Duration of psoriatic arthritis as a risk factor for myocardial infarction

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Published in:
Rheumatology advances in practice

DOI:
10.1093/rap/rky011

Publication date:
2018

Document version
Final published version

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Citation for published version (APA):
Egeberg, A., Skov, L., Hansen, P. R., Gislason, G. H., Wu, J. J., Thyssen, J. P., & Mallbris, L. (2018). Duration of psoriatic arthritis as a risk factor for myocardial infarction. Rheumatology advances in practice, 2(1), [rky011]. https://doi.org/10.1093/rap/rky011

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Download date: 08. May. 2020
Objective
The aim was to examine the association between disease duration and risk of myocardial infarction (MI) in patients with PsA.

Methods
We used nationwide registry data from Denmark to estimate incidence rates per 1000 person-years and the risk of MI [adjusted hazard ratios (HRs) with 95% CIs] in rheumatologist-diagnosed patients with PsA using Cox regression models. The study period was between 1 January 2008 and 31 December 2012.

Results
The study population comprised a total of 8071 patients with PsA and 4 348 857 general population control subjects. A total of 156 and 54 215 MIs occurred during follow-up among patients with PsA and the reference population, respectively. There was a significant association between the duration of PsA and risk of MI (adjusted HR = 1.02; 95% CI: 1.01, 1.03 for each additional year after PsA diagnosis). Stratified based on short (<2 years) and long (>2 years) disease duration, the adjusted HRs were 0.96 (95% CI: 0.60, 1.52; \( P = 0.8487 \)) and 1.29 (95% CI: 1.09, 1.53; \( P = 0.0026 \)), respectively. Other significant predictors included age, sex, socio-economic status, smoking, alcohol abuse, diabetes, hypertension and previous cardiovascular disease.

Conclusions
We observed an increased risk of MI associated with longer duration of PsA. Our findings call for increased focus on disease duration in the cardiovascular risk assessment among patients with PsA.

Key words: psoriatic arthritis, myocardial infarction, cardiovascular risk, epidemiology

Introduction
PsA is a chronic inflammatory arthropathy that is frequently associated with skin and/or nail psoriasis. In recent years, cutaneous psoriasis has been associated with increased risk of cardiovascular disease (CVD), in particular myocardial infarction (MI) [1]. However, data on the relationship between PsA and MI are less clear cut [2, 3]. Chronic systemic inflammation in psoriasis
Studies in Epidemiology recommendations [9]. The Danish health-care system is tax supported and provides access to general practitioners, specialists in private clinics and public hospitals for all citizens without charge. A permanent and unique civil registration number is given to each resident upon birth or migration. This number allows for unambiguous linkage at an individual level of a range of administrative registries and clinical databases [10–13]. This allows for complete and accurate information on all health-care consultations (e.g. diagnoses), pharmacy-dispensed prescriptions, vital statistics and socio-economic status. Data are encrypted and rendered anonymous when used for research purposes. Diagnoses are coded as International Classification of Diseases (ICD) codes, and pharmacotherapy according to the Anatomical Therapeutic Chemical classification. Hospital-administered pharmacotherapy is coded as treatment procedure [SundhedsvI`senets Klassifikationssystem (SKS)] codes. The majority of prescriptions in Denmark are claimed at pharmacies; however, certain drugs, for example, systemic immunosuppressant agents (including biologics and MTX) are predominantly given directly from hospital clinics.

The present study comprised all adults (≥18 years) alive and resident in Denmark on 1 January 2008 (i.e. the study start date). All individuals were followed from the start of the study until 31 December 2012, death, migration or the occurrence of an end point, whichever came first. Patients were classified as having PsA if they had received a diagnosis (inpatient or ambulatory) of PsA (ICD-10 M07.0-3 or ICD-8 696.09) before the start of the study.

**Methods**

**Data sources and study population**

Study approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015; int. ref. GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for registry studies in Denmark. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology recommendations [9].

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**Pharmacotherapy, co-morbidity and socio-economic status**

We identified baseline pharmacotherapy 6 months before study inclusion for the following therapies: adalimumab, cholesterol-lowering drugs, ciclosporin, etanercept, infliximab, LEF, MTX, SSZ and systemic CSs. Certolizumab pegol, ustekinumab and golimumab were not marketed in Europe at the time of study initiation and were thus not included. We assessed baseline co-morbidity as those of the following conditions that occurred in the 5-year period before study inclusion: alcohol abuse, CVD, diabetes and hypertension. Cardiovascular disease was defined as a composite of selected medical conditions and revascularization procedures as previously described [14]. Diabetes was defined by either ICD-code or use of glucose-lowering drugs. Collection of data on hypertension, smoking and alcohol abuse has been described elsewhere [15–17]. Socio-economic status was calculated as age-standardized quintiles of the average 5-year gross annual income at baseline.

**Statistical analysis**

SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The duration of PsA was calculated as the time difference between PsA onset and study start. Incidence rates were summarized per 1000 person-years, and Cox regression analyses were performed to estimate hazard ratios (HRs). In multivariable models, we adjusted for age, sex, socio-economic status, cholesterol-lowering drugs, smoking, alcohol abuse, diabetes, hypertension and CVD, respectively. We performed separate analyses, in which patients with previous MI were excluded. Sensitivity analyses were performed, with additional adjustment for use of systemic anti-PsA treatment and duration of cutaneous psoriasis, respectively. Patients were stratified based on whether they had PsA for <2 years (‘short duration’) or ≥2 years (‘long duration’). This cut-off has been established previously [18]. Model assumptions, including the linearity of continuous variables, absence of interactions and the proportional hazards assumptions, were tested and found to be valid unless otherwise specified. The proportional hazards assumptions were tested through significance tests and graphically assessed using log–log plots. Statistically significant results were defined as those with P < 0.05, and we report results with 95% CIs were appropriate.

**Results**

The study population comprised a total of 8071 patients with PsA and 4 348 857 general population control subjects (Table 1). Among patients with PsA, there was a slight (56%) female predominance, whereas the reference population had an equal gender distribution. Patients with PsA were slightly older (mean age 54.7 vs 48.7 years) at
baseline and had a mean disease duration of 8 years. The prevalence of CVD, alcohol abuse, smoking and hypertension, respectively, was higher among patients with PsA, and a greater proportion of PsA patients had received systemic treatment within the last 6 months before the start of the study compared with the reference population. Among patients with concurrent cutaneous psoriasis, the mean (s.d.) disease duration was 9.2 (7.7) and 4.3 (6.6) years for patients with PsA and the reference population, respectively.

A total of 156 PsA patients and 54,215 control subjects experienced a MI during the study period. The incidence rates per 1000 person-years were 4.06 and 2.61 among patients with PsA and the reference population, respectively. Stratified by disease duration, the incidence rates were 2.15 and 4.59 among patients with short duration and long duration, respectively (supplementary Table S1, available at Rheumatology Advances in Practice online).

There was a significant association between the duration of PsA and the risk of MI in crude (HR = 1.05; 95% CI: 1.04, 1.06) and adjusted (HR = 1.02; 95% CI: 1.01, 1.03) analyses, respectively (Fig. 1). Stratified based on short and long disease duration, the adjusted HRs were 0.96 (95% CI: 0.60, 1.52; \( P = 0.8487 \)) and 1.29 (95% CI: 1.09, 1.53; \( P = 0.0026 \)) respectively. When patients with previous MI were excluded, that is, in analyses of first-time MI, the adjusted HR of MI associated with an additional year of disease duration was 1.02 (95% CI: 1.00, 1.03; \( P < 0.05 \)). In analyses stratified based on short and long disease duration, the adjusted results were 0.99 (95% CI: 0.61, 1.62; \( P = 0.9737 \)) and 1.29 (95% CI: 1.07, 1.55; \( P = 0.0085 \)) (Table 2). The results were not significantly altered by adjustment for systemic anti-PsA treatment (adjusted HR = 1.02; 95% CI: 1.01, 1.03) or the duration of cutaneous psoriasis (adjusted HR = 1.02, 95% CI: 1.00, 1.03; \( P < 0.05 \)), respectively. Other significant predictors of MI included older age, male sex, low socio-economic status, hypertension, diabetes, smoking, alcohol abuse, diabetes and previous CVD (supplementary Table S2, available at Rheumatology Advances in Practice online).

**Discussion**

In this nationwide study of the Danish population, we observed a significantly increased risk of MI associated with the duration of PsA. Our results remained consistent in adjusted models and suggest that disease duration might be an easily obtainable risk marker when evaluating cardiovascular risk in patients with PsA, and possibly also in other inflammatory diseases. Traditional established MI risk factors, such as age, sex and lifestyle factors, were also significantly associated with the risk of MI, supporting the robustness of our findings.

Data suggest that cutaneous psoriasis lesions manifests on average 10 years before development of PsA [19]. Consequently, epidemiological studies tend to identify patients with a shorter duration of PsA...
Comparison of disease duration for the risk of CVD [5–8]. On studies of RA and diabetes have highlighted the importance of disease duration for the risk of CVD [5–8]. We previously found increased CVD risk [20], whereas a larger study found a significantly increased risk of CVD associated with duration of psoriasis [14].

Contrasting the present findings, one previous study [21] failed to find an association between disease duration and the extent of atherosclerosis among patients with PsA, albeit that only 44% of patients were seen in the clinic within the first 2 years after the diagnosis. Certain limitations apply to the interpretation of our study results, the most important being the observational nature of our data. Indeed, observational studies cannot establish a causal relationship, and although our results are biologically plausible and remained consistent in a number of sub-analyses, the results should be considered hypothesis generating. Moreover, it is likely that some patients might not seek medical treatment in very early and mild stages of PsA, leading to an underestimation of the disease duration. We did not include adjustment for NSAIDs because these are also available over the counter in Denmark. Lastly, we lacked data on obesity/BMI and on clinical and radiographic findings, and whether differences in PsA severity might have affected our results remains unclear.

In conclusion, we observed an increased risk of MI associated with a longer duration of PsA. Our findings call for increased focus on disease duration in CVD risk assessment among patients with PsA.

### Acknowledgements

Author contributions: Drs A.E. and G.H.G. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: A.E. Acquisition, analysis and interpretation of data: all authors. Drafting of the manuscript: A.E. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: A.E. and G.H.G. Obtained funding: A.E. and L.M. Administrative, technical or material support: A.E. and G.H.G. Study supervision: A.E. and G.H.G.

Funding: Dr A.E. has received research funding from Pfizer and Eli Lilly, and honoraria as consultant and/or speaker from Pfizer, Eli Lilly, Novartis, Galderma and Janssen Pharmaceuticals. Dr L.S. has been a paid speaker for Pfizer, AbbVie, Eli Lilly, Novartis and LEO Pharma, and has been a consultant or served on Advisory Boards with Pfizer, AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma and Sanofi. She has served as an investigator for Pfizer, AbbVie, Eli Lilly, Novartis, Amgen, Regeneron and LEO Pharma and received research and educational grants from Pfizer, AbbVie, Novartis, Sanofi, Janssen Cilag and LEO Pharma. Dr P.R.H. is supported by a non-restricted grant from the LEO Foundation and a Borregaard Clinical Scientist Fellowship from the Novo Nordisk Foundation. Dr H.G.H. is supported by an unrestricted research scholarship from the Novo Nordisk Foundation. Dr J.W.J. is an investigator for AbbVie, Amgen, Eli Lilly, Janssen, Novartis and Regeneron. Dr J.P.T. is supported by an unrestricted grant from the Lundbeck Foundation and has attended advisory boards for Roche and Sanofi-Genzyme, and been a speaker for LEO Pharma. Dr L.M. is a full-time employee of Eli Lilly and Company and owns stock.

Declaration Statement: The funding sources participated in interpretation of the final analysed study results, but had no access to the raw data, and did not participate in data collection, management or analysis.

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| TABLE 2 Risk of myocardial infarction in patients with PsA |
|-----------------------------------------------------------|
| Risk of myocardial infarction (including patients with previous myocardial infarction) | Crude HR (95% CI) | P-value | Adjusted* HR (95% CI) | P-value |
|-----------------------------------------------------------|-------------------|---------|----------------------|---------|
| Duration of PsA, per year 1.05 (1.04, 1.06) | <0.0001 | 1.02 (1.01, 1.03) | 0.0038 |
| Duration < 2 years 0.82 (0.52, 1.31) | 0.4084 | 0.96 (0.60, 1.52) | 0.8487 |
| Duration ≥ 2 years 1.76 (1.49, 2.08) | <0.0001 | 1.29 (1.09, 1.53) | 0.0026 |
| Risk of first-time myocardial infarction | | | | |
| Duration of PsA, per year 1.05 (1.03, 1.06) | <0.0001 | 1.02 (1.00, 1.03) | 0.0131 |
| Duration < 2 years 0.88 (0.54, 1.44) | 0.6173 | 0.99 (0.61, 1.62) | 0.9737 |
| Duration ≥ 2 years 1.71 (1.41, 2.06) | <0.0001 | 1.29 (1.07, 1.55) | 0.0085 |

*Adjusted for age, sex, socio-economic status, cholesterol-lowering drugs, smoking, alcohol abuse, diabetes, hypertension and previous cardiovascular disease. HR: hazard ratio.
Supplementary data

Supplementary data are available at Rheumatology Advances in Practice online.

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