Psoriasis May Not be an Independent Risk Factor for Acute Ischemic Heart Disease Hospitalizations: Results of a Large Population-Based Dutch Cohort

Marlies Wakkee¹, Ron M.C. Herings²,³ and Tamar Nijsten¹

Although psoriasis has been associated with components of the metabolic syndrome, its association with myocardial infarction is less clear. A cohort study was conducted using hospital and pharmacy records of 2.5 million Dutch residents between 1997 and 2008. The risk of ischemic heart disease (IHD) hospitalizations was compared between psoriasis patients and a matched reference cohort. Additional adjustments were made for healthcare consumption and use of cardiovascular drugs. A total of 15,820 psoriasis patients and 27,577 reference subjects were included, showing an incidence rate of 611 and 559 IHD per 100,000 person-years, respectively (P = 0.066). The age- and gender-adjusted risk of IHD was comparable between both cohorts (hazard ratio (HR) = 1.10, 95% confidence interval 0.99–1.23). Before cohort entry, psoriasis patients used more antihypertensive, antidiabetic, and lipid-lowering drugs and were more often hospitalized. Adjusting for these confounders decreased the HR for IHD, but it remained comparable between both populations. There was no different risk of IHD between the subgroup of patients who only used topicals versus those who received systemic therapies or inpatient care for their psoriasis. This study, therefore, suggests that psoriasis is not a clinically relevant risk factor for IHD hospitalizations on the population level.

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INTRODUCTION

In the past 5 years, the interest in the association between psoriasis and comorbidities, especially cardiovascular diseases, has revived (Gelfand et al., 2006; Neumann et al., 2006; Cohen et al., 2007; Wakkee et al., 2007; Kimball et al., 2008; Wakkee and Nijsten, 2009). Several observational studies found an increased risk of cardiovascular diseases. The primary underlying hypothesis is that the increased systemic inflammatory status of psoriasis patients leads to and/or aggravates other chronic (low-grade) inflammatory diseases including atherosclerosis. However, psoriasis is also associated with a considerable health-related quality of life impairment, depression, altered life styles, increased use of systemic drugs, and healthcare consumption, which may affect the relationship between psoriasis and the metabolic syndrome as well (Nijsten and Wakkee, 2009; Wakkee and Nijsten, 2009). Although several studies adjusted in part for potential confounders, such as diabetes, dyslipidemia, obesity, and smoking, residual confounding may be substantial (Nijsten and Wakkee, 2009; Wakkee et al., 2009).

More recently, psoriasis has been associated with an increased risk of myocardial infarction (MI) using the data from the UK general practice research database (GPRD) (Gelfand et al., 2006; Kaye et al., 2008). Another study analyzing the same cohort could not confirm an overall increased risk of MI (Brauchli et al., 2009). Moreover, a Swedish population-based study found that the risk of MI was only increased in females with psoriasis, whereas another US study observed a particularly higher rate of occlusive vascular disease in male psoriasis patients (McDonald and Calabresi, 1973; Lindegard, 1986). In the PUVA (psoralen plus ultraviolet light A) Follow-Up Study, cardiovascular mortality was comparable with the expected incidence (Stern and Lange, 1988).

Although psoriasis is associated with components of the metabolic syndrome, its association with MI is still less clear. The objective of this study was therefore to conduct an exploratory study on the association between psoriasis and ischemic heart disease (IHD) by comparing the incidence of hospitalizations for IHD in psoriasis patients with controls in a large sample of the Dutch population using hospital and pharmacy-linked databases.

RESULTS

Study population
The cohort study included 43,397 subjects of whom 15,820 (37%) had psoriasis. The mean age at cohort entry was

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Abbreviations: CI, confidence interval; GPRD, general practice research database; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; PUVA, psoralen plus ultraviolet light A

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Psoriasis patients were significantly more likely to have been hospitalized for non-cardiovascular diseases in the 6 months before start of follow-up (7.1% versus 5.1%, \( P < 0.001 \)) and to have filled prescriptions for lipid-lowering, antihypertensive, and antidiabetic drugs.

Almost all patients with psoriasis had used a topical antipsoriatic therapy (99%), and 13% had used a systemic antipsoriatic therapy or were hospitalized for their psoriasis.

### Event rate and univariate analyses

The median follow-up time was about 6 years in both cohorts. In the psoriasis population, 3.7% were hospitalized for an IHD (583 events) resulting in an incidence rate of 611 IHDs (95% confidence interval (CI) 562–663) per 100,000 person-years (Table 2). In the matched cohort population, 846 IHDs occurred in 3.1% of the controls representing an incidence rate of 559 IHDs (95% CI 522–598) per 100,000 person-years. Psoriasis patients and controls had an equal likelihood of developing an IHD in time (\( P = 0.066 \), Figure 1).

The age- and gender-matched hazard ratio (HR) for IHD was borderline significantly increased for psoriasis (crude HR 1.10, 95% CI 0.99–1.23).

Acute MIs were observed 234 and 235 times per 100,000 person-years in the psoriasis and control cohort, respectively. The age- and gender-adjusted survival analysis did not show a different risk of acute MI (crude HR 0.99, 95% CI 0.84–1.17).

### Multivariate survival analyses

The risk of IHD decreased but remained comparable between the psoriasis and reference cohort (adjusted HR 1.05, 95% CI 0.95–1.17, Table 2) after adjusting for the healthcare consumption proxy, metabolic drugs, and an interaction term between psoriasis and healthcare consumption. The multivariate model for MI, which did not include any significant interaction variables, showed that psoriasis was not associated with a different risk of acute MI.

### Sensitivity analyses

Restricting the analysis to individuals without cardiovascular disease-associated hospitalizations in their 6 months history showed that the risk of developing an IHD remained comparable between psoriasis patients and matched references (crude HR 1.09, 95% CI 0.98–1.22).

In the cohort of psoriasis patients, those who had used PUVA, systemic antipsoriatic therapies, or were treated as in patients who had had no different risk of IHD than the psoriasis patients who had only used topical therapies (\( P = 0.10 \)).

Stratifying for age group showed that the HRs of 35,509 people of 65 years or younger and 7,888 persons older than 65 years (HR 1.06, 95% CI 0.92–1.23 and HR 1.09, 95% CI 0.93–1.28, respectively) were comparable with the HRs of the total population.

### DISCUSSION

The results of this large cohort study with valid and clinically relevant outcomes suggest that psoriasis is not a risk factor for acute IHD hospitalizations on the population level. Psoriasis

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**Table 1. Baseline characteristics of the psoriasis and reference cohorts**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Psoriasis cohort</th>
<th>Reference cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>15,820 (36.5)</td>
<td>27,577 (63.5)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>7,583 (47.9)</td>
<td>13,306 (48.3)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>8,237 (52.1)</td>
<td>14,271 (51.7)</td>
</tr>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>48.9 (16.1)</td>
<td>48.1 (16.1)</td>
</tr>
<tr>
<td>Earlier hospitalizations(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>1,130 (7.1%)(^2)</td>
<td>1,415 (5.1%)(^2)</td>
</tr>
<tr>
<td>Total</td>
<td>1,676</td>
<td>1,979</td>
</tr>
<tr>
<td>Unique</td>
<td>1,447</td>
<td>1,802</td>
</tr>
<tr>
<td>Medical history(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering drugs (%)</td>
<td>1,102 (7.0)(^3)</td>
<td>1,701 (6.2)(^3)</td>
</tr>
<tr>
<td>Antihypertensive drugs (%)</td>
<td>3,076 (19.4)(^4)</td>
<td>4,519 (16.4)(^4)</td>
</tr>
<tr>
<td>Antidiabetic drugs (%)</td>
<td>699 (4.4)(^5)</td>
<td>993 (3.6)(^5)</td>
</tr>
<tr>
<td>Psoriasis therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topicals only</td>
<td>13,851 (87.5)</td>
<td></td>
</tr>
<tr>
<td>Systemic therapy and/or hospitalization(^6)</td>
<td>1,969 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Specific therapies ever used since start of follow-up(^6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical antipsoriotic</td>
<td>15,646 (98.9)</td>
<td></td>
</tr>
<tr>
<td>Therapies(^7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PUVA therapy</td>
<td>505 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>122 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>424 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Acitretin</td>
<td>789 (5.0)</td>
<td></td>
</tr>
<tr>
<td>Fumarates</td>
<td>14 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Biologics(^8)</td>
<td>84 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

PUVA, psoralen plus ultraviolet light A; SD, standard deviation.

\(^1\) In 6 months before cohort entry (excluding hospitalizations for cardiovascular diseases, \( n=100 \) and \( n=124 \) for the psoriasis and control cohorts, respectively).

\(^2\) \( P < 0.001 \).

\(^3\) \( P = 0.001 \).

\(^4\) \( P < 0.001 \).

\(^5\) Systemic drugs include PUVA therapy, and hospitalization should be specific for psoriasis.

\(^6\) Total adds up to more than 100% because of the possibility of multiple therapies per patient.

\(^7\) Coal tar, topical corticosteroids, dithranol, calcipotriol, calcitriol, tacrolimus, and pimecrolimus.

\(^8\) Adalimumab (\( n=19 \)), efalizumab (\( n=8 \)), etanercept (\( n=65 \)), infliximab (\( n=2 \)).
patients initially seemed to have an increased risk of IHD, but after adjusting for metabolic drug use and healthcare consumption, this association seemed to be strongly affected by confounding. We observed that psoriasis patients may have a different cardiovascular risk profile for which they receive subsequent therapies, and that the risk of IHD and MI were similar to the reference population. This may seem contradictory, but it has previously been shown that there is a weak or even no association between the metabolic syndrome and the occurrence of cardiovascular events (Sattar et al., 2008). This corresponds with a prospective cohort study of mortality causes among psoriasis patients, which showed no increased cardiovascular mortality (Stern and Lange, 1988).

Our data differ from the interpretations of the results of the study performed in the GPRD by Gelfand et al. (2006). Despite these differences, the factual information between the GPRD-based study and our study is marginal. Their HRs for MI were 1.11 (95% CI 1.07–1.17) for mild psoriasis and 1.43 (95% CI 1.18–1.72) for severe psoriasis (Gelfand et al., 2006). Moreover, another recent cohort study of the GPRD on incident psoriasis patients could not confirm previous GPRD findings and showed no overall increased risk of incident MI in psoriasis (Brauchli et al., 2009). The risk of IHD tended to be increased in our study, but the analyses of our data suggest that other factors, for example, referral bias for other disease, are important for interpretation of our results. It might well be that the results that were found in the GPRD study have been biased likewise.

On the basis of the theory that a high inflammatory state accelerates the atherosclerotic process and increases the risk of cardiovascular events, one might expect a relationship between the severity of psoriasis and the occurrence of IHD. By using the applied therapies as proxies for psoriasis severity, our data did not show a different risk of IHD between patients with more severe psoriasis (that is, systemic antipsoriatic therapies or inpatient treatments) compared with mild psoriatic patients (that is, only topicals), even after adjusting for confounders. However, using a secondary database does not allow us to draw any conclusions about the natural history of longstanding uncontrolled severe psoriasis.

We also found that psoriasis patients generally use more healthcare than “healthy” individuals. This may increase the risk of diagnosing other conditions such as cardiovascular diseases, for which additional drugs may be prescribed or patients are hospitalized (Wakkee et al., 2009). MI s are, for example, asymptomatic or clinically unrecognized in 21–68% of all cases (Aronow, 2003; de Torbal et al., 2006). As testing for interaction showed a significant interaction between psoriasis and the number of earlier hospitalizations, we reduced surveillance bias and assured a more equal comparison between cohorts by adjusting for this healthcare consumption variable. Remarkably, most other studies investigating the risk of cardiovascular events among psoriasis patients did not examine whether surveillance bias

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events</th>
<th>Person-years</th>
<th>Incidence rate</th>
<th>95% CI</th>
<th>Crude HR</th>
<th>95% CI</th>
<th>Adjusted HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>846</td>
<td>151,303</td>
<td>559</td>
<td>522,598</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>583</td>
<td>95,437</td>
<td>611</td>
<td>562,663</td>
<td>1.10</td>
<td>0.99,1.23</td>
<td>1.05</td>
<td>0.95,1.17</td>
</tr>
<tr>
<td>Acute MI</td>
<td>360</td>
<td>153,514</td>
<td>235</td>
<td>211,260</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>223</td>
<td>97,029</td>
<td>234</td>
<td>201,262</td>
<td>0.99</td>
<td>0.84,1.17</td>
<td>0.94</td>
<td>0.80,1.11</td>
</tr>
</tbody>
</table>

CI, confidence interval.

1 Incidence rate per 100,000 person-years.

2 HR adjusted for age and gender by matching.

3 Adjusted for age, gender, earlier use of antihypertensive, antidiabetic, and lipid-lowering drugs, the number of earlier non-cardiovascular hospitalizations in 180 days before cohort entry, and significant interaction terms.

4 IHD includes hospitalizations for acute myocardial infarction, angina pectoris, and other acute IHDs.
may have influenced their results. Nevertheless, this hospital- and pharmacy-based study did not have patient characteristics data such as type of psoriasis, body mass index, socioeconomic status, and life-style factors. The absence of these and other unknown risk factors for IHD may, thus, have led to overestimated risk estimates (Nijsten and Wakkee, 2009).

In this large population-based cohort study, clinically relevant outcomes of cardiovascular disease based on hospital discharge diagnosis were used as end points. The PHARMO Record Linkage System collected data prospectively and irrespective of our hypothesis, which excludes recall bias. The longitudinal National Medical Register, from which the hospital data were extracted, has almost complete coverage (99%) of all hospital admissions in the Netherlands. The observed MI incidence in the reference population was comparable with that estimated by the Dutch Heart Association in the Dutch population (235 versus 227 per 100,000 person-years, respectively), confirming the validity of the study outcome (Dutch Heart Association, 2009). The outcomes we studied are somewhat different from the GPRD study in which MI diagnoses were based on GP data, which may be more sensitive to misclassification basis than hospitalization records (Hammad et al., 2008).

A caveat of our study was that we based the definition of psoriasis on drug and hospitalization records, potentially resulting in misclassification, and hence, regression to the nil to show exposure-related disease. The prevalence of actively treated psoriasis patients was 0.6% (15,820 subjects). As expected, this was lower than the estimated psoriasis prevalence of 2–3% in Western populations that includes patients without prescription drugs (Stern et al., 2004; Nijsten et al., 2005). Psoriasis patients without psoriasis-specific therapies, such as vitamin-D derivatives, PUVA, or inpatient treatments, were also missed in this study. However, those subjects who had only used possible drug dispensings for psoriasis, such as corticosteroids or methotrexate, were also excluded from the reference cohort. The prevalence of more severe psoriasis was 13% in the psoriasis cohort, which is more in line with a recent estimate of 17% moderate-to-severe psoriasis in the US adults than the 3% severe psoriasis patients observed in the GPRD data set (Gelfand et al., 2006; Kurd and Gelfand, 2009). However, this therapy-based classification of severity remains a proxy, as no data were available on clinical disease severity. Validation of our psoriasis definition by GP medical files has been described available on clinical disease severity. Validation of our classification of severity remains a proxy, as no data were available or if they were hospitalized for dermatological diseases or the conditions listed above.

Our data showed only a slight and borderline-significant increased risk of IHD among psoriasis patients. We reason that this association resulted from residual confounding such as increased healthcare consumption. Previous studies in which psoriasis was found to be an independent risk factor for cardiovascular events may have been biased likewise. Owing to the modest positive association between psoriasis and cardiovascular diseases, correction for confounders is critical and requires prospective studies designed to address this research hypothesis. Of course, clinicians should be attentive for risk factors or internal conditions that can affect their patients’ health other than their skin disease.

MATERIALS AND METHODS

Data source

For this study, we used data from the PHARMO Record Linkage System, which links various medical databases including those on hospital discharge information, drug dispensing, and clinical laboratory records concerning 2.5 million individuals who were or have been the residents in defined areas in the Netherlands (Lau et al., 1997; Herings et al., 1999, 2000; Erkens et al., 2005; Pharmo, 2009). The hospital records included detailed information on primary and secondary diagnoses (coded according to the International Classification of Diseases, ninth Revision (WHO, 1987)), medical procedures, and dates of hospital admission and discharge. The drug dispensing records (coded according to the Anatomical Therapeutic Chemical Classification (WHO, 1999) consisted of the dispensing date, amount dispensed, and prescription dose regimens and length.

Study population

Patients with psoriasis were identified from the Pharmo Record Linkage System database using a five-step algorithm that focused on maximizing case sensitivity based on hospitalizations and drug dispensing records. This algorithm categorized individuals according to the likelihood of having been diagnosed with psoriasis (none, possible, probable, or definite), from which only those who definitely had psoriasis were selected. In the algorithm, individuals with a hospital discharge diagnosis of psoriasis and/or psoriatic arthritis, dispensings for psoralen, calcipotriol, calcitriol or dithranol, fumaric acid, and/or efalizumab were considered as definite psoriasis patients. Patients were classified as possibly or probably having psoriasis if they did not meet any of the abovementioned criteria, but had prescriptions for topical corticosteroids, coal tar, systemic glucocorticosteroids, retinoids, methotrexate, ciclosporin, adalimumab, etanercept, and/or infliximab. UV-B was not assessed, because this therapy is administered without pharmacy prescription. In the last step of the algorithm, identified definite psoriasis patients were excluded if they had been hospitalized for skin conditions other than psoriasis, had <6 months of history before start of follow-up (which is twice the maximum prescription time allowed in the Netherlands), and/or were <18 years of age at index date. Patients were also excluded if they had a history of diseases that could, theoretically, affect the development of psoriasis or its severity (that is, HIV, immune disorders, inflammatory bowel diseases, hepatitis B and C, multiple sclerosis, rheumatoid arthritis, and status after organ transplant).

From the pool of people with no likelihood of having psoriasis, reference subjects were selected and matched in a 1:2 ratio for age, gender, and presence of a database record within 30 days of cohort entry of a definite psoriasis patient. Similar to the psoriasis patients, reference subjects were excluded if <6 months of history was available or if they were hospitalized for dermatological diseases or the conditions listed above.
Follow-up period
Patients with psoriasis were followed from the first available date of an active treatment or hospitalization for psoriasis between 1998 and 2007. Subjects in the comparison cohort were followed from random drug dispensing or hospitalization occurring within 30 days of the start of follow-up of their matched psoriasis patient. For all subjects, follow-up time ended with the last drug dispensing available before 2008, an IHD, or death, whichever came first.

Study outcomes
The primary study outcome was hospitalization for acute IHD (that is, acute MI, other acute IHD, and angina pectoris). In addition, acute MI was studied separately.

Potential confounders
For each subject, we explored dispensings of antihypertensives, lipid-lowering, and antidiabetic drugs in 6 months before cohort entry to provide a proxy for the presence of treated dyslipidemia, hypertension, and diabetes mellitus. To adjust for healthcare utilization, we calculated the total number of hospitalizations (except for cardiovascular diseases to avoid overadjustment) in 6 months before cohort entry (Smitten et al., 2008). No information was available on lifestyle factors such as physical exercise, diet, smoking, alcohol consumption, or health-related quality of life.

Statistical analysis
Continuous variables are presented as means (standard deviations) or median (interquartile range) and were tested for statistically significant differences using the Student’s t-test and the Mann–Whitney test, respectively. Incidence rates and 95% CIs, which were calculated using Byar’s approximation (Breslow and Day, 1987), are presented as events per 100,000 person-years. Kaplan–Meier, and univariate and multivariate Cox proportional hazard analyses were performed to compare the likelihood of registering the study outcome between the two cohorts. Owing to age and gender matching, the “crude” HRs already take into account these potential confounders. Biologically plausible and available confounding variables such as antihypertensives, antidiabetic and lipid-lowering drug use, and number of hospitalizations in 180 days before cohort entry, all changed the HR for psoriasis by 10% or more in the bivariate analyses and were therefore included in the multivariate model (von Elm et al., 2007). In the multivariate model, these confounders were also tested for interaction with psoriasis. Visual inspection of the log(–log) survival plots against time that confirmed the proportional hazard assumptions were met.

Several sensitivity analyses were performed. First, the analyses were restricted to patients without a cardiovascular event in the 6 months before cohort entry to increase the likelihood of examining incident events. Effect modification by age on the risk estimates was explored by stratification for age (≤65 and >65 years) and by testing for interaction with psoriasis. Subgroup survival analyses were conducted to analyse whether there was a different risk of IHD between psoriasis patients who only used topical therapies versus those who used PUVA, systemic antipsoriatic drugs, and/or were hospitalized. All statistical tests were two-sided and a P-value <0.05 was considered statistically significant. The analyses were performed using SPSS 15.0 (SPSS, Chicago, IL). Adherence to the STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, especially for the multivariate analysis, assured the reporting of this observational study (von Elm et al., 2007).

CONFLICT OF INTEREST
RMC Herings is the scientific director of the PHARMO Institute. This research institute performs financially supported studies for several pharmaceutical companies such as Wyeth Pharmaceuticals.

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REFERENCES


