Clinical Management Guidelines for Friedreich Ataxia

Chapter 4. The heart and cardiovascular system in Friedreich ataxia

Contents

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4. The heart and cardiovascular system in Friedreich ataxia

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This chapter gives an extensive overview of the effects of Friedreich ataxia on the heart and cardiovascular system and the functional consequences of these effects. It also covers strategies for monitoring cardiac function and managing arrhythmias and heart failure in individuals with Friedreich ataxia. In making recommendations, the authors were tasked with answering the following questions:

For individuals with Friedreich ataxia, what surveillance strategies could be implemented to monitor cardiac function routinely? (see 4.2)

For individuals with Friedreich ataxia, what management strategies could be implemented for arrhythmias? (see 4.3)

For individuals with Friedreich ataxia, what management strategies could be implemented for heart failure? (see 4.4)

4.1 Overview of the heart effects of Friedreich ataxia

4.1.1 Cardiac effects of Friedreich ataxia

Friedreich ataxia (FRDA) is commonly accompanied by abnormalities of both cardiac structure and function, and cardiac disease is the main cause of death (1). Individuals with FRDA can experience arrhythmias, most commonly of atrial origin, and symptoms include palpitations, dizziness, dyspnea and chest discomfort. Individuals with FRDA can also develop heart failure (HF) with its associated symptoms, and the combination of HF and arrhythmia conveys a poorer prognosis (1). Deficiency of the protein frataxin is the fundamental abnormality which leads to expression of the cardiac phenotype of FRDA (2). As a result of mutations in both alleles of the *FXN* gene, most commonly due to a GAA repeat expansion, and the decreased levels of frataxin there is impaired assembly of iron–sulphur clusters that are critical to key enzyme functions in mitochondria and throughout the cell.

There has been no consistent definition or terminology used in published studies to describe the features of the cardiac involvement in FRDA (3-14), and this lack of consistency has made interpretation of, and comparison between, studies difficult. The most common description of the cardiac phenotype in FRDA has been “hypertrophic cardiomyopathy”, yet there are a number of reasons to question whether this is the best terminology in FRDA. One concern is that this can lead to confusion with the autosomal dominant conditions that are also termed hypertrophic cardiomyopathies. This is an important distinction as there are fundamental molecular and clinical differences between FRDA and these autosomal dominant conditions, which have implications for both outcomes and treatment. First, the mechanism which underlies the cardiac changes in FRDA is based on frataxin deficiency in the mitochondria, whereas in the autosomal dominant hypertrophic cardiomyopathies it is sarcomere abnormalities and myocardial fiber disarray (15). Second, the pattern of hypertrophy in FRDA is generally concentric, asymmetric septal involvement is not common, and there is rarely any outflow tract obstruction (6, 9). This is unlike the pattern seen in the autosomal dominant hypertrophic cardiomyopathies in which asymmetric septal hypertrophy is more frequent, and are more commonly associated with a resting or inducible dynamic outflow tract gradient (15). Furthermore, the term hypertrophic implies an increase in left ventricular mass index (LVMI), whereas the most common pattern of LV geometry in FRDA is an increase in relative wall

thickness (RWT) (9, 16). Even in the absence of any definite increase in RWT or LVMI, abnormalities on the electrocardiogram can occur (17), suggesting that there is at least some degree of myocardial abnormality in the majority of FRDA individuals. Individuals with FRDA can also have a dilated left ventricle with reduced LV ejection fraction (LVEF), that is, a phenotype consistent with a dilated cardiomyopathy. LV dilatation and reduced LVEF are generally not seen in FRDA at first presentation (9, 10, 18), indicating that there is evolution of this cardiac phenotype later in the disease process (18, 19). On the basis of the issues discussed above, the heterogeneous and unique collection of cardiac abnormalities seen in FRDA might be better described as “FRDA cardiomyopathy”.

To determine the direct effects of frataxin deficiency on the heart in FRDA, possible cardiac effects from coexistent conditions which are more common in FRDA as well as other common unrelated conditions need to be considered. Diabetes mellitus occurs in approximately 10% of individuals with FRDA (20, 21) and is recognized to have effects on cardiac structure and function (22-24). Sleep apnea is also recognized to have effects on the heart (25-27), is more common in FRDA than in the non-FRDA population, and has been reported to occur in young adults with FRDA even in the absence of morbid obesity (28). Hypertension and ischemic heart disease both become more common with age in FRDA, as they do in the non-FRDA population. Hypertension can lead to, and in FRDA presumably contribute to, similar LV geometric patterns (concentric remodeling and concentric hypertrophy) as seen early in the course of FRDA in the absence of hypertension (29). On the other hand, ischemic heart disease can lead to regional and possibly global hypokinesis of the left ventricle and these cardiac abnormalities can also occur late in the disease course in FRDA. Other acquired heart disease is not common in the FRDA population but should also be kept in mind. For example, myocarditis is not common but can occur at any age. Because of the underlying FRDA related cardiac abnormality, individuals with FRDA could be more susceptible to the effects of myocarditis.

4.1.2 Literature review of the structural and functional cardiac effects of Friedreich ataxia

The literature in FRDA can be loosely divided into studies before and after 1996, the year when the mutation in the *FXN* gene was first described. Most studies published after 1996 have included subjects with genetic confirmation of the diagnosis of FRDA. The early studies still provide useful information about the cardiac phenotype in FRDA, but due to the lack of genetic confirmation it is very likely that these studies also included some subjects without FRDA (30, 31). Furthermore, individuals who were homozygous for GAA expansions in the *FXN* gene but with atypical neurological presentations would not have been included in studies prior to 1996 (32, 33). In addition, point mutations in the *FXN* gene are now recognized to occur in more than 2% of people with FRDA (34-36), and it likely that some of the individuals in the early studies will have had such point mutations. There may be systematic differences in the cardiac phenotype of individuals with FRDA due to a point mutation compared to homozygotes for GAA expansions.

Cardiac involvement in FRDA has been assessed by a number of non-invasive techniques, including electrocardiography (EKG), echocardiography and cardiac magnetic resonance (CMR). There is only limited data regarding the natural history of cardiac disease in FRDA both before and after 1996. Part of this limitation is because cardiac disease is not usually diagnosed until after FRDA diagnosis, which is dependent on an individual presenting with neurological symptoms. There is limited pathological and histological data from post mortems and almost no cardiac biopsy data or catheterization-based data from living people with FRDA.

Electrocardiographic findings

Most individuals with FRDA have evidence of cardiac involvement as determined by the presence of an abnormal EKG (3, 17, 37, 38). A recent study of 239 children and adults, 79% of whom had genetically confirmed FRDA, found EKG abnormalities in 90% (17). The most common findings were nonspecific ST-T wave changes (53%), right axis deviation (32%), left ventricular hypertrophy (19%), and right ventricular hypertrophy (17). Females and those with smaller GAA repeats in the shorter allele of *FXN* (GAA1) were less likely to have EKG abnormalities. Longitudinal follow-up data is still required to determine whether an EKG can assist in early diagnosis of FRDA-associated cardiomyopathy, aid in the assessment of prognosis, or help to define the underlying pathophysiological processes.

Echocardiography and cardiac magnetic resonance imaging

Structural abnormalities frequently described in echocardiographic studies in FRDA are increase in left ventricular wall thickness (12, 13, 16, 39-42) and increase in left ventricular mass index (LVMI) (13, 16, 42, 43). However, the most common abnormality in FRDA is an increase in RWT, with only a proportion of subjects with increased RWT also having an increase in LVMI (9, 16, 39, 42). RWT is a simple and useful measure for the assessment of LV structural change in FRDA, although it is greater in males than females sex (44-46) and different thresholds in adults and children are appropriate for the diagnosis of an abnormal RWT (9, 45). While an increase in RWT without accompanying increase in LVMI (concentric remodeling pattern) could just be an earlier stage of the hypertrophic process than an increase in both RWT and LVMI (concentric hypertrophy pattern), there are alternative explanations for the relative lack of increase in LVMI in FRDA. One important component of the relative lack of increase in LVMI compared to RWT is that the LV remodeling in FRDA is not just reflected in an increase in wall thickness but also by a decrease in LV end-diastolic cavity size (9, 16, 39, 40, 43), the latter change necessarily associated with a lower LVMI than if the cavity size had not decreased. Another important observation from several cross-sectional studies in adults is that LVMI is inversely correlated with age (9, 41, 43), and therefore additional possible explanations for the relative lack of LVMI increases in FRDA could be aging-related LV remodeling, premature mortality or morbidity in individuals with FRDA with a higher LVMI, or a combination of both.

A definition of hypertrophy based on Henry's nomograms has been used in a number of studies in FRDA (10, 12, 13, 47). However, a diagnosis of the absence of cardiomyopathy based on a normal LV wall thickness using Henry’s nomograms not only has the intrinsic limitation of lacking consideration of the sex effects on LV mass index in healthy people and individuals with FRDA (9), but it has also been demonstrated in previous FRDA studies to fail in identifying an increase in RWT in a proportion of individuals. Thus, a RWT of 0.42±0.08 was found in a subgroup of 64/205 children and adults who were classified to be free of cardiomyopathy, indicating that a substantial proportion of the individuals in this subgroup would have had an abnormal RWT (i.e. 0.43 or above in adults) (12). Similarly, in another study in a subgroup of 56/133 individuals who were classified as not having LV hypertrophy, the RWT was 0.43±0.07 (10).

An additional accompaniment of the reduced LV end-diastolic volume in FRDA, in the absence of an increase in, rather than just preservation of LVEF, must be a reduction in stroke volume (39, 43). This would be predicted to lead to a decrease in the cardiac output even in the face of preserved LVEF. However, the cardiac output is at least partly preserved in FRDA despite the lower stroke volume because individuals with FRDA have a higher heart rate compared to controls (16, 39).

There is only limited data on the effects of FRDA on Doppler measures of left ventricular relaxation and filling, including transmitral E and A, their ratio (E/A) and isovolumic relaxation time (IVRT), in

comparison with age- and sex-matched controls. Furthermore, the results have not been consistent (5, 16, 39, 40, 48). An issue not considered in previous studies is that E is negatively correlated with heart rate, A is positively correlated with heart rate, and therefore the E/A ratio is inversely correlated with heart rate (49). The higher heart rate in individuals with FRDA should have been, but was generally not, adjusted for in comparisons with controls.

While LVEF is generally preserved in FRDA, some of the markers used to assess LV systolic function are reduced. Both systolic (and early diastolic) myocardial velocity gradients of left ventricular short axis function (reflecting radial systolic and early diastolic strain) were reduced compared to controls in a group of individuals with FRDA who were free of cardiac symptoms (40). Tissue Doppler measurements of longitudinal function in individuals with FRDA with preserved LVEF showed reduced peak velocities of both systolic and early diastolic left ventricular motion when compared to controls (16). Global longitudinal strain and peak systolic twist are also reduced in individuals with FRDA with normal LVEF and LVMI, but RWT is increased (39).

Left atrial (LA) dilatation is a sign of chronic elevation of left atrial pressure (50) and left atrial size is thus of considerable interest in FRDA as it might also be expected to increase in the setting of a small thick left ventricle. However, while there is limited information about left atrial size in FRDA, available data suggests that it is not routinely increased in individuals with increased RWT and normal ejection fraction (16, 39). In turn, this raises the possibility that the ratio of E/e`, which is elevated in FRDA (39), and increases with LA pressure in other cardiac conditions (50), may not be an accurate reflection of left atrial pressure in FRDA.

A number of studies have reported an association between the number of GAA repeats in the GAA1 allele and LV structural changes in FRDA, but the findings have not been consistent. GAA1 has been noted to be higher in people with a “cardiomyopathy” (4, 51) and other reports include positive correlations of GAA1 with wall thickness (31, 47, 52), RWT (11), LV mass (31, 43), LVMI (12, 47) and an inverse correlation of GAA1 with LV end-diastolic dimension (53). On the other hand, there have also been recent moderate-sized studies which have not replicated previous findings (13, 42). Potential explanations for these differences in results between studies include differences in the cohort characteristics and the limited size of individual cohorts. There has also been heterogeneity between studies in the statistical methods, for example, whether adjustments were made for potential confounding factors such as sex, age or body size. Neither is it clear that an adjustment for age is possible when children and adults are included in the same study, due to the complex nature of the differences between children and adults with FRDA (45, 54, 55). Furthermore, any FRDA cohort will necessarily be missing those individuals who have died prematurely from heart disease. As mortality is more likely to affect adults than children with FRDA (1), and occurs earliest in those with the most severe cardiac involvement (1), absence of individuals due to early mortality is likely to confound any analysis which includes adults and children together.

To address some of these issues a recent study investigated the correlation of GAA1 with LV echocardiographic measures separately in 68 children and 148 adults with FRDA (9). Increases in RWT and age-normalized RWT were the most frequent LV structural abnormalities, sex and body size were important determinants of most other LV structural variables in both children and adults, and GAA1 was associated with a smaller left ventricle and increased LV wall thickness in adults, but not associated with either LV size or wall thickness in children.

With regard to LV function, GAA1 has not generally been correlated with LVEF or LV fractional shortening, but has been reported to be inversely correlated with both systolic and early diastolic radial strain (40). GAA1 has also been reported to be an inverse correlate of right ventricular s` and e`, whereas a negative correlation of the number of GAA repeats in the longer allele (GAA2) with LV

regional s` (anterior and lateral walls) has also been reported (56). In other studies which have reported associations of GAA2 with cardiac variables, it has not been clear whether this association was independent of a positive correlation of GAA2 with GAA1 within the same study (10).

Using CMR spectroscopy, the cardiac phosphocreatine to ATP ratio was lower in individuals with FRDA with and without hypertrophy, implying that cardiac metabolic dysfunction in FRDA precedes hypertrophy and may play a role in its development (57, 58). In another CMR study, myocardial perfusion reserve index quantification revealed significantly lower endocardial-to-epicardial perfusion reserve in subjects with FRDA versus controls, whereas there was no difference in myocardial iron between the two groups using the CMR technique of T2* (11). The former finding suggests a greater potential for subendocardial ischemia in FRDA in situations where cardiac perfusion reserve is under stress (e.g., atrial fibrillation with a rapid ventricular response). The latter finding implies that the intra-mitochondrial iron particles in FRDA are relatively isolated compared with the large iron aggregates seen in transfusion-associated myocardial iron overload, making CMR measurement of iron content in the FRDA heart uninformative for guiding therapeutic interventions.

CMR has also been used to determine the presence of LV focal fibrosis using late gadolinium enhancement (LGE), and diffuse myocardial fibrosis using T1 mapping techniques. The proportion of people with LGE in studies in FRDA has been variable. Raman et al (11) reported the presence of LGE in 58% of adult subjects with a normal LVEF (age range 18-57 years). Weidemann et al (19) reported the presence of LGE in 66% of 32 subjects (age 33±13 years; number of children in the study not reported), 25% of whom had a LVEF <55%. All those with a reduced LVEF were positive for LGE, whereas 13/25 (52%) with a normal LVEF had LGE. That children with FRDA can develop LGE was also reported in 3 children with a normal LVEF by Mavrogeni et al (59). In contrast, Takazaki et al (60) reported only 15% LGE positivity in 27 subjects with a normal LVEF (age = 28±10 years). There is currently no explanation for the substantial variation in LGE positivity in the different studies. T1 mapping data has only been reported in one study in FRDA, and suggested the presence of diffuse myocardial fibrosis (60). However, there were a number of methodologic issues with this study, including the use of different CMR machines for the FRDA and control groups, and the lack of age matching.

Natural history studies and predictors of reduced left ventricular ejection fraction

Until recently there have only been limited natural history data regarding the cardiac manifestations of FRDA, with most studies performed before the identification of the *FXN* gene (61-63). However, several studies have been published since 1997. In a prospective echocardiographic study with a median 5-year follow-up of individuals with FRDA, most of whom (61/70) were taking idebenone, there were decreases in posterior wall thickness, LVMI and ejection fraction (12). In a retrospective analysis of LV structural and functional changes during follow-up in 23 children with FRDA there was a slow non-linear decline in LVEF, with more rapid decreases as age increased, but with maintenance of LVEF within the normal range until the age of 22 years (64). Of the 12 children with reduced LVEF and follow-up echocardiograms, 10 showed improvement to the normal LVEF range on at least one echocardiogram, and 5 remained normal through the last study. However, this cannot be concluded to reflect spontaneous improvement as LVEF is dependent on and therefore will vary with loading conditions. Furthermore, echocardiographic assessment of LVEF is recognized to have substantial variability. In a longitudinal study of 138 individuals with FRDA, with a mean follow-up of 10.5 (range 0.6-23.0) years, there was a decrease in LVEF accompanied by an increase in LV size and a reduction in LV wall thickness (10). In a study of 115 adults with FRDA and a baseline LVEF of 65±7%, LV systolic dysfunction with a LVEF<50 % occurred in 12 individuals after a mean follow-up of 13±6 years (18). Individuals with a GAA1 >800 were classified as high risk in this study.

Mortality studies and predictors of mortality

A number of mortality studies predate 1996. A study of 82 fatal cases of FRDA showed that over half died of HF while nearly three-quarters had evidence of cardiac dysfunction during life (38). In a population-based study of survival in FRDA in northwestern Italy, 58 individuals were identified and followed to death or to December 31, 1984 (whichever came first) to determine the patterns of survival (65). The 10-, 20-, and 30-year survival rates were 96%, 80%, and 61%, respectively. Survival for males was poorer than for females even after adjustment for expected survival. Somewhat unexpectedly, age of onset of FRDA was not a significant prognostic factor. In a follow-up study of 61 individuals with FRDA, cardiac failure was evident in 5% and was the most common cause of death (61).

There have also been mortality studies after 1996. A retrospective study of individuals with FRDA was performed to determine cause of death followed by a case-control analysis comparing characteristics of deceased individuals with living, age- and sex-matched FRDA controls (1). Causes of death were cardiac dysfunction (59%), probable cardiac dysfunction (3.3%), a non-cardiac cause (27.9%) or unknown (9.8%). Compared to non-cardiac deaths, cardiac deaths occurred earlier in the disease course (median 29 vs. 17 years duration of FRDA). Congestive HF and arrhythmia were common causes of cardiac-related death. Compared to living matched FRDA controls, deceased individuals had longer GAA1, higher rates of an arrhythmia and reduced LVEF. The presence of the diagnosis of a “hypertrophic cardiomyopathy” did not differ between the deceased and living groups.

In a study of 138 adults with FRDA with a mean follow-up of 10 years, the 10-year survival rate was 88.5% (10). In 80% (12/15) of individuals with FRDA who died during the study period, death was due to a cardiac cause, and predictors of mortality were a longer GAA1, a reduced LVEF and an increased LVMI. A longitudinal study from the same group, of 140 individuals with FRDA, showed LVEF to be an independent predictor of mortality, whereas global longitudinal strain (measured from apical 4 chamber view only) was not an independent predictor of mortality after adjusting for LVEF (66).

Post mortem and biopsy studies

There have been a number of post mortem studies in FRDA (3, 67-71), but only a few of these postdated genetic confirmation techniques (69-71). In a post mortem study of 16 hearts from people with FRDA, including three complete hearts (67), all hearts showed extensive interstitial fibrosis with considerable focal degeneration of muscle fibers. One heart showed extensive active muscle necrosis. Antemortem cardiac thrombus and thromboembolism were common findings. The main coronary arteries showed no gross disease. In a clinical study of 75 individuals with FRDA in which two died, post mortem revealed a minimally dilated but flabby left ventricle in both (3). Post mortem cardiac findings from 3 individuals with FRDA who died of congestive HF and had atrial arrhythmias showed pleomorphic nuclei and focal fibrosis and degeneration throughout each heart, including in the conduction system (68). There were distinctive abnormalities of both large and small coronary arteries, and focal degeneration of nerves and ganglia.

In 18 post mortem specimens of individuals with genetically confirmed FRDA, histological sections revealed abnormal cardiomyocytes, muscle fiber necrosis, reactive inflammation, and increased endomysial connective tissue (69). Scattered muscle fibers displayed perinuclear collections of minute iron-positive granules in rows between myofibrils, but total iron in the left ventricular wall of individuals with FRDA was not significantly higher than normal. In a further study from the same group, regions of significantly increased iron were irregularly distributed throughout the working

myocardium (71). These observations are at odds with the concept of selective iron toxicity only in cardiac mitochondria, and the role of iron in mediating the cardiomyopathy of FRDA remains unclear.

There is minimal data available from cardiac biopsy in FRDA (69) and thus little information about the cardiac histology in individuals with early stages of the cardiac disease process. Based on post mortem data from individuals with more advanced cardiac disease, it might be assumed that there is a combination of myocyte loss, myocyte hypertrophy and interstitial fibrosis in the left ventricular wall of an individual with FRDA and increased RWT or LVMI. However, the age at which these individual components develop, whether they occur simultaneously or in some sequence, and the temporal progression of these changes is unknown.

Late onset Friedreich ataxia

Late onset FRDA, defined as the onset of neurologic symptoms after age 25, is generally found in people with very short GAA1, and may not be, or at least is less likely to be, associated with cardiac abnormalities (7, 72-74). Whether this means that cardiac screening is not necessary in late onset FRDA is not yet clear as there are only a small number of cases described in the literature. Until greater natural history data has accumulated, a conservative recommendation is to perform cardiac screening in all individuals with a diagnosis of FRDA.

4.1.3 Arrhythmias in Friedreich ataxia

Atrial tachyarrhythmias

Atrial tachyarrhythmias occur frequently in FRDA, particularly in the later stages of the course of cardiac disease, and cause morbidity, and may also contribute to mortality (1, 38). In a longitudinal study of 138 individuals with FRDA, 6 had a previous history of atrial fibrillation (AF) at baseline, and over 0.6 to 23 years of follow-up, supraventricular arrhythmias were reported to occur in 16.5%, although the type of supraventricular arrhythmia was not reported (10). Intermittent palpitations have also been described in FRDA and the cause of these has not always been determined (37). AF is the most common reported tachyarrhythmia and may be paroxysmal or persistent (12, 38), but atrial flutter also occurs (37, 75). The combination of palpitations and angina has been reported in young people with FRDA (38), and it is feasible that individuals with a very thick walled left ventricle and a strain pattern on the resting EKG could develop angina due to subendocardial ischemia in the setting of a tachycardia and the absence of epicardial coronary artery disease.

Tsou and colleagues reported that arrhythmias were present or associated in approximately 16% of the deaths in FRDA (1). Although arrhythmia was listed either as the cause of death, or at least of playing a significant role in the death, there was insufficient detail from the records to determine the type of arrhythmia. Thus, the nature of the relationship of atrial arrhythmias with mortality in FRDA remains unclear.

Ventricular arrhythmias and death

Ventricular tachycardia (VT) and ventricular fibrillation (VF) have rarely been described in FRDA and there are few reports of sudden unexpected death or syncope due to arrhythmia. Current evidence suggests that such events are not likely to be common in FRDA cardiomyopathy, particularly in the absence of LV dilatation and a reduction in ejection fraction. On the other hand, it cannot yet be concluded that these arrhythmias occur rarely in FRDA as natural history studies are lacking. Furthermore, a single episode of either type of ventricular arrhythmia could result in sudden death in FRDA and yet not be documented. There is a single case report of syncope due to a ventricular

arrhythmia in an individual with FRDA which was managed with the insertion of an internal cardioverter-defibrillator (76). Cases of sudden death have been reported (70, 77, 78), but the cause of death has not been certain. Further information is required about the nature and frequency of ventricular arrhythmias in FRDA. There should be a low threshold for investigation with Holter monitoring and/or Loop monitoring in individuals with FRDA and palpitations, dizziness or syncope.

4.1.4 Heart failure in Friedreich ataxia

The symptoms of HF may be recognized late in FRDA because dyspnea and/or fatigue with exertion may be less prominent clinical features in an individual who is wheelchair bound. The spontaneous development of HF symptoms or signs in individuals with FRDA and normal ejection fraction is rare, even if there is a severe increase in RWT or LVMI. The presence of HF symptoms and signs therefore generally suggests the presence of a reduced LVEF. In a retrospective review, Tsou and colleagues (1) identified a history of HF in approximately 65% of people dying from FRDA.

Classification of heart failure in Friedreich ataxia

The New York Heart Association (NYHA) HF classification scheme is commonly used to assess the severity of functional limitations (ability to exercise) and there is a correlation of this classification with outcomes (Table 4.1) (79). However, the NYHA classification scheme has limitations for the assessment of individuals with neuromuscular disorders due to the inability of some individuals to perform exercise. NYHA Stage I is when there are no symptoms related to the heart even during exercise, such as climbing two flights of stairs. This stage may be easy to determine in a person newly diagnosed with FRDA, but becomes more difficult to assess as the neurologic features of FRDA advance and lead to limitations of mobility. Stages II and III are difficult to assess in FRDA because loss of ability to exercise is common in advanced neurologic disease. Thus, it could be difficult to tell if HF is advancing using this classification. Stage IV is easier to assess as cardiac symptoms with rest or minimal activity and particularly orthopnea and paroxysmal nocturnal dyspnea are more specific for cardiac disease.

Table 4.1 New York Heart Association stages of heart failure (79)

Stage	
I	No limitations with normal physical activity
II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitations, dyspnea or angina pectoris.
III	Marked limitation of physical activity. Less than ordinary activity results in symptoms.
IV	Unable to carry out any physical activity without discomfort. Symptoms are present at rest.

4.2 Surveillance strategies to monitor cardiac function in Friedreich ataxia

It is recommended that all individuals with a diagnosis of FRDA have an EKG and echocardiogram performed as part of their initial evaluation and that the EKG and echocardiogram are repeated at least yearly thereafter, irrespective of the initial findings. Cardiology consultation should be considered for all individuals with FRDA, but is definitely indicated if there are cardiac symptoms or an abnormality on the EKG. Although there is much current interest in cardiology in the measurement of strain and left ventricular long-axis strain is reduced in FRDA at an early stage in the

disease course (39), the role of routine measurement of long-axis strain by either echocardiography or cardiac magnetic resonance in FRDA is unclear. Similarly, cardiac magnetic resonance studies have demonstrated that there can be focal myocardial fibrosis in the left ventricular myocardium in FRDA based on the presence of LGE (11, 19, 59, 60), but whether this finding provides clinically useful information in FRDA is unknown.

Best practice statements

An EKG and an echocardiogram should be performed at diagnosis of Friedreich ataxia and then at least annually.
Either 24-hour Holter monitoring or Loop monitoring, or possibly both tests, are indicated for individuals with palpitations or other symptoms suggesting the possibility of an arrhythmia. A Loop monitor will be an appropriate additional test when symptoms are infrequent.
Evaluation by a cardiologist should take place if an individual with Friedreich ataxia has cardiac symptoms or abnormal results on cardiac testing.
Individuals with Friedreich ataxia being considered for scoliosis surgery, or other major surgery, are at risk of a poor outcome and require a multi-disciplinary approach to the management of heart function during surgery and in the postoperative period.

Recommendations

Grading for strength of recommendation and level of evidence

For the rating of the **strength** of the recommendation, in addition to evidence from studies in FRDA, evidence from like conditions, clinical experience and expert consensus are taken into account when published evidence is not available.

The **level of evidence** is based on published evidence from studies in FRDA. If there is no published evidence in FRDA, evidence from other like conditions or clinical expertise may have been used to make the recommendation – this is graded as 'very low' or in some cases 'low' level evidence. See the table below for an explanation of the symbols used to grade recommendations.

Strength of recommendation	Symbol	Level of evidence	Symbol
Strong for intervention	↑↑	High	⊕⊕⊕⊕
Conditional for intervention	↑	Moderate	⊕⊕⊕◯
Neither intervention nor comparison	—	Low	⊕⊕◯◯
Conditional against intervention	↓	Very low	⊕◯◯◯
Strong against intervention	↓↓		

Advanced imaging

Should advanced imaging techniques in echocardiography and/or cardiac magnetic resonance imaging (e.g., strain and late gadolinium enhancement) versus standard imaging techniques (e.g., measurement of left ventricular ejection fraction, size and wall thickness) be used for identification of at-risk individuals with Friedreich ataxia?	**Strength**	**Level of evidence***

There is not sufficient evidence to make a recommendation for or against using advanced imaging techniques over standard echocardiography for identifying at-risk individuals with Friedreich ataxia.	—	⊕◯◯◯
Justification: Echocardiography is the standard technique for screening for cardiac disease in Friedreich ataxia.		
Subgroup considerations: None		

Routine Holter monitoring

Should routine surveillance Holter monitors (e.g., at least annually) versus Holter monitors only to investigate symptoms be performed for individuals with Friedreich ataxia?	**Strength**	**Level of evidence***
There is not sufficient evidence to make a recommendation about Holter monitoring for individuals with Friedreich ataxia who do not have symptoms suggesting they might have an arrhythmia.	—	⊕◯◯◯
Justification: There is a lack of evidence for benefit of Holter monitoring for individuals with Friedreich ataxia without symptoms suggesting an arrhythmia, while risks include over-medicalization with unnecessary testing and detection of abnormalities of uncertain significance (e.g., premature atrial contractions without sustained arrhythmia).		
Subgroup considerations: None		

Lay summary

Lay summary of clinical recommendations for monitoring cardiac function in Friedreich ataxia

Why these recommendations?

People with Friedreich ataxia often experience heart (cardiac) problems and cardiac disease is a common cause of death. These recommendations are to help guide the selection and frequency of cardiac testing for individuals with Friedreich ataxia.

The authors suggest that for all individuals with Friedreich ataxia an electrocardiogram (EKG) and echocardiogram should be performed at diagnosis of Friedreich ataxia and then at least annually. However, at this stage it is unclear whether advanced imaging techniques such as cardiac magnetic resonance imaging should be used over standard echocardiography for identifying individuals with Friedreich ataxia who are at risk of heart disease.

In addition, a Holter monitor should be used if an individual with Friedreich ataxia has heart palpitations, but at this time it is unclear whether routine Holter monitoring should be done when there are no symptoms of heart problems.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It may be important for you to speak with your healthcare professional about Friedreich ataxia and cardiac monitoring and what it means for you.

Who are these recommendations specifically for?

These recommendations are for all individuals with Friedreich ataxia.

4.3 Management strategies for arrhythmias in Friedreich ataxia

4.3.1 Atrial tachyarrhythmias

Rate controlling agents

No randomized controlled trial (RCT) has evaluated rate control of AF in FRDA, but there are no specific reasons why standard guidelines for rate control should not apply in FRDA. Recommendations for heart rate control in atrial fibrillation are provided in the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation (80).

In general, rate control is not the preferred option for long-term management in atrial arrhythmias in FRDA, as attaining and maintaining rate control, particularly during exercise in young people, can be difficult. Furthermore, young people tend to remain symptomatic when in AF even if reasonable rate control can be achieved. Nevertheless, in certain circumstances, rate control may still be a reasonable option. In such cases digoxin can be used irrespective of the left ventricular ejection fraction. A beta blocker will be the preferred option if there is a history of HF or reduced ejection fraction, but needs to be commenced slowly. If there is a reduced LVEF, verapamil and diltiazem are contraindicated because of their negative inotropic action.

Antiarrhythmic therapy

There are no RCTs which have examined the effectiveness or safety of antiarrhythmic drugs in FRDA for either reversion of atrial tachyarrhythmias or for maintenance of sinus rhythm following spontaneous, chemical or electrical cardioversion. However, the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation (80) can be used as a guide to antiarrhythmic treatment of AF in FRDA. There are important concerns raised in these guidelines about the safety of some of the antiarrhythmic medications in the setting of “organic heart disease” and it should be assumed that similar concerns apply to the abnormal heart in FRDA.

Antithrombotic therapy for prevention of thromboembolism related to atrial tachyarrhythmias

Based on data in subjects with AF and a dilated cardiomyopathy due to causes other than FRDA, a high risk of thromboembolism would be predicted for individuals with FRDA with AF and a reduced LVEF (80). Indeed, intracardiac thrombosis and systemic thromboembolism was described as a frequent finding in one post mortem study in FRDA (67). In the absence of a reduction in LVEF, where the risk of thromboembolism can be considered to be high, there are no specific reasons why the standard risk factors for thromboembolism in AF should not also apply to FRDA, and these may be a reasonable way to determine the need for anticoagulant therapy in FRDA. Anticoagulation with new oral anticoagulants, including dabigatran, rivoroxaban and apixaban, rather than a vitamin K antagonist, is recommended for individuals with FRDA and paroxysmal or permanent AF for the prevention of thromboembolism, unless there is a contraindication (81).

Ablation therapy

If the symptoms or ventricular response of atrial tachyarrhythmias are unable to be controlled with antiarrhythmic and/or ventricular rate control medications then there are electrophysiological options for management. Atrial flutter may be amenable to ablation therapy to prevent further episodes of atrial flutter. Atrial fibrillation can be treated with the percutaneous procedure of pulmonary vein isolation; however, the effectiveness of this technique in FRDA is currently unknown. There is also an option for atrioventricular (AV) node ablation or modification in combination with pacemaker insertion to prevent both a rapid ventricular response and bradycardia (80).

4.3.2 Ventricular arrhythmias

Antiarrhythmic therapy

There are no RCTs addressing the effectiveness or safety of antiarrhythmic drugs in FRDA for the treatment of ventricular arrhythmias. Furthermore, as there are few reports of symptomatic VT, syncope due to VT or resuscitated sudden death in FRDA, antiarrhythmic therapy to prevent recurrent ventricular arrhythmias will rarely be indicated. With the exception of beta blockers, no currently available antiarrhythmic drugs have been shown in RCTs to be effective in the primary management of people with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death (SCD) (82). On the other hand, beta blockers are effective in suppressing ventricular ectopic beats and arrhythmias as well as in reducing SCD in a spectrum of cardiac disorders in people with and without HF (82). As a general rule, antiarrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia-prone individuals under special circumstances. Because of potential adverse side effects of the available antiarrhythmic drugs, these agents must be used with considerable caution.

If individuals with FRDA develop ventricular arrhythmias, then beta blockers should be considered first-line therapy for secondary prevention, but if not effective at full therapeutic doses, then amiodarone or sotalol can be tried, with careful monitoring for adverse effects during administration. Amiodarone is the only option if beta blockers are contraindicated. Both sotalol and amiodarone have also been shown to reduce the frequency of internal cardioverter-defibrillator (ICD) shock therapy. Sotalol should be used with caution in individuals with HF, severely reduced LVEF or renal dysfunction.

ICD for primary and secondary prevention of ventricular arrhythmias

There are no RCT data regarding ICD implantation for either primary or secondary prevention of ventricular arrhythmias in FRDA. Multiple clinical trials in other cardiac conditions have demonstrated a survival benefit of ICD use compared to antiarrhythmic therapy for secondary prevention of resuscitated SCD, sustained VT or sustained VF. It is recommended that the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities be used to guide ICD placement for the secondary prevention of SCD or sustained VT/VF in FRDA (83). Importantly, these guidelines do not support ICD placement if the predicted lifespan from other causes is less than a year.

Primary prevention of SCD refers to the use of ICDs in individuals who are at risk for, but have not yet had an episode of sustained VT, VF, or resuscitated cardiac arrest. Clinical trials have evaluated the risks and benefits of ICD implantation in prevention of sudden death and have shown improved survival with ICD in multiple patient populations, including those with HF due to non-ischemic dilated cardiomyopathy (83). However, making a recommendation to use an ICD for primary prevention in FRDA is not possible at this time due to absence of evidence for ventricular arrhythmias as a common cause of death.

One series of five subjects with FRDA who received ICD implantation has been reported (ages from 14-26 years) (84). However, none of this cohort had syncope, near syncope, symptomatic VT or a dilated cardiomyopathy with reduced LVEF (i.e. there were no standard indications for an ICD).

Best practice statement

For treatment of symptomatic arrhythmias in Friedreich ataxia, antiarrhythmic medications (other than betablockers) which are negatively inotropic or are recognized to have a high risk for proarrhythmic effects cannot be assumed to be safe and should rarely, if ever, be used.

Recommendations

Anticoagulation for atrial fibrillation

Should anticoagulation versus no anticoagulation be used for individuals with permanent, persistent or paroxysmal atrial fibrillation with Friedreich ataxia?	**Strength**	**Level of evidence***
We conditionally recommend anticoagulation over no anticoagulation in individuals with Friedreich ataxia with permanent, persistent or paroxysmal atrial fibrillation.	↑	⊕◯◯◯
Justification: There is no evidence to suggest treatment should be different for individuals with Friedreich ataxia versus individuals without Friedreich ataxia, where anticoagulation therapy would be appropriate for individuals with permanent, persistent or paroxysmal atrial fibrillation unless there is a contraindication. Shared decision-making should consider younger age of this cohort in the context of increased risk of falls, stroke, females with concomitant heavy menstrual bleeding and desire to maintain autonomy in decisions related to health.		
Subgroup considerations: The recommendation is for individuals with Friedreich ataxia with permanent, persistent or paroxysmal atrial fibrillation. Stroke happens across the age spectrum in Friedreich ataxia. The recommendation does need to encourage clinicians to think across all ages; however, be mindful of specific groups as specified in the justification above.		

Rhythm control for atrial fibrillation

Should rhythm control versus rate control be used for atrial fibrillation/flutter with Friedreich ataxia?	**Strength**	**Level of evidence***
We conditionally recommend attempts to maintain a normal cardiac rhythm over rate control in individuals with Friedreich ataxia and atrial tachyarrhythmias, and also recommend consideration of ablation for those who remain severely symptomatic due to a persistent atrial tachyarrhythmia or frequent paroxysms of an atrial tachyarrhythmia.	↑	⊕◯◯◯
Justification: Highly symptomatic individuals who are younger in particular require careful consideration regarding intervention. Some consideration should be given for moderate risks of pharmacological intervention versus higher risks with ablation, including prolonged anesthesia.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with atrial fibrillation/flutter, with particular considerations as described in the justification above.		

Lay summary

Lay summary of clinical recommendations for arrhythmias in Friedreich ataxia

Why these recommendations?

Individuals with Friedreich ataxia can experience arrhythmias (irregular heart rate), with symptoms including palpitations, dizziness, shortness of breath and chest discomfort.

These recommendations are about the use of medication or procedures to treat individuals with Friedreich ataxia who have permanent or episodic atrial fibrillation (an irregular and often rapid heart rate).

We suggest using anticoagulation medication for people with Friedreich ataxia with atrial fibrillation because the overall benefits (e.g., preventing a stroke) are likely to be greater than the risks (bleeding is the most common risk).

For individuals with Friedreich ataxia who have persistent or episodic atrial fibrillation, we also suggest that medication and possibly procedures (i.e. cardioversion) can be used to obtain a normal heart rhythm, as well as medication to maintain a normal heart rhythm. This is because maintaining a normal heart rhythm may lead to an improvement in symptoms. Even if there is no immediate improvement in symptoms, the treatment might help to look after heart function in the medium term. On the other hand, the risks of the use of cardioversion and medication for this purpose are small.

For those individuals who continue to have severe symptoms due to atrial fibrillation even after using medication, we suggest considering a procedure that can help break up the electrical signals that cause irregular heartbeats (called an ablation).

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It may be important for you to speak with your healthcare professional about the investigation of palpitations you may be having. Making a diagnosis of atrial fibrillation has important management implications. If atrial fibrillation is confirmed, then it is important to discuss the management options with a cardiologist.

Who are these recommendations specifically for?

These recommendations are for individuals with Friedreich ataxia who have permanent or episodic atrial fibrillation.

4.4 Management strategies for heart failure

There is currently no evidence to support any cardiac treatment for individuals with FRDA with normal LV ejection fraction and without cardiac symptoms or signs. A number of studies have investigated the effects of idebenone on LV wall thickness and/or LV mass but most of these studies have been small and the findings have not been consistent (2). Furthermore, a reduction of wall thickness or LV mass cannot be assumed to be a beneficial outcome of treatment in FRDA.

Spontaneous onset of HF symptoms is rarely seen in individuals with FRDA with increased LV wall thickness in the setting of a normal LVEF and normal sinus rhythm, and so regular HF medication therapy is unlikely to be indicated in such individuals. However, individuals with FRDA with such patterns of LV remodeling are more likely to develop symptoms and signs of acute HF in

circumstances of stress, such as surgery and serious infections, particularly when accompanied by changes in intravascular volume. Careful fluid management to avoid depletion or overload is recommended in such situations and diuretic therapy could be required if symptoms or signs develop due to fluid overload.

4.4.1 Pharmacologic treatment of heart failure with reduced left ventricular ejection fraction

Adults

There are no RCT data regarding the treatment of either asymptomatic people with FRDA with reduced LVEF or of individuals with FRDA and with HF associated with reduced LVEF (HFREF). However, in the absence of any evidence for any FRDA disease-specific harmful effects of standard HF treatments it is reasonable to use standard HF guidelines as a guide to therapy in FRDA, recognizing that there could be differences in the pathophysiology of FRDA heart disease. The fundamentals of medication management for symptomatic HFREF are provided in the 2013 ACCF/AHA guideline for the management of HF (79) and in the 2017 ACC/AHA/HFSA update on the 2013 ACCF/AHA guideline (85).

Children

There are no RCTs investigating the treatment of reduced LVEF with or without HF in children with FRDA. Neither is there even much data available from trials in children with HF due to a cardiomyopathy with reduced LVEF and causes other than FRDA. This is due in part to the difficulty of performing RCTs in children given the low prevalence of pediatric HFREF. Treatment of HFREF in children has been based on the results from adult studies.

4.4.2 Lifestyle factors and cautions to aid in management of heart failure

Lack of physical activity, poor diet, excessive consumption of salt and fluids and being overweight can exacerbate HF. Exercise-based rehabilitation can lead to reductions in hospitalizations for HF and improved quality of life and does not increase mortality in people with stable HF. Individuals who are requiring diuretics should generally be on a fluid restriction of less than 2L/day and more strict fluid restrictions may be necessary depending on the severity of the HF, the sodium level and the required doses of diuretics.

4.4.3 Device therapy and heart transplantation for heart failure

Prolongation of the QRS interval occurs in a proportion of people with advanced HF and has been associated with ventricular electromechanical delay (“dyssynchrony”) (83). QRS duration, dyssynchrony of contraction, and left bundle branch block (LBBB) in particular, have been identified as predictors of worsening HF, SCD, and total mortality. Modification of ventricular electromechanical delay with multisite ventricular pacing (biventricular pacing and cardiac resynchronization therapy (CRT)) can improve ventricular systolic function, ameliorate functional mitral regurgitation, and, in some individuals, induce favorable remodeling with reduction of cardiac chamber dimensions. Individuals with FRDA can develop HF due to severe systolic LV systolic dysfunction and can have a LBBB so CRT should be considered in such circumstances. There is a single case report of the successful use of a ventricular assist device in a patient with FRDA and heart failure due reduced LVEF (86).

Guidelines for CRT in patients with severe systolic HF are included in the 2013 ACCF/AHA guideline for the management of HF (79).

Transplantation of the heart in FRDA is not common but has been reported (87-91). Individuals with FRDA appear to do well after transplantation.

4.4.4 Fluid and operative management of individuals with and without heart failure

The increased thickness of the left ventricle in FRDA results in a reduction in coronary flow reserve and less tolerance to tachycardia. The reduced size of the LV cavity in FRDA means a greater reliance on heart rate to maintain cardiac output and a reduction in stroke volume reserve. Hearts of individuals with FRDA will therefore have less tolerance for changes in hemodynamics such as bradycardia, tachycardia, low blood pressure, and increases or decreases in LV filling. Careful monitoring of fluid balance is essential in individuals with FRDA undergoing stressful events, such as scoliosis surgery or hydration therapy in the emergency room setting. In addition, rapid access to advanced technologies for supporting cardiac output following major surgery, such as dialysis and left ventricular assist devices, may be required.

Although significant advances have been made in understanding the molecular biology of FRDA, there remain substantial and fundamental gaps in our understanding of the clinical disease and natural history of FRDA. Furthermore, there are no RCTs of the treatment or prevention of arrhythmias or the treatment of HF and no trials showing any benefit of treatment to delay the onset of or prevent the development of left ventricular dysfunction in FRDA.

Best practice statements

There is no therapy with proven cardiac benefits for asymptomatic people with Friedreich ataxia with echocardiographic or cardiac magnetic resonance findings of either a normal heart or increased left ventricular wall thickness but normal ejection fraction.
In adults with Friedreich ataxia and a reduction in left ventricular ejection fraction there is a case for treating according to standard heart failure guidelines.
In individuals with Friedreich ataxia and symptomatic heart failure there is a case for treating according to standard heart failure guidelines.
Women with Friedreich ataxia and a reduction in left ventricular ejection fraction should be advised that pregnancy could result in cardiac decompensation and a greater maternal and fetal risk.
Treatment options such as an ICD and heart transplantation are not contraindicated in Friedreich ataxia, but the appropriateness of such therapy requires careful consideration of the individual's functional status and their prognosis from non-cardiac morbidities.

Recommendations

Heart failure medication/devices (preserved left ventricular ejection fraction)

Should heart failure medication and/or devices vs. no medication and/or devices be used for individuals with Friedreich ataxia and a preserved left ventricular ejection fraction (i.e. >55%)?	**Strength**	**Level of evidence***

We do not suggest using heart failure medication and/or devices for individuals with Friedreich ataxia with a preserved left ventricular ejection fraction.	↓	⊕◯◯◯
Justification: There is no evidence that the use of medication and/or devices has any benefit in reducing the occurrence of cardiac dysfunction in individuals with Friedreich ataxia with preserved ejection fraction and there are risks of side effects and over-medication if such treatments are used.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia and a preserved left ventricular ejection fraction (i.e. >55%).		

Heart failure medication (reduced ejection fraction)

Should heart failure medication versus no medication be used for individuals with reduced ejection fraction with Friedreich ataxia?	**Strength**	**Level of evidence***
We conditionally recommend treating individuals with Friedreich ataxia with a reduced left ventricular ejection fraction with medications according to current American Heart Association/American College of Cardiology heart failure guidelines (2013 & 2017 update).	↑	⊕◯◯◯
Justification: Medical treatment of an individual with Friedreich ataxia with reduced ejection fraction should include those with a LVEF <50%, but could also be considered for those with a significant downward trend in ejection fraction over time. This is based on current recommendations of the AHA/ACC (79, 85) for treatment of heart failure as there is no evidence to suggest that individuals with Friedreich ataxia should be treated differently to other people with heart failure and reduced ejection fraction.		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia and a reduced ejection fraction, and as indicated in the justification above.		

Advanced heart failure treatments (reduced left ventricular ejection fraction)

Should advanced heart failure treatments (e.g., biventricular pacemaker, internal cardioverter-defibrillator, left ventricular assist device, heart transplantation) versus supportive care be used for individuals with Friedreich ataxia in the advanced stages of heart failure due to a reduced left ventricular ejection fraction?	**Strength**	**Level of evidence***
Advanced heart failure therapies such as a left ventricular assist device, implantable cardioverter-defibrillator, biventricular pacemaker and heart transplantation should be considered for individuals with Friedreich ataxia and heart failure due to a reduced left ventricular ejection fraction, based on consideration of both their cardiac and overall health status.	↑	⊕◯◯◯
Justification: Based on the current evidence, advanced heart failure therapies should be considered based on individual circumstances. A diagnosis of Friedreich ataxia alone should not preclude such consideration. Evidence from case reports indicates positive outcomes (86-91).		
Subgroup considerations: This recommendation is for individuals with Friedreich ataxia with a reduced left ventricular ejection fraction (i.e. <55%).		

Lay summary

Lay summary of clinical recommendations for heart failure in Friedreich ataxia

Why these recommendations?

Heart failure is a condition where your heart function is impaired and it can result in loss of exercise tolerance, breathlessness and leg swelling. Heart failure can also result in abnormal heart rhythms.

These recommendations did not find that any specific heart failure medication or devices had evidence of benefit in individuals with Friedreich ataxia with a normal left ventricular ejection fraction (a commonly used measure of the percentage of blood pumped by the left ventricle with each heart beat). On the other hand, if an individual has a reduced left ventricular ejection fraction, we suggest that treatment should follow the same guidelines as for individuals with a reduced left ventricular ejection fraction who do not have Friedreich ataxia.

In the case of advanced heart failure, and after considering both the heart and general health of the individual concerned, we suggest that devices that can help to maintain heart output or heart transplantation could be considered.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It may be important for you to speak with your healthcare professional about Friedreich ataxia and heart failure and what it means for you.

Who are these recommendations specifically for?

These recommendations are for individuals with Friedreich ataxia who have been diagnosed with heart failure.

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