Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major

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Background—The goal of this study was to determine the predictive value of cardiac T2* magnetic resonance for heart failure and arrhythmia in thalassemia major.

Methods and Results—We analyzed cardiac and liver T2* magnetic resonance and serum ferritin in 652 thalassemia major patients from 21 UK centers with 1442 magnetic resonance scans. The relative risk for heart failure with cardiac T2* values <10 ms (compared with >10 ms) was 160 (95% confidence interval, 39 to 653). Heart failure occurred in 47% of patients within 1 year of a cardiac T2* <6 ms with a relative risk of 270 (95% confidence interval, 64 to 1129). The area under the receiver-operating characteristic curve for predicting heart failure was significantly greater for cardiac T2* (0.948) than for liver T2* (0.589; P<0.001) or serum ferritin (0.629; P<0.001). Cardiac T2* was <10 ms in 98% of scans in patients who developed heart failure. The relative risk for arrhythmia with cardiac T2* values <20 ms (compared with >20 ms) was 4.6 (95% confidence interval, 2.66 to 7.95). Arrhythmia occurred in 14% of patients within 1 year of a cardiac T2* of <6 ms. The area under the receiver-operating characteristic curve for predicting arrhythmia was significantly greater for cardiac T2* (0.747) than for liver T2* (0.514; P<0.001) or serum ferritin (0.518; P<0.001). The cardiac T2* was <20 ms in 83% of scans in patients who developed arrhythmia.

Conclusions—Cardiac T2* magnetic resonance identifies patients at high risk of heart failure and arrhythmia from myocardial siderosis in thalassemia major and is superior to serum ferritin and liver iron. Using cardiac T2* for the early identification and treatment of patients at risk is a logical means of reducing the high burden of cardiac mortality in myocardial siderosis.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00520559.

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Key Words: magnetic resonance imaging ■ heart ■ iron overload ■ siderosis ■ thalassemia

Thalassemia is the most common single-gene disorder worldwide, with ≈94 million heterozygotes for β-thalassemia and 60,000 homozygotes born each year.1 Although survival is improving in cohorts of patients in whom deferoxamine was introduced at a younger age,2 myocardial siderosis resulting in heart failure remains the major cause of death (50% to 70%) in thalassemia major patients.2,3 This occurs at a strikingly young age, with between 15% to 50% of patients dying by 35 years of age.2,3

Severe myocardial siderosis causes a toxic dilated cardiomyopathy that can be reversed if aggressive chelation is begun early,4 but clinical diagnosis is often delayed because of the typically late onset of symptoms. Catastrophic deterioration in cardiac function resulting in death may occur rapidly once clinically obvious heart failure is present. Methods for predicting heart failure have been developed that are based on established measures of iron loading, most importantly, time-averaged serum ferritin >2500 μg/L2,5 and liver iron concentration >15 mg/kg dry weight.6 However, the persistently high mortality rate from heart failure indicates that high-risk patients are not being identified in time for effective intervention. Measurement of ventricular function such as alteration over time in ejection fraction has also been proposed in thalassemia, but it identifies patients at a relatively late stage,7 and dysfunction may be masked because of supranormal left ventricular function in thalassemia patients in the absence of myocardial iron loading.8 Most
recently, direct assessment of myocardial iron with magnetic resonance (MR) relaxation has been used because iron deposits shorten T1, T2, and T2*. Of these, the measurement of T2* has become the most widely used in the heart because it is easily combined with cardiac gating, is fast and robust, and is the most sensitive to iron deposition.9 The cardiac T2* technique is transferrable with good interscanner agreement10 and has been implemented in at least 50 centers worldwide on 1.5T scanners from the 3 largest scanner manufacturers. Direct calibration of the cardiac T2* value to the myocardial iron concentration has been reported in animals11 and humans.12 However, although this work is important for complete scientific understanding, the relationship between cardiac T2* and prediction of cardiac events can be made independently of these data and, in terms of patient care, is the more important. Here, we report the value of cardiac T2* MR for predicting cardiac events from a large prospective database of thalassemia major patients compared with the established predictors of outcome, liver iron and serum ferritin.

Methods

Patient Population
A total of 652 patients (1442 scans) with β-thalassemia major were included in this study. Their clinical care was undertaken at 21 hematology centers throughout the United Kingdom, and they were scanned at the Cardiovascular MR Unit of Royal Brompton Hospital, London, UK, between 1999 and 2006. This is a substantial majority of the UK thalassemia major patients (~800 patients) and therefore represents a multicenter national sample. Patients were referred for clinical evaluation according to local practice at each caring center and were unscreened. All patients were included in the database, but 17 were excluded from the predictive analysis reported in this study because of clinical heart failure (n=11) or arrhythmia (n=6) at the time of their first MR scan. Of these patients, 319 were male and 333 female, with a mean age at time of their first scan of 27.1±9.6 years. Detailed patient demographics are shown in Table 1. The prospective database of all patients was maintained from local patient records, and follow-up was complete (100%) for a total of 1285 patient-years. Detailed patient demographics are shown in Table 1. The prospective database of all patients was maintained from local patient records, and follow-up was complete (100%) for a total of 1285 patient-years. At the time of the first scan, 22 patients were receiving no chelation, 66%9,13 and the caring clinician made the clinical diagnosis of heart failure. A diagnosis of arrhythmia was made only if the patient complained of palpitations and arrhythmia was objectively demonstrated by ECG with 24-hour monitoring or a standard 12-lead recording. Arrhythmias were categorized according to American Heart Association/American College of Cardiology guidelines14 and included atrial fibrillation, defined as a cardiac arrhythmia arising from the atrium with an atrial rate >300 bpm and an irregular ventricular response in the presence of conduction (>10 minutes of sustained arrhythmia); supraventricular tachycardia, defined as a tachycardia that emanates from or requires participation of supraventricular tissue other than atrial fibrillation/flutter (>10 minutes of sustained arrhythmia); ventricular tachycardia, defined as ≥3 con-
secutive complexes in duration emanating from the ventricles at a rate of >100 per minute; and ventricular fibrillation, defined as rapid, usually >300 per minute, grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology, and amplitude. Cardiac T2* values >20 ms were considered normal.9 A liver T2* value of <0.96 ms is calibrated to a dry weight equivalent of >15 mg/g dry weight.8

**Magnetic Resonance**

Patients were scanned with a 1.5T scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany) using previously reported techniques.15 In brief, cardiovascular MR was performed with a cardiac-gated, single-breath-hold, 8-echo sequence (2.6 to 16.7 ms, increasing in 2.02-ms increments) of a single midventricular short-axis slice. A single-breath-hold, 20-echo sequence (1.07 to 0.21 ms) of a transaxial slice of the liver was also acquired. Long-axis cines and a contiguous stack of short-axis cines were also acquired to assess left ventricular dimensions and function using standard techniques.16 Data analysis was performed using CMRtools and its plug-in ThalassemiaTools (Cardiovascular Imaging Solutions, London, UK) for the liver T2* (a large region of interest excluding vascular structures) and heart T2* (a large region of the interventricular septum excluding regions in proximity to the coronary veins), as well as left ventricular ejection fraction using semiautomated planimetry of endocardial borders.16 All scans were reported at the time of acquisition by multiple operators, and a clinical report was generated for the referring physician.

**Statistics**

All statistical analyses were performed by the Medical Statistics Department at our institution (M.R.). Because many patients in this study had multiple scans, we used a mixed-model Poisson regression with nested values (n=1442 scans) to produce univariate and multivariate analyses of cardiac T2*, liver T2*, and serum ferritin for cardiac outcomes and presented as relative risk (RR; with 95% confidence intervals [CIs]). Nesting incorporates all data from all scans in the predictive model for cardiac outcomes, and all repeated scans from any patient are modeled as nonindependent. Therefore, the unit of analysis is each individual scan with the 1 year of follow-up that follows it. Scans from the same patient are then nested within that patient. Each scan is assessed with regard to the outcomes following that individual scan, with the patient entered as a random effect to account for within-patient correlation. For purposes of comparison only, the RRs were also calculated per scan (nonnested analysis in which all scans are considered to be independent; n=1442 scans) and for patient first scans only (nonnested analysis considering each patient’s first scan only, with any repeated scans ignored; n=652 scans). These data are given in tables in the online-only Data Supplement because they show results similar to the main analysis. Patients were censored from further analysis after a first outcome. All patient demographics are presented according to the first scan for each patient. The distributions of liver T2*, cardiac T2*, ferritin, and ejection fraction were not significantly deviated from normal by Kolmogorov-Smirnov testing and therefore are presented using mean and SD and per scan. Receiver-operating characteristic graphs were produced for cardiac T2*, liver T2*, and serum ferritin to compare predictive accuracy for cardiac outcomes across the full range of measured values using the area under the curve. Kaplan–Meier curves for time to heart failure and arrhythmia were generated. Data with a normal distribution are presented as mean±SD; those with nonnormal distributions are presented as median and interquartile range. Statistical significance was set at P<0.05, and all P values are 2 tailed. All analyses were performed with STATA 10.2 (StataCorp, College Station, Tex).

**Results**

**Summary of Primary End-Point Events**

At 1 year of follow-up, there were 80 episodes of heart failure and 98 episodes of arrhythmia. There were 4 deaths: 3 patients died of sepsis after bone marrow transplantation, and 1 patient died after an episode of ventricular tachycardia. There were 32 instances in which a patient was recorded as having both a heart failure event and an arrhythmia event within 1 year of a scan.

**Heart Failure**

For the 80 heart failure episodes, 60 presented in New York Heart Association class II, 16 were class III, and 4 were class IV. The mean ejection fraction of these 80 patients at the time of diagnosis of heart failure was 43.1±7.2%. The median time of onset from the time of the T2* MR scan to an episode of heart failure was 158 days (quartiles 1 and 3, 52 and 342 days). In these heart failure patients, the preceding cardiac T2* was 6.7±1.8 ms, liver T2* was 3.9±3.7 ms, and ferritin was 2713±1686 µg/L. The distribution of cardiac T2* values in those patients who went on to develop heart failure compared with the T2* values of those patients who remained free of heart failure is shown in Figure 1A. The RRs associated with cardiac T2*, liver T2*, and ferritin are given in Table 2. The cardiac T2* was <10 ms in 98% of patients who developed heart failure. The 1-year incidence of heart failure in patients with the lowest cardiac T2* of <6 ms was 47%. Compared with cardiac T2* values >10 ms, there was a significantly increased risk of heart failure associated with cardiac T2* values <10 ms, with an RR of 160 (95% CI, 39 and 653) in the nested analysis. The RR for cardiac T2* <6 ms was 270 (95% CI, 64 and 1129). Serum ferritin using the conventional threshold (>2500 µg/L) was a significant but weaker predictor of heart failure, with an RR of 0.56 (95% CI, 0.34 and 0.91) versus ferritin <2500 µg/L (Table 2). Liver T2* <0.96 ms (equivalent to the conventional threshold of >15 mg/g dry weight iron) was not a significant predictor of heart failure, with an RR of 0.81 (95% CI, 0.23 and 2.80) versus liver T2* >0.96 ms. Receiver-operating characteristic curves for the prediction of heart failure by cardiac T2*, liver T2*, and serum ferritin are shown in Figure 1B. The areas under the curve for serum ferritin (0.629) and liver T2* (0.589) were similar (P=0.21), but the area under the curve for cardiac T2* (0.948) was substantially and significantly greater (P<0.001 versus liver T2*; P<0.001 versus serum ferritin). The RRs for the first scan only (nonnested) and per scan (nonnested) groups gave similar conclusions (Table I of the online-only Data Supplement). The Kaplan–Meier curves for the occurrence of heart failure stratified into 4 levels of cardiac T2* shown in Figure 1C illustrate a significant increase in risk with increasing cardiac iron loading (P<0.001). Overall, the T2* threshold of 10 ms predicted heart failure with a sensitivity of 97.5% (95% CI, 91.3 to 99.7) and specificity of 85.3% (95% CI, 83.3 to 87.2). The data were also analyzed for prediction of asymptomatic left ventricular dysfunction at the time of the scan and showed significant incremental RR for each level of cardiac T2* <10 ms (T2* 8 to 10 ms, 2.97; T2* 6 to 8 ms, 3.48; T2* <6 ms, 4.51; all P<0.001).

**Arrhythmia**

For the 98 patients who developed arrhythmias within 1 year of MR scanning, 78 patients had atrial fibrillation, 14 patients had supraventricular tachycardia, 5 patients had ventricular
tachycardia, and 1 patient had ventricular fibrillation. In these patients, at the time of first MR scan, the mean cardiac T2* was 13.5 ± 9 ms, mean liver T2* was 6.0 ± 6.4 ms, mean serum ferritin was 2140 ± 1540 g/L, and mean ejection fraction was 60.7 ± 9.3%. The median time to developing arrhythmia was 133 days. The distribution of cardiac T2* values in the patients who went on to develop arrhythmia compared with those who remained free of arrhythmia is shown in Figure 2A. The RRs associated with cardiac T2*, liver T2*, and ferritin are given in Table 3. A cardiac T2* ≤ 20 ms was present in 83% of patients who developed arrhythmia. The incidence of arrhythmia at 1 year in patients with the lowest cardiac T2* of ≤ 10 ms was 14%. The mean cardiac T2* in the arrhythmia patients was as follows: atrial fibrillation, 13.6 ± 9.9 ms; supraventricular tachycardia, 11.9 ± 7.1 ms; ventricular tachycardia, 16.5 ± 9.3 ms; and ventricular fibrillation, 9.0 ms. There was no significant difference between the cardiac T2* values for atrial and ventricular arrhythmias (P = 0.28). Compared with cardiac T2* values > 20 ms, there was a significantly increased risk of arrhythmia associated with cardiac T2* values < 20 ms, with an RR of 4.60 (95% CI, 2.66 to 7.95). The RR for a cardiac T2* < 6 ms was 8.79 (95% CI, 4.03 to 19.2). There was no significant predictive value using the conventional thresholds of ferritin (≥ 2500 g/L), with an RR of 0.90 (95% CI, 0.55 to 1.45) versus ferritin < 2500 g/L, or liver T2* (≥ 6.3 ms), with an RR of 0.81 (95% CI, 0.24 to 2.74) versus liver T2* < 6.3 ms.

**Table 2. Heart Failure**

| No. in Group | No. With Heart Failure | RR 95% CI | P   |
|--------------|-----------------------|-----------|-----|
| Cardiac T2*, ms |
| < 6          | 72                    | 270       | 64–1129 | <0.001 |
| 6–<8         | 98                    | 171       | 41–718  | <0.001 |
| 8–<10        | 108                   | 81        | 19–357  | <0.001 |
| ≥10          | 1164                  | 1         | Reference |
| Liver T2*, ms |
| <0.96        | 63                    | 3         | 1.25     | 0.33–4.76 | 0.74 |
| 0.96–<1.4    | 136                   | 14        | 2.59     | 1.16–5.79 | 0.021 |
| 1.4–<2.7     | 382                   | 26        | 1.68     | 0.85–3.31 | 0.13 |
| 2.7–<6.3     | 484                   | 22        | 1.22     | 0.61–2.45 | 0.57 |
| ≥6.3         | 377                   | 15        | 1        | Reference |
| Ferritin, μg/L |
| ≥2500        | 450                   | 35        | 0.56     | 0.34–0.91 | 0.02 |
| <2500        | 992                   | 45        | 1        | Reference |

Heart failure RRs for increments in cardiac T2* from < 6 to 10 ms vs reference value of T2* > 10 ms. Heart failure RRs for increments in liver T2* from < 0.96 ms vs reference value of > 6.3 ms. Heart failure RRs for serum ferritin > 2500 and < 2500 μg/L.

Figure 1. A, Frequency distribution of cardiac T2* values in the 80 patients who developed heart failure within 1 year of scan (bottom) vs the other 572 patients (top). Note the segregation of cardiac T2* in the patients who went on to develop heart failure into the lowest values; 98% of patients who developed heart failure had a cardiac T2* of < 10 ms. The solid vertical red line is the median; dashed red lines are the upper and lower quartiles. B, Receiver-operating characteristic curve for the prediction of heart failure within 1 year of MR scanning. The diagonal line shows the performance of a nondiagnostic test. Although the points marked on each line indicate a threshold of 10 ms for cardiac T2*, 0.96 ms for liver T2* (equivalent to 15 mg/kg dry weight), and 2500 μg/L for serum ferritin. C, Kaplan–Meier curves showing the occurrence of heart failure over 1 year according to baseline cardiac T2* values of > 10, 8 to 10, 6 to < 8, and < 6 ms (P < 0.001).
Receiver-operating characteristic curves for the prediction of arrhythmia by cardiac T2*, liver T2*, and serum ferritin are shown in Figure 2B. The areas under the curve for serum ferritin (0.518) and liver T2* (0.514) were similar (P>0.99), but the area under the curve for cardiac T2* (0.747) was substantially and significantly greater (P<0.001 versus liver T2*; P<0.001 versus serum ferritin). The RRs for the first scan only (nonnested) and per scan (nonnested) groups give similar conclusions and are shown in Table II of the online-only Data Supplement. The Kaplan–Meier curves for the occurrence of arrhythmia stratified into 3 levels of cardiac T2* shown in Figure 2C illustrate a significant increase in risk with increasing cardiac iron loading (P<0.001). Overall, the T2* threshold of 20 ms predicted arrhythmia with a sensitivity of 82.7% (95% CI, 73.7 to 89.6) and specificity of 53.5% (95% CI, 50.8 to 56.2).

### Table 3. Arrhythmia

| T2* Threshold (ms) | No. in Group | No. With Arrhythmia | RR (95% CI) | P  |
|-------------------|--------------|---------------------|------------|----|
| <6                | 72           | 14                  | 8.79 (4.03–19.2) | <0.001 |
| 6–10              | 98           | 20                  | 7.5 (3.71–15.2) | <0.001 |
| 8–15              | 108          | 16                  | 6.82 (3.28–14.2) | <0.001 |
| 10–15             | 263          | 21                  | 3.23 (1.65–6.3)  | 0.001  |
| 15–20             | 165          | 10                  | 2.21 (0.97–5.02) | 0.058  |
| ≥20               | 736          | 17                  | 1           | Reference |

Liver T2*, ms

| T2* Threshold (ms) | No. in Group | No. With Arrhythmia | RR (95% CI) | P  |
|-------------------|--------------|---------------------|------------|----|
| <0.96             | 63           | 3                   | 0.82 (0.23–2.96) | 0.77 |
| 0.96–1.4          | 136          | 10                  | 1.21 (0.54–2.69) | 0.64 |
| 1.4–2.7           | 382          | 28                  | 1.13 (0.64–2)   | 0.68 |
| 2.7–6.3           | 484          | 27                  | 0.83 (0.48–1.46) | 0.52 |
| ≥6.3              | 377          | 30                  | 1           | Reference |

Ferritin, g/L

| Ferritin Threshold (μg/L) | No. in Group | No. With Arrhythmia | RR (95% CI) | P  |
|--------------------------|--------------|---------------------|------------|----|
| ≥2500                    | 450          | 30                  | 0.9 (0.55–1.45) | 0.65 |
| <2500                    | 992          | 68                  | 1           | Reference |

**Effect of MR Result on Risk**

The reporting of the cardiac T2* value may have caused alterations in treatment that could have affected the outcome events. Therefore, we analyzed the RRs for an increase or decrease in each chelator (relative to not changing dose) and T2* >0.96 ms. Receiver-operating characteristic curves for the prediction of arrhythmia by cardiac T2*, liver T2*, and serum ferritin are shown in Figure 2B. The areas under the curve for serum ferritin (0.518) and liver T2* (0.514) were similar (P=0.99), but the area under the curve for cardiac T2* (0.747) was substantially and significantly greater (P<0.001 versus liver T2*; P<0.001 versus serum ferritin). The RRs for the first scan only (nonnested) and per scan (nonnested) groups give similar conclusions and are shown in Table II of the online-only Data Supplement. The Kaplan–Meier curves for the occurrence of arrhythmia stratified into 3 levels of cardiac T2* shown in Figure 2C illustrate a significant increase in risk with increasing cardiac iron loading (P<0.001). Overall, the T2* threshold of 20 ms predicted arrhythmia with a sensitivity of 82.7% (95% CI, 73.7 to 89.6) and specificity of 53.5% (95% CI, 50.8 to 56.2).

**Figure 2 (Continued).** Receiver-operating characteristic curve for prediction of arrhythmia within 1 year of MR scanning. The diagonal line shows the performance of a nondiagnostic test. The liver T2* and serum ferritin are not predictive. The cardiac T2* is significantly superior to both these conventional measures (P<0.001). The points marked on each line indicate a threshold of 10 ms for cardiac T2*, 0.96 ms for liver T2* (equivalent to 15 mg/kg dry weight), and 2500 μg/L for serum ferritin. C, Kaplan–Meier curves showing the occurrence of arrhythmia over 1 year according to cardiac T2* values of >20, 10 to 20, and <10 ms (P<0.001).
included these in an adjusted analysis examining heart T2* for the prediction of heart failure or arrhythmia. There was no statistically significant effect of changing dose, except that an increased dose of deferoxamine was associated with a small increased RR of arrhythmia and the adjusted RR relating heart T2* to outcomes remained very similar to the unadjusted ones. Therefore, there is little statistical evidence from the database that short-term changes in chelation dose after scans altered the ability of T2* to predict outcomes over the period of collection of data.

**Effect of Prior History of Heart Failure or Arrhythmia on Outcomes**

All patients reported in this study did not have heart failure or arrhythmia at the time of first MR scan, but 9 patients had a prior (and resolved) history of heart failure, and 1 patient had a prior (and resolved) history of arrhythmia. Therefore, we reanalyzed the predictive power of cardiac T2* using prior history of heart failure or arrhythmia as covariates and including in the analysis those patients who developed end points within 1 year of follow-up who had additional MR scans. The RR of prior heart failure predicting future heart failure was 1.93 (95% CI, 1.19 to 3.13), and the RR of prior heart failure or arrhythmia predicting future heart failure was 1.60 (95% CI, 0.92 to 2.81) and 1.59 (95% CI, 0.84 to 3.02), respectively. The RR of prior arrhythmia predicting future arrhythmia was 2.67 (95% CI, 1.41 to 5.09), and the RR of prior arrhythmia or heart failure predicting future arrhythmia was 1.84 (95% CI, 0.86 to 3.94) and 2.08 (95% CI, 1.07 to 4.02), respectively. There was no significant interaction between heart T2* and prior heart failure in analyses of heart failure and no significant interaction between heart T2* and prior arrhythmia in analyses of arrhythmia. Overall, therefore, these results show that there were significant associations between prior disease and new disease, but they were independent of the predictive ability of T2*, and T2* was still a much more powerful predictor.

**Regression Between Iron Parameters**

There were significant relationships between all 3 iron variables (cardiac T2* versus liver T2*: \( R^2 = 0.003, \ P = 0.040 \); cardiac T2* versus ferritin: \( R^2 = 0.003, \ P = 0.041 \); liver T2* versus ferritin: \( R^2 = 0.37, \ P < 0.001 \)). These results should be interpreted in the context of the large sample size \( n = 1442 \), which was highly powered to find significant results for regression analysis, and on data inspection, only the relationship between liver T2* and ferritin is meaningful.

**Effect of Age, Gender, and Baseline Medication on Heart Failure**

Neither age nor gender was significantly associated with either study outcome \( (P > 0.3 \) for all). There was no association between baseline treatment and heart failure events when assessed either as a single variable \( (P > 0.2 \) for all) or in conjunction with T2* \( (P > 0.4 \) for all).

**Discussion**

Failure to control serum ferritin and liver iron over sustained periods has been linked to increased risk of heart disease\(^2,5,6,7\) and other complications of iron overload.\(^7\) However, low values of liver iron or serum ferritin do not necessarily signify low risk of iron-induced cardiomyopathy.\(^9\) This may arise because iron chelation therapy can remove iron more rapidly from the liver than from the heart, which may normalize liver iron while myocardial iron remains high.\(^9,18,19\) Other mechanisms may be involved, including potential genetic variations in function of cardiac iron transport channels such as the L-type calcium channel and the divalent metal transporter 1.\(^1,20,21\) Therefore, there is often a need to identify those patients most at risk of cardiomyopathy even when serum ferritin and liver iron values are currently well controlled. Although sequential quantification of heart function identifies a patient group at increased risk of cardiac mortality,\(^7\) it would be preferable to identify high-risk patients early before cardiomyopathy develops and use targeted treatment.\(^22,23\) The estimation of heart iron by MR offers this possibility. We have used the MR relaxation parameter T2*, which is sensitive to the presence of storage iron microaggregates, which disturb the homogeneity of the magnetic microenvironment. Evidence has been accumulating that low values of cardiac T2*, which reflect high cardiac iron levels, are associated with heart failure. In a cross-sectional study of 28 patients presenting with heart failure, 89% of cases had a cardiac T2* <10 ms.\(^24\) Limited other data have supported this experience.\(^25\) Therefore, in the present study, we analyzed our prospective database on all thalassemia major patients living in the United Kingdom who had a cardiac T2* scan since 1999. The data unequivocally demonstrate that cardiac T2* is a powerful predictor of the subsequent development of heart failure. The RR was substantial at 270 for the highest-risk group with a cardiac T2* <6 ms compared with a cardiac T2* of >10 ms. Analysis of the incidence of heart failure following the finding of a cardiac T2* of <6 ms was impressive, with 47% of such patients developing this ominous complication within 12 months. The receiver-operating characteristic analysis showed that the predictive value of cardiac T2* for heart failure was significantly and substantially greater than for conventional iron measures for the prediction of cardiac complications (liver iron, serum ferritin).

The results for the prediction of arrhythmia by cardiac T2* are also significant but of lower magnitude than for the prediction of heart failure. In addition, the distribution of cardiac T2* in patients presenting with arrhythmia had a greater spread with higher cardiac T2* values. However, 83% of cases occurred in patients with cardiac T2* values <20 ms, indicating myocardial siderosis as the primary cause. The majority of the arrhythmias were atrial in origin and were not dependent on failing ventricular function because they were observed at higher (although still abnormal) T2* levels than those seen with heart failure. The atrial myocardium might be more sensitive to iron deposition than the ventricle in the causation of arrhythmias; this hypothesis is supported somewhat by historical data before the use of iron chelators, which suggested that iron deposition is greater in the ventricles than in the atria.\(^26\) Unfortunately, T2* measurements of the thin atrial myocardium are limited by partial volume effects and are unlikely to be robust; therefore, this issue is not easy to address with current noninvasive MR techniques. Thalasse-
mia patients are also susceptible to non–iron-dependent causation of atrial arrhythmia because of chronically raised cardiac output and atrial dilation.

Our study has some limitations. We have not formally validated our results in a different cohort. However, we did not attempt to build a multivariate model from a number of available factors but looked at a small number of prespecified iron measures and prospectively showed their relation to the outcomes of interest. However, it would still be of interest to reproduce these results in another cohort. We used the widely accepted normal cardiovascular MR threshold for the lower limit of normality of left ventricular ejection fraction of 56% to categorize ventricular dysfunction, although data from a single center, which have not been reproduced, suggest that slightly higher threshold values may pertain to thalassemia major patients in the absence of cardiac siderosis.27

Conclusions

This study shows that cardiac T2* is highly predictive over 1 year for the development of heart failure and arrhythmia and is significantly more predictive than contemporaneous measures of liver iron and serum ferritin. This indicates that the inclusion of cardiac T2* assessment, in concert with conventional long-term assessments of tissue iron loading, is mandatory for the comprehensive evaluation of iron loading. A widespread program using cardiac T2* in β-thalassemia major has considerable potential for reducing mortality from heart failure by the early identification and treatment of patients at risk. These data will also be of direct value in the management of different iron loading conditions such as hemochromatosis and other transfusion-dependent anemias.

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Patients with transfusion-dependent anemias such as thalassemia major die primarily of heart failure caused by myocardial siderosis. Significant recent advances in the prevention of cardiac mortality include the robust identification of the level of iron loading in the heart with T2* cardiovascular magnetic resonance and improved treatments to remove cardiac iron quickly while reducing the toxicity of iron-mediated reactive oxygen species. However, the drive to treat myocardial siderosis aggressively has not been guided by an understanding of the clinical outcomes in relation to the severity of myocardial siderosis. In this multicenter prognostic study of thalassemia major patients, we show that the risk of progression to heart failure is present dominantly with myocardial T2* <10 ms and that the risk climbs steeply with further reductions in T2* (increasing myocardial siderosis). Likewise, there is increased likelihood of progression to both atrial and ventricular arrhythmias with increasing myocardial siderosis but with a higher T2* threshold, indicating that other factors such as increased atrial sensitivity to iron and chronic atrial stretch from raised cardiac output may be involved. These data form a new bedrock for risk assessment in clinical practice for the need to treat myocardial siderosis and in particular show that cardiac T2* is a significantly better predictor of cardiac events than the established measures of liver iron and serum ferritin. T2* cardiovascular magnetic resonance has significant potential to lead to the eradication of heart failure–related death in transfusion-dependent anemias when it is available and effective cardiac chelation can be instituted and maintained.
Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major
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### SUPPLEMENTAL Tables

**Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major**
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#### Supplemental Table 1: Heart failure

| Cardiac T2* (ms) | No. in group | No. with heart failure | Per scan (non-nested) | No. in group | No. with heart failure | First scan only |
|------------------|--------------|-----------------------|-----------------------|--------------|-----------------------|-----------------|
|                  |              |                       | RR  95% CI  p         |              |                       | RR  95% CI  p   |
| <6               | 72           | 34                    | 275  66  1144  0.001  | 30           | 16                    | 4.44  1.74  11.4  0.002  |
| 6 to <8          | 98           | 29                    | 172  41  722  0.001   | 49           | 11                    | 1.87  0.69  5.06  0.22   |
| 8 to <10         | 108          | 15                    | 81   18  353  0.001   | 50           | 6                     | 1 Reference     |
| 10+              | 1164         | 2                     | 1 Reference          | 523          | 0                     | Not estimable due to zero events |

| Liver T2* (ms) | No. in group | No. with heart failure | Per scan (non-nested) | No. in group | No. with heart failure | First scan only |
|----------------|--------------|-----------------------|-----------------------|--------------|-----------------------|-----------------|
| <0.96          | 63           | 3                     | 1.20  0.35  4.13  0.78 | 31           | 1                     | 0.78  0.09  6.52  0.82  |
| 0.96 to <1.4   | 136          | 14                    | 2.59  1.25  5.36  0.011 | 78           | 8                     | 2.50  0.87  7.19  0.09   |
| 1.4 to <2.7    | 382          | 26                    | 1.71  0.91  3.23  0.098 | 188          | 11                    | 1.42  1.42  3.85  0.49   |
| 2.7 to <6.3    | 484          | 22                    | 1.14  0.59  2.20  0.69  | 209          | 7                     | 0.81  0.27  2.43  0.71   |
| 6.3+           | 377          | 15                    | 1 Reference          | 146          | 6                     | 1 Reference     |

| Ferritin µg/L  | No. in group | No. with heart failure | Per scan (non-nested) | No. in group | No. with heart failure | First scan only |
|----------------|--------------|-----------------------|-----------------------|--------------|-----------------------|-----------------|
| 2500+          | 450          | 35                    | 0.58  0.38  0.91  0.017 | 215          | 18                    | 0.41  0.21  0.81  0.011  |
| <2500          | 992          | 45                    | 1 Reference          | 437          | 15                    | 1 Reference     |
## Supplemental Table 2: Arrhythmia

| Cardiac T2* (ms) | No. in group | No. with arrhythmia | Per scan (non-nested) | No. in group | No. with arrhythmia | First scan only |
|------------------|--------------|---------------------|-----------------------|--------------|---------------------|-----------------|
|                  |              |                     | RR  | 95% CI  | p     | RR  | 95% CI  | p     |
| <6               | 72           | 14                  | 8.42 | 4.15   | 17.1  | <0.001 | 30           | 6             | 14.4 | 4.39 | 47.2  | <0.001 |
| 6 to <8          | 98           | 20                  | 8.84 | 4.63   | 16.9  | <0.001 | 49           | 9             | 13.2 | 4.43 | 39.5  | <0.001 |
| 8 to <10         | 108          | 16                  | 6.41 | 3.24   | 12.7  | <0.001 | 50           | 7             | 10.1 | 3.20 | 31.8  | <0.001 |
| 10 to <15        | 263          | 21                  | 3.46 | 1.82   | 6.55  | <0.001 | 106          | 8             | 5.43 | 1.78 | 16.6  | 0.003  |
| 15 to <20        | 165          | 10                  | 2.62 | 1.20   | 5.73  | 0.015  | 57           | 1             | 1.26 | 0.15 | 10.8  | 0.83   |
| 20+              | 736          | 17                  | 1    | Reference |      |       | 360          | 5             | 1    | Reference |

| Liver T2* (ms)  | No. in group | No. with arrhythmia | Per scan (non-nested) | No. in group | No. with arrhythmia | First scan only |
|-----------------|--------------|---------------------|-----------------------|--------------|---------------------|-----------------|
|                  |              |                     | RR  | 95% CI  | p     | RR  | 95% CI  | p     |
| <0.96           | 63           | 3                   | 0.60 | 0.18   | 1.96  | 0.40  | 31           | 2             | 1.35 | 0.28 | 6.48  | 0.71   |
| 0.96 to <1.4    | 136          | 10                  | 0.92 | 0.45   | 1.89  | 0.83  | 78           | 5             | 1.34 | 0.42 | 4.21  | 0.62   |
| 1.4 to <2.7     | 382          | 28                  | 0.92 | 0.55   | 1.54  | 0.76  | 188          | 13            | 1.44 | 0.58 | 3.61  | 0.44   |
| 2.7 to <6.3     | 484          | 27                  | 0.70 | 0.42   | 1.18  | 0.18  | 209          | 9             | 0.90 | 0.33 | 2.41  | 0.83   |
| 6.3+            | 377          | 30                  | 1    | Reference |      |       | 146          | 7             | 1    | Reference |

| Ferritin μg/L   | No. in group | No. with arrhythmia | Per scan (non-nested) | No. in group | No. with arrhythmia | First scan only |
|-----------------|--------------|---------------------|-----------------------|--------------|---------------------|-----------------|
|                  |              |                     | RR  | 95% CI  | p     | RR  | 95% CI  | p     |
| 2500+           | 450          | 30                  | 1.03 | 0.67   | 1.58  | 0.90  | 215          | 14            | 0.77 | 0.40 | 1.51  | 0.45   |
| <2500           | 992          | 68                  | 1    | Reference |      |       | 437          | 22            | 1    | Reference |