

Original Investigation

Comparative Risk of Anaphylactic Reactions Associated With Intravenous Iron Products

Cunlin Wang, MD, PhD; David J. Graham, MD, MPH; Robert C. Kane, MD; Diqiong Xie, PhD; Michael Wernecke, BA; Mark Levenson, PhD; Thomas E. MaCurdy, PhD; Monica Houstoun, PharmD; Qin Ryan, MD, PhD; Sarah Wong, MPH; Katrina Mott, MPH; Ting-Chang Sheu, MPH; Susan Limb, MD; Chris Worrall, BS; Jeffrey A. Kelman, MD, MSc; Marsha E. Reichman, PhD

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IMPORTANCE All intravenous (IV) iron products are associated with anaphylaxis, but the comparative safety of each product has not been well established.

OBJECTIVE To compare the risk of anaphylaxis among marketed IV iron products.

DESIGN, SETTING, AND PARTICIPANTS Retrospective new user cohort study of IV iron recipients (n = 688 183) enrolled in the US fee-for-service Medicare program from January 2003 to December 2013. Analyses involving ferumoxytol were limited to the period January 2010 to December 2013.

EXPOSURES Administrations of IV iron dextran, gluconate, sucrose, or ferumoxytol as reported in outpatient Medicare claims data.

MAIN OUTCOMES AND MEASURES Anaphylaxis was identified using a prespecified and validated algorithm defined with standard diagnosis and procedure codes and applied to both inpatient and outpatient Medicare claims. The absolute and relative risks of anaphylaxis were estimated, adjusting for imbalances among treatment groups.

RESULTS A total of 274 anaphylaxis cases were identified at first exposure, with an additional 170 incident anaphylaxis cases identified during subsequent IV iron administrations. The risk for anaphylaxis at first exposure was 68 per 100 000 persons for iron dextran (95% CI, 57.8-78.7 per 100 000) and 24 per 100 000 persons for all nondextran IV iron products combined (iron sucrose, gluconate, and ferumoxytol) (95% CI, 20.0-29.5 per 100 000), with an adjusted odds ratio (OR) of 2.6 (95% CI, 2.0-3.3; $P < .001$). At first exposure, when compared with iron sucrose, the adjusted OR of anaphylaxis for iron dextran was 3.6 (95% CI, 2.4-5.4); for iron gluconate, 2.0 (95% CI 1.2, 3.5); and for ferumoxytol, 2.2 (95% CI, 1.1-4.3). The estimated cumulative anaphylaxis risk following total iron repletion of 1000 mg administered within a 12-week period was highest with iron dextran (82 per 100 000 persons, 95% CI, 70.5- 93.1) and lowest with iron sucrose (21 per 100 000 persons, 95% CI, 15.3- 26.4).

CONCLUSIONS AND RELEVANCE Among patients in the US Medicare nondialysis population with first exposure to IV iron, the risk of anaphylaxis was highest for iron dextran and lowest for iron sucrose.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Cunlin Wang, MD, PhD, Division of Epidemiology I, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20903 (cunlin.wang@fda.hhs.gov).

JAMA. 2015;314(19):2062-2068. doi:10.1001/jama.2015.15572

In 2010, anemia affected one third of the global population, and iron deficiency was the most common cause.¹ A model using data throughout 2010 estimated that moderate iron deficiency anemia (IDA) affects approximately 610 million people worldwide.² Oral iron replacement is the primary treatment strategy for iron deficiency anemia but may be inadequate for some patients due to intolerance, impaired absorption, significant ongoing bleeding, or nonadherence.³ For these patients, intravenous (IV) iron may be indicated. Compared with oral iron, IV iron can significantly increase levels of hemoglobin, serum ferritin, and transferrin saturation.⁴ As of June 2013, there were 5 IV iron products marketed in the United States. While their efficacy is established, the most important safety concern relates to the risk of serious and fatal anaphylaxis,⁵⁻⁸ which may occur at both first and subsequent exposures.

No sufficiently large randomized trials have been conducted to determine the comparative risk of anaphylaxis for IV iron products. Based on a meta-analysis of published studies of iron dextran, the estimated incidence of anaphylaxis was 0.61%.⁹ Although the newer IV iron products are purportedly safer,^{10,11} anaphylactic reactions also occur with these products.^{8,12} In a randomized, placebo-controlled trial involving more than 2500 patients treated with iron gluconate, the incidence of life-threatening reactions was 0.04%.⁹ In another trial of 750 patients treated with ferumoxytol, 1 patient developed anaphylaxis.¹³

To our knowledge, there have been no large population-based observational studies that evaluate the risk of anaphylaxis among different IV iron products. Such a study is important because large head-to-head comparative safety trials to detect rare adverse reactions like anaphylaxis may not be feasible. The purpose of this study was to compare the risk of anaphylaxis among patients receiving different IV iron products in a large, nondialysis, US Medicare patient population.

Methods

Study Population

This study used a retrospective new user cohort design. Patients enrolled in fee-for-service Medicare Part A (hospitalization) and Part B (office-based care) between January 2003 and December 2013 entered the IV iron new user cohort on the date of their first outpatient claim with a Healthcare Common Procedure Coding System (HCPCS) code for an IV iron product (index date). Patients were included in the study if on their index date they were not receiving dialysis, were continuously enrolled in Medicare A and B for the previous 12 months, had no IV iron exposure in the preceding 12 months, and were exposed to only 1 type of IV iron product. Also, patients who had a claim for a blood transfusion on the index date or a diagnosis of anaphylaxis in the 30 days before the index date were excluded. Since ferumoxytol received US Food and Drug Administration (FDA) approval in mid-2009, analyses involving this agent were limited to the period from January 2010 to end of study (December 2013). This study was approved by the Research Involving Human Subjects Committee of the FDA prior

to initiation. Patient consent was waived because the study used deidentified health care claims data.

Exposure of Interest

The primary comparison of interest was the use of dextran vs nondextran IV iron products. A secondary analysis compared anaphylaxis risk between iron dextran and 3 approved nondextran products individually (iron gluconate, iron sucrose, and ferumoxytol). Although it was not possible to distinguish between the 2 FDA-approved iron dextrans (high-molecular-weight dextran, low-molecular-weight dextran) based on claims data during most of the study interval because they shared the same HCPCS code, all iron dextran claims were combined into 1 group.

Outcome Definition and Identification

Cases of anaphylaxis were identified using a predefined, validated algorithm, based on *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis/procedure and HCPCS codes for inpatient and outpatient claims, which was developed using the National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.^{14,15} The algorithm had a positive predictive value (PPV) of 63% for anaphylaxis, and 76% for the composite outcome of anaphylaxis or serious *allergic reaction*, the latter of which was defined as an allergic reaction that is highly likely to evolve into anaphylaxis if untreated. False-positive events identified as anaphylaxis by this algorithm in the validation study included mild allergic reactions, isolated hives, rash, and respiratory distress.¹⁴ This algorithm was used to identify anaphylaxis cases when multiple procedure and diagnosis codes were present (eAppendix 1 in the [Supplement](#)). Because IV iron-associated anaphylaxis cases reported from clinical trials and spontaneous adverse events indicate that anaphylaxis generally occurs within a few hours of IV iron administration,^{8,12} anaphylaxis cases in this study were limited, for the primary analysis, to only those captured on the same date as the IV iron administration, which may plausibly increase the positive predictive value of the algorithm.

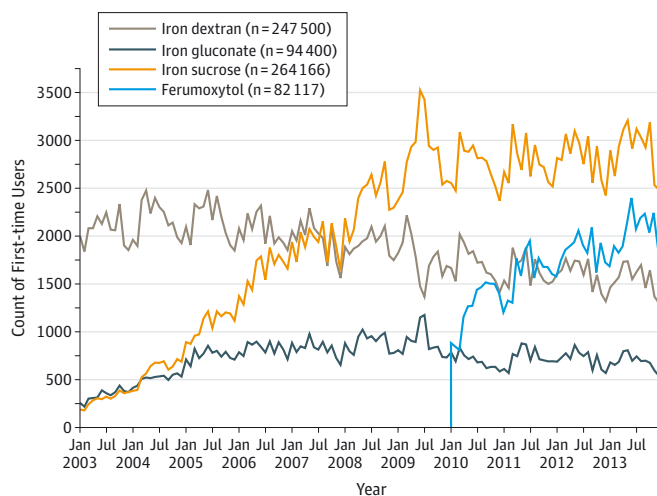
Cohort Follow-up and Censoring

In addition to the analysis of anaphylaxis at the first administration, patients were also followed up to identify the risks of anaphylaxis at subsequent administrations. Follow-up began on index date. Censoring occurred for disenrollment from Medicare Part A or B, switching to another IV iron product, dialysis initiation, occurrence of an anaphylaxis event, death, or end of study (December 31, 2013), whichever occurred first.

Covariates

In addition to age and sex, data on the following potential confounders were collected from Medicare claims during the 12-month period preceding the index date: history of food allergies, history of drug allergy, asthma, chronic obstructive pulmonary disease, coronary heart disease, hypertension, and indications for IV iron use (eAppendixes 2 and 3 in the [Supplement](#)). In the sensitivity analysis that included patients with Medicare part D (prescription drug) coverage, concomitant use

Figure 1. Trend of First-Time Use by IV Iron Product



IV indicates intravenous.

of antibiotics, β -blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors was also included.^{16,17}

Statistical Analysis

The risk of anaphylaxis and corresponding 95% CIs was calculated for each IV iron product and for the combined non-dextran products.¹⁸ Imbalances in baseline characteristics between treatment groups were assessed using standardized mean differences (SMDs). Multivariable logistic regression was used to estimate the risk of anaphylaxis at first administration after adjusting for imbalanced covariates. The Tukey range test was used to adjust for multiple comparisons.¹⁹ The 95% CIs of the adjusted odds ratios (ORs) were estimated based on likelihood ratio tests. The combined nondextran group was used as the reference group when compared with iron dextran. Iron sucrose was used as the reference group for comparisons involving individual IV iron products. Because IV iron products differ by iron dose per administration, the cumulative risk of anaphylaxis was analyzed based on a clinically relevant repletion level of iron (1000 mg) achieved within 12-weeks per recommended dose and schedule. First, the number of exposures necessary to achieve an iron repletion of 1000 mg were obtained by calculating the average number of administrations required for each IV iron product (eTable 1 in the Supplement). Under the assumption that the first administration carried a higher risk of anaphylaxis than subsequent administrations, logistic regression was used to model risk at the first administration. Poisson regression was used to model risk of subsequent administrations. The risk of anaphylaxis with 95% CIs for each treatment regimen was calculated by multiplying the observed number of exposures needed to receive 1000 mg of iron with the risk of anaphylaxis at each administration.

Prespecified sensitivity analyses examined the robustness of the results to variations in the outcome definition, including (1) anaphylaxis cases diagnosed up to 2 days after IV iron administration, (2) anaphylaxis or death occurring on the

same day as IV iron administration, (3) cases only meeting anaphylaxis criteria A and B as defined in eAppendix 1 in the Supplement, and (4) restricting the population to patients with Medicare Part D information to account for potential imbalance on relevant concomitant medications. Furthermore, following the approval of ferumoxytol, a generic code J3490 (unclassified drugs) was used temporarily for reimbursement before a specific HCPCS code was assigned. We also conducted sensitivity analysis that removed ferumoxytol users who had a J3490 code during the period of July 2009 through December 2009. $P < .05$ was considered the threshold for statistical significance. All tests were 2-sided. All analyses were performed using SAS version 9.2 (SAS Institute Inc) and R 3.0.2 (R Foundation for Statistical Computing).

Results

There were 247 500 iron dextran and 440 683 nondextran new IV iron users during the study period. New iron dextran use decreased slightly over time, while nondextran use increased, particularly for iron sucrose. Ferumoxytol use began following its 2009 marketing approval (Figure 1). At baseline, patients receiving dextran or nondextran IV irons were comparable with age, sex, race, and relevant health conditions except for coronary heart disease and hypertension (Table 1). The products differed with respect to the underlying conditions leading to IV iron administration, reflecting differences in FDA-approved indications for use (iron dextran is approved for use in broad iron deficiency anemia indications and nondextran products are approved only for use in patients with chronic kidney disease). Among the individual nondextran products, baseline demographics and anaphylaxis-related characteristics were similar, except for the ferumoxytol cohort, which had the highest proportion of patients with chronic kidney disease (60%) and lowest proportion of patients with gastrointestinal tract and genitourinary tract bleeding (12%) (eTable 2 in the Supplement).

Table 1. Baseline Characteristics for Incident Users Receiving Iron Dextran and Nondextran Intravenous Iron (2003-2013)

	No. (%) of Patients		Standardized Mean Difference
	Iron Dextran (n = 247 500)	Nondextran Intravenous Iron (n = 440 683)	
Baseline Characteristics ^a			
Age, mean (SD), y	73.2 (11.3)	74.0 (11.4)	0.07
Sex			
Men	83 312 (33.7)	167 097 (37.9)	0.09
Women	164 188 (66.3)	273 586 (62.1)	0.09
Race			
White	214 962 (86.9)	374 436 (85.0)	0.05
Black	23 683 (9.6)	48 449 (11.0)	0.05
Asian	1718 (0.7)	4222 (1.0)	0.03
Hispanic	4231 (1.7)	6926 (1.6)	0.01
Other/unknown	2906 (1.2)	6650 (1.5)	0.03
Regions			
Northeast	25 935 (10.5)	86 661 (19.7)	0.26
Midwest	50 782 (20.5)	119 670 (27.2)	0.16
South	135 108 (54.6)	169 783 (38.5)	0.33
West	35 106 (14.2)	63 529 (14.4)	0.01
Other	569 (0.2)	1040 (0.2)	0.00
Indications			
Anemia			
CKD	53 141 (21.5)	233 229 (52.9)	0.69
GI/GU bleeding	53 681 (21.7)	63 956 (14.5)	0.19
Other	140 678 (56.8)	143 498 (32.6)	0.50
Conditions			
Asthma	33 179 (13.4)	60 044 (13.6)	0.01
COPD	72 391 (29.2)	132 620 (30.1)	0.02
Coronary heart disease	101 419 (41.0)	207 127 (47.0)	0.12
Depression	41 481 (16.8)	77 570 (17.6)	0.02
Drug allergy	16 151 (6.5)	33 355 (7.6)	0.04
Food allergy	958 (0.4)	1968 (0.4)	0.01
Hypertension	204 701 (82.7)	394 991 (89.6)	0.20
Beneficiaries With Part D Enrollment ^a			
No. of patients	83 627	211 132	
Concomitant medications			
NSAIDs	5977 (7.1)	10 404 (4.9)	0.09
Antibiotics	1916 (2.3)	5420 (2.6)	0.02
β-Blockers	27 616 (33.0)	86 856 (41.1)	0.17
ACE inhibitors	20 692 (24.7)	52 376 (24.8)	0.00

Abbreviations: ACE, angiotensin-converting enzyme; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GI/GU, gastrointestinal tract and genitourinary tract; NSAIDs, nonsteroidal anti-inflammatory drugs.

^a Data on concomitant medications were collected for those patients who were enrolled in Medicare Part D (prescription drugs) in 2007-2013.

There were 274 anaphylaxis cases identified at first exposure to an IV iron product. The risk for anaphylaxis was 68 per 100 000 persons (95%CI, 57.8-78.7/ per 100 000) in the iron dextran group compared with 24 per 100 000 persons (95% CI, 20.0-29.5 per 100 000) in the nondextran IV iron group. The OR was 2.6 (95% CI, 2.0-3.3 $P < .001$), after adjustments for age, indication, history of coronary heart disease, and hypertension. Compared with iron sucrose, both iron dextran and iron gluconate were associated with an increased risk of anaphylaxis (OR, 3.6; 95% CI, 2.4-5.4 and OR, 2.0; 95% CI, 1.2-3.5, respectively). Using data from 2010 to 2013, ferumoxytol was also associated with a higher risk of anaphylaxis compared with sucrose (OR, 2.2; 95% CI, 1.1-4.3; Table 2). Results

of sensitivity analyses were consistent with the main results (eTables 3-6 and eFigures 1-4 in the Supplement). We found less than 1% (548 of 82 117) ferumoxytol users had the generic J3490 code during the June 2009-December 2009 period. Removing these patients had little change to the results (eTable 7 and eFigure 5 in the Supplement).

An additional 170 anaphylaxis events were observed at subsequent IV iron administrations. For all IV iron products, the rate of anaphylaxis was highest at the first administration and decreased thereafter. The decrease was particularly pronounced for iron gluconate and iron sucrose (Figure 2). The cumulative risk of anaphylaxis over multiple administrations was highest for iron dextran, followed in decreasing order by

Table 2. Risk of Anaphylaxis at First Administration by Intravenous Iron Products

Intravenous Iron	2003-2013			2010-2013		
	Nondextran	Iron Dextran	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose
No. of anaphylaxis cases	107	167	45	167	34	21
No. of new users	440 683	247 500	264 166	247 500	94 400	134 836
Rate per 100 000 persons (95% CI)	24.3 (20.0-29.5)	67.5 (57.8-78.7)	17.0 (12.6-23.0)	67.5 (57.8-78.7)	36.0 (25.3-50.9)	15.6 (9.9-24.3)
AOR (95% CI) ^a	1 [Reference]	2.6 (2.0-3.3)	1 [Reference]	3.6 (2.4-5.4)	2.0 (1.2-3.5)	1 [Reference]
P value ^b		<.001		<.001	.005	.02

Abbreviation: AOR, adjusted odds ratio.

^a Adjusted for age, indication, coronary heart disease, and hypertension.^b P value adjusted for multiple comparisons.

ferumoxytol, iron gluconate, and iron sucrose (eFigure 6 in the Supplement). To reach an aggregate iron dose of 1000 mg in the cumulative dose analysis, dextran and ferumoxytol users required 2 administrations on average, whereas sucrose users needed 5 and iron gluconate users needed 7. For cumulative doses of 1000-mg iron administered, as estimated from modeling, iron dextran was also associated with the highest risk of anaphylaxis (82 per 100 000 persons, 95% CI, 70.5- 93.1 per 100 000), whereas iron sucrose was associated with the lowest risk (21 per 100 000 persons, 95% CI, 15.3- 26.4 per 100 000) (Figure 3).

The 2 marketed iron dextran products (high-molecular-weight dextran, low-molecular-weight dextran) shared the same HCPCS code during most of the study period. Thus, the individual risk of each iron dextran product could not be fully studied. However, during a brief interval from January 2006 to March 2008, separate HCPCS codes were used for each dextran product. During this period, of 53 914 new iron dextran users, 48 772 (90.5%) received low-molecular-weight dextran and 5142 (9.5%) received high-molecular-weight dextran, suggesting that during the study period, most dextran use in this population was low-molecular weight. Among first administrations of iron dextran during this period, a total of 43 anaphylaxis events were observed, of which 40 (93%) were in those taking low-molecular-weight dextran (eTable 8 in the Supplement).

Discussion

Among more than 680 000 US Medicare nondialysis beneficiaries who initiated IV iron use from 2003 to 2013, iron dextran was associated with increased anaphylaxis risk compared with nondextran formulations at first administration. Among the nondextran products, the risk of anaphylaxis at first administration was higher with both iron gluconate and ferumoxytol than with iron sucrose. Because each IV iron product has a specific recommended dose and schedule of administration, the cumulative risk of anaphylaxis was also calculated based on both the number of administrations and clinically relevant repletion level of iron (1000 mg) achieved within 12 weeks. Both analyses showed iron dextran was associated with the highest cumulative risk of anaphylaxis and iron sucrose with the lowest risk.

All IV iron formulations studied consist of an elemental iron core surrounded by a carbohydrate shell intended to shield the iron core and facilitate iron delivery to the reticuloendothelial system following intravenous administration. The formulations differ from each other in the size of the iron core and the identity and density of the carbohydrate shell.²⁰ Although iron dextran is asserted to have a greater risk of serious adverse events than the more recently approved nondextran IV iron products, most of the clinical trials that supported the approval of nondextran IV irons used a placebo or oral iron comparator and not iron dextran. Only a few head-to-head trials prospectively compared IV iron formulations, and they were small in sample size, had few or no anaphylaxis events, and were not designed to establish comparative safety.^{9,21,22} To our knowledge, the present study represents the largest

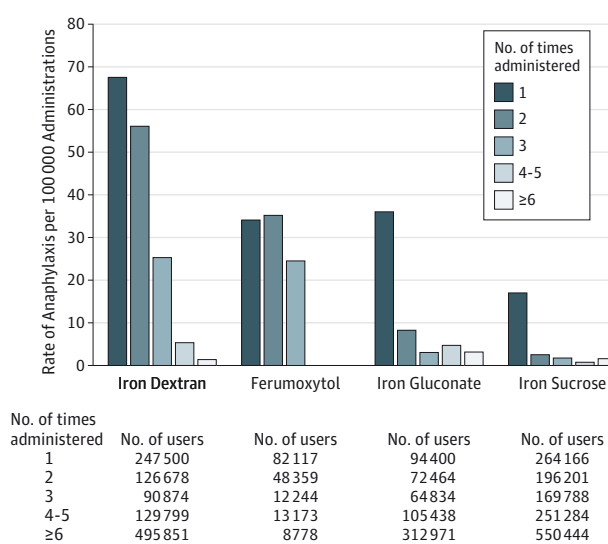
comparative safety assessment of anaphylaxis risk for the IV iron products. In contrast to prior efforts to assess safety,²³⁻²⁵ our study was not based on postmarket passive case reporting, such as the FDA's spontaneous adverse events reporting system, which is limited in its ability to support comparative safety analyses due to different approval dates and indication of IV iron products, variations in reporting over time, choice of denominator used, and variations in the diagnostic criteria of anaphylaxis. Our study provides a more reliable estimate of the relative risk between individual IV iron products based on a prespecified algorithm for anaphylaxis, a well-defined and characterized population at risk, and adjustment for imbalances in baseline risk factors for anaphylaxis.

The mechanism of anaphylactic reaction after IV iron remains unknown. Dextran may be immunogenic, even to patients who have not been previously exposed, because of cross-reactivity of dextran to native polysaccharide antibodies.²¹ The mechanism of anaphylaxis associated with nondextran IV iron is also unclear. Possibilities include reactions to the carbohydrate shell or to release of unbound iron into the circulation that then may cause oxidative stress, hypotension, and cardiac failure in addition to the typical anaphylactic reaction. A recent review of ferumoxytol suggested that the structure of carbohydrate coating surrounding the iron oxide core also may be associated with immunogenicity.²⁶ The possible adverse effects of more rapid administration of higher doses of IV iron are also not well characterized.

This study has several limitations. The study population consisted of US Medicare beneficiaries not receiving dialysis treatment; thus, our results may not extend to dialysis patients or younger age populations. Patients receiving dialysis were not included because iron dextran and ferumoxytol were rarely used in this population. Another limitation was that the low- and high-molecular-weight dextran products could not be individually identified during most of study period. However, the very low use of high-molecular-weight iron dextran from January 2006 through March 2008, during which we could distinguish the use of 2 dextran products, suggests that our results likely represent the risk of the low-molecular-weight dextran, especially the most recent data from 2010-2013.

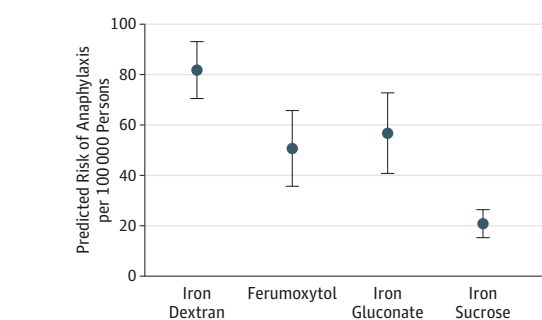
Based on the incidence rates observed in clinical trials of ferumoxytol, in which the rate of anaphylaxis or serious hypersensitivity reaction varied between 0.2% and 0.9%, depending on the patient population,²⁷ our results may indicate low sensitivity (8%-35%) in detecting anaphylaxis. One possible explanation is that the patient populations included in the randomized clinical trials and our large observational study were different. The ferumoxytol trial that reported an anaphylaxis incidence of 0.9% was conducted in a general population of patients with iron deficiency anemia to support an unapproved indication (Miya Paterniti, MD, US FDA, written communication, July 10, 2015), whereas the majority of patients in our study had anemia related to chronic kidney disease per approved indication, and the baseline risk of anaphylaxis may have been different in these 2 populations. Also, anaphylaxis can present in a variety of ways with varying degrees of severity. In clinical trials, there is generally a well-defined case definition, whereas in the general practice set-

Figure 2. Rate of Anaphylaxis by IV Iron Products and Number of Administrations



IV indicates intravenous.

Figure 3. Adjusted Predicted Risk of Anaphylaxis at Cumulative Dose of 1000 mg



Adjusted for age, coronary heart disease, and hypertension. Error bars indicate 95% CIs.

ting, physicians may code severe or textbook anaphylaxis as *anaphylaxis* but code less severe or atypical anaphylaxis in terms of its component symptoms or as an allergic reaction. Compared with anaphylaxis criteria used in the adjudication of clinical trial data, our algorithm might have missed the cases presenting with skin and mucosal symptoms that could have been treated with corticosteroids, which may be milder in nature than cases presenting with systemic symptoms (such as respiratory compromise, syncope). The skin and mucosal symptoms were not included in our algorithm because they are not specific to anaphylaxis, so including them would negatively affect the positive predictive value. While balancing between positive predictive value and sensitivity, our algorithm should have captured the typical and severe anaphylaxis cases diagnosed by the physician. The validity of our analyses should not be biased by the under ascertainment of anaphylaxis cases since it seems unlikely that physician coding practices for completing Medicare billing claims would differ

depending on which IV iron product was used. Although random variation in the sensitivity could create a spurious difference between products, especially at very low levels of sensitivity, this is unlikely to have affected this study because the relative risks between individual IV iron products were all greater than 2, and greater than 5 in the comparison between iron dextran and sucrose.

In addition, given the difference in indication between iron dextran and nondextran products, patients treated with dextran and nondextran IV iron may be different relative to the risk of anaphylaxis. We examined important baseline charac-

teristics that are relevant to the risk of anaphylaxis and adjusted for those that were not balanced in the final analysis. However, residual confounding is possible due to additional factors not captured by this study.

Conclusions

Among patients in the US Medicare nondialysis population with first exposure to IV iron, the risk of anaphylaxis was highest for iron dextran and lowest for iron sucrose.

ARTICLE INFORMATION

Author Contributions: Dr MaCurdy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Author Affiliations: Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (Wang, Graham, Mott, Reichman); Office of New Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (Kane, Houstoun, Ryan, Limb); Dr Kane is now retired. (Kane); Office of Biostatistics, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (Xie, Levenson); Acumen LLC, Burlingame, California (Wernecke, MaCurdy, Wong, Sheu); Harvard School of Public Health, Boston, Massachusetts (Mott); Genentech Inc, San Francisco, California (Limb); Centers for Medicare & Medicaid Services, Washington, DC (Worrall, Kelman).

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors are employees or contractors of the Centers for Medicare & Medicaid Services or the US Food and Drug Administration. No other disclosures were reported.

Funding/Support: This study was funded through an intraagency agreement between the Centers for Medicare & Medicaid Services and the US Food and Drug Administration.

Role of the Funder/Sponsor: The Centers for Medicare & Medicaid Services and the US Food and Drug Administration had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; the preparation of the manuscript; or the decision to submit the manuscript for publication.

Disclaimer: The views expressed are those of the authors and not necessarily those of the Department of Health and Human Services, the Centers for Medicare & Medicaid Services, or the US Food and Drug Administration.

REFERENCES

1. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood*. 2014;123(5):615-624.
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289

diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163-2196.

3. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol*. 2004;76(1):74-78.

4. Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev*. 2012;1:CD007857.

5. Barton JC, Barton EH, Bertoli LF, Gothard CH, Sherrer JS. Intravenous iron dextran therapy in patients with iron deficiency and normal renal function who failed to respond to or did not tolerate oral iron supplementation. *Am J Med*. 2000;109(1):27-32.

6. Fishbane S, Ungureanu VD, Maesaka JK, Kaupke CJ, Lim V, Wish J. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kidney Dis*. 1996;28(4):529-534.

7. Fletes R, Lazarus JM, Gage J, Chertow GM. Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis*. 2001;37(4):743-749.

8. Bailie GR. Comparison of rates of reported adverse events associated with IV iron products in the United States. *Am J Health Syst Pharm*. 2012;69(4):310-320.

9. Michael B, Coyne DW, Fishbane S, et al; Ferrlecit Publication Committee. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. *Kidney Int*. 2002;61(5):1830-1839.

10. Bailie GR, Johnson CA, Mason NA. Parenteral iron use in the management of anemia in end-stage renal disease patients. *Am J Kidney Dis*. 2000;35(1):1-12.

11. Fishbane S. Safety in iron management. *Am J Kidney Dis*. 2003;41(5)(suppl):18-26.

12. Wysowski DK, Swartz L, Borders-Hemphill BV, Goulding MR, Dormitzer C. Use of parenteral iron products and serious anaphylactic-type reactions. *Am J Hematol*. 2010;85(9):650-654.

13. Singh A, Patel T, Hertel J, Bernardo M, Kausz A, Brenner L. Safety of ferumoxytol in patients with anemia and CKD. *Am J Kidney Dis*. 2008;52(5):907-915.

14. Walsh KE, Cutrona SL, Foy S, et al. Validation of anaphylaxis in the Food and Drug Administration's Mini-Sentinel. *Pharmacoepidemiol Drug Saf*. 2013;22(11):1205-1213.

15. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary

report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117(2):391-397.

16. Simons FE. Anaphylaxis. *J Allergy Clin Immunol*. 2010;125(2)(suppl 2):S161-S181.

17. Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol*. 2008;153(suppl 1):7-11.

18. Agresti A. *Categorical Data Analysis*. New York, NY: John Wiley & Sons; 2002.

19. Tukey JW. The problem of multiple comparisons. In: *The Collected Works of John W. Tukey VIII. Multiple Comparisons*. New York, NY: Chapman & Hall; 1953.

20. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program*. 2010;2010:338-347.

21. Kosch M, Bahner U, Bettger H, Matzkies F, Teschner M, Schaefer RM. A randomized, controlled parallel-group trial on efficacy and safety of iron sucrose (Venofer) vs iron gluconate (Ferrlecit) in haemodialysis patients treated with rHuEpo. *Nephrol Dial Transplant*. 2001;16(6):1239-1244.

22. Macdougall IC, Strauss WE, McLaughlin J, Li Z, Dellanna F, Hertel J. A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clin J Am Soc Nephrol*. 2014;9(4):705-712.

23. Bailie GR, Clark JA, Lane CE, Lane PL. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant*. 2005;20(7):1443-1449.

24. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21(2):378-382.

25. Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. *Am J Kidney Dis*. 1999;33(3):464-470.

26. Pai AB, Garba AO. Ferumoxytol: a silver lining in the treatment of anemia of chronic kidney disease or another dark cloud? *J Blood Med*. 2012;3:77-85.

27. FDA Drug Safety Communication: FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol). <http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm>. Updated April 2, 2015. Accessed September 13, 2015.

Supplementary Online Content

Wang C, Graham DJ, Kane RC, et al. Comparative Risk of anaphylactic reactions associated with intravenous iron products. *JAMA*. doi:10.1001/jama.2015.15572.

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eFigure 6. Cumulative Risk of Anaphylaxis by Number of Administration and IV Iron Products

Appendix 1. Anaphylaxis Definition

Appendix 2. International Classification of Disease, 9th edition, Clinical Modification (ICD-9-CM) Codes used to define covariates in the study

This supplementary material has been provided by the authors to give readers additional information about their work.

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e-Table 1. Average Number of Administrations to Reach a Cumulative Dose of 1000mg of Iron Repletion

IV Iron Product	Recommended Maximum Daily Dose	# of Administrations*
Iron Dextran	100mg	2.0
Iron Gluconate	125mg	7.0
Iron Sucrose	200mg	4.9
Ferumoxytol	510mg	1.9

*An administration is identified as a single billing claim for an IV iron injection or infusion. The actual iron dose in a given administration of iron can differ.

e-Table 2. Baseline Characteristics at Incidence for Patients Receiving IV Iron (2003-2013)

Baseline Covariates	Iron Dextran (N = 247,500)	Iron Gluconate (N = 94,400)	Iron Sucrose (N = 264,166)	Ferumoxytol (N = 82,117)
<i>Age Mean(SD)</i>	73.2 (11.3)	73.4 (11.8)	73.8 (11.5)	75.3 (10.5)
Gender				
<i>Male</i>	33.7%	36.9%	37.8%	39.4%
<i>Female</i>	66.3%	63.1%	62.2%	60.6%
Race				
<i>White</i>	86.9%	83.3%	85.8%	84.1%
<i>Black</i>	9.6%	12.3%	10.3%	11.7%
<i>Asian</i>	0.7%	0.9%	0.9%	1.1%
<i>Hispanic</i>	1.7%	2.0%	1.5%	1.4%
<i>Other/Unknown</i>	1.2%	1.5%	1.5%	1.6%
Regions				
<i>Northeast</i>	10.5%	23.0%	20.2%	14.2%
<i>Midwest</i>	20.5%	22.2%	30.9%	20.9%
<i>South</i>	54.6%	40.3%	34.1%	50.7%
<i>West</i>	14.2%	14.0%	14.7%	14.1%
<i>Other</i>	0.2%	0.5%	0.2%	0.2%
Indications				
<i>Anemia - CKD</i>	21.5%	42.6%	54.5%	59.9%
<i>Anemia - GI/GU Bleeding</i>	21.7%	18.2%	14.0%	11.9%
<i>Anemia - Other</i>	56.8%	39.3%	31.5%	28.2%
Conditions				
<i>Asthma</i>	13.4%	13.9%	13.5%	13.6%
<i>COPD</i>	29.2%	30.4%	30.1%	29.7%
<i>Coronary Heart Disease</i>	41.0%	46.6%	47.1%	47.1%
<i>Depression</i>	16.8%	17.1%	17.8%	17.7%
<i>Drug Allergy</i>	6.5%	6.5%	7.2%	10.0%
<i>Food Allergy</i>	0.4%	0.4%	0.4%	0.6%
<i>Hypertension</i>	82.7%	87.4%	89.8%	91.6%
With Part D Enrollment*	Iron Dextran (N = 83,627)	Iron Gluconate (N = 37,614)	Iron Sucrose (N = 127,472)	Ferumoxytol (N = 46,046)
Concomitant Medications				
<i>NSAIDs</i>	7%	6%	5%	5%
<i>Antibiotics</i>	2%	2%	3%	2%
<i>Beta-blockers</i>	33%	38%	41%	43%
<i>ACE Inhibitors</i>	25%	24%	25%	25%

**Note: Data on concomitant medications were only collected for the subset of beneficiaries who were enrolled in Medicare Part D (prescription drugs) in 2007- 2013 for the six months prior to index date.*

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Sensitivity Analysis Results

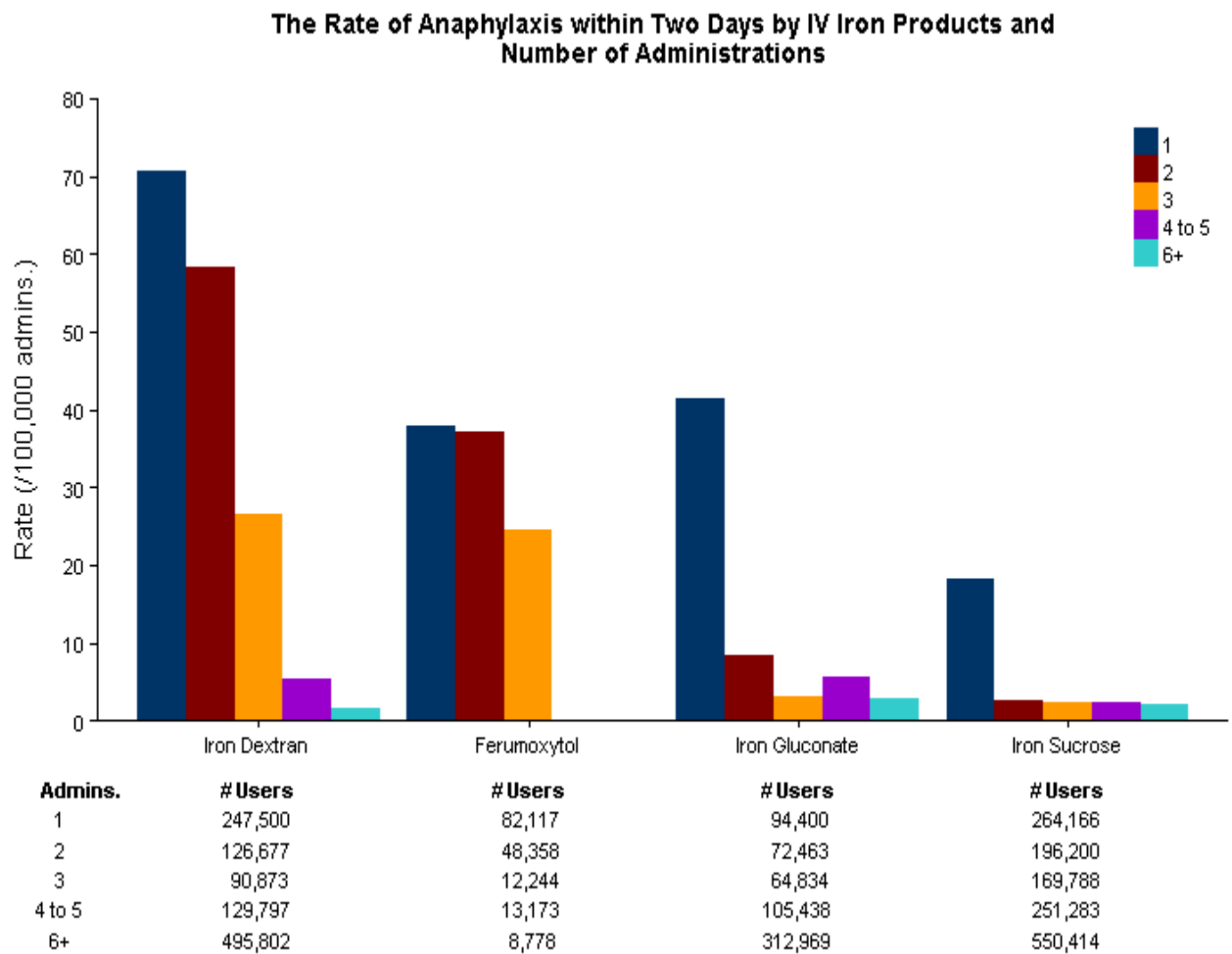
e-Table 3. Risk of Anaphylaxis at First Administration for Incident Users within Two-Days of IV Iron Administration

IV Iron	2003-2013			2010 to 2013			
	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
# Anaphylaxis Cases	48	175	39	21	31	69	18
# New Users	264,166	247,500	94,400	134,836	82,117	77,935	34,029
Rate per 100,000 persons (95% CI)	18.2 (13.5, 24.3)	70.7 (60.8, 82.2)	41.3 (29.8, 57.1)	15.6 (9.9, 24.3)	37.8 (26.1, 54.3)	88.5 (69.4, 112.7)	52.9 (32.3, 85.4)
Adjusted Odds Ratio (95% CI)*	Reference	3.6 (2.5, 5.2)	2.2 (1.4, 3.5)	Reference	2.5 (1.3, 4.8)	5.4 (3.0, 9.8)	3.3 (1.6, 7.0)
p-value**		<0.001	<0.001		0.004	<0.001	<0.001

*: adjusted for age, indication, CHD, hypertension.

**: P value adjusted for multiple comparisons.

e-Figure 1.



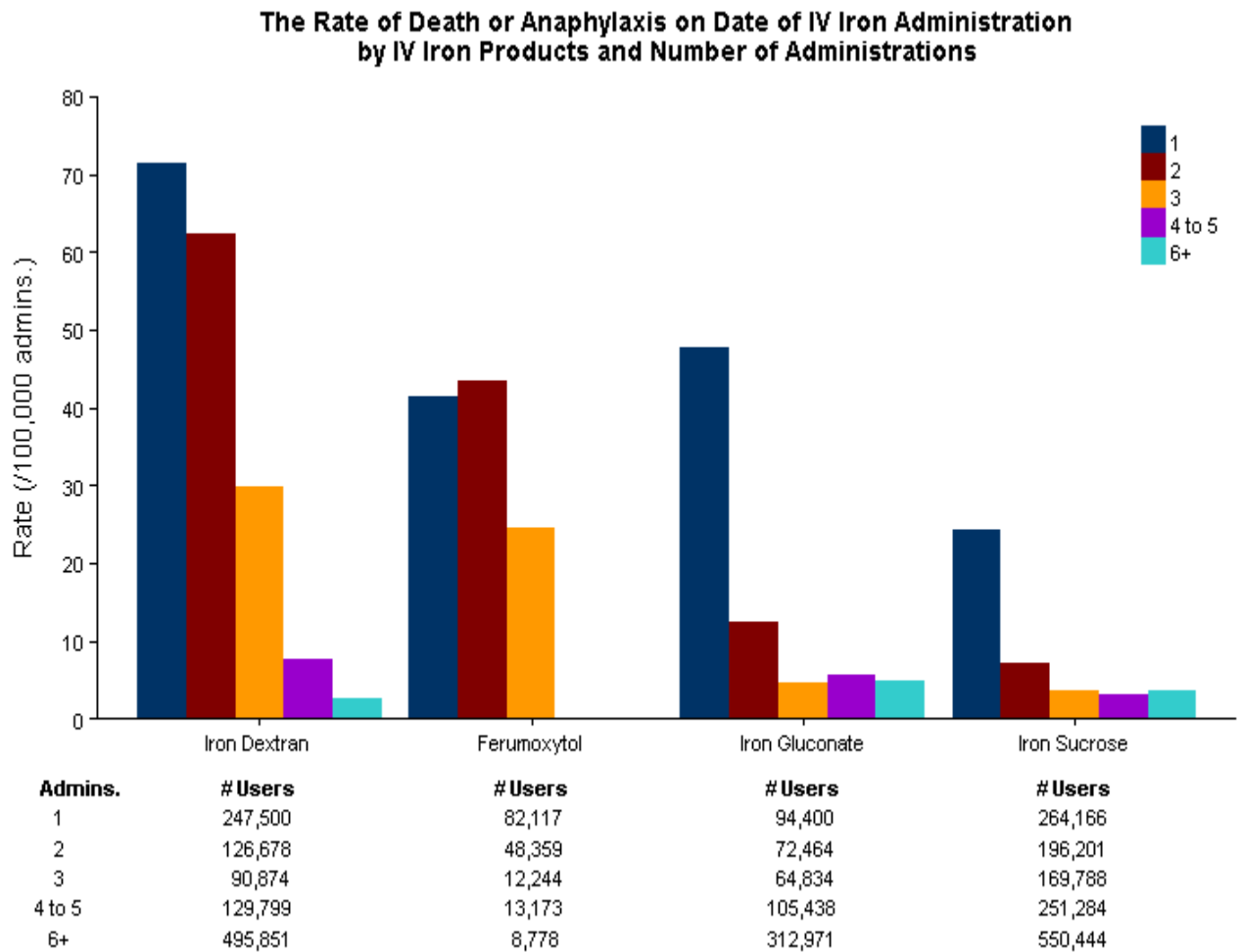
e-Table 4. Risk of Death or Anaphylaxis on the Date of First IV Iron Administration for Incident IV Iron Users

IV Iron	2003-2013			2010 to 2013			
	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
# Death or Anaphylaxis Cases	64	177	45	33	34	69	18
# New Users	264,166	247,500	94,400	134,836	82,117	77,935	34,029
Rate per 100,000 persons (95% CI)	24.2 (18.7, 30.9)	71.5 (61.4, 82.9)	47.7 (34.8, 63.8)	24.5 (16.8, 34.4)	41.4 (28.7, 57.9)	88.5 (68.9, 112.0)	52.9 (31.3, 83.6)
Adjusted Odds Ratio (95% CI)*	Reference	2.8 (2.0, 3.9)	1.9 (1.2, 2.9)	Reference	1.7 (0.9, 3.0)	3.7 (2.2, 6.1)	2.2 (1.1, 4.3)
p-value**		<0.001	0.00		0.08	<0.001	0.024

*: adjusted for age, indication, CHD, hypertension.

**: P value adjusted for multiple comparisons.

e-Figure 2.



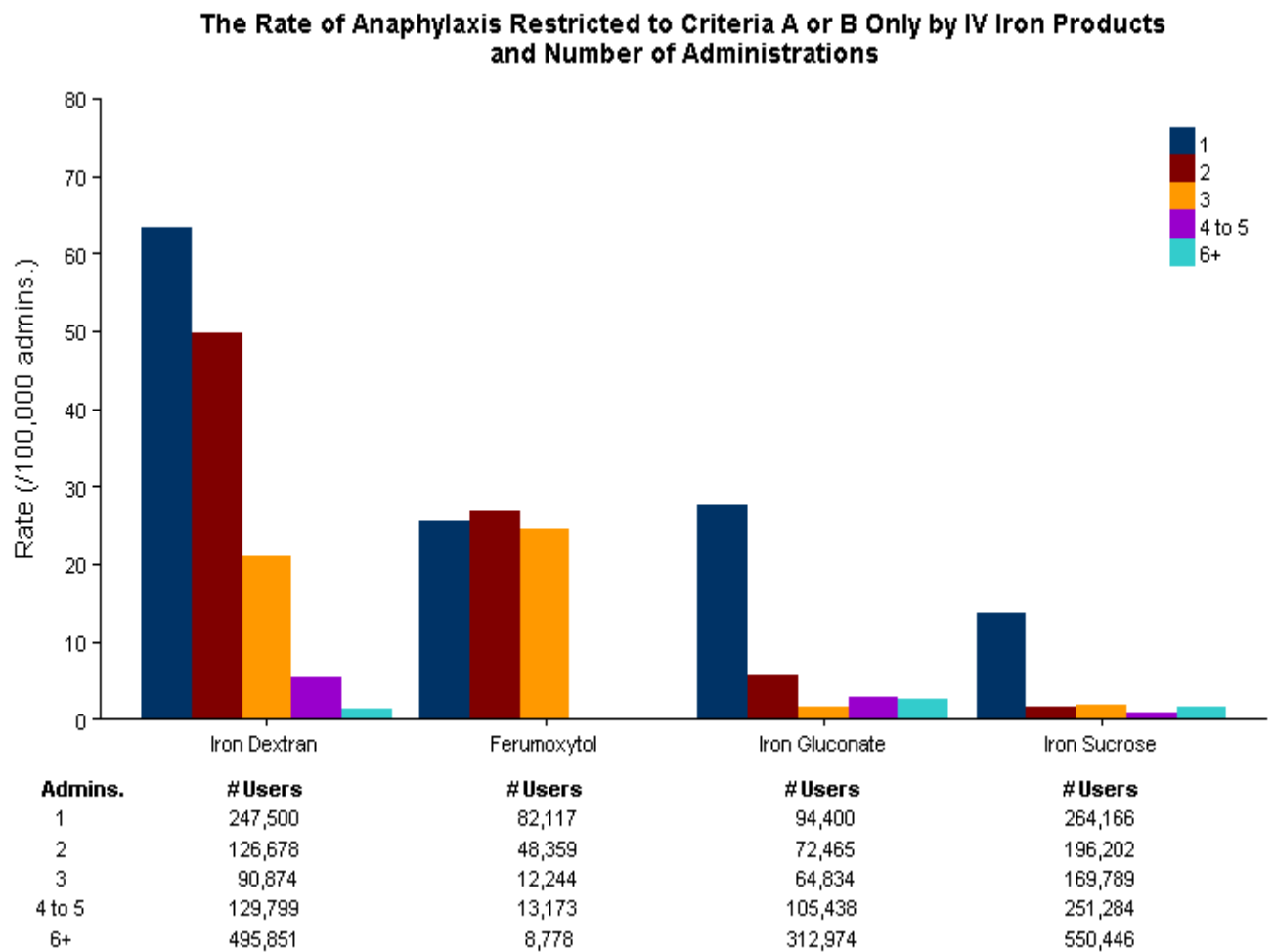
e-Table 5. Risk of Anaphylaxis Restricted to Criteria A or B Only at First Administration for Incident IV Iron Users

IV Iron	2003-2013			2010 to 2013			
	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
# Anaphylaxis Cases	36	157	26	15	21	58	9
# New Users	264,166	247,500	94,400	134,836	82,117	77,935	34,029
Rate per 100,000 persons (95% CI)	13.6 (9.7, 19.1)	63.4 (54.1, 74.4)	27.5 (18.4, 41.0)	11.1 (6.5, 18.8)	25.6 (16.2, 39.8)	74.4 (57, 96.9)	26.4 (12.9, 52.2)
Adjusted Odds Ratio (95% CI)*	Reference	4.3 (2.8, 6.5)	2.0 (1.1, 3.4)	Reference	2.4 (1.1, 5.2)	6.3 (3.2, 12.6)	2.3 (0.9, 6.2)
p-value**		<0.001	0.02		0.03	<0.001	0.116

*: adjusted for age, indication, CHD, hypertension.

**: P value adjusted for multiple comparisons.

e-Figure 3.



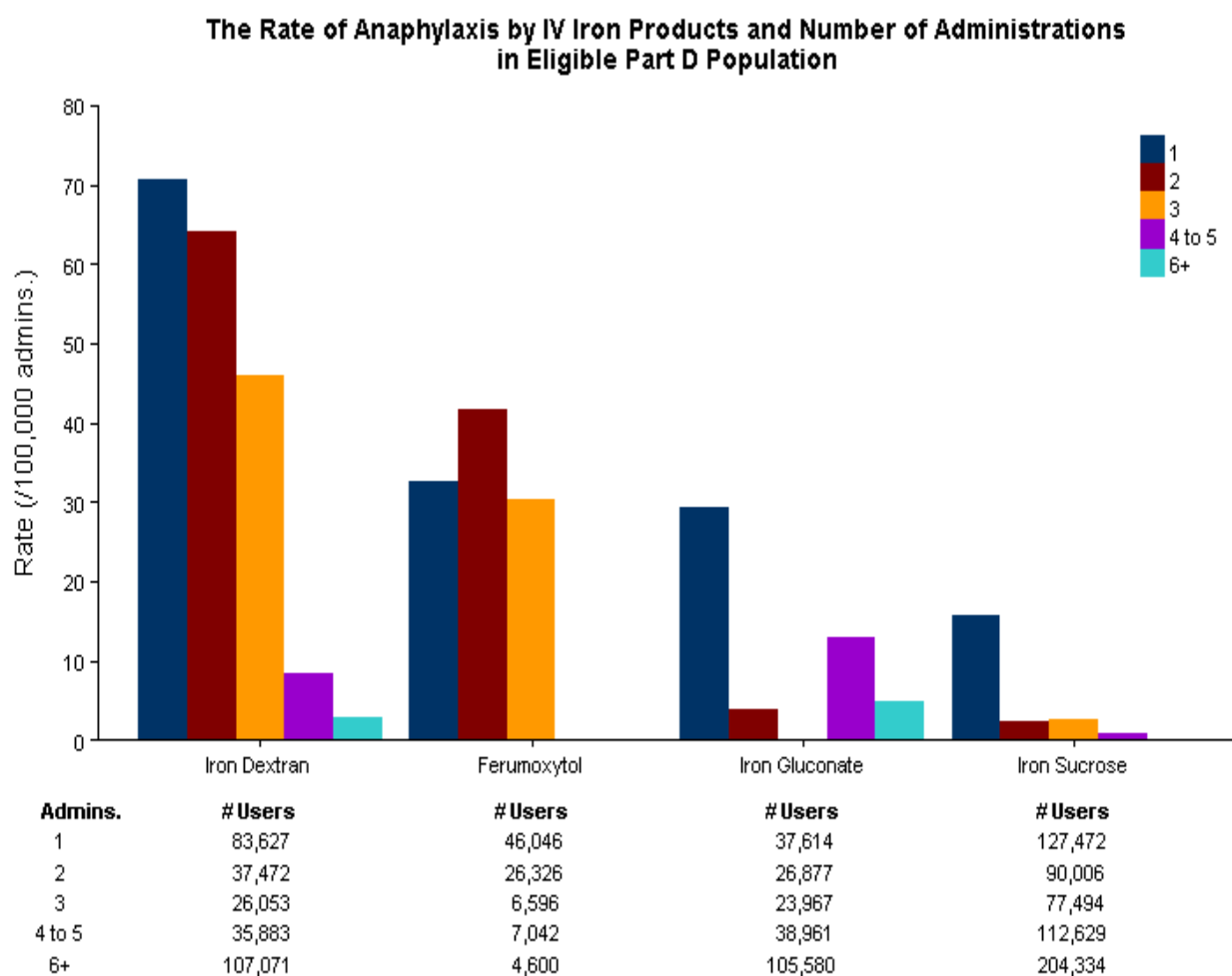
e-Table 6. Risk of Anaphylaxis at First Administration for Incident IV Iron Users in Part D Enrolled Population

IV Iron	2003-2013			2010 to 2013			
	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
# Anaphylaxis Cases	20	59	11	11	15	45	8
# New Users	127,472	83,627	37,614	80,127	46,046	45,313	20,348
Rate per 100,000 persons (95% CI)	15.7 (9.8, 24.7)	70.6 (54.2, 91.7)	29.2 (15.4, 54.1)	13.7 (7.2, 25.4)	32.6 (18.9, 55.1)	99.3 (73.3, 134.1)	39.3 (18.3, 80.8)
Adjusted Odds Ratio (95% CI)*	Reference	4.2 (2.3, 7.6)	1.8 (0.8, 4.2)	Reference	2.4 (1.0, 6.2)	6.7 (3.0, 14.9)	2.7 (0.9, 8.1)
p-value**		<0.001	0.20		0.06	<0.001	0.075

*: adjusted for age, indication, CHD, hypertension, antibiotics, ACE inhibitors, beta-blockers.

**: P value adjusted for multiple comparisons.

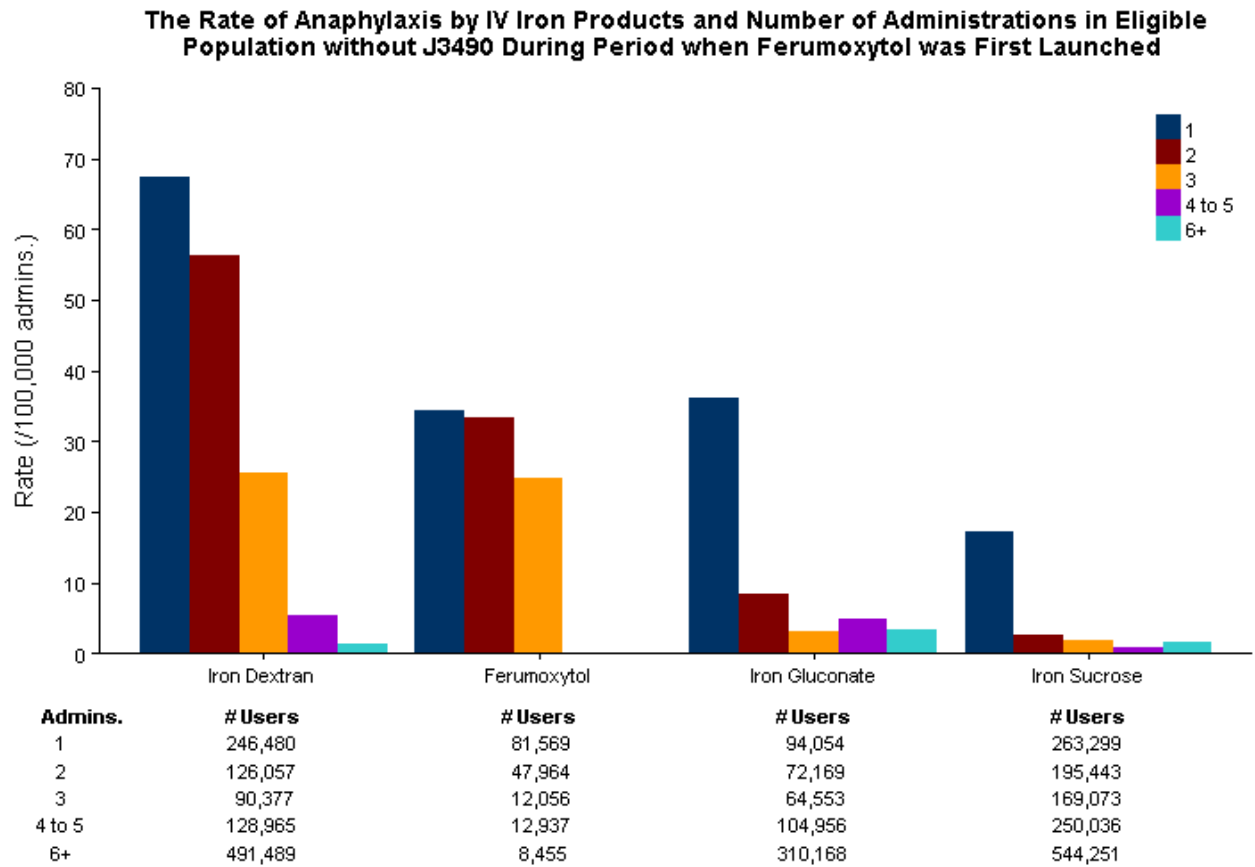
e-Figure 4.



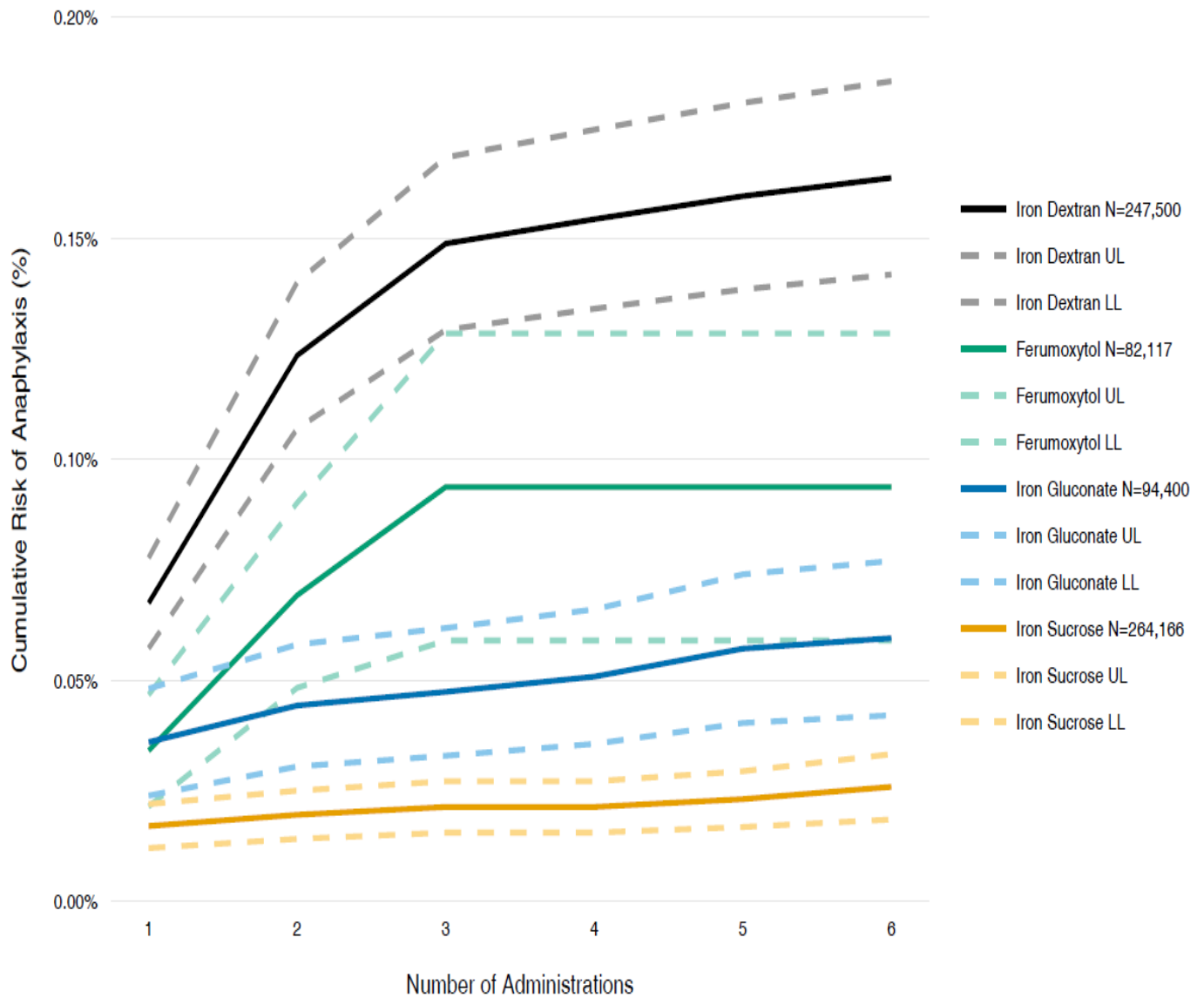
**e-Table 7. Risk of Anaphylaxis at First Administration for Incident IV Iron Users
(without J3490 code during 06/2009-12/2009)**

IV Iron	2003-2013			2010 to 2013			
	Iron Sucrose	Iron Dextran	Iron Gluconate	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
# APH Cases	45	166	34	21	28	66	16
# New Users	263,299	246,480	94,054	134,427	81,569	77,641	33,897
Rate per 100,000 persons (95% CI)	17.1 (12.6, 23.1)	67.3 (57.7, 78.6)	36.1 (25.4, 51.1)	15.6 (9.9, 24.3)	34.3 (23.3, 50.3)	85.0 (66.3, 108.8)	47.2 (27.9, 78.5)
Adjusted Odds Ratio (95% CI)*	Reference	3.6 (2.5, 5.3)	2.0 (1.2, 3.4)	Reference	2.2 (1.1, 4.4)	5.2 (2.9, 9.4)	2.9 (1.4, 6.4)
p-value**		<0.001	<0.001		0.01	<0.001	<0.001
*: adjusted for age, indication, CHD, hypertension.							
**: P value adjusted for multiple comparisons.							

e-Figure 5.



e-Figure 6. Cumulative Risk of Anaphylaxis by Number of Administration and IV Iron Products



e-Table 8. Risk of Anaphylaxis at First Administration by IV Iron Products (01/2006 to 03/ 2008) when Iron Dextran could be distinguished

IV Iron Products	# Anaphylaxis	# Patients	Rate of Anaphylaxis (per 100,000 persons)
Infed[®]	40	48,772	82.0 (59.4, 112.8)
Dexferrum[®]	3	5,142	58.3 (15.1, 185.8)
Iron Gluconate	8	22,241	36.0 (16.7, 73.9)
Iron Sucrose	6	48,828	12.3 (5.0, 28.2)

e-Table 9. Rate of Anaphylaxis by Daily Dosage Category by IV Iron Products

IV Iron Cohort	Daily Dosage	# Patients	# Anaphylaxis	Rate (/100,000 Persons)	95% CI (/100,000 Persons)
Iron Dextran	Within Recommended Dosage ($\leq 100\text{mg}$)	66,075	108	163.5	(134.7,198.1)
	100mg < Dosage $\leq 1000\text{mg}$	109,302	35	32.0	(22.6,45.1)
	1000mg < Dosage $\leq 2500\text{mg}$	68,305	21	30.7	(19.5,47.9)
	Outlier (Dosage > 2500mg)	3,818	3	78.6	(20.3,250.1)
Iron Gluconate	Within Recommended Dosage ($\leq 125\text{mg}$)	78,076	19	24.3	(15.1,38.8)
	Above Recommended Dosage ($>125\text{mg}$)	16,308	15	92.0	(53.4,155.5)
Iron Sucrose	Within Recommended Dosage ($\leq 200\text{ mg}$)	197,544	9	4.6	(2.2,9.0)
	Above Recommended Dosage ($>200\text{mg}$)	66,599	36	54.1	(38.4,75.7)
Ferumoxytol	Within Recommended Dosage ($\leq 510\text{mg}$)	78,944	26	32.9	(22.0,49.0)
	Above Recommended Dosage ($>510\text{mg}$)	3,171	2	63.1	(10.9,254.0)

Appendix I. Anaphylaxis Definition

■ Criterion A: Encounter with ICD-9 code- 995.0 [other anaphylactic shock] inpatient or emergency department encounter ■ Criterion B: Encounter with ICD-9 code 995.0 [other anaphylactic shock] outpatient encounter <u>PLUS</u> a code for one of the following symptoms/procedures/treatments: • bronchospasm (519.11) or • stridor (786.1) or • hypotension (458.9) or • epinephrine (J0170 or J0171) or • injection of diphenhydramine (J1200) or • CPR (92950 or 99.60) ■ Criterion C: Encounter with ICD-9 code- (995.3 [allergy unspecified] or 995.2 [other unspecified adverse effect of drug] or E930-E949 [drugs, medicinal and biological substances causing adverse effects in therapeutic use]) <u>inpatient or emergency department encounter PLUS a code for one of the following symptoms/procedures/treatments:</u> • bronchospasm (519.11) or • stridor (786.1) or • injection of diphenhydramine (J1200) • and <u>a code for one</u> of the following symptoms/procedures/treatments • hypotension (458.9) or • epinephrine (J0170 or J0171) or • CPR (92950 or 99.60)	
Notes: <i>Diagnosis codes in any position are accepted</i>	
<i>All codes must occur on the same day as the IV Iron administration</i>	
<i>Patients must meet at least one of the criteria A-C to count as having anaphylaxis</i>	

Appendix II. International Classification of Disease, 9th edition, Clinical Modification (ICD 9-CM) codes used to define covariates in the study

Covariates	ICD-9 Codes
CHD	414.x
Hypertension	401.x, 402.x, 403.x, 404.x, 405.x, 997.91
Indication - Chronic Kidney Disease	585.x
Indication – Gastrointestinal or Genitourinary Bleeding	455.x, 456.0, 456.20, 530.1, 530.7, 530.82, 531.0, 531.1, 531.2, 531.3, 531.4, 531.5, 531.6, 531.7, 531.9, 532.0, 532.1, 532.2, 532.3, 532.4, 532.5, 532.6, 532.7, 532.9, 533.0, 533.1, 533.2, 533.3, 533.4, 533.5, 533.6, 533.7, 533.9, 534.0, 534.1, 534.2, 534.3, 534.4, 534.5, 534.6, 534.7, 534.9, 535.00, 535.01, 535.10, 535.11, 535.20, 535.21, 535.30, 535.31, 535.40, 535.41, 535.50, 535.51, 535.60, 535.61, 537.83, 562.00, 562.01, 562.02, 562.03, 562.10, 562.11, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9, 593.81, 599.7, 599.70, 599.71, 599.72, 623.8, 626.2, 626.6
Indication – Other	218.x, 579.x, 627.0, 627.1, 640.x, 641.x, 642.x, 643.x, 645.x, 646.x, 647.x, 648.x, 649.x, V22.x, V23.x
Asthma	493.x
COPD	ICD-9 DGN: 491.x, 492.x, 494.x, 496.x ICD-9 HCPC: 32141, 32491, G8093, G8094
Drug Allergy	995.27, 692.3, 693.0, V14.x
Food Allergy	692.5, 693.1, 995.6, 995.7, V15.01, V15.02, V15.03, V15.04, V15.05

Appendix III. International Classification of Disease, 9th edition, Clinical Modification (ICD 9-CM) HCPCS codes used to define IV Iron exposure

IV Iron	ICD-9 HCPCS	Description
iron dextran	J1750	Injection, iron dextran, 50 mg
	J1751*	Injection, iron dextran, 165, 50 mg
	J1752*	Injection, iron dextran, 267, 50 mg
	J1760	Injection, iron dextran, 2 cc
	J1770	Injection, iron dextran, 5 cc
	J1780	Injection, iron dextran, 10 cc
	Q4098	Injection, iron dextran, 50 mg
iron gluconate	J2915	Injection, sodium ferric gluconate complex in sucrose injection, 62.5 mg
	J2916	Injection, sodium ferric gluconate complex in sucrose injection, 12.5 mg
iron sucrose	J1755	Injection, iron sucrose, 20 mg
	J1756	Injection, iron sucrose, 1 mg
ferumoxytol	Q0138	Injection, ferumoxytol, for treatment of iron deficiency anemia, 1 mg
	Q0139	Injection, ferumoxytol, for treatment of iron deficiency anemia, 1 mg

*These codes were used to define INFeD (J1751) and Dexferrum (J1752) during the 27 month period when they were coded differently. These codes were discontinued in March 2008.