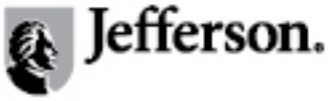

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Long-term persistency and costs associated with the use of iron chelation therapies in the treatment of Sickle cell disease within Medicaid programs.

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Abstract (250 word maximum as a single paragraph)

This study evaluated iron chelating therapy discontinuation and costs in Medicaid recipients with Sickle cell disease (SCD). This retrospective study evaluated healthcare claims from 2006 to 2010. Patients with ≥ 1 SCD diagnosis claim, ≥2 claims for deferoxamine (DFO) or deferosirox (DFX), and continuous enrollment ≥6 months prior to and 18 months following iron chelation therapy (ICT) initiation were included. Outcomes included treatment discontinuation, adherence and persistence (i.e., medication possession ratio (MPR), refill gaps ≥6 weeks) and total healthcare costs. The average age among 404 SCD patients meeting study inclusion criteria was 18.7 (±11.0) years with 45.8% being males and 66.7% were African Americans. Switches from DFO to DFX occurred in 29.0% (n =117) of patients, while 2.2% (n =9) switched from DFX to DFO. The Cox regression assessing long-term medication persistency indicated a 1.30 times higher likelihood of treatment discontinuation with DFO compared to DFX (95% CI: 1.06-1.61). Some 19.7% of patient remained on DFX relative to 4.8% on DFO. Rates of SCD crises related hospitalizations and total costs were similar in DFX-only and DFO-only treatment groups. Following one year of treatment, 37.4% remained on DFX compared to 15.7% on DFO. Meaningful differences in treatment discontinuation between the two treatment groups did not occur until 220+ days during the study period. At 18-months, treatment discontinuation rates were high in both groups; 95% for DFO and 80% for DFX. This study of SCD Medicaid patients found more therapeutic switches from DFO to DFX and a higher medication persistency rate with DFX than DFO.

Introduction

Sickle cell disease (SCD) is an inherited disorder of the blood that leads to the production of an abnormal sickle hemoglobin and manifests as hemolysis and red blood cell rigidity and endothelial adhesion, wherein abnormal red blood cells may agglomerate and block blood from flowing to organs and tissues [1, 2]. Within the United States alone, SCD has been recently reported to affect between 88,494 to 89,664 persons of which 80,151 were black and 8,928 were Hispanic [3]. The total fees (charges) for 50 years of life expectancy for SCD patients have been estimated to be as much as $8.7 million per patient [4].

The key clinical manifestations of SCD include recurrent acute painful crises, fatigue, hemolytic anemia, and chronic organ damage especially to the heart, lung, spleen, kidneys, bones, brain, skin, muscle, liver, and biliary tract [1, 2, 5]. Persons with SCD are hence subject to an increased prevalence of stroke, occlusive disease, acute chest syndrome, and immunologic or infectious conditions [1, 6]. The prevention of early complications remains central to the treatment of SCD [7, 8]. Although transfusion therapy is recommended in persons with SCD that express anemic signs and symptoms, multiple red blood cell transfusions may produce iron overload, potentially leading to cellular damage and organ failure [2, 7-9].

SCD patients requiring blood transfusions have been shown to be hospitalized more frequently than SCD patients not requiring transfusions [10]. Multiple blood transfusions chronically may lead to excessive accumulation of iron [11]. SCD patients with iron overload may be at increased risk to develop organ failure compared to patients with normal iron stores. In addition, a positive relationship has been shown that higher ferritin levels were associated with more frequent hospitalizations [10]. Adult SCD patients requiring transfusions were 1.4 times more likely to be hospitalized than pediatric SCD patients.

Iron-chelation therapies (ICTs) help to eliminate iron overload by binding with labile plasma iron to form non-toxic conjugates that can be safely excreted from the body. These treatments are often necessary in persons requiring long-term red-cell transfusions, including those with sickle cell disease, thalassemia major, or myelodysplastic syndromes [9]. Specific guidelines and consensus statements for SCD explicitly address ICT use for iron overload associated with transfusions, wherein prophylactic therapy is generally preferred among those requiring chronic transfusions [7-9]. Deferoxamine (DFO) (Desferal®, Novartis) is a parenterally-administered siderophore whose feroxamine complex is excreted primarily by the kidneys; it is most often administered via a portable pump for 8-10 hours each day from 5-7 days per week [9, 12]. Approved in 2005, deferasirox (DFX) (Exjade®, Novartis) is an orally-administered chelator that forms a complex with plasma iron that is excreted in the bile [12]. Due in part to its once-a-day dosing and oral administration route, research has found that DFX is associated with improved health-related quality of life (HRQOL), medication adherence, and patient satisfaction [13-15]. A third chelating agent, deferiprone (Ferriprox®, Apotex; Kelfer®, Cipla), was recently approved in the U.S. for persons with thalassemia major when the therapeutic response to current chelation therapy is inadequate [9, 16].

Limited empirical research has sought to investigate the long-term persistency of ICTs, and many initial investigations relied upon subjective measures of medication adherence [15]. Furthermore, even though pharmacoeconomic investigations of DFX have found that the treatment is cost-effective relative to DFO, little attention has focused in the scientific literature upon actual, real-world expenditures associated with both DFO and DFX [12, 15, 17-22]. Given that patients with SCD that receive chronic blood transfusions require ICTs, good adherence is intuitively warranted to avoid morbidity and mortality associated with iron overload. As such, the purpose of this study was to evaluate ICT persistency and costs in Medicaid beneficiaries across 10 states in the U.S. from 2006 to 2010.

Methods

Data. This retrospective cohort study investigated persistency and costs among Medicaid recipients from 2006 to 2010 that were present within the Thomson Reuters Medicaid Marketscan database. These multiyear longitudinal data, collected across 10 states in the U.S., include comprehensive hospital inpatient and outpatient medical claims, outpatient prescription drug claims, and Medicaid enrollment and eligibility information for approximately 6 million beneficiaries.

Study sample. Patients included in this study had one or more diagnosis of SCD as identified by an International Classification of Disease, 9th edition, Clinical Manifestation (ICD-9-CM) code of 282.6x, two or more claims for ICT medications (i.e., DFO or DFX), and continuous enrollment for at least 6 months prior to ICT initiation through 18 months follow up period . Thus, the study's index date was defined to correspond with first ICT prescription claim and the 6-month pre-index period was employed to measure relevant baseline patient characteristics. Although the study's entire time frame spanned five years, subjects were included only if they were continuously eligible to receive Medicaid benefits for 24 months study period (i.e., 6-months pre-index and 18-months post-index). Based on the ICT exposure, patients were classified in 3 groups: patients treated with DFO only, patients treated with DFX only, and those switching from DFO to DFX.

Outcomes assessed. The principal outcomes analyzed within the current study included: 1) total direct healthcare costs associated with SCD related complications from the perspective of the payer for the 18-month time period following ICT treatment initiation. A hematologist provided a list of specific SCD-related complications and the database was searched to identify patients with ICD-9 codes for these complications. 2) persistence with ICTs, defined as time to discontinuation of treatment according to a 6 week or greater medication refill gap. Notably, in determining ICT persistence based upon a refill gap of 6 weeks or more, a medication possession ratio (MPR) was first measured according to Steiner and Prochazka, defined as the total days of drug supply for each ICT, divided by the number of days between the first and last dispensing of the medication plus the days' supply of last dispensing [23]. The

utilization of ICTs was captured using National Drug Classification codes (NDC) across all cohorts of DFO and DFX use; procedural codes (i.e., Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS)) were also employed for DFO given its route of administration. Other variables measured were age (including an age categorization of 18 years or older), sex, race/ethnicity (i.e., African American, Hispanic, White, other), number of transfusion episodes based upon the number of transfusion days observed, capitated Medicaid coverage, Deyo-Charlson Comorbidity Index as a validated measure of comorbid disease severity, 6-month pre-index baseline total healthcare costs, and other cost categories (i.e., hospitalization, outpatient, medication) [24, 25]. Multiple transfusion claims occurring on a single day were counted only once to calculate number of transfusion episodes for each patient. ICT medication switches from DFO to DFX and vice a versa were also assessed during the study period.

Statistical Analysis. Descriptive statistics were presented overall and for three cohorts of ICT medication use: 1) DFO-only; 2) DFX-only; and 3) combination ICT treatment, including switches. A Kaplan-Meier curve was employed to graphically present crude treatment discontinuations, with a log-rank test for equality of survivor functions employed to assess group differences between DFO and DFX. Subsequently, a Cox proportional hazards regression model was used to evaluate the risk of treatment discontinuation associated with DFO and DFX after controlling for covariates including age (i.e., 18 years or older), sex, Deyo-Charlson Comorbidity Index, number of baseline transfusion episodes, and capitated Medicaid coverage. The outcome of healthcare costs in the 18-month study period following ICT treatment initiation was assessed via generalized linear models (i.e., gamma distribution family with log link) using maximum likelihood estimation and controlling for the aforementioned predictor variables plus baseline pre-ICT healthcare costs [26]. A post-hoc sensitivity analysis was additionally conducted for this gamma regression to include the number of continuous days of ICT medication use as an offset variable to adjust for potentially differential exposures. Results of both the Cox and gamma regressions

yielded relative risk measures, denoted a hazard ratio or *exp(b)*, respectively. Residual diagnostics were conducted to assess model fit for both the Cox regression (e.g., Schoenfeld and Martingale residuals) and the gamma regression (e.g., Anscombe residuals); deviances were also assessed. Statistical significance for all inferential analyses was assessed using an *a priori* alpha level of 0.05.

Results

Overall, 404 Medicaid enrollees met the study's inclusion criteria; complete baseline descriptive information is presented in Table 1. Across all individuals, the average age was 18.7 (±11.0) years with 44.8% (n = 181) being 18 years of age or older. Males comprised 45.8% (n = 185), and 66.7% (n = 269) were African Americans. A majority (62.4%, n=252) were enrolled within capitated Medicaid coverage plans. The DFO-only group comprised 10.4% (n = 42) of the study participants versus 56.4% (n = 228) for the DFX-only group overall; individuals whose therapy was switched over time and received a combination of DFO and DFX comprised the remaining 33.2% (n = 134). The number of blood transfusions in the baseline period was 2.3 (±2.6), 2.7 (±3.3), 4.0 (±3.2), and 3.1 (±3.3) in the DFO-only, DFX-only, combination DFO-DFX, and overall, respectively.

Blood transfusions in the post-index period averaged 6.6 (±8.4), 8.9 (±10.3), and 13.0 (±9.4) for DFO-only, DFX-only, or combinations, respectively. DFO-only and DFX-only did not differ (p=0.373); however, combination therapy had higher transfusion episodes than both DFO-only and DFX-only groups (p<0.001).

Persistency and Treatment Discontinuation Analysis

Figure 1 shows the Kaplan-Meier graph of treatment discontinuations indicated that long-term persistency was low. Bivariate analysis showed that treatment discontinuation significantly differed between DFO and DFX (p = 0.004), and meaningful differences did not appear to occur until over seven months into the study period. After 12 months, 15.7% remained on DFO compared to 37.4% on DFX, decreasing 4.8% for DFO and 19.7% for DFX at 18 months. Overall, the average treatment duration

across the 18-month study period was 6.5 (±4.8) months for DFO and 7.6 (±6.5) months for DFX (p = 0.041). Concerning changes in patterns of medication use during this 18-month study period, switches from DFO to DFX occurred in 29.0% (n = 117) of patients, while 2.2% (n = 9) switched from DFX to DFO. Compared to the pre-ICT period, the number of transfusion episodes increased in all three cohorts during the 18-month treatment period, with the mean difference being +4.3 in the DFX-only group, +6.2 in the DFO-only group, and +9.0 in the combination treatment group.

The Cox proportional hazards regression that assessed long-term treatment discontinuation after controlling for various predictors indicated a significant 1.305 times higher likelihood of treatment discontinuation with DFO compared to DFX (95% CI: 1.059-1.607, p = 0.012). Persons 18 years of age or older were significantly associated with a 1.304 times likelihood of treatment discontinuation (95% CI: 1.059-1.605, p = 0.013). Other predictors were not significantly associated with treatment discontinuation (i.e., number of transfusion episodes, male sex, capitated Medicaid coverage, Deyo-Charlson comorbidity index). The full results of the Cox regression are presented in Table 2.

Cost Analysis

The average unadjusted total healthcare costs per patient per month (PMPM) 6-month pre-ICT baseline and 18-month study period costs are presented in Table 3. Across the overall sample, average total pre-ICT costs were $4,988 (±7,592) PMPM, or $29,927 (±45,554) per patient during the 6-month baseline period. The average total study period costs were $6,532 (±8,575) PMPM, or $117,569 (±154,348) during the 18 month post-index study period. Compared to the pre-ICT period, mean monthly costs across the three descriptive cohorts during the 18-month treatment period changed, with the mean average PMPM difference being $775 reduction in the DFO-only group, $2,314 increase in the DFX-only group, and $960 increase in the combination treatment group.

The gamma regression presented in Table 4 found that significant predictors of total healthcare costs included the number of baseline pre-index transfusion episodes, age of 18 years or older, Deyo-

Charlson comorbidity index, and baseline pre-ICT healthcare costs. The number of pre-index blood transfusion episodes was associated with higher costs by a factor of 1.028 (95% CI: 1.001-1.053, p = 0.021) higher costs. Age greater than 18 years was associated with higher costs by a factor of 1.559 (95% CI: 1.308-1.859, p < 0.001). The Charlson Comorbidity Index, Deyo modification (a measure of comorbidities) was associated with higher costs by a factor of 1.100 (95% CI: 1.021-1.185, p = 0.012). Lastly, healthcare costs in the baseline period were associated with higher costs by a factor of 1.011 (95% CI: 1.001-1.014, p < 0.001). The use of DFO versus DFX was not significantly associated with overall healthcare costs, nor was male sex or capitated Medicaid coverage. Results of the post-hoc sensitivity analysis that controlled for the number of continuous days of ICT medication exposure across the 18-month study period as an offset variable yielded consistent results wherein no significant differences were noted in total healthcare costs between DFO versus DFX (*exp(b)* = 1.163, 95% CI: 0.632-2.138, p = 0.628). This post-hoc analysis was conducted, in part, due to the earlier observation that the unadjusted average treatment durations of DFO versus DFX were statistically different, and hence suggestive of different exposures which could have been associated with changes in total healthcare costs.

Discussion

Using a national database of Medicaid enrollees across 10 states in the U.S., this study assessed the 18-month persistency and direct costs associated with the use of DFO and DFX in the treatment of SCD. For the 404 beneficiaries that met the study's inclusion criteria between 2006 and 2010, treatment discontinuation was high and statistically different at 95.2% for DFO versus 80.3% for DFX (p = 0.004). After controlling for several predictors (i.e., age category, transfusion episodes, sex, capitated Medicaid coverage, Deyo-Charlson comorbidity index), a Cox proportional hazard regression found DFO use to be significantly associated with a 1.305 times higher likelihood of treatment discontinuation relative to DFX (p = 0.012). These findings become particularly relevant when also considering results of the multivariate cost analysis, which indicated that no significant difference was present in total healthcare

costs between DFO and DFX after controlling for various predictors. Rather, significant associations with total healthcare costs were found with baseline transfusion episodes, age category, baseline costs, and case-mix comorbid risk adjustment.

Although other authors have broadly investigated adherence to ICTs and costs of SCD based across various settings and populations, the current study extends these findings by assessing the comparative, real-world patterns of care surrounding the persistence and costs specifically associated with parenteral versus oral ICTs. Grosse et al. (2010) articulated the importance of using large administrative datasets in addressing health services research for hemoglobinopathies, including SCD, particularly in the objective measurement of cost and resource utilization outcomes. To the authors' knowledge, the current study represents the first investigation to also comprehensively evaluate real-world direct medical costs according to either DFO or DFX utilization.

Early investigations of ICT adherence were conducted using subjective physician observations or patient self-assessments. Therein, Gabutti and Piga reported an average adherence of 64% for DFO over a 30-year time horizon, while Weissman et al. reported that 62% of persons with thalassemia or SCD were adherent to DFO treatment [27, 28]. In more closely-related work comparing patterns of use with DFO and DFX, Trachtenberg et al. measured adherence through patient self-reports and medical chart reviews from 2007-2009 among 265 individuals on DFO or DFX [29]. Results for the short-term nonadherence at one month were low, at 8% for DFO and 3% for DFX, though these values worsened with age; comparative results for treatment discontinuations in the current study using claims data were 17% for DFO and 15% for DFX. Alvarez et al. reported via pill counts and patient self-reports that 29% of 21 children with SCD using DFX were nonadherent with therapy after one year, while Raphael et al. reported 24% nonadherence based upon a retrospective chart review of 59 children; the current study found high percentages of discontinuation at 84% for DFO and 63% for DFX after one year that continued to decrease by month 18 [30, 31]. Based exclusively upon objective claims data, Jordan et al.

investigated Medicaid beneficiaries within 3 states and found median times to treatment discontinuation ranged from 86 days (any DFO patients) to 253 days (deferasirox switchers) [15]. Comparatively, the current study found the median time of treatment discontinuation across all subjects to be 182 days (mean = 214) and, according to treatment groups: 162 days (mean = 199) for the DFO-only cohort; 172 days (mean = 230) for DFX-only cohort; and 220 days (mean = 190) for combination treatment cohort. Multivariate analyses within both Jordan et al. and the current investigation consistently found that DFO was associated with statistically higher likelihood of treatment discontinuation relative to DFX after controlling for other predictors [15].

Several studies have investigated overall costs associated with SCD at both the national and state level [4, 17, 32-34]. Pertaining to medication use, however, Delea et al. studied DFO use alone for chelation due to iron overload from repeated blood transfusions in 39 thalassemia and 106 SCD patients (which included 17 Medicaid enrollees) using a large U.S. health insurance claims database of 40 million members in over 70 health plans from 1997 to 2004 [20]. Average annual total medical costs in SCD patients were reported to be $59,233 ($4,936 per month) [$90,044, $7,504 per month, USD 2011], with DFO plus additional costs for ICT administration averaging $19,621 per year ($1,635 per month) [$29,827, $2,486 per month, USD 2011]; no multivariate analyses were presented by Delea et al. to ascertain the association of DFO with costs after controlling for other predictors [20]. Mvundura et al. and Amendah et al. reported that medication claims among children enrolled in Medicaid were higher than those enrolled in commercial insurance plans at $1,049 versus $531 [$1,288 versus $652, USD 2011], although average total expenditures were lower in Medicaid at $11,075 versus $14,722 [$13,601 versus, $18,081, USD 2011] despite similar number of outpatient blood transfusions [35, 36]. In descriptive terms, the current study found annualized total overall medical costs of $78,384 ($6,532 per month) [$85,839, $7,153 per month, USD 2011]. Therein, combined annualized medication plus outpatient costs were $23,640 ($1,970 per month) [$25,888, $2,157 per month, USD 2011] for the DFO-

only cohort versus $36,240 ($3,020 per month) [$39,687, $3,307 per month, USD 2011] for the DFX-only cohort. Although the lower descriptive cost observation for DFO versus DFX in the current investigation may have been driven by its significantly higher treatment discontinuation rate, no significant difference in total cost was ultimately found between the two ICTs after controlling for various predictors in the multivariate analysis.

The present investigation allowed for actual patterns of care to be analyzed, focusing upon naturalistic settings (i.e., effectiveness) rather than clinical trial settings (i.e., efficacy) [37]. Given that this study was retrospective in design, patient randomized to either DFO or DFX could not be conducted, hence multivariate statistics were used to account for patient heterogeneity and risk factors [26]. Despite this, several limitations must be noted. Foremost, severity of SCD could not be determined given the retrospective and administrative nature of the national database. While an 18-month treatment horizon was studied, this time frame may be insufficient to measure long-term effectiveness of either ICT or SCD complications. As the population being evaluated were Medicaid enrollees, any reimbursement restrictions that might have limited the use of ICT treatment from 2006 to 2010 were not assessed due to lack of specific location-related information for each patient. Furthermore, while total direct healthcare costs were measured from the perspective of Medicaid, results may not be generalizable other patient populations or health systems that utilize different coverage mechanisms.

The implications of the current study are particularly important when considering the role of payers and providers in a public health context [38, 39]. The economic, clinical, and humanistic impact of iron overload may become substantial, and poor adherence to ICTs has been shown to result in serum ferritin targets to not be achieved, which negatively impacts costs, morbitidy and mortality, and health-related quality of life [31, 40-42]. The long-term ramifications of nonadherence to ICTs in persons with iron overload may manifest in severe clinical complications, particularly hepatic failure, iron-induced cardiomyopathy, or pancreatic iron deposition [9]. Based upon cost-effectiveness and cost-utility

analyses, DFX has been reported to be cost-effective relative to DFO in the treatment of transfusional iron overload from the perspective of payers both in the U.S. and U.K [12, 17-22]. These models, however, assumed high compliance across patient populations, which do not appear to correspond to actual patterns of care [12]. It is also important to note that persons with SCD have reported significant barriers in access to health care, particularly those associated with delays in treatment [43]. Predictors of nonadherence in SCD remain complex and multifaceted, and current suggestions state that an integrated team approach involving healthcare providers, family caregivers, and treatment centers be utilized to achieve optimal results with chronic therapies [29, 42].

Overall, the current findings suggest that payers and providers should review the care of SCD patients with a goal of identifying those that may have prematurely discontinued ICT treatment. Approximately 5% remained on DFO versus 20% for DFX after 18 months in this investigation. Despite this, overall healthcare costs did not differ between DFO versus DFX. As persons with SCD may alter the utilization of their medications for several reasons, future research should be directed toward identifying and implementing multifaceted patient-centered programs to optimize long-term persistency and outcomes.

Conclusion

The investigation of real-world ICT utilization patterns among Medicare beneficiaries with SCD across 10 states from 2006-2010 in the U.S. found that approximately 95% individuals discontinued use of DFO and 80% of individuals discontinued use of DFX 18-months following treatment initiation. After multivariate analyses controlled for various predictors, total healthcare costs did not differ between DFO and DFX even though treatment discontinuation was 1.305 times higher with DFO. Public health concerns surrounding patient persistency with ICTs places a responsibility on payers and providers to evaluate drug utilization patterns in order to identify poor persistence and risk of discontinuation in this vulnerable population.

Disclosure (to be included in the cover letter, not the manuscript submission per author guidelines for the American Journal of Hematology)

Drs. Armstrong and Skrepnek are consultants to Novartis through Strategic Therapeutics, LLC. Drs. Sasane, Kwock, and Snodgrass are employees of Novartis. Dr. Ballas is a consultant to Novartis.

Table 1. Baseline Descriptive Characteristics

Characteristic	Deferoxamine Only (n = 42)	Deferasirox Only (n = 228)	Combination Treatment (n = 134)	Overall (n = 404)
Age in years	20.5	19.2	17.3	18.7
Mean, standard deviation	(±9.9)	(±12.0)	(±9.5)	(±11.0)
Age ≥ 18 years	24[†]	106	51[†]	181
N, (%)	(57.1%)	(46.5%)	(38.1%)	(44.8%)
Sex, Male	21	93[†]	71[†]	185
N, (%)	(50.0%)	(40.8%)	(53.0%)	(45.8%)
Deyo-Charlson				
Mean, standard deviation	0.93	0.76	0.81	0.79
	(±1.24)	(±1.18)	(±0.96)	(±1.12)
Race				
African American N, (%)	32	147	90	269
	(76.2%)	(64.5%)	(67.2%)	(66.7%)
Hispanic N, (%)	0	2	1	3
	(0.0%)	(0.9%)	(0.7%)	(0.7%)
White N, (%)	0	5	1	6
	(0.0%)	(2.2%)	(0.7%)	(1.5%)
Other N, (%)	10	74	42	126
	(23.8%)	(32.5%)	(31.3%)	(31.2%)

Capitated Medicaid Coverage	25	150	77	252
N, (%)	(59.5%)	(65.8 %)	(57.5%)	(62.4%)
Number of Baseline Period Transfusions	2.3‡	2.7‡	4.0‡	3.1
Mean, standard deviation	(±2.6)	(±3.3)	(±3.2)	(±3.3)
Comorbidities				
Coronary Heart Disease	1	5	1	7
	(2.4%)	(2.2%)	(0.7%)	(1.7%)
Chronic Liver Disease	1	4	5	10
	(2.4%)	(1.8%)	(3.7%)	(2.5%)
Chronic Renal Disease	1	7	2	10
	(2.4%)	(3.1%)	(1.5%)	(2.5%)
Coronary Occlusion with Infarction	1	9	11	24
	(2.4%)	(3.9%)	(8.2%)	(5.9%)
Diabetes	1	2	2	5
	(2.4%)	(0.9%)	(1.5%)	(1.2%)
Hypertension	5	18	5	28
	(11.9%)	(7.9%)	(3.7%)	(6.9%)
Other Cerebrovascular Disease	2†	26	22†	50
	(4.8%)	(11.4%)	(16.4%)	(12.4%)

‡ Significantly different between groups (Analysis of Variance, Tukey post-hoc for multiple comparisons, $p \leq 0.05$)

† Statistically different between groups (χ^2 , $p \leq 0.05$)

Table 2. Predictors of Treatment Discontinuation

Variable	Hazard Ratio	Standard Error	Test statistic	p-value	95% CI, lower bound	95% CI, upper bound
Deferoxamine Use (versus Deferasirox)	1.305*	0.139	2.50	0.012	1.059	1.607
Number of Pre-Index Transfusion Episodes	0.982	0.017	−1.08	0.281	0.951	1.015
18 years of age or older	1.304*	0.138	2.50	0.013	1.059	1.605
Male	1.049	0.108	0.45	0.641	0.857	1.285
Capitated Medicaid coverage	1.118	0.117	1.06	0.287	0.911	1.372
Deyo-Charlson	0.988	0.042	−0.29	0.772	0.908	1.074

Cox Proportional Hazard Regression, Efron method for ties; N = 404; time at risk 86,336; Log-likelihood -2015.97; p = 0.009

* Statistically significant at $p \leq 0.05$

Table 3. Baseline and Study Period Per Patient Per Month (PMPM) Average Costs According to Treatment Groups

Characteristic	Deferoxamine Only (n = 42)	Deferasirox Only (n = 228)	Combination Treatment (n = 134)	Overall (n = 404)
Inpatient PMPM Costs [mean (±std dev)]				
Baseline	$3,838 (±8,729)	$3,559 (±8,005)	$2,497 (±4,874)	$3,236 (±7,209)
Study	$3,560 (±7,303)	$4,034 (±9,509)	$2,630 (±5,130)	$3,519 (±8,091)
Outpatient PMPM Costs [mean (±std dev)]				
Baseline	$1,459 (±1,491)	$924 (±1,340) ‡	$1,648 (±1,445) ‡	$1,220 (±1,430)
Study	$1,315 (±1,181)	$890 (±1,287) ‡	$1,383 (±1,094) ‡	$1,098 (±1,236)
Medication PMPM Costs [mean (±std dev)]				
Baseline	$1,009 (±832) ‡	$256 (±689) ‡	$851 (±797) ‡	$532 (±805)
Study	$655 (±592) ‡	$2,130 (±1,499) ‡	$1,942 (±1,267) ‡	$1,915 (±1,422)
Total PMPM Costs [mean (±std dev)]				
Baseline	$6,306 (±9,244)	$4,740 (±8,485)	$4,996 (±4,978)	$4,988 (±7,592)

Study	$5,531 (±7,672)	$7,054 (±9,956)	$5,956 (±5,861)	$6,532 (±8,575)

‡ Significantly different between groups (Analysis of Variance, Tukey post-hoc for multiple comparisons, $p \leq 0.05$

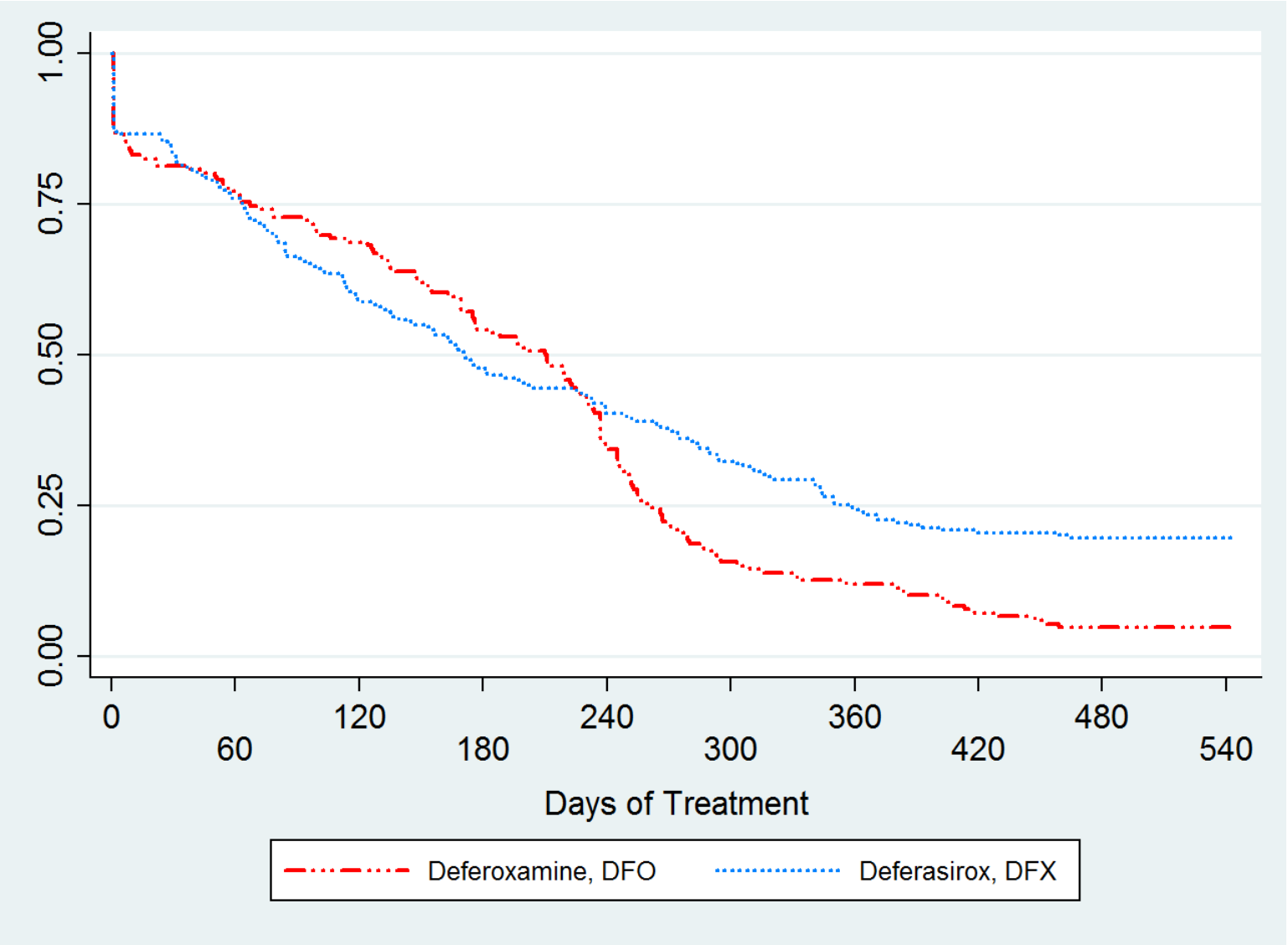
Table 4. Predictors of Total Healthcare Costs

Variable	*exp(b)*	Standard Error	z	p-value	95% CI, lower bound	95% CI, upper bound
Deferoxamine Use (versus Deferasirox)	0.924	0.077	–0.95	0.340	0.784	1.087
Number of Pre-Index Transfusion Epsiodes	1.028*	0.012	2.31	0.021	1.001	1.053
18 years of age or older	1.559*	0.140	4.96	<0.001	1.308	1.859
Male	0.948	0.080	–0.63	0.526	0.804	1.118
Capitated Medicaid coverage	0.989	0.082	–0.14	0.892	0.841	1.162
Deyo-Charlson	1.100*	0.042	2.51	0.012	1.021	1.185
Baseline Healthcare Costs (per thousand dollars)	1.011*	0.001	9.68	<0.001	1.001	1.014

Generalized Linear Model, gamma distribution family, log link; Maximum likelihood estimation, n = 404; Observed Information Matrix (OIM) Log-likelihood = –5031.28; Deviance = 202.06; Akaike information criteria, AIC = 24.95

* Statistically significant at $p \leq 0.05$

Figure 1. Kaplan-Meier Graph for Treatment Discontinuation between Deferoxamine and Deferasirox



Time at risk = 86,336; Log rank test for equality of survivor functions p = 0.004

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