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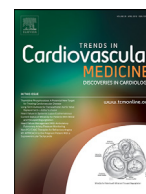


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Trends in Cardiovascular Medicine

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A B S T R A C T

Patients with myotonic dystrophy, the most common neuromuscular dystrophy in adults, have a high prevalence of arrhythmic complications with increased cardiovascular mortality and high risk for sudden death. Sudden death prevention is central and relies on annual follow-up and prophylactic permanent pacing in patients with conduction defects on electrocardiogram and/or infrahisian blocks on electrophysiological study. Implantable cardiac defibrillator therapy may be indicated in patients with ventricular tachyarrhythmia.

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Introduction

Myotonic dystrophies are autosomal dominant multi-system disorders that were first recognized as a clinical entity more than a century ago. Myotonic dystrophies are the most common myopathies presenting in adulthood. They are characterized by myotonia and progressive muscle degeneration leading to disabling weakness and wasting. Their combined prevalence is estimated to be 1 in 8000 persons (12.5/100,000 persons) based on clinical diagnoses [1]. Myotonic dystrophies are classified into type 1 (DM1, also known Steinert disease) and type 2 disease (DM2, proximal myotonic myopathy, or proximal myotonic dystrophy). DM1 is associated with the abnormal expansion of a CTG trinucleotide repeat in the *DMPK* gene on chromosome 19q13.3 [2], while DM2, a less common disorder that was described more recently, is associated with a CCTG repeat in the *ZNF9* gene on chromosome 3q21 [3].

Patients with DM1 have a reduced life expectancy mainly due to respiratory involvement and sudden death. This review aims to provide insights into the cardiac manifestations of DM1, the impact of these manifestations on patient prognosis, and the molecular pathomechanisms underlying DM1 and specifically the cardiac involvement in DM1, in order to facilitate the development of strategies for the clinical management of patients with DM1.

Molecular genetics and pathomechanisms

DM1 mutation

The genetic mutation responsible for the autosomal dominant DM1 is an expanded CTGn repeat in the 3' untranslated region of

the *DMPK* gene [2]. This CTG tract ranges from 5 to 37 repeats in healthy individuals, whereas it ranges from 51 to several thousands of repeats in DM1 patients. Repeat lengths of 38–50 are considered a protomutation allele. Globally, the size of the CTG expansion correlates with disease severity and age of onset [4]. This microsatellite expansion is unstable at both the somatic and intergenerational levels. That is to say, the size of the expanded CTG tract increases during the patient's lifetime as well as over successive generations. Tissues in which the CTG expansion is larger are more severely affected, such as the skeletal muscles, heart, and brain [5], and the increase in CTG expansion size with each successive generation results in pronounced anticipation.

RNA toxicity and aberrant splicing

At the molecular level, both the wild-type and mutant *DMPK* allele are transcribed; however, mutant *DMPK* transcripts containing expanded CUG repeats are not exported to the cytoplasm but rather retained in the nucleus as discrete aggregates or foci, leading to *DMPK* haploinsufficiency [6]. This reduction in the levels of *DMPK*, a serine–threonine protein kinase, was found to have no major phenotypic impact, especially on cardiac or muscle function, in adult mice, confirming that haploinsufficiency is not a key factor in DM1 pathogenesis [7].

A growing body of evidence shows that the triplet repeat expansion in DM1 leads to a toxic RNA gain-of-function mechanism. The expanded CUG repeats alter the function of RNA-binding proteins, and consequently, alter a number of heterologous RNA targets and pathways in a tissue-specific manner. Nuclear-retained CUG-expanded transcripts sequester MBNL proteins, which regulate developmental alternative splicing and polyadenylation events, particularly during the transition of a subset of gene products from the fetal to the adult isoforms [8]. Thus, the functional loss of MBNL results in the re-expression of fetal isoforms in adult

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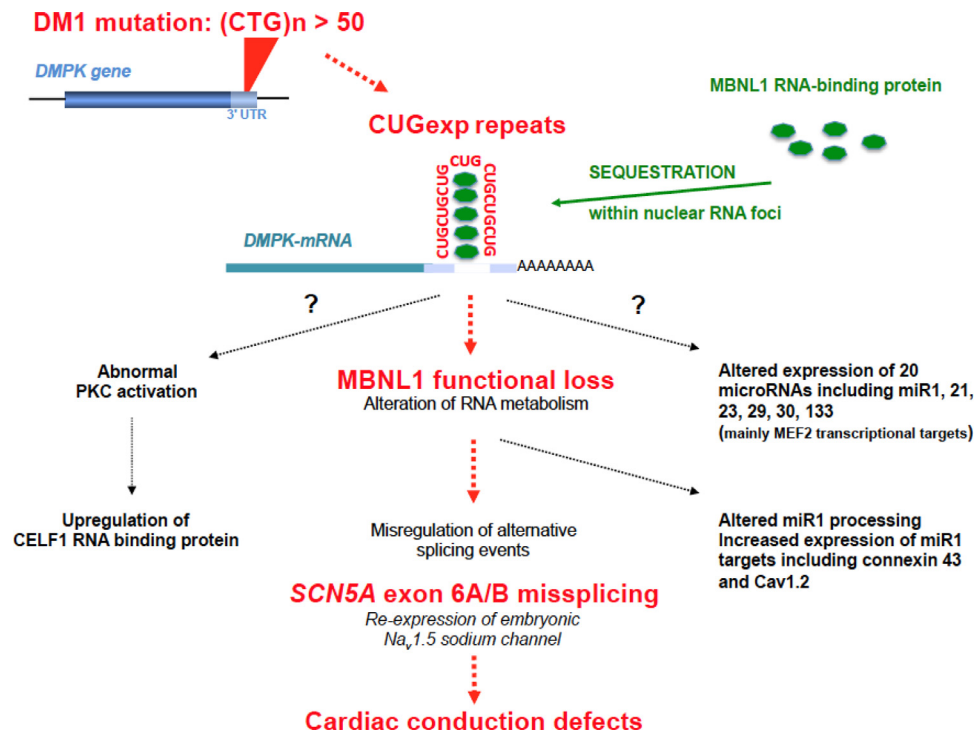


Fig. 1. Molecular genetics and pathomechanisms of myotonic dystrophy type 1.

tissues. This mechanism is reinforced by CELF1 upregulation in DM1 tissues, as MBNL1 and CELF1 act antagonistically in the regulation of several splicing events and mRNA expression [9]. For example, myotonia has been associated with the inclusion of a premature termination codon and reduced levels of the skeletal muscle-specific chloride channel CLCN1 [10]. Several other splicing events in *INSR*, *BIN1*, *CACNA1S*, and *DMD* pre-mRNAs that are also regulated by MBNL1 have been associated with insulin resistance, muscle weakness, and dystrophies. Although DM1 is often considered a “spliceopathy,” additional mechanisms may contribute to the development of this complex disease.

Cardiac involvement: *SCN5A* missplicing and other mechanisms

In accordance with functional loss of MBNL proteins due to their sequestration by expanded CUG repeats, *Mbnl* deficient mouse models recapitulate cardinal DM1 cardiac defects and display several splicing changes including events affecting sodium and calcium channels [11,12]. Abnormal sodium current properties were also correlated with conduction defects in a mouse model the human *DMPK* gene with expanded CTG repeats and misregulation of *SCN5A* mRNA splicing was identified in heart samples of DM1 patients by RNAseq [13]. *SCN5A* gene encodes $Na_v1.5$, the alpha-subunit of the cardiac voltage-gated sodium channel that is responsible for the rapid depolarization of cardiac cells and is involved in the cardiac action potential duration as well as the propagation of the impulse throughout the myocardium. The loss of $Na_v1.5$ function results in arrhythmic disorders, such as autosomal dominant conduction system disease and Brugada syndrome [14].

In DM1, aberrant splicing of the mutually exclusive 6A/B exons within *SCN5A* pre-mRNA leads to a switch from the adult exon 6B towards the fetal exon 6A, resulting in the re-expression of fetal $Na_v1.5$ that has lower excitability than the adult isoform (Fig. 1). To determine its functional impact, the DM1 missplicing of endogenous *Scn5a* pre-mRNA was reproduced in the heart tissue of wild-type adult mice using an AAV-U7 snRNA antisense system

[13]. These *Scn5a*-skipped mice re-expressed approximately 30% fetal exon 6A and developed conduction system disease with marked PR-interval prolongation, increased QRS duration, supraventricular arrhythmias, and sudden death in 20% of cases. Involvement of *SCN5A* missplicing as a prominent mechanism underlying cardiac electrical abnormalities in DM1 was reinforced recently by a CRISPR/Cas9 approach allowing the re-expression of fetal *Scn5a* isoform in adult mice [15].

Several additional mechanisms could contribute to the cardiac involvement in DM1. Thus, CELF1 upregulation due to the abnormal activation of the PKC signaling pathway was identified in a heart-specific mouse model expressing interrupted 960CTG repeats and displaying dilated cardiomyopathy and arrhythmia [16]. In addition, altered expression of 22 microRNAs, mainly direct MEF2 transcriptional targets, were identified in this mouse model and validated in heart samples from DM1 patients [17]. Among them, it was proposed that (i) the altered expression of miR-21, miR-29, miR-30, and miR-133, which regulate a network of genes associated with fibrosis, could contribute to interstitial cardiac fibrosis in DM1 patients, and (ii) reduced miR-1 expression could contribute to conduction defects, as low miR-1 levels were correlated with cardiac abnormalities and arrhythmias in transgenic mice [18]. Moreover, miR-1 biogenesis is regulated by MBNL1, and the loss of MBNL1 function observed in DM1 results in miR-1 downregulation and increased levels of miR-1 targets such as GJA1 gap-junction proteins and *CACNA1C* calcium channels, which could also contribute to cardiac dysfunctions [19].

General clinical manifestations

Clinical phenotypes

DM1 has four distinct clinical phenotypes depending on the age at onset and global disease severity: the adult-onset, congenital, childhood-onset, and late-onset oligosymptomatic forms [1]. Globally, disease severity correlates with mutation size: >100 repeats are usually present in patients with adult-onset disease; >1000 re-

Table 1
Clinical manifestations of myotonic dystrophy type 1.

Skeletal muscle	Muscle weakness Myotonia
Digestive	Dysphagia Constipation Diarrhea Anal incontinence Gallbladder disorders
Respiratory	Respiratory insufficiency Aspiration pneumonia
Brain	Neuropsychological Daytime sleepiness
Cardiac	Conduction system disease Supraventricular and ventricular arrhythmias Left ventricular systolic dysfunction
Ocular	Cataract (posterior, iridescent, subcapsular opacities)
Endocrinal	Diabetes Hypothyroidism Hypogonadism, infertility
Others	Frontal balding

peats, in patients with congenital disease; and 51–100 repeats, in oligosymptomatic patients.

Adult-onset disease, the most prevalent form, usually presents during the 2nd-to-4th decade of life with muscle weakness, myotonia, and/or cataract. Progression of skeletal muscle weakness can lead to severe disability, respiratory insufficiency, and dysphagia [1]. The other clinical manifestations are summarized in Table 1. Congenital DM1 is a severe developmental disorder characterized by reduced fetal movements, polyhydramnios, severe global hypotonia, and respiratory failure at birth. In the childhood-onset form, mental retardation and learning difficulties precede the other manifestations.

Prognosis

Life expectancy is greatly shortened in DM1 patients due to an increased risk of respiratory complications and sudden cardiac death, which were the primary causes of death in 33% and 31% patients, respectively, in the largest cohort published to date [20,21]. A risk-prediction score to estimate long-term survival probability was recently developed based on the following: age, diabetes, need for support when walking, heart rate, systolic blood pressure, first-degree atrioventricular and bundle branch blocks, and vital capacity. This score can be helpful to estimate the competing risk of death when pacemakers or implantable cardioverter defibrillators (ICDs) are considered for the primary prevention of sudden death [21].

Cardiovascular manifestations

The prevalence of the cardiac manifestations of DM1 is shown in Table 2. Most manifestations are arrhythmic and can lead to

sudden death. Cardiac fibrosis and fatty infiltration affect the cardiac conduction system at all levels (sinoatrial and atrioventricular nodes, His–Purkinje system), providing a substrate for conduction defects, ectopic activity, and re-entrant arrhythmias.

Cardiovascular mortality

Among the cardiovascular causes of death in DM1 patients, sudden cardiac death is the most frequent (43% patients), followed by pulmonary embolism (25%), terminal heart failure (17%), myocardial infarction (5%), and ischemic stroke (3%) [21]. The annual incidence of sudden death has been estimated at 0.53%–1.16% [20–23]. The progression of conduction system disease to complete atrioventricular block and asystole and ventricular tachyarrhythmias are generally assumed to be the main mechanisms underlying sudden death. Advanced atrioventricular block has been documented in 12% patients at 10 years of follow-up in the largest cohort published to date [24]. It is noteworthy that mechanisms underlying sudden cardiac death are difficult to determine and remain controversial, especially the proportion of sudden deaths attributable to major conduction defects or primary ventricular tachyarrhythmias. As DM1 is a complex disease involving multiple systems, non-cardiac causes can also be involved. For example, massive pulmonary embolism has been suspected or identified at autopsy in cases of sudden death after ICD or pacemaker implantation with no record of ventricular arrhythmias in the implanted device [24].

Independent predictors of sudden death are (i) clinical diagnosis of atrial tachyarrhythmia and electrocardiogram (ECG) with one of the following features: any rhythm other than sinus rhythm, PR interval ≥ 240 ms, QRS duration ≥ 120 ms, and second- or third-degree atrioventricular block [20], and (ii) age, family history of sudden death, and left bundle branch block [25].

Conduction system disease

Conduction system disease is the most prevalent cardiac manifestation of DM1. First-degree atrioventricular, fascicular, or bundle branch blocks have been identified in 28%–45% patients at diagnosis [20–23]. Most patients with mild conduction defects on surface ECG are found to have infrahisian conduction defects on electrophysiological studies, with the HV interval significantly correlated with PR interval ($r=0.34$, $P=0.002$) and QRS widening ($r=0.42$, $P=0.0001$) [25]. Moreover, among patients with normal ECG findings, 55% had infrahisian conduction defects (HV = 60–80 ms). Progression to complete atrioventricular block occurred in 19% patients in a large cohort of unselected DM1 patients during a 12-year follow-up (median age, 50 years) [24] and in 55% patients with HV interval ≥ 70 ms during a 55 months follow-up [26]. Independent predictors of advanced atrioventricular block include age, male sex, atrial fibrillation, syncope, and evidence of any conduction defect on ECG [24]. In another multicenter registry where 62 patients out of 406 were implanted with pacemakers, mostly

Table 2
Prevalence of cardiac manifestations of myotonic dystrophy type 1.

	Groh et al. [16] (n = 406)	Wahbi et al. [17] (n = 914)	Petri et al. [20] (n = 1828)
Age, years	42.3	38.4	–
Male sex	50.7%	47.0%	–
Conduction system disease			
First-degree atrioventricular block	45.0%	34.1%	28.2%
QRS > 120 ms	16.5%	18.4%	19.9%
Atrial fibrillation/flutter	12.8%	7.6%	5.0%
Ventricular arrhythmias	1.9%	1.0%	–
Left ventricular dysfunction	11.3%	8.4%	7.2%

prophylactically for ECG conduction abnormalities, 17 (27.4%) were pacemaker-dependent at last follow-up [25].

Supraventricular arrhythmias

Supraventricular arrhythmias, including atrial fibrillation, flutter, and tachycardia, are present in 5%–12% patients at presentation [20–23]. Supraventricular arrhythmias usually occur in patients without significant atrial remodeling. Rapid atrial fibrillation can manifest as lightheadedness and syncope in young patients and be the first sign of disease [28]. The risk of arterial thromboembolism in patients with supraventricular arrhythmias remains unknown, but several cases of stroke have been reported among patients with CHADS-VASC scores of 0 [29].

Increased P wave duration and dispersion and echocardiographic atrial electromechanical delay (intra-left and inter-atrial) are common in DM1 patients and are associated with presence or further development of atrial fibrillation [30,31].

Ventricular arrhythmias

Re-entry circuits promoted by fibrotic foci, fatty infiltration, and delayed conduction in the His–Purkinje system along with bundle branch re-entry tachycardia [32] may lead to ventricular arrhythmias. The exact prevalence of premature ventricular contractions in DM1 has not been established in large cohort studies with systematic Holter ECG; however, a meta-analysis of published cases suggested a prevalence of 14% [23]. In the largest cohort published to date, the prevalence rates of non-sustained and sustained ventricular tachycardia were 2.2% and 0.8%, respectively [24]. The incidence of sustained ventricular tachycardia was 2.3% in a large cohort of unselected DM1 patients during a 12-year follow-up and non-sustained ventricular tachycardia was the only independent predictor of sustained ventricular tachycardia [24]. The prognostic implications of inducible ventricular tachycardia during electrophysiological studies is uncertain in this patient population.

Several studies have shown evidence of increased dispersion of ventricular repolarization (QTc dispersion, JTc dispersion, transmural dispersion of repolarization, QT variability index) and sympatho-vagal balance in patients with DM1 (Heart Rate Variability) suggesting a potential interest of these measures to predict ventricular arrhythmias [33–35].

Venous thromboembolism

Venous thromboembolism, defined as deep vein thrombosis and/or pulmonary embolism, occurred in 10.3% of 1148 DM1 patients over a 10-year follow-up [36]. Furthermore, 58% patients who developed thromboembolism had no predisposing factors. The standardized rate ratio for venous thromboembolism was 7.5 between this cohort and an age- and sex-matched community-based population. The risk of venous thromboembolism was 5.5 higher than that in patients with other inherited myopathies, after adjustments for potential confounding factors. These observations indicate that a systematic venous thromboembolism prophylaxis that can be applied in any medical or surgical setting is required. Venous thromboembolism in DM1 may be attributable to complex pathogenic mechanisms such as altered mRNA processing of coagulation factors. The following predict venous thromboembolism in DM1: older age, history of venous thromboembolism, obesity, Walton score, cancer, conduction disease, and ambulation loss.

Other manifestations

Arterial systolic hypotension

Systolic blood pressure \leq 110 mmHg occurs in 24% patients and is independently associated with greater all-cause mortality [21]. It

is unclear whether systolic hypotension is a specific complication of the disease or a non-specific marker of disease severity.

Sleep apnea

Sleep apnea is a common, multifactorial complication that precipitates both atrial and ventricular tachyarrhythmias [37]. The effect of nocturnal mechanical ventilation on arrhythmias in DM1 is not known.

Myocardial dysfunction

Left ventricular dysfunction occurs in 7.2%–11.3% patients [18–20] and remains asymptomatic in most patients. Subclinical myocardial systolic dysfunction can be detected using strain rate imaging echocardiography [38] and correlates with conduction system disease. Reduced global and regional coronary flow reserve is demonstrable with positron emission tomography with oxygen-labeled water, but its clinical implications remain unknown [39].

Mitral valve prolapse

Mitral valve prolapse is associated with DM1 [40], but its prevalence has not been estimated in large prospective cohorts, and severe mitral regurgitation is rare in DM1.

Genotype–phenotype correlations

The size of the CTG amplification correlates significantly with the severity of cardiac involvement (conduction defects on ECG and left ventricular systolic dysfunction), major conduction defects, and sudden death [41], even adjusting for confounders such as age, gender, and diabetes mellitus. However, all DM1 patients, including those with CTG amplifications $<$ 100 repeats, are at risk for life-threatening complications.

Cardiac clinical investigations

Risk stratification for sudden death

The prevention of sudden death is central to the management of DM1 patients, and the main objective of cardiac diagnostic workup is risk stratification. Two main approaches—*invasive* and *non-invasive*—are used to identify high-risk patients who require an implantable device.

Non-invasive approach

This is based on 12-lead ECG and 24-h ambulatory ECG. The combination of any cardiac rhythm other than sinus rhythm, PR interval \geq 240 ms, QRS duration \geq 120 ms, and second- or third-degree atrioventricular block [20] is independently associated with sudden death. The sensitivity, specificity, and positive and negative predictive values of these criteria were 74.1%, 61.7%, 12.1%, and 97.1%, respectively.

Invasive approach

This is based on 12-lead ECG and electrophysiology study in patients with mild conduction defects on ECG. Patients with HV interval \geq 70 ms [22,26,27] are at a high risk for complete atrioventricular block and sudden death. In a prospective study including 49 patients with HV interval \geq 70 ms who underwent pacemaker implantation, 51% had advanced atrioventricular blocks stored in their device memory.

The accuracy of these two approaches in the prediction of sudden death and/or advanced atrioventricular block has been studied in different populations, but no direct comparison has yet been performed. Current data suggest that the *invasive* strategy has greater positive predictive value, but its specificity and negative predictive values are not known. Prophylactic pacing with patient selection based on the *invasive* approach reduces the risk of

sudden death in observational, non-randomized studies (see paragraph on cardiac treatments); [22] the potential clinical benefit of pacing using the non-invasive criteria is unknown.

Other investigations

Cardiac workup in DM1 is also used for the early detection of other cardiac manifestations such as supraventricular tachyarrhythmias and left ventricular dysfunction, which may be present even in asymptomatic patients [24].

Recommendations for cardiac workup

Annual follow-up is recommended in DM1 patients, including asymptomatic patients. Considering the prognostic implications and complexity of the cardiac involvement in DM1, follow-up should be undertaken by a cardiologist with experience in managing DM1 patients. The cardiac workup should include 12-lead ECG at diagnosis and at least yearly thereafter. Patients with cardiac symptoms, conduction block on ECG, and/or supraventricular or ventricular arrhythmias should also undergo echocardiogram and 24-h ambulatory ECG.

Electrophysiological study can be useful in patients with cardiac symptoms or conduction disease, such as first-degree atrioventricular, fascicular, and bundle branch block, on ECG. It may be repeated in patients who develop symptoms or show progression of conduction disease on the follow-up ECG [42].

Cardiac treatments

Sudden death prevention: pacing and defibrillator implantation

Pacing therapy is the first-line treatment for sudden death prevention in DM1 [43] and an ICD may be considered to minimize the risk of sudden death from VT if meaningful survival of greater than 1 year is expected. Prophylactic pacing is recommended in patients with conduction system disease due to the risk of rapid unpredictable progression to complete atrioventricular block. No randomized trial has assessed the prognostic impact of prophylactic pacing yet. However, propensity-score analysis of data from a large registry with 900 DM1 patients showed significantly greater overall survival (hazard ratio, 0.47–0.61) among patients with mild conduction defects on ECG who underwent electrophysiological study and permanent pacing if the HV interval ≥ 70 ms rather than follow-up ECG and ambulatory ECG assessment [22]. This benefit was largely attributable to a lower incidence of sudden death (hazard ratio, 0.24–0.28).

In DM1 patients, permanent pacing

- is recommended in the presence of symptomatic or asymptomatic third-degree or advanced second-degree atrioventricular block.
- may be considered in patients with first-degree atrioventricular, fascicular, or bundle branch block. (Thresholds values of 240 and 120 ms for PR interval and QRS duration, respectively, may represent a good compromise in terms of sensitivity and specificity.)
- may be considered in patients with HV interval ≥ 70 ms on electrophysiological study, regardless of symptoms.

ICDs can be considered to minimize the risk of sudden death from VT if meaningful survival of greater than 1 year is expected and more specifically in patients with the following indications:

- sustained ventricular tachyarrhythmias (for secondary prevention),
- the same indications as in non-ischemic dilated cardiomyopathy (for primary prevention),

- any indication for permanent pacing along with non-sustained ventricular tachycardia on ambulatory ECG or sustained ventricular tachycardia induced by programmed ventricular stimulation.

Prophylactic pacemaker/ICD is considered if the life expectancy exceeds 1 year. Additionally, the high risk of competing causes of death such as respiratory failure should be taken into account [19]. Multidisciplinary evaluation of global disease severity is warranted and should include an estimation of survival probability using a specific survival score [21].

Atrial pacing in the Bachmann bundle region was associated with a reduction of atrial electromechanical delay and the risk of R-wave oversensing on the atrial lead, compared with right atrial stimulation, but showed no benefit for the prevention of atrial fibrillation [44–46].

Supraventricular arrhythmias

It remains unclear whether DM1 patients with atrial fibrillation or other atrial arrhythmias should be treated similarly to patients from the general population. Given the lack of data on the risk of thromboembolic complications in DM1, the indications for anticoagulation should probably be the same as in the general population. Preliminary data suggest that class I antiarrhythmic drugs should be used very cautiously or be contraindicated in patients with conduction system disease or a history of ventricular or supraventricular arrhythmias owing to the ventricular arrhythmogenic effects of these drugs. The efficacy of radiofrequency ablation appears to be similar to that reported in the general population for the prevention of atrial flutter recurrence [29], but remains unknown for atrial fibrillation. Minimal ventricular pacing has been shown to be an efficient strategy to reduce the risk of atrial fibrillation in DM1 patients implanted with a pacemaker [47]. An increase of the incidence of paroxysmal atrial fibrillation has been shown in patients with a higher rate of right ventricular pacing and a lower rate of atrial stimulation [48].

Left ventricular dysfunction and heart failure therapy

The management of heart failure in DM1 should follow current American College of Cardiology/American Heart Association guidelines. The up-titration of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers is often difficult because many patients develop symptomatic hypotension. Hyperkalemia is a frequent complication of ACE inhibitors and aldosterone antagonists in these patients even when renal function is preserved.

Venous thromboembolism

More systematic venous thromboembolism prophylaxis and treatments should be offered to patients with DM1 than usually dispensed [27]. The most appropriate management strategy for venous thromboembolism in DM1 remains to be defined and should probably be similar to that in patients with inherited thrombophilic diseases, such as protein C or protein S deficiency. The decision to initiate prolonged curative anticoagulation in patients with venous thromboembolism is difficult, as the risk of bleeding complications may be high in this population who are at an increased risk of falls and whose compliance with treatment might be variable. In women, careful counseling on the use of oral contraceptives and postmenopausal estrogen replacement therapy is required since the risk of venous thromboembolism is highest between 20 and 59 years of age [29].

Class I antiarrhythmic drugs safety

Some concerns have been raised regarding the safety of class I antiarrhythmic drugs in DM1 patients. The indications for mexiletine are frequently discussed in DM1 patients, as this drug is the most efficient treatment for myotonia. The use of these medications may exacerbate the loss of cardiac sodium channel function, which contributes to the development of cardiac arrhythmias [49]. Several case series have shown that intravenous flecainide or ajmaline can trigger severe ventricular tachyarrhythmias or unmask a type 1 Brugada pattern in DM1 patients [50]. Therefore, these drugs should be used very cautiously, and their risk-benefit ratio should be assessed on an individual basis.

Specific populations

Pediatric patients

The prevalence of cardiac involvement and the risk of adverse events have not been estimated in large pediatric populations with DM. However, several case reports have shown that pediatric DM1 patients can present with atrial arrhythmias and less commonly with sustained ventricular tachyarrhythmias, which may cause sudden death [51]. These events have been exclusively reported after the age of 10 years and were triggered in most cases by exercise. Complete atrioventricular block has not yet been reported in DM1 patients before the age of 18 years. A Danish nationwide study showed that pediatric DM patients had a higher prevalence of heart disease than the general population, with a standardized incidence ratio of 19.4 (95% CI, 4.92–52.7) [52].

These data suggest that the early detection of cardiac involvement should be considered after the age of 10 years, particularly in patients who practice sports. Indications for 12-lead ECG, echocardiography, and ambulatory ECG should probably be the same as in adults.

Myotonic dystrophy type 2

Patients with DM2 present with similar cardiac manifestations as patients with DM1, but with a lower prevalence and later age of onset [53,54]. Complete atrioventricular block occurs in most patients in their 70s. A higher proportion of patients develop left ventricular dysfunction and ischemic stroke, particularly, patients with atrial fibrillation. The risk of sudden death is lower in DM2 patients than in DM1 patients [55]. DM2 patients may benefit from the same approach for risk stratification and preventive treatments for sudden death as in DM1 patients.

Future directions

There is an unmet need for research on risk stratification in DM1 and DM2 to improve the criteria for prophylactic permanent pacing and ICD therapy. The accuracy of non-invasive workup versus electrophysiological study should be compared in large populations. Considering the high risk of sudden death, randomized trials to assess the impact of preventive measures on prognosis are hardly feasible; therefore, analysis of large multicenter registries will be of great importance.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.tcm.2019.06.001](https://doi.org/10.1016/j.tcm.2019.06.001).

References

- [1] Harper PS. Myotonic dystrophy. 3rd ed. London: WB Saunders; 2001.
- [2] Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H, 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* 1992;69:385.
- [3] Ranum LP, Rasmussen PF, Benzow KA, Koob MD, Day JW. Genetic mapping of a second myotonic dystrophy locus. *Nat Genet* 1998;19:196–8.
- [4] Hunter A, Tsilfidis C, Mettler G, Jacob P, Mahadevan M, Surh L, Korneluk R. The correlation of age of onset with CTG trinucleotide repeat amplification in myotonic dystrophy. *J Med Genet* 1992;29:774–9.
- [5] Thornton CA, Johnson K, Moxley RT. Myotonic dystrophy patients have larger CTG expansions in skeletal muscle than in leukocytes. *Ann Neurol* 1994;35:104–7.
- [6] Furling D, Lam le T, Agbulut O, Butler-Browne GS, Morris GE. Changes in myotonic dystrophy protein kinase levels and muscle development in congenital myotonic dystrophy. *Am J Pathol* 2003;162:1001–9.
- [7] Carrell ST, Carrell EM, Auerbach D, Pandey SK, Bennett CF, Dirksen RT. Dmpk gene deletion or antisense knockdown does not compromise cardiac or skeletal muscle function in mice. *Hum Mol Genet* 2016;25:4328–38.
- [8] Lin X, Miller JW, Mankodi A, Kanadia RN, Yuan Y, Moxley RT, Swanson MS, Thornton CA. Failure of MBNL1-dependent post-natal splicing transitions in myotonic dystrophy. *Hum Mol Genet* 2006;15:2087–97.
- [9] Wang ET, Ward AJ, Cherone JM, Giudice J, Wang TT, Treacy DJ, et al. Antagonistic regulation of mRNA expression and splicing by CELF and MBNL proteins. *Genome Res* 2015;25:858–71.
- [10] Charlet BN, Savkur RS, Singh G, Philips AV, Grace EA, Cooper TA. Loss of the muscle-specific chloride channel in type 1 myotonic dystrophy due to misregulated alternative splicing. *Mol Cell* 2002;10:45–53.
- [11] Lee KY, Li M, Manchanda M, Batra R, Charizanis K, Mohan A, et al. Compound loss of muscleblind-like function in myotonic dystrophy. *EMBO Mol Med* 2013;5:1887–900.
- [12] Dixon DM, Choi J, El-Ghazali A, Park SY, Roos KP, Jordan MC, et al. Loss of muscleblind-like 1 results in cardiac pathology and persistence of embryonic splice isoforms. *Sci Rep* 2015;5:9042.
- [13] Freyermuth F, Rau F, Kokunai Y, Linke T, Sellier C, Nakamori M, et al. Splicing misregulation of SCN5A contributes to cardiac-conduction delay and heart arrhythmia in myotonic dystrophy. *Nat Commun* 2016;7:11067.
- [14] Wang DW, Viswanathan PC, Balsler JR, George AL, Benson DW. Clinical, genetic, and biophysical characterization of SCN5A mutations associated with atrioventricular conduction block. *Circulation* 2002;105:341–6.
- [15] Pang PD, Alsina KM, Cao S, Koushik AB, Wehrens XHT, Cooper TA. CRISPR-mediated expression of the fetal scn5a isoform in adult mice causes conduction defects and arrhythmias. *J Am Heart Assoc* 2018;7:e010393.
- [16] Wang GS, Kuyumcu-Martinez MN, Sarma S, Mathur N, Wehrens XH, Cooper TA. PKC inhibition ameliorates the cardiac phenotype in a mouse model of myotonic dystrophy type 1. *J Clin Invest* 2009;119:3797–806.
- [17] Singh RK, Gurha P, Ward AJ, Creighton CJ, Cooper TA. The Mef2 transcription network is disrupted in myotonic dystrophy heart tissue, dramatically altering miRNA and mRNA expression. *Cell Rep* 2014;6:336–45.
- [18] Zhao Y, Ransom JF, Li A, Vedantham V, von Drehle M, Muth AN, et al. Dysregulation of cardiogenesis, cardiac conduction, and cell cycle in mice lacking miRNA-1-2. *Cell* 2007;129:303–17.
- [19] Rau F, Freyermuth F, Fugier C, Villemain J-P, Fischer M-C, Jost B, Dembele D, et al. Misregulation of miR-1 processing is associated with heart defects in myotonic dystrophy. *Nat Struct Mol Biol* 2011;18:840–5.
- [20] Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. *N Engl J Med* 2008;358:2688–97.
- [21] Wahbi K, Porcher R, Laforêt P, Fayssol A, Bécane HM, Lazarus A, et al. Development and validation of a new scoring system to predict survival in patients with myotonic dystrophy type 1. *JAMA Neurol* 2018;75:573–81.
- [22] Wahbi K, Meune C, Porcher R, Bécane HM, Lazarus A, Laforêt P, et al. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. *JAMA* 2012;307:1292–301.
- [23] Petri H, Vissing J, Witting N, Bundgaard H, Køber L. Cardiac manifestations of myotonic dystrophy type 1. *Int J Cardiol* 2012;160:82–8.
- [24] Wahbi K, Babuty D, Probst V, Wissocque L, Labombarda F, Porcher R, 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* 2017;38:751–8.
- [25] Bhakta D, Shen C, Kron J, Epstein AE, Pascuzzi RM, Groh WJ. Pacemaker and implantable cardioverter-defibrillator use in a US myotonic dystrophy type 1 population. *J Cardiovasc Electrophysiol* 2011;22:1369–75.
- [26] Lazarus A, Varin J, Ounnoughene Z, Radvanyi H, Junien C, Coste J, et al. Relationships among electrophysiological findings and clinical status, heart function, and extent of DNA mutation in myotonic dystrophy. *Circulation* 1999;99:1041–6.
- [27] Lazarus A, Varin J, Babuty D, Anselme F, Coste J, Duboc D. Long-term follow-up of arrhythmias in patients with myotonic dystrophy treated by pacing: a multicenter diagnostic pacemaker study. *J Am Coll Cardiol* 2002;40:1645–52.
- [28] Brembilla-Perrot B, Schwartz J, Huttin O, Frikha Z, Sellal JM, Sadoul N, et al. Atrial flutter or fibrillation is the most frequent and life-threatening arrhythmia in myotonic dystrophy. *Pacing Clin Electrophysiol* 2014;37:329–35.

- [29] Wahbi K, Sebag FA, Lellouche N, Lazarus A, Bécane HM, Bassez G, et al. Atrial flutter in myotonic dystrophy type 1: patient characteristics and clinical outcome. *Neuromuscul Disord* 2016;26:227–33.
- [30] Russo V, Di Meo F, Rago A, Papa AA, Molino A, Mosella M, Politano L, Russo MG, Nigro G. Paroxysmal atrial fibrillation in myotonic dystrophy type 1 patients: p wave duration and dispersion analysis. *Eur Rev Med Pharmacol Sci* 2015;19(Apr (7)):1241–8.
- [31] Russo V, Rago A, Ciardiello C, Russo MG, Calabrò P, Politano L, Nigro G. The role of the atrial electromechanical delay in predicting atrial fibrillation in myotonic dystrophy type 1 patients. *J Cardiovasc Electrophysiol* 2016;27(Jan (1)):65–72.
- [32] Merino JL, Carmona JR, Fernández-Lozano I, Peinado R, Basterra N, Sobrino JA. Mechanisms of sustained ventricular tachycardia in myotonic dystrophy: implications for catheter ablation. *Circulation* 1998;98:541–6.
- [33] Russo V, Papa AA, Rago Anna, Nigro G. Arrhythmic risk evaluation in myotonic dystrophy: the importance of selection criteria and methodological approach. *Clin Auton Res* 2017;27:203–4.
- [34] Magri D, Piccirillo G, Bucci E, et al. Increased temporal dispersion of myocardial repolarization in myotonic dystrophy type 1: beyond the cardiac conduction system. *Int J Cardiol* 2012;156:259–64.
- [35] Hardin BA, Lowe MR, Bhakta D, Groh WJ. Heart rate variability declines with increasing age and CTG repeat length in patients with myotonic dystrophy type 1. *Ann Noninvasive Electrocardiol* 2003;8:227–32.
- [36] Sochala M, Porcher R, Stojkovic T, Bécane HM, Béhin A, Laforêt P, et al. High risk of fatal and non-fatal venous thromboembolism in myotonic dystrophy. *Circulation* 2018;138.
- [37] Lazarus A, Varin J, Jauvert G, Alonso C, Duboc D. Relationship between cardiac arrhythmias and sleep apnoea in permanently paced patients with type 1 myotonic dystrophy. *Neuromuscul Disord* 2007;17:392–9.
- [38] Wahbi K, Ederhy S, Bécane HM, Meune C, Béhin A, Stojkovic T, Laforet P, Eymard B, Duboc D, Cohen A. Impaired myocardial deformation detected by speckle-tracking echocardiography in patients with myotonic dystrophy type 1. *Int J Cardiol* 2011;152:375–6.
- [39] Annane D, Merlet P, Radvanyi H, Mazoyer B, Eymard B, Fiorelli M, et al. Blunted coronary reserve in myotonic dystrophy. An early and gene-related phenomenon. *Circulation* 1996;94:973–7.
- [40] Gottdiener JS, Hawley RJ, Gay JA, DiBianco R, Fletcher RD, Engel WK. Left ventricular relaxation, mitral valve prolapse, and intracardiac conduction in myotonia atrophica: assessment by digitized echocardiography and noninvasive his bundle recording. *Am Heart J* 1982;104:77–85.
- [41] Chong-Nguyen C, Wahbi K, Algalarrondo V, Bécane HM, Radvanyi-Hoffman H, Arnaud P, et al. Association between mutation size and cardiac involvement in myotonic dystrophy type 1: an analysis of the DM1-Heart registry. *Circ Cardiovasc Genet* 2017;10.
- [42] Lallemand B, Clementy N, Bernard-Brunet A, Pierre B, Corcia P, Fauchier L, et al. The evolution of infrahisian conduction time in myotonic dystrophy patients: clinical implications. *Heart* 2012;98:291–6.
- [43] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American college of cardiology/American heart association task force and the European society of cardiology committee for practice Guidelines; developed in collaboration with the European heart rhythm association and the heart rhythm society. *Circulation* 2006;114:e385–484.
- [44] Nigro G, Russo V, Politano L, Della Cioppa N, Rago A, Arena G, et al. Does Bachmann's bundle pacing prevent atrial fibrillation in myotonic dystrophy type 1 patients? A 12 months follow-up study. *Europace* 2010;12:1219–23.
- [45] Russo V, Rago A, Papa AA, Arena G, Politano L, Nigro G. Bachmann bundle pacing reduces atrial electromechanical delay in type 1 myotonic dystrophy patients. *J Interv Card Electrophysiol* 2018;51:229–36.
- [46] Russo V, Nigro G, Papa AA, Rago A, Di Meo F, Cristiano A, Far field R-wave sensing in myotonic dystrophy type 1: right atrial appendage versus Bachmann's bundle region lead placement. *Acta Myol* 2014;33:94–9.
- [47] Russo V, Papa AA, Rago A, Ciardiello C, Nigro G. Effect of dual-chamber minimal ventricular pacing on paroxysmal atrial fibrillation incidence in myotonic dystrophy type 1 patients: a prospective, randomized, single-blind, crossover study. *Heart Rhythm* 2018;15:962–8.
- [48] Russo V, Rago A, Papa AA, Politano L, Golino P, Russo MG, et al. Does a high percentage of right ventricular pacing influence the incidence of paroxysmal atrial fibrillation in myotonic dystrophy type 1 patients? *Kardiol Pol* 2013;71:1147–53.
- [49] Otten RF, Scherschel JA, Lopshire JC, Bhakta D, Pascuzzi RM, Groh WJ. Arrhythmia exacerbation after sodium channel blockade in myotonic dystrophy type 1. *Muscle Nerve* 2009;40:901–2.
- [50] Wahbi K, Algalarrondo V, Bécane HM, Fressart V, Beldjord C, Azibi K. Brugada syndrome and abnormal splicing of SCN5A in myotonic dystrophy type 1. *Arch Cardiovasc Dis* 2013;106:635–43.
- [51] Bassez G, Lazarus A, Desguerre I, Varin J, Laforêt P, Bécane HM, et al. Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1. *Neurology* 2004;63:1939–41.
- [52] Lund M, Diaz LJ, Ranthe MF, Petri H, Duno M, Juncker I, et al. Cardiac involvement in myotonic dystrophy: a nationwide cohort study. *Eur Heart J* 2014;35:2158–64.
- [53] Sansone VA, Brigonzi E, Schoser B, Villani S, Gaeta M, De Ambroggi G, et al. The frequency and severity of cardiac involvement in myotonic dystrophy type 2 (DM2): long-term outcomes. *Int J Cardiol* 2013;168:1147–53.
- [54] Wahbi K, Meune C, Bécane HM, Laforêt P, Bassez G, Lazarus A, et al. Left ventricular dysfunction and cardiac arrhythmias are frequent in type 2 myotonic dystrophy: a case control study. *Neuromuscul Disord* 2009;19:468–72.
- [55] Schoser BG, Ricker K, Schneider-Gold C, Hengstenberg C, Dürre J, Bültmann B, et al. Sudden cardiac death in myotonic dystrophy type 2. *Neurology* 2004;63:2402–4.