


# openheart Cardiac care of children with dystrophinopathy and females carrying DMD-gene variations

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## ABSTRACT

**Objective** We provide succinct, evidence-based and/or consensus-based best practice guidance for the cardiac care of children living with Duchenne muscular dystrophy (DMD) as well as recommendations for screening and management of female carriers of mutations in the *DMD*-gene.

**Methods** Initiated by an expert working group of UK-based cardiologists, neuromuscular clinicians and DMD-patient representatives, draft guidelines were created based on published evidence, current practice and expert opinion. After wider consultation with UK-cardiologists, consensus was reached on these best-practice recommendations for cardiac care in DMD.

**Results** The resulting recommendations are presented in the form of a succinct care pathway flow chart with brief justification. The guidance signposts evidence on which they are based and acknowledges where there have been differences in opinion. Guidelines for cardiac care of patients with more advanced cardiac dystrophinopathy at any age have also been considered, based on the previous published work of Quinlivan *et al* and are presented here in a similar format. The recommendations have been endorsed by the British Cardiovascular Society.

**Conclusion** These guidelines provide succinct, reasoned recommendations for all those managing paediatric patients with early or advanced stages of cardiomyopathy as well as females with cardiac dystrophinopathy. The hope is that this will result in more uniform delivery of high standards of care for children with cardiac dystrophinopathy, so improving heart health into adulthood through timely earlier interventions across the UK.

## Key messages

### What is already known about this subject?

- ⇒ The heart is abnormal from the start. However, cardiac symptoms only occur late in the involvement of the heart in Duchenne muscular dystrophy (DMD).
- ⇒ Timely introduction of heart medications improves heart health as DMD progresses.
- ⇒ Preserving cardiac function is a prerequisite for longer survival in DMD.
- ⇒ Females with *DMD*-gene variations are at increased risk of cardiomyopathy.

### What does this study add?

- ⇒ This work provides, for the first time in the UK, a clear care pathway to advise on how to best preserve cardiac function from the beginning in dystrophinopathy. This was based on evidence and a consensus building exercise among UK experts and patient representatives.
- ⇒ Furthermore, it gives guidance for the monitoring and management of females with *DMD*-gene mutations from their genetic diagnosis.

### How might this impact on clinical practice?

- ⇒ Clinicians—neuromuscular and cardiologist—treating those with *DMD*-gene variations will have access to the same clinical practice guidance for cardiac management at all stages of cardiac involvement. Patients will also be able to access the same information.
- ⇒ Endorsed by the British Cardiovascular Society, and having sought input from multiple centres, we expect uptake and implementation to be widespread. This will both improve standards of care and harmonise care between different centres across the UK

## INTRODUCTION

Duchenne muscular dystrophy (DMD) is a severe, progressive, muscle-wasting, life-limiting condition that affects just under 20 in every 100 000 live male births around the world.<sup>1</sup> There are currently around 2500 boys and men living with the condition in the UK.<sup>2</sup> DMD is caused by mutations in the *DMD*-gene, located on the X-chromosome, that encodes for the protein dystrophin.<sup>3</sup> This means that the vast majority of those

diagnosed with DMD are boys; although rarely girls may develop significant skeletal muscle weakness. DMD can also have phenotypic affects in female carriers in terms of their cardiac health.<sup>4</sup>

The lack of functional dystrophin causes muscle damage over time, fibrosis and replacement of skeletal muscle with fat. From



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the average age of diagnosis at 4 years in the UK,<sup>5</sup> it is primarily the skeletal muscles that are most noticeably affected at first with a gradual decline in motor function and loss of ambulation usually early in the second decade of life. As boys become older and grow to young men, they usually require ventilator support because of intercostal and diaphragm muscle weakness.<sup>6</sup> Dystrophin is also expressed in the heart. The lack of dystrophin in the myocardium leads to progressive loss of myocytes with fibro-fatty replacement and clinically, to a progressive form of dilated cardiomyopathy.

There is currently no effective treatment for DMD. Glucocorticoid steroid therapy is routinely recommended from a young age because it slows the rate of decline in skeletal muscle function and prolongs ambulation.<sup>7</sup> Steroids also delay the onset and rate of progress of cardiomyopathy. Preserving cardiac function for as long as possible is critical to prolonged survival in DMD and is the focus of this paper. With current standards of care in the UK, median life expectancy is around 29–30 years of age.<sup>8</sup>

The International Care Standards for DMD include recommendations for cardiac management.<sup>9</sup> However, that guidance is somewhat vague on choices of medication other than advocating the early introduction of an ACE inhibitor (ACEi). This may have contributed to variations in the cardiac care offered to patients with DMD in different parts of the UK. Families have expressed this concern over several years, and their views are supported by the findings of a recent survey of patients and carers about their care experiences (paper in preparation).

In order to address the diversity of care being provided, DMD Care UK was launched as a 3-year initiative between Duchenne UK, the wider patient community and Newcastle University, in collaboration with the North Star Network of neuromuscular centres<sup>10</sup> to agree, publish and promote high-quality DMD care uniformly across the UK through evidence-based consensus building.

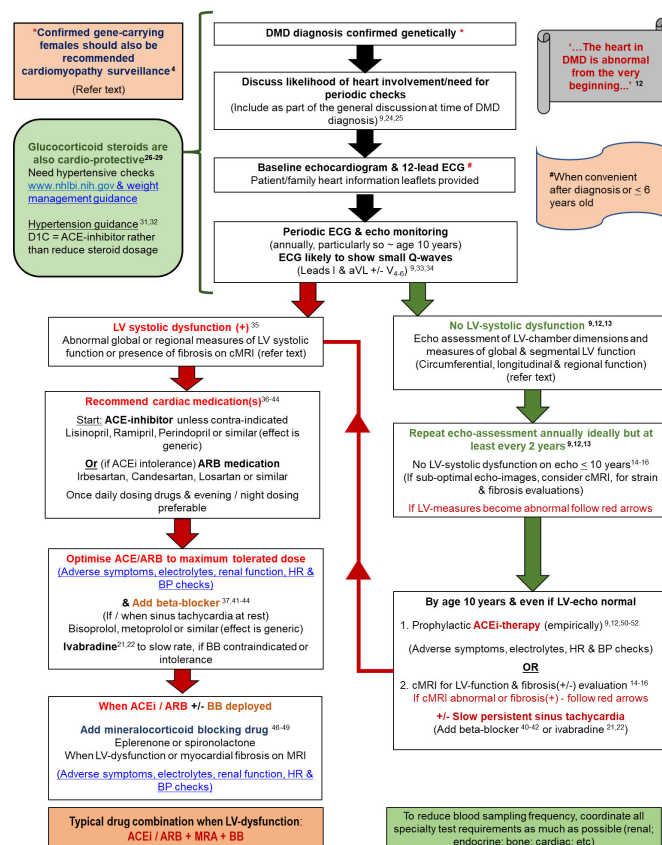
This paper presents the methods and outputs of the cardiac care group within DMD Care UK.

The guidance presented here aims to promote a uniform high standard of cardiac care for children with dystrophinopathy, regardless of where they live and is intended to complement the recently published UK adult DMD guidelines.<sup>11</sup> We have also included recommendations on the cardiac care of females at risk of cardiomyopathy because they carry mutations in the *DMD*-gene.

## METHODS

### Preparation of this guidance

This is a consensus summary from an expert cardiac working group (WG) of UK adult and paediatric cardiologists, neuromuscular specialists, specialist nurses and patient representatives from across the UK's North Star Network—all with experience in the management of people with DMD. The work builds on the evidence and international expert opinion, including that published by



**Figure 1** Recommended schedule of testing and therapy for children with DMD. ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; BP, blood pressure; cMRI, cardiac MRI; D1C, drug of first choice; DMD, Duchenne muscular dystrophy; HR, heart rate; ICD, Implantable cardioverter-defibrillator; LV, left ventricular; MRA, mineralocorticoid receptor antagonist.

Birnkrant *et al*,<sup>9</sup> and the proceedings of the 238th European Neuromuscular Centre Workshop Study Group, 2018.<sup>12</sup>

The WG members were identified and invited from among cardiologists based at expert North Star Centres with significant experience in the management and treatment of people with DMD. Patient representatives were invited to join through Duchenne UK's networks. The literature and evidence for both optimum surveillance and treatment was reviewed by a core group, who then drafted the initial version of figure 1. This was then circulated to the rest of the WG. Through a subsequent series of WG meetings, held virtually, final consensus was reached, and penultimate versions were circulated more widely to paediatric and adult cardiologists in the UK for comment. The guidance presented here is the 18th iteration of the original document and is intended to cover all stages of heart involvement in dystrophinopathy.

## RESULTS

### Cardiac involvement in DMD

The heart is 'abnormal from the start' in boys with DMD.<sup>12</sup> The main manifestation of cardiac involvement

in DMD is left ventricular (LV) systolic dysfunction. As part of early discussions, parents/carers should be made aware that progressive heart muscle weakness is part of the natural history of DMD.<sup>13</sup> This is to help them understand why baseline heart checks are advisable soon after diagnosis followed by a schedule of regular checks thereafter. It also prepares them for discussions about the use of prophylactic heart medication from an early age in order to realise their established benefits.

The multidisciplinary dystrophinopathy care team should include, as an integral member, a cardiologist who has expertise in inherited neuromuscular disorders and in heart failure management. He or she should oversee the cardiac management of patients with dystrophinopathy.<sup>12</sup> Although remote oversight of cardiac test results, performed to schedule, in younger boys reduces the need to attend a separate cardiology clinic, it is preferable for boys and their families to be familiar with 'their cardiologist' well ahead of the time when heart medications are recommended. Families who were consulted through a UK survey and within DMD Care UK's focus groups reported that they would welcome early, direct contact with the cardiac team to enable them to better understand the cardiac implications of DMD and to have the opportunity to discuss timely introduction of heart therapies. A multidisciplinary outpatient clinic, in which several different specialty assessments can take place on the same day, is probably the ideal arrangement for follow-up, but one that has not been implemented in the UK to date.<sup>12</sup>

Females with *DMD*-gene mutations should also be made aware of their risk of developing cardiomyopathy and offered a baseline cardiac assessment at the time of their genetic diagnosis and subsequent ongoing cardiac review.<sup>4</sup>

### Heart surveillance in dystrophinopathy

LV dysfunction is an inevitable consequence of DMD.<sup>13</sup> So, it is not a question of whether a patient with DMD will benefit from cardioactive medications but rather one of when they are best deployed in a particular patient. Cardiac symptoms only occur late in the involvement of the heart in DMD and so are a very poor guide to the state of cardiac function, which can only be determined by objective testing.<sup>9</sup>

A 12-lead ECG should be performed serially to detect inappropriate sinus tachycardia, arrhythmias or atrio-ventricular block.<sup>14</sup> Cardiomyopathy in DMD initially develops with segmental dysfunction affecting inferobasal or basolateral LV regions. So, the earliest changes will not necessarily be detected by semi-qualitative assessments or by measures of LV-fractional shortening alone. Therefore, from as soon as convenient after diagnosis, echo examinations should include both measures of global (ie LV chamber dimensions; fractional shortening, ejection fraction and assess radial and longitudinal function) and regional LV function. The sensitivity of these assessments is further increased by including tissue Doppler measures

of LV lateral wall longitudinal function and, if obtainable reliably, global LV-'strain' by speckle-tracking.<sup>12 15 16</sup> The detection of LV dysfunction should trigger the cascade of cardiac medications summarised in figure 1, acknowledging that some treatments may already have been initiated prophylactically based empirically on age alone. It is now also recognised that the finding of LV dysfunction by echo and tissue-Doppler is a relatively late indicator of cardiac involvement in dystrophinopathy. By the time dysfunction is evident, destructive processes have long been underway in the myocardium.<sup>12</sup>

Cardiac MRI is an even more sensitive imaging modality which provides detailed structural and functional information about the heart. It is particularly useful in clarifying equivocal findings and in those in whom reliable echo measures cannot be obtained. Furthermore, its ability to provide tissue characterisation allows detection of heart involvement before it has resulted in LV dysfunction.<sup>12 15 16</sup> Late-gadolinium enhanced imaging sequences allow detection of diffuse or focal myocardial fibrosis, which generally precedes the development of LV dysfunction. The pattern of sub-epicardial fibrosis seen in dystrophinopathy helps distinguish it from other patterns of unknown significance sometimes seen in scans of healthy young adults.<sup>17</sup> Although more sensitive than echo in detecting early abnormalities, cMRI is absolutely contraindicated in some patients (eg. presence of MRI-incompatible metal implants) and may require general anaesthesia or sedation to reduce motion artefacts (eg. in children below age 6 years or in adolescents with learning difficulties or contractures). Some patients do not tolerate the confined space of the MR-scanner (eg. steroid-related obesity or claustrophobia). In practice, the use of sedation or general anaesthesia for cMRI in younger children is rarely justified unless the results are thought likely to change clinical management.

There are also safety concerns about patients having serial cMRIs which include administration of a gadolinium contrast agent (ie nephrogenic systemic fibrosis, potential neuro-toxicity). Therefore, if cMRIs are performed serially, some will not include assessment of myocardial fibrosis to minimise the risk of these adverse effects.<sup>18 19</sup>

The cardiac biomarker, N-terminal pro-brain natriuretic peptide (pro-BNP) is not sensitive enough to guide early treatment of cardiac dystrophinopathy because measures only become abnormally elevated when LV dysfunction is well advanced.<sup>20</sup> However, it may have a role in helping distinguish heart failure from respiratory insufficiency and assessing response to therapy at more advanced stages of cardiomyopathy. In the future, it may become possible to use serial measures of highly sensitive DMD-specific biomarkers in peripheral blood to guide cardiac management throughout the course of DMD.<sup>21</sup>

Contemporary echo and/or cMRI allow detection of cardiac abnormalities at an earlier stage and at a younger age than was possible for the previous generation of patients. Today's patients have the potential to benefit



from more sensitive heart assessments through the earlier introduction and escalation of drugs aimed at preserving LV function for as long as possible.

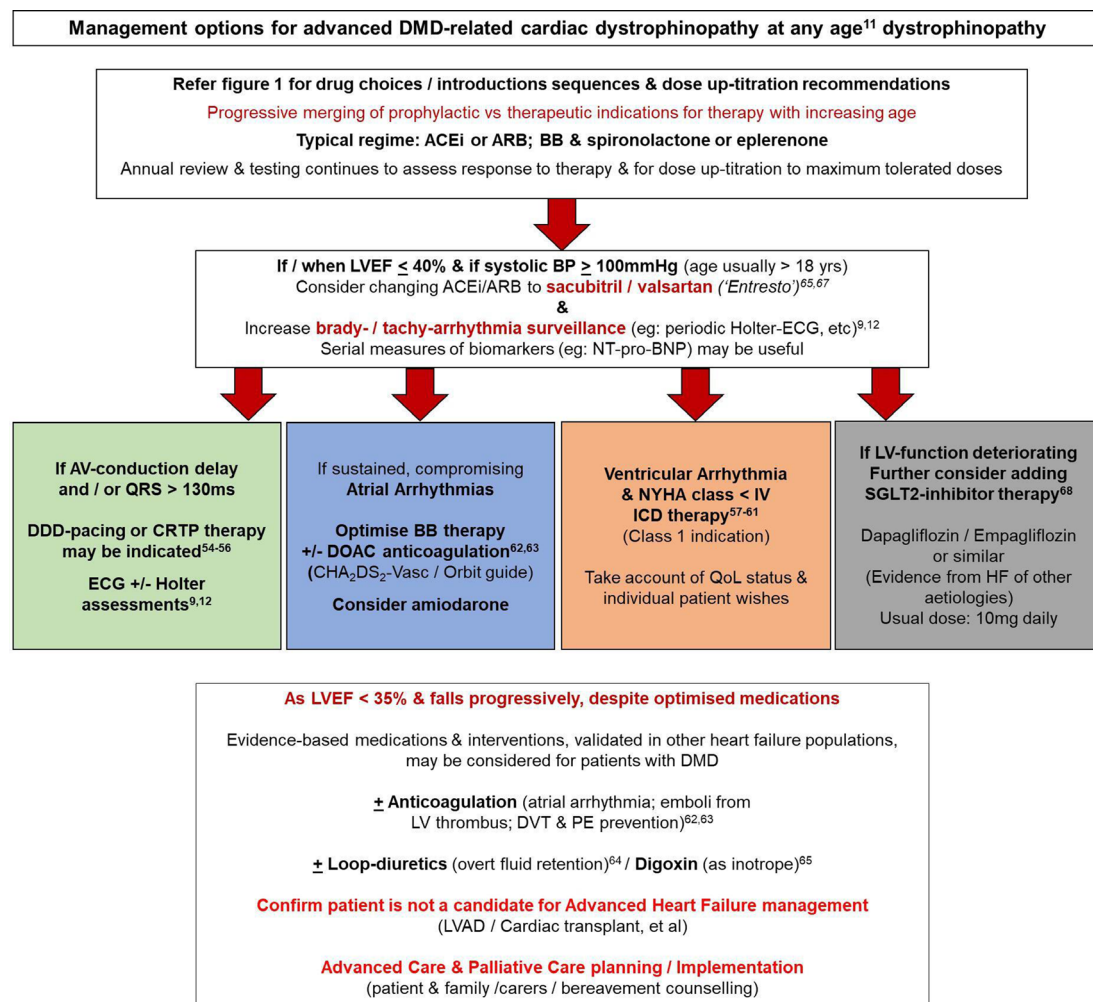
### Justification for heart imaging in more advanced cardiomyopathy

The justification for performing regular cardiac tests after the initiation of therapies to preserve LV function is sometimes questioned, since this is not routine practice, for patients with idiopathic forms of cardiomyopathy (IDCM), for example. However, the course of these two conditions differs in several key respects. Unlike in IDCM, the multisystem implications of DMD and particularly the severity of immobility, mean that cardiac symptoms occur very late in the course of LV dysfunction, providing no guide for either patient or cardiologist about the progression of cardiomyopathy or its response to treatment. Objective testing is, therefore, needed to help optimise

therapy and dosing and to provide feedback to patients regarding the function of their heart. Crucially, the cardiomyopathy of DMD is progressive, meaning that serial testing is required to assess for other changes that only occur later in the course of the condition. Imaging then is to detect atrial dilatation as a forerunner to possible atrial arrhythmias, right ventricular dysfunction and the presence of LV dyssynchrony or thrombus; standard and Holter-ECGs to screen for tachy-arrhythmias or brady-arrhythmias of prognostic importance.

### Rationale for introducing heart medications

Despite the increased sensitivity of cardiac imaging techniques in detecting cardiac involvement in recent years, recognition of the way in which dystrophin-deficiency affects the myocardium ‘from the beginning’<sup>12</sup> is justification for recommending empiric use of an ACEi therapy prophylactically no later than age 10 years to preserve



**Figure 2** Management options for advanced cardiac dystrophinopathy at any age ACE. ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; AV, atrioventricular; BB, beta-blocker; BP, blood pressure; CRT, cardiac resynchronisation pacing device (P)±defibrillator capability (D); DDD, dual chamber pacemaker; DMD, Duchenne muscular dystrophy; DOAC, direct oral anticoagulant; DVT, deep venous thrombosis; EF%, (left ventricular) ejection fraction; HF, heart failure; Holter (ECG), continuous ECG recording; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LV, left ventricular; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonist; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Failure Classification; PE, pulmonary embolism; QoL, quality of life; SGLT2-inhibitor, sodium-glucose co-transporter-2 inhibitor.

### Box 1 Self-assessment minimum cardiac care standards audit for boys with Duchenne muscular dystrophy (DMD)

1. Does a dedicated cardiologist supervise the cardiac care of boys with DMD?
2. What evidence can you provide to show that parents/carers have been made aware that cardiomyopathy is almost invariably part of DMD?
3. What percentage of boys with DMD had their first echo assessment before their 6th birthday?
4. What percentage of boys with DMD undergo echo and ECG annually from age 10 years?
5. What percentage of boys under follow-up have been prescribed an ACE-inhibitor or angiotensin-receptor blocker by age 10 years?
6. What percentage of boys with left ventricular dysfunction are on 'triple-therapy' (ie, ACE inhibitor (ACEi)+beta-blocker (BB)+mineralocorticoid receptor antagonist (MRA)-blocker)?
7. What was your 'child not brought to appointment' rate for boys >10 years last year?

### Self-assessment cardiac-care standards audit for females with *DMD*-gene variations

1. What was your 'failure to reattend for scheduled cardiac review' rate for females aged 30–60 years with *DMD*-gene variations in the last 12 months?
2. What percentage of females with confirmed cardiac dystrophinopathy are taking combination cardiac medications (ie, ACEi+MRA; ACEi+BB or similar)?

cardiac function.<sup>9</sup> Recognition of the progressive nature of cardiac dystrophinopathy means that the finding of myocardial fibrosis on cMRI, if the test is performed, confirms that LV dysfunction will shortly follow, even if not already detectable. This justifies addition of a mineralocorticoid receptor antagonist (MRA) to inhibit the myocardial scarring process. Confirmation of LV dysfunction should prompt further escalation to maximum tolerated doses and addition of any medications not already deployed.

It is common for boys with DMD to develop a resting sinus tachycardia with faster rates observed at serial attendances (eg, 100–130 bts/min)—sometimes even before there is echoevidence of LV dysfunction. A persistently fast heart rate acts as an additional cardiac stressor accelerating decline in function. Although evidence for the use of rate slowing medications such as a beta-blocker or ivabradine prophylactically is lacking, slowing the heart rate in the context of persistent tachycardia is desirable and coherent with established recommendations for optimising heart rate in patients at more advanced stages of cardiomyopathy in other contexts.<sup>22–24</sup>

Figure 1 summarises current best practice recommendations in the cardiac care of paediatric patients with cardiac dystrophinopathy, including the need for observations and checks of renal function and biochemistry.<sup>9–68</sup> The three-drug combination outlined may have to be reduced or suspended temporarily during serious

illness such as sepsis, but it should be restarted during convalescence.

It is rare for children with cardiac dystrophinopathy to have developed advanced LV dysfunction (eg. LV ejection fraction <40%) but it can occur—particularly in those with very large deletions and early onset of cardiomyopathy or following a super-added episode of viral myocarditis. Although typically only relevant for older patients with DMD, figure 2 has been included to summarise drug and device options that can be considered for patients at any age with advanced LV dysfunction.<sup>9 11 12 54 56–63 65 67 68</sup>

### Female carriers of *DMD*-gene variants

Care arrangements for females carrying a variant in the *DMD*-gene are even less well established and more variable around the UK than for boys with DMD. Although the majority experience neither signs nor symptoms at any stage, some develop progressive skeletal myopathy or cardiomyopathy or have cognitive impairment.<sup>4 69 70</sup>

Because of the diversity in clinical effects, it seems timely to discard the older terminology of 'DMD/BMD carrier' to describe these girls/women and replace it with a more accurate term, 'dystrophinopathy carrier'. Furthermore, even the term 'carrier' seems inadequate to describe those with clinical signs or symptoms. It is preferable, therefore, to limit the use 'carrier' to describing those without clinical effects (ie. no skeletal or cardiac signs or symptoms on testing, no cognitive effects and normal creatine kinase levels).<sup>69 70</sup> Those with signs or symptoms should be considered to have a dystrophinopathy and managed accordingly as for affected males.

Even in the absence of skeletal muscle manifestations, females with *DMD*-gene variations have an estimated 7.3%–16.7% lifetime risk of developing cardiomyopathy, from which symptoms typically only occur when LV dysfunction is well advanced.<sup>69 70</sup> Detecting cardiomyopathy requires surveillance, using the same heart imaging techniques as outlined for males with DMD. A baseline cardiac assessment, comprising 12-lead ECG and echocardiography, should be undertaken once carrier status is confirmed genetically. Assessments should follow a standard echo-imaging protocol, to provide measures of global and regional LV function that allow for serial comparisons—similar to that outlined above for boys with DMD. Results of this initial assessment provide the basis for decision-making and future comparisons. If initial results are reassuring, repeat testing can usually be undertaken at 3 yearly intervals, modifying the schedule if needed in discussion with families/patients for the very young and elderly. Equivocal findings on echo require repeat testing after a shorter interval or cMRI to clarify uncertainties. As for males with DMD, the finding of clinically significant myocardial fibrosis on cMRI or any degree of regional or global LV dysfunction on echo or cMRI justifies the same schedule of cardiac medications as outlined for males with cardiac dystrophinopathy. The finding of myocardial fibrosis in the typical DMD distribution indicates that LV dysfunction will follow, even if not

already present. Management of cardiac involvement in females with cardiac dystrophinopathy comprises introducing an ACEi or ARB, up-titrating to the maximum tolerated dose and adding an MRA for its additional anti-fibrosis benefits. Females with cardiac dystrophinopathy seldom develop the resting sinus tachycardia seen in boys with DMD during early cardiomyopathy and so rate slowing medications (ie, beta-blocker or ivabradine) are less often indicated initially. The overarching aim of therapy is to prevent progressive loss of cardiac function. For women of childbearing age who may become pregnant or who are planning pregnancy, the cardiac drug regimen will need to be modified.<sup>71 72</sup> Figure 2 outlines additional drug and/or non-pharmacological options that may be considered in the management of those with advanced cardiac dystrophinopathy.

## CONCLUSION

It is now widely accepted that the late initiation or over-cautious use of cardio-protective medications in children with cardiac dystrophinopathy leads to lost opportunities to mitigate the cardiac effects of the condition, which cannot be compensated for even by optimised cardiac management later in adulthood. Preserving cardiac function is a prerequisite for longer survival in DMD. This guidance is intended to contribute to achieving that goal more consistently across the UK.

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