2022 HRS expert consensus statement on evaluation and management of arrhythmic risk in neuromuscular disorders

Groh, W.J.; Bhakta, D.; Tomaselli, G.F.; Aleong, R.G.; Teixeira, R.A.; Amato, A.; ... ; Zeppenfeld, K.

2022 HRS expert consensus statement on evaluation and management of arrhythmic risk in neuromuscular disorders

William J. Groh, MD, MPH, FHRS (Chair),[1]
Deepak Bhakta, MD, MBA, FHRS, FACC, FAHA, FACP, CCDS (Vice-Chair),[2]
Gordon F. Tomaselli, MD, FHRS (Vice-Chair),[3] Ryan G. Aleong, MD, FHRS,[4]
Ricardo Alkmim Teixeira, MD, PhD,[5,*] Anthony Amato, MD,[6,†]
Samuel J. Asirvatham, MD, FHRS,[7] Yong-Mei Cha, MD, FHRS,[7]
Domenico Corrado, MD, PhD, FESC,[8,‡] Denis Duboc, MD, PhD,[9]
Zachary D. Goldberger, MD, FHRS,[10] Minoru Horie, MD, PhD,[11,§]
Joseph E. Hornyak, MD, PhD,[12,¶] John Lynn Jefferies, MD, MPH, FACC, FAHA, FHFSA,[13,#]
Stefan Kääb, MD, PhD,[14,‡] Jonathan M. Kalman, MBBS, PhD, FHRS,[15]
Naomi J. Kertesz, MD, FHRS, CEPS-P,[16,**] Neal K. Lakdawala, MD,[6,††]
Pier D. Lambiase, BCH, BM, MBChB, PhD, FHRS,[17,‡] Steven A. Lubitz, MD, MPH,[18,‡‡]
Hugh J. McMillan, MD, MSc,[19,§§] Elizabeth M. McNally, MD, PhD,[20,#]
Margherita Milone, MD, PhD,[7,†] Narayanan Namboodiri, MBBS, MD,[21,¶¶]
Saman Nazarian, MD, PhD, FHRS,[22] Kristen K. Patton, MD, FHRS,[23]
Vincenzo Russo, MD, PhD,[24,‡] Frederic Sacher, MD, PhD,[25,‡]
Pasquale Santangeli, MD, PhD,[22] Win-Kuang Shen, MD, FHRS,[26]
Dario C. Sobral Filho, MD, PhD,[27,##] Bruce S. Stambler, MD, FHRS,[28]
Claudia Stöllberger, MD,[29] Karim Wahbi, MD, PhD,[9]
Xander H.T. Wehrens, MD, PhD, FHRS,[30] Menachem Mendel Weiner, MD,[31,***]
Matthew T. Wheeler, MD, PhD,[32,#] Katja Zeppenfeld, MD, PhD[33,‡]

Document Reviewers: Diana Anca, MD; Andreas S. Barth, MD, PhD; Ratna Bhavaraju-Sanka, MD; Alfred E. Buxton, MD; Gonzalo Calvimontes, MD; Richard J. Czosek, MD; Alexsandro A. Fagundes, MD; Jeff S. Healey, MD, MSc, FRCPC, FHRS; Daniel P. Judge, MD; Jodie L. Hurwitz, MD, FHRS; Pamela K. Mason, MD, FHRS; Christian Meyer, MD, MA, FESC, FEHRA, FHRS; Soraya M. Samii, MD, PhD, FHRS; Kazuhiro Satomi, MD, PhD; Martin K. Stiles, MBChB, PhD, FHRS; Robert Rinaldi, MD, FAAPMR

From the [1]Ralph H. Johnson VA Medical Center and Medical University of South Carolina, Charleston, South Carolina, [2]Indiana University School of Medicine, Indianapolis, Indiana, [3]Albert Einstein College of Medicine, Bronx, New York, [4]University of Colorado Hospital, Aurora, Colorado, [5]Hospital Renascentista, Pouso Alegre, Brazil, [6]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, [7]Mayo Clinic, Rochester, Minnesota, [8]Department of Cardiac, Thoracic, and Vascular Sciences, University of Padova, Padova, Italy, [9]Cardiology Department, Hôpital Cochin, AP-HP, Université de Paris, Paris, France, [10]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, [11]Shiga University of Medical Sciences, Otsu, Japan, [12]University of Michigan, Ann Arbor, Michigan, [13]University of Tennessee Health Science Center, Memphis, Tennessee, [14]Department of Medicine I, University Hospital, LMU Munich, Munich, Germany, [15]Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia, [16]Nationwide Children's Hospital, Columbus, Ohio, [17]Barts Heart Centre, St Bartholomew's Hospital, University College London, and St Bartholomew's Hospital London, London, United Kingdom, [18]Massachusetts General Hospital, Boston, Massachusetts, [19]Montreal Children's Hospital, McGill University,

 https://doi.org/10.1016/j.hrthm.2022.04.022

Montreal, Quebec, Canada, [20]*Northwestern University Feinberg School of Medicine, Chicago, Illinois,* [21]*Sree Chitra Institute for Medical Sciences and Technology, Thiruvananthapuram, India,* [22]*University of Pennsylvania, Philadelphia, Pennsylvania,* [23]*University of Washington, Seattle, Washington,* [24]*University of Campania Luigi Vanvitelli, Naples, Italy,* [25]*Bordeaux University Hospital, LIRYC Institute, Bordeaux, France,* [26]*Mayo Clinic College of Medicine, Phoenix, Arizona,* [27]*PROCAPE University Hospital, Recife, Brazil,* [28]*Piedmont Heart Institute, Atlanta, Georgia,* [29]*Second Medical Department with Cardiology and Intensive Care Medicine, Klinik Landstraße, Vienna, Austria,* [30]*Baylor College of Medicine, Houston, Texas,* [31]*Icahn School of Medicine at Mount Sinai, New York, New York,* [32]*Stanford University, Stanford, California, and* [33]*Leiden University Medical Center, Leiden, The Netherlands.*

**Representative of the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC)*
†Representative of the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM)
‡Representative of the European Heart Rhythm Association (EHRA)
§Representative of the Japanese Heart Rhythm Society (JHRS)
¶Representative of the American Academy of Physical Medicine and Rehabilitation (AAPM&R)
#Representative of the American College of Cardiology (ACC)
***Representative of the Pediatric and Congenital Electrophysiology Society (PACES)*
††Representative of the Heart Failure Society of America (HFSA)
‡‡Representative of the American Heart Association (AHA)
§§Representative of the Child Neurology Society (CNS)
¶¶Representative of the Asia Pacific Heart Rhythm Society (APHRS)
##Representative of the Latin American Heart Rhythm Society (LAHRS)
****Representative of the American Society of Anesthesiologists (ASA)*

KEYWORDS Atrial fibrillation; Atrioventricular block; Cardiomyopathy; ICD; Implantable cardioverter-defibrillator; Muscular dystrophy; Myotonic dystrophy; Pacemaker; Sudden death; Ventricular fibrillation; Ventricular tachycardia

ABBREVIATIONS **AAV** = adeno-associated virus; **ACE** = angiotensin-converting enzyme; **AF** = atrial fibrillation; **AFL** = atrial flutter; **AV** = atrioventricular; **BBRVT** = bundle branch reentrant ventricular tachycardia; **BMD** = Becker muscular dystrophy; **bpm** = beats per minute; **CIED** = cardiovascular implantable electronic device; **CMR** = cardiac magnetic resonance imaging; **COR** = class of recommendation; **CRT** = cardiac resynchronization therapy; **CRT-D** = cardiac resynchronization therapy defibrillator; **CRT-P** = cardiac resynchronization therapy pacemaker; **DM** = myotonic dystrophy; **DM1** = myotonic dystrophy type 1; **DM2** = myotonic dystrophy type 2; **DMD** = Duchenne muscular dystrophy; **ECG** = electrocardiogram; **EDMD** = Emery-Dreifuss muscular dystrophy; **EDMD1** = Emery-Dreifuss muscular dystrophy type 1; **EDMD2** = Emery-Dreifuss muscular dystrophy type 2; **FA** = Friedreich ataxia; **FSHD** = facioscapulohumeral muscular dystrophy; **FSHD1** = facioscapulohumeral muscular dystrophy type 1; **FSHD2** = facioscapulohumeral muscular dystrophy type 2; **ICD** = implantable cardioverter-defibrillator; **LBBB** = left bundle branch block; **LGMD** = limb-girdle muscular dystrophy; **LGMD1B** = limb-girdle muscular dystrophy type 1B; **LGMD2** = limb-girdle muscular dystrophy type 2; **LOE** = level of evidence; **LVEF** = left ventricular ejection fraction; **MELAS** = mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke-like episodes; **NMD** = neuromuscular disorder; **NYHA** = New York Heart Association; **RBBB** = right bundle branch block; **RCT** = randomized controlled trial; **RWI** = relationship with industry and other entities; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia (Heart Rhythm 2022;19:e61–e120)

Developed in collaboration with the American Academy of Physical Medicine and Rehabilitation (AAPM&R), the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), the American College of Cardiology (ACC), the American Heart Association (AHA), the American Society of Anesthesiologists (ASA), the Asia Pacific Heart Rhythm Society (APHRS), the Child Neurology Society (CNS), the European Heart Rhythm Association (EHRA), the Heart Failure Society of America (HFSA), the Japanese Heart Rhythm Society (JHRS), the Latin American Heart Rhythm Society (LAHRS), the Pediatric and Congenital Electrophysiology Society (PACES), and the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC). Endorsed by AANEM, ACC, AHA, APHRS, CNS, EHRA, HFSA, JHRS, LAHRS, PACES, and SOBRAC. AAPM&R and ASA affirmed the value.
 Correspondence: Heart Rhythm Society, 1325 G St NW, Suite 400, Washington, DC 20005. E-mail address: clinicaldocs@hrsonline.org.

Abstract

This international multidisciplinary document is intended to guide electrophysiologists, cardiologists, other clinicians, and health care professionals in caring for patients with arrhythmic complications of neuromuscular disorders (NMDs). The document presents an overview of arrhythmias in NMDs followed by detailed sections on specific disorders: Duchenne muscular dystrophy, Becker muscular dystrophy, and limb-girdle muscular dystrophy type 2; myotonic dystrophy type 1 and type 2; Emery-Dreifuss muscular dystrophy and limb-girdle muscular dystrophy type 1B; facioscapulohumeral muscular dystrophy; and mitochondrial myopathies, including Friedreich ataxia and Kearns-Sayre syndrome, with an emphasis on managing arrhythmic cardiac manifestations. End-of-life management of arrhythmias in patients with NMDs is also covered. The document sections were drafted by the writing committee members according to their area of expertise. The recommendations represent the consensus opinion of the expert writing group, graded by class of recommendation and level of evidence utilizing defined criteria. The recommendations were made available for public comment; the document underwent review by the Heart Rhythm Society Scientific and Clinical Documents Committee and external review and endorsement by the partner and collaborating societies. Changes were incorporated based on these reviews. By using a breadth of accumulated available evidence, the document is designed to provide practical and actionable clinical information and recommendations for the diagnosis and management of arrhythmias and thus improve the care of patients with NMDs.

TABLE OF CONTENTS

Top 10 take-home messages

1. Shared decision-making among patients, their families, and clinicians is essential whenever diagnostic studies or therapies, particularly those that are invasive, are being utilized or contemplated. Counseling and education may result in patients' refusal or withdrawal of such measures if inconsistent with their goals of care, and this should be respected.
2. Cardiac testing is appropriate in most patients with neuromuscular disorders to evaluate cardiac involvement. The type of cardiac test and the need for and frequency of repeat testing are governed by the underlying disorder, results of previous or new studies, and the patient's symptomatic status. It should be noted that skeletal muscle impairment may mask or confound cardiovascular symptoms, requiring heightened vigilance to cardiac involvement and modification of testing.
3. Previously published guideline-based indications for cardiovascular implantable electronic device (CIED) use, including cardiac resynchronization therapy, and for management of cardiomyopathy and heart failure may be applied in patients with neuromuscular disorders. For some indications, the level of evidence and/or class of recommendation in the current document have been modified from prior guidelines to reflect the underrepresentation of patients with neuromuscular disorders in past studies.
4. A patient's overall prognosis may be affected by the impact of their underlying neuromuscular condition. Condition-specific technical challenges including body habitus (such as kyphoscoliosis), respiratory muscle weakness, and sedation-related risks may influence clinical management. These effects may dominate a patient's clinical picture and prognosis, possibly attenuating the benefit of arrhythmia therapy, particularly CIED implantation, when compared with other patient populations.
5. Patients with Duchenne muscular dystrophy, Becker muscular dystrophy, and recessive forms of limb-girdle muscular dystrophy rarely develop bradyarrhythmias, but cardiomyopathy, heart failure, and ventricular arrhythmias may occur with increased frequency. When indicated, CIED therapy in these patients may pose technical challenges and limited benefit, particularly in those with advanced neuromuscular impairment.
6. In addition to established indications, pacemaker implantation, or, in selected individuals, pacing-capable implantable cardioverter-defibrillator placement, is indicated in patients with myotonic dystrophy type 1 or type 2 who have evidence of abnormal atrioventricular (AV) conduction, marked by PR interval $\geq$240 ms, QRS duration $\geq$120 ms, and/or HV interval $\geq$70 ms, even when asymptomatic.
7. Patients with Emery-Dreifuss muscular dystrophy or limb-girdle muscular dystrophy type 1B with abnormal AV conduction, including PR interval $\geq$230 ms or HV interval $\geq$70 ms, are at higher risk of arrhythmic events including sudden death, even when asymptomatic. Transvenous (or equivalent pacing-capable) implantable cardioverter-defibrillator placement is indicated in such patients.
8. Patients with mitochondrial myopathies, such as Kearns-Sayre syndrome, are susceptible to developing advanced distal conduction disease. Pacemaker implantation is indicated in these patients who demonstrate AV conduction abnormalities, particularly if progressive, including fascicular block.
9. Initiation of oral anticoagulation in patients with neuromuscular disorders who develop atrial fibrillation should be based on established risk criteria (eg, CHA_2DS_2-VASc and HAS-BLED in adults). Individuals with Emery-Dreifuss muscular dystrophy or limb-girdle muscular dystrophy type 1B and atrial fibrillation should be treated with oral anticoagulation regardless of CHA_2DS_2-VASc score because of the association with atrial standstill and suspected heightened risk of thromboembolism.
10. Early but limited experience with gene modification in some heritable diseases has been promising and is now being employed in patients with neuromuscular disorders. The hope for additional advances must be tempered by the complexity of these therapeutics and the small number of patients with neuromuscular disorders who qualify for such treatment.

Section 1 Introduction

1.1. Document scope and rationale

Technological advances and progress in the diagnosis and treatment of neuromuscular disorders (NMDs) have increased patient longevity and the prevalence of associated arrhythmia risk. This multidisciplinary expert consensus statement led by the Heart Rhythm Society (HRS), in collaboration with the American Academy of Physical Medicine and Rehabilitation (AAPM&R), the American Association

of Neuromuscular & Electrodiagnostic Medicine (AANEM), the American College of Cardiology (ACC), the American Heart Association (AHA), the American Society of Anesthesiologists (ASA), the Asia Pacific Heart Rhythm Society (APHRS), the Child Neurology Society (CNS), the European Heart Rhythm Association (EHRA), the Heart Failure Society of America (HFSA), the Japanese Heart Rhythm Society (JHRS), the Latin American Heart Rhythm Society (LAHRS), the Pediatric and Congenital Electrophysiology Society (PACES), and the Sociedade Brasileira de Arritmias Cardíacas (SOBRAC), is intended to guide electrophysiologists, cardiologists, neurologists, and other clinicians in caring for patients with arrhythmic complications of NMDs.

The document presents an overview of arrhythmias in NMDs followed by detailed sections on specific disorders with an emphasis on arrhythmic cardiac manifestations. Conditions with similar clinical presentations and demonstrated cardiac involvement are grouped into sections: Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and limb-girdle muscular dystrophy (LGMD) type 2 (LGMD2) (see Section 3.1, Table 4 for additional nomenclature); myotonic dystrophy (DM) type 1 (DM1) and type 2 (DM2); Emery-Dreifuss muscular dystrophy (EDMD) and LGMD type 1B (LGMD1B); facioscapulohumeral muscular dystrophy (FSHD); and mitochondrial myopathies, including Friedreich ataxia (FA) and Kearns-Sayre syndrome. It is noted that the 229th European Neuromuscular Centre (ENMC) workshop[1] has suggested a reclassification and revised nomenclature for LGMD, in which autosomal dominant type 1 LGMD is classified as specific myopathies or as LGMD D (dominant) variants (D1–D4) and autosomal recessive LGMD2 is renamed LGMD R1–R24 in addition to descriptive names for some of the recessive variants. In this revised nomenclature, *LMNA*-associated myopathies (LGMD1B, Emery-Dreifuss muscular dystrophy type 2 [EDMD2], and Emery-Dreifuss muscular dystrophy type 3 [EDMD3]) are named EDMD. In this document, we have retained the LGMD1B and EDMD naming convention. Each section covers general concepts specific to that disorder followed by condition-specific recommendations. These sections are further categorized into diagnostic testing and risk stratification, bradycardias/conduction disease and the use of pacing and cardiac resynchronization therapy (CRT), atrial arrhythmias, and ventricular arrhythmias/sudden cardiac death and the use of implantable cardioverter-defibrillators (ICDs). A framework and recommendations for end-of-life management of arrhythmias in patients with NMDs are also covered.

Where possible, recommendations put forth in this document are based on published evidence with the understanding that NMDs are rare and the referenced evidence base is largely observational. Studies using small sample sizes and larger randomized controlled trials (RCTs) marked by underrepresentation of patients with NMDs were frequently encountered throughout this document's development. Although summaries of clinical conditions are presented, this document is not a comprehensive review; rather, it serves to provide practical and actionable clinical information and management recommendations, with the goal of improving overall patient care. As with many guideline statements, this document is designed to help guide shared decision-making with the individual patient and is not intended to dictate management.

Throughout this document, the term "clinical status" is used to refer to a patient's overall level of functioning and may include objective and subjective measures of ambulatory capability, level of respiratory impairment, and degree of frailty, as examples.[2] This is a particularly germane concept, as the noncardiac consequences of NMDs may dominate a patient's clinical picture and prognosis, influencing clinical decision-making. Clinical status also encompasses a patient's age; children, in particular, require special consideration. Many recommendations, particularly those involving ICD implantation and anticoagulation for atrial arrhythmias, are based on research conducted in adult individuals. Although applying these studies in the care of children may be reasonable in some circumstances, extrapolating such evidence in all children is not appropriate and calls for clinician discretion and careful discussion. The recommendations should therefore be tempered by the clinician's judgment regarding the expected impact and appropriateness of a particular intervention while taking into account mitigating factors that may affect its benefit.

This consensus document provides recommendations for care of these complex patients based on current evidence for best practice in the assessment and management of arrhythmia risk in patients with NMDs. When evidence was lacking or contradictory, a consensus expert opinion was developed. For both adult and pediatric patients, the health benefits, side effects, and risks were comprehensively considered in formulating the recommendations. The document is intended to provide practical guidance and advice for management and is expected to improve the quality of care. Adherence to recommendations can be enhanced by patient engagement and a shared decision-making process. Recommendations are not a replacement for clinical judgment and are not intended to dictate management.

1.2. Organization of the writing committee

The writing committee consisted of internationally recognized experts from 12 countries in the fields of cardiac electrophysiology, cardiology, pediatric cardiology, neurology, physical medicine and rehabilitation, congestive heart failure, and anesthesiology, representing AANEM, AAPM&R, ACC, AHA, APHRS, ASA, CNS, EHRA, HFSA, HRS, JHRS, LAHRS, PACES, and SOBRAC, and selected according to each society's procedures. The HRS strives to ensure diversity in formation of the writing group. Disclosure of any relationships with industry and other entities (RWIs) was required from the writing committee members (Appendix 1) and from the peer reviewers (Appendix 2), in accordance with the HRS policies; of the 38 committee members, 20 (53%) had no relevant RWIs. Sections with

recommendations were drafted by the writing committee members who did not have relevant RWIs. The HRS policy on relationships with industry can be found at https://www.hrsonline.org/sites/default/files/2020-06/HRS_Code-of-Ethics.pdf.

1.3. Methodology and evidence review

The HRS Scientific and Clinical Documents Committee establishes, reviews, and updates clinical practice document methodology, with the aim to align with Institute of Medicine standards.[3] This document was developed in accordance with the processes detailed in the *HRS Clinical Document Development Methodology Manual and Policies*.[4] To ensure that clinical practice documents remain current, new data are reviewed on an ongoing basis, and the full documents are formally reviewed every 5 years.

Consensus statements are evidence based, and recommendations are derived from the synthesis of published data or from a consensus of expert opinion when data are not available. Members of the writing committee conducted comprehensive literature searches of electronic databases, including MEDLINE (via PubMed) and Google Scholar; key evidence

Table 1 ACC/AHA recommendation system: Applying class of recommendation and level of evidence to clinical strategies, interventions, treatments, and diagnostic testing in patient care (updated May 2019)*

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

was summarized in standardized evidence tables (Appendix 3), with attention to the study type, size, inclusion criteria, and key findings. RCTs were prioritized, if available, and meta-analyses or systematic reviews and descriptive observational studies and case series were included. Search terms included, but were not limited to, muscular dystrophy, DMD, Becker muscular dystrophy, limb girdle muscular dystrophy, myotonic dystrophy, Steinert, PROMM, DM1, DM2, cardiac, arrhythmia, ECG, electrocardiogram, echocardiogram, Holter, pacemaker, ICD, sudden death, atrial fibrillation, atrioventricular block, ventricular tachycardia, ventricular fibrillation, Emery Dreifuss, lamin, cardiac arrest, implantable cardioverter-defibrillator, Emery-Dreifuss and heart, Limb-Girdle, dystrophy, neuromuscular disease, lamin A/C, emerin, laminopathy, conduction, atrial standstill, guidelines, anesthesia, stroke, facioscapulohumeral, facioscapulo-humeral, heart, syncope, loop recorder, mexiletine, cardiac resynchronization therapy, risk stratification, cardiac involvement, conduction disease, mitochondrial myopathies, genetic testing, GAA repeat frataxin gene, cardiac resynchronization, atrial arrhythmias, ventricular arrhythmias, indications for defibrillators, mitochondrial myopathies, end of life decision-making, end of life care, and palliative care. Searches were limited to human subjects, and no time limits or language restrictions were required. Listed references are representative and not necessarily inclusive. Both literature searches and initial drafts were written by writing committee members free of relevant RWIs. Writing committee members were asked to weigh the strength of evidence for or against a particular diagnostic or management option and consider the range of potential outcomes, including variations due to patient comorbidities or preferences.

Recommendations and explicative text are presented in a modular knowledge chunk format, with each chunk including a table of recommendations, a brief synopsis, recommendation-specific supportive text, and flow diagrams or tables as appropriate. All recommendations were discussed by the writing committee before voting. Initial failure to reach consensus was resolved by subsequent discussions, revisions as needed, and re-voting. Although the consensus threshold was set at 67%, the mean consensus over all recommendations was 99%. A quorum of two-thirds of the writing committee was met for all votes.[4] Recommendations are constructed to be accessible and implementable at the point of care. When feasible, recommendations are formatted to allow for audit and monitoring of quality of care. Due to the paucity of data for this population of patients with rare disorders, cost or resource analysis was not practicable.

The recommendations were formulated according to the ACC/AHA class of recommendation (COR) and level of evidence (LOE) system (Table 1).[5] The COR denotes the strength of the recommendation based on a careful assessment of the estimated magnitude and certainty of the benefit in proportion to the risk; COR 1 indicates that the benefit of the intervention strongly exceeds the risk; COR 2a indicates that the benefit of the intervention moderately exceeds the risk; COR 2b indicates that the benefit weakly exceeds the risk; and COR 3 recommendations are subdivided into two categories: the benefit is equal to the risk (No benefit) or the risk exceeds the benefit (Harm). The LOE reflects the quality of the evidence that supports the recommendation based on type, quantity, and consistency of data from clinical trials and other sources. LOE A is derived from high-quality RCTs; LOE B-R is derived from moderate-quality RCTs; LOE B-NR is derived from well-designed nonrandomized studies; LOE C-LD is derived from randomized or nonrandomized studies with limitations of design or execution; and LOE C-EO indicates that a recommendation was based on expert opinion.[5] Case reports were included in the evaluation of evidence due to the limited randomized data available for the NMD patient population. For each recommendation, the COR and LOE were critically appraised to account for the unique features of patients with NMDs to resolve the disparity between published evidence and its applicability to the population with muscular dystrophy.

Table 2 Relevant clinical practice documents

Title	Publication year
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[6]	2019
2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay[7]	2019
2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death[8]	2017
Management of Cardiac Involvement Associated with Neuromuscular Diseases: A Scientific Statement from the American Heart Association[9]	2017
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure[10]	2017
2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[11]	2016
2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[12]	2014
2013 ACCF/AHA Guideline for the Management of Heart Failure[13]	2013
2012 ACCF/AHA/HRS Focused Update Incorporated into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities[14]	2013
HRS Expert Consensus Statement on the Management of Cardiovascular Implantable Electronic Devices (CIEDs) in Patients Nearing End of Life or Requesting Withdrawal of Therapy[15]	2010

1.4. Document review and approval

The draft document underwent review by the HRS Scientific and Clinical Documents Committee and was approved by the writing committee. The recommendations were subject to a period of public comment. The entire document underwent rigorous peer review by each of the participating societies and revision by the document chairs before endorsement.

1.5. Relevant clinical practice documents

Table 2 lists pertinent guidelines and consensus statements that the writing committee considered for this document. The included documents contain relevant information for the diagnosis and treatment of patients with NMDs.

Section 2 General principles for arrhythmic risk in neuromuscular disorders

2.1. Cardiac manifestations

NMDs often involve the cardiovascular system and can limit life expectancy in affected patients. Cardiac manifestations are varied and may include cardiomyopathy, bradyarrhythmias, or tachyarrhythmias. When present, dilated cardiomyopathy is most common, but hypertrophic cardiomyopathy has been described in conditions such as FA. Arrhythmias are commonplace in these rare diseases and may be primary or the consequence of an associated cardiomyopathy. Atrial and ventricular arrhythmias as well as sudden cardiac death have been observed. Importantly, many of these patients are disproportionately affected by conduction system disease requiring pacing.

The cardiovascular presentation and management of patients with NMDs is dependent on the specific disorder. This document focuses on the muscular dystrophies exhibiting prominent cardiac and arrhythmic manifestations, including DMD, BMD, LGMD2 and LGMD1B, DM1 and DM2, EDMD, FSHD, and mitochondrial myopathies including FA and Kearns-Sayre syndrome. The genetic basis and cardiac manifestations of these disorders are shown in Table 3.

The care of NMD patients requires a team of practitioners, often led by a neurologist or physical medicine and rehabilitation physician, with input from experts in cardiology, electrophysiology, pulmonary medicine, gastroenterology, endocrinology, and orthopedic and general surgery. It is important that the treatment of cardiac complications of NMDs accounts for the coexistence of other potentially life-limiting comorbidities. As an example, much of this document details procedural care typically requiring moderate sedation. The use of even mild sedatives can result in respiratory impairment in these patients due to skeletal muscle weakness, which may in turn cause significant pulmonary and procedure-related complications.[16,17] Therefore, the importance of involving pulmonologists and anesthesiologists in the preprocedural setting as well as in the intraprocedural and postprocedural care of NMD patients cannot be overstated, such as with diagnostic electrophysiological testing, catheter ablation, and cardiovascular implantable electronic device (CIED) implantation.

Table 3 Genetics, cardiovascular complications, and neuromuscular disorders

Neuromuscular disorder	Section	Heritance	Gene locus	Disease protein	Cardiac manifestations			
					CM	Conduction abnormality	Ventricular arrhythmia	Atrial arrhythmia
DMD	3	XL	Xp21	Dystrophin	+++	+	++	+
BMD	3	XL	Xp21	Dystrophin	+++	+	++	+
LGMD2*	3	AR	Various	Various	+++	+	++	++
DM1	4	AD	19q13	DMPK	+	+++	+	++
DM2	4	AD	3q21	ZNF9	Rare	+	+	+
EDMD	5	XL	Xq28	Emerin	++	+++	+++	++
LGMD1B*	5	AD	1q11-21	Lamin A/C	+	++	+++	++
FSHD	6	AD	4q D4Z4	DUX4	Rare	Rare	Rare	Rare
FA	7	AR	9q21.11	Frataxin	+++ (HCM)	+++	+++	+
Kearns-Sayre syndrome	7	AD	mtDNA	Various	+	+++	+	++

The table includes the section of the document that covers the specific neuromuscular disorder. The relative frequencies of the type of cardiac manifestation are included. The type of cardiomyopathy is dilated unless otherwise indicated.[9] *A reclassification and revised nomenclature for LGMD has been suggested by the 229th European Neuromuscular Centre workshop, with recessive LGMD2 renamed LGMD R1–R24 (see Table 4) in addition to descriptive names for some of the recessive variants and with *LMNA*-associated myopathies (LGMD1B, EDMD2, and EDMD3) named EDMD.[1] +++ = high, ++ = moderate, and + = low relative frequency of cardiac manifestations; AD = autosomal dominant; AR = autosomal recessive; BMD = Becker muscular dystrophy; CM = cardiomyopathy; DM1 = myotonic dystrophy type 1; DM2 = myotonic dystrophy type 2; DMD = Duchenne muscular dystrophy; DMPK = myotonic dystrophy protein kinase; DUX4 = double homeobox 4; EDMD = Emery-Dreifuss muscular dystrophy; FA = Friedreich ataxia; FSHD = facioscapulohumeral muscular dystrophy; HCM = hypertrophic cardiomyopathy; LGMD = limb-girdle muscular dystrophy; LGMD1B = limb-girdle muscular dystrophy type 1B; LGMD2 = limb-girdle muscular dystrophy type 2; mtDNA = mitochondrial DNA; XL = X-linked; ZNF9 = zinc finger 9.

2.2. Genetic testing and counseling

The NMDs included in the consensus statement are inherited and have defined genetic causes. This document targets cardiac and arrhythmia management. Therefore, recommendations specific to genetic testing and counseling are not included, as they are beyond the intended scope of this document. Most decisions on genetic testing and counseling will be made by other members of the multidisciplinary team rather than the cardiologist or cardiac electrophysiologist. However, the cardiology care providers may field questions from patients and families regarding genetic testing and counseling and will make management decisions on appropriate cardiac evaluation based on those results. Thus, the cardiologist or cardiac electrophysiologist should understand the genetic basis of different NMDs, as well as the appropriate timing and candidates for genetic testing and counseling. This section provides a brief overview. In addition, a review of the genetic basis of each disorder is provided in the introductory paragraphs preceding the recommendations. Table 3 includes the inheritance, genes, and protein(s) involved in NMDs.

It should be noted that when genetic testing is referenced, the words "and counseling" typically follow or are presumed to be included. A genetic counselor is a key member of the multidisciplinary care team who assists patients, families, and other members of the team in making the initial decisions on whether testing is warranted and the interpretation and consequences of test results.

In the X-linked recessive disorders, DMD and BMD, genetic testing is reliable and definitive and has replaced more invasive measures such as skeletal muscle biopsy.[18] Genetic testing may inform the decisions on benefits of specific therapies.[19] Cascade screening of family members through genetic testing may also be informative. Such testing should be directed toward at-risk male relatives of patients with genetically confirmed DMD or BMD and male relatives of mothers of DMD and BMD patients. As DMD typically presents at an early age, screening younger brothers of a patient and their mother can yield diagnostic and prognostic information and provide a basis for management and counseling. Families affected by DMD and BMD typically include females who are asymptomatic carriers. Their identification can allow for preconception genetic testing, counseling, and cardiac testing as female carriers can develop late cardiac disease.[20-22]

Genetic testing in autosomal recessive LGMD2 can both provide a diagnosis and identify the specific genetic abnormality.[1,23] There are at least 25 genetic variants encompassing the broad category of recessive LGMD2. Some of the variants rarely have cardiac involvement, whereas others have the potential for significant cardiac morbidity and mortality. Genetic classification is required to make informed decisions on the type and frequency of cardiac testing and therapy.

Patients with a clinical diagnosis of autosomal dominant DM1 or DM2 should undergo genetic confirmation. In addition to providing a definitive diagnosis for symptomatic patients, screening of appropriate relatives through genetic testing and counseling can identify those at preclinical stages of disease and allow for decisions on surveillance. In DM1, CTG repeat length predicts status and progression of neuromuscular impairment and, in the majority of studies, cardiac involvement.[24-27] In DM2, the CCTG repeat length does not correlate with disease severity. Cascade screening based on genetic test results assures that affected relatives are identified.

EDMD is classically inherited in an X-linked recessive fashion, but there is heterogeneity with families that fit an X-linked dominant, autosomal dominant, or autosomal recessive inheritance pattern. LGMD1B, with a cardiac phenotype similar to that of EDMD, is inherited in an autosomal dominant mode. Patients with EDMD and LGMD1B are at high risk for cardiac disease, often identified with initially asymptomatic abnormalities on electrocardiogram (ECG). Genetic testing in affected patients with appropriate cascade screening of relatives, with or without symptoms, allows proper surveillance and treatment and, in some case series, improves clinical outcomes.[28] The type of mutation is a predictor of sudden death—specifically, truncation (nonsense) mutations in *LMNA*.[29,30] X-linked EDMD confers a higher risk for sudden death, as well.[31,32]

FSHD is inherited in an autosomal dominant fashion.[33] Genetic testing and cascade screening can identify affected individuals. Cardiac involvement in FSHD is rare, and genetic testing does not predict risk.

FA is inherited in an autosomal recessive fashion. An earlier age of symptom onset, increasing severity of neurological symptoms, and worsening left ventricular hypertrophy are observed in patients in whom genetic testing shows a greater expansion of the GAA triplet repeat in frataxin (*FXN*).[34,35] Therefore, genetic testing of patients and their siblings is appropriate. It does not appear, however, that transformation to dilated cardiomyopathy correlates with the size of the repeat expansion.

Mitochondrial disorders are heterogenous with variable inheritance.[36,37] Mitochondrial DNA is inherited maternally and mitochondrial disorders are transmitted from a mother to children of both sexes. The penetrance and expressivity of the maternally inherited diseases can be affected by the presence of more than one mitochondrial DNA type, termed heteroplasmy. The genetic variability of these disorders is further enhanced by other modes of inheritance, such as X-linked or autosomal, while sporadic occurrences are also observed. Decisions on genetic testing in these disorders will be typically made in consultation with a medical geneticist and/or neuromuscular specialist.

2.3. Pediatric considerations

The pediatric patient with NMD raises special considerations, as these individuals have been largely excluded from the arrhythmia-management literature. The document mentions this discordance, for example, when using criteria developed for adults to assess thromboembolic risk due to atrial arrhythmias. A significant portion of the document, however, deals with the use of CIEDs. CIED implantation may be readily performed in an adult with NMD, but such surgery may have significantly greater consequences in a child, including the possible need for epicardial approach, frequent system modifications, psychosocial implications, and, in the case of ICD implantation, the specter of inappropriate shock.[38] These concerns are also underscored by the potentially limited benefit in children with NMDs, as the vast majority of evidence pertaining to CIED use (and arrhythmia management in general) has been conducted in adult patients without NMDs. Through collaboration with pediatric cardiology societies, the document aims to balance these perspectives, making arrhythmia-related care available to children with NMDs based on existing evidence and experience while emphasizing the importance of shared decision-making and clinician judgment, coupled with the understanding that some interventions may not always be appropriate or desired in some pediatric patients. It is expected that further research and experience will provide greater clarity regarding arrhythmia care in the pediatric NMD patient.

Section 3 Duchenne, Becker, and recessive limb-girdle muscular dystrophies

3.1. General principles of Duchenne, Becker, and recessive limb-girdle muscular dystrophies

DMD, BMD, and recessive LGMD2 are X-linked and autosomal recessive disorders involving genes encoding dystrophin, those associated with the dystrophin-glycoprotein complex, and sarcomeric proteins. Disruption of the dystrophin complex underlies the degeneration of cardiac and skeletal muscles. DMD and BMD both arise from a mutation in the dystrophin gene but differ in that DMD is characterized by near absence of dystrophin, whereas in BMD, dystrophin is reduced in size and/or amount. DMD is typically diagnosed in early childhood and affects 1 of every 5,000 live male births. Without medical intervention, boys with DMD typically die in their teens. Glucocorticoid use prolongs ambulation in DMD and is associated with improved cardiopulmonary outcomes; however, there are significant accompanying side effects, such as obesity, metabolic syndrome, delayed puberty, and osteoporosis. With steroid use and increased use of noninvasive respiratory support, males with DMD are living into their 20s and 30s,[39] and the use of angiotensin-converting enzyme (ACE) inhibitors in conjunction with steroids may further extend their life span. With this extended life span and enhanced respiratory care, cardiomyopathy has become an increasing cause of morbidity and mortality. In contrast, BMD and recessive LGMD2 present at varying ages, from adolescence to adulthood. Dilated cardiomyopathy can occur with all these muscular dystrophy subtypes without direct correlation to the severity of skeletal muscle involvement.[40-47] Because not all forms of LGMD2 are associated with development of cardiomyopathy, genetic testing in these conditions is critical. Further delineation of LGMD2 associated with cardiomyopathy can be found in Table 4. Maternal genetic carriers of DMD and BMD have been found to have cardiomyopathy as well, although the typical time of onset and progression are currently under investigation.[20]

Patients with DMD, BMD, and LGMD2 were largely excluded from significant enrollment in clinical trials where the benefits of CIED therapy, such as ICD and cardiac resynchronization therapy with pacemaker (CRT-P) implantation, were established. Their underrepresentation in these analyses raises the question as to whether they can expect comparable benefits from such interventions, as demonstrated in more representative study populations. Individuals diagnosed with one of these forms of muscular dystrophy are generally younger and often have extracardiac comorbidities that may impact survival and subsequent CIED benefit.

Table 4 Recessive forms (type 2) of limb-girdle muscular dystrophies associated with cardiomyopathy, listed according to the subtype nomenclature used in this document, with the new classification system in parentheses[1]

Subtype (prior name)	Gene	Protein	Cellular localization
LGMD2D (LGMD R3)	*SGCA*[48]	α-Sarcoglycan	Sarcolemma
LGMD2E (LGMD R4)	*SGCB*[49,50]	β-Sarcoglycan	Sarcolemma
LGMD2C (LGMD R5)	*SGCG*[51]	γ-Sarcoglycan	Sarcolemma
LGMD2F (LGMD R6)	*SGCD*[52]	δ-Sarcoglycan	Sarcolemma
LGMD2G (LGMD R7)	*TCAP*[53]	Telethonin	Sarcomere
LGMD2I (LGMD R9)	*FKRP*[54]	Fukutin-related protein	Golgi apparatus
LGMD2J (LGMD R10)	*TTN*	Titin	Sarcomere
LGMD2N (LGMD R14)	*POMT2*	Protein *O*-mannosyltransferase 2	Endoplasmic reticulum
LGMD2Q (LGMD R17)	*PLEC*	Plectin	Intermediate filament

LGMD = limb-girdle muscular dystrophy; LGMD2 = limb-girdle muscular dystrophy type 2.

3.2. Diagnostic testing and risk stratification in Duchenne, Becker, and recessive limb-girdle muscular dystrophies

Recommendations for diagnostic testing and risk stratification in Duchenne, Becker, and recessive limb-girdle muscular dystrophies			
COR	LOE	Recommendations	References
1	B-NR	1. Coordinated care of patients with DMD, BMD, or LGMD2 should be conducted in a medical setting where there is access to expertise in the neurological, cardiac, arrhythmic, pulmonary, and genetic manifestations of these disorders.	55-57
1	B-NR	2. In patients with DMD, BMD, or LGMD2, guideline-directed evaluation and therapy for heart failure is recommended.	58
1	B-NR	3. In patients with DMD, BMD, or LGMD2, cardiac evaluation including physical examination, ECG, ambulatory ECG, and cardiac imaging (echocardiography or cardiac magnetic resonance imaging [CMR]) at diagnosis with periodic retesting is recommended even in the absence of cardiac symptoms.	40-44,46,47,59-69
1	B-NR	4. In females who are carriers of a pathogenic or likely pathogenic variant for DMD or BMD, screening cardiac imaging (echocardiography or CMR) is recommended in adulthood even in the absence of cardiac symptoms.	20-22,70,71
2a	C-LD	5. In patients with DMD, BMD, or LGMD2 who have symptoms of conduction disorder or arrhythmias without an obvious cause, implantable cardiac monitoring is reasonable.	59,65,72

Synopsis

As the survival of patients with muscular dystrophies has improved, the diagnostic and therapeutic approaches of the multidisciplinary care teams have shifted to more anticipatory and proactive strategies. Furthermore, a clear underlying diagnosis obtained through clinical evaluation and genetic testing, as described in Section 2.2, are required for prescribing disease-specific therapy, prognostic assessment, and counseling. Identification of the causative neuromuscular condition will also guide the nature, timing, and frequency of cardiovascular treatment and testing. In many cases, mutation identification may influence clinical management.

Recommendation-specific supportive text

1. Centers with multidisciplinary specialty experience in managing patients with NMDs are best equipped to manage patients with DMD, BMD, or LGMD2, including those with pulmonary/respiratory and documented or suspected cardiac involvement. Given the multiorgan system involvement in patients with DMD, BMD, or LGMD2, a multidisciplinary team is crucial to improve the care of patients. Several case series have demonstrated the benefits of a multispecialist approach to care in DMD patients, arguably the most vulnerable patients in this category of NMDs.[39,55-57,73] It stands to reason that this approach would yield similar benefits in those with BMD or LGMD2.
2. As respiratory care has improved, death due to cardiovascular disease is more prevalent. Given the overlap of respiratory, cardiovascular, and neurological symptoms, the identification of heart failure and treatment optimization can be challenging in DMD, and possibly in BMD and LGMD2, patient populations. It is important to start an ACE inhibitor in DMD as early as possible in the ambulatory stage and no later than 10 years of age to prevent the development of cardiomyopathy and clinical heart failure.[58] In a small, randomized, double-blind study, DMD patients with mild cardiomyopathy who were treated with an angiotensin II receptor blocker had equivalent improvement in left ventricular function as those treated with an ACE inhibitor.[74] Therefore, therapy with angiotensin II receptor blockers are an option for DMD patients who are intolerant of ACE inhibitors. The role of neprilysin inhibition to prevent the development or progression of cardiomyopathy has not been studied and is an area for future research. In the late ambulatory stage of DMD, symptoms of heart failure may be subtle due to the complications of NMDs, such as weakness and limited mobility, favoring heightened surveillance strategies to detect ventricular systolic dysfunction and aggressive medical interventions prior to the development of manifest heart failure. In BMD, there are no data regarding the prophylactic initiation of an ACE inhibitor prior to evidence of cardiac dysfunction, although the small size of this population makes it difficult to conduct studies to address this question. Small studies have shown that aldosterone and eplerenone have a similarly protective effect in patients with DMD prior to the development of overt left ventricular dysfunction.[75,76] Management of BMD is extrapolated from the DMD data given the shared pathological mechanisms.[39,77] In all cases, guideline-directed medical therapy is indicated in patients with DMD, BMD, or LGMD2 when systolic dysfunction (left ventricular ejection fraction [LVEF] $\leq$40%) is observed, particularly when symptoms are present.[10,13]

3. Arrhythmias are seen with all dystrophin-associated muscular dystrophies, and worsening left ventricular function correlates with higher-grade arrhythmias. Data suggest that late gadolinium enhancement on CMR is independently predictive of mortality, cardiovascular events, and ventricular arrhythmias. Its predictive value may persist even in those with relatively mild left ventricular dysfunction and even preserved left ventricular function, suggesting additive prognostic value beyond echocardiography.[69,78]
4. Women who are carriers of disease-causing DMD or BMD mutations have a low but measurable risk of cardiomyopathy.[20-22,70,71] Early data suggest that CMR may be superior in identifying myocardial scar even with normal ventricular function, although an echocardiogram is suitable to screen for cardiovascular involvement. This information can be of particular benefit in women and adolescent females who are of childbearing age.[20,22,70,71]
5. Insertable loop recorder implantation and emerging mobile/smart phone–based applications may assist in determining the frequency and burden of arrhythmias in patients with concerning symptoms and where noninvasive strategies have not been diagnostic. This may be particularly useful in those with unexplained syncope.[72]

3.3. Bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in Duchenne, Becker, and recessive limb-girdle muscular dystrophies

Recommendations for bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in Duchenne, Becker, and recessive limb-girdle muscular dystrophies

COR	LOE	Recommendations	References
1	B-NR	1. In patients with DMD, BMD, or LGMD2 with documented symptomatic bradycardia due to any degree of sinus node dysfunction or AV block, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.	79-82
1	B-NR	2. In patients with DMD, BMD, or LGMD2 and third-degree or advanced second-degree AV block at any anatomical level, with or without symptoms, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.	79-81
2a	B-NR	3. In patients with DMD, BMD, or LGMD2 with an LVEF ≤35% despite guideline-directed medical therapy with a combination of sinus rhythm, left bundle branch block (LBBB), QRS duration ≥150 ms, and New York Heart Association (NYHA) class II to class IV symptoms, or in those with suspected right ventricular pacing–induced cardiomyopathy or anticipated right ventricular pacing ≥40%, CRT is reasonable if concordant with the patient's goals of care and clinical status.	83-88

Synopsis

Clinically relevant sinus bradycardia and AV block are not frequently encountered with DMD, BMD, and LGMD2.[64,89] Therefore, no condition-specific recommendations are made in favor of applying traditional pacing indications. Pacemaker implantation may pose special challenges in patients with DMD, BMD, or LGMD2, rendering a relatively less favorable outlook with such interventions.[81] This may be particularly germane when asymptomatic or minimally symptomatic individuals are encountered, where deferral of pacing may be appropriate depending on the patient's goals of care.

CRT may be appropriate in patients with DMD, BMD, or LGMD2 with usual criteria for such treatment in the face of maximally tolerated guideline-directed medical therapy. Large studies examining CRT in patients with NMDs have not been published, and it is unlikely that available trials enrolling subjects with these conditions in significant numbers exist. Data from available studies are therefore carefully extrapolated to patients with DMD, BMD, or LGMD2. Clinical scenarios for the management of pacemaker implantation in these populations are discussed in Table 5.

Recommendation-specific supportive text

1. Bradyarrhythmias are relatively rare in patients with DMD or BMD, and if they occur, they are typically in conjunction with cardiomyopathy.[61] Traditional practice patterns based on expert opinion are thereby used to guide decision-making for permanent pacemaker implantation with the device type governed by clinical features and operator discretion.[7] The patient's overall clinical status and goals of care may modify a selected treatment approach. Procedural risks in this population are often higher owing to complications arising from the use of sedatives and anesthesia accompanied by a patient's compromised ventilatory status, justifying assistance from

Table 5 Clinical scenarios for the management of arrhythmias in Duchenne muscular dystrophy, Becker muscular dystrophy, and recessive limb-girdle muscular dystrophy type 2

Clinical scenario	Management strategies	Key points
DMD		
1. A 27-year-old man with DMD is found to have progressive left ventricular dysfunction (most recent LVEF 29%) despite maximally tolerated guideline-directed medical therapy for >1 year. ECG shows sinus rhythm, PR interval 140 ms, QRS duration 100 ms, and a prominent R wave in lead V_1. He requires a power wheelchair and full assistance for daily needs. Mechanical ventilation via tracheostomy is required, and nutrition is provided through enterostomy due to recurrent aspiration pneumonitis. Hospitalization for heart failure has not been observed.	• Management options considered included primary prevention ICD implantation. • Continued cardiovascular medical therapy was recommended regardless of arrhythmia management strategy. • Values elicited in discussion included current quality of life, actual anticipated benefit of ICD implantation, and expected surgical risks and recovery. • Deferral of ICD implantation was ultimately recommended and preferred due to unfavorable risk–benefit of device insertion.	• Limited quality of life was raised as the main driver of the final management decision. • Lack of representation of patient substrate in previously published trials was noted. • Likely nonarrhythmic mechanism of death limits the benefit of ICD implantation. • Technical/procedural aspects of ICD implantation—kyphoscoliosis, sedation-related risks including respiratory infection, and possible prolonged recovery—were cited as additional determinants to defer ICD implantation.
BMD		
2. A 31-year-old man with BMD is found to have stable left ventricular dysfunction (most recent LVEF 32%) despite maximally tolerated guideline-directed medical therapy for >1 year. He has exertional dyspnea and fatigue corresponding to NYHA function class III. He ambulates most of the day, uses a wheelchair for long distance mobility, and has a service animal to assist with activities of daily living. ECG shows sinus rhythm with LBBB with PR interval 160 ms, and QRS duration 150 ms.	• Management options discussed included continued medical therapy, implantation of CRT-P, or implantation of CRT-D. • Values elicited in discussion included options to improve quality of life through treatment of heart failure symptoms and desire for protection against ventricular arrhythmias. • CRT-D implantation was successfully performed to address the above issues.	• CRT-D was indicated based on traditional guideline-based criteria. • Risk of sudden death due to VT or VF and ventricular dyssynchrony due to LBBB was addressed by CRT-D implantation. Relatively mild neuromuscular impairment, patient preference, and young age all lend themselves well to CRT-D (as opposed to CRT-P) implantation. • Following lengthy discussion, CRT-D was deemed compatible with patient's goals of care by all stakeholders.
LGMD2		
3. A 38-year-old woman with LGMD2 reports several episodes of recurrent, unprovoked syncope, some resulting in minor injury. ECG shows sinus rhythm and right bundle branch block. Echocardiogram shows normal LVEF with biatrial dilation. The 30-day event recorder shows sinus pauses with ventricular asystole (2.5–4.0 seconds) with overall heart rate range 60–110 bpm. She ambulates with assistance from her husband and the use of a rolling walker.	• Management options discussed included observation, loop recorder insertion, and pacemaker implantation (leadless, transvenous single-chamber versus dual-chamber). • Values elicited in discussion included desire to avoid recurrent syncope and injury, simplicity of treatment, and preference for quick recovery. • Leadless pacemaker was chosen by the patient to provide protection against arrhythmia recurrence and the most likely cause of syncope and associated injury.	• Relatively simple procedures (pacemaker implantation) may be associated with a higher rate of complications or prolonged recovery in this and similar populations. • Dual-chamber pacemaker implantation with atrial lead implantation for underlying sinus node dysfunction is unlikely to provide significant additional benefit but may be accompanied by a higher frequency of procedural risks and prolonged recovery (such as infectious and respiratory complications, including pneumothorax). • Therapies targeting quality of life remain the primary focus in patients with advanced neuromuscular involvement.

BMD = Becker muscular dystrophy; bpm = beats per minute; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DMD = Duchenne muscular dystrophy; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LGMD2 = limb-girdle muscular dystrophy type 2; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

pulmonologists and anesthesiologists even when mild or moderate sedation is anticipated.[81] Although no direct data are available, when compared with DMD and BMD bradyarrhythmias, conduction disturbances in particular are felt to occur with relatively lower frequency in individuals with LGMD2.[7,89]

2. Advanced second-degree (2:1 block or two or more consecutive nonconducted P waves) and most forms of third-degree AV block are associated with adverse prognosis, even in asymptomatic individuals. The level of conduction impairment may be surmised with reasonable accuracy through noninvasive means such as 12-lead ECG. While these rhythm disturbances are not observed with a significantly higher frequency in patients with DMD, BMD, or LGMD2 when compared with the general population, the prognosis associated with this type of AV conduction impairment in patients with these NMDs is felt to be similar to that observed in other patient series.[79,80] As expected, the indications for permanent pacing in patients with DMD, BMD, or LGMD2 mirror those in the general population with the qualifier that the patient's overall clinical status and goals of care may mitigate (or modify) the treatment approach.[7] The special procedural considerations outlined above also apply in this circumstance, possibly warranting additional specialty expertise in the perioperative setting
3. Case reports and series have evaluated the use of CRT-P in the DMD and BMD patient populations, and their results are felt to be applicable to patients with LGMD2.[83,90] Studies specifically addressing the benefit and outcome of CRT-P in these populations are lacking and are unlikely to be performed with a significantly large number of subjects. However, CRT-P is still felt to offer similar benefit and advantages in appropriately selected candidates, as has been seen in conventional study populations.[84-88] Although some patients with QRS duration 120–149 ms may also derive benefit from CRT, a QRS duration $\geq$150 ms is utilized because the evidence for clinical benefit from CRT is strongest for this threshold cutoff.[91]

3.4. Atrial arrhythmias in Duchenne, Becker, and recessive limb-girdle muscular dystrophies

Recommendations for atrial arrhythmias in Duchenne, Becker, and recessive limb-girdle muscular dystrophies

COR	LOE	Recommendations	References
1	B-NR	**1. In patients with DMD, BMD, or LGMD2, anticoagulation according to established guidelines and clinical context is recommended for atrial fibrillation (AF) or atrial flutter (AFL) taking into consideration the risks of thromboembolism and bleeding on oral anticoagulation.**	64,92-94

Synopsis

AF and AFL have been reported in DMD, BMD, and LGMD2.[64] When seen, their occurrence appears to be closely associated with the development of cardiomyopathy.[89] The natural history of atrial arrhythmias has not been well documented, and studies specifically evaluating thromboembolic risk in this population are lacking.[95]

Recommendation-specific supportive text

1. There are no known contraindications or increased risks with anticoagulant use in DMD, BMD, and LGMD2 populations; therefore, standard treatment guidelines for management of atrial arrhythmias including prevention of thromboembolic complications are applicable in this population.[6,12] The clinical context in which this decision arises must also be considered, factoring in items such as patient age, dosing of anticoagulants particularly in children, patient frailty, and limitations in thromboembolic and bleeding risk assessment in patients not well represented in studies where these criteria were determined. The risk for thromboembolic complications is based on well-established CHA_2DS_2-VASc risk criteria that were validated in an older patient cohort with more comorbidities than what would be expected in the typically younger DMD, BMD, and LGMD2 patient subset with fewer expected risk factors.[92] Nevertheless, while this algorithm is deemed appropriate for use in adults with DMD, BMD, or LGMD2, these patients are less likely to meet criteria for anticoagulant therapy.[95] Though uncommon, children with DMD, BMD, or LGMD2 who develop atrial arrhythmias present a special circumstance where evidence and experience with oral anticoagulants are lacking. Traditional algorithms including CHA_2DS_2-VASc and HAS-BLED, the latter to determine hemorrhagic risk, comprise several risk factors that are wholly absent in children. The decision to initiate anticoagulation in a child is based on clinician judgment incorporating their best assessment of a patient's thromboembolic and bleeding risks, patient and family preferences, and an understanding that evidence in this area is absent, largely due to the infrequency of this situation.

3.5. Ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in Duchenne, Becker, and recessive limb-girdle muscular dystrophies

Recommendations for ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in Duchenne, Becker, and recessive limb-girdle muscular dystrophies

COR	LOE	Recommendations	References
1	B-NR	1. In patients with DMD, BMD, or LGMD2 with spontaneously occurring hemodynamically significant sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), ICD therapy is indicated if concordant with the patient's goals of care and clinical status.	96
2a	B-NR	2. In patients with DMD, BMD, or LGMD2 with an LVEF ≤35% despite guideline-directed medical therapy, ICD therapy is reasonable if concordant with the patient's goals of care and clinical status.	68,97-99

Synopsis

As patients with muscular dystrophies, specifically DMD, are living longer due to improved respiratory care, more attention is directed to cardiac failure and arrhythmias. Sudden death and ventricular arrhythmias have been reported in DMD, BMD, and LGMD2 and attributed to both respiratory and cardiac etiologies.[67,98] The exact incidence of sudden cardiac death is not fully known, although it appears to be low, and the role of ICD implantation requires further evaluation.[99] Specific procedural risks, in particular those associated with sedative use and anesthesia, are similarly applicable when ICD implantation is anticipated and are described in Section 3.3. The decision as to whether ICD implantation should be considered may be far less straightforward in this patient subgroup, and examples highlighting these complexities are included in Table 5.[77,81] An algorithm outlining the relevant concepts and decision making with regard to CIED implantation is shown in Figure 1.

Recommendation-specific supportive text

1. Although the morbidity of implantation and the success of ICDs in terminating ventricular arrhythmias in DMD, BMD, and LGMD2 have not been well documented, there is expert consensus that secondary prevention ICD implantation is appropriate in survivors of spontaneously occurring significant ventricular arrhythmias or cardiac arrest, provided this is accepted by the patient and consistent with their goals of care.[8,96,100]
2. Current treatment guidelines support the widely accepted practice of primary prevention ICD implantation in patients with nonischemic cardiomyopathy (LVEF ≤35%) on guideline-directed medical therapy.[8,10,13,91,100] The supportive data for this recommendation are predominantly derived from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) that enrolled patients with median age 60 years and included those with ischemic cardiovascular substrate.[97] Although published data regarding the prevention of sudden death through ICD implantation in patients may possibly be generalized to the BMD and LGMD2 populations whose clinical features are similar to typical ICD recipients, it is unclear if these results and documented benefit can be readily extrapolated to the much younger dystrophin-associated muscular dystrophy population, particularly those with DMD.[77] There are further data from the Pediatric Cardiomyopathy Registry and other similar series that demonstrate a very low rate of sudden arrhythmic death in the pediatric population in contrast to their adult counterparts.[68,98,99] Consequently, it is unclear at what age the incidence of sudden arrhythmic death increases and when ICD implantation is most beneficial. Although the threshold age of ICD benefit in DMD, BMD, and LGMD2 is unknown, available data may be more applicable to adults, particularly those with relatively limited neuromuscular and respiratory impairment and fewer associated comorbidities (ie, patients with BMD or LGMD2) rendering a lower risk of nonarrhythmic death and therefore a higher likelihood of ICD benefit in such patients. Previously published studies indicated a benefit from primary prevention ICD implantation in patients with mild heart failure symptoms based on NYHA functional class. However, this classification scheme is less reliable in patients with neuromuscular impairment; hence, heart failure status is omitted from this recommendation. Additional considerations include the difficulties of ICD implantation brought about by varying body habitus including severe kyphoscoliosis, accompanying respiratory muscle weakness, and sedation-related complications. Pulmonary function studies typically demonstrate a pattern of restrictive dysfunction, often further increasing sedation-related risks. The importance of shared decision-making is once again emphasized.

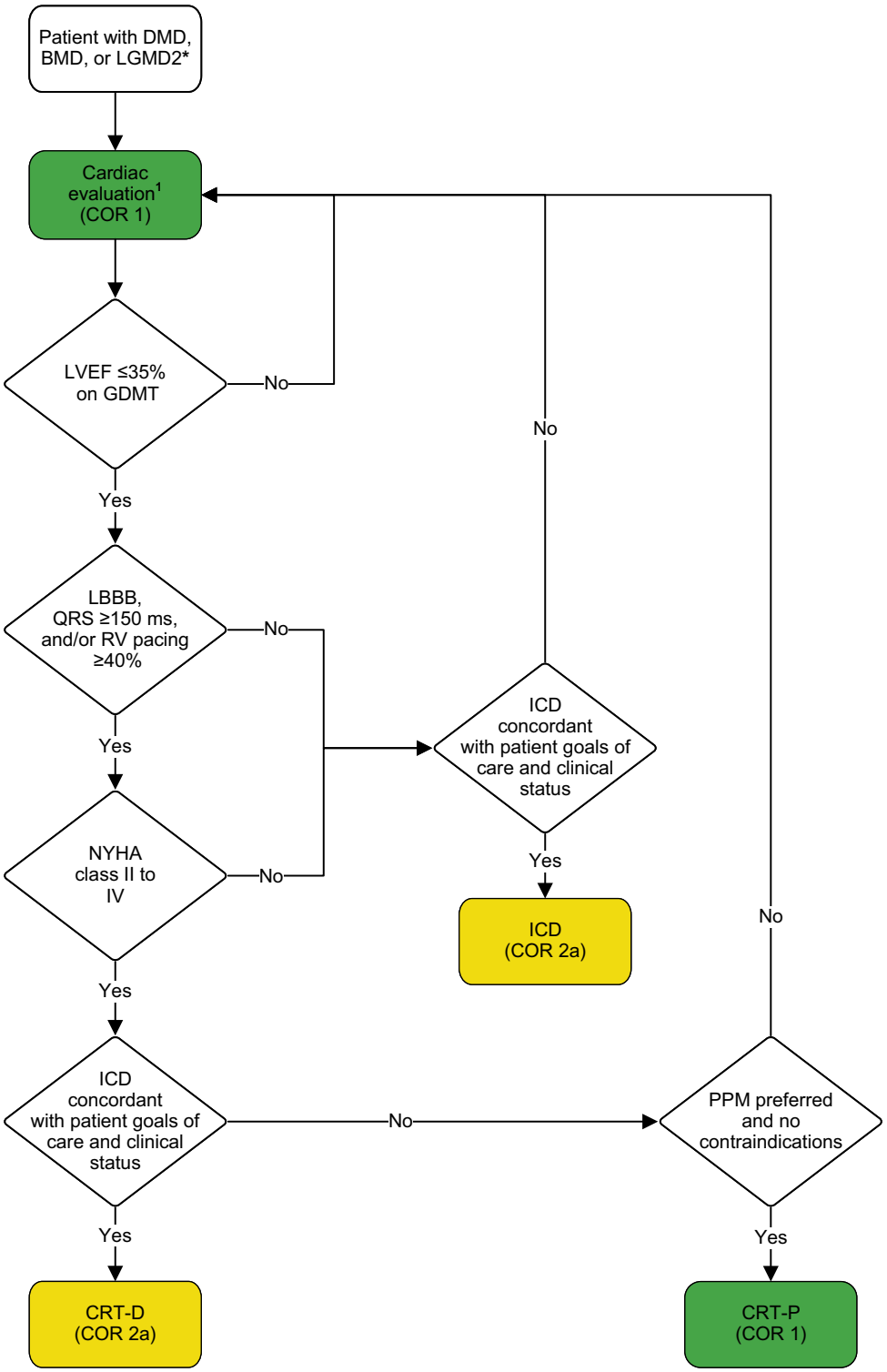

Figure 1 Flowchart for rhythm management and cardiovascular implantable electronic device implantation in patients with Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), or recessive limb-girdle muscular dystrophy type 2 (LGMD2) and left ventricular dysfunction. *Patients with standard indications for pacemaker or secondary prevention implantable cardioverter-defibrillator (ICD) may be managed based on previously published recommendations. [1]Physical examination, electrocardiogram, ambulatory electrocardiogram, and cardiac imaging (echocardiography or cardiac magnetic resonance imaging) at diagnosis with periodic retesting. Colors correspond to the class of recommendation (COR) in Table 1. CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; GDMT = guideline-directed medical therapy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PPM = permanent pacemaker; RV = right ventricular.

Section 4 Myotonic dystrophy types 1 and 2

4.1. General principles for myotonic dystrophy types 1 and 2

DM1 (Latin name *dystrophica myotonica type 1*, also known as Steinert disease or MD1) is the most common inherited NMD in adults, with a worldwide prevalence of 1:8,000 (reaching 1:500 in eastern Canada due to a founder effect).[101] DM1 is an autosomal dominant disorder caused by the expansion of a (CTG) triplet repeat in the untranslated 3′ region of the myotonic dystrophy protein kinase (*DMPK*) gene. Greater expansion of the CTG triplet repeat typically occurs in successive generations—a phenomenon termed anticipation. The disease involves the skeletal muscles, as well as the respiratory, cardiac, endocrine, ocular, and central nervous systems. Life expectancy is greatly shortened due to sudden death that occurs in up to one-third, presumably from AV conduction disturbances and ventricular arrhythmias, although catastrophic nonarrhythmic causes may also be implicated. Progressive respiratory failure is also a common mechanism of death.[102-104] At the molecular level, the pathophysiology of DM1 relies on a toxic RNA gain of function: *DMPK* mutant RNAs with expanded CTG repeats are retained in the nuclei as discrete aggregates or foci and cause alternative splicing deregulation of a subset of pre-mRNAs. Abnormal splicing of *SCN5A* with subsequent cardiac sodium channel dysfunction has been identified as an important contributor to the genesis of arrhythmias in DM1.[105] Cardiac manifestations of DM1 include conduction system disease (prevalence of first-degree AV block, 28.2%–45.0%; prevalence of bundle branch block, 16.5%–19.9%), supraventricular arrhythmias (prevalence, 5.0%–12.5%), and nonsustained and sustained VT (prevalence, 2.2%–4.1% and 1.0%–2.7%, respectively).[104,106,107] Genotype–phenotype correlation studies have shown that larger CTG amplification size is associated with a higher prevalence of all cardiac manifestations of the disease; however, it is noteworthy that life-threatening cardiac events can also occur in patients with smaller expansions.[24,25]

In pediatric patients with DM1, a higher prevalence of heart disease than in the general population has been observed in a Danish nationwide study with standardized prevalence ratios of 19.4 (95% CI, 4.92–52.7).[108] One series showed that pediatric patients with DM1 can present with atrial arrhythmias and, to a lower extent, with sustained VT, after the age of 10 years.[109] Third-degree AV block has thus far not been reported in DM1 patients aged <18 years. In most cases, supraventricular and ventricular arrhythmias were triggered by exercise.[109] At the present time, the recommendations for cardiovascular evaluation provided in this section are the same for both pediatric and adult DM patients.

DM2 (also called MD2 in some literature), also known as proximal myotonic myopathy, is caused by a CCTG expansion in the zinc finger 9 (*ZNF9*) gene and has a prevalence of 1:20,000. Patients with DM2 present with cardiac manifestations similar to those in DM1, although they are less prevalent and appear in older age.[110-113] While similar cardiovascular and arrhythmic events are seen in DM2, they appear to occur less frequently than in DM1. The proposed arrhythmia management of DM1 is hereby extrapolated to those with DM2. Further studies may yield management and risk stratification approaches specific to DM2.

4.2. Diagnostic testing and risk stratification in myotonic dystrophy types 1 and 2

Recommendations for diagnostic testing and risk stratification in myotonic dystrophy types 1 and 2

COR	LOE	Recommendations	References
1	C-EO	**1. Coordinated care of patients with DM1 or DM2 should be conducted in a medical setting where there is access to expertise in the neurological, cardiac, arrhythmic, pulmonary, and genetic manifestations of these disorders.**	
1	B-NR	**2. In patients with DM1 or DM2, cardiac evaluation including physical examination, ECG, ambulatory ECG, and cardiac imaging (echocardiography or CMR) at diagnosis with periodic retesting is recommended even in the absence of cardiac symptoms.**	24,26,104,106,108,110,114,115
1	C-LD	**3. In patients with DM1 or DM2 and cardiac conduction disorder, close monitoring for arrhythmic complications is recommended when using mexiletine (or other sodium channel blockers).**	116-119
2a	B-NR	**4. In patients with DM1 or DM2 with symptoms consistent with bradycardia and with ECG evidence of mild to moderate conduction disorder and when noninvasive testing is nondiagnostic, electrophysiological testing is reasonable for risk stratification for AV block and sudden cardiac death.**	26,120-123
2b	B-NR	**5. In patients with DM1 or DM2 with symptoms suggestive of ventricular tachyarrhythmias and when noninvasive testing is nondiagnostic, electrophysiological testing to assess the risk of sustained arrhythmias may be considered.**	120,123-126

Synopsis

The main objective of diagnostic testing in DM1 and DM2 is the assessment of sudden death risk. A noninvasive 12-lead and/or ambulatory ECG-based approach in search of severe ECG abnormality or an invasive strategy using 12-lead ECG and electrophysiological study[106,120,123] has been utilized to stratify this risk. Ultimately, such testing assists in deciding which patients are potentially eligible for prophylactic permanent pacing or primary prevention ICD. The predictive utility, comparative effectiveness, and cost-effectiveness of these two approaches have not been systematically compared; hence, at the present time, these approaches are comparable. Annual follow-up and arrhythmia evaluation, even in asymptomatic patients, may detect subclinical progression of arrhythmic manifestations that are known to occur. This progression may occur in an unpredictable manner, underscoring the importance of regular vigilant follow-up.[24,108] Genetic testing and counseling, as outlined in Section 2.2, can also be of clinical value and guide management.

Recommendation-specific supportive text

1. Centers with multidisciplinary specialty experience in managing patients with NMDs are best equipped to manage DM1 and DM2 patients, including those with pulmonary/respiratory, ophthalmologic, endocrine, gastrointestinal, and documented or suspected cardiac involvement. Recognition of DM1 and DM2 patients who are at high risk for serious cardiovascular complications, in particular malignant arrhythmias, requires familiarity with cardiac manifestations of NMDs.
2. The ECG is a powerful tool to detect conduction system disease (especially prolonged PR interval and QRS duration, and LBBB) or non-sinus rhythm on 12-lead ECG, all of which are predictive of sudden cardiac death in DM1.[106,107,115] Echocardiogram and ambulatory ECG monitoring are useful for the diagnosis of left ventricular systolic dysfunction, paroxysmal supraventricular and ventricular arrhythmias, and paroxysmal advanced AV block.[104] Echocardiogram and ambulatory ECG monitoring are generally reserved for patients with symptoms or evidence of conduction system disease, as most observational studies showed that these modalities rarely demonstrated significant abnormalities aside from these two indications; however, there are circumstances where initial screening and subsequent repeated evaluations would be indicated in asymptomatic patients without known conduction system disease, such as in patients over the age of 40 years.[24] Serial imaging and ECG evaluation may be of highest yield when identifying progression of cardiovascular disease, particularly if symptoms develop or worsen.
3. Concern has been raised regarding the safety of Vaughan-Williams class I antiarrhythmic drugs in DM1, especially mexiletine, which is frequently used to treat skeletal muscle myotonia. These medications may increase loss of function of the cardiac sodium channel, resulting in cardiac arrhythmias in DM1 patients. Intravenous injections of flecainide or ajmaline can trigger severe ventricular tachyarrhythmias or unmask type 1 Brugada pattern in DM1.[117,127] While widespread data are lacking, small series have demonstrated benefit from use of mexiletine in the treatment of myotonia without apparent arrhythmic complication or ECG changes, but with only limited follow-up duration ($\leq$7 weeks).[116,118] Although not formally studied, reasonable monitoring strategies to confirm safety when initiating such drugs include inpatient telemetry monitoring or, alternatively, serial outpatient ECG over several days, for example, with comparison to baseline QRS morphology and duration in particular, in carefully selected patients. The presence of a previously implanted pacemaker or ICD may also influence the need and type of monitoring, although this scenario has also not been widely studied. Inpatient monitoring may be preferred in those with evidence of AV conduction impairment including prolonged PR interval and/or bundle branch block, while outpatient monitoring may suffice for those without significant baseline ECG abnormalities.[119]
4. Invasive electrophysiological testing is generally used when arrhythmic risk is not fully characterized by results of noninvasive studies or when a high index of suspicion for elevated arrhythmic risk persists despite normal or minimally abnormal findings. While patients with PR interval $\geq$240 ms or QRS duration $\geq$120 ms are at higher risk of sudden death, the risk carried by patients with evidence of mild to moderate AV conduction impairment, for example, with PR interval or QRS duration of 200–240 ms and 100–120 ms, respectively, especially when coupled with symptoms suggestive of bradycardia, is uncertain.[104,106] Electrophysiological testing may therefore help characterize such patients' susceptibility to future serious arrhythmic events. A prolonged HV interval, for instance, may indicate that a patient is at increased risk for complete AV block and sudden death.[26] In one prospective study including 49 patients with DM1, patients with an HV interval $\geq$70 ms (mean HV interval, 79 $\pm$ 11 ms; range, 70–125 ms) had an incidence of advanced AV block or sinus node dysfunction of 51.0% over a mean follow-up of 4.4 years.[120,123] Serial electrophysiological testing in DM1 patients was examined in one retrospective study where mean prolongation of the HV interval of 1.2 ms/y was reported in those undergoing two or more electrophysiological studies. Predictors of HV interval prolongation were development of cardiac symptoms or significant prolongation of conduction intervals on 12-lead ECG during follow-up. In these situations, repeat electrophysiological testing could possibly be avoided in favor of proceeding to device-based therapy.[122]
5. While induction of ventricular arrhythmias including bundle branch reentrant ventricular tachycardia (BBRVT) has been observed in DM1 patients, the predictive value of programmed ventricular stimulation has not been thoroughly evaluated in patients with DM1 but may be helpful

in patients with symptoms of unexplained syncope, presyncope, or palpitations. Stimulation protocols favoring induction of BBRVT have been described and may be utilized in this setting.[26,124,125,128,129] Unlike with other substrates, no data exist regarding appropriateness of ICD implantation in DM1 and DM2 patients who are found to have inducible ventricular arrhythmias, although inducibility in carefully selected patients suggests the presence of substrate prone to developing future VT or VF. Further studies are required to better clarify this issue.[124,125,128,129]

4.3. Bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in myotonic dystrophy types 1 and 2

Recommendations for bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in myotonic dystrophy types 1 and 2

COR	LOE	Recommendations	References
1	B-R	1. In patients with DM1 or DM2 with LVEF ≤35%, sinus rhythm, LBBB with QRS duration ≥150 ms, and NYHA class II to class IV symptoms, or suspected right ventricular pacing–induced cardiomyopathy despite guideline-directed medical therapy, CRT is recommended if concordant with the patient's goals of care and clinical status.	84-88,130
1	B-NR	2. In patients with DM1 or DM2 and documented symptomatic bradycardia due to any degree of sinus node dysfunction or AV block, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.	79,80,82,131
1	B-NR	3. In patients with DM1 or DM2 and third-degree or advanced second-degree AV block at any anatomical level, with or without symptoms, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.	104,106
2a	B-NR	4. In patients with DM1 or DM2 and marked first-degree AV block (PR interval ≥240 ms) or intraventricular conduction delay (native QRS duration ≥120 ms), permanent pacemaker implantation is reasonable if concordant with the patient's goals of care and clinical status.	106
2a	B-NR	5. In patients with DM1 or DM2 with HV interval ≥70 ms on electrophysiological study, permanent pacemaker implantation is reasonable if concordant with the patient's goals of care and clinical status.	120,123-126

Synopsis

The annual incidence of sudden death in DM1 and DM2 is between 0.53% and 1.16% and is most often attributed to malignant bradyarrhythmias resulting from advanced conduction system disease.[104] However, the observation of sudden death in pacemaker and even ICD recipients suggests that other mechanisms may be involved, such as ventricular tachyarrhythmias including BBRVT or noncardiac causes such as pulmonary embolism.[2,104,106,132,133] Based on noninvasive or invasive criteria, prophylactic pacemaker implantation is historically performed in patients with evidence of conduction system disease prior to the development of advanced or complete AV block. Utilization of a documented multidisciplinary evaluation of global disease severity with estimation of survival probability by a specific survival score may help identify candidates in whom a pacemaker may be of greatest yield.[2] Clinical scenarios for pacemaker implantation in patients with DM1 and DM2 are shown in Table 6.

Recommendation-specific supportive text

1. One recent study showed echocardiographic benefit from increased implementation and tolerance of guideline-directed medical therapy following CRT.[130] However, this study was conducted in a small number of DM1 patients with relatively limited follow-up and end points. Additionally, assigning symptoms due to heart failure rather than underlying neuromuscular impairment may prove challenging. Nevertheless, while criteria used for determining CRT eligibility have been established through studies conducted in the general population, these approaches may be reasonably implemented in patients with DM1 and DM2.[91] While some patients with QRS duration 120–149 ms may also derive benefit from CRT, a QRS duration ≥150 ms is utilized as the evidence for clinical benefit from CRT is strongest for this threshold cutoff.[91]
2. Criteria for permanent pacing in patients with symptomatic bradycardia in the general population are similarly applied in DM1 and DM2 patients, despite the lack of published evidence. Although not specifically studied, pacemaker implantation in DM1 patients with second-degree or third-degree AV block, even when asymptomatic, is likely to offer the highest likelihood of benefit against sudden death (see further discussion below).[7,14,104,106,123,132]

3. Patients with DM1 or DM2 and third-degree or advanced second-degree AV block are at dramatically higher risk for sudden death, even in the absence of symptoms.[104,106] These forms of AV block are felt to represent the most concerning findings in DM1 and DM2 patients owing to their association with unreliable, unstable escape rhythms that may precede asystole, bradycardia-mediated ventricular arrythmias, and sudden death. Nevertheless, recognition of significant bradycardia in a DM1 or DM2 patient is suggestive of advanced, likely infra-His conduction disease and indicates a circumstance where sudden death can possibly be prevented.[7,106,120,123]
4. While conduction defects on 12-lead ECG in individuals with DM1 have a prevalence of up to 45% at diagnosis, permanent pacemaker implantation is not indicated in all DM1 patients who demonstrate such findings. Published threshold values of PR interval $\geq$240 ms and QRS duration $\geq$120 ms, indicating increased risk of sudden death, represent a reasonable compromise to identify the maximum number of patients who may benefit from pacing while possibly minimizing unnecessary pacemaker implantation. Along with these criteria, rhythm other than sinus, second-degree or third-degree AV block had sensitivity of 74.1% for the prediction of sudden death, with specificity of 61.7%, positive predictive value of 12.1%, and negative predictive value of 97.1%.[106,110] It should be noted that these criteria have only been examined in adults; hence, with the knowledge that this degree of conduction impairment in children is relatively uncommon, their application may be deemed too aggressive in children.
5. In a retrospective observational study, the use of an electrophysiological study followed by implantation of a pacemaker in patients with DM1 with an HV interval $\geq$70 ms was associated with an improvement in overall survival (adjusted hazard ratios ranging from 0.47 [95% CI, 0.26–0.84; P = .01] to 0.61 [95% CI, 0.38–0.99; P = .047]) and reduction of sudden death (adjusted hazard ratios ranging from 0.24 [95% CI, 0.10–0.56; P = .001] and 0.28 [95% CI, 0.13–0.61; P = .001]) compared with patients followed by ECG assessment alone.[123]

4.4. Atrial arrhythmias in myotonic dystrophy types 1 and 2

Recommendations for atrial arrhythmias in myotonic dystrophy types 1 and 2

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with DM1 or DM2, anticoagulation according to established guidelines and clinical context is recommended for AF or AFL, taking into consideration the risks of thromboembolism and the risks of bleeding on oral anticoagulation.**	92-94

Synopsis

Atrial arrhythmias, including AF, AFL, and atrial tachycardia, are present in 5%–12% of patients at presentation.[2,106,107,123,134] Supraventricular arrhythmias can occur in patients without significant atrial remodeling. AF with rapid AV conduction and accompanying syncope can occur in young patients and may be the first sign of cardiovascular involvement in DM1 or DM2.[134,135] As in all patients, the risks of bleeding must be counterbalanced against the risk of thromboembolism. While difficult to objectively characterize, frailty, fall risk, and patient tolerance of such risks may influence the decision to prescribe anticoagulant therapy, as in Table 6, clinical scenario 4.

Recommendation-specific supportive text

1. It remains unclear whether DM1 or DM2 patients with atrial arrhythmias have the same risk for thromboembolic events as those in the general population. Given the lack of such data, at the present time, the indications for prevention of thromboembolic complications and assessment of bleeding risk are the same as in the general population.[6,12,93,95] The clinical context in which this decision arises must also be considered, factoring in items such as patient age, dosing of anticoagulants particularly in children, patient frailty, and limitations in thromboembolic and bleeding risk assessment in patients not well represented in studies where these criteria were determined. Though uncommon, children with DM1 or DM2 who develop atrial arrhythmias present a special circumstance where evidence and experience with oral anticoagulants are lacking. Traditional algorithms including CHA_2DS_2-VASc and HAS-BLED, the latter to determine hemorrhagic risk, comprise several risk factors that are wholly absent in children. The decision to initiate anticoagulation in a child is based on clinician judgment incorporating their best assessment of a patient's thromboembolic and bleeding risks, patient and family preferences, and an understanding that evidence in this area is absent, largely due to the infrequency of this situation. Finally, independent of thromboembolic risk, AF and AFL have been associated with a higher risk of sudden death in one large series of DM1 patients, although the exact mechanism of this increased risk and mitigation strategies have yet to be elucidated.[106]

4.5. Ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in myotonic dystrophy types 1 and 2

Recommendations for ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in myotonic dystrophy types 1 and 2

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with DM1 or DM2 in whom ICD therapy is planned, an ICD system with permanent pacing capability is recommended.**	104,106,110,121,132
1	B-NR	2. **In patients with DM1 or DM2 who are survivors of spontaneously occurring hemodynamically significant sustained VT or VF, ICD therapy is indicated if concordant with the patient's goals of care and clinical status.**	96,104,132,133
1	B-NR	3. **In patients with DM1 or DM2 and an LVEF ≤35% despite guideline-directed medical therapy, ICD therapy is indicated if concordant with the patient's goals of care and clinical status.**	97,132
1	B-NR	4. **In patients with DM1 or DM2 in whom clinically relevant ventricular arrhythmias are induced during electrophysiological study, ICD therapy is recommended if concordant with the patient's goals of care and clinical status.**	110,124-126,132,133
2b	B-NR	5. **In patients with DM1 or DM2 in whom permanent pacemaker implantation is indicated, ICD therapy may be considered if concordant with the patient's goals of care and clinical status.**	106,121,132

Synopsis

Fibrotic foci, fatty infiltration, and delayed conduction in the His–Purkinje system may lead to ventricular arrhythmias including BBRVT in DM1 and DM2 patients.[133] The incidence of sustained VT was 2.3% in a large cohort of unselected DM1 and DM2 patients during 12-year follow-up, and nonsustained VT was the only independent predictor of sustained VT.[104] Identifying asymptomatic DM1 and DM2 patients at high risk of sudden death can be challenging, and debate continues regarding the most effective means to protect against its occurrence. A screening history, ECG, and a combination of electrophysiological testing and pacemaker and ICD implantation may be employed to evaluate and address this risk, as outlined in Figure 2. DM1 and DM2 patients with traditional guideline-based indications for CIED implantation may be managed accordingly.[10,13] The decision to proceed with ICD implantation may be quite complex in patients with DM1 or DM2, as comorbidities, clinical status, and patient wishes need to be considered. Based on these features, attenuation of overall benefit from ICD implantation may also be observed. Finally, the potential need for permanent pacing also deserves consideration, as a transvenous (or pacing-capable) ICD system can provide pacing support not achievable with currently available subcutaneous ICD systems. Utilization of available diagnostic information regarding conduction system integrity, clinician expertise, and patient preference may provide guidance and help determine appropriateness for the type of CIED to be implanted. See Table 6 for clinical scenarios describing management decisions for patients with DM1.

Recommendation-specific supportive text

1. Patients with DM1 or DM2 and evidence of cardiac involvement are known to be at higher risk of sudden death, generally due to bradyarrhythmias and tachyarrhythmias.[104,106,110,121,132] While evidence of AV conduction impairment is predictive of sudden death, pacemaker implantation provides incomplete protection against this event, indicating a coexisting susceptibility to both types of these rhythm disturbances once cardiac involvement is confirmed.[121,132] Therefore, once ICD implantation is indicated, due to either due to induced/spontaneously occurring ventricular arrhythmias or left ventricular dysfunction, the risk for serious bradyarrhythmias is elevated, even in patients who do not demonstrate evidence for significant AV conduction disease at the time of device implantation. Considering this, and the known progressive nature of cardiac disease in DM1 and DM2, an ICD system capable of providing rate support is the most protective.[110,121,132]
2. Specific studies evaluating the benefit of secondary prevention ICD implantation in DM1 and DM2 patients are lacking, and it is unlikely that such studies will be conducted. Hence, the implementation of data from studies conducted in the general population and their extrapolation to patients with DM1 or DM2 is felt to be appropriate.[8,96,100]
3. Specific studies evaluating the benefit of primary prevention ICD implantation in DM1 and DM2 patients with systolic ventricular dysfunction and heart failure have yet to be published. However, the risk of sudden arrhythmic death associated with systolic left ventricular dysfunction of nonischemic etiology is well established.[10,13] Hence, the implementation of data from studies conducted in the general population and their extension to patients with DM1 or DM2 is felt to be appropriate.[8,97,100] Previously published studies indicated a benefit from primary prevention ICD implantation in patients with mild heart failure symptoms based on NYHA functional class. However, this

classification scheme is less reliable in patients with neuromuscular impairment; hence, heart failure status is omitted from this recommendation.

4. The induction of clinically relevant ventricular arrhythmias, most notably monomorphic VT, during electrophysiological study in DM1 and DM2 patients is felt to be indicative of scarring due to myocardial fibrosis, providing a substrate for future development of spontaneously occurring VT or VF leading to sudden death. This is further supported by the occurrence of sudden death due to presumed ventricular tachyarrhythmias in a subset of pacemaker recipients with DM1, who are similarly felt to have myocardial fibrosis of AV conduction structures.[26,106,110,132,133] Risk predictors for sudden death and future VT or VF in DM1 and DM2 are limited; however, it is often the case that multiple known predictors of sudden death and ventricular arrhythmias in DM1 and DM2 patients such as LBBB, nonsustained VT, and AV conduction abnormalities[104] do not occur in isolation. The occurrence of BBRVT in DM1 and DM2 is well known.[133] Though BBRVT can be effectively cured with catheter ablation, those with this rhythm disturbance are felt to have the substrate (ie, myocardial infiltration/scar) that may lead to other rhythm disturbances including AV conduction disturbances and intramyocardial reentry. The former is underscored by the observation of residual, prolonged HV interval in patients with BBRVT. Additionally, Wahbi et al[104] demonstrated the presence of LBBB as an independent predictor for sudden death in those with DM1. LBBB is arguably almost uniformly present in patients with DM1 and BBRVT; therefore, while ablation may eliminate BBRVT, some element of increased risk may still be apparent, which is best addressed by ICD implantation. However, cautiously avoiding ICD implantation may be justified in DM1 and DM2 patients in whom no further ventricular arrhythmias are induced with comprehensive ventricular stimulation following successful curative catheter ablation of BBRVT, without other indicators of arrhythmic risk. Pacemaker implantation or observation as deemed appropriate per the clinician's discretion and patient's preferences may be employed thereafter in this situation.
5. The benefit of ICD therapy for sudden death prevention in DM1 and DM2 has not been conclusively determined. However, pacemaker-eligible patients with accompanying conduction disease, particularly those with HV interval $\geq$70 ms, are felt to have the substrate to develop ventricular arrhythmias that may only be addressed by ICD. This theory is underscored by the observation of sudden death in pacemaker recipients.[106,110,121,132] Detection of nonsustained VT on ambulatory ECG may similarly indicate the presence of arrhythmogenic substrate where pacemaker alone may provide insufficient protection against sudden death.[104,106]

Table 6 Clinical scenarios for the management of arrhythmias in myotonic dystrophy type 1

Clinical scenario	Management strategies	Key points
1. A 63-year-old man with DM1 and minimal neuromuscular impairment presents with a single episode of unprovoked syncope and facial injury. ECG shows sinus rhythm, PR interval 180 ms, and RBBB (QRS duration 140 ms). Echocardiogram shows global LVEF 50% and mild mitral regurgitation.	• Management options discussed included use of further noninvasive and invasive diagnostic strategies versus empiric arrhythmia therapies as follows: ○ Prolonged ambulatory monitoring or loop recorder insertion ○ Empiric pacemaker implantation given evidence of conduction system disease ○ EP testing to assess AV conduction and evaluate the inducibility of ventricular arrhythmias, followed by CIED insertion • Values elicited in discussion included likelihood of recurrence with further injuries, potential for life-threatening brady- and tachyarrhythmias as causative etiology, and favorable functional status with reasonable expected longevity. • Given age, high functional status, and potentially serious causative arrhythmias, EP testing was performed. Pacemaker implantation was planned with possible ICD insertion if clinically relevant ventricular arrhythmias were induced.	• Age, high functional status, and serious nature of syncope with injury prompted aggressive evaluation. • Empiric pacemaker implantation without further testing could be considered given existing RBBB. • Normal LVEF suggests absence of significant myocardial involvement. • Clinical benefit of empiric ICD implantation in this situation remains uncertain. • EP study was primarily utilized to determine the suitability of ICD implantation, as pacemaker implantation was appropriate with clinical features at presentation.

Table 6 (*Continued*)

Clinical scenario	Management strategies	Key points
2. A 52-year-old man with DM1 and mild neuromuscular impairment reports limiting exertional dyspnea when ambulating and climbing stairs. ECG and 48-Holter monitor show sinus rhythm with 3:2 and 4:3 type 1 second-degree AV block (Wenckebach type), and RBBB. Echocardiogram demonstrates LVEF 39% with global hypokinesis and mild to moderate mitral regurgitation. He is normotensive on losartan with avoidance of beta-adrenergic blockade due to bradycardia.	• Management options discussed included implantation of dual-chamber pacemaker, biventricular pacemaker (CRT-P), and biventricular ICD (CRT-D) implantation. • Values elicited in discussion included desire for improved functional capacity, reduction of symptoms attributed to bradycardia and left ventricular dysfunction, and prevention of sudden death due to malignant brady- and tachyarrythmias. • The decision was made to proceed with biventricular ICD (CRT-D) implantation, as this would address all the relevant cardiovascular issues described.	• Restoration of AV synchrony with alleviation of related symptoms was accomplished by permanent pacing. • Anticipated right ventricular pacing $\geq$40% coupled with moderate preexisting left ventricular dysfunction warrants implantation of CRT device. • ICD implantation may be considered in DM1 patients who require pacing due to ongoing risk of sudden death, possibly due to ventricular arrhythmias. • Moderate left ventricular dysfunction indicates myocardial involvement/infiltration due to DM1. • Beta-adrenergic blockade for left ventricular dysfunction may be safely used following device insertion without concern for aggravating bradycardia.
3. A 72-year-old woman with DM1 and significant skeletal muscle weakness presents with recurrent dizziness and falling over the past year. ECG shows sinus rhythm, PR interval 260 ms, and LBBB (QRS 160 ms). Echocardiogram shows LVEF 52% without wall motion abnormality. The 30–day event recorder shows sinus rhythm, occasional multiform premature ventricular complexes, and no symptomatic episodes.	• Management options discussed included use of further noninvasive and invasive diagnostic strategies versus preemptive arrhythmia therapies as follows: ○ Prolonged arrhythmia monitoring with loop recorder insertion ○ EP testing to assess AV conduction and evaluate the inducibility of ventricular arrhythmias, followed by CIED insertion ○ Empiric pacemaker implantation ○ Empiric transvenous ICD implantation • Values elicited in discussion included desire to avoid complications from symptomatic episodes, most expeditious management strategy, and focus on quality of life. • Although several risk indicators for sudden death were present (PR interval 260 ms and LBBB), the most likely serious etiology for observed episodes remained bradyarrhythmias due to high-grade AV block. Advanced functional impairment and primary emphasis on quality of life led to the decision to pursue empiric pacemaker implantation.	• Age, significant functional impairment, patient wishes, and suggestive clinical features were key points in determining ultimate management strategy. • Transvenous ICD would accomplish protection against brady- and tachyarrhythmias, but limited evidence, possible longer adjustment (compared to pacemaker), and patient wishes favored pacemaker implantation.
4. A 68-year-old woman with DM1 and advanced neuromuscular impairment resulting in repeated falls is found to have asymptomatic rate-controlled AF during hospitalization for trochanteric fracture. She is expected to be confined to bed indefinitely. Other comorbidities include diabetes and chronic kidney disease stage 2. She has never had stroke/thromboembolism or serious bleeding. Ventricular function is normal; she has intact cognition and reports favorable quality of life with frequent family visitation.	• Management options discussed included prescribing direct oral anticoagulant/warfarin, left atrial appendage occlusion, and avoidance of anticoagulation altogether. • Values elicited in discussion included reduced though acceptable quality of life, desire to avoid preventable life-threatening/life-altering medical complications, preference for noninvasive therapy, increased thromboembolic risk balanced by limited bleeding risk using conventional risk calculators, and limited fall risk given bed-confined status. • With CHA_2DS_2-VASc and HAS-BLED risk scores of 3 and 2, respectively, oral anticoagulation was recommended and accepted.	• Conventional risk calculators are recommended for use in DM1 patients and support the use of oral anticoagulation here. • Fall risk and frailty are difficult to quantify but must be considered when considering anticoagulation. • Patient wishes to avoid serious preventable complications through noninvasive means were heeded; anticoagulation will reduce the risk of systemic thromboembolism due to AF.

Scenarios cover different degrees of muscle impairment. AF = atrial fibrillation; AV = atrioventricular; CIED = cardiovascular implantable electronic device; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DM1 = myotonic dystrophy type 1; ECG = electrocardiogram; EP = electrophysiological; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block.

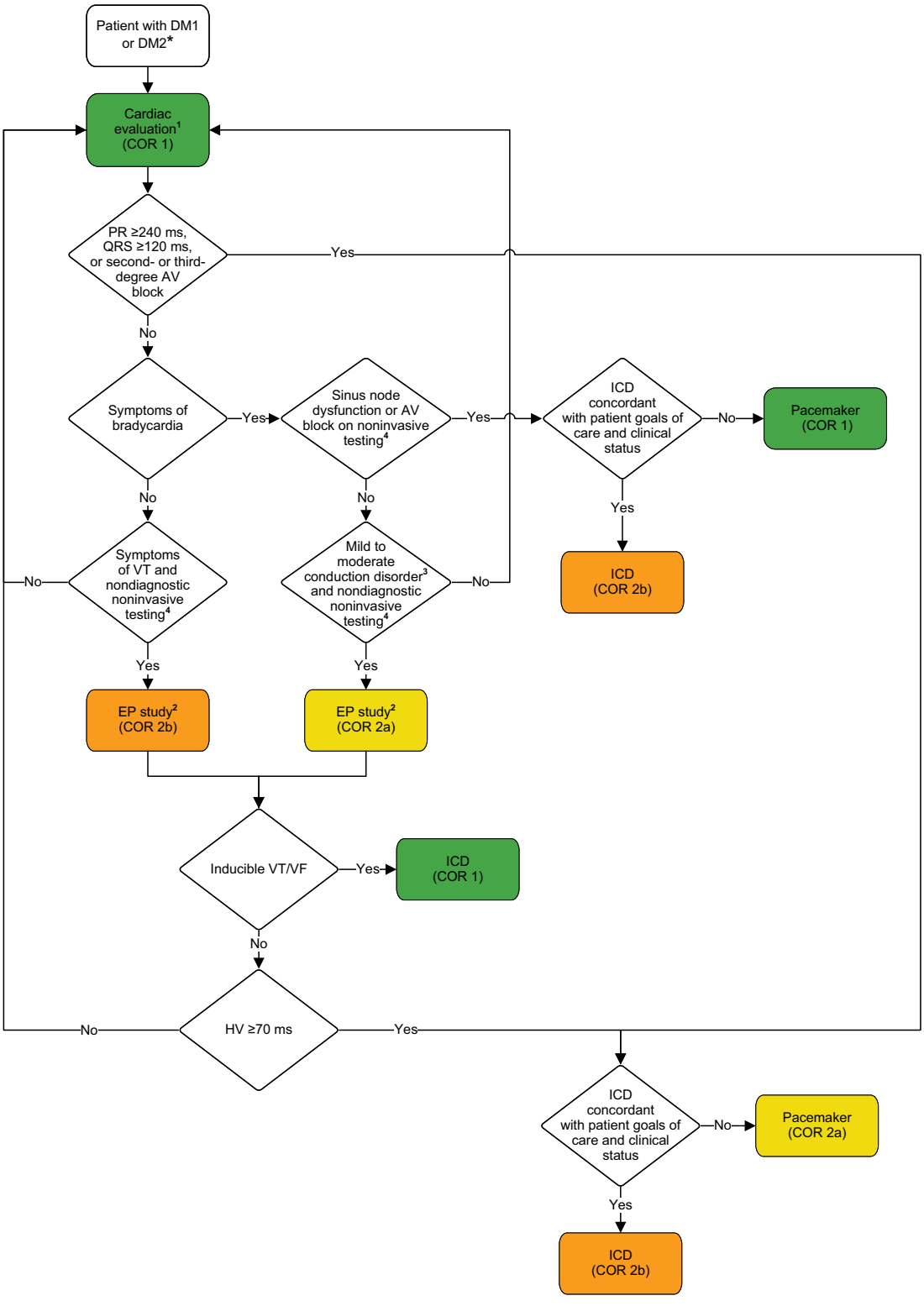

Figure 2 Flowchart for rhythm management and cardiovascular implantable electronic device implantation in patients with myotonic dystrophy type 1 (DM1) or myotonic dystrophy type 2 (DM2) with normal ventricular function, with a focus on the risk stratification for the prevention of sudden death. *Patients with indications for pacemaker or implantable cardioverter-defibrillator (ICD) implantation, including cardiac resynchronization therapy, based on recommendations from previously published guidelines are not represented in this flow diagram. [1]Physical examination, electrocardiogram (ECG), ambulatory ECG, and cardiac imaging (echocardiography or cardiac magnetic resonance imaging) at diagnosis with periodic retesting. [2]The purpose of electrophysiological (EP) testing for risk stratification for sudden death is to assess the integrity of atrioventricular conduction, in particular the His–Purkinje system with measurement of the HV interval, as well as to determine the inducibility of clinically significant ventricular arrhythmias. A suggested stimulation protocol used in DM1 patients has been published,[26] and other protocols primarily used in patients with ischemic heart disease may also be useful.[128,129] The discussion of device implantation should be carried out prior to electrophysiological testing to confirm the patient's preference and willingness to undergo cardiovascular implantable electronic device implantation. [3]Mild to moderate conduction disorder is defined as PR interval 200–240 ms and/or QRS duration 100–120 ms. [4]Noninvasive testing includes 12-lead ECG, telemetry recordings, ambulatory ECG, or insertable loop recorder. Colors correspond to the class of recommendation (COR) in Table 1. AV = atrioventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

Section 5 Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

5.1. General principles for Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

EDMD is inherited in an X-linked or autosomal dominant pattern—Emery-Dreifuss muscular dystrophy type 1 (EDMD1) and Emery-Dreifuss muscular dystrophy type 2 (EDMD2), respectively. Similarly, limb-girdle muscular dystrophy 1B (LGMD1B) is inherited in an autosomal dominant pattern, which is in contrast to LGMD2 (see Section 3). The 229th European Neuromuscular Centre workshop in 2017 suggested a reclassification and revised nomenclature for LGMD; this document retains previous nomenclature.[1] Autosomal dominant LGMD1B is classified as specific myopathies or as LGMD D (dominant) variants (D1–D4). Autosomal recessive LGMD2 is renamed as LGMD R1–R24 in addition to descriptive names for some of the recessive variants.[1] EDMD1 results from mutations in the *STA* gene (Xq28), which encodes the nuclear membrane protein emerin. In contrast, EDMD2 and LGMD1B are due to *LMNA* mutations (1q21-q23 [EDMD2] and 1q11-21 [LGMD1B] loci). Each encodes lamin A/C proteins, which are components of the inner nuclear membrane.[30,136,137] Both forms of EDMD are characterized by juvenile-onset joint contractures (eg, Achilles tendon, spine, and elbows), with progressive humeroperoneal muscle weakness.[138] LGMD1B can be distinguished from EDMD by predominant proximal myopathy and lack of early contractures. EDMD and LGMD1B both confer a high risk of progressive conduction system disease, sudden cardiac death due to ventricular arrhythmias, and dilated cardiomyopathy.[139-141] Characteristic early ECG changes in EDMD1 include bradycardia, with low-amplitude P waves, and a prolonged PR interval.[89,142] As the disease advances, there are characteristic histopathologic myocardial changes (ie, atrial thinning and apoptosis), and arrhythmias including AF, AFL, and complete heart block may develop. One of the hallmarks of EDMD1 is atrial standstill.[143] *LMNA* mutations confer high risk for AV block, often in concert with dilated cardiomyopathy (Figure 3). Patients with EDMD2 and LGMD1B are at exceedingly high risk of sudden death, likely higher than patients with EDMD1. Given the genetic overlap in EDMD2 and LGMD1B, and the similar cardiac manifestations with EDMD1, the following recommendations pertain to all three conditions.

5.2. Diagnostic testing and risk stratification in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

Recommendations for diagnostic testing and risk stratification in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

COR	LOE	Recommendations	References
1	C-EO	1. **Coordinated care of patients with EDMD or LGMD1B should be conducted in a medical setting where there is access to expertise in the neurological, cardiac, arrhythmic, pulmonary, and genetic manifestations of these disorders.**	
1	B-NR	2. **In patients with EDMD or LGMD1B, cardiac evaluation including physical examination, ECG, ambulatory ECG, and cardiac imaging (echocardiography or CMR) at diagnosis with periodic retesting is recommended even in the absence of cardiac symptoms.**	29,139,144-151
1	B-NR	3. **First-degree relatives of patients with genetically confirmed EDMD or LGMD1B who do not have access to or have opted out of genetic testing should be screened with ECG and cardiac imaging (echocardiography or CMR).**	137,145,146,152-154
2a	C-EO	4. **In patients with EDMD or LGMD1B who have symptoms of conduction disorder or arrhythmias, implantable cardiac monitoring is reasonable, even in the setting of a normal 12-lead ECG, normal ambulatory ECG monitoring, and/or normal transthoracic echocardiogram.**	
2b	C-LD	5. **In patients with EDMD or LGMD1B with symptoms consistent with bradycardia and ECG evidence of mild to moderate conduction disorder, or symptoms consistent with ventricular tachyarrhythmias, and when noninvasive testing is nondiagnostic, electrophysiological testing may be considered for risk stratification for sustained arrhythmias, AV block, and sudden cardiac death.**	124-126,137,141,155

Synopsis

EDMD (types 1 and 2) and LGMD1B are associated with a high risk of cardiac involvement, particularly arrhythmias and sudden cardiac death. *LMNA*-related heart disease is associated with myopathy and malignant arrhythmias. In addition, there is considerable phenotypic variation and penetrance; some patients with EDMD or LGMD1B may present with only cardiac or musculoskeletal manifestations. As such, there are relatively aggressive recommendations regarding definitive diagnosis (including genetic testing) and the treatment of arrhythmias and cardiomyopathy. It is critical to recognize that cardiac manifestations may develop at any age and are often independent of the severity and degree of NMD.

Genetic screening is the foundation for diagnosis (Table 7, clinical scenario 3). Once disease is established, cardiovascular testing should be performed and repeated periodically, even in the absence of symptoms suggestive of arrhythmia or heart failure (Figure 3). Furthermore, first-degree relatives should undergo genetic screening and initial cardiovascular testing (eg, ECG and/or echocardiogram). Details of genetic testing in EDMD and LGMD1B are further discussed in Section 2.2. Resting and ambulatory electrocardiography are the cornerstone of the evaluation. Cardiac imaging, specifically transthoracic echocardiography, should be used to assess left ventricular function, although there is a growing role for CMR. Electrophysiological testing with programmed electrical stimulation is sometimes performed in select patients to assess the risk of ventricular tachyarrhythmias (Table 7, clinical scenario 4).

Recommendation-specific supportive text

1. Centers with multidisciplinary specialty experience in managing patients with NMDs are best equipped to manage EDMD and LGMD1B patients, including those with pulmonary/respiratory, musculoskeletal, and documented or suspected cardiac involvement. Recognition of EDMD and LGMD1B patients who are at high risk for serious cardiovascular complications, particularly cardiomyopathy and malignant arrhythmias, requires familiarity with cardiovascular manifestations of NMDs.
2. A longitudinal cohort study of 94 patients followed for a median of 57 months found that dilated cardiomyopathies caused by pathogenic variants of *LMNA* are highly penetrant, adult-onset, malignant diseases characterized by a high rate of heart failure and life-threatening arrhythmias.[145] In a longitudinal series of 122 patients with pathogenic variants of *LMNA*, there was an increase in the frequency of ECG findings on a median 7-year follow-up.[146] Specifically, there was an increase in AV block (46% to 57%) as well as atrial (39% to 63%) and ventricular (16% to 34%) arrhythmias. Ongoing surveillance for arrhythmia after the index evaluation is of paramount importance with EDMD and LGMD1B. One meta-analysis of 299 patients with pathogenic variants of *LMNA* found that sudden death was the most frequently reported mode of death (46%), and arrhythmias were reported in 92% of patients after the age of 30 years.[139] This is consistent with other reports in which the majority of patients developed severe AV block requiring pacemakers after age 35 years.[147,148,156] One retrospective cohort of 78 patients with pathogenic variants of *LMNA* found that most presented with cardiac symptoms prior to 50 years of age.[149] Overall, cardiac involvement occurred earlier in patients with EDMD2 than in those with LGMD1B; the age at ICD or permanent pacemaker implantation was lower for patients with EDMD2 (39.6 ± 10.8 years) than for those with LGMD1B (48.4 ± 8.3 years). Another longitudinal cohort study followed 21 patients with pathogenic variants of *LMNA* over 6 years; over 70% had bradyarrhythmias, the median age of the first evidence of cardiac compromise was 40 years, and the median age of detection of severe signs of cardiac involvement was 48 years.[150]
3. Cascade genetic testing can identify family members at risk of EDMD and LGMD1B and inform cardiac evaluation. Family members in whom one of the pathogenic variants of EDMD or LGMD has been identified benefit from longitudinal screening for cardiac involvement, both cardiomyopathy and arrhythmias, often with echocardiography and ECG.[157] There is considerable variability in the phenotypic expression of EDMD2 and LGMD. Some patients have isolated cardiac involvement, and this could be the only manifestation in first-degree relatives. Bonne et al[137] described the variability in the phenotype of pathogenic variants in autosomal dominant EDMD2, in which 12 of 53 patients demonstrated only cardiac involvement, with many needing permanent pacing. Other studies also describe the protean manifestations of laminopathies, which can present antecedent to, or in the absence of any, neuromuscular symptoms.[146,152,158] One longitudinal study of X-linked and autosomal dominant EDMD2 in 18 patients with 30-year follow-up showed that the majority developed bradyarrhythmias and AF or AFL; however, there was no correlation between neuromuscular impairment and cardiac manifestations.[152] In addition, patients with X-linked EDMD1 may manifest atrial and ventricular tachyarrhythmias without skeletal muscle involvement.[152-154]
4. Long-term cardiac monitoring may be needed to identify subclinical conduction system disease or tachyarrhythmias. External event recorders and Holter monitoring are limited in this capacity, and longer-duration implantable loop monitoring increases the diagnostic yield. There are considerable data supporting the use of implantable loop recorders in unexplained syncope.[72,159] Furthermore, there is strong evidence of benefit in patients with syncope and in detecting occult AF.[160] However, there is a paucity of evidence directly measuring the efficacy of implantable cardiac monitoring in patients with EDMD and LGMD1B. Not identifying subclinical arrhythmias, especially AF and AFL, in these patients may lead to adverse outcomes. Indeed, atrial standstill is a common feature in EDMD1, and patients are at risk for thromboembolism.[152]
5. Patients with pathogenic variants of *LMNA* have a high risk of ventricular tachyarrhythmia and often receive

ICDs, especially when there is an indication for a pacemaker for bradyarrhythmia. While electrocardiographic criteria indicative of abnormal AV conduction, such as PR interval ≥230 ms, and abnormal intraventricular conduction are predictive of serious arrhythmias, patients with *LMNA* mutations who demonstrate mild to moderately abnormal ECG abnormalities (PR interval 200–230 ms or QRS duration 100–120 ms), accompanied by symptoms of unexplained syncope, presyncope, or palpitations, warrant more aggressive evaluation.[139,144-146] Electrophysiological testing evaluating the integrity of AV conduction, in particular the HV interval, is well suited for this purpose. While studies have not demonstrated a high correlation between the incidence of clinical ventricular arrhythmias and inducibility during electrophysiological testing, programmed ventricular stimulation in this setting may possibly provide additive information regarding a patient's future arrhythmic risk and is generally adjunctive to invasive AV conduction system assessment.[141,155] One prospective series followed 19 patients with pathogenic variants of *LMNA* (9 with EDMD2 and 1 with LGMD1B) who received an ICD. Over a mean of 34 months, 8 (42%) received appropriate shocks; 6 of these patients were found to have VF, and ICD therapies were not correlated with inducible VT or VF.[141] Furthermore, programmed electrical stimulation in the setting of catheter ablation for VT poses challenges and does not clearly improve outcomes. In one series of 25 patients with pathogenic variants of *LMNA* referred for catheter ablation for VT, inducibility of nonclinical VT was seen in 50% and persistent inducibility of clinical VT was seen in only 12.5%.[155] Stimulation protocols used during electrophysiological testing and interpretation of test results are largely extrapolated from published data in other clinical substrates, mainly coronary artery disease and survivors of myocardial infarction. Induction of sustained, hemodynamically significant monomorphic VT is of greatest clinical significance, while initiation of polymorphic VT and/or VF may be nonspecific. Interpretation of electrophysiological study results and their predictive value for future arrhythmic events including sudden death ultimately falls to operator discretion.[124,125,128,129]

5.3. Bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

Recommendations for bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with EDMD or LGMD1B with an LVEF ≤35% despite guideline-directed medical therapy, with a combination of sinus rhythm, LBBB, QRS duration ≥150 ms, and NYHA class II to class IV symptoms, or in those with suspected right ventricular pacing–induced cardiomyopathy or anticipated right ventricular pacing ≥40%, CRT is recommended if concordant with the patient's goals of care and clinical status.**	84-88
1	C-EO	2. **In patients with EDMD or LGMD1B in whom pacing is indicated and ICD therapy is not concordant with the patient's goals of care and clinical status, a permanent pacemaker or, if appropriate, CRT-P implantation is recommended.**	

Synopsis

CRT has demonstrated clinical benefit in patients who have developed or are at risk for worsening heart failure due to intraventricular dyssynchrony despite maximally tolerated guideline-directed medical therapy.[14] Such benefits include improvement in symptoms due to heart failure, reduction in heart failure hospitalization, objective improvement in measures of ventricular function, and, possibly, reduced mortality.[84-88] Implantation of cardiac resynchronization therapy with defibrillator (CRT-D) in selected individuals may provide further mortality benefit.[8] Although there is a paucity of literature demonstrating the efficacy and outcomes in patients with EDMD and LGMD1B who have received a CRT-D, there are no compelling reasons to believe that such individuals would not receive the same benefit as others who meet criteria for resynchronization (Table 7, clinical scenario 3).

Recommendation-specific supportive text

1. EDMD and LGMD1B are commonly associated with dilated cardiomyopathy. There is a large evidence base

and clinical guidelines to support the use of CRT in terms of mortality benefit in patients with heart failure due to left ventricular systolic dysfunction taking guideline-directed medical therapy, LBBB with a wide QRS duration, or need for frequent pacing.[8,10,13] While benefit may be observed with QRS duration 120–150 ms, the clearest benefit is in patients with longer QRS durations (≥150 ms). Patients with EDMD and LGMD1B are not specifically addressed in these studies but by extrapolation may be appropriate candidates for CRT or CRT-D.[11,84-88,100] However, there are no prospective randomized trials in these patients.

2. Patients with EDMD and LGMD1B are susceptible to malignant AV conduction disturbances and may also demonstrate ventricular dysfunction. Given the progressive nature of cardiac disease, involvement of the cardiac conduction system resulting in bradycardia may precede development of cardiomyopathy and/or elevated risk of ventricular arrhythmias. While transvenous (or pacing-capable) ICD implantation will potentially address all arrhythmic issues, patient wishes and clinical circumstances may favor pacemaker over ICD implantation. Patients and families may be guided in making these decisions with the assistance of counseling and decision tools.[7,100,141,148,152,161-163]

5.4. Atrial arrhythmias in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

Recommendations for atrial arrhythmias in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with EDMD or LGMD1B, anticoagulation is recommended for AF or AFL, taking into consideration the risk of bleeding on oral anticoagulation.**	152
1	B-NR	2. **In patients with EDMD, anticoagulation is recommended for atrial standstill, taking into consideration the risk of bleeding on oral anticoagulation.**	152

Synopsis

Clinical practice guidelines are unequivocally supportive of anticoagulation for the prevention of thromboembolism in patients with AF or AFL, and risk stratification scores such as CHA_2DS_2-VASc have been developed to identify patients whose risk of stroke would be reduced by oral anticoagulants.[6] Patients with EDMD (especially EDMD1) and LGMD1B are at high risk of developing AF or AFL associated with atrial thinning and apoptosis.[95] One of the hallmarks of EDMD1 is atrial standstill,[143,164] which imparts a highly thrombogenic substrate given sluggish blood flow in the left atrium and left atrial appendage from the loss of effective atrial systole (akin to AF or AFL).[165] Atrial standstill, which is estimated to be present in 30% of patients with EDMD,[166] can develop at any time and may be clinically silent. Stroke is often the first presentation of EDMD, often at a young age.[167] The risk of stroke in these patients subsequent to AF or AFL is exceedingly high. With atrial standstill, anticoagulation should be initiated irrespective of the risk identified by traditional risk factors (eg, CHA_2DS_2-VASc) (Table 7, clinical scenario 1).

Recommendation-specific supportive text

1. In one small series of patients with genetically confirmed EDMD (aged 42.8 ± 9.6 years), 11 of 18 (61%) developed AF or AFL during 1- to 30-year follow-up, 7 had X-linked EDMD, and 4 had autosomal dominant EDMD with *LMNA* mutations.[152] Four patients (3 with *LMNA* mutations) with a history of permanent AF or AFL developed a stroke, and none were on anticoagulation prior to the event. In a separate series, AF with bradycardic ventricular response was observed in young adults several years prior to their being diagnosed with EDMD, underscoring the occurrence of cardiac involvement prior to manifest neurologic involvement and the need for heightened suspicion for NMD, particularly EDMD, in young patients with apparent lone AF.[135] Children with EDMD or LGMD1B who develop atrial arrhythmias present a special circumstance where evidence and experience with oral anticoagulants are lacking. Traditional algorithms including CHA_2DS_2-VASc and HAS-BLED, the latter to determine hemorrhagic risk, comprise several risk factors that are wholly absent in children. The decision to initiate anticoagulation in a child is based on clinician judgment incorporating their best assessment of a patient's thromboembolic and bleeding risks, patient and family preferences, and an understanding that evidence in this area is absent, largely due to the infrequency of this situation. A lower threshold to begin anticoagulation may be present in carefully selected children with EDMD or LGMD1B due to reports of stroke in younger

patients and the well-documented occurrence of atrial standstill.[152,167]

2. In the small series noted previously, with genetically confirmed EDMD, atrial standstill occurred in 5 of 18 patients after the development of paroxysmal AF or AFL.[152] Of the 4 patients who suffered a stroke, 2 had atrial standstill at the time of the event. Another series reported atrial standstill in 2 young adults (<40 years of age) who were ultimately diagnosed with EDMD associated with low-voltage electrograms with right atrial mapping and absence of right atrial capture with high-output pacing and noted during electrophysiological study.[135] Atrial standstill may therefore represent an end-stage manifestation following the natural progression of atrial arrhythmias in these patients due to underlying myocardial fibrosis and infiltration.[168] Though apparently uncommon in children, the relationship between atrial arrhythmias/atrial standstill and stroke underscores the importance of anticoagulation when these conditions are observed. While rare, children who develop AF or AFL or atrial standstill are appropriate candidates for oral anticoagulation when prescribed in conjunction with shared decision making. Finally, while experience and data are limited, the presence of atrial standstill may render left atrial appendage occlusion less effective in preventing thromboembolic complications. An illustrative case is presented in Table 7, clinical scenario 3.

5.5. Ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

Recommendations for ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in Emery-Dreifuss and limb-girdle type 1B muscular dystrophies

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with EDMD or LGMD1B in whom ICD therapy is planned, an ICD system with permanent pacing capability is recommended.**	141,148,161-163,169
1	B-NR	2. **In patients with EDMD or LGMD1B who are survivors of spontaneously occurring hemodynamically significant sustained VT or VF, ICD therapy is indicated if concordant with the patient's goals of care and clinical status.**	96,162,163
1	B-NR	3. **In patients with EDMD or LGMD1B with at least one of the following: second-degree or third-degree AV block, PR interval ≥230 ms, or spontaneous HV ≥70 ms, ICD therapy is recommended if concordant with the patient's goals of care and clinical status.**	141,148,161-163
1	B-NR	4. **In patients with EDMD or LGMD1B with an LVEF ≤35% despite guideline-directed medical therapy, ICD therapy is indicated if concordant with the patient's goals of care and clinical status.**	141,162
1	B-NR	5. **In patients with EDMD or LGMD1B in whom clinically relevant ventricular arrhythmias are induced during electrophysiological study, ICD therapy is recommended if concordant with the patient's goals of care and clinical status.**	124-126,141,155
2a	B-NR	6. **In patients with EDMD or LGMD1B with LVEF <45% and nonsustained VT, an ICD is reasonable if concordant with the patient's goals of care and clinical status.**	29,146
2a	C-LD	7. **In patients with EDMD or LGMD1B with at least one of the following: LBBB, right bundle branch block (RBBB), or AF or AFL with slow ventricular response (ventricular rate <50 bpm), ICD therapy is reasonable if concordant with the patient's goals of care and clinical status.**	141,148,161,163
2b	C-LD	8. **In patients with EDMD or LGMD1B with symptomatic sinus node dysfunction or sinus bradycardia with heart rate <40 bpm, ICD therapy may be considered if concordant with the patient's goals of care and clinical status.**	170,171

Synopsis

ECG and electrophysiological testing identify high-risk features suggesting the need for permanent pacing (ie, prolonged PR and HV intervals and advanced AV/infranodal block). When patients with EDMD or LGMD1B are candidates for a permanent pacemaker, they often receive a transvenous (or comparable pacing-capable) ICD system as an initial device (Table 7, clinical scenario

2). This is primarily due to the concomitant risk of sudden death. The data for device therapy for sinus node dysfunction are less clear. Subcutaneous ICDs are not an optimal choice for patients with EDMD or LGMD1B given the high likelihood of needing atrial/ventricular pacing or antitachycardia pacing. Similarly, CRT may prevent development or worsening of left ventricular dysfunction in circumstances when frequent ventricular pacing is anticipated (Figure 3).

Recommendation-specific supportive text

1. Patients with EDMD and LGMD1B are at high risk for potentially lethal ventricular tachyarrhythmia. However, they are at high risk for bradyarrhythmias as well. There is a significant body of evidence supporting implantation of a transvenous ICD when there is an indication for permanent pacing. While the subcutaneous ICD has a high efficacy for treating VT and VF,[172,173] when transvenous access is available, a subcutaneous ICD is a suboptimal choice given the high likelihood that pacing would be needed. Data are limited on subcutaneous ICDs in patients with NMDs, but the need for pacing for malignant bradyarrhythmias that may lead to sudden death and associated risk of bradycardia/pause-dependent VT or VF strongly favors transvenous ICD over subcutaneous ICD.[141,148,161,162] As noted above, a prospective cohort study showed that in lamin A/C patients, conduction system disease was significantly associated with the development of VT or VF.[163] EDMD and LGMD1B patients with other CRT criteria who develop left ventricular dysfunction can benefit from an upgrade to a CRT-D system (ie, upgrading from a preexisting transvenous ICD would avoid a de novo transvenous implant).[169]
2. As in the general population, patients with EDMD or LGMD1B who have experienced spontaneously occurring ventricular arrhythmias are at risk for recurrent VT or VF and sudden death.[96] This is further supported by the observation of appropriate, and at times recurrent, shock delivery in EDMD and LGMD1B patients with existing ICDs.[155,162,163] While limited published evidence exists, adjunctive therapies such as antiarrhythmic drugs and catheter ablation may also be required for further management of repeated VT/VF episodes.[155]
3. Patients with *LMNA* mutations are at high risk for AV block, supraventricular arrhythmias, and ventricular arrhythmias. One observational study of 41 patients with *LMNA* mutations (5 with LGMD1B and 4 with EDMD) explored ECG predictors associated with ventricular arrhythmias.[161] Of the 21 patients with ventricular arrhythmias, a PR interval $\geq$230 ms was able to robustly discriminate between those with and without ventricular arrhythmias, with both sensitivity and specificity of 87%. Eight patients with VT or VF uniformly had concomitant AV block with a markedly prolonged PR interval (310 $\pm$ 71 ms), and a high frequency of AF (5 of 8 [63%]).[161] Another study described the results of 8 of 10 patients with EDMD who underwent an electrophysiological study based on abnormalities on ECG and/or Holter monitoring.[148] A pacemaker was implanted in 3 patients, all of whom had prolonged HV intervals. None of the patients who were asymptomatic with normal or nonspecific ECG findings received a pacemaker.[148] One prospective series found that of 19 patients with *LMNA* mutations who received an ICD when referred for permanent pacemaker, 8 (42%) received appropriate shocks over a mean 34-month follow-up.[141] A prospective cohort study evaluated 47 patients for permanent pacemakers based on the presence of bradycardia, or PR interval $\geq$240 ms with either LBBB or nonsustained VT. Of 21 patients who received a prophylactic ICD in lieu of permanent pacemakers, 11 (52%) received appropriate ICD therapy during 62-month medical follow-up.[163] Nonsustained VT occurred in 8 of 10 patients who had no other evidence of malignant ventricular arrhythmia. Inappropriate shocks occurred in 7 of 21 (33%); none of the patients had sudden death. The presence of significant conduction disease (primarily second- or third-degree but also first-degree AV block and slowly conducted AF) was significantly correlated with the development of VT or VF. LBBB was predictive of sudden death only when seen in conjunction with first-degree AV block. Whether RBBB, bifascicular block, or isolated fascicular block is predictive of sudden death in the absence of any other conduction impairment is unknown and deserves further study, underscoring the limited data available in patients with these conditions. One case series of 15 patients with EDMD2 with known *LMNA* mutations reported 8 cases of sudden cardiac death, most in the context of left ventricular dysfunction and documented ventricular arrhythmias, 3 of which occurred after pacemaker implantation.[162] Finally, based on the evidence that catheter ablation of ventricular arrhythmias in patients with *LMNA* mutations may be of limited benefit,[155] ICDs are of special importance in this population.
4. Consistent with other recommendations from clinical practice guidelines,[8] patients with EDMD and LGMD1B are eligible to receive an ICD for the same indications as patients with nonischemic cardiomyopathy on guideline-directed medical therapy.[10,13,97,174] While specific randomized trials are lacking, one prospective series found that of 19 patients with *LMNA* mutations[141] who received an ICD when referred for permanent pacemaker, 8 (42%) received appropriate shocks over a mean 34-month follow-up. One case series of 15 patients[162] with

EDMD2 with known *LMNA* mutations reported 8 cases of sudden cardiac death, most in the context of left ventricular dysfunction and documented ventricular arrhythmias, 3 of which occurred after pacemaker implantation. Previously published studies indicated a benefit from primary prevention ICD implantation in patients with mild heart failure symptoms based on NYHA functional class. However, this classification scheme is less reliable in patients with neuromuscular impairment; hence, heart failure status is omitted from this recommendation.

5. Inducibility of clinically relevant ventricular arrhythmias, most notably monomorphic VT, is felt to have a predictive value of future arrhythmic risk in patients with EDMD or LGMD1B, even in light of limited evidence, by identifying individuals with an arrhythmogenic cardiac substrate that may lead to sudden death.[141,155] ICD implantation is the most effective means to prevent death in patients found to have elevated risk of ventricular arrhythmias.[124-126,128,129]
6. Two large cohort studies show that a mild decrease in left ventricular systolic function is a risk factor associated with ventricular arrhythmias and sudden cardiac death in patients with *LMNA* mutations.[29,146] In the largest of these studies, analysis included nonsustained VT on ambulatory monitoring, and this was found to be an independent risk factor associated with malignant ventricular arrhythmias.[29] The presence of both left ventricular systolic dysfunction and nonsustained VT was additive. The largest study used an LVEF cutoff of $<45\%$. Both studies also found that male sex and a non-missense *LMNA* mutation were independent risk factors. However, if either or both male sex and an *LMNA* non-missense mutation were not accompanied by left ventricular systolic dysfunction or nonsustained VT, no ventricular arrhythmia events occurred.[29] The recommendation is consistent with the *2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy*.[175] It is important to note that entry into these studies required only the presence of an *LMNA* mutation and not muscular dystrophy. Only 15%–20% of patients had a diagnosis or family history of muscular dystrophy. The presence of muscular dystrophy was not an independent risk factor for ventricular arrhythmias in these *LMNA* mutation carriers.
7. Objective markers of advanced AV conduction impairment such as prolonged PR interval and HV interval are clearly associated with sudden death and ventricular arrhythmias in patients with EDMD and LGMD1B.[161-163] A PR interval $\geq$240 ms in conjunction with LBBB was significantly associated with VT or VF in one series, though the effect of isolated LBBB remains unclear.[163] Along these lines, the implications of RBBB and bifascicular block have not been established. However, as these types of conduction delays are indicative of some level of AV conduction system involvement due to myocardial fibrosis, their occurrence, particularly in younger patients with EDMD or LGMD1B, is felt to be significant and associated with a degree of increased sudden death risk, either to malignant bradyarrhythmias or to VT and VF. These concerns are further amplified when considering the progressive nature of conduction disturbances in this population.[148] Similarly, AF and AFL are observed with increased frequency in EDMD and LGMD1B patients due to atrial thinning, myocyte apoptosis, and eventual fibrosis.[95,163] This same cascade of events is felt to result in damage to the AV conduction system and, later, ventricular myocytes.[161] The increased risk of sudden death in EDMD and LGMD1B is therefore extrapolated to those patients with slowly conducted atrial arrhythmias. As described before, patients with EDMD or LGMD1B demonstrating findings suggestive of AV conduction system impairment are more suited to ICD implantation, as pacemaker implantation appears to offer incomplete protection in preventing sudden death.[141,148,161,163]
8. One case report describes an asymptomatic 27-year-old man who received a prophylactic pacemaker due to PR interval $\geq$240 ms, incomplete RBBB, and left anterior fascicular block.[170] The electrophysiological study showed an HV interval of 60 ms and normal sinus node recovery time. The number of bradycardia episodes with sinus pauses on pacer interrogation increased from 6 at the beginning to 39 at the end of the 3-year observation.[170] Another case report describes the follow-up study of a boy who underwent pacemaker implantation for PR interval prolongation and sick sinus syndrome at 9 years of age and who ultimately died of heart failure at age 26 years.[171] Difficulty in achieving successful atrial pacing may be observed owing to significant atrial scarring and associated standstill, or even previously undetected "fine" AF.[168]

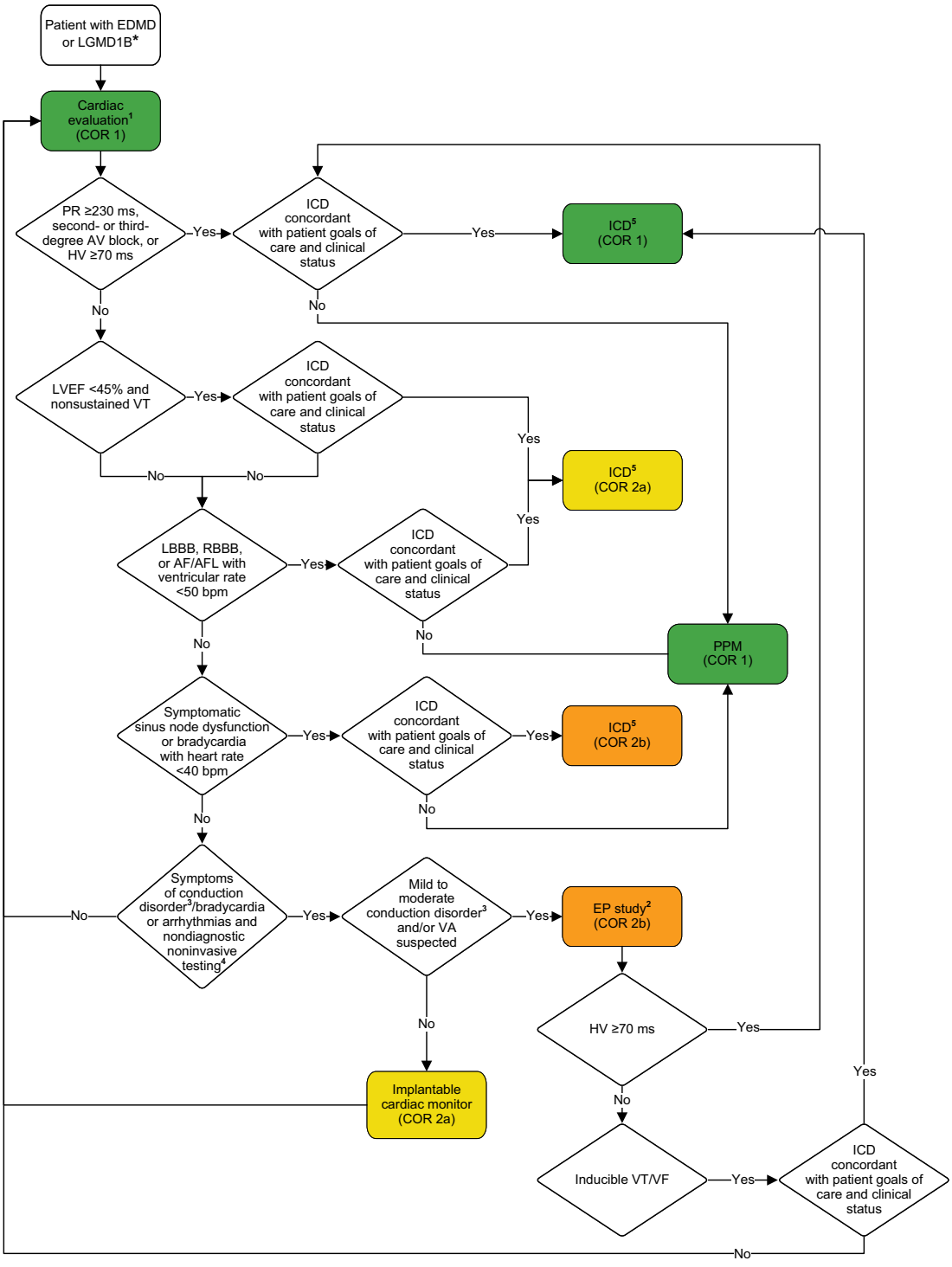

Figure 3 Flowchart for rhythm management and cardiovascular implantable electronic device implantation in patients with Emery-Dreifuss muscular dystrophy (EDMD) or limb-girdle muscular dystrophy type 1B (LGMD1B). *Patients with indications for pacemaker or implantable cardioverter-defibrillator (ICD) implantation, including cardiac resynchronization therapy, based on recommendations from previously published guidelines are not represented in this flow diagram. [1]Physical examination, electrocardiogram (ECG), ambulatory ECG, and cardiac imaging (echocardiography or cardiac magnetic resonance imaging) at diagnosis with periodic retesting. [2]The purpose of electrophysiological (EP) testing is to assess the integrity of atrioventricular (AV) conduction, in particular the His–Purkinje system and HV interval, and inducibility of clinically significant ventricular arrhythmias. The discussion of device implantation should be carried out prior to electrophysiological testing to confirm a patient's preference, desire, and willingness to undergo implantation. [3]Mild to moderate conduction disorder is defined as PR interval 200–230 ms and/or QRS duration 100–120 ms. [4]Noninvasive testing includes 12-lead ECG, telemetry recordings, ambulatory ECG, or implantable loop recorder. [5]ICD system with permanent pacing capability. Colors correspond to the class of recommendation (COR) in Table 1. AF = atrial fibrillation; AFL = atrial flutter; bpm = beats per minute; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; PPM = permanent pacemaker; RBBB = right bundle branch block; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 7 Clinical scenarios for the management of arrhythmias in Emery-Dreifuss muscular dystrophy and limb-girdle muscular dystrophy type 1B

Clinical scenario	Management strategies	Key points
EDMD		
1. A 25-year-old man presents with left upper extremity weakness and difficulty speaking. The neurological findings resolve spontaneously in the emergency department over a period of 1 hour. The patient has a history of elbow and ankle contractures since childhood and a presumptive diagnosis of EDMD. There are no other family members with a similar phenotype. ECG reveals sinus bradycardia, low-amplitude P waves, a PR interval of 260 ms, and nonspecific intraventricular conduction delay with a QRS duration of 110 ms. Transthoracic echocardiogram reveals biatrial dilation, left ventricle chamber size at the upper limits of normal, moderate mitral and tricuspid regurgitation, and an LVEF of 55%.	• Acute management included brain magnetic resonance imaging and computed tomography to evaluate the presumptive transient ischemic attack; empiric anticoagulation was initiated, as intracerebral hemorrhage and other contraindications were absent. • Cardiac magnetic resonance imaging and electrophysiological testing with programmed ventricular stimulation were performed to assess myocardial involvement and conduction system disease, and to determine ventricular arrhythmic risk. The patient may be a candidate for a primary prevention ICD with pacing capability, if significant conduction disease or ventricular arrhythmias are observed. • Because the patient was young and otherwise functional with presumptive transient ischemic attack, long-term management included anticoagulation, in the absence of contraindications, with periodic assessment of left ventricular function and surveillance for brady- or tachyarrhythmias.	• EDMD is associated with chamber dilation, especially atrial. • AF and atrial standstill with an increased risk of thromboembolic complications including stroke in EDMD are well known. • Low-normal LVEF with AV valve incompetence may reflect mild left ventricular dysfunction in this context. • A directed assessment of arrhythmic risk is warranted in this patient population based on presenting symptoms, physical findings, and clinical index of suspicion for serious rhythm disturbances.
2. A 64-year-old man with EDMD2 presents to the clinic to discuss ICD generator change. He was diagnosed with EDMD2 when he was 25 years old, after developing elbow and Achilles joint contractures and progressive humeroperoneal muscle weakness. Genetic testing confirmed an *LMNA* mutation (1q21-q23 locus). He underwent implantation of a dual-chamber ICD 15 years ago after developing significant symptomatic bradycardia in the setting of high-grade AV block. He has never had shocks from his device. His interrogation reveals normal device function and stable lead parameters. His ventricular pacing frequency is $<0.1\%$. His ICD is now at elective replacement indicator, and generator change is scheduled in 1 month. His neuromuscular symptoms have been progressively worsening, and he expresses reluctance to have his generator replaced.	• Management options discussed centered on the risks and benefits of the generator exchange procedure and the alternatives to not having generator change. • EDMD2 puts him at high risk for the development of potentially lethal ventricular tachyarrhythmias. • The patient had not had any shocks, and his pacing requirements were minimal. • Discussion of his reluctance for ICD generator exchange centered on the risk and on the risks and benefits of the procedure and the alternatives to not having generator change. • ICD generator change was ultimately deferred based on shared decision making.	• Patients with EDMD2 are at high risk for the development of potentially lethal ventricular tachyarrhythmias. • Patients with NMDs who have implantable devices need to be counseled about the need for device and long-term maintenance prior to implantation. • Eliciting the patient's overall medical care goals and preferences with consideration of the individual's neuromuscular prognosis is recommended when the option of discontinuing device therapy is present. • Generator change presents an opportunity to discuss goals of care and patient preferences including their desire to downgrade or avoid CIED therapy.

(*Continued*)

Table 7 (*Continued*)

Clinical scenario	Management strategies	Key points
3. A 12-year-old boy with EDMD, whose father required transplant due to EDMD-related cardiomyopathy, presented with frequent episodes of nonsustained atrial tachycardia at 10 years of age. His arrhythmia burden was ~14% with a maximum rate of 241 bpm. At that time, his LVEF was normal and his baseline ECG demonstrated a PR interval of 202 ms and a QRS duration of 92 ms. Despite medical therapy, he developed incessant atrial tachycardia with periods of brady cardia due to variable AV conduc-tion. He underwent an electrophysiology study at 12 years of age. He was found to have diffuse scarring of both atria. He had multiple arrhythmia circuits. His HV interval was 50 ms in tachycardia. Control of the atrial tachycardia was not achieved with ablation attempts. Subsequent ambulatory monitoring demonstrated periods of high-grade AV block with pauses up to 3 seconds with continued underlying atrial tachycardia.	• Management options discussed included anticoagulation and device placement (ICD versus pacemaker) due to AV block. • Continued cardiovascular medical therapy was recommended regardless of arrhythmia management strategy due to risk of cardiomyopathy. • Values elicited in discussion included options to preserve quality of life and desire for protection against stroke and sudden cardiac death. • Therapy with warfarin was begun with plans for ICD placement. • Upon arrival for ICD placement, the patient was in complete AV block. ICD implantation was successfully performed.	• Due to lack of representation of pediatric patients with NMDs in previously published trials of anticoagulation for atrial arrhythmias and single-chamber ICD placement, extrapolation of data from adults was required in conjunction with clinical decision making. • Family history of progression of EDMD to cardiomyopathy requiring transplant at 17 years of age was factored into decision making. • Anticoagulation is warranted due to scarred atria with incessant arrhythmia and poor atrial transport as a nidus for thrombus. • As direct oral anticoagulants are not approved for use in children, warfarin was prescribed.
LGMD1B		
4. A 42-year-old woman is admitted after a transient episode of sudden loss of consciousness. She has a history of ankle contractures since adolescence. Over the past 5 years, she has developed progres sive muscle weakness with difficulty climbing stairs. She had an older sister with similar muscular disease and heart disease who died at age 38 years after complications of a stroke. Genetic testing revealed a missense mutation in *LMNA*. Her ECG revealed sinus tachycardia with a PR interval of 300 ms, incomplete RBBB, and left axis deviation. Transthora cic echocardiogram revealed left ventricle dilation with reduced function and an estimated LVEF of 40%. Ambulatory ECG recording revealed atrial tachycardia with 3:1 and 4:1 conduction.	• Management options discussed included an aggressive evaluation of syncope and consideration of ICD implantation because of the patient's cardiac involvement—both conduction system disease and dilated cardiomyopathy—in the setting of LGMD1B. • Values elicited included patient preference for pacemaker over ICD. • She was treated with hydralazine, beta-blockers, and diuretics. After discussion with the patient and her family, a CRT-P pacemaker was placed.	• Syncope in this context is a serious symptom and mandates aggressive evaluation. • Dilated cardiomyopathy in this context requires treatment of left ventricular dysfunction and heart failure. • Biventricular pacing is used if the burden of ventricular pacing is expected to be significant. • Shared decision making is important in consideration of the type of device to be implanted.
5. A 35-year-old man with LGMD1B presents to the clinic to discuss the possibility of pacemaker placement. He was suspected to have LGMD1B when he was 15 years old, after developing proximal muscle weakness, in the absence of contractures. Genetic testing confirmed an *LMNA* mutation (1q11-21 locus). Since that time, he has had progressive lightheadedness. His 12-lead ECG and recent Holter monitoring are normal, and transthoracic echocardiography was unremarkable.	• Management options discussed included periodic assessment for brady- or tachyarrhythmias and the high risk of conduction disease and sudden death associated with LGMD1B that could require device implantation. • The absence of documented abnormalities on ECG and especially symptom-rhythm correlation on ambulatory monitoring supported avoiding empiric CRM device implantation in favor of long-term cardiac rhythm monitoring.	• Patients with LGMD1B are at high risk for both conduction disease and sudden death. • Symptoms are often the main driver of long-term monitoring, in the absence of arrhythmia or high-risk features on ECG or ambulatory ECG monitoring. • PR interval $\geq$240 ms and LBBB or fascicular block are known to be risk factors for future need for pacemaker or ICD. • Electrophysiological testing can be employed for patients where there is high suspicion of conduction disease, with consideration of programmed ventricular stimulation.

AF = atrial fibrillation; AV = atrioventricular; bpm = beats per minute; CIED = cardiovascular implantable electronic device; CRM = cardiac rhythm management; CRT-P = cardiac resynchronization therapy with pacemaker; ECG = electrocardiogram; EDMD = Emery-Dreifuss muscular dystrophy; EDMD2 = Emery-Dreifuss muscular dystrophy type 2; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LGMD1B = limb-girdle muscular dystrophy type 1B; LVEF = left ventricular ejection fraction; NMD = neuromuscular disorder.

Section 6 Facioscapulohumeral muscular dystrophy

6.1. General principles for facioscapulohumeral muscular dystrophy

FSHD is the third most common muscular dystrophy, with a prevalence of 1:15,000–1:20,000 using a diagnosis based on clinical phenotype with genetic confirmation.[33] FSHD is characterized by an initial regional distribution of weakness involving facial, periscapular, and humeral muscles. FSHD symptoms typically develop in the second decade of life but can begin at any age from infancy to late adulthood. FSHD typically progresses slowly. About 20% of individuals become wheelchair dependent after 50 years of age. Respiratory compromise may occur. Life expectancy is not reduced.

Two genetically distinct but clinically indistinguishable forms of FSHD occur. More than 95% of patients have FSHD type 1 (FSHD1), characterized by contraction of D4Z4 repeats on the long arm of chromosome 4. Patients with fewer D4Z4 repeats have a more severe phenotype, including earlier symptom onset. FSHD1 is inherited as autosomal dominant, but up to 30% of cases are sporadic. A minority of patients have FSHD type 2 (FSHD2), caused by a combined heterozygous mutation in the *SMCHD1* gene on the short arm of chromosome 18 and a permissive double homeobox 4 (*DUX4*) allele on chromosome 4. FSHD2 is inherited in a digenic fashion. Both FSHD1 and FSHD2 have a common downstream mechanism resulting in hypomethylation in the D4Z4 region and transcriptional de-repression of DUX4 in muscle, believed to cause disease through a toxic gain-of-function mechanism.[176]

Compared to many of the other muscular dystrophies, significant cardiac involvement in FSHD is rare. It has not been proven that cardiac findings in patients with FSHD are attributable to the pathophysiology of the disease. FSHD is included in the consensus document because it is a common muscular dystrophy and cardiologists or electrophysiologists might be asked to evaluate the FSHD patient. Patients with FSHD can be older, and cardiac disease may be present due to other causes. The recommendation provided addresses baseline diagnostic testing in these patients. Guidelines apply to FSHD patients as in any general population in the diagnosis and management of cardiac arrhythmias.

6.2. Diagnostic testing and risk stratification in facioscapulohumeral muscular dystrophy

Recommendations for diagnostic testing and risk stratification in facioscapulohumeral muscular dystrophy

COR	LOE	Recommendations	References
2a	B-NR	1. **In patients with FSHD, cardiac evaluation including examination, ECG, ambulatory ECG, and cardiac imaging (echocardiography or CMR) at diagnosis with periodic retesting are reasonable even in the absence of cardiac symptoms.**	177-183

Synopsis

There are only a moderate number of cardiac studies in patients with FSHD. The studies showed mild to moderate ECG abnormalities in about one-half of patients, most commonly the presence or development of incomplete or complete RBBB. In general, the ECG changes were not associated with progressive conduction system disease or the development of structural cardiomyopathy over a moderate duration of follow-up.[179,180] In a series of 100 FSHD patients, 1 patient was observed to develop symptomatic high-grade AV block.[177] The presence of symptomatic supraventricular tachycardia associated with palpitations has been noted. In a series of 83 patients, there was evidence for arrhythmias (primarily supraventricular tachycardia) in 12% of patients with FSHD, half of whom experienced palpitations. Whether the ECG changes and arrhythmias are more common than in an age-matched general population has not been determined. Genetic testing and counseling may be used for diagnostic and screening purposes, as described in Section 2.2.

Recommendation-specific supportive text

1. The limited literature notes a moderate prevalence of ECG abnormalities and possibly arrhythmias, and baseline cardiac evaluation in FSHD is reasonable. The diagnostic yield of echocardiography may be low in asymptomatic FSHD patients. There are indications that CMR may provide useful information about myocardial involvement.[183] Whether the abnormalities detected are clinically relevant is uncertain. In the absence of cardiovascular symptoms or other findings, the value of serial cardiovascular testing in FSHD is likely limited. Until new evidence suggests otherwise, a directed evaluation at the clinician's discretion is appropriate.[179,180]

Section 7 Mitochondrial myopathies including Friedreich ataxia

7.1. General principles for mitochondrial myopathies including Friedreich ataxia

7.1.1. Mitochondrial myopathies

Mitochondrial myopathies, encephalomyopathies, and respiratory chain disorders are a group of diseases resulting from abnormalities in mitochondrial DNA or nuclear DNA involved in mitochondrial function.[36] Mitochondrial myopathies can be inherited maternally or autosomally. Tissue with a high respiratory workload, including brain, skeletal muscle, extraocular muscle, retinal, and cardiac muscle, is primarily affected.

Mitochondrial disorders that have cardiac and arrhythmia manifestations include several clinical phenotypes.[37,184] Chronic progressive external ophthalmoplegia is characterized by involvement of the extraocular and oropharyngeal muscles. Kearns-Sayre syndrome, a subtype of chronic progressive external ophthalmoplegia, is characterized by ocular myopathy, pigmentary retinopathy, and onset before age 20 years. Cardiac involvement, when observed, is typically characterized by advanced, distal AV conduction impairment, with heart failure and sudden death also being reported.[184] Myoclonus epilepsy with red ragged fibers (MERRF) is characterized by myoclonus, seizures, ataxia, dementia, and skeletal muscle weakness. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is the most common form of the maternally inherited mitochondrial disorders. MERRF and MELAS are typically associated with hypertrophic (symmetric or asymmetric) cardiomyopathy, but dilated cardiomyopathy and rarely arrhythmogenic histiocytoid cardiomyopathy have been observed. Preexcitation can be observed in MELAS. Leber hereditary optic neuropathy causes subacute blindness, primarily in young men. It can be associated with hypertrophic cardiomyopathy and a short PR interval or preexcitation syndromes. Other mitochondrial point mutation disorders including NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa) and Leigh syndrome (subacute necrotizing encephalomyelopathy) cause neurodegenerative disorders primarily in children. Point mutations are associated with hypertrophic or dilated cardiomyopathy, often in children. Barth syndrome is a rare X-linked recessive mitochondrial disease manifested by hypotonia, growth retardation, cyclic neutropenia, and 3-methylglutaconic aciduria in children. It is associated with left ventricular noncompaction and endocardial fibroelastosis or hypertrophic or dilated cardiomyopathy. Heart failure and ventricular arrhythmias occur, often in young children.[185,186]

7.1.2. Friedreich ataxia

FA is grouped with mitochondrial myopathies due to their shared mitochondrial pathology. FA is the most common form of inherited ataxia and is due to a GAA triplet repeat expansion in intron 1 of the frataxin gene that is inherited as an autosomal recessive trait.[187] A minority of FA patients have a different mutation on the other frataxin allele (compound heterozygous) in addition to a GAA expansion.[188] The normal GAA repeat size is <30 repeats, but affected individuals typically have a repeat size ≥ 70. The genetic defect encoding frataxin leads to deficiency in the synthesis of iron–sulfur clusters and subsequent mitochondrial iron accumulation and free radical accumulation.[189] The severity of the clinical manifestations in FA has been correlated with the smaller of the 2 expanded GAA repeats.[34,190] Clinical manifestations include progressive cerebellar dysfunction, scoliosis, diabetes mellitus, impaired speech, and loss of vision and hearing. Cardiac manifestations are found in the majority of FA patients and include left ventricular hypertrophy that can progress to heart failure with reduced ejection fraction. Associated arrhythmias occur in $>50\%$ of FA patients, predominantly in those with structural cardiac abnormalities.

7.2. Diagnostic testing and risk stratification in mitochondrial myopathies including Friedreich ataxia

Recommendations for diagnostic testing and risk stratification in mitochondrial myopathies including Friedreich ataxia

COR	LOE	Recommendations	References
1	B-NR	1. **Coordinated care of patients with mitochondrial myopathies including FA should be conducted in a medical setting where there is access to expertise in the neurological, cardiac, arrhythmic, pulmonary, and genetic manifestations of these disorders.**	34,184
1	B-NR	2. **In patients with mitochondrial myopathies including FA, cardiac evaluation including examination, ECG, ambulatory ECG, and cardiac imaging (echocardiography or CMR) at diagnosis with periodic retesting is recommended even in the absence of cardiac symptoms.**	34,184

Synopsis

Given the often silent and progressive nature of cardiac involvement, screening ECGs and echocardiography can identify subclinical cardiac involvement and patients at risk for cardiovascular events, regardless of neurological status. Serial testing may have additive value when changes in symptomatology are observed.[34] Screening ambulatory ECG monitoring may provide further

information even in asymptomatic patients, particularly in those demonstrating ECG changes. Serious arrhythmias may develop unpredictably in previously asymptomatic individuals and are a cause of death in mitochondrial myopathy and FA patients.[9] CMR is a useful means of detecting early cardiac fibrosis. CMR-derived T2* relaxation time can be employed to quantitate iron overload in FA; however, not all patients have access to CMR.[35,191] Arrhythmias are observed in FA patients with ventricular hypertrophy and are attributed as a cause of death in ~10% of FA patients, but are less common than in other genetic causes of hypertrophic cardiomyopathy.[192] Patients with decreased left ventricular systolic function (LVEF ≤35%) are at higher risk of sudden death.[91,97] Ventricular arrhythmias have been described in patients with normal left ventricular function, underscoring the need for monitoring in patients who present with palpitations, syncope, or other symptoms suggestive of arrhythmias, with careful screening in asymptomatic patients (Figure 4).[193] AF has also been found to be common as cardiac disease progresses.[6,12] An increased prevalence of ECG preexcitation has been reported in mitochondrial disorders, especially in MELAS, but is rarely associated with symptomatic arrhythmias.[37,194,195] The principles of genetic evaluation of the mitochondrial disorders may be complex and are further discussed in Section 2.2.

Recommendation-specific supportive text

1. Centers with multidisciplinary specialty experience in managing patients with NMDs are best equipped to manage mitochondrial myopathies and FA patients, including those with pulmonary/respiratory and documented or suspected cardiac involvement. Patients with mitochondrial myopathies and FA might not have cardiac symptoms even with significant cardiac involvement due to physical limitations from their underlying NMD. Cardiac disease does not correlate with the degree of skeletal muscle disease in these populations. Patients with mitochondrial myopathies may have unique sensitivity to anesthesia, especially volatile anesthetics.[196] Therefore, a multidisciplinary approach involving neurology, cardiology, and other knowledgeable consultants is desirable from the onset of disease diagnosis.[34,184]
2. In mitochondrial myopathies, the rate of progression of cardiac disease does not correlate with the severity of peripheral muscular disease, and cardiac involvement can be mildly symptomatic or asymptomatic. A high index of suspicion is required whenever patients describe or present with even mild arrhythmia symptoms or findings. The nature and frequency of surveillance monitoring is at the discretion of the treating provider, as no studies have clearly demonstrated the best diagnostic strategy, particularly in asymptomatic individuals.[34,184]

7.3. Bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in mitochondrial myopathies including Friedreich ataxia

Recommendations for bradycardias, conduction disorders, and use of pacing or cardiac resynchronization therapy in mitochondrial myopathies including Friedreich ataxia

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with mitochondrial myopathies including FA and documented symptomatic bradycardia due to sinus node dysfunction or any degree of AV block, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.**	79,80,82,197-199
1	B-NR	2. **In patients with mitochondrial myopathies including FA and third-degree or advanced second-degree AV block at any anatomical level, with or without symptoms, permanent pacemaker implantation is indicated if concordant with the patient's goals of care and clinical status.**	79,80,184
2a	B-NR	3. **In patients with FA with an LVEF ≤35% despite guideline-directed medical therapy, with a combination of sinus rhythm, LBBB, QRS duration ≥150 ms, and NYHA class II to class IV symptoms, or in those with suspected right ventricular pacing–induced cardiomyopathy or anticipated right ventricular pacing ≥40%, CRT is reasonable if concordant with the patient's goals of care and clinical status.**	84-88,200
2a	B-NR	4. **In patients with mitochondrial myopathies including FA with progressive ECG conduction disorder including any degree of AV or fascicular block, permanent pacemaker implantation is reasonable if concordant with the patient's goals of care and clinical status.**	184,197-199

Synopsis

In chronic progressive external ophthalmoplegia, most commonly in the Kearns-Sayre syndrome variant, cardiac involvement manifests primarily as conduction abnormalities including sinus node dysfunction and progressive AV block.[184,197-199,201-203] In Kearns-Sayre syndrome, AV block is observed usually after the onset of eye involvement. The HV interval is prolonged, consistent with distal conduction disease. Advanced conduction impairment can be observed in asymptomatic individuals. Other mitochondrial disorders generally have a lower risk of conduction disease. Conduction disease with progression to complete heart block is not common in FA, although when seen, it is generally accompanied by progression of left ventricular hypertrophy or the onset of dilated cardiomyopathy. An algorithm to guide rhythm management and pacemaker implantation in patients with mitochondrial disorders including FA is shown in Figure 4.

Recommendation-specific supportive text

1. The development of bradycardia symptoms in patients with mitochondrial myopathies may serve as a sentinel event, signaling the development of potentially life-threatening bradycardia. Those with mitochondrial myopathies are much more susceptible to developing symptomatic AV (particularly infranodal) conduction disturbances rather than sinoatrial node dysfunction, with the former generally being considered more severe and associated with progression.[184,197,199,203] Discovery of significant bradycardia following the onset of mild or transient symptoms, particularly that due to AV block, may therefore provide a critical opportunity to offer early pacemaker implantation to a patient with mitochondrial myopathy, possibly avoiding the occurrence of more serious symptoms and even death from evolution to advanced persistent AV block.
2. Patients with mitochondrial myopathies or FA are known to develop symptomatic bradycardia most seriously due to advanced, distal conduction disease. Pacemaker implantation may not only lead to symptomatic improvement but may provide prognostic benefit.[184,197-199,201-203]
3. CRT has not been specifically studied in mitochondrial myopathies or FA, although evidence derived from the CRT literature has been extrapolated to these conditions with appropriate cardiovascular substrate, clinical features, and guideline-directed medical therapy.[10,13,84,85,200] Competing comorbidities can limit the functional benefit of resynchronization. A QRS duration of $\geq$150 ms is where the greatest benefit is expected. In these mitochondrial disorders, especially FA, judging the severity of heart failure class can be difficult due to the underlying neuromuscular limitations. Many patients are nonambulatory, and that status cannot aid in assessing heart failure class.
4. Advanced distal conduction disease may occur in mitochondrial diseases, especially Kearns-Sayre syndrome, and can be observed without premonitory symptoms. Progressive AV conduction impairment may lead to bradycardia, asystole, and sudden death in an unpredictable manner. Aside from traditional ECG findings, no additional clinical features or markers have been discovered to improve risk stratification in affected individuals. The severity of conduction disease at which pacing should be instituted is not clear but should reflect a significant burden or progression of impairment.[184,197-199,201-203]

7.4. Atrial arrhythmias in mitochondrial myopathies including Friedreich ataxia

Recommendations for atrial arrhythmias in mitochondrial myopathies including Friedreich ataxia

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with mitochondrial myopathies including FA, anticoagulation according to established guidelines and clinical context is recommended for AF or AFL, taking into consideration the risks of thromboembolism and the risks of bleeding on oral anticoagulation.**	92-94

Synopsis

AF has been observed in patients with mitochondrial disorders primarily in chronic progressive external ophthalmoplegias and FA, and its presence may signify progression of underlying structural cardiac involvement.[95] Atrial arrhythmias are more common in FA patients who have ventricular hypertrophy.[9] However, no studies specifically examining the risk of thromboembolic events complicating AF in mitochondrial disorders or FA are available, and existing guidelines and evidence are therefore referenced.[6,93]

Recommendation-specific supportive text

1. The CHA_2DS_2-VASc risk score has been shown to apply across a wide range of AF patients to decrease the risk of stroke. Indicators of bleeding risk with anticoagulation are also applicable with the knowledge that those with neuromuscular impairment may be at heightened risk of fall-related bleeding complications.[92-94] Accordingly, the clinical context in which this decision arises must also be considered, factoring in items such as patient age, dosing

of anticoagulants particularly in children, patient frailty, and limitations in thromboembolic and bleeding risk assessment in patients not well represented in studies where these criteria were determined. Children with mitochondrial myopathies including FA who develop atrial arrhythmias present a special circumstance where evidence and experience with oral anticoagulants are lacking. Traditional algorithms including CHA_2DS_2-VASc and HAS-BLED, the latter to determine hemorrhagic risk, comprise several risk factors that are wholly absent in children. The decision to initiate anticoagulation in a child is based on clinician judgment incorporating their best assessment of a patient's thromboembolic and bleeding risks, patient and family preferences, and an understanding that evidence in this area is absent, largely due to the infrequency of this situation.

7.5. Ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in mitochondrial myopathies including Friedreich ataxia

Recommendations for ventricular arrhythmias, sudden cardiac death, and use of implantable cardioverter-defibrillators in mitochondrial myopathies including Friedreich ataxia

COR	LOE	Recommendations	References
1	B-NR	1. **In patients with mitochondrial myopathies including FA with spontaneously occurring VF or sustained hemodynamically significant VT, ICD therapy is indicated if concordant with the patient's goals of care and clinical status.**	96,204,205
2a	B-NR	2. **In patients with mitochondrial myopathies including FA with an LVEF ≤35% despite guideline-directed medical therapy, ICD therapy is reasonable if concordant with the patient's goals of care and clinical status.**	97

Synopsis

Premature ventricular contractions and nonsustained VT have been observed in a small percentage of patients with mitochondrial disorders. Sudden death of unknown cause is responsible for 6% of deaths (1.5 sudden deaths per 1,000 person-years) in a middle-aged population with genetically verified mitochondrial diseases.[184] Although placement of an ICD in a single patient with Kearns-Sayre syndrome presenting with wide complex tachycardia who was noninducible during electrophysiological study has been reported, larger studies evaluating the benefit of primary and secondary prevention ICDs in mitochondrial myopathies are absent.[203] Premature ventricular complexes, distal conduction disease, left ventricular hypertrophy on echocardiography, and diabetes have been found to be independent risk factors for nonarrhythmic and arrhythmic cardiac events. The risk of ventricular arrhythmias and sudden death in patients with cardiac conduction disturbances treated with pacemakers appears to be low.[184]

Patients with FA typically have an underlying substrate of hypertrophic cardiomyopathy.[192] Systolic dysfunction is less common but can be observed. Ventricular arrhythmias and decreased left ventricular systolic function (LVEF ≤35%) are associated with an elevated risk of sudden cardiac death[91,97] A diagram to facilitate ICD decision making in patients with mitochondrial myopathies and FA is provided in Figure 4. A case scenario for a patient with FA is outlined in Table 8.

Recommendation-specific supportive text

1. Patients with underlying cardiac disease who develop spontaneous sustained ventricular arrhythmias have an increased risk of subsequent sudden death, and ICD implantation has a demonstrated survival benefit.[96,204,205] It is acknowledged that no studies specific to FA or mitochondrial myopathy patients have been published demonstrating survival benefit from primary or secondary prevention ICDs. Results and conclusions from device trials are extrapolated to these conditions. Although the majority of evidence proving this benefit is derived from patients with ischemic cardiomyopathy, published studies enrolled a modest proportion of subjects with nonischemic cardiomyopathy.
2. The risk of sustained ventricular arrhythmias resulting in sudden death is increased with the development of ventricular dysfunction in FA patients. While left ventricular dysfunction is less common in other mitochondrial myopathies, a higher risk of ventricular arrhythmias would be expected with its development, as seen in other substrates. Therefore, existing criteria

for primary prevention ICD implantation are appropriate in patients with either FA or mitochondrial myopathy who develop cardiomyopathy with LVEF ≤35% in the setting of guideline-directed medical therapy. Furthermore, previously published studies indicate a benefit from primary prevention ICD implantation in patients with heart failure symptoms based on NYHA functional class. However, assessment of NYHA functional class is typically less reliable in patients with neuromuscular impairment; hence, heart failure status is omitted from this recommendation. Similarly, the potential limitations of benefits due to competing comorbidities have led to assigning primary prevention ICD implantation a 2a COR.[10,13,97]

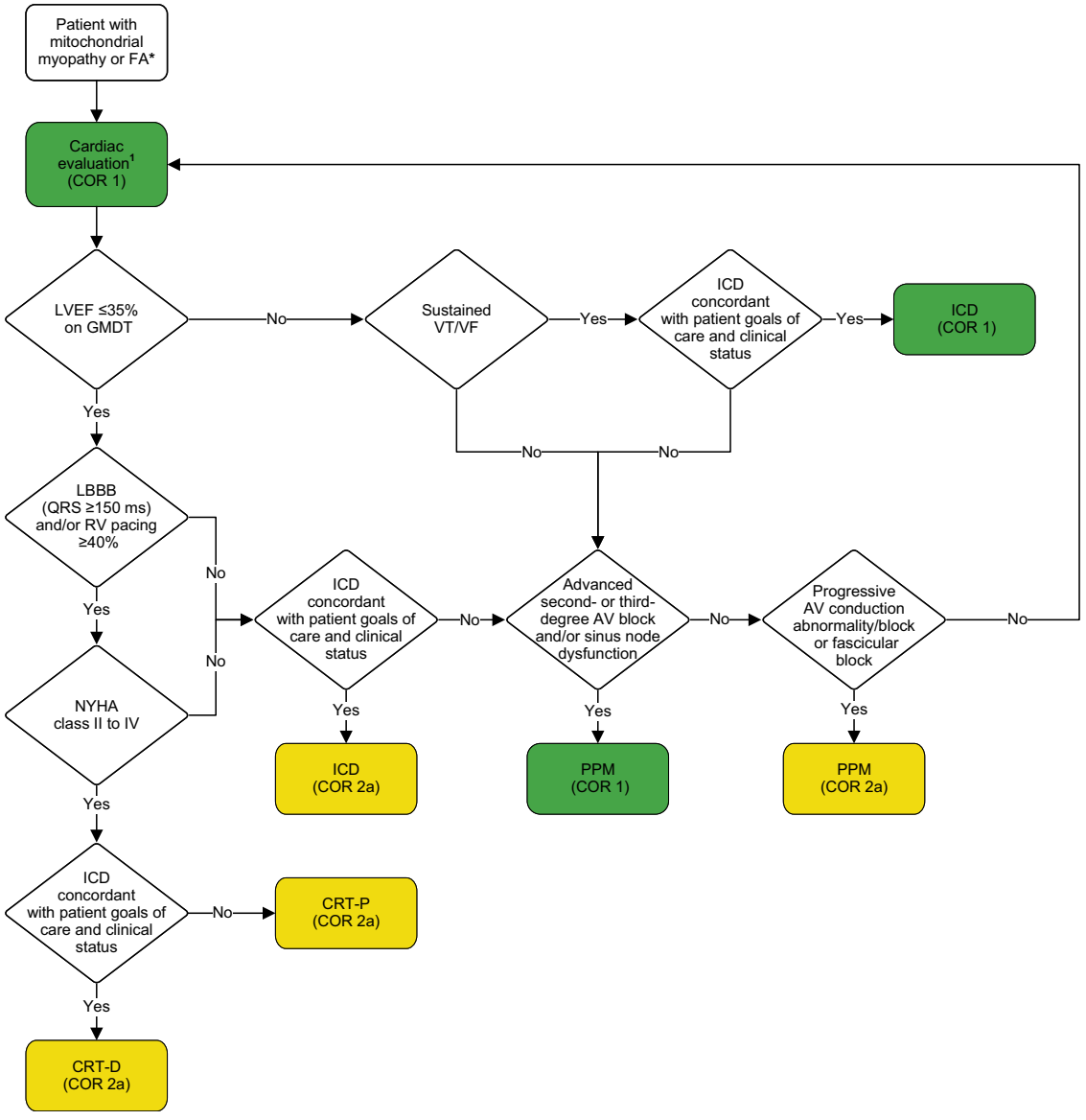

Figure 4 Flowchart for rhythm management and cardiovascular implantable electronic device implantation in patients with mitochondrial myopathies including Friedreich ataxia (FA). *Some patients with indications for pacemaker implantation or secondary prevention implantable cardioverter-defibrillator (ICD) based on recommendations from previously published guidelines may not be represented in this flow diagram. [1]Physical examination, electrocardiogram, ambulatory electrocardiogram, and cardiac imaging (echocardiography or cardiac magnetic resonance imaging) at diagnosis with periodic retesting. Colors correspond to the class of recommendation (COR) in Table 1. AV = atrioventricular; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; GDMT = guideline-directed medical therapy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PPM = permanent pacemaker; RV = right ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 8 Clinical scenarios for management of patients with Friedreich ataxia

Clinical scenario	Management strategies	Key points
A 30-year-old man with FA is referred for consideration of primary prevention ICD from general cardiology. FA diagnosis occurred at age 15 years with the slow progression of skeletal muscle weakness until the patient became nonambulatory at age 25 years. Echocardiogram at age 25 years showed concentric hypertrophy. Echocardiogram 10 months before the current visit showed dilated cardiomyopathy with calculated ejection fraction 32%. The patient was initiated on GDMT. Repeat echocardiography at 4 months before the current visit showed no improvement in LVEF. The patient remained asymptomatic from a cardiac standpoint. He is independent, lives alone with a service dog, and is employed as a clerk at a medical facility. He has ongoing family support.	• The consensus from neurology, general cardiology, and pulmonary medicine was that the patient is currently stable with reasonable prognosis at least for the next several years. • A discussion with the patient and his accompanying father was held to review the risks and benefits of a primary prevention ICD in FA. The risk of sudden cardiac death was discussed and shared decision making was carried out to elicit the medical care goals. • Options discussed included ongoing heart failure therapy with or without ICD placement. • Values elicited included the patient's desire for protection against sudden death in light of young age and satisfactory functional capacity. • The patient and family elected to proceed with a single-chamber ICD. • The procedure was performed without complications. The postprocedural hospital stay was prolonged due to slow recovery, with eventual return to baseline functioning after a 10-day acute rehabilitation stay. • Two years following ICD placement, the patient was doing well. The patient was no longer employed due to difficulty with transportation. No ICD therapies for ventricular arrhythmias occurred since implantation. ICD interrogation revealed episodes of irregular tachycardia in a monitoring zone consistent with asymptomatic atrial fibrillation. A 14-day event monitor showed atrial fibrillation episodes lasting up to 24 hours with rates of 80–160 bpm. The patient was placed on anticoagulation, and the beta-blocker dosage was increased.	• Progressive loss of muscle function with wheelchair dependence 10–20 years after symptom onset is common. • Concentric hypertrophy is often observed. It does not increase the risk of sudden death as in other genetic causes of hypertrophic cardiomyopathy. • About 10% of patients develop left ventricular systolic dysfunction. The role of GDMT in limiting the progression of left ventricular systolic dysfunction has not been studied but is extrapolated from other populations. • Left ventricular systolic dysfunction increases the risk of atrial and ventricular arrhythmias like in other disease states. • Eliciting the overall goals of care and preferences led to the patient's decision to move ahead with primary prevention ICD. • Patients with NMDs can have protracted admissions at CIED placement due to underlying skeletal muscle dysfunction including respiratory involvement. Therapy to return patients to preimplant level of functioning is necessary. • Progressive noncardiac issues typically limit the quality and duration of life.

bpm = beats per minute; CIED = cardiovascular implantable electronic device; FA = Friedreich ataxia; GDMT = guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NMD = neuromuscular disorder.

Section 8 Shared decision-making and end-of-life care

8.1. General principles for shared decision-making and end-of-life care

This expert consensus statement details the management of arrhythmias in the most common NMDs. The recommendations describe the evaluation and treatment of arrhythmias and the use of pacemakers and ICDs, for both prevention and treatment. All NMDs have prominent nonarrhythmic manifestations that can limit both quality and quantity of life. As patients approach the end stages of the disease process, they and their families may not wish for therapies that further prolong life, especially if they are subject to the discomfort of ICD shocks. Some may not desire the risks associated with device implantation, especially given the respiratory muscular involvement common in many of the diseases that can be exacerbated by procedural sedation. In addition, the natural history of the NMD may impact the decisions that patients and families make regarding arrhythmia therapy even prior to an advanced disease state. Every reasonable attempt should be made to respect their desire not to pursue, continue, or even withdraw care. The majority of the recommendations in this document call for thoughtful patient and family counseling and shared decision making. Open and periodic discussions should take place with the patient and, if appropriate, their family, regarding the diagnosis and treatment of arrhythmias and placement and deactivation of pacemakers or ICDs. The discussion takes place in the context of the patients' preferences and goals of care. The dialogue will need to be recurring as goals of care evolve. Engagement with consultants specializing in palliative or hospice care is often useful. This section synthesizes the recommendations regarding end-of-life decisions that apply to all the previously reviewed diseases. Table 9 reviews these diseases and the most common manifestations that can impact quality and quantity of life.

Table 9 The neuromuscular disorders, use of pacemakers and implantable cardioverter-defibrillators, shared decision-making principles, and end-of-life care decisions

Neuromuscular disorder	Frequency of pacemaker implant	Typical pacemaker indications	Likelihood of pacemaker dependency	Frequency of ICD implant	Typical ICD indications	Typical issues affecting nonarrhythmic quality of life and mortality
Duchenne muscular dystrophy	Infrequent	Symptomatic bradycardia, heart block	Infrequent	Infrequent	Primary prevention due to cardiomyopathy	Respiratory failure Heart failure
Becker muscular dystrophy, limb-girdle muscular dystrophy type 2	Infrequent	Symptomatic bradycardia, heart block	Infrequent	Moderate	Primary prevention due to cardiomyopathy	Respiratory failure Heart failure
Myotonic dystrophy type 1	Frequent	Primary prevention due to heart block risk Symptomatic bradycardia	Moderate	Moderate	Primary prevention due to ventricular arrhythmia risk	Respiratory failure Heart failure
Myotonic dystrophy type 2	Moderate	Primary prevention due to heart block risk Symptomatic bradycardia	Infrequent	Infrequent	Primary prevention due to ventricular arrhythmia risk	Normal general population causes
Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy type 1B	Moderate	Primary prevention due to heart block risk	Frequent	Frequent	Primary prevention due to ventricular arrhythmia risk	Heart failure
Facioscapulohumeral muscular dystrophy	Rare	Normal general population indications	Rare	Rare	Normal general population indications	Normal general population causes
Mitochondrial myopathies	Moderate	Primary prevention due to heart block risk Symptomatic bradycardia	Moderate	Rare	Primary prevention due to left ventricular dysfunction	Respiratory failure Heart failure
Friedreich ataxia	Rare	Symptomatic bradycardia	Infrequent	Moderate	Primary prevention due to left ventricular dysfunction	Heart failure Respiratory failure

ICD = implantable cardioverter-defibrillator.

8.2. Shared decisionmaking and end-of-life decisions

Recommendations for shared decision-making and end-of-life decisions			
COR	LOE	Recommendations	References
1	C-EO	1. **In patients with NMDs who are considering or have a pacemaker or ICD, education on function including deactivation should be periodically discussed with the patient, their family members, and/or health care decision makers.**	
1	C-EO	2. **In patients with NMDs in whom the presence of conduction disorder portends a risk of ventricular arrhythmias, the decision of whether to implant a pacemaker or ICD should be concordant with the patient's overall medical care goals and clinical status.**	
1	C-EO	3. **In patients with NMDs who are considering ICD replacement and are undertaking advanced care planning, discussing the options of deferring ICD replacement is recommended.**	
1	C-EO	4. **In patients with NMDs who have an ICD and are undertaking advanced care planning, discussing the option of deactivation of ICD shock therapy is recommended.**	
1	C-EO	5. **In patients with NMDs who have an ICD and are experiencing ventricular arrhythmias with shocks refractory to available therapies, discussion of management of ICD therapy including shock deactivation is recommended, with careful attention to the patient's goals of care.**	
2a	C-EO	6. **In patients with NMDs who have a pacemaker or ICD and are nearing the end of life, if the patient or their health care decision maker requests pacing inactivation, it is reasonable to comply after education on the consequences of inactivation, with careful attention to the patient's goals of care.**	

Synopsis

The six recommendations on end-of-life decisions focus on education and goals of care in patients with NMDs who are considering or have a pacemaker or ICD. The evidence is graded as expert opinion due to limited nonrandomized observational data evaluating end-of-life decisions in pacemaker and ICD patients, and the problems associated with extrapolating available information to the special circumstances accompanying NMDs. It is important that patients and their families understand their autonomy in making decisions regarding health care, including care for arrhythmias. Education, at appropriate levels, regarding what therapies are available, how they work, their impact on quality and quantity of life, and options for changing or deactivating are topics that may be germane for discussion. It is important that discussions regarding the patient's autonomy in managing their arrhythmia care be initiated as early as possible, ideally prior to implantation. Advanced care planning will limit the misperceptions that can occur later in the course of illness. The ethical and legal tenets behind cardiac device management at end of life are covered in the *2010 HRS Expert Consensus Statement on the Management of Cardiovascular Implantable Electronic Devices (CIEDs) in Patients Nearing End of Life or Requesting Withdrawal of Therapy*.[15] Clinical scenarios for end-of-life decisions in patients with NMDs are provided in Table 10.

Recommendation-specific supportive text

1. The education of patients and their health care decision makers on the functions, benefits, and limitations of pacemakers and ICDs should occur prior to and periodically after implantation. The educational session may be led by the physician or another knowledgeable member of the care team. The discussion should include the options for programming changes to adjust or limit therapies. Patients and care providers should understand that programming can continue some device functions (eg, bradycardia pacing support) but inactivate other device functions (eg, tachyarrhythmia therapies). Concepts of shared decision making and patient autonomy on care should be emphasized.
2. Patients with DM, EDMD, or LGMD1B often develop conduction disease that increases the risk of advanced heart block and ventricular arrhythmias, both of which can lead to sudden death. Primary prevention pacemakers or ICDs are often used in these conditions. The pre–device implantation conversation is an opportunity to enlighten patients and their families regarding the risks and benefits of therapy. Similarly, it provides an opportunity for the implanting clinician to obtain the patient's long-term goals of care and preferences.[206] This discussion, coupled with known information on expectations of quality of life, prognosis specific to the underlying NMD, and the relative risks of advanced heart block versus ventricular arrhythmias, can facilitate device selection (specifically pacemaker versus ICD) and further counseling. Ideally, the care team, patient, family members, and/or health care decision makers will have a discussion regarding advance planning prior to a decision about device therapy. However, specific information and education related to the pacemaker or ICD remains the responsibility of the implanting electrophysiologist.
3. Discussion prior to ICD generator change provides an opportunity to reeducate and counsel patients regarding options pertaining to ICD programming, deactivation, and replacement. Patients may be unaware, for example, that deferring ICD replacement is acceptable if they desire and that programmed therapies can be noninvasively adjusted in the future if their goals of care change.[207-209] This issue is most germane in patients with limitations due to significant NMD and in those with advanced heart failure who are not candidates for specialized therapies such as ventricular assist device insertion or cardiac transplantation.
4. NMDs can lead to progressive skeletal muscle dysfunction typically manifesting as respiratory failure in the later stages of illness. Cardiac involvement can lead to progressive heart failure. In addition, other diseases (cancer, dementia, etc) can impact a patient's quality of life or shorten life span. The advancement in disease state can prompt a recognition that the end of natural life is approaching and further lead to dialogue on what medical care the patient desires. A discussion when advanced care directives are being planned is another key opportunity to reeducate patients regarding ICD programming options and deactivation and that ICD therapies can be noninvasively adjusted or deactivated in the future should their goals of care change.[207-209] Involvement of hospice medicine and palliative care specialists may be of particular benefit in these situations.
5. Patients with NMDs may experience refractory ventricular arrhythmias resulting in multiple ICD shocks, and in some patients, traditional options such as ablation, drug therapy, or transplantation and further steps such as cervical sympathectomy and radiation ablation may not be viable or effective. A significant number of ICD patients receive shocks in the final weeks of their lives.[210,211] In patients with ICDs particularly those who have received multiple shocks, ICD therapies for ventricular arrhythmias may no longer be perceived as beneficial.[210,212,213] As the end-of-life situation is recognized and goals of care shift to quality of life and patient comfort, it is important for patients and their families to understand their options regarding reprogramming and deactivation of ICD therapies and the generally painless manner of death from untreated ventricular arrhythmias.[210,212,214]
6. Pacemaker dependence may be present in several of the NMDs. In comparison to inactivation of cardioversion/defibrillation function, inactivation of pacing may be immediately life-threatening and thus has distinct implications and ethical concerns. Requests for inactivation of pacing are fortunately an uncommon scenario and require attention and further education on an individual basis. Patients and family may misunderstand that ongoing pacing may prolong suffering and will not allow for a natural death. Guidance from palliative care and hospice medicine

Table 10 Clinical scenarios for end-of-life management in patients with neuromuscular disorders

Clinical scenario	Management strategies	Key points
1. A 62-year-old woman with DM1, nonischemic cardiomyopathy (LVEF 24%), left bundle branch block, and previous biventricular ICD implantation is admitted with recurrent aspiration pneumonitis. She uses a wheelchair for all mobility, has a tracheostomy from prior pneumonia requiring prolonged mechanical ventilation, and had an enterostomy inserted 1 year ago. End-of-life management and planning is discussed.	• Acute management options included patient preference for enteral feeds, medical management of aspiration pneumonitis, and escalation of care if further deterioration was observed. • ICD management options discussed included unchanged programming and inactivation of tachyarrhythmia therapies with or without inactivation of pacing/CRT function. • Values elicited in discussion include decision for do-not-resuscitate status versus comfort measures with hospice referral. • Decision was made to continue nutrition via enterostomy, administering intravenous antibiotics with supplemental oxygen and inactivating tachyarrhythmia therapies, and maintaining pacing/CRT programming. • Do-not-resuscitate status was requested in keeping with focus on quality of life.	• Advanced neuromuscular impairment and associated medical conditions negatively impact quality of life. • Given poor overall prognosis, focus was shifted to maintaining quality over quantity of life. • Therapies targeting acute and possible reversible medical conditions were planned with avoidance of care escalation given unlikely benefit from aggressive measures and maintaining palliative therapies such as pacing/CRT. • Involvement of hospice medicine and palliative care specialists may be helpful in guiding and/or leading these discussions, with a focus on shared decision making.
2. A 39-year-old woman with EDMD1, atrial fibrillation, and a history of lower extremity arterial thromboembolism is hospitalized following traumatic intracranial hemorrhage associated with an accidental fall while on warfarin therapy. At baseline, she required assistance with activities of daily living and ambulated with a walker or wheelchair only. She remains lethargic and noncommunicative.	• Management options discussed included resumption of oral anticoagulation with warfarin or direct oral anticoagulant, left atrial appendage occlusion when appropriate, or observation without further intervention. • Values elicited in discussion included addressing preventable causes of morbidity and mortality and minimizing/avoidance of complications from medical/surgical thromboembolism prevention. • Patient's family declined resuming oral anticoagulation and deferred left atrial appendage indefinitely in favor of monitoring for further clinical neurological improvement given preference for conservative management.	• Traditional appropriate management strategies may be fraught with an increased risk of complications in patients with neuromuscular conditions. • Invasive strategies may be poorly tolerated, associated with increased procedural risk, and less appropriate in patients with advanced neuromuscular impairment and associated complexities. • The benefit of commonly indicated therapies may be overshadowed by comorbidities related to the underlying condition.
3. A 17-year-old adolescent male with DMD was admitted with heart failure, increasing dyspnea, nausea, and peripheral edema. He had undergone primary prevention, single-lead ICD implantation for left ventricular dysfunction and premature ventricular contractions with a dilated left ventricle with an ejection fraction of 22% 4 years earlier. He has been wheelchair bound for the past 8 years for progressive muscle weakness. He has been treated with aspirin, metoprolol, angiotensin receptor neprilysin inhibitor, and furosemide. His LVEF on this admission is estimated to be 20%, and he has developed an intraventricular conduction delay with a QRS duration of 130 ms. He was treated with intravenous milrinone with modest improvement of symptoms. An upgrade of the ICD to a CRT-D was discussed with the patient and his parents. The patient was reluctant despite the urging of his parents. He was discharged to home with intravenous milrinone in addition to his admission heart failure medical regimen.	• Management options included upgrade from ICD to CRT-D in a patient with advanced heart failure in the setting of progressive DMD. Other possible therapies included mechanical support devices and transplantation. • Values elicited in discussion were the role of the patient (still a minor) and parents in the shared decision-making, and assessment of the balance of benefit of more aggressive device therapy. • Decision for management and rationale were driven by the progressive nature of the neuromuscular disorder complicated with heart failure. The use of intravenous inotropes afforded the patient some improvement in heart failure symptoms.	• Although upgrade of an ICD in most contexts is reasonably safe, this was not the case here. • Shared decision-making should include the patient even if he/she is a minor. • Optimization of quality of life, even if limited in time, is paramount.

Table 10 (*Continued*)

Clinical scenario	Management strategies	Key points
4. A 46-year-old woman with DM1 and severe neuromuscular impairment (nonambulatory, nocturnal oxygen supplementation) presents for first cardiac electrophysiological evaluation with referral from neurology service. No symptoms attributable to cardiac involvement or arrhythmias are noted. The ECG shows sinus rhythm, PR interval 260 ms, right bundle branch block, and left anterior fascicular block with QRS duration 140 ms. Echocardiogram shows LVEF 55% without other significant abnormalities.	• Referral for evaluation by pulmonary medicine showed restrictive pulmonary function testing consistent with severe respiratory muscle involvement. • Coordinated care of patient was conducted with discussion with neurology, pulmonary medicine, and cardiac electrophysiology regarding neuromuscular prognosis. Consensus that the likelihood of poor cardiac or respiratory outcome over the next 2–4 years was high. • Conference with the patient and husband held to elicit the medical care goals. The discussion included the high risk for both cardiac and pulmonary complications of DM1. The risk of sudden cardiac death was discussed based on the severe cardiac conduction disease on the ECG. Included in the discussion was a review of the potential benefit of a primary prevention pacemaker or ICD. An option discussed included ongoing follow-up without device implantation. • The patient and family elected to proceed with a dual-chamber pacemaker implantation. • The procedure was done with anesthesia support and required intubation. Pacemaker was implanted without complications. However, there was failure to wean off the ventilator post-procedure. The patient remained in the intensive care unit for 2 weeks due to neuromuscular-related respiratory failure. • Despite marginal respiratory status, the patient was able to wean off the ventilator with nocturnal bi-level positive airway pressure support, and the patient was discharged 3 weeks post-implantation. • At 6-month follow-up after pacemaker implantation, complete heart block was observed with pacing suppression. No escape rhythm was observed with pacing at 30 beats/min. • The patient had progressive respiratory insufficiency and succumbed to pneumonia 2 years after pacemaker implantation. • The husband sent a thank you note to the care team for providing his wife with additional time to spend with him and their son who had congenital DM1.	• Poor functional status portends the high risk for poor mid- to long-term outcomes. • Empiric pacemaker implantation without further testing is reasonable given the ECG with severe conduction disease. • Clinical benefit of empiric ICD placement remains uncertain and would be potentially less advantageous as long-term outcome in the patient is poor. • Eliciting the overall goals of care and preferences led to the patient's decision to go ahead with pacemaker implantation. • Coordinated care between neurology, pulmonary medicine, cardiac electrophysiology, and anesthesiology led to a procedure with the anticipated issues but overall favorable outcome.

CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; DM1 = myotonic dystrophy type 1; DMD = Duchenne muscular dystrophy; ECG = electrocardiogram; EDMD1 = Emery-Dreifuss muscular dystrophy type 1; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

specialists to help lead these discussions may be helpful. However, if, after full discussion of the consequences of turning off versus continuing pacing, a patient and/or their health care decision makers request cessation of pacing, the patient's autonomy in medical decision making remains the primary directive. If a provider has ethical concerns in carrying out the patient's request, referral to another provider is appropriate.[15]

Section 9 Future directions and studies

9.1. Optimal therapy for heart failure

Clinical evidence regarding the use of heart failure therapies in NMDs is generally lacking. Antifibrotic therapies (ACE inhibitors and angiotensin II receptor blockers) alone, or in combination with beta-blockers or corticosteroids, seem to have a beneficial impact on prohibiting disease progression, improving cardiac function and survival in DMD and BMD.[215] Selective aldosterone receptor antagonism also appears effective for cardiac protection in DMD.[76] Further prospective studies are necessary to investigate the utility and optimal timing for use of standard and novel heart failure medications to prevent or delay the onset of myocardial impairment in NMDs.[216] The role of CRT that has been proven to be effective in treating ischemic cardiomyopathy and dilated cardiomyopathy remains unclear for NMDs. To date, very few studies have reported cardiac resynchronization in DMD and BMD[83,90,217,218] and DM1.[219-221] There are no data regarding His bundle or left bundle pacing in patients with NMDs, which are both promising strategies to minimize perioperative risks while potentially preserving the benefits of CRT. Early resynchronization in patients with LBBB or wide QRS complex inferring His–Purkinje disease may eliminate the detrimental effects of desynchronized ventricular conduction and further deterioration of LVEF. However, the diffuse nature of conduction system disease in NMDs may limit and even preclude the benefit of such approaches. The utility and ethics of mechanical circulatory support and cardiac transplantation in advanced heart failure due to NMDs remain undefined.

9.2. Risk stratification and prevention of sudden death

The risk of arrhythmic sudden death in many of the NMDs is not as closely related to left ventricular function as in other causes of cardiomyopathy. For example, the severity of underlying conduction disease is a risk factor for sudden death in many of the NMDs independent of left ventricular function.[89] The best methodology to risk stratify patients with NMDs for ventricular arrhythmias and sudden death remains unclear in most of the NMDs.[222] Studies are needed to determine the optimal timing of electrophysiological study, the threshold HV interval for prophylactic pacing in some NMDs, the utility of procainamide or other drug infusions to examine latent conduction disease, and the role of VT induction in the guidance of decisions on ICD placement. National or international registries should strongly be considered to further evaluate cardiac and arrhythmia therapies in NMDs.

Sleep disorders, such as sleep apnea, are common in NMDs and can modulate arrhythmia susceptibility. An ongoing observational prospective cohort clinical trial (NCT02375087) is investigating the relationship between the severity of oxygen desaturations during sleep and nocturnal arrhythmias and the specific proarrhythmic role of sleep disorders in DM1 patients.[223]

Imaging of the myocardial substrate, including late gadolinium delayed enhancement for focal fibrosis and T1 mapping for assessment of diffuse fibrosis in the setting of non-NMD cardiomyopathies, has been helpful for identification of arrhythmia susceptibility. Several clinical trials are examining the prognostic value of CMR in the presence of NMDs and the clinical impact of myocardial fibrosis in various NMD states.[224-226] Substrate ablation could play a role in decreasing sudden cardiac death if extensive fibrosis is determined to be a significant risk factor.[224-226]

9.3. Gene therapy

Genome engineering tools, including targeted gene editing, exon skipping, and gene regulation, have become available to correct the underlying genetic mutations that cause some of the NMDs.[227-231] Genome engineering can target RNA, and this is accomplished via antisense oligonucleotides, which are synthetic single-stranded strings of nucleic acids. Alternatively, systemic delivery of gene editing tools, which can target DNA or RNA, holds tremendous promise for treatment of NMDs. There are three antisense oligonucleotides—eteplirsen, golodirsen, vitolarsen—approved by the U.S. Food and Drug Administration to treat specific mutations in DMD, and additional agents are being evaluated in clinical trials. There are also multiple strategies in preclinical or clinical testing to target the primary defect and/or mitigate secondary and downstream pathological mechanisms.[232] Preclinical studies of gene therapy in DMD and BMD patients extensively explored the role of adeno-associated virus (AAV) vector–mediated delivery of microdystrophin in halting dystrophic progression and restoring muscle function.[233] There are three ongoing in-human clinical trials of AAV-delivered microdystrophin in DMD males.[234-236] PF-06939926 (NCT03362502),[236] SGT-001 (NCT03368742),[235] and SRP-9001 (NCT03375164)[234] are investigational recombinant AAV capsids carrying an internally truncated or shortened version of the human dystrophin gene (microdystrophin) under the control of a human muscle-specific promoter, which is also expected to be expressed in the heart. In DM1, antisense oligonucleotides that bind to and neutralize mutant RNA appear promising but require methods to gain better entry into muscle and heart.[237] The tri- or tetranucleotide expansions that cause DM1 and DM2, respectively, lead to long RNA sequences of $(CUG)_n$ or $(CCUG)_n$. These abnormal RNA molecules cause toxic effects through RNA-binding proteins such as muscleblind-like protein 1 and CUG-binding protein 1.[238] Downstream effects include disruption of alternative splicing,

which contributes to multiple features of DM1 including arrhythmias. Splice-switching oligonucleotides are short, synthetic, antisense, modified nucleic acids that base pair with pre-RNA and disrupt the normal splicing of a transcript by blocking the RNA–RNA base pairing or protein–RNA binding interaction that occur between components of the splicing machinery and pre-RNA. Splice-switching oligonucleotides may be utilized in the future to specifically correct alternative splicing changes linked to DM-related disease manifestations.[239]

9.4. Clinical science

Future advances in mechanistic, clinical, and therapeutic research in NMDs must surmount challenges posed by rare diseases. By necessity, NMD clinical trials enroll small sample sizes and, when combined with individual variability in clinical course, diminish study power to detect important clinical attributes and effect sizes. Thus, alternative trial designs and statistical techniques that maximize data from a small and heterogeneous group of subjects are necessary. Additionally, the geographic dispersion of enrolled patients, small numbers of adequately trained investigators, and significant variability in clinical practices limit the generalizability of results and homogeneity of pooled data. Thus, future efforts to effectively consolidate resources, homogenize treatment plans and data measurement practices, minimize biases, and streamline research efforts are necessary. We propose the following investigational priorities to increase the understanding of NMD disease- and mutation-specific arrhythmia pathogenesis and potential therapeutic targets:

- Increase worldwide NMD expert center collaborations with prospective disease-specific enrollment, data collection and processing through registry participation, multidisciplinary (myologists, geneticists, neurologists, cardiologists, and cardiac electrophysiologists) disease management, and follow-up protocols.
- Increase knowledge of the prevalence and impact of NMDs and their associated conditions through campaigns generating patient awareness and enhanced research support, financial and otherwise, from government and private sources.
- Enhance awareness of the need and requirements for training to develop the next generation of NMD arrhythmia providers and investigators.

Appendix 3

Supplementary data

Supplementary data (Appendix 3) associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.04.022.

References

1. Straub V, Murphy A, Udd B; LGMD workshop study group. 229th ENMC international workshop: limb girdle muscular dystrophies—nomenclature and reformed classification Naarden, the Netherlands, 17–19 March 2017. Neuromuscul Disord 2018;28:702–710.
2. Wahbi K, Porcher R, Laforet P, et al. Development and validation of a new scoring system to predict survival in patients with myotonic dystrophy type 1. JAMA Neurol 2018;75:573–581.
3. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical Practice Guidelines We Can Trust. National Academies Press; 2011.
4. Indik JH, Patton KK, Beardsall M, et al. HRS clinical document development methodology manual and policies: executive summary. Heart Rhythm 2017;14:e495–e500.
5. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;67:1572–1574.
6. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2019;16:e66–e93.
7. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2019;16:e128–e226.
8. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline 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 on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2018;15:e73–e189.
9. Feingold B, Mahle WT, Auerbach S, et al. Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American Heart Association. Circulation 2017;136:e200–e231.
10. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.
11. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200.
12. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–e76.
13. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–e239.
14. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;61:e6–e75.
15. Lampert R, Hayes DL, Annas GJ, et al. HRS expert consensus statement on the management of cardiovascular implantable electronic devices (CIEDs) in patients nearing end of life or requesting withdrawal of therapy. Heart Rhythm 2010;7:1008–1026.
16. Nikhanj A, Yogasundaram H, Miskew Nichols B, et al. Cardiac intervention improves heart disease and clinical outcomes in patients with muscular dystrophy in a multidisciplinary care setting. J Am Heart Assoc 2020;9:e014004.
17. Sommerville RB, Vincenti MG, Winborn K, et al. Diagnosis and management of adult hereditary cardio-neuromuscular disorders: a model for the multidisciplinary care of complex genetic disorders. Trends Cardiovasc Med 2017;27:51–58.
18. Takeuchi F, Komaki H, Yamagata Z, et al. A comparative study of care practices for young boys with Duchenne muscular dystrophy between Japan and European countries: implications of early diagnosis. Neuromuscul Disord 2017;27:894–904.
19. van Deutekom JC, Janson AA, Ginjaar IB, et al. Local dystrophin restoration with antisense oligonucleotide PRO051. N Engl J Med 2007;357:2677–2686.
20. Florian A, Rosch S, Bietenbeck M, et al. Cardiac involvement in female Duchenne and Becker muscular dystrophy carriers in comparison to their first-degree male relatives: a comparative cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging 2016;17:326–333.

21. Politano L, Nigro V, Nigro G, et al. Development of cardiomyopathy in female carriers of Duchenne and Becker muscular dystrophies. JAMA 1996;275:1335–1338.
22. McCaffrey T, Guglieri M, Murphy AP, Bushby K, Johnson A, Bourke JP. Cardiac involvement in female carriers of Duchenne or Becker muscular dystrophy. Muscle Nerve 2017;55:810–818.
23. Bushby K. Diagnosis and management of the limb girdle muscular dystrophies. Pract Neurol 2009;9:314–323.
24. Groh WJ, Lowe MR, Zipes DP. Severity of cardiac conduction involvement and arrhythmias in myotonic dystrophy type 1 correlates with age and CTG repeat length. J Cardiovasc Electrophysiol 2002;13:444–448.
25. Chong-Nguyen C, Wahbi K, Algalarrondo V, 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:e001526.
26. Lazarus A, Varin J, Ounnoughene Z, et al. Relationships among electrophysiological findings and clinical status, heart function, and extent of DNA mutation in myotonic dystrophy. Circulation 1999;99:1041–1046.
27. Bhakta D, Lowe MR, Groh WJ. Prevalence of structural cardiac abnormalities in patients with myotonic dystrophy type I. Am Heart J 2004;147:224–227.
28. Sakata K, Shimizu M, Ino H, et al. High incidence of sudden cardiac death with conduction disturbances and atrial cardiomyopathy caused by a nonsense mutation in the STA gene. Circulation 2005;111:3352–3358.
29. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers: a European cohort study. J Am Coll Cardiol 2012;59:493–500.
30. Muchir A, Bonne G, van der Kooi AJ, et al. Identification of mutations in the gene encoding lamins A/C in autosomal dominant limb girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B). Hum Mol Genet 2000; 9:1453–1459.
31. Fishbein MC, Siegel RJ, Thompson CE, Hopkins LC. Sudden death of a carrier of X-linked Emery-Dreifuss muscular dystrophy. Ann Intern Med 1993; 119:900–905.
32. Vytopil M, Vohanka S, Vlasinova J, et al. The screening for X-linked Emery-Dreifuss muscular dystrophy amongst young patients with idiopathic heart conduction system disease treated by a pacemaker implant. Eur J Neurol 2004; 11:531–534.
33. Tawil R, Kissel JT, Heatwole C, et al. Evidence-based guideline summary: evaluation, diagnosis, and management of facioscapulohumeral muscular dystrophy: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology 2015;85:357–364.
34. Pousset F, Legrand L, Monin ML, et al. A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. JAMA Neurol 2015;72:1334–1341.
35. Weidemann F, Stork S, Liu D, et al. Cardiomyopathy of Friedreich ataxia. J Neurochem 2013;126:88–93.
36. Pfeffer G, Chinnery PF. Diagnosis and treatment of mitochondrial myopathies. Ann Med 2013;45:4–16.
37. Berardo A, Musumeci O, Toscano A. Cardiological manifestations of mitochondrial respiratory chain disorders. Acta Myol 2011;30:9–15.
38. Shah MJ, Silka MJ, Silva JNA, et al. 2021 PACES expert consensus statement on the indications and management of cardiovascular implantable electronic devices in pediatric patients. Heart Rhythm 2021;18:1888–1924.
39. McNally EM, Kaltman JR, Benson DW, et al. Contemporary cardiac issues in Duchenne muscular dystrophy. Circulation 2015;131:1590–1598.
40. Politano L, Nigro V, Passamano L, et al. Evaluation of cardiac and respiratory involvement in sarcoglycanopathies. Neuromuscul Disord 2001;11:178–185.
41. Wahbi K, Meune C, Hamouda el H, et al. Cardiac assessment of limb-girdle muscular dystrophy 2I patients: an echography, Holter ECG and magnetic resonance imaging study. Neuromuscul Disord 2008;18:650–655.
42. Fayssoil A, Ogna A, Chaffaut C, et al. Natural history of cardiac and respiratory involvement, prognosis and predictive factors for long-term survival in adult patients with limb girdle muscular dystrophies type 2C and 2D. PLoS One 2016; 11:e0153095.
43. Petri H, Sveen ML, Thune JJ, et al. Progression of cardiac involvement in patients with limb-girdle type 2 and Becker muscular dystrophies: a 9-year follow-up study. Int J Cardiol 2015;182:403–411.
44. Fanin M, Melacini P, Boito C, Pegoraro E, Angelini C. LGMD2E patients risk developing dilated cardiomyopathy. Neuromuscul Disord 2003;13:303–309.
45. Melacini P, Fanin M, Danieli GA, et al. Myocardial involvement is very frequent among patients affected with subclinical Becker's muscular dystrophy. Circulation 1996;94:3168–3175.
46. Poppe M, Bourke J, Eagle M, et al. Cardiac and respiratory failure in limb-girdle muscular dystrophy 2I. Ann Neurol 2004;56:738–741.
47. Semplicini C, Vissing J, Dahlqvist JR, et al. Clinical and genetic spectrum in limb-girdle muscular dystrophy type 2E. Neurology 2015;84:1772–1781.
48. Piccolo F, Roberds SL, Jeanpierre M, et al. Primary adhalinopathy: a common cause of autosomal recessive muscular dystrophy of variable severity. Nat Genet 1995;10:243–245.
49. Bonnemann CG, Modi R, Noguchi S, et al. Beta-Sarcoglycan (A3b) mutations cause autosomal recessive muscular dystrophy with loss of the sarcoglycan complex. Nat Genet 1995;11:266–273.
50. Lim LE, Duclos F, Broux O, et al. Beta-Sarcoglycan: characterization and role in limb-girdle muscular dystrophy linked to 4q12. Nat Genet 1995;11:257–265.
51. Noguchi S, McNally EM, Ben Othmane K, et al. Mutations in the dystrophin-associated protein γ-sarcoglycan in chromosome 13 muscular dystrophy. Science 1995;270:819–822.
52. Nigro V, de Sa Moreira E, Piluso G, et al. Autosomal recessive limb-girdle muscular dystrophy, LGMD2F, is caused by a mutation in the δ-sarcoglycan gene. Nat Genet 1996;14:195–198.
53. Moreira ES, Wiltshire TJ, Faulkner G, et al. Limb-girdle muscular dystrophy type 2G is caused by mutations in the gene encoding the sarcomeric protein telethonin. Nat Genet 2000;24:163–166.
54. Brockington M, Yuva Y, Prandini P, et al. Mutations in the fukutin-related protein gene (FKRP) identify limb girdle muscular dystrophy 2I as a milder allelic variant of congenital muscular dystrophy MDC1C. Hum Mol Genet 2001; 10:2851–2859.
55. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord 2002;12:926–929.
56. Passamano L, Taglia A, Palladino A, et al. Improvement of survival in Duchenne muscular dystrophy: retrospective analysis of 835 patients. Acta Myol 2012;31:121–125.
57. Saito T, Kawai M, Kimura E, et al. Study of Duchenne muscular dystrophy long-term survivors aged 40 years and older living in specialized institutions in Japan. Neuromuscul Disord 2017;27:107–114.
58. Duboc D, Meune C, Pierre B, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. Am Heart J 2007; 154:596–602.
59. Chenard AA, Becane HM, Tertrain F, de Kermadec JM, Weiss YA. Ventricular arrhythmia in Duchenne muscular dystrophy: prevalence, significance and prognosis. Neuromuscul Disord 1993;3:201–206.
60. Corrado G, Lissoni A, Beretta S, et al. Prognostic value of electrocardiograms, ventricular late potentials, ventricular arrhythmias, and left ventricular systolic dysfunction in patients with Duchenne muscular dystrophy. Am J Cardiol 2002;89:838–841.
61. Perloff JK. Cardiac rhythm and conduction in Duchenne's muscular dystrophy: a prospective study of 20 patients. J Am Coll Cardiol 1984;3:1263–1268.
62. Yanagisawa A, Miyagawa M, Yotsukura M, et al. The prevalence and prognostic significance of arrhythmias in Duchenne type muscular dystrophy. Am Heart J 1992;124:1244–1250.
63. Shah AM, Jefferies JL, Rossano JW, Decker JA, Cannon BC, Kim JJ. Electrocardiographic abnormalities and arrhythmias are strongly associated with the development of cardiomyopathy in muscular dystrophy. Heart Rhythm 2010;7:1484–1488.
64. Villa CR, Czosek RJ, Ahmed H, et al. Ambulatory monitoring and arrhythmic outcomes in pediatric and adolescent patients with Duchenne muscular dystrophy. J Am Heart Assoc 2015;5:e002620.
65. Chiang DY, Allen HD, Kim JJ, et al. Relation of cardiac dysfunction to rhythm abnormalities in patients with Duchenne or Becker muscular dystrophies. Am J Cardiol 2016;117:1349–1354.
66. Punnoose AR, Kaltman JR, Pastor W, McCarter R, He J, Spurney CF. Cardiac disease burden and risk of mortality in hospitalized muscular dystrophy patients. Pediatr Cardiol 2016;37:1290–1296.
67. Ng W, Lau CP. Cardiac arrhythmias as presenting symptoms in patients with limb-girdle muscular dystrophy. Int J Cardiol 1997;59:157–160.
68. Connuck DM, Sleeper LA, Colan SD, et al. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. Am Heart J 2008;155:998–1005.
69. Florian A, Ludwig A, Engelen M, et al. Left ventricular systolic function and the pattern of late-gadolinium-enhancement independently and additively predict adverse cardiac events in muscular dystrophy patients. J Cardiovasc Magn Reson 2014;16:81.
70. Florian A, Patrascu A, Tremmel R, et al. Identification of cardiomyopathy-associated circulating miRNA biomarkers in muscular dystrophy female carriers using a complementary cardiac imaging and plasma profiling approach. Front Physiol 2018;9:1770.

71. Soltanzadeh P, Friez MJ, Dunn D, et al. Clinical and genetic characterization of manifesting carriers of DMD mutations. Neuromuscul Disord 2010; 20:499–504.
72. Krahn AD, Klein GJ, Yee R, Skanes AC. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. Circulation 2001;104:46–51.
73. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol 2018;17:251–267.
74. Allen HD, Flanigan KM, Thrush PT, et al. A randomized, double-blind trial of lisinopril and losartan for the treatment of cardiomyopathy in Duchenne muscular dystrophy. PLoS Curr 2013;5.
75. Raman SV, Hor KN, Mazur W, et al. Stabilization of early Duchenne cardiomyopathy with aldosterone inhibition: results of the multicenter AIDMD trial. J Am Heart Assoc 2019;8:e013501.
76. Raman SV, Hor KN, Mazur W, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: results of a two-year open-label extension trial. Orphanet J Rare Dis 2017;12:39.
77. Bourke JP, Guglieri M, Duboc D, et al. 238th ENMC international workshop: updating management recommendations of cardiac dystrophinopathy: Hoofddorp, The Netherlands, 30 November - 2 December 2018. Neuromuscul Disord 2019;29:634–643.
78. Menon SC, Etheridge SP, Liesemer KN, et al. Predictive value of myocardial delayed enhancement in Duchenne muscular dystrophy. Pediatr Cardiol 2014; 35:1279–1285.
79. Dhingra RC, Denes P, Wu D, Chuquimia R, Rosen KM. The significance of second degree atrioventricular block and bundle branch block: observations regarding site and type of block. Circulation 1974;49:638–646.
80. Shaw DB, Kekwick CA, Veale D, Gowers J, Whistance T. Survival in second degree atrioventricular block. Br Heart J 1985;53:587–593.
81. Fayssoil A, Lazarus A, Wahbi K, et al. Cardiac implantable electronic devices in tracheotomized muscular dystrophy patients: safety and risks. Int J Cardiol 2016;222:975–977.
82. Kay R, Estioko M, Wiener I. Primary sick sinus syndrome as an indication for chronic pacemaker therapy in young adults: incidence, clinical features, and long-term evaluation. Am Heart J 1982;103:338–342.
83. Fayssoil A, Nardi O, Annane D, Orlikowski D. Successful cardiac resynchronisation therapy in Duchenne muscular dystrophy: a 5-year follow-up. Presse Med 2014;43:330–331.
84. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–1853.
85. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–2150.
86. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–880.
87. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834–1843.
88. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352:1539–1549.
89. Groh WJ. Arrhythmias in the muscular dystrophies. Heart Rhythm 2012; 9:1890–1895.
90. Stollberger C, Finsterer J. Left ventricular synchronization by biventricular pacing in Becker muscular dystrophy as assessed by tissue Doppler imaging. Heart Lung 2005;34:317–320.
91. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Heart Rhythm 2012;9:1737–1753.
92. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263–272.
93. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093–1100.
94. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation 1991; 84:527–539.
95. Finsterer J, Stollberger C. Atrial fibrillation/flutter in myopathies. Int J Cardiol 2008;128:304–310.
96. Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337:1576–1584.
97. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
98. Pahl E, Sleeper LA, Canter CE, et al. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. J Am Coll Cardiol 2012;59:607–615.
99. Dimas VV, Denfield SW, Friedman RA, et al. Frequency of cardiac death in children with idiopathic dilated cardiomyopathy. Am J Cardiol 2009; 104:1574–1577.
100. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Heart Rhythm 2013;10:e11–e58.
101. Mathieu J, De Braekeleer M, Prevost C. Genealogical reconstruction of myotonic dystrophy in the Saguenay-Lac-Saint-Jean area (Quebec, Canada). Neurology 1990;40:839–842.
102. de Die-Smulders CE, Howeler CJ, Thijs C, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain 1998;121:1557–1563.
103. Mathieu J, Allard P, Potvin L, Prevost C, Begin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology 1999; 52:1658–1662.
104. Wahbi K, Babuty D, Probst V, 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;38:751–758.
105. Freyermuth F, Rau F, Kokunai Y, et al. Splicing misregulation of *SCN5A* contributes to cardiac-conduction delay and heart arrhythmia in myotonic dystrophy. Nat Commun 2016;7:11067.
106. Groh WJ, Groh MR, Saha C, et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. N Engl J Med 2008;358:2688–2697.
107. Petri H, Vissing J, Witting N, Bundgaard H, Kober L. Cardiac manifestations of myotonic dystrophy type 1. Int J Cardiol 2012;160:82–88.
108. Lund M, Diaz LJ, Ranthe MF, et al. Cardiac involvement in myotonic dystrophy: a nationwide cohort study. Eur Heart J 2014;35:2158–2164.
109. Bassez G, Lazarus A, Desguerre I, et al. Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1. Neurology 2004;63:1939–1941.
110. Ha AH, Tarnopolsky MA, Bergstra TG, Nair GM, Al-Qubbany A, Healey JS. Predictors of atrio-ventricular conduction disease, long-term outcomes in patients with myotonic dystrophy types I and II. Pacing Clin Electrophysiol 2012;35:1262–1269.
111. Sansone VA, Brigonzi E, Schoser B, et al. The frequency and severity of cardiac involvement in myotonic dystrophy type 2 (DM2): long-term outcomes. Int J Cardiol 2013;168:1147–1153.
112. Wahbi K, Meune C, Becane HM, et al. Left ventricular dysfunction and cardiac arrhythmias are frequent in type 2 myotonic dystrophy: a case control study. Neuromuscul Disord 2009;19:468–472.
113. Schoser BG, Ricker K, Schneider-Gold C, et al. Sudden cardiac death in myotonic dystrophy type 2. Neurology 2004;63:2402–2404.
114. Cudia P, Bernasconi P, Chiodelli R, et al. Risk of arrhythmia in type I myotonic dystrophy: the role of clinical and genetic variables. J Neurol Neurosurg Psychiatry 2009;80:790–793.
115. Breton R, Mathieu J. Usefulness of clinical and electrocardiographic data for predicting adverse cardiac events in patients with myotonic dystrophy. Can J Cardiol 2009;25:e23–e27.
116. Kwiecinski H, Ryniewicz B, Ostrzycki A. Treatment of myotonia with antiarrhythmic drugs. Acta Neurol Scand 1992;86:371–375.
117. 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;40:901–902.
118. Logigian EL, Martens WB, Moxley RT, et al. Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. Neurology 2010; 74:1441–1448.
119. Vio R, Zorzi A, Bello L, et al. Evaluation of mexiletine effect on conduction delay and bradyarrhythmic complications in patients with myotonic dystrophy type 1 over long-term follow-up. Heart Rhythm 2020;17:1944–1950.
120. 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;40:1645–1652.

121. Laurent V, Pellieux S, Corcia P, et al. Mortality in myotonic dystrophy patients in the area of prophylactic pacing devices. Int J Cardiol 2011; 150:54–58.
122. Lallemand B, Clementy N, Bernard-Brunet A, et al. The evolution of infrahissian conduction time in myotonic dystrophy patients: clinical implications. Heart 2012;98:291–296.
123. Wahbi K, Meune C, Porcher R, et al. Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease. JAMA 2012;307:1292–1301.
124. Moss AJ, Hall WJ, Cannom DS, et al. Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335:1933–1940.
125. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882–1890.
126. Buxton AE, Lee KL, DiCarlo L, et al. Multicenter Unsustained Tachycardia Trial Investigators. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000; 342:1937–1945.
127. Wahbi K, Algalarrondo V, Becane HM, et al. Brugada syndrome and abnormal splicing of SCN5A in myotonic dystrophy type 1. Arch Cardiovasc Dis 2013; 106:635–643.
128. MADIT Executive Committee. Multicenter Automatic Defibrillator Implantation Trial (MADIT): design and clinical protocol. Pacing Clin Electrophysiol 1991;14:920–927.
129. Buxton AE, Fisher JD, Josephson ME, et al. Prevention of sudden death in patients with coronary artery disease: the Multicenter Unsustained Tachycardia Trial (MUSTT). Prog Cardiovasc Dis 1993;36:215–226.
130. Nikhanj A, Sivakumaran S, Yogasundaram H, et al. Comparison of usefulness of cardiac resynchronization therapy in patients with type 1 myotonic dystrophy with versus without left bundle branch block. Am J Cardiol 2019; 124:1770–1774.
131. Strasberg B, Amat YLF, Dhingra RC, et al. Natural history of chronic seconddegree atrioventricular nodal block. Circulation 1981;63:1043–1049.
132. 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;22:1369–1375.
133. Merino JL, Carmona JR, Fernandez-Lozano I, Peinado R, Basterra N, Sobrino JA. Mechanisms of sustained ventricular tachycardia in myotonic dystrophy: implications for catheter ablation. Circulation 1998;98:541–546.
134. Brembilla-Perrot B, Schwartz J, Huttin O, et al. Atrial flutter or fibrillation is the most frequent and life-threatening arrhythmia in myotonic dystrophy. Pacing Clin Electrophysiol 2014;37:329–335.
135. Stoyanov N, Winterfield J, Varma N, Gollob MH. Atrial arrhythmias in the young: early onset atrial arrhythmias preceding a diagnosis of a primary muscular dystrophy. Europace 2014;16:1814–1820.
136. Bonne G, Di Barletta MR, Varnous S, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nat Genet 1999;21:285–288.
137. Bonne G, Mercuri E, Muchir A, et al. Clinical and molecular genetic spectrum of autosomal dominant Emery-Dreifuss muscular dystrophy due to mutations of the lamin A/C gene. Ann Neurol 2000;48:170–180.
138. Raffaele Di Barletta M, Ricci E, Galluzzi G, et al. Different mutations in the LMNA gene cause autosomal dominant and autosomal recessive Emery-Dreifuss muscular dystrophy. Am J Hum Genet 2000;66:1407–1412.
139. van Berlo JH, de Voogt WG, van der Kooi AJ, et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? J Mol Med (Berl) 2005;83:79–83.
140. Ben Yaou R, Becane HM, Demay L, et al. [Autosomal dominant limb-girdle muscular dystrophy associated with conduction defects (LGMD1B): a description of 8 new families with the LMNA gene mutations]. Rev Neurol (Paris) 2005;161:42–54 [in French].
141. Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D. Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med 2006;354:209–210.
142. Buckley AE, Dean J, Mahy IR. Cardiac involvement in Emery Dreifuss muscular dystrophy: a case series. Heart 1999;82:105–108.
143. Madej-Pilarczyk A. Clinical aspects of Emery-Dreifuss muscular dystrophy. Nucleus 2018;9:268–274.
144. Taylor MR, Fain PR, Sinagra G, et al. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. J Am Coll Cardiol 2003;41:771–780.
145. Pasotti M, Klersy C, Pilotto A, et al. Long-term outcome and risk stratification in dilated cardiolaminopathies. J Am Coll Cardiol 2008;52:1250–1260.
146. Kumar S, Baldinger SH, Gandjbakhch E, et al. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. J Am Coll Cardiol 2016; 68:2299–2307.
147. Kitaguchi T, Matsubara S, Sato M, et al. A missense mutation in the exon 8 of lamin A/C gene in a Japanese case of autosomal dominant limb-girdle muscular dystrophy and cardiac conduction block. Neuromuscul Disord 2001;11:542–546.
148. Sanna T, Dello Russo A, Toniolo D, et al. Cardiac features of Emery-Dreifuss muscular dystrophy caused by lamin A/C gene mutations. Eur Heart J 2003; 24:2227–2236.
149. Maggi L, D'Amico A, Pini A, et al. LMNA-associated myopathies: the Italian experience in a large cohort of patients. Neurology 2014;83:1634–1644.
150. Carboni N, Sardu C, Cocco E, et al. Cardiac involvement in patients with lamin A/C gene mutations: a cohort observation. Muscle Nerve 2012;46:187–192.
151. Draminska A, Kuch-Wocial A, Szulc M, et al. Echocardiographic assessment of left ventricular morphology and function in patients with Emery-Dreifuss muscular dystrophy. Int J Cardiol 2005;102:207–210.
152. Boriani G, Gallina M, Merlini L, et al. Clinical relevance of atrial fibrillation/flutter, stroke, pacemaker implant, and heart failure in Emery-Dreifuss muscular dystrophy: a long-term longitudinal study. Stroke 2003;34:901–908.
153. Nigro G, Russo V, Ventriglia VM, et al. Early onset of cardiomyopathy and primary prevention of sudden death in X-linked Emery-Dreifuss muscular dystrophy. Neuromuscul Disord 2010;20:174–177.
154. Karst ML, Herron KJ, Olson TM. X-linked nonsyndromic sinus node dysfunction and atrial fibrillation caused by emerin mutation. J Cardiovasc Electrophysiol 2008;19:510–515.
155. Kumar S, Androulakis AF, Sellal JM, et al. Multicenter experience with catheter ablation for ventricular tachycardia in lamin A/C cardiomyopathy. Circ Arrhythm Electrophysiol 2016;9:e004357.
156. Merlini L, Granata C, Dominici P, Bonfiglioli S. Emery-Dreifuss muscular dystrophy: report of five cases in a family and review of the literature. Muscle Nerve 1986;9:481–485.
157. Lakdawala NK. Using genetic testing to guide therapeutic decisions in cardiomyopathy. Curr Treat Options Cardiovasc Med 2013;15:387–396.
158. Cattin ME, Muchir A, Bonne G. 'State-of-the-heart' of cardiac laminopathies. Curr Opin Cardiol 2013;28:297–304.
159. Solbiati M, Costantino G, Casazza G, et al. Implantable loop recorder versus conventional diagnostic workup for unexplained recurrent syncope. Cochrane Database Syst Rev 2016;4:CD011637.
160. Healey JS, Alings M, Ha A, et al. Subclinical atrial fibrillation in older patients. Circulation 2017;136:1276–1283.
161. Hasselberg NE, Edvardsen T, Petri H, et al. Risk prediction of ventricular arrhythmias and myocardial function in lamin A/C mutation positive subjects. Europace 2014;16:563–571.
162. Becane HM, Bonne G, Varnous S, et al. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. Pacing Clin Electrophysiol 2000;23:1661–1666.
163. Anselme F, Moubarak G, Savoure A, et al. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. Heart Rhythm 2013;10:1492–1498.
164. Boriani G, Biagini E, Ziacchi M, et al. Cardiolaminopathies from bench to bedside: challenges in clinical decision-making with focus on arrhythmia-related outcomes. Nucleus 2018;9:442–459.
165. Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. JAMA 2015;313:1950–1962.
166. Bensaid J. Persistent atrial standstill documented over a 22-year period. Am Heart J 1996;131:404–407.
167. Wang J, Zhu Q, Kong X, et al. A combination of left ventricular hypertrabeculation/noncompaction and muscular dystrophy in a stroke patient. Int J Cardiol 2014;174:e68–e71.
168. Varma N, Helms R, Benson DW, Sanagala T. Congenital sick sinus syndrome with atrial inexcitability and coronary sinus flutter. Circ Arrhythm Electrophysiol 2011;4:e52–e58.
169. de Bie MK, Thijssen J, van Rees JB, et al. Suitability for subcutaneous defibrillator implantation: results based on data from routine clinical practice. Heart 2013;99:1018–1023.
170. Rakovec P, Zidar J, Sinkovec M, Zupan I, Brecelj A. Cardiac involvement in Emery-Dreifuss muscular dystrophy: role of a diagnostic pacemaker. Pacing Clin Electrophysiol 1995;18:1721–1724.
171. Yoshioka M, Saida K, Itagaki Y, Kamiya T. Follow up study of cardiac involvement in Emery-Dreifuss muscular dystrophy. Arch Dis Child 1989; 64:713–715.
172. Burke MC, Gold MR, Knight BP, et al. Safety and efficacy of the totally subcutaneous implantable defibrillator: 2-year results from a pooled analysis of the IDE study and EFFORTLESS registry. J Am Coll Cardiol 2015; 65:1605–1615.

173. Weiss R, Knight BP, Gold MR, et al. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. Circulation 2013;128:944–953.
174. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–2158.
175. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. Heart Rhythm 2019;16:e301–e372.
176. Statland JM, Tawil R. Facioscapulohumeral muscular dystrophy. Continuum (Minneap Minn) 2016;22:1916–1931.
177. Laforet P, de Toma C, Eymard B, et al. Cardiac involvement in genetically confirmed facioscapulohumeral muscular dystrophy. Neurology 1998;51:1454–1456.
178. Chen TH, Lai YH, Lee PL, et al. Infantile facioscapulohumeral muscular dystrophy revisited: expansion of clinical phenotypes in patients with a very short EcoRI fragment. Neuromuscul Disord 2013;23:298–305.
179. van Dijk GP, van der Kooi E, Behin A, et al. High prevalence of incomplete right bundle branch block in facioscapulohumeral muscular dystrophy without cardiac symptoms. Funct Neurol 2014;29:159–165.
180. Labombarda F, Maurice M, Simon JP, et al. Cardiac abnormalities in type 1 facioscapulohumeral muscular dystrophy. J Clin Neuromuscul Dis 2017;18:199–206.
181. Kimura T, Moriwaki T, Sawada J, Naka T, Hazama T, Nakata T. [A family with facioscapulohumeral muscular dystrophy and hereditary long QT syndrome]. Rinsho Shinkeigaku 1997;37:690–692 [in Japanese].
182. Trevisan CP, Pastorello E, Armani M, et al. Facioscapulohumeral muscular dystrophy and occurrence of heart arrhythmia. Eur Neurol 2006;56:1–5.
183. Blaszczyk E, Grieben U, von Knobelsdorff-Brenkenhoff F, et al. Subclinical myocardial injury in patients with facioscapulohumeral muscular dystrophy 1 and preserved ejection fraction—assessment by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2019;21:25.
184. Wahbi K, Bougouin W, Behin A, et al. Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases. Eur Heart J 2015;36:2886–2893.
185. Towbin JA, Jefferies JL. Cardiomyopathies due to left ventricular noncompaction, mitochondrial and storage diseases, and inborn errors of metabolism. Circ Res 2017;121:838–854.
186. Kang SL, Forsey J, Dudley D, Steward CG, Tsai-Goodman B. Clinical characteristics and outcomes of cardiomyopathy in Barth syndrome: the UK experience. Pediatr Cardiol 2016;37:167–176.
187. Campuzano V, Montermini L, Molto MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271:1423–1427.
188. Becker AB, Qian J, Gelman BB, Yang M, Bauer P, Koeppen AH. Heart and nervous system pathology in compound heterozygous Friedreich ataxia. J Neuropathol Exp Neurol 2017;76:665–675.
189. Babcock M, de Silva D, Oaks R, et al. Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin. Science 1997;276:1709–1712.
190. Durr A, Cossee M, Agid Y, et al. Clinical and genetic abnormalities in patients with Friedreich's ataxia. N Engl J Med 1996;335:1169–1175.
191. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001;22:2171–2179.
192. Tsou AY, Paulsen EK, Lagedrost SJ, et al. Mortality in Friedreich ataxia. J Neurol Sci 2011;307:46–49.
193. Asaad N, El-Menyar A, Al Suwaidi J. Recurrent ventricular tachycardia in patient with Friedreich's ataxia in the absence of clinical myocardial disease. Pacing Clin Electrophysiol 2010;33:109–112.
194. Sproule DM, Kaufmann P, Engelstad K, Starc TJ, Hordof AJ, De Vivo DC. Wolff-Parkinson-White syndrome in patients with MELAS. Arch Neurol 2007;64:1625–1627.
195. Wahbi K, Larue S, Jardel C, et al. Cardiac involvement is frequent in patients with the m.8344A>G mutation of mitochondrial DNA. Neurology 2010;74:674–677.
196. Morgan PG, Hoppel CL, Sedensky MM. Mitochondrial defects and anesthetic sensitivity. Anesthesiology 2002;96:1268–1270.
197. Roberts NK, Perloff JK, Kark RA. Cardiac conduction in the Kearns-Sayre syndrome (a neuromuscular disorder associated with progressive external ophthalmoplegia and pigmentary retinopathy): report of 2 cases and review of 17 published cases. Am J Cardiol 1979;44:1396–1400.
198. Welzing L, von Kleist-Retzow JC, Kribs A, Eifinger F, Huenseler C, Sreeram N. Rapid development of life-threatening complete atrioventricular block in Kearns-Sayre syndrome. Eur J Pediatr 2009;168:757–759.
199. Yesil M, Bayata S, Postaci N, Arikan E. Progression of conduction system disease in a paced patient with Kearns-Sayre syndrome. Clin Cardiol 2009;32:E65–E67.
200. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–1338.
201. Charles R, Holt S, Kay JM, Epstein EJ, Rees JR. Myocardial ultrastructure and the development of atrioventricular block in Kearns-Sayre syndrome. Circulation 1981;63:214–219.
202. Florian A, Ludwig A, Stubbe-Drager B, et al. Characteristic cardiac phenotypes are detected by cardiovascular magnetic resonance in patients with different clinical phenotypes and genotypes of mitochondrial myopathy. J Cardiovasc Magn Reson 2015;17:40.
203. Kabunga P, Lau AK, Phan K, et al. Systematic review of cardiac electrical disease in Kearns-Sayre syndrome and mitochondrial cytopathy. Int J Cardiol 2015;181:303–310.
204. Connolly SJ, Hallstrom AP, Cappato R, et al. Investigators of the AVID, CASH and CIDS studies. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. Eur Heart J 2000;21:2071–2078.
205. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748–754.
206. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. N Engl J Med 2002;346:1061–1066.
207. Braun TC, Hagen NA, Hatfield RE, Wyse DG. Cardiac pacemakers and implantable defibrillators in terminal care. J Pain Symptom Manage 1999;18:126–131.
208. Fried TR, Byers AL, Gallo WT, et al. Prospective study of health status preferences and changes in preferences over time in older adults. Arch Intern Med 2006;166:890–895.
209. Schoenfeld MH. Deciding against defibrillator replacement: second-guessing the past? Pacing Clin Electrophysiol 2000;23:2019–2021.
210. Goldstein NE, Lampert R, Bradley E, Lynn J, Krumholz HM. Management of implantable cardioverter defibrillators in end-of-life care. Ann Intern Med 2004;141:835–838.
211. Ahmad M, Bloomstein L, Roelke M, Bernstein AD, Parsonnet V. Patients' attitudes toward implanted defibrillator shocks. Pacing Clin Electrophysiol 2000;23:934–938.
212. Goldstein NE, Mehta D, Siddiqui S, et al. "That's like an act of suicide" patients' attitudes toward deactivation of implantable defibrillators. J Gen Intern Med 2008;23:7–12.
213. Wiegand DL, Kalowes PG. Withdrawal of cardiac medications and devices. AACN Adv Crit Care 2007;18:415–425.
214. Grassman D. EOL considerations in defibrillator deactivation. Am J Hosp Palliat Care 2005;22:179; author reply 179–180.
215. Russo V, Papa AA, Williams EA, et al. ACE inhibition to slow progression of myocardial fibrosis in muscular dystrophies. Trends Cardiovasc Med 2018;28:330–337.
216. Russo V, Sperlongano S, Gallinoro E, et al. Prevalence of left ventricular systolic dysfunction in myotonic dystrophy type 1: a systematic review. J Card Fail 2020;26:849–856.
217. Kono T, Ogimoto A, Nishimura K, Yorozuya T, Okura T, Higaki J. Cardiac resynchronization therapy in a young patient with Duchenne muscular dystrophy. Int Med Case Rep J 2015;8:173–175.
218. Andrikopoulos G, Kourouklis S, Trika C, et al. Cardiac resynchronization therapy in Becker muscular dystrophy. Hellenic J Cardiol 2013;54:227–229.
219. Russo V, Rago A, Antonio Papa A, Nigro G. Cardiac resynchronization improves heart failure in one patient with myotonic dystrophy type 1: a case report. Acta Myol 2012;31:154–155.
220. Russo V, Rago A, D'Andrea A, Politano L, Nigro G. Early onset "electrical" heart failure in myotonic dystrophy type 1 patient: the role of ICD biventricular pacing. Anadolu Kardiyol Derg 2012;12:517–519.
221. Kilic T, Vural A, Ural D, et al. Cardiac resynchronization therapy in a case of myotonic dystrophy (Steinert's disease) and dilated cardiomyopathy. Pacing Clin Electrophysiol 2007;30:916–920.
222. Dello Russo A, Mangiola F, Della Bella P, et al. Risk of arrhythmias in myotonic dystrophy: trial design of the RAMYD study. J Cardiovasc Med (Hagerstown) 2009;10:51–58.
223. Sleep breathing disorders, a main trigger for cardiac arrhythmias in type I myotonic dystrophy? (STAR). ClinicalTrials.gov identifier: NCT02375087. Accessed January 24, 2020. https://clinicaltrials.gov/ct2/show/NCT02375087
224. Cardiac involvement in patients with Duchenne/Becker muscular dystrophy. ClinicalTrials.gov identifier: NCT02470962. Accessed January 24, 2020. https://clinicaltrials.gov/ct2/show/NCT02470962

225. Validating cardiac MRI biomarkers and genotype-phenotype correlations for DMD. ClinicalTrials.gov identifier: NCT02834650. Accessed January 24, 2020. https://clinicaltrials.gov/ct2/show/NCT02834650
226. Assessment of cardiopulmonary function in Duchenne muscular dystrophy. ClinicalTrials.gov identifier: NCT02195999. Accessed January 24, 2020. https://clinicaltrials.gov/ct2/show/NCT02195999
227. Lim LE, Rando TA. Technology insight: therapy for Duchenne muscular dystrophy—an opportunity for personalized medicine? Nat Clin Pract Neurol 2008; 4:149–158.
228. Tabebordbar M, Zhu K, Cheng JKW, et al. In vivo gene editing in dystrophic mouse muscle and muscle stem cells. Science 2016;351:407–411.
229. Amoasii L, Hildyard JCW, Li H, et al. Gene editing restores dystrophin expression in a canine model of Duchenne muscular dystrophy. Science 2018; 362:86–91.
230. Young CS, Mokhonova E, Quinonez M, Pyle AD, Spencer MJ. Creation of a novel humanized dystrophic mouse model of Duchenne muscular dystrophy and application of a CRISPR/Cas9 gene editing therapy. J Neuromuscul Dis 2017;4:139–145.
231. Long C, Amoasii L, Bassel-Duby R, Olson EN. Genome editing of monogenic neuromuscular diseases: a systematic review. JAMA Neurol 2016;73:1349–1355.
232. Guiraud S, Davies KE. Pharmacological advances for treatment in Duchenne muscular dystrophy. Curr Opin Pharmacol 2017;34:36–48.
233. Ramos J, Chamberlain JS. Gene therapy for Duchenne muscular dystrophy. Expert Opin Orphan Drugs 2015;3:1255–1266.
234. A gene transfer therapy study to evaluate the safety of SRP-9001 in participants with Duchenne muscular dystrophy (DMD). ClinicalTrials.gov identifier: NCT03375164. Accessed April 14, 2021. https://www.clinicaltrials.gov/ct2/show/NCT03375164
235. Microdystrophin gene transfer study in adolescents and children with DMD (IGNITE DMD). ClinicalTrials.gov identifier: NCT03368742. Accessed April 14, 2021. https://www.clinicaltrials.gov/ct2/show/NCT03368742
236. A study to evaluate the safety and tolerability of PF-06939926 gene therapy in Duchenne muscular dystrophy. ClinicalTrials.gov identifier: NCT03362502. Accessed April 14, 2021. https://clinicaltrials.gov/ct2/show/NCT03362502
237. Wheeler TM, Leger AJ, Pandey SK, et al. Targeting nuclear RNA for in vivo correction of myotonic dystrophy. Nature 2012;488:111–115.
238. Lee JE, Cooper TA. Pathogenic mechanisms of myotonic dystrophy. Biochem Soc Trans 2009;37:1281–1286.
239. Havens MA, Hastings ML. Splice-switching antisense oligonucleotides as therapeutic drugs. Nucleic Acids Res 2016;44:6549–6563.

Appendix 1 Author disclosure table

Writing group member	Employment	Honoraria/ speaking/ consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ partnership/ principal/majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
Ryan G. Aleong, MD, FHRS	University of Colorado Hospital, Aurora, Colorado	None	None	None	None	None	None	None	None
Ricardo Alkmim Teixeira, MD, PhD	Hospital Renascentista, Pouso Alegre, Brazil	None	None	None	None	None	None	None	None
Anthony Amato, MD	Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts	None	None	None	None	None	None	None	None
Samuel J. Asirvatham, MD, FHRS	Mayo Clinic, Rochester, Minnesota	0: AliveCor 2: Biosig Technologies 2: Biotronik 2: Boston Scientific 2: MediLynx 2: Medtronic 2: Abbott	None	None	None	None	None	2: AliveCor	None
Deepak Bhakta, MD, MBA, FHRS, FACC, FAHA, FACP, CCDS (Vice-Chair)	Indiana University School of Medicine, Indianapolis, Indiana	None	None	1: Medtronic	None	None	None	None	None
Yong-Mei Cha, MD, FHRS	Mayo Clinic, Rochester, Minnesota	None	None	2: Medtronic	None	None	None	None	None
Domenico Corrado, MD, PhD, FESC	Department of Cardiac, Thoracic, and Vascular Sciences, University of Padova, Padova, Italy	None	None	None	None	None	None	None	None
Denis Duboc, MD, PhD	Cardiology Department, Hôpital Cochin, AP-HP, Université de Paris, Paris, France	None	None	None	None	None	None	None	None
Zachary D. Goldberger, MD, FHRS	University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin	None	None	None	None	None	None	1: Elsevier	None
William J. Groh, MD, MPH, FHRS (Chair)	Ralph H. Johnson VA Medical Center and Medical University of South Carolina, Charleston, South Carolina	None	None	None	None	None	None	None	None
Minoru Horie, MD, PhD	Shiga University of Medical Sciences, Otsu, Japan	None	None	None	None	None	None	None	None

(*Continued*)

Appendix 1 (*Continued*)

Writing group member	Employment	Honoraria/ speaking/ consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ partnership/ principal/majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
Joseph E. Hornyak, MD, PhD	University of Michigan, Ann Arbor, Michigan	None	None	None	None	None	None	None	None
John Lynn Jefferies, MD, MPH, FACC, FAHA, FHFSA	University of Tennessee Health Science Center, Memphis, Tennessee	1: Abbott 1: AstraZeneca 1: Audentes Therapeutics 1: Bayer Healthcare Pharmaceuticals 1: Bristol Myers Squibb 1: Chiesi Pharmaceutical 1: HeartBeam 1: Novartis 1: Pfizer 2: Daxor 2: Medtronic 2: Nuwellis 2: Sanofi	1: Bristol Myers Squibb 1: NS Pharma 1: Nuwellis 1: Pfizer 1: Sanofi	0: University of Tennessee Health Science Center 1: Ionis 2: HeartBeam 3: Daxor 4: Abbott 4: Alnylam Pharmaceuticals 4: AstraZeneca 4: Bayer Healthcare Pharmaceuticals 4: Biocardia 4: Chiesi Pharmaceutical 4: Merck 4: MyoKardia 4: NS Pharma 4: Sanofi 4: Veru 5: American College of Cardiology 5: Bristol Myers Squibb 5: Eli Lilly 5: Medtronic 5: NIH 5: Novartis 5: Nuwellis 5: Pfizer 5: Regeneron	None	None	None	None	None

Stefan Kääb, MD, PhD	Department of Medicine I, University Hospital, LMU Munich, Munich, Germany	0: AstraZeneca 1: Bayer Healthcare Pharmaceuticals 1: Boehringer Ingelheim 1: Pfizer/BMS	None	0: Biotronik 0: Boston Scientific 0: Medtronic	None	None	None	None	None
Jonathan M. Kalman, MBBS, PhD, FHRS	Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia	None	None	3: Medtronic	3: Abbott 3: Biosense Webster 3: Medtronic	None	None	None	2: Abbott 2: Biosense Webster 3: Medtronic
Naomi J. Kertesz, MD, FHRS, CEPS-P	Nationwide Children's Hospital, Columbus, Ohio	None	None	None	None	None	None	None	None
Neal K. Lakdawala, MD	Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts	1: Array BioPharma 1: MyoKardia 1: Sarepta Therapeutics 2: Bristol Myers Squibb	None	None	None	None	None	None	None
Pier D. Lambiase, BCH, BM, MBChB, PhD, FHRS	Barts Heart Centre, St Bartholomew's Hospital, University College London, and St Bartholomew's Hospital London, London, United Kingdom	2: Boston Scientific	None	5: Medtronic	4: Abbott 4: Boston Scientific	None	None	None	None
Steven A. Lubitz, MD, MPH	Massachusetts General Hospital, Boston, Massachusetts	1: Bayer Healthcare Pharmaceuticals 1: Blackstone Life Sciences 1: Bristol Myers Squibb 1: Invitae	None	0: IBM 0: Fitbit 2: Medtronic 2: Premier 5: American Heart Association 5: Boehringer Ingelheim 5: Bristol Myers Squibb 5: NIH	None	None	None	None	None
Hugh J. McMillan, MD, MSc	Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada	1: Novartis	None	1: Hoffmann-La Roche	None	None	None	None	None

(*Continued*)

Appendix 1 (*Continued*)

Writing group member	Employment	Honoraria/ speaking/ consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ partnership/ principal/majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
Elizabeth M. McNally, MD, PhD	Northwestern University Feinberg School of Medicine, Chicago, Illinois	1: Amgen 1: AstraZeneca 1: Avidity Biosciences 1: Cytokinetics 1: Invitae 1: Johnson & Johnson 1: Pfizer 1: Stealth Biopharma 2: Exonics 2: PepGen 2: Tenaya Therapeutics	None	None	None	0: Ikaika Therapeutics	None	None	None
Margherita Milone, MD, PhD	Mayo Clinic, Rochester, Minnesota	1: American Academy of Neurology	None	4: Mayo Clinic	None	None	None	None	None
Narayanan Namboodiri, MBBS, MD	Sree Chitra Institute for Medical Sciences and Technology, Thiruvananthapuram, India	None	None	None	None	None	None	None	None
Saman Nazarian, MD, PhD, FHRS	University of Pennsylvania, Philadelphia, Pennsylvania	0: Abbott 0: CardioSolv, LLC 1: Biosense Webster 1: Circle Software	None	2: Siemens Heathcare 3: ADAS 3D 5: Biosense Webster 5: Imricor	None	None	None	None	None
Kristen K. Patton, MD, FHRS	University of Washington, Seattle, Washington	1: ABIM 1: FDA Circulatory System Devices Panel 1: Great Wall International Congress of Cardiology	None	None	None	None	None	None	0: ACGME RC Internal Medicine 0: ACC Electrophysiology Section Leadership Council 0: AHA Clinical Cardiology Council 0: FDA
Vincenzo Russo, MD, PhD	University of Campania Luigi Vanvitelli, Naples, Italy	None	None	None	None	None	None	None	None

Frederic Sacher, MD, PhD	Bordeaux University Hospital, LIRYC Institute, Bordeaux, France	0: Abbott 0: Bayer Healthcare Pharmaceuticals 0: Biosense Webster 0: Boehringer Ingelheim 0: Boston Scientific 0: inHEART 0: MicroPort 0: Pfizer	None	None	None	None	None	None	None
Pasquale Santangeli, MD, PhD	University of Pennsylvania, Philadelphia, Pennsylvania	1: Medtronic 2: Biosense Webster 3: Abbott	None	None	None	None	None	None	None
Win-Kuang Shen, MD, FHRS	Mayo Clinic College of Medicine, Phoenix, Arizona	None	None	None	None	None	None	None	None
Dario C. Sobral Filho, MD, PhD	PROCAPE University Hospital, Recife, Brazil	None	None	None	None	None	None	None	None
Bruce S. Stambler, MD, FHRS	Piedmont Heart Institute, Atlanta, Georgia	0: Milestone 1: Boston Scientific	None	0: Milestone 4: Biotronik	None	None	None	None	None
Claudia Stöllberger, MD	Second Medical Department with Cardiology and Intensive Care Medicine, Klinik Landstraße, Vienna, Austria	None	None	None	None	None	None	None	None
Gordon F. Tomaselli, MD, FHRS (Vice-Chair)	Albert Einstein College of Medicine, Bronx, New York	0: Leducq Foundation	None	None	None	0: Domicell, LLC	None	None	0: Amgen
Karim Wahbi, MD, PhD	Cardiology Department, AP-HP, Cochin Hospital, Université de Paris, Paris, France	None	None	None	None	None	None	None	None
Xander H.T. Wehrens, MD, PhD, FHRS	Baylor College of Medicine, Houston, Texas	None	None	None	None	None	None	None	None
Menachem Mendel Weiner, MD	Icahn School of Medicine at Mount Sinai, New York, New York	None	None	None	None	None	None	None	None

(*Continued*)

Appendix 1 (*Continued*)

Writing group member	Employment	Honoraria/ speaking/ consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ partnership/ principal/majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
Matthew T. Wheeler, MD, PhD	Stanford University, Stanford, California	None	None	None	None	None	None	None	None
Katja Zeppenfeld, MD, PhD	Leiden University Medical Center, Leiden, The Netherlands	None	None	5: Biosense Webster	None	None	None	None	None

Number value: **0** = $0; **1** = ≤$10,000; **2** = >$10,000 to ≤$25,000; **3** = >$25,000 to ≤$50,000; **4** = >$50,000 to ≤$100,000; **5** = >$100,000. ABIM = American Board of Internal Medicine; ACC = American College of Cardiology; ACGME RC = Accreditation Council for Graduate Medical Education Review Committee; AHA = American Heart Association; FDA = U.S. Food and Drug Administration.

*Research and fellowship support are classed as programmatic support. Sources of programmatic support are disclosed but are not regarded as a relevant relationship with industry for writing group members or reviewers.

Appendix 2 Reviewer disclosure table

Peer reviewer	Employment	Honoraria/speaking/consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/partnership/principal/majority stockholder	Stock or stock options	Intellectual property/royalties	Other
Diana Anca, MD	Weill Cornell Medicine, New York, New York	None	None	None	None	None	None	None	None
Andreas S. Barth, MD, PhD	Johns Hopkins Hospital, Baltimore, Maryland	1: Guidepoint Global Advisors	None	None	None	None	None	None	None
Ratna Bhavaraju-Sanka, MD	UT Health San Antonio, San Antonio, Texas	1: Argenx	None	None	None	None	None	None	None
Alfred E. Buxton, MD	Beth Israel Deaconess Medical Center, Boston, Massachusetts	None	None	None	None	None	None	None	None
Gonzalo Calvimontes, MD	Unidad de Cirugía Cardiovascular de Guatemala UNICAR, Guatemala City, Guatemala	None	None	None	None	None	None	None	None
Richard J. Czosek, MD	Cincinnati Children's Medical Center, Cincinnati, Ohio	None	None	None	None	None	None	None	None
Jeff S. Healey, MD, MSc, FRCPC, FHRS	Hamilton Health Sciences, Hamilton, Ontario, Canada	1: Cypher Pharma 1: Servier 1: Boston Scientific 1: MyoKardia 1: Bayer Healthcare Pharmaceuticals	2: Bristol Myers Squibb	5: Boston Scientific 5: Bristol Myers Squibb 5: Medtronic 5: Pfizer 5: Servier	2: Novartis	None	None	None	None
Alexsandro A. Fagundes, MD	Universidade Federal da Bahia, Salvador, Brazil	1: Medtronic	None	None	None	None	None	None	None

(*Continued*)

Appendix 2 (*Continued*)

Peer reviewer	Employment	Honoraria/speaking/ consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/partnership/ principal/majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
Daniel P. Judge, MD	Medical University of South Carolina, Charleston, South Carolina	1: ADRx, Inc 1: Cytokinetics 1: Pfizer 1: Tenaya Therapeutics	None	None	None	None	None	None	None
Jodie L. Hurwitz, MD, FHRS	North Texas Heart Center, Dallas, Texas	1: Abbott	None	None	None	None	None	None	None
Pamela K. Mason, MD, FHRS	University of Virginia Health System, Charlottesville, Virginia	1: Boston Scientific 1: Cook Medical 1: Medtronic	None	1: Medtronic	None	None	5: Apple	None	None
Christian Meyer, MD, MA, FESC, FEHRA, FHRS	Evangelisches Krankenhaus Düsseldorf, Dusseldorf, Germany	None	None	None	None	None	None	None	None
Soraya M. Samii, MD, PhD, FHRS	Hershey Medical Center, Hershey, Pennsylvania	None	None	None	None	None	None	None	None
Kazuhiro Satomi, MD, PhD	Tokyo Medical University, Tokyo, Japan	2: Abbott Japan 2: Japan Lifeline 2: Medtronic Japan	None	None	None	None	None	None	None
Martin K. Stiles, MBChB, PhD, FHRS	Waikato Clinical School, University of Auckland, Hamilton, New Zealand	1: Boehringer Ingelheim 1: Boston Scientific 1: Medtronic 1: Other	None	None	None	None	None	None	None
Robert Rinaldi, MD, FAAPMR	University of Texas Southwestern Medical Center, Dallas, Texas	None	None	None	None	None	None	None	None

Number value: **0** = $0; **1** = ≤$10,000; **2** = >$10,000 to ≤$25,000; **3** = >$25,000 to ≤$50,000; **4** = >$50,000 to ≤$100,000; **5** = >$100,000.

*Research and fellowship support are classed as programmatic support. Sources of programmatic support are disclosed but are not regarded as a relevant relationship with industry for writing group members or reviewers.