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ORIGINAL ARTICLE

Epidemiology and Genetics

Secondary prevention measures in anaphylaxis patients: Data from the anaphylaxis registry

Magdalena Kraft[1] | Macarena Pia Knop[2] | Jean-Marie Renaudin[3] | Kathrin Scherer Hofmeier[4] | Claudia Pföhler[5] | Maria Beatrice Bilò[6,7] | Roland Lang[8] | Regina Treudler[9] | Nicola Wagner[10] | Thomas Spindler[11] | Jonathan O'B Hourihane[12] | Ioana Maris[13] | Alice Koehli[14] | Andrea Bauer[15] | Lars Lange[16] | Sabine Müller[17] | Nikolaos G. Papadopoulos[18,19] | Bettina Wedi[20] | Anne Moeser[21] | Luis F. Ensina[22] | Montserrat Fernandez-Rivas[23,24] | Ewa Cichocka-Jarosz[25] | George Christoff[26,27] | Blanca E. Garcia[28] | Iwona Poziomkowska-Gęsicka[29] | Victoria Cardona[24,30] | Tihomir B. Mustakov[31] | Uta Rabe[32] | Vera Mahler[33] | Linus Grabenhenrich[1,34] | Sabine Dölle-Bierke[1] | Margitta Worm[1] | on behalf of The Network for Online Registration of Anaphylaxis (NORA)

[1]Division of Allergy and Immunology, Department of Dermatology Venerology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

[2]Department of Dermatology and Allergy, University Hospital, LMU Munich, Munich, Germany

[3]Presidency, Allergy Vigilance Network, Nancy, France

[4]Division of Allergy, Department of Dermatology, University Hospital Basel, University of Basel, Basel, Switzerland

[5]Department of Dermatology, The Saarland University Medical Center, Homburg/Saar, Germany

[6]Allergy Unit, Department of Internal Medicine, University Hospital Ospedali Riuniti di Ancona, Ancona, Italy

[7]Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy

[8]Department of Dermatology, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria

[9]Department of Dermatology, Venereology and Allergology, Leipzig Interdisciplinary Allergy Center (LICA)-Comprehensive Allergy Center, University Hospital, Leipzig, Germany

[10]Department of Dermatology, University Hospital of Erlangen-Nürnberg, Erlangen, Germany

[11]Allergy Campus Hochgebirgsklinik Davos, Davos, Switzerland

[12]DM University College Cork and Cork University Hospital, Cork, Ireland

[13]Bon Secours Hospital Cork/Department of Paediatrics and Child Health, University College Cork, Cork, Ireland

[14]Division of Allergology, University Children's Hospital Zurich, Zurich, Switzerland

[15]University Allergy Center, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany

[16]Department for Pediatrics, St. Marien-Hospital, Bonn, Germany

[17]Department of Dermatology, Medical Center-University of Freiburg, Freiburg, Germany

[18]Allergy Department, 2nd Pediatric Clinic, National and Kapodistrian University of Athens, Athens, Greece

[19]Division of Infection, Immunity & Respiratory Medicine, University of Manchester, Manchester, UK

[20]Department of Dermatology and Allergy, Comprehensive Allergy Center, Hannover Medical School, Hannover, Germany

Participating centers can be found under www.anaphylaxie.net (NORA)

[21]Institute for Infectious Diseases and Infection Control, Jena University Hospital, Jena, Germany
[22]Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil
[23]Department of Allergy, Hospital Clinico San Carlos, Universidad Complutense, IdISSC, Madrid, Spain
[24]ARADyAL Research Network
[25]Department of Pediatrics, Pulmonology, Allergy and Dermatology Clinic, Jagiellonian University Medical College, Krakow, Poland
[26]Faculty of Public Health, Medical University-Sofia, Sofia, Bulgaria
[27]Allergy Out-patient Department, Acibadem CityClinic, Tokuda Medical Centre, Sofia, Bulgaria
[28]Service of Allergology, Complejo Hospitalario de Navarra, Pamplona, Spain
[29]Clinical Allergology Department, Pomeranian Medical University in Szczecin, Szczecin, Poland
[30]Allergy Section, Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain
[31]Chair of Allergy, Medical University Sofia, Sofia, Bulgaria
[32]Department for Allergy and Asthma, Johanniter Hospital, Treuenbrietzen, Germany
[33]Paul-Ehrlich-Institut, Langen, Germany
[34]Department for Infectious Disease Epidemiology, Robert Koch-Institut, Berlin, Germany

Correspondence
Margitta Worm, Department of Dermatology, Venerology and Allergology, Charité-Universitätsmedizin Berlin, Berlin, Germany.
Email: margitta.worm@charite.de

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Abstract

Background: Patients with a history of anaphylaxis are at risk of future anaphylactic reactions. Thus, secondary prevention measures are recommended for these patients to prevent or attenuate the next reaction.

Methods: Data from the Anaphylaxis Registry were analyzed to identify secondary prevention measures offered to patients who experienced anaphylaxis. Our analysis included 7788 cases from 10 European countries and Brazil.

Results: The secondary prevention measures offered varied across the elicitors. A remarkable discrepancy was observed between prevention measures offered in specialized allergy centers (84% of patients were prescribed adrenaline autoinjectors following EAACI guidelines) and outside the centers: Here, EAACI guideline adherence was only 37%. In the multivariate analysis, the elicitor of the reaction, age of the patient, mastocytosis as comorbidity, severity of the reaction, and reimbursement/availability of the autoinjector influence physician's decision to prescribe one.

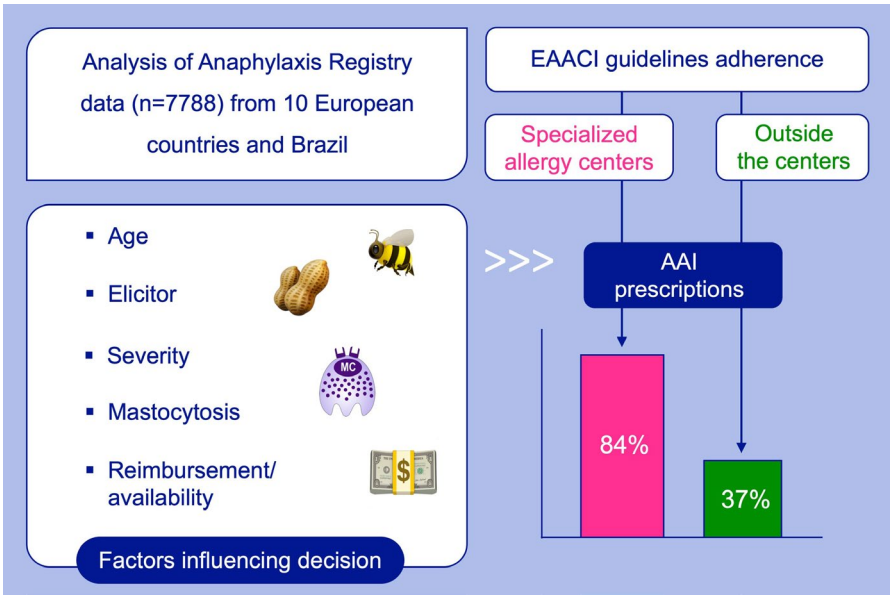
Conclusions: Based on the low implementation of guidelines concerning secondary prevention measures outside of specialized allergy centers, our findings highlight the importance of these specialized centers and the requirement of better education for primary healthcare and emergency physicians.

KEYWORDS
adrenaline autoinjector, anaphylactic reaction, anaphylaxis, epinephrine autoinjector, secondary prevention

1 | INTRODUCTION

Anaphylaxis is a rapid, potentially life-threatening event. Because of its sudden occurrence, immediate professional management cannot be realized in most cases. Therefore, preventive measures are particularly important. Patients with a history of anaphylaxis have an increased risk of severe reactions in the future.[1] Thus, in this group individual secondary prevention measures are particularly indicated. The identification, consequent avoidance of triggers, and specific immunotherapy (SIT) may decrease the probability of repeated anaphylactic reactions.[2,3] Emergency medication and management training may diminish the severity of the reaction and prevent fatal outcome.[4-6] Providing detailed information regarding the cause, nature, and countermeasures decreases insecurity and increases the patients' quality of life.[7] Therefore, different international guidelines emphasize the importance of secondary prevention measures.[8,9]

In this study, we analyzed the data acquired from the Anaphylaxis Registry regarding the range of secondary prevention measures offered to patients in specialized allergy centers and by primary care providers. The availability of an adrenaline autoinjector is one of the



GRAPHICAL ABSTRACT

Data from the Anaphylaxis Registry were analyzed to identify secondary prevention measures offered to patients who experienced anaphylaxis. In specialized allergy centers 84% of patients were prescribed adrenaline autoinjectors following EAACI guidelines and only 37% outside the centers. The secondary prevention measures offered to the anaphylaxis patients varied with the elicitor, and to some extent with other factors such as patients' age, comorbidities, and reaction severity.

Abbreviation: AAI, adrenaline autoinjector

most important preventive measures to reduce the risk for severe outcome; therefore, we focused on whether the European Academy of Allergy and Clinical Immunology (EAACI) standards[8] for adrenaline autoinjector prescription are followed.

2 | PATIENTS AND METHODS

2.1 | Database

The Anaphylaxis Registry is a real-life database that collects data regarding moderate and severe anaphylactic reactions. The registry was described elsewhere.[10-12] One hundred and thirty-seven specialized tertiary allergy centers from eleven countries (Germany, Austria, Switzerland, Poland, Italy, Spain, Ireland, Greece, France, Bulgaria, and Brazil) contribute currently to the registry. Pseudonymized data of patients with anaphylaxis in the previous year are locally captured by trained health professionals through a web interface. Elicitor, symptoms, course, and treatment of the reaction, along with diagnostic procedures and preventive measures, are the focus of the registry. Furthermore, patients' demographic and medical data are collected. The registry was established in 2007 (initially in German-speaking countries and in other countries since 2011), and the questionnaire evolved over time, including additional topics (current version 7.0). The project was approved by the ethics committee at Charité—University Medicine Berlin, Germany, and accredited by the local ethic committees in all participating centers.

2.2 | Patients

We included cases reported between June 2011 and March 2018 fulfilling the modified National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.[13] Cases reported prior to this time period were excluded, because the previous questionnaire versions did not contain all items required for this analysis.

The scope of the registry is moderate and severe anaphylactic reactions; however, it contains a small proportion of cases with mild anaphylactic symptoms, which were excluded from the analysis (defined as skin/mucosa and/or gastrointestinal symptoms only). Reactions with skin/mucosal and severe gastrointestinal symptoms (vomiting/incontinence) caused by a parenteral elicitor were defined as moderate reactions and remained in the dataset.

The dataset contained 7788 cases fulfilling the inclusion criteria (Figure S1, Table S1).

2.3 | Variables

The secondary prevention measures following the anaphylactic reaction were asked in the questionnaire in a standardized form:

1. *What prophylactic measures have been instigated following the episode?* The answers' options (multiple selections possible) were as follows: "Counseling about avoidance of the trigger," "Prescription of emergency drugs," "Training in emergency management plan, including drug training," "SIT," and "Others" (with an option to describe a measure in a free text form). For each measure, the time point of the introduction was asked as follows (multiple selections possible): "Already in place prior to reaction," "At the emergency department/ primary care prior to discharge," "In primary care during a follow-up visit," and "In specialist center during a follow-up visit."

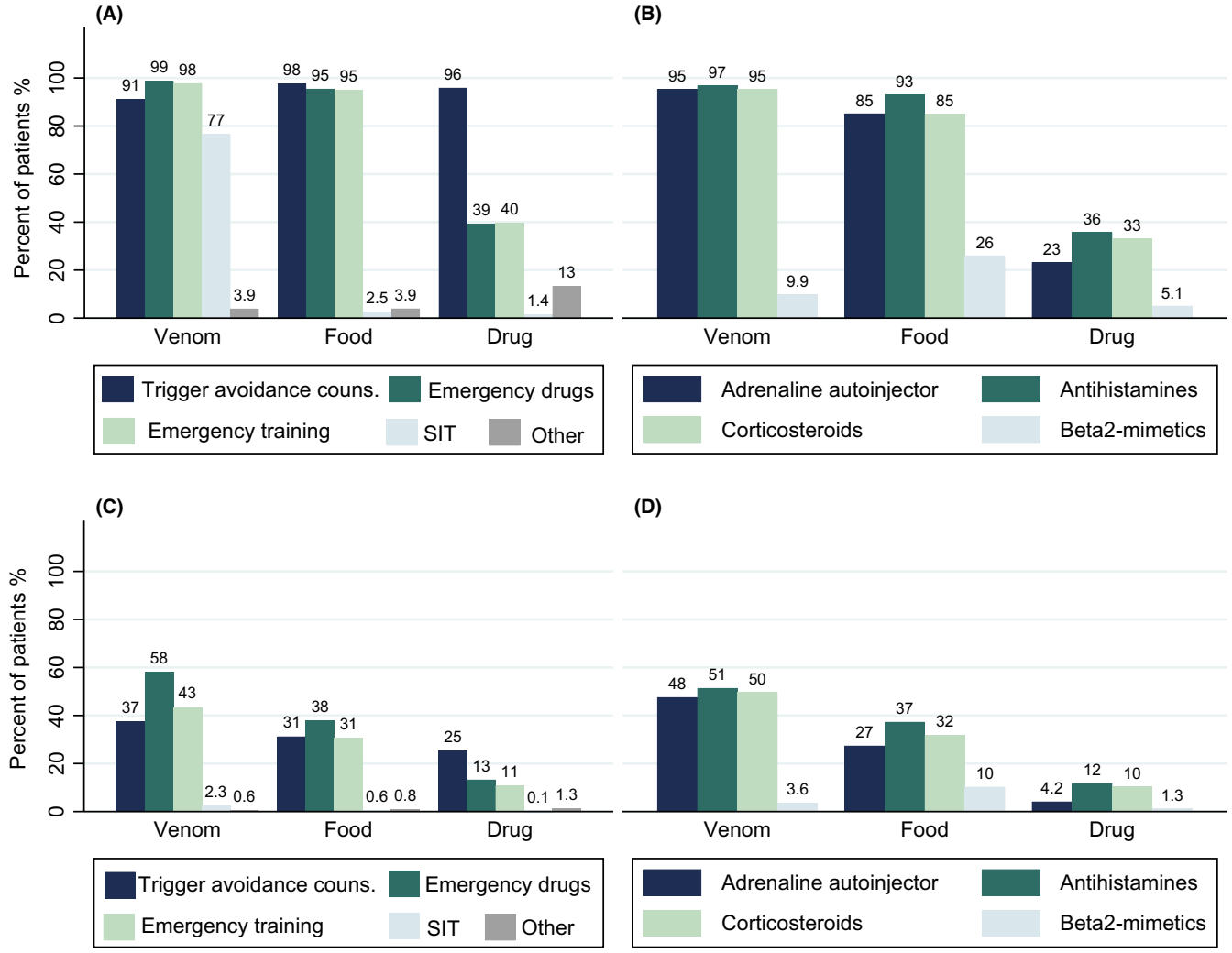


FIGURE 1 Proportion of venom (Panel A: n = 2861; B: n = 2800 C: n = 2607; D: n = 2546), food (Panel A: n = 2676; B: n = 2637 C: n = 1926; D: n = 1894), or drug (Panel A: n = 1388; B: n = 1371; C: n = 1191; D: n = 1187) allergic patients who were offered different secondary measures (A and C) and prescribed different emergency medication (B and D) at any time (A and B) or before visiting the specialized allergy center (C and D)

2. *What kind of emergency drugs were prescribed following the recovery of the reaction?* Here, the multiple selections of the following medication were offered: "Adrenaline autoinjector," "Adrenaline inhaler," "Antihistamines," "β2-mimetics," "Corticosteroids," and "Other" (free text possible). The time point of the prescription was asked as described for the question mentioned above.
3. Beginning with version 7.0 of the questionnaire (since March 2017; 597 cases in our dataset were reported during this time period) the following additional information was asked: *Which adrenaline autoinjector was prescribed? How many adrenaline autoinjectors were prescribed? Which dosage of one adrenaline autoinjector was prescribed?*

2.4 | Statistical analysis

The data were analyzed with STATA® 15.0 statistical software (Stata Corp.). To determine predictors influencing the probability of obtaining an autoinjector prescription, logistic regression analysis with robust standard errors (with study centers as clustering variable) was performed. Results are presented as odds ratio (OR) with 95% confidence intervals and *P*-values.

3 | RESULTS

3.1 | Secondary prevention measures vary across elicitors

Almost all patients with venom allergy received emergency medication prescription (99%) and emergency management training (98%) at some point after the reaction (Figure 1A; absolute numbers are described in the figure legends). In 77% of the cases, SIT was initiated. Most patients in this group were prescribed adrenaline autoinjector (95%), antihistamines (97%), and corticosteroids (95%; Figure 1B).

Among patients with food allergy, trigger avoidance counseling was the most frequent preventive measure (98%), followed by

emergency drug prescription (95%) and emergency management training (95%; Figure 1A). Moreover, SIT was initiated in 2.5% of these patients. Special extensive training programs and individual nutritional counseling were offered in a few cases. Patients with food allergy were less likely to receive an adrenaline autoinjector prescription than those with venom allergy (85% vs 95%). Furthermore, the prescription rates of antihistamines (93%) and corticosteroids (85%) were slightly lower (Figure 1B).

Education regarding trigger avoidance was the most frequent preventive measure offered to patients with drug allergy (96%). Interestingly, despite that in case of drug allergy the identified allergen can be avoided without a great risk of accidental intake, 40% of these patients received emergency medication prescribed, particularly antihistamines and/or corticosteroids; however, 23% were also prescribed an adrenaline autoinjector (Figure 1A and B).

"Other" secondary prevention measures were offered to 14% of the patients with drug allergy: Testing and provocation to provide alternative safe medication were the most common answers appearing in this category.

To investigate which factors have an influence on the secondary prevention measures offered, we performed the analysis (separate for venom and food allergy) differentiating among severity grades of the reaction according to the Ring and Messmer scale,[14] age groups and gross domestic product (GDP)[15] per capita of the country where the center is located (low < 15 000 $: Brazil, Bulgaria, and Poland n = 242; middle > 15 000 $ and < 40 000 $: Greece, Italy, Spain, and France; n = 1216; and high > 40 000 $: Austria, Germany, Ireland, and Switzerland n = 4079). Here, we observed that babies (n = 61) and the elderly (>80 years, n = 29) received less emergency medication, and particularly fewer autoinjectors prescribed (approximately 70% of the patients in these age groups received an adrenaline autoinjector prescribed compared with approximately 90% of those in other age groups; data not shown). Severity of the reaction had a slight influence on the prescription pattern (data not shown). As suspected, patients from

TABLE 1 Predictors for patients[a] to get an adrenaline autoinjector prescription (results of two separate logistic regression models)

Number of observations	A) At all (after or during the visits in a specialized allergy center) n = 3608		B) Before visit in a specialized allergy center n = 4410	
	Odds ratio [95%-CI]	*P*-value	Odds ratio [95%-CI]	*P*-value
Male sex	1.13 [0.92-1.39]	.233	0.94 [0.78-1.15]	.593
Age (in years)	0.98 [0.98-0.99]	<.001	0.98 [0.98-0.99]	<.001
Elicitor (vs venom)				
Food	0.36 [0.2-0.66]	.001	0.28 [0.18-0.43]	<.001
Others (including latex, exercise, and unknown causes of anaphylaxis)	0.18 [0.1-0.34]	<.001	0.28 [0.18-0.43]	<.001
Comorbidities				
Cardiovascular comorbidities	1.38 [0.88—2.17]	.159	1.12 [0.97-1.3]	.130
Asthma	1.25 [0.92-1.7]	.153	1.22 [0.99-1.5]	.068
Mastocytosis	3.03 [1.26-7.28]	.036	1.53 [0.99-2.36]	.053
Severity grade III or IV (vs grade II[b])	1.54 [1.27-1.87]	<.001	1.36 [1.19-1.55]	<.001
Access to autoinjector in the country of residence[c] (vs European countries with reimbursement)				
European without reimbursement	0.53 [0.31-0.91]	.02	0.44 [0.148-1.3]	.135
Brazil as country of residence	0.11 [0.08-0.16]	<.001	Omitted[d]	
Year of reaction	1.06 [0.97-1.16]	.176	1.1 [1.01-1.19]	.026
Model constant	3.96e-51 [7.4e-126- 2.11e-24]	.186	4.36e-83 [1.5e-155-1.29e-10]	.026

[a]Only patients with absolute indication for an adrenaline autoinjector according to EAACI guidelines were included.
[b]Reactions grade I was excluded from the analysis during database adjustment (Figure S1).
[c]We assumed that patients are residents of the country where their specialized center is localized.
[d]As there were no cases from Brazil in which adrenaline autoinjector was prescribed before visit in the specialized center, this variable was omitted in this model.

countries with lower gross domestic product were prescribed less emergency medication (5%-24% less than in the countries with a high gross domestic product; data not shown).

3.2 | The majority of patients with anaphylaxis were offered adequate prophylaxis measures for the first time in a specialized center

As these data show the great majority of patients were offered adequate secondary prevention measures at some point, we aimed to further examine whether these measures were introduced during a visit to a specialized allergy center or previously in a primary care setting/emergency department. For this analysis, the patients who directly received emergency treatment in a specialized center or were visited by a center member during hospitalization immediately after the reaction had to be excluded to avoid bias. Thus, only patients who presented in the center for the first time at least 2 days after the reaction were included in this part of the analysis. Therefore, the total number of cases decreased from n = 7788 to n = 6354.

The most common secondary prevention measure offered to the patients before consultations in a specialized center was emergency drug prescription (58% and 38% of patients with venom and food allergies, respectively; Figure 1C). In the venom group, the percentage of patients who received antihistamines (51%), corticosteroids (50%), and an adrenaline autoinjector (48%) prescribed by the primary care/emergency physicians was similar (Figure 1D). Among patients with food allergy, a nonspecialist was more likely to prescribe antihistamines (37%) and corticosteroids (32%) than an adrenaline autoinjector (27%).

Antihistamines and corticosteroids for drug-allergic patients were prescribed similarly often in and outside the allergy centers; adrenaline autoinjectors were surprisingly provided mainly by specialists (17% vs 4%; Figure 1B and D).

Trigger avoidance counseling and emergency management training (including drug training) were offered to approximately 40% of patients with venom allergy, 30% of patients with food allergy, and 25% (counseling) and 11% (training) of patients with drug allergy before visiting the specialized center.

These data reveal that the standard of care for anaphylaxis patients in specialized centers is high. However, before the visit to a center less than half of the patients were offered adequate prophylaxis to handle the next reaction.

3.3 | Eighty-four percent of the patients with an absolute indication for an adrenaline autoinjector according to EAACI guidelines were prescribed one

The EAACI guidelines defined six groups of patients with an absolute indication for an adrenaline autoinjector: history of food, latex, or aeroallergens anaphylaxis (a); exercise-induced anaphylaxis (b); idiopathic anaphylaxis (c); coexisting asthma and food allergy (d); venom allergy without receiving SIT (e); and venom allergy and mast cell disorder (f). In our dataset, 4032 cases fulfilled one of these criteria. The information on adrenaline autoinjector prescription was provided in 3817 cases. Of these, 84% were prescribed an adrenaline autoinjector (before or during a consultation in a specialized center; Figure 2A). Guideline adherence was very good in patients with venom allergy (91%), followed by food-induced anaphylaxis (85%; Figure 2C). Patients with latex allergy, idiopathic anaphylaxis, and anaphylaxis caused by other elicitors were less often prescribed an autoinjector (67%, 70%, and 72%, respectively; Figure 2C).

The group of patients that required adrenaline autoinjector prescription before visiting a specialized center was larger (n = 6088) because in the majority of cases venom immunotherapy was initiated at first at a specialized center and these patients were not protected by immunotherapy until then; thus, they must be prescribed an adrenaline autoinjector. Within this group, the information on adrenaline autoinjector prescription was provided in 4751 cases. Despite the EAACI guidelines, 63% of the patients did not receive an autoinjector prescription before visiting a specialized center (Figure 2B). The patients with venom allergy (47%) were most likely to receive an adrenaline autoinjector prescription, followed by patients with food allergy (27%) and idiopathic anaphylaxis (24%; Figure 2D).

3.4 | Patients from countries without reimbursement were prescribed fewer adrenaline autoinjectors

Next, we analyzed whether the reimbursement status has an impact on the frequency of adrenaline autoinjector prescription. Among the countries contributing to the registry, autoinjectors are not reimbursed in Poland, Bulgaria, and Brazil. Moreover, in Brazil autoinjectors are not available at local pharmacies and have to be ordered from specialized companies. This situation was reflected in our data, as patients from Brazil received notably less adrenaline autoinjector prescriptions than patients from other countries (38% (n = 48) vs 79% (n = 163) in European countries without reimbursement and 85% (n = 3607) in European countries with reimbursement; data not shown).

3.5 | Elicitor and severity of the reaction, age of the patient, mastocytosis as comorbidity, and reimbursement/availability of the autoinjector influence physician's decision to prescribe one

To compare factors influencing the physicians' decision regarding adrenaline autoinjector prescription, a multivariate analysis was performed (Table 1). Panel A presents results based on EAACI guideline adherence in total; panel B presents the analysis of the adherence to the guidelines among emergency and primary care physicians. In both models, the reaction severity (Ring & Messmer, grades III and IV vs grade II) and venom as the elicitor were associated with a higher probability to receive an adrenaline autoinjector ($P \leq .001$). Higher age ($P < .001$ in both models) and the country of residence with no reimbursement ($P = .02$ in the overall model) were negatively associated. Mastocytosis was an important predictor in the overall model

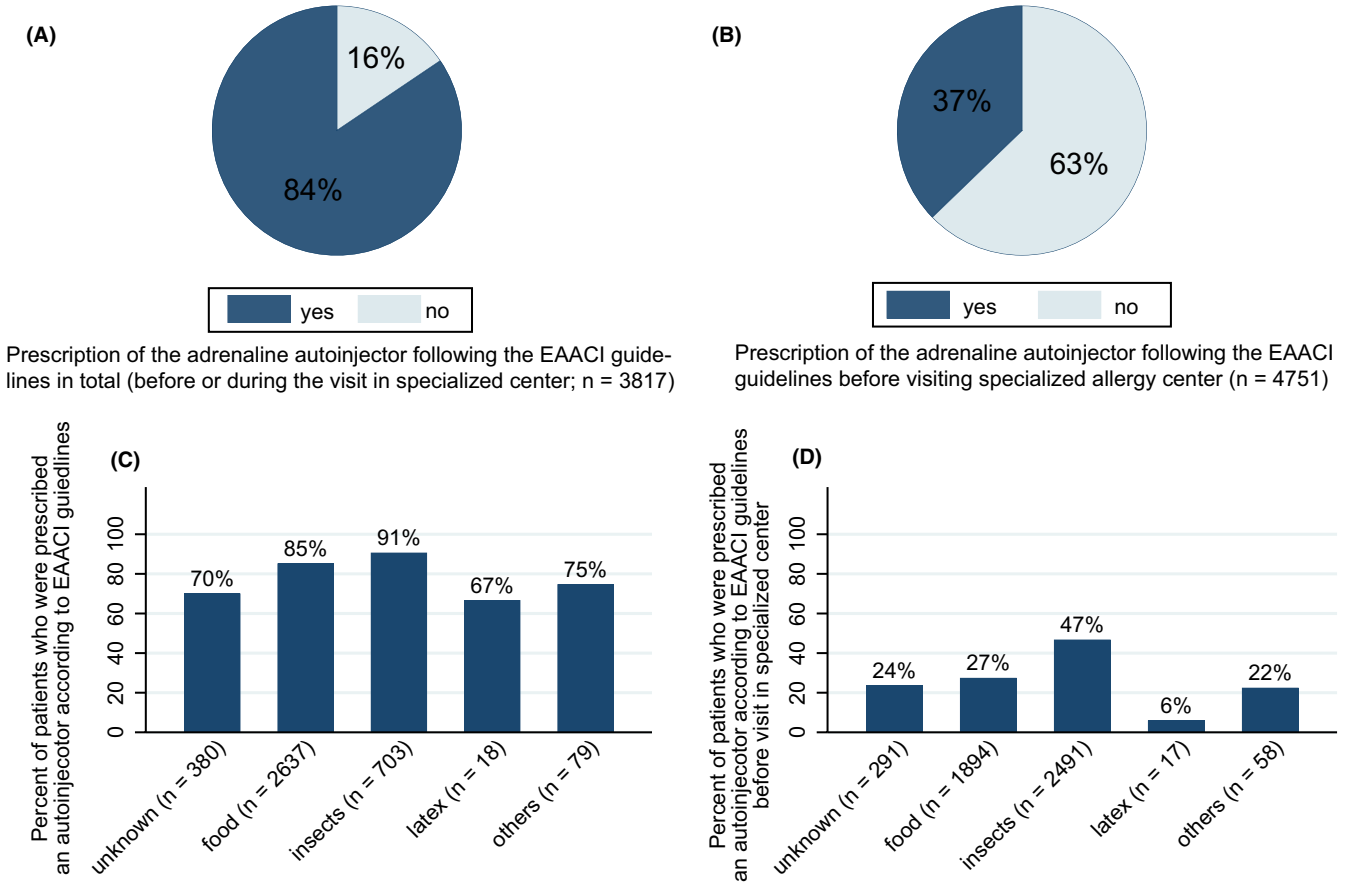


FIGURE 2 Proportion of patients who were prescribed an adrenaline autoinjector according to absolute indications of EAACI guidelines at any time (before or during the visit in the specialized center) (A and C; n = 3817) or before visiting the specialized allergy center (B and D; n = 4751). In panels C and D, the results for different elicitors are shown: unknown (Panel C: n = 380; D: n = 291), food (Panel C: n = 2637; D: n = 1894), insects (Panel C: n = 703; D: n = 2491), latex (Panel C: n = 18; D: n = 17), and others (Panel C: n = 77; D: n = 58) containing mostly Anisakis (Panel C: n = 31; D: n = 27), aeroallergens (Panel C: n = 21, D: n = 19), and exercise-induced anaphylaxis (Panel C: n = 11; D n = 6). The differences in absolute numbers between panel A and C vs panel B and D result from 1) the exclusion of patients presenting within or directly after the anaphylactic reaction in the specialized center in panel B and D, and 2) number of patient with venom allergy undergoing SIT and therefore not having an absolute indication for an autoinjector according to EAACI guidelines

(OR = 3.03, P = .036). In addition, Brazilian patients had a remarkably lower probability to receive an adrenaline autoinjector (OR = 0.11, P < .001). Sex and cardiovascular diseases of the patient had no influence on physicians' decision.

3.6 | Prescription of more than one adrenaline autoinjector

Of 597 patients, 65%, 33%, and 2% were prescribed one, two, and more than two autoinjectors, respectively (Figure S2A). In the multivariate analysis (Table S2), the probability to receive two devices was increased in patients with mastocytosis (OR = 5.74, P = .026), whereas it was decreased in patients with food allergy compared with those with venom allergy (OR = 0.31, P = .011). Pediatric patients were more often prescribed two or more autoinjectors than adult patients with a clear cutoff during the transition from childhood to adulthood (Table S2, Figure S2B). The dosage of adrenaline (150 vs 300 µg) was usually selected according to weight (300 µg for >30 kg; data not shown).

4 | DISCUSSION

Our data provide basically a positive outcome regarding the range of preventive measures offered to anaphylaxis patients. In most cases, adequate measures were offered, and EAACI guideline adherence regarding autoinjector prescription (84%) was satisfying. However, this perspective is strongly influenced by the structure of the registry; the cases entered into the database were recorded by allergists in a cooperating center, and we had no data regarding the patients who never reach these healthcare facilities (which may be depending on the country/region the majority of the patients). The second main source of bias may be the definition of particular measures, such as "counseling about avoidance of the trigger" or "training in emergency management plan, including drug training" that can strongly vary with regard to their extent, as no minimal standards for those measures were defined in the questionnaire.

A more differentiated image of secondary prevention measures appears on analyzing the data regarding prescription and counseling

patterns outside specialized centers; the data revealed that the minimal protection in the form of an adrenaline autoinjector prescription was offered to 37% of the patients, who had an absolute indication for it. This low emphasis on secondary prevention measures might be related to the fact that patients may not always be advised before the proper allergological work-up, and that the primary care physician referred the patient to a specialized allergy center. However, the fact that 70% of patients who had an anaphylaxis to food with severity grade III/IV left the emergency department and went through primary care without a prescription for an autoinjector is alarming. Our findings are in line with a population-based study by Kilger et al[16] who analyzed the emergency medication prescribed to children after anaphylaxis in Dresden (Germany) and showed that only 26% of the children were prescribed an autoinjector. Another population-based study conducted in Canada reported that 45%-55% of patients with food allergy have an autoinjector.[17]

Interestingly, the elicitor of the reaction appears to be an important factor, influencing physicians' decision regarding emergency drug recommendation; patients with food allergy were prescribed emergency medication less frequent than those with venom allergy. This difference was substantial, particularly with regard to autoinjector prescription outside an allergy center (48% vs 27%). As this effect remained significant in the multivariate analysis, it cannot be explained by the difference in the patients' age or reaction severity.

Most cases in the registry are from high GDP European countries, and no data on the individual socioeconomic background are collected. Therefore, the Anaphylaxis Registry is not the appropriate database to analyze the differences regarding this issue. However, the data sample from Brazil gives a hint, how unequally the access to adequate secondary prevention measures is distributed worldwide. The differences according to gross domestic product per capita/reimbursement of the autoinjector (no by chance the two European countries from the registry without reimbursement are also the ones with the lowest gross domestic income) were present and significant in the multivariate analysis; however, the differences were not as notable as expected. This can be partially related to the fact that our collaborating centers in the countries without reimbursement are mainly placed in big cities; therefore, they may attract a selected, higher-income population. On the other hand, we have no information, if the prescriptions issued by the physicians were later filled in the pharmacy and, as studies from the United States show, not being able to afford medication is the most common reason for not well-off patients to not fill the prescriptions.[18,19]

Individual characteristics of the patients had little influence on preventive measures offered to them. Two groups received autoinjector prescriptions less frequently: babies and elderly patients (data not shown). This can be explained by the fact that there are no devices with an accurate dosage for babies, and elderly patients are prescribed adrenaline less often possibly because of multiple comorbidities, even though cardiovascular diseases themselves seem to have no influence on physicians' decision. These findings should be addressed by further research as elderly patients are particularly prone to severe reactions.[20,21]

Children were significantly more often prescribed two autoinjectors, which is striking because of the rough cutoff at the end of second decade (Figure S2B). This may reflect the differences in behavior of pediatric allergist and other specialties or be caused by physician's emphasis on special needs of children. In this case, the European Medicines Agency (EMA) recommendations to prescribe additional adrenaline autoinjector for the use in the school might have been crucial.

Overall, our data highlight the importance of specialized allergy centers and allergists in terms of providing adequate secondary prevention measures to individuals with anaphylaxis. Healthcare standards, except for those of specialized facilities, were found to be insufficient as in most cases the international guidelines were not followed. This implicates the requirement of better education for emergency doctors and primary healthcare providers to emphasize the importance of the secondary prevention measures in anaphylaxis patients.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

M Kraft performed data analysis and wrote the manuscript. M Knop, JM Renaudin, K Scherer Hofmeier, C Pföhler, MB Bilò, R Lang, R Treudler, N Wagner, T Spindler, JO'B Hourihane, I Maris, A Koehli, A Bauer, L Lange, S Müller, NG Papadopoulos, B Wedi, A Moeser, LF Ensina, M Fernandez-Rivas, E Cichocka-Jarosz, G Christoff, BE Garcia, I Poziomkowska-Gęsicka, V Cardona, TB Mustakov, U Rabe, V Mahler L Grabenhenrich, and S Dölle-Bierke 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.

ORCID

Magdalena Kraft https://orcid.org/0000-0002-2770-9947
Lars Lange https://orcid.org/0000-0003-1104-5848
Bettina Wedi https://orcid.org/0000-0002-9868-6308
Victoria Cardona https://orcid.org/0000-0003-2197-9767
Margitta Worm https://orcid.org/0000-0002-3449-1245

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SUPPORTING INFORMATION

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

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