

## Gout management in Swiss primary care – a retrospective observational study

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### Summary

**BACKGROUND:** Gout is the most common form of inflammatory arthritis worldwide and its prevalence is rising. In Switzerland, there are no data available on the characteristics and treatment of gout patients. In this study, we aimed to describe numbers of patients affected by gout and hyperuricaemia and unveil approaches Swiss primary care physicians (PCPs) use for the management.

**METHODS:** This was a retrospective observational study using electronic medical routine data provided from 242 Swiss PCPs. Included were all their patients receiving urate-lowering therapy (ULT), with a diagnostic code for gout or who had a serum uric acid (SUA) measurement. According to their disease status, patients were classified into four subgroups (normal urate, hyperuricaemia, untreated gout, treated gout). For treatment analysis, patients with SUA measurements before and after ULT initiation were included. Comorbidities and risk factors for secondary causes relevant in the context of gout were collected. Outcomes were prevalence of gout and hyperuricaemia, characteristics of patients according to subgroup, number of SUA measurements, levels of SUA and patients who reached the treatment goal of a SUA level <360 µmol/l.

**RESULTS:** We assessed 15,808 patients and classified them into the subgroups. This yielded a prevalence of 1.0% for gout and 1.2% for hyperuricaemia. 2642 patients were diagnosed with gout of whom 2420 (91.6%) received a ULT. Overall; 41.3% of patients with a gout treatment had at least one SUA measurement; 15.0% of patients with treated gout had a record of SUA measurements before and after ULT initiation; and 57.5% reached the treatment goal of <360 µmol/l after allopurinol treatment.

**CONCLUSION:** Swiss gout patients received comprehensive treatment, which is reflected in a high number of patients treated with ULT, laboratory tests per person and a high treatment success rate, although there is no systematic approach to the treatment of gout.

**Keywords:** *gout, hyperuricaemia, urate lowering therapy, variety of care, electronic medical routine data*

### Introduction

Gout is the most common form of inflammatory arthritis worldwide and its prevalence is rising. The highest prevalence has been reported in occidental countries and among oceanic populations, affecting up to 7.6% of the population, which is a doubling in occidental countries in the last 15 years [1–7]. Similar in its clinical appearance to gout, hyperuricaemia is reported to be rising with a reported prevalence of up to 21.4% [4–6, 8]. In contrast to gout, which is diagnosed clinically, the diagnosis of hyperuricaemia is solely defined by serum uric acid (SUA) levels above 400 µmol/l (6.8 mg/dl) [7, 9–11].

There is international evidence that the management of these non-communicable entities varies widely. Previous studies investigating primary care populations in different occidental countries reported that 9–74% of all patients diagnosed with gout had SUA measurements, and 40–84.5% of all patients were treated with urate-lowering therapy (ULT) [3, 12–17]. Among treated patients, 21–50% reached the treatment target of <360 µmol/l (<6 mg/dl) recommended in most guidelines [18–20]. A recent Swiss guideline is in concordance with the international guidelines and recommends the treatment target of <360 µmol/l for gout patients, whereas it is not recommended to treat hyperuricaemia [21]. However, data on prevalence and the actual management of gout and hyperuricaemia in primary care is lacking for Switzerland.

Therefore, the aims of this study were:

- To investigate numbers and prevalence of patients affected by gout or hyperuricaemia to describe population characteristics and to assess differences in subpopulations
- To describe approaches Swiss primary care physicians (PCPs) used for the management of gout and to assess if the treatment goal (SUA level ≤ 360 µmol/l) was reached and which factors were associated with doing so.

### Methods

#### Study design and setting

We conducted a retrospective observational database analysis based on the FIRE (family medicine International

**Author contributions**  
RM, SZ and TR developed the study protocol. FV and SG extracted and analysed the data. RM, SZ, SG and TR wrote the final manuscript. All authors read, revised and approved the manuscript.

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Classification of Primary Care [ICPC] research using electronic medical records) database, which was established in 2009 [22]. The FIRE database is a continuous collection of structured medical routine data from Swiss primary care practices. Until August 2019, more than 540 PCPs (approximately 10% of general practitioners working in the German-speaking region of Switzerland [23]) from more than 180 practices participated on a voluntary basis. This resulted in records from more than 600,000 patients and more than 7 million consultations. In brief, the database covers patient demographics, vital signs, laboratory data, prescribed medication according to anatomical therapeutic chemical (ATC) coding and diagnoses based on ICPC Version 2 [24, 25]. For this analysis, data from 1 January 2009 to 31 August 2018 were included. According to the Local Ethics Committee of the Canton of Zurich, the project did not fall under the scope of the law on human research [26] and therefore no ethical consent was necessary (BASEC-Nr: Req-2017-00797).

### Eligibility and inclusion criteria

Practices were eligible if they provided SUA measurements for FIRE. Within these practices, all patients alive and aged between 18 and 90 were included if one of the following criteria were fulfilled: (a) at least one prescription of ULT (ATC code M04); (b) ICPC code of gout (T92); (c) at least one SUA measurement.

### Patient subgroups

The following subgroups were defined for further assessments of patient characteristic: normal urate (first SUA level <400 µmol/l, no ULT, no ICPC T92), hyperuricaemia (first SUA level >400 µmol/l, no ULT, no ICPC T92), untreated gout (ICPC T92, no ULT) and treated gout (ICPC T92, use of a ULT). For the analysis of the disease management, treated gout patients with available SUA measurements before and after treatment initiation were analysed according to their received treatment (allopurinol: ATC M04AA01; febuxostat: ATC M04AA03) and sex. The patient selection process is visualised in the study flowchart (fig. 1).

### Database query and variables

From the FIRE database, we retrieved the following information at PCP level: age, sex, practice location (urban vs rural [27]) and practice type (single vs group practice). At patient level we retrieved: (a) demographic data (age, sex and body mass index [BMI]); (b) treatment data (number of SUA measurements, level of SUA measurements, type of medication); (c) information about comorbidities (alcohol abuse, obesity, hypertension, diabetes mellitus, dyslipidaemia, cardiovascular disease); and risk factors influencing SUA levels by increasing SUA production (psoriasis, high cell turnover diseases, cytotoxic chemotherapeutics) or by decreasing excretion (chronic kidney disease [CKD] stage 3a and higher, congestive heart failure, diuretics, laxatives) [28, 29]. Comorbidities and risk factors were defined using ICPC codes, laboratory measurements and ATC-codes (for detailed identification schemes see supplementary tables S1 and S2 in appendix 1) [30, 31].

### Statistical analysis

We described patient level categorical data as numbers and proportions (n, %) and patient level continuous data as means and standard deviations (SDs). The percentage of missing observations was reported when necessary. To compare patient characteristics between patient subgroups, we used the chi-squared test for categorical variables and the analysis of variance (ANOVA) test for continuous variables. When testing difference in means or proportions between two groups, we reported results as 95% confidence intervals (CIs). A logistic multivariable mixed model, correcting for sex and repeated measurements (nested random effects: PCPs/patients) was used to examine treatment success. We specified the model as follows:

SUA level  $\leq 360$  µmol/l ~ fixed effects ( $X$ ) + random effects of intercept (PCPs/patients)

where  $X$  = treatment indicator, sex.

We represented the results of the model as odds ratios (ORs) with 95% CI. The observations with missing values were excluded for regression analysis, but still included in the descriptive analysis. A p-value  $\leq 0.05$  was considered statistically significant. All statistical analyses were carried out using the R statistical package [32].

## Results

### Population characteristics

Within the FIRE network, 97 distinct practices with 242 PCPs covered 15,808 eligible patients (fig. 1). The PCPs' mean age was 51.7 years (SD 10.4), 148 (61.2%) were male, 219 (90.5%) worked in a double or group practice and 130 (53.7%) practiced in an urban area. At the patient level, 15,808 patients met the inclusion criteria. Their mean age was 58.9 years (SD 16.2) and 8,840 (55.9%) were male; 49.1% (n = 7764) of the patient population had at least two comorbidities of which dyslipidaemia (n = 10,569, 66.9%), hypertension (n = 8990, 56.9%) and diabetes (n = 1704, 10.8%) were the most prevalent. We identified 4672 (29.6%) patients having risk factors for secondary causes of which the three most common were the use of diuretics (n = 3266, 20.7%), CKD stage 3a or higher (n = 2066, 13.1%) and the use of laxatives (n = 1187, 7.5%).

Subgroup classification revealed that 5773 (36.5%) of all eligible patients were affected by hyperuricaemia or gout, which resulted in a prevalence of 1.0% for gout and 1.2% for hyperuricaemia. All patient characteristics differed statistically significantly between the four different subgroups (table 1).

### Disease management

#### SUA measurements

Overall, 22,169 SUA measurements were available. The mean number of SUA measurements per patient was 1.4 (SD 1.3) and mean SUA level was 339.4 µmol/l (SD 98.0). The SUA level was significantly higher among men (376.7 µmol/l, SD 89.6) than women (296.3 µmol/l, SD 89.3) with a 95% CI for the difference of -83.3 to -77.4 µmol/l. Moreover, SUA level rose with CKD grade. The number and the level of SUA measurements differed significantly

between patient subgroups (table 1). Among the gout patients (treated and untreated), 1090 patients (41.3%) had at least one SUA measurement. Of the treated gout patients 364 (15.0%) had at least one SUA measurement before and after ULT initiation and were therefore eligible for the treatment effect analysis.

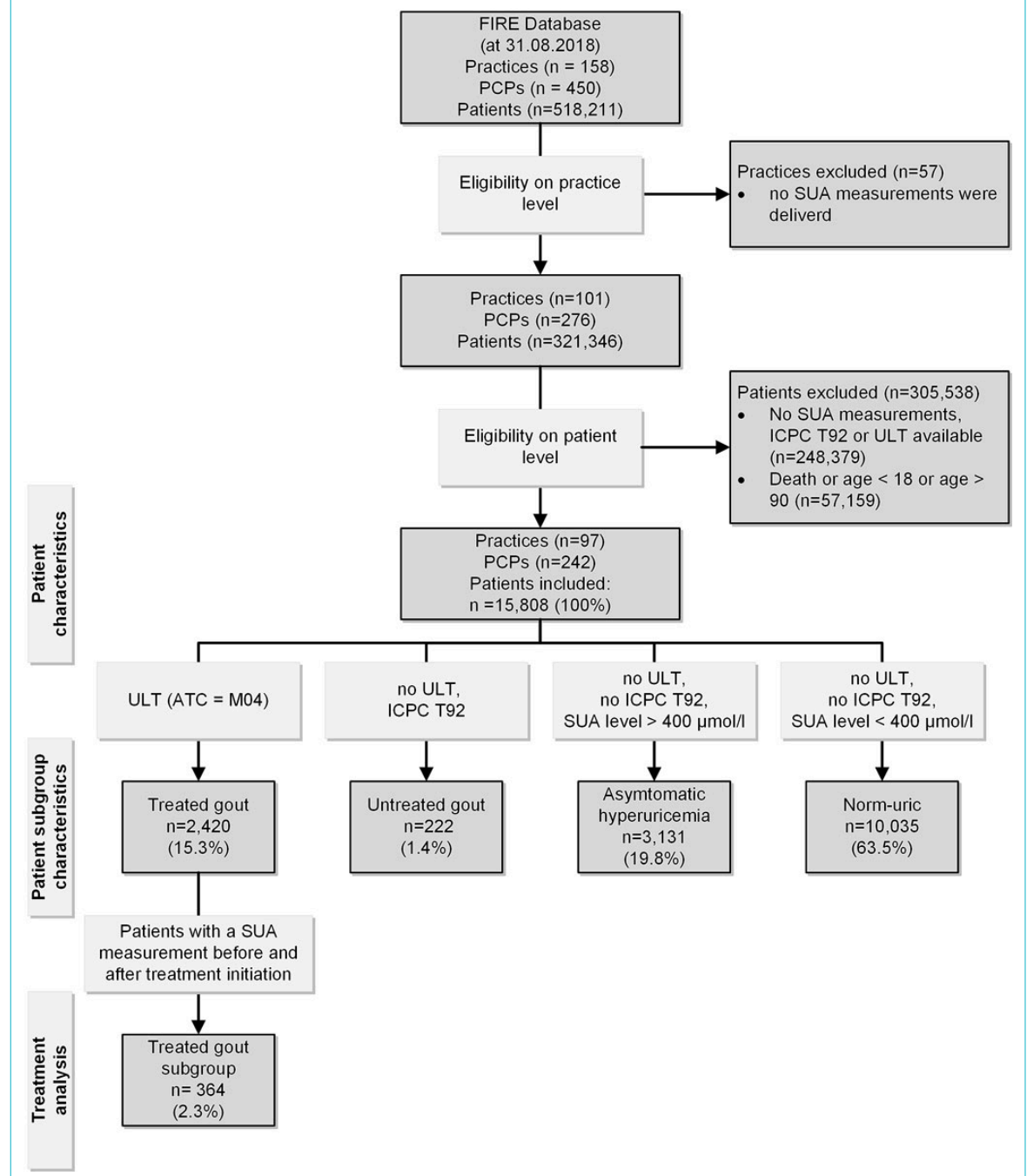
### Treatment

Of all patients affected with gout, 2,420 (91.6%) were treated. The proportion of treated patients did not differ significantly between the sexes (1832, 91.4% of men and 588, 92.2% of women,  $p = 0.610$  with a 95% CI for the difference of  $-0.02$  to  $0.03$ ). Treatment with allopurinol led to a statistically significant average drop in SUA level

of  $67 \mu\text{mol/l}$  (95% CI 53.8 to 79.5) (table 2). The drop was  $77 \mu\text{mol/l}$  in women (95% CI 49.5 to  $104.3 \mu\text{mol/l}$ ) and  $60 \mu\text{mol/l}$  in men (95% CI 46.2 to  $75.0 \mu\text{mol/l}$ ). The treatment goal of  $\text{SUA} \leq 360 \mu\text{mol/l}$  was reached by 199 patients (57.5%), 69 female patients (68.3% of all treated women), and 130 male patients (53.1% of all treated men). The OR for achieving the treatment goal with treatment was 4.34, ( $p < 0.001$ , 95% CI 3.15 to 6.08). Female patients were more likely to achieve the treatment goal: OR 2.36 ( $p < 0.001$ , 95% CI 1.53 to 3.69).

Only 28 patients in our sample had SUA measurements before and after treatment initiation with febuxostat (table 3). Febuxostat led to a drop in SUA level, of  $71 \mu\text{mol/l}$

**Figure 1:** Flow chart of the study design and inclusion/exclusion criteria including number and proportions of patients. FIRE = family medicine ICPC Research using electronic medical records; ICPC = international classification of primary care; PCP = primary care physician; SUA = serum uric acid; ULT: urate-lowering therapy



1 ( $p < 0.001$ , 95% CI  $-3.2$  to  $143.5$ ). The mean drop was  $112 \mu\text{mol/l}$ , (95% CI  $64.8$  to  $157.7 \mu\text{mol/l}$ ) in men and  $36 \mu\text{mol/l}$ , (95% CI  $-138.7$  to  $211.9$ ) in women. Treatment success was reached in 67.9% of the 28 treated patients (in men 66.7%, in women 71.4%).

### Treatment patterns

To investigate the treatment pattern of PCPs, we assessed SUA measurements before and after initiating ULT. Figure 2 displays a random sample of patients treated with ULT. As can be seen, SUA measurements before and after ULT

initiation show a high variation in absolute numbers as well as in time intervals before and after treatment started.

### Discussion

Our data analysis of Swiss primary care patients yielded a low prevalence of gout and hyperuricaemia. However, within all those eligible, 35% of patients were affected by gout or hyperuricaemia and more than 50% of those affected by gout had risk factors for secondary causes. The majority (91.6%) of patients affected by gout received treatment, of whom the vast majority (97.4%) received allopurinol. The number of SUA measurements among indi-

**Table 1:** Patient characteristics according to defined subgroups.

Patient characteristics		Normal urate	Hyperuricaemia	Untreated gout	Treated gout	p-value	
Patient characteristics	Number of patients	10,035	3131	222	2420		
	Age (years), mean (SD)	55.5 (16.0)	62.3 (15.6)	63.4 (15.6)	68.1 (13.0)	<0.001	
	Sex male, n (%)	4411 (44.0)	2425 (77.5)	172 (77.5)	1832 (75.7)	<0.001	
	BMI class, n (%)	Normal weight	17 (7.7)	236 (7.5)	69 (2.9)	1596 (15.9)	<0.001
		Obese	50 (22.5)	485 (15.5)	302 (12.5)	748 (7.5)	
		Overweight	44 (19.8)	542 (17.3)	263 (10.9)	1475 (14.7)	
Underweight		0 (0.0)	12 (0.4)	9 (0.4)	286 (2.9)		
Number of chronic diseases, mean (SD)	1.33 (0.95)	1.75 (1.01)	2.08 (1.53)	2.04 (1.21)	<0.001		
Risk factors and comorbidities, n (%)	Dyslipidaemia	6901 (68.8)	2284 (72.9)	117 (52.7)	1267 (52.4)	<0.001	
	Hypertension	4733 (47.2)	2111 (67.4)	150 (67.6)	1988 (82.4)	<0.001	
	Diabetes	662 (6.6)	411 (13.1)	47 (21.1)	584 (24.1)	<0.001	
	Cardiovascular disease	270 (2.7)	191 (6.1)	48 (21.6)	200 (8.3)	<0.001	
	Risk factors	1874 (18.7)	1100 (35.1)	111 (50)	1587 (65.6)	<0.001	
	Diuretics	1092 (10.9)	891 (28.5)	66 (29.7)	1217 (50.3)	<0.001	
	CKD	684 (6.8)	751 (23.9)	49 (22.1)	582 (24.0)	<0.001	
Laxatives	640 (6.4)	240 (7.7)	19 (8.6)	288 (11.9)	<0.001		
SUA measurements, mean (SD)	SUA measurements	1.37 (0.91)	1.79 (1.46)	0.62 (0.91)	1.10 (2.12)	<0.001	
	SUA level*	293.5 (60.3)	458.1 (67.9)	439.3 (112.5)	419.0 (111.6)	<0.001	
Treatment, n (%)	Allopurinol	0 (0.0)	0 (0.0)	0 (0.0)	2,357 (97.4)		
	Febuxostat	0 (0.0)	0 (0.0)	0 (0.0)	91 (3.8)		
	Probenecid	0 (0.0)	0 (0.0)	0 (0.0)	13 (0.5)		

BMI = body mass index; CKD= chronic kidney disease 3b or higher; SD = standard deviation; SUA = serum uric acid \* Percentages were calculated including missing values. Missing were: BMI 61.2%, SUA levels 9.8%. Reported p-values result from chi-square test (categorical variables) or ANOVA test (continuous variables). BMI classes are: underweight = BMI <20 kg/m<sup>2</sup>; normal weigh = BMI ≥20 and <25 kg/m<sup>2</sup>; overweight = BMI ≥25 and <30 kg/m<sup>2</sup>; obese = BMI ≥30 kg/m<sup>2</sup>

**Table 2:** Treatment effect of allopurinol.

		Patients (n)	SUA measurements (n)	SUA levels (μmol/l)		SUA ≤360 μmol (%)
				Mean	SD	
Total	Before	346	581	480	127	21.7%
	After	346	933	413	119	57.5%
Male	Before	245	434	485	120.7	19.6%
	After	245	651	425	115.2	53.1%
Female	Before	101	147	463	143.4	26.7%
	After	101	282	386	123.2	68.3%

SD = standard deviation; SUA = serum uric acid

**Table 3:** Treatment effect of febuxostat.

		Patients (n)	SUA measurements (n)	SUA levels (μmol/l)		SUA ≤360 μmol (%)
				Mean	SD	
Total	Before	28	69	525	146.6	14.3%
	After	28	85	454	300.6	67.9%
Male	Before	21	50	504	111.7	9.5%
	After	21	50	392	122.3	66.7%
Female	Before	7	19	579	206.9	28.6%
	After	7	35	543	433.6	71.4%

SD = standard deviation; SUA = serum uric acid

vidual patients varied widely, indicating that most PCPs do not have a systematic approach to hyperuricaemia or gout. In recent studies, the prevalence of gout varied widely and was conflated to the range of 1–4% by Kuo et al. 2015. In studies reporting the prevalence of both, the prevalence of hyperuricaemia was three to five times higher than the prevalence of gout [4–6]. Our study reported a gout prevalence on the lower end of the range found in literature. Interestingly, survey data resulted generally in a rather higher gout prevalence than results from administrative or patient record data, which supports the validity of our data for gout [3, 4, 6, 12]. In contrast, the prevalence of hyperuricaemia reported in our study is much lower and suggests a large underestimation in our data [33]. This is mainly explained by the absence of a systematic screening within our “real world” primary care study population – which is not recommended by any guideline and benefit of which has not yet been studied [34, 35]. With regard to comorbidities and risk factors for secondary gout and hyperuricaemia, our results are comparable to the prevalence and proportions reported in previous studies [3, 6, 16].

Treatment rate of gout patients with ULT ranged among the highest ever reported; similarly high treatment rates were only documented in Germany (84.5%) and France (83%) [3, 14], where for many other countries, for instance the United Kingdom, the United States or Australia, treatment rates of 34%, 40% or 57% were reported [12, 15, 17, 36]. Moreover, besides the treatment rate, treatment success in patients who recorded a SUA before and after treatment initiation with allopurinol was achieved in 36% of cases, and was among the highest reported rates so far in primary care populations (21–40.9%) [12, 14, 15, 17, 36]. Treatment success in patients receiving with febuxostat was even higher, but owing to the small sample size, the result might not be very robust. The regression analysis revealed that female patients were more likely to achieve

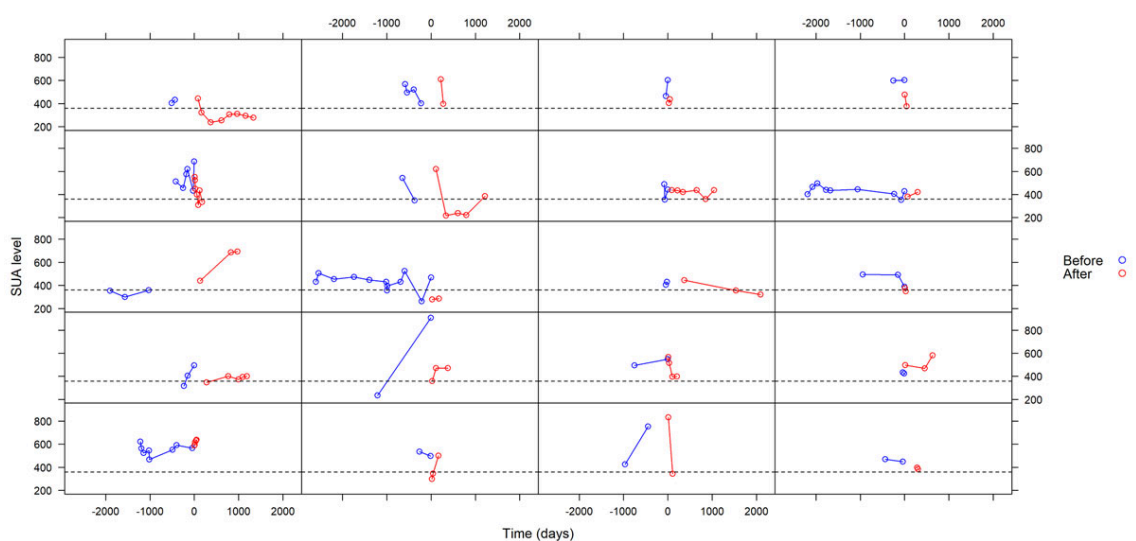
the treatment goal than male patients. This might be partially because female patients started with a lower SUA level than male patients, but it is also known that female patients are generally more closely monitored than male patients [37]. In general, the high treatment success rates in our sample might be influenced by the subgroup identification, which selected the patients most closely monitored.

The high variability in the number of SUA measurements among individual patients and treatment patterns is in line with previous observational studies (9–79% of those diagnosed with gout had at least one SUA measurement) [3, 12, 36]. This high variability persisted, regardless of sex, treatment status and after correction for PCP as a cluster. Even among the subgroup of patients receiving ULT, a uniform and systematic approach via frequent SUA measurements, reflecting monitoring as it is established in many other chronic diseases, could not be detected. Obviously, gout does not receive the same awareness as, for instance, diabetes, and considerable gaps in disease knowledge and education among PCPs and patients exist [38].

### Strengths and limitations

There are a number of limitations that should be considered when interpreting the results of our study. An important limitation of this study is missing information from electronic medical record as we could only assess structured data entries. Data entries such as free text diagnoses are lost. We would like to point out that we cannot exclude the possibility of misclassification within different patient subgroups as the definition of untreated gout was based solely on ICPC2-codes, which were not systematically provided by all PCPs. Therefore, the number of untreated gout cases might be underestimated, which also influences the reported prevalence for gout. The reported prevalence for hyperuricaemia must be considered with caution, as systematic hyperuricaemia screening is lacking in Swiss

**Figure 2:** The variation of SUA measurements among a randomly chosen sample of treated patients (men and women). Blue circles define SUA level measurement before treatment was started. Red circles define SUA level measurements after treatment was started. The zero-point on the timeline is defined as the day when treatment was started. SUA = serum uric acid





primary care and only patients who had a SUA measurement at their PCP's practice could be covered. Further, information on the dosage was not systematically available within our data and hence we could not address treatment aspects concerning the dosage.

On the other hand, our study has some important strengths. First, our sample of PCPs is representative of the Swiss PCP community in terms of gender, but slightly over-represents younger PCPs, PCPs working in group practices in urban settings [23]. Further, the validity of laboratory data is high since they are directly imported from the laboratory machines. Similarly, prescribed drugs are digitally recorded and effectively reflect PCPs' real-life treatment of gout. To our knowledge, we are the first to examine the situation of gout and hyperuricaemia in Switzerland and how patients are treated in the Swiss primary care setting.

## Conclusion

Swiss gout patients received comprehensive treatment, which is reflected in a high number of patients treated with ULT, laboratory tests per person and a high treatment success rate, although there is no systematic approach to the treatment of gout. As gout and hyperuricaemia are among the fastest rising non-communicable diseases, affecting the quality of life of patients tremendously, awareness and knowledge of the need for a systematic approach to patient treatment should be increased.

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## Disclosure statement

The institute of primary care received an unrestricted grant from Menarini AG. The author(s) declared no other potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Data sharing statement

The data are gathered within the ongoing FIRE project. Additional data that are regularly gathered are stored in the FIRE database. The FIRE database can be accessed at any time by the scientific team of the institute. For external requests, access has to be requested from the head of the institute.

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## Appendix 1

## Supplementary tables

**Table S1:** Details of definitions to identify comorbidities.

Alcohol abuse	ICPC-2 = 'P15 P16' OR ATC = 'N07BB01'
Obesity	ICPC-2 = T83 OR BMI $\geq 25$ and $< 30$ THEN 'overweight' ICPC-2 = T82 OR BMI $\geq 30$ THEN 'obese'
Hypertension	ICPC-2 = 'K8[5–7]' OR ATC = 'C02 C03A C03EA01 C07 C08 C09A C09B C09C C09D' OR $\geq 2$ prescriptions in $\geq 6$ months OR BDSYST $\geq 140$ (at least twice)
Diabetes	ICPC-2 = (T89, T90) OR (ATC IN ('A10 ABX') OR HbA1c $> 6.5\%$ )
Dyslipidaemia	ICPC-2 = T93 OR (ATC = C10A AND $\geq 2$ prescriptions in $\geq 6$ months) OR triglyceride $> 1.7$ mmol/l OR total-cholesterol $> 4.9$ mmol/l OR LDL-cholesterol $> 3$ mmol/l OR (sex = 'female' AND HDL-cholesterol $\leq 1.2$ mmol/l) OR (sex = 'male' AND HDL-cholesterol $\leq 1$ mmol/l)
Cardiovascular diseases	ICPC-2 = 'K74 K75 K76 K77 K78 K79  F83 K89 K90 K91 K92'

**Table S2:** Details of definitions to identify risk factors.

<b>Increasing serum uric acid production</b>	
Psoriasis	ICPC-2 = 'S91'
Myeloma, lymphoma	ICPC-2 = 'B7[2–4]'
Solid tumours	ICPC-2 = A79   D7[4–8]   L71   N74   R8[4, 5]   X7[5–7]   Y77'
Cytotoxic therapy	ATC = 'L04   L01D   A12AA05   C04AC   V06DC02   C10AD   C10BA01   C04AC01   C10AD02   C10AD52   G04CB   G03FA05   G03BA02   G03EK01   G03EA01   G03BA03   G03EA02   A12AA06   B05CA08   D08AA01   A12CC06   B05XA15'
<b>Decreasing serum uric acid excretion</b>	
Chronic kidney disease stage 3a and higher	GFR (CKD-EPI) $\leq 60$ AND before OR after 30 days of inclusion
Congestive heart failure	ICPC-2 = 'K77'
Diuretics	ATC = C03   C02L   C07C   C07D   C08G   C02LA   C02LB   C02LC   C02LE   C02LF   C02LG   C02LK   C02LL   C02LN   C02LX   C07CA   C07CB   C07CG   C07DA   C07DB   C08GA   C09BA   C09DA   C08GA02   C07CB03 C07CB53   C07DB01   C09DA09   C09BA07   C02LA07   C07CA17   C09DA06   C09BA01   C09BA08   C02LC01   C02LC51   C02LA50   C09BA12   C02LA03   C02LG01   C02LG51   C09BA02   C09DA02   C09DA10   C09BA09   C02LF01   C02LG02   C09DA04   C07CG01   C09BA03   C09DA01   C02LA04   C02LB01   C07CB02   C09BA13   C02LC05   C08GA01   C07CA02   C02LL01   C07CA23   C09BA04   C02LG03   C02LG73   C02LX01   C07CA03   C02LE01   C09BA06   C09BA05   C02LA08   C02LA02   C02LA52   C02LA01   C02LA51   C02LA71   C02LA09   C09DA07   C07DA06   C09DA03   C02LK01   C09BA15
Laxatives	ATC = 'A06AD'
Ethambutol, pyrazinamide	ATC = 'J04AK02 J04AK01'
Aspirin	ATC = 'B01AC06'
Levodopa	ATC = 'N04BA'