Use of intravenous iron and risk of anaphylaxis: A multinational observational post-authorisation safety study in Europe

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Abstract

Purpose: This post-authorisation safety study estimated the risk of anaphylaxis in patients receiving intravenous (IV) iron in Europe, with interest in iron dextran and...
1 | INTRODUCTION

Intravenous (IV) iron therapy was introduced in the 1950s for the treatment of severe iron deficiency anaemia.1 In the last decades, the use of IV iron has grown worldwide owing to a better understanding of the management of moderate and severe anaemia related to numerous conditions, including chronic kidney disease, heavy uterine bleeding, pregnancy and postpartum anaemia, and chemotherapy-induced anaemia.2

Anaphylaxis in IV iron treatment is rare. Hypersensitivity reactions in association with IV iron preparations have been reported in the scientific literature, from spontaneous adverse events–reporting studies and population-based epidemiologic studies.2–7 Population-based studies in the United States have reported anaphylaxis risks of 2.0 to 2.4 per 10 000 first IV iron non-dextran administrations and 4.0 to 6.8 per 10 000 first IV iron dextran administrations.3,4 Population-based studies in Europe are lacking.

This study addressed concerns by the European Medicines Agency regarding the risk of anaphylaxis related to IV iron use in routine clinical practice in European populations, with a particular interest in comparing the risk between iron non-dextrans and dextran-containing preparations.

The study was registered in the European Union electronic Register of Post-Authorisation Studies (EUPAS Number: EUPAS20720) and was conducted under the ENCePP Seal.

2 | METHODS

2.1 | Study design

The study cohort comprised adults from six data sources in five European countries (Table S1, Supplementary Material): Denmark (Danish National and Regional Linked Registries and Databases), France (Système National des Données de Santé [SNDS]), Germany (German Pharmacoepidemiological Research Database [GePaRD] and Board of Trustees for Dialysis and Kidney Transplantation and its Quality in Nephrology programme [KfH QiN]), the Netherlands (PHARMO Database Network [PHARMO-NL]), and Sweden (Swedish national registers).

Patients who had a first-recorded IV iron treatment (new users) during the study period and were registered for at least 12 months before the first-recorded iron treatment were included in the study (Figure 1). The KfH QiN dialysis registry captured medical and treatment information from the date dialysis is initiated; therefore, the 12-month lookback period did not apply to this data source. Table 1 shows the IV iron compounds studied. A cohort of parenteral penicillin users in some study data sources was used as a positive control to test the case-identification algorithm. New users were individuals with a first recorded IV iron treatment or IV penicillin without a record of dispensing/administration of these drugs during the 12 months before the cohort entry date (i.e. the date of the first eligible IV iron or IV
penicillin treatment). Users with a second and third or subsequent IV iron treatment meeting the inclusion criteria were included to assess the risk beyond the first treatment.

The study period (1999–2017) varied across data sources and was defined as the time between the date of the first eligible dispensing/administration (i.e., treatment) of IV iron and the latest date of data availability in the data source. Patients were followed from the cohort entry date until the date of first occurrence of any of the censoring events: study outcome, death, end of study period, switch between types of IV iron (for main analysis) or disenrollment from the data source.

Diagnosis codes for medical conditions were retrieved from outpatient, inpatient, or emergency department encounters by using International Classification of Diseases (ICD), Ninth or Tenth Revisions, or International Classification of Primary Care codes. Medications were retrieved mostly from ambulatory pharmacy dispensing and primary care prescriptions and, in some data sources, from inpatient hospitals’ data, hospital outpatient specialists’ clinics, and administered treatments in dialysis centres. Medications were identified by using the Anatomical Therapeutic Chemical (ATC) Classification System codes and data source–specific codes.
2.2 | Outcome

Anaphylaxis events were identified through an adaptation of the algorithm consisting of diagnoses, symptoms and treatment codes developed and validated by Walsh et al.10 (Figure 2), which was based on the clinical criteria by Sampson et al.11 Criterion A used only anaphylaxis diagnosis codes. The symptoms, procedures or treatment codes in Criterion B and Criterion C (Figure 2) were used only in conjunction with anaphylaxis diagnostic codes (Criterion B) or allergic reactions (Criterion C). In a sensitivity analysis, the algorithm was expanded to increase its sensitivity (expansions highlighted in boxes in bold italic font in Figure 2). Outcomes were validated through review of medical records of potential cases in Denmark and in the PHARMO-NL. The algorithm used in GePaRD-Germany was indirectly validated through confirmation of potential anaphylaxis events due to any trigger (i.e. not restricted to IV iron) by using data from the Oldenburg University Hospital in Germany.

FIGURE 2  Main and expanded anaphylaxis algorithms. ICD-10, International Classification of Diseases, Tenth Revision.
2.3 | Time at risk

For the main analysis, time at risk was Day 0 (the day of administration of a study drug) for data sources capturing drug administration data. For data sources capturing drug dispensing or lacking an exact date of anaphylaxis diagnosis, the time at risk was Day 0 and Day 1 after dispensing/administration of a study drug (Figure 3). In a sensitivity analysis, an extended risk window of 7 days was considered for data sources capturing drug dispensing or lacking an exact date of anaphylaxis diagnosis (Figure 3).

2.4 | Statistical analysis

Data analyses occurred in two stages: (1) an analysis conducted at each data source and (2) a combined analysis of aggregated data conducted at RTI Health Solutions, the coordinating centre. Descriptive statistics of baseline variables, obtained from the same sources of outcome and exposure data, selected based on their potential for confounding of the association between IV iron treatment and risk of anaphylaxis, were generated for each study cohort.

Incidence proportions (IPs) during the defined time at risk were calculated at each data source as the number of patients with an incident anaphylaxis event divided by the total number of patients/treatments at risk (data not shown). Corresponding 95% confidence intervals (CIs) were derived from the Wilson score method, which has robust coverage for rare events. Risk ratio (RR) and risk difference (RD) estimates were calculated, respectively, by dividing and subtracting relevant IP estimates. Corresponding 95% CIs were derived from the Miettinen-Nurminen method.

Beta-binomial regression was implemented by using the finite mixture model procedure in SAS with default iteration and convergence parameters and the dual quasi-Newton optimisation technique to obtain maximum likelihood estimates. The logit link was used to estimate regression coefficients, and the inverse logit function was applied to these regression coefficients to derive IP point estimates for each compound of interest. For comparative analyses, RR point estimates were derived by dividing corresponding model-derived IP estimates, and RD point estimates were derived by subtracting corresponding model-derived IP estimates.

Sensitivity analyses were used to calculate the IPs, RRs and RDS of anaphylaxis among the different groups of IV iron compounds assuming different scenarios of risk. These risk scenarios included expansion of the case-identification algorithm, extension of the risk window from Day 0 until Day 7, risk among IV iron switchers, and risk among IV iron users excluding patients receiving dialysis. Detailed descriptions of these scenarios are presented in Table S1 (Supplementary Material).

For the validation analyses, the positive predictive value (PPV) was computed as the proportion of algorithm-identified anaphylaxis cases confirmed by medical record review.

For all analyses, owing to the data protection regulations for cell counts below five in Denmark, the exact number of events and IPs for some estimates from the meta-analyses cannot be disclosed and are reported as minimum and maximum range.

3 | RESULTS

3.1 | Descriptive data

Overall, 304,210 first IV iron treatments were identified during the study period across all data sources. The number of first IV iron events, particularly when some studies have zero events. Beta-binomial regression was implemented by using the finite mixture model procedure in SAS with default iteration and convergence parameters and the dual quasi-Newton optimisation technique to obtain maximum likelihood estimates. The logit link was used to estimate regression coefficients, and the inverse logit function was applied to these regression coefficients to derive IP point estimates for each compound of interest. For comparative analyses, RR point estimates were derived by dividing corresponding model-derived IP estimates, and RD point estimates were derived by subtracting corresponding model-derived IP estimates.

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treatments varied from 5825 in PHARMO-NL to 140 916 in GePaRD-Germany. IV iron dextran treatments represented 2.1% of all first IV iron treatments (Figure 4). However, in PHARMO-NL iron dextran represented 41.1% of the first IV iron treatments (Figure 4). There were 148 099 second IV iron treatments across data sources ranging from 1850 treatments in PHARMO-NL to 67 895 treatments in GePaRD-Germany (Figure 4). For the third or subsequent IV iron treatments, a total of 3 103 486 treatments in 105 634 patients were identified, of which 2 620 795 (84.4%) were contributed by the KfH QiN dialysis registry and 348 945 (11.2%) from the GePaRD in Germany (Figure 4).

Selected baseline characteristics of patients by data source are presented in Table S2 (Supplementary Material). The distributions by age and sex were similar in all study populations: mean age (standard deviation) was 57 (19.3) years, 70% were females. The prevalence of the conditions shown in Table 2 varied greatly across study populations, for example, the prevalence of asthma ranged from 1% to 14% and allergies from 3% to 56%, depending on the type of available data (e.g. outpatient diagnoses vs. hospital discharge diagnoses).

3.2 | Outcomes

The pooled numbers of potential anaphylaxis events (identified through the main algorithm) and IPs, overall and by iron group (i.e. dextran and non-dextran), for first IV iron treatments are shown in the first column of Table 3. The number of potential anaphylaxis events, reported as a range to comply with data protection regulations, among patients that had a first exposure to IV iron (N = 304 210 patients) ranged from 13 to 16 events; the IP of anaphylaxis ranged from 0.38 (95% CI, 0.17–0.88) to 0.51 (95% CI, 0.28–0.97) per 10 000 first treatments. All events were identified in iron non-dextrans. The RD of anaphylaxis between iron dextran and non-dextrans ranged from 0.44 to 0.55 per 10 000 treatments, favouring the iron dextran. The IP of anaphylaxis for IV penicillins was 1.16 per 10 000 first treatments, based on 30 potential events, whereas at any treatment, the IP was 0.45 per 10 000 treatments (data not shown).

Among patients with second IV iron treatments (N = 148 099 patients), three potential anaphylaxis events were identified, for an IP of anaphylaxis of 0.25 per 10 000 second treatments (Table 4). One event was identified among iron dextran and two events among iron non-dextrans. The estimated RR of anaphylaxis with iron non-dextrans as comparator was 13.1 and the RD was 3.08 per 10 000 second treatments, favouring iron non-dextrans. None of the patients with a second or third IV iron exposure had an anaphylaxis reaction to an earlier dose.

For third or subsequent IV iron treatments (N = 3 103 486 treatments), 10 potential events were identified for an IP of anaphylaxis of 0.02 per 10 000 third or subsequent treatments (Table 4). All events were found among iron non-dextrans. The RD for iron dextran minus iron non-dextrans was –0.03 per 10 000 third or subsequent treatments in favour of iron dextran.
The low number of events identified in this study precluded the conduct of adjusted analyses and the interpretation of the results based on groups and types of IV iron.

### 3.3 Sensitivity analyses

Results of the sensitivity analyses are presented in Table 3. The expanded case-identification algorithm identified between 19 and 22 potential anaphylaxis events among first IV iron treatments (i.e. 6 additional events compared with the main algorithm), yielding an IP ranging from 0.63 (95% CI, 0.38–1.05) to 2.81 (95% CI, 0.60–13.8) per 10 000 first iron treatments. For the 7-day risk window scenario, between 24 and 27 anaphylaxis events were identified at first IV iron treatment (i.e. 11 additional events compared with the main risk window), yielding an IP ranging from 0.74 (95% CI, 0.43–1.29) to 0.88 (95% CI, 0.56–1.39) per 10 000 first iron treatments. In the analysis that excluded dialysis patients, between 13 and 16 potential anaphylaxis events were identified in first IV iron treatments, resulting in an IP ranging from 0.77 (95% CI, 0.41–1.47) to 1.75 (95% CI, 0.71–4.46) per 10 000 first iron treatments. When assessing the risk after switching between IV iron groups, no anaphylaxis occurred after a switch from an iron dextran to an iron non-dextran. However, two potential anaphylaxis events occurred after a first switch from an iron non-dextran to an iron dextran for an IP of 32.9 per 10 000 first switches (data not shown).
TABLE 3 Beta-binomial pooled risk of anaphylaxis after a first IV iron treatment—overall and by IV iron dextran and iron non-dextrans groups—and parenteral penicillin: main algorithm, expanded algorithm, 7-day risk window, and exclusion of dialysis patients

| Groups | Main analysis | Sensitivity analyses |
|--------|--------------|---------------------|
|        | Overall IV iron |                     |
|        | Main algorithm | Expanded algorithm  |
| Anaphylaxis events, n<sup>a</sup> | Min, 13; max, 16 | Min, 13; max, 16 |
| Treatments, n<sup>b</sup> | 304 210 | 304 210 |
| IP, 95% CI | Min, 0.38 (0.17–0.88); max, 0.51 (0.28–0.97)<sup>b</sup> | Min, 0.74 (0.43–1.29); max, 0.88 (0.56–1.39) |
|   | 176 261 | 176 261 |
| Iron dextran |                     |
| Anaphylaxis events, n | 0 | 0 |
| Treatments, n<sup>b</sup> | 6387 | 6387 |
| IP, 95% CI | 0 (0 to >9995) | 0 (0 to >9995) |
| Iron non-dextrans |                     |
| Anaphylaxis events, n<sup>a</sup> | Min, 13; max, 16 | Min, 13; max, 16 |
| Treatments, n<sup>b</sup> | 297 813 | 297 813 |
| IP, 95% CI | Min, 0.44 (0.16–1.24); max, 0.55 (0.23–1.34) | Min, 1.00 (0.42–2.42); max, 1.24 (0.62–2.53) |
| RR, 95% CI<sup>c</sup> | Min, 0 (0.00 to >9995); max, 0 (0.00 to >9995) | Min, 0 (0–NE); max, 0 (0 to >9995) |
| RD, 95% CI<sup>c</sup> | Min, –0.44 (–1.02 to >9995); max, –0.55, (–1.14 to >9995) | Min, –1.00 (NE–NE); max, –1.24 (–2.22 to >9995) |
| Penicillin (positive control) |                     |
| Anaphylaxis events, n | 30 | 48 |
| Treatments, n<sup>b</sup> | 231 294 | 984 000 |
| IP, 95% CI | 1.16 (0.78–1.73) | 0.53 (0.40–0.71) |

Abbreviations: CI, confidence interval; IP, incidence proportion; IV, intravenous; max, maximum; min, minimum; NA, not applicable; NE, not estimable; RD, risk difference; RR, risk ratio.

<sup>a</sup>The number of events identified in Denmark was between 1 and 4, the exact number cannot be disclosed because of data protection regulations aimed at prevention of identification of individuals. Therefore, number of events and IPs per 10 000 first treatments are reported as minimum and maximum range.

<sup>b</sup>Treatments included the Danish data which were rounded to the nearest 10 to comply with data protection regulations aimed at prevention of identification of individuals. Therefore, number of events and IPs per 10 000 first treatments are reported as minimum and maximum range.

<sup>c</sup>RRs calculated for iron dextran versus non-dextrans; RDs calculated for iron dextran minus iron non-dextrans.

3.4 | Validation

The direct validation of the case-identification algorithms in Denmark yielded a PPV of 70% (95% CI, 50%–86%) based on 42 evaluable potential cases combined across the IV iron and IV penicillin cohorts (cases in the penicillin cohort accounted for more than 90% of all potential cases validated).

In PHARMO-NL, one evaluable potential anaphylaxis event identified through the main algorithm in the IV penicillin cohort was confirmed: PPV was 100% (95% CI, 2.5%–100%). The expanded algorithm based on 10 evaluable potential cases showed a PPV of 10% (95% CI, 0.25%–45%).

The indirect external validation of the main case-identification algorithm used in GeParD-Germany, showed a PPV of 62.3% (95% CI, 49.8%–73.7%) based on 78 patients with potential anaphylaxis events due to any trigger identified through specific anaphylaxis diagnostic codes captured in the in-hospital setting at Oldenburg University Hospital in Germany (presented in Figure 2) and 43 confirmed events. No potential outpatient events were identified.

4 | DISCUSSION

This study identified 304 210 patients with a first IV iron treatment: 6367 (2.1%) first treatments were iron dextran. The overall IP of anaphylaxis among IV iron users ranged from 0.38 (95% CI, 0.17–0.88) to 0.51 (95% CI, 0.28–0.97) per 10 000 first treatments, corresponding to the maximum and the minimum of the true (masked) number of cases. The IPs of anaphylaxis among repeat users were 0.25 per 10 000 for second treatments and 0.02 per 10 000 for third or subsequent treatments (the latter mostly in dialysis patients). Data on dosing of IV iron was not available. However, for anaphylaxis, dose is not considered critical.17
TABLE 4 Main results for second and third and subsequent IV iron treatments

|                | Second treatments | Third and subsequent treatments |
|----------------|-------------------|---------------------------------|
| Overall IV iron|                   |                                 |
| Treatments (patients) | 148 099          | 3 103 486 (105 634)             |
| Anaphylaxis events (n) | 3               | 10                             |
| IP (95% CI)b  | 0.25 (0.07–0.94)  | 0.02 (0.00–0.13)               |
| Iron dextran |                   |                                 |
| Treatmentsa | 3084              | 9508                           |
| Anaphylaxis events (n) | 1               | 0                             |
| IP (95% CI)b  | 3.33 (0.48–23.3)  | 0 (0 to >9995)                |
| Iron non-dextrans |                   |                                 |
| Treatmentsa | 145 015           | 3 093 988                      |
| Anaphylaxis events (n) | 2               | 10                            |
| IP (95% CI)b  | 0.25 (0.06–1.06)  | 0.03 (0.00–0.19)              |
| RR (95% CI)c  | 13.1 (1.26–146)   | 0 (0 to >9995)                |
| RD (95% CI)b  | 3.08 (0.12–23.1)  | −0.03 (−0.13 to >9995)        |

Abbreviations: CI, confidence interval; IP, incidence proportion; IV, intravenous; RR, risk ratio; RD, risk difference.

*Treatments included the Danish data which were rounded to the nearest 10 to comply with data protection regulations aimed at preventing the identification of individuals.

The number of events identified in Denmark was between 1 and 4. The exact number cannot be disclosed because of data protection regulations aimed at preventing the identification of individuals. Therefore, IPs per 10 000 first treatments are reported as a minimum and maximum range.

The first-use estimates are lower than those reported in the U.S. studies: 2.4 and 6.8 per 10 000 first treatments (IV iron non-dextrans and iron dextran, respectively) in Wang et al.4 or those by Walsh et al.3: 2.0 and 4.0 per 10 000 first treatments (IV iron non-dextrans and iron dextran, respectively). One reason for the observed differences in the incidence of anaphylaxis between our study and the U.S. studies3,4 may be that repeated IV iron use was, potentially, misclassified as new use in our study. The underlying assumption is that the first treatment with IV iron carries the highest risk of anaphylaxis because subsequent treatments are likely to be avoided in patients with a prior hypersensitivity reaction. In our study, the identification of first IV iron treatment was affected by the limited capture of hospital use of IV iron, the setting where first administrations of this drug are most likely to happen. Indeed, data from Sweden suggest that 50%–80% of IV iron treatments occur in hospital.18 In contrast, the U.S. studies3,4 had ascertainment of treatment with IV iron, irrespective of administration setting, and could therefore determine new-user status more accurately. However, in Wang et al.4 the incidence of fatal anaphylaxis among users of IV iron dextran was lower than that among users of IV iron non-dextrans. This could relate to a differential misclassification of anaphylaxis by type of IV iron and/or to differences in baseline characteristics of users across different IV iron types.

A large proportion (84%) of all third or subsequent IV iron treatments were identified through the KfH QIN dialysis registry in Germany, reflecting the need for repeated iron use in patients undergoing dialysis.

Both U.S. studies excluded dialysis patients. Our study included dialysis patients in the main analysis. However, we conducted a sensitivity analysis excluding dialysis patients to account for the different patterns (i.e. chronic) of use of IV iron and the impossibility of ascertaining new-user status among these patients, especially in the KfH QIN dialysis registry. This sensitivity analysis showed an IP of anaphylaxis among first IV iron treatments ranging from 0.77 to 1.75 per 10 000 first treatments (compared with a range from 0.38 to 0.51 per 10 000 first IV iron treatments when dialysis patients were included in the main analysis), consistent with a reduced misclassification of first treatment.

Other sensitivity analyses such as the expanded case-identification algorithm and the 7-days risk window yielded RRs >1 when comparing the risk of anaphylaxis for iron dextran versus iron non-dextrans (Table 3); however, these analyses were based on very few cases, all of which had important validity concerns, and therefore, conclusions cannot be drawn.

Another reason to explain the lower risk of anaphylaxis in our study compared with U.S. studies relates to a potential underascertainment of anaphylaxis events. While underascertainment remains a possibility, we think it is unlikely to play a major role because we used an adapted case-identification algorithm developed and validated by Walsh et al.3 Moreover, the risk of anaphylaxis in our positive control—the penicillin cohort (1.16 per 10 000 first treatments)—was consistent with the published estimates (ranging from 0.1 to 5 per 10 000). In our opinion, this evidence supports the adequateness of the case-identification algorithm used in our study.

The low number of potential anaphylaxis events identified despite the use of multiple large, population-based data sources prevented the conduct of adjusted analyses. Beta-binomial regression meta-analyses were undertaken instead, which account for the weight of each data source but may be subject to confounding. Differences in risk of anaphylaxis between IV iron types in Europe could be assessed if enough data on first IV iron administration become available.

5 | CONCLUSIONS

This study found IPs of anaphylaxis per 10 000 first treatments across all IV iron types ranging from 0.38 (95% CI, 0.17–0.88) to 0.51 (95% CI, 0.28–0.97) and from 0.44 to 0.55 for iron non-dextrans; IPs were not assessable for iron dextran as no events were identified. These IPs were lower than the estimates of 2 and 6.8 per 10 000 first treatments (IV iron non-dextrans and iron dextran, respectively) reported in studies in the United States.

Our study identified a large number of IV iron and IV penicillin users in Europe, but it captured only a small fraction of treatments in in-hospital and specialty clinics, the settings where the most first use
of these drugs is likely to happen. Due to this data capture limitation, the study could not exclude a differential risk of anaphylaxis between iron dextran and iron non-dextrans. However, the results are reassuring for repeat users of IV iron in the ambulatory setting.

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CONFLICT OF INTEREST
The study was funded by a consortium of IV iron marketing authorisation holders and was conducted under a contract including the ENCePP Seal granting the research team independent publication rights.

ETHICS STATEMENT
The study was determined by the RTI International institutional review board as research not involving human subjects (RTI-HS had no interaction with human subjects). Approvals or notifications were obtained/processed from the ethics committees and other bodies as applicable, by participating research centres that contributed to the study according to the applicable requirements for access to data and analysis.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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APPENDIX A.

IV Iron Consortium
The Intravenous Iron Consortium is a consortium of 17 iron manufacturing companies sponsoring this Joint post-authorisation safety study:

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