



Published in final edited form as:

Pediatrics. 2018 October ; 142(Suppl 2): S72–S81. doi:10.1542/peds.2018-03331.

Cardiac Management of the Patient With Duchenne Muscular Dystrophy

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Abstract

Duchenne muscular dystrophy (DMD) results in a progressive cardiomyopathy that produces significant morbidity and mortality. To improve the quality of life in patients with DMD, cardiac care is focused on surveillance and management, with the goal of slowing the onset and progression of heart failure complications. The current article is intended to be an expanded review on the cardiac management data used to inform the 2018 DMD Care Considerations recommendations as well as be a discussion on clinical controversies and future management directions. The new cardiac guidance includes changes regarding noninvasive imaging surveillance of cardiac function and pharmacologic therapy. Many emerging therapies lack sufficient evidence-

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Dr Cripe served as chairperson for the Duchenne Muscular Dystrophy Care Considerations Cardiology Management Working Group convened by the Centers for Disease Control and Prevention, drafted the initial outline for the manuscript, drafted sections of the manuscript, and reviewed and revised the manuscript; Dr Olson served as cochairperson for the Duchenne Muscular Dystrophy Care Considerations Cardiology Management Working Group convened by the Centers for Disease Control and Prevention, drafted the initial outline for the manuscript, drafted sections of the manuscript, and reviewed and revised the manuscript; Ms Buddhé served on the Duchenne Muscular Dystrophy Care Considerations Cardiology Management Working Group convened by the Centers for Disease Control and Prevention, contributed to the development of corresponding recommendations, drafted the initial outline for the manuscript, drafted sections of the manuscript, and reviewed and revised the manuscript; Drs Friedland-Little and Kertesz served on the Duchenne Muscular Dystrophy Care Considerations Cardiology Management Working Group convened by the Centers for Disease Control and Prevention, contributed to the development of corresponding recommendations, drafted sections of the manuscript, and reviewed and revised the manuscript; Drs Eghtesady, Finder, Hor, Judge, McNally, Raman, Thompson, and Wagner and Ms Kinnett served on the Duchenne Muscular Dystrophy Care Consideration Cardiology Management Working Group convened by the Centers for Disease Control and Prevention, contributed to the development of corresponding recommendations, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

based data to be recommended in the 2018 DMD Care Considerations. These are discussed in the present article as clinical controversies and future directions. Important emerging therapies include new heart failure medications, mechanical circulatory support with ventricular assist devices, heart transplantation, and internal cardiac defibrillators. Future research studies should be focused on the risks and benefits of these advanced therapies in patients with DMD. We conclude this review with a brief discussion on the relationship between the heart and the recently developed medications that are used to directly target the absence of dystrophin in DMD.

The loss of dystrophin in Duchenne muscular dystrophy (DMD) results in a progressive skeletal myopathy as well as a cardiomyopathy.^{1,2} As cardiac function worsens, clinical heart failure develops. Improved care in other specialties, especially respiratory support, has positioned cardiomyopathy as a principal source of morbidity and mortality.³⁻⁷

The patient who is nonambulatory makes the identification of traditional heart failure symptoms challenging. Thus, regular cardiac evaluations are the core tenet for care guidelines, including the 2018 DMD Care Considerations sponsored by the Centers for Disease Control and Prevention.⁸ The goal is to identify early myocardial changes and initiate therapy to favorably affect ventricular remodeling, thus improving cardiac outcomes and quality of life.⁹⁻¹¹ Unfortunately, the importance of cardiac surveillance is underappreciated in the care of the patient with DMD, as demonstrated in a recent natural history study in which researchers looked at the use of noninvasive imaging in DMD.¹² Recommendations for optimal cardiac care are clearly outlined in recent care guidelines.^{8,13}

In this companion article, we review the data and thought processes used to inform the important changes included in the 2018 DMD Care Considerations (see Fig 1 for an overview of the recommended assessments and interventions organized by stage of disease).⁸ Changes in imaging surveillance and recommendations regarding pharmacologic therapy will be discussed. The use of implantable defibrillators and mechanical circulatory support (ventricular assist devices) as well as heart transplantation are addressed. We conclude this review with a brief but important discussion on emerging therapies that are used to directly target the absence of dystrophin in DMD. This article is not intended to be a complete review of cardiac issues in DMD. The interested reader is referred to many excellent recent reviews.¹⁴⁻¹⁶

CORE CHANGES

Early diagnosis and treatment of cardiomyopathy leads to favorable ventricular remodeling in patients with DMD,⁹⁻¹¹ which is expected to maximize the duration and quality of life. The 2018 DMD Care Considerations reaffirmed that regular cardiac evaluations are an essential foundation of DMD care. In the updated guidance, the need for cardiac assessment at the time of diagnosis is emphasized. This initial cardiac visit should include a past and present cardiac medical and family history. In addition, the clinician should perform a physical examination, electrocardiogram, and noninvasive imaging with either an echocardiogram or cardiac MRI (CMRI) on the basis of the child's age and ability to cooperate. In previous guidelines, cardiac visits were recommended every 2 years before age 10 years, and at least a yearly evaluation was recommended thereafter depending on the

presence of ventricular dysfunction. Because of a growing recognition that adverse myocardial changes occur before overt cardiac dysfunction and at a younger age than previously thought, it is now recommended in the 2018 DMD Care Considerations that yearly cardiac screening begins at diagnosis. For patients with established cardiac abnormalities, more frequent visits may be needed.

Noninvasive Imaging to Assess Cardiac Function

Because traditional heart failure symptoms are difficult to identify in the patient with DMD who is nonambulatory, noninvasive imaging to assess cardiac function is an integral part of the cardiac evaluation. In the update, CMRI is recommended as the preferred noninvasive imaging modality for patients with DMD for reasons provided below. Echocardiography has historically been the primary imaging modality. In some patients with DMD, a significant limitation with echocardiography is inadequate acoustic imaging windows, secondary to body habitus.^{17,18} CMRI image quality is less affected by body habitus, and multiple studies have revealed that CMRI is superior to echocardiography for diagnosing DMD-related ventricular dysfunction.^{19–21} Soslow et al¹⁹ found that echocardiographic image quality was suboptimal in approximately half of patients with DMD. Suboptimal echocardiographic image quality frequently causes a significant over- or underestimate of left ventricular systolic function compared with CMRI.²⁰ Buddhe et al²¹ showed that an echocardiography-based ventricular functional assessment had a weak correlation with CMRI measurements, even in patients with adequate echocardiographic image quality. These studies reveal that CMRI is superior to an echocardiogram for detecting ventricular dysfunction, especially when echocardiographic scanning windows are suboptimal.

Histopathologic studies in DMD reveal subepicardial myocardial fibrosis, degeneration, and fatty infiltration.^{22,23} In addition to improved image quality, CMRI can detect fibrosis before changes in standard functional measurements (ie, ejection fraction [EF] and/or fractional shortening) occur.²⁴ Gadolinium-based contrast agents used in CMRI allow for the noninvasive assessment of pathologic myocardial fibrosis by the extent of late gadolinium enhancement (LGE).^{24–26} The time course and distribution of this LGE positivity within the myocardium may be an important clinical biomarker to aid in the management of DMD-associated cardiac disease.²⁷ Also, myocardial fibrosis detected by CMRI can be an independent predictor of adverse cardiac remodeling, ventricular arrhythmias, death, or a need for a cardiac transplant in DMD.^{28,29} Serial studies are thus warranted to determine if early medical management is useful in preventing the progression of ventricular dysfunction once LGE is documented.

Fibrotic changes in the myocardium in patients with DMD usually have a heterogeneous distribution, leading to regional wall motion abnormalities. Strain imaging, a relatively new technique that is used to quantify regional tissue deformation, improves the detection of regional wall motion abnormalities both by echocardiography and CMRI. However, an echocardiographic strain is sometimes limited by inadequate image quality. CMRI strain has better correlation with CMRI left ventricular ejection fraction (LVEF) than echocardiographic strain.²¹ Strain imaging analysis by CMRI tissue tagging is sufficiently sensitive to diagnose occult regional cardiac dysfunction.³⁰ Hor et al³¹ compared a novel

CMRI feature tracking-based assessment of peak average circumferential myocardial strain with peak average circumferential myocardial strain derived from tagged images and found high correlation in a large population of patients with DMD who had a wide range of cardiac dysfunction. Unlike tissue tagging, a feature-tracking analysis can be performed on routine images without additional scanning.³¹ Increased DMD heart disease severity was found to be associated with a reduced composite of CMRI-measured circumferential strain, diminished regional circumferential strain heterogeneity, and positive LGE imaging.³² Circumferential strain in particular has qualified as the most robust parameter with the best agreement when different vendors for CMRI feature-tracking strain assessment were compared.³³ Previous studies have consistently revealed that myocardial strain abnormalities are prevalent in young patients with DMD despite a normal EF, and these strain values continue to decline with advancing age. Also, a reduction in strain may precede fibrosis detected by LGE and is thus an attractive early biomarker of dysfunction, particularly because it can be detected by echocardiography. Thus, strain analysis in combination with standard echocardiography, CMRI, and LGE imaging has the potential to provide a means to risk stratify DMD cardiomyopathy.³⁴

Clinical Controversy—Transthoracic echocardiograms remain appropriate and useful in certain clinical situations. CMRI may not be feasible because of limitations, including cost, availability, required expertise, patient discomfort secondary to contractures and body positioning, and the need for sedation in some patients. This is particularly true in children with developmental delay, claustrophobia, or who are at younger ages. Echocardiograms are also preferred when urgent results are needed, such as in the emergency department or critical care unit.

In recent reports, researchers identified gadolinium deposition in brains after multiple administrations of gadolinium-based contrast agents.^{35,36} The clinical significance of this is unclear; however, an adverse effect has not been established in any studies. Newer gadolinium agents may have less deposition. Further research is needed to define the incidence and significance of these gadolinium depositions.³⁷

Future Directions—The ultimate goal is to find the most reliable, sensitive, and specific indicator of early myocardial involvement in DMD. In future studies, researchers should continue to evaluate novel imaging techniques for detecting subtle early myocardial abnormalities. T1 mapping by CMRI, a technique for assessing extracellular volume, was found to be abnormal in patients with DMD compared with that in controls (even in patients with DMD who otherwise had normal CMRIs).³⁸ T1 mapping can be used to identify diffuse fibrosis in the myocardium (unlike LGE, which detects focal lesions). Myocardial T1 mapping and extracellular volume are examples of emerging imaging techniques in DMD-related cardiomyopathy that may eventually become a standard of care.^{39,40} Prospective longitudinal studies that link early CMRI changes to long-term clinical outcomes are necessary to determine which established and/or novel CMRI techniques are most important for DMD-related clinical management. This information could also be extremely important in future clinical trials. Finally, in agreement with the 2014 National Institutes of Health Working Group,¹⁵ clinical trials for DMD muscle therapies should include CMRI as the

primary measure of cardiac safety monitoring and therapeutic efficacy rather than primarily echocardiograms.

Medical Management

Given the lack of specific therapies for DMD-related cardiomyopathy, the 2018 DMD Care Considerations endorse following traditional heart failure treatment strategies, as delineated previously and by other committees.^{13,15,41} Briefly, first-line therapy is angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). Recent studies revealed that combination therapy with the mineralocorticoid receptor antagonist eplerenone and an ACEi versus an ACEi alone in patients with DMD lessened the decline in left ventricular function after 2 years.^{42,43} Thus, consideration may be given for including mineralocorticoid receptor antagonists in first-line therapy with monitoring of kidney function and blood chemistry, β -adrenergic blockers are typically added with continued ventricular dysfunction or elevated heart rates. Additional medications, such as diuretics or digoxin, should be considered in situations in which additional heart failure therapy is required. It should be noted that patients with DMD often have low systolic blood pressure, which limits the up-titration of heart failure medications.

Additional research is needed to establish optimal cardiac pharmacotherapy in DMD, including research on issues such as timing for initiating medications (discussed below), appropriate dosing, specific indications for adding additional medications, and the utility of new heart failure medications (discussed below). However, performing robust cardiac clinical trials in patients with DMD is challenging. Adult heart failure studies (non-DMD) have large patient numbers, with a relatively high incidence of clinical heart failure events (ie, hospitalizations or changes in heart failure functional classes) and mortality. In contrast, DMD is a relatively rare disorder with a long delay (possibly decades) between the onset of cardiac functional changes and mortality. Cardiac-related morbidity is also difficult to assess in DMD because of the nonambulatory status of older patients and the involvement of other organ systems. Thus, patients with DMD do not fit in traditional heart failure functional classes. This leaves noninvasive imaging measures of cardiac function to inform the benefit in most DMD cardiac trials.

Clinical Controversy—Controversy exists regarding the age to start heart failure medications in patients with DMD who have a normal cardiac evaluation, including imaging. A consensus exists for initiating medications with symptoms of heart failure, ventricular dysfunction on imaging, myocardial fibrosis (LGE on CMRI), or abnormal chamber size. The 2014 National Institutes of Health Working Group recommended that all patients with DMD start an ACEi or ARBs by age 10 years on the basis of work by Duboc et al.^{15,44,45} In their randomized, double-blinded, placebo-controlled study, patients with DMD between the ages of 9.5 and 13 years (mean \pm SD: 10.7 \pm 1.2 years) with a normal LVEF ($>55\%$) by echocardiogram were randomly assigned to 3 years of the ACEi perindopril or a placebo. After 3 years, all patients received open-label perindopril. Although cardiac function was similar after 3 years, the early perindopril group had fewer patients with significantly decreased ventricular function (EF of $<45\%$) after 5 years and reduced mortality at 10 years.^{44,45} In the 2018 DMD Care Considerations, it was agreed that these

results were sufficiently compelling to recommend starting an ACEi or ARB around age 10 years in patients with a normal cardiac evaluation. ACEis and ARBs are generally well-tolerated, so some families and providers may decide to start medications before age 10 years.

Future Directions—The Food and Drug Administration recently approved 2 new classes of heart failure medications.^{46,47} Sacubitril/valsartan is a combination drug containing a first-in-class neprilysin inhibitor (sacubitril) and a previously approved ARB (valsartan). Compared with standard treatment with an ACEi, sacubitril/valsartan significantly reduced the composite end point of death and heart failure hospitalizations in adult patients with heart failure.^{46,48} A second newly approved medication is ivabradine, which is used to target the sinoatrial node to reduce heart rate. Ivabradine is recommended for patients with heart failure who have a heart rate of >70 beats per minute despite optimal β -adrenergic blocker usage.⁴⁹ Neither sacubitril/valsartan nor ivabradine has been evaluated in patients with DMD. These new medications have a theoretical benefit for DMD but are costly, so insurance companies may be unwilling to cover the higher costs unless a benefit in DMD is demonstrated.

Heart Transplant and Mechanical Circulatory Support

Guidelines for treating severe heart failure in non-DMD cardiomyopathy include indications for medical devices (such as internal cardiac defibrillators and mechanical circulatory support) and heart transplantation. A paucity of information regarding the use of these advanced therapies in patients with DMD prevents specific recommendations for their use in DMD-related cardiomyopathy. It is clear, however, that these therapies are emerging therapeutic considerations.

Heart transplantation is the standard of care for patients with refractory end-stage heart failure.⁵⁰ Given the scarcity of donor organs, however, a consensus exists among the transplantation community that to be a candidate for a heart transplant, a patient must have a reasonable chance to achieve a significant survival benefit from the transplanted heart. Heart transplantation is not considered an effective therapy in the setting of irreversible dysfunction of other organ systems.⁵¹ Some reports reveal good outcomes after a heart transplant in patients with muscular dystrophy.^{52,53} However, in most cases, the degree of respiratory insufficiency and muscular weakness generally found in patients with DMD who have developed severe myocardial dysfunction is thought to be a contraindication to a transplant because of the high associated risk of posttransplant mortality.⁵⁴

In the adult heart failure population, mechanical circulatory support with a left ventricular assist device (LVAD) as a destination therapy (rather than as a bridge to transplantation) is now an accepted strategy to provide survival and quality-of-life benefits to patients with advanced heart failure who are not candidates for a heart transplant.⁵⁵ The use of LVADs for destination therapy has grown considerably over the past decade,⁵⁶ and destination therapy is currently the indication for >45% of LVADs implanted in adult patients.⁵⁷ The pediatric heart failure community has been slower to adopt the concept of destination LVAD therapy, likely in part because of concerns regarding the disparity between optimistic estimates of

survival on an LVAD and what would be considered a normal life expectancy for a child.⁵⁸ However, recent case reports of LVADs placed as a destination therapy in patients with DMD have revealed some favorable early outcomes.^{59–62}

Clinical Controversy—Identifying patients with DMD who will achieve a real benefit from LVAD placement remains a challenge. In a recent registry analysis, ~30% of adult patients who receive a destination LVAD were found to have a poor outcome, which was defined as either mortality or persistently poor quality of life at 1 year after device placement.⁶³ Decreased functional status pre-LVAD implant was associated with an increased likelihood of poor outcome after implant in this analysis by Arnold et al,⁶³ and numerous earlier studies have likewise revealed a correlation between pre-LVAD health status and post-LVAD survival.^{64,65} In the reports of destination LVAD placement in patients with DMD, the authors emphasize the postoperative challenges posed by the respiratory insufficiency, muscle weakness and wasting, and an increased risk of bleeding found in this population.^{58,59,61,62} Despite improvements in device design, adverse events remain a concern for all patients on an LVAD, with bleeding, infection, and stroke being important causes of morbidity and mortality.⁵⁷ The balance of risks versus benefit may shift considerably on the basis of patient-specific factors, and the noncardiac sequelae of DMD place these patients on the higher-risk end of the spectrum.

Future Directions—At this time, the severe noncardiac manifestations of DMD preclude most patients with DMD from being considered candidates for a heart transplant. If new therapies are able to reduce the noncardiac morbidity and mortality in this population, then heart transplantation may become a more realistic option. The role of destination LVAD therapy is continuing to evolve. It is essential to develop criteria for identifying patients with DMD who are most likely to benefit from LVAD placement. This process will involve a multidisciplinary assessment by a care team, including in cardiology, cardiac surgery, anesthesiology, neurology, pulmonology, orthopedic surgery, and physical therapy. The involvement of psychology and the palliative care team is also essential. (For additional details, see the psychosocial care specialty article that is part of this supplement.⁶⁶) End-of-life issues related to destination LVAD placement in pediatric and young adult patients, including the inevitable eventual withdrawal of support, require careful consideration and honest discussion before device placement.⁶⁷

Arrhythmias and Device Therapy

Arrhythmias are an important potential contributor to mortality in DMD. Recent studies reveal the presence of atrial and ventricular premature beats, atrial tachycardia, ventricular couplets, and nonsustained and sustained ventricular tachycardia (VT) in these patients.^{68–70} Decreased EF is strongly correlated with the incidence of nonsustained and sustained VT. Nonsustained VT occurs in ~30% of patients with DMD and an LVEF of <35%. In evaluating the usefulness of arrhythmias predicting sudden death in DMD, LVEF was the only predictor of mortality, and ventricular arrhythmias were not.^{68–70} The benefit of an implantable cardioverter defibrillator (ICD) has not been established for patients with DMD. However, an ICD benefit in the adult population (non-DMD) with a reduced LVEF (<35%) on maximal medical therapy as a primary prevention strategy has been well established

through the Sudden Cardiac Death Heart Failure Trial, which revealed that ICD therapy reduced overall mortality by 23%.⁷¹ In this context, primary prevention refers to an approach to prevent sudden cardiac death on the basis of predictive factors, whereas secondary prevention refers to the prevention of a second occurrence of resuscitated sudden cardiac death. For patients with DMD who have sustained VT or resuscitated sudden cardiac death, the decision for an ICD implant is straightforward because these are accepted class I indications for use as a secondary prevention.

Clinical Controversy—The dilemma is what to do for patients with DMD who have nonsustained VT and/or an LVEF of <35%. In the adult heart failure population, the Sudden Cardiac Death Heart Failure Trial (n = 1211; average age: 58 years) revealed that the benefit outweighed the risk for ICDs in favor of implant among patients with an LVEF of <35%.⁷¹ However, it is unknown whether the DMD population, which is younger and has a nonischemic cardiomyopathy, would similarly benefit. In addition, placement of an ICD in patients with DMD may confer a higher risk because of accompanying skeletal muscle and respiratory compromise. Pediatric studies provide little additional guidance. In a 2009 study, Dimas et al⁷² reviewed all patients with idiopathic dilated cardiomyopathy (DCM) seen at Texas Children's Hospital over a 14-year period. The study included 85 patients (median age: 3.8 years) with a median LVEF of 23%. In that cohort, 1 sudden cardiac death event occurred. In 2012, Pahl et al⁷³ conducted a similar review of 1803 patients with DCM (mean age: 5.3 years) in patients enrolled in the Pediatric Cardiomyopathy Registry. At most, a 3% 5-year incidence of sudden death occurred, and EF and sudden death were not correlated. Other case reports and small case series include small numbers of patients with DMD who have received ICDs.^{28,70,74} The majority of patients with ICDs in these reports had no documented sustained ventricular arrhythmias, and only 1 patient received appropriate shocks (treatment of VT or ventricular fibrillation); the patient died of ventricular fibrillation despite multiple appropriate device discharges.²⁸

Future Directions—A better understanding of the risks and benefits is necessary before recommending ICDs as a primary prevention in patients with DMD. An international registry is currently enrolling patients to evaluate the incidence of arrhythmias and ICD use specifically among the DMD population (principal investigator: Kertesz and co-workers⁷⁵; Nationwide Children's Hospital). The risk of ICD placement in children and adolescents is not insignificant, with 21% of youth receiving inappropriate shocks (shocks for rhythms that should not be defibrillated) and 12% of youth having complications within 30 days of implantation. Unfortunately, there may be an increased risk of ICD placement in the DMD population because of anesthesia risks, respiratory compromise, and contractures.

Therapies Directly Targeting Dystrophin Deficiency

In September 2016, the Food and Drug Administration granted accelerated approval for the first drug that was used to directly target the underlying dystrophin deficiency in DMD. Eteplirsen is an exon-skipping drug with the potential to improve skeletal myopathy in a subset of patients with DMD. Animal studies, however, reveal that this class of exon-skipping medications (phosphorodiamidate morpholino oligimers) is significantly less efficacious in the heart compared with in the skeletal muscle.^{76–78} The cardiac effects of

eteplirsen are unknown in humans. It is hoped that eteplirsen approval will accelerate the development of similar disease-targeting medications. However, even if treatments are found to ameliorate the skeletal myopathy, mortality will not be affected unless improved cardiac treatments are discovered. Cardiomyopathy has the potential of limiting the overall functional benefit of the new therapies in which the skeletal muscle is targeted. It is essential that research includes an analysis of novel therapies on cardiac function.

FUNDING:

Supported in part by Cooperative Agreement NU38OT000167, funded by the Centers for Disease Control and Prevention.

POTENTIAL CONFLICT OF INTEREST: Northwestern University receives grant support on behalf of Dr McNally from Solid Biosciences. In addition, Dr McNally is a consultant to Exonics and Invitae. She is a founder of Ikaika Therapeutics and holds a patent relevant to muscular dystrophies; Dr Wagner has received an honorarium from FibroGen, Hoffmann-La Roche, and Wave Life Sciences; the other authors have indicated they have no potential conflicts of interest to disclose.

ABBREVIATIONS

ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
CMRI	cardiac MRI
DMD	Duchenne muscular dystrophy
EF	ejection fraction
ICD	implantable cardioverter defibrillator
LGE	late gadolinium enhancement
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
VT	ventricular tachycardia

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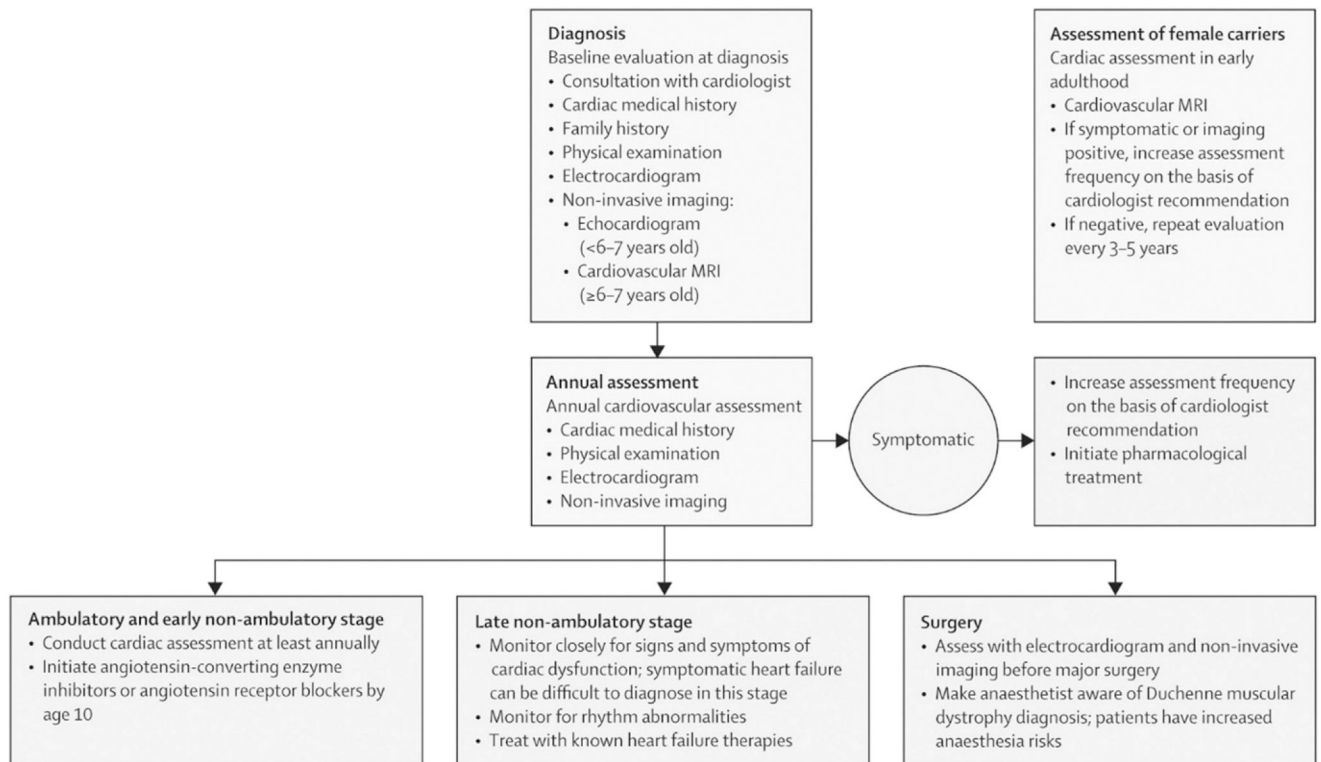
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**FIGURE 1.**

Cardiac monitoring, diagnosis, and treatment algorithm for patients with DMD. In this figure, the process of monitoring, diagnosing, and treating cardiac issues in patients with DMD is illustrated.