Co-Morbidities and Treatment of Gout

Co-morbidities and treatment of gout: from trials to clinical practice

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CO-MORBIDITIES AND TREATMENT OF GOUT:
FROM TRIALS TO CLINICAL PRACTICE.

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General introduction

Parts of this introduction have been published in the book "The Heart in Rheumatic, autoimmune and inflammatory disorders" (1).

Gout is the most prevalent inflammatory rheumatic disease. It is caused by the deposition of monosodium urate (MSU) crystals in synovial joints. Gout is known to be associated with multiple comorbidities such as cardiovascular disease, diabetes and reduced renal function. The pathophysiological mechanisms that possibly link comorbidities to gout are complex, and further confounded by the role of shared common risk factors. Both symptoms related to gout and its co-morbidities are almost equally associated with impaired health-related Quality of Life (hrQOL), especially physical hrQOL (hrQOL) (2). Although gout is a well-treatable disease, its management remains too often suboptimal. (3-5). This suboptimal treatment could be explained by poor adherence of the patient to the treatment (6) or of the physician to the guidelines (7). Furthermore, co-morbidities can impact gout treatment. More severe gout is associated with more co-morbidities and although it requires a more aggressive treatment of gout, the associated co-morbidities might preclude the use of some of the possible drugs used in the treatment of gout (8). Challenges in the treatment of gout and the role of comorbidities in gout care are the focus of this thesis. The main objective of this thesis was to improve management of gout patients in clinical practice: the **first part** will focus on different aspects relevant to the management of patients with gout. The **second part of this thesis**, will focus on epidemiological evidence on the role of gout itself in the occurrence of co-morbidities.

1.1 EPIDEMIOLOGY

The prevalence of gout in Europe ranges from 1% to 4% (9). Several reports suggest the prevalence of gout is increasing (10-15). This rise in gout prevalence coincides with a rise in the prevalence of obesity and ageing of the population (9). Fructose, abundantly present in sugar-sweetened beverages, has also been incriminated as a possible explanation of the increasing prevalence of gout as, during fructolysis, ATP degrades to AMP, which contributes to the production to uric acid (16-20).

1.2 PATHOPHYSIOLOGY OF GOUT

Uric acid, the main risk factor for gout, is the end product of the purine metabolism (Figure 1). Twenty percent of the purines present in the body stems from the diet and 80% from endogenous sources (cell turnover and de novo synthesis of nucleic acids). Purines are degraded into hypoxanthine and xanthine, which are in turn converted into uric acid by the enzyme xanthine oxidase (XO). Xanthine oxidase is one of the two interchangeable forms of the enzyme xanthine oxidoreductase (XOR): xanthine oxidase (XO) and xanthine dehydrogenase (XD) (21). XOR is present in the liver, the gut, the intestinal epithelium, the kidney, the heart, the blood vessels and the brain (22).

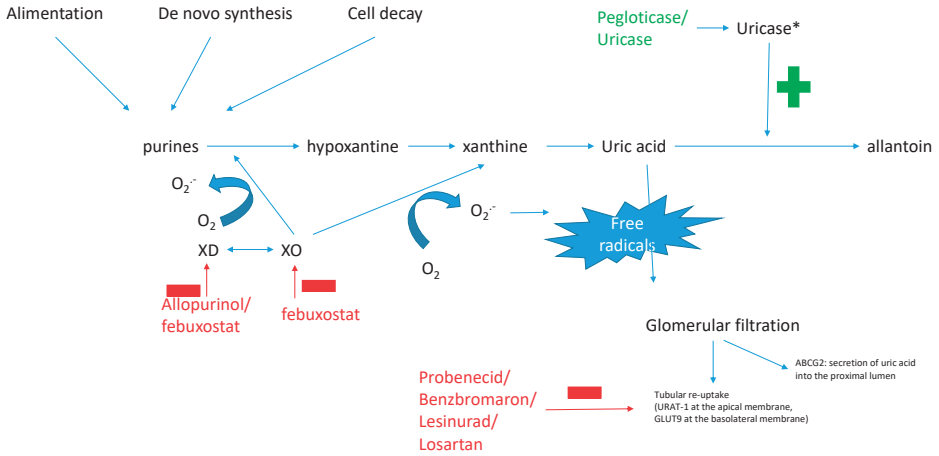

Figure 1 Formation, elimination of uric acid and impact of drugs (25, 43)

All species, except humans and primates, further break uric acid down to allantoin by uricase. Allantoin is water-soluble and is therefore excreted in the urine. In humans and primates who lack this uricase, uric acid is mostly filtered through the kidneys, and a small part is excreted through the intestine. In the kidneys, 90% of the filtered uric acid is reabsorbed, mostly through URAT-1 and GLUT9 (23). For the past few years, there has been an increased interest for the role of the intestine in the development of hyperuricemia. A novel urate-transporter ABCG2 has been discovered and could play a role in this process as well as the intestinal microbiota (24, 25).

Under physiological condition, uric acid exists in his ionized form, urate. Monosodium urate (MSU) crystals may form if the urate concentration of 6.8mg/dL (0.41mmol/L) is surpassed (26). The solubility of urate decreases by increasing sodium concentration, by decreasing temperature and by decreasing pH (23). During an acute gout attack, the uric acid precipitates in crystals, which in turn will activate the immune system through the inflammasome. This inflammasome will induce the production of IL-1 that will eventually lead to inflammation (27).

1.3 RISK FACTORS FOR GOUT

Besides hyperuricemia, the key risk factor for gout, demographic risk factors, including sex, age and ethnicity, constitute the main risk factors (10). The lower risk of gout in women has been, at least partially, attributed to the uricosuric effects of oestrogens (28). In the post-menopausal period, the prevalence of gout in women tends to rise, but never attains the same levels as in men (12, 29-31). In men, gout prevalence rises from the age of 35 onward (12, 29, 31). The prevalence of gout is also strongly dependent of the ethnicity: gout being more prevalent in African-Americans, New-Zealand Maori 's and Hmong Chinese (31-33).

Dietary factors also play a role in the risk of gout (34). Generally known dietary risk factors for gout are consumption of alcohol, red meat and seafood. For the last few years, sugar-sweetened beverages have also been incriminated (see paragraph 1.1 Epidemiology of gout). Diuretics are also commonly reported as risk factors for gout but this influence could be biased by the indication for this type of medication, such as hypertension and heart failure (35). Some comorbidities present in patients with gout share common risk factors with gout itself, such as for example obesity and diabetes or cardiovascular diseases. The extent to which co-morbidities are independent risk factors for gout or whether this association could be explained by those shared risk factors is an important focus of this thesis. The complex relationship between comorbidities, gout and their management is further discussed in paragraph 1.5 Co-morbidities.

1.4 CLINICAL MANIFESTATIONS OF GOUT

The spectrum of gout distinguishes different states: a pre-clinical state defined as asymptomatic hyperuricaemia, and a clinical state characterized by the presence of gout flares, the presence of tophi (MSU crystal deposition in soft tissue) or bone/joint damage (36).

Patients with asymptomatic hyperuricaemia are at risk of developing gout but they do not have any clinical symptoms yet. While hyperuricaemia predisposes to clinical gout, the association is not strong enough to have imminent clinical repercussions (37).

The typical clinical presentation of an acute gout flare is also known as "podagra", which means "foot trap" in Greek. It presents with a suddenly occurring, extremely painful, red and swollen 'big toe' that usually spontaneously resolves within a few days. The arthritis typically starts by the end of the night, in the early morning (38). Usually, the presentation is mono-or oligoarticular, but 3-14% of the patients present with polyarticular arthritis (39). Any joint can be affected by gout but the disease more often affects the lower limbs; spine, shoulder and hip-joints are rarely affected (39). The period between the flares is called "intercurrent" gout: during this period, the patient is asymptomatic, meaning that he does not have signs and symptoms of arthritis. However, when left untreated and given unaltered metabolism, patients will often develop a second attack within 6 months to 2 years (39).

At last, gout can also be associated with complications, such as tophi in subcutaneous tissue, bone, soft tissues surrounding the joint (40). Tophi are accumulations of MSU crystals in in subcutaneous tissue, bone, soft tissues surrounding the joint (40). Those MSU crystal deposition are surrounded by inflammatory cells (41). When clinically apparent, tophi are subcutaneous nodules that often appear white. They are mostly located in the fingers (pulp or joints), the elbows, the hallux, the Achilles' tendon and in the ears, but may appear everywhere (39, 41).

When present near the joint, tophi can damage the bone and therefore the joint. Imaging can be used to confirm the presence and magnitude of joint damage.

1.5 GOUT TREATMENT

The treatment of gout has two goals: one is treating the inflammation during an acute gout attack and the second one is lowering the uric acid concentration in order to prevent future attacks of gout and deposition of MSU crystals in soft tissues, which may evolve into the formation of tophi and destruction of joints.

Treatment of acute gout includes: colchicine, non-steroidal-anti-inflammatory drugs (NSAIDs), oral glucocorticoids, intra-articular glucocorticoids and the more recently developed interleukin 1 inhibitors (anti-IL1). It is, however, not known whether this new class of drugs is more effective or has a more favourable profile for side effects compared to the other drug classes. The high prevalence of co-morbidities in gout makes it often difficult to choose for the most appropriate drug as some co-morbidities are actual or relative contra-indications for the use of certain of these drugs available for treating acute gout attacks. It is therefore important to have accurate information on their efficacy and safety, as such information could help physicians in treatment decisions. Unfortunately, a quantitative summary of the safety and efficacy of the available drugs for treating acute gout attacks was lacking at the start of this thesis. This is unfortunate, as such valuable information might help physicians and patients make an evidence-based choice when initiating treatment in case of acute gout attacks.

The second phase of treatment consists of lowering the uric acid levels. This can be achieved by xanthine-oxidase inhibitors (allopurinol and febuxostat) or by uricosurics (benzbromarone, probenecid and lesinurad) (figure 1). Uricase, which breaks uric acid further down to allantoin which can then be excreted by the kidneys, is only recommended in severe refractory tophaceous gout (figure 1) (37). Because starting urate-lowering-therapy (ULT) can provoke acute gout attacks, it is recommended to use a prophylaxis during the first 3 to 6 months. Commonly, low dose colchicine (0.5mg to 1 mg daily) is used for this purpose (42). As of this moment, there is a debate regarding the targets when treating patients with gout. Most guidelines recommend to aim for a serum uric acid (sUA) level <0.36 mmol/l or 0.30 mmol/L (43, 44). However, the Nederlands Huisartsen Genootschap (NHG) recommends to seek a for patient acceptable frequency of acute gout attacks rather than a specific sUA level. In fact, there is no evidence which approach (uric acid targeted or symptom targeted approach) is more effective in reducing acute gout attacks, preventing the development of tophi, or reduce existing tophi. Also, there are no studies that compare the effect of specific sUA thresholds on gout outcomes. Moreover, a strictly sUA targeted strategy might have disadvantages as higher dosing schedules,

combination treatment, and treatment switches may cause more side effects, reduce therapy adherence from patients and eventually cause more health consumption. There is a clear need to collect evidence on effectiveness, safety and (cost)-effectiveness on the two approaches, to enhance evidence base shared decisions by physicians and patients.

A further step beyond treating to target might be to aim to reach remission. In gout, criteria for remission were developed that encompass as sub-domains: sUA level, tophi, flare, pain and patient global assessment (45). Consensus was reached on a definition of remission for each domain, but not on the timeframe over which these domains should indicate absence of disease activity and therefore remission. With regards to tophi, there was no consensus on the assessment of the tophus response (absence, regression in size or number, regression in size alone). When tophi are visible, they can be assessed with a Vernier calliper or tape measurement (46). Tophi, however, can also cause joint damage, which cannot be assessed with those measuring methods. Conventional Radiography (XR) are already use in Rheumatoid Arthritis and other inflammatory joint diseases to assess joint damage. XR are inexpensive, widely available and capture abnormalities specific for gout. They are therefore a logical choice in assessment of structural joint damage due to tophi in gout. However, there are no comprehensive data on the construct validity of radiographically scored structural joint damage in gout. Furthermore, it is not known if such structural damage scored by XR is associated with functioning and disability which would make it a relevant measure when evaluating outcomes of treatment.

1.6 COMORBIDITIES

Epidemiological studies have shown that gout is associated with a large number of co-morbidities, especially cardiovascular disease and cardiovascular risk factors. The NHANES 2007-2008 study showed, for example, that patients with gout have a 2-3 times higher prevalence of cardiovascular risk factors, such as hypertension, diabetes and obesity (33). Two main mechanisms suggest a causal relationship between gout and cardiovascular disease. The first one is oxidative stress which is known to induce endothelial dysfunction, the initial process of atherosclerosis. (Fig.1). During the oxidation of hypoxanthine to uric acid, superoxide radicals ($O_2^{\cdot-}$), also called reactive oxygen species (ROS), are produced. These ROS can then react with hydrogen (H+) ions and form hydrogen peroxide (H_2O_2) and hydroxyl radicals (-OH) (21). Furthermore, the generated ROS can react with Nitric Oxide (NO) to form peroxynitrite, which in turn leads to more free radicals. The second mechanism is the inflammatory process that is associated with MSU crystals. MSU crystals induce this inflammation through a cytoplasmic complex containing multiple proteins called the inflammasome, more specifically NLRP3-inflammasome. Research from the last decade has demonstrated that the same NLRP3-inflammasome also plays a role in atherosclerosis (47).

Besides a potential direct causal relation between gout or uric acid and certain co-morbidities, the association could be explained by the presence of risk factors common to gout and co-morbidities. In gout research, the question remains whether or not there is a true causal relationship between gout and certain co-morbidities and if present, what the clinical implications would be when treating gout patients. At the time of this thesis, the focus of research had been essentially on uric acid and cardiovascular diseases and risk factors and to a lesser extent to gout and cardiovascular diseases and risk factors. A summary of the actual evidence of association between gout and co-morbidities, besides cardiovascular diseases was lacking. If gout/hyperuricaemia causes comorbidities, physicians caring for gout patients should be recommended to treat gout or hyperuricaemia more strictly and even screen gout patients for those co-morbidities. We therefore conducted a systematic literature review in order to answer the following question: "In patients with hyperuricemia and/or a diagnosis of gout, should we routinely screen for comorbidities and cardiovascular risk factors?".

A frequently associated co-morbidity with gout is diabetes. The relation between gout and diabetes is rather intriguing. Studies have shown lower uric acid concentrations in individuals with type 2 diabetes mellitus (T2DM) compared with those without diabetes, suggesting a lower risk of gout. Two mechanisms are thought to explain this possible lower uric acid concentrations in patients with diabetes. First, it has been demonstrated that there is a bell-shaped relationship between uric acid and HbA1c: uric acid levels increase following increasing levels of HbA1c up to 6.9%, upon which there is a decrease in uric acid levels with increasing HbA1c levels (48). This phenomenon is thought to be explained by the uricosuric effect of glycosuria (49). Second, patients with T2DM have an impaired inflammatory response which may further protect those patients against gout (49). On the other hand, epidemiological studies only found an increased prevalence of gout in patients with diabetes (50, 51). The question remains whether there is an increased risk of gout in patients with diabetes and whether this risk depends on diabetes control (duration HB A1C) or the presence of common risk factors gout and diabetes share, such as obesity.

Over the past years, the association between Obstructive Sleep Apnea and gout has gained interest. Various pathophysiological mechanisms suggest there might be a causal association between gout and OSA. First, OSA-induced hypoxemia causes a rise in adenosine triphosphate (ATP) degradation which eventually increases purine concentrations and their end product uric acid (52). Second, hypercapnia and acidosis caused by OSA could influence the likelihood of MSU precipitation (53). Third, excretion of lactic acid, generated during the hypoxic episodes in OSA, can result in a higher renal reabsorption of uric acid (54). Alternatively, the relationship could also be explained by shared risk factors of gout and OSA, such as age, obesity, metabolic syndrome, renal impairment and heart failure (55). Another unanswered question is, if

an increased risk is present for patients with gout to develop OSA, is it high enough to warrant screening in all patients with gout?

1.7 MAIN OBJECTIVES

The main objective of this thesis was to focus evidence the management of acute and chronic gout patients and to further add to the insight of the association between gout and several comorbidities using epidemiological studies.

The specific objectives of this thesis are:

1. To compare the efficacy and safety of NSAIDs to other NSAIDs or to different drug classes used for the treatment of acute gout.
2. To compare benefits and harms of a strict SUA-target approach to patient centred-approach in in gout patients requiring ULT treatment.
3. To assess validity of X-rays of the feet as an outcome instrument to assess structural damage in gout.
4. To summarize the literature regarding the association between hyperuricemia and gout and different comorbidities, especially cardiovascular risk factors and events.
5. To assess the risk of gout in patients with diabetes and obstructive sleep apnea and its independence of shared risk factors.

Outline of this thesis

In this thesis, we focussed on different clinical aspects of the management of patients with gout and on the association of gout and co-morbidities. In **Chapter 2**, we compared non-steroidal inflammatory drugs (NSAIDs) to each other and to other commonly prescribed drugs for the treatment of acute gout with regards to efficacy and safety. For this purpose, we conducted a Cochrane Review of the published literature. In **Chapter 3**, we evaluated a patient-centred approach to a strict uric acid-approach in the treatment of patients with gout. We compared data from to daily life registries, one of the Maastricht University Medical Centre +, the other from VieCuri hospital. In **Chapter 4**, we investigated the construct validity of radiographs of the feet as an instrument to assess joint damage in patients with gout. The data from a cross-sectional study of 126 patients attending the outpatient clinic of the rheumatology department at the Maastricht University Medical Centre+, were used. In **Chapter 5-7**, we investigated the relationship between gout and frequent co-morbidities. In **Chapter 5**, we aimed to answer the question whether gout patients or patients with hyperuricemia should be screened for certain co-morbidities. We conducted a systematic review of the literature to assess the risk of gout patients or patients with hyperuricemia to develop certain comorbidities including mortality from co-morbidities. In **Chapter 6**, we investigated the hypothesis that the risk of gout in

patients with diabetes can be explained by comorbidities. We used a population-based cohort from the Clinical Practice Research Datalink (CPRD) (http://www.cprd.com) which contains the computerized medical records of approximately 6.9% of the total UK population (56, 57). In **Chapter 7**, we investigated the risk of gout in patients with obstructive sleep apnea (OSA). As both diseases share common risk factors, we hypothesized that the increased risk of gout in patients with OSAS could be explained by those shared risk factors. We conducted a case control study, using the same CPRD-database as in Chapter 6. **Chapter 8** encompasses a summary and discussion of our main findings and a reflection about the implication for patients, healthcare and research.

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2

Non-steroidal anti-inflammatory drugs for acute gout

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ABSTRACT

Background

Gout is an inflammatory arthritis resulting from the deposition of monosodium urate crystals in and around joints. Non-steroidal anti- inflammatory drugs (NSAIDs) are commonly used to treat acute gout. This is an update of a Cochrane Review first published in 2014.

Objectives

To assess the benefits and harms of non-steroidal anti-inflammatory drugs (NSAIDs) (including cyclo-oxygenase-2 (COX-2) inhibitors (COXIBs)) for acute gout.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase for studies to 28 August 2020. We applied no date or language restrictions.

Selection criteria

We considered randomised controlled trials (RCTs) and quasi-RCTs comparing NSAIDs with placebo or another therapy for acute gout. Major outcomes were pain, inflammation, function, participant-reported global assessment, quality of life, withdrawals due to adverse events, and total adverse events.

Data collection and analysis

We used standard methodological procedures as expected by Cochrane.

Main results

We included in this update 28 trials (3406 participants), including 5 new trials. One trial (30 participants) compared NSAIDs to placebo, 6 (1244 participants) compared non-selective NSAIDs to selective cyclo-oxygenase-2 (COX-2) inhibitors (COXIBs), 5 (712 participants) compared NSAIDs to glucocorticoids, 13 compared one NSAID to another NSAID (633 participants), and single trials compared NSAIDs to rilonacept (225 participants), acupuncture (163 participants), and colchicine (399 participants). Most trials were at risk of selection, performance, and detection biases.

We report numerical data for the primary comparison NSAIDs versus placebo and brief results for the two comparisons - NSAIDs versus COX-2 inhibitors and NSAIDs versus glucocorticoids.

Low-certainty evidence (downgraded for bias and imprecision) from 1 trial (30 participants) shows NSAIDs compared to placebo. More participants (11/15) may have a 50% reduction in pain at 24 hours with NSAIDs than with placebo (4/15) (risk ratio (RR) 2.7, 95% confidence

interval(CI)1.1to6.7),withabsoluteimprovementof47%(3.5%moreto152.5%more).NSAIDsmay-havelittletonoeffectoninflammation (swelling) after four days (13/15 participants taking NSAIDs versus 12/15 participants taking placebo; RR 1.1, 95% CI 0.8 to 1.5), with absolute improvement of 6.4% (16.8% fewer to 39.2% more). There may be little to no difference in function (4-point scale; 1 = complete resolution) at 24 hours (4/15 participants taking NSAIDs versus 1/15 participants taking placebo; RR 4.0, 95% CI 0.5 to 31.7), with absolute improvement of 20% (3.3% fewer to 204.9% more). NSAIDs may result in little to no difference in withdrawals due to adverse events (0 events in both groups) or in total adverse events; two adverse events (nausea and polyuria) were reported in the placebo group (RR 0.2, 95% CI 0.0, 3.8), with absolute difference of 10.7% more (13.2% fewer to 38% more). Treatment success and health-related quality of life were not measured.

Moderate-certainty evidence (downgraded for bias) from 6 trials (1244 participants) shows non-selective NSAIDs compared to selective COX-2 inhibitors (COXIBs). Non-selective NSAIDs probably result in little to no difference in pain (mean difference (MD) 0.03, 95% CI 0.07 lower to 0.14 higher), swelling (MD 0.08, 95% CI 0.07 lower to 0.22 higher), treatment success (MD 0.08, 95% CI 0.04 lower to 0.2 higher), or quality of life (MD -0.2, 95% CI -6.7 to 6.3) compared to COXIBs. Low-certainty evidence (downgraded for bias and imprecision) suggests no difference in function (MD 0.04, 95% CI -0.17 to 0.25) between groups. Non-selective NSAIDs probably increase withdrawals due to adverse events (RR 2.3, 95% CI 1.3 to 4.1) and total adverse events (mainly gastrointestinal) (RR 1.9, 95% CI 1.4 to 2.8).

Moderate-certainty evidence (downgraded for bias) based on 5 trials (712 participants) shows NSAIDs compared to glucocorticoids. NSAIDs probably result in little to no difference in pain (MD 0.1, 95% CI -2.7 to 3.0), inflammation (MD 0.3, 95% CI 0.07 to 0.6), function (MD -0.2, 95% CI -2.2 to 1.8), or treatment success (RR 0.9, 95% CI 0.7 to 1.2). There was no difference in withdrawals due to adverse events with NSAIDs compared to glucocorticoids (RR 2.8, 95% CI 0.5 to 14.2). There was a decrease in total adverse events with glucocorticoids compared to NSAIDs (RR 1.6, 95% CI 1.0 to 2.5).

Authors' conclusions

Low-certainty evidence from 1 placebo-controlled trial suggests that NSAIDs may improve pain at 24 hours and may have little to no effect on function, inflammation, or adverse events for treatment of acute gout. Moderate-certainty evidence shows that COXIBs and non-selective NSAIDs are probably equally beneficial with regards to improvement in pain, function, inflammation, and treatment success, although non-selective NSAIDs probably increase withdrawals due to adverse events and total adverse events. Moderate-certainty evidence shows that systemic glucocorticoids and NSAIDs probably are equally beneficial in terms of pain relief, improvement in function, and treatment success. Withdrawals due to adverse events were also similar

between groups, but NSAIDs probably result in more total adverse events. Low-certainty evidence suggests no difference in inflammation between groups. Only low-certainty evidence was available for the comparisons NSAID versus rilonacept and NSAID versus acupuncture from single trials, or one NSAID versus another NSAID, which also included many NSAIDs that are no longer in clinical use. Although these data were insufficient to support firm conclusions, they do not conflict with clinical guideline recommendations based upon evidence from observational studies, findings for other inflammatory arthritis, and expert consensus, all of which support the use of NSAIDs for acute gout.

BACKGROUND

Description of the condition

Gout is an inflammatory arthritis that is characterised by the deposition of monosodium urate (MSU) crystals within synovial fluid and other tissues. The natural history of articular gout is generally characterised by two different states: a preclinical state consisting of asymptomatic hyperuricaemia and a clinical state of gout defined by the presence of flares, with or without tophi and bone erosions (Bursill 2019). Gout often heralds its presence by an exquisitely painful acute monoarthritic flare of sudden onset; oligoarticular and polyarticular flares are less common and often occur in patients with poorly controlled disease or during hospitalisation (Dalbeth 2021). Gout occurs in the backdrop of hyperuricaemia, which is necessary but not sufficient to cause gout (Dalbeth 2021). Hyperuricaemia itself is most commonly caused by insufficient secretion of uric acid, rarely by overproduction, and sometimes by both (Dalbeth 2021). Lower limb joints, particularly the big toe, are the most commonly involved, followed by followed by the mid- tarsal, ankle, knee, and upper limb joints. Subsequent acute flares tend to be longer lasting and polyarticular and tend to affect upper limb joints, such as wrist or elbow (Dalbeth 2021).

Description of the intervention

Non-steroidal anti-inflammatory drugs (NSAIDs) including selective cyclooxygenase-2 (COX-2) inhibitors are commonly used to treat inflammatory conditions (Garner 2009; Garner 2010; Wienecke 2008). Published guidelines recommend their use for treating acute attacks, with maximum doses given for a short time (Jordan 2007; Khanna 2012; Zhang 2006). These guidelines state that all NSAIDs are equally effective.

How the intervention might work

NSAIDs inhibit inflammation by binding cyclo-oxygenase (COX) enzymes. Evidence has shown that COX-2 expression in monocytes is induced in response to MSU microcrystal formation (Pouliot 1998). Therefore, it is likely that NSAIDs exert their beneficial effects in gout by inhibiting the production of COX-2-mediated pro-inflammatory prostaglandins. Most NSAIDs are non-selective inhibitors; this means they inhibit both COX-1 and COX-2. Because non-selective NSAIDs also act on COX-1, they may decrease protective stomach prostaglandin levels, which explains the main adverse event of NSAIDs: ulcers and eventually bleeding. A newer class of NSAIDs are the COXIBs: they selectively inhibit COX-2, which is not involved in the formation of prostaglandins for the stomach and, therefore, may have fewer adverse effects on the gastric mucosa; they are recommended for people at risk for development of ulcers. The main problem with the use of NSAIDs, including COXIBs, is the potential risk of cardiovascular and renal disease (Feenstra 2002; Kearney 2006; Marks 2011).

Why it is important to do this review

Acute gout is an extremely painful condition that has a significant impact on health-related quality of life (HRQoL), as well as on productivity and ability to function (Rhody 2007; Singh 2006). Without treatment, flares resolve on average only after seven days (Bellamy 1987). Therefore, it is important to rapidly relieve the symptoms caused by acute gout. NSAIDs are known to be among the physician's first choice for treatment of acute gout, but due to potential adverse effects, their use is limited in people with comorbidities such as cardiovascular disease, renal impairment, and a history of peptic ulcer or gastrointestinal bleeding (Borer 2005). The benefits and harms of NSAIDs in treating acute gout were systematically reviewed in 2014 (van Durme CMPG 2014); it is important to update this review to include relevant new evidence.

OBJECTIVES

To assess the benefits and harms of non-steroidal anti- inflammatory drugs (NSAIDs) (including cyclooxygenase-2 (COX-2) inhibitors (COXIBs)) for acute gout.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all published randomised controlled trials (RCTs) or quasi-randomised controlled clinical trials (CCTs) that compared NSAIDs to another therapy (active or placebo, including non- pharmacological therapies) for acute gout. We included only trials that were published as full articles or were available as full trial reports.

Types of participants

We included studies of adults (aged 18 years or older) with a diagnosis of acute gout. We excluded populations that included a mix of people with acute gout and other musculoskeletal pain unless results for the acute gout population could be separately analysed.

Types of interventions

All trials that evaluated NSAIDs were included, other than those for NSAIDs that are no longer available (e.g. rofecoxib (trademark: Vioxx)).

Comparator treatments could be:

- placebo;
- no treatment;

- paracetamol;
- colchicine;
- systemic or intra-articular glucocorticoids;
- interleukin-1(IL-1) inhibitors;
- non-pharmacological treatments;
- one NSAID versus another NSAID; or
- combination therapy (any of the above in combination).

Types of outcome measures

For the purposes of this review, we included outcome measures that were considered to be of greatest importance to people with acute gout and the clinicians who care for them.

OMERACT (Outcome Measures in Rheumatology Clinical Trials) has proposed a set of recommended outcome measures to be used for evaluation of resolution of acute attacks (Grainger 2009; Schumacher 2009). Intense pain is the hallmark of an acute gout attack, hence pain has been proposed as an OMERACT outcome measure; it also has been a consistent outcome measure in clinical trials involving acute gouty arthritis, although the instruments and time intervals used to measure pain vary (Grainger 2009). Other proposed OMERACT outcome measures include joint swelling and tenderness, participant global assessment, and harms (Grainger 2009; Schumacher 2009).

It is recognised that interpreting the meaning of mean changes in continuous measures of pain (e.g. mean change on a 100- mm visual analogue scale (VAS)) is hampered when participants report either very good or very poor pain relief (Moore 2010). For trials of interventions for chronic pain, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended that dichotomous pain outcomes (the proportion of participants improved by 30% or greater and by 50% or greater) be reported (Dworkin 2008), although no recommendations have yet been published for acute pain. Therefore, we elected to include a dichotomous pain outcome measure (the proportion of participants reporting 30% or greater pain relief) as the primary benefit measure in this review. However, as most trials of interventions for acute gout report continuous measures, we included mean change in pain score as a secondary benefit measure.

Major outcomes

- Pain: the proportion of participants who reported pain relief of 50% or greater; if not found, the following data were extracted: proportion of participants who achieved pain relief of 30% or greater, or proportion of participants achieving a pain score below 30/100 on VAS, or pain measured as a continuous outcome (e.g. VAS, numerical rating scale)

- Inflammation (joint swelling, erythema, tenderness): if more than one measure was reported in an individual trial, we extracted only one according to the following hierarchy: swelling, erythema, and tenderness. We extracted data (when applicable) both for an index joint and for the total number of inflamed joints
- Function of target joint (e.g.measuredbytheHealthAssessment Questionnaire (HAQ))
- Participants'global assessment of treatment success
- HRQoL as reported by generic questionnaires (e.g.36-ItemShort Form (SF-36)) or by disease-specific questionnaires (e.g. Gout Assessment Questionnaire (GAQ), Gout Impact Scale (GIS))
- Study participant withdrawal due to adverse events(AEs)
- Total number of adverse events

Minor outcomes

• Serious adverse events

We planned to include outcomes at all time points measured in the included trials. We planned to pool available data into short- term (up to two weeks), medium-term (two to six weeks), and long- term (more than six weeks) outcomes, but only short-term data were available. When available, we chose to include the earliest time point for the outcome pain, swelling, and function, as this was more clinically relevant. For the other outcomes (participants' global assessment of treatment success and HRQoL), we chose the latest time point/end of treatment, as we also considered this to be more clinically relevant.

Search methods for identification of studies

Electronic searches

We searched a registry of all randomised controlled trials (RCTs) in gout, established by Cochrane Musculoskeletal to facilitate the updates of a series of reviews of interventions for gout, including this review update. The search for the gout registry was designed not to include terms for any interventions, to establish a registry of all randomised trials in this condition, regardless of the intervention. The following electronic databases were searched to establish the registry. The search strategy combined standard Cochrane search filters for 'gout' and 'randomised trial', with no language restrictions.

- Cochrane Central Register of Controlled Trials(CENTRAL),in the Cochrane Library, via Ovid, to 28 August 2020 (Appendix 1).
- MEDLINE via Ovid, 1948 to 28 August 2020 (Appendix 2).
- Embase via Ovid, 1980 to 28 August 2020 (Appendix 3).

We also searched the clinical trials register clinicaltrials.gov and the World Health Organization (WHO) trials register for relevant trials, using the search term 'gout'. Details of search strategies used for the previous version of this review are given in van Durme CMPG 2014.

Searching other resources

We handsearched the bibliographies of all included papers for information on any other relevant studies.

Data collection and analysis

Selection of studies

Editorial staff from Cochrane Musculoskeletal initially screened titles and abstracts in the gout registry and retrieved full texts for all records that they identified as RCTs of an intervention for people with gout. Editorial staff annotated the population, intervention, and comparator for each full-text article and assigned it to the appropriate gout review. They imported relevant records to Covidence to select studies eligible for inclusion in this review update (www.covidence.org).

Two review authors (CD and MW) independently screened each title and abstract for suitability for inclusion in the review. They decided independently of each other upon the eligibility of each article according to the pre-determined selection criteria (see Criteria for considering studies for this review). If more information was required to establish whether inclusion criteria were met, we obtained the full text of the paper. We documented all reasons for excluding studies. We resolved disagreements by consensus after review of the full-text article. A third review author (RL) resolved differences when necessary. We translated studies into English when necessary.

Data extraction and management

Two review authors (CD and MW) independently extracted data from included trials, including study design, characteristics of the study population, treatment regimen and duration, relevant outcomes, timing of outcome assessment, and duration of follow- up. We extracted data using a standardised form.

We extracted raw data (means and standard deviations (SDs) for continuous outcomes, number of events or participants for dichotomous outcomes) for the outcome of interest. We resolved differences in data extraction by referring back to the original articles. When needed, we consulted a third review author (RL).

Assessment of risk of bias in included studies

Two review authors (CD and MW) assessed the risk of bias of included studies using the methods recommended by Cochrane for the following items (Higgins 2017): random sequence

generation; allocation concealment; blinding of participants, care provider, and outcome assessor for each outcome measure; incomplete outcome data; selective reporting; and other sources of bias such as deviation from the study protocol in a way that did not reflect clinical practice, inappropriate administration of an intervention, presence of unequal co-interventions, or funding by pharmacological industry.

We assessed these criteria as showing low, high, or unclear risk of bias. Review authors discussed disagreements at a consensus meeting. A third review author (RL) made the final decision when consensus could not be reached.

Measures of treatment effect

To assess benefit, we extracted, if available from published reports, raw data for outcomes of interest (means and SDs for continuous outcomes, numbers of events for dichotomous outcomes) as well as numbers of participants. If we needed to convert or impute reported data, we recorded this in the notes section of the Characteristics of included studies table. We plotted the results of each trial as point estimates with 95% confidence intervals (CIs). We planned to present point estimates as risk ratios (RRs) for dichotomous outcomes and as mean differences (MDs) for continuous outcomes. An RR greater than 1.0 indicates a beneficial effect of NSAIDs (Deeks 2020). RRs are considered clinically relevant if the 95% CI is smaller than 0.7 in favour of the intervention, or larger than 1.5 in favour of the control. This resembles an absolute difference of 25%.

For continuous data, we analysed MD results between intervention and comparator groups, with corresponding 95% CIs. The MD between groups was weighted by the inverse of the variance in the pooled treatment estimate. However, if different scales were used to measure the same conceptual outcome (e.g. functional status, pain), we calculated standardised mean differences (SMD) instead, with corresponding 95% CIs. SMDs were calculated by dividing the MD by the SD, resulting in a unit-less measure of treatment effect (Deeks 2020). SMDs greater than zero indicate a beneficial effect in favour of NSAIDs for management of symptoms in acute gout attacks. We computed a 95% CI for the SMD when needed. The SMD can be interpreted as described by Cohen (Cohen 1988), that is, an SMD of 0.2 is considered to indicate a small beneficial effect, 0.5 a medium effect, and 0.8 a large effect of NSAIDs for management of symptoms in acute gout attacks. SMDs are considered to indicate a clinically relevant effect if they are larger than 0.5. Upon completion of the analysis, we had planned to translate the SMD back into an MD, using the control group SD at baseline to represent the population SD on a common scale (e.g. 0- to 10-point pain scale), which can be better appraised by clinicians.

In the Effects of interventions section under Results and in the 'Comments' column of the 'Summary of findings' table, we provided the absolute percentage difference and the number

needed to treat for an additional beneficial outcome (NNTB), or the number needed to treat for an additional harmful outcome (NNTH) (NNTB or NNTH only for dichotomous outcomes with a clinically significant difference). For dichotomous outcomes, the absolute percentage change was calculated from the difference in risk between intervention and control groups using GRADEpro (GRADEpro 2015), expressed as a percentage. We calculated the NNTB or the NNTH from the control group event rate and the RR by using the Visual Rx NNT calculator (Cates 2008).

Unit of analysis issues

We did not expect unit of analysis problems in this review. In the event that we had identified cross-over trials in which reporting of continuous outcome data precluded paired analysis, we did not plan to include these data in a meta-analysis, to avoid unit of analysis error. When carry-over effects were thought to exist, and when sufficient data were found, we planned to include only data from the first period in the analysis (Higgins 2020a). When outcomes were reported at multiple follow-up times, we planned to extract data at the following time points: short term (up to two weeks), medium term (more than two weeks to six weeks), and long term (more than six weeks). However, in the included trials, only short-term outcomes were presented. If more than one time point was reported within the time frame (e.g. at one-week follow-up, at two-week follow-up), we planned to extract the later time point (i.e. two weeks).

Dealing with missing data

We contacted the study authors when important data were missing. In case individuals were missing from reported results and no further information was forthcoming from the study authors, we assumed missing values to indicate a poor outcome. For dichotomous outcomes (e.g. number of withdrawals due to adverse events), we planned to calculate the withdrawal rate using the number of participants randomised in the group as the denominator (worst-case analysis). For continuous outcomes (e.g. mean change in pain score), we planned to calculate the MD or the SMD based on the number of participants analysed at that time point. If the number of participants analysed was not presented for each time point, we planned to use the number of randomised participants in each group at baseline.

When possible, we computed missing SDs from other statistics such as standard errors, confidence intervals, or P values, according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). If we could not calculate SDs, we planned to impute them (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

We assessed studies for clinical homogeneity with respect to intervention groups (type of NSAID), control groups, timing of outcome assessment, and outcome measures. For any studies

judged as clinically homogeneous, we planned to assess statistical heterogeneity using the I2 statistic based on the following approximate guide (Deeks 2020): 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% may represent considerable heterogeneity. In cases of considerable heterogeneity (defined as I2 greater than 75%), we planned to explore the data further, including subgroup analyses, in an attempt to explain the heterogeneity.

Assessment of reporting biases

We planned an assessment of reporting biases through screening of the Clinical Trial Register at the International Clinical Trials Registry Platform of the WHO to determine whether the protocol of the RCT had been published before study participant recruitment was started (DeAngelis 2004).

Furthermore, we planned a comparison between the fixed-effect estimate and the random-effects model (to assess the possible presence of small-sample bias), as well as a funnel plot (to assess the possible presence of reporting bias), if data were available (Page 2020). However, data were insufficient to permit these analyses.

Data synthesis

If we considered studies sufficiently homogeneous, we pooled data in a meta-analysis using a random-effects model, irrespective of I2 statistic results. We performed analyses using Review Manager 5 (RevMan 2020), and we produced forest plots for all analyses for the following comparisons: NSAIDs versus placebo; non-selective NSAIDs versus COXIBs; and NSAIDs versus glucocorticoids.

Subgroup analysis and investigation of heterogeneity

When sufficient data were available, we planned the following three subgroup analyses.

- Disease severity (monoarticular versus polyarticular).
- Presence or absence of comorbidities (such as cardiovascular or renal disease, history of peptic ulcer).
- Duration of treatment: short term (up to two weeks) versus long term (longer than six weeks).

If trial data were available, we planned to extract major outcomes for the above subgroups within each trial (e.g. monoarticular versus polyarticular) and to informally compare the magnitude of effects between subgroups by assessing the overlap of CIs for the effect estimate (for the main benefit outcome only). Non-overlap of CIs indicates statistically significant responses between subgroups. However, data were insufficient for any subgroup analyses to be performed.

Sensitivity analysis

When sufficient studies existed, we planned sensitivity analyses to assess the impact of any bias attributable to inadequate or unclear treatment allocation (including studies with quasi-randomised designs) or to lack of blinding. However, data were insufficient for sensitivity analyses to be performed.

Interpreting results and reaching conclusions

We followed the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 15 (Schunemann 2020a), when interpreting results, and we were aware of distinguishing lack of evidence of effect from lack of effect. We based our conclusions only on findings from the quantitative synthesis of studies included in this review. We avoided making recommendations for practice; our implications for research suggest priorities for future research and outline remaining uncertainties in this area.

Summary of findings and assessment of the certainty of the evidence

We produced 'Summary of findings' (SoF) tables using GRADEpro software (GRADEpro 2015). These tables include an overall grading of evidence based on the GRADE approach as recommended by Cochrane (Schünemann 2020). We produced a summary of available data on the following seven major outcomes: mean improvement in pain, reduction of inflammation measured by swelling, function of target joint, participant global assessment, HRQoL, number of withdrawals due to adverse events, and total adverse events. We have presented three SoF tables for the following comparisons: NSAIDs versus placebo; and two of the most clinically relevant comparisons with multiple trials that allowed pooling of outcomes (non-selective NSAIDs versus COXIBs and NSAIDs versus glucocorticoids). We did not produce SoF tables for comparisons with single trials of only low-certainty evidence (NSAID versus rilonacept, NSAID versus acupuncture), nor for comparison of one NSAID versus another NSAID, as these were mostly single-trial comparisons and included many NSAIDs that are no longer in clinical use.

We originally intended to include in the SoF tables the proportions of participants who reported pain relief of 50% or greater. However, as this information was not included for most trials, we included a continuous measure of pain instead because this is how most trials measured pain.

Two people (CD and MW) used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to independently assess the certainty of a body of evidence related to studies that contributed data to the meta-analyses for prespecified outcomes, and we reported the certainty of evidence as high, moderate, low, or very low. We used methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020). We justified all decisions to downgrade the certainty of

studies by using footnotes, and we made comments to aid readers' understanding of the review when necessary. We provided the NNTB or the NNTH and absolute percentage change in the Comments column of the SoF table for dichotomous outcomes, as described in the Measures of treatment effect section above.

Those SoF are available in the supplementary document presented aside this thesis and are available upon request.

RESULTS

Description of studies

Results of the search

Cochrane Musculoskeletal updated the search for all gout review updates on 28 August 2020, searching for studies from July 2011 to August 2020. Searches for this update yielded a total of 4511 new records from the following databases: MEDLINE (2125), Embase (1537), and Cochrane CENTRAL (849). We also identified 1 eligible study from the references of other studies. After removing duplicates, we excluded 3245 records based on title and abstract screening. We then assessed 571 full-text articles for eligibility. Of these, we included 5 new studies in this review update (Li 2013; Rainer 2016; Roddy 2020; Xu 2016; Zhang 2014). We excluded 566 full- text articles for the following reasons: 164 because of wrong study design, 65 because of wrong patient population, and 298 because of wrong intervention. Thirteen reports were duplicates from the same studies, and 2 studies used the wrong comparator. A total of 21 studies were already included in the previous version of this review, 2 studies are awaiting classification, and 1 study is ongoing. A flow diagram summarising the study selection process is shown in Figure 1.

Included studies

The 28 included trials involved 3406 participants (mean 122 participants; range 20 to 416, with study duration ranging from 90 hours to 14 days). A full description of the included studies is provided in the Characteristics of included studies table. Twenty-six trials were reported in English, 1 in Portuguese (Klumb 1996), and 1 in German (Siegmeth 1976).

Diagnosis of gout and participant features

All included trials were RCTs. The diagnosis of gout was made on clinical grounds in 8 trials (Butler 1985; Douglas 1970; Eberl 1983; Lederman 1990; Maccagno 1991; Roddy 2020; Smyth 1973; Sturge 1977). Ten trials used the 1977 classification criteria of the American College of Rheumatology (ACR 1977) (Cheng 2004; Li 2013; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Terkeltaub 2013; Willburger 2007; Xu 2016; Zhang 2014), and 1 trial included only participants with gout confirmed by identification of MSU crystals in synovial

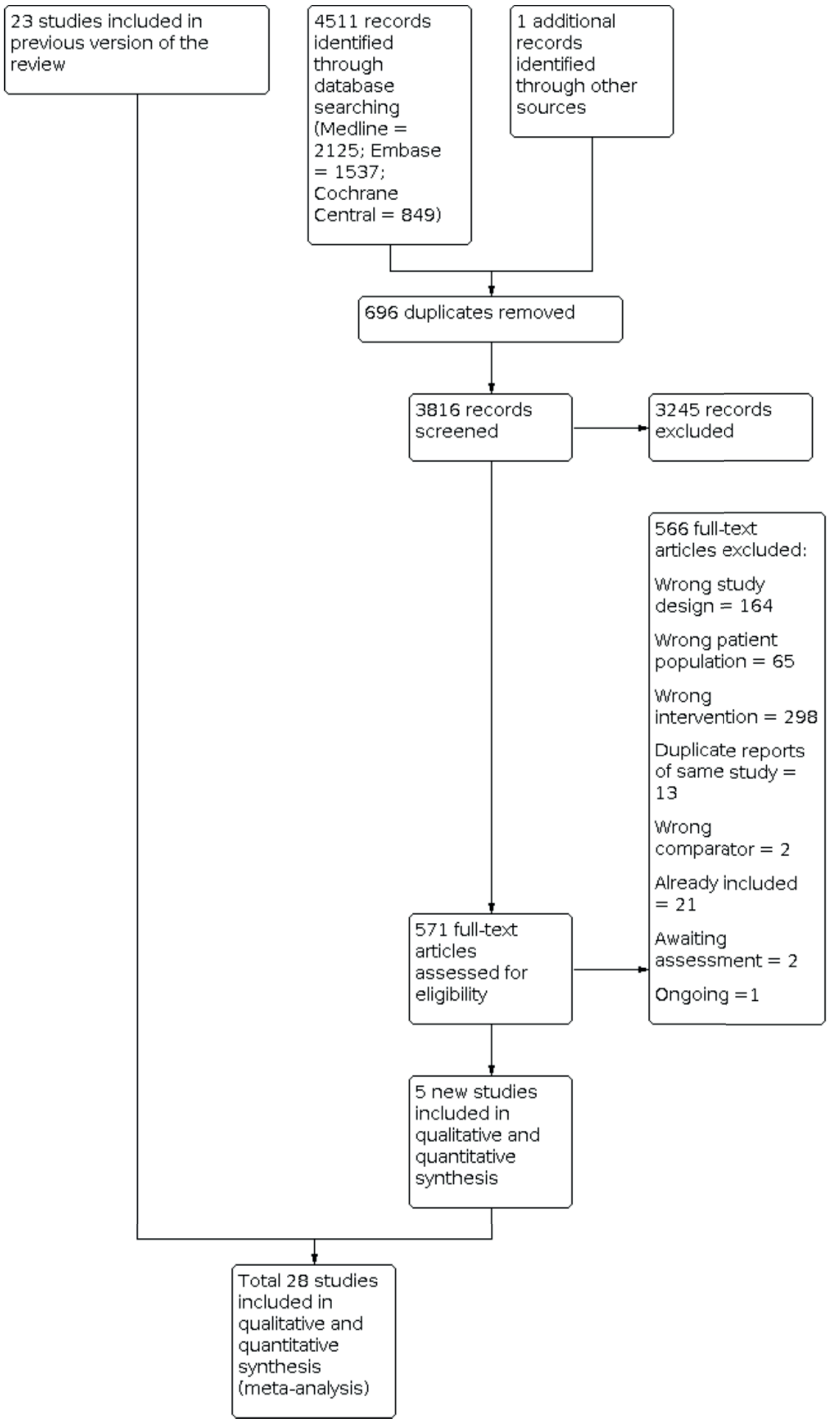


Figure 1. Study flow diagram

fluid (Janssens 2008a). Eight trials used either clinical inclusion criteria (a clear history - or the observation - of at least two attacks of acute arthritis with abrupt onset and remission, history/observation of podagra, presence of tophi, history/observation of response to colchicine within 48 hours of therapy) or positive identification of MSU crystals in the synovial fluid for inclusion (Altman 1988; Axelrod 1988; Garcia de la Torre 1987; Klumb 1996; Lomen 1986; Man 2007; Rainer 2016; Siegmeth 1976). Zhou 2012 used the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Medicine (Traditional Chinese Medicine 1994).

All included studies recruited adults, and all but 1 study reported mean age of the study population (Lomen 1986); mean age of the whole study population ranged from 44 to 66 years. Twenty-one trials included both males and females (Altman 1988; Cheng 2004; Douglas 1970; Garcia de la Torre 1987; Janssens 2008a; Lederman 1990; Li 2013; Maccagno 1991; Man 2007; Rainer 2016; Roddy 2020; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Smyth 1973; Sturge 1977; Terkeltaub 2013; Willburger 2007; Xu 2016; Zhang 2014). In these trials, the proportion of males varied between 69% and 97%. Five trials included only males (Axelrod 1988; Eberl 1983; Klumb 1996; Siegmeth 1976; Zhou 2012), and 2 trials did not describe gender distribution (Butler 1985; Lomen 1986).

Seven trials reported the mean duration of disease, which ranged from 5 to 17 years (Douglas 1970; Klumb 1996; Lomen 1986; Siegmeth 1976; Terkeltaub 2013; Xu 2016; Zhou 2012). Four trials included only participants with monoarthritis (Janssens 2008a; Lederman 1990; Lomen 1986; Maccagno 1991). Two trials included participants with monoarthritis and oligoarthritis (maximum three joints involved) (Schumacher 2012; Terkeltaub 2013). Nine trials included participants regardless of the number of joints involved: 66% to 96% of participants had monoarthritis, and 5% to 34% had more than one joint involved (Axelrod 1988; Eberl 1983; Klumb 1996; Man 2007; Roddy 2020; Rubin 2004; Schumacher 2002; Willburger 2007; Zhang 2014). Nine trials described affected sites: the first metatarsophalangeal joint was affected in 27% to 100%, the knee in 18% to 47%, the ankle in 19% to 27%, the thumb in 5%, the wrist in 5% to 14%, and the elbow in 3% to 10% of participants (Axelrod 1988; Eberl 1983; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Li 2013; Roddy 2020; Schumacher 2002; Xu 2016).

Comparisons

Only 1 trial compared an NSAID (tenoxicam 40 mg) to placebo (Garcia de la Torre 1987).

Thirteen trials compared one NSAID to another NSAID (Altman 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Klumb 1996; Lederman 1990; Lomen 1986; Maccagno 1991; Shrestha 1995; Siegmeth 1976; Smyth 1973; Sturge 1977). Although many of the studied NSAIDs are still registered, many are no longer commonly used in practice: NSAIDs studied included diclofenac (Cheng 2004), etodolac (Lederman 1990; Maccagno 1991), flufenamic acid (Douglas

1970), flurbiprofen (Butler 1985; Lomen 1986), ketorolac (Shrestha 1995), ketoprofen (Altman 1988; Siegmeth 1976), meclofenamate (Eberl 1983), meloxicam (Cheng 2004), nimesulide (Klumb 1996), and phenylbutazone (Butler 1985; Douglas 1970; Siegmeth 1976; Smyth 1973; Sturge 1977). The duration of treatment ranged from 5 days in Altman 1988, Lomen 1986, and Shrestha 1995 to 10 days in Butler 1985; follow-up ranged from 24 hours in Maccagno 1991 to 14 days in Altman 1988 and Eberl 1983.

Six trials compared a non-selective NSAID (indomethacin, 50 mg 3 times daily) to a selective COX-2 inhibitor (etoricoxib 120 mg once daily; celecoxib 50, 200, or 400 mg twice daily, or lumiracoxib 400 mg once daily) (Li 2013; Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007; Xu 2016). Treatment was given for 4 days in Xu 2016, 7 days in Willburger 2007, and 8 days in Rubin 2004Schumacher 2002 and Schumacher 2012; follow-up ranged from 4 days in Xu 2016 to 14 days in Schumacher 2012.

Four trials compared NSAIDs (naproxen 500 mg twice daily or indomethacin 50 mg 3 times daily) to oral glucocorticoids (prednisolone 30 or 35 mg once daily) (Janssens 2008a; Man 2007; Rainer 2016; Xu 2016). Drugs were given for 4 days in Xu 2016, Janssens 2008a, and Rainer 2016 and for 6 days in Man 2007; follow- up ranged from 90 hours in Janssens 2008a and Xu 2016 to 14 days in Man 2007 and Rainer 2016.

One trial compared NSAIDs (diclofenac 75 mg twice daily for 7 days) to intramuscular glucocorticoids (betamethasone 7 mg once intramuscularly) (Zhang 2014). Participants were followed up for 7 days.

One trial compared an NSAID (indomethacin 50 mg 4 times daily) to adrenocorticotropin hormone (ACTH) (40 international units (IU) intramuscularly in a single dose) (Axelrod 1988). Participants were followed for 1 year, and every attack during that year was treated with either indomethacin or ACTH.

One trial compared an NSAID (indomethacin 50 mg 3 times daily for 3 days, followed by 25 mg 3 times daily for up to 9 days) to rilonacept (320 mg subcutaneously) and to NSAID plus rilonacept (Terkeltaub 2013).

One trial compared an NSAID (indomethacin 25 mg 3 times daily for 5 days) to acupuncture combined with infrared irradiation (Zhou 2012).

One trial compared an NSAID (naproxen 250 mg 3 times daily) to colchicine (500 mcg 3 times daily) (Roddy 2020).

Outcomes

Four trials included our primary benefit endpoint of proportion of participants improved by 50% or more (Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Lomen 1986), and 20 trials included our primary harms endpoint of withdrawal due to adverse events (Altman 1988; Axelrod 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Garcia de la Torre 1987; Janssens 2008a; Lederman 1990; Li 2013; Lomen 1986; Maccagno 1991; Man 2007; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Terkeltaub 2013; Willburger 2007; Xu 2016). Other endpoints were variably reported.

NSAID versus placebo (1 trial)

The primary outcomes of this trial were time to improvement and time to resolution; pain and the presence of inflammation were assessed as secondary outcomes. In addition, both of our primary outcomes were reported (Garcia de la Torre 1987).

One NSAID versus another NSAID (13 trials)

Only 3 trials reported proportions of participants improved by 50% or more (Eberl 1983; Klumb 1996; Lomen 1986). All trials used ordinal scales to report pain, with the exception of Klumb 1996, which used a VAS.

Seven trials assessed 'inflammation' as an outcome, but the method of assessment varied across trials (Cheng 2004; Douglas 1970; Eberl 1983; Lederman 1990; Lomen 1986; Maccagno 1991; Smyth 1973). Cheng 2004 used an inflammatory score that assessed tenderness, swelling, and restriction of function of the inflamed joint. Douglas 1970 reported the number of days needed for the redness, swelling, tenderness, or heat to resolve. Eberl 1983 reported numbers of participants who had no redness, swelling, or function restriction at the end of treatment. Lederman 1990 and Lomen 1986 assessed pain, swelling, erythema, and tenderness on a 5-point scale.

Five trials assessed function (Altman 1988; Cheng 2004; Eberl 1983; Lederman 1990; Maccagno 1991). Altman 1988 and Cheng 2004 assessed function as part of a total 'inflammatory' score. The other 3 trials reported whether there was a limitation in motion of the index joint (absent/none or present).

Five trials included a measure of participants' global assessment (Altman 1988; Cheng 2004; Lederman 1990; Lomen 1986; Maccagno 1991), and no trials included a measure of HRQoL.

Twelve trials included the numbers of participants with AEs and provided a description of the AEs (Altman 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Klumb 1996; Lederman 1990; Lomen 1986; Maccagno 1991; Shrestha 1995; Smyth 1973; Sturge 1977).

Non-selective NSAIDs versus selective cyclo-oxygenase-2 inhibitors (6 trials)

None of these trials measured our primary benefit endpoint, but they all reported withdrawals due to AEs. All 6 trials measured pain as a primary outcome, using a Likert scale (Li 2013; Rubin 2004; Schumacher 2012; Willburger 2007; Xu 2016), or a 5-point ordinal scale (Schumacher 2002). FIve trials measured inflammation and participants' global assessment as secondary outcomes (Li 2013; Rubin 2004; Schumacher 2002; Willburger 2007; Xu 2016). One trial assessed function (Xu 2016). Willburger 2007 was the only trial that measured HRQoL as a secondary outcome, using SF-36 and EuroQoL Group Quality of Life Questionnaire based on 5 dimensions (EQ-5D) questionnaires. Six trials included numbers of participants with AEs and provided a description of the AEs (Li 2013; Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007; Xu 2016).

NSAIDs versus oral glucocorticoids (4 trials) or intramuscular (IM) glucocorticoids (1 trial) or adrenocorticotropin hormone (1 trial)

Neither of the 4 trials comparing NSAID versus oral glucocorticoid included our primary benefit endpoint; all trials included numbers of withdrawals due to AEs (Janssens 2008a; Man 2007; Rainer 2016; Xu 2016). All 4 trials measured pain as mean pain reduction. Three trials measured function (Janssens 2008a; Rainer 2016; Xu 2016). Two trials included measures of inflammation (redness, tenderness, and swelling) (Rainer 2016; Xu 2016). Rainer 2016 and Xu 2016 assessed participants' global assessment. Only Rainer 2016 assessed HRQoL (SF-36) but did not report the results of this outcome (these also were not obtained from study authors). All trials included the numbers of participants with AEs and provided a description of the AEs. Three trials reported withdrawals due to AEs (Janssens 2008a; Man 2007; Xu 2016).

The trial that compared NSAIDs to intramuscular glucocorticoids reported our main benefit outcome (number of patients without pain) after assessing pain on a Likert scale (Zhang 2014). Other outcomes that were assessed were measures of inflammation (swelling,tenderness)andp atients'andphysicians'assessmentsof global response to therapy.

The trial that compared NSAIDs to ACTH did not include any of our main benefit outcomes but did assess pain as the number of hours needed to achieve complete pain relief (Axelrod 1988). This trial also reported withdrawals due to AEs and numbers and types of adverse events.

NSAIDs versus rilonacept (interleukin-1 inhibitors) (1 trial)

One trial compared NSAID to rilonacept (Terkeltaub 2013). This trial measured change in pain from baseline using both Likert and numerical scales and withdrawals due to adverse events but none of the other relevant measures in this review.

NSAIDs versus acupuncture (1 trial)

One trial compared NSAID to acupuncture. This trial measured only mean change in pain (Zhou 2012).

NSAIDs versus colchicine (1 trial)

Roddy 2020 compared NSAID to colchicine. This trial measured change in pain intensity from baseline as a primary outcome on a 0 to 10 numerical rating scale (NRS). No measure of inflammation was included. Quality of life was assessed using the EuroQoL Group Quality of Life Questionnaire based on 5 dimensions and a 5- level scale (EQ-5D-5L). Adverse events and descriptions of adverse events were provided.

Excluded studies

We excluded 20 trials after detailed review. Reasons for exclusion are described in the Characteristics of excluded studies table. Nine studies were not RCTs (Arnold 1988; Bach 1979; Cunovic 1973; Cuq 1973; Ecker-Schlipf 2009; Janssens 2009; Navarra 2007; Steurer 2016; Werlen 1996). We excluded 1 study because participants with renal insufficiency, history of gastrointestinal AEs to NSAIDs, peptic ulcer or gastritis, or any other

contraindication to indomethacin were placed in the triamcinolone group (non-randomised), and other participants were randomised (Alloway 1993). Data for randomised participants were not reported separately. One trial did not include participants with acute gout (Kudaeva 2007). We excluded 3 trials because the NSAIDs used (feprazone, proquazone, and fenoprofen) are no longer available (Reardon 1980; Ruotsi 1978; Weiner 1979). We excluded 1 trial because the inclusion population consisted of patients with peptic haemorrhage ulcers who were having an acute gout flare (Xu 2015). We excluded 2 trials because they compared two different doses of the same drug (Tumrasvin 1985; Valdes 1987). We identified an additional trial comparing apremilast to indomethacin from the trial registry search, but the trial had been withdrawn (NCT00997581).

Studies awaiting classification

For one trial, only the conference abstract was available at the time of publication of this review (Katona 1988). Another study is written in Chinese and is awaiting translation (Yin 2005). We categorised trials as awaiting classification (see Characteristics of studies awaiting classification table).

Ongoing studies

One ongoing trial - ChiCTR1800019612 - is recruiting participants to study effects of NSAID plus ozone treatment of autologous blood versus ozone treatment of autologous blood.

Risk of bias in included studies

We judged most trials (26/28; 93%) as having unclear - Altman 1988; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Lomen 1986; Maccagno 1991; Man 2007; Rainer 2016; Rubin 2004; Schumacher 2002; Schumacher 2012; Siegmeth 1976; Smyth 1973; Terkeltaub 2013; Willburger 2007 - or high risk of bias - Axelrod 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Lederman 1990; Roddy 2020; Sturge 1977; Xu 2016; Zhang 2014; Zhou 2012. We judged only 2 trials (8%) as having low risk of bias (Li 2013; Shrestha 1995).

A description of the risk of bias of included studies is presented in the Characteristics of included studies table. Summaries of the risk of bias of included trials as a group are shown in Figure 2 and of of individual trials in Figure 3.

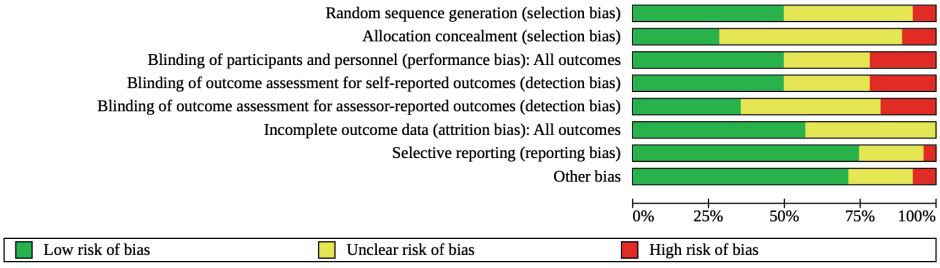


Figure 2. Risk of bias graph: review author's judgements about each risk of bias item presented as percentages across all included studies.

Sequence generation (selection bias)

Fourteen trials reported an appropriate sequence generation (Cheng 2004; Douglas 1970; Janssens 2008a; Li 2013; Man 2007; Rainer 2016; Roddy 2020; Schumacher 2002; Schumacher 2012; Shrestha 1995; Smyth 1973; Willburger 2007; Xu 2016; Zhou 2012). For 12 trials, the method of sequence generation was unclear (Altman 1988; Butler 1985; Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Lomen 1986; Maccagno 1991; Rubin 2004; Siegmeth 1976; Sturge 1977; Terkeltaub 2013; Zhang 2014). We judged 2 trials as having high risk of bias for the item sequence generation: 1 trial because participants were alternately assigned to one of the two treatment groups (Axelrod 1988), and the other trial because although stated as randomised with no description of the randomisation method, baseline characteristics were significantly different between the two treatment groups (Lederman 1990).

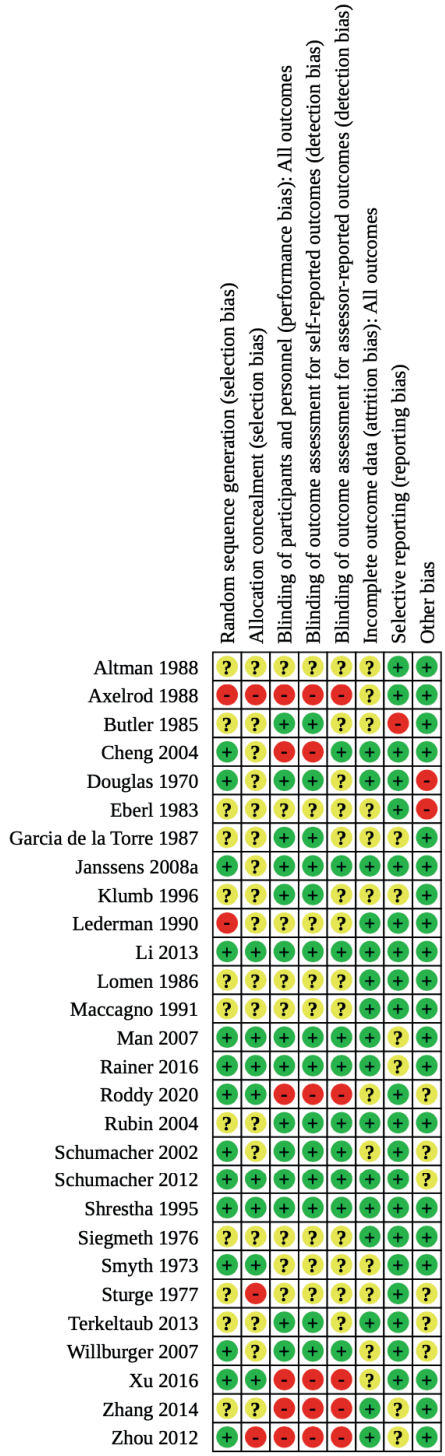


Figure 3. Risk of bias summary: review author's judgements about each risk of bias item for each included study.

Allocation

For 17 trials, concealment of drug allocation was inappropriately described or was not described at all, and we judged them to be at unclear risk of bias (Altman 1988; Butler 1985; Cheng 2004; Douglas 1970; Eberl 1983; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Lederman 1990; Lomen 1986; Maccagno 1991; Rubin 2004; Schumacher 2002; Siegmeth 1976; Terkeltaub 2013; Willburger 2007; Zhang 2014). We assigned 3 trials to be at high risk of allocation bias because the treatment was not concealed (Axelrod 1988; Sturge 1977; Zhou 2012). Eight trials were at low risk of selection bias, as the method of allocation concealment was clearly described (Li 2013; Man 2007; Rainer 2016; Roddy 2020; Schumacher 2012; Shrestha 1995; Smyth 1973; Xu 2016).

Blinding

We judged 8 trials as having unclear risk of performance bias regarding blinding of study personnel (Altman 1988; Eberl 1983; Lederman 1990; Lomen 1986; Maccagno 1991; Siegmeth 1976; Smyth 1973; Sturge 1977). For 6 trials (Axelrod 1988; Cheng 2004; Roddy 2020; Xu 2016; Zhang 2014; Zhou 2012), we considered risk of performance bias to be high because participants were not blinded. We judged 14 trials to be at low risk of performance bias, as the method of blinding participants and study personnel was adequately described (Butler 1985; Douglas 1970; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Li 2013; Man 2007; Rainer 2016; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Terkeltaub 2013; Willburger 2007). We judged 8 trials as having unclear risk of detection bias for self-reported outcomes because blinding of participants was not described or was unclear (Altman 1988; Eberl 1983; Lederman 1990; Lomen 1986; Maccagno 1991; Siegmeth 1976; Smyth 1973; Sturge 1977). We assigned 6 trials high risk of bias because the trials were not blinded (Axelrod 1988; Cheng 2004; Roddy 2020; Xu 2016; Zhang 2014; Zhou 2012). We judged 14 trials to be at low risk of detection bias for self-reported outcomes, as the method used to blind participants was adequately described (Butler 1985; Douglas 1970; Garcia de la Torre 1987; Janssens 2008a; Klumb 1996; Li 2013; Man 2007; Rainer 2016; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Terkeltaub 2013; Willburger 2007).

We judged 13 trials to be at unclear risk of detection bias for assessor-reported outcomes because blinding of outcome assessors was not described or was unclear (Altman 1988; Butler 1985; Douglas 1970; Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Lederman 1990; Lomen 1986; Maccagno 1991; Siegmeth 1976; Smyth 1973; Sturge 1977; Terkeltaub 2013). We assigned 5 trials high risk of detection bias for assessor-reported outcomes because the trials were not blinded (Axelrod 1988; Roddy 2020; Xu 2016; Zhang 2014; Zhou 2012). We judged 10 trials to be at low risk of detection bias for assessor-reported outcomes, as the method of blinding outcome assessors was adequately described (Cheng 2004; Janssens 2008a; Li 2013; Man 2007; Rainer 2016; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Willburger 2007).

Incomplete outcome data

We judged 12 trials as having unclear risk of bias for incomplete outcome data because they did not report if there were withdrawals or missing data, or how withdrawals or missing data (or both) were handled (Altman 1988; Axelrod 1988; Butler 1985; Eberl 1983; Garcia de la Torre 1987; Klumb 1996; Roddy 2020; Schumacher 2002; Smyth 1973; Sturge 1977; Willburger 2007; Xu 2016). We judged the remaining 16 trials to be at low risk of attrition bias (Cheng 2004; Douglas 1970; Janssens 2008a; Lederman 1990; Li 2013; Lomen 1986; Maccagno 1991; Man 2007; Rainer 2016; Rubin 2004; Schumacher 2012; Shrestha 1995; Siegmeth 1976; Terkeltaub 2013; Zhang 2014; Zhou 2012).

Selective reporting

Twenty trials were at low risk of reporting bias (Altman 1988; Axelrod 1988; Cheng 2004; Douglas 1970; Eberl 1983; Janssens 2008a; Lederman 1990; Li 2013; Lomen 1986; Maccagno 1991; Rubin 2004; Schumacher 2002; Schumacher 2012; Shrestha 1995; Siegmeth 1976; Smyth 1973; Sturge 1977; Terkeltaub 2013; Willburger 2007; Xu 2016). We assigned 6 trials unclear risk of selective reporting bias (Garcia de la Torre 1987; Klumb 1996; Man 2007; Rainer 2016; Zhang 2014; Zhou 2012). Man 2007 reported secondary outcomes, but not in the prespecified manner. Klumb 1996 did not provide a clear description of outcomes and provided inappropriate between-group comparisons (only status scores). Garcia de la Torre 1987 and Rainer 2016 did not report all prespecified outcomes. Zhang 2014 reported an outcome that was not prespecified and did not report anywhere whether there was a statistically significant difference in this reported outcome. Other prespecified outcomes were reported, but again, it was not reported whether differences were statistically significant. Zhou 2012 did not report inflammation but named it in the methods section, so it is unclear if this was going to be a separate outcome.

We judged 1 trial as having high risk of bias for this criterion because it did not report one prespecified outcome - pain measured on an ordinal scale (Butler 1985).

Other potential sources of bias

Two trials were judged to be at high risk of other bias (Douglas 1970; Eberl 1983). Eberl 1983 used a higher initial meclofenamate dose compared with the indomethacin dose used in the control group, which may have biased the results in favour of the meclofenamate group. In Douglas 1970, the mean age of participants was significantly higher in the flufenamic acid group (57.2 years) than in the phenylbutazone group (47.6 years).

In Sturge 1977, there was also a difference in age between the two groups: participants in the naproxen group were older (mean age 58.8 years, range 34 to 84) than those in the phenylbutazone group (mean age 50.4 years, range 30 to 73).

Four studies were subject to funding by manufacturers, but these relationships did not appear to affect reporting of study results, and it is unclear if there was any bias in the study design as a result of the funding relationships.

The rilonacept study was funded by Regeneron Pharmaceutics Inc. (manufacturers of rilonacept); employees of Regeneron Pharmaceutics Inc. participated in study design, data analysis, and writing of the manuscript (Terkeltaub 2013). It is unclear if this relationship resulted in any biased conduct in the trial.

For Schumacher 2002, Merck Research Laboratory provided funding to all participating investigators to cover the costs of patient procedures and investigations; one study author was on the Merck advisory board, one was a consultant for Merck, and four were employed by Merck and owned shares of Merck common stock.

Editorial support was funded by Pfizer for Schumacher 2012.

Four authors of Willburger 2007 were employed by Novartis Pharma; one author was a speaker for Novartis. It is unclear if this relationship resulted in any biased reporting of results in the trial.

Roddy 2020 reported a difference in length of treatment; naproxen was given for 4 days and colchicine for 7 days.

Effects of interventions

See: **Summary of findings 1** NSAIDs compared to placebo for acute gout; **Summary of findings 2** Non-selective NSAIDs versus selective cyclo-oxygenase-2 inhibitors; **Summary of findings 3** NSAIDs compared to glucocorticoids for acute gout. *Those SoF tables are available in the supplementary document presented aside this thesis (available upon request).*

NSAIDs versus placebo

Benefits

One trial of 30 participants compared an NSAID (tenoxicam 40 mg) with placebo (Garcia de la Torre 1987). All results are summarised in Summary of findings 1. NSAIDs may result in decreased pain (higher proportion of participants achieving ≥ 50% improvement in pain). Low-certainty evidence downgraded for bias and imprecision suggests there may be a clinically significant improvement in the number of patients who achieve more than 50% reduction in overall pain (reported as 'spontaneous pain') at 24 hours (11/15 in the tenoxicam group, 4/15 in the placebo group; risk ratio (RR) 2.7, 95% confidence interval (CI) 1.1, 6.7), with absolute change of 47% more (3.5% more to 152.5% more) with NSAIDs and number needed to treat

for an additional beneficial outcome (NNTB) of 3 (95% CI 2 to 12; Analysis 1.1). There was no difference in the number of participants who achieved more than 50% reduction in pain with movement at 24 hours (4/15 in the NSAIDs group versus 1/15 in the placebo group; RR 4.0, 95% CI 0.5 to 31.7) and at day 4 (13/15 in the NSAIDs group versus 14/15 in the placebo group; RR 0.9, 95% CI 0.7 to 1.2; Analysis 1.1).

Low-certainty evidence downgraded for bias and imprecision suggests no reported between-group differences in the proportions of participants with more than 50% improvement in joint swelling at 24 hours (5/15 in the NSAIDs group versus 2/15 in the placebo group; RR 2.5, 95% CI 0.6 to 10.9) or at day 4 (13/15 in the NSAIDs group versus 12/15 in the placebo group; RR 1.1, 95% CI 0.8 to 1.5), with absolute change of 6.4% more patients (16.8% fewer to 39.2% more).

NSAIDs may have no effect on function (≥ 50% improvement in pain with movement at 24 hours assessed on a 4-point scale (1 = complete resolution to 4 = increased pain); RR 4.0 (95% CI 0.5 to 31.7)), with absolute change of 20% more (3.3% fewer to 204.9% more).

The trial did not measure global assessment of treatment success nor health-related quality of life (HRQoL).

Harms

There were no withdrawals due to adverse events in either group in this trial and no significant between-group differences in numbers of adverse events (0/15 in the NSAIDs group versus 2/15 in the placebo group; RR 0.2, 95% CI 0.0 to 3.8), with absolute change of 10.6% fewer (13.2% fewer to 38% more; Analysis 1.3).

Non-selective NSAIDs versus cyclo-oxygenase-2 inhibitors

Six trials including 1266 participants compared NSAIDs (indomethacin 50 mg 3 times daily or 75 mg twice daily) to COXIBs (etoricoxib 120 mg once daily; celecoxib 50, 200, or 400 twice daily; or lumiracoxib 400 mg once daily), and data could be pooled (Li 2013; Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007; Xu 2016). Two trials were at unclear risk of selection bias (Rubin 2004; Willburger 2007), 1 was at high risk of performance and detection bias (Xu 2016), and it is unclear whether funding in 3 trials provided by the manufacturer resulted in any bias (Schumacher 2002; Schumacher 2012; Willburger 2007). One trial was at low risk of bias (Li 2013). All results are summarised in Summary of findings 2.

Benefits

Six trials (1044 participants) showed no between-group differences with respect to mean pain change from baseline on a 0 to 4 Likert scale (where 0 is no pain) at day 1 or 2 (mean difference

(MD) 0.0, 95% CI -0.1 to 0.1; Analysis 2.1). There was no statistically or clinically significant difference between NSAIDs and COXIBs with regards to inflammation measured on a 0 to 3 Likert scale (0 is no swelling; MD 0.1, 95% CI -0.1 to 0.2; 6 trials with 1044 participants; moderate-certainty evidence downgraded for bias; Analysis 2.2). Xu 2016 assessed function as pain with activity. There was no mean difference from baseline between the two groups (MD -0.0, 95% CI -0.2 to 0.2; low-certainty evidence downgraded for bias and imprecision; Analysis 2.3). Moderate-certainty evidence (downgraded for bias) from 4 trials (730 participants) showed no between-group differences with respect to patients' global assessment of treatment success (MD 0.1, 95% CI -0.0 to 0.2; Analysis 2.4). One trial with 222 participants reported no between- group differences with respect to HRQoL measured by the 36-Item Short Form questionnaire (SF-36) Mental Health component (MD -0.2, 95% CI -6.7 to 6.3; low-certainty evidence downgraded for bias and imprecision; Analysis 2.5; Willburger 2007).

Harms

Moderate-certainty evidence (downgraded for bias) from four trials (1266 participants) showed significantly fewer withdrawals due to adverse events among participants treated with COXIBs versus non- selective NSAIDs (21/729 (3.0%) in the COXIB group versus 32/514 (7.0%) in the non-selective NSAIDs group; RR 2.3, 95% CI 1.3 to 4.1), with absolute change of 4% more (1% more to 9% more) and number needed to treat for an additional harmful outcome (NNTH) of 26 (NNTH 11 to 105; Analysis 2.6). There were significantly fewer total adverse events among participants treated with COXIBs (168/727; 23%) compared with participants treated with NSAIDs (193/505; 45%) (RR 1.9, 95% CI 1.4 to 2.8; Analysis 2.7).

There were significantly fewer gastrointestinal adverse events with COXIBs compared with non-selective NSAIDs (RR 2.4, 95% CI 1.6 to 3.4; 1232 participants, 6 studies; 43/727 (6%) in the COXIBs group versus 72/505 (14%) in the non-selective NSAIDs group; Analysis 2.8). There were no significant between-group differences in cardiovascular events (RR 2.4, 95% CI 1.0 to 5.7), other adverse events (RR 1.7, 95% CI 0.9 to 3.2), or serious adverse events (RR 2.3, 95% CI 0.5 to 11.2; Analysis 2.9; Analysis 2.10; Analysis 2.11).

NSAIDs versus oral glucocorticoids or intramuscular glucocorticoid or adrenocorticotropic hormone

Benefits

Four trials (712 participants) compared NSAIDs to oral glucocorticoids (Janssens 2008a; Man 2007; Rainer 2016; Xu 2016), 1 compared NSAIDs to adrenocorticotropin hormone (ACTH) (Axelrod 1988), and 1 compared NSAIDs to intramuscular glucocorticoid (Zhang 2014). Two trials that compared NSAIDs to oral glucocorticoids were at low risk of bias (Janssens 2008a; Man 2007), 1 at unclear risk of bias (Rainer 2016), and 3 at high risk of bias Axelrod 1988; Xu 2016; Zhang 2014). Pain was assessed as mean decrease per hour on a visual analogue scale

(VAS) (Janssens 2008a; Man 2007; Rainer 2016), and per time interval at zero to 90 hours (Janssens 2008a). One trial reported pain as mean decrease 4 hours following treatment on each day for 7 days on a Likert scale (Zhang 2014). All results are summarised in Summary of findings 3.

Moderate-certainty evidence downgraded for bias showed no significant differences in mean pain reduction on a VAS scale (0 to 100; 0 no pain) between groups (MD 0.1, 95% CI -2.7 to 3.0; 3 trials, 584 participants; Analysis 3.1). One trial that compared NSAIDs (indomethacin 50 mg 4 times daily) to ACTH (40-mg single dose intramuscularly) reported that complete pain relief was achieved significantly sooner in the ACTH group compared with the indomethacin group (mean ± SD; 24 ± 10 hours in indomethacin group versus 3 ± 1 hours in ACTH group; Axelrod 1988), but we were unable to verify this from the data presented.

Three trials reported measures of inflammation (Rainer 2016; Xu 2016; Zhang 2014). Xu 2016 and Zhang 2014 reported swelling as a measure of inflammation, and only Xu 2016 reported it as mean difference from baseline. There was a significant difference in mean change in swelling from day 0 to day 4 on a 4-point Likert scale in favour of oral glucocorticoids (MD 0.3, 95% CI 0.1 to 0.6; low- certainty evidence downgraded for bias and imprecision; Analysis 3.2).

Two trials reported a measure of function (Janssens 2008a; Rainer 2016). Moderate-certainty evidence downgraded for bias showed no significant difference in reduction in loss of function between groups (MD -0.2, 95% CI -2.2 to 1.8; Analysis 3.3).

Two trials assessed patients' global assessment on a 5-point Likert scale (Rainer 2016; Xu 2016). There were no differences between groups (RR 0.9, 95% CI 0.7 to 1.2), with absolute change of 8.4% more (5.6% fewer to 25.8% more; moderate-certainty evidence downgraded for bias; Analysis 3.4).

Rainer 2016 also assessed HRQoL using SF-36 but did not present these results in the article.

Harms

Five trials with 772 participants reported withdrawals due to adverse events (Janssens 2008a; Man 2007; Rainer 2016; Xu 2016; Zhang 2014). Moderate-certainty evidence downgraded for bias showed there was no statistically significant difference between NSAIDs (10/389) versus oral glucocorticoid (3/383) (RR 2.8, 95% CI 0.5 to 14.2), with absolute change of 1.4% more (0.4% fewer to 10.4% more; Analysis 3.5). The trial comparing NSAIDs to ACTH - Altman 1988 - reported significantly more withdrawals due to adverse events in the indomethacin group (10/50 in the indomethacin group versus 0/50 in the ACTH group; RR 21, 95% CI 1.3 to 348.9; Analysis 5.1).

A pooled analysis of 5 trials comparing NSAIDs with corticosteroids - Janssens 2008a; Man 2007; Rainer 2016; Xu 2016; Zhang 2014 - showed more total adverse events in the NSAID group (248/379 (65%)) than in the glucocorticoid group (195/374 (52%); RR 1.6, 95% CI 1.0 to 2.5; Analysis 3.6). There were no significant between-group differences with respect to cardiovascular (RR 2.9, 95% CI 0.1 to 68.7), gastrointestinal (RR 1.8, 95% CI 0.9 to 3.7), or other adverse events (RR 1.1, 95% CI 0.7 to 1.8), nor serious adverse events (RR 12.4, 95% CI 0.7 to 214.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10).

In the trial of NSAID versus ACTH, significantly more adverse events were reported in the NSAIDs group compared to the ACTH group (49/50 (98%) in NSAID group versus 0/50 (0%) in ACTH group; RR 99, 95% CI 6.3 to 1562; Analysis 5.2).

One NSAID versus another NSAID

Two trials including 121 participants that compared naproxen with etodolac could be pooled for two outcomes (Lederman 1990; Maccagno 1991). Lederman 1990 had high risk of bias and Maccagno 1991 had unclear risk of bias.

Benefits

There was no between-group difference with respect to participants' global assessment of treatment success reported as proportions of people who considered themselves markedly improved at the end of treatment (53/60 (88%) in the etodolac group versus 53/61 (87%) in the naproxen group; RR 1.0, 95% CI 0.9 to 1.1; Analysis 4.1).

Harms

There were no withdrawals due to adverse events. There was no between-group difference with respect to numbers of adverse events (4/60 (7%) in the etodolac group versus 2/61 (3%) in the naproxen group; RR 1.7, 95% CI 0.4 to 7.9; Analysis 4.2).

Four trials including 142 participants compared indomethacin to another NSAID (nimesulide (Klumb 1996), flurbiprofen (Lomen 1986), meclofenamate (Eberl 1983), or ketoprofen (Altman 1988)). These trials had unclear - Altman 1988; Klumb 1996; Lomen 1986 - or high - Eberl 1983 risk of bias, and no between-group differences in benefits or harms outcomes were reported in individual trials or in the limited number of pooled analyses that were possible (data not shown).

NSAIDs versus rilonacept (interleukin-1 inhibitor)

Benefits

One trial at high risk of bias that included 225 participants found that NSAIDs provided greater pain relief from 24 to 72 hours than rilonacept (interleukin-1 inhibitor), as measured on a 0 to

10 numerical rating scale (MD -2.1, 95% CI -3.14 to -1.1; Analysis 6.1). Combination therapy (NSAIDs plus rilonacept) versus NSAIDs did not provide greater pain relief from baseline to a mean of pain at 24 to 72 hours as measured on a 0 to 10 numerical rating scale (MD -0.5, 95% CI -1.5 to 2.4; Analysis 7.1).

This trial did not measure inflammation, function, participants' global assessment of treatment success, nor HRQoL.

Harms

There was no between-group difference with regards to withdrawals due to adverse events (2/77 (2%) in the NSAIDs group versus 1/75 (1%) in the rilonacept group; RR 1.9, 95% CI 0.2 to 21.0; Analysis 6.2) nor in total number of adverse events (23/77 (30%) for the NSAIDs group versus 27/75 (36%) for the rilonacept group; RR 0.8, 95% CI 0.5 to 1.3; Analysis 6.3). There were no serious adverse events.

For combination therapy (NSAIDs plus rilonacept) versus NSAIDs, there were also no differences in study withdrawals due to adverse events (2/76 (3%) in the NSAIDs group versus 2/74 (3%) in the combination group; RR 1.0, 95% CI 0.1 to 6.7; Analysis 7.2), in risk of adverse events (23/76 (30%) in the NSAIDs group versus 34/74 (46%) in the combination group; RR 0.7, 95% CI 0.4 to 1.0), nor in risk of serious adverse events. (0/76 (0%) in the NSAIDs group versus 3/74 (4%) in the combination group; RR 0.1, 95% CI 0.0 to 2.6; Analysis 7.3; Analysis 7.4).

NSAIDs versus acupuncture combined with infrared irradiation

Benefits

One trial at high risk of bias that included 163 participants found that acupuncture and infrared irradiation resulted in better benefit with respect to mean pain score after treatment compared with NSAIDs (MD 2.2, 95% CI 1.8 to 2.7; Analysis 8.1Zhou 2012). This trial did not measure inflammation, function, participants' global assessment of treatment success, nor HRQoL.

Harms

Withdrawals due to adverse events and total adverse events were not reported.

NSAIDs versus colchicine

Benefits

Roddy 2020, which included 399 participants, found no difference in mean change in worst pain intensity over days 1 to 7 with NSAIDs compared to colchicine using a 0 to 10 NRS (MD 0.3, 95% CI -0.4 to 1.0). Quality of life was measured on the EuroQoL Group Quality of Life Questionnaire based on 5 dimensions and a 5-level scale (EQ-5D-5L), and there was no difference between groups (MD 0.0, 95% CI -0.0 to 0.0; Analysis 9.1; Analysis 9.2).

Harms

Withdrawals due to adverse events were not reported. There was no difference with regards to total number of adverse events (91/200 (46%) in the NSAID group versus 101/199 (51%) in the colchicine group; RR 0.9, 95% CI 0.7 to 1.1). There were no differences in gastrointestinal adverse events (RR 0.8, 95% CI 0.7 to 1.0) nor in other adverse events (RR 1.0, 95% CI 0.2 to 4.9; Analysis 9.3; Analysis 9.4; Analysis 9.5).

DISCUSSION

Summary of main results

We studied 28 trials and included 5 new trials in this review update, with a total of 3406 participants with acute gout who received treatment with non-steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs versus placebo

Low-certainty evidence was based on 1 trial comparing tenoxicam (NSAID) to placebo. There was a gain in benefit, measured as more than 50% improvement in pain after 24 hours. This benefit was lost after 4 days. There was no difference in benefit, measured as more than 50% improvement in swelling at 24 hours or at day 4. There were no data on joint function, participants' global assessment, nor health-related quality of life (HRQoL).

With regards to harms, there was no evidence of a difference in numbers of withdrawals, total numbers of adverse events, nor serious adverse events between NSAIDs and placebo.

Non-selective NSAIDs versus cyclo-oxygenase-2 inhibitors

Overall, moderate-certainty evidence is available from 6 trials that compared NSAIDs (indomethacin 50 mg 3 times daily or 75 mg twice daily) to cyclo-oxygenase-2 inhibitors (COXIBs) (etoricoxib 120 mg once daily; celecoxib 50, 200, or 400 twice daily; or lumiracoxib 400 mg once daily). With regards to benefit, assessed as mean differences from baseline in pain, inflammation, function, quality of life, and patients' global assessment, there were no differences between non-selective NSAIDs and COXIBs.

With regards to harms, significantly fewer adverse events and fewer withdrawals due to adverse events were noted among people treated with COXIBs. Although more gastrointestinal adverse events were reported among people who received non-selective NSAIDs, there was no significant difference in serious adverse events between those taking NSAIDs and those given COXIBs. One trial reported fewer cardiac events in the COXIBs group (etoricoxib) compared with the NSAIDs group (indomethacin) (Rubin 2004).

NSAIDs versus oral or intramuscular glucocorticoids

Overall, moderate-certainty evidence is available from 4 trials comparing NSAIDs to oral glucocorticoids. With regards to benefit, assessed as mean decrease in pain per time interval, joint function (walking disability), and participants' global assessment of response, there were no statistically significant differences between groups. With regards to inflammation, a statistically significant difference favoured prednisolone. No data on HRQoL were provided.

With regards to harms, more total adverse events were reported with NSAIDs than with glucocorticoids. There were no differences in numbers of serious adverse events nor in gastrointestinal or cardiovascular adverse events.

Other comparisons

We are uncertain of the benefits or harms of the other comparisons, as only low-certainty to very low-certainty evidence is available from single trials for NSAID versus rilonacept, NSAID versus acupuncture, one NSAID versus another NSAID (most were single- trial comparisons and included some NSAIDs that are no longer in use), or NSAIDs versus colchicine.

Overall completeness and applicability of evidence

Demographic data for participants in these studies seem representative of the average gout population. The age of trial participants ranged from 44 to 66 years. Twenty-one trials included both females and males, and the proportion of males was higher than that of females, ranging from 69% to 97%. Nine trials included participants regardless of the number of joints involved. The proportion of participants with monoarthritis ranged from 66% to 96%.

One of the problems regarding applicability of evidence concerns external validity. This is especially important with regards to comorbidities, which are present in most people with gout and were excluded by most included trials. The short follow-up duration of the included trials may have precluded the detection of certain adverse events that could have occurred after multiple short periods of drug use. Garcia de la Torre 1987 (comparing NSAIDs to placebo) excluded people with gastrointestinal or cardiac disease. In the comparison of COXIBs versus NSAIDs, all trials excluded people with a history of myocardial infarction or cerebral thrombotic ischaemic disease (or both) or a history of peptic ulcer haemorrhage (Li 2013; Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007; Xu 2016); 5 of the 6 trials also excluded people with other significant medical problems and those who had a concurrent medical condition that could confound or interfere with efficacy evaluations (Li 2013; Rubin 2004; Schumacher 2002; Schumacher 2012; Willburger 2007). Trials that compared NSAIDs to oral glucocorticoids also excluded people with common comorbid conditions such as coronary heart disease, heart failure, history of upper gastrointestinal disease, renal failure, or bleeding disorder. Man 2007 excluded people with a condition that could interfere with assessment without specifying

which one, along with people with dementia and confusion. Also the trial comparing NSAIDs to colchicine excluded participants with ischaemic heart disease or impaired liver function (Roddy 2020).

The single trial comparing NSAIDs versus an interleukin (IL)-1 inhibitor did not exclude people with significant comorbidities, resulting in a population with greater external validity (Terkeltaub 2013).

Quality of the evidence

Generation of an adequate randomisation sequence, concealment of treatment allocation, and blinding of outcome assessment were among the domains that were addressed most poorly, rendering many trials susceptible to selection and detection biases.

Three of the 4 (75%) studies comparing NSAIDs to COXIBs and 1 trial comparing NSAIDs to an IL-1 inhibitor were sponsored and supported by the company manufacturing etoricoxib and lumiracoxib (1 trial did not mention any funding in the article). Although pharmaceutical industry sponsoring is very common, it has been shown that industry-sponsored drug studies can lead to more favourable results than sponsorship from other sources (Lundh 2012).

We assessed the certainty of evidence according to the GRADE method.

For the comparison NSAIDs versus placebo, we downgraded the certainty of evidence to low for all outcomes due to study design flaws, making the results susceptible to selection and reporting biases, and because the evidence came from 1 study with 30 participants, we downgraded the results for imprecision.

For the comparison NSAIDs versus COXIBs, we downgraded the certainty of evidence to moderate for pain, inflammation, participants' global assessment of treatment success, study participant withdrawal due to adverse events, and total number of adverse events because of possible bias in study design. We downgraded the certainty of evidence to low for function and quality of life because of bias and imprecision, as evidence for these two outcomes came from a single trial with a small number of participants (45 in each arm).

For the comparison NSAIDs versus glucocorticoids, we downgraded the certainty of evidence to moderate for all outcomes (except inflammation) because of possible bias in study design and because participants in the NSAIDs group in Man 2007 were given an intramuscular injection of NSAIDs while the glucocorticoid group received placebo. We downgraded the certainty of evidence to low for inflammation because of bias and imprecision, as the evidence came from a single trial with a small number of participants (68 in both arms).

The other comparisons (NSAID versus rilonacept, NSAID versus acupuncture, one NSAID versus another NSAID) were not graded, as most were single-trial comparisons and included many NSAIDs that are no longer in clinical use.

Potential biases in the review process

We believe that we have identified all relevant studies up until the date of the search. We devised a thorough search strategy and searched all major databases for relevant studies, and we applied no language restriction.

Two review authors assessed trials for inclusion in the review, extracted data, and assessed risk of bias independently; a third review author adjudicated in case of any discrepancies, minimising risk errors and bias in the review.

Agreements and disagreements with other studies or reviews

This review is an update of a systematic review we conducted in 2014 (van Durme CMPG 2014), and our conclusions are in agreement with those presented in the previous review.

We have not identified any other systematic review on the use of NSAIDs for acute gout.

In one Cochrane systematic review on the use of systemic glucocorticoids for acute gout (Janssens 2008b), review authors identified the same trial as we did comparing NSAIDs and systemic glucocorticoids (Man 2007), and they concluded that systemic glucocorticoids could be an alternative to NSAIDs for treatment of acute gout, although the evidence was graded as B (moderate risk of bias, moderate-certainty evidence).

In another Cochrane systematic review on the use of NSAIDs for treatment of low back pain (Roelofs 2008), review authors similarly concluded that NSAIDs were probably equivalent to COXIBs with regards to benefits and harms based on evidence graded as strong by the review authors. With regards to COXIBs, review authors concluded that benefit was similar but that the total number of adverse events was less in the COXIBs group. Gastrointestinal and cardiovascular adverse events were not assessed separately. In our analysis, we also found similar benefit but less harm of COXIBs when compared to NSAIDs based on moderate-certainty evidence. COXIBs were safer with regards to total adverse events and gastrointestinal and even cardiovascular events. The fact that COXIBs led to fewer cardiovascular events than NSAIDs in the reviewed trials could be due to the short follow-up duration of included trials and to selection of participants, because 2 trials were published after the upheaval of COXIBs, potentially causing cardiovascular events (Schumacher 2012; Willburger 2007). As NSAIDs and COXIBs are most often used for short periods among people with gout, this issue seems to be less relevant here.

AUTHORS' CONCLUSIONS

Implication for practice

Guidelines recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 (COX-2) inhibitors (COXIBs), low- dose colchicine, or glucocorticoids for treatment of acute gout flares (FitzGerald 2020Qaseem 2017; Richette 2017). They do not rank any particular therapeutic class above the others but suggest that the choice of first-line therapy should be individualised depending upon the presence of any comorbidities. Our review lends support to these guidelines. We found only low-certainty evidence from 1 placebo-controlled trial (Richette 2010). We downgraded the evidence due to potential selection and reporting biases and imprecision. This study indicated there may be short- term benefit with NSAIDs during the first 24 hours, which was not evident after 4 days. However, this may be explained by the self- limiting course of the disease with a mean duration of a few days. Although clinical experience and consensus views based on their effects in other inflammatory arthritis support the use of NSAIDs for acute gout, this low-certainty single study provides inconclusive evidence to inform guidelines adequately (Richette 2010).

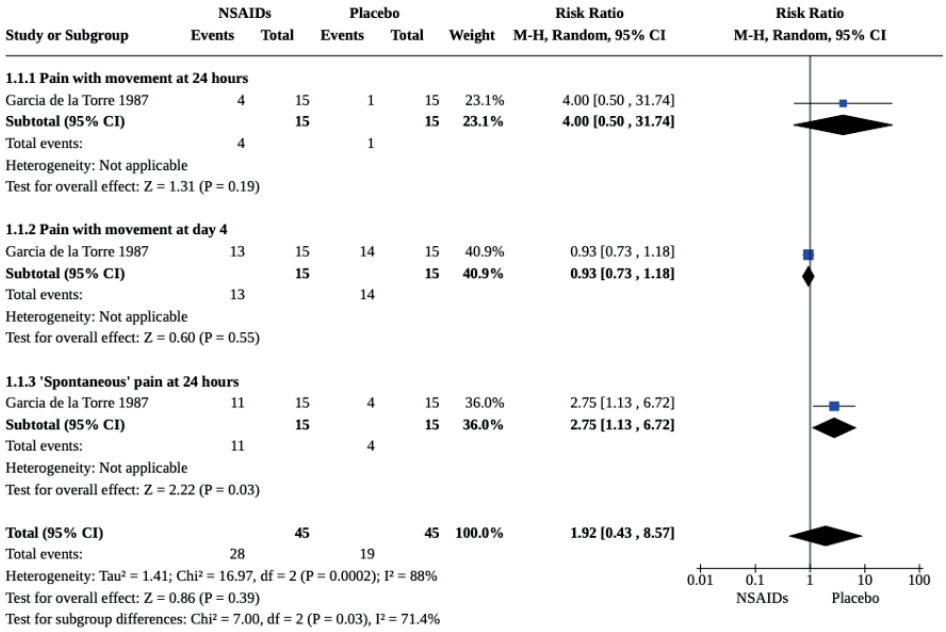
Moderate-certainty evidence based on 6 trials showed that selective COX-2 inhibitors and non-selective NSAIDs were equally beneficial, although COXIBs were associated with significantly fewer total and gastrointestinal adverse events. We downgraded the evidence due to unclear risk of selection and detection bias. Moderate-certainty evidence based on 5 trials showed that systemic glucocorticoids and NSAIDs are equally beneficial with regards to pain; there could be a beneficial effect of glucocorticoids with regards to reduction of swelling, but this is based on a single trial at high risk of bias for blinding of participants and personnel. Glucocorticoids seem to be associated with fewer adverse events. Researchers found no differences with regards to withdrawal due to adverse events. We found insufficient data regarding interleukin (IL)-1 inhibitors for treatment of acute gout (1 trial at unclear risk of bias). A single trial at high risk of bias suggests that NSAIDs and colchicine are equally beneficial, but that there is more harm with colchicine with regards to gastrointestinal side effects, especially diarrhoea.

Implications for research

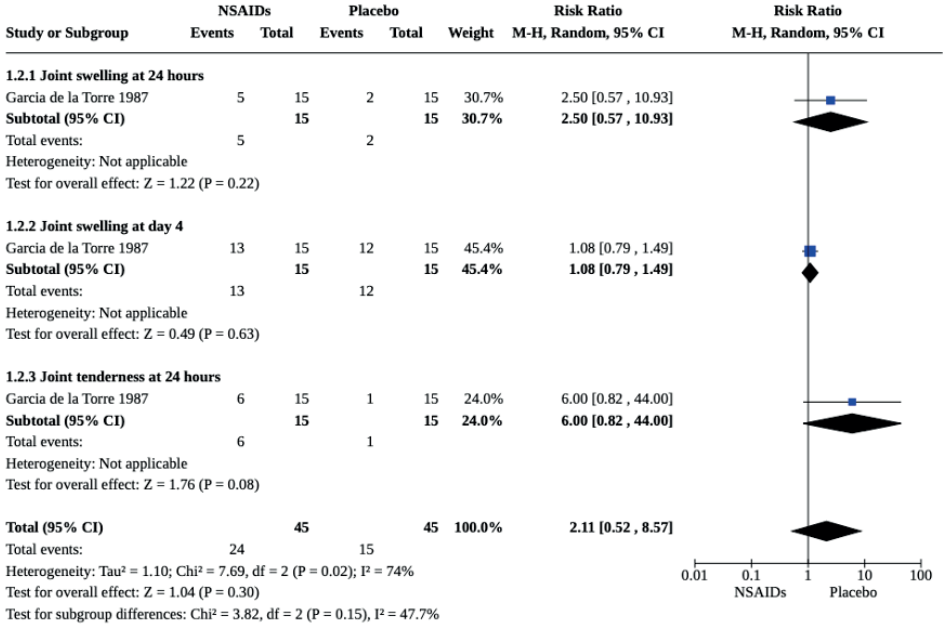
Further data concerning the comparative benefits and harms of NSAIDs compared with colchicine and intra-articular glucocorticoids are needed. As both COXIBs and glucocorticoids seem to be better tolerated than NSAIDs for the same efficacy, trials directly comparing COXIBs to glucocorticoids and glucocorticoids to colchicine are needed. Xu 2016 compared COXIBs and glucocorticoids and did not find any difference in benefit nor harm between these two dug classes. However, as this trial was at high risk of bias for blinding of personnel and participants, this finding will need to be confirmed in further trials. Also, the observation made by Zhang 2014 that glucocorticoids might act more quickly than NSAIDs when given intramuscularly

needs to be confirmed, as this was an open-label trial and thus was at high risk of bias. The single observation that an IL-1 inhibitor (rilonacept) was not superior to NSAIDs (indomethacin) needs confirmation in other trials, although the cost of these new drugs might preclude their use in routine care. A recent systematic literature review pointed out that canakinumab may be more efficacious than NSAIDs for pain reduction (Zeng 2021), but this needs to be confirmed in larger randomised controlled trials. Another important implication for research should be analysis of the cost-effectiveness of different drugs. The trial comparing NSAIDs to colchicine is the only trial that assessed cost-effectiveness (Roddy 2020). Naproxen seemed to be slightly less costly and more effective than colchicine: at a willingness-to-pay of £20,000 per quality-adjusted life-year (QALY), naproxen had an 80% chance of being cost-effective compared with colchicine.

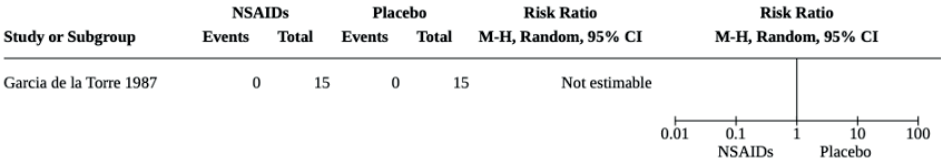
Trial reporting should include methods of randomisation and treatment allocation concealment; blinding of study participants, study personnel, and outcome assessment; follow-up numbers for all participants who entered the trial; and complete reporting of outcomes. Sample sizes should be reported and should have adequate power to answer the research question; ideally trials should assess both benefits and risks of an intervention. To enable comparison and pooling of the results of randomised controlled trials, we suggest that future trials report means with standard deviations for continuous measures, and numbers of events and total numbers analysed for dichotomous measures, and they should assess outcomes recommended by OMERACT (Outcome Measures in Rheumatology Clinical Trials) for studies of acute gout, including pain, joint swelling, joint tenderness, participants' global assessment, and activity limitations (Schumacher 2009). However, how these outcomes have to be assessed exactly still needs to be determined by OMERACT. Therefore, we suggest use of dichotomous measures to report pain as recommended by the International Measurement and Pain Assessment in Clinical Trials (IMMPACT) (the proportions of participants improved by 30% or greater and by 50% or greater) (Dworkin 2008).



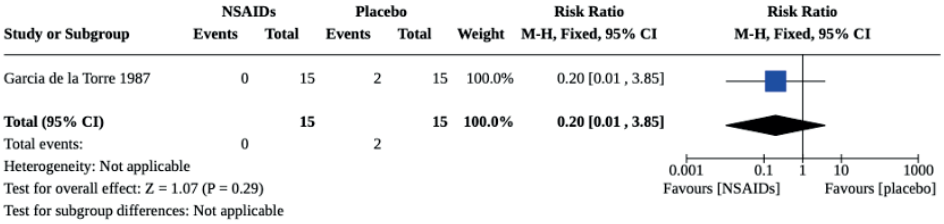
Analysis 1.1. Comparison 1: NSAIDs versus placebo, Outcome 1: Pain ≥ 50% improvement in pain



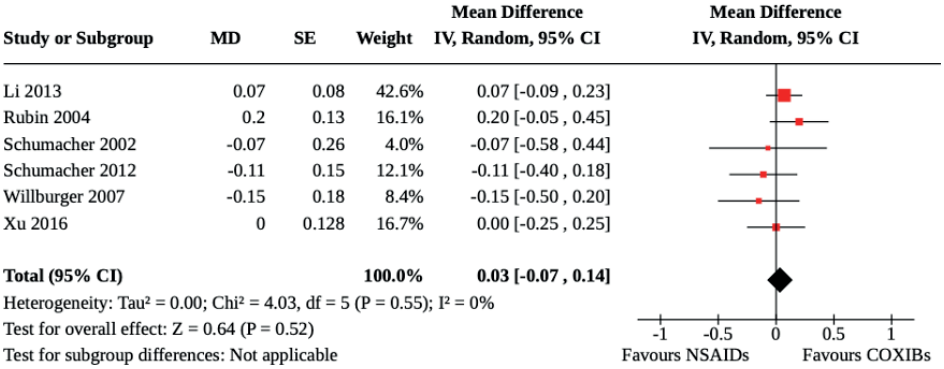
Analysis 1.2. Comparison 1: NSAIDs versus placebo, Outcome 2: Inflammation ≥ 50% improvement in joint swelling or tenderness



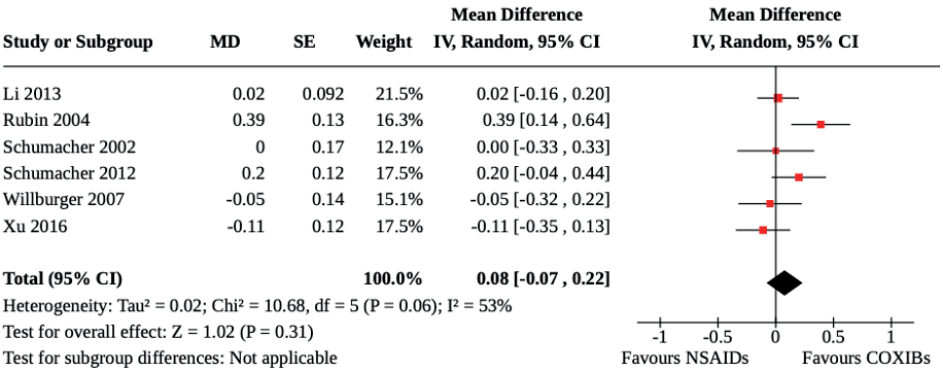
Analysis 1.3 Comparison 1: NSAIDs versus placebo, Outcome 3: Withdrawals due to adverse events



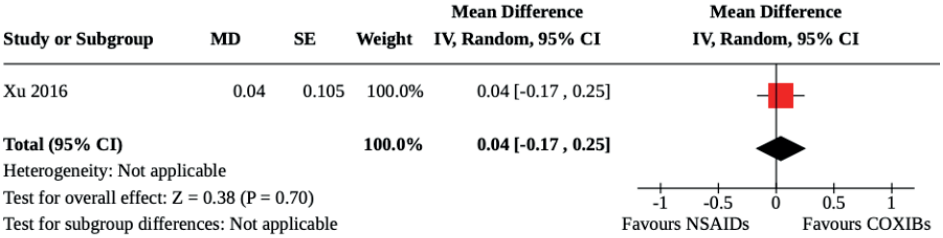
Analysis 1.4 Comparison 1: NSAIDs versus placebo, Outcome 4: Total adverse events



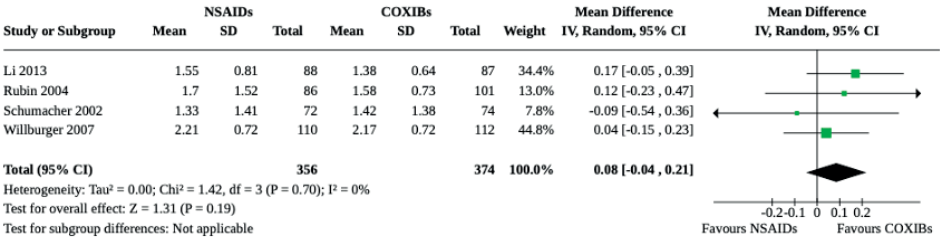
Analysis 2.1 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 1: Pain: mean change difference from baseline on a 5-point Likert scale



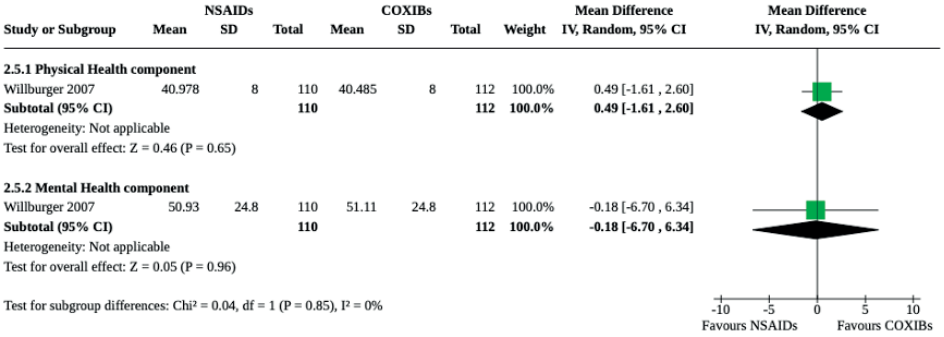
Analysis 2.2 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 2: Swelling: mean change difference in swelling from baseline



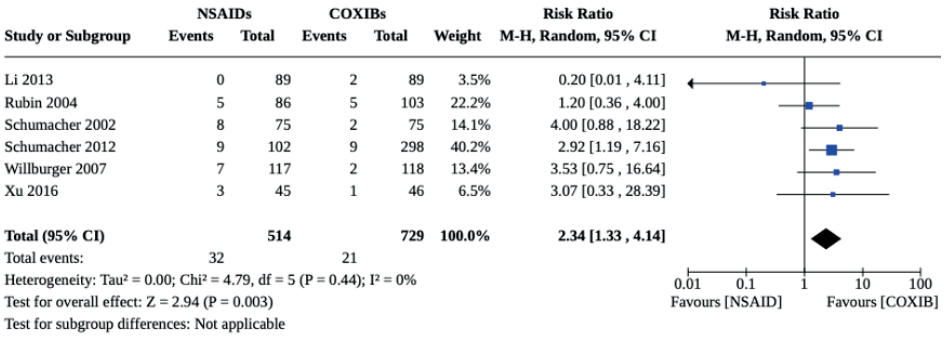
Analysis 2.3 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 1: Function: mean change difference in pain with activity from baseline



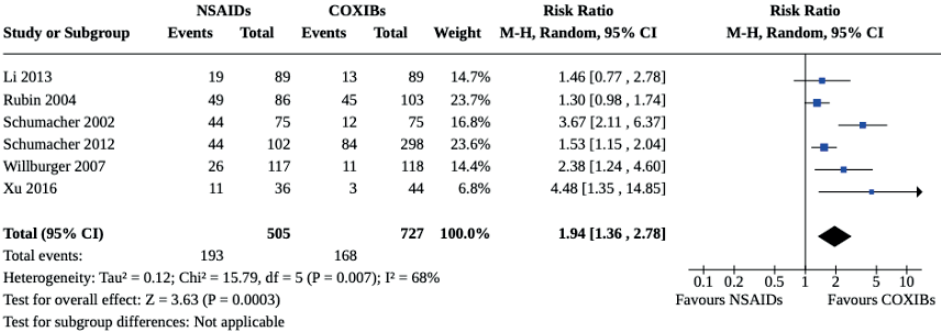
Analysis 2.4 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 4: Participant's global assessment of treatment success



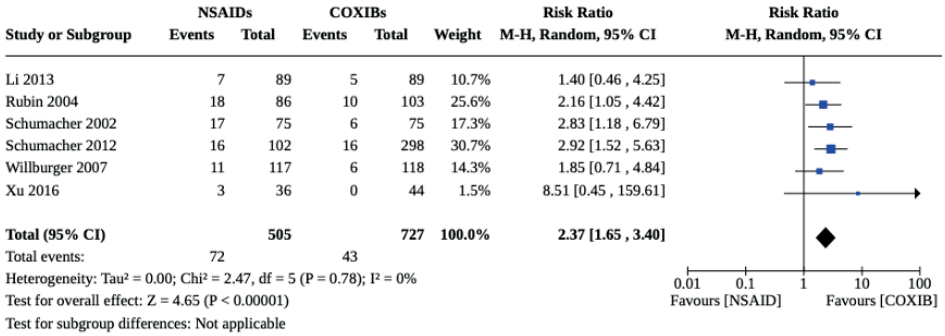
Analysis 2.5 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 5: Health-related quality of life measured by 36-item Short Form



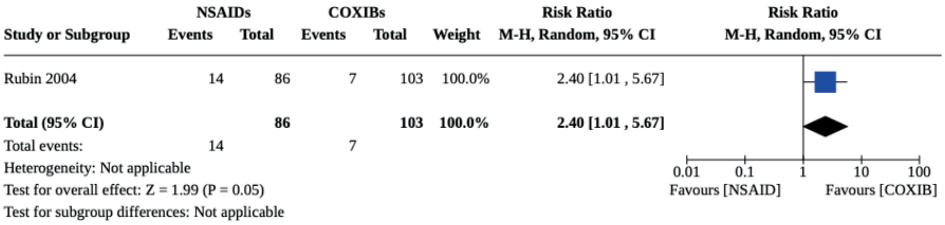
Analysis 2.6 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 6: Withdrawals due to adverse events



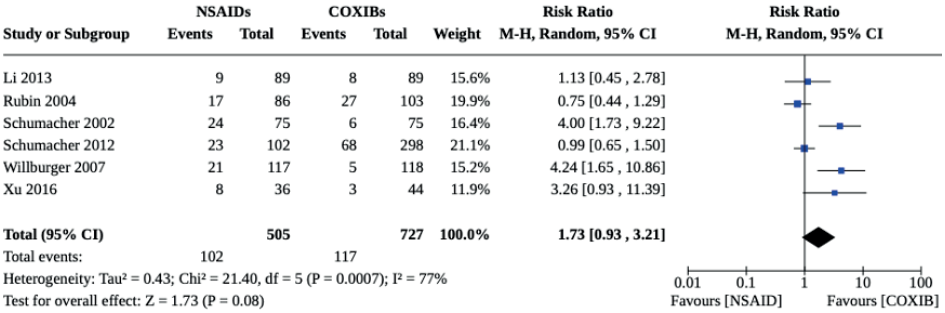
Analysis 2.7 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 7: Total adverse events



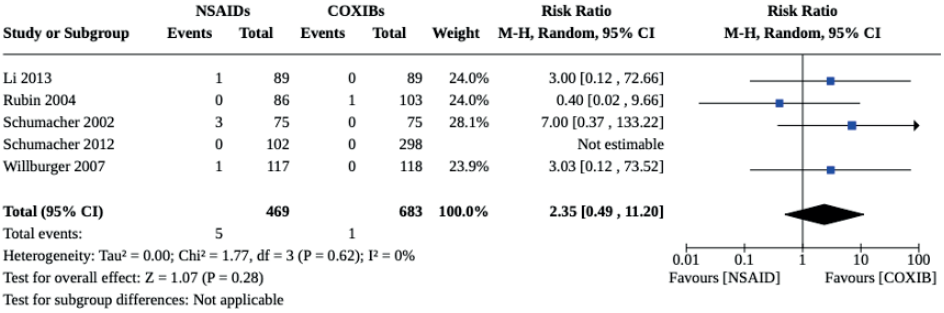
Analysis 2.8 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 8: Gastrointestinal adverse events



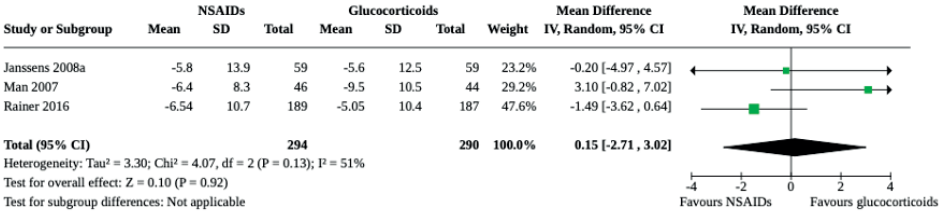
Analysis 2.9 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 9: Cardiovascular adverse events



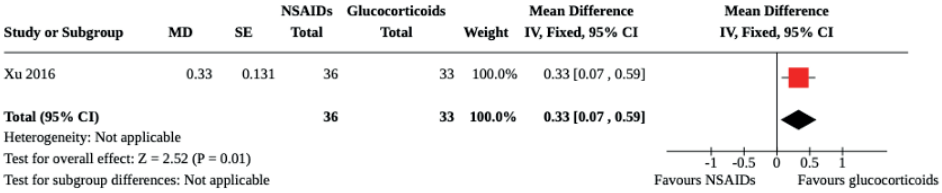
Analysis 2.10 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 10: Other adverse events



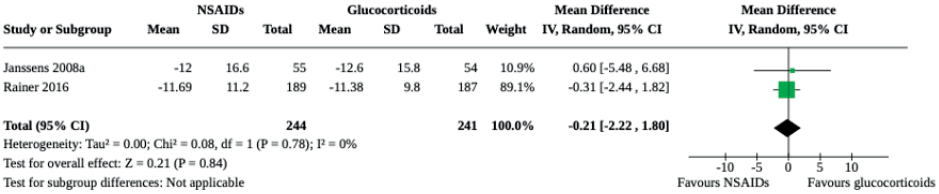
Analysis 2.11 Comparison 2: NSAIDs versus cyclo-oxygenase (COX)-2 inhibitors (COXIBs), Outcome 11: Serious adverse events



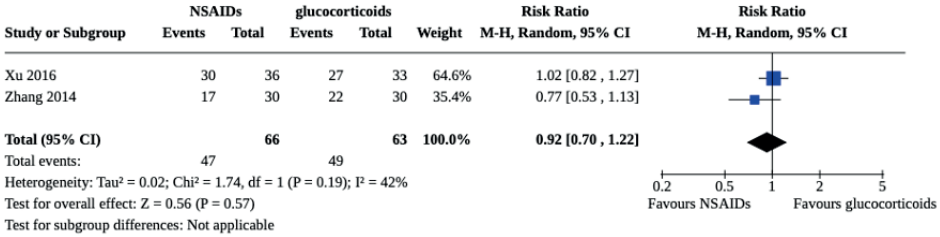
Analysis 3.1 Comparison 3: NSAIDs versus glucocorticoids, Outcome 1: Pain: mean reduction over visual analogue scale per hour during first 6 hours



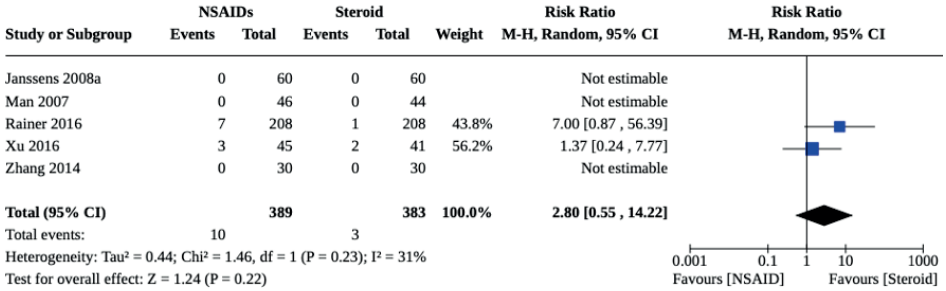
Analysis 3.2 Comparison 3: NSAIDs versus glucocorticoids, Outcome 2: Inflammation: swelling mean difference in change from day 0 to day 14



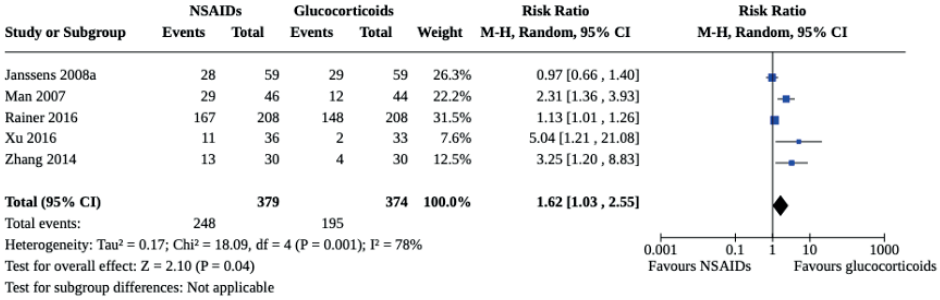
Analysis 3.3 Comparison 3: NSAIDs versus glucocorticoids, Outcome 3: Walking disability during first 6 hours



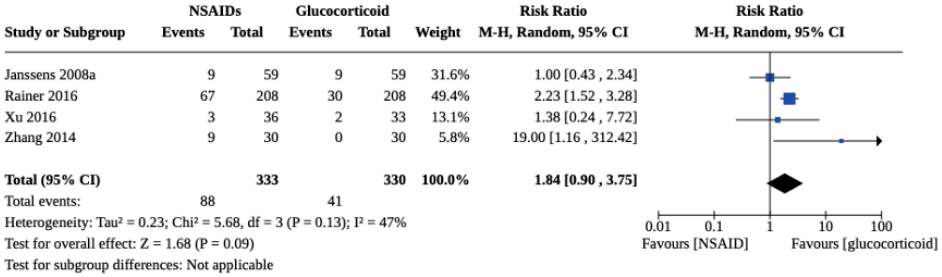
Analysis 3.4 Comparison 3: NSAIDs versus glucocorticoids, Outcome 4: Patient's Global Assessment of response to treatment: good to very good response at day 3 to 4



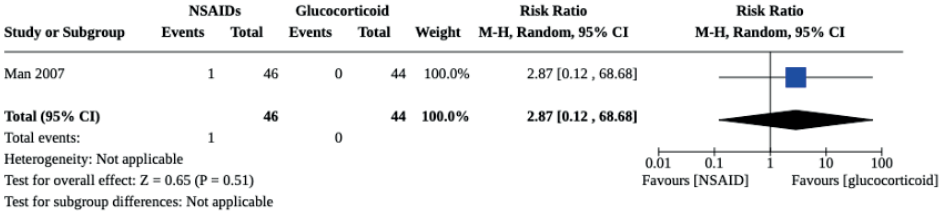
Analysis 3.5 Comparison 3: NSAIDs versus glucocorticoids, Outcome 5: Withdrawals due to adverse events



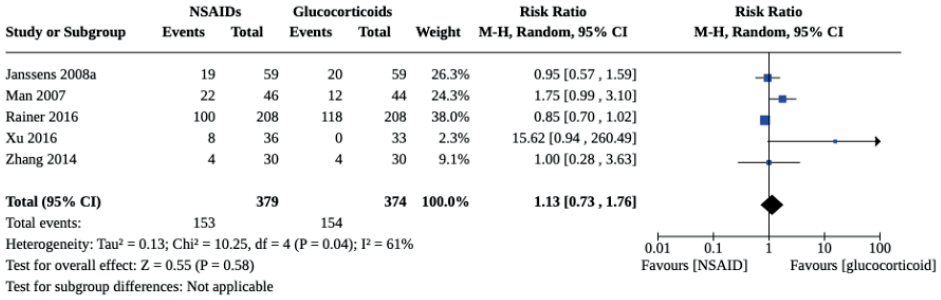
Analysis 3.6 Comparison 3: NSAIDs versus glucocorticoids, Outcome 6: Total adverse events



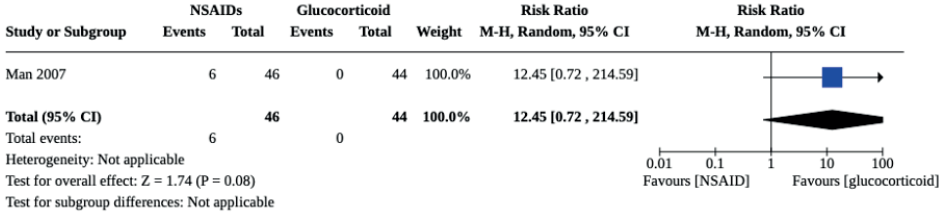
Analysis 3.7 Comparison 3: NSAIDs versus glucocorticoids, Outcome 7: Gastrointestinal adverse events



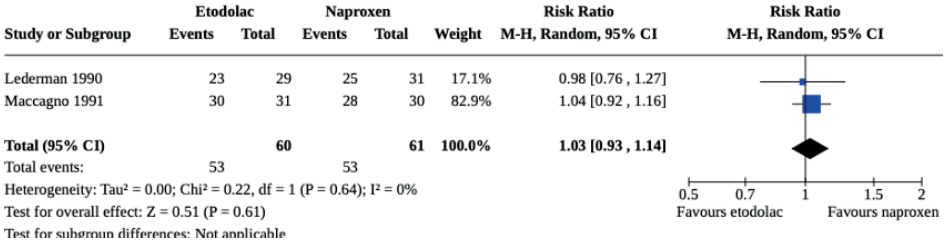
Analysis 3.8 Comparison 3: NSAIDs versus glucocorticoids, Outcome 8: Cardiovascular adverse events



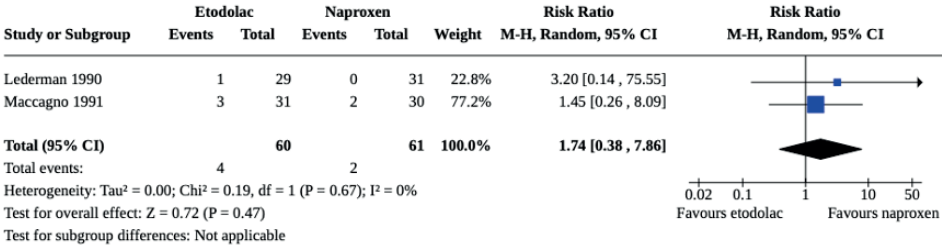
Analysis 3.9 Comparison 3: NSAIDs versus glucocorticoids, Outcome 9: Other adverse events



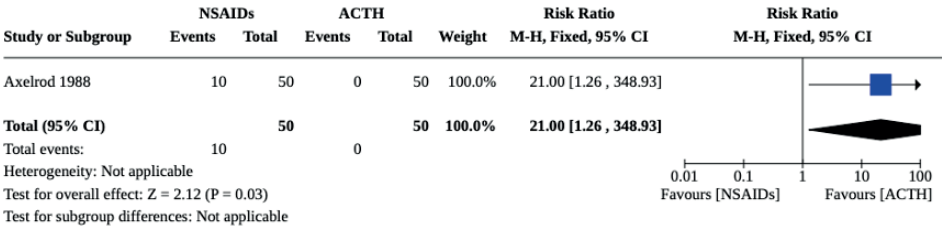
Analysis 3.10 Comparison 3: NSAIDs versus glucocorticoids, Outcome 10: Serious adverse events



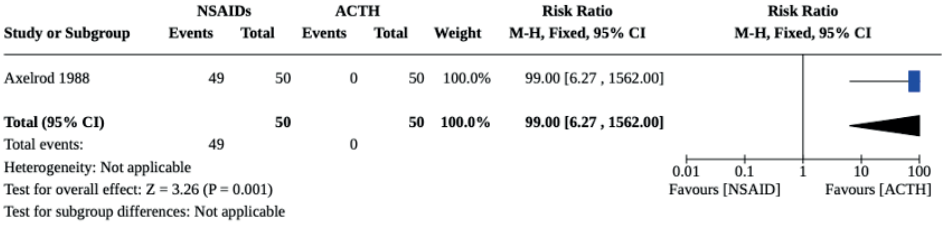
Analysis 4.1 Comparison 4: Etodolac versus naproxen, Outcome 1: Participant's global assessment at end of therapy: markedly improved



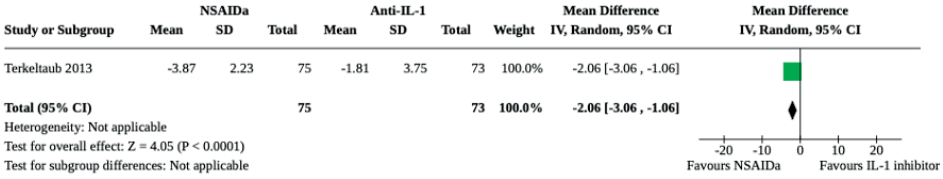
Analysis 4.2 Comparison 4: Etodolac versus naproxen, Outcome 2: Total adverse events



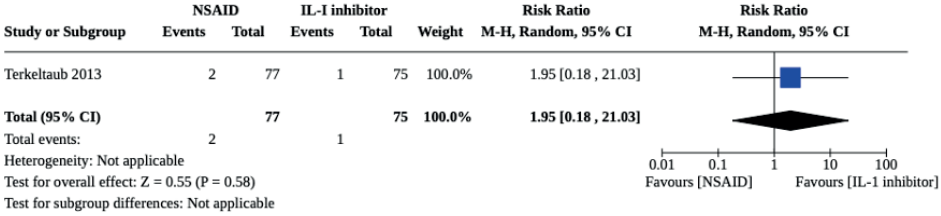
Analysis 5.1 Comparison 5: NSAIDs versus adrenocorticotropin hormone (ACTH), Outcome 1: Withdrawals due to adverse events



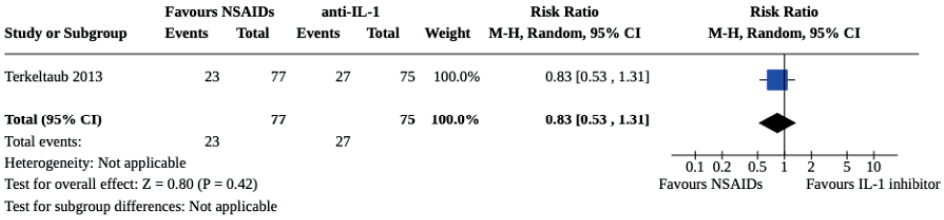
Analysis 5.2 Comparison 5: NSAIDs versus adrenocorticotropin hormone (ACTH), Outcome 2: Total adverse events



Analysis 6.1 Comparison 6: NSAIDs versus interleukin (IL)-1 inhibitor, Outcome 1: Pain: mean pain reduction on numerical rating scale

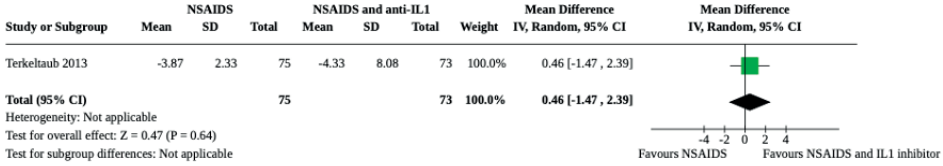


Analysis 6.2 Comparison 6: NSAIDs versus interleukin (IL)-1 inhibitor, Outcome 2: Withdrawals due to adverse events



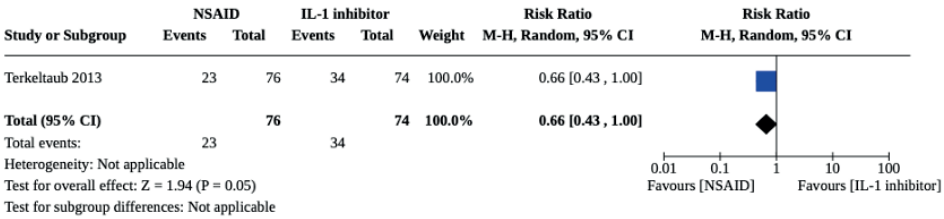
Analysis 6.3 Comparison 6: NSAIDs versus interleukin (IL)-1 inhibitor, Outcome 3: Total adverse events

Analysis 6.5 Comparison 6: NSAIDs versus interleukin(IL)-1 inhibitor, Outcome 5: Serious adverse events

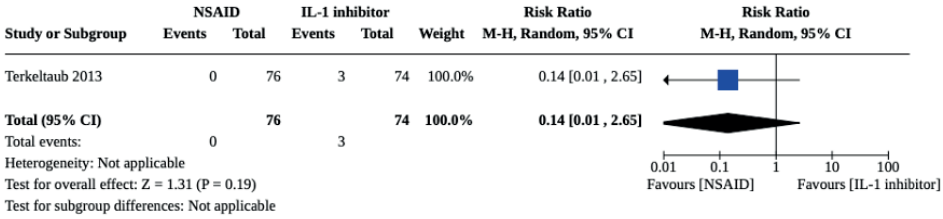


Analysis 7.1 Comparison 7: NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs, outcome 1: Pain (change 24 to 72 hours numerical rating scale)

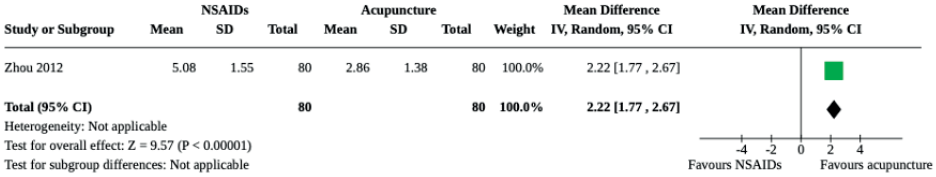
Analysis 7.2 Comparison 7: NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs, outcome 2: Withdrawals due to adverse events



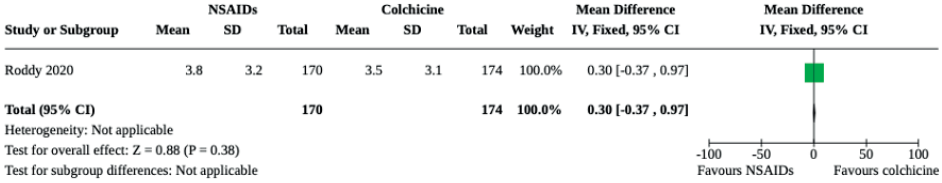
Analysis 7.3 Comparison 7: NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs, outcome 3: Total adverse events



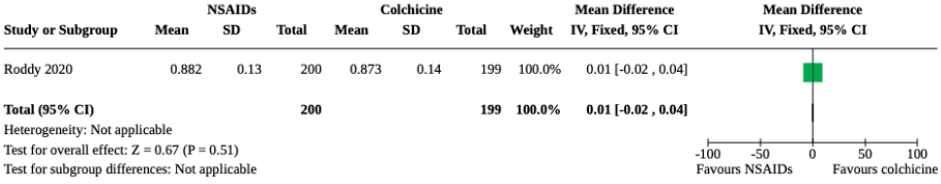
Analysis 7.4 Comparison 7: NSAIDs versus interleukin (IL)-1 inhibitor plus NSAIDs, outcome 4: Serious adverse events



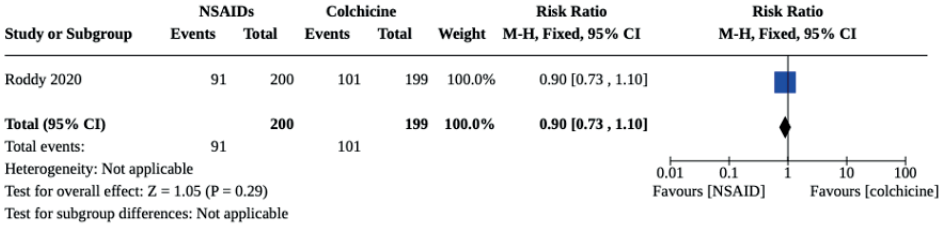
Analysis 8.1 Comparison 8: NSAIDs versus acupuncture combined with infrared irradiation, Outcome 1: Pain: mean score on visual analogue scale after treatment



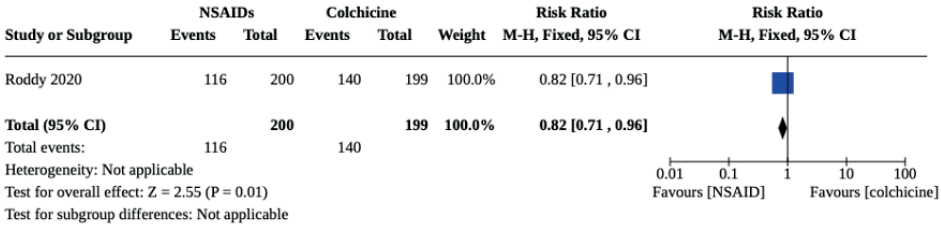
Analysis 9.1 Comparison 8: NSAIDs versus colchicine, Outcome 1: Pain: mean change over days 1 to 7



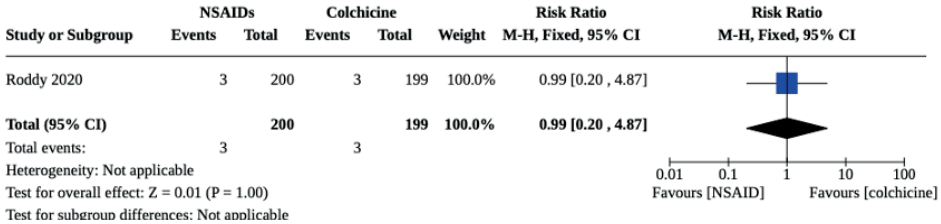
Analysis 9.2 Comparison 8: NSAIDs versus colchicine, Outcome 2: Quality of life: EQ-5D at day 7



Analysis 9.3 Comparison 8: NSAIDs versus colchicine, Outcome 3: Total adverse events



Analysis 9.4 Comparison 8: NSAIDs versus colchicine, Outcome 4: Gastrointestinal adverse events



Analysis 9.5 Comparison 8: NSAIDs versus colchicine, Outcome 5: Other adverse events

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3

A comparative study of real-life management strategies in gout: data from two protocolized gout clinics

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ABSTRACT

Objective

To compare outcomes of two gout clinics that implemented a different treatment strategy. One clinic adopted a strict serum uric acid (sUA) (≤0.30 mmol/L) target (UA-) strategy - with early addition of uricosuric to allopurinol - and the other a patient-centred (PC-) strategy emphasizing shared decision based on sUA and patient satisfaction with gout control.

Methods

Patients newly diagnosed with gout and a follow-up of 9-15 months were included. Co-primary outcomes were proportion of patients reaching a sUA ≤0.36 mmol/L, and free of flares. Secondary outcomes were proportion of patients requiring treatment intensification, and experiencing adverse events. Independent t-tests or chi-square were used to test differences in outcomes, and logistic regressions to adjust the effect of centre on outcomes for confounders.

Results

In total, 126 and 86 patients had a follow-up of 11.3±1.8 vs 11.1±1.9 months. In the UA-strategy 105/126 (83%) compared to 63/86 (74%) patients in the PC-strategy (p=0.10), reached the threshold of ≤0.36 mmol/L; and 58/126 (46%) vs 31/86 (36%) were free of flares (p=0.15). In the UA-strategy 76/126 (60%) patients were on allopurinol monotherapy compared to 63/86 (73%) in the PC-strategy (p=0.05), yet the number of adverse events was not different (n=25 (20%) vs n=20 (23%), p=0.55). Adjusting for confounders did not substantially change these associations.

Conclusion

A strict UA-strategy resulted in a non-significant higher proportion of patients reaching a sUA ≤0.36 mmol/L and being free of flares. This was accomplished with significantly more therapy intensification. The small sample-size plays a role in significance of results.

INTRODUCTION

Gout is the most common type of inflammatory arthritis worldwide, with an estimated prevalence ranging from 0.9% in Europe to 3.9% in the United States (1-3). The disability-adjusted life years (DALYs), quantifying the burden of disease due to mortality and morbidity, increased by 26% between 2005 and 2015 (4). Hyperuricemia is the main risk factor for gout. Inflammation of the joints and surrounding tissues results from the activation of the inflammasome triggered by deposition of monosodium urate (MSU) crystals (5, 6). In addition to articular manifestations, gout has been associated with a number of comorbidities, such as cardiovascular diseases and chronic kidney disease (7, 8).

Fortunately, gout is a well-treatable disease. Lifestyle advice (e.g., promoting weight loss) can result in a decrease of serum uric acid (sUA) of about 0.10 mmol/L (9). When gout flares occur frequently or when tophi are present, urate-lowering therapy (ULT) should be started (10, 11). ULT has been shown to decrease sUA, lower the risk of future flares, reduce tophaceous load, and repair structural damage of the joints (12, 13). Recent European League Against Rheumatism (EULAR) guidelines even recommend that clinicians consider ULT after a first gout flare (10). However, it remains unclear which target should be recommended in the treatment of gout: a 'Treat-to-Uric-Acid' target (ACR/EULAR), or a 'Treat-to-Avoid-Symptoms' (T2AS) target (ACP guidelines) (10, 11). Also, the optimal sUA threshold in a 'Treat-to-Uric-Acid' target remains discussed. In the EULAR recommendations the sUA-target hinges upon urate levels below the threshold of ≤0.36 mmol/L, the level of saturation of sUA and of crystal formation (14). When tophi are present, or in case of frequent flares, a sUA target ≤0.30 mmol/L is recommended, to accelerate the dissolution of tophi (10). The British Society for Rheumatology (BSR) even recommends a sUA target ≤0.30 mmol/L for all gout patients (15). Finally, while several types of drugs are available to reduce sUA, comprising xanthine oxidase inhibitors (XOI), uricosuric agents, or uricases, there is as yet no consensus on whether or when to include a combination of two Modes of Action (2MoA), i.e. a XOI plus an add-on of a uricosuric in the treatment (16).

Despite multiple recommendations and the wide availability of ULT drugs, the treatment of gout patients in clinical practice remains suboptimal (3, 17, 18). Suboptimal treatment has been attributed to an underestimation of the burden of gout by professionals and patients resulting in delays and poor adherence to treatment (18). Additionally, the lack of evidence about the optimal target and most effective drug strategy - creating distrust in guidelines - and limited attention for compliance to treatment have been identified by healthcare professionals as other barriers to optimal treatment (11, 19, 20).

To improve the quality of care for patients with gout in clinical practice, two hospitals started a gout clinic based on applying a protocolized treatment approach. Interestingly, each clinic

has adopted a different strategy. One clinic adopted a strict sUA (≤0.30 mmol/L) target (UA-) strategy – with early addition of uricosurics to XOI if the target was not reached and fractional excretion of uric acid (FEUa) was <4% (2MoA) – and the other clinic a patient-centred (PC-) strategy emphasizing patient education and shared decision about ULT based on sUA and patient satisfaction with gout control. In the absence of a head-to-head comparison of gout treatment strategies, we aimed to compare the proportions of patients in both clinical practices reaching a sUA ≤0.36 mmol/L and ≤0.30 mmol/L, being free of flares, requiring combination therapy and experiencing adverse events. The use of real-life data can lead to a better understanding of the gap between clinical research and daily practice of gout treatment (21). We expected a priori that a strict UA-strategy results in a lower sUA level, a comparable proportion of patients free of flares but more patients requiring combination therapy and having adverse events compared to patients treated according to a PC-strategy.

PATIENTS AND METHODS

Clinical care protocols in each centre

One regional non-university hospital and one university centre with regional function implemented a gout clinic applying a protocolized treatment strategy (figure 1). Approval was given by the ethical committees of both centres (METC 16-4-032.1) and patients provided written informed consent.

UA-strategy

In the non-university centre, a UA-strategy aimed at strictly targeting sUA to ≤0.30 mmol/L, independently of the presence of tophi, and includes combined 2MoA therapy early in the treatment protocol depending on FEUa. ULT is started with 100-150mg/day allopurinol for the first week, up-titrated to 300mg/day if estimated glomerular filtration rate (eGFR) ≥50 ml/min, otherwise 200mg/day. If the sUA target is not reached at 2-3 months follow-up, the FEUa is used to determine cases (FEUa<4%) where the sUA target can better be reached by adding a uricosuric or cases where it is better to up-titrate allopurinol (till 600mg/day max. depending on eGFR) or switch to febuxostat. The FEUa represents the percentage of sUA filtered in the kidney and distinguishes under-excretors from overproducers (normal range 6-8%) (22). Colchicine or prednisone are used as a first-line gout flare prophylaxis. Dietary advice is provided during the consultation session with an information letter, containing dietary guidance and advice about weight reduction (if obese). After each treatment adjustment, patients are re-evaluated after three months. Once the sUA target is attained, patients received one additional follow-up after 6 months. If they maintain a sUA ≤0.30 mmol/L, patients are referred back to their general practitioner (GP).

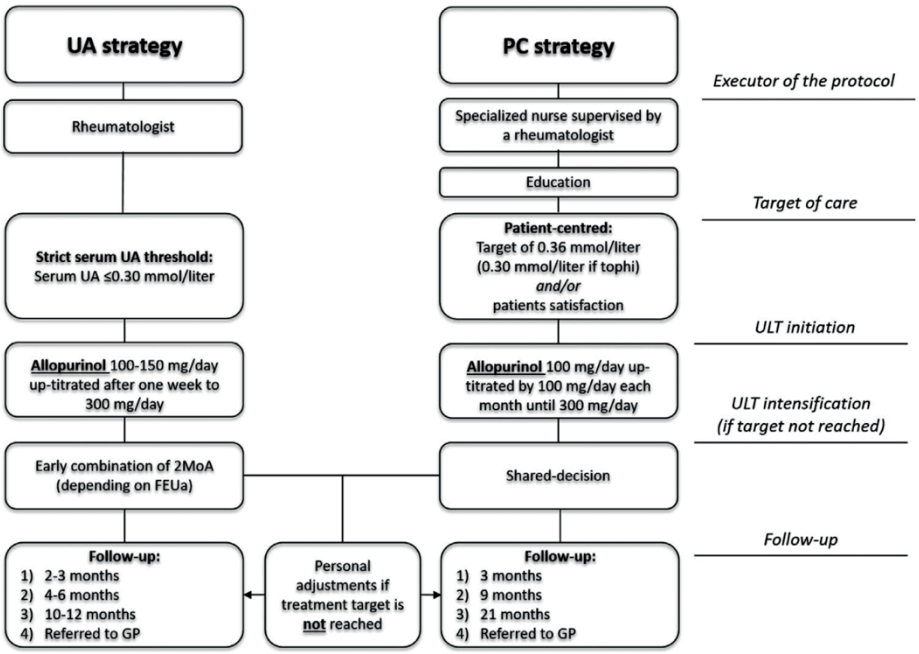

Figure 1: Flow-chart of the two treatment strategies for newly referred gout patients in this study. UA-strategy= uric acid target strategy, PC-strategy= patient-centred strategy, sUA= serum uric acid, ULT= urate-lowering therapy, 2MoA= two modes of action, FEUa= fractional excretion of uric acid, GP= general practitioner.
[a] = regional non-university outpatient clinic, [b] = university outpatient clinic (with regional function)

PC-strategy

In the university centre, a PC-strategy aimed to align the physician's point of treatment goals towards a sUA target of ≤0.36 mmol/L (or ≤0.30 mmol/L when tophaceous), with patients' satisfaction about the number and severity of gout flares. Patients are seen by a specialized nurse supervised by a rheumatologist experienced in gout. The strategy focuses on patient education in terms of the pathophysiology of gout, lifestyle, and importance of attaining the specified sUA level. The ULT starts with 100mg/day allopurinol which is up-titrated by 100mg/day every month until 300mg/day is reached. If the sUA concentration is not been reached a level ≤0.36 mmol/L and/or if the patient is unsatisfied with the number and severity of gout flares after 3 months, allopurinol is further up-titrated or benzbromarone is added if eGFR ≥30 ml/min in the context of a shared decision process. Colchicine is used as first-line gout flare prophylaxis. After each treatment adjustment patients are re-evaluated at three months. Once the sUA target is attained, patients are seen after 6 and 12 months. If the treatment target for physicians and patients remains maintained, patients are referred back to their GP.

Study sample

The sample for the current study comprised all newly referred gout patients attending the outpatient rheumatology clinic at one of the two hospitals between January 2015 and October 2017. Patients who had at least one outpatient follow-up appointment after 9-15 months were included in the current analyses. All patients were diagnosed by a rheumatologist with expertise in gout. Patients could be referred by the primary care physician, or another rheumatologist who had diagnosed a new case of gout at the outpatient clinic or during inpatient consultations.

Data collection

The following data were collected from the (standardized) medical records at baseline and follow-up: patient characteristics (i.e. age, sex, weight, and length), the presence of tophi, medication use (diuretics, prophylaxis of gout and ULT drugs), comorbidities (baseline only), and uric acid and creatinine concentration in serum and urine. Additional information on presence of gout flares, adverse events, and outpatient visits were collected between baseline and follow-up. Obesity was defined as body mass index (BMI) ≥30 kg/m^2. Comorbidities were defined as present if formally recorded in the past history of the hospital record or the current use of comorbidity specific drugs treatment and included: hypertension, dyslipidaemia, type 2 diabetes mellitus (DM2), peripheral arterial disease, cerebral vascular accident, myocardial infarction, heart failure, nephrolithiasis, obstructive sleep apnoea syndrome, coronary artery disease, cancer, transient ischemic attack, renal transplantation, heart arrhythmia, and hepatic steatosis. Renal function was calculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation to eGFR. Renal failure was defined as eGFR ≤30 ml/min. To facilitate phenotyping of gout based on comorbidities, patients were grouped following the previously subdivided clusters of Richette et al. into five distinctive phenotype groups: (1) only hypertension, (2) obesity, (3) DM2, (4) dyslipidaemia, and (5) with renal and/or cardiovascular diseases (23). Group two to five could also contain patients with hypertension.

Outcomes

Co-primary outcomes were the proportion of patients reaching a sUA ≤0.36 mmol/L, and the proportion of patients free of gout flares. Secondary outcomes were the mean sUA level, mean number of outpatient visits, and the proportion of patients reaching a sUA ≤0.30 mmol/L, requiring treatment intensification beyond allopurinol (and especially 2MoA), and experiencing adverse events of ULT drugs.

Statistical analysis

Characteristics of patients in both centres at baseline and outcomes at follow-up were compared using independent t-test for continuous variables and $\chi 2$ test for categorical variables. Multivariable logistic and linear (when sUA was the outcome) regressions were performed to quantify the magnitude of the effect of the treatment strategy on each of the outcomes after

adjusting for baseline confounders. Potential covariates were age, sex, eGFR, use of diuretics, presence of tophi, baseline sUA, BMI, and gout phenotypes. The outcome 'free of flares' was additionally adjusted for prophylaxis. Covariates were included if statistically significant in the univariate analyses ($p<0.05$) or those deemed important from a clinical perspective. In an additional series of models, the role of the interaction-term treatment strategy*gout phenotypes in relation to each of the outcomes was tested. Statistical analyses were performed using IBM SPSS, version 25.0 (IBM Corp).

RESULTS

Patients

In total, 255 and 142 newly referred gout patients attended the UA and PC-strategy in the period of interest, respectively. Of these, 77/255 (30.2%) and 24/142 (16.9%) in the UA and PC strategy, respectively, had not yet a control-visit in the pre-specified period and were therefore not eligible for the current study sample. Furthermore, 29/178 (16.3%) vs 13/118 (11.0%) patients were lost to follow-up and 6/178 (3.4%) vs 11/118 (9.3%) patients died. Finally, 126 UA-strategy and 86 PC-strategy patients had a follow-up assessment of 11.3±1.8 vs 11.1±1.9 months after inclusion (p=0.527) and were considered for the current analyses (figure 2).

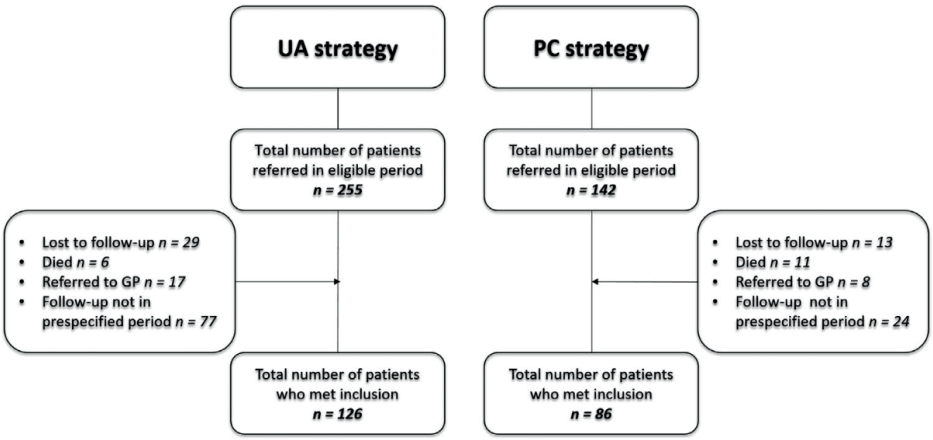

Figure 2: Flow-chart of patients eligible and included in the centres providing a UA- or PC strategy. UA-strategy= uric acid target strategy, PC-strategy= patient-centred strategy, GP= general practitioner.

Baseline characteristics are shown in table 1. The presence of tophi (n=27 (21.4%) vs n=52 (60.5%), p<0.001), the use of diuretics (n=39 (31.0%) vs n=41 (47.7%), p=0.014), the presence of hypertension (n=70 (55.6%) vs n=70 (81.4%), p<0.001), and dyslipidaemia (n=29 (23.0%) vs n=43 (50.0%), p<0.001) were significantly lower in the UA-strategy vs the PC-strategy.

Notwithstanding, the patients were not significantly differently distributed (p=0.157) across the phenotypes of the classification clusters of Richette et al. Yet, 28/126 (26.4%) patients in the UA-strategy had isolated gout without comorbidities compared to 16/86 (18.6%) patients in the PC-strategy. In both strategies, the phenotype with renal and/or cardiovascular diseases represented the largest number of patients.

Table 1: Baseline characteristics of gout-patients receiving the PC- or UA-strategy.

	UA-strategy (n=126)	**PC- strategy (n=86)**	**p-value**
Females; *n (%)*	17 (13.5)	19 (22.1)	0.101
Age; *mean (SD)*	64.8 (11.9)	64.0 (13.5)	0.668
MSU crystal confirmed; *n (%)*	120 (95.2)	18 (20.9)	<0.001
Tophaceous; *n (%)*	27 (21.4)	52 (60.5)	<0.001
Diuretics use; *n (%)*	39 (31.0)	41 (47.7)	0.014
sUA at baseline; *mean (SD)*	0.51 (0.14)	0.48 (0.15)	0.194
BMI (kg/m^2); *mean (SD)*	29.0 (5.0)[a]	29.7 (4.8)	0.378
Obesity; *n (%)*	40 (36.7)	37 (43.0)	0.370
Comorbidities; *n (%)*			
Hypertension	70 (55.6)	70 (81.4)	<0.001
Heart Failure	16 (12.7)	5 (5.8)	0.099
Heart arrhythmia	29 (23.0)	19 (22.1)	0.875
CV events	51 (40.5)	37 (43.0)	0.712
Dyslipidaemia	29 (23.0)	43 (50.0)	<0.001
DM2	40 (31.7)	24 (27.9)	0.550
OSAS	14 (11.1)	10 (11.6)	0.907
Cancer	8 (6.3)	6 (7.0)	0.857
Hepatic steatosis	4 (3.2)	8 (9.3)	0.058
Renal transplantation	1 (0.8)	3 (3.5)	0.157
Nephrolithiasis	13 (10.3)	13 (15.1)	0.296
CKD; *mean (SD)*	58.4 (21.8)[b]	56.3 (22.5)	0.497
Phenotype of gout; *n (%)*	*n=106*	*n=86*	0.157
Only hypertension	28 (26.4)	16 (18.6)	
Obesity	12 (11.3)	20 (23.3)	
DM2	16 (15.1)	9 (10.5)	
Dyslipidaemia	8 (7.5)	9 (10.5)	
Renal and CV diseases	42 (39.6)	32 (37.2)	

PC-strategy= patient-centred strategy, UA-strategy= uric acid target strategy, MSU= monosodium urate, BMI= Body Mass Index, sUA= serum uric acid, DM2= Diabetes Mellitus type 2, CV= cardiovascular, CKD= Chronic Kidney Disease, OSAS= Obstructive Sleep Apnoea Syndrome. CV events includes peripheral arterial disease, cerebral vascular accident, myocardial infarction, coronary artery disease, and transient ischemic attack. [a] n=109 (17 missing data), [b] n=122 (4 missing data).

Primary outcomes

sUA ≤0.36 mmol/L

In the UA-strategy 105/126 (83.3%) patients compared to 63/86 (74.1%) patients in the PC-strategy, respectively, reached the threshold of ≤0.36 mmol/L (p=0.103). Univariate logistic regression for a sUA ≤0.36 mmol/L showed that the treatment strategy (OR 1.75; 95% CI 0.89-3.43) was not significantly related to the achievement of the treatment target. This remained unchanged (OR 1.65; 95% CI 0.77-3.56) after adjustment for confounders (table 2). Disease phenotype had no significant influence as confounder on the relationship of treatment strategies for the achievement of the treatment target (OR 1.63; 95% CI 0.80-3.31) and did not modify the effect of centre on outcome.

Table 2: Uni- and multivariable logistic and linear (sUA) regression analyses for all outcomes*

	UA-strategy (n= 126)	PC-strategy (n=86)	Univariate (n=212)		Multivariable (n=207)	
	N (%)	N (%)	Odds ratio	95% CI	Odds ratio	95% CI
Co-primary						
sUA ≤ 0.36 mmol/L	105 (83.3)	63 (74.1)	1.75	0.89-3.43	1.65	0.77-3.56
Free of flares	58 (46.0)	31 (36.0)	1.51	0.86-2.66	1.61	0.83-3.10
Secondary						
sUA ≤ 0.30 mmol/L	83 (65.9)	44 (51.8)	1.80	1.03-3.16	1.97	1.00-3.85
Adverse events	25 (19.8)	20 (23.3)	0.82	0.42-1.59	1.04	0.49-2.21
Allopurinol monotherapy	76 (60.3)	63 (73.3)	0.56	0.31-1.01	0.40	0.20-0.82
	Mean (SD)	**Mean (SD)**	**B**		**B**	
sUA	0.30 (0.10)	0.34 (0.11)	0.04	0.01-0.07	0.04	0.01-0.07

*Values are the number (%), unless indicated otherwise. Multivariable model includes treatment strategy (centre), age, sex, estimated glomerular filtration rate (eGFR), use of diuretics, presence of tophi, and baseline serum uric acid. sUA= serum uric acid, UA-strategy= uric acid target strategy, PC-strategy= patient-centred strategy

Free of gout flares

During follow-up, 58/126 (46.0%) vs 31/86 (36.0%) patients in the UA and PC-strategy, respectively, were free of flares (p=0.148). Univariate logistic regression for gout flares showed that the treatment strategy (OR 1.51; 95% CI 0.86-2.66) was not significantly related to the proportion of patients free of flares. This remained unchanged (OR 1.61; 95% CI 0.83-3.10) after adjustment for confounders (table 2). Again, disease phenotype had no independent contribution (OR 1.64; 95% CI 0.90-3.00) and did not modify the effect of centre on outcome.

Secondary outcomes

Mean sUA

Both the UA-strategy and the PC-strategy resulted in a significant decrease of sUA (p<0.001) over time during the treatment period. At follow-up, the mean sUA was significantly lower in the UA-strategy patients compared to the PC-strategy (0.30±0.10 vs 0.34±0.11 mmol/L, p=0.004).

Multivariable linear regression analyses showed that sUA was 0.04 mmol/L lower (95% CI 0.01-0.07) in patients treated in the UA-strategy compared to the PC-strategy (table 2).

Table 3: Total number (N) and percentages (%) of treatment intensifications after the first and follow-up visit

	At (end of) the first visit				At follow-up			
	UA-strategy		PC-strategy[a]		UA-strategy		PC-strategy	
	N	%	N	%	N	%	N	%
Allopurinol monotherapy	96	76.2	67	77.9	76	60.3	63	73.3
Benzbromarone monotherapy	2	1.6	6	7.0	2	1.6	4	4.7
Febuxostat monotherapy	5	4.0	2	2.3	20	15.9	8	9.3
Allopurinol/benzbromarone combination therapy	9	7.1	0	0.0	18	14.3	1	1.2
Febuxostat/benzbromarone combination therapy	2	1.6	0	0.0	3	2.4	0	0.0
No ULT	12	9.5	10	11.6	7	5.6	10	11.6

PC-strategy= patient-centred strategy, UA-strategy= uric acid target strategy, ULT= urate-lowering therapy. [a] n=85 (One patient was using rasburicase)

sUA ≤0.30 mmol/L

A sUA target of ≤0.30 mmol/L has been reached significantly (p=0.040) more often in the UA-strategy, 83/126 (65.9%) patients vs 44/86 (51.8%) patients in the PC-strategy. In multivariable analyses, reaching a treatment target ≤0.30 mmol/L was 1.97 more likely (95% CI 1.00-3.85) among patients receiving the UA-strategy (table 2).

ULT intensifications and outpatient visits

At end of the first visit a similar proportion of patients received ULT; 114/126 (90.5%) in the UA-strategy and 75/86 (88.4%) in the PC-strategy. Allopurinol monotherapy was distributed similarly in both strategies (n=96 (76.2%) vs n=67 (77.9%)) (table 3). At follow-up, 76/126 (60.3%) patients in the UA-strategy were on allopurinol monotherapy compared to 63/86 (73.3%) in those receiving the PC-strategy (p=0.052). 2MoA therapy was observed significantly more often in the UA-strategy. Already at end of the first visit there were 11/126 (8.7%) patients on combination therapy in the PC-strategy. At follow-up, 21/126 (16.7%) patients of the UA-strategy vs 1/86 (1.2%) of PC-strategy were using combination therapy (p<0.001) (table 3). Multivariable analyses showed that patients in the UA-strategy were 0.40 times less likely (95% CI 0.20-0.82) to have allopurinol monotherapy (table 2). During follow-up, patients in the UA-strategy had a mean of 4.4 (1.0) outpatient visits versus 3.9 (1.1) visits in the PC-strategy (p=0.001).

Adverse events

Adverse events with regard to ULT drugs were registered by 25/126 (19.8%) patients of the UA-strategy and 20/86 (23.3%) patients of the PC-strategy (p=0.551). The adverse events of ULT include discomfort in the gastrointestinal tract (n=19), musculoskeletal (n=3), skin (n=25), and

psychiatric adverse events (n=1). Multivariable logistic regression showed that the two strategies did not differ in the likelihood of an adverse event (OR 1.04; 95% CI 0.49-2.21) (table 2).

DISCUSSION

In this study we compared the clinical outcomes of real-life gout management according to two protocolized treatment strategies: one following a strict sUA (≤0.30 mmol/L) target with early combining 2MoA strategy (UA-strategy), the other a PC-strategy integrating information on sUA with patient satisfaction about gout management. Patients receiving the strict UA-strategy reached, although not significantly, more frequent the sUA target (≤0.36 mmol/L) and were more often free of flares, but they required significantly more ULT treatment intensification and visited more frequently the rheumatology outpatient clinic. Reassuringly, frequent drug-treatment intensification was not accompanied by more frequent adverse events or withdrawals from follow-up. Based on our results, a sUA level below ≤0.36 mmol/L is a realistic clinical goal for the majority of gout patients with both protocolized strategies, but a stricter UA-strategy seems to ensure better short-term outcomes.

One randomized controlled trial (RCT) showed that nurse-led care providing ULT in a treat-to-UA-target approach (sUA ≤0.36mmol/L) combined with education to gout patients with ongoing gout flares in primary care, was efficacious in reaching a sUA level ≤0.36mmol/L (95% vs 30%) and in improving health related quality of life compared to usual care by the GP after 2 years (24, 25). Effects on sUA were seen early and were sustained during the 2 years duration of the study. Our study was the first to compare real-life data of two protocolized approaches in a rheumatology outpatient setting. Although the difference in the proportion of patients reaching the sUA ≤0.36 mmol/L target and being free of flares was not significant the point estimates do show a difference, it should be noted that the lack of statistical significance is a reflection of the small sample-size and thus lack of power (type II error). Also, patients treated in the centre adopting the stricter sUA target of 0.30 mmol/L reached significantly more frequently the lower sUA level (≤0.30 mmol/L) and a significant lower mean sUA. Although this was not unexpected, this finding also indicates that even lower targets are feasible. In view of a possible causal relation between sUA and cardiovascular events, it cannot be excluded that stricter control of sUA might have (also) longer-term benefits on cardiovascular risk. However, low sUA levels have also been associated with dementia, further complicating the issue of the preferred target (26). Unfortunately, information on patients' knowledge of gout, on confidence and satisfaction with treatment and on (long-term) medication adherence or lifestyle changes was not collected in both centres. Lack of this information hampers us to understand whether the differences in outcomes can (partly) be explained by influence of strategies on patients' lifestyle and medication behaviour (14, 18, 25, 27). With regard to treatment adherence, it should be mentioned first

that adherence received attention of specialists in both centres, and second that the literature provides some evidence that adherence to ULT in specialist care is better than in primary care. Therefore differences in adherence are unlikely to influence our results (28).

Centres clearly differed in drug choice when failing first-line allopurinol monotherapy. Recent studies suggest combining XOI with a uricosuric drug when monotherapy is ineffective in reducing sUA (12, 29, 30), and this approach was adopted in the UA-strategy. While this approach has a biological advantage that it influences the main biological path of hyperuricemia (22, 31), it cannot be concluded from our study design that early combination therapy is better to reach a low sUA as in the treatment strategy with early add-on of uricosuric, the sUA target was ≤0.30 mmol/L. Of note, in the PC-strategy, the majority of patients were still on allopurinol 300mg/day, and this would allow further up-titration of allopurinol if a stricter sUA would be preferred. Notwithstanding, a recent retrospective chart review by Janssen et al. found added value of a UA-strategy with 2MoA in reaching a sUA ≤0.36 mmol/L for the treatment of patients not achieving the target despite monotherapy allopurinol, but this was not compared to further up-titration of allopurinol (16). While decisions in the healthcare system should be mainly taken based on effectiveness and safety, cost-effectiveness is the 'third' hurdle of technology assessment. In the earlier mentioned RCT on nurse-led gout care in primary care, a lifetime cost-effectiveness Markov model was computed. At 2-years follow-up, quality adjusted life years (QALY) had been gained at the expense of more visits, but the cost-effectiveness was still favourable at £506/QALY. At 10-years follow-up, further QALYs were gained while cost-saving were noted, as patients had less resource utilisation. Important for our study, gout control in the nurse-led trial was achieved without combination therapy. Of note, our study was conducted in a secondary care setting and the sUA target was ≤0.30 mmol/L in the UA-strategy (25). In future strategy studies, the potential extra cost of the stricter UA-strategy with early add-on of 2MoA should also be considered in relation to the cost-effectiveness compared to a PC-strategy. Furthermore, the sUA target level in a stricter sUA targeted approach might play a role in the cost-effectiveness, when small differences in sUA levels would translate (independent of type or dose of drug) in benefits on cardiovascular outcomes and other comorbidities.

In view of the importance of comorbidities in gout and an expected difference in gout phenotype between the centres, we explored the possible role of comorbidities on outcome. Overall, the prevalence of the comorbidities in the total samples was slightly higher than in previously published population studies, which is not surprising as our sample considered patients referred to rheumatologists and such participants likely differ from gout patients followed in primary care settings (23, 32, 33). Between centres, the prevalence of tophi, the use of diuretics, and the presence of hypertension and dyslipidaemia were significantly higher in the PC-strategy group. This case mix could be related to the difference in setting (university or non-university), but also to regional differences in lifestyle habits. Reassuringly, disease phenotype did not modify

the effect of centre on outcome. It is important to conduct future research to examine the role of gout phenotypes on treatment strategies, in which patient education, lifestyle advice and cardiovascular risk management is an important part.

The conclusion we formulated on the different treatment strategies, was based on a comparison of real-life data from two protocolized gout clinics, and not on results of an experimental study. The use of real-life data gained renewed interest due to the increasing accessibility of digital health data and may bridge the evidentiary gap between strictly RCTs and daily practice of gout treatment. Moreover, it compares results of strategies more easily and cheaply (21). Notwithstanding, real-life data has specific challenges, mainly related to offer insufficient possibility to control for potential confounders and less controlled interventions compared to RCTs. On this line, specific limitations should be discussed, some of which actually also relate to more strict experimental studies. Firstly, patients in the PC-strategy were diagnosed with gout based on clinical diagnosis and not strictly based on fulfilment of any diagnostic criteria. In the UA-strategy on the other hand patients were diagnosed strictly based on crystal identification and ACR/EULAR gout classification criteria. Secondly, there are limitations regarding the standardized measurement of outcomes including number of gout flares and adverse events. Only recently a standardized approach to validate a definition for gout flares with patients' self-reported criteria was suggested by a Gaffo et al. (34). As a consequence misclassification of cases as well as of outcomes may have influenced the results. Further, due to differences in approaches and frequency of assessments of (the number of) gout flares, it was not possible to differentiate between the numbers of flares in the initial period and later periods of time after initiating ULT. The majority of the gout flares commonly take place during the first six months of ULT, however, due to the consultation protocol, no distinction could be made in this study. Data on type (but not dosage) of gout flare prophylaxis was only available for the first and follow-up visit. However, in additional multivariate analysis, prophylaxis did not meaningful influence the effect of strategy on flare (data not shown). Overall, findings underline the need for a carefully designed treat-to-target trial with an appropriate sample size, exploring the effectiveness and cost-effectiveness of different sUA targets with or without an explicit role of the patient in a shared decision making context, and with attention for short as well as long-term outcomes.

CONCLUSION

Real-life data from two gout clinics reveal that a stricter UA-strategy resulted in a non-significant higher proportion of patients reaching a sUA ≤0.36 mmol/L and being free of flares, though significantly more patients reached a sUA ≤0.30 mmol/L without experiencing more adverse events. This was accomplished through significantly more therapy intensification from allopurinol monotherapy to combination therapy.

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4

Construct validity of radiographs of the feet to assess joint damage in patients with gout

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ABSTRACT

Objective

To investigate construct validity of radiographic damage of the feet in gout.

Methods

Radiographs of the feet were scored using the Sharp-van der Heijde method. Factors associated with damage were investigated by a negative binomial model. The contribution of damage to health was assessed by linear regression.

Results

Age, disease duration, serum uric acid and tophi were associated with being erosive and erosion scores. Tophi were associated with joint space narrowing. Erosions were associated (β:0.47, 95%CI:0.09-0.84) with physical function, but damage was not associated with overall physical health.

Conclusion

Our results support construct validity for radiographs of the feet when assessing joint damage in gout.

INTRODUCTION

Gout is worldwide the most prevalent inflammatory arthritis (1). It is therefore surprising that outcome research in gout is more limited when compared to other rheumatic diseases. To fill this gap, the Outcome Measures in Rheumatology (OMERACT) gout working group, reached consensus on outcome domains that should be measured in clinical trials and studies in gout and proposed instruments to measure domains (2). With joint damage being endorsed as a core outcome domain, joint imaging was proposed as instrument (3).

To date, radiographic damage measured by conventional radiography (XR) is still considered a feasible approach to measure joint damage because of its widespread availability, low patient burden and easy scoring method. For scoring XR damage, a highly reliable scoring method, namely, the gout-modified Sharp-van der Heijde score (SvdH-mG) is available (4). The SvdH-mG includes the same joints in hands and feet of the SvdH system for rheumatoid arthritis, plus the distal interphalangeal joints of the hand. Joints are scored for erosions and joint space narrowing (JSN), each reflecting features that can be distinguished on XR (5).

While XR has intuitively high face validity to assess joint damage in gout, no comprehensive data on the construct validity of radiographic damage are available. Construct validity assesses the ability of the instrument to measure the 'construct' it intends to measure. Although construct validity of XR to measure joint damage is supported by comparisons of damage scores assessed by other imaging modalities (6), there is only one study (n= 20) that assessed whether radiographic damage was associated with functioning (7). It was shown that radiographic damage on XR had an impact on hand function. Another aspect of construct validity can be found in the expectation that a series of biological factors that reflect the disease process (such as serum uric acid (sUA) or tophi) would be associated with radiographic damage as it is generally assumed that joint damage is the resultant of progressive accumulation of uric acid. Bringing together more pieces of evidence that radiographic damage relates in expected directions with physical function and biological factors, would add confidence in the construct validity of XR and enhance the systematic inclusion of XR in any gout trial.

Therefore, the aim of this study was to evaluate the construct validity of radiographic damage in the feet by exploring which biological factors of gout contribute to radiographic damage and by investigating the relationship between radiographic damage and health outcomes.

MATERIALS AND METHODS

Patient population

Data from patients with gout were obtained from a cross-sectional study of 126 patients attending the outpatient clinic of rheumatology at the Maastricht University Medical Centre (MUMC+) , which serves as a regional hospital for patients with gout. During the study visit, comprising a structured interview and clinical examination, demographic and disease characteristics were assessed, including disease duration, sUA levels, use of uric-acid lowering therapy (ULT), location and number of clinical tophi, and confirmation of number of self-reported gout flares (past year). Based on physician confirmed comorbidities, the Rheumatic Diseases Comorbidity Index (RDCI) was calculated (8). Physical function was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI; range 0-3) and physical health using the physical component score of the Short-Form-36 (SF-36 PCS) (9, 10). Plain radiographs of the feet were obtained as part of standard clinical care within 1 month before or after the study visit. The principles of the Declaration of Helsinki were followed and the study was approved by the ethics committee of the MUMC+.

Radiographic damage

The radiographs were independently scored by two trained and experienced rheumatologists (CvD, TS) blinded for the clinical characteristics and for each other's score. Radiographs were scored using the SvdH-mG assessing erosions in MTP I-V and IP I (score 0-10 per joint; 0-5 per articular surface) and JSN (score 0-4 per joint) resulting in a maximum combined score of 168 for both feet (5). Intra- and interobserver ICCs (two-way mixed, average measures) were calculated for erosion-, JSN-, and total damage scores separately.

Statistical analysis

The sample characteristics are presented as mean (SD) or median (IQR) depending on the distribution of the data. To explore biological factors associated with radiographic damage, a negative binomial regression (NB) and a zero-inflated negative binomial regression (ZINB) were performed for JSN- and erosions score respectively, as data were non-normally distributed with overdispersion (for JSN) and an excess of zeros (for erosions). In the multivariable models, age and sex were included by default, and the remaining variables were added using manually forward selection ($p<0.05$). To explore the relative contribution of JSN and erosions to HAQ-DI and SF-36 PCS, linear regressions analyses, adjusted for age, sex, disease duration and comorbidities were performed. Data were analysed using IBM SPSS statistics v19.0 and Stata Release 12 (for NB and ZINB).

RESULTS

Study population

Eighty-one patients with gout (81/126; 64.3%) had radiographs and were included. The demographic and clinical characteristics are presented in Table 1. The patients contributing to the current analyses did not differ significantly from the 45 patients with no radiographs with regard to age, sex, use of ULT or presence of tophi.

Table 1 Baseline characteristics (n=81)

Characteristics	Value
Age (years)	66.4 (10.5)
Male sex, n (%)	65 (80.2)
Ethnicity, n (%)	
White	79 (97.5)
Asian	2 (2.5)
Body Mass Index (kg/m^2)	29.4 (4.6)
Disease duration (years)	11.1 (10.0)
No. of gout flares last year, median [IQR]	1 [0 to 3]
Last flare in foot/anle, n (%)	70 (86.4)
Currently on uric acid lowering therapy, n (%)	57 (70.4)
Uric acid level (mmol/L)	0.40 (0.13)
Uric acid level <0.36 mmol/L, independent of ULT, n (%)	38 (46.9)
Tophaceous gout, n (%)	38 (46.9)
Tophi in foot, n (%)	15 (18.5)
Number of tophi, mean, (median) [IQR]	2.0 (0) [0 to 2]
RDCI (0-9), mean (median) [IQR]	2.8 (3) [2 to 4]
Chronic kidney disease, n (%)	
MDRD < 60 ml/min/1.73 m^2	30 (37.0)
MDRD < 30 ml/min/1.73 m^2	11 13.6)
Gout-modified SvdH-score foot	
Total (0-168), mean, (median)	5.1 (4.5)
[IQR]	[1.5 to 7.5]
Erosion (0-120), mean, (median)	1.6 (0.5)
[IQR]	[0.0 to 2.0]
JSN score (0-48), mean, (median)	3.5 (3)
[IQR]	[1.0 to 5.3]
HAQ-DI (0-3)	0.65 (0.59)
SF-36 PCS (0-100)	38.7 (11.9)
SF-36 MCS (0-100)	49.2 (12.7)

Values are expressed as mean (SD) unless stated otherwise.
RDCI: Rheumatic Disease Comorbidity Index, MDRD: Modification of Diet in Renal Disease,
SvdH-score: Sharp/van der Heijde-score, JSN: Joint Space Narrowing, HAQ-DI: Health Assessment Questionnaire – Disability Index, SF-36 PCS: Short Form-36 Physical Component Score,
SF-36 MCS: Short Form-36 Mental Component Score.

Radiographic damage

The ICCs (95% CI) for intraobserver reliability (of 10 radiographs) for erosion-, JSN-, and total scores were 0.98 (0.95-0.99), 0.87 (0.57-0.96) and 0.96 (0.87-0.99) for observer 1 and 0.92 (0.72-0.98), 0.71 (0.20-0.92) and 0.88 (0.60-0.97) for observer 2, respectively. For interobserver reliability the total sample ICCs (95% CI) for erosion-, JSN-, and total scores were 0.94 (0.90-0.96), 0.85 (0.76-0.90) and 0.93 (0.90-0.96).

Seventy-one patients (71/81, 87.7%) had radiographic damage, of which thirty-eight (46.9%) had erosions (score>0.5) and 63 (77.8%) had JSN (score>0.5). Median [IQR] erosion, JSN and total SvdH-mG scores were 0.5 [0-2], 3 [1.0-5.3] and 4.5 [1.5-7.5] respectively for the entire group.

Factors associated with radiographic damage

Table 2 shows the final model of the NB and ZINB analyses. Older age and having not reached the sUA target level (i.e., sUA <0.36 mmol/L) were significantly associated with the chance of being erosive. Older age, longer disease duration and higher number of clinical tophi were positively associated with erosion scores. Presence of clinical tophi was associated with having more JSN.

Table 2

a) Multivariable Zero-Inflated Negative Binomial regression analysis exploring determinants of erosive disease in patients with gout

b) Multivariable Negative Binomial regression analysis exploring determinants of joint space narrowing (JSN) in patients with gout

	Multivariable regression Being non-erosive*				**Multivariable regression Erosion-score (count)¥**			
a)	**B**	**OR†**	**95% CI (OR)**	**P-value**	**B**	**Exp(β)‡**	**95% CI (Exp(β))**	**P-value**
Age (years)	-0.15	0.86	0.74 to 0.99	**0.036**	0.05	1.06	1.02 to 1.09	**0.002**
Sex (female)	3.36	28.8	0.87 to 955.74	0.06	0.50	1.65	0.72 to 3.75	0.23
Disease duration (years)					0.04	1.04	1.01 to 1.07	**0.018**
Number of tophi (n)					0.07	1.07	1.03 to 1.12	**0.001**
sUA ≤0.36mmol/L (yes/no)	4.39	80.53	1.25 to 5192.79	**0.039**				
b)					**JSN-score (count)¥**			
Age (years)	#	#	#	#	0.01	1.01	0.99 to 1.02	0.63
Sex (female)	#	#	#	#	-0.13	0.88	0.55 to 1.39	0.58
Tophaceous gout (yes/no)	#	#	#	#	0.57	1.76	1.23 to 2.53	**0.002**

*Logistic model, predicting being non-erosive (the amount of erosions being a 'certain zero')

¥Negative binomial model, predicting expected count.

†Factor change in odds for one unit increase in the independent variable.

‡Factor change in expected count for one unit increase in the independent variable.

Significant values are shown in bold typeface

The contribution of radiographic damage to outcome

In Table 3, the results of the uni- and multivariable regression analyses to explore the impact of radiographic damage scores on HAQ-DI and SF-36 PCS are shown. In multivariable analysis, higher erosion scores were significantly associated with higher HAQ-DI, although contribution to the variation in outcome (+6.0% after adjustment) was limited. The multivariable analysis of SF-36 PCS revealed no significant influence of erosions or JSN.

Table 3. Uni- and multivariable linear regressions exploring the impact of radiographic damage on physical functioning and health-related quality of life, measured with HAQ-DI and SF-36 PCS.

		HAQ-DI			
		Univariable Analysis		Multivariable Analysis	
		B (95% CI)	P-value	B (95% CI)	P-value
Erosion score (per 10 points worsening) *		0.51 (0.10 to 0.91)	**0.015**	0.47 (0.09 to 0.84)	**0.015**
JSN score (per 10 points worsening) *		0.02 (-0.43 to 0.46)	0.94	-0.09 (-0.32 to 0.49)	0.68
R^2 model, %				26%	
Variance (R^2) explained by radiographic damage scores, %	Erosion			6.0%	
	JSN			0.2%	

		SF-36 PCS			
		Univariable Analysis		Multivariable analysis	
		B (95% CI)	P-value	B (95% CI)	P-value
Erosion score (per 10 points worsening) *		-2.02 (-10.28 to 6.22)	0.63	-1.44 (-9.46 to 6.58)	0.72
JSN score (per 10 points worsening) *		4.08 (-4.64 to 12.80)	0.36	3.03 (-5.39 to 11.44)	0.48
R^2 model, %				14%	
Variance (R^2) explained by radiographic damage scores, %	Erosion			0.2%	
	JSN			0.6 %	

*Tested separately in multivariable analysis

HAQ-DI: Health Assessment Questionnaire – Disability Index, SF-36 PCS: Short Form 36 Physical Component Score, JSN: Joint Space Narrowing.

Multivariable analyses are adjusted for age, sex, disease duration and comorbidity (calculated by the Rheumatic Diseases Comorbidity Index)

DISCUSSION

The current study further supports the construct validity of radiographic damage of the feet when assessing outcome in gout. First, patients who were older, had longer disease duration, had not reached the sUA target level, and had more tophi were more likely to be erosive or to have more erosions. In addition, patients with tophaceous gout had higher JSN scores. Second, radiographic damage showed an association with physical function assessed by HAQ, but not with overall physical health measured by the SF-36.

The finding that age, disease duration, sUA level and tophi were associated with radiographic damage was recently also reported by Dalbeth et al., who found that sUA level, tophi but also disease duration were at least moderately associated with radiographic damage of hands and feet (11). A study showing that profound reduction of sUA levels lead to improvement of the SvdH-mG (erosion) score, further supports the role of sUA and clinical tophi in the pathophysiology of erosions (12).

On the other hand, radiographic damage was not consistently associated with health outcome in our study. A reason for the inconsistent and at most moderate (for HAQ-DI) association might be the fact the natural course of gout is difficult to capture, as radiographic damage seems reversible with ULT. Another explanation might be the overall low scores of radiographic damage, but this is likely the clinical reality of unselected patients under care of a rheumatologist, as observed damage scores are in line with those reported in other studies by patients not selected for trials (13). Further, self-reported HAQ-DI and SF-36 might insufficiently capture lower limb impairments. Especially SF-36, a health-related quality of life instrument, is strongly influenced by different aspects of health such as vitality. Last but not least, it is known that patients with slowly progressive disease, as is the case for chronic gout, can often adapt to impairments, indicating reference shift (14).

We recognize that this study is not without limitations. First, the sample size is small and patients were recruited from a university hospital, although for patients with gout it serves as a regional hospital. Although this would not hamper the internal validity, it might be possible that the relation between radiographic damage and health outcomes is stronger in selected subgroups with more severe disease. Second, only radiographs of the feet were obtained in standard clinical care, as clinical manifestations occur most frequently in the feet. Third, we need to be cautious when interpreting our results, since joint damage scored with SvdH-mG, might be attributable to osteoarthritis rather than gout, especially since both diseases often occur together (15). The study by Dalbeth et al. (11) showed that JSN was the imaging feature least associated with crystal deposition (assessed using dual-energy CT). Therefore, we believe that JSN, present in both gout and osteoarthritis lacks discriminative validity and might be

reconsidered in the future. Nevertheless, our study convincingly confirmed that the SvdH-mG is a highly reproducible method to score radiographic damage. Finally, this is a cross-sectional study and therefore knowledge about how radiographic damage evolves over time could not be obtained.

In conclusion, our findings support the construct validity of XR to evaluate joint damage in gout. Together with the widespread availability, low patient burden and low costs, this suggests a role for XR to monitor joint damage in patients with gout. More research is still needed to understand whether in clinical practice, information on XR would influence currently recommended treatment strategies.

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5

Cardiovascular Risk Factors and Comorbidities in Patients with Hyperuricemia and/or Gout: A Systematic Review of the Literature

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ABSTRACT

Objective

To review the available literature on the likelihood of having cardiovascular (CV) risk factors and on developing CV comorbidities in patients with gout and/or asymptomatic hyper-uricemia as an evidence base for generating multinational clinical practice recommendations in the 3e (Evidence, Expertise, Exchange) Initiative in Rheumatology.

Methods

A systemic literature search was carried out using MEDLINE EMBASE, and the Cochrane Library, and abstracts presented at the 2010/2011 meetings of the American College of Rheumatology (ACR) and the European Against Rheumatism, searching for CV risk factors and new CV comorbidities in patients with asymptomatic hyperuricemia and/or a diagnosis of gout. Trials that fulfilled predefined inclusion criteria were systematically reviewed.

Results

A total of 66 out of 8918 identified publications were included in this review. After assessment of the risk of bias, 32 articles with a high risk of bias were excluded. Data could not be pooled because of clinical and statistical heterogeneity. In general, both for asymptomatic hyper-uricemia and for gout the hazard ratios for CV comorbidities were only modestly increased (1.5 to 2.0) as were the hazard ratios for CV risk factors, ranging from 1.4 to 2.0 for hypertension and from 1.0 to 2.4 for diabetes.

Conclusion

Unlike the common opinion that patients with gout or hyperuricemia are at higher risk of developing CV disease, the actual risk to develop CV disease is either rather weak (for hyper-uricemia) or poorly investigated (for gout).

INTRODUCTION

The association of uric acid and cardiovascular disease is well known (1). Whether an elevated uric acid is the cause or the consequence of a worse cardiovascular (CV) risk profile, however, is still unsure. To date, there is no consensus on how to deal with this association in the management of patients with gout.

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Diagnosis and management of Gout (2). The objective of the current report was to systematically review the literature concerning one of the 10 selected questions as an evidence base for generating the recommendations. The question was: In patients with hyperuricemia and/or the diagnosis of gout, should we routinely screen for comorbidities and CV risk factors?

MATERIALS AND METHODS

A systematic review was carried out in several steps following the guidelines for Cochrane systematic reviews (3). First, the research question was rephrased into epidemiological terms according to the PICO (Patients, Interventions, Comparator, Outcome) method (3). Patients were defined as adults (older than 18 years) with a diagnosis of gout or hyperuricemia. In our research question there was no intervention. The comparator was considered the healthy population without gout or hyperuricemia. The outcome variables were CV risk factors (hypertension, diabetes, dyslipidemia, and metabolic syndrome), CV disease [CVD; stroke, coronary heart disease (CHD), peripheral arterial disease (PAD)] and other comorbidities. Only comorbidities that could be screened for and treated, such as renal disease and cancer, were included in the search. As outcomes for chronic kidney disease "mortality" and "start of renal replacement therapy" were chosen. For cancer, only trials on the incidence and/or mortality of site-specific cancers were selected. We also decided to include only prospective observational studies with patients free of gout and comorbidities at baseline.

Next, a systematic literature review was conducted in MEDLINE, EMBASE, and the Cochrane Library, using a comprehensive search strategy (see Appendix 1, available from www.3egout.com). There was no time restriction; languages were restricted to those spoken by members of the 3e Initiative: English, French, Spanish, German, and Dutch. Review articles were also retrieved to identify additional references via hand search. The abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) from 2010 and 2011 were also searched to find unpublished trials. Each selected study was assessed for risk of bias using a tool by Hayden, et *al* (4), designed especially for prospective cohort studies. A predefined data extraction sheet was used to extract all data from the trials.

RESULTS

A total of 8918 trials were identified with our search (Figure 1). After title and abstract screening, 117 trials were retrieved for full-text review, of which 64 met the inclusion criteria. Two congress abstracts were also included as full-text trials. Thirty-two articles with a high risk of bias were excluded. Table 1 presents a summary of the key findings of our review. More detailed tables of every outcome assessed can be found in the online Appendix, available from www.3egout.com.

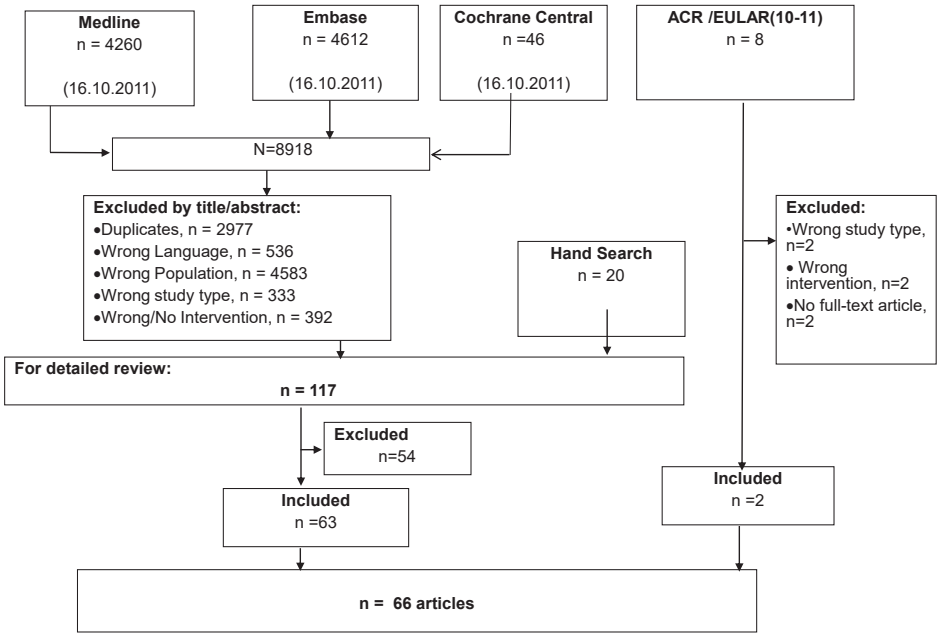

Figure 1 The systematic literature review.

Hypertension

Fifteen trials describing the risk of hypertension in patients with hyperuricemia were retrieved (5-19). Six of the 15 trials had a moderate risk of bias, and the other 9 had a high risk of bias and were excluded (Table 1). Studies showed a higher risk for women than for men [hazard ratio (HR) 1.9 vs 1.4).

Diabetes

Seven trials describing the risk of diabetes in patients with hyperuricemia were retrieved (19-25). Four of the 7 studies had a moderate risk of bias (19-23), and the other 3 had a high risk of bias and were excluded (Table 1). Unadjusted HR ranged from 1 to 4.8 and decreased to 1.0 to 2.4 after adjustment. The risk was higher in women.

Table 1. Overview of the results of the systematic literature review for each cardiovascular risk factors and each comorbidity

		No. Trials in Hyperuricemia/ No. Trials in Gout	HR, All Trials, range	
			Hyperuricemia	Gout
Hypertension	All	6/0	1.4-2.0	NA
	F	2/0	1.7-1.9	NA
	M	2/0	1.4-1.5	NA
Diabetes	All	4/0	1.0-2.4	NA
	F	1/0	2.0	NA
	M	1/0	1.07*	NA
Incidence of PAD	All	1/0	1.23*	NA
	F		NA	NA
	M		NA	NA
Stroke	All	6/1	1.25*-1.50*	NA
	F	1/0	1.50*	NA
	M	1/0	0.9*-1.3*	NA
CHD	All	7/4	0.7*-2.1*	1.3-1.6
	F	4/2	1.0*-2.1*	1.2*-1.4
	M	4/4	0.7*-1.5*	1.3-1.6
CKD	All	2/1	2.1-5.8	NR
	F	1/0	5.8	NA
	M	1/0	2.0*	NA
Cancer	All	2	1.0*-1.1*	1.2
	F	1/	1.0*	NA
	M	2/	1.0-1.1*	NA
Mortality due to Stroke	All	2/1	1.20	1.06*
	F	1/1	1.12*	1.45*
	M	1/1	1.71*	0.85*
CHD	All	13/4	1.12*-8.5*	0.97*-1.35
	F	4/2	1.3-8.5*	1.3*-1.8
	M	3/3	1.1*-1.7	1.2*-1.4*
CKD	All	0/1	NA	4.35
	F	0/1	NA	4.76
	M	0/1	NA	3.78
Cancer	All	1/0	1.4	NA
	F	0/0	NA	NA
	M	1/0	1.4	NA

* Reported HR not statistically significant. HR: hazards ratio; NA: not available: NR: HR not reported in study, authors found not statistically significant; PAD: peripheral arterial disease; CHD: chronic heart disease; CKD: chronic kidney disease.

Stroke

Fifteen trials (26-37,39-40, 48) on risk of stroke in patients with hyperuricemia were retrieved. Six of the 15 studies in hyperuricemic patients had a moderate risk of bias (27-28, 30-31, 37, 39) and the remaining 7 a high risk of bias and were excluded (Table 1). Stroke-related mortality (30, 39) and stroke incidence (27-28, 31, 37) were investigated. Stroke incidence and mortality were not increased. One article (moderate risk of bias) described the risk of stroke in patients with gout (41). Mortality was not increased.

Coronary heart disease

Twenty-three trials describing the risk of manifest CHD in hyperuricemic patients (26-35, 40, 42-49, 50-51, 53, 57) were identified. Thirteen of these 23 trials had a moderate risk of bias (27-28, 30-31, 42-46, 48, 51, 53). Of those 13 trials, 6 have looked at mortality (30, 45-46, 49, 51, 53), and 7 trials investigated incidence (27-28, 31, 42-44, 48). The risk for incident CHD was not increased (Table 1). Mortality was slightly increased in women (HR 1.3) but not in men.

Nine trials described the risk of CHD in patients with gout (41, 50, 54-59). Eight of these had a moderate risk of bias (41, 54-57, 59). Four trials looked at CHD mortality (41, 55-57) and another 4 examined CHD incidence (54-56, 59). Adjusted HR for mortality (HR 1.4 to 1.8) and new CHD (HR 1.3 to HR 1.6) were only slightly increased.

Peripheral arterial disease

One article on the risk of peripheral arterial disease in patients with hyperuricemia was found (60). The risk was not increased (Table 1).

Cancer

Four trials describing the risk of site-specific cancer in patients with hyperuricemia were retrieved (52, 61-63). Three of the 4 trials had a moderate risk of bias (61-63) and one a high risk of bias (excluded). Mortality due to site-specific cancers (63) and incidence of site-specific cancers (61-62) were investigated. Cancer incidence was not increased. Cancer mortality was slightly increased (HR 1.4), due to cancers of the digestive tract, respiratory tract, and the nervous system (Table 1).

One article describing the risk of cancer in patients with gout (64) revealed a moderate risk of bias. Cancer incidence (prostate) was slightly increased (HR 1.2) (see Appendix, available from www.3egout.com).

Chronic kidney disease

Three trials describing the risk of endstage kidney disease (40, 65-66) in hyperuricemic patients were retrieved. Two of these 3 trials (65-66) had a moderate risk of bias. Endstage renal disease

(ESRD) was defined as the start of replacement therapy (dialysis or renal transplant), and mortality was investigated in 1 trial (65). The adjusted risk for chronic kidney disease was increased (HR 2.1–5.8), particularly in women (HR 5.8) (Table 1). Two trials describing the risk of ESRD in gout patients were retrieved (41, 65). These trials had a moderate risk of bias. Mortality was increased in 1 (HR 4.4) (41), but not in the other.

* Reported HR not statistically significant. HR: hazards ratio; NA: not available: NR: HR not reported in study, authors found not statistically significant; PAD: peripheral arterial disease; CHD: chronic heart disease; CKD: chronic kidney disease.

DISCUSSION

This systematic review gives an overview of the available literature on the presence of CV risk factors and other comorbidities in patients with gout and hyperuricemia, and on the risk of developing these comorbidities over time. This overview served as an evidence base for generating 1 of the 10 clinical recommendations on the diagnosis and management of gout. A detailed description of all the final recommendations can be found elsewhere[2]. Because of multiple sources of heterogeneity among the included trials, a formal metaanalysis with data pooling was not performed. This review shows that the risk to develop CV risk factors or CV diseases is not, or is only slightly, increased. With regard to cancer, the available data are too weak to support any conclusions. The risk of developing ESRD is markedly elevated in patients with hyperuricemia. With regard to gout, the results did not allow a clear conclusion. The development of ESRD in hyperuricemic patients could be explained by the deposition of urate crystals in the kidney, which contributes to the deterioration of kidney function. Two studies[67,68] monitoring kidney function in patients with gout and chronic kidney diseases who were taking urate-lowering therapies showed improvement in kidney function during treatment. Such an observation warrants further investigation on the effects of urate-lowering therapy in preventing ESRD in patients with hyperuricemia and gout.

An interesting finding in this review is that, while in men hyperuricemia does not seem to increase the risk of CV diseases, this seems to be different in women. A hypothetical explanation is that women are more sensitive to the harmful effects of uric acid on endothelial function, and to oxidative and inflammatory changes, thus affecting the risk of developing hypertension and metabolic syndrome[2].

An important limitation of the prospective studies included in this review is that patients who already had experienced a CV event were excluded from the analysis. This may lead to left-censorship bias: the event that the investigators are interested in had occurred before the start

of follow-up. This problem can only be solved by performing large inception cohort studies, where individuals will be included as soon as hyperuricemia or gout is diagnosed. And even then, especially in the case of hyperuricemia, it will be unclear for how long the patient had already been at risk of developing the CV outcome.

During the systematic literature search, 5 metaanalyses discussing the risk of CV comorbidities in patients with hyperuricemia were identified[67,68,69,70,71]. The most important reasons for exclusion of these metaanalyses in the present study were as follows; the studies included in the metaanalyses did not always start with a "healthy cohort," of which some already had reached the endpoint, and some studies did not provide clear and useful definitions of the different uric acid categories. Another important limitation was related to the risk-of-bias assessment tool used in the metaanalysis: the Newcastle-Ottawa scale, based on which the authors of the excluded metaanalysis concluded that most included studies were of good quality. The Newcastle-Ottawa scale was designed to access nonrandomized studies rather than prognosis studies, and thus mainly assesses the "reporting" of study methods rather than how well the study methods limit bias. However, although the risk ratio in the metanalyses might be slightly overestimated, the main results are still in accord with our results presented here.

In summary, the well-grounded assumption that gout and hyperuricemia are risk factors for clinically manifest CV disease is based mainly on cross-sectional association studies. In the prospective cohort studies, we analyzed in the review, the risk did not seem to be increased at all or was shown to be only slightly increased. Another important finding of our review is that, if an increased risk of CV disease was found in univariate analysis, this increased risk disappeared or at least was drastically lowered after adjustment or confounders. This may suggest that hyperuricemia should be seen as a risk indicator (and part of the metabolic syndrome) rather than as an individual and independent risk factor.

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6

Individuals with type 2 diabetes mellitus are at an increased risk of gout but this is not due to diabetes: a population-based cohort study

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ABSTRACT

Objective

The relationship between type 2 diabetes and gout is complex. The objective of this study was to understand the role of diabetes itself and its comorbidities within the association between type 2 diabetes and gout.

Methods

We conducted a retrospective cohort study using the UK Clinical Practice Research Datalink (CPRD) GOLD. Persons with type 2 diabetes were identified as persons on a non-insulin anti-diabetic drug (NIAD) between 2004 and 2012, and were matched to one control based on age, sex, and general practice. We estimated gout risk in NIAD users using Cox regression analysis. All analyses were stratified for sex.

Results

221,117 NIAD users were identified. NIAD users had an increased risk of gout (Hazard Ratio (HR) 1.48; 95%CI 1.41-1.54). This association was stronger in women (HR 2.23; 95%CI 2.07-2.41) compared to men (HR 1.19; 95%CI 1.13-1.26). After adjustments for BMI, eGFR, hypertension, renal transplantation, diuretics, statins, low dose aspirin, ciclosporin, and tacrolimus, the risk disappeared in women (HR 1.01; 95% CI 0.92-1.11) and reversed in men (HR 0.61; 95% CI 0.58-0.66) (p for interaction <0.001). When stratifying gout risk according to HbA1c in male and female NIAD users, we found an inverse association between raising HbA1c and incident gout in men only. Further adjustment gave similar results.

Conclusion

Individuals with type 2 diabetes are at increased risk of gout. This is not due to diabetes itself, but to the comorbid conditions. Diabetes itself is apparently associated with a decreased risk of gout, especially in men.

INTRODUCTION

Gout is the most common inflammatory joint disease worldwide and affects up to 1-2% of adults in western societies (1). The disease has been associated with multiple comorbidities, including type 2 diabetes. However, the relationship between type 2 diabetes and gout is complex as several pathophysiological mechanisms that occur in diabetes can have opposite effects on the risk of gout (2-5).

On the one hand, diabetes may be associated with an increased risk of gout. As compared with the general population, individuals with type 2 diabetes generally have a higher BMI (Body Mass index), an increased prevalence of hypertension (6) and a decline in renal function (7). These comorbid conditions are well known risk factors of gout (8,9). Indeed, higher prevalences of gout have been identified in individuals with type 2 diabetes (2,3). On the other hand, studies have shown lower uric acid concentrations in individuals with type 2 diabetes compared to those without diabetes, suggesting a lower risk of gout (10,11). Glycosuria, which occurs when blood glucose levels rise above ~10 mmol/l (11), has been suggested to be the underlying mechanism for these low concentrations (12). An impaired inflammatory response in individuals with type 2 diabetes may further protect against the development of gout (4). In agreement, a case-control study in The Health Improvement Network (THIN), a British primary care database, has shown that individuals with type 2 diabetes are at a lower risk of gout than controls (4). This risk was even lower if diabetes was poorly controlled (5).

In view of the above, the objective of this study was to determine the risk of gout in individuals with type 2 diabetes as compared with population-based controls, and to understand the role of diabetes itself and its comorbidities within gout risk. Since it has been suggested that risk factors for gout are more prevalent in women with type 2 diabetes than in men (13), we additionally investigated potential sex-related differences in the association between type 2 diabetes and incident gout.

METHODS

Data source

Using data from the CPRD GOLD, we performed a retrospective cohort study. CPRD GOLD contains computerized medical records of general practitioners in the United Kingdom (UK) and is formerly known as the General Practice Research Database. Currently, the database includes data on more than 13 million individuals from 678 practices in England, Northern Ireland, Scotland and Wales. The data comprises demographic information, data on lifestyle, prescription details, clinical events, specialist referrals, and hospital admissions and major out-

comes. In addition, CPRD GOLD contains data on indicators of the Quality and Outcomes Framework (QOF) since 2004. The QOF is an incentive scheme for General Practitioners (GPs) in order to increase the quality of recording of indicators of various diseases, including diabetes mellitus. This has resulted in the recording of smoking status and body mass index (BMI) of 90-95% individuals in CPRD. For persons with diabetes, the QOF awards recent recording of variables such as HbA1c, eGFR, BMI, and smoking status. The GPRD Group has obtained ethical approval from a multicentre research ethics committee for all purely observational research using anonymised records from the general practice research database. This study was approved by the general practice research database Independent Scientific Advisory Committee.

Study population

In order to select individuals with type 2 diabetes, we identified all persons aged 18 years or older who received at least one prescription for a non-insulin antidiabetic drug (NIAD) recorded between April 1th 2004 and August 31th 2012. NIADs included metformin, sulphonurea derivatives, incretin agents, meglitinides, thiazolidinediones, and acarbose. The index date was defined as the date of the first NIAD prescription since the start of the study period. The study population included, therefore, both prevalent and incident NIAD users. After start of valid data collection, each NIAD user was matched with one randomly selected control by sex, year of birth (within 5 years), and practice. The controls were individuals without a NIAD or insulin prescription during the whole study period. Every control was assigned the index date of its matched NIAD user. Every control was assigned the index date of its matched NIAD user. All individuals were then followed-up from their index date until the date of death, end of data collection (August 31th 2012), the date of transfer of the person out of the practice, or the end date of data collection of the practice in CPRD, whichever came first. At baseline, individuals were excluded from the analysis if they had a history of gout, or if they had used colchicine, allopurinol, probenecid, benzbromaron, febuxostat, rasburicase, sulfinpyrazone or pegloticase before or on the index date.

Exposure

The follow-up time of the NIAD users was divided into intervals based on the length of NIAD prescriptions, i.e. for every prescription a new interval was created. This person-time was classified as "current NIAD use". After a washout period exceeding 90 days, person-time was considered "past NIAD use". When a new NIAD was prescribed, person-time was considered "current NIAD use" again. The follow-up time of controls was divided into intervals of 90 days.

Study outcome and covariates

Outcome of interest was the first-time clinical diagnosis of gout, identified using READ codes. READ codes are a set of clinical codes used in primary care in the United Kingdom for the registration of clinical diagnosis, processes of care (tests, screening, symptoms, patient admin-

istration etc.), and medication. This case definition has previously been validated by analysis of medical records and laboratory results of a sample of 38 anti-ulcer drug exposed subjects with a first-time diagnosis of gout (14).

The following variables were assessed in the period prior to the index date, using dummy variables: sex, smoking status (never/current/past/unknown), BMI (classified according to the World Health Organization (15)), and alcohol use (yes/no/unknown). At each time interval we assessed age, eGFR, and whether individuals had a history of hypertension, underwent a renal transplantation or had a postmenopausal status/oophorectomy. In addition, the following variables were determined 6 months prior to the start of each time interval: the use of insulin, thiazide diuretics, loop diuretics, low dose aspirin (≤100mg), ciclosporin, tacrolimus or statins.

Statistical analysis

All statistical analyses were performed with SAS 9.2. Results were considered significant if P value was <.05. We estimated incidence rates (IRs) of gout between April 1, 2004 and August 31, 2012 in NIAD and non-NIAD users. IRs were calculated as the number of incident cases divided by the total number of person-years (PYs) at risk. Using time-dependent Cox proportional hazard models we estimated hazard ratios (HRs) for the risk of developing gout in NIAD users (with and without insulin use) versus controls, by sex and by age (<50 years and ≥50 years). The age-sex adjusted hazard ratios (model 1) were first adjusted for smoking status, alcohol use, and postmenopausal status/oophorectomy (model 2). Thereafter, we adjusted for variables which theoretically may act as intermediates, i.e. BMI, eGFR, hypertension, and the use of thiazide diuretics, loop diuretics, statins, low dose aspirin (≤100mg), renal transplantation, ciclosporin, and tacrolimus (model 3). Model 3 was also repeated in men and women according to age (<50 years and ≥ 50 years).In addition, to further examine the gout risk in NIAD users, we performed subgroup analyses by HbA1c. We classified HbA1c values into the following categories in order to increase comparability with a previous study [14]: <6% (<42mmol/mol), 6-6.9% (42-52mmol/mol), 7-7.9% (53-63mmol/mol), 8-8.9% (64-74mmol/mol), ≥9% (≥75 mmol/mol) and missing. When covariates were missing, the cases were analysed in a separate "missing" group. All analyses were stratified by sex.

To explore the influence of misclassification, we performed a sensitivity analysis in which the case-definition of gout was restricted to those individuals with a diagnosis (READ code) of gout and at least one prescription for its treatment: colchicine, allopurinol, non-steroidal anti-inflammatory drug (NSAID), systemic glucocorticoid, probenecid, benzbromaron, febuxostat, rasburicase, sulfinpyrazone or pegloticase, within 14 days before or after a registration of a gout diagnosis. The earliest recording of the gout diagnosis or its treatment after the start of follow-up defined the outcome.

RESULTS

Figure 1 shows how the final study population was defined. Table 1 shows the baseline characteristics of the study population. Since NIAD users with insulin did not significantly differ from NIAD users without insulin (data not shown), we combined the results of these subgroups into a single NIAD users group. As a result, the cohort encompassed 221,117 NIAD users and a similar number of controls with a mean age of 60.4 ± 15.4 years, of whom 50.6% were women. The mean duration of follow-up was 4.3 years among NIAD users and 4.5 years among controls. On average, NIAD users had a higher BMI, suffered more frequently of hypertension, and more often had used statins. As compared with males, female NIAD users had a higher BMI, more often had an eGFR below 60 mL/min/1.73m, and more often had hypertension (supplementary Table 1 and 2). HbA1c concentrations were slightly lower in women at baseline. In addition, the differences in mean BMI and the proportion of individuals with an eGFR below 60 mL/min/1.73m² in NIAD users as compared with controls was larger in women.

Risk of gout in NIAD users as compared with controls

Table 2 shows that current NIAD use was associated with a 1.5-fold age- and sex-adjusted increased risk of gout (HR 1.48; 95% CI 1.41-1.54) (model 1). This result only slightly changed after adjustment for confounding variables in model 2, including smoking status, alcohol use, and postmenopausal status/oophorectomy (HR 1.41; 95%CI 1.35-1.47). However, after full statistical adjustment, current NIAD use was no longer associated with an increased risk, but with a 27% reduced risk of gout (HR 0.73; 95%CI 0.69-0.77) (model 3). The following confounders were mainly responsible for this shift: BMI, the use of statins, the use of loop diuretics, and a history of hypertension.

Sex modified the association between NIAD use and incident gout (p for interaction <0.001). Although both male and female users of NIADs had a higher age-adjusted risk of gout in comparison with their controls, the increased risk was more pronounced in women (HR 2.23 95%CI 2.07-2.41) than in men (HR 1.19 95%CI 1.13-1.26) (model 1). After full adjustments in model 3, male NIAD users had an almost 40% reduced risk of gout (HR 0.61; 95%CI 0.58-0.66), whereas in female NIAD users the risk disappeared (HR 1.01; 95%CI 0.92-1.11). After further stratification by age, female NIAD users aged <50 years (N=29,413) had a 40% reduced risk of developing gout (HR 0.59; 95%CI 0.46-0.77) in comparison with their controls. In contrast, there was no difference in gout risk between female NIAD users aged 50+ years (n=82,465) (HR 1.01; 95%CI 0.93-1.11) (N=82,465) and controls. Both male NIAD users aged <50 years (N=22,445) and 50+ years (N=86,794) had an almost 40% reduced risk of gout as compared to their controls (respectively; HR 0.61 (95% CI 0.52-0.71) and HR 0.62 (95% CI 0.58-0.66).

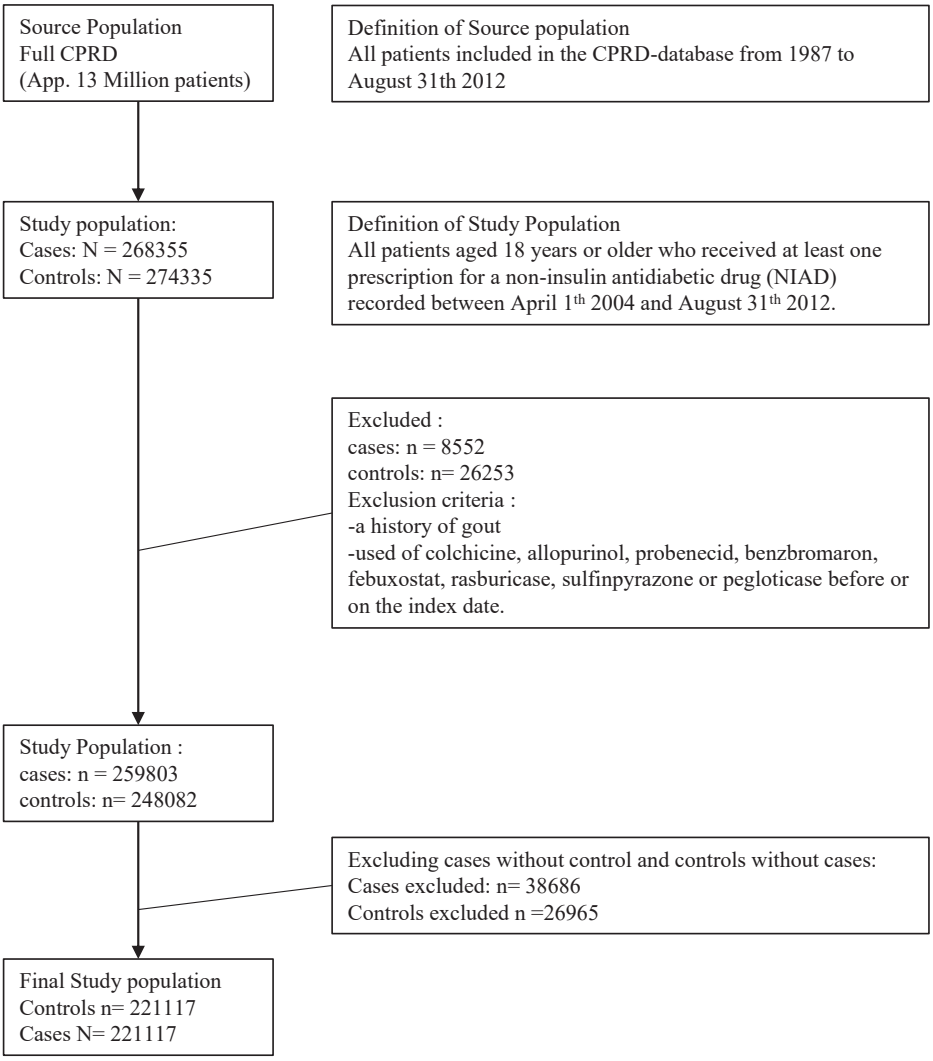

Figure 1. Flowchart Participants Selection

Risk of gout among NIAD users by HbA1c

Exploration of the influence of HbA1c on the risk of gout within NIAD users, showed an inverse association between higher HbA1c values and gout risk (Table 3). As compared to NIAD users with a HbA1c <6.0% (<42mmol/mol), the age- and sex-adjusted risk of gout was more than 20% reduced among those with recent HbA1c values of 8.0-8.9% (64-74mmol/mol) (HR 0.75; 95%CI 0.63-0.90) and even almost 40% reduced among those with recent HbA1c ≥9.0% (≥75 mmol/mol) (HR 0.61; 95%CI 0.51-0.74). Further adjustment in models 2 and 3 gave similar results.

Table 1. Baseline characteristics of NIAD-users and matched non-NIAD-users

Characteristics	NIAD-users N=221,117	Non-NIAD-users N=221,117
Mean follow-up time (years, SD)	4.3 ± 2.9	4.5 ± 2.8
Females	111,878 (50.6%)	111,878 (50.6%)
Age		
Mean age at index date (years, SD)	60.4 ± 15.4	60.4 ± 15.4
18-49 years	51,858 (23.5%)	51,858 (23.5%)
50-59 years	46,422 (21.0%)	46,422 (21.0%)
60-69 years	56,055 (25.4%)	56,055 (25.4%)
70+ years	66,782 (30.2%)	66,782 (30.2%)
BMI		
Mean BMI at index date (kg/m^2, SD)	31.2 ± 6.7	26.6 ± 5.1
<24.9 kg/m^2	32,887 (14.9%)	78,419 (35.5%)
25.0-29.9 kg/m^2	69.698 (31.5%)	74,742 (33.8%)
30.0-34.9 kg/m^2	59,343 (26.8%)	29,498 (13.3%)
≥35.0 kg/m^2	52,325 (23.7%)	11,902 (5.4%)
Missing	6,864 (3.1%)	26,556 (12.0%)
HbA1c		
<6.0 % (<42mmol/mol)	2,160 (1.0%)	1,542(0.7%)
6.0-6.9 % (42-52mmol/mol)	9,852(4.5%)	1,105 (0.5%)
7.0-7.9 % (53-63mmol/mol)	17,622 (8.0%)	126 (0.1%)
8.0-8.9 % (64-74mmol/mol)	10.557 (4.8%)	12 (0.0%)
≥9.0 % (≥75 mmol/mol)	16.781 (7.6%)	6 (0.0%)
Missing	164,145 (74.2%)	218,326 (98.7%)
eGFR		
≥90 mL/min/1.73m²	38,030 (17.2%)	12,055 (5.5%)
60-89 mL/min/1.73m²	84,450 (38.2%)	43,885 (19.8%)
30-59 mL/min/1.73m²	29,710 (13.4%)	16,504 (7.5%)
45-59 mL/min/1.73m²	22,224 (10.1%)	12,544 (5.7%)
30-45 mL/min/1.73m²	6,450 (2.9%)	3,093 (1.4%)
15-29 mL/min/1.73m²	1,254 (0.6%)	537 (0.2%)
<15 mL/min/1.73m²	188 (0.1%)	99 (0.0%)
Missing	67,485 (30.5%)	148,037 (66.9%)

Characteristics	NIAD-users N=221,117	Non-NIAD-users N=221,117
Smoking status		
Never	111,404 (50.4%)	116,514 (52.7%)
Current	45,797 (20.7%)	47,400 (21.4%)
Ex	62,287 (28.2%)	49,782 (22.5%)
Missing	1,629 (0.7%)	7,421 (3.4%)
Alcohol use		
No	65,912 (29.8%)	40,842 (18.5%)
Yes	141,204 (63.9%)	152,751 (69.1%)
Missing	14,001 (6.3%)	27,524 (12.4%)
History of diseases		
Hypertension	85,541 (38.7%)	46,022 (20.8%)
Renal failure acute	645 (0.3%)	248 (0.1%)
Renal failure chronic	1,741 (0.8%)	835 (0.4%)
Renal failure total	2,293 (1.0%)	1,040 (0.5%)
Postmenopausal status	18,704 (8.5%)	21,242 (9.6%)
Oophorectomy	5,129 (2.3%)	4,243 (1.9%)
Drug use six months before index date		
Thiazide diuretics	38,591 (17.5%)	26,411 (11.9%)
Loop diuretics	21,537 (9.7%)	10,074 (4.6%)
Low dose aspirin	96 (0.0%)	39 (0.0%)
Statins	93,729 (42.4%)	35,120 (15.9%)
Ciclosporine	68 (0.0%)	60 (0.0%)
Tacrolimus	178 (0.1%)	100 (0.0%)
Diabetes medication six months before index date		
Metformin	55,038 (24.9%)	n/a
Sulfonylureaderivatives	35,326 (16.0%)	n/a
Thiazolidinediones	8,260 (3.7%)	n/a
Insulin	18,089 (8.2%)	n/a
Incretins	523 (0.2%)	n/a
Meglitinides	721 (0.3%)	n/a

Table 2. Risk of gout in NIAD users compared with controls

	Number of gout events	Gout	Model 1	Model 2	Model 3	P-value for interaction
	N=8322[a]	IR (/1000 PY)	HR (95%CI)	HR (95%CI)	HR (95%CI)	
By NIAD use						
No NIAD use	3594	3.60	Reference	Reference	Reference	
Current NIAD use	4476	5.25	1.48 (1.41-1.54)	1.41 (1.35-1.47)	0.73 (0.69-0.77)	
By sex[b]						
Males	2630	5.99	1.19 (1.13-1.26)	1.13 (1.07-1.19)	0.61 (0.58-0.66)	
Females	1846	4.46	2.23 (2.07-2.41)	2.14 (1.98-2.31)	1.01 (0.92-1.11)	<0.001

Abbreviations: NIAD=non-insulin antidiabetic drug; IR=incidence rate; PY=person years; HR=hazard ratio; CI=confidence interval

Model 1: adjusted for sex and age

Model 2: model 1+ additionally adjusted for smoking status, alcohol use, and postmenopausal status/oophorectomy

Model 3: model 2 + additionally adjusted for BMI, eGFR, hypertension, renal transplantation, and use of low dose aspirin, statins, tacrolimus,
ciclosporin, loop diuretics, and thiazide diuretics

[a] total number of 252 gout events occurred in past NIAD users, who were part of the multivariate model in the analyses in the table

[b] reference group is no NIAD use with same sex

Subgroup analysis by sex, however, showed that higher HbA1c values were inversely associated with incident gout in male, but not in female NIAD users (p for interaction ≤0.01 for all categories). As compared to male NIAD users with HbA1c <6.0% (<42mmol/mol), the age-adjusted risk of gout was more than 30% reduced among those with HbA1c values of 8.0-8.9% (64-74mmol/mol) (HR 0.63; 95%CI 0.50-0.79) and even 50% reduced among those with HbA1c ≥9.0% (≥75 mmol/mol) (HR 0.50; 95%CI 0.39-0.63) (Table 3). Further adjustment in model 2 and 3 gave similar results.

Sensitivity analysis

After changing the case-definition of gout from a READ code for gout to a READ code for gout and a prescription for gout-specific medication, the total number of gout events decreased by approximately 25%. Notwithstanding, after full adjustments, NIAD-users still had a decreased risk of developing gout (HR 0.67; 95% CI 0.63-0.72) as compared with controls. Men had a 40% reduced risk of gout (HR 0.58; 95% CI 0.54-0.63) whereas this was not the case in women (HR 0.92; 95% CI 0.83-1.02). Results were similar for the subgroups analyses according to HbA1c.

Table 3. Risk of gout in NIAD users according to Hba1c stratified by sex

	Number of gout events	Gout	Model 1	Model 2	Model 3
	N=2602	IR (/1000 PY)	HR (95%CI)	HR (95%CI)	HR (95%CI)
By most recent Hba1c[a]					
Total population					
<6.0 % (<42mmol/mol)	201	6.71	Reference	Reference	Reference
6.0-6.9 % (42-52mmol/mol)	930	6.51	0.95 (0.81-1.10)	0.94 (0.80-1.09)	1.01 (0.87-1.18)
7.0-7.9 % (53-63mmol/mol)	728	5.48	0.82 (0.70-0.95)	0.81 (0.70-0.95)	0.88 (0.75-1.03)
8.0-8.9 % (64-74mmol/mol)	306	4.78	0.75 (0.63-0.90)	0.76 (0.64-0.91)	0.79 (0.66-0.94)
>9.0 % (≥75 mmol/mol)	245	3.52	0.61 (0.51-0.74)	0.62 (0.52-0.75)	0.62 (0.51-0.75)
Missing	2066	4.99	0.77 (0.66-0.90)	0.78 (0.66-0.90)	0.82 (0.70-0.96)
Males[b]					
<6.0 % (<42mmol/mol)	127	8.43	Reference	Reference	Reference
6.0-6.9 % (42-52mmol/mol)	560	7.72	0.89 (0.74-1.08)	0.89 (0.73-1.08)	0.96 (0.79-1.17)
7.0-7.9 % (53-63mmol/mol)	405	5.76	0.68 (0.56-0.83)	0.68 (0.56-0.83)	0.74 (0.61-0.91)
8.0-8.9 % (64-74mmol/mol)	174	4.99	0.63 (0.50-0.79)	0.64 (0.51-0.80)	0.67 (0.53-0.84)
>9.0 % (≥75 mmol/mol)	138	3.63	0.50 (0.39-0.63)	0.51 (0.40-0.65)	0.51 (0.40-0.66)
Missing	1226	5.89	0.72 (0.59-0.87)	0.73 (0.60-0.88)	0.77 (0.64-0.94)
Females[b]					
<6.0 % (<42mmol/mol)	74	4.98	Reference	Reference	Reference
6.0-6.9 % (42-52mmol/mol)	370	5.26	1.04 (0.81-1.34)	1.03 (0.81-1.33)	1.10 (0.86-1.41)
7.0-7.9 % (53-63mmol/mol)	323	5.17	1.06 (0.82-1.37)	1.06 (0.82-1.37)	1.14 (0.88-1.46)
8.0-8.9 % (64-74mmol/mol)	132	4.54	0.99 (0.75-1.32)	1.00 (0.75-1.33)	1.00 (0.75-1.33)
>9.0 % (≥75 mmol/mol)	107	3.38	0.83 (0.61-1.11)	0.83 (0.62-1.12)	0.81 (0.60-1.09)
Missing	840	4.08	0.86 (0.67-1.10)	0.87 (0.67-1.11)	0.91 (0.70-1.17)

Abbreviations: NIAD=non-insulin antidiabetic drug; IR=incidence rate; PY=person years; HR=hazard ratio; CI=confidence interval

Model 1: adjusted for sex and age

Model 2: model 1+ additionally adjusted for smoking status, alcohol use, and postmenopausal status/oophorectomy

Model 3: model 2 + additionally adjusted for BMI, eGFR, hypertension, renal transplantation, and use of insulin, low dose aspirin, statins, tacrolimus, ciclosporin, loop diuretics, and thiazide diuretics

a) in the year before the date of a new time interval

b) model not adjusted for sex

DISCUSSION

The relationship between type 2 diabetes and gout is complex. On the one hand, individuals with type 2 diabetes being at an increased risk of gout, possibly due to type 2 diabetes -associated comorbidities. On the other hand, the decreased inflammatory response and the uricosuric effect of glycosuria might protect against the development of gout. This study showed that individuals with type 2 diabetes, especially women, had a strongly increased risk to develop

gout as compared with controls. However, this risk can be fully attributed to classic risk factors for gout (high BMI, hypertension, reduced renal function). Interestingly, when taking into account these factors, male but not female individuals with type 2 diabetes were in fact at lower risk to develop gout as compared to controls. The protective effect of type 2 diabetes in men could be attributed to high HbA1c levels.

Our main finding of a 40% increased risk of gout in individuals with type 2 diabetes supports the formerly identified higher prevalence of gout in these individuals as compared with controls (2,3). Classic risk factors for gout, which may partly mediate the association between type 2 diabetes and gout, are likely responsible for this additional risk. When accounting for gout risk factors such as hypertension, we found that individuals with type 2 diabetes had a 27% lower risk to develop gout. This finding is in line with the THIN study (4). Note that comparison of our unadjusted results with the THIN study was hampered due to the direct adjustment for the number of GP visits in the latter. The number of GP visits is a very non-specific covariate and may reflect the presence or severity of comorbidities, such as hypertension and kidney failure. We want to emphasize that it is difficult to disentangle the role of variables in the association between type 2 diabetes and gout. Factors may theoretically act as a confounder, a mediator, or both. Careful assessment of the respective role may provide a more comprehensive picture of the association between type 2 diabetes and gout and can prevent confounded conclusions.

The role of increasing HbA1c concentrations to explain the reduced risk of gout in individuals with type 2 diabetes has been reported in two other studies (5, 16). The risk of gout was almost 40% reduced among individuals with type 2 diabetes having a HbA1c ≥ 9% (≥75 mmol/mol), as compared to those with HbA1c values below 6.0%. The inverse association between HbA1c and incident gout may be caused by the uricosuric effect of glycosuria, which occurs when the blood glucose level rise above ~10 mmol/l (HbA1c≈ 8%) (11). Osmotic diuresis and/or higher filtration rate, induced by glycosuria, may therefore play an important role (17). An alternative mechanism relates to a newly discovered urate transporter, i.e. hUAT (18). hUAT can be activated by sugars and could, at least partially, explain low uric acid concentrations in the presence of high glucose concentrations. However, the level of evidence for a role of hUAT in the renal urate transport is still weak.

Of interest are our sex-stratified analyses of the association between type 2 diabetes and HbA1c on the one hand and incident gout on the other. First, we showed that the increased risk of gout was more pronounced in women than in men. In the present study, females with type 2 diabetes had a higher prevalence of classic risk factors for gout as compared with their male counterparts. Also, the risk difference between individuals with type 2 diabetes and controls with regard to gout risk factors such as BMI and the proportion of individuals with an eGFR<60 ml/min/1.73m2, was greater in women than it was in men. Less favourable CVD risk profiles in

female than in male individuals with type 2 diabetes have been identified by prior studies (19-21). Second, we showed that after adjustment for classic risk factors, the risk for gout between women with type 2 diabetes compared to controls disappeared while the risk of gout in men became lower. Interestingly, further stratification for age (<50 years and ≥ 50 years), revealed that women younger than 50 years were also at lower risk of gout compared to women older than 50 years while such difference was not found in men. The decreased risk in men compared to women may be explained by a sex difference in the association between high HbA1c and incident gout in individuals with type 2 diabetes; a significant association between high HbA1c and a decreased risk of gout in men, but no association in women. It is unclear why HbA1c was only associated with a decreased gout risk in men and women younger than 50 years. A possible hypothesis for this sex difference is a different effect of glucose on uric acid reabsorption in the kidney in men and women. The effect of sex on the association between HbA1c and incident gout clearly needs further exploration. The difference between women younger or older than 50 years old might be related to the menopausal status which might influence directly or indirectly the risk of gout. The menopausal status might also influence the risk of gout (22).

Our study had several strengths. First, the findings of this study are likely to be generalizable to the general population as it was performed in a large UK general practice database. Second, a cohort design was used, which is the best observational design for determining the incidence of a certain condition. Third, we used data from 2004 onwards. HbA1c and eGFR recordings have improved dramatically since 2004, because of GP´s incentives for routinely recording these data under the QOF. Finally, a validated algorithm (READ codes) for identifying a first-time diagnosis of gout was used (14). Our study had also several limitations. Despite a substantial number of missing values at baseline, HbA1c was regularly recorded for the majority of the individuals with type 2 diabetes over time. A detection bias may have occurred because persons with type 2 diabetes having higher HbA1c values may more often visit their GP as compared to those who are well-controlled. This could increase the likelihood of being diagnosed with gout. However, we found that in individuals with high HbA1c levels the risk of gout is actually lower. Furthermore, we included only persons with type 2 diabetes who were treated with NIADs or insulin and therefore our results are not applicable to individuals with type 2 diabetes who are not treated with NIADs or insulin. Another limitation is the fact that postmenopausal status is probably under recorded in CPRD as reflected by the small proportion in table 1. This may have led to residual confounding. In the same line, individuals with type 2 diabetes have lower numbers of missing values for possible confounders such as alcohol consumption, smoking status and BMI due to their regular contact with GPs.

In conclusion, our data show that individuals with type 2 diabetes are at an increased risk of gout, and that this association is stronger in women. The increased risk was not caused by diabetes itself, but by the presence of comorbidities such as hypertension and reduced renal

function, which may counterbalance the risk reducing effect of HbA1c in individuals with type 2 diabetes. Health care professionals treating individuals with diabetes should be knowledgeable about diagnosis and treatment of gout, especially in patients with well controlled diabetes. Although it is still heavily debated whether gout or hyperuricemia are independent risk factors for cardiovascular disease and mortality[23], such evidence might even change the treatment approach towards a more aggressive use of uric acid lowering drugs in patients with diabetes.

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7

Obstructive sleep apnea and the risk of gout: a population-based case-control study

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ABSTRACT

Background

Patients with Obstructive Sleep Apnea(OSA) might be at risk of gout because of pathophysiological mechanisms that can lead to hyperuricemia and eventually gout or because of shared risk factors between both diseases. The objective of the present study was to investigate the risk of gout in patients with OSA.

Methods

A population-based case-control study using the UK Clinical Practice Research Datalink GOLD including all patients aged 40 years and older with a first diagnosis of gout between 1987-2014. Gout cases were matched by year of birth, sex and practice to non-gout controls. Conditional logistic regression estimated the risk of gout with an earlier diagnosis of OSA. Analyses were adjusted for lifestyle factors, comorbidities and recent drug use.

Results

111,509 cases were matched with 210,241 controls. Patients with OSA were at increased risk of gout (OR 1.86;95%CI (1.71-2.02). However, this association disappeared (OR 1.05;95%CI 0.96-1.16) after adjustment for smoking status, body mass index (BMI), alcohol use, a history of heart failure, diabetes mellitus, renal function, and recent use of diuretics and other medications. Among females with OSA and patients with OSA associated with heart failure, renal impairment or higher BMI, the risk of gout was however still increased when compared to the total control population.

Conclusion

This study showed that the observed association between OSA and gout disappeared after adjustment.

INTRODUCTION

Gout is the most common inflammatory arthritis (1), affecting up to 1-2% of adults, and leads to disability and reduced quality of life (2). Gout is characterised by the deposition of monosodium urate (MSU) crystals in synovial fluids and other tissues. Individuals suffering from gout often have a complex profile of comorbidities, including cardiovascular disease, diabetes mellitus, and kidney disease (3). One of the comorbidities in gout that has received more attention over past years is Obstructive Sleep Apnea (OSA) (4). Various underlying mechanisms may explain an association between gout and OSA. First, OSA-induced hypoxemia causes a rise in adenosine triphosphate (ATP) degradation which eventually increases purine concentrations and their end product uric acid (5). Second, hypercapnia and acidosis caused by OSA could influence the likelihood of MSU precipitation (6). Third, excretion of lactic acid, generated during the hypoxic episodes in OSA, could result in a higher renal reabsorption of uric acid (7).

Alternatively, the relationship could also be explained by shared risk factors of gout and OSA, such as age, obesity, metabolic syndrome, renal impairment and heart failure (8).

Two prospective studies in large United Kingdom (UK) primary care databases have demonstrated a 1.5-fold increased risk of developing gout among patients with OSA (4, 9) with the overall risk peaking one to two years after OSA diagnosis (9). While both papers statistically adjusted their analyses for body mass index (BMI), type 2 diabetes mellitus, ischaemic heart disease, hypertension, the use of diuretics of an unspecified class and alcohol consumption, renal impairment was either ignored or considerably under-recorded (4). Under-recording could be explained by selecting only medical diagnoses of chronic kidney disease (CKD), not taking >30 million records of estimated glomerular filtration (eGFR) rates into consideration (that are available as of 2018) (4). As CKD is a well-known risk factor for gout (10, 11), adequate statistical adjustment for this risk factor is important. Furthermore, both studies ignored the presence of heart failure, which is associated with both gout (12) and with sleep disorders, especially OSA (13).

The objective of the present study was to investigate the risk of gout in patients with OSA, while accounting for all relevant potential confounders, including CKD and heart failure.

METHODS

Data source

Data for the present study were obtained from the Clinical Practice Research Datalink (CPRD) in the UK, previously known as the General Practice Research Database (http://www.cprd.com).

CPRD contains the computerized medical records of approximately 13 million patients under care of general practitioners (GPs) in the UK, representing 6.9% of the total UK population (14). Practices contribute to CPRD only if their data quality meets research standards. Since 1987, data recorded in the CPRD include demographic information, prescription details, lifestyle parameters, clinical events, preventive care provided and specialist referrals. CPRD has been extensively validated (15) and has been previously used to study gout (16).

Study population

We conducted a population-based case-control study (fig.1). The cases consisted of all patients aged 40 years and older with a first diagnosis of gout during the period of valid data collection (from 1 January 1987 to 30 June 2014). Each case with gout was identified using READ codes (17). READ codes are a set of clinical codes used in primary care in the UK for the registration of clinical diagnosis, processes of care (tests, screening, symptoms, patient administration etc.), and medication. . Each case with gout was matched by year of birth, sex, and practice to up to two randomly selected controls without a diagnosis of gout using incidence density sampling (18). The date of the first recorded diagnosis of gout defined the index date for the cases and controls were assigned the same index date as their matched case. Cases and controls with a history of exposure to colchicine and uric acid-lowering therapy (ULT) (allopurinol, febuxostat and/or uricosuric drugs) before the index date as well as their matched case or control were excluded.

Exposure and potential confounders

Clinical READ codes were used to determine OSA exposure. Cases and controls with a read code for OSA before the index date were classified as being exposed to OSA.

The following variables were considered as potential confounders and were assessed prior to the index date: smoking status, BMI, alcohol use, socioeconomic status, a history of hypertension, diabetes mellitus (as recorded by either a diagnostic code for diabetes mellitus or a history of prescription(s) for anti-diabetic treatment, British National Formulary Chapters 6.1.1 & 6.1.2), hypercholesterolemia, postmenopausal status / hysterectomy, acute myocardial infarction, stroke or heart failure. The use of the following medication was assessed in the six months before the index date: thiazide diuretics, loop diuretics, beta-blockers, calcium channel blockers, Angiotensin-Converting-Enzyme inhibitors (ACE-inhibitors), Angiotensin II Receptor Blockers (ARBs), low dose aspirin, statins, Non-Insulin AntiDiabetic Drugs (NIADDs), insulin or benzodiazepines. In addition, the most recent eGFR before the index date was assessed. Electronic lab test data were used to extract the eGFR. Furthermore, when only serum creatinine measurements were available, these were used to estimate the eGFR by use of the abbreviated MDRD formula ($186 \times (\text{serum creatinine} / 88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$). In addition, we identified diagnostic codes for stages of CKD. When there were multiple records on the

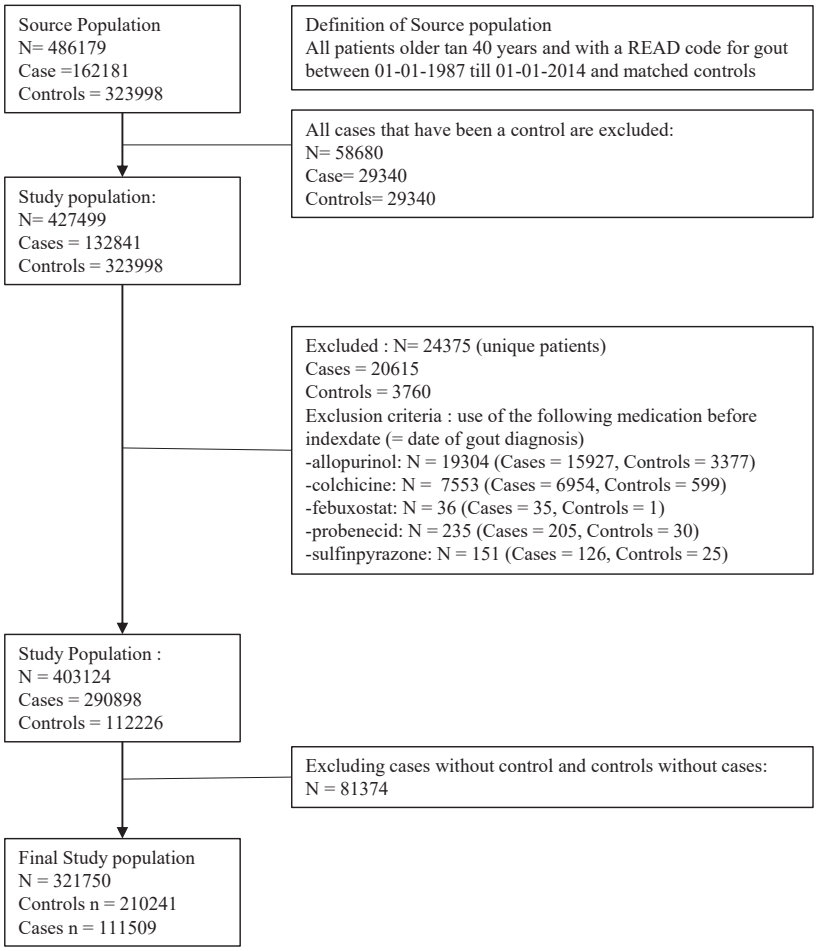

Figure 1 Flow chart Study Population

same day the best eGFR was chosen. The following categories were used to stratify for renal function by eGFR: CKD 1 (eGFR>90ml/min), CKD 2 (eGFR 60-89 ml/min), CKD 3 (eGFR 30-59 ml/min), CKD 4 (eGFR 15-29 ml/min) and CKD 5 (<15 ml/min).

Statistical analysis

Conditional logistic regression was used to estimate the risk of gout associated with a diagnosis of OSA (SAS version 9.4, PHREG procedure). In the analyses, risk was expressed as odds ratios (OR) with corresponding 95% confidence intervals (CIs). Potential confounders were included in the final model if they independently changed the beta-coefficient for OSA by at least 5% or when a consensus about inclusion existed within the team of researchers, supported by clinical evidence from the literature. Missing data of confounders such as BMI, smoking status, alcohol

use and renal function were treated as separate levels using dummy variables. OSA exposure was further stratified by gender, age categories and the presence of important confounders. Finally, we studied the effect of univariately adding the most important confounders to the main analyses as well as adjusting simultaneously for these confounders.

RESULTS

Table 1 shows the baseline characteristics of the study population. The cohort encompassed 111,509 gout cases and 210,241 controls with a mean age of 62 years (standard deviation SD 13.3), of whom 27% were female. Gout cases had a higher BMI than controls (29 kg/m^2 SD 5.3 in cases vs. 26.8 kg/m^2 SD 4.8 in controls). On average, gout cases used alcohol more often (73.9% in cases vs. 65.5% in controls) and were more likely to be ex-smokers than controls (34.2% cases vs. 26% controls). With regard to comorbidities, gout cases more often had a history of hypertension, heart failure or reduced renal function. They were also more frequently recent users of diuretics.

Patients with OSA had an almost doubled risk of gout (crude odds ratio [OR] 1.86; 95% Confidence Interval [CI] 1.71-2.02, Table 2). However, the effect disappeared after statistical adjustment for alcohol use, a history of diabetes mellitus, renal function, the most recently recorded eGFR measurement, heart failure, smoking status, BMI category and recent use of statins, beta-blockers, ACE-inhibitors, ARBs, calcium channel blockers, loop diuretics or thiazide diuretics (adjusted [adj.] OR 1.05; 95% CI 0.96-1.16). Further exploration identified that this shift was almost entirely explained by statistical adjustment for BMI, heart failure, recent use of diuretics and renal function (Table 3).

Stratification of the fully adjusted models (Table 2) revealed that as compared to patients without OSA, those with OSA and with a high BMI remained at an increased risk of gout (BMI 30-35 kg/m2: adj. OR 1.34; 95% CI 1.13-1.59; BMI >35 kg/m2: 1.56; 95% CI 1.33-1.83). Also, in comparison to patients without OSA, those with OSA and a history of heart failure had an almost doubled risk of gout (adj. OR 1.82; 95% CI 1.21-2.73). Furthermore, recent use of loop diuretics (adj. OR 1.73; 95% CI 1.33-2.26) and use of thiazide diuretics (adj. OR 1.85; 95% CI 1.47-2.33) was also associated with an increased risk of gout. The risk of gout among patients with OSA also further rose with increasing renal impairment (adj. OR 2.22; 95% CI 1.70-2.91 for CKD 3 (eGFR 30-59 ml/min), adj. OR 3.93; 95% CI 1.06-14.56 for CKD 4 (eGFR 15-29 ml/min) (Table 2). With regard to sex, women with OSA remained at an increased risk of gout in contrast to men with OSA (adj. OR 1.64; 95% CI 1.19-2.27).

Table 1 Baseline characteristics of cases and matched controls

Characteristics	Cases		Controls	
	N=111,509	%	N=210,241	%
No. of females	30,461	27.3	58,715	27.9
Age (mean, [SD], years)	62.8	13.3	62.5	13.3
By class				
18-49	22,050	19.8	43,103	20.5
49-59	25,927	23.3	50,025	23.8
60-69	26,127	23.4	48,424	23.0
≥70	37,405	33.5	68,689	32.7
Smoking status				
Never	46,790	42.0	86764	41.3
Current	16,077	14.4	39182	18.6
Ex	38,146	34.2	54754	26.0
Missing	10,496	9.4	29541	14.1
BMI, kg/m^2 (mean [SD])	29	5.3	26.8	4.8
By category				
<25	18,938	17.0	60497	28.8
25-30	39,492	35.4	65842	31.3
31-35	22,075	19.8	24369	11.6
>35	10,992	9.9	8925	4.2
Missing	20,012	17.9	50608	24.1
Alcohol				
No	16,639	14.9	34934	16.6
Yes	82,405	73.9	137605	65.5
Missing	12,465	11.2	37702	17.9
Renal function*				
CKD 1	8,382	7.5	18529	8.8
CKD 2	31,838	28.6	56712	27.0
CKD 3	19,230	17.2	16744	8.0
CKD 4	2,001	1.8	611	0.3
CKD 5	206	0.2	146	0.1
Missing	49,852	44.7	117499	55.9
History of comorbidities				
Acute myocardial infarction	7,858	7.0	8318	4.0
Stroke	5,952	5.3	8283	3.9
Heart failure	8,954	8.0	5213	2.5
Hypertension	49,488	44.4	54166	25.8
Diabetes mellitus	10,928	9.8	16058	7.6
Hypercholesterolemia	8,699	7.8	10891	5.2
OSA	1,094	1.0	1126	0.5
Use of diuretics$^+$				
Loop diuretics	17,976	16.1	11377	5.4
Thiazide diurectics	24,049	21.6	22012	10.5

Abbreviations: N=number, SD=standard deviation, BMI=Body Mass Index, CKD=Chronic Kidney disease, OSA= Obstructive Sleep Apnea

* CKD 1 (eGFR>90ml/min), CKD 2 (eGFR 60-89 ml/min), CKD 3 (eGFR 30-59 ml/min), CKD 4 (eGFR 15-29 ml/min), CKD 5 (<15 ml/min); $^+$ within six months prior to index date

Table 2 Risk of gout in patients with OSA, stratified by gender, age, BMI, CKD, co-morbidities and recent use of diuretics

Exposure	Cases		Controls		Crude	Fully adj.
	N=111,509	%	N=210,241	%	OR (CI)	OR
No OSA	110,415	99.0	209,115	99.5	Referent	Referent
OSA	1,094	0.98	1,126	0.54	1.86 (1.71-2.02)	1.05 (0.96-1.16)
By gender						
Male	953	0.85	1043	0.50	1.74 (1.59-1.90)	1.05 (0.95-1.16)
Female	141	0.13	83	0.04	3.36 (2.56-4.42)	1.64 (1.19-2.27)
By age class						
40-49 years	210	0.19	186	0.09	2.22 (1.82-2.71)	1.12(0.90-1.41)
50-59 years	346	0.31	392	0.19	1.73 (1.50-2.00)	0.96 (0.82-1.13)
60-69 years	316	0.28	341	0.16	1.75 (1.49-2.04)	1.02 (0.86-1.22)
>70 years	222	0.20	207	0.10	1.96 (1.62-2.37-1.13)	1.20 (0.96-1.50)
By BMI kg/m2[a]						
<25	40	0.04	113	0.05	0.67 (0.47-0.97)	0.67 (0.45-0.98)
25-29	224	0.20	305	0.15	1.38 (1.16-1.64)	1.15 (0.95-1.39)
30-34	318	0.29	325	0.15	1.88 (1.61-2.20)	1.34 (1.13-1.59)
≥35	456	0.41	322	0.15	2.74 (2.37-3.16)	1.56 (1.33-1.83)
Missing	56	0.05	61	0.03	1.78 (1.24-2.57)	1.91 (1.30-2.81)
By renal function[+,a]						
CKD 1	151	0.14	250	0.12	1.17 (0.95-1.43)	0.61 (0.49-0.76)
CKD 2	492	0.44	527	0.25	1.80 (1.59-2.03)	1.02 (0.89-1.17)
CKD 3	233	0.21	92	0.04	4.76 (3.72-6.07)	2.22 (1.70-2.91)
CKD 4	19	0.02	<5[#]	0.00	11.24 (3.34-37.81)	3.93 (1.06-14.56)
CKD 5	<5[#]	0.00	<5[#]	0.00	1.00 (0.09-11.03)	0.41 (0.04-4.59)
Missing	198	0.18	252	0.12	1.50 (1.24-1.81)	1.15 (0.94-1.40)
By history of comorbidities						
Acute myocardial infarction [a]						
Yes	80	0.07	73	0.03	2.08 (1.51-2.86)	0.80 (0.56-1.15)
No	1014	0.91	1053	0.50	1.84 (1.69-2.01)	1.07 (0.97-1.18)
Stroke [a]						
Yes	52	0.05	42	0.02	2.29 (1.52-2-3.44)	1.05 (0.66-1.66)
No	1042	0.93	1084	0.52	1.84 (1.69-2.01)-2.21)	1.05 (0.96-1.16)
Heart failure [a]						
Yes	128	0.11	37	0.02	6.61 (4.58-9.54)	1.82 (1.21-2.73)
No	966	0.87	1089	0.52	1.70 (1.56-1.85)	1.01 (0.92-1.12)
Diabetes mellitus [a]						
Yes	265	0.24	258	0.12	1.96 (1.65-2.33)	0.70 (0.58-0.85)
No	829	0.74	868	0.41	1.83 (1.66-2.01)	1.16 (1.05-1.30)

Exposure	Cases		Controls		Crude	Fully adj.
	N=111,509	%	N=210,241	%	OR (CI)	OR
Hypertension [a]						
Yes	659	0.59	466	0.22	2.71 (2.40-3.05)	1.14 (1.00-1.30)
No	435	0.39	660	0.31	1.27 (1.12-1.43)	0.98 (0.86-1.12)
Hypercholesterolemia [a]						
Yes	553	0.50	521	0.25	2.02 (1.79-2.28)	0.94 (0.82-1.08)
No	541	0.49	605	0.29	1.72 (1.53-1.94)	1.16 (1.02-1.32)
By use of loops diuretics*, [a]						
Yes	260	0.23	91	0.04	5.41 (4.26-6.87)	1.73 (1.33-2.26)
No	834	0.75	1035	0.49	1.55 (1.41-1.69)	1.01 (0.91-1.12)
By use of thiazide diuretics*, [a]						
Yes	274	0.25	129	0.06	4.10 (3.32-5.06)	1.85 (1.47-2.33)
No	820	0.74	997	0.47	1.58 (1.43-1.73)	0.93 (0.84-1.04)

Abbreviations: N=number, OR= Odds ratio, CI = Confidence interval, Fully adj.=Fully adjusted: adjusted for smoking status, alcohol use, body mass index, history of diabetes mellitus, heart failure and the most recently recorded eGFR measurement. In addition, we adjusted analyses for the use of statins, beta-blockers, Angiotensin-Converting-Enzyme inhibitors, Angiotensin II Receptor Blockers, calcium-channel blockers and thiazide or loop diuretics six months before the index date, OSA= Obstructive Sleep Apnea, CKD=Chronic Kidney disease, BMI=Body Mass Index.

+by the most recently recorded eGFR prior to index date. CKD 1 (estimated glomerular filtration rate [eGFR]>90ml/min), CKD 2 (eGFR 60-89 ml/min), CKD 3 (eGFR 30-59 ml/min), CKD 4 (eGFR 15-29 ml/min), CKD 5 (<15 ml/min). #According to the Independent Scientific Advisory Committee (ISAC) guidance on the content of protocols for research using CPRD data, no cell containing <5 cases or controls are reported. * within six months prior to index date. [a] the stratified analysis was not adjusted for the factor by which it was stratified.

Table 3 Statistical adjustment by body mass index, heart failure and renal function and the association between OSA and gout.

	Odds Ratio
Exposure	(95% Confidence Interval)
No OSA	**Reference**
OSA	
Crude odds ratio	1.86 (1.71-2.02)
Adjusted by	
BMI	1.22 (1.12-1.33)
Most recently recorded renal function	1.61 (1.47-1.75)
History of heart failure	1.77 (1.63-1.93)
Use of thiazide diuretics in previous 6 months	1.69 (1.55-1.85)
Use of loop diuretics in previous 6 months	1.59 (1.46-1.73)
All of the above mentioned confounders	1.05 (0.96-1.16)

Abbreviations: OSA= Obstructive sleep apnea, Renal Function=renal function was estimated by lab data containing the most recently recorded eGFR. When only creatinine values were available the MDRD formula was used to calculate the eGFR. In addition, read codes for the stage of chronic kidney disease were used to determine renal function. BMI= Body Mass Index

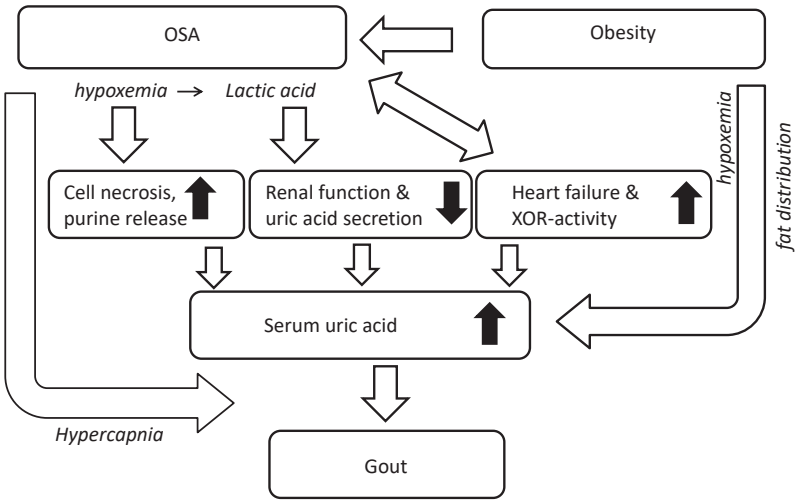

Figure 2 Possible biological pathways linking OSA to gout.

Compared to patients without OSA, patients with OSA and diabetes mellitus had a statistically significant decreased risk of gout (adj. OR 0.70; 95%CI 0.58-0.85). Patients with OSA and hypercholesterolemia, also had a 6% decreased risk, although not statistically significant (adj. OR 0.94; 95%CI 0.82-1.08).

DISCUSSION

Our study showed that the almost doubled risk of gout with OSA disappeared after adequate statistical adjustment for BMI, renal function, heart failure and recent use of diuretics. Notwithstanding, subgroups of patients with OSA, more specifically women and those with a history of heart failure, who had recently used diuretics, who had an eGFR between 59 and 15 ml/min or had a BMI above 30 kg/m2, still had a 2- to 4-fold increased risk of gout.

The absence of an overall association between OSA and gout in our study contrasts with a 1.5-fold increased risk of gout with OSA that was reported by two previous studies (4, 9) which had used the same data source i.e. the CPRD GOLD database, or a data source (THIN) that partly overlaps with CPRD (19). Table 3 shows that this difference can be largely explained by more comprehensive statistical adjustment for potential confounding in the current study, in particular for renal impairment as measured by eGFR and READ codes, and heart failure. When renal function declines, less uric acid is excreted which leads to hyperuricaemia and eventually gout (20) (Figure 2).

Heart failure is probably under-recorded in large observational studies based on diagnostic codes (21). Specific for the UK primary care databases, under-diagnosis might be related to manual coding of cardiology discharge letters by general practice staff. Therefore, we statistically adjusted our analyses for proxy indicators of heart failure such as recent use of diuretics. We also statistically adjusted our analysis for use of other medications that are commonly used for heart failure, including beta-blockers, ACE-inhibitors and ARBs (22).. Since (repeated) prescriptions, including outpatient prescriptions of cardiologists are generally issued by GPs every four weeks, this proxy indicator is likely to be better captured and therefore more likely to further reduce the level of residual confounding. Notwithstanding, heart failure remained associated with gout, even after full adjustment. The explanation might be found in insufficient adjustment for the known increased xanthine oxidoreductase (XOR) activity in the myocardium of the failing heart which leads to an elevation of uric acid (23) (Figure 2). Filippatos et al. demonstrated in their study that hyperuricemia was associated with poor outcomes in patients with heart failure without CKD but not in those with CKD, confirming the hypothesis that hyperuricemia in patients with heart failure could not only be explained by reduced uric acid excretion because of a poor kidney function (24). Otaki et al. also demonstrated an association between XOR activity and severity and clinical outcomes in patients with heart failure (25). Further evidence on a possible role of an increased XOR activity in heart failure can be found in studies demonstrating a beneficial effect of adding allopurinol to the treatment of patients with heart failure (26, 27). This beneficial effect was not demonstrated with benzbromarone, which is an uricosuric drug and therefore decreases the uric acid concentration by increasing its excretion (28). An alternative explanation for the independent contribution of heart failure to OSA can also be found in the influence of overnight rostral fluid shifts to the neck and lungs in patients with heart failure (29).

Unexpectedly, we found that the risk of gout with OSA disappeared in men after adjustment for confounders, while in women the risk remained elevated. It is widely accepted that females are at lower risk of gout, as a result of the uricosuric effect of oestrogens in women before menopause (30). However, even after menopause, the risk in females remains lower and we can therefore assume that other causal factors probably play a role. Sex differences have also been noted in the prevalence and severity of OSA, with women presenting with less severe and less prevalent disease. These differences are decreased after menopause (31). Differences in fat distribution, upper airway anatomy (in particular the posterior tongue region), mechanisms affecting ventilatory stability and sex hormones might explain the differences between men and women in OSA (31). In this line, it is of note that a study by Wang et al. showed that fat accumulation around the head measured by dual-energy X-ray absorptiometry was positively correlated with uric acid levels in women but not in men (32).

Obesity, which itself is associated with hypoxemia, is the main risk factor for the development of OSA. In more obese patients OSA is aggravated with more severe oxygen desaturations and hypoxemia, which may explain why the risk of gout remains high in the highest BMI category (33, 34) (Figure 2).

Our study had several limitations. First, there probably is underreporting of both OSA and gout, especially in the less severe cases (17, 35). Misclassification of both exposure (OSA) and our outcome of interest, i.e. gout, is probably random and may therefore lead to regression towards null (36). It could have masked a true association between OSA and gout among men. Among women, it could have masked a higher true association,. With respect to confounders, although our data regarding renal function were more accurate, renal function is not routinely measured in primary care. This could lead to residual confounding. Another limitation in our study, which is present in all epidemiological studies where researchers try to estimate the total causal effect of an exposure on an outcome of interest, is the problem of potential over-adjustment. Ideally, one should not control for factors which lie in the causal pathway between exposure and outcome, as it leads to a regression of the risk towards null (37). In our case, renal function could also be influenced by OSA itself as nocturnal hypoxemia present in OSA could accelerate decline in kidney function and therefore reduce uric acid excretion and induce or exacerbate hyperuricemia and eventually the risk of gout (38). Renal function would then be in the causal pathway from OSA to gout. Another limitation concerns the limited number of patients present in some subgroups, especially women and the groups with the worst CKD (CKD 4 and 5). The conclusion drawn from those results should therefore be interpreted with caution.

Our study had several strengths. First, we were able to include a large number of patients with gout and controls. The findings of this study are therefore likely to be generalizable to patients with gout and OSA in the total UK population (14). Second, the large amount of clinical information routinely and longitudinally collected in clinical practice, allowed us to statistically adjust for many potential confounders such as, age, sex, smoking status, alcohol use, kidney function, comorbidity and use of medication.

Conclusion/key message

This study showed that the observed association between OSA and gout disappeared after extensively adjusting for BMI, heart failure, diuretics and renal function, in particular. As the latest guidelines for the treatment of gout by the British Society of Rheumatology recommend to discuss the use of ULT with every patient, even after a first attack of gout, we think that it is important that physicians are aware that gout occurs more frequently in the presence of various comorbidities, among which OSA. Our study also emphasizes the importance of using frequently recorded electronic lab test data to assess renal function in UK primary care data, rather than READ codes.

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8

Summary and general discussion

In this part of the thesis, we first summarize results of the included studies followed by a general discussion of the main findings.

SUMMARY

Part 1 Management of gout

In **chapter 2**, we present the findings of a Cochrane systematic literature review on the efficacy and safety of non-selective non-steroidal inflammatory drugs (NSAIDs) compared to other NSAIDs or to other drug classes in the treatment of acute gout flares. We included 28 trials (3406 participants). The following comparisons were found: NSAIDs versus placebo (1 trial), NSAIDs versus other NSAIDs (13 trials), NSAIDs versus Cox-2 selective inhibitors (COXIBs) (6 trials), NSAIDs versus glucocorticoids (4 trials versus oral glucocorticoids, 1 trial versus im glucocorticoids), NSAIDs versus anti-IL1 (1 trial), NSAIDs versus acupuncture (1 trial), NSAIDs versus colchicine (1 trial). The outcome measures of interest in this review followed the recommendations by Outcome Measures in Rheumatology Clinical Trails (OMERACT) for trials in acute gout: pain, inflammation, function of the target joint and participant's assessment of response to treatment. Health-related Quality of Life (HRQoL) and safety were added as recommended by the Cochrane Collaboration. Overall, the certainty of the evidence was low to moderate. NSAIDs seemed to be more efficacious than placebo in the first 24hours after treatment initiation on pain (number of patients with at least 50% reduction in pain at 24 hours; risk ratio (RR) 2.7, 95% confidence interval (CI) 1.1 to 6.7) (low-certainty evidence). There was no difference regarding our other outcomes. Two trials comparing two NSAIDs (naproxen and etodolac) could be pooled and found no between-group differences with regards to efficacy (response to treatment success reported as proportions of people who considered themselves markedly improved at the end of treatment, RR 1.0, 95% CI 0.9 to 1.1) and safety (no withdrawals due to adverse events, number of adverse events: RR 1.7, 95% CI 0.4 to 7.9). NSAIDs seemed as efficacious as COXIBs with regards to pain (0-10 scale 0, no pain; mean difference (MD) 0.0, 95% CI -0.1 to 0.1) as well as with the other efficacy outcomes (moderate-certainty evidence). However, NSAIDs compared to COXIBs were associated with a higher risk for side effects, especially gastro-intestinal side effects (total number of adverse events: RR 1.9, 95% CI 1.4 to 2.8, gastro-intestinal adverse events: RR 2.4, 95% CI 1.6 to 3.4) (moderate-certainty evidence). NSAIDs seemed as efficacious as glucocorticoids for pain (0 to 100 VAS, 0= no pain, MD 0.1, 95% CI -2.7 to 3.0) (moderate-certainty evidence), but less efficacious for the reduction of swelling (4-point Likert Scale, 0= no inflammation; MD 0.3, 95% CI 0.1 to 0.6) (low-certainty evidence). Furthermore, NSAIDs seemed associated with more adverse events (RR 1.6, 95% CI 1.0 to 2.5) (moderate-certainty evidence). Low-certainty evidence based on a single trial suggested that NSAIDs are as efficacious as colchicine with regards to efficacy, but that NSAIDs are associated with less gastro-intestinal effects. A single trial, low-certainty evidence, suggested that anti-IL1 (canakinumab) is less efficacious than NSAIDs with regards to efficacy. There was no difference in safety.

In **chapter 3,** we compared outcomes of two different treatment strategies using a different target when treating gout: one being a strict uric acid-targeted (sUA ≤0.30 mmol/L) (sUA) strategy (126 patients) (UA-strategy), and the other adopting a patient-centered (PC) strategy (86 patients), emphasizing patient education and a shared decision about ULT based on sUA and patient satisfaction with gout control. In the UA-strategy 105/126 (83%) compared to 63/86 (74%) patients in the PC-strategy (p=0.10), reached the recommended threshold of ≤0.36 mmol/L; and 58/126 (46%) vs 31/86 (36%) patients were free of flares (p=0.15), after an average follow-up time of 11 months. In the UA-strategy 76/126 (60%) patients were on allopurinol monotherapy compared to 63/86 (73%) in the PC-strategy (p=0.05), at follow-up. In the UA-strategy, 21/126 (16.7%) patients vs 1/86 (1.2%) of PC-strategy were using combination therapy (p<0.001). The remaining patients were using benzbromarone or febuxostat monotherapy. The number of registered adverse events was not different (n=25 (20%) vs n=20 (23%), p=0.55). After adjustment for confounders, the UA-strategy remained only significantly associated with frequent therapy intensification.

In **Chapter 4,** we evaluated the construct validity of conventional radiography (XR) to measure structural joint damage (erosions) in patients with gout in a cross-sectional study. The XR of the feet were part of the baseline data of a cohort of patients with gout who were seen at the outpatient clinic of the Rheumatology Department of the Maastricht University Medical Centre+. XR were independently scored by two trained and experienced rheumatologists blinded for the characteristics and for each other's score. We used the gout-modified Sharp/van der Heijde (SvdH-mG) score. In total 81 out of a cohort of 126 patients (64.3%) had XR available and were included, 71 (71/81, 87.7%) had radiographic damage, of which 38 (46.9%) had erosions and 63 (77.8%) had joint space narrowing (JSN). Intraclass correlation coefficient for intra- and interobserver variability was above 0.75 which is considered excellent agreement We found that higher sUA levels, presence of tophi and longer disease duration were significantly associated with higher erosion scores on XR. Presence of tophi was also associated with more joint space narrowing. Patients with radiographic damage experienced worse physical function measured by the Health Assessment Questionnaire (HAQ) but not when measured with the physical component of the Short Form (36) Health Survey SF-36. Of note, the HAQ was initially developed to assess difficulties in physical activities of patients with arthritis, while the SF-36 is a generic instrument. We concluded that these findings support the construct validity of XR to assess joint damage in the feet, and reflect to some extent also the biological cumulative burden of monosodium uric acid crystals.

Part 2 Co-morbidities

In chapter 5, we conducted a systematic literature review of longitudinal observational studies to understand whether patient with hyperuricemia and/or a diagnosis of gout, should be routinely screen for comorbidities and CV risk factors. In total 66 studies were included, 34

studies with moderate or good quality were used for the summary. Six studies with a moderate risk of bias reported a higher risk of *hypertension* in patients with hyperuricemia (adjusted Hazard Ratio (HR) ranging across studies from 1.4 to 2.0), especially in women (adjusted HR ranging across studies from 1.7 to 1.9 vs adjusted HR ranging from 1.4 to 1.5 in men). For the risk of *diabetes*, the four included studies reported an increased risk which decreased after adjustment, adjusted HR ranging from 1.0 to 2.4. This risk of diabetes was higher in women (significant adjusted HR 2.0 vs not significant adjusted HR 1.24 in men). There were no studies exploring the risk of hypertension and diabetes in gout. Six trials investigated the risk of *stroke* in patients with hyperuricemia and one trial investigated the risk of stroke in patients with gout. Nor incidence nor mortality were increased. For *coronary heart disease* (CHD), 13 studies with a moderate risk of bias explored the risk of coronary heart diseases in patients with hyperuricemia and 8 studies the risk of CHD in patients with gout. In patients with hyperuricemia, the *incident risk for CHD* (7 studies) was not increased, *CHD-related mortality* (6 studies) was only increased in women (adjusted HR 1.3). In patient with gout, adjusted HR for *incident CHD* (4 studies) (adjusted HR ranging from 1.3 to 1.6) and for *CHD-related mortality* (4 studies) (adjusted HR ranging from 1.4 to 1.8) were only slightly increased. With regards to other comorbidities, two studies suggested an increased risk of *chronic kidney disease* (CKD) defined as End Stage Renal Disease (ESRD, start of replacement therapy such as dialysis or renal transplant) in hyperuricemia (average adjusted HR ranging from 2.1 to 5.8), particularly in females (average adjusted HR 5.8). There was no study on the risk of CKD mortality in hyperuricemia. In gout, the mortality due to CKD seemed to be elevated (adjusted HR 4.4) (one study), the incidence of ESRD was not increased (one study, HR not reported). The association with *cancer* was only poorly investigated in both hyperuricemia and gout. In conclusion, unlike the common opinion that patients with gout or hyperuricemia are at higher risk of developing cardiovascular diseases, the actual risk to develop CV disease is either rather weak (for hyper-uricemia) or poorly investigated (for gout). Women with hyperuricemia (less clear for gout) might have a higher risk of incidence of cardiovascular risk factors such as hypertension and diabetes as well as a higher incidence for and mortality from cardiovascular disease, especially coronary heart disease, when compared to males.

In **chapter 6**, we investigated the risk of gout in patients with T2DM (defined as persons on a noninsulin antidiabetic drug (NIAD) in a retrospective analysis of a cohort study, the UK Clinical Practice Research Datalink (CPRD) GOLD. In total, 221.117 T2DM patients were identified. Overall, patients with T2DM were at increased risk of gout (HR 1.48;95%CI 1.41-1.54), however this increased risk disappeared after adjustments for confounders (HR 1.01;95%CI 0.92-1.11). In adjusted analyses, we even found a reversed risk of gout in men with diabetes (HR 0.61;95%CI 0.58-0.66). We concluded that individuals with type 2 diabetes have an increased chance to develop gout. However, this is not due to diabetes itself, but to lifestyle and common comorbid conditions of the patients. Diabetes itself seems to decrease the risk of gout among men. In

Chapter 7, we investigated the risk of patients with OSA to develop gout, to understand if OSA contribute to gout, independently shared risk factors, in case-control study using the UK CPRD database. 111,509 cases with gout were matched with 210,241 controls. Patients with OSA were at increased risk of gout (OR 1.86;95%CI (1.71-2.02). However, this association disappeared (OR 1.05;95%CI 0.96-1.16) after adjustment for confounders. For females with OSA and for patients with OSA and heart failure, renal impairment or higher BMI, the risk of gout remained higher when compared to the total control population.

GENERAL DISCUSSION

Decision making is central in health care. For centuries, medical decisions were mainly grounded on experience and authority, and only to a small extent based on knowledge derived from observations. The second half of the 19th and the 20th century saw an exponential growth in knowledge in all medical areas, resulting in improved understanding of diseases and innovations in treatment with unprecedented efficacy. This questioned common clinical practice and stimulated research that was more directly useful for clinical care (1). In 1948, the first randomized controlled trial (RCT) was published " Streptomycin treatment of pulmonary tuberculosis", co-designed by Sir Austin Bradford Hill, the father medical statistics (2). With scientific evidence accumulating, multiple initiatives arose to bring more certainty to clinical decision making. The concept of Evidence-based medicine (EBM) was coined in 1991 and is defined as the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients (3). RCTs and synthesis of evidence from RCTs in systematic literature reviews are the backbone of EBM.

Today physicians are used to apply the concept of EBM in their clinical practice. However, after three decades of success, some limits of EBM have been identified, for even well-conducted trials can be inapplicable or inappropriate for the individual patient. A new source of evidence that arose the last few years, is the real-life data which were generally used in drug safety monitoring and now offers new opportunities for research in health care (4). Real-world data have been defined by the Food Drug Administration (FDA) as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (5).

Part 1. Gout management

1.1 Treatment of acute gout flares.

Multiple drugs from different classes are available to treat an acute flare of gout: from the oldest known drug, colchicine, to the recently developed IL-1 antagonists. In our Cochrane Review we

compared the efficacy and safety of different Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) against each other and of multiple drug classes, which are commonly used to treat acute gout flares, against NSAIDs. Despite a clear methodological guidance by the Cochrane Collaboration, the conduct of this systematic review was not without challenges(6). Essential in a Cochrane review is the choice of the outcome of interest in order to predefine and prioritize the different outcome domains and measures. The choice of the outcomes domains of our review was based on the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Core Domain Set for acute gout and comprised: pain, joint swelling, joint tenderness, patient global assessment of response to treatment (7). The choice of these outcome domains was the result of evidence from the literature combined with opinion of expert and patients. We further added Health-related Quality of life (HRQoL) and safety (withdrawal due to adverse events and total number of adverse events), as recommended by the Cochrane Collaboration(8). Not all studies reported on all the pre-selected outcomes, but a more important challenge was heterogeneity of measurement instruments, the time points for assessment of the outcomes and the reporting of the result. As an example, for our primary outcome self-reported pain, we agreed upon the proportion of participants who experienced pain relief of 50% or greater as the preferred reporting outcome measure for pain, as this would be the most clinically relevant outcome. If not present the following data were extracted: proportion of participants who achieved pain relief of 30% or greater or proportion of participants achieving a pain score below 30/100 on Visual Analogue Scale (VAS) or pain measured as a continuous outcome (e.g., VAS, numerical rating scales). Eventually, only one trial met our preferred outcome measure (proportion of participants who reported pain relief of 50% or more), most trials used mean change from baseline on a VAS or Likert Scale to report pain. Across trials pain was measured at different moments (varying from 6 hours up to 10 days), contributing to difficulties to compile the results.

Beside heterogeneity in outcome measurement and reporting, an important issue of this review, is generalizability. The evidence of this review arose from randomized controlled trials. A randomized controlled trial assures that both the intervention and the comparison group are the same, limiting the risk of confounding. By compiling all those trials together, we increase the sample size and therefore diminish the possibility of type 1 and type 2 errors. However, in most randomized controlled trials, patients with comorbidities are often excluded to minimize the risks associated with the use of drugs. As patients with gout often have co-morbidities such as renal insufficiency and cardiovascular diseases that might preclude the use of NSAIDs or influence the safety profile or even the efficacy of the NSAIDs, the exclusion of some comorbidities limits the generalizability of the results of the trials in patients with gout and co-morbidities. In this category of patients, the question remains whether the NSAIDs have the similar safety and efficacy as other drug classes.

A further issue for discussion concerns the choice of indomethacin as a comparator (17 trials out of 26), which was the case for 6 out of 13 NSAIDs versus other NSAIDs trials, 3 out of 5 glucocorticoids RCTs, all Cyclo-Oxygenase InhiBitors (COXIBs) studies and the anti-IL1 trial. In the Netherlands, the National Healthcare Institute advices to use other NSAIDs than indomethacin because of more frequent (serious) side effects of indomethacin (such as bone marrow suppression, gastric ulcer and hemorrhages, alteration of renal function) which are experienced more often with indomethacin than with other NSAIDs. The use of indomethacin as comparator could therefore have influenced the safety outcome results of our systematic reviews: there were less adverse events with COXIBs and glucocorticoids compared to NSAIDs), fewer withdrawals due to adverse events with COXIBs compared to NSAIDs. Manufacturers of innovative drugs are highly likely to choose a drug that has the most contrasting safety profile as comparator in RCTs, to increase the chance of a difference in safety of the new drug. Of note, our review could not find evidence for differences in efficacy nor safety between different kind of NSAIDs (two trials pooled, indomethacin not included in pooled analysis).

In view of the lack of generalizability, more efforts should be invested in pragmatic RCTs that are designed from a clinical practice perspective. A nice example of a pragmatic RCT is the recently published trial investigating the use of Anakinra (an IL-1 antagonist) as a treatment of gout flare (9). This non-inferiority randomized trial compared anakinra to naproxen, colchicine or prednisone, and left the choice of the comparator to the appreciation of the physician and the patient. This allowed the trial to be more connected to clinical reality. Treatment with Anakinra showed to be non-inferior to treatment as usual for treatment of acute gout flares. Last but not least in an era of patient centered care, the role of patient's preferences, that can differ from physician's, should also be taken into account if there is no clear safety or efficacy difference between the available drugs(10).

1.2 Treatment strategies

As of this moment, there is a debate regarding the preferred strategy when starting uric acid lowering treatment (ULT), and specifically about the benefits and harms when treating strictly towards a predefined threshold for serum uric acid (sUA). Rheumatology guidelines recommend to treat toward a sUA level <0.36 mmol/l or 0.30 mmol/L (11, 12), while guidelines from family medicine recommend to seek for a for patient acceptable frequency of gout flares and question the value of monitor serum UA and the need to reach a specific sUA target when managing gout(11, 13). To add evidence to this ongoing discussion about treat to a strict uric-acid target versus a less strict strategy that balances sUA against the patient needs and believes, we compared real-world data from two different clinics applying a different treatment strategy: one clinic followed a strict treat-to-target uric acid strategy and the other a patient-centred (PC (strategy), emphasizing patient education and a shared decision about urate-lowering therapy (ULT) based on serum uric acid and patient satisfaction with gout control. Although numerically

results were in favour of treating towards a stricter uric-acid target, there was no significant difference between the two strategies in reaching sUA threshold nor in number of patients free of flares

In this retrospective study, we used increasingly relevant real-world data. Although from a clinical perspective, real-world data are a useful source of evidence, much can be improved to increase the quality of such studies. In our study, data collection was not matched between both hospitals for variables other than uric acid, in particular number of flares and side effects were not entirely comparable. Furthermore, outcomes such as patient satisfaction with gout control, medication adherence or changes in lifestyle or cardiovascular risk were only assessed in one clinic. All those outcomes are important by themselves when evaluating real-world effects of a treatment strategy. More importantly, these variables are important when making sense of the data as they can confound, modify or mediate the effect of the strategy. Assessing treatment efficacy using pragmatic trials allows studying effect modification of the above factors (4). In addition, the influence of several other covariates that can be relevant in daily practice could be explored, such as level of self-efficacy, health literacy, presence of tophi or co-medication.

An insufficiently resolved but key aspect of outcome measurement in gout concerns the assessment of flares for use in trials or daily practice registers. In 2018, an approach to assess flare has been proposed and validated in a cross-sectional study but is only poorly known and used in clinical trials (14, 15). On a same line, valid measures are also lacking for several of the outcome domains and covariates mentioned above such as patient satisfaction with care and confidence in treatment, patient self-management skill, etc…. It could also be that the choice of the treatment strategy should be based on the presence of co-morbidities as different cluster studies have shown that there were different phenotypes in gout.

Overall, based on our research, we believe that there is insufficient evidence to prefer a strict treat-to-target approach above a patient centered approach. Presently, a RCT addressing this research question is being conducted in the Netherlands.

In order to enhance quality of gout management, there is a need to stimulate real world research and collect data in clinical practice in a way that will make it possible to use those data in research. Adopting the **FAIR** principles for scientific data management and stewardship will increase the usefulness of such efforts. The aim of those guiding principles, published in 2016, is to improve **F**indability, **A**ccessibility, **I**nteroperability and **R**euses of the collected data sets. An important barrier that should not be underestimated, is the behavioural changes that this will need from doctors and scientists with regards to collaboration and integration of data. Also, the creation of G-CAN (Gout and Crystal-Associated Network) has the potential to improve collaboration among researchers and stimulate this common data collection. The consensus

statement of the G-CAN regarding labels and definitions of disease states in gout is a first step in that direction(16).

1.3 Conventional Radiography

We demonstrated the validity of conventional radiography (XR) of the feet to assess joint damage in the feet. Intra-ossal tophi detected by XR of the feet might reflect the biological cumulative burden of monosodium uric acid crystals. XR could therefore play a role in assessing the disease stage: tophaceous versus non-tophaceous as well as disease severity. Assessing tophi on XR of the feet could also be used to assess 'remission' when the principle of treating to 'remission' has proven value with regards to function and health. This issue was not the specific objective of or study, and future research should focus on the role and value of assessing cumulative joint damage with XR in clinical practice:

1.4 Comorbidities

In 1945 by Le Roy Steinberg published the first longitudinal study on gout and the cardiovascular system with data of 46 gout patients (45 men) followed-up from one week to 40 years(17). He concluded that gout is not an etiological factor in hypertension, that there was no evidence that gout led to renal lithiasis nor to angina pectoris (17). To this date, the causality between uric acid or gout and CV disease remains an issue of debate and expands to many other comorbidities. The importance of this issue cannot be underestimated as causality would imply that hyperuricemia should be treated with ULT to reduce the risk of those comorbidities. In this thesis, we contributed to the discussion on causality between gout and co-morbid diseases, more specifically cardiovascular risk factors and diseases, type II diabetes and Obstructive Sleep Apnea (OSA).

While humans instinctively assume causal connections, scientific proof of causality is complex. In medicine, the randomized controlled trial (RCT) is the best available approach to designate causality and is the 'gold standard' to assess effectiveness and safety of drugs. Of note, in the 21st century also biological plausibility and safety have to be proven before being able to move towards an RCT. Due to its complexity and costs, an RCT is not always feasible, especially when outcomes/side effects can be expected in the long term only. Therefore, observational studies are often conducted to quantify the effect or side effects. However, such observational studies are difficult to interpret partly due to bias, especially when trying to assess causality. In 1965, Sir Bradford Hill established a group of 9 principles that can be used to establish causality in epidemiological studies (18): strength, consistency, specificity temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. When applying these Bradford Hill criteria to the relationship between gout/hyperuricaemia and gout, criteria plausibility and experimental evidence were sufficiently met. However, strength of association, consistency and temporality were the most questionable. Across different studies in our systematic review,

adjustment for cofounding drastically diminished the strength of the association, independent of the morbidity considered. Furthermore, the results of the different studies of our systematic literature review were not consistent. This could be partly explained by difference in the definitions used for hyperuricemia or gout or for the outcomes. Other possible explanations are follow-up time of the different studies included or the choice and measurement of confounders that were adjusted for. Finally, the temporal relation between gout and comorbidities is not straight ward. Although we only considered prospectively collected data in our observational study as well as for studies included in our SLR, it should be noted that the onset of the exposure (gout) and outcome (CV event/OSA and even CV risk factors such as hypertension) are difficult to establish. For example, hyperuricemia precedes gout, CV-events generally requires a longer period of, clinically unnoticed, atherosclerosis. Overall, when testing our findings against the classic Bradford Hill criteria for causality, there is insufficient support for causal relationship between hyperuricemia, gout and cardiovascular diseases OSA or diabetes. Although use of a set of criteria to determine causality is quite tempting, they are not without reservations and exceptions, as noted by Rothman and acknowledge by Sir Bradford Hill himself (19).

Nowadays, a novel method emerged to investigate causality: the Mendelian randomization. Mendelian randomization is a method based on the variation of genes in a population which is known to be random and thus independent of environmental confounders. This method is used to examine the causal effect of a modifiable exposure on a certain disease. Various Mendelian randomization studies have been published on uric acid and multiple comorbidities, none indicating causal relationships. No adequately powered mendelian randomization studies have been published on gout and co-morbidities (20). Mendelian randomization studies by genetically determined BMI, suggested a small but causal effect on sUA level and risk of gout, that was deemed insufficient to explain a large amount of the observed associations with co-morbidities (20). However, Mendelian randomization studies, might lack power and robustness to demonstrate causality when the proportion of trait variance explained by the genetic instruments is small (21). Furthermore, no Mendelian randomization studies have been performed to assess a possible causal role of inflammation in gout on comorbidities.

In conclusion, based on our research, evidence for a causal relationship between hyperuricemia/gout and cardiovascular co-morbidities, cardiovascular risk factors and OSA is lacking, despite pathophysiological plausibility. Our conclusion is further supported by an umbrella review by Li et al published after our review.

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Addendum

Impact Paragraph
Nederlandse samenvatting
Résumé en français
CV
List of publications
Dankwoord/Remerciements

IMPACT PARAGRAPH

This chapter focusses on the societal, scientific and clinical implications of this thesis. Overall, the thesis addressed research gaps in improving quality of care for patients with gout. First, we summarized the literature on efficacy of different types of drugs to treat acute gout flares. We did not find clear difference in efficacy nor safety. Second, we compared outcomes of applying different targets when starting urate-acid lowering therapy (ULT) in gout patients. We revealed that the strategy treating towards a specific serum Uric Acid (sUA) did not result in a statistically significant difference in the number of flares, nor in the achievement of the recommended sUA target, when compared to a patient-centred strategy integrating patient education and a shared decision about adjusting ULT. However, the treat to sUA strategy required more treatment intensifications. Finally, in a literature review and two new cohort studies, we could not find a causal relationship between gout and several co-morbidities. We mainly showed that the strong associations are explained by shared risk factors.

Impact for research

All manuscripts have been published in peer reviewed journals. In addition, our Cochrane Review "NSAIDs for acute gout" was summarized in JAMA as a Clinical Evidence Synopsis following its publication in the Cochrane Database of Systematic Reviews. Results of several articles were presented at national and international meetings.

In our strategy study, the treat to sUA strategy had no undisputable advantages. On this line, treat to target in gout, was selected as one of the 11 eleven knowledge gaps at the 2019 Research Agenda of the Dutch Society of Rheumatology. Recently, a consortium of three centers – including ours - initiated a randomized-controlled trial to assess cost-effectiveness, of a strict uric acid targeted strategy versus a symptom-controlled approach, hoping to finally resolve this issue.

Despite cumulating epidemiological evidence that hyperuricaemia and gout have no strong causal role in onset or course of comorbidities, some experimental studies cannot be ruled out that causal relationship exists in subgroups of patients. This is relevant, as it would have clinical implications when treating gout patients. Answering those research questions is complex, and requires the long-term data that allow matching of data of persons with treatment according to the different strategies (counterfactual principle). Research in this thesis highlights the need to establish a network of clinician researchers that collect data in clinical practice in an uniform manner, following the earlier mentioned FAIR principles. To improve the value of such real world data, researchers have to agree on a well-defined set of outcomes (benefits and harms) as well as contextual factors (e,g. comorbidities, treatments). Without correctly collected data and well-defined research questions, it is impossible to evaluate the value of care innovations.

Impact for patients

Patients rank control of flares as the most relevant outcome of treatment. Evidence from our studies can reassure patients that the available drug types for treating acute flares are equally effective and safe. Of note, physicians still have to account for comorbidities that preclude the use of certain drug classes in subgroups of patients. Our Cochrane review served as scientific support for the formulation of the European Alliance of Rheumatology recommendation for the treatment of acute gout flares. To prevent (recurrent) flares, urate-lowering therapy can be started or should at least be discussed after a first flare with each patient. In view of the ongoing discussion about the preferred target when treating with ULT, patients should be more involved in decisions to start and intensify ULT, so that the final treatment choice also accounts for the patients' preferences and values. For this reason, we have been developing a decision aid to support patients and their healthcare provider in choosing the best treatment option for the patient, based on available evidence.

Impact for Society

Our observational studies and literature review on comorbidity underlined the importance of lifestyle and especially obesity in the relationship between gout and comorbidity. The obesity epidemic faced by industrialized countries, demands a behavioral change of medical specialists involved in treatment of gout: instead of treating a disease, we should emphasize more the impact of lifestyle on health and motivate the patient to change its behavior. For this reason, we highlighted the role of lifestyle in our ULT decision aid and the ULT adherence tool we developed, as lifestyle – and especially weight control - is a corner stone in the management of our patients, not only to control gout flares but to prevent other comorbidities. Obesity should be recognized as a societal problem and should be addressed as such by policy makers and health insurers.

The association of gout and comorbidity but also the increasing number of patients with gout underlines the importance of collaboration between different specialties but also between the first- and the second-line. Policy makers should stimulate but also facilitate such collaborations between healthcare providers and various researchers.

NEDERLANDSE SAMENVATTING

Jicht is de meest voorkomende vorm van gewrichtsontsteking (artritis). De belangrijkste risicofactor voor jicht is de aanwezigheid van een verhoogd urinezuur concentratie in het bloed (hyperuricemie). Naast een verhoogd urinezuur, spelen leeftijd, geslacht maar ook leefstijlfactoren zoals overgewicht, een rol bij het ontstaan van jicht. Na een periode van verhoogd urinezuur, kan dat urinezuur neerslaan in de vorm van kristallen in de gewrichten, waar het een gewrichtsontsteking veroorzaakt. Het urinezuur kan ook in de huid of rondom de gewrichten neerslaan waar het jichtknobbels (tophi) veroorzaakt. Deze jichtknobbels kunnen op den duur gewrichtsschade veroorzaken. Deze schade kan op een röntgenfoto worden aangetoond. Röntgenfoto's zouden dus gebruikt kunnen worden om de schade als gevolg van jicht te meten.

Het klassieke beeld van jicht, welke in de Oudheid al zo beschreven was, is een plotse aanval van pijn, roodheid en zwelling van een gewricht, vaak de grote teen. Deze aanvallen kunnen door verschillende ontstekingsremmers worden behandeld. De meest gebruikte middelen zijn: colchicine, ontstekingsremmers zoals ibuprofen die NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) worden genoemd en corticosteroïden, zoals prednison. Daarnaast wordt geadviseerd om bij meerdere aanvallen per jaar te starten met urinezuurverlagende geneesmiddelen zoals allopurinol, benzbromaron of febuxostat. Er zijn verschillende opvattingen over hoe jichtpatiënten behandeld moeten worden: de meeste richtlijnen adviseren om urinezuurconcentratie in het bloed van 0.30 mmol/L of 0.36 mmol/L na te streven (afhankelijk van het land en/of de aanwezigheid van jichtknobbels en/of gewrichtsschade), anderen vinden dat het doel is om een voor patiënten aanvaardbare aantal aanvallen per jaar te streven.

Een ander belangrijk kenmerk van jicht is dat het vaak voorkomt met andere ziekten, zoals hypertensie, diabetes, hart- en vaatziekten, etc. De aanwezigheid van een of meerdere ziekten, ook co-morbiditeiten genoemd, resulteert in verschillende klinische vragen. Zo is nog onduidelijk welke medicamenteuze behandeling van acute jichtaanvallen de beste balans heeft tussen werkzaamheid en veiligheid bij mensen met een of meerdere co-morbiditeiten omdat sommige van deze co-morbiditeiten het gebruik van bepaalde geneesmiddelen belet. Een andere vraag is of er een oorzakelijk verband is tussen jicht of een verhoogd urinezuur en bepaalde co-morbiditeiten. Dit is belangrijk omdat dit zou betekenen dat door jicht en dus het verhoogd urinezuur te behandelen, men ook de co-morbiditeiten kan behandelen of in ieder geval hun invloed op het beloop van de gezondheid kan veranderen Zo een oorzakelijk verband zou betekenen dat bij aanwezigheid van jicht, patiënten gescreend moeten worden op de aanwezigheid van bepaalde co-morbiditeiten of dat je patiënten met bepaalde co-morbiditeiten sneller en/of strikter moet behandelen in geval van jicht of misschien zelfs al bij de aanwezigheid van een te hoog urinezuur.

De doelen van dit proefschrift zijn:

1. Het vergelijken van de werkzaamheid en veiligheid van NSAIDs met andere vormen van ontstekingsremmers in de behandeling van jichtaanvallen.
2. Het vergelijken van een behandelstrategie waarbij strikt naar het urinezuur wordt gekeken bij het starten van urinezuurverlagende therapie met een behandelstrategie waarbij beslissing om op te hogen samen met de patiënt wordt genomen.
3. De geldigheid van röntgenfoto's van de voeten om gewrichtsschade als gevolg van de jichtknobbels bij patiënten met jicht, te meten.
4. Het samenvatten van de bestaande literatuur over het oorzakelijk verband tussen hyperuricemie, jicht en verschillende co-morbiditeiten.
5. Het meten van het risico op jicht bij patiënten met suikerziekte (diabetes mellitus, DM) en obstructieve slaapapnoe (OSA).

We hebben in de gepubliceerde literatuur alle studies die de werkzaamheid en veiligheid van NSAIDs (soort ontstekingsremmer) vergeleken hebben met andere ontstekingsremmers opgezocht en samengevat. De ontstekingsremmers die vergeleken zijn, zijn:

- Cox-2 Inhibitors (COXIBs), een speciale groep NSAIDs die specifieker gericht is tegen de ontsteking en dus minder bijwerkingen veroorzaken
- prednison
- colchicine
- anti-Interleukine 1, een geneesmiddel gericht tegen een specifiek ontstekingseiwit die een belangrijke rol speelt bij een jichtaanval.

Om werkzaamheid te beoordelen hebben we gekeken of er verschillen waren in de afname van pijn in het ontstoken gewricht, de afname van zwelling van het ontstoken gewricht en de bewegingsbeperking van het ontstoken gewricht. Daarnaast hebben we ook gekeken naar de beoordeling van patiënten over het succes van de behandeling en de kwaliteit van leven die gerelateerd is aan gezondheid. Om veiligheid te beoordelen hebben we gekeken naar het aantal en de ernst van de bijwerkingen. Alle studies werden ook beoordeeld op hun wetenschappelijke kwaliteit. In totaal, hebben we 28 studies gevonden. Over het algemeen was de wetenschappelijke kwaliteit van de studies die we vonden matig tot slecht. We concludeerden dat het gebruik van conventionele NSAIDs effectiever was dan het gebruik van een placebo om pijn te verminderen. Conventionele NSAIDs zijn even effectief als Cox-2 Inhibitors. Zoals te verwachten gaven conventionele NSAIDs meer bijwerkingen vergeleken met COXIBs. Corticosteroïden lijken iets effectiever te zijn om de zwelling te verminderen dan NSAIDs maar hebben hetzelfde effect op pijn. Ook hier lijken NSAIDs meer bijwerkingen te geven.

Daarnaast hebben we twee behandelstrategieën om urinezuur te verlagen bij patiënten met jicht met elkaar vergeleken. Bij de eerste behandelstrategie werden patiënten behandeld met

urinezuurverlagende medicatie tot een urinezuurwaarde van ≤0.30 mmol/L werd bereikt in het bloed (UA-strategie). Bij de andere behandelstrategie werd – naast urinezuurverlagende medicatie - ook de nadruk gelegd op patiëntenvoorlichting en gezamenlijke besluitvorming over de urinezuur-verlagende medicatie (PC-strategie). Voor deze studie werden data gebruikt die in de klinische praktijk verzameld worden, zoals urinezuur concentratie in het bloed, het aantal aanvallen, etc…Hoewel er meer patienten in de UA-strategie waren die een voldoende laag urinezuurconcentratie (≤0.36 mmol/L) hadden en minder vaak aanvallen hadden na een jaar, waren deze verschillen niet stastistisch significant. Dit betekent dat we niet zeker zijn dat het verschil niet op toeval berust omdat het meten van uitkomsten en vertroebelende factoren in de dagelijkse praktijk een uitdaging vormen. Wel was het zo dat patiënten in de PC-strategie vaker meerdere geneesmiddelen nodig hadden om tot een laag urinezuurconcentratie te bereiken en vaker de arts bezochten. Er leek geen verschil in het aantal bijwerkingen dat genoteerd werd in het patietnendossier.

Gewrichtsschade is een belangrijke uitkomst in de praktijk omdat het een mate kan zijn voor de opstapeling van urinezuur in het lichaam en het een rol speelt bij de beslissing om met urinezuurverlagende middelen te starten. Ook zou het een rol kunnen gaan spelen bij het bepalen van remissie. Remissie betekent dat er geen ziekteverschijnselen meer van jicht zijn na een behandeling. We hebben dus gekeken naar de geldigheid van de jicht-gemodificeerde Sharp- van der Heijde score (SvdH-mG) om gewrichtschade op röntgenfoto's te meten onderzocht. De Sharp-van der Heijde score is een score die oorspronkelijk ontwikkeld is om de mate van gewrichtsschade bij patiënten met reumatoïde artritis (een andere vorm van gewrichtsontstekingsziekte) te meten en die aangepast is voor het meten van gewrichtschade bij jicht. Om de geldigheid van de methode na te gaan werd de relatie tussen bekende kenmerken van jicht (zoals urinezuur en jichtknobbels) en de mate van schade (score) op de röntgenfoto's van de voeten onderzocht. We hebben de röntgenfoto's van de voeten van 71 patiënten onderzocht. Bijna de helft had gewrichtsschade in de vorm van erosies. Een erosie is een onderbreking van het bot dat waarschijnlijk wijst op stapeling van urinezuurkristallen bij jicht. Ook vonden we een relatie tussen het aantal erosies en zowel de hoogte van urinezuurconcentratie, als de aanwezigheid van jichtknobbels en de duur van de ziekte. Patiënten met meer schade op de röntgenfoto's hadden ook meer moeite met lichamelijke activiteiten. We concludeerden dat de röntgenfoto's van de voeten gebruikt kunnen worden om gewrichtsschade ten gevolge van jicht te meten en mogelijk een rol kunnen gaan spelen bij het bepalen van remissie (afwezigheid van afwijkingen passend bij jicht).

Tenslotte, hebben we in dit proefschrift in diverse hoofdstukken de relatie onderzocht tussen een verhoogd urinezuur, jicht en co-morbiditeiten. We hebben gekeken of patiënten met een verhoogd urinezuur en patiënten met jicht vaker cardiovasculaire risicofactoren hebben, zoals hypertensie (hoge bloeddruk) en diabetes mellitus (suikerziekte) en of ze vaker co-morbiditeiten

hadden zoals hart- en vaatziekten en nierziekten. Hiervoor deden we een literatuurstudie. We vonden 66 studies, 34 hadden een matig tot goede wetenschappelijk kwaliteit en hebben we gebruikt om tot onze conclusies te komen. Alle studies beschreven het risico van patiënten met jicht of hyperuricemie om cardiovasculaire risicofactoren of hart-en vaatziekten of andere ziekten te krijgen. We hebben al deze risico's samengevoegd. We vonden een verhoogd risico op hypertensie en diabetes, bij patiënten met een hyperuricemie, vooral vrouwen met hyperuricemie. Wat betreft hartziekten, was er geen verhoogd risico op het krijgen van coronair lijden (ziekte waarbij de kransslagaders (slagaders van het hart) vernauwd zijn) bij patiënten met een hyperuricemie en het risico om te overlijden aan coronair lijden was enkel verhoogd bij vrouwen met een hyperuricemie. In geval van jicht was het risico op het krijgen van coronair lijden en om te overlijden aan coronair lijden slechts licht verhoogd. Het risico op het krijgen van chronisch nierfalen leek wel verhoogd bij patiënten met een hyperuricemie en bij patiënten met jicht lijkt het overlijden als gevolg van nierfalen verhoogd maar niet het ontwikkelen van nierfalen. We concludeerden op basis van deze data dat er geen verhoogd of enkel licht verhoogd risico is op het krijgen van hart en vaatziekten bij patiënten met hyperuricemie of jicht. Vrouwen met hyperuricemie lijken een hoger risico op cardiovasculair risicofactoren en om te overlijden aan hartziekte dan mannen met hyperuricemie.

Tenslotte, hebben we gekeken of er een omgekeerd verband bestaat, namelijk of patiënten met diabetes een hoger risico om jicht te krijgen. We vonden dat patiënten met diabetes een verhoogd risico hadden op net ontwikkelen jan jicht over een periode van xx jaatr. , maar dit verhoogd risico verdween als er in de analyses rekening werd gehouden met de aanwezigheid van onder andere co-morbiditeiten en het gewicht. We vonden zelfs dat mannen met diabetes een verlaagd risico hadden op het ontwikkelen van jicht had als je met deze factoren rekening hield. We concludeerden dus dat het risico op het krijgen van jicht bij patienten met diabetes verhoogd is maar dat dit veroorzaakt worden door andere factoren zoals co-morbiditeiten en overgewicht. Dezelfde analyses hebben we gedaan voor patienten met slaapapnoe. We vonden dat het risico op jicht enkel verhoogd was in patienten met slaapapnoe en hartfalen, nierfunctiestoornisen of overgewicht.

Samenvattend hebben we in dit proefschrift bijgedragen aan het behandelen van een acute jichtaanval, de discussie over welke behandelstrategie toegepast moet worden als patienten starten met urinezuurverlagende therapieen en het verband tussen jicht, hyperuricemie en co-morbiditeiten. In de toekomst zal, onder andere, verder gekeken moeten worden naar het verbeteren van de rol van de patiënten in hun eigen behandeling en de invloed van co-morbiditeiten op de behandeling.

RÉSUMÉ EN FRANÇAIS

La goutte est la forme la plus courante d'arthrite. Le facteur de risque le plus important pour la goutte est la présence d'une concentration accrue d'acide urique dans le sang (hyperuricémie). Outre un taux élevé d'acide urique, l'âge, le sexe et des facteurs liés au mode de vie, comme l'obésité, jouent un rôle dans le développement de la goutte. Cette hyperuricémie peut, après une certaine durée, provoquer une précipitation d'acide urique sous forme de cristaux dans les articulations, où ces cristaux provoquent une inflammation (arthrite). L'acide urique peut également précipiter dans la peau ou autour des articulations, où il provoque des nodules de cristaux d'urate (tophi). Ces nodules peuvent, à terme, provoquer des lésions articulaires. Ces lésions peuvent être mises en évidence sur une radiographie. Les radiographies pourraient donc être utilisées pour mesurer les dommages causés par la goutte.

L'image classique de la goutte, qui était déjà décrite dans l'Antiquité, est une crise soudaine de douleur, de rougeur et de gonflement d'une articulation, souvent le gros orteil. Ces crises peuvent être traitées par divers agents anti-inflammatoires. Les médicaments les plus couramment utilisés sont : la colchicine, les anti-inflammatoires comme l'ibuprofène appelés AINS (anti-inflammatoires non stéroïdiens) et les corticostéroïdes, comme la cortisone. En outre, s'il y a plusieurs crises par an, il est recommandé de commencer à prendre des médicaments pour réduire le taux d'acide urique dans le sang, comme l'allopurinol, le benzbromarone ou le fébuxostat. Les avis divergent sur la manière dont les patients souffrant de goutte doivent être traités : la plupart des directives recommandent de viser une concentration d'acide urique dans le sang de 0,30 mmol/L ou 0,36 mmol/L (selon le pays et/ou la présence de nodules de goutte et/ou de lésions articulaires), d'autres pensent que l'objectif est d'avoir un nombre acceptable de crises par an pour les patients.

Une autre caractéristique importante de la goutte est qu'elle survient souvent en même temps que d'autres maladies, comme l'hypertension, le diabète, les maladies cardiovasculaires, etc. La présence d'une ou plusieurs de ces maladies, également appelées comorbidités, entraîne des questions cliniques différentes. Par exemple, on ne sait toujours pas quel traitement médicamenteux lors de crises de goutte aiguës présente le meilleur équilibre entre efficacité et sécurité chez les personnes présentant une ou plusieurs comorbidités, car certaines de ces comorbidités empêchent l'utilisation de certains médicaments. Une autre question est de savoir s'il existe une relation de cause à effet entre la goutte ou un taux élevé d'acide urique et certaines comorbidités. Un lien de causalité signifierait qu'en traitant la goutte et donc l'augmentation de l'acide urique, on pourrait également traiter les comorbidités ou du moins modifier leur influence sur l'évolution de la santé. Un lien de causalité signifierait qu'en présence de la goutte, les patients devraient être dépistés pour la présence de certaines comorbidités ou que les patients présentant certaines comorbidités devraient être traités plus rapidement et/

ou plus strictement en cas de goutte ou peut-être même en présence d'un taux d'acide urique élevé.

Les objectifs de cette thèse sont :

1. Comparer l'efficacité et la sécurité des AINS avec d'autres formes de médicaments anti-inflammatoires dans le traitement des crises de goutte.
2. Comparer une stratégie de traitement dans laquelle l'acide urique est strictement surveillé lors de l'instauration d'un traitement hypo-uricémiant avec une stratégie de traitement dans laquelle la décision d'augmenter est prise avec le patient.
3. La validité des radiographies du pied pour mesurer les dommages articulaires dus aux nodules de goutte chez les patients atteints de goutte.
4. Résumer la littérature existante sur la relation de cause à effet entre l'hyperuricémie, la goutte et diverses comorbidités.
5. Mesurer le risque de goutte chez les patients atteints de diabète et d'apnée obstructive du sommeil (AOS).

Nous avons recherché dans la littérature publiée toutes les études qui comparaient l'efficacité et la sécurité des anti-inflammatoires non stéroïdiens (AINS) avec d'autres anti-inflammatoires. Les anti-inflammatoires qui ont été comparés sont les suivants :

- Les inhibiteurs de la COX-2 (COXIBs), un groupe spécial d'AINS qui ciblent directement l'enzyme COX-2 qui joue un rôle dans l'inflammations, ils causent donc moins d'effets secondaires.
- la prednisolone (cortisone)
- la colchicine
- l'anti-Interleukine 1, un médicament qui cible une protéine inflammatoire spécifique ;

Pour évaluer l'efficacité des AINS, nous avons cherché à savoir s'il y avait des différences dans la réduction de la douleur dans l'articulation enflammée, la réduction du gonflement de l'articulation enflammée et la restriction des mouvements de l'articulation enflammée. Nous avons également examiné l'évaluation par les patients de la réussite du traitement et de la qualité de vie liée à leur santé. Pour évaluer la sécurité des AINS, nous avons examiné le nombre et la gravité des effets secondaires. Toutes les études ont également été évaluées quant à leur qualité scientifique. Au total, nous avons trouvé 28 études. En général, la qualité scientifique des études que nous avons trouvées était modérée à médiocre. Nous avons conclu que l'utilisation d'AINS classiques était plus efficace que l'utilisation d'un placebo pour réduire la douleur. Les AINS classiques sont aussi efficaces que les inhibiteurs de la Cox-2. Comme prévu, les AINS classiques ont produit plus d'effets secondaires que les COXIB. La cortisone semble être légèrement plus efficace pour réduire le gonflement que les AINS, mais a le même effet sur la douleur. Là encore, les AINS semblent avoir plus d'effets secondaires.

Nous avons également comparé deux stratégies de traitement pour réduire l'acide urique chez les patients atteints de goutte. Dans la première stratégie de traitement, les patients étaient traités par des médicaments abaissant le taux d'acide urique jusqu'à ce qu'un taux d'acide urique de ≤0,30 mmol/L soit atteint dans le sang (stratégie UA). L'autre stratégie de traitement - en plus des médicaments hypo-uricémiant - mettait également l'accent sur l'éducation du patient et la prise de décision partagée concernant les médicaments hypo-uricémiants (stratégie PC). Cette étude a utilisé des données recueillies dans la pratique clinique, telles que la concentration d'acide urique dans le sang, le nombre de crises, etc. Bien que davantage de patients de la stratégie UA aient eu une concentration d'acide urique suffisamment basse (≤0,36 mmol/L) et aient eu moins de crises après un an, ces différences n'étaient pas statistiquement significatives. Cela signifie que nous ne pouvons pas être sûrs que la différence ne soit pas due au hasard, car la mesure des résultats et des facteurs de confusion est difficile dans la pratique quotidienne. Cependant, les patients de la stratégie PC étaient plus susceptibles d'avoir besoin de plusieurs médicaments pour atteindre de faibles concentrations d'acide urique et étaient plus susceptibles de consulter un médecin. Il ne semble pas y avoir de différence dans le nombre d'événements indésirables enregistrés dans le dossier du patient.

L'atteinte articulaire est un résultat important dans la pratique car elle peut être une mesure de l'accumulation d'acide urique dans l'organisme et elle joue un rôle dans la décision de commencer un traitement hypo-uricémiant. Elle pourrait également jouer un rôle dans la détermination de la rémission. La rémission signifie que les symptômes de la goutte disparaissent après le traitement. Nous avons donc examiné la validité du score Sharp-van der Heijde modifié pour la goutte (SvdH-mG) pour mesurer les dommages articulaires sur les radiographies. Le score de Sharp-van der Heijde est un score qui a été développé à l'origine pour mesurer le degré d'atteinte des articulations chez les patients atteints de polyarthrite rhumatoïde (une autre forme d'arthrite). Celui-ci a été modifié pour pouvoir être utilisé dans la goutte. Pour vérifier la validité de la méthode, nous avons examiné la relation entre les caractéristiques connues de la goutte (telles que l'acide urique et les nodules de goutte) et le degré de dommage (score) sur les radiographies des pieds. Nous avons examiné les radiographies des pieds de 71 patients. Près de la moitié d'entre eux présentaient des lésions articulaires sous forme d'érosions. Une érosion est une lésion de l'os qui, dans la goutte, indique probablement une accumulation de cristaux d'acide urique. Nous avons également trouvé une relation entre le nombre d'érosions et le niveau de concentration d'acide urique, la présence de nodules de goutte et la durée de la maladie. Les patients présentant des dommages plus importants sur les radiographies avaient également plus de difficultés avec les activités physiques. Nous avons conclu que les radiographies des pieds peuvent être utilisées pour mesurer les dommages articulaires dus à la goutte et peuvent jouer un rôle dans la détermination de la rémission (absence d'anomalies associées à la goutte).

Enfin, dans cette thèse, nous avons examiné dans plusieurs chapitres la relation entre un taux d'acide urique élevé, la goutte et les comorbidités. Nous avons cherché à savoir si les patients présentant des taux élevés d'acide urique et les patients souffrant de goutte présentent plus souvent des facteurs de risque cardiovasculaire, tels que l'hypertension (pression artérielle élevée) et le diabète sucré (diabète), et s'ils ont plus souvent des comorbidités telles que des maladies cardiovasculaires et rénales. Pour cela, nous avons effectué une recherche dans la littérature scientifique. Nous avons trouvé 66 études, dont 34 de qualité scientifique moyenne à bonne, que nous avons utilisées pour tirer nos conclusions. Toutes les études ont décrit le risque que les patients souffrant de goutte ou d'hyperuricémie développent des facteurs de risque cardiovasculaire ou des maladies cardiovasculaires ou autres. Nous avons mis en commun tous ces risques. Nous avons constaté un risque accru d'hypertension et de diabète chez les patients atteints d'hyperuricémie, en particulier chez les femmes. En ce qui concerne les maladies cardiaques, il n'y avait pas d'augmentation du risque de maladie coronarienne (maladie dans laquelle les artères coronaires (artères du cœur) sont rétrécies) chez les patients atteints d'hyperuricémie, et le risque de mourir d'une maladie coronarienne n'était augmenté que chez les femmes atteintes d'hyperuricémie. En cas de goutte, le risque de développer une maladie coronarienne est plus élevé. Le risque de développer une insuffisance rénale chronique semble être accru chez les patients souffrant d'hyperuricémie et chez les patients souffrant de goutte, le décès dû à l'insuffisance rénale semble être accru mais pas le développement de l'insuffisance rénale. Nous avons conclu de ces données qu'il n'y a pas de risque accru ou seulement un risque légèrement accru de développer une maladie cardiovasculaire chez les patients souffrant d'hyperuricémie ou de goutte. Les femmes souffrant d'hyperuricémie semblent avoir un risque plus élevé de présenter des facteurs de risque cardiovasculaire et de mourir d'une maladie cardiaque que les hommes atteints d'hyperuricémie.

Enfin, nous avons cherché à savoir s'il existe une relation inverse, à savoir si les patients diabétiques ont un risque plus élevé de développer la goutte. Nous avons constaté que les patients diabétiques présentaient un risque accru de développer la goutte. Mais ce risque accru disparait lorsque la présence de comorbidités et le poids, entre autres, sont pris en compte dans les analyses. Nous avons même constaté que les hommes diabétiques présentaient un risque réduit de développer la goutte lorsque ces facteurs étaient pris en compte. Nous avons donc conclu que le risque de développer la goutte est accru chez les patients diabétiques, mais que cela est dû à d'autres facteurs tels que les comorbidités et le surpoids. Nous avons effectué les mêmes analyses pour les patients souffrant d'apnée du sommeil. Nous avons constaté que le risque de goutte n'était accru que chez les patients souffrant d'apnée obstructive du sommeil (AOS) et d'insuffisance cardiaque, d'insuffisance rénale ou d'obésité.

En résumé, cette thèse a contribué à la prise en charge de la crise de goutte aiguë, à la discussion sur la stratégie de traitement à appliquer lorsque les patients commencent à prendre des

médicaments réduisant l'acide urique et à la relation entre la goutte, l'hyperuricémie et les comorbidités. À l'avenir, d'autres recherches devront être menées, notamment pour améliorer le rôle des patients dans leur propre traitement et l'influence des comorbidités sur le traitement.

CURRICULUM VITAE

Caroline van Durme is geboren op 22 januari 1980, en opgegroeid in Luik. Na het behalen van haar algemeen secundair onderwijs diploma op de Onbevlekte Ontvangenis Humaniora te Tongeren, ging zij in 1998 geneeskunde studeren aan de Erasmus Universiteit Rotterdam. Ze behaalde haar artsendiploma in 2004.

In 2005 werkte ze als arts niet in opleiding tot specialist op de afdeling Interne Geneeskunde in het Oosterschelde Ziekenhuis in Goes (opleider dr. P. Leurs), eind 2005 begon ze aan haar vooropleiding Interne Geneeskunde in het Amphia Ziekenhuis in Breda (opleider: dr. C. van Guldener). In 2009 startte ze met haar vervolgopleiding Reumatologie (opleider: prof.dr. S. van der Linden) die ze afrondde in 2012. Tijdens haar vervolgopleiding, nam ze, onder begeleiding van prof.dr. R. Landewé, deel aan de 3E (Evidence, Expertise, Exchange) Initiative over jicht. Dit werd het begin van een groeiend interesse in het ziektebeeld wat uiteindelijk tot een promotietraject onder begeleiding van prof.dr. A. Boonen en em.prof.dr. F. de Vries heeft geleid.

Ze is als reumatoloog werkzaam gebleven in het Maastricht Universitair Medisch Centrum, daarnaast werkte ze eerst aan de Centre Hospitalier Universitaire de Liège die ze in 2015 verliet voor het Centre Hospitalier Chrétien, ook in Luik gelegen, waar ze met veel plezier spreekuur in het Frans kan doen.

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