



Duration of psoriatic arthritis as a risk factor for myocardial infarction

Egeberg, Alexander; Skov, Lone; Hansen, Peter Riis; Gislason, Gunnar H.; Wu, Jashin J.; Thyssen, Jacob P.; Mallbris, Lotus

Published in:
Rheumatology Advances in Practice

DOI:
[10.1093/rap/rky011](https://doi.org/10.1093/rap/rky011)

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

Document license:
[CC BY-NC](https://creativecommons.org/licenses/by-nc/4.0/)

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), 1-5. <https://doi.org/10.1093/rap/rky011>

Concise report

Duration of psoriatic arthritis as a risk factor for myocardial infarction

Alexander Egeberg¹, Lone Skov¹, Peter Riis Hansen², Gunnar H. Gislason^{2,3,4}, Jashin J. Wu⁵, Jacob P. Thyssen¹ and Lotus Mallbris⁶

Abstract

Objectives 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

Key messages

- Risk of myocardial infarction remains poorly understood in patients with PsA.
- Duration of PsA was significantly associated with future risk of myocardial infarction.
- Physicians should enquire about disease duration when assessing cardiovascular risk in patients with PsA.

¹Department of Dermatology and Allergy, ²Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, ³The Danish Heart Foundation, Copenhagen, ⁴The National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark, ⁵Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA and ⁶Eli Lilly and Company, Indianapolis, IN, USA

Submitted 3 November 2017; revised version accepted 4 April 2018

Correspondence to: Alexander Egeberg, Department of Dermatology and Allergy, Herlev and Gentofte Hospital, Kildegårdsvej 28, 2900 Hellerup, Denmark.
E-mail: alexander.egeberg@gmail.com

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

and PsA may hypothetically increase the risk of MI, because cumulative exposure to systemic low-grade inflammation has been associated with atherosclerotic CVD [4]. This suggests that a longer duration of inflammatory disease, such as PsA, might increase the risk of CVD, including MI. Therefore, features such as PsA disease duration, which are easily obtainable by interview or review of the patient history, might identify those at higher risk for CVD. Indeed, a small study of angiographic coronary artery disease in psoriasis, and larger studies in RA and diabetes, have demonstrated that patients with a longer duration of disease have a higher risk of CVD, but these studies were limited to either clinical coronary artery disease or non-population-based methods [5–8]. We therefore examined the effects of PsA duration on the risk of MI in a nationwide cohort study in Denmark.

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].

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 [Sundhedsvisensets 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.

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

TABLE 1 Baseline characteristics of the study population

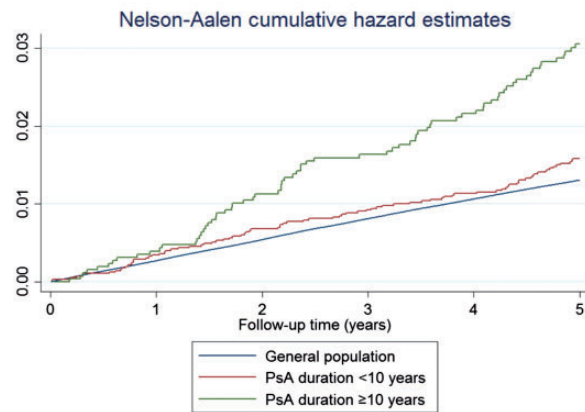
Characteristics	Reference population (n = 4 348 857)	PsA population (n = 8071)
Age, mean (s.d.), years	48.7 (18.0)	54.7 (14.0)
Sex, n (%)		
Women	2 208 599 (50.8)	4517 (56.0)
Men	2 140 258 (49.2)	3554 (44.0)
Duration of PsA, mean (s.d.), years	NA	8.0 (7.0)
Age at disease onset, mean (s.d.), years	NA	46.7 (13.8)
Socio-economic status, n (%)		
Lowest	870 786 (20.0)	743 (9.2)
Below average	869 301 (20.0)	2053 (25.4)
Average	869 276 (20.0)	2071 (25.7)
Above average	869 680 (20.0)	1667 (20.7)
Highest	869 814 (20.0)	1537 (19.0)
Smoking, n (%)	430 808 (9.9)	1316 (16.3)
Co-morbidity, n (%)		
Alcohol abuse	60 779 (1.4)	145 (1.8)
Cardiovascular disease	378 124 (8.7)	1252 (15.5)
Diabetes	157 384 (3.6)	583 (7.2)
Hypertension	526 298 (12.1)	1714 (21.2)
Medication ^a , n (%)		
Adalimumab	991 (0.0)	199 (2.5)
Cholesterol-lowering drugs	399 843 (9.2)	1294 (16.0)
Ciclosporin	1126 (0.0)	47 (0.6)
Biologics ^b	943 (0.0)	226 (2.8)
Infliximab	1224 (0.0)	108 (1.3)
LEF	123 (0.0)	8 (0.1)
MTX	15 224 (0.4)	2028 (25.1)
SSZ	8874 (0.2)	649 (8.0)
Systemic CSs	88 881 (2.0)	776 (9.6)

^aBiologics include etanercept, infliximab, adalimumab, certolizumab pegol and golimumab. Certolizumab pegol, ustekinumab and golimumab were not marketed in Europe at the time of study start.

^bWithin the last 6 months. NA, not applicable.

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 a 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,

Fig. 1 Cumulative risk of myocardial infarction

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

TABLE 2 Risk of myocardial infarction in patients with PsA

	Crude HR (95% CI)	P-value	Adjusted ^a HR (95% CI)	P-value
Risk of myocardial infarction (including patients with previous myocardial infarction)				
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

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

compared with psoriasis. This might explain why the epidemiological data on the risk of CVD is not as consistent for PsA as for RA and psoriasis [2, 3]. Previously, studies of RA and diabetes have highlighted the importance of disease duration for the risk of CVD [5–8]. On the contrary, a small single-centre study found no relationship between increased duration of psoriasis and 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 G.H.G. is supported by an unrestricted research scholarship from the Novo Nordisk Foundation. Dr J.J.W. 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.

Design and conduct of the study	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
Collection, management, analysis and interpretation of data	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Preparation, review or approval of the manuscript	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Decision to submit the manuscript for publication	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

References

- Gelfand JM, Neimann AL, Shin DB et al. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;296:1735–41.
- Egeberg A, Thyssen JP, Jensen P, Gislason GH, Skov L. Risk of myocardial infarction in patients with psoriasis and psoriatic arthritis: a nationwide cohort study. *Acta Derm Venereol* 2017;97:819–24.
- Ogdie A, Yu Y, Haynes K et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;74:326–32.
- Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol* 2009;54:2129–38.
- Armstrong AW, Harskamp CT, Ledo L, Rogers JH, Armstrong EJ. Coronary artery disease in patients with psoriasis referred for coronary angiography. *Am J Cardiol* 2012;109:976–80.
- Li WQ, Han JL, Manson JE et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. *Br J Dermatol* 2012;166:811–8.
- Masuda H, Miyazaki T, Shimada K et al. Disease duration and severity impacts on long-term cardiovascular events in Japanese patients with rheumatoid arthritis. *J Cardiol* 2014;64:366–70.
- Banerjee C, Moon YP, Paik MC et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. *Stroke* 2012;43:1212–7.
- von Elm E, Altman DG, Egger M et al. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453–7.
- Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
- Andersen TF, Madsen M, Jørgensen J, Møller-Nielsen L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–8.
- Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(7 Suppl):38–41.
- Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health* 2011;39(7 Suppl):103–5.
- Egeberg A, Skov L, Joshi AA et al. The relationship between duration of psoriasis, vascular inflammation and cardiovascular events. *J Am Acad Dermatol* 2017;77: 650–6.e3.
- Olesen JB, Lip GY, Hansen ML et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;342:d124.
- Egeberg A, Mallbris L, Gislason GH, Skov L, Hansen PR. Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. *J Invest Dermatol* 2016; 136:93–8.
- Egeberg A, Gislason GH, Hansen PR. Risk of major adverse cardiovascular events and all-cause mortality in patients with hidradenitis suppurativa. *JAMA Dermatol* 2016;152:429–34.
- Kirkham B, de Vlam K, Li W et al. Early treatment of psoriatic arthritis is associated with improved patient-reported outcomes: findings from the etanercept PRESTA trial. *Clin Exp Rheumatol* 2015;33: 11–9.
- Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs* 2014;74:423–41.
- Gisoni P, Farina S, Giordano MV, Girolomoni G. Usefulness of the Framingham risk score in patients with chronic psoriasis. *Am J Cardiol* 2010;106:1754–7.
- Eder L, Thavaneswaran A, Chandran V, Cook R, Gladman DD. Increased burden of inflammation over time is associated with the extent of atherosclerotic plaques in patients with psoriatic arthritis. *Ann Rheum Dis* 2015;74:1830–5.