

# AHA Consensus Statement

## Cardiovascular Function and Treatment in $\beta$ -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  $\beta$ -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

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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  $\beta$ -thalassemia major (TM) in cohort studies.<sup>1-4</sup> Significant advances in the identification and risk stratification of patients with myocardial siderosis have occurred since 2001 with magnetic resonance (MR) technology,<sup>5-7</sup> 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.<sup>8-10</sup> There is evidence that this approach has contributed to the significant reduction in cardiac mortality in TM.<sup>3,11-14</sup> 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 cardiologic 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<sup>15-20</sup> 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 $\beta$ -Thalassemia Major

TM is a genetic condition with severe reduction or absent production of the  $\beta$ -globin chain constituent of hemoglobin (Hb) A. This results in ineffective erythropoiesis caused by an excess of  $\alpha$ -globin chains and profound anemia that is life-threatening from  $\approx 1$  to 2 years of age. Blood transfusions are required lifelong; however, the iron load of  $\approx 200$  mg per unit combined with mildly increased gastrointestinal iron uptake related to hepcidin suppression<sup>21</sup> 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.<sup>22</sup> TM varies greatly in frequency around the world, being most prevalent in

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.<sup>23,24</sup> 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- $\beta$ -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.<sup>25</sup> 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

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<sup>26</sup> suggest that maintaining a pre-transfusion 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.<sup>27</sup> 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  $\approx 70\%$  of cases.<sup>1,2,28,29</sup>

## 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.<sup>30</sup> 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.<sup>2</sup> Improvements in survival with deferoxamine treatment by later birth cohort have been confirmed in other countries.<sup>3,31,32</sup>

## 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).

## 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.<sup>28</sup> In a US survey in 2004, the number of TM patients of all ages receiving cardiac medication was found to be 10% (35/341).<sup>22</sup> 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.<sup>42</sup> In a worldwide survey conducted in 2012, the incidence of HF at first T2\* scan was 3.1% (107/3445).<sup>41</sup> 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%).<sup>38</sup> 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<sup>43</sup> 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.<sup>27,44</sup> 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<sup>28,31,45</sup>; however, 5-year survival for patients presenting in HF (ages 24 $\pm$ 5 years) was only 48%.<sup>46</sup> 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.<sup>47-49</sup> The clearance of cardiac iron substantially lagged improvements in systolic function,<sup>47</sup> which explains the high risk of relapse observed with premature termination of intensive chelation therapy.<sup>48,49</sup> 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.<sup>50</sup> 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.<sup>11,51</sup> 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

**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 <sup>5</sup>	109	20	43	37
Hong Kong <sup>33</sup>	180	26	24	50
Turkey <sup>34</sup>	28	46	39	14
Australia <sup>35</sup>	30	37	27	37
Oman <sup>36</sup>	81	24	22	54
United States <sup>37</sup>	141	13	21	66
Italy <sup>38</sup>	167	13 ( $<8$ ms)	52 (8–20 ms)	35
Italy <sup>39</sup>	220		30% $<20$ ms	66
Greece <sup>40</sup>	159		68% $<20$ ms	32
Worldwide	3445	20	22	58

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.<sup>52</sup> In children with hemoglobinopathy who received transfusion and chelation, the cardiac T2\* was <20 ms only after 10 years of age.<sup>53,54</sup> However, occasional younger onset of cardiac iron, as young as 7 years, has been recorded in TM, especially when access to chelation is limited.<sup>55</sup>

### 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,<sup>56,57</sup> as well as the T-type calcium channels,<sup>58</sup> although another pathway may be involved for ferric (Fe)<sup>3+</sup> ions.<sup>59</sup> Non-transferrin-bound iron uptake has been shown to be rapid in isolated cardiomyocytes.<sup>60</sup> Nifedipine was shown to hinder iron uptake into cardiac cells, and this therapeutic possibility is being explored in a pilot study in humans.<sup>61</sup> Anecdotal evidence from individual cases<sup>62</sup> and family studies of discrepant cardiac iron loading, as well as evidence from a worldwide survey of cardiac T2\*,<sup>41</sup> 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.<sup>63,64</sup> GSTM1 has also been implicated in liver iron loading.<sup>65</sup>

### 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,<sup>66,67</sup> including (1) damage to membranes by lipid peroxidation; (2) damage to mitochondria and the respiratory enzyme chain<sup>68,69</sup>; (3) interference with electrical function, including ryanodine release channel interference<sup>70,71</sup>; (4) promotion of cardiac fibrosis, which was prominently reported in early autopsy studies,<sup>72</sup> although it is rare with greater access to chelation<sup>73</sup>; and (5) altered gene expression.<sup>74</sup>

### 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 sur-

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.<sup>70,75,76</sup> 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.<sup>27,72</sup> 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,<sup>27,72</sup> but this is now rare in more modern cohorts of patients dying of HF.<sup>73</sup> More minor patches of myocardial fibrosis have been identified in vivo with late gadolinium-enhancement CMR in Italian patients with TM,<sup>77</sup> but this has not been reproduced in the United Kingdom.<sup>78</sup> This difference probably results from higher levels of myocarditis resulting from hepatitis C infection in Italy.<sup>79</sup> 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.<sup>7</sup> 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.<sup>39</sup> 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),<sup>76,80</sup> 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



endothelial function has been documented with deferiprone<sup>9</sup> and deferasirox.<sup>83</sup> (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.<sup>85,86</sup> Impaired diastolic function shown by CMR also had low sensitivity for identification of cardiac iron loading.<sup>87</sup>

### 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.<sup>88</sup>

## 3. Diagnostic Strategies for Cardiac Involvement in TM

### 3.1 Basic Tests

New-onset electrocardiographic abnormalities are usually evident in TM patients with HF<sup>89</sup> and may include supraventricular arrhythmias, electrocardiographic findings that suggest right-sided heart involvement (S<sub>1</sub>Q<sub>3</sub> pattern and right-axis deviation), new-onset T-wave inversion beyond lead V<sub>1</sub>, 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.<sup>90</sup> Electrocardiographic changes most specifically associated with cardiac iron include repolarization abnormalities and relative bradycardia.<sup>91</sup> 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.<sup>92</sup> However, one study showed poor correlation of BNP against low myocardial T2\*, which predicts future HF.<sup>50</sup> 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,<sup>93</sup> 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.<sup>94</sup> Echocardiography

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,<sup>95</sup> 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.<sup>96</sup> 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.<sup>97</sup>

#### 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.<sup>98</sup> 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

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