

Clinical Presentation, Diagnosis, Treatment, and Outcome of Heart Disease in Becker Muscular Dystrophy

ABSTRACT

Becker muscular dystrophy (BMD) is a primary myopathy caused by mutations in the dystrophin gene on chromosome Xq21.2, which often affects the myocardium and cardiac conduction system. However, there is limited experience with cardiac disease in BMD. This review aims to summarize and discuss recent advances and future perspectives regarding the clinical presentation, diagnosis, treatment, and outcome of cardiac involvement in BMD. Data were retrieved by searching for relevant articles in the PubMed and Google Scholar databases. Cardiac disease in BMD is characterized by myocardial fibrosis, can be subclinical or clinical, and manifests as left or right ventricular systolic dysfunction with/without heart failure due to dilated or hypertrophic cardiomyopathy, diastolic dysfunction with preserved/decreased systolic function, conduction disturbances and supraventricular/ventricular arrhythmias, thrombus formation, arterial hypertension, pulmonary hypertension, left ventricular hypertrabeculation, coronary artery disease, and valve defects. Cardiac involvement in BMD must be detected and treated at an early stage, because it progresses over time and has a significant impact on the course of the disease. Established treatment methods include non-invasive therapies with small molecules and catheter-based invasive therapies (stent implantation, endocardial and epicardial ablation), device-related treatments (pacemaker, implantable cardioverter-defibrillator, cardiac resynchronization therapy, left ventricular assist device), and heart surgery. Cardiac involvement in BMD occurs in about two-thirds of patients, is subclinical in the early stages but becomes symptomatic as the heart disease progresses, requires early diagnosis, and can be treated with non-invasive and invasive therapies, with prognosis improving with early detection and adequate treatment.

Keywords: Arrhythmias, Becker muscular dystrophy, cardiomyopathy, dystrophin, noncompaction

INTRODUCTION

Becker muscular dystrophy (BMD) is a rare primary myopathy that is usually caused by large in-frame duplications or deletions affecting one or more exons, and rarely by small deletions/duplications/insertions, splice site variants that maintain the reading frame, or point mutations, including nonsense mutations that generate a stop codon and missense mutations that disrupt the reading frame in the *dystrophin* gene on chromosome Xq21.2.¹ Becker muscular dystrophy manifests phenotypically as skeletal muscle myopathy,¹ significant cardiovascular complications,² occasional epilepsy,³ and occasional cognitive impairment.^{4,5} Joints, ligaments, and bones may be secondarily affected due to skeletal muscle weakness, joint dislocations, and contractures.⁶ Becker muscular dystrophy differs from allelic Duchenne muscular dystrophy (DMD) by the presence of dystrophin in Western blot or immunohistochemistry. Becker muscular dystrophy is an X-linked recessive disorder that is either transmitted via female carriers of a dystrophin mutation in one of their X-chromosomes or occurs spontaneously in males due to germline mutations in the X-chromosome.¹ Not only males but also female carriers show phenotypic symptoms if the major part of the chromosome carrying the mutation is not inactivated according to the Lyon hypothesis.⁷ The prevalence of BMD is estimated at 1 in 18 000 male births.⁸ This narrative review aims to summarize and discuss recent advances and future perspectives regarding the clinical

REVIEW

Josef Finsterer 

Department of Neurology, Neurology &
Neurophysiology Center, Vienna, Austria

Corresponding author:

Josef Finsterer
✉ ffigs1@yahoo.de

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presentation, diagnosis, treatment, and outcome of cardiac involvement in BMD.

METHODS

Data for this review were obtained through a literature search in the PubMed, Embase, and Google Scholar databases using the search terms "Becker muscular dystrophy," "dystrophinopathy," "dystrophin," and "X-linked myopathy" in combination with "heart," "myocardium," "arrhythmias," "heart failure," "systolic dysfunction," "diastolic dysfunction," "thrombus," "heart valve," "cardiac conduction," "treatment," and "therapy." In addition, reference lists were searched for articles that met the search criteria. Articles containing original data on the occurrence, diagnosis, treatment, and course of heart disease in BMD were included. Articles that did not contain original data, were not available as full articles, were not written in English, or were duplicates were excluded (Figure 1).

RESULTS

Clinical Manifestations

A total of 86 articles meeting the inclusion criteria were identified (Figure 1). Heart disease within the BMD encompasses not just a single disease, but several different clinical entities.

Types of Cardiac Involvement

The most common manifestation of cardiac involvement in BMD is dilated cardiomyopathy (dCMP), which results from the replacement of cardiomyocytes by fibrous tissue, leading to impaired contractility and thus dilation of the left and right ventricles (Table 1).^{9,10} In rare cases, BMD can also manifest as hypertrophic cardiomyopathy.^{11,12} If systolic dysfunction exceeds a certain level, patients develop heart failure, which is clinically characterized by jugular vein enlargement, exertional dyspnea, and leg edema. Liver congestion may also cause pain in the upper abdomen. Reduced myocardial contractility can lead not only to left ventricular systolic dysfunction, but also to left ventricular diastolic dysfunction, which is classified into four degrees of severity: 1. impaired relaxation (E/A ratio <1), 2. pseudonormal filling, 3. reversible restrictive filling pattern (E/A ratio >2), and 4. irreversible restrictive filling pattern.¹³ Patients with BMD often also show cardiac conduction disorders (atrial, Hisian, and infra-Hisian)¹⁴ or supraventricular and ventricular arrhythmias,¹³ including sinus tachycardia, atrial fibrillation (AFIB),¹⁵ atrial flutter (AFLU), ventricular extrasystoles, non-sustained or sustained

ventricular tachycardia, or cardiac arrest.¹⁶ Depending on the stage of the disease, ECG abnormalities can be detected in up to 77% of patients.¹⁴ The classic pattern of ECG abnormalities in patients with BMD includes high R-waves, Q-waves in the left precordial leads, right axis deviation, and complete right bundle branch block.¹⁷ These ECG abnormalities correlate with a predilection for myocardial fibrosis in the posterobasal wall.^{17,18} Rare manifestations of cardiac involvement include arterial hypertension,¹⁹ pulmonary hypertension,³ coronary artery disease,²⁰ valvular heart disease (mitral regurgitation),²¹ left ventricular hypertrabeculation (LVHT) (Figure 2),²²⁻²⁴ congenital heart disease (bicuspid aortic valve),²⁵ coronary artery dissection,¹⁹ or Takotsubo syndrome (broken heart syndrome) (Table 1).²⁶ Early-onset cardiomyopathy is associated with mutations that disrupt the spectrin repeat in the rod domain region, as well as with mutations in exons 12, 14-17, or 31-42, whereas late-onset cardiomyopathy is associated with a deletion of exons 2-9 and 45-49.²⁷

Prevalence of Cardiac Involvement

The frequency of cardiac involvement in BMD is between 60% and 75%.¹⁹ In the vast majority of cases, heart disease develops after the onset of muscular symptoms,²⁰ but there are rare cases in which cardiomyopathy preceded the muscular manifestations.^{22,28,29} In a recent study of 163 patients with BMD, heart disease occurred before the onset of muscle symptoms in only 5 patients with an average age of 33 years.²⁹ Another case of heart disease occurring before muscle disease has also been reported.³⁰ The prevalence of heart disease increases with age.³¹

Symptoms and Signs

Symptoms that patients with CMP and BMD may experience include fatigue, exercise intolerance, shortness of breath at rest or during exertion, edema, palpitations, chest pain, fainting, headache, dizziness, polyuria, or nocturia. Cardiologic signs may include arrhythmias, ventricular extrasystoles, tachycardia, bradycardia, abnormal heart sounds, crackles, crepitus, leg edema, liver enlargement, or jugular venous distension.

Diagnosis

The diagnosis of heart disease in BMD is usually made by a cardiologist based on medical history, clinical examination, standard ECG, long-term ECG, loop recording, stress testing, transthoracic or transesophageal echocardiography, stress echocardiography, cardiac MRI (cMRI), coronary angiography, or scintigraphy (e.g., TC-99m single photon emission computed tomography (SPECT) or methoxyisobutylisonitrile (MIBI) SPECT. Cardiac MRI is preferable to echocardiography, as echocardiography can be difficult in patients with scoliosis, chest deformities, ventilation disorders, and contractures. In addition, cMRI can detect late gadolinium enhancement (LGE), which occurs predominantly in the postero-basal region in a subendocardial distribution. Late gadolinium enhancement correlates with myocardial fibrosis, increases with age, and correlates with the decline in ejection fraction (EF).³¹

Treatment

The treatment of heart disease in BMD can be classified as approved (established) or in development/experimental/

HIGHLIGHTS

- Cardiac involvement in Becker muscular dystrophy (BMD) occurs in about two-thirds of patients.
- Cardiac involvement is subclinical in the early stages but becomes symptomatic as the heart disease progresses.
- Cardiac involvement requires early diagnosis.
- Cardiac disease in BMD can be treated with non-invasive and invasive therapies, with prognosis improving with early detection and adequate treatment.

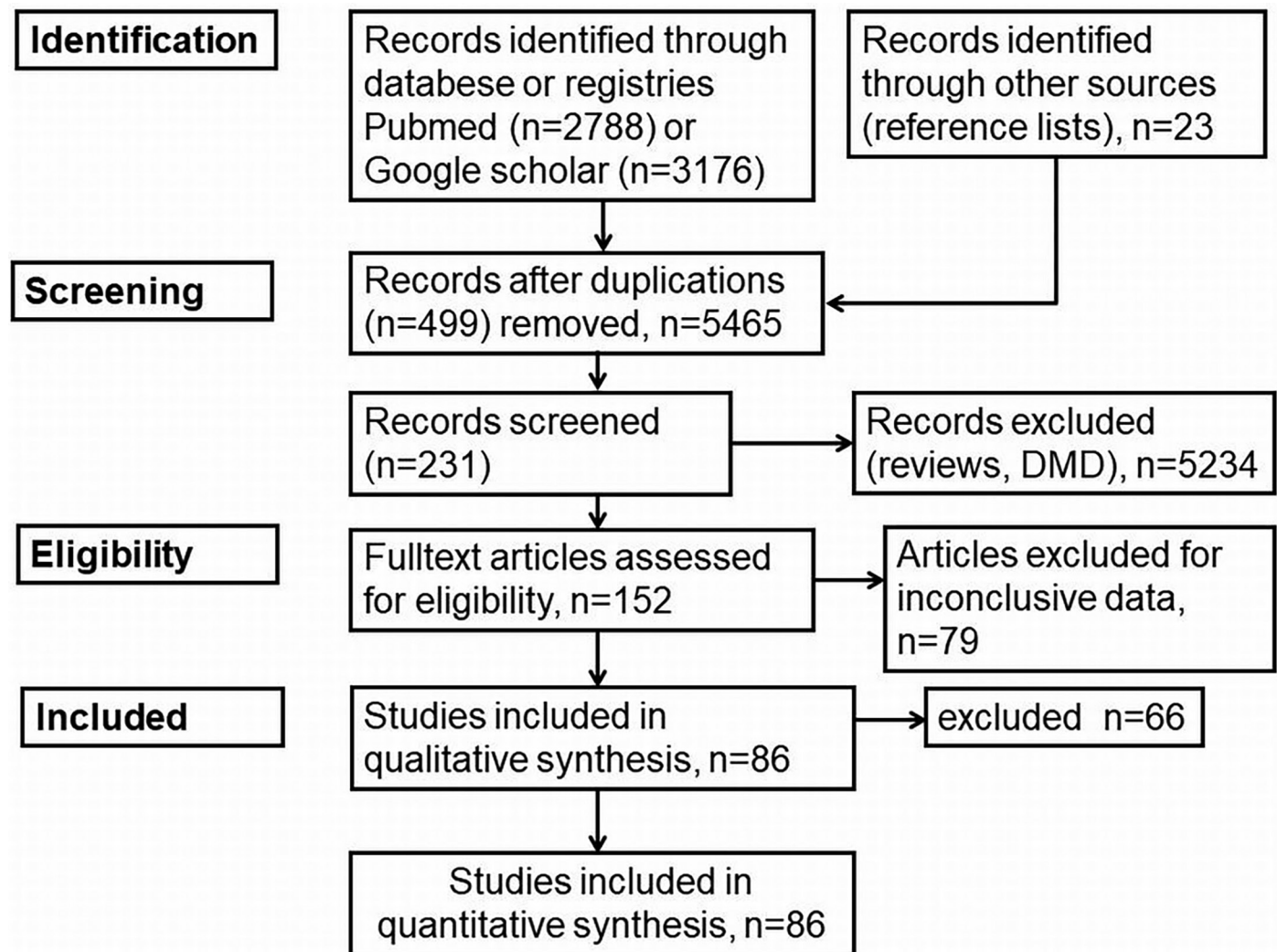


Figure 1. Flow chart of literature search results and study selection process.

innovative (Table 2). Approved therapies can be further subdivided into non-invasive or invasive, as well as prophylactic (presymptomatic) or symptomatic therapies. Established non-invasive therapies include physical therapy, pharmacological treatment, avoidance of cardiotoxic drugs, and partially gene therapies (read-through, exon skipping, gene editing, and gene replacement) (Table 2). Invasive treatments can be classified as catheter-based (minimally invasive), device-related, or surgical (HTX, aortocoronary bypass, left atrial appendage resection, trabecular resection in LVHT, valve replacement, thoracic or spinal stabilization). Future therapies can be classified as pharmacological, cell-based, or gene therapies. The question of who should treat heart disease in BMD can be answered clearly. The cardiologist should treat symptomatic patients, while prophylaxis can also be prescribed by the treating neurologist.

Standard (Established) Therapies

There is evidence that several medications can have a positive effect on heart function in patients with BMD and carriers. However, drug therapy for heart disease is often only

effective to a limited extent, as heart disease can progress rapidly and require a switch to invasive therapy. In advanced stages of cardiac involvement, only a combination of different therapies is often beneficial.

Non-invasive Therapies

Pre-symptomatic Treatment

The question of whether asymptomatic patients with BMD with normal systolic function should receive drugs that prevent or delay the development of myocardial fibrosis has not yet been investigated in large-scale studies. However, there is evidence from studies with patients with DMD that angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and glucocorticoids delay the development of fibrosis and dCMP.^{32,33} Angiotensin-converting enzyme inhibitors and ARBs are known to not only reduce cardiac afterload but also mitigate myocardial fibrosis by interfering with the renin-angiotensin system (RAS) and blocking angiotensin II,³⁴ transforming growth factor-beta

Table 1. Cardiac Abnormalities in Becker Muscle Dystrophy and Their Treatment

Abnormality	Treatment
Hypertrophic cardiomyopathy	GDMT
Dilated cardiomyopathy	GDMT
Systolic dysfunction	GDMT
Diastolic dysfunction	GDMT
Conduction defects	GDMT
Supra-ventricular arrhythmias	GDMT
Ventricular arrhythmias	GDMT
Thrombus formation	OAC
Coronary heart disease	GDMT
Arterial hypertension	GDMT
Pulmonary hypertension	GDMT
Mitral valve insufficiency	Valve replacement
Congenital heart disease	GDMT
LVHT	Depends on type of complications
Takotsubo syndrome	Beta-blockers

GDMT, guideline-directed medical treatment; LVHT, left ventricular hypertrabeculation; OAC, oral anticoagulation.

(TGF1b), an important mediator of fibrosis, fibroblast proliferation, collagen synthesis, and the overall development of fibrotic tissue.³⁵ Similarly, ARBs reduce myocardial fibrosis by counteracting the pro-fibrotic effects of the RAS by reducing inflammation, myofibroblast differentiation, and the production of extracellular matrix proteins involved in the fibrotic process.³⁶ Mineralocorticoid receptor antagonists are known to counteract fibrosis and improve ventricular function by blocking the action of aldosterone, which stimulates the transcription of collagen genes.³⁷ Angiotensin-converting enzyme inhibitor, ARBs, and MRAs are typically

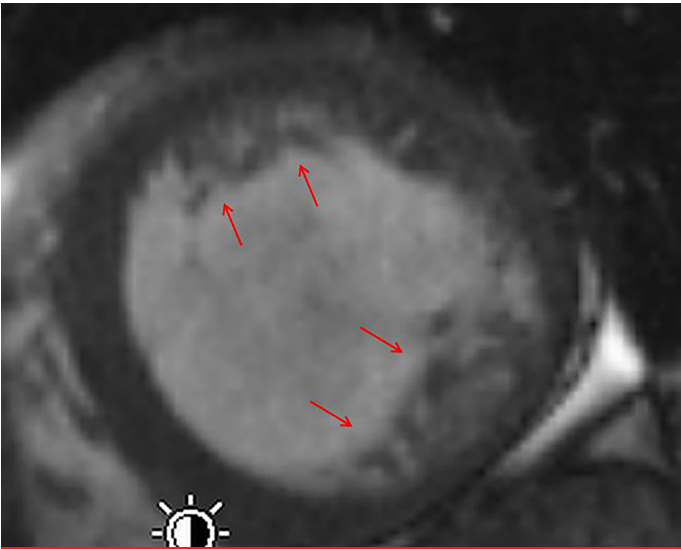


Figure 2. cMRI of a female carrier of a dystrophin deletion showing extensive left ventricular hypertrabeculation in the short axis view. cMRI, cardiac MRI.

Table 2. Classification of Established and Experimental Therapies for Cardiac Disease in Becker Muscular Dystrophy

Approved Standard Therapies
Non-invasive therapies
Drug (pharmaceutical)
Pre-symptomatic
Symptomatic
Systolic dysfunction
Diastolic dysfunction
Arrhythmias and conduction disturbances
Thrombus formation
Other cardiac abnormalities
Avoidance of cardiotoxic compounds
Resistance training
Invasive therapy
Catheter-based
Implants
Surgery
Upcoming therapies
Pharmacological
Cell-based therapies
Genetic therapy
Targeting the disease causing gene
Correction of the genetic defect
Read through therapies
Exon skipping
Gene editing
DNA editing
RNA editing
Gene replacement therapy (mini-/micro-dystrophin)
Targeting non-disease-causing genes (SERCA2a, Trm63, S100A1, ARC)

used when myocardial fibrosis is documented on cardiac magnetic resonance tomography (cMRT) but systolic function is preserved, there is an asymptomatic decrease in ejection fraction (EF), EF is <55%, or asymptomatic arrhythmias occur. Whether glucocorticoids (e.g., deflazacort, prednisone, and prednisolone) can delay myocardial fibrosis in asymptomatic patients with BMD has not yet been systematically investigated. However, studies in patients with DMD have shown that glucocorticoids can delay the decline in cardiac function by suppressing TGF1b and the inflammatory immune response following fibrosis.³⁸ In a study of 21 patients with DMD treated with deflazacort for 3 years, the prevalence of dCMP was lower compared to the control group.³⁹ In a study of 48 patients with DMD who received either deflazacort or prednisone, the patients treated with steroids had higher fractional shortening (FS) than the untreated patients.⁴⁰ In a study of 14 patients with DMD who received steroids over a period of 4.5 years, the patients treated with steroids had less ventricular dilation and systolic dysfunction than the untreated patients.⁴¹ In a study involving 462 patients with DMD, the onset of dCMP was delayed by 2.1 years in patients treated with steroids.⁴² The limitations of all these studies are that they are retrospective and that the steroid doses administered varied considerably.³¹ As a rule, only a few patients with BMD are treated with prednisone in the long term (9 in a study involving 163 cases).²⁹

Symptomatic Treatment

Pharmacological

Systolic Dysfunction

The treatment of systolic dysfunction (EF <50%, FS <28%) with/without heart failure in patients with BMD is carried out according to the established American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines from 2022.⁴³ This guideline-directed drug therapy (GDMT) is based on the administration of a combination of 4 drug classes (quad therapy): 1. A neprilysin inhibitor (e.g., sacubitril) together with an ARB (e.g., valsartan) or an ACEI, 2. Beta-blockers (e.g., bisoprolol), 3. MRAs (e.g., eplerenone, spironolactone, vamorolone), and 4. Sodium-glucose cotransporter 2 inhibitors (SGLT-2) (e.g., sitagliptin, dapagliflozin).⁴³ Additionally, loop diuretics (e.g., furosemide) and fibrates (e.g., fenofibrate) may be administered. Beta-blockers are known to reduce heart rate and myocardial oxygen demand. However, there is also evidence that perindopril and bisoprolol do not improve ventricular function in patients with DMD.⁴⁴ Arterial hypotension may limit the use of beta-blockers. Mineralocorticoid receptor antagonists are usually administered to patients with New York Heart Association class III or IV who are already optimally controlled with ACEI and beta-blockers.⁴⁵ In a study of 20 patients with DMD with preserved EF, eplerenone resulted in a smaller reduction in left ventricular circumferential strain compared to 20 controls.⁴⁶ In a single patient with BMD, heart failure was treated with sacubitril/valsartan (2x50 mg/day), furosemide (2x20 mg/day), spironolactone (25 mg/day), dapagliflozin (10 mg/day), fenofibrate (160 mg/day), and bisoprolol (2.5 mg/day).⁴⁷

Whether steroids (e.g., deflazacort, prednisone, and prednisolone), which are used to inhibit the progression of fibrosis and dystrophy in skeletal muscle, are also beneficial in symptomatic heart disease, particularly dCMP, has not been systematically investigated in patients with BMD. However, there is evidence from studies in patients with DMD that steroids, especially deflazacort (0.9 mg/kg/day) and prednisone (0.75 mg/kg/day or 10 days of treatment, 10 days off), can improve systolic function and increase cardiac output.³⁸ Steroids are known to modulate gene expression by activating/suppressing transcription, inhibit or delay secondary inflammation after muscular dystrophy by inhibiting TGF- β , and modulate metabolic stress even in symptomatic patients.³⁴ Givinostat, a histone deacetylase inhibitor approved by the FDA and EMA for the treatment of patients with DMD aged 6 years and older with all genetic variants of DMD, has not been studied for a potential effect on heart disease in BMD.

Diastolic Dysfunction

Treatment of stage I diastolic dysfunction focuses on treating the underlying causes, such as high blood pressure, diabetes, and coronary heart disease, as well as lifestyle changes (e.g., healthy diet, regular exercise, avoiding nicotine, balanced nutrition, aerobic exercise, reducing saturated fats, sugar, and sodium intake, stress reduction, and adequate sleep). In pseudonormalization (stage II), medications such

as ACEI, calcium channel blockers, and diuretics may be helpful, whereas other medications may control blood pressure or heart rate. In severe cases (stages III and IV), treatments may include advanced options such as left ventricular assist devices (LVADs) or, in rare cases, heart transplantation (HTX).

Arrhythmias and Conduction Disturbances

Arrhythmias and conduction disturbances are thought to be caused by fibrosis of the cardiac conduction system (Purkinje fibers).⁴⁸ Beta-blockers are usually administered to reduce the heart rate in cases of sinus tachycardia. If beta-blockers are ineffective or cause side effects, amiodarone is usually tried.⁴⁹ If amiodarone is ineffective, ivabradine, a selective I(f) current blocker in sinus node cells, is an option.⁵⁰ Unlike beta-blockers, ivabradine does not cause hypotension. In a 22-year-old patient with BMD, dCMP, systolic dysfunction, and sinus tachycardia, ramipril was successfully replaced with candesartan, ivabradine, and furosemide.⁵⁰ Discontinuation of ivabradine led to recurrence of sinus tachycardia and arterial hypotension.⁵⁰ In a DMD rat model, ivabradine reduced the progression of cardiomyopathy and lowered the heart rate to normal values.⁵¹ Premature ventricular complexes (beats) usually do not require treatment, but if they cause syncope or non-sustained ventricular tachycardia, or if they are associated with a positive family history of sudden cardiac death (SCD), treatment with beta-blockers, calcium channel blockers, or ablation is indicated. Non-sustained ventricular tachycardias are treated with beta-blockers and, if these are ineffective, with an implantable cardioverter defibrillator (ICD) according to the 2017 AHA/ACC guidelines for ventricular arrhythmias.⁵² QT dispersion has been shown to be increased in BMD, which is associated with an increased risk of SCD.⁵³ Wolff-Parkinson-White (WPW) syndrome has been shown to be the first manifestation of BMD, but no accessory pathways could be identified during attempted radiofrequency ablation.⁵⁴ Atrial fibrillation or AFLU should be treated according to the established AHA/ACC guidelines from 2023.⁵⁵ Atrial, Hissian, or infra-Hissian conduction disturbances are a domain of invasive therapy.

Thrombus Formation

The question of whether and when patients with BMD should receive oral anticoagulants (OAC) has not yet been clarified. However, according to the 2024 AHA/ACC guidelines, patients with AFIB or AFLU should receive OAC if the CHA2DS2-VASc score is >1 in men and >2 in women⁵⁶ and if the HAS-BLED score is below 3. However, the decision should be made on an individual basis, using the HAS-BLED score to assess bleeding risk, not to deny treatment, but to identify and treat modifiable bleeding factors. The AHA/ACC guidelines also recommend OAC for patients with severe systolic dysfunction, especially shortly after diagnosis of heart failure (HF) or if there is a history of thromboembolism or AFIB.⁴³ A case of cardioembolic thromboembolism with ischemic stroke has been reported in a 65-year-old BMD patient who was treated with OAC in addition to diuretics and dopamine.¹⁵ The question of whether patients with BMD and LVHT should receive OAC due to the risk of cardioembolic thromboembolism remains unresolved. However,

if thrombi are documented in the intertrabecular spaces on cMRI, experts recommend the administration of OAC.^{57,58} Medications used as OACs include vitamin-K antagonists (e.g., phenprocoumon and warfarin), direct thrombin antagonists (e.g., dabigatran, argatroban, bivalirudin, and lepirudin), thrombin receptor antagonists (e.g., vorapaxar), and factor-X-inhibitors (e.g., rivaroxaban, apixaban, and edoxaban). Only vitamin K antagonists should be used in patients with mechanical heart valves.

Other Cardiac Abnormalities

Pulmonary hypertension is treated in accordance with established guidelines using endothelin receptor antagonists (e.g., ambrisentan and bosentan), phosphodiesterase inhibitors (e.g., sildenafil), and OAC.^{16,59} Heart transplants should only be considered in cases of treatment-resistant disease. If patients with BMD also suffer from coronary heart disease, valve stenosis, or valve insufficiency, GDMT should be used. The use of statins or PCSK-9 inhibitors for hyperlipidemia and elevated low density lipoprotein (LDL) or elevated Lp(a) should be considered.⁶⁰ However, statins and fibrates should be administered with caution as they can trigger rhabdomyolysis, cause cardiomyopathy, and lead to HF.

Avoidance of Cardiotoxic Compounds: Side effects of cardiac therapy may include myopathies caused by beta-blockers or statins. There is evidence that statins can also cause cardiomyopathy and heart failure.⁶¹ Amiodarone is known to cause thyroid dysfunction and visual disturbances. Volatile halogenated anesthetics and succinylcholine can cause malignant hyperthermia with tachycardia, ventricular arrhythmias, and disseminated intravascular coagulation. Therefore, beta-blockers (e.g., propranolol, labetalol), statins, amiodarone, succinylcholine, and volatile anesthetics should be administered with caution.^{19,62,63} It is also recommended to avoid QT-prolonging drugs (e.g., amiodarone, sotalol, haloperidol, ziprasidone, macrolides, fluoroquinolones, citalopram, and tricyclics). Nonsteroidal anti-inflammatory drugs have been shown to exacerbate heart failure in patients with isolated BMD.⁶⁴ Certain chemotherapeutic agents can cause heart failure, and local anesthetics and proton pump inhibitors can trigger ventricular arrhythmias.

Resistance Training: Although resistance training can improve muscle strength, functional ability, and quality of life in patients with BMD, its effects on cardiac function are less clear. This is because no systematic studies have been conducted on the effect of resistance training on cardiac function in patients with BMD. A study involving a single patient with BMD who completed 12 weeks of resistance training failed to demonstrate any positive effect on cardiac function.⁶⁵ In a study involving 5 patients with BMD who completed a 12-week resistance training program, the mean maximum voluntary contraction increased, and the time taken to move from sitting to standing and to climb and descend stairs became significantly faster, but the effects on the myocardium were not investigated.⁶⁶ In a study involving 11 patients with BMD, 12 weeks of training improved VO_2max by 47% and maximum work capacity by 80%.⁶⁷ However, systolic function did not change.⁶⁷

Invasive Therapy

There are no systematic studies on the benefits of catheter-based intervention, device-based treatment, or surgical treatment of heart disease in patients with BMD, but case reports and case studies provide promising results. There is also evidence from patients with DMD that invasive therapies are becoming increasingly important for the treatment of heart disease in patients with BMD.

Catheter Based

In cases of non-valvular AFIB or AFLU where OAC is not possible, ablation of the left atrium may be attempted.^{16,68} If patients with non-valvular AFIB have a high risk of stroke but also a high risk of bleeding or other reasons that prevent long-term OAC, closure of the left atrial appendage (LAA) is a therapeutic option.⁶⁹ However, it must be considered that the LAA is an actuator in a control loop for intravascular volume regulation and may lose this function upon closure. Closure of the LAA aims to prevent embolization of clots from the LAA into the general circulation. However, this goal cannot be achieved if the closure leaks.⁷⁰ In patients with BMD presenting with acute symptomatic or asymptomatic coronary artery disease, a stent should be inserted in accordance with established guidelines.⁷¹ In chronic coronary artery disease, aortocoronary bypass surgery (ACBP) is indicated.⁷¹ In cases of concomitant congenital heart disease (e.g., tetralogy of Fallot),⁷² closure of an atrial septal defect (ASD) or ventricular septal defect (VSD) using catheter-based implants may be considered. If, despite the indication for valve reconstruction, thoracotomy and the use of a heart-lung machine or general anesthesia are contraindicated, this can be performed by transcatheter valve implantation (e.g., TAVI).

Implants

In cases of sick sinus syndrome, atrioventricular-block, or symptomatic sinoatrial-block, implantation of a pacemaker (PM) should be considered.⁷³ In cases of survived cardiac arrest or persistent ventricular tachycardia, an ICD should be implanted in accordance with the AHA/ACC guidelines.⁷³ Cardiac resynchronization therapy (CRT) with or without a defibrillator (CRT-D) is indicated if heart failure is present together with asynchrony between the innervation of the right and left ventricles.^{22,73} Left ventricular assist devices may be indicated for mechanical circulatory support when conventional drug therapies or CRT/CRT-D systems are ineffective for treating heart failure and patients with BMD are not eligible for HTX.⁷⁴ Left ventricular assist devices can be implanted in patients on the waiting list for HTX to bridge the time until surgery. In a female BMD carrier with dCMP as the only symptom of the disease, heart failure progressed so rapidly that she required an LVAD prior to HTX.⁷⁴

Surgery

Heart transplant is an established alternative to drug and device-based cardiac therapy when these prove unsuccessful in BMD presenting with heart failure (refractory systolic dysfunction). It is indicated for patients with end-stage heart failure who cannot be treated with other means, especially in cases of refractory heart failure or life-threatening

ventricular arrhythmias.⁷⁵ In a study of 29 patients with muscular dystrophy (52% had BMD), the results in terms of infection rates, rejection, and allograft vasculopathy were similar to those of 275 controls.⁷⁶ Aortocoronary bypass surgery is indicated when stent implantation is no longer indicated for coronary artery disease or when chronic coronary artery stenosis is present. Valve replacement is indicated for severe secondary mitral regurgitation, but can also be performed transcatheterously. Resection of the left atrial appendage in AFIB has been proposed, but its effectiveness is controversial. Whether patients with LVHT could benefit from trabecular resection, as has been suggested,⁷⁷ is also controversial, as such procedures do not guarantee that the trabeculae will not recur. If valve replacement cannot be performed transcatheterously, thoracotomy with open-heart surgery remains an option. All cardiac surgery can only be performed if respiratory function is not impaired and the overall survival rate is considered sufficient. Since all cardiac surgeries are usually performed under general anesthesia, there is a risk of malignant hyperthermia, which is why individual patients may need to be tested for susceptibility to malignant hyperthermia before surgery. It should also be noted that some of the immunosuppressants administered to prevent transplant rejection after heart transplantation may be cardiotoxic and may impair not only cardiac function but also the function of striated skeletal muscle.⁷⁸ Because scoliosis or thoracic deformities can also be a feature of BMD, especially in patients who are wheelchair-bound, the scoliosis can become so severe that it impairs heart and lung function. In this case, patients can benefit cardiologically from surgical correction of scoliosis using Harrington rods.⁷⁹ Overall, there is currently only limited experience with applicable invasive cardiac therapies in patients with BMD. In a study of 163 patients with BMD, 8 patients had a PM implanted, 11 had an ICD implanted, 4 had an LVAD implanted, and 7 had undergone HTX.²⁹ Left-sided cardiac sympathetic denervation is a surgical technique that could be used to prevent malignant arrhythmias.

Upcoming (Experimental) Therapies

Pharmacological

To counteract the loss of sarcolemmal integrity, synthetic amphiphilic copolymers, in particular poloxamer-188, have been investigated as membrane-stabilizing therapy in pre-clinical animal models for DMD (mdx mice and dystrophic dogs) and have shown promising results.⁸⁰ Poloxamer-188 works by selectively attaching itself to sites of membrane damage where mechanical stress or micro-tears expose the hydrophobic interior of the lipid bilayer.⁸¹ It is unknown whether this effect also applies to BMD animal models (dmd del 52-55 mice, dmd del exon 3-16 rats, and del 45-47 bmx mice⁸²). Poloxamer-188 localizes and seals membrane disturbances and effectively reduces membrane permeability. Treated animals showed improved cardiac output and better structural preservation, underscoring the potential for membrane repair.⁸⁰ An initial clinical trial with patients with DMD is currently underway to investigate the safety and efficacy of the approach, but no results are available yet. However, there are also reports that demonstrate a positive effect on the heart muscle but a harmful effect on skeletal muscle.⁸³

Cell Based

CAP-1002 [Deramiciocel®] is derived from mesenchymal stem cells from the heart and is a cell-based therapy based on the ability of stem cells to secrete regulatory, regenerative, and anti-inflammatory factors that support muscle repair. CAP-1002 aims to improve regenerative capacity to reduce inflammation, promote tissue healing, and potentially regenerate damaged cardiomyocytes. CAP-1002 was evaluated in a phase-2 study of 26 patients with DMD who received either CAP-1002 or placebo quarterly for 1 year.⁸⁴ The primary endpoint was the change in Performance of Upper Limb version 1.2 (PUL 1.2) scores for the mid-elbow after 12 months.⁸⁴ The mean change in PUL 1.2 score in the mid-elbow region after 12 months compared to baseline favored CAP-1002 over placebo.⁸⁴ It was concluded that CAP-1002 is safe and effective in reducing the deterioration of upper limb function in patients with late-stage DMD. Under CAP-1002, various measures of cardiac function and structure (e.g., FS, EF, wall thickness, and LVEDD) determined by cMRI improved.⁸⁴ In a study of 13 patients with DMD who received 75 million mesenchymal stem cells (MSCs) injected into the right circumflex artery, areas of fibrosis decreased visibly on cMRI and regional wall motion abnormalities improved.

Genetic Therapy

Gene therapy aims to restore the production of functional dystrophin protein in affected muscle and heart muscle tissue.⁸¹ Gene therapy is necessary because sustained dystrophin expression is essential for the continuous protection of cardiomyocytes.⁸⁵ Gene therapy can be divided into therapies that target the disease-causing gene and therapies that target non-disease-causing genes (e.g., *S100A1*, *SERCA2a*, and *ARC*).

Targeting Disease-Causing Gene

Gene therapy targeting the disease-causing gene is performed either by correcting the underlying mutation in the dystrophin gene (e.g., exon skipping, read-through approach, and gene editing) or by introducing a new functional copy of the gene into the patient's cells.⁸⁶

Correction of the Genetic Defect:

Read-through Therapies

In patients with a nonsense mutation (10%-20% of BMD cases), in which premature stop codons interrupt dystrophin production, read-through therapy with agents that enable the ribosome to bypass the faulty stop signal and continue translation, thereby potentially restoring functional dystrophin, is justified.⁸¹ One drug that showed promising results in mice in bypassing stop codons was gentamicin.⁸¹ However, gentamicin failed in human trials.⁸⁷ It is unknown whether read-through therapies can also be beneficial for the myocardium in BMD, but data from a few patients with DMD show that ataluren, an oxadiazole for which the EMA did not extend approval in 2024, has shown not only motor improvement but also a positive effect on the myocardium.⁸⁸ In a study of 7 ambulatory patients with DMD who received ataluren for an average of 4 years at an average age of 7.5 years, only 1 of them developed dCMP at the age of 11 and suffered acute myocardial injury.⁸⁸ In a study of 4 patients with DMD

who received ataluren over a period of 4 years, FS improved in 3 patients. Only 1 patient developed dCMP.⁸⁹

Exon Skipping

Exon skipping is another promising approach to restore the disrupted reading frame and generate a truncated but functional dystrophin protein. Exon skipping utilizes antisense oligonucleotides (AONs) such as phosphodiarnidate morpholino oligomers (PMOs), the 2'OMe modification, or tricycloDNA oligomers. These bind to specific splice sites and mask certain exons during the splicing process, thereby promoting the exclusion of the target exons.⁹⁰ The application of AONs led to an improved EF in mdx mice.⁹¹ However, FDA-approved AONs such as eteplirsén, golodirsén, viltolarsén, brogirdirsén, and casimersén showed only a moderate improvement in muscle performance and a limited effect on the heart.⁹⁰ In a retrospective study of 122 patients with DMD who received eteplirsén (targets exon 51), the annual decline in EF was -0.66% in the eteplirsén-treated patients compared to -1.38% in the control group.⁹⁰ Patients treated with eteplirsén had a lower risk of developing heart failure.⁹⁰ Golodirsén and viltolarsén target exon 53, casimersén targets exon 45, and brogirdirsén targets exon 44, but so far none have shown benefit for cardiac function or the prevention of myocardial fibrosis in patients with DMD. Drisapersén, a 2'OMe-based ASO targeting exon 51 in DMD, also failed to demonstrate clinical benefit in a phase-3 trial despite promising initial results.⁹² Its effect on the heart has not been investigated. To overcome the challenges of administering AONs to myocardial tissue, peptide-conjugated PMOs (PPMOs) represent a promising alternative to single AONs. In a study in dystrophic dogs, intracoronary administration of PPMOs for multiexon skipping resulted in a reduction of Q-amplitude and Q/R ratio, as well as restoration of dystrophin expression in the Purkinje fibers of the heart, leading to improvement or prevention of cardiac conduction abnormalities.⁹³ Another new generation of AONs is tricyclo-DNA, which improved cardiorespiratory function in mdx mice.⁹¹

Gene Editing

DNA Editing

CRISPR/Cas9 gene editing technologies are used to repair specific mutations, either by knock-in of deleted exons or knock-out of mutated exons, and have shown promising results in preclinical models and hold potential for personalized mutation-specific interventions.⁹⁴ In mdx mice, removal of the mutated exon 23 from the dystrophin gene by administration of the CRISPR/Cas9 system via adeno-associated viruses (AAV) for expression of the modified dystrophin gene led to partial restoration of functional dystrophin protein in myofibers and heart muscles and improved muscle function.⁹⁵ Delivery of the CRISPR/Cas9 system via AAV to express the modified *dystrophin* gene resulted in partial restoration of functional dystrophin protein in myofibers and heart muscles, improvement in muscle biochemistry, and increased muscle strength.⁹⁴ In a DMD mouse model with deletion of exons 52-54 that develops an early-onset cardiac phenotype, CRISPR/Cas9 administered intravenously via AAV restored functional dystrophin expression by excision or

skipping of exon 55.⁹⁵ Transcript editing and dystrophin restoration were primarily limited to cardiac tissue.⁹⁵ In a mouse model with a deletion of exon 44 in the *dystrophin* gene, single-swap editing, in which an adenine base editor edits a single base pair at a splice donor site or splice acceptor site to enable exon skipping, restored dystrophin protein expression in cardiomyocytes derived from induced pluripotent stem cells (iPSCs) by restoring the 3 most therapeutically relevant exons, 45, 51, and 53.⁹⁶

By applying this knock-in approach to correct all mutations downstream of exon 44 in DMD-specific iPSC lines harboring mutations in exons 45 and 51, the expression of mini-dystrophin was confirmed by Western blot and immunofluorescence staining.⁹⁷ Transplantation of gene-edited myogenic progenitor cells derived from DMD iPSCs into NSG/mdx4Cv mice resulted in the formation of donor-derived myofibers, as evidenced by the dual expression of human dystrophin and lamin A/C. This provided proof-of-concept for the use of programmable nucleases to develop an autologous iPSC-based therapy for muscular dystrophies.⁹⁷ In a study of DMD iPSCs with deletion of exon 50, full-length dystrophin expression and membrane localization in cardiomyocytes were restored by targeted addition of exon 50 at the junction of exon 49 and intron 49 using homologous recombination (HDR).⁹⁸

RNA Editing

Using a mini-dCas13X-mediated RNA adenine base editing strategy (mxABE) for the treatment of the nonsense point mutation c.4174CYT in the dystrophin gene, robust expression of the dystrophin protein was achieved at over 50% of the wild-type (WT) level by enabling premature termination codon (PTC) read-through in muscle tissue and by 54% in the myocardium.⁹⁹

Gene Replacement Therapy

Gene replacement therapies can be classified as in vivo gene therapy, in which genetic material is introduced directly into the patient's body, often via infusion or targeted treatment of a specific organ, whereas in ex vivo gene therapy, the patient's cells are isolated, modified in the laboratory, and then reinfused to the body. In vivo therapy is used for organs that are difficult to access, whereas ex vivo therapy is used for diseases that affect accessible tissues such as blood. Both methods use a vector, often derived from a modified virus, to transport the therapeutic genes to the cells.

Gene replacement therapy involves the administration of a mini-dystrophin or micro-dystrophin gene (μ -dys) that is engineered to fit within the packaging limits of the most commonly used AAV.^{100,101} In mini-dystrophins, part of the rod domain is removed, whereas in μ -dys, a significant portion of the rod domain and C-terminus is removed. These truncated versions of the gene encode truncated forms of dystrophin that retain essential functional domains of full-length dystrophin and may offer significant clinical benefit.⁸¹ Gene therapy using AAV to deliver mini-/ μ -dys is currently the most promising strategy for DMD.¹⁰² Mini-dystrophin transferred into a DMD mouse model resulted in normalization of the ECG, reduction of fibrosis, and improvement in EF. Similarly, μ -dys normalized heart rate, PR- and QT-intervals,

and cardiomyocyte integrity.¹⁰³ In a study of a site-specific gene addition strategy in iPSCs derived from a DMD patient with exon 50 deletion, a mini-dystrophin cassette was precisely targeted to the ribosomal RNA gene locus by homologous recombination using transcription activator-like effector nickases (TALENickases).¹⁰⁴ After differentiation of the target clone into cardiomyocytes, dystrophin expression and membrane localization were restored, and increased spontaneous contraction was observed in the modified cardiomyocytes.¹⁰⁴ Howard et al¹⁰⁵ recently developed the first DMD mouse model (Fiona mice) that reproducibly led to heart failure. This model shows that heart inflammation and fibrosis occur before functional decline. Fibrosis does not progress further, but inflammation persists after functional loss. The model was also used to test the efficacy of μ -dys therapy for the prevention of heart failure.¹⁰⁵ μ -dys therapy prevented a decline in heart function and suppressed the occurrence of inflammation and fibrosis.¹⁰⁵

Another gene replacement therapy is the intravenous administration of delandistrogen moxeparvovec [Elevidys®] from Sarepta Therapeutics, which has been approved by the FDA.⁸¹ However, there are still some challenges regarding the immune response, efficient administration, long-term expression, and safety.⁸¹ Reports of myocarditis-like reactions due to immune responses targeting either the AAV vector or the μ -dys have emerged in ongoing studies. In addition, a recently published report showed that a Phase 3 study with Elevidys failed to demonstrate a significant therapeutic effect. There have also been 3 deaths of patients who suffered acute liver failure after receiving experimental gene therapy for DMD.⁸¹ The severe hepatotoxicity underscores the need for a better understanding of dose thresholds for vectors, patient susceptibility, and long-term safety. Rigorous evaluation of these side effects, particularly immune-related complications, is essential. The combination of AAV therapy with PPMO resulted in a significant improvement in myocardial structure.¹⁰⁶ Several other μ -dys-based gene replacement therapies are currently in clinical trials to evaluate safety and efficacy.⁸¹

Numerous other microgen configurations and different AAV serotypes have been investigated in animal models in many laboratories. Bottlenecks in gene therapy for DMD/BMD using mini/ μ -dys administration include the fact that most of these approaches are only suitable for infants with strong muscle cell regeneration and immature immune systems and require a high dose of rAAV.¹⁰² However, a high dose of rAAV can cause an immune response and acute liver toxicity.¹⁰²

Targeting Non-disease Genes

Gene therapy targeting non-disease-causing genes is based on the upregulation and expression of non-dystrophin genes whose gene products have a positive effect on cardiac function.⁸⁶ Increasing calcium concentration in the endoplasmic reticulum through *SERCA2q* expression restores calcium homeostasis and prevents cell death. Gene therapy through *SERCA2a* gene expression is based on pumping calcium from the cytoplasm into the sarcoplasmic reticulum.⁸⁶ Increasing the expression of *SERCA2a* in mice using AAV

serotype-9 led to normalization of the ECG.⁸⁶ In a phase-2 study, *SERCA2a* gene therapy improved heart failure, systolic function, and diastolic volume.¹⁰⁷ Dual overexpression of *S100A1* and *ARC* in mdx mice improved diastolic dysfunction, long-term cardiac outcome, and heart failure caused by μ -dys expression.¹⁰⁸

Monitoring

Patients with heart disease in BMD must be monitored regularly in order to start, adjust, or intensify cardiac therapy. Patients with BMD should be examined regularly (at least once/year) for heart disease from the age of 10 years [<https://www.mda.org/disease/becker-muscular-dystrophy/medical-management>]. If cardiac involvement in BMD progresses rapidly during the course of the disease,¹⁰⁹ follow-up intervals may need to be shortened to 6 months or less. During follow-up examinations, patients should undergo long-term ECG and echocardiography. In patients with non-compaction, it is advisable to perform repeated cMRT with contrast medium to determine whether intraventricular or intertrabecular thrombus formation is present, so that the appropriate time for OAC to prevent cardiac embolism is not missed. If patients develop ventricular arrhythmias, a decision must be made as to whether they require implantation of a pacemaker or an ICD to prevent SCD. If the heart disease cannot be treated with medication or devices, HTX should be considered, as the survival rate without severe COI is usually quite good.¹¹⁰

Outcome

The course of heart disease in BMD depends heavily on the quality of diagnostic and therapeutic treatment of heart defects. Although there are few systematic studies on the optimal treatment of heart disease in BMD, it can be assumed that early detection, the use of prophylaxis, and optimized symptomatic treatment could be factors that determine the course of heart disease in these patients. Despite improved cardiac therapies for heart disease in BMD, these patients still die mainly from difficult-to-treat systolic dysfunction or difficult-to-treat malignant arrhythmias.⁴⁵ In addition, some patients die of SCD despite having an implanted ICD.¹¹⁰ In a study of 163 patients with BMD, no association was found between heart disease and loss of walking ability.²⁹ There may also be deterioration of systolic and diastolic dysfunction similar to patients with DMD.¹¹¹

CONCLUSIONS

Cardiac involvement is now a well-established phenotypic feature of male patients with BMD, female carriers, and animal models of BMD, and has been extensively described and discussed in the literature. Patients with BMD must be prospectively evaluated for cardiac disease, as it may be subclinical at onset and early treatment may prevent or delay potentially difficult-to-treat complications of the myocardium and intracardiac conduction system. Symptomatic cardiac therapy should remain in the hands of cardiologists and cardiac surgeons, as specialists are required to adequately treat the complex abnormalities that can occur during the course of the disease. There is growing evidence that steroids, read-through approaches, exon skipping, or

gene replacement therapies may be beneficial not only for muscle impairment but also for cardiac involvement in BMD. Various approaches to gene therapy are promising for the future, and some of them have already found their way into clinical application. There is also evidence that early treatment leads to better outcomes than late initiation of cardiac therapy. Much work remains to be done in the future to clarify open questions regarding the optimal and most effective therapeutic treatment of cardiac disease in BMD. Overall, the hearts of patients with BMD require proactive treatment within the framework of a multidisciplinary care model.

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