About gout: Studying potential targets for improvement of care

Veenstra, F.

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Chapter 1

General introduction

Gout

Gout is a common inflammatory rheumatic disease. The typical presentation of gout is an acute painful inflammatory arthritis, better known as a gout flare[1]. A gout flare can be extremely painful and can be a burden in daily life. Without treatment a flare is usually self-limiting for one to two weeks[1]. The typical index joint for gout is the first metatarsophalangeal joint[2]. Ankle and other foot joints are also frequently affected[1]. Other joints can be affected, but involvement of the joints of the upper limbs is mostly seen in patients with severe, uncontrolled gout. If left untreated, advanced gout can develop, characterised by chronic arthritis in one or more joints and/or the development of tophi. Tophi are chalk-like subcutaneous nodules present amongst others in joints, tendons, olecranon bursae and auricles[1]. Severe and untreated tophaceous gout can eventually lead to damage of the joint and bone.

The most important risk factor for gout is a state of hyperuricemia, a chronically elevated serum urate (SU) level ≥ 0.42 mmol/l[1,3]. However, most people with hyperuricemia are asymptomatic and do not develop gout[1]. Gout often occurs with comorbidities as hypertension, cardiovascular disease, renal impairment and diabetes mellitus type 2[1]. Women with gout have a higher comorbidity burden compared to men[4-6].

The prevalence of gout is estimated between 0.7% and 3.9% in adults worldwide[7]. This number is increasing in developed countries[7]. In the Netherlands, the prevalence in 2021 was 4.5% for men and 1.7% for women[8,9]. Male to female ratio ranges between 2:1 & 4:1[7]. Prevalence of gout in men increases with age and plateaus at the age of 70 and older. In women the prevalence sharply increases after menopause[7,10].

During a gout flare a patient can feel disabled, not able to work, might need emergency care and in worst case needs to be hospitalised[1,11]. As the prevalence of gout is expected to increase further, due to among others the aging population, the burden of gout on healthcare costs is expected to rise accordingly[10]. In The Netherlands the estimated costs of hospital care for gout will increase with 24.2% to € 17.6 million from 2017 to 2030[10].

Diagnosis of gout

The diagnosis gout is often based on the clinical presentation of symptoms in patients. The presence of monosodium urate crystals in synovial fluid or tophi, as detected under polarisation microscope, is considered as the gold standard for the diagnosis[1]. However, in primary care settings joint fluid analysis under polarisation microscope is seldom possible. Therefore a diagnostic rule was developed and validated in primary care settings based on evaluation of clinical symptoms and signs excluding joint fluid analysis. This diagnostic rule can help quantify the risk of gout[12]. Furthermore, X-rays, ultrasound and dual-energy computed tomography (DECT) scan can be useful low impact imaging techniques in clinical practice to help in diagnosing gout in case synovial fluid aspiration is not possible or inconclusive[13-15]. For research purposes the European Alliance of Associations for Rheumatology (EULAR) and the American College for Rheumatology (ACR) classification criteria for gout are developed that have a high sensitivity (92%) and specificity (89%)[13].

Pharmacological treatment of gout

Short term management of a gout flare aims to rapidly reduce and resolve the burden of the flare. A short term treatment with either colchicine, a non-steroidal anti-inflammatory drugs (NSAID) (e.g. naproxen or ibuprofen), or glucocorticoids is the treatment of first choice[1]. In case of contra-indications or no effect of first line medication, treatment with IL-1 inhibitors, anakinra or canakinumab, should be considered.

The cornerstone of long-term management of gout is urate-lowering therapy (ULT). ULT aims to lower SU levels which eventually leads to dissolving the monosodium urate (MSU) deposits[1]. The long term usage of ULT leads to suppression of gout flares and dissolving of tophi and aims to prevent future joint damage[1,16-18]. Guidelines of the EULAR and ACR advise to escalate the dose of ULT until a target SU of < 0.36 mmol/l, or 0.30 mmol/l in case of severe gout, is reached[19,20]. As initiation of ULT can trigger gout flares, concomitant treatment with colchicine or NSAID's is advised for the first 3 to 6 months[1].

In clinical practice in the Netherlands the most commonly used ULTs are allopurinol, febuxostat and benzbromarone[21,22]. Both allopurinol and febuxostat are xanthine oxidase inhibitors, they inhibit the production of urate. Benzbromarone is a uricosuric drug, it promotes urate excretion in the kidney. Benzbromarone can be used as monotherapy but can also be used in combination with a xanthine oxidase inhibitor (both allopurinol and febuxostat).

Suboptimal gout treatment

Although gout is a treatable disease, the majority of gout patients does not reach the SU target and is therefore at greater risk for recurrent gout flares, tophi and joint damage[23-25]. There are several known psychological and social barriers on the level of both patients and physicians preventing patients to reach the treatment target in gout. Regarding patients, these include a negative stereotypical image of gout patients in society, medication non-adherence, and lack of knowledge on gout, including cause, consequences, and its treatment[26-28]. Barriers for physicians include lack of knowledge on gout and its treatment, suboptimal guideline adherence and an underestimation of long-term effects of gout[23,24,29].

A few studies have shown promising results to improve gout outcomes in patients. A nurse-led intervention consisting of intensified individual patient support, regular assessment of SU and ULT dose titration based on SU levels until target was reached, led to a higher adherence to ULT compared to usual care. The higher adherence to ULT eventually led to a higher percentage of patients who reached SU target in the intervention group. Furthermore, flare frequency and tophi improved substantially in the nurse-led care group. The intervention was cost effective as well[16]. Another feasibility study showed that patients who were given a self-testing urate meter, supported by the GoutSMART app, an app providing physicians advise on dose escalation of ULT, were more likely to reach SU target compared to usual care[30]. However, implementation strategies must be formed in each health care system to integrate these types of care.

Outline of the thesis

A possible opportunity to improve gout treatment outcomes is a more personalised therapeutical approach. Potential ways to achieve this might be a personalised medication strategy based on specific patient characteristics (sex, presence of comorbidities, use of comedication), or by using DECT imaging. Also, understanding which barriers, both patient and physician related, result in suboptimal treatment in gout patients can help us find opportunities for improvement, on which interventions can be developed. For instance, knowledge of the arguments on which patients decide to continue or not continue their ULT when they have achieved remission on can prove to be valuable information for physicians to use in shared decision making. Lastly, beliefs on ULT of patients and physicians might be an intervention target in improving gout management and guidelines adherence. These opportunities and barriers are studied in this thesis, a short rationale per study is described below.

Sex differences in response to ULT

In patients with gout a strong male predominance is present. Medication studies mostly include men and so far, limited data is published separately for women[31,32]. A Cochrane review was not able to present their intended sub-analyses on women due to lack of data in the included trials[31]. Within a retrospective analysis of 3 phase III trials only 226 out of 4101 included patients were women[32]. Men and women might experience different effects of the same medication[33]. Women excrete less uric acid compared to men[34-37]. This might indicate that uricosuric agents like benzbromarone could be more beneficial in women over xanthine oxidase inhibitors like allopurinol. Therefore, it is of interest to study possible between-sex differences in response to allopurinol and benzbromarone, as well as within sex differences in response to allopurinol and benzbromarone.

In Chapter 2 sex differences in response to allopurinol and benzbromarone are investigated using data of a retrospective cohort.

The role of metformin in gout

Gout patients often have comorbidities including diabetes mellitus type 2[1]. One of the most common medicines prescribed in patients with diabetes mellitus type 2 is metformin. A recent review showed that metformin might have complementary anti-inflammatory and urate lowering effects[38]. Metformin might therefore be the medicine of first choice for patients with gout and diabetes mellitus. However, these effects were found in small sample size studies[39,40] and the relevance for clinical practice is unknown. It is therefore important to examine whether the effect of metformin is relevant in the clinical context of patients with both gout and diabetes mellitus starting ULT.

In Chapter 3 the effect of metformin on the clinical outcomes and serum urate in gout patients with diabetes mellitus are studied, using data of a retrospective cohort.

Presence of MSU deposits on DECT scan in gout patients in remission

Radiological imaging can be a supportive tool in clinical decision making. A DECT scan can provide information on the presence, number, and volume of MSU deposits in the scanned area and this can be helpful in situations of diagnostic uncertainty. Previous research showed that

DECT scan results are helpful by making physicians more confident in their decision making regarding ULT initiation or discontinuation[41]. However, less is known about the usefulness of a DECT scan in patients in remission. One criterium in the preliminary gout remission criteria states that patients must be free of visible tophi[42]. However, deposition monosodium urate can be present internally and not visible during physical examination. It is of interest to know whether patients in clinical remission have MSU deposits assessed by a DECT scan and whether these deposits are related with other patient-, disease-, and treatment characteristics. Results might help in decision making when considering further treatment of patients in remission if shown that DECT scan results have prognostic value in these cases.

In Chapter 4 DECT scan results in patients with gout in clinical remission are described.

Patients' perspective on (dis)continuation of ULT

Currently, most gout guidelines in rheumatology advice to prescribe ULT, when indicated, lifelong in a Treat to Target (T2T) strategy[19,20]. In daily practice however, a large proportion of patients stop their therapy at some point in time. Like other rheumatic diseases gout patients in remission might be suitable for (temporarily) tapering or discontinuation of their ULT in a Treat to avoid Symptoms (T2S) strategy[43]. This is currently studied in a clinical trial (GO TEST Finale)[44]. Complementary to the clinical outcomes of the trial it is important to know the patients' perspective on continuation and discontinuation of ULT when in remission. Knowledge on facilitators and barriers of ULT (dis)continuation might help physicians and patients in the process of shared decision making when considering ULT (dis)continuation.

In Chapter 5 the factors reported by patients as being important in their decision making when having the choice for (dis)continuation of their ULT are described. Using a mixed methods study including interviews and a max-difference exercise.

Beliefs of rheumatologists and general practitioners on ULT

As stated above, current gout treatment is often suboptimal. A proportion of patients do not reach their treatment target, often due to non-adherence. Known barriers within physicians are lack of knowledge, non-adherence to guidelines and conflicting guidelines[23,24,29,46]. Less is known about the beliefs of physicians about ULT. Beliefs about ULT can possibly influence prescribing behaviour of physicians and also influence the beliefs of their patients[46]. It is therefore important to know these ULT beliefs and their influence on prescribing behaviour and their patients' beliefs, as it might be an intervention target in improving gout management.

In Chapter 6 the beliefs of rheumatologist and general practitioners about ULT and the associations of these beliefs with their prescribing behaviour, gout outcomes in patients and the beliefs of their patients are reported.

A general discussion on the results of this thesis and further implications for care and research will be provided in chapter 7.

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Chapter 2

Sex differences in response to allopurinol and benzbromarone in gout: a retrospective cohort study.

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Abstract

Objectives
Due to lower mean uric acid excretion in women compared to men, uricosuric agents might be preferred in women over xanthine oxidase (XO) inhibitors. We therefore investigated the differences in response to two different mode of action urate lowering therapies (ULT) within and between sexes.

Methods
This retrospective cohort study included patients with a clinical diagnosis of gout who started allopurinol and/or benzbromarone. Successful response to ULT, defined as reaching serum uric acid (sUA) target <0.36 mmol/l within six months after start of ULT, was compared between allopurinol and benzbromarone in women and men. Effect modification by sex on response differences was evaluated.

Results
Allopurinol was started in 255 women and 1045 men. Benzbromarone in 60 women and 205 men. After six months, the proportions of women reaching sUA target were 58.4% and 66.7% for allopurinol and benzbromarone (difference -8%, 95% CI -22% to 5%). The respective proportions in men were 61.0% and 75.6% (difference -15%, 95% CI -21% to -8%). Corrected for confounding, the odds ratio (OR) of reaching target on benzbromarone versus allopurinol within women was 0.91 (95% CI 0.47 to 1.75), and within men 1.55 (95% CI 1.04 to 2.32). Corrected for confounding, sex was not an effect modifier of the difference in allopurinol and benzbromarone response (OR 0.59, 95% CI 0.28 to 1.24).

Conclusion
This study did not demonstrate between sex differences regarding response to either a uricosuric agent or a XO inhibitor, negating different treatment choices by sex.

Introduction

Gout is a preferential male disease, with a male:female prevalence ratio of 3-4:1[1]. Given this distribution, less is known about gout in women, although the incidence of gout in women has doubled over the past two decades[2]. In recent years the attention for gout in women has increased. Studies show that the clinical manifestation of gout is different between women and men. For example, gout occurs in women at a higher age, is more frequently accompanied with comorbidities and women with gout use diuretics more frequently[3-5]. To our knowledge, there are few data on a possible difference in response to urate lowering therapy (ULT) between women and men. Medication studies mostly include men and no separate data for women are published, which precludes subgroup analyses[6,7]. However, this is a subject of interest, as women and men differ on many levels such as lifestyle and biological processes, which could influence the response to medication[8,9].

An important difference is that women with gout seem to have a lower mean uric acid excretion compared to men with gout[10-12]. Also, in a large cohort of patients, without gout, who suffered from renal stones, female patients showed a significantly lower uric acid excretion compared to male patients[13]. This, possibly more common, renal underexcretion of uric acid in women with gout leads to two hypotheses regarding response to ULT. Firstly, a better response to a uricosuric agent (benzbromarone) compared to a xanthine oxidase (XO) inhibitor (allopurinol) in female patients. Secondly, a relatively better response to a uricosuric agent compared to a XO inhibitor might be expected in female gout patients compared to male gout patients.

Therefore, in this retrospective cohort study in secondary rheumatology care, the differences in response to two different modes of action ULT within and between sexes, were investigated.

Methods

Study design

A retrospective cohort study was conducted in two rheumatology clinics, the Sint Maartenskliniek Nijmegen and Rijnstate Hospital Arnhem, the Netherlands. Data on patient-, disease- and treatment characteristics were collected from electronic health records. Approval from the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, 2018-4692) was obtained. Patient informed consent was sought according to Dutch law and the local rules of each participating center.

Participants

Patients, ≥18 years, with a clinical diagnosis of gout (according to 2015 ACR/EULAR gout classification criteria and/or clinical diagnosis by a rheumatologist[14]) who had a minimum follow-up of 6 months between January 2010 and September 2018, were ULT naive and started allopurinol and/or benzbromarone during follow-up were included in this cohort. ULT naive patients were selected to create a clear starting point. As allopurinol is the first-choice medication in the participating hospitals, patients who used benzbromarone were often switching from or adding benzbromarone to allopurinol during follow-up. If a patient had a treatment period on both ULT, both periods were included in the study. A treatment period was defined from start of ULT until discontinuation or end of follow up (either due to lost

to follow up or study end). Patients without any serum uric acid (sUA) measurements after initiation of ULT were excluded.

Outcomes measures

At baseline (moment of start of the ULT treatment period, either allopurinol or benzbromarone), patient- and disease characteristics were assessed. To measure difference in response, successful response to ULT was defined as reaching sUA target <0.36 mmol/l[15] within six months after start of ULT. Secondary outcomes were time to reach sUA target any time during follow-up after start of ULT, and ULT dose at time of reaching sUA target.

Statistical analyses

No formal sample size calculation was made as a convenient sample was used. All comparisons were made between sexes and between allopurinol and benzbromarone. Baseline differences were, depending on distribution, evaluated using two-sample t-test or Mann-Whitney U test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. The primary outcome for successful response to ULT treatment was presented as proportions, differences in proportions and 95% confidence interval (CI), evaluated by two sample proportion Z test. Using logistic regression, after univariate analysis of baseline characteristics, the multivariate model included correction for the confounders sUA baseline levels, baseline eGFR level and use of diuretics. Effect modification of sex on between drug response differences was analysed using an interaction term sex*ULT. Time to reach target (any time during follow-up) was analysed by Cox proportional hazard modelling with correction for sUA baseline levels. Here, also the interaction term for sex*ULT was tested for significance. Furthermore, the model included an interaction term for time*ULT to meet the proportional hazard assumption of stable hazard rate (HR) over time, with time being divided in the first 120 days after initiation ULT and period after 120 days, based on HR distribution over time. Finally, ULT dose at moment of reaching target was evaluated by linear regression corrected for sUA baseline levels, baseline eGFR levels and age. All analyses were done using cluster variance analyses to account for interdependency between groups, as patients could be included in both the allopurinol and benzbromarone treatment group. Analyses were conducted using STATA/IC v 13.1 and using complete case analysis.

Results

Demographics

In this cohort 1300 and 265 patient treatment periods were included in the allopurinol and benzbromarone group, respectively. Of the patients who started benzbromarone during follow up, 251 patients did so in addition to allopurinol (n=91) or switched from allopurinol (n=160), 14 patients were naive starters.

Clinical characteristics at time of start of ULT are described in Table 1. Women in both ULT treatment groups had a significantly higher mean age, more comorbidities, more frequent use of diuretics and higher baseline sUA, compared to men. Both women and men had a lower baseline level of sUA at the start of benzbromarone treatment compared to baseline level before start of allopurinol. Also, both women and men treated with benzbromarone had a lower eGFR renal function compared to allopurinol users.

Successful response to ULT

Within six months after start of ULT, the proportions of women who had reached target sUA were 58.4% and 66.7 % for allopurinol and benzbromarone, respectively (difference -8%, 95% CI -22% to 5%). The proportions in men were 61.0% and 76.1% in allopurinol and benzbromarone users, respectively (difference -15%, 95% CI -22% to -9%). The corrected odds ratio (OR) of response to benzbromarone versus allopurinol within women was 0.91 (95% CI 0.47 to 1.75), and within men 1.61 (95% CI 1.08 to 2.41). The corrected OR of response to allopurinol in women compared to men was 1.38 (95% CI 0.95 to 2.02), and the OR for benzbromarone response for women compared to men was 0.79 (95% CI 0.40 to 1.58). Corrected for confounding, sex was not an effect modifier of the difference in allopurinol and benzbromarone response (OR 0.57, 95% CI 0.27 to 1.20).

Table 1. Baseline patient and disease characteristics

	Allopurinol			Benzbromarone		
	Women (n =255)	Men (n = 1045)	p-value[a]	Women (n=60)	Men (n=205)	p-value[a]
Age (years), median (IQR[b])	74.9 (67.3-81.6)	63.7 (54.4-72.4)	<0.001	75.8 (67.5-81.9)	66.3 (57.6-75.5)	<0.001
Current alcohol use, n (%)	88 (34.5)	696 (66.7)	<0.001	18 (30)	133 (64.9)	<0.001
Comorbidities, n (%)						
Hypertension	176 (69.0)	496 (47.5)	<0.001	43 (71.7)	104 (50.7)	0.004
Renal impairment	95 (37.3)	195(18.7)	<0.001	25 (41.7)	48 (23.4)	0.005
Diabetes mellitus	93 (36.5)	204 (19.5)	<0.001	24 (40)	45 (22.0)	0.009
Diuretics use, n (%)	169 (66.3)	403 (38.6)	<0.001	45 (75)	99 (48.3)	<0.001
Renal function, eGFR (ml/min/1.73m2), median (IQR[b])	46 (34-60)	70 (57-87)	<0.001	38.5 (31.5-50.5)	65.5 (46.5-82)	<0.001
History or presence of tophi, n (%)	97 (38.0)	276 (26.4)	<0.001	29 (48.3)	75 (36.6)	0.101
Erosive, n (%)	41 (16.1)	188 (18.0)	0.472	10 (16.7)	48 (23.4)	0.266
Crystal proven gout, n (%)	190 (74.5)	734 (70.2)	0.177	46 (76.7)	144 (70.2)	0.331
Baseline serum uric acid (mmol/l), mean (SD)	0.56 (0.12)	0.52 (0.10)	<0.001	0.48 (0.14)	0.46 (0.13)	0.289
Follow-up time (days), median (IQR[b])	371 (163-657)	379 (194-652)	0.506	295.5 (70.5-614.5)	270 (95-565)	0.996

[a] P-values for categorical variables were calculated by chi-square analysis, for continuous variables the appropriate (non) parametric analysis was used based on Gaussian distribution.
[b] IQR = inter quartile range

Time to reach target 0.36 mmol/l (any time during follow-up)

Figure 1 shows the Kaplan Meier curves for time to reach target. During the first 120 day period, both women and men using benzbromarone reached target sUA faster compared to using allopurinol (HR 2.74, 95% CI 1.70 to 4.43 for women and HR 2.78, 95% CI 2.16 to 3.59 for men). The time to reach target sUA was not significantly different in women compared to men for both allopurinol and benzbromarone, HR 0.95 (95% CI 0.81 to 1.11) and 0.93 (95% CI 0.57 to 1.52), respectively.

For the period after 120 days, for both women and men the HRs were inversely lower for benzbromarone compared to allopurinol, HR 0.57 (95% CI 0.34 to 1.06) and HR 0.57 (95% CI 0.38 to 0.86) for women and men, respectively. Again, corrected for confounding, sex was not an effect modifier of the difference in time to reach target sUA to allopurinol and benzbromarone during follow up (HR 0.98, 95% CI 0.60 to 1.61).

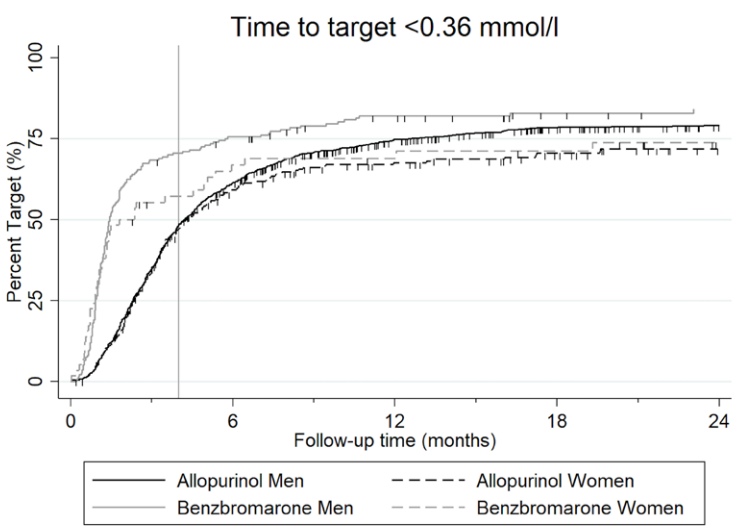

Figure 1: Kaplan–Meier curve for time to reach the target at any time during follow-up

ULT dose at target serum uric acid <0.36 mmol/l

The mean dose of allopurinol at time of reaching target sUA was lower in women compared to men, 216 mg and 271 mg, respectively (difference -55 mg, 95% CI -73 to -37). After correction, this difference remained statistically significant, -45 mg (95% CI -67 to -23). The mean dose of benzbromarone at target sUA was similar for women and men, 86 mg and 88 mg respectively (difference -2 mg, 95% -15 to 11). After correction, this difference was 4 mg (95% -9 to 18). For the subset of patients using benzbromarone in addition to allopurinol, mean doses were similar for women and men at time of reaching target sUA.

Discussion

Our results show that, although women have lower urate excretion than men[10,11], this does not translate in relevant differences between women and men in response rates to a XO inhibitor or a uricosuric drug. Therefore, the choice of urate lowering drug does not have to be based on the supposed sex differences.

Three interesting additional findings were observed. Firstly, the significantly shorter time to reach sUA target for benzbromarone compared to allopurinol. Secondly, more men on benzbromarone reached the sUA target within 6 months than on allopurinol. Thirdly, women reached the sUA target at a lower mean allopurinol dose than men.

Starting with the first observation, there are several explanations for the more swift response to benzbromarone. Firstly, this might be caused by lower baseline sUA before start of benzbromarone, because this treatment is often given as add-on to allopurinol. However, this was accounted for in the analyses. Also, benzbromarone is often started in a higher dose relative to its maximum dose than allopurinol. Another reason for this finding might be that benzbromarone is a more potent drug with regard to sUA lowering. Renal handling of uric acid plays a key role in the pathophysiology of gout in most patients[16]. As benzbromarone inhibits uric acid reabsorption, it provides a more logical pharmacological approach to hyperuricemia in most patients. When using this drug in clinical practice, this faster response should be taken into account when using this drug in a treatment strategy. The second finding follows the same reasoning as the first, with the statistically significant difference possibly only found in men because of the smaller sample of women in our cohort.

Regarding the third finding, the lower effective allopurinol dose in women can be caused by residual confounding, for example body mass index was not corrected due to a large number of missing values. Another reason might be different pharmacokinetic or -dynamic effects in women compared to men. Unfortunately, reliable subgroup analyses by sex are very rare in existing allopurinol studies because the proportion of women is often 10% or less. In a previous study looking at efficacy of febuxostat and allopurinol in women using data of three RCTs, only 226 women of the more than 4000 patients were included[7].

Strengths of this study include a relatively large population of both sexes, especially women and comparison between allopurinol and benzbromarone, a drug of which data is relatively scarce. Although the latter might also limit generalisability, our goal was to study comparison of an XO inhibitor with a uricosuric drug in light of the lower sUA excretion in women. Although benzbromarone is not used worldwide, newer uricosuric drugs have been developed and marketed recently. Considering the same working mechanism, we hypothesize that other uricosuric drugs might have similar effects as benzbromarone, making this a comparison of interest. Our cohort is considered a good representation of gout patients in secondary rheumatology care as the male:female ratio, patient- and disease characteristics and the differences in these characteristics between women and men are comparable to previous studies in secondary care[3-5]. Limitations of our study are firstly the retrospective design, mostly because of incomplete outcome assessment. This is also the reason why we chose to use sUA target instead of flare incidence, as the former is better assessed in this study. Also, nearly all patients who used benzbromarone previously failed allopurinol, and this might result in

biased efficacy estimates for benzbromarone and for the comparison between allopurinol and benzbromarone. However, this should not hamper comparison between sexes, also because we used cluster variance analyses to account for interdependency.

In conclusion, this study did not demonstrate between sex differences regarding response to either a uricosuric agent or a XO inhibitor, negating different treatment choices by sex.

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Chapter 3

Effect of metformin use on clinical outcomes and serum urate in gout patients with diabetes mellitus: a retrospective cohort study.

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Abstract

Objective
Gout and diabetes mellitus type 2 (DM) frequently co-exist. The pharmacological effects of metformin may include anti-inflammatory and urate lowering effects. The objective of this study was to test these effects in patients with gout starting uric acid lowering treatment (ULT) in secondary care.

Methods
Retrospective cohort study including patients with gout and DM starting ULT. Differences in the incidence density of gout flares, proportion of patients reaching target sUA in the first six months after starting ULT, and difference in mean allopurinol dose at sUA target were compared between users of metformin and users of other or no anti-diabetic drugs (control group). Correction for confounding was applied.

Results
A total of 307 patients were included, of whom 160 (52.1%) used metformin. The incidence of flares was 1.61 and 1.70 in the first six months for respectively the metformin group and control group. The incidence rate ratio for gout flares was not significant (0.95, 95% CI 0.78 to 1.14). At six months, 62.8% and 54.9% reached target sUA in the metformin and control group respectively, corrected odds ratio of 1.09 (95% CI 0.66 to 1.80). There was no difference in mean allopurinol dose at sUA target 266 mg for metformin users and 236 mg for the control group, difference 30 mg (95% CI -4.7 to 65.5).

Conclusions
In conclusion we could not confirm a clinically relevant anti-inflammatory or urate lowering effect of metformin in patients starting ULT treatment and receiving usual care flare prophylaxis.

Introduction

Gout is one of the most prevalent inflammatory rheumatic diseases worldwide and its prevalence is increasing[1]. Drug treatment of gout focuses on treating acute gout flares with anti-inflammatory drugs and reducing serum uric acid (sUA) levels with urate lowering therapy (ULT)[2]. Patients with gout often have comorbidities, like diabetes mellitus (DM) which is present in a quarter of patients with gout[3].

Metformin is the first-choice medication for patients with type 2 DM. Recently, it has been suggested that metformin also has anti-inflammatory effects in gout. These effects are mainly mediated by 5'Adenosine Monophosphate-activated Protein Kinase (AMPK) through different mechanisms[4]. A downstream target of AMPK is mammalian target of rapamycin (mTOR), which is one of the biological mechanisms involved in the process of inflammation[5,6]. Metformin has shown to reduce mTOR signalling in cells contacted with monosodium urate crystals[7]. A small retrospective study found that diabetic gout patients who used metformin and allopurinol had a significantly lower number of gout attacks, compared to diabetic gout patients who used allopurinol alone[7].

In addition to putative anti-inflammatory effects, metformin is believed to have a sUA lowering effect by improving insulin sensitivity. There are two proposed mechanisms for this effect. First, urinary uric acid clearance appears to increase with higher insulin sensitivity, leading to a decrease in sUA[8-10]. Second, insulin resistance causes lipolysis which leads to higher levels of free fatty acids, that are eventually metabolised into uric acid[9,11]. This effect was indeed found in a small controlled intervention study with metformin in patients with gout who did not use ULT[12].

In conclusion, there is some evidence on the anti-inflammatory and sUA lowering effects of metformin, but relevance for clinical practice is unknown[4]. We therefore conducted this retrospective cohort study, to examine whether metformin has a relevant anti-inflammatory and sUA-lowering effects in a clinical practice context.

Methods

Study design
We conducted a retrospective cohort study in secondary care setting. Eligible patients were included from the rheumatology departments of three hospitals (Sint Maartenskliniek, Rijnstate and Radboudumc) in The Netherlands. Data was collected from electronic health records, including patient-, disease- and treatment characteristics. The local ethics committee (Commissie Mensgebonden Onderzoek regio Arnhem-Nijmegen, 2018-4692) assessed the study and provided exemption, as ethical approval for this type of study is not required under Dutch law.

Participants
The retrospective cohort included patients ≥ 18 years with the diagnosis gout and at least six months follow-up. Eligible for this study were patients with a diagnosis of DM, a first prescription of ULT after inclusion in the cohort and at least six months follow-up after

initiation of ULT. Metformin use was operationalised as prescription coverage of metformin in any dose for at least 80% (145 days) of the six months follow-up. This cut-off point was chosen in line with the minimal use of 80% to be adherent to medication[13]. Patients without a minimum prescription coverage of 80% were excluded from the study. DM patients with other or no medication were placed in the control group.

Outcome measures

Anti-inflammatory effect

To evaluate the anti-inflammatory effect of metformin, we assessed the incidence rate ratio (IRR) of gout flares in the first six months after start of ULT. We defined gout flares as a clinical diagnosis of gouty arthritis by the physician, based on physical examination and laboratory inflammation parameters when available. In addition, flares in the period before consultation and reported by patients at the consultation were included as total of flares over the period between each consultation. Incidence of gout flares during the first six months of start ULT was calculated by attributing the number of flares reported during a consultation to the time since the last consultation. Total number of flares divided by sum of person-time was used to calculate the incidence density (ID) over the six month period of interest. When no information was reported, it was assumed that no flares had occurred.

Serum uric acid lowering effect

To evaluate the sUA lowering effect of metformin, we assessed sUA levels at baseline, sUA change over the first six months, the proportion of patients who reached sUA target (<0.36 mmol/l) within six months and the dose of allopurinol at sUA target. sUA levels were collected from their respective lab files in the electronic health record. The last known sUA measurement was used for the proportion of patients who reached target within six months, if there was no measurement available in the last month, but available within two weeks after six months, we used the latter one. Patients were excluded from these specific analyses if there were no sUA measurements available within this period. A sUA target of <0.36 mmol/l was used, following the EULAR/ACR guidelines[2]. Dose of ULT was collected from the medication sheets in the electronic health record.

Statistical analysis

No formal sample size calculation was made as a convenient sample was used. All comparisons were made for metformin users compared to the control group as reference. Baseline characteristics were evaluated using two-sample t-test or Mann-Whitney U test, depending on distribution for continuous variables. For categorical variables chi-square test or Fisher's exact test were used. To evaluate the difference in ID of flares in the first six months after starting ULT, Poisson regression was used. At first, in univariate analysis all variables which changed the estimate for more than 10% were selected as confounders in the full analysis. These included age, alcohol use, colchicine use, usage of anti-inflammatory drugs, prednisone use, renal impairment, sUA at baseline, crystal proven gout, insulin use and presence of tophi. Difference in sUA levels at baseline was evaluated by linear regression. The full linear model included renal impairment, diuretic use, insulin use and crystal proven gout as confounders. ULT dose at time of reaching target was evaluated by linear regression as well. There were no confounders included. A linear mixed model with random intercept was used to compare the course of sUA levels over the first six months. This model included sUA at baseline and renal impairment as confounders. To compare the number of patients that reached or did not reach sUA target levels, logistic regression was used. This model included renal impairment, use of diuretics and sUA at baseline as confounders. Statistical analyses were performed in STATA/IC v 13.1.

Results

Of a total of 1401 naive ULT starters with six months follow-up, 307 (22%) patients with DM were included in this study (table 1). The metformin group consisted of 160 patients and the control group 147. Metformin users were somewhat younger and had a better renal function compared to non-metformin users. Most patients started with allopurinol as ULT.

Gout flares

In the metformin group, the ID of gout flares in the first six months after starting ULT was 1.61 (95% CI 1.22 to 2.01), compared to 1.70 (95% CI 1.38 to 2.01) in the control group. The adjusted incidence rate ratio (IRR) was 0.95 (95% CI 0.78 – 1.14) (for unadjusted estimates see table 2).

SUA levels

Mean sUA levels at baseline were 0.54 mmol/l and 0.56 mmol/l, for the metformin group and control group, respectively. Adjusted linear regression showed that sUA levels at baseline did not differ between both groups (difference -0.02, 95% CI -0.04 to 0.01) (unadjusted estimates see table 2). Mean sUA levels at last known measurement before six months were 0.35 mmol/l and 0.38 mmol/l, for the metformin group and control group, respectively. As illustrated in Figure 1 we found no differences in change over six months in sUA levels between both groups (adjusted difference -0.01, 95% CI -0.02 to 0.01) (unadjusted estimates see table 2).

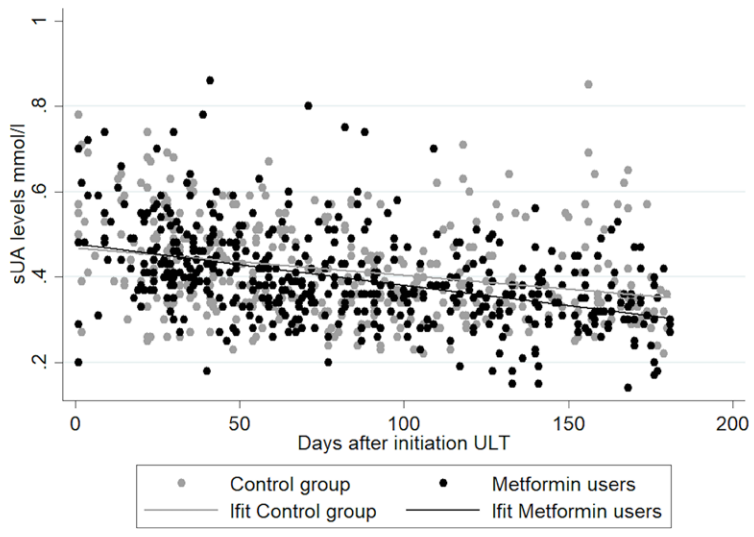

Figure 1: Change in sUA levels over the first six months after initiation ULT

*Lfit gives an indication of the decrease in sUA over time in both groups

Table 1: Baseline and disease characteristic

Baseline characteristics	Metformin group (n = 160)	Control group (n = 147)	P-value
Age (years) Median (IQR)	70.6 (65.1-77.2)	74.4 (66.7-79.6)	**0.0187**
Male gender (%)	114 (71.3)	104 (70.8)	0.923
BMI (kg/m^2) Median (IQR)*	30.1 (27.3-33.2)	31.2 (26.2-35.7)	0.8495
Alcohol use (%)	69 (43.1)	59 (40.1)	0.248
Comorbidities **			
Hypertension (%)	109 (68.1)	92 (62.6)	0.308
Hypercholesterolemia (%)	35 (21.9)	31 (21.1)	0.867
Kidney stones (%)	7 (4.4)	10 (6.8)	0.353
Renal impairment (%)	37 (23.1)	63 (42.9)	**0.000**
Serum uric acid baseline (mmol/l) Mean (+/- SD)	0.54 (+/- 0.12)	0.56 (0.12)	0.1339
Renal function, eGFR (ml/min/1.73m^2) Median (IQR)	60 (48-70)	50 (34-68)	**0.0008**
Medication			
Diuretics (%)	111 (69.4)	93 (63.3)	0.257
Insulin (%)***	32 (20)	39 (26.5)	0.175
Other oral diabetics (%)***	75 (46.9)	56 (38.1)	0.1194
Number of involved joints			0.396
Mono articular disease: 1 joint (%)	33 (20.8)	22 (15)	
Oligo articular disease: 2-4 joints (%)	77 (48.4)	79 (53.7)	
Poly articular disease: >4 joints (%)	49 (30.8)	46 (31.3)	
MTP-1 involved (%)	100 (70.4)	95 (74.8)	0.422
Tophi (%)	53 (33.1)	57 (38.8)	0.302
Crystal-proven gout (%)	117 (73.1)	119 (81)	0.104
Erosions (%)	26 (16.3)	30 (20.4)	0.346
ULT started Allopurinol (%) Benzbromarone (%) Febuxostat (%)	 156 (97.5) 4 (2.5) 0	 144 (98) 2 (1.4) 1 (0.7)	0.450
Start dose allopurinol (mg/day) Median (IQR)	100 (100-100)	100 (100-100)	0.3469
Colchicine use (%)	115 (71.9)	102 (69.4)	0.632

BMI = body mass index (kg/m^2), eGFR = estimated glomerular filtration rate (ml/min/1.73m^2), MTP = (metatarsophalangeal joint). ULT = urate lowering therapy.
Two-sample t-test or Mann-Whitney U test, depending on distribution for continuous variables. For categorical variables chi-square test or Fisher's exact test.
* > 50% of data is missing
** As stated in the electronic patient record
*** Some patients used both insulin and other oral diabetics

Target serum uric acid

Within the first six months, 62.8% of the metformin group had reached target sUA levels compared to 54.9% in the control group (adjusted odds ratio 1.09 (95% CI 0.66 – 1.80)) (unadjusted estimates see table 2). Mean daily dosages of allopurinol at target were 266 (+/- 121) and 236 (+/- 100) for the metformin group and control group, respectively. Linear regression showed no significant between group differences (difference 30mg/day, 95% CI -4.7 to 65.5).

Table 2: Uncorrected and corrected analyses per outcome measure

		Outcome	Confounders
Gout flares	Uncorrected	0.95 IRR (95% CI 0.80 – 1.13)	
	Corrected	0.95 IRR (95% CI 0.78 – 1.14)	Age, alcohol use, colchicine use, prednisone use, use anti-inflammatory drugs, renal impairment, sUA at baseline, crystal proven gout, presence of tophi and insulin use.
sUA levels baseline	Uncorrected	-0.02 mmol/l difference (95% CI -0.05 – 0.01)	
	Corrected	-0.02 mmol/l difference (95% CI -0.04 – 0.01)	Renal impairment, diuretic use, insulin use and crystal proven gout
sUA levels over 6 months	Uncorrected	-0.02 mmol/l difference (95% CI -0.04 – 0.00)	
	Corrected	-0.01 mmol/l difference (95% CI -0.02 – 0.01)	sUA at baseline and renal impairment
Reaching target sUA	Uncorrected	1.39 OR (95% CI 0.87 – 2.20)	
	Corrected	1.09 OR (95% CI 0.66 – 1.80)	Renal impairment, history of kidney stones sUA at baseline, insulin use and use of diuretics
Dose at target allopurinol	Uncorrected	30.4 mg difference (95% CI -4.7– 65.5)	

sUA = serum uric acid, IRR = Incidence rate ratio, OR = Odds ratio

Discussion

We did not observe a relevant anti-inflammatory or sUA lowering effect of metformin during the first six months after starting ULT in a real-world setting. Although these effects of metformin are supported by pharmacological and empirical evidence, several contextual factors can lead to a null effect when treating gout patients in a real-world setting.

Firstly, the anti-inflammatory effect of metformin might be too weak to have a clinically relevant contribution in gout treatment in a phase where strong anti-inflammatory treatments like colchicine are prescribed as prophylactic treatment[3]. Another explanation for the lack of difference in gout flares in this study is the effect of other possible variables that interfere with the proposed anti-inflammatory mechanism of metformin, for example state of diabetes regulation. Poorly controlled diabetes is described to decrease the risks of gout flares in some studies[14,15]. This suggested mechanism in diabetes mellitus might counteract the possible effect of metformin, however we did not have the data to correct for this possible mechanism.

The lack of sUA lowering effect of metformin might be driven by differences in study context and design. The study by Barskova et al[12] was a small intervention study with metformin in which the included patients did not use ULT. In our study all patients started ULT. Also, in our study only prevalent metformin users were included. It is therefore possible that through index event bias[16] our sample disproportionally included patients in whom metformin did not have a sUA lowering effect, or not enough to prevent the development of gout. However, index event bias would also reduce the proportion of DM patients and metformin users in our cohort, but with 22% DM patients of which 52% used metformin our cohort stays well within the expected ranges[3,17]. Furthermore, other anti-diabetic medication may have this sUA lowering effect in gout as well, thus resulting in a net null result. Whether this effect is unique for metformin has indeed not been tested. Of note, previous studies have shown that even drugs within the same class can have different off-target effects, for example in a study comparing losartan and irbesartan, only losartan showed a sUA lowering effect in patients with gout[18].

This retrospective study might have some general limitations, such as underreporting of gout flares and a possibility of double reported flares. However, firstly we assume that this would be the case in both groups and probably should not result in a biased between group difference, secondly our flare rate is comparable with other studies[19,20]. Also, we had no data on the type of DM. However, it is likely that most patients have type 2 DM since this accounts for 90 to 95% of all DM, and gout is mainly associated with type 2 DM[3,21]. Also, we had no data on the state of diabetes regulation, including HbA1c levels, which may interact with the risk of gout flares as well[14,15]. In the non-metformin group mean age was slightly higher and renal function lower, resulting in confounding by indication. However, our analyses were corrected for these differences when necessary.

Strengths of this study include the considerable sample size, resulting in adequate precision while excluding any relevant effect considering the confidence intervals, and correction for confounders. Due to the non-limiting inclusion criteria, multi-centre data collection and a prevalence of DM in the cohort within the expected range, the generalisability of the study

seems solid. Also, the uricosuric effect of metformin was assessed using different outcome measures, including correction for second order effects such as differences in ULT use.

In conclusion, although pharmacological effects of metformin probably include anti-inflammatory and urate lowering effects, we could not confirm a clinically relevant effect in patients starting ULT treatment and receiving usual care flare prophylaxis.

3

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Chapter 4

Presence and characteristics of MSU crystal depositions on dual-layer spectral computed tomography in gout patients in clinical remission.

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Abstract

Objectives

Objectives of this study are to determine the proportion of gout patients in remission who have monosodium urate (MSU) crystal depositions measured by dual-layer spectral computed tomography (dlSCT) and to examine characteristics of MSU positive and MSU negative patients.

Methods

This study was embedded in the GOut TrEatment STrategy Finale study, comparing a continued urate-lowering therapy (ULT) treat-to-target strategy with a treat-to-symptom ULT tapering to stop strategy in gout patients in clinical remission for at least 12 months. The proportion of patients with MSU crystal depositions, the number of MSU crystal depositions and (total) volume were calculated. Differences in characteristics between MSU positive and MSU negative patients were evaluated using Mann-Whitney U or Fisher's exact tests.

Results

Of 30 patients dlSCT scans were available, 17 patients had one or more MSU crystal depositions. Median (range) number of depositions and total volume were 4 (1 – 14) and 53.6mm^3 (0.6 mm^3 – 567.5 mm^3), respectively. Patients with MSU crystal depositions had a lower median renal function (71 ml/min/1.73m^2 (56 - 83) versus 88 ml/min/1.73m^2 (79 - 90) (p-value 0.002)), no other differences were found.

Conclusion

MSU crystal depositions are prevalent in ULT using gout patients in long term clinical remission, and are associated with lower renal function. The clinical significance of these depositions – especially the predictive value for gout flares after ULT stopping – deserves further attention.

Introduction

Gout is an inflammatory rheumatic disease and is characterized by an elevated serum urate (SU)[1]. If the saturation point for SU is exceeded, monosodium urate (MSU) crystals can precipitate in joints and soft tissues[1]. This may result in acute painful episodes of arthritis (gout flares), development of tophi (macroaggregate of MSU crystals surrounded by a rim of immune cells), and irreversible joint damage[2].

Long term gout treatment is based on urate-lowering therapy (ULT), with a treatment target <0.36mmol/l, or even <0.30 mmol/l in presence of erosions, chronic or tophaceous gout[3]. The goal of gout treatment is absence of gout flares and tophi, and being free of clinical visible tophi is therefore one of the domains of the preliminary remission criteria for gout[4]. The significance of subclinical tophi has not be elucidated yet however.

A suitable low-impact imaging technique to assess the presence of (subclinical) tophi is the dual-energy computed tomography (DECT) scan. Due to the dual-energy component, a DECT scan is able to differentiate between MSU crystal depositions and other substances, especially calcium. A DECT scan can be useful in the diagnostic phase as supportive tool in clinical decision making for physicians[5,6]. MSU crystal depositions present on DECT scan have been found to decrease under ULT treatment over a period of 2 years[7], and are predictive for flares in a group of patients with and without ULT[8]. Spectral CT using a dual-layer detector (dlSCT) is a relative new form of dual-energy CT (DECT), using a detector with two layers to capture the low and high-energy spectrum simultaneously, offering a more accurate material decomposition[9].

More knowledge on the presence of MSU crystal depositions and its' determinants in gout patients in remission is needed to explore the potential value of the DECT scan to guide treatment choices in gout patients in remission. Potential uses include whether ULT should be intensified, or if ULT can be (temporarily) stopped.

The aim of this study is therefore to estimate the prevalence of MSU crystal depositions assessed by a dlSCT scan in gout patients in clinical remission on ULT, and to examine associations with patient, disease and treatment characteristics.

Methods

This study was performed within the treat-to-symptom (T2S) ULT discontinuation arm of the GOut TrEatment STrategy (GO TEST) Finale study (ICTRP NL9245)[10]. The GO TEST Finale study is a randomised clinical trial, comparing a continued ULT T2T strategy (treatment target serum urate < 0.36mmol/l) with a strategy with an attempted switch to a T2S ULT discontinuation strategy in which ULT is tapered to stop and T2T is restarted in case of flaring in gout patients in remission (for at least 12 months, defined by preliminary gout remission criteria)[10]. Ethical approval for the trial was obtained from the METC Oost-Nederland (dossier number: NL74350.091.20). In a subgroup of patients in the T2S arm, a dual-layer spectral CT scan before ULT tapering was available.

Measurements

Baseline data of the GO TEST Finale used for this study were sex, age, history of flares, number of joints involved, history of clinical tophi, comorbidities, current and previously ULT use, last use of anti-inflammatory medication, gout related laboratory parameters (including SU levels and CKD-EPI) and presence of erosive disease on X-rays of both feet.

Dual-layer Spectral CT

All scans were performed using the Philips IQON dual-layer spectral-CT (dlSCT) following a standardized protocol. A single scan was performed of both feet and ankles with 140 kiloVolt and 55 milliampères, acquiring images with a sample collimation of 128 and pitch of 0.4. Postprocessing of images was performed using a bone, soft tissue and an uric acid removed algorithm. The uric acid removed reconstruction shows MSU crystal depositions as black.

Scoring of dlSCT scan

Two radiologists (SJ and SB) independently scored the dlSCT images on MSU crystal depositions; both radiologists had no information on any previous visible locations of tophi. Scoring was done within Philips IntelliSpace Portal (ISP). As dlSCT images are prone to artifacts[11], we defined suspicious spots for MSU crystal depositions as spots being both black in the uric acid removed reconstruction and dense on the soft tissue reconstruction. Both radiologists reported the number of depositions and their location within the feet and ankles, including the series (uric acid removed reconstruction) and slice number on which the deposition was seen. The radiologists scored the following areas on presence and number of depositions in the area: first metatarsophalangeal joint(MTP1), other MTP joints, midfoot, ankle (both talocrural ankle joint and subtalar joint), Achilles heel and other tendons, for both sides. In addition to tophi, erosions were scored in the same areas. Consensus meetings were performed to resolve discrepancies in scored MSU crystal depositions and erosions.

Volume measurement of tophi

After consensus on the presence and location of MSU deposits, a certified radiographer (FV) performed volume measurements. Within ISP every MSU crystal deposition was marked, followed by automated volume measurement in mm^3.

Statistical analyses

Considering the explorative nature of this study, no formal sample size calculation was performed. dlSCT scan findings were described by descriptive statistics. Baseline patients characteristics were described by descriptive statistics using, median and IQR (25-75 percentile). Differences in characteristics between patients with and without MSU crystal depositions were evaluated using Mann-Whitney U test for continuous variables, and Fisher's exact test for categorical variables. All analyses were performed in STATA version 17, without correction for multiple testing, using two sided $p<0.05$ as significance level.

Results

A total of 30 patients were included in this study, of whom 29 (97%) were men. Median age was 68.7 year (IQR 62.0 to 71.1). 17 patients (57%) had MSU crystal depositions on dlSCT scan. Comparisons between MSU positive and MSU negative patients on patients-, disease-, and treatment characteristics are shown in table 1. Groups were comparable on all characteristics except for a lower renal function and (non-significant) higher SU levels in MSU positive patients .

The number of observed MSU crystal depositions ranged between 1 and 14 with a median of 4. Most prone position for depositions was the MTP1 joint with 32% of the measured depositions (Table 2). The total volume of depositions ranged between 0.6 mm^3 and 567.5 mm^3 with median volume of 53.6 mm^3.

More patients showed erosions on the dlSCT scan than on foot x-ray. Presence of erosions was not associated with presence of MSU crystal depositions.

Table 1: Baseline patient, disease and treatment characteristics

	MSU negative (n=13)	MSU positive (n=17)	p-value
Age, median (IQR)	67.8 (59.0 to 69.3)	69.0 (63.6 to 72.1)	0.305
Male, N (%)	13 (100%)	16 (94%)	1.000
Alcohol use, N (%)	10 (77%)	12 (71%)	1.000
Currently smoking/smoked in past, N (%)	8 (62%)	6 (35%)	0.200
Hypertension, N (%)	6 (46%)	8 (47%)	1.000
Diabetes mellitus type 2, N (%)	3 (23%)	5 (29%)	1.000
BMI (kg/m^2) baseline, median (IQR)	29.9 (27.5 to 33.5)	31.3 (28.3 to 32.9)	0.808
Years since diagnosis, median (IQR)	9.7 (4.1 to 13.3)	7.8 (4.9 to 9.6)	0.786
Visible tophi in history, N (%)	3 (23%)	4 (24%)	1.000
Last flare, N (%)			0.741
≤ 2 years ago	5 (39%)	5 (29%)	
3 years ago	2 (15%)	5 (29%)	
≥ 4 years ago	6 (46%)	7 (42%)	
SU baseline (mmol/l), median (IQR)	0.25 (0.23 to 0.30)	0.29 (0.26 to 0.34)	0.059
CKD-EPI (ml/min/1.73m^2) baseline, median (IQR)	88 (79 to 90)	71 (56 to 83)	0.002
Years since first ULT prescription, median (IQR)	6.0 (3.7 to 11.0)	5.9 (3.6 to 8.2)	0.525
ULT used at baseline, median, N (%)			0.256
Allopurinol	12 (92%)	12 (71%)	
Benzbromarone		3 (18%)	
Febuxostat		1 (6%)	
Allopurinol + benzbromarone	1 (8%)		
Benzbromarone + febuxostat		1 (6%)	
Presence erosions on baseline x-ray, N (%)	1 (8%)	2 (12%)	0.872
Presence erosions on baseline dlSCT, N (%)	9 (69%)	16 (94%)	0.138

MSU: monosodium urate; IQR: Inter quartile range; BMI: Body mass index; SU: Serum urate; ULT: Urate lowering therapy; dlSCT: dual-layer Spectral CT. Mann-Whitney U test for continuous variables, and Fisher's exact test for categorical variables

Table 2: MSU crystal depositions per location and patient

Location deposition	Number of depositions (n=85)	Number of patients (n =17)
MTP 1	27	10
Other MTP joints	4	1
Midfoot	18	4
Ankle	10	5
Achilles tendon	2	2
Other tendons	24	5
Total	85	17

MTP: metatarsophalangeal joint

Discussion

Our study showed that – interestingly – more than half of patients with gout using ULT and in remission for at least 12 months still have subclinical MSU crystal depositions, especially at the MTP 1 joint. Presence of MSU crystal depositions on dlSCT scan was associated with a reduced renal function, but not with other patient-, disease- and treatment characteristics.

Our study shows a similar percentage of patients with MSU crystal depositions as a previous study using a DECT scan in patients complying with the gout remission criteria for at least three months[12]. In the latter study, a higher SU after use of ULT was associated with MSU crystal depositions, a trend we also found in the current study. The association we found between the presence of MSU crystal depositions and a lower renal function is in line with findings from a previous reporting that reduced clearance of creatinine was associated with the early development of tophi in patients with gout[13]. It is plausible that resolving of MSU crystal depositions also might by delayed due to a lower renal function.

This study had several strengths and limitations. First of all, artefacts on dlSCT/DECT scans are a very common phenomenon[11], also in our study. To limit false positive findings in our study, the possible deposition had to be visible on two different reconstructions. In addition, there were multiple consensus meetings organised to discuss the differences in scoring between the radiologists. Secondly, the volume measurements were performed by hand, which might be more prone to measurement errors. However, our volumes lay within ranges presented in other studies[7,8,12]. Lastly, the study is rather small, resulting in a lack of power to provide more than a first exploration of the value of DECT scans in gout patients in remission. The latter is however a major strength of the study, as this might well be a clinical context were DECT scans might provide valuable information for clinical decision making. Indeed, as the study is embedded within the GO-TEST Finale study, the predictive value of these DECT scan findings on long-term clinical outcomes after ULT stopping can be estimated. Presence of MSU crystal depositions might indicate that patients are not able to stop with their medication or even might indicate that these patients have not reached remission or even might need a higher ULT dose.

In conclusion, a relevant proportion of gout patients in remission while using ULT still have MSU crystal depositions on dlSCT scan. The implication of these finding for prognosis and guiding treatment choices has to be determined.

4

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Chapter 5

Gout patients' perspective on continuation or discontinuation of urate-lowering therapy during remission: a mixed methods study.

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Abstract

Background
Long-term gout management is based on reducing serum urate by using urate-lowering therapy (ULT)[1,2]. A lifelong treat-to-target approach is advocated, though a ULT (taper to) stop attempt can be considered (treat-to-avoid symptoms approach) during remission. Exploring gout patients' beliefs on long-term ULT strategies during remission is important for optimising gout management.

Objective
To identify factors that influence the decision for continuation or discontinuation of ULT and to determine their relative importance according to gout patients in remission.

Methods
A mixed methods design was used. First, semi-structured interviews (substudy 1) were conducted to identify barriers and facilitators for (dis)continuation of ULT using inductive thematic analysis. Afterwards these barriers/facilitators were summarized into neutrally phrased items and used in a Maximum Difference Scaling study (MaxDiff, substudy 2) to determine their relative importance using the rescaled probability score (RPS).

Results
Substudies 1 and 2 included 18 and 156 patients, respectively. Substudy 1 yielded 22 items, within 10 overarching themes. Substudy 2 revealed that the perceived risk of joint damage and gout flares and the reassurance of ULT use were the most important items.
The costs, ease of receiving ULT and its practical use were the least important items.

Conclusion
These results can aid shared decision making and provide input for what's important to discuss with gout patients in remission, when they consider ULT discontinuation.

Introduction

Gout is the most prevalent inflammatory rheumatic disease worldwide[1,2]. Long-term pharmacologic treatment is focused on reducing serum urate below its' saturation point by using urate-lowering therapy (ULT). Treatment goals are prevention of recurrent flares and the development of irreversible joint damage, and the dissolution of tophi[2,3].

In clinical practice, two ULT treatment strategies are frequently followed. Current (inter) national guidelines recommend initiating ULT according to a treat-to-target strategy (T2T), increasing ULT dosage or combining therapies until the serum urate treatment target has been reached and gout flares and tophi are absent[4-7]. It is advised to continue ULT medication lifelong[4,7]. However, the American College of Physicians states that evidence is insufficient to use ULT T2T lifelong in gout patients[8]. They advocate a strategy in which the intensity of ULT is solely based on avoiding recurrent flares, without monitoring serum urate, a so-called treat-to-avoid-symptoms (T2S) approach[8]. Doherty et al. have shown that a nurse-led T2T approach is efficacious and cost-effective when compared to usual care[9]. However, it is not clear yet if ULT should be continued T2T indefinite when remission has been achieved for a certain period of time. Current rheumatology guidelines advise continuing ULT indefinitely over ULT discontinuation, but due to the lack of strong evidence, tapering or discontinuation can both be considered and discussed when remission is achieved[4,10].

ULT non-adherence in gout is very common, and reasons have been studied thoroughly[11-13]. A recent study identified that major reasons behind the patients' decision not take allopurinol is the desire to lead a normal life and to test if ULT dose can be lowered or stopped altogether without getting symptoms[14]. However, studies focusing on preference for ULT (dis)continuation in patients in whom remission has been achieved while following a ULT T2T strategy is lacking.

The primary aim of this study was to identify barriers and facilitators for gout patients in remission when considering continuation or discontinuation of their ULT, and to determine the relative importance of the identified topics. A secondary objective was to investigate differences in the ranking of items between subgroups of patients (e.g. age, disease duration, treating physician).

Methods

Two consecutive studies were carried out in this mixed methods design. For both studies an exemption was obtained from the Medical Ethical Committee Oost-Nederland (file numbers 2020-6575 and 2021-7479) as under Dutch law ethical approval was not required. Both studies have been peer reviewed on design and feasibility by the internal review board of the Sint Maartenskliniek Nijmegen. These studies comply with the declaration of Helsinki. All participants gave informed consent to participate in either one of the two studies. A patient research partner (EP) was involved throughout the entire process and helped developing the interview guide and formulating the neutral items.

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Substudy 1: Semi-structured interviews

Semi-structured interviews were performed to determine facilitators and barriers for a ULT treat-to-target (T2T) strategy and a treat-to-avoid-symptoms (T2S) strategy as perceived by patients in remission[15].

In a T2T strategy ULT is dosed and continued based on an acceptable patient symptom state and a serum urate target ≤0.36mmol (6mg/dl)[4,7]. In our proposed T2S strategy, ULT is tapered to discontinuation and restarted following shared decision making in case of (recurrent) flaring, a T2T is once again followed from this point forward.

Participants recruitment

Patients were recruited in the Netherlands from the rheumatology outpatient clinic of the Sint Maartenskliniek Nijmegen and from one general practice in Nijmegen in June and July 2020. Patients had to be ≥ 18 years, mentally competent, clinically diagnosed with gout, with current or past ULT use (allopurinol, benzbromarone and/or febuxostat), in remission (free of gout flares and/or visible tophi and (if known), serum urate level ≤ 0.36 mmol/l for at least 12 months)[15] and had to be proficient in Dutch. We used purposive sampling[16], since this results in variation of patient characteristics that might influence the patient's perspective on the topic so that insight into the whole range of barriers/facilitators is obtained. We aimed to include a variety of patients regarding sex, duration of ULT use (or no ULT use) and treating physician (general practitioner (GP) or rheumatologist). After approval of the treating physician, patients were selected by two researchers (SW, medical student and IRP, resident rheumatology and PhD candidate). Before the study, there was no physician-patient relationship between SW and IRP and the interviewed participants. Selection and recruitment continued until data saturation was reached (when no new information emerged in three consecutive interviews).

Semi-structured Interviews

The interview guide was developed by SW and IRP using the proposed phases by Kallio et al.[17].

For the interview guide we focused on patients' thoughts and feelings on their gout diagnosis and continuation (T2T) and discontinuation (T2S) of ULT. Two pilot interviews were conducted. All interviews were conducted by telephone and were performed by either SW or IRP and were audio-recorded and transcribed verbatim by a professional transcription company (TiptopGlobal). All participants received a Dutch summary of their interview to assure data validity.

Analysis

Inductive thematic analysis was used to analyze the transcriptions using the qualitative data analysis software ATLAS.ti (version 9.0). The phases of thematic analysis as described by Braun and Clarke were followed[18] and three consecutive coding steps were performed: open, axial and selective coding[19]. Three researchers (SW, FV and IRP) analyzed all transcripts separately and all codes were discussed. Differences were reviewed until consensus was achieved and all individual codes and final codes after consensus were kept in a codebook. This inductive thematic analysis resulted in barriers and facilitators and overarching themes. These were subsequently summarized in neutrally formulated items by the multidisciplinary study team consisting of researchers, rheumatologists, clinical-pharmacologist and a patient partner. We chose neutrally formulated items, since our primary aim of the overall study was to determine which topics are important, and not necessarily the direction (pro or con discontinuation) of the patients beliefs.

Substudy 2: Maximum difference scaling survey

The items derived from the interview study were used in a Maximum Difference Scaling survey (MaxDiff). This method was chosen to be able to determine the relative importance of each item.

In a MaxDiff survey participants are shown several choice sets of items and choose the most and least important item within that subset. This facilitates the ranking of a considerable number of items and is not subjected to scale related biases. For all items a utility score is calculated which reflects the relative importance for patients when deciding on discontinuation of their ULT during remission. The higher the score, the more important the factor. This method has been used previously in patients with inflammatory arthritis[20,21].

Participants recruitment

Patients were recruited in the Netherlands from the rheumatology outpatient clinic of the Sint Maartenskliniek and five general practices (Nijmegen area, the Netherlands). Since we expected bias based on the setting (primary versus secondary care), we aimed to include sufficient participants per setting, so that subgroup analysis would be possible later on. No standard method to determine a sample size for the MaxDiff method is yet available[22,23], so we aimed to include at least 200 respondents (100 currently treated by a GP and 100 currently treated by a rheumatologist). Gout patients could participate if they were in remission for at least 12 months based on preliminary gout remission criteria[15]. Patients could be either actively using ULT (with or without previous discontinuation attempts in case of remission) or could have stopped ULT during remission. Patients at the rheumatology outpatient clinic were screened for eligibility and invited on behalf of their treating rheumatologist. Patients from the general practices were selected by their GP and invited to participate. To be certain that patients met the inclusion criteria, all patients first completed a screening survey in Castoredc. If inclusion criteria were met, the MaxDiff survey was sent per email. If uncertain, patients were contacted by telephone (IRP).

MaxDiff survey

The MaxDiff survey started with an entry question "How do you feel about discontinuation of your urate lowering therapy when your gout is in remission" with a 5-point likert scale answer option (very positive, positive, neutral, negative, very negative, I don't know) and was merged into three categories for the analyses. Also patient- and disease characteristics were collected. The Sawtooth Software's Discover was used to design and execute the MaxDiff exercise (Sawtooth Software Inc. 2013). All participants ranked each of the 22 items three times, so the MaxDiff survey consisted of 14 questions in which five items were shown each time (22x3 / 5=13.2, so 14 questions were needed). An example of a question is shown in figure 1. The survey was pilot tested on comprehensibility and time required to complete the survey by EP, NvH, MF and LV and small changes in the wording and instructions were made.

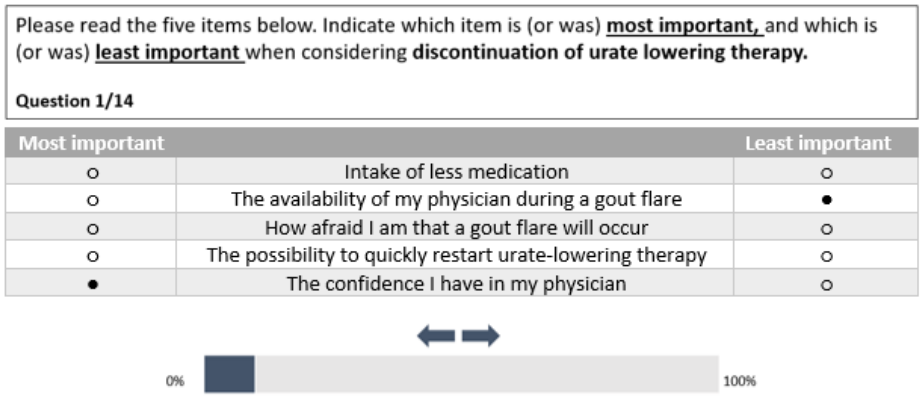

Figure 1: Example of a question of the Maximum Difference Scaling survey (MaxDiff)

Analysis

Descriptive analyses were used to provide insight into patient characteristics. The Sawtooth software calculated a utility score (preference score) for all items in the MaxDiff survey. Empirical Bayesian modeling was used to generate individual utility scores[24]. An average score was calculated by using iteration. To ease the interpretation of the utility scores, a rescaled probability score (RPS) was generated with a 0-100 range (the higher the score the more important the factor). For example, a factor with an RPS of 8, is twice as important as a factor with a RPS of 4. So, the RPS scores represent the relative importance of the items in our MaxDiff survey. Root likelihood was used to exclude patients with inconsistent answers (Root likelihood <0.269)[25].

Different subgroups were created by categorizing variables, which in advance were expected to possibly influence the ranking; age divided by <67/≥67 years, disease duration <10/≥10 years, current treatment by either general practitioner, previously by rheumatologist but currently by GP and currently by rheumatologist, attitude towards ULT discontinuation positive (positive and very positive), negative (negative and very negative) and neutral/no opinion, education level was categorized by the International Standard Classification of Education (ISCED) low (no diploma, primary/pre-vocational education, general secondary education), medium (secondary vocational education and training) and high (higher professional education and university education) and working status divided by no paid work and paid work.

Possible associations between the RPS scores and patients' characteristics (e.g. age, disease duration, treating physician) were explored using Kendall's coefficient of concordance (Kendall's W)[26].

When working with ranked data at an ordinal level of measurement Kendall's W, a non-parametric statistic, can be used to determine the degree of agreement between groups. It can be used for assessing agreement among raters. The Kendall's W score ranges from 0 (no agreement) to 1 (complete agreement). With a p-value <0.05 the null-hypothesis can be rejected that there is no agreement in ranking between groups. StataIC 17 was used for all analyses, SPSS version 29.0.0. was used for Kendall's W analysis.

Results

Study population characteristics

Table 1 shows the patients characteristics of both studies.

In substudy 1 (semi-structured interviews) data saturation was reached when 18 patients were interviewed (29 patients were invited, response rate 62%). Four patients (all currently using ULT) were treated by a general practitioner and 14 patients were treated by a rheumatologist (10 currently using ULT, 1 intermittent and 3 previously).

For substudy 2 (MaxDiff survey) 1242 patients were approached of whom 519 filled in the screenings questionnaire. Eventually 160 out of 218 patients completed the full survey. The overall response rate was 17% (160/ (1242-315). Four patients were excluded from analyses due to inconsistent answers (determined by a Root Likelihood <0.269), so 156 patients were included in the analyses (see figure 2).

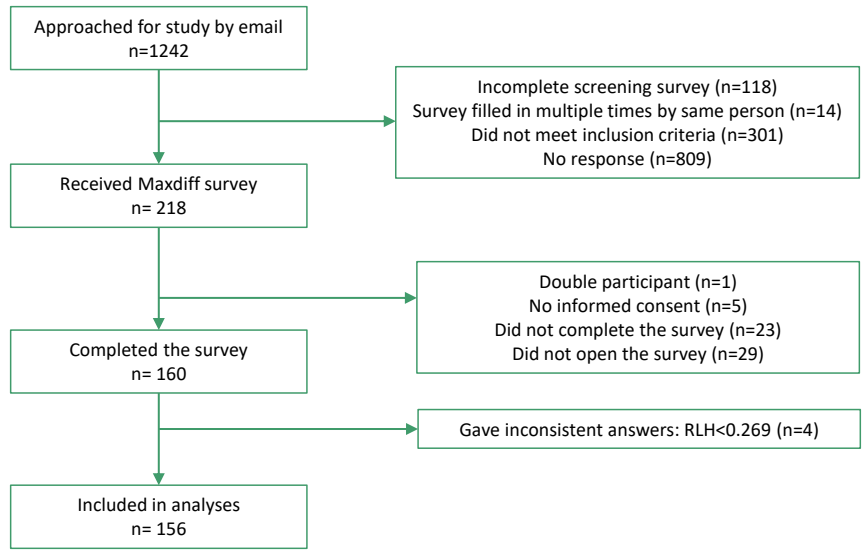

Figure 2: Flowchart of inclusion in substudy 2

Table 1: Patient characteristics of substudy 1 and 2.

Characteristic	Substudy 1 (n=18)	Substudy 2 (n=156)
Sex, male N (%)	16 (89)	147 (94)
Age, mean (SD), years	67 (9.4)	65.9 (10.1)
Disease duration, median, (IQR), years	8.4 (4-10)	10 (6-16.5)
Currently or previously treated by rheumatologist (%)	14 (78)	132 (85)
Current ULT use N (%)	None 2 (11) Allopurinol 14 (78) Febuxostat 2 (11)	None 24 (15) Allopurinol 116 (74) Benzbromarone 9 (6) Febuxostat 6 (4) Allopurinol + benzbromarone 1 (1)
Experience with ULT discontinuation N (%)	Yes 4 (22) No 14(78)	Yes 45 (29) No 106 (68) Don't know 5 (3)
General attitude towards ULT discontinuation (entry question) N (%)		Positive 88 (57) Negative 35 (22) Neutral /no opinion 33 (21)

MaxDiff: maximum difference scaling survey; SD: standard deviation; IQR: interquartile range, ULT: urate lowering therapy.

Semi-structured interviews (substudy 1)

Interview durations ranged from 20-65 minutes. The semi-structered interviews yielded 46 facilitators and barriers when gout patients in remission considered (dis)continuation of their ULT. These factors were categorized in 10 overarching themes (gout flares, use of anti-inflammatory medication for gout flare, use of ULT, long-term gout effects, general medication use, role of the physician, role of serum urate, current scientific knowledge, logistics/costs of gout treatment, lifestyle). See table 2 for exemplary quotes per theme and supplement 1 for an elucidation of the 10 themes. The list of barriers and facilitators were then summarized in a list of 22 neutral phrased sentences. These neutral sentences were then used as input for substudy 2, the MaxDiff survey. See table 2.

Table 2: Themes and examples of quotes of substudy 1, semi-structured interviews.

Theme	Quote	Neutrally phrased sentences
1. Gout flares	''If I am not mobile during a gout flare, that can always be solved. I can always call someone or call a cab'' *R_1* ''Gout flares are not acceptable during tapering or discontinuation of urate-lowering therapy'' *R_12*	1. The risk of having a gout flare 2. How a possible gout flare would affect my daily life 3. How afraid I am that a gout flare will occur
2. Use of anti-inflammatory medication for gout flare	'' I rather take 10 pills (anti-inflammatory), than (ULT) the whole year rounds' *GP_1* '' Use of Colchicine is not acceptable, I am more sick of it than of the gout flare itself'' *R_13*	4. How quickly a gout flare can be treated with medication (such as colchicine, glucocorticoids and/or NSAIDs) 5. My willingness to take medication (such as colchicine, glucocorticoids and/or NSAIDs) to resolve a gout flare
3. Use of ULT	'' I prefer one gout flare a year, above the side effects of chronic benzbromarone use'' *R_13* '' I've resigned myself to lifelong medication'' *R_7* '' First hours after I take my Allopurinol I am woozy, but these side effects are acceptable for me'' *R_6*	6. The ability to quickly restart urate-lowering therapy 7. How satisfied I am with using urate-lowering therapy 8. The reassurance that the use of urate-lowering therapy gives me 9. Practical use of urate-lowering therapy (such as intake of the medication) 10. (Possible) Side-effects of using urate-lowering therapy
4. Long-term gout effects	''There is risk of damage of the cartilage when you are having gout flares'' *R_1* '' If I let go of my ULT, I would be anxious that my gout (symptoms) would return. *R_2*	11. The risk of developing joint damage
5. General medication use	'' Taking the same medication day after day cannot be good, the body must be damaged somehow'' *GP_1* '' Don't take unnecessary medication and don't accept that it is lifelong, if you get a toothache once a year you don't have your teeth remove preventively'' *R_11* '' It is all poison, with beneficial side effects'' *R_4*	12. Intake of less medication

6. Role of physician	'' Physician just follows standard protocol, the protocol says that a physician needs to prescribe medication (ULT)'' *R_1* '' Physician advice is to take the medication (ULT) and take a blood test once every two years, I follow that'' *GP_3* "Physician is the designated person to advise on ULT use, I am just a layman'' R_5	13. The advice of my physician on continuing or discontinuing my urate-lowering therapy 14. The trust I have in my physician 15. To what extent my personal circumstances (e.g. lifestyle) are considered in the treatment 16. The accessibility of my physician in case of a gout flare
7. Role of serum urate	'' It is nice that my serum urate levels are checked, feels safe'' *R_3* '' When you taper or discontinue your ULT you let go of the measurements (blood checks), then there is less fuss'' *R_4*	17. The level of serum urate determines the treatment
8. Current scientific knowdlegde	'' I take a medicine that has not been proven that I need it, and the health insurer just pays for everything'' *GP_1* '' If the body cannot do it itself, it (ULT) is a good remedy, but that has not yet been demonstrated in my opinion'' *R_1*	18. What is known about the pros and cons of (dis)continuing urate-lowering therapy
9. Logistics / costs of gout treatment	'' I don't want extra costs for consultations in case of flaring'' *R_9* '' Taking medication is easy, I get an automatic notification if I need a repeat prescription'' *GP_2*	19. How much my gout treatment costs 20. To what extent my physician monitors my gout (e.g. frequency of visits) 21. The ease with which I receive my urate-lowering therapy
10. Lifestyle	''Since two years I don't drink alcohol anymore, since then I am free of gout flares'' *R_9* '' I am willing to change my lifestyle If I don't have to use ULT anymore'' *R_14*	22. To what extent my lifestyle changes reduce the risk of having a gout flare

GP= patient in general practioner care, R= patient in rheumatology care.

Maximum difference scaling questionnaire (substudy 2)

The majority of respondents (56.4%) was positive about ULT discontinuation, 22.4% was negative and 21.2% was neutral / didn't know. The 22 items and their RPS are shown in figure 3 and supplement 2. The three highest ranked items when gout patients in remission consider discontinuation of their ULT were: ''the risk of joint damage''; ''reassurance that ULT use gives me''; ''risk of having gout flare(s)'', with a mean RPS (SD) of 8.77 (3.9), 8.52 (4.1) and 8.03 (4.4) respectively. The three least important items were: ''Practical use of ULT (administration of ULT)'', ''Ease of receiving ULT (repeat prescription)'', ''the costs of my gout treatment'', with a mean RPS (SD) of 1.72 (1.7), 1.36 (1.6) and 0.34 (0.5) respectively.

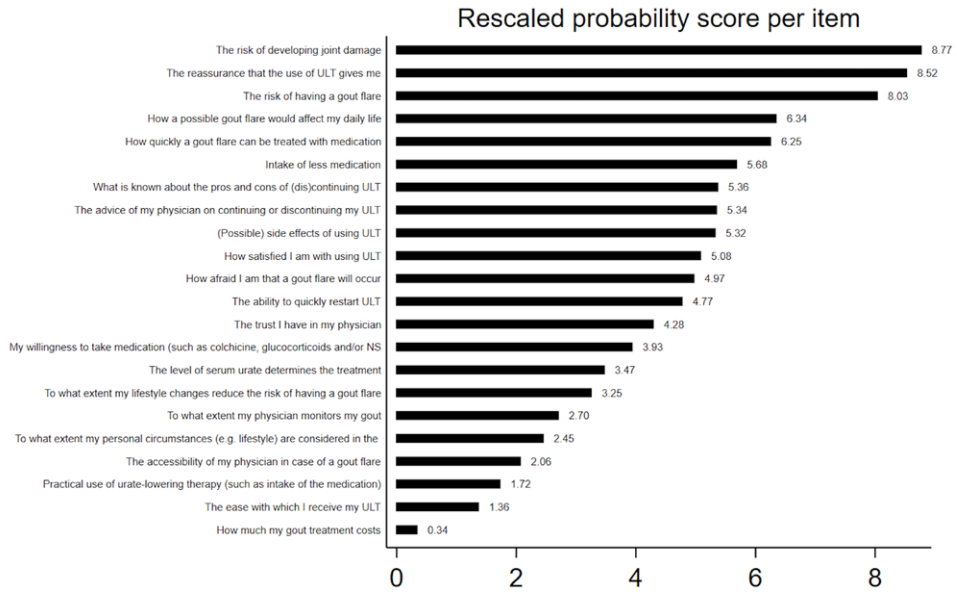

Figure 3: Relative importance of items of the maximum difference scaling study.
Relative importance of the 22 items based on their rescaled probability score (RPS). ULT; urate-lowering therapy.

Agreement in ranking between patient subgroups.

The ranking of subgroups had a high level of agreement according to the Kendall's W analyses in which a score of 0 indicates no agreement and 1 complete agreement. The Kendall's W scores ranged from 0.85-0.99 for treating physician (KW 0.93, *p*-value <0.001), age (KW 0.97, *p*-value 0.005), attitude towards ULT discontinuation (KW 0.89, *p*-value <0.001), working status (KW 0.96, *p*-value 0.006), disease duration (KW 0.99, *p*-value 0.004) and current ULT use (KW 0.85, *p*-value 0.022). Since alle Kendall's W are above 0.8 there were no major differences in ranking between subgroups.

Discussion

This mixed methods study shows that the perceived risk of developing joint damage and control of disease activity play an important role when gout patients in remission consider discontinuation of urate-lowering therapy. Costs and the ease with which ULT is received were deemed less important.

In our interviews (substudy 1) patients expressed their desire to test if they truly need to continue their ULT indefinitely. Previous qualitative research on ULT (dis)continuation has mostly been performed in the initiation phase or the phase when clinical remission has not been achieved yet, and has mostly been focused on non-intentional non-adherence. Limited gout knowledge (of both patients and physicians), interactions with health-care providers, medication side effects and practical barriers of taking long-term medication were determined as important factors based on a systematic review[27]. This is in line with a recent study on intentional nonadherence in gout patients using allopurinol[14]. They found that the wish to lead a normal life, consider themselves a healthy person and to test if they really needed the ULT were important reasons for intentional nonadherence. Another recent study focused on barriers and facilitators to allopurinol during three stages of medication adherence (initiation, implementation and discontinuation)[28]. Patients discontinued their allopurinol due to infrequent flares, (self) identified dietary triggers for flares or concern of long-term allopurinol use. These findings are also consistent with the results of our semi-structured interviews.

A continued ULT T2T strategy is currently advised by international rheumatology guidelines[4-7], and perceived superior by most rheumatologist. This study adds the patient perspective and their perceived risks and opinions on ULT discontinuation during remission. The risk of joint damage and gout flares are deemed important by gout patients in remission when considering ULT discontinuation. Although it is not uncommon to have irreversible joint damage at time of gout diagnosis[2,29], it is unclear yet what the risk of developing joint damage after ULT discontinuation after prolonged remission is. The same applies to the risk of having gout flares. Results of the ongoing GO TEST FINALE on comparing a continued ULT treat-to-target strategy to a ULT taper to stop treat-to-avoid symptoms strategy (with the possibility of restarting ULT)[30], will help answer these questions, and will enable physicians to provide better information to their patients.

Several potential limitations of this study need to be mentioned. We aimed to include 200 patients, instead 156 patients were included in the analysis, which is still a fairly decent sample. Also fewer general practitioner patients participated than aimed for, however the subgroup analyses per setting did not show that treatment setting influenced the results. Inherent to performing a qualitative study there are some potential biases. We cannot exclude the possibility that patients were not aware of important barriers/facilitators or did not mention them for example due to fear or social desirability. As the interviewers were junior researchers that did not have a prior physician-patient relationship, we think that the threshold for sharing their true opinions was low. Additionally, semi-structured interviews are a suitable method to explore patients' views and experiences and the use of purposive sampling in combination with reaching data saturation makes us confident that no important items were missed. Another potential concern could be that interviews were held by telephone due to the COVID-19 pandemic. However, telephone interviews do not lead to inferior results compared to face-to-face interviews[31]. Lastly, it should be mentioned that results are perhaps not generalizable to other countries with other healthcare systems. In this Dutch cohort, patients ranked the "costs of my gout treatment" as least important. This can perhaps be explained by the fact that most gout patients often have other comorbidities, so their compulsory deductible is often already paid, as well as the yearly mandatory personal contribution for medicines of maximum €250.

An important strength of our study is that it is the first study which solely focuses on gout patients in remission. Another strength is our mixed methods approach. Firstly, a broad insight was gained into what is important for gout patients in remission when considering ULT (dis) continuation. Then a ranking took place, yielding an overview of most and least important items. The results of this study are therefore usable for daily practice.

In conclusion, particular the perceived occurrence of possible joint damage and control of disease activity play an important role when gout patients in remission consider discontinuation of ULT. The results of this study can further aid in further optimising personalised medicine and aid adequate education on topics gout patients in remission deem important.

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5

Supplement 1: Thematic overview of substudy 1, semi-structured interviews.

Theme 1: Gout flares

The risk, and being afraid of the possibility of having gout flares after urate-lowering therapy (ULT) discontinuation was mentioned and perceived as very unpleasant. Gout flares were deemed very painful and led to temporarily immobility in the past. So, high risk of having gout flares after ULT discontinuation or high impact on daily life was mentioned as a reason to keep continuing ULT during remission.

In contrast, some patients weighed their pros and cons of discontinuing their ULT, and determined when they would find it worthy stopping their ULT. Some would accept gout flare(s) after ULT discontinuation, since they had a previous experience of gout flares being treated fast and stated that immobility during a gout flare can always be solved easily. Others stated that it would be worth being without ULT if flares only occurred 1-3 times a year, others would not accept one flare at all after ULT discontinuation.

Theme 2: Use of anti-inflammatory medication for gout flare

The short-term use of anti-inflammatory medication such as colchicine, non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids during a gout flare was experienced positively as well as negatively. Some patients would trade their ULT for short-term flare treatment, since they would rather take a week of anti-inflammatory medication instead of daily ULT chronically. On the other hand it was stated that anti-inflammatory medication (colchicine) causes more discomfort then the gout flare itself, so ULT was continued to not risk having to take anti-inflammatory medication once more.

Theme 3: Use of ULT

Using ULT was perceived as comforting. Using it gives a safe feeling, since ULT induced gout remission. Stopping ULT did not occur to some patients, they were happy the way things are and accepted lifelong ULT themselves to continuing ULT lifelong. Others had asked their physician in the past if they could lower or stop their ULT. They wondered if ULT is necessary once low serum urate levels have been achieved, some were convinced that gout flares remain absent even if they discontinue their ULT. Others were convinced that ULT is harmful to liver and kidneys, especially when renal function is already reduced. A few patients already stopped their ULT during remission, due to the absence of flares and side-effect of chronic benzbromarone use. A few patients stated that the ULT tablets are very large and therefore difficult to swallow.

Theme 4: Long-term gout effects

The risk of damage to cartilage, tendons and joints due to gout flares was mentioned as a reason to continue ULT during remission. Anxiety that damage could occur on the long-term when ULT is continued was also mentioned.

Theme 5: General medication use

Patients were negative about medication use in general. They stated that taking the same medication day after day cannot be good and the body will be damaged somehow. They described medication as a poison with beneficial side effects. Others stated that you should not accept that medication use if lifelong, 'if you get a toothache once a year, you don't remove all your teeth preventively'.

Theme 6: Role of physician

A number of patients followed the advice of their physician. If the physician stated that ULT is necessary as well as a blood sample once in a while, they complied. They assumed that what the physicians says is true and correct. In contrast, other patients stated that physicians simply follow a standard protocol, which tells them to prescribe ULT, regardless of patient's personal circumstances.

Theme 7: Role of serum urate

Patients mentioned that checking their serum urate levels from time to time feels safe. If serum urate levels are low, their gout is fine. Others on the other hand stated that letting go of serum urate levels give less hassle, since no more blood samples before a physicians consult are needed. Some stated that serum urate levels could be used to lower ULT dose, so that the lowest needed ULT dose is determined but serum urate levels are kept within a certain range.

Theme 8: Current scientific knowledge

Patients are ambivalent towards ULT and current scientific knowledge. Patients stated that when the body itself cannot regulate its serum urate levels, it is convenient that ULT could help and it is a good remedy. However, they mentioned that they feel it is not proven yet that they need to take all the time. It was opted that treatment, if possible, should be personalized based on patients characteristics, for example if it could be that serum urate targets are different based on sex, age and weight.

Theme 9: Logistics / costs of gout treatment

Patients mentioned that the ease with which they receive their ULT enabled them to continue their ULT. Some patients automatically received a timely signal from their pharmacy to pick up a new prescription, others stated that their partner helps them to remind them to take their medication on a daily basis. Others experienced that making sure they have enough ULT in stock is a hassle. One patient stated that when he decides to go on a spontaneous holiday / stay over, he continuously worries about having a gout flare since he was not able to take his ULT. Patients also mentioned the costs of their gout treatment. Some patients indicated that gout flares costs extra, since they need to take anti-inflammatory medication or need to consult their rheumatologist and therefore rather continue their ULT. Others stated that following a lifelong strategy of which it is not certain that it is the best treatment strategy, could perhaps costs society more. They stated that 10 days of anti-inflammatory medication is cheaper than daily ULT use, especially since patients pay for their medication themselves by a deductible.

Theme 10: Lifestyle

Patients mentioned that lifestyle and having gout flares are strongly connected. They received lifestyle advice in the past from their general practitioner, rheumatologist or rheumatism nurse, mainly dietary advice. Patients stated that changing your diet, mainly stop consuming alcohol, results in having no more gout flares. Patients also stated that they are willing to change their lifestyle and diet, if this would mean they could be without their ULT and still be gout flare free.

Supplementary table 1: Relative importance of items of the maximum difference scaling study.

RANK	RPS (SD)	Factor	Theme
1	8.77 (3.93)	The risk of developing joint damage	Long-term gout effects
2	8.52 (4.07)	The reassurance that the use of urate-lowering therapy gives me	Use of ULT
3	8.03 (4.40)	The risk of having a gout flare	Gout flares
4	6.34 (4.28)	How a possible gout flare would affect my daily life	Gout flares
5	6.25 (3.96)	How quickly a possible gout flare can be treated with medication (like colchicine, prednisone and/or naproxen)	Use of anti-inflammatory for gout flares
6	5.68 (4.80)	Intake of less medication	General medication use
7	5.36 (3.73)	What is known about the pros and cons of (discontinuing urate-lowering therapy)	Current scientific knowledge
8	5.34 (3.74)	The advice of my physician on continuing or discontinuing my urate-lowering therapy	Role physician
9	5.32 (4.09)	(Possible) Side-effects of using urate-lowering therapy	Use of ULT
10	5.08 (3.48)	How satisfied I am with using urate-lowering therapy	Use of ULT
11	4.97 (4.36)	How afraid I am that a gout flare will occur	Gout flares
12	4.77 (3.30)	The ability to quickly restart urate-lowering therapy	Use of ULT
13	4.28 (3.72)	The trust I have in my physician	Role physician
14	3.93 (3.42)	My willingness to take medication (such as colchicine, glucocorticoids and/or NSAIDs) to resolve a gout flare	Use of anti-inflammatory for gout flares
15	3.47 (2.75)	19; The level of serum urate determines the treatment	Role of serum urate
16	3.25 (2.91)	To what extent my lifestyle changes reduce the risk of having a gout flare	Lifestyle
17	2.70 (2.48)	To what extent my physician monitors my gout (e.g. frequency of visits)	Logistics
18	2.45 (2.51)	To what extent my personal circumstances (e.g. lifestyle) are considered in the treatment	Role physician
19	2.06 (2.59)	The accessibility of my physician in case of a gout flare	Role physician
20	1.72 (1.68)	Practical use of urate-lowering therapy (such as intake of the medication)	Use of ULT
21	1.36 (1.62)	The ease with which I receive my urate-lowering therapy	Logistics
22	0.34 (0.53)	How much my gout treatment costs	Costs

Chapter 6

Beliefs of rheumatologists and general practitioners on urate lowering therapy: a cross-sectional study.

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Abstract

Objective

To describe beliefs about urate lowering therapy (ULT) of physicians and patients in primary and secondary care, to examine differences in physicians' medication beliefs, and to examine the association of physicians' medication beliefs with prescribed dosage of ULT, gout outcomes, and patients' medication beliefs.

Methods

Cross-sectional study among rheumatologists and general practitioners(GPs) and their patients using ULT in The Netherlands. All participants filled out the *Beliefs about Medication questionnaire* (BMQ). Demographics of physicians were collected through questionnaires. Patient and disease characteristics were collected through questionnaires and electronic medical records. Differences between rheumatologists and GPs in BMQ subscales *Necessity* and *Concern*, and the necessity concern difference(NCD) score were analysed by two-sample T-tests. Multilevel analyses were performed to examine the association of physicians' BMQ scores with the prescribed dosage of ULT, gout outcomes (number of gout flares, serum urate) and patients' BMQ scores.

Results

Twenty-eight rheumatologists, 443 rheumatology patients, 45 GPs and 294 GP patients were included. Mean NCD scores were 7.1±3.6, 4.0±4.0, and 4.2±5.0 for rheumatologists, GPs and patients respectively. Rheumatologists scored higher on necessity beliefs (mean diff=1.4; 95%CI 0.0;2.8) and lower on concern beliefs(mean diff=-1.7; 95%CI -2.7;-0.7) compared to GPs.

No associations between physicians' beliefs and prescribed dosage of ULT, gout outcomes, or patients' beliefs were found.

Conclusion

Rheumatologists had higher necessity and lower ULT concern beliefs, compared to GPs and patients. Physicians' beliefs were not related to prescribed ULT dosage and patient outcomes. The role of physicians' beliefs in gout management in patients using ULT seems limited. Future qualitative research can provide more insight into physicians' views of gout management.

Introduction

Gout is the most common form of inflammatory arthritis with an estimated prevalence of 1.4% in the European population[1]. It is caused by depositions of monosodium urate crystals within joints and soft tissue[1]. Urate lowering therapy (ULT) effectively lowers serum urate (SU) levels below the proposed targets, serum urate (SU) < 0.36 mmol/l, or in case of tophaceous gout <0.30 mmol/l[2,3]. This results in the resolution of gout symptoms and reduces the risk for recurrent gout flares[2,3]. In a clinical setting with nurse-led care, personalized information, and a treat-to-target strategy SU targets can be reached in more than 90% of patients with gout[4]. However, despite proven effectiveness a large proportion of patients does not reach SU targets in both primary and secondary care[5,6], resulting in recurrent flares, tophi, and, consequently, a higher disease burden for patients and societal costs[7].

Considerable attention has been paid to the barriers of effective treatment in patients with gout. Barriers that have been reported are patients' lack of knowledge of the disease and the potential benefit of lifestyle adjustments, and non-adherence to ULT medication[8-10]. A small number of educational and behavioural intervention studies in patients with gout addressed patients' disease perceptions and were effective in improving knowledge on gout and adherence to ULT medication[4,11].

Less is known about the potential impact of physician related factors on the management of gout. Studies indicate the presence of various health care related barriers on gout management, such as suboptimal guideline adherence, lack of physician's knowledge about gout and ULT medication, and underestimation of long-term gout complications[5,6,12].

Furthermore, at present two different treatment strategies are being used in clinical practice, i.e., treat to target and treat to avoid symptoms. Although most guidelines advocate a treat-to-target strategy, including the Dutch gout guidelines for both primary and secondary care, the American College Of Physicians promotes a treat to avoid symptom strategy[3,13-16]. Solid proof on which treatment strategy is superior, however, is missing[13]. In absence of a clear consensus on the therapeutic strategy, the individual beliefs of physicians can be a factor of importance in gout management.

According to the Theory of Planned Behaviour[17], physicians' beliefs towards medication can shape prescribing behaviour and in turn, gout management. Health beliefs models such as the Theory of Planned Behaviour[17] and the Necessity-Concern framework[18], postulate that beliefs about illness and medication can shape an individual's intentions and behaviour. Hence, physicians' beliefs towards ULT medication (i.e., the necessity of and concerns with ULT medication) may influence gout management, specifically prescribed dosage of ULT.

Empirical findings about the relations between physicians' medication beliefs, clinical management, and patients' beliefs and outcomes are scarce and inconclusive[19-24].

A systematic review in low back pain (LBP) showed that the attitudes and beliefs of the health professional were associated with the attitudes and beliefs of their consulting patients with LBP. In addition, health care professionals (HCP) attitudes and beliefs were associated with clinical management and guideline adherence[23]. Regarding cholesterol-lowering medication,

Foley et al. (2006) showed that physicians' attitudes and beliefs about hyperlipidaemia were associated with the decision to increase the statin dose in high-risk patients with lipid therapy[24]. Whereas another study among physicians, pharmacy staff and patients found no association between HCPs beliefs about statins and patients' statin beliefs and their medication-taking behaviour[20]. In rheumatology, only one study examined the relations between physicians (implicit and explicit) beliefs about disease-modifying antirheumatic drugs (DMARD) and the attitudes and beliefs, medication taking behaviour, and disease activity of patients with rheumatoid arthritis and found no associations[18]. Considering the variety in gout treatment strategies in clinical practice and the high non-adherence rates for ULT among gout patients, insight into physicians' beliefs about ULT and whether these beliefs influence prescribed dosage of ULT is warranted.

Therefore, the aim of this study was 1) to describe the medication beliefs of physicians and patients in both primary and secondary gout care, 2) to examine differences in beliefs between rheumatologists and GPs and 3) to assess the association of physicians' medication beliefs with their prescribed dosage of ULT, gout outcomes, and their patients' medication beliefs.

Patients and Methods

Study design and participants

A cross-sectional study among physicians and their patients with gout was conducted. Physicians and patients were recruited simultaneously in the period May-December 2020. The local ethical review board (CMO region Arnhem-Nijmegen, dossier number: 2019-5268) exempted the study from ethical approval since the study was not subject to the Dutch Medical Research Involving Human Subjects act (WMO). The study was approved by the internal review board of the Sint Maartenskliniek, the Netherlands. All participants gave written informed consent. The STROBE checklist was used to ensure complete and transparent reporting[25].

Participating physicians

All physicians (including trainees and physicians assistants) at the rheumatology department of the Sint Maartenskliniek Nijmegen and general practitioners (GPs) participating in the practice-based research network (PBRN) Family Medicine network in the Nijmegen region were invited to participate. The PBRN consists of 17 primary care practices with 75 GPs in the East of the Netherlands (Nijmegen and surrounding area). There were no additional eligibility criteria for physicians.

Participating patients

Retrospectively, patients (≥18 years) with a clinical diagnosis of gout according to treating physician and use of ULT were identified and extracted from the electronic medical record in both the Sint Maartenskliniek and the PBRN. To be eligible, patients had to use ULT in the year prior to inclusion and were still on ULT, were able to understand the Dutch language, and had no cognitive impairments.

Procedure and measures

Demographic characteristics and medication beliefs of physicians and patients were collected by a questionnaire. Clinical characteristics of the rheumatology patients were extracted from the electronic medical record by the researchers. For GP patients the data was provided by the PBRN network. Questionnaires for all physicians (digital format) and patients (paper-and-pencil format) from the rheumatology department were sent by the researchers; questionnaires for GP patients (paper-and-pencil format) were sent through their GP practice.

Demographic and clinical characteristics

For the physicians the following demographic characteristics were collected by questionnaire: sex, age, years of working experience, estimated hours of direct patient contact per week, and gout consultations per week.

For the patients, sex, age, and number of self-reported flares over the past 3 months were collected by questionnaire. GP patients were asked if they were currently under treatment by a rheumatologist for their gout.

From the electronic medical records, the following patient data were extracted: latest ULT use including type and dosage, latest available lab history on serum urate and renal function over the past two years, and all known comorbidities.

Medication beliefs: Beliefs about Medicines Questionnaire

To assess medication beliefs the Beliefs about Medicines Questionnaire (BMQ), reflecting/quantifying the underlying Necessity-Concern framework, was used[26]. The BMQ consists of a specific part regarding the medication of interest (BMQ-specific) and a part about medication in general (BMQ-general).[26] The BMQ-specific consists of two subscales, a necessity and concern scale with both five items. All items are scored on a 5-point Likert scale 1 (strongly disagree) to 5 (strongly agree) resulting in a sum score range of 5 to 25. The BMQ-general consists of two subscales, a harm and overuse scale with both 4 items. All items are scored on a 5-point Likert scale 1 (strongly disagree) to 5 (strongly agree) resulting in a sum score range of 4 to 20.

In addition, the necessity concern difference (NCD) score can be derived from the BMQ-specific. For this score the concern score is subtracted from the necessity score (range minus 20 to plus 20). A positive score reflects that necessity score outweighs concern score; a negative score reflects that the concern score outweighs the necessity score.

Finally, four attitudinal profiles can be derived from the BMQ-specific: acceptant, ambivalent, sceptic, and indifferent[27]. Respondents are classified into these attitudinal groups according to the median cut-off score of the necessity and concern subscale. Only for physicians the attitudinal profiles were calculated.

For patients, the Dutch version of the BMQ was used[28]. For physicians, an adapted version of the BMQ was used[21]. Only complete BMQs were applicable for analyses.

Statistical analyses

Descriptive statistics were used to describe participant characteristics. For normally distributed data mean and SD were calculated, otherwise median and IQR (25-75 percentile) were calculated. BMQ scores and attitudinal profiles were grouped according to primary vs secondary care en described for both physicians and patients.

Differences between rheumatologists and GPs regarding the BMQ subscales, necessity, concern, harm and overuse, and the NCD score were analysed by two-sample T-tests. Differences in attitudinal groups between rheumatologists and GPs was assessed by chi-square test.

Series of multilevel analyses were performed, as patient data (level 0) was nested within physicians (level 1), to examine the association of physicians' medication beliefs (i.e., necessity and concern scores as independent variable) with the following dependent variables: prescribed dosage of ULT (measured with the maximum dosage of allopurinol, the most common ULT) per patient, the latest SU levels in their patients, patients' necessity or concern score, the proportion of patients who reached SU target <0.36 mmol/l, and the presence of gout flares (yes/no) in the past 3 months. To perform the multilevel analyses with patients nested within physicians, it was necessary that both had responded in order to be matched. Furthermore, only complete BMQs were included in these analyses.

First, collinearity between potential physician-related and patient-related covariates was assessed. Physicians' age and years of work experience had a r > 0.7, therefore only work experience was taken into further analyses. Next, bivariate analyses were performed to determine which physician-related (Primary vs secondary care, sex, years of work experience, hours of direct patient contact/week, and number of gout consults/week) and patient-related (age, sex, diabetes mellitus, hypertension, renal failure and start ULT past year Yes/No) factors were associated with the necessity or concern score of physicians. Covariates with a p-value <0.157 (according Akaike information criterion[29]) were included in their respective full adjusted multilevel models. A linear multilevel model was used for the following continuous dependent variables: dosage of allopurinol, SU level, patients' necessity score, and patients' concern score, presenting the unstandardized beta coefficient. A logistic multilevel model was used for the following binary dependent variables: proportion of patients who reached SU target, and the presence of gout flares (yes/no) in the past 3 months, presenting the corresponding odds ratio (OR). Likelihood ratio tests were used to assess multilevel model fit. For all models, a multilevel model with a random intercept for physician level (patients nested within physicians) deemed to be most suitable. Intraclass correlation coefficient (ICC), which quantifies the degree to which data at the lower level are correlated, is presented as well[30]. Post hoc analyses without patients who received both GP and rheumatology care were performed with the same full models.

No formal sample size calculation was made as a convenient sample was used. Data was analysed using STATA version 17.

Results

Characteristics of study participants

In figure 1, the study flow diagram of participants is displayed.

In total 111 physicians were invited to participate, 28 of 36 from the rheumatology department (78%), including 19 rheumatologists , 7 residents and 2 physician assistants and 45 of 75 GPs (60%) from 16 out of 17 general practices responded. Their characteristics are described in table 1.

Table 1: Characteristics physicians.

	Rheumatologists (n= 28)	General practitioners (n=45)
Sex, male (%)	9 (32.1%)	20 (44.4%)
Age, mean (SD)	43.1 (10.6)	46.1 (8.3)
Working experience, years, median (IQR)	8.5 (IQR 3 – 14)	13 (IQR 8-20)
Direct patient contact, hours/week, median (IQR)	15 (IQR 8.5 – 20)	24 (IQR 20 – 30)
Gout consults/week median (IQR)	4 (IQR 1 – 6.5)	1 (IQR 0.2– 1)

SD= standard deviation, IQR = Interquartile range (25°-75°), n=number.

In total 443/1087 (40.8%) of the invited rheumatology patients and 294/593 (49.6%) of the invited GP patients responded. Patient characteristics are shown in detail in supplementary table S1. Most patients were male (respectively 85.3% in rheumatology patients vs 88.1% in GP patients) with a mean age of 68.3±10.52 year and 68.6±10.32 year for rheumatology patients and GP patients, respectively. There were no differences in relevant chronic comorbidities between rheumatology patients and GP patients.

Of rheumatology patients 25.7% reported one or more flares in the previous 3 months, whereas GP patients 17.7% reported one or more flares. Mean SU levels in rheumatology patients were 0.30±0.08 vs 0.37±0.08 in GP patients. Target SU (<0.36 mmol/l) was reached in 79% of the rheumatology patients, whereas 48.6% of GP patient reached SU target. Most frequently used ULT was for both groups allopurinol with a median (IQR) dosage of 300 mg (IQR = 50 to 900 mg) for rheumatology patients and 200 mg (IQR = 100 to 700 mg) for GP patients.

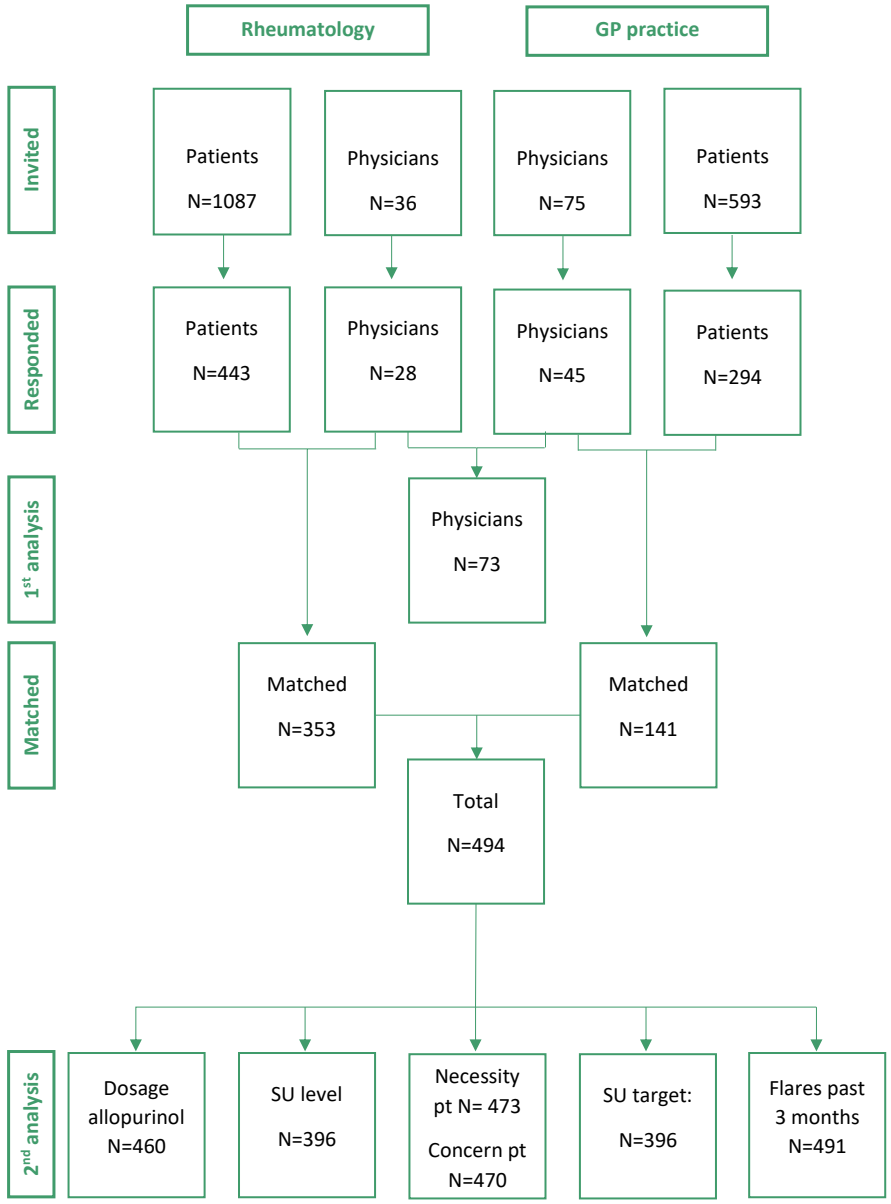

Figure 1: Study flowchart: from invitation to analyses

1st analysis: Beliefs about medication physicians
2nd analysis: Multilevel analyses including all patient-physicians matches
Pt= patient, SU= serum urate level.

Beliefs about medication physicians and patients

The BMQ scores for physicians are displayed in table 2. Rheumatologists scored higher on the BMQ necessity scale (17.5± 2.4 vs 16.1±3.2), and lower on the BMQ concern scale (10.4±2.0 vs 12.1±2.1) compared to GPs. Rheumatologists scored lower on both overuse (9.9±2.1 vs 11.3±2.1) and harms (7.1±1.6 vs 8.3±1.4) subscales compared to GPs. Rheumatologists were mostly classified in the attitudinal group acceptant (46.4%), whereas the GPs were mostly classified in two attitudinal groups, sceptic (31.1%) and indifferent (33.3%) (X^2= 9.0, p=0.029). The NCD difference score was 3.1 (95%CI 1.2 to 5.0), reflecting that for rheumatologists the necessity beliefs outweighed the concern beliefs more than it did for GPs.

Table 2: Medication beliefs and attitudinal medication profiles of rheumatologists and general practitioners on ULT.

	Rheumatologists (N=28)	GPs (N=45)	Difference (95%CI)
Necessity score, mean (SD)	17.5 (2.4)	16.1 (3.2)	1.4 (0.0 to 2.8)
Concern score, mean (SD)	10.4 (2.0)	12.1 (2.1)	-1.7 (-2.7 to -0.7)
Overuse score, mean (SD)	9.9 (2.1)	11.3 (2.1)	-1.5 (-2.5 to -0.5)
Harm score, mean (SD)	7.1 (1.6)	8.3 (1.4)	-1.2 (-1.9 to -0.5)
Attitudinal profiles#*			
Acceptant, n (%)	13 (46.4)	7 (15.6)	
Ambivalent, n (%)	5 (17.9)	9 (20.0)	
Sceptic, n (%)	6 (21.4)	14 (31.1)	
Indifferent, n (%)	4 (14.3)	15 (33.3)	
NCD score, mean (SD)	7.1 (3.6)	4.0 (4.0)	3.1 (1.2 to 5.0)

SD= standard deviation, GP= general practitioner, CI= confidence interval, n=number.
Range necessity score: 5 to 25 , range concern score: 5 to 25, range overuse score: 4 to 20, range harm score: 4 to 20.
*Attitudinal profiles of physicians based on median cut-off scores: acceptant (necessity > 17, concern ≤ 11), ambivalent (necessity > 17, concern > 11), sceptic (necessity ≤ 17, concern > 11) and indifferent (necessity ≤ 17, concern ≤ 11).
p=0.029

Overall patients had a mean necessity score of 16.8±4.2 and a mean concern score of 12.6±3.7. The mean NCD score of patients was 4.2±5.0. They had the following attitudinal profile distribution: 29.0% acceptant, 25.8% ambivalent, 14.5% sceptic and 30.6% indifferent. For specific group scores see table 3.

Table 3: Medication beliefs and attitudinal medication profiles of patients on ULT.

	Patients rheumatologists	Patients GP
Necessity score, mean (SD)	17.3 (4.2)	16.1 (4.1)
Concern score, mean (SD)	13.1 (3.7)	11.9 (3.7)
Overuse score, mean (SD)	11.2 (2.7)	10.8 (2.6)
Harm score, mean (SD)	10.1 (2.4)	9.9 (2.4)
*Attitudinal profiles**		
Acceptant, n (%)	93 (19.8)	61 (18.0)
Ambivalent, n (%)	177 (37.6)	113 (33.3)
Sceptic, n (%)	107 (22.7)	69 (20.4)
Indifferent, n (%)	94 (20.0)	96 (28.3)
NCD score, mean (SD)	4.2 (5.1)	4.2 (4.9)

SD= standard deviation, GP= general practitioner, n=number.
Range necessity score: 5 to 25 , range concern score: 5 to 25, range overuse score: 4 to 20, range harm score: 4 to 20.
* Attitudinal profiles of patients based on median cut-off scores: acceptant (necessity > 17, concern < 13), ambivalent (necessity > 17, concern ≥ 13) , sceptic (necessity ≤ 17, concern ≥ 13) and indifferent (necessity ≤ 17, concern < 13)

Association of physician' beliefs with allopurinol dosage, gout outcomes and patients' beliefs

Table 4 and 5 show the results of the multilevel analyses exploring the association of physician's medication beliefs (separate for necessity and concern score) with their highest prescribed dosage of allopurinol, the latest SU levels in their patients, patients' necessity or concern score, the proportion of patients who reached SU target <0.36 mmol/l, and the presence of gout flares (yes/no) in the past 3 months. Unadjusted, a higher physician's concern score was associated with a lower dosage of allopurinol. Adjusted models, as seen in table 4 and 5 did not show any associations between physicians' beliefs and the outcome measures. Similar results were found for the association between the NCD of physicians and prescribed dosage of allopurinol, gout outcomes, and patients' NCD (see supplementary table S2). Post hoc analyses without 32 patients who received both GP and rheumatology care did not show any differences to the primary analyses (see supplementary table S3 and S4).

Table 4: The association between physicians' necessity beliefs and prescribed dosage of allopurinol, gout outcomes, and patients' necessity beliefs.

	Allopurinol dosage (mg)		Serum urate level (mmol/l)		Necessity score patients		Targets SU y/n		Flares past 3 months y/n	
	b (95% CI)	Adj* (95% CI)	b (95% CI)	Adj^ (95% CI)	b (95% CI)	Adj# (95% CI)	OR (95% CI)	Adj^^ (95% CI)	OR (95% CI)	Adj** (95% CI)
Necessity score physician	3.83 (-3.00; 10.65)	0.56 (-4.49; 5.82)	-0.00 (-0.01; 0.01)	0.00 (-0.00; 0.01)	0.03 (-0.11; 0.17)	0.00 (-0.15; 0.15)	1.01 (0.81; 1.25)	0.95 (0.83; 1.10)	1.03 (0.96; 1.11)	1.00 (0.92 ;1.08)
ICC	0.18	0.06	0.43	0.20	0.01	0.02	0.48	0.11	0.00	0.00

b= unstandardized beta, OR= odds ratio, ICC= Intraclass correlation coefficient, SU= serum urate level, adj= adjusted, CI= confidence interval.
* Adjusted for: **Primary vs secondary care**, hours of patient contact, number of gout consultations, **age patient**, sex patient, diabetes mellitus, renal failure and **start ULT past year**. ^ Adjusted for: **Primary vs secondary care, work experience**, hours of patient contact, number of gout consultations, **age patient**, **sex patient**, **renal failure** and **start ULT past year**. # Adjusted for: Primary vs secondary care, hours of patient contact, and **hypertension**. ^^ Adjusted for: **Primary vs secondary care**, sex physician, **work experience**, hours of patient contact, number of gout consultations, age patient, sex patient, **renal failure** and **start ULT past year**. ** Adjusted for: Primary vs secondary care, work experience, number of gout consultations and **start ULT past year**. Covariates denoted in **bold** are significantly associated with outcome parameter (p<0.05)

Table 5: The association between physicians' concern beliefs and prescribed dosage of allopurinol, gout outcomes, and patients' concern beliefs.

	Allopurinol dosage (mg)		Serum urate level (mmol/l)		Concerns score patients		Targets SU y/n		Flares past 3 months y/n	
	b (95% CI)	Adj* (95% CI)	b (95% CI)	Adj^ (95% CI)	b (95% CI)	Adj# (95% CI)	b (95% CI)	Adj* (95% CI)	b (95% CI)	Adj^ (95% CI)
Concern score physician	-11.42 (-19.58; -3.25)	-1.66 (-8.48; 5.16)	0.01 (-0.00; 0.02)	-0.00 (-0.01; 0.01)	-0.11 (-0.28; 0.05)	-0.02 (-0.18; 0.14)	0.84 (0.65; 1.10)	1.05 (0.87; 1.25)	1.01 (0.92; 1.11	1.04 (0.94; 1.16)
ICC	0.16	0.07	0.41	0.20	0.02	0.00	0.46	0.11	0.00	0.00

b= unstandardized beta, OR= odds ratio, ICC= Intraclass correlation coefficient, SU= serum urate level, adj= adjusted, CI= confidence interval.
* Adjusted for: **Primary vs secondary care**, work experience, hours of patient contact, number of gout consultations, **age patient**, sex patient, diabetes mellitus, renal failure and **start ULT past year**. ^ Adjusted for: **Primary vs secondary care**, **work experience**, hours of patient contact, number of gout consultations, **age patient**, **sex patient**, **renal failure** and **start ULT past year**. # Adjusted for: **Primary vs secondary care**, work experience, number of gout consultations and start ULT past year. ^^ Adjusted for: **Primary vs secondary care**, sex physician, **work experience**, hours of patient contact, number of gout consultations, age patient, sex patient, **renal failure** and **start ULT past year**. * Adjusted for: Primary vs secondary care, work experience, hours of patient contact, number of gout consultations and **start ULT past year**. Covariates denoted in **bold** are significantly associated with outcome parameter (p<0.05)

Discussion

In this cross-sectional study the role of medication beliefs in gout management was examined. In both physicians (rheumatologists and GPs) and patients the need for ULT outweighed the concern. Rheumatologists reported higher medication necessity beliefs and lower concern beliefs than GPs and patients. Physician's medication beliefs were not associated with dosage of prescribed allopurinol, treatment outcomes, or medication beliefs of patients.

In line with other studies, we found that physicians reported a greater need and fewer concerns for their prescribed medication[19-21]. The average necessity score falls in the range of previous described studies regarding beliefs on statins and DMARDs (13.9 to 20.9)[19-21]. The average concern score of rheumatologists, however, is slightly lower than the range of previous studies prescribing DMARDs and statins (11.5 to 13.5)[19-21]. A plausible explanation for this is that ULT is relatively safe and well tolerated[2].

Rheumatologists had higher necessity beliefs and lower concern beliefs compared to GPs. There are a few explanations that could account for these subgroup differences. First, rheumatologists in our study treated more gout patients individually and therefore are likely to have more accurate knowledge of gout management[12]. Second, the Dutch gout population in secondary care tends to have a more severe gout phenotype, which often necessitates a more intensive treatment. Although we did not collect specific data on gout severity, like presence of erosions or tophi, more flares and higher dosage of allopurinol were reported in the population treated by a rheumatologist.

We found no associations between physicians' medication beliefs with their prescribed dosage of allopurinol, gout outcomes or the medication beliefs of patients. This is in line with earlier research in rheumatology[19]. Of note, in our unadjusted model a higher concern score was associated with a lower prescribed dosage of allopurinol. This is in line with other studies[23,24]. In our adjusted model, however, the relationship between concern beliefs and prescribed dosage of allopurinol disappeared. The concern beliefs were outweighed by other covariate factors, including primary vs secondary care, age of the patient and recent start of ULT influencing the prescribed dosage of allopurinol. Overall, in our adjusted multilevel analyses, the covariate primary vs secondary care was the strongest factor independently associated with prescribed dosage of allopurinol and clinical outcomes.

In this study some limitations must be considered. First, only patients treated with ULT were included. Medication beliefs may also influence physician's decision whether or not to initiate ULT. In hindsight, including patients who are not treated with ULT would have given a broader perspective. However, in our opinion, specific beliefs on medication are stable and are therefore not likely to change in different contexts. Second, not all patients could be paired with their physician due to non-response in either of them resulting in a slightly smaller sample size for the multilevel analyses, particularly in the GP setting. However, we do not think that this had any major influence on our results as the unadjusted results show differences which are expected and disappearing after correction for potential confounding factors. Third, we were not able to identify possible duplication between GP and rheumatology patients. In total 32 GP patients stated that they were being treated by a rheumatologist (not necessarily our included rheumatologists) as well. Post hoc analyses excluding these

32 patients did not show any different results. Fourth, participation bias may have occurred as physicians, who responded to the questionnaire might be more involved with their gout patients and therefore be more willing to participate in this study. If beliefs of responding and non-responding physicians should differ this may have led to biased estimates of our study findings. Similarly, participation bias may also have occurred in responding patients and may have led to a non-representative group. However, our response rate can be considered as high, and the patient characteristics reflect the average gout population. Fifth, no formal power calculation was performed as the primary objective was descriptive. A post hoc power analysis for the second objective showed a slight underpowered sample (73 responders included where 87 needed). Therefore, these results should be interpreted with caution. For the third objective the study was sufficiently powered. Last, physicians from one specialised hospital were included in this cross-sectional study limiting study generalizability. A multi-site study is needed to confirm or refute our findings. Furthermore, a qualitative study (e.g., focus groups, interviews) can provide more in depth understanding of the beliefs of physicians and their possible influencing role in gout management. Also, a longitudinal study is needed to firmly ascertain the influence of physicians' medication beliefs on gout management. This first study might be a starting point for further studies on the role of physicians' beliefs in gout.

Despite the limitations, there are strengths as well. To our knowledge, this is the first study wherein beliefs of physicians regarding urate-lowering therapy for gout are subject of study. With previous studies focussing on patient barriers in effective treatment[8-10] it is important to know which role the beliefs of physicians play in an effective gout management. Second, both primary and secondary care physicians involved in gout management were included in this study, covering the entire spectrum of gout patients. Last, the response rates of 76% and 60% in rheumatologists and GPs, and 40.8% and 49.6% in their patients, respectively, can be considered as high.

In conclusion, the results show that rheumatologists scored higher on necessity and lower on concern beliefs compared GPs. We found no associations between physicians' beliefs with the prescribed dosage of ULT and clinical outcomes in their patients. The role of physicians' beliefs in gout management in patients being treated with ULT seems limited. Future qualitative research can provide more insight into physicians' views of gout management.

6

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Supplementary table s1: Patient and disease characteristic

	Patients rheumatologists (n=443)	Patients GP (n=294)
Sex, male n(%)	378 (85.3%)	259 (88.1%)
Age, mean (SD)	68.3 (10.52)	68.6 (10.32)
Hypertension, n(%)	244 (55.1%)	182 (61.9%)
Hypercholesterolemia , n(%)	94 (21.2%)	79 (26.9%)
Renal failure, n(%)	92 (20.8%)	78 (26.5%)
Diabetes mellitus, n(%)	97 (21.9%)	75 (25.5%)
3 months		
No flares, n(%)	324 (73.1%)	241 (82.0%)
1 flare, n(%)	53 (12.0%)	22 (7.5%)
2 flares, n(%)	29 (6.6%)	13 (4.4%)
3 flares, n(%)	16 (3.6%)	10 (3.4%)
4 flares, n(%)	6 (1.4%)	5 (1.7%)
5 or more flares, n(%)	10 (2.3%)	2 (0.7%)
ULT type[$]		
Allopurinol, n(%)	377 (85.1%)	283 (69.3%)
Benzbromarone, n(%)	37 (8.6%)	7 (2.4%)
Febuxostat, n(%)	27 (6.1%)	4 (1.4%)
ULT dose		
Allopurinol, median min/max	300 (50 – 900)	200 (100 – 700)
Benzbromarone, median min/max	100 (25 – 200)	100 (50 – 300)
Febuxostat, median min/max	80 (20 – 120)	60 (40 -80)
SU, mean mmol/l (SD)	0.30 (0.08)	0.37 (0.08) **
Reached target <0.36 mmol/l, n(%)	350 (79.0%)	51 (48.6) ***
Start ULT past year (since June 2019), n(%)	127 (28.7%)	18 (6.12)

** Only known for 105 (35.7%) of GP patients

*** Calculated for patients with known SU level (426 rheumatology patients and 105 GP patients)

Supplementary table s2: Multilevel model of the association between physicians' NCD score and prescribing behaviour, gout outcomes, and patients' NCD score.

		Model		Adjusted model		
		Value b of OR	ICC	Value b of OR	ICC	Adjusted for
Latest known SU level (b)	NCD physician	-0.002 (95% CI -0.007 to 0.002)	0.419	0.001 (95% CI -0.003 to 0.005)	0.202	Primary vs secondary care, sex[b] Work experience, hours of patient contact, number of gout consultations, age[b], , renal failure, start ULT past year.
SU target reached with latest known sUA level (OR)	NCD physician	1.06 (95% CI 0.91 to 1.24)	0.470	0.96 (95% CI 0.86 to 1.07)	0.113	Primary vs secondary care, sex[a,b], work experience, hours of patient contact, number of gout consultations, Age[b] renal failure, start ULT past year.
Highest prescribed dose allopurinol (b)	NCD physician	5.57 (95% CI 0.87 to 10.27)	0.166	0.80 (95% CI -2.96 to 4.57)	0.065	Primary vs secondary care, hours of patient contact, number of gout consultations, age[b], Sex[b] diabetes mellitus, renal failure, start ULT past year.
Flares past 12 months (OR)	NCD physician	1.03 (95% CI 0.98 to 1.08)	0.009	1.00 (95%CI 0.95 to 1.06)	0.00	Primary vs secondary care, work experience, hours of patient contact, number of gout consultations, hypertension, start ULT past year.
NCD patients (b)	NCD physician	0.04 (95% CI -0.09 to 0.18)	0.036	0.08 (95% CI -0.06 to 0.22)	0.027	Primary vs secondary care, number of gout consultations, diabetes mellitus.

NCD = Necessity concern difference, b = b coefficient, OR = Odds Ration, ICC = Intra class correlation coefficient

[a]= physician

[b] = patient

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Supplementary table s3: The association between physicians' necessity beliefs and dose of allopurinol, gout outcomes, and patients' necessity beliefs.

	Allopurinol dose (mg)	Serum urate level (mmol/l)	Necessity score patients	Targets SU y/n	Flares past 3 months y/n
	b Adj* (95% CI)	b Adj^ (95% CI)	b Adj# (95% CI)	OR Adj^^ (95% CI)	OR Adj** (95% CI)
Necessity score physician	0.17 (-5.08; 5.42)	0.00 (-0.00; 0.01)	0.04 (-0.12; 0.19)	0.95 (0.82; 1.10)	1.00 (0.92 ;1.09)
ICC	0.07	0.20	0.02	0.11	0.00

b= unstandardized beta, OR= odds ratio, ICC= Intraclass correlation coefficient, SU= serum urate level, adj= adjusted, CI= confidence interval.
* Adjusted for: **Primary vs secondary care**, hours of patient contact, number of gout consultations, **age patient**, sex patient, diabetes mellitus, renal failure and **start ULT past year**. ^ Adjusted for: **Primary vs secondary care**, **work experience**, hours of patient contact, number of gout consultations, **age patient**, **sex patient**, **renal failure** and **start ULT past year**. # Adjusted for: Primary vs secondary care, hours of patient contact, and **hypertension**. ^^ Adjusted for: **Primary vs secondary care**, sex physician, **work experience**, hours of patient contact, number of gout consultations, age patient, sex patient, **renal failure** and **start ULT past year**. ** Adjusted for: Primary vs secondary care, work experience, number of gout consultations and **start ULT past year**. Covariates denoted in **bold** are significantly associated with outcome parameter ($p < 0.05$)

Supplementary table s4: The association between physicians' concern beliefs and dose of allopurinol, gout outcomes, and patients' concern beliefs.

	Allopurinol dose (mg)	Serum urate level (mmol/l)	Concerns score patients	Targets SU y/n	Flares past 3 months y/n
	b Adj* (95% CI)	b Adj^ (95% CI)	b Adj# (95% CI)	OR Adj* (95% CI)	OR Adj^ (95% CI)
Concern score physician	-2.09 (-9.08; 4.91)	-0.00 (-0.01; 0.01)	-0.02 (-0.18; 0.14)	1.05 (0.87;1.26)	1.06 (0.95;1.18)
ICC	0.07	0.19	0.00	0.11	0.00

b= unstandardized beta, OR= odds ratio, ICC= Intraclass correlation coefficient, SU= serum urate level, adj= adjusted, CI= confidence interval.
* Adjusted for: **Primary vs secondary care**, work experience, hours of patient contact, number of gout consultations, **age patient**, sex patient, diabetes mellitus, renal failure and **start ULT past year**. ^ Adjusted for: **Primary vs secondary care**, **work experience**, hours of patient contact, number of gout consultations, age patient, **sex patient**, **renal failure** and **start ULT past year**. # Adjusted for: **Primary vs secondary care**, work experience, number of gout consultations and start ULT past year. ^^ Adjusted for: **Primary vs secondary care**, sex physician, **work experience**, hours of patient contact, number of gout consultations, age patient, sex patient, **renal failure** and **start ULT past year**. * Adjusted for: Primary vs secondary care, work experience, hours of patient contact, number of gout consultations and **start ULT past year**. Covariates denoted in **bold** are significantly associated with outcome parameter ($p < 0.05$)

Chapter 7

General discussion

In this thesis the value of several potential targets, both patient and physician related, to improve suboptimal treatment in gout patients were explored.
In this discussion main outcomes of this thesis will be discussed within the following themes:
- Personalisation of care for gout patients
- Role of beliefs about urate-lowering therapy and beliefs regarding gout in general on treatment of gout patients
- Further possibilities to improve treatment outcomes of gout

Personalisation of care for gout patients

Personalised pharmacological care is already used in clinical practise as dose of urate-lowering therapy is titrated based on serum urate levels and disease activity. Furthermore, urate-lowering therapy is changed in case of side effects. However, in usual care a relevant number of patients does not reach their treatment target[1-3]. Therefore, personalised care could be further investigated in gout patients. A more personalised treatment strategy might yield a better treatment response. A more personalised approach during consultations might lead to better involvement and adherence to therapy and eventually lead to a higher number of patients reaching their treatment target.

In this thesis the value of several potential targets in further personalising the care for gout patients were studied. We studied the influence of characteristics of patients on treatment response in our retrospective cohort of secondary care gout patients. Furthermore, we studied whether patients in remission have monosodium urate crystal depositions visible on dual-layer spectral computed tomography (dlSCT) scan. The presence of monosodium urate crystal depositions might be a valuable biomarker and influence further treatment choices in patients in clinical remission. In addition, we explored which factors are important for patients when stopping or continuing of their urate-lowering therapy, while in remission, is considered.

Personalisation of pharmacotherapy

Our hypotheses that women might respond better on benzbromarone compared to allopurinol and that metformin would have an additional anti-inflammatory and serum urate lowering effect were not confirmed[4,5]. Our findings indicate that personalised treatment strategies based on sex and use of metformin are not in place.

However, it is conceivable that personalising treatment in patients with gout and comorbidities might be valuable, considering that a substantial number of gout patients have underlying comorbid conditions[6]. There are pharmacological treatment options indicated for patients with heart failure and type 2 diabetes mellitus which (possibly) have a serum urate lowering effect. Next to metformin, these include among others losartan and SGLT2 inhibitors such as canagliflozin[7-9]. Especially the SGLT2 inhibitors show promising results in recently published studies. Patients using a SGLT2 inhibitor have a lower risk for incident gout compared to patients using a DPP4 inhibitor such as linagliptin[9]. It would be valuable to examine whether these medications also have a serum urate lowering effect in patients already using urate-lowering therapy.

In conclusion, it is recommended to continue studying the potential of medicines already used for comorbidities in gout patients, specifically focusing on their anti-inflammatory and serum

urate lowering effects. This approach can provide valuable insights into the therapeutic benefits of these medications for managing gout and its associated comorbidities. They might play a role in patients who fail to reach treatment target with solely urate-lowering therapy, or even in patients who are not able to use general urate-lowering therapies due to side effects or contraindication based on comorbidities.

Personalisation based on dlSCT scan results

Another potential way to personalise gout care is to use imaging techniques to support treatment decisions. One of the potential imaging techniques is the dlSCT scan. Presence of monosodium urate depositions on a dual-energy computed tomography (DECT) scan, a scan technique leading to similar results compared to dlSCT[10], already showed to be predictive for recurrent flares in a group of patients treated with urate-lowering therapy[11]. In chapter 4 we showed that a substantial proportion (57%) of patients who are treated with urate-lowering therapy and in clinical remission for at least one year still have monosodium urate depositions detected by a dlSCT scan. Presence of urate depositions might be a biomarker for recurrent gout flares for patients in remission stopping with their urate-lowering therapy. If this is indeed the case will be investigated in the ongoing GO-TEST Finale trial[12]. Together with other potential predictive biomarkers, such as lab markers, this might lead to a personalised treatment strategy for urate-lowering therapy in patients in remission. Ideally, a predictive model should be developed to determine the strongest predictors for (un)successful stopping with urate-lowering therapy.

Important factors for patients when considering stopping with urate-lowering therapy

In chapter 5 we explored which factors are important for patients in remission when considering stopping or continuing with urate-lowering therapy. Factors important for patients include perceived risk of joint damage, a feeling of reassurance that urate-lowering therapy gives, and risk of recurrent flares. These factors can provide physicians valuable information on which topics are important for patients treated with urate-lowering therapy in remission and should be discussed during shared decision making regarding further treatment. Although in a different treatment phase, patients not in remission might find additional information on these factors helpful as well.

In conclusion, our studies on personalisation of pharmacotherapy did lead to new insights on between-sex differences and use of metformin. However our results do not warrant adaptation of current treatment guidelines, as further research is necessary. The results of a dlSCT scan might be a promising biomarker in treatment choices in patients in remission and with the factors stated as important by patients in remission physicians might be better informed in what to discus to optimise shared decision making. Considering the latest research results, it is important to study the effect on gout outcomes of promising medications like SGLT2 inhibitors. Specifically, investigating their potential usefulness in patients who fail to reach their treatment targets with urate-lowering therapy is a valuable area of exploration.

Role of beliefs about urate-lowering therapy and beliefs regarding gout in general on treatment of gout patients

In chapter 6 we studied the beliefs of physicians and their patients about urate-lowering therapy[13]. We found that rheumatologists had higher necessity beliefs and lower concern beliefs about urate-lowering therapy compared to general practitioners. These differences

in beliefs had no influence on prescribed dosage of urate-lowering therapy and other gout treatment outcomes like serum urate levels and flares and beliefs of patients and are therefore not an intervention target to improve the number of patients reaching their treatment target.

Beliefs on gout in general

In addition to the beliefs on urate-lowering therapy, beliefs on gout in general and knowledge on gout might play a role in gout treatment. Following the theory of planned behaviour, beliefs of physicians can influence their disease management[14].

There are multiple studies performed on beliefs in general and/or knowledge regarding gout in patients, physicians, and the general population. These studies show some outcomes of interest which might influence gout treatment and gout outcomes in patients. They mention for example a lack of knowledge, possibly inducing false beliefs about gout and its treatment in both patients and physicians[15,16]. Furthermore, it was found that patients feel stigmatised and experience a negative stereotypical image[15,16]. In addition, a survey showed that the general population described gout as a self-induced disease. However, when performing the same survey with the term crystal arthritis it was seen as a serious chronic condition that needs treatment[17]. Above mentioned studies did not test if their results were associated with gout treatment outcomes, which might be of interest to study in future research.

Therefore, despite the results of our study, treating physicians must be aware of their own beliefs and state of knowledge on gout and urate-lowering therapy and how they might influence their patients. Furthermore, these, in general, negative images may impact the adherence to urate lowering of gout patients unknowingly. It is important to be aware of this and address this during consultations.

Further possibilities to improve treatment outcomes of gout

The major challenge within gout treatment is the relevant number of patients who do not reach their treatment target due to suboptimal treatment[1,3], resulting in recurrent flares, tophi and joint damage. As stated above, shared decision making, where patients and physicians make treatment decisions together based on all available evidence and preferences of patients, is important during consultations[18]. Getting patients more involved in decision-making will increase their knowledge on gout and its treatment and may help increasing the adherence numbers among gout patients[19].

In addition to shared decision making it is important to stay connected with the patient. Multiple studies on gout and treatment outcomes showed promising results regarding serum urate levels and reduction of flares in patients who had more time/contact, either in person or through digital applications, with a physician or specialised nurse[20-22].

Although these studies show promising results, implementation strategies have not been proposed. All studies worked around an intervention wherein patients have more contact with their health care provider or have more external stimulations, like reminders in applications to take their medication. Staying connected seems to be an important condition for patients to adhere to their therapy. More implementation studies should be performed to study which strategy or device or combination is most feasible and cost effective. A combination of more intensified contact with health care providers during the first year of treatment followed by

an e-health solution could be successful in raising the number of patients who reach their serum urate targets and disease remission.

Methodological considerations

Retrospective cohort data; challenges and benefits

In chapter 2 and chapter 3 we used data of our created retrospective secondary care cohort to answer the research questions. The use of retrospective cohort data is challenging, but also has its benefits. First challenge is the development of the retrospective cohort, which was quite a task. In our case we used over fifteen different research assistants to manually fill our cohort with data from three hospitals, all using different electronic health record systems, which took an average of one hour per patient resulting in a combined workload of over 2000 hours. This made the development sensitive for errors and missing data. Multiple data checks were performed and adjustments in the data were made to optimise data completeness and correctness. However, with the current developments in the field of artificial intelligence and machine learning there might by a more robust solution in building cohort data from different electronic health record systems. Hospitals wishing to perform research on their data should accommodate this. Secondly, physicians' notes of consultations are very heterogeneous, especially on gout flares, and made it difficult to fully fill every consult file in our cohort. This can be easily solved if hospitals use standardised forms for several types of consults.

Major benefit of our retrospective cohort is the amount of data which can be collected within a brief period of time. Our cohort had data of three types of hospitals, an academic hospital, a general hospital, and a hospital specialised in movement disorders. With over 2400 patients our cohort has an extensive amount of data which facilitates to study several research questions and sub populations within gout as we did with women and gout patients with diabetes. It is also easy to add data to the cohort if needed. In our case, after deciding to study diabetic gout patients, we added more specific data on their medicine use. Furthermore, the development of a retrospective cohort is less expensive compared to a prospective cohort.

Thus, in my view the use of retrospective cohort data is valuable in research if the data source is well documented, and the development of the cohort can be done automatically with manual checks.

In addition, since the majority of gout patients is treated within primary care settings (18), it is important to not only limit retrospective cohorts to secondary care patients, but to include primary care patients as well. Fortunately, there are initiatives that collect data of multiple primary care practice and make them available for research. Researchers should include this data when studying gout and its treatment in clinical setting.

Generalisability of the presented studies

As mentioned above, the majority of the gout patients is treated in primary care setting[23]. What does that mean for the generalisability of the results from our retrospective cohort studies (chapter 2 and 3) to the whole gout population? Although the patients included in these studies do reflect the current gout population in secondary care where patients often present with more severe gout and there is more intensified monitoring, our results might still be applicable to the gout population in primary care, because in the Netherlands treatment strategies are

similar between primary and secondary care[24,25]. Therefore, results of our retrospective cohort regarding treatment choices are applicable in primary care as well. Nevertheless, I would still advise to use primary care data in cohorts to be more inclusive as mentioned earlier. This also might give an opportunity to perform extensive sub group analyses.

In the studies presented in chapters 5 and 6 we also included patients and physicians (chapter 6) from primary care practices. However, their number was lower than patients and physicians in secondary care which led to a slightly underpowered study due to a small group of general practitioners (chapter 6) and underrepresentation within the primary care group (chapter 5). However, in my opinion this does not lead to results which cannot be used in primary care practice due to the observational design of the studies and the separate presentation of results for primary and secondary care.

Conclusions and implications for clinical practice

The following conclusion and implications for clinical practice come forward from the main findings and general discussion:

- We found no between-sex differences regarding response to either benzbromarone or allopurinol.
- Metformin has no clinically relevant anti-inflammatory and serum urate lowering effect in patients starting with urate-lowering therapy and flare prophylaxis.
- Patients in remission are frequently not free of monosodium urate crystal depositions.
- Factors which are most important when considering continuation or discontinuation of urate-lowering therapy for patients include perceived risk of joint damage, the certainty that urate-lowering therapy provides and risk of recurrent flares. These should be discussed with patients in a process of shared decision making when considering (dis)continuation of urate-lowering therapy.
- Beliefs on urate-lowering therapy differ between rheumatologists and general practitioners, but these differences have no major impact on gout outcomes in patients treated with urate-lowering therapy.

Future research

The following research topics should be addressed in the future, based on the results of the studies and general discussion presented in this thesis:

- Studying effect of medication for comorbidities (for example SGLT2).
- To determine what is the best long term ULT treatment approach in patients with gout in clinical remission while using ULT and if dISCT/DECT scan can help in decision making in this phase.
- In addition to the beliefs on urate-lowering therapy, beliefs in general on gout in physicians and patients and their relation to gout outcomes should be studied. Furthermore more awareness on gout and its impact should be created to improve the negative stereotypical image of gout.
- Research on how to effectively implement successful trial strategies in current care to improve gout treatment, including self-management and e-health strategies and to determine which strategies are most effective.

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Nederlandse samenvatting

Jicht is een ontstekingsreuma die wordt gekenmerkt door aanvallen van gewrichts-ontstekingen. Behandeling van aanvallen van jicht bestaat uit het gebruik van ontstekingsremmende medicijnen zoals colchicine. Bij terugkerende aanvallen wordt urinezuurverlagende therapie geadviseerd. Ondanks dat jicht goed te behandelen is, is de behandeling in de praktijk vaak suboptimaal en halen veel mensen niet het beoogde behandelresultaat. Er zijn verschillende barrières bekend die een optimale behandeling in de weg staan zoals gebrek aan kennis bij patiënten en artsen, suboptimale therapietrouw bij patiënten en het niet optimaal volgen van richtlijnen door artsen. In dit proefschrift zijn mogelijke aangrijpingspunten onderzocht om de behandeling met urinezuurverlagende therapie te optimaliseren.

In hoofdstuk 2 is onderzocht of er verschillen zijn tussen vrouwen en mannen in het profijt van verschillende vormen van urinezuurverlagende therapie. We vonden geen verschillen tussen vrouwen en mannen in hun reactie op diverse typen urinezuurverlagende therapie. Daarom is het niet noodzakelijk om richtlijnen ten aanzien van het voorschrijven van urinezuurverlagende therapie te baseren op sekse.

Hoofdstuk 3 heeft de toegevoegde waarde van metformine, een veel gebruikt diabetes medicijn, onderzocht in de behandeling van jicht patiënten. Onze bevindingen tonen aan dat metformine geen aanvullend ontstekingsremmend of urinezuur verlagend effect heeft bij patiënten die al urinezuurverlagende en ontstekingsremmende medicatie gebruiken.

In Hoofdstuk 4 is onderzocht of jichtpatiënten, die met behandeling al meer dan een jaar volledig klachtenvrij zijn ('in remissie'), ook vrij zijn van ophopingen van jicht kristallen in hun gewrichten. Met behulp van een relatief nieuwe beeldvormende techniek, de dual-energy CT scan, kunnen betrouwbaar jicht kristallen in het lichaam worden aangetoond. In deze studie bleek dat bij ruim de helft van de patiënten nog kristalophopingen aanwezig waren. Het is echter nog onduidelijk of deze kristalophopingen, niet zichtbaar bij lichamelijk onderzoek, een rol spelen bij het optreden van nieuwe opvlammingen van jicht bij patiënten in remissie.

Hoofdstuk 5 heeft onderzocht welke factoren patiënten in remissie belangrijk vinden bij het overwegen om door te gaan met of te stoppen met hun urinezuurverlagende therapie. De drie belangrijkste aspecten waren het risico op gewrichtsschade, het gevoel van geruststelling die urinezuurverlagende therapie geeft en het risico op terugkerende jichtaanvallen. Deze informatie kan door artsen worden gebruikt tijdens gesprekken over het doorgaan of stoppen van urinezuurverlagende therapie.

Hoofdstuk 6 heeft de opvattingen die artsen hebben over urinezuurverlagende therapie onderzocht. Reumatologen bleken een grotere overtuiging te hebben van de noodzaak van deze therapie en minder zorgen over gebruik ervan in vergelijking met huisartsen. Dit verschil in opvattingen had in deze studie echter geen invloed op de dosering van urinezuurverlagende therapie, uitkomsten van de behandeling en opvattingen van patiënten.

Samenvattend concluderen we dat er geen noodzaak is om verschillende behandelstrategieën te hanteren op basis van geslacht of het gebruik van metformine. Patiënten in remissie kunnen nog langdurig kristalophopingen houden, die niet zichtbaar zijn bij lichamelijk onderzoek. Het risico op gewrichtsschade blijkt een belangrijke factor te zijn voor patiënten terwijl

overtuigingen van artsen geen invloed lijken te hebben op de dosering van urinezuurverlagende therapie. Toekomstig onderzoek is nodig om te bepalen hoe de behandeling van jicht verder verbeterd kan worden.

Fryske gearfetting

Jicht is in ûntstekkingsreuma dy't skaaimerke wurdt troch oanfallen fan gewrichtsûntstekkingen. Behanneling fan jichtoanfallen bestiet út it gebrûk fan ûntstekkinsferminderjende medisinen lykas colchicine. By weromkommende oanfallen wurdt urinesoerferleegjende terapy advisearre. Nettsjinsteande dat jicht goed te behanneljen is, is de behanneling yn de praktyk faak suboptimaal en helje in soad minsken net it bedoelde behannelresultaat. Der binne ferskillende barriêres bekend dy't in optimale behanneling ferhinderje, lykas it gebrek oan kennis by pasjinten en dokters, it net trou ûndergean fan terapy by pasjinten en it net foldwaande folgjen fan richtlinen troch dokters. Yn dit proefskrift binne mooglike oangripingspunten ûndersocht om de behanneling mei urinesoerferleegjende terapy te optimalisearjen.

Yn haadstik 2 is ûndersocht of der ferskillen binne tusken froulju en manlju yn it profyt hawwen fan ferskillende foarmen fan urinesoerferlaagjende terapy. Wy fûnen gjin ferskillen tusken froulju en manlju yn harren reaksje op ferskate typen urinesoerferlaagjende terapy. Dêrom is it net needsaaklik om rjochtlinen ta oansjen fan it foarskriuwen fan urinesoerferlaagjende terapy te basearjen op sekse.

Haadstik 3 hat de tafoege wearde fan metformine, in faak brûkt diabetesmedisyn, ûndersocht yn de behanneling fan jichtpasjinten. Us ûnderfiningen toane oan dat metformine gjin oanfoljend ûnstekkingsremjend of urinesoerferleegjend effekt hat by pasjinten dy't al urinesoerferleegjende en ûnstekkingsremjende medikaasje brûke.

Yn haadstik 4 is ûndersocht oft jichtpasjinten, dy't mei in behanneling al mear as in jier folslein klachtefrij binne ('yn remisje'), ek frij binne fan opheappingen fan jichtkristallen yn harren gewrichten. Mei help fan in relatyf nije byldfoarmjende technyk, de dual-ernegy CT scan, kinne jichtkristallen yn it lichem betrouber oantoand wurde. Ut dizze stúdzje die bliken dat by rom de helte fan de pasjinten noch kristalopheappingen oanwêzich wiene. It is lykwols noch ûndúdlik oft dizze kristalopheappingen, net sichtber by lichaamlik ûndersyk, in rol spylje by it optreden fan nije opflammingen fan jicht by pasjinten yn remisje.

Haadstik 5 hat ûndersocht hokker faktoaren pasjinten yn remisje wichtich fine by it oerwegen om troch te gean of op te hâlden mei harren urinesoerferleegjende terapy. De trije wichtichste aspekten wiene it risiko op gewrichtsskea, it gefoel fan gerêststelling dy't urinesoerferleegjende terapy jout en it risiko op weromkommende jichtoanfallen. Dy ynformaasje kin troch dokters brûkt wurde yn petearen oer it trochgean of ophâlden mei urinesoerferleegjende terapy.

Haadstik 6 hat de opfettingen dy't dokters hawwe oer urinesoerferleegjende terapy ûndersocht. Reumatologen blieken in gruttere oertsjûging te hawwen fan de needsaak fan dizze terapy en ek minder soargen te hawwen oer it gebrûk derfan yn ferliking mei húsdokters. Dit ferskil yn opfettingen hie yn dizze stúdzje lykwols gjin ynfloed op de dosearring fan urinesoerferleegjende terapy, de útkomsten fan de behanneling en de opfettingen fan pasjinten.

Gearfetsjend konkludearje wy dat der gjin needsaak is om ferskillende behannelstrategyen te hantearjen op basis fan slachte of it gebrûk fan metformine. Pasjinten yn remisje kinne noch langduorjend kristalopheappingen hâlde, dy't net sichter binne by lichaamlik ûndersyk. It risiko op gewrichtsskea blykt in wichtige faktor te wêzen foar pasjinten wylst oertsjûgingen

fan dokters gjin ynfloed lykje te hawwen op de dosearring fan urinesoerferleegjende terapy. Takomstich ûndersyk is nedich om te bepalen hoe't de behanneling fan jicht fierder ferbettere wurde kin.

Research data management

Research data management

The research data in this thesis was collected at the department of Rheumatology in the Sint Maartenskliniek, the department of Rheumatology in the Radboudumc, the department of Rheumatology in Rijnstate hospital and participating general practices. Research Data Management was conducted according to the FAIR principles. A detailed description of how these FAIR principles were applied is provided below.

Ethics and privacy

The data collected for this thesis was obtained from human subjects. For the studies described in chapter 2, 3, 5 and 6 a waiver for ethical approval by the Medical Ethical Committee Oost-Nederland, the Netherlands was provided. Ethical approval for the study described in chapter 4 was obtained from the same medical and ethical review board under registration number: NL74350.091.20. Patients of whom data was used in studies described in chapter 2 and 3 gave consent via opt-in or opt-out procedure depending on institution guidelines. Patients participating in studies described in chapter 4, 5 and 6 all gave written informed consent. The privacy of all patients was warranted by using unique and encrypted identification codes. Keys were stored separately from study data and only accessible by study team members.

Fair principles

Findable: All the data that was obtained during the studies is stored on department servers (Sint Maartenskliniek under V:\research_reuma_studies). Non-electronical data were stored at the research department of the Sint Maartenskliniek and after completion stored at the archive of the research department of the Sint Maartenskliniek.
Accessible: All data will be available upon reasonable request to the corresponding author or by contacting the staff secretary of the research department of the Sint Maartenskliniek (secretariaat.research@maartenskliniek.nl). Data, codes and syntaxes are stored on the server of the research department which is only accessible by assigned employees (V:\ research_reuma_studies).

Interoperability: Data of studies described in chapters 2, 3, 4, and 6 were collected by electronic case reports forms in CASTORedc and for analyses stored in Excel. Data of the study described in chapter 5 was first collected through Sawtooth discover software and later stored in Excel. Data of all studies was analysed in STATA vs 13 or 17. One sub analysis described in chapter 5 was performed in SPSS.

Reusable: Data will be saved for 15 years after termination of the individual studies. Using these data in the future is only possible if patients gave permission in their informed consents (if applicable) or if renewed permission is gained.

List of publications

List of publications

This thesis

Veenstra F, Wanten SAC, Verhoef LM, Ter Stal M, Kwok WY, van den Hoogen FHJ, Flendrie M, van Herwaarden N. Sex differences in response to allopurinol and benzbromarone in gout: a retrospective cohort study. Rheumatol Adv Pract. 2021 Jan 28;5(1):rkab002.

Veenstra F, Verhoef LM, Opdam M, den Broeder AA, Kwok WY, Meek IL, van den Ende CHM, Flendrie M, van Herwaarden N. Effect of metformin use on clinical outcomes and serum urate in gout patients with diabetes mellitus: a retrospective cohort study. BMC Rheumatol. 2022 May 31;6(1):27.

Veenstra F, Peeters IR, Jens S, Boks S, den Broeder AA, van den Ende CHM, van Herwaarden N, Flendrie M. Presence and characteristics of tophi on dual-energy computed tomography in gout patients in clinical remission. [Submitted]

Peeters IR, **Veenstra F**, Wanten SAC, Vriezekolk JE, van den Ende CHM, den Broeder AA, van Herwaarden N, Verhoef LM, Flendrie M. Gout patients' perspective on continuation or discontinuation of urate-lowering therapy during remission: a mixed methods study. [Submitted]

Veenstra F, Vriezekolk JE, van den Bemt BJF, Schers HJ, Sloot B, van den Ende CHM, van Herwaarden N, Flendrie M. Beliefs of rheumatologists and general practitioners on urate lowering therapy: a cross-sectional study. Rheumatol Adv Pract. 2023 Apr 10;7(2):rkad033.

Conference abstracts

Veenstra F, Verhoef LM, Nieboer LM, den Broeder AA, Kwok WY, Meek I, van den Hoogen FHJ, van Herwaarden N, Flendrie M. No difference in gout flares after initiation of urate lowering therapy between once or twice daily 0.5 mg colchicine prophylaxis. ECN congress 2020 (poster presentation), EULAR congress 2020 (poster presentation)

Veenstra F, Verhoef LM, Opdam M, den Broeder AA, Kwok WY, Meek IL, van den Ende CHM, Flendrie M, van Herwaarden N. Effect of metformin use on clinical outcomes and serum urate in gout patients with diabetes mellitus: a retrospective cohort study. ECN congress 2020 (oral presentation), EULAR congress 2020 (poster presentation)

Peeters IR, **Veenstra F**, Wanten SAC, Vriezekolk JE, van den Ende CHM, den Broeder AA, van Herwaarden N, Verhoef LM, Flendrie M. Gout patients' perspective on continuation or discontinuation of urate-lowering therapy during remission: a mixed methods study. EULAR congress 2023 (poster presentation)

Veenstra F, Vriezekolk JE, van den Bemt BJF, Schers HJ, Sloot B, van den Ende CHM, van Herwaarden N, Flendrie M. Beliefs of rheumatologists and general practitioners on urate lowering therapy: a cross-sectional study. ECN congress 2021 (poster presentation), EULAR 2021 (Abstract book)

PhD portfolio

PhD portfolio of Frouwke Veenstra

Department: Research Sint Maartenskliniek
PhD period: 02/09/2019 – 15/01/2024
PhD Supervisor(s): Dr. CHM van den Ende, Prof. Dr. FHJ van den Hoogen
PhD Co-supervisor(s): Dr. M Flendrie, Dr. N van Herwaarden

Training activities	Hours
Courses	
RIHS - Introduction course for PhD candidates (2020)	15.00
RU - Projectmanagement voor Promovendi (2020)	45.00
RU - Scientific Writing for PhD candidates (2021)	84.00
Longitudinal and multilevel anlaysis (2021)	84.00
Radboudumc - Scientific integrity (2021)	20.00
EBrok course (2021)	14.00
Loopbaanmanagement voor promovendi (2021)	28.00
RU - The Art of Finishing Up (2022)	10.00
Seminars	
Regionale refereeravond (2019) (Oral presentation)	12.00
Weten en eten (2019)	4.00
Weten en eten (2021)	4.00
Regionale refereeravond (2022)	4.00
Junior refereren Epidemiologie (2022)	154.00
Regionale refereeravond (2023) (Oral presentation)	12.00
Conferences	
EULAR 2020 (2020) (Poster presentation)	24.00
ECN 2020 (2020) (Oral presentation & poster presentation)	32.00
ECN 2021 (2021) (Poster presentation)	16.00
PhD retreat (2022)	16.00
EULAR 2022 (2022)	32.00
WEON (2022)	16.00
Other	
Research lunches (2022)	28.00
Teaching activities	
Supervision of internships / other	
Supervision master student physician assistant (2020)	56.00
Supervision master student medicine (2020)	56.00
Research your own data (2022)	28.00
Total	**794.00**

Dankwoord

Dankwoord

Promoveren is een reis met pieken en dalen, een reis die zo nu en dan vertraging kent en een reis waar halverwege het plan wordt aangepast. Gelukkig is het een reis die je nooit in je eentje volbrengt. Ik wil graag al mijn reisgenoten die mij hebben bijgestaan danken voor hun wijze woorden, luisterend oor, wandelingen, goede gesprekken, thee momenten, momenten met een lach, momenten met een traan, muzikale momenten, sportieve momenten en alles wat we nog meer hebben meegemaakt afgelopen 4,5 jaar.

Curriculum vitae

Curriculum vitae

Frouwke Veenstra werd op 16 juli 1992 geboren in Enschede. In 2010 haalde zij haar HAVO diploma aan het csg Liudger te Drachten. Datzelfde jaar startte ze met de opleiding Medische Beeldvormende en Radiotherapeutische technieken aan de Hanze Hogeschool te Groningen. Na het behalen van haar bachelor diploma in 2014 startte ze met de pre-master en de daarop volgende de master Biomedical Sciences aan de Radboud universiteit te Nijmegen. Tijdens haar master volgde ze een wetenschappelijke stage bij het Koninklijk instituut voor de Tropen en een consultancy stage bij GGD Gelderland-Zuid.

In 2019 startte Frouwke als promovenda bij de afdeling research van de Sint Maartenskliniek. Ze werd daarbij begeleidt door Dr. Els van den Ende, Prof. Dr. Frank van den Hoogen, Dr. Marcel Flendrie en Dr. Noortje van Herwaarden. Ze heeft verschillende onderzoeken gedaan om de behandeling van jicht te optimaliseren. Deze staan beschreven in dit proefschrift.

Afgelopen anderhalf jaar heeft zij gewerkt als projectmedewerker Gezondheidsmonitors bij GGD GHOR Nederland. In februari zal zij weer aan de slag gaan in de Sint Maartenskliniek. Dit keer op de afdeling radiologie als Medisch Beeldvormings- en Bestralingsdeskundige.

Theses Sint Maartenskliniek

Theses Sint Maartenskliniek

De Jong, L.A.F. (2023). *Effects of lower limb orthotic devices in people with neurological disorders.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Michielsens, C. (2023). *Tapering strategies of biologics in inflammatory disorders*. Radboud University Nijmegen, Nijmegen. The Netherlands.

Pouls, B. (2023). *Supporting patients'medication management using eHealth. Test cases in rheumatology*. Radboud University Nijmegen, Nijmegen. The Netherlands.

Stöcker, J. (2023). *Accessible and effective non-pharmacological care for persons with systemic sclerosis*. Radboud University Nijmegen, Nijmegen. The Netherlands.

Mulder, M. (2022). *Going off-road. Exploring and mapping psoriatic arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Huiskes, V. (2022). *The synergistic role of patients and healthcare providers in reducing drug-related problems.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Marsman, D. (2022). *Polymyalgia rheumatica. Clinical characteristics and new treatment opportunities.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Alingh, J. (2021). *Effect of robotic gait training on the post-stroke gait pattern. Evaluation of LOPES II.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Dijsseldonk, R. (2021). *Step into the future: mobility after spinal cord injury*. Radboud University Nijmegen, Nijmegen, The Netherlands.

Pelle, T. (2021). *Beating osteoarthritis by e-self management in knee or hip osteoarthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Heuckelum, M (2020). *Novel approaches to improve medication adherence in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Mathijssen, E. (2020). *The voice of patients with rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bakker, S. (2019). *Regional anesthesia and total knee arthroplasty. Anesthetic and pharmacological considerations.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Claassen, A. (2019). *Strategies for patient education in rheumatic diseases.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Fenten, M. (2019). *Optimizing locoregional anesthesia in fast track orthopaedic surgery.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Minten, M. (2019). *On the role of inflammation and the value of low dose radiation therapy in osteoarthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Verhoef, L. (2019). *Effective and efficient use of bDMARDs in rheumatoid arthritis.* Radboud University Nijmegen, Nijmegen. The Netherlands.

Bekker, C. (2018). *Sustainable use of medication. Medication waste and feasibility of redispensing.* Utrecht University, Utrecht. The Netherlands.

Bikker, I.(2018). *Organizing timely treatment in multi-disciplinary care.* University of Twente, The Netherlands.

Bouman, C. (2018). *Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors.* Radboud University Nijmegen, The Netherlands.

Mahler, E. (2018). *Contributors to the management of osteoarthritis.* Utrecht University, The Netherlands.

Tweehuysen, L. (2018). *Optimising biological treatment in inflammatory rheumatic diseases. Predicting, tapering and transitioning.* Radboud University Nijmegen, Nijmegen, The Netherlands.

Geerdink, Y. (2017). *Getting a grip on hand use in unilateral cerebral palsy.* Radboud University, Nijmegen, The Netherlands.

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Van Hooff, M. (2017). *Towards a paradigm shift in chronic low back pain? Identification of patient profiles to guide treatment.* VU University Amsterdam, Amsterdam, The Netherlands.

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enning, L. (2015). *The effectiveness of injections in cuffdisorders and improvement of diagnostics.* Maastricht University, Maastricht, The Netherlands.

Stegeman, M. (2015). *Fusion of the tarsal joints: outcome, diagnostics and management of patient expectations.* Utrecht University, Utrecht, The Netherlands.

Van Herwaarden, N. (2015). *Individualised biological treatment in rheumatoid arthritis.* Utrecht University, Utrecht, The Netherlands.

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Smulders, E. (2011). *Falls in rheumatic diseases. Risk factors and preventive strategies in osteoporosis and rheumatoid arthritis.* Radboud University, Nijmegen, The Netherlands.

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Groen, B. (2010). *Martial arts techniques to reduce fall severity.* Radboud University, Nijmegen, The Netherlands.

Van Koulil, S. (2010). *Tailored cognitive behavioral therapy in fibromyalgia.* Radboud University, Nijmegen, The Netherlands.

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