IJC Heart & Vasculature 62 (2026) 101851

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Genetic anticipation and cardiac conduction abnormalities in myotonic dystrophy type 1: implications for early stratification from a multicenter registry

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Abbreviations: AF, Atrial fibrillation; AVB-I, First-degree atrioventricular block; AVB-II, Second-degree atrioventricular block; AVB-III, Third-degree atrioventricular block; CCA, Cardiac conduction abnormalities; CVA, Cerebrovascular accident; CTG, Cytosine–Thymine–Guanine (trinucleotide repeat expansion); DM1, Myotonic dystrophy type 1; DMPK, Dystrophia myotonica protein kinase; ECG, Electrocardiogram; EPS, Electrophysiological study; HR, Hazard ratio; ICD, Implantable cardioverter-defibrillator; L-BBB, Left bundle branch block; MVA, Major ventricular arrhythmias; PM, Pacemaker; R-BBB, Right bundle branch block; SCD, Sudden cardiac death; SD, Standard deviation; VT, Ventricular tachycardia; VF, Ventricular fibrillation.

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https://doi.org/10.1016/j.ijcha.2025.101851
Received 31 October 2025; Received in revised form 4 December 2025; Accepted 6 December 2025
Available online 11 December 2025

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ARTICLE INFO

Keywords:
Myotonic dystrophy type 1 (DM1)
Inherited cardiac disease
Cardiac conduction abnormalities (CCA)
Sudden cardiac death (SCD)
Cardiovascular genetics

ABSTRACT

Background: DM1 is an autosomal dominant disorder caused by unstable CTG repeats that expand over lifetime and in successive generations, contributing to genetic anticipation. Cardiac conduction abnormalities (CCAs) are a major source of morbidity and premature death in DM1, yet the influence of age at diagnosis, generation, and CTG repeat length on the timing and progression of cardiac involvement remains poorly defined.
Method: This multicentric retrospective study included 549 adult DM1 patients from 16 hospitals in Spain. The primary composite endpoint comprised significant CCAs, device implantation, malignant ventricular arrhythmias and cardiac syncope. Patients were stratified by age-at-diagnosis (<40, 40–59, and ≥60 years); birth generation (1920–1965, 1966–1990, 1991–2015), and CTG repeat length (<100, 100–599, and ≥600).
Results: During follow-up, 33.1 % of patients experienced the primary endpoint. This risk was 4.7-fold higher in the youngest group versus the oldest group (HR 4.70; $p < 0.001$); 35-fold higher in the 3rd generation versus the 1st and increased progressively with longer CTG expansions. Device implantation rates were likewise higher in younger patients, later generations, and those with larger repeat lengths.
Conclusion: The results demonstrate a striking anticipation pattern in the cardiac phenotype of DM1, with progressively earlier and more severe electrical disease paralleling CTG expansion across generations. Incorporating age at diagnosis, generational cohort, and genetic repeat burden into clinical assessment may enhance risk stratification and enable earlier, targeted rhythm surveillance and device therapy to prevent sudden cardiac death in DM1.

1. Introduction

Myotonic dystrophy type 1 (DM1 or Steinerťs disease; OMIM 160900) is the most prevalent adult-onset muscular dystrophy [1]. DM1 is an autosomal dominant hereditary neuromuscular disorder with variable expressivity [2], caused by an unstable CTG (Cytosine–Thymine–Guanine) trinucleotide repeat expansion in the DMPK (DM protein kinase) gene [3,4]. The unstable CTG repeat expansion tends to further increase over an individual's lifetime and in successive generations, accounting for the genetic anticipation phenomenon, defined as earlier onset and greater symptom severity in subsequent generations [5,6]. The age of onset and clinical severity broadly correlate with both generation and CTG repeat length [2]. Mildly affected DM1 patients usually have 50 to 100 repeats, whereas classically affected patients typically have between 100 and 1000 CTG repeats [2].

DM1 is a multisystem disorder with manifestations extending beyond progressive muscle weakness and myotonia, including intellectual impairment, cataracts, respiratory insufficiency, endocrine disturbances, and cardiac disease [1,5]. Cardiac disease encompasses cardiomyopathy but is predominantly characterized by conduction abnormalities. In fact, cardiac involvement is currently recognized as a major contributor to morbidity and premature death in DM1 patients. However, the severity of cardiac manifestations often does not correlate with the extent of peripheral muscular impairment [6]. Significant gaps remain in understanding the determinants, timing, and progression of cardiac conduction disease in this population. As efforts move towards targeted therapies [7], the lack of robust longitudinal data on the natural course and complications of conduction abnormalities remains a major obstacle to developing optimal risk stratification and monitoring strategies.

Against this background, the present study aimed to characterize the lifetime burden and temporal pattern of cardiac conduction abnormalities (CCAs) in a large DM1 cohort, specifically assessing the influence of age at diagnosis, generational cohort, and CTG repeat length on disease progression.

2. Methods

2.1. Study population

The study cohort comprised adult patients with DM1 who had a definite diagnosis based on clinical and neurophysiological features and/or genetic determination of CTG repeat expansion. They were followed at 16 specialized inherited cardiac disease units and cardiomyopathy clinics across Spain.

Exclusion criteria included pediatric patients, patients without any cardiovascular evaluation data or inadequate cardiovascular follow-up, and patients under follow-up who refused to participate in the registry.

The multicenter study was approved by the Local Ethics Committee (CEImPA 2023.206) and conducted in accordance with the principles of the Declaration of Helsinki (1964) and its subsequent amendments. Participating investigators at each center ensured data quality and integrity.

2.2. Data acquisition

Each center extracted and anonymized clinical data from their medical records using standardized procedures. General information included demographics, sex, age at diagnosis, the reason for medical consultation or referral, family history, occupation, muscular

[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

involvement, and the need for a wheelchair. Cardiovascular tests, including electrocardiogram (ECG), 24-hour Holter ECG and transthoracic echocardiogram, and electrophysiological study (EPS), when available, at baseline, follow-ups, and last evaluation, were recorded.

Follow-up events included death, sudden cardiac death (SCD), aborted SCD, cardiac syncope, device implantation, and the development of cardiac conduction disturbances.

Cardiac syncope was defined according to ESC guidelines as a transient loss of consciousness, characterized by a rapid onset, short duration, and spontaneous complete recovery, and considered highly suggestive of intermittent arrhythmias or structural cardiac abnormalities [8,9].

The indication for EPS was individualized, based on the clinical judgment of the local cardiologist and contemporary ESC guideline recommendations, and incorporated a shared decision-making process in which patients were informed of the rationale, potential risks, and clinical implications of the procedure and could decline participation. EPS was specifically used to evaluate the risk of progression of cardiac conduction abnormalities through HV-interval measurement. It was typically performed in the presence of syncope, on the appearance of new conduction disturbances, or in cases of progression of previously documented PR or QRS prolongation. However, standardized EPS screening protocols were not uniformly implemented across participating sites.

Subsequent device implantation—either pacemaker (PM) or implantable cardioverter-defibrillator (ICD)—was undertaken according to the treating clinician's assessment and in alignment with relevant clinical guideline recommendations [9,10]. Decisions regarding device therapy similarly involved shared decision-making, ensuring that patient values and preferences were explicitly considered when discussing potential benefits and risks.

Muscular involvement was recorded to reflect the presence of any known muscle impairment in the patient, based on neurologist reports, and coded as a dichotomous variable (yes/no). For each patient, significant muscular involvement was defined by the need for wheelchair dependency (yes/no). No clinical grading scale was applied, in order to avoid inter-center variability in assessment. This variable was collected to provide a global picture of disease severity, rather than for detailed muscular evaluation.

Cerebrovascular accidents (CVA) and all-cause mortality were also collected. The cause of death was determined from available medical records, including hospital admission reports preceding death, primary care documentation, or autopsy reports when available. Causes of death were categorized by each submitting center as cardiological, non-cardiological, or unknown.

When available, the number of CTG repeats was recorded.

For analytical purposes, DM1 patients were stratified into three categories, in three different ways, according to:

(a) **Age at DM1 diagnosis**: older group (diagnosed at 60 years old or older), intermediate group (diagnosed between 40 and 59 years of age), and younger group (diagnosed before 40 years) [11];
(b) **Generation**: based on birth year: 1920 to 1965 (1st generation), 1966 to 1990 (2nd generation) and 1991 to 2015 (3rd generation);
(c) **CTG repeat length**, when available: <100; 100 to 599, and > 600 repeats.

2.3. Study endpoints

The primary endpoint was a composite of adverse cardiovascular events, which included lifetime development of significant CCA, device implantation (PM and/or ICD), major ventricular arrhythmias (MVA), and/or cardiac syncope.

Significant CCAs were defined by the presence of at least one of the following: (1) first-degree atrioventricular block (AVB-I; defined by PR interval $\geq$ 200 ms) plus QRS $\geq$ 120 ms, including right or left bundle branch blocks (R-BBB, L-BBB); (2) HV interval > 70 ms on electrophysiological evaluation; (3) second-degree or third-degree atrioventricular block (AVB-II or AVB-III).

MVA included documented SCD, aborted SCD, sustained ventricular tachycardia (VT), and ventricular fibrillation (VF).

Secondary endpoints included device implantation and lifetime CCAs development. Atrial fibrillation (AF) as well as AVB-I and QRS prolongation were also evaluated separately.

2.4. Statistical analyses

Categorical variables were described as n (%) and quantitative variables as mean ± SD. Categorical variables were compared using the chi-square or Fisher's exact test, and quantitative variables with appropriate parametric tests. Cox proportional-hazard models were employed to assess survival rates and the timing of arrhythmias across generations.

Time-to-event was defined as the interval between the baseline evaluation and the first documented ECG showing CCA, MVA and/or cardiac syncope, whichever occurred first. Patients were censored at the date of death, last documented clinical follow-up, or loss to follow-up. Kaplan–Meier analyses illustrated time to first event using this censoring structure. P-values < 0.05 were considered significant. Statistical analyses were performed using the Stata/IC version 15.1 (StataCorp, College Station, TX).

3. Results

3.1. Study population

Clinical information from 549 DM1 patients was collected across 16 Spanish centers. The geographical distribution of DM1 patients from Spain is displayed in the Central Figure. Baseline characteristics of the overall cohort and comparisons according to age-at-diagnosis groups are presented in Table 1. Nearly half of the patients were women (48.1 %). The mean age at diagnosis was 33.6 ± 16.2 years old. Most patients were diagnosed through family screening (56.3 %), although this proportion was lower in the oldest group ($\geq$ 60 years), who were more frequently diagnosed on the basis of symptoms. By generation, most patients belonged to the 2nd generation (322 patients, 58.6 %), followed by the 1st (155, 28.2 %) and 3rd generation (72, 13.1 %). Despite the relatively young mean age of the cohort, most patients had muscular involvement, and it was significantly higher in the youngest group. However, fewer than 10 % of them required wheelchair assistance, and approximately half of the patients were active workers.

During follow-up, 66 patients (12 %) died, with a mean age of 59.6 ± 10.4 years. Only 18.2 % of deaths (12 patients) were attributable to cardiovascular causes, with a similar mean age of death of 58.3 ± 12.8 years (p = 0.64). CVA occurred in 13 patients (2.4 %) at a mean age of 50.7 ± 20.9 years (Table 1).

3.2. Primary composite endpoint

During follow-up, the primary composite endpoint (CCA, PM/ICD implantation, MVA, and cardiac syncope) was present in 182 patients (33.15 %) (Central Figure, Fig. 1A). When analyzed by age at DM1 diagnosis, the lifetime incidence of the composite primary endpoint was significantly greater in the youngest group (<40 years; Fig. 1B, p < 0.001). Compared with the oldest group ($\geq$ 60 years), the risk of the primary endpoint in the youngest group was 4.7–fold higher (HR: 4.70 CI95%: 2.4–9.1; p < 0.001) and 2.4-fold higher (HR: 2.42 CI95%: 1.2–4.7; p = 0.008) in the intermediate group (40–59 years; Fig. 2A).

The risk of the primary endpoint was also increased across generations, being 35–fold higher in the 3rd generation compared with the 1st generation (Fig. 1C).

Among the 274 (59.9 %) DM1 patients with available CTG-repeat

Table 1
General characteristics of the Myotonic dystrophy type 1 cohort.

BASALINE CHARACTERISTICS	Total N = 549	First group (≥ 60yo) N = 27	Second group N = 172	Third group (<40yo) N = 350	P value
Age at diagnosis (±SD)	33.6 (±16.2)	66.9 (±6.7)	47.7 (±5.7)	24.1 (±10.8)	–
Men, n (%)	285 (51.9 %)	16 (59.3 %)	80 (46.5 %)	189 (5 %)	0.202
Reason for diagnosis:					0.440
- Family screening	309 (56.3 %)	12 (44.4 %)	97 (56.4 %)	200 (57.1 %)	
- Symptoms	226 (41.2 %)	14 (51.9 %)	73 (42.4 %)	139 (39.7 %)	
- Casual	14 (2.6 %)	1 (3,7%)	2 (1,16 %)	11 (3.1 %)	
Muscular involvement	487 (88.7 %)	14 (51.9 %)	148 (86.1 %)	325 (92.9 %)	<0.001*
Wheelchair	53 (9.7 %)	3 (11.1 %)	20 (11.6 %)	30 (8.6 %)	0.522
Active worker	217 (51.3 %)	7 (43.8 %)	55 (43.3 %)	155 (55.4 %)	0.066
CTG-Expansion	234.9 (±388.8)	134.9 (±175.9)	172.2 (±247.1)	274.6 (±450.1)	0.012*
Cerebrovascular accident	13 (2.4 %)	2 (7, %)	6 (3,5%)	5 (1,4 %)	0.073
	50.7 (±20.9)	74,20 (±11.5)	52,80 (±15.3)	39,15 (±21.9)	
FOLLOW-UP					
Pacemaker	108 (19.7 %)	6 (22.2 %)	45 (26.2 %)	57 (16.3 %)	0.027*
ICD	22 (4.0 %)	2 (7.4 %)	8 (4.6 %)	12 (3.4 %)	0.522
Atrial Fibrillation	75 (13.7 %)	8 (26.6 %)	28 (16.3 %)	39 (11.1 %)	0.012*
AVB-I	233 (42.4 %)	10 (37.0 %)	82 (47.7 %)	141 (40.3 %)	0.233
AVB-II	30 (5.5 %)	4 (14.8 %)	11 (6.4 %)	15 (4.3 %)	0.055
AVB-III	10 (1.8 %)	0	5 (2.9 %)	5 (1.4 %)	0.380
QRS prolongation	170 (31.0 %)	11 (40.7 %)	74 (43.0 %)	85 (24.3 %)	<0.001*
Deaths	66 (12 %)	9 (33.3 %)	35 (20.4 %)	22 (6.3 %)	<0.001
Mean Age at death	59.1 (±10.8)	67.7 (±7.2)	48.1 (±5.5)	31.3 (±10.3)	
CV deaths / Deaths	12 (18.2 %)	9 (22,2%)	8 (22,9%)	2 (9.2 %)	0.405
Mean Age at CV death	58.40(±13.5)	74.9 (±15.6)	45.6 (±5.2)	18 (±24)	

AVB-I: first degree auriculoventricular block; AVB-II: second degree auriculoventricular block; AVB-I: third degree auriculoventricular block; ICD: Implantable Cardioverter Defibrillator; CV: cardiovascular.

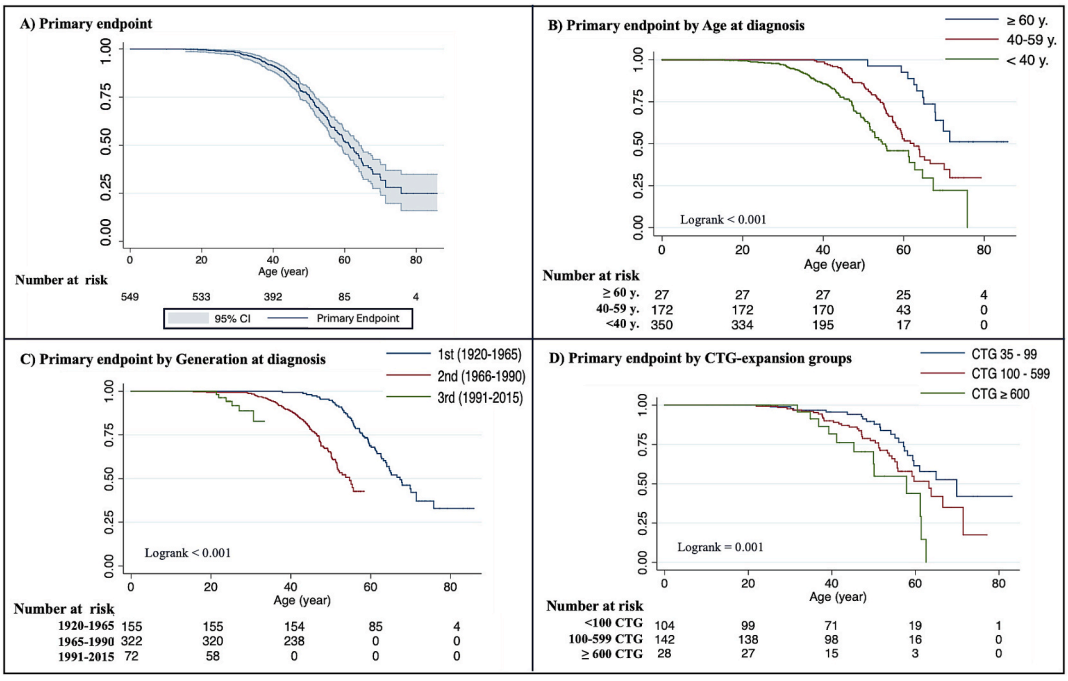

Fig. 1. (A) Primary composite endpoint during lifetime. (B) Primary composite endpoint during lifetime divided by age of diagnosis groups. (C) Primary composite endpoint during lifetime divided by generation groups. (D) Primary composite endpoint during lifetime divided by CTG repeat groups.

data, the mean repeat length was 234.9 ± 388.8 (range 35 – 4000). Most patients (n = 142; 38 %) had < 100 repeats or 100–599 (n = 142; 51.8 %), and only 28 patients (10.2 %) had ≥ 600 repeats. The incidence of the primary endpoint rose significantly with increasing CTG expansion length (Fig. 1D).

Comparison and lifetime incidence of the primary endpoint components by groups are shown in Table 2.

3.3. Device implantation.

The lifetime incidence of device implantation in the DM cohort is shown in Fig. 2A. During follow-up, 108 patients (19.7 %) required PM implantation, with a mean implantation age of 49.8 ± 10.8 years. The main indication for PM implantation was HV-interval prolongation (38 patients, 35.2 %), followed by cardiac syncope (9 patients, 8.3 %). In total, cardiac syncope was documented during follow-up in 16 patients (2.9 %), and EPS was performed in 89 (16.2 %), contributing to many of

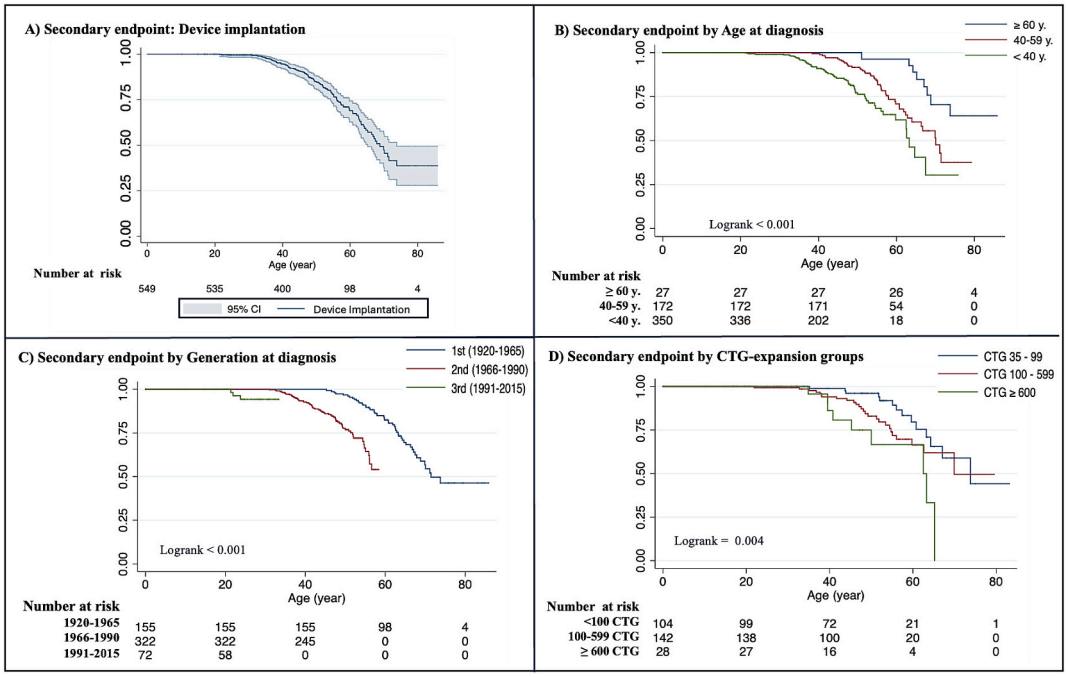

Fig. 2. (A) Device implantation during lifetime. (B) Device implantation during lifetime divided by age of diagnosis groups. (C) Device implantation during lifetime divided by generation groups. (D) Device implantation divided by CTG repeat groups.

Table 2
Primary and secondary endpoints.

Age at Diagnosis	First older group N = 27	Second group (40–59 years old) N = 172			Third younger group (<40 years old) N = 350		
		HR	CI95%	p	HR	CI95%	p
Primary Endpoint	Ref.	2.42	1.2–4–7	0.008*	4.70	2.4–9.1	<0.001*
CCA	Ref.	1.86	0.9–2.9	0.098	3.6	1.7–7.6	0.001*
ICD/PM	Ref.	2.53	1.2–5.5	0.018*	4.80	2.2–10.6	<0.001*
AVB-I	Ref.	3.47	1.7–6.9	<0.001*	8.86	4.4–17.8	<0.001*
QRS prolongation	Ref.	2.66	1.4–5.1	0.003*	4.30	2.2–8.4	<0.001*
Atrial Fibrillation	Ref.	1.85	0.8–4.5	0.171	3.73	1.5–9.2	0.004*
Generations	1st Gen	2nd Generation			3rd Generation		
	N = 155	N = 322			N = 72		
		HR	CI95%	p	HR	CI95%	p
Primary Endpoint	Ref	4.21	2.8–6.3	<0.001*	35.3	11.5–108.4	<0.001*
CCA	Ref.	3.03	1.9–4.9	<0.001*	18.96	5.0–71.4	<0.001*
ICD/PM	Ref.	4.57	2.7–7.7	<0.001*	90.41	13.5–605.9	<0.001*
AVB-I	Ref.	4.51	3.1–6.5	<0.001*	35.83	14.5–88.3	<0.001*
QRS prolongation	Ref.	5.38	3.4–8.5	<0.001*	31.07	8.8–110.3	<0.001*
Atrial Fibrillation	Ref.	2.83	1.5–5.5	0.002*	76.83	10.3–575.5	<0.001*
CTG-Expansion	<100 CTG	100–599 CTG			≥600 CTG		
	N = 104	N = 142			N = 28		
		HR	CI95%	p	HR	CI95%	p
Primary Endpoint	Ref.	1.73	1.0–2.9	0.039*	3.43	1.7–7.0	0.001*
CCA	Ref.	1.60	0.9–2.9	0.125	2.23	0.9–5.7	0.094
ICD/PM	Ref.	1.68	0.9–3.2	0.118	3.76	1.6–8.8	0.002*
AVB-I	Ref.	1.56	1.0–2.4	0.039*	2.29	1.2–4.3	0.010*
QRS prolongation	Ref.	1.56	0.9–2.6	0.093	2.60	1.2–5.5	0.013*
Atrial Fibrillation	Ref.	1.14	0.5–2.4	0.717	1.71	0.5–5.3	0.353

AVB-I: first degree auriculoventricular block; CCA: cardiac conduction abnormalities, defined as AVB-I plus QRS duration of ≥ 120 msec; HV ≥ 70 msec and/or AVB-II/III; ICD: Implantable Cardioverter Defibrillator; PM: pacemaker.

these indications.

Twenty patients (3.6 %) received an ICD, 15 (7 %) for primary prevention and 5 (25 %) for secondary prevention.

The crude rates of PM/ICD implantation were similar in the oldest and intermediate groups, but lower in the youngest group (<40 years). Nevertheless, after adjustment by age at implantation, the incidence of PM or ICD implantation was significantly higher for the youngest group. Compared to the oldest group (≥60 years), the risk of PM/ICD

implantation was 4.8–fold higher in the youngest group (HR: 4.80 CI95%: 1.2–5.5; p < 0.001) and 2.5-fold higher in the intermediate group (HR: 2.53 CI95%: 1.2–4.7; p = 0.018) (Fig. 2B and Table 2). Device implantation rates also increased in the 3rd generation and in those patients with larger CTG repeat expansions (Fig. 2C, D, and Table 2).

3.4. Cardiac conduction abnormalities

The burden of significant CCA increased progressively across the lifespan (Fig. 3A). The risk of developing significant CCA was higher in the youngest age group, in later generations, and among those with longer CTG expansions (Fig. 3B–D).

Holter monitoring identified 30 patients with AVB-II, 10 with AVB-III, and 9 non-sustained VT (Table 1). AVB-I on ECG was present in 233 patients (42.4 %) and QRS prolongation was found in 170 (31.0 %) (Table 1). Cox regression indicated earlier onset of these abnormalities in younger age groups: the risk of AVB-I was 8.9-fold higher (HR 8.86, 95 % CI 4.4–17.8; p < 0.001) in the youngest group and 3.5-fold higher (HR 3.47, 95 % CI 1.7–6.9; p < 0.001) in the intermediate group vs. the oldest group. AF was detected in 75 patients (13.7 %, Table 1). By generation, the 3rd generation had a higher risk of AF, AVB-I, and QRS prolongation than the 1st generation (Table 2).

Over a mean follow-up of 7 years, marked changes were observed in PR interval (from 189.7 ± 39.4 ms to 199.8 ± 45.8 ms; p < 0.001) and QRS duration (from 103.8 ± 22.4 ms to 112.6 ± 28 ms; p < 0.001) (Fig. 4D).

4. Discussion

This multicenter study of 549 DM1 patients demonstrates that the risk of developing significant cardiac conduction abnormalities or requiring a device implantation increases steadily with age, but occurs much earlier in patients diagnosed young, in successive generations, and in those with greater CTG expansions (Fig. 1). These age- and generation-related gradients persisted when analyzing device implantation, significant CCA, or isolated AVB-I and QRS prolongation (Table 2).

Previous large DM1 cohorts have described the lifetime cardiac phenotype but rarely incorporated age at diagnosis or generational factors into risk assessment (Table 3, [6,11–20]). Only few studies examined the association with CTG repeat length [18,19], and none explored the potential combined impact of generation and age at diagnosis on the timing of cardiac manifestations. The earlier onset of CCA observed in younger generations and in patients diagnosed at a younger age in this study supports the concept of genetic anticipation, whereby successive generations experience earlier and more severe cardiac involvement driven by progressive CTG repeat expansion.

In this cohort, stratification by age, generation, and repeat length revealed broadly concordant anticipation patterns (Figs. 1–3). These findings suggest that age at diagnosis and generational information may serve as pragmatic surrogates markers for cardiac risk stratification, particularly when comprehensive genetic data are unavailable or incomplete.

With regard to the prevalence of CCA and device implantation, this cohort showed modest differences compared with previous large series, which may reflect variation in phenotype expression across generations, differences in surveillance intensity, and disparities in clinical practice patterns among centers and countries.

Earlier studies reported major conduction defects in roughly one-fifth of DM1 patients [14], noting that substantial PR and QRS prolongation predicts adverse outcomes. In the current cohort, AVB-I and QRS prolongation more frequent than in the 2012 meta-analysis by Petri et al. [13] (42.4 % and 31 % vs 28.2 % and 19.9 %, respectively). Likewise, PM and ICD implantation rates were also higher than in some historical series (19.7 % and 4 % vs 4.1 % and 1.1 %, respectively) [13], but consistent with more recent registries, such as those by Chong-Nguyen et al. (21 % PM) [18] and Wahbi et al. (19.8 % PM) [14].

As previously reported, larger CTG expansions correlated with increased device implantation and significant CCA development, reinforcing the role of repeat length as a cardiac risk marker in DM1. Similar to our cohort, Chong-Nguyen et al. found that larger CTG expansions were significantly associated with the need for PM implantation [18]. Likewise, patients with longer CTG repeats were at a higher risk, in line with prior evidence that repeat size predicts cardiac risk [19].

AF occurred in 13.7 % of this cohort, with higher prevalence among older patients, in line with patterns observed in the general population

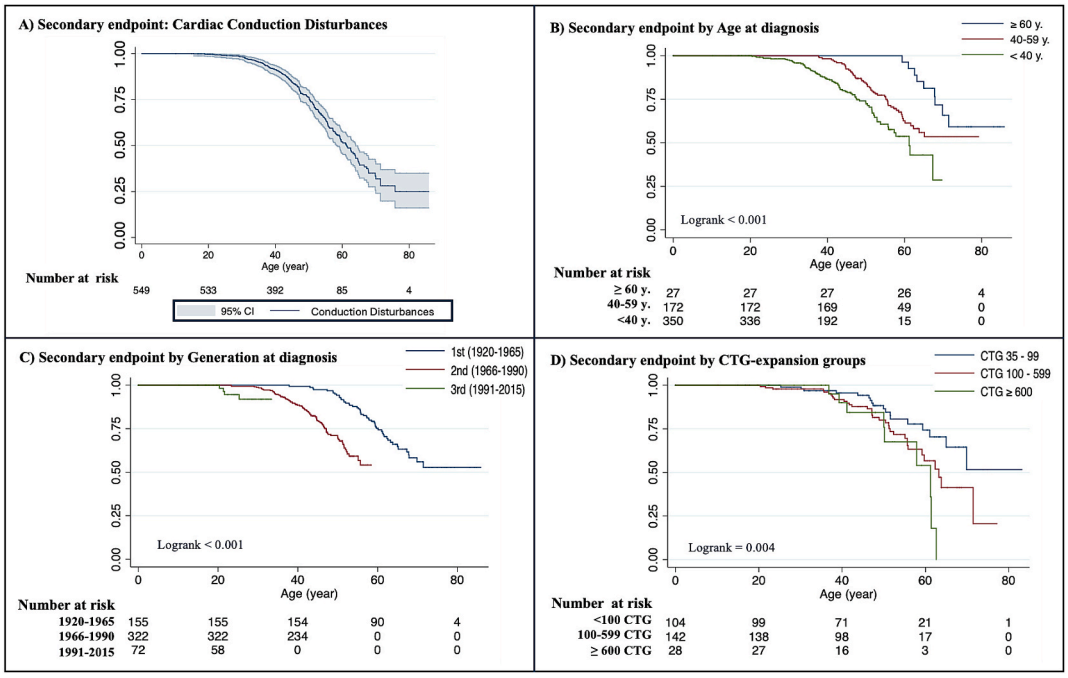

Fig. 3. (A) Cardiac conduction abnormalities during lifetime. (B) Cardiac conduction abnormalities during lifetime divided by age of diagnosis groups. (C) Cardiac conduction abnormalities during lifetime divided by generation groups. (D) Cardiac conduction abnormalities during lifetime divided by CTG repeat groups.

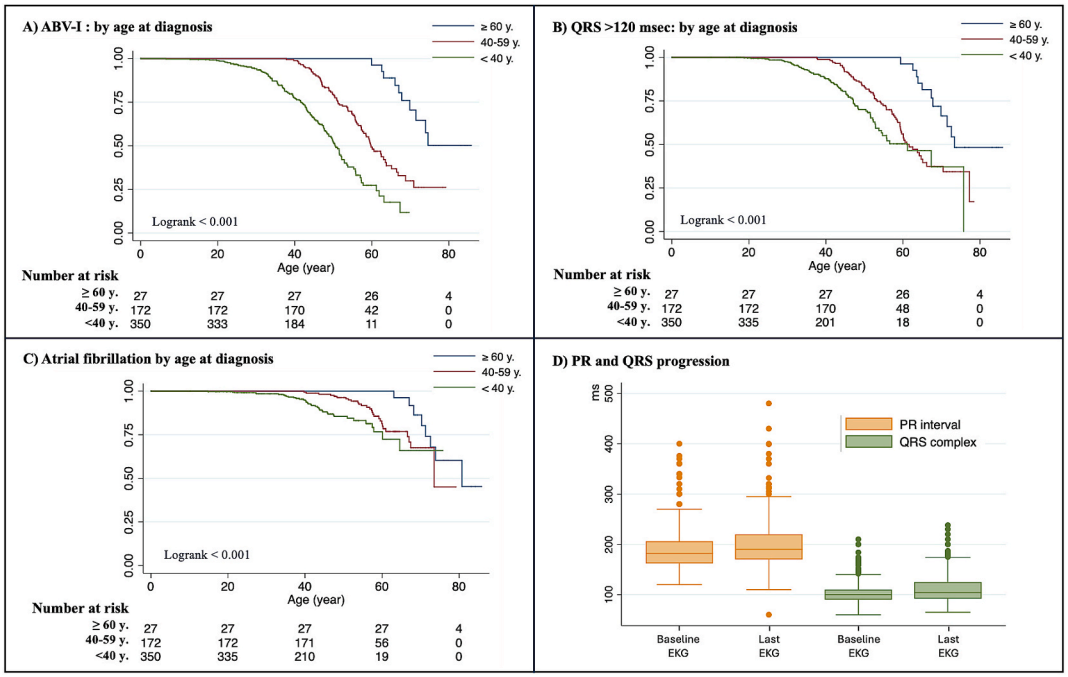

Fig. 4. (A) Auriculo-ventricular block during lifetime divided by age of diagnosis groups. (B) QRS > 120 ms development during lifetime divided by age of diagnosis groups. (C) Atrial fibrillation occurrence during lifetime divided by age of diagnosis groups. (D) PR and QRS duration progression during follow-up.

Table 3
Clinical studies including cohorts of more that 400 patients with Myotonic dystrophy type 1 and cardiovascular evaluation.

Paper characteristics	Number of DM1 patients included	Cardiovascular evaluation/ Main cardiovascular outcomes
Systematic review. Russo et al [19], 2021.	3677	Prevalence and risk of atrial fibrillation in DM1.
Meta-analysis. Petri et al [12], 2012	1828	Global description of cardiac involvement across multiple DM1 cohorts.
Systematic review. Russo et al [14], 2020.	647	Prevalence of left ventricular systolic dysfunction.
Multicentric Cohort study (France). Wahbi et al [13], 2017	1388	Conduction system disease and incidence of malignant ventricular arrhythmias.
Nationwide cohort study (Denmark). Lund et al [10], 2014.	1146 (only 485 genetically confirmed)	Cardiovascular disease burden in DM1 compared with the general population.
DM1-Heart Registry (2 French Centers). Chong-Nguyen et al [17], 2017.	855	Association between CTG-repeat length and cardiac complications.
Multicentric Cohort study (Japan). Itoh et al [15], 2020.	506	Prevalence and progression of cardiac conduction disorders.
Multicentric Cohort study (Japan). Itoh et al [18], 2024.	496	Relationship between CTG-repeat expansion and cardiac phenotype.
Single center (DM1-Heart French Registry). Wahbi K et al [16], 2012.	486 (from 914; 212 matched with 106 non-invasive group)	Comparison between electrophysiological study and non-invasive risk-stratification strategies.
Multicentric Cohort study (USA). Groh et al [6], 2008	406	ECG abnormalities as predictors of future cardiac events.
Multicentric Cohort study (USA). Bhakta et al [11], 2010.	180 (from 406; TTE subgroup,(6))	Left ventricular systolic dysfunction and incidence of heart failure.

DM1 = Myotonic Dystrophy type 1; USA = United States of America; TTE = transthoracic echocardiogram; ECG = electrocardiogram.

(Table 1). This prevalence exceeded that of the systematic review by Russo et al. (10.9 %) [20] and Chong-Nguyen et al. (7 %) [18], but matched the 12.5 % reported in the French registry [21]. Lifetime analysis again demonstrated higher AF risk among those diagnosed earlier and in the 3rd generation, mirroring the anticipation pattern observed for conduction disease. Meanwhile, CVA incidence remained low (2.4 %), suggesting either adequate AF management or limited follow-up to capture stroke risk fully.

These observations have direct clinical implications for the management of DM1 patients. Age at diagnosis, generational background, and CTG repeat burden may help identify patients at highest risk for early conduction disturbances and device requirement. Such patients might benefit from closer rhythm surveillance and considering lower thresholds for EPS. Integrating these parameters into decision-making could support more proactive device implantation strategies in selected patients and enhance prevention of life-threatening arrhythmias and sudden cardiac events.

Recent ESC guidelines for cardiomyopathies [10] and for the management of ventricular arrhythmias and SCD [9] recognize DM1 as a neuromuscular condition with relevant arrhythmic risk, emphasizing awareness of AVB progression. However, they do not yet incorporate age at diagnosis, generation, or CTG repeat burden as formal modifiers in risk stratification algorithms. These guidelines also highlight the challenge of identifying asymptomatic DM1 patients at high risk of sudden cardiac events and the uncertainty regarding optimal timing of ICD implantation for primary prevention. In this context, the present findings underscore the potential value of incorporating age-, generation-, and genetics-based information future guideline refinements and personalized monitoring strategies.

5. Study limitations

This was a retrospective longitudinal cohort study. Although it represents the largest national DM1 cohort to date, the total sample size and the event counts in some subgroups limit the generalizability of our findings to other populations with different demographic or clinical characteristics. Furthermore, because this multicenter registry spanned several decades, variability in ECG screening intervals, EPS indications,

device implantation thresholds, and genetic testing practices across centers may have introduced heterogeneity and residual confounding. Differences in real-world practice patterns, including evolving guideline recommendations over time, inherent to real-world clinical care, should be considered when interpreting the results. In addition, the very large hazard ratios observed in the 3rd generation and in some high-risk strata may partly reflect small-event numbers, differences in surveillance intensity between generations, and unmeasured confounders, raising the possibility of small-sample bias in subgroup analyses. Finally, CTG repeat length was not available for all patients, and somatic mosaicism as well as age-dependent repeat instability were not systematically assessed, which may have led to misclassification of genetic severity in some cases. Therefore, we emphasize that the findings should be interpreted cautiously. However, despite these limitations, the findings remain biologically plausible and consistent with anticipation phenomena.

6. Conclusion

This large multicenter cohort provides new insights into the natural history of cardiac conduction disease in DM1. Patients diagnosed earlier and those from younger generations exhibited earlier onset of significant CCA and higher lifetime device implantation rates, consistent with genetic anticipation driven by CTG expansion. Similar anticipation-like risk gradients were evident in groups with longer CTG repeat lengths, reinforcing the role of genetic burden in cardiac risk stratification in DM1. Taken together, these findings support the integration of age at diagnosis, generational cohort, and CTG repeat burden into clinical evaluation and follow-up strategies, helping to identify patients who may benefit from closer cardiac monitoring, earlier invasive risk assessment, and timely device implantation to prevent life-threatening events.

Disclosures

There are no relationships with industry regarding this paper.

CRediT authorship contribution statement

Rebeca Lorca: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Alberto Alen:** Writing – review & editing, Data curation. **Carlos Moliner-Abós:** Investigation. **Fernando de Frutos:** . **Néstor Báez-Ferrer:** Investigation. **María Luisa Peña-Peña:** Investigation. **Eduardo Villacorta:** Investigation. **Tomas Ripoll-Vera:** Investigation. **Esther Zorio:** Resources, Investigation. **Aaron Martínez-Gimeno:** Investigation. **José Bermúdez-Jiménez:** . **Javier Limeres:** Investigation. **Coloma Tiron:** Investigation. **José M. Larrañaga-Moreira:** Investigation. **Eva Cabrera-Romero:** Investigation. **Pablo García-Pavía:** Writing – review & editing, Validation, Supervision. **María Angeles Espinosa:** Investigation. **Jesús Piqueras:** Investigation. **Soledad García-Hernández:** Investigation. **Julián Palomino-Doza:** Investigation. **Marc Soriano-Amores:** Investigation. **German Moris:** Validation, Resources, Data curation. **Lidia María Carrillo-Mora:** . **Petros Syris:** Writing – review & editing, Validation. **Rut Alvarez-Velasco:** Software, Methodology, Formal analysis, Data curation. **Juan Ramón Gimeno:** Writing – review & editing, Visualization, Validation, Conceptualization. **Carmen Muñoz:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Formal analysis, Conceptualization.

Funding

This research was funded by Health Institute Carlos III, grant number PI22/00705, and Sociedad Española de Cardiología, grant code "SECARIT-INV-MUL 24/01".

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] T. Ashizawa, H.F. Epstein, Ethnic distribution of myotonic dystrophy gene, Lancet Lond Engl. 338 (8767) (1991) 642–643.
[2] B.A. Seifert, H.V. Reddi, B.E. Kang, L.J.H. Bean, A. Shealy, N.C. Rose, Myotonic dystrophy type 1 testing, 2024 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG), Genet. Med. 26 (8) (2024) 101145.
[3] J.D. Brook, M.E. McCurrach, H.G. Harley, A.J. Buckler, D. Church, H. Aburatani, et al., Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3′ end of a transcript encoding a protein kinase family member, Cell 68 (4) (1992) 799–808.
[4] M. Mahadevan, C. Tsilfidis, L. Sabourin, G. Shutler, C. Amemiya, G. Jansen, et al., Myotonic dystrophy mutation: an unstable CTG repeat in the 3′ untranslated region of the gene, Science 255 (5049) (1992) 1253–1255.
[5] C. Dogan, M. De Antonio, D. Hamroun, H. Varet, M. Fabbro, F. Rougier, Gender as a modifying factor influencing myotonic dystrophy type 1 phenotype severity and mortality: a nationwide multiple databases cross-sectional observational study, in: R. Artero (Ed.), PLOS ONE, vol. 11(2), 2016 e0148264.
[6] W.J. Groh, M.R. Groh, C. Saha, J.C. Kincaid, Z. Simmons, E. Ciafaloni, et al., Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1, N. Engl. J. Med. 358 (25) (2008) 2688–2697.
[7] L. Wood, G. Bassez, B. Van Engelen, H. Lochmüller, B. Schoser, A. Atalaia, et al., 222nd ENMC international workshop, Neuromuscul. Disord. 28 (5) (2018) 463–469.
[8] M. Brignole, A. Moya, F.J. De Lange, J.C. Deharo, P.M. Elliott, A. Fanciulli, et al., 2018 ESC guidelines for the diagnosis and management of syncope, Eur. Heart J. 39 (21) (2018) 1883–1948.
[9] K. Zeppenfeld, J. Tfelt-Hansen, M. de Riva, B.G. Winkel, E.R. Behr, N.A. Blom, et al., 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, Eur. Heart J. 43 (40) (2022) 3997–4126.
[10] Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023 Aug 25;ehad194.
[11] M. Lund, L.J. Diaz, M.F. Ranthe, H. Petri, M. Duno, I. Juncker, et al., Cardiac involvement in myotonic dystrophy: a nationwide cohort study, Eur. Heart J. 35 (32) (2014) 2158–2164.
[12] D. Bhakta, M.R. Groh, C. Shen, R.M. Pascuzzi, W.J. Groh, Increased mortality with left ventricular systolic dysfunction and heart failure in adults with myotonic dystrophy type 1, Am. Heart J. 160 (6) (2010) 1137–1141, 1141.e1.
[13] H. Petri, J. Vissing, N. Witting, H. Bundgaard, L. Køber, Cardiac manifestations of myotonic dystrophy type 1, Int. J. Cardiol. 160 (2) (2012) 82–88.
[14] K. Wahbi, D. Babuty, V. Probst, L. Wissocque, F. Labombarda, R. Porcher, et al., Incidence and predictors of sudden death, major conduction defects and sustained ventricular tachyarrhythmias in 1388 patients with myotonic dystrophy type 1, Eur. Heart J. 38 (10) (2017) 751–758.
[15] V. Russo, S. Sperlongano, E. Gallinoro, A. Rago, A.A. Papa, P. Golino, et al., Prevalence of left ventricular systolic dysfunction in myotonic dystrophy type 1: a systematic review, J. Card. Fail. 26 (10) (2020) 849–856.
[16] H. Itoh, T. Hisamatsu, T. Tamura, K. Segawa, T. Takahashi, H. Takada, et al., Cardiac conduction disorders as markers of cardiac events in myotonic dystrophy type 1, J. Am. Heart Assoc. 9 (17) (2020) e015709.
[17] K. Wahbi, C. Meune, R. Porcher, H.M. Bécane, A. Lazarus, P. Laforêt, et al., Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease, JAMA 307 (12) (2012) 1292–1301.
[18] C. Chong-Nguyen, K. Wahbi, V. Algalarrondo, H.M. Bécane, H. Radvanyi-Hoffman, P. Arnaud, et al., Association between mutation size and cardiac involvement in myotonic dystrophy type 1: an analysis of the DM1-heart registry, Circ. Cardiovasc. Genet. 10 (3) (2017) e001526.
[19] Itoh H, Hisamatsu T, Segawa K, Takahashi T, Sato T, Takada H, et al. CTG repeat length underlying cardiac events and sudden death in myotonic dystrophy type 1. Eur Heart J Open. 2024 Sep;4(5):oeae078.
[20] V. Russo, A.A. Papa, M. Lioncino, A. Rago, F. Di Fraia, A. Palladino, et al., Prevalence of atrial fibrillation in myotonic dystrophy type 1: a systematic review, Neuromuscul Disord NMD. 31 (4) (2021 Apr) 281–290.
[21] L.H. Lund, L.B. Edwards, A.I. Dipchand, S. Goldfarb, A.Y. Kucheryavaya, B. J. Levvey, et al., The registry of the international society for heart and lung transplantation: thirty-third adult heart transplantation report-2016; focus theme: primary diagnostic indications for transplant, J. Heart Lung Transpl. Off. Publ. Int. Soc. Heart Transpl. 35 (10) (2016) 1158–1169.