Optimizing the management of patients with gout in daily practice

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CHAPTER 1

General introduction

Gout

Gout is the most common form of inflammatory arthritis worldwide (1). The prevalence and incidence of gout vary widely according to the population studied and methods employed but ranges from a prevalence of <1% to 6.8% and an incidence of 0.58–2.89 per 1,000 person-years (1). The prevalence of gout varies considerably due to geographic regions, or demographic factors such as age and sex. Gout is caused by monosodium urate (MSU) crystal deposition. An elevated serum uric acid (sUA) level (hyperuricemia) is the major risk factor for MSU crystal deposition and development of gout. Gout typically presents as an acute, self-limiting inflammatory mono-arthritis that affects the joints (2). Some patients experience only a few gout flares in their life, usually in the first metatarsophalangeal joint or midfoot. However, in the majority of patients gout becomes a chronic disease with relapsing gout flares in an increasing number of joints. In these patients' deposits of MSU crystals, so-called tophi, frequently emerge in the subcutaneous, sub-periostal or intra-osseous tissues, the latter resulting in structural joint damage. In a smaller subgroup of patients with chronic gout, flares occur without complete resolution of inflammation between flares and thus evolving to chronic arthritis.

In the last two decades, gout regained new interest and is worldwide rapidly increasing, partly because of longevity of populations, and increasing incidence in Western countries as a consequence of the obesity epidemic and partly because of the survival of patients with chronic heart and kidney disease with often complicated gout (3-5). Therefore, major progress has been made in the understanding of the pathogenesis, impact, diagnostic approaches to, and treatment of this disorder.

In this thesis, we aimed to improve our understanding of several aspects related to the management of gout in daily practice and investigate the role of patient-centered management of gout. This introductory chapter will provide background on these topics, and will specify the research objective and outline of the thesis.

Management of gout

Although gout is associated with a substantial burden of disease, it is a well-treatable disease. Lifestyle advices (e.g. weight loss, diminution of alcohol consumption if present, lower consumption of red meat) can result in a decrease of sUA level of about 0.10 mmol/L, but play a limited role in controlling gout (6). In the treatment of gout, a distinction is made between treatment of acute gout flares with different symptom-relieving drugs (colchicine, non-steroidal anti-inflammatory drugs or prednisone), and long-term management with urate-lowering therapy (ULT). The most recent European League Against Rheumatism (EULAR) guideline recommends to consider and discus initiation of ULT after a first gout flare and to treat towards a sUA level below 0.36 mmol/L, or below 0.30 mmol/L in complex cases (7). However, it remains unclear which target should be recommended in the treatment of gout: a 'Treat-to-Uric-Acid' target (American College of Rheumatology (ACR)/EULAR guidelines), or a 'Treat-to-Avoid-Symptoms' (T2AS) target (American College of Physicians (ACP) guidelines) (7-9). Also, the optimal sUA threshold in a 'Treat-to-Uric-Acid' target is being questioned. In the EULAR recommendations the sUA-target hinges upon urate levels below the threshold of ≤0.36 mmol/L, the level of saturation of sUA and of crystal formation (10). When tophi are present, or in case of frequent flares, a sUA target ≤0.30 mmol/L is recommended, to accelerate the dissolution of tophi (7). The British Society for Rheumatology (BSR) even recommends a sUA target ≤0.30 mmol/L for all gout patients (11). Finally, while several types of ULT drugs are available to reduce sUA, comprising xanthine oxidase inhibitors (XOI), uricosuric agents, or uricases, there is as yet no consensus on whether or when to consider combination of two Modes of Action (2MoA), i.e. a XOI plus an add-on of a uricosuric in the treatment (12). Currently, allopurinol is the first-line ULT by the EULAR recommendations, based on efficacy, safety and cost-effectiveness and febuxostat is indicated as second-line option (7). Uricosurics are recommended, where available, alone or in combination with allopurinol in patients without proper control with allopurinol alone.

Despite multiple recommendations and the wide availability of ULT drugs, the treatment of gout patients in clinical practice remains suboptimal (13-15). Suboptimal treatment has been attributed to an underestimation and unawareness of the burden of gout by both healthcare professionals and patients resulting in delays and poor adherence to treatment (16). Additionally, the lack of evidence

about the optimal target and most effective treatment strategy - creating distrust in guidelines - and limited attention for compliance to treatment have been identified by healthcare professionals as barrier to optimal treatment (9, 17, 18). To improve the quality of care (QoC) for patients with gout in clinical practice, there is high need to investigate and compare different treatment strategies for gout management.

Factors influencing gout treatment

Sex differences

As gout is the most common inflammatory arthritis globally, understanding trends in gout prevalence is of great importance. The prevalence of gout is influenced by demographic factors, such as ethnicity, age, and sex. Among patients with gout ≤ 65 years, the prevalence in men is four times higher than in women (19). Above this age, the prevalence of gout narrows to a more equal sex distribution, especially due to the sharper increase of the incidence in gout among older women (20, 21). There are a number of potential biological pathways explaining sex differences in the occurrence of gout, and most evidence points to the role of the uricosuric effect of oestrogens (22-25). In addition to the biological pathways explaining sex differences in hyperuricemia and onset of gout, differences in risk factors and clinical manifestations require attention (26, 27). Despite the increasing prevalence of gout, particularly in the aging female population, most studies are performed in predominantly male populations and few studies examine the differences between sexes (20, 28-30). To improve insight into sex differences, clinical characteristics and comorbidities between female and male gout patients need to be explored and compared, and specifically the influence of menopausal state on these differences.

Comorbidities

Besides the sex differences, gout is often accompanied by various comorbidities, including cardiovascular disease, chronic kidney disease, obesity and other conditions (1). In recent years, considerable advances have been made in understanding in particular the importance of obesity, lifestyle factors, comorbidities and genetics. Comorbidities and their treatment may have an effect on the development of gout and on the management choice (31, 32).

In an era that aims to make steps towards personalized health, research into differential responses to treatment across contextual factors becomes increasingly important as it allows to understand which subgroup of patients respond differently to available drugs or drug strategies. If differences in effect sizes across contextual factors are considered clinically relevant, clinical practice should be adapted. From a methodological point of view a contextual factor is defined as *"a variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers"* (33, 34). In 2018, a list of potential generic contextual factors that should be considered in trials for effect modification was identified by Outcome Measures in Rheumatology (OMERACT) based on scarce evidence from the literature and expert opinion; gender/sex, comorbidities, health care system, psychological wellbeing, adherence to treatment, age, and previous exposure to drugs were perceived as the seven most important factors. This set of potential contextual factors still needs to be confirmed in different rheumatic diseases. Further, it might be that in specific conditions or interventions other contextual factors might play a clinical important role. Currently it is (still) unclear if there is a different treatment response of ULT effectiveness across patients based on the presence of specific contextual factors such as comorbidities (e.g. heart and kidney diseases and obesity) and sex. Unraveling the influence of (different) contextual factors on effectiveness of gout treatment could lead to more guided and tailored strategies with better outcomes.

Patient needs

Healthcare professionals are critical to improving health outcomes for patients with gout by building understanding and knowledge about the disease, reducing stigmatization, and supporting patient involvement for gout management choices. Notwithstanding, several factors contribute to suboptimal gout care such as unawareness of disease severity and its management among healthcare professionals and patients, poor healthcare professionals' guideline adherence, poor patient medication adherence, and finally failure, intolerance or contra-indications (presence of comorbidities) of ULT (35, 36).

Around the turn of the 21st century, the call of patients to account for their personal situation and needs and to be involved in disease management decisions gave an impetus for healthcare to be more patient-centered (37). On that line, the Institute of Medicine emphasized the importance of patient-centeredness in addition to the effectiveness, safety, timeliness, equitability and efficiency as part of the six pillars of QoC (38). Patient-centered care is defined as measuring and responding to patient needs, experiences, and satisfaction with disease control (39). This paradigm shift urged healthcare providers to integrate patients' needs, goals, experiences, and satisfaction into the traditional biomedical and the patient reported health outcomes (38-40). While patients' experiences of care can be pertinent outcomes by themselves, they also might give insight why treatments may not reach the expected health outcomes in a real-world setting. In gout, there is little knowledge on the impact of gout on patient-centered outcomes, and its relationship with clinical health outcomes (41, 42). Furthermore, patients experiences is a multidimensional and complex construct, which can be measured as patients experiences towards the process of care or towards the outcome of care, complementary, but separate, components of treatment (43). Finally, to fully understand the outcomes of care, it has been repeatedly shown that not only patient- and care characteristics, but also country characteristics play a role (44-46). Knowledge about variations in gout health outcomes and the impact of experiences of care and relationships with patient and care characteristics on these outcomes might help healthcare professionals across countries to understand the reasons for suboptimal treatment and how to set priorities when enhancing QoC for gout patients.

Support tools for gout management

Shared decision-making is an important aspect of patient-centered care, in general as for the treatment of gout (47-50). Shared decision-making tools on the one hand can improve the implementation of treatment recommendations as it might be a support for healthcare professionals to consider all treatment possibilities (51). It can also enhance patients' confidence with a treatment as the patient contributes to the choice and believes and expectations of patients can be included in the decision (51). In this line, clinical guidelines increasingly recommend that healthcare professionals should involve patients in decisions about screening, treatment, and other interventions, to help them to arrive at informed choices (52).

Last but not least, when evaluating care, shared decision making tools, such as decision aids (DAs) may also reveal which treatments patients would prefer, even if that treatment option in not accounted for in management guidelines. To improve QoC in daily practice, there is need for a DA to support informed decisions and increase involvement for gout patients with one or more gout flares that need to start with (initial) ULT. A patient DA should be carefully developed, user-tested and open to scrutiny, with a well-documented and systematically applied development process exemplified in the International Patient Decision Aid Standards (IPDAS) recommendations (53).

Medication adherence to prescribed ULT is one of the main complex health-behavior contributing to suboptimal gout care. Medication adherence refers to the process by which patients take their medication as prescribed. Adherence to prescribed ULT ranged from 20% to 70% and is considered to be among the poorest of all chronic conditions (36, 54, 55). Patients' self-care behavior is a key determinant of medication adherence (36, 56). Interventions to support patients in dealing with challenges for self-care lead to more effective care, including better adherence to prescribed medication (57). Yet, such interventions can be time consuming in clinical setting. Support tools such as eHealth offers the opportunity to enhance self-management, while remaining efficient in a clinical healthcare setting and foster patient-centered care. eHealth interventions have shown to be easy to use, have fewer availability restrictions, and can temper pressure on healthcare systems (58-60). Moreover, computer-tailored technology allows patients to receive highly tailored and personalized feedback about their personal situations and advices on how to improve where needed. Several socio-cognitive models can be used to design the content of these models aimed at increasing awareness, motivation and action. One of these models is the Integrated Change (I-Change) model which consist of an assessment of current individual behavior and motivation regarding a desired behavior, and integrates the answers given during an online assessment into personalized advice and feedback generated by unique algorithms (61, 62). Computer-tailored support tools based on the I-Change model have proven to be (cost)-effective in changing various complex health-related behaviors and their determinants. Therefore, a patient-tailored tool to support ULT adherence among gout patients in a clinical setting to [1] identify personal factors that can be barriers or facilitators of adherence (lifestyle and

drugs) and [2] provide personalized advices as well as immediate tips and tricks to improve ULT adherence to the recommended treatment should be developed.

Despite the growing popularity of DAs and computer-tailored support tools and their proven efficacy, patients may still experience difficulties with the user interface and may therefore discontinue use (63, 64). Usability studies enable developers to discover potential difficulties with support tools and to explore engagement and users' experiences. The perceived usability has been demonstrated as an important determinant of an individual's intention to continue using the support tools (65).

Objectives

The main aim of this thesis is to explore the impact of several aspects related to the management of gout. First, the role of different treatment strategies on gout outcomes and the role of contextual factors (e.g. sex and comorbidities) herein will be studied. Next, patient needs will be explored and eventually innovations to improve patient-centered care in gout.

Outline of the thesis and sources

In **Chapter 2**, we investigated in the absence of randomized-controlled trials comparing different gout treatment strategies the outcomes of two gout clinics that implemented a different treatment strategy. Newly referred gout patients attending the outpatient rheumatology clinic at one regional non-university hospital and one university centre with regional function implemented a gout clinic applying a protocolized treatment strategy participated within the study.

In **Chapter 3**, we investigated clinical characteristics and comorbidities differences between female and male patients with newly diagnosed gout, and explored the role of gout onset ≥ 55 years, as a surrogate for the disappearance of the protective effect of oestrogens. Newly diagnosed gout patients referred to one of two regional non-academic rheumatology outpatient clinics in the Netherlands were considered for this cross-sectional study.

In **Chapter 4**, we conducted a systematic review with meta-regression analysis to investigate the hypothesis whether contextual factors modify the efficacy of ULT drugs on sUA as outcome domain in gout patients. For the study setting, only randomized controlled trials were included to minimize inclusion to studies that actually reported effect modification.

In **Chapter 5**, we evaluated the impact of gout on gout specific and generic health outcomes, as well on patient-centered outcomes in a real-world setting across 14 European countries. The study was a cross-sectional international European online survey. Patients with self-reported physician-diagnosed gout were primarily recruited from open panels of an online market research organization and from patients associations, and incidentally by rheumatologists or general practitioner.

In **Chapter 6** and **Chapter 7**, we described the development and usability process of the user-interface for an easy-to-use DA and a web-based patient-tailored support tool. A cross-sectional mixed methods design was used in both studies to evaluate usability among gout patients and healthcare professionals.

Finally, in **Chapter 8** we first summarize the individual chapters. Next, we discuss our findings in light of theoretical or methodological challenges and the directions for future research.

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PART I

Drug strategies and contextual factors

CHAPTER 2

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

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Abstract

Objective

To compare outcomes of 2 gout clinics that implemented different treatment strategies.

Methods

Patients newly diagnosed with gout and a follow-up of 9–15 months were included. Co-primary outcomes were the proportion of patients reaching a serum uric acid (sUA) ≤0.36 mmol/L and free of flares. Secondary outcomes were the proportion of patients requiring treatment intensification and experiencing adverse events. One clinic adopted a strict serum UA (≤0.30 mmol/L target) strategy, with early addition of a uricosuric to allopurinol, and the other clinic adopted a patient-centered (PC) strategy emphasizing a shared decision based on sUA and patient satisfaction with gout control. Independent t-tests or chi-square tests were used to test differences in outcomes, and logistic regressions were used to adjust the effect of the treatment center on outcomes for confounders.

Results

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

Conclusion

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

Introduction

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

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

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

To improve the quality of care for patients with gout in clinical practice, 2 hospitals started a gout clinic based on applying a protocolized treatment approach. Interestingly, each clinic has adopted a different strategy. One clinic adopted a strict serum UA (≤0.30 mmol/L) target strategy, with early addition of uricosurics to xanthine oxidase inhibitors if the target was not reached and if fractional excretion of UA was <4% (2 modes of action). The other clinic used a patient-centered (PC) strategy, emphasizing patient education and shared decisions about ULT, based on sUA and patient satisfaction with gout control. In the absence of a head-to-head comparison of gout treatment strategies, we aimed to compare the proportions of patients in both clinical practices who reached a sUA ≤0.36 mmol/L and ≤0.30 mmol/L, who were free of flares, who required combination therapy, and who experienced adverse events. The use of real-life data can lead to a better understanding of the gap between clinical research and daily practice of gout treatment (21). We expected a priori that a strict UA strategy would result in a lower sUA level and a comparable proportion of patients free of flares, but with more patients requiring combination therapy and having adverse events, compared to patients treated according to a PC strategy.

Methods

Clinical care protocols in each center

One regional nonuniversity hospital and 1 university center with a regional function implemented a gout clinic applying a protocolized treatment strategy (Figure 1). Approval was given by the ethics committees of both centers (METC 16-4-032.1) and patients provided written informed consent.

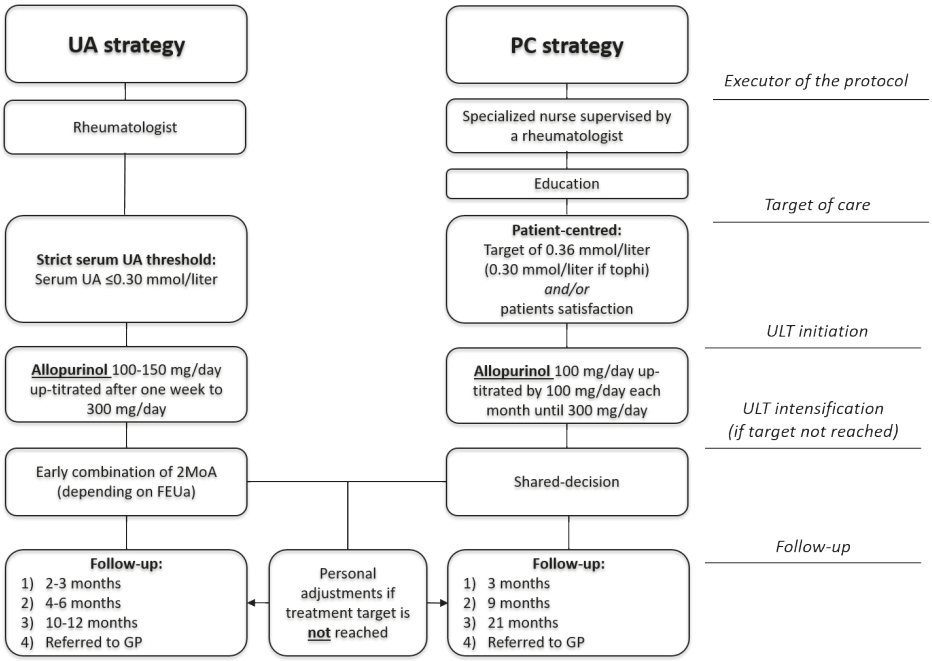

Figure 1: Flow chart of the 2 treatment strategies for newly referred gout patients in this study. The UA strategy (uric-acid-target strategy) was at a regional nonuniversity outpatient clinic. The PC strategy (patient-centered strategy) was at a university outpatient clinic with regional function. UA = uric acid; ULT = urate-lowering therapy; 2MoA = 2 modes of action; FEUa = fractional excretion of uric acid; GP = general practitioner.

UA strategy

In the nonuniversity center, a UA strategy aimed at strictly targeting sUA to ≤0.30 mmol/L, independently of the presence of tophi, and included combined 2-modes-of-action therapy early in the treatment protocol, depending on fractional excretion of UA. ULT is started with 100–150 mg/day allopurinol for the first week, uptitrated to 300 mg/day if the estimated glomerular filtration rate (eGFR) is ≥50 ml/minute, otherwise to 200 mg/day. If the sUA target is not reached at 2–3 months follow-up, the fractional excretion of UA is used to determine cases (fractional excretion of UA <4%) where the sUA target can better be reached by adding a uricosuric, or cases where it is better to uptitrate allopurinol (up to 600 mg/day maximum, depending on the eGFR) or switch to febuxostat. The fractional excretion of UA represents the percentage of sUA filtered in the kidney and distinguishes underexcretors from overproducers (normal range 6–8%) (22). Colchicine or prednisone are used as a first-line gout flare prophylaxis. Dietary advice is provided during the consultation

session with an information letter, containing dietary guidance and advice about weight reduction (if the patient is obese). After each treatment adjustment, patients are reevaluated after 3 months. Once the sUA target is attained, patients receive 1 additional follow-up after 6 months. If they maintain a sUA ≤0.30 mmol/L, patients are referred back to their general practitioner (GP).

PC strategy

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

Study sample

The sample for the current study comprised all newly referred gout patients attending the outpatient rheumatology clinic at 1 of the 2 hospitals between January 2015 and October 2017. Patients who had at least 1 outpatient follow-up appointment after 9–15 months were included in the current analyses. All patients were diagnosed by a rheumatologist with expertise in gout. Patients could be referred by the primary care physician or by another rheumatologist who had diagnosed a new case of gout at the outpatient clinic or during inpatient consultations.

Data collection

The following data were collected from the standardized medical records at baseline and follow-up: patient characteristics (i.e., age, sex, weight, and height), the presence of tophi, medication use (diuretics, prophylaxis of gout, and ULT drugs), comorbidities (baseline only), and UA and creatinine concentrations in serum and urine. Additional information on the presence of gout flares, adverse events, and outpatient visits was collected between baseline and follow-up. Obesity was defined as body mass index (BMI) ≥30 kg/m². Comorbidities were defined as present if formally recorded in the past history of the hospital record, or if the patient was currently receiving comorbidity-specific drug treatment, and included hypertension, dyslipidemia, type 2 diabetes mellitus, peripheral arterial disease, cerebral vascular accident, myocardial infarction, heart failure, nephrolithiasis, obstructive sleep apnea syndrome, coronary artery disease, cancer, transient ischemic attack, renal transplantation, heart arrhythmia, and hepatic steatosis. Renal function was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation for eGFR. Renal failure was defined as eGFR ≤30 ml/minute. To facilitate phenotyping of gout based on comorbidities, patients were grouped following the previously subdivided clusters of Richette et al (23) into 5 distinct phenotype groups: 1) only hypertension, 2) obesity, 3) type 2 diabetes mellitus, 4) dyslipidemia, and 5) renal and/or cardiovascular diseases. Groups 2 to 5 could also contain patients with hypertension.

Outcomes

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

Statistical analysis

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

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

Results

Patients

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

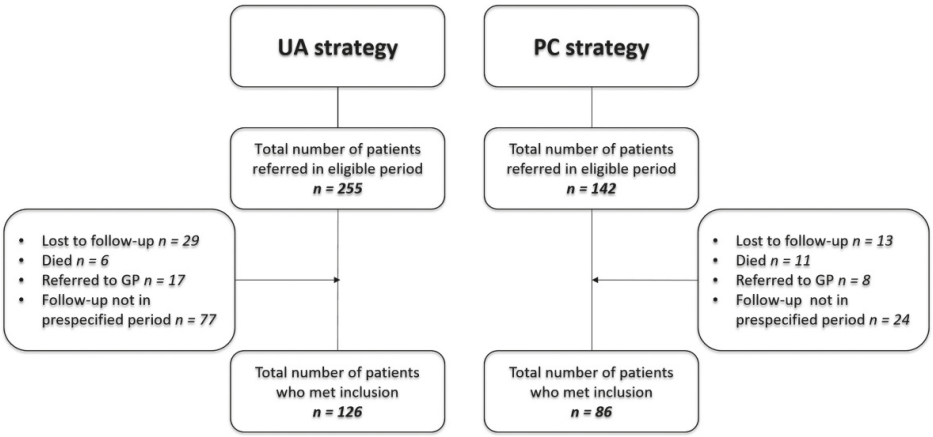

Figure 2: Flow chart of patients deemed eligible and included in the centers providing a UA strategy (uric-acid-target strategy) or PC strategy (patient-centered strategy). GP = general practitioner.

Table 1: Baseline characteristics of gout patients in the UA or PC strategy[a]

Characteristic	UA-strategy (n=126)	PC- strategy (n=86)	*P*
Female	17 (13.5)	19 (22.1)	0.101
Age, mean ± SD years	64.8 ± 11.9	64.0 ± 13.5	0.668
MSU crystals confirmed	120 (95.2)	18 (20.9)	<0.001
Tophaceous	27 (21.4)	52 (60.5)	<0.001
Diuretics use	39 (31.0)	41 (47.7)	0.014
sUA at baseline, mean ± SD mmol/L	0.51 ± 0.14	0.48 ± 0.15	0.194
BMI, mean ± SD kg/m^2	29.0 ± 5.0[b]	29.7 ± 4.8	0.378
Obesity	40 (36.7)	37 (43.0)	0.370
Comorbidities			
Hypertension	70 (55.6)	70 (81.4)	<0.001
Heart failure	16 (12.7)	5 (5.8)	0.099
Heart arrhythmia	29 (23.0)	19 (22.1)	0.875
CV events	51 (40.5)	37 (43.0)	0.712
Dyslipidaemia	29 (23.0)	43 (50.0)	<0.001
Type 2 diabetes mellitus	40 (31.7)	24 (27.9)	0.550
OSAS	14 (11.1)	10 (11.6)	0.907
Cancer	8 (6.3)	6 (7.0)	0.857
Hepatic steatosis	4 (3.2)	8 (9.3)	0.058
Renal transplantation	1 (0.8)	3 (3.5)	0.157
Nephrolithiasis	13 (10.3)	13 (15.1)	0.296
CKD, mean ± SD ml/min/1.73m^2	58.4 ± 21.8[c]	56.3 ± 22.5	0.497
Phenotype of gout[d]			0.157
Only hypertension	28 (26.4)	16 (18.6)	
Obesity	12 (11.3)	20 (23.3)	
Type 2 diabetes mellitus	16 (15.1)	9 (10.5)	
Dyslipidaemia	8 (7.5)	9 (10.5)	
Renal and CV diseases	42 (39.6)	32 (37.2)	

[a]Values are the number (%) unless indicated otherwise. Cardiovascular (CV) events include peripheral arterial disease, cerebral vascular accident, myocardial infarction, coronary artery disease, and transient ischemic attack. UA strategy = uric-acid-target strategy; PC strategy = patient-centered strategy; MSU = monosodium urate; BMI = body mass index; OSAS = obstructive sleep apnea syndrome; CKD = chronic kidney disease.
[b]N = 109 (17 missing data).
[c]N = 122 (4 missing data).
[d]UA strategy (n = 106), PC strategy (n = 86).

Baseline characteristics are shown in Table 1. The presence of tophi (n = 27 [21.4%] versus n = 52 [60.5%]; P < 0.001), the use of diuretics (n = 39 [31.0%] versus n = 41 [47.7%]; P = 0.014), the presence of hypertension (n = 70 [55.6%] versus n = 70 [81.4%]; P < 0.001), and dyslipidemia (n = 29 [23.0%] versus n = 43 [50.0%]; P < 0.001) were significantly lower in the UA strategy versus the PC strategy. Notwithstanding, the patients were not significantly differently distributed (P = 0.157) across the phenotypes of the classification clusters of Richette et al. Nevertheless, 28 of 106 patients (26.4%) in the UA strategy had isolated gout without comorbidities compared to 16 of 86 patients (18.6%) in the PC strategy. In both strategies, the phenotype with renal and/or cardiovascular diseases represented the largest number of patients.

Primary outcomes

sUA ≤0.36 mmol/L

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

Free of gout flares

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

Table 2: Univariable and multivariable logistic and linear sUA regression analyses for all outcomes[a]

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

[a]Values are the number (%) unless indicated otherwise. Multivariable model includes treatment strategy (treatment center), age, sex, estimated glomerular filtration rate, use of diuretics, presence of tophi, and baseline serum uric acid (sUA). UA strategy = uric-acid-target strategy; PC strategy = patient-centered strategy; OR = odds ratio; 95% CI = 95% confidence interval.

Secondary outcomes

Mean sUA

Both the UA strategy and the PC strategy resulted in a significant decrease of sUA ($P < 0.001$) over time during the treatment period. At follow-up, the mean sUA was significantly lower in the UA strategy patients compared to the PC strategy patients (mean ± SD 0.30 ± 0.10 versus 0.34 ± 0.11 mmol/L; $P = 0.004$). Multivariable linear regression analyses showed that sUA was 0.04 mmol/L lower (95% CI 0.01–0.07) in patients treated in the UA strategy compared to the PC strategy (Table 2).

sUA ≤0.30 mmol/L

A sUA target of ≤0.30 mmol/L was reached significantly ($P = 0.040$) more often in the UA strategy, with 83 of 126 patients (65.9%) versus 44 of 86 (51.8%) in the PC strategy. In multivariable analyses, reaching a treatment target ≤0.30 mmol/L was 1.97 times more likely (95% CI 1.00–3.85) among patients in the UA strategy (Table 2).

ULT intensifications and outpatient visits

At end of the first visit, a similar proportion of patients received ULT: 114 of 126 patients (90.5%) in the UA strategy and 75 of 86 (87.2%) in the PC strategy. Allopurinol monotherapy was distributed similarly in both strategies (n = 96 [76.2%] versus n = 67 [77.9%]) (Table 3). At follow-up, 76 of 126 patients (60.3%) in the UA strategy were receiving allopurinol monotherapy compared to 63 of 86 (73.3%) in the PC strategy (P = 0.052). Two-modes-of-action therapy was observed significantly more often in the UA strategy. Already at the end of the first visit there were 11 of 126 patients (8.7%) using combination therapy in the PC strategy. At follow-up, 21 of 126 patients (16.7%) in the UA strategy versus 1 of 86 (1.2%) in the PC strategy were using combination therapy (P < 0.001) (Table 3). Multivariable analyses showed that patients in the UA strategy were 0.40 times less likely (95% CI 0.20–0.82) to have allopurinol monotherapy (Table 2). During follow-up, patients in the UA strategy had a mean ± SD of 4.4 ±1.0 outpatient visits versus 3.9 ± 1.1 visits in the PC strategy (P = 0.001).

Table 3: Total number (%) of treatment intensifications after the first and follow-up visits[a]

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

[a]UA strategy = uric-acid-target strategy; PC strategy = patient-centered strategy; ULT = urate-lowering therapy.
[b]N = 85 (1 patient was taking rasburicase).

Adverse events

Adverse events with regard to ULT drugs were registered by 25 of 126 patients (19.8%) in the UA strategy and 20 of 86 (23.3%) in the PC strategy (P = 0.551). The adverse events of ULT included discomfort in the gastrointestinal tract (n = 19), and musculoskeletal (n = 3), skin (n = 25), and psychiatric (n = 1) adverse events. Multivariable logistic regression showed that the 2 strategies did not differ in the likelihood of an adverse event (OR 1.04 [95% CI 0.49–2.21]) (Table 2).

Discussion

In this study, we compared the clinical outcomes of real-life gout management according to 2 protocolized treatment strategies: 1 following a strict sUA (≤0.30 mmol/L) target with early combining 2-modes-of-action strategy (UA strategy), and the other a PC strategy integrating information on sUA with patient satisfaction about gout management. Patients receiving the strict UA strategy reached more frequently, although not significantly, the sUA target (≤0.36 mmol/L) and were more often free of flares, but they required significantly more ULT treatment intensification and more frequently visited the rheumatology outpatient clinic. Reassuringly, frequent drug-treatment intensification was not accompanied by more frequent adverse events or withdrawals from follow-up. Based on our results, a sUA level below ≤0.36 mmol/L is a realistic clinical goal for the majority of gout patients with both protocolized strategies, but a stricter UA strategy seems to ensure better short-term outcomes.

One randomized controlled trial (RCT) showed that nurse-led care providing ULT in a treat-to-UA-target approach (sUA ≤0.36 mmol/L) combined with education to gout patients with ongoing gout flares in primary care was efficacious in reaching a sUA level ≤0.36 mmol/L (95% versus 30%) and in improving health-related quality of life, compared to usual care by the GP after 2 years (24, 25). The effects on sUA were seen early and were sustained during the 2-year duration of the study. To the best of our knowledge, our study was the first to compare real-life data of 2 protocolized approaches in a rheumatology outpatient setting. Although the difference in the proportion of patients reaching the sUA ≤0.36 mmol/L target and being free of flares was not significant, the point estimates do show a difference. Notably, the lack of statistical significance is a reflection of the small sample-size and thus lack of power (type II error). In addition, patients treated in the center adopting the stricter sUA target of 0.30 mmol/L reached significantly more frequently the lower sUA level (≤0.30 mmol/L), and they had a significantly lower mean sUA. Although not unexpected, this finding also indicates that even lower targets are feasible. In view of a possible causal relation between sUA and cardiovascular events, it cannot be excluded that stricter control of sUA might also have longer-term benefits on cardiovascular risk. However, low sUA levels have also been associated with dementia, further complicating the issue of the preferred target (26). Unfortunately, information on patients' knowledge of gout, on confidence and

satisfaction with treatment, and on long-term medication adherence or lifestyle changes was not collected in both treatment centers. Lack of this information hampers us from understanding whether the differences in outcomes can partly be explained by the influence of strategies on patients' lifestyle and medication behavior (14, 18, 25, 27). With regard to treatment adherence, adherence received the attention of specialists in both treatment centers, and the literature provides some evidence that adherence to ULT in specialist care is better than in primary care. Therefore differences in adherence are unlikely to influence our results (28).

The 2 treatment centers clearly differed in drug choice when first-line allopurinol monotherapy was failing in patients. Recent studies suggest combining xanthine oxidase inhibitors with a uricosuric drug when monotherapy is ineffective in reducing sUA (12, 29, 30) and this approach was adopted in the UA strategy. While this approach has a biologic advantage in that it influences the main biologic path of hyperuricemia (22, 31) we cannot conclude from our study design that early combination therapy is better to reach a low sUA, because in the treatment strategy with early add-on of a uricosuric, the sUA target was ≤0.30 mmol/L. Of note, in the PC strategy, the majority of patients were still on allopurinol 300 mg/day, and this dose would allow further uptitration of allopurinol if a stricter sUA level would be preferred. Nevertheless, a recent retrospective chart review by Janssen et al (16) found added value of a UA strategy with 2 modes of action in reaching a sUA ≤0.36 mmol/L for the treatment of patients not achieving the target despite monotherapy allopurinol, but UA strategy with 2 modes of action was not compared to further uptitration of allopurinol. While decisions in the health care system should be mainly based on effectiveness and safety, cost-effectiveness is the third hurdle of technology assessment. In the above mentioned RCT on nurse-led gout care in primary care, a lifetime cost-effectiveness Markov model was computed. At 2 years of follow-up, quality-adjusted life years (QALYs) had been gained at the expense of more visits, but the cost-effectiveness was still favorable at £506/QALY. At 10-years of follow-up, further QALYs were gained while cost savings were noted, because patients had less resource utilization. Important for our study, gout control in the nurse-led trial was achieved without combination therapy. Of note, our study was conducted in a secondary care setting and the sUA target was ≤0.30 mmol/L in the UA strategy (25). In future strategy studies, the potential extra cost of the stricter UA strategy with early add-on of 2 modes of action should also be considered in relation to the cost-effectiveness compared

to a PC strategy. Furthermore, the sUA target level in a stricter sUA targeted approach might play a role in the cost-effectiveness, when small differences in sUA levels would translate (independent of type or dose of drug) into benefits on cardiovascular outcomes and other comorbidities.

In view of the importance of comorbidities in gout and an expected difference in gout phenotype between the treatment centers, we explored the possible role of comorbidities on outcome. Overall, the prevalence of the comorbidities in the total samples was slightly higher than in previously published population studies, which is not surprising, because our sample considered patients referred to rheumatologists, and such participants likely differ from gout patients followed in primary care settings (23, 32, 33). Between treatment centers, the prevalence of tophi, the use of diuretics, and the presence of hypertension and dyslipidemia were significantly higher in the PC strategy group. This case mix could be related to the difference in setting (university versus nonuniversity) but also to regional differences in lifestyle habits. Reassuringly, the disease phenotype did not modify the effect of the treatment center on outcome. Conducting future research will be important to examine the role of gout phenotypes on treatment strategies, in which patient education, lifestyle advice, and cardiovascular risk management are an important part.

The conclusion we formulated on the different treatment strategies was based on a comparison of real-life data from 2 protocolized gout clinics and not on results of an experimental study. The use of real-life data gained renewed interest due to the increasing accessibility of digital health data and may bridge the evidentiary gap between strictly RCTs and daily practice of gout treatment. Moreover, the use of real-life data compares results of strategies more easily and cheaply (21). Nevertheless, real-life data have specific challenges, mainly related to an insufficient possibility to control for potential confounders and less controlled interventions compared to RCTs. In this regard, specific limitations should be discussed, some of which actually relate as well to more strict experimental studies. First, patients in the PC strategy were diagnosed with gout based on clinical diagnosis and not strictly based on fulfilment of any diagnostic criteria. In the UA strategy, on the other hand, patients were diagnosed strictly based on crystal identification and ACR/EULAR gout classification criteria. Second, there are limitations regarding the standardized measurement of outcomes, including the number of gout flares and

adverse events. Only recently, a standardized approach to validate a definition for gout flares with patients' self-reported criteria was suggested by Gaffo et al (34). As a consequence, misclassification of cases as well as of outcomes may have influenced the results. Further, due to differences in approaches and frequency of assessments of the number of gout flares, we could not differentiate between the numbers of flares in the initial period and later periods of time after initiating ULT. The majority of gout flares commonly take place during the first 6 months of ULT, but due to the consultation protocol, no distinction could be made in this study. Data on type (but not dosage) of gout flare prophylaxis were only available for the first and follow-up visit. However, in additional multivariate analysis, prophylaxis did not meaningfully influence the effect of the strategy on flare (data not shown). Overall, our findings underline the need for a carefully designed treat-to-target trial with an appropriate sample size, exploring the effectiveness and cost effectiveness of different sUA targets with or without an explicit role of the patient in a shared decision-making context, and with attention for short- and long-term outcomes.

Conclusion

Real-life data from 2 gout clinics reveal that a stricter UA strategy resulted in a nonsignificantly higher proportion of patients reaching a sUA ≤0.36 mmol/L and being free of flares, though significantly more patients reached a sUA ≤0.30 mmol/L without experiencing more adverse events. This result was accomplished through significantly more therapy intensification from allopurinol monotherapy to combination therapy.

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CHAPTER 3

Sex differences in the clinical profile among patients with gout: cross-sectional analyses of an observational study

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Abstract

Objective

Research findings in gout result predominantly from studies about men and might not be generalizable to women. To improve insight into sex differences in gout, our study compared clinical characteristics and comorbidities of female and male patients with gout, and explored the influence of menopause on these differences.

Methods

Data from patients referred to 2 rheumatology clinics and diagnosed with gout were used. Clinical characteristics and comorbidities of each sex were compared univariately. Sex difference in comorbidities were further explored in multivariate logistic regression analyses adjusting for age, BMI, smoking, and alcohol consumption in both the total group and in those with gout onset ≥ 55 years (as a surrogate for menopausal state).

Results

There were 954 patients, including 793 (83%) men, included. Women were on average older (65 vs 62 yrs), were more often obese (54% vs 36%), had a higher serum uric acid (sUA) level (0.53 vs 0.49 mmol/L), used diuretics more often (60% vs 30%), and consumed alcohol less frequently (47% vs 72%). Additionally, women more frequently had reduced renal function (64% vs 31%), hypertension (78% vs 56%), heart failure (23% vs 12%), and type 2 diabetes (39% vs 17%; all $P < 0.05$). In those with gout onset ≥ 55 years, differences in comorbidities were less pronounced and disappeared after adjusting for lifestyle.

Conclusion

Our study confirmed sex differences in clinical characteristics and comorbidities among newly diagnosed patients with gout, and revealed that sex differences in comorbidities among those with gout onset beyond the age of female menopause were strongly attenuated and fully explained by lifestyle.

Introduction

Gout, the most common type of inflammatory arthritis, is a predominantly male disease (1). Among patients with gout ≤ 65 years, the prevalence in men is 4-times higher than in women (2). Above this age, the prevalence of gout narrows to a more equal sex distribution, especially due to the sharp increase in the incidence of gout among older women (3, 4). Despite the increasing prevalence of gout, particularly in the aging female population, most studies are performed on predominantly male populations and few studies examine the differences between sexes (4-7).

There are a number of potential biological pathways explaining sex differences in the occurrence of gout, and most evidence points to the role of the uricosuric effect of estrogen (8-11). The uricosuric effect of estrogen was initially emphasized by epidemiological research, showing an increase in serum uric acid (sUA) levels among postmenopausal women (12-14). Previously, a study of patients undergoing male-to-female gender reassignment demonstrated that estrogen therapy reduced sUA concentrations and increased urinary uric acid (UA) excretion (8, 10). Apart from estrogen, other sex-specific differences on the effect of genetic variants on sUA levels have been found. In a study on gout risk with a large population of European ancestry, a gene-sex interaction was identified for ABCG2, a unidirectional secretory urate transporter in the proximal renal tubule (15), and PDZK1, a key regulatory protein for several secretory urate transporters (16, 17), with a greater influence on sUA in men than in women. In addition, SLC2A9, encoding the GLUT9 protein and facilitating reabsorption of urate, explains approximately 3% of the effect of variance in urate levels. Although SLC2A9 has a stronger effect on sUA in women, it would not explain differences in the occurrence of gout between men and women (16-19). Overall, gene-sex interactions suggest a greater influence of secretory urate transporters on sUA and gout risk in men, yet the overall effect size on sUA levels and on the occurrence of gout remains unclear.

In addition to the biological pathways explaining sex differences in hyperuricemia and the onset of gout, differences in risk factors and clinical manifestations also require attention (20, 21). A systematic literature review of 9 (mainly small) studies on differences between male and female patients with gout (3), completed by 2 previous gout cohort studies (22, 23), consistently showed that female patients with gout tend to be older, have lower levels of alcohol consumption, have a higher

BMI, and are prescribed diuretics more often. Compared to male patients with gout, women also more commonly presented with a polyarticular pattern, and suffered more frequently from common gout-related comorbidities, such as hypertension (HTN), type 2 diabetes mellitus (T2DM), osteoarthritis, and renal insufficiency (13, 22-26). However, none of these studies explored sex-specific differences in excretion of urate, which is especially important considering the existing evidence on the uricosuric effect of estrogen. Further, none of these studies investigated the effect of onset of gout ≥ 55 years (when the protective effect of estrogen disappears, since by age 55 almost all women have gone through menopause) on sex differences in clinical manifestations (27). It would be expected that the clinical profile of gout with regard to risk factors and comorbidities would become more comparable between sexes in this age group (28).

The objectives of this study were therefore first, to add data on the clinical differences between female and male patients with newly diagnosed gout, and second, to explore the role of gout onset ≥ 55 years to represent the disappearance of the protective effect of estrogen. We expected to confirm previously reported sex differences and hypothesized that (1) the differences in clinical characteristics and comorbidities between sexes would be strongly reduced in those with a first gout flare ≥ 55 years, and (2) that no difference in urinary UA excretion would be present between male and female patients with gout ≥ 55 years.

Methods

Study sample

New patients referred to 1 of 2 regional nonacademic rheumatology outpatient clinics in the Netherlands and diagnosed with gout were considered for this cross-sectional study. Sample A included patients at Clinic A between January 2015 and October 2017 and Sample B included patients at Clinic B between July 2011 and May 2016. All patients were diagnosed using the American College of Rheumatology/European League Against Rheumatism gout classification criteria, and most patients had monosodium urate (MSU) crystal-proven gout (29). Patients could have been referred by either the primary care physician or other specialists within the hospital. Our study was approved by the ethical committee at the hospital of Sample A (METC 16-4-032.1). Ethical approval for this type of study was not required according the policy of the hospital of Sample B. All patients provided written informed consent.

Data collection

Data collected at the first visit comprised demographics (age, sex); lifestyle factors [BMI (with BMI ≥ 30 kg/m^2 being obese), current smoking status (yes/no; Sample B only), and current alcohol consumption (yes/no; Sample B only)]; date of first gout flare (Sample B only); the presence of tophi in clinical examination (yes/no); use of specific medication types (diuretics, colchicine prophylaxis for gout, and sUA-lowering drugs); laboratory tests [UA and creatinine concentration in serum and spot urine (Sample A only)]; and comorbidities confirmed by rheumatologists [HTN, peripheral arterial disease, cerebrovascular accident, myocardial infarction, heart failure, heart arrhythmia, dyslipidemia, T2DM, nephrolithiasis, and hepatic steatosis (all yes/no answers)]. Laboratory tests were used to calculate renal function and fractional excretion of uric acid (FEUa). Renal function is presented as the estimated glomerular filtration rate (eGFR) and was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (30). The FEUa was only available for Sample A and was calculated using the following equation: (urinary UA × serum creatinine) ÷ (sUA x urinary creatinine). The FEUa represents the percentage of sUA filtered in the kidneys and distinguishes underexcretors (FEUa < 4.0%) from overproducers (31). Among healthy subjects, average FEUa ranges from 6% to 8%, whereas patients with gout have generally an average FEUa of 3–5% (31, 32). Since the UA urine-plasma ratio will increase significantly with the use of a uricosuric (e.g., benzbromarone) and is independent of the use of a xanthine oxidase inhibitor (e.g., allopurinol or febuxostat), FEUa was not calculated for the patients treated with uricosurics (31).

Statistical analyses

Univariable comparisons of clinical characteristics and comorbidities between women and men were performed using independent t-tests for continuous and normally distributed variables and chi-square test for categorical variables. In the sample comprising data on age of gout onset (Sample B), logistic regression was performed to explore the adjusted role of sex (female compared to male) on the presence of comorbidities and clinical characteristics, first in the total sample and then in those with gout onset ≥ 55 years (representing postmenopausal women). Multivariate regression analyses were limited to comorbidities and clinical characteristics that were significantly (P < 0.05) associated with sex in univariate analyses. Potential confounders were defined a priori based on plausibility, and comprised age (Model 1) and lifestyle factors [i.e., smoking, alcohol consumption

and BMI (if obesity was not the outcome); Model 2]. In the sample comprising laboratory data of spot urine (Sample A), the FEUa was compared between sexes among patients ≥ 55 years. Statistical analyses were performed using IBM SPSS, version 25.0 (IBM Corp). A P value < 0.05 (2-tailed) was considered to be statistically significant.

Results

Sex differences in clinical characteristics in the total sample

In the total sample, 954 patients with gout were included, of which 161 (17%) were female and 793 (83%) were male (Figure 1). Clinical characteristics of female and male patients for the total sample are shown in Table 1, and for Samples A (n = 255) and B (n = 699) in Supplementary Table 1 (available with the online version of this article). In the total sample, some relevant and significant differences between sexes were found: women were 2.6 years older than men, had a 2.2 kg/m2 higher BMI with a 2.09-times higher prevalence of obesity (95% CI 1.47–2.98), and used diuretics 3.51-times more frequently (95% CI 2.48–4.99; Table 1 and Supplementary Table 2). sUA level was 0.04 mmol/L higher in women (P < 0.001), and no differences in the presence of tophi were seen (95% CI 0.76–1.68) between sexes. Women also had a significantly higher prevalence of comorbidities, including a 2.76-times higher prevalence of HTN (95% CI 1.86–4.10), a 2.30-times higher prevalence of heart failure (95% CI 1.50–3.53), a 3.11-times higher prevalence of T2DM (95% CI 2.15–4.48), and an eGFR 14.9 mL/min/1.73 m2 lower than men (all P < 0.05; Supplementary Table 2). Additional logistic regression (Model 1) revealed that the differences between sexes on (significantly different) comorbidities and clinical characteristics could not be explained by age (Supplementary Table 2).

Table 1: Baseline characteristics of female and male patients with gout (total sample).

Variable	Females, n=161	Males, n=793	*P*
Age, yrs, mean (SD)	64.9 (14.9)	62.3 (13.0)	0.04
BMI, kg/m^2, mean (SD)	31.1 (7.4)	28.9 (4.9)	0.001
<25 kg/m^2	29 (19.2)	125 (16.6)	
25–29.9 kg/m^2	40 (26.5)	357 (47.3)	
≥30 kg/m^2	82 (54.3)	273 (36.2)	
Tophi	40 (25.0)	180 (22.7)	0.53
MSU crystal-proven	142 (93.4)	688 (90.8)	0.29
sUA, mmol/L, mean (SD)	0.53 (0.13)	0.49 (0.11)	<0.001
Current smoking[a]	17 (13.9)	100 (18.1)	0.23
Alcohol consumption[a]	57 (47.1)	400 (71.9)	<0.001
Comorbidities			
Hypertension	125 (77.6)	442 (55.7)	<0.001
Peripheral arterial disease	9 (5.6)	61 (7.7)	0.35
CVA	16 (9.9)	50 (6.3)	0.10
MI	20 (12.4)	118 (14.9)	0.42
Heart failure	37 (23.0)	91 (11.5)	<0.001
Heart arrhythmia	36 (22.4)	141 (17.8)	0.17
Dyslipidaemia	41 (25.5)	168 (21.2)	0.23
T2DM	63 (39.1)	136 (17.2)	<0.001
Nephrolithiasis	15 (9.3)	65 (8.2)	0.64
Hepatic steatosis	24 (14.9)	85 (10.7)	0.13
eGFR, ml/min/1.73m^2, mean (SD)	58.3 (66.3)	73.2 (30.7)	<0.001
eGFR <60 ml/min/1.73m^2	100 (64.1)	237 (30.6)	<0.001
Diuretic use	97 (60.2)	239 (30.1)	<0.001

Values are presented as n (%) unless otherwise stated. [a]Data only available in Sample B. CVA = cerebrovascular accident; T2DM = type 2 diabetes mellitus; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; MSU = monosodium urate; sUA = serum uric acid.

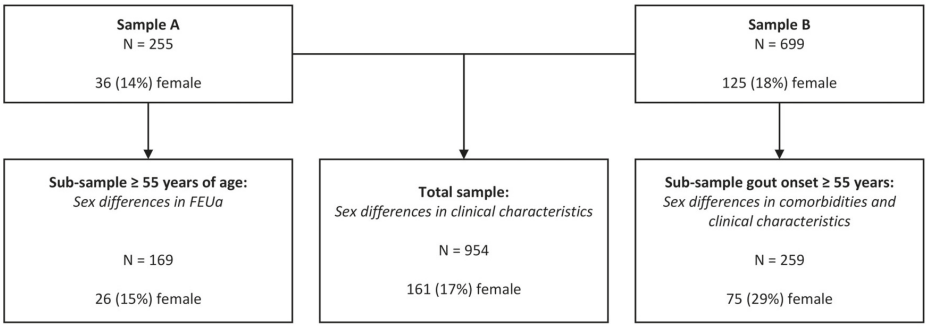

Figure 1: Flowchart of the study and data analyses. FEUa = fractional excretion of uric acid.

Sex differences in comorbidities and clinical characteristics in patients with gout onset ≥ 55 years (Sample B)

When exploring the effect of postmenopausal status on clinical characteristics in Sample B, the age of the first gout flare was available for 484 (69%) patients, with 259 having had their first gout flare ≥ 55 years [75 (29%) women and 184 (71%) men; Table 2]. The sex differences in the group of patients without age of onset available (n = 215) were comparable to the sex differences in those with age of onset available (n = 484), except for a lower prevalence of tophi among men with missing date of gout onset. In patients with gout onset ≥ 55 years, women were 3.0 years older and their sUA levels were almost comparable to men with gout onset ≥ 55 years. Further, 0.61-times fewer women with gout onset ≥ 55 were smokers (95% CI 0.24–1.56). Women were 0.38-times less likely to consume alcohol (95% CI 0.22–0.67) and had a 2.4 kg/m2 higher BMI compared to men with gout onset ≥ 55 years (Supplementary Table 3, available with the online version of this article). Multivariate regression analysis of sex on comorbidities and clinical characteristics (Table 2) revealed that the age-adjusted association between sex and outcomes (Model 1) was clearly lower among patients with gout onset ≥ 55 years when compared to the total group, and only significant for T2DM, diuretic use, and obesity (Table 2). When adjusting additionally for lifestyle factors (Model 2), the strength of association decreased in both groups (decrease of coefficient between 8–22% in the total group and between 15–28% in the subsample with gout onset ≥ 55 years) and became insignificant for all outcomes in those with gout onset ≥ 55 years, except for the association between female sex and obesity (Table 2).

Table 2: Uni- and multivariate logistic regressions presenting the influence of sex (female vs male) on comorbidities and clinical characteristics in the subsample with date of gout onset and lifestyle factors available (Sample B).

	Descriptive Data		Univariable Association		Multivariable model 1[a]		Multivariable model 2[b]	
	Females, n (%)	**Males, n (%)**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Total group	**n= 87**	**n=397**		**n=484**		**n=484**		**n=484**
Comorbidities, n (%)								
Hypertension	70 (80.5)	248 (62.5)	2.47	1.40-4.36	2.46	1.39-4.34	2.10	1.15-3.83
Heart failure	24 (27.6)	50 (12.6)	2.64	1.52-4.61	2.67	1.53-4.66	2.14	1.17-3.92
T2DM	30 (34.5)	61 (15.4)	2.90	1.72-4.87	2.99	1.78-5.04	2.33	1.34-4.08
eGFR<60 ml/min/1.73m^2	50 (60.2)	107 (27.6)	3.98	2.43-6.51	4.10	2.49-6.75	3.77	2.21-6.43
Clinical characteristics, n (%)								
Diuretic use	57 (65.5)	144 (36.3)	3.34	2.05-5.43	3.46	2.11-5.68	2.79	1.67-4.68
Obesity	48 (55.2)	154 (39.4)	1.89	1.19-3.03	1.95	1.21-3.12	1.94	1.19-3.18
Gout onset ≥ 55 yrs	**n=75**	**n=184**		**n=259**		**n=259**		**n=259**
Comorbidities; n (%)								
Hypertension	61 (81.3)	137 (74.5)	1.50	0.77-2.92	1.48	0.75-2.92	1.12	0.54-2.35
Heart failure	22 (29.3)	35 (19.0)	1.77	0.95-3.28	1.62	0.86-3.04	1.30	0.65-2.60
T2DM	29 (38.7)	34 (18.5)	2.78	1.53-5.05	2.69	1.47-4.91	2.05	1.06-3.97
eGFR<60 ml/min/1.73m^2	46 (64.8)	86 (47.8)	2.01	1.14-3.55	1.63	0.89-3.00	1.39	0.72-2.66
Clinical characteristics, n (%)								
Diuretic use	53 (70.7)	98 (53.5)	2.11	1.19-3.76	1.99	1.11-3.56	1.43	0.77-2.67
Obesity	43 (57.3)	67 (36.6)	2.33	1.35-4.02	2.83	1.59-5.04	2.77	1.53-5.03

[a]Multivariable Model 1 includes age. [b]Multivariable Model 2 includes age, BMI (where appropriate), smoking, and alcohol consumption. eGFR = estimated glomerular filtrate rate; T2DM = type 2 diabetes mellitus.

Sex differences in FEUa in patients ≥ 55 years (Sample A)

When exploring FEUa among male and female patients ≥ 55 years in Sample A, data were available for 169 (66%) patients, including 26 (15%) female and 143 (85%) male subjects (Table 3). Two female patients and 1 male patient with extremely high FEUa (≥ 10%) were excluded, as this was likely due to unusual contextual effects on UA excretion. Average FEUa in Sample A was similar between women and men [4.6% (1.9) vs 4.4% (1.5); P = 0.51]. Notwithstanding, women ≥ 55 years [n = 9 (35%)] were somewhat less frequently underexcretors compared to males ≥ 55 years [n = 64 (45%); P = 0.34). When including the 3 outliers, results were comparable.

Table 3: Biochemical gout characteristics of the female and male patients with gout older than 55 years (Sample A).

	Females, n=26	**Males, n=143**	***P***
sUA, mmol/L	0.46 (0.13)	0.45 (0.12)	0.73
Urinary UA	1.5 (1.1)	1.8 (1.2)	0.29
Serum creatinine	108.6 (38.9)	121.7 (51.1)	0.21
Urinary creatinine	71.1 (45.4)	97.8 (66.6)	0.05
eGFR, ml/min/1.73m^2	49.8 (20.1)	59.2 (20.7)	0.04
FEUa, %	4.6 (1.9)	4.4 (1.5)	0.51
<4.0%, n (%)	9 (34.6)	64 (44.8)	0.34
≥4.0%, n (%)	17 (65.4)	79 (55.2)	

Values are presented as mean (SD) unless otherwise stated. eGFR = estimated glomerular filtrate rate; FEUa = fractional excretion of uric acid; sUA= serum uric acid; UA = uric acid.

Discussion

Our study confirms that female patients referred to a rheumatologist and diagnosed with gout differ significantly from male patients. On a homogeneous group level, the female patient is older, has a higher BMI with increased prevalence of obesity, is prescribed diuretics more often, less frequently consumes alcohol, has a higher sUA level at presentation, and has more frequent comorbidities, such as HTN, heart failure, T2DM, and advanced renal insufficiency. In those with gout onset ≥ 55 years, sex differences in comorbidities were strongly attenuated, while lifestyle factors continued to play a relevant role in explaining sex differences.

When comparing our results with those of 11 previously published studies on sex differences in patients with gout (1, 5, 12, 13, 22, 23, 33-37) (Table 4), our findings support evidence that women with gout are on average older (7/10 studies) (1, 12, 13, 22, 23, 33-37); more often suffer from renal insufficiency (6/9 studies) (1, 12, 13, 22, 23, 33-36), obesity (3/4 studies) (5, 13, 22, 23), and HTN (6/10 studies) (1, 12, 13, 22, 23, 33-37); used diuretics more frequently (8/9 studies) (1, 5, 12, 13, 22, 23, 33, 34, 37); and were less likely to heavily consume alcohol (7/8 studies) (5, 12, 13, 22, 23, 33, 34, 37). Further, no sex differences were noted in the presence of tophi (5/6 studies) (12, 13, 22, 23, 33-35), while findings on articular manifestations were conflicting. In our study, we used age of onset ≥ 55 years to represent postmenopausal women in order to explore the role of estrogen on gout characteristics. The mean age of menopause in western European women is 51 years of age, and therefore almost all women above 55 years are postmenopausal (27). We demonstrated first that age of onset ≥ 55 years attenuated the sex differences in comorbidities. Our results therefore suggest that < 55 years, women are protected by estrogen against the effect of classic gout risk factors, such as decreased renal function, HTN, heart failure, and frequency of alcohol consumption. Notably, independent of age of onset, lifestyle factors always played a role in sex differences, since sex differences were attenuated when adjusting for BMI, smoking, and alcohol consumption. Lifestyle factors consistently attenuated the association between sex and comorbidities, but the effect was somewhat stronger among those with gout onset ≥ 55 years. Interestingly, obesity played a more important role in sex differences in patients ≥ 55 years.

In gout, the relationship between sUA and comorbidities is a complex interaction, whereby comorbidities can be both the cause and effect of elevated sUA levels. Moreover, comorbidities are interrelated, complicating the exploration of their independent roles. Finally, lifestyle factors and medication (especially diuretics) play a key role in the complex interplay of sUA and comorbidities in patients with gout (38). Nonetheless, we cannot ignore the role of sex in the presentation of gout characteristics. It was a remarkable finding that women referred to gout clinics used diuretics 3.51-times more frequently. Starting diuretics has previously been associated with hyperuricemia, and thus an increased risk of gout in women (39, 40). Although diuretic use has been shown to be a safe and effective first-line treatment for HTN, our population of females with gout was characterized by more frequent diuretic use compared to the male gout population, which was

partly related to the higher prevalence of HTN. Yet the differences in diuretic use disappeared in the group with gout onset ≥ 55 years after adjustments had been made for age and lifestyle factors (Model 2). When including HTN in multivariate analyses, no influence on the observed association was found, although confounding between obesity and HTN was found (data not shown). Possibly, obese women are prescribed diuretics more frequently. Also, striking differences in the prevalence of T2DM were revealed even after adjustments for lifestyle factors (including BMI) were made. While the reduced renal function of the female patients might mediate the relation between T2DM and sUA, and therefore gout, sUA has also been identified as an independent risk factor for T2DM, and it has been suggested that female patients with gout are at a higher risk of developing T2DM than male patients with gout (41, 42). This could be a possible explanation for the striking differences in T2DM, seen also when limiting the analyses to those with gout onset above the age of menopause. Moreover, T2DM, together with HTN, independently increases the risk of heart failure in women (43), and this relationship is 3-fold stronger in women compared to men (44).

Further, we compared the FEUa between sexes for patients ≥ 55 years, when the presumed protective uricosuric effect of estrogen disappears. The average FEUa was similar in women ≥ 55 years as it was in men in the same age group, yet the classic male gout profile of underexcretor was still less frequently encountered in the population of females with gout ≥ 55 years. Adjusting the relationship between sex and FEUa with potential confounders (age, diuretics use, and BMI) had no relevant effect on the results (data not shown). While we hypothesized that women ≥ 55 years would be underexcretors as frequently as men, we could not confirm this hypothesis. Whether this is due to residual confounding, the small sample size or a gene-sex interaction of the urate transporter genes cannot be further analyzed/studied in our sample, but warrants exploration since this may have therapeutic implications.

Studies on clinical differences between men and women have received much attention in the last decade. In this research area, it is recommended to distinguish gender difference from sex differences (20). In gout, a limited number of studies have explored the potential role of biological differences (i.e., sex-related research), but fewer studies have explored the role of gender in areas such as behavior, lifestyle, life experience, and healthcare access (i.e., gender-associated research)

(20, 21). In our study, it seems contradictory to make a strong distinction between gender and sex since both aspects seem to play a role in the observed sex differences in gout. For example, women are more often obese compared to men, both in our study population and in the general population (45). Differences in obesity can partly be explained by the influence of chromosomal, hormonal, and neuroendocrine influences on energy balance and fat distribution (sex differences); however, they can also be explained by behavioral and sociocultural factors (gender-specific). Moreover, HTN is more prevalent among obese gout patients and may be treated more frequently with diuretics in women compared to men, partly based on biological grounds but partly also on the behavioral choices of the prescribing physician.

Results from this study should be interpreted in consideration of several limitations. Strong conclusions on pathways explaining sex differences and the role of menopause on sUA metabolism and clinical characteristics were impeded by the cross-sectional nature of this study; incomplete information on the dates of onset for comorbidities, gout onset, age of menopause, and urinary UA excretion; actual data on menopause and the effect of estrogen on plasma levels; and residual confounding. For example, the number of females with a first gout flare < 55 years or with data on FEUa ≥ 55 years was too small (n = 12 and n = 26, respectively) to perform a meaningful comparison on sex differences in these subgroups. Despite these limitations, the current study, is the first, to our knowledge, to provide a better understanding of sex differences in gout patient profiles, and highlights the need for awareness and the potential effect of sex-specific pathophysiology and management of gout.

Conclusion

Analyses of our currently identified population confirmed the existence of sex differences in clinical characteristics and comorbidities, but revealed that differences were attenuated in patients with an onset of gout ≥ 55 years. Further studies are needed to understand whether prevention and management of gout should be different between sexes before and after the age of menopause.

Table 4: Literature review of sex differences in patients with gout according to 11 articles

First Author (Yr)	Country	Study Design	Population	Diagnosis	Sample Size, n (%)	Age, Yrs (SD)
Lally (1986)	USA	Cross-sectional	Rheumatology clinic	MSU	M: 75 (77) F: 23 (23)	M: 50 (-) F: 58 (-)[a]
Meyers (1986)	South Africa	Retrospective cohort	Rheumatology clinic	ACR	M: 178 (66) F: 92 (34)	M: 58 (-) F: 67 (-)
Deesomchok (1989)	Thailand	Cross-sectional	Rheumatology clinic	ACR	M: 172 (89) F: 22 (11)	M: 52 (14) F: 59 (11)[a]
Puig (1991)	Spain	Cross-sectional	Rheumatology clinic	MSU/ACR	M: 220 (86) F: 37 (14)	M: 51 (13) F: 61 (14)*
Tickly (1998)	South Africa	Case-control	Rheumatology clinic	ACR	M: 69 (77) F: 21 (23)	M: 54 (-) F: 55 (-)
Chang (2004)	Taiwan	Population-based cohort	GP	ACR	M: 101 (79) F: 27 (21)	M: 49 (15) F: 63 (11)[a]
Souza (2005)	Brazil	Observational cohort	Rheumatology clinic	MSU/ACR	M: 31 (53) F: 27 (47)	M: 61 (9) F: 64 (11)
Harrold (2006)	USA	Population-based cohort	GP	ACR	M: 4975 (81) F: 1158 (19)	M: 58 (14) F: 70 (12)[a]
Bhole (2010)	USA	Longitudinal cohort	Rheumatology clinic	ACR	M: 200 (66) F: 104 (34)	M: - F: -
Harrold (2017)	USA	Observational cohort	Rheumatology clinic	ACR	M: 1011 (79) F: 262 (21)	M: 61 (14) F: 71 (11)[a]
Drivelegka (2018)	Sweden	Case-control	GP	ICD	M: 9513 (67) F: 4600 (33)	M: 65 (15) F: 71 (15)[a]

[a]P < 0.05 in univariate analyses. ACR = American College of Rheumatology; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CCr =creatinine clearance; HTN = hypertension; ICD = International Classification of Diseases; F = female; FEUa = fraction excretion of uric acid; GP = general practice; M = male; MSU = monosodium urate crystals; OA = osteoarthritis; sUA = serum uric acid; T2DM = type 2 diabetes mellitus.

Female After Menopause, n (%)	Differences in Outcomes in Females vs Males[a]		Nonsignificant Outcomes
	Clinical and Lifestyle Factors	Comorbidities	
21 (91%)	Alcohol intake (10 vs 45%) Diuretics (78 vs 25%)	Renal insufficiency (30 vs 12%)	Podagra, tophi, HTN
-	- Diuretics (78 vs 48%) - Monoarticular gout (27 vs 61%) - Alcoholism (2 vs 11%)	Renal insufficiency (25 vs 15%)	Tophi, HTN, dyslipidaemia, T2DM
18 (82%)	- Podagra (32 vs 69%)	Haematologic malignancy (23 vs 3%)	Articular features, HTN, T2DM, renal insufficiency
32 (86%)	Alcohol intake (14 vs 55%) sUA (0.55 vs 0.50 mmol/L) FEUa (7.0 vs 4.7%) Tophi (27 vs 10%) Diuretics (57 vs 14%)	Renal insufficiency (54 vs 12%) HTN (78 vs 33%) OA (81 vs 40%)	Articular features, obesity, T2DM
20 (95%)	Alcohol intake (57 vs 82%) Diuretics (50 vs 33%)	HTN (65 vs 59%)	T2DM
22 (81%)	Ccr (5.6 vs 8.6 mmol/L)	Renal dysfunction (85 vs 65%)	Tophi
19 (70%)	Less podagra[a] More upper limb manifestation[a]	OA (56 vs 26%)	Diuretics, alcohol intake, tophi, HTN, T2DM, renal insufficiency, dyslipidaemia
-	- Diuretics (77 vs 40%)	Renal insufficiency (18 vs 10%) HTN (81 vs 57%) Dyslipidaemia (42 vs 38%) T2DM (30 vs 17%) Peripheral arterial disease (7 vs 4%) Renal failure (12 vs 6%)	Nephrolithiasis
-	- Obesity (36 vs 26%) - Diuretics (47 vs 29%) - Heavy alcohol intake (13 vs 43%)	HTN (82 vs 69%)	-
-	- BMI (33.5 vs 31.9 kg/m^2) - Alcohol intake (OR: 0.13) - Diuretics (51 vs 22%)	HTN (77 vs 57%) T2DM (28 vs 17%) Renal disease (24 vs 13%) OA (46 vs 25%)	Tophi, heart disease
-	- Obesity (12 vs 10%) - Diuretics (53 vs 39%) - Alcoholism (2 vs 5%)	- T2DM (18 vs 15%) - HTN (72 vs 65%) - CHF (21 vs 16%) - COPD (7 vs 5%) - Thromboembolism (14 vs 10%)	Coronary heart disease, renal disease

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CHAPTER 4

Effect modification by contextual factors of urate-lowering therapy on serum uric acid in patients with gout: a systematic review with meta-regression analysis

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Abstract

Objective

To synthesize evidence of the effect of contextual factors (CFs) on efficacy of urate-lowering therapy (ULT) on serum uric acid (sUA) as outcome in gout patients.

Methods

Randomised controlled trials (RCTs) from (updated) Cochrane reviews were the starting point. RCTs were included if they explored the role of any CF on efficacy of ULT on sUA in gout patients. For CFs with sufficient data (i.e. ≥3 trials), a mixed-effects meta-regression analysis was performed with trial and comparison as random effects, whereas specific CFs were modelled as fixed factors.

Results

Eight RCTs were included. Effect modification by CFs was explored for age, sex, race, renal function, cardiovascular comorbidity, tophi, thiazide-diuretic use, and previous ULT use. Crude data stratified by renal function were available for four trials (36 randomised comparisons), and suitable for meta-analysis. Pooled estimates revealed that gout patients with a normal, mildly-, or moderately impaired renal function were consistently more likely to achieve sUA target with ULT compared to control. Among RCTs comparing ULT to placebo (30 comparisons), effects of ULT on achieving sUA target were not statistically different for those with normal (OR:66.87;[11.39-392.75]) compared to mildly (OR:28.54;[5.11-159.46]) and moderately (OR:21.45;[3.20-143.64]) impaired renal function, but seemed lower in those with severely impaired (OR:9.13;[0.96-86.97]) renal function. Data were insufficient to draw conclusions on effect modification by other CFs.

Conclusion

Few RCTs report stratified analyses exploring the role of CFs. ULT seemed effective in reaching the sUA target in all levels of renal function, though severely impaired renal function appeared to render a slight disadvantage.

Introduction

When moving towards personalised medicine, research into contextual factors (CFs) is increasingly relevant, as it allows to understand which subgroup(s) of patients respond differently to available drugs or drug strategies (1, 2). In the most recent framework, Outcome Measures in Rheumatology (OMERACT) recognises the importance of CFs as an integral part of outcome assessment. A CF is defined as *"a variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results"* (3, 4). CFs can be classified into three main types that are methodologically relevant for clinical studies: effect modifying, outcome influencing, and measurement affecting CFs (5). Effect modifying CFs are variables that influence the magnitude of the effect of the treatment on outcome, and therefore may be relevant for personalised medicine (5). In an attempt to identify CFs that should be explored for effect modification in all trials in rheumatology, OMERACT selected seven CFs (gender/sex, comorbidities, healthcare system, psychological well-being, treatment adherence, age, and previous drugs exposure) as potentially relevant for all trials in rheumatology (4, 6). Studies are needed to confirm effect modification by these factors in specific rheumatologic diseases. Also, it might be that for specific conditions or interventions additional CFs play a clinical important role.

Gout is worldwide a common disease for which the prevalence is increasing (7). Serum uric acid (sUA) is considered the main risk factor for symptomatic gout. Gout occurs more frequently in men and is associated with various comorbidities including cardiovascular diseases, renal insufficiency, and obesity (7). In patients with recurrent flares and/or tophi, it is recommended to start urate-lowering therapy (ULT) (8). Different classes of ULT are available to lower sUA, including xanthine oxidase inhibitors, uricosuric agents, or uricases. The most frequent outcome domain of ULT-trials in gout is sUA (9-11), as sUA is accepted as a biomarker for flares and tophi load, which are more relevant to patients (9). Currently, it is unclear whether treatment response to ULT is different between patient subgroups by presence/absence of specific CFs such as sex/gender or comorbidities that are strongly associated with gout, such as cardiovascular diseases, renal insufficiency, and obesity (12).

The objective of this systematic review was to determine the CFs for which effect modification has been reported of ULT on sUA as outcome, and to assess the direction and magnitude of the effect modification by CFs.

Methods

Recommendations by Cochrane Collaboration were followed for conducting the review (13) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) for reporting (14) this review (see online Appendix 1). The protocol was submitted to PROSPERO on March 17th, 2021. However, PROSPERO was not accepting registrations at that moment; therefore we did not obtain a registration number.

Eligibility criteria

As a first step, the PICOCT framework (Patients, Intervention, Comparator, Outcome, Context, and Time) was specified to find randomised controlled trials (RCTs) assessing the efficacy of ULT on sUA. Studies were eligible if they addressed adult (≥18 years) patients with gout (physician diagnosed and/or fulfilling ACR/EULAR classification criteria) and starting one of the currently available ULTs (allopurinol, febuxostat, benzbromarone, or lesinurad). Controls were receiving placebo, another ULT, or a different dose of ULT. The outcome of primary interest was sUA (10, 11). Any type of CF (e.g. personal, disease-related, and environmental) and any follow-up period was considered for eligibility.

Information sources, search strategy and study selection

As evidence from RCTs on ULTs of interest in gout had been summarised in Cochrane reviews, these systematic reviews were used as the starting point of the study selection (15-19). Whenever the last search of a review was older than 12 months, an update was conducted using the original search strategy. The records retrieved by this new search were screened and selected by two independent reviewers (RtK and IH) following the selection criteria of the original review. RCTs from Cochrane reviews and their subsequent updates were included when they reported to explore the effect of ULT on sUA by any CF. Any methodological approach to assess effect modification was accepted. Based on expert knowledge, predefined classes of CFs distinguished: *demographics*: e.g. sex/gender, education, or race; *lifestyle factors*: e.g. body mass index; *gout/*

health-related factors: e.g. disease duration, tophaceous disease, renal function. Only RCTs were included to minimize bias in conclusions on effect modification. For each selection step, discrepancies were solved by consensus in consultation with a third reviewer (CvD). EndNote X8 software was used to manage the records retrieved from the searches.

Data extraction

Data extraction was conducted by two reviewers (RtK and IH) blinded for each other using a predefined, standardised data extraction form developed in Microsoft Excel 2010 and pilot tested. The data extraction form was consistent with the Cochrane Collaboration's recommendations (20) and addressed characteristics of included studies (including superiority or non-inferiority design), participants' characteristics, type of interventions, and overall efficacy. Furthermore, the extraction sheet was complemented to determine: (a) which CF was considered (type and definition); (b) crude data on effectiveness of ULT by CF; and (c) the methodological approach to assess effect modification (e.g. stratified randomisation, stratified analyses, statistical interaction test), and (d) interpretation (i.e. relevance) of the effect modification. Discrepancies were solved by consensus in consultation with a third reviewer (CvD).

Risk of bias in individual studies

The Cochrane risk of bias tool for RCTs (RoB 2) was used to assess the risk of bias assessments (21, 22). Criteria were graded for each domain of interest by the two blinded reviewers (RtK and IH) as 'high risk', 'some concerns' or 'low risk'. A third reviewer (CvD) solved disagreements. From these assessments, each RCT was assigned an *overall* risk of bias in terms of low risk (low for all key domains), high risk (high for ≥1 key domains), and unclear risk (unclear for ≥1 key domains).

Statistical analyses and evidence synthesis

Quantitative synthesis

Trials with multiple ULT arms were treated as individual trials (i.e. 3-arm trials with 2 active interventions generated 2 randomised comparisons with the comparator). Treatment effects (net benefits) for each individual intervention arm in contrast to the comparator arm, that were reported separately for subgroups by CFs, were expressed using odds ratios (ORs). Coded so, OR >1 indicated a beneficial effect in favour of the experimental ULT intervention compared with the control comparator

(i.e. randomised comparison). For binary outcomes, these were directly calculated as logORs and SE(logOR), and applied a continuity correction of 0.5 in case of zero-cells (23). For continuous outcomes, however, we initially calculated standardised mean differences (SMDs) and the corresponding SEs, and converted these into logORs and SE(logOR) by multiplying by π/√3 (24, 25). For each CF, a separate meta-analysis was performed if there was sufficient data (i.e. available for at least 3 of the trials); see prespecified protocol (online Appendix 1). In the overall model, heterogeneity was investigated across all randomised comparisons, applying the combination between the standard Q-statistic followed by the inconsistency index (I^2 statistic); interpreted as the percentage of total variation across several studies due to heterogeneity (26-28). We used mixed-effects models based on Restricted Maximum Likelihood (REML)-based parameter estimates with CF as a fixed effect factor while trial and (sub-) comparison were random effects, accounting for the hierarchical structure of the data, i.e. comparisons nested within trials (29). Inconsistency for the multilevel model was estimated according to the method described by Nakagawa and Santos (30). Analyses were performed using R Software (31) with the *metafor*-package (32). Furthermore, we conducted a *post hoc* sensitivity analysis excluding head-to-head comparisons (e.g. 'active' ULT in the comparator group) (33).

Qualitative analyses

For all eligible trials, a summary table was created, describing the effect of CFs on sUA efficacy as described in the original manuscript.

Results

Study eligibility and selection

Five Cochrane reviews (15-19) - comprising 17 individual RCTs - addressed effectiveness of the ULTs of interest. Of these, two RCTs were eligible for our qualitative synthesis. As presented in Figure 1, the updated searches for the Cochrane reviews identified 3,739 records after removal of duplicates. Screening the titles and abstracts and subsequently the full-texts according to the review's original eligibility criteria left us with 20 full-texts to be assessed for eligibility for the current study. Of these, six RCTs were eligible, so a total of 8 RCTs were included in our qualitative synthesis. Four trials could be included in the quantitative synthesis, as they provided stratified data on effect of ULT on sUA by one CF (Figure 1).

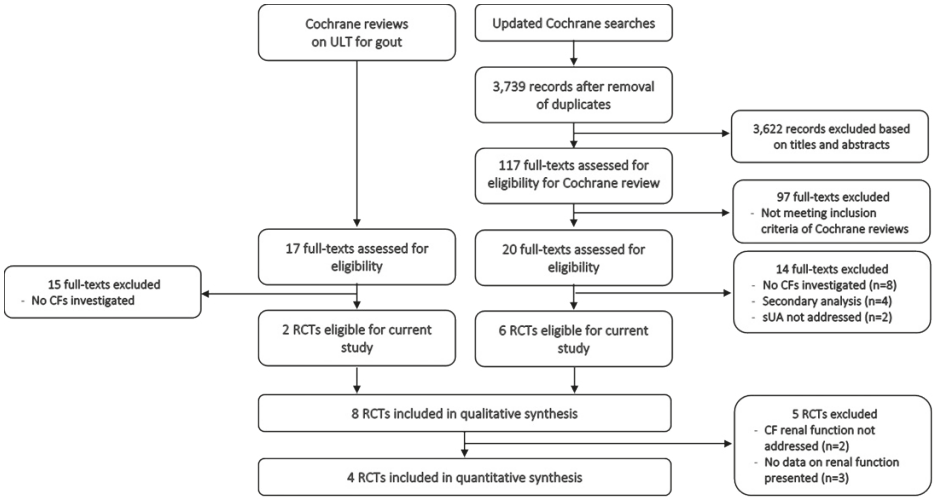

Figure 1: Flow diagram showing the selection of trials.

4

Study characteristics

Table 1 presents the study characteristics of the eight trials included. Trials were published between 2008 and 2019. The mean trial duration was 26 weeks (range, 4–52 weeks), mean disease duration was 10 years (range, 3–12 years), and 6% of patients were female (range, 3–12%). Five studies compared experimental ULT intervention (febuxostat n=2, and lesinurad n=3) to placebo, while three studies compared ULT to an active control ULT (febuxostat vs allopurinol n=3). ULT dosing was fixed for the duration of the study, except for initial up-titration of the intended dose in some RCTs. Febuxostat and lesinurad studies included treatment arms with different doses of the interventional drug, independent of renal function (40, 80, 120, 240 mg febuxostat and 200, 400, 600 mg lesinurad, respectively). In contrast, allopurinol dosage was (per study protocol) reduced to 100 mg or 200 mg in persons with (moderately) renal impairment in two studies where allopurinol was the active intervention or active comparator, respectively. Reaching a sUA level ≤0.36 mmol/L was the outcome in seven trials, while in one trial the percent reduction in sUA from baseline was the outcome.

Table 1: Study characteristics of RCTs included

Author, year	Trial duration (weeks)	No. of patients randomised	Disease duration (years)	Female (%)	ULT intervention
Schumacher (2008)*	28	1072	11	6	Febuxostat Febuxostat Febuxostat Allopurinol
Becker (2010)*	26	2269	12	6	Febuxostat Febuxostat
Xu (2015)	24	504	3	5	Febuxostat Febuxostat
Bardin (2016)	52	611	12	4	Lesinurad + allopurinol Lesinurad + allopurinol
Perez-Ruiz (2016)*	4	227	8	2	Lesinurad + allopurinol Lesinurad + allopurinol Lesinurad + allopurinol
Yu (2016)	12	109	-	3	Febuxostat
Saag (2017)	52	607	12	6	Lesinurad + allopurinol Lesinurad + allopurinol
Saag (2019)*	12	1790	-	12	Febuxostat IR Febuxostat IR Febuxostat XR Febuxostat XR

ULT = urate-lowering therapy, CF = contextual factor, IR = immediate release, XR = extended release, CV = cardiovascular. Bold contextual factors have presented data. *included in meta-analysis, #obligatory for renal impairment, ❜obligatory for moderate renal impairment

	Daily dose (mg)	No. of patients receiving intervention	ULT comparison	Daily dose (mg)	No. of patients receiving comparison	CF investigated
	80	267	Placebo	-	134	**Renal function**
	120	269				
	240	134				
	100#/300	268				
	40	757	Allopurinol	200¶/300	756	**Renal function, tophi**
	80	756				
	40	160	Allopurinol	300	159	**Sex**
	80	158				
	200+200# /≥300	204	Allopurinol + placebo	200# /≥300	206	Renal function, sex, age, race, CV comorbidity, diuretic use
	400+200# /≥300	200				
	200+200# /≥300	46	Allopurinol + placebo	200# /≥300	72	**Renal function, previous ULT use**
	400+200# /≥300	42				
	600+200# /≥300	48				
	80	54	Allopurinol	300	55	**Tophi**
	200+200# /≥300	201	Allopurinol + placebo	200# /≥300	201	Renal function, sex, age, race, CV comorbidity, diuretic use
	400+200# /≥300	201				
	40	357	Placebo	-	357	**Renal function**
	80	357				
	40	355				
	80	357				

Effect of CF on sUA

CFs in the eight trials comprised age (n=2), sex (n=3), race (n=2), renal function (n=6), cardiovascular comorbidity (n=2), tophi (n=2), thiazide-diuretic use (n=2), and previous ULT use (n=1). The number of CFs evaluated per study varied from one to six (Table 1 and Supplementary Table S1 and S2). For several CF types, heterogeneity or lack of measurement description of the CF was noticed. In three RCTs randomisation was stratified by renal function (34-36), in two trials by renal function and tophus status (37, 38), and in another RCT by pre-study allopurinol dose (39). All trials evaluated effect modification by CF using subgroup analyses (stratified analyses) of randomised treatment comparisons, of which five provided data (crude or effect sizes). Interaction tests were never performed/reported.

Quantitative synthesis

Four of the six studies that explored the role of renal function on ULT efficacy in sUA, presented crude data stratified by renal function for each treatment arm (36 treatment comparisons) and could be meta-analysed. Renal function was classified in each study as normal, mildly, moderately, and severely impaired renal function (for detailed definition see Supplementary Table S2) on sUA target achievement with ULT (34-36, 39). Three were placebo-controlled (30 randomised comparisons) and one compared febuxostat to allopurinol. The meta-analysis of 36 randomised comparisons identified a considerable heterogeneity (I^2=92.8%). Effect sizes were significant in subgroups having a normal (OR: 13.49 [2.18-83.31]), mildly impaired (OR: 18.50 [3.00-113.93]), and moderately impaired renal function (OR: 25.90 [4.12-162.85]), respectively (Figure 2). In the subgroup with severely impaired renal function, a non-significant effect size (OR: 6.43 [0.61-68.37]) was found. In most comparisons, the effect was (significantly) in favour of the experimental intervention group compared with the control comparator in achieving the sUA target. The comparisons of febuxostat 40 mg compared to allopurinol 200/300 mg were not statistically significantly different in any subgroup by renal function despite lower doses. Yet, febuxostat 80 mg was statistically significantly more beneficial compared to allopurinol 200/300 mg for patients with normal, mildly, and moderately impaired renal function (Figure 2). Furthermore, between subgroups, patients with mildly (Relative Odds Ratio (ROR): 1.37 [1.01-1.87]) or moderately impaired (ROR: 1.92 [1.27-2.90]) renal function were statistically more likely to achieve sUA target compared to a normal renal function. Patients with severely impaired (ROR: 0.48 [0.10-2.33]) renal function were less likely to achieve sUA

target compared to a normal renal function. Of note, on the level of individual studies, the study by Schumacher (assessing different doses of febuxostat vs placebo in all strata) revealed that the beneficial treatment effects became smaller in patients with mildly impaired compared to normal renal function (34). The post hoc sensitivity analyses excluding trials with an active comparison (febuxostat vs allopurinol (35)), confirmed estimates for ULT on sUA were significant in subgroups having a normal (OR: 66.87 [11.39-392.75]), mildly impaired (OR: 28.54 [5.11-159.46]), and moderately impaired (OR 21.45 [3.20-143.65]) renal function (but not for severely impaired renal function (OR: 9.13 [0.96-86.97])) (I^2=59.4%) (Figure 3). Between subgroups, those with normal opposed to mildly (ROR: 0.43 [0.15-1.23]), moderately (ROR: 0.32 [0.08-1.22]) were not significantly different. Those with severely impaired renal function (ROR: 0.14 [0.02-0.83]) seemed less likely to achieve sUA target compared to persons with normal renal function.

Qualitative synthesis

Six trials reported results of efficacy of ULT on sUA by CF that could not be pooled, because (a) crude data to assess estimates per treatment comparison for CF were not available, (b) subsamples were too small, or (c) insufficient studies were available for pooling (Supplementary Table S1). For subgroup analyses by age (n=2), sex (n=3), race (n=2), cardiovascular comorbidity (n=2), and thiazide-diuretic use (n=2), authors reported 'subgroup analyses did not differ from the main analysis'. Two placebo-controlled trials (lesinurad or placebo in persons on allopurinol) reported subgroup analyses by renal function (37, 38), without providing crude data. Each concluded on a small, non-significant, decrease in efficacy of ULT in reaching the sUA target in persons with mildly or moderately impaired compared to normal renal function (37, 38). Dosing of allopurinol background was lower in those with renal impairment (200 mg), but it is unlikely this affects efficacy of interventional ULT. For other CFs, results were more uncertain. For analyses by tophi, two trials provided data per treatment arm (35, 40), and suggested that the presence of tophi was associated with lower rates of sUA achievement within the active treatment arms. However, in stratified analyses of the treatment comparisons (febuxostat vs allopurinol), the presence of tophi did not change the likelihood of ULT to achieve the sUA target. Previous use of ULT resulted in significantly larger mean percent reduction in sUA in each lesinurad arm (at different doses) compared with placebo (39).

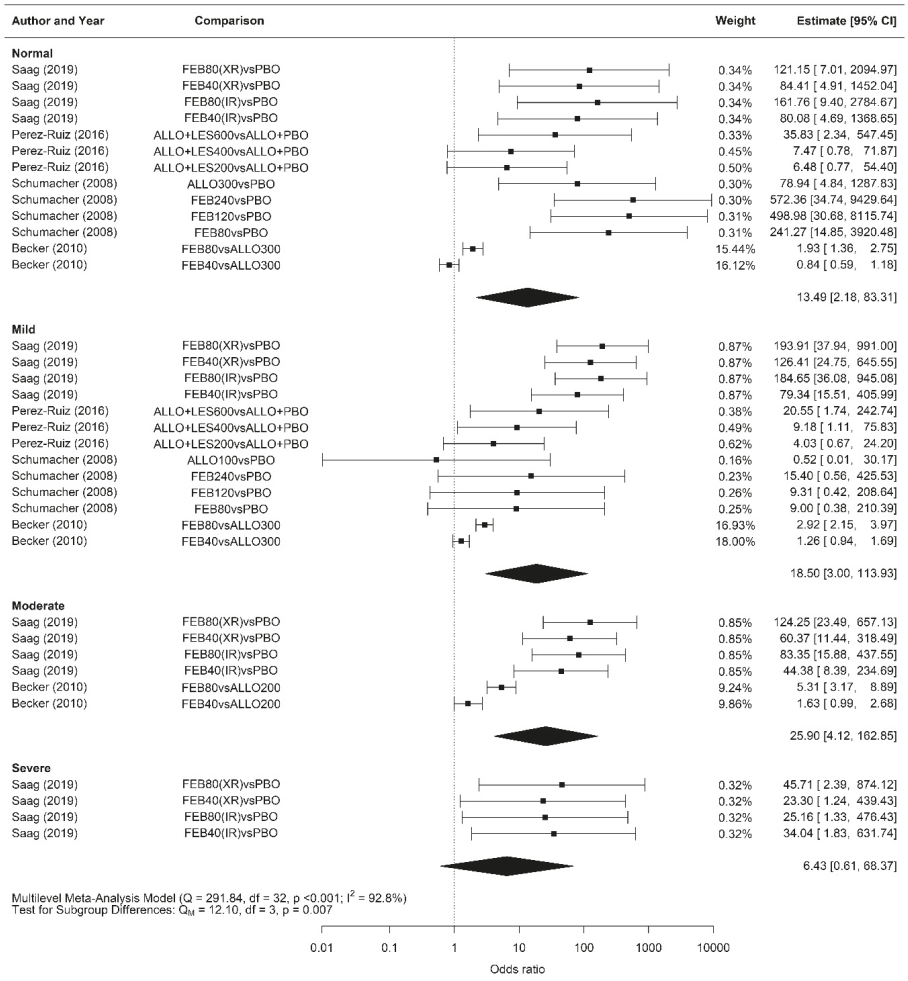

Figure 2: Forest plot of the results of the meta-analysis of sUA target achievement according to the level of renal function shown as pooled OR with 95% CIs. FEB = febuxostat, PBO = placebo, ALLO = allopurinol, LES = lesinurad, IR = immediate release, XR = extended release. The square represents the point estimate of the intervention effect. Horizontal lines join lower and upper limits of the 95% CI of this effect. Diamonds represent the subgroup pooled OR.

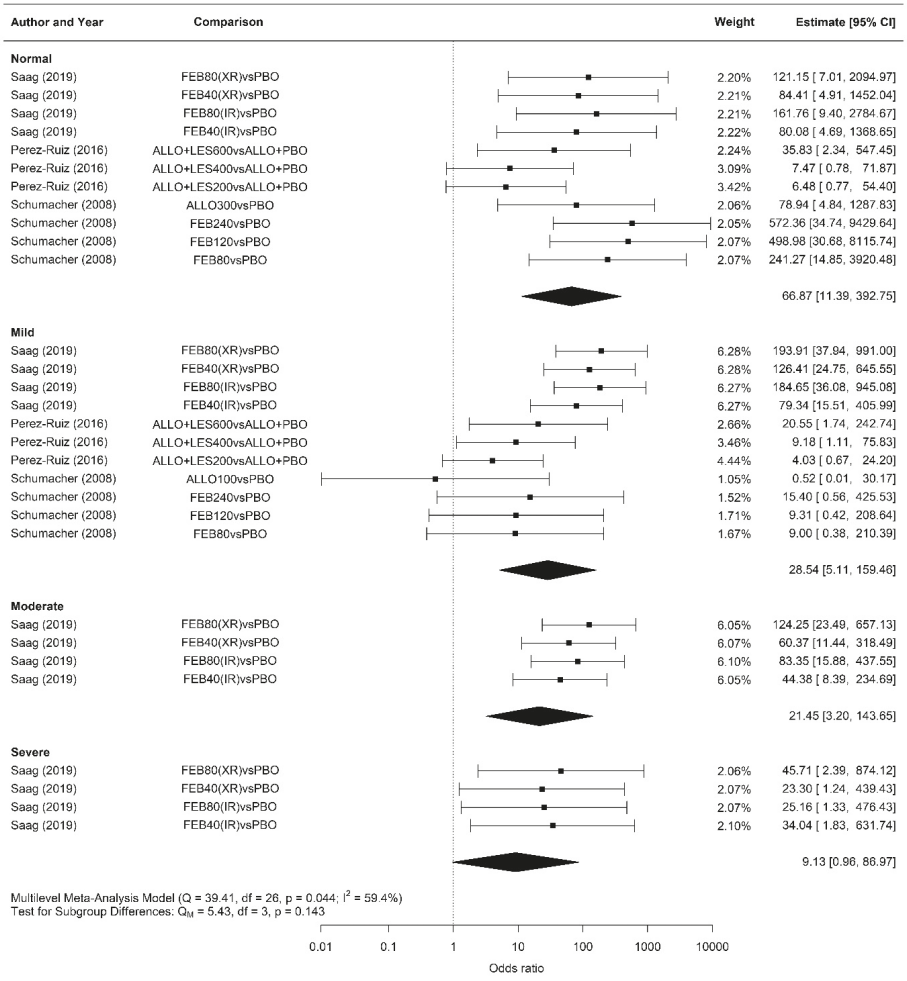

Figure 3: Forest plot of the sensitivity analyses of sUA target achievement according to the level of renal function shown as pooled OR with 95% CIs. FEB = febuxostat, PBO = placebo, ALLO = allopurinol, LES = lesinurad, IR = immediate release, XR = extended release. The square represents the point estimate of the intervention effect. Horizontal lines join lower and upper limits of the 95% CI of this effect. Diamonds represent the subgroup pooled OR.

Risk of bias of included RCTs

Six of the trials were classified as low risk of bias (Figure S1). As there was limited variability in risk of bias between trials, risk of bias is unlikely to influence the results.

Discussion

The importance of effect modification of treatment by CFs is increasingly recognized, as such evidence will support personalized treatment decisions. In gout, eight RCTs considered effect modification of ULT on sUA for age, sex, race, renal function, cardiovascular comorbidity, tophi, thiazide-diuretic use, and previous ULT use. Pooled estimates by renal function showed that patients with a normal, mildly, and moderately impaired renal function were more likely to achieve sUA target with ULT (febuxostat or lesinurad) compared to any comparator (placebo or allopurinol), though severely impaired renal function seemed to render a slight disadvantage. Further, patients with mildly or moderately impaired compared to a normal renal function seemed more likely to achieve sUA target in the main analyses. However, when considering only placebo-controlled studies in the sensitivity analysis, the likelihood to achieve the sUA target decreased – although not significantly - when renal function decreased. For all other CFs studied, there was insufficient evidence to make any conclusion on potential effect modification.

We focussed on RCTs to avoid inherent problems of confounding when investigating effect modifiers in non-RCTs (41). While performing the current review, lesinurad was withdrawn from the market in the United States for business reasons and by the European Commission at the request of the marketing authorization holder, making the current results related to lesinurad of less value for gout management. Yet, we decided to follow our study protocol, as inclusion would add to the evidence that effect of ULT on sUA would differ by CFs. Meta-analysis after excluding lesinurad, provided the similar conclusion for effectiveness of ULT by renal function. While other ULTs are available on the market (e.g. benzbromarone or peglocticase), no RCTs were found that investigated effect modification of other ULTs on sUA. Our review included RCTs that were placebo-controlled but also head-to-head comparisons. Placebo-controlled studies indicate whether a specific ULT has differential efficacy depending on the presence of a specific CF, while the head-to-head comparisons are useful complements as

they provide information on whether the choice of treatment matters. The latter is more interesting when moving towards personalised medicine. In the head-to-head comparison between febuxostat and allopurinol, febuxostat seemed more effective not only in the patient group with normal renal function, but also in those mildly or moderately impaired renal function. On a same line, the study including allopurinol compared to placebo, suggested lower effectiveness of allopurinol when renal function declined. However, the lower effectiveness of allopurinol could be explained by under-dosing of allopurinol, which was dosed at 100 mg or 200 mg in those with (moderately) renal impairment in both studies respectively. Clearly, our meta-analysis does not allow to compare effectiveness of different drug classes by renal function. The number of randomised comparisons was too small to perform further subgroup analysis by ULT classes or dosing. Of note, none of the trials allowed dose escalation, which would be common in daily practice. Also, results on effectiveness in case of severely impaired renal function should be interpreted with caution as this conclusion was drawn from four treatment comparisons of only one trial (2 doses febuxostat vs placebo). Last but not least, subgroups by CF are not necessarily prognostically similar at baseline. Even despite randomised stratification by renal function in three out of four studies of the meta-analysis, the reported estimates by the CF are not fully de-confounded by other CFs such as age, BMI, or gender.

Of the seven CFs proposed by the OMERACT Contextual Factors Working Group as potentially relevant to be evaluated in all RCTs in rheumatology, four were explored at least once, namely: sex, age, comorbidities (renal function and cardiovascular), and previous drugs exposure (4, 6). Only for renal function sufficient data were available to perform a meta-analysis. None of the studies in our review explored the role of the remaining OMERACT CFs: healthcare system, psychological well-being, and treatment adherence. Additionally, three other CFs were explored in our review that were not part of the OMERACT set, but potentially relevant in gout and treatment with ULT, namely: BMI, presence of tophi, and concomitant use of diuretics. Within treatment arms, presence of tophi reduced the likelihood of achieving the predefined sUA target, but this was not confirmed by the randomised comparisons. Of note, the randomised comparisons concerned two active treatments (febuxostat vs allopurinol) and were not placebo-controlled. Also, previous use of ULT seemed to infer a larger effect in mean percent reduction of sUA in a placebo-controlled randomised comparison. We did not include baseline

sUA as a CF in our study, as baseline values of the outcome are methodologically inherently related to the outcome, and thus not health/disease, personal or environmental factors (5).

The definition and measurement approach of the CFs studied was heterogeneous for some but not for all CFs. Five of six studies used the CKD-EPI equation for estimated glomerular filtration rate (eGFR) to classify renal function (42), while one study used serum creatinine levels (34). It could be that a small number of patients from the latter study would have been classified differently if the CKD-EPI criteria were used. For tophi, definitions about assessment were generally absent. Furthermore, methodological approaches to assess effect modification in the individual studies were heterogeneous and suboptimal. As indicated and to reduce dissimilarity of subgroup analysis, a randomised stratification for the CF of main interest should be performed. Of note, even if differences in effect sizes between predefined subgroups are found, this does not necessarily infer causality of the CF, confounding can persist. Analyses for CFs should be pre-specified, consistently reported, and appropriate methods for evaluating effect modification must be applied (43). Future research should also focus on effect modification of ULT on other outcomes besides SU such as gout flares and tophi, but also on cardiovascular outcomes or other comorbidities. Relevant examples are the trials of White et al. or Mackenzie et al., in which effect modification by several CFs on cardiovascular outcome was studied (44, 45).

Conclusion

Our study aimed to contribute to the clinical question whether, in gout patients, the presence of specific CFs influence the efficacy and potentially choice of ULT. Only few RCTs addressed the role of CFs and/or few RCTs addressed differences in effect modification by CFs between treatments. ULT seemed effective in reaching the sUA target in all levels of renal function, though severely impaired renal function might render a slight disadvantage. Differences in effect modification between types of ULT remain unclear. Overall, there is need for a research agenda that prioritizes outcomes (including gout flares and adverse events) and CFs for which effect modification should be explored, with attention to appropriate study design and analyses.

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PART II

Patient needs and support tools

CHAPTER 5

Outcomes of care among patients with gout in Europe: a cross-sectional survey

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J Rheumatol. 2021:jrheum.210009

Abstract

Objective

To assess health- and patient-centered outcomes in gout across Europe, and explore patient-, care-, and country-level characteristics associated with these outcomes.

Methods

Patients with self-reported physician-diagnosed gout from 14 European countries completed an online survey. Multivariable mixed-effect logistic and linear regressions were computed for health outcomes (gout flare recurrence) and patient-centered outcomes (patient satisfaction with current medication, and unaddressed goals), accounting for clustering within countries. The role of patient-, care-, and country-level factors was explored.

Results

Participants included 1029 patients, predominantly diagnosed by a general practitioner (GP). One or more gout flares were reported by 70% of patients and ≥ 3 flares by 32%. Gout patients reported 1.1 ± 1.2 unaddressed goals, and 80% were satisfied with current medication. Patients with ≥ 3 and ≥ 1 flares were less likely to be treated with urate-lowering therapy (ULT) (OR 0.52, 95% CI 0.39–0.70 and OR 0.38, 95% CI 0.28–0.53, respectively), but more likely to have regular physician visits (OR 2.40, 95% CI 1.79–3.22 and OR 1.77, 95% CI 1.30–2.41). Three or more gout flares were also associated with lower satisfaction (OR 0.39, 95% CI 0.28–0.56) and more unaddressed goals (β 0.36, 95% CI 0.19–0.53). Notwithstanding, the predicted probability of being satisfied was still between 57% and 75% among patients with ≥ 3 flares but who were not receiving ULT. Finally, patients from wealthier and Northern European countries more frequently had ≥ 3 gout flares.

Conclusion

Across Europe, many patients with gout remain untreated despite frequent reported flares. Remarkably, a substantial proportion of them were still satisfied with gout management. A better understanding of patients' satisfaction and its role in physicians' gout management decisions is warranted to improve quality of care and gout outcomes across Europe.

Introduction

Gout is highly prevalent and affects 1–4% of the population within Europe (1, 2). Gout flares are both unpredictable and recurrent, and are characterized by severe pain and limitations in physical function. If left untreated, a chronic course may occur, with persistent joint inflammation and development of tophi, potentially causing joint damage and disability (3-6). In addition, the increased prevalence of comorbidities, such as cardiovascular and chronic kidney diseases and type 2 diabetes mellitus (T2DM), contribute to the effect of gout on overall functioning and health, healthcare costs, and even mortality (7-10). Fortunately, the majority of patients with gout can be managed adequately. Different symptom-relieving drugs (colchicine, nonsteroidal antiinflammatory drugs, or prednisone) are available to control acute gout flare, and for long-term management, urate-lowering therapy (ULT) can be prescribed. The most recent European Alliance of Associations for Rheumatology (EULAR) guideline recommends consideration and discussion of starting ULT after a first gout flare (11). Notwithstanding, outcomes of gout remain suboptimal (5, 6, 12, 13), and population studies show that 37–72% of patients have 1 or more gout flares (14-16). Several factors contribute to suboptimal gout care, including low awareness of disease severity and its management among both physicians and patients, poor adherence to physicians' guidelines, poor adherence to medication, and finally the failure, intolerance, or contraindications (presence of comorbidities) of ULT (17-20).

Around the turn of the 21st century, calling patients to account for their personal situation, needs, and involvement in disease management decisions gave impetus to more patient-centered healthcare (21). In line with this, the Institute of Medicine emphasized the importance of patient-centeredness in addition to effectiveness, safety, timeliness, equitability, and efficiency as part of the 6 pillars of quality of care (22). Patient-centered care is defined as measuring and responding to patient needs, experiences, and satisfaction with disease control (23). This paradigm shift urged healthcare providers to integrate patients' needs, goals, experiences, and satisfaction with the traditional biomedical and patient-reported health outcomes (22-24). While patient experiences of care can be pertinent outcomes by themselves, they might also provide insight into why treatments may not reach the expected health outcomes in a real-world setting. In gout, substantial research clarified the effect of gout on health outcomes (25, 26). However, there is little

knowledge on the effect of care on patients' experiences (e.g., unaddressed goals, satisfaction) (4, 27), nor about the relationship between these experiences and health outcomes. Finally, to fully understand the outcomes of care, it has been shown repeatedly that not only patient and care characteristics but also country characteristics play a role. For example, patients from higher-income countries had lower disease activity in rheumatoid arthritis (RA) and spondyloarthritis. This was partly explained by higher uptake of innovative (and expensive) medication. Moreover, a paradox was seen, as patients with RA living in less wealthy countries had higher disease activity but reported better well-being and lower fatigue (28-30). Little is known about the association of country characteristics and geographic variation on gout health outcomes and experiences of care (31). Knowledge about variations in these outcomes and their relationships with patient and care characteristics might help physicians across countries to understand priorities when enhancing quality of care for patients with gout.

The objective of this study was (1) to evaluate the impact of gout on gout-specific and generic health outcomes as well as on patient-centered outcomes in a real-world setting across 14 European countries; and (2) to explore which patient, care, or country characteristics contribute to variations in outcomes.

Methods

This study was a cross-sectional international European online survey. Data were collected between June 13 and September 30, 2018.

Patients

Patients aged > 18 years with self-reported physician-diagnosed gout from 14 European countries (Austria [AT], Belgium [BE], Denmark [DK], France [FR], Germany [GE], Ireland [IE], Italy [IT], Malta [MT], Netherlands [NL], Norway [NO], Portugal [PT], Spain [SP], Sweden [SE], and Switzerland [CH]) were considered eligible to participate in the study. Patients were primarily recruited from open panels of an online market research organization (Dynata and Toluna) and from patient associations, and incidentally by rheumatologists or general practitioners (GPs) who were aware of the study and could hand out a leaflet to potential participants. It was planned to include at least 1000 patients, with a sample size per country varying between 25 and 150, depending on country size. Prior to the

survey's initiation, the participants received information on the objective of the study, were made aware that Grünenthal financed this study, and gave explicit consent. Following standards of market research, ethical approval was not needed for a study with anonymous data collection (Market Research Society; www.mrs.org.uk).

Data collection

The content of the questionnaire has been determined by a working group comprising both patients and clinical experts in gout, to ensure that outcomes relevant to evaluating gout care were covered. The survey can be found in the Supplementary Data 1 (available with the online version of this article). The online survey took approximately 15 minutes and contained 5 parts: (1) patient sociodemographics (e.g., age, sex, country of residence, and employment status); (2) history of gout diagnoses (e.g., healthcare provider who diagnosed gout); (3) patient knowledge about gout and lifestyle; (4) current gout management, including patient perspective (e.g., gout treatment, satisfaction with current medication, number of flares in the past year, physician visits in the past year, and comorbidities); and (5) impact of gout (e.g., effect on mental and physical health, number of missed work days in the past year, treatment goals). In the absence of a validated measurement instrument for some of the domains, the working group formulated items to assess these goals. The English questionnaire was translated into 11 different languages and checked for user-friendly language.

Outcomes

Outcomes for the current study included recurrence of gout flares (≥ 3 gout flares and ≥ 1 gout flare in the past year), self-reported impact of gout on mental and physical health (mean of 8 5-point Likert scale statements dichotomized as impact higher than median (3–5) vs impact below median (< 3), missed work (for those employed, ≥ 1 work day missed in past year due to gout), patient satisfaction with current medication (5-point Likert scale dichotomized as satisfied [very satisfied and satisfied] vs less satisfied [very dissatisfied, dissatisfied, and neutral]), and finally, patients' unaddressed treatment goals. The unaddressed treatment goals were calculated as the sum of the treatment goals that patients indicated were relevant to them but were not addressed by their physician (max score = 9; Supplementary Data 1, questions D3 and D4, available with the online version of this article).

Explanatory factors

Explanatory factors were selected a priori as relevant covariables or confounders across 3 main domains. Patient factors were as follows: sex (male vs female), age (> 55 vs ≤ 55 yrs), employment status (employed vs not employed), highest level of education achieved (higher education [university and postgraduate] vs other qualifications), comorbidities (sum score [0–5] of chronic kidney disease, T2DM, obesity, hypertension, and hypercholesterolemia), and knowledge about disease and lifestyle

(anchors range from 1 to 5: not knowledgeable [score 1–3] vs knowledgeable [score 4–5]). Care factors were as follows: currently treated with ULT (yes vs no), number of follow-up visits in the past year (dichotomized as ≥ 2), and type of physician who diagnosed gout (GP vs other). Country factors were as follows: gross domestic product (GDP) and healthcare expenditures (HCE) per capita in international dollars (Int$) extracted from the Organisation for Economic Co-operation and Development (2018 or latest available; www.oecd.org) and geographic regions (West [NL, BE, FR, IR], middle [GE, AT, and CH], South [IT, PT, SP, MT], and North [DK, NO, SE]).

Statistical analysis

The study sample, including outcomes and explanatory factors of interest, was described for the total group as well as subsamples from different geographic regions. Multivariable mixed-effect logistic and linear (for unaddressed treatment goals) regression models were computed for each outcome of interest, accounting for clustering of patients within countries (random intercept). In a first step, all patient- and care-related explanatory factors were introduced in the model for each outcome. Of note, the number of gout flares (≥ 3) was included as a covariate when the outcome was the impact on mental and physical health, ≥ 1 day of work missed, satisfaction, or unaddressed treatment goals. In a second step, country-level factors (GDP, HCE, and geographic region) were each included separately in the final models to assess their independent contribution and the confounding effect of the country factors in the model. To avoid overadjustment, the role of the geographic region was explored in the 1-level model. Statistical analyses were performed using IBM SPSS, version 25.0 (IBM Corp.).

Results

A total of 1029 patients with gout from 14 European countries (range 12–186 patients per country) participated in this survey. Overall, approximately 90% of patients were recruited by research panels, except for Malta (n = 12). Inclusion by rheumatologists or GPs was incidental. Overall, 228/1029 (22%) patients were female, 554/1029 (54%) were older than 55 years, and 398/1029 (39%) had a higher education (Table 1; Supplementary Table 1 for characteristics per country, available with the online version of this article). Patients had on average 1.8 ± 1.5 comorbidities. Patients were mainly diagnosed by their GP (746/1029 [73%]); 423/1029 (41%) patients had regular follow-ups (≥ 2 in the past year), and 604/1029 (59%) patients were currently being treated with ULT. Among geographic regions, patients from Southern Europe were more likely to be younger than 55 years, employed, knowledgeable about the disease, and frequently treated with ULT. Southern European countries also had a markedly lower GDP and HCE.

Gout outcomes across Europe

In Europe, the proportion of patients with ≥ 3 and ≥ 1 gout flare in the past year was 32% (324/1029) and 70% (724/1029), respectively (Table 1; Supplementary Table 1 for characteristics per country, available with the online version of this article). The impact of gout on mental and physical health that was higher than median was reported by 43% (443/1029) of the patients, and 52% of the employed patients (264/512) missed at least 1 day of work due to gout in the past year. A total of 80% (818/1029) of patients were satisfied with current medication, and patients revealed on average 1.1 (SD 1.2) unaddressed treatment goals. The top 3 unaddressed goals were to "forget about gout" (24%), "manage/minimize pain" (19%), and "prevent tophi" (18%; Figure 1).

Table 1: Patient, care, country characteristics, and gout health outcomes and patient-experienced outcomes overall and per geographic region

	Western Europe, n=331	Middle Europe, n=210	Southern Europe, n=388	Northern Europe, n=100	Total, n=1029
Patient characteristics					
Females	70 (21)	43 (21)	88 (23)	27 (27)	228 (22)
Age > 55 yrs	221 (64)	118 (56)	166 (43)	59 (59)	554 (54)
Higher education	146 (44)	46 (22)	181 (47)	25 (25)	398 (39)
Employed	124 (38)	105 (50)	242 (62)	41 (41)	512 (50)
Comorbidities, mean (0-5)	1.5 (1.3)	1.8 (1.4)	2.0 (1.6)	1.5 (1.2)	1.8 (1.5)
Knowledgeable about disease	104 (31)	58 (28)	228 (59)	20 (20)	410 (40)
Knowledgeable about lifestyle	235 (71)	187 (89)	332 (86)	75 (75)	829 (81)
Care characteristics					
Treated with ULT	179 (54)	116 (55)	262 (68)	47 (47)	604 (59)
Regular follow-ups (≥2)	141 (43)	93 (44)	172 (44)	17 (17)	423 (41)
Diagnosed by GP	258 (78)	150 (71)	262 (68)	76 (76)	746 (73)
Country characteristics[a], mean (SD)					
GDP (Int$, in thousands)	53.4 (10.2)	56.6 (4.9)	41.3 (2.1)	58.2 (5.5)	49.9 (9.5)
HCE (Int$, in thousands)	5.0 (0.1)	6.1 (0.5)	3.4 (0.1)	5.6 (0.3)	4.7 (1.1)
Gout health outcomes					
≥3 gout flares in past year	106 (32)	61 (29)	116 (30)	41 (41)	324 (32)
≥1 gout flare in past year	235 (71)	128 (61)	296 (76)	65 (65)	724 (70)
Patient experienced outcomes; n (%)					
Impact of gout on mental and physical health	131 (40)	60 (29)	218 (56)	34 (34)	443 (43)
Missed ≥1 day of work[b]	58 (47)	51 (49)	140 (58)	15 (37)	264 (52)
Satisfaction with current medication	273 (83)	165 (79)	306 (79)	74 (74)	818 (80)
Unaddressed treatment goals (0-9), mean (SD)	1.1 (1.3)	1.1 (1.3)	1.2 (1.1)	1.2 (1.4)	1.1 (1.2)

Values are expressed as n (%) unless otherwise indicated. [a]International dollars (Int$) extracted from the Organisation for Economic Co-operation and Development (2018 or latest available; www.oecd.org). [b]Only employed patients (512/1029 [50%]). GDP = gross domestic product; GP = general practitioner; HCE = healthcare expenditures; ULT = urate-lowering therapy

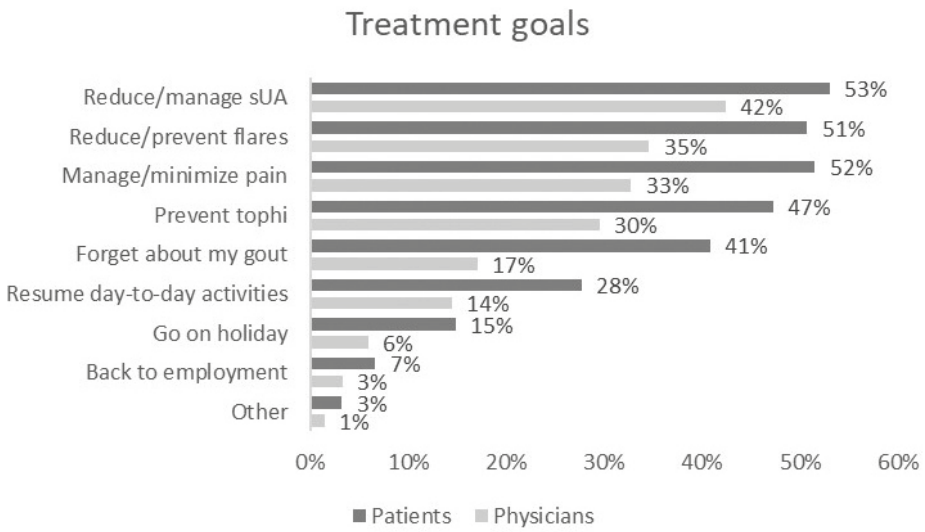

Figure 1: Treatment goals. sUA = serum uric acid.

Factors associated with gout outcomes

Patients with ≥ 3 gout flares in the past year were less likely to be treated with ULT (OR 0.52, 95% CI 0.39–0.70) in comparison to patients with < 3 flares. Also, patients with ≥ 3 flares visited a physician more frequently for their gout (OR 2.40, 95% CI 1.79–3.22), were more likely to report more comorbidities (OR 1.15, 95% CI 1.04–1.27), and were more likely to consider themselves knowledgeable about gout (OR 1.53, 95% CI 1.13–2.07; Table 2; for univariate associations for all outcomes, see Supplementary Table 2, available with the online version of this article).

Table 2: Results from multilevel multivariable logistic (OR and 95% CI) and linear (β and 95% CI) regressions for the various outcomes of interest.

	≥3 Gout Flares, n=1029		≥1 Gout Flare, n=1029		Impact of Gout on Mental and Physical Health, n=1029		Missed ≥1 Day of Work, n=512		Satisfaction, n=1029		Unaddressed Goals, n=1029	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	β	**95% CI**
Patient factors												
Sex (male vs female)	0.81	0.58-1.13	**0.67**	**0.46-0.99**	1.19	0.85-1.67	1.02	0.63-1.65	**2.02**	**1.39-2.93**	0.03	-0.16-0.22
Age (>55 vs ≤55 yrs)	0.76	0.55-1.06	**0.55**	**0.39-0.78**	**0.72**	**0.52-0.99**	**0.36**	**0.23-0.58**	1.01	0.68-1.51	-0.03	-0.21-0.15
Education (high vs other)	0.75	0.55-1.02	0.76	0.56-1.04	0.86	0.64-1.16	0.78	0.51-1.20	0.86	0.59-1.24	0.08	-0.08-0.24
Employment (work vs nonwork)	1.04	0.75-1.45	1.15	0.82-1.61	1.22	0.89-1.69	-	-	1.01	0.68-1.50	0.05	-0.13-0.23
Comorbidities, mean (0-5)	**1.15**	**1.04-1.27**	1.06	0.95-1.18	**1.22**	**1.10-1.35**	**1.16**	**1.01-1.33**	1.06	0.94-1.19	-0.02	-0.08-0.03
Gout flares past year (≥3 vs <3)	-	-	-	-	**2.59**	**1.91-3.50**	**2.48**	**1.59-3.87**	**0.39**	**0.28-0.56**	**0.36**	**0.19-0.53**
Knowledgeable about disease (yes vs no)	**1.53**	**1.13-2.07**	1.25	0.91-1.71	**1.35**	**1.01-1.81**	1.30	0.85-1.99	**1.68**	**1.15-2.44**	-0.03	-0.19-0.13
Knowledgeable about lifestyle (yes vs no)	0.92	0.64-1.32	1.18	0.82-1.70	**1.96**	**1.36-2.84**	1.60	0.91-2.80	**2.73**	**1.86-4.00**	0.20	-0.01-0.39
Care factors												
ULT treatment (yes vs no)	**0.52**	**0.39-0.70**	**0.38**	**0.28-0.53**	**0.59**	**0.44-0.80**	0.76	0.50-1.16	**2.85**	**2.00-4.06**	0.02	-0.14-0.19
Regular follow-ups (≥2 vs <2)	**2.40**	**1.79-3.22**	**1.77**	**1.30-2.41**	1.02	0.76-1.36	**2.75**	**1.82-4.17**	1.04	0.73-1.48	**-0.17**	**-0.33- -0.01**
Diagnosed by GP (yes vs no)	0.77	0.56-1.05	1.02	0.73-1.42	**0.69**	**0.50-0.94**	**0.48**	**0.31-0.75**	1.18	0.81-1.72	-0.02	-0.19-0.16

Values in bold are statistically significant. GP = general practitioner; ULT = urate-lowering therapy.

Patients with ≥ 1 gout flares in the past year were even less likely to be treated with ULT (OR 0.38, 95% CI 0.28–0.53) in comparison to those with ≥ 3 flares. In comparison with those with ≥ 3 flares, patients with ≥ 1 flares were more likely to visit their physician more regularly (OR 1.77, 95% CI 1.30–2.41). The reverse association between male sex and older age (> 55 yrs) for ≥ 1 gout flares was significant (OR for men: 0.67, 95% CI 0.46–0.99, and OR for > 55 yrs: 0.55, 95% CI 0.39–0.78; Table 2).

Patients experiencing a higher-than-median impact of gout on their mental and physical health were less frequently treated with ULT (OR 0.59, 95% CI 0.44–0.80) in comparison to patients with a below-median impact on their mental and physical health (Table 2). Moreover, patients who experienced ≥ 3 gout flares (OR 2.59, 95% CI 1.91–3.50) were more likely to report more comorbidities (OR 1.22, 95% CI 1.10–1.35). Nevertheless, these patients considered themselves knowledgeable about lifestyle (OR 1.96, 95% CI 1.36–2.84) and gout (OR 1.35, 95% CI 1.01–1.81). Of note, patients diagnosed by a GP (OR 0.69, 95% CI 0.50–0.94) or who were older than 55 years (OR 0.72, 95% CI 0.52–0.99) experienced less impact from gout on their mental and physical health (Table 2).

Patients missing ≥ 1 working days due to gout in the past year were more likely to have experienced frequent gout flares (OR 2.48, 95% CI 1.59–3.87), visited a physician more frequently (OR 2.75, 95% CI 1.82–4.17), and had a 1.16 (95% CI 1.01–1.33) increased risk of having comorbidities. On the other hand, patients diagnosed by a GP (OR 0.48, 95% CI 0.31–0.75), or who were older than 55 years (OR 0.36, 95% CI 0.23–0.58) were less likely to have missed working days (Table 2).

Patients satisfied with their current medication were less likely to experience frequent gout flares (OR 0.39, 95% CI 0.28–0.56) and were more likely to be in treatment with ULT (OR 2.85, 95% CI 2.00–4.06). These patients scored themselves as being knowledgeable about lifestyle (OR 2.73, 95% CI 1.86–4.00) and gout (OR 1.68, 95% CI 1.15–2.44), and were more likely male (OR 2.02, 95% CI 1.39–2.93; Table 2).

While frequent gout flares (β 0.36, 95% CI 0.19–0.53) were independently associated with a higher number of unaddressed treatment goals, more regular visits to their physician (β –0.17, 95% CI –0.33 to –0.01) were associated with fewer unaddressed treatment goals (Table 2).

Role of country characteristics

Country of residence (n = 14) as a second level did not contribute significantly to variance in any of the gout outcomes explored (random intercept covariance P > 0.05). Further exploration of specific country characteristics revealed that per thousand Int$ GDP and HCE, there was a 1.02 (95% CI 1.00–1.05) and 1.27 (95% CI 1.01–1.61) increased risk of having ≥ 3 gout flares, and a negative association with higher impact on mental and physical health (significant only for HCE; Table 3). No associations were seen for GDP and HCE on patient-centered outcomes. In comparison with patients from Western European countries, patients from Northern Europe more frequently reported having ≥ 3 gout flares (OR 1.77, 95% CI 1.08–2.90), and those residing in Middle Europe less frequently had ≥ 1 flare (OR 0.51, 95% CI 0.34–0.77) and less impact on mental and physical health (OR 0.45, 95% CI 0.30–0.68). Also, patients from Southern and Middle Europe were less satisfied (OR 0.44, 95% CI 0.28–0.68 and OR 0.56, 95% CI 0.34–0.92, respectively), in comparison with patients in Western European countries. Of note, there was no relevant confounding of country characteristic factors on covariates of the final model.

Table 3: Results from multilevel multivariable logistic (OR and 95% CI) and linear (β and 95% CI) regressions for the various outcomes of interest

	≥3 Gout Flares, n=1029		≥1 Gout Flare, n=1029		Impact of Gout on Mental and Physical Health, n=1029		Missed ≥1 Day of Work, n=512		Satisfaction, n=1029		Unaddressed goals, n=1029	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95%CI**	**OR**	**95% CI**	**OR**	**95% CI**	β	**95% CI**
Country factors[a]												
GDP (Int$, in thousands)	**1.02**	**1.00-1.05**	1.01	0.98-1.03	0.98	0.96-1.01	1.01	0.99-1.04	1.01	0.98-1.04	0.00	-0.01-0.01
HCE (Int$, in thousands)	**1.27**	**1.01-1.61**	0.93	0.74-1.17	**0.70**	**0.56-0.87**	1.16	0.92-1.45	1.16	0.88-1.52	-0.01	-0.09-0.06
European geographic region												
Western Europe	Ref		Ref		Ref		Ref		Ref		Ref	
Middle-Europe	0.77	0.51-1.15	**0.51**	**0.34-0.77**	**0.45**	**0.30-0.68**	1.01	0.56-1.84	**0.56**	**0.34-0.92**	0.06	-0.22-0.23
Southern Europe	0.71	0.50-1.02	1.16	0.80-1.68	**1.55**	**1.10-2.17**	1.27	0.76-2.13	**0.44**	**0.28-0.68**	0.05	-0.15-0.24
Northern Europe	**1.77**	**1.08-2.90**	0.74	0.44-1.23	0.64	0.38-1.06	0.63	0.28-1.43	0.66	0.37-1.19	0.02	-0.26-0.30

GDP and HCE are derived from separate models; only minor differences were observed in individual covariates between the separate models. The European geographic region was derived from a separate 1-level model. Values in bold are statistically significant. [a]International dollars (Int$) extracted from the Organisation for Economic Co-operation and Development (2018 or latest available; www.oecd.org). GDP = gross domestic product; HCE = healthcare expenditures.

Discussion

Among patients from different European countries, this study observed a substantial impact of gout on a broad range of health outcomes, whereas the effect on patient-centered outcomes was less striking. Overall, 70% of the patients reported at least 1 gout flare in a 12-month period, and 32% at least 3 flares. In addition, 43% of patients reported an effect on mental and physical health, and 52% of those employed missed at least 1 working day due to gout in the past year. Nevertheless, 80% of the patients were satisfied with their current medication, and patients experienced on average 1.1 unaddressed treatment goal. Multivariable exploration revealed that gout flares contributed substantially to worse health and patient-centered outcomes. As expected, current ULT was consistently associated with better health and patient-centered outcomes, except for unaddressed treatment goals. Contrary to our hypothesis, patients from wealthier countries reported more frequent gout flares.

Findings on the frequency of gout flares in this study are comparable to other European studies within population settings, where the frequency of patients diagnosed with gout with at least 1 gout flare within a 12-month period varied between 37% to 72% (14-16). Similarly, the ULT prescription rate of 59% in our study was within the reported range of 25–73% in other GP and population settings (14, 15, 32-36). Importantly, our study pointed to an inverse relationship between low ULT use and gout flares (15, 32). This raises the important question of why patients were not treated adequately despite recurrent flares. Strikingly, these patients also visited their physician more frequently. While we adjusted for comorbidities, including obesity, there might be residual confounding, as the severity (not the number) of comorbidities might play a role in either causing more severe gout and/or being a contraindication for a more aggressive disease, thus leading to suboptimal care (undertreatment). Unfortunately, we had no data on contraindications, past failure, or intolerance of ULT. Of note, Harrold, et al reported that only 9.6% of the GPs were aware of the guidelines and adhered to recommended treatment for gout flares in only 47% of the cases (37, 38). Somewhat counterintuitively, patients with more flares considered themselves more knowledgeable about gout. This seems to indicate that knowledge is not always a barrier to optimal treatment, as suggested by Rai et al (13). It remains difficult to know whether patients experiencing frequent gout flares had truly

difficult gout to treat or whether physicians were insufficiently aware of treatment options (39). Gout flares were not benign but had large impact on mental and physical health and on work participation. Literature affirms that patients who reported ≥ 3 gout flares within a 12-month period had nearly a 3-fold increase in the odds of reporting symptoms of depression (40). In addition, a 1-year prospective observational study showed loss of working days due to flares in 78% of patients (41).

In addition to health outcomes, we demonstrated a negative association between frequent flares and patient-centered outcomes. The overall satisfaction rate of 80% was comparable to Khanna, et al, where satisfaction with current ULT ranged from 75% to 95% in a managed care setting (42). Of interest, knowledge about gout and about lifestyle were both associated with higher satisfaction, supporting the relevance of patient-centered care. Gout flares were also related to unaddressed goals. While 54% (164/305) of patients without gout flares had at least 1 unaddressed treatment goal, this increased to 73% (235/324) in those with ≥ 3 gout flares. Interestingly, "forget about my gout" was the most frequent unaddressed treatment goal. It is likely that this domain integrates the worries gout causes for patients, such as the unexpected nature of gout flares, the need to adhere to lifestyle changes and medication intake, and anxiety about the longterm effects of gout. The unaddressed treatment goals highlight the importance of actively addressing goals, needs, and expectations in the patient–physician relationship.

The high satisfaction rate, in contrast to the high proportion of patients with untreated gout flares, was striking. Further analyses indicated that the predicted probability of patients with ≥ 3 gout flares, but who are not being treated with ULT, and were nevertheless satisfied, was as high as 57–75%; this was independent of frequency of physician visits (but dependent on the remaining explanatory factors of satisfaction). In other words, "suboptimal" gout treatment does not result in a dissatisfied patient, and more insight into the role of satisfaction with quality of care and health outcomes is needed. Currently, it remains difficult to answer the question of what an acceptable pain level or frequency of gout flares is for patients without increasing medication (43). In particular, the ongoing debate of a "treat to uric acid" target opposed to a "treat to avoid symptoms" target requires attention on the relation between patient satisfaction and flares (44). In line with this, regular longitudinal assessments of satisfaction with gout management in a daily practice

cohort can provide more insight into factors contributing to satisfaction and its causal relation with health outcomes.

This study specifically aimed to understand similarities and differences in health and patient-centered outcomes across European countries. Results were interesting but challenging. While it was expected that patients from wealthier countries had better health outcomes, patients from countries with a higher HCE and GDP more frequently had ≥ 3 gout flares. It is possible that lifestyle, specifically alcohol use and obesity (partially adjusted for), is a strong risk factor for gout. In addition, it might be that in wealthier countries, patients have more difficult gout to treat in view of more severe comorbidities, as patients with heart or kidney failure might survive longer in those countries. Another striking finding was the lower satisfaction rate among patients from Southern and Middle Europe. We can only speculate about potential causes such as communication, accessibility, and out-of-pocket costs for treatments. Insight into population health and satisfaction with healthcare in the different countries would have been useful as a benchmark for interpreting our data (45, 46).

Limitations that are inherent to cross-sectional and survey-based studies should be discussed. First, enrolled gout patients might not be fully representative of the average gout patients in each of the participating European countries. Moreover, included patients had self-reported gout, further contributing to potential selection bias. However, self-reported physician-diagnosed gout has acceptable reliability and sensitivity, and seems more appropriate for epidemiologic studies (47, 48). Third, as this was an online self-reported survey, misclassification (information bias) and recall bias might have affected the findings of this study. While proposals have been made to improve assessment of self-reported gout flares, consensus on the most accurate approach has not been reached (49, 50). Further, stigma may influence health beliefs and coping plans, and may affect people seeking health services. Importantly, in order to assess largely unexplored domains, specifically for patient-centered outcomes, several of the survey questions were self-composed. Nevertheless, care was taken that questions were unambiguous, unidimensional, and tested among patients. Last but not least, in view of the cross-sectional nature of our study, conclusions about causality related to confounding by indication cannot be made.

Conclusion

In Europe, a substantial proportion of patients with gout experience gout flares but receive no ULT. Patients with frequent flares were more likely to visit their physician regularly. Interestingly, a substantial proportion of these patients were not dissatisfied with their gout management. Findings suggest that more stringent control of gout flares by physicians, even if patients seem satisfied, would contribute to improved gout outcomes, leading to eventually fewer unaddressed treatment goals and even higher satisfaction.

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CHAPTER 6

Development of a patient decision aid for the initiation of urate-lowering therapy in gout patients

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Abstract

Objective

Shared decision-making improves patients' experiences with care, satisfaction with management decisions and possibly health outcomes. This study describes the development of a decision aid (DA) that supports patients with gout and their physicians in a face-to-face clinical setting to (a) decide whether or not to (re)start urate-lowering therapy (ULT) and (b) agree on the preferred ULT.

Methods

Recommendations of the International Patient Decision Aid Standards group guided the development. A steering group of experts in gout and health services research specified the scope. Nominal group technique meetings were organised in which patients ranked the importance of preidentified potential characteristics/attributes of ULT and discussed further needs regarding the DA. A literature search was conducted to collect evidence on gout outcomes with and without ULT. Subsequently, the DA prototype was designed and adjusted using feedback from the steering group and results of cognitive debriefing interviews among five gout patients.

Results

The final DA consists of six pages. First, the DA clarifies the decision at stake and describes gout including its risk factors, the role of lifestyle and treatment of flares. Next, risk of future flares with and without ULT in relation to serum uric acid levels is described and visualised. Relevant attributes of ULT are presented in an option grid distinguishing first-line and second-line ULT. Finally, patients' believes and preferences are explicitly addressed before making the shared decision.

Conclusion

This study provides initial support for usability of a DA for gout patients eligible for starting ULT.

Introduction

Gout is worldwide the most common form of inflammatory arthritis and is a well treatable disease (1). Serum uric acid (sUA) is the main risk factor for gout. Lifestyle modifications, especially weight loss in case of obesity, play a relevant but limited role in controlling gout (2, 3). Therefore, most patients will require pharmacological urate-lowering therapy (ULT) to prevent recurrent gout flares and damage related to tophi, and possibly to reduce risk for comorbidities (4).

Several ULTs are available to reduce sUA. Allopurinol and febuxostat inhibit the activity of xanthine oxidase and, thus, reduce uric acid production. Benzbromaron and lesinurad are examples of uricosuric drugs and increase the renal excretion of sUA (5, 6). Despite the availability of an increasing number and mode of actions of ULT, gout management is far from optimal (7-10). Suboptimal treatment is related to various key barriers among both physicians and patients (11-13). Importantly, a qualitative study revealed that a substantial proportion of patients receives contradictory information from different physician, contributing to poor treatment initiation and adherence (14).

Several initiatives have been proposed to improve outcomes of gout treatment in daily practice (15). Shared decision-making (SDM) is increasingly considered to constitute an essential part of quality of care and is grounded in the paradigm that care should be based on best evidence and should be respectful of, and responsive to, individual patient preferences, needs and values (16). Decision aids (DAs) are tools that support patients and physicians in the choices when decisions about screening, treatment or other interventions have to be made (17-19). Shared decisions involve at minimum a patient and physician, although other healthcare providers or friends and family members may be invited to participate (20, 21). The process ensures that correct and complete information is readily available for patients and physicians (22). While effectiveness of DAs on disease outcomes is as yet contradictory, patients exposed to Das feel more knowledgeable, better informed and more clear about their values (22).

The European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) recommends to initiate ULT after a first gout flare (23, 24). EULAR recommendation specifically stated that: '*Patients*

with gout should receive full information and be fully involved in decision-making concerning the use of ULT to increase uptake and adherence of ULT' (23). To support the implementation of this recommendation and, thus, improve quality of care, this paper describes the development of a DA for patients with gout that have an indication to (re-) start ULT in a clinical setting.

Methods

The study protocol was determined within a steering group consisting of four rheumatologists and two health service researchers including an expert on DAs. Recommendations by the International Patient Decision Aid Standards (IPDAS) group guided the development and comprised four phases: *scoping, design (patients and physicians needs assessment and literature searches), development of a prototype and pilot testing with patients* (18, 25). The study was approved by the ethical committee of Maastricht University Medical Center (2018–0801).

Phase 1: scope

The aim was to develop a DA to support the decision whether or not to start ULT in gout patients in a face-to-face clinical setting and to agree which ULT would be preferred. Initial specifications of the content required for a decision (eg, type of ULT) and format of the DA were discussed within the steering group.

Phase 2: design

IPDAS certification criteria for DA

The IPDAS collaboration states a DA needs to present information on the decision at stake, the health condition including risk factors, the available options (first and second line) and positive (benefits) as well as negative (harms) features of each option (26). Furthermore, the DA has to offer structured guidance on deliberation which option to select.

Needs assessment: patients and physicians

A nominal group technique (NGT) was chosen to understand which characteristics/attributes of ULT are relevant for patients and should be included in the DA. The NGT facilitates quick agreement on the relative importance of an issue (in this case, the attributes of ULT) (27, 28). Patients were recruited in the outpatient clinic of a regional and university hospital. All participants provided written informed consent.

The discussion was facilitated by a rheumatologist and audio-recorded. Following an introduction on DAs, the purpose procedures of the meeting, participants were presented potential attributes of ULT, as obtained from a literature search preceding the NGT meetings (29). Next, patients were asked to rank individually the attributes by importance from 1 (most important) to 10 (least important) on a worksheet. Patients also had the opportunity to add missing attribute(s). The individual ranks were summed across patients to obtain a ranking order. Using the initial sum scores of each attribute, a group discussion was stimulated on the initial scores. Eventually, patients were asked to rerank to support a final decision on selection of attributes to be included.

Ensuing the NGT, participants were further invited to specify the content of the attributes of ULT. For example, 'efficacy' of ULT is a key attribute, but can be specified as effect on number of gout flares, sUA and/or tophi reduction, cardiovascular risks or a combination of those. Finally, participants discussed general aspects of content and layout, including benefits and harms of the planned DA. Discussions were transcribed verbatim and content was used when developing the different parts of the prototype.

To reveal potential discrepancy between patients' and physicians' views, which attributes of ULT should be included in the DA, the ranking exercise was also carried out among rheumatologists who were not part of the steering group.

Literature search

Two literature searches were performed. The first concerned identification of potential attributes of ULT and aimed to inform the NGT meetings. A non-systematic search was performed in PubMed for literature on DAs to support decisions on initiating a drug in a chronic disease. Keywords concerned 'chronic diseases', 'decision aid' and 'treatment'. Drug attributes were extracted and summarised into domains (eg, side effects) and specifications (eg, type of side effects, severity of side effects and frequency of side effects). The second search aimed to find data on effect of gout and its treatment on outcomes selected by patients as relevant for a decision (30-32). Using a hierarchical approach, evidence from systematic literature reviews (SLRs) of randomized controlled trials (RCTs) in patients with gout comparing the effect of ULT to placebo (outcome with opposed to without ULT) or other ULT (comparative effectiveness) would be considered

as best evidence. In case of absence of SLRs or eligible RCTs, observational studies would be used. Searches and data extraction were performed by the junior researcher (RtK), and data extraction was checked by a senior researcher (CvD).

Phase 3: development of prototype

Based on preceding qualitative and quantitative steps (needs formulated by experts, results NGT meetings including needs among patients and literature searches), recommendations on development of DAs and expectations on outcome of SDM interventions, a prototype was developed (22, 33, 34). During the process, members of the steering group were regularly consulted regarding the content and selection of attributes to include within the DA. For design of the DA, expertise of a design academy was consulted. To ensure readability across literacy levels, text was tested against language level (B1).

Phase 4: pilot testing

Design and participants

Pilot testing consisted of individual cognitive debriefing interviews followed by questions assessing usability of the DA. Patients were recruited in the outpatient clinic of a regional and university hospital. Patients should not have taken part in the NGT meetings and were further eligible if they were ≥18 years, proficient in the Dutch language, diagnosed with gout and currently using ULT. Interviews were conducted at the outpatient clinic. All participants provided written informed consent.

Cognitive debriefing

Participants were instructed to read aloud each page of the DA in the presence of the researcher and verbalise any comments, thoughts or difficulties regarding wording, clarity, completeness of the information, visualisation, navigation through the programme and content being actionable. The researcher took field notes and prompted questions seeking clarifying comments and observations about the DA. The cognitive debriefing was audio recorded, transcribed verbatim, anonymised and analysed. The comments of the participants were summarized around the main elements of the prototype of the DA. Based on the remarks, revisions were made and the adapted prototype was tested with other participants.

Usability questions

Following the cognitive debriefing, participants completed 10 questions, adapted from the Ottawa acceptability tool, to assess the comprehensibility and usability (35). Eight closed ended items address respondents' perceptions about the DA (eg, information (n=3 items), design (n=2 items), usefulness for decision-making (n=3 items)) with Likert-scale response options (varying between 2 and 4 options) and two open-ended questions asking for potential improvements (Online Supplemental Table S1).

Results

Phase 1: specification of the scope

The scope of the DA was to facilitate a shared decision whether or not to (re)start ULT in a clinical encounter between a physician and a gout patient who has an indication to (re)start ULT. In line with the SDM paradigm, a patient can decline participation in the SDM process and rely on the physicians' decision. To enhance usability in daily practice, the content of the DA was aligned to the national and international recommendations. On that line, experts agreed that lifestyle changes should be positioned as integral part of gout management and flare prophylaxis before initiating ULT should be emphasised. Also, the potential of sUA target in management should be mentioned, and a distinction should be made between first-line and second-line ULT (first-line allopurinol and second-line febuxostat and benzbromaron). Rasburicase was not included as it is not registered for chronic urate lowering. Lesinurad was finally not included as by the time of the pilot testing, the European Medicines Agency withdrawn lesinurad on request of the market. Within these boundaries, patients can choose between available ULTs.

Phase 2: design

Patient needs for information on ULT attributes

Ten potentially important attributes of ULT (Table 1) were selected from high-quality DAs retrieved from the literature search and were used in the NGT meetings. Four NGT meetings were organised within total 20 gout patients. Patients were 60±12 years old, 18 (90%) were men, disease duration was 4.1±4.9 years and 18 (90%)) used currently ULT. Of note, one patient did not participate in the ranking experiment, as he trusted his physician to make the best choice for him personally.

Table 1 presents the result of the initial and final ranking. Based on a gap in the final sum score, it was agreed to include the six highest ranked attributes (effectiveness, side effects, interactions with concomitant medications, biological mechanism of action, frequency of administration and requirement for combination ULT therapy) in the DA. Patients agreed effectiveness to be the most important goal of a treatment:

"Actually, as a patient, you always want that the complaints for which you visit the doctor to stop. That can be pain or other complaints. Then you are satisfied and afterwards you will probably continue to look at whether it is harmful to your body or side effects and costs for people and yourself".

However, when using daily ULT for long periods of time, patients felt strongly the drug should be safe and have no interactions with concomitant medications:

"Imagine I get something prescribed now but I also take something else that can clash. Does that work together? So I think that's pretty important".

When continuing the discussion of the specific information on effectiveness (attribute ranked first), patients revealed both sUA target achievement and gout flare recurrence as most important as these were applicable to all patients. For side effects, it was preferred to be informed about the type of side effects in relation to the frequency. Patients also expressed the need for general gout information (eg, causes and risk factors) and information about lifestyle and need for flare prophylaxis. Finally, patients preferred the visualisation of risk communication on the most important outcome as icon arrays.

When comparing the rank order of attributes between patients and rheumatologist, the latter had underestimated the importance for patients of potential interactions of ULT with other drugs.

Table 1: Initial and final sum score and ranking by patients and final ranking by rheumatologists of the attributes during the nominal group technique meetings (order of attributes according to patients' final rank)

Attributes	Patients (n=19)				Rheumatologists (n=5)
	Initial sum score*	Initial rank	Final sum score*	Final rank	Rank
Effectiveness	26	1	26	1	1
Side effects	53	2	53	2	2
Interactions with concomitant medications	77	3	78	3	6
Biological mechanism of action	96	4	93†	4	4
Combination therapy required	101	6	93†	5	5
Frequency of administration	97	5	98	6	3
Out-of-pocket cost	137	7	141	7	7
Time on market	146	8	146	8	8
Branded or generic specification	151	9	155	9	9
Cost for the society	161	10	162	10	10

*Sum score of the ranks provides to the patients across all nominal group technique meetings in which '1' indicate the most important attribute.†Equal final sum score by patients, but biological mechanism of action was more often (36% vs 11%) prioritised in the top three as attribute.

Literature search

Three SLRs were identified, synthetising efficacy of allopurinol, febuxostat and uricosurics (30-32). As the last search of each review was older than 12 months, updates were conducted using each SLR's original search strategy. Overall, six RCTs were selected comparing effect of ULT to placebo or other ULTs on flares as outcome (the preferred outcome for patients) (36-41). After tabulating the study characteristics, data turned out to be too heterogeneous (eg, exclusion criteria, definition of flares, sUA level at inclusion) and follow-up time was too short to provide meaningful data on efficacy on flares (as flares provoked by ULT initiation distorts long-term efficacy). Therefore, an available review of five longitudinal studies reporting data on the association of flares according to sUA category was used (42). The study best fitting our target population, concerned patients with rheumatologists diagnosed gout and clinically confirmed flares (43). Of note, the majority of patients were (not yet) treated with ULT during follow-up. As the

relation between sUA and flare was steep, it was decided to distinguish two sUA categories, differing in future flares risk. In patients with an sUA of >0.36–<0.55 mmol/L, future flares risk was 48/100 and in patients with a sUA ≥0.55 mmol/L future flare risk was 90/100 within a follow-up period of at least 1 year. Patients who would reach the sUA target (≤ 0.36 mmol/L) would have a future flares risk of 12/100. To understand the relative efficacy of the different ULTs, one head-to-head RCT comparing allopurinol, febuxostat and placebo concluded a stronger impact of febuxostat compared with allopurinol on sUA but not on flares (30, 36).

Phase 3: development of prototype

A six-page paper DA, personalised according to the patient's current sUA level, being >0.36 but <0.55 mmol/L or ≥0.55 mmol/L, was developed (see Table 2 for sources of content). The first page explicitly stated the decision that had to be taken, described the health condition and explored the (personalised) risk factors (eg, comorbidities, gender, tophi, sUA) for gout, and previous ULT (and potential side effects) use. Page two visualised the (personalised) risk on future gout flares without ULT by icons arrays of a gout flare in the first metatarsophalangeal joint (first MTP). Page three described the role of lifestyle changes, comprising weight loss if obese and diminution of alcohol consumption if present and the treatment of flares. Page four introduced the benefits of ULT on the risk of future flares when reaching a sUA target (≤0.36 mmol/L), again visualised by icons arrays. The chance of sUA target achievement when initiating ULT was added as text below the icon arrays. Additionally, the recommendation to lower sUA ≤0.30 mmol/L in tophaceous gout, and the need for flare prophylaxis on initiation of ULT was emphasised. An option grid (page five) provided an overview of the attributes selected by patients and the steering group distinguishing the available first-line and second-line ULT options. The attribute combination ULT required was removed, as lesinurad had not received reimbursement in the Netherlands, and none of the other ULT required combination with another ULT. The last page asked patients whether they have remaining unanswered questions and offered them the opportunity to discuss personal views, worries and believes about gout and gout treatment. Finally, patients were invited to make a decision, whether or not to start ULT and to consent with the chosen ULT option. Of note, the same DA can be used for patients starting or restarting ULT, as only the ULT options available according to the healthcare professional in the option grid might differ (eg, change from one ULT to another in case of previous side effects). Clearly, our DA is a

professional administered tool and healthcare professionals usually require some level of training/experience to apply the tool.

Table 2: Information sources used for the various sections of the decision aid.

Sections of prototype	Information sources
I: Health condition and personal risk factors	Landmark gout literature provided by the steering group.
II: The personalised risk on future gout flares without ULT	Literature search of Cochrane database did not meet the needs; a review on the relation between sUA and gout flares was used instead.
III: Lifestyle changes and treatment of acute flares	SLR on effectiveness and side effect treatment acute gout flares. SLR on effect lifestyle in gout outcomes provided by the steering group. National and international recommendations on gout management. Dutch exercise norm.
IV: Effect of ULT	Literature search of Cochrane database did not meet the needs; a review on the relation between sUA and gout flares was used instead. Role of flare prophylaxis added per advice of the steering group.
V: Option grid	Literature search on available decision aids provided a list of attributes that informed the NGT meetings. NGT ranked attributes (six highest were included). Cochrane review on comparative effectiveness of ULT on gout flares. National and international recommendations on gout management. For side effects information and data provided by the Dutch Healthcare Institute (www.farmacotherapeutischkompas.nl).
VI: Final treatment decision	Example retrieved from literature search for decision aids (to inform NGT) informed the design of this page.

NGT = nominal group technique; SLR = systematic literature review; sUA = serum uric acid; ULT = urate-lowering therapy.

Phase 4: pilot testing

Five gout patients participated, mean age was 66.0±9.3 years, all were men, average disease duration was 16.4±15.1 years, educational level was high (n=2), intermediate (n=2) and low (n=1), and all used currently ULT.

Cognitive debriefing

Overall, patients appreciated the provision of valuable information of different ULT options and attributes:

"Very clear and informative. If I had seen this DA earlier, I would have started with ULT sooner now that I have seen all the pros and cons".

Minor improvements were suggested for every page on language (eg, replacing words, shortening or rephrasing of sentences), font and symbols (Table 3). Patients confirmed that the general gout information and lifestyle information were useful and necessary in obtaining a complete picture of gout:

"Using your ULT tablets is very important, yet it is always additional to lifestyle. You should always eat healthy and have enough daily activity".

Notwithstanding, one patient suggested to provide more practical advices on healthy lifestyle, for example, maximum units of alcohol consumptions and this information was added to the DA.

Finally, patients pointed to the large amount of information and potential cognitive burden, and recommended to take the DA home after consultation. For this reason, also the telephone and email address of the gout clinic were included in the DA in case further questions would raise.

Usability questions

Patients appreciated the information, design and usefulness for SDM (Online Supplemental Table S1). The open-ended questions revealed no new information compared with the cognitive debriefing.

Table 3: Comments by patients in the pilot test on every page of the decision aid and adaptations made by the steering group

Main element	Comments	Adaptations made
I: Health condition and personal risk factors	Gout flares can occur in more body parts than the big toe, for example in the ears	Other commonly involved joints added to the text
	Gout can give more severe problems than only flares and pain. Elaborate on other severe problems	Tophi in skin and bone explicitly mentioned
	Some risk factors are not applicable for individual patients	The risk factor personalized by adding tick boxes
II: The personalised risk on future gout flares without ULT	Not clear that the icon arrays are gout flares in the first metatarsophalangeal joint	Specifically added that the most common gout flare location was illustrated
	Not clear if the risk of future gout flares was independent of the personal sUA level	The DA was personalized for patients with an initial sUA level between (>0.36-<0.55 mmol/L and ≥0.55 mmol/L).
III: Lifestyle changes and treatment of acute flares	Give more detailed information for advices related to proportions (eg, drinks or red meat)	Detailed for alcohol consumption
	Specify the non-citrus fruits with examples	Overruled/rejected by the steering group
IV: Effect of ULT	Mention the specific sUA target of ULT	Added the sUA target of ≤0.36 mmol/L
	Mention number of future flares that will occur within the period considered in the figure with icon arrays	Added icon arrays presenting number of patients with at least one gout flare
V: Option grid	Mention here also the generic name of ULTs. A patient that used desuric, did not know this was also called benzbromaron	Generic names were added to the option grid for all the ULTs
	Increase font style within the option grid	Font of symbols and text was increased
	Add rasburicase	The DA clarifies only ULTs for long-term control of sUA are included
VI: Final treatment decision	Include the day of the follow-up in the DA	Added a section were the next visit can be mentioned (eg, time and date)

DA = decision aid; sUA = serum uric acid; ULT = urate-lowering therapy

Discussion

A systematic process was followed to develop a DA to facilitate a shared decision whether or not to (re)start ULT in gout patients with an indication to initiate ULT. Patients and physicians were involved in the design, prototype development and pilot testing of the DA. Overall, participants found the DA valuable to facilitate the treatment decision, optimise communication and increase patient empowerment. In line with SDM principles, a first question when engaging in SDM is whether a patient wants to be involved or prefers that the physician makes the decision whether or not to (re)start ULT. Among the 25 patients providing input for the DA, only one patient preferred the physician to make the final treatment decision. Patients appreciated the option grid, including the information on alternative options when the initial choice option would fail. Notwithstanding, patients also recognised the intellectual burden and recommended to take home the DA. On this line, we chose to create a paper-based DA (opposed to web-based) to facilitate a face-to-face clinical setting. In a COVID-19 era with remote visits, a web-based version that remains accessible to patients may be more appropriate. A study in the USA on rheumatologists' views and practices related to SDM in gout treatment revealed that 70% of the rheumatologists reported to offer patients offering a choice whether or not to start ULT without a DA (44). Our DA might support patients and physicians in this shared decision.

To enhance usability of a DA in daily practice, it is essential to adhere to national and/or international recommendations (EULAR/ACR). The distinction in the current DA between the first-line (allopurinol) and second-line (febuxostat and benzbromaron) ULT options, advice on lifestyle changes, need for prophylaxis on ULT initiation and the role of a sUA target are all supported in national as well as international recommendations.

The development of the DA posed some challenges, especially regarding evidence-based information on the risk of flares with and without ULT (45). Flares, the most important indicator of effectiveness for patients, are not or inconsistently reported in RCTs and follow-up is often too short to provide meaningful data on risks and benefits for clinical care. Fortunately, observational studies on the relation between sUA and flares with and without ULT were helpful, the discussion on sUA as biomarker for gout is ongoing (43). An advantage of this approach was

that we could 'personalise' the DA, by presenting different risk for future flares depending on the initial sUA level while keeping the relative effectiveness of ULT. Some studies suggest that febuxostat has exacerbation of acute gout flares at the start of treatment, which is less the case for allopurinol, but evidence is weak (36). In other words, while febuxostat is more effective in sUA target achievement compared with allopurinol at the recommended dose, this does not translate into better effectiveness on flare reduction. Yet, the relationship between sUA and gout flares is complex.

In the literature, only one DA prototype was designed in an Asian community for gout treatment (46). However, information on flares risk with and without ULT was lacking. Notwithstanding, this is a key aspect of a DA. This lack of state of the art development of current DAs highlights the value of our stepwise and transparent description of the development process of our DA.

Some limitations should be recognised. Due to practical circumstances, among which consequences of COVID-19 restrictions, only five patients were included in the pilot test. As a consequence, feedback might have been homogenous. Therefore, when further testing effectiveness of the DA-specific needs of patients who are ULT naïve or with lower health literacy should receive attention. Fortunately, our DA is flexible for adaptation to new or personalised evidence on (treatment of) gout or needs of patients. Appropriate testing of the (cost)-effectiveness of the DA will require, a (semi)experimental trial. Consistent with the paradigm of patient-centred care, Outcome Measures in Rheumatology reached consensus that not only adherence to the chosen outcome is an important core outcome but also (1) knowledge of options, their potential benefits and harms; (2) chosen option aligned with each patient's values and preferences; (3) confidence in the chosen option; (4) satisfaction with the decision-making process and (5) potential negative consequences (eg, time and costs). Implementation of SDM and the use of a DA in clinical practices require changes in patient–physician communication. Even before evidence on the effectiveness on different outcomes in various subgroups will be available, our DA can be used to gain experience with SDM in the context of patient-centred care.

Conclusion

We systematically developed and pilot tested a DA to (re)start with ULT. This study provides initial support for usability of a DA for gout patients eligible to start or restarting ULT. Testing of effectiveness on gout outcome and patient experiences in clinical practice is a necessary step.

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CHAPTER 7

Development and usability of a web-based patient-tailored tool to support adherence to urate-lowering therapy in gout

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Abstract

Objective

The aim of this study is to develop and assess usability of a web-based patient-tailored tool to support adherence to urate-lowering therapy (ULT) among gout patients in a clinical setting.

Methods

The content of the tool was based on the Integrated Change (I-Change) model. This model combines various socio-cognitive theories and assumes behavioral change is a result of becoming aware of the necessity of change by integrating pre-motivational, motivational, and post-motivational factors. An expert group (five gout experts, three health services researchers, and one health behavior expert) was assembled that decided in three meetings on the tool's specific content (assessments and personalized feedback) using information from preparatory qualitative studies and literature reviews. Usability was tested by a think aloud approach and validated usability questionnaires.

Results

The I-Change Gout tool contains three consecutive sessions comprising 80 questions, 66 tailored textual feedback messages, and 40 tailored animated videos. Navigation through the sessions was determined by the patients' intention to adapt suboptimal ULT adherence. After the sessions, patients receive an overview of the personalized advices and plans to support ULT adherence. Usability testing among 20 gout patients that (ever) used ULT and seven healthcare professionals revealed an overall score for the tool of 8.4±0.9 and 7.7±1.0 (scale 1-10). Furthermore, participants reported a high intention to use and/or recommend the tool to others. Participants identified some issues for further improvement (e.g. redundant questions, technical issues, and text readability). If relevant, these were subsequently implemented in the I-Change Gout tool, to allow further testing among the following participants.

Conclusion

This study provides initial support for the usability by patients and healthcare professionals of the I-Change Gout tool to support ULT adherence behavior.

Introduction

Gout is the most common type of inflammatory arthritis worldwide (1, 2). The prevalence and incidence of gout vary widely according to the population studied and methods employed, but range from a prevalence of <1% to 6.8% and an incidence of 0.58 to 2.89 per 1,000 person-years (2). An elevated serum uric acid (sUA) is the main risk factor for gout. Both lifestyle and comorbidities contribute to hyperuricemia and possibly independently also to gout. Fortunately, gout is well treatable and a combination of non-pharmacological and pharmacological treatments is recommended (3). Urate-lowering therapy (ULT) should be considered and discussed with every patient after a first gout flare (3-5). Yet, the management of gout in real-life is far from optimal. This has been attributed to patient, physician, and system factors (4, 6).

Adherence to prescribed ULT ranges from 20% to 70% and is considered to be among the poorest of all chronic conditions (7-9). Patients' barriers have been categorized into four areas: [1] limited gout knowledge; [2] few cues and feedback from direct environment and low frequency and quality of interactions with physicians; [3] negative attitudes towards and experiences with medication; and [4] failure to cope with practical barriers for long-term medication use (4, 10). Patients' self-care behavior is a key determinant to modify these barriers of medication adherence (7, 11, 12). Also, as part of quality of care, physicians are called upon to promote patient-centered care. This encompasses care that is responsive to the needs and preferences of patients (13). Yet, self-management interventions can be time consuming in clinical setting. eHealth offers the opportunity to enhance self-management, while remaining efficient in a clinical healthcare setting. eHealth interventions have shown to be easy to use, have fewer availability restrictions, and temper pressure on healthcare systems (14-16). Moreover, computer-tailored technology allows patients to receive highly tailored and personalized feedback about their personal situations and advices on how to improve where needed. Eight eHealth programs were launched to enhance gout self-management in general (17-19). Yet, none of these focused on ULT adherence behavior. Similarly, interventions to improve adherence to ULT are limited and none of them addressed self-care behavior, a key determinant of adherence (7, 17, 20).

The Integrated Change (I-Change) model consist of an assessment of the individual's current behavior and motivation regarding a desired health behavior, and integrates the answers given during an online assessment into personalized advice and feedback generated by unique algorithms (21, 22). Computer-tailored support tools based on the I-Change model have proven to be (cost)-effective in changing various complex health-related behaviors and their determinants, including: smoking cessation (23), reducing alcohol consumption (24), reducing fat nutrition intake (25), increasing physical activity (26), and improving type 2 diabetes mellitus (T2DM) medication adherence (16).

Despite the growing popularity of computer-tailored support tools and their proven efficacy, patients may still experience difficulties with the user interface of the support tool and may therefore discontinue program use (27, 28). Usability studies enable developers to discover potential difficulties with the support tool and to explore engagement and users' experiences. Perceived usability has been demonstrated to be an important determinant of an individual's intention to implement behavioral change, but also of actual use of the proposed intervention in clinical practice (29-31).

The aim of this study is to develop and assess usability of a web-based patient-tailored I-Change tool to support ULT adherence among gout patients in a clinical setting.

Methods

Scope

The I-Change Gout tool aims to be used in clinical care to support ULT adherence among gout patients who are using ULT for at least 1 month, in whom ULT is adjusted, or in whom medication adherence was (suspected to be) suboptimal. While the focus is on ULT adherence, the I-Change Gout aimed explicitly to address lifestyle as an integral part of management.

Development I-Change Gout Tool

The I-Change model combines various socio-cognitive theories and assumes that behavioral change is a result of becoming aware of the necessity to adjust one's own behavior by integrating three phases: pre-motivational, motivational,

and post-motivational (21, 32, 33). The I-Change Gout tool assesses these 3 phases of behavioral change along three consecutive sessions and integrates pre-motivational factors (6 factors), motivational factors (3 factors), and post-motivational factors (2 factors) (Figure 1) (34). Details on the factors are described in Table 1. After each session, patients receive tailored feedback in the form of animated videos and text messages individualized to their answers on the questions (Supplementary Table S1). As shown in Figure 1, patients can navigate through the system following two trajectories, depending on (a) stated and revealed health behavior, and (b) the intention to adjust behavior. If the patient is considered to have a fully desirable health behavior following session 1, the patient is directed immediately to session 3. If the patient has suboptimal health behavior following session 1, the intention to adapt the behavior is assessed. In case of a low intention (i.e. not motivated to adapt), the patient is directed to session 2 (motivational session). A patient with a high intention (i.e. motivated to adapt), is immediately directed to session 3 (post-motivational session). All patients follow session 3, in which a patient is prompted to set specific goals and plans to adjust health behavior. The I-Change Gout tool ends by providing the patient an overview of the received advices and the plans for action made.

To develop the I-Change Gout tool a project group was assembled consisting of five gout experts, three health services researchers, and one health behavior expert. The perspective of the gout patients (the potential end-users) was explicitly included in the development by a qualitative study that was performed in preparation of the current study (35). Three meetings of 2 hours were scheduled to decide on the content of each of the three sessions. The project group had to agree on: (a) the questions and questionnaires required to assess various factors in the three sessions, (b) the cut-off points of scores on questions and questionnaires decisive for personalized feedback and navigation through the system, and (c) the content of the personalized feedback. A researcher (RtK) prepared the content of the meetings based on the preceding qualitative study among gout patients (35), literature on ULT adherence (4, 7, 8, 36), and individual contact with experts. Preparatory materials were sent two weeks before each meetings to the project group. An existing successful I-Change tool to support medication adherence in T2DM was used as basis (16).

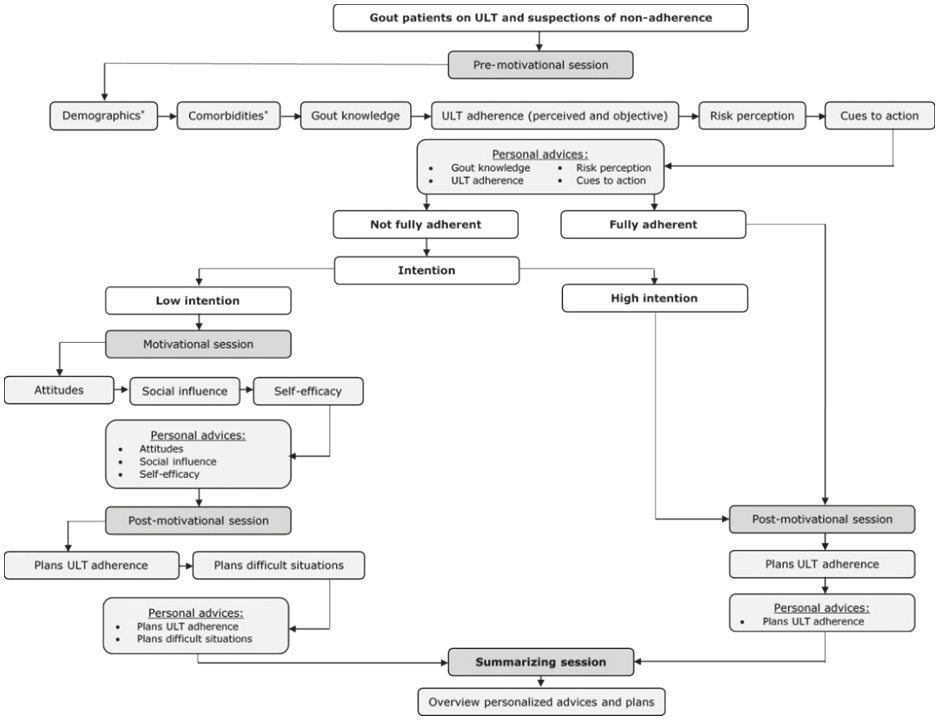

Figure 1: Flowchart of the I-Change Gout tool to support urate-lowering therapy adherence. ULT = urate-lowering therapy. *Demographics and comorbidities were not used to provide patient-tailored advices. Yet, demographic information on marital status was used in the algorithm of social influence.

Usability study

A cross-sectional mixed methods design was used to evaluate usability among gout patients and healthcare professionals. A cognitive debriefing study using a think aloud approach was performed among patients and a series of validated usability questionnaires was completed by patients and healthcare professionals. Cognitive debriefing by individual think aloud sessions is an accepted approach to evaluate usability among patients and healthcare professionals (37). The ethical committee of Maastricht University Medical Center (METC 2019-1040) approved this study and all participants provided written informed consent.

Participants and procedure

Patients were eligible if they were ≥18 years, had sufficient knowledge of the Dutch language, and were currently using ULT. Patients were recruited from one regional non-university and one university hospital with a regional function. Patients

were purposefully sampled to ensure representation of relevant age categories (≤50, 51-70, 71-85 and ≥86 years), gender (20% female), education levels (low, intermediate, and high), and disease duration (range 0-10 years). Healthcare professionals were recruited in hospitals and general practitioner practices in the south of the Netherlands and eligible if they were involved in gout management, but not in the development of the I-Change Gout tool. A sample size of ± 20 patients and ± 6 healthcare professionals was considered, as it is widely assumed that 5 participants suffice for usability testing and with 20 users 95% of the problems are captured (38).

Think aloud

The think aloud study was conducted at the outpatient clinics in the presence of a researcher and was audio recorded. Patients were invited to log on and follow the instructions presented in the program, and complete the full program. Patients were asked to verbalize their thoughts and opinions while using the I-Change Gout tool, to assess patients reasoning and source of their problems. The researcher emphasized that the intention was to evaluate the program and not the participants' behavior in order to encourage the participants to talk freely and express their positive and negative experiences.

Usability questionnaire

After completing the full program all patients and healthcare professionals were invited to rate the usability of the I-Change Gout tool by completing a series of five validated questionnaires assessing four domains of usability:

S*ystem usability* comprises four subdomains of the System Usability Scale (39, 40) evaluating: *strengths* (4 items; e.g. "I thought the program was easy to use"); *weaknesses* (3 items; e.g. "I thought there was too much inconsistency in the program"); *barriers* (2 items; e.g. "I needed to learn a lot before I could get going with the program"); and *intention* (2 items; "I think that I would like to use this system frequently" and "I think I would recommend others to use the system").

Engagement consists of 3 items (e.g. "The program made me curious"), adapted from of the Digital Behavior Change Interventions Engagement Scale (41, 42).

User experience addresses 5 subdomains evaluating: *effectiveness* (3 items; e.g. "The program gives important information on the benefits of using ULT"); *trustworthiness* (3 items; e.g. "The program is trustworthy"); *enjoyment* (3 items; e.g. "I found the use of this program enjoyable"); *active trust* (3 items; e.g. "I know now how to use my ULT drugs better"); and *design aesthetics* (3 items; e.g. "I think the design of the program is attractive") (43). The original questionnaire also employs the subdomain "efficiency", which measures the ease of searching and accessing information (43). As searching information was not applicable, instead, the subdomain *design aesthetics* was added (44).

Program clarity is measured by 11 items (e.g. "To what extent do you think this part of the gout tool [e.g. knowledge] is clear to use?")

All questionnaire items are scored on a 5-point Likert scale. For the first three (sub)-domains, the anchors ranges from 1="I totally disagree" to 5="I totally agree". For the domain *program clarity* the anchors ranges from 1="very unclear" to 5="very clear". The total score for (sub)-domains is calculated as the average of the items, except for *intention* where the individual items are considered separately.

Finally, *program end score* was measured by asking participants to grade the gout tool on a numeric rating scale ranging from 1="very bad" to 10="very good".

All questionnaires were rephrased to fit the perspective of the healthcare professionals. Following the questionnaires, participants were prompted to further clarify some response by written feedback in a single textbox.

Analyses

Results of questions of the usability questionnaire were analyzed using descriptive statistics (e.g. mean and standard deviation) using IBM SPSS, version 25.0 (IBM Corp). Feedback in the textbox was linked by the researcher (RtK) to (sub)-domains of the usability questionnaire. The think aloud sessions were transcribed verbatim, anonymized, and analyzed (categorized in themes for each of the I-Change (sub)-sections) by a junior researcher (RtK) trained in qualitative research, and were checked by a senior researcher (AB). The Standards for Reporting Qualitative Research (SRQR) guided the transparency of all aspects of this qualitative research (45). Textual remarks on written and spoken text or feedback on animated videos

were collected per page of the I-Change Gout tool. All citations of patients were linked to the different (sub)-domains of the usability questionnaire. Expressed thoughts and opinions were used as input to improve the I-Change Gout tool if considered relevant after discussion within the project group. The revised I-Change Gout tool was tested among the following participants.

Results

Development I-Change Gout Tool

The project group decided on the specific content of the I-Change Gout tool during the three meticulously prepared meetings. Details of the content and source feeding the content can be found in Table 1 and in the Supplementary Data S1 and Table S1. ULT adherence behavior is a key determinant for navigation through the system. In the I-Change Gout tool, patients are classified as optimal (opposed to suboptimal) adherence by combining questions on perceived and objective adherence. The Probabilistic Medication Adherence Scale (ProMAS) was chosen to assess objective adherence, as this instruments provides insight in the broad spectrum of (non)-adherence behavior (46). To classify a person as optimal adherent, a strict cut-off point was chosen (fully self-perceived adherence combined with a 100% score on the ProMAS). Although a score ≥80% on the ProMAS is the formal threshold for acceptable adherence, the project group considered there would be room for improvement and potential value for patients to follow the I-Change Gout tool (46). Patients with a suboptimal adherence and a low intention to adjust behavior navigate through all 3 sessions. Patients with a suboptimal adherence and high intention navigate after session one immediately to session three (as they can skip the motivational setting) (Figure 1). Overall, the three sessions of the I-Change Gout tool consisted of 80 questions, 66 tailored textual feedback messages, and 40 tailored animated videos. Additionally, all patients have the opportunity to view evidence-based lifestyle advices (47). After finalizing the content, the design (e.g. avatar) was discussed, and textual information was adapted to health literacy basic reading levels.

Table 1: Description of the sessions and the different factors assessed along the I-Change Gout tool, and the source of the questions.

Sessions	I-Change factors	Content specific for the I-Change Gout tool	Source
I: Pre-motivational		To improve person's awareness of the importance of ULT and their personal behavior towards ULT adherence	
	Demographics	Socio-economic background (e.g. age, gender, educational level, marital status, and work situation)	Adapted from previous effective I-Change tool and input from experts
	Comorbidities	Common diagnosed comorbidities influencing the management and control of gout	Rheumatic Disease Comorbidity Index questionnaire adapted for the purpose of the tool
	Gout knowledge	The understanding of factual information regarding gout related to the pathogenesis, treatment of acute attacks and also management of chronic gout	Gout Knowledge Questionnaire adapted for purpose of the tool
	Perceived ULT adherence	Person's perception about his or her own ULT adherence behavior	Previous effective I-Change tools
	Objective ULT adherence	The degree to which the person's ULT adherence behavior corresponds with recommended ULT use from a health care provider	ProMAS questionnaire adapted for ULT use
	Risk perception	The perceived risk of gout flares or other gout problems as a result of non-adherence to ULT	Adapted from previous effective I-Change tool and input from experts
	Cues to action	Hints or signals a person is perceiving within his/her environment (external) or within him/herselff (internal) that trigger an action linked to the ULT adherence behavior	Adapted from previous effective I-Change tool and input from experts
	Intention	A person's motivation in the sense of his or her conscious plan or decision to improve the ULT adherence behavior. The intention to adapt behavior detemines the navigation of the sessions. Decisive to move first to session II or immediately to session III	As in previous effective I-Change tool

Table 1: Continued.

Sessions	I-Change factors	Content specific for the I-Change Gout tool	Source
II: Motivational		To improve motivation to take action regarding their ULT adherence behavior	
	Attitudes	A person's overall evaluative opinion about their ULT adherence behavior as a result of the perceived advantages and disadvantages of the ULT adherence for this person	Adapted from previous effective I-Change tool and literature
	Social influence	The processes whereby person's thougths, feelings, and actions about ULT adherence are directly or indirectly influenced by others	Adapted from previous effective I-Change tool
	Self-efficacy	The level of one's own belief to successfully carry out the desired ULT adherence behavior in certain difficult situations	Adapted from previous effective I-Change tool and input from experts
III: Post-motivational		To support patients in translating intentions into pre-formulated actions and coping plans to promote desired behavior	
	Plans ULT adherence	The process of choosing and planning specific actions and plans that may help to successfully adopt and maintain the ULT adherence behavior.	Adapted from previous effective I-Change tool
	Plans difficult situations	The types of plans needed to maintain a behavioral change attempt and can contribute in a person's pursuit to cope and overcome obstacles and difficulties by anticipating how to address these obstacles and difficult situation	Adapted from previous effective I-Change tool

ULT = urate-lowering therapy

Usability study

Twenty gout patients and seven healthcare professionals participated in the usability study. Patients were 69.6±14.7 years old, 85% (17/20) were male, had a mean disease duration of 8.3±9.7 years (median: 5.0), with education levels ranging from high (n=5; 25%), intermediate (n=7; 35%), to low (n=8; 40%). Healthcare professionals were 38.0±13.7 years old, 43% (3/7) were male, working experience was 10.4±11.8 years (median: 5.0), and professional background ranged from general practitioner (n=2; 29%), rheumatologist (n=2; 29%), occupational physician (n=1; 14%), to a physician assistant (n=2; 29%).

Usability questionnaires

Table 2 presents the scores of the patients and healthcare professionals on the usability domains. The *program end score* rating was on average 8.4±0.9 (range 6-10) for patients and 7.7±1.0 (range 6-9) for healthcare professionals. Intention to use the system in the future and recommend it to others was high among patients (average: 4.4±0.6 and 4.6±0.6, respectively) and healthcare professionals (average: 4.0±0.0 and 4.0±0.6, respectively).

Overall, no striking low scores were observed. Among healthcare professionals, average scores were more frequently below four (Table 2). The lowest score by healthcare professionals were found for engagement (3.4±0.3) and enjoyment (3.6±0.4).

In the open questions, healthcare professionals appreciated the interactive and personalized provision of valuable information of gout management and ULT adherence:

"*Short, clear and good supporting animations, that is the strength of this intervention*" (HP3).

Notwithstanding, one healthcare professional raised worries on the ability of patients to become an actor of their own health behavior:

"*I am afraid that unmotivated gout patients may not be motivated by this [program] either, it will not achieve its goal and it will only be developed for the small group that is already serious about his/her disease*" (HP5).

Further, professionals questioned the skills of the elderly gout patients, and their health literacy. In the open questions, some patients mentioned technical issues with regard to the use of the I-Change Gout tool.

Table 2: Usability according to patients and healthcare professionals

Domains	Subdomains	Patients (n=20)	Healthcare professionals (n=7)
System usability[a]	Strengths	4.4 (0.6)	4.3 (0.5)
	Weaknesses	1.3 (0.6)	1.8 (0.5)
	Barriers	1.6 (1.0)	1.4 (0.5)
	Intention		
	to use the system	4.4 (0.6)	4.0 (0.0)
	to recommend the system	4.6 (0.6)	4.0 (0.6)
Engagement[a]	Engagement	4.2 (0.7)	3.4 (0.3)
User experience[a]	Effectiveness	4.0 (0.8)	3.9 (0.8)
	Trustworthiness	4.5 (0.5)	4.4 (0.5)
	Enjoyment	4.3 (0.6)	3.6 (0.4)
	Active trust	4.1 (0.8)	4.1 (0.4)
	Design aesthetics	4.4 (0.7)	4.0 (0.1)
Program clarity[b]	Program clarity	4.1 (0.4)	3.9 (0.4)
Program end score[c]	Program end score	8.4 (0.9)	7.7 (1.0)

[a] 1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree
[b] 1 = very unclear, 2 = unclear, 3 = neutral, 4 = clear, 5=very clear
[c] 1 = very bad to 10 = very good

Think aloud

Patients appreciated the information and application of the three sessions, and described them as positive, useful, and clear. The variation and interaction between video- and text-based advices was experienced positively (Table 3). Furthermore, patients appreciated videos and text length, stating it was short and informative:

"*The written material describes gout well and focuses on the importance of regularly taking ULT*" (PT 13).

Patients indicated that the I-Change Gout tool was effective and gave important information on the benefits and importance of ULT. The program helped to consider taking ULT as prescribed:

"*With the information I have just heard, I understand I should use my tablets daily, even if I have no gout complaints. I will start using my pill box again*" (PT 1)

"*This is the first time I hear that allopurinol is involved in the treatment of gout"* (PT7).

Improvements were suggested in language use of written text such as shortening or rephrasing some feedback messages, and replace words. In addition, patients suggested explaining the system navigation more explicitly at different parts of the three sessions to improve the effective use. Furthermore, categories on education and work situations were revealed to be missing on the initial page asking patients to tell about their socio-economic background. Finally, one additional ULT adherence plan was suggested (see text PT8). These smaller changes were immediately implemented in the I-Change Gout tool.

"*Add 'using a reminder app on your smartphone' as specific plan; this slightly differs from an alarm as an alarm is easy to click away. I will then still forget the ULT*" (PT8).

Four patients had some critical remarks regarding the objective ULT adherence questionnaire (ProMAS) in session 1. One patient stated for example:

"I don't feel taken seriously by this questionnaire, too often it boils down to the same thing and this annoys me" (PT2).

Yet, another patient indicated to clearly recognize the added value of the ProMAS questionnaire:

"*There are often repetitive questions, yet there is a difference in dimensions and this makes you really think about your use of tablets*" (PT8).

To avoid feedback messages for each individual item of the ProMAS (n=15), feedback was clustered by items addressing a similar construct after discussion within the project group.

For a minority of patients that were adherent to ULT, according to the ProMAS questionnaire during completing the program, the program had less added value:

"*I already have a lot of gout knowledge, and use my tablets daily, so the system may be less effective for me. However, the program would certainly be valuable for patients who are new with gout or do not have the gout knowledge like me*" (PT6).

On a same line, adherent patients did not entirely recognize the benefit of making plans to stay adherent as they already made specific plans for ULT use. However, for patients with ULT adherence issues, reminders to take ULT on a daily basis were frequently mentioned as a useful coping plan. Overall, making coping plans and having a daily routine was reported by almost every patient as necessary for daily tablet use:

"*Place the tablets in a fixed place, and be very precise in this. This is also necessary to take them properly*" (PT19).

Table 3: Citations of patients during the think aloud study related to the different subdomains of the usability questionnaires

Domains	Subdomains	Citations
System usability	Strengths	Informative and easy to use – it is patient friendly
	Weaknesses	The medication questionnaire has often repetitive questions
	Barriers	I need support to use a digital program, not using a computer in daily life
	Intention	I definitely will use the program if it is available for me
Engagement	Engagement	I am going to implement these plans and I am very curious about the program.
User experience	Effectiveness	With the information I have just heard, I think I should use my tablets daily, even if I have no gout complaints. I will start using my pill box again
	Trustworthiness	The written material described gout well and focused on the importance of regularly taking ULT
	Enjoyment	I liked the lay-out of the program, and it was interesting to go through the program
	Active trust	I have made plans to improve my tablet use, and my advices were clear
	Design aesthetics	Short, clearly and good supporting video's
Program clarity	Program clarity	The entire program is clear and I have no trouble filling in the questions

Discussion

This study describes the development and usability of web-based patient-tailored tool to support adherence to ULT in gout patients in a clinical setting. Both patients and healthcare professionals reported a high intention to use and/or recommend the tool to others. No major problematic issues were identified across the domains of usability questionnaires, yet healthcare professionals raised some worries about engagement of elderly patients, those that have poor digital literacy, and those intrinsically unmotivated. The specific points for further improvements (e.g. repetition of questions, technical issues, and readability of text) revealed by participants were immediately adjusted following each interview until the current final version of the I-Change Gout tool.

Lack of knowledge has been identified as an important determinant of ULT adherence (4). Patients indicated that the current I-Change Gout tool was effective as it addressed knowledge gaps and inadequate risk perceptions effectively by actively improving patients' knowledge and risk perception, and rectified several misconceptions with tailored animated videos and text messages.

In addition to knowledge, patients' motivation is key in changing the self-care behavior. The I-Change Gout tool was developed with the intention to improve patients' motivation and support the complex ULT adherence behavior within three sessions. The motivational session ensured that patients with suboptimal adherence and a low intention became aware of the added value of ULT adherence, by addressing attitudes (pros and cons of ULT), social influence (support and norm to use ULT), and self-efficacy (action plans on ULT use) effectively to promote desired behavior regarding ULT use. Notwithstanding, healthcare professionals doubted whether the I-Change Gout tool would truly reach the desired medication adherence behavior in less motivated patients. To gain insight into the magnitude and potential solutions for this problem, more in depth qualitative and quantitative evaluation of the I-Change Gout tool in less motivated patients will be required. For patients that are less motivated, direct support and encouragement to follow the I-Change Gout tool by healthcare professionals, who should be aware of their role as social influencer, may still be needed.

Furthermore, in the post-motivational session patients' clearly revealed that coping plans and a daily routine are valuable for ULT adherence. Literature supports the fact that coping plans were associated with ULT adherence among gout patients (48, 49). Although adherent patients did not entirely recognize the benefit of making plans to stay adherent, it remains important to make coping and action plans in the post-motivational session to remain adherent.

The current I-Change Gout tool is the first web-based patient-tailored tool that specifically addressed ULT adherence in gout patients based on various theories that influence health behavior through self-management. The I-Change Gout tool was designed to complement usual care at the first visit following implementation of ULT, and addresses desired lifestyle behavior in addition to importance of adherence to ULT. In the current study, patients highlighted that voiced animated video-based advices were preferred over long pieces of text. The videos were rated as informative, of adequate length, and sufficiently personalized to foster good acceptance, engagement, and intention to use the program. That video tailoring can be effective and may be preferred over text tailoring was confirmed by existing studies (50, 51).

A randomized controlled trial will be required to assess the efficacy and (cost-) effectiveness of the I-Change Gout tool in daily practice. Such a trial should also clarify what the uptake of the tool is and in which subgroups of gout patients (at risk) the tool will be effective (i.e. most relevant target group). Patients with lower computer or health literacy skills may be less likely to use the tool (52) and direct support by healthcare professionals or social support may still be needed for those patients. The Netherlands ranks among the European top in digital skills, yet health literacy is still considered problematic or inadequate in respectively 26.9% and 1.8% of persons in the general population (53). Patients with gout have shown to score even lower in various domains of health literacy than patients with other rheumatic diseases (54). The I-Change Gout tool specifically tried to reduce reading burden and increased accessibility to low-literacy patients by using short sentences and plain language, multimedia formats including pictures and videos, and dropdown options to reduce reading time and improving comprehension (55). Of note, when providing patient-centered care, it is equally important identify patients that prefer individual learning opposed to those in which person-to-person contact is more effective.

A review of 18 interventions that aimed to improve medication adherence of gout patients (20), found that nurse-led interventions with patient education is the most promising in achieving improved adherence compared to usual care (56, 57). The authors discussed that none of the interventions addressed to develop self-care behavior (e.g. action plans), despite evidence of its relevance in medication taking behavior. Potentially, the I-Change Gout tool could be efficacious and even more cost-effective compared to nurse-led approaches (16). An interesting review of mobile applications to improve adherence through self-management of gout patients build upon effectiveness of regular feedback on disease control (17). They found six apps that educate patients and help them to monitor their sUA. One of these fulfilled predefined quality criteria (17). As it is known that informed decision (as I-Change) improves uptake and short-term adherence to medications, such an app could be considered as part of the action plans to ensure long-term adherence.

Although several challenges of the tool have been mentioned above, one limitation should be specifically discussed. The ProMAS was chosen to estimate objective medication taking behavior. The questionnaire yielded some negative feedback (e.g. repeating questions). Adaptations (e.g. clustered feedback messages on the answers from repeating questions of the ProMAS) and more clarification of its reasoning (e.g. to make the tool personal tailored) were implemented and should potentially lead to better enjoyment. Additionally, the ProMAS was not validated as objective adherence measurement among gout patients. However, the ProMAS is a better way to quantify adherence behavior, as it assesses a range of medication taking dispositions with varying difficulty levels using a Rasch model approach (46). The ProMAS yielded insight in a broader spectrum of adherence behaviors compared to the most frequently widely used Medication Adherence Report Scale (MARS) (58). Furthermore, the ProMAS was tested among patients receiving medication for chronic conditions. Although it may be unlikely that the validity will differ between various chronic diseases, specific research is needed to be able to answer this question. Overall, based on all the methodological considerations, we feel the ProMAS was the best fit for our purpose as objective medication adherence measurement Lastly, for the purpose of the I-Change Gout tool, we had to adapt several questionnaires from the literature in order to comply as closely as possible with the I-Change model factors, yet the tool can be easily adopted when better/validated instruments are published. The current study demonstrated that

a systematic development process based on evidence from literature, views of experts, and perspectives of gout patients is important. Although the synthesis and interpretation of the findings of the cognitive debriefing and the open answers of the usability questionnaire were intensively discussed within the project group, coding and analysis of the think aloud sessions was conducted by only one researcher. As the feedback was quite straightforward, and the themes syntheses of the verbatim transcripts and themed summaries were checked by a senior researcher, it is unlikely that the interpretation might be biased. A transparent description of the development is a first and essential step towards understanding effectiveness of any support tool. Other researchers or tool developers can use the methodological development process of the I-Change Gout tool as guidance in their own development process.

Conclusion

This study provides initial support for the usability by patients and healthcare professionals of an I-Change Gout tool to support ULT adherence behavior. Further studies need to be conducted to assess its efficacy and (cost-) effectiveness in daily practice.

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CHAPTER 8

Summary and general discussion

Summary and general discussion

This thesis explored several aspects relevant for the management of gout in clinical practice. First, we studied effectiveness and side-effects of different treatment targets when starting urate-lowering treatment (ULT), and the role of contextual factors (CFs) on outcomes of gout and gout treatment. Secondly, patient needs were explored and support tools, aiming to improve patient-centered management of gout, were developed and tested for usability. In this final chapter, we first summarize the results of the individual studies. Next, we discuss our findings in light of theoretical or methodological challenges and the directions for future research.

Summary of the main findings

In the absence of randomized controlled trials (RCTs) that compare the benefits and harms of different targets when treating gout with ULT, we analyzed real-life data that had been collected in the gout clinic of two centers. One clinic followed a strict serum uric acid (sUA) (≤0.30 mmol/L) target strategy with early combination therapy (uric acid (UA)-strategy), whereas the other clinic adopted a patient-centered (PC) target, integrating information on sUA with patient satisfaction regarding gout control. Results were reported in **Chapter 2**, and revealed that the strict sUA-strategy resulted in more patients reaching the sUA target (≤0.36 mmol/L) (83% vs 74%) and being free of flares (46% vs 36%) when compared to the PC-strategy after an average of follow-up of 11.3±1.8 vs 11.1±1.9 months. However, statistically, these differences were not significant. On the other hand, patients receiving the stricter sUA strategy required significantly more frequently ULT intensification (0.40 times less likely to be treated with allopurinol monotherapy) and they visited more often the rheumatology outpatient clinic (4.4 vs 3.9 visits). Drug-treatment intensification seemed not associated with more frequent adverse events or withdrawals from follow-up.

Gout is considered as a typical male disease. Among persons ≤ 65 years, gout occurs four times more frequently in men compared to women (1). Above this age, the prevalence of gout narrows to a more equal sex distribution, due to the sharper increase of the incidence of gout among elderly women (2, 3). Most evidence on sex differences points to the role of the uricosuric effect of oestrogens, protecting

pre-menopausal women against onset of gout (4-7). However, it is unknown whether the menopausal state influences clinical manifestations between sexes (8, 9). In line with the available literature, our findings described in **Chapter 3** indicate that – in a cross-sectional sample of gout patients - women compared to men are on average 2.6 years older, suffer more frequently from renal insufficiency (a 14.9 mL/min per 1.73m^2 lower eGFR), have a 2.1 times increased prevalence of obesity, a 3.1 times increased prevalence of type 2 diabetes mellitus (T2DM), and 2.8 times increased prevalence of hypertension. Women also used 3.5 times more frequently diuretics, and were 0.4 times less likely to be heavy consumers of alcohol. No difference in the presence of tophi was observed. As the role of menopause on these associations was unknown, we repeated these analyses in a subgroup of patients with an age of gout onset above 55 years (n=259/484), i.e. the age commonly beyond menopause. In these older gout patients, women were on average still older, had more often obesity (2.3 times), T2DM (2.8 times), and renal impairment (2.0 times), and used more frequently diuretics (2.1 times) compared to men, although these differences were less pronounced than in the total sample. No differences were seen for hypertension. Compared to effects in the total samples, sex differences in comorbidities among those with gout onset ≥ 55 years were attenuated more strongly when adjusting for body mass index (BMI), smoking, and alcohol consumption. Also, the average fractional excretion of uric acid (FEUa) was similar in women ≥ 55 years as it was in men ≥ 55 years, adding to the evidence of the uricosuric effect of oestrogens in premenopausal women. Data suggest that before the age of menopause, other factors play a role in differences in comorbidities between sexes and women might be protected from the adverse effect of obesity, potentially by the uricosuric effect of oestrogens.

An important question in the era of stratified medicine is whether treatment response on sUA lowering drugs in gout patients differs depending on the presence or absence of specific CFs such as comorbidities (e.g. heart and kidney diseases and obesity) or socio-demographic factors (e.g. sex) (10, 11). Therefore, in **Chapter 4** we searched the literature for RCTs exploring effect modification of ULT on reaching the sUA target by CFs. Eight of the 37 available RCTs reported subgroup analyses by CFs, addressing age (n=2), sex (n=3), race (n=2), renal function (n=6), cardiovascular comorbidity (n=2), tophi (n=2), thiazide-diuretic use (n=2), and previous ULT (n=1). Four trials presented the crude trial results per treatment arm and stratified by renal function (normal, mildly-, moderately- and severely impaired).

These studies were eligible for quantitative analyses, i.e. meta-analysis. This meta-analysis across 36 randomized comparisons revealed significant heterogeneity (I^2=92.8%). Pooled estimates showed that patients with a normal (OR:13.49;[2.18-83.31]), mildly (OR:18.50;[3.00-113.93]), or moderately (OR:25.90;[4.12-162.85]) impaired renal function were all highly likely to achieve the sUA target with the ULT intervention when compared to the comparator, while severely impaired renal function rendered a slight disadvantage. Between groups analysis by renal impairment revealed that mildly and moderately impaired renal function rendered a statistical significant advantage in achieving sUA target compared to normal renal function. Sensitivity analysis with only placebo-controlled studies confirmed large beneficial effects of ULT on reaching the sUA target when (compared to placebo) in persons with normal, mildly or moderately impaired renal function. Between subgroup analysis by renal impairment showed no statistical advantage for normal opposed to mildly or moderately impaired renal function. Qualitative summaries of studies for which quantitative analysis were not possible, suggested that patients with tophi were less likely to achieve sUA targets. However, influence of tophi in reaching sUA target was observed within head-to-head comparisons and not placebo-controlled. No clear conclusions could be drawn for effect modification by other CFs.

In addition to health outcomes, patient's experiences of care (patient-centeredness) are increasingly considered as an indicator of quality of care (QoC). While patient experiences of care can be pertinent outcomes by themselves, they might also give insight on why (drug) treatments may not reach the expected health outcomes. In **Chapter 5**, we evaluated the impact of gout on generic and gout specific health outcomes, as well as on patient-centered outcomes in a real-world setting across 14 European countries. Overall, the proportion of patients with ≥3 and ≥1 gout flares the past year was 32% and 70%, respectively. Multivariable exploration revealed that patients with ≥3 and ≥1 flares were less likely to be treated with ULT (OR: 0.52 and OR: 0.38), but more likely to have regular physician visits (OR: 2.40 and OR: 1.77). Gout flares (≥3) contributed substantially to worse health and patient-centered outcomes such as satisfaction with gout management and unaddressed treatment goals. Notwithstanding, 80% of patients were satisfied with gout treatment. Even patients with ≥3 gout flares and not treated with ULT, 57% to 75% was still satisfied among various subgroups, and this was independent of frequency of physician visits. In other words, "suboptimal" gout outcome (and

treatment) does not result in a dissatisfied gout patient. Unexpectedly, patients from wealthier and Northern-European countries reported more frequently ≥3 gout flares.

To further improve QoC in daily practice for patients with gout, we developed two tools to support patient-centered care for patients and healthcare professionals. In **Chapter 6**, we described the development and usability of a decision aid (DA) for gout patients that have an indication to (re)-start ULT. The paper-based DA was developed for use during the face-to-face clinical outpatient visit. Recommendations of the International Patient Decision Aid Standards (IPDAS) group guided the development. Patients and physicians' played a key role in the design, prototype development, and pilot testing of the DA. The paper DA, personalized according to the patient's current sUA level, consisted of six pages addressing: (1) general information on health condition including risk factors; (2) clarification of the decision that needs to be considered (starting ULT on top of lifestyle changes and prophylaxis); (3) the role of lifestyle changes and treatment of acute gout flares; (4) the risk for gout flares with or without ULT; (5) a description of ULT options (first and second-line) including side effects in an option grid; and (6) the personal perceptions and believes before making the final shared decision. The pilot test provided initial support for usability of a DA to support shared decision making (SDM) in gout patients, eligible for (re)-starting ULT. Some suggestions for improvement of the content (e.g. more practical in advices on healthy lifestyle) and wording (e.g. shortening sentences) were revealed. This resulted in several adaptations and improvements of the DA.

Patient involvement in care is considered not only relevant in treatment decisions but requires attention during the entire patient journey. Adherence to prescribed ULT ranges from 20% to 70% and is considered to be among the poorest of all chronic conditions (12-14). Yet, interventions to improve adherence to ULT are limited and none of them addresses self-care nor focuses on ULT adherence behavior (12, 15). Patients' self-care behavior is a key determinant to modify adherence behavior. In **Chapter 7**, the development and usability of the I-Change Gout tool to support ULT adherence among gout patients in a clinical setting are described. The I-Change Gout tool discusses awareness (pre-motivational), motivational factors, and action plans (post-motivational) in order to promote the desired ULT use. The I-Change Gout tool aimed to support ULT adherence

among gout patients who are using ULT, in whom ULT is adjusted, or in whom medication adherence was (suspected to be) suboptimal. While the focus was on ULT adherence, the I-Change Gout also addressed lifestyle as an integral part of management. Existing I-Change tools were the starting point of the I-Change Gout tool. An expert group was assembled that decided on the tool's specific content (assessments and personalized feedback) using information from a preparatory qualitative study and literature reviews. Patients perceived and predicted actual ULT adherence behavior was the key determinant for navigation through the system. Overall, the three predefined sessions (pre-motivational, motivational, and post-motivational) of the I-Change Gout tool consisted of 80 questions, 66 tailored textual feedback messages, and 40 tailored animated videos. During initial testing, patients and healthcare professionals reported a high intention to use and/or recommend the I-Change Gout tool to support ULT adherence behavior. Doubts remained among healthcare professionals whether the I-Change Gout tool could change behavior of less motivated persons towards desired behaviors.

General discussion

Management of gout

Compared to the management of other chronic inflammatory diseases such as rheumatoid arthritis and spondyloarthritis, management of the auto-inflammatory disorder gout remains much more debated and **Chapter 2** contributed to this discussion. Several national and international guidelines on the management of chronic gout are available, among them the American College of Rheumatology (ACR) (16), European Alliance of Associations for Rheumatology (EULAR) (17), American College of Physicians (ACP) (18), British Society of Rheumatology (BSR) (19), Dutch Association of Rheumatologists, and Dutch national guideline for general practitioners (GPs) (NHG-standard) (20). Common areas concern the management of lifestyle and comorbidities, timing of initiating of ULT, role of sUA monitoring, and need for prophylaxis when starting ULT (21). Despite agreement in the content of the recommendations for several of the common areas, disagreement exists on recommendations for timing of initiating ULT and even more strongly on the sUA target of ULT. Most guidelines proposed a treat-to-target (T2T) strategy with achievement of a sUA level below 0.36 mmol/L as target (16, 17). Especially the ACP guideline emphasizes that there is no experimental evidence showing the health benefit of treating to sUA level and points to the

absence of trial data comparing a T2T strategy with a treat-to-avoid-symptoms strategy (22). On that line, they call for evidence to determine whether the benefits of escalating ULT to reach a sUA target level outweigh the harms associated with repeated monitoring and increased medication (18, 22).

To fully appreciate the above discussion on the role of treating to a predefined target (T2T) in the management of gout with ULT, it is important to remind the theoretical concept of T2T (Table 1). T2T is a process in which a specific relevant outcome (target) of the disease should be reached in order to prevent subsequent disability on the long-term (23). In other words, treatment should target a reversible surrogate marker that predisposed to this hard irreversible and deleterious endpoint (23). According to the concept, (a) a precise and pre-defined determination about the target is required and also (b) the level of target that should be reached should be pre-defined (preferably based on evidence). Last but not least, the patient and treating healthcare professional should decide in advance to intensify the treatment until the target is reached, unless contraindicated (24). A T2T strategy has demonstrated benefits in chronic diseases such as T2DM and hypertension (25, 26). Also, it has become a fundamental principle in a number of inflammatory diseases, most notably rheumatoid arthritis (27). Using the example of T2DM, the hard irreversible and deleterious endpoint (e.g. risk of the disease) can be defined by the occurrence of blindness due to retinopathy (but also renal insufficiency and major cardiovascular events might be considered) (28). A sustained abnormal level of glycaemia is the evidence based and strong predisposing factor of the hard endpoint (e.g. retinopathy) (29). The marker (e.g. HbA1c) is considered as a relevant surrogate marker (target) and the HbA1c level ≤6.0% has been shown to be the threshold of the predisposing factor. This marker is therefore considered a valid surrogate endpoint for clinical trials.

Based on this theoretical framework, evidence is required to decide whether the T2T concept with a specific sUA level as target should be applied in the management of chronic gout (Table 1). Below we address each of the components of the T2T concept.

Table 1: The different components of the treat-to-target concept within gout management

Components of the treat-to-target concept	Specific for gout management
(1) Definition of the disease	Gout
(2) Definition of the main irreversible and detrimental risk(s) of the disease	Potentially candidates; gout flares, tophi, bone erosions, or cardiovascular disease
(3) Definition of the irreversible predisposing factors of the risk	Candidate: sUA
(4) Definition of the threshold of the predisposing factors below which the risk is significantly decreased (the target)	Candidate: sUA level below 0.36 mmol/L
(5) Definition of the time to reach the target	Some guidelines advise to start targeting sUA after a first gout flare
(6) Definition of the process permitting to check the sustainability of the success	Regularly monitoring sUA level after initiation or up-titration

sUA = serum uric acid

An agreed upon **definition for gout** was proposed by the Gout, Hyperuricaemia and Crystal-Associated Disease Network (G-CAN): "*Gout is a disease caused by monosodium urate (MSU) crystal deposition with any of the following clinical presentations (current or prior): gout flare, chronic gouty arthritis, or subcutaneous tophus*" (30). This definition acknowledges sUA as a causal factor for gout, and flare and tophi as typical symptoms/manifestations of disease (31, 32)**.** On this line, **potential hard endpoints** that reflect the risks of the disease are gout flares, number or size of tophi (including bone erosions). Some consider cardiovascular disease or other comorbidities as potential hard endpoints. However, for each of these hard endpoints, it can be discussed whether they are irreversible or whether some of those candidate hard endpoints are a direct consequence of gout. Flare and subcutaneous or intraosseous tophi are not irreversible (33). Only in untreated gout, tophi can have a deleterious outcome, but the question in T2T is not whether or not to treat but whether to treat strictly to a target. As for cardiovascular diseases (or other comorbidities), it has been repeatedly shown there is no causal relation between sUA level and cardiovascular outcomes or other gout associated comorbidities (34, 35). Some studies even suggested that sUA might protect against various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, or amyotrophic lateral sclerosis (36-40). As indicated previously, it is generally accepted that sUA is a bio-marker (e.g. **the predisposing factor**) for flares and tophi, but no unequivocal evidence exists that sUA is a surrogate endpoint for these outcomes (32). Research on the

(causal) relation between sUA and flares is challenging. Also the **threshold of the predisposing factor** below which the risk is significantly decreased is debatable, as there is no clinical evidence to support an absolute target value for sUA i.e. below 0.36 mmol/L or 0.30 mmol/L for patients with severe gout (tophi, chronic arthropathy, frequent flares) to serve as recommended sUA threshold (17, 41-44). The choice of a sUA level target below 0.36 mmol/L is widely based on laboratory studies indicating MSU reaches its solubility limit (depending on temperature and pH value), above a concentration of 0.36 mmol/L (45). To facilitate faster dissolution of crystals in patients with severe gout (tophi, chronic arthropathy, frequent gout flares) it is recommended to focus on 0.30 mmol/L to deplete urate stores and prevent flares and tophi, followed by the 0.36 mmol/L target after sustained debulking phase (46, 47). The evidence on **time to reach the target** and **the sustainability of the success** is also not (entirely) clear. While some guidelines recommend to start systematically ULT after a first gout flare no clear evidence is available to support this advice. Less doubt exists that treatment with ULT should be maintained over time, unless the risk factors for gout disappear/ reduce as is the case when a patient loses a lot of weight. Finally, and in light of the above, the role of **tight control** of sUA, and thus intense **monitoring** could be questioned. When patients are satisfied with the treatment, experience no gout flares and have no tophi but sUA is still above the target (e.g. 0.36 mmol/L), there is no evidence ULT should be intensified.

With the above mentioned arguments in mind, the results of our real-world comparison of outcomes of a treat-to-strict sUA target opposed to a treat-to-avoid-symptoms argue for the need of a RCT. Our data indicate health outcomes (≤0.36 mmol/L sUA target and flares) were numerically better in the strict treat-to-sUA strategy although not statistically significant. However, implementation of a strict sUA target was at the expense of more frequent treatment escalations with potential extra costs. Clearly, real-world data have evident methodological challenges regarding comparability of assessment of outcome - including flares and adverse events - and insufficient data to account for potential confounders related to patient or center characteristics. Currently, in the Netherlands, the Gout TrEatment STrategy project (GO TEST) Overture superiority RCT is carried out to assess (cost)-effectiveness of the T2T strategy versus the treat-to-avoid symptoms strategy (European Union Clinical Trials Register Number:2020-005721-82) (48). The primary outcome of the still enrolling GO TEST trial is remission defined as

absence of tophi, absence of flares, numeric rating scale (NRS) pain due to gout < 2, NRS disease activity <2 over the last six months of 24 months follow up. A main secondary outcome is the number of gout flares according baseline to last follow up.

A challenge for clinical studies but also for evaluation of daily care in gout patients - as in our treatment strategy comparison - is the measurement of self-reported flare. Flares are the most relevant outcomes for gout patients (49-51). For our 'treatment strategy' study, we had merely information on the number of flares, while three aspects would have been relevant: (1) can patients accurately assess current flares, and can we reliably assess flare frequency over a specific past period in time; (2) can we assess flare severity, and (3) what is the number of flares that are acceptable for patients. To assess a *current self-reported flare*, Gaffo et al. defined in 2012 flare bases on the fulfillment of at least 3 of 4 patient-reported criteria (i.e. patient-defined gout flare, pain at rest score of >3 on a 0–10-point NRS, presence of at least 1 swollen joint, and presence of at least 1 warm joint) (52, 53). This definition was sensitive (85%), specific (95%), and accurate (92%) for an investigator defined–flare as a diagnostic standard (52). The Gaffo criteria will also be used in the GO TEST trial as outcome measure for flares at time point of the assessment. While this definition is an important step to homogenize assessment of flare across the course of studies, a valid approach to assess past frequency is still missing. Diaries including the Gaffo criteria might be a solution, but in real-life adherence to diaries is low. *Flare severity* is at least equally important as presence of flare when evaluating gout severity or effect of medication. Past research identified four key themes relating to flare severity: (1) flare characteristics (e.g. pain intensity, duration, and location), (2) impact on function (e.g. walking, activities of daily living, and sleep), (3) impact on family and social life (e.g. dependency on others, social connection, and work), and (4) psychological impact (e.g. depression, anxiety, and sense of control) (54). While the Gaffo criteria include level of pain intensity to assess the presence of a flare, severity of flares across these key dimensions are not routinely measured. This is a shortcoming, as ULT might (also) have impact on flare severity. Finally, when asking patients to indicate *which number of flares* over the past 6-12 months are consistent with hypothetical remission state over 6 and 12 months, patients consistently answer 'zero flares' (49). This contrasts to our findings from real-life data reported in **Chapter 5** which showed that between 57% and 75% of gout patients with ≥3 flares in the last year and not receiving ULT were still satisfied

with gout treatment. Clearly, remission and acceptability/satisfaction are different constructs, and likely severity of flare influences whether relative frequent flares (≥3 in the past year) are acceptable. Overall, consensus on an approach to collect data on flare (presence, past frequency, severity) would advance knowledge on gout outcomes in clinical studies and real-world settings.

Contextual factors and outcomes of gout

To generate evidence on personalized or stratified medicine, several methodological challenges as encountered in **Chapter 3**, **4** and also **5**, remain unresolved. Outcome Measures in Rheumatology (OMERACT) - a platform of researchers that aims to improve outcome assessment in rheumatology - defines a CFs as *"a variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results"* (55, 56). From a methodological perspective, CFs can be classified into three main types that are methodologically relevant for clinical studies: effect modifying, outcome influencing, and measurement affecting CFs (57). Content wise, CFs can be classified as personal (e.g. age or sex), disease-related (e.g. disease duration or severity), or environmental factors (e.g. place of resident or healthcare system) (57). Sex/gender, a personal CF, receives much attention in medicine the last 25 years. In gout striking sex differences in the prevalence and incidence of gout were already observed by Hippocrates in the fifth century BC (58). **Chapter 3** describes large differences in disease manifestations between genders in patents with gout. We now describe the known differences in comorbidities between sexes become less apparent in patients with gout onset beyond the age of menopause and are mainly explained by differences in lifestyle factors (specifically BMI). Clearly, sex/gender is a so-called 'outcome affecting' CF as it determines the relation between sex and comorbidities in gout. However, this relation is different in those with gout onset before and after the age of menopause, indicating the latter (age) is an effect modifying factor of the relation between sex and comorbidities. Unfortunately, we could not test an interaction between age and sex in view of the small sample size of women with gout before age of menopause. Moreover, in these persons with onset of gout beyond the age of menopause, BMI had a stronger attenuating effect on the sex differences in comorbidities, turning BMI into a confounder. Insight into the role of various 'covariates' can essentially contribute to the understanding of disease when moving to stratified medicine. **Chapter 4** concentrated on effect modification of ULT on sUA by CF in patients with gout and summarized the literature on this topic. Limited conclusions could be

made, as few available RCTs (22%) explored the role of CFs on ULT effectiveness. More-over, limitations in reporting relevant details on stratified analyses hampered meta-analysis. Only for one CF (renal function) sufficient data were available to perform a meta-analysis. For other CFs, even the magnitude of effect modification in individual studies could be rarely extracted from the original RCTs: although studies mentioned stratified analyses would be performed, these data were rarely presented in the manuscript or appendix.

Our studies highlighted three relevant research gaps that can pertain (in varying importance) to the three methodological types of CFs (effect modifying, outcome influencing, and measurement affecting): (1) which CFs are potentially relevant to address, (2) how should CFs been measured, and (3) how to assess and report the role of CFs. Firstly, regarding identification of potential relevant CFs, the OMERACT community agreed on a set of generic CFs to provide guidance on addressing CFs in rheumatology trials (59). This set of CFs was based on expert opinion. Our systematic literature review (SLR) indicates CFs can be specific to diseases, interventions, or outcomes of interest. For example, the presence of tophi - a gout specific factor- is potentially relevant as an effect modifying CF when selecting a ULT. Additionally to a generic set of CFs, experts should select additional CFs based on literature and personal knowledge that might be relevant for specific diseases, interventions, or outcomes of interest. The classification of environmental contextual factors in the International Classification of Functioning, Disability and Health (ICF) could support experts in their choice (60).

Secondly, measurement of CFs should be valid (reflect the 'truth'). However, it is still unclear which clinimetric properties a CF should fulfill. Clearly, a CF should first reflect the construct ('truth') that we want to measure. Second, the clinimetric properties such as reliability and discrimination should be known. Many CFs will not be stable over time, which might pose additional challenges. As an example, tophi as 'effect modifier' was not well described in our SLR in **Chapter 4**. When tophi are included as outcome, the number, the size of an index tophus, or location of tophus has been proposed. Technically, tophi can be measured by clinical examination (e.g. counting), use of Vernier calipers, computed tomography (CT), X-rays, or dual energy computed tomography (DECT) (61). It is unclear which approach for measurement is most relevant when presence of tophi is explored as an effect modifier in an intervention study. In other words, research

into measurement of tophi should distinguish the purpose of management: as a CF (outcome influencing or effect modifying) or as an outcome. Also, tophi can disappear, which might change the risk profile of a patient and influence the choice of treatment. Another example in this thesis pertains to "country of residence" as a CF. This example concerns the role of country of residence when exploring health- and patient-centered outcomes in a European study among gout patients. We expected that patients residing in wealthier countries had better health outcomes. However, we found that in countries with higher Health Care Expenditures (HCE) per capita in international dollars, patients more frequently had ≥3 gout flares (also after adjusting for available clinical confounders). While the finding might indicate gout is more severe in richer countries or less well treated in first-line care, we lacked data to gain better insight into the signification of those results. Clearly, it is insufficiently clear what "country of residence" actually represents. Country of residence may be a surrogate for the type or quality of the healthcare system (e.g. communication, accessibility, and out-of-pocket costs), the culture (e.g. lifestyle including food preferences, expectations of medical care, experiences and coping with stressors, support from family, patient-physician interaction), or the socioeconomic inequalities. This example underlines the need to better define the constructs we wish to explore when trying to understand differences in health outcomes based on socio-economic factors.

Thirdly, consensus on analyzing and reporting the role of CFs is a key factor to enhance validity of CFs research. For example, with regard to effect modification, a stratified design would be preferred as in such case the subgroups are similar in terms of prognostics (62). However, in practice this is not straightforward. Designing RCTs with large sample sizes is both costly and not always feasible in practice. Notwithstanding, adequate power is necessary to detect the same target difference in subgroups (e.g. males vs females, or normal renal function vs impaired renal function) (63). In a step up process towards identification of key effect modifiers, initial exploration of potential effect modification could be evaluated in observational studies or non-stratified analyses. This could provide initial support to justify an (expensive) stratified trial. To ensure trials provide information that is useful for clinical practice, preferably patients with a broad range of background characteristics should be enrolled (64).Overall, researchers and clinicians are searching for alternative study designs addressing the rapid evolving clinically relevant research objectives in the 21st century which are difficult to answer with the classic RCTs.

Support tools for gout management

Since 2001, patient-centered care has is one of the six official pillars of QoC, additionally to effectiveness, safety, timeliness, equitability, and sustainability (65). Patient-centered care is defined as measuring and responding to patient needs, experiences, and satisfaction with disease control (66). Healthcare professionals are called upon to promote patient-centered care (65). To assist healthcare professionals to facilitate patient-centered care and address patients' needs, we developed two support tools for gout patients. Essential for the development of any support tool is a clearly defined scope and a systematic development process based on evidence from literature, views of experts, and perspectives of patients (67). A transparent description of the development is a first and essential step towards understanding effectiveness of any support tool. Next, a usability test is required to ensure actual use. Testing of effectiveness and efficiency in clinical practice are the final steps before adopting such support tools in clinical care.

In a context of patient-centered care, international and national management recommendations for gout state that patients should be fully involved in decision-making concerning the initiation of ULT after a first gout flare (16, 17). There is some evidence that SDM between patients and their healthcare professional increases patients' knowledge, and the feeling of being informed and involved, which in turn improves adherence to treatment resulting in improved health outcomes (68). Therefore, we developed a paper-based DA to support patients and physicians with the decision to (re-)start ULT for patients with gout. In the literature only one DA prototype was published, designed in accordance with the Ottawa decision support framework (69). However, information on flares risk with and without ULT was lacking. Some important (methodological) lessons were learned during our development, which can be used as guidance in the development process of other researchers or DA developers.

While the choice of a theoretical model is definitely at the core of *the development* of a support tool, the most challenging issue during the development of the DA was related to the (lack of) availability of evidence for ULT effectiveness on outcomes relevant for patients. First, patients highlighted the need to be informed about the long-term benefits of ULT on gout flares and sUA, which are not or inconsistently reported in RCTs. It was therefore challenging to provide meaningful data on risk and benefits for clinical care. Observational studies were helpful, although

more data on the relation between sUA and flares with and without ULT would be welcome. Second, insufficient data towards personalized medicine (effect of CFs) did not allow individualized predictions of benefits and harms of ULT within the current DA. Yet, the DA was personalized according to the patient's current sUA level. Third, (numeric) health literacy remains a point of attention, despite the fact that the patients included in the study considered the DA clear and informative, some patients were somewhat cautious about the cognitive burden. Especially weighing benefits and harms is challenging. For this reason, we believe healthcare professionals should ensure understanding of patients (teach back) during the consultation and reveal misconceptions of patients that should be addressed before a final treatment decision. Healthcare professionals will need to develop new skills in guiding decisional conversations that acknowledge the expanded role of the patient in the SDM process, mainly related to risk communication competencies (helping patients understand treatment options and risks).

The I-Change Gout tool, the second support tool described in this thesis, is aimed to be used in clinical care to support ULT adherence among gout patients, in a setting that promotes patient-centered and efficient care. Poor medication adherence is a multi-dimensional problem (70). Yet, patients' self-care behavior is a key determinant to lower or break through the barriers of medication adherence (12, 71, 72). The I-Change Gout tool was developed with the intention to improve patients' motivation and support the complex ULT adherence behavior within three sessions. While the focus is on ULT adherence, the I-Change Gout tool aimed also to address lifestyle as an integral part of management. It is the first web-based patient-tailored tool that specifically addressed ULT adherence in gout patients based on various theories where health behavior is influenced through self-management. With the I-Change Gout tool, we aimed to fill the existing gap in healthcare with respect to combining evidence based support tools and self-care behavior to improve ULT adherence, which is feasible for use in busy clinics. A literature review showed that nurse-led interventions consisting of patient education was the most promising in achieving improved adherence compared to usual gout care (73, 74). Yet, none of these interventions addressed self-care behavior, despite evidence of its relevance. A trial of Doherty et al. revealed that nurse-led care, including providing patients with individualized information and engaging them in their care, along with a strategy of T2T ULT, resulted in very high treatment uptake and adherence (73). Potentially, the I-Change Gout tool could be

efficacious and even more cost-effective compared to nurse-led approaches, as the I-Change model have proven to be (cost)-effective in changing various complex health-related behaviors and their determinants (75-79). Of note, when providing patient-centered care, it is equally important to identify patients that prefer individual learning opposed to those where personal contact is more effective.

The greatest challenge during the development of the I-Change Gout tool was related to the availability of an objective measuring method (such as electronic medication packaging devices, pill count) related to self-reported medication adherence. The ProMAS was chosen to estimate 'objective' medication intake behavior. This questionnaire is a relatively new, self-reported questionnaire for medication adherence. The ProMAS is developed as many other current adherence measurements suffer from several limitations, resulting in adherence rates that often deviate substantially from the objective measurements and highly overestimated adherence (80). The development of the ProMAS relied on testing whether one latent variable (adherence disposition) can be inferred from the range of adherence behaviors. Compared to the MARS-5, one of the most frequently used self-reported medication adherence questionnaire, the ProMAS provided less skewed data with more variance, which is more in line with adherence data assessed with objective methods (81). However, the ProMAS is developed as a generic instrument and was tested among a broad scale of patients with various chronic diseases receiving different medication (and varying corresponding schedules). Also, there is no validation of the ProMAS compared to objective measurements (as golden standard). Yet, taking into account all methodological considerations we believe that the ProMAS best fits our purpose as 'objective medication adherence measurement' compared to other self-reported medication adherence scales.

Following development, *usability* is an essential part of both above mentioned support tools to ensure actual use in clinical practice. Regarding the qualitative approach and rationale of the qualitative part of our studies, we aimed to receive feedback from patients and healthcare professionals to ensure the final prototype of the support tools is understandable and attractive to potential users. Cognitive debriefing by individual think aloud sessions was chosen as accepted approach to evaluate usability among patients and healthcare professionals. Furthermore, in **Chapter 6** and **7** the validated usability questionnaires were rephrased and

composed to match the purpose of the individual studies. Therefore, care was taken that questions were unambiguous, unidimensional, and tested among patients to diminish the influence on the final results. During the usability testing, healthcare professionals doubted whether the I-Change Gout tool would truly reach the desired outcome of improving medication adherence behavior in less motivated patients visiting their outpatient clinics. This also applies to other specific subgroups such as patients attending the GPs, or patients with low health literacy. More in depth qualitative and quantitative evaluation of the I-Change Gout tool is required to gain insight into the magnitude and potential solutions for this problem. Selection bias likely occurred due to the fact that a subset of the intended population was selected for participation in the studies, partly due to practical issues including COVID-19 restrictions. Therefore, in order to be of impact on health and patient-centered outcomes, research of both tools needs to be extended beyond our usability studies in which the final step, namely effectiveness of the tools in clinical practice, should be examined.

Research on the potential effect of support tools for managing gout is still in its infancy. Our preliminary research on support tools shows potential for their usability, however follow-up research is still needed on their effectiveness on health and patient-centered outcomes. To understand the effectiveness of SDM on outcomes, an (semi)-experimental trial will be required. OMERACT reached consensus that not only adherence is an important core outcome, but also (1) knowledge of options, their potential benefits and harms; (2) chosen option aligned with each patient's values and preferences; (3) confidence in the chosen option; (4) satisfaction with the decision-making process; and (5) potential negative consequences (e.g. time and costs) (82). Furthermore, to answer the challenging question regarding potential end-users of the I-Change Gout tool, we should gain insight into uptake as well as effectiveness of the I-Change Gout tool in gout patients with varying levels of motivation, preferably an experimental study. In such trial a process analysis will be relevant and should explore (a) motivation to go through the program (various sessions), and (b) motivation to change behavior and implement actions. Even before such specific knowledge, there is evidence that a minimal level of motivation should be present for a patient to engage in (any) change program. Also, it has been well known that uptake and adherence of patients will critically depend on the believes and attitudes of healthcare professionals towards patient-centered care in general and the two support tools

specifically (healthcare professionals are part of the social influence). In that line, healthcare professionals should ask patients to provide feedback on the support tools and start a discussion on the tool(s), adherence and behavioral change when applicable. In the end, both support tools will improve individualized education and engagement of patients, which are shown as important elements in successful gout management for health and patient-centered outcomes.

Conclusion

The studies presented in this thesis explored several aspects related to the management of gout in clinical practice. We contribute to the paradigm of the 21st century that management of gout context and patients' experiences should be considered. We showed that a treatment towards sUA target with ULT might have some advantages, but also at the expense of more healthcare visits and developed support tools to facilitate SDM and improve adherence to ULT. The studies in this dissertation have contributed to the achievement of a culture shift in patient-tailored management and patient-centered care. Even if it accounts only for a small proportion of gout patients, addressing more patient-tailored management and patient-centered care may lead to better health- and patient-centered outcomes, and thereby a better public health.

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ADDENDUM

Impact paragraph
Nederlandse samenvatting
Dankwoord
Curriculum Vitae

Impact paragraph

This thesis contributes to a better understanding of several aspects of gout management relevant for clinical practice, and describes the development of two tools that aim to support patient-centered care. In this final paragraph, we reflect on the dissemination of the thesis' results, and the implications for society, research, and patients as well as healthcare professionals. Impact occurs when research generates benefits (health, economic, cultural) in addition to building the academic knowledge (1).

Dissemination of findings

Spreading knowledge and making it accessible and usable is a fundamental part of research (2). Even in the 21st century, publishing research in peer-reviewed journals and presenting and discussing research findings at scientific meetings remains the core of academic research. At the time the thesis was published, all the six original manuscripts had been accepted in peer-reviewed journals. Also, findings of the individual articles had been presented at various national and international conferences. Yet, other channels can be relevant to disseminate findings to a broader audience and potential users. On this line, the development of the I-Change Gout tool was introduced in the 'VieCuri Innovation and Science magazine', and 'Physician's Weekly' published an interview on the article related to sex differences in gout. The editor of Journal of Rheumatology selected the latter article and article on outcomes of gout care in Europe as an 'Editor's Pick of the Month', indicating the relevance of the findings of our research to the rheumatology community.

Implications for society

Gout is an underestimated public health problem. It affects 1% to 6.8% of the adult population and is worldwide the most common type of inflammatory arthritis. In addition, gout is associated with considerable costs to the healthcare system and the society as a whole (3). In the Netherlands, 480.000 persons suffered from gout in 2017, and this number will increase by 22% to about 580.000 by 2030 (4). Increased serum uric acid (sUA) is the main risk factor for gout. Several types of anti-inflammatory drugs are available to treat gout flares, and sUA can be successfully controlled by different classes of urate-lowering therapy (ULT).

Recommendations for diagnosis and management of gout have been developed at national level and at the level of several continents. Despite all these advances and efforts, gout management remains highly suboptimal (5). Our data revealed that across Europe, the proportion of patients with ≥3 gout flares within 12 months was 32%. Untreated gout can have on longer-term adverse health effects when recurrent gout flares reflect increased sUA, as this is likely an indicator of progression to chronic gout. When sUA accumulates in the body, there is also a high likelihood tophi will develop. Intra-osseous tophi can cause bone damage and cutaneous tophi can infect, potentially resulting in life threatening sepsis. Additionally, patients with chronic gout incur more frequent sick leave and can potentially lose their job. On a societal level, there should be more awareness about the potential severity of under-treatment of gout among patients as well among healthcare providers. Balancing of under-treatment against overtreatment of gout should be brought more to the attention in the medical curriculum and post-graduate education of several disciplines.

Based on evidence and large consensus among several stakeholders, patient-centered care been endorsed since 2001 as one of the six official pillars of quality of care. Yet, healthcare professionals often lack the time and means to facilitate the concept of patient-centered care. Though we are striving towards patient-centered care, we must accept that patient–healthcare professionals' interactions are driven by a medical priority. The I-Change Gout tool offers the opportunity to enhance patients' self-management, while remaining efficient in a clinical healthcare setting. Healthcare professionals often lack time to engage actively in patient education and improvement of self-management skills. The availability of the I-Change Gout tools allows healthcare professionals to adopt and implement the support tool in their management to be more time effective. Of note, a support tool is not aimed to be a substitute for personal contact between patients and healthcare professionals. During its initial application in clinical practice, a need for further adaptations might be revealed to optimize suitability for broader implementation, a process also referred to as reinvention in Roger's Diffusion of Innovation Theory (6). The gout decision aid (DA), was specifically developed to be responsive to individual patient preferences, needs and values when (re)-starting ULT in patient with gout. With the DA, we hope to contribute to successful long-term gout management, with improved patients' individual health outcomes, improved patients' and healthcare

professionals' satisfaction, and a reduced financial and societal burden of gout. Regular updates of the DA, when relevant new information emerges, is essential.

Implications for research

This thesis describes several findings which have (had) a beneficial impact on research. The studies in this thesis have added to scientific knowledge regarding several aspects of gout management, and in particular to the debate of a treat-to-target versus a treat-to-avoid-symptoms strategy. No randomized controlled trial has yet been undertaken to assess health benefits, side effects and costs of treating to a sUA level compared to with a treat-to-avoid-symptoms strategy (7). In the treatment strategy article, we confirmed the need for a carefully designed treat-to-target randomized controlled trial, likely with quality of life, number of flares and sUA as co-primary outcomes. Partly based on our findings, the Dutch Association of Rheumatologists addressed the lack of evidence of (cost)-effectiveness of a treat-to-target strategy as a formal knowledge gap in the 'KennisAgenda' of 2019. Currently, in the Netherlands the Gout TrEatment STrategy project (GO TEST) Overture superiority RCT is carried out to assess (cost)-effectiveness of the treat-to-target strategy versus the treat-to-avoid symptoms strategy (European Union Clinical Trials Register Number:2020-005721-82) (8).

Implications for patients and healthcare professionals

The most important area for impact of the research described in this thesis is probably the persons or groups of persons deriving advantage or benefit from this research: gout patients and healthcare professionals dealing with these patients. Two hands-on innovative support tools were developed which gives healthcare professionals, primary and secondary caregivers, the opportunity to provide more patient-centered care. As a result, patients can benefit from the results of this thesis. The I-Change Gout tool was designed for a complement to usual care, specifically to the first follow-up visit after implementation of ULT, and addressed besides ULT also lifestyle. Patients can benefit directly by gaining insight into their disease and its course, and by becoming empowered and more involved in the care they receive. Personalized advice as provided with eHealth, has the advantage that it can be accessed at any time and in a desired pace. eHealth has a practical implication for patients, healthcare professionals, and society to facilitate the right

care in the right place. It should be noted that these support tools can also be valuable for healthcare professionals. The I-Change Gout tool can be time saving for the healthcare professionals and the DA will support healthcare professionals to provide evidence based and recommended care. The latter might contribute to the healthcare professionals' satisfaction.

A remarkably result of this thesis was that a substantial proportion of gout patients were satisfied with their gout management despite frequent flares. An open question is whether during the consultation the number of flares is a specific point of discussion between patients and their healthcare professionals. We would like to encourage healthcare professionals to discuss in more detail the number and severity of flares as a first step towards the shared decision whether or not to start ULT to improve control of gout flares.

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Nederlandse samenvatting

Jicht is de meest voorkomende reumatologische aandoening. De ziekte wordt veroorzaakt door een te hoog urinezuurgehalte in het bloed. Dit kan ontstaan doordat te weinig urinezuur het lichaam verlaat of doordat te veel urinezuur wordt aangemaakt. Het urinezuur in het bloed kan neerslaan als urinezuurkristallen in en rondom de gewrichten. Urinezuurkristallen vormen zich vooral op plekken in het lichaam waar de temperatuur iets lager is bijvoorbeeld in de grote teen, enkel, voet of in de vingers. Het immuunsysteem wil deze kristallen opruimen en dit zorgt voor een hevige ontsteking. Deze ontsteking wordt 'een jichtaanval' of 'acute jicht' genoemd. Als deze aanvallen vaker en/of in meer gewrichten voorkomen, spreekt men van chronisch jicht. Bij 2 op de 3 mensen gaat één enkele aanval over in chronische jicht. Bij chronische jicht kunnen urinezuurkristallen zich ophopen. Deze ophopingen worden jichtknobbels of tophi genoemd. Jichtknobbels komen het vaakst voor onder de huid of in de botten van de gewrichten. Deze jichtknobbels kunnen uiteindelijk ook de gewrichten beschadigen.

Te veel urinezuur in het lichaam kan dus jicht veroorzaken. Toch krijgen maar 1 op de 100 volwassenen te maken met jicht. Er zijn een aantal factoren die het risico op een te hoog urinezuurgehalte in het bloed, en dus op jicht, verhogen. Jicht komt vaker voor bij mannen dan bij vrouwen. De meeste vrouwen zijn beschermd tegen jicht tot aan de overgang. Na de overgang hebben vrouwen een vrijwel even grote kans op jicht als mannen. Andere zaken die de kans op jicht vergroten zijn voeding en leefstijl, bepaalde medicijnen, zoals plastabletten, of ziekten, zoals hart- en vaatziekten.

Jicht en de bijbehorende comorbiditeiten vormen een grote last voor zowel de patiënt als voor de gezondheidszorg. Het is daarom van belang meer inzicht te krijgen in de behandeling van jicht en de rol van patiëntgerichte zorgverlening omtrent jicht.

In dit proefschrift worden verschillende onderzoeken gepresenteerd op het gebied van jicht. Het doel van dit proefschrift was tweeledig:

I. Het onderzoeken van de impact van verschillende aspecten die verband houden met de behandeling van jicht, zoals de rol van verschillende behandelstrategieën en de rol van contextuele factoren (bijvoorbeeld geslacht en comorbiditeiten) op jicht uitkomsten.
II. Het in kaart brengen van de behoefte(s) van patiënten en uiteindelijk hulpmiddelen introduceren om patiëntgerichte zorg bij jicht te verbeteren.

Het onderzoek in dit proefschrift werd uitgevoerd in verschillende observationele studies. Voor het beantwoorden van de twee doelen werd daarnaast de literatuur omtrent contextuele factoren bestudeerd en werden patiënten en zorgprofessionals ondervraagt naar de bruikbaarheid van de ontwikkelde hulpmiddelen.

Deel I: Behandelstrategieën en contextuele factoren

Hoofdstuk 2: Geprotocolleerde behandelstrategieën voor jicht patiënten
Momenteel is er nog veel discussie welke strategie moet worden aanbevolen bij de behandeling van jicht: een 'Treat-to-Target' (T2T) strategie (behandelen tot aan een vooraf bepaald doel/target), of een 'Treat-to-Avoid-Symptoms' (T2AS) strategie (behandelen tot er geen/aanvaardbare klachten zijn). Bij de afwezigheid van een gerandomiseerde gecontroleerde studie die de voor- en nadelen onderzoekt van de verschillende behandelingen van jicht, analyseerden we in **Hoofdstuk 2** de resultaten van een klinische audit van *real-life* jicht patiënten die behandeld worden in twee behandelcentra met verschillende geprotocolleerde behandelstrategieën. Eén centrum hanteerde een strikt serum urinezuur doel (0.36 mmol/L) met vroege combinatietherapie als strategie (T2T-strategie). Het andere centrum hanteerde een patiëntgerichte strategie waarbij informatie over het urinezuurniveau wordt geïntegreerd met informatie over patiënt tevredenheid van de jicht behandeling (T2AS-strategie). Voor deze retrospectieve studie zijn er medische patiëntdossiers van jicht patiënten uit twee verschillende ziekenhuizen in Nederland onderzocht. De resultaten beschreven dat patiënten die de strikte T2T-strategie kregen, vaker (hoewel niet significant) het urinezuurniveau van 0.36 mmol/L bereikten (83%

vs. 74%) en vaker vrij waren van jichtaanvallen (46% vs. 36%) vergeleken met patiënten in de T2AS-strategie tijdens een gemiddelde periode van 11.3±1.8 vs. 11.1±1.9 maanden. Ze hadden echter significant vaker een intensievere urinezuur verlagende therapie nodig (en hierdoor 0.4 keer minder kans om behandeld te worden met allopurinol monotherapie) en bezochten vaker de polikliniek (4.4 vs. 3.9 bezoeken). Het is geruststellend dat frequente intensivering van de medicamenteuze behandeling niet gepaard ging met frequentere bijwerkingen of stopzetting van de vervolgbezoeken.

Hoofdstuk 3: Geslachtsverschillen bij jicht patiënten

Jicht wordt beschouwd als een typisch mannelijke ziekte. Bij patiënten ≤65 jaar komt jicht vier keer vaker voor bij mannen dan bij vrouwen. Boven deze leeftijd vernauwt de prevalentie van jicht tot een gelijkere verdeling over de geslachten, vooral door de sterke toename van de incidentie van jicht bij oudere vrouwen. Het meeste bewijs wijst naar de rol van het uricosurische effect van oestrogenen, waardoor premenopauzale vrouwen beschermd worden tegen het ontstaan van jicht. Het is echter onbekend welke invloed de menopauze heeft op de verschillen in risicofactoren en klinische manifestaties tussen de geslachten. In overeenstemming met de beschikbare literatuur ondersteunt **Hoofdstuk 3** het bewijs dat vrouwen ten opzichte van mannen met jicht gemiddeld 2.6 jaar ouder zijn, vaker last hebben van nierinsufficiëntie (een 14.9 ml/min per 1.73m^2 lagere nierfunctie), een 2.1 keer verhoogde prevalentie van obesitas, een 3.1 keer verhoogde prevalentie van diabetes mellitus type 2 en een 2.8 keer verhoogde prevalentie van hypertensie. Vrouwen gebruikten ook 3.5 keer vaker diuretica en waren 0.4 keer minder snel zware alcoholconsumenten. Er werden geen verschillen in aanwezigheid van tophi waargenomen. Bij het herhalen van de analyses in een subgroep met patiënten ≥55 jaar om postmenopauzale vrouwen te vertegenwoordigen en hiermee de rol van oestrogeen te onderzoeken toonden we aan dat bij het ontstaan van jicht in patiënten ≥55 jaar de geslachtsverschillen in comorbiditeiten verzwakten. Onafhankelijk van de beginleeftijd speelden leefstijlfactoren altijd een rol bij geslachtsverschillen, aangezien geslachtsverschillen minder sterk waren bij correctie voor body mass index (BMI), roken en alcoholgebruik. Leefstijlfactoren verzwakten consequent de associatie tussen geslacht en comorbiditeit, iets duidelijker bij diegenen met een beginleeftijd van jicht ≥55 jaar. Verder vergeleken we de fractionele uitscheiding van urinezuur tussen geslachten voor patiënten ≥55 jaar. De gemiddelde uitscheiding was vergelijkbaar bij vrouwen ≥55 jaar

als bij mannen in dezelfde leeftijdsgroep, wat bijdraagt aan het bewijs van het uricosurische effect van oestrogenen bij premenopauzale vrouwen.

Hoofdstuk 4: Systematisch literatuur overzicht van contextuele factoren bij jicht patiënten

Een belangrijke vraag in het tijdperk van gestratificeerde geneeskunde is of de respons op serum urinezuur verlagende medicijnen bij jicht patiënten verschilt, afhankelijk van de aan-of afwezigheid van specifieke contextuele factoren zoals comorbiditeiten (bijv. hart- en nierziekten en obesitas) of sociaal-demografische factoren (bijv. geslacht). Daarom hebben we in **Hoofdstuk 4** de literatuur doorzocht naar gerandomiseerde gecontroleerde studies die effect modificatie van urinezuur verlagende therapie op het bereiken van het serum urinezuur doel (0.36 mmol/L) door contextuele factoren onderzochten. Acht van de 37 beschikbare gerandomiseerde gecontroleerde studies rapporteerden subgroep analyses op basis van contextuele factoren, namelijk leeftijd (n=2), geslacht (n=3), ras (n=2), nierfunctie (n=6), cardiovasculaire comorbiditeit (n=2), tophi (n=2), gebruik van diuretica (n=2), en voorafgaande urinezuur verlagende therapie (n=1). Vier studies presenteerden de ruwe onderzoeksresultaten per behandelarm en gestratificeerd naar nierfunctie (normaal, mild, matig en ernstig verminderd). Deze studies kwamen in aanmerking voor kwantitatieve analyses, oftewel meta-analyse. De meta-analyse van 36 gerandomiseerde vergelijkingen bracht significante heterogeniteit aan het licht (I^2=92.8%). Gepoolde schattingen lieten zien dat patiënten met een normale (OR:13.49;[2.18-83.31]), mild (OR:18.50;[3.00-113.93]), of matig verminderde nierfunctie zeer waarschijnlijk het serum urinezuur doel bereiken met een interventie van urinezuur verlagende therapie in vergelijking met de comparator, terwijl een ernstig verminderde nierfunctie een klein nadeel opleverde. Analyses tussen groepen op basis van nierinsufficiëntie bracht aan het licht dat een milde en matige nierfunctiestoornis een statistisch significant voordeel opleverde bij het bereiken van een serum urinezuur doel in vergelijking met een normale nierfunctie. Sensitiviteitsanalyse met alleen placebogecontroleerde studies bevestigde grote gunstige effecten van urinezuur verlagende therapie op het bereiken van een serum urinezuur doel (in vergelijking met placebo) bij personen met normale, milde of matige nierfunctiestoornis. Analyses tussen subgroepen op basis van nierinsufficiëntie toonde geen statistisch voordeel voor normale versus milde of matige nierfunctiestoornis. Kwalitatieve samenvattingen van studies waarvoor kwantitatieve analyses niet mogelijk was, suggereerden dat patiënten met tophi

minder kans hadden om het serum urinezuur doel te bereiken. De invloed van tophi bij het bereiken van een serum urinezuur doel werd echter waargenomen bij rechtstreekse vergelijkingen en niet in placebogecontroleerde studies. Er konden geen duidelijke conclusies worden getrokken voor effect modificatie door andere contextuele factoren.

Deel II: Patiëntbehoeften en hulpmiddelen

Hoofdstuk 5: Patiëntbehoeften bij jicht patiënten in Europa

Naast de gezondheidsuitkomsten worden de ervaringen van patiënten met zorg (patiëntgerichtheid) steeds meer beschouwd als een indicator van kwaliteit van zorg. Hoewel de zorgervaringen van patiënten op zichzelf relevante uitkomsten zijn, kunnen ze ook inzicht geven in waarom (medicamenteuze) behandelingen mogelijk niet de verwachte gezondheidsresultaten opleveren. In **Hoofdstuk 5** hebben we de impact van jicht op generieke en jicht specifieke gezondheidsresultaten geëvalueerd, evenals op patiëntgerichte uitkomsten in een praktijksituatie in 14 Europese landen. Gemiddeld was het percentage patiënten met ≥3 en ≥1 jichtaanvallen het afgelopen jaar respectievelijk 32% en 70%. Multivariabele exploratie toonde aan dat patiënten met ≥3 en ≥1 jichtaanvallen minder kans hadden om met urinezuur verlagende therapie behandeld te worden (OR: 0,52 en OR: 0,38), maar meer kans hadden op regelmatige doktersbezoeken (OR: 2,40 en OR: 1,77). Jichtaanvallen (≥3) droegen substantieel bij aan een slechtere gezondheid en patiëntgerichte resultaten, zoals tevredenheid met de behandeling en ongeadresseerde behandeldoelen. Desalniettemin was 80% van de patiënten tevreden met de jichtbehandeling. Zelfs bij patiënten met ≥3 jichtaanvallen die niet met urinezuur verlagende therapie werden behandeld, was 57% tot 75% nog steeds tevreden in verschillende subgroepen, en dit was onafhankelijk van de frequentie van doktersbezoeken. Met andere woorden, 'suboptimale' jichtuitkomsten (en behandeling) resulteren niet per definitie tot een ontevreden patiënt. Onverwacht rapporteerden patiënten uit rijkere en Noord-Europese landen vaker ≥3 jichtaanvallen.

Hoofdstuk 6: Bruikbaarheid van een keuzehulp voor urinezuur verlagende therapie

Om de kwaliteit van de zorg voor jicht patiënten in de dagelijkse praktijk verder te verbeteren, hebben we twee hulpmiddelen ontwikkeld om patiëntgerichte

zorg te ondersteunen, zowel voor patiënten als zorgprofessionals. In **Hoofdstuk 6** hebben we de ontwikkeling en bruikbaarheid beschreven van een keuzehulp voor jicht patiënten die een indicatie hebben om urinezuur verlagende therapie te (her)starten. De keuzehulp is ontwikkeld op papier voor gebruik tijdens het 'face-to-face' polikliniekbezoek. Aanbevelingen van de International Patient Decision Aid Standards (IPDAS)-groep hebben de ontwikkeling geleid. Patiënten en zorgprofessionals speelden een sleutelrol bij het design, de ontwikkeling van het prototype, en de pilottest van de keuzehulp. De papieren keuzehulp, gepersonaliseerd op basis van het huidige serum urinezuurniveau van de patiënt, bestond uit zes pagina's die betrekking hadden op: (1) algemene informatie over gezondheidstoestand inclusief risicofactoren; (2) verduidelijking van de beslissing die moet worden overwogen (starten met urinezuur verlagende therapie bovenop veranderingen in leefstijl en profylaxe); (3) de rol van de verandering in leefstijl en behandeling van acute jichtaanvallen; (4) het risico op jichtaanvallen met of zonder urinezuur verlagende therapie; (5) een beschrijving van de urinezuur verlagende therapie opties (eerste- en tweedelijns) inclusief bijwerkingen in een optieraster; en (6) de persoonlijke percepties en overtuigingen voordat de uiteindelijke gedeelde beslissing wordt genomen. De pilottest biedt een eerste inzicht in de bruikbaarheid van de keuzehulp ter ondersteuning van een gedeelde besluitvorming in de behandeling van jicht patiënten, die in aanmerking kwamen voor (her)starten van urinezuur verlagende therapie. Enkele suggesties voor verbetering van de inhoud (bijv. meer praktische adviezen over een gezonde leefstijl) en bewoordingen (bijv. het verkorten van zinnen) werden gedaan. Dit resulteerde in verschillende aanpassingen en verbeteringen van de keuzehulp.

Hoofdstuk 7: Bruikbaarheid van een eHealth systeem voor therapietrouw

Betrokkenheid van de patiënt bij zijn/haar zorg is relevant, niet alleen bij behandelbeslissingen, maar gedurende het hele traject van de patiënt. Het naleven van voorgeschreven urinezuur verlagende therapie varieert van 20% tot 70% en wordt beschouwd als een van de slechtste therapietrouw van alle chronische aandoeningen. Toch zijn interventies om de naleving van urinezuur verlagende therapie te verbeteren beperkt en geen van hen heeft betrekking op zelfzorg, een belangrijke bepalende factor voor therapietrouw. In **Hoofdstuk 7** wordt de ontwikkeling en bruikbaarheid beschreven van de '*I-Change Gout Tool*' om therapietrouw van urinezuur verlagende therapie te verbeteren bij jicht patiënten in een klinische setting. De 'I-Change Gout Tool' integreert bewustzijn

(pre-motiverend), motivatiefactoren en actieplannen (post-motiverend) om het gewenste gebruik van urinezuur verlagende therapie te bevorderen. De 'I-Change Gout Tool' is bedoeld om therapietrouw te ondersteunen bij jicht patiënten die urinezuur verlagende therapie gebruiken, bij wie de urinezuur verlagende therapie is aangepast, of bij wie de therapietrouw (vermoedelijk) suboptimaal is. Terwijl de focus lag op therapietrouw van urinezuur verlagende therapie, richtte de 'I-Change Gout Tool' zich ook op leefstijl als integraal onderdeel van jicht management. Bestaande I-Change tools waren het uitganspunt van de 'I-Change Gout Tool'. Er werd een expertgroep samengesteld die de specifieke inhoud van de tool (beoordelingen en gepersonaliseerd feedback) besliste op basis van informatie van voorbereidend kwalitatief onderzoek en literatuuronderzoek. Patiënt waargenomen en daadwerkelijk voorspelde therapietrouw was de belangrijkste bepalende factor voor navigatie door het systeem. In totaal bestonden de drie sessies (pre-motiverende, motiverende en post-motiverende sessie) van de 'I-Change Gout Tool' uit 80 vragen, 66 op maat gemaakte tekstuele feedbackberichten en 40 op maat gemaakte geanimeerde video's. Tijdens de eerste bruikbaarheidstest meldden patiënten en zorgprofessionals een hoge intentie om de 'I-Change Gout Tool' te gebruiken en/of aan te bevelen om urinezuur verlagende therapie therapietrouw te ondersteunen. Onder zorgprofessionals bleef twijfel bestaan of de 'I-Change Gout Tool' het gedrag van minder gemotiveerde personen zou kunnen veranderen in de richting van het gewenste gedrag.

De studies die in dit proefschrift worden gepresenteerd, hebben verschillende aspecten onderzocht die verband houden met de behandeling van jicht in de klinische praktijk. We dragen bij aan het paradigma van de 21ste eeuw dat ervaringen van patiënten overwogen moeten worden tijdens de behandeling van jicht. We tonen aan dat een behandeling naar een serum urinezuur doel met urinezuur verlagende therapie enkele voordelen zou kunnen hebben, maar ook ten koste gaat van meer doktersbezoeken. Daarnaast hebben we ondersteunende hulpmiddelen ontwikkeld om gedeelde besluitvorming te vergemakkelijken en de therapietrouw van urinezuur verlagende therapie te verbeteren. De studies in dit proefschrift hebben bijgedragen aan het bereiken van een cultuuromslag in patiëntgerichte management en patiëntgerichte zorg. Zelfs als het slechts een klein deel van de jicht patiënten betreft, kan een meer op de patiënt afgestemde zorg leiden tot betere gezondheids- en patiëntgerichte resultaten, en daarmee een betere volksgezondheid.

Dankwoord

Wat een rit! Tijdens het schrijven van mijn proefschrift ben ik er pas achter gekomen hoeveel er kan gebeuren in 4 jaar tijd. Een terugblik leert dat er vele (bijzondere) gebeurtenissen hebben plaatsgevonden in deze afgelopen 4 jaar, welke uiteindelijk ook een vrij grote impact hebben gehad op het tot stand komen van dit proefschrift. Wie had in september 2017 kunnen bedenken dat ongeveer 50% van de tijd van het schrijven dit proefschrift zich in de thuissituatie zou afspelen. Ik wil graag iedereen van harte bedanken voor een fantastische tijd. Enkele personen zou ik graag in het bijzonder willen bedanken voor hun waardevolle bijdrage.

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te functioneren bij een minder moment tijdens het traject. We hebben lief en leed met elkaar gedeeld, want moge een ding duidelijk zijn, bij een promotietraject zijn er veel lastige momenten. Gelukkig hadden we de vaste afspraak dat leuke momenten gevierd werden met vlaai! Ook de maandelijkse Dönderdag zorgde voor de nodige afwisseling. Ik wil jullie bedanken voor de ontzettend leuke tijd, en hoop jullie dan ook nog vaker te zien in de toekomst. Het provisorium blijft onze ruimte.

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Curriculum Vitae

Ritchie Riccardo Eloy (Ritch) te Kampe was born on 5th June 1994 in Heerlen, the Netherlands. In 2012, he graduated from secondary school (VWO) at Sophianum College in Gulpen. Afterwards, Ritch studied Biomedical Sciences at the Maastricht University in Maastricht, the Netherlands. After choosing Human Movement Sciences as direction in the second study year and obtaining his Bachelor degree in 2016, Ritch continued his education at Maastricht University and graduated from the Human Movement Sciences Master in 2017.

In September 2017, Ritch started working as a PhD candidate at the department of Functioning and Rehabilitation of the Maastricht University in close collaboration with the department of Rheumatology of VieCuri Medical Center in Venlo. The PhD project was supervised by prof. dr. Annelies Boonen, prof. dr. Hein de Vries, dr. Caroline van Durme, and dr. Tim Jansen. During his time as a PhD researcher he presented his work at national and international meetings, published in peer-reviewed journals, tutored students, and was a member of the CAPHRI PhD Panel. Currently, Ritch is working as policy advisor strategy and support at Zuyderland Medical Centre.