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Original article

Gout and rheumatoid arthritis, both to keep in mind in cardiovascular risk management: A primary care retrospective cohort study

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ABSTRACT

Objectives: To assess in one time window cardiovascular risks for both patients with gout and patients with rheumatoid arthritis in a Dutch primary care population.
Methods: Retrospective matched cohort study with data from the electronic health records of 51 Dutch general practices. Participants were patients aged 30 years or older with an incident diagnosis of gout ($n=2655$) or rheumatoid arthritis ($n=513$), and matched non-disease controls ($n=7891$ and $n=1850$ respectively). At disease incidence date, patients and controls were compared for prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and prior cardiovascular diseases. Patients without prior cardiovascular disease were followed for a first cardiovascular disease, and compared to controls using Kaplan-Meier survival curves and Cox proportional hazard analyses.
Results: Compared to controls, gout patients suffered more from hypertension (44.8%), diabetes (20.1%), hypercholesterolemia (13.7%), and prior cardiovascular disease (30%) ($P<0.01$), whereas rheumatoid arthritis patients (hypertension 28.5%; diabetes 11.7%; hypercholesterolemia 7.4%; prior cardiovascular disease 11.3%) did not ($P>0.05$). After adjustment, both gout and rheumatoid arthritis patients without prior cardiovascular disease were more likely to get a cardiovascular disease: hazard ratio (95% confidence interval) 1.44 (1.18 to 1.76), and 2.06 (1.34 to 3.16) respectively.
Conclusions: This primary care study indicates that gout and rheumatoid arthritis are both independent risk factors for cardiovascular diseases, rheumatoid arthritis to some greater extent, whereas gout patients at first diagnosis had already an increased cardiovascular risk profile. It gives strong arguments for implementation of both rheumatic diseases in primary care guidelines on cardiovascular risk management.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death, with more than 17 million deaths per year, and a major cause of disability worldwide [1]. Therefore, case finding, screening and management of CVD needs continuous attention in daily medical practice. This applies particularly to primary health care, where patients at risk for CVD have easily access to physicians or other health workers who can manage these risks, in general or more specifically according to guidelines.

Gout, an auto-inflammatory joint disease and also considered a systemic and metabolic disorder [2], has been linked to CVDs [2,3]. It is the most prevalent inflammatory joint disease, with an estimated increasing prevalence of at least 1–2% in the general and 3–4% in the adult population [2,4]. Gout is a very painful disease characterized by joint redness, recurrent course, and involvement of the metatarso-phalangeal joint of the first toe as most affected site [2,5]. It is caused by intra-articular deposition of monosodium urate (MSU) crystals, which can be identified as the gold standard for the diagnosis by microscopic investigation of synovial fluid aspirated from the affected joint [5,6]. Despite its strong link with CVD, gout has hardly been implemented in general or specific primary care cardiovascular risk management (CVRM) as a factor to pay continuous attention to. As the severe pain will urge almost every gout patient to consult a physician and considering that ca. 90% of the patients with gout are managed in primary care [7], general practitioners (GPs) can easily identify without special efforts the vast majority of them for subsequent involvement in regular care [8]. Opposite to gout, rheumatoid arthritis (RA), another inflammatory but autoimmune systemic joint disease with a painful chronic

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course [9], which showed to be also a risk factor for CVDs [10–14], has already a certain established status in CVRM in primary and secondary care guidelines with a weight equally to diabetes [15]. However, despite this status, its independent association with CVD has not yet been confirmed in a primary care population.

If gout turns out to be a substantial risk factor for CVD in a comparable degree to RA, implementing it in CVRM possibly with the same status as RA currently has, should be considered seriously. Gout with its high and increasing prevalence, much higher when compared to RA [16], implies absolutely many patients [4,17], and implementing it in CVRM might have in that case substantially beneficial impact on the total prevention of CVD and its burden for society [3].

This study aimed to assess the cardiovascular risk profile in primary care patients from the same population with an incident diagnosis of gout or RA, and the independent association of these rheumatic diseases with a first future CVD during one time window.

2. Methods

2.1. Design, setting and data source

We designed a retrospective cohort study to assess the prevalence, the incidence and the independent risk of CVD in primary care patients aged over 30 years with gout or RA, by comparing them with matching controls. The study was conducted with data from the General Practitioner Database (GP Database) of the Department of Primary and Community Care at the Radboud University Medical Center, Nijmegen. This database contains patients' demographic, and GPs' diagnosis and management information from electronic health records of general practices in the Eastern part of the Netherlands. All patients' encounters are coded as diagnoses according to the International Classification of Primary Care (ICPC), expanded with the Dutch ICPC sub-codes [18]. These diagnoses provide a good indication of the health status of the Dutch general population, because almost all inhabitants in the Netherlands are registered with a general practice, with the GP acting as "gatekeeper" for referral to secondary health care.

Practices were included if follow-up data from gout or RA patients were available during the study period from 1st January 2008 till 28 February 2014. Extracted data for this study were age, sex, practice, studied diseases, starting date of the disease, date of practice registration or deregistration, and date of death.

2.2. Patient and control selection

Patients were selected for study inclusion if they had an ICPC code for gout (T92) or RA (L88 or L88.01) during the study period. At the incidence date of gout (start of the disease), i.e. the matched index date, a maximum of four controls without gout was included for each patient, matched for sex, age and practice. The same procedure was done to include controls for the RA patients, leading to two separate study groups, first a gout patient group with matched non-gout controls, and later, a RA patient group with matched non-RA controls. After that, we selected from these groups subjects who were free of prior CVD at the incidence or index date (baseline) for follow-up.

2.3. Outcome measures

Outcomes were incidence dates of the first CVD, defined as diseases with an atherothrombotic pathophysiology, including angina pectoris (AP; K74-74.02), myocardial infarction (K75, K76-76.02), heart failure (HF; K77-77.02), transient ischemic accident (K89), cerebral vascular accident (K90, K90.02-90.03), peripheral arterial disease (K92-92.01) and aortic aneurysm (K99-99.01). Hypertension (K86-87), diabetes mellitus (T90-90.02), and hypercholesterolemia (T93-93.01, T93.03), proven risk factors for CVD, were included as possibly confounding comorbidities. When the incidence date of an included disease was missing, it was set before the index date.

2.4. Statistical analysis

Patients of the groups formed at the first step were compared with their respective non-disease controls for age, sex, presence of hypertension, diabetes, hypercholesterolemia, and prior CVD, using independent samples *t*-test for continuous variables and Chi^2 analysis for categorical variables. The same comparisons were done for the subjects without prior CVD. For them, occurrence of any CVD (real end-point), practice deregistration, death by any cause or reaching end of follow-up (censored end-points) were assessed and crudely evaluated by Kaplan-Meier survival curves using log rank tests. Beside any CVD (pooled outcome), occurrence of separate CVDs was also assessed. For gout and RA patients, the crude incidence density rate (IDR) of CVD as pooled outcome was calculated by dividing the number of new cases of CVD in the first follow-up year by the sum of follow-up time of all patients during a 1-year period after index date, and expressed per 1000 patient-years with a 95% confidence interval (95% CI). Cox proportional analysis of the real end-point was performed with adjustment for age, sex, and comorbidities hypertension, diabetes, and hypercholesterolemia. All comorbidities recorded at the index date as well as during follow-up but before any end-point, were included. The results both for gout and RA were expressed as hazard ratios (HR) with 95% CI. Additional analyses were done for possible interactions of gout or RA with age, sex or comorbidities. In all analyses, statistical significance was set at a two-sided *P*-value ≤ 0.05. Analyses were performed using IBM SPSS Statistics version 20 as statistical package.

3. Results

3.1. Patients and characteristics

As first step, 2655 patients with gout, 7891 non-gout controls, 513 RA patients, and 1850 non-RA controls were selected from 51 practices. Next, subjects with prior CVD were excluded, leaving 1859 gout patients with 6334 non-gout controls, and 455 RA patients with 1607 non-RA controls for follow-up.

Gout patients without exclusion of prior CVD (Table 1) were mostly male (66.9%), whereas RA patients were mostly female (65.3%). Gout patients (mean age: 62.5 year; SD: 14.1) suffered more from hypertension (44.8%), diabetes (20.1%), hypercholesterolemia (13.7%) and prior CVD (30.0%) at the index date when compared with controls, while RA patients (mean age: 59.2 years;; SD: 14.8) did not (hypertension: 28.5%; diabetes: 11.7%; hypercholesterolemia: 7.4%; and prior CVD: 11.3%). Excluding patients with prior CVD (Table 2) did not change gender difference between gout and RA patients. Prevalence at the index date of hypertension (38.8%), diabetes (14.6%), and hypercholesterolemia (10.4%) was still higher in gout patients compared to their controls, which was, again, not seen in RA patients.

3.2. Occurrence of CVD

After a mean follow-up time of 29.8 months (SD: 20.2), 8.3% of gout patients ($n = 154$) developed a first CVD, versus 5% non-gout controls ($n = 318$) after a mean time of 26.8 months (SD: 19.9). A percentage of 7.7 of RA patients ($n = 35$) developed a CVD versus