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Risks for Anaphylaxis With Intravenous Iron Formulations

A Retrospective Cohort Study

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Background: The risks for anaphylaxis among intravenous (IV) iron products currently in use have not been assessed.

Objective: To compare risks for anaphylaxis among 5 IV iron products that are used frequently.

Design: Retrospective cohort study using a target trial emulation framework.

Setting: Medicare fee-for-service data with Part D coverage between July 2013 and December 2018.

Participants: Older adults receiving their first administration of IV iron.

Measurements: The primary outcome was the occurrence of anaphylaxis within 1 day of IV iron administration, ascertained using a validated case definition. Analysis was adjusted for 40 baseline covariates using inverse probability of treatment weighting. The adjusted incidence rates (IRs) for anaphylaxis per 10 000 first administrations and odds ratios (ORs) were computed.

Results: The adjusted IRs for anaphylaxis per 10 000 first administrations were 9.8 cases (95% CI, 6.2 to 15.3 cases) for iron dextran, 4.0 cases (CI, 2.5 to 6.6 cases) for ferumoxytol, 1.5 cases (CI, 0.3 to 6.6 cases) for ferric gluconate, 1.2 cases (CI, 0.6 to 2.5 cases) for iron sucrose, and 0.8 cases (CI, 0.3 to 2.6 cases) for ferric carboxymaltose. Using iron sucrose as the referent category, the adjusted ORs for anaphylaxis were 8.3 (CI, 3.5 to 19.8) for iron dextran and 3.4 (CI, 1.4 to 8.3) for ferumoxytol. When cohort entry was restricted to the period after withdrawal of high-molecular-weight iron dextran from the U.S. market in 2014, the risk for anaphylaxis associated with low-molecular-weight iron dextran (OR, 8.4 [CI, 2.8 to 24.7]) did not change appreciably. Anaphylactic reactions requiring hospitalizations were observed only among patients using iron dextran or ferumoxytol.

Limitation: Generalizability to non-Medicare populations.

Conclusion: The rates of anaphylaxis were very low with all IV iron products but were 3- to 8-fold greater for iron dextran and ferumoxytol than for iron sucrose.

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Anaphylaxis is an acute and potentially deadly systemic allergic reaction that is poorly understood but may be mediated by mast cell and basophil degranulation. Anaphylactic reactions can occur with any intravenous (IV) iron formulation, but with the current formulations—low-molecular-weight iron dextran (INFeD [Allergan] in the United States and CosmoFer [Pharmacosmos] in Europe), ferumoxytol (Feraheme [AMAG Pharmaceuticals] in the United States and Rienso [Takeda] in Europe), ferric gluconate (Ferrlecit [Sanofi]), iron sucrose (Venofer [American Regent]), and ferric carboxymaltose (Injectafer [American Regent] in the United States and Ferinject [Vifor Pharma] in Europe)—the risks seem to be very low. Randomized controlled trials are generally considered the most rigorous method for assessing the efficacy and safety of medications. However, given the rarity of anaphylactic events, clinical trials—or meta-analyses of such trials—are not adequately powered to detect differences in anaphylaxis among formulations. For instance, a relatively large trial of 1997 patients using ferric carboxymaltose and ferumoxytol found 0 cases of anaphylaxis, whereas another trial of more than 700 patients recorded a single case (1, 2).

When the prevalence of adverse events is very low, large-scale epidemiologic investigations may provide the best guide to assess the relative risks for these events, but few studies have examined the risk for anaphylaxis among the IV iron formulations. One such study used Medicare data from 2003 to 2013 (3). During this period, high-molecular-weight iron dextran—known to be associated with hypersensitivity reactions—was still in use (4–6). Since this Medicare study, another IV iron product, ferric carboxymaltose (approved in the United States in 2013), has become widely used. Since 2013, IV iron has been used more frequently to treat iron deficiency (7, 8). In uncomplicated iron deficiency (9), oral iron remains the treatment of choice, given its safety, effectiveness, availability, and low cost, but gastrointestinal symptoms are the principal limitation to its use (10). Intravenous iron formulations may be preferred in patients who do not tolerate oral iron or who have an unsatisfactory response. Intravenous formulations may also be the treatment of choice for iron deficiency if rapid correction is needed or when complicated by chronic blood loss, malabsorption, inflammatory bowel disease, some forms of functional iron deficiency, chronic heart failure, or rare genetic disorders, such as iron-refractory iron deficiency anemia.

Consequently, a new large-scale, epidemiologic investigation that directly compares the risks for anaphylaxis across frequently used IV iron products is timely. Using a target trial emulation approach within Medicare fee-for-service data from 2013 to 2018, our study compares this risk for current IV iron products among older adults, who have a higher risk for drug-related anaphylaxis (11); separates the effects of low-molecular-weight from high-molecular-weight iron dextran; and includes ferric carboxymaltose.

Table 1. Specification and Emulation of a Target Trial Evaluating 5 IV Iron Formulations and Risk for Anaphylaxis

Protocol Component	Target Trial Specification	Target Trial Emulation Using Medicare Data
Eligibility criteria	Age >65 y between July 2013 and December 2018 Indication for IV iron (e.g., intolerance to oral iron) Exclusion criteria: 1. Prior use of IV iron products 2. History of anaphylaxis 3. Recent transfusion or use of an erythropoietin-stimulating agent within 30 d 4. ESRD or HIV	Age >65 y between July 2013 and December 2018 in Medicare using IV iron Exclusion criteria: 1. Patients required to be new users of IV iron with at least 365 d of nonuse before the index date; all available look-back going back to January 2007 was used to exclude prior IV iron use Exclusion criteria 2, 3, and 4 were the same as in the target trial
Treatment strategies	First administration of 1) either low- or high-molecular-weight iron dextran (only low-molecular-weight version after 2014), 2) ferumoxytol, 3) ferric gluconate, 4) iron sucrose, or 5) ferric carboxymaltose	Treatment strategies were the same as in the target trial; IV iron administration was ascertained using HCPCS codes
Treatment assignment	Individuals are randomly assigned to 1 of the 5 treatment strategies at baseline Neither patient nor provider was blinded to the intervention	Patients were classified according to their IV iron Randomization was emulated by adjusting for imbalances in 40 baseline covariates using a multinomial extension of the inverse probability of treatment weighting approach Neither patient nor provider was blinded to the intervention
Follow-up	Starts on the day of first IV iron administration and ends on the day after administration	Same as in the target trial
Outcomes	Anaphylaxis	Same as in the target trial; see text for details
Causal contrasts	Per protocol effect	Same as in the target trial
Statistical analysis	IRs of anaphylaxis per 10 000 patients Relative risks for anaphylaxis, using iron sucrose as referent category	Adjusted IRs and relative risks were estimated via inverse probability of treatment weighing

ESRD = end-stage renal disease; HCPCS = Healthcare Common Procedure Coding System; IR = incidence rate; IV = intravenous.

METHODS

The study was approved by the Rutgers Institutional Review Board, and the appropriate data use agreements were in place.

Target Trial Emulation

Our target trial emulation framework has 2 steps (12). First, we specified the protocol of a hypothetical, pragmatic, unblinded clinical trial that aims to elucidate the risk for anaphylaxis across the 5 formulations of IV iron examined. Table 1 summarizes the key design elements of such a trial. In brief, the population of this target trial comprises adults older than 65 years with iron deficiency anemia who have an indication for IV iron use and have not previously used IV iron. The individual iron formulations represent the 5 treatment strategies. The outcome of interest is anaphylaxis, which is assessed within 1 day of administration of IV iron. Second, we used a large database of Medicare beneficiaries to emulate this target trial. The design elements of our emulation approach are articulated in further detail in the following sections and summarized in Table 1.

Data Sources

Study participants were drawn from insurance claims from Medicare, a U.S. federal program that provides health care to U.S. citizens aged 65 years or older. We used a 50% sample of Medicare fee-for-service patients with Part D prescription claims between January 2007 and December 2018. Data elements of interest included patient sociodemographic characteristics, medical and pharmacy enrollment status, pharmacy dispensing files, and inpatient and outpatient medical use files—which provided information on International Classification of Diseases, 9th and 10th Revision, codes; Current Procedural Terminology (CPT), Fourth Edition, codes; and Healthcare Common Procedure Coding System (HCPCS) codes. Our study had no missing data.

Eligibility Criteria and Treatment Strategies

We used HCPCS codes to identify a cohort of older adults receiving their first administration of one of the following IV iron formulations between July 2013 and December 2018: ferric carboxymaltose, ferumoxytol, ferric gluconate, iron dextran, or iron sucrose. We restricted the study cohort entry to July 2013 onward to coincide with the approval of ferric carboxymaltose. Ferric derisomaltose (Monoferric [Pharmacosmos] in the United States and Monofer [Pharmacosmos] in Europe) was approved in 2020 and was not included in our analysis. To mitigate concerns about confounding and emulate the eligibility criterion of new use, cohort membership was restricted to patients receiving their first administration of IV iron. This date of first administration was designated as the index date. New users were defined as those initiating treatment with the study medication without evidence of having used it for a minimum of 365 days before this index date. To better emulate the criterion of no prior use, we used all available prior baseline data for each patient going back as far as January 2007 to exclude those who had used IV iron products before July 2013 (13).

Other patient characteristics, including the baseline characteristics and eligibility criteria, were ascertained using a fixed look-back window of 365 days before the index date (that is, the baseline period). We excluded

persons who were not continuously enrolled in Medicare Parts A, B, and D or were enrolled in managed care for any time during the baseline period. We also excluded those with a diagnosis of end-stage renal disease, HIV, a history of anaphylactic reactions, or a recent (<30 days before index date) blood transfusion or use of an erythropoietin-stimulating agent (see the **Appendix Figure**, available at Annals.org, for the study design).

Treatment Assignment

To emulate the randomization procedure in the target trial, we accounted for imbalances in patient characteristics across the IV iron formulations using a multinomial extension of the propensity score–based inverse probability of treatment weights (IPTW) (14, 15). Propensity scores were estimated using a multinomial logistic regression that modeled the probability of initiating treatment with 1 of the 5 IV iron formulations as the dependent variable, and 40 baseline patient characteristics as the independent variables. These covariates corresponded to the domains of sociodemographic characteristics (such as age, sex, and race), comorbid conditions, potential indications for IV iron use (such as chronic kidney disease), use of other pertinent medications putatively associated with risk for anaphylaxis (such as angiotensin-converting enzyme inhibitors), and markers of health care use (such as number of hospitalizations). All analyses were done using SAS, version 9.4 (SAS Institute).

Follow-up and Outcomes

The primary study end point was the occurrence of anaphylaxis, which was ascertained using a validated case definition based on the combination of International Classification of Diseases, CPT, and HCPCS codes (16). The algorithm has an overall positive predictive value (PPV) of 75% and comprises the following 3 components: 1) anaphylaxis resulting in hospitalization (PPV = 77%), 2) an outpatient or emergency department visit due to anaphylactic shock accompanied by codes relating to the administration of cardiopulmonary resuscitation or epinephrine or the occurrence of hypotension (PPV = 73%), and 3) 2 separate encounters for anaphylactic shock within the same day representing different encounter types (that is, inpatient, outpatient, or emergency department visit; PPV = 88%). On the basis of the onset of such reactions observed in clinical trials and spontaneous adverse drug reaction reporting (17, 18), cases of anaphylaxis were restricted to those occurring within 1 day of IV iron administration.

Statistical Analysis

We assessed the performance of IPTW in adjusting for differences in baseline characteristics by cross-tabulating patient characteristics before and after IPTW weighting. The per protocol effect was the primary causal contrast of interest. We calculated the incidence rates (IRs) of anaphylaxis by formulation type (per 10 000 first administrations) and estimated adjusted odds ratios (ORs) along with their corresponding 95% CIs using IPTW-weighted logistic regressions that modeled anaphylaxis as the outcome and individual IV iron formulations as the dependent variable (with iron sucrose as the referent category). We also calculated the E-value to assess the potential for unmeasured confounding (19). In brief, the E-value estimates the minimum strength of association required for an unmeasured confounder to move the observed causal effect toward a null value of 1.

Six additional analyses were conducted. First, we reported the incidence for each contributing component of the composite end point of anaphylaxis. Second, because the criterion requiring 2 separate encounter types for anaphylaxis within the same day was the most frequently occurring component with the highest PPV (88%), we also separately estimated ORs for this component. Similar analyses for the other 2 components were considered but were not estimated because we lacked sufficient power. Third, because HCPCS codes identifying iron dextran cannot distinguish high-molecular-weight iron dextran from its low-molecular-weight counterpart, we did an analysis restricting the study period to after 2014, when the last available high-molecular-weight iron dextran (that is, Dexferrum [American Regent]) was withdrawn from the U.S. market (20). Fourth, we examined a composite outcome of anaphylaxis or death occurring within 1 day of IV iron administration. Fifth, we varied the minimum look-back window defining new use from 1 year to 2 years. Sixth, although our primary analysis excluded patients with a history of anaphylaxis, we did sensitivity analyses assessing the effect of including such patients in our analysis.

Role of the Funding Source

This study was not funded.

RESULTS

After the inclusion and exclusion criteria were applied, 167 925 eligible patients had received their first administration of an IV iron product between July 2013 and December 2018. Patients were categorized into 1 of the 5 treatment groups according to the medication received. **Table 2** shows the unadjusted distribution of baseline characteristics across the iron products. Iron sucrose (n = 59 755) and ferumoxytol (n = 40 778) were the most commonly prescribed therapies, followed by ferric carboxymaltose (n = 36 399), iron dextran (n = 19 225), and ferric gluconate (n = 11 768). Before IPTW adjustment, clinical characteristics differed among the iron products (**Table 2**). Chronic kidney disease was more prevalent among users of iron sucrose and ferumoxytol than among iron dextran users, reflecting the differences in their approved indications for use. Of note, patients with a history of drug allergies were least likely to receive iron dextran. After IPTW adjustment, all baseline characteristics were well balanced across the 5 products (**Table 3**). Although all patients in our cohort had not received IV iron for at least 1 year preceding their index date, the mean time without IV iron use before the index date was much higher at 5.9 years (SD, 3.1).

Primary Analysis

Table 4 shows the adjusted IRs (per 10 000 first administrations) for the composite end point of anaphylaxis. Use

Table 2. Baseline Characteristics Before Weighting*

Characteristic	Ferumoxytol (*n* = 40 778)	Iron Dextran (*n* = 19 225)	Ferric Carboxymaltose (*n* = 36 399)	Iron Sucrose (*n* = 59 755)	Ferric Gluconate (*n* = 11 768)
Sociodemographic characteristics					
Male sex	14 911 (36.6)	6325 (32.9)	12 634 (34.7)	21 714 (36.3)	4055 (34.5)
Mean age (SD), *y*	77.9 (7.4)	76.8 (7.2)	77.0 (7.2)	77.7 (7.5)	78.1 (7.6)
Age quartile					
1	9472 (23.2)	5470 (28.5)	9863 (27.1)	14 819 (24.8)	2762 (23.5)
2	9521 (23.3)	4767 (24.8)	9133 (25.1)	13 846 (23.2)	2715 (23.1)
3	10 263 (25.2)	4589 (23.9)	8874 (24.4)	14 712 (24.6)	2828 (24.0)
4	11 532 (28.3)	4399 (22.9)	8529 (23.4)	16 378 (27.4)	3463 (29.4)
Race					
White	34 538 (84.7)	15 976 (83.1)	31 201 (85.7)	47 855 (80.1)	9072 (77.1)
Black	3385 (8.3)	1491 (7.8)	2566 (7.0)	5417 (9.1)	1238 (10.5)
Other	2865 (7.0)	1758 (9.1)	2632 (7.2)	6483 (10.8)	1458 (12.4)
Year					
2013	2126 (5.2)	1244 (6.5)	701 (1.9)	2801 (4.7)	574 (4.9)
2014	7609 (18.7)	4218 (21.9)	2199 (6.0)	11 100 (18.6)	2054 (17.5)
2015	7011 (17.2)	4016 (20.9)	3440 (9.5)	10 514 (17.6)	2050 (17.4)
2016	7251 (17.8)	3559 (18.5)	5184 (14.2)	10 891 (18.2)	2012 (17.1)
2017	6842 (16.8)	4506 (23.4)	8527 (23.4)	11 352 (19.0)	2557 (21.7)
2018	9949 (24.4)	1682 (8.7)	16 348 (44.9)	13 097 (21.9)	2521 (21.4)
Comorbid conditions					
Chronic kidney disease	20 610 (50.5)	5150 (26.8)	12 564 (34.5)	31 846 (53.3)	4974 (42.3)
Gastrointestinal bleeding	20 462 (50.2)	10 359 (53.9)	19 739 (54.2)	30 149 (50.5)	6280 (53.4)
Asthma	5637 (13.8)	2827 (14.7)	5298 (14.6)	8539 (14.3)	1783 (15.2)
COPD	12 230 (30.0)	5770 (30.0)	10 549 (29.0)	18 973 (31.8)	3718 (31.6)
Cancer	23 984 (58.8)	10 768 (56.0)	23 154 (63.6)	28 352 (47.4)	5609 (47.7)
Anxiety	8661 (21.2)	4219 (21.9)	8643 (23.7)	12 933 (21.6)	2509 (21.3)
Heart failure	13 265 (32.5)	5031 (26.2)	10 246 (28.1)	23 037 (38.6)	4312 (36.6)
Hypertension	37 022 (90.8)	16 907 (87.9)	32 470 (89.2)	54 973 (92.0)	10 655 (90.5)
Diabetes	20 212 (49.6)	8987 (46.7)	17 123 (47)	32 306 (54.1)	6151 (52.3)
Stroke	8654 (21.2)	3732 (19.4)	7158 (19.7)	12 919 (21.6)	2608 (22.2)
Medication use					
NSAIDs	6599 (16.2)	4118 (21.4)	6635 (18.2)	9231 (15.4)	2064 (17.5)
ACE inhibitors	11 869 (29.1)	5413 (28.2)	9832 (27.0)	17 051 (28.5)	3278 (27.9)
ARBs	8964 (22.0)	3763 (19.6)	8193 (22.5)	13 261 (22.2)	2479 (21.1)
β-Blockers	21 092 (51.7)	8845 (46.0)	17 645 (48.5)	32 195 (53.9)	6018 (51.1)
Food allergy	72 (0.2)	36 (0.2)	57 (0.2)	90 (0.2)	20 (0.2)
Drug allergy	4215 (10.3)	1358 (7.1)	5717 (15.7)	5886 (9.9)	1134 (9.6)
Health care use					
Number of distinct outpatient medications					
Tercile 1	13 399 (32.9)	6659 (34.6)	12 458 (34.2)	19 669 (32.9)	4184 (35.6)
Tercile 2	13 948 (34.2)	6399 (33.3)	12 225 (33.6)	19 512 (32.7)	3719 (31.6)
Tercile 3	13 441 (33.0)	6167 (32.1)	11 716 (32.2)	20 574 (34.4)	3865 (32.8)
Number of hospitalizations					
0	23 833 (58.4)	10 980 (57.1)	23 867 (65.6)	32 632 (54.6)	6474 (55.0)
1	9145 (22.4)	4574 (23.8)	7194 (19.8)	13 494 (22.6)	2749 (23.4)
>1	7810 (19.1)	3671 (19.1)	5338 (14.7)	13 629 (22.8)	2545 (21.6)
Number of ED visits					
0	19 552 (47.9)	8841 (46.0)	20 015 (55.0)	25 634 (42.9)	5016 (42.6)
1	9620 (23.6)	4799 (25.0)	8017 (22.0)	14 304 (23.9)	2872 (24.4)
>1	11 616 (28.5)	5585 (29.1)	8367 (23.0)	19 817 (33.2)	3880 (33.0)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blockers; COPD = chronic obstructive pulmonary disease; ED = emergency department; NSAID = nonsteroidal anti-inflammatory drug.
* Values are numbers (percentages) unless otherwise specified. Brand names for the IV iron formulations are as follows: low-molecular-weight iron dextran: INFeD (Allergan) in the United States and CosmoFer (Pharmacosmos) in Europe; ferumoxytol: Feraheme (AMAG Pharmaceuticals) in the United States and Rienso (Takeda) in Europe; ferric gluconate: Ferrlecit (Sanofi); iron sucrose: Venofer (American Regent); and ferric carboxymaltose: Injectafer (American Regent) in the United States and Ferinject (Vifor Pharma) in Europe.

of iron dextran was associated with the highest rates of anaphylaxis (adjusted IR, 9.8 cases [95% CI, 6.2 to 15.3 cases] per 10 000), followed by ferumoxytol (IR, 4.0 cases [CI, 2.5 to 6.6 cases] per 10 000). Rates of anaphylaxis were lower for ferric gluconate (IR, 1.5 cases [CI, 0.3 to 6.6 cases] per 10 000), iron sucrose (IR, 1.2 cases [CI, 0.6 to 2.5 cases] per 10 000), and ferric carboxymaltose (IR, 0.8 cases [CI, 0.3 to 2.6 cases] per 10 000).

When iron sucrose was used as the referent category (**Figure**), the adjusted ORs for anaphylaxis were 8.3 (CI,

Table 3. Baseline Characteristics After IPTW Weighting*

Characteristic	Ferumoxytol	Iron Dextran	Ferric Carboxymaltose	Iron Sucrose	Ferric Gluconate
Sociodemographic characteristics					
Male	35.5	35.0	35.2	35.4	35.6
Mean age (SD), *y*	77.5 (7.3)	77.6 (7.5)	77.3 (7.3)	77.5 (7.4)	77.5 (7.4)
Age quartile					
1	25.4	24.8	26.3	25.1	25.3
2	23.9	23.8	24.4	23.8	23.7
3	24.6	24.8	24.1	24.6	24.6
4	26.1	26.6	25.3	26.5	26.4
Race					
White	82.6	82.5	82.9	82.6	82.8
Black	8.4	8.3	8.1	8.3	8.3
Other	9.0	9.2	8.9	9.1	8.9
Year					
2013	6.1	6.0	6.1	5.9	6.1
2014	16.1	16.0	15.9	16.3	16.3
2015	17.1	17.2	17.1	17.2	17.1
2016	19.2	19.5	19.3	19.2	19.2
2017	15.3	14.9	15.1	15.5	15.5
2018	26.2	26.4	26.5	25.9	25.9
Comorbid conditions					
Chronic kidney disease	44.6	45.0	43.2	44.7	45.1
Gastrointestinal bleeding	52.0	52.1	52.2	52.1	52.3
Asthma	14.4	14.4	14.4	14.4	14.3
COPD	30.5	30.7	30.3	30.6	30.7
Cancer	54.9	55.1	54.6	54.8	54.6
Anxiety	22.0	22.2	22.5	22.1	22.1
Heart failure	33.3	32.1	32.5	33.1	33.8
Hypertension	90.5	90.4	90.3	90.5	90.9
Diabetes	50.5	49.9	49.6	50.3	50.5
Stroke	20.9	20.7	21.0	20.9	20.9
Medication use					
NSAIDs	17.0	17.4	17.4	17.2	17.0
ACE inhibitors	28.4	28.5	28.2	28.3	28.7
ARBs	21.9	21.8	22.1	21.9	22.0
β-Blockers	51.1	49.8	50.9	51.0	51.8
Food allergy	0.2	0.1	0.1	0.2	0.2
Drug allergy	11.0	11.2	11.1	10.9	11.1
Health care use					
Number of distinct outpatient medications					
Tercile 1	33.5	34.1	33.9	33.5	33.1
Tercile 2	33.3	32.9	32.9	33.2	33.5
Tercile 3	33.2	33.0	33.2	33.3	33.4
Number of hospitalizations					
0	58.1	56.7	59.5	58.3	57.9
1	22.2	23.1	22.3	22.1	22.3
>1	19.7	20.2	18.2	19.6	19.8
Number of ED visits					
0	47.1	45.3	48.2	47.0	46.8
1	23.6	24.1	23.8	23.6	23.7
>1	29.3	30.7	28.0	29.4	29.5

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blockers; COPD = chronic obstructive pulmonary disease; ED = emergency department; NSAID = nonsteroidal anti-inflammatory drug.
* Values are percentages unless otherwise indicated. Brand names for the IV iron formulations are as follows: low-molecular-weight iron dextran: INFeD (Allergan) in the United States and CosmoFer (Pharmacosmos) in Europe; ferumoxytol: Feraheme (AMAG Pharmaceuticals) in the United States and Rienso (Takeda) in Europe; ferric gluconate: Ferrlecit (Sanofi); iron sucrose: Venofer (American Regent); and ferric carboxymaltose: Injectafer (American Regent) in the United States and Ferinject (Vifor Pharma) in Europe.

3.5 to 19.8) for iron dextran and 3.4 (CI, 1.4 to 8.3) for ferumoxytol. The risk for anaphylaxis did not differ significantly with gluconate or ferric carboxymaltose compared with iron sucrose. For iron dextran, the E-value corresponding to the lower bound of the 95% CI of the OR was 6.5 and that corresponding to the point estimate was 16.1; the corresponding E-values for ferumoxytol were 2.2 and 6.3.

Secondary Analysis

The increase in risk for anaphylaxis for both iron dextran and ferumoxytol was primarily driven by the outcome

Table 4. Adjusted IRs of Anaphylaxis (per 10 000 First Administrations) Among New Initiators of IV Iron Products*

Product†	Anaphylaxis‡	Components‡		
		Anaphylactic Hospitalizations	Anaphylaxis With CPR, Hypotension, or Epinephrine	Anaphylaxis With Multiple Encounter Types on the Same Day
Iron sucrose	1.2 (0.6–2.5)	0.0	1.0 (0.5–2.3)	0.7 (0.3–1.8)
Ferric carboxymaltose	0.8 (0.3–2.6)	0.0	0.4 (0.1–2.0)	0.7 (0.2–2.4)
Ferric gluconate	1.5 (0.3–6.6)	0.0	1.0 (0.2–6.1)	0.5 (0.0–6.5)
Ferumoxytol	4.0 (2.5–6.6)	1.8 (0.9–3.7)	1.2 (0.5–2.9)	3.6 (2.2–6.0)
Iron dextran	9.8 (6.2–15.3)	3.8 (1.8–7.8)	5.0 (2.7–9.4)	8.0 (4.8–13.2)

CPR = cardiopulmonary resuscitation; IR = incidence rate; IV = intravenous.
* Values are IRs (95% CIs) per 10 000 first administrations. Analyses were adjusted for the baseline covariates described in Table 1 using a multinomial inverse probability of treatment weighting approach. See text for additional details.
† Brand names for the IV iron formulations are as follows: low-molecular-weight iron dextran: INFeD (Allergan) in the United States and CosmoFer (Pharmacosmos) in Europe; ferumoxytol: Feraheme (AMAG Pharmaceuticals) in the United States and Rienso (Takeda) in Europe; ferric gluconate: Ferrlecit (Sanofi); iron sucrose: Venofer (American Regent); and ferric carboxymaltose: Injectafer (American Regent) in the United States and Ferinject (Vifor Pharma) in Europe.
‡ The primary end point of anaphylaxis was defined as a composite of the following 3 outcomes: 1) anaphylaxis resulting in a hospitalization, 2) outpatient or emergency department visit related to anaphylaxis plus codes relating to administration of epinephrine or CPR or occurrence of hypotension, and 3) codes for anaphylactic shock evident in 2 of 3 encounter types within the same day (i.e., inpatient, outpatient, or emergency department). See text for additional details.

criterion specifying 2 separate encounter types for anaphylaxis within the same day (**Table 4**). Anaphylactic reactions requiring hospitalizations were observed only among patients using iron dextran or ferumoxytol. For the sensitivity analysis examining the third contributing component of the composite outcome (that is, 2 separate encounter types for anaphylaxis), findings were similar to those of the primary analysis, showing an increase in risk for both iron dextran (OR, 11.9 [CI, 4.0 to 35.6]) and ferumoxytol (OR, 5.3 [CI, 1.8 to 16.1]). In the analysis where cohort entry was restricted to the period after withdrawal of high-molecular-weight iron dextran in 2014, the risk associated with the use of low-molecular-weight iron dextran remained elevated (OR, 8.4 [CI, 2.8 to 24.7]).

The risk for the combined outcome of anaphylaxis or death was elevated only for iron dextran (OR, 3.2 [CI, 1.9 to 5.3]) (**Appendix Table**, available at Annals.org). Study findings were robust to changes in the length of the minimum look-back window to define new use, as well as the inclusion of patients with a history of anaphylaxis.

DISCUSSION

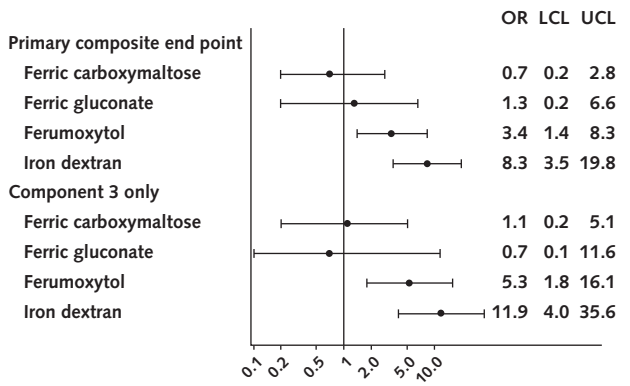
Using a cohort of more than 167 000 Medicare beneficiaries, we found that the risk for anaphylaxis was low with all 5 IV iron products studied. Nonetheless, the comparison among IV iron medications showed that ferumoxytol and iron dextran were associated with 3- and 8-fold increases, respectively, in risk for anaphylaxis when compared with iron sucrose.

Like the study using Medicare data from 2003 to 2013, we found an increased risk for anaphylaxis with iron dextran (3). We also showed that low-molecular-weight iron dextran may have the highest risk for anaphylaxis among the 5 IV iron preparations currently in use by restricting our analysis to the time after high-molecular-weight dextran was removed from the U.S. market. These conclusions should be cautiously interpreted because the anaphylaxis rate was very low and the 95% CIs were wide. We used a validated case definition for anaphylaxis, which had a higher PPV (75% for the composite primary outcome and 88% for the criterion requiring 2 separate encounter types for anaphylaxis within the same day) than the definition used in the prior Medicare study (63%) (16). Finally, in contrast to the earlier analysis, our case definitions did not include administration of diphenhydramine, which may have been preferentially used with iron dextran administrations, introducing differential outcome misclassification bias (21).

Compared with the IRs (per 10 000 first administrations) and ORs (compared with iron sucrose) of anaphylaxis reported for iron dextran in prior epidemiologic investigations, the point estimates of our IRs and ORs of 9.8 and 8.3, respectively, are higher than the IR of 6.8 and OR of 3.6 observed in the older Medicare study (2003 to 2013) but similar to the IR of 8.5 and OR of 5.4 reported for later years (2010 to 2013) (16). Of note, a U.S. Food and Drug Administration report using data from 2000 to 2013 examined 26 606 iron dextran administrations but found a lower rate of anaphylaxis (3.2 cases per 10 000 first administrations) (22), whereas a European study used multinational data from 1999 to 2017 to examine 6387 iron dextran administrations and found no cases of anaphylaxis (23). Our higher observed IRs and ORs for anaphylaxis may be explained by 2 factors. First, our cohort exclusively comprised older adults, who have a higher risk for medication-related anaphylaxis (11). By comparison, participants were younger in both the European study (mean age, 57 years [SD, 19]) and the Food and Drug Administration report, where 68% of patients were younger than 65 years (mean age not reported). Second, unlike prior studies, we used an all-available look-back approach using up to 6 additional years of older data, thereby potentially excluding the subset of patients using IV iron on an intermittent basis (that is, every few months or years for chronic iron deficiency). Compared with new users of IV iron, intermittent users are expected to have a lower risk for anaphylaxis given their prior experience with IV iron products.

Other data examining the comparative safety of IV iron formulations have also come from randomized clinical trials and from analyses of spontaneous reports. However, clinical

Figure. Adjusted risk for anaphylaxis in patients newly administered IV iron products.



Analyses were adjusted for baseline covariates described in Table 1 using a multinomial inverse probability of treatment weighting approach. See text for additional details. The primary end point of anaphylaxis was defined as a composite of the following 3 outcomes: 1) anaphylaxis resulting in a hospitalization, 2) outpatient or emergency department visit related to anaphylaxis plus codes relating to administration of epinephrine or cardiopulmonary resuscitation or occurrence of hypotension, and 3) codes for anaphylactic shock evident in 2 of 3 encounter types within the same day (i.e., inpatient, outpatient, or emergency department). We report a separate analysis for the third component because it was the most frequently occurring one and had the highest positive predictive value. See text for details. IV = intravenous; LCL = lower confidence limit; OR = odds ratio; UCL = upper confidence limit.

trials are inadequately powered to detect differences for very infrequent outcomes, such as anaphylactic reactions (1, 2). Meanwhile, analyses based on postmarketing reporting systems, such as the Food and Drug Administration Adverse Event Reporting System, the World Health Organization VigiBase, and the European Medicines Agency EudraVigilance, are limited by low internal validity and the inability to compute IRs (24).

The IRs of anaphylaxis per 10 000 administrations of IV iron products in our study ranged from 0.8 to 1.5 cases for ferric carboxymaltose, ferric gluconate, and iron sucrose and were 4.0 and 9.8 cases for ferumoxytol and iron dextran, respectively. Of note, these observed estimates for nondextran IV iron products are similar to the reported rate of 2 to 5 cases of anaphylaxis per 10 000 courses for penicillins—the leading cause of drug-induced anaphylaxis in the United States—and approximately 2-fold greater for iron dextran (compared with the higher end of the estimated range for penicillins) (25, 26). Although these comparisons help contextualize the risks for anaphylaxis with IV iron by juxtaposing IV iron against another drug class, these risks may not be directly comparable for 2 reasons. First, data informing rates for penicillin are older, predating 1990; meanwhile, the overall incidence of drug-related anaphylaxis has continued to trend upward over the ensuing decades (27, 28). Second, unlike in our study, these estimates were not derived from a population exclusively comprising older adults.

Although the exact pathophysiologic mechanisms responsible for anaphylactic reactions due to IV iron use remain elusive, several have been proposed (29, 30). All IV iron products are iron–carbohydrate complexes with a carbohydrate shell encapsulating the elemental iron core (31). The characteristics of this carbohydrate structure—which influences drug stability, rate of iron release, and immunogenicity—can vary between formulations (30, 32). The unique propensity for anaphylactic reactions for dextran-containing iron products may be explained by dextran's high affinity and cross-reactivity with polysaccharide antibodies (33).

Our study has several limitations. First, anaphylaxis can manifest in many ways and with varying degrees of severity that range from milder, self-limiting cases with skin or mucosal involvement to severe, life-threatening ones with systemic and cardiopulmonary symptoms. Because our case definitions capture the more serious manifestations of anaphylaxis, the overall rates of such reactions may have been underestimated because of exclusion of milder cases. Second, like all observational studies, we may have residual confounding. However, we took several steps to reduce the likelihood of confounding by adjusting for relevant patient characteristics using a multinomial IPTW approach, restricting our cohort to new users of study medications, and excluding potential confounders, such as history of anaphylaxis. Despite these precautions, we could not account for factors that were not directly captured in Medicare data. Nevertheless, except for history of anaphylaxis and a general risk factor of older age, no well-established patient characteristics associated with the development of anaphylaxis due to IV iron have been identified, potentially mitigating concerns for residual confounding. Third, our cohort exclusively comprised older adults, and therefore the study findings may not generalize to younger patients, who are at lower risk for drug-related anaphylaxis, or those receiving IV iron for certain indications (such as anemia in pregnancy). Fourth, because ferric derisomaltose was approved in the United States in 2020, we could not assess the relative risk of this formulation.

Our investigation offers an important step in understanding the differences in the risk for anaphylaxis due to IV iron use. Although the risk for such events with all IV iron products remained very low, our study implicated both iron dextran and ferumoxytol with an increased risk for anaphylaxis. Clinically, factors guiding the choice of parenteral iron preparation should include not only the risk for anaphylaxis but also medical history, clinical indication, setting, dose, number and duration of administrations needed, risk for other adverse events, and cost. Our findings also provide reassuring data with respect to the risk for anaphylaxis with ferric carboxymaltose, which has seen a rapid increase in use after favorable clinical trial data in various clinical indications, including chronic kidney disease and heart failure. By clarifying the risk for this rare but severe adverse reaction, this information can contribute to the choice of IV iron preparations.

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Rutgers University, Piscataway, and Department of Veterans Affairs New Jersey Health Care System, East Orange, New Jersey (C.V.D.); Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, New York (G.M.B.); Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey (J.L.C.); and Center for Pharmacoepidemiology and Treatment Science, Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, and Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, New Jersey (S.S.).

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Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Dave (e-mail, cdave@ifh.rutgers.edu). *Data set:* Available from data vendors through a data use agreement.

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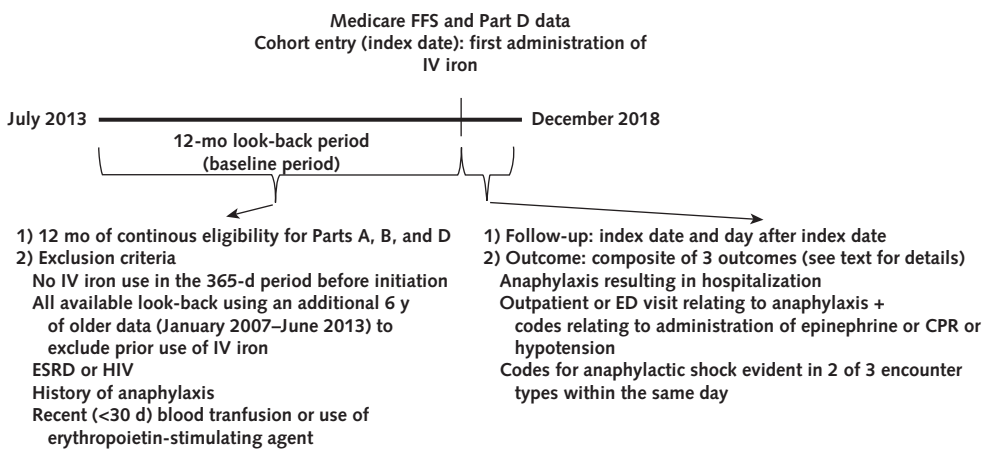
Administrative, technical, or logistic support: C.V. Dave, S. Setoguchi.
Collection and assembly of data: C.V. Dave, S. Setoguchi.

Appendix Table. Secondary Analysis: Adjusted IRs of Anaphylaxis (per 10 000 First Administrations) and ORs Among New Initiators of IV Iron Products*

Product	Minimum Look-Back Window to Define New Use (2 Years)†		Inclusion of Patients With History of Anaphylaxis		Composite of Anaphylaxis or Death	
	IR (95% CI)‡	OR (95% CI)	IR (95% CI)‡	OR (95% CI)	IR (95% CI)‡	OR (95% CI)
Iron sucrose	1.2 (0.6–2.8)	Reference	1.2 (0.5–2.4)	Reference	4.9 (3.4–7.0)	Reference
Ferric carboxymaltose	1.0 (0.3–2.9)	0.9 (0.3–3.8)	0.8 (0.3–2.6)	1.1 (0.3–3.9)	1.0 (0.4–2.9)	0.2 (0.1–0.6)
Ferric gluconate	0.5 (0.0–7.4)	0.8 (0.1–7.0)	1.5 (0.3–6.5)	1.7 (0.3–8.4)	6.1 (2.9–12.7)	1.2 (0.5–2.8)
Ferumoxytol	4.4 (2.7–7.2)	4.1 (1.6–10.5)	4.0 (2.4–6.3)	4.4 (1.7–11.0)	5.9 (3.7–8.4)	1.1 (0.7–1.9)
Iron dextran	11.3 (7.1–17.7)	8.4 (3.2–21.5)	9.7 (6.2–15.3)	8.3 (3.2–21.2)	15.7 (11.0–22.5)	3.2 (1.9–5.3)

IR = incidence rate; IV = intravenous; OR = odds ratio.
* Analyses were adjusted for the baseline covariates described in Table 1 using a multinomial inverse probability of treatment weighting approach. See text for additional details. The primary end point of anaphylaxis was defined as a composite of the following 3 outcomes: 1) anaphylaxis resulting in a hospitalization, 2) outpatient or emergency department visit related to anaphylaxis plus codes relating to administration of epinephrine or cardiopulmonary resuscitation or occurrence of hypotension, and 3) codes for anaphylactic shock evident in 2 of 3 encounter types within the same day (i.e., inpatient, outpatient, or emergency department). See text for details.
† The mean and median numbers of years that patients were enrolled in our data without having used IV iron before their index date were 5.9 years (SD, 3.1) and 6.0 years (interquartile range, 3.2–8.3 years), respectively, for the primary analysis and 6.5 years (SD, 2.8) and 6.5 years (interquartile range, 4.1–8.7 years), respectively, for the secondary analysis, where we extended the minimum look-back window to define new use to 2 years.
‡ Per 10 000 patients.

Appendix Figure. Study design.



CPR = cardiopulmonary resuscitation; ED = emergency department; ESRD = end-stage renal disease; FFS = fee-for-service; IV = intravenous.