, 2022. Accessed April 19, 2023. https://www.nice.org.uk/guidance/ng219
58. Cipolletta E, Tata LJ, Nakafero G, et al. Association between gout flare and subsequent cardiovascular events among patients with gout. JAMA 2022;328(5):440–450.
59. Phillips R, Hazell L, Sauzet O, et al. Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open 2019; 9(2):e024537.
60. Maher D, Ailabouni N, Mangoni AA, et al. Alterations in drug disposition in older adults: a focus on geriatric syndromes. Expert Opin Drug Metab Toxicol 2021;17(1):41–52.
61. Li Q, Li X, Kwong JS, et al. Diagnosis and treatment for hyperuricaemia and gout: a protocol for a systematic review of clinical practice guidelines and consensus statements. BMJ Open 2017;7(6): e014928.
62. Stamp LK, Grainger R, Frampton C, et al. Effect of omega-three supplementation on serum urate and gout flares in people with gout a pilot randomized trial. BMC Rheumatol 2022;6(1):31.
63. Zhang M, Zhang YQ, Terkeltaub R, et al. Effect of dietary and supplemental omega-3 polyunsaturated fatty acids on risk of recurrent gout flares. Arthritis Rheumatol 2019;71(9):1580–1586.
64. Fatima T, McKinney C, Major TJ, et al. The relationship between ferritin and urate levels and risk of gout. Arthritis Res Ther 2018;20(1):179.
65. Rashid N, Levy GD, Wu YL, et al. Patient and clinical characteristics associated with gout flares in an integrated healthcare system. Rheumatol Int 2015;35(11):1799–1807.
66. Morlock R, Taylor DC, Baumgartner S. Characteristics of patients with gout treated to sua target that continue to experience flares: data from France, Germany, Italy, Spain, UK and US. Ann Rheum Dis 2017;76-(Supplement 2):763.
67. Pascart T, Grandjean A, Capon B, et al. Monosodium urate burden assessed with dual-energy computed tomography predicts the risk of flares in gout: a 12-month observational study: MSU burden and risk of gout flare. Arthritis Res Ther 2018;20(1):210.
68. Ebstein E, Forien M, Norkuviene E, et al. Ultrasound evaluation in follow-up of urate-lowering therapy in gout phase 2 (USEFUL-2): duration of flare prophylaxis. Joint Bone Spine 2020;87(6):647–651.
69. Stewart S, Tallon A, Taylor WJ, et al. How flare prevention outcomes are reported in gout studies: a systematic review and content analysis of randomized controlled trials. Semin Arthritis Rheum 2020;50(2): 303–313.
70. Dalbeth N, Gosling AL, Gaffo A, et al. Gout. Lancet 2021;397(10287): 1843–1855.

21514658, 2024, 6, Downloaded from https://rheumatology.onlinelibrary.wiley.com/doi/10.1002/acr.25309 by National Health And Medical Research Council, Wiley Online Library on [18/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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LETTER

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Reply

To the Editor:

We would like to thank Professor Schlesinger and colleagues for the interest and comment on our recently published systematic review with network meta-analysis of gout flares when initiating or escalating urate-lowering therapy (ULT).[1] As pointed out by the authors, trials of the interleukin-1 inhibitor canakinumab were not included in our review. Our strict inclusion and exclusion criteria (full details provided in the Supplementary Methods[1]) excluded phase 1 and 2 trials, such as the large randomized, controlled (phase 2) prophylaxis trial of canakinumab versus colchicine.[2] Various phase 3 and open-label extension trials investigating canakinumab for the treatment of acute flares and subsequent prevention of new flares did not meet our inclusion criteria.[3,4]

Canakinumab is currently approved by the US Food and Drug Administration and European Medicines Agency for the symptomatic treatment of gout flares in adults with frequent flares who cannot tolerate, are contraindicated, or do not benefit from nonsteroidal anti-inflammatory drugs and colchicine and for whom repeated courses of corticosteroids are not appropriate.[5,6] Although canakinumab prophylaxis trials are encouraging,[2] these somewhat limited approval criteria, which encompass treatment of an acute attack rather than prophylaxis after ULT initiation or intensification, coupled with the findings of our review highlight that more research is required to better define both the benefits and harms of existing and newer medications for gout flare prophylaxis.[1] The unique dosing regimen of canakinumab may have significant implications for quality of life in a population for whom nonadherence is prevalent.[7]

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1. Maher D, Reeve E, Hopkins A, et al. Comparative risk of gout flares when initiating or escalating various urate-lowering therapy: a systematic review with network meta-analysis. Arthritis Care Research (Hoboken) 2024;76(6):871–81.
2. Schlesinger N, Mysler E, Lin HY, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis 2011; 70(7):1264–1271.
3. Schlesinger N, Alten RE, Bardin T, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 2012;71(11):1839–1848.
4. Canakinumab in the treatment of gouty arthritis flare(s) and prevention of new flares in patients with chronic kidney disease (study withdrawn). ClinicalTrials.gov identifier: NCT01593527. Updated April 20, 2017. Accessed December 10, 2024. https://clinicaltrials.gov/study/NCT01593527
5. Novartis Pharmaceuticals Corporation. Medication guide: ILARIS® (canakinumab) injection. US Food and Drug Administration. 2023. Accessed December 20, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125319s107lbl.pdf
6. Novartis Europharm Limited. Ilaris: EPAR - product information. European Medicines Agency. 2024. Accessed December 20, 2024. https://www.ema.europa.eu/en/documents/product-information/ilaris-epar-product-information_en.pdf
7. Scheepers LEJM, van Onna M, Stehouwer CDA, et al. Medication adherence among patients with gout: a systematic review and meta-analysis. Semin Arthritis Rheum 2018;47(5):689–702.

5 Characterising gout in complex populations: exploring age-related differences and flare patterns

Chapter overview

The previous chapter (**Chapter 4)** investigated the influence of different ULT strategies and flare prophylaxis on gout flare rates using data from randomised controlled trials. However, as highlighted in **Chapter 2**, complex patients such as older adults or those with co-morbidities like chronic kidney disease or extensive cardiovascular disease are often excluded or underrepresented from these trials. To address this gap, **Chapter 5** presents a prospective observational cohort study to describe a complex cohort of individuals with gout and understand their patterns of gout flares. Key differences between complex younger and older adults with gout are described and potential influencers of gout flares are also explored.

Data for this chapter was drawn from the Central Adelaide Gout Clinic Database and Biobank (CAGCD), an initiative established during my PhD candidature to facilitate multiple concurrent and future research projects. I played a key role in its development by contributing to the ethics application, assisting with the design of baseline and follow-up questionnaires, selecting quality of life and adherence assessment tools, developing and testing the gout diary, and helping establish the biobank. My involvement extended to participant recruitment, creating reminder tools and educating participants on their blood collection times, and gathering flare information from the gout diary. Additionally, I collected and prepared biobank samples in the UniSA laboratory for future analyses.

Due to unforeseen circumstances related to staff at the Central Adelaide Gout Clinic, I also took over the responsibility for completing, testing, and refining the electronic CAGCD database, as well as creating and validating the data extraction tools. I entered data and maintained the database until completion of my sub-study, after which I provided training to new staff to ensure its ongoing maintenance. While my sub-study was the first to utilise the CAGCD and included a limited number of participants, it provided the groundwork to ensure all necessary information was systematically collected and extractable for future studies. Since then, the CAGCD has expanded significantly and is now a valuable and comprehensive data source for gout research.

Abstract

Objectives. To characterise a complex cohort of younger and older individuals with gout, examine their patterns of gout flares, and explore potential factors influencing these flare patterns.

Methods. Participants were recruited from a newly established longitudinal observational cohort of adults with gout, who were managed using a treat-to-target serum urate protocol. Data were collected between July 2020 and December 2021 through clinic visits every three months and monthly phone assessments. Data included baseline demographics, clinical assessments, patient-reported outcomes, laboratory measures, and gout flare documentation using gout diaries. Comparisons were made between younger (<65) and older (≥65) participants, and factors influencing gout flares were explored using an independent-sample t-test for continuous variables, Wilcoxon-Mann-Whitney test for continuous nonparametric variables and chi-square or Fisher's exact test for dichotomous/categorical variables.

Results. Of the 39 participants included in this analysis, 17 (44%) were younger and 22 (56%) were older. The most common co-morbidities were hypertension (24/39, 62%), cardiovascular disease (18/39, 46%), gastrointestinal disease (17/39, 44%) and hypercholesterolemia (16/39, 41%). Nearly half (19/39) had tophaceous gout, a quarter (10/39) had chronic gouty arthritis and over half (22/39) had joint erosions. Younger participants had significantly higher rates of smoking (11.8% vs 0%), alcohol consumption per week (median 3.0 vs 1.5 standard drinks), and body mass index (median 32.9 vs 25.1 kg/m^2). Older participants had significantly worse renal function (95.4% vs 41.2% had a creatinine clearance <90ml/min), more co-morbidities (median 8.0 vs 4.0), a greater number of regular medications (median 9.5 vs 4.0), and more joint erosions (72.7% vs 35.3% had erosions). The median flare rate was 0.33 flares per month in months 0-3, 0.34 in months 4-6 and 0.14 after the first six months. Participants with tophaceous gout had notably higher flare rates (median 0.47 vs 0.18 per month), which remained elevated throughout the study and affected various joints. Younger participants experienced significantly shorter flare durations (median 4.0 vs 7.0 days), and flare prophylaxis was associated with fewer affected joints (1.0 vs 2.0) and lower pain scores during a flare (6.0 vs 8.0 on a 10-point pain scale).

Conclusion. In this complex gout population, age-related differences in gout presentation were evident and flare patterns varied, with tophaceous gout associated with persistently higher flare rates. These findings highlight the need for early intervention and sustained management to prevent progression to complex gout.

Significance and Innovations

- Younger individuals had more modifiable gout risk factors, such as obesity and alcohol consumption, whereas older individuals had greater co-morbidities and associated medications, which may influence serum urate concentrations and treatment decisions.
- Flare patterns were highly variable, but individuals with tophaceous gout experience persistently higher flare rates, highlighting the impact of a high monosodium urate crystal burden.
- A treat-to-target serum urate strategy can effectively achieve serum urate targets and improve clinical outcomes in gout, even in complex patient cohorts.

Introduction

Gout, a chronic inflammatory arthritis caused by monosodium urate (MSU) crystal deposition, remains one of the most common and debilitating forms of arthritis worldwide (1). Characterised by acute, painful flares and the potential for long-term joint damage (71), gout significantly impairs quality of life and functional status (13, 206). While effective urate-lowering therapies (ULTs) exist (71), many patients fail to achieve serum urate (SU) targets due to various challenges such as sub-optimal ULT prescribing and monitoring, poor medication adherence, poor disease perception, and the impact of comorbid conditions (18, 207). As a result, some individuals experience refractory or difficult to manage gout, often requiring specialist management by a rheumatologist.

These 'complex' individuals typically present with severe and ongoing disease manifestations, including frequent flares, tophaceous gout and chronic gouty arthritis, and often experience challenges with treatment adherence and sub-optimal response (63, 208-210). However, disease complexity extends beyond condition-related and therapy-related factors, encompassing broader social/economic, patient-related and health-system related factors (184). Lifestyle factors such as obesity and alcohol use can contribute to poor response to ULT (211), while patient-related factors such as multiple comorbidities and polypharmacy further complicate management, as treatments must account for drug-disease and drug-drug interactions (140). For instance, renal impairment and cardiovascular comorbidities may make some treatment options contraindicated or may necessitate dose adjustments, close monitoring or narrower treatment options to ensure safety and efficacy (140). Timely access to healthcare may also influence gout outcomes, with difficulty in accessing healthcare associated with psychological stress (212). Additionally, studies have shown that a key factor in improving medication adherence and reaching SU targets in gout is ensuring patients receive sufficient education on their disease and medications (121). Although these factors are often considered in isolation, few studies have examined how they collectively contribute to the overall complexity of gout.

With an ageing population and gout disproportionately affecting older adults, age-related multimorbidity and polypharmacy is expected to drive an increased prevalence of complex cases (5, 213). At the same time, gout incidence is increasing in younger adults (214), and it can also be severe, particularly in early-onset gout with a genetic

predisposition (215, 216). The degree and type of complexity, however, may vary between the age groups. For instance, age-related changes in drug disposition can increase the risk of adverse drug reactions in older adults (217). Additionally, the development of geriatric syndromes (143), such as frailty, may influence the presentation and severity of gout. In contrast, younger patients may face different challenges, such as how their gout treatment affects their ability to work, particularly if they have frequent or ongoing flares. Exploring these differences between age groups may help inform the development of more tailored management strategies, particularly as the gout population continues to evolve.

A key feature of disease complexity in gout is the occurrence of flares, which remains one of the most distressing and disabling aspects of the disease (218, 219). For complex patients, flares may be more frequent, prolonged, or severe, heightening the disease burden and contributing to poorer health outcomes (210). Beyond physical pain, flares can disrupt daily functioning and contribute to psychological stress (14). Despite their clinical significance, the predictors and patterns of flares in complex gout populations remain inadequately explored. Furthermore, there is a limited understanding of how key factors such as tophaceous gout, flare prophylaxis, SU concentrations, age and ULT strategies influence flare patterns in more complex populations. Investigating these aspects in a well-defined cohort of complex gout patients may help identify modifiable factors that could reduce flare burden and improve patient outcomes. Additionally, in a population with high rates of drug-disease and drug-drug interactions (140), understanding protective factors against gout flares, such as omega-3 fatty acids (220), may have broader applications.

Thus, this study aimed to characterise a complex cohort of younger and older individuals with gout, examine their flare patterns, and explore potential factors influencing these patterns within this population.

Methods

Study population

The study population was drawn from a newly established longitudinal observational cohort of patients with gout (Central Adelaide Gout Clinic Database and Biobank (CAGCD)) who were managed at the Royal Adelaide Hospital Urate Crystal Arthritis Clinic, a tertiary referral hospital in Adelaide, Australia. Individuals are referred to the

clinic from tertiary or primary care and are generally considered to have more complex or difficult to manage gout requiring specialist management by a rheumatologist. Clinic patients were eligible for inclusion in the CAGCD if they were adults aged 18 years or older with gout as defined by the 2015 ACR-EULAR classification criteria (70), and were willing to participate in the assessment, monitoring and treatment protocols. Participants were excluded if they were unable to provide written, informed consent, were unable to attend clinical assessments due to geographic, transport or mobility factors or were unable to engage in assessments.

Individuals who consented to participate in the CAGCD were eligible for inclusion in this sub-study upon providing additional written, informed consent. Ethics approval was obtained from the Central Adelaide Local Health Network (protocol numbers: 12131 and 13017) and the University of South Australia (protocol number: 203170) Human Research Ethics Committees.

Study protocol

For this sub-study, participants were recruited from the 10th July 2020 until the 2nd July 2021, and followed up until the 2nd December 2021 to allow for collection of sufficient follow up data. Patients were reviewed in clinic every 3-months, starting from their first clinic visit (baseline), and received monthly phone reviews between clinic visits. Patients who attended the clinic were managed using a standardised protocol (**Appendix 2**) for treat-to-target ULT, with the aim of achieving a SU target concentration of below 0.30 mmol/L. First line ULT was allopurinol. If the SU target was not achieved with the maximum tolerated dose of allopurinol monotherapy, probenecid was added. If allopurinol was not tolerated, or if the maximum tolerated combination of allopurinol with probenecid did not achieve the SU target, allopurinol was ceased and febuxostat was commenced. Gout flare prophylaxis with either colchicine or naproxen or second-line low-dose prednisolone was considered for all participants during the first 6-months of ULT initiation or during any ULT escalation and was dependent on consideration of comorbidities and participant preference. Participants were prescribed colchicine, an NSAID or prednisolone for the treatment of gout flares, with dosing based on 2012 ACR Guidelines for the Management of Gout (135). For flares that failed to respond to oral therapy, some participants were offered intramuscular methylprednisolone injections at clinic appointments (full details including dosing is provided in **Appendix 2**).

Data collection

Data was collected prospectively in electronic and paper-format and stored in a custom-built CAGCD database. Data extracted for this sub-study included baseline information such as age, gender, body mass index, employment history, smoking and alcohol history, past medical conditions, current medications, gout history, and other relevant information collected at each follow-up visit. Participants had baseline x-rays taken of their hands and feet and underwent joint and tophi assessments at each clinic visit including the measurement of tender joint counts, swollen joint counts, and tophus counts. For participants with tophaceous gout, up to three index tophi, where one dimension was at least 5mm at baseline, were designated for serial measurement of the shortest and longest perpendicular at each clinic visit. In addition to the data collected as part of the CAGCD, the sub-study included three additional questionnaires (see below) and a single omega-3 fatty acid level.

The baseline assessment date refers to when participants consented to the CAGCD and completed the baseline assessment questionnaire. For most participants this was their first visit to the Urate Crystal Arthritis Clinic. However, as the clinic was operational prior to the establishment of the CAGCD, and with reduced capacity to see new patients during the COVID19 pandemic, some existing clinic patients were also recruited to the CAGCD. Baseline information for these participants was drawn from their first clinic visit record, which was slightly less detailed than the baseline assessment questionnaire. The same treatment protocol (**Appendix 2**) was used in all participants including those recruited before the establishment of the CAGCD.

Data collection – questionnaires

At each clinic visit, participants completed the Short Form 36-questionnaire (SF-36) (221), the Gout Impact Scale (GIS) (222), the Tophus Impact Questionnaire (TIQ) (for participants with tophi) (223), and the 5-item Medication Adherence Report Scale (MARS-5) (sub-study participants only) (197). Additional baseline only questionnaires for sub-study participants included the Beliefs about Medicines Questionnaire Specific (BMQ-Specific) (180) and the Satisfaction with Information about Medicines Scale (SIMS) (224). Descriptions and brief scoring systems of each questionnaire are provided below:

- The SF-36 is a general health questionnaire used in clinical practice to assess various aspects of an individual's physical and psychological wellbeing and has been validated for use in gout (225). The SF-36 is scored across eight domains, each with a total score ranging between 0 and 100.
- The GIS is a 24-item questionnaire assessing the impact of gout on five scales: (i) concern overall; (ii) medication side effects; (iii) unmet treatment needs; (iv) well-being during attack; and (v) concern over attack. The total GIS score was calculated if at least 13 items were completed by the participant.
- The TIQ is a 20-item tool designed to assess the burden of tophi on individuals with gout (223). Questions are asked on a agree or disagree scale, with a final rasch model adjusted score ranging from 0 to 10 (223).
- The MARS-5 is a 5-item self-reported adherence tool which is aimed at assessing both intentional and non-intentional nonadherence (197). Each item is graded on a 5-point Likert scale ranging from 'Never' (1-point) to 'Very Often' (5-points). The total MARS-5 score ranges from 5 to 25, with higher scores indicating better adherence and scores above 20 generally considered as adherent (197).
- The BMQ-specific consists of two 5-item sub-scales which measure the individual's beliefs on the necessity and concerns of their prescribed medicines (180). Each item is assessed on a 5-point Likert scale, ranging from strongly agree (5-points) to strongly disagree (1-point). Scores from each 5-item sub-scale are summed to provide an overall sub-scale score ranging from 5 to 25 for medication 'necessity' and medication 'concerns'. A 'necessity-concerns differential' is calculated by comparing the difference between the necessity and concerns sub-scale scores, with the final score ranging from -20 (highest medication concerns beliefs) to +20 (highest medication necessity beliefs).
- The SIMS is a 17-item tool aimed at understanding how satisfied individuals are with the information they have received about their prescribed medicines (224). Responses of "about right" or "none needed" are considered satisfactory and scored as 1. Responses of "too much", "too little" or "none received" are considered non-satisfactory and are scored as 0. Scores are summed and reported as a total satisfaction rating ranging from 0 to 17, with higher scores indicating greater satisfaction with the information received, as well as by sub-

scale (action and usage of medication (scores ranging from 0-9) and potential problems of medication (scores ranging from 0-8)).

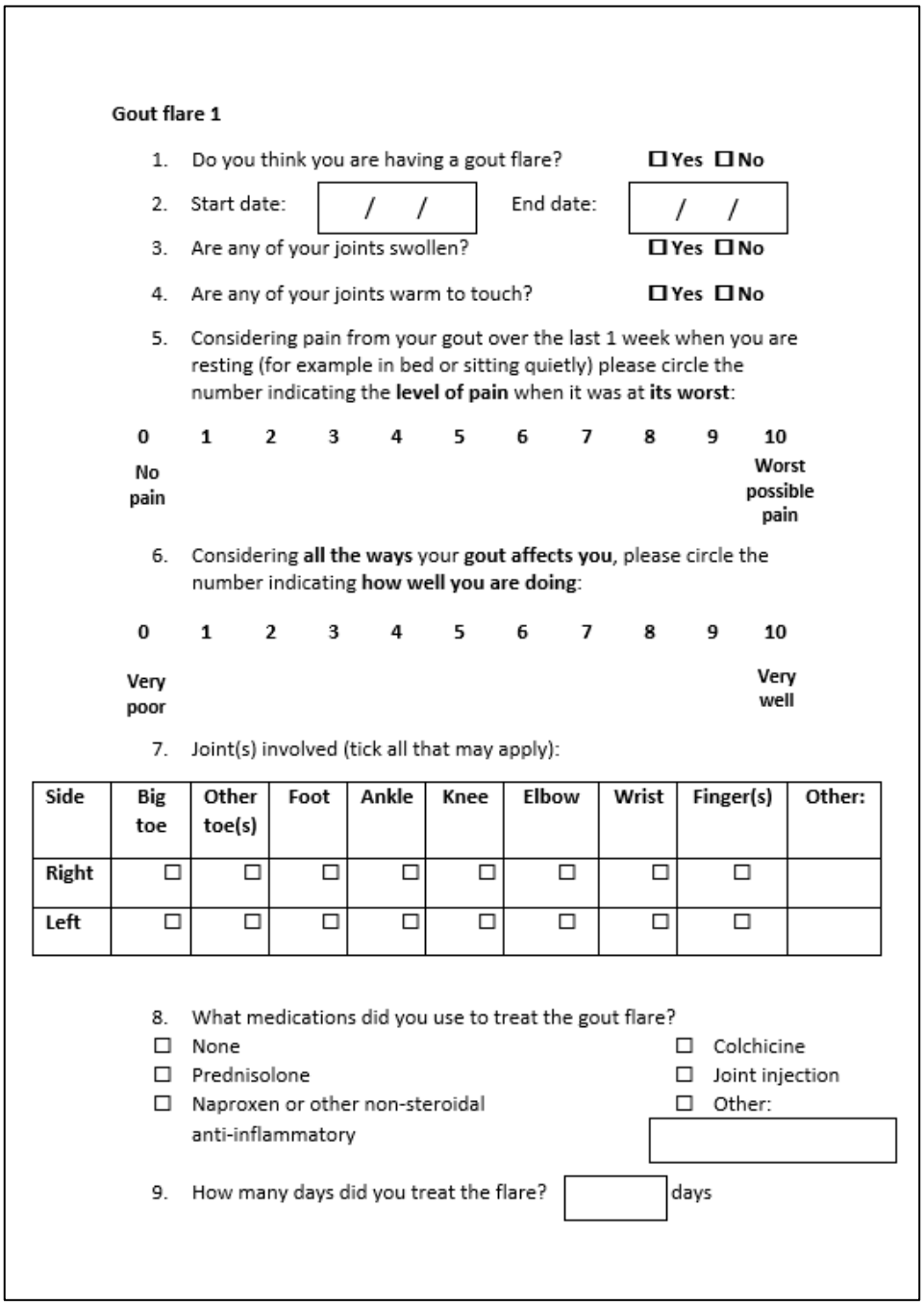
Data collection – laboratory investigations

Relevant laboratory investigations included SU concentrations and measures of renal function and were processed by standard pathology laboratories. Blood samples for SU were requested at monthly intervals before each phone or clinic appointment. A single blood sample was collected after the baseline assessment to analyse red blood cell (RBC) Omega-3 fatty acid status, which reflects long-term fatty acid intake (226). RBCs were obtained by centrifuging whole blood at 2000 relative centrifugal force at 4°C for 10 minutes. Plasma was removed and the sample was washed and centrifuged three times with Phosphate Buffered Saline (PBS). Red blood cells were stored at minus 80 degrees until defrosted, aliquoted, and sent for fatty acid profiling (% composition) by QmegaQuant, LLC. The Omega-3 Index (Eicosapentaenoic acid (EPA) + Docosahexaenoic acid (DHA)) was used for analysis (226).

Data collection – gout diary

A gout diary (**Appendix 3**) including information on gout, the participants individualised treatment plan, SU target, blood sampling schedule, and gout flare and adverse event documentation was developed and pilot tested. Based on initial feedback from several participants, the gout dairy was updated to improve clarity and functionality. Participants were instructed to use the gout diary at home and to bring it to each clinic appointment for review and updating. Using the gout diary, a comprehensive measure of each gout flare was captured within real-time. Each flare was recorded on a single page of the gout diary using checkbox and multiple-choice questioning (**Figure 1**) and was based on Gaffo et al's (227) validated definition of a gout flare. Gout flare data collected included the flare start and end date, whether any joints were swollen or warm to touch, the joints affected, medications used to treat the flare, treatment duration, gout pain on a 10-point scale, and overall quality of life on a 10-point scale. If participants did not complete or forgot to bring their gout diary, they were asked to retrospectively record a less comprehensive flare record which included the start and end date of any flares that occurred from their last clinic review, the joints involved, medications used to treat the flare and the treatment duration.

Figure 1. Excerpt of gout flare recording from the gout diary



Gout flare 1

1. Do you think you are having a gout flare? ☐ Yes ☐ No
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ Yes ☐ No
4. Are any of your joints warm to touch? ☐ Yes ☐ No
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0 1 2 3 4 5 6 7 8 9 10

No pain — **Worst possible pain**

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0 1 2 3 4 5 6 7 8 9 10

Very poor — **Very well**

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?

☐ None
☐ Prednisolone
☐ Naproxen or other non-steroidal anti-inflammatory
☐ Colchicine
☐ Joint injection
☐ Other:

9. How many days did you treat the flare? ____ days

Outcome measures

The study population were described at baseline using the World Health Organisation Adherence to long-term therapies guidance categories (184) including: (i) social- and economic-factors such as age and sex; (ii) patient-related factors such as co-morbidities; (iii) health system/health care team-related factors such as history of management; (iv); condition-related factors such as duration of gout or presence of palpable tophi and (v) therapy-related factors such as use of flare prophylaxis.

Socio-economic status was determined using the participants residential post code, with a State or Territory postal area index of relative socio-economic advantage and disadvantage ranking of <25% classified as low, 25-75% classified as medium, and >75% classified as high socio-economic status (228). The closest measurement of SU either before or after the baseline review date was used as the participants baseline SU concentration. This SU concentration does not represent pre-ULT treatment levels for all participants. Creatinine clearance (CrCl) was calculated using the Cockcroft and Gault formula. For participants in which ideal body weight could not be calculated, the estimated glomerular filtration rate was used in lieu of CrCl. Chronic gouty arthritis status was assigned by the rheumatologist and was based on the presence of persistent inflammation induced by MSU crystals (7). Flares were classified as meeting the validated definition of a gout flare (227) if they met at least 3 of 4 criteria: (i) patient-defined gout flare; (ii) pain at rest score >3 (on a 10-point scale); (iii) presence of at least 1 swollen joint; and (iv) presence of at least 1 warm joint.

Flare outcome measures included the mean number of flares per month during month 0-3, 4-6 and >6 from baseline and the proportion of flare days per month from baseline. Individual flare characteristics were also assessed, including the flare duration, presence of at least one swollen joint, presence of at least one warm joint, pain scale (ranging from no pain (0) to worst possible pain (10)), patient global assessment (ranging from very poor (0) to very well (10)), number of affected joints, whether the flare was treated, and the treatment duration. Heatmaps were developed for flaring joints across months 0-3, 4-6 and >6 from baseline and against different participant characteristics. Other outcome measures included the percentage change from baseline in SU concentrations, index tophi diameter, tender joint count, swollen joint count, medication adherence and health-related quality of life scores (GIS and SF-36). Other monthly reported measures included the mean SU concentration, the individual percentage change in index tophi diameter, and the change in participant flare prophylaxis use.

Statistical analysis

Data is presented using descriptive statistics including mean with standard deviation, median with interquartile range, and counts with percentages. Normality was assessed using the Shapiro-Wilk test. Baseline characteristics were compared between younger participants (<65 years at baseline) and older participants (≥65 years old at baseline) using an independent-sample t-test for continuous variables, Wilcoxon-Mann-Whitney

test for continuous nonparametric variables and chi-square or Fisher's exact test for dichotomous/categorical variables. All data was analysed using R version 4.3.2. Heatmap data was produced in R and transferred to PowerPoint for conversion into schematic format.

For flares that did not have a specified start date, an arbitrary start date was imputed based on whether the flare was known to start early, mid, or late in that month. Flares occurring early in the month were imputed with the date of the first Monday of that month, mid-month flares were imputed with the Monday closest to the 15th day of that month, and late-month flares were imputed with the date of the last Monday of that month. For flares that did not have a specified end date, the treatment duration for that flare was used to impute a flare end date. If there was no treatment duration, the participants median duration for all other flares was used to impute a flare end date. Participants with chronic flares who were unable to differentiate and document episodes of flares were excluded from flare related analyses.

Individual flares were analysed by: (i) flares that met the criteria for a flare versus those that either did not meet the criteria or had insufficient recording of flares; (ii) flares occurring in participants receiving flare prophylaxis versus those not receiving flare prophylaxis at the time of the flare; (iii) flares occurring in younger participants (<65 years at baseline) versus older participants (≥65 years old at baseline); (iv) flares occurring in participants with subcutaneous tophi versus those without tophi at the time of the flare; (v) flares occurring in participants who initiated ULT versus those who escalated their ULT at baseline; and (iv) flares occurring in participants with a baseline omega-3 index of <6% versus those with a baseline index of ≥6% (groups were based on the omega-3 index study mean).

The mean flare rate per month was calculated using the following formula:

$$\text{Mean Flare Rate per Month} = \left(\frac{\text{Total Number of Flares}}{\text{Observation Period (in days)}}\right) \times \left(\frac{365 \text{ days}}{12 \text{ months}}\right)$$

Flare rates per month were reported over the entire study period, as well as for months 0-3, 4-6 and >6 months from baseline. Flare rates per month were compared by prophylaxis status (prophylaxis at baseline versus no prophylaxis), age category (<65 versus ≥65 years old at baseline), tophi status (subcutaneous tophi at baseline versus no

tophi), ULT category (ULT initiation at baseline versus ULT escalation), and omega-3 index (<6% versus ≥6%, based on the study mean). The proportion of flare days per month were calculated for each participant by dividing their total number of flaring days in each 30-day period from baseline by 30. The mean proportion of flare days per month across all participants was used for reporting.

Results

Baseline Demographics

Of the 41 participants who consented to this study, 39 had follow-up data following the baseline assessment and were therefore included in this analysis. Two participants with chronic gouty arthritis were excluded from specific analyses of gout flares, as there was an inability to differentiate and document episodes of flares. One participant was censored at the point of known unintentional non-adherence to ULT, while another participant was censored when they were no longer able to record their flare data. No participant withdrew consent from the study. Three participants (7.7%) died during the study period for reasons unrelated to gout and five participants (12.8%) were lost to follow up. Participants were followed up for an average of 8.3 months (± Standard deviation (SD) = 4.0 months). Overall, 17 (44%) participants were younger adults (<65 years) and 22 (56%) were older adults (≥65 years).

Social and economic factors

Participant social and economic factors are presented in **Table 1.** Participants were predominately male (84.6%) and had a mean age of 64.9 years (range 26 to 95 years). Most of the younger participants were employed (82.4%), while the older participants were predominately retired (81.8%). One quarter of those who were employed (26.7%) had taken between 4 and 30 days off work due to gout in the last 3-months. Over half of the cohort (56.4%) reported drinking alcohol, with beer (77.3%) the most consumed type, followed by wine (50.0%). Almost half (47.1%) of the younger participants reported reductions in alcohol consumption prior to their baseline visit. However, younger participants still consumed a greater number of standard drinks per week than older participants (P=0.025). Over half of the participants (53.8%) were classified as obese and on average, younger participants had a higher body mass index (P=0.023). Almost all the older participants (95.5%) and 41.2% of the younger participants had a CrCl <90 mL/min, indicating some form of renal impairment.

Table 1. Social and economic factors

Characteristic	**<65 years** n= 17	**≥65 years** n= 22	**P-value**[a]	**Total** n=39
Sex, Male, n (%)	15 (88.2)	18 (81.8)	0.68	33 (84.6)
Age, years, mean ± SD	49.7 ± 11.3	76.6 ± 8.1	-	64.9 ± 16.5
Employment status, n (%)				
Employed	14 (82.4)	1 (4.6)	**<0.001**	15 (38.5)
Unemployed	0 (0)	0 (0)		0 (0)
Retired	0 (0)	18 (81.8)		18 (46.2)
Other[b]	3 (17.6)	3 (13.6)		6 (15.4)
Socio-economic status, n (%)				
Low <25%	4 (23.5)	7 (31.8)	0.92	11 (28.2)
Medium 25-75%	6 (35.3)	6 (27.3)		12 (30.8)
High >75%	7 (41.2)	9 (40.9)		16 (41.0)
Alcohol drinker, n (%)	11 (64.7)	11 (50.0)	0.55	22 (56.4)
Alcohol days per week, median (IQR)*	2.0 (1.5-2.0)	3.0 (1.0-3.5)	0.34	2.0 (1.0-3.0)
Standard drinks per week[c], median (IQR)*	3.0 (2.3-3.9)	1.5 (1.0-2.0)	**0.025**	2.0 (1.5-3.0)
Smoking, n (%)				
Never	7 (41.2)	17 (77.3)	**0.028**	24 (61.5)
Former	8 (47.1)	5 (22.7)		13 (33.3)
Current	2 (11.8)	0 (0)		2 (5.1)
Renal function				
Creatinine concentration (mg/dL), median (IQR)*	90.0 (80.0-95.0)	128.0 (91.0-156.0)	**0.011**	97 (85.5-136.0)
CrCl category (mL/min), n (%)				
≥90	10 (58.8)	1 (4.6)	**<0.001**	11 (28.2)
>60 - <90	4 (23.5)	4 (18.2)		8 (20.5)
>30 - <60	3 (17.6)	10 (45.5)		13 (33.3)
≤30	0 (0)	7 (31.8)		7 (17.9)
Body mass index (kg/m^2), median (IQR)*	32.9 (28.7-35.8)	25.1 (20.5-29.3)	**0.023**	31.1 (26.8-35.3)
≥ 30 kg/m^2, n (%)	12 (70.6)	9 (40.9)	0.17	21 (53.8)
Lifestyle changes made prior to baseline visit, n (%)				
Dietary changes	6 (35.3)	9 (40.9)	0.98	15 (38.5)
Increase exercise	5 (29.4)	4 (18.2)	0.46	9 (23.1)
Weight loss	5 (29.4)	4 (18.2)	0.46	9 (23.1)
Decrease alcohol	8 (47.1)	3 (13.6)	**0.033**	11 (28.2)
None	2 (11.8)	6 (27.3)	0.43	8 (20.5)

* Data was non-normally distributed

[a] P-values were calculated using an independent-sample t-test, Wilcoxon-Mann-Whitney test, or Chi-square or Fisher's exact test. Significant P-values are shown in bold.

[b] other category includes students, homemakers, ill health and disability and/or selection of ≥2 employment categories.

[c] 1 standard drink = 10g alcohol

CrCl = creatinine clearance. IQR = interquartile range. SD = standard deviation.

Patient related factors

Patient related factors are presented in **Table 2**. Participants had an average of six medical conditions including gout (range 1-13). Older participants had significantly more medical conditions (median 8 vs 4, P<0.001), and they also had higher rates of

hypertension (P=0.049), cardiovascular disease (P<0.001) and chronic kidney disease (P=0.004). The most common concurrent medications included statins (51.3%), angiotensin converting enzyme and angiotensin-II receptor blockers (46.2%), beta-blockers (41.0%) and proton pump inhibitors (38.5%). Older participants were taking more medications (median 9.5 vs 4, P=0.002) than younger participants, and they also had higher usage of statins (P=0.038), diuretics (P=0.024) and low-dose aspirin (P=0.027). Older participants also had significantly lower physical functioning and role-physical scores in the SF-36 questionnaire, indicating reduced physical health at baseline.

Table 2. Patient related factors

Characteristic	**<65 years** n= 17	**≥65 years** n= 22	**P-value[a]**	**Total** n=39
Medical conditions, total[b], median (IQR)	4 (3.0-6.0)	8 (6.3-9.0)	**<0.001**	6 (4-8)
Hypertension, n (%)	7 (41.2)	17 (77.3)	**0.049**	24 (61.5)
Cardiovascular disease[c], n (%)	1 (5.6)	17 (77.3)	**<0.001**	18 (46.2)
Gastrointestinal disease[d], n (%)	6 (35.3)	11 (50.0)	0.55	17 (43.6)
Hypercholesterolaemia, n (%)	4 (23.5)	12 (54.5)	0.10	16 (41.0)
Chronic kidney disease, n (%)	1 (5.6)	11 (50.0)	**0.004**	12 (30.8)
Lung disease[e], n (%)	3 (17.6)	6 (27.3)	0.70	9 (23.1)
Cancer, n (%)	3 (17.6)	5 (22.7)	1.00	8 (20.5)
Type 2 Diabetes Mellitus, n (%)	1 (5.6)	5 (22.7)	0.21	6 (15.4)
Liver disease, n (%)	1 (5.6)	2 (9.1)	1.0	3 (7.7)
Concurrent medications, total (regular meds), median (IQR)	4 (2.0-7.0)	9.5 (5.5-11.8)	**0.002**	7 (2.5-10)
Statin, n (%)	5 (29.4)	15 (68.2)	**0.038**	20 (51.3)
ACE inhibitor or A2RB[f], n (%)	5 (29.4)	12 (54.5)	0.21	17 (43.6)
Beta-blocker, n (%)	4 (23.5)	12 (54.5)	0.10	16 (41.0)
PPI, n (%)	5 (29.4)	10 (45.5)	0.49	15 (38.5)
Calcium channel blocker, n (%)	4 (23.5)	7 (31.8)	0.72	11 (28.2)
Diuretic[g], n (%)	1 (5.6)	9 (40.9)	**0.024**	10 (25.6)
Low-dose aspirin (100mg/day), n (%)	0 (0)	6 (27.3)	**0.027**	6 (15.4)
Omega-3 index (%)[h], mean ± SD	6.08 ± 1.03	5.82 ± 1.62	0.60	5.9 ± 1.4
Range	4.50-7.38	3.38-9.92		3.4-9.9
<6%, n (%)	5 (41.7)	10 (58.8)	0.59	15 (51.7)
≥6%, n (%)	7 (58.3)	7 (41.2)		14 (48.3)
Patient global assessment, (0-10 scale)[i], mean ± SD	5.9 ± 2.0	6.3 ± 2.6	0.60	6.1 ± 2.3
Short Form 36 scores, (0-100)[j], mean ± SD				
Physical Functioning	59.9 ± 29.8	39.0 ± 24.3	**0.027**	48.1 ± 28.5
Role-Physical	60.9 ± 41.8	25.4 ± 35.4	**0.014**	40.8 ± 41.7
Role-Emotional	64.6 ± 44.7	47.6 ± 42.9	0.25	55.0 ± 43.9
Vitality (Energy and Fatigue)	51.5 ± 22.4	44.6 ± 20.6	0.27	47.6 ± 21.4
Emotional Well-Being	63.1 ± 23.3	69.5 ± 22.8	0.34	66.7 ± 22.9
Social Functioning	66.9 ± 25.0	63.6 ± 30.8	0.71	65.1 ± 28.1
Bodily Pain	55.4 ± 31.0	46.6 ± 24.2	0.36	50.7 ± 27.5
General Health	49.1 ± 21.3	44.3 ± 21.9	0.55	46.4 ± 21.5

[a] P-values were calculated using an independent-sample t-test, Wilcoxon-Mann-Whitney test, or Chi-square or Fisher's exact test. Significant P-values are shown in bold.
[b] includes gout
[c] includes coronary artery disease (n=13), heart failure (n=2), stroke/transient ischemic attack (n=4), and vascular disease (n=6).
[d] primarily gastro-oesophageal reflux disease and peptic ulcerative disease
[e] primarily asthma and chronic obstructive pulmonary disease
[f] ACE inhibitor (n=10) and A2RB (n= 7)
[g] non-thiazide (n=8) and thiazide (n=2) diuretics
[h] includes data for 29 participants
[i] measured with a numerical rating scale, where 0=very poor and 10=very well
[j] a higher score indicates better health
ACE = angiotensin-converting enzyme. A2RB = angiotensin-II receptor blocker. BMI = body mass index. CrCl = creatine clearance. IQR = interquartile range. PPI= proton pump inhibitor. SD = standard deviation.

Health system / health care team related factors

Thirty participants provided information regarding their gout management in the year prior to enrolment, of which 27 received long-term management from either a general practitioner (GP) (59.3%) or rheumatologist (44.4%). Most participants sought advice and treatment for their gout flares from a GP (83.3%) and/or rheumatologist (46.7%), and/or 13.3% required an emergency department visit.

Participants demonstrated generally high satisfaction levels with the information they received about their gout medication from the rheumatologist at their baseline visit, with an overall mean (± SD) score of 14.3 ± 2.6 out of 17 in the Satisfaction with Information About Medicines Questionnaire (8). Specifically, they reported feeling well-informed about the action and usage of their medication, with a mean score of 8.3 ± 1.0 out of 9, indicating a strong understanding of how to use their medication effectively. Perceptions on potential problems associated with their gout medications were lower, with an average score of 6.0 ± 2.1 out of 8. There was no difference in Satisfaction with Information About Medicines Questionnaire scores between younger and older participants (P>0.8).

Condition related factors

Condition related factors are presented in **Table 3**. Over one quarter of participants (28.2%) reported a family history of gout in one (63.6%) or two (36.4%) first degree relatives. Younger participants had lived with gout for a median of 6 years before the study period whereas older participants had lived with gout for 16.1 years. Older participants had more tophi (63.6%) compared to younger participants (29.4%). Older participants also had significantly more joint erosions visible on x-ray (72.7%) compared to younger participants (35.3%). Over half (51.3%) of participants had

experienced more than five flares in the previous 12-months and a quarter (25.6%) of participants were considered to have chronic gouty arthritis. Participants with tophi (48.7%) reported a moderate tophus burden as measured by TIQ (5) (mean (± SD) TIQ-20 score 5.1 ± 1.3 out of 10). Based on the GIS (4), participants reported moderate impact of gout on their health, with a mean (± SD) total GIS score of 49.4 ± 17.6. GIS scores were similar between younger and older participants.

Table 3. Condition related factors

Characteristic	**<65 years** n= 17	**≥65 years** n= 22	**P-value**[a]	**Total** n=39
Family history of gout (first degree relative), n (%)	5 (29.4)	6 (27.3)	1.00	11 (28.2)
Duration of gout, years, median (IQR)*	6.0 (4.7-14.5)	16.1 (5.3-27.9)	0.17	9.3 (4.5-22.2)
Number of gout flares in previous year, n (%)				
0	1 (5.6)	0 (0)	0.66	1 (2.6)
1-2	3 (17.6)	3 (13.6)		6 (15.4)
3-5	4 (23.5)	6 (27.3)		10 (25.6)
6-10	2 (11.8)	6 (27.3)		8 (20.5)
>10	6 (35.3)	6 (27.3)		12 (30.8)
Unknown	1 (5.9)	1 (4.6)		2 (5.1)
Chronic gouty arthritis, n (%)	6 (35.3)	4 (18.2)	0.28	10 (25.6)
Tender joint count, median (IQR)*	1.0 (0-5.0)	1.5 (1.0-3.0)	0.95	1 (0-3.5)
Swollen joint count, median (IQR)*	1.0 (0-3.0)	1.0 (1.0-4.0)	0.71	1 (0.2-3.8)
Tophi present, n (%)	5 (29.4)	14 (63.6)	0.07	19 (48.7)
Tophus count, n (%)				
0	12 (70.6)	8 (36.4)	0.08	20 (51.3)
1-5	3 (17.6)	5 (22.7)		11 (28.2)
>5	2 (11.8)	9 (40.9)		8 (20.5)
Tophus Impact Scale, (0-10)[b], mean ± SD	5.2 ± 2.1	5.0 ± 0.9	0.85	5.1 ± 1.3
Joint erosions, n (%)	6 (35.3)	16 (72.7)	**0.044**	22 (56.4)
Pain from gout in last week, (0-10 scale)[c], mean ± SD	5.9 ± 2.0	6.3 ± 2.6	0.60	6.1 ± 2.3
GIS scores, (0-100)[d], mean ± SD				
Total GIS Score	53.3 ± 18.2	46.4 ± 17.0	0.24	49.4 ± 17.6
Gout concern Overall	69.9 ± 16.7	59.9 ± 23.0	0.13	64.3 ± 20.9
Gout Medication Side Effects	52.9 ± 24.4	43.5 ± 26.4	0.26	47.7 ± 25.6
Unmet Gout Treatment Need	47.1 ± 17.9	44.3 ± 16.9	0.63	45.5 ± 17.2
Well-Being During Attack	51.9 ± 24.8	48.0 ± 25.7	0.65	49.7 ± 25.1
Gout Concern During Attack	55.5 ± 24.2	46.8 ± 24.6	0.27	50.6 ± 24.5

* Data was non-normally distributed

[a] P-values were calculated using an independent-sample t-test, Wilcoxon-Mann-Whitney test, or Chi-square or Fisher's exact test. Significant P-values are shown in bold.

[b] a higher score indicates worse health. Calculated using Rasch-modelled Score.

[c] measured with a numerical rating scale, where 0=very poor and 10=very well.

[d] a higher score indicates worse health

GIS = gout impact scale. IQR = interquartile range. SD = standard deviation.

Therapy related factors

Therapy related factors are summarised in **Table 4**. Most participants had previously used ULT and approximately half had previously used gout flare prophylaxis. Prednisolone and colchicine were the predominant treatments used for acute gout flare management in the 12-months prior to baseline. At study baseline, 17 participants (43.6%) were commenced on ULT (94.1% allopurinol), 20 (51.3%) had their ULT dose escalated (95.0% allopurinol), one (2.6%) switched from allopurinol to probenecid due to side effects and one participant (2.6%) was on a stable therapeutic dose of allopurinol. Gout flare prophylaxis was provided to 61.5% of the cohort, with the majority receiving colchicine (87.5%) and/or prednisolone (29.2%). Four participants (16.7%) received both colchicine and prednisolone, one participant received a NSAID (4.2%), and one received both colchicine and NSAID (4.2%). For those receiving flare prophylaxis, the average duration of prophylaxis was 5.6 (IQR 3.5-8.1) months, noting that for eight participants prophylaxis was still ongoing at their censor date (censor dates ranging from 1.8 to 9.9 months after commencing prophylaxis). Colchicine prophylaxis was ceased in four participants (16.7%) due to gastrointestinal adverse events, while prednisolone was ceased in one participant (4.2%) due to skin thinning and blood spotting.

On average, participants held high beliefs on the necessity of their medication with a mean (± SD) specific necessity score of 20.0 ± 3.6 out of 25.0 as measured by the Beliefs about Medicines Questionnaire Specific (7). The overall necessity minus concerns differential was positive, with a score of 5.6 ± 4.3 in younger participants and 8.1 ± 3.8 in older participants (possible range -20 to 20) (P=0.08). Participants were assessed as having high adherence to their medications with a median 5-item Medication Adherence Report Scale of 24.0 (IQR 22.0-25.0) (possible range 5-25).

Table 4. Therapy related factors

Characteristic	<65 years n= 17	≥65 years n= 22	P-value[a]	Total n=39
Previous ULT use ever, n (%)	16 (94.1)	18 (81.8)	0.36	34 (87.2)
Previous flare prophylaxis use ever, n (%)	10 (58.8)	10 (45.5)	0.61	20 (51.3)
Previous treatment flares (last 12-months), n (%)				
Prednisolone	10 (58.8)	14 (63.6)	1.00	24 (61.5)
Colchicine	12 (70.6)	11 (50.0)	0.33	23 (59.0)
NSAID	9 (52.9)	5 (22.7)	0.11	14 (35.9)
Corticosteroid injection	5 (29.4)	4 (18.2)	0.46	9 (23.1)
Other	3 (17.6)	5 (22.7)	1.00	8 (20.5)
Urate-lowering therapy at baseline, n (%)				
Initiation	5 (29.4)	12 (54.5)	0.29	17 (43.6)
Escalation	11 (64.7)	9 (40.9)		20 (51.3)
Other	1 (5.9)	1 (4.6)		2 (5.13)
Prophylaxis use at baseline, n (%)	13 (76.5)	11 (50.0)	0.11	24 (61.5)
Serum urate (mmol/L)				
Mean ± SD	0.44 ± 0.10	0.45 ± 0.13	0.77	0.45 ± 0.12
Range	0.24-0.61	0.20-0.70		0.20-0.70
Beliefs about Medicines Questionnaire, mean ± SD				
Specific Necessity Score (5-25)	19.4 ± 3.9	20.5 ± 3.4	0.36	20.0 ± 3.6
Specific Concerns Score (5-25)	13.8 ± 4.6	12.4 ± 3.0	0.32	13.1 ± 3.9
Necessity minus Concerns Differential (-20 to +20)[b]	5.6 ± 4.3	8.1 ± 3.8	0.08	6.9 ± 4.2
5-item Medication Adherence Report Scale (5-25)[c], median (IQR)*	23.5 (21.2-25.0)	24.0 (23.0-25.0)	0.56	24.0 (22.0-25.0)

* Data was non-normally distributed

[a] P-values were calculated using an independent-sample t-test, Wilcoxon-Mann-Whitney test, or Chi-square or Fisher's exact test. Significant P-values are shown in bold.

[b] a negative score indicates higher medication concerns beliefs and a positive score indicates higher medication necessity beliefs.

[c] a higher score indicates higher adherence

IQR = interquartile range. SD = standard deviation.

Change in factors over time

The percentage change from baseline to the end of the study period for various condition, clinical and treatment related factors are summarised in **Table 5** (mean follow up period of 8.3 (± SD 4.0) months). There was a significant reduction in SU concentrations, tender joint counts and swollen joint counts in both younger and older participants. The index tophi diameter decreased in both groups (significantly in the older participants), but no significant changes were noted in participant tophus impact scale scores. Medication adherence significantly increased in the older participants. Changes in gout impact scale and SF-36 scores varied between the younger and older participants but in general, both scales were improved (i.e., gout impact scale scores reduced and SF-36 scores increased).

Table 5. Percentage change from baseline

Variable	<65 years n= 17	P-value[a]	≥65 years n= 22	P-value[b]	Total n=39
SU concentration	-22.1 ± 24.9	**0.001**	-23.8 ± 24.0	**<0.001**	-23.1 ± 24.1
Index tophi diameter	-59.1 ± 31.5	0.13	-32.2 ± 27.2	**<0.001**	-38.5 ± 29.7
Tender joint count	-68.4 ± 69.5	**0.032**	-74.3 ± 42.3	**0.001**	-72.0 ± 53.1
Swollen joint count	-70.4 ± 67.6	**0.031**	-85.0 ± 28.8	**0.014**	-78.1 ± 50.0
5-item medication adherence report scale[c]	4.4 ± 18.0	0.89	7.6 ± 10.8	**0.037**	6 ± 14.5
Tophus impact scale[d]	6.8 ± 90.0	0.60	-17.3 ± 32.0	0.09	-12.1 ± 46.2
GIS[d]					
Total GIS Score	-10.3 ± 34.2	**0.042**	-21.6 ± 27.0	**<0.001**	-17.1 ± 30.1
Gout concern Overall	-13.6 ± 19.5	**0.026**	-18.9 ± 39.5	0.055	-16.8 ± 32.7
Gout Medication Side Effects	-23.2 ± 31.8	**0.0097**	-12.5 ± 73.7	0.33	-17.2 ± 58.6
Unmet Gout Treatment Need	-19.8 ± 40.8	**0.014**	-12.2 ± 52.3	0.19	-15.4 ± 47.2
Well-Being During Attack	-24.3 ± 34.4	**0.011**	-33.8 ± 38.3	**0.0014**	-30.2 ± 36.6
Gout Concern During Attack	13.5 ± 45.4	1.00	-13.2 ± 59.8	**0.021**	-2.5 ± 55.4
Short Form 36 scores[e]					
Physical Functioning	27.2 ± 47.4	**0.014**	66.7 ± 178.0	0.61	51.2 ± 142.0
Role-Physical	30.0 ± 106.0	0.46	60.0 ± 171.0	0.07	45.0 ± 140.0
Role-Emotional	16.7 ± 79.1	0.27	42.3 ± 104.0	**0.022**	31.8 ± 93.3
Vitality (Energy and Fatigue)	41.3 ± 130.0	0.48	15.0 ± 56.3	0.29	25.9 ± 93.0
Emotional Well-Being	16.9 ± 64.2	0.89	18.4 ± 71.6	0.40	17.8 ± 67.6
Social Functioning	2.0 ± 41.1	0.46	8.8 ± 62.9	0.77	6.0 ± 54.3
Bodily Pain	53.2 ± 102.0	**0.022**	29.4 ± 93.8	0.33	38.9 ± 96.0
General Health	-4.2 ± 34.9	0.34	19.3 ± 73.1	0.81	9.9 ± 61.2

Mean ± SD percentage change calculated per participant.

[a] P-values were calculated using a paired-sample t-test or paired Wilcoxon-Mann-Whitney test. P-values are for % change from baseline for participants aged <65 years old at baseline. Significant P-values are shown in bold.

[b] P-values were calculated using a paired-sample t-test or paired Wilcoxon-Mann-Whitney test. P-values are for % change from baseline for participants aged ≥65 years old at baseline.

[c] a positive score indicates improved adherence

[d] a negative score indicates improved health

[e] a positive score indicates improved health

GIS = gout impact scale. IQR = interquartile range. SD = standard deviation. SU = serum urate.

Flare analysis

A total of 126 gout flares were reported in 28 (out of 37) participants during the study period. Of these, 4.8% (6/126) had imputed start dates, 17.5% (22/126) had imputed end dates, and 3.2% (4/126) had an imputed flare duration. Based on the valid definition for a flare by Gaffo et al (227), of the 86 flares (68.3%) with sufficient recording of flares, 79.1% (68/86) met the criteria for a flare. Reported symptoms were not different between flares that met the flare criteria and those that either did not meet the criteria or had insufficient recording of flares, except for a greater proportion of flares with at least one swollen or warm joint in the group that met the flare criteria (**Table 6**).

Table 6. Flare analysis comparing flares that met the valid definition of a flare versus those that did not

Analysis of individual flares	Met flare criteria		Did not meet flare criteria		P-value[a]
	N	Result	N	Result	
Flare duration, days, median (IQR)	68	5.5 (4.0-9.0)	58	5.0 (3.0-9.0)	0.78
≥1 swollen joint, n (%)	68	64 (94.1)	18	1 (5.6)	**<0.0001**
≥1 warm joint, n (%)	67	60 (89.6)	16	1 (6.3)	**<0.0001**
Pain, scale 0-10[b], median (IQR)	67	7.0 (5.0-8.0)	29	6.0 (4.0-8.0)	0.10
Patient global assessment, scale 0-10[c], median (IQR)	63	6.0 (4.5-7.0)	20	6.0 (4.8-7.0)	0.70
Number of affected joint(s), median (IQR)	68	2.0 (1.0-2.0)	58	1.0 (1.0-2.0)	0.16
Treated flare, n (%)	68	64 (94.1)	58	52 (89.7)	0.51
Duration of flare treatment, days, median (IQR)	61	4.0 (3.0-9.0)	39	6 (3.0-9.0)	0.41

Valid definition for a flare based on Gaffo 2018 *et al* (227)

[a] P-values were calculated using an independent-sample t-test, Wilcoxon-Mann-Whitney test, or Chi-square or Fisher's exact test. Significant P-values are shown in bold.

[b] measured with a numerical rating scale, where 0=no pain and 10=worst possible pain.

[c] measured with a numerical rating scale, where 0=very poor and 10=very well.

All data was non-normally distributed.

IQR = interquartile range. SD = standard deviation.

Due to the high rates of missing data, all documented flares were used in the analyses. An analysis of individual gout flares by prophylaxis status, age category, tophi status, ULT status, and omega-3 index are presented in **Table 7.** On average, younger participants had shorter gout flares than older participants, with a median flare duration of 4 versus 7 days (P=0.005), respectively. Flares in participants with tophi and those escalating ULT were significantly more likely to have at least one swollen joint (P=0.008 and P=0.002, respectively) or at least one warm joint (P=0.02 and P=0.01, respectively) compared to participants without tophi and those initiating ULT, respectively. Participants not receiving flare prophylaxis were more likely to have flares with multiple joint involvement compared to flares occurring in participants receiving flare prophylaxis (Median 2 versus 1 joint involved, P=0.03). Flares occurring in participants who were not receiving flare prophylaxis were also rated 2 points higher on the pain scale compared to those occurring in participants who were receiving flare prophylaxis, indicating higher pain at rest during a flare (median 8 versus 6 on a 10-point scale (P=0.008)). Older participants were also more likely to report higher pain scores than younger participants (median 7.5 versus 5.5, P=0.04). Most flares (88.9%) were treated by protocol with prednisolone, NSAID or colchicine. Paracetamol or

paracetamol with an opiate were added in 20.6% of flares and 7.9% of flares were untreated. As with flare duration, treatment duration was shorter in younger compared to older participants, as well as those with an omega-3 index of ≥6% compared to those with an index <6% (3 versus 5 days, P=0.02 for both respectively).

Table 7. Analysis of individual gout flares by prophylaxis status, age category, tophi status, and ULT category

	No Prophylaxis n=65	**Prophylaxis** n=61	**P-value**	**Age <65 years** n=50	**Age ≥65 years** n=76	**P-value**	**No tophi** n=43	**Tophi** n=83	**P-value**	**ULT initiation** n=57	**ULT escalation** n=69	**P-value**	**Omega-3 index <6%** n=34	**Omega-3 index ≥6%** n=32	**P-value**
Flare duration, days, median (IQR)	6.0 (4.0-9.0)	5.0 (3.0-8.0)	0.13	4.0 (3.0-7.8)	7.0 (4.0-10.0)	**0.005**	6.0 (3.5-9.0)	5.0 (3.5-9.0)	0.60	5.0 (3.0-9.0)	6.0 (4.0-9.0)	0.57	6.5 (4.0-10.0)	5.0 (4.0-7.0)	0.17
≥1 swollen joint, n (%)	37 (75.5)	28 (75.7)	1.00	22 (71.0)	43 (78.2)	0.63	20 (58.8)	45 (86.5)	**0.008**	22 (57.9)	43 (89.6)	**0.002**	15 (53.6)	24 (92.3)	**0.004**
≥1 warm joint, n (%)	34 (72.3)	27 (75.0)	0.98	23 (74.2)	38 (73.1)	1.00	20 (58.8)	41 (83.7)	**0.023**	21 (58.3)	40 (85.1)	**0.013**	16 (61.5)	22 (88.0)	0.06
Pain, scale 0-10[b], median (IQR)	8.0 (6.0-9.0)	6.0 (4.0-8.0)	**0.008**	5.5 (4.0-8.0)	7.5 (6.0-9.0)	**0.04**	7.0 (4.0-8.0)	7.0 (5.0-9.0)	0.09	7.0 (4.3-8.0)	7.0 (5-8.8)	0.37	7.0 (4.5-8.0)	7.0 (5.0-8.0)	0.57
Patient global assessment, scale 0-10[c], median (IQR)	5.5 (4.0-7.0)	6.0 (5.0-7.0)	0.25	6.0 (5.0-7.0)	5.0 (4.0-7.0)	0.47	6.0 (4.3-7.0)	6.0 (5.0-7.0)	0.91	6.0 (5.0-7.0)	5.0 (4.0-7.0)	0.12	6.0 (5.0-7.0)	5.0 (4.0-6.0)	0.12
Number of affected joint(s), median (IQR)	2.0 (1.0-2.0)	1.0 (1.0-2.0)	**0.03**	1.0 (1.0-2.0)	2.0 (1.0-2.3)	0.08	1.0 (1.0-2.0)	2.0 (1.0-2.5)	0.09	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.78	2.0 (1.0-2.8)	1.0 (1.0-2.0)	0.31
Treated flare, n (%)	62 (95.4)	54 (88.5)	0.20	48 (96.0)	68 (89.5)	0.31	39 (90.7)	77 (92.8)	0.73	52 (91.2)	64 (92.8)	1.00	32 (94.1)	30 (93.8)	1.00
Duration of flare treatment, days, median (IQR)	5.0 (3.0-9.0)	4.0 (3.0-8.0)	0.84	3.0 (2.0-7.0)	5.0 (3.0-9.0)	**0.02**	4.0 (2.5-9.0)	4.0 (3.0-9.0)	0.79	5.0 (3.0-9.0)	4.0 (2.0-8.8)	0.25	5.0 (3.0-9.0)	3.0 (2.3-5.5)	**0.02**

[a] P-values were calculated using an independent-sample t-test, Wilcoxon-Mann-Whitney test, or Chi-square or Fisher's exact test. Significant P-values are shown in bold.
[b] measured with a numerical rating scale, where 0=no pain and 10=worst possible pain.
[c] measured with a numerical rating scale, where 0=very poor and 10=very well.
All data was non-normally distributed. For the no prophylaxis versus prophylaxis group, flares were grouped based on flare prophylaxis use at the time of the flare. For the age <65 years versus age ≥65 years, flares were grouped based on the participants age at baseline. For the no tophi versus tophi group, flares were grouped based on tophi status at the time of flare.
IQR = interquartile range.

Of the 126 gout flares there were 189 joints involved, and the site of the joint was most commonly the knee (42.9%), elbow (21.4%), foot (19.8%) and fingers (19.0%). Of note, 68.3% of all flaring joints were reported to be on the right side of the participant's body (P<0.001). A heatmap of the proportion of flaring joints between months 0-3, 4-6 and >6 months from baseline showed no discernible pattern of the flaring joints over time (**Figure 2)**. A heatmap illustrating the proportion of flaring joints by prophylaxis status (A), age category (B), tophi status (C), ULT status (D) and omega-3 index (E) are presented in **Figure 3A-E**. For flares occurring in individuals receiving prophylaxis at the time of flare, the right knee (25%) and fingers (16%) were major flaring joints. In comparison, the joints flaring in participants without prophylaxis were more evenly distributed, with the major differences being involvement of the right elbow (16%) and left knee (15%). Older participants had more flares in their right elbow (13%) and left knee (14%) compared to younger participants (3 and 5%, respectively). Participants without tophaceous gout predominantly had flares in their lower extremities (86.7%, P<0.001), most notably the right knee (28%). In contrast, those with tophaceous gout had an even distribution of flares between the upper (46.5%) and lower extremities (53.5%) but had a greater proportion of flares in their right fingers and elbow (16 and 15% versus 2 and 5%, respectively). There were no major differences in flaring joints observed when flares occurred in those initiating ULT compared to those who were escalating ULT. There was a greater involved of the left knee in participants with an omega-3 index <6% (18 vs 5%) and greater involvement of the left toes in those with an omega-3 index ≥6% (4 vs 20%).

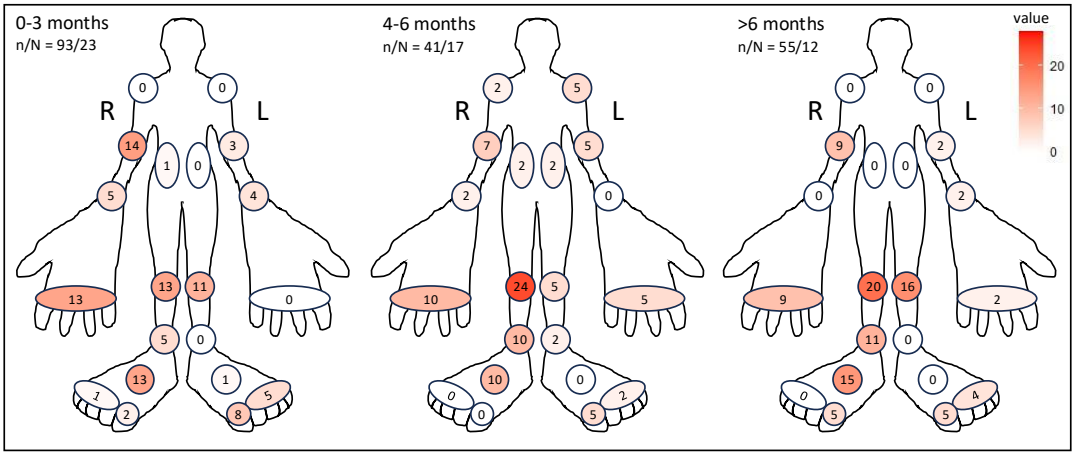


Figure 2. Heatmap of flaring joints by time period

Heatmaps illustration of the aggregate distribution of gout flares across joints during each time period, measured from the baseline assessment date. Values are expressed as percentages and represent how

frequently each joint was affected by a flare relative to all flares recorded across all joints during that period. n/N represents the number of flares observed in each period (n) relative to the number of participants who had at least one flare during that period (N).

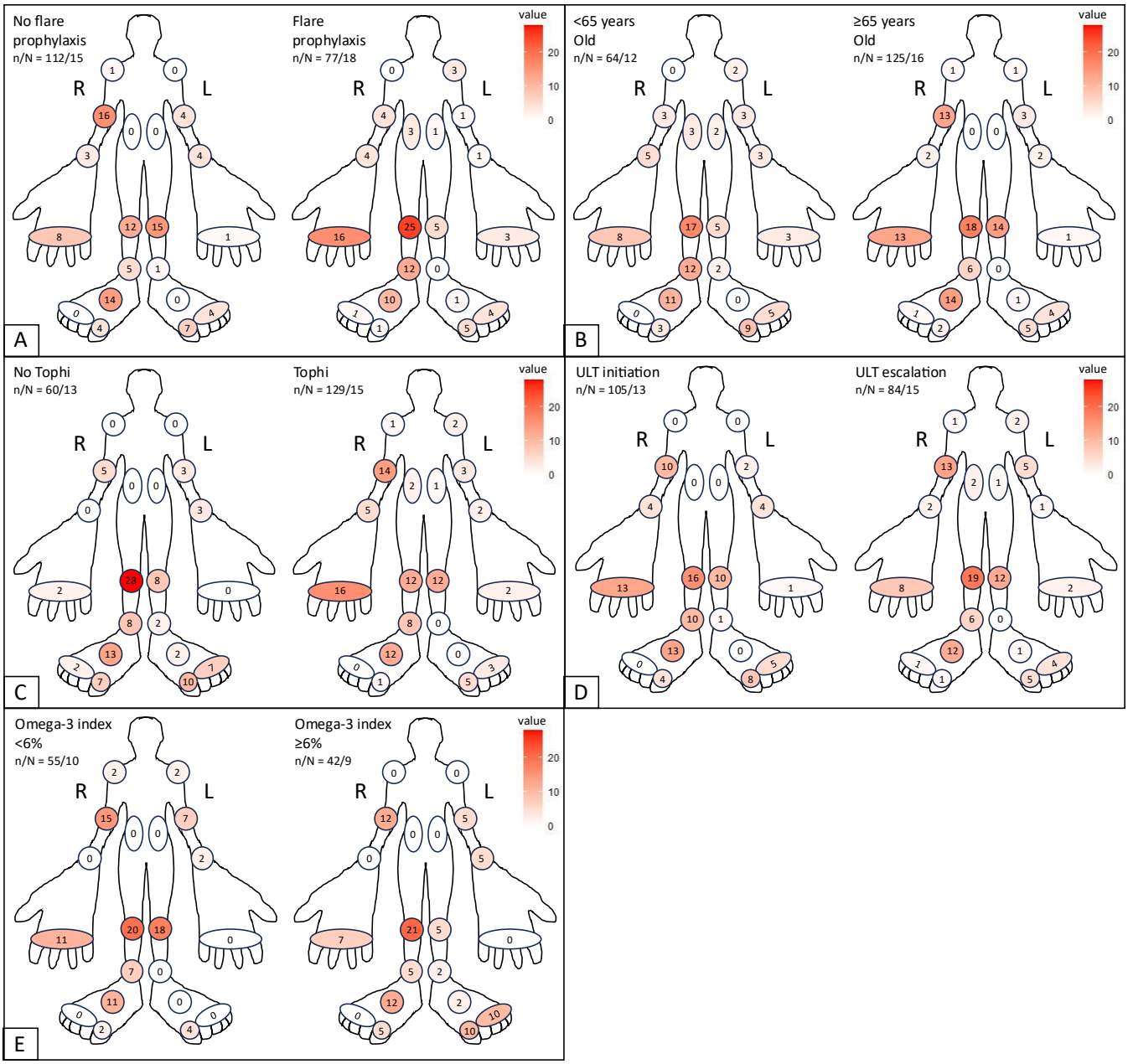


Figure 3. Heatmap of flaring joints by clinical and demographic groups

Heatmaps illustration of the aggregate distribution of gout flares across joints over the entire study period within each group. Values are expressed as percentages and represent how frequently each joint was affected by a flare relative to all flares recorded across all joints. n/N represents the number of flares observed in each period (n) relative to the number of participants who had at least one flare during that period (N). In Figure 3A, flares were grouped depending on whether the participant was on flare prophylaxis at the time of the flare. In Figure 3B, flares were grouped by the participants age at baseline. In Figure 3C, flares were grouped depending on whether the participant had tophi at the time of the flare. In Figure 3D, flares were grouped based on whether the participant initiated or escalated ULT at baseline and one participant that switched ULT at baseline was assigned to the ULT initiation group. In Figure 3E, flares were grouped based on whether the participant had an omega-3 index of <6% or ≥6% at baseline.
ULT = urate lowering therapy

Over the whole study period, the median flare rate was 0.33 (Interquartile range (IQR) 0.08-0.60) flares per month per participant. The flare rate reduced from a median rate of 0.33 (IQR 0-1.0) and 0.34 (IQR 0-0.66) flares per month in months 0-3 and 4-6 respectively, to a rate of 0.14 (IQR 0-0.53) flares per month after the first 6-months (**Figure 4A**). There was no difference when comparing flare rates per month between participants who received prophylaxis versus those who did not (P=0.67), younger participants versus older participants (P=0.42), participants initiating ULT versus those escalating ULT (P=0.96), or participants with an omega-3 index <6% versus ≥6% (P=0.84). Similarly, although there was visible variability, there was no significant difference in flare rates per month between months 0-3, 4-6, and >6 months for those same categories (**Figure 4B-C and 4E-F**). However, flare rates per month were significantly higher in participants with tophaceous gout versus those without tophaceous gout over the whole study period (median 0.47 (IQR 0.31-0.82) versus 0.18 (IQR 0-0.41), P=0.01) and during months 4-6 (median 0.45 (IQR 0.25-0.67) versus 0.38 (IQR 0-0.38), P=0.04) (**Figure 4D**). No discernible patterns were apparent between gout flares and SU concentrations or prophylaxis use as displayed within individual level data in **Figure 5**. A high rate of flares was visible in participants with tophaceous gout (**Figure 5B**). Most participants trended towards or achieved the SU target of <0.30 mmol/L during their individual observation periods of this sub-study (**Figure 5**).

The proportion of days per month from baseline that participants experienced a gout flare peaked at month three at 13.6% and then gradually declined to 3.3% by month seven (**Figure 6A**). However, the proportion of flare days per month between months eight and 14 were quite variable. The mean plasma SU concentration steadily declined over time and reached a concentration of 0.36 mmol/L within approximately four and a half months from baseline and further declined to below the SU target concentration of 0.30 mmol/L by approximately eight and half months from baseline (**Figure 6B**). For most participants with tophaceous gout, there was a decrease in the size of their tophi over time as shown by the percentage change in their total index tophi area in **Figure 6C**. The number of participants prescribed flare prophylaxis also declined steadily during the study period, with only 50% of the total population who were prescribed prophylaxis at baseline remaining on prophylaxis by month seven (**Figure 6D**).

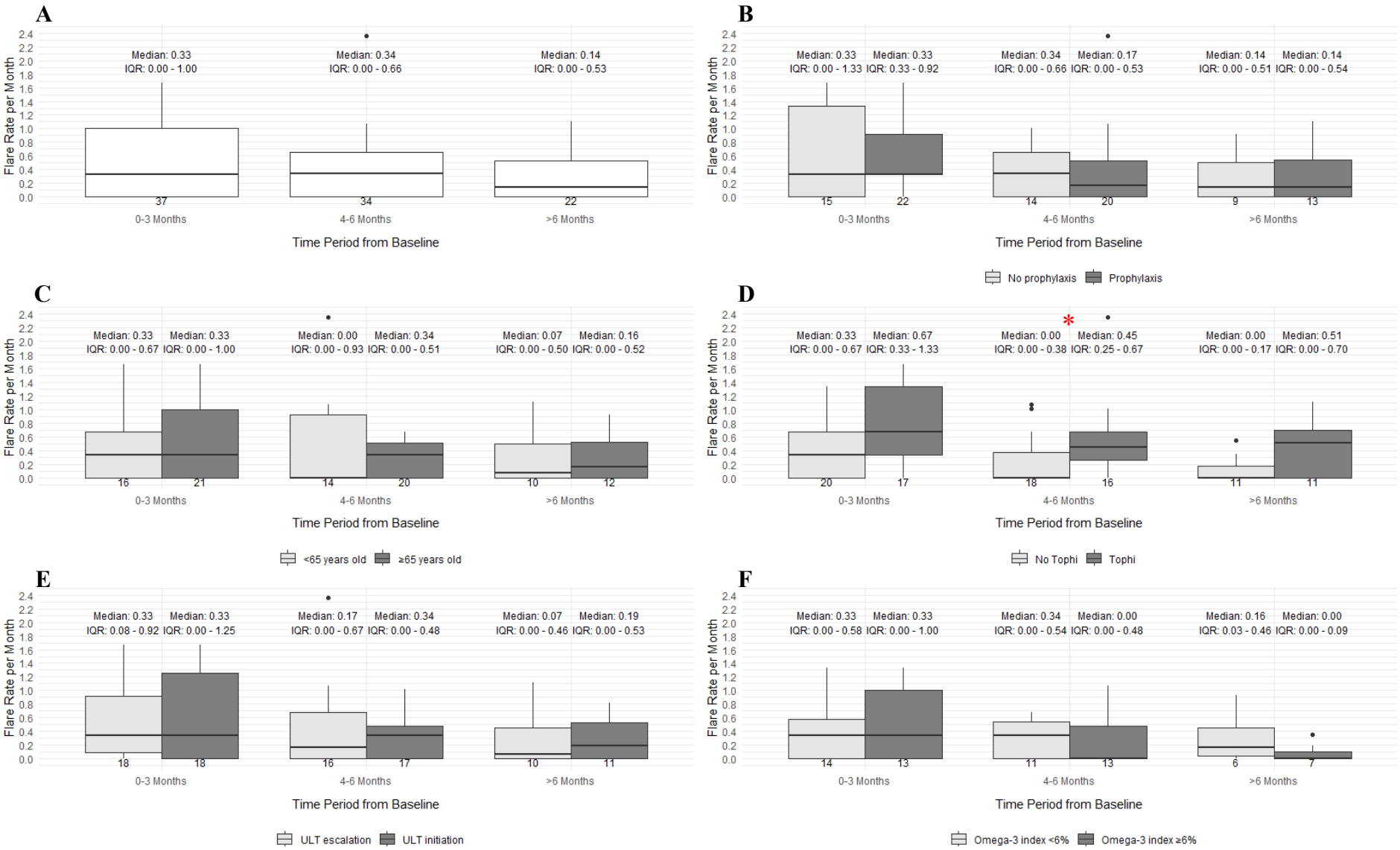


Figure 4. Flare rates per month during months 0-3, 3-6 and >6 from baseline

[a] For Figures 4B-F, P-values were calculated using an independent Wilcoxon-Mann-Whitney test and compared each of the two groups within each time period. Significant P-values are shown by a red asterisk. The number of participants included within each group is displayed below each boxplot. Figure 4A displays flare rates for all participants. In Figure 4B, participants were grouped based on prophylaxis use at baseline. In Figure 4C, participants were grouped based on their age at baseline. In Figure 4D, participants were grouped based on whether they had tophi at baseline. In Figure 3D, participants were grouped based on whether they initiated or escalated ULT at baseline. In Figure 4E, one participant that switched ULT at baseline was assigned to the ULT initiation group and one participant who was on a stable therapeutic ULT dose at baseline was excluded. In Figure 5E, participants were grouped based on their omega-3 fatty index at baseline. All data was non-normally distributed.

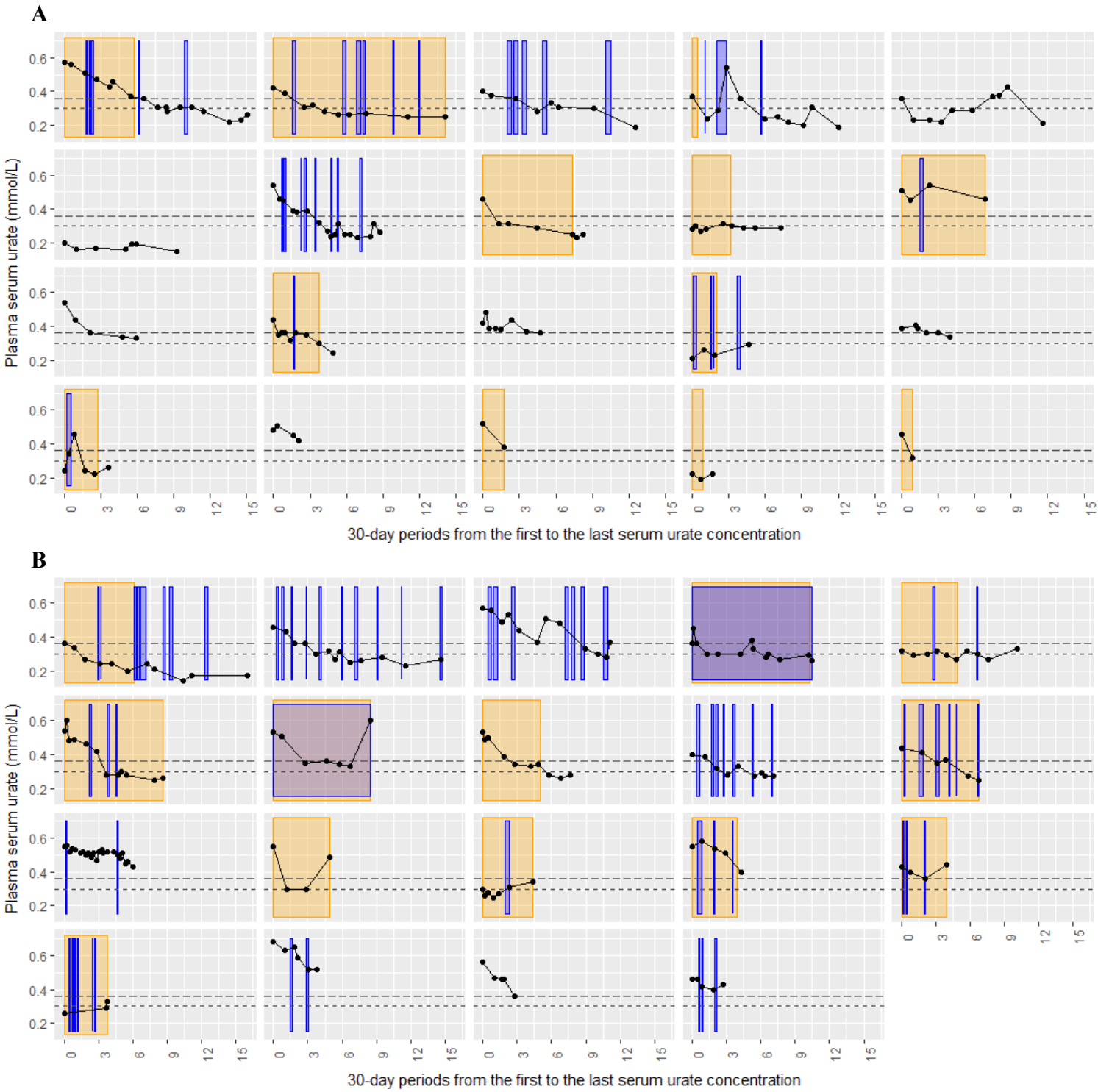


Figure 5. Individual level serum urate concentrations, prophylaxis use and flares over time grouped by tophaceous gout status

Each plot represents one study participant (N=39). Figure 5A displays participants without tophaceous gout. Figure 5B displays participants with tophaceous gout. The data displayed is from the participants first serum urate concentration post baseline to their last serum urate concentration before their censor date. Participants have been ordered from longest to shortest follow up.
SU concentrations are displayed as dots and connected by solid black lines. A SU concentration of 0.36 is shown by the long dashed line and a SU concentration of 0.30 is shown by the short, dashed line. The duration of prophylaxis is shown as yellow rectangles. Each individual gout flare is shown as a blue rectangle with the flare duration spanning the width of the rectangle. Two participants with chronic gouty arthritis who were unable to differentiate episodes of flare are displayed with a continuous gout flare over the study period.
SU = serum urate

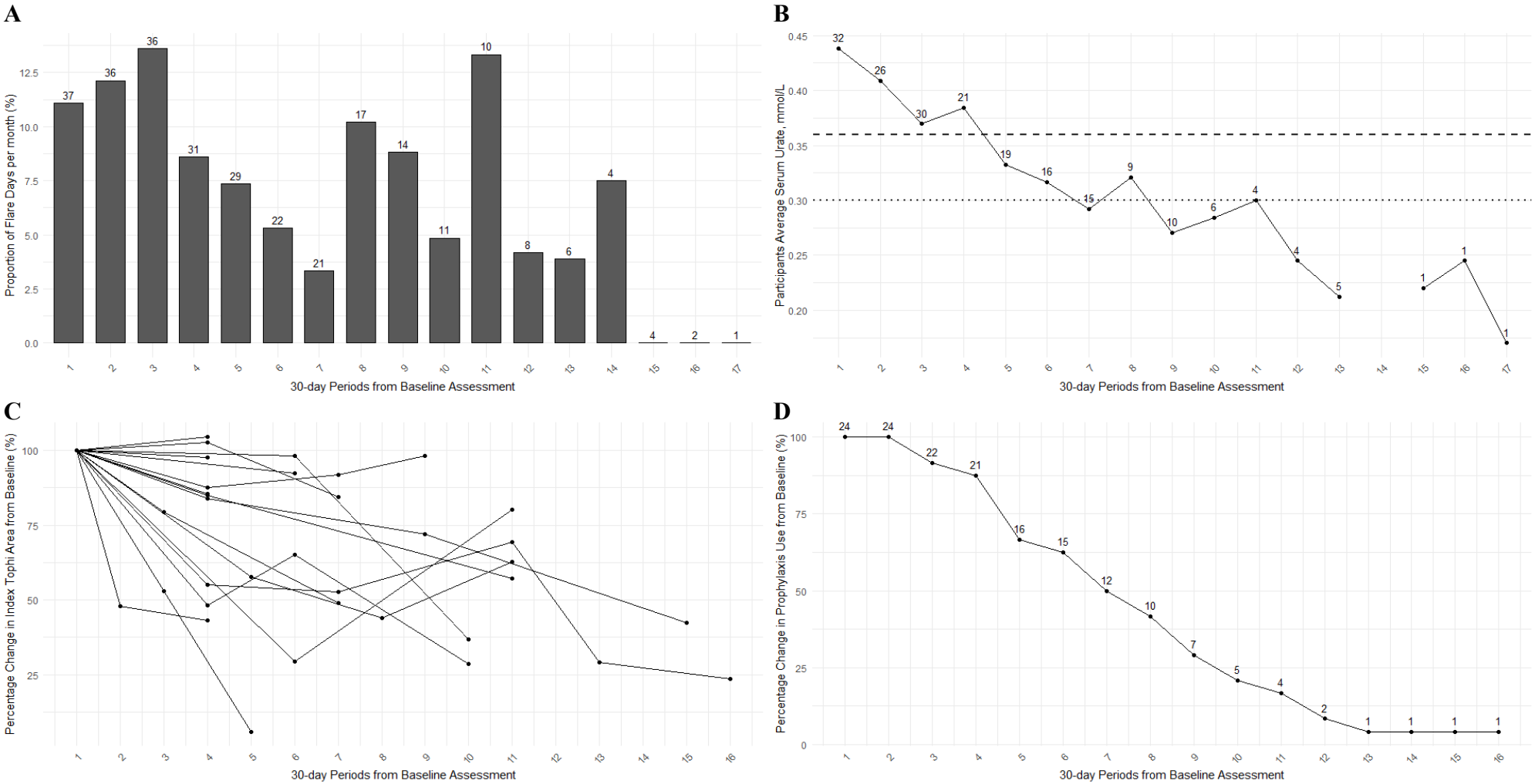


Figure 6. Changes in flares, serum urate, tophi diameter and prophylaxis use from baseline

Figure 6A shows the proportion of days per month that participants were experiencing a gout flare, taking into consideration the number of participants in the study per month. Figure 6B shows the mean serum urate concentration per month, which was averaged per participant per month. Figure 6C shows the percentage change in the index tophi area from baseline for each individual participant. Figure 6D shows the percentage change in prophylaxis use per month from baseline for the proportion of the total population who were prescribed prophylaxis at baseline. For Figure 6A, B and D the number of participants included within each period are displayed on each plot. The number of participants in Figure 6C was 19.

Discussion

This study provides valuable insights into the social, clinical, and patient-related characteristics of individuals with complicated or difficult to manage gout and explores their flare patterns. Key differences between younger (<65 years) and older (≥65 years) participants were observed. Younger participants had higher rates of smoking, alcohol consumption per week, and body mass index, while older participants had worse renal function, more co-morbidities including hypertension, cardiovascular disease and chronic kidney disease, and were taking a greater number of regular medications including statins, diuretics, and low-dose aspirin. Older adults also had more joint erosions and lower physical functioning scores compared to younger participants. Gout flares were common in the whole cohort, particularly within the first six months, with variations in flare patterns. Flare prophylaxis was associated with fewer affected joints and lower pain scores during a flare, and younger participants experienced shorter flare durations. Participants with tophaceous gout had a notably higher flare rate, which remained elevated throughout the study, and various joints were affected.

The baseline demographics such as age, gender, duration of gout and co-morbidities were similar to those observed in other outpatient-based cohort studies (43, 229, 230) and primary care-based studies (231-233) conducted internationally. However, compared to the primary care-based studies (231-233), our cohort exhibited very high rates of flares and tophi at baseline, suggesting a more substantial disease burden. There were also distinct differences between our younger and older participants. Notably the younger cohort had more modifiable risk factors such as obesity and alcohol intake (234), while the older cohort exhibited more age-related decline in organ function, including renal impairment and cardiovascular diseases. The older cohort also had a greater number of medications, resulting in a higher rate of polypharmacy to manage their conditions (149, 217). Not only are these factors less amenable to lifestyle modifications (234), they also complicate the management of gout due to the increased risk of drug-disease and drug-drug interactions. These interactions are particularly relevant when considering the use of gout flare prophylaxis with colchicine, NSAIDs or corticosteroids (213), potentially explaining why only half of our older cohort received flare prophylaxis. Given these challenges, gout management strategies could be tailored to better account for the differences between younger and older adults. However, current guidelines provide limited or no specific recommendations for older adults

(235), highlighting a significant gap in addressing the unique needs of this growing and increasingly complex patient population.

Older participants in our cohort were, on average, twice as likely to have tophi and had lived with gout for approximately 2.5 times longer (16 vs 6 years) than younger participants. These factors likely contributed to over two thirds of older participants displaying evidence of joint erosions on x-ray (17, 236), whereas erosions were only present in one third of the younger participants. This high level of joint erosions is not entirely surprising, given that almost half of the participants were not prescribed ULT at the time of their first appointment at the clinic, and the remainder were on sub-therapeutic doses. Studies have shown that persistence with ULT is challenging, with approximately 63% of individuals discontinuing allopurinol within 12 months (237). This reiterates the need for early and sustained gout management to reduce the MSU burden, prevent tophi development, and minimise the risk of irreversible joint damage. What was unexpected, however, were the high rates of self-reported adherence and the strong beliefs amongst participants regarding the necessity of their medications, particularly when compared to other studies in individuals with gout (238). Additionally, four out of five participants had actively made lifestyle changes in an effort to manage their gout prior to attending the clinic, inferring a highly motivated cohort. This could reflect selection bias, as participants who are less motivated may have cancelled or not attended their baseline appointments. Despite these positive indicators of patient engagement, the progression to complex gout requiring specialist care highlights a gap in early and effective management. This suggests a need for improved gout education and management strategies at the primary care level (239), as well as potentially earlier access to specialised gout clinics to prevent irreversible complications of gout.

Gout flares impose a significant disease burden with impact on various aspects of an individual's life (11, 14). Approximately two thirds of our participants reported at least one gout flare during the study period, with considerable variation in flare frequency between individuals, consistent with findings by Teoh and colleagues (240) in a population experiencing frequent flares (241). A key challenge in assessing gout flares is ensuring accurate and complete flare documentation (240, 242). While the gout diary developed for this study was useful, anecdotally, entries were sometimes incomplete, or the diary was not brought to clinic appointments. As a result, approximately 30% of

flares could not be validated against the current valid definition of a flare (227). However, there were no major differences in the symptoms associated with flares that met the criteria and those that did not or had insufficient data, except for a greater proportion of flares with at least one swollen or warm joint. Previous literature has highlighted that discordance between patient and physician reported flares often arise from flares that are not associated with swollen or warm joints and have lower pain scores, which may reflect milder flare episodes but are still considered to be clinically relevant by patients (243). Interestingly, we found that flares in individuals without tophi and those initiating rather than escalating ULT were significantly less likely to have swollen or warm joints but similar pain levels and quality of life scores. Given that the presence of swollen or warm joints is a key criterion in the currently accepted valid definition of a gout flare (227), our findings suggest that further research is needed to explore the relationship between observable joint symptoms and patient-reported impacts. Such investigations may potentially help identify diverse presentations of flares and inform future refinements in flare assessment and management strategies.

Swollen joints were also less likely to be observed in participants with a lower omega-3 index, which is inconsistent with the anti-inflammatory properties of omega-3s. Pilot studies have suggested that omega-3 fatty acid supplementation may be a promising alternative for gout flare prophylaxis (220, 244), particularly for individuals at high risk of adverse events. However, we were unable to determine whether any participants were actively taking omega-3 supplements. Our findings may reflect a small sample size and low baseline omega-3 levels, with the average omega-3 index being only 6%, which is slightly higher than the average 5.44% reported in the Australian population (245). Although we found no strong association between omega-3 fatty acid index and the frequency or severity of gout flares, improving the omega-3 index to ≥8% (226) could still provide cardiovascular benefits (246), which may be important for overall health in the gout population. Other unexpected findings were that younger participants had shorter flare durations, duration of acute gout flare treatment and lower pain scores during a flare. While the reasons for these age-related differences are unclear, they could potentially reflect younger individuals' ability to recognise and treat flares sooner, leading to reduced severity and shorter symptom duration. In contrast, older adults often face challenges such as multi-morbidity and the physiological complexities of ageing, including altered immune responses and delayed return to homeostasis, which may

result in longer flare duration and greater symptom severity (149, 247). Differences were also observed in the location of flaring joints, which can significantly contribute to the burden of a flare (12). Flares in larger joints, such as the knees, or those required for mobility, like the feet and ankles, have been associated with a greater impact on functional activities (13). This emphasises the potential benefit observed in our study of prophylaxis in reducing the number of affected joints during a flare and lowering pain intensity. While not statistically significant, there was also a trend of fewer joints being affected in younger participants and those without tophi. Further validation of these trends could help explain variations in flare patterns between individuals and help to tailor flare prophylaxis for those most in need.

Overall, the rate of flares decreased in the 6-months following baseline, however an increase in flare days per month was observed around months 7-9 and month 11. This may have been influenced by a 50% reduction in the use of flare prophylaxis by month 7. Additionally, this increase in flares coincided with slight elevations in SU concentrations and index tophi area in some participants. However, this observation may be due to chance and the small number of participants who had a follow up of greater than 6-months. It is also possible that the observed increase in tophus diameter was due to larger tophi breaking down into smaller, more diffused components during the dissolution process. Improvements in quality of life scores (SF-36 and GIS) were also observed throughout the study period, potentially associated with a reduction in gout flares. Notably, participants with tophaceous gout experienced significantly higher flare rates throughout the study, while those without tophi were typically flare free by months 4-6. Prior studies also report an association between tophi and increased flare risk (44, 248, 249), with Ebstein and colleagues (250) showing higher relapse rates when flare prophylaxis ceased in patients with less than a 50% reduction in tophi size. Recognising the association between tophi and flare risk, many guidelines now recommend an initial lower SU target of <0.30 mmol/L in individuals with tophaceous or otherwise severe gout (i.e., frequent flares, chronic gouty arthritis) (35, 92), to facilitate faster crystal dissolution (251, 252). This lower SU target was part of the protocol used for this cohort.

Participants with tophaceous gout tended to experience flares in more atypical joints such as those in the upper extremities including the shoulder, back, and fingers, which is likely due to a higher crystal burden, while participants without tophi showed more

typical lower extremity involvement. Although subcutaneous tophi are a good indicator for very high crystal burden, and rates were elevated in our study, in the broader literature approximately 70-85% of individuals lack visible tophi (61, 62, 253) but crystal deposits can still be present (254). Dual-energy CT can detect MSU crystals and provide an accurate measure of the crystal burden (255), with studies identifying that a higher urate load is associated with flares (43, 254). This likely contributes to the variability and difficulty in showing an association between achieving the SU target and observing a reduction in gout flares whilst a crystal load is still present (256). However, long term data has demonstrated that a treat-to-target SU approach can successfully reduce flares (90, 257). These findings suggest that flare prophylaxis may be particularly beneficial for individuals with tophi, given the elevated flare rates associated with higher crystal burden. Additionally, our results indicate that a longer duration of prophylaxis may be advantageous in this population, although the optimal treatment duration remains to be determined. However, given that tophaceous gout has been associated with an increased risk of cardiovascular disease and associated mortality (33, 61), selection and duration of prophylaxis requires careful clinical consideration and patient involvement.

Strengths and limitations

Our study had several strengths, including a prospective study design and the use of a gout diary, which enabled real-time measurement of flares and minimised recall bias. Data collection was comprehensive, covering social, economic, clinical, and other relevant participant related factors. However, the study also had some limitations. COVID-19 impacted new participant recruitment, leading to some individuals who previously attended the clinic prior to the study commencement date being enrolled to the study during follow up appointments. These participants had a different baseline assessment form, resulting in some missing data, although most of it was retrospectively retrieved from electronic medical records. Other limitations included small participant numbers and varying following up periods, which may have affected result significance. Given the relatively small sample size, the large number of statistical comparisons increases the risk of type 1 error (false positives), thus the findings should be interpreted with caution. The study was conducted in a single rheumatology clinic, potentially limiting generalisability. Questionnaires specific to the sub-study (BMQ, SIMS and MARS at baseline) were completed after the individuals consult with the

rheumatologist, which may have introduced some bias. Due to the limited sample size, we did not perform multivariate analysis, and therefore covariates in the data cannot be ruled out. Additionally, as individual flares were analysed as separate observations, the assumption of independence required for the statistical tests used (t-tests and chi-squared tests) may have been violated for participants with multiple flares. This introduces the possibility of intra-individual correlation, whereby flares from the same participant may be more similar to each other than flares from different participants. More complex approaches, such as generalised linear models, were not applied due to concerns about model instability, sparce data, and overfitting. Therefore, these analyses should be considered as hypothesis generating, illustrating potential differences or associations between groups that warrant future exploration in larger datasets. Finally, analyses of the quality of life measures collected in this study were limited. Future research could explore these outcomes in greater depth, ideally by combining quantitative scores with qualitative approaches to better understand the quality of life in individuals with more complex or difficult to manage gout.

Future research/unanswered questions

Our findings highlight several areas for future investigation. Given the differences between younger and older individuals, future research should focus on tailoring gout management strategies to address age-related variations in disease presentation and progression. The persistently high flare rates in individuals with tophi, particularly in atypical locations such as the upper extremities, highlights the need to investigate the optimal duration and effectiveness of prophylaxis in this population. The variability in flare frequency and the discordance between physician-assessed and patient-reported flares further emphasises the importance of understanding diverse flare presentations. Investigating the relationship between observable joint symptoms, such as swollen and warm joints, and patient-reported impacts, such as pain and quality of life scores, may help refine flare assessment tools and management strategies, especially for milder or atypical flare episodes. Additionally, our study suggests a need for continued exploration of early gout management, particularly in those with advanced disease, to better understand how to intervene before progression to complex gout occurs.

Conclusion

In this complex cohort with high rates of tophi and comorbidities, a treat-to-target SU approach was able to successfully lower SU concentrations, reduce tophi size, and improve clinical outcomes. Age-related differences in gout presentation were evident. Flare patterns varied between participants, with tophaceous gout associated with a higher flare burden. These findings provide insights into key factors that may influence gout flares, particularly in refractory or more difficult to manage gout, and may help to guide the development of future flare assessment tools and disease management strategies.

6 Thesis Discussion

This thesis explored the challenges of gout management, focusing on patient complexity, flare risk during treatment initiation and escalation, the role of prophylaxis in preventing flares, and adherence to urate-lowering therapy (ULT). Using a combination of literature reviews, cross-sectional and cohort studies, and a systematic review with network meta-analysis, this research provides new insights into how gout affects different patient populations, particularly older adults, and highlights key areas for improving clinical care.

Summary of research findings

Complexity and the impact of ageing

The real-world cohort study described in this thesis (**Chapter 5**) highlighted the significant burden that gout can place on individuals, including recurrent flares, chronic gouty arthritis, tophaceous gout, irreversible joint damage and work disability due to illness-related absences. Many individuals with gout presented as clinically complex, with multiple comorbidities and polypharmacy that would need to be taken into account for treatment decisions. Similarly, participants in **Chapter 3** also had high rates of polypharmacy and metabolic comorbidities. Despite these challenges, findings from **Chapter 5** demonstrate that optimal treatment outcomes can still be achieved using a treat-to-target serum urate (SU) approach. However, this still requires careful consideration of individual patient factors, particularly in older adults and those with multimorbidity.

One of the key findings from **Chapter 5** was the distinct differences in gout presentation between younger (<65 years) and older (≥65 years) individuals. Younger individuals tended to have more modifiable risk factors, such as obesity and alcohol use. This highlights the importance of lifestyle modifications in younger individuals with gout, as addressing these risk factors could improve disease control and reduce long-term medication burden. In contrast, older individuals had more chronic kidney disease, multiple comorbidities, and polypharmacy, all of which can complicate gout management and are mostly irreversible. This paired with the knowledge discussed in **Chapter 2** regarding the physiological changes associated with ageing and the impact on drug metabolism and clearance, shows the complexity in caring for older adults with gout.

Chapters 2 and 5 collectively emphasised the complex interplay between gout, its treatment, and coexisting medical conditions, particularly in older adults. For example, comorbidities and concurrent medications not only influence the choice of gout treatment, such as avoiding NSAIDs in individuals with cardiovascular disease, but they can also impact gout itself, with conditions such as chronic kidney disease and medications like thiazide diuretics raising SU concentrations. Furthermore, **Chapter 2** highlighted the increasing prevalence of geriatric syndromes, including frailty, sarcopenia, polypharmacy and dementia, which further complicate gout management in this population. Despite these challenges, recent reviews of gout guidelines indicate a lack of specific recommendations for managing gout in older adults (88, 258). Additionally, as demonstrated in **Chapter 2**, older adults and those with significant renal impairment are frequently excluded or underrepresented in clinical trials, limiting the available evidence to guide treatment decisions in these populations.

Given the ageing population and the rising prevalence of complex multimorbidity, it is essential to develop more tailored approaches to gout management that address the unique challenges faced by older adults, as also highlighted in recent literature (4). Equipping primary care providers with a strong understanding of these complexities will be important in facilitating early and effective treatment for this growing patient population (259). This need was highlighted in **Chapter 5**, where most individuals had lived with gout for an average of nine years before being seen in a rheumatology clinic, suggesting potential gaps in current primary care management.

Gout flares and ULT-induced flares

The systematic review with network meta-analysis conducted in **Chapter 4** provided new insights into the rise in gout flares that may occur shortly after starting ULT or escalating sub-therapeutic ULT. While the exact mechanism remains unclear, we identified that historical higher-dose ULT regimens used predominately in trial settings, such as fixed high-dose febuxostat (i.e. 80-240mg) or febuxostat combined with lesinurad, were more likely to trigger flares compared to more gradual dosing strategies. However, these regimens have largely been replaced by gradual up-titration strategies, such as initiating febuxostat at 40mg daily and increasing to a maximum of 120mg over weeks to months (146). Additionally, lesinurad has been discontinued for manufacturer-related reasons (260). As a result, ULT-induced flares may now be less frequent than

previously reported, though they remain a significant clinical concern. Our findings support that a slower up-titration of ULT may help reduce the risk of ULT-induced flares, which is particularly relevant for older adults, where prophylactic options are limited and carry a higher risk of harm. However, despite a start-low, go-slow approach, some individuals may still benefit from flare prophylaxis, with research in this area expanding since our review (261).

A key finding of the systematic review with network meta-analysis (**Chapter 4**) was the substantial variability in how flares were reported across trials. Flare definitions were highly inconsistent and often inadequately described, and only trials that randomised flare prophylaxis reported on the severity and duration of gout flares. Additionally, no study provided flare rates per study arm for participants who did or did not achieve the SU target or for those with and without tophaceous gout. This inconsistency made it difficult to draw definitive conclusions on the influence of these and other factors, such as health-related quality of life, on flare incidence and characteristics. The lack of standardised flare reporting in clinical trials has also been identified in previous systematic reviews (262), and remains a critical area for improvement.

Building upon these findings, **Chapter 5** provided real-world insights that helped address some of the gaps in trial data. This cohort study revealed that gout flare patterns in clinical practice are highly variable, with individuals experiencing an average of 0.33 flares per month over the study period. Flare rates fluctuated month per month, a pattern often not detailed in clinical trial reporting. Individuals with tophaceous gout experienced more frequent and persistent flares, with greater involvement of the upper extremities and a higher likelihood of swollen and warm joints compared to those without tophi. Younger individuals (<65 years) experienced shorter flares and flare treatment durations and reported lower pain scores compared to older individuals (≥65 years). While no significant differences in flare rates were observed between those who did or did not receive flare prophylaxis, new insights emerged, such as greater involvement of the right knee and fingers in those who continued to flare despite prophylaxis, whereas flares in individuals without prophylaxis were more evenly distributed across joints. Flare prophylaxis was also associated with fewer affected joints per flare and lower pain scores, an outcome that is rarely reported in ULT clinical trials.

Another important finding from **Chapter 5** was that the currently accepted valid definition of a gout flare (227), which has been utilised in recent clinical trials (263), may not capture flares in all individuals, particularly those without tophi and those initiating rather than escalating ULT. Since this criteria relies on the presence of swollen or warm joints, which was less prominent in this subgroup, this different flare presentation suggests that the current definition may need to be expanded to include other symptoms or measures of flare severity. While this finding requires further validation, it contributes to the growing body of research on understanding the patient experience of gout flares and identifying clinically meaningful outcomes (13, 14, 263). This may have implications for future flare assessment methods and clinical trial reporting outcomes.

Preventing gout flares

As highlighted in **Chapter 5**, some individuals with gout, such as those with tophaceous gout and high urate crystal loads, are more prone to frequent flares. For these individuals, flare prophylaxis may be beneficial. However, as discussed in **Chapter 1** and further confirmed in **Chapter 4**, evidence on the efficacy, safety and optimal duration of prophylactic treatments remains limited. **Chapter 4** demonstrated that colchicine and rilonacept effectively reduced flare risk during ULT initiation or escalation, although rilonacept was associated with a higher risk of treatment-related adverse events. However, commonly used treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids had insufficient or very limited data within the analyses. Additionally, newer agents like rilonacept and other interleukin-1 inhibitors (e.g., canakinumab) remain unavailable in many regions or lack sufficient evidence or safety for routine prophylactic use (**Chapter 4**).

In the absence of newer available prophylactic therapies, ensuring the safe and appropriate use of currently approved options is paramount. Given the lack of comprehensive safety data on gout flare prophylaxis, **Chapter 2** provided important insights into key prescribing and monitoring considerations for colchicine, NSAIDs, and corticosteroids, particularly in older and more complex patients. Factors such as altered drug clearance and increased susceptibility to adverse effects in these populations may shift the benefit-to-harm ratio unfavourably, highlighting the need for careful, individualised decision making when prescribing flare prophylaxis.

Adherence to urate-lowering therapy

Despite the availability of effective treatments, **Chapter 5** revealed that nearly half of patients entering a gout clinic were not on ULT, and many had already developed long-term, irreversible complications of gout. This highlights the importance of maintaining adherence to therapy to prevent disease progression. However, **Chapter 3** identified significant challenges in detecting non-adherence, partly due to the variability in adherence rates depending on the assessment tool used and the inconsistent correlation between different tools. This highlights the benefit of having multiple, complementary measures to assess both intentional and unintentional non-adherence behaviours.

One potential quick measure of adherence identified in our study was the simplified 3-item version of the Compliance Questionnaire Rheumatology (CQR). While this tool may be useful in routine clinical practice, further validation is required to determine its accuracy and clinical utility. Similar strategies have been applied in rheumatoid arthritis, where a 5-item version of the CQR has been validated for monitoring adherence to disease-modifying antirheumatic drugs (193).

While various clinical interventions to improve adherence to ULT have been explored and continue to expand (117, 119), **Chapter 3** adds to this complex issue by providing further insights into factors that may influence adherence to allopurinol. Many of the factors identified in our study, such as the number of concomitant medications, flare frequency, comorbidities and treatment duration, may be particularly relevant in older or more complex individuals with gout.

A particularly notable finding was that individuals often prioritised medications for other conditions, such as cardiovascular disease, over their gout medication. This suggests that gout may not carry the same level of concern or urgency as other chronic conditions. Similarly, a recent qualitative study in Australia found that due the episodic nature of gout, general practitioners often deprioritised its management when patients were not experiencing an active flare (259). However, growing evidence highlights the significant impact of gout on cardiovascular health and mortality (34, 264). In particular, gout flares have been associated with a transient increase in subsequent cardiovascular events (265), reinforcing the importance of long-term ULT to lower the monosodium urate-crystal burden and prevent flare activation. Given the strong relationship between gout and metabolic comorbidities (26), improving adherence to

ULT will not only prevent the chronic complications of gout but also reduce broader health risks.

Future directions

Building on the findings of this thesis, several important areas for future research have been identified. As the complexity of the gout population increases, particularly in older adults and those with comorbidities, innovative approaches are required to better predict, prevent, and manage gout flares. Moving forward, integrating new technologies, improving clinical trial reporting, and exploring alternative strategies for flare prophylaxis may help to enable more personalised treatment approaches. The following sections highlight these key areas and suggest potential directions for further investigation.

Artificial intelligence tools and machine learning algorithms

Building on the insights gained from the cohort study (**Chapter 5**), we envision that the knowledge generated from this research will provide a strong foundation for developing a time-to-repeated-event model to predict gout flares and enable personalised use of gout flare prophylaxis. With advances in artificial intelligence (AI) tools and machine learning (ML) algorithms in healthcare, exciting new opportunities now exist to achieve this and more (266).

Real-world, complex, comprehensive datasets, such as the one developed within this PhD (**Chapter 5**), offer a valuable foundation for AI and ML analysis. These methodologies can analyse large volumes of complex data, leveraging advanced algorithms to uncover non-linear relationships, interactions, and subtle patterns that traditional statistical methods, which often depend on pre-defined assumptions and linear models, may miss (266). This capability enables more accurate and nuanced predictions, offering novel insights into treatment responses and flare patterns. Additionally, Natural Language Processing (NLP) techniques could further augment this data by extracting valuable insights from unstructured data sources, such as electronic health records, clinic notes, and patient-reported outcomes (267). These insights could provide a deeper understanding of patient behaviours, barriers to treatment adherence, and other factors that might influence both flare development and treatment response.

However, developing such models is inherently complex and requires accurate, high-quality data, rigorous coding and testing, and thorough validation across diverse populations (268). Despite these challenges, progress in this field is underway. For example, ML-based prediction models have been developed to identify individuals with hyperuricemia who are at risk of developing gout (269) and AI-driven gout management systems have shown promise in reducing the incidence of chronic kidney disease and improving SU target achievement (270). Additionally, NLP and ML techniques have been used to retrospectively identify gout flares from clinical notes (271). The GOUT-36 prediction rule for inpatient gout flares, while not a full ML-based model, also shows promise in this area (272).

By integrating clinical data, SU concentrations, adherence metrics, comorbidities, and other relevant factors, ML algorithms have the potential to predict the timing and/or severity of gout flares. Such models could also assess an individual's position within a risk matrix that evaluates the risk-benefit ratio for flare prophylaxis (**Figure 1**). This would enable more tailored flare prevention strategies, reducing unnecessary prophylaxis use in low flare risk patients and mitigating potential harms such as medication-related adverse events, increased healthcare associated costs, and pill burden for these individuals.

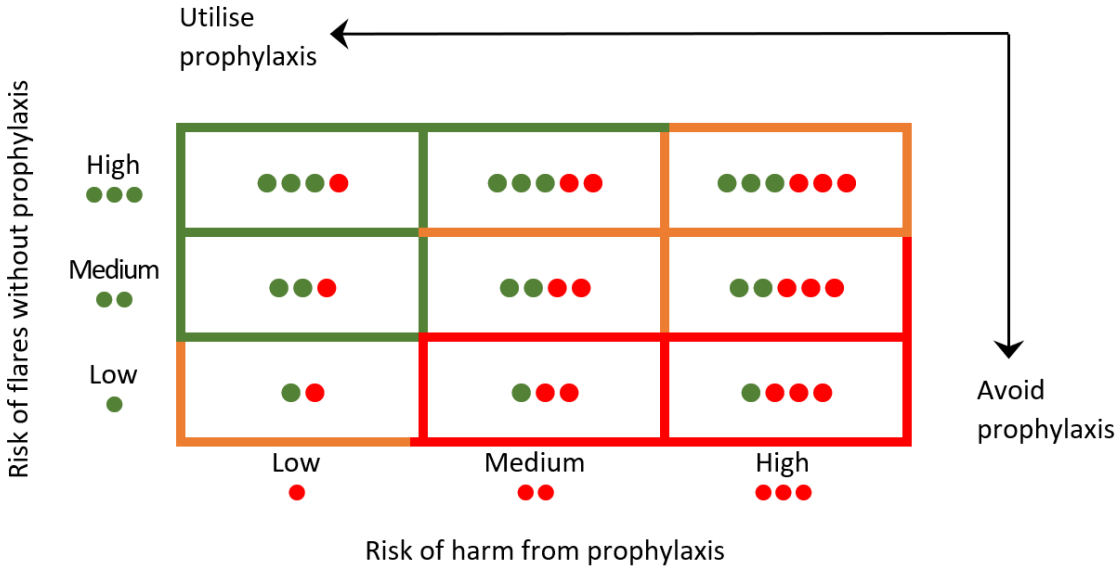


Figure 1. A risk matrix evaluating the potential risk of flare occurrence after initiating or escalating urate-lowering therapy without flare prophylaxis against the potential risk of using prophylaxis. An individual's position within the matrix will vary based on their

specific risk factors, urate-lowering therapy dosing schedule, and the prophylactic drug used.

As AI and ML innovations continue to rapidly evolve, it will be important to integrate these advancements with insights gained from more traditional research methods. Specifically, real-world evidence studies and implementation research will be required to understand how these models can be effectively applied in clinical practice. Several other important research gaps are also discussed below.

Improved clinical trial reporting

One of the key findings from the systematic review (SR) with network meta-analysis (NMA) (**Chapter 4**) conducted in this thesis was the significant variability and limitations in the reporting of gout flares and flare prophylaxis in clinical trials. Previous literature has emphasised the need for standardised reporting methods, particularly when flare prevention is the primary outcome (262, 273). From **Chapter 5** and the existing literature (12-14, 242), it is evident that the number of flares alone may not fully capture the burden of flares and additional factors, such as flare duration, severity, and affected joints are also important. This suggests that a more comprehensive reporting framework is necessary for clinical trials to ensure meaningful patient outcomes are also considered. Improving these reporting standards would enhance the quality and comparability of future research and clinical recommendations.

The availability of global clinical research data-sharing platforms, such as Vivli (274), has opened up new opportunities to re-analyse clinical trial data at the individual participant level. These platforms now make it possible to investigate the benefits and harms of NSAIDs and corticosteroids as flare prophylaxis, which was not possible in our SR with NMA (**Chapter 4**), as flare and adverse event data were rarely reported at the individual flare prophylactic drug level within the included trials. Such re-analysis would allow for a direct comparison of these commonly used prophylactic drugs against alternative therapies, such as colchicine and emerging interleukin-1 inhibitors, and may reduce the need for new trials to investigate these outcomes. Re-analysis of clinical trial data might also help to better understand the optimal duration of prophylaxis for different patient groups and strengthen guideline recommendations, given the limited number of trials specifically investigating this outcome identified in **Chapter 4**. However, additional trials may still be necessary to address specific gaps.

These data-sharing platforms could also help explore and confirm the effects of factors identified in this thesis using large clinical trial datasets such as the association between certain co-morbidities and adherence patterns observed in **Chapter 3** or the influence of age and tophi burden on gout flare patterns in **Chapter 5**. Furthermore, individual patient-level meta-analyses can address research gaps involving complex patient groups, such as those aged over 80 years or those with significant comorbidities, who are often underrepresented in clinical trials (as discussed in **Chapter 2).** While clinical trial data may not fully reflect real-world settings, combining data from multiple trials can provide a larger sample size, enhancing the power to determine the benefits and harms for medications in this population, including those seen in more complex, real-world clinical settings. This information could inform specific recommendations for certain patient populations such as those with geriatric syndromes such as frailty or sarcopenia, where current clinical guidelines for gout lack tailored guidance (235, 258).

Alternative approaches to gout flare prophylaxis

Rheumatic diseases like rheumatoid arthritis require rapid disease control to prevent permanent joint damage and to manage daily, continuous pain (275). While early intervention remains important in gout, treatment is generally more gradual, with dose adjustments occurring over several weeks to months. A single study included in our SR with NMA (**Chapter 4**) explored an even slower, stepwise dose increase in ULT, specifically febuxostat, compared to standard initiation dosing (137). This stepwise approach showed promise in reducing the need for flare prophylaxis, however, the randomised-controlled evidence is currently limited to this single study. Additionally, the limited tablet strengths available for ULT in Australia (e.g. only 80 mg febuxostat tablets) makes this strategy less practical in clinical settings.

A very gradual stepwise dose increase approach to initiation might only be suitable for certain patient subgroups. For example, **Chapter 5** highlighted that individuals with tophaceous gout experience persistently higher flare rates, suggesting that a slower up-titration strategy may not sufficiently reduce flare burden in this group and that prophylaxis may still be necessary. Furthermore, in those with a high monosodium urate crystal load, faster crystal dissolution may be preferable to prevent long-term joint damage (251, 252). Thus, the role of stepwise, very gradual ULT up-titration approaches requires further investigation not just regarding its effectiveness in

preventing ULT induced flares, but also in identifying who is suitable and how to implement this in practice. Future research could explore individualised ULT up-titration strategies tailored to patient characteristics, such as tophaceous versus non-tophaceous gout, with the goal of integrating these approaches into clinical practice guidelines to optimise treatment strategies.

Beyond ULT dosing strategies, alternative prophylaxis methods also warrant further investigation. In **Chapter 5**, we examined omega-3 fatty acids as a potential modifier of gout flares but found no significant reduction in flare rates. Similarly, a pilot randomised trial of omega-3 supplementation versus no supplementation found no statistically significant difference, likely due to being underpowered (220). Despite these findings, identifying safe and well-tolerated strategies to reduce gout flares remains a significant area for future research. This is particularly important as the gout population becomes increasingly complex, with a growing risk of adverse effects and contraindications associated with existing prophylactic therapies.

Implementation into clinical practice

To ensure future research meaningfully improves patient care, it is essential to focus on how these findings can be translated into real-world practice. One example is to increase education for clinicians and patients, particularly around flare expectations when commencing or up-titrating ULT. This may be especially important for patients with tophaceous gout and/or higher disease burden, who may experience more frequent flares and a longer overall period of flares after starting ULT. Providing more realistic expectations may also help support improved medication adherence. Other examples include exploring how very gradual ULT initiation without prophylaxis could be integrated into routine care without adding unnecessary treatment complexity. Likewise, AI and ML tools designed to support decisions around flare risk and ULT dosing must be tested not only for accuracy but also for usability in routine care. Implementation research will play a key role in understanding how these tools can be embedded into different healthcare systems, how to build clinician trust in AI-driven decision support, and how to ensure they enhance rather than complicate care. Combined with efforts to strengthen the evidence base for underrepresented populations, this future research will help to ensure that patients with gout receive timely, effective, and sustainable treatment, ultimately reducing the burden of this significant disease.

Conclusion

This thesis provides valuable insights into the clinical characteristics and treatment considerations for gout in both older and younger populations, addressing the challenges posed by an ageing demographic and increasing patient complexity. These findings have the potential to inform the development of tailored management strategies moving forward. Additionally, this thesis offers comprehensive information on the changes in drug disposition associated with ageing and geriatric syndromes, contributing to a more comprehensive understanding of gout treatment in older adults.

This thesis highlights the challenges in measuring adherence to ULT and identifies factors that may influence adherence, such as disease prioritisation. Novel insights were gained into ULT-induced flares, revealing a higher frequency of flares in historical high-dose clinical trial regimens compared to contemporary “start low, go slow” approaches. Furthermore, this thesis exposes a significant gap in the literature regarding the efficacy and safety of two primary gout flare prophylaxis medications: NSAIDs and corticosteroids.

Analysis of real-world flare patterns in individuals with more complex or refractory gout revealed high variability, with tophi playing a key role in recurrent flares. This observation highlights the importance of considering tophaceous burden in gout management strategies. Future studies should build upon these findings, focusing on improved reporting in clinical trials and investigate factors that may help predict gout flares. Such research could help to tailor flare prevention strategies, reducing unnecessary gout flare prophylaxis use in low flare risk patients. This is particularly significant in the ageing gout population, to reduce the risk of unnecessary drug exposure and potential harm.

References

1. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nature reviews Rheumatology. 2020;16(7):380-90.
2. Singh JA, Gaffo A. Gout epidemiology and comorbidities. Seminars in arthritis and rheumatism. 2020;50(3):S11-S6.
3. Elfishawi MM, Zleik N, Kvrgic Z, Michet CJ, Crowson CS, Matteson EL, et al. The Rising Incidence of Gout and the Increasing Burden of Comorbidities: A Population-based Study over 20 Years. Journal of Rheumatology. 2018;45(4):574-9.
4. Li Y, Chen Z, Xu B, Wu G, Yuan Q, Xue X, et al. Global, regional, and national burden of gout in elderly 1990-2021: an analysis for the global burden of disease study 2021. BMC public health. 2024;24(1):3298.
5. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. [Review]. 2021;1(10287):1843-55.
6. Taylor WJ, Fransen J, Jansen TL, Dalbeth N, Schumacher HR, Brown M, et al. Study for Updated Gout Classification Criteria: Identification of Features to Classify Gout. Arthritis care & research (2010). 2015;67(9):1304-15.
7. Bursill D, Taylor WJ, Terkeltaub R, Kuwabara M, Merriman TR, Grainger R, et al. Gout, Hyperuricemia, and Crystal-Associated Disease Network Consensus Statement Regarding Labels and Definitions for Disease Elements in Gout. Arthritis Care Res (Hoboken). 2019;71(3):427-34.
8. Gaffo AL, Schumacher HR, Saag KG, Taylor WJ, Dinnella J, Outman R, et al. Developing a provisional definition of flare in patients with established gout. Arthritis Rheum. 2012;64(5):1508-17.
9. Janssen CA, Oude Voshaar MAH, Ten Klooster PM, Vonkeman HE, Van De Laar M. Development and validation of a patient-reported gout attack intensity score for use in gout clinical studies. Rheumatology (united kingdom). 2019;58(11):1928-34.
10. Elgafy H, Liu X, Herron J. Spinal gout: A review with case illustration. World journal of orthopedics. 2016;7(11):766-75.
11. Tatlock S, Rudell K, Panter C, Arbuckle R, Harrold LR, Taylor WJ, et al. What Outcomes are Important for Gout Patients? In-Depth Qualitative Research into the Gout Patient Experience to Determine Optimal Endpoints for Evaluating Therapeutic Interventions. Patient. 2017;10(1):65-79.
12. Holyer J, Taylor WJ, Gaffo A, Hosie G, Horne A, Mihov B, et al. Which Attributes Are Most and Least Important to Patients When Considering Gout Flare Burden Over Time? A Best-worst Scaling Choice Study. Journal of Rheumatology. 2022;49(2):213-8.
13. Garcia-Guillen A, Stewart S, Su I, Taylor WJ, Gaffo AL, Gott M, et al. Gout Flare Severity From the Patient Perspective: A Qualitative Interview Study. Arthritis care & research (2010). 2022;74(2):317-23.
14. Stewart S, Guillen AG, Taylor WJ, Gaffo A, Slark J, Gott M, et al. The experience of a gout flare: a meta-synthesis of qualitative studies. Seminars in arthritis and rheumatism. 2020;50(4):805-11.
15. Chandratre P, Mallen CD, Roddy E, Liddle J, Richardson J. "You want to get on with the rest of your life": a qualitative study of health-related quality of life in gout. Clin Rheumatol. 2016;35(5):1197-205.
16. Singh JA. The impact of gout on patient's lives: a study of African-American and Caucasian men and women with gout. Arthritis Res Ther. 2014;16(3):R132.
17. Ji Z, Huang Y, Liang L, Lin P, Guo X, Huang Q, et al. Clinical characteristics and risk factors associated with bone erosion in patients with tophi. Adv Rheumatol. 2024;64(1):18.
18. Rai SK, Choi HK, Choi SHJ, Townsend AF, Shojania K, De Vera MA. Key barriers to gout care: a systematic review and thematic synthesis of qualitative studies. Rheumatology (Oxford). 2018;57(7):1282-92.

19. Australian Govenement Australian Institute of Health and Welfare. Chronic musculoskeletal conditions: Gout 2024 [Available from: https://www.aihw.gov.au/reports/chronic-musculoskeletal-conditions/gout.
20. Wertheimer A, Morlock R, Becker MA. A revised estimate of the burden of illness of gout. Curr Ther Res Clin Exp. 2013;75:1-4.
21. Global, regional, and national burden of gout, 1990-2020, and projections to 2050 : a systematic analysis of the Global Burden of Disease Study 2021. The Lancet Rheumatology. 2024;6(8):507.
22. Shiozawa A, Szabo SM, Bolzani A, Cheung A, Choi HK. Serum Uric Acid and the Risk of Incident and Recurrent Gout: A Systematic Review. Journal of Rheumatology. 2017;44(3):388-96.
23. Pascart T, Liote F. Gout: state of the art after a decade of developments. Rheumatology (Oxford, England). 2019;58(1):27-44.
24. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. Curr Opin Rheumatol. 2011;23(2):192-202.
25. Major TJ, Topless RK, Dalbeth N, Merriman TR. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. BMJ (Online). 2018;363:k3951-k.
26. Kuo C-F, Grainge MJ, Mallen C, Zhang W, Doherty M. Comorbidities in patients with gout prior to and following diagnosis: case-control study. Ann Rheum Dis. 2016;75(1):210-7.
27. Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women--the Third National Health and Nutrition Examination Survey. Arthritis Res Ther. 2008;10(5):R116-R.
28. Halperin Kuhns VL, Woodward OM. Sex Differences in Urate Handling. Int. 2020;21(12):4269.
29. Leask MP, Crisan TO, Ji A, Matsuo H, Kottgen A, Merriman TR. The pathogenesis of gout: molecular insights from genetic, epigenomic and transcriptomic studies. Nature reviews Rheumatology. 2024;20(8):510-23.
30. Cho C, Kim B, Kim DS, Hwang MY, Shim I, Song M, et al. Large-scale cross-ancestry genome-wide meta-analysis of serum urate. Nature communications. 2024;15(1):3441-.
31. Tin A, Marten J, Halperin Kuhns VL, Li Y, Wuttke M, Kirsten H, et al. Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels. Nat Genet. 2019;51(10):1459-74.
32. Cox P, Gupta S, Zhao SS, Hughes DM. The incidence and prevalence of cardiovascular diseases in gout: a systematic review and meta-analysis. Rheumatol Int. 2021;41(7):1209-19.
33. Disveld IJM, Zoakman S, Jansen T, Rongen GA, Kienhorst LBE, Janssens H, et al. Crystal-proven gout patients have an increased mortality due to cardiovascular diseases, cancer, and infectious diseases especially when having tophi and/or high serum uric acid levels: a prospective cohort study. Clin Rheumatol. 2019;38(5):1385-91.
34. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation (New York, NY). 2007;116(8):894-900.
35. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Annals of the Rheumatic Diseases. 2017;76(1):29-42.
36. Qaseem A, Harris RP, Forciea MA, Clinical Guidelines Committee of the American College of P. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017;166(1):58-68.
37. Ben Salem C, Slim R, Fathallah N, Hmouda H. Drug-induced hyperuricaemia and gout. Rheumatology (Oxford). 2017;56(5):679-88.

38. Caspi D, Lubart E, Graff E, Habot B, Yaron M, Segal R. The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. Arthritis and rheumatism. 2000;43(1):103-8.
39. Shiozawa A, Buysman EK, Korrer S. Serum uric acid levels and the risk of flares among gout patients in a US managed care setting. Current Medical Research and Opinion. 2017;33(1):117-24.
40. Rothenbacher D, Primatesta P, Ferreira A, Cea-Soriano L, Rodriguez LA. Frequency and risk factors of gout flares in a large population-based cohort of incident gout. Rheumatology (Oxford). 2011;50(5):973-81.
41. Uhlig T, Karoliussen LF, Sexton J, Kvien TK, Haavardsholm EA, Perez-Ruiz F, et al. One- and 2-year flare rates after treat-to-target and tight-control therapy of gout: results from the NOR-Gout study. Arthritis Res Ther. 2022;24(1):11.
42. Cipolletta E, Abhishek A, Di Battista J, Grassi W, Filippucci E. Ultrasonography in the prediction of gout flares: a 12-month prospective observational study. Rheumatology (Oxford). 2023;62(3):1108-16.
43. Pascart T, Grandjean A, Capon B, Legrand J, Namane N, Ducoulombier V, et al. Monosodium urate burden assessed with dual-energy computed tomography predicts the risk of flares in gout: A 12-month observational study: MSU burden and risk of gout flare. Arthritis Research and Therapy. 2018;20 (1)(210).
44. Liu S, Sun H, Yang S, Liang N, Gao Y, Qu S, et al. Clustering of gout-related comorbidities and their relationship with gout flares: a data-driven cluster analysis of eight comorbidities. Journal of endocrinological investigation. 2024;47(5):1119-28.
45. Fatima T, McKinney C, Major TJ, Stamp LK, Dalbeth N, Iverson C, et al. The relationship between ferritin and urate levels and risk of gout. Arthritis Research and Therapy. 2018;20 (1) (179).
46. Zhang M, Zhang YQ, Terkeltaub R, Chen C, Neogi T. Effect of Dietary and Supplemental Omega-3 Polyunsaturated Fatty Acids on Risk of Recurrent Gout Flares. Arthritis rheumatol. 2019;71(9):1580-6.
47. El Ridi R, Tallima H. Physiological functions and pathogenic potential of uric acid: A review. J Adv Res. 2017;8(5):487-93.
48. Bardin T. Hyperuricemia starts at 360 micromoles (6 mg/dL). Joint Bone Spine. 2015;82(3):141-3.
49. Zhang WZ. Why Does Hyperuricemia Not Necessarily Induce Gout?. [Review]. 2021;1(2).
50. Mandal AK, Mount DB. The Molecular Physiology of Uric Acid Homeostasis. Annual review of physiology. 2015;77(1):323-45.
51. Yin H, Liu N, Chen J. The Role of the Intestine in the Development of Hyperuricemia. Frontiers in immunology. 2022;13:845684-.
52. Chhana A, Lee G, Dalbeth N. Factors influencing the crystallization of monosodium urate: a systematic literature review. BMC Musculoskelet Disord. 2015;16(1):296-.
53. Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. Clin Pharmacokinet. 2007;46(8):623-44.
54. Dalbeth N, House ME, Aati O, Tan P, Franklin C, Horne A, et al. Urate crystal deposition in asymptomatic hyperuricaemia and symptomatic gout: a dual energy CT study. Annals of the rheumatic diseases. 2015;74(5):908-11.
55. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440(7081):237-41.
56. Liu-Bryan R, Scott P, Sydlaske A, Rose DM, Terkeltaub R. Innate immunity conferred by toll-like receptors 2 and 4 and myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal–induced inflammation. Arthritis Rheum. 2005;52(9):2936-46.

57. Martinon F, Burns K, Tschopp J. The Inflammasome: A Molecular Platform Triggering Activation of Inflammatory Caspases and Processing of proIL-β. Molecular cell. 2002;10(2):417-26.
58. Schauer C, Janko C, Munoz LE, Zhao Y, Kienhöfer D, Frey B, et al. Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. Nature medicine. 2014;20(5):511-7.
59. Dalbeth N, Pool B, Gamble GD, Smith T, Callon KE, McQueen FM, et al. Cellular characterization of the gouty tophus: A quantitative analysis. Arthritis and rheumatism. 2010;62(5):1549-56.
60. Aati O, Taylor WJ, Horne A, Dalbeth N. Toward Development of a Tophus Impact Questionnaire: A Qualitative Study Exploring the Experience of People With Tophaceous Gout. Journal of clinical rheumatology. 2014;20(5):251-5.
61. Perez-Ruiz F, Martinez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. Annals of the Rheumatic Diseases. 2014;73(1):177-82.
62. Oh Y-J, Moon KW. Presence of tophi is associated with a rapid decline in the renal function in patients with gout. Sci. 2021;11(1):5684-.
63. Stamp LK, Dalbeth N. What Is Allopurinol Failure and What Should We Do About It? The Journal of rheumatology. 2024;51(6):556-62.
64. Yip K, Braverman G, Yue L, Fields T. Pipeline Therapies for Gout. Current rheumatology reports. 2024;26(3):69-80.
65. Pascual E, Batlle-Gualda E, Martínez A, Rosas J, Vela P. Synovial fluid analysis for diagnosis of intercritical gout. Ann Intern Med. 1999;131(10):756-9.
66. Singh JA, Budzik J-F, Becce F, Pascart T. Dual-energy computed tomography vs ultrasound, alone or combined, for the diagnosis of gout: a prospective study of accuracy. Rheumatology (Oxford, England). 2021;60(10):4861-7.
67. Janssens H, Fransen J, van de Lisdonk EH, van Riel P, van Weel C, Janssen M. A Diagnostic Rule for Acute Gouty Arthritis in Primary Care Without Joint Fluid Analysis. Arch Intern Med. 2010;170(13):1120-6.
68. Mandl P, D'Agostino MA, Navarro-Compan V, Gesl I, Sakellariou G, Abhishek A, et al. 2023 EULAR recommendations on imaging in diagnosis and management of crystal-induced arthropathies in clinical practice. Annals of the Rheumatic Diseases. 2024;83(6):752-9.
69. Zhang J, Sun W, Gao F, Lu J, Li K, Xu Y, et al. Changes of serum uric acid level during acute gout flare and related factors. Frontiers in endocrinology. 2023;14:1077059.
70. Neogi T, Jansen T, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annals of the Rheumatic Diseases. 2015;74(10):1789-98.
71. Dalbeth N, Te Karu L, Stamp LK. Gout and its management. Intern Med J. 2024;54(5):716-23.
72. Slobodnick A, Shah B, Krasnokutsky S, Pillinger MH. Update on colchicine, 2017. Rheumatology (Oxford, England). 2018;57(suppl_1):i4-i11.
73. Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four–hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis and rheumatism. 2010;62(4):1060-8.
74. Gaffo AL. Gout: Treatment of flares. In: UpToDate Wolters Kluwer; 2024.
75. Terkeltaub RA, Furst DE, DiGiacinto JL, Kook KA, Davis MW. Novel Evidence-Based Colchicine Dose-Reduction Algorithm to Predict and Prevent Colchicine Toxicity in the Presence of Cytochrome P450 3A4/P-Glycoprotein Inhibitors. Arthritis and Rheumatism. 2011;63(8):2226-37.

76. Stamp LK, Horsley C, Te Karu L, Dalbeth N, Barclay M. Colchicine: the good, the bad, the ugly and how to minimize the risks. Rheumatology (Oxford, England). 2024;63(4):936-44.
77. Hansten PD, Tan MS, Horn JR, Gomez-Lumbreras A, Villa-Zapata L, Boyce RD, et al. Colchicine Drug Interaction Errors and Misunderstandings: Recommendations for Improved Evidence-Based Management. Drug safety. 2023;46(3):223-42.
78. Vane JR, Botting RM. Mechanism of Action of Nonsteroidal Anti-inflammatory Drugs. The American Journal of Medicine. 1998;104(3, Supplement 1):2S-8S.
79. van Durme CM, Wechalekar MD, Landewé RB, Pardo Pardo J, Cyril S, van der Heijde D, et al. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev. 2021;12(12):Cd010120.
80. Borer JS, Simon LS. Cardiovascular and gastrointestinal effects of COX-2 inhibitors and NSAIDs: achieving a balance. Arthritis Res Ther. 2005;7 Suppl 4(Suppl 4):S14-S22.
81. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. Journal of pharmacy & pharmaceutical sciences. 2013;16(5):821-47.
82. Williams DM. Clinical Pharmacology of Corticosteroids. Respiratory care. 2018;63(6):655-70.
83. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016;388(10055):2039-52.
84. Buchman AL. Side Effects of Corticosteroid Therapy. Journal of clinical gastroenterology. 2001;33(4):289-94.
85. Schlesinger N, Pillinger MH, Simon LS, Lipsky PE. Interleukin-1β inhibitors for the management of acute gout flares: a systematic literature review. Arthritis Res Ther. 2023;25(1):128-.
86. Sivera F, Wechalekar MD, Andrés M, Buchbinder R, Carmona L, Sivera F. Interleukin-1 inhibitors for acute gout. Cochrane Database Syst Rev. 2014;2014(9):CD009993-CD.
87. Thiele RG, Schlesinger N. Ultrasonography shows disappearance of monosodium urate crystal deposition on hyaline cartilage after sustained normouricemia is achieved. Rheumatol Int. 2010;30(4):495-503.
88. Conley B, Bunzli S, Bullen J, O'Brien P, Persaud J, Gunatillake T, et al. What are the core recommendations for gout management in first line and specialist care? Systematic review of clinical practice guidelines. BMC Rheumatol. 2023;7(1):15-.
89. Kiltz U, Smolen J, Bardin T, Cohen Solal A, Dalbeth N, Doherty M, et al. Treat-to-target (T2T) recommendations for gout. Annals of the Rheumatic Diseases. 2017;76(4):632-8.
90. Stamp LK, Frampton C, Morillon MB, Taylor WJ, Dalbeth N, Singh JA, et al. Association between serum urate and flares in people with gout and evidence for surrogate status: a secondary analysis of two randomised controlled trials. Lancet Rheumatol. 2022;4(1):e53-e60.
91. Doherty M, Jenkins W, Richardson H, Sarmanova A, Abhishek A, Ashton D, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet. 2018;392(10156):1403-12.
92. Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology (Oxford). 2017;56(7):E1-E20.
93. Pisano A, Cernaro V, Gembillo G, D'Arrigo G, Buemi M, Bolignano D. Xanthine Oxidase Inhibitors for Improving Renal Function in Chronic Kidney Disease Patients: An Updated Systematic Review and Meta-Analysis. Int J Mol Sci. 2017;18(11).
94. Higgins P, Dawson J, Lees KR, McArthur K, Quinn TJ, Walters MR. Xanthine oxidase inhibition for the treatment of cardiovascular disease: a systematic review and meta-analysis. Cardiovasc Ther. 2012;30(4):217-26.

95. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012;64(10):1431-46.
96. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med. 2018;378(13):1200-10.
97. Kim SC, Neogi T, Kim E, Lii J, Desai RJ. Trends in Utilization of Urate-Lowering Therapies Following the US Food and Drug Administration's Boxed Warning on Febuxostat. Arthritis rheumatol. 2021;73(3):542-3.
98. Mackenzie IS, Ford I, Nuki G, Hallas J, Hawkey CJ, Webster J, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet. 2020;396(10264):1745-57.
99. FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis rheumatol. 2020;72(6):879-95.
100. Soskind R, Abazia DT, Bridgeman MB. Updates on the treatment of gout, including a review of updated treatment guidelines and use of small molecule therapies for difficult-to-treat gout and gout flares. Expert Opin Pharmacother. 2017;18(11):1115-25.
101. Australian Medicines Handbook (online). Benzbromarone: Adelaide: Australian Medicines Handbook Pty Ltd; 2024 July. Available from: https://amhonline.amh.net.au/.
102. Sundy JS, Baraf HSB, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment Two Randomized Controlled Trials. JAMA-J Am Med Assoc. 2011;306(7):711-20.
103. Proudman C, Lester SE, Gonzalez-Chica DA, Gill TK, Dalbeth N, Hill CL. Gout, flares, and allopurinol use: a population-based study. Arthritis Res Ther. 2019;21:8.
104. Day RO, Kannangara DRW, Stocker SL, Carland JE, Williams KM, Graham GG. Allopurinol: insights from studies of dose-response relationships. Expert Opinion on Drug Metabolism and Toxicology. 2017;13(4):449-62.
105. Yin RL, Li L, Zhang G, Cui YF, Zhang LJ, Zhang QX, et al. Rate of adherence to urate-lowering therapy among patients with gout: a systematic review and meta-analysis. BMJ Open. 2018;8(4):9.
106. Ramasamy SN, Korb-Wells CS, Kannangara DRW, Smith MWH, Wang N, Roberts DM, et al. Allopurinol hypersensitivity: A systematic review of all published cases, 1950-2012. Drug Safety. 2013;36(10):953-80.
107. Stamp LK, Barclay ML. How to prevent allopurinol hypersensitivity reactions? Rheumatology (Oxford). 2018;57:i35-i41.
108. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med. 1984;76(1):47-56.
109. Stamp LK, Chapman PT, Barclay ML, Horne A, Frampton C, Tan P, et al. How much allopurinol does it take to get to target urate? Comparison of actual dose with creatinine clearance-based dose. Arthritis Res Ther. 2018;20:7.
110. Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. Journal of Rheumatology. 2006;33(8):1646-50.
111. Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum. 2012;64(8):2529-36.
112. Stamp LK, Chapman PT, Barclay ML, Horne A, Frampton C, Tan P, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to

achieve target serum urate in people with gout. Annals of the Rheumatic Diseases. 2017;76(9):1522-8.
113. Wright DFB, Hishe HZ, Stocker SL, Dalbeth N, Horne A, Drake J, et al. The development and evaluation of dose-prediction tools for allopurinol therapy (Easy-Allo tools). Br J Clin Pharmacol. 2024;90(5):1268-79.
114. Wallace MC, Roberts RL, Nanavati P, Miner JN, Dalbeth N, Topless R, et al. Association between ABCG2 rs2231142 and poor response to allopurinol: replication and meta-analysis. Rheumatology (Oxford). 2018;57(4):656-60.
115. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of Drug Adherence Rates Among Patients with Seven Different Medical Conditions. Pharmacotherapy. 2008;28(4):437-43.
116. Spencer K, Carr A, Doherty M. Patient and provider barriers to effective management of gout in general practice: a qualitative study. Ann Rheum Dis. 2012;71(9):1490-5.
117. Spragg JCJ, Michael TJF, Aslani P, Coleshill MJ, Chan JS, Day RO, et al. Optimizing adherence to allopurinol for gout: patients' perspectives. Br J Clin Pharmacol. 2023;89(7):1978-91.
118. Singh JA. Challenges Faced by Patients in Gout Treatment: A Qualitative Study. Journal of clinical rheumatology. 2014;20(3):172-4.
119. Sinnappah KA, Stocker SL, Chan JS, Hughes DA, Wright DFB. Clinical interventions to improve adherence to urate-lowering therapy in patients with gout: a systematic review. Int J Pharm Pract. 2022;30(3):215-25.
120. Gill I, Dalbeth N, Ofanoa M, Goodyear-Smith F. Interventions to improve uptake of urate-lowering therapy in patients with gout: a systematic review. BJGP open. 2020;4(3):bjgpopen20X101051.
121. Ramsubeik K, Ramrattan LA, Kaeley GS, Singh JA. Effectiveness of healthcare educational and behavioral interventions to improve gout outcomes: a systematic review and meta-analysis. Ther Adv Musculoskelet Dis. 2018;10(12):235-52.
122. Michael TJF, Wright DFB, Chan JS, Coleshill MJ, Aslani P, Hughes DA, et al. Patient-Led Urate Self-Monitoring to Improve Clinical Outcomes in People With Gout: A Feasibility Study. ACR Open Rheumatol. 2024;6(7):403-11.
123. Kvarnström K, Westerholm A, Airaksinen M, Liira H. Factors Contributing to Medication Adherence in Patients with a Chronic Condition: A Scoping Review of Qualitative Research. Pharmaceutics. 2021;13(7):1100.
124. Jose J, Jimmy B. Patient Medication Adherence: Measures in Daily Practice. Oman Med J. 2011;26(3):155-9.
125. Schlesinger N, Etzel CJ, Greenberg J, Kremer J, Harrold LR. Gout Prophylaxis Evaluated According to the 2012 American College of Rheumatology Guidelines: Analysis from the CORRONA Gout Registry. Journal of Rheumatology. 2016;43(5):924-30.
126. Becker MA, MacDonald PA, Hunt BJ, Lademacher C, Joseph-Ridge N. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. Nucleosides Nucleotides Nucleic Acids. 2008;27(6):585-91.
127. Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. Rheumatology (United Kingdom). 2014;53(11):1920-6.
128. Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis Rheum. 1974;17(5):609-14.
129. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. Journal of Rheumatology. 2004;31(12):2429-32.
130. Stamp L, Horne A, Mihov B, Drake J, Haslett J, Chapman PT, et al. Is colchicine prophylaxis required with start-low go-slow allopurinol dose escalation in gout? A non-inferiority randomised double-blind placebo-controlled trial. Annals of the rheumatic diseases. 2023;82(12):1626-34.

131. Becker MA, Schumacher HR, Jr., Wortmann RL, MacDonald PA, Eustace D, Palo WA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353(23):2450-61.
132. Schumacher HR, Jr., Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum. 2008;59(11):1540-8.
133. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial. Arthritis Research and Therapy. 2010;12 (2):R63.
134. Wortmann RL, Macdonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clin Ther. 2010;32(14):2386-97.
135. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012;64(10):1447-61.
136. George M, Pullman-Mooar S, Hussain F, Schumacher HR. Evaluating appropriate use of prophylactic colchicine for gout flare prevention. Arthritis Care Res (Hoboken). 2014;66(8):1258-62.
137. Yamanaka H, Tamaki S, Ide Y, Kim H, Inoue K, Sugimoto M, et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. Annals of the Rheumatic Diseases. 2018;77(2):270-6.
138. Li X, Shao Q, Shen J, Ren S, Li L, Lu H, et al. Association between the initial dose urate-lowering drugs and gout flares in adult males with gout. Rheumatology (Oxford, England). 2024;63(6):1599-606.
139. Lee JS, Oh JS, Kim Y-G, Lee C-K, Yoo B, Hong S. Rapid reduction in uric acid by a urate-lowering agent is associated with recurrent cardiovascular events. Medical hypotheses. 2020;141:109740-.
140. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med. 2017;15:10.
141. Choi HK, Soriano LC, Zhang Y, Garcia Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: Population based case-control study. BMJ (Online). 2012;344 (7843) (no pagination)(d8190).
142. Würzner G, Gerster J-C, Chiolero A, Maillard M, Fallab-Stubi C-L, Brunner HR, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. Journal of hypertension. 2001;19(10):1855-60.
143. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric Syndromes: Clinical, Research, and Policy Implications of a Core Geriatric Concept. Journal of the American Geriatrics Society (JAGS). 2007;55(5):780-91.
144. Nicolaus S, Crelier B, Donzé JD, Aubert CE. Definition of patient complexity in adults: A narrative review. Journal of Multimorbidity and Comorbidity. 2022;12:26335565221081288-.
145. Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. Nat Rev Rheumatol. 2016;12(4):235-42.
146. Australian Medicines Handbook (online). Febuxostat: Adelaide: Australian Medicines Handbook Pty Ltd; 2025 January. Available from: https://amhonline.amh.net.au/.
147. Stamp LK, Farquhar H, Pisaniello HL, Vargas-Santos AB, Fisher M, Mount DB, et al. Management of gout in chronic kidney disease: a G-CAN Consensus Statement on the research priorities. Nature reviews Rheumatology. 2021;17(10):633-41.

148. Muth C, Blom JW, Smith SM, Johnell K, Gonzalez-Gonzalez AI, Nguyen TS, et al. Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus. J Intern Med. 2019;285(3):272-88.
149. Abhishek A. Managing Gout Flares in the Elderly: Practical Considerations. Drugs and Aging. 2017;34(12):873-80.
150. Thomas MC. Diuretics, ACE inhibitors and NSAIDs — the triple whammy. Med J Aust. 2000;172(4):184-5.
151. Leete J, Wang C, López-Hernández FJ, Layton AT. Determining risk factors for triple whammy acute kidney injury. Mathematical biosciences. 2022;347:108809-.
152. Dodds R, Sayer AA. Sarcopenia and frailty: new challenges for clinical practice. Clinical medicine (London, England). 2016;16(5):455-8.
153. Lim RH, Sharmeen T. Medicines management issues in dementia and coping strategies used by people living with dementia and family carers: A systematic review. International journal of geriatric psychiatry. 2018;33(12):1562-81.
154. Australian Medicines Handbook (online). Colchicine: Adelaide: Australian Medicines Handbook Pty Ltd; 2025 January. Available from: https://amhonline.amh.net.au/.
155. Abdu N, Mosazghi A, Teweldemedhin S, Asfaha L, Teshale M, Kibreab M, et al. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Usage and co-prescription with other potentially interacting drugs in elderly: A cross-sectional study. PLoS One. 2020;15(10):e0238868.
156. Australian Government Department of Health and Aged Care. Therapeutic Goods Order No. 95 - Child-resistant packaging requirements for medicines 2017. Therapuetic Goods Administration; 2017.
157. Adenuric Febuxostat Abbreviated PI [Internet]. MIMS Australia. 2022 [cited 13 March 2025]. Available from: https://emims.plus/.
158. Allopurinol Sandoz Allopurinol Abbreviated PI [Internet]. MIMS Australia. 2024 [cited 13 March 2025]. Available from: https://emims.plus/.
159. Xia Y, Wu Q, Wang H, Zhang S, Jiang Y, Gong T, et al. Global, regional and national burden of gout, 1990–2017: a systematic analysis of the Global Burden of Disease Study. Rheumatology (Oxford, England). 2020;59(7):1529-38.
160. Dalbeth N, Choi HK, Joosten LAB, Khanna PP, Matsuo H, Perez-Ruiz F, et al. Gout. Nat Rev Dis Primers. 2019;5:17.
161. Fisher MC, Rai SK, Lu N, Zhang Y, Choi HK. The unclosing premature mortality gap in gout: a general population-based study. Ann Rheum Dis. 2017;76(7):1289-90.
162. Chandratre P, Roddy E, Clarson L, Richardson J, Hider SL, Mallen CD. Health-related quality of life in gout: a systematic review. Rheumatology (Oxford). 2013;52(11):2031-40.
163. Vaccher S, Kannangara DRW, Baysari MT, Reath J, Zwar N, Williams KM, et al. Barriers to Care in Gout: From Prescriber to Patient. Journal of Rheumatology. 2016;43(1):144-9.
164. Scheepers L, van Onna M, Stehouwer CDA, Singh JA, Arts ICW, Boonen A. Medication adherence among patients with gout: A systematic review and meta-analysis. Semin Arthritis Rheum. 2018;47(5):689-702.
165. Zandman-Goddard G, Amital H, Shamrayevsky N, Raz R, Shalev V, Chodick G. Rates of adherence and persistence with allopurinol therapy among gout patients in Israel. Rheumatology (Oxford). 2013;52(6):1126-31.
166. Harrold LR, Andrade SE, Briesacher BA, Raebel MA, Fouayzi H, Yood RA, et al. Adherence with urate-lowering therapies for the treatment of gout. Arthritis Res Ther. 2009;11(2):R46-R.
167. McGowan B, Bennett K, Silke C, Whelan B. Adherence and persistence to urate-lowering therapies in the Irish setting. Clin Rheumatol. 2016;35(3):715-21.
168. Scheepers L, Burden AM, Arts ICW, Spaetgens B, Souverein P, de Vries F, et al. Medication adherence among gout patients initiated allopurinol: a retrospective

cohort study in the Clinical Practice Research Datalink (CPRD). Rheumatology (Oxford). 2018;57(9):1641-50.
169. Singh JA, Richman J, Yang S, Bridges SL, Saag K. Allopurinol adherence and its predictors in gout: a national cohort study in US veterans. Lancet Rheumatol. 2020;2(5):e281-e91.
170. Rashid N, Coburn BW, Wu YL, Cheetham TC, Curtis JR, Saag KG, et al. Modifiable factors associated with allopurinol adherence and outcomes among patients with gout in an integrated healthcare system. Journal of Rheumatology. 2015;42(3):504-12.
171. Horsburgh S, Norris P, Becket G, Arroll B, Crampton P, Cumming J, et al. Allopurinol use in a New Zealand population: prevalence and adherence. Rheumatol Int. 2014;34(7):963-70.
172. Sarawate CA, Brewer KK, Yang W, Patel PA, Schumacher HR, Saag KG, et al. Gout Medication Treatment Patterns and Adherence to Standards of Care From a Managed Care Perspective. Mayo Clin Proc. 2006;81(7):925-34.
173. Riedel AA, Nelson M, Joseph-Ridge N, Wallace K, MacDonald P, Becker M. Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. The Journal of Rheumatology. 2004;31(8):1575-81.
174. Mantarro S, Capogrosso-Sansone A, Tuccori M, Blandizzi C, Montagnani S, Convertino I, et al. Allopurinol adherence among patients with gout: an Italian general practice database study. Int J Clin Pract. 2015;69(7):757-65.
175. Halpern R, Mody RR, Fuldeore MJ, Patel PA, Mikuls TR. Impact of noncompliance with urate-lowering drug on serum urate and gout-related healthcare costs: administrative claims analysis. Curr Med Res Opin. 2009;25(7):1711-9.
176. Lee S, So MW, Ahn E. Long-term adherence and persistence with febuxostat among male patients with gout in a routine clinical setting. Modern Rheumatology. 2019;29(4):662-8.
177. Wroe AL. Intentional and unintentional nonadherence: a study of decision making. J Behav Med. 2002;25(4):355-72.
178. Shi L, Liu J, Koleva Y, Fonseca V, Kalsekar A, Pawaskar M. Concordance of Adherence Measurement Using Self-Reported Adherence Questionnaires and Medication Monitoring Devices. Pharmacoeconomics. 2010;28(12):1097-107.
179. de Klerk E, van der Heijde D, van der Tempel H, van der Linden S. Development of a questionnaire to investigate patient compliance with antirheumatic drug therapy. J Rheumatol. 1999;26(12):2635-41.
180. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1-24.
181. Lam WY, Fresco P. Medication Adherence Measures: An Overview. Biomed Res Int. 2015;2015:1-12.
182. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther. 1999;21(6):1074-90.
183. Stocker SL, McLachlan AJ, Savic RM, Kirkpatrick CM, Graham GG, Williams KM, et al. The pharmacokinetics of oxypurinol in people with gout. Br J Clin Pharmacol. 2012;74(3):477-89.
184. World Health O, Project WHOAtLTT, Global Adherence Interdisciplinary N, Irgun ha-beri'ut h-', Maailman tr, Munaẓẓamat al-Ṣiḥḥah a-'ly, et al. Adherence to long-term therapies : evidence for action. Geneva: Geneva : World Health Organization; 2003.
185. de Klerk E, van der Heijde D, Landewe R, van der Tempel H, van der Linden S. The compliance-questionnaire-rheumatology compared with electronic medication event monitoring: A validation study. Journal of Rheumatology. 2003;30(11):2469-75.
186. Neame R, Hammond A. Beliefs about medications: a questionnaire survey of people with rheumatoid arthritis. Rheumatology (Oxford). 2005;44(6):762-7.

187. Robinson JP, Shaver PR, Wrightsman LS. CHAPTER 1 - Criteria for Scale Selection and Evaluation. Elsevier Inc; 1991. p. 1-16.
188. Mukaka MM. A guide to appropriate use of Correlation coefficient in medical research. Malawi medical journal. 2012;24(3):69-71.
189. Silva L, Miguel ED, Peiteado D, Villalba A, Mola M, Pinto J, et al. Compliance in gout patients. Acta Reumatol. 2010;35(5):466-74.
190. Singh JA, Shah N, Edwards NL. A cross-sectional internet-based patient survey of the management strategies for gout. BMC Altern Med. 2016;16:90.
191. Tan CSL, Teng GG, Chong KJ, Cheung PP, Lim AYN, Wee HL, et al. Utility of the Morisky Medication Adherence Scale in gout: a prospective study. Patient Prefer Adherence. 2016;10:2449-57.
192. Yin R, Cao H, Fu T, Zhang Q, Zhang L, Li L, et al. The rate of adherence to urate-lowering therapy and associated factors in Chinese gout patients: a cross-sectional study. Rheumatol Int. 2017;37(7):1187-94.
193. Hughes LD, Done J, Young A. A 5 item version of the Compliance Questionnaire for Rheumatology (CQR5) successfully identifies low adherence to DMARDs. BMC Musculoskelet Disord. 2013;14(1):286-.
194. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive Validity of a Medication Adherence Measure in an Outpatient Setting. J Clin Hypertens. 2008;10(5):348-54.
195. Chua XHJ, Lim S, Lim FP, Lim YNA, He HG, Teng GG. Factors influencing medication adherence in patients with gout: A descriptive correlational study. J Clin Nurs. 2018;27(1-2):E213-E22.
196. Zwikker HE, van Dulmen S, den Broeder AA, van den Bemt BJ, van den Ende CH. Perceived need to take medication is associated with medication non-adherence in patients with rheumatoid arthritis. Patient Prefer Adherence. 2014;8:1635-45.
197. Chan AHY, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. Br J Clin Pharmacol. 2020;86(7):1281-8.
198. George J, Cross AJ, Elliott RA, Petrie K, Kuruvilla L, George J. Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. Cochrane Database Syst Rev. 2020;2020(5):CD012419-CD.
199. Uhlig T, Karoliussen LF, Sexton J, Borgen T, Haavardsholm EA, Kvien TK, et al. 12-month results from the real-life observational treat-to-target and tight-control therapy NOR-Gout study: achievements of the urate target levels and predictors of obtaining this target. RMD Open. 2021;7(1):e001628.
200. Kleinstäuber M, Wolf L, Jones ASK, Dalbeth N, Petrie KJ. Internalized and Anticipated Stigmatization in Patients With Gout. ACR Open Rheumatol. 2020;2(1):11-7.
201. Rashid N, Levy GD, Wu YL, Zheng CY, Koblick R, Cheetham TC. Patient and clinical characteristics associated with gout flares in an integrated healthcare system. Rheumatol Int. 2015;35(11):1799-807.
202. Aung T, Myung G, FitzGerald JD. Treatment approaches and adherence to urate-lowering therapy for patients with gout. Patient Prefer Adherence. 2017;11:795-800.
203. Stamp LK, Merriman T, Frampton C, Zhang M, Wallace M, Miner JN, et al. Plasma oxypurinol as a measure of adherence in clinical trials. Annals of the Rheumatic Diseases. 2018;77(2):313-4.
204. Baumgartner PC, Haynes RB, Hersberger KE, Arnet I. A Systematic Review of Medication Adherence Thresholds Dependent of Clinical Outcomes. Front Pharmacol. 2018;9:1290.
205. Schlesinger N, Dwyer J, Carson J, Brunetti L. Gout flare prophylaxis trials: comment on the article by Maher et al. Arthritis care & research (2010). 2025.
206. Watson L, Belcher J, Nicholls E, Chandratre P, Blagojevic-Bucknall M, Hider S, et al. Factors associated with change in health-related quality of life in people with gout:

a 3-year prospective cohort study in primary care. Rheumatology (Oxford). 2022;62(8):2748-56.
207. Rogenmoser S, Arnold MH. Chronic gout: Barriers to effective management. Aust J Gen Pract. 2018;47(6):351-6.
208. Strand V, Pillinger MH, Oladapo A, Yousefian C, Brooks D, Kragh N. Patient Experience with Chronic Refractory Gout and Its Impact on Health-Related Quality of Life: Literature Review and Qualitative Analysis. Rheumatol Ther. 2024;11(5):1271-90.
209. Perez-Ruiz F, Desideri G. Improving adherence to gout therapy: an expert review. Ther Clin Risk Manag. 2018;14:793-802.
210. Brook RA, Forsythe A, Smeeding JE, Lawrence Edwards N. Chronic gout: epidemiology, disease progression, treatment and disease burden. Current medical research and opinion. 2010;26(12):2813-21.
211. Latourte A, Bardin T, Clerson P, Ea HK, Flipo RM, Richette P. Dyslipidemia, Alcohol Consumption, and Obesity as Main Factors Associated With Poor Control of Urate Levels in Patients Receiving Urate-Lowering Therapy. Arthritis Care Res (Hoboken). 2018;70(6):918-24.
212. Singh JA, Edwards NL. Gout management and outcomes during established COVID-19 pandemic in 2020–2021: a cross-sectional Internet survey. Ther Adv Musculoskelet Dis. 2022;14:1759720X221096381-1759720X.
213. Day RO, Lau W, Stocker SL, Aung E, Coleshill MJ, Schulz M, et al. Management of gout in older people. Journal of Pharmacy Practice and Research. 2019;49(1):90-7.
214. Zhang J, Jin C, Ma B, Sun H, Chen Y, Zhong Y, et al. Global, regional and national burdens of gout in the young population from 1990 to 2019: a population-based study. Rheumatic & musculoskeletal diseases open. 2023;9(2):e003025.
215. Amatucci AJ, Padnick-Silver L, LaMoreaux B, Bulbin DH. Comparison Between Early-Onset and Common Gout: A Systematic Literature Review. Rheumatol Ther. 2023;10(4):809-23.
216. Matsuo H, Ichida K, Takada T, Nakayama A, Nakashima H, Nakamura T, et al. Common dysfunctional variants in ABCG2 are a major cause of early-onset gout. Sci. 2013;3(1):2014-.
217. Maher D, Ailabouni N, Mangoni AA, Wiese MD, Reeve E. Alterations in drug disposition in older adults: a focus on geriatric syndromes. Expert Opin Drug Metab Toxicol. 2021;17(1):41-52.
218. Singh JA. Goals of gout treatment: a patient perspective. Clin Rheumatol. 2018;37(9):2557-66.
219. Khanna PP, Nuki G, Bardin T, Tausche AK, Forsythe A, Goren A, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. Health and Quality of Life Outcomes. 2012;10 (no pagination)(117).
220. Stamp LK, Grainger R, Frampton C, Drake J, Hill CL. Effect of omega-three supplementation on serum urate and gout flares in people with gout a pilot randomized trial. BMC Rheumatol. 2022;6(1):31-.
221. Ware JE, Sherbourne CD. THE MOS 36-ITEM SHORT-FORM HEALTH SURVEY (SF-36) .1. CONCEPTUAL-FRAMEWORK AND ITEM SELECTION. Med Care. 1992;30(6):473-83.
222. Wallace B, Khanna D, Aquino-Beaton C, Singh JA, Duffy E, Elashoff D, et al. Performance of Gout Impact Scale in a longitudinal observational study of patients with gout. Rheumatology (Oxford). 2016;55(6):982-90.
223. Aati O, Taylor WJ, Siegert RJ, Horne A, House ME, Tan P, et al. Development of a patient-reported outcome measure of tophus burden: the Tophus Impact Questionnaire (TIQ-20). Annals of the Rheumatic Diseases. 2015;74(12):2144-50.
224. Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. Qual Health Care. 2001;10(3):135-40.

225. Janssen CA, Oude Voshaar MAH, Ten Klooster PM, Jansen TLTA, Vonkeman HE, Van De Laar MAFJ. A systematic literature review of patient-reported outcome measures used in gout: An evaluation of their content and measurement properties. Health and Quality of Life Outcomes. 2019;17 (1) (no pagination)(63).
226. Harris WS, von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med. 2004;39(1):212-20.
227. Gaffo AL, Dalbeth N, Saag KG, Singh JA, Rahn EJ, Mudano AS, et al. Validation of a Definition of Flare in Patients With Established Gout. Arthritis rheumatol. 2018;70(3):462-7.
228. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA), Australia [Internet] Canberra: ABS; 2021 [Available from: https://www.abs.gov.au/statistics/people/people-and-communities/socio-economic-indexes-areas-seifa-australia/latest-release.
229. Rasmussen C, Larsen JW, Christensen HM, Larsen MB, Thomsen AM, Leishmann T, et al. Optimising gout treatment: insights from a nurse-led cohort study. RMD Open. 2024;10(2):24.
230. Ankli B, Berger CT, Haeni N, Kyburz D, Hugle T, So AK, et al. The target uric acid level in multimorbid patients with gout is difficult to achieve: data from a longitudinal Swiss single-centre cohort. Swiss Med Wkly. 2019;149:w20121.
231. Chandratre P, Mallen C, Richardson J, Muller S, Hider S, Rome K, et al. Health-related quality of life in gout in primary care: Baseline findings from a cohort study. Seminars in Arthritis and Rheumatism. 2018;48(1):61-9.
232. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Annals of the Rheumatic Diseases. 2013;72(6):826-30.
233. Primatesta P, Plana E, Rothenbacher D. Gout treatment and comorbidities: a retrospective cohort study in a large US managed care population. BMC Musculoskelet Disord. 2011;12(1):103-.
234. MacFarlane LA, Kim SC. Gout: a review of non-modifiable and modifiable risk factors. Rheum Dis Clin North Am. 2014;40(4):581-604.
235. Li QR, Li XD, Wang J, Liu HD, Kwong JSW, Chen H, et al. Diagnosis and treatment for hyperuricemia and gout: a systematic review of clinical practice guidelines and consensus statements. BMJ Open. 2019;9(8):13.
236. Wu M, Liu FJ, Chen J, Chen L, Wei C, Hu ZM, et al. Prevalence and Factors Associated With Bone Erosion in Patients With Gout. Arthritis care & research (2010). 2019;71(12):1653-9.
237. Coleshill MJ, Day RO, Tam K, Kouhkamari M, Caillet V, Aung E, et al. Persistence with urate-lowering therapy in Australia: A longitudinal analysis of allopurinol prescriptions. Br J Clin Pharmacol. 2022;88(11):4894-901.
238. Uhlig T, Karoliussen LF, Sexton J, Kvien TK, Haavardsholm EA, Taylor WJ, et al. Beliefs about medicines in gout patients: results from the NOR-Gout 2-year study. Scand J Rheumatol. 2023;52(6):664-72.
239. Stamp LK, Chapman P, Hudson B, Frampton C, Hamilton G, Judd A. The challenges of managing gout in primary care: Results of a best-practice audit. Aust J Gen Pract. 2019;48(9):631-7.
240. Teoh N, Gamble GD, Horne A, Taylor WJ, Palmano K, Dalbeth N. The challenges of gout flare reporting: mapping flares during a randomized controlled trial. BMC Rheumatol. 2019;3:27.
241. Dalbeth N, Ames R, Gamble GD, Horne A, Wong S, Kuhn-Sherlock B, et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. Annals of the Rheumatic Diseases. 2012;71(6):929.
242. Stewart S, Dalbeth N, Gaffo A. The challenge of gout flare measurement. Best Pract Res Clin Rheumatol. 2021;35(4):12.

243. Jagpal A, Rahn EJ, Mudano AS, Dalbeth N, Taylor W, Saag KG, et al. Which factors predict discordance between a patient and physician on a gout flare? Rheumatology (Oxford). 2021;60(2):773-9.
244. Abhishek A, Fuller A, Nakafero G, Zhang WY, Dumbleton J, Hawkey C, et al. Feasibility of conducting a randomized, placebo-controlled study assessing whether omega-3 fatty acids prevent gout flares when starting urate-lowering treatment. Rheumatol Adv Pract. 2022;6(3):8.
245. Schuchardt JP, Beinhorn P, Hu XF, Chan HM, Roke K, Bernasconi A, et al. Omega-3 world map: 2024 update. Progress in Lipid Research. 2024;95:101286.
246. Khan SU, Lone AN, Khan MS, Virani SS, Blumenthal RS, Nasir K, et al. Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis. eClinicalMedicine. 2021;38.
247. Pomatto LCD, Davies KJA. The role of declining adaptive homeostasis in ageing. J Physiol. 2017;595(24):7275-309.
248. Jatuworapruk K, Grainger R, Dalbeth N, Taylor WJ. Development of a prediction model for inpatient gout flares in people with comorbid gout. Annals of the Rheumatic Diseases. 2020;79(3):418-23.
249. Yoon MJ, Yang JA, Joo SH, Lee SJ, Moon JY, Kwon HM, et al. Risk factors for gout attack recurrence during urate-lowering allopurinol treatment. Arthritis and Rheumatology. 2014;10):S69.
250. Ebstein E, Forien M, Norkuviene E, Richette P, Mouterde G, Daien C, et al. UltraSound evaluation in follow-up of urate-lowering therapy in gout phase 2 (USEFUL-2): Duration of flare prophylaxis. Joint, bone, spine : revue du rhumatisme. 2020;87(6):647-51.
251. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Care and Research. 2002;47(4):356-60.
252. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two-stage approach to the treatment of hyperuricemia in gout: the "dirty dish" hypothesis. Arthritis Rheum. 2011;63(12):4002-6.
253. Lioté F, Lancrenon S, Lanz S, Guggenbuhl P, Lambert C, Saraux A, et al. GOSPEL: Prospective survey of gout in France. Part I: Design and patient characteristics (n = 1003). Joint, bone, spine : revue du rhumatisme. 2012;79(5):464-70.
254. Dalbeth N, Nicolaou S, Baumgartner S, Hu J, Fung M, Choi HK. Presence of monosodium urate crystal deposition by dual-energy CT in patients with gout treated with allopurinol. Annals of the Rheumatic Diseases. 2018;77(3):364-70.
255. Bongartz T, Glazebrook KN, Kavros SJ, Murthy NS, Merry SP, Franz WB, et al. Dual-energy CT for the diagnosis of gout: an accuracy and diagnostic yield study. Annals of the Rheumatic Diseases. 2015;74(6):1072.
256. Stamp L, Morillon MB, Taylor WJ, Dalbeth N, Singh JA, Lassere M, et al. Serum urate as surrogate endpoint for flares in people with gout: A systematic review and meta-regression analysis. Semin Arthritis Rheum. 2018;48(2):293-301.
257. Morillon MB, Christensen R, Singh JA, Dalbeth N, Saag K, Taylor WJ, et al. Serum urate as a proposed surrogate outcome measure in gout trials: From the OMERACT working group. Seminars in Arthritis and Rheumatism. 2021;51(6):1378-85.
258. Yu Y, Wang D, Zhou Q, Wang C, Ma X, Gao Y, et al. Recommendations in clinical practice guidelines on gout: systematic review and consistency analysis. Clinical & Experimental Rheumatology. 2020;38(5):964-72.
259. Hoon E, Edwards J, Robinson P, Rowett D, Stocks N, Keen HI, et al. How is gout currently managed, and is there interest in changing the way we deliver care? A qualitative exploratory study. Aust J Gen Pract. 2024;53(11):864-71.
260. Huddleston EM, Gaffo AL. Emerging strategies for treating gout. Current opinion in pharmacology. 2022;65:102241-.

261. Stamp LK, Horne A, Mihov B, Drake J, Haslett J, Chapman P, et al. Predicting Gout Flares in People Starting Allopurinol Using the Start-Low Go-Slow Dose Escalation Strategy. Arthritis Care Res (Hoboken). 2024;76(10):1371-8.
262. Stewart S, Tallon A, Taylor WJ, Gaffo A, Dalbeth N. How flare prevention outcomes are reported in gout studies: A systematic review and content analysis of randomized controlled trials. Semin Arthritis Rheum. 2020;50(2):303-13.
263. Sutherland C, Gaffo AL. Investigating gout flares: beyond a definition. Curr Opin Rheumatol. 2024;36(4):309-13.
264. Vargas-Santos AB, Neogi T, da Rocha Castelar-Pinheiro G, Kapetanovic MC, Turkiewicz A. Cause-Specific Mortality in Gout: Novel Findings of Elevated Risk of Non-Cardiovascular-Related Deaths. Arthritis rheumatol. 2019;71(11):1935-42.
265. Lee DY, Moon JS, Jung I, Chung SM, Park SY, Yu JH, et al. Risk acceleration by gout on major adverse cardiovascular events and all-cause death in patients with diabetes and chronic kidney disease. Diabetes, obesity & metabolism. 2025;27(3):1554-63.
266. Alowais SA, Alghamdi SS, Alsuhebany N, Alqahtani T, Alshaya AI, Almohareb SN, et al. Revolutionizing healthcare: the role of artificial intelligence in clinical practice. BMC medical education. 2023;23(1):1-689.
267. Khurana D, Koli A, Khatter K, Singh S. Natural language processing: state of the art, current trends and challenges. Multimedia tools and applications. 2023;82(3):3713-44.
268. Myllyaho L, Raatikainen M, Männistö T, Mikkonen T, Nurminen JK. Systematic literature review of validation methods for AI systems. The Journal of systems and software. 2021;181:111050.
269. Brikman S, Serfaty L, Abuhasira R, Schlesinger N, Bieber A, Rappoport N. A machine learning-based prediction model for gout in hyperuricemics: a nationwide cohort study. Rheumatology (Oxford). 2024;63(9):2411-7.
270. Qi H, Lu J, Dalbeth N, Sun M, Liu Z, Ji X, et al. An Artificial Intelligence-Based Gout Management System Reduced Chronic Kidney Disease Incident and Improved Target Serum Urate Achievement. Rheumatology (Oxford, England). 2024.
271. Zheng C, Rashid N, Wu YL, Koblick R, Lin AT, Levy GD, et al. Using natural language processing and machine learning to identify gout flares from electronic clinical notes. Arthritis Care Res (Hoboken). 2014;66(11):1740-8.
272. Jatuworapruk K, Grainger R, Dalbeth N, Lertnawapan R, Hanvivadhanakul P, Towiwat P, et al. The GOUT-36 prediction rule for inpatient gout flare in people with comorbid gout: derivation and external validation. Rheumatology (Oxford). 2022;61(4):1658-62.
273. Stamp LK, Morillon MB, Taylor WJ, Dalbeth N, Singh JA, Lassere M, et al. Variability in the reporting of serum urate and flares in gout clinical trials: Need for minimum reporting requirements. Journal of Rheumatology. 2018;45(3):419-24.
274. Vivli. Vivli Center for Global Clinical Research Data 2025 [Available from: https://vivli.org/.
275. Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, et al. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract. 2018;27(6):501-7.
276. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012;64(10):1447-61.

Note: References contained within published papers are not included in the above list.

Appendices

Appendix 1: Supplementary appendix for the systematic review with network meta-analysis

Supplementary Materials

Supplement to:

Comparative risk of gout flares when initiating or escalating various urate-lowering therapy: a systematic review with network meta-analysis

Dorsa Maher, Emily Reeve, Ashley Hopkins, Jiun Ming Tan, Mahsa Tantiongco, Nagham Ailabouni, Richard Woodman, Lisa Stamp, David Bursill, Susanna Proudman, Michael Wiese

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- Full list of items sought for extraction
- Details of publication bias assessment
- Details of the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (ROB-2)

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Supplementary References

Supplementary Table 1: PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2-3 Supplementary Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 2 Supplementary Exhibit 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Exhibit 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2-3 Supplementary Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 2-3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3 Supplementary Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 3 Supplementary Methods
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3 Supplementary Methods
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 2-3

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 2-3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3 Supplementary Methods
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 3 Supplementary Table 4 and Exhibit 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 3-4 Supplementary Figures 1-4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 3 and 6 Supplementary Tables 3, 5-7 Supplementary Exhibits 3-6 Supplementary Figures 5-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 3-8 Supplementary Figure 1-4

Section and Topic	Item #	Checklist item	Location where item is reported
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 3-8 Figure 3 and 6 Supplementary Exhibits 5-9, Figures 5-25
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 8 Supplementary Exhibits 5, 7-8 Supplementary Figures 12-18
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 8 Supplementary Figures 19-25
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 8-9
	23b	Discuss any limitations of the evidence included in the review.	Page 9
	23c	Discuss any limitations of the review processes used.	Page 9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplementary Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Table 2: PRISMA NMA checklist

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***Page 1***
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***Page 1-2***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 2
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Page 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	***Page 2-3 Supplementary Methods***
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 2 Supplementary Exhibit 1

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Exhibit 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 2-3 Supplementary Methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 2-3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 2-3 Supplementary Methods
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***Page 3 Figure 2***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 3 Supplementary Methods
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	Page 2-3
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	Page 3
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**Page 3 Supplementary Methods**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment*	***N/A***

		network; and • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 3 Figure 1
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***Figure 2***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***Page 3-8***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 3-8 Supplementary Table 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Page 3-4 Supplementary Figures 1-4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***Page 3-8*** ***Figure 3 and 6*** ***Supplementary Exhibits 5-9, Figures 5-25***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***Page 3-8*** ***Figure 3 and 6*** ***Supplementary Exhibits 5-9, Figures 5-25***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	***Page 8*** ***Supplementary Exhibits 5, 7-8*** ***Supplementary Figures 12-18***
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 3 Supplementary Figures 1-4
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***Page 8*** ***Supplementary Exhibits 3-4***
DISCUSSION			

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Page 8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Page 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***Page 1***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplementary Exhibit 1: Search strategy

1. Ovid MEDLINE(R) ALL 1946 to November 08, 2021

1	exp Gout/
2	Hyperuricemia/
3	(gout* or hyperuric?emi* or antihyperuric?emi* or anti-hyperuric?emi* or gouty arthritis).ti,ab,kw.
4	1 or 2 or 3
5	(flare* or attack* or pain* or acute gout or gout flare or gout attack or acute gouty arthritis or acute gout attack or acute attack or acute flare or acute attack* of gout or attack* of gout or gouty attack or acute gouty attack or gouty inflammation or recurrent gout attacks or gouty flare or recurrent attacks or acute arthritis or acute gouty inflammation or acute gouty flare or attack* of gouty arthritis or flare of gout or MSU crystal induced inflammation or recurrent flares or acute attacks of gouty arthritis or acute episode of gout or acute inflammatory flare or acute episode or flare up).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	Allopurinol/
7	Febuxostat/
8	Probenecid/
9	Benzbromarone/
10	Sulfinpyrazone/
11	uricosuric agent/
12	(Allohexa? or allop?rin?? or allorin or allpargin or allural or apulonga or apurin or atisuril or bleminol or caplenal or capurate or cellidrin or embarin or foligan or hamarin or jenapurinol or lopurin or lysuron or milurit? or novopurol or pan quimica or progout or pureduct or purinol or remid or rimapurinol or roucol or suspendol or tipuric or uribenz or uridocid or uripurinol or urosin or urtias or xanthomax or xanturic or zygout or zyloprim or Zyloric or febuxostat or tei 6720 or tei6720 or uloric or benecid or benemid or benuryl or pro?cid or probecid or probenecid or acifugan or benzbromarone or besuric or desuric or narcaricin or urinorm or anturan? or apo sulfinpyrazone or aposulfinpyrazone or sul??inpyrazone or nusulfinpyrazone or sulfoxyphenylpyrazolidin or lesinurad or pegloticase or rasburicase or topiroxostat).ti,ab,kw.
13	(ULT or urate-lowering or urate lowering or uric-acid lowering or uric acid lowering or xanthine oxidase or xanthine oxidase inhibitor* or uricosuric* or recombinant uricase* or antigout agent or antiurolithiasis agent or uricosuric agent).ti,ab,kw.
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	Colchicine/
16	anti-inflammatory agents, non-steroidal/ or celecoxib/ or diclofenac/ or etoricoxib/ or ibuprofen/ or indomethacin/ or ketoprofen/ or ketorolac/ or mefenamic acid/ or meloxicam/ or naproxen/ or piroxicam/ or sulindac/
17	cyclooxygenase 2 inhibitors/ or celecoxib/
18	adrenal cortex hormones/ or glucocorticoids/ or dexamethasone/ or prednisolone/ or prednisone/

19	(canakinumab or rilonacept or interleukin 1 inhibitor* or celebrex or dichlofenal or diclonate p or diclophenac or dicrofenac or feloran or novapirina or orthofen or orthophen or ortofen or sodium diclofenac or voltaren or voltarol or arcoxia or brufen or ibumetin or motrin or nuprin or rufen or salprofen or amuno or indocid or indocin or indometacin or metindol or osmosin or alrheumat or alrheumum or benzoylhydratropic acid or orudis or profenid or contraflam or coslan or dysman or mefac or mefacit or mefenaminic acid or mefic or parkemed or pinalgesic or ponalar or ponalgic or ponmel or ponstan or ponstan forte or ponstel or ponsyl or pontal or Masflex or meloxicam or mobec or Mobic or mobicox or movalis or movicox or parocin or reumoxicam or uticox or aleve or anaprox or methoxypropiocin or naprosin or naprosyn or naproxen sodium or proxen or sodium naproxenate or synflex or feldene or aclin or apo sulin or apo-sulin or arthrobid or arthrocine or chibret or clinoril or copal or kenalin or klinoril or mk 231 or mk-231 or mk231or novo sundac or novo-sundac or nu sulindac or nu-sulindac or sulindac or sulindal or celebrex or sc 58635 or sc-58635 or sc58635 or corticoids or corticosteroids or decaject or decameth or decaspray or dexamethasone or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or di adreson f or di-adreson-f or diadresonf or predate or predonine or apo-prednisone or cortan or cortancyl or cutason or dacortin or decortin or decortisyl or dehydrocortisone or deltasone or encorton or encortone or enkortolon or kortancyl or liquid pred or meticorten or orasone or panafcort or panasol or predni tablinen or prednidib or predniment or prednison acsis or prednison galen or prednison hexal or prednisone or pronisone or rectodelt or sone or sterapred or ultracorten or winpred or delta-cortisone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
20	15 or 16 or 17 or 18 or 19
21	14 or 20
22	4 and 5 and 21
23	exp Adult/
24	(adult? or man or men or women or woman or middle-age? or middle age? or elder* or geriatric or old* people or old* person).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
25	23 or 24
26	22 and 25
27	limit 26 to english language
28	limit 27 to humans
29	limit 28 to animals
30	27 not 29
31	28 or 30

2. Ovid EMBASE Classic+Embase 1947 to November 08, 2021

1	exp gout/
2	hyperuricemia/
3	(gout* or hyperuric?emi* or antihyperuric?emi* or anti-hyperuric?emi* or gouty arthritis).ti,ab,kw.
4	1 or 2 or 3
5	(flare* or attack* or pain* or acute gout or gout flare or gout attack or acute gouty arthritis or acute gout attack or acute attack or acute flare or acute attack* of gout or attack* of gout or gouty attack or acute gouty attack or gouty inflammation or recurrent gout attacks or gouty flare or recurrent attacks or acute arthritis or acute gouty inflammation or acute gouty flare or attack* of gouty arthritis or flare of gout or MSU crystal induced inflammation or recurrent flares or acute attacks of gouty arthritis or acute episode of gout or acute inflammatory flare or acute episode or flare up).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6	allopurinol/
7	allopurinol plus benzbromarone/
8	allopurinol plus lesinurad/
9	febuxostat/
10	probenecid/
11	colchicine plus probenecid/
12	benzbromarone/
13	sulfinpyrazone/
14	lesinurad/
15	verinurad/
16	rasburicase/
17	pegloticase/
18	topiroxostat/
19	xanthine oxidase inhibitor/
20	uricosuric agent/
21	antigout agent/
22	antiurolithiasis agent/
23	(Allohexa? or allop?rin?? or allorin or allpargin or allural or apulonga or apurin or atisuril or bleminol or caplenal or capurate or cellidrin or embarin or foligan or hamarin or jenapurinol or lopurin or lysuron or milurit? or novopurol or pan quimica or progout or pureduct or purinol or remid or rimapurinol or roucol or suspendol or tipuric or uribenz or uridocid or uripurinol or urosin or urtias or xanthomax or xanturic or zygout or zyloprim or Zyloric or febuxostat or tei 6720 or tei6720 or uloric or benecid or benemid or benuryl or pro?cid or probecid or probenecid or acifugan or benzbromarone or besuric or desuric or narcaricin or urinorm or anturan? or apo sulfinpyrazone or aposulfinpyrazone or sul??inpyrazone or nusulfinpyrazone or sulfoxyphenylpyrazolidin or lesinurad or pegloticase or rasburicase or topiroxostat).ti,ab,kw.

24	(ULT or urate-lowering or urate lowering or uric-acid lowering or uric acid lowering or xanthine oxidase or xanthine oxidase inhibitor* or uricosuric* or recombinant uricase* or antigout agent or antiurolithiasis agent or uricosuric agent).ti,ab,kw.
25	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	colchicine/
27	nonsteroid antiinflammatory agent/
28	celecoxib/ or diclofenac/ or etoricoxib/ or ibuprofen/ or indometacin/ or ketoprofen/ or ketorolac/ or mefenamic acid/ or meloxicam/ or naproxen/ or piroxicam/ or sulindac/
29	cyclooxygenase 2 inhibitor/ or celecoxib/
30	corticosteroid/ or steroid hormone/ or glucocorticoid/
31	prednisolone/
32	dexamethasone/
33	prednisone/
34	canakinumab/
35	rilonacept/
36	recombinant interleukin 1 receptor blocking agent/
37	(canakinumab or rilonacept or interleukin 1 inhibitor* or celebrex or dichlofenal or diclonate p or diclophenac or dicrofenac or feloran or novapirina or orthofen or orthophen or ortofen or sodium diclofenac or voltaren or voltarol or arcoxia or brufen or ibumetin or motrin or nuprin or rufen or salprofen or amuno or indocid or indocin or indometacin or metindol or osmosin or alrheumat or alrheumum or benzoylhydratropic acid or orudis or profenid or contraflam or coslan or dysman or mefac or mefacit or mefenaminic acid or mefic or parkemed or pinalgesic or ponalar or ponalgic or ponmel or ponstan or ponstan forte or ponstel or ponsyl or pontal or Masflex or meloxicam or mobec or Mobic or mobicox or movalis or movicox or parocin or reumoxicam or uticox or aleve or anaprox or methoxypropiocin or naprosin or naprosyn or naproxen sodium or proxen or sodium naproxenate or synflex or feldene or aclin or apo sulin or apo-sulin or arthrobid or arthrocine or chibret or clinoril or copal or kenalin or klinoril or mk 231 or mk-231 or mk231or novo sundac or novo-sundac or nu sulindac or nu-sulindac or sulindac or sulindal or celebrex or sc 58635 or sc-58635 or sc58635 or corticoids or corticosteroids or decaject or decameth or decaspray or dexamethasone or dexasone or dexpak or hexadecadrol or hexadrol or maxidex or methylfluorprednisolone or millicorten or oradexon or di adreson f or di-adreson-f or diadresonf or predate or predonine or apo-prednisone or cortan or cortancyl or cutason or dacortin or decortin or decortisyl or dehydrocortisone or deltasone or encorton or encortone or enkortolon or kortancyl or liquid pred or meticorten or orasone or panafcort or panasol or predni tablinen or prednidib or predniment or prednison acsis or prednison galen or prednison hexal or prednisone or pronisone or rectodelt or sone or sterapred or ultracorten or winpred or delta-cortisone).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
38	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39	25 or 38

40	4 and 5 and 39
41	exp adult/
42	(adult? or man or men or women or woman or middle-age? or middle age? or elder* or geriatric or old* people or old* person).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
43	41 or 42
44	40 and 43
45	limit 44 to english language
46	limit 45 to humans
47	limit 46 to animals
48	45 not 47
49	46 or 48

3. Web of Science

ALL FIELDS: gout* OR hyperuric*emi* OR antihyperuric*emi* OR anti-hyperuric*emi* OR "gouty arthritis"

AND

ALL FIELDS: flare* OR attack* OR pain* OR "acute gout" OR "gout flare" OR "gout attack" OR "acute gouty arthritis" OR "acute gout attack" OR "acute attack" OR "acute flare" OR "acute attack* of gout" OR "attack* of gout" OR "gouty attack" OR "acute gouty attack" OR "gouty inflammation" OR "recurrent gout attacks" OR "gouty flare" OR "recurrent attacks" OR "acute arthritis" OR "acute gouty inflammation" OR "acute gouty flare" OR "attack* of gouty arthritis" OR "flare of gout" OR "MSU crystal induced inflammation" OR "recurrent flares" OR "acute attacks of gouty arthritis" OR "acute episode of gout" OR "acute inflammatory flare" OR "acute episode" OR "flare up"

AND

TOPIC: Allopurinol OR Febuxostat OR Probenecid OR Benzbromarone OR Sulfinpyrazone OR Allohexa* OR allop*rin** OR allorin OR allpargin OR allural OR apulonga OR apurin OR atisuril OR bleminol OR caplenal OR capurate OR cellidrin OR embarin OR foligan OR hamarin OR jenapurinol OR lopurin OR lysuron OR milurit* OR novopurol OR "pan quimica" OR progout OR pureduct OR purinol OR remid OR rimapurinol OR roucol OR suspendol OR tipuric OR uribenz OR uridocid OR uripurinol OR urosin OR urtias OR xanthomax OR xanturic OR zygout OR zyloprim OR Zyloric OR febuxostat OR tei6720 OR uloric OR benecid OR benemid OR benuryl OR pro*cid OR probecid OR probenecid OR acifugan OR benzbromarone OR besuric OR desuric OR narcaricin OR urinorm OR anturan* OR "apo sulfinpyrazone" OR aposulfinpyrazone OR sul**inpyrazone OR nusulfinpyrazone OR sulfoxyphenylpyrazolidin OR lesinurad OR verinurad OR pegloticase OR rasburicase OR topiroxostat OR ULT OR urate-lowering OR "urate lowering" OR "uric-acid lowering" OR "uric acid lowering" OR "xanthine oxidase" OR "xanthine oxidase inhibitor*" OR uricosuric* OR "recombinant uricase*" OR "antigout agent" OR "antiurolithiasis agent" OR "uricosuric agent" OR Colchicine OR "non-steroidal anti-inflammatory agent*" OR "non-steroidal anti-inflammatory drug*" OR NSAID* OR celecoxib OR diclofenac OR etoricoxib OR ibuprofen OR indomethacin OR ketoprofen OR ketorolac OR "mefenamic acid" OR meloxicam OR naproxen OR piroxicam OR sulindac OR "cyclooxygenase inhibitors" OR

celecoxib OR "adrenal cortex hormones" OR glucocorticoids OR dexamethasone OR prednisolone OR prednisone OR canakinumab OR rilonacept OR "interleukin inhibitor*"

4. Cochrane library and Cochrane Central Register of Controlled Trials

1	(ULT OR urate-lowering OR "urate lowering" OR "uric-acid lowering" OR "uric acid lowering" OR "xanthine oxidase" OR "xanthine oxidase inhibitor*" OR "uricosuric*" OR "recombinant uricase*" OR "antigout agent" OR "antiurolithiasis agent" OR "uricosuric agent" OR allopurinol OR febuxostat OR probenecid OR benzbromarone OR sulfinpyrazone OR lesinurad OR verinurad OR rasburicase OR pegloticase OR topiroxostat OR colchicine OR nsaid* OR "non-steroidal anti-inflammatory drug*" OR corticosteroid* OR canakinumab OR rilonacept OR "interleukin 1 inhibitor*"):ti,ab,kw AND (flare* OR attack* OR pain* OR "acute gout" OR "gout flare" OR "gout attack" OR "acute gouty arthritis" OR "acute gout attack" OR "acute attack" OR "acute flare" OR "acute attack* of gout" OR "attack* of gout" OR "gouty attack" OR "acute gouty attack" OR "gouty inflammation" OR "recurrent gout attacks" OR "gouty flare" OR "recurrent attacks" OR "acute arthritis" OR "acute gouty inflammation" OR "acute gouty flare" OR "attack* of gouty arthritis" OR "flare of gout" OR "MSU crystal induced inflammation" OR "recurrent flares" OR "acute attacks of gouty arthritis" OR "acute episode of gout" OR "acute inflammatory flare" OR "acute episode" OR "flare up") (Word variations have been searched)
2	MeSH descriptor: [Gout] explode all trees
3	#1 AND #2

5. Australian New Zealand Clinical Trials Register

Registry: ANZCTR

Health condition: Gout

Age group: Adult (18yrs and over)

Healthy volunteers: No

6. ClinicalTrials.gov

Condition = “GOUT”

7. EU Clinical Trials Register

(gout* OR hyperuric*emi* OR antihyperuric*emi* OR anti-hyperuric*emi* OR "gouty arthritis")

AND

(flare* OR attack* OR pain* OR "acute gout" OR "gout flare" OR "gout attack" OR "acute gouty arthritis" OR "acute gout attack" OR "acute attack" OR "acute flare" OR "acute attack* of gout" OR "attack* of gout" OR "gouty attack" OR "acute gouty attack" OR "gouty inflammation" OR "recurrent gout attacks" OR "gouty flare" OR "recurrent attacks" OR "acute arthritis" OR "acute gouty inflammation" OR "acute gouty flare" OR "attack* of gouty arthritis" OR "flare of gout" OR "MSU crystal induced inflammation" OR "recurrent flares" OR "acute attacks of gouty arthritis" OR "acute episode of gout" OR "acute inflammatory flare" OR "acute episode" OR "flare up")

AND

(ULT OR urate-lowering OR "urate lowering" OR "uric-acid lowering" OR "uric acid lowering" OR "xanthine oxidase" OR "xanthine oxidase inhibitor*" OR "uricosuric*" OR "recombinant uricase*" OR "antigout agent" OR "antiurolithiasis agent" OR "uricosuric agent" OR allopurinol OR febuxostat OR probenecid OR benzbromarone OR sulfinpyrazone OR lesinurad OR verinurad OR rasburicase OR pegloticase OR topiroxostat OR colchicine OR nsaid* OR "non-steroidal anti-inflammatory drug*" OR corticosteroid* OR canakinumab OR rilonacept OR "interleukin 1 inhibitor*")

8. Other

Title search from reference lists of key articles:

1. “Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities”
2. “Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout”
3. “Clinically Insignificant Effect of Supplemental Vitamin C on Serum Urate in Patients With Gout: A Pilot Randomized Controlled Trial”
4. “Comparison of two plasma urate assays in patients receiving vitamin C supplementation”
5. “Diabetes and gout: efficacy and safety of febuxostat and allopurinol”
6. “Effect of pegloticase on renal function in patients with chronic kidney disease: a post hoc subgroup analysis of 2 randomized, placebo-controlled, phase 3 clinical trials”
7. “Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout”
8. “Pegloticase Treatment Significantly Decreases Blood Pressure in Patients With Chronic Gout”
9. “Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in healthy subjects”
10. “Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients”
11. “Relationship Between Serum Urate and Plasma Oxypurinol in the Management of Gout: Determination of Minimum Plasma Oxypurinol Concentration to Achieve a Target Serum Urate Level”
12. “The efficacy of febuxostat and allopurinol in the treatment of gout with hyperuricemia”
13. “The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial”
14. “Tophus burden reduction with pegloticase: results from phase 3 randomized trials and open-label extension in patients with chronic gout refractory to conventional therapy”
15. “Treating hyperuricemia of gout: safety and efficacy of febuxostat and allopurinol in older versus younger subjects”
16. “Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment”

Supplementary Methods

Amendments from protocol

The review protocol has been registered on PROSPERO and is available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=178479

The following amendments were made to the protocol during the abstract/title screening phase of the review:

(1) The criteria for defining ULT initiation was updated to provide clarity for studies that did not explicitly state a washout period however were assumed to be initiating ULT.
    - **Previous criteria:** Participants had no ULT drug in the 1-week prior to commencing the study ULT drug.
    - **Updated criteria:** Participants had no ULT drug in the 1-week prior to commencing the study ULT drug. Studies that did not report on a washout period were included if the study authors explicitly stated or reasonably suggested that participants were initiating ULT for the first time.

(2) The criteria for defining ULT escalation was updated to provide clarity for studies that add an additional ULT drug as escalation rather than increasing the dose of the existing ULT drug
    - **Previous criteria:** Participants entering a study on a subtherapeutic dose of ULT (as defined by study authors) and during the study period their ULT dose was escalated with an aim to achieve a target dose, target SU concentration or a reduction in flares or other symptoms
    - **Updated criteria:** Participants entering a study on a subtherapeutic dose of ULT (as defined by study authors) and during the study period their ULT dose was escalated (or an additional ULT was commenced) with an aim to achieve a target dose, target SU concentration or a reduction in flares or other symptoms

(3) The protocol incorrectly stated that the comparator/control arm could include no comparator. The following amendment was made to the protocol:
    - **Previous criteria:** A different intervention as described above [referring to the Intervention/exposure section of the protocol], placebo, or no comparator
    - **Updated criteria:** A different intervention as described above [referring to the Intervention/exposure section of the protocol] or placebo

(4) The following exclusion criteria were added to the review
    - Phase 1 or 2 RCTs
        - **Rational:** During the title and abstract screening phase, we noticed that many of the phase 1 and 2 studies included ULT doses, protocols and treatment approaches that are not applicable to clinical practice. Phase 1 studies are also less likely to be published and therefore inclusion of the published studies may lead to publication bias (1).
    - Studies investigating ULT initiation during an active flare
        - **Rational:** The inclusion of these studies extended beyond the scope of this review

(5) The following outcome measure was added to the review
    - Total treatment related adverse events related to the prophylactic drug

- **Rational:** We had pre-specified study withdrawal due to adverse events, total adverse events and serious adverse events. We decided it was important to extract total treatment related adverse event data separately from total adverse events as it may provide additional information of prophylaxis related harms.

Full inclusion and exclusion criteria

Inclusion:

- Adult human population, aged 18 years or older
- Confirmed gout, as defined by meeting one of the following criteria:
    - 1977 American Rheumatism Association preliminary classification criteria for gout (2);
    - 2015 American College of Rheumatology / European League Against Rheumatism classification criteria for gout (3);
    - Confirmed MSU crystal positive synovial fluid aspirate; OR
    - Diagnosis of gout as described by the authors

(6) Initiating ULT or escalating the dose of subtherapeutic ULT, with or without concurrent administration of one or more flare prophylaxis drugs

- ULT was defined as any one or more of the following drugs – allopurinol, febuxostat, probenecid, benzbromarone, sulfinpyrazone, lesinurad (with either allopurinol or febuxostat), verinurad (with either allopurinol or febuxostat), rasburicase, pegloticase or topiroxostat
- Flare prophylaxis was defined as any one or more of the following drugs or drug classes reported by the authors as prophylactic use (i.e. not for treatment of a gout flare) – colchicine, NSAIDs (including selective cyclooxygenase II (COX-II) inhibitors), corticosteroids, or interleukin 1 (IL-1) inhibitors (canakinumab or rilonacept)
- Initiating ULT was defined as having no ULT drug in the 1-week prior to commencing the study ULT drug. Studies that did not report on a washout period were included if the study authors explicitly stated or reasonably suggested that participants were initiating ULT for the first time.
- Escalating the dose of subtherapeutic ULT was defined as participants entering a study on a subtherapeutic dose of ULT (as defined by study authors) and during the study period their ULT dose was escalated (or an additional ULT was commenced) with an aim to achieve a target dose, target SU concentration or a reduction in flares or other symptoms

Exclusion:

- Studies that did not report at least one primary outcome of interest (gout flares or prophylaxis-related adverse events)
- Studies designed solely to assess treatments for gout flares
- Studies investigating ULT initiation during an active flare
- Studies that did not report outcomes separately for the different ULT arms/groups (for flare outcomes)
- Studies that did not separate results for participants with gout and participants without gout
- Conference abstracts, studies performed solely using medication or administrative claims data, interrupted time series, case controlled, case series, cross-sectional studies, retrospective studies, narrative or systematic reviews, phase 1 or 2 randomised controlled trials, unpublished studies that did not have a final report available, and non-human studies.
- Studies not published in English

Full list of items sought for extraction

Study reference	Study outcome level for flares
Publication type	Serum urate target (if applicable)
Study title	Total number randomised
Year of publication	Age of participants
Country in which study conducted	Sex of participants
Clinical trial number	Race/ethnicity of participants
Study aim	Baseline serum urate concentration
Study design	Flare history
RCT phase (if applicable)	Tophus status
Number of study sites	Sub-groups measured
How ULT was allocated	Type of intervention
How/if prophylaxis was allocated	Washout period (if applicable)
Study start and end date	ULT drug, dose, frequency, route, duration and number of participants for each arm/group
Duration of follow up	Proportion of treatment naïve participants
Population of interest	Prophylactic drug, dose, frequency, route, duration and number of participants for each arm/group (if applicable)
Study setting	Gout flare treatment
Type of analysis	Frequency of observations
Inclusion criteria	Gout flares (frequency, severity/pain score, duration)
Exclusion criteria	Adverse events related to prophylaxis
Gout diagnosis criteria	Health-related quality of life
Flare definition criteria	Study funding sources

Details of publication bias assessment

Comparison-adjusted funnel plots were used to explore publication bias for all direct comparisons with treatments ordered by P-scores. We used Egger's regression test to assess asymmetry. However, the results of the Egger's test should be interpreted with caution as all of our networks included fewer than 10 studies (K <10) (4). When the number of studies is low, the statistical power of the Egger's test may not be sufficient to detect real asymmetry (4).

Details of the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (ROB-2)

We used the Revised Cochrane Risk-of-Bias Tool for Randomized trials (ROB-2) to access trial bias (5). It is structured into five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported results. Each domain includes signalling questions with response options of "Yes", "Probably yes", "Probably no", "No" and "No information". Based on responses to the signalling questions, each domain is judged as either "Low risk of bias", "Some concerns" or "High risk of bias". An overall risk of bias is determined for each trial based on the trials highest risk of bias score across the five domains. Two independent reviewers critically appraised each included study twice, using the ROB-2 tool: once for gout flares and once for adverse events related to prophylaxis. Discrepancies were resolved by consensus or through consensus with a senior reviewer (ER).

Supplementary Table 3: Summary of gout flare results

Reporting method and details, including duration of ULT and prophylaxis within each trial			Treatment groups (N)			P-value
FLARE PROPHYLAXIS BASED TRIALS						
Paulus 1974	**ULT: 6-months, Prophylaxis: 6-months**		**Probenecid + C (N=20)**	**Probenecid + PBO (N=18)**		**P-value**
Mean number of gout flares per patient	Per month, mean ± SD	All subjects	0.19 ± 0.05	0.48 ± 0.12		**<0.05**
		Subjects with SU conc. <6.5mg/dL	0.13 ± 0.06 (N=9)	0.49 ± 0.13 (N=9)		**<0.05**
Total number of gout flares	During whole study period		23 (over 109 months)	35 (over 94 months)		NR
Borstad 2004	**ULT: >3 months, Prophylaxis: >3 months**		**A + C (N=21)**	**A + PBO (N=22)**		**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, months 0-6, %		33	77		**0.008**
	≥ 2 gout flares, months 0-6, %		14	63		**0.004**
Mean number of gout flares per patient*	Months 0-3		0.6	1.9		**0.022**
	Months 3-6		0.03	1.05		**0.033**
	Months 0-6		0.5	2.9		**0.008**
Total number of gout flares	Months 0-6		12	65		NR
Severity of gout flare	Mean severity, measured by VAS		3.64	5.08		**0.018**
Duration of gout flare	Mean duration, days		6.0	5.56		0.566
Other	SU conc. in subjects that flared, mg/dL	At baseline	9.15	9.15		NR
		At 3-months	6.07	6.13		NR
	Change in SU conc. from baseline to 3-months	All participants	-			0.552
		Participants that had a flare	-			0.648
Karimzadeh 2006	**ULT: 12-months, Prophylaxis: variable duration**		**A + C3-6 (N=63)**	**A + C7-9 (N=62)**	**A + C10-12 (N=65)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, %	Months 0-6	46	11	6	NR
		Months 0-12	54	27.5	23	**<0.001 vs C3-6** 0.1 for C7-9 vs C10-12
Other	Time until gout flare recurrence, months, mean [95% CI]		8 [7-9]	11 [10-11]	11 [11-12]	**<0.001 vs C3-6** 0.09 for C7-9 vs C10-12
	Participants that flared vs had no flares	Mean SU conc.	-			NS
		Age	-			NS
Schumacher 2012	**ULT: 20-weeks , Prophylaxis: 16-weeks**		**A + R80 (N=80)**	**A + R160 (N=81)**	**A + PBO (N=79)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, weeks 0-16, %		18.8	16.3	46.8	**<0.001 vs PBO**
	≥ 2 gout flares, weeks 0-16, %		5.0	3.8	31.6	**<0.001 vs PBO**
	Either flare definition, ≥ 1 gout flare, weeks 0-16, %		25.0	23.5	54.4	**<0.001 vs PBO**
Mean number of gout flares per patient	Met flare definition of main analysis, mean	Weeks 0-4*	0.10	0.06	0.35	**<0.001 R160 vs PBO** **<0.002 R80 vs PBO**

		Weeks 0-8*	0.20	0.14	0.71	**<0.001 vs PBO**
		Weeks 0-12*	0.29	0.17	0.93	**<0.001 vs PBO**
		Weeks 0-16, mean [95% CI]	0.29 [0.12-0.46]	0.21 [0.09-0.33]	1.06 [0.71-1.42]	**<0.001 vs PBO**
	Met alternative flare definition, weeks 0-16, mean [95% CI]		0.40 [0.20-0.60]	0.28 [0.14-0.41]	1.19 [0.80-1.58]	NR
Total number of gout flares	Weeks 0-16		23	17	84	**<0.001 vs PBO**
	Weeks 16-20 (safety follow-up – only allopurinol continued)		8	11	14	NS
Severity of gout flare	Days per patient with pain severity score ≥5, mean [95% CI]		0.85 [0.00-1.72]	0.35 [0.06-0.64]	2.13 [1.41-2.84]	**<0.0001 vs PBO**
Duration of gout flare	Gout flare days per patient, mean [95% CI]		2.36 [0.00-4.89]	0.98 [0.32-1.63]	5.52 (3.34-7.70)	**<0.0001 vs PBO**
	Gout flare days per flare, mean ± SD		8.52 ± 17.99	5.12 ± 3.30	5.19 ± 5.54	NS
Other	Number needed to treat for a reduction of at least 1 gout flare		~ 2	~ 2	-	-
	Risk ratio [95% CI] for ≥ 1 flare compared to placebo		0.40 [0.24-0.67]	0.35 [0.20-0.60]	-	-
Mitha 2013	**ULT: 20-weeks, Prophylaxis: 16-weeks**		**A + R80 (N=82)**	**A + R160 (N=84)**	**A + PBO (N=82)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, weeks 0-16, %		25.6	20.5	56.1	**<0.0001 vs PBO**
	≥ 2 gout flare, weeks 0-16, %		8.5	6.0	32.9	**<0.001 vs PBO**
Mean number of gout flares per patient	Pre-specified exploratory analysis, mean ± SD	Week 1	NR	0.10 ± 0.3	0.22 ± 0.42	**<0.05**
		Week 2	0.18 ± 0.45	NR	0.46 ± 0.67	**<0.01**
	Weeks 0-16, mean [95% CI]		0.35 [0.21-0.50]	0.34 [0.15-0.52]	1.23 [0.89-1.58]	**<0.0001 vs PBO**
	That met alternative flare definition, mean [95% CI]		0.62 [0.33-0.91]	0.48 [0.27-0.70]	1.51 [1.10-1.92]	**≤0.0001 vs PBO**
Total number of gout flares	Cumulative number	Week 4	19	14	50	**<0.001 vs PBO**
		Week 8	25	21	75	**<0.001 vs PBO**
		Week 12	27	26	88	**<0.001 vs PBO**
		Week 16	29	28	101	**<0.001 vs PBO**
Severity of gout flare	Days per patient with pain severity score ≥5, mean [95% CI]		1.7 [0-3.5]	0.9 [0.3-1.5]	4.3 [2.6-6.0]	**<0.0001 vs PBO**
Duration of gout flare	Gout flare days per patient, mean [95% CI]		4.3 [0.5-8.1]	1.9 [0.6-3.1]	11.2 [6.6-15.8]	**<0.0001 vs PBO**
Other	Median time to first gout flare, days		Study could not determine		34	**<0.0001 (PBO was earlier than either R group)**
	Risk ratio [95% CI] for ≥ 1 flare compared to placebo		0.46 [0.30-0.69]	0.37 [0.23-0.58]	-	-
	Risk reduction for ≥ 1 flare compared to placebo, % [95% CI]		54.3 [30.8-69.9]	63.5 [41.9-77.1]	-	-
	Risk reduction for ≥ 2 flare compared to placebo, % [95% CI]		74.1 [43.8-88.0]	81.7 [54.8-92.6]	-	-
NCT01451645 (study unpublished)	**ULT: 16-weeks, Prophylaxis: 16-weeks**		**A + C (N=41)**		**A + PBO (N=41)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, weeks 0-16, % [95% CI]		24.4 [12.36-40.30]		43.9 [28.47-60.25]	NR
	≥ 2 gout flares, weeks 0-16, % [95% CI]		4.9 [0.60-16.53]		24.4 [12.36-40.30]	NR
Mean number of gout flares per patient	Weeks 0-16, mean ± SD		0.3 ± 0.56		1.1 ± 1.90	NR
Duration of gout flare	Gout flare days per patient, mean ± SD		1.6 ± 3.75		6.6 ± 13.20	NR
NCT01459796 (study terminated)	**ULT: 52-weeks, Prophylaxis: 52-weeks**		**A + R (N=126)**		**A + P (N=94)**	**P-value**

Other	Proportion of participants that required rescue medication after having ≥ 2 flares during the treatment period (unclear duration due to termination, possibly 0-51 weeks), %		8.7	22.3		NR
Yamanaka 2018	**ULT: 24-weeks, Prophylaxis: 12-weeks (one arm only)**		**Stepwise F (N=96)**	**F + C (N=95)**	**F (N=50)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, %	Weeks 0-12 ‡	20.8	18.9	36.0	**0.048 Stepwise F vs F** **0.024 F + C vs F** 0.744 Stepwise F vs F + C
		Weeks 0-12, no history of having ULT	16.9	18.8	35.3	No previous ULT vs previous ULT overall: 0.273 for Stepwise F 1.000 for F + C and F
		Weeks 0-12, previous history of having ULT	29.0	19.4	37.5	
		Weeks 0-24	31.3	29.5	38.0	-
	1 gout flare, %	Weeks 0-12	14.6	14.7	20.0	NR
		Weeks 13-24	12.5	10.5	10.0	NR
		Weeks 0-24	19.8	15.8	16.0	NR
	2 gout flares, %	Weeks 0-12	5.2	3.2	6.0	NR
		Weeks 13-24	3.1	5.3	0.0	NR
		Weeks 0-24	7.3	6.3	10.0	NR
	≥3 gout flares, %	Weeks 0-12	1.0	1.1	10.0	NR
		Weeks 13-24	0.0	2.1	2.0	NR
		Weeks 0-24	4.2	7.4	12.0	NR
Mean number of gout flares per patient	Weeks 0-12		1.35	1.33	2.06	NS vs F
	Weeks 13-24		1.20	1.53	1.33	NS
	Weeks 0-24		1.50	1.79	2.37	NR
Total number of gout flares	Weeks 0-12		27	24	37	NS vs F
	Weeks 13-24		18	26	8	NS
	Weeks 0-24		45	59	45	NR
URATE-LOWERING THERAPY BASED TRIALS						
Becker 2005	**ULT: 52-weeks, Prophylaxis: 8-weeks**		**F80 (N=256)**	**F120 (N=251)**	**A (N=253)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, %	Weeks 0-8	22	36	21	**<0.001 F120 vs F80 or A**
		Weeks 9-52	64	70	64	NR
		Weeks 0-4 *	15	22	13	NR
		Weeks 5-8 *	10	25	12	NR
		Weeks 9-12 *	36	43	32	NR
		Weeks 13-16 *	33	26	23	NR

		Weeks 17-20 *	25	28	20		NR
		Weeks 21-24 *	21	21	19		NR
		Weeks 25-28 *	15	22	16		NR
		Weeks 29-32 *	18	10	16		NR
		Weeks 33-36 *	13	14	13		NR
		Weeks 37-40 *	13	7	12		NR
		Weeks 41-44 *	10	11	12		NR
		Weeks 45-48 *	9	7	11		NR
		Weeks 49-52	8	6	11		NR
		Weeks 49-52, where mean post-baseline SU <6.0mg/dL †	6				0.005
		Weeks 49-52, where mean post-baseline SU >6.0mg/dL †	14				
Schumacher 2008	**ULT: 28-weeks, Prophylaxis: 8-weeks**		**F80 (N=267)**	**F120 (N=269)**	**F240 (N=134)**	**A (N=268)**	**PBO (N=134)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, %	Weeks 0-8	28	36	46	23	20	**≤0.05 for F120 or F240 vs F80, A or PBO**
		Weeks 8-28	NR	NR	NR	NR	NR	NS
Reinders 2009	**ULT: 4-months, Prophylaxis: until SU target reached**		**A (N=30)**		**B (N=25)**			**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, months 0-4, %		0		4			NR
Becker 2010	**ULT: 6-months, Prophylaxis: 6-months**		**F40 (N=757)**		**F80 (N=756)**	**A (N=755)**		**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, with no prior participation in the open-label ULT extension trials, % *	-	N=659		N=668	N=665		**≤0.001 in each treatment group compared to subjects in the corresponding group without prior participation in the open-label ULT extension trials**
		Weeks 1-<4	12		13	11		
		Weeks 4-<8	13		14	8		
		Weeks 8-<12	7		9	9		
		Weeks 12-<16	8		9	6		
		Weeks 16-<20	8		8	4		
		Weeks 20-<24	7		7	5		
		Weeks 24-<28	4		6	4		
	≥ 1 gout flare, with prior participation in the open-label ULT extension trials, % *	-	N=98		N=88	N=90		
		Weeks 1-<4	0		1	1		
		Weeks 4-<8	0		3	0		
		Weeks 8-<12	2		0	1		
		Weeks 12-<16	1		0	0		
		Weeks 16-<20	1		0	0		
		Weeks 20-<24	0		0	0		
		Weeks 24-<28	0		0	0		
Jackson 2012	**ULT: 6-months, Prophylaxis: 6-months**		**F40 (N=115)**		**F80 (N=128)**	**A (N=131)**		**P-value**

Proportion of patients with gout flares	≥ 1 gout flare, in participants ≥65 years of age, % †	Weeks 0-8	16.5	18.0	4.6	**≤0.05 vs A**
		Weeks 20-28	9.5	6.6	0.9	**≤0.05 F40 vs A**
Sundy 2011	**ULT: 6-months, Prophylaxis: 6-months**		**Pg biweekly (N=85)**	**Pg monthly (N=84)**	**PBO (N=43)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, % [95% CI]	Months 1-3	75 [65-84]	81 [71-89]	53 [38-69]	**0.02 Pg biweekly vs PBO** **0.002 Pg monthly vs PBO**
		Months 4-6	41 [29-53]	57 [44-68]	67 [51-81]	**0.007 Pg biweekly vs PBO** 0.32 Pg monthly vs PBO
		Overall (reported as a treatment-emergent adverse event)	76	85	81	NR
Mean number of gout flares per patient	Mean ± SD, [95% CI]	Months 1-3	2.3 ± 2.1, [1.8-2.7]	2.7 ± 2.4, [2.2-3.2]	1.2 ± 1.6, [0.7-1.7]	**0.001 Pg biweekly vs PBO** ≤0.001 Pg monthly vs PBO
		Months 4-6	0.8 ± 1.2, [0.5-1.1]	1.5 ± 2.0, [1.1-2.0]	1.3 ± 1.5, [0.8-1.7]	**0.06 Pg vs PBO biweekly** 0.45 Pg monthly vs PBO
Huang 2014	**ULT: 28-weeks, Prophylaxis: 8-weeks**		**F40 (N=172)**	**F80 (N=172)**	**A (N=172)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, weeks 9-28, %		5.23	4.07	9.30	0.6086 F40 vs F80 0.0521 F80 vs A 0.1460 A vs F40
Xu 2015	**ULT: 24-weeks, Prophylaxis: 24-weeks**		**F40 (N=160)**	**F80 (N=158)**	**A (N=159)**	**P-value**
Proportion of patients with gout flares*	≥ 1 gout flare, %	Weeks 1-<4	14.4	17.0	18.3	>0.05
		Weeks 4-<8	9.7	16.8	12.5	>0.05
		Weeks 8-<12	8.6	9.2	16.2	>0.05
		Weeks 12-<16	8.1	10.5	7.9	>0.05
		Weeks 16-<20	6.7	7.3	5.7	>0.05
		Weeks 20-<24	6.0	5.3	6.4	>0.05
Yu 2016	**ULT: 12-weeks, Prophylaxis: 12-weeks**		**F (N=54)**		**A (N=55)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, weeks 0-12, %		40.7		34.6	0.556
Bardin 2017	**ULT: 12-months, Prophylaxis: 5-months**		**A + L200 (N=204)**	**A + L400 (N=200)**	**A + PBO (N=206)**	**P-value**
Proportion of patients with gout flares*	≥ 1 gout flare, %	Months 0-<1	14	18	12	NR
		Months 1-<2	12	19.5	7.5	NR
		Months 2-<3	7.5	12.5	13	NR

		Months 3-<4	12	12.5	8	NR
		Months 4-<5	12	12.5	9	NR
		Months 5-<6	10	12	11	NR
		Months 6-<7	14	12	17	NR
		Months 7-<8	11.5	10	12	NR
		Months 8-<9	9	11	13	NR
		Months 9-<10	10.5	12	9.5	NR
		Months 10-<11	11	8	8	NR
		Months 11-<12	8.5	4.5	7	NR
Mean number of gout flares per patient	Months 7-12, mean ± SD		0.73 ± 0.12	0.77 ± 0.13	0.83 ± 0.13	0.57 A + L200 vs A + PBO 0.75 L400 vs A + PBO
Dalbeth 2017	**ULT: 12-months, Prophylaxis: 5-months**		**F + L2 (N=106)**	**F + L4 (N=109)**	**F + PBO (N=109)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, %	End of month 1	25.5	35.8	17.4	NR
		End of month 11 to end of month 12	10.1	6.0	9.2	NR
Mean number of gout flares per patient	Months 7-12, mean ± SD		1.4 ± 2.5	0.7 ± 1.2	1.2 ± 2.7	0.55 F + L2 vs F + PBO **0.04 F + L4 vs F + PBO**
Saag 2017	**ULT: 52-weeks, Prophylaxis: 5-months**		**A + L200 (N=201)**	**A + L400 (N=201)**	**A + PBO (N=201)**	**P-value**
Mean number of gout flares per patient	Months 7-12, mean ± SD		0.57 ± 0.10	0.51 ± 0.09	0.58 ± 0.10	0.98 A + L2 vs PBO 0.61 A + L4 vs PBO
Other	"Notably, discontinuation of prophylaxis at month 5 was not followed by an increase in the rate of gout flares requiring treatment in the lesinurad groups compared with the allopurinol-alone group."					
Stamp 2017	**ULT: 12-months, Prophylaxis: up to 12-months**		**A DE (n=90)**	**A control (N=93)**		**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, %	Months 0-12	54	59		0.58
		Months 0-3*	50	54		NR
		Months 4-6*	51	57		NR
		Months 7-9*	52	49		NR
		Months 10-12*	48	50		NR
Zhang 2017	**ULT: 6-months, Prophylaxis: none**		**F (N=31)**	**A (N=15)**		**P-value**
Mean number of gout flares per patient	Months 0-6, mean ± SD		3.3 ± 3.2	3.3 ± 2.8		0.81
Wang 2018	**ULT: 6-months, Prophylaxis: use not reported**		**F (N=80)**	**A (N=80)**		**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, months 0-6, %		3.75	12.5		**<0.05**
White 2018	**ULT: unclear, median of 2-years, Prophylaxis: 6-months**		**F (N=3098)**	**A (N=3092)**		**P-value**
Mean number of gout flares per patient	Rates of gout flare per patient-year		0.68	0.63		NR
Hao 2019	**ULT: 3-months, Prophylaxis: 3-months**		**F (N=40)**	**A (N=40)**		**P-value**
Mean number of gout flares per patient	Mean ± SD	At 1-week	1.3 ± 0.2	2.3 ± 0.1		**<0.001**
		At 1-month	1.1 ± 0.1	1.8 ± 0.1		**<0.001**
		At 3-months	0.9 ± 0.1	1.5 ± 0.2		**<0.001**

Liang 2019	**ULT: 12-weeks, Prophylaxis: none**		**F (N=105)**			**B (N=109)**		**P-value**
Proportion of patients with gout flares	Weeks 0-12, %	1 gout flare	16.19			23.85		NR
		≥ 1 gout flare	22.85			33.94		>0.05
		2 gout flares	4.76			10.09		NR
		≥ 2 gout flare	6.66			10.09		>0.05
		≥ 3 gout flares	1.9			0		NR
Saag 2019	**ULT: 3-months, Prophylaxis: 3-months**		**F40 IR (N=357)**	**F40 XR (N=355)**	**F80 IR (N=357)**	**F80 XR (N=357)**	**PBO (N=357)**	**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, months 0-3, %	All participants	21.0	22.8	27.2	26.6	20.7	NS
		Severely impaired renal function (n=100)	8.7	14.3	15.0	33.3	11.1	NS
		Moderately impaired renal function (n=483)	27.5	26.9	26.4	33.0	20.4	NS
		Mildly impaired renal function (n=965)	20.3	18.9	28.6	23.7	18.6	**<0.05 F80 IR vs PBO**
		Normal renal function (n=235)	17.6	35.6	28.3	22.0	32.7	NS
Desideri 2021	**ULT: 36-weeks, Prophylaxis: duration unclear**		**F (N=98)**			**A (N=98)**		**P-value**
Proportion of patients with gout flares	≥ 1 gout flare, weeks 0-36, %	Defined as a "treatment-emergent adverse event"	10.2			15.3		NR
		Defined as a "treatment-related adverse event"	6.1			8.2		NR

Treatment groups: A = allopurinol, B = benzbromarone, F = febuxostat, L = lesinurad, Pg = pegloticase, PBO = placebo, R = rilonacept

Footnote: CI = confidence interval, conc. = concentration, DE = dose escalation , IR = immediate release, NR = not reported, NS = not significant, SD = standard deviation, SU = serum urate, ULT = urate lowering therapy, VAS = visual analogue scale, XR = extended release

NOTE: * Result estimated from figure, † Results from post hoc analyses, ‡ In this trial, the flare rate from weeks 0-12 was used in the network meta-analysis instead of data from the longest available time period from time zero (weeks 0-24) as prophylaxis was given from week 0-12. Wortman 2010 has been omitted from this table as the flare data was unsuitable for inclusion (cannot separated flare results for the different urate-lowering therapies or from placebo).

Supplementary Table 4: Summary of characteristics of studies included in the systematic review

Trial design	Treatment groups (method of allocation), treatment duration, number of participants	Notable inclusion/exclusion criteria	Country	No. sites	Age (Mean ± SD or as specified)	Sex (% male)	Race (% white)	Baseline SU (Mean ± SD) (mg/dL)	Flare rate prior to study	Tophaceous gout (%)
FLARE PROPHYLAXIS BASED TRIALS										
Paulus 1974										
Double-blind, placebo-controlled trial	**ULT (all participants), 6-months:** Probenecid 500mg three times a day **NOTE:** at one study site, participants were stabilized on probenecid for 2-weeks before randomisation, while the other site had a 2-week washout from all ULT **Prophylaxis (randomised), 6-months:** **G1**: Colchicine 0.5mg three times a day (N= 29 (20 analysed)) **G2:** Placebo three times a day (N= 23 (18 analysed))	**Inclusion:** males with a SU conc. >7.5mg/dL. History of typical gout flares that respond promptly to intensive colchicine therapy **Exclusion:** SeCr >1.2mg/dL	United States	2	Mean (range) **G1:** 53 (34-77) **G2:** 52 (43-73)	100	NR	**G1:** 8.4±0.4 **G2:** 9.2±0.6	Mean ± SD (prior year) **G1:** 4.2±1.1 **G2:** 3.2±0.4	**G1:** 15.0 **G2:** 22.2
Borstad 2004										
Double-blind, placebo-controlled trial	**ULT (all participants), 3 months post attaining SU of <6.5mg/dL (6-month study):** Allopurinol 100mg once daily initially increased by 50-100mg increments (depending on renal function) every 2-3 weeks, until a SU conc. of <6.5mg/dL attained **Prophylaxis (randomised), 3 months post attaining SU of <6.5mg/dL (6-month study):** **G1:** Colchicine 0.6mg twice a day (N=21) **G2:** Placebo twice a day (N=22) **NOTE:** dosed once daily in participants with chronic renal insufficiency or reduced to once daily in the event of gastrointestinal side effects	**Inclusion:** (unclear) possibly presence of tophi and/or frequent flares (≥3 flares/year) **Exclusion:** aged <19 years. CrCl <20ml/min	United States	1	Mean 63	86	G1: 67 G2: 73	Mean **G1:** 9.49 **G2:** 9.15	Mean (prior year) **G1:** 2.48 **G2:** 2.09	**G1:** 62 **G2:** 64
Karimzadeh 2006										
Open-label, duration-ranging study	**ULT (all participants), duration unclear (possibly 12-months):** Allopurinol (dose and frequency not reported) **Prophylaxis (duration randomised), see durations below:** **G1:** Colchicine 1mg daily for 3-6 months (N=63) **G2:** Colchicine 1mg daily for 7-9 months (N=62) **G3:** Colchicine 1mg daily for 10-12 months (N=65)	**Inclusion:** greater than one year post gout diagnosis	Iran	1	46.6 ± 8.1	96.3	NR	Mean 8.5	NR	NR
Schumacher 2012										

Phase III, double-blind, placebo-controlled trial (PRESURGE-1)	**ULT (all participants), 20-weeks (including 4-week safety follow up):** Allopurinol 300mg once daily initially (or lower in renal impairment), increased by 50-100mg increments (depending on renal function) every 2-weeks up to a maximum daily dose of 800mg to achieve a SU conc. of <6mg/dL **Prophylaxis (randomised), 16-weeks:** **G1:** Rilonacept 160mg SC loading dose on day 1, then 80mg SC weekly (N=80) **G2:** Rilonacept 320mg SC loading dose on day 1, then 160mg SC weekly (N=81) **G3:** Placebo SC weekly (N=79)	**Inclusion:** ages 18-80 years. SU ≥7.5mg/dL and frequent flares (≥2 flares in the past year) **Exclusion:** chronic active gouty arthritis. eGFR <30ml/min/1.73m^2	United States and Canada	64	52.3 ± 12.6	92.9	80.4	**G1:** 9.03±1.24 **G2:** 9.07±1.23 **G3:** 9.42±1.35	Mean ± SD (per year) **G1:** 4.6±2.9 **G2**: 4.5±3.6 **G3:** 4.6±3.6	**G1:** 12.5 **G2:** 9.9 **G3:** 10.1
Mitha 2013										
Phase III, double-blind, placebo-controlled trial (PRESURGE-2)	**ULT (all participants), 20-weeks (including 4-week safety follow up):** Allopurinol 300mg once daily initially, titrated every 2-weeks, as needed, up to a maximum of 800mg per day to achieve a SU conc. of <6mg/dL (starting dose and titration increment were adjusted for renal impairment) **Prophylaxis (randomised), 16-weeks:** **G1:** Rilonacept 160mg SC loading dose on day 1, then 80mg SC weekly (N=82) **G2:** Rilonacept 320mg SC loading dose on day 1, then 160mg SC weekly (N=84) **G3:** Placebo SC weekly (N=82)	**Inclusion:** ages 18-79 years. SU ≥7.5mg/dL and frequent flares (≥2 flares in the past year)	Germany, India, Indonesia, Republic of South Africa and Taiwan	57	51.1 ± 12.1	93.1	53.2	**G1:** 9.4±1.5 **G2:** 9.5±1.5 **G3:** 9.4±1.4	Mean (per year) **G1:** 6.8±5.4 **G2:** 7.0±5.7 **G3:** 7.1±6.9	**G1:** 25.0 **G2:** 25.6 **G3:** 22.0
NCT01451645 (study unpublished)										
Phase IV, double-blind, placebo-controlled trial	**ULT (all participants), 16-weeks:** Allopurinol (dose and frequency not reported) **Prophylaxis (randomised), 16-weeks:** **G1:** Colchicine 0.6mg daily (N=41) **G2:** Placebo daily (N=41)	**Inclusion:** ages 18-70 years. Tophi present and/or a history of flares in 2 or 3 joints. SU ≥7.5mg/dL and frequent flares (≥2 flares in the past year). **Exclusion:** >3 gout affected joints	United States	20	90.2% were aged 18-65 years and 9.8% were aged ≥65 years	91.5	NR	NR	NR	NR
NCT01459796 (study prematurely terminated at sponsors discretion)										

Phase III, double-blind, placebo-controlled trial	**ULT (all participants), 52-weeks:** Allopurinol 50 or 100mg daily **Prophylaxis (randomised), 52 weeks:** **G1:** Rilonacept 160mg SC loading dose on day 1, then 80mg SC weekly (N=126 (0 completed)) **G2:** Placebo SC weekly (N=94 (0 completed))	**Inclusion:** ages 18-80 years. SU ≥7.5mg/dL and frequent flares (≥2 flares in the past year).	United States	60	51.9 ± 10.95	89.5	73.6	NR	NR	NR
Yamanaka 2018										
Open-label, comparative study (FORTUNE-1)	**ULT +/- prophylaxis (randomised), 24-weeks:** **G1:** Febuxostat 10mg daily for 4-weeks, then 20mg daily for 4-weeks, then 40mg daily for 16-weeks (N=96) **G2:** Febuxostat 40mg daily + colchicine 0.5mg daily for 12 weeks, then Febuxostat 40mg daily for 12 weeks (N=95) **G3:** Febuxostat 40mg daily for 24-weeks (N=50)	**Inclusion:** males with SU >7.0mg/dL and had flare in the past year. **Exclusion:** aged <20 years. SeCr ≥2.0mg/dL	Japan	24	**G1:** 47.4 ± 10.5 **G2:** 47.6 ± 11.1 **G3:** 46.4 ± 12.7	100	NR	**G1:** 8.67±1.38 **G2:** 8.51±1.19 **G3:** 8.57±1.17	History of ≥2 flares (%) **G1:** 77.1 **G2:** 73.7 **G3:** 76.0	NR
URATE-LOWERING THERAPY BASED TRIALS										
Becker 2005										
Phase III, double-blind, active-comparator trial (FACT)	**ULT (randomised), 52-weeks:** **G1:** Febuxostat 80mg once daily (N=256) **G2:** Febuxostat 120mg once daily (N=251) **G3:** Allopurinol 300mg once daily (N=253) **Prophylaxis (investigator discretion), initiated during washout and first 8-weeks:** Colchicine 0.6mg once daily (N=NR) or naproxen 250mg twice daily (N=NR)	**Inclusion:** ages 18-85 years. SU ≥8.0mg/dL **Exclusion:** eCrCl of <50ml/min/1.73m^2	United States and Canada	112	51.8 ± 12.1	96	77	9.84 ± 1.25	NR	24
Schumacher 2008										
Phase III, double-blind, active- and placebo-controlled trial (APEX)	**ULT (randomised), 28-weeks:** **G1:** Febuxostat 80mg once daily (N=267) **G2:** Febuxostat 120mg once daily (N=269) **G3:** Febuxostat 240mg once daily (N=134) **G4:** Allopurinol 100 or 300mg once daily (based on renal function) (N=268) **G5:** Placebo once daily (N=134) **Prophylaxis (investigator discretion), initiated during washout and first 8-weeks:** Colchicine 0.6mg once daily (N=NR) or naproxen 250mg twice daily (N=NR)	**Inclusion:** ages 18-85 years. SU ≥8.0mg/dL. CrCl >20ml/min	United States	167	**G1:** 51 ± 12 **G2:** 51 ± 12 **G3:** 54 ± 13 **G4:** 52 ± 12 **G5:** 52 ± 12	94	78	9.85 ± 1.26	NR	**G1:** 24 **G2:** 30 **G3:** 27 **G4:** 28 **G5:** 33

	NOTE: colchicine recommended if serum creatinine was >1.5mg/dL									
Reinders 2009										
Open-label, active-comparator study	**<u>ULT (randomised), 4-months:</u>** **G1:** Allopurinol in a step-up dose scheme (100 to 200 to 300mg/day, dose raised every week). If tolerated but SU target ≤5.0mg/dL not reached by 2-months, dose increased to 300mg twice a day (N=36 (30 analysed)) **G2:** Benzbromarone 100mg once daily, increasing to 200mg once a day if tolerated but SU target ≤5.0mg/dL not reached by 2-months (N=29 (25 analysed)) **<u>Prophylaxis (colchicine tolerance), until target SU (≤5.0mg/dL) reached:</u>** Colchicine 0.5-1mg daily (N=NR) or non-specified NSAID (N=NR)	**Inclusion:** CrCl ≥50ml/min, presence of tophi or frequent flares (>2/year)	The Netherlands	3	**G1:** 58.6 ± 12.3 **G2:** 59.6 ± 11.3	**G1:** 81 **G2:** 83	NR	**G1:** 9.08±1.51 **G2:** 8.57±1.34	% with >2 flares/year **G1:** 81 **G2:** 83	**G1:** 53 **G2:** 48
Becker 2010										
Phase III, double-blind, active-comparator trial (CONFIRMS)	**<u>ULT (randomised), 6-months:</u>** **G1:** Febuxostat 40mg once daily (N=757) **G2:** Febuxostat 80mg once daily (N=756) **G3:** Allopurinol 200 or 300mg once daily (based on renal function) (N=755) **<u>Prophylaxis (investigator discretion), during washout and then 6-months:</u>** Colchicine 0.6mg once daily (N=NR) or naproxen 250mg twice daily (N=NR) **NOTE:** Some participants received other prophylaxis (prednisone or other NSAID). Participants with eCrCl of <50ml/min were not to receive naproxen. Naproxen co-administered with lansoprazole 15mg daily	**Inclusion:** ages 18-85 years. SU ≥8.0mg/dL **Exclusion:** eCrCl of <30ml/min	United States	324	**G1:** 52.5 ± 11.68 **G2:** 53.0 ± 11.79 **G3:** 52.9 ± 11.73	94	82	**G1:** 9.6±1.15 **G2:** 9.6±1.20 **G3:** 9.5±1.19	NR	NR
Jackson 2012										
Post-hoc analysis	Post-hoc analysis of the CONFIRMS trial in participants aged ≥65 years of age **<u>Description as above in the CONFIRMS trial:</u>** **G1:** N=115 **G2:** N=128 **G3:** N=131 **Colchicine:** 83.7% **Naproxen:** 10.4% **Other prophylaxis:** 5.9%	-	-	-	**Mean** 71	85.8	84.8	**G1:** 9.4±1.14 **G2:** 9.5±1.17 **G3:** 9.3±1.04	NR	**G1:** 19.1 **G2:** 18.8 **G3:** 19.8
Wortmann 2010										

Post-hoc analysis	Analysis of data from three, phase III, double-blind studies (FACT, APEX and CONFIRMS) **Refer to each individual study for full details** **Prophylaxis:** Colchicine (54.7% in FACT trial, 53.8% in APEX trial, 79.6% in CONFIRMS trial) or naproxen (44.6% in FACT trial, 45.7% in APEX trial, 15.2% in CONFIRMS trial) or other prophylaxis (5.1% in CONFIRMS trial) or no prophylaxis (<1% in both the FACT and APEX trials) **NOTE:** In CONFIRMS trial, naproxen co-administered with lansoprazole 15mg daily	-	-	-	NR	94.5	80.1	-	-	**CONFIRMS trial:** 21.1
Sundy 2011										
Two identical phase III, double-blind, placebo-controlled trials (Trial C0405 and C0406)	**ULT (randomised), 6-months:** **G1:** Pegloticase 8mg SC 2-weekly (N=85 (Trial C0405=43 and Trial C0406=42)) **G2:** Pegloticase 8mg alternating with placebo SC 2-weekly (N=84 (Trial C0405=41 and Trial C0406=43)) **G3:** Placebo SC 2-weekly (N=43 (Trial C0405=20 and Trial C0406=23)) **Prophylaxis (investigator discretion), initiated week -1 and then 6-months:** Colchicine 0.6mg once or twice daily (N=NR) or non-specified NSAID (N=NR)	**Inclusion:** aged >18 years. SU ≥8.0mg/dL and symptomatic gout (frequent flares (≥3 flares in the past 18 months) or tophi or gouty arthropathy). Conventional therapy is contraindicated or has been ineffective.	United States, Canada and Mexico	56	**Trial C0405:** **G1:** 58.2 ± 15 **G2:** 55.1 ± 13 **G3:** 57.2 ± 13	**G1:** 69.8 **G2:** 85.4 **G3:** 75.0	**G1:** 74.4 **G2:** 78.0 **G3:** 70.0	**G1:** 9.8±1.6 **G2:** 10.4±1.8 **G3:** 9.4±1.6	Unclear	**G1:** 67.4 **G2:** 75.6 **G3**: 70.0
					Trial C0406: **G1:** 54.3 ± 16 **G2:** 53.9 ± 14 **G3:** 53.8 ± 11	**G1:** 91.5 **G2:** 79.1 **G3:** 91.3	**G1:** 52.4 **G2:** 62.8 **G3:** 69.6	**G1:** 9.5±1.7 **G2:** 9.6±1.7 **G3:** 9.8±1.6	Unclear	**G1:** 78.6 **G2:** 76.7 **G3:** 65.2
Huang 2014										
Double-blind, active-comparator study	**ULT (randomised), 28-weeks :** **G1:** Febuxostat 40mg once daily (N=172) **G2:** Febuxostat 80mg once daily (N=172) **G3:** Allopurinol 300mg once daily (N=172) **Prophylaxis (method of allocation NR), initiated during washout and first 8-weeks:** Colchicine 0.5mg once daily (N=NR) or meloxicam 7.5mg once daily (N=NR)	**Inclusion:** aged 18-70 years. SU ≥8.0mg/dL.	China	14	**G1:** 46.42 ± 10.90 **G2:** 47.40 ± 11.18 **G3:** 46.17 ± 11.56	**G1:** 97.1 **G2:** 98.3 **G3:** 97.7	0	**G1:** 9.89±1.36 **G2:** 9.98±1.39 **G3:** 9.95±1.35	NR	NR
Xu 2015										
Phase III, double-	**ULT (randomised), 24-weeks:** **G1:** Febuxostat 40mg once daily (N=168 (160 analysed)) **G2:** Febuxostat 80mg once daily (N=168 (158 analysed))	**Inclusion:** aged 18-70 years. SU ≥8.0mg/dL	China	13	**G1:** 45.5 ± 11.9 **G2:** 48.2 ± 12.0 **G3:** 46.6 ± 10.7	**G1:** 98.8	0	**G1:** 9.43±1.23	NR	**G1:** 15.0 **G2:** 16.5 **G3:** 16.4

blind, active-comparator study	**G3:** Allopurinol 300mg once daily (N=168 (159 analysed)) **<u>Prophylaxis (all participants), 24-weeks:</u>** Ibuprofen 200mg twice daily					**G2:** 92.4 **G3:** 93.7 (P=0.024)		**G2:** 9.50±1.27 **G3:** 9.65±1.31		
Yu 2016										
Phase IIIb, open-label, active-comparator study	**<u>ULT (randomised), 12-weeks:</u>** **G1:** Febuxostat 80mg once daily (N=54) **G2:** Allopurinol 300mg once daily (N=55) **<u>Prophylaxis (all participants), initiated during washout and then 12-weeks:</u>** Colchicine 0.5mg twice daily	**Inclusion:** aged 20-65 years. SU ≥8.0mg/dL if not taking ULT at screening **Exclusion:** presence of the HLA-B*5801 allele	Taiwan	6	**G1:** 46.0 ± 11.0 **G2:** 45.2 ± 12.0	**G1:** 98.1 **G2:** 96.4	0	% with SU ≥9 mg/DL **G1:** 83.3 **G2:** 80.0	NR	**G1:** 46.3 **G2:** 56.4
Bardin 2017										
Phase III, double-blind, placebo-controlled trial (CLEAR 2) (Escalation study)	**<u>ULT (randomised), 12-months:</u>** **G1:** Allopurinol (pre-study dose) + lesinurad 200mg once daily (N=204) **G2:** Allopurinol (pre-study dose) + lesinurad 400mg once daily (N=200) **G3:** Allopurinol (pre-study dose) + placebo once daily (N=206) **NOTE:** Allopurinol was required to be stabilised for ≥8-weeks prior to screening at a dose of 300-900mg daily (200mg permitted in moderate renal impairment) **<u>Prophylaxis (colchicine tolerance), initiated day -14 and continued until month 5 unless became intolerant or developed toxicity to prophylaxis:</u>** Colchicine 0.5 or 0.6mg once daily (G1= 88.7%, G2= 83.5%, G3= 77.2%) or non-specified NSAID (G1= 11.3%, G2= 18.0%, G3= 24.8%) **NOTE:** Some patients received colchicine + NSAID (2.5%) and some received other prophylaxis/no prophylaxis (1.3%). NSAID could be co-administered with a PPI	**Inclusion:** aged 18-85 years. Inadequate response to standard-of-care allopurinol and frequent flares (≥2 flares in the past year). SU ≥6.5mg/dL at screening. **Exclusion:** eCrCl <30ml/min. Previously received pegloticase	Europe, North America, South Africa, Australia and New Zealand	152	51.2 ± 10.9	96.2	79.0	6.9 ± 1.2	Mean ± SD (prior year) 6.2 ± 5.93	23.6
Dalbeth 2017										
Phase III, double-blind, placebo	**<u>ULT (febuxostat initiated on day -21, then randomisation on day 0), 12-months:</u>** Febuxostat 80mg once daily + lesinurad 200mg once daily (N=106) Febuxostat 80mg once daily + lesinuard 400mg once daily (N=109) Febuxostat 80mg once daily + placebo once daily (N=109)	**Inclusion:** aged 18-85 years. SU ≥8.0mg/dL if not currently on a ULT or ≥6.0mg/dL if on ULT.	North America, Europe, Australi	102	54.1 ± 11.0	95.4	79.9	(At screening) 8.7 ± 1.6	Mean ± SD (prior year) 6.7 ± 8.2	100

- controlled trial (CRYSTAL)	**<u>Prophylaxis (colchicine tolerance), initiated at day -21 and continued until month 5 unless became intolerant or developed toxicity to prophylaxis:</u>** Colchicine 0.5 or 0.6mg once daily (G1= 89.6%, G2= 86.2%, G3= 79.8%) or non-specified NSAID (G1= 8.5%, G2= 13.8%, G3= 20.2%) **NOTE:** NSAID could be co-administered with a PPI	Have ≥1 measurable tophus. **Exclusion:** eCrCl <30ml/min. Previously received pegloticase	a and New Zealand							
Saag 2017										
Phase III, double-blind, placebo-controlled trial (CLEAR 1) (Escalation study)	**<u>ULT (randomised), 12-months:</u>** **G1:** Allopurinol (pre-study dose) + lesinurad 200mg once daily (N=201) **G2:** Allopurinol (pre-study dose) + lesinurad 400mg once daily (N=201) **G3:** Allopurinol (pre-study dose) + placebo once daily (N=201) **NOTE:** Allopurinol was required to be stabilised for 8-weeks prior to screening at a dose of 300-800mg daily (200mg permitted in moderate renal impairment) **<u>Prophylaxis (colchicine tolerance), initiated at day -14 and continued until month 5 unless became intolerant or developed toxicity to prophylaxis:</u>** Colchicine 0.5 or 0.6mg once daily (G1= 84.6%, G2= 83.6%, G3= 82.6%) or non-specified NSAID (G1= 13.9%, G2= 16.4%, G3= 16.9%) **NOTE:** Some patients received colchicine + NSAID (1%). NSAID could be co-administered with a PPI.	**Inclusion:** aged 18-85 years. Inadequate response to standard-of-care allopurinol and frequent flares (≥2 flares in the past year). SU ≥6.5mg/dL at screening. **Exclusion:** eCrCl <30ml/min. Previously received pegloticase	United states	138	51.90 ± 11.28	94.0	76.3	6.94 ± 1.27	Mean ± SD (prior year) 4.8 ± 3.6	14.3
Stamp 2017										
Phase IV, open-label, active-comparator trial (Escalation study)	**<u>ULT (randomised), 12-months:</u>** **G1:** Allopurinol pre-study dose was increased by 50 or 100mg/day (depending on renal function) at monthly intervals until SU was <6mg/dL on three consecutive visits or adverse effects occurred (N=90) **G2:** Allopurinol at pre-study dose (N=93) **<u>Prophylaxis (investigator discretion, prescribing optional), up to 12-months:</u>** Colchicine (dose and frequency not reported) (G1= 38%, G2= 38%) or non-specified NSAID (G1=17%, G2=10%) or prednisone (dose and frequency not reported) (G1= 13%, G2=13%)	**Inclusion:** receiving CrCl based dose of allopurinol for at least one month and SU ≥6.0mg/dL	New Zealand	2	60.2 ± 12.5	87.4	41.5	7.15 ± 1.6	Median (IQR) (prior year) 3 (1-8)	44.2
Zhang 2017										

Phase III, double-blind, active-comparator trial	**ULT (randomised), 6-months:** **G1:** Febuxostat 40-80mg once daily (N=31) **G2:** Allopurinol 300mg once daily (N=15) **Prophylaxis:** None	**Inclusion:** aged 18-80 years. SU ≥7mg/dL	China	NR	49 ± 11	98	NR	9.5 ± 1.6	% with >2 flares (prior year) 52.1	19.6
Wang 2018										
Open-label, active-comparator trial	**ULT (randomised), 6-months:** **G1:** Febuxostat 80mg once daily (N=80) **G2:** Allopurinol 100mg three times a day (N=80) **Prophylaxis:** Use not reported	-	China	1	**G1:** 60.8 ± 3.2 **G2:** 62.5 ± 4.0	**G1:** 53.8 **G2:** 56.3	NR	**G1:** 6.14±0.80 **G2:** 6.21±0.78	NR	NR
White 2018										
Phase III, double-blind, active comparator trial (CARES)	**ULT (randomised), duration unclear (median duration of exposure was ~2-years):** **G1:** Febuxostat 40mg initially once daily. If after 2-weeks SU >6mg/dL, dose increased to 80mg once daily (N=3098) **G2:** Allopurinol 200 or 300mg initially once daily (depending on renal function), increasing by 100mg per month until SU conc. <6mg/dL or maximum dose reached (400 or 600mg daily, based on renal function) (N=3092) **Prophylaxis (colchicine tolerance, prescribing optional if prophylaxis unsuitable), first 6-months of treatment:** Colchicine 0.6mg once daily (G1=22.4%, G2=22.6%) or naproxen 250mg twice daily (N=NR) **NOTE:** Some participants received other prophylaxis (prednisone or other NSAID). Participants with eCrCl of <50ml/min were not to receive naproxen. Naproxen was co-administered with lansoprazole 15mg daily.	**Inclusion:** aged ≥50 (males) or ≥55 (females) with gout and a history of major cardiovascular or cerebrovascular disease. SU ≥7mg/dL or ≥6mg/dL with uncontrolled gout (≥1 flare in the past year and/or the presence of a tophus)	North America	320	Median (IQR) **G1:** 64.0 (58-71) **G2:** 65.0 (58-71)	**G1:** 84.1 **G2:** 83.8	**G1:** 69.7 **G2:** 69.2	8.7 ± 1.7	NR	**G1:** 21.6 **G2:** 21.0
Hao 2019										
Open-label, active-comparator trial	**ULT (randomised), 3-months:** **G1:** Febuxostat 40mg once daily (N=40) **G2:** Allopurinol 100mg three times a day (N=40) **Prophylaxis (all participants), 3-months:** Colchicine 0.5mg three times a day	-	China	1	**G1:** 42.3 ± 2.1 **G2:** 42.4 ± 2.0	**G1:** 75.0 **G2:** 77.5	NR	**G1:** 6.36±0.16 **G2:** 6.37±0.16	Unclear	NR

Liang 2019										
Open-label, active-comparator trial	**<u>ULT (randomised), 12-weeks:</u>** **G1:** Febuxostat 20mg once daily (N=120 (105 analysed)) **G2:** Benzbromarone 25mg once daily (N=120 (109 analysed)) **<u>Prophylaxis:</u>** None	**Inclusion:** Males with SU ≥7mg/dL	China	1	**G1:** 52.42 ± 11.73 **G2:** 50.27 ± 14.15	100	0	**G1:** 9.43±1.20 **G2:** 9.33±1.12	NR	**G1:** 23.9 **G2:** 20.0
Saag 2019										
Phase III, double-blind, placebo-controlled trial	**<u>ULT (randomised), 3-months:</u>** **G1:** Febuxostat 40mg IR once daily (N=357) **G2:** Febuxostat 40mg XR once daily (N=355) **G3:** Febuxostat 80mg IR once daily (N=357) **G4:** Febuxostat 80mg XR once daily (N=357) **G5:** Placebo once daily (N=357) **<u>Prophylaxis (colchicine tolerance), during washout and then 3-months:</u>** Colchicine 0.6mg once daily (or alternate daily in reduced renal function) (N=NR) or naproxen 250mg twice daily (N=NR) **NOTE:** Some participants received other prophylaxis (prednisone or other NSAID). Participants with eGFR of <50ml/min were not to receive naproxen. Naproxen was co-administered with lansoprazole 15mg daily	**Inclusion:** aged ≥18 years. SU ≥8mg/dL and ≥1 flare in the past year. An eGFR of 15-59ml/min was required in 30% of participants, with 85% of these participants having an eGFR on 15-29ml/min	United States	217	Mean (range) 55.1 (24-94)	88.4	64.3	9.61 ± 1.27	NR	NR
Desideri 2021										
Phase IV, open-label, active-comparator trial (FORWARD)	**<u>ULT (randomised), 36-weeks:</u>** **G1:** Febuxostat 80mg once daily, up-titrated to a maximum dose of 120mg once daily (N=98) **G2:** Allopurinol 100mg once daily, up-titrated to a maximum dose of 600mg once daily (based on kidney function and tolerability) (N=98) **NOTE:** Up-titration was during weeks 2-10 only if SU target of <6mg/dL not attainted **<u>Prophylaxis (colchicine tolerance), duration not specified:</u>** Colchicine 0.5-1mg once daily (N=NR) or naproxen 550mg twice daily (N=NR) **NOTE:** Naproxen was co-administered with omeprazole 20-40mg once daily	**Inclusion:** aged ≥18 years. SU >8mg/dL. Overall cardiovascular risk of between 5-15% (or ≤7% for participants with type 2 diabetes mellitus) **Exclusion:** CrCl <30ml/min. Contraindication or intolerance of NSAIDs or colchicine.	Europe	29	Mean (range) 59.6 (30-83)	82.1	NR	**G1:** 9.47±1.05 **G2:** 9.19±1.04	NR	NR

Footnotes: CrCl = creatinine clearance, eCrCl = estimated creatinine clearance, eGFR = estimated glomerular filtration rate, G = group, IQR = interquartile range, IR = immediate release, No.

= number, NR = not reported, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor, SC = subcutaneous, SD = standard deviation, SeCr = serum creatinine, SU = serum urate, ULT = urate-lowering therapy, XR = extended release

Note: Sundy 2011 included two identical phase III, double-blind, placebo-controlled trials (Trial C0405 and C0406) and therefore two sets of participant characteristic are reported.

Supplementary Exhibit 2: List of included studies

Bardin 2017

- Bardin T, Keenan RT, Khanna PP, et al. Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). Annals of the Rheumatic Diseases 2017; 76(5): 811-20.

Becker 2010

- Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial. Arthritis Research and Therapy 2010; 12 (2): R63.

Becker 2005

- Becker MA, Schumacher HR, Jr., Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353(23): 2450-61.

Borstad 2004

- Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. Journal of Rheumatology 2004; 31(12): 2429-32.

Dalbeth 2017

- Dalbeth N, Jones G, Terkeltaub R, et al. Lesinurad, a Selective Uric Acid Reabsorption Inhibitor, in Combination With Febuxostat in Patients With Tophaceous Gout: Findings of a Phase III Clinical Trial. Arthritis and Rheumatology 2017; 69(9): 1903-13.

Desideri 2021

- Desideri G, Rajzer M, Gerritsen M, et al. Effects of intensive urate lowering therapy with febuxostat in comparison with allopurinol on pulse wave velocity in patients with gout and increased cardiovascular risk: the FORWARD study. Eur Heart J Cardiovasc Pharmacother 2021; 07: 07.

Hao 2019

- Hao G, Duan W, Sun J, Liu J, Peng B. Effects of febuxostat on serum cytokines IL-1, IL-4, IL-6, IL-8, TNF-alpha and COX-2. Experimental and Therapeutic Medicine 2019; 17(1): 812-6.

Huang 2014

- Huang X, Du H, Gu J, et al. An allopurinol-controlled, multicenter, randomized, double-blind, parallel between-group, comparative study of febuxostat in Chinese patients with gout and hyperuricemia. Int J Rheum Dis 2014; 17(6): 679-86.

Jackson 2012

- Jackson RL, Hunt B, MacDonald PA. The efficacy and safety of febuxostat for urate lowering in gout patients >=65 years of age. BMC Geriatr 2012; 12: 11.

Karimzadeh 2006

- Karimzadeh H, Nazari J, Mottaghi P, Kabiri P. Different duration of colchicine for preventing recurrence of gouty arthritis. Journal of Research in Medical Sciences 2006; 11(2): 104-7.

Liang 2019

- Liang N, Sun MS, Sun RX, et al. Baseline urate level and renal function predict outcomes of urate-lowering therapy using low doses of febuxostat and benzbromarone: a prospective, randomized controlled study in a Chinese primary gout cohort. Arthritis Res Ther 2019; 21(1): 9.

Mitha 2013

- Mitha E, Ralph Schumacher H, Fouche L, et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: Results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology (United Kingdom) 2013; 52(7): 1285-92.

Paulus 1974

- Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R. Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients. Arthritis Rheum 1974; 17(5): 609-14.

NCT01451645

- Pharmaceuticals R. Efficacy and Safety of Colchicine for the Prevention of Gout Flares During the Initiation of Allopurinol. https://ClinicalTrials.gov/show/NCT01451645; 2014.

NCT01459796

- Pharmaceuticals R. Study of the Safety and Efficacy of Long-Term Rilonacept Treatment for the Prevention of Gout Flares. https://ClinicalTrials.gov/show/NCT01459796; 2017.

Reinders 2009

- Reinders MK, Haagsma C, Jansen T, et al. A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day in patients with gout. Annals of the Rheumatic Diseases 2009; 68(6): 892-7.

Saag 2019

- Saag KG, Becker MA, Whelton A, et al. Efficacy and Safety of Febuxostat Extended and Immediate Release in Patients With Gout and Renal Impairment: A Phase III Placebo-Controlled Study. Arthritis rheumatol 2019; 71(1): 143-53.

Saag 2017

- Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad Combined With Allopurinol: A Randomized, Double-Blind, Placebo-Controlled Study in Gout Patients With an Inadequate Response to Standard-of-Care Allopurinol (a US-Based Study). Arthritis rheumatol 2017; 69(1): 203-12.

Schumacher 2008

- Schumacher HR, Jr., Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008; 59(11): 1540-8.

Schumacher 2012

- Schumacher HR, Jr., Evans RR, Saag KG, et al. Rilonacept (interleukin-1 trap) for prevention of gout flares during initiation of uric acid-lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. Arthritis Care Res (Hoboken) 2012; 64(10): 1462-70.

Stamp 2017

- Stamp LK, Chapman PT, Barclay ML, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Annals of the Rheumatic Diseases 2017; 76(9): 1522-8.

Sundy 2011

- Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment Two Randomized Controlled Trials. JAMA-J Am Med Assoc 2011; 306(7): 711-20.

Wang 2018

- Wang S. The efficacy of febuxostat and allopurinol in the treatment of gout with hyperuricemia. Pak J Pharm Sci 2018; 31(4): 1623-7.

White 2018

- White WB, Saag KG, Becker MA, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med 2018; 378(13): 1200-10.

Wortmann 2010

- Wortmann RL, Macdonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clin Ther 2010; 32(14): 2386-97.

Xu 2015

- Xu S, Liu X, Ming J, et al. A phase 3, multicenter, randomized, allopurinol-controlled study assessing the safety and efficacy of oral febuxostat in Chinese gout patients with hyperuricemia. Int J Rheum Dis 2015; 18(6): 669-78.

Yamanaka 2018

- Yamanaka H, Tamaki S, Ide Y, et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. Annals of the Rheumatic Diseases 2018; 77(2): 270-6.

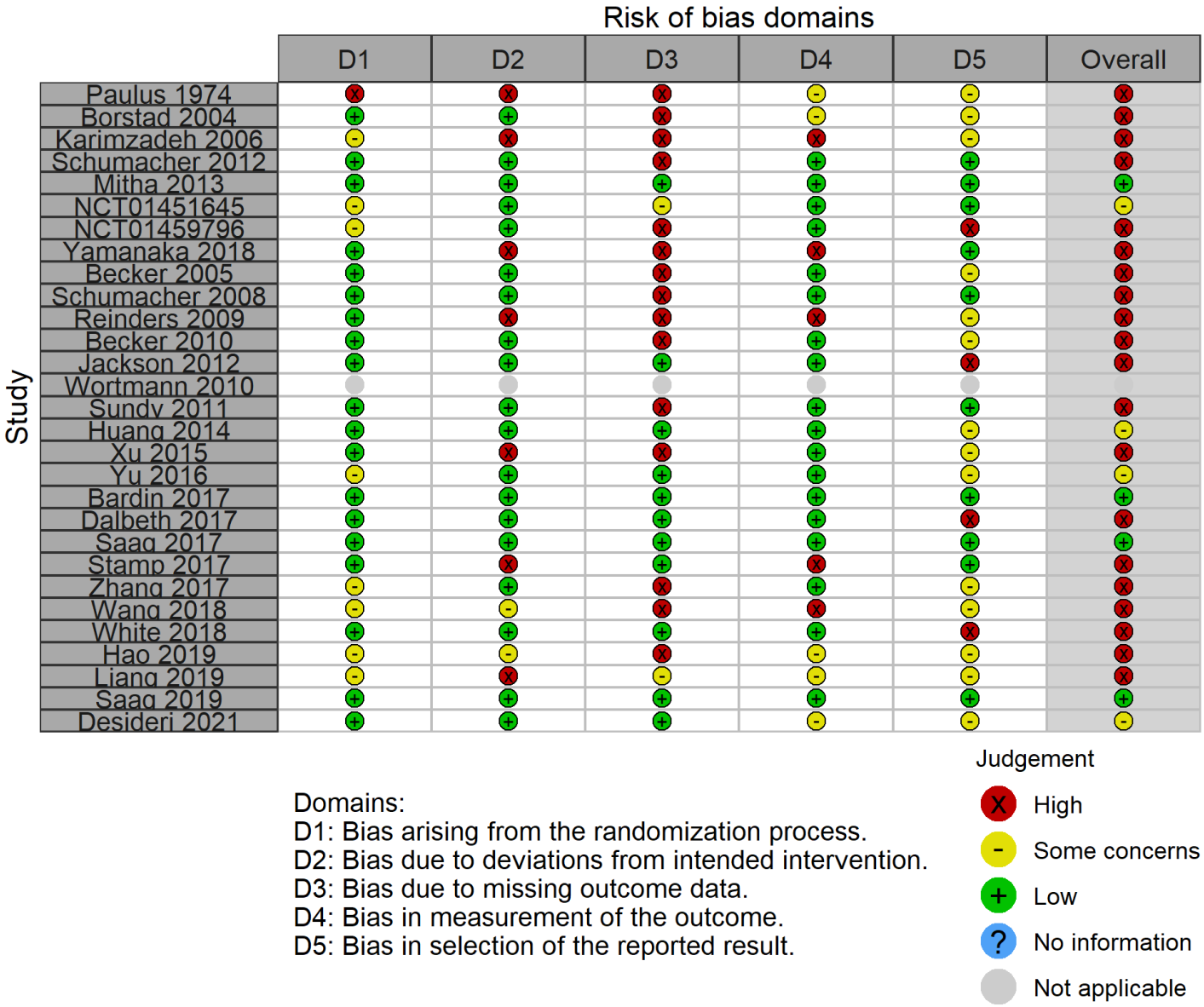
Yu 2016

- Yu KH, Lai JH, Hsu PN, Chen DY, Chen CJ, Lin HY. Safety and efficacy of oral febuxostat for treatment of HLA-B5801-negative gout: a randomized, open-label, multicentre, allopurinol-controlled study. Scand J Rheumatol 2016; 45(4): 304-11.

Zhang 2017

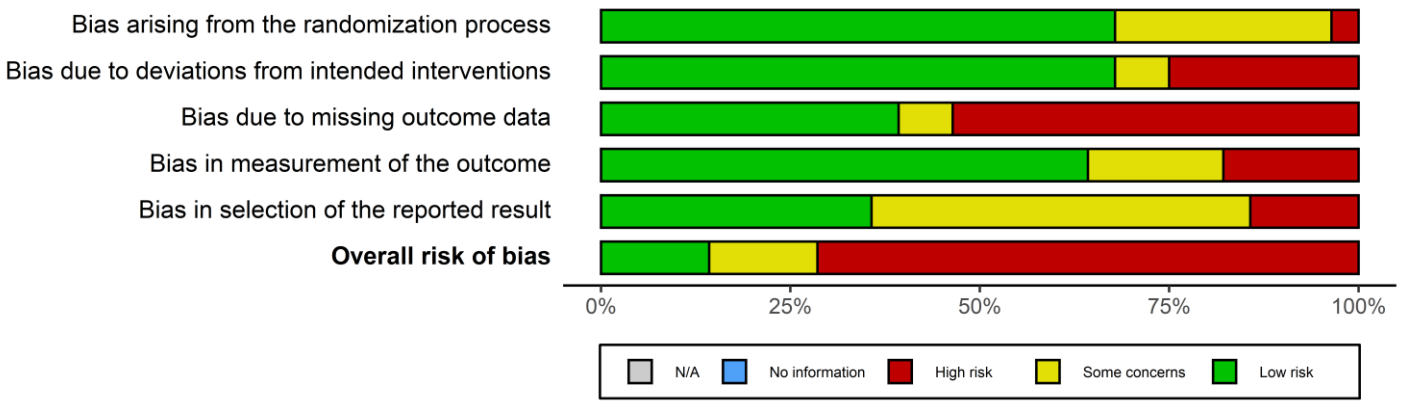
- Zhang Z, Zhang X, Sun Y, et al. New urate depositions on dual-energy computed tomography in gouty arthritis during urate-lowering therapy. Rheumatol Int 2017; 37(8): 1365-72.

Supplementary Figure 1: Quality assessment for gout flares summarised per trial

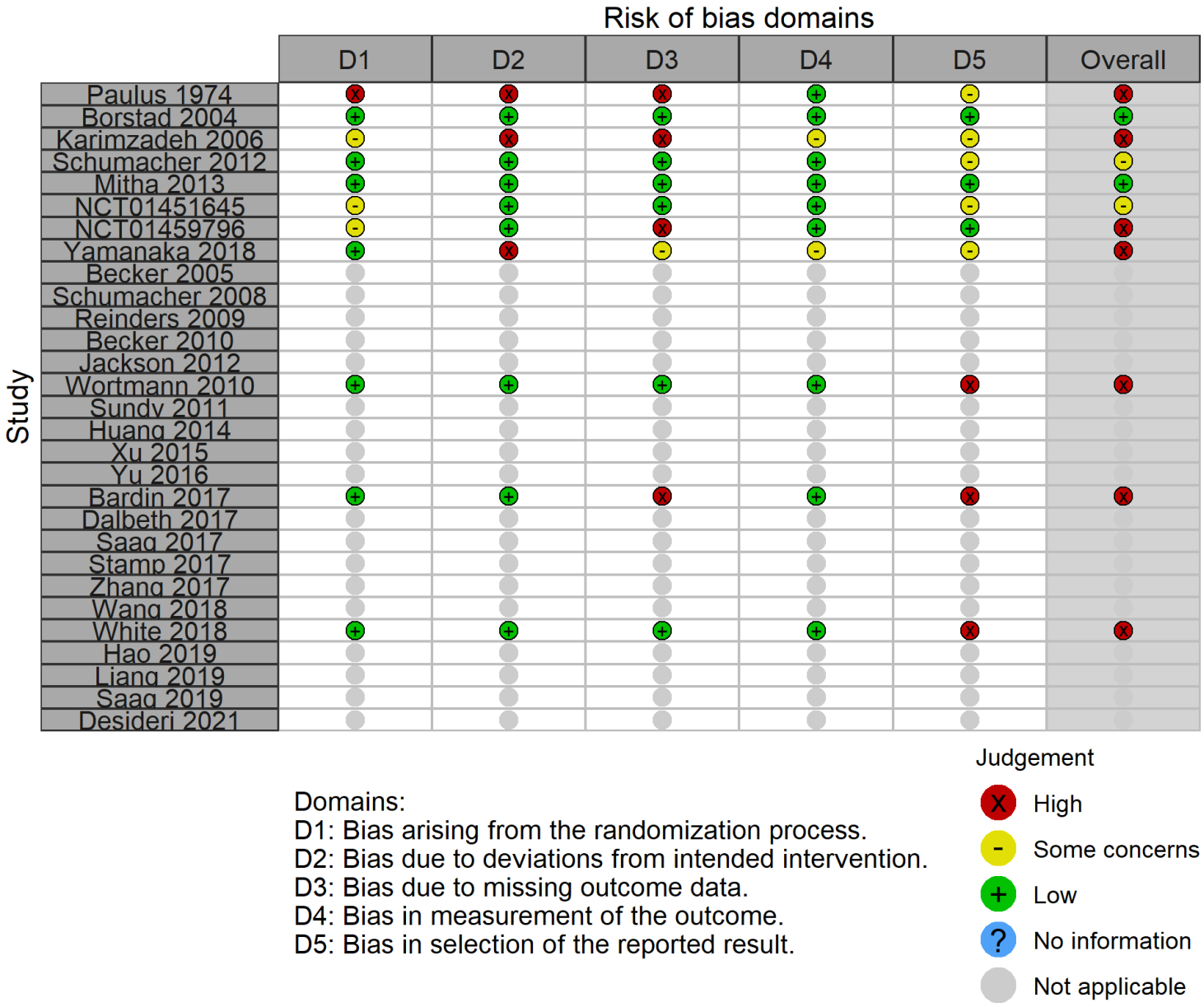


Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Supplementary Figure 2: Quality assessment for gout flares summarised per domain

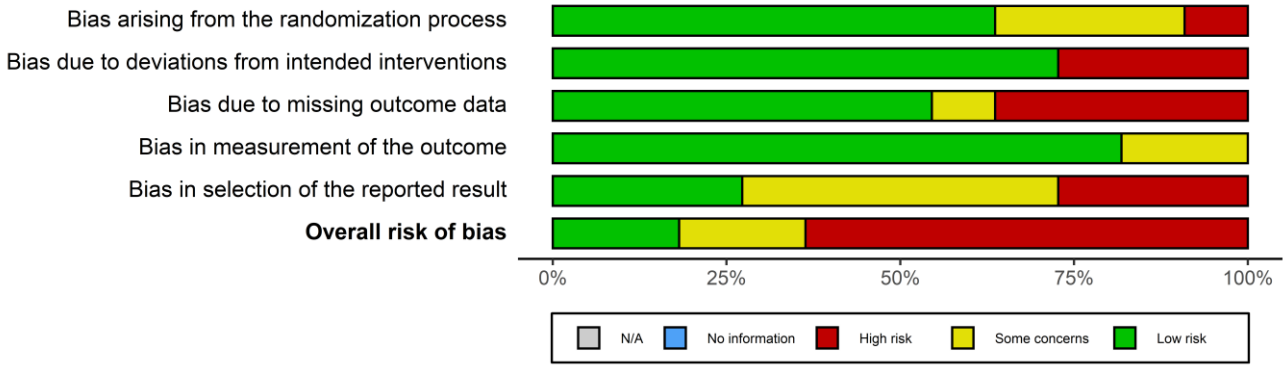


Supplementary Figure 3: Quality assessment for prophylaxis related adverse events summarised per trial



NOTE: Quality assessment of adverse events associated with prophylaxis was not considered applicable for: (i) Dalbeth 2017 and Saag 2017 due to the limited nature of the adverse event reporting; and (ii) Zhang 2017, Wang 2018 and Liang 2019, as prophylaxis was not used in these trials.

Supplementary Figure 4: Quality assessment for prophylaxis related adverse events summarised per domain



Supplementary Table 5: Summary of prophylaxis related adverse event results

Treatment groups		Withdrawal due to AE (%)	Total AE (%)	Serious AE (%)	Total treatment related AE (%)	Other notable AE data		
FLARE PROPHYLAXIS BASED TRIALS								
Paulus 1974						**Diarrhea (%)**		
Probenecid + C		0	NR	NR	75.0	45.0		
Probenecid + PBO		0			44.4	33.3		
P-value		-			>0.05	NR		
Borstad 2004						**Diarrhea (%)**		
A + C		4.8	43	0	NR	38		
A + PBO		9.1	36	0		4.5		
P-value		NR	0.760	NR		0.009		
Karimzadeh 2006						**Liver enzymes raised <2x ULN (%)**		
A + C 3-6 months		NR	NR	NR	NR	4.8		
A + C 7-9 months						8.1		
A + C 10-12 months						9.2		
P-value					0.2	NR		
Schumacher 2012						**Injection site reactions (%)**		
A + R 80mg		5.0	61.3	3.8	17.5	8.8		
A + R 160mg		3.7	65.4	3.7	32.1	19.8		
A + PBO		5.1	60.8	3.8	7.6	1.3		
P-value		NR	NR	NR	NR	NR		
Mitha 2013						**Injection site reactions (%)**		
A + R 80mg		3.7	68.3	6.1	31.7	12.2		
A + R 160mg		0	61.9	3.6	25.0	17.9		
A + PBO		0	61.0	4.9	8.5	1.2		
P-value		NR	NR	NR	NR	NR		
NCT01451645 (study unpublished)						**Diarrhea (%)**		
A + C		7.3	51.2	2.4	NR	2.4		
A + PBO		0	48.8	0		7.3		
P-value		NR	NR	NR		NR		
NCT01459796 (study terminated)						**Injection site erythema (%)**		
A + R		6.3	68.3	4.0	19.0	7.1		
A + PBO		10.6	68.1	5.3	12.8	2.1		
P-value		NR	NR	NR	NR	NR		
Yamanaka 2018						**Diarrhea (%)**		
Stepwise F		NR	21.9	0	NR	0		
F + C			20.0	0		1.1		
F			22.0	0		0		
P-value			NS	NS		NR		
URATE-LOWERING THERAPY BASED TRIALS								
Wortmann 2010						**Diarrhea (%)**		
FACT+APEX trial (F, A or PBO)	C	NR	55.1	NR	NR	8.4		
	N		44.3			2.7		
	P-value		0.001			<0.001		
CONFIRMS trial (F or A)	C	NR	55.1	NR	NR	5.1		
	N		54.9			6.4		
	P-value		NS			NS		
Bardin 2017						**Serum creatinine elevation ≥1.5x baseline (%)**		
						C	**NSAID**	**P-value**
A + L 200mg	C or NSAID	NR	NR	NR	NR	6.1	8.7	NR
A + L 400mg						14.4	19.4	NR
A + PBO						3.1	3.9	NR

Dalbeth 2017						Other description
F + L 200mg F + L 400mg F + PBO	C or NSAID	NR	NR	NR	NR	"Evaluation of CV and renal safety in this subgroup [NSAID group] did not demonstrate notable treatment differences."
Saag 2017						**Other description**
A + L 200mg A + L 400mg A + PBO	C or NSAID	NR	NR	NR	NR	"There was also no apparent association between serum creatinine elevations and either of the gout flare prophylaxis medications (colchicine or NSAID) (data not shown)."

White 2018						Composite of CV death, nonfatal MI, nonfatal stroke, or urgent re-vascularization due to unstable angina (%) *			
						Initial flare prophylaxis		Overall flare prophylaxis	
						C	Non-C	C	No C used
F	C, NSAID or other	NR	NR	NR	NR	11.3	8.1	14.9	9.6
A						10.9	7.6	12.1	9.9
P-value						0.91		0.15	

Treatment groups: A = allopurinol, C = colchicine, F = febuxostat, L = lesinurad, N = naproxen, PBO = placebo, R = rilonacept

Footnote: AE = adverse event, CV = cardiovascular, MI = myocardial infarction, NR = not reported, NS = not significant, NSAID = non-steroidal anti-inflammatory drug, ULN = upper limit of normal

NOTE: * Results from post hoc analyses. Adverse event rates presented represent the combined treatment of urate-lowering therapy with prophylaxis or placebo, as presented in the treatment groups column. We were not able to determine if the adverse events presented are a result of the prophylactic drug or the urate-lowering therapy. Within the flare prophylaxis adverse event network meta-analyses, prophylactic drug ± dose combinations are compared to a different prophylactic drug ± dose and/or to no prophylaxis/placebo and the urate-lowering therapy use is the same or similar between each group.

Supplementary Table 6: Summary of health-related quality of life results

Assessment detailing and timing		Treatment groups (N)			P-value
URATE-LOWERING THERAPY BASED TRIALS					
Sundy 2011	**ULT: 6-months, Prophylaxis: 6-months**	**Pg biweekly**	**Pg monthly**	**PBO**	**P-value**
HAQ pain score	At baseline, mean ± SD	44.2 ± 27.7	45.1 ± 27.0	53.9 ± 28.1	0.07 Pg biweekly and 0.09 Pg monthly vs PBO
	Change at final visit, mean ± SD	-11.4 ± 33.8	-6.9 ± 27.0	1.4 ± 30.0	**0.03 Pg biweekly** and 0.14 Pg monthly vs PBO
HAQ-DI	At baseline, mean ± SD	1.10 ± 0.86	1.21 ± 0.86	1.24 ± 0.95	0.43 Pg biweekly and 0.86 Pg monthly vs PBO
	Change at final visit, mean ± SD	-0.22 ± 0.64	-0.20 ± 0.55	0.02 ± 0.41	**0.01 Pg biweekly and 0.01 Pg monthly vs PBO**
SF-36 physical component summary score	At baseline, mean ± SD	35.2 ± 10.9	33.3 ± 9.8	31 ± 11.1	0.05 Pg biweekly and 0.26 Pg monthly vs PBO
	Change at final visit, mean ± SD	4.4 ± 9.4	4.9 ± 8.5	-0.3 ± 9.0	**0.01 Pg biweekly and 0.002 Pg monthly vs PBO**
Stamp 2017	**ULT: 12-months, Prophylaxis: up to 12-months**	**Allopurinol dose escalation**		**Allopurinol control**	**P-value**
HAQ	At baseline, mean ± SD	0.57 ± 0.07		0.53 ± 0.07	0.51 for change from baseline to 12-months
	At month 12, mean ± SD	0.62 ± 0.09		0.51 ± 0.09	

Footnote: HAQ = Health Assessment Questionnaire, HAQ-DI = Health Assessment Questionnaire Disability Index, PBO = placebo, Pg = pegloticase, SF-36 = 36-Item Short Form Health Survey, SD = standard deviation, ULT = urate-lowering therapy

Supplementary Table 7: Summary of gout flare measurement and data capture

Trial definition of a gout flare	Method of flare identification and recording	Acute management of a flare	Outcome level of flare data	Flare defined as expected manifestation or adverse event	Time period used to report gout flares
FLARE PROPHYLAXIS BASED TRIALS					
Paulus 1974					
Patient-reported pain in the joint with accompanying swelling and tenderness or investigator observed flare (taking into consideration the observed temperature of the involved joint, tenderness, swelling and area of redness).	Retrospectively at each monthly visit	Additional colchicine, indomethacin or phenylbutazone	NR	NR (Presume expected manifestation)	Monthly rate and over the entire treatment period
Borstad 2004					
NR	In real-time using patient information sheets	NSAIDs	NR	NR (Presume expected manifestation)	Months 0-3, 3-6 and 0-6
Karimzadeh 2006					
NR	NR	Not specified - "If patients relapsed before the end of one year, exclude from study and treated for acute gouty arthritis."	NR	NR (Presume expected manifestation)	End of month 6 and 12
Schumacher 2012					
For the primary analysis, all of the following criteria were required: 1) the presence of patient-reported acute articular pain typical of a gout attack deemed by the patient and/or the investigator to require treatment with an anti-inflammatory therapeutic agent; 2) the presence of at least 2 additional key signs/symptoms of joint swelling, redness, and tenderness; and 3) the presence of at least one of the following additional clinical variables of rapid onset of pain, decreased range of motion, joint warmth, or other symptoms similar to a prior gout flare. For the secondary analysis, flares were defined as patient-reported articular pain typical of a gout attack deemed to require treatment with an anti-inflammatory agent.	In real-time using a daily telephone interactive voice response system	NSAID and/or oral glucocorticoid	Primary and secondary	Expected manifestation	Total 16-week treatment period and week 16-20 (safety follow up)
Mitha 2013					
For the primary analysis, all of the following criteria were required: 1) the presence of patient-reported acute articular pain typical of a gout attack that is deemed (by patient and/or investigator) to require treatment with an anti-	In real-time using a daily telephone interactive voice response system	NSAID and/or oral glucocorticoid	Primary and secondary	Expected manifestation	Total 16-week treatment period

inflammatory therapeutic; 2) the presence of at least two of the following three signs/symptoms: joint swelling, tenderness and redness; and 3) the presence of at least one of the following clinical variables: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare. For the secondary analysis, flares were defined as patient-reported articular pain typical of a gout attack that is deemed to require treatment with an anti-inflammatory agent.					and week 16-20 (safety follow up)
NCT01451645 (study unpublished)					
NR	In real-time using a flare diary	NR	Primary and secondary	NR (Presume expected manifestation)	Total 16-week treatment period
NCT01459796 (study terminated)					
Acute articular pain typical of a gout attack that required treatment with an anti-inflammatory therapeutic and had at least 3 of the following 4 signs or symptoms: joint swelling, tenderness, redness, and pain; and with at least 1 of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare.	NR	NR	Secondary	NR (Presume expected manifestation)	Unclear due to study termination
Yamanaka 2018					
Gout flares requiring analgesic treatment with NSAIDs or adrenal corticosteroids to manage symptoms	In real-time on a specified patient record form which was verified by the attending investigator at next study visit (every 4 weeks)	NSAIDs or adrenal corticosteroids	Primary and secondary	NR (Presume expected manifestation)	Weeks 0-12, 13-24 and 0-24
URATE-LOWERING THERAPY BASED TRIALS					
Becker 2005					
Gout flares requiring treatment	NR	Investigator's discretion	Secondary	NR (Presume expected manifestation)	Weeks 0-8, 9-52, and every 4-weeks
Schumacher 2008					
Gout flares requiring treatment	NR	Investigator's discretion	Secondary	Expected manifestation	Weeks 0-8 and 8-28
Reinders 2009					
NR	NR	NR	NR	Adverse event	Over study period (4-months)
Becker 2010 and Jackson 2012					

Gout flares requiring treatment. Jackson 2012 defined flares as acute episodes of joint swelling, pain, exquisite tenderness and warmth, and redness at the joint, along with the overlying skin being tense, warm, shiny, and purplish or red in color.	NR	NR	NR	Expected manifestation	Every 4-weeks
Sundy 2011					
Acute joint pain and swelling requiring treatment	Reported in real-time by patients and confirmed by investigator interview	NR	Secondary	Expected manifestation and adverse event	Months 1-3 and 4-6
Huang 2014					
Gout flares requiring treatment	NR	NR	Secondary	Expected manifestation	Weeks 9-28
Xu 2015					
NR	NR	Temporarily increase ibuprofen or change to another medication (e.g. colchicine or celecoxib) for treatment	NR	Expected manifestation	Week 0-4, 4-8, 8-12, 12-16, 16-20, and 20-24
Yu 2016					
NR	NR	NR	NR	Adverse event	Weeks 0-12
Bardin 2017					
Clinically relevant gout flares requiring either an increase in current medication or new medication	In real-time using a daily electronic patient diary	Colchicine, analgesics and/or anti-inflammatory medications, including oral and intra-articular corticosteroids	Secondary	NR (Presume expected manifestation)	Monthly and months 7-12
Dalbeth 2017					
Gout flares requiring treatment	In real-time using a daily electronic patient diary	NR	Secondary	NR (Presume expected manifestation)	Months 7-12
Saag 2017					
Gout flares requiring treatment	In real-time using a daily electronic patient diary	Colchicine, analgesics, and/or anti-inflammatory medications, including oral and intraarticular corticosteroids	Secondary	NR (Presume expected manifestation)	Months 7-12
Stamp 2017					

NR	Retrospectively via monthly phone calls and at each 3-monthly study visit	Investigator's discretion	Secondary	NR (Presume expected manifestation)	Total 12-month treatment period and 3-monthyly
Zhang 2017					
Sudden-onset pain and swelling, with raised local skin temperature, followed by articular dyskinesia of the affected joints within a week	Retrospectively at each monthly visit	Etoricoxib	NR	NR (Presume expected manifestation)	Total 6-month treatment period
Wang 2018					
NR	NR	NR	NR	NR	Total 6-month treatment period
White 2018					
NR	Reported in the trial protocol: In real-time using a gout flare assessment worksheet and confirmed by investigator interview	Investigator's discretion	NR	NR (Presume expected manifestation)	Over entire treatment period
Hao 2019					
Gout flares requiring medical intervention	NR	NSAIDs	Unclear	NR	At 1-week, 1-month and 3-months
Liang 2019					
NR	Retrospectively at the next follow-up visit	Colchicine and/or etoricoxib	Secondary	Adverse event	Total 12-week treatment period
Saag 2019					
The presence of all of the following: 1) patient-reported acute articular pain typical of a gout attack that was deemed (by patient and/or investigator) to require treatment (and was treated) with colchicine, NSAIDs, or steroids; 2) presence of at least three or more of joint swelling, redness, tenderness, and pain; and 3) patient experienced at least one or more of rapid onset of pain, decreased range of motion, joint warmth, and other symptoms similar to a prior gout flare. Patients who discontinued the double-blind study drug due to gout flares were considered to have experienced a gout flare during the 3-month treatment period	NR	Colchicine, NSAIDs, or steroids	Secondary	NR (Presume expected manifestation)	Total 3-month treatment period
Desideri 2021					
NR	NR	Naproxen or other NSAID. In case of	NR	Adverse event	Total 36-week treatment period

		NSAIDs intolerance/contraindication or lack of efficacy, oral colchicine and/or steroids (oral or intraarticular injection) could be used.			

Footnote: NSAID = non-steroidal anti-inflammatory drug, NR = not reported

Note: Wortman 2010 has been omitted from this table as it is a post-hoc analysis of three other included trials (Becker 2005, Schumacher 2008 and Becker 2010).

Supplementary Exhibit 3: Summary of secondary outcomes

The severity and duration of gout flares was reported only by the flare prophylaxis-randomised RCTs **(Supplementary Table 3)**. Borstad *et al* (6) reported a significantly lower (P=0·018) mean flare severity as measured by the visual analogue scale (VAS) for subjects who received colchicine prophylaxis as compared to placebo (3·64 vs 5·08 respectively). There was no significant difference in mean flare duration (6·0 vs 5·6 days, respectively). Schumacher 2012 *et al* (7) and Mitha *et al* (8) both reported significantly fewer overall flare days and days with a pain severity score ≥5 out of 10 for rilonacept 80mg and 160mg as compared to placebo (P<0·0001). Only two studies reported on health related quality of life (HRQOL), with one reporting no difference from baseline in a study that compared allopurinol dose escalation to allopurinol control (9), while the other reported improvements in HRQOL with pegloticase treatment compared to placebo (10) **(Supplementary Table 6).**

Supplementary Exhibit 4: Summary of sub-group analysis

There was insufficient data to perform the pre-specified sub-group analyses of flare risk categorised by definition of a flare **(Supplementary Table 7)**, participants who achieved the SU target of <0·36mmol/l, participants with tophaceous gout and ULT treatment naïve versus treatment established participants. Definition of a flare was highly varied and often inadequately described across the studies**.** No study reported flare rates per study arm for participants that either did or did not achieve the SU target or for participants with and without tophaceous gout. Two studies provided flare data in treatment-naïve compared with treatment-established subjects **(Supplementary Table 3)**. Yamanaka *et al* (11) found no significant difference in the incidence of gout flares in participants with or without previous ULT, both within each treatment group and within the entire study population. In contrast, Becker 2010 *et al* (12) reported significantly lower flare rates in participants with prior participation in long-term ULT extension trials compared to subjects who were newly initiated on ULT, for each 4-weekly time period over the 28-week trial duration.

Supplementary Table 8: Summary of treatment acronyms

The following treatment acronyms are used within the network meta-analysis results:

Treatment acronyms	
A_P	Allopurinol ~300mg + Prophylaxis
A_t	Allopurinol up-titration
A_t_p	Allopurinol up-titration + Prophylaxis
B_t_p	Benzbromarone up-titration + Prophylaxis
F_120mg_p	Febuxostat 120mg + Prophylaxis
F_240mg_p	Febuxostat 240mg + Prophylaxis
F_40mg	Febuxostat 40mg
F_40mg_p	Febuxostat 40mg + Prophylaxis
F_80mg_p	Febuxostat 80mg + Prophylaxis
F_L_200mg_p	Febuxostat 80mg + Lesinurad 200mg + Prophylaxis
F_L_400mg_p	Febuxostat 80mg + Lesinurad 400mg + Prophylaxis
F_t	Febuxostat 10mg up-titrated to 40mg
F_t_p	Febuxostat up-titration + Prophylaxis
Placebo_p	Placebo + Prophylaxis
ULT	Urate-lowering therapy
ULT_C	Urate-lowering therapy + Colchicine
ULT_N	Urate-lowering therapy + Naproxen
ULT_R160mg	Urate-lowering therapy + Rilonacept 160mg
ULT_R80mg	Urate-lowering therapy + Rilonacept 80mg

Supplementary Exhibit 5: Network summaries

ULT-based flare subnetwork 1

```
## Title: ULT-based subnetwork 1
##
## Original data (with adjusted standard errors for multi-arm studies):
##
##                      treat1      treat2      TE   seTE seTE.adj narms multiarm
## Yamanaka 2018      F_40mg_p         F_t -0.0949 0.2909   0.3671     3        *
## Yamanaka 2018        F_40mg         F_t  0.5470 0.2741   0.3262     3        *
## Yamanaka 2018        F_40mg    F_40mg_p  0.6419 0.2839   0.3479     3        *
## Becker 2005       F_120mg_p    F_80mg_p  0.4942 0.1452   0.1666     3        *
## Becker 2005             A_p    F_80mg_p -0.0433 0.1699   0.2410     3        *
## Becker 2005             A_p   F_120mg_p -0.5375 0.1485   0.1722     3        *
## Schumacher 2008   F_120mg_p    F_80mg_p  0.2498 0.1272   0.1752     5        *
## Schumacher 2008   F_240mg_p    F_80mg_p  0.4991 0.1351   0.2009     5        *
## Schumacher 2008         A_p    F_80mg_p -0.1941 0.1483   0.2403     5        *
## Schumacher 2008    F_80mg_p   Placebo_p  0.3322 0.1979   0.3712     5        *
## Schumacher 2008   F_120mg_p   F_240mg_p -0.2493 0.1235   0.1666     5        *
## Schumacher 2008         A_p   F_120mg_p -0.4439 0.1378   0.1993     5        *
## Schumacher 2008   F_120mg_p   Placebo_p  0.5820 0.1902   0.3078     5        *
## Schumacher 2008         A_p   F_240mg_p -0.6931 0.1451   0.2285     5        *
## Schumacher 2008   F_240mg_p   Placebo_p  0.8313 0.1956   0.3529     5        *
## Schumacher 2008         A_p   Placebo_p  0.1382 0.2049   0.4221     5        *
```

```
## Becker 2010        F_40mg_p    F_80mg_p -0.1092 0.1462   0.1753     3         *
## Becker 2010             A_p    F_40mg_p -0.0627 0.1534   0.1931     3         *
## Becker 2010             A_p    F_80mg_p -0.1719 0.1491   0.1817     3         *
## Xu 2015            F_40mg_p    F_80mg_p -0.1729 0.2606   0.3294     3         *
## Xu 2015                 A_p    F_40mg_p  0.2381 0.2558   0.3156     3         *
## Xu 2015                 A_p    F_80mg_p  0.0651 0.2427   0.2866     3         *
## Yu 2016                 A_p    F_80mg_p -0.1650 0.2478   0.2478     2
## Dalbeth 2017    F_L_200mg_p F_L_400mg_p -0.3398 0.2099   0.2335     3         *
## Dalbeth 2017       F_80mg_p F_L_200mg_p -0.3793 0.2666   0.3794     3         *
## Dalbeth 2017       F_80mg_p F_L_400mg_p -0.7191 0.2448   0.2930     3         *
## Saag 2019          F_40mg_p    F_80mg_p -0.2048 0.0939   0.1029     3         *
## Saag 2019          F_40mg_p   Placebo_p  0.0554 0.1254   0.1726     3         *
## Saag 2019          F_80mg_p   Placebo_p  0.2603 0.1205   0.1506     3         *
##
## Number of treatment arms (by study):
##                  narms
## Yamanaka 2018        3
## Becker 2005          3
## Schumacher 2008      5
## Becker 2010          3
## Xu 2015              3
## Yu 2016              2
## Dalbeth 2017         3
## Saag 2019            3
##
## Results (random effects model):
##
##                      treat1      treat2     RR           95%-CI
## Yamanaka 2018      F_40mg_p         F_t 0.9095 [0.5143; 1.6084]
## Yamanaka 2018        F_40mg         F_t 1.7280 [1.0098; 2.9571]
## Yamanaka 2018        F_40mg    F_40mg_p 1.9000 [1.0892; 3.3143]
## Becker 2005       F_120mg_p    F_80mg_p 1.4292 [1.2067; 1.6928]
## Becker 2005             A_p    F_80mg_p 0.8754 [0.7537; 1.0167]
## Becker 2005             A_p   F_120mg_p 0.6125 [0.5128; 0.7315]
## Schumacher 2008   F_120mg_p    F_80mg_p 1.4292 [1.2067; 1.6928]
## Schumacher 2008   F_240mg_p    F_80mg_p 1.7566 [1.3980; 2.2072]
## Schumacher 2008         A_p    F_80mg_p 0.8754 [0.7537; 1.0167]
## Schumacher 2008    F_80mg_p   Placebo_p 1.2899 [1.0599; 1.5697]
## Schumacher 2008   F_120mg_p   F_240mg_p 0.8136 [0.6475; 1.0223]
## Schumacher 2008         A_p   F_120mg_p 0.6125 [0.5128; 0.7315]
## Schumacher 2008   F_120mg_p   Placebo_p 1.8435 [1.4521; 2.3404]
## Schumacher 2008         A_p   F_240mg_p 0.4983 [0.3933; 0.6314]
## Schumacher 2008   F_240mg_p   Placebo_p 2.2658 [1.7148; 2.9938]
## Schumacher 2008         A_p   Placebo_p 1.1291 [0.8978; 1.4199]
## Becker 2010        F_40mg_p    F_80mg_p 0.8369 [0.7251; 0.9660]
## Becker 2010             A_p    F_40mg_p 1.0459 [0.8707; 1.2564]
## Becker 2010             A_p    F_80mg_p 0.8754 [0.7537; 1.0167]
## Xu 2015            F_40mg_p    F_80mg_p 0.8369 [0.7251; 0.9660]
## Xu 2015                 A_p    F_40mg_p 1.0459 [0.8707; 1.2564]
## Xu 2015                 A_p    F_80mg_p 0.8754 [0.7537; 1.0167]
## Yu 2016                 A_p    F_80mg_p 0.8754 [0.7537; 1.0167]
```

```
## Dalbeth 2017    F_L_200mg_p F_L_400mg_p 0.7119 [0.4718; 1.0743]
## Dalbeth 2017       F_80mg_p F_L_200mg_p 0.6843 [0.4058; 1.1539]
## Dalbeth 2017       F_80mg_p F_L_400mg_p 0.4872 [0.3015; 0.7872]
## Saag 2019          F_40mg_p    F_80mg_p 0.8369 [0.7251; 0.9660]
## Saag 2019          F_40mg_p   Placebo_p 1.0795 [0.8730; 1.3349]
## Saag 2019          F_80mg_p   Placebo_p 1.2899 [1.0599; 1.5697]
##
## Number of studies: k = 8
## Number of pairwise comparisons: m = 29
## Number of observations: o = 7034
## Number of treatments: n = 10
## Number of designs: d = 7
##
## Random effects model
##
## Treatment estimate (sm = 'RR', comparison: other treatments vs 'Placebo_p'):
##                 RR           95%-CI    z  p-value
## A_p         1.1291 [0.8978; 1.4199] 1.04   0.2991
## F_120mg_p   1.8435 [1.4521; 2.3404] 5.02 < 0.0001
## F_240mg_p   2.2658 [1.7148; 2.9938] 5.75 < 0.0001
## F_40mg      2.0510 [1.1307; 3.7206] 2.36   0.0181
## F_40mg_p    1.0795 [0.8730; 1.3349] 0.71   0.4802
## F_80mg_p    1.2899 [1.0599; 1.5697] 2.54   0.0111
## F_L_200mg_p 1.8848 [1.0786; 3.2936] 2.23   0.0260
## F_L_400mg_p 2.6476 [1.5766; 4.4462] 3.68   0.0002
## F_t         1.1869 [0.6460; 2.1809] 0.55   0.5809
## Placebo_p        .                .    .        .
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0; tau = 0; I^2 = 0% [0.0%; 64.8%]
##
## Tests of heterogeneity (within designs) and inconsistency (between designs):
##                   Q d.f. p-value
## Total          3.08    8  0.9295
## Within designs 1.18    2  0.5548
## Between designs 1.90    6  0.928
```

ULT-based flare subnetwork 2

```
## Title: ULT-based subnetwork 2
##
## Original data:
##
##                 treat1 treat2      TE   seTE
## Borstad 2004       A_t  A_t_p  0.8408 0.3296
## Schumacher 2012    A_t  A_t_p  0.9907 0.2095
## Mitha 2013         A_t  A_t_p  0.8963 0.1727
## Reinders 2009    A_t_p  B_t_p -1.2777 1.6108
## Desideri 2021    A_t_p  F_t_p  0.4055 0.3824
##
## Number of treatment arms (by study):
##                 narms
```

```
## Borstad 2004        2
## Schumacher 2012     2
## Mitha 2013          2
## Reinders 2009       2
## Desideri 2021       2
##
## Results (random effects model):
##
##                 treat1 treat2     RR           95%-CI
## Borstad 2004       A_t  A_t_p 2.5127 [1.9723; 3.2011]
## Schumacher 2012    A_t  A_t_p 2.5127 [1.9723; 3.2011]
## Mitha 2013         A_t  A_t_p 2.5127 [1.9723; 3.2011]
## Reinders 2009    A_t_p  B_t_p 0.2787 [0.0119; 6.5498]
## Desideri 2021    A_t_p  F_t_p 1.5000 [0.7089; 3.1741]
##
## Number of studies: k = 5
## Number of pairwise comparisons: m = 5
## Number of observations: o = 782
## Number of treatments: n = 4
## Number of designs: d = 3
##
## Random effects model
##
## Treatment estimate (sm = 'RR', comparison: other treatments vs 'A_t'):
##           RR            95%-CI     z  p-value
## A_t        .                 .     .        .
## A_t_p 0.3980 [0.3124;  0.5070] -7.46 < 0.0001
## B_t_p 1.4281 [0.0602; 33.8756]  0.22   0.8254
## F_t_p 0.2653 [0.1207;  0.5833] -3.30   0.0010
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0; tau = 0; I^2 = 0% [0.0%; 89.6%]
##
## Tests of heterogeneity (within designs) and inconsistency (between designs):
##                     Q d.f. p-value
## Total            0.19    2  0.9092
## Within designs   0.19    2  0.9092
## Between designs  0.00    0      --
```

Prophylaxis-based flare network

```
## Title: Prophylaxis-based network
##
## Original data (with adjusted standard errors for multi-arm studies):
##
##                       treat1     treat2      TE   seTE seTE.adj narms multiarm
## Borstad 2004             ULT      ULT_C  0.8408 0.3296   0.3296     2
## Schumacher 2012 ULT_R160mg  ULT_R80mg -0.1555 0.3446   0.6018     3        *
## Schumacher 2012          ULT  ULT_R80mg  0.9154 0.2618   0.2839     3        *
## Schumacher 2012          ULT ULT_R160mg  1.0710 0.2810   0.3100     3        *
## Mitha 2013       ULT_R160mg  ULT_R80mg -0.2354 0.2870   0.5064     3        *
## Mitha 2013               ULT  ULT_R80mg  0.7841 0.2121   0.2284     3        *
```

```
## Mitha 2013             ULT ULT_R160mg  1.0195 0.2376   0.2629     3         *
## NCT01451645            ULT      ULT_C  0.5878 0.3268   0.3268     2
## Yamanaka 2018          ULT      ULT_C  0.6419 0.2839   0.2839     2
##
## Number of treatment arms (by study):
##                  narms
## Borstad 2004         2
## Schumacher 2012      3
## Mitha 2013           3
## NCT01451645          2
## Yamanaka 2018        2
##
## Results (random effects model):
##
##                      treat1     treat2     RR           95%-CI
## Borstad 2004            ULT      ULT_C 1.9830 [1.3945; 2.8200]
## Schumacher 2012 ULT_R160mg  ULT_R80mg 0.8152 [0.5292; 1.2558]
## Schumacher 2012         ULT  ULT_R80mg 2.3075 [1.6706; 3.1871]
## Schumacher 2012         ULT ULT_R160mg 2.8306 [1.9836; 4.0394]
## Mitha 2013       ULT_R160mg  ULT_R80mg 0.8152 [0.5292; 1.2558]
## Mitha 2013              ULT  ULT_R80mg 2.3075 [1.6706; 3.1871]
## Mitha 2013              ULT ULT_R160mg 2.8306 [1.9836; 4.0394]
## NCT01451645             ULT      ULT_C 1.9830 [1.3945; 2.8200]
## Yamanaka 2018           ULT      ULT_C 1.9830 [1.3945; 2.8200]
##
## Number of studies: k = 5
## Number of pairwise comparisons: m = 9
## Number of observations: o = 758
## Number of treatments: n = 4
## Number of designs: d = 2
##
## Random effects model
##
## Treatment estimate (sm = 'RR', comparison: other treatments vs 'ULT'):
##                RR           95%-CI     z  p-value
## ULT             .                .     .        .
## ULT_C      0.5043 [0.3546; 0.7171] -3.81   0.0001
## ULT_R160mg 0.3533 [0.2476; 0.5041] -5.73 < 0.0001
## ULT_R80mg  0.4334 [0.3138; 0.5986] -5.07 < 0.0001
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0; tau = 0; I^2 = 0% [0.0%; 79.2%]
##
## Tests of heterogeneity (within designs) and inconsistency (between designs):
##                    Q d.f. p-value
## Total           0.49    4  0.9743
## Within designs  0.49    4  0.9743
## Between designs 0.00    0      --
```

Prophylaxis-based adverse-event network: withdrawal due to adverse events

```
## Title: Withdrawal due to adverse events
##
## Original data (with adjusted standard errors for multi-arm studies):
##
##                     treat1     treat2      TE   seTE seTE.adj narms multiarm
## Borstad 2004           ULT      ULT_C  0.6466 1.1861   1.2357     2
## Schumacher 2012 ULT_R160mg  ULT_R80mg -0.3001 0.7473   1.0295     3        *
## Schumacher 2012        ULT  ULT_R80mg  0.0126 0.6891   0.9095     3        *
## Schumacher 2012        ULT ULT_R160mg  0.3127 0.7472   1.0292     3        *
## Mitha 2013      ULT_R160mg  ULT_R80mg -1.9699 1.5039   1.6479     3        *
## Mitha 2013             ULT  ULT_R80mg -1.9459 1.5038   1.6478     3        *
## Mitha 2013             ULT ULT_R160mg  0.0240 1.9940   4.0827     3        *
## NCT01451645            ULT      ULT_C -1.9459 1.4958   1.5355     2
## NCT01459796            ULT  ULT_R80mg  0.2930 0.6176   0.7082     2
##
## Number of treatment arms (by study):
##                  narms
## Borstad 2004         2
## Schumacher 2012      3
## Mitha 2013           3
## NCT01451645          2
## NCT01459796          2
##
## Results (random effects model):
##
##                     treat1     treat2     RR           95%-CI
## Borstad 2004           ULT      ULT_C 0.6890 [0.1044; 4.5465]
## Schumacher 2012 ULT_R160mg  ULT_R80mg 0.5466 [0.1411; 2.1168]
## Schumacher 2012        ULT  ULT_R80mg 0.9109 [0.3476; 2.3867]
## Schumacher 2012        ULT ULT_R160mg 1.6665 [0.4115; 6.7494]
## Mitha 2013      ULT_R160mg  ULT_R80mg 0.5466 [0.1411; 2.1168]
## Mitha 2013             ULT  ULT_R80mg 0.9109 [0.3476; 2.3867]
## Mitha 2013             ULT ULT_R160mg 1.6665 [0.4115; 6.7494]
## NCT01451645            ULT      ULT_C 0.6890 [0.1044; 4.5465]
## NCT01459796            ULT  ULT_R80mg 0.9109 [0.3476; 2.3867]
##
## Number of studies: k = 5
## Number of pairwise comparisons: m = 9
## Number of observations: o = 833
## Number of treatments: n = 4
## Number of designs: d = 3
##
## Random effects model
##
## Treatment estimate (sm = 'RR', comparison: other treatments vs 'ULT'):
##                RR           95%-CI     z p-value
## ULT             .                .     .       .
## ULT_C      1.4513 [0.2200; 9.5765]  0.39  0.6988
## ULT_R160mg 0.6001 [0.1482; 2.4304] -0.72  0.4742
```

```
## ULT_R80mg  1.0979 [0.4190; 2.8767]  0.19  0.8493
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0.1201; tau = 0.3466; I^2 = 11% [0.0%; 81.5%]
##
## Tests of heterogeneity (within designs) and inconsistency (between designs):
##                    Q d.f. p-value
## Total           4.49    4  0.3432
## Within designs  3.87    3  0.2758
## Between designs 0.62    1  0.4294
```

Prophylaxis-based adverse-event network: total adverse events

```
## Title: Total adverse events
##
## Original data (with adjusted standard errors for multi-arm studies):
##
##                               treat1     treat2      TE   seTE seTE.adj narm
s
## Borstad 2004                     ULT      ULT_C -0.1643 0.3782   0.3874
2
## Schumacher 2012           ULT_R160mg  ULT_R80mg  0.0660 0.1201   0.1770
3
## Schumacher 2012                  ULT  ULT_R80mg -0.0080 0.1268   0.1910
3
## Schumacher 2012                  ULT ULT_R160mg -0.0741 0.1212   0.1790
3
## Mitha 2013                ULT_R160mg  ULT_R80mg -0.0982 0.1140   0.1699
3
## Mitha 2013                       ULT  ULT_R80mg -0.1133 0.1160   0.1736
3
## Mitha 2013                       ULT ULT_R160mg -0.0151 0.1230   0.1887
3
## NCT01451645                      ULT      ULT_C -0.0488 0.2210   0.2364
2
## NCT01459796                      ULT  ULT_R80mg -0.0025 0.0932   0.1255
2
## Yamanaka 2018                    ULT      ULT_C  0.0916 0.2579   0.2712
2
## Wortmann 2010 - FACT+APEX      ULT_C      ULT_N  0.2186 0.0484   0.0970
2
## Wortmann 2010 - CONFIRMS       ULT_C      ULT_N  0.0037 0.0531   0.0995
2
##                            multiarm
## Borstad 2004
## Schumacher 2012                   *
## Schumacher 2012                   *
## Schumacher 2012                   *
## Mitha 2013                        *
## Mitha 2013                        *
## Mitha 2013                        *
## NCT01451645
```

```
## NCT01459796
## Yamanaka 2018
## Wortmann 2010 - FACT+APEX
## Wortmann 2010 - CONFIRMS
##
## Number of treatment arms (by study):
##                            narms
## Borstad 2004                   2
## Schumacher 2012                3
## Mitha 2013                     3
## NCT01451645                    2
## NCT01459796                    2
## Yamanaka 2018                  2
## Wortmann 2010 - FACT+APEX      2
## Wortmann 2010 - CONFIRMS       2
##
## Results (random effects model):
##
##                               treat1     treat2     RR            95%-CI
## Borstad 2004                     ULT      ULT_C 0.9812 [0.7144; 1.3477]
## Schumacher 2012           ULT_R160mg  ULT_R80mg 0.9927 [0.8211; 1.2001]
## Schumacher 2012                  ULT  ULT_R80mg 0.9609 [0.8212; 1.1245]
## Schumacher 2012                  ULT ULT_R160mg 0.9680 [0.7977; 1.1746]
## Mitha 2013                ULT_R160mg  ULT_R80mg 0.9927 [0.8211; 1.2001]
## Mitha 2013                       ULT  ULT_R80mg 0.9609 [0.8212; 1.1245]
## Mitha 2013                       ULT ULT_R160mg 0.9680 [0.7977; 1.1746]
## NCT01451645                      ULT      ULT_C 0.9812 [0.7144; 1.3477]
## NCT01459796                      ULT  ULT_R80mg 0.9609 [0.8212; 1.1245]
## Yamanaka 2018                    ULT      ULT_C 0.9812 [0.7144; 1.3477]
## Wortmann 2010 - FACT+APEX      ULT_C      ULT_N 1.1206 [0.9780; 1.2840]
## Wortmann 2010 - CONFIRMS       ULT_C      ULT_N 1.1206 [0.9780; 1.2840]
##
## Number of studies: k = 8
## Number of pairwise comparisons: m = 12
## Number of observations: o = 5049
## Number of treatments: n = 5
## Number of designs: d = 4
##
## Random effects model
##
## Treatment estimate (sm = 'RR', comparison: other treatments vs 'ULT'):
##                RR           95%-CI     z p-value
## ULT             .                .     .       .
## ULT_C      1.0191 [0.7420; 1.3998]  0.12  0.9068
## ULT_N      0.9095 [0.6439; 1.2846] -0.54  0.5901
## ULT_R160mg 1.0331 [0.8513; 1.2536]  0.33  0.7417
## ULT_R80mg  1.0407 [0.8893; 1.2178]  0.50  0.6193
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0.0071; tau = 0.0841; I^2 = 43.2% [0.0%; 76.1%]
```

```
##
## Tests of heterogeneity (within designs) and inconsistency (between designs):
##                     Q d.f. p-value
## Total           10.57    6  0.1027
## Within designs  10.30    5  0.0672
## Between designs  0.27    1  0.6033
```

Prophylaxis-based adverse-event network: serious adverse events

```
## Warning: Comparisons with missing TE / seTE or zero seTE not considered in
## network meta-analysis.

## Comparisons not considered in network meta-analysis:
##        studlab treat1 treat2 TE seTE
##   Borstad 2004  ULT_C    ULT NA   NA
##  Yamanaka 2018  ULT_C    ULT NA   NA

## Title: Serious adverse events
##
## Original data (with adjusted standard errors for multi-arm studies):
##
##                     treat1     treat2      TE   seTE seTE.adj narms multiarm
## Schumacher 2012 ULT_R160mg  ULT_R80mg -0.0124 0.8011   0.9813     3        *
## Schumacher 2012        ULT  ULT_R80mg  0.0126 0.8009   0.9808     3        *
## Schumacher 2012        ULT ULT_R160mg  0.0250 0.8010   0.9811     3        *
## Mitha 2013      ULT_R160mg  ULT_R80mg -0.5349 0.7136   0.8735     3        *
## Mitha 2013             ULT  ULT_R80mg -0.2231 0.6524   0.7514     3        *
## Mitha 2013             ULT ULT_R160mg  0.3118 0.7478   0.9830     3        *
## NCT01451645            ULT      ULT_C -1.0986 1.6182   1.6182     2
## NCT01459796            ULT  ULT_R80mg  0.2930 0.6176   0.6176     2
##
## Number of treatment arms (by study):
##                 narms
## Schumacher 2012     3
## Mitha 2013          3
## NCT01451645         2
## NCT01459796         2
##
## Results (random effects model):
##
##                     treat1     treat2     RR           95%-CI
## Schumacher 2012 ULT_R160mg  ULT_R80mg 0.7999 [0.2946; 2.1720]
## Schumacher 2012        ULT  ULT_R80mg 1.0368 [0.4816; 2.2321]
## Schumacher 2012        ULT ULT_R160mg 1.2962 [0.4688; 3.5841]
## Mitha 2013      ULT_R160mg  ULT_R80mg 0.7999 [0.2946; 2.1720]
## Mitha 2013             ULT  ULT_R80mg 1.0368 [0.4816; 2.2321]
## Mitha 2013             ULT ULT_R160mg 1.2962 [0.4688; 3.5841]
## NCT01451645            ULT      ULT_C 0.3333 [0.0140; 7.9482]
## NCT01459796            ULT  ULT_R80mg 1.0368 [0.4816; 2.2321]
##
## Number of studies: k = 4
## Number of pairwise comparisons: m = 8
```

```
## Number of observations: o = 790
## Number of treatments: n = 4
## Number of designs: d = 3
##
## Random effects model
##
## Treatment estimate (sm = 'RR', comparison: other treatments vs 'ULT'):
##                RR            95%-CI     z p-value
## ULT             .                 .     .       .
## ULT_C      3.0000 [0.1258; 71.5336]  0.68  0.4972
## ULT_R160mg 0.7715 [0.2790;  2.1331] -0.50  0.6171
## ULT_R80mg  0.9645 [0.4480;  2.0763] -0.09  0.9263
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0; tau = 0; I^2 = 0% [0.0%; 84.7%]
##
## Tests of heterogeneity (within designs) and inconsistency (between designs):
##                    Q d.f. p-value
## Total           0.53    3  0.9131
## Within designs  0.24    2  0.8882
## Between designs 0.29    1  0.5910
```

Prophylaxis-based adverse-event network: total treatment related adverse events

```
## Title: Total treatment related adverse events
##
## Original data (with adjusted standard errors for multi-arm studies):
##
##                     treat1     treat2      TE   seTE seTE.adj narms multiarm
## Paulus 1974            ULT      ULT_C -0.5232 0.2934   0.5212     2
## Schumacher 2012 ULT_R160mg  ULT_R80mg  0.6066 0.2916   0.5862     3        *
## Schumacher 2012        ULT  ULT_R80mg -0.8347 0.4615   0.8446     3        *
## Schumacher 2012        ULT ULT_R160mg -1.4413 0.4244   0.7477     3        *
## Mitha 2013      ULT_R160mg  ULT_R80mg -0.2377 0.2490   0.5621     3        *
## Mitha 2013             ULT  ULT_R80mg -1.3122 0.3961   0.7412     3        *
## Mitha 2013             ULT ULT_R160mg -1.0745 0.4079   0.7701     3        *
## NCT01459796            ULT  ULT_R80mg -0.4002 0.3262   0.5403     2
##
## Number of treatment arms (by study):
##                 narms
## Paulus 1974         2
## Schumacher 2012     3
## Mitha 2013          3
## NCT01459796         2
##
## Results (random effects model):
##
##                     treat1     treat2     RR           95%-CI
## Paulus 1974            ULT      ULT_C 0.5926 [0.2134; 1.6459]
## Schumacher 2012 ULT_R160mg  ULT_R80mg 1.3017 [0.6608; 2.5643]
## Schumacher 2012        ULT  ULT_R80mg 0.4360 [0.2257; 0.8423]
## Schumacher 2012        ULT ULT_R160mg 0.3349 [0.1566; 0.7162]
```

```
## Mitha 2013      ULT_R160mg  ULT_R80mg 1.3017 [0.6608; 2.5643]
## Mitha 2013             ULT  ULT_R80mg 0.4360 [0.2257; 0.8423]
## Mitha 2013             ULT ULT_R160mg 0.3349 [0.1566; 0.7162]
## NCT01459796            ULT  ULT_R80mg 0.4360 [0.2257; 0.8423]
##
## Number of studies: k = 4
## Number of pairwise comparisons: m = 8
## Number of observations: o = 746
## Number of treatments: n = 4
## Number of designs: d = 3
##
## Random effects model
##
## Treatment estimate (sm = 'RR', comparison: other treatments vs 'ULT'):
##                RR           95%-CI    z p-value
## ULT             .                .    .       .
## ULT_C      1.6875 [0.6076; 4.6868] 1.00  0.3154
## ULT_R160mg 2.9857 [1.3962; 6.3849] 2.82  0.0048
## ULT_R80mg  2.2936 [1.1872; 4.4313] 2.47  0.0135
##
## Quantifying heterogeneity / inconsistency:
## tau^2 = 0.1855; tau = 0.4307; I^2 = 61.8% [0.0%; 87.2%]
##
## Tests of heterogeneity (within designs) and inconsistency (between designs):
##                    Q d.f. p-value
## Total           7.85    3  0.0493
## Within designs  4.85    2  0.0885
## Between designs 3.00    1  0.0834
```

Supplementary Exhibit 6: Pairwise meta-analysis results

ULT-based flare subnetwork 1

```
## Number of studies: k = 8
## Number of pairwise comparisons: m = 29
## Number of observations: o = 16103
##
## Results for pairwise comparisons (random effects model):
##                              m     RR           95%-CI  tau^2    tau    Q
I^2
## F_40mg_p vs F_t              1 0.9095 [0.5143; 1.6084]     --     -- 0.00
--
## F_40mg vs F_t                1 1.7280 [1.0098; 2.9571]     --     -- 0.00
--
## F_40mg vs F_40mg_p           1 1.9000 [1.0892; 3.3143]     --     -- 0.00
--
## F_120mg_p vs F_80mg_p        2 1.4361 [1.1311; 1.8233] 0.0112 0.1060 1.60 37
.6%
## A_p vs F_80mg_p              5 0.8834 [0.7560; 1.0322]      0      0 1.19  0
.0%
## A_p vs F_120mg_p             2 0.6144 [0.5040; 0.7489]      0      0 0.21  0
.0%
## F_240mg_p vs F_80mg_p        1 1.6472 [1.2640; 2.1466]     --     -- 0.00
--
## F_80mg_p vs Placebo_p        2 1.3228 [1.0812; 1.6184]      0      0 0.10  0
.0%
## F_120mg_p vs F_240mg_p       1 0.7794 [0.6118; 0.9928]     --     -- 0.00
--
## F_120mg_p vs Placebo_p       1 1.7896 [1.2328; 2.5980]     --     -- 0.00
--
## A_p vs F_240mg_p             1 0.5000 [0.3762; 0.6645]     --     -- 0.00
--
## F_240mg_p vs Placebo_p       1 2.2963 [1.5652; 3.3689]     --     -- 0.00
--
## A_p vs Placebo_p             1 1.1481 [0.7684; 1.7155]     --     -- 0.00
--
## F_40mg_p vs F_80mg_p         3 0.8381 [0.7227; 0.9720]      0      0 0.30  0
.0%
## A_p vs F_40mg_p              2 1.0182 [0.7841; 1.3222] 0.0008 0.0277 1.02  1
.7%
## F_L_200mg_p vs F_L_400mg_p   1 0.7119 [0.4718; 1.0743]     --     -- 0.00
--
## F_80mg_p vs F_L_200mg_p      1 0.6843 [0.4058; 1.1539]     --     -- 0.00
--
## F_80mg_p vs F_L_400mg_p      1 0.4872 [0.3015; 0.7872]     --     -- 0.00
--
## F_40mg_p vs Placebo_p        1 1.0570 [0.8267; 1.3514]     --     -- 0.00
--
##
## Details on meta-analytical method:
```

```
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

ULT-based flare subnetwork 2

```
## Number of studies: k = 5
## Number of observations: o = 782
##
## Results for pairwise comparisons (random effects model):
##                   m     RR           95%-CI tau^2 tau    Q  I^2
## A_t_p vs A_t      3 0.3980 [0.3124; 0.5070]     0   0 0.19 0.0%
## A_t_p vs B_t_p    1 0.2787 [0.0119; 6.5498]    --  -- 0.00   --
## A_t_p vs F_t_p    1 1.5000 [0.7089; 3.1741]    --  -- 0.00   --
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

Prophylaxis-based flare network

```
## Number of studies: k = 5
## Number of pairwise comparisons: m = 9
## Number of observations: o = 1246
##
## Results for pairwise comparisons (random effects model):
##                            m     RR           95%-CI tau^2 tau    Q  I^2
## ULT_C vs ULT               3 0.5043 [0.3546; 0.7171]     0   0 0.34 0.0%
## ULT_R160mg vs ULT_R80mg    2 0.8165 [0.5300; 1.2580]     0   0 0.03 0.0%
## ULT_R80mg vs ULT           2 0.4334 [0.3138; 0.5986]     0   0 0.15 0.0%
## ULT_R160mg vs ULT          2 0.3531 [0.2474; 0.5039]     0   0 0.02 0.0%
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

Prophylaxis-based adverse-event network: withdrawal due to adverse events

```
## Number of studies: k = 5
## Number of pairwise comparisons: m = 9
## Number of observations: o = 1321
##
## Results for pairwise comparisons (random effects model):
##                            m     RR            95%-CI  tau^2    tau    Q   I^
2
## ULT_C vs ULT               2 1.6314 [0.1311; 20.2999] 1.5384 1.2403 1.84 45.8
%
## ULT_R160mg vs ULT_R80mg    2 0.5322 [0.1434;  1.9757]      0      0 0.99  0.0
%
## ULT_R80mg vs ULT           3 1.0128 [0.4277;  2.3982]      0      0 1.90  0.0
%
## ULT_R160mg vs ULT          2 0.7580 [0.1923;  2.9870]      0      0 0.02  0.0
%
##
## Details on meta-analytical method:
```

```
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

Prophylaxis-based adverse-event network: total adverse events

```
## Number of studies: k = 8
## Number of pairwise comparisons: m = 12
## Number of observations: o = 5537
##
## Results for pairwise comparisons (random effects model):
##                           m     RR           95%-CI  tau^2    tau    Q   I^2
## ULT_C vs ULT              3 1.0183 [0.7539; 1.3754]      0      0 0.35  0.0%
## ULT_R160mg vs ULT_R80mg   2 0.9798 [0.8332; 1.1522]      0      0 0.98  0.0%
## ULT_R80mg vs ULT          3 1.0372 [0.9167; 1.1736]      0      0 0.62  0.0%
## ULT_R160mg vs ULT         2 1.0461 [0.8832; 1.2390]      0      0 0.12  0.0%
## ULT_C vs ULT_N            2 1.1188 [0.9064; 1.3810] 0.0205 0.1432 8.94 88.8%
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

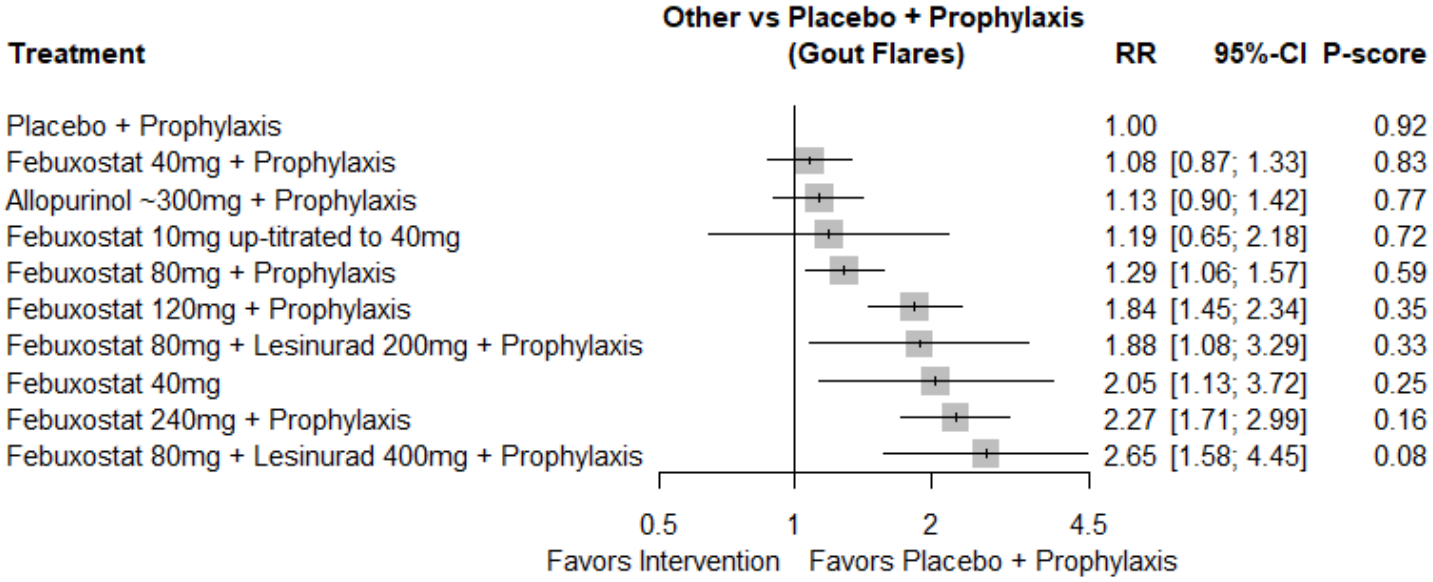
Prophylaxis-based adverse-event network: serious adverse events

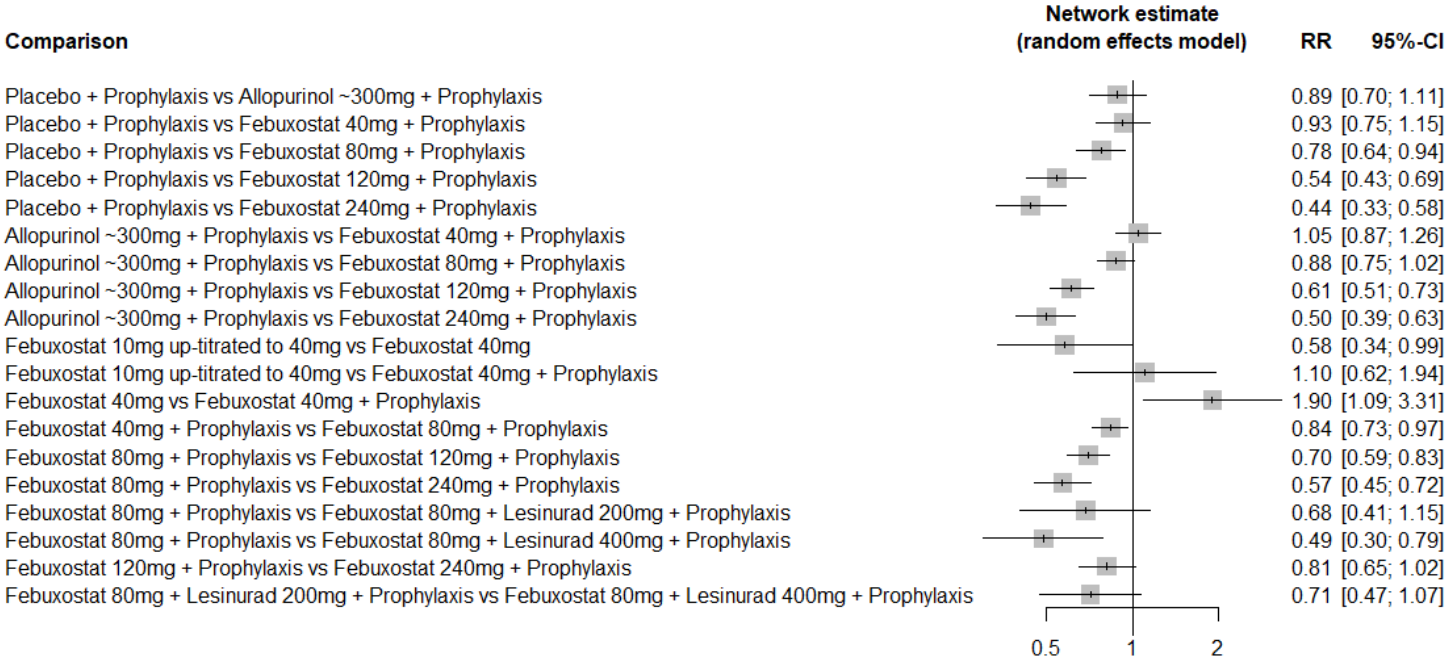
```
## Number of studies: k = 4
## Number of pairwise comparisons: m = 8
## Number of observations: o = 1278
##
## Results for pairwise comparisons (random effects model):
##                           m     RR            95%-CI tau^2 tau    Q  I^2
## ULT_R160mg vs ULT_R80mg   2 0.7380 [0.2597;  2.0973]     0   0 0.24 0.0%
## ULT_R80mg vs ULT          3 0.9605 [0.4460;  2.0681]     0   0 0.33 0.0%
## ULT_R160mg vs ULT         2 0.8367 [0.2866;  2.4428]     0   0 0.07 0.0%
## ULT_C vs ULT              1 3.0000 [0.1258; 71.5336]    --  -- 0.00   --
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

Prophylaxis-based adverse-event network: total treatment related adverse events

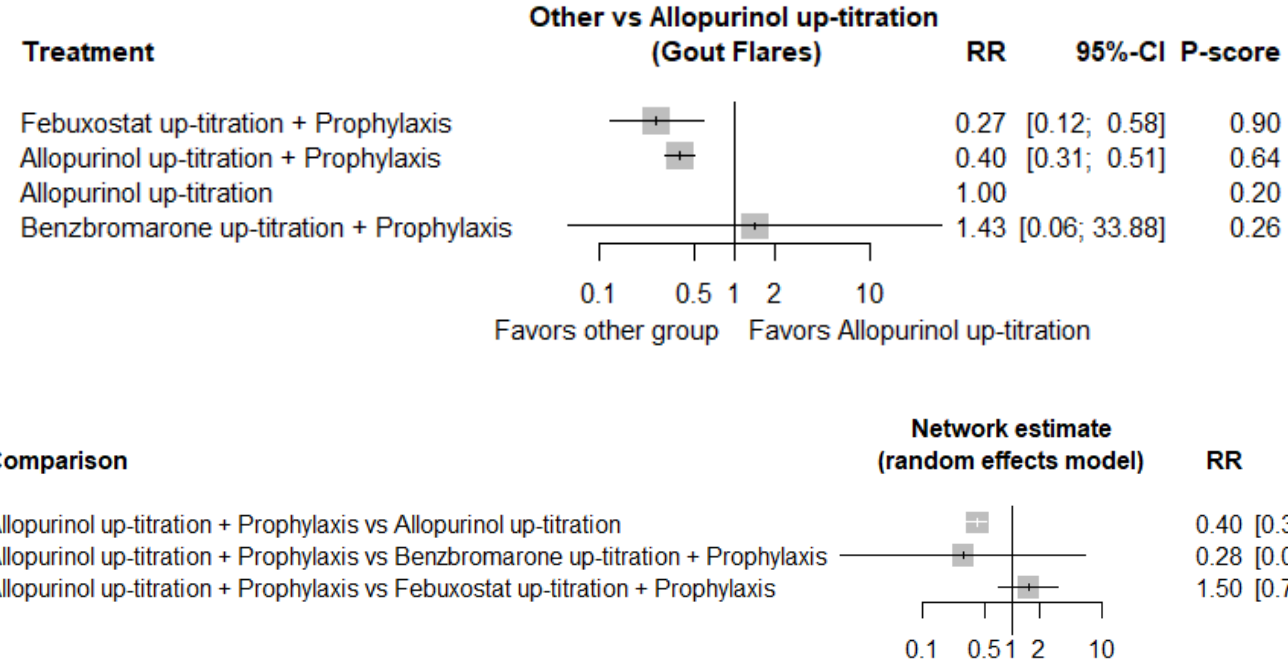
```
## Number of studies: k = 4
## Number of pairwise comparisons: m = 8
## Number of observations: o = 1234
##
## Results for pairwise comparisons (random effects model):
##                           m     RR           95%-CI  tau^2    tau    Q   I^2
## ULT_C vs ULT              1 1.6875 [0.9494; 2.9993]     --     -- 0.00    --
## ULT_R160mg vs ULT_R80mg   2 1.1863 [0.5189; 2.7122] 0.2829 0.5319 4.85 79.4%
## ULT_R80mg vs ULT          3 2.2530 [1.2930; 3.9258] 0.0897 0.2995 3.17 37.0%
## ULT_R160mg vs ULT         2 3.4926 [1.9625; 6.2155]      0      0 0.39  0.0%
##
## Details on meta-analytical method:
## - Inverse variance method
## - DerSimonian-Laird estimator for tau^2
```

Supplementary Figure 5: Forrest plots - ULT-based flare subnetwork 1

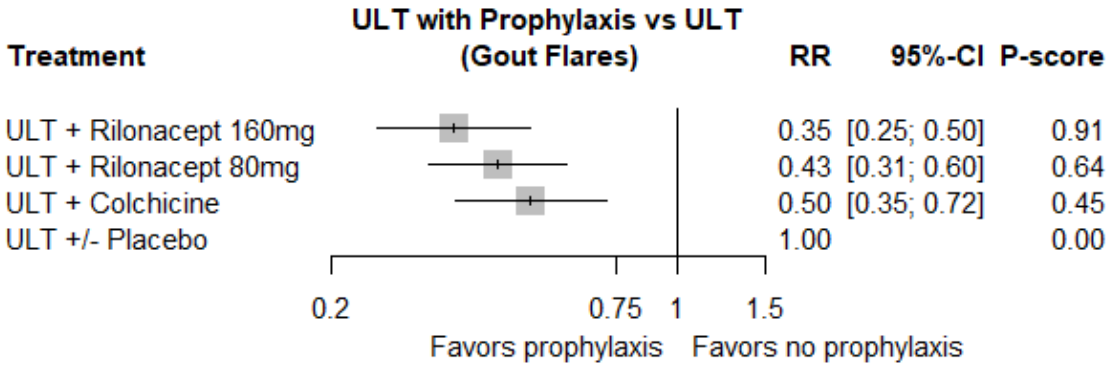


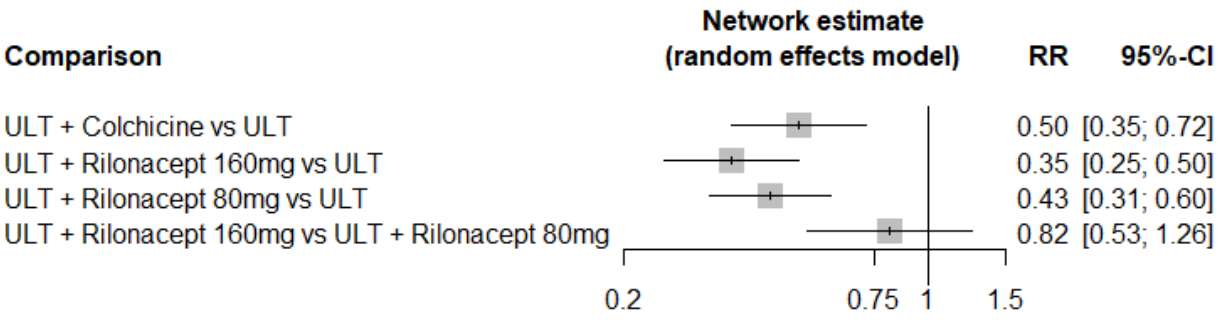


Supplementary Figure 6: Forrest plots - ULT-based flare subnetwork 2

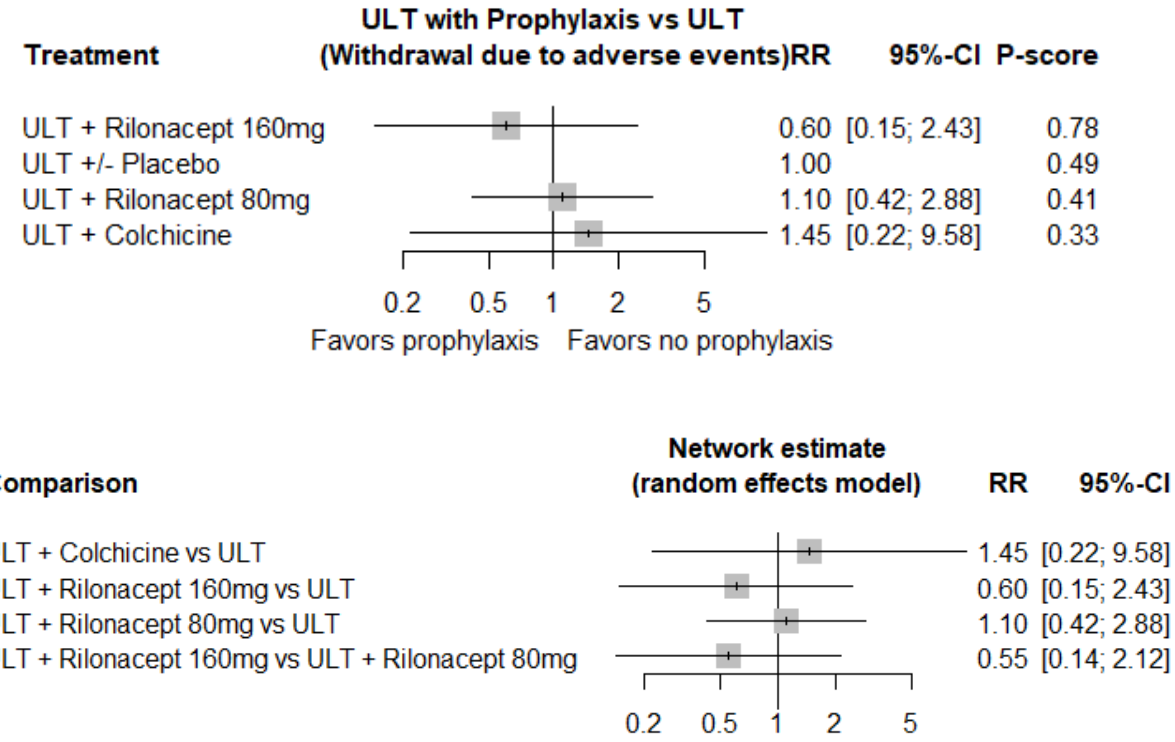


Supplementary Figure 7: Forrest plots - Prophylaxis-based flare network

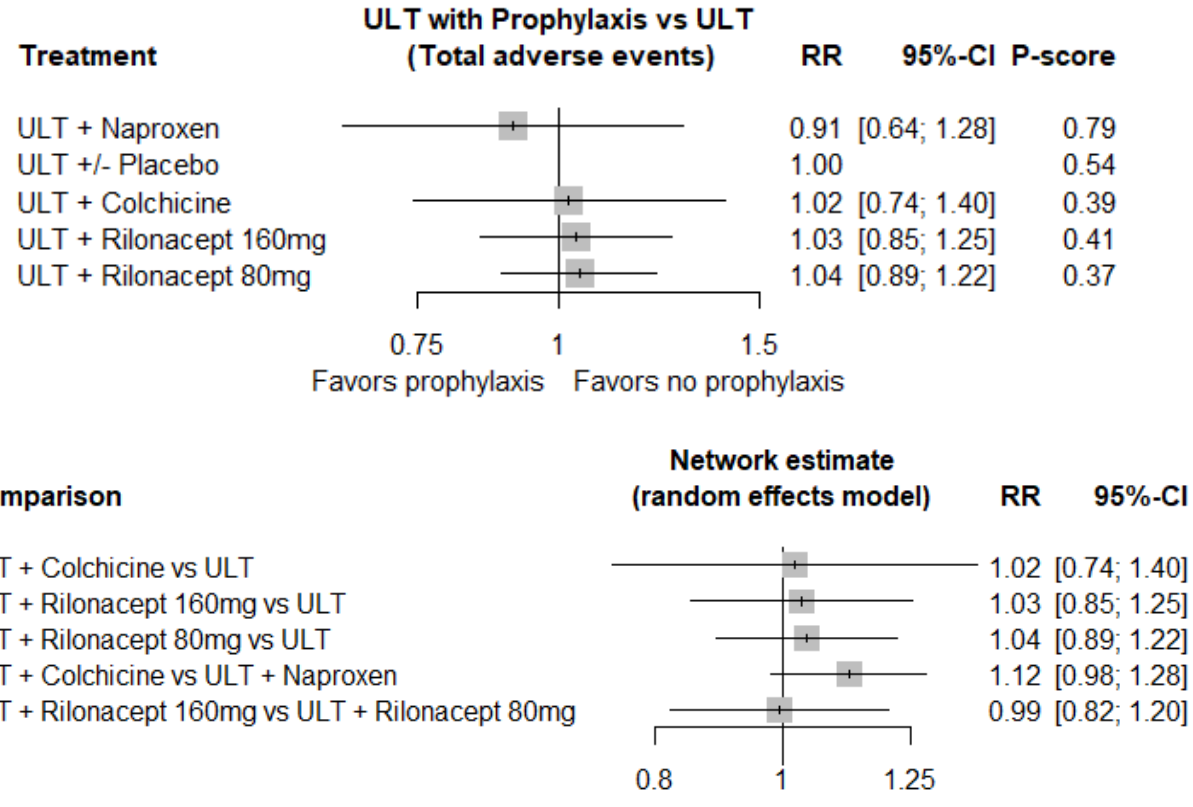




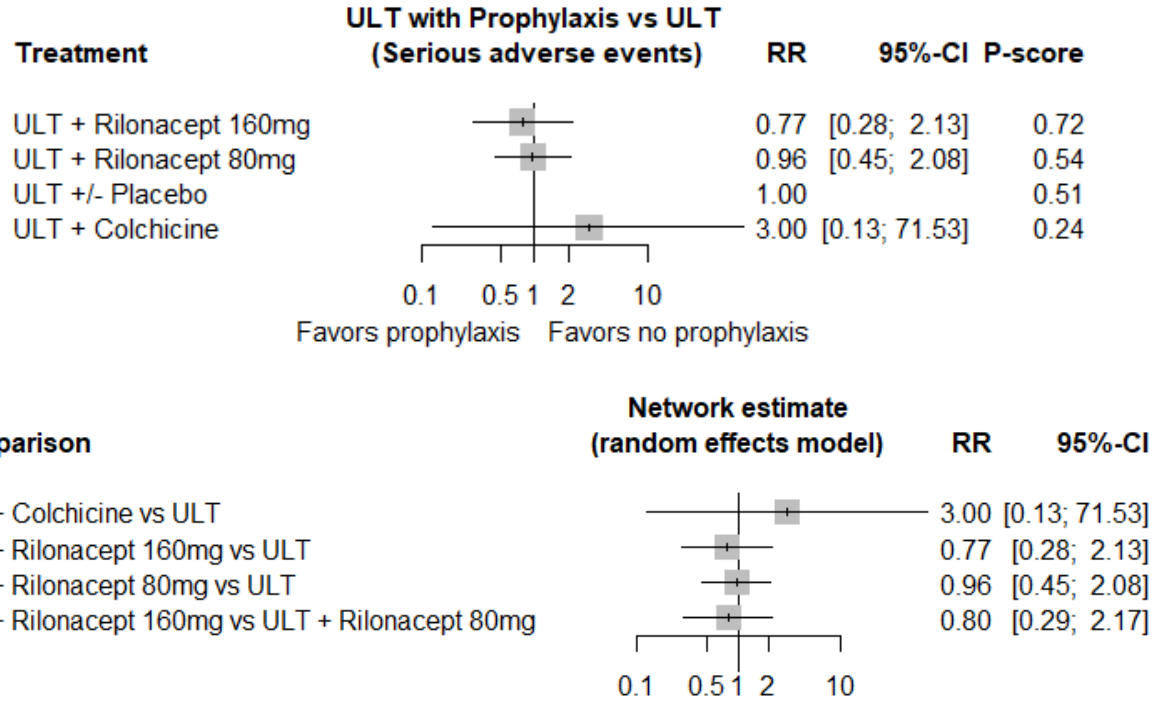
Supplementary Figure 8: Forrest plots - Prophylaxis-based adverse-event network: withdrawal due to adverse events



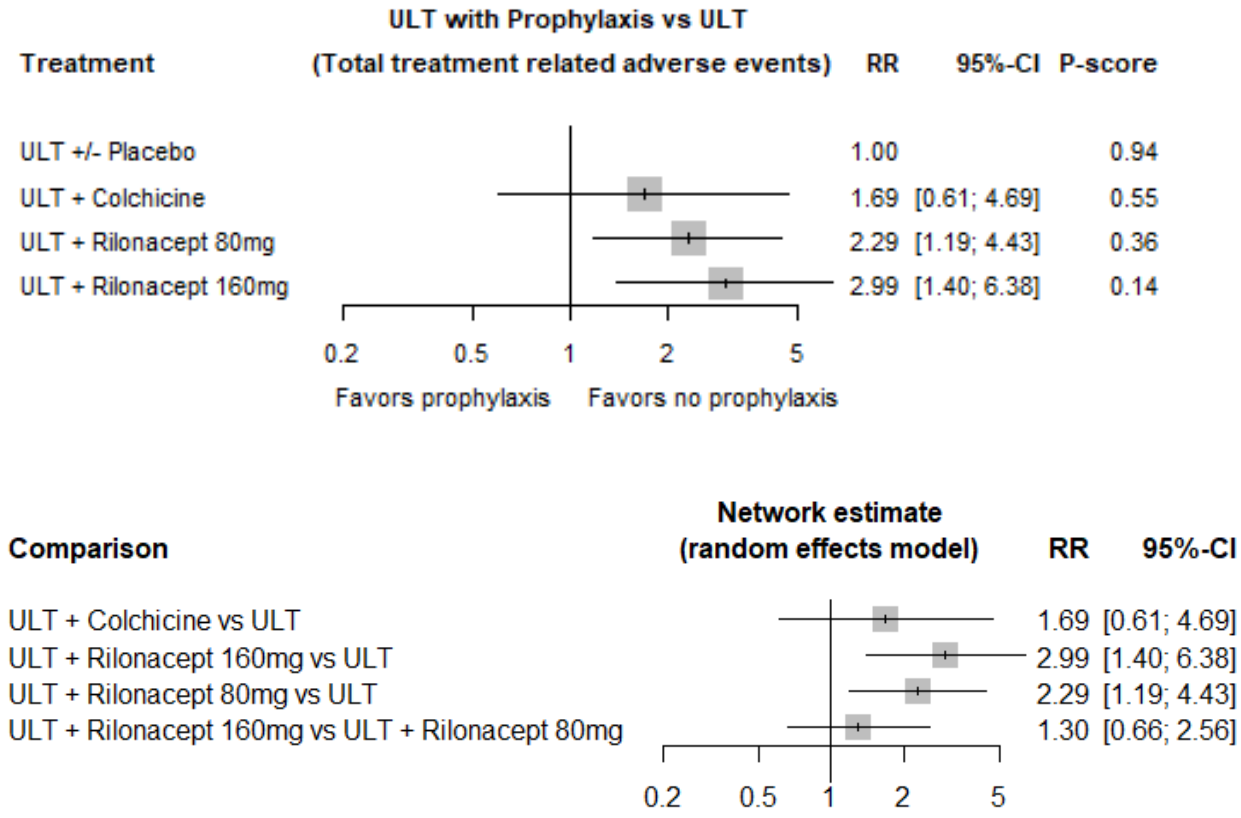
Supplementary Figure 9: Forrest plots - Prophylaxis-based adverse-event network: total adverse events



Supplementary Figure 10: Forrest plots - Prophylaxis-based adverse-event network: serious adverse events



Supplementary Figure 11: Forrest plots - Prophylaxis-based adverse-event network: total treatment related adverse events



Supplementary Exhibit 7: Evaluation of global inconsistency

ULT-based flare subnetwork 1

```
## Q statistics to assess homogeneity / consistency
##
##                     Q df p-value
## Total            3.08  8  0.9295
## Within designs   1.18  2  0.5548
## Between designs  1.90  6  0.9289
##
## Design-specific decomposition of within-designs Q statistic
##
##                         Design    Q df p-value
##  A_p vs F_40mg_p vs F_80mg_p 1.18  2  0.5548
##
## Between-designs Q statistic after detaching of single designs
##
##                     Detached design    Q df p-value
##                     A_p vs F_80mg_p 1.88  5  0.8656
##       A_p vs F_120mg_p vs F_80mg_p 0.47  4  0.9761
##        A_p vs F_40mg_p vs F_80mg_p 1.62  4  0.8051
##  Placebo_p vs F_40mg_p vs F_80mg_p 1.66  4  0.7976
##
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                     Q df p-value tau.within tau2.within
## Between designs 1.90  6  0.9289          0           0
```

ULT-based flare subnetwork 2

```
## Q statistics to assess homogeneity / consistency
##
##                     Q df p-value
## Total            0.19  2  0.9092
## Within designs   0.19  2  0.9092
## Between designs  0.00  0      --
##
## Design-specific decomposition of within-designs Q statistic
##
##        Design    Q df p-value
##  A_t vs A_t_p 0.19  2  0.9092
##
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                     Q df p-value tau.within tau2.within
## Between designs 0.00  0      --          0           0
```

Prophylaxis-based flare network

```
## Q statistics to assess homogeneity / consistency
##
```

```
##                      Q df p-value
## Total             0.49  4  0.9743
## Within designs    0.49  4  0.9743
## Between designs -0.00  0      --
##
## Design-specific decomposition of within-designs Q statistic
##
##                           Design    Q df p-value
##                     ULT vs ULT_C 0.34  2  0.8458
##  ULT vs ULT_R160mg vs ULT_R80mg 0.16  2  0.9248
##
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                      Q df p-value tau.within tau2.within
## Between designs -0.00  0      --          0           0
```

Prophylaxis-based adverse-event network: withdrawal due to adverse events

```
## Q statistics to assess homogeneity / consistency
##
##                     Q df p-value
## Total            4.49  4  0.3432
## Within designs   3.87  3  0.2758
## Between designs  0.62  1  0.4294
##
## Design-specific decomposition of within-designs Q statistic
##
##                           Design    Q df p-value
##                     ULT vs ULT_C 1.84  1  0.1745
##  ULT vs ULT_R160mg vs ULT_R80mg 2.03  2  0.3632
##
## Between-designs Q statistic after detaching of single designs
##
##   Detached design    Q df p-value
##  ULT vs ULT_R80mg 0.00  0      --
##
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                     Q df p-value tau.within tau2.within
## Between designs  0.48  1  0.4890     0.6763      0.4574
```

Prophylaxis-based adverse-event network: total adverse events

```
## Q statistics to assess homogeneity / consistency
##
##                      Q df p-value
## Total            10.57  6  0.1027
## Within designs   10.30  5  0.0672
## Between designs   0.27  1  0.6033
##
## Design-specific decomposition of within-designs Q statistic
```

```
##
##                          Design    Q df p-value
##                   ULT vs ULT_C 0.35  2  0.8396
##                  ULT_C vs ULT_N 8.94  1  0.0028
##  ULT vs ULT_R160mg vs ULT_R80mg 1.01  2  0.6037
##
## Between-designs Q statistic after detaching of single designs
##
##   Detached design    Q df p-value
##  ULT vs ULT_R80mg 0.00  0      --
##
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                    Q df p-value tau.within tau2.within
## Between designs 0.13  1  0.7195     0.0980      0.0096
```

Prophylaxis-based adverse-event network: serious adverse events

```
## Q statistics to assess homogeneity / consistency
##
##                    Q df p-value
## Total           0.53  3  0.9131
## Within designs  0.24  2  0.8882
## Between designs 0.29  1  0.5910
##
## Design-specific decomposition of within-designs Q statistic
##
##                          Design    Q df p-value
##  ULT vs ULT_R160mg vs ULT_R80mg 0.24  2  0.8882
##
## Between-designs Q statistic after detaching of single designs
##
##   Detached design    Q df p-value
##  ULT vs ULT_R80mg 0.00  0      --
##
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                    Q df p-value tau.within tau2.within
## Between designs 0.29  1  0.5910          0           0
```

Prophylaxis-based adverse-event network: total treatment related adverse events

```
## Q statistics to assess homogeneity / consistency
##
##                    Q df p-value
## Total           7.85  3  0.0493
## Within designs  4.85  2  0.0885
## Between designs 3.00  1  0.0834
##
## Design-specific decomposition of within-designs Q statistic
##
```

```
##                           Design    Q df p-value
##  ULT vs ULT_R160mg vs ULT_R80mg 4.85  2  0.0885
##
## Between-designs Q statistic after detaching of single designs
##
##   Detached design    Q df p-value
##  ULT vs ULT_R80mg 0.00  0      --
##
## Q statistic to assess consistency under the assumption of
## a full design-by-treatment interaction random effects model
##
##                    Q df p-value tau.within tau2.within
## Between designs 1.15  1  0.2831     0.3943      0.1555
```

Supplementary Exhibit 8: Evaluation of local inconsistency

ULT-based flare subnetwork 1

```
## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##                  comparison k prop    nma direct indir.    RoR     z p-value
##           A_p vs F_120mg_p 2 0.80 0.6125 0.6144 0.6047 1.0160  0.07  0.9447
##           A_p vs F_240mg_p 1 0.69 0.4983 0.5000 0.4946 1.0110  0.04  0.9666
##              A_p vs F_40mg 0    0 0.5505      . 0.5505      .     .       .
##            A_p vs F_40mg_p 2 0.51 1.0459 1.0170 1.0764 0.9448 -0.30  0.7614
##            A_p vs F_80mg_p 5 0.92 0.8754 0.8834 0.7843 1.1263  0.41  0.6790
##         A_p vs F_L_200mg_p 0    0 0.5990      . 0.5990      .     .       .
##         A_p vs F_L_400mg_p 0    0 0.4265      . 0.4265      .     .       .
##                A_p vs F_t 0    0 0.9513      . 0.9513      .     .       .
##           A_p vs Placebo_p 1 0.33 1.1291 1.1481 1.1200 1.0251  0.10  0.9207
##     F_120mg_p vs F_240mg_p 1 0.89 0.8136 0.7794 1.1507 0.6773 -1.05  0.2944
##        F_120mg_p vs F_40mg 0    0 0.8988      . 0.8988      .     .       .
##      F_120mg_p vs F_40mg_p 0    0 1.7078      . 1.7078      .     .       .
##      F_120mg_p vs F_80mg_p 2 0.81 1.4292 1.4275 1.4370 0.9933 -0.03  0.9760
##   F_120mg_p vs F_L_200mg_p 0    0 0.9781      . 0.9781      .     .       .
##   F_120mg_p vs F_L_400mg_p 0    0 0.6963      . 0.6963      .     .       .
##           F_120mg_p vs F_t 0    0 1.5532      . 1.5532      .     .       .
##     F_120mg_p vs Placebo_p 1 0.41 1.8435 1.7896 1.8819 0.9510 -0.20  0.8390
##        F_240mg_p vs F_40mg 0    0 1.1047      . 1.1047      .     .       .
##      F_240mg_p vs F_40mg_p 0    0 2.0989      . 2.0989      .     .       .
##      F_240mg_p vs F_80mg_p 1 0.74 1.7566 1.6472 2.1167 0.7782 -0.94  0.3471
##   F_240mg_p vs F_L_200mg_p 0    0 1.2021      . 1.2021      .     .       .
##   F_240mg_p vs F_L_400mg_p 0    0 0.8558      . 0.8558      .     .       .
##           F_240mg_p vs F_t 0    0 1.9089      . 1.9089      .     .       .
##     F_240mg_p vs Placebo_p 1 0.53 2.2658 2.2963 2.2321 1.0288  0.10  0.9207
##         F_40mg vs F_40mg_p 1 1.00 1.9000 1.9000      .      .     .       .
##         F_40mg vs F_80mg_p 0    0 1.5901      . 1.5901      .     .       .
##       F_40mg vs F_L_200mg_p 0    0 1.0882      . 1.0882      .     .       .
##       F_40mg vs F_L_400mg_p 0    0 0.7747      . 0.7747      .     .       .
```

```
##               F_40mg vs F_t 1 1.00 1.7280 1.7280      .      .     .       .
##         F_40mg vs Placebo_p 0    0 2.0510      . 2.0510      .     .       .
##        F_40mg_p vs F_80mg_p 3 0.94 0.8369 0.8381 0.8190 1.0233  0.08  0.9390
##     F_40mg_p vs F_L_200mg_p 0    0 0.5727      . 0.5727      .     .       .
##     F_40mg_p vs F_L_400mg_p 0    0 0.4077      . 0.4077      .     .       .
##             F_40mg_p vs F_t 1 1.00 0.9095 0.9095      .      .     .       .
##       F_40mg_p vs Placebo_p 1 0.75 1.0795 1.0570 1.1486 0.9203 -0.33  0.7387
##     F_80mg_p vs F_L_200mg_p 1 1.00 0.6843 0.6843      .      .     .       .
##     F_80mg_p vs F_L_400mg_p 1 1.00 0.4872 0.4872      .      .     .       .
##             F_80mg_p vs F_t 0    0 1.0867      . 1.0867      .     .       .
##       F_80mg_p vs Placebo_p 2 0.95 1.2899 1.3228 0.8192 1.6147  1.07  0.2855
##  F_L_200mg_p vs F_L_400mg_p 1 1.00 0.7119 0.7119      .      .     .       .
##          F_L_200mg_p vs F_t 0    0 1.5880      . 1.5880      .     .       .
##    F_L_200mg_p vs Placebo_p 0    0 1.8848      . 1.8848      .     .       .
##          F_L_400mg_p vs F_t 0    0 2.2306      . 2.2306      .     .       .
##    F_L_400mg_p vs Placebo_p 0    0 2.6476      . 2.6476      .     .       .
##            F_t vs Placebo_p 0    0 1.1869      . 1.1869      .     .       .
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (RR) in network meta-analysis
##  direct     - Estimated treatment effect (RR) derived from direct evidence
##  indir.     - Estimated treatment effect (RR) derived from indirect evidence
##  RoR        - Ratio of Ratios (direct versus indirect)
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

ULT-based flare subnetwork 2

```
## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##      comparison k prop    nma direct indir. RoR z p-value
##    A_t_p vs A_t 3 1.00 0.3980 0.3980      .   . .       .
##    B_t_p vs A_t 0    0 1.4281      . 1.4281   . .       .
##    F_t_p vs A_t 0    0 0.2653      . 0.2653   . .       .
##  A_t_p vs B_t_p 1 1.00 0.2787 0.2787      .   . .       .
##  A_t_p vs F_t_p 1 1.00 1.5000 1.5000      .   . .       .
##  B_t_p vs F_t_p 0    0 5.3824      . 5.3824   . .       .
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (RR) in network meta-analysis
##  direct     - Estimated treatment effect (RR) derived from direct evidence
##  indir.     - Estimated treatment effect (RR) derived from indirect evidence
##  RoR        - Ratio of Ratios (direct versus indirect)
```

```
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

Prophylaxis-based flare network

```
## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##               comparison k prop    nma direct indir. RoR z p-value
##             ULT_C vs ULT 3 1.00 0.5043 0.5043      .   . .       .
##        ULT_R160mg vs ULT 2 1.00 0.3533 0.3531      .   . .       .
##         ULT_R80mg vs ULT 2 1.00 0.4334 0.4334      .   . .       .
##      ULT_C vs ULT_R160mg 0    0 1.4274      . 1.4274   . .       .
##       ULT_C vs ULT_R80mg 0    0 1.1636      . 1.1636   . .       .
##  ULT_R160mg vs ULT_R80mg 2 1.00 0.8152 0.8165      .   . .       .
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (RR) in network meta-analysis
##  direct     - Estimated treatment effect (RR) derived from direct evidence
##  indir.     - Estimated treatment effect (RR) derived from indirect evidence
##  RoR        - Ratio of Ratios (direct versus indirect)
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

Prophylaxis-based adverse-event network: withdrawal due to adverse events

```
## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##               comparison k prop    nma direct  indir.    RoR     z p-value
##             ULT_C vs ULT 2 1.00 1.4513 1.4513       .      .     .       .
##        ULT_R160mg vs ULT 2 0.88 0.6001 0.7621  0.1125 6.7756  0.89  0.3754
##         ULT_R80mg vs ULT 3 0.99 1.0979 1.0531 47.6115 0.0221 -0.81  0.4201
##      ULT_C vs ULT_R160mg 0    0 2.4186      .  2.4186      .     .       .
##       ULT_C vs ULT_R80mg 0    0 1.3220      .  1.3220      .     .       .
##  ULT_R160mg vs ULT_R80mg 2 0.90 0.5466 0.5115  1.0172 0.5029 -0.29  0.7690
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (RR) in network meta-analysis
##  direct     - Estimated treatment effect (RR) derived from direct evidence
##  indir.     - Estimated treatment effect (RR) derived from indirect evidence
##  RoR        - Ratio of Ratios (direct versus indirect)
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

Prophylaxis-based adverse-event network: total adverse events

```
## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##               comparison k prop    nma direct indir.    RoR     z p-value
##             ULT_C vs ULT 3 1.00 1.0191 1.0191      .      .     .       .
##             ULT_N vs ULT 0    0 0.9095      . 0.9095      .     .       .
##         ULT_R160mg vs ULT 2 0.89 1.0331 1.0459 0.9378 1.1153  0.35  0.7261
##          ULT_R80mg vs ULT 3 1.00 1.0407 1.0395      .      .     .       .
##            ULT_C vs ULT_N 2 1.00 1.1206 1.1206      .      .     .       .
##       ULT_C vs ULT_R160mg 0    0 0.9865      . 0.9865      .     .       .
##        ULT_C vs ULT_R80mg 0    0 0.9793      . 0.9793      .     .       .
##       ULT_N vs ULT_R160mg 0    0 0.8803      . 0.8803      .     .       .
##        ULT_N vs ULT_R80mg 0    0 0.8739      . 0.8739      .     .       .
##  ULT_R160mg vs ULT_R80mg 2 0.90 0.9927 0.9812 1.1065 0.8868 -0.37  0.7138
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (RR) in network meta-analysis
##  direct     - Estimated treatment effect (RR) derived from direct evidence
##  indir.     - Estimated treatment effect (RR) derived from indirect evidence
##  RoR        - Ratio of Ratios (direct versus indirect)
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

Prophylaxis-based adverse-event network: serious adverse events

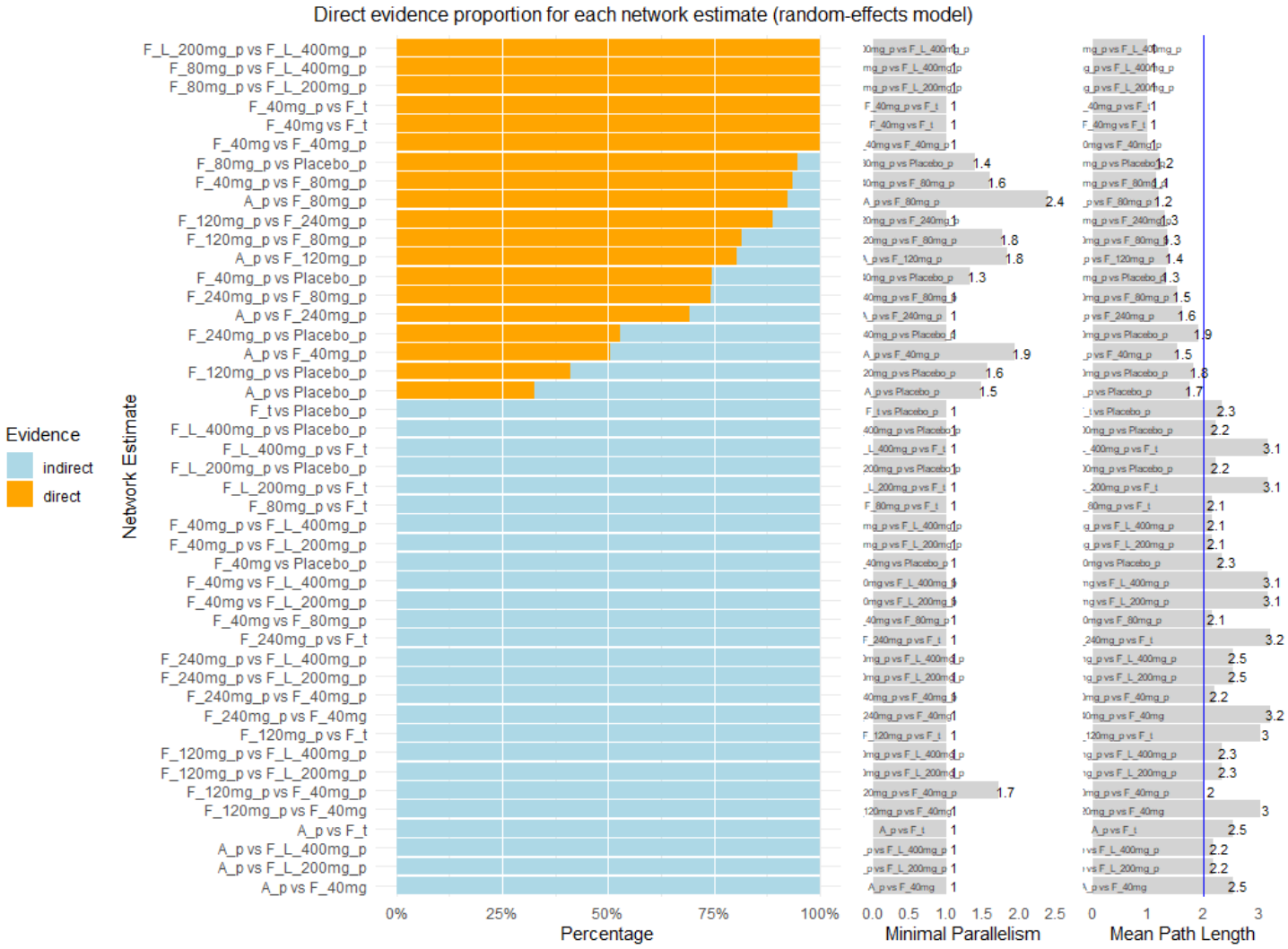
```
## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##               comparison k prop    nma direct    indir.    RoR     z p-value
##             ULT_C vs ULT 1 1.00 3.0000 3.0000         .      .     .       .
##         ULT_R160mg vs ULT 2 0.90 0.7715 0.8367    0.3680 2.2739  0.47  0.6365
##          ULT_R80mg vs ULT 3 1.00 0.9645 0.9605 1208.2852 0.0008 -0.44  0.6593
##       ULT_C vs ULT_R160mg 0    0 3.8887      .    3.8887      .     .       .
##        ULT_C vs ULT_R80mg 0    0 3.1105      .    3.1105      .     .       .
##  ULT_R160mg vs ULT_R80mg 2 0.91 0.7999 0.7380    1.8979 0.3889 -0.52  0.6049
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (RR) in network meta-analysis
##  direct     - Estimated treatment effect (RR) derived from direct evidence
##  indir.     - Estimated treatment effect (RR) derived from indirect evidence
##  RoR        - Ratio of Ratios (direct versus indirect)
```

```
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

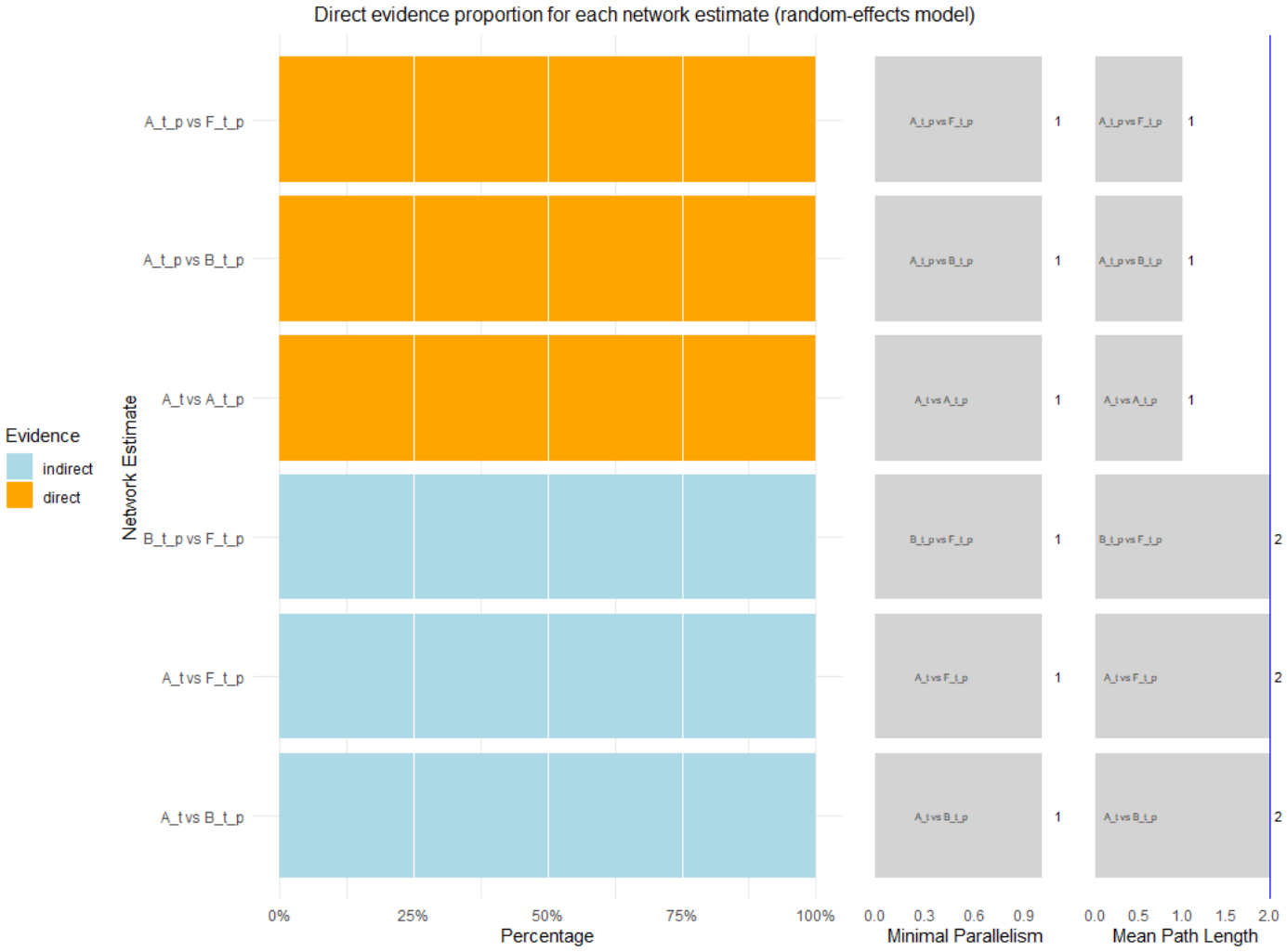
Prophylaxis-based adverse-event network: total treatment related adverse events

```
## Separate indirect from direct evidence (SIDE) using back-calculation method
##
## Random effects model:
##
##               comparison k prop    nma direct indir.    RoR     z p-value
##             ULT_C vs ULT 1 1.00 1.6875 1.6875      .      .     .       .
##        ULT_R160mg vs ULT 2 0.84 2.9857 3.5058 1.2955 2.7061  0.94  0.3451
##         ULT_R80mg vs ULT 3 1.00 2.2936 2.2798      .      .     .       .
##      ULT_C vs ULT_R160mg 0    0 0.5652      . 0.5652      .     .       .
##       ULT_C vs ULT_R80mg 0    0 0.7357      . 0.7357      .     .       .
##  ULT_R160mg vs ULT_R80mg 2 0.93 1.3017 1.1802 4.4162 0.2672 -1.00  0.3171
##
## Legend:
##  comparison - Treatment comparison
##  k          - Number of studies providing direct evidence
##  prop       - Direct evidence proportion
##  nma        - Estimated treatment effect (RR) in network meta-analysis
##  direct     - Estimated treatment effect (RR) derived from direct evidence
##  indir.     - Estimated treatment effect (RR) derived from indirect evidence
##  RoR        - Ratio of Ratios (direct versus indirect)
##  z          - z-value of test for disagreement (direct versus indirect)
##  p-value    - p-value of test for disagreement (direct versus indirect)
```

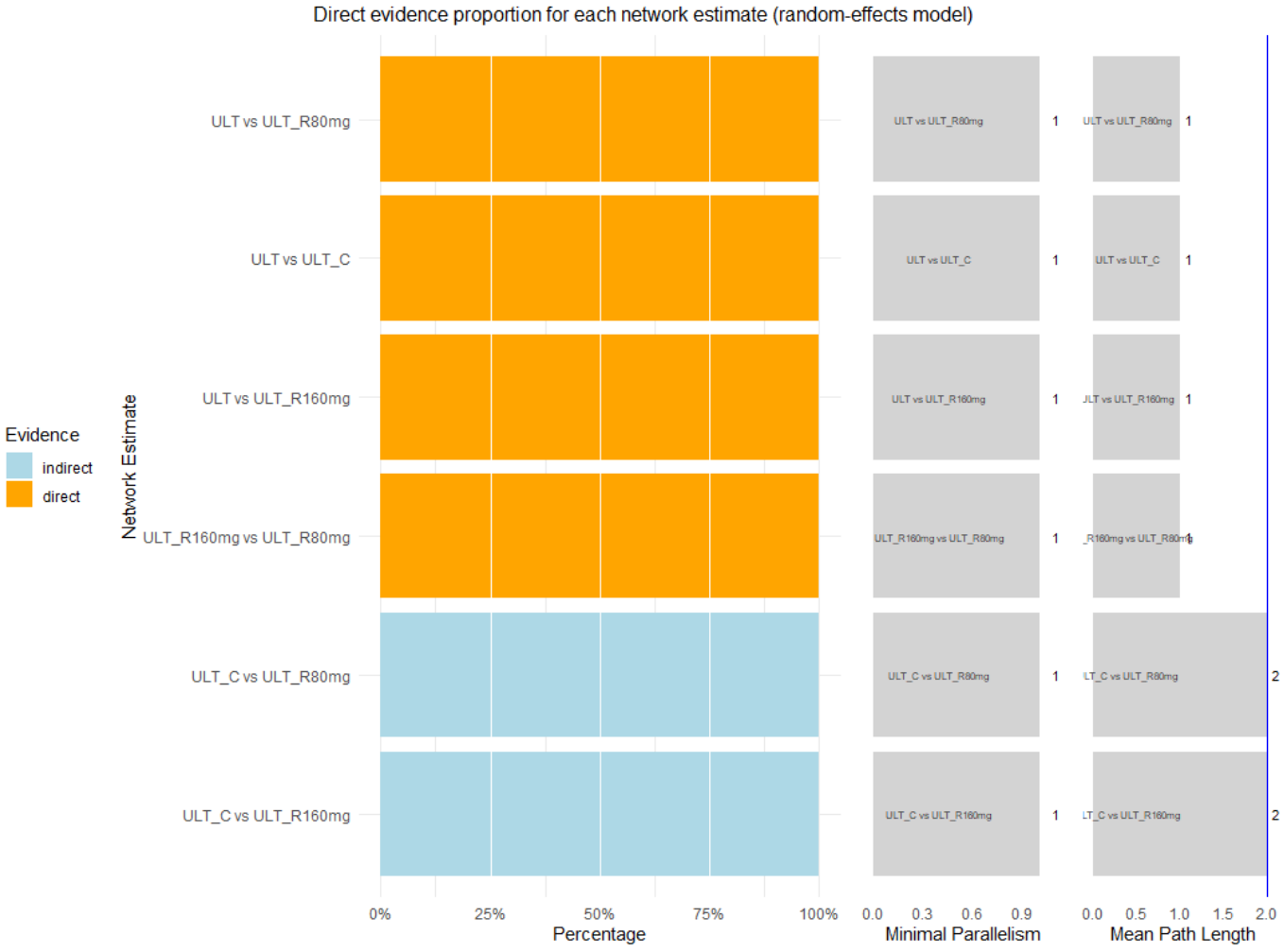
Supplementary Figure 12: Direct evidence proportions - ULT-based flare subnetwork 1



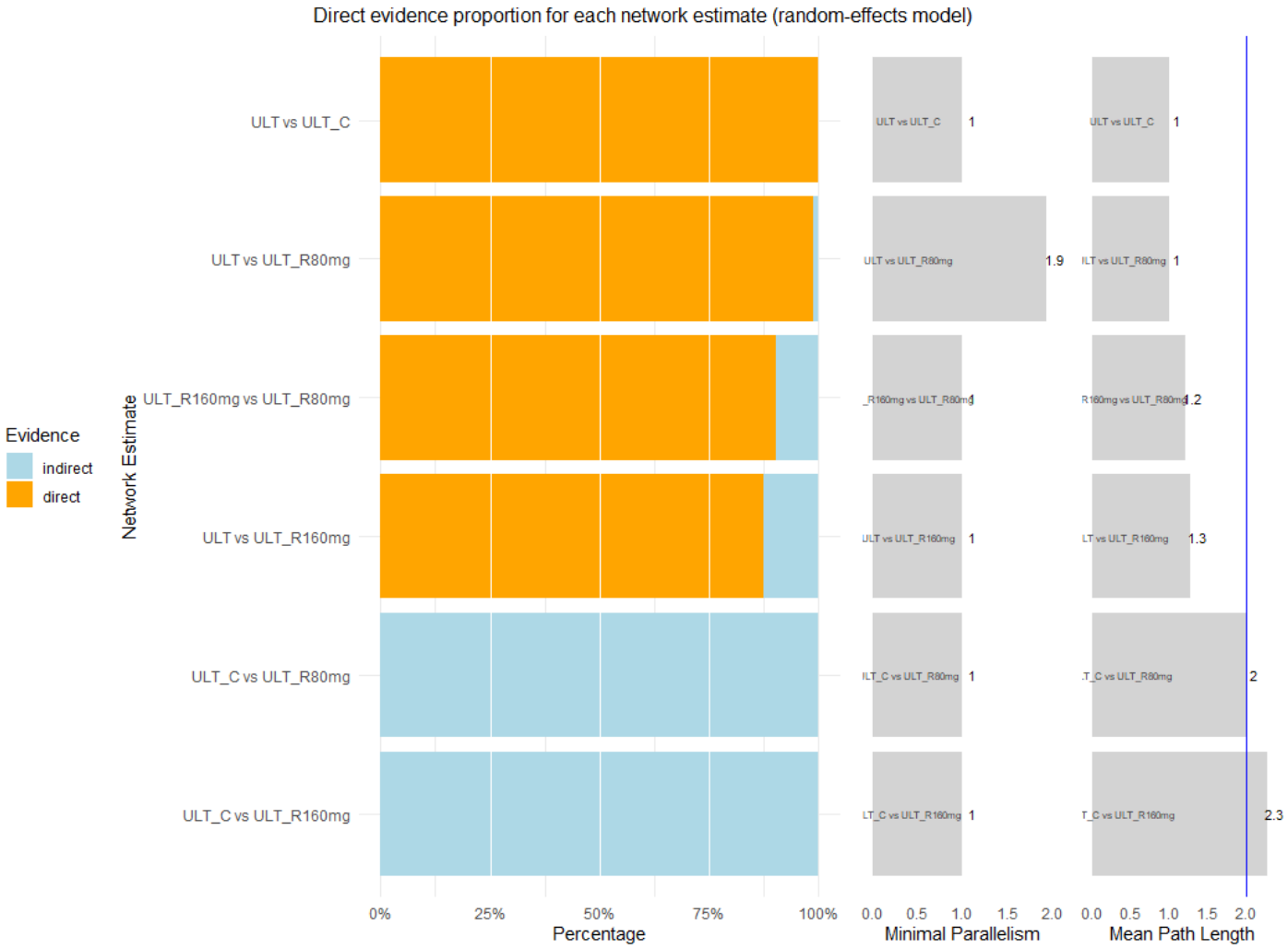
Supplementary Figure 13: Direct evidence proportions - ULT-based flare subnetwork 2



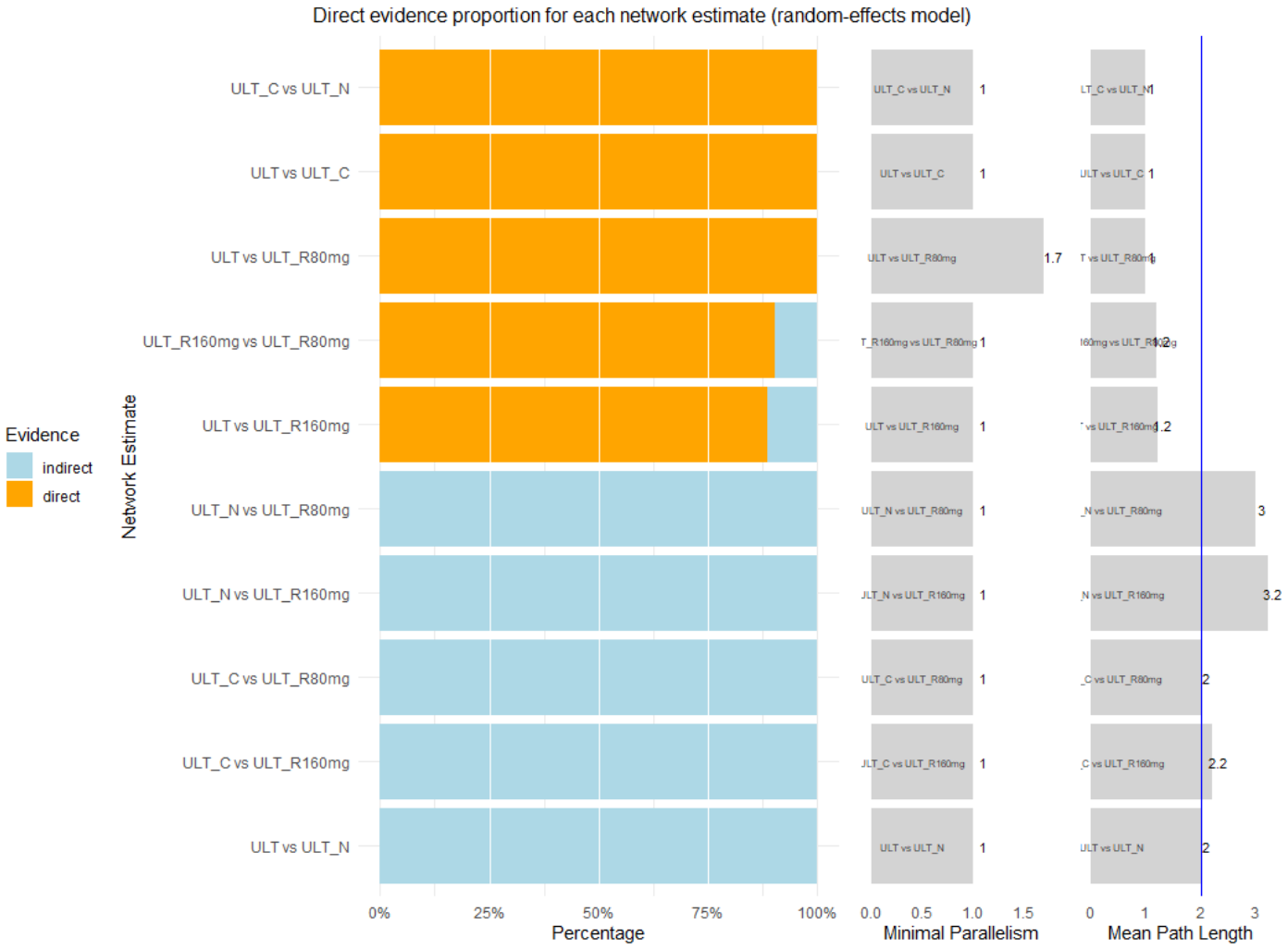
Supplementary Figure 14: Direct evidence proportions - Prophylaxis-based flare network



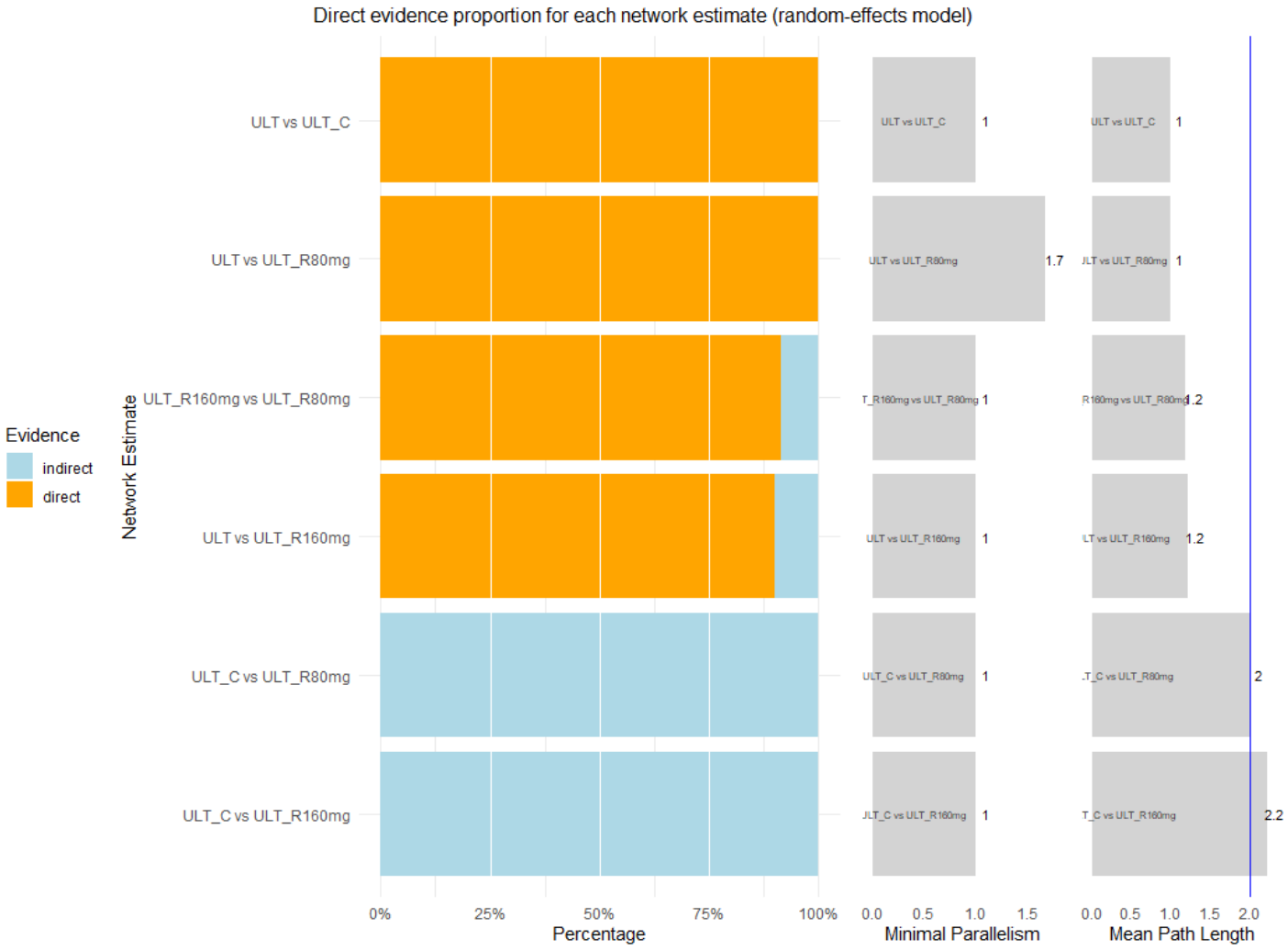
Supplementary Figure 15: Direct evidence proportions - Prophylaxis-based adverse-event network: withdrawal due to adverse events



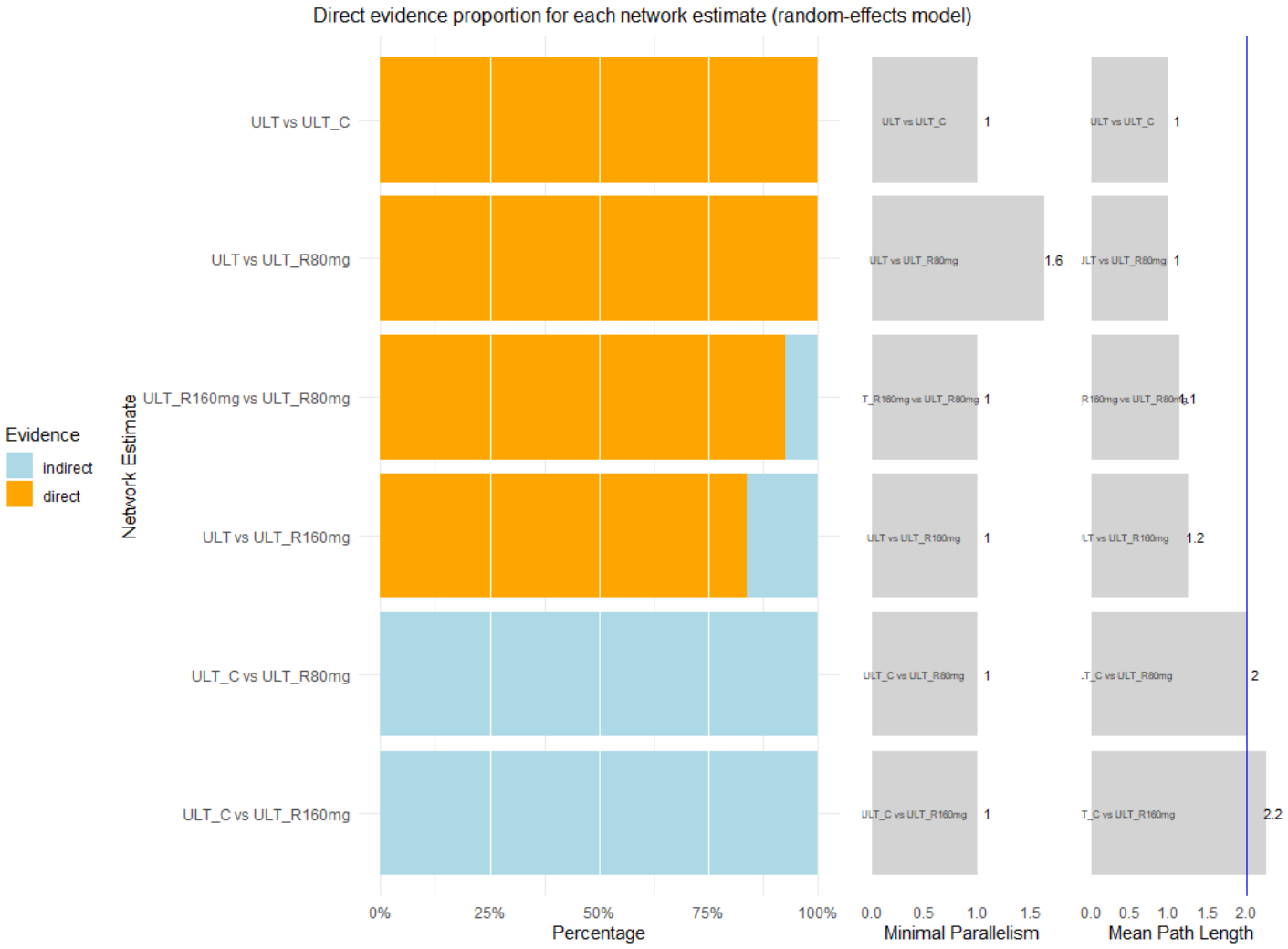
Supplementary Figure 16: Direct evidence proportions - Prophylaxis-based adverse-event network: total adverse events



Supplementary Figure 17: Direct evidence proportions - Prophylaxis-based adverse-event network: serious adverse events



Supplementary Figure 18: Direct evidence proportions - Prophylaxis-based adverse-event network: total treatment related adverse events



Supplementary Exhibit 9: P-scores

ULT-based flare subnetwork 1

```
##                                                P-score
## Placebo + Prophylaxis                           0.9214
## Febuxostat 40mg + Prophylaxis                   0.8346
## Allopurinol ~300mg + Prophylaxis                0.7704
## Febuxostat 10mg up-titrated to 40mg             0.7156
## Febuxostat 80mg + Prophylaxis                   0.5898
## Febuxostat 120mg + Prophylaxis                  0.3474
## Febuxostat 80mg + Lesinurad 200mg + Prophylaxis 0.3340
## Febuxostat 40mg                                 0.2527
## Febuxostat 240mg + Prophylaxis                  0.1573
## Febuxostat 80mg + Lesinurad 400mg + Prophylaxis 0.0767
```

ULT-based flare subnetwork 2

```
##                                          P-score
## Febuxostat up-titration + Prophylaxis     0.9001
## Allopurinol up-titration + Prophylaxis    0.6436
## Benzbromarone up-titration + Prophylaxis  0.2604
## Allopurinol up-titration                  0.1959
```

Prophylaxis-based flare network

```
##                        P-score
## ULT + Rilonacept 160mg  0.9138
## ULT + Rilonacept 80mg   0.6366
## ULT + Colchicine        0.4496
## ULT                     0.0000
```

Prophylaxis-based adverse-event network: withdrawal due to adverse events

```
## Title: Withdrawal due to adverse events
##
##                        P-score
## ULT + Rilonacept 160mg  0.7805
## ULT                     0.4877
## ULT + Rilonacept 80mg   0.4058
## ULT + Colchicine        0.3260
```

Prophylaxis-based adverse-event network: total adverse events

```
## Title: Total adverse events
##
##                        P-score
## ULT + Naproxen          0.7868
## ULT                     0.5403
## ULT + Rilonacept 160mg  0.4091
## ULT + Colchicine        0.3946
## ULT + Rilonacept 80mg   0.3692
```

Prophylaxis-based adverse-event network: serious adverse events

```
## Title: Serious adverse events
##
##                        P-score
```

```
## ULT + Rilonacept 160mg  0.7162
## ULT + Rilonacept 80mg   0.5399
## ULT                     0.5077
## ULT + Colchicine        0.2361
```

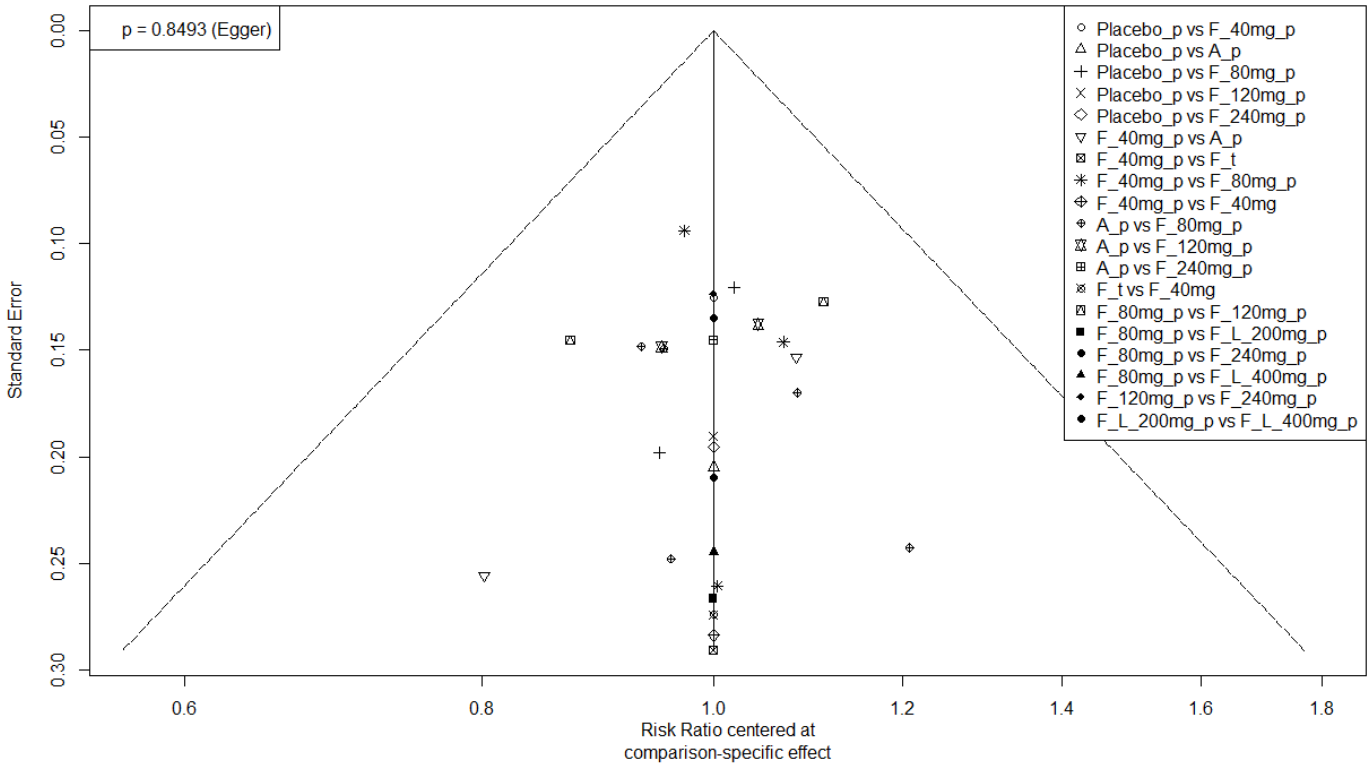
Prophylaxis-based adverse-event network: total treatment related adverse events

```
## Title: Total treatment related adverse events
##
##                        P-score
## ULT                     0.9444
## ULT + Colchicine        0.5525
## ULT + Rilonacept 80mg   0.3647
## ULT + Rilonacept 160mg  0.1384
```

Supplementary Figure 19: Comparison adjusted funnel plots - ULT-based flare subnetwork 1

```
funnel(m.netmeta_ULTa,
       order = c("Placebo_p", "F_40mg_p", "A_p", "F_t", "F_80mg_p", "F_120mg_p",
"F_L_200mg", "F_40mg", "F_240mg_p", "F_L_400mg"),
       linreg = TRUE)

## Warning: Use argument 'method.bias' instead of 'linreg' (deprecated).
```

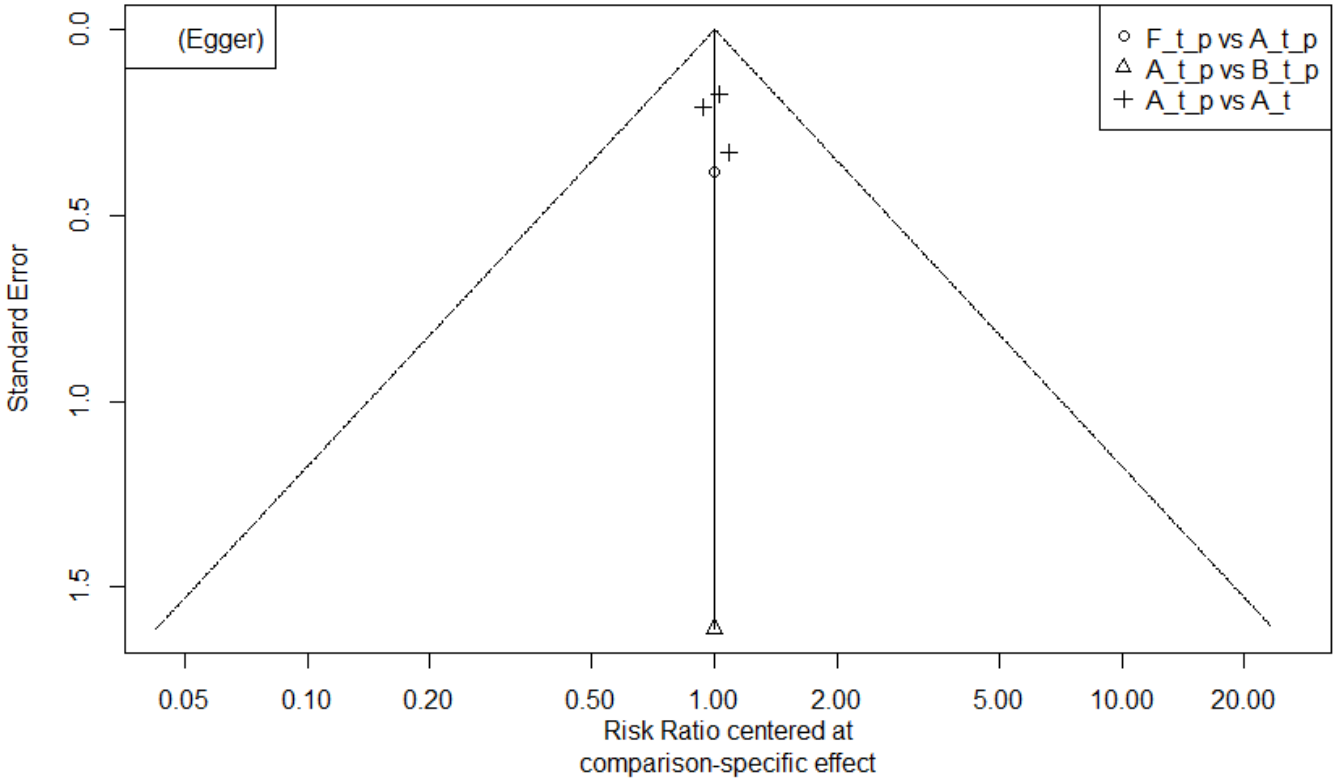



```
## Linear regression test of funnel plot asymmetry
##
## Test result: t = -0.19, df = 27, p-value = 0.8493
##
## Sample estimates:
##     bias se.bias intercept se.intercept
##  -0.0491  0.2556    0.0076       0.0416
##
## Details:
## - multiplicative residual heterogeneity variance (tau^2 = 0.1635)
## - predictor: standard error
## - weight:    inverse variance
## - reference: Egger et al. (1997), BMJ
```

Supplementary Figure 20: Comparison adjusted funnel plots - ULT-based flare subnetwork 2

```
funnel(m.netmeta_ULTb,
       order = c("F_t_p", "A_t_p", "B_t_p","A_t"),
       linreg = TRUE)

## Warning: Use argument 'method.bias' instead of 'linreg' (deprecated).
```

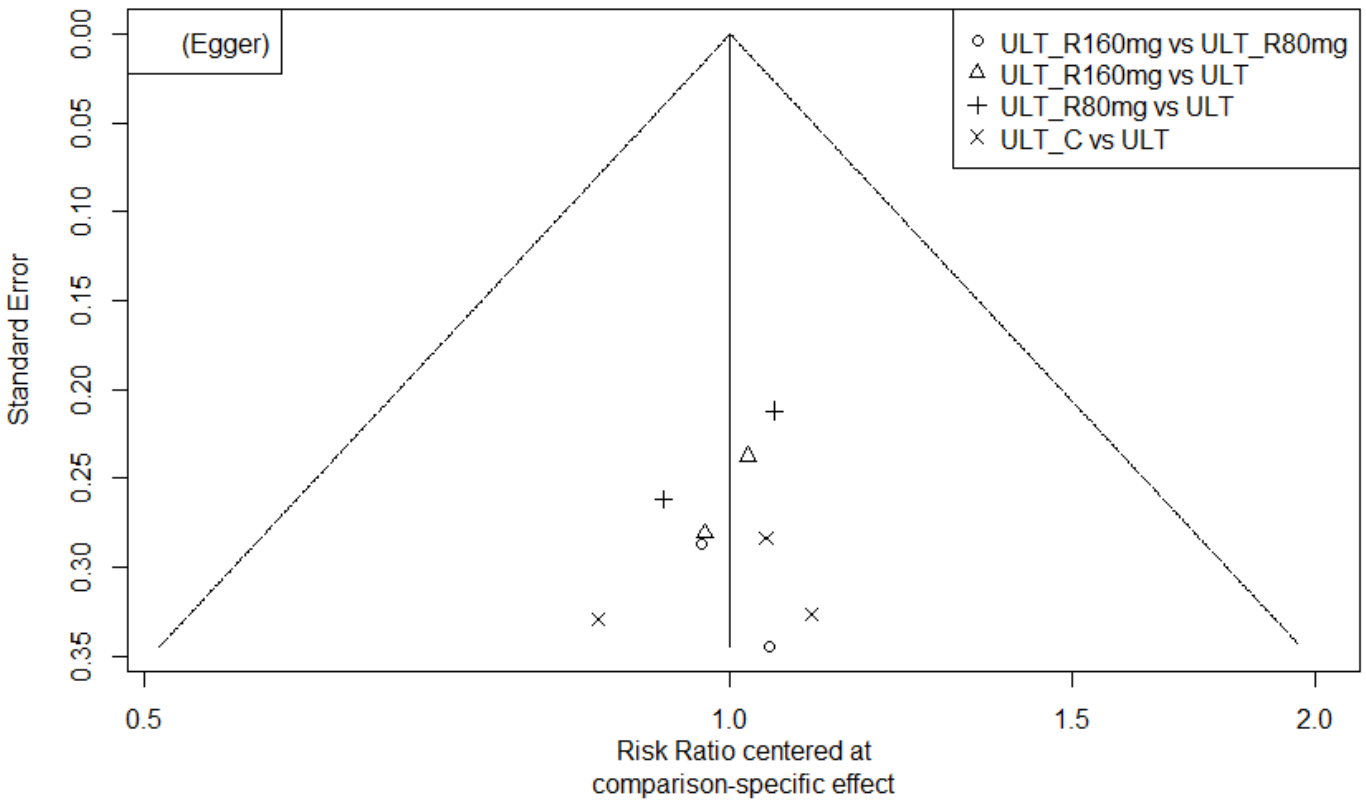



```
## Linear regression test of funnel plot asymmetry
##
## Test result: t = 0.22, df = 3, p-value = 0.8385
##
## Sample estimates:
##    bias se.bias intercept se.intercept
##  0.0528  0.2377   -0.0122       0.0623
##
## Details:
## - multiplicative residual heterogeneity variance (tau^2 = 0.0624)
## - predictor: standard error
## - weight:    inverse variance
## - reference: Egger et al. (1997), BMJ
```

Supplementary Figure 21: Comparison adjusted funnel plots - Prophylaxis-based flare network

```
funnel(m.netmeta_proph,
       order = c("ULT_R160mg", "ULT_R80mg", "ULT_C","ULT"),
       linreg = TRUE)

## Warning: Use argument 'method.bias' instead of 'linreg' (deprecated).
```

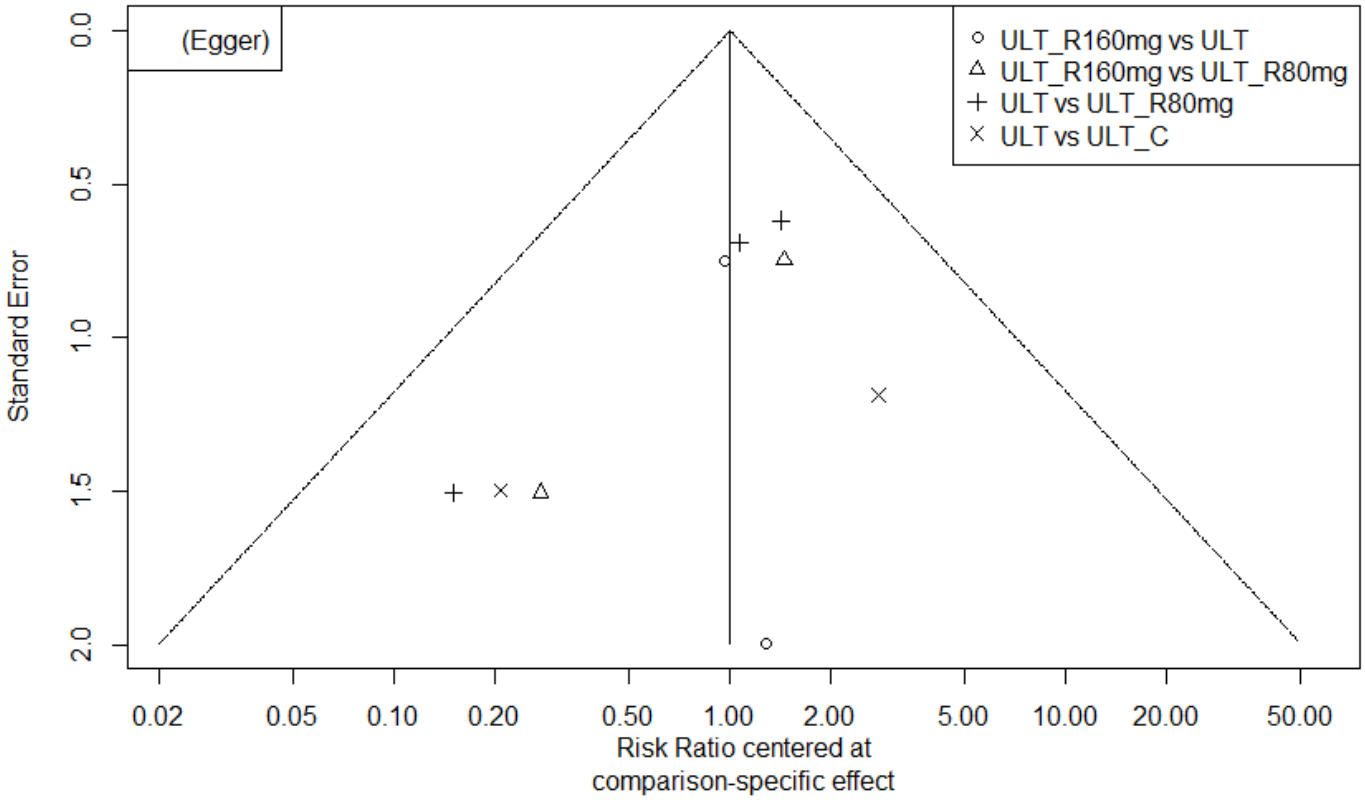



```
## Linear regression test of funnel plot asymmetry
##
## Test result: t = -0.63, df = 7, p-value = 0.5494
##
## Sample estimates:
##     bias se.bias intercept se.intercept
##  -0.3695  0.5876    0.1005       0.1618
##
## Details:
## - multiplicative residual heterogeneity variance (tau^2 = 0.0728)
## - predictor: standard error
## - weight:    inverse variance
## - reference: Egger et al. (1997), BMJ
```

Supplementary Figure 22: Comparison adjusted funnel plots - Prophylaxis-based adverse-event network: withdrawal due to adverse events

```
funnel(m.netmeta_AE_w,
       order = c("ULT_R160mg", "ULT", "ULT_R80mg","ULT_C"),
       linreg = TRUE)

## Warning: Use argument 'method.bias' instead of 'linreg' (deprecated).
```

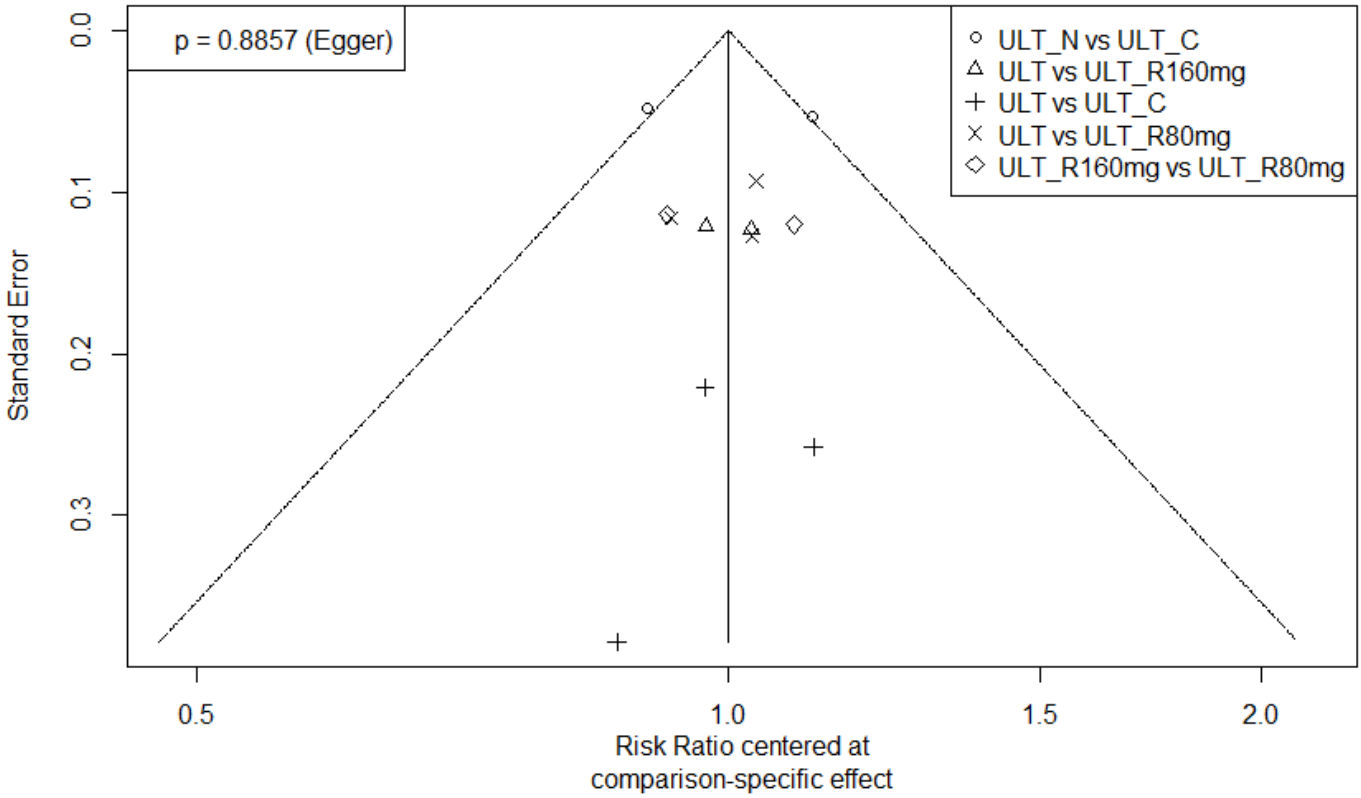



```
## Linear regression test of funnel plot asymmetry
##
## Test result: t = -1.82, df = 7, p-value = 0.1117
##
## Sample estimates:
##     bias se.bias intercept se.intercept
##  -1.1242  0.6180    0.9920       0.5694
##
## Details:
## - multiplicative residual heterogeneity variance (tau^2 = 0.4611)
## - predictor: standard error
## - weight:    inverse variance
## - reference: Egger et al. (1997), BMJ
```

Supplementary Figure 23: Comparison adjusted funnel plots - Prophylaxis-based adverse-event network: total adverse events

```
funnel(m.netmeta_AE_t,
       order = c("ULT_N", "ULT", "ULT_R160mg", "ULT_C", "ULT_R80mg" ),
       linreg = TRUE)

## Warning: Use argument 'method.bias' instead of 'linreg' (deprecated).
```

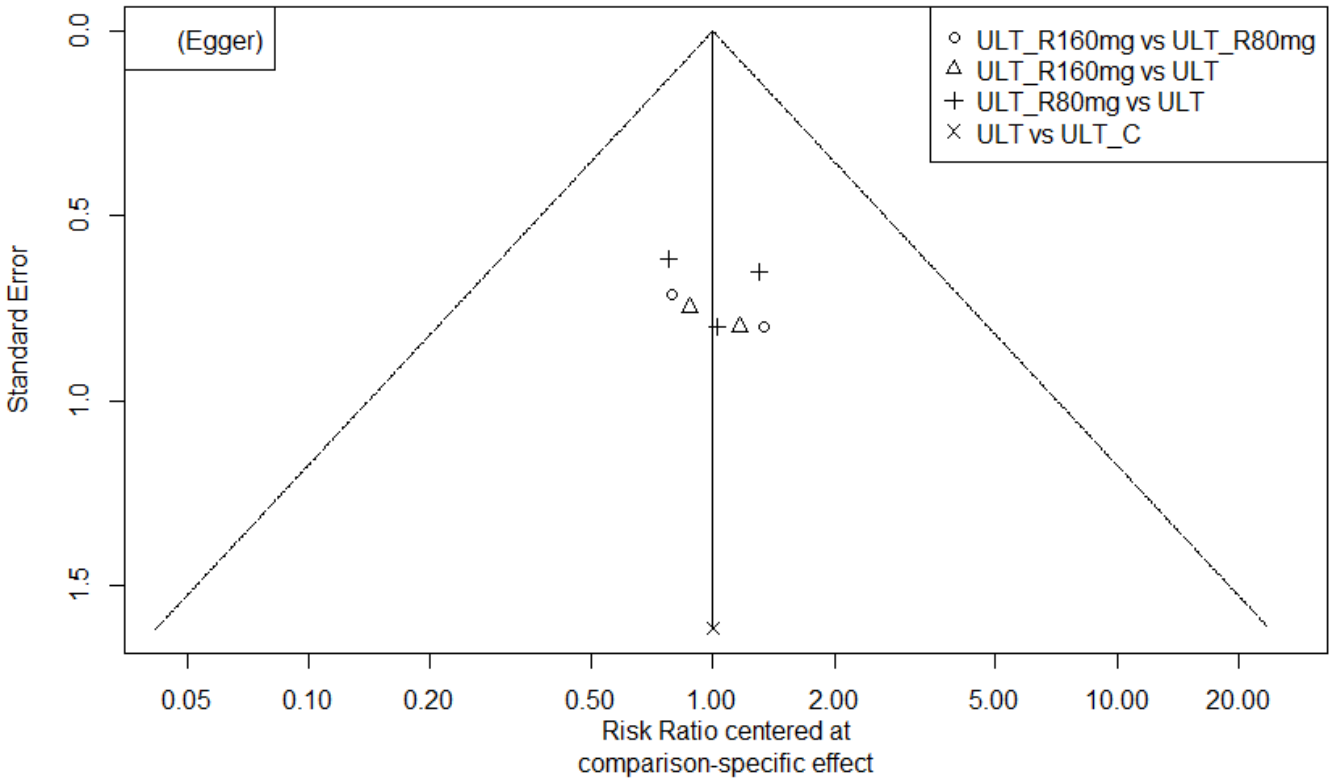



```
## Linear regression test of funnel plot asymmetry
##
## Test result: t = 0.15, df = 10, p-value = 0.8857
##
## Sample estimates:
##    bias se.bias intercept se.intercept
##  0.0913  0.6190   -0.0115       0.0582
##
## Details:
## - multiplicative residual heterogeneity variance (tau^2 = 1.1010)
## - predictor: standard error
## - weight:    inverse variance
## - reference: Egger et al. (1997), BMJ
```

Supplementary Figure 24: Comparison adjusted funnel plots - Prophylaxis-based adverse-event network: serious adverse events

```
funnel(m.netmeta_AE_s,
       order = c("ULT_R160mg", "ULT_R80mg", "ULT", "ULT_C"),
       linreg = TRUE)

## Warning: Use argument 'method.bias' instead of 'linreg' (deprecated).
```

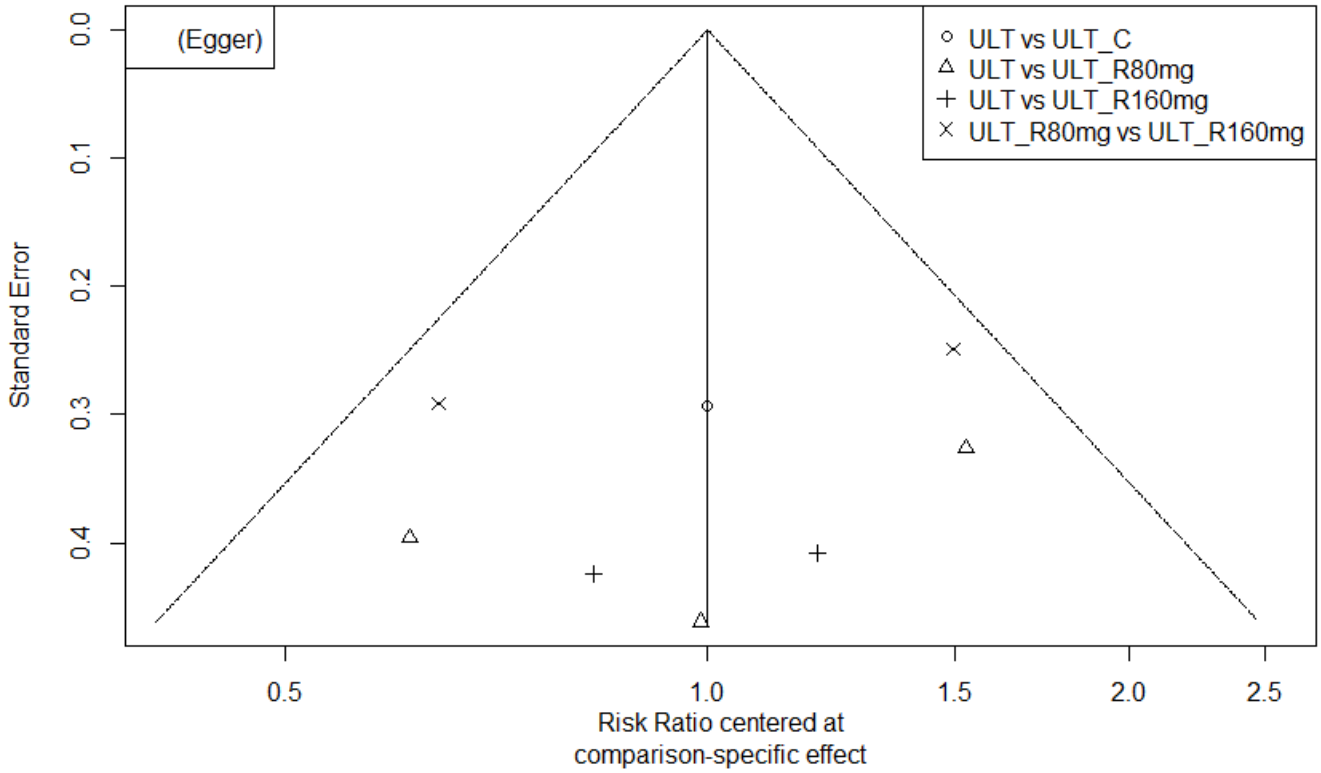



```
## Linear regression test of funnel plot asymmetry
##
## Test result: t = 0.42, df = 6, p-value = 0.6899
##
## Sample estimates:
##    bias se.bias intercept se.intercept
##  0.2211  0.5278   -0.1645       0.4021
##
## Details:
## - multiplicative residual heterogeneity variance (tau^2 = 0.1032)
## - predictor: standard error
## - weight:    inverse variance
## - reference: Egger et al. (1997), BMJ
```

Supplementary Figure 25: Comparison adjusted funnel plots - Prophylaxis-based adverse-event network: total treatment related adverse events

```
funnel(m.netmeta_AE_tr,
       order = c("ULT", "ULT_C", "ULT_R80mg", "ULT_R160mg"),
       linreg = TRUE)

## Warning: Use argument 'method.bias' instead of 'linreg' (deprecated).
```




```
## Linear regression test of funnel plot asymmetry
##
## Test result: t = -0.87, df = 6, p-value = 0.4157
##
## Sample estimates:
##     bias se.bias intercept se.intercept
##  -1.6908  1.9345    0.5841       0.6469
##
## Details:
## - multiplicative residual heterogeneity variance (tau^2 = 1.2478)
## - predictor: standard error
## - weight:    inverse variance
## - reference: Egger et al. (1997), BMJ
```

Supplementary References

1. van den Bogert CA, Souverein PC, Brekelmans CTM, Janssen SWJ, Koeter GH, Leufkens HGM, et al. Non-Publication Is Common among Phase 1, Single-Center, Not Prospectively Registered, or Early Terminated Clinical Drug Trials. PLoS One. 2016;11(12):e0167709-e.
2. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum. 1977;20(3):895-900.
3. Neogi T, Jansen T, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annals of the Rheumatic Diseases. 2015;74(10):1789-98.
4. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis With R: A Hands-On Guide. 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021 2021.
5. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898-l.
6. Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA. Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. Journal of Rheumatology. 2004;31(12):2429-32.
7. Schumacher HR, Jr., Evans RR, Saag KG, Clower J, Jennings W, Weinstein SP, et al. Rilonacept (interleukin-1 trap) for prevention of gout flares during initiation of uric acid-lowering therapy: results from a phase III randomized, double-blind, placebo-controlled, confirmatory efficacy study. Arthritis Care Res (Hoboken). 2012;64(10):1462-70.
8. Mitha E, Ralph Schumacher H, Fouche L, Luo SF, Weinstein SP, Yancopoulos GD, et al. Rilonacept for gout flare prevention during initiation of uric acid-lowering therapy: Results from the PRESURGE-2 international, phase 3, randomized, placebo-controlled trial. Rheumatology (United Kingdom). 2013;52(7):1285-92.
9. Stamp LK, Chapman PT, Barclay ML, Horne A, Frampton C, Tan P, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Annals of the Rheumatic Diseases. 2017;76(9):1522-8.
10. Sundy JS, Baraf HSB, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment Two Randomized Controlled Trials. JAMA-J Am Med Assoc. 2011;306(7):711-20.
11. Yamanaka H, Tamaki S, Ide Y, Kim H, Inoue K, Sugimoto M, et al. Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study. Annals of the Rheumatic Diseases. 2018;77(2):270-6.
12. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald P, Lloyd E, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial. Arthritis Research and Therapy. 2010;12 (2):R63.

Appendix 2: Standardised protocol for treat-to-target urate lowering therapy

Urate lowering therapy (ULT) escalation protocol

Allopurinol

- Commenced at 100mg daily (50mg if estimated glomerular filtration rate (eGFR) <60ml/min).
- Allopurinol will be increased monthly according to serum urate results until a target serum urate of <0.30mmol/L (the primary endpoint) is achieved.
- Allopurinol will be increased by 100mg monthly (50mg monthly if eGFR <60ml/min) to a maximum tolerated dose not exceeding 900mg daily.
- If allopurinol is not tolerated at any dose, xanthine oxidase inhibitor therapy will be continued with febuxostat.

Probenecid

- If the serum urate target is not reached with maximum tolerated allopurinol monotherapy, probenecid will be added at 500mg twice a day.
- The initial dose will be increased to 1g twice a day after one month if the serum urate target has not been met.

Febuxostat

- Commenced if allopurinol is not tolerated at any dose, or if the maximum tolerated combination of allopurinol and probenecid does not achieve the serum urate target. Allopurinol and febuxostat **will not** be used concurrently.
- The initial dose will be 40mg daily, increased by 40mg every month if the serum urate target has not been met, to a maximum of 120mg daily.

Gout flare prophylaxis protocol

Gout flare prophylaxis will be considered for all participants during the first 6 months of the study, and during any ULT escalation, dependent on careful consideration of comorbidities and patient preference.

First line:

- Colchicine - 500microg daily or twice a day, or
- Naproxen - 250mg twice a day.

Second line:

- Low dose prednisolone - up to 5mg daily.

Gout flare management protocol

Gout flares will be managed with either colchicine, a non-steroidal anti-inflammatory drug (NSAID) or prednisolone according to the 2012 ACR Guidelines for Management of Gout (276).

Appendix 3: Gout Diary

Patient Label

Gout diary

RAH Crystal Arthritis Clinic

This booklet has been given to you because you have a medical condition known as gout.

Please use this booklet to record information about your symptoms, treatment and results to help better manage your gout.

If you have any questions about the information in this booklet, please ask a doctor or nurse at the clinic.

Please bring this booklet to all of your clinic appointments

BACKGROUND

What is gout?

Gout is an inflammatory arthritis caused by the presence of urate crystals. Urate crystals form when levels of urate are too high in the blood.

Urate crystals may cause episodes of acute inflammation, called **gout flares.** During these flares, your joints may become painful, swollen and tender to touch. The skin over the joint may also feel warm and look red compared to surrounding skin. Although gout flares will usually settle, the crystals causing the inflammation will remain until gout is treated.

Urate crystals can cause damage to the joints. Lumps of urate crystals may also form under the skin, called **tophi**.

Gout is a common problem in the community and can be effectively treated with long-term medication.

BACKGROUND

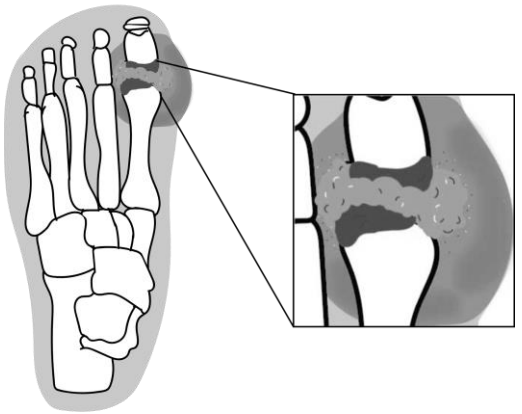
How is gout diagnosed?

Gout can be diagnosed by the presence of characteristic symptoms and signs on examination. Sometimes, fluid is removed from a joint using a needle and urate crystals are found in the fluid using a microscope. Radiology tests, such as ultrasound and dual-energy CT scanning, may also identify urate crystals.

How is gout managed?

Gout management is divided into:

- Urate lowering therapy
- Gout flare management
- Gout flare prophylaxis
- These individual components will be explained on the following pages.



Crystals can cause joint inflammation and damage

FURTHER INFORMATION

Further information on gout medications can be found on the following websites:

Urate lowering therapy

- Allopurinol: https://rheumatology.org.au/patients/documents/Allopurinol_2018.pdf
- Probenecid: https://rheumatology.org.au/patients/documents/Probenecid_2019_Apr.pdf
- Febuxostat: https://rheumatology.org.au/patients/documents/Febuxostat_2018.pdf

Gout flare management and prophylaxis

- Colchicine: https://rheumatology.org.au/patients/documents/Colchicine_2019.pdf
- Prednisolone: https://rheumatology.org.au/patients/documents/Prednisolone_2019.pdf
- Non-steroidal anti-inflammatory drugs (NSAIDs): https://rheumatology.org.au/patients/documents/NSAIDS_2019.pdf

MY TREATMENT PLAN

Urate lowering therapy

These medications lower the level of urate in your blood. This causes urate crystals to dissolve so that they can be removed from the body and stop further inflammation.

Date	Medication	Dose	Frequency

MY TREATMENT PLAN

Gout flare prophylaxis

While lowering blood urate levels, there may be a temporary increase in the number of gout flares. Sometimes medications are given to help reduce the frequency of these gout flares. They are usually not continued forever and may be used for 3 to 6 months, depending on the circumstances.

- ☐ Colchicine 0.5mg tablets:
  - 1 tablet, frequency _____
- ☐ Naproxen 250mg tablets:
  - 1 tablet morning and night.
- ☐ Prednisolone 5mg tablets:
  - ___tablet daily, in the morning

MY TREATMENT PLAN

Gout flare treatment

Gout crystals may cause episodes of acute inflammation, called gout flares. During these flares, your joints may become painful, swollen and tender to touch. The skin over the joint may also feel warm and look red compared to surrounding skin. Treatment for gout flares should be started early, as this tends to shorten the duration.

The following medications have been recommended for treatment of your gout flares:

- ☐ Prednisolone ___mg tablets:
  - ___tablets in the morning for 3 days; then
  - ___tablets in the morning for 3 days; then
  - ___tablets in the morning for 3 days.
- ☐ Naproxen ___mg tablets:
  - 1 tablet morning and night, with food for 5 to 7 days.
- ☐ Colchicine 0.5mg tablets:
  - 2 tablets; then, after 1 hour
  - 1 tablet.

APPOINTMENTS

Appointments may be either clinic visits or phone calls. Please have your blood tests performed at any **SA Pathology** outlet **in the week prior** to your appointment, ideally on the **Monday or Tuesday prior** to allow time for the results to be available. The blood tests **do not require fasting**.

Date	Appointment type (Please circle)	Blood test done before date?
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
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	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐
	Clinic review / phone call	☐

BLOOD TEST RESULTS

Your blood test results will include **serum urate**. Your urate lowering therapy will be increased until you reach your serum urate target.

My **serum urate target** is: _____ mmol/L

Date of blood test	**Serum urate result** (mmol/L)

Date of blood test	**Serum urate result** (mmol/L)

GOUT FLARES

If you have any gout flares, please record them in the following pages.

It is best to record gout flares as they happen, so the details are accurate.

If you are unsure whether you are actually having a gout flare, please still complete the questions.

You will be asked about the details of these gout flares when you are seen in clinic.

Gout flare 1

1. Do you think you are having a gout flare? ☐ **Yes** ☐ **No**
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ **Yes** ☐ **No**
4. Are any of your joints warm to touch? ☐ **Yes** ☐ **No**
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0 1 2 3 4 5 6 7 8 9 10

No pain — **Worst possible pain**

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0 1 2 3 4 5 6 7 8 9 10

Very poor — **Very well**

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?

☐ None
☐ Prednisolone
☐ Naproxen or other non-steroidal anti-inflammatory
☐ Colchicine
☐ Joint injection
☐ Other:

9. How many days did you treat the flare? ____ days

Gout flare 2

1. Do you think you are having a gout flare? ☐ Yes ☐ No
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ Yes ☐ No
4. Are any of your joints warm to touch? ☐ Yes ☐ No
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0	1	2	3	4	5	6	7	8	9	10
Very poor										Very well

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

Gout flare 3

1. Do you think you are having a gout flare? ☐ Yes ☐ No
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ Yes ☐ No
4. Are any of your joints warm to touch? ☐ Yes ☐ No
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0	1	2	3	4	5	6	7	8	9	10
Very poor										Very well

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

Gout flare 4

1. Do you think you are having a gout flare? ☐ **Yes** ☐ **No**
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ **Yes** ☐ **No**
4. Are any of your joints warm to touch? ☐ **Yes** ☐ **No**
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0 1 2 3 4 5 6 7 8 9 10

No pain — **Worst possible pain**

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0 1 2 3 4 5 6 7 8 9 10

Very poor — **Very well**

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

Gout flare 5

1. Do you think you are having a gout flare? ☐ **Yes** ☐ **No**
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ **Yes** ☐ **No**
4. Are any of your joints warm to touch? ☐ **Yes** ☐ **No**
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0 1 2 3 4 5 6 7 8 9 10

No pain — **Worst possible pain**

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0 1 2 3 4 5 6 7 8 9 10

Very poor — **Very well**

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

Gout flare 6

1. Do you think you are having a gout flare? ☐ Yes ☐ No
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ Yes ☐ No
4. Are any of your joints warm to touch? ☐ Yes ☐ No
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0	1	2	3	4	5	6	7	8	9	10
Very poor										Very well

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

Gout flare 7

1. Do you think you are having a gout flare? ☐ Yes ☐ No
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ Yes ☐ No
4. Are any of your joints warm to touch? ☐ Yes ☐ No
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0	1	2	3	4	5	6	7	8	9	10
Very poor										Very well

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

Gout flare 8

1. Do you think you are having a gout flare? ☐ **Yes** ☐ **No**
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ **Yes** ☐ **No**
4. Are any of your joints warm to touch? ☐ **Yes** ☐ **No**
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0 1 2 3 4 5 6 7 8 9 10

No pain — **Worst possible pain**

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0 1 2 3 4 5 6 7 8 9 10

Very poor — **Very well**

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other:
9. How many days did you treat the flare? ☐ days

Gout flare 9

1. Do you think you are having a gout flare? ☐ **Yes** ☐ **No**
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ **Yes** ☐ **No**
4. Are any of your joints warm to touch? ☐ **Yes** ☐ **No**
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst**:

0 1 2 3 4 5 6 7 8 9 10

No pain — **Worst possible pain**

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0 1 2 3 4 5 6 7 8 9 10

Very poor — **Very well**

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other:
9. How many days did you treat the flare? ☐ days

Gout flare 10

1. Do you think you are having a gout flare? ☐ Yes ☐ No
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ Yes ☐ No
4. Are any of your joints warm to touch? ☐ Yes ☐ No
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst:**

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0	1	2	3	4	5	6	7	8	9	10
Very poor										Very well

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

Gout flare 11

1. Do you think you are having a gout flare? ☐ Yes ☐ No
2. Start date: / / End date: / /
3. Are any of your joints swollen? ☐ Yes ☐ No
4. Are any of your joints warm to touch? ☐ Yes ☐ No
5. Considering pain from your gout over the last 1 week when you are resting (for example in bed or sitting quietly) please circle the number indicating the **level of pain** when it was at **its worst:**

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

6. Considering **all the ways** your **gout affects you**, please circle the number indicating **how well you are doing**:

0	1	2	3	4	5	6	7	8	9	10
Very poor										Very well

7. Joint(s) involved (tick all that may apply):

Side	Big toe	Other toe(s)	Foot	Ankle	Knee	Elbow	Wrist	Finger(s)	Other:
Right	☐	☐	☐	☐	☐	☐	☐	☐	
Left	☐	☐	☐	☐	☐	☐	☐	☐	

8. What medications did you use to treat the gout flare?
   - ☐ None
   - ☐ Prednisolone
   - ☐ Naproxen or other non-steroidal anti-inflammatory
   - ☐ Colchicine
   - ☐ Joint injection
   - ☐ Other: _____
9. How many days did you treat the flare? _____ days

SIDE EFFECTS

If you have any side effects from your medications, please write them in this table:

Date	Medication	Side effect(s)

OTHER MEDICATIONS

If you would like to, write your other medications in this table:

Medication name	Dose	Frequency

YOUR PERSONAL NOTES

Please feel free to use the space provided to write any notes.

Appendix 4: Author contributions and journal permissions

University of South Australia

Statement of Authorship

Title of Paper	Alterations in drug disposition in older adults: a focus on geriatric syndromes
Publication Status	■ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details Relevant reference details	Maher, D., Ailabouni, N., Mangoni, A. A., Wiese, M. D., & Reeve, E. (2021). Alterations in drug disposition in older adults: a focus on geriatric syndromes. Expert Opinion on Drug Metabolism & Toxicology, 17(1), 41–52. https://doi.org/10.1080/17425255.2021.1839413
PRINCIPAL AUTHOR	
Name of Principal Author (Candidate)	Dorsa Maher
Contribution to the Paper Brief description of your work in this publication	Initial review and contribution to the selection of included geriatric syndromes. Original draft of the introduction, chronological age-related changes in drug disposition, conclusion, expert opinion and article highlights. Review and edit of full manuscript.
Overall Percentage (%)	60%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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Approval Date: 1st May 2025

University of South Australia

Statement of Authorship

Title of Paper	Investigating adherence to allopurinol in patients with gout using three approaches
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☒ Unpublished and Unsubmitted work written in manuscript style
Publication Details Relevant reference details	

PRINCIPAL AUTHOR

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Contribution to the Paper Brief description of your work in this publication	Methodology, data analysis, original draft and editing.
Overall Percentage (%)	50%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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Title of Paper	Comparative Risk of Gout Flares When Initiating or Escalating Various Urate-Lowering Therapy: A Systematic Review With Network Meta-Analysis
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details Relevant reference details	Maher, D., Reeve, E., Hopkins, A., Tan, J. M., Tantiongco, M., Ailabouni, N., Woodman, R., Stamp, L., Bursill, D., Proudman, S., & Wiese, M. (2024). Comparative Risk of Gout Flares When Initiating or Escalating Various Urate-Lowering Therapy: A Systematic Review With Network Meta-Analysis. Arthritis Care & Research (2010), 76(6), 871–881. https://doi.org/10.1002/acr.25309

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Name of Principal Author (Candidate)	Dorsa Maher
Contribution to the Paper Brief description of your work in this publication	Study conception and design, literature search, title and abstract screening, full-text review, data extraction, data analysis and original draft and editing.
Overall Percentage (%)	60%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
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Statement of Authorship

Title of Paper	Reply to: "Gout flare prophylaxis trials"
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Publication Details Relevant reference details	Maher D, Reeve E, Wiese M. Reply to: "Gout flare prophylaxis trials". Arthritis care & research (2010). 2025. https://doi.org/10.1002/acr.25498.

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Name of Principal Author (Candidate)	Dorsa Maher	
Contribution to the Paper Brief description of your work in this publication	Reply conception and design, original drafting and editing	
Overall Percentage (%)	80%	
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