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Insights from a nationwide cohort

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DR. ADELINA YAFASOVA (Orcid ID: 0000-0003-3889-0080)

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Increased long-term risk of heart failure and other adverse cardiac outcomes in dermatomyositis and polymyositis: Insights from a nationwide cohort

Running title: Cardiac outcomes in DM/PM

Adelina Yafasova, MD,a Louise P. Diederichsen, MD, PhD,b Morten Schou, MD, DMSc,c Guoli Sun, MD,a Christian Torp-Pedersen, MD, DMSc,d Gunnar H. Gislason, MD, PhD,c,e,f Emil L. Fosbøl, MD, PhD,a Lars Køber, MD, DMSc,a Jawad H. Butt, MDa

† Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
b Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
c Department of Cardiology, Herlev and Gentofte University Hospital, Herlev, Denmark
d Department of Cardiology, Nordsjællands Hospital, Hillerød, Denmark
e The National Institute of Public Health, University of Southern Denmark, Odense, Denmark.
f The Danish Heart Foundation, Copenhagen, Denmark

ABSTRACT

Background: Mounting evidence suggests that dermatomyositis/polymyositis (DM/PM) are associated with increased risk of atherosclerotic events and venous thromboembolism. However, data on the association between DM/PM and other cardiac outcomes, especially heart failure (HF), are scarce.

Objectives: To examine the long-term risk and prognosis associated with adverse cardiac outcomes in patients with DM/PM.

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Methods: Using Danish administrative registries, we included all patients ≥18 years with newly diagnosed DM/PM (1996-2018). Risks of incident outcomes were compared with non-DM/PM controls from the background population (matched 1:4 by age, sex, and comorbidity). In a secondary analysis, we compared mortality following HF diagnosis between DM/PM patients with HF and non-DM/PM patients with HF (matched 1:4 by age and sex).

Results: The study population included 936 DM/PM patients (median age 58.5 years, 59.0% women) and 3,744 matched non-DM/PM controls. The median follow-up was 6.9 years. Absolute 10-year risks of incident outcomes for DM/PM patients vs matched controls were: HF, 6.98% (CI, 5.16-9.16%) vs 4.58% (3.79-5.47%) (P=0.002); atrial fibrillation, 10.17% (7.94-12.71%) vs 7.07% (6.09-8.15%) (P=0.005); the composite of ICD implantation/ventricular arrhythmias/cardiac arrest, 1.99% (1.12-3.27%) vs 0.64% (0.40-0.98%) (P=0.02); all-cause mortality, 35.42% (31.64-39.21%) vs 16.57% (15.10-18.10%) (P<0.0001). DM/PM with subsequent HF was associated with higher mortality compared with HF without DM/PM (adjusted hazard ratio 1.58 [CI, 1.01-2.47]).

Conclusion: Patients with DM/PM had a higher associated risk of HF and other adverse cardiac outcomes compared with matched controls. Among patients developing HF, a history of DM/PM was associated with higher mortality.

Keywords: Heart failure; atrial fibrillation; autoimmune disease; inflammation; cohort study.

ABBREVIATIONS
DM/PM: Dermatomyositis/polymyositis
HF: Heart failure
ICD: Implantable cardioverter-defibrillator
ICD-8 and ICD-10: International Classification of Diseases, 8th and 10th revision
HR: Hazard ratio
CI: Confidence interval

INTRODUCTION
Dermatomyositis/polymyositis (DM/PM) are rare idiopathic inflammatory myopathies characterized by muscle inflammation and proximal muscle weakness; other relevant subgroups on the same spectrum include inclusion body myositis, immune-mediated necrotising myopathy, and antisynthetase syndrome. Cutaneous involvement is one of the clinical features distinguishing DM from PM. Other extramuscular manifestations include the joints, lungs, gastrointestinal tract, and heart.[1-3] Cardiac involvement is well-documented in other rheumatic diseases, including rheumatoid arthritis[4] and systemic lupus erythematosus;[5] however, there is a paucity of large-scale data on the association between DM/PM and cardiac manifestations. Population-based studies have shown that DM/PM are associated with increased risk of atherosclerotic disease (including myocardial infarction, ischaemic stroke, and peripheral artery disease)[6-11], venous thromboembolism,[12] and mortality due to cardiovascular disease.[13] Other cardiac manifestations, including heart failure (HF) and arrhythmic outcomes, have also been reported, but the estimated prevalence varies substantially.[14-21] Most data were derived from case reports[22, 23] or studies limited by small study populations, including imaging and autopsy studies.[20, 21, 24] Cardiac involvement is a frequent cause of death in patients with DM/PM,[14-17] yet data on the long-term risk of adverse cardiac outcomes, especially HF, in patients with DM/PM are lacking. Given the generally high morbidity and mortality of HF,[25] it is important to quantify the risk of its development and prognosis in patients with DM/PM. Such data are warranted prior to developing cardiac screening recommendations for DM/PM patients and future investigation of treatment strategies in DM/PM patients with cardiac involvement. We therefore conducted a nationwide cohort study to assess the long-term risk of incident HF and other adverse cardiac outcomes in adults diagnosed with DM/PM compared with age-, sex-, and comorbidity-matched controls from the background population. Further, we compared long-term mortality in patients with incident HF with and without a history of DM/PM.

MATERIALS AND METHODS

Data sources

Denmark has a universal, tax-funded healthcare system. All Danish residents are assigned a unique personal registration number which enables individual-level linkage between nationwide registries. This study used data from the following administrative registries: 1) The Danish National Patient Registry, which contains information on all hospital contacts including discharge diagnoses according to the International Classification of Diseases (ICD-
8 until 1994, ICD-10 thereafter) and all surgical procedures according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures;[26] 2) The Danish National Prescription Registry, which contains information on all claimed drug prescriptions in Danish pharmacies;[27] and 3) The Danish Civil Registration System, which contains information on birth date, sex, and vital status, including date of death and emigration.[28]

**Study population**

We identified all residents in Denmark ≥18 years with a first-time primary or secondary in- or outpatient diagnosis of DM or PM in the period between January 1, 1996 and June 30, 2018. A diagnosis of DM/PM was defined as at least two in- or outpatient hospital contacts with DM/PM within one year. Patients with a diagnosis code of juvenile DM were not included. Patients were excluded from the study population if they met the following exclusion criteria (eTable 1 for diagnosis and procedure codes): 1) Prior implantation of a pacemaker or implantable cardioverter-defibrillator (ICD) or 2) a prior primary or secondary in- or outpatient diagnosis of HF or cardiac arrhythmia (atrial fibrillation/flutter, ventricular arrhythmia [ventricular tachycardia, flutter, or fibrillation], cardiac arrest, atrioventricular block [advanced 2nd or 3rd degree], sinoatrial dysfunction). In order to avoid immortal time bias, the index date was defined as the date of the second diagnosis of DM or PM, and controls from the background population received the same index as a DM/PM patient and were subject to the same exclusion criteria. Each case was matched in a 1:4 ratio with controls from the background population by year of index date, sex, age (maximum difference of one year), and comorbidity (ischaemic stroke, ischaemic heart disease, peripheral artery disease, venous thromboembolism [deep venous thrombosis or pulmonary embolism], hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease) using risk-set matching.

**Comorbidity and concomitant pharmacotherapy**

Comorbidity was defined using primary and secondary in- and outpatient diagnosis codes prior to index (eTable 1 for diagnosis codes) with the following exceptions: hypertension was identified using claimed drug prescriptions within six months prior study inclusion, while diabetes was defined using diagnosis codes and/or claimed drug prescriptions within six months prior to study inclusion. Information on pharmacotherapy at baseline was obtained using claimed prescriptions within the last six months prior to index. Medical treatment after diagnosis of HF was defined using claimed prescriptions within four months after HF.
diagnosis. Treatment with immunosuppressants was defined as claimed prescriptions within six months after DM/PM diagnosis. See eTable 2 for Anatomical Therapeutic Chemical Classification System codes.

Outcomes
Outcomes were defined as primary or secondary in- or outpatient diagnoses (eTable 1 for diagnosis and procedure codes). The primary outcome was HF, while secondary outcomes were atrial fibrillation or flutter; a composite of ICD implantation/ventricular arrhythmias (ventricular tachycardia, flutter, or fibrillation)/cardiac arrest; a composite of pacemaker implantation/advanced 2nd or 3rd degree atrioventricular block/sinoatrial dysfunction; and all-cause mortality. Diagnosis codes for outcomes have been validated in the Danish National Patient Registry with high positive predictive values, [29-32] including 84-100% for HF[29, 31], 100% for ICD and pacemaker implantation[32], >90% for atrial fibrillation and cardiac arrest[30], and 80-90% for ventricular tachycardia/fibrillation.[30] We followed patients from index until outcome, emigration, death, or end of the study (December 31, 2018), whichever came first.

Secondary analysis
In a secondary analysis, patients with DM/PM who developed HF were matched 1:4 by sex, age (maximum difference of one year), type of diagnosis (in- or outpatient), and year of HF diagnosis with HF patients without a prior diagnosis of DM/PM. All-cause mortality was the primary outcome.

Statistics
Baseline characteristics were reported as medians with interquartile ranges for continuous variables or frequencies and percentages for categorical variables. Differences in baseline characteristics between the DM/PM population and the background population were tested using the Wilcoxon test for continuous variables and the chi-square or Fisher’s exact test for categorical variables. The Aalen-Johansen estimator was used to estimate absolute risks of all outcomes except all-cause mortality, taking the competing risk of death into account; differences between groups were examined with Gray’s test. The Kaplan-Meier estimator was used to estimate the absolute risk of all-cause mortality; differences between groups were
examined with the log-rank test. We calculated incidence rates per 1,000 person-years with 95% confidence intervals (CI) for all outcomes. Rates of outcomes were examined using Cox regression conditional on the matching (comparing cases with their matched controls), with the background population as the reference. Due to differences in baseline characteristics, hazard ratios (HRs) were adjusted for prior liver disease and malignancy. The assumption of proportional hazards was not met for two outcomes: HF and all-cause mortality. Therefore, incidence rates and HRs for these outcomes were reported for two periods in landmark analyses (day 0 to 365; day 366 day to full follow-up). There was no interaction between DM/PM status and sex, age (neither as a continuous nor categorical [below/above the median age] variable), or calendar year on the rate of outcomes. For the secondary analysis of all-cause mortality following HF diagnosis, the proportional hazards assumption was fulfilled, and HRs were adjusted for a history of ischaemic stroke, ischaemic heart disease, atrial fibrillation, venous thromboembolism, diabetes, hypertension, peripheral artery disease, malignancy, chronic obstructive pulmonary disease, chronic kidney disease, liver disease, and use of lipid-lowering medication.

A P-value below 0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software (SAS 9.4, Cary, NC, USA).

Sensitivity analyses
To test the robustness of the findings, we restricted the primary outcome to 1) primary HF diagnoses and 2) inpatient HF diagnoses. Further, to detect patients with possible antisynthetase syndrome or cancer-associated myositis, we performed a sensitivity analysis which excluded DM/PM cases and controls who had a diagnosis of cancer or interstitial lung disease prior to index.

Ethics
This study is approved by the Capital Region of Denmark (approval number: P-2019-348) in accordance with the General Data Protection Regulation. In Denmark, there is no requirement for ethics committee approval in registry-based studies in which individuals cannot be identified.

RESULTS
From January 1, 1996 to June 30, 2018, 1,061 patients ≥18 years were diagnosed with DM/PM in Denmark. After application of exclusion criteria, 965 patients were included in the
study; of these, 936 patients were matched with 3,744 controls without DM/PM. Table 1 shows baseline characteristics for the DM/PM population and background population. The median age was 58.5 years (interquartile range 46.4-68.9 years), and 59.0% were women. The median follow-up from the index date until emigration, death, or end of the study was 6.9 years (interquartile range 3.1-12.4 years). Within six months after diagnosis of DM/PM, 645 patients (68.9%) claimed a prescription of glucocorticoids; 242 patients (25.9%) claimed a prescription of azathioprine; 153 patients (16.4%) claimed a prescription of methotrexate.

**Heart failure**

Figure 1 depicts the absolute risk of incident HF for the DM/PM and background population. The absolute 10-year risk of incident HF was 6.98% (CI, 5.16-9.16%) for DM/PM patients and 4.58% (CI, 3.79-5.47%) for the background population. From day 0 till day 365, the incidence rate of HF per 1,000 person-years was 18.76 (CI, 11.49-30.63) in DM/PM patients and 2.99 (CI, 1.65-5.39) in the matched background population (adjusted HR 8.42 [CI, 3.26-21.78]). From day 366 till the end of follow-up, the incidence rate of HF per 1,000 person-years was 8.20 (CI, 6.10-11.02) in DM/PM patients and 5.46 (CI, 4.65-6.41) in the matched background population (adjusted HR 1.91 [CI, 1.30-2.79]).

**All-cause mortality after diagnosis of heart failure**

During follow-up, 60 patients with DM/PM developed HF; they were matched with 240 non-DM/PM controls with HF based on age and sex. The median follow-up from diagnosis of HF until emigration, death, or end of the study was 3.1 years (interquartile range 0.9-6.2 years) and 4.0 years (interquartile range 1.3-8.0 years) years for the DM/PM population and the non-DM/PM population, respectively. Table 2 summarizes characteristics for the two groups of HF patients. Though not statistically significant, treatment with renin-angiotensin system inhibitors/beta blockers and mineralocorticoid receptor antagonists within four months after HF diagnosis was less common in DM/PM patients with HF compared with matched controls without DM/PM. The unadjusted all-cause mortality rate per 1,000 person-years was 142.49 (CI, 103.68-195.82) for the DM/PM population with HF and 101.00 (CI, 85.10-119.86) for the non-DM/PM population with HF (adjusted HR 1.58 [CI, 1.01-2.47]).

**Secondary outcomes**

Figure 2 shows the absolute risks of secondary outcomes. Absolute 10-year risks of outcomes were: atrial fibrillation or flutter, 10.17% (CI, 7.94-12.71%) for DM/PM patients and 7.07%
for DM/PM patients and 0.64% (CI, 0.40-0.98%) for the matched background population; a composite of ICD implantation/ventricular arrhythmia/cardiac arrest, 1.99% (CI, 1.12-3.27%) for DM/PM patients and 1.00% (CI, 0.67-1.45%) for the matched background population; all-cause mortality, 35.42% (CI, 31.64-39.21%) for DM/PM patients and 16.57% (CI, 15.10-18.10%) for the matched background population. Figure 3 shows unadjusted incidence rates and adjusted HRs of outcomes. For all outcomes, DM/PM was associated with a significantly higher rate of outcomes compared with the background population in the Cox regression model. As for the primary outcome of HF, HRs were highest within the first 365 days after diagnosis for all-cause mortality.

Sensitivity analyses
We found results similar to the main analysis when restricting the primary outcome to primary diagnoses of HF only (0-365 days: HR 10.02 [CI, 3.11-32.30], >365 days: HR 2.02 [CI, 1.27-3.21]) and inpatient diagnoses of HF only (0-365 days: HR 8.05 [CI, 2.41-26.85], >365 days: HR 2.26 [CI, 1.50-3.41]). After excluding cases and controls with a previous diagnosis of cancer or interstitial lung disease, we matched 785 patients with DM/PM with 3,140 controls. This sensitivity analysis also yielded results similar to the main analysis for the primary outcome of HF (0-365 days: HR 6.83 [CI, 2.86-16.28]; 365 days to full follow-up: HR 2.33 [CI, 1.52-3.57]).

DISCUSSION
This nationwide cohort study on long-term cardiac outcomes in patients with DM/PM yielded three main findings. First, DM/PM patients had a higher long-term risk of HF compared with a matched background population. Second, a history of DM/PM was associated with higher all-cause mortality among patients developing HF. Finally, DM/PM patients had higher long-term risks of arrhythmic outcomes and all-cause mortality compared with a matched background population.

Heart failure
Although HF is reported to be one of the most frequent cardiac manifestations in DM/PM,[14-16] most data are derived from case reports[22, 23], cardiac imaging studies,[20] and autopsy studies.[24] To our knowledge, no large population-based studies have examined the long-
term risk of HF in patients with DM/PM. In the present study, we found that DM/PM was associated with a higher long-term risk of HF compared with matched controls from the background population. The rate of HF was highest within the first 365 days after DM/PM diagnosis, but also remained elevated compared with matched controls beyond the first 365 days. Similar trends have been observed for ischaemic stroke and myocardial infarction in other studies. We also found that DM/PM patients developing HF had higher associated all-cause mortality compared with non-DM/PM controls with HF. Although speculative, there are several possible explanations for this finding. First, it is possible that HF is diagnosed at a late stage in DM/PM patients. Second, DM/PM patients with HF may not receive the optimal treatment for their HF. Third, it is possible that the higher mortality is, at least partly, due to the myositis itself and its non-cardiovascular manifestations. Though cardiovascular involvement is reported to be among the leading causes of death in patients with DM/PM, specific recommendations for cardiac screening, monitoring and treatment of patients with DM/PM and cardiac involvement are non-existing. Our findings stress the need for surveillance and prevention of cardiac complications in DM/PM and investigation of optimal treatment strategies in this patient group.

Although we did not have information on HF aetiology and pathophysiology in our DM/PM cohort, there are several interesting observations to be noted. The prevalence of ischaemic heart disease, hypertension, and atrial fibrillation was similar in patients with DM/PM who developed HF and age- and sex-matched HF controls without DM/PM. Although speculative, this indicates that development of HF in patients with DM/PM can at least partly be explained by traditional risk factors, which further underlines the importance of risk factor prevention in these patients. Use of lipid-lowering medication was lower in patients with DM/PM developing HF compared with non-DM/PM controls who developed HF. It is possible that clinicians are hesitant in prescribing statins to patients with DM/PM due to the risk of muscular adverse effects, which could lead to the development of endothelial dysfunction and coronary artery disease and ultimately HF. Previous studies have found that pathologic findings in the heart of patients with DM/PM revealed myocardial inflammation and necrosis similar to that in skeletal muscles, indicating that inflammation also plays a role in cardiac manifestations of DM/PM. Treatment with glucocorticoids may also play a role in the development of HF in DM/PM. Further investigation of the pathogenesis of HF in DM/PM is warranted. Interestingly, we also found that although not statistically significant, treatment with guideline-recommended therapy for HF with reduced ejection fraction was less common in patients with DM/PM developing HF than non-DM/PM patients with HF. In
Denmark, a diagnosis of HF combined with renin-angiotensin-system inhibitor and beta blocker treatment by 120 days after discharge can accurately be used to identify patients with HF with reduced ejection fraction.[33] Though these are only speculations, these findings may suggest that DM/PM patients with HF develop HF with preserved ejection fraction (i.e., HF with diastolic dysfunction). This is in accordance with a previous imaging study reporting that DM/PM is associated with left ventricular diastolic dysfunction.[20]

Secondary outcomes
DM/PM was also associated with a higher risk of arrhythmic outcomes and all-cause mortality compared with matched controls from the background population. As for HF, an association between DM/PM and other adverse cardiac outcomes has been reported in the literature,[14, 16, 18] but most data were derived from case reports,[23] imaging studies,[20] and autopsy studies.[24] The most common cardiac outcome in both the DM/PM and background population was atrial fibrillation. A Korean cohort study of 343 patients with idiopathic inflammatory myopathies found that the prevalence of atrial fibrillation was higher in idiopathic inflammatory myopathies compared with other autoimmune rheumatic diseases, including rheumatoid arthritis and systemic lupus erythematosus.[21] We also found that DM/PM was associated with a higher rate of the composite of ICD implantation/ventricular arrhythmia/cardiac arrest, further underlining the importance of cardiac monitoring in this patient group. For the composite of pacemaker implantation/atrioventricular block/sinoatrial dysfunction, our results showed that while absolute 10-years risks were similar in the two groups, DM/PM was associated with a higher rate of this outcome in the adjusted Cox regression analysis; thus, further data are warranted. As for all-cause mortality, it is important to note that the excess all-cause mortality is not necessarily only related to cardiovascular events, though it has been reported that cardiovascular disease is a major cause of death in DM/PM.[14, 17]

Strengths and limitations
The primary strength of this study is the nationwide design with complete data, a long follow-up period, and no loss to follow-up. The DM/PM cohort is substantially larger than in previous studies. There are several limitations which deserve acknowledgement. Due to the observational nature of the study, we cannot assess causal relationships. Despite adjustment and matching, we cannot exclude the possibility of residual confounding. Validation of diagnosis codes for DM/PM in the Danish National Patient Registry has not been performed;

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however, the registry has been thoroughly validated and generally shows high validity.[26] In order to improve the validity of the diagnosis further, we restricted the definition of DM/PM to at least two in- or outpatient hospital contacts with DM/PM within one year. The use of glucocorticoids was lower than expected in our cohort. However, as follow-up started at the time of the second diagnosis of DM/PM, some patients may have claimed a prescription of glucocorticoids between the first and the second diagnosis; the true proportion of patients treated with glucocorticoids may therefore be higher than reported. Polymyositis may sometimes be considered an exclusion diagnosis; as it is not possible to differentiate between subgroups of idiopathic inflammatory myopathies based on diagnosis codes, we cannot be entirely sure if some patients in our cohort have other subtypes of idiopathic inflammatory myopathies. Further, although very few, some patients may only be followed in the primary care sector, and their cardiovascular diagnoses would therefore not be included in the study. Finally, we did not have data on certain important covariates, including body mass index, smoking, socioeconomic status, HF aetiology, left ventricular ejection fraction, natriuretic peptides, and New York Heart Association functional class.

CONCLUSION

In this nationwide cohort study, we found that patients with adult-onset DM/PM had a higher associated risk of a wide range of adverse cardiac outcomes, including HF, compared with age-, sex-, and comorbidity-matched controls from the background population. Among patients developing HF, a history of DM/PM was associated with higher mortality. Our results stress the importance of monitoring of cardiac manifestations on a regular basis in patients with DM/PM. Cooperation between rheumatologists and cardiologists is necessary to expand our knowledge in the area.

CONFLICTS OF INTEREST

None.

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**ADDRESS FOR CORRESPONDENCE**

Adelina Yafasova, MD
Department of Cardiology
Rigshospitalet, Copenhagen University Hospital
Blegdamsvej 9, 2100 København Ø, Denmark
E-mail: adelinav@hotmail.com

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ALTERNATIVE PROOFREADER

Jawad Haider Butt, MD
Department of Cardiology
Rigshospitalet, Copenhagen University Hospital
Blegdamsvej 9, 2100 København Ø, Denmark
E-mail: jawad_butt91@hotmail.com

FIGURE LEGENDS

Figure 1: Absolute risk of HF in patients with DM/PM and matched controls from the background population

Figure 2: Absolute risks of secondary outcomes in patients with DM/PM and matched controls from the background population
A. Atrial fibrillation/flutter. B. The composite of ICD implantation/ventricular arrhythmia/cardiac arrest. C. The composite of pacemaker implantation/atrioventricular block (advanced 2nd or 3rd degree)/sinoatrial dysfunction. D. All-cause mortality.

Figure 3: Unadjusted incidence rates and adjusted HRs of outcomes
For HF and all-cause mortality, estimates are reported for day 0 to 365 and day 366 to full follow-up. For the other secondary outcomes, estimates are reported for the full follow-up period.

TABLES

Table 1: Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Background population N=3,744</th>
<th>DM/PM population N=936</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (interquartile range)</td>
<td>58.5 (46.4-68.9)</td>
<td>58.5 (46.4-68.9)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Table 2: Characteristics of heart failure patients with and without DM/PM

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-DM/PM population N=240</th>
<th>DM/PM population N=60</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (interquartile range)</td>
<td>70.0 (62.2-78.1)</td>
<td>70.0 (62.2-78.1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>116 (48.3)</td>
<td>29 (48.3)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Comorbidities, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (10.8)</td>
<td>7 (11.7)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Abbreviations: ADP, adenosine diphosphate; DM/PM, dermatomyositis/polymyositis; N/A, not applicable; RAS, renin-angiotensin system.
<table>
<thead>
<tr>
<th>Condition</th>
<th>N (%)</th>
<th>N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>99 (41.3)</td>
<td>27 (45.0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>71 (29.6)</td>
<td>15 (25.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (52.9)</td>
<td>36 (60.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>22 (9.2)</td>
<td>8 (13.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>13 (5.4)</td>
<td>6 (10.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes</td>
<td>60 (25.0)</td>
<td>13 (21.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>20 (8.3)</td>
<td>8 (13.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>40 (16.7)</td>
<td>9 (15.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Malignancy</td>
<td>39 (16.3)</td>
<td>10 (16.7)</td>
<td>0.94</td>
</tr>
<tr>
<td>Liver disease</td>
<td>6 (2.5)</td>
<td>(\leq 3 \text{ (\leq 5.0%)}) *</td>
<td>*</td>
</tr>
</tbody>
</table>

**Pre-diagnosis medical treatment, N (%)\(^1\)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N (%)</th>
<th>N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid-lowering medication</td>
<td>83 (34.6)</td>
<td>12 (20.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>89 (37.1)</td>
<td>21 (35.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>ADP receptor inhibitors</td>
<td>19 (7.9)</td>
<td>4 (6.7)</td>
<td>0.74</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>80 (33.3)</td>
<td>19 (31.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>53 (22.1)</td>
<td>19 (31.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>93 (38.8)</td>
<td>21 (35.0)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

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\(^1\) Adjusted for age, sex, 

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<table>
<thead>
<tr>
<th>Medical treatment after diagnosis, N (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HF medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>142 (59.2)</td>
<td>29 (48.3)</td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>133 (55.4)</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>Beta blockers and RAS inhibitors</td>
<td>101 (42.1)</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td>67 (27.9)</td>
<td>11 (18.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ADP, adenosine diphosphate; DM/PM, dermatomyositis/polymyositis; HF, heart failure; N/A, not applicable; RAS, renin-angiotensin system.

* ≤3 events in at least one of the groups. In Denmark, ethics approval is not required for registry-based studies in which individuals cannot be identified; in order to ensure that data are not identifiable, we are not allowed to report estimates for outcomes where N ≤3.

1 Claimed prescriptions within six months prior to HF diagnosis.

2 Claimed prescriptions within four months after HF diagnosis.

**FIGURES**

**Figure 1:** Absolute risk of HF in patients with DM/PM and matched controls from the background population
Figure 2: Absolute risks of secondary outcomes in patients with DM/PM and matched controls from the background population

2A. Atrial fibrillation/flutter

2B. The composite of ICD implantation/ventricular arrhythmia/cardiac arrest
2C. The composite of pacemaker implantation/atrioventricular block (advanced 2\textsuperscript{nd} or 3\textsuperscript{rd} degree)/sinoatrial dysfunction

2D. All-cause mortality
Figure 3: Unadjusted incidence rates and adjusted HRs of outcomes

Log-rank test P-value < 0.0001

<table>
<thead>
<tr>
<th>Years after inclusion</th>
<th>Background population</th>
<th>DM/PM population</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
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<tr>
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<tr>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Numbers at risk

| Background population | 3744 | 3217 | 2653 | 2132 | 1716 | 1377 |
| DM/PM population      | 936  | 696  | 557  | 439  | 337  | 248  |
Heart failure
0 to 365 days
- Background population: 2.99 [1.65-5.39]
- DM/PM population: 18.76 [11.49-30.63]

366 days to full follow-up
- Background population: 5.46 [4.65-6.41]
- DM/PM population: 8.20 [6.10-11.02]

Atrial fibrillation or flutter
- Background population: 8.49 [7.52-9.58]

ICD implantation, ventricular arrhythmia, and cardiac arrest
- Background population: 1.10 [0.79-1.54]
- DM/PM population: 2.64 [1.64-4.24]

Pacemaker implantation, atrioventricular block, and sinoatrial dysfunction
- Background population: 1.30 [0.96-1.76]
- DM/PM population: 1.86 [1.05-3.27]

All-cause mortality
0 to 365 days
- Background population: 11.39 [8.41-15.41]
- DM/PM population: 118.37 [97.49-143.73]

366 days to full follow-up
- Background population: 22.70 [21.01-24.53]
- DM/PM population: 35.92 [31.29-41.23]