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ORIGINAL ARTICLE

Drug Allergy, Insect Sting Allergy, and Anaphylaxis

# Different phenotypes of drug-induced anaphylaxis—Data from the European Anaphylaxis Registry

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Abbreviation: DIA, drug-induced anaphylaxis

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## Abstract

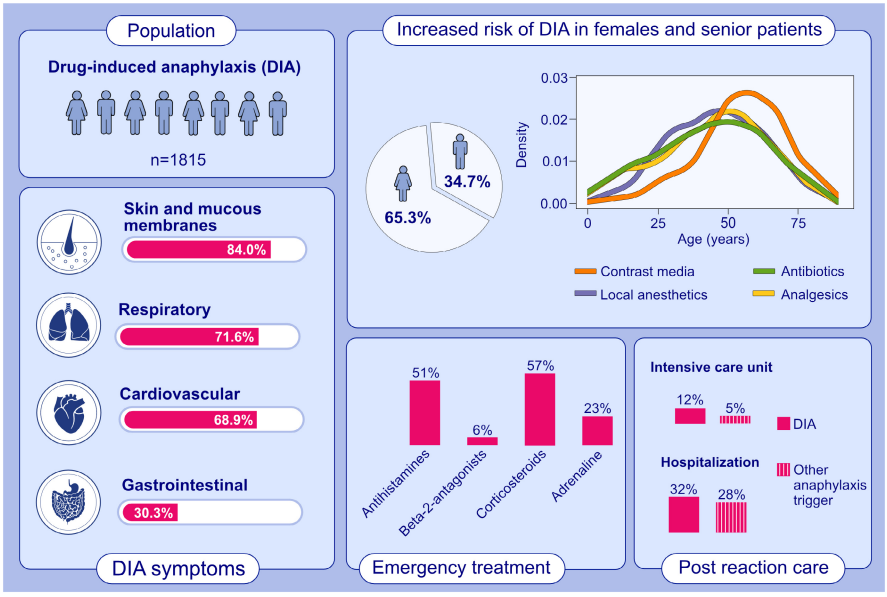
**Background:** Drugs are a frequent cause of severe anaphylactic reactions. Here, we analyze a large dataset on drug induced anaphylaxis regarding elicitors, risk factors, symptoms, and treatment.

**Methods:** Data from the European Anaphylaxis Registry (2007–2019) with 1815 reported cases of drug-induced anaphylaxis were studied accordingly.

**Results:** Drugs are the third most frequent cause of anaphylaxis reported in the Anaphylaxis Registry. Among the eliciting groups of drugs analgesics and antibiotics were far most often reported. Female and senior patients were more frequently affected, while the number of children with DIA was low. DIA patients had symptoms affecting the skin and mucous membranes ($n$ = 1525, 84.02%), the respiratory ($n$ = 1300, 71.63%), the cardiovascular ($n$ = 1251, 68.93%) and the gastrointestinal system ($n$ = 549, 30.25%). Drugs caused significant more severe reactions, occurred more often in medical facilities and led to increased hospitalization rates in comparison to food and insect venom induced anaphylaxis. Adrenaline was used more often in patients with DIA than in anaphylaxis due to other causes. Patients with skin symptoms received more antihistamines and corticosteroids in the acute treatment, while gastrointestinal symptoms led to less adrenaline use.

**Conclusion:** The study contributes to a better understanding of DIA, with a large number of cases from Europe supporting previous data, e.g., analgesics and antibiotics being the most frequent culprits for DIA. Female gender and higher age are relevant risk factors and despite clear recommendations, the emergency treatment of DIA is not administered according to the guidelines.

KEYWORDS
anaphylaxis, drug hypersensitivity, drugs, multicenter study




## GRAPHICAL ABSTRACT

This study analyzes data from the European Anaphylaxis Registry (2007–2019) with 1815 reported cases of drug-induced anaphylaxis (DIA). We show that female gender and higher age are relevant DIA risk factors. DIA symptoms affect the skin and mucous membranes (84.0%), respiratory (71.6%), cardiovascular (68.9%), and gastrointestinal systems (30.3%). Intensive care admission and hospitalization rates are higher in DIA than in case of anaphylaxis caused by other elicitors (food- and insect venom-induced).
Abbreviations: DIA, drug-induced anaphylaxis

## 1 | INTRODUCTION

Anaphylaxis is a potentially life-threatening systemic hypersensitivity reaction, defined as any acute onset illness with typical skin features, plus involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms; or any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.[1] The most common culprits for anaphylaxis are drugs, insects, and foods.[2] For decades, drug consumption has been rising, in part driven by changes in clinical practice in age-related and chronic diseases.[3] The purpose of this manuscript is to analyze the clinical epidemiology of drug-induced anaphylaxis (DIA) in the European Anaphylaxis Registry (EAR).

There are numerous data sources on DIA worldwide, with geographical differences in prevalence, emergency treatment, and postreaction care. Estimates of anaphylaxis suggest incidence rates between 1.5 and 7.9 per 100,000 population per year in Europe.[4] Published data from the European Anaphylaxis Registry show a calculated incidence of 4.5 per 100,000 population.[5] While data from the US suggest an anaphylaxis incidence of up to 50 per 100,000 population,[6] numbers for England are much lower with 6–8 cases per 100,000 inhabitants.[7] Anaphylaxis is generally assumed to be underdiagnosed and underreported, making its incidence underestimated.[8] Adverse drug reactions occurring both inside and outside of medical facilities are serious and potentially fatal.[9,10] In recent years, an increase in hospital admissions for severe anaphylaxis was shown.[11]

While clinical guidelines help standardize anaphylaxis treatment, there is still a need for more data on adverse reactions to various drug groups. Current data show that the diagnosis is often missed, with underuse of the few available specific test methods for some drugs and a lack of specific and sensitive test methods for many drug groups.[12] However, appropriate management of patients with anaphylaxis is fundamentally dependent on a correct diagnosis and immediate treatment.

This study unravels the most frequent elicitors, symptoms, and possible cofactors of anaphylactic reactions triggered by drugs in a large cohort from the European Anaphylaxis Registry.

## 2 | METHOD

The Anaphylaxis Registry collects data regarding the culprit causing anaphylaxis through a web-based data entry system. The multilingual online questionnaire with an assembly of 375 variables was filled out by allergists from 75 tertiary referral centers in 11 countries.

Experienced allergy centers are participating on a voluntary basis in the register. Study centers were asked to enter their most severe cases, usually with respiratory and/or cardiovascular symptoms, but more moderate anaphylaxis could be recorded as well. After the allergic work-up in the questionnaire, the clinical specialist decided whether the respective trigger was confirmed or highly suspected. Confirmed cases were those that could be clearly attributed to one specific trigger (clear history of exposure and onset of symptoms and/skin tests and/or provocation test). Highly suspected were the cases in which experts assumed with a high degree of probability that there was an anaphylactic reaction that could be attributed to one specific trigger but were not able to confirm this with absolute certainty (no skin and/or provocation test). Cases with more than one suspected trigger were not included into this analysis. Originally developed for the German Anaphylaxis Registry, the questionnaire has been translated for international use. Interrater reliability was assessed by using repeated data entry by two independent professionals. Medical records, including laboratory measures, were retrospectively retrieved by trained professionals in each study center. Raw study data were stored with pseudonyms on a server at Charité—Universitätsmedizin Berlin.

Drug-induced anaphylactic cases are distributed by country as follows: Germany ($n = 905$), Switzerland ($n = 285$), France ($n = 158$), Austria ($n = 135$), Spain ($n = 99$), Bulgaria ($n = 52$), Italy ($n = 80$), Brazil ($n = 48$), Poland ($n = 38$), Ireland ($n = 9$), and Greece ($n = 6$). Within countries involved in the European Anaphylaxis Registry, we observed a large variety in percentages of anaphylactic reactions. Different variables such as sex, age, symptoms, severity, location, emergency treatment, postreaction care and concomitant factors regarding the different drug groups were analyzed.

### 2.1 | Ethics

The study was approved by the ethics committee at Charité—Universitätsmedizin Berlin, Germany (EA1/079/06), accredited by the local ethics committees in the participating centers, and is registered on ClinicalTrials.gov (Identifier: NCT05210543).

### 2.2 | Statistical analysis

We performed the analysis using R (Version 1.2.5033[13]). The differences between groups were assessed with the Chi-squared or the Fisher's exact test. $p$-values $< .05$ were considered statistically significant. In case of multiple comparisons or post hoc tests, the $p$-value was corrected using the Holm's method. We compared each drug group with the other drug groups of the same hierarchical group or subgroup level.

## 3 | RESULTS

### 3.1 | Drugs are the third most frequent cause of anaphylaxis

The entire dataset includes 12,848 cases of anaphylactic reactions, recorded between July 2007 and March 2019. Of these, 4350 cases are food related (37.37%), 4945 are insect related (42.48%), and

2346 (20.15%) cases are drug-induced, making DIA the third most frequent elicitor of anaphylaxis.

The flowchart in Figure 1 illustrates the detailed case selection process and the number of remaining samples after each step. In the first step, we excluded all nondrug-related cases ($n$ = 10, 138). Subsequently, we sorted out cases with more than one suspected trigger ($n$ = 144) and did not include moderate cases (Ring & Messmer grade I, $n$ = 233) or reactions that occurred due to specific immunotherapy (SIT). After data processing, 1815 cases remained for further analysis.

## 3.2 | Analgesics and antibiotics are the main causes of DIA

*Most represented ATC groups* (see Table 1 and Table S6):

Analgesics ($n$ = 749, 41.27%), antibiotics ($n$ = 602, 33.17%), local anesthetics ($n$ = 134, 7.38%), radiocontrast media ($n$ = 94, 5.18%), antineoplastic and immunomodulating agents ($n$ = 66, 3.64%) and other drugs: proton-pump inhibitors ($n$ = 49, 2.70%) and other drugs ($n$ = 121, 6.67%). We found that in most countries analgesics and antibiotics were the main trigger for DIA, see Table S5 for subgroup analysis per country.

## 3.3 | Demographics of drug-induced anaphylaxis

An overview of our findings on characteristics of drug-induced anaphylaxis versus anaphylaxis caused by foods or insects (Table 2):

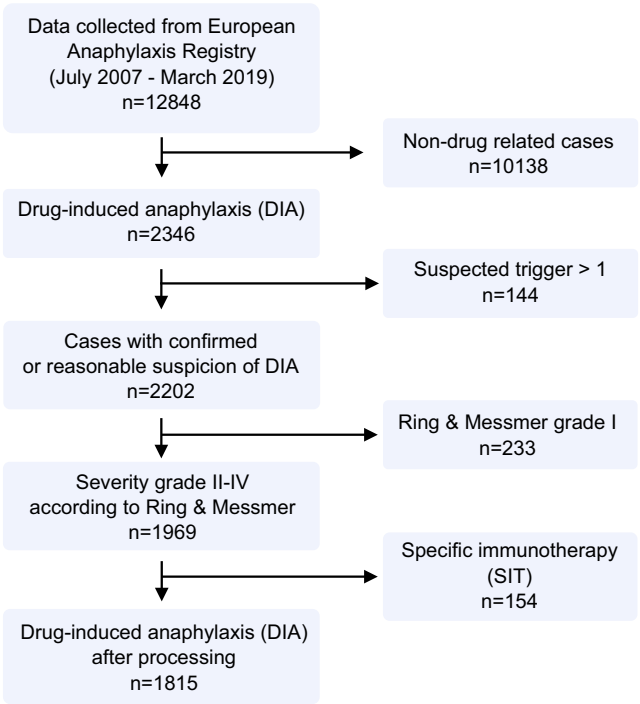



**FIGURE 1** Flowchart of the case selection process for the analysis presented in this publication.

The analysis of sex groups showed the proportion of female patients suffering from drug-induced anaphylaxis to be higher than in other anaphylactic reactions ($n$ = 1186, 65.34%, $p$ < .0001), while DIA in males was less reported ($n$ = 629, 34.66%, $p$ < .0001). Nevertheless, male patients were admitted to hospital (29.01% vs. 36.57%, $p$ < .05) and the intensive care unit (ICU) (9.61% vs. 16.10%, $p$ < .05) significantly more often. Also, we found significant differences among age groups. The number of children (≤17 years) with anaphylaxis to drugs ($n$ = 153, 8.43%) was low compared with anaphylaxis induced by other triggers ($n$ = 3091, 32.01%), while seniors (≥65 years) were more frequently affected ($n$ = 308, 16.97%, $p$ < .0001). However, children were significantly more likely to be admitted to hospital than adults (18–64 years) and seniors (44.44% vs. 30.44%, $p$ < .05). Furthermore, the mortality rate in DIA was significantly higher ($n$ = 12, 0.67%) than in anaphylaxis caused by foods or insects (0.21%, $p$ < .05). The levels of tryptase after a reaction in patients with anaphylaxis due to drugs were analyzed but were not reported due to limited numbers available ($n$ = 589).

## 3.4 | Symptom profile of DIA

We differentiated between four different groups of symptoms. DIA patients had symptoms affecting the skin and mucous membranes ($n$ = 1525, 84.02%), the respiratory ($n$ = 1300, 71.63%), the cardiovascular ($n$ = 1251, 68.93%), and the gastrointestinal systems ($n$ = 549, 30.25%). Cutaneous manifestations as angioedema and urticaria in DIA were reported significantly more often in children (angioedema 62.09% and urticaria 62.75%) and were likewise less frequent in the age group of seniors (angioedema 33.77% and urticaria 31.17%, $p$ < .0001). Moreover, our analysis revealed that the emergency treatment differed according to the predominating symptom (see Table 3 and Table S7).

DIA patients with cutaneous symptoms ($n$ = 1525, 84.02%) received significantly more antihistamines ($n$ = 836, 54.82%, $p$ < .0001) and corticosteroids ($n$ = 935, 61.31%, $p$ < .0001). DIA patients with respiratory symptoms ($n$ = 1300, 71.63%) received beta-2-agonists more often ($n$ = 98, 7.54%, $p$ < .0001). DIA patients with cardiovascular symptoms ($n$ = 1251, 68.93%) received adrenaline significantly more often ($n$ = 346, 27.66%, $p$ < .0001), and DIA patients suffering from gastrointestinal symptoms ($n$ = 549, 30.25%) were less likely to receive adrenaline in the emergency room ($n$ = 101, 18.40%, $p$ < .05).

## 3.5 | Severity, hospitalization, and treatment of DIA

The analysis of the severity of drug-induced anaphylaxis indicates that drugs caused more severe reactions (Ring & Messmer grade IV 5.62%, $p$ < .0001) than foods (Ring & Messmer grade IV 0.84%) and insect venom (Ring & Messmer grade IV 2.28%). Not surprisingly, we also found that significantly more reactions to drugs occurred in

**TABLE 1** Most represented ATC groups described in main drug group, sub drug group, and subsub drug group—distinguished in confirmed and highly suspected

| Drug group | Subgroup | Subsubgroup | Confirmed, *n* | Highly suspected, *n* | Total, *n* (%) |
|---|---|---|---|---|---|
| All drugs | | | 1153 | 662 | 1815 (100) |
| Analgesics | | | 424 | 325 | 749 (41.27) |
| | NSAID | | 254 | 233 | 490 (65.42) |
| | | Propionic acid derivatives | 83 | 87 | 170 (34.69) |
| | | Acetic acid derivatives and related substances | 89 | 78 | 167 (34.08) |
| | | Salicylic acid and derivatives | 70 | 45 | 115 (23.47) |
| | | Other NSAID (fenamates and coxibs) | 15 | 23 | 38 (7.76) |
| | Other analgesics and antipyretics (specified) | | 165 | 83 | 248 (33.11) |
| | | Pyrazolones | 143 | 48 | 191 (77.02) |
| | | Anilids | 18 | 16 | 34 (13.71) |
| | | Unspecified other analgesics and antipyretics | 7 | 16 | 23 (9.27) |
| | Opioids | | 4 | 7 | 11 (1.47) |
| Antibiotics | | | 441 | 161 | 602 (33.17) |
| | Beta-lactams | | 332 | 110 | 442 (73.42) |
| | | Penicillins | 197 | 49 | 246 (55.66) |
| | | Cephalosporins | 135 | 61 | 195 (44.12) |
| | Quinolones | | 65 | 28 | 93 (15.45) |
| | Macrolides, lincosamides, and streptogramins | | 19 | 11 | 30 (4.98) |
| | Other antibiotics | | 25 | 12 | 37 (6.15) |
| Local anesthetics | | | 66 | 68 | 134 (7.38) |
| Contrast media | | | 74 | 20 | 94 (5.18) |
| Antineoplastic agents/ immunomodulating agents | | | 44 | 22 | 66 (3.64) |
| Proton-pump inhibitors | | | 30 | 19 | 49 (2.70) |
| Other drugs | | | 74 | 47 | 121 (6.67) |

medical facilities ($n = 847$, 46.67%, $p < .0001$) compared with foods and insects. Likewise, 84.31% of all RM grade IV reactions occurred inside medical facilities.

Regarding postreaction care, the hospitalization ($n = 574$, 31.63%, $p < .05$) and the ICU ($n = 215$, 11.85%, $p < .0001$) admission rates were higher in DIA than in anaphylaxis to other elicitors. Children suffering from DIA were more likely to undergo hospital admission than other age groups ($p < .05$). Female DIA patients were significantly less likely to be admitted to the hospital ($n = 344$, 29.01%, $p < .05$) or ICU ($n = 114$, 9.61%, $p < .05$). As pointed out earlier, however, older patients were treated more often in ICUs due to higher reaction severity with advanced age (10.46% in children; 11.30% in adults; and 14.94% in seniors).

Subsequently, we examined the emergency treatment that patients received for an anaphylactic reaction. Here, we found that patients received significantly more therapeutic agents compared with other elicitors of anaphylactic reactions, except for beta-2-agonists ($n = 107$, 5.90%, $p < .05$) (see Table 2). For the treatment of drug-induced anaphylactic reactions, corticosteroids were administered 57% of the time, followed by antihistamines (51%), adrenaline (23%) as well as beta-2-agonists (6%) and glucagon (0.06%).

### 3.6 | Elicitor-specific analysis

To improve the medical management of DIA, it is necessary to examine individual drug groups in more detail, as shown in the subsequent sections. Table 1 gives an overview of the groups, their structure, and the proportion of all drugs that triggered anaphylaxis. Further analysis focused on the main drug groups with more than 50 registered anaphylactic reactions, while PPIs were included in the figures.

### 3.7 | Analgesics

Analgesics are the most common culprits for drug-induced anaphylaxis in the European Anaphylaxis Registry ($n = 749$, 41.27%). According to the Anatomical Therapeutic Chemical (ATC) classification system,[14] analgesics are classified into three subgroups: Nonsteroidal anti-inflammatory drugs (NSAIDs), other analgesics and antipyretics (pyrazolones and anilids) and opioids. Opioids were not analyzed any further since opioid-triggered anaphylaxis was reported only four times in the dataset. The results obtained from this analysis are shown in Table 4 and reveal that analgesics as a trigger for anaphylaxis occurred significantly

TABLE 2 Demographics of drug-induced anaphylaxis: characteristics of drug-induced anaphylaxis versus anaphylaxis caused by other triggers (foods or insects)

| | Drugs, *n* (%) | Anaphylaxis induced by other triggers, *n* (%) | Chi$^2$ test |
|---|---|---|---|
| Total | 1815 (100) | 9657 (100) | |
| Sex | | | |
| Female | 1186 (65.34) | 4633 (47.98) | $p < .0001$ |
| Male | 629 (34.66) | 5024 (52.02) | $p < .0001$ |
| Age | | | |
| Children | 153 (8.43) | 3091 (32.01) | $p < .0001$ |
| Adults | 1354 (74.60) | 5545 (57.42) | $p < .0001$ |
| Seniors | 308 (16.97) | 1021 (10.57) | $p < .0001$ |
| Symptoms | | | |
| Gastrointestinal | 549 (30.25) | 4106 (42.52) | $p < .0001$ |
| Severity according to Ring & Messmer | | | |
| Grade III | 637 (35.10) | 4220 (43.70) | $p < .0001$ |
| Grade IV | 102 (5.62) | 161 (1.67) | $p < .0001$ |
| Setting | | | |
| Inside medical facility | 847 (46.67) | 449 (4.65) | $p < .0001$ |
| Outside medical facility | 751 (41.38) | 7507 (77.74) | $p < .0001$ |
| Emergency treatment | | | |
| Antihistamines | 928 (51.13) | 4479 (46.38) | $p < .05$ |
| Beta-2-agonists | 107 (5.90) | 733 (7.59) | $p < .05$ |
| Corticosteroids | 1039 (57.25) | 4907 (50.81) | $p < .05$ |
| Adrenaline | 421 (23.20) | 1721 (17.82) | $p < .0001$ |
| Postreaction care | | | |
| Hospital admission | 574 (31.63) | 2663 (27.58) | $p < .05$ |
| ICU | 215 (11.85) | 526 (5.45) | $p < .0001$ |

*Note*: The differences between groups were assessed with the Chi-squared or the Fisher's exact test. *p*-values <.05 were considered statistically significant.

more often in male patients ($n = 289$, 38.58%, $p < .05$) and children ($n = 77$, 10.28%, $p < .05$) compared with other drugs. Cardiovascular symptoms ($n = 461$, 61.55%, $p < .05$) and severe reactions (RM Grade IV $n = 27$, 3.60%, $p < .05$) were recorded significantly less in comparison with other drug groups, as illustrated in Figure 2.

Analgesic-triggered anaphylaxis occurred more frequently outside of medical facilities ($n = 375$, 50.07%, $p < .0001$) and led to fewer ICU admissions ($n = 73$, 9.75%, $p < .05$), although there was no significant difference in hospital admissions in general. In emergency treatment, adrenaline was used significantly less ($n = 138$, 18.42%, $p < .05$). However, no significance regarding other emergency drugs, such as antihistamines, beta-2-agonists, and corticosteroids was observed.

## 3.8 | Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs were the primary cause of analgesic-induced anaphylaxis ($n = 490$, 65.42%, Table 5). The data indicate that anaphylaxis triggered by NSAIDs occurs significantly more often in seniors ($n = 88$, 17.96%, $p < .05$) compared with other analgesics. Severe reactions ($n = 4$, 0.82%, $p < .0001$) and ICU admissions ($n = 33$, 6.73%, $p < .05$) were recorded significantly less frequently than in other analgesic-induced anaphylaxis. Furthermore, we observed that anaphylactic reactions happened less often inside medical facilities ($n = 73$, 14.90%, $p < .0001$). Also, patients with anaphylaxis triggered by NSAID received more antihistamines ($n = 254$, 51.84%, $p < .05$) and more corticosteroids ($n = 269$, 54.90%, $p < .05$) compared with reactions due to other analgesics.

The NSAID subgroup analysis is summarized in Table S1, and although it shows some statistically significant findings, the data must be taken with caution due to low case numbers.

## 3.9 | Antibiotics

After analgesics, antibiotics were the second most frequent culprit of DIA ($n = 602$, 33.17%). We found that anaphylactic reactions occurred more often outside medical facilities ($n = 185$, 30.73%, $p < .0001$), but then led to hospital admissions ($n = 220$, 36.54%, $p < .05$) because of severe reactions (Table S2 and Figure 2).

During the emergency treatment, patients reacting to antibiotics were more likely to be treated with adrenaline ($n = 184$, 30.56%, $p < .0001$) and received corticosteroids more often ($n = 389$, 64.62%, $p < .05$). We also analyzed the different subgroups of antibiotics (as detailed in Table 1); however, the number of cases was limited, and therefore, we did not examine the subgroups further.

**TABLE 3** Symptom profile of DIA (skin symptoms, gastrointestinal symptoms, respiratory symptoms, and cardiovascular symptoms) and significant differences in emergency treatment

| | DIA cutaneous symptoms, *n* (%) | DIA all other symptoms, *n* (%) | Chi² test |
|---|---|---|---|
| Total | 1525 (100) | 290 (100) | |
| Emergency treatment | | | |
| Antihistamines | 836 (54.82) | 92 (31.72) | $p < .0001$ |
| Corticosteroids | 935 (61.31) | 104 (35.86) | $p < .0001$ |
| | **DIA gastrointestinal symptoms, *n* (%)** | **DIA all other symptoms, *n* (%)** | **Chi² test** |
| Total | 549 (100) | 1266 (100) | |
| Emergency treatment | | | |
| Adrenaline | 101 (18.40) | 320 (25.28) | $p < .05$ |
| | **DIA respiratory symptoms, *n* (%)** | **DIA all other symptoms, *n* (%)** | **Chi² test** |
| Total | 1300 (100) | 515 (100) | |
| Emergency treatment | | | |
| Beta-2- agonists | 98 (7.54) | 9 (1.75) | $p < .0001$ |
| | **DIA cardiovascular symptoms, *n* (%)** | **DIA all other symptoms, *n* (%)** | **Chi² test** |
| Total | 1251 (100) | 564 (100) | |
| Emergency treatment | | | |
| Adrenaline | 346 (27.66) | 75 (13.30) | $p < .0001$ |

*Note*: The differences between groups were assessed with the Chi-squared or the Fisher's exact test. *p*-Values < .05 were considered statistically significant.

**TABLE 4** Characteristics of analgesics in comparison with anaphylaxis induced by other triggers

| | Analgesics, *n* (%) | Anaphylaxis induced by other triggers, *n* (%) | Chi² test |
|---|---|---|---|
| Total | 749 (100) | 1066 (100) | |
| Sex | | | |
| Male | 289 (38.58) | 340 (31.89) | $p < .05$ |
| Age | | | |
| Children | 77 (10.28) | 76 (7.13) | $p < .05$ |
| Symptoms | | | |
| Cardiovascular | 461 (61.55) | 790 (74.11) | $p < .05$ |
| Severity according to Ring & Messmer | | | |
| Grade IV | 27 (3.60) | 75 (7.04) | $p < .05$ |
| Setting | | | |
| Inside medical facility | 165 (22.03) | 682 (63.98) | $p < .0001$ |
| Emergency treatment | | | |
| Adrenaline | 138 (18.42) | 283 (26.55) | $p < .05$ |
| Postreaction care | | | |
| ICU | 73 (9.75) | 142 (13.32) | $p < .05$ |

*Note*: The differences between groups were assessed with the Chi-squared or the Fisher's exact test. *p*-Values < .05 were considered statistically significant.

### 3.9.1 | Local anesthetics

Beyond analgesics and antibiotics, local anesthetics were the third largest ATC drug group given as an elicitor of anaphylaxis in our dataset ($n = 134$, 7.38%). However, only 49.25% of all registered DIA to local anesthetics were confirmed ($n = 66$), while all others were only suspected (see Table 1). The deeper data analysis identified that 65 of these 134 cases were reports provided from a single center. Comparing these single-center DIA to local anesthetics with all other reports to local anesthetics, we found no significant differences, see Table S8. We address this fact in more detail in the discussion.

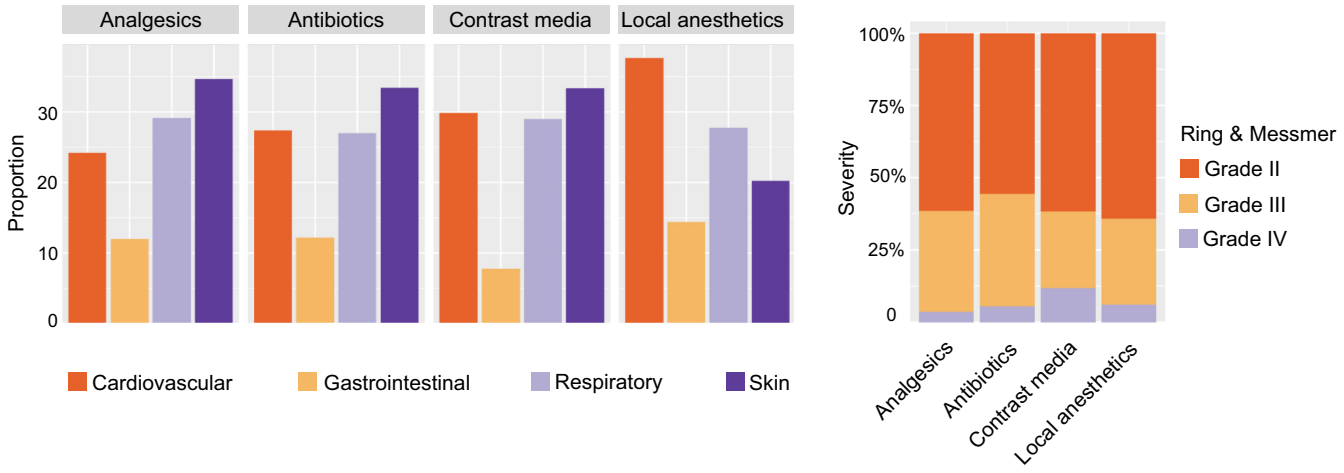



FIGURE 2 Symptom/severity proportion among age groups in main drug groups.

TABLE 5 Characteristics of anaphylaxis in nonsteroidal anti-inflammatory drugs compared with anaphylaxis induced by other analgesics

| | NSAID, *n* (%) | Anaphylaxis induced by other analgesics, *n* (%) | $Chi^2$ test |
|---|---|---|---|
| Total | 490 (100) | 259 (100) | |
| Age | | | |
| Seniors | 88 (17.96) | 28 (10.81) | $p < .05$ |
| Severity according to Ring & Messmer | | | |
| Grade IV | 4 (0.82) | 23 (8.88) | $p < .0001$ |
| Setting | | | |
| Inside healthcare facility | 73 (14.90) | 92 (35.52) | $p < .0001$ |
| Emergency treatment | | | |
| Antihistamines | 254 (51.84) | 99 (38.22) | $p < .05$ |
| Corticosteroids | 269 (54.90) | 91 (35.14) | $p < .05$ |
| Postreaction care | | | |
| Intensive Care Unit | 33 (6.73) | 40 (14.44) | $p < .05$ |
| Concomitant diseases | | | |
| Current infection | 39 (7.96) | 9 (3.47) | $p < .05$ |
| Mastocytosis | 8 (1.63) | 24 (9.27) | $p < .0001$ |
| Medication as cofactor | | | |
| Statins | 15 (3.06) | 17 (6.56) | $p < .05$ |

*Note*: The differences between groups were assessed with the Chi-squared or the Fisher's exact test. *p*-Values < .05 were considered statistically significant.

Abbreviation: NSAID, nonsteroidal anti-inflammatory.

In Table S3, we show the analysis of anaphylaxis due to local anesthetics vs. other drugs. Skin symptoms were less often described in anaphylaxis to local anesthetics than with other drugs ($n = 59$, 44.03%, $p < .0001$). Regarding emergency treatment, patients reacting to local anesthetics received significantly less antihistamines ($n = 29$, 21.64%, $p < .0001$), less corticosteroids ($n = 34$, 25.37%, $p < .0001$), and less adrenaline ($n = 13$, 9.70%, $p < .05$). Patients with anaphylaxis to local anesthetics presented significantly more often with stress/anxiety ($n = 29$, 21.64%, $p < .05$) and thyroid disease ($n = 20$, 14.93%, $p < .05$) but less often in association with infections.

### 3.10 | Radiocontrast media (RCM)

Anaphylactic reactions to RCM accounted for 5.18% (n = 94) of all DIA. Table S4 compares RCM vs. other drugs. While there was no significance regarding the patients' sex, we found that anaphylaxis due to RCM was rare in children ($n = 1$, 1.06%, $p < .05$), while seniors are significantly more often affected ($n = 28$, 29.79%, $p < .05$), compared with other drugs. Furthermore, we found that anaphylactic reactions due to radiocontrast media were significantly more severe ($n = 11$, 11.70%, $p < .05$) and occurred almost only inside medical facilities ($n = 92$, 97.87%, $p < .0001$). Regarding concomitant diseases,

significantly more cardiovascular disease ($n = 38$, 40.43%, $p < .05$), thyroid disease ($n = 17$, 18.09%, $p < .05$), as well as malignant disease ($n = 20$, 21.28%, $p < .0001$) compared with other drugs were reported. The co-medication of ACE inhibitors and thyroxine was taken significantly more in patients reacting anaphylactic to RCM.

### 3.11 | Tryptase

Tryptase values were not provided from all registered cases and only measured outside the reaction. The mean value for drug-induced anaphylaxis was 7.50 µg/L ($n = 704$), insect-induced anaphylaxis 6.55 µg/L ($n = 3057$), and in food-induced anaphylaxis 5.37 µg/L ($n = 1071$), which is statistically significant due to the high numbers of values.

## 4 | DISCUSSION

In this study, we analyzed a large dataset of drug-induced anaphylaxis covering more than one decade. Drugs are the third most common cause of anaphylaxis after foods and insect venom in the European Anaphylaxis Registry. However, severe reactions and reactions that needed to be treated in hospital and ICU occurred significantly more often with DIA compared with other elicitors, which is consistent with other studies.[15] Furthermore, hospitalization rates in DIA reported within the European Anaphylaxis Registry were significantly higher than in anaphylaxis caused by other triggers, eventually linked to the most common location of occurrence: medical facilities.

### 4.1 | Age as a factor

Anaphylaxis affects people of all ages, according to this study. The age group that presented most frequently with DIA were adults, leaving children and seniors far behind[16] (Figure 3). While medication use differs by age group, polypharmacy is common among the elderly and time necessary for sensitization is shorter compared with younger patients.[17] As published earlier, the average severity of reactions increases with age.[18,19] This might contribute to the higher absolute numbers of DIA in this group.[20]

### 4.2 | Sex as a factor

The majority of anaphylaxis occurred in women, as also reported in numerous other studies.[21–24] Interestingly enough, data from Korean databases show different sex proportions.[17,25] The hormone estradiol has been discussed as a potentiator for sex differences in anaphylaxis,[26] as it may reinforce mast cell releasability.[27] We found that male patients, however, developed significantly more severe reactions than female patients.[16] A possible cause might be that with increasing age men tend to be multimorbid compared with women of the same age.[28]

### 4.3 | Symptoms

In concordance with other studies, we found that the most frequent symptoms in DIA were skin symptoms and the least frequent were gastrointestinal symptoms.[29] Nevertheless, these symptoms still occurred in one in three patients in our database, contradicting other studies from Portugal or Korea, where the proportion of gastrointestinal (GIT) symptoms was lower.[23,25,30] This may partly be explained by the greater use of analgesics[23] in the regions covered by the European Anaphylaxis Registry (EAR). We showed that children presented more often with skin symptoms than adults and seniors, which is in concordance with previous studies.[29,31] However, we found no significant difference in the occurrence of cardiovascular symptoms compared with other culprits—which contradicts other studies.[32]

### 4.4 | Severity and emergency treatment

Our findings are in line with previous research, as higher age and male sex are associated with severe anaphylaxis.[33,34] The analysis of emergency treatment based on symptoms has revealed that the

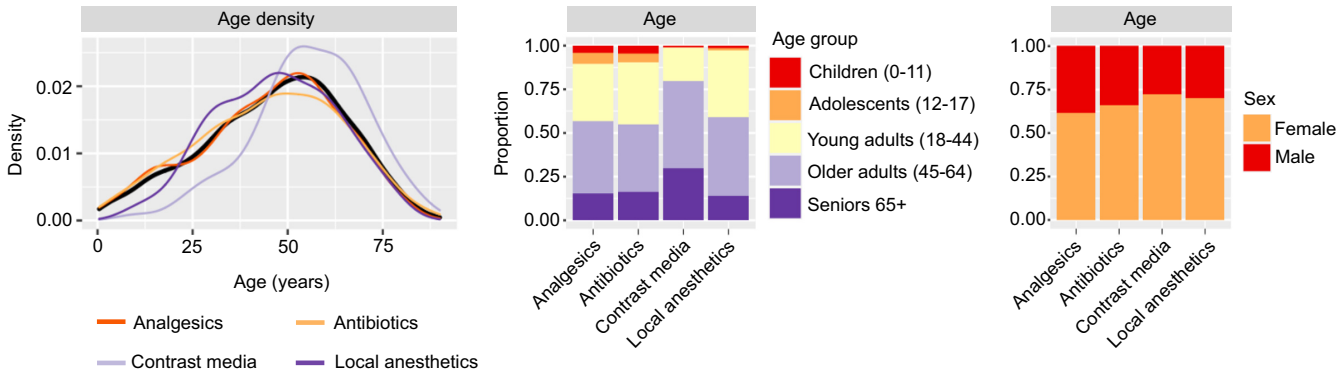



FIGURE 3 Age/sex comparison in main drug groups.

more detrimental the symptom (e.g., skin symptoms vs. cardiovascular symptoms), the more likely a patient was to receive adrenaline.[35] Our data show that adrenaline was only administered in 23.20% of cases (see Table 2), but significantly more than with other culprits, which is in concordance with other studies.[36] According to the guidelines, however, adrenaline is supposed to be given in any case of anaphylaxis.[1,37] We conclude that anaphylaxis is often not recognized as such and hence not treated appropriately.[35,38] Previous reports also found that anaphylaxis is frequently not treated according to the guidelines.[16,31,39]

### 4.5 | Drug groups

Coinciding with previous studies,[20,40–43] we identified analgesics and antibiotics as the most common cause for drug-induced anaphylaxis followed by local anesthetics and radiocontrast media.

### 4.6 | Analgesics: NSAIDs

Within the group of analgesics, NSAIDs were the most often administered drug group,[44] with ibuprofen being the most frequently reported individual drug. We found that drugs of this group were commonly used, compared with other age groups, seniors reacted significantly more. At the same time, anaphylaxis triggered by NSAID presented with significantly less severe reactions and symptoms that rarely lead to hospital admissions.[20] However, this seems to make these cases difficult for practitioners to recognize as anaphylaxis.[45,46] The fact that patients rarely received adrenaline as emergency treatment supports this assumption.

Among the subgroups of NSAIDs, we found that propionic acid derivatives and acetic acid derivatives are mainly characterized by the age group they are administered to. In this database, most of the reported DIA to NSAIDs in children were due to propionic acid derivatives and in seniors due to acetic acid derivatives—both do not seem to cause severe reactions.

For salicylic acid, however, we found that people with respiratory diseases are more susceptible to hypersensitivity reactions.[47] This should be considered when prescribing medications. For the group of pyrazolones, we found that they lead to severe reactions. However, this could be attributed to the fact they are often given after surgery, that is, to patients in a state of physical vulnerability.

### 4.7 | Antibiotics

As also shown in prior studies, we found that antibiotics cause a significant proportion of DIA—they were found to be the second largest group of anaphylaxis-triggering drugs.[4,16,43,45,48] We found that the reactions often occur at home; where these drugs are taken but patients frequently end up in hospital due to the severity of symptoms.[49] Beta-lactams are by far the most common antibiotic class causing anaphylaxis.[30]

### 4.8 | Local anesthetics

An interesting finding occurred when we analyzed local anesthetics. Reactions occur very rarely, and if they occur, they show inconspicuous symptoms.[50] We found that these cases of anaphylaxis are therefore not adequately treated. This might be concerning, because the severity of the caused reactions is comparable to those of other drugs. As mentioned before, more than half of the reported cases stemmed from one single center. Local anesthetics may cause a vasovagal reaction.[50] Symptoms (e.g., fainting) may or may not (e.g., when skin symptoms are missing) resemble an anaphylactic reaction. However, we did not find significant differences within the reports of single centers to DIA by local anesthetics. The high number of cases from one center may not be related to a quality deviation. If these cases are excluded from all DIA for this analysis, local anesthetics drop to the fourth most common drug group ($n = 69$, 3.8%).

### 4.9 | Radiocontrast media (RCM)

RCM has been previously reported as a common cause of anaphylactic reactions.[48] We observed that anaphylaxis to RCM occurs more frequently in the elderly and leads to more severe reactions.

### 4.10 | Tryptase

We do not have tryptase levels from all DIA patients, and if available, it has not only been determined outside the reaction (baseline). Although tryptase levels were slightly higher in drug-induced anaphylaxis versus insects and food—which was also statistically significant due to the high sample size, this finding needs a further analysis in the future (e.g., subgroups, age and sex match, etc.).

### 4.11 | Limitations

A weakness of the study is that different application methods (intramuscular, intravenous, and oral) of the anaphylaxis-inducing drugs are not distinguished. To address this, the EAR data entry form would need adjustment. The high numbers of DIA triggered by local anesthetics must be taken with great care as allergy testing including provocation tests have often not been performed in supposingly affected patients and a vasovagal reaction is a well-known potentially likely differential diagnosis. Moreover, the local anesthetic preparations may contain additives, which could also be a possible trigger factor (e.g., sulfite) rather than the anesthetic substance itself.

Another limitation is that it remains unclear how the specialists drew the line between confirmed and highly suspected cases when applying the EACCI guidelines since this can be strongly influenced by experience and local best practices. Data may not be representative for a given country and may be biased depending on the focus of the given allergy center.

## 5 | CONCLUSION

Anaphylaxis is a severe, life-threatening reaction that requires prompt evaluation and management. To recognize and treat anaphylactic reactions in a timely manner, health professionals need to be trained appropriately. We provide scientific evidence, with a large number of cases from Europe for what has been suspected for a long time, for example, analgesics and antibiotics being the most frequent culprits for DIA.

Adrenaline is only administered in a small fraction of anaphylaxis cases despite clear national and international recommendations. Improvement can only be achieved by a better dissemination of guidelines, but also a better knowledge to recognize anaphylaxis and their elicitors.[37] The study improves the understanding of certain drug groups in different age groups and gender. Symptom patterns of drug groups contribute to better clinical management, especially for immediate emergency treatment. The findings of this study shed light on the characteristics and risk patterns of DIA.

### AUTHOR CONTRIBUTIONS

T Hanschmann performed data analysis and wrote the manuscript. W Francuzik, S Dölle-Bierke, K Scherer Hofmeier, L Grabenhenrich, F Ruëff, JM Renaudin, C Pföhler, R Treudler, MB Bilò, R Lang, LF Ensina, G Christoff, V Cardona, N Wagner, N Reider, S Müller, and H Dickel collected the data, contributed to the interpretation of data, and revised the manuscript critically for important intellectual content. M Worm created the conception and design of the study, managed data acquisition, contributed to the interpretation of data, and revised the manuscript critically. All authors approved the final version of the manuscript for publication.

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### CONFLICT OF INTEREST

MW declares honoraria for lectures and consulting from ALK-Abelló Arzneimittel GmbH, Mylan Germany GmbH, Leo Pharma GmbH, Sanofi-Aventis Deutschland GmbH, Regeneron Pharmaceuticals, DBV Technologies S. A, Stallergenes GmbH, HAL Allergie GmbH, Allergopharma GmbH & Co.KG, Bencard Allergie GmbH, Aimmune Therapeutics UK Limited, Actelion Pharmaceuticals Deutschland GmbH, Novartis AG, Biotest AG, AbbVie Deutschland GmbH & Co. KG and Lilly Deutschland GmbH. KS reports honoraria for lectures and consulting from Allergopharma, Sanofi-Aventis, Abbvie, Menarini and Takeda, outside submitted work. NW is or recently

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## SUPPORTING INFORMATION

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

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