RESEARCH ARTICLE

Differential effects of iron chelators on iron burden and long-term morbidity and mortality outcomes in a large cohort of transfusion-dependent β-thalassemia patients who remained on the same monotherapy over 10 years

Short title: Iron chelation outcomes in TDT

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ABSTRACT

We conducted a retrospective cohort study on 663 transfusion-dependent β-thalassemia patients receiving the same iron chelation monotherapy with deferoxamine, deferiprone, or deferasirox for up to 10 years (median age 31.8 years, 49.9% females). Patients on all three iron chelators had a steady and significant decline in serum ferritin over the 10 years (median deferoxamine: -170.7 ng/mL, *P* = 0.049, deferiprone: -236.7 ng/mL, *P* = 0.001; deferasirox: -323.7 ng/mL, *P* <0.001) yet had no significant change in liver iron concentration or cardiac T2*; while noting that patients generally had low hepatic and cardiac iron levels at study start. Median absolute, relative, and normalized changes were generally comparable between the three iron chelators. Patients receiving deferasirox had the highest morbidity and mortality-free survival probability among the three chelators, although the difference was only statistically significant when compared with deferoxamine (*P* = 0.037). On multivariate Cox regression analysis, there was no significant association between iron chelator type and the composite outcome of morbidity or mortality. In a real-world setting, there is comparable long-term iron chelation effectiveness between the three available iron chelators for patients with mild-to-moderate iron overload.

Keywords: deferoxamine; deferiprone; deferasirox; iron overload; thalassemia.

INTRODUCTION

The introduction of iron chelation therapy since the 1960s to prevent and manage secondary iron overload in patients with transfusion-dependent β-thalassemia (TDT) changed the prospect of the disease from one known for early childhood mortality to a chronic condition of adulthood [1-3]. However, improvements in survival attributed to deferoxamine (DFO) use were immediately challenged by the burden of subcutaneous treatment and poor adherence [4-8]. Subsequent development of the oral iron chelators deferiprone (DFP, three time daily) and deferasirox (DFX, once daily, dispersible tablet [DT] and later film-coated tablet [FCT] forms) helped address limitations with compliance at a comparable or superior iron chelation efficacy compared with DFO [9-20]. Such advances in oral iron chelation therapy coupled with parallel advances in iron overload monitoring by MRI have led to continued improvement in disease morbidity and patient survival [21-32]. However, the differential effects of specific iron chelators on such long-term clinical outcomes have been rarely studied. In fact, even for iron chelation efficacy measured through serum ferritin (SF), liver iron concentration (LIC), or cardiac T2* (cT2*), head-to-head comparative trials with oral iron chelators are extremely limited [33], making data from real-world evidence studies essential [34-39]. Although combination therapy has been commonly used to manage patients with severe iron overload or established organ dysfunction, most patients today are maintained on monotherapy.

With this background, the current study aims to evaluate and compare the iron chelation effectiveness and impact on long-term morbidity and mortality outcomes

between the three available iron chelators through analysis of a large cohort of patients who remained on the same monotherapy for up to 10 years.

METHODS

This was a retrospective cohort study of β-thalassemia patients attending treatment centers in Italy, using pooled data from DB-INTHEM. DB-INTHEM is a database that automatically collects data of Italian patients with β-thalassemia who are followed by centers using Webthal®, a computerized medical record software currently owned by the Italian Society of Thalassemias and Hemoglobinopathies (SITE), which was developed in 2000 to aid in standardized clinical, laboratory, and imaging data recording across participating centers. A Secure Socket Layer system and passwords are used to ensure data safety and confidentiality. At each center, an Ethics Committee approval is obtained and written informed consents for data collection and use are retrieved from patients.

For this study, we retrieved data for all patients who had a diagnosis of β-thalassemia major and had an average of at least ten red blood cell units per year during the observation period, to confirm their transfusion-dependence. Patients also had to receive the same iron chelation monotherapy (DFO, DFP, or DFX) for the entirety of the 10-year observation period. Patients on combinations and those who had to discontinue/switch their monotherapy for any reason within the 10-year period were excluded. A total of 663 patients out of 912 available in our dataset met these eligibility criteria and were included in the analyses. Patients were followed from 01 January 2010 until 31 December 2019, death, transplant, or loss to follow-up. This

period was chosen to represent a long-term 10-year observation, and to reflect modern management of the disease with MRI monitoring of organ-specific iron overload and oral iron chelation therapy being routinely available. It also represents a period prior to the Covid-19 pandemic which may have disrupted standard patient management.

For each patient, we retrieved data on age at study start, sex, center of treatment, pretransfusion hemoglobin (observation period average), annual iron intake (observation period average), iron chelator dose and compliance (observation period average), and status at last follow-up date (dead, alive, transplant, lost to follow-up). For patients receiving DFX FCT in more recent years, doses were imported in the database using their equivalent in DT to ensure harmonization. Compliance was measured using pill count at every visit.

We also retrieved data on active iron-related morbidities at study start and development of new (including worsening) iron-related morbidities during the 10-year observation period. These included the following morbidities which were diagnosed per local standards: heart failure, cardiac arrythmia, liver fibrosis or cirrhosis, hepatocellular carcinoma, and diabetes mellitus.

We also retrieved data on SF, LIC (measured using hepatic MRI T2* with standard calibration techniques), cT2*, alanine aminotransferase (ALT), and serum creatinine (Cr). For all these variables, we considered the annual average of all available records for each consecutive year during the 10-year observation period. For the purposes of this analysis, we also assigned the following for each variable: Y_1 *and*

Y_{10} value (annual average in 2000 and 2019, respectively), *First* value (first annual average during the 10-year observation period), *Last* value (last annual average during the 10-year observation period), *Period Average* (average of all annual averages during the 10-year observation period), *Absolute Change* (the difference between *First* and *Last* value or Y_{10} and Y_1 values, as indicated), *Relative Change* (the difference between *First* and *Last* value or Y_{10} and Y_1 values, as indicated, divided by *First* or Y_1 value, respectively; and multiplied by 100), *Normalized Change* (the difference between *First* and *Last* value divided by the duration of years in between).

Statistical analysis

Data did not follow a normal distribution (Shapiro Wilk test P <0.001 for key study variables), hence nonparametric tests were used. Descriptive statistics are represented as median (interquartile range [IQR], min, max) or percentages. Bivariate associations were evaluated using the Mann Whitney U t-test (continuous, 2 variables), Kruskal Wallis H text (continuous >2 variables), Chi-square test (nominal), Wilcoxon signed-rank test (paired, continuous), and McNemar's test (paired, nominal); and correlations were evaluated using the Spearman's correlation coefficient (rs). Kaplan-Meier survival curves were constructed to estimate cumulative morbidity and mortality-free survival, and the Log-rank test was used for comparisons of survival curves. Cox regression analyses were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of the composite outcome of morbidity or mortality. Multivariate forward stepwise models were used to adjust for confounding effects of age, sex, center of treatment, pretransfusion hemoglobin,

annual iron intake, and active morbidity at study start. All *P*-values were two-sided with the level of significance set at <0.05.

RESULTS

A total of 663 TDT patients were included in this analysis, with 331 (49.9%) being female. The median age at study start was 31.8 years (IQR: 22.4.1-36.4, min: 0.1, max: 61), including 120 (18.1%) children (<18 years) and 543 (81.9%) adults. Eighty-four (12.7%) of patients were maintained on DFO, 151 (22.8%) on DFP, and 428 (64.6%) on DFX monotherapy during the 10-year observation period. The median dose of DFO (observation period average per individual patient) was 33.7 mg/kg/day (IQR: 29.4.1-39.1, min: 18.9, max: 52.2), of DFP was 81.9 mg/kg/day (IQR: 69.3-87.4, min: 43.5, max: 101.1), and of DFX was 24.7 mg/kg/day (IQR: 19.4-28.9, min: 4.1, max: 44.3). The median compliance for DFO (observation period average per individual patient) was 87.6% (IQR: 75-93, min: 50.4, max: 100), for DFP was 96.9% (IQR: 92.4-98.4, min: 11.1, max: 100), and for DFX was 97.6% (IQR: 95.4-99.1, min: 26.4, max: 100). Comparisons of patients' characteristics between the three iron chelators are summarized in **Table 1**. In general, patients receiving DFO were slightly older and more likely to be female than patients on DFP or DFX. They were also more likely to have an active morbidity at study start than patients on DFP or DFX. Patients on the three iron chelators had comparable annual iron intake from transfusions during the 10-year observation period (**Table 1**).

Changes in iron parameters

Patients on DFO, DFP, and DFX had comparable SF at study start (median *Y_1 SF* DFO: 1104.9 ng/mL; DFP: 1144.6 ng/mL; DFX: 1334.5 ng/mL; *P* = 0.544). Patients on all three iron chelators had a steady and significant decline in SF over the 10 years (median *Absolute Change SF [Y_{10}-Y_1]* DFO: -170.7 ng/mL, *P* = 0.049, DFP: -236.7 ng/mL, *P* = 0.001; DFX: -323.7 ng/mL, *P* <0.001) (**Table 2**, **Figure 1A**). Similar findings were noted when the *First SF* and *Last SF* values were considered for each patient, with a median duration of 10 years in between both values for all three iron chelators (**Table 2**). Median *Absolute Change SF (Y_{10}-Y_1, and Last-First)*, *Relative Change SF (Y_{10}-Y_1, and Last-First)*, and *Normalized Change SF (Last-First)* were comparable between the three iron chelators (*P* ≥0.05 for all) (**Table 2**).

Patients on DFO, DFP, and DFX had slightly different LIC at study start (median *Y_1 LIC* DFO: 2.2 mg/g; DFP: 5 mg/g; DFX: 3 mg/g; *P* = 0.015). Patients on all three iron chelators had no significant change in LIC over the 10 years (median *Absolute Change LIC [Y_{10}-Y_1]* DFO: +0.5 mg/g, *P* = 0.943, DFP: +0.7 mg/g, *P* = 0.400; DFX: +0.8 mg/g, *P* = 0.209), with a trend towards a slight increase (**Table 2**, **Figure 1B**). Similar findings were noted when the *First LIC* and *Last LIC* values were considered for each patient, with a median duration of 4, 3, and 4 years in between both values for DFO, DFP, and DFX, respectively (**Table 2**). Median *Absolute Change LIC (Y_{10}-Y_1, and Last-First)*, *Relative Change LIC (Y_{10}-Y_1, and Last-First)*, and *Normalized Change LIC (Last-First)* were comparable between the three iron chelators (*P* ≥0.05 for all) (**Table 2**).

Patients on DFO, DFP, and DFX had comparable cT2* at study start (median *Y_1 cT2** DFO: 31.1 ms; DFP: 37.9 ms; DFX: 36.9 ms; *P* = 0.198). Patients on all three

iron chelators had no significant change in cT2* over the 10 years (median *Absolute Change cT2* [Y_{10}-Y_1]* DFO: +11.5 ms, *P* = 0.069, DFP: -2.4 ms, *P* = 0.959; DFX: +2.5 ms, *P* = 0.230), with a trend towards an increase in DFO and DFX and a decrease in DFP (**Table 2**, **Figure 1C**). Similar findings were noted when the *First LIC* and *Last cT2** values were considered for each patient, with a median duration of 4, 3, and 4 years in between both values for DFO, DFP, and DFX, respectively (**Table 2**) – while the increase for DFX was statistically significant. Median *Absolute Change cT2* (Y_{10}-Y_1, and Last-First)*, *Relative Change cT2* (Y_{10}-Y_1, and Last-First)*, and *Normalized Change cT2* (Last-First)* were comparable between the three iron chelators (*P* ≥0.05 for all), yet significantly different between DFX and DFP for *Absolute* and *Relative Change cT2* (Last-First)* (**Table 2**).

Transitions in iron overload risk categories (defined based on conventional, literature-based thresholds [40]) between *First* and *Last* values are summarized in **Figure 2A** for SF, **Figure 2B** for LIC, and **Figure 2C** for cT2*. Although overall, patients tended to move to lower SF risk categories across all three iron chelators, transitions were more pronounced and significant for DFX (37.9% to 59.7% for SF <1000 ng/mL and 19.2% to 11.8% for SF >2500 ng/mL; *P* <0.001) but not DFP (44.1% to 56.6% for SF <1000 ng/mL and 16.1% to 14.7% for SF >2500 ng/mL; *P* = 0.051) or DFO (45.3% to 57.3% for SF <1000 ng/mL and 16% to 16% for SF >2500 ng/mL; *P* = 0.119) (**Figure 2A**). Transitions for LIC were not significant for any iron chelator, although the proportion of patients with LIC >7 mg/g tended to substantially decrease for DFO (20% to 13.3%; *P* = 0.801) and less so for DFP (33.6% to 30.6%; *P* = 0.213), while it increased for DFX (17% to 20.2%; *P* = 0.442) (**Figure 2B**). Transitions for cT2* were also not significant for any iron chelator, although the

proportion of patients with cT2* <20 ms decreased for all three iron chelators: DFO (22% to 16.1%; *P* = 0.727), DFP (11.1% to 5.6%; *P* = 0.1000), and DFX (6.8% to 4.3%; *P* = 0.248) (**Figure 2C**).

Changes in laboratory markers of hepatic and renal function

Patients on DFO, DFP, and DFX had comparable ALT at study start (median Y_1 *ALT* DFO: 39.3 IU/L; DFP: 38.3 IU/L; DFX: 34.5 IU/L; *P* = 0.111). Patients on all three iron chelators had a steady and significant decline in ALT over the 10 years (median *Absolute Change ALT* [Y_{10}-Y_1] DFO: -14 IU/L, *P* <0.001, DFP: -10.8 IU/L, *P* <0.001; DFX: -13.4.7 IU/L, *P* <0.001) (**Table 2**, **Figure 1D**). Similar findings were noted when the *First ALT* and *Last ALT* values were considered for each patient, with a median duration of 10 years in between both values for all three iron chelators (**Table 2**). Median *Absolute Change ALT* (Y_{10}-Y_1, *and Last-First)*, *Relative Change ALT* (Y_{10}-Y_1, *and Last-First)*, and *Normalized Change ALT (Last-First)* were comparable between the three iron chelators (*P* ≥0.05 for all) (**Table 2**).

Patients on DFO, DFP, and DFX also had comparable Cr at study start (median Y_1 *Cr* DFO: 0.67 mg/dL; DFP: 0.62 mg/dL; DFX: 0.64 mg/dL; *P* = 0.523). Patients on all three iron chelators had a steady, minimal, yet significant increase in Cr over the 10 years (median *Absolute Change Cr* [Y_{10}-Y_1] DFO: +0.07 mg/dL, *P* <0.001, DFP: +0.05 mg/dL, *P* = 0.400; DFX: +0.06 mg/dL, *P* = 0.209) (**Table 2**, **Figure 1E**). Similar findings were noted when the *First Cr* and *Last Cr* values were considered for each patient, with a median duration of 8 years in between both values for all three iron chelators (**Table 2**). Median *Absolute Change Cr (Last-First)*, *Relative Change Cr (Last-First)*, and *Normalized Change Cr (Last-First)* were significantly different

between the three iron chelators, primarily due to higher median increases in DFX (**Table 2**).

Morbidity and mortality outcomes

All patients were followed for the full 10 years, except for 11 patients who were lost to follow up/transferred outside the Webthal® network, 6 patients who underwent bone marrow transplantation, and 10 (1.5%) patients who died during the observation period. The crude incidence of death was comparable between the three iron chelators (*P* = 0.259), although numerically lower for DFX (n = 4, 0.9%), compared to DFO (n = 2, 2.4%) and DFP (n = 4, 2.6%). Half of the deaths in each chelator group were attributed to cardiovascular disease (**Table 3**). Similarly, the crude incidence of new morbidity (n = 27, 4.1%) was comparable between the three iron chelators (*P* = 0.206), although numerically lower for DFX (n = 13, 3.3%), compared to DFO (n = 6, 7.1%) and DFP (n = 8, 5.3%) (**Table 3**).

Kaplan-Meier survival curves for the composite outcome of morbidity or mortality were comparable between the three iron chelators, although with a significantly shorter survival time for DFO compared with DFX (*P* = 0.037, **Figure 3**). The HR for the outcome of morbidity or mortality was 0.739 (95%CI: 0.297-1.837; *P* = 0.515) for DFP and 0.423 (95%CI: 0.184-0.974; *P* = 0.043) for DFX compared to DFO. Upon adjustment on multivariate Cox regression for age, sex, center of treatment, pretransfusion hemoglobin, annual iron intake, and active morbidity at study start, the association between iron chelator type the composite outcome of morbidity or mortality was no longer significant, and primarily driven by age and center or

treatment: 0.724 (95%CI: 0.286-1.834; *P* = 0.496) for DFP and 0.621 (95%CI: 0.264-1.462; *P* = 0.276) for DFX compared to DFO.

DISCUSSION

Our data generally show that in a real-world setting, there is comparable long-term iron chelation effectiveness between the three available iron chelators DFO, DFP, and DFX as evident from patients who remained on the same monotherapy over a period of 10 years. SF levels showed continuous reduction while LIC and cT2* values remained largely unchanged. These effects may be considered clinically favorable for a regularly transfused patient population that mostly had mild-to-moderate iron overload in the liver and no cardiac siderosis, probably reflecting that iron chelation targets were mostly for maintenance rather than reduction of iron burden. However, a considerable proportion of patients across the three iron chelators (up to ~30%) still had SF >2500 ng/mL, LIC values >7 mg/g, or cT2* values <20 ms at final evaluation, and remain at risk for future morbidity or mortality [38,40-50]. Adherence to oral iron chelation exceeded 90% and iron chelators were used within approved dose levels. For the subset of patients not achieving target iron levels, treatment optimization would need to be considered through higher doses, when feasible, or switching to alternate or combined therapy [40].

Our study is in general agreement with previous real-world data of smaller cohorts from the US, Europe or Asia [34-39], which often showed the ability of the three iron chelators to reduce or maintain iron levels at varying magnitudes, although no common pattern favoring one iron chelator over others could be observed – although

this can be largely attributed to the observational nature of such comparisons, including those in our study, with baseline variations of patient characteristics and iron burden within and between studies. Our study extends observations on iron chelation effectiveness to data on long-term clinical outcomes, by also highlighting general similarity in the risk of morbidity and mortality during iron chelation therapy with any of the three iron chelators.

Reductions in ALT paralleled reductions in SF levels. Although these remained in the normal reference range, they may indicate subclinical improvement in hepatic function in the context of reduced iron overload. The impact of DFX therapy on improvement in liver disease in patients with TDT has been previously reported [51] and earlier concerns of hepatic toxicity effects of DFP have been disputed [52]. Elevations were also noted for Cr, mostly within the normal reference range. Previous long-term studies highlighted some effects of DFX on renal hemodynamics, but these were mild without progressive worsening of renal function over time [53,54].

Our study has some limitations. Findings may not be generalizable to other geographies and primarily reflect patients managed in Western countries with adequate resources. This study also only included patients receiving the same iron chelator monotherapy for the entire 10-year observation period. Accordingly, patients switching iron chelator or on combination therapy due to side effects or lack of efficacy were not included or represented. Subsequently, our cohort mainly included patients with mild-to-moderate hepatic and no cardiac iron overload and could only represent outcomes for patients with similar iron profiles. Additionally, a large

proportion of patients did not have any MRI measurements for hepatic or cardiac iron overload, and this may not necessarily be random as it may reflect patients with lower iron levels that did not require annual follow up [55] – this still, however, reflects real-world disease management decisions. Nonetheless, the subset of patients with available MRI values was still large to present interpretable findings.

Our findings confirm that in the era of modern disease management, the majority of patients with TDT and mild-to-moderate iron overload who are compliant and remained on the same iron chelation monotherapy had adequate long-term iron control irrespective of the type of chelator; while in a subset of patients, treatment optimization is still necessary to achieve safe iron levels. Balancing iron intake with effective iron overload prevention and management is associated with a low morbidity and mortality burden in the TDT patient population.

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Authorship contribution

Study conception and design: KMM, GLF. Data collection: SB, RO, GBF, RL, AP, FL, BG, GLF. Statistical analysis: KMM, BG. Review and interpretation of results: KMM, SB, RO, GBF, RL, AP, FL, BG, GLF. Manuscript drafting: KMM, GLF. Manuscript review for important intellectual content: SB, RO, GBF, RL, AP, FL, BG. All authors approved the manuscript before submission.

Data availability and sharing

Data can be made available upon reasonable request to the corresponding author.

Declaration of competing interest

KMM reports consultancy fees from Novartis, Celgene Corp (Bristol Myers Squibb), Agios Pharmaceuticals, CRISPR Therapeutics, Vifor Pharma, and Pharmacosmos; and research funding from Agios Pharmaceuticals and Pharmacosmos. SB reports being on the advisory board of Vertex Pharmaceuticals and Bristol Myers Squibb and receiving speaker honoraria from Bristol Myers Squibb and Chiesi. RO reports being on the advisory board of Chiesi and Bristol Myers Squibb and consultancy fees from Vertex Pharmaceuticals and Bristol Myers Squibb. GBF reports consultancy fees from Bristol Myers Squibb, Agios Pharmaceuticals, FORMA Therapeutics, Vertex Pharmaceuticals. RL reports receiving speaker honoraria from Bristol Myers Squibb. AP reports receiving speaker honoraria from Bristol Myers Squibb. FL reports being on the advisory board of Vertex Pharmaceuticals and Bristol Myers Squibb. GLF reports receiving speaker honoraria and being on the advisory board Vertex Pharmaceuticals, Bristol Myers Squibb, Hemanext and Garuda Pharmaceuticals. The remaining authors have no relevant financial or non-financial interests to disclose.

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Table 1. Comparisons of patients' characteristics between the three iron chelators.

Parameter	**DFO (n = 84)**	**DFP (n = 151)**	**DFX (n = 428)**	***P*-value**
Age at study start in years, median (IQR)	34.9 (31-39)	32.4 (26.9-36.6)	30.1 (17.5-35.3)	**<0.001**
Age categories in years, n (%)				
<2	2 (2.4)	0 (0)	13 (3)	**<0.001**
2 to <6	1 (1.2)	2 (1.3)	30 (7)	
6 to <12	1 (1.2)	3 (2)	38 (8.9)	
12 to <18	0 (0)	4 (2.6)	26 (6.1)	
≥18 years	80 (95.2)	142 (94)	321 (75)	
Female, n (%)	46 (54.8)	60 (39.7)	225 (52.6)	**0.016**
Pretransfusion Hb in g/dL*, median (IQR)	9.8 (9.5-10.1)	9.8 (9.5-10.1)	9.7 (9.4-9.9)	**0.005**
Annual iron intake in mg*, median (IQR)	7762.5 (5999.8-8863.7)	7628 (6424.6-9604.5)	7212.5 (5866.4-9101.8)	0.114
Active morbidity at study start, n (%)				
Any	22 (26.2)	26 (17.2)	65 (15.2)	**0.049**
Heart failure	15 (17.9)	12 (7.9)	51 (11.9)	0.077
Cardiac arrythmia	0 (0)	0 (0)	0 (0)	-
Liver fibrosis or cirrhosis	4 (4.8)	1 (0.7)	0 (0)	**<0.001**
Hepatocellular carcinoma	0 (0)	0 (0)	1 (0.2)	0.760
Diabetes mellitus	6 (7.1)	16 (10.6)	19 (4.4)	**0.024**

*Observation period average. DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Table 2. Comparisons of changes in iron parameters and hepatic/renal function measures over 10 years between the three iron chelators.

Parameter	DFO (n = 84)		DFP (n = 151)		DFX (n = 428)		*P*-value			
							DFO vs DFP vs DFX	***DFO vs DFP***	***DFO vs DFP***	***DFP vs DFX***
	n	**median (IQR)**	**n**	**median (IQR)**	**n**	**median (IQR)**				
SF										
Y_1 (ng/mL)	74	1104.9 (618.6-2046.1)	135	1144.6 (676-2050)	346	1334.5 (743.4-2188.2)	0.544	0.890	0.401	0.377
Y_{10} (ng/mL)	73	773.1 (328.3-1949)	138	821.2 (408.7-1801.8)	374	733.1 (405.2-1313.5)	0.775	0.629	0.874	0.494
Absolute Change (Y_{10}-Y_1) (ng/mL)	65	-170.7 (-700-276.5)	125	-236.7 (-667.5-112.3)	316	-323.7 (-983.1-162.2)	0.245	0.692	0.149	0.244
Relative Change (Y_{10}-Y_1) (%)	65	-24.5 (-55.7-19.3)	125	-26.5 (-53.8-21.5)	316	-30.5 (-63.1-22)	0.580	0.939	0.403	0.421
Y_1 vs Y_{10} *P*-value	**0.049**		**0.001**		**<0.001**					
Period Average (ng/mL)	84	978.1 (590.1-1970.3)	151	1066.7 (601.6-1858)	413	1067.5 (606.7-1860.8)	0.879	0.898	0.723	0.669
Duration between First and Last (years)	84	10 (8-10)	151	10 (9-10	413	10 (9-10)	0.493	0.248	0.521	0.398
First (ng/mL)	84	1064.9 (593.1-1986.1)	151	1130 (609.5-2050)	413	1275 (669.7-2184.4)	0.543	0.692	0.319	0.497
Last (ng/mL)	75	791.7 (388.1-2033.8)	143	833.7 (420.3-1772.3)	380	795.2 (435.5-1587.7)	0.978	0.884	0.823	0.981
Absolute Change (Last-First) (ng/mL)	75	-158.4 (-668.2-238.6)	143	-191 (-674.7-117.5)	380	-315.6 (-971.1-179.8)	0.214	0.567	0.113	0.273
Relative Change (Last-First) (%)	75	-23.4 (-52-19.2)	143	-22.7 (-052.7-20.6)	380	-30.1 (-62.4-24.3)	0.538	0.789	0.345	0.434
Normalized Change (Last-First) (ng/mL)	75	-15.8 (-74.2-31.4)	143	-23.7 (-70.7-13.1)	380	-32.9 (-110.3-20)	0.161	0.497	0.082	0.246
First vs Last *P-value*	**0.047**		**0.001**		**<0.001**					
LIC										

Y_1 (mg/g)	14	2.2 (1.5-4.1)	24	5 (2.3-11.3)	57	3 (1.6-5.5)	**0.015**	**0.011**	0.288	**0.016**
Y_{10} (mg/g)	16	2.7 (1.8-5.5)	23	4.7 (2.1-9.5)	68	2.9 (1.8-6.1)	0.216	0.143	0.829	0.107
Absolute Change (Y_{10}-Y_1) (mg/g)	8	0.5 (-0.3-1.9)	9	0.7 (-6.9-6)	20	0.8 (-1.4-6)	0.808	1.000	0.746	0.532
Relative Change (Y_{10}-Y_1) (%)	8	25.7 (-14.6-62.5)	9	38.7 (-71.9-184.6)	20	46.5 (-38.3-215.7)	0.692	0.743	0.746	0.417
Y_1 vs Y_{10} *P*-value	0.655		1.000		0.059					
Period Average (mg/g)	37	2.9 (1.7-5.6)	68	4.9 (2.4-8.2)	201	3 (1.9-5.6)	**0.002**	**0.012**	0.722	**0.001**
Duration between First and Last (years)	37	4 (2-6)	68	3 (1-5)	201	4 (2-5)	0.289	0.134	0.240	0.395
First (mg/g)	37	2.4 (1.6-5.5)	68	4.6 (2.1-9.2)	201	2.7 (1.5-6.1)	**0.009**	**0.025**	0.830	**0.003**
Last (mg/g)	30	2.4 (1.7-4.9)	49	4.3 (2.1-9.1)	153	2.8 (1.7-6.1)	**0.012**	**0.010**	0.424	**0.009**
Absolute Change (Last-First) (mg/g)	30	-0.1 (-0.7-1.5)	49	0.2 (-1.4-1.6)	153	0.3 (-1.1-1.8)	0.803	0.476	0.578	0.866
Relative Change (Last-First) (%)	30	-6.6 (-33.1-62.9)	49	4.2 (-30.4-85.2)	153	9.3 (-38.6-75.9)	0.867	0.565	0.635	0.954
Normalized Change (Last-First) (mg/g)	30	-0.03 (-0.26-0.28)	49	0.05 (-0.38-0.51)	153	0.07 (-0.25-0.39)	0.618	0.342	0.365	0.932
First vs Last *P-value*	0.943		0.400		0.209					
cT2*										
Y_1 (ms)	15	31.1 (18-36)	26	37.9 (29.9-43.4)	62	36.1 (27.5-43.9)	0.198	0.101	0.095	0.794
Y_{10} (ms)	16	38.4 (24.3-43.6)	25	38.2 (33.7-42.1)	70	39.1 (32.9-43.3)	0.766	0.831	0.461	0.731
Absolute Change (Y_{10}-Y_1) (ms)	8	11.5 (3.4-16.6)	10	-2.4 (-8.5-23.8)	24	2.5 (-3.6-13.1)	0.427	0.360	0.220	0.696
Relative Change (Y_{10}-Y_1) (%)	8	48.6 (10.4-100.9)	10	-5.4 (-17.8-131.2)	24	7.7 (-8.4-47.3)	0.293	0.360	0.113	0.642
Y_1 vs Y_{10} *P*-value	0.069		0.959		0.230					
Period Average (ms)	43	35 (26.4-41)	77	39 (33.1-42.7)	215	37.1 (31-42.4)	0.087	**0.033**	0.081	0.307
Duration between First and Last (years)	43	4 (1-5)	77	3 (1-5)	215	4 (2-5)	0.647	0.427	0.692	0.438
First (ms)	43	32 (28.3-41.1)	77	39 (32.7-44)	215	36 (29.8-43)	0.055	**0.033**	0.148	0.086

Last (ms)	31	36.5 (26.5-43.1)	54	39.1 (34.2-43.6)	162	39 (32.3-44.4)	0.204	0.143	0.083	0.749
Absolute Change (Last-First) (ms)	31	1.6 (-5.6-8.7)	54	-1.6 (-8.9-4.5)	162	2.1 (-4.2-7.9)	0.104	0.320	0.611	**0.032**
Relative Change (Last-First) (%)	31	3.6 (-25.5-38.9)	54	-5 (-18.5-14.3)	162	7 (-9.8-24.3)	0.135	0.460	0.666	**0.040**
Normalized Change (Last-First) (ms)	31	0.25 (-1.76-1.53)	54	-0.47 (-2.22-1.8)	162	0.56 (-1.24-1.85)	0.159	0.648	0.444	0.057
First vs Last *P-value*	0.610		0.278		**0.017**					
ALT										
Y_1 (IU/L)	74	39.3 (23.8-79.9)	135	38.3 (27.5-63.7)	345	34.5 (20.7-61.3)	0.111	0.687	0.117	0.091
Y_{10} (IU/L)	73	19.7 (15.5-28)	132	22.7 (16.4-39.3)	368	19.5 (14.6-28.7)	**0.009**	0.163	0.424	**0.002**
Absolute Change (Y_{10}-Y_1) (IU/L)	65	-14 (-44.4-[-]1.6)	121	-10.8 (-31.9-0)	312	-13.4 (-39.3-[-]0.6	0.608	0.518	0.922	0.327
Relative Change (Y_{10}-Y_1) (%)	65	-40.7 (-78.1-[-]5.6)	121	-31.8 (-60.9-0)	312	-40.9 (-66.5-[-]3.1)	0.460	0.452	0.922	0.216
Y_1 vs Y_{10} *P*-value	**<0.001**		**<0.001**		**<0.001**					
Period Average (IU/L)	84	31.9 (20.6-61.6)	149	35.2 (24.6-56.9)	410	26.5 (18.9-41.6)	**<0.001**	0.467	0.016	**<0.001**
Duration between First and Last (years)	84	10 (8-10)	149	10 (9-10)	410	10 (8-10)	0.763	0.466	0.571	0.736
First (IU/L)	84	37.5 (19.8-76.1)	149	37.4 (26.8-61.9)	410	31.1 (18.4-56.4)	**0.010**	0.878	0.051	**0.007**
Last (IU/L)	76	22.2 (16-38)	144	23.2 (16.4-40.1)	381	19.5 (14.5-29.8)	**0.002**	0.601	**0.044**	**0.001**
Absolute Change (Last-First) (IU/L)	76	-12.6 (-41.4-0.8)	144	-10.1 (-26.2-[-]0.7)	381	-11.7 (-36.3-1.1)	0.782	0.574	0.896	0.519
Relative Change (Last-First) (%)	76	-37.2 (-66.7-1.7)	144	-28.1 (-58.5-[-]1.9)	381	-37.2 (-64.4-5.4)	0.627	0.608	0.903	0.331
Normalized Change (Last-First) (IU/L)	76	-1.4 (-4.4-0.1)	144	-1.3 (-3.1-[-]0.1)	381	-1.2 (-4-0.2)	0.884	0.661	0.811	0.696
First vs Last *P-value*	**<0.001**		**<0.001**		**<0.001**					
Cr										
Y_1 (mg/dL)	73	0.66 (0.55-0.75)	132	0.62 (0.55-0.72)	338	0.64 (0.5-0.75)	0.523	0.378	0.258	0.844
Y_{10} (mg/dL)	42	0.67 (0.60-0.75)	85	0.68 (0.55-0.8)	248	0.7 (0.6-0.85)	0.094	0.980	0.127	0.069

Absolute Change (Y_{10}-Y_1) (mg/dL)	39	0.07 (0-0.15)	75	0.05 (-0.03-0.14)	207	0.06 (0.01-0.17)	0.263	0.393	0.694	0.106
Relative Change (Y_{10}-Y_1) (%)	39	13.1 (0-29)	75	6.7 (-4.8-22)	207	10.5 (1.1-27.8)	0.188	0.245	0.898	0.072
Y_1 vs Y_{10} *P*-value	**<0.001**		**<0.001**		**<0.001**					
Period Average (mg/dL)	78	0.64 (0.55-0.74)	147	0.64 (0.56-0.73)	391	0.66 (0.54-0.8)	0.617	0.839	0683	0.331
Duration between First and Last (years)	78	8 (5-10)	147	8 (5-10)	391	8 (6-10)	0.722	0.667	0.434	0.714
First (mg/dL)	78	0.64 (0.53-0.74)	147	0.62 (0.55-0.72)	391	0.64 (0.5-0.75)	0.662	0.591	0.370	0.727
Last (mg/dL)	74	0.7 (0.6-0.82)	144	0.68 (0.57-0.8)	378	0.69 (0.58-0.83)	0.637	0.470	0.939	0.369
Absolute Change (Last-First) (mg/dL)	74	0.04 (-0.03-0.12)	144	0.02 (-0.04-0.13)	378	0.06 (0-0.16)	**0.017**	0.728	0.114	**0.008**
Relative Change (Last-First) (%)	74	5.5 (-4.5-23.3)	144	4.1 (-5.2-20.1)	378	11.1 (-0.3-29.4)	**0.006**	0.567	0.106	**0.002**
Normalized Change (Last-First) (mg/dL)	74	0.01 (0-0.02)	144	0 (0-0.02)	378	0.01 (0-0.02)	**0.021**	0.786	0.105	**0.011**
First vs Last *P-value*	**0.002**		**<0.001**		**<0.001**					

Hb, hemoglobin; SF, serum ferritin; LIC, liver iron concentration; cT2*, cardiac T2*; ALT, alanine aminotransferase; Cr, serum creatinine; IQR, interquartile range; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Table 3. Comparisons of morbidity and mortality outcomes over 10 years between the three iron chelators.

Parameter	DFO (n = 84)	DFP (n = 151)	DFX (n = 428)	*P*-value			
				DFO vs DFP vs DFX	***DFO vs DFP***	***DFO vs DFP***	***DFP vs DFX***
Status at last observation, n (%)				0.259	0.901	0.260	0.121
Alive	82 (97.6)	147 (97.4)	424 (99.1)				
Completed 10-year observation	80 (95.2)	143 (94.7)	413 (96.5)				
Transplant	1 (1.2)	0 (0)	5 (1.2)				
Transferred	1 (1.2)	3 (2)	5 (1.2)				
Lost to follow up	0 (0)	1 (0.7)	1 (0.2)				
Dead	2 (2.4)	4 (2.6)	4 (0.9)				
Cardiovascular disease-related	1 (1.2)	2 (1.3)	2 (0.5)				
Other cause	1 (1.2)	2 (1.3)	2 (0.5)				
New morbidity development, n (%)				0.206	0.567	0.094	0.263
Any	6 (7.1)	8 (5.3)	14 (3.3)				
Heart failure	0 (0)	0 (0)	3 (0.7)				
Cardiac arrythmia	1 (1.2)	2 (1.3)	0 (0)				
Liver fibrosis or cirrhosis	3 (3.6)	4 (2.6)	3 (0.7)				
Hepatocellular carcinoma	0 (0)	1 (0.7)	0 (0)				
Diabetes mellitus	3 (3.6)	2 (1.3)	8 (1.9)				

DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

FIGURE LEGENDS

Figure 1. Serial (annual) changes in iron parameters and hepatic/renal function measures for the three iron chelators. (A) SF, **(B)** LIC, **(C)** cT2*, **(D)**, ALT, **(E)** Cr. SF, serum ferritin; LIC, liver iron concentration; cT2*, cardiac T2*; ALT, alanine aminotransferase; Cr, serum creatinine; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Figure 2. Transitions in the distribution of iron overload risk categories between *First* and *Last* values for all three iron chelators. (A) SF, **(B)** LIC, **(C)** cT2*. SF, serum ferritin; LIC, liver iron concentration; cT2*, cardiac T2*; DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Figure 3. Kaplan-Meier survival curves for the composite outcome of morbidity or mortality. DFO, deferoxamine; DFP, deferiprone; DFX, deferasirox.

Figure 1


(A)
Median SF (ng/mL)
1,334.5
1,144.6
1,104.9
821.2
773.1
733.1
Year
P-value
DFO 74 69 72 69 70 60 68 67 70 73 0.049
DFP 135 132 137 135 136 123 124 128 128 138 0.001
DFX 346 346 361 358 358 323 338 348 348 374 <0.001
(B)
Median LIC (mg/g)
5.0
3.0
2.2
4.7
2.9
2.7
Year
P-value
DFO 14 9 19 18 16 16 11 20 13 16 0.655
DFP 24 24 23 25 20 19 24 23 24 23 1.000
DFX 57 64 66 82 97 67 67 92 63 68 0.059
(C)
Median cT* (ms)
37.9
36.1
31.1
39.1
38.4
38.2
Year
P-value
DFO 15 10 23 21 18 16 11 20 15 16 0.069
DFP 26 29 35 29 21 19 27 26 26 25 0.959
DFX 62 71 79 94 98 66 73 93 69 70 0.230
(D)
Median ALT (IU/L)
39.3
38.3
34.5
22.6
19.7
19.5
Year
P-value
DFO 74 69 72 69 70 60 66 67 70 73 <0.001
DFP 135 134 137 136 134 120 121 128 127 132 <0.001
DFX 345 346 362 358 358 323 330 342 343 368 <0.001
(E)
Median Cr (mg/dL)
0.67
0.64
0.62
0.70
0.68
0.66
Year
P-value
DFO 73 69 71 68 70 51 44 44 44 42 <0.001
DFP 132 132 136 135 132 96 89 87 85 85 <0.001
DFX 338 344 359 358 356 265 263 243 227 248 <0.001

Figure 2

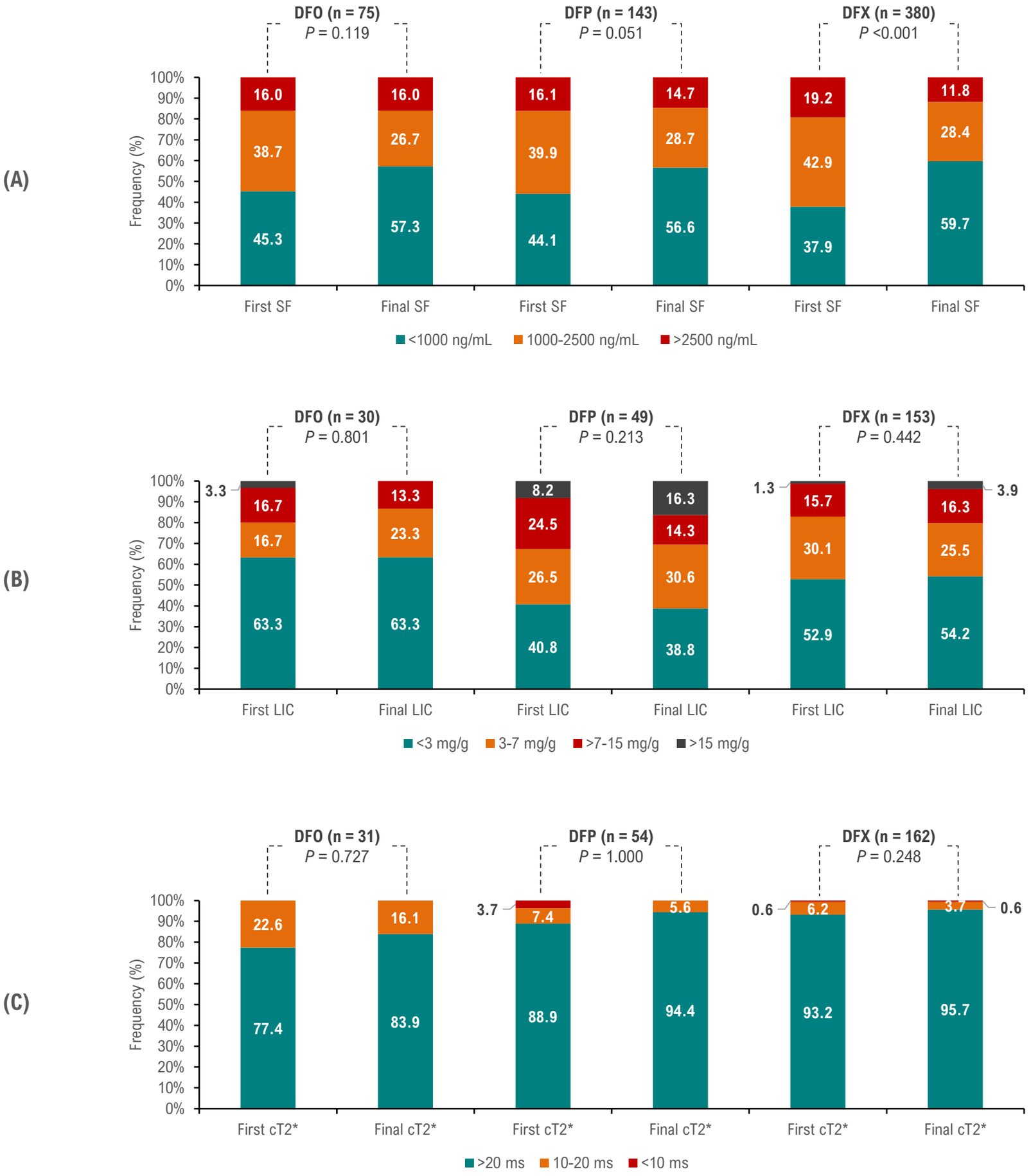
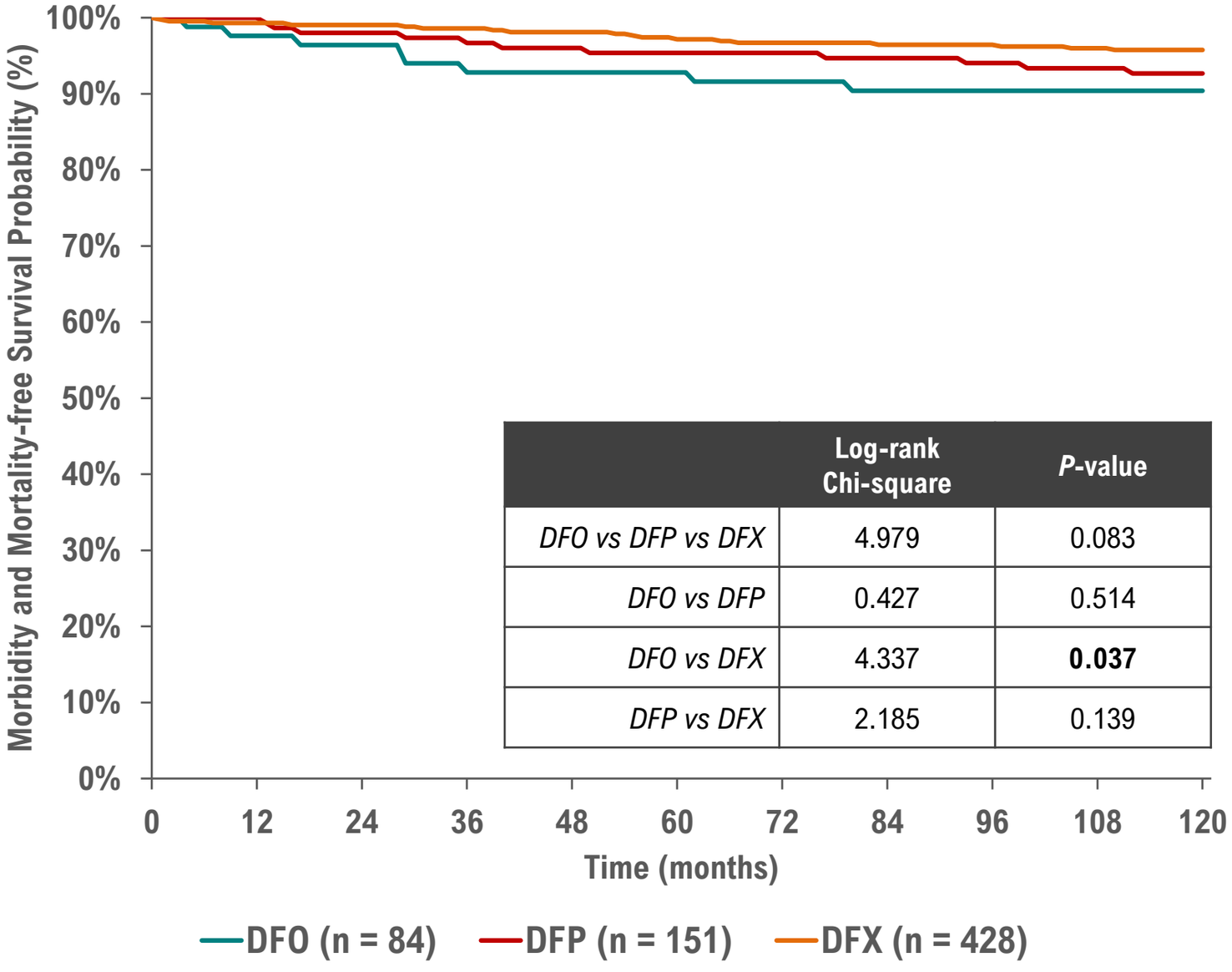

(A)
DFO (n = 75)
P = 0.119
DFP (n = 143)
P = 0.051
DFX (n = 380)
P <0.001
Frequency (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
16.0
38.7
45.3
16.0
26.7
57.3
16.1
39.9
44.1
14.7
28.7
56.6
19.2
42.9
37.9
11.8
28.4
59.7
First SF
Final SF
First SF
Final SF
First SF
Final SF
<1000 ng/mL
1000-2500 ng/mL
>2500 ng/mL
(B)
DFO (n = 30)
P = 0.801
DFP (n = 49)
P = 0.213
DFX (n = 153)
P = 0.442
Frequency (%)
3.3
16.7
16.7
63.3
13.3
23.3
63.3
8.2
24.5
26.5
40.8
16.3
14.3
30.6
38.8
1.3
15.7
30.1
52.9
16.3
25.5
54.2
3.9
First LIC
Final LIC
First LIC
Final LIC
First LIC
Final LIC
<3 mg/g
3-7 mg/g
>7-15 mg/g
>15 mg/g
(C)
DFO (n = 31)
P = 0.727
DFP (n = 54)
P = 1.000
DFX (n = 162)
P = 0.248
Frequency (%)
22.6
77.4
16.1
83.9
3.7
7.4
88.9
5.6
94.4
0.6
6.2
93.2
3.7
95.7
0.6
First cT2*
Final cT2*
First cT2*
Final cT2*
First cT2*
Final cT2*
>20 ms
10-20 ms
<10 ms

Figure 3



	Log-rank Chi-square	*P*-value
DFO vs DFP vs DFX	4.979	0.083
DFO vs DFP	0.427	0.514
DFO vs DFX	4.337	**0.037**
DFP vs DFX	2.185	0.139