Original Article

Association Between Mutation Size and Cardiac Involvement in Myotonic Dystrophy Type 1

An Analysis of the DM1-Heart Registry

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Background—In myotonic dystrophy type 1, the association between mutation size (CTG expansion) and the severity of cardiac involvement is controversial.

Methods and Results—We selected 855 patients with myotonic dystrophy type 1 (women, 51%; median age, 37 years), with genetic testing performed at the moment of their initial cardiac evaluation, out of 1014 patients included in the Myotonic Dystrophy Type 1-Heart Registry between January 2000 and December 2015. We studied the association between CTG expansion size and other baseline characteristics and (1) cardiac involvement at baseline and (2) the incidence of death, sudden death, and other cardiac adverse events. At initial presentation, the median CTG expansion size was 530 (interquartile range, 300–830). In multivariate analysis, larger expansions were associated with the presence at baseline of conduction defects on the ECG and left ventricular systolic dysfunction. In a median 11.5 years of follow-up period, 210 patients died (25%), including 32 suddenly (4%). Supraventricular arrhythmias developed over lifetime in 166 patients (19%), sustained ventricular tachyarrhythmias in 17 (2%), and permanent pacemakers were implanted in 181 (21%). In Cox regression analyses, larger CTG expansions were significantly associated with (1) total death, sudden death, and pacemaker implantation in a model, including CTG expansion size, age, sex, diabetes mellitus, and (2) all end points except sudden death in a model including all baseline characteristics.

Conclusions—The size of the CTG expansion in the blood of myotonic dystrophy type 1 patients is associated with total and sudden deaths, conduction defects, left ventricular dysfunction, and supraventricular arrhythmias.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique Identifier: NCT01136330

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With a 1:8000 incidence, myotonic dystrophy type 1 (DM1), also known as Steinert's disease, is the most common neuromuscular disease in adults.[1] This autosomal, dominant disorder is caused by the expansion of a (CTG) n triplet repeat in the 3′ untranslated region of the *DMPK* gene.[2] The manifestations of the disease include muscle wasting and weakness, myotonia, multiple endocrine disorders, respiratory insufficiency, early-onset cataract, cognitive impairment, and cardiac disease, including conduction defects, ventricular dysfunction, supraventricular, and ventricular arrhythmias.[3,4]

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The size of the CTG expansion, which may range from 50 to 4000 repeats,[5,6] has been positively correlated with the global severity of the disease.[7,8] The most severe clinical forms of the disease, such as congenital or early childhood DM1, have been exclusively observed in patients with the largest mutations. However, the relationship between CTG expansion size and cardiac manifestations of the disease remains unclear. Correlations with conduction system disease have been addressed in several studies, mainly with a cross-sectional design, showing contradictory findings.[9–14] Besides, the occurrence of supraventricular arrhythmias or severe conduction system disease and patient long-term cardiac prognosis according to the size of the CTG mutation are unknown.

Our objective was to study in a large cohort of DM1 patients the relationship between the size of the CTG expansion and (1) the prevalence of cardiac manifestations of the disease at initial presentation and (2) the long-term cardiac

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outcome, with an analysis taking into account other confounding factors, such as age or sex.

Methods

The DM1-Heart Registry

The DM1-Heart Registry was designed and organized by the Cardiology Department of Cochin Hospital and the Neurological Unit of the Myology Institute at the Pitié Salpêtrière Hospital. We retrospectively included in this Registry consecutive patients >18 years old, admitted to our Institutions between January 2000 and December 2015 for the management of DM1, diagnosed by the presence of ≥50 CTG triplets in the 3′ untranslated region of the *DMPK* gene on blood leukocytes.

We retrospectively reviewed the patients' medical records and entered the results of their genetic testing and all of their cardiac investigations in a dedicated database. During each yearly visit, a clinical examination, an ECG, and an echocardiography were performed. The vital status of patients who were not seen after December 2015 was ascertained by consulting the National Death Registry or by contacting their primary physician.

This study, which is in compliance with the ethical principles formulated in the declaration of Helsinki, was approved by our local Ethics Committee, and all patients, except those who had died before initiation of the study, granted their informed, written consent to participate in the Registry.

Patient Selection, Clinical Definitions, and Study End Points

Of the 1014 patients included in the Registry, only those who underwent genetic analysis at the time of the baseline cardiac investigations entered the final analysis (n=855 patients). Because CTG expansion is unstable and tends to increase during life, we studied the association between CTG expansion size and (1) the patient baseline characteristic, including the prevalence of cardiac manifestations of the disease and the findings of ECG and echocardiography, and (2) the lifetime occurrence of total death, sudden death, conduction system disease requiring the implantation of a permanent pacemaker, and supraventricular arrhythmias.

Conduction defect was defined as first-degree atrioventricular (AV) block, left or right bundle branch block, and left anterior or left posterior fascicular block on the surface ECG.[15] According to the guidelines issued by the American Society of Echocardiography, the left ventricular (LV) dysfunction, measured by the Simpson's biplane method, was considered abnormal when the LV ejection fraction was <55%.[16]

We classified sustained ventricular tachyarrhythmias as ventricular tachycardia or fibrillation based on the analysis of the cardiac rhythm during cardiopulmonary reanimation, or stored in the pacemaker memories, or both. A sustained ventricular tachyarrhythmias stored in the pacemaker memory was classified as ventricular tachycardia when the ventricular rhythm was regular and as a ventricular fibrillation when the rhythm was irregular and the rate >200 bpm.

Death was classified as sudden if it occurred unexpectedly (1) within 1 hour of onset of cardiac manifestations, in absence of prior hemodynamic deterioration, (2) during sleep, or (3) within 24 hours after the patient was last seen alive and apparently stable clinically.[17] Indications for permanent pacing included third-degree AV block, type II second-degree AV block, sinus node dysfunction, and infrahissian conduction defects with a HV interval >70 ms. HV interval is measured on the His bundle electrogram from beginning of the His deflection to the earliest identified ventricular activity on the surface ECG. Supraventricular arrhythmia was defined as a sustained atrial tachycardia with a duration of >30 second recorded on an ECG, a 24-hour ambulatory ECG, or in the memories of cardiac devices. Premature ventricular complexes were defined as >15 premature ventricular events per hour recorded on a 24-hour ambulatory ECG.[18]

Genetic Analysis

The size of CTG repeat expansion was analyzed by Southern blot analysis. DNA was extracted from peripheral blood samples as previously reported. Ten microgram of DNA was digested using 2 restriction enzymes (*Eco*RI and *Bam*HI) following the manufacturer's conditions and electrophoresed on agarose gel (0.8%) for 24 hours at 50 V. The gel was depurinated, denatured, and neutralized, and the DNA fragments were transferred to a positive nitrocellulose membrane (Roche). Filter was hybridized to the (a-^{32}P)-dCTP-labeled cDNA25 probe at 65°C for 18 hours. Before autoradiography, the filter was washed to a final stringency of 0.1×saline–sodium citrate, 0.1% sodium dodecyl sulfate at 65°C for 10 to 30 minutes. Since 2014, filters were probed with cDNA25 labeled using the nonradioactive PCR DIG probe synthesis kit (Roche). Probe hybridization and detection was made following the manufacturer's conditions (DIG Easy Hyb, Anti-Digoxigenin AB, CDP Star; Roche).

Statistical Analysis

Continuous variables are expressed as median (interquartiles). Categorical variables were presented as frequencies and percentages. To analyze the relationship between CTG expansion size and patients' characteristics at baseline, the continuous variable CTG expansion size was split into 4 quartiles, and comparisons were made using analysis of variance on ranks (Kruskall–Wallis test) followed by the Dunn's test. The combining effects of age, sex, and CTG expansion size were taken into account by forcing these 3 variables into multivariate analyses: categorial variables were analyzed using logistic regression, and analysis of covariance was performed for continuous variables. For overall survival, sudden death, supraventricular and ventricular arrhythmia, and pacemaker implantation, Kaplan–Meier curves were constructed for each quartile of CTG expansion size, and curves were compared using the log-rank test. Then, we analyzed in 2 separate models the combining effects of (1) age, sex, CTG expansion size, and diabetes mellitus, and (2) all baseline characteristics using a multivariate Cox model for each end point. Statistical softwares used were Statview (version 5.0) and Sigmaplot (version 11.0). A value of $P<0.05$ was considered statistically significant.

Results

Study Population

From the 1014 adult patients with genetically proven DM1 of our registry, we identified and included in the present study 855 patients who underwent the quantification of the CTG expansion size at the moment of their baseline investigations. Their median age at initial presentation was 37 years (27–49), and 420 (49%) patients were male. The median mutation size was 530 repeats (300–830; additional Figure 1). Their baseline characteristics and findings of ECG and echocardiography are summarized in Table 1. An electrophysiology study was performed in 442 patients. Conduction system defect was present in 423 patients (49%), supraventricular arrhythmias in 75 patients (10%), and LV dysfunction in 75 patients (9%). Among patients with LV dysfunction, 40 (53%) were treated with angiotensin-converting enzyme inhibitors, 3 (4%) with angiotensin II receptor blockers, 19 (25%) with β-blockers, and 4 (5%) with diuretics. Of patients who suddenly died, 2 (6%) were treated with amiodarone, 2 (6%) with β-blockers, and 1 (3%) with antiarrhythmic agents class I.

Relationship Between CTG Expansion Size and Baseline Characteristics

Patient baseline characteristics and findings of ECG and echocardiography are presented in Table 1 for each CTG expansion size quartile.

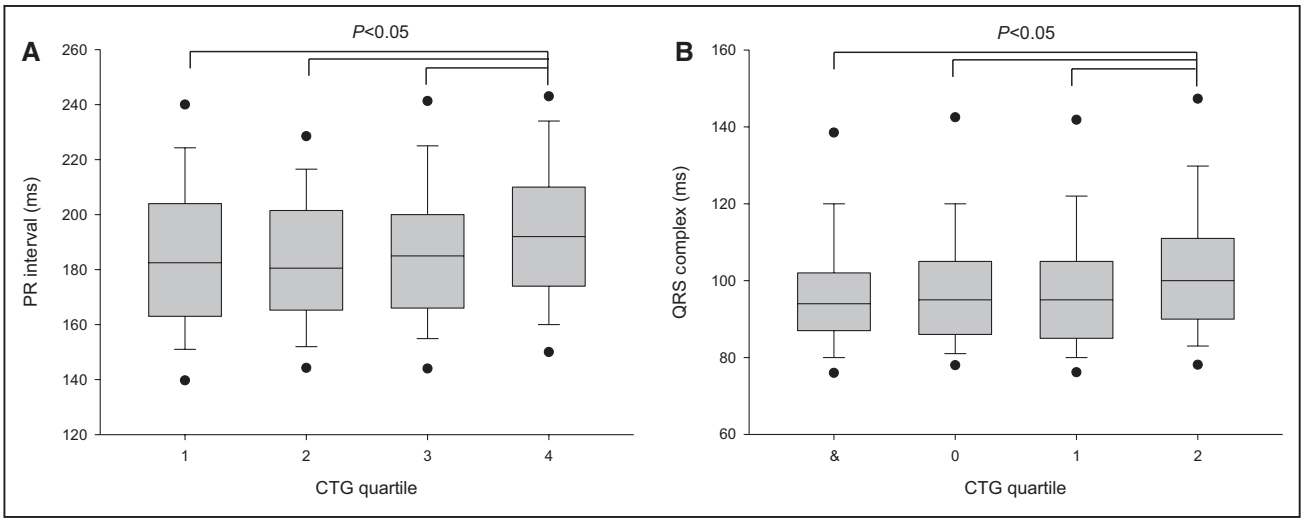

Figure 1. Association between CTG expansion size and ECG findings: PR interval (**A**), QRS complex (**B**). Boxes represent the 25th–75th interquartiles (splitted by the median), bars the 10th–90th interquartiles, and scatters the 5th–95th interquartiles.

Patients with larger mutations were significantly younger, had earlier onset of the disease, with more severe muscular involvement, higher Muscular disability Rating Scale score,[19] and had more frequently diabetes mellitus. CTG expansion size was significantly correlated with heart rate (R=0.148; P<0.0001). The prevalence of conduction system disease and left bundle branch block on the ECG was significantly higher, and PR and QRS intervals were longer in patients with larger mutation (Figure 1). No difference was observed for LV ejection fraction (P=0.94) or the prevalence of LV systolic dysfunction (P=0.44), supraventricular arrhythmias (P=0.89), atrial fibrillation (P=0.88), or premature ventricular contractions (P=0.99).

The analysis of the relationship between patient characteristics at baseline and CTG expansion size, age, sex, and diabetes mellitus is presented in Table 2 and Table I in the Data Supplement. By multiple variable analysis, CTG expansion size was significantly associated with (1) all conduction defects on the ECG, including first-degree AV block, left and right bundle branch block, (2) LV systolic dysfunction, but not with PR and QRS intervals and LV ejection fraction on the echocardiography. Age and male sex were significantly associated with (1) conduction defects and more prolonged time intervals, (2) lower LV ejection fraction and LV dysfunction.

Patient Outcome and Predictors of Cardiac Events

Over a 11.5 (8.2–14.7) years median follow-up duration, 210 patients died (25%), including 68 from respiratory death and 32 suddenly, whose 8 (25%) ventricular arrhythmias were reported. Twenty-five patients (3%) were lost to follow-up. The lifetime incidence of study end points in the total population and by mutation size quartiles is presented in Table 3 and Figure 2. Supraventricular arrhythmias developed in 166 patients (19%). A permanent pacemaker was implanted in 181 patients (21%). Indications for permanent pacing included (1) third-degree or type II second-degree AV block or sinus node dysfunction in 57 patients and (2) first-degree AV or fascicular block on the surface ECG or a HV interval >70 ms in 124 patients. Ventricular arrhythmias were detected in 17 patients (2%), including 6 with pacemakers. Death from heart failure occurred in 12 patients (1%).

The lifetime incidence of death, sudden death, supraventricular arrhythmias, and implantations of pacemakers was significantly higher in patients with larger mutations. No difference was observed for sustained ventricular arrhythmias, whose incidence was by far lower than that for other end points (log rank, P=0.23).

The multiple variable analysis of the relationship between (1) CTG expansion size, age, sex, and diabetes mellitus, and (2) study end points is presented in Table 4. CTG expansion size was significantly associated with all end points except supraventricular arrhythmias. Each increase of 500 repeats in triplet expansion was associated with a 1.5-fold higher hazard of death from any causes. Age was associated with all end points and male sex, with total death, supraventricular arrhythmias, and pacemaker implantation. Diabetes mellitus was associated with total death and supraventricular arrhythmias.

The univariate and multivariate analyses of the relationship between (1) CTG expansion size and all other baseline characteristics, and (2) study end points are, respectively, shown in Table II in the Data Supplement and in Table 5. By multivariate analysis, (1) age, age of disease onset, male sex, CTG expansion size, and diabetes mellitus were associated with total death, (2) age and age of disease onset were associated with sudden death, (3) age, male sex, CTG expansion size, and supraventricular arrhythmia were associated with supraventricular arrhythmia, and (4) age, CTG expansion size, supraventricular arrhythmia, premature ventricular complexes, and any conduction defect were associated with pacemaker implantation.

Discussion

Our study shows a strong association between the size of the CTG expansion and the severity of cardiac involvement in DM1. We found a significant association between mutation size and (1) conduction defects on the ECG and LV dysfunction on echocardiography, (2) the occurrence of death of any cause, sudden death, and permanent pacemaker implantation in

Table 1. Baseline Characteristics of the Study Population

	Total Population (n=855)	CTG Expansion Size				*P* Value
		First Quartile <300 (n=228)	Second Quartile 300–530 (n=211)	Third Quartile 530–830 (n=207)	Fourth Quartile ≥830 (n=209)	
Age	37 (27–49)	45 (34–56)	32 (24–44)	36 (26–45)	37 (29–48)	<0.001
Male sex	420 (49)	109 (52)	108 (52)	101 (48)	102 (44)	0.373
Age of disease onset	22 (14–35)	32 (23–49)	22 (16–35)	19 (14–29)	15 (10–30)	<0.001
MDRS	3 (2–3)	2 (2–3)	2 (2–3)	3 (2–3)	3 (2–4)	<0.001
Diabetes mellitus	63 (7)	10 (5)	8 (4)	20 (10)	25 (11)	0.009
Personal medical history						
Atrial fibrillation	57 (7)	13 (6)	12 (6)	15 (7)	17 (7)	0.884
SVA	75 (10)	16 (8)	19 (9)	18 (9)	22 (10)	0.89
PVCs	53 (6)	14 (7)	13 (6)	12 (6)	14 (6)	0.986
ECG						
Heart rate	68 (60–77)	66 (59–75)	68 (60–74)	69 (61–78)	70 (61–81)	0.001
PR interval	185 (166–203)	181 (162–203)	181 (166–201)	185 (166–200)	192 (174–210)	0.002
QRS duration	96 (87–106)	94 (87–102)	95 (86–105)	95 (85–105)	100 (90–111)	0.001
Any conduction defect	423 (49)	95 (45)	92 (44)	96 (46)	140 (61)	<0.001
First-degree AV block	268 (31)	64 (30)	61 (29)	58 (28)	85 (37)	0.143
Left BBB	92 (11)	17 (8)	18 (9)	17 (8)	40 (18)	0.002
Right BBB	55 (6)	9 (4)	10 (5)	18 (9)	18 (8)	0.173
Echocardiography						
LVEF, %	65 (60–67)	64 (60–67)	65 (60–67)	64 (60–67)	65 (60–68)	0.939
LV dysfunction	75 (9)	16 (8)	16 (8)	3 (8)	26 (11)	0.435
Mild	59 (7)	12 (5)	13 (6)	13 (6)	21 (10)	
Moderate	14 (2)	4 (2)	3 (1)	3 (1)	4 (2)	0.83
Severe	2 (0.2)	0 (0)	0 (0)	1 (0.5)	1 (0.5)	
LVEDD, mm	45 (42–49)	46 (43–49)*	56 (42–49)	45 (42–48)	45 (42–48)	0.029
IVS, mm	8 (7–10)	8 (7–10)	8 (7–9)	8 (7–10)	9 (8–10)	0.032
PW, mm	8 (7–9)	8 (7–9)	7 (7–8)	8 (7–9)	8 (7–9)	0.002
End diastolic LV volume, mL	92 (78–112)	97 (87–112)*¤	97 (83–112)	92 (78–112)	92 (78–107)	0.001
LV mass, g/m^2	148 (121–184)	153 (127–190)	142 (116–179)	146 (121–184)	153 (119–180)	0.09
LV hypertrophy	160 (19)	42 (21)	26 (13)	36 (18)	56 (25)	0.016
Cardiac device						
Pacemaker	181 (21)	44 (19)	36 (17)	37 (18)	64 (31)	0.020
ICD	11 (1)	2 (1)	4 (2)	2 (1)	3 (1)	0.789
Medical treatment						
Amiodarone	29 (3)	8 (4)	9 (4)	4 (2)	8 (4)	0.59
Antiarrhythmic class I	15 (2)	1 (0.4)	2 (1)	6 (3)	6 (3)	0.14
Beta-blockers	60 (7)	18 (8)	11 (5)	11 (5)	20 (10)	0.29
ACE inhibitor	61 (7)	13 (6)	10 (5)	16 (8)	22 (11)	0.22
ARB	9 (1)	3 (1)	3 (1)	1 (0.5)	2 (1)	0.74
Diuretic	4 (0.5)	1 (0.4)	1 (0.5)	1 (0.5)	1 (0.5)	0.99
Aspirin	31 (4)	6 (4)	5 (2)	8 (4)	12 (6)	0.38
Vitamin K antagonist	35 (4)	8 (4)	10 (5)	7 (3)	10 (5)	0.89

Values are median (quartile) or numbers (%) of observations. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AV, atrioventricular; BBB, bundle branch block; EF, ejection fraction; ICD, implantable cardioverter defibrillator; IVS, interventricular septum; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MDRS, Muscular Disability Rating Scale; PVC, premature ventricular complex; PW, posterior wall; and SVA, supraventricular arrhythmia.

Table 2. Multivariate Analysis of the Association Between CTG Expansion Size, Age, Sex, Diabetes Mellitus, and Baseline Characteristics

	CTG Expansion Size		Age		Male Sex		Diabetes Mellitus	
	OR (95% CI)*	*P* Value	OR (95% CI)†	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Conduction defects	1.12 (1.08–1.17)	<0.001	1.79 (1.59–2.01)	<0.001	1.84 (1.38–2.48)	<0.001	1.05 (0.59–1.86)	0.87
First-degree AV block	1.06 (1.02–1.10)	0.0031	1.71 (1.51–1.93)	<0.001	1.73 (1.27–2.36)	0.0005	1.14 (0.66–1.99)	0.64
Left BBB	1.11 (1.06–1.17)	<0.001	1.83 (1.52–2.19)	<0.001	1.30 (0.82–2.06)	0.26	0.91 (0.42–1.98)	0.81
Right BBB	1.06 (1.00–1.12)	0.049	1.31 (1.06–1.63)	0.0124	1.91 (1.07–3.40)	0.028	2.02 (0.92–4.45)	0.08
LV dysfunction	1.07 (1.02–1.13)	<0.001	1.64 (1.35–1.99)	<0.001	3.47 (2.01–5.99)	<0.0001	0.82 (0.35–1.93)	0.65

BBB indicates bundle branch block; CI, confidence interval; LV, left ventricle; and OR, odds ratios.
*Odds ratios calculated with a step of 100 triplets.
†Odds ratios calculated with a step of 10 y.

a multivariate model, including also age, sex, diabetes mellitus, and (3) total death, supraventricular arrhythmias, and permanent pacing in a model, including all baseline characteristics.

Our study is the first to describe the relationship between mutation expansion size and cardiac manifestations of DM1 based on (1) long-term outcomes, in addition to detailed cardiac workups, (2) a large sample of ≈800 patients, and (3) a multivariate analysis regarding potential confounding factors, such as age, sex, diabetes mellitus, and large set of other characteristics. Our analysis was performed exclusively on DM1 patients for whom the size of the CTG expansion has been determined at the moment of their initial cardiac evaluation.

In addition, analysis of longitudinal rather than cross-sectional data and the use a multiple variable modeling contributed to identify a strong genotype–phenotype correlation contrarily to several prior studies, including studies from our group.[11] Thus, as an example, no significant association between mutation size and personal history of supraventricular arrhythmias has been identified at baseline, while this association is found to be significant by Kaplan–Meier and multivariate Cox analysis of lifetime outcome.

We also found in this study that the size of the CTG expansion is associated with a worse long-term outcome, including a higher total mortality as shown previously[20] and a higher incidence of sudden death (in one of the 2 multivariate models). Furthermore, sudden death represents the most frequent cause of death related to cardiac involvement in DM1. Previous studies have identified conduction defects on the ECG or a personal history of supraventricular arrhythmia as the only independent predictors of this event.[9] In this study, the size of the CTG tract was found to be strongly associated with conduction time intervals and supraventricular arrhythmias. Therefore, our findings and those from prior studies concordantly show strong relationship between the size of the CTG expansion, the development of conduction system disease, the occurrence of major conduction defects requiring permanent pacing, and the risk for sudden death. However, even though DM1 patients with larger CTG tract are exposed to a worse long-term cardiac outcome, strategies for the prevention of sudden death should probably mainly be based on the evaluation of conduction system defects and other cardiac manifestations of the disease, particularly with regards to high hazard ratios associated with these variables.

At the pathophysiological level, clinical manifestations of DM1, including heart disease, are likely related to a toxic RNA gain-of-function mechanism caused by the expression of mutant *DMPK* transcripts carrying expanded repeats tract that alters the activities of RNA splicing factor, such as Muscleblind-like Protein 1 and CUG-binding protein 1 as CUG is a triplet repeat nucleotide, and affects the splicing of multiple genes. Several abnormal splicing events have been identified in heart samples of DM1 patients, and recently, it has been shown that missplicing of *SCN5A*, the gene encoding the cardiac sodium channel, contributes to conduction system disease and arrhythmias in this disease.[21] Moreover, it also is important to keep in mind that the CTG expansion is unstable at the somatic level and tends to increase in different tissues, including the heart,

Table 3. Incidence of Total Death, Sudden Death, and Cardiac Events

	Total Population (n=855)	CTG expansion size			
		First Quartile <300 (n=228)	Second Quartile 300–530 (n=211)	Third Quartile 530–830 (n=207)	Fourth Quartile ≥830 (n=209)
Total death	210 (25)	47 (21)	40 (19)	45 (22)	78 (37)
Sudden death	32 (4)	6 (3)	5 (2)	7 (3)	14 (7)
SVA	166 (19)	32 (14)	39 (18)	40 (19)	55 (26)
Pacemaker implantation	181 (21)	44 (19)	36 (17)	37 (18)	64 (31)
Sustained VTA	17 (2)	4 (2)	2 (1)	3 (1)	8 (4)
LV dysfunction	75 (9)	16 (7)	16 (8)	17 (8)	26 (12)

Values are numbers (%) of observations or median (quartile). LV indicates left ventricular, SVA, supraventricular arrhythmia; and VTA, ventricular tachyarrhythmias.

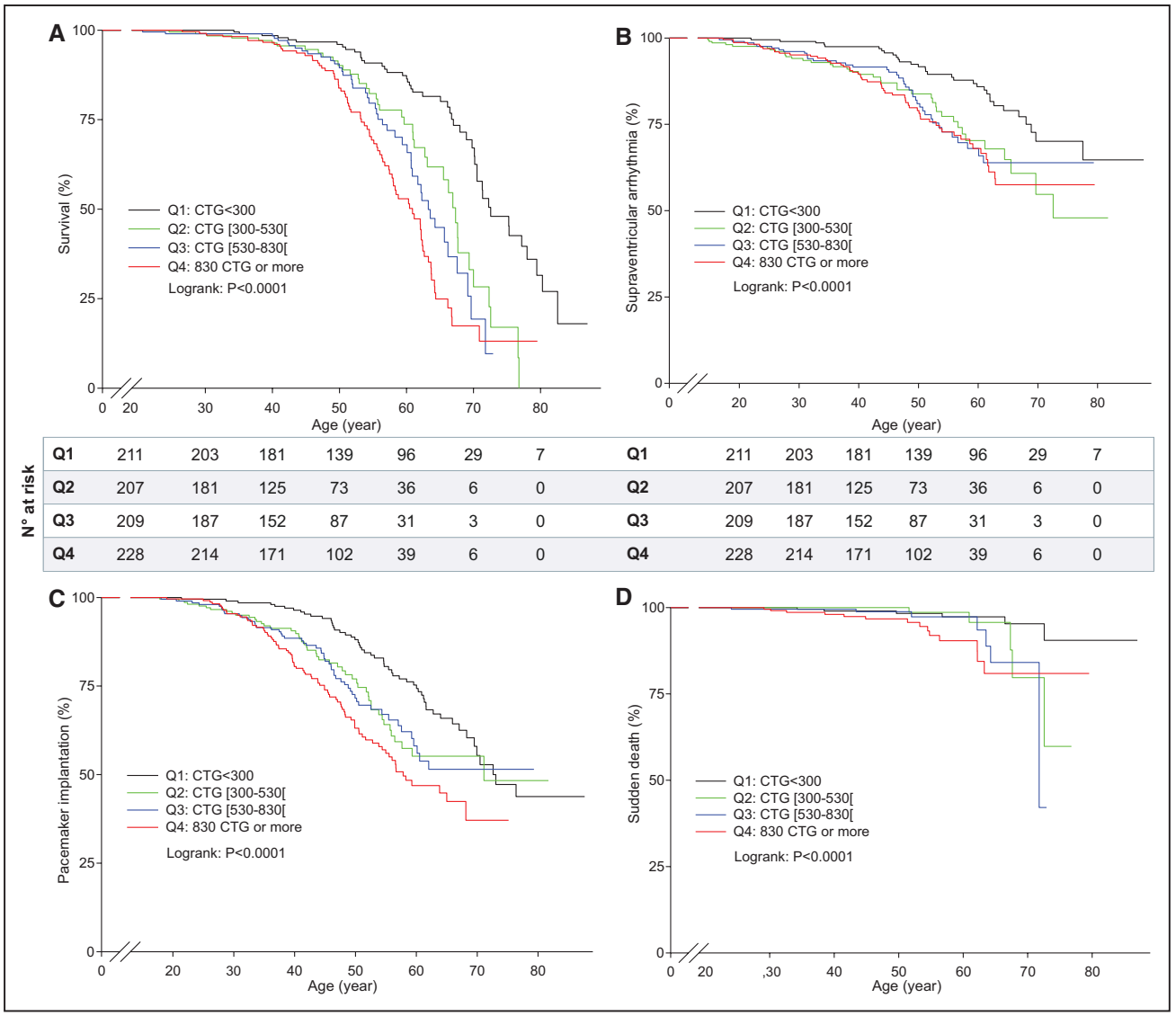

Figure 2. Kaplan–Meier estimates of overall survival (**A**), supraventricular arrhythmias (**B**), pacemaker implantations (**C**), and sudden death (**D**) in the 855 patients presenting with myotonic dystrophy type 1 (DM1).

during the life of DM1 patients, influencing, therefore, both onset and progression of the disease because the mutation size of the CTG tract may theoretically be higher in the heart than in the blood. However, correlations between CTG expansion size in heart tissues and cardiac dysfunctions have not been studied yet, probably because of low myocardial tissue availability.[22,23] Nevertheless, our study shows that the expansion size measured on peripheral lymphocytes correlates significantly with clinical manifestations of the disease at the cardiac level.

Conclusion

In DM1, larger CTG amplification size is associated with the development of conduction system defect, LV dysfunction, supraventricular arrhythmias, sudden death, and total mortality.

Table 4. Multivariate Analysis of the Correlation Between CTG Repeats, Age, Male Sex, Diabetes Mellitus, and Clinical Outcomes

	Total Death		Sudden Death		Supraventricular Arrhythmia		Pacemaker Implantation	
	HR (95% IC)	*P* Value	HR (95% IC)	*P* Value	HR (95% IC)	*P* Value	HR (95% IC)	*P* Value
CTG repeats	1.49 (1.30–1.71)	<0.0001	1.53 (1.09–2.14)	0.0130	1.15 (0.976–1.37)	0.0939	1.32 (1.16–1.51)	<0.0001
Age	0.88 (0.86–0.90)	<0.0001	0.88 (0.82–0.93)	<0.0001	0.94 (0.92–0.96)	<0.0001	0.95 (0.94–0.97)	<0.0001
Male sex	1.51 (1.14–1.99)	0.0037	1.46 (0.72–2.96)	0.29	1.82 (1.33–2.51)	0.0002	1.37 (1.06–1.77)	0.0164
Diabetes mellitus	1.99 (1.37–2.89)	0.0003	1.98 (0.75–5.25)	0.17	1.98 (1.29–3.04)	0.0019	1.12 (0.74–1.70)	0.60

HR indicates hazard ratio.
*HR for CTG number are calculated for 500 CTG steps.

Table 5. Multiple Variable Analysis of Association Between Baseline Characteristics and Clinical Outcomes

	Total Death		Sudden Death		Supraventricular Arrhythmia		Pacemaker Implantation	
	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age, y	0.89 (0.86–0.91)	<0.0001	0.9 (0.84–0.96)	0.0008	0.9 (0.88–0.92)	<0.0001	0.91 (0.90–0.93)	<0.0001
Age of onset, y	0.98 (0.97–0.99)	0.0032	0.96 (0.94–0.99)	0.0060	…	…	…	…
Male sex	1.54 (1.17–2.04)	0.0023	…	…	1.52 (1.04–2.23)	0.0324	…	…
CTG expansion (500 CTG)	1.39 (1.20–1.61)	<0.0001	…	…	1.25 (1.01–1.55)	0.042	1.24 (1.08–1.43)	0.0032
Diabetes mellitus	1.96 (1.35–2.84)	0.0004	…	…	…	…	…	…
Supraventricular arrhythmia	…	…	…	…	16.3 (11.1–23.9)	<0.0001	2.26 (1.60–3.18)	<0.0001
PVC	…	…	…	…	…	…	4.31 (3.05–6.09)	<0.0001
Any conduction defect	…	…	…	…	…	…	8.49 (5.64–12.76)	<0.0001
LV dysfunction	…	…	…	…	…	…	…	…

CI indicates confidence interval; HR, hazard ratio; LV, left ventricular; and PVC, premature ventricular complex.

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Disclosures

Arnaud Lazarus, MD, is a board member of Boston Scientific, a consultant for Sorin Group France, and an employee of Biotronik France. The other authors report no conflicts.

Appendix

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CLINICAL PERSPECTIVE

Myotonic dystrophy type 1, the most common neuromuscular disease in adults, is caused by the expansion of a (CTG)n triplet repeat in the *DMPK* gene. In our study, which included 855 patients, expansion size was significantly correlated with the presence of conduction defects on the ECG and left ventricular systolic dysfunction at initial presentation, independently to age, sex, or diabetes mellitus. Expansion size was also independently associated, over a median 11.5 years follow-up period, with total mortality, conduction defects requiring permanent pacing, and supraventricular arrhythmias in a model, including all patient characteristics at initial presentation. These results suggest that expansion size is independently associated with the severity of cardiac involvement in myotonic dystrophy type 1.

Association Between Mutation Size and Cardiac Involvement in Myotonic Dystrophy Type 1: An Analysis of the DM1-Heart Registry

Caroline Chong-Nguyen, Karim Wahbi, Vincent Algalarrondo, Henri Marc Bécane, Hélène Radvanyi-Hoffman, Pauline Arnaud, Denis Furling, Arnaud Lazarus, Guillaume Bassez, Anthony Béhin, Abdallah Fayssoil, Pascal Laforêt, Tanya Stojkovic, Bruno Eymard and Denis Duboc

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Multivariate analysis of the association between CTG expansion size, age, gender, diabetes and baseline ECG and echocardiography findings.

	CTG expansion size		**Age**		**Male gender**		**Diabetes**	
	F	***P***	**F**	***P***	**F**	***P***	**F**	***P***
PR interval	0.07	0.79	6.52	0.011	2.52	0.11	0.94	0.33
QRS interval	0.06	0.79	1.42	0.23	5.48	0.020	0.38	0.54
LV ejection fraction (%)	0.31	0.58	0.45	0.50	0.58	0.45	0.53	0.47

Abbreviations: LV: left ventricular.

*F: adjusted variance ratio

Supplemental Table 2: Single variable analysis of association between baseline characteristics and clinical outcomes

	Total death		**Sudden death**		**Supraventricular arrhythmia**		**Pacemaker implantation**	
	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (years)	0.88 (0.86 to 0.90)	<0.0001	0.87 (0.82 to 0.93)	<0.0001	0.95 (0.93 to 0.97)	<0.0001	0.95 (0.94 to 0.96)	<0.0001
Age of onset (years)	0.96 (0.96 to 0.97)	<0.0001	0.95 (0.93 to 0.97)	<0.0001	0.98 (0.97 to 0.99)	0.0053	0.98 (0.97 to 0.98)	<0.0001
Sex: Male	1.42 (1.08 to 1.87)	0.0121	1.41 (0.70 to 2.85)	0.34	1.89 (1.31 to 2.74)	0.0007	1.25 (0.97 to 1.61)	0.0862
CTG expansion (500 CTG)	1.56 (1.39 to 1.75)	<0.0001	1.60 (1.20 to 2.12)	0.0012	1.21 (1.02 to 1.44)	0.029	1.37 (1.21 to 1.55)	<0.0001
Diabetes	2.14 (1.48 to 3.08)	<0.0001	1.97 (0.76 to 5.14)	0.16	1.63 (0.99 to 2.69)	0.0557	1.18 (0.79 to 1.78)	0.42
Supraventricular arrhythmia	0.94 (0.63 to 1.38)	0.74	1.52 (0.46 to 5.04)	0.50	10.7 (7.5 to 15.3)	<0.0001	2.04 (1.46 to 2.86)	<0.0001
PVC	0.74 (0.44 to 1.23)	0.24	0.63 (0.15 to 2.63)	0.52	1.59 (0.92 to 2.72)	0.095	3.38 (2.44 to 4.67)	<0.0001
Any Conduction defect	1.37 (1.01 to 1.86)	0.043	1.46 (0.67 to 3.19)	0.34	3.26 (2.05 to 5.18)	<0.0001	6.23 (4.20 to 9.24)	<0.0001
LV dysfunction	1.34 (0.93 to 1.94)	0.12	1.39 (0.53 to 3.64)	0.51	1.8 (1.14 to 2.84)	0.0111	1.68 (1.20 to 2.36)	0.0028

Abbreviations: LV: LV dysfunction; PVC: premature ventricular complex

Supplemental Figure 1: Distribution of the number of CTG repeats in the DM1 Heart Registry. Additional bars delimitate the median (full line) and the 25/75th quartiles (dotted lines). The quartiles (Q1-Q4) are represented accordingly.