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Cardiovascular risk in patients with new gout: should we reclassify the risk?

M. Gamala[1,2], J.W.G. Jacobs[1], S.P. Linn-Rasker[3], M. Nix[4], B.G.F. Heggelman[4], P.C.M. Pasker-de Jong[5], J.M. van Laar[1], R. Klaasen[3]

[1]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, The Netherlands; [2]Department of Rheumatology, Northwest Clinics, Alkmaar and Den Helder, The Netherlands; [3]Department of Rheumatology, Meander Medical Center Amersfoort, The Netherlands; [4]Department of Radiology, and [5]Meander Academy, Meander Medical Center Amersfoort, The Netherlands.

Mihaela Gamala
Johannes W.G. Jacobs
Suzanne P. Linn-Rasker
Maarten Nix
Ben G.F. Heggelman
Pieternel C.M. Pasker-de Jong
Jacob M. van Laar
Ruth Klaasen

Please address correspondence to:
Mihaela Gamala, MD,
Department of Rheumatology and Clinical Immunology,
University Medical Center Utrecht,
Box 85500,
3508 GA Utrecht, The Netherlands.
E-mail: m.gamala@umcutrecht.nl

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ABSTRACT

Objective. *Chronic inflammation, as seen in gout, may contribute to an increased risk of developing cardiovascular (CV) events (CVE). The aim of the study was to explore the effect of adding gout as a chronic inflammatory disease to the Dutch SCORE, a tool predicting 10-year CV mortality and morbidity.*

Methods. *This was a cross-sectional substudy including new patients with gout according the 2015 EULAR/ACR classification criteria who had participated in a trial on diagnostic accuracy of DECT with mono or oligoarthritis. Patients underwent a structured CV consultation, including assessment of CVE-history and of CV risk factors with the Dutch risk prediction SCORE. Chi-square test for trends was used to test for significance reclassification of the CV risk before and after adding gout to the Dutch SCORE.*

Results. *Seventy-six gout patients were included. SCORE was applied in 60 patients; 16 patients had experienced a prior CVE. The 10-year risk scores without gout as risk factor were high in 29 patients (48.3%), moderate in 6 (10%) and low in 25 (41.7%); with gout, the risk of 23/60 patients (38.3%) was reclassified from low to moderate in 6 patients (10%), from low to high in 11 (18.3%) and from moderate to high in 6 (10%), p<0.001 for trend.*

Conclusion. *Adding gout to the risk prediction tools led to significant and clinically relevant reclassification of CV risk in new gout patients. Studies with large follow-up are warranted to validate these findings.*

Introduction

It is well established that gout is associated with an increased risk of cardiovascular disease (CVD) (1, 2) and likely relates to persistent inflammation (3, 4). As inflammation present in chronic diseases such as rheumatoid arthritis (RA), gout, diabetes is a contributor to the hallmark oxidative stress associated with most CVD (5), gout would be a CV risk factor comparable to RA and diabetes. In a study in new gout patients (6), those initially not classified as 'very high' risk underwent carotid ultrasound; 56% had their risk upgraded, and 46% moved in the *very high* risk stratum, based on atheroma plaque. The European League Against Rheumatism recommends treating gout as soon as possible after diagnosis to prevent gout attacks, and possibly cardiovascular events (CVE) (7).

In the Dutch SCORE (5), a modification of the Systematic Coronary Risk Evaluation (SCORE), estimating the 10-year risk of fatal and nonfatal CVD (6), RA is a risk factor because of its chronic inflammatory action, but gout is not.

The objective of this study was to explore the theoretical effect of adding gout as risk factor to the Dutch SCORE for patients with gout.

Methods

Study subjects

Seventy-six patients from a study on accuracy of dual energy-CT (DECT) with undifferentiated mono and oligoarthritis (1–3 swollen joints) who were classified with gout according the 2015 EULAR/ACR gout classification criteria (8), between 1 April 2016 and 30 September 2018 at the Rheumatology outpatient clinic of the Meander Medical Center, The Netherlands, were included in the current substudy. The study was conducted according to the ethical principles of the declaration of Helsinki and approved by the Medical Research Ethics Committee - United on research involving human subjects (MEC-U) at Nieuwegein, the Netherlands and is registered at the trial register of the Netherlands (NTR) with number 5826 and at the ClinicalTrials.gov with number NCT03038386. All included subjects provided informed consent.

Material and methods

Gender, age, body length and weight, joint symptom duration, conventional CV risk factors (CRF), CVE (via review of medical records), and serum urate levels) were assessed; for details, see Supplementary Table S1.

Gout classification criteria

These criteria consist of clinical symptoms and signs, detection of urate cristals in joint fluid and DECT results (8). Testing of Syncytial Fluid (SF) with polarisation microscopy was performed

on all samples. Two experienced rheumatologists performed this examination within one hour of sample acquisition. A definite diagnosis of crystal proven gout was made if needle-shaped, negatively birefringent crystals were seen (9), For DECT, subjects were scanned within 6 weeks of joint aspiration. Scans of index joint and, in addition, of hands/wrists, feet/ankles, and knees, all bilaterally, were performed. The technical details of our imaging method have been described elsewhere (10). A radiologist who was blinded to the subject's polarisation microscopy results evaluated the images. The radiologist excluded artefacts known to produce green pixels near a joint: *e.g.* nail beds and metal prostheses, before classifying DECT results as positive or negative.

Cardiovascular risk assessment

The 10-year CV risk was calculated using the Dutch SCORE table (11), which uses gender, age, smoking status, SBP, the TC:HDL ratio and rheumatic disease (rheumatoid arthritis). In this score, patients with a prior CVE are automatically classified as having the highest risk, and for patients over 70 years the score of a 70-year-old patient is calculated. To account for RA or diabetes as risk factor, the Dutch CVRM guideline adds 15 years to the actual age to calculate the 10-year CV risk. A risk <10% is classified as low, 10–20% as intermediate and ≥20% as high. Risk scores were calculated separately without gout and after adding gout to the algorithm, based on hypothesis that gout is an independent risk factor for CVE, with an overall impact similar to that of RA or diabetes. According to the Dutch CVRM guideline, preventative treatment with an antihypertensive drug or statin is indicated in high risk patients with a systolic blood pressure >140mmHg or an LDL>2.5 mmol/l.

In addition, the 10-year CV mortality risk was calculated using the European Systematic Coronary Evaluation (SCORE), stratified as low (<1%); moderate (1-4%); high (5–9%) and very high (>9%) (12).

Statistical analysis

Standard descriptive statistics were used: numerical data are given as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) in case of skewed distribution, and categorical variables as frequencies and percentages. Chi-square trend test was used to compare the CV risk stratification before and after adding gout to the risk tool. Differences in patient characteristics between reclassified and non-reclassified patients were assessed through Student-t, Mann-Whitney U, dependent of normal distribution or not, and chi-square, or Fisher's exact tests. Statistical analyses were performed using SPSS for Windows, v. 22.0 (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was considered as statistically significant.

Results

Seventy-six patients with new gout according to the EULAR/ACR 2015 classification criteria were included; patients' characteristics are summarised in Table I. Median symptom duration suggestive of intermittent gout was 12 month (IQR 0.7–48). Fifty-three (70%) subjects had MSU crystal proven gout. Sixty-four (84%) subjects had a positive DECT result.

Table I. Characteristics of included patients

	Total (n=76)
Age in years, mean (SD)	61.4 (14.3)
Male	63 (82.9)
BMI, kg/m^2, mean, SD	28.7 (3.7)
CV risk factors present	
Hypertension	42 (55.3)
Diabetes mellitus	13 (17.1)
hypercholesterolaemia	64 (72)
Smoking habit (n=73)	9 (12)
History of CV disease	
Coronary heart disease	8 (10.5)
Peripheral artery disease	2 (2.6)
Stroke	6 (7.8)
GFR <60 ml/min	10 (13.1)
Use of medication	
diuretics	19 (25)
treatment for hypertension	37 (48.7)
hypolipidaemic treatment	33 (43.4)
antidiabetic treatment	10 (13.2)
Lipid spectrum	
TCh, mmol/l, mean (SD)	5 (1.2)
TG, mmol/l, median (IQR)	1.9 (1.5-2.7)
HDL, mmol/l, mean (SD)	1.7 (0.3)
LDL, mmol/l, mean (SD)	3 (0.9)
Urate burden	
serum urate, mmol/l, mean (SD)	484.1 (95.1)

Data shown as n (%) unless otherwise specified. BMI: body mass index, calculated as weight:(height)^2; CV: cardiovascular; GFR: glomerular filtration rate; HDLc: high-density lipoprotein cholesterol; LDLc: low-density lipoprotein cholesterol; SUA: serum uric acid; TCh: total cholesterol; TG: triglycerides; DECT: dual-energy computed tomography.

CV risk stratification

The Dutch SCORE was applied to 60 patients (79%) as all other 16 patients (21%) had a history of CVE, classifying them in the highest risk score, which prohibits reclassification. Median risk score was 18% (IQR 6–34%). The 10-year risk scores were high in 29/60 patients (48%), moderate in 6 (10%) and low in 25 (42%). After adding gout as risk factor, the risk of 23/60 patients (38%) was upgraded: from low to moderate in 6 patients (10%), from low to high in 11 (18%) and from moderate to high in 6 (10%). Figure 1 shows the CV risk reclassification, which is statistically significant (p<0.001 for trend test); before reclassification, 29/60 patients (48%) were at high CV risk level and after reclassification, 46/60 patients (77%).

The patients with CV risk reclassification had a significantly higher BMI (p=0.04), used antihypertensive and hypolipidaemic drugs less frequently (p=0.02 and 0.04, respectively) and were significantly younger (p=0.01). Frequency of diabetes, smoking habits and lipid levels did not differ significantly between the reclassified en not reclassified patients group (for details see Suppl. Table S2). According to the European SCORE, the 10-year CV mortality risk score was very high in 3/60 patients (5%), high in 15/60 patients (25%), moderate in 34/60 patients (57%) and low in 8/60 patients (13%). After adding gout as risk factor, by multiplying the score by 1.5 according to guidelines (13), the risk of 23/60 patients (38%) was reclassified: from moderate to high in 11 patients (18%), from high to very high in 12 (20%).

Discussion

After adding gout as risk factor to the Dutch SCORE, 23/60 (38%) of patients with new gout according to the 2015 EULAR/ACR classification criteria had their CV risk upgraded; 17/60 (28%) of the patients moved into the high-risk class. The patients group who did not

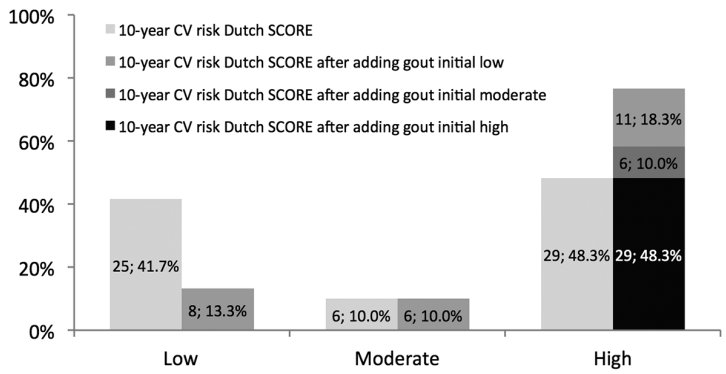

Fig. 1. Cardiovascular (CV) risk stratification of included new diagnosed gout patients.
Left light grey bars in each category show the risk before adding gout to the Dutch SCORE, while right dark grey bars show the CV risk after adding gout to the Dutch SCORE, mentioning how many patients moved in a higher category.
Data shown as number of patients per each subgroup and percentage of total sample.

have their risk upgraded used antihypertensive and hypolipidaemic treatment more often, lowering the risk of presence of the traditional CV risk factors, *i.e.* hypertensive and hyperlipidaemic states, respectively. The non-reclassified patients were also older; an explanation is that in the higher risk group before reclassification, patients predominantly were old, prohibiting many older patients to be upgraded more (ceiling effect). Our results that the Dutch SCORE classifications were upgraded when including gout as risk factor corroborate with the results of SCORE for the 10 year CVE mortality risk, when taking gout as risk factor into account.

In another study in patients with new gout diagnosis (6), 142 patients not initially classified as *very high* risk underwent carotid ultrasound; 80 (56%) had their risk upgraded, 66 (46%) moved in the *very high* risk stratum, based on atheroma plaques.

Our findings indicate that if gout is a CV risk factor comparable to RA, the consequences are clinically very relevant; our findings reinforce the recommendation to screen gout patients at diagnosis. The goal is to prevent the onset of CVE in patients with gout.

There are limitations to our study. First, the relatively small sample size with relatively low statistical power and the cross sectional design. Second, our study was based on the hypothesis that gout is an independent risk factor for CVE, with an overall impact similar to that of RA and diabetes (14). A long-term prospective study after the diagnosis of gout assessing the incidences of CVE and validating the reclassification would be warranted.

A strength of our study is that we highlighted the clinical relevance of considering gout as CV risk factor comparable to RA in patients with new gout diagnosis.

In RA patients in whom CVD risk is substantially elevated compared with the general population (15), anti-rheumatic treatment lead to switch in CV risk category and preventive treatment advice in 13% of the patients in a recent study (16). The presence of gout should alert physicians to screen, diagnose, and promptly treat cardiovascular risk factors (hypertension, hyperlipidaemia) in addition to treat gout early.

Conclusion

Adding gout as risk factor to the Dutch risk prediction tool leads to relevant reclassification of CV risk. Studies with large follow-up are warranted to validate our results.

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