Cardiac involvement in myotonic dystrophy: a nationwide cohort study

Marie Lund1*, Lars Jorge Diaz1, Mattis Flyvholm Ranthe1, Helle Petri2, Morten Duno3, Inger Juncker4, Hans Eiberg5, John Vissing6, Henning Bundgaard2, Jan Wohlfahrt1, and Mads Melbye1,7

1Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, Copenhagen S, Denmark; 2Unit for Inherited Cardiac Diseases, Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; 3Department of Clinical Genetics, Molecular Genetic Laboratory, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; 4Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark; 5Department of Cellular and Molecular Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; 6Neuromuscular Research Unit, Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; and 7Department of Medicine, Stanford School of Medicine, Stanford, CA, USA

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Aims
To quantify the association between myotonic dystrophy (DM) and cardiac disease in a nationwide cohort.

Methods and results
We identified a nationwide cohort of 1146 DM patients (period 1977–2011) using the National Patient Registry (NPR) and a subcohort of 485 patients who had undergone genetic testing for DM1. Information on incident cardiac diseases was obtained from the NPR. We estimated standardized incidence ratios (SIRs) of cardiac disease compared with the background population, overall and according to selected diagnostic subgroups (cardiomyopathy, heart failure, conduction disorders, arrhythmias, and device implantation). In the DM cohort, SIR for any cardiac disease was 3.42 [95% confidence interval (CI) 3.01–3.86]; for a cardiac disease belonging to the selected subgroups 6.91 (95% CI: 5.93–8.01) and for other cardiac disease 2.59 (95% CI: 2.03–3.25). For a cardiac disease belonging to the selected subgroups, the risk was particularly high in the first year after DM diagnosis [SIR 15.4 (95% CI: 10.9–21.3)] but remained significantly elevated in subsequent years [SIR 6.07 (95% CI: 5.11–7.16)]. The risk was higher in young cohort members [e.g. 20–39 years: SIR 18.1 (95% CI: 12.3–25.8)] compared with older [e.g. 60–79 years: SIR 3.99 (95% CI: 2.98–5.23)] but remained significantly increased in all age categories. Results were similar in separate analyses of the genetically confirmed DM1 patients.

Conclusion
Myotonic dystrophy is strongly associated with cardiac disease. The risk is pronounced in the young and remains elevated throughout life, stressing the importance of lifelong cardiac follow-up from time of DM diagnosis.

Keywords
Myotonic dystrophy • Cardiac disease • Epidemiology

Introduction
Myotonic dystrophies (DMs) are autosomal dominantly inherited neuromuscular disorders and the most common form of primary muscle disease in adults. Aside from skeletal muscle involvement, multigenerational involvement is common, typically affecting cardiac, endocrine, and central nervous system tissues.1 Two genetically distinct subtypes of disease exist, DM type 1 (DM1; Online Mendelian Inheritance of Man [OMIM] 160900) and DM type 2 (DM2; OMIM 602668). The combined prevalence of DM based on a clinical diagnosis is ~1–2 per 8000.2 Cardiac involvement is seen in both subtypes of disease3,4 but DM1 patients often have a more complex and progressive cardiac phenotype.5

In a cross-sectional study of 245 DM1 patients, the prevalences of conduction disorders, supraventricular tachycardia and ventricular tachycardia, have been reported to be 16, 9 and 3%, respectively.6 The risk of sudden cardiac death in DM1 patients has in a meta-analysis been reported as 0.56% per year.7 Since preventive means are available such as permanent pacing or implantation of an intra-cardiac defibrillator, more focus on cardiac involvement in patients with DM1 is pivotal.7–10 Accordingly, knowledge of the magnitude of the risk of cardiac involvement in DM1 patients is highly warranted.

* Corresponding author. Tel: +45 32683956, Fax: +45 32683165, Email: mxd@ssi.dk

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Cardiac involvement in myotonic dystrophy

Originating from tertiary referral centres, previous prevalence estimates of cardiac involvement in DM1 rely on highly surveyed and possibly also severely affected patient populations. This, in conjunction with the lack of control groups, likely introduces a selection bias in the estimation of the true extent of cardiac involvement in DM1. Therefore, the magnitude of the increased risk of cardiac disease in patients with DM1 compared with a matched unselected population remains an unanswered question.

In the present study, we quantified the risk of incident cardiac disease in a nationwide cohort of >1000 clinically and/or genetically diagnosed DM1 patients from 1977 to 2011, compared with the general population. In subanalyses, we focused on the subcohort of 485 genetically confirmed DM1 patients.

Materials and Methods

We established a nationwide cohort of individuals with DM diagnosed from 1977 to 2011. Using the unique personal identification number assigned to all Danish citizens, we linked individual-level information on DM and cardiac disease from various Danish health registers and demographic information from the Civil Registration System (CRS). The CRS contains information on sex, date of birth, and updated information on vital status and emigration, thus minimizing loss to follow-up.11

Identification of myotonic dystrophy patients

Patients with DM were identified by a diagnosis of DM in the National Patient Registry (NPR) and/or by genetic testing for DM1. The NPR contains information from all Danish hospitals on inpatient discharge diagnoses assigned since 1977, and outpatient diagnoses since 1995. Reporting of discharge diagnoses to the NPR is mandatory and diagnoses have been registered using the International Classification of Disease version 8 (ICD8) from 1977 to 1993 and ICD10 from 1994 onwards. Patients with DM were identified from the NPR using the following diagnoses: ICD8 33090 (myotonic dystrophy), ICD10 G711A (myotonic dystrophy), or ICD10 G711 (myotonic disorders); for the latter except if ever presence of G711B to G711K (myotonic disorders other than myotonic dystrophy) or ICD8 33091 (myotonic dystrophy, Thomsen). Since the NPR did not allow for distinction between whether a myotonic dystrophy (DM) diagnosis was based on a clinical evaluation or a genetic test or both, we further collected information on genetic testing for DM directly from all Danish laboratories where this had been performed during the study period. Genetic testing was performed using Southern blotting of genomic DNA or by PCR-fragment-length analysis and triplet-repeat primed-PCR.13 Combining diagnoses from the NPR and results of genetic testing yielded a final study cohort of 1146 individuals with DM, of which a subcohort of 485 individuals were genetically verified as DM1 patients; of note the 18 DM2 patients that had been genetically diagnosed during the study period were excluded from the study (Figure 1). Date of DM diagnosis was defined among the 1146 cohort members (in order of priority) as first: date of withdrawal of DNA used for genetic testing, n = 436; second: date of diagnosis with one of the diagnostic codes used to define DM, n = 709; and third: date of diagnosis of any primary muscle disease (ICD10: DG710), n = 1 (an individual with an undated genetic test for DM1).

Identification of incident cardiac disease

Information on cardiac disease was obtained from the NPR and was assessed as: Any Cardiac Disease overall and with further subdivision into Selected Cardiac Disease and Other Cardiac Disease. Selected Cardiac Disease comprised selected diagnostic subgroups of Any Cardiac Disease that we a priori, on the basis of the existing literature, suspected to be associated with DM. Selected Cardiac Disease was assessed as a composite estimate and according to subgroups: cardiomyopathy, heart failure, atrio-ventricular conduction disorders, bundle branch block or fascicular block including asystole, supraventricular tachycardia, ventricular arrhythmias (including sudden cardiac death and aborted sudden cardiac death), and implantation of a pacemaker or an implantable cardioverter defibrillator (for specific diagnostic codes used to define cardiac disease, see Supplementary material online, Table S1).

Statistical analysis

We calculated standardized incidence ratios (SIRs) for cardiac disease. Each SIR was calculated by dividing the number of observed events of cardiac disease in the DM cohort by the expected number based on general population rates. Expected numbers of cardiac disease were calculated by applying age-, sex-, and calendar-time-specific national incidence rates to the person-years of follow-up observed in the DM cohort. Mid-P tests and confidence intervals (CIs) were used throughout.14 Tests for homogeneity of SIR by current age, time since DM diagnosis and age at DM diagnosis were performed using log-likelihood test. The association between current age and SIR of Selected Cardiac Disease was evaluated using categorical age groups and further illustrated by fitting a restricted cubic spline with four knots at the following percentiles: 5% (6.7 years), 35% (34.1 years), 65% (52.6 years), and 95% (75.1 years). To prevent survival bias from affecting estimates of cardiac disease, follow-up started at date of DM diagnosis and ended at date of first diagnosis with the specific subgroup of cardiac disease studied, death, emigration, designated missing as defined by the CRS or 31 December 2011, whichever occurred first. For each subgroup of cardiac disease studied, patients with a subgroup diagnosis prior to a DM diagnosis were excluded from those specific analyses. Thus, the size of the DM cohort followed for subgroups of cardiac disease was not identical for the individual subgroups studied (Supplementary material online, Table S2).

As an additional analysis, we performed the opposite design and estimated SIR of DM among all patients diagnosed with cardiac disease. In this analysis, we excluded patients with a DM diagnosis prior to a diagnosis of the specific subgroup of cardiac disease studied and follow-up started at date of first cardiac disease diagnosis and ended at date of DM diagnosis, death, emigration, designated missing as defined by the CRS or 31 December 2011, whichever occurred first. Analyses were performed using SAS software (version 9.3), and R (version 2.15.1) was used for graphs.

Ethics

The study was approved by the Danish Data Protection Agency (journal number 2008-54-0472). According to the Danish legislation research based only on register data are exempted from approval by a biomedical ethics committee.

Results

The study included a main cohort of 1146 DM patients (53.1% male) of which a subcohort of 485 had undergone genetic testing for DM1 (48.7% male). Median age at DM diagnosis was 41 (range 0–85) years among subjects in the main cohort and 38 (range 0–81) years among subjects in the subcohort. During follow-up for Any Cardiac Disease, 22.3% (224 of 1005) died among the main cohort. Further characteristics of the main cohort and subcohort are found in Table 1 and number of cohort members followed for cardiac disease and

{Fig. 1...
corresponding person-years of follow-up (overall and by diagnostic subgroups of cardiac disease) in Supplementary material online, Table S2.

**Main results: standardized incidence ratio of cardiac disease, main cohort and subcohort**

As presented in Table 2, for the main cohort, SIRs of Any Cardiac Disease, Selected Cardiac Disease (cardiomyopathy, heart failure, conduction disorders, arrhythmias and implantation of a pacemaker or an implantable cardioverter defibrillator) and Other Cardiac Disease in patients with DM were 3.42 (95% CI: 3.01–3.86), 6.91 (95% CI: 5.93–8.01), and 2.59 (95% CI: 2.03–3.25), respectively; results were similar for the subcohort. Standardized incidence ratios for Selected Cardiac Disease according to diagnostic subgroups are shown in Supplementary material online, Table S3A (main cohort) and Supplementary material online, Table S3B (subcohort).

To examine whether high SIRs of Selected Cardiac Disease could partly be explained by increased medical attention in the time following DM diagnosis, we stratified according to time since DM diagnosis. Standardized incidence ratio of Selected Cardiac Disease was 15.4 (95% CI: 10.9–21.3) within the first year and 6.07 (95% CI: 5.11–7.16) one or more years after DM diagnosis. Results with further subdivisions of time since DM diagnosis are presented for the main cohort in Figure 2.

We further examined whether SIR of Selected Cardiac Disease was modified by current age; results are presented in Figure 3 for the main cohort and in Supplementary material online, Table S4 for the DM1 subcohort.

**Additional analyses, main cohort**

Investigating the underlying absolute rates of Selected Cardiac Disease, we did not find that the lower SIR in the older age groups (i.e. as illustrated in Figure 3) reflected that DM patients had the same excess rate regardless of current age; i.e. that such a common excess rate just meant relatively less in the older ages, when compared with the rate in general population (data not shown). Moreover, as seen in Table 3, the observation of decreasing SIR of Selected Cardiac Disease with increasing current age, was seen regardless of age at DM diagnosis and no effect of age at DM diagnosis was seen within
Cardiac involvement in myotonic dystrophy among a cohort of all patients with cardiac disease (rationale: association between DM and cardiac disease, we estimated SIR of DM from 1977 to 2011. These were followed for 3 314 805 person-years and 81 persons were diagnosed with DM, corresponding to an overall SIR of DM of 5.50 (95% CI: 4.40–6.80). Supplementary material online, Table S5 shows SIRs of DM in patients with Any Cardiac Disease, Selected Cardiac Disease and Other Cardiac Disease, overall and according to time since DM diagnosis.

Finally, we estimated the positive predictive value of a DM diagnosis in the National Patient Registry representing a DM1 patient as 395/93 (83%). Following this, overall an estimated (0.83 × 692 + 1.0 × 494)/1146 = 93% of the main study cohort were DM1 patients (Figure 1).

Discussion

In this nationwide cohort of DM patients, we found an overall increased risk of cardiac disease. This association was particularly strong for selected diagnostic subgroups (cardiomyopathy, heart failure, conduction disorders, arrhythmias, or device implantation) and remained significant in subgroup analyses irrespective of current age and time since DM diagnosis. Compared with the general population, the risk was increased by 10 or more fold in the youngest DM patients and by three- or more fold in DM patients 60–80 years old. The same pattern was observed in the subgroup of genetically confirmed DM1 patients.

The present study is the first population based study to quantify the association between DM1 and cardiac disease by comparison with the general population. Our finding of a particularly increased risk for selected subgroups of cardiac disease (including conduction disorders and arrhythmias) is in line with prevalence and incidence estimates from previous cross-sectional or cohort studies reporting a high degree of cardiac involvement in DM1, particularly conduction disorders and arrhythmias. However, since prevalences and incidences are both age- and calendar-time dependent, these outcomes from previous studies are difficult to compare with the results of the present study. Compared with previous studies originating from tertiary centres, our nationwide cohort likely reflected an unselected spectrum of patients both with respect to neuromuscular disease, as well as to degree of cardiac investigation performed.

The increased risk of Selected Cardiac Disease was most pronounced in individuals younger than 60 years. In theory, an explanation for this finding might be that DM patients had the same excess rate of cardiac disease regardless of current age and that such a common excess rate just meant relatively less in the older ages when compared with the rate in the general population; however, as explained in the results section this was most likely not the case. Instead, a more plausible explanation for the particularly high SIR of Selected Cardiac Disease in young DM patients could be that the DM patients surviving beyond 60 years of age were those with milder or asymptomatic disease.

A strength of our study was the ability to evaluate the association between DM and cardiac disease in two different study designs: from cardiac disease to DM and from DM to cardiac disease. In particular, in the cohort of patients with cardiac disease followed for DM, the strata of current age. Thus, current age rather than age at DM diagnosis seemed important with respect to risk of Selected Cardiac Disease.

Since ischaemic heart disease may lead to many of the specific cardiac outcomes encompassed by Selected Cardiac Disease, we examined risk of Selected Cardiac Disease with censoring if ischaemic heart disease occurred after DM diagnosis, but prior to the remaining cardiac outcomes studied. The resulting SIRs were 6.69 (95% CI: 5.71–7.79) overall, 15.2 (95% CI: 10.6–21.1) within the first year after DM diagnosis and 5.84 (95% CI: 4.89–6.93) excluding the first year after DM diagnosis.

To evaluate the impact of surveillance bias on the observed association between DM and cardiac disease, we estimated SIR of DM among a cohort of all patients with cardiac disease (rationale: among a cohort of all patients with any cardiac disease the a priori suspicion of DM is minimal, i.e. this cohort would be less susceptible to surveillance bias compared with the cohort of DM patients followed for cardiac disease). A total of 634 805 individuals had a diagnosis of Selected Cardiac Disease from 1977 to 2011. These were followed for 3 314 805 person-years and 81 persons were diagnosed with DM, corresponding to an overall SIR of DM of 5.50 (95% CI: 4.40–6.80). Supplementary material online, Table S5 shows SIRs of DM in patients with Any Cardiac Disease, Selected Cardiac Disease and Other Cardiac Disease, overall and according to time since DM diagnosis.

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A strength of our study was the ability to evaluate the association between DM and cardiac disease in two different study designs: from cardiac disease to DM and from DM to cardiac disease. In particular, in the cohort of patients with cardiac disease followed for DM, the
clinician would a priory not be concerned about DM. Irrespective of study design, we found an equally increased and strong association between DM and cardiac disease, arguing against surveillance bias having a significant influence on the result. Furthermore, from clinical experience, DM patients tend not to seek medical attention due to cognitive impairment and often do not report symptoms related to their cardiac disease. Since no formal cardiac screening programs have been part of DM management in Denmark, apart from the last couple of years of the study period, we do not expect the DM patients to have been particularly highly surveyed compared with the general population. However, while increased surveillance might well exist, we find it assuring that SIRs of cardiac disease

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Standardized incidence ratio of cardiac disease in a nationwide cohort of 1146 patients with myotonic dystrophy, overall, and according to time since myotonic dystrophy diagnosis</th>
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<tr>
<td></td>
<td>Overall</td>
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<td></td>
<td>Obsa</td>
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<td>Main cohort of 1146 DM patients</td>
<td></td>
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<tr>
<td>Any cardiac disease</td>
<td>251</td>
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<tr>
<td>Selected cardiac disease</td>
<td>170</td>
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<tr>
<td>Other cardiac disease</td>
<td>193</td>
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<tr>
<td>Subcohort of 485 DM1 patients identified by genetic testing</td>
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<tr>
<td>Any cardiac disease</td>
<td>69</td>
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<tr>
<td>Selected cardiac disease</td>
<td>44</td>
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<tr>
<td>Other cardiac disease</td>
<td>47</td>
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SIR, standardized incidence ratio; DM, myotonic dystrophy; obs, observed number of cases; CI, confidence interval; SCD, sudden cardiac death.

aObserved numbers of Selected Cardiac Disease and Other Cardiac Disease do not add up to the observed numbers of Any Cardiac Disease, since follow-up for each subgroup of cardiac disease was performed independently of the remaining subgroups.

bSelected Cardiac Disease comprises cardiomyopathy and heart failure, conduction disorders, arrhythmias and implantation of pacemaker or implantable cardioverter defibrillator. For estimates according to diagnostic subgroups of Selected Cardiac Disease for main cohort and subcohort, see Supplementary material online, Table S3A and B.

**Figure 2.** Standardized incidence ratio of selected cardiac disease according to time since diagnosis of myotonic dystrophy. Selected Cardiac Disease comprises cardiomyopathy and heart failure, conduction disorders, arrhythmias and implantation of pacemaker or implantable cardioverter defibrillator. The standardized incidence ratio of 15.4 is the standardized incidence ratio of Selected Cardiac Disease within the first year of myotonic dystrophy diagnosis and the standardized incidence ratio of 6.07 is the standardized incidence ratio of Selected Cardiac Disease beyond the first year of myotonic dystrophy diagnosis. Standardized incidence ratios and 95% CIs in the figure are also found in Supplementary material online, Table S6. SIR, standardized incidence ratio; DM, myotonic dystrophy; CI, confidence interval.
remained increased beyond 1 year after DM diagnosis in analyses with stratification according to time since DM diagnosis. For instance, the SIR of Selected Cardiac Disease was increased by more than five-fold, 10 years or more after DM diagnosis.

Our study had other strengths. It was based on a large cohort of DM patients and the population- and register-based design minimized selection bias by inclusion of all patients with a discharge diagnosis of DM from a Danish hospital. Selection bias was further limited by healthcare being free of charge in Denmark. The use of nationwide discharge registers maximized follow-up for cardiac disease, including also cardiac disease treated at local hospitals. With the mapping of the chromosomal locus for DM1 in 1992\textsuperscript{15–17} the DM1 diagnosis was genetically confirmed in the subcohort of 485 individuals. Genetic testing for DM2 was generally introduced in Denmark in 2006 and since, very few DM2 patients have been identified. Thus, to make the main cohort as representative of a DM1 population as possible we chose to exclude genetically confirmed DM2 patients from the study population. Still, misclassification could exist for the 661 individuals with a register based, but not genetically confirmed DM diagnosis. To address the extent of possible misclassification, we estimated the positive predictive value of the DM case definition used in the present study reflecting a patient having DM1 as 93\% (Figure 1). The majority of the remaining 7\% likely reflected patients with myotonic disorders other than DM or a small proportion could be patients with DM2. For myotonic disorders other than the myotonic dystrophies, cardiac disease is not part of the phenotype\textsuperscript{18} and for DM2 the cardiac phenotype is often less progressive compared with DM1.\textsuperscript{2,5} Thus, in the present study, possible misclassification has likely lead to conservative estimates of the association between cardiac disease and DM1. The observation of similar
results in separate analyses of the main cohort of both clinically and genetically identified DM patients and the DM1 subcohort is reassuring with respect to inference about cardiac disease in DM1 patients from the present study, whereas inferences about cardiac disease in DM2 patients cannot be made from the present study.

Our finding of a high risk of cardiac involvement in DM1 patients throughout life stresses the importance of continued thorough cardiac evaluation and follow-up including a particular focus on development of conduction disorders, arrhythmia, and left ventricular impairment. A severe abnormality on the electrocardiogram and a diagnosis of atrial tachyarrhythmia have been reported to be predictive of a sudden death in patients with DM1. Moreover, a recent study reported improved survival in DM1 patients with major conduction delays and who were managed by an invasive strategy (electrophysiological study and prophylactic pacemaker) as opposed to a non-invasive strategy. Findings further underlining the importance of early detection of cardiac complications among DM1 patients.

Supplementary material

Supplementary material is available at European Heart Journal online.

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Conflicts of interest: M.L., L.J.D., M.F.R., and M.M. report grants from Lundbeck Foundation, during the conduct of the study; M.L. reports grants from University of Copenhagen, during the conduct of the study; J.V. reports personal fees from Genzyme Incorporation, outside the submitted work; the remaining co-authors declare no conflicts of interest.

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