# Cardiovascular Function and Treatment in β-Thalassemia Major: A Consensus Statement From the American Heart Association

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on behalf of the American Heart Association Committee on Heart Failure and Transplantation of the Council on Clinical Cardiology and Council on Cardiovascular Radiology and Imaging

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AHA Consensus Statement

# Cardiovascular Function and Treatment in β-Thalassemia Major

## A Consensus Statement From the American Heart Association

*Endorsed by the Thalassaemia International Federation, European Society of Cardiology Working Group on Cardiovascular Magnetic Resonance, and Society for Cardiovascular Magnetic Resonance*

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***Abstract*—**This aim of this statement is to report an expert consensus on the diagnosis and treatment of cardiac dysfunction in β-thalassemia major (TM). This consensus statement does not cover other hemoglobinopathies, including thalassemia intermedia and sickle cell anemia, in which a different spectrum of cardiovascular complications is typical. There are considerable uncertainties in this field, with a few randomized controlled trials relating to treatment of chronic myocardial siderosis but none relating to treatment of acute heart failure. The principles of diagnosis and treatment of cardiac iron loading in TM are directly relevant to other iron-overload conditions, including in particular Diamond-Blackfan anemia, sideroblastic anemia, and hereditary hemochromatosis.

Heart failure is the most common cause of death in TM and primarily results from cardiac iron accumulation. The diagnosis of ventricular dysfunction in TM patients differs from that in nonanemic patients because of the cardiovascular adaptation to chronic anemia in non–cardiac-loaded TM patients, which includes resting tachycardia, low blood pressure, enlarged end-diastolic volume, high ejection fraction, and high cardiac output. Chronic anemia also leads to background symptomatology such as dyspnea, which can mask the clinical diagnosis of cardiac dysfunction. Central to early identification of cardiac iron overload in TM is the estimation of cardiac iron by cardiac T2* magnetic resonance. Cardiac T2* <10 ms is the most important predictor of development of heart failure. Serum ferritin and liver iron concentration are not adequate surrogates for cardiac iron measurement. Assessment of cardiac function by noninvasive techniques can also be valuable clinically, but serial measurements to establish trends are usually required because interpretation of single absolute values is complicated by the abnormal cardiovascular hemodynamics in TM and measurement imprecision.

Acute decompensated heart failure is a medical emergency and requires urgent consultation with a center with expertise in its management. The first principle of management of acute heart failure is control of cardiac toxicity related to free iron by urgent commencement of a continuous, uninterrupted infusion of high-dose intravenous deferoxamine, augmented by

†Deceased.

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This consensus statement was reviewed and endorsed by the ESC Working Group on Cardiovascular Magnetic Resonance, at the request of the American Heart Association. Although there is agreement with the general concepts of this document and confidence in the methodology used by the American Heart Association, the ESC Working Group on Cardiovascular Magnetic Resonance may not agree with every identified statement and/or specific wording. This document was not published by the ESC Working Group on Cardiovascular Magnetic Resonance and is not considered official ESC policy.

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oral deferiprone. Considerable care is required to not exacerbate cardiovascular problems from overuse of diuretics or inotropes because of the unusual loading conditions in TM.

The current knowledge on the efficacy of removal of cardiac iron by the 3 commercially available iron chelators is summarized for cardiac iron overload without overt cardiac dysfunction. Evidence from well-conducted randomized controlled trials shows superior efficacy of deferiprone versus deferoxamine, the superiority of combined deferiprone with deferoxamine versus deferoxamine alone, and the equivalence of deferasirox versus deferoxamine. (***Circulation*. 2013;128:281-308.**)

**Key Words:** AHA Scientific Statement ■ CT and MRI ■ heart failure ■ other heart failure ■ other treatment ■ thalassemia

# 1. Introduction

## 1.1 Need for Consensus Document

Heart disease has been the predominant cause of death in β-thalassemia major (TM) in cohort studies.[1–4] Significant advances in the identification and risk stratification of patients with myocardial siderosis have occurred since 2001 with magnetic resonance (MR) technology,[5–7] and with this, it has been possible to focus on the heart as the target lethal organ in TM and tailor chelation treatment and prevention accordingly.[8–10] There is evidence that this approach has contributed to the significant reduction in cardiac mortality in TM.[3,11–14] These advances give room for a consensus document in a rapidly evolving field in both diagnostics and therapeutics. The aim of the present document is to bring together broad-ranging cardiological and hematologic experience in the heart and heart failure (HF) in TM, summarize how to measure cardiac iron and function, identify and treat patients at high risk to prevent HF, and diagnose and treat HF. A primary premise of this review document is that cardiac disease is easier and safer to treat at an early stage rather than a late stage when the hazard of death is high. We build on previous, more focused summary reviews and consensus statements on the heart in TM[15–20] and build a consensus of the assessment of cardiac function and treatment of HF in TM.

# 2. Fundamentals of TM and the Heart

## 2.1 Iron-Loading Conditions

### *2.1.1 β-Thalassemia Major*

TM is a genetic condition with severe reduction or absent production of the β-globin chain constituent of hemoglobin (Hb) A. This results in ineffective erythropoiesis caused by an excess of α-globin chains and profound anemia that is life-threatening from ≈1 to 2 years of age. Blood transfusions are required lifelong; however, the iron load of ≈200 mg per unit combined with mildly increased gastrointestinal iron uptake related to hepcidin suppression[21] increases total body iron, which leads to a requirement for lifelong iron chelation treatment to prevent or reverse iron-related complications. A broad phenotypic characterization of TM is the requirement for >8 transfusion events per year (may have multiple units at each transfusion) in an adult aged >16 years.[22] TM varies greatly in frequency around the world, being most prevalent in areas with endemic population exposure to malaria (Asia, the Middle East, Mediterranean Europe), and this is considered to have created positive pressure for the accumulation of hemoglobin genetic mutations that in heterozygote form provide innate resistance to parasitization by plasmodia of red cells. In countries with no historical exposure to endemic malaria, TM occurs through immigration. Thus, the United States and the United Kingdom each have <1000 TM patients, whereas Indonesia has many thousands of registered TM patients with likely high levels of underreporting.

### *2.1.2 Thalassemia Intermedia*

The cardiovascular manifestations of thalassemia intermedia are beyond the scope of this document but typically include a greater propensity to pulmonary hypertension and thrombosis.[23,24] In thalassemia intermedia, there is a very variable increase in gastrointestinal iron uptake. Patients with thalassemia intermedia generally do not require transfusions to maintain the hemoglobin level and form part of the spectrum of non–transfusion-dependent thalassemia, which also includes other genotypes, such as some patients with E-β-thalassemia and HbH disease. As patients with thalassemia intermedia get older, however, they may require transfusions to prevent complications, including those in the cardiovascular system. This leads to iron loading and an increased requirement for iron chelation.

### *2.1.3 Sickle Cell Anemia*

The cardiovascular manifestations of sickle cell anemia are beyond the scope of this document but typically include a greater propensity to sickle cell crisis (severe generalized attacks of pain), as well as pulmonary hypertension, thrombosis, and stroke.[25] Patients with sickle cell anemia are increasingly being transfused to prevent cardiovascular complications, which leads to iron loading and an increased requirement for iron chelation. Although the risks of extrahepatic iron deposition and organ toxicity are lower in sickle cell anemia than in other transfusional anemias, they increase proportionally to the duration of chronic transfusion therapy.

### *2.1.4 Other Iron-Loading Conditions*

There are other causes of iron overload, including conditions such as hereditary hemochromatosis, Diamond-Blackfan anemia, sideroblastic anemia, myelodysplasia, and α-thalassemia, for which these guidelines are relevant but for which the evidence base is lower than for TM. Patients

with transfusion-dependent Diamond-Blackfan anemia and sideroblastic anemia appear to be at particularly high risk for extrahepatic iron deposition and toxicity.

### 2.2 Aims of Transfusion in TM

The main aim of blood transfusion in TM, beyond prolonging life, is the suppression of ineffective erythropoiesis. To achieve this, clinical experience and guidelines[26] suggest that maintaining a pretransfusion hemoglobin level of 9 to 10 g/dL with a posttransfusion hemoglobin level of 13 to 14 g/dL leads to a balance between minimization of iron loading and maximization of symptom relief. Transfusions reduce the expansion of blood volume seen in chronic anemia, which is a driver of increased cardiac index.

### 2.3 Cause of Death in TM

Before the introduction of chelation, the most common cause of death in TM patients receiving regular transfusions in the 1960s was HF.[27] In the era of deferoxamine iron chelation, mortality was postponed considerably, but mortality from cardiac iron overload continued to dominate the causes of death, accounting for ≈70% of cases.[1,2,28,29]

### 2.4 Age at Cardiac Death

The age of cardiac death in TM depends on a number of factors, including access to transfusions and chelation. In transfused but unchelated patients, the typical age at death was 10 years, primarily of cardiac causes.[30] With the introduction of deferoxamine treatment in the late 1970s, the median age of survival improved and was strongly dependent on birth cohort. In the United Kingdom, by the year 2000, the median age at death was 35 years.[2] Improvements in survival with deferoxamine treatment by later birth cohort have been confirmed in other countries.[3,31,32]

### 2.5 Frequency of Cardiac Iron Overload

Samples of TM patients in a number of countries across the world have shown cardiac iron overload to be common using definitions from T2* cardiovascular magnetic resonance (CMR) of severe cardiac iron loading of <10 ms and mild to moderate cardiac iron loading of 10 to 20 ms (refer to Section 3.3 for measurement of iron by T2* CMR; Table 1).

**Table 1. Frequency of Cardiac Iron Overload**

| Country | Sample Size, n | Frequency, % | | |
|---|---|---|---|---|
| | | Severe: T2* <10 ms | Mild to Moderate: T2* >10–20 ms | Normal: T2* >20 ms |
| United Kingdom[5] | 109 | 20 | 43 | 37 |
| Hong Kong[33] | 180 | 26 | 24 | 50 |
| Turkey[34] | 28 | 46 | 39 | 14 |
| Australia[35] | 30 | 37 | 27 | 37 |
| Oman[36] | 81 | 24 | 22 | 54 |
| United States[37] | 141 | 13 | 21 | 66 |
| Italy[38] | 167 | 13 (<8 ms) | 52 (8–20 ms) | 35 |
| Italy[39] | 220 | 30% <20 ms | | 66 |
| Greece[40] | 159 | 68% <20 ms | | 32 |
| Worldwide survey[41] | 3445 | 20 | 22 | 58 |

### 2.6 Frequency of Cardiomyopathy

There are 2 ways by which cardiomyopathy prevalence can be measured. The first is by prevalence of the clinical syndrome of HF. The prevalence varies by patient age and by year of birth. In a cohort of 97 patients born before 1976, 37% had heart disease, as defined by need for inotropic or antiarrhythmic medications.[28] In a US survey in 2004, the number of TM patients of all ages receiving cardiac medication was found to be 10% (35/341).[22] In an Italian cohort, the prevalence of HF by 15 years of age was 5% in patients born between 1970 and 1974 and 2% in those born between 1980 and 1984.[42] In a worldwide survey conducted in 2012, the incidence of HF at first T2* scan was 3.1% (107/3445).[41] Alternatively, the prevalence of detectable left ventricular (LV) dysfunction is higher than the prevalence of clinically manifest HF. In one study of 167 Italian patients, LV dysfunction was found in 19 patients (11.4%).[38] Another more recent Italian study found a high prevalence of LV dysfunction of 19%. This higher figure may represent the high prevalence of hepatitis C infection[43] and aging of the Italian TM population compared with clinical experience elsewhere.

### 2.7 HF and Survival

The natural history and clinical course in untreated patients is one of clinically silent myocardial iron accumulation for many years, followed by malignant arrhythmias and acutely impaired myocardial function in early adulthood.[27,44] The time from symptom appearance to death was short, typically approximately 6 to 12 months. With improved access to iron chelation in the 1970s, life expectancy improved, with patients expected to survive to their mid-30s[28,31,45]; however, 5-year survival for patients presenting in HF (ages 24±5 years) was only 48%.[46] These data were disconcerting given the ample evidence that intensive iron chelation therapy could completely restore cardiac function in most patients with preclinical dysfunction and some with overt HF.[47–49] The clearance of cardiac iron substantially lagged improvements in systolic function,[47] which explains the high risk of relapse observed with premature termination of intensive chelation therapy.[48,49] Recognition of severe cardiac siderosis by T2* CMR and intervention with suitable treatment, before the onset of symptomatic HF, is associated with improvements in ventricular function.[50] As a result, recent improvements in life expectancy for TM patients in the United Kingdom can be explained by the increasing availability of T2* CMR and earlier escalation of therapy.[11,51] The acute mortality of New York Heart Association stage IV HF in thalassemia remains high (probably in excess of 50% in hospital mortality) simply because support for the heart and other failing organs, especially the kidneys and liver, often cannot be continued long enough for iron chelation to stabilize myocardial function, a process that may take many months. Nonetheless, futility cannot be predicted, and intensive chelation and prolonged cardiopulmonary support should be attempted in all patients with iron cardiomyopathy, because survival to an excellent

quality of life may be achieved in a significant proportion of patients.

### 2.8 Age, Transfusions, and Cardiac Loading

There are few data relating the age of onset of cardiac iron loading with age and transfusion history. Among patients with myelodysplasia who received transfusions but no chelation, those with cardiac T2* <20 ms had received >100 U of blood.[52] In children with hemoglobinopathy who received transfusion and chelation, the cardiac T2* was <20 ms only after 10 years of age.[53,54] However, occasional younger onset of cardiac iron, as young as 7 years, has been recorded in TM, especially when access to chelation is limited.[55]

### 2.9 Cardiac Uptake of Iron

There is an incomplete understanding of iron loading into the heart, and no studies have been performed in humans. Cell and animal studies have indicated that cardiac entry of iron is mediated by the divalent metal transporter 1 (DMT1) and L-type calcium channels,[56,57] as well as the T-type calcium channels,[58] although another pathway may be involved for ferric $(Fe)^{3+}$ ions.[59] Non–transferrin-bound iron uptake has been shown to be rapid in isolated cardiomyocytes.[60] Nifedipine was shown to hinder iron uptake into cardiac cells, and this therapeutic possibility is being explored in a pilot study in humans.[61] Anecdotal evidence from individual cases[62] and family studies of discrepant cardiac iron loading, as well as evidence from a worldwide survey of cardiac T2*,[41] suggests that genetic modifiers of cardiac iron uptake may be present and clinically relevant. The only genetic influence known to date is the glutathione S-transferase-M1 (GSTM1) null genotype, which was associated with an increased level of cardiac iron.[63,64] GSTM1 has also been implicated in liver iron loading.[65]

### 2.10 Cardiac Pathophysiology in TM

In untreated TM, chronic profound anemia causes high–cardiac-output HF and is fatal at a young age. The early start of regular transfusion prevents early cardiac death and other complications of anemia but results in progressive iron accumulation toxicity. In the heart, increased levels of intracellular free iron are toxic through a number of mechanisms,[66,67] including (1) damage to membranes by lipid peroxidation; (2) damage to mitochondria and the respiratory enzyme chain[68,69]; (3) interference with electrical function, including ryanodine release channel interference[70,71]; (4) promotion of cardiac fibrosis, which was prominently reported in early autopsy studies,[72] although it is rare with greater access to chelation[73]; and (5) altered gene expression.[74]

### 2.11 Adaptive Cardiac Physiology in TM in Absence of Cardiac Iron Loading

Because hemoglobin is responsible for oxygen transport, to preserve oxygen delivery, the body compensates for low hemoglobin levels by increasing the cardiac output and cardiac index, which is the cardiac output normalized to body surface area, up to 60% compared with normal control subjects. The increased cardiac index is usually achieved by an increase in end-diastolic volume, stroke volume, and heart rate. TM therefore represents a chronic high-output state produced by volume-loaded ventricles (high preload). To maintain normal systemic blood pressure in the presence of high cardiac output, the body has to lower the systemic vascular resistance through peripheral arterial vasodilation, which leads to wide pulse pressures and low diastolic blood pressure.[70,75,76] The increased cardiac output may lead to flow murmurs on cardiac auscultation. The ejection fraction is increased because of decreased afterload and increased preload.

### 2.12 Clinical Cardiac Manifestations of Iron Overload

In the absence of regular iron chelation, historical series show a broad range of cardiac complications, including pericarditis, myocarditis, HF, and arrhythmias.[27,72] In the modern era, with iron chelation treatment, the clinical manifestation of cardiac disease has changed, and pericarditis and myocarditis are now rare. Historical postmortem studies showed severe replacement cardiac fibrosis,[27,72] but this is now rare in more modern cohorts of patients dying of HF.[73] More minor patches of myocardial fibrosis have been identified in vivo with late gadolinium-enhancement CMR in Italian patients with TM,[77] but this has not been reproduced in the United Kingdom.[78] This difference probably results from higher levels of myocarditis resulting from hepatitis C infection in Italy.[79] The most common clinical manifestations of cardiac disease are now dilated cardiomyopathy (with restrictive features) and arrhythmia, predominantly atrial fibrillation (AF). In severe cardiac iron loading, ventricular arrhythmias become more common, and ectopic atrial tachycardia, flutter, and chaotic atrial rhythms may also occur. Recent autopsy data show that iron deposition in the myocardium in TM patients occurs preferentially in the subepicardium, no systematic variation occurs between myocardial regions, and iron in the interventricular septum is highly representative of total cardiac iron.[7] Some authors advocate use of multislice T2* data to characterize heterogeneity in myocardial iron distribution, but this technique requires corrections for large, patient-specific magnetic susceptibility artifacts. Although global sampling of cardiac T2* potentially offers a more complete picture of cardiac iron burden, anatomic correlations for this approach are lacking.[39] Other relevant iron-overload complications that may affect the heart include hypothyroidism, diabetes mellitus, hypoadrenalism, growth hormone deficiency, and hypoparathyroidism.

Changes in the heart in addition to ventricular systolic impairment include the following: (1) Decreased left atrial function, which is attributable to ventricular stiffening or direct atrial toxicity. Limited data suggest that decreased left atrial function is a more sensitive marker of iron toxicity than left ventricular ejection fraction (LVEF),[76,80] but further data are needed. (2) Impaired right ventricular (RV) function, which may be caused by the increased vulnerability of the RV to the effects of iron deposition because of its thin wall. Tissue Doppler imaging velocity and strain imaging suggest early RV impairment in iron overload.[81] (3) Impaired endothelial function in iron overload.[9,82–84] Improvement in

endothelial function has been documented with deferiprone[9] and deferasirox.[83] (4) Impaired diastolic function as shown by tissue Doppler imaging has been reported with cardiac iron overload, but only in small studies, and its low sensitivity limits its use for diagnosis and as a prognostic tool.[85,86] Impaired diastolic function shown by CMR also had low sensitivity for identification of cardiac iron loading.[87]

### 2.13 Vascular Effects of Iron Loading

Patients with TM and normal cardiac iron levels documented by T2* and no clinical signs of cardiac dysfunction have increased aortic stiffness as assessed by pulse-wave velocity (carotid-femoral) and augmentation index compared with normal control subjects.[88]

## 3. Diagnostic Strategies for Cardiac Involvement in TM

### 3.1 Basic Tests

New-onset electrocardiographic abnormalities are usually evident in TM patients with HF[89] and may include supraventricular arrhythmias, electrocardiographic findings that suggest right-sided heart involvement ($S_1Q_3$ pattern and right-axis deviation), new-onset T-wave inversion beyond lead $V_1$, and a consistent decrease in QRS height. In patients without HF, an abnormal ECG was found in 46% (T-wave abnormalities in 34% and right bundle-branch block in 12%), which was weakly associated with lower myocardial T2* and mild myocardial fibrosis, probably from hepatitis C myocarditis.[90] Electrocardiographic changes most specifically associated with cardiac iron include repolarization abnormalities and relative bradycardia.[91] It is not known whether progressive alterations in electrocardiographic tracings occur before HF develops.

The chest radiograph may show cardiomegaly caused by the hyperdynamic circulation, signs of congestive HF, and, on occasion, extramedullary hematopoiesis as indicated by the lobulated soft tissue opacities of the ribs anteriorly and posteriorly. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are significantly increased in documented LV diastolic dysfunction, whereas NT-proBNP appears to have better predictive value in detecting latent LV diastolic dysfunction.[92] However, one study showed poor correlation of BNP against low myocardial T2*, which predicts future HF.[50] One possible explanation for this finding is cardiac endocrinopathy and reduced BNP secretion caused by iron toxicity. More recent data suggest that NT-proBNP levels may be useful,[93] and further studies are needed.

### 3.2 Noninvasive Techniques to Measure Cardiac Function

#### *3.2.1 Echocardiography*

A number of factors affect cardiac function measurements by different techniques, and this makes comparisons between techniques and different laboratories difficult.[94] Echocardiography is a very useful cardiac examination because its application is widespread, safe, economical, and routine in clinical practice; however, image acquisition depends on the operator and the availability of good acoustic windows. Reproducibility is reasonable in normal ventricles, but the quantification of volumes and mass relies on geometric assumptions that do not apply in ventricles undergoing asymmetrical cardiac remodeling, such as in cardiomyopathy,[95] and measurements show significant interobserver variability. In a small study of 36 patients, a resting LVEF <60% by echocardiography correlated with increased cardiac mortality over a 12-year period.[96] Echocardiography provides less accurate quantification than CMR, and accuracy decreases with worsening LV function as geometric assumptions lose validity. In addition, typical echocardiography measurements include the papillary muscles in the blood pool, which leads to systematic overestimation of volumes. Echocardiography is the preferred second-line technique after CMR, and 3-dimensional is preferable to 2-dimensional because of improved longitudinal reproducibility. It is important that echocardiography be performed in experienced centers that are used to scanning TM patients in large numbers. Echocardiography is the easiest way to evaluate the diastolic LV function/dysfunction in patients with TM with published guidelines.[97]

#### *3.2.2 Radionuclide Ventriculography*

Radionuclide ventriculography during exercise is reported as a sensitive technique for detecting preclinical myocardial dysfunction in patients with systemic iron overload.[98] However, its use is limited in the current era because of concerns about radiation dose in young people, considerable intercenter variation in normal values of ejection fraction related to differences in background radiation–subtraction techniques, and the availability of other techniques such as echocardiography and CMR, which are usually preferred.

#### *3.2.3 Cardiovascular Magnetic Resonance*

CMR is also free of ionizing radiation, noninvasive, and highly reliable. In addition, CMR is independent of geometric assumptions for assessment of LV volumes and function and has been shown to be accurate and reproducible. However, it is more expensive than echocardiography, is performed in a claustrophobic environment, and is limited in patients with cardiac devices (although CMR-compatible devices are now available). Despite the special expertise required to perform and interpret CMR, it is considered the "gold standard" today for the measurement of all LV and RV indexes. With the introduction in recent years of the steady-state free precession technique with much improved blood-myocardium contrast, faster acquisition, and improved temporal resolution of the cine images, the image quality is superior to the spoiled gradient echo sequences, which are more of a historical issue at this point. Steady-state free precession end-expiratory breath-hold cines should be acquired in the vertical and horizontal long-axis planes, with subsequent contiguous short-axis cines from the atrioventricular ring to the apex. LV mass should be calculated from the end-diastolic frames after the epicardial and endocardial borders of the LV are delineated and should include the papillary muscles. End-systolic and end-diastolic volumes are best calculated from the LV volume-time curves generated from all frames of all cines, should exclude the papillary muscles, and should

model LV blood pool changes from systolic valve descent. Such rigorously derived CMR cardiac volumes have the benefit of having recognized normalized values for sex, body surface area, and age for both the LV[99] and the RV.[100] These covariates have substantial impact on the normal ranges. However, many CMR analysis software packages do not have this full modeling capability, and in that case, normal values appropriate to the software should be used. CMR is more reproducible than other techniques over time[101,102]; therefore, it is preferred for follow-up of patients over time when it is available. Finally, it is important to compare normal values for LV[103] and RV[104] function with values obtained in nonanemic TM patients to prevent misdiagnosis of abnormality, as detailed below. Such comparisons are now also available for children.[105,106] A further value of CMR is related to the use of late gadolinium enhancement, which identifies myocardial replacement fibrosis. This can be useful to identify myocarditis and myocardial infarction, which are uncommon differential diagnoses in HF in TM patients.[107] CMR with late gadolinium enhancement should be considered in any patient who has a positive test result for hepatitis C, has abnormal cardiac function in the absence of cardiac iron, or has other known cardiovascular risk factors, such as chronic diabetes mellitus. Diastolic cardiac function is measured in clinical practice by echocardiography, and CMR is not generally used for this assessment despite the fact that it provides absolute peak filling rates from the volume-time curves[108] that are at higher spatial resolution than provided by radionuclide ventriculography. Performance of CMR requires training and experience to obtain results of the required quality, as detailed in guidelines.[109,110]

#### *3.2.4 Cardiac Computed Tomography and Exercise Testing*

There are few data on the use of cardiac computed tomography in TM, but it is a fast technique to assess cardiac function,[111] and liver attenuation correlates with MR-derived liver iron concentration, but only at moderately to severely increased levels of iron in the liver.[112] No significant data exist on measurement of cardiac iron by computed tomography. β-Blockers are generally used as premedication, which can affect the functional analysis, and radiation exposure is significant with repeated use. Exercise stress testing might be considered useful to unmask subclinical LV dysfunction in TM, but in practice, it appears to have limited value. Exercise capability is affected by chronic anemia, the typical small body habitus of TM patients, and other factors.

### 3.3 T2* CMR Measurement of Cardiac Iron

Myocardial iron deposition can be quantified reproducibly with myocardial T2*,[5,113–115] a relaxation parameter that arises principally from local magnetic field inhomogeneities that are increased with iron deposition. T2* is the time taken for decay of the myocardial signal by 63% and is measured in milliseconds. T2* is related to T2 by summation of tissue relaxation (T2) and magnetic inhomogeneity, known as T2 prime (T2′), in the form $1/T2^*=1/T2+1/T2'$. In clinical medicine, it is usual to use these decay times to assess magnetic relaxation, but basic science–based investigations typically use the rate of relaxation (R), and this relation can be rewritten as $R2^*=R2+R2'$, with the units of measurement being inverse seconds ($s^{-1}$).

As myocardial stores increase in the heart, ferritin breakdown increases into particulate hemosiderin, which is a form of ferrihydrite (hydrated iron oxide). The hemosiderin to ferritin ratio is significantly higher in cardiac siderosis than in normal hearts.[116] This disrupts the local magnetic field homogeneity, causing reduced T2* values in inverse relation to iron concentration. Iron that is safely stored in ferritin or hemosiderin is nontoxic, yielding hearts with low T2* and normal function; however, high iron stores predispose patients to development of cardiac dysfunction in the future.[5,38] An improvement in myocardial T2* resulted in improvement in LVEF in observational, prospective, and randomized controlled studies of iron chelation in thalassemia patients.[8,9] Myocardial iron deposition is also strongly associated with RV dysfunction, which mirrors the decrease in LV function seen with worsening cardiac iron loading and decreasing T2*.[117] Further studies are required to determine the relative importance of RV function compared with LV function and establish whether novel treatment strategies targeted to the RV may prove useful.

For measurements of myocardial T2*, imaging of a single short-axis mid-LV slice is performed at multiple separate echo times to measure the signal decay of the myocardium. Gradient-echo T2* CMR is the preferred technique rather than a spin-echo T2 sequence because of its greater sensitivity to iron deposition and lower sensitivity to motion. The first described method required multiple separate image acquisitions, each of which required a breath hold.[5] This was time consuming and prone to artifacts that made it difficult to assess the exact myocardial borders with longer echo times, and it created problems with image registration between the images. A multiecho sequence is now standard, because this allows the acquisition of a single short-axis midventricular slice at multiple echo times in a single breath hold.[118] This also has the advantage of T1 independence because of the constant repetition time between all echo times in contrast to the lengthening repetition time with increasing echo time in the multiple breath-hold T2* measuring sequence. A gating delay of 0 ms after the R wave is chosen to obtain myocardial images in a consistent position in the cardiac cycle irrespective of the heart rate. The most recent technical improvement in the T2* sequence has been the development of the black-blood sequence.[119,120] This sequence greatly reduces blood signal, which significantly reduces the blood artifact propagating in the phase-encoding direction that typically spreads across the interventricular septum. This reduces measurement variability. A reproducible multislice T2* sequence has been reported,[121] but no clinical advantage of this more complex protocol has been demonstrated. In particular, the T2* and iron concentration in the septum have been shown to be highly representative of mean total cardiac iron concentration,[7,122,123] and the variation in iron between ventricular myocardial segments appears clinically insignificant.[7]

For analysis of the images, software that is clinically validated for this application should be used. Such software incorporates safeguards against incorrect handling and

interpretation of the data, which can have clinical implications.[124] A full-thickness region of interest is measured in the LV myocardium that encompasses both epicardial and endocardial borders. This is best located in the interventricular septum and distant from the superior and inferior cardiac veins, which can cause susceptibility artifacts and falsely lower the T2* measurement.

Currently, all T2* MR measurements have been validated at a field strength of 1.5 T. Although 3T scanners are now commonly installed, there is very little clinical experience of their use in TM. T2* values at 3T are shorter than at 1.5 T,[125,126] and the potential for artifacts is greater. In view of the importance of the measurement of myocardial T2* and the very limited clinical experience at 3T, we recommend that all clinical T2* MR be performed at 1.5 T.

### 3.4 Normal Ranges in TM

In healthy, nonanemic subjects, LV and RV volumes and function (systolic and diastolic) vary with sex, age, and body surface area. Identification of early abnormality requires rigorous analysis and appropriate reference ranges that normalize for all 3 variables. These ranges are available in both tabular and graphic form for analysis, including papillary muscles as myocardium and modeling for systolic valve descent, and are of significant clinical and research utility for the correct and accurate interpretation of CMR studies.[99,100] Values for young patients are also available.[105,106]

In TM patients without cardiac iron overload, LV end-diastolic volume is increased and LV end-systolic volume is decreased, which leads to increased LV stroke volume, LVEF, and cardiac output compared with healthy control subjects after normalization for body surface area.[103] The hyperdynamic circulation also leads to an increased LV mass. The same is true for the RV indexes: RV stroke volume and cardiac output are higher, and RV ejection fraction is also higher, mostly secondary to increased RV end-diastolic volume compared with healthy, nonanemic control subjects.[104] The observed differences in LV indexes seen in TM patients without iron overload are more pronounced than the RV indexes compared with healthy, nonanemic control subjects. It is important to use the "normal for TM" ranges for TM patients, because this may enhance diagnostic accuracy for detection of cardiomyopathy.

## 4. Treatment of TM: The Iron Chelators

### 4.1 Basic Chelation Principles

Iron has 6 electrochemical coordination sites that need to be tightly bound by an iron chelator to block the ability of the iron ions to catalyze redox reactions and to allow efficient transport and excretion without iron redistribution. Iron chelators should reduce tissue iron levels, prevent excessive organ iron accumulation, and neutralize toxic labile iron pools. Based on the number of the coordination sites, iron ligands are termed hexadentate, tridentate, and bidentate. Denticity is directly related to the molecular weight: Hexadentate chelators have a higher molecular weight than tridentate and bidentate molecules. However, diffusion through biological membranes and hence absorption from the gastrointestinal tract and cellular penetration are governed not only by molecular size but also by lipophilicity and net molecular charge.[127] Selectivity and affinity for the ferric $(Fe)^{3+}$ oxidation state are important characteristics of an iron chelator. These properties reduce the chelation of other biologically important bivalent metals, such as copper and zinc, whereas the effect on nonessential trivalent cations, such as aluminum and gallium, remains negligible. Under biological conditions, the affinity of chelators for iron and the stability of ligand-metal complexes is expressed as $pF^{3+}$ value, that is, the negative logarithm of the concentration of the free $Fe,^{3+}$ measured in a solution of 10 μmol/L ligand and 1 μmol/L $Fe^{3+}$ at pH 7.4. The larger the $pF^{3+}$, the higher the stability of the ligand-metal complex. There are 3 commercially available iron chelators, each with very different properties (Table 2).

### 4.2 Deferoxamine

Deferoxamine was the first approved iron chelator to be introduced into clinical use in the 1960s. It is a hexadentate ligand that binds to iron in a 1:1 molar ratio. Deferoxamine is not absorbed effectively by the gastrointestinal tract and must be administered parenterally. Its plasma half-life is very short at ≈20 minutes[128]; therefore, the drug is usually given as a 10% solution subcutaneously by use of a small portable pump. When intensive chelation is needed, deferoxamine can be given as a continuous intravenous infusion. Parenteral administration of deferoxamine is cumbersome, which can adversely affect adherence to treatment. The most common deferoxamine side effects are local infusion-site reactions (induration, erythema, swelling, and itch). Serious adverse events have occurred, particularly in patients taking higher deferoxamine doses relative to their iron burden.[129,130] Ophthalmologic and audiological tests and growth monitoring are recommended. *Yersinia* and *Klebsiella* infections have been reported in patients treated with deferoxamine.[131,132] Renal toxicity and acute respiratory distress syndrome, particularly after excessively high intravenous doses, have been described.[133]

### 4.3 Deferiprone

Deferiprone is a bidentate ligand that binds to iron in a 3:1 molar ratio.[134] Deferiprone is absorbed rapidly from the upper gastrointestinal tract, and the peak serum concentration occurs 45 to 60 minutes after oral ingestion in fasted patients and up to 2 hours in fed patients.[135] Deferiprone is mainly metabolized to a glucuronide conjugate that lacks iron-binding capability. Given its relatively short plasma half-life of 1.5 to 2.5 hours, the drug is usually administered 3 times daily. Free deferiprone, glucuronide metabolite, and the iron-deferiprone complex are mainly excreted renally.[135] The drug is available as tablets or as oral solution. The most common adverse reactions associated with deferiprone are gastrointestinal symptoms (nausea, vomiting, abdominal pain) and a transient increase of liver enzymes.[134] Arthropathy may occur, ranging from mild pain in 1 or more joints (usually knee) to severe arthritis, and low plasma zinc levels have been reported in a minority of patients. Agranulocytosis (absolute neutrophil count $<0.5\times10^9$/L), the most serious adverse

**Table 2. Main Features of the Iron Chelators**

| Drug | FDA Approved | EU Approved | Route | Typical Chronic Dosing, $mg \cdot kg^{-1} \cdot d^{-1}$ | Frequency | Excretion | Main Adverse Effects |
|---|---|---|---|---|---|---|---|
| Deferoxamine | Yes | Yes | SC (IV in heart failure) | 20–50 | 8- to 14-h infusion for 5–7 d/wk | 60% Urine; 40% feces | Sensorineural deafness, visual disturbance, skeletal abnormality, growth retardation |
| Deferiprone | Yes | Yes | Oral | 75–100 | ×3/d | 75%–90% Urine | Agranulocytosis, GI disturbance, arthropathy |
| Deferasirox | Yes | Yes | Oral | 20–40 | ×1/d | ≈90% Feces | Rash, GI disturbance, rise in creatinine |

EU indicates European Union; FDA, US Food and Drug Administration (United States); GI, gastrointestinal; IV, intravenous; and SC, subcutaneous.

reaction with deferiprone, has been reported in ≈1% of treated patients (0.6 cases per 100 patient-years of treatment). A less severe form of neutropenia (absolute neutrophil count 0.5–1.5×$10^9$/L) has been reported in ≈5% of patients treated with deferiprone, particularly nonsplenectomized patients and in association with viral infections.[134] The neutrophil count should therefore be monitored every week to detect early signs of agranulocytosis. Temporary discontinuation or dose adjustment may be beneficial for the common adverse events, whereas in the case of agranulocytosis or neutropenia, the drug should be stopped immediately, and patients should contact their physician. Patients should also be advised to report immediately to their physician any symptoms indicative of infection, such as fever, sore throat, and flulike symptoms.

### 4.4 Deferasirox

Deferasirox is an orally active tridentate chelator that binds iron in a 2:1 molar ratio. Single oral doses of deferasirox are absorbed rapidly, achieving peak plasma levels within 1 to 3 hours after administration; with a mean elimination half-life of 8 to 16 hours, plasma levels are maintained within a therapeutic range over 24 hours, which supports once-daily administration.[136] Feces are the main route of excretion.[137] Deferasirox is available as orally dispersible tablets that are dissolved in water or juice and given at least 30 minutes before a meal. Deferasirox has a clinically manageable safety profile with appropriate patient monitoring. The most common adverse events are mild to moderate transient gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain), diffuse maculopapular skin rash, and increased alanine aminotransferase and serum creatinine levels.[136] Such events rarely require discontinuation of treatment but are frequently resolved either spontaneously or after dose interruption/adjustment. Safety data on long-term usage accord with short-term data.[138] Mild elevations in serum creatinine levels occur in ≈33% of patients, but few experience elevations beyond the normal range.[139] Although the changes in serum creatinine are usually nonprogressive, deferasirox is currently contraindicated in patients with creatinine clearance <40 mL/min or serum creatinine greater than twice the age-appropriate normal threshold.[140] Several cases of Fanconi syndrome have been reported with deferasirox.[140] In some cases, overdosage related to low total iron burden has been reported. Cases were reversible with cessation of the drug. Auditory and ocular toxicities occur in ≈1% of patients treated with deferasirox. Patient monitoring, including tests of renal and hepatic function, is recommended for all patients receiving deferasirox.

## 5. Diagnosis of HF in TM

### 5.1 Diagnosis of HF With Impaired Ventricular Function in Nonanemic Subjects

HF can be defined as an abnormality of cardiac structure or function that leads to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures).[141] For the purposes of these guidelines, HF is defined clinically as a syndrome in which patients have typical symptoms (eg, breathlessness, ankle swelling, and fatigue) and signs (eg, elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function.

### 5.2 Diagnosis of HF in TM

Many symptoms typically present in HF are common in anemia, which can make the diagnosis of HF difficult to make on clinical grounds alone. More reliable clinical markers for the development of HF are changes in symptoms, such as increased exertional dyspnea. Additional symptoms that are prevalent in the TM population relate to liver congestion (abdominal or back pain and nausea) and dizziness/presyncope (arrhythmias).[142] Other symptoms include failure to tolerate standard transfusions. Orthopnea and peripheral edema are late symptoms. The absence of the clinical features of HF (such as hepatomegaly, peripheral edema, raised jugular venous pressure, and lung crackles) does not exclude severe cardiac impairment. The classic signs of HF may appear late, and this has the potential to delay diagnosis and appropriate intensification of chelation.[142] As in conventional HF, blood tests are frequently abnormal. Liver function tests and serum ferritin may be raised because of congestion. An elevated BNP is expected but is a late sign.[50]

## 6. Prediction of HF in TM

The association between biomarkers and HF can be studied through cross-sectional studies that show the contemporaneous

relation of the biomarker to HF, although this approach ignores previous levels of the biomarker, or by longitudinal studies that relate a biomarker to future outcome in a prospective fashion either with single or serial measurements. The latter study design has significant advantages but is harder to execute.

### 6.1 Ferritin

Trends in ferritin level are useful in monitoring the direction of body iron loading but may not predict cardiac iron loading. Long-term elevations in ferritin predict cardiac mortality. Studies suggest that a ferritin level >2500 μg/L indicates a raised risk,[28,42,143] but there is no threshold effect, and risk is increased even down to ferritin levels of 1000 μg/L. A low ferritin level does not guarantee freedom from HF. Single cross-sectional ferritin measurements may be misleading because they may not reflect long-term ferritin levels and do not correlate with cardiac iron levels.[5] Ferritin levels may also be increased by inflammation or infection (especially in hepatitis C, which is highly prevalent worldwide in adult TM) and may be decreased by vitamin C deficiency. Therefore, in individual patients, the serum ferritin level may not reflect the individual total body iron load and cardiac risk.[5,96,143]

### 6.2 Liver Iron

The relation between liver iron and cardiac iron is complex. Single cross-sectional liver iron measurements in patients on long-term iron chelation may be misleading because they may not reflect long-term liver iron levels and do not correlate with cardiac iron levels.[5] It is likely that failure to control liver iron over the long term increases the risk of cardiac iron loading.[143,144] Levels of liver iron >15 to 20 mg/g Fe dry weight are associated with liver damage, liver fibrosis, and the presence of increasing levels of free plasma labile iron and free chelatable iron.[145] It has been shown that noncompliance with iron chelation treatment is a major predictive factor for cardiac iron loading in patients with high ferritin levels, which implies high liver iron loading.[146] However, high levels of free plasma labile iron may be the actual source of iron that loads into the heart.[147] Therefore, high liver iron levels per se may not be the best way to view the cardiac risk associated with liver iron loading. Long-term excessive liver iron loading with poor current compliance with iron chelation therapy may be the worst combination of factors for cardiac iron loading. Thus, although control of liver iron over time is likely to be important in prevention of cardiac iron accumulation, single or even repeated measurements showing low liver iron do not guarantee protection from cardiac disease.[148]

### 6.3 Cardiac Iron (T2*)

Cardiac T2* has been calibrated to cardiac iron in animals and humans.[7,123,149] The lower limit of normal is 20 ms,[5] a threshold below which myocardial T2* in normal subjects does not occur. However, this is recognized as a conservative threshold, because T2* calibration data suggest 20 ms equates to 1.1 mg/g iron dry weight, which is approximately twice the historically reported normal mean level of human myocardial iron.[150] The probability of a reduced ejection fraction increases as cardiac iron increases (cardiac T2* falls).[5,38,43] The longitudinal follow-up of patients has shown that cardiac T2* <10 ms predicts HF. Of patients who developed HF, 98% had a cardiac T2* <10 ms. Patients with a cardiac T2* <6 ms have a 50% likelihood of developing HF within 12 months if no change in iron chelation treatment is instituted.[6] A 3-tier risk model was established on the basis of this finding (low risk, >20 ms; intermediate risk, 10–20 ms; and high risk, <10 ms). A normal cardiac T2* has a very high predictive value for exclusion of HF for 12 months.[35]

### 6.4 LV Ejection Fraction

An increased risk of clinical HF has been demonstrated for patients with falling LVEF or absolute values below the lower limit of the normal range[96,151]; however, there are problems with the use of LVEF. Reproducible measurements of LVEF require excellent attention to detail in acquisition and analysis. CMR has superior reproducibility compared with echocardiography for measurement of LVEF.[101,102] In addition, the absolute level of LVEF varies between imaging techniques and between centers. Finally, changes in LVEF are a late event compared with the early warning of cardiac loading seen with intermediate levels of cardiac T2* (10–20 ms). This occurs because as iron accumulates in the heart, the early decrement in LVEF may be modest and within the normal range until iron storage capacity is exhausted. The relation between the measured T2* and LVEF is therefore shallow until a critical level is reached, after which rapid deterioration may occur. Therefore, the T2* technique can identify those patients who may benefit from earlier chelation therapy to avoid overt HF, which can be difficult to reverse. Because T2* measures storage iron in the form of hemosiderin, and acute toxicity is related to free iron, LVEF can improve faster than the cardiac T2* with acute chelation treatment, which can drive the free iron to zero despite the presence of high tissue levels of hemosiderin. Alternative measures of systolic LV function such as tagging and myocardial phase mapping may be more sensitive to myocardial T2*, but further experience is needed to evaluate their possible clinical role.[152]

### 6.5 Diastolic Function and Compliance

There are few data relating diastolic function to outcome. In one report of 45 patients with 15 years of follow-up, 11 patients died, and restrictive LV filling was predictive of death.[153]

### 6.6 Relative Predictive Power

Direct comparison of cardiac T2* against cross-sectional measurements of liver iron and serum ferritin shows that cardiac T2* is the most significant predictor of the development of HF.[6] There is no direct comparison of cardiac T2* and LVEF for prediction of HF. In the presence of low T2*, the imperative for aggressive cardiac chelation, antifailure therapy, and hospitalization is increased if the LVEF is reduced or falling on closely repeated measurements.

### 6.7 Age

In children who have received regular transfusions and iron chelation, cardiac loading before the age of 10 years is

uncommon.[54] Cardiac iron loading in younger children has been seen in patients receiving little or no iron chelation treatment.[55]

### 6.8 Exercise Capacity

There are contradictory reports regarding exercise capacity in TM patients compared with healthy subjects. TM patients have been reported to have limited exercise capacity,[154] with increasing cardiac iron correlated with decreasing exercise capacity.[155] Others have found normal exercise capacity but a decreased ratio between cardiac index and oxygen extraction at peak exercise in TM patients, which shows a lower contribution of the cardiovascular system to maintain oxygen uptake.[156] Another study showed similar or reduced exercise capacity in TM patients, with normal oxygen delivery but reduced utilization.[157] Consensus opinion is that exercise capacity is often consistent with the degree of anemia and does not appear to be useful to diagnose preclinical disease.[158]

## 7. Conventional Medical Treatment of HF

The medical management of chronic HF without hemoglobinopathy is based on published guidelines.[159–164] In general, the recommendations are similar among guidelines. Overall, management of TM with chronic HF and cardiomyopathy should follow these guidelines unless specified in the following sections.

## 8. Why Treatment of HF in TM Is Different

### 8.1 Introduction

Although the main aspects of the diagnosis and management of HF are well known, the acute and chronic care of HF that complicates TM differ in a number of important ways. First, the age of the population being treated is much younger.[165] Second, it is a toxic cardiomyopathy related to myocardial iron accumulation, so that there is the important prospect of complete resolution of ventricular dysfunction with treatments directed at iron removal rather than directly at myocardial performance. Third, there may be important comorbidities that require recognition and specific treatment in their own right.

### 8.2 Reversibility

Iron cardiomyopathy is the most common and feared complication of TM, but because it is caused by iron toxicity, it is reversible.

### 8.3 Endocrine, Metabolic, and Infectious Comorbidities

TM patients with cardiac iron overload also have iron overload in many endocrine glands,[166,167] including the pancreas, pituitary, thyroid, parathyroid, and adrenal gland. The endocrine and metabolic deficiencies can mimic or exacerbate HF. Primary myocardial dysfunction can be caused by hypoparathyroidism[168–170] and hypothyroidism,[171,172] and these conditions may exacerbate iron cardiomyopathy. Decreased adrenal reserve is also common in TM,[173–178] and patients in HF should be treated as though they have adrenal insufficiency until proven otherwise. Hypogonadotrophic hypogonadism is the most common endocrinopathy observed in TM,[1,179] and low sex steroids may exacerbate HF symptoms.[180,181] Growth hormone deficiency must also be considered and may contribute to HF. Many TM patients have diabetes mellitus, and insulin resistance and type 2 diabetes mellitus are strongly associated with cardiac iron deposition. Cardiac metabolism is altered, and a propensity to cardiac dysfunction is associated with chronic hyperglycemia and insulin resistance, in which there occurs a shift of cardiac metabolism from glucose to fatty acid oxidation, with associated lipotoxicity, activation of the renin-angiotensin-aldosterone axis, hypertrophy, altered calcium homeostasis, fibrosis, and microvascular disease.[182] Thus, the phenotype of iron-overload cardiomyopathy may have some overlap with the cardiovascular changes typically associated with type 2 diabetes mellitus. Glucose control must be considered in acute and chronic HF management, ideally by the use of insulin infusions, with meticulous avoidance of hypoglycemia and hyperglycemia.

The chronic anemia and ineffective erythropoiesis of thalassemia are associated with a hypermetabolic state that leads to deficiencies in a number of metabolically important cofactors such as thiamine, B6, and folate.[183] Fat-soluble vitamins are decreased,[184–186] as are trace elements such as zinc, copper, and selenium.[183,185,187] Carnitine deficiency is also common, and carnitine replacement therapy has been associated with clinical improvement in uncontrolled studies.[188,189] Hence, in any TM patient presenting with decreased cardiac function, it is prudent to eliminate possible contributions from thiamine, carnitine, or extreme vitamin D deficiencies (25 hydroxyvitamin D levels <10 ng/dL),[190–192] given the benign nature of replacement therapy.

Sepsis is the second-leading cause of death in TM patients and may precipitate HF. Whether sepsis disrupts iron stores in the heart or whether the hemodynamic stress induced by sepsis merely unmasks compensated HF is unknown. Many older TM patients have been subjected to splenectomy and are therefore vulnerable to severe infection by encapsulated organisms[193]; in patients treated with the chelator deferoxamine, increased iron stores may also predispose to bacterial infection, particularly with some unusual pathogens, including *Yersinia enterocolitica*.[131] Chronic antigen exposure with blood transfusion also downregulates cell-mediated immunity and may leave TM patients at risk for fulminant infections.[194–197]

Myocarditis prevalence in 1995 was estimated to be 4% among a cohort of Greek TM patients, and it was suggested that such infections were the cause of LV failure.[198] The same group hypothesized an association of the major histocompatibility subtypes HLA-DRB1*1401 and HLA-DQA1*0501 with LV HF.[199] Since these reports were published, improved access to iron chelation appears to have decreased the incidence of myopericarditis significantly.[5,200,201] The clinical presentations of myocarditis and decompensated HF attributable to severe iron overload have considerable overlap, except that iron-induced cardiomyopathy does not typically manifest with chest pain, diffuse ST-T–wave changes, or increased cardiac enzyme levels. Given the overlap and the possibility that iron may exacerbate myopericarditis, all TM patients with acute reductions in cardiac function should receive intensified iron

chelation therapy empirically until cardiac iron loading can be confirmed by CMR.

### 8.4 Different Baseline Hemodynamics and Different Response to Loading

Patients with TM have an increased cardiac index as a consequence of their chronic anemia.[53,103,200] The heart rate and stroke volume may both be elevated compared with age- and sex-matched control subjects. Thus, mild tachycardia and cardiomegaly must be viewed as physiological compensation for the anemia rather than pathological associations that imply myocardial iron overload. The hyperdynamic circulation characteristic of this group accounts in part for the increased reference ranges for ventricular ejection fractions in thalassemia.[103] Despite having an increased cardiac index, TM patients also have lower systolic blood pressure and a blunted temporal variability of blood pressure, consistent with a markedly decreased systemic vascular resistance.[75,202] Despite having lower blood pressure and higher cardiac index, measurements of aortic and peripheral vascular compliance reveal decreased values in TM patients that worsen with iron overload and with age.[82,83,203–205] Iron overload exacerbates oxidative stress in the vasculature, accelerating age-related increases in vascular stiffness.[205] Flow-mediated dilation, a marker of endothelial function, is proportional to cardiac T2*, which suggests commonality between cardiac and vascular iron overload.[9] Chelation therapy for 1 year improves endothelial function, which suggests that the relationships are causal rather than correlative.[9,83] Increased systemic vascular elastance creates a ventricular-vascular mismatch in TM patients that can lead to unfavorable ventricular remodeling and increased cardiac oxygen consumption.[206,207]

The aforementioned physiological differences affect the success of HF treatment in thalassemia. Baseline preload is high because of chronic anemia. Therefore, although diuresis can lower wall stress and improve symptoms attributable to fluid overload, overdiuresis can precipitate acute renal failure by excessive reduction of preload, especially in the setting of compromised oncotic status with chronic liver disease (iron induced, hepatitis C) and hypoalbuminemia.[18] Older patients may have a restrictive physiology that does not tolerate either overfilling or underfilling. Although there are no clear data, maintaining higher hemoglobin levels in patients with HF may be beneficial. Afterload reduction is often the mainstay of conventional acute HF treatment and can improve ventricular-vascular coupling in dilated cardiomyopathy. Unfortunately, chronic anemia results in low systemic afterload, and additional poor vascular compliance in the TM patient may limit the afterload reduction that is tolerated (even relatively young patients may have stiff vessels). Afterload reduction should be titrated very carefully against urine output and clinical response rather than target pressures, which are often derived from experience in non-TM populations and not applicable in this hemodynamically unusual group of patients. Overall, there are no data on the use of conventional HF treatments in TM patients with HF, but it is inadvisable to withhold such treatments that have been shown to have significant mortality and morbidity benefits in patients without thalassemia. However, exceptional caution is required in the setting of acute decompensated HF, and this is discussed further in the next section.

Although positive inotropes are often used to improve ventricular-vascular coupling, their use comes with significant penalties in iron cardiomyopathy. Most inotropes increase intramyocyte calcium levels, may worsen oxidative stress, and increase electrical automaticity, which may act synergistically with iron-mediated toxicity to the detriment of myocyte function. Thus, we recommend that inotropes should be used with great caution and reserved for desperate situations and that doses should be minimized whenever possible.

### 8.5 Unique Electrophysiology

Arrhythmias in TM are a mixture of triggered and reentrant arrhythmias.[208] Chronic volume overload creates an anatomic substrate suitable for atrial and ventricular reentrant tachycardias and fibrillation by lengthening the conduction paths and increasing dispersion of repolarization. However, patients with thalassemia intermedia, who have larger chamber volumes but little cardiac iron, have fewer cardiac arrhythmias than TM patients, which implies a critical role for iron toxicity.[200,209] Atrial iron cannot be measured by CMR, but atrial arrhythmia risk correlates with ventricular T2* estimates.[6] Iron deposition is most common in working muscle and tends to spare the conduction system.[72,210] Postulated mechanisms for the electrophysiological effects include inhibition of fast inward sodium currents, blockage of ryanodine calcium release channel, and oxidative stress–mediated changes in sarcoplasmic calcium release and reuptake.[71,211–213]

Clinically, intra-atrial reentrant tachycardia and AF are the most common serious rhythm disturbances.[214] Ectopic atrial tachycardia and chaotic atrial rhythm may also be seen, particularly in the presence of significant cardiac iron loading.[27,44] Amiodarone is often successful in controlling atrial arrhythmias and can be a powerful temporizing measure during intensive iron chelation. Long-term therapy may be complicated by hypothyroidism because of iron-mediated thyroid damage[215]; however, amiodarone therapy can often be terminated successfully after 6 to 12 months. Ablation should be reserved for patients who have undergone successful removal of cardiac iron (documented by CMR). Ventricular arrhythmias are more specific for iron cardiotoxicity.[214] Frequent premature ventricular contractions, by themselves, are not specific for iron cardiomyopathy, but couplets, nonsustained ventricular tachycardia, or mixtures of frequent atrial and ventricular premature contractions should raise clinical suspicion. Historically, sudden death accounts for ≈5% of cardiac deaths in TM and is associated with severe iron overload and increased QT dispersion, which suggests iron-mediated repolarization abnormalities and torsade de pointes as a causative mechanism.[46,216] Ventricular late potentials have also been described in thalassemia and are correlated with serum ferritin levels.[217] Treatment of potentially life-threatening ventricular arrhythmias in patients with severe cardiac iron burdens is problematic, because the physiological substrate is potentially reversible, and device therapy should be avoided if possible because it precludes further monitoring of cardiac iron stores by CMR. A defibrillation vest may represent a viable therapeutic bridge during intensive iron chelation therapy.

## 9. Treatment of Acute Decompensated HF With Reduced Ejection Fraction

### 9.1 Recognition of Acute HF

Acute decompensated HF is recognized as a clinical syndrome that includes progressive dyspnea and significant fluid retention. A significant presenting feature in TM can be abdominal (or other location) pain from distended organs such as the liver. This is usually associated with reduced ventricular function and raised BNP.

### 9.2 Mortality Rate in Acute HF

The death rate attributable to HF in historical series was 50% within 1 year.[27,44] In 52 patients with mean LVEF of 36%, there was 48% survival after 5 years with no change in iron chelator and use of cardiac medications.[46] In recent years, with the introduction of continuous intravenous deferoxamine treatment, survival has improved, with a report of this treatment showing survival of 6 of 7 patients.[47] Deferoxamine intensification (continuous intravenous or subcutaneous) showed survival in 17 of 20 patients.[218]

### 9.3 Where Should Patients With HF Be Treated?

This is a medical emergency and requires specialized medical care. Delay in starting appropriate chelation therapy can be life-threatening. On presentation, advice should be sought about treatment from a specialist center that is experienced in treatment of HF in thalassemia patients. Such a center is expected to have a larger volume of TM patients under care and have experience with less common complications. Early transfer of the patient to the specialist center is strongly advised where possible to allow integrated cardiological and hematologic care with doctors skilled in handling HF in TM. There are some data supporting this approach to improve cardiac outcomes.[219,220] When admission to a specialist center is not possible, close liaison with such a center is mandatory.

### 9.4 Management of Acute Decompensated HF in TM

The aim of treatment in acute HF is to keep the patient alive so that iron chelator treatment can detoxify the cardiac iron. We recommend the following management strategy:

1. Immediate commencement of 24-hour-per-day continuous (uninterrupted) intravenous iron chelation treatment with deferoxamine 50 $mg \cdot kg^{-1} \cdot d^{-1}$.[47–49,151]
2. The patient should have continuous electrocardiographic and hemodynamic monitoring.
3. As soon as is practical, perform bedside echocardiography to confirm the diagnosis of HF and exclude other cardiovascular conditions, including pulmonary embolism.
4. Introduce deferiprone as soon as possible at a dose of 75 $mg \cdot kg^{-1} \cdot d^{-1}$ (the total dose given in 3 divided doses).[50,221–226]
5. Supportive hemodynamic therapy should be geared to maintain cerebral and renal perfusion, avoiding aggressive inotropic therapy, which can be detrimental. Blood pressure is typically low in TM patients and should not attract specific therapy if renal and cerebral perfusion is maintained.
6. Only minimum diuretic treatment should be used because of the importance of maintaining preload. Consideration should be given to the alternative maneuver of venous ultrafiltration to remove excess fluid as a means to prevent reduction in preload,[227,228] but recent results have shown more renal failure and adverse events with its use in non-TM patients with decompensated HF,[229] and further trials are needed to establish its role.
7. Cardiac arrhythmias are common and often respond to continuous iron chelation treatment. Meticulous attention should be given to normalization of electrolyte abnormalities, and consideration should be given to the use of magnesium infusion to stabilize ventricular arrhythmia. Nevertheless, amiodarone is the drug of choice to treat hemodynamically significant arrhythmias. β-Blockers can be used if the hemodynamic status allows. There is no published evidence for the use of these interventions.
8. Maintain meticulous glucose control with insulin/potassium infusion. This may also help with cardiac inotropic status.[230]
9. Give hydrocortisone on the presumption of inadequate adrenal response to stress.[175]
10. Check thyroid, liver, and renal function and calcium, magnesium, vitamin D, carnitine, and other metabolic parameters and correct these when necessary.
11. Maintain hemoglobin between 10 and 12 g/dL. This may require frequent small-volume transfusions.
12. Search for precipitating conditions such as infections.
13. There is no evidence to support the initiation of angiotensin-converting enzyme inhibitors or angiotensin 2 receptor blockers to manage acute decompensation, and the successful introduction of these drugs is often compromised by poor tolerance caused by low blood pressure. The introduction of β-blockers as an antifailure treatment has the merit of reducing the propensity to arrhythmia and may take priority over angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers. The introduction of these drugs can be considered for management of chronic HF, after the patient is stabilized and is past the acute decompensation period.
14. Cardiac T2* should be performed as soon as is practical. If cardiac T2* is >20 ms, then myocarditis should be considered as a cause of HF, using a standard CMR myocarditis protocol.[231]

### 9.5 Additional Notes

1. Clinical stabilization can occur within 14 days after commencement of continuous iron chelation treatment but can also take months.
2. Patients with renal failure may require early dialysis to remove the iron chelator and, although experience with this is limited, efficacy is not proven and may vary by chelator.
3. Deferasirox has not been evaluated in acute HF and may be ill-advised in the presence of marginal renal perfusion.
4. Consideration should be given to mechanical support devices to support both ventricles, bearing in mind the RV is often compromised. There is no published evidence for this approach.

5. Cardiac transplantation has been used, but its relevance is questionable in the modern chelation era.[232–235]
6. Cardiac storage iron is removed very slowly from the heart, even with intensive iron chelation. Treatment will need to be continued for several years and should be monitored by regular T2* and cardiac function assessments. Iron chelation treatment may require adjustment according to liver iron and serum ferritin levels to prevent chelator-mediated toxicity.
7. Compliance with iron chelation treatment is essential for long-term survival of acute cardiac failure, but long-term follow-up by a specialist center is essential to achieve optimal outcomes.[219,220]
8. Long-term intravenous deferoxamine treatment requires careful management of the intravenous line, anticoagulation, and scrupulous sterile access techniques. Careful consideration of the risk and benefits of this approach must be given on a case-by-case basis.
9. Conversion from 24 hours/day intravenous to 24 hours/day subcutaneous deferoxamine iron chelation treatment can be considered after the acute period.[151]
10. Combination therapy with daily subcutaneous deferoxamine and daily oral deferiprone (for the avoidance of doubt, both drugs are taken together every day) has been used extensively for long-term management of patients with impaired LV function without decompensated HF.[50] The use of subcutaneous deferoxamine infusion avoids the infection risk of long-term intravenous infusion.
11. After resolution of decompensated HF, treatment may need to continue for several years to remove cardiac iron in thalassemia.[47] In hemochromatosis, cardiac iron has been shown to persist even when venesection has resulted in hypoferremia and iron deficiency anemia.[236]
12. Treatment should be monitored by assessing clinical status, LVEF (which can improve substantially within weeks), cardiac T2* (which improves over months), and ferritin trend.

## 10. Treatment of Myocardial Iron Overload Without Cardiac Decompensation

### 10.1 Level of Urgency

Many factors come into play when considering whether to escalate therapy in response to detection of cardiac iron (T2* <20 ms) in an asymptomatic patient with normal or near-normal LVEF. These include the severity of cardiac iron loading, whether there is any evidence of preclinical cardiac toxicity, longitudinal trends in cardiac iron, liver iron burden, and patient compliance.

Without escalation in therapy, the prospective risk for developing HF in 1 year is 47% if cardiac T2* is <6 ms, with a relative risk of 270 compared with patients having a T2* >10 ms.[6] In an observational study of 652 patients followed up for up to 7 years, only 1 of 80 HF episodes occurred in a patient who had a T2* >10 ms.[6] Because outcomes for symptomatic HF are poor,[48] many thalassemia centers will treat patients who have T2* <6 ms similar to those with overt HF. Patients having T2* between 6 and 10 ms are often placed on intensified but not necessarily maximal chelation therapy. Patients with T2* between 10 and 20 ms can often be managed more conservatively, with modifications of chelator dose, efforts to improve patient compliance, or alternative or additional chelators. Preclinical reductions in heart function also warrant escalation in chelation therapy.[151] Many patients with mild reductions in heart function are completely asymptomatic but are at significantly increased risk for progression to HF and death.[151] CMR estimates of cardiac function can also be collected easily at the time of cardiac T2* assessment. As noted above, the role of other preclinical markers of cardiac iron toxicity, including arrhythmias, QT prolongation, and exercise capacity, in guiding chelation therapy is currently unknown.[6,155,216]

Longitudinal trends in cardiac T2* values are also important.[148] Cardiac iron clears slowly, with a half-life of ≈13.5 months (5% per month) during continuous intravenous deferoxamine,[47] and a third as fast with intermittent deferoxamine therapy.[8,9] Therefore, normalization of cardiac iron lags improvements in total body iron burden. A patient whose cardiac T2* has improved from 6 to 8 ms in 1 year should clearly be handled differently from one whose cardiac T2* has declined from 10 to 8 ms over the same interval.

Liver iron burden also plays a role in determining how aggressively one should respond to the presence of cardiac iron. The chelatable iron pool increases with total body iron stores,[145,237,238] although the mechanisms of this phenomenon are not well understood. Chelators such as deferasirox and intermittently dosed deferoxamine primarily interact with intravascular or hepatic labile iron. When hepatic iron stores are high, changes in cardiac iron may be quite modest until the liver iron levels drop below 5 mg/g.[148,239] Chelators with better intracellular permeability, such as deferiprone, appear to have superior cardiac iron clearance when liver iron is high.[8,240]

Lastly, knowledge of patient compliance with medication is essential in determining appropriate chelation for any given patient with cardiac iron overload. Compliance is an important predictor of cardiac chelation efficacy,[146] particularly for chelators such as deferoxamine and deferasirox that act primarily as intravascular sinks to clear cardiac iron. Cardiac T2* measures primarily insoluble, inert hemosiderin, which exists in equilibrium with the toxic labile iron pool. If free drug is available around-the-clock to soak up toxic labile iron, increases in cardiac iron deposition or progression to HF may be less likely, regardless of the measured cardiac T2*. However, labile iron rebounds quickly in the absence of iron chelation,[241,242] so anything short of perfect compliance is likely to place the heart at risk.[146,243] Because the intensity of labile iron exposure increases with liver iron concentration,[145,237,238] the cardiac penalty for noncompliance is likely to be worse for higher liver iron stores.[144,239]

### 10.2 Cardiac Iron Chelation Strategies

Deferoxamine, deferasirox, and deferiprone all remove cardiac iron if given in adequate doses and if patient compliance is good. However, each medication has advantages and disadvantages, and optimal therapy must be tailored to each patient. There are many excellent reviews on this subject.[244–246] The following recommendations are specific to patients with detectable, asymptomatic cardiac iron overload.

#### 10.2.1 Deferoxamine Monotherapy

The half-life of deferoxamine is only 30 minutes, and labile iron rebounds (often with an overshoot) within hours of infusions being stopped. When the drug is given in standard, intermittent subcutaneous infusions, it will clear cardiac iron at 1.1% to 2.2% per month.[8,9] By contrast, continuously administered deferoxamine clears cardiac iron at nearly 5% per month because labile iron is scavenged continuously, leaving a gradient between the heart and intravascular space. Thus, increasing the days and duration of deferoxamine therapy will tend to improve cardiac iron clearance. The primary limitation of this approach is patient discomfort and inconvenience, which leads to poor patient acceptance. Local skin reactions prevent subcutaneous therapy in some subjects, introducing the known risks of chronic intravascular access. Others are unable or unwilling to undergo chelation during the day because of job or social considerations. We recommend a change in chelation treatment in patients with cardiac siderosis if there is poor compliance with deferoxamine.

#### 10.2.2 Deferiprone Monotherapy

Retrospective studies suggest that deferiprone monotherapy offers superior cardiac protection[240,247,248] and improves survival compared with routine deferoxamine therapy.[249,250] Improvements in myocardial iron loading in national strategic programs with treatment regimens including deferiprone have also been reported,[3,251] with associated improvements in outcomes.[3,14,252] These survival data are recognized by the European Medicines Agency.[253] There is only 1 prospective randomized study comparing deferoxamine and deferiprone monotherapy.[8] Deferiprone given at 92 $mg \cdot kg^{-1} \cdot d^{-1}$ cleared cardiac iron at a rate of 2.2% per month, nearly double the rate produced by deferoxamine in the same trial. Deferiprone significantly improved LVEF in contrast to no change in LVEF with deferoxamine,[8] despite statistically insignificant improvements in hepatic iron concentration. Separate analysis showed that deferiprone also improved RV ejection fraction more than deferoxamine.[254] We recommend the use of deferiprone monotherapy in patients with cardiac siderosis, and it is also suitable for patients with reduced LVEF or asymptomatic LV dysfunction. Deferiprone combined with deferoxamine (both given daily together) is commonly prescribed in severe cardiac siderosis for maximum effect (Section 10.2.4).

#### 10.2.3 Deferasirox Monotherapy

Publications from 2 open-label, single-arm trials with multiple reports (cardiac substudy of the EPIC trial [Evaluation of Patients' Iron Chelation With Exjade][10,255,256] and US04[239,257] trial) showed that deferasirox monotherapy can be used successfully in patients with detectable cardiac iron and normal cardiac function. Data from a small case series were in accord.[258] However, no change in LVEF was seen in these trials. Cardiac iron clearance rates were 1.3% to 1.5% per month, comparable to those published for deferoxamine. Iron clearance rates, however, may be a function of initial hepatic[238,239,257] or cardiac[10,255,256] iron burden. The results of a large randomized controlled trial presented late in 2012 showed the efficacy of deferasirox for removal of cardiac iron (mean dose 36.7 $mg \cdot kg^{-1} \cdot d^{-1}$), with noninferiority of deferasirox compared with deferoxamine, but no change in LVEF with treatment.[259] We recommend that deferasirox is suitable to treat cardiac siderosis, but we do not recommend the use of deferasirox as first-choice treatment for cardiac T2* <6 ms or in patients with reduced LVEF because of the limited data on efficacy available at this time. We recommend caution in the use of deferasirox monotherapy to treat cardiac siderosis in patients with high liver iron loading, in whom high doses (>40 $mg \cdot kg^{-1} \cdot d^{-1}$) may be needed and cardiac efficacy may be delayed.

#### 10.2.4 Combined Drug Therapies

Deferoxamine and deferiprone have been combined successfully (both drugs taken together every day or most days) to improve cardiac and hepatic iron clearance.[260,261] There is evidence of a synergistic shuttle effect between deferiprone and deferoxamine in improving iron clearance.[69,262] Reversal of cardiac siderosis and improvement in LVEF have been shown in several small trials.[263–265] In one open-label, single-arm trial of patients with depressed LVEF and severe cardiac iron (T2* <8 ms), combined subcutaneous deferoxamine and oral deferiprone 75 $mg \cdot kg^{-1} \cdot d^{-1}$ for 7 days a week improved cardiac T2* 3.3% per month and normalized LVEF in all individuals with cardiac dysfunction.[50] In a randomized controlled trial, patients having T2* between 8 and 20 ms received either deferoxamine monotherapy or deferoxamine combined with deferiprone (both given together, with deferoxamine dosed at 5–6 days per week).[9] Combined therapy increased cardiac T2* 4.2% per month compared with only 2.2% per month for deferoxamine therapy. RV function was also shown to improve significantly more with combination treatment.[266] However, the addition of even as little as 2 deferoxamine doses per week to daily deferiprone appears to greatly improve overall iron balance.[267] The use of combination therapy has been associated with improved outcomes in severe cardiac iron loading compared with the use of deferoxamine alone.[226,268] The use of the combination of deferoxamine and deferiprone is widespread, and this combination is used especially in patients with moderate to severe cardiac iron overload or when LVEF is impaired. We recommend its use in these circumstances, and clinical experience suggests that there are no significant toxicity issues for the combination, although safety reports are limited compared with trials of chelator monotherapy.[269] The combination of daily deferiprone with daily deferasirox is currently under investigation, but there are currently very few data to support this attractive regimen.[270] Deferasirox has also been combined with deferoxamine.[271]

#### 10.2.5 Sequential Drug Therapies

One randomized trial also suggested that alternating deferoxamine and deferiprone therapies (drugs taken sequentially on different days, but not taken on the same day together) provided comparable cardiac protection to deferiprone monotherapy, with improved control of liver iron concentration.[272] This therapy represents another option in patients with mild cardiac siderosis.

### 10.3 Treatment of Patients With Cardiac Siderosis With Abnormal or Falling LVEF

Patients with myocardial iron loading who have reduced LVEF for TM,[103] or a consistent trend over time with several

measurements toward abnormality, form a subset of patients identifiable clinically as having early HF, which is usually asymptomatic. The measurement technique used to determine cardiac function will vary according to local availability but can include LVEF, cardiac dimensions, or possibly tissue Doppler parameters. If repeated measures of cardiac function are compared, this must be done using a consistent technology (eg, CMR or echocardiography for all measurements, using the same acquisition technique). Such patients require intensification of chelation. This may only require dose adjustment of current treatment or measures to improve compliance. Should these measures prove ineffective within a few months, or should clinical concern exist, a change in iron chelator regimen is required. We recommend the use of deferoxamine with deferiprone in combination in these circumstances.[50] This approach is consistent with data from randomized controlled trials, [9,128] as well as an analysis of the decreased risk of developing HF in patients whose LVEF improved with treatment.[273]

## 11. Monitoring Treatment With Respect to the Heart

### 11.1 Monitoring of Body Iron Load

Regular monitoring is recommended of ferritin (at least every 3 months) and of liver iron concentration by MRI (annually). The trend indicates the direction of body iron loading, which reflects the balance of transfusional iron intake and iron chelator–mediated iron excretion (chelator regimen and patient compliance). There is little useful relation clinically between single measurements of ferritin and cardiac T2* in patients already receiving chelation therapy.[5] Failure to control ferritin on a long-term basis increases the likelihood of heart disease. Increased cardiac risk been shown with long-term ferritin >2500 μg/L,[28,143,146,151] as well as for values >1000 μg/L.[1] Ferritin as a single measure of total body iron can be misleading, however, and liver iron concentration can be used as an additional measure to provide quantification of total body iron stores[274] and hence the risk of progressive liver damage.[275] Single estimates of liver iron concentration by T2* do not correlate with cardiac T2* in patients receiving chelation therapy[5]; however, there is a relationship between a single liver iron concentration measurement and cardiac survival.[143]

### 11.2 Clinical Cardiac Monitoring

Patients receiving regular transfusion and iron chelation should be assessed formally for their cardiac status (history, physical examination, and auscultation) beginning at the age of 10 years and annually thereafter. Ideally, this assessment should be performed by a cardiologist with expertise in iron-related cardiac disease, working closely with clinicians at a reference center. Such an approach, including the cardiac investigations, increases the likelihood of identifying preclinical cardiac disease, which permits early intensification of treatment and prevents the development of HF.

### 11.3 Cardiac Investigations

It is recommended that annual electrocardiography and echocardiography (chamber dimension and function) be performed. The first CMR for cardiac T2* should be performed as soon as the child can cooperate without sedation or anesthetic, which is typically between the age of 6 and 10 years. After this, annual assessment of T2* CMR is typical, but individual patient factors will determine the frequency of repetition. For example, patients at high risk (T2* <10 ms, reduced LVEF, poor compliance, treatment interruption) may require scanning every 6 months. In the patient with stable chelation and stable cardiac T2* >20 ms, scans can be repeated less frequently (every 2–3 years).

### 11.4 LVEF Response During Chelation

The trend in LVEF and cardiac dimensions is useful to monitor response to treatment. A worsening in cardiac function is a poor prognostic sign[151] and an indication for intensification of treatment. Different responses in the LVEF to iron chelators have been demonstrated in cardiac siderosis without decompensation. Data from control arms of 2 randomized controlled trials showed subcutaneous deferoxamine did not significantly improve LVEF in mild to moderate cardiac iron overload,[8,9] whereas the active arms of these trials showed significant increases in LVEF with deferiprone,[8,9] and this has been found in other trials.[276] These findings are in accordance with those of cross-sectional studies.[240,248] LVEF does not increase with deferasirox treatment in cardiac siderosis.[10,239,255,256] The improvement in LVEF probably reflects relief of subclinical cardiotoxicity; it is associated with a lower risk of developing HF and is a good prognostic sign.[273] If cardiac function fails to improve, it is important to also consider additional contributory factors, such as other cardiomyopathy or other concomitant pathology. It is likely that trends in cardiac T2* have similar importance for prognosis, but this has not been addressed in published studies. Where T2* CMR is not readily available, serial cardiac function measurements become paramount as an important indicator for increased risk of HF from cardiac iron overload.

## 12. Cardiac Mortality and Iron Chelation

The introduction of deferoxamine infusion in the 1970s had a profound effect on reducing mortality in TM,[2,277] and this was dominated by a reduction in iron overload–related cardiac mortality. More recently, deferiprone was introduced into clinical care in many countries (European approval in 1999 and US Food and Drug Administration approval in 2011), either as monotherapy or in combination with deferoxamine. Its use has been associated with reduced cardiac mortality in the United Kingdom, Italy, Cyprus, and Hong Kong.[11,14,249,250,268,278,279] In the United Kingdom, treatment with deferiprone has been linked to the finding of normal cardiac iron concentration with cardiac T2* >20 ms.[240] The mechanism for the improved mortality is probably multifactorial but may include early identification of patients at cardiac risk by cardiac T2*, improved compliance with chelation therapy, or specific cardiac actions of deferiprone, including greater access to cardiac iron stores or mitochondrial iron. There have been no reports since the introduction of deferasirox (US Food

and Drug Administration approval in 2005) that have documented any effects on cardiac mortality in TM.

## 13. Pregnancy

Recent advances in the management of TM have substantially reduced complications and improved quality of life and life expectancy of patients, with a consequent increase in their reproductive potential and desire to have children. An increasing number of woman with TM have a successful pregnancy, with >500 pregnancies reported.[22,280–283] Spontaneous fertility can occur in well-transfused and chelated women with TM. Unfortunately, the majority have impaired fertility caused by hypogonadism and require induction of ovulation, which may produce a high number of twin or triplet pregnancies.[283–286] The maternal and fetal risks depend primarily on preexisting maternal complications and iron-related organ damage.[287] Iron overload may result in cardiac complications, and therefore, we recommend assessment of heart T2* and cardiac function and dimensions before conception. Blood consumption may increase during pregnancy to maintain a hemoglobin level of ≈10 g/dL and ensure optimal fetal growth,[283] and when combined with the interruption of chelation because of teratogenic considerations, this may significantly worsen iron overload. These factors, the increased blood volume and changes in blood pressure, may compromise heart function, which should be monitored carefully during pregnancy.

The rate of cardiac complications in pregnancy ranges from 1.1% to 15.6%.[284,288] In patients with severe heart or liver iron overload, a restarting of iron chelation with deferoxamine toward the end of the second trimester should be considered. Spontaneous miscarriage and fetal loss have been reported in 9% to 33.3% of pregnancies in women with thalassemia.[285,289] Preterm births for underlying maternal or obstetric complications have occurred at increased rates. Obstetric complications, including gestational diabetes, preeclampsia, and hypertension, have been reported frequently.[287] The rate of cesarean delivery because of fetopelvic disproportion, osteoporosis, maternal HIV infection, or patient choice varies between 24% and 100%.[283,284] Prophylaxis for thromboembolism with heparin or low-molecular-weight heparin is indicated, particularly in splenectomized patients and in patients with thalassemia intermedia. In conclusion, provided that a multidisciplinary team is available, pregnancy is possible with a favorable outcome, but such pregnancies are best handled in expert centers because of the increased risk to mother and baby, especially in women who have preexisting cardiac disease or large amounts of cardiac iron.

## 14. Late Consequences of Transfusion

### 14.1 Arrhythmias and Iron Loading

From the earliest reporting of the cardiovascular complications of thalassemia, it was noted that arrhythmia and conduction disturbance were featured prominently.[27] AF was the most common arrhythmia (12 of 20) encountered in transfused but not chelated patients, with ventricular arrhythmias being less common (2 of 20). Abnormalities of conduction disturbance from complete heart block (4 of 20) to more minor electrocardiographic abnormalities were also seen (15 of 20).[27] The follow-up of this cohort revealed that 50% of patients had cardiac rhythm disturbances by the age of 20 years, and 40% developed heart block, although this complication was uncommon (6%) before the age of 15 years.[45] Early pathological examination of hearts affected by iron overload emphasized the patchiness of iron overload,[72] with evidence of atrioventricular nodal and conducting tissue having variable iron content that was not always associated with clinical evidence of arrhythmia or heart block.[210] A role of severe, untreated iron overload in the development of conduction disturbance would appear likely. The incidence of heart block has diminished drastically with effective chelation therapy in TM patients.[290] In a prospective series, ≈14% of patients with severe iron overload (T2* <6 ms) experienced an arrhythmia within 1 year of the CMR scan; most of these arrhythmias were AF (78 of 98 patients), although a few patients had ventricular arrhythmia (5/98), including 1 patient who died.[6] Arrhythmias may occur in patients with normal myocardial T2*,[6] and a number of explanations for this finding are possible, including the existence of atrial iron loading separate from the ventricle, vulnerability of the atria to arrhythmias, persistence of atrial iron loading despite ventricular clearance, myocarditis, and the longstanding proarrhythmic atrial effects of volume loading and high cardiac output caused by chronic anemia.

### 14.2 Arrhythmias in Relation to HF

Arrhythmias in TM may be a consequence of the development of HF, may precipitate HF, or may occur in the context of good LV function with or without current evidence of iron overload. This is particularly the case for AF; in the aging cohort of well-chelated individuals, AF may be encountered in otherwise apparently healthy hearts. Ventricular arrhythmia is more often associated with severe iron overload, although this distinction between acute presentations and more chronic incidence of arrhythmia has not always been demonstrated.[6] There are numerous case reports that attest to the association of severe siderotic cardiomyopathy and ventricular arrhythmia, as well as sudden death, assumed to be arrhythmic in origin. The nature of sudden death, by definition, is not clear, but it would be consistent with ventricular arrhythmia as the primary cause in most instances. In this regard, the toxic cardiomyopathy of iron overload would mimic the situation that prevails in other nonischemic and ischemic cardiomyopathies, although the presence of LV dysfunction would not be expected to be a prerequisite for the risk to be elevated in the TM population. The potential mechanisms for such enhanced risk include increased QT dispersion, autonomic dysfunction, high redox potential, and low resting heart rate, and are all to be encountered in more or less severe form in patients with TM.

### 14.3 Causation of Arrhythmia

Animal studies suggest that the toxicity of iron is first manifest by changes in electrical conduction and arrhythmia, before the onset of contractile failure.[291] Iron-loaded myocytes have abnormal action potentials, with decreased overshoot and shortened action potential duration compared with non–iron-overloaded cells[212]; these features are likely to occur in a patchy distribution at a microscopic level and

would be recognized electrical substrates for arrhythmogenesis. In the TM patient, such inhomogeneity of action potential duration would be associated with increased variability of repolarization recorded by the ECG. Increased variability of the QT duration (QT or JT dispersion) has been noted in association with iron overload, and it has been suggested to be a marker for the risk of ventricular arrhythmia and sudden death, presumed to be caused by malignant ventricular arrhythmia.

### 14.4 Sudden Death

A recent study suggested a high incidence of sudden death among young men without clinical evidence of cardiac disease, with a 27% occurrence rate over a 26-year observation period.[216] Those who experienced sudden death had ECGs that demonstrated a higher degree of QT and JT dispersion than the cohort who survived. Other groups have not observed such a high incidence of sudden death,[11,200,290] although sporadic cases are not uncommon in TM. The implications of such increased risk would mandate consideration of the use of implantable cardioverter-defibrillator devices, a prospect not yet considered for the majority of the TM population. There is a need to reassess the thalassemia population for the incidence of electrocardiographic abnormalities that might increase the propensity to malignant ventricular arrhythmia. Careful analysis of the ECG for QT and JT dispersion plus the consideration of "blind" Holter ECG monitoring may be required for subgroups deemed to be at particular risk.

### 14.5 Treatment of Arrhythmias With Hemodynamic Compromise

Once the diagnosis of ventricular arrhythmia has been made, treatment is urgent and consists of intense, uninterrupted chelation therapy. The evidence, mostly anecdotal, supports the use of deferoxamine by intravenous infusion in a continuous regimen at doses of up to 75 $mg \cdot kg^{-1} \cdot d^{-1}$ or more.[47,48,292,293] In general, patients are supported at these times by concurrent treatment with antiarrhythmic medication, which in this context usually consists of an infusion of amiodarone by central vein.[294] Alternative medication, such as β-blockers and class I antiarrhythmic agents, are usually ruled out by hypotension in the decompensated TM patient. Adjunctive supportive treatment would include normalization of electrolyte deficiencies, particularly potassium (target >4.5 mmol/L), and the infusion of magnesium,[295,296] plus careful management of associated endocrine abnormalities, such as diabetes mellitus, hypoparathyroidism, and thyroid disorders. Blood glucose should be maintained within appropriate ranges (4.0–6.0 mmol/L) by flexible, sliding-scale insulin infusions. In hemodynamically compromised patients, direct current defibrillation may be required.

For acute AF complicated by hemodynamic compromise, for overt HF, or in the context of known severe myocardial iron overload (pragmatic definition of T2* <10 ms), the immediate approach should be the same as for ventricular arrhythmia. In both instances, there should be attention given to anticoagulation. There is at least a theoretical potential for systemic embolization for these patients because of the combined features of the arrhythmia, possibly enlarged atrial size, and procoagulant features of the hematologic condition, exacerbated in many by asplenia.[297–299]

### 14.6 Treatment of Arrhythmias in Ambulatory Patients

In many of the aging population of thalassemia patients, even in those with current excellent iron status and good ventricular function, paroxysmal supraventricular tachycardia and AF in particular are frequently encountered in the clinic. The precise incidence and associated features of this growing population are not yet clear. The management of AF for this group should parallel that advocated for the general population, in whom AF is seen increasingly more often in the aging population, albeit at considerably older ages than for the TM group. Strategies for managing paroxysmal AF, persistent AF, and established, permanent AF revolve around the choices of rhythm control versus acceptance of the arrhythmia, with attention directed to rate control. Special considerations apply to the TM patient. The general population's attributable risk of systemic embolization (mostly manifest by stroke) cannot be assumed to apply. It is possible that the risk of stroke in this significantly younger group would be increased by virtue of the documented prothrombotic tendencies. Permanent anticoagulation would need to be considered at an early stage for all but the mildly affected group, who experience infrequent, short-lasting bouts of AF. For those patients intolerant of antiarrhythmic drugs and those whose AF is poorly controlled despite the use of such medication, consideration should be given to the newer techniques used to control arrhythmia. Ablation techniques have evolved into a mainstay of treatment for AF patients who fall into the above categories. Currently, success rates for AF are quoted as being between 70% and 80% for the eradication of the arrhythmia, albeit with a 10% to 15% likelihood of requiring >1 ablation procedures.[300,301] The pathophysiology of supraventricular tachycardia and AF in the TM population may be different, so that equivalent success rates seen in the general population of AF patients should not be assumed to apply to this special group. On the positive side, TM patients are likely to be younger, but to counterbalance this, the atria may be much more difficult to treat by virtue of the widespread but patchy distribution of fibrosis and residual iron deposits. Patients with TM must not be denied the possibility of ablation treatment, but caution needs to be expressed with regard to longer-term outcome until more prospective data become available, most likely through registries rather than formal trials.

Although heart block was documented in early series of iron-overloaded patients,[302] this complication has all but disappeared with better treatment. However, sporadic cases do occur and will require the use of pacemakers. Historically, this would have meant the loss of the ability to use CMR in these individuals; however, manufacturers have now successfully produced pacemakers and leads that are compatible for use in MR scanners.[303] The units carry a specific x-ray opaque identification marker to allow confirmation that an MR-safe pacemaker is in place before any scan, should the patient's details not be known to the imaging unit.

### 14.7 Liver Disease

Liver disease is frequent in TM because of transfusion-transmitted hepatitis and iron overload. Chronic hepatitis C infection is the most common form of hepatitis infection worldwide, whereas infection with hepatitis B virus is more prevalent in Asia.[304] In many countries, the incidence of both infections in thalassemia fell significantly in the 1990s with the screening of blood donors and the hepatitis B virus vaccine. Today, the residual risk of transfusion-transmitted infection is <2 per 1 million,[305] whereas the prevalence of chronic hepatitis C is high in patients born before 1990. Both viral hepatitis and iron overload are independently associated with liver fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma. When both factors are present, as in TM, the effect is synergistic, and in the individual patient, it may be impossible to distinguish the role of each. The prevalence of cirrhosis in adult TM patients ranges from 10% to 20%.[306] Cirrhosis predisposes to long-term end-stage liver failure and is the main risk factor for hepatocellular carcinoma. Once rare, hepatocellular carcinoma now has a rising prevalence in TM.[307–310]

### 14.8 Renal Disease

Awareness of underlying renal dysfunction is critical because it is a surrogate and independent marker for an increased risk of stroke, HF, and myocardial infarction.[311] With increasing patient survival, renal disease has become more prevalent in patients with TM. Various abnormalities of renal function, including both glomerular and tubular dysfunction, have been reported,[312–314] but there are no systemic longitudinal studies. A recent cross-sectional study in TM patients has shown an abnormally high creatinine clearance in 20.8%, low creatinine clearance in 7.8%, hypercalciuria in 28.7%, and albuminuria in up to 59% of patients.[315] Mechanisms of kidney dysfunction are numerous and only partially clarified, but chronic anemia, hypoxia, iron, and iron chelators are potentially toxic to renal parenchyme.[316] Acute kidney injury has also been reported, and the probable mechanism in many cases is prerenal from sepsis or complications of HF (cardiorenal syndrome) and liver failure that affects renal perfusion. Labile iron may also lead to acute kidney injury.[317,318] Several renal side effects have been reported in association with the use of deferoxamine and deferasirox. Deferoxamine causes acute renal dysfunction at high doses or at normal doses in high-risk patients (those with diabetes mellitus, hypertension, or proteinuria; elderly patients; and those with underlying renal dysfunction), especially when given intravenously.[319–321] Deferasirox has been associated with several renal side effects, including nonprogressive increases in serum creatinine and cases of reversible mild or even life-threatening Fanconi syndrome.[139,322–327]

## 15. Future Directions

There are ongoing clinical trials that are relevant to treatment of cardiac iron overload by deferasirox. One that is relevant is the Novartis 2214 trial, with open-label treatment in TM patients with combined deferoxamine with deferasirox. In addition, clinical trials of new chelators are ongoing. There are many unanswered questions in the management and treatment of cardiac disease in TM patients. The most obvious general gap relates to the relative paucity of high-quality studies of large sample sizes to determine treatment preferences. However, there is also a need to better understand trends (as opposed to absolute values) in iron biomarkers as prognostic indicators. The clinical importance of endothelial dysfunction in iron overload needs clarifying. The possible clinical value of complex, more fragile measurements of iron components by CMR, other than hemosiderin (such as ferritin), needs evaluation.[328] The application of noninvasive iron measurement technology needs to be evaluated in other iron-overload conditions after a report of its use in hereditary hemochromatosis.[329] Finally, a randomized controlled trial of long-term amlodipine treatment, which is a new strategy to prevent cardiac iron loading, is under way.[61,330]

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# Correction

In the article by Pennell et al, "Cardiovascular Function and Treatment in β-Thalassemia Major: A Consensus Statement From the American Heart Association," which published online June 17, 2013, and appeared with the July 16, 2013, issue of the journal (*Circulation*. 2013;128:281–308), a correction was needed.

On page 294, section 10.2.4, first paragraph, the second sentence read, "There is evidence of a synergistic shuttle effect between deferiprone and deferasirox in improving iron clearance." It has been changed to read, "There is evidence of a synergistic shuttle effect between deferiprone and deferoxamine in improving iron clearance." The authors regret the error.

This correction has been made to the current online version of the article, which is available at http://circ.ahajournals.org/content/128/3/281.

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