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SPECIAL REPORT

Clinical Care Recommendations for Cardiologists Treating Adults With Myotonic Dystrophy

Elizabeth M. McNally, MD, PhD; Douglas L. Mann, MD; Yigal Pinto, MD, PhD; Deepak Bhakta, MD; Gordon Tomaselli, MD; Saman Nazarian, MD, PhD; William J. Groh, MD, MPH; Takuhisa Tamura, MD; Denis Duboc, MD; Hideki Itoh, MD, PhD; Leah Hellerstein, LCSW, MPH; Pradeep P. A. Mammen, MD

***Abstract*—**Myotonic dystrophy is an inherited systemic disorder affecting skeletal muscle and the heart. Genetic testing for myotonic dystrophy is diagnostic and identifies those at risk for cardiac complications. The 2 major genetic forms of myotonic dystrophy, type 1 and type 2, differ in genetic etiology yet share clinical features. The cardiac management of myotonic dystrophy should include surveillance for arrhythmias and left ventricular dysfunction, both of which occur in progressive manner and contribute to morbidity and mortality. To promote the development of care guidelines for myotonic dystrophy, the Myotonic Foundation solicited the input of care experts and organized the drafting of these recommendations. As a rare disorder, large scale clinical trial data to guide the management of myotonic dystrophy are largely lacking. The following recommendations represent expert consensus opinion from those with experience in the management of myotonic dystrophy, in part supported by literature-based evidence where available. **(*J Am Heart Assoc*. 2020;9:e014006. DOI: 10.1161/JAHA.119.014006.)**

Key Words: arrhythmias • conduction system disease • heart failure • management • myotonic dystrophy

Myotonic dystrophy (DM) arises from nucleotide repeat expansions and is inherited in an autosomal dominant manner. Myotonic dystrophy type 1 (DM1), estimated as high as 1:2500, arises from a CTG expansion in the *DMPK* gene, ranging from 51 to >1500 copies, and is a multisystem disorder associated with cardiac complications.[1,2] Myotonic dystrophy type 2 (DM2) is attributable to a CCTG repeat expansion in the *CNBP* gene, often to >5000 copies.[1] Like DM1, DM2 is associated with an increased risk for atrial arrhythmias, conduction system slowing, ventricular arrhythmias, cardiomyopathy, and heart failure. Not every DM patient will develop these cardiac complications. However, the incidence of cardiac abnormalities remains significant in DM, potentially affecting >50% of patients,[3] and as such, it is recommended that DM patients undergo regular screening by a cardiologist familiar with neuromuscular disease and specifically with DM, if available. Cardiac conduction system disturbances can have sudden and catastrophic presentations, and at the same time are preventable through proper management. Therefore, cardiac surveillance in DM can be lifesaving. This document represents expert opinion derived from cardiologists with experience treating cardiac complications in myotonic dystrophy. Because DM is a rare disorder, literature-based evidence for DM-specific recommendations is often lacking and in the absence of published support, the group relied on clinical experience. The Myotonic Foundation organized this collection of information, and this document was developed to provide guidance to cardiologists who may not regularly evaluate myotonic dystrophy in their practice. It should also be emphasized that these recommendations were developed for the patient with a known diagnosis of DM, which typically implies the presence of accompanying neuromuscular symptoms like weakness and myotonia. The first presentation of DM may be cardiac arrhythmias, which can precede the onset of neuromuscular symptoms. Thus, in young patients with unusual arrhythmias, the cardiologist should assess

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neuromuscular symptoms and consider DM as a possible underlying diagnosis. The methods used for this document development were similar to those used to formulate overall care recommendations for myotonic dystrophy.[4]

Mechanisms of Dysrhythmias in DM

In DM1, cardiac dysrhythmia is the second leading cause of death after respiratory failure.[5] The precise mechanisms by which DM1 promotes cardiac conduction system dysfunction are not well understood. Characterized by toxic gain-of-function RNA-mediated mis-splicing, abnormal splicing of the *SCN5A* gene has been implicated in cardiac conduction system disease.[6] In addition, upregulation of NKX2.5 has also been suggested to play a role in cardiac dysfunction in DM.[7] For DM2, less is known about the specific molecular causes of cardiac dysrhythmia and dysfunction, and although not well documented, DM2 is thought to share some molecular defects with DM1.

DM is identified as a neuromuscular disease with a cardiac dysrhythmia risk requiring special management.[8] For DM patients, cardiac dysrhythmias may be symptomatic. Therefore, patients should be instructed to report events including palpitations, syncope, near syncope, dizziness, and lightheadedness. However, not all DM patients exhibit symptoms of arrhythmias since some rhythm disturbances may not produce clinical symptoms yet still be present. Regular monitoring includes regular surface 12-lead ECG, signal averaged ECG, 24- to 48-hour Holter monitors, patch monitors, event monitors, and implantable loop recorders. The precise frequency of using these surveillance modalities depends on whether the surface ECG is normal or not and the presence of symptoms and/or left ventricular dysfunction. In the DM patient with evidence for prolonged ECG intervals and/or left ventricle (LV) dysfunction, it may be necessary to monitor yearly or even more frequently. In the DM patient with a normal ECG and normal LV function, monitoring may be pursued with less frequency. Whether wearable or implantable devices will increase detection of cardiac dysrhythmias in DM has not yet been well addressed, and future studies may address this need.

Atrial Arrhythmias in DM

Atrial arrhythmias are commonly observed in DM1 and include atrial tachycardias such as typical and atypical atrial flutter, as well as atrial fibrillation.[5,9,10] Atrial tachyarrhythmias may have a slower than expected ventricular response owing to concomitant atrioventricular nodal slowing, resulting in slower than expected heart rates. Atrial arrhythmias may be among the earliest presentation of DM1, preceding even the recognition of muscle involvement.[11] Typical criteria for anticoagulation should be followed with special attention to 1) limitations of the DM population in making frequent appointments for monitoring therapeutic targets for vitamin K antagonists, and 2) the risk of falls and intracerebral hemorrhage in those with advanced muscular involvement. Ablation for atrial dysrhythmias can be successful with durable results.[12] Ideally, ablations should be performed by experienced clinicians, preferably with a team also familiar with the sedation and anesthesia needs of neuromuscular patients.

Atrioventricular Node Dysfunction in DM

Cardiac conduction system disease affecting the atrioventricular node is well described as a progressive event in DM1 and also occurs in DM2, although less well characterized. Like atrial arrhythmias, cardiac conduction defects can occur in the absence of left ventricular dysfunction and often progress slowly. As such, regular 12-lead surface ECGs are recommended to follow atrioventricular nodal prolongation. Pacemaker implantation is recommended with a PR interval >240 ms and a QRS duration >120 ms (Class IIb).[13–15]

Embolic Events and Stroke Risk in DM

Embolic events and stroke risk are believed to be increased in DM and are thought to relate to an increased incidence of atrial fibrillation and flutter. However, population-based studies are lacking. Scoring systems such as the Congestive heart failure, Hypertension, Age, Diabetes, Stroke and Vascular disease (also known as CHADS-Vasc) system can be applied, acknowledging that these scoring systems are not designed for younger patients with genetically mediated diseases.[16] The decision regarding anticoagulation should consider the increased fall risk related to underlying neuromuscular disease and muscle weakness. Both warfarin-based and newer oral anticoagulants can be used for anticoagulation in DM. Additionally, DM is not specifically associated with hypertension, and younger DM patients may be hypotensive, potentially altering stroke risk and consequent recommendations for anticoagulation.[17] In addition, autonomic dysfunction is a feature of DM1,[18] and this may further complicate blood pressure response and management of embolic risk. Anticoagulation can be pursued in DM, but with concomitant neuromuscular weakness, fall risk is increased. Data are lacking as to whether aspirin is beneficial in DM.

Ventricular Arrhythmias in DM

Ventricular arrhythmias are challenging to predict in DM because of atrioventricular conduction system disease.[19–23] A widened or widening QRS on serial ECGs may portend

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increased risk. Regular monitoring is recommended to evaluate the presence of ventricular arrhythmias, and the determination for internal cardioverter defibrillator (ICD) implant relies on standard guidelines.[24,25] In the presence of left ventricular dysfunction, left ventricular ejection fraction <35%, ICDs should be considered for primary prevention of ventricular arrhythmias. Given the propensity for atrioventricular block, subcutaneous ICD systems are likely to be suboptimal unless no evidence of conduction system disease is noted. When possible, a dual chamber system is preferred. Additionally, biventricular pacing should be considered in the setting of left bundle branch or complete atrioventricular block. The use of His selective or non-selective pacing has not been assessed in this population and may be limited to the diffuse nature of infra-Hisian conduction system disease. In DM, with associated skeletal muscle disease, patients have limited exercise tolerance and usual symptoms of exercise intolerance and other heart failure symptoms may not be present. Symptoms of syncope and presyncope should be considered carefully in the presence of a widened QRS.

Invasive electrophysiological studies may be useful to risk stratify DM patients, especially in the presence of an abnormal surface ECG and unclear but potentially linked symptoms.[26] In this setting, an ECG with prolonged PR and/or QRS intervals, bundle branch, or fascicular block, along with potential arrhythmia linked symptoms, electrophysiological studies can be used to evaluate His bundle-ventricular prolongation and/or presence of VT/VF after extrasystoles. However, this area remains relatively understudied, and additional recommendations are expected in forthcoming guidelines from the Heart Rhythm Society specific to neuromuscular disease.

Heart Failure With Reduced Ejection Fraction in DM

LV dysfunction occurs in up to 40% of DM patients, reflecting an increased propensity to develop cardiomyopathy and heart failure in DM.[27] Heart failure symptoms may be largely absent because of neuromuscular disease limiting exercise tolerance. Right ventricular failure can develop, but generally occurs in the presence of untreated respiratory muscle weakness and accompanying pulmonary hypertension (see comments below about respiratory management).

Left ventricular size and function should be routinely monitored through regular cardiac imaging. Cardiac imaging should be performed in every DM patient at baseline and every 1 to 5 years thereafter, if the initial imaging study is normal. As LV dysfunction increases with age, regular annual monitoring should be undertaken in the DM1 patient aged >40 years, especially in the presence of an abnormal ECG, including, but not limited to, PR interval >200 ms, QRS >120 ms (including right or left bundle branch block), presence of fascicular block, second or third degree atrioventricular block, atrial fibrillation or flutter, or development of ventricular arrhythmias or with any evidence of prolonged QRS duration on routine surface ECG. In the presence of change of symptoms including worsening fatigue, dyspnea or other symptoms, it is reasonable to obtain additional cardiac imaging studies.

Imaging the Heart in DM

Echocardiography constitutes a mainstay imaging modality for its ease of use, even in wheelchair bound patients, and its ready availability and safety. Strain rate imaging can be utilized to improve detection of subtle left ventricular dysfunction. Cardiac magnetic resonance imaging (CMR) is also a highly useful modality that provides additional information with regard to cardiac fibrosis when using gadolinium imaging.[28,29] Strain defects are readily detected using CMR and can be used as an early sign of cardiac involvement. Although useful, CMR can be challenging to complete successfully in a neuromuscular patient with limited mobility and associated respiratory muscle weakness. An experienced imaging team should be familiar with mobility needs, limits on sedation and respiratory status before and during the study. Furthermore, interpretation of CMR images should be completed by those familiar with interpreting cardiomyopathy findings.

Treating Cardiomyopathy in DM

In other forms of progressive LV dysfunction associated with neuromuscular disease, early treatment has been shown to slow progression of LV dysfunction.[30–32] Guideline-directed medical therapy should be used to treat LV dysfunction, as blood pressure tolerates, acknowledging that hypotension may limit uptitration of medications. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-adrenergic blockers are well tolerated in DM, although the DM patient may tolerate only low doses of these medications attributable to hypotension. The efficacy of mineralocorticoid receptor antagonism with agents like aldactone (spironolactone) or eplerenone is not well described in DM patients, but use of these agents is assumed to have the same benefit as in other forms of heart failure. Of particular note, the use of mineralocorticoid receptor antagonism agents in DM patients may be noteworthy as there is some clinical data demonstrating these agents are able to suppress atrial arrhythmias in patients with cardiomyopathies.[33–36] As in other uses of these agents, patients should be monitored for hyperkalemia. Additional agents such as angiotensin receptor neprolysin inhibitors (known as ARNIs) may also be useful, although relative hypotension may limit the use of this agent. Similarly,

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ivabradine may be less helpful in the myotonic setting, as heart rates tend to be low because of cardiac conduction disease. In the setting of LV dysfunction and the presence of a QRS >140 ms, cardiac resynchronization therapy can be considered if heart failure persists after optimizing medical therapies for heart failure.

Additional Considerations in Managing the DM Heart

Muscle disease and its effect on serum biomarkers of renal function

With muscle disease, serum creatinine cannot be used to monitor renal clearance because serum creatinine is low to non-detectable in the setting of low muscle mass. Alternatively, serum cystatin C has been shown to be of use in neuromuscular disease.[37,38] This is an important consideration if renally-cleared novel oral anticoagulants are used for stroke prophylaxis in patients with atrial dysrhythmia.

Managing skeletal muscle myotonia in DM

Mexiletine, a class IB antiarrhythmic agent, has been promoted for the management of grip myotonia symptoms.[39,40] The decision to use this agent should be made in consultation between the neurologist and cardiologist to assess risk/benefit. Notably, this agent did appear to be well tolerated in clinical studies to assess its use for treating muscle myotonia symptoms. However, as with all class I antiarrhythmic agents, proarrhythmic effects may be increased.

Fatigue and daytime sleepiness

DM patients frequently note excessive daytime sleepiness and fatigue.[41] Fatigue arises from many factors including but not limited to ill-defined central nervous system aspects of DM, sleep disordered breathing, and restless leg syndrome in DM2.[42] Sleep disorders are common in DM, and extend beyond neuromuscular respiratory disease. Stimulants like modafinil are used to treat excessive fatigue with benefit.[43] The use of stimulants, in principle, may increase the risk for cardiac arrhythmias and cardiac complications. However, risk and benefit must be considered in making the decision for the management of the DM patient's fatigue.[44] A shared decision-making model should be used, involving the patient and providers as some degree of risk is usually well accepted by DM patients for the symptomatic benefit that stimulants provide.[44] It may be reasonable to increase frequency of monitoring for arrhythmias in the myotonic patient treated with stimulants.

Neuromuscular respiratory disease

With respiratory muscle weakness, hypoventilation with corresponding hypercapnia and hypoxia is a common feature in DM and is a predictor of mortality in DM.[5] Management of the DM patient requires close collaboration with experts in managing neuromuscular respiratory weakness. Non-invasive nocturnal ventilatory support can and should be applied to improved daytime fatigue. Episodes of irregular heart rhythms may be more frequent with inadequate nocturnal support.[45]

Hyperlipidemia, metabolic syndrome, and exercise in DM

As with many neuromuscular disorders, DM patients have limited exercise capacity and may become obese and exhibit metabolic syndrome findings. In DM1, mis-splicing of the insulin receptor is thought to contribute to an increased presence of diabetes mellitus.[46,47] Metabolic syndrome and hyperlipidemia have been described in DM.[48,49] Diabetes mellitus and hyperlipidemia should be treated for target goals. Statins can be used in neuromuscular patients, and it may be helpful to monitor the serum creatine kinase before initiating these medications. Exercise has been suggested to be beneficial in DM patients, but larger studies are needed.[50,51] However, not all DM patients are capable of exercising. In one report, acute onset exercise was associated with an increase arrhythmia propensity.[52] Adequate warm up and cool down periods before and after exercise may help DM patients participate in exercise. The increased risk for diabetes mellitus and metabolic syndrome, coupled with a reduced ability to exercise, may limit the capacity to detect significant coronary artery disease because exertional symptoms may be minimal. Pharmacologic stress evaluation or coronary artery angiography can be used to detect flow limiting stenosis. The management of flow-limiting epicardial coronary artery disease does not differ for the DM patient and conventional guidelines should be followed. Renal impairment may be present in DM, and if serum creatinine is markedly diminished because of low muscle mass, serum cystatin C can be monitored.[53]

Advanced management/end-of-life management

The leading cause of death in DM is neuromuscular-associated respiratory weakness and hypoventilation, followed by cardiac complications.[54] However, there are many exceptions, and some patients may exhibit more significant cardiac complications in the absence of severe neuromuscular involvement. When contemplating advanced management options like cardiac transplantation or ventricular assist support, the degree of neuromuscular involvement, especially respiratory function, must be weighed in decisions regarding advanced options.[55] Improved non-invasive ventilation options have prolonged survival in neuromuscular disease. However, even with this success, progressive muscle weakness and impaired quality of life should promote dialog among patients, caregivers and healthcare providers regarding end-

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of-life options. In this setting, device deactivation for ICDs should be discussed.

Summary Recommendations

1. Baseline 12-lead ECG should be performed in all patients upon confirmation of DM diagnosis and annually thereafter if asymptomatic.
2. Cardiac imaging should be performed in every DM patient at baseline and every 1 to 5 years thereafter if the initial imaging study is normal. If the baseline study is abnormal, then imaging can be done more frequently and should accompany a change in status like increasing shortness of breath, or to monitor medical and/or arrhythmia management. The preferred imaging modalities include echocardiography with strain rate imaging and CMR. Echocardiogram and CMR are both acceptable options for screening patients. Choosing which modality to use should be based on local expertise and accessibility. The risk of a cardiomyopathy being present in DM1 is enhanced in 1 of the following observations:
   a. Abnormal ECG including (but not limited to) PR interval >200 ms, QRS >120 ms (including right or left bundle branch block), presence of fascicular block, second or third degree atrioventricular block, atrial fibrillation or flutter, or development of ventricular arrhythmias.
   b. Symptoms suggestive of heart failure (ie, dyspnea, edema) or arrhythmias (palpitations, syncope).
   c. Consideration may be given to performing more frequent cardiac imaging in the absence of the above findings in those with a combination of the following: significantly increased CTG repeat length in DM1 (ie, in excess of 500–1000 repeats), and age >40 years.
3. Ambulatory monitoring may be used to detect ambient or asymptomatic arrhythmias including advanced (nocturnal) atrioventricular block and non-sustained ventricular arrhythmias. Such monitoring should be considered in patients with the aforementioned baseline ECG abnormalities or in those with symptoms suggestive of arrhythmias (see point 5 below).
4. Because of the possibility of sudden death in DM, invasive electrophysiology testing should be considered if non-invasive testing indicates elevated risk for serious conduction block or arrhythmias. Electrophysiological testing should be directed at evaluation for distal conduction impairment (His-Purkinje disease) and inducibility for ventricular arrhythmias, particularly bundle branch reentrant ventricular tachycardia.
5. Syncope, presyncope, dizziness, or lightheadedness should be considered as potential cardiogenic symptoms in patients with DM and prompt an evaluation for tachy- or brady-, arrhythmias and cardiomyopathy.
6. Patients and family members should be educated that symptoms such as palpitations, syncope, or near-syncope require prompt attention.
7. Pharmacologic treatment can be used cautiously to control atrial fibrillation in DM. Mexiletine, a class 1B anti-arrhythmic with pro-arrhythmic effects, is used to treat myotonia and may provide modest relief from atrial fibrillation. However, the use of any anti-arrhythmic medications/treatments in DM1 requires prior evaluation of the heart for underlying structural or functional abnormalities like left ventricular dysfunction that may complicate its use. Additionally, monitoring during drug initiation is warranted. At a minimum, anti-arrhythmic agents should be used with caution in particular in any patient with conduction system disease and cardiomyopathy in the absence of a pacemaker or ICD. Specific guidelines for managing atrial fibrillation do not exist for DM, so the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines can be used.[56] Advanced management options, including ablation, Maze procedure, and left atrial appendage occlusion, can be considered to reduce atrial fibrillation and reduce thromboembolic risk.
8. Anti-myotonic medications, stimulants, and general anesthetics should be used with caution, as these agents can elevate the risk of cardiorespiratory complications and malignant hyperthermia. Patients should be evaluated preoperatively and cared for by anesthesiologists familiar with DM1. See https://www.myotonic.org/mdf-releases-updated-anesthesia-guidelines
9. Management of hypotension is required only if it becomes symptomatic.
10. DM patients with a reduced ejection fraction (EF <40%) should be managed using the updated American College of Cardiology/American Heart Association/Heart Failure Society of America or European Society of Cardiology guidelines. It is reasonable to treat DM patients with left ventricular ejection fraction <50% similarly, given the known progression of cardiomyopathy in DM. Guidelines for the treatment of heart failure with reduced ejection fraction serve as a general approach for managing these patients. Recognizing that DM patients are prone to the development of hypotension and hyperkalemia, it may be necessary to individualize the management of symptomatic heart failure in DM patients.
11. Beta-adrenergic blockers, angiotensin-converting enzyme inhibitors, or ARBs may be considered in DM patients with LV structural/function abnormalities including left atrial dilatation, left ventricular dilatation, mild LV dysfunction (EF 40%–50%), and regional wall motion abnormalities not

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attributable to non-DM conditions (ie, coronary artery disease, hypertensive heart disease).

12. A primary or secondary prevention pacemaker or ICD is reasonable based on the ACC/American Heart Association/Heart Rhythm Society "Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities." A primary prevention pacemaker or ICD in a DM patient found to be at high risk of cardiac arrest or sudden cardiac death from abnormalities detected via non-invasive or invasive cardiac testing may be considered without a guideline. Patient and family preference with careful informed consent and the assessment of other risk factors affecting morbidity and mortality should be considered in the decision to implant a pacemaker or ICD.
13. Cardiac resynchronization therapy may be offered to DM patients with left ventricular ejection fraction ≤0.35, NYHA functional class III (or ambulatory class IV) symptoms, normal sinus rhythm, and intraventricular conduction delay (QRS duration >150 ms with left bundle branch block pattern) while on optimal guideline-directed medical therapy.
14. Coronary artery disease can develop in DM patients, and exercise stress testing may not be possible with concomitant neuromuscular involvement. Statins can be used in DM.
15. Multidisciplinary management is needed for DM patients including neurology, pulmonology, and anesthesiology physicians with expertise in DM when considering cardiovascular therapeutics, particularly invasive procedures that require sedation/anesthesia.

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Disclosures

None.

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