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ORIGINAL ARTICLE

Prevalence and distribution of iron overload in patients with transfusion-dependent anemias differs across geographic regions: results from the CORDELIA study

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Abstract

Objectives: The randomized comparison of deferasirox to deferoxamine for myocardial iron removal in patients with transfusion-dependent anemias (CORDELIA) gave the opportunity to assess relative prevalence and body distribution of iron overload in screened patients. *Methods:* Patients aged ≥10 yr with transfusion-dependent anemias from 11 countries were screened. Data were summarized descriptively, overall and across regions. *Results:* Among 925 patients (99.1% with β-thalassemia major; 98.5% receiving prior chelation; mean age 19.2 yr), 36.7% had myocardial iron overload (myocardial T2* ≤20 ms), 12.1% had low left ventricular ejection fraction. Liver iron concentration (LIC) (mean 25.8 mg Fe/g dw) and serum ferritin (median 3702 ng/mL) were high. Fewer patients in the Middle East (ME; 28.5%) had myocardial T2* ≤20 ms vs. patients in the West (45.9%) and Far East (FE, 40.9%). Patients in the West had highest myocardial iron burden, but lowest LIC (26.9% with LIC <7 mg Fe/g dw) and serum ferritin. Among patients with normal myocardial iron, a higher proportion of patients from the ME and FE had LIC ≥15 than <7 mg Fe/g dw (ME, 56.7% vs. 17.2%; FE, 78.6% vs. 7.8%, respectively), a trend which was less evident in the West (44.6% vs. 33.9%, respectively). Transfusion and chelation practices differed between regions. *Conclusions:* Evidence of substantial myocardial and liver iron burden across regions revealed a need for optimization of effective, convenient iron chelation regimens. Significant regional variation exists in myocardial and liver iron loading that are not well explained; improved understanding of factors contributing to differences in body iron distribution may be of clinical benefit.

Key words thalassemia; heart; liver; iron; prevalence; distribution

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Iron-induced cardiomyopathy has long been recognized as a leading cause of death in patients with transfusion-dependent anemias (1–4). However, liver iron concentration (LIC) and serum ferritin, both established markers of liver iron overload, may not reliably reflect the presence of myocardial iron deposition (5, 6). Prompted by such observations, the development of reliable noninvasive techniques has facilitated investigation of myocardial iron burden in the setting of transfusion-related iron overload in clinical practice. Cardiovascular magnetic resonance (CMR), which provides an estimate of myocardial iron load through the measurement of myocardial T2*, has been validated and recently calibrated (5, 7). A myocardial T2* value <20 ms indicates clinically significant myocardial iron above the normal limit which is associated with an increased risk of impaired ventricular function, with T2* <10 ms (i.e., severe myocardial

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iron overload) being associated with the highest risk of heart failure (8–10). Advances in the ability to measure myocardial T2* for the management of myocardial siderosis (10–15) [including the relationship between T2* and heart failure (10)]; a greater understanding of normal ventricular function in patients with thalassemia (16); and the availability of iron chelators with demonstrated efficacy for the removal of myocardial iron (15, 17–22) have all contributed to the decrease in cardiac-related mortality and morbidity over the last 10 yr (23–25). Although cardiac-related mortality continues to remain a key challenge in treating these patients, an increasing number of deaths due to the long-term effects of iron-induced liver toxicity are also being observed (25).

With these evolving management advances and challenges, it is important to re-examine the prevalence of iron overload among chronically transfused patients. Additionally, little is known about the distribution of iron burden across different geographic regions, as few studies had sufficient sample size to enable such assessment. CORDELIA (NCT00600938) was an international, multicenter, open-label, randomized, Phase II clinical trial, which demonstrated the non-inferiority of deferasirox vs. deferoxamine (DFO) for the removal of myocardial iron in patients with β-thalassemia major (22). Overall, 925 patients were screened for entry into CORDELIA. We examined the prevalence and distribution of body iron burden and in particular myocardial iron overload, overall and by geographic region, in this large and representative cohort of patients with transfusion-dependent anemias.

Methods

CORDELIA was a Phase II, open-label, randomized study (NCT00600938) conducted between April 10, 2008 and March 1, 2012 to verify the non-inferiority of deferasirox vs. DFO in myocardial iron removal (22). Patients were screened for study entry from countries within three regions: West [Canada (n = 4), Cyprus (n = 10), Italy (n = 2), Turkey (n = 232), UK (n = 11)]; Middle East (ME) [Egypt (n = 387), UAE (n = 45), Lebanon (n = 31)]; and Far East (FE) [Taiwan (n = 22), Thailand (n = 122), China (n = 59)]. Turkey was included in the Western region by definition of the World Health Organization assignment to their European region, and to balance patient numbers between regions assessed here.

Patients

Patients who underwent screening for entry into CORDELIA were aged ≥10 yr with a diagnosis of β-thalassemia major, Diamond–Blackfan anemia (DBA), sideroblastic anemia, or low/int-1 risk myelodysplastic syndromes (MDS). Patients were also required to have a lifetime history of ≥50 red blood cell (RBC) transfusions (predominantly leucodepleted packed red cells, but also included whole blood, non-leucodepleted red cells, or washed red cells) and to be receiving RBC transfusions amounting to ≥10 units/yr. Prior chelation or requirement for chelation therapy was also a criterion.

Patients unable to undergo the study assessments [including magnetic resonance imaging (MRI)] or who had psychiatric or addictive disorders that prevented them from giving their informed consent were ineligible for screening.

Patients provided written informed consent prior to any screening assessment. The design and protocol of the CORDELIA study were approved by the relevant Ethics Committees at each study site. The study was conducted in accordance with the guidelines for Good Clinical Practice stipulated by the International Conference on Harmonisation and Declaration of Helsinki.

Screening assessments

Assessments were performed at screening for evaluation of myocardial siderosis (T2*), cardiac function [as evaluated by left ventricular ejection fraction (LVEF), %], and other iron parameters [as evaluated by LIC, mg Fe/g dry weight (dw) and serum ferritin, ng/mL level].

Myocardial T2* was measured using a standardized CMR protocol for multigradient-echo T2* acquisition (5). Briefly, 10-mm midventricular short-axis slices were acquired at nine separate echo times (5.6–17.6 ms, with 1–2-ms increments) in a single breath hold. The signal intensity at each echo time was measured using CMR tools software (Thalassemia-Tools; Cardiovascular Imaging Solutions, London, UK), and an exponential fit was used to derive the myocardial T2* in milliseconds. The resulting images were assessed by a central CMR expert reader. LVEF was also measured by CMR. LVEF below the lower limit of normal (LLN) was identified using Westwood criteria (LLN for LVEF of 59% in males and 63% in females) (16).

LIC was evaluated by measurement of the transverse relaxation parameter, R2, using a single breath-hold MRI technique that previously demonstrated high sensitivity and specificity of R2 to liver biopsy LIC thresholds (26). Measurements were read centrally.

Serum ferritin levels were obtained from blood samples drawn at screening and were analyzed by a central laboratory using a validated standard kit assay.

Statistical analysis

All screened patients were included in the analysis population. Patient characteristics were summarized by myocardial T2* categories of myocardial iron overload (<6 ms, 6–<10 ms, 10–≤20 ms, normal threshold >20 ms), by three geographic regions (West, ME, and FE) and by splenectomy status (yes/no).

Results are presented descriptively. For measures of iron burden, myocardial T2* is shown as the geometric mean (anti-log of the mean of the log data) with 95% confidence

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intervals (CI), while LIC and serum ferritin are recorded as mean [standard deviation (SD)] and median (range), respectively. Data for cardiac function (LVEF) are summarized as mean (SD).

Correlations between myocardial T2* and other iron parameters, as well as age and LVEF were assessed using Pearson's correlation coefficient (*r*).

Results

Patient characteristics

Overall, 925 patients screened for entry into CORDELIA were included in this analysis, including patients from the West (n = 259), ME (n = 463), and FE (n = 203) regions. The characteristics of patients are summarized in Table 1.

Transfusion and chelation history

Despite a similar mean age, patients from the West region had received the greatest number of transfusions (exposures to a transfusion episode) in their lifetime [median 257 (range 21–1950)], in comparison with patients from the ME and FE regions. However, the volume of blood per transfusion [median 200 mL (range 185–1400)] was lowest in the West when compared with the ME and FE regions. The most recent transfusion policy (in the previous year) demonstrated a shift towards more frequent transfusion exposure in patients from the ME and FE regions; in the year prior to screening, 91.4% of patients in the West region were transfused monthly, whereas in the ME region, patients were largely transfused monthly or every 2 wk, with a similar observation in patients in the FE region (Table 2).

Most patients (98.5%) had received previous iron chelation therapy with a range of agents for a median of 12.3 yr (0.0–37.1; Table 3). In the West region, deferasirox was most frequently used (54.8%) just prior to study entry, compared with 8.0% in the ME and 15.2% in the FE regions. DFO was the most frequent last prior therapy in both the ME (46.4%) and FE (36.4%) regions. Time since initiation of chelation therapy was shortest in patients in the FE region [9.1 yr (0.1–31.3)], indicating that these patients, who had a mean age at screening for the study similar to patients from other regions, initiated chelation therapy at a later age than in other regions – although these patients had also started transfusions more recently (Table 2). Indeed, the median (range) time difference between start of transfusions and initiation of chelation therapy was longest in patients in the FE region [4.8 yr (–7.0 to 35.2)] compared with the West [2.8 yr (8.0 to 27.3)] and ME regions [3.0 yr (–16.1 to 26.0)]. Patients in the West and FE regions had no interruption of chelation therapy after it was initiated (median of 0 months without chelation), while for patients in the ME region, the median duration of interruption was 10.0 months (0.0–600.0; Table 3).

Myocardial iron overload

In the overall population, geometric mean myocardial T2* was 21.8 ms (n = 764; Table 4). Overall, 36.7% of

Table 1 Patient demographics and clinical characteristics[1]

Characteristic	Overall (n = 925)	West (n = 259)	Middle East (n = 463)	Far East (n = 203)
Male : female (%)	54.5 : 45.5	55.6 : 44.4	57.5 : 42.5	46.3 : 53.7
Age, yr				
Mean (SD)	19.2 (7.8)	19.6 (7.4)	19.3 (7.4)	18.8 (9.2)
Median (range)	18.0 (9.0–80.0)	18.0 (10.0–49.0)	18.0 (9.0–66.0)	16.0 (9.0–80.0)
Race, *n* (%)				
Caucasian	672 (72.6)	249 (96.1)	423 (91.4)	–
Asian	251 (27.1)	10 (3.9)	38 (8.2)	203 (100)
Other	2 (0.2)	–	2 (0.4)	–
Weight, kg				
Mean (SD)	46.6 (13.3)	49.7 (12.8)	47.0 (13.9)	41.8 (10.8)
Median (range)	47.0 (16.0–96.0)	49.9 (19.2–95.0)	47.0 (16.0–96.0)	41.8 (21.6–75.5)
Disease, *n* (%)				
β-thalassemia major	902 (99.1)	257 (99.2)	446 (99.6)	199 (98.0)
DBA	1 (0.1)	1 (0.4)	–	–
Low/int-risk MDS	4 (0.4)	–	1 (0.2)	3 (1.5)
Other[2]	3 (0.3)	1 (0.4)	1 (0.2)	1 (0.5)
Splenectomy, *n* (%)	460 (49.7)	151 (58.3)	236 (51.0)	73 (36.0)
Hepatitis C, *n* (%)	101 (10.9)	14 (5.4)	76 (16.4)	11 (5.4)

DBA, Diamond–Blackfan anemia; MDS, myelodysplastic syndromes; SD, standard deviation.

[1]Values are reported for patients with non-missing data.

[2]β-thalassemia intermedia, congenital dyserythropoietic anemia, paroxysmal nocturnal hemoglobinuria (n = 1 each).

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Table 2 History of blood transfusion by geographic region

	Overall	West	Middle East	Far East
Time since start of transfusions, yr				
Patients, *n*	839	257	383	199
Mean (SD)	17.6 (7.0)	18.6 (7.1)	18.0 (6.9)	15.8 (6.7)
Median (range)	16.5 (0–49.1)	17.3 (5.1–49.1)	17.4 (0–44.1)	14.2 (2.2–38.8)
Number of transfusion episodes				
Patients, *n*	770	248	324	198
Mean (SD)	256 (184)	315 (228)	228 (145)	229 (163)
Median (range)	216 (15–1950)	257 (21–1950)	207 (15–840)	188 (30–1000)
Volume per blood transfusion, mL				
Patients, *n*	774	201	375	198
Mean (SD)	364 (157)	279 (170)	400 (79)	380 (212)
Median (range)	350 (148–1400)	200 (185–1400)	350 (148–700)	300 (150–1000)
Usual transfusion frequency in the previous year, *n* (%)				
Patients, *n*	859	257	401	201
Every 2 wk	157 (18.3)	16 (6.2)	80 (20.0)	61 (30.3)
Every month	633 (73.7)	235 (91.4)	269 (67.1)	129 (64.2)
Every 6 wk	30 (3.5)	5 (1.9)	23 (5.7)	2 (1.0)
Every 2 months	19 (2.2)	1 (0.4)	11 (2.7)	7 (3.5)
Every 3 months	12 (1.4)	–	10 (2.5)	2 (1.0)
Every 4 months	3 (0.3)	–	3 (0.7)	–
Every 6 months	5 (0.6)	–	5 (1.2)	–

Table 3 Prior chelation therapy by geographic region

	Overall (*n* = 888)	West (*n* = 259)	Middle East (*n* = 427)	Far East (*n* = 202)
Previous chelation, *n* (%)	875 (98.5)	259 (100.0)	418 (97.9)	198 (98.0)
DFO	300 (34.5)	37 (14.3)	191 (46.4)	72 (36.4)
Deferiprone	113 (13.0)	29 (11.2)	51 (12.4)	33 (16.7)
DFO + deferiprone	205 (23.6)	50 (19.3)	104 (25.2)	51 (25.8)
Deferasirox	205 (23.6)	142 (54.8)	33 (8.0)	30 (15.2)
Other[1]	46 (5.3)	1 (0.4)	33 (8.0)	12 (6.1)
Time since start of chelation, yr				
Mean (SD)	12.8 (6.7)	14.0 (7.2)	13.8 (6.1)	9.4 (5.7)
Median (range)	12.3 (0–37.1)	13.2 (0–37.1)	13.4 (0.2–34.1)	9.1 (0.1–31.3)
Time without chelation after initiation, months				
Mean (SD)	12.8 (38.0)	1.7 (10.9)	28.7 (54.2)	1.4 (8.6)
Median (range)	0 (0–600.0)	0 (0–108.0)	10.0 (0–600.0)	0 (0–87.0)

DFO, deferoxamine; SD, standard deviation.
[1]Unknown or patients received irregular deferiprone and/or DFO therapy.

Table 4 Iron overload and cardiac function parameters in patients with transfusion-dependent anemias across geographic regions

	Overall (*n* = 925)	West (*n* = 259)	Middle East (*n* = 463)	Far East (*n* = 203)
Geometric mean myocardial T2* (95% CI), ms	21.8 (20.8, 22.9)	19.4 (17.8, 21.2)	24.5 (22.9, 26.3)	20.0 (18.0, 22.2)
Mean LVEF (SD), %	66.9 (5.8)	66.7 (5.5)	66.1 (6.1)	68.6 (5.2)
Mean LIC (SD), mg Fe/g dw	25.8 (17.1)	19.4 (14.6)	25.1 (16.5)	35.1 (16.9)
Median serum ferritin (range), ng/mL	3702 (64–23 640)	2316 (334–11 682)	3742 (64–16 736)	5261 (685–23 640)

CI, confidence interval; LIC, liver iron concentration; LVEF, left ventricular ejection fraction; SD, standard deviation.

patients had myocardial iron loading with myocardial T2* ≤20 ms, 19.9% with a myocardial T2* of 10–≤20 ms (mild-to-moderate myocardial iron), 11.4% with T2* of 6–<10 ms (severe myocardial iron), and 5.4% having T2* <6 ms (severe myocardial iron and high risk of heart failure).

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Geometric mean myocardial T2* differed across geographic regions, with the highest value (indicating lower myocardial iron burden) in patients from the ME region (Table 4). The distribution of myocardial iron overload severity categories also varied between geographic regions, as well as in comparison with the overall population (Fig. 1). In contrast to patients in the West (45.9%) and the FE (40.9%) regions, fewer patients in the ME regions had myocardial iron loading with T2* ≤20 ms (28.5%).

Geometric mean myocardial T2* also differed by splenectomy status, with a slightly higher value in non-splenectomized patients vs. splenectomized patients [23.2 ms (95% CI 21.7, 24.7) vs. 20.6 ms (19.2, 22.1), respectively]. More non-splenectomized patients had myocardial T2* >20 ms (67.7% vs. 59.3% of splenectomized patients), and 12.5% of non-splenectomized patients had severe myocardial siderosis compared with 20.7% of splenectomized patients.

Cardiac function

There were no differences across geographic regions in mean LVEF, which was in the normal range among all patient populations (Table 4). Among T2* categories, mean (SD) LVEF was lowest in patients with severe myocardial iron overload [T2* 6–<10 ms: 63.8% (6.2%); T2* <6 ms: 63.8% (6.1%)], compared with those patients having mild-to-moderate [T2* 10–≤20 ms: 66.4% (6.4%)] or no significant myocardial iron overload [>20 ms: 67.9% (5.2%)].

As shown in Fig. 2, 24.4% of patients with T2* <6 ms had an LVEF below the LLN [59% (males) or 63% (females)], compared with 8.2% of patients with myocardial T2* >20 ms and 12.1% overall.

Other iron parameters

Liver iron concentration. Mean (SD) LIC was severely elevated in the overall population of screened patients [25.8 (17.1) mg Fe/g dw] and when analyzed by geographic region (Table 4). However, the magnitude of mean LIC elevations differed according to region, with the lowest and highest LIC values observed in the West and FE regions, respectively (Table 4).

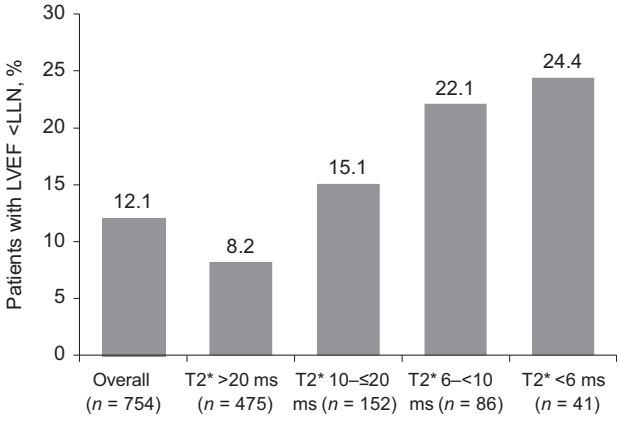

Figure 2 Prevalence of abnormal cardiac function across the T2* categories in patients with transfusion-dependent anemias. †Westwood criteria (males <59%; females <63%) (16). LLN, lower limit of normal.

The proportions of patients meeting predefined categories of LIC severity (<7.7–<15 and ≥15 mg Fe/g dw) are shown by geographic region in Fig. 1. Overall, 64.1% of patients had severe liver iron burden, as shown by LIC ≥15 mg Fe/g dw. The distribution of patients across categories of LIC severity varied between the West, FE, and ME regions. The overwhelming majority (82.0%) of patients in the FE region had LIC ≥15 mg Fe/g dw compared with approximately half (51.2%) of patients from the West region and 63.4% from the ME region (Fig. 1). The proportion of patients with low liver iron burden (LIC <7 mg Fe/g dw) was more than threefold higher in the West region than in the FE region (Fig. 1).

Distribution of myocardial and liver iron burden. We also examined the pattern of myocardial and liver iron distribution among screened patients with data available for both assessments. Only four patients (all from the West region) had severe myocardial iron burden, but low LIC (T2* <10 ms and LIC <7 mg Fe/g dw). Among patients with normal myocardial iron (T2* >20 ms), more than half (58.5%) had an LIC ≥15 mg Fe/g dw, while 19.6 and 21.9% had LIC <7 or 7–<15 mg Fe/g dw, respectively. Within regions, a higher

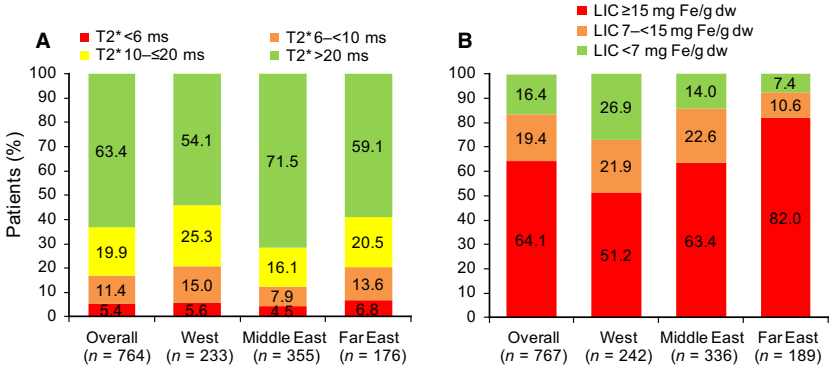

Figure 1 Prevalence of (A) myocardial and (B) liver iron overload in patients with transfusion-dependent anemias across geographic regions.

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proportion of patients with T2* >20 ms from the ME and FE regions had severe liver iron burden (LIC ≥15 mg Fe/g dw) compared with those having LIC <7 mg Fe/g dw (ME region, 56.7% vs. 17.2%; FE region, 78.6% vs. 7.8%, respectively; Table 5). This within-region trend for differences in liver iron loading among patients with normal myocardial iron was less evident among patients from the West region (44.6% had LIC ≥15 mg Fe/g dw vs. 33.9% with LIC <7 mg Fe/g dw).

In the overall population of patients with severe liver iron burden (LIC ≥15 mg Fe/g dw; $n = 455$), 56.5% had a myocardial T2* >20 ms. Analysis by geographic region of myocardial T2* categories in patients with LIC ≥15 mg Fe/g dw revealed a relatively higher proportion of patients from the ME region with a T2* >20 ms than from the FE or West regions (Table 5). The distribution of severely liver iron-overloaded patients among the remaining mild-to-moderate (T2* 10–≤20 ms) or severe categories (T2* <6 or 6–<10 ms) of myocardial iron burden was generally comparable (Table 5).

Serum ferritin. Median (range) serum ferritin level was 3702 (64–23 640) ng/mL overall. Across regions, median serum ferritin level was lower in patients in the West region than their counterparts in the FE region (Table 2). Correspondingly, markedly fewer patients in the West region (47.3%) recorded serum ferritin concentrations exceeding 2500 ng/mL compared with patients from the ME and FE region (Table 6).

Correlation analyses

Weak correlations were observed between myocardial T2* and age ($r = -0.053$), LIC ($r = -0.224$), serum ferritin ($r = -0.258$), and LVEF ($r = 0.183$).

Table 5 Distribution of myocardial and liver iron overload across geographic regions in patients with transfusion-dependent anemias

	Geographic regions *n* (%)[1]		
Category	West	Middle East	Far East
Myocardial T2* >20 ms	*n* = 121	*n* = 215	*n* = 103
Liver iron concentration (LIC), mg Fe/g dw			
<7	41 (33.9)	37 (17.2)	8 (7.8)
7–<15	26 (21.5)	56 (26.0)	14 (13.6)
≥15	54 (44.6)	122 (56.7)	81 (78.6)
LIC ≥15 mg Fe/g dw	*n* = 116	*n* = 195	*n* = 144
Myocardial T2*, ms			
>20	54 (46.6)	122 (62.6)	81 (56.3)
10–≤20	28 (24.1)	38 (19.5)	29 (20.1)
6–<10	22 (19.0)	24 (12.3)	22 (15.3)
<6	12 (10.3)	11 (5.6)	12 (8.3)

[1]Totals are calculated by region; values are reported for patients with non-missing data for both LIC and T2*.

Discussion

Although cardiac-related mortality remains a leading cause of death in patients with transfusion-dependent anemias, changing management strategies have brought about a reduction in the number of deaths attributed to iron-induced cardiomyopathy (23–25). As there is a lack of awareness of the impact of these changes on the prevalence of myocardial iron, the CORDELIA study (a randomized comparison of deferasirox vs. DFO) provided the opportunity to investigate the prevalence of myocardial iron overload from a broader geographical perspective, as well as body iron burden overall.

The overall prevalence of myocardial iron overload (T2* ≤20 ms) observed in this analysis (36.7%) is slightly lower than previous observations (27–29). Most patients screened for CORDELIA fell into the category for severe liver iron burden (LIC >15 mg Fe/g dw), but with myocardial T2* in the normal range (>20 ms). However, we observed several differences in the distribution of iron overload among patients across the regions. Patients in the West region had the highest myocardial iron burden, but the lowest liver iron burden and serum ferritin levels. Myocardial iron burden was lowest in the ME region, although the majority of these patients with T2* in the normal range also had severely elevated LIC, a trend which was observed least often in patients from the West region. Patients in the West and Middle Eastern regions were of a similar age and had a similar duration since initiation of transfusions, so these factors were unlikely to have significant impact on the differences in body iron distribution across these groups. El-Beshlawy *et al.* (30) recently reported similar observations in Middle Eastern patients. Finally, the proportion of patients with T2* ≤20 ms reported in the ME region here (28.5%) contrasts with data reported in 2009 among 81 patients from Oman, where 46% of patients had abnormal myocardial T2* (27). These differences in prevalence may reflect the smaller patient population in the Omani study, but could also follow on from differences in patient management among Middle Eastern countries.

Table 6 Comparison of the prevalence of iron overload, measured by serum ferritin, across geographic regions in patients with transfusion-dependent anemias

	Geographic regions *n* (%)[1]		
	West	Middle East	Far East
Serum ferritin, ng/mL	*n* = 256	*n* = 452	*n* = 201
≤1000	34 (13.3)	26 (5.8)	3 (1.5)
1000–≤2500	101 (39.5)	116 (25.7)	27 (13.4)
>2500	121 (47.3)	310 (68.6)	171 (85.1)

[1]Totals are calculated by region; values are reported for patients with non-missing data.

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Age at starting transfusion or chelation therapy, the nature of transfusion or chelation regimens and patient age at screening may all contribute to iron accumulation and distribution. It is possible that variations in the way blood is delivered over time – a small amount per transfusion episode often or a larger amount infrequently – could have differential effects on iron distribution, despite similar rates of iron loading. It is well known that inefficient blood supply and/or difficulty in patient access leads to a lower frequency of transfusion in some countries (31). Furthermore, the majority of patients from the FE region were not splenectomized. If hypersplenism was present in these patients, perhaps as a result of inadequate transfusion policies in the past, it could explain the observed higher transfusion frequency in the year prior to screening and volume per blood transfusion compared with Western patients and could also contribute to the higher body iron burden despite lower transfusion chronicity. Later onset of transfusion dependency in patients from the FE region (despite being of a similar mean age at screening compared to patients from the other regions) may explain the shorter exposure to prior chelation therapy. It is possible that some individuals from this region were patients with non-transfusion-dependent thalassemia (NTDT) who later became regularly transfused, a scenario that is quite common in patients with HbE/β-thalassemia in the FE. This could also help clarify why the highest liver iron burden was seen in this group. Unfortunately, pretransfusional hemoglobin levels were not available in the data collected, as this would given further insight into the local transfusion practices and the implications on iron loading and distribution.

Although information on adherence was not systematically collected, deferasirox was reported as last prior chelation in over half of patients in the West region, but only a small proportion of patients in the Middle and FE regions. In these latter regions, DFO use was most common, perhaps due to limited patient access to oral therapies. A recent longitudinal analysis highlighted differences between myocardial and liver iron changes depending on the type of chelation regimen utilized, suggesting that chelation therapy should ideally be tailored based on individual patient body iron burden (32).

As the spleen may have a role in iron regulation (28, 33), differences in splenectomy practices may also influence the disparity in body iron distribution across the regions. A greater proportion of patients from the West region had undergone splenectomy, which could contribute to the higher myocardial iron burden in these patients as splenectomy has been implicated in increased myocardial siderosis (28). However, multiple confounding factors could also contribute to this observation, such as local transfusion practices and attitude to the safety of splenectomy. Furthermore, the kinetics of iron accumulation may differ across geographic regions depending on the genetic background of patients and may play an underlying role in the observed differences in both the extent and pattern of iron burden between the regions (34–37).

There was no clinically meaningful correlation between myocardial T2* and age, LIC, serum ferritin, or LVEF in this analysis, which is consistent with previous observations (6, 38). Nevertheless, high LIC may be relevant as preliminary data suggest an association between LIC and the rate of myocardial iron removal in patients treated with deferasirox (22, 39). Additionally, although a strong relationship between LVEF and myocardial T2* was not shown in this analysis – likely to be related to the substantial number of patients with myocardial T2* in the normal range (5) – we did observe that nearly one-quarter of patients with very severe myocardial iron loading (T2* <6 ms) had cardiac dysfunction as observed by LVEF below the LLN for patients with thalassemia. There was also a trend for a greater proportion of cardiac dysfunction at lower myocardial T2* categories. Kirk *et al.* (10) provided convincing evidence to support a relationship between the severity of myocardial siderosis (T2* <20 ms) and the risk of heart failure or arrhythmias, thus supporting the validity of myocardial T2* as an early predictor of heart complications. Interestingly, however, in our study, 8% of patients with normal myocardial T2* had abnormal LVEF, highlighting the importance of monitoring both myocardial iron burden and cardiac function.

Despite the majority of patients having documented receipt of some prior iron chelation therapy, total body iron burden in this large cohort was severe, indicating that compliance and/or dosage may have been suboptimal. Liver iron burden in particular was severely elevated, providing evidence to support recent observations that liver complications are increasing, relative to heart complications (25, 40). The fact that a significant proportion of patients continue to show myocardial iron loading, as well as substantial liver iron burden, demonstrates that there remains a need for the optimization of effective and convenient iron chelation treatment regimens.

As with studies of a non-interventional design, the potential influence of patient selection bias for screening should be a consideration when interpreting these results. CORDELIA entry criteria were stringent with regard to body iron burden and transfusion dependence, and physicians may have been mindful of these when identifying patients who were appropriate for screening for a study on myocardial iron overload, possibly selecting those patients most likely to have myocardial iron. Additionally, a high number of patients screened for entry originated from the ME region (463 of 925 patients). Observations of a lower prevalence of myocardial iron burden in these patients may have impacted the findings of the results reported here. Local country transfusion and chelation practices may influence regional observations, particularly when groups were unbalanced, such as the large number of patients from Turkey compared with

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other countries in the West region. Finally, cross-sectional analyses such as these should be interpreted with caution, particularly as differences in previous chelation practices and patient compliance are likely to impact on iron chelation efficacy and the relationship between heart and liver iron unloading (32). It should also be noted that the results from this exploratory analysis are presented descriptively, as the study was neither designed nor powered to detect statistical differences between different populations.

In summary, myocardial siderosis was observed in approximately one-third of patients screened for entry into the CORDELIA study. The burden of liver iron loading in particular was severe, despite prior chelation therapy in almost all patients examined. We observed differences in the pattern of iron accumulation across geographic regions examined, which may be the result of patient age, transfusion, chelation, and other disease management practices, as well as inherent population differences; further investigation into these differences is warranted. Collectively, these results suggest a need to optimize effective and convenient chelation regimens for personalized treatment to better manage both myocardial and liver iron burden in patients with transfusion-dependent anemias.

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Authors' contributions

AE-B, AY, JBP, ME, VV, YA, and YK served as investigators on this trial, screening patients. They contributed to data interpretation, reviewed, and provided their comments on this manuscript. AP, DJP, JBP, and YA served as Study Steering Committee members overseeing the conduct of the trial, from study design to analysis plan and data interpretation. DH assisted in developing the trial protocol, coordinating the execution of the trial and contributing to the analysis, interpretation and reporting of the study data. EQF served as the study analysis statistician. All authors approved the final manuscript.

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References

1. Ehlers KH, Giardina PJ, Lesser ML, Engle MA, Hilgartner MW. Prolonged survival in patients with beta-thalassemia major treated with deferoxamine. *J Pediatr* 1991;**118**:540–5.
2. Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, Allen CJ, Farrell DE, Harris JW. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med* 1994;**331**:567–73.
3. Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A, Martin M, Koren G, Cohen AR. Survival in medically treated patients with homozygous beta-thalassemia. *N Engl J Med* 1994;**331**:574–8.
4. Borgna-Pignatti C, Rugolotto S, De Stefano P, *et al.* Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica* 2004;**89**:1187–93.
5. Anderson LJ, Holden S, Davis B, *et al.* Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J* 2001;**22**:2171–9.
6. Di Tucci AA, Matta G, Deplano S, Gabbas A, Depau C, Derudas D, Caocci G, Agus A, Angelucci E. Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias. *Haematologica* 2008;**93**:1385–8.

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7. Carpenter J-P, He T, Kirk P, *et al.* On T2* magnetic resonance and cardiac iron. *Circulation* 2011;**123**: 1519–28.
8. Tanner MA, Galanello R, Dessi C, Westwood MA, Smith GC, Nair SV, Anderson LJ, Walker JM, Pennell DJ. Myocardial iron loading in patients with thalassemia major on deferoxamine chelation. *J Cardiovasc Magn Reson* 2006;**8**:543–7.
9. Chouliaras GL, Kattamis A, Berdoukas V, Gotsis ED, Mavrogeni S, Ladis V. Cardiac magnetic resonance in transfusion dependent thalassaemia: assessment of iron load and relationship to left ventricular ejection fraction. *Br J Haematol* 2010;**151**:397–401.
10. Kirk P, Roughton M, Porter JB, *et al.* Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation* 2009;**120**:1961–8.
11. Anderson LJ, Westwood MA, Holden S, Davis B, Prescott E, Wonke B, Porter JB, Walker JM, Pennell DJ. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. *Br J Haematol* 2004;**127**:348–55.
12. Ghugre NR, Enriquez CM, Gonzalez I, Nelson MD Jr, Coates TD, Wood JC. MRI detects myocardial iron in the human heart. *Magn Reson Med* 2006;**56**:681–6.
13. Tanner MA, He T, Westwood MA, Firmin DN, Pennell DJ. Multi-center validation of the transferability of the magnetic resonance T2* technique for the quantification of tissue iron. *Haematologica* 2006;**91**:1388–91.
14. Pepe A, Positano V, Santarelli MF, Sorrentino F, Cracolici E, De Marchi D, Maggio A, Midiri M, Landini L, Lombardi M. Multislice multiecho T2* cardiovascular magnetic resonance for detection of the heterogeneous distribution of myocardial iron overload. *J Magn Reson Imaging* 2006;**23**:662–8.
15. Pennell DJ, Berdoukas V, Karagiorga M, *et al.* Randomized controlled trial of deferiprone or deferoxamine in beta-thalassemia major patients with asymptomatic myocardial siderosis. *Blood* 2006;**107**:3738–44.
16. Westwood MA, Anderson LJ, Maceira AM, Shah FT, Prescott E, Porter JB, Wonke B, Walker JM, Pennell DJ. Normalized left ventricular volumes and function in thalassemia major patients with normal myocardial iron. *J Magn Reson Imaging* 2007;**25**:1147–51.
17. Pennell D, Porter JB, Cappellini MD, *et al.* Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with beta-thalassemia major. *Haematologica* 2012;**97**:842–8.
18. Pepe A, Lombardi M, Positano V, Cracolici E, Capra M, Malizia R, Prossomariti L, De Marchi D, Midiri M, Maggio A. Evaluation of the efficacy of oral deferiprone in beta-thalassemia major by multislice multiecho T2*. *Eur J Haematol* 2006;**76**:183–92.
19. Tanner MA, Galanello R, Dessi C, *et al.* A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation* 2007;**115**:1876–84.
20. Porter JB, Tanner MA, Pennell DJ, Eleftheriou P. Improved myocardial T2* in transfusion dependent anemias receiving ICL670 (deferasirox). *Blood* 2005;**106**:abst 3600.
21. Wood JC, Kang BP, Thompson A, Giardina P, Harmatz P, Glynos T, Paley C, Coates TD. The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores. *Blood* 2010;**116**:537–43.
22. Pennell DJ, Porter JB, Piga A, *et al.* A 1-year randomized controlled trial of deferasirox versus deferoxamine for myocardial iron removal in beta-thalassemia major (CORDELIA). *Blood* 2014;**123**:1447–54.
23. Thomas AS, Garbowski M, Ang AL, Shah FT, Walker JM, Moon JC, Pennell DJ, Porter JB. A decade follow-up of a thalassemia major (TM) cohort monitored by cardiac magnetic resonance imaging (CMR): significant reduction in patients with cardiac iron and in total mortality. *Blood* 2010;**116**:abst 1011.
24. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008;**10**:42.
25. Voskaridou E, Ladis V, Kattamis A, *et al.* A national registry of haemoglobinopathies in Greece: deducted demographics, trends in mortality and affected births. *Ann Hematol* 2012;**91**:1451–8.
26. St Pierre TG, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E, Lindeman R. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005;**105**:855–61.
27. Daar S, Pathare AV, Jain R, Zadjali SA, Pennell DJ. T2* cardiovascular magnetic resonance in the management of thalassemia patients in Oman. *Haematologica* 2009;**94**:140–1.
28. Aydinok Y, Bayraktaroglu S, Yildiz D, Alper H. Myocardial iron loading in patients with thalassemia major in Turkey and the potential role of splenectomy in myocardial siderosis. *J Pediatr Hematol Oncol* 2011;**33**:374–8.
29. Carpenter JP, Roughton M, Pennell DJ. International survey of T2* cardiovascular magnetic resonance in beta-thalassemia major. *Haematologica* 2013;**98**:1368–74.
30. El-Beshlawy A, El-Tagui M, Hamdy M, El Ghamrawy M, Azim KA, Salem D, Said F, Samir A, Pierre TS, Pennell DJ. Low prevalence of cardiac siderosis in heavily iron loaded Egyptian thalassemia major patients. *Ann Hematol* 2013;**93**:375–9.
31. Viprakasit V, Gattermann N, Lee JW, Porter JB, Taher AT, Habr D, Martin N, Domokos G, Cappellini MD. Geographical variations in current clinical practice on transfusions and iron chelation therapy across various transfusion-dependent anaemias. *Blood Transfus* 2013;**11**:108–22.
32. Danjou F, Origa R, Anni F, Saba L, Cossa S, Podda G, Galanello R. Longitudinal analysis of heart and liver iron in thalassemia major patients according to chelation treatment. *Blood Cells Mol Dis* 2013;**51**:142–5.
33. Brewer CJ, Coates TD, Wood JC. Spleen R2 and R2* in iron-overloaded patients with sickle cell disease and thalassemia major. *J Magn Reson Imaging* 2009;**29**:357–64.

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34. Gordeuk VR, Caleffi A, Corradini E, *et al.* Iron overload in Africans and African-Americans and a common mutation in the *SCL40A1* (ferroportin 1) gene. *Blood Cells Mol Dis* 2003;**31**:299–304.
35. Barton JC, Acton RT, Lee PL, West C. SLC40A1 Q248H allele frequencies and Q248H-associated risk of non-HFE iron overload in persons of sub-Saharan African descent. *Blood Cells Mol Dis* 2007;**39**:206–11.
36. Oudit GY, Trivieri MG, Khaper N, Liu PP, Backx PH. Role of L-type Ca2+ channels in iron transport and iron-overload cardiomyopathy. *J Mol Med* 2006;**84**:349–64.
37. Lin H, Lian WS, Chen HH, Lai PF, Cheng CF. Adiponectin ameliorates iron-overload cardiomyopathy through the PPARalpha-PGC-1-dependent signaling pathway. *Mol Pharmacol* 2013;**84**:275–85.
38. Jensen PD. Evaluation of iron overload. *Br J Haematol* 2004;**124**:697–711.
39. Porter JB, Taher AT, Aydinok Y, Cappellini MD, Kattamis A, El-Ali A, Martin N, Pennell D. Impact of liver iron overload on myocardial T2* response in transfusion-dependent thalassemia major patients treated with deferasirox for up to 3 years. *Blood* 2013;**122**:abst 1016.
40. Lobo C, Angulo IL, Aparicio LR, Drelichman GI, Zanichelli MA, Cancado R. Retrospective epidemiological study of Latin American patients with transfusional hemosiderosis: the first Latin American epidemiological study in iron overload–the RELATH study. *Hematology* 2011;**16**:265–73.

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