

Psoriasis and Cardiovascular Disease

Epidemiological Studies

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1. PAPERS

This PhD thesis is based on scientific work completed while working as a research fellow at the department of cardiology at Copenhagen University Hospital Gentofte. The following 4 papers form the backbone of the dissertation:

Paper I: Ahlehoff O, Gislason GH, Charlott M, Jørgensen C, Lindhardsen J, Olesen JB, Abildstrøm SZ, Skov L, Torp-Pedersen C, and Hansen PR. Psoriasis is associated with clinically significant cardiovascular risk - a Danish nationwide cohort study. *J Intern Med.* 2011 Aug;270(2):147-57.

Paper II: Ahlehoff O, Gislason GH, Jørgensen C, Lindhardsen J, Charlott M, Olesen JB, Abildstrøm SZ, Skov L, Torp-Pedersen C, and Hansen PR. Psoriasis and risk of atrial fibrillation and ischaemic stroke - a Danish nationwide cohort study. *Eur Heart J.* 2011 Aug 25. [Epub ahead of print]

Paper III: Ahlehoff O, Gislason GH, Charlott M, Lindhardsen J, Jørgensen C, Olesen JB, Bretler DM, Skov L, Torp-Pedersen C, and Hansen PR. Psoriasis carries an increased risk of venous thromboembolism - a Danish nationwide cohort study. *PLoS One.* 2011 Mar 25;6(3):e18125.

Paper IV: Ahlehoff O, Gislason GH, Lindhardsen J, Olesen JB, Charlott M, Skov L, Torp-Pedersen C, and Hansen PR. Prognosis following first-time myocardial infarction in patients with psoriasis - a Danish nationwide cohort study. *J Intern Med.* 2011 Sep;270(3):237-44.

2. INTRODUCTION

Psoriasis (PS) is a chronic inflammatory disease affecting approximately 2% of the population, most commonly as the clinical variant termed psoriasis vulgaris, which is characterized by the presence of, raised well-demarcated erythematous plaques covered by silvery scales due to hyperproliferation and premature maturation of epidermal keratinocytes.^{1,2} Other manifestations of psoriasis include scalp psoriasis, nail disease, and sero-negative arthritis known as psoriatic arthritis.¹ Like patients with other chronic diseases individuals with psoriasis suffer from a range of disabling conditions, including impaired social-life and depression due to embarrassment of their appearance and patients with PS have reduced levels of employment and income.^{1,2} Evidence has also indicated that PS is associated with conventional cardiovascular risk factors, e.g. hypertension, diabetes mellitus (DM), obesity, smoking, and hyperlipidaemia.³⁻¹⁵ Furthermore, PS may, like other chronic inflammatory disorders including rheumatoid arthritis and systemic lupus erythematosus, confer independent risk of atherothrombotic disease.^{11,16-27} More than 3 decades ago McDonald et al. published a small study of highly selected patients with PS suggestive of an increased risk of arterial and venous thrombosis.¹⁶ The scientific discussion in this area of research has become more prolific in the last few years, not least after the 2006 publication of epidemiological data by Gelfand et al. in *Journal of the American Medical Association* indicating an increased risk of myocardial infarction (MI) in patients with severe PS independent of classic cardiovascular risk factors.¹⁷

Epidemiological studies of atherothrombotic risk with PS have, however, yielded conflicting results as demonstrated first by Brauchli et al., and more recently in a smaller study by Schmitt et al., which both were unable to confirm the results of Gelfand's group.^{28, 29} Indeed, increased prevalence of established cardiovascular risk factors, other comorbidities, and surveillance bias caused by increased healthcare consumption in patients with PS, have been proposed as important contributors for the observed association between PS and increased cardiovascular risk.^{30, 31} PS is characterised by T-helper cell (Th) 1/Th17-driven inflammation and there is an overlap of the underlying inflammatory mechanisms with those seen in atherosclerosis.³²⁻³⁵ Participation of similar immunoinflammatory and prothrombotic mechanisms in PS and atherothrombotic disease is supported by evidence that systemic immunosuppressive treatment with methotrexate in patients with PS is associated with reduced risk of cardiovascular disease, including MI.³⁶ PS has also been associated with surrogate markers of cardiovascular disease, e.g. endothelial dysfunction and coronary calcification, and with markers of increased platelet activity.³⁷⁻⁴⁴ Moreover, atrial fibrillation/flutter (AF) is highly prevalent and is associated with increased risk of heart failure, cardiovascular morbidity, and stroke,^{45, 46} and studies have linked inflammatory mechanisms to the pathogenesis of AF, e.g. by demonstration of atrial infiltration of inflammatory cells, and raised circulating levels of inflammatory markers, and markers of oxidative stress in patients with AF.⁴⁷⁻⁵⁴ In addition, venous thromboembolism (VTE), i.e. deep venous thrombosis and pulmonary embolism, is a prevalent and potentially lethal disease associated with cancer, prolonged immobilization, surgery and trauma (secondary or provoked VTE).⁵⁵ VTE may also be associated with certain cardiovascular risk factors (e.g. obesity, hypertension, and smoking), atherothrombotic events, and markers of inflammation.⁵⁵⁻⁵⁹ Recent results have also demonstrated increased risk of VTE in patients with inflammatory bowel disease.⁶⁰ The sum of evidence therefore suggests that considerations of shared immunoinflammatory pathways as discussed with PS and atherothrombotic disease can also be applied to AF and VTE, but very little is known about the specific impact of PS on the risk of the latter important cardiovascular conditions.

Since PS is a prevalent disease affecting approximately 120 million people worldwide improved understanding of a potential PS-associated impact on

cardiovascular risk could contribute to reduction of cardiovascular disease burden, e.g. by providing the background for changes in primary and secondary cardiovascular disease prevention strategies in patients with PS.²

OBJECTIVES

With the underlying hypothesis that PS has detrimental effects on all examined adverse cardiovascular endpoints the thesis had the following objectives:

To examine the risk of atherothrombotic events in patients with PS and compare this risk to that of patients with a well-established cardiovascular risk factor, i.e. diabetes mellitus (DM).

To examine the risk of AF and ischemic stroke in patients with PS.

To examine the risk of VTE in patients with PS.

To examine the post-MI prognosis in patients with PS.

The nationwide Danish registries on hospitalisations, prescription claims, causes of death, and socioeconomic data provide a unique opportunity to conduct large scale epidemiological studies of these endpoints in an entire population and with completeness of follow-up.

Therefore, to fulfil the objectives of the present thesis 4 historical cohort studies (i.e. retrospectively collected information analysed in a prospective manner by use of Poisson regression and Cox regression, respectively) of the Danish population as of January 1, 1997 was done.

3. METHODS

DATABASES

In Denmark, all citizens have a unique personal civil registration number that enables individual-level linkage of information across nationwide registries. Morbidity was obtained from the Danish National Patient Register in which all hospital admissions, diagnoses, and invasive procedures have been recorded since 1978 according to the World Health Organisation's International Classification of Diseases (ICD), i.e. before 1994 the eighth revision (ICD-8) and the tenth revision (ICD-10) thereafter. All medications dispensed from pharmacies were obtained from the Danish Registry of Medicinal Product Statistics (the National Prescription Registry), where all dispensed prescriptions have been recorded since 1995, including data on the dispensing date, and drug dose, formulation and quantity, and the affiliation (general practitioner

or hospital doctor) of the prescribing physician. All deaths were identified from the Central Population Register where all deaths are recorded within 2 weeks. Causes of death were obtained from the National Causes of Death Register, in which immediate, contributory, and underlying causes of death were recorded using ICD-10 codes by the physician who completed the death certificate. Socioeconomic status was defined as average yearly income in a 5 year period prior to study start. Data on death, comorbidity, concomitant medication, and socioeconomic data were linked on individual case level.

STUDY POPULATION

The present thesis evaluates the cardiovascular risk of patients with incident PS after 1997 as defined by prescriptions claimed for topical vitamin-D derivatives and classified as PS at the time of their second prescription claim. Patients with severe PS were identified by hospitalisations for PS (ICD-10 L40) or psoriatic arthritis (M070-M073) and the disease was classified as severe at the time of their third (in-patient or out-patient) diagnosis. For sensitivity analyses, a definition of PS by first prescription claim and first hospital diagnosis for severe PS was used in paper I-III, in order to address bias related to differences of health-care consumption and medical surveillance. Subjects who immigrated to Denmark after January 1, 1997 were not eligible for analyses. Patients were followed until Dec 31, 2006, emigration, death, or the occurrence of a study endpoint.

Paper I: The study comprised the entire Danish population aged ≥ 18 on January 1, 1997. After the exclusion of patients with prevalent PS, prevalent DM (defined by claimed prescriptions for glucose-lowering drugs), and patients with prior cerebrovascular disease, or MI a total of 4,040,257 subjects were eligible for analyses.

Paper II: The study included the entire Danish population aged ≥ 10 on January 1, 1997. Following exclusion of patients with prevalent PS, prior AF, and prior stroke 4,518,484 subjects were eligible for analyses.

Paper III: The study included the entire Danish population aged ≥ 18 on January 1, 1997. After exclusion of patients with prevalent PS, previous VTE, and patients who received vitamin K antagonists at or prior to

baseline a total of 4,164,740 subjects were eligible for analyses.

Paper IV: This study comprised the entire Danish population, who experienced a first-time MI in the period 2002-2006. The population was followed from the date of first-time MI.

Pharmacological treatment and comorbidity
Due to the national health care reimbursement scheme for drug expenses, pharmacies in Denmark are required to register all dispensed prescriptions ensuring complete registration.⁶¹ Drugs are registered according to the international Anatomical Therapeutic Chemical (ATC) classification system. Prescriptions claimed for topical vitamin D derivatives (ATC D05AX), i.e. treatment used exclusively for PS,⁶² were used for determination of subjects with PS. Treatment for cardiovascular diseases and cardiovascular risk factors were identified by prescriptions for platelet inhibitors (B01AC), beta-blockers (C07), angiotensin-converting enzyme inhibitors (ACEI) /angiotensin 2 receptor antagonists (C09), loop diuretics (C03C), spironolactone (C03D), vitamin K antagonists (B01AA), statins (C10A), and glucose-lowering drugs (A10) claimed up to 6 months prior to study initiation.

The Charlson comorbidity index, developed by Charlson et al. in 1987, is widely used in epidemiological studies and was developed based on a longitudinal study of patients admitted to a medical service, where 19 conditions were found to significantly influence survival in the study population and were given a weighted score based on the relative mortality risk.⁶³ In papers I-III, comorbidity at study entry was described by the Charlson comorbidity index, as defined by the 19 prespecified diagnoses at study entry and up to 1 year previously, and modified to ICD-10.⁶⁴ The Ontario acute MI mortality prediction rules, as defined by the 9 prespecified diagnoses modified to ICD-10, are well-validated for post-MI populations and we therefore used these rules to define comorbidity in paper IV on post-MI prognosis.⁶⁵

OUTCOMES

The diagnoses of MI, stroke, AF, and VTE in the Danish National Patient Register have previously been validated with very high positive predictive values for MI, stroke, and AF and with acceptable values for

VTE.⁶⁶⁻⁶⁹ The following endpoints (ICD-10 codes) were assessed:

Paper I: MI (I21-I22), stroke (I60-I61, I63-I64), coronary revascularisation (percutaneous coronary intervention and coronary artery bypass grafting), all-cause mortality, cardiovascular death (I00-I99), and the composite of stroke, MI, and cardiovascular death, respectively.

Paper II: AF (I48) and ischaemic stroke (I63, I64).

Paper III: VTE (I26, I80.1-I80.9) as the primary endpoint, and the specific diagnosis of pulmonary embolism (I26) as the secondary endpoint.

Paper IV: All-cause mortality and a composite of recurrent MI (I21-I22), stroke (I60-I61, I63-I64), and cardiovascular death (I00-I99).

STATISTICAL ANALYSES

Baseline characteristics are presented as percentages and means with standard deviations. Unadjusted event rates are summarized as incidence per 1000 person-years. A two-sided p-value < 0.05 was considered statistically significant. Assessment of the impact of an unmeasured confounder was made by use of the 'rule out' approach, as described by Schneeweiss et al.⁷⁰ All statistical analyses were performed with the use of SAS statistical software version 9.2 and Stata statistical software version 11.

Papers I-III: The rate ratio (RR) and 95% confidence interval (CI) of study endpoints was estimated multivariable Poisson regression models controlling for age, calendar year, concomitant medication, comorbidity, socioeconomic data, and gender. PS status was included as a time-dependent variable so that patients were only considered at risk from the time they complied with the PS criteria. Age and calendar year were also included as time-dependent variables, while information on comorbidity and concomitant medication as of January 1, 1997 were included as fixed variables.

Sensitivity analyses matched for age and gender with updated baseline characteristics to time of PS onset for cases and corresponding controls were made to assess the impact of changes in comorbidity and concomitant medication, respectively. In papers I and II propensity score-matched sensitivity analyses were

applied to establish study populations with comparable baseline characteristics. A propensity score for the likelihood of receiving topical vitamin D derivatives was quantified by multivariate logistic regression. Furthermore, analyses were made to address the concerns of surveillance bias raised in previous papers,^{30, 31} i.e. by identification of patients with PS by their first vitamin D prescription claim (instead of second claim as used in the primary analyses), and patients with severe PS by their first hospital diagnosis (instead of third diagnosis as used in the primary analyses), and by exclusion of subjects with a history of hospitalisations up to 1 year prior to study start, respectively. In paper II sensitivity analyses with exclusion of patients with coronary artery disease, and censoring of patients at the time of a surgical procedure or of a prescription claim for anti-thyroid treatment, respectively, were made to address the potential impact of these important risk factors for AF. In addition, in paper III we made a sensitivity analysis addressing the impact of surgery and immobilization on risk of VTE by censoring study subjects at the time of a surgical procedure. Model assumptions, including the proportional hazard/risk assumption in each time-band, absence of interaction between model covariates, and linearity of continuous variables were tested and found to be valid. However, statistically significant interactions between PS and age, and (paper I) DM and age were present for all examined endpoints and age-stratified estimates were therefore presented.

Paper IV: The hazard ratios (HRs) and corresponding CIs were estimated by Cox regression models controlling for confounding factors including age, gender, calendar year, concomitant medication, comorbidity, and socioeconomic data. Sensitivity analyses of non-fatal MI with start of follow-up 30 days after the index MI, and with inclusion of revascularisation strategy and post-MI medication in the regression model were made to assess the impact of differences in treatment strategies between the two groups on the prognosis. Model assumptions, including absence of interaction between model covariates, linearity of continuous variables and fulfilment of the proportional hazard assumption, were tested and found to be valid.

ETHICS

The protocol was approved by the Faculty of Health Sciences, University of Copenhagen. Data at the indi-

vidual case level were made available to us by the national registries in anonymised form. This was approved by The Danish Data Protection Agency (2007-41-1667), and retrospective registry studies do not require ethical approval in Denmark.

4. RESULTS

The following section provides an abstracted overview of the 4 papers that are included in the thesis. For each paper a brief presentation of background and aims, methods, results, and main conclusions is provided. For details of the studies please refer to the appendix section wherein all 4 papers are apparent in full.

PAPER I: Psoriasis is associated with clinically significant cardiovascular risk - a Danish nationwide cohort study

Background and aim:

The cardiovascular risk associated with PS, including psoriatic arthritis is debated. We therefore investigated the PS- and psoriatic arthritis-related risk of cardiovascular morbidity and mortality and compared the risk to that of patients with an established cardiovascular risk factor, i.e. DM.

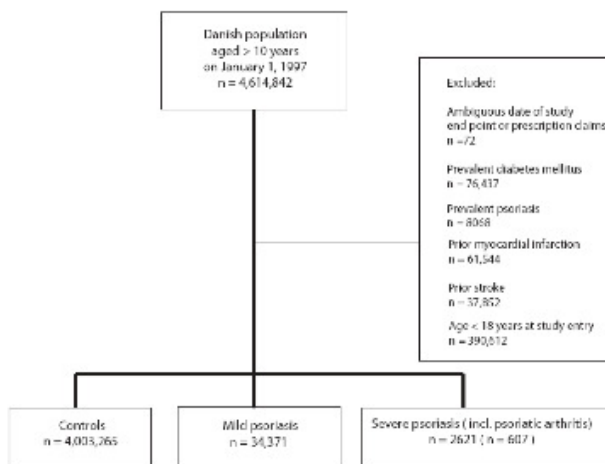


Figure 1 Flow chart of the study population selection

Methods:

Cohort study of the entire Danish population followed from 1997 to 2006 by individual level-linkage of nationwide registries. Poisson regression models were applied to assess overall and age-stratified cardiovascular risk in patients with PS, including psoriatic arthritis, and patients with DM. The following endpoints were assessed: all-cause mortality, cardiovascular

mortality, MI, stroke, and coronary revascularisation including percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG).

Results:

In the study period a total of 34,371 patients with mild PS and 2621 with severe PS, including 607 patients with psoriatic arthritis, were identified and compared with the general population. A flow chart of study population selection is presented in Figure 1. The event rates and adjusted RRs of all endpoints were increased in all patients with PS. Age-stratified analyses demonstrated highest risk in young patients with severe disease. Results from the multivariable adjusted Poisson regression are presented in Table 2. A total of 127,449 patients with incident DM were identified in the study period. They were generally older (mean age 55.6 years) and more often of male gender (54.1%) compared to patients with PS. The cardiovascular risk estimates were similar in patients with severe skin affection alone, those with psoriatic arthritis, and in patients with DM, e.g. for the composite cardiovascular end point DM conferred an increased risk with RR 1.58 (CI 1.56-1.61), that was comparable to the increased risk observed in severe psoriasis (p=0.68) and psoriatic arthritis (p=0.46). Sensitivity analyses including propensity score-matched models confirmed the results of the primary analysis.

Conclusion:

PS is associated with increased risk of adverse cardiovascular events and all-cause mortality. The risk in patients with severe PS, including psoriatic arthritis is comparable to the risk with DM. Patients with PS may benefit from early cardiovascular risk factor modification.

PAPER II: Psoriasis and risk of atrial fibrillation and ischaemic stroke – a Danish nationwide cohort study

Background and aims:

PS is a common chronic inflammatory disease. Although inflammation contributes to the pathogenesis of AF and ischaemic stroke, the possible association between PS and AF has not been studied previously and little evidence is available about the effect of PS on the risk of ischaemic stroke. We therefore investigated the risk of AF and ischaemic stroke in patients with PS in a nationwide cohort.

Methods:

A historical cohort study of the entire Danish population aged ≥ 10 years followed from 1997 to 2006 by individual level-linkage of nationwide registries. Poisson regression models controlling for age, gender, comorbidity, concomitant medication, and socioeconomic status were applied together with sensitivity analyses.

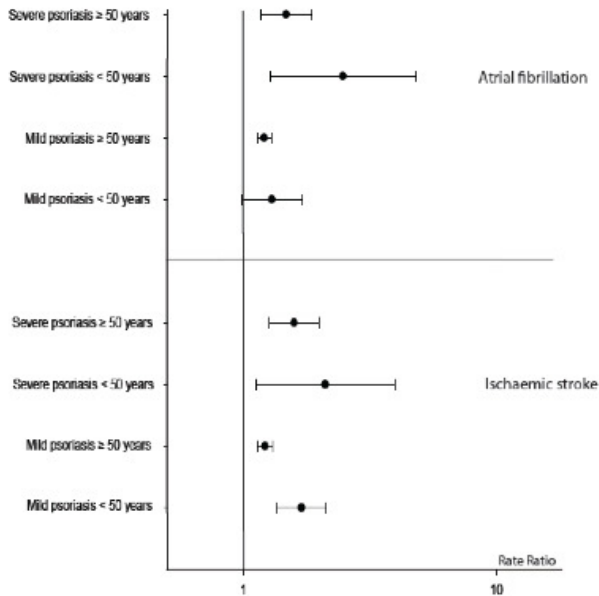


Figure 2 Age-stratified rate ratios (RRs) and 95% confidence intervals. RR = 1 (vertical line) for controls

Results:

A total of 39,558 patients with PS, including 2793 patients with severe PS were compared with 4,478,926 controls, i.e. the general population. An overview of the study population selection is given in Figure 2. AF rates per 1000 person-years were higher in patients with PS (0.26, 0.36, and 0.59 vs. 6.10, 7.21, 9.10 for controls, and subjects with mild and severe PS, in patients aged < 50 vs. ≥ 50 years, respectively) and a similar pattern of increased risk was seen for ischaemic stroke (0.24, 0.61, 1.56 vs. 5.94, 6.74, 8.88, respectively). In patients aged < 50 and ≥ 50 years with mild PS, the RR for AF was 1.30 (CI 0.99 to 1.72) and 1.21 (1.13 to 1.30), respectively. Patients with severe PS were at higher risk of AF (RR 2.48 [1.28 to 4.83] in patients aged < 50 years and 1.48 [1.17 to 1.86] in patients aged ≥ 50 years). Furthermore, PS was associated with increased risk of ischaemic stroke, i.e. RR 1.70 (1.35 to 2.13) and 1.22 (1.13 to 1.31) in patients with mild PS aged < 50 years and ≥ 50 years, respectively. The risk of ischaemic stroke in patients with severe PS was higher, i.e. RR 2.11 (1.12

to 3.97) in patients aged < 50 years and 1.59 (1.27 to 2.00) in patients aged ≥ 50 years. The results of the age-stratified and multivariable adjusted Poisson regression are presented in Figure 2. Sensitivity analyses controlling for surgical procedures, hyperthyroidism and MI yielded comparable results as the primary analysis. Furthermore, the censoring of subjects at time of AF-onset did not eliminate the association between PS and ischaemic stroke.

Conclusion:

PS is associated with an age- and severity-dependent increased risk of AF and ischaemic stroke. The study is the first to evaluate the risk of AF in patients with PS. The results add novel data to a growing body of evidence suggesting that patients with PS are at increased cardiovascular risk.

PAPER III: Psoriasis carries an increased risk of venous thromboembolism - a Danish nationwide cohort study

Background and aim:

PS is an immunoinflammatory disease associated with cardiovascular risk factors, atherothrombotic events, and hypercoagulability. VTE is prevalent, potentially lethal, and shares risk factors with PS, but the risk of VTE associated with PS is unknown. The present study investigated the potential association between PS and increased risk of VTE.

Methods:

Information from nationwide prospectively recorded registries was used to establish an unselected nationwide cohort. Multivariate Poisson regression models controlling for age, gender, comorbidity, concomitant medication, socioeconomic data, and calendar year were used to assess the overall and age-stratified risk estimates. Sensitivity analyses controlling for increased risk of secondary (provoked) VTE was also applied.

Results:

In the 10 year study period a total of 35,138 patients with mild and 3526 patients with severe PS were identified and compared with 4,126,075 controls. A flowchart of the study population selection is presented in Figure 4. Patients with PS had higher incidence rates of VTE than controls (1.29, 1.92, and 3.20 per 1000 person-years for controls, mild PS, and severe PS, respectively). The RR of VTE was elevated in all patients with PS with overall RR 1.35 (CI 1.21–1.49) and RR 2.06 (CI 1.63–2.61) for mild and severe PS,

respectively. Sensitivity analyses accounting for secondary VTE, including censoring of subjects undergoing surgical procedures did not significantly alter the results. Age-stratified analyses demonstrated that the PS-related risk was highest in younger patients with severe disease.

Conclusion:

This nationwide cohort study indicated that patients with PS are at increased risk of VTE. Physicians should be aware that patients with PS may be at increased risk of both venous and arterial thromboembolic events and may therefore be candidates for earlier cardiovascular risk factor modification than predicted by ordinary risk assessment schemes.

PAPER IV: Prognosis following first-time myocardial infarction in patients with psoriasis: a Danish nationwide cohort study

Background and aim:

The prognostic impact of PS in patients with MI is unknown. Therefore, we investigated the risk of adverse cardiovascular events and mortality in patients with PS following a first-time MI.

Methods:

Historical cohort study of the entire Danish population aged ≥ 10 years that experienced a first-time MI in the period 2002–2006. Multivariable Cox regression models were used to assess risk the composite endpoint of recurrent MI, stroke, and cardiovascular death and all-cause mortality associated with PS.

Results:

A total of 462 patients with PS (69.5 years) and 48,935 controls (70.6 years) were identified with a first-time MI in the study period. There were no statistical differences in the proportion of fatal index MIs between the two groups (18.0 vs. 16.9 %; $p=0.53$). Patients with psoriasis surviving the index MI received significantly more statins than controls and demonstrated a non-significant trend for decreased use of betablockers, and increased use of glucose-lowering drugs, loop diuretics and angiotensin converting enzyme inhibitors/angiotensin 2 receptor antagonists, respectively. Significant differences in rates of invasive coronary revascularization, i.e. PCI or CABG, following the index MI, were not apparent between the two groups. Baseline characteristics are presented in Table 5. For all-cause mortality, the incidence rates were 119.4 (CI 117.2 - 138.3) and 138.3 (CI 114.1 -

167.7) per 1000 patient-years for controls and patients with PS, respectively. The adjusted HR for all-cause mortality was 1.18 (CI 0.97-1.43). For the composite endpoint the IRs were 149.7 (CI 147.1 - 152.4) and 185.6 (CI 155.8 - 221.0) for controls and patients with PS, respectively. The HR for the composite endpoint was 1.26 (CI 1.04-1.54). A sensitivity analysis accounting for post-MI differences in pharmacological and invasive treatment did not attenuate the association between PS and adverse prognosis following first-time MI.

Conclusion:

This first study of the PS-related risk of cardiovascular morbidity and mortality in patients with MI demonstrated an increased risk of adverse cardiovascular events compared to patients without PS. Furthermore, the study demonstrated a trend towards PS-related increased all-cause mortality. The study supports available evidence of PS as being a clinically significant cardiovascular risk factor and suggests a need for aggressive cardiovascular secondary prophylaxis in these high-risk patients.

5. METHODOLOGICAL CONSIDERATIONS

STUDY DESIGN

We decided only to include new-onset PS and this approach was particularly important in paper I where we made a direct comparison between the cardiovascular risk in patients with PS and DM. This model enabled the establishment of PS and DM study populations with comparable disease durations, although it should be recognised that the precise time of onset of chronic diseases, e.g. PS and DM, is not possible to determine in these administrative databases.

POISSON REGRESSION VS. COX REGRESSION

In cohort studies with varying follow-up time, a large amount of observations, and a relatively rare outcome, Poisson regression provides a reasonable statistical approach. The decision to choose Poisson regression or Cox regression is in most circumstances a choice of convenience or preference, since the models normally provide very similar results. However, Poisson regression is far more efficient when analysing large datasets with time-varying covariates and therefore we decided to use Poisson regression models. In paper IV on the prognosis following MI, however, the dataset was considerably smaller and time-varying variables were not included and therefore the

Cox regression was applied allowing for the best possible controlling for baseline hazard.

SELECTION BIAS, PROTOPATHIC BIAS, AND CONFOUNDING BY INDICATION

Selection bias is a systematic error in epidemiological studies that arises from the population selection where the association between exposure and outcome differs between those included and those not included, i.e. patients with PS treated with vitamin D derivatives may generally have a different cardiovascular risk profile than PS patients treated with corticosteroids or other topical agents. As discussed below, however, there is no apparent reason to believe that this should be the case since the different topical PS treatments are all generally used as first-line treatments regardless of the cardiovascular risk profile. However, we cannot fully refute that patients with severe PS included in our study by hospital contacts may differ from those treated by non-hospital dermatologists. The use of nationwide registries of hospitalisations and dispensed prescriptions from all pharmacies in Denmark where healthcare is readily accessible and essentially free of charge minimized selection bias related to e.g. subject gender, age, socioeconomic status, healthcare insurance provision, and labour market association.

The use of pharmacological treatment to identify the main exposure in epidemiological studies may lead to important bias and misleading conclusions. The term prothopathic bias refers to the situation in which the initial symptoms of the outcome of interest is the very reason for the initiation of the pharmacological treatment used as the exposure measure, i.e. if topical vitamin D therapy was initiated because of early manifestations of cardiovascular disease. Since vitamin D is solely used for the treatment of PS skin lesions there is, however, no reason to suspect any impact of such bias in the presented studies. Along this line, confounding by indication, a source of bias in non-randomized studies with potentially important differences in determinants of the outcome of interest between exposed and unexposed, is unlikely to be an important issue in our studies. Indeed, in our study design, the treatment used to define exposure (vitamin D analogues) was initiated because of PS (which is associated with increased cardiovascular risk) but merely served as a specific indicator of PS.

6. DISCUSSION

The present thesis has provided the first nationwide examination of the association between PS and cardiovascular disease. The unique Danish administrative registries of hospitalisations, drug prescriptions, causes of death, and socioeconomic data enabled individual level-linkage of the entire Danish population with a very low loss to follow-up and with use of validated study endpoints. The main results of the thesis were that all patients with PS were at increased risk of all-cause mortality and of a range of atherothrombotic events, including MI, stroke, coronary revascularisation, and cardiovascular death. Patients with severe PS had a comparable risk to that of patients with DM. Furthermore, the thesis provided novel evidence of PS as a possible risk factor for AF and VTE and we demonstrated an association between PS and adverse outcomes following first-time MI. In summary, the results add importantly to the evidence indicating that PS is a significant cardiovascular risk factor.

PSORIASIS, INFLAMMATION, PROTHROMBOSIS, AND CARDIOVASCULAR DISEASE

PS is a common chronic disease affecting approximately 2 % of the world's population. The disease is characterised by the cutaneous psoriasis elements which are infiltrated skin lesions covered by silvery scales, other manifestations include affection of the nails, and 10-20% of the patients have joint disease, i.e. psoriatic arthritis.^{1, 2} Psoriasis treatment varies with disease severity PS and range from topical treatment (i.e. vitamin D, tar preparations, or topical steroid) to phototherapy, vitamin-A derivatives and systemic immunosuppression (e.g. methotrexate, ciclosporine and biological agents).⁶² Atherosclerosis and PS are both chronic inflammatory diseases characterized by Th1/Th17-driven inflammation and there is a considerable overlap of identified inflammatory markers and mediators in cutaneous psoriatic elements and atherosclerotic plaques.^{1, 2, 34, 35} Like other Th1-mediated inflammatory diseases, e.g. systemic lupus erythematosus and rheumatoid arthritis, PS has been associated with conventional cardiovascular risk factors, including obesity, dyslipidaemia, hypertension, smoking, and DM and to surrogate markers of atherothrombotic disease, including endothelial dysfunction, coronary calcification, and carotid intima-media thickening.^{3-15, 37-41} The presence of endothelial dysfunction in patients with PS was, however, very recently questioned when this early vascular abnor-

mality was not found in patients with PS after exclusion of those with classic cardiovascular risk factor or manifest atherosclerosis.⁷¹

Inflammation is associated with increased levels of pro-thrombotic markers and plays a key role in all steps of atherosclerosis from fatty streak formation to plaque instability and thrombosis.^{32, 72} Furthermore, platelet activity regeneration time after aspirin intake appear to be accelerated in patients with PS compared to controls.⁴² Hyperhomocysteinaemia, which may be associated with augmented risk of both arterial and venous thrombosis, has also been reported in these patients, further suggestive of a prothrombotic environment.^{43, 73, 74} Along this line, immunosuppressive therapy with methotrexate and tumour necrosis factor- α inhibitors may decrease cardiovascular risk in patients with psoriasis, and observations that statins may have favourable effects on psoriasis also suggest that coincident pathological mechanisms contribute to the clinical manifestations of PS and cardiovascular disease.^{36, 75-77}

As in atherosclerosis, inflammation and oxidative stress have been suggested to play a role in the initiation, recurrence, and perpetuation of AF.^{52-54, 78-83} For example, atrial infiltration of inflammatory cells has been observed in histological samples from patients undergoing invasive treatment for lone AF but not for Wolf-Parkinson-White syndrome.⁴⁷ Conditions such as hypertension, DM, obesity, and smoking that increase the risk of AF are also associated with markers of inflammation and oxidative stress, and in patients with AF increased circulating levels of inflammatory markers (e.g. plasma C-reactive protein) seem to correlate with decreased probability of successful electrical cardioversion and increased recurrence of AF following cardioversion.^{51, 84-86} Interestingly, lower rates of AF recurrences after cardioversion and post-operative AF after cardiac surgery by anti-inflammatory therapy with methylprednisolone and statins have also been reported.^{87, 88} The association between inflammation and VTE is unclear at present.^{58, 89} VTE has been associated with increased risk of atherothrombotic events and, interestingly, VTE was recently linked to inflammatory bowel disease with marked fluctuations in risk with disease activity as measured by hospitalisations and drug use.^{55-57, 60} Statins, which have pleiotropic effects including anti-inflammatory properties, may also attenuate the risk of VTE in healthy individuals as well as in patients with atherosclerosis.^{76, 90} Altogether, the considerations above, and especially the high likeli-

hood of shared immunoinflammatory pathophysiological pathways, appear to position PS as a plausible and potentially important risk factor for a variety of cardiovascular diseases, including atherothrombotic events, AF, and VTE.

Atherosclerosis and atherothrombosis

PS has previously been linked to risk of cardiovascular disease and mortality independent of conventional risk factors in studies of healthcare databases.^{10, 11, 17-23, 91} The work by Gelfand et al. published in 2006 demonstrated an association between severe psoriasis and MI where the risk was age-dependent and the highest risk was observed in younger patients.¹⁷ These results were, however, more recently questioned when Brauchli et al. were unable to confirm the results using the same British General Practice Research Database.²⁸ The latter study exclusively examined the risk in patients with presumed short duration of PS and excluded patients with prevalent coronary artery disease, and these differences in study design may serve as potential explanations for the divergent results. Absence of independent risk with PS was also reported recently in a smaller study, which, however, only had moderate power due to occurrence of relatively few cardiovascular events.²⁹ Furthermore, it was recently suggested that increased prevalence of comorbidities including previous cardiovascular disease and presence of surveillance bias contributed to the findings of Gelfand et al.^{30, 31}

Our results are consistent with the epidemiological data connecting PS to augmented risk of cardiovascular morbidity and mortality.^{17-23, 92} It is notable, that our study (paper I) excluded patients with prevalent atherosclerotic disease, i.e. prior MI and prior stroke, and patients with prevalent PS, and provided a direct cohort-based comparison between cardiovascular risk with PS, psoriatic arthritis, and DM. We were, to our knowledge, the first to demonstrate an association between PS and invasive coronary revascularisation and this novel finding supports the notion of an increased occurrence of clinically significant coronary artery disease in patients with PS. Our use of hospitalisations (including out-patient visits) to define severe PS may, however, have increased the presence of cardiometabolic comorbidities and decreased the threshold for detection of study outcomes in these patients (surveillance bias). This consideration is probably less relevant for outcomes such as MI, stroke, coronary revascularisation, and death, but it may have influenced the detection threshold for AF

as further discussed below. We made efforts to reduce these sources of bias by making multiple adjustments (e.g. for Charlson comorbidity index and concomitant medication) and by performing sensitivity analyses with less restrictive inclusion criteria (i.e. first vitamin D prescription claim and first hospitalisation). These analyses yielded results that were comparable to the primary model which further supported that surveillance bias was not a likely explanation for the observed association between PS and study endpoints. We were also, to our knowledge, the first to demonstrate that PS was associated with an impaired prognosis following first-time MI (paper IV), thus expanding the evidence of augmented cardiovascular risk in patients with PS to comprise the high risk post-MI population, where the potential impact of surveillance bias is likely to be markedly attenuated since all Danish patients with recent MI are subject to extensive and comparable healthcare provision irrespective of a PS diagnosis. These results are in agreement with data on worsened post-MI prognosis in patients with other inflammatory diseases, i.e. systemic lupus erythematosus and rheumatoid arthritis.^{26, 93-95}

ATRIAL FIBRILLATION/FLUTTER

AF is the most frequently occurring cardiac arrhythmia and is associated with increased risks of thromboembolic complications (including ischaemic stroke), heart failure, coronary artery disease, and cardiovascular death.^{46, 96, 97} Except for a small study that has linked PS to raised heart rate and increased frequency of supraventricular extrasystoles the association between PS and cardiac arrhythmias has not been explored previously.⁹⁸ We were, to our knowledge, the first to demonstrate an increased risk of AF in patients with PS and our demonstration of a consistent disease severity-dependent association between PS and AF supports the hypothesis of shared inflammatory mechanisms between these two diseases (paper II). These results are supported by recent preliminary data from our group suggestive of increased risk of AF in patients with rheumatoid arthritis.⁹⁹ It is notable that controlling for comorbidity including with exclusion of patients with prior MI and censoring of subjects undergoing surgical procedures or diagnosed with hyperthyroidism as determined by claims of antithyroid drugs did not cancel out the observed association. This observation suggests that the risk of AF in patients with PS was not procedure-related, comorbidity-dependent, or entirely driven by the

presence of coronary artery disease. As mentioned above, surveillance bias could influence the detection threshold for AF, but sensitive analyses, with use of PS inclusion criteria less reliant on repeated physician visits, i.e. inclusion by first vitamin D prescription claim and classified as severe on first hospital visit, did not significantly attenuate the association between PS and AF, which supports that our results were not caused by surveillance bias. AF is an important risk factor for ischaemic stroke¹⁰⁰ and we demonstrated an increased risk of ischaemic stroke in patients with PS. Interestingly, censoring of patients with AF did not cancel out the PS-associated increased risk of ischaemic stroke. This finding suggests that patients with PS are at an increased risk of ischaemic stroke that exceeds the risk attributable to AF and it thus lends significant support to previous studies that have suggested that PS was a contributor to stroke.^{11, 16-23}

VENOUS THROMBOEMBOLISM

In 1978 a study by McDonald et al. suggested that the risk of VTE and other adverse cardiovascular events was increased in a group of highly selected patients with PS.¹⁶ Since then, however, while the association between PS and atherothrombosis has been studied in different settings, the impact of PS on risk of VTE has not been investigated.^{10, 11, 17-21} We were the first, to our knowledge, to evaluate the risk of VTE with PS in a nationwide unselected cohort and we found a clear and severity-dependent increased risk in patients with PS (paper III). These data parallel our finding with regards to risk of atherothrombotic events and the results are in agreement with previous findings on the VTE risk with other inflammatory diseases, including inflammatory bowel disease, systemic lupus and rheumatoid arthritis.^{60, 101-104} The results were robust for multivariable adjustment and were further supported by the sensitivity analyses that indicated that the elevated VTE risk was not driven by malignancies or secondary VTE after surgery.

7. STUDY STRENGTHS

The studies presented in this thesis were strengthened by the large number of participants, the nationwide coverage of prospectively recorded registries, the use of validated endpoints, the real-life contemporary clinical setting, and the completeness of follow-up. The use of study populations comprising

the entire Danish population attenuated the potential impact of surveillance bias, and as described above the study was further enhanced by relevant sensitivity analyses and by direct comparison with/within populations with a high healthcare consumption, i.e. patients with DM and patients with recent MI. The possibility of a causal relationship between PS and the examined cardiovascular endpoints was strengthened by our study design which controlled for important measured confounders (i.e. comorbidity, concomitant pharmacological treatment, and age), the finding of a consistent dose-response relationship between psoriasis severity and cardiovascular risk. The consistency of the results across several cardiovascular endpoints and sensitivity analyses consolidates the robustness of the thesis results.

8. STUDY WEAKNESSES

Observational studies may reveal disease associations but cannot establish causal relationships, and our result should be interpreted in this context. Some potentially important sources of bias in epidemiological studies of administrative registries, i.e. surveillance bias, selection bias, confounding by indication, and prothopathic bias, deserves to be mentioned again. As discussed in greater detail previously we made every effort to avoid selection bias and surveillance bias and further addressed these important weaknesses in sensitivity analyses. Likewise, confounding by indication and prothopathic bias are unlikely to play important roles, but still it is impossible to completely refute an impact of one or more of these biases on the results presented in this thesis. Furthermore, while the endpoints used in the four papers have all been validated in the Danish registries this was not the case for most diagnoses used to establish comorbidity and the use of hospitalisations are likely to underestimate the true prevalence of these diseases. The psoriasis cohort was defined by claimed prescriptions for topical vitamin D derivatives and our results may not apply to patients treated with topical corticosteroids only. It is, however, important to remember that topical treatment, including vitamin D derivatives are used as first-line PS treatment^{34, 62, 105} and there are no apparent reasons to suspect important differences in patient characteristics between patients with PS treated with topical corticosteroids alone or vitamin D derivatives. Also, the proportion of patients with PS who were never treated with vitamin D is likely to be small as illus-

trated by sensitivity analyses that provided a period prevalence (1997-2006) that was very close to the expected PS prevalence of approximately 2%. Patients with mild PS who were not treated with vitamin D would, however, have been misclassified as controls and thus inflict an uncertainty on the risk estimates towards the null hypothesis. Since the registration of systemic immunosuppressive treatment managed by dermatological departments is incomplete we were unable to use systemic treatment for PS to define our cohort, and also unable to assess any differences in the impact of varying treatment regimens on the cardiovascular risk in patients with PS. The Danish population is predominantly of Caucasian descent the results should only be extrapolated to other ethnicities with caution. In addition, the possibility of residual confounding is present in all observational studies, and the registries do not hold information on some potentially important confounders, e.g. obesity, blood pressure, left ventricular ejection fraction, lipid levels, glucose levels, and smoking.

9. NOVELTY OF THE RESULTS

This thesis comprises four papers based on analyses of Danish nationwide administrative registries. The ability to conduct large-scale contemporary epidemiological studies of an entire population is somewhat unique for Denmark, and while the association between PS and atherosclerosis has previously been studied in various hospital- and population-based settings we were the first to present nationwide unselected data. Furthermore, we were able to do a direct cohort based comparison of cardiovascular risk with PS to that of patients with DM, a well-established cardiovascular risk factor. We thus provided important and reasonably easily interpretable data that are likely to influence future management of cardiovascular risk in the very large group of patients with PS. The novel findings of an association between PS, AF, and VTE serve to further establish PS as an important contributor to cardiovascular disease, and have provided results that add to the current understanding of inflammatory diseases as contributory to AF and VTE.

10. CONCLUSION

The main results of this thesis were that all patients with PS were at increased risk of all-cause mortality and of a range of adverse cardiovascular events in-

cluding MI, stroke, coronary revascularization, cardiovascular death, AF, and VTE. These novel results add to evidence indicating that PS is a clinically significant cardiovascular risk factor and may form background for future interventional studies aimed at improved primary and secondary prevention of cardiovascular disease in patients with PS.

Clinical implications and future research

The present thesis confirmed and extended the available epidemiological evidence of the association between PS and cardiovascular disease. Future epidemiological studies of administrative registries could provide further confirmatory data in independent populations, especially if such registries hold supplementary information on confounders that were not assessed in the present work (see study limitations above). The Danish registries could, however, be used to provide novel information on the impact of PS on prognosis following invasive coronary revascularisation, including data on risk of post-PCI restenosis, in-stent thrombosis and reinterventions. Along this line, large-scale epidemiologic studies of PS and the risk of other immunoinflammatory conditions, cancer, and psychiatric conditions (including depression) are clearly warranted. The ongoing development of the Danish registries to comprise information on clinical data, i.e. from DM registries and databases on general anaesthesia procedures, and the continuous increase of follow-up time will allow for future expansion of the epidemiological data on the association between PS and cardiovascular disease.

Furthermore, prospective studies accounting more completely for PS severity and for differences in systemic immunomodulatory treatment may provide clinically important information, e.g. by exploring the notion that aggressive treatment of PS may diminish the risk of future cardiovascular events. Also, whether more aggressive primary and secondary cardiovascular risk factor modification is beneficial in these patients is unknown, and studies aimed at evaluating such interventions are urgently needed. These studies will more precisely define the diagnostic, therapeutic, and prognostic consequences of PS in the context of cardiovascular disease and such data will form the background for guidelines aimed at cardiovascular risk management in patients with PS.

11. SUMMARY

Atherosclerosis and PS are prevalent chronic immunoinflammatory diseases with pathophysiological,

clinical and epidemiological similarities. Results suggest that PS may be an independent risk factor for cardiovascular disease. Participation of similar immunoinflammatory and prothrombotic mechanisms in PS and cardiovascular disease is supported by evidence that treatment with methotrexate in patients with PS is associated with reduced cardiovascular risk. Furthermore, PS is associated with surrogate markers of cardiovascular disease, e.g. endothelial dysfunction and coronary calcification, and with markers of increased platelet activity. However, results of epidemiological studies of the risk of cardiovascular disease in PS have been conflicting, and surveillance bias has been proposed to contribute to the observed association. Although similar considerations of shared immunoinflammatory pathways with PS can be applied to AF and VTE very little is known about the interaction between PS and these common diseases.

With the underlying hypothesis that PS had detrimental effects on all prespecified adverse cardiovascular endpoints the objective of the current thesis was to examine in these patients: 1) the risk of atherothrombotic events and compare it with the risk in patients with DM; 2) the risk of AF and ischaemic stroke; 3) the risk of VTE; and 4) the prognosis after first-time MI.

By use of the unique Danish nationwide registries approximately 40,000 patients with PS, including approximately 3000 patients with severe PS were identified in the study period 1997-2006. Paper I provided a comparison of cardiovascular risk between patients with PS, approximately 127,000 patients with DM, and the general population, respectively. Patients with PS were at increased risk of all endpoints including, MI, stroke, invasive coronary revascularization, cardiovascular death, and a composite cardiovascular endpoint (MI, stroke, and cardiovascular death). For the composite endpoint the rate ratios (RRs) were 1.20 (95% confidence interval [CI] 1.14-1.25), 1.58 (CI 1.36-1.85), and 1.59 (CI 1.56-1.63) for mild PS, severe PS, and DM, respectively. Paper II documented an up to 2.5 fold increase in risk of AF and ischaemic stroke in patients with PS, with the highest risk estimates for young patients with severe disease. The main results of paper III were that patients with PS had an increased risk of VTE with RR 1.35 (CI 1.21-1.49) and RR 2.06 (CI 1.63-2.61) for mild and severe PS, respectively. Paper IV on post-MI prognosis included 615 patients with PS and a recent MI. The results docu-

mented that after first-time MI, these patients had an increased risk of a composite of recurrent MI, stroke, and cardiovascular death with hazard ratio 1.26 (CI 1.12-1.41) as compared to patients without PS.

In conclusion, this thesis demonstrated that all patients with PS were at increased risk of atherothrombotic events and that the risk with severe PS was comparable to that of patients with DM. Furthermore, the thesis provided novel evidence of PS as a possible risk factor for AF and VTE. Finally, we demonstrated an association between PS and adverse prognosis following first-time MI. The results add importantly to evidence indicating that PS is an independent cardiovascular risk factor and should form the background for studies of interventions aimed at improved primary and secondary prevention of cardiovascular disease in patients with PS.

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