

CLINICAL REPORT

Risk of Acute Myocardial Infarction or Stroke in Patients with Mycosis Fungoides and Parapsoriasis

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Mycosis fungoides (MF) and parapsoriasis display increased inflammation, which may be associated with increased risk of arterial cardiovascular events. The aim of this Danish nationwide population-based cohort study was to assess the relative risk (RR) of acute myocardial infarction (AMI) or stroke in patients with MF and parapsoriasis. In patients with MF, the RR of AMI or stroke was 1.0 (95% confidence interval (95% CI) 0.7–1.3). In the second half of the study period, the RR was 1.8 (95% CI 1.1–2.9) during the first 5 years of follow-up. In men with parapsoriasis, the RR of AMI or stroke was 1.7 (95% CI 1.1–2.7) within the first 5 years of follow-up, whereas the RR of AMI during the first 5 years of follow-up was 2.0 (95% CI 1.2–3.4). In conclusion, patients with MF and parapsoriasis have an increased RR of AMI or stroke within the first 5 years of follow-up. Key words: mycosis fungoides; parapsoriasis; cutaneous T-cell lymphoma; comorbidities; acute myocardial infarction; stroke.

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Mycosis fungoides (MF) is an extranodal non-Hodgkin lymphoma with malignant proliferation of T lymphocytes in the skin (1, 2). In early disease stages, MF presents as erythematous skin patches and plaques, which may progress to tumour formation, and may disseminate to lymph nodes and internal organs (1, 2).

Parapsoriasis is an inflammatory skin disorder, whose manifestations resemble the clinical and histopathological findings in early MF. It has been regarded as a distinct entity or an early form of MF, although this remains a matter of debate (3–12).

MF and parapsoriasis display increased low-grade systemic inflammation (1, 13–15) similar to that observed in patients with psoriasis (13) and other immune inflammatory diseases, that are associated with an increased risk of arterial cardiovascular events (16). The inflammation in psoriasis and other immune inflammatory diseases is regarded as a risk factor for arterial cardiovascular events (16, 17). A correlation with the degree of inflammation has been indicated, as evidenced by a heightened risk

of acute myocardial infarction (AMI) in patients with severe disease (18). Furthermore, evidence is mounting that inflammation plays a key role in the pathogenesis of atherosclerosis and that inflammation can elicit arterial cardiovascular events (19).

We therefore hypothesized that both MF and parapsoriasis are associated with an increased risk of arterial cardiovascular events. Because of the implications for clinical treatment of MF and parapsoriasis, it is important to expand our sparse knowledge of arterial cardiovascular events in these patients. The aim of this study was to conduct a nationwide population-based cohort study to assess the risk of AMI or stroke in patients with MF and parapsoriasis, using data from the unique Danish medical and administrative registries.

METHODS

The study was conducted using data from the Danish Cancer Registry (DCR) and the Danish National Registry of Patients (DNRP). The DCR has been recording data on the incidence of cancer in Denmark since 1943. Diagnoses have been coded according to the modified Danish version of the International Classification of Diseases, 10th revision (ICD-10), since 1978 (20). Registration is based on notification forms from hospitals, including departments of pathology and forensic medicine, and from practicing physicians (20). Comprehensive assessment has shown that the DCR is 95–98% complete and valid (20). The DNRP was established in 1977 and records 99.4% of all discharges from Danish non-psychiatric acute-care hospitals (21). Information in the DNRP includes dates of hospital admission and discharge, surgical procedures performed, and discharge diagnoses classified according to the Danish version of the International Classification of Diseases, 8th revision (ICD-8) until 31 December 1993, and the 10th revision (ICD-10) thereafter (21). Diagnostic data from outpatient visits have been recorded since 1995 (21). Parapsoriasis is considered a non-malignant disease, and it is most commonly treated in outpatient clinics. This diagnosis has therefore been registered in the DNRP only since 1995.

Patients can be linked among Danish registries at the level of the individual by means of the unique civil registration number (CRN) assigned to all Danish residents at birth. The CRN is recorded in the Danish Civil Registration System (CRS), along with date of birth, residency status, and dates of immigration, emigration and death (22).

We established a cohort of all patients with a first-time diagnosis of MF in the DCR between 1 January 1980 and 31 December 2010, and a cohort of all patients with a first-time diagnosis of parapsoriasis recorded in the DNRP from 1 January 1995 to 31 December 2011. All MF and parapsoriasis patients were diagnosed by trained dermatologists and pathologists, and were all treated at a department of dermatology. The criteria

for the parapsoriasis diagnosis were clinical findings of scaly erythematous patches combined with histopathological findings of a superficial lymphocytic infiltrate with pleomorphism, and absence of Pautrier's microabscesses and epidermotropism.

The CRS was used to link all patients to the DNRP in order to identify and exclude those with a previous diagnosis of AMI and/or stroke. Patients under the age of 25 years were also excluded because AMI and stroke are very rare in these patients and may be caused by other disposing risk factors than MF. Patients with parapsoriasis, who progressed to MF ($n=19$), were censored from the parapsoriasis group at the time of progression, and they were included in the MF group. The date of the first MF/parapsoriasis diagnosis was considered the index date.

Utilizing the CRS, 10 population comparison cohort members were randomly selected from the general population for each patient, matched by sex and age on the index date. The 2 patient cohorts and their respective population comparison cohorts were linked to the DNRP in order to identify all hospitalizations for AMI and stroke after the index date. Cohort members were followed until the occurrence of a first hospitalization for AMI or stroke, emigration, death, or 31 December 2011, whichever came first.

Statistical analysis

The number of patients who had a first-time AMI and/or stroke during the follow-up period were counted. Proportional hazards regression was used to compute hazard ratios and 95% confidence intervals (95% CIs) as a measure of the relative risk (RR) of AMI or stroke in patients with MF and parapsoriasis.

The regression analysis was stratified by sex and age below/above 70 years, as previously used (10, 23). As time from onset of symptoms to diagnosis is thought to have decreased over time for patients with MF (24–26), we stratified the analysis on time of diagnosis. The study period was therefore divided into 2 equal parts: the first part of the study period from 1980 to 1995 and the second part of the study period from 1995 to 2010. Patients diagnosed in the first part of the study period could have been at a more advanced stage of their disease at time of diagnosis, and therefore more likely to have experienced arterial cardiovascular events before they had their MF diagnosis, which would have excluded them from the study.

In the regression analysis, we adjusted for the following covariates: diabetes mellitus, hypertension, angina pectoris, chronic ischaemic heart disease, chronic heart failure, and transient cerebral ischaemic attack. RRs were also computed separately for AMI and stroke. Statistical analyses were carried out using SAS software (version 9.2).

The study was approved by the Danish Data Protection Agency (record no. 1-16-01-1-18). No further ethical approval is needed for register-based studies in Denmark.

RESULTS

A total of 483 patients with incident MF and 623 patients with incident parapsoriasis were identified. Of these, 44 MF patients and 53 parapsoriasis patients were diagnosed with AMI or stroke before their index date, and they were therefore excluded from further analysis. Patient characteristics for the remaining 439 MF patients and 570 parapsoriasis patients are shown in Table I. The mean age on the index date was 66 years (range 26–95 years) in patients with MF and 60 years (25–100 years) in patients with parapsoriasis. The youngest patient diagnosed with AMI was 63.1

Table I. Characteristics of patients with mycosis fungoides (MF) and parapsoriasis

Patient characteristics	MF cohort $n=439$	Parapsoriasis cohort $n=570$
Sex: F/M	161/278	264/306
Age: <70 years	257	399
>70 years	182	171
Index year: 1980–1995	205	–
1995–2010	234	–

years in the MF cohort and 40.3 years in the parapsoriasis cohort. For patients diagnosed with stroke, the youngest patient was 48.2 years in the MF cohort and 50.4 years in the parapsoriasis cohort. The female:male ratio was 1:1.7 in patients with MF and 1:1.2 in patients with parapsoriasis. The median follow-up time was 5.1 years (0–32 years) in patients with MF and 6.2 years (0–17 years) in patients with parapsoriasis. The total follow-up time was 3,199 person-years in MF and 4,010 person-years in parapsoriasis.

The overall incidence rate of AMI or stroke was largely the same in patients with MF (14.7 per 1,000 person-years; cumulative incidence 10.7%) and their population comparison cohort (15.6 per 1,000 person-years; cumulative incidence 15.1%). During the study period, the overall RR of AMI or stroke was 1.0 (95% CI 0.7–1.3) in patients with MF (Table II). In separate analyses of the 2 endpoints, no increased RR of either AMI or stroke was found in patients with MF (Table II). However, MF patients diagnosed in the second half of the study period (1995–2010) did have an increased RR of AMI or stroke within the first 5 years of follow-up (RR=1.8; 95% CI 1.1–2.9) (Table III).

The overall incidence rate of AMI or stroke was 12.0 per 1,000 person-years in patients with parapsoriasis (cumulative incidence 8.4%) and 9.9 per 1,000 person-years (cumulative incidence 7.5%) in their population comparison cohort. The overall RR of AMI or stroke was 1.2 (95% CI 0.9–1.6). A slightly elevated RR of AMI or stroke was found in men with parapsoriasis (RR=1.3; 95% CI 0.9–1.9), but not in women (RR=1.0; 95% CI 0.6–1.6) (Table II). Notably, within the first 5 years of follow-up, the RR of AMI or stroke was increased in men with parapsoriasis (RR=1.7; 95% CI 1.1–2.7) (Table III). In an analysis in which the 2 endpoints were examined separately, the RR of AMI was 1.4 (95% CI 0.9–2.2) (Table II). After stratifying by follow-up time, we found an increased RR of AMI in patients with parapsoriasis during the first 5 years of follow-up (RR=2.0; 95% CI 1.2–3.4) (Table III).

DISCUSSION

This nationwide cohort study investigates the risk of AMI or stroke in patients with MF and parapsoriasis. The results showed that, within the first 5

Table II. Relative risk of acute myocardial infarction (AMI) or stroke in patients with mycosis fungoides (MF) and parapsoriasis

	Mycosis fungoides						Parapsoriasis					
	Cohort (n=439)			Population comparison (n=4,390)			Cohort (n=570)			Population comparison cohort (n=5,700)		
	No./1,000 person-years	Relative risk crude (95% CI)	Relative risk adjusted ^a (95% CI)	No./1,000 person-years	Relative risk crude (95% CI)	Relative risk adjusted ^a (95% CI)	No./1,000 person-years	Relative risk crude (95% CI)	Relative risk adjusted ^a (95% CI)	No./1,000 person-years	Relative risk crude (95% CI)	Relative risk adjusted ^a (95% CI)
AMI or stroke	47	14.7	1.0 (0.7-1.3)	665	15.6	1.0 (0.7-1.3)	48	12.0	1.2 (0.9-1.7)	428	9.9	1.2 (0.9-1.6)
Females	14	10.6	1.0 (0.6-1.7)	200	11.5	1.0 (0.6-1.7)	17	8.4	1.0 (0.6-1.7)	174	8.2	1.0 (0.6-1.6)
Males	33	17.6	1.0 (0.7-1.4)	465	18.5	1.0 (0.7-1.4)	31	15.6	1.4 (0.9-2.0)	254	11.4	1.3 (0.9-1.9)
<70 years	26	11.2	1.1 (0.7-1.6)	351	11.5	1.1 (0.7-1.6)	23	7.3	1.2 (0.8-1.8)	205	6.2	1.2 (0.8-1.8)
>70 years	21	24.4	1.0 (0.6-1.5)	314	25.8	1.0 (0.6-1.5)	25	28.8	1.4 (0.9-2.1)	223	21.5	1.3 (0.9-2.0)
1980-1995	27	14.2	0.9 (0.6-1.3)	444	16.5	0.9 (0.6-1.3)	-	-	-	-	-	-
1995-2010	20	15.6	1.1 (0.7-1.8)	221	14.1	1.1 (0.7-1.8)	-	-	-	-	-	-
AMI	24	7.3	1.1 (0.7-1.6)	313	7.1	1.1 (0.7-1.6)	25	6.1	1.5 (1.0-2.3)	184	4.2	1.4 (0.9-2.2)
Stroke	27	8.3	1.0 (0.7-1.5)	370	8.5	1.0 (0.7-1.5)	25	6.1	1.1 (0.7-1.7)	240	5.4	1.1 (0.7-1.7)

Data are number of events, unless otherwise specified.

^aAdjusted for diabetes mellitus, hypertension, angina pectoris, chronic ischaemic heart disease, chronic heart failure, and transient cerebral ischaemic attack. CI: confidence interval.

Table III. Adjusted relative risk of acute myocardial infarction (AMI) or stroke during follow-up of patients with mycosis fungoides (MF) and parapsoriasis

	MF population comparison cohort (n=4,390)						Parapsoriasis population comparison cohort (n=5,700)					
	MF cohort (n=439)			Parapsoriasis cohort (n=570)			MF cohort (n=439)			Parapsoriasis cohort (n=570)		
	0-5 years' follow-up	>5 years' follow-up	Relative risk adjusted ^a (95% Confidence interval)	0-5 years' follow-up	>5 years' follow-up	Relative risk adjusted ^a (95% Confidence interval)	0-5 years' follow-up	>5 years' follow-up	Relative risk adjusted ^a (95% Confidence interval)	0-5 years' follow-up	>5 years' follow-up	Relative risk adjusted ^a (95% Confidence interval)
AMI or stroke	27	20	1.3 (0.9-1.9)	246	419	0.8 (0.5-1.2)	27	21	1.3 (0.9-1.9)	219	209	1.1 (0.7-1.8)
Females	7	7	1.6 (0.7-3.5)	50	150	0.7 (0.3-1.6)	6	11	0.7 (0.3-1.7)	85	89	1.3 (0.7-2.5)
Males	20	13	1.2 (0.7-1.9)	196	269	0.8 (0.5-1.4)	21	10	1.7 (1.1-2.7)	134	120	1.0 (0.5-1.9)
<70 years	13	13	1.6 (0.9-2.8)	93	258	0.8 (0.5-1.4)	11	12	1.3 (0.7-2.5)	86	119	1.1 (0.6-2.0)
>70 years	14	7	1.1 (0.7-1.9)	153	161	0.8 (0.4-1.7)	16	9	1.4 (0.8-2.3)	133	90	1.4 (0.7-2.7)
1980-1995	9	18	0.8 (0.4-1.6)	128	316	0.9 (0.6-1.5)	-	-	-	-	-	-
1995-2010	18	2	1.8 (1.1-2.9)	103	103	0.3 (0.1-1.1)	-	-	-	-	-	-
AMI	14	10	1.3 (0.8-2.3)	124	189	0.8 (0.4-1.6)	16	9	2.0 (1.2-3.4)	86	98	1.0 (0.5-2.0)
Stroke	13	14	1.3 (0.7-2.3)	118	252	0.9 (0.5-1.5)	12	13	1.0 (0.5-1.8)	129	111	1.3 (0.7-2.3)

Data are number of events, unless otherwise specified.

^aAdjusted for diabetes mellitus, hypertension, angina pectoris, chronic ischaemic heart disease, chronic heart failure, and transient cerebral ischaemic attack.

years of being diagnosed, these patients have a higher RR of AMI or stroke than a matched general population cohort after adjustment for potential confounders. The RR of AMI was 2-fold increased in patients with parapsoriasis during the first 5 years of follow-up. Furthermore, the combined RR of AMI and stroke was increased by 70% in male parapsoriasis patients during the first 5 years of follow-up. In MF patients diagnosed in the second part of the study period (1995–2010), the RR of AMI or stroke was increased by 80% during the first 5 years of follow-up.

An increased risk of arterial cardiovascular events has previously been described in patients with other chronic immune inflammatory diseases, such as psoriasis and rheumatoid arthritis (16, 17, 27, 28). In these diseases, the inflammatory Th1/Th2 imbalance has been related to formation of atherosclerosis and the increased risk of arterial cardiovascular events (17, 28). The inflammatory properties in psoriasis and rheumatoid arthritis essentially resemble those of MF and parapsoriasis with increased Th1 inflammation (1, 13–15); and it is therefore plausible that they induce the same pro-atherogenic effects as those described for psoriasis and rheumatoid arthritis.

It has been reported previously, that patients with MF as well as patients with parapsoriasis have an increased mortality within the first 5 years of follow-up (10). These findings indicate that a particular subgroup of MF and parapsoriasis patients harbour a clinically aggressive form of their disease (10). This subgroup of patients may respond with severe inflammation, which increases their risk of arterial cardiovascular events. Thus, these previous data accord with the present findings of an increased risk of arterial cardiovascular events in MF and parapsoriasis patients within the first 5 years of follow-up (10). Patients with more than 5 years follow-up may have a more indolent clinical course of their disease and a lower degree of systemic inflammation, which may explain that they have no increased risk of arterial cardiovascular events.

The time elapsed from symptom onset to diagnosis of MF and parapsoriasis is usually several years (29). The inflammatory process therefore exerts its effects on the mechanisms underlying arterial cardiovascular events long before a firm diagnosis of MF or parapsoriasis is established. Consequently, AMI or stroke often occurs shortly after the MF or parapsoriasis diagnosis is made. A similar pattern of immediate increase in the RR of arterial cardiovascular events has been observed in persons shortly after they were diagnosed with rheumatoid arthritis (30).

Over the study period, growing awareness and better tools for diagnosis of patients with MF may have shortened the time from symptom onset to diagnosis of MF (24–26). Earlier recognition of MF could have reduced the risk of exclusion from the study due to AMI or stroke before the MF diagnosis was established. This argument is consistent with the finding that more MF-related arterial cardiovascular events were recorded in the second half of the study period than during the first half of the study period.

Systemic retinoids used in treatment of MF may induce dyslipidaemia and therefore increase the risk of arterial cardiovascular disease. However, time from exposure of increased blood lipids to development of arterial cardiovascular events may last several years. Furthermore, systemic retinoid treatment is always accompanied by monitoring of blood lipids and treatment of dyslipidaemia, which may avoid or postpone occurrence of arterial cardiovascular events, thus systemic retinoids are not believed to cause cardiovascular events, especially not within the first 5 years of follow-up (31, 32). Patients with parapsoriasis are primarily treated with skin-directed therapies (e.g. topical corticosteroids, nitrogen mustard, psoralen plus ultraviolet A irradiation (PUVA), and narrow-band ultraviolet B irradiation) (11), which have no known adverse cardiovascular effects (23, 33). Collectively, the clinical treatment of MF and parapsoriasis patients is not believed to influence the risk of subsequent arterial cardiovascular events.

A strength of the study is its population-based cohort study design, with complete long-term follow-up, and without selection bias. Since the Danish National Health Service provides free access to healthcare, referral and diagnostic biases are also largely avoided. The validity of our data depends mainly on the accuracy of the coding of MF and parapsoriasis and the endpoint diagnoses. The Danish registries have a high validity for cancer diagnoses with high classification specificity (20). To ensure a high validity of the parapsoriasis diagnosis, the cohort was restricted to patients treated at hospital departments of dermatology.

Discharge diagnoses have been documented to have a positive predictive value of 90% for AMI (34, 35), and the predictive value is slightly lower for stroke (36, 37). However, a limited specificity of these diagnoses would have biased the relative risk estimates towards the null. As we lacked data on disease stage of MF, we could draw no conclusions as to the relative importance of disease severity for the risk of arterial cardiovascular events, which is a study limitation.

The most prominent finding of the present study is that both patients with MF and parapsoriasis have an increased risk of AMI or stroke within the first 5 years of follow-up. It is plausible that the excess cardiovascular risk is mediated by chronic inflammation, which emphasizes the importance of adequate treatment of MF and parapsoriasis. Thus, early diagnosis, treatment and intervention against cardiovascular risk factors should be emphasized in the clinical management of patients with newly diagnosed MF and parapsoriasis.

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