Analyses of Spontaneous Adverse Drug Reaction Databases Using Descriptive and Inferential Statistics

Dissertation

zur Erlangung des Doktorgrades (PhD)

der Medizinischen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität

Bonn

Diana Ivonne Dubrall

aus Heidenheim an der Brenz

2020

Angefertigt mit der Genehmigung
der Medizinischen Fakultät der Universität Bonn

1. Gutachter: Prof. Dr. rer. nat. Matthias Schmid

2. Gutachter: Prof. Dr. med. Bernhardt Sachs

Tag der mündlichen Prüfung: 04.09.2020

Aus dem Institut für Medizinische Biometrie, Informatik und Epidemiologie
Direktor: Prof. Dr. rer. nat. Matthias Schmid

Table of content

List of abbreviations

ACEi	Angiotensin-Converting Enzyme Inhibitor
ADR	Adverse Drug Reaction
ARB	Angiotensin-Receptor Blocker
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinpodukte)
EMA	European Medicines Agency
EudraVigilance	European Adverse Drug Reaction Database
CI	Confidence Intervals
DEGS1	German Health Interview and Examination Survey for Adults
EEA	European Economic Area
HCP	Health Care Professionals
IMBIE	Institute for Medical Biometry, Informatics and Epidemiology
Non-HCP	Non-Health Care Professionals
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratios
OTC	Over the Counter Drugs
RAS	Renin-Angiotensin System
SMQ	Standardised MedDRA Query
USA	United States of America

1. Summary

The presented cumulative dissertation summarizes four scientific research papers of analyses assessing data of the adverse drug reaction (ADR) database of the Federal Institute for Drugs and Medical Devices (BfArM) and the European ADR database (EudraVigilance) of the European Medicines Agency (EMA). The objective was to analyse all ADR reports contained in BfArM's ADR database descriptively for the first time and subsequently with regard to three relevant pharmacovigilance questions. Therefore, research strategies for the identification of the cases depending on the research question were established and different statistical methods were used. Two of the known limitations of analysis performed in ADR databases are the lack of matching control groups and exact exposure data. To overcome these issues, we generated control groups within the ADR database and used external data sources to set the number of ADR reports in relation to the number of inhabitants and assumed drug-exposed inhabitants. All research articles have been published in international peer-reviewed journals (see Appendix A-D).

2. Introduction

Prior to the approval of a drug, its safety and efficacy have to be investigated in clinical trials. In these only a limited number of patients are included, which are often selected according to strictly pre-defined inclusion and exclusion criteria (EMA, 2020). Especially vulnerable patients such as very old as well as very young patients or patients with comorbidities are often not involved. Thus, the complete extent of ADRs is unknown when a drug is released to the market. Therefore, post-authorisation monitoring of the approved drugs remains crucial. Among others, ADR databases are one of the suitable tools to monitor drug safety. In the past, ADR reports served as one of the sources of evidence in 94.4 % of all regulatory actions due to safety issues in Europe (Lane et al., 2018).

In Germany, ADRs are reported by Health Care Professionals (HCP) e.g. physicians and non-Health Care Professionals (non-HCP) e.g. consumers (Kommas et al., 2019). A detailed description about reporting channels and reporting obligations can be found elsewhere (Kommas et al., 2019). In brevity, all ADR reports of chemical defined drugs were stored in BfArM's ADR database until November 22, 2017 (BfArM, 2013 a). Since then all ADR reports are being sent to the European ADR database (EudraVigilance).

The first study of this cumulative dissertation represents a descriptive analysis of all ADR reports contained in BfArM's ADR database (Appendix A). Descriptive analyses of ADR databases were also published for other countries (Ozcan et al., 2016; Thiessard et al, 2005). However, the results from other countries cannot be transferred to Germany, since these may vary significantly due to different prescribing behaviours and differences between the patient populations involved (e.g. genetic differences).

In Germany, nearly 2.4 % - 6.4 % of all hospital admissions were ADR related and increased with rising age (Schneeweiss et al., 2002; Schurig et al., 2018). Likewise, the number of ADR reports per inhabitants referring to older adults (> 65 years) compared to younger adults was higher in other ADR database analysis (Aagaard et al., 2012). With regard to drug therapy in older adults, information on safety and efficacy are contained in less than half of initial drug approval documents (Ruiter at al., 2019). However, older adults are more prone to develop ADRs, since they exhibit numerous risk factors such as multimorbidity, polypharmacy, as well as changes in pharmacokinetics, due to reduced kidney and liver function (Davies and O'Mahony, 2015). Additionally, the forthcoming demographic change will shift the proportion of older adults in the German population. An increase up to 24-30 % until the year 2060 (2018: ~ 19 %) is expected (Destatis, 2019). Hence, the impact and significance of ADRs in older adults is supposed to gain further medical and economic relevance in the future. In our second study we analysed, whether an increase in the number of ADR reports referring to older adults in relation to the number of inhabitants and assumed drug-exposed inhabitants could already be observed in the past. Further on, we investigated whether there are differences in the reported characteristics in ADR reports of older and younger adults, which may highlight ADRs of particular importance for older adults (Appendix B).

Opposed to older adults, ADR related hospital admissions are reported to be less common in children (Impicciatore et al., 2001). Based on emergency department records the incidence of drug-induced anaphylaxis for children (< 19 years) was estimated to be 0.5/100,000 person-years (West et al., 2007). Anaphylaxis is defined as a potentially severe generalized or systemic hypersensitivity reaction, in which the skin (e.g. urticaria, angioedema), the respiratory tract (e.g. dyspnea), the gastrointestinal tract (e.g. vomiting) and the cardiovascular system (e.g. hypotension, cardiovascular shock) may be involved

(Muraro et al., 2014). Among others, drugs are one of the most frequent elicitors reported to induce anaphylactic reactions in children (Cavkaytar et al., 2017; Thong and Tan, 2011; Xing et al., 2018). To be noted, only a few studies investigated risk factors of drug-induced anaphylactic reactions in patients aged 0-17 years. In these studies antibiotics, in particular beta-lactams, and non-steroidal anti-inflammatory drugs (NSAIDs) were mostly reported as suspected drugs. With regard to possible risk factors allergy and atopy are discussed but literature is contradictory (Demir et al., 2019; Montañez et al., 2017; Muraro et al., 2014). However, risk factors may differ depending on the drugs used. In order to identify possible associated factors, a comparative analysis of anaphylactic reaction reports compared to all other ADRs (exclusive anaphylactic reactions) and a drug-stratified analysis was conducted in our third study (Appendix C).

For patients of all ages, the rate of hospital admissions has not only increased in the past for anaphylactic reactions but also for angioedema (Gupta et al., 2003). An angioedema is a well known ADR of drugs acting on the renin-angiotensin system (RAS). Angioedema is defined as a deep dermal, subcutaneous swelling that typically affects the face, lips, tongue, larynx or pharynx (Byrd et al., 2006; Sachs et al., 2018). It may be life-threatening (Bas, 2017; Stauber et al., 2014), especially when airways are involved. In roughly 0.1 to 0.7 % of patients treated with angiotensin-converting enzyme inhibitors (ACEi) an angioedema is estimated to occur (Bas, 2017). For angiotensin-receptor blockers (ARBs) lower, and for aliskiren (renin inhibitor) lower and equal angioedema incidences are reported compared to ACEi (Makani et al., 2012; Toh et al.,2012; Withe et al., 2010). Concerning the pathophysiological mechanism, ACEi-associated angioedema is assumed to be caused by accumulation of bradykinin (Bas et al., 2015). Female gender (Costis et al., 2005), smoking (Bezalel et al., 2015; Morimoto et al., 2004), allergies, and some co-medications (e.g. immunosuppressives, fibrinolytics) (Brown et al., 2017; Lin et al., 2014) have been reported as risk factors for ACEi-associated angioedema. In contrast, little isknown about the pathophysiological mechanism and risk factor of ARBs and aliskiren-associated angioedema. Hence, in our fourth study, we compared angioedema reports of ACEi versus ARBs and aliskiren, in order to identify differences, which may give a hint to the underlying pathophysiology and the risk factors of ARBs and aliskiren-associated angioedema (Appendix D).

3. Objectives

We performed the first descriptive analysis of all ADR reports contained in BfArM's ADR database, in order to analyse the characteristics (e.g. drugs, ADRs) most frequently reported (Appendix A). Subsequently, external data sources were used to set the number of ADR reports referring to older and younger adults in relation to the number of inhabitants and assumed drug-exposed inhabitants to investigate, if the number of ADR reports increased in the past and with rising age (Appendix B). The aims of the three comparative analyses were to analyse (i) ADRs of particular importance for older adults (Appendix B), (ii) the drugs and associated factors most frequently reported in ADR reports of anaphylactic reactions (Appendix C), and (iii) the characteristics reported in angioedema reports of ARBs and aliskiren, which may provide further insight concerning their pathophysiological mechanism and associated factors (Appendix D).

4. Methods

4.1 BfArM's ADR database

Roughly 555,000 ADR reports originating from Germany were contained in BfArM's ADR database. The majority of these ADR reports (69.8 %) were spontaneous reports, in which the reported ADRs occurred in everyday life (study reports: 28.2 %, unknown: 2.0 %). In order to avoid any stimulated reporting bias through study reports, all performed analyses were restricted to spontaneous reports. In 82.5 % of these spontaneous reports a HCP and in 15.6 % a non-HCP was involved in the reporting of the ADR (in 4.5 % both, a HCP and a non-HCP reported, and in 6.4 % the reporter was unknown).

4.2 EudraVigilance

The comparative analysis of ACEi, ARBs and aliskiren-associated angioedemas was additionally performed in EudraVigilance (Appendix D). This database includes all ADR reports of medicinal products, which have been authorised or being studied in clinical trials in the European Economic Area (EEA). Up to the data lock point of December 31, 2019, roughly 3.0 million spontaneous reports from the EEA were stored in EudraVigilance. In 81.4 % of these, a HCP was involved in the reporting of the ADR, whereas 17.8 % were exclusively reported by a non-HCP.

4.3 Descriptive analysis of all ADR reports

All spontaneous ADR reports received between 1978 and December 31, 2016 originating from Germany, in which the drugs were reported as "suspected/interacting" were identified (n= 369,778). Further, we excluded all ADR reports, that reported a medication error, intentional misuse or suicide/self-injury behavior (in the following “unintended drug use”). The final dataset contained 345,662 ADR reports.

4.4 Adverse drug reactions in older adults

For the comparative analysis, we identified all spontaneous reports registered between January 1, 2000 and October 31, 2017 with German origin, in which the drugs were designated as "suspected/interacting" for patients > 65 years ("older adults", n= 74,950) and patients 19-65 years ("younger adults", n= 128,652). After exclusion of ADR reports, for which an unintended drug use or an unknown primary source were reported, the final datasets of older and younger adults consisted of 69,914 and 111,463 ADR reports.

4.5 Drug-induced anaphylactic reactions in children

At first, we extracted all spontaneous ADR reports submitted to the BfArM in the time frame January 1, 2000 up to December 31, 2016 with German origin referring to children (0-17 years) (n= 14,508). The ADR reports of anaphylactic reactions were identified by application of the standardized MedDRA Query (SMQ) “anaphylactic reaction (narrow)” (n= 505, other ADR reports n= 14,003) (MedDRA, 2020). An individual case assessment of the identified anaphylactic reaction reports according to the correctness of diagnosis and the causal relationship was performed (see Appendix C). After exclusion of ADR reports, in which an unintended drug use was reported, 159 validated cases and 12,168 other ADR reports remained.

4.6 Comparative analysis of ACEi, ARBs and aliskiren angioedema reports

In EudraVigilance, all spontaneous ADR reports registered between January 1, 2010 and June 31, 2017 originating from one of the member states of the EEA, in which either an ACEi, ARB or aliskiren was reported as "suspected/interacting" drug, were identified. Each of the three datasets were divided in angioedema cases and controls (all other ADR reports exclusive the identified angioedema cases) by application of the SMQ "angioedema (narrow)".

4.7 Statistical analysis

Descriptive analyses with regard to (i) patients demographics, (ii) seriousness of the ADR reports in accordance with legal requirements (EMA, 2017), (iii) the drug substances reported most frequently as suspected and (iv) the ADRs reported most frequently, were conducted in all of the four analyses.

4.7.1 Odds Ratios

Odds ratios (OR) and Bonferroni adjusted confidence intervals (CI) were calculated in all comparative analyses using a 2 x 2 frequency table (Morris and Gardner, 1988) (see example Table 1)). The aim was to identify conditions of interest which are more often associated with cases or controls.

Table 1)	Cases	Controls	Calculation OR +/- adjusted CI
Number of ADR reports with condition of interest (e.g. ADR)	A	B	*OR = (A/B)/(C/D)* *α = 0.05; k =number of hypothesis tests* *α' = α/k significance level corrected for multiple testing by Bonferroni correction* *CI = OR + / - Z(1 – (α'/ 2)) ** $\sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}$
Number of ADR reports without condition of interest (e.g. ADR)	C	D	

α = significance level of hypothesis test; Z(1-(α'/2)) = critical value Z of the standard normal distribution in a two-tailed hypothesis test on significance level α'; OR = 1 condition does not affect the outcome; OR > 1 condition more often associated with cases; OR < 1 condition more often associated with controls; if CI excludes 1 the association is statistically significant

In the comparative analyses of angioedema reports of ACEi versus ARBs and aliskiren, ORs +/- 95 % CI were additionally calculated using logistic regression analyses. Logistic regression was used to calculate OR in the presence of several explanatory variables (conditions of interest) in order to reduce confounding by analyzing the association of all variables at the same time (Petrie, 2020). The relationship between the explanatory variables and the response variable can be described by the following mathematical equation:

$$log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots. + \beta_m x_m$$

p = probability of outcome (e.g. case or control); β_i =regression coefficients; x_i = explanatory variables

4.7.2 ADR reports per 100,000 inhabitants/assumed drug-exposed inhabitants

The mean numbers of ADR reports per 100,000 inhabitants and per 100,000 assumed drug-exposed inhabitants were calculated in the analysis of ADR reports referring to older

adults. Therefore, the number of inhabitants was extracted from the Federal Statistical Office in Germany (Destatis, 2020). To calculate the number of assumed drug-exposed inhabitants, the number of inhabitants was multiplied by the proportion of patients taken any medications according to the DEGS1 study (Knopf and Grams, 2013). Afterwards, the number of ADR reports was set in relation to the number of inhabitants/assumed drug-exposed inhabitants for each year distributed by age and gender. The results are presented as the mean number of ADR reports per 100,000 inhabitants/assumed-drugs exposed inhabitants for the timespan.

Example calculation of the mean number of ADR reports per 100,000 inhabitants:

1) *The number of ADR reports per 100,000 inhabitants per year =*

   (number of ADR reports per year / number of inhabitants per year) × 100,000

2) *The mean number of ADR reports per 100,000 inhabitants =*

   $\sum$ *number of ADR reports per 100,000 inhabitants per year*$_i$ */ the number of years*

5. Results

Only an overview of the most important results is presented. For a detailed presentation of the results please refer to the Appendix A-D.

5.1 Descriptive analysis of all ADR reports

Since 1978 the number of ADR reports in BfArM's ADR database steadily increased. On the highest aggregated analysis level, drugs for the treatment of nervous system disorders were most frequently reported as suspected in nearly one quarter of all ADR reports (23.1 %). However, differences in the most commonly reported drug classes and ADRs were observed between ADR reports from physicians and consumers. Overall, patients reported subjectively perceived ADRs more frequently, while physicians more commonly reported findings or diagnoses that require medical expertise.

5.2 Adverse drug reactions in older adults

In relation to 100,000 inhabitants the increase of the number of ADR reports was higher for older compared to younger inhabitants. The highest number of ADR reports per 100,000 inhabitants and assumed drug-exposed inhabitants, was detected for the age groups 76-84 years (25 ADR reports) and 70-79 years (27 ADR reports), respectively. Per 100,000 males/females, an even higher number of ADR reports for males in general and

classified as serious was observed compared to females. Nearly one-fifth (19.8 %) of all ADR reports referring to older adults reported an antithrombotic agent as suspected drug (younger adults: 5.1 %). Concerning antithrombotic agents, gastrointestinal and cerebral haemorrhages were reported more frequently for older compared to younger adults.

5.3 Drug-induced anaphylactic reactions in children

In general, the number of ADR reports per year increased, while the number of anaphylactic reaction reports was almost stable. Antibiotics (30.2 %, cefaclor most reported) and analgesics/antipyretics (22.0 %, ibuprofen most reported) were the drug classes reported most often in anaphylactic reaction reports. Both drug classes and the intravenous application of medicinal products, were statistically significantly more often reported in anaphylactic reaction reports compared to all other ADR reports ($p < 0.001$). In drug-stratified analysis, more atopic/allergic patients were included in analgesics/antipyretics (42.9 %) compared to antibiotics cases (14.6 %).

5.4 Comparative analysis of ACEi, ARBs, and aliskiren angioedema reports

Among others, "allergy" (OR 1.8 [1.4-2.3]) and "previous/recurrent angioedema" (OR 36.8 [18.5-73.3]) were reported more often in the history of the patients of ACEi angioedema reports versus ACEi controls. In comparison to ACEi (4.3 %), even more patients with allergies were included in ARBs (6.8 %) and aliskiren (13.6 %) angioedema reports. Regarding the reported ADRs, "urticaria" was more frequently observed in ARBs (18.5 %) and aliskiren (9.0 %) than ACEi-associated angioedemas (5.0 %). In contrast, ACEi-associated angioedemas were more often designated as "life-threatening" compared to ARBs (OR 2.2 [1.6-2.9]) and aliskiren (OR 14.2 (3.5-57.4)).

6. Discussion

The continuous increase in the number of ADR reports per year in BfArM's ADR database may be caused by stricter legal requirements for the pharmaceutical companies to forward these ADR reports to the BfArM (Appendix A). A general increase in willingness of all reporters (HCPs and non-HCPs) to report ADRs as result of an increased awareness (i) of ADRs due to an increased access to information (e.g. internet) and (ii) of the opportunities to report ADRs such as via the online platforms since 2009, are additional possible explanations. Furthermore, an increase in the number of ADR reports sent by non-HCPs,

may also be stimulated by the request to report ADRs contained in the package leaflet since 2013 (BfArM, 2013 b). Especially, subjectively perceived ADRs reported by consumers may be very important to complement the ADR reports from physicians, since these ADRs may affect the patient's quality of life and consequently the adherence of the patient (Aagaard et al., 2009).

With regard to older adults, the increase of the number of ADR reports may be associated with the increase of the proportion of older adults in the German population in the analysed time frame (Destatis, 2019). The higher proportion of multi-morbid (RKI, 2012), drug-exposed and polymedicated older inhabitants (Knopf and Grams, 2013), may influence the higher frequency of ADR reports for older adults. An increase in the number of ADR reports in general and for older adults was also observed in other European ADR databases (Cutroneo et al., 1999; Ozcan et al., 2016; Thiessard et al., 2005).

Despite the enormous increase of ADR reports in the past, the number of anaphylactic reaction reports in our analysis remained stable between 2000 and 2016. In contrast, in literature the frequency of anaphylactic reactions increased (Montañez et al., 2017). Differences regarding the study designs may be responsible for this difference.

In other descriptive ADR databases analyses, drugs for the treatment of nervous system disorders were also one of the most common reported drugs to induce ADRs (Ozcan et al., 2016; Thiessard et al., 2005). However, this drug class (21.2 %) was only the third commonly used in German adults between 2008 and 2011 (Knopf and Grams, 2013). Nevertheless, the reference to our study is, among others, at least hampered by another analysis period.

Concerning older adults, antithrombotics were the drug class most frequently reported in roughly one-fifth of all ADR reports. This may reflect the huge and increasing number of antithrombotics prescribed in general and with rising age (Hein and Wille, 2019). Antithrombotics were also in other studies identified as the top ranking drugs responsible for ADRs in older adults (Cutroneo et al., 1999; Schurig et al., 2018). Likewise, gastrointestinal and nervous system haemorrhages were more often associated with direct oral anti-

coagulants for older (≥ 60 years) opposed to younger adults in the USA and Japan (Shimada et al., 2019). Hence, our data underlines the recommendation to monitor older patients taking antithrombotics.

In our analysis of drug-induced anaphylactic reactions, ibuprofen was the most reported analgesic/antipyretic and cefaclor the most reported antibiotic. Concerning ibuprofen, the high number of reports may reflect the high frequency of exposure. According to others, ibuprofen was the most prescribed analgesic (76 %) to children in Germany in 2013 (Kapellen et al., 2015). In the same study, cefaclor accounted for 18.6 % of all antibiotic prescriptions beyond amoxicillin, which was the most frequently prescribed antibiotic (28.7 %). Based on this result, one may speculate, that cefaclor induces anaphylactic reactions in children more often than amoxicillin. However, without references to the exact exposure, no conclusions can be made whether the aforementioned drugs actually cause more ADRs.

Unexpectedly, more ADR reports in general as well as more serious ADRs per 100,000 older males compared to females were observed. Literature is inconsistent whether older males develop i) ADRs and ii) serious ADRs more often (Holm et al., 2017; Hopf and Mathias, 1988; Mann et al., 1992; Montastruc et al., 2002; Thiessard et al., 2005; Watson et al., 2019; Wester et al., 2007; Zopf et al., 2008). Differences regarding the study designs could be responsible for the deviating results. However, in a German survey serious ADRs were more often reported by physicians (Hasford et al., 2002) which could impact on the number of ADR reports per 100,000 older males to an unknown extent. Nevertheless, as a conclusion from our findings, more emphasis should be put on the occurrence of ADRs and serious ADRs in older males.

In our analysis of anaphylactic reactions, roughly one quarter of the children were atopic/allergic, which is in line with other studies (Bohlke et al., 2004; Dinakar, 2012). With regard to our results, atopy/allergy is possibly a drug-specific associated factor, since the proportion of allergic/atopic children differed between drug classes. Likewise to our analysis, atopy was not associated with beta-lactam allergy in children by others (Ponvert et al., 1999, 2011). Concerning analgesics/antipyretics, one study reported atopy as a risk factor to induce only selected forms of NSAID hypersensitivity (Quiralte et al., 2007), whereas no differences were found by others in patients of all ages (Faria et al., 2014).

In contrast to anaphylactic reactions in children, the risk factors for ACEi-associated angioedemas are well studied. Among these, seasonal allergies (Kostis et al., 2005) and previous angioedemas (Hoover et al., 2010) were reported, which was consistent with our analysis and could also observed in ARBs- and aliskiren-associated angioedemas.

In literature, angioedema is mainly differentiated into histamine- and bradykinin-mediated angioedema (Kaplan, 2011; Sachs et al., 2018). Histamine-mediated reactions often manifest with urticaria and pruritus, while this is not the case for bradykinin-mediated angioedema. In our analysis, urticaria and pruritus were more often reported in angioedema cases of ARBs and aliskiren compared to ACEi. Based on this observation one may speculate, that there is a higher proportion of histamine-mediated angioedema in ARBs and aliskiren than ACEi angioedema reports. However, this cannot be concluded with certainty, since (among others) laboratory investigations are lacking. The observed differences could also be caused by differences in the patient populations (e.g. allergy) involved in ACEi, ARBs and aliskiren angioedema reports.

The strengths of our analysis are a large population coverage, including real world data, as well as vulnerable patient populations (e.g. older adults, comorbid patients), a long-term data collection and the inclusion of all types of drugs such as over the counter (OTC) drugs (Kommas et al., 2019).

One of the major limitations is the unknown amount of underreporting (Hazell and Shakir, 2006), which may depend on the type of ADR and drugs taken (Hasford et al., 2002). Another limitation is the lack of matching exact exposure data. As a consequence of both limitations, exact incidences and prevalences cannot be calculated. Differences regarding the documentation of ADR reports may influence the results to an unknown extent.

7. Acknowledgement

First of all, I would like to thank Prof. Dr. Matthias Schmid and Prof. Dr. Bernhardt Sachs for the opportunity to work on this project. Thanks for all the productive meetings and the great cooperation. I really enjoyed being part of the project and it gave me a great opportunity to develop professionally and personally. I would particularly like to thank Prof. Dr. Matthias Schmid for the great support from the Institute of Medical Biometry, Epidemiology and Informatics (IMBIE) and to be available for statistical queries at any time.

Special thanks to Prof. Bernhardt Sachs for the close cooperation, the lively exchange and the constant availability. I also want to thank the other two members of the dissertations committee: Prof. Dr. Julia Carolin Stingl and Prof. Dr. Klaus Weckbecker.

I want to express my gratitude to all of my colleagues from the BfArM and the IMBIE for the continuous exchange and the great lunch breaks, especially, Dr. Matthias Vogel and Denna Tabari who were always a pillar for me and critically proofread my work. I also want to thank Division 7 of the BfArM for the continuous exchange, especially, Barbara Koch and Christine Röhl who trained and helped me with any difficulties in the use of databases.

A heartfelt thanks to my family and friends, which have always provided me with the necessary balance. Special thanks to my parents Karin and Wolfgang Dubrall, who were always there for me, believed in me and supported me at any time, Tom and Yasmin for proofreading and for the great times we have together. I also want to thank all other relatives and friends who enrich my life so much.

8. References

Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. Drug Saf 2009; 32: 1067–1074

Aagaard L, Strandell J, Melskens L, Petersen PS, Holme Hansen E. Global patterns of adverse drug reactions over a decade: analyses of spontaneous reports to VigiBase™. Drug Saf 2012; 35(12): 1171-1182

Bas M. The Angiotensin-Converting-Enzyme-Induced Angioedema. Immunol Allergy Clin North Am 2017; 37(1): 183-200

Bas M, Greve J, Strassen U, Khosravani F, Hoffmann TK, Kojda G. Angioedema induced by cardiovascular drugs: new players join old friends. Allergy 2015; 70(10):1196-1200

Bezalel S, Mahlab-Guri K, Asher I, Werner B, Sthoeger ZM. Angiotensin-converting enzyme inhibitor-induced angioedema. Am J Med 2015; 128(2): 120-125

Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. J Allergy Clin Immunol 2004; 113(3): 536-542

Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: A review of the literature. J Clin Hypertens 2017; 19: 1377-1382

Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. Immunol Allergy Clin North Am 2006; 26(4): 725-737

Cavkaytar O, Karaatmaca B, Cetinkaya PG, Esenboga S, Arik Yilmaz E, Sahiner UM, Sekerel BE, Soyer O. Characteristics of drug-induced anaphylaxis in children and adolescents. Allergy Asthma Proc 2017; 38 (5): 56-63

Cutroneo P, Greco S, Cucinotta G, Arcoraci V, Caputi AP. SPONTANEOUS REPORTING OF ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS IN SICILY (ITALY). Pharmacological Research 1999; 40(1): 41-46

Davies EA, O'Mahony MS. Adverse drug reactions in special populations – the elderly. Br J Clin Pharmacol 2015; 80 (4): 796-807

Demir S, Erdenen F, Gelincik A, Unal D, Olgac M, Coskun R, Colakoglu B, Buyukozturk S. Evaluation of the Potential Risk Factors for Drug-Induced Anaphylaxis in Adult Patients. Int Arch Allergy Immunol 2019; 178(2): 167-176

Dinakar C. Anaphylaxis in Children: Current Understanding and Key Issues in Diagnosis and Treatment. Curr Allergy and Asthma Rep 2012; 12(6): 641-649

European Medicines Agency (EMA), 2017: Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf (17.04.2020)

European Medicines Agency (EMA), 2020: Legal framework: Pharmacovigilance. https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance/legal-framework-pharmacovigilance (17.04.2020)

Faria E, Rodrigues-Cernadas J, Gaspar Â, Botelho C, Castro E, Lopes A, Gomes E, Malheiro D, Cadinha S, Campina-Costa S, Neto M, Sousa N, Rodrigues-Alves R, Romeira A, Caiado J, Morais-Almeida M, Portuguese Society of Allergology and Clinical Immunology (SPAIC) Drug Allergy Interest Group. Drug-induced anaphylaxis survey in Portuguese Allergy Departments. J Investig Allergol Clin Immunol 2014; 24(1): 40-48

Federal Institute for Drugs and Medical Devices (BfArM), 2013 a: European Database on Adverse Drug Reaction Reports. https://www.bfarm.de/EN/Drugs/vigilance/ReportingRisks/uawDB/_node.html (17.04.2020)

Federal Institute for Drugs and Medical Devices (BfArM), 2013 b: Gemeinsame Bekanntmachung über die zu verwendenden Standardsätze in der Fachinformation und Packungsbeilage zum Berichten von Nebenwirkungen sowie für Arzneimittel, die einer zusätzlichen Überwachung unterliegen, gemäß § 11 Absatz 1b und § 11a Absatz 1 Satz 9 des Arzneimittelgesetzes (AMG). https://www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Pharmakovigilanz/bm-phvig-20130807-standardsaetze.html (17.04.2020)

Federal Statistical Office (Destatis), 2019: Bevölkerung im Wandel Annahmen und Ergebnisse der 14. koordinierten Bevölkerungsvorausberechnung. https://www.destatis.de/DE/Presse/Pressekonferenzen/2019/Bevoelkerung/pressebroschuere-bevoelkerung.pdf;jsessionid=72A29C555C8C41F92C1CC37AA48FCFC8.internet8742?_blob=publicationFile (17.04.2020)

Federal Statistical Office (Destatis), 2020: GENESIS-online - Database of the Federal Statistical Office of Germany. https://www-genesis.destatis.de/genesis/online/logon?language=en (17.04.2020)

Gupta R, Sheikh A, Strachan D, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. BMJ 2003; 327(7424): 1142–1143

Hasford J, Goettler M, Munter KH, Müller-Oberlinghausen B. Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. J Clin Epidemiol. 2002; 55(9): 945-950

Hazell L, Shakir SA. Under-Reporting of Adverse Drug Reactions. Drug Saf 2006; 29(5): 385-396

Hein L, Wille H. Antithrombotika und Antihämorrhagika. In: Schwabe U, Paffrath D, Ludwig WD, Klauber J (eds). Arzneiverordnungsreport 2019. Berlin Heidelberg: Springer Verlag Berlin-Heidelberg, 2019: 531-555

Holm L, Ekman E, Jorsäter Blomgren K. Influence of age, sex and seriousness on reporting of adverse drug reactions in Sweden. Pharmacoepidemiol Drug Saf 2017; 26(3): 335-343

Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin convertingenzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. Clin Exp Allergy 2010; 40(1): 50-61

Hopf G, Mathias B. ADVERSE REACTIONS REPORTING AND AGE. The Lancet 1988; 332(8619): 1079-1080

Impicciatore P, Choonara I, Clarkson A, Provasi D, Pnadol C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol 2001; 52: 77-83

Kapellen T, Telschow C, Zawinell A. Trends bei der Verordnung von Arzneimitteln bei Kindern und Jugendlichen. In: Klauber J, Günster C, Gerste B, Robra BP, Schmacke N (eds). Versorgungsreport 2015/2016. Schwerpunkt: Kinder und Jugendliche. Stuttgart: Schattauer, 2015: 71-88

Kaplan AP. Drug-induced angioedema. Journal of Angioedema 2011; 1(2): 14-22

Knopf H, Grams D. Arzneimittelanwendung von Erwachsenen in Deutschland. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsbl 2013; 56: 868-877

Kommas E, Lex D, Huber M, Paeschke N. Verdachtsfälle melden - Warum am behördlichen Nebenwirkungsmelde-System kein Weg vorbeiführt. DAZ 2019; 37: 44-49

Kostis JB, Kim HJ, Rusnak J, Casale T, Kaplan A, Corren J, Levy E. Incidence and characteristics of angioedema associated with enalapril. Arch Intern Med 2005; 165(14): 1637-1642

Lane S, Lynn E, Shakir S. Investigation assessing the publicly available evidence supporting postmarketing withdrawals, revocations and suspensions of marketing authorisations in the EU since 2012. BMJ Open 2018; 8(1): e019759

Lin SY, Tang SC, Tsai LK, Yeh SJ, Hsiao YJ, Chen YW, Chen KH, Yip BS, Shen LJ, Wu FL, Jeng JS. Orolingual angioedema after alteplase therapy of acute ischaemic stroke: incidence and risk of prior angiotensin-converting enzyme inhibitor use. Eur J Neurol 2014; 21(10): 1285-1291

Makani H, Messerli F, Romero J, Wever-Pinzon O, Korniyenko A, Berrios R, Bangalore S. Meta-Analysis of Randomized Trials of Angioedema as an Adverse Event of Renin–Angiotensin System Inhibitors. Am J Cardiol 2012; 110(3): 383-391

Mann RD, Rawlins MD, Fletcher P, Wood SM. Age and the Spontaneous Reporting of Adverse Reactions in the United Kingdom. Pharmacoepidemiol Drug Saf 1992; 1: 19-23

Medical Dictionary for Regulatory Activities (MedDRA), 2020: Introductory Guide for Standardised MedDRA Queries (SMQs) Version 23.0. https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_23_0_english.pdf (17.04.2020)

Montañez MI, Mayorga C, Bogas G, Barrionuevo E, Fernandez-Santamaria R, A Martin-Serrano, Laguna JJ, Torres MJ, Fernandez TD, Doña I. Epidemiology. Mechanisms, and Diagnosis of Drug-induces anaphylaxis. Front Immunol 2017; 8: 614

Montastruc JL, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. Fundam Clin Pharmacol 2002; 16: 343-346

Morimoto T, Gandhi TK, Fiskio JM, Seger AC, SO JW, Cook EF, Fukui T, Bates DW. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract 2004; 10(4): 499-509

Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. British Medical Journal 1988, 296: 1313-1316

Muraro A, Roberts G, Worm M, Bil MB, Brockow K, Fernandes-Rivas M, Santos AF, Zolkipli Q, Bellou A, Beyer K, Bindslev-Jensen C, Cardona V, Clark AT, Demoly P, Dubois AEJ, DunnGalvin A, Eigenmann P; Halken S, Harada L, Lack G, Jutel M, Niggemann B, Rue F, Timmermans F, Vlieg–Boerstra BJ, Werfel T, Dhami S, Panesar S, Akdis CA, Sheikh A on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014; 69: 1026–1045

Ozcan G, Aykac E, Kasap Y, Nemutlu NT, Sen E, Aydinkarahaliloglu ND. Adverse Drug Reaction Reporting Pattern in Turkey: Analysis of the National Database in the Context of the First Pharmacovigilance Legislation. Drugs Real World Outcomes 2016; 3(1):33-43

Petrie A, Sabin C. Binary outcomes and logistic regression. In: Medical Statistics at a Glance – Fourth Edition. Hoboken (NY): Wiley-Blackwell, 2020: 85-88

Ponvert C, Le Clainche L, de Blic J, Le Bourgeois M, Scheinmann P, Paupe J. Allergy to beta-lactam antibiotics in children. Pediatrics 1999; 104: e45

Ponvert C, Perrin Y, Bados-Albiero A, Le Bourgeois M, Karila C, Delacourt C, Scheinmann P, De Blic J. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. Pediatr Allergy Immunol 2011; 22: 411–418

Quiralte J, Blanco C, Delgado J, Ortega N, Alcntára M, Castillo R, Anguita JL, Sáenz de San Pedro B, Carrillo T. Challenge-based clinical patterns of 223 spanish patients with nonsteroidal anti-inflammatory-drug-induced-reactions. J Investig Allergol Clin Immunol 2007; 17(3): 182-188

Robert Koch Institut (RKI), 2012: Daten und Fakten:Ergebnisse der Studie »Gesundheit in Deutschland aktuell 2012«. Beiträge zur Gesundheitsberichterstattung des Bundes. https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/GEDA12.pdf?_blob=publicationFile (17.04.2020)

Ruiter R, Burggraaf J, Rissmann R. Under-representation of elderly in clinical trials: An analysis of the initial approval documents in the Food and Drug Administration database. Br J Clin Pharmacol 2019; 85(4): 838–844

Sachs B, Meier T, Nöthen MM, Stieber C, Stingl J. Drug-induced angioedema; Focus on bradykinin. Hautarzt 2018; 69(4): 298-305

Schneeweiss S, Hasford J, Göttler M, Hoffmann A, Riethling AK, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol 2002; 58: 285–291

Schurig AM, Böhme M, Just KS, Scholl C, Dormann H, Plank-Kiegele B, Seufferlein T, Gräff I, Schwab M, Stingl JC. Adverse Drug Reactions (ADR) and Emergencies. The prevalence of suspected ADR in four emergency departments in Germany. Dtsch Arztebl Int 2018; 115: 251-258

Shimada K, Hasegawa S, Nakao S, Mukai R, Sasaoka S, Ueda N, Kato Y, Abe J, Mori T, Yoshimura T, Kinosada Y, Nakamura M. Adverse reaction profiles of hemorrhagic adverse reactions caused by direct oral anticoagulants analyzed using the Food and Drug Administration Adverse Event Reporting System (FAERS) database and the Japanese Adverse Drug Event Report (JADER) database. Int J Med Sci. 2019; 16(9): 1295-1303

Stauber T, Confino-Cohen R, Goldberg A. Life-threatening angioedema induced by angiotensin-converting enzyme inhibitors: characteristics and risk factors. Am J Rhinol Allergy 2014; 28(1): 54-58

Thiessard F, Roux E, Miremont-Salamé G, Fourrier-Réglat A, Haramburu F, Tubert-Bitter P, Bégaud B. Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986-2001). Drug Saf 2005; 28(8): 731-740

Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol 2011; 71(5): 684-700

Toh S, Reichmann ME, Houston M, Ross Southworth M, Ding X, Hernandez AF, Levenson M, Li L, McCloskey C, Shoaibi A, Wu E, Zornberg G, Hennessy S. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med 2012; 172(20): 1582-1589

Watson S, Caster O, Rochon PA, den Ruijter H. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine 2019; 17: 100188

West SL, D'Aloisio AA, Ringel-Kulka T, Waller AE, Clayton Bordley W. Population-based drug-related anaphylaxis in children and adolescents captured by South Carolina Emergency Room Hospital Discharge Database (SCERHDD) (2000–2002). Pharmacoepidemiol Drug Saf 2007; 16(12): 1255-1267

Wester K, Jönsson A, Spigset O, Hägg S. Spontaneously reported fatal suspected adverse drug reactions: a 10-year survey from Sweden. Pharmacoepidemiol Drug Saf 2007; 16(2): 173-180

Withe WB, Bresalier R, Kaplan A, Palmer BF, Riddell RH, Lesogor A, Chang W, Keefe DL. Safety and Tolerability of the Direct Renin Inhibitor Aliskiren: A Pooled Analysis of Clinical Experience in More Than 12,000 Patients With Hypertension. J Clin Hypertens 2010; 12(10): 765-775

Xing Y, Zhang H, Sun S, Ma X, Pleasants RA, Tang H, Zheng H, Zhai S, Wang T. Clinical features and treatment of pediatric patients with drug-induced anaphylaxis: a study based on pharmacovigilance data. Eur J Pediatr 2018; 177(1): 145-154

Zopf Y, Rabe C, Neubert A, Gaßmann KG, Rascher W, Hahn EG, Brune K, Dormann H. Women encounter ADRs more often than do men. Eur J Clin Pharmacol 2008; 64: 999-1004

Appendix A

Dubrall D, Schmid M, Alešik E, Paeschke N, Stingl J, Sachs B. Frequent Adverse Drug Reactions, and Medication Groups under Suspicion. Dtsch Arztebl Int 2018; 115(23): 393-400.

Full title:

Frequent Adverse Drug Reactions, and Medication Groups under Suspicion. A Descriptive Analysis Based on Spontaneous Reports to the German Federal Institute for Drugs and Medical Devices from 1978 to 2016.

Authors' full names:

Diana Dubrall[1,2], Matthias Schmid[1], Eva Alešik[2], Norbert Paeschke[2], Julia Stingl, Bernhardt Sachs

Authors' institutional affiliations including city and country

1) Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), University Hospital of Bonn, Bonn, North Rhine-Westphalia, Germany

2) Federal Institute for Drugs and Medical Devices (BfArM), Bonn, North Rhine-Westphalia, Germany

3) Center for Translational Medicine, Universität Bonn, North Rhine-Westphalia, Germany

4) Department for Dermatology and Allergy, University Hospital of the RWTH Aachen, Aachen, North Rhine-Westphalia, Germany

Disclaimer:

The information and views set out in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Federal Institute for Drugs and Medical Devices.

Abstract

Background: The adverse drug reaction database of the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM) contains reports of suspected adverse drug reactions (ADRs) that are spontaneously submitted by physicians, pharmacists, or patients. The aim of the present study was a descriptive analysis of all of these spontaneous reports.

Methods: 345,662 spontaneously submitted reports were analyzed with respect to the number of reports per year, the sources of the reports, demographic variables, the most commonly reported ADRs, and the drug classes most commonly suspected.

Results: The number of reports submitted spontaneously each year has grown steadily since 1978. At the least detailed level of analysis, “drugs for the treatment of nervous system disorders” were the most common class of drugs under suspicion of causing the reported adverse drug reactions (23.1%). In a more detailed analysis by therapeutic subgroup, the three subgroups most commonly reported as suspected of causing side effects were antithrombotic agents, systemic antibiotics, and psycholeptics -causing thrombocytopenia, diarrhea, and drug dependency as the most frequently reported ADRs, respectively. The order of drug classes most commonly causing ADRs differed markedly between the physicians’ reports (diazepines, fluoroquinolones, heparins) and the patients’ reports (interferons, antithrombotic drugs, selective immunosuppressant drugs). Patients more commonly reported subjectively perceived ADRs, while physicians more commonly reported findings or diagnoses that require medical expertise.

Conclusion: The increasing number of spontaneous reports is mainly due to reports forwarded from pharmaceutical companies to the BfArM. This, in turn, is probably a result of increasingly strict legal reporting requirements in Germany. The detected differences between physicians’ and patients’ ADR reports can be taken to indicate that patients should be more specifically informed and questioned about potential ADRs. By reporting adverse drug reactions, physicians may improve drug safety.

Key messages

- Spontaneous reports of ADRs from physicians, pharmacists, or patients in everyday use of an already approved medicinal product are crucial for ensuring drug safety.
- The number of spontaneous reports registered annually with the German Federal Institute for Drugs and Medical Devices (BfArM; Bundesinstitut für Arzneimittel und Medizinprodukte) has increased steadily since 1978. This is mainly due to an increase in reports sent to the BfArM by pharmaceutical companies. Stricter legal requirements for reporting ADRs are likely to be behind this increase.
- At the top hierarchy level, drugs for treatment of nervous system disorders are the most common to be reported as drugs under suspicion (23.1%). At the level of the specific drug groups, the most commonly reported medicinal products are antithrombotics, systemic antibiotics, and psycholeptics.
- Physicians typically report ADRs that can be detected by a physician, such as specific diagnoses or laboratory findings. In contrast, patients often report ADRs that are perceived subjectively and/or that affect their quality of life.

Introduction

One of the central tasks of the German Federal Institute for Drugs and Medical Devices (Bundesinstituts für Arzneimittel und Medizinprodukte, BfArM) is to monitor the safety of medicinal products. An essential methodological element in the regulatory monitoring of medicinal product safety is the spontaneous reporting system (1–3). Spontaneous reports are unsolicited reports by physicians, pharmacists, patients, or other sources, of suspected cases of adverse drug reactions (ADRs) with widespread, everyday use of a medicinal product, which is not in the context of systematic investigations (for example, studies).

Spontaneous reports play an important role, as clinical trials prior to medicinal product approval can include only a limited number of selected patients. The limitations of these studies means that rare ADRs, as well as those that only occur in certain vulnerable patients or after prolonged use, cannot be reliably detected (1, 2, 4, 5). Additionally, new ADRs may occur during the drug lifecycle, such as in the event of other indications for use or novel co-medications (1, 6).

Complementary, active programs for medicinal product safety monitoring have increasingly been developed in the past decade, including the analysis of so-called Big Data (7) (from electronic health records [from insurance companies], scientific literature, and social media). These systems, like the spontaneous reporting system, are subject to method-inherent limitations (7, 8). Thus, analysis of spontaneous reports still is of central importance (3, 7–9).

Signals from spontaneous reports can provide a major impetus for regulatory action (for instance, leading to changes in product information or to new studies) (10). A 2013 study found that 44% (11/25) of safety-related withdrawals of medicinal products in the USA or the EU were due to spontaneous reports (1).

In Germany, spontaneous reports can be submitted directly to the competent federal authorities via the BfArM/ Paul-Ehrlich-Institut (PEI) website according to the respective area of responsibility (BfArM, chemically-defined active substances, among others; PEI, monoclonal antibodies and vaccines, among others) (11, 12 , 13). However, reports may

also be directed to the medicinal product commissions of the drug commissions of healthcare professions or to pharmaceutical companies, which then forward them (14). Physicians are required by their professional code to report ADRs (15). An overview of what physicians should be aware of when reporting ADRs is given in eBox 1.

Since 22 November 2017, pharmaceutical companies send their reports exclusively to the European database EudraVigilance at the European Medicines Agency (EMA) (16, 17) (restricted access rights: www.adrreports.eu/en/access_policy.html).

The BfArM forwards the adverse reaction reports that it receives directly (e.g. from physicians) to EudraVigilance. Future analyses within the framework of monitoring medicinal product safety will be carried out in EudraVigilance; country-specific analyses are also possible. Therefore, direct reports, e.g. from physicians and pharmacists in Germany, to the BfArM continue to be of great importance, as these may differ from ADR reports from other EU countries, for example due to difference in frequency of use of medicinal products.

The aim of this investigation was to determine the importance of ADR reports and databases for ensuring safety of medicinal product use by carrying out a retrospective descriptive analysis of all spontaneous reports contained in the adverse drug reaction database.

Methods

The starting point of the analysis comprised of all suspected ADR reports contained in BfArM's adverse drug reaction database, from the first registration in 1978 until 31 December 2016 (N = 528,539). Of these suspected ADR reports, about 70% (n = 369,778) were spontaneous reports, about 28.2% (n = 149,034) were from systematic investigations/studies ("solicited reports"), and about 1.8% (n = 9,728) were of unclear origin. This analysis only included spontaneous reports within Germany of ADRs due to suspected or interacting medicinal product(s) (herein termed "drugs under suspicion") that did not report unintended use. The final analysis dataset contained 345,662 spontaneous reports (65.4% of all reports of the ADR database, and 93.5% of all spontaneous reports) (eFigure 1, eMethods).

All spontaneous reports were of suspected ADRs of medicinal products. Case numbers were determined by computer-based database queries; no single-case evaluation was performed (for example, for causality assessment). Active substances are coded in the ADR database according to the official classification for active pharmacologically ingredients according to the ATC code (anatomic therapeutic chemical classification system) (18) (eFigure 2) and the World Health Organization's Drug Dictionary (19), and ADRs according to MedDRA terminology (MedDRA, Medical Dictionary for Regulatory Activities) (20) (eMethods). Suitable hierarchy levels were selected for each evaluation.

The primary reporting source provides information from whom the report originated (e.g. physician) regardless of the reporting channel (e.g. pharmaceutical company). Healthcare professionals (HCPs) are defined as those with medical qualifications; this includes physicians, pharmacists, and nurses (21). Consumers and non-HCPs are defined as people who are not HCPs; this includes patients and relatives (herein referred to as "patients"). Ratios were calculated as appropriate to investigate possible associations between the number of reports and population size (22), number of prescriptions (23), or number of physicians (24) in Germany.

The classification "serious adverse drug reaction" takes into account criteria from the legal definition (e.g., it results in death, is life-threatening, requires inpatient

hospitalization, results in permanent disability, and/or is a congenital anomaly). These criteria differ from clinical criteria (11).

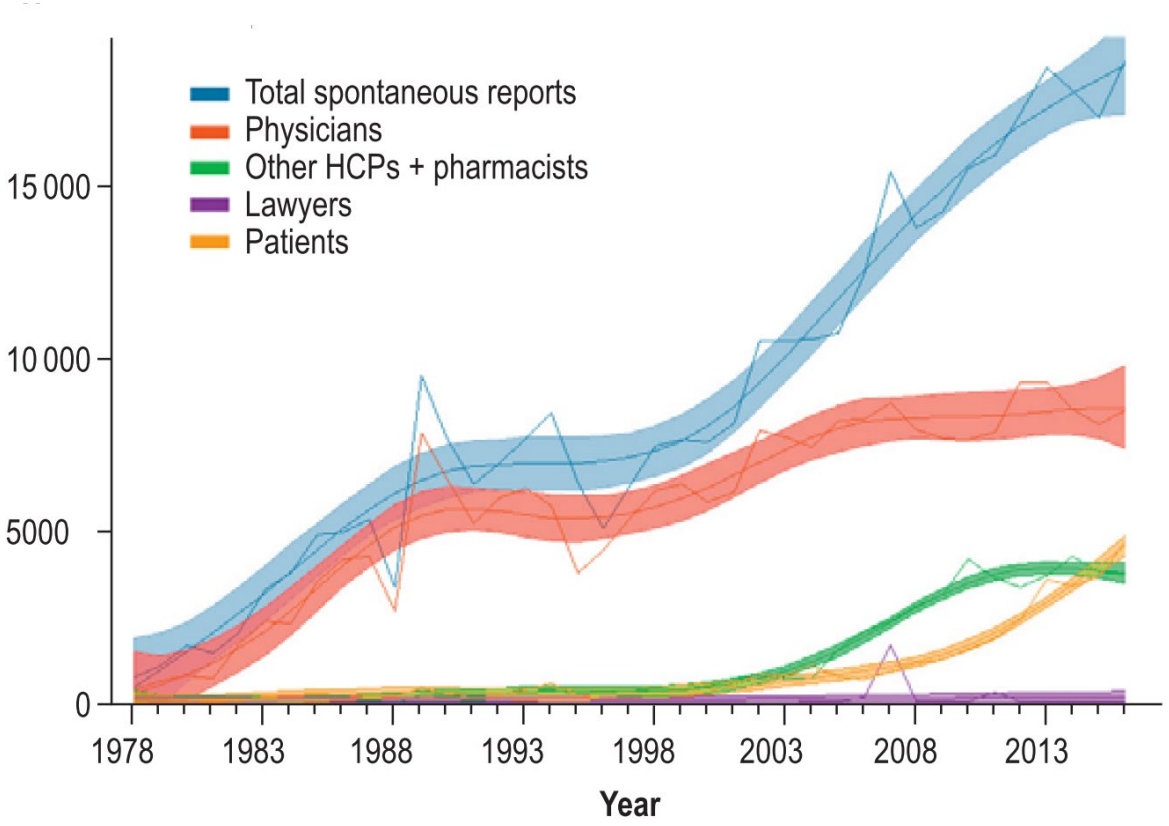
Approval for the study protocol was obtained from the ethics committee of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn (Lfd. Nr. 009/17).

Results

The 345,662 spontaneous reports comprised more than 904,242 ADRs, which were associated with 421,581 drugs under suspicion or combinations of drugs under suspicion. The primary reporting sources were physicians (64.1%; 221,427) and pharmacists (10.3%; 35,776), other HCPs (2.6%; 9,011), patients (9.5%; 32,992), and lawyers (0.6%; 2,138).

The total number of spontaneous reports per year has been rising steadily since 1978 (Figure 1). Reporting from physicians has had a slower rate of increase since 2002; in contrast, reporting has noticeably increased from pharmacists and other HCPs since 2005, and from patients since 2008. Reporting from lawyers show peak levels that can be traced back to special factors (for example, the case of rofecoxib in 2007).

Figure 1. Number of spontaneous reports received per year according to primary reporting source.



The primary source refers to the person who generated the ADR report, not to the sender [such as the pharmaceutical company] who submitted the report to the German Federal Institute for Drugs and Medical Devices. The color-coded curves indicate the respective 95% confidence intervals. In 6% of the 345,662 cases, more than one reporting source was named (for example, physician and patient both reported the same case independently from each other). To avoid double counting, this analysis was based on reports that only named one source.

HCP, healthcare professionals

The time course of spontaneous reports in total and of those sent to the BfArM by pharmaceutical companies has been very similar since 1988 (Figure 2). In contrast, there are no clear associations between the increasing number of spontaneous reports and changes in population size (22), prescription data (23), or the number of working physicians (24) (Figure 3).

The observed increase in the number of spontaneous reports from 1989 to 1996 is not reflected in the number of spontaneous reports sent to the BfArM from other sources. This increase could therefore be the result of other statutory reporting obligations in this period (25), as pharmaceutical companies also were required to report non-serious ADRs to the BfArM during that time (eBox 2).

Around 66.9% of all spontaneous reports are classified as serious (11). The proportion of spontaneous reports including the serious criterion “fatal” was 5.5%.

Figure 2. Number of spontaneous reports per year that are forwarded by pharmaceutical companies to the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM).

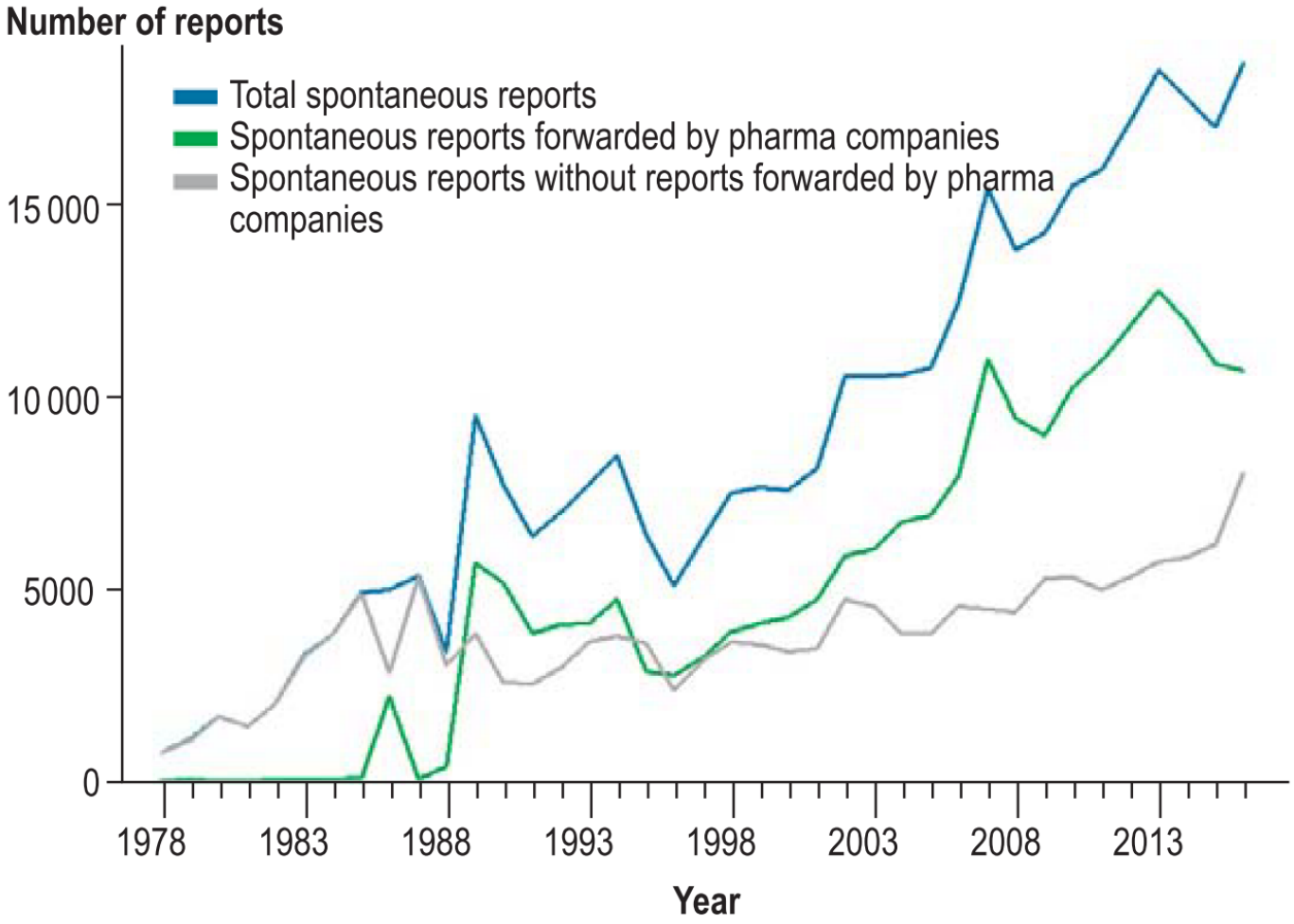
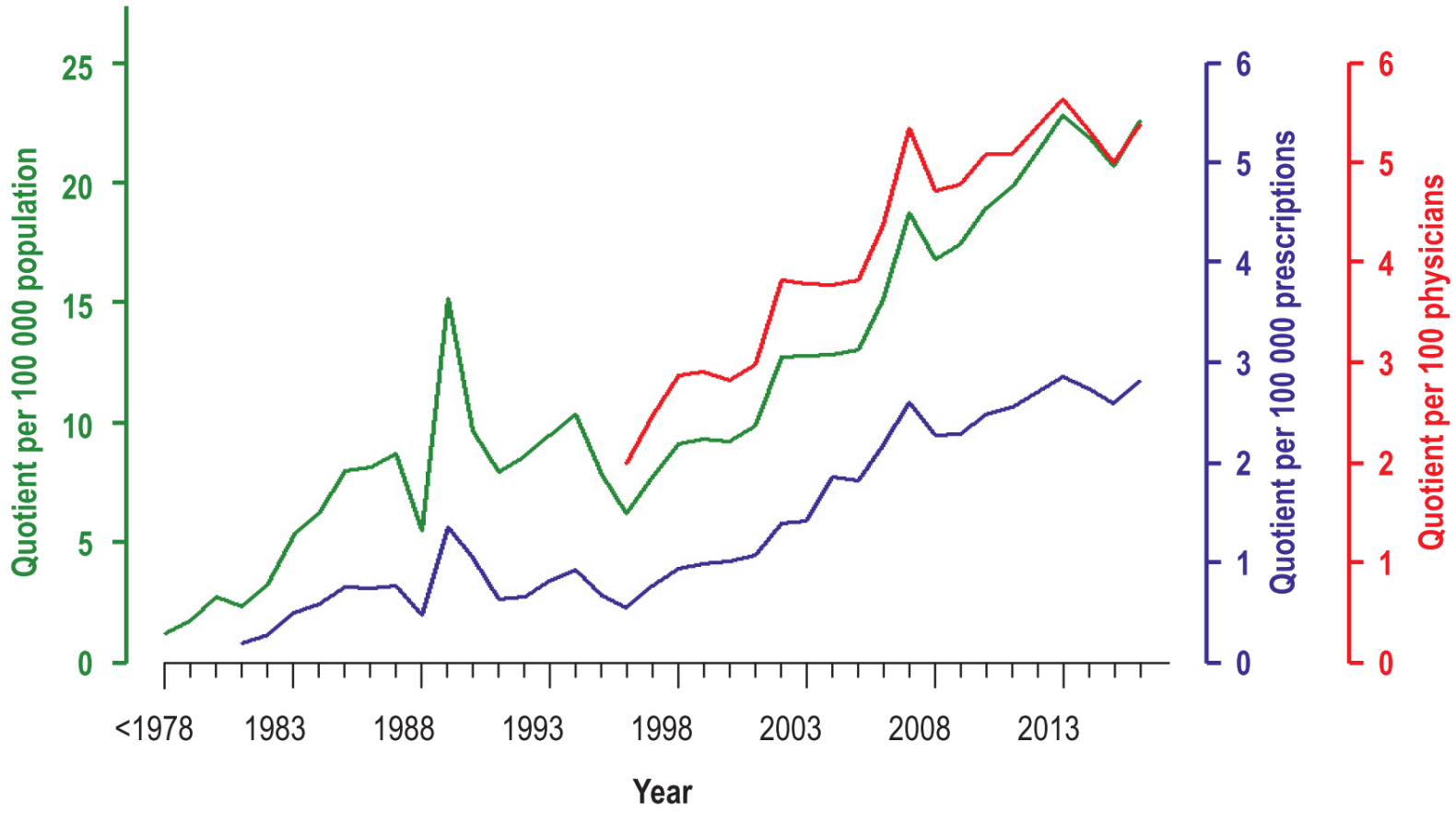


Figure 3. Quotient spontaneous reports per 100,000 population, 100,000 prescriptions or per 100 physicians over time.



Limitations of the analysis are described in eBox 3.

Stratification according to patient age shows a continuous increase in accumulated reports for patients from 11 to 70 years of age (eFigure 3). The most spontaneous reports refer to the age group 66–70 years.

Overall, 54.6% of spontaneous reports refer to females, and 38.8%, refer to males (with 6.6% not specified). For children aged ≤ 15 years, more spontaneous reports are made for males.

For this age group the most frequent ADRs are for the drug group of “nervous system disorders” with the most reports for the subgroup of “psychostimulants, ADHD medication, and nootropics” (11.9%, 830). The most commonly reported ADRs are aggression (6.1%; 51), suicidal thoughts (6.1%; 51), and headache (5.9%; 49).

For adolescent women (> 15 to ≤ 20 years), the most frequent ADRs are for the drug group of “hormonal contraceptives for systemic use” (23.7%; 1,046). The most commonly reported ADRs are pulmonary embolism (20.1%; 217), deep vein thrombosis (17.4%; 182), and pelvic vein thrombosis (11.9%; 124).

The three ADRs that were cumulatively reported most frequently for all groups (irrespective of age or sex) during the observation period were nausea, pruritus, and dizziness (eTable 1). Many other nonspecific general symptoms (such as vomiting, headache, and pyrexia) are also among the 15 most common ADRs. Three of these 15 ADRs are visible cutaneous ADRs (skin rash, erythema, and urticaria); two others (hypersensitivity and pruritus) may show visible cutaneous symptoms.

If the reported drugs under suspicion are analyzed at the highest hierarchical level of the ATC drug groups, the drugs for nervous system disorders are clearly in first place (23.1%), as four of the ten most reported therapeutic subgroups, all of which are listed in Table 1 (psycholeptics, psychoanaleptics [antidepressants], analgesics, and antiepileptics) are comprised in this drug group. This is followed by drugs for the treatment of cardiovascular disorders (13.0%) and “antineoplastics and immunomodulating agents” (12.4%) (eTable 2).

Table 1 shows the ten therapeutic subgroups that are most frequently reported as suspicious, with their most commonly reported ADRs. The aim of this study was to

obtain a descriptive analysis of all spontaneous reports. Therefore, Table 1 lists many known associations, such as bleeding events related to antithrombotic agents.

Table 1. The most frequently reported medication groups under suspicion, and their most frequently reported ADRs in the total dataset (n= 345,662).

Rank	Therapeutic subgroup under suspicion (pharmacological subgroup)*1	Proportion of generated dataset (N = 345 662), in %*2 (number of spontaneous reports)	Proportion of most frequently reported ADRs in medication subgroups under suspicion, in %*2 (number of spontaneous reports)
1st	Antithrombotic agents (heparin group, factor Xa inhibitors/ direct thrombin inhibitors*3)	8.4% (29 185)	7.1% thrombocytopenia (2074) 5.9% gastrointestinal hemorrhage (1722) 4.9% hemorrhage (1430)
2nd	Antibacterials for systemic use (quinolones, other beta-lactam antibacterials [e. g. cephalosporin])	8.4% (29 014)	6.5% diarrhea (1885) 6.2% skin rash (1803) 6.0% pruritus (1741)
3rd	Psycholeptics (antipsychotics)	7.9% (27 363)	4.0% drug dependence (1098) 3.7% leukopenia (1025) 3.5% fever (947)
4th	Psychoanaleptics (antidepressants)	6.0% (20 828)	5.4% nausea (1125) 4.7% dizziness (975) 3.1% headache (640)
5th	Antineoplastic agents (other antineoplastic agents [e. g. protein kinase inhibitors], antimetabolites)	6.0% (20 793)	6.2% dyspnea (1284) 5.4% fever (1125) 5.2% thrombocytopenia (1087)
6th	Antiinflammatory and antirheumatics (antiinflammatory and antirheumatic non-steriods [coxibs, e. g. rofecoxib; acetic acid derivatives, e. g. diclofenac)	5.7% (19 650)	6.2% hypertension (1209) 5.0% nausea (980) 4.5% cerebral infarction (887)
7th	Analgesics (salicylic acid and derivatives [e. g. ASA], pyrazolones [e. g. phenazone], anilides [e. g. paracetamol], opioids)	4.0% (13 723)	7.9% nausea (1085) 5.1% drug dependence (695) 4.8% agranulocytosis (657)
8th	Antiepileptics (other antiepileptics [e. g. levetiracetam, lamotrigine], carboxamide derivates [e. g. carbamazepine])	3.7% (12 898)	7.1% seizure (920) 4.4% dizziness (575) 4.3% hyponatremia (557)
9th	Agents acting on the renin-angiotensin system (ACE inhibitors plain, angiotensin II antagonists plain)	3.7% (12 713)	9.0% angioedema (1139) 7.0% cough (893) 6.2% dizziness (782)
10th	Sex hormones and modulators of the genital system (hormone contraceptives for systemic use)	3.4% (11 906)	9.5% pulmonary embolism (1132) 8.1% deep vein thrombosis (961) 4.4% unintended pregnancy (519)

*1 For the analysis presented in Table 1, medications were grouped according to the 2nd level of the ATC code (the therapeutic subgroup), with the most frequent pharmacological subgroups shown in brackets; for the analysis presented in Table 2, medications were grouped according to the 4th level of the ATC code. Adverse drug reactions (ADRs) were analyzed at the 4th level of MedDRA (Medical Dictionary for Regulatory Activities) terminology (as preferred terms).

[*2] When interpreting percentages, it should be noted that a report may contain several drugs under suspicion and multiple ADRs.

[*3] For definition of the therapeutic/pharmacological subgroup “factor Xa inhibitors/direct thrombin inhibitors”, please see eFigure 2.

Reported ADRs from physicians and patients are similar in terms of the most commonly reported ADRs but differ in ranking (eTable 3). However, among the 50 ADRs most frequently reported by physicians, those that are typically diagnosed by physicians, such as specific diagnoses (e.g., pulmonary embolism, ranked #35) and laboratory findings (e.g., leukopenia, ranked #14), are prevalent. In contrast, ADRs reported by patients are mainly those that can be subjectively perceived (e.g., anxiety, ranked #29; taste disturbances, ranked #45) and/or those that limit individual quality of life (e.g., weight increased, ranked #40; alopecia, ranked #28). This distinction is also evident when the medicinal products most frequently reported by either physicians or patient are directly compared (Table 2). On average, patients report more ADRs per report than physicians (3.5 versus 2.5) as well as more serious ADRs (75.6% versus 65.8%). Only three of the drug groups most frequently reported by physicians as suspicious were also among the top ten from patients. Notably, patients were more likely than physicians to report immunostimulants (e.g., interferons, ranked #1) and contraceptives (progestogens and estrogens, fixed combination, ranked #5; intrauterine contraceptives, ranked #6); these were ranked #18, #16, and #21, respectively, by physicians.

Table 2. Physician reports (n= 221,427) compared to patient reports (n= 32,992): Comparison of the most frequently reported ADRs in the frequently reported medication groups under suspicion (based on physician reporting) [*1]

Rank: physicians	Most frequent medication groups under suspicion in physician reports	Frequency in physician reports in % (*n* = 221 427)	Physicians: Proportion of most common ADRs in reported medication groups under suspicion in % (number of spontaneous reports)	Rank: patients	Frequency in patient reports in % (n = 32 992)[*2]	Patients: Proportion of most common ADRs in reported medication groups under suspicion in % (number of spontaneous reports)
1st	Diazepine[*3], oxazepine, thiazepine, oxepine (e. g. clozapine, olanzapine)	3.3% (7324)	8.5% leukopenia (626) 8.4% pyrexia (615) 5.8% agranulocytosis (426)	22nd	1.1% (361)	14.1% weight increased (51) 8.6% dizziness (31) 8.0% fatigue (29)
2nd	Fluoroquinolones	3.0% (6577)	5.5% nausea (359) 5.4% diarrhea (357) 5.1% dyspnoea (333)	4th	2.7% (880)	13.6% arthralgia (120) 13.6% tendinopathy (120) 10.3% dizziness (91)
3rd	Heparins	2.6% (5861)	24.1% thrombocytopenia (1 411) 14.6% drug-specific antibodies (856) 13.5% pulmonary embolism (792)	26th	1.0% (321)	7.2% thrombocytopenia (23) 6.2% thrombosis (20) 5.9% hematoma (19)
4th	HMG CoA reductase inhibitors	2.4% (5343)	27.6% myalgia (1477) 16.6% blood creatine phosphokinase increased (887) 10.0% rhabdomyolysis (535)	12th	1.4% (475)	28.0% myalgia (133) 11.2% muscle weakness (53) 10.1% muscle spasms (48)
5th	Factor Xa inhibitors/ direct thrombin inhibitors[*4] (e.g. rivaroxaban, lepirudin)	2.2% (4912)	6.3% cerebral hemorrhage (311) 6.2% gastrointestinal hemorrhage (304) 5.5% hemoglobin decreased (271)	2nd	3.0% (1006)	13.1% epistaxis (132) 8.8% dizziness (89) 7.5% blood in urine (75)
6th	Antithrombotic agents	2.1% (4752)	12.8% gastrointestinal hemorrhage (608) 7.9% melena (374) 7.5% thrombocytopenia (358)	20th	1.1% (371)	7.3% dizziness (27) 6.2% hematoma (23) 5.9% bleeding (22)
7th	Non-selective monoamine reuptake inhibitors, and other antidepressants (e. g. venlafaxin, mirtazapine)	2.1% (4708)	4.5% nausea (210) 4.0% dizziness (187) 3.5% alanine aminotransferase increased 167)	9th	1.8% (590)	11.4% nausea (67) 10.2% dizziness (60) 9.7% fatigue (57)
8th	ACE inhibitors, plain	2.0% (4373)	13.7% angioedema (599) 8.8% cough (387) 4.1% nausea (180)	25th	1.0% (328)	11.6% cough (38) 10.1% dizziness (33) 7.9% dyspnea (26)
9th	Other antipsychotics (e.g. risperidone)	1.8% (4002)	5.2% extrapyramidal symptoms (208) 4.6% dyskinesia (185) 4.5% akathisia (180)	42nd	0.7% (231)	14.3% weight increased (33) 8.7% restlessness (20) 6.9% fatigue (16)
10th	Selective serotonin reuptake inhibitors (SSRI) (e. g. citalopram, fluoxetine)	1.7% (3865)	6.2% nausea (238) 3.7% dizziness (144) 3.7% drug interaction (143)	18th	1.3% (420)	10.0% dizziness(42) 7.6% nausea (32) 7.4% headache (31)

[*1] To avoid double counting, this analysis was based on reports with only one reporter source.

[*2] Ranking of the most commonly reported medication groups under suspicion in patient reports: 1st, interferons (5.1%); 2nd, other antithrombotic agents (3.0%); 3rd, selective immunosuppressants (2.9%); 4th, fluoroquinolones (2.7%); 5th, progestogens and estrogens, fixed combinations (2.4%); 6th, intrauterine contraceptives (2.2%), 7th, other immunostimulants (1.9%), 8th, dopa and dopa derivatives (1.9%); 9th, other antidepressants (1.8%); and 10th, angiotensin II antagonists, plain (1.7%).

[*3] These refer to diazepines that are assigned to antipsychotics, such as clozapine and olanzapine, but not to benzodiazepines.

[*4] For definition of the therapeutic/pharmacological subgroup “factor Xa inhibitors/direct thrombin inhibitors”, please see eFigure 2.

Discussion

To our knowledge, this is the first and largest cumulative evaluation of spontaneous reports from Germany in the BfArM adverse drug reaction database, and it revealed a continuous increase in reports from 1978 to 2016. Furthermore, the number of reports increased with patient age (11–70 years), and more reports involving women. The three most commonly reported medication groups (with the most common ADRs in parentheses) were: antithrombotic agents (thrombocytopenia, gastrointestinal hemorrhage, and hemorrhage), antibacterials for systemic use (diarrhea, skin rash, and pruritus), and psycholeptics (drug dependence, leukopenia, and pyrexia).

The steady increase in number of spontaneous reports in the BfArM database is mainly due to more reports being sent to the BfArM by pharmaceutical companies. Various factors could be behind this, such as a general increase in willingness to report by physicians and patients (as primary reporting sources); this could be due to increased awareness of ADRs and of reporting options, and having more in- formation sources (Internet). However, the proportion of direct reports to the BfArM (spontaneous reports without reports from pharmaceutical companies) did not show a comparably strong increase (Figure 2). Likewise, there was no clear association between the increase in spontaneous reports and population size, the number of prescriptions made, or the number of working physicians (Figure 3), although certain limitations must be taken into account (eBox 3). Therefore, modified or tightened legal requirements for reporting ADR reports to the BfArM were probably more important for increasing the number of reports sent to the BfArM by the pharmaceutical companies (eBox 3).

About every tenth spontaneous report comes from a patient. Reports from this source have increased substantially since 2008. This could be due to increased sensitivity to the topic due to high-profile medicinal product scandals, the possibility since 2009 to report ADRs online to the BfArM, and the calls for reporting suspected ADRs in the package leaflet (26). Patients in other European countries also have reported more frequently over time (27, 28).

The relatively high proportion of reports classified as serious (66.9%) (11) is likely due to regulatory reporting requirements for pharmaceutical companies. It is not possible to

determine how many ADRs were fatal, as the calculated proportion (5.5%) does not provide any statement about the cause of death. In other words, many reports do not indicate whether death was due to the ADR itself, to the consequences of the ADR, or to underlying diseases.

ADRs are known to increase with age (from 11 to 70 years) (29–31) and may be due to increased medicinal product use in older people (32, 33). A higher risk of ADRs in older people may also be the result of comorbidity, polymedication, and/or decreased liver or kidney function (32, 34–36).

A prevalence of the female sex in ADR reports (54.6% versus 38.8%) has also been described previously in other analyses (29–31). Explanations for this could be more frequent visits to the physician by women (34, 37), a higher use of medicines by women (29, 33), and sex differences in pharmacokinetics (38).

Thirteen of the 15 most commonly reported ADRs were nonspecific general symptoms. This could be due to the fact that, in addition to the ADR leading to the report, nonspecific general symptoms associated with the main ADR were (co-)reported and therefore appeared overly frequently in the analysis.

One-fifth of the most common ADRs are cutaneous, and one-third of the reported ADRs were related to skin. Adverse drug reactions should therefore be considered when making a differential diagnosis of skin lesions.

It is striking that in our study, as well as in other studies (29, 31), “medicinal products for the treatment of the nervous system disorders” were most frequently reported as suspect in the top-level drug groups. However, based on these data, no conclusions can be made about whether these medicines actually cause more ADRs or are only reported more frequently, as the corresponding frequency of use is not known (among other reasons). Nonetheless, in Germany in the period from 2008 to 2011, the highest prevalence of medicinal product use was observed for treating cardiovascular disorders (28.4%), followed by varia (22.5%), and then for nervous system disorders (21.2%) (33).

The importance of medical expertise becomes clear with regard to ADRs typically determined by a physician, such as specific diagnoses (pulmonary embolism) or

laboratory findings (thrombocytopenia). Patients, on the other hand, are more likely than physicians to report ADRs that are subjectively perceived, as well as those that may be of particular importance to their personal quality of life (for example, weight changes, sleep disorders, or alopecia). In this respect, patient reports can be an important supplement to reports from physicians. Furthermore, ADRs that affect the patient's quality of life may affect adherence. Together with an appropriate patient education, patient knowledge about such ADRs and their significance can be relevant to the success of a therapy.

The benefits of the spontaneous reporting system include monitoring the full spectrum of medicinal products (including over-the-counter [OTC] medications), a large population coverage that includes high-risk groups (e.g., children and pregnant women), and acquisition without a time limit. Among the inherent limitations of the spontaneous reporting system is underreporting (3, 14, 39); while this is estimated to be around 90% (40), it depends on the type, severity, and familiarity of the ADR, and of the drug under suspicion (old/new), as was shown in a German study (e1). Other limitations include partially incomplete documentation of case reports and the inability to determine ADR frequency.

The BfArM regularly informs about new risks identified within the framework of medicinal product safety monitoring. Analysis of spontaneous reports contributes substantially to risk recognition of new medical products and can provide the basis for a range of various regulatory measures, such as intensified surveillance, obligation of studies, inclusion of new contraindications in the product information of medicinal products, and revocation of authorization.

Examples of BfArM measures that were based on spontaneous reports include:

- changes in monitoring requirements due to progressive multifocal leukoencephalopathy with the use of fumarates (e2);
- obligation to determine liver values during treatment with kava-kava–containing medicinal products due to hepatotoxic events (e3);

- withdrawal of approval of topically applied bufexamac-containing medicinal products due to contact allergic reactions (e4).

As regulatory measures required to ensure medicinal product safety are based on relevant data and information, ADR reports and the quality of these reports are of major importance for medicinal produce safety. Therefore, the BfArM would also like to use this article to strongly encourage reporting of suspected ADRs (14).

Acknowledgments

We would like to thank the teams responsible for “database search” and “processing/capturing of ADR reports” from the Division of Pharmacovigilance at the BfArM.

We also thank our colleagues at the Institute for Medical Biometry, Informatics, and Epidemiology (IMBIE) at the University Hospital of Bonn for their support.

References

1. Coloma PM, Trifirò G, Patadia V, Sturkenboom M: Postmarketing safety surveillance: where does signal detection using electronic healthcare records fit into the big picture? Drug Saf 2013; 36: 183–97.

2. Paludetto MN, Olivier-Abbal P, Montastruc JL: Is spontaneous reporting always the most important information supporting drug withdrawals for pharmacovigilance reasons in France? Pharmacoepidemiol Drug Saf 2012; 21: 1289–94.

3. Huang YL, Moon J, Segal JB: A comparison of active adverse event surveillance systems worldwide. Drug Saf 2014; 37: 581–96.

4. Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM: The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. Drug Saf 2014; 37: 283–94.

5. Amery WK: Why there is a need for pharmacovigilance. Pharmacoepidemiol Drug Saf 1999; 8: 61–4.

6. Pacurariu AC, Coloma PM, van Haren A, Genov G, Sturkenboom MC, Straus SM: A description of signals during the first 18 months of the EMA pharmacovigilance risk assessment committee. Drug Saf 2014; 37: 1059–66.

7. Harpaz R, DuMochel W, Shah NH: Big data and adverse drug reaction detection. Clin Pharmacol & Ther 2016; 99: 268–70.

8. Pacurariu AC, Straus SM, Trifirò G, et al.: Useful interplay between spontaneous ADR reports and electronic healthcare records in signal detection. Drug Saf 2015; 38: 1201–10.

9. Robb MA, Racoosin JA, Sherman RE, et al.: The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf 2012; 21: 9–11.

10. European Medicines Agency: Guideline on good pharmacovigilance practices (GVP). Module IX - signal management (Rev 1). www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/10/WC500236408.pdf (last accessed on 9 October 2017).

11. Arzneimittelgesetz: Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz – AMG). Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), zuletzt geändert durch Artikel 5 des GKV-Arzneimittelversorgungsstärkungs- gesetzes (AMVSG) vom 4. Mai 2017 (BGBl. I S. 1050).

12. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM): Neben-wirkungsmeldung durch Angehörige der Heilberufe. www.bfarm.de/SharedDocs/Formulare/DE/Arzneimittel/Pharmakovigilanz/aa-uaw-melde-bogen.pdf?blob=publicationFile&v=17.

13. Paul-Ehrlich-Institut (PEI): Meldung von Verdachtsfällen unerwünschter Arzneimittelwirkungen und Impfkomplikationen. www.pei.de/DE/infos/fachkreise/meldeformulare-fach/meldeformulare-fach-node.html (last accessed on 17 April 2018).

14. Stammschulte T, Pachl H, Gundert-Remy U, et al.: Einführung in die Grundlagen der Pharmakovigilanz (Teil II): Spontanmeldesystem zur Erfassung von Verdachtsfällen unerwünschter Arzneimittelwirkungen (UAW). Bulletin zur Arzneimittelsicherheit 2010; 4: 18–26.

15. Bundesärztekammer: (Muster-)Berufsordnung für die in Deutschland tätigen Ärztinnen und Ärzte – MBO-Ä 1997 – in der Fassung des Beschlusses des 118. Deutschen Ärztetages 2015 in Frankfurt am Main, Stand: 27.05.2015.

16. European Medicines Agency: EudraVigilance. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5 (last accessed on 17 April 2018).

17. EudraVigilance. Häufig gestellte Fragen rund um das Meldesystem. www.adrreports.eu/de/faqs.html (last accessed on 17 April 2018).

18. Deutsches Institut für Medizinische Dokumentation und Information (DIMDI): Anatomisch-Therapeutisch-Chemische (ATC) Klassifikation. www.dimdi.de/static/de/amg/atcddd/index.htm (last accessed on 17 April 2018).

19. WHO Collaborating Centre for Drug Statistics Methodology: Anatomisch-Therapeutisch-Chemische (ATC) Klassifikation. www.whocc.no/atc_ddd_index/ (last accessed on 17 April 2018).

20. MedDRA: Medical Dictionary for Regulatory Activities. www.meddra.org/how-to-use/support-documentation (last accessed on 17 April 2018).

21. European Medicines Agency: Guideline on good pharmacovigilance practices (GVP). Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf (last accessed on 28 July 2017).

22. Statistisches Bundesamt: Bevölkerungsstand. www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand/Tabellen_/lrbev03.html (last accessed on 17 April 2018).

23. Schwabe U, Ludwig WD: Arzneiverordnungen 2016 im Überblick. In: Schwabe U, Paffrath D, Ludwig WD, Klauber J (eds.): Arzneiverordnungsreport 2017. Berlin, Heidelberg: Springer 2017; 3–32.

24. Bundesärztekammer: Ärztestatistik zum 31. Dezember 2016. www.bundesaerztekammer.de/fileadmin/user_upload/downloads/pdf-Ordner/Statistik2016/Stat16AbbTab.pdf (last accessed on 17 April 2018).

25. Einführung der Meldepflicht 1987 und Bekanntmachung dazu vom 28.10.1987. Anzeige von Nebenwirkungen, Wechselwirkungen mit an- deren Arzneimitteln und Arzneimittelmissbrauch nach §2 Abs. Satz 2 AMG vom 28.10.1987.

26. Gemeinsame Bekanntmachung über die zu verwendenden Standardsätze in der Fachinformation und Packungsbeilage zum Berichten von Nebenwirkungen sowie für Arzneimittel, die einer zusätzlichen Überwachung unterliegen, gemäß § 11 Absatz 1b

und § 11a Absatz 1 Satz 9 des Arzneimittelgesetzes (AMG), vom 3. Juli 2013. www.bfarm.de/SharedDocs/Bekanntmachungen/DE/Pharmakovigilanz/bm-phvig-20130807-standardsaetze.pdf?blob=publicationFile&v=6 (last accessed on 17 April 2018).

27. Inch J, Watson MC, Anakwe-Umeh S: Patient versus healthcare professional spontaneous adverse drug reaction reporting: a systematic review. Drug Saf 2012; 35: 807–18.

28. European Medicines Agency: Annual Report 2016. www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2017/05/WC500227334.pdf (last accessed on 17 April 2018).

29. Thiessard F, Roux E, Miremont-Salame G, et al.: Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986–2001). Drug Saf 2005; 28: 731–40.

30. Ozcan G, Aykac E, Kasap Y, Nemutlu NT, Sen E, Aydinkarahaliloglu ND: Adverse drug reaction reporting pattern in Turkey: analysis of the national database in the context of the first pharmacovigilance legislation. Drugs Real World Outcomes 2016; 3: 33–43.

31. Aagaard L, Strandell J, Melskens L, Petersen PS, Holme Hansen E: Global patterns of adverse drug reactions over a decade. Drug Saf 2012; 35: 1171–82.

32. Alhawassi TM, Krass I, Bajorek BV, Pont LG: A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging 2014; 9: 2079–86.

33. Knopf H, Grams D: Arzneimittelanwendung von Erwachsenen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsbl 2013; 56: 868–77.

34. Telschow C, Schröder M: Arzneimittelverordnungen nach Alter und Geschlecht. In: Schwabe U, Paffrath D, Ludwig WD, Klauber J (eds.): Arzneiverordnungs-Report 2017. Berlin, Heidelberg: Springer 2017; 783–792.

35. Klotz U: Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 2009; 41: 67–76.

36. Hämmerlein A, Derendorf H, Lowenthal DT: Pharmacokinetic and pharmacodynamic changes in the elderly. Clin Pharmacokinet 1998; 35: 49–64.

37. Glaeske G, Gerdau-Heitmann C, Höfel F, Schicktanz C: „Gender-specific drug prescription in Germany“ results from prescription analysis. In: Regitz-Zagrosek V (ed.): Sex and gender differences in pharmacology. Berlin, Heidelberg: Springer 2012; 149–67.

38. Zopf Y, Rabe C, Neubert A, et al.: Gender-based differences in drug prescription: relation to adverse drug reactions. Pharmacology 2009; 84: 333–9.

39. Lütkehermölle W, Paeschke N: Einführung in die Grundlagen der Pharmakovigilanz (Teil I) – Verdachtsfälle von unerwünschten Arznei- mittelwirkungen. Bulletin zur Arzneimittelsicherheit 2010; 1: 14–7.

40. Hazell L, Shakir SA: Under-reporting of adverse drug reactions. Drug Saf 2006; 29: 385–96.

eReferences

e1. Hasford J, Goettler M, Munter KH, Müller-Oerlinghausen B: Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. J Clin Epidemiol 2002; 55: 945–50.

e2. BfArM: Dimethylfumarathaltige Arzneimittel und progressive multifo- kale Leukencephalopathie (PML). Stand: 7. April 2015. www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RI/2015/RI-dimethylfumarat.html (last accessed on 17 April 2018).

e3. BfArM: Kava-Kava, Widerruf der Zulassung. Stand: 31. August 2015. www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakvigilanz/DE/RV_STP/g-l/kavakava3.html (last accessed on 17 April 2018).

e4. BfArM: Bufexamac-haltige Arzneimittel: Kontaktallergische Reaktionen. Feststellungsbescheid. Stand 5. Mai 2010. www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RV_STP/af/bufexamac.html (last accessed on 17 April 2018).

e5. BfArM: Glossar: over the counter OTC. www.bfarm.de/SharedDocs/ Glossareintraege/DE/O/OTC.html (last accessed on 17 April 2018).

e6. MedDRA: Standardised MedDRA queries. www.meddra.org/standardised-meddra-queries (last accessed on 17 April 2018).

e7. Farzan J: Neue Pharmakovigilanz-Gesetzgebung in der EU. Bulletin zur Arzneimittelsicherheit 2011; 3: 14–7.

e8. BfArM: Glossar: Schwarzes Dreieck. www.bfarm.de/SharedDocs/Glossareintraege/DE/S/Schwarzes_Dreieck.html (last accessed on 17 April 2018).

eBOX 1

Authors

Felix Wolfrum[1], Diana Dubrall[2,3], Norbert Paeschke[2], Eva Alešik[2], Bernhardt Sachs[2,4], Rainer Riedel[1], Maria Wittmann[1,5]

1) Institute for Health-Economics & Health-Care Research, University of Applied Sciences, Cologne.

2) BfArM, Bonn.

3) Institute for Medical Biometry, Informatics, and Epidemiology (IMBIE), University Hospital of Bonn, Germany.

4) Clinic for Dermatology and Allergology, University Hospital (RWTH), Aachen, Germany.

5) Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Germany.

What should physicians be aware of when reporting ADRs?

- Why should ADRs be reported after approval?

Clinical trials prior to approval of a medicinal product include a limited number of preselected patients. In this situation, ADRs that are rare or that only occur in certain vulnerable patients or after prolonged use cannot be reliably detected. Therefore, spontaneous reports of ADRs from physicians with everyday use of a medicinal product on a wide range of patients after its approval are of major importance for medicinal product safety.

- To whom can ADRs be reported in Germany?

ADRs can be reported to:

a) the Drug Commission of the German Medical Association (AkdÄ; Arzneimittelkommission der deutschen Ärzteschaft);

b) the competent federal authorities according to their respective areas of responsibility (for the German Federal Institute for Drugs and Medical Devices [BfArM], chemically-defined active substances, among others; and for the Paul-Ehrlich-Institut [PEI], monoclonal antibodies and vaccines, among others);

c) pharmaceutical companies, which then forward them.

As the reports are exchanged between institutions, parallel reports to several institutions are not required.

- How can ADRs be reported?

ADRs are best reported via the online platforms of AkdÄ, BfArM, or PEI, respectively. If this is not possible, reporting can alternatively be done either using the reporting form, which should be printed and filled out and then sent by fax, scan, or postal mail, or directly (without a form) by postal mail, fax, or email. Nonetheless, using the online platforms is explicitly recommended, as all relevant information is specifically queried there.

- Which information should be included in the ADR report?

The relevant information is requested in the reporting form. Of particular importance are the following:

a) the demographic background of the patient (including initials, age, and sex), to allow detection of double reporting, among other things;

b) the type of ADR, time of occurrence, duration, and outcome;

c) the suspected (or, where appropriate, interacting) medicinal product(s) and its use (exact name [active substance, trade name], and if available, lot number), route of administration (oral, intravenous, etc.), dose used, starting and (if appropriate) stopping time/date of therapy, and indication;

d) any concomitant medication (exact name [active substance, trade name] and if available, lot number), route of application (oral, intravenous, etc.), dose used, starting and (if appropriate) stopping time/date of therapy, and indication;

e) medical history, potential risk factors, and accompanying factors (e.g., comorbidities, nicotine or alcohol abuse);

f) information for assessment of a causal relationship (for example, description of the temporal association, course, and treatment of the ADR [including discontinuation of the suspect medicine]), re-exposure, assessment of a causal relationship by the reporting physician;

g) information that provides a more detailed description of the ADR, such as laboratory parameters;

h) information about the reporter (including address, e-mail, and qualifications).

Treating physician letters and hospital discharge letters can be very helpful if they contain relevant information.

- Which ADRs are of particular interest?

All ADRs can be reported. A causal relationship with the use of the medicinal product does not have to be clearly demonstrated; it is sufficient if it is assessed as “possible”. Of particular interest are reports on:

– all serious ADRs

– all ADRs in children and pregnant or breast-feeding women

– ADRs of newly introduced active substances (e.g., up to five years after approval)

– previously unknown ADRs, or those that are not listed in the product information

– ARs occurring after prolonged use or after a medicinal product has been discontinued (long-term effects)

– observed accumulation of a certain AR (for example, allergic reactions as an indication of possible defects in pharmaceutical quality)

– ADRs in case of use outside of the approved indications (off-label use)

– medication errors, abuse

- What happens to the report?

– After pseudonymisation, the report is stored in EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance, the European database for adverse drug reaction), where analyses are continuously performed to ensure drug safety. Signals from ARs can be a major cause of regulatory action (for example, changes in product information, conducting trials).

eBox 2

ADR reporting by pharmaceutical companies

Changes to the statutory reporting obligations of 1987–2016. The following aspects must be taken into consideration with respect to Figure 2:

The increasing number of spontaneous report in the database of the Federal Institute for Drugs and Medical Devices (BfArM) over time is mainly due to an increase in reports forwarded to the BfArM by pharmaceutical companies. In particular, modified or tightened legal requirements for pharmaceutical companies to forward ADRs which they have become aware of, may have contributed to this increase. The reporting obligation for pharmaceutical companies - that is, their obligation to forward spontaneous reports - to the competent federal authorities, has existed since 1987. Various legislative changes were made up to 2016. For example, in October 2012, the second law amending medicinal products and other legislation redefined the term „ADR“. In the 1987 definition, unintended ADRs under the intended use of a medicinal product had to be reported; the definition of ADRs since 2012, in contrast, includes any reaction to the use of a medicinal product, including, for example, those due to medication errors.

Modifications in the form and scope of the reporting requirements of individual cases (serious/non-serious) could have influenced the course as well. Specifically, in 1987, ADRs with temporary, minor harm that did not impair health were not yet notifiable. In stark contrast, in the period 1989–1995, all ADRs (serious and non-serious) had to be reported. Differences also existed in the reporting forms and the timing of the deadlines, depending on whether the reported ADR was known or not. Starting from 1996, non-serious ADRs could be listed in periodic safety reports (instead of submitting an ADR report). The new EU legislation in 2012 (e7) created the conditions for suspected non-serious ADRs to be reported regularly as single-case reports. The obligation to forward such suspected cases from the EU Member States to the EudraVigilance database applies both to the respective competent authorities in the EU and to pharmaceutical companies (for the latter, since 22 November 2017) across the EU.

With the beginning of the legal reporting obligations, ADR reports were required to provide information about the so-called „identifiability“ of the data source and the patient (to exclude multiple registrations of one case report from different reporting sources), in addition to information about at least one medicinal product under suspicion of inducing an ADR and about at least one ADR due to use of the product. The requirements of providing a minimum criteria of information for identifiability have been reduced over time, in part for data protection reasons but also to ensure that not having certain information does not obstruct reporting an ADR. However, this has made merging information about the same case from different reporting sources much more difficult, and having multiple registrations cannot be ruled out for all individual cases. In addition, the general monitoring and documentation requirements for pharmaceutical companies have been increasingly tightened. These now includes the obligation to perform a weekly literature search in at least one literature database (since 2005), and the obligation to report ADRs that have become known; the obligation to notify was (and is) also valid for ADRs reported via the Internet.

Other reasons for the increased volume of reporting are: the obligatory inclusion since 2013 of a reference in the product information and patient information leaflets for reporting ADRs, as well as the labeling of newly approved medicinal products with additional monitoring (black triangle).

Explanations for the terms used:

Medicinal products under additional monitoring ▼

Since 2013 (26), medicinal products under additional monitoring are marked with a black triangle ▼ in all EU member states (e8). Additional monitoring usually covers medicinal products when there is less available information about them than for other medicines, which may be due to the product being new to the market or having insufficient data for its long-term use. The black triangle indicates that this medicinal product is being monitored even more strictly than others. Notably, it does not mean that the medicinal product is not safe. The black triangle urges patients to report any suspicion of a possible ADR when using the medicine. The black triangle is printed both in the patient

information leaflet and in the prescribing information for healthcare professionals (the so-called summary of medicinal product characteristics). It is not shown on the outer wrapper or on the product label.

eBox 3

Limitations on the evaluation of the time course of the quotient of spontaneous reports per 100,000 population, 100,000 prescriptions, and 100 physicians in Germany

Overview of the evolution of population size, prescriptions, and number of working physicians over time

Since the reunification of Germany (1990), the population size has remained almost constant (data: German Federal Statistical Office [Statistisches Bundesamt]) (22). In contrast, the number of spontaneous reports has increased over time. This has led to an increase in the ratio of spontaneous reports/100,000 population in Germany.

The total number of prescriptions (data: drug prescription report [Arzneiverordnungsreport]) (23) increased in the years 1991/1992 (this is not visible in the quotient) and then slowly decreased. In 2004, the total number of regulations decreased sharply (due to the Statutory Health Insurance Modernization Act [GKV-Modernisierungsgesetz]) and then began to slowly rise again. The number of spontaneous reports has greatly increased over time. Therefore, the quotient of spontaneous reports/100,000 prescriptions shows a slight increase.

The number of working physicians in the out- and inpatient areas (data: physician statistics of the German Medical Association [Bundesärztekammer]) (24) has steadily increased. The number of spontaneous reports has greatly increased over time. Therefore, the quotient of spontaneous reports/100 physicians shows a slight increase.

For interpreting the quotients in Figure 3, various limitations must be taken into account:

The data on the population are provided by the German Federal Statistical Office (Statistisches Bundesamt) (22). In particular, there may be restrictions in the accuracy in recent years due to the increased level of immigration and the consequent problems in registration. Another aspect is an increase in the aged population in Germany over the

analysis period (1978–2016) and increased life expectancy, as an older population is associated with higher prevalence rates for the presence of disease. The presence of disease or comorbidity, and the therapies for these (and in particular polypharmacy), may be associated with an increase in ADRs and reports of ADRs.

The total number of prescriptions was taken from the Arzneiverordnungsreporte (drug prescription reports) (23). This included finished medicinal products that have been prescribed for outpatients and covered by the statutory health insurance funds; among other things, data on medicinal product prescriptions for private patients are missing. Further, over-the-counter (OTC) use is not included. In addition, data do not allow any conclusion to be drawn as to whether the medicines were actually used. The indication of the total number of prescriptions in DDD (defined daily dose) is also problematic, as using DDD is not suitable for all medicinal products and may not correspond to the actual prescribed/ applied daily dose.

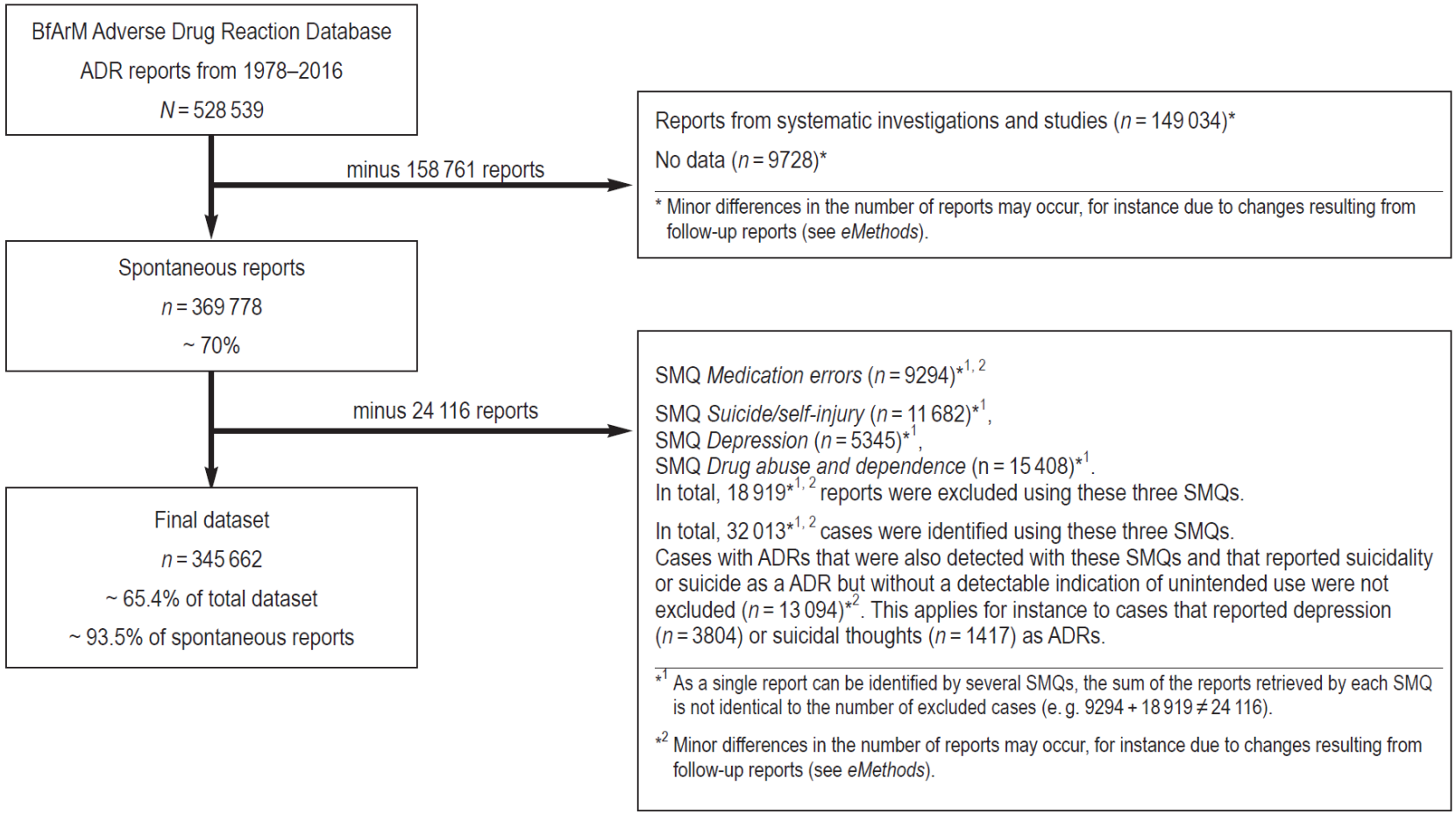
Data on the number of working physicians come from the medical statistics of the German Medical Association (Bundesärztekammer) (24). The increase in the number of working physicians in the out- and inpatient sectors did not take into account the individual disciplines. Due to different prescription frequencies in the various disciplines, this may also be of importance.

Explanations for the terms used:

DDD (defined daily dose)

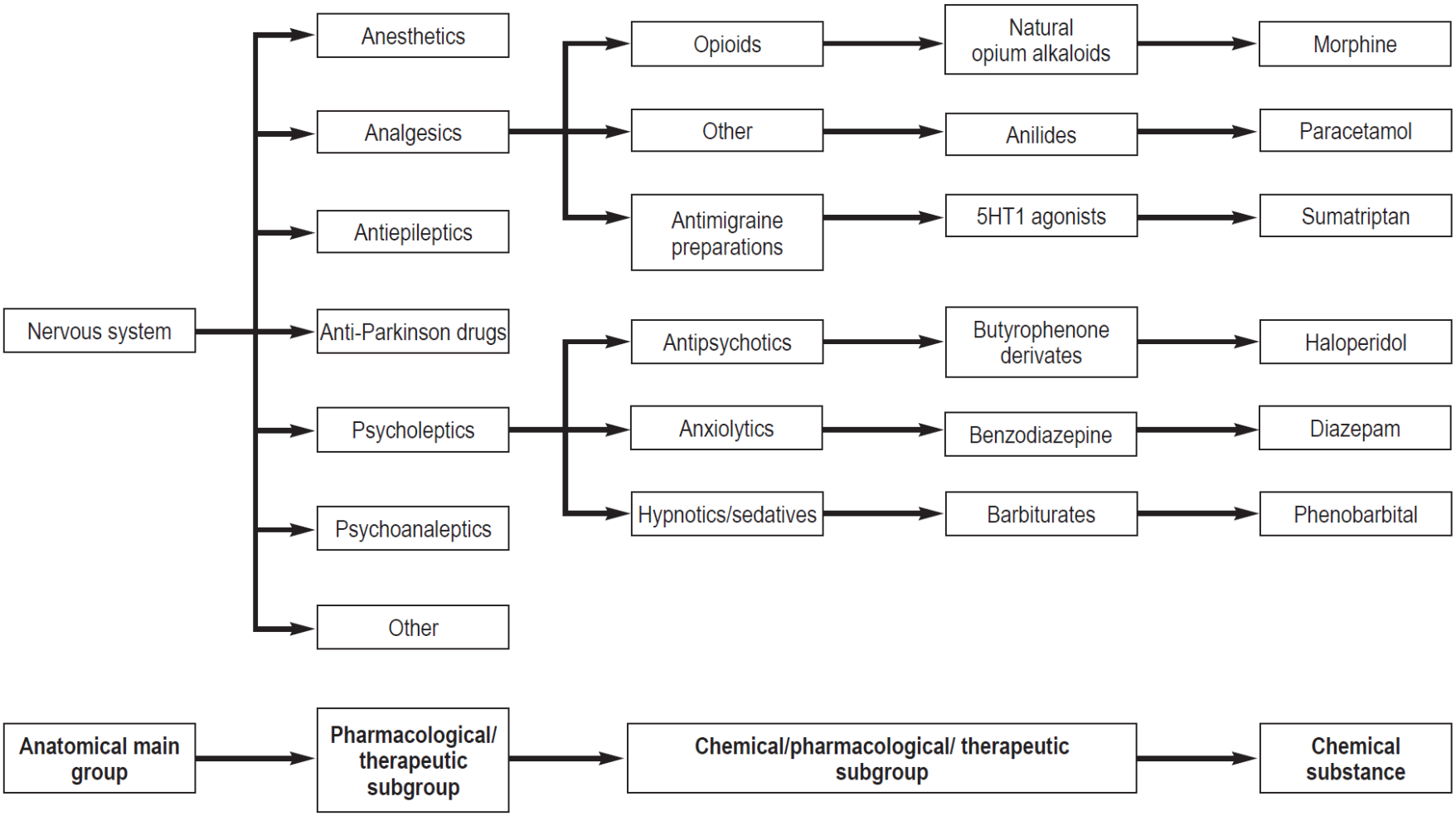
The defined daily dose is based on the amount of active substance or medicinal product that should typically be used for the main indication per day. It should be noted that the DDD does not necessarily reflect the recommended or actual daily dose of a medicinal product but mainly provides a technical means of measurement and comparison (23).

eFigure 1. Flow chart depicting generation of final dataset.



German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM); SMQ, standardized MedDRA queries; MedDRA, Medical Dictionary for Regulatory Activities.

eFigure 2. Description and schematic depiction of ATC * (anatomical therapeutic classification using morphine as an example.



Example: morphine

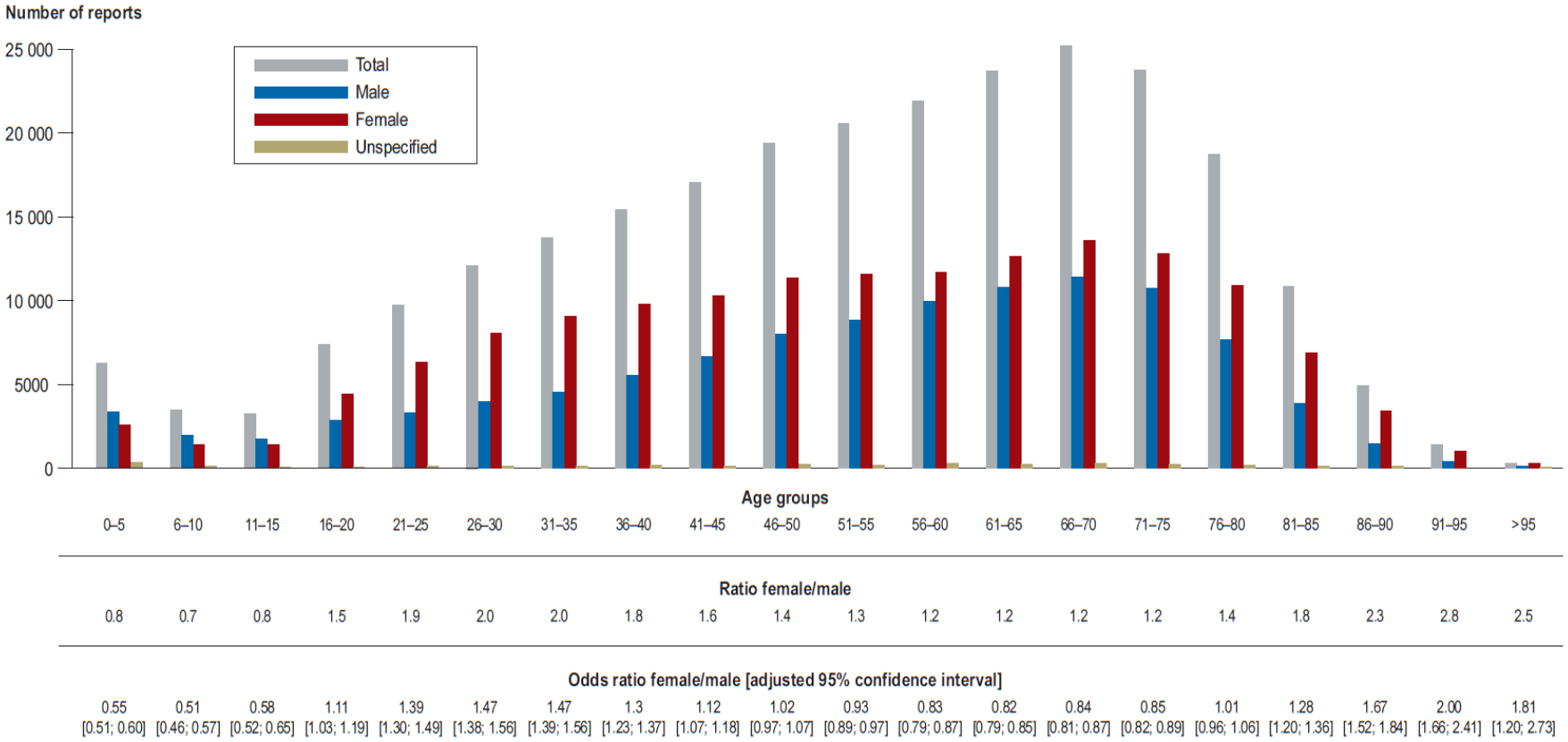
The ATC classification system has a hierarchy with five different levels. *There are fourteen major anatomical groups (for example, 1st level: the nervous system). Active substances are each assigned to the anatomical systems in which they are effective. The 2nd level identifies the associated pharmacological/therapeutic subset (for example, analgesics). The 3rd and 4th levels reflect the chemical, pharmacological, or therapeutic subgroup (3rd level, opioids; 4th level, natural opium alkaloids). At the last (5th) level, the chemical substance is described (morphine). Graphical depiction using the example “Medicinal products for the treatment of diseases of the nervous system“ (not given in full).

* ATC-Structure and Principles: www.whocc.no/atc/structure_and_principles/

Clarification for Tables 1 and 2: Other antithrombotic agents

In the ADR database (and deviating from the ATC code classification), the active substances rivaroxaban and lepirudin (4th level ATC code) are assigned to the pharma- cological subgroup “other antithrombotic agents”. Other direct factor Xa inhibitors (e.g., apixaban, edoxaban) are included in the pharmacological subgroup “factor Xa inhibitors”, while another direct thrombin inhibitor (dabigatran) is included in the pharmacological subgroup “direct thrombin inhibitors”. To facilitate understanding, the term “other antithrombotic agents” in Tables 1 and 2 has been renamed „Factor Xa inhibitors/direct thrombin inhibitors“. Thus, only the name of the group, but not the assigned substances, was changed. Note that there was no summation of the three pharmacological subgroups.

eFigure 3.Stratification of spontaneous reports by age and sex.



eFigure 3 shows the cumulative stratification of spontaneous reports with respect to age (in 5-year age groups) of affected patients and their sex. Reports within one age group can be from different years. In addition to the sex ratio (female/male), the odds ratio for each age group with respect to the other age groups was calculated using the Bonferroni confidence interval adjustment.

eTable 1.The 15 most frequently reported ADRs in the generated dataset.

Rank	Most frequently reported ADRs	Proportion of generated dataset (*N* = 345 662) in % (number of spontaneous reports)
1st	Nausea	5.2% (18 074)
2nd	Pruritus	3.8% (12 984)
3rd	Dizziness	3.7% (12 833)
4th	Dyspnea	3.4% (11 762)
5th	Vomiting	2.8% (9781)
6th	Skin rash	2.8% (9610)
7th	Headache	2.7% (9353)
8th	Diarrhea	2.7% (9338)
9th	Pyrexia	2.5% (8709)
10th	Hypersensitivity	2.4% (8225)
11th	Urticaria	2.3% (7985)
12th	Thrombocytopenia	2.1% (7279)
13th	Fatigue	2.0% (7044)
14th	Erythema	1.9% (6508)
15th	Tachycardia	1.8% (6150)

The fifteen most frequently reported ADRs are shown as the proportion of the generated dataset of 345,662 spontaneous report (as percentage) and their absolute number (in brackets).

As a report may describe several ADRs, the number of reported ADRs exceeds the total number of reports. For the analysis presented in eTable 1, ADRs were chosen at the 4th level (PT, preferred term) of the MedDRA (Medical Dictionary for Regulatory Activities) terminology.

eTable 2.The ten most frequently reported medication groups under suspicion at the top level.

Rank	First level medication groups under suspicion (and the three most frequent therapeutic sub-groups of medication under suspicion)	Proportion in generated dataset (*N* = 345 662) in %- (absolute number of spontaneous reports)
1st	Nervous system (psycholeptics; psychoanaleptics [antidepressants]; analgesics)	23.1% (79 976)
2nd	Cardiovascular system (agents acting on the renin-angiotensin system; lipid modifying agents; cardiac therapy)	13.0% (44 787)
3rd	Antineoplastic and immunomodulationg agents (antineoplastic agents; immunosuppressants; immunostimulants)	12.4% (43 006)
4th	Blood and blood forming organs (antithrombotic agents; blood substitutes and perfusion solutions; antianemic preparations)	10.9% (37 661)
5th	Antiinfectives for systemic use (antibacterials; antivirals; antimycotics)	10.5% (36 327)
6th	Musculo-skeletal system (antiinflammatory and antirheumatic products; drugs for treatment of bone diseases; muscle relaxants)	8.7% (30 217)
7th	Alimentary tract and metabolism (drugs used in diabetes; drugs for acid related disorders; drugs for functional gastrointestinal disorders)	7.3% (25 139)
8th	Genitourinary system and sex hormones (sex hormones and modulators of the genital system; other gynecologicals; urologicals)	6.1% (21 223)
9th	Various (contrast media; all other therapeutic products; dental preparations)	4.7% (16 089)
10th	Respiratory system (drugs for obstructive airway diseases; cough and cold preparations; antihistamines for systemic use)	3.9% (13 365)

The ten most frequently reported medication groups under suspicion are shown as their percentage share of the generated dataset of spontaneous reports (n = 345,662). and as absolute numbers (in brackets). The three most frequent therapeutic subgroups of medication under suspicion are shown in brackets. As a report may describe several

drugs under suspicion, the number of reported ADRs exceeds the total number of reports.

The analysis presented in eTable 2 is based on the ATC code and depicts the most frequent 1st level (anatomical main group) medication groups and their three most frequent 2nd level medication subgroups.

eTable 3. The ten most frequent reported ADRs by physicians and patients.

Rank	Physicians: most frequently reported ADRs	Proportion in physician reports (*n* = 221 427) in % (number of spontaneous reports)
1.	Nausea*	4.7 % (10 382)
2.	Pruritus*	3.5% (7734)
3.	Dyspnea*	3.1% (6876)
4.	Vomiting	2.8% (6267)
5.	Pyrexia	2.8% (6262)
6.	Dizziness*	2.8% (6256)
7.	Thrombocytopenia	2.7% (6009)
8.	Urticaria	2.6% (5721)
9.	Skin rash	2.6% (5681)
10.	Diarrhea*	2.3% (5180)

Rank	Patients: most frequently reported ADRs	Proportion in patient reports (*n* = 32 992) in % (number of spontaneous reports)
1.	Dizziness*	7.1% (2346)
2.	Nausea*	6.3% (2074)
3.	Headache	5.3% (1747)
4.	Fatigue	5.1% (1696)
5.	Dyspnoea*	4.6% (1527)
6.	Diarrhea*	4.1% (1353)
7.	Pruritus*	3.7% (1209)
8.	Visual impairment	3.4% (1135)
9.	Asthenia	3.3% (1088)
10.	Arthralgia	3.1% (1038)

The ten most frequently reported ADRs in spontaneous reports from physicians (n = 221,427) and patients (n = 32,992) are shown as the percentage share of the corresponding dataset (e.g., for physicians or patients) and their absolute number (in brackets).

ADRs that are in the top ten for both physicians and patients are indicated with an asterisk (*). As a report may describe several ADRs, the number of reported ADRs exceeds the total number of reports. The remaining ADRs (until #50) are not listed here.

For the analysis presented in eTable 3, ADRs were chosen at the fourth level (PT, preferred term) of the MedDRA (Medical Dictionary for Regulatory Activities) terminology.

eMethods

Explanation of terms used

To facilitate understanding, the following terms were used in the article “Frequent Adverse Drug Reactions, and Medication Groups Under Suspicion”:

- “ADR/s” as an abbreviation of “adverse drug reaction/s ”
- “patient” rather than “consumer and non-healthcare professional”;
- “pharmaceutical company” rather than “holder of the authorization” or “marketing authorization holder”. Differences in reporting obligations are not further discussed within the article.

OTC medicinal products:

OTC (over-the-counter) refers to all non-prescription medications (e5).

Generation of the final analysis dataset (N = 345,662)

Only spontaneous reports were used for the analysis, to produce a homogeneous database. Spontaneous reports (including reports from the Internet and digital media) are unsolicited reports about suspected ADRs that occur under everyday conditions (and not in the framework of clinical trials, for instance). According to the guidelines of the European Medicines Agency (EMA) (21), however, the definition of “unsolicited reports” covers both spontaneous reports and literature reports.

Solicited reports

According to an EMA guideline (21), solicited reports are all ADR reports that arise from organized data collection systems, including clinical trials, non-interventional studies,

and surveys of patients or healthcare professionals. These reports are not considered to be spontaneous.

Causality assessment

Because of the high volume of ADR reports, no routine causality assessment can be made of all submitted spontaneous reports. Instead, causality assessments are conducted on an ad hoc basis, for instance when a signal arises in the context of computer-based signal detection. Such a signal may result, for example, from a relatively high number of ADR reports on a particular medicinal product within a given time span.

MedDRA terminology

MedDRA terminology (MedDRA, Medical Dictionary for Regulatory Activities) is a standardized medical terminology that can be used to index reported ADRs, for example in an ADR database (20). Keywording makes it easier to standardize such research and to perform it in a reproducible manner.

SMQ (standardized MedDRA queries)

SMQs are a predefined set of terms used in the MedDRA catalog for summarizing ADRs (e6).

Preferred term (PT)

A PT is a self-contained descriptor (a single medical concept) for a symptom, sign, disease, diagnosis, therapy indication, examination, or surgical or medical intervention. A PT is also an independent descriptor for a medical, social, or family history characteristic (according to MedDRA).

Restriction to medicinal products used as intended

The aim of this study was to generate a dataset of ADRs that were due to the intended use of the medicinal products. In the case of unintended use, for example in the case of suicide, much higher doses are typically taken, so that ADRs can be significantly different from those with the intended use. For this purpose, using SMQs (e6) removed ADR reports from the dataset that were based for instance on a medication error or an intended overdose (such as a suicide attempt)

Exclusion of ADR reports associated with medication errors

Spontaneous reports of ADRs that were coded as medication errors were excluded from the analysis using the SMQ medication errors (n = 9,304)*[1,2]. However, one can assume that this does not exclude all ADR reports that were due to medication errors, as some ADRs contained in the database can be related to a medication error that is neither explicitly stated in the report nor can be directly deduced from the report.

Exclusion of cases with intentional overdoses

The SMQs depression and suicide/self-injury and drug abuse and dependence identified 32,013 cases*[1,2]. Of these, 18,919*[1,2] reports were excluded that were of ADRs after intentional overdose (e.g., suicide attempts). For this exclusion process, two reviewers of the SMQs depression and suicide/self-injury and drug abuse and dependence (total n = 32,013 cases)*[1,2] identified subordinated preferred terms (PTs; referred to herein as “adverse drug reactions” or “ADRs”) that indicated suicide or intentional overdose. In this way, 5,345*[2] and 11,682*[2] cases were identified with the SMQs depression and suicide/ self-injury, respectively, and 15,408*[2] cases were identified with the SMQ drug abuse and dependence.

Cases with ADRs that were also detected with these SMQs, and that reported suicidality or suicide as a ADR but without a detectable indication of intentional use, were not

excluded (n = 13,097)*[1,2]. This applies for instance to cases that reported depression (n = 3,804) or suicidal thoughts (n = 1,417) as ADRs.

Due to the high number of cases, it was not possible to evaluate individual cases. Therefore, it could be possible that some cases of intentional overdose were included in the final dataset.

Cases with unknown primary reporting source

Spontaneous reports in which the primary reporting source was unknown (6.9% of the 345,662 cases; e.g., those from an anonymous reporting source) were analyzed separately. As this separate analysis did not reveal any substantial differences as compared to the overall dataset, these reports were not excluded from the final analysis.

*[1] Within the framework of an internal review process, a recommendation was made after the first analysis had been completed to list the overall number of cases identified for the SMQ depression and suicide/self-injury and the SMQ drug abuse and dependence, to facilitate understanding (n = 32,013 cases). Since this analysis was performed at a later date, there is a minimum deviation of three cases from the summation of 18,919 (= cases excluded by this SMQ) and 13,097 (= cases included in the analysis). (18,919 + 13,097 = 32,016, rather than 32,013). There was also a minimal deviation of ten cases for cases that had been coded as medication error, between the first and the most recent case retrieval (from 9,304 cases to 9,294, respectively). These marginal deviations may have been caused by, for example, recoding as a result of follow-up reports.

*[2] A single report can be included in multiple SMQs, hence the sum of reports collected via different SMQs is not the same as the number of excluded cases.

Appendix B

Dubrall D, Just KS, Schmid M, Stingl JC, Sachs B. Adverse drug reactions in older adults: a retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices. BMC Pharmacol Toxicol 2020; 21: 25.

Full title:

Adverse drug reactions in older adults: a retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices

Short title:

Adverse drug reactions in older adults

Authors' full names:

Diana Dubrall [1,2], Katja S Just[3], Matthias Schmid[1], Julia C Stingl[3], Bernhardt Sachs[2,4]

Authors' institutional affiliations including city and country

1) Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), University Hospital of Bonn, Bonn, North Rhine-Westphalia, Germany

2) Research Division, Federal Institute for Drugs and Medical Devices (BfArM), Bonn, North Rhine-Westphalia, Germany

3) Institute of Clinical Pharmacology, University Hospital of the RWTH Aachen, Aachen, North Rhine-Westphalia, Germany

4) Department for Dermatology and Allergy, University Hospital of the RWTH Aachen, Aachen, North Rhine-Westphalia, Germany

Disclaimer:

The information and views set out in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Federal Institute for Drugs and Medical Devices.

Abstract

Background: Older adults are more prone to develop adverse drug reactions (ADRs) since they exhibit numerous risk factors. The first aim was to analyse the number of spontaneous ADR reports regarding older adults (> 65) in the ADR database of the German Federal Institute for Drugs and Medical Devices (BfArM) and to set them in relation to i) the number of ADR reports concerning younger adults (19-65), and ii) the number of inhabitants and assumed drug-exposed inhabitants. The second aim was to analyse, if reported characteristics occurred more often in older vs. younger adults.

Methods: All spontaneous ADR reports involving older or younger adults within the period 01/01/2000-10/31/2017 were identified in the ADR database. Ratios concerning the number of ADR reports/number of inhabitants and drug-exposed inhabitants were calculated. The reports for older (n= 69,914) and younger adults (n= 111,463) were compared using descriptive and inferential statistics.

Results: The absolute number of ADR reports involving older adults increased from 1,615 (2000) up to 5,367 ADR repots (2016). The age groups 76-84 and 70-79 had the highest number of ADR reports with 25 ADR reports per 100,000 inhabitants and 27 ADR reports per 100,000 assumed drug-exposed inhabitants. For both ratios, the number of reports was higher for males (26 and 28 ADR reports) than for females (24 and 26 ADR reports). Fatal outcome was reported almost three times more often in older vs. younger adults. Six out of ten drug substances most frequently suspected were antithrombotics (vs. 1/10 in younger adults). For some drug substances (e.g. rivaroxaban) the ADRs reported most frequently differed between older (epistaxis) and younger adults (menorrhagia).

Conclusions: There is a need to further investigate ADRs in older adults since they occurred more frequently in older vs. younger adults and will likely increase in future. Physicians should be aware of different ADRs being attributed to the same drug substances which may be more prominent in older adults. Regular monitoring of older adults taking antithrombotics is recommended.

Key words

Adverse drug reactions, spontaneous reports, ADR database, adverse drug reactions older adults, side effects, older adults

List of abbreviation

ADR: adverse drug reaction
ATC classification: Anatomical Therapeutic Chemical classification
AVP: drug prescription reports (Arzneiverordnungs-Reporte)
BfArM: Federal Institute for Drugs and Medical Devices
CI: confidence interval
DDD: defined daily doses
EMA: European Medicines Agency
HCPs: Health Care Professionals
MedDRA: Medical Dictionary for Regulatory Activities
non-HCPs: Non-Health Care Professionals
OR: odds ratio
OTC drugs: over-the-counter drugs
PEI: Paul-Ehrlich-Institut
PIMs: potentially inappropriate medications
PT: preferred term

Background

Older adults usually present with many risk factors promoting the occurrence of adverse drug reactions (ADRs) [1] like e.g. multimorbidity which can lead to polypharmacy [2]. In Germany, up to 58 % of older adults suffer from at least one chronic disease [3], and around 50 % in the age group of 70-79 years exhibit polypharmacy [4]. Further risk factors for ADRs in older adults include changes in renal and hepatic clearance, distribution and metabolism leading to prolonged half-lives or higher plasma concentrations if not taken into consideration [5].

With regard to spontaneously reported ADRs roughly three times more ADR reports per million inhabitants per year are reported for older adults aged 65-74 years compared to younger adults aged 5-19 years for high-income countries [6]. Since ADRs are an important cause for morbidity and death [7], they have a significant impact on healthcare systems, especially in older adults [8]. For example, ADR-related hospital admissions are common in older adults in two German observational studies [9, 10]. Concerning ADRs resulting in death, the highest number of reported fatal ADRs is reported for the older adults aged 71-80 years in a Swedish study [11].

Since the proportion of older adults within the German population is steadily increasing [12] (in 2060 roughly every third person will be ≥ 65 years [13]) the impact and significance of ADRs in older adults is supposed to gain further medical and economic relevance in the future.

In general, ADRs in older adults may be difficult to recognise as they often present with unspecific symptoms or are attributed to underlying diseases. Therefore, the causal association with drug treatment is difficult to assess [10, 14] and the prevalence of ADRs in older adults might even be higher. With regard to the reporting of ADRs, some (older) studies found that ADRs in older adults are less often reported [15, 16] whereas a recent study describes the opposite [17].

Since some drugs were found to be associated more often with ADRs in older adults, lists of potentially inappropriate medications (PIMs) for older adults (e.g. PRISCUS list, international Beers Criteria) have been published [18, 19, 20]. Irrespective of these lists of PIMs, in spontaneous reports from Italy and Sweden the drug classes reported most

frequently to be associated with ADRs in older adults are cardiovascular drugs and drugs acting on the blood and blood forming organs [17, 21]

The present study is the first retrospective analysis of spontaneous ADR reports (specified as "ADR reports" in the following) concerning older adults (> 65 years) performed in the large ADR database of the Federal Institute for Drugs and Medical Devices (BfArM) [22]. The first aim of the study was to determine the number of ADR reports regarding older adults (> 65 years) and to set these reports in relation to i) the number of spontaneous ADR reports regarding younger adults (19-65), and ii) the number of inhabitants [23] and assumed drug-exposed inhabitants [4], and to oppose the ADR reports to the number of defined daily doses (DDD) used per insured person [24]. The second aim was to analyse, if some of the reported characteristics are more often described in the ADR reports of older adults compared to younger adults.

Materials and Methods

Reporting channels

Physicians in Germany are obliged by their professional code of conduct to report ADRs to their professional councils which forward these reports to either BfArM (responsible for chemically defined drugs) or Paul-Ehrlich-Institut (PEI) (responsible for monoclonal antibodies, vaccines etc.) as described elsewhere [25]. BfArM and PEI are independent federal higher authorities within the portfolio of the Federal Ministry of Health (so called competent authorities) [26].

Both, Health Care Professionals (HCPs) and Non-Health Care Professionals (non-HCPs, e.g. consumer) may also directly report to one of these two competent authorities, or to the respective marketing authorization holders.

ADRs can be reported online [27, 28] or by using standardized reporting forms. Alternatively a reporting by fax, scan, or postal mail, or directly (without a form) by postal mail, fax, or email is also possible. However, the online platforms are explicitly recommended for ADR reporting as all relevant information is specifically queried there.

Until 22 November 2017 [29] marketing authorization holders forwarded the ADR reports to the aforementioned competent authorities. After the changes to the pharmaceutical legislation in 2012 marketing authorization holders had to report transitionally to BfArM or PEI, and additionally to the European Medicines Agency (EMA). However, this transitional period ended on 22 November 2017 and BfArM's ADR database was closed. From that date onwards marketing authorization holders, BfArM, and PEI now forward serious and non-serious ADRs directly to the EMA.

The public access to the restricted set of data elements of BfArM's ADR database is no longer available since the closure of the database [29]. Due to data privacy requirements, it is not possible to make the individual case reports available to the readership. Nevertheless, researchers and/or readers who are interested can perform the same analysis in the ADR database EudraVigilance of the EMA [30]. However, different levels of access are granted for different stakeholders [31].

BfArM's ADR database

BfArM's ADR database contains about 555,000 ADR reports from Germany up to the data lock point November, 22 2017. The majority of these ADR reports (69.8 %) were reported spontaneously (voluntary reporting), whereas 28.2 % were reported in studies. In 2.0 % it was unknown whether the ADR report originated from spontaneous reporting or from a study [25]. We restricted the present analysis to spontaneous reports for consistency and to avoid any bias through stimulated reporting. In the vast majority of these spontaneous reports a HCP (82.5 %) was involved in the reporting of the ADR. In contrast, in 15.6 % of the spontaneous reports a non-HCP reported (in 4.5 % both, a HCP and a non-HCP reported, and in 6.4 % the reporter was unknown).

In the database, drugs are coded according to the WHO Drug Dictionary [32] and the Anatomical Therapeutic Chemical (ATC) classification system [33]. ADRs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology [34]. Both terminologies include five different hierarchical levels for coding and, thus for the analysis of the reported drug substances and ADRs, respectively. The five hierarchical levels represent different levels of analysis with regard to granularity and specificity. In both the highest level of the terminology represents the analysis level of aggregated data (coarse-grained data) with lowest specificity. In contrast, the lowest level of the terminology represents the finer-grained analysis level with highest specificity.

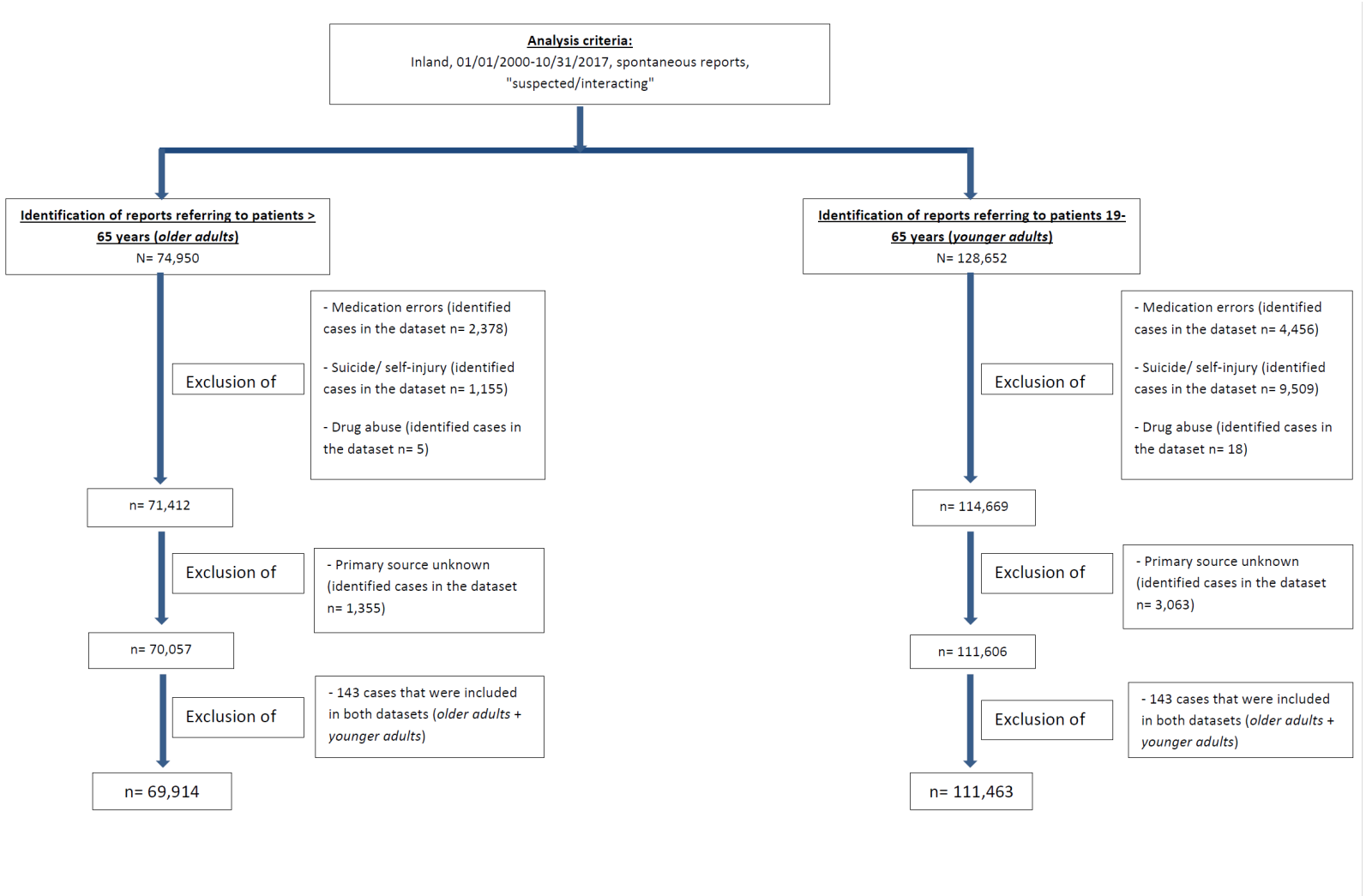
According to the legal definition an ADR is a noxious and unintended reaction caused by a medicinal product [35]. In 2012 the definition of an ADR was extended to the use outside the marketing authorisation including off-label use, overdose, misuse, abuse, and medication errors [36]. A more detailed description of the changes to the legal reporting obligation in the time period from 1987-2016 is published elsewhere [25]. The defined time period of our analysis covers both, the new and the old legal definition. For consistency, we restricted our analysis to ADRs associated with the intended use of a drug.

Identification of cases and reference group

We identified all spontaneous reports of ADRs referring to patients > 65 years ("*older adults*" aligned with the most frequently applied definition for older adult in developed

countries [37]), registered between 01/01/2000 – 10/31/2017, from Germany (n= 74,950) in which drugs were designated as "suspected/interacting" (Figure 1). All ADR reports coded as medication errors, intentional suicide/self-injury, or drug abuse were excluded by application of respective standardised MedDRA queries [25, 34] (n= 71,412). Subsequently, 1,355 cases with an unknown primary source were excluded (resulting in n= 70,057). In order to analyse i) if more ADR reports of *older adults* are contained in BfArM's ADR database, and ii) if some of the reported characteristics are more often reported in ADR reports of *older adults* a reference group with patients aged 19-65 years ("*younger adults*") was generated. For this reference group the same inclusion and exclusion criteria were used (n= 111,606). We excluded 143 cases contained in both datasets. Finally, the dataset *older adults* consisted of 69,914 reports whereas the dataset of *younger adults* included 111,463 reports.

Figure 1. Flowchart: identification of ADR reports for *older adults* and *younger adults*



Assessment of ADR reports with regard to quality of documentation and causal association

Due to the large sample size in our analysis (n=69,914 reports) it was not possible to assess each case individually. Instead, we assessed a random sample of 250 ADR reports of *older adults*. This random sample was drawn by using the sample function in R [38]. First, 15 of the randomly selected cases were assessed together by the three evaluators KJ (physician), BS (physician), and DD (pharmacist) in order to harmonise the application of the VigiGrade completeness score [39] and the WHO criteria [40].

VigiGrade evaluates the documentation quality of the ADR reports. A report with a completeness score higher than 0.8 is considered as well documented [39]. The WHO criteria were applied to assess the causal relationship between administration of the suspected drug substances and the ADR. After 50 cases had been assessed we calculated the mean completeness score and its standard deviation. Based on this result we estimated how many cases we would have to evaluate to achieve a completeness score of 0.8. According to this calculation a random sample of 250 cases was necessary. Therefore, we set the case number to 250 for our assessment of quality of documentation and causal association.

The calculation of the completeness score (VigiGrade, [39]) was, however, modified as it was not computed for every reported drug-ADR pair (in case more than one ADR had been reported) and then aggregated to an average, to yield an overall score for the corresponding report. Instead, the score was only calculated for the leading ADR [41].

Finally, the completeness score of our 250 randomly selected cases was 0.75 (95 % CI = [0.69-0.81]) with the upper limit of the confidence interval including 0.8. "Time to onset" was the most imprecise criterion (40.4 % of reports) due to the fact that it was not documented exactly (19.2 %) or was even missing (21.2 %).

The assessment of the causal relationship based on the WHO criteria [40] was chosen since it is an internationally used method and due to already existing experiences of the study team regarding its application. In 199/250 reports (79.6 %) the causal relationship was considered to be "at least possible" (i.e. 1.6 % (4/250) certain plus 22.0 % (55/250) probable plus 56.0 % possible (140/250). Hence, if the random sample was representa-

tive for the whole dataset, one could expect a dataset of well-documented cases in which about 80 % of the reported ADRs have an "at least possible" causal relationship.

Strategy of analysis

For each group we analysed the number of reports per year, demographic parameters, reported history, seriousness criteria, administration route of the applied drugs, the drugs most frequently reported as suspected together with their most frequently reported ADRs, and the 20 ADRs which were reported most often (irrespective of the drug concerned). Additionally, age-stratified analyses (age intervals: 66 - 75, 76 – 85, 86+) were performed in *older adults*.

In order to analyse the reported history, suitable hierarchy levels of the MedDRA code [34] were selected. According to the legal definition, an ADR was considered serious if it led to death, was life-threatening, required or prolonged hospitalisation, resulted in persistent or significant disabilities, and/or was a congenital anomaly/birth defect [42]. Hence, this classification of seriousness of the ADR report may differ from the clinical severity of the perceived ADR.

For an overview on drugs classes frequently suspected to cause an ADR, we performed the analysis on the second level of the ATC-code [32, 33] which is a more aggregated level (with lower specificity). Additionally, the drug substance level was selected for a more specific analysis. The ADRs reported most frequently overall and the ADRs associated with the most frequently reported drug classes and drug substances were analysed in both, *older* and *younger adults* on the preferred term (PT) level of the MedDRA code [34].

With regard to PIMS we analysed the number of respective ADR reports separately for *older adults*. For this purpose the PRISCUS list [18] was applied as it was the recommendation used presumably most often by physicians in Germany with regard to drug prescribing in older adults. However, the PRISCUS list was lastly revised in 2011. Hence, we also discuss (see discussion) the 10 drug classes and drug substances most frequently reported as suspected in *older adults* with regard to the recommendations of the Beers Criteria [19].

In general, in *older adults* 88,968 suspected drug substances and 206,666 ADRs (PT-level) were coded compared to 136,791 suspected drug substances and 338,046 ADRs (PT-level) in *younger adults*. Only 3.2 % and 1.7 % of the ADR reports for the *older adults* and *younger adults* were explicitly designated as "interacting". Hence, these ADR reports were not separately analysed in the context of this study.

The study was designed as a retrospective ADR database analysis which was linked to population-related data about inhabitants[23], assumed drug-exposed inhabitants [4], and DDD per insured person [24], and which incorporates a comparative analysis of ADR reports of *older adults* and *younger adults*.

Number of DDD per insured person

In order to describe the prescribing behaviours in Germany with rising age we extracted the number of defined daily doses (DDD) per insured person per age group for each of the years 2000-2016 in the German drug prescription reports [24]. Averages (+/-SD) of the mean number of DDD per insured person were calculated for the 16 years per age group. The average number of DDD per insured person of the 16 years per age group was divided by 365 days to calculate the mean number of DDD used per day per insured person per age group.

The drug prescription reports contain all outpatient drug prescriptions of statutory insured patients [24]. Hence, the drug prescription report covers about 80-90 % of the German population. The number of prescribed drugs is not patient-related and is available in DDD only. Further limitations refer to missing data on privately insured patients, over-the-counter (OTC) drug use, and inpatient treatments. There is also no exact data referring to the DDD per insured males/ females.

Number of inhabitants and assumed number of drug-exposed inhabitants

The exact number of drug-exposed inhabitants and drug-exposed males/ females in Germany is unknown as already described in the previous section [24]. Hence, data about the German population distributed by age and gender for each of the years 2000-

2016 (since data of 2017 were limited to October) was extracted from the GENESIS database of the Federal Statistical Office [23] to calculate reporting rates. First, averages (+/-SD) were calculated for the number of ADR reports divided by the number of inhabitants identified for the 16 years for i) each age group, and ii) each of the reported seriousness criteria in the age and gender-stratified analysis. The results are presented as the number of ADR reports per 100,000 inhabitants. However, not all inhabitants are exposed to medication and the proportion of drug exposure may vary between age and gender. Therefore, we estimated the number of assumed drug-exposed inhabitants and drug-exposed males/ females based on the number of German inhabitants and German males/ females per age group for each year multiplied by the proportion of drug-exposed patients published by a study about the medication use of German adults (DEGS1) [4]. In order to match the conditions of that study, the analysis was adapted to the period of the aforementioned study (2008-2011). Averages (+/-SD) were calculated for the number of ADR reports divided by the number of assumed drug-exposed inhabitants identified for each age group for each of the four years. The results are presented as the number of ADR reports per 100,000 assumed drug-exposed inhabitants. Both calculations were based on the date of the ADR report and not of the ADR. However, any inaccuracy would apply to all years, thus diminishing any effects.

Statistical analysis

Means and medians were calculated for the patients' age, the annual increase of ADR reports, and frequency distributions for all other results. The chi-squared test was applied to assess differences between the frequency distributions of the datasets for *older adults* and *younger adults*. P-values below 0.05 were considered statistically significant. Odds ratios with Bonferroni adjusted confidence intervals (CI) to account for multiple testing were calculated for demographic parameters, comorbidities, the drug classes and drug substances reported most often, the respective ADRs reported most frequently, and for the 20 ADRs reported most frequently, irrespective of the drug.

To analyse if the number of reports for *older adults* have increased proportionally to the number of reports for *younger adults* a ratio (*older adults*/*younger adults*) was calculated for each year.

Regression slopes for the number of ADR reports per 100,000 *older adults* and *younger adults* per year were estimated using linear regression analysis. In order to model the differences in the yearly increase of the slopes for ADR reports per 100,000 *older adults* vs. *younger adults,* an interaction effect between the number of ADR reports per 100,000 *younger adults* and years was included. Differences in the variances of the two groups were taken into account by weighting the observations in the linear model by inverse residuals.

Wilcoxon-Mann-Whitney test was used to detect differences in the medians of the number of ADR reports per 100,000 German males/ females for each age group.

All analyses were performed using R, version 3.3.3. The study was approved by the local ethics committee of the Medical Faculty of Bonn (009/17).

Results

Characteristics of the reports

Overall age groups more ADR reports referred to females than to males (absolute numbers, without any relation to inhabitants and drug-exposed inhabitants) (Table 1). The relative proportion was slightly higher in *younger adults* than in *older adults* (60.3 % vs. 55.9 %, OR 0.8 [0.8-0.9]), and increased with rising age within *older adults*.

The reports of *older adults* were more often designated as "serious" (83.9 % vs. 78.9 %; p<0.001) or "required or prolonged hospitalisation" (40.2 % vs. 32.7 %; <0.001), and were even 3 times more often designated as "fatal" (9.1 % vs. 3.4 %; <0.001) compared to the reports of *younger adults.*

More comorbidities were reported in *older adults* compared to *younger adults*. For instance, pre-existing vascular hypertensive disorders and renal disorders were mentioned in 24.5 % and 8.9 % of the reports from *older adults* compared to 9.2 % and 2.8 % of the reports from *younger adults* (OR 3.2 [3.1-3.3], OR 3.4 [3.2-3.6]) (Table 1). There were no substantial differences regarding either the oral or intravenous route of administration between *older adults* and *younger adults*.

Table 1. Demographic parameters, comorbidities and reported seriousness criteria in *younger versus older adults*.

	younger adults **(19-65) (n= 111,463)**	***older adults*** **(> 65) (n= 69,914)**	**OR [+/- adj. CI] *older* vs. *younger adults***	**patients aged 66-75 (n= 37,370)**	**OR [+/- adj. CI] patients aged 66-75 vs. *younger adults***	**patients aged 76-85 (n= 24,149)**	**OR [+/- adj. CI] patients aged 76-85 vs. *younger adults***	**patients aged ≥ 86 (n= 5,649)**	**OR [+/- adj. CI] patients aged ≥ 86 vs. *younger adults***
Demographic parameters									
mean age (+/- SD) (median, IQR) [yr][a]	46.4 (+/- 12.8) (48 [37-57])	75.4 (+/-7.2) (75 [70-80])	-	70.5 (+/- 2.8) (70 [68-73])	-	79.7 (+/- 2.7) (79 [77-82])	-	89.1 (+/- 2.9) (88 [87-91])	-
female	60.3 % (67,249)	55.9 % (39,065)	0.8 [0.8-0.9]*	52.8 % (19,731)	0.7 [0.7-0.8]*	58.2 % (14,049)	0.9 [0.9-0.9]*	68.3 % (3,861)	1.4 [1.3-1.5]*
male	38.4 % (42,824)	43.2 % (30,230)		46.4 % (17,355)		41.0 % (9,907)		30.9 % (1,744)	
(un-known)	(1.2 % (1,390))	(0.9 % (619))		(0.8 % (284))		(0.8 % (193))		(0.8 % (44))	
Reported patients' history									
hyperten-sion[b]	9.2 % (10,302)	24.5 % (17,105)	3.2 [3.1-3.3]*	22.8 % (8,538)	2.9 [2.8-3.1]*	27.5 % (6,652)	3.7 [3.5-3.9]*	28.0 % (1,583)	3.8 [3.5-4.2]*
cardiac disorders[c]	7.3 % (8,180)	24.5 % (17,163)	4.1 [3.9-4.3]*	20.8 % (7,776)	3.3 [3.2-3.5]*	29.5 % (7,115)	5.3 [5.0-5.6]*	33.6 % (1,898)	6.4 [5.8-7.0]*
diabetes [d]	4.3 % (4,830)	11.2 % (7,837)	2.8 [2.6-3.0]*	10.8 % (4,047)	2.7 [2.5-2.9]*	12.5 % (3,012)	3.2 [2.9-3.4]*	11.4 % (643)	2.8 [2.5-3.3]*
renal disorders[e]	2.8 % (3,138)	8.9 % (6,224)	3.4 [3.2-3.6]*	7.1 % (2,670)	2.7 [2.4-2.9]*	11.0 % (2,646)	4.3 [3.9-4.6]*	13.4 % (759)	5.4 [4.7-6.1]*
hepatic impair-ments[f]	3.3 % (3,669)	2.5 % (1,765)	0.8 [0.7-0.8]*	2.9 % (1,068)	0.9 [0.8-1.0]	2.4% (569)	0.7 [0.6-0.8]*	1.6 % (90)	0.5 [0.3-0.7]*

Reported Seriousness criteria									
serious [g]	78.9 % (87,954)	83.9 % (58,681)	1.4 [1.3-1.5]*	82.1 % (30,669)	1.2 [1.2-1.3]*	84.8 % (20,482)	1.5 [1.4-1.6]*	88.2 % (4,982)	2.0 [1.8-2.3]*
death [g]	3.4 % (3,755)	9.1 % (6,340)	2.9 [2.7-3.0]*	6.9 % (2,595)	2.1 [2.0-2.3]*	10.6 % (2,570)	3.4 [3.2-3.7]*	15.7 % (886)	5.3 [4.7-6.0]*
hospitali-zation [g]	32.7 % (36,460)	40.2% (28,094)	1.4 [1.3-1.4]*	37.8 % (14,131)	1.3 [1.2-1.3]*	43.4 % (10,490)	1.6 [1.5-1.7]*	46.1 % (2,603)	1.8 [1.6-1.9]*
life-threaten-ing [g]	8.2 % (9,171)	11.9 % (8,332)	1.5 [1.4-1.6]*	11.3 % (4,223)	1.4 [1.3-1.5]*	13.1 % (3,172)	1.7 [1.6-1.8]*	14.6 % (825)	1.9 [1.7-2.1]*
disabling [g]	2.7 % (3,020)	3.0 % (2,118)	1.1 [1.0-1.2]	3.2 % (1,179)	1.2 [1.1-1.3]*	3.0 % (731)	1.1 [1.0-1.3]	2.7 % (151)	1.0 [0.8-1.3]

*: OR=1 is not included; OR > 1 reported more often in *older adults* or the stratified age groups; OR < 1 reported more often in *younger adults*.

[a] in some cases only the age group (e.g. 7. decade; *older adults* (> 65)) and not the exact age of the patient was reported. If so, these patients were not included in the calculation of the average and median age for *older adults*, *younger adults*, and stratified age groups.

[b) -f)] Suitable hierarchical levels of the MedDRA terminology were chosen for the analysis of the reported patients' history [25]. b) High Level Group Term vascular hypertensive disorder; c) System organ class cardiac disorders; d) High level term diabetes mellitus including subtypes; e) High Level Group Term renal disorders exclusive nephropathies; f) High Level Group Term hepatic and hepatobiliary disorders.

[g] According to the legal definition an ADR was considered serious if it led to death, was life-threatening, required or prolonged hospitalisation, resulted in persistent or significant disabilities, and/or was a congenital anomaly/birth defect [42].

Table 1 shows the absolute numbers of ADR reports and the calculated odds ratios with Bonferroni adjusted confidence intervals for the demographic parameters, the reported comorbidities and the reported seriousness criteria of the patients. The dataset *younger adults* served as a reference for the calculation of the odds ratios. One ADR report may inform about more than one comorbidity and seriousness criteria. Hence, the number of reported comorbidities and seriousness criteria may exceed the number of ADR reports.

Annual number of ADR reports (absolute numbers)

The number of ADR reports contained in the ADR database (absolute numbers, without any relation to inhabitants and assumed drug-exposed inhabitants) increased from 2000-2016 for *younger adults* and *older adults* with an annual mean increase of 177 and 165 ADR reports, respectively. The calculated ratio of ADR reports for *older adults*/*younger adults* slightly increased from 0.4 in the year 2000 to 0.7 in the year 2017 (mean ratio for the time period 2000-2017: 0.6; range: 0.4-0.8). The age-stratified mean increase of the number of ADR reports per year for the age groups 66-75 years and 76-85 years was approximately the same (both 66 reports/year), while it was notably lower for the age group 86+ years (15 reports/year) (see Supplementary Figure 1 and Supplementary Table 1, Additional File 1).

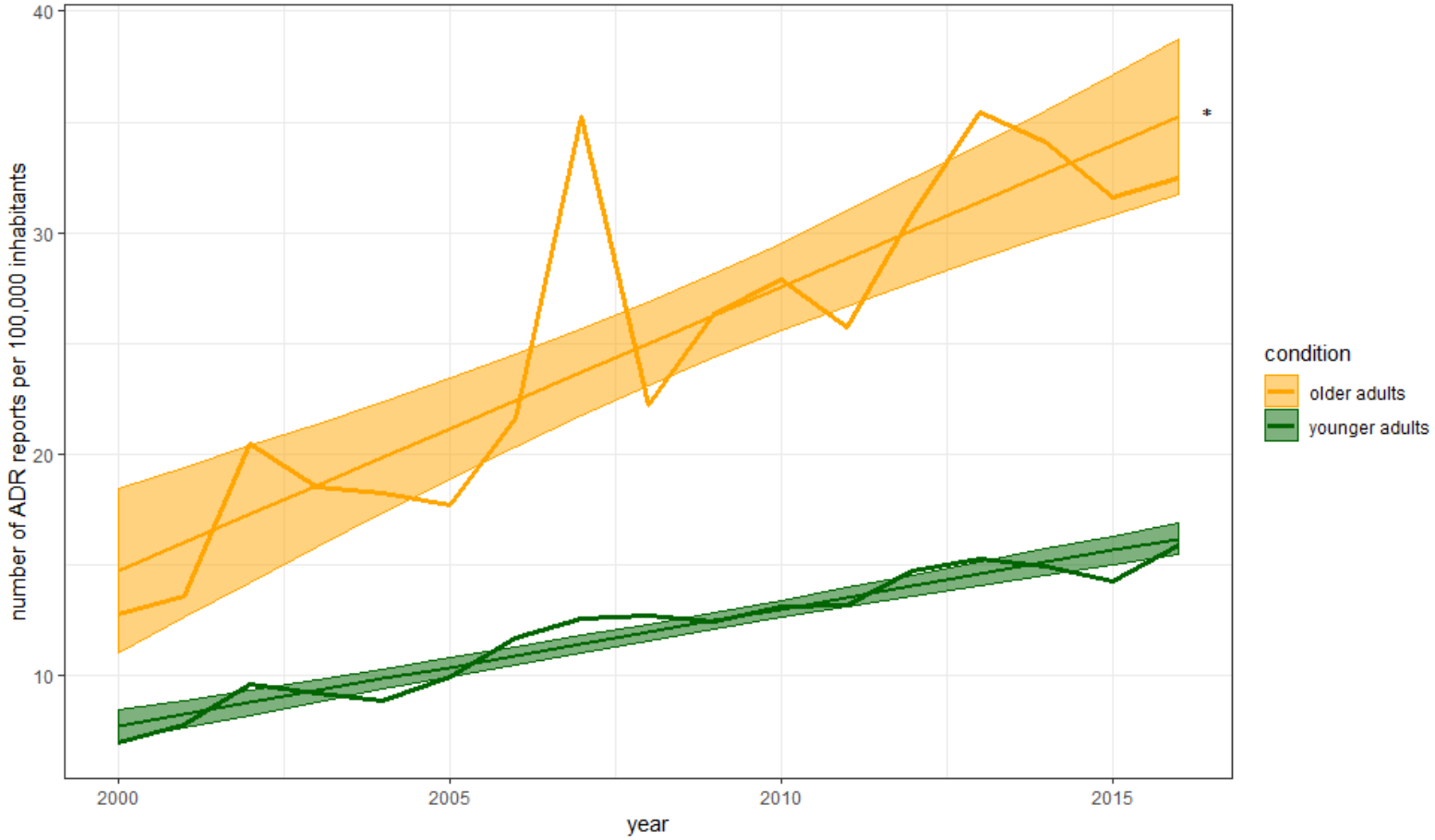
Number of reports in relation to inhabitants, assumed drug-exposed inhabitants, and DDD per insured person

The annual number of ADR reports for *older adults* and *younger adults* per 100,000 inhabitants increased from 2000 (12.7 and 6.9) to 2016 (32.6 and 15.8) (Figure 2). Analysis of the regression slopes revealed a significantly larger increase in *older adults* (p-value for interaction effect < 0.001). Across eight age groups the average number of ADR reports/100,000 inhabitants was highest for the age groups 66-75, 76-84, and 85+ (Figure 3). This finding remained stable if the number of reports was related to the assumed proportion of drug-exposed inhabitants in the respective age group (see Supplementary Document 1, Additional File 2). Notably, the average number of DDD per insured person per age group increased from the youngest age group (25-34) to the age group 75-84 (Figure 4). The youngest age group (25-34) used on average 0.3 DDD per insured person per day in contrast to 3.8 DDD per insured person for the age group 75-84.

If the number of ADR reports was set in context to inhabitants and exposure more reports referred to males for the age groups > 65 years per 100,000 inhabitants and for the age group > 70 years per 100,000 drug-exposed inhabitants (see Figure 3 and Supplementary Document 1 Additional File 2). In relation to the number of inhabitants, slight-

ly more ADR reports for all of the reported seriousness criteria were observed for males (Table 2).

Figure 2. Number of ADR reports per 100,000 younger/older German inhabitants per year.

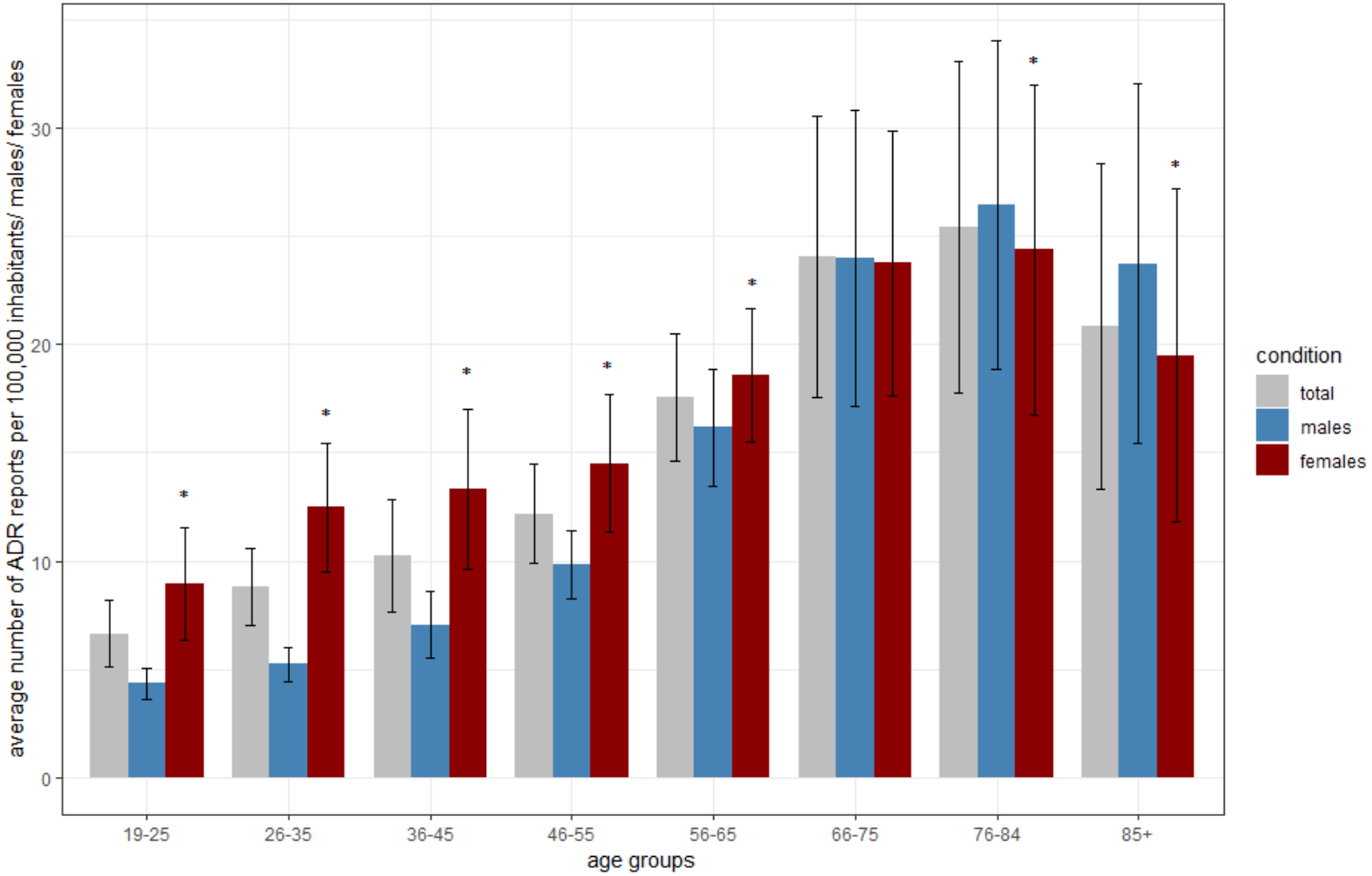


*interaction test of the slopes: p < 0.001; slope *older adults*: 1.3 [0.9-1.7]; slope *younger adults*: 0.5 [0.5-0.6].

Figure 2 shows the number of ADR reports for *younger adults* per 100,000 German inhabitants (19-65) and the number of ADR reports for *older adults* per 100,000 German inhabitants (> 65) [23] per year. The increases in the number of ADR reports for *older adults* and *younger adults* are presented as weighted linear regression slopes. There was a significant higher increase of the slope for the number of reports per 100,000 older adults than per 100,000 younger adults ($p < 0.001$).

The obvious higher number of ADR reports for *older adults* in 2007 is mainly due to reports for rofecoxib (withdrawn in 2004). Roughly 30.0 % of these ADR reports in 2007 referred to rofecoxib as suspected drug substance compared to 5.2 % of the reports for *younger adults*. About 98.7 % of the reports concerning rofecoxib in 2007 were reported by lawyers. Hence, the delayed increase of the number of ADR reports referring to rofecoxib may likely be due to lawsuit after its withdrawal. The limitations of both data sources have to be considered [23; 25].

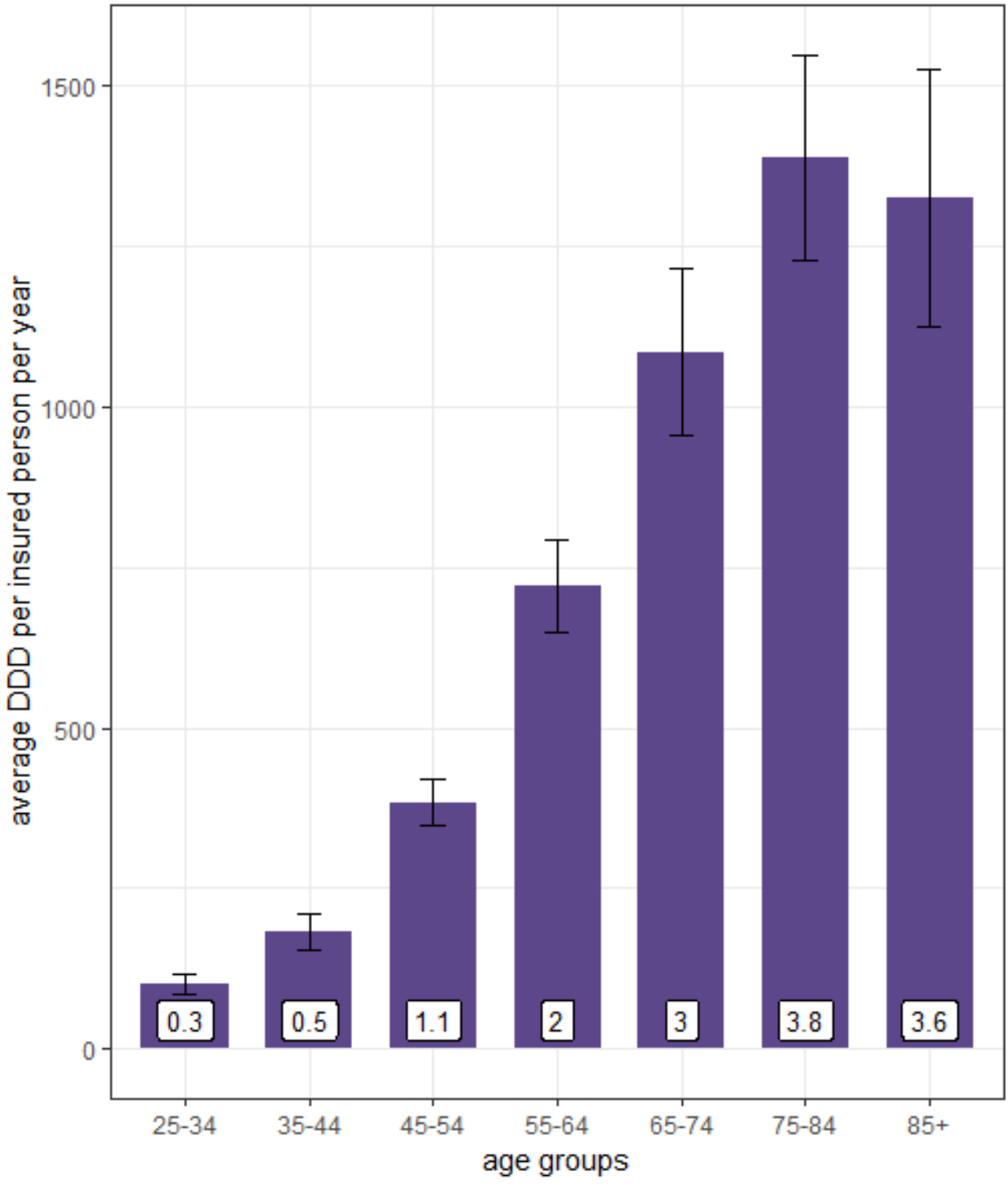
Figure 3. Average number of ADR reports per 100,000 German inhabitants distributed by age and gender.



*Wilcoxon-Mann-Whitney test < 0.05

The figure 3) shows the average number (+/- SD) of ADR reports per 100,000 German inhabitants distributed by age and gender [23]. The age groups were adapted for this analysis since inhabitants older than 85 years could not be stratified further in the database queried. All ADR reports (male, female and unknown gender) were considered for the calculation of the total average number of spontaneous reports per 100,000 inhabitants (grey bars). Thus, the grey bars possibly do not lie exactly in the middle between the blue and red bars for males and females.

Figure 4. Average number of DDD per insured person.



*Wilcoxon-Mann-Whitney test < 0.05

Figure 4) shows the average (+/- SD) of DDD per insured person per age group per year [24]. The mean DDD per day was inserted at the bottom of the bars for each age group. The data stemmed from the German drug prescription reports for the years 2001-2017.

The defined age groups of the drug prescription reports were adapted for this analysis since they did not match the defined age groups of the ADR database analysis

Defined daily dose (DDD): The DDD is based on the amount of active substances or medicinal product that should typically be used for the main indication per day. The DDD does not necessarily reflect the recommended or actual administered dose of a drug substance or medicinal product. It mainly provides a technical means of measurement and comparison [24].

Table 2) Reported seriousness criteria per 100,000 inhabitants in the stratified age groups.

	patients aged 66-75 years (n= 37,370)	**patients aged 76-84 years (n= 22,761)**	**patients aged ≥ 85 years (n= 7,036)**
ADR reports per 100,000 inhabitants			
female	23.7 (+/- 6.1)	24.4 (+/- 7.6)	19.5 (+/- 7.7)
males	24.0 (+/- 6.8)	26.4 (+/- 7.6)	23.7 (+/- 8.3)
ADR reports "serious" per 100,000 inhabitants			
female	19.2 (+/- 6.2)	20.6 (+/- 8.0)	17.2 (+/- 8.0)
male	20.1 (+/- 6.5)	22.8 (+/- 7.7)	21.0 (+/- 8.1)
ADR reports "death" per 100,000 inhabitants			
female	1.4 (+/- 0.6)	2.4 (+/- 1.6)	3.0 (+/- 3.2)
male	2.0 (+/- 0.6)	3.0 (+/- 1.2)	3.5 (+/- 2.4)
ADR reports "hospitalization" per 100,000 inhabitants			
female	8.8 (+/- 2.6)	10.6 (+/- 4.9)	9.6 (+/- 5.2)
male	9.6 (+/- 2.6)	11.7 (+/- 4.0)	10.9 (+/- 3.9)
ADR reports "life-threatening" per 100,000 inhabitants			
female	2.5 (+/- 0.8)	3.3 (+/- 1.5)	3.1 (+/- 2.2)
male	3.2 (+/- 0.9)	3.7 (+/- 1.3)	3.5 (+/- 1.8)

Table 2) shows the average number (+/- SD) of ADR reports per 100,000 German inhabitants distributed by gender and reported seriousness criteria. The age groups were adapted for this analysis since inhabitants older than 85 years could not be stratified further in the database queried [23]. One ADR report may inform about more than one seriousness criteria. Hence, one ADR reports can be assigned to several seriousness criteria.

Most frequently suspected drug classes and drug substances

The analysis of the drug **classes** reported most often as suspected (second level ATC-code) (Table 3.1) yielded that antithrombotics were reported almost 5 times more often in *older adults* compared to *younger adults* (1st rank; 19.8 % of *older adults*; OR 4.6 [4.3-4.9]). Likewise, among the ten drug **substances** most often suspected in *older adults*, there were six antithrombotics (acetylsalicylic acid was mostly used as an anti-platelet agent, Table 3.2). Three of the ten drug **classes** (Table 3.1) are used for the treatment of nervous system disorders (6th rank psychoanaleptics, 7th rank psycholeptics, and 10th rank analgesics). Antineoplastic agents ranked 2nd, and antiphlogistics and antirheumatics ranked 3rd.

In contrast, psycholeptics were the drug **class** most frequently reported in *younger adults* (10.0 % of the reports; OR 0.4 [0.4-0.5], Table 3.1). Likewise, four of the ten drug **substances** most frequently suspected within the reports for *younger adults* were antipsychotics (only one being an antithrombotic; rivaroxaban ranking 10th) (Table 3.2).

Only 3,611 (4.1 % of 88,968) suspected drug substances reported in *older adults* were PIMs according to the PRISCUS list. Olanzapine was the most often reported PIM in *older adults* (45th rank in *older adults* with 0.5 % of *older adults* reports) (see Supplementary Table 2, Additional File 3). In contrast, olanzapine ranked fourth in the reports of *younger adults* (Table 3.2).

Table 3.1. The ten drug classes (with their drug substances and ADRs) most frequently suspected in *older adults* and *younger adults*.

rank	*older adults* (> 65) % most frequently reported drug classes (number of reports) [(%) three most frequently reported suspected drug substances within the respective drug class]	OR [+/- 95 % adj. CI] *older* vs. *younger adults*	% three most frequently reported ADRs (number of reports) within the respective drug class	OR [+/- 95 % adj. CI] of reported ADRs *older* vs. *younger adults*
1.	19.8 % (13,831) antithrombotic agents (B01) [32.0 % rivaroxaban, 12.7 % phenprocoumon, 11.8 % acetylsalicyclic acid]	4.6[4.3-4.9]*	7.6 % (1,051) gastrointestinal haemorrhage 5.9 % (812) cerebral haemorrhage 4.9 % (677) haemorrhage	2.3[1.7-2.9]* 2.3[1.7-3.1]* 1.3[1.0-1.7]
2.	9.1 % (6,336) antineoplastic agents (L01) [7.4 % paclitaxel, 6.1 % oxaliplatin, 5.6 % imatinib]	1.3[1.2-1.3]*	7.3 % (463) dyspnea 6.8 % (428) diarrhoea 5.9 % (375) nausea	1.0[0.8-1.2] 1.4[1.1-1.8]* 1.2[0.9-1.5]
3.	6.9 % (4,831) antiphlogistics and antirheumatics (M01) [46.6 % rofecoxib, 17.1 % diclofenac, 9.3 % ibuprofen]	1.7[1.6-1.8]*	16.5 % (797) hypertension 15.5 % (748) cerebral infarction 12.2 % (588) death	2.9[2.3-3.6]* 6.3[4.6-8.7]* 13.3[8.0-21.9]*
4.	6.4 % (4,454) systemic antibiotics (J01) [15.6 levofloxacin, 13.7 % ciprofloxacin, 11.4 % moxifloxacin]	0.8[0.8-0.9]*	9.1 % (406) diarrhea 5.0 % (221) nausea 4.9 % (218) pruritus	1.2[0.9-1.4] 0.7[0.5-0.9]* 0.6[0.5-0.8]*
5.	6.0 % (4,225) agents acting on the renin-angiotensin system (C09) [19.5 % ramipril, 9.5 % enalapril, 7.9 % valsartan]	2.2[2.0-2.4]*	8.1 % (344) angioedema 8.0 % (340) dizziness 5.4 % (230) nausea	0.9[0.6-1.2] 1.1[0.8-1.4] 1.0[0.7-1.4]
6.	4.7 % (3,273) psycholanaleptics (N06) [15.0 % mirtazapine, 10.6 % venlafaxine, 9.9 % rivastigmin]	0.7[0.7-0.8]*	8.5 % (279) hyponatraemia 6.7 % (218) dizziness 6.6 % (217) nausea	6.9[4.6-10.3]* 1.2[0.9-1.5] 1.1[0.9-1.5]
7.	4.5 % (3,138) psycholeptics (N05) [22.8 % risperidone, 11.9 % quetiapine, 11.4 % olanzapine]	0.4[0.4-0.5]*	6.0 % (188) drug interaction 5.1 % (161) somnolence 4.0 % (125) parkinsonism	1.6[1.2-2.2]* 2.3[1.6-3.3]* 1.8[1.2-2.6]*
8.	4.0 % (2,764) lipid modifying agents (C10) [33.5 % simvastatin, 23.9 % atorvastatin, 11.9 % fluvastatin]	1.2[1.1-1.3]*	22.7 % (628) myalgia 13.4 % (370) blood creatine phosphokinase increased 12.9 % (356) rhabdomyolysis	0.6[0.5-0.8]* 0.8[0.6-1.0] 1.9[1.4-2.5]*

9.	3.9 % (2,747) antidiabetics (A10) [19.5 % metformin, 17.0 % insulin human, 8.5 % glibenclamid]	1.5[1.4-1.7]*	21.5% (590) hypoglycaemia 7.2 % (198) lactic acidosis 5.9 % (161) nausea	2.4[1.8-3.0]* 2.8[1.7-4.3]* 0.9[0.6-1.3]
10.	3.7 % (2,581) analgesics (N02) [25.2 % metamizole, 14.8 % fentanyl, 9.0 % tramadol]	1.0[0.9-1.1]	10.0 % (259) nausea 6.9 % (177) vomiting 6.2 % (161) agranulocytosis	1.0[0.7-1.3] 1.3[0.9-1.8] 1.0[0.7-1.5]
rank	***younger adults* (19-65) % most frequently reported drug classes (number of reports) [(%) three most reported frequently suspected drug substances within the respective drug class]**	**OR [+/- 95 % adj. CI] *older* vs. *younger adults***	**% three most frequently reported ADRs (number of reports) within the respective drug class**	**OR [+/- 95 % adj. CI] of reported ADRs *older* vs. *younger adults***
1.	10.0 % (11,126) psycholeptics (N05) [16.8 % clozapine, 16.7 % risperidone, 15.7 % olanzapine]	0.4[0.4-0.5]*	6.0 % (670) weight increased 3.8 % (426) drug interaction 3.6 % (398) leukopenia	0.1[0.1-0.3]* 1.6[1.2-2.2]* 0.8[0.5-1.2]
2.	7.5 % (8,400) systemic antibiotics (J01) [13.1 % moxifloxacin, 11.5 % clindamycin, 11.4 ciprofloxacin]	0.8[0.8-0.9]*	8.0 % (672) rash 7.9 % (667) diarrhoea 7.9 % (667) pruritus	0.6[0.4-0.8]* 1.2[0.9-1.4] 0.6[0.5-0.8]*
3.	7.4 % (8,225) antineoplastic agents (L01) [11.6 % paclitaxel, 6.5 % docetaxel, 6.5 % oxaliplatin]	1.3[1.2-1.3]*	7.3 % (601) dyspnea 5.4 % (441) pyrexia 5.1 % (416) nausea	1.0[0.8-1.2] 1.0[0.8-1.3] 1.2[0.9-1.5]
4.	6.4 % (7,188) psychoanaleptics (N06) [15.6 % venlafaxine, 12.4 % mirtazapine, 9.8 % duloxetine]	0.7[0.7-0.8]*	5.9 % (423) nausea 5.8 % (417) dizziness 4.8 % (344) drug interaction	1.1[0.9-1.5] 1.2[0.9-1.5] 1.2[0.9-1.7]
5.	5.1 % (5,689) immunostimulants (L03) [25.0 % interferon, 22.4 % glatiramer, 21.9 % interferon beta-1a]	0.1[0.1-0.1]*	18.0 % (1,022) multiple sclerosis relapse 4.7 % (266) pyrexia 4.6 % (260) dyspnoea	0.1[0.0-0.3]* 1.8[1.0-3.4] 0.7[0.3-1.8]
6.	5.1 % (5,676) antithrombotic agents (B01) [20.6 % rivaroxaban, 13.5 % phenprocoumon, 9.9 % enoxaparin]	4.6[4.3-4.9]*	6.5 % (367) thrombocytopenia 6.3 % (358) pulmonary embolism 3.7 % (211) haemorrhage	0.7[0.5-0.8]* 0.4[0.3-0.5]* 1.3[1.0-1.7]
7.	4.9 % (5,515) immunosupressivs (L04) [28.7 % etanercept, 15.6 % fingolimod, 13.1 % ciclosporin]	0.6[0.5-0.6]*	4.4 % (243) multiple sclerosis relapse 3.4 % (189) diarrhoea 3.4 % (186) nausea	0.0[0.0-0.2]* 0.8[0.5-1.4] 0.8[0.5-1.4]
8.	4.8 % (5,323) sex hormones (G03)	0.1[0.1-0.1]*	11.1 % (590) pulmonary embolism	0.5[0.3-1.1]

	[12.9 % dienogest/ethyinylestradiol, 11.6 % drospirenone/ethinylestradiol, 7.5 % ethinylestradiol/levonorgestrel]		8.2 % (438) deep vein thrombosis 5.2 % (279) unintended pregnancy	0.4[0.2-1.1] -
9.	4.7 % (5,228) antiepileptics (N03) [16.5 % carbamazepine, 15.6 % levetiracetam, 15.3 % pregabalin]	0.6[0.5-0.6]*	7.5 % (392) seizure 5.1 % (266) dizziness 4.9 % (257) hyponatriaemia	0.6[0.4-0.9]* 1.7[1.2-2.4]* 1.3[0.9-1.8]
10.	4.3 % (4,740) antiphlogistics and antirheumatics (M01) [22.6 % rofecoxib, 19.2 % diclofenac, 18.4 % ibuprofen]	1.7[1.6-1.8]*	6.5 % (306) hypertension 6.1 % (287) nausea 5.7 % (269) dizziness	2.9[2.3-3.6]* 0.7[0.5-1.0] 0.7[0.5-0.9]*

*OR=1 is not included; OR > 1 reported more often in *older adults*; OR < 1 reported more often in *younger adults*

Table 3.1 shows the relative and absolute numbers of ADR reports for the ten drug **classes** reported most frequently as suspected in *older adults* (> 65) and *younger adults* (19-65), with their three most frequently suspected *drug substances* in relative numbers, and the three most frequently reported ADRs within the respective drug class in relative and absolute numbers. For the analysis of the drug classes the second level, and for the analysis of the drug substances the fifth level of the ATC-code was applied [24]. For the analysis of ADRs reported most frequently the PT-level of the MedDRA terminology [25] was used. One ADR report can contain several drug substances and classes as suspected (hence, multiple assignment of one report to more than one drug class is possible) and inform about several ADRs. Therefore, the number of drug substances and ADRs exceeds the number of ADR reports. The table presents the most frequently reported ADRs within the respective drug class independent of the applied drug substance. Hence, the three most frequently reported ADRs related to the respective drug class may not necessarily be identical to the three most often reported drug substances of the respective drug class.

Different drug substances belonging to the same respective drug class may account for the discrepancies in ADRs between *older adults* and *younger adults*. For example, "thrombocytopenia" as the ADR most often reported in *younger adults* for the drug class antithrombotics was due to heparin administration in 44.9 % of the "thrombocytopenia" cases. Likewise, "pulmonary embolism" was due to certoparin administration in 29.6 % of the "pulmonary embolism" cases in *younger adults*. However, rivaroxaban accounted for only 3.3 % of these "thrombocytopenia" cases and 15.9 % of these "pulmonary embolism" cases although it was the drug substance suspected most often for *younger adults* among the drug class of antithrombotics. In *older adults* rivaroxaban was also the most frequently

reported drug substance in the drug class of antithrombotics and accounted for 26.9 % of all "gastrointestinal haemorrhage" cases, and was the most reported drug substance in "cerebral haemorrhage", and "haemorrhage" cases.

Table 3.2. The ten drug substances (with their ADRs) most frequently reported as suspected in *older adults* and *younger adults*.

rank	*older adults* (> 65) % most frequently reported drug substances (number of reports)	OR [+/- 95 % adj. CI] *older* vs. *younger adults*	% three most frequently reported ADRs (number of reports)	OR [+/- 95 % adj. CI] of reported ADRs *older* vs. *younger adults*
1.	6.3 % (4,425) rivaroxaban	6.4[5.7-7.0]*	7.8 % (346) epistaxis 6.9 % (307) cerebral haemorrhage 5.8 % (257) haemoglobin decreased	2.2[1.3-3.9]* 3.6[1.7-7.3]* 1.5[0.9-2.6]
2.	3.2 % (2,253) rofecoxib	3.4[3.1-3.8]*	32.8 % (739) cerebral infarction 32.0 % (721) hypertension 25.3 % (571) death	3.6[2.6-5.2]* 1.7[1.3-2.3]* 8.5[4.9-14.9]*
3.	2.5 % (1,763) acetylsalicylic acid	3.9[3.4-4.4]*	18.3 % (323) gastrointestinal haemorrhage 12.4 % (218) melaena 9.4 % (165) gastric ulcer haemorrhage	1.4[0.9-2.2] 1.0[0.7-1.6] 1.2[0.7-2.1]
4.	2.5 % (1,762) phenprocoumon	3.7[3.3-4.3]*	13.3 % (235) gastrointestinal haemorrhage 9.0 % (158) drug interaction 8.9 % (157) prothrombin time prolonged	1.9[1.1-3.2]* 1.4[0.8-2.4] 0.8[0.5-1.3]
5.	2.3 % (1,635) apixaban	9.1[7.5-11.0]*	7.6 % (125) cerebral haemorrhage 7.3 % (120) haemorrhage 6.6 % (108) off label use	2.3[0.8-7.2] 2.0[0.7-5.9] 1.4[0.5-3.7]
6.	2.0 % (1,427) dabigatran	10.6 [8.5-13.3]*	10.3 % (147) gastrointestinal haemorrhage 7.9 % (113) cerebrovascular accident 6.9 % (99) haemorrhage	2.0[0.7-5.5] 0.7[0.3-1.5] 1.0[0.4-2.6]
7.	1.6 % (1,118) diclofenac	1.6[1.4-1.8]*	10.0 % (112) gastrointestinal haemorrhage 6.9 % (77) pruritus 6.5 % (73) nausea	3.0[1.6-5.6]* 0.6[0.4-1.0] 0.9[0.5-1.6]
8.	1.5 % (1,067) zoledronic acid	2.0[1.8-2.3]*	47.8 % (510) osteonecrosis of jaw 11.1 % (118) osteonecrosis 9.7 % (104) tooth extraction	1.0[0.8-1.4] 0.7[0.4-1.1] 0.7[0.4-1.1]
9.	1.4 % (956) clopidogrel	3.9[3.2-4.6]*	12.0 % (115) gastrointestinal haemorrhage	2.1[1.0-4.7]

			6.5 % (62) thrombocytopenia 5.0 % (48) anaemia 5.0 % (48) melaena	0.9[0.4-1.8] 1.2[0.5-3.1] 0.9[0.4-2.1]
10.	1.3 % (925) simvastatin	1.6[1.4-1.9]*	19.7 % (182) myalgia 18.8 % (174) rhabdomyolysis 15.5 % (143) blood creatine phosphokinase increased	0.4[0.3-0.6]* 1.8[1.2-2.8]* 0.8[0.5-1.1]
rank	***younger adults* (19-65)** **% most frequently reported drug substances (number of reports)**	**OR [+/- 95 % adj. CI] *older* vs. *younger adults***	**% three most frequently reported ADRs (number of reports)**	**OR [+/- 95 % adj. CI] of reported ADRs *older* vs. *younger adults***
1.	2.9 % (3,232) levonorgestrel	0	14.0 % (451) uterine perforation 13.7 % (444) device dislocation 12.2 % (395) pregnancy with contraceptive device	- - -
2.	1.7 % (1,868) clozapine	0.2[0.1-0.2]*	10.9 % (204) pyrexia 10.1 % (189) leukopenia 8.1 % (152) c-reactive protein increased	1.6[0.8-3.1] 1.4[0.7-2.8] 0.8[0.3-2.1]
3.	1.7 % (1,856) risperidone	0.6[0.5-0.7]*	7.0 % (129) weight increased 6.6 % (122) galactorrhoea 6.0 % (111) akathisia	0.2[0.1-0.5]* 0.0[0.0-0.6]* 0.3[0.1-0.8]*
4.	1.6 % (1,749) olanzapin	0.3[0.3-0.4]*	15.6 % (273) weight increased 5.3 % (93) blood creatine phosphokinase increased 5.0 % (87) alanine aminotransferase increased	0.1[0.0-0.4]* 0.7[0.2-1.8] 0.1[0.0-1.6]
5.	1.4 % (1,585) etanercept	0.7[0.6-0.8]*	7.4 % (118) condition aggravated 6.5 % (103) rheumatoide arthritis 4.9 % (78) drug ineffective	0.9[0.5-1.6] 1.6[0.9-2.7] 0.8[0.4-1.7]
6.	1.3 % (1,420) interferon	0.1[0.1-0.1]*	20.8 % (295) multiple sclerosis relapse 4.4 % (63) pyrexia 3.8 % (54) headache	0.1[0.0-0.9]* 1.0[0.2-5.7] 0.3[0.0-8.3]
7.	1.1 % (1,272) glatiramer	0.02[0.01-0.04]*	23.0 % (293) multiple sclerosis relapse 11.2 % (142) dyspnea	0.3[0.0-9.1] -

			7.1 % (90) injection site necrosis	1.1[0.0-36.1]
8.	1.1 % (1,258) quetiapine	0.5[0.4-0.6]*	7.7 % (97) drug interaction	1.3[0.6-2.5]
			7.7 % (97) weight increased	0.1[0.0-0.7]*
			6.0 % (76) leukopenia	0.5[0.2-1.4]
9.	1.1 % (1,243) Interferon beta 1a	0.03[0.02-0.06]*	19.4 % (241) multiple sclerosis relapse	0.5[0.1-4.3]
			8.4 % (104) influenza like illness	0.4[0.0-13.5]
			4.8 % (60) alanine aminotransferase increased	1.6[0.1-20.0]
10.	1.1 % (1,173) rivaroxaban	6.4[5.7-7.0]*	8.7 % (102) menorrhagia	0.0[0.0-0.1]*
			5.5 % (65) deep vein thrombosis	0.3[0.2-0.5]*
			5.1 % (60) pulmonary embolism	0.4[0.2-0.6]*

*OR=1 is not included; OR > 1 reported more often in *older adults*; OR < 1 reported more often in *younger adults*

Table 3.2 shows the relative and absolute numbers of ADR reports of the ten **drug substances** most frequently reported as suspected in *older adults* (> 65) and *younger adults* (19-65) with their relative and absolute numbers of the three most frequently reported ADRs. For the drug substances the fifth level of the ATC-code was applied [24]. For the analysis of ADRs reported most frequently the PT-level of the MedDRA terminology [25] was used. One ADR report can contain several drug substances as suspected and inform about several ADRs. Therefore, the number of drug substances and ADRs exceeds the number of ADR reports. Since we did not perform an individual case assessment for all ADR reports (e.g. with regard to the causal association with the drug intake), it cannot be excluded that the most frequently reported ADRs may also stand in a causal relation to other drug substances that were also reported as suspected within the ADR report. However, one may assume that the three most frequently reported ADRs are more likely to be causally related to the listed drug substance since they are reported so often.

Most frequently reported ADRs

There is broad consistency along with some differences concerning the 20 ADRs reported most frequently in *older adults* and *younger adults* irrespective of the suspected drug substance (see Supplementary Table 3, Additional File 4). In the top ranks of both, mainly unspecific ADRs ("nausea", "dizziness", "dyspnoea", "diarrhoea", "pruritus", "vomiting", "rash", "headache") are listed. Interestingly, those mainly unspecific ADRs were less often reported in patients older than 86 years (see Supplementary Table 3, Additional File 4). The highest odds ratios (and thus more frequently reported in *older adults* compared to *younger adults*) were observed for "gastrointestinal haemorrhage" (15th rank; OR 5.1 [4.2-6.1]), "death" (9th rank; OR 3.8 [3.3-4.4]), "fall" (18th rank; OR 3.0 [2.6-3.6]), and "cerebrovascular accident" (19th rank; OR 3.0 [2.6-3.6]). Conversely, for *younger adults* the lowest odds ratios compared to *older adults* (and thus being more reported in *younger adults*) were found for "urticaria" (12th rank; OR 0.5 [0.4-0.5]), "paraesthesia" (19th rank; OR 0.5 [0.4-0.6]), and "hepatic enzyme increased" (18th rank; OR 0.6 [0.5-0.7]). The calculated odds ratios for "death", "gastrointestinal haemorrhage", "fall", "cerebrovascular accident", "cerebral infarction", "syncope", "cerebral haemorrhage", and "haemoglobin decreased" increased with rising age. It should be noted though, that "death" itself is not an ADR but an outcome coded by MedDRA terminology [25].

Drug classes reported as suspected most frequently and their ADRs

The ADRs reported most frequently differed for some drug **classes** between *older adults* and *younger adults*. This becomes obvious with antithrombotics, psychoanaleptics, and psycholeptics (Table 2.1). For instance, for antithrombotics, "gastrointestinal and cerebral haemorrhage" were the ADRs reported most frequently for *older adults*. In contrast "thrombocytopenia" and "pulmonary embolism" were the ADRs reported most frequently for *younger adults* (possibly suggesting ineffectiveness of the drug). Similarly, "hyponatraemia" was the ADR reported most frequently for psychoanaleptics in *older adults* but ranked only 29th in the respective reports of *younger adults*.

Different drug **substances** belonging to the same respective drug **class** (Table 3.1) may account for the discrepancies in ADRs between *older adults* and *younger adults* (further description see legend Table 2.1).

Drug substances reported as suspected most frequently and their ADRs

Likewise, Table 2.2 shows that for some drug **substances** the most frequently reported ADRs between *older adults* and *younger adults* differed. The ADRs most frequently reported for rivaroxaban were "epistaxis" (OR 2.2 [1.3-3.9]), and "cerebral haemorrhage" (OR 3.6 [1.7-7.3]) in *older adults* vs. "menorrhagia" (OR 0.0 [0.0-0.1]), and "deep vein thrombosis" (OR 0.3 [0.2-0.5]) in *younger adults*. Further analysis with regard to rivaroxaban revealed that the indications most often reported differed between *older adults* and *younger adults* (see Supplementary Table 5, Additional File 6). Hence, not only the drug **substance** itself but the difference in the indications (i.e. the underlying diseases) could have affected the ADR profile. Among the other antithrombotic agents (acetylsalicylic acid (3rd rank), phenprocoumon (4th rank), and apixaban (5th rank)) differences concerning the ADRs most frequently reported were less striking (see Supplementary Table 6, Additional File 7). However, "gastrointestinal haemorrhage" (OR 1.9 [1.1-3.2]) related to phenprocoumon, "cerebral haemorrhage" (OR 2.3 [0.8-7.2]) related to apixaban, "gastrointestinal haemorrhage" related to dabigatran (OR 2.0 [0.7-5.5]) and clopidogrel (OR 2.1 [1.0-4.7]), respectively, were reported more often in *older adults* than *younger adults*. Further differences were observed with regard to the ADRs most frequently reported for risperidone and olanzapine. "Falls" were reported about 10 times more often for risperidone and "parkinsonism" was reported about 4 times more often for olanzapine in *older adults* compared to younger adults.

Discussion

This study is the first retrospective analysis of ADR reports referring to older adults in the national ADR database of the competent authority BfArM in Germany. In order to strengthen the significance of the ADR database analysis, parallel analysis with other external data sources providing complementary data about the number of inhabitants [23], the medication use (prescription-only medicine and OTC) [4], and drug prescriptions [24] were also conducted. Furthermore, the ADR reports of *older adults* were compared to ADR reports of *younger adults* in order to identify differences among both patient populations. We saw a significant higher increase of ADR reports in *older adults* per 100,000 inhabitants vs. *younger adults* per 100,000 inhabitants in the last years, underlining the importance of ADRs in older adults. Interestingly, the ADRs reported the most frequently differed for some drug classes and drug substances between *older* vs. *younger adults*.

An increase of the absolute number of ADR reports with rising age up to the age group 66-70 years was already shown in our previous descriptive analysis of all ADR reports contained in BfArM's ADR database [25]. In the present study, however, the number of ADR reports was set in relation to the number of inhabitants and assumed drug-exposed inhabitants distributed by age and gender [4, 23]. We found an increase in the number of ADR reports per 100,000 inhabitants and assumed drug-exposed inhabitants with rising age up to the age groups 76-84 years and 70-79 years, respectively. Our finding may reflect the increase of older inhabitants in the same time frame in Germany [23] which may have led to an increase of drug-exposed inhabitants and, thus, more patients with ADRs.

In an analysis of the global ADR database *Vigibase* the highest mean number of ADR reports per million inhabitants for high-income countries has been observed for the age group 65-74 years [6]. The slight shift compared to our age strata may be explained by differences of the underlying data. Our analysis was restricted to Germany only, whereas the analysis in *Vigibase* included several high-income countries.

The rising frequency of ADRs with older age per inhabitants has also been described in ADR database analysis of other countries [21, 43, 44]. A higher proportion of ADRs in inpatients older than 65 years compared to younger inpatients has been reported in two medical record studies performed in German hospitals as well [10, 45]. Various factors may account for this finding, e.g. a higher proportion of multi-morbid persons and a higher proportion of drug-exposed and polymedicated patients, which has been described in two German surveys [3, 4]. Polypharmacy and comorbidities have been assumed to correlate with the seriousness of spontaneously reported ADRs in a study from Italy [21]. This may also explain the increase of serious ADRs with rising age in our analysis (see below).

ADRs itself and ADR related hospital admissions are associated with costs for the Health Care System [46] which are estimated to be even higher for patients older than 65 years [9]. Assuming that the number of ADR reports will further increase in the future, we would expect almost a doubling of ADR reports per 100,000 older inhabitants (78.9 [62.1-95.7] ADR reports) in the year 2050 based on the linear trend displayed in Figure 2. If so, a further increase of health care costs can be expected in the future. However, this prediction is associated with considerable uncertainty due to the distance of the year 2050 to the analysed time period (2000-2016) and possible unknown variables (e.g. legislative changes) that may occur in the future and could impact on this scenario.

Known risks for ADRs in older patients are age-related changes in pharmacodynamics and pharmacokinetics, e.g. reduced kidney and liver function leading to a higher variability in drug response [5, 47]. Likewise, we also found a higher proportion of patients with one of the queried comorbidities (e.g. cardiac disorders) with rising age, except for hepatobiliary disorders. The higher number of patients with hepatobiliary disorders in *younger adults* compared to *older adults* could be due to a reduced life expectancy of patients with severe - and thus possibly also more often reported - hepatobiliary disorders. Compared to a German survey [3] the proportion of individuals older than 65 years with hypertension was much lower in our analysis (50 % vs. 24.5 %). This discrepancy could be due to incomplete or missing data in the ADR reports or differences in the recording of diseases inherent to the different study designs.

In the present study an ADR was considered serious if it led to death, and/ or hospitalization or prolonged hospitalization, and/ or congenital anomalies or was life-threatening [42]. A higher proportion of "serious" ADRs and ADRs "leading to/ or prolonging hospitalisation" with increasing age has been seen in spontaneously reported ADRs from Italy and Sweden as well [11, 21]. Likewise, in a German cohort study an increase of ADR related hospital admissions has been reported with increasing age [9]. However, differences regarding the study designs have to be considered.

Like the Swedish study which focussed on fatal ADR reports [11] we observed an increase of ADR reports informing about a fatal outcome with rising age, as well. However, it should be noted that we did not specifically assess fatal ADR reports with regard to their causal relationship. Hence, we cannot elucidate the number of cases in which the fatal outcome was due to other causes like underlying comorbidities or natural death.

As also observed in other ADR database analysis [17, 48, 49] we found a higher absolute number of ADR reports referring to older females with rising age. This finding may be explained by (i) sex differences in pharmacokinetics and pharmacodynamics [50], (ii) differences in reporting behaviours (females tend to report ADRs more often than males [48, 51]), (iii) the higher number of female inhabitants in the older German population [23, 52], and (iiii) more older females in the German population taking drugs and having comorbidities compared to older males [3, 4].

Unexpectedly, slightly more ADR reports referred to *older males* than *females* when related to either 100,000 inhabitants or assumed drug-exposed inhabitants in our analysis. With regard to gender related differences concerning ADRs in older adults there is conflicting data in literature [15, 17, 44, 53, 54 55]. Different study designs (e.g. observational studies versus analysis of ADR reports) and different denominators (e.g. drug prescriptions versus inhabitants) may account for these differences. For instance, female gender as a risk factor for ADRs has been reported in a prospective multicentre cohort study involving three German hospitals and one hospital in Jerusalem overall and for females older than 65 years even after adjusting for age, body mass index and the number of prescribed drugs [53]. In a Swedish study the number of ADR reports for females

related to the number of drug prescriptions in DDD was similar or only slightly lower in the age groups 75-84 years and ≥ 85 years but significantly higher in the age group 65-74 years compared to males [17]. In an older study from West Germany Hopf et al. [15] found more ADR reports per 1,000,000 million inhabitants for males from the age group 60-69 years onwards. However, this was only observed before adjusting for drug exposure in DDD [15]. Our results that more ADR reports referred to older males for both denominators (inhabitants and drug exposed-inhabitants) are thus in line with the first but not the second finding (different denominators) from Hopf et al. [15].

In some database analyses a higher proportion of "serious" ADR reports and/ or ADR reports with fatal outcome were found in older males [11, 17, 49]. In our study, a slightly higher number of ADR reports for all seriousness criteria in all stratified age groups was only observed when related to 100,000 inhabitants (not for all age groups in absolute numbers). In a French analysis, a preponderance of male gender for serious ADRs in relation to inhabitants has been observed for the age group 60-69 years only [54]. Possibly the higher number of ADR reports per 100,000 older male inhabitants in our analysis may be due to serious ADRs which are more often reported by German physicians [56]. However, as a conclusion from our findings, female gender should not be considered as a risk factor for *all* age groups. Especially in older adults more emphasis should be put on the occurrence of ADRs and serious ADRs in older males.

In the last few years the number of drug prescriptions for antithrombotics (especially for rivaroxaban) increased enormously [24] and drug-exposure in terms of DDD increased with rising age [24]. Likewise, in our analysis almost one fifth (19.8 %) of all ADR reports of *older adults* reported an antithrombotic agent as "suspected/interacting" drug (and the number of these reports has increased over the last years). However, we cannot elucidate whether antithrombotics actually cause more ADRs or if these are only reported more frequently, due to the huge number of drug prescriptions. Nevertheless, antithrombotics were identified as the top ranking drugs responsible for ADR in older adults in ADR database studies from Italy and France [21, 57] and in medical record studies from Germany and US [10, 58]. In contrast, psycholeptics ranked first in *younger adults* in our analysis accounting for 10.0 % of all reports in *younger adults* (4.5 % of all reports in

older adults). This finding is in line with studies showing that ADRs associated with drugs acting on the nervous system were more often reported for *younger adults* [17, 21] vs. *older adults* [59].

Interestingly, for some drug substances and drug classes the ADRs reported most often differed between *older adults* and *younger adults*. This was striking for rivaroxaban. Differences regarding the reported indications for rivaroxaban between *younger* and *older adults* and, thus, a more common chronic use (e.g. atrial fibrillation) in *older adults* may account for this finding. A cohort study has shown that the risk for bleeding, especially gastrointestinal bleeding, inherently increases with rising age [60], it may then be potentiated by antithrombotics. In this respect, higher numbers of ADR reports with regard to gastrointestinal and nervous system haemorrhages associated with direct oral anticoagulants have been seen in patients aged 60 years or older compared to younger patients in a study performed in two large ADR databases from USA and Japan [61]. Haemorrhages were the cause of death reported most often in the Swedish study of fatal ADR reports [11]. Within these reports, antithrombotics were most frequently suspected. Hence, our data in conjunction with the data from literature underline the recommendation to monitor older patients taking antithrombotics.

Likewise to the increase of prescription-only drugs, the use of OTC drugs increases with rising age [4]. Two out of the 10 most frequently reported drug substances in *older adults* are also available as OTC drugs in Germany (acetylsalicylic acid (3^{rd}) and diclofenac (7^{th})). In our analysis we cannot differentiate, if acetylsalicylic acid or diclofenac had been prescribed or taken as an OTC drug. However, since OTC drugs may also cause ADRs or interact with prescribed therapy [62] the importance of taking a full medical history inclusive OTC drugs and food supplements still remains.

In our study, "parkinsonism" was reported as an ADR for psycholeptic drugs and olanzapine 1.8 times and 4 times more often in *older adults* compared to *younger adults*, respectively. In general, the prevalence of Parkinson disease increases with rising age

[63]. However, "parkinsonism" as an example for an ADR may be difficult to distinguish from the onset of the disease itself, the progression of the disease or signs of aging, which illustrates the challenge of ADR recognition in older adults. Hence, in order to avoid prescription cascades new symptoms should be critically examined and their aetiology clarified.

The exact exposure of older adults with PIM in the German population is unknown. In our analysis PIMs according to PRISCUS [18] were not very frequently reported as suspected in *older adults*. One explanation for this observation could be that non-PIM related ADRs are more frequently in our analysis due to the higher number of drug prescriptions for non-PIMs. This may lead to an underrepresentation of ADRs related to PIMs. In a prospective medical record study performed in Germany the prevalence of ADRs associated with a PIM was rather low [45]. Likewise, more ADR reports related to non-PIMs than to PIMs according to the Laroche list have also been reported in a study conducted in a French Pharmacovigilance database [57]. However, differences in PIM lists and PIM prescription behaviours between Germany and France complicate the comparability of this study with our study. In addition, an underreporting of PIMs e.g. due to fear of legal consequences cannot be excluded. This limitation, however, would probably also apply to the French study.

In our analysis, risperidone and mirtazapine were the psycholeptic and psychoanaleptic drug substances reported most frequently in *older adults*. Both are recommended in the PRISCUS list [18] to be prescribed instead of other psycholeptics and psychoanaleptics. Conversely, the international Beers Criteria [19] advises caution when using both drug substances in older adults and recommend a close monitoring of sodium levels when prescribing mirtazapine and psychoanaleptics. In our analysis "hyponatraemia" was infact about 7 times more often reported for the drug class psychoanaleptics in *older adults* than in *younger adults*.

In the Beers Criteria [19] the chronic use of diclofenac is discouraged in older adults due to an increased risk of gastrointestinal (GI) bleeding. In contrast, diclofenac is not re-

ported as inappropriate drug for older adults in the PRISCUS list [18]. In our analysis, "GI haemorrhage" associated with diclofenac (7th rank) was roughly three times more often reported in *older adults* compared to *younger adults*. It should be noted that diclofenac is also available as an OTC drug in Germany. Hence, diclofenac intake will even be higher, and subsequently may impact on the number of ADR reports referring to diclofenac. In summary, our findings with regard to risperidone, mirtazapine, and diclofenac are consistent with the recommendation of the Beers Criteria.

The seven ADRs reported most frequently for *older adults* and *younger adults* are rather unspecific and may be co-reported to the main ADR triggering the report [25]. Among the 20 ADRs reported most often for *older adults*, were "gastrointestinal haemorrhage", "death", "fall", and "cerebrovascular accident" (see Supplementary File 4, Supplementary Table 3). An increase in the frequency of these four ADRs was observed with rising age in our dataset and is also reported in literature [11, 58]. This observation may reflect the increase of serious ADRs with rising age as discussed above.

Falls in general, as well as ADRs which may favour falls like syncope or confusional states (also more often reported with rising ages in our analysis) are associated with a higher mortality, morbidity and immobility [64, 65]. These may lead to more intense need of care in older adults, resulting in an enormous increase of health care costs [64]. Hence, physicians should critically examine the current and intended drugs taken with respect to their potential to favour falls.

The monitoring of drugs used in older adults remains of major importance since data about efficacy and safety in older adults are still underrepresented in initial drug approval documents [66]. Despite its limitations the spontaneous reporting system has proved to be a useful tool to recognize ADRs after marketing approval [25]. Its strengths are based on a large population coverage including real world data as well as vulnerable patient populations (e.g. older adults, comorbid patients), a long-term data collection, and the inclusion of all types of drugs like OTC drugs [25].

One of its major limitations is the unknown amount of underreporting [67], which may depend on the type of ADR and drugs taken, or the recognition of the symptoms as an ADR, especially in older adults [56]. Another limitation is the lack of matching exact exposure data. As a consequence of these both limitations, exact incidences and prevalences cannot be calculated, which also applies to our results. To address this limitation, we set the number of ADR reports in relation to the number of inhabitants and assumed drug-exposed patients. This allows for an estimation of the dimension but should not be misunderstood as exact prevalences and/or incidences.

The distribution of ADR reports originating from physicians, pharmacists and patients was equal in *older* and *younger adults*. Hence, published differences in reporting behaviours among these three reporter types [25, 56, 68, 69] are not assumed to play a role for the detected differences between *younger* and *older adults* in our analysis.

We could not account for any impact of the medical speciality of the reporter since respective data is only rarely available. The chronological age and biological age may differ individually, as well as the degree of frailty, which also could have an impact that cannot be accounted for in our analysis.

Finally, a full case validation with regard to the causal relationship and the quality and completeness of the reports was not possible due to the large sample sizes. However, we would like to point out that all ADR reports have been submitted to BfArM because the reporter assumed an underlying causal association. However, if an equal distribution of cases with poor documentation quality and lack of causal relationship is expected, the same tendency of the results would be observed with a smaller number of cases.

Conclusion

In summary, our analysis underlines the need to further investigate ADRs in older adults since these reports are expected to significantly increase in the future. Also, more attention should be payed to the occurrence of ADRs in older males. Moreover, physicians should be aware of different ADRs being associated with the same drug depending on age. Our findings may also be helpful for the regular update of PIMs lists. Physicians should continue their caution and monitoring when prescribing antithrombotics to older adults. Finally, HCPs should report ADRs, particularly in older adults, as this gives regulators and researches the possibility to further investigate ADRs in older adults and to develop strategies to prevent them.

Acknowledgement

The authors would like to thank the ADR database research team of BfArM's pharmacovigilance division for their excellent support and Catharina Scholl for critically reading the manuscript.

References

1. Halter JB, Ouslander JG, Tinetti ME, Studenski S, High KP, Asthana S. *Hazzard's Geriatric Medicine & Gerontology*. 6th ed. New York: McGraw-Hill, 2009.
2. Davies EA, O'Mahony MS. *Adverse drug reactions in special populations – the elderly.* Br J Clin Pharmacol. 2015; 80 (4): 796-807.
3. Robert Koch Institut. *Daten und Fakten:Ergebnisse der Studie »Gesundheit in Deutschland aktuell 2012«. Beiträge zur Gesundheitsberichterstattung des Bundes.* https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/GEDA12.pdf?__blob=publicationFile. Accessed: 2014.
4. Knopf H, Grams D. *Arzneimittelanwendung von Erwachsenen in Deutschland. Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1).* Bundesgesundheitsbl. 2013; 56: 868-877.
5. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003; 38(8): 843-53.
6. Aagaard L, Strandell J, Melskens L, Petersen PS, Holme Hansen E. Global patterns of adverse drug reactions over a decade: analyses of spontaneous reports to VigiBase™. Drug Saf. 2012; 35(12): 1171-82.
7. Routledge PA, O'Mahony MS, Woodhouse KW. *Adverse drug reactions in elderly patients.* Br J Clin Pharmacol. 2004; 57(2): 121-126.
8. Wu C, Bell CM, Wodchis WP. *Incidence and economic burden of adverse drug reactions among elderly patients in Ontario emergency departments: a retrospective study.* Drug Saf. 2012; 35(9): 769-81.
9. Schneeweiss S, Hasford J, Göttler M, Hoffmann A, Riethling AK, Avorn J. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol. 202; 58(4): 285-91.
10. Schurig AM, Böhme M, Just KS, Scholl C, Dormann H, Plank-Kiegele B, et al. Adverse Drug Reactions (ADR) and Emergencies. The prevalence of suspected ADR in four emergency departments in Germany. Dtsch Arztebl Int. 2018; 115: 251-8.

11. Wester K, Jönsson A, Spigset O, Hägg S. Spontaneously reported fatal suspected adverse drug reactions: a 10-year survey from Sweden. Pharmacoepidemiol Drug Saf. 2007; 16(2): 173-80.
12 Statistisches Bundesamt. *Bevölkerung*. https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand/Tabellen_/lrbev01.html%20D_STATIS.
13. Statistisches Bundesamt. Bevölkerung Deutschlands bis 2060 - 13. koordinierte Bevölkerungsvorausberechnung. https://www.destatis.de/DE/Publikationen/Thematisch/Bevoelkerung/VorausberechnungBevoelkerung/BevoelkerungDeutschland2060Presse5124204159004.pdf?__blob=publicationFile. Accessed: April 2015.
14. Lavan AH, Gallagher P. *Predicting risk of adverse drug reactions in older adults.* Ther Adv Drug Saf. 2016; 7(1): 11-22.
15. Hopf G, Mathias B. *ADVERSE REACTIONS REPORTING AND AGE.* The Lancet. 1988; 332(8619): 1079-1080.
16. Ann Tanner L, Baum C. *SPONTANEOUS ADVERSE REACTION REPORTING IN THE ELDERLY.* The Lancet. 1988; 332(8610): 580.
17. Holm L, Ekman E, Jorsäter Blomgren K. *Influence of age, sex and seriousness on reporting of adverse drug reactions in Sweden.* Pharmacoepidemiol Drug Saf. 2017; 26(3): 335-343.
18. Holt S, Schmiedl S, Thürmann PA. *Potentially Inappropriate Medications in the Elderly: The PRISCUS List*. Dtsch Arztebl Int. 2010; 107 (31-32): 543-51.
19. Fick DM, Semla TP, Beizer J, et al. *American Geriatrics Society 2019 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older adults*. J Am Geriatr Soc. 2019; 67(4): 674-694.
20. Kuhn-Thiel AM, Weib C, Wehling M. *Consensus validation of the FORTA (Fit fOR The Aged) list: a clinical tool for increasing the appropriateness of pharmacotherapy in the elderly.* Drugs Aging. 2014; 31 (2): 131-40.
21. Cutroneo P, Greco S, Cucinotta G, Arcoraci V, Caputi AP. SPONTANEOUS REPORTING OF ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS IN SICILY (ITALY). Pharmacological Research. 1999; 40(1): 41-46.
22. Federal Institute for Drugs and Medical Devices (BfArM).

http://www.bfarm.de/EN/Home/home_node.html

23. Statistische Bundesamt. GENESIS-online. https://www-genesis.destatis.de/genesis/online/logon?language=en. Accessed: 2019.
24. Schwabe U, Paffrath D, Ludwig WD, Klauber J. *Arzneiverordnungsreport 2017.* Berlin Heidelberg: Springer Verlag Berlin-Heidelberg; 2017.
25. Dubrall D, Schmid M, Alešik E, Paeschke N, Stingl J, Sachs B. *Frequent Adverse Drug Reactions, and Medication Groups under Suspicion.* Dtsch Arztebl Int. 2018; 115(23): 393-400.
26. European Medicines Agency. National competent authorities (human). https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human.
27. Federal Institute for Drugs and Medical Devices and Paul-Ehrlich-Institut. Online reporting of side effects. https://nebenwirkungen.pei.de/nw/DE/home/home_node.html.
28. European Medicines Agency. EudraVigilance - European database of suspected adverse drug reaction reports. http://www.adrreports.eu/en/index.html.
29. Federal Institute for Drugs and Medical Devices. European Database on Adverse Drug Reaction Reports. https://www.bfarm.de/EN/Drugs/vigilance/ReportingRisks/uawDB/_node.html;jsessionid=3AA69F0B3C9EFE14A8A1605332865F3D.1_cid354.
30. European Medicines Agency. EudraVigilance. https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance.
31. European Medicines Agency. Access to EudraVigilance data. https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data.
32 WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutical Chemical (ATC) Classification. https://www.whocc.no/atc_ddd_index/. Accessed: 13 December 2018.
33. German Institute of Medical Documentation and Information (DIMDI). ATC-Classification.

https://www.dimdi.de/dynamic/en/drugs/atc-classification/index.html

34. MedDRA: Medical Dictionary for Regulatory Activities. Introductory Guide MedDRA Version 21.0. https://www.meddra.org/sites/default/files/guidance/file/intguide_21_0_english.pdf Accessed: March 2018.
35. DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
36. European Medicines Agency. Guidline on good pharmacovigilance practices (GVP): Annex I - Definitions (Rev 4). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf. Accessed: 9 October 2017.
37. World Health Organization. Health statistics and information systems: Proposed working definition of an older person in Africa for the MSD Project. https://www.who.int/healthinfo/survey/ageingdefnolder/
38. RDocumentation. Random Samples and Permutations. https://www.rdocumentation.org/packages/base/versions/3.6.1/topics/sample.
39. Bergvall T, Noren GN, Lindquist M. *vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues.* Drug Saf. 2014; 37(1): 65-77.
40. Edwards R, Aronson JK. *Adverse drug reactions: definitions, diagnosis, and management.* Lancet. 2000; 356(9237): 1255-1259.
41. Sachs B, Dubrall D, Fischer-Barth W, Schmid M, Stingl J. Drug-induced anaphylactic reactions in children: A retrospective analysis of 159 validated spontaneous reports. Pharmacoepidemiol Drug Saf. 2019; 28(3): 377-88.
42. Arzneimittelgesetz: Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz – AMG). Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), zuletzt geändert durch Artikel 5 des GKV-Arzneimittelversorgungsstärkungsgesetzes (AMVSG) vom 4. Mai 2017 (BGBl. I S. 1050).

43. Ozcan G, Aykac E, Kasap Y, Nemutlu NT, Sen E, Aydinkarahaliloglu ND. Adverse Drug Reaction Reporting Pattern in Turkey: Analysis of the National Database in the Context of the First Pharmacovigilance Legislation. Drugs Real World Outcomes. 2016; 3(1): 33-43.
44. Thiessard F, Roux E, Miremont-Salamé G, Fourrier-Réglat A, Haramburu F, Tubert-Bitter P, et al. Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986-2001). Drug Saf. 2005; 28(8): 731-40.
45. Dormann H, Sonst A, Müller F, Vigler R, Patapovas A, Pfistermeister B, et al. Adverse Drug Events in Older Patients Admitted as an Emergency-the Role of Potentially Inappropriate Medication in Elderly People (PRISCUS). Dtsch Arztebl Int. 2013; 110(13): 213-219.
46. Rottenkolber D, Schmiedl S, Rottenkolber M, Farker K, Saljé K, Mueller S, et al. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. Pharmacoepidemiol Drug Saf. 2011; 20(6): 626-634.
47. Bégaud B, Martin K, Fourrier A, Haramburu F. Does age increase the risk of adverse drug reactions? Br J Clin Pharmacol. 2002; 54(5): 550-2.
48. Tran C, Knowles SR, Liu BA, Shear NH. *Gender Differences in Adverse Drug Reactions*. J Clin Pharmacol. 1998; 38(11): 1003-9.
49. Watson S, Caster O, Rochon PA, den Ruijter H. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine. 2019; 17: 100188.
50. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009; 48(3): 143-57.
51. Rademaker M. *Do women have more adverse drug reactions?* Am J Clin Dermatol. 2001; 2(6): 349-351.
52. Statistisches Bundesamt. Deaths, life expectancy. https://www.destatis.de/EN/FactsFigures/SocietyState/Population/Deaths/Deaths.html.
53. Zopf Y, Rabe C, Neubert A, Gaßmann KG, Rascher W, Hahn EG, et al. Women encounter ADRs more often than do men. Eur J Clin Pharmacol. 2008; 64: 999-1004.

54. Montastruc JL, Lapeyre-Mestre M, Bagheri H, Fooladi A. Gender differences in adverse drug reactions: analysis of spontaneous reports to a Regional Pharmacovigilance Centre in France. Fundamental and Clinical Pharmacology. 2002; 16: 343-6.
55. Mann RD, Rawlins MD, Fletcher P, Wood SM. Age and the Spontaneous Reporting of Adverse Reactions in the United Kingdom. Pharmacoepidemiol Drug Saf. 1992; 1: 19-23.
56. Hasford J, Goettler M, Munter KH, Müller-Oberlinghausen B. Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. J Clin Epidemiol. 2002; 55(9): 945-950.
57. Montastruc F, Duguet C, Rousseau V, Bagheri H, Montastruc JL. Potentially inappropriate medications and adverse drug reactions in the elderly: a study in a PharmacoVigilance database. Eur J Clin Pharmacol. 2014; 70(9): 1123-1127.
58. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. *Emergency Hospitalizations for Adverse Drug Events in Older Americans.* N Engl J Med. 2011; 365(21): 2002-2012.
59. Greil W, Häberle A, Schuhmann T, Grohmann R, Baumann P. Age and adverse drug reactions from psychopharmacological treatment: data from the AMSP drug surveillance programme in Switzerland. Swiss Med Wkly. 2013; Jul 2: 143.
60. Selak V, Kerr A, Poppe K, Wu P, Harwood M, Grey C, et al. Annual Risk of Major Bleeding Among Persons Without Cardiovascular Disease Not Receiving Antiplatelet Therapy. JAMA. 2018; 319(24): 2507-2520.
61. Shimada K, Hasegawa S, Nakao S, Mukai R, Sasaoka S, Ueda N, et al. Adverse reaction profiles of hemorrhagic adverse reactions caused by direct oral anticoagulants analyzed using the Food and Drug Administration Adverse Event Reporting System (FAERS) database and the Japanese Adverse Drug Event Report (JADER) database. Int J Med Sci. 2019; 16(9): 1295-1303.
62. Fugh-Berman A. Herb-drug interactions. Lancet . 2000; 355(9198): 134-8.
63. von Campenhausen S, Bornschein B, Wick R, Bötzel K, Sampaio C, Poewe W, et al. Prevalence and incidence of Parkinson’s disease in Europe. European Neuropsychopharmacology. 2005; 15: 473-90.

64. Berg RL, Cassels JS, editors. The Second Fifty Years: Promoting Health and Preventing Disability. Washington (DC): National Academies Press; 1992.

65. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med. 2009; 169 (21): 1952-60.

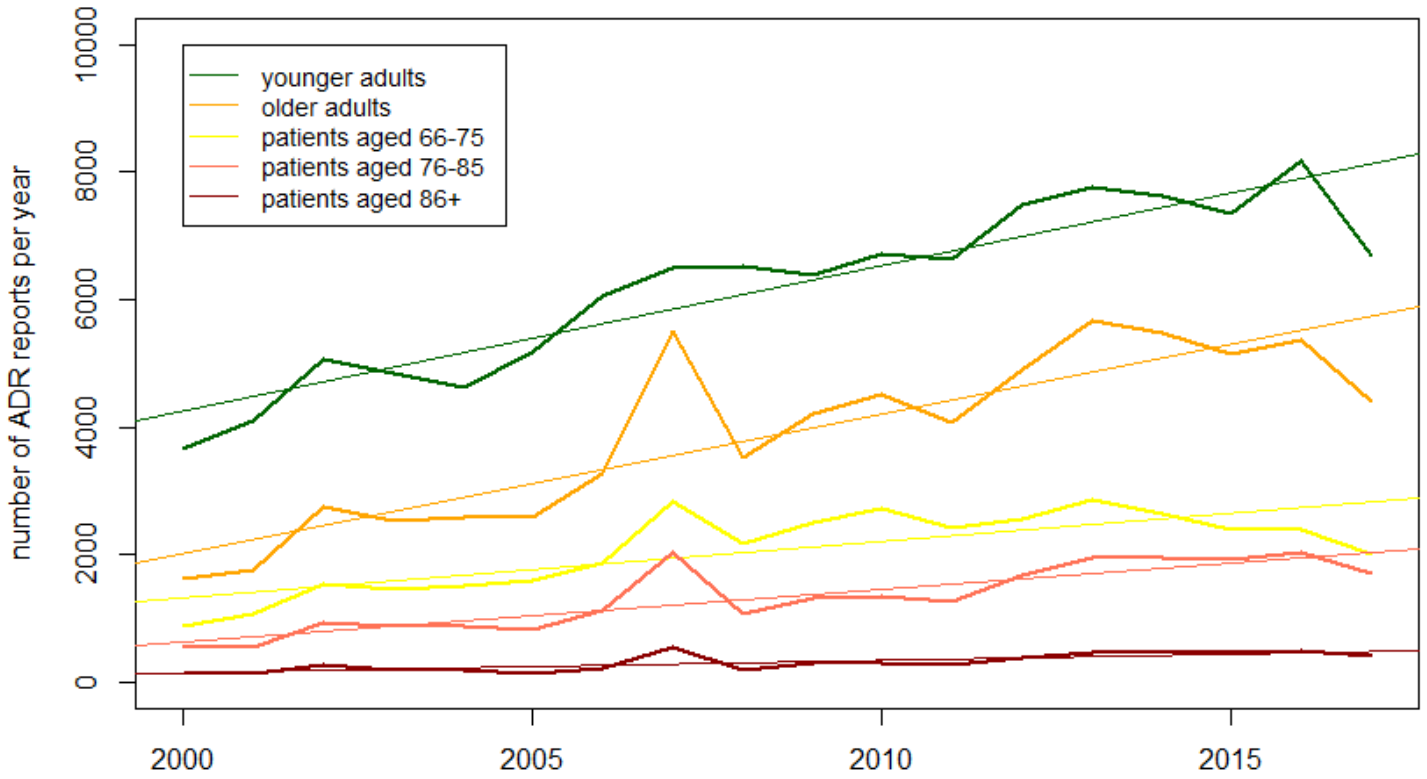
66. Ruiter R, Burggraaf J, Rissmann R. Under-representation of elderly in clinical trials: An analysis of the initial approval documents in the Food and Drug Administration database. Br J Clin Pharmacol 2019; 85(4): 838-44.

67. Hazell L, Shakir SA. *Under-Reporting of Adverse Drug Reactions.* Drug Saf. 2006; 29(5): 385-396.

68. Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. Health Technology Assessment. 2011; 15(20): 23-32.

69. Green CF, Mottram DR, Rowe PH, Pirmohamed M. Attitudes and knowledge of hospital pharmacists to adverse drug reaction reporting. Br J Clin Pharmacol. 2001; 51(1): 81-6.

Supplementary Figure 1. The number of ADR reports per year for *younger adults*, *older adults*, patients aged 66-75 years, patients aged 76-85 years, patients aged ≥ 86 years (absolute numbers).



Supplementary Figure 1 shows the absolute number of ADR reports for *younger adults* (19-65 years), *older adults* (> 65 years), and the stratified age groups patients aged 66-75 years, patients aged 76-85 years and patients aged ≥ 86 years per year. The stratified age groups are subgroups of the *older adults*. In some cases, only the age group (e.g. 7. decade; older adults (> 65)) and not the exact age of the patient was reported. If so, these patients cannot assigned to the stratified age groups. Hence, the sum of the number of ADR reports of all three stratified age groups is not equal to the number of ADR reports for *older adults*.

The absolute number of ADR reports for *older adults*, *younger adults*, and the stratified age groups increased over the years with an annual mean increase of 165 ADR reports for *older adults*, 177 ADR reports for *younger adults*, 66 ADR reports for patients aged 66-75 and patients aged 76-85, and 15 ADR reports for patients aged ≥ 86, respectively. The obvious higher number of ADR reports for *older adults* (and the stratified age groups) in 2007 is mainly due to reports for rofecoxib (withdrawn in 2004). Roughly 30.0 % of these ADR reports in 2007 contained rofecoxib as suspected drug substance compared to 5.2 % of the reports for *younger adults*.

Supplementary Table 1. The calculated ratio "number of ADR reports for *older adults*/ number of ADR reports for *younger adults*" per year.

year	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
ratio *older adults/ younger adults*	0.44	0.43	0.54	0.52	0.56	0.50	0.54	0.85	0.54	0.66	0.67	0.61	0.65	0.73	0.72	0.70	0.66	0.66

Supplementary Table 1 shows the calculated ratio of the number of ADR reports for *older adults* (> 65 years) divided by the number of ADR reports for *younger adults* (19-65 years) per year. The calculated ratio increased slightly over the years.

Supplementary Document 1. The average number of ADR reports per 100,000 inhabitants/males/females and estimation of the number of ADR reports per 100,000 assumed drug-exposed inhabitants/males/females per age group.

Introduction:

The exact number of drug-exposed inhabitants/males/females in Germany is unknown since published data of the German drug prescription reports (AVP) [24] are not patient-related. They include data on the number of prescribed drugs in DDD only, and have some further limitations like missing data on privately insured patients, over-the-counter (OTC) drug use, and lack of exact data concerning the DDD per insured males/females. Therefore, we related the number of ADR reports to the number of German inhabitants/males/females per age group for each year [23] and estimated the number of assumed drug-exposed inhabitants/males/females based on published medication use of German younger adults in the DEGS1 study [4].

Methods:

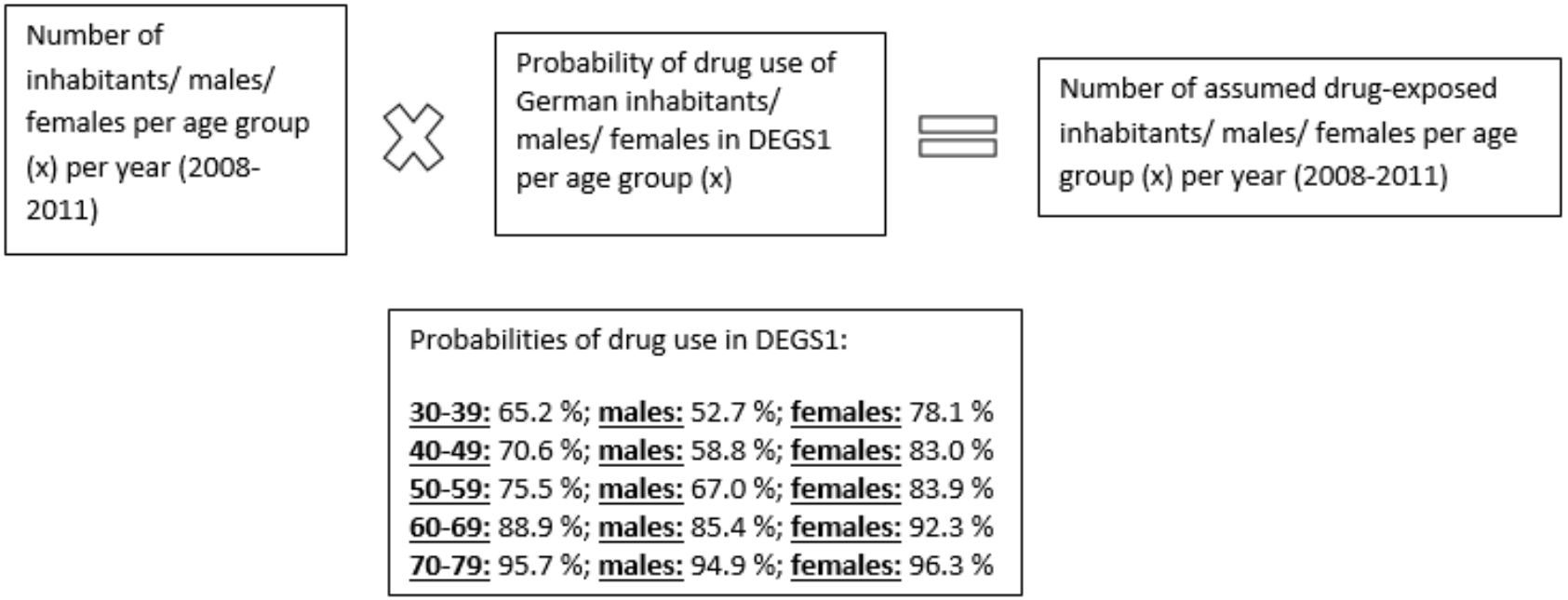
Assumptions:

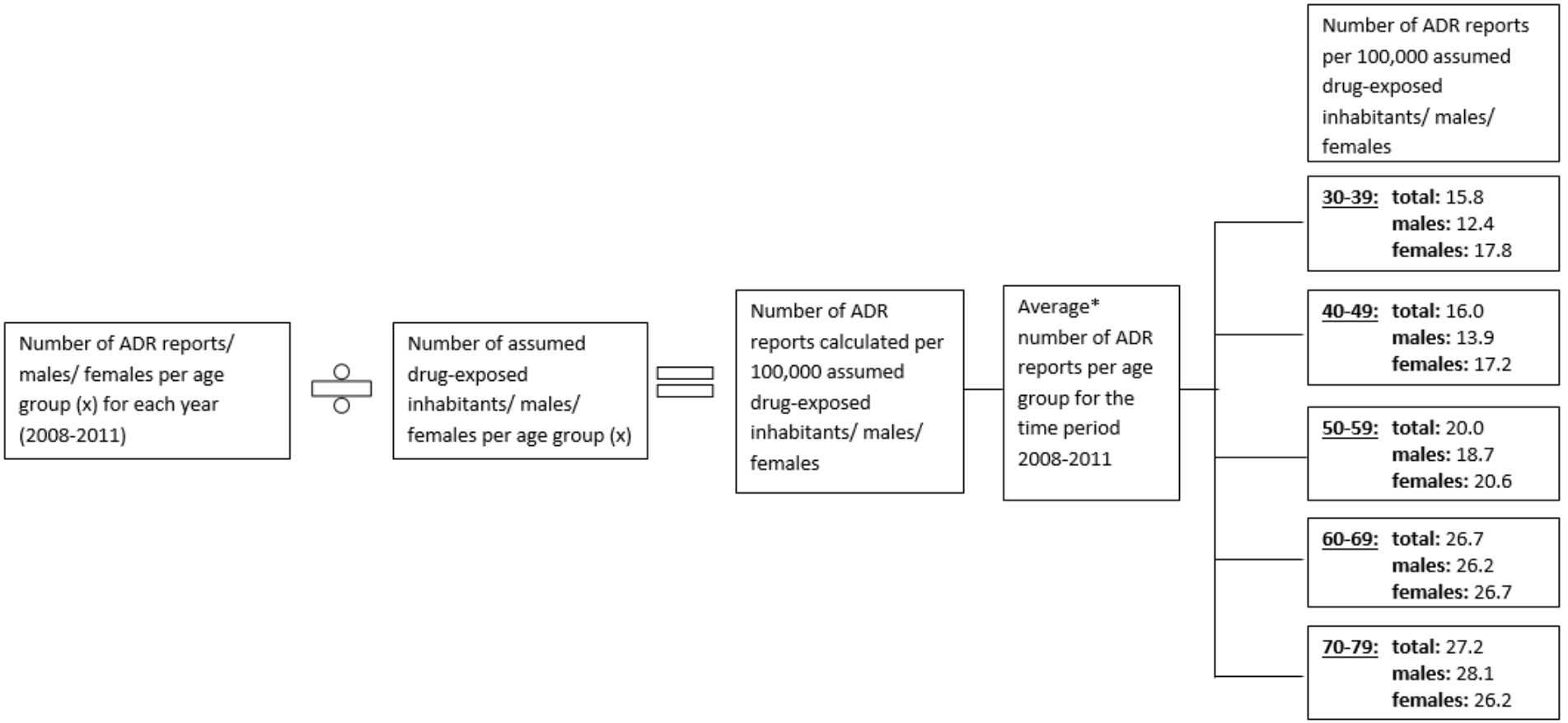
Underreporting is equally distributed by age and gender

*

*

1) Calculation of the number of ADR reports per 100,000 assumed drug-exposed inhabitants/males/females using DEGS1 data [4] (2008-2011)





*average number of ADR reports of the four years per age group

The figure 1) shows the average number of ADR reports per 100,000 assumed drug-exposed inhabitants/males/females per age group. For this analysis, the time period and the age groups were adapted according to the DEGS1 analysis. All ADR reports (male, female and unknown gender) were considered for the calculation of the total average number of ADR reports per 100,000 assumed

drug-exposed inhabitants. Thus, the total number of ADR reports per 100,000 assumed drug-exposed inhabitants do not lie exactly in the middle between the number of ADR reports per 100,000 assumed drug-exposed male/female inhabitants.

Results:

- In each age group the average numbers of ADR reports per 100,000 assumed **drug-exposed inhabitants** exceeds the average numbers of ADR reports per 100,000 inhabitants (larger denominator when all inhabitants are included) (see figure 3 manuscript)
    - The greatest deviations were observed for the youngest age group 30-39 (15.8 ADR reports) with a greater deviation for males (12.4 ADR reports) due to the lower drug exposure rates in younger inhabitants, especially in younger males
    - The smallest deviation was observed for the oldest age group 70-79 (27.2 ADR reports) due to the approximation of drug exposure to 100.0 % of the older inhabitants
    - More ADR reports were observed for 70-79 year old males than females

- The average number of ADR reports per 100,000 assumed **drug-exposed inhabitants** increased with advancing age. However, the increase was slightly lower than the increase of the average number of ADR reports per 100,000 inhabitants reflecting different age and gender dependent drug-exposure rates.

Discussion:

Both analysis (average number of ADR reports per 100,000 inhabitants/assumed **drug-exposed inhabitants**) yielded similar results. The number of ADR reports per 100,000 inhabitants and per 100,000 assumed drug-exposed inhabitants increased with rising ages. The number of ADR reports referring to males was higher in relation to 100,000 male inhabitants from the age group 66-75 onwards, and in relation to 100,000 assumed drug-exposed male inhabitants for the age group 70-79 compared to the number of ADR reports referring to females per 100,000 female inhabitants and per 100,000 assumed drug-exposed female inhabitants. The presented analysis in the manuscript regarding the observed higher increase of the number of ADR reports for older adults compared to younger adults per 100,000 inhabitants per year (Figure 2) is supported by the increase of the number of ADR reports per 100,000 inhabitants (see manuscript Figure 3) and drug-exposed inhabitants with rising age groups (in the presented supplement). The same accounts for the increase of ADR reports for *older adults* in relation to *younger adults* in the past few years (derived from the calculated ratio "number of ADR reports for *older adults*/number of ADR reports for *younger adults*") (Additional File 1). These additional analyses support our finding that more ADR reports were seen with rising ages up to the age group 76-84 years in relation to the number of inhabitants in Figure 3.

Besides the limitations of the data sources [4, 23, 25] used, the different periods of time and age groups need to be respected when comparing the results.

Deviating from literature, we assumed that the underreporting is equally distributed by age and gender. According to literature, underreporting for males is discussed to be higher compared to females [49]. Therefore, we assume that the number of ADR reports per 100,000 males in relation to the number of inhabitants and assumed drug-exposed inhabitants could be even higher as evaluated in our analysis.

Supplementary Table 2. The number of ADR reports of the potentially inappropriate medications (PIMs) contained in the PRISCUS list in *older adults* (> 65 years).

rank (of PIMs)	potentially inappropriate medications according to PRISCUS list [18]	number of ADR reports	% of *older adults* reports (n= 69,914)
1.	olanzapine	357	0.51
2.	etoricoxib	294	0.42
3.	haloperidol	275	0.39
4.	clozapine	220	0.31
5.	lorazepam	196	0.28
6.	amitriptyline	132	0.19
7.	nitrofurantoin	104	0.15
8.	sotatol	99	0.14
9.	prasugrel	95	0.14
10.	doxepin	88	0.13
11.	zolpidem	87	0.12
12.	diazepam	80	0.11
13.	nifedipine	77	0.11
14.	zopiclone	73	0.10
15.	flecainide	71	0.10
16.	trimipramine	69	0.10
17.	pentoxifylline	62	0.09
18.	doxazosin	58	0.08
18.	clonidine	58	0.08
18.	oxazepam	58	0.08
19.	solifenacin	52	0.07
20.	indometacin	51	0.07
21.	beta-actetyldigoxin	36	0.05
21.	baclofen	36	0.05
22.	dimetindene	34	0.05
22.	dimenhydrinate	34	0.05
22.	bromazepam	34	0.05
23.	piracetam	32	0.05
24.	tolterodine	31	0.04
24.	ticlopidine	31	0.04
25.	meloxicam	30	0.04
26.	oxybutynin	28	0.04
26.	clomipramine	28	0.04
27.	reserpine/ clopamide	26	0.04
27.	naftidrofuryl	26	0.04
28.	acemetacin	25	0.04

28.	tranylcypromine	25	0.04
29.	fluoxetine	24	0.03
29.	terazosin	24	0.03
30.	dimenhydrinat/cinnarizine	22	0.03
31.	tetrazepam	21	0.03
32.	digoxin	20	0.03
32.	clemastine	20	0.03
32.	doxylamine	20	0.03
33.	levomepromazine	19	0.03
33.	nitrazepam	19	0.03
33.	alprazolam	19	0.03
34.	piroxicam	16	0.02
35.	maprotiline	15	0.02
36.	brotizolam	14	0.02
37.	flunitrazepam	13	0.02
38.	lormetazepam	12	0.02
39.	fluphenazine	11	0.02
40.	reserpine/dihydralazine/hydrochlorothaizide	10	0.01
40.	dihydroergocryptine	10	0.01
41.	methyldopa	9	0.01
41.	clobazam	9	0.01
41.	temazepam	9	0.01
41.	diphenhydramine	9	0.01
42.	hydroxyzine	8	0.01
42.	chlorphenamin/ascorbic acid/paracetamol	8	0.01
43.	pethidine	7	0.01
43.	triazolam	7	0.01
44.	ketoprofen	6	0.01
44.	nitrofurantoin/pyridoxine	6	0.01
44.	perphenazine	6	0.01
44.	phenobarbital	6	0.01
45.	imipramine	5	0.01
45.	thioridazine	5	0.01
45.	chlordiazepoxide	5	0.01
45.	chloral hydrate	5	0.01
46.	phenylbutazone	4	0.01
46.	metildigoxin	4	0.01
46.	dihydroergocristine/reserpine/clopamide	4	0.01
46.	atenolol/nifedipine	4	0.01
46.	doxylamine/dextrometorphan/ephedrine/paracetamol	4	0.01
47.	acteyldigoxin	3	0.00
47.	dihydroergocryptine/reserpine/clopamide	3	0.00
47.	medazepam	3	0.00
47.	diphenhydramine/cyanocobalamin/dexamethasone/ lido-caine/pyridoxine	3	0.00

48.	chlorphenamine/codeine	2	0.00
48.	triprolidine/pseudoephedrine	2	0.00
48.	prazosin	2	0.00
48.	nifedipine/metoprolol	2	0.00
48.	ergotamin/phenobarbital/belladonna	2	0.00
48.	dihydroergocryptine/dihydroergocristine/ dihydroergocornine	2	0.00
48.	paraffin liquid	2	0.00
48.	diazepam/benzoic acid/benzyl alcohol/propylene glycol/sodium benzoat	2	0.00
48.	prazepam	2	0.00
48.	diphenhydramine/lupus/valariana	2	0.00
48.	diphenhydramine/carbromal	2	0.00
48.	nicergoline	2	0.00
48.	phenobarbital/belladonna/ergotamine	2	0.00
48.	phenobarbi-tal/caffeine/ethaverine/paracetamol/propylphenazone	2	0.00
49.	nitrofurantoin/phenazopyridine/sulfadiazine	1	0.00
49.	nitrofurantoin/sulfadiazine	1	0.00
49.	dimenhydrinate/pyridoxine	1	0.00
49.	reserpine/hydrochlorothiazie	1	0.00
49.	reserpine/ajmaline/belladonna/pentaerithrityl tetranitrate	1	0.00
49.	ergotamine	1	0.00
49.	ergotamine/caffeine/cyclizine	1	0.00
49.	ergotamine/caffeine	1	0.00
49.	dihydroergotamine/etilefrine	1	0.00
49.	dihydroergotamine/heparin/lidocaine	1	0.00
49.	dihydroergotamine/heparin	1	0.00
49.	chlordiazepoxide/amitriptyline	1	0.00
49.	chlordiazepoxide/clidinium	1	0.00
49.	flurazepam	1	0.00
49.	zalpeplon	1	0.00
49.	diphenhydramine/caffeine/polistirex	1	0.00
49.	diphenhydramine/methaqualone	1	0.00
49.	diphenhydramine/passiflora/valeriana	1	0.00
49.	phenobarbital/acetylsalicyclic acid/caffeine/ codeine	1	0.00
49.	phenobarbital/phenytoin	1	0.00
-	chinidin	0	0.00
-	chlorphenamin	0	0.00
-	triprolidine/pseudoephedrine	0	0.00
-	reserpine	0	0.00
-	dihydroergotoxin	0	0.00
-	dikaliumchlorazepat	0	0.00

Supplementary Table 2 shows the absolute and relative number of ADR reports in which one or several monosubstances and/or combination products of the PIMs contained in

the PRISCUS list [18] were reported as suspected. Monosubstances and combination products are listed separately. One ADR report can contain several drug substances as suspected. Therefore, the number of drug substances may exceed the number of ADR reports.

Supplementary Table 3. The 20 ADRs reported most frequently in the ADR reports of *younger adults*, *older adults* and stratified age groups.

rank	*younger adults* (19-65) (n= 111,463)	OR [+/- 95 % CI] *older* vs. *younger adults*	*older adults* (> 65) (n= 69,914)	OR [+/- 95 % CI] *older* vs. *younger adults*	patients aged 66-75 (n= 37,370)	patients aged 76-85 (n= 24,149)	OR [+/- 95 % CI] patients aged 76-85 vs. 66-75	patients aged 86+ (n= 5,649)	OR [+/- 95 % CI] patients aged ≥ 86 vs. 66-75
1.	6.0 % (6,694) nausea	0.9 [0.8-1.0]	5.4 % (3,756) nausea	0.9 [0.8-1.0]	5.9 % (2,206) nausea	5.1 % (1,228) nausea	0.9 [0.8-1.0]	5.3 % (299) death [a]	3.9 [3.0-4.9]*
2.	4.4 % (4,959) dizziness	1.0 [0.9-1.1]	4.5 % (3,177) dizziness	1.0 [0.9-1.1]	4.6 % (1,731) dizziness	4.8 % (1,148) dizziness	1.0 [0.9-1.2]	4.3 % (244) gastrointestinal haemorrhage	3.3 [2.6-4.3]*
3.	4.2 % (4,678) dyspnoea	1.0 [0.9-1.0]	4.0 % (2,821) dyspnoea	1.0 [0.9-1.0]	4.4 % (1,641) dyspnoea	3.7 % (884) dyspnoea	0.8 [0.7-0.9]*	3.9 % (223) nausea	0.7 [0.5-0.8]*
4.	4.0 % (4,421) pruritus	0.8 [0.7-0.9]*	3.4 % (2,404) diarrhoea	1.1 [1.0-1.2]	3.7 % (1,401) diarrhoea	3.1 % (754) vomiting	1.0 [0.9-1.2]	3.8 % (214) dizziness	0.8 [0.6-1.0]
5.	3.4 % (3,786) rash	0.8 [0.7-0.8]*	3.2 % (2,265) pruritus	0.8 [0.7-0.9]*	3.7 % (1,367) pruritus	3.1 % (745) diarrhoea	0.8 [0.7-0.9]*	3.2 % (180) diarrhoea	0.8 [0.7-1.1]
6.	3.3 % (3,673) headache	0.6 [0.5-0.7]*	3.1 % (2,142) vomiting	1.1 [1.0-1.2]	3.1 % (1,168) vomiting	3.0 % (719) pruritus	0.8 [0.7-0.9]*	3.2 % (178) fall	2.8 [2.1-3.7]*
7.	3.1 % (3,432) diarrhoea	1.1 [1.0-1.2]	2.6 % (1,808) rash	0.8 [0.7-0.8]*	3.0 (1,122) rash	2.7 % (648) death [a]	1.9 [1.6-2.3]*	3.1 % (174) vomiting	1.0 [0.8-1.3]
8.	2.9 % (3,238) vomiting	1.1 [1.0-1.2]	2.3 % (1,595) thrombocy-	1.3 [1.2-1.5]*	2.6 % (973) erythema	2.5 % (610) hyperten-	1.3 [1.1-1.5]*	2.9 % (161) cerebrovas-	2.4 [1.8-3.2]*

			topenia			sion		cular acci-dent	
9.	2.8 % (3,146) erythema	0.8 [0.7-0.8]*	2.3 % (1,581) death [a]	3.8 [3.3-4.4]*	2.4 % (909) myalgia	2.3 % (566) rash	0.8 [0.7-0.9]*	2.8 % (157) cerebral infarction	2.8 [2.1-3.9]*
10.	2.7 % (3,033) fatigue	0.8 [0.7-0.9]*	2.2 % (1,543) hyperten-sion	1.6 [1.5-1.8]*	2.4 % (903) headache	2.3 % (563) gastrointes-tinal haem-orrhage	1.8 [1.4-2.2]*	2.7 % (154) dyspnoea	0.6 [0.5-0.8]*
11.	2.6 % (2,855) hypersensi-tivity	0.6 [0.6-0.7]*	2.2 % (1,518) fatigue	0.8 [0.7-0.9]*	2.3 % (878) fatigue	2.3 % (562) thrombocy-topenia	1.0 [0.8-1.2]	2.5 % (141) cerebral haemor-rhage	2.6 [1.9-3.6]*
12.	2.4 % (2,681) urticaria	0.5 [0.4-0.5]*	2.2 % (1,518) erythema	0.8 [0.7-0.8]*	2.3 % (874) thrombocy-topenia	2.2 % (534) fall	1.9 [1.6-2.4]*	2.5 % (141) haemoglo-bin de-creased	2.3 [1.7-3.2]*
13.	2.2 % (2,507) pyrexia	0.8 [0.7-0.9]*	2.0 % (1,421) headache	0.6 [0.5-0.7]*	2.1 % (801) pyrexia	2.1 % (511) cerebrovas-cular acci-dent	1.8 [1.4-2.2]*	2.5 % (139) hyperten-sion	1.2 [0.9-1.7]
14.	2.2 % (2,503) myalgia	0.8 [0.8-0.9]*	2.0 % (1,405) asthenia	1.3 [1.2-1.5]*	2.0 % (755) hypersensi-tivity	2.0 % (490) asthenia	1.0 [0.9-1.2]	2.3 % (131) asthenia	1.2 [0.9-1.6]
15.	2.0 %	0.8 [0.7-0.9]*	1.9 %	5.1 [4.2-6.1]*	2.0 %	2.0 %	2.0 [1.6-2.5]*	2.3 %	0.6 [0.5-0.8]*

	(2,259) drug ineffective		(1,343) gastrointestinal haemorrhage		(754) hypertension	(473) cerebral infarction		(130) pruritus	
16.	1.8 % (2,047) tachycardia	0.7 [0.6-0.8]*	1.9 % (1,334) myalgia	0.8 [0.8-0.9]*	2.0 % (736) asthenia	1.9 % (458) fatigue	0.8 [0.7-1.0]	2.2 % (125) confusional state	2.2 [1.6-3.0]*
17.	1.7 % (1,915) thrombocytopenia	1.3 [1.2-1.5]*	1.8 % (1,248) pyrexia	0.8 [0.7-0.9]*	1.7 % (631) drug ineffective	1.9 % (458) syncope	1.3 [1.1-1.6]*	2.2 % (122) cardiac failure	2.0 [1.4-2.7]*
18.	1.7 % (1,914) hepatic enzyme increased	0.6 [0.5-0.7]*	1.7 % (1,219) fall	3.0 [2.6-3.6]*	1.6 % (595) hyperhidrosis	1.9 % (453) erythema	0.7 [0.6-0.9]*	2.2 % (122) hypoglycaemia	3.2 [2.3-4.6]*
19.	1.7 % (1,888) paraesthesia	0.5 [0.4-0.6]*	1.7 % (1,187) cerebrovascular accident	3.0 [2.6-3.6]*	1.6 % (580) arthralgia	1.9 % (449) cerebral haemorrhage	1.9 [1.5-2.5]*	2.2 % (122) syncope	1.5 [1.1-2.1]*
20.	1.7 % (1,865) arthralgia	0.8 [0.7-0.9]*	1.6 % (1,151) syncope	1.7 [1.5-2.0]*	1.5 % (560) acute kidney injury	1.8 % (441) heamoglobin decreased	1.7 [1.3-2.1]*	2.1 % (119) melaena	2.9 [2.0-4.1]*

*OR=1 is not included; OR > 1 reported more often in *older adults,* patients aged 66-75; OR < 1 reported more often in *younger adults* or the respective age groups

[a] except for ADRs also diagnosis, results of investigations, or social histories can be coded according to MedDRA terminology [25]. The preferred term (PT) "death" itself is not an ADR but an outcome coded by MedDRA terminology [25].

Supplementary Table 3 shows the relative and absolute numbers of the 20 ADRs reported most frequently in the ADR reports of *older adults*, *younger adults* and the stratified age groups with the calculated odds ratios with Bonferroni adjusted confidence intervals. The dataset *younger adults* served as a reference for the calculation of the odds ratios for *older adults* vs. *younger adults*. The dataset patients aged 66-75 years served as a reference for the calculation of the odds ratios for patients aged 76-85 years and patients aged ≥ 86 years vs. patients aged 66-75 years. The ADR evaluation refers to the PT-level of MedDRA terminology [25]. One ADR report can inform about several ADRs. Therefore, the number of ADRs exceeds the number of ADR reports.

Interestingly, allergic-type reactions like "erythema", "pruritus", "rash", and "hypersensitivity" were reported more often for *younger adults* than for *older adults*. This may be explained by differences with regard to (i) the used drugs between older and younger adults, (ii) an overrepresentation of other, non-allergic type ADRs in older adults, or (iii) differences in immunological response between older and younger adults. Further research is needed to evaluate if older adults are less prone to develop allergic-type reactions than younger adults.

Supplementary Table 4. The three drug substances most frequently suspected for the three most frequently reported ADRs in the ADR reports of antithrombotic agents of *younger adults* and *older adults*.

rank	***younger adults*** **(19-65) the three most frequently reported ADRs in the ADR reports of antithrombotic agents (n= 5,676)**	**the three most frequently reported drug substances (number of reports) per ADR**	**rank**	***older adults*** **(> 65) the three most frequently reported ADRs in the ADR reports of antithrombotic agents (n= 13,831)**	**the three most frequently reported drug substances (number of reports) per ADR**
1.	6.5 % (367) thrombocytopenia	44.9 % (165) heparin 15.8 % (58) tirofiban 8.2 % (30) clopidogrel 8.2 % (30) enoxaparin	**1.**	7.6 % (1,051) gastrointestinal haemorrhage	26.9 % (283) acetylsalicyclic acid 23.0 % (242) rivaroxaban 21.6 % (227) phenprocoumon
2.	6.3 % (358) pulmonary embolism	29.6 % (106) certoparin 21.5 % (77) enoxaparin 15.9 % (57) rivaroxaban	**2.**	5.9 % (812) cerebral haemorrhage	35.2 % (286) rivaroxaban 14.8 % (120) apixaban 13.4 % (109) phenprocoumon
3.	3.7 % (211) haemorrhage	19.9 % (42) rivaroxaban 17.0 % (36) enoxaparin 11.4 % (24) phenprocoumon	**3.**	4.9 % (677) haemorrhage	30.2 % (205) rivaroxaban 17.6 % (119) apixaban 13.7 % (93) dabigatran

Supplementary Table 4 shows the relative and absolute numbers of the three drug substances most frequently reported as suspected in the ADR reports of antithrombotic agents of *younger adults* (19-65) and *older adults* (> 65). One ADR report can contain several drug substances as suspected. Therefore, the number of drug substances exceeds the number of ADR reports.

Supplementary Table 5. Characteristics, drug indications, and ADRs in the ADR reports of *younger adults* and *older adults* in which rivaroxaban was suspected before and after extension of the indication (13.01.2012).

	receipt date before 13.01.2012		**receipt data after 13.01.2012 (incl. 13.01.2012)**	
	***younger adults* (19-65)**	***older adults* (> 65)**	***younger adults* (19-65)**	***older adults* (> 65)**
number of reports	73	138	1,100	4,287
mean age (median) [yr]	55.8 (59.0)	75.3 (75.0)	52.4 (55.0)	78.6 (78.0)
female/ male/ unknown	45.2 % (33) 53.4 % (39) 1.4 % (1)	65.2 % (90) 34.8 % (48) 0 % (0)	49.5 % (545) 49.6 % (546) 0.8 % (9)	50.8 % (2,179) 47.9 % (2,055) 1.2 % (53)
the 5 most frequently reported indication terms				
1.	41.1 % (30) thrombosis prophylaxis	57.2 % (79) thrombosis prophylaxis	27.0 % (297) venous thromboembolism	57.7 % (2,473) atrial fibrillation
2.	15.1 % (11) venous thrombolism	11.6 % (16) total knee replacement	23.7 % (261) cerebrovascular accident prophylaxis	52.6 % (2,257) cerebrovascular accident prophylaxis
3.	12.3 % (9) total knee replacement	10.1 % (14) knee arthroplasty	23.0 % (253) atrial fibrillation	14.0 % (600) unknown
4.	8.2 % (6) unknown	6.5 % (9) hip arthroplasty	17.0 % (187) deep vein thrombosis	7.8 % (336) venous thromboembolism
5.	5.5 % (4) total hip replacement	5.1 % (7) total hip replacement	16.7 % (184) pulmonary embolism	5.2 % (222) pulmonary embolism

the 5 most frequently reported ADRs				
1.	21.9 % (16) deep vein thrombosis	18.1 % (25) deep vein thrombosis	9.2 % (101) menorrhagia	8.0 % (343) epistaxis
2.	13.7 % (10) haematoma	13.0 % (18) pulmonary embolism	5.2 % (57) dizziness	7.1 % (305) cerebral haemor-rhage
3.	11.0 % (8) pheripheral swelling	7.2 % (10) dyspnea	4.8 % (53) pulmonary embolism	5.8 % (249) haemoglobin de-creased
4.	9.6 % (7) pulmonary embolism	7.2 % (10) haematoma	4.7 % (52) drug ineffective	5.8 % (247) gastrointestinal haemorrhage
5.	8.2 % (6) haemarthrosis	7.2 % (10) thrombosis	4.5 % (49) deep vein thrombosis	5.1 % (217) haemorrhage

Supplementary Table 5 shows the characteristics, reported drug indication terms, and reported ADRs in the ADR reports of *younger adults* and *older adults* in which rivaroxaban was reported as suspected drug substance before and after the extension of the indication (13.01.2012). One report may inform about more than one drug indication term and several ADRs. Therefore, the number of indication terms and ADRs exceeds the number of reports.

Supplementary Table 6. The five most frequently reported ADRs of *younger adults* in which phenprocoumon, acytylsalicyclic acid, and apixaban were reported as suspected drug substance.

rank	phenprocoumon (n= 768; 0.7 %)	rank	acetylsalicyclic acid (n= 736; 0.7 %)	rank	apixaban (n= 293; 0.3 %)
1.	10.5 % (81) prothrombin time prolonged	**1.**	13.6 % (100) gastrointestinal haemorrhage	**1.**	4.8 % (14) cerebrovascular accident
2.	7.4 % (57) gastrointestinal haemorrhage	**2.**	12.0 % (88) melaena	**1.**	4.8 % (14) off label use
3.	6.8 % (52) drug interaction	**3.**	7.9 % (58) nausea	**1.**	4.8 % (14) pulmonary embolism
3.	6.8 % (52) hepatic enzyme increased	**4.**	7.9 % (58) gastric ulcer haemorrhage	**2.**	4.4 % (13) nausea
4.	5.9 % (45) international normalised ratio increased	**5.**	7.2 % (53) abdominal pain upper 7.2 % (53) vomiting	**3.**	4.1 % (12) dizziness

Supplementary Table 6 shows the five most frequently reported ADRs in the ADR reports of *younger adults* (19-65) (n= 111,463) in which phenprocoumon, acetylsalicyclic acid, and apixaban were reported as suspected drug substance. One ADR report may inform about several ADRs. Therefore, the number of ADRs exceeds the number of ADR reports.

Appendix C

Sachs B, Dubrall D, Fischer-Barth W, Schmid M, Stingl J. Drug-induced anaphylactic reactions in children: A retrospective analysis of 159 validated spontaneous reports. Pharmacoepidemiol Drug Saf 2019; 28(3): 377–388.

Full title:

Drug-induced anaphylactic reactions in children: a retrospective analysis of 159 validated spontaneous reports

Running title:

Drug-induced anaphylaxis in children

Authors' full names:

Bernhardt Sachs[1,2], Diana Dubrall[*1,3], Wilma Fischer-Barth[*1], Matthias Schmid[3], Julia Stingl[1,4]

Authors' institutional affiliations including city and country

1) Federal Institute for Drugs and Medical Devices (BfArM), Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany

2) Department for Dermatology and Allergy, University Hospital Aachen, RWTH Aachen, Pauwelsstraße 30, 52074 Aachen, Germany

3) Institute for Medical Biometry, Informatics and Epidemiology, (IMBIE), University Hospital Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany

4) Centre for Translational Medicine, Medical Faculty, University Hospital Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany

*: both authors contributed equally to the study and the manuscript

Key words:

adverse drug reaction, anaphylactic reaction, anaphylaxis, atopy, spontaneous reports

Key points:

- Only few studies have investigated drug-induced anaphylactic reactions in children.
- The adverse drug reaction (ADR) database of the German Federal Institute for Drugs and Medical Devices provided the opportunity to examine this rare ADR on a larger scale.
- Intravenous administration was noted for 38 % of incriminated drugs. In 13.8 % of cases (11.3% if excluding repeated re-administration in one person) previous hypersensitivity to the drug had been reported and these cases appeared to be more severe than cases designated as “drug never used before”.
- Antibiotics, analgesics, and MRI contrast media were most frequently suspected of having induced the anaphylactic reaction in validated cases.
- Cefaclor accounted for 27 % and amoxicillin for 8.3 % of cases induced by antibiotics although exposure to amoxicillin seems to outweigh cefaclor exposure.

Disclaimer:

The information and views set out in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Federal Institute for Drugs and Medical Devices.

Abstract

Purpose: The main objective of this study was to analyze validated cases of drug-induced anaphylactic reactions in children with regard to incriminated drugs, clinical characteristics, and associated factors. A further objective was to compare differences in incriminated drugs and characteristics between validated cases and a reference excluding anaphylactic reaction cases (basic dataset).

Methods: Spontaneous reports of anaphylactic reactions in children (0-17 years) registered between 01/2000-12/2016 were extracted from the adverse drug reaction database of the German Federal Institute for Drugs and Medical Devices. These reports were restricted to drugs for which at least four cases were found. After case validation, 159 reports remained (validated dataset) and were compared to the basic dataset (n=12.168 reports) using inferential statistics.

Results: Estimated yearly increase of reports (36.8 vs. 0.1), most frequently incriminated drugs (antibiotics 30.2 % vs. 11 %, analgesics/antipyretics 22.0 % vs 5.6 %; p-values <0.001), and route of administration (38.4 % vs. 6.7 %) differed between the validated dataset and the basic dataset. Validated cases differed in severity (higher with atracurium), reported symptoms (urticaria leading with analgesics), and associated factors (atopy/allergy rarely reported with antibiotics) depending on the incriminated drug class. In 13.8 % (11.3% if excluding repeated re-administration in one person) of the cases the drug had not been tolerated before.

Conclusions: A heterogeneous clinical phenotype with differences in associated factors was observed, suggesting different underlying mechanisms triggered by the different drug groups. Occurrence of serious drug-induced anaphylactic reactions in children could be reduced by carefully considering patient history.

Introduction

According to the allergy for global use nomenclature, anaphylaxis is defined as a severe, life-threatening generalized or systemic hypersensitivity reaction (1) resembling an immediate-type reaction (2,3).

The distal pathophysiological pathway in immune-mediated and non-immune mediated anaphylaxis involves the release of mediators such as histamine, tryptase, and other bioactive mediators from basophils and mast cells (4).

Drugs rank either second (5,6) or third (7-9) behind food and insect venoms as elicitors of anaphylaxis in children. One study reported an incidence of 0.5 / 100,000 person-years based on the clinical evaluation of these cases (10).

Antibiotics, particularly beta-lactams, and NSAIDs are reported as frequent elicitors of drug-induced anaphylaxis in children (11-15). However, these observations are based on a limited number of anaphylaxis cases in children (<100).

Some publications have reported atopy and allergy as risk factors for severe courses of anaphylaxis (16,17) whereas others have not (12,14,15,18). However, risk factors and co-factors may differ between age groups or according to the underlying pathophysiology and are not sufficiently studied in children (19).

This paucity of data prompted us to further investigate drug-induced anaphylaxis in children on a larger scale and over a longer period of time (i.e. 159 validated cases in 16 years) by exploring the adverse drug reaction (ADR) database of the German Federal Institute for Drugs and Medical Devices (BfArM).

The main objective was to analyze validated cases with regard to incriminated drugs, clinical phenotype, and associated factors. One limitation of spontaneous ADR data is the lack of control groups. A further objective was thus to compare differences in incriminated drugs and characteristics between validated cases and a reference excluding anaphylactic reaction cases (basic dataset).

Material and Methods

BfArM's ADR database

As described earlier (20,21), physicians in Germany are obliged by their professional conduct code to report adverse drug reactions (ADRs) to their professional councils which forward these reports to either BfArM (responsible for chemically defined drugs) (22) or Paul-Ehrlich-Institut (PEI) (responsible for monoclonal antibodies, vaccines etc.)(23,24). These reports can also be reported directly to BfArM, PEI, or marketing authorization holders who then forward the reports to the authorities.

In BfArM's ADR database, drugs are coded according to the WHO Drug Dictionary and the Anatomical Therapeutic Chemical (ATC) classification system (25). ADRs are coded using MedDRA terminology (26).

The data lock point of the present analysis was 12/2016.

Case identification

We identified all spontaneous ADR reports (no study reports) referring to children (0-17 years), registered between 1/2000 -12/2016, and originating from Germany (n= 14,508). Subsequently, we selected all anaphylactic reaction cases (n= 505) by application of the MedDRA Query (SMQ) "anaphylactic reaction" (version 19.1 as of 9/2016) (26). The 505 cases were restricted to reports where the "suspected/interacting" drug was reported more than 3 times in order to exclude influence by single reports. This resulted in 242 reports. All ADR reports coded as medication errors or with evidence of ADRs due to intentional suicide/self-injury were excluded by application of respective SMQs (pertains to each of the three datasets).

Validation of cases with anaphylactic reactions

The 242 reports were assessed by one of two (either B.S. or W.F-B) board certified specialists in dermatology and allergology. Only cases in which (i) the correctness of the

diagnosis "anaphylactic reaction" according to a national guideline (3) and (ii) the causal relationship with the incriminated drug according to WHO criteria (27) was at least possible were considered for further analysis. Reports with only few symptoms or reports where symptoms were already transformed into the diagnosis "anaphylaxis" were also considered if

- respective treatment or treatment in an intensive/emergency care unit was reported,
- the patient had to be hospitalized,
- the event occurred under medical surveillance (e.g. during anesthesia),
- the case was reported as *life-threatening*,
- or the physician already had classified the anaphylactic reaction suggesting medical expertise concerning anaphylactic reactions.

For quality assurance the final dataset was reviewed by a pharmacist. Eventually, the validated dataset consisted of 159 cases including 164 incriminated drugs (equal causal probability for two drugs in 5 cases). The analysis of the incriminated drugs and routes of administration referred to the 164 drugs whereas all other analyses referred to the 159 cases (see figure 1).

Figure 1. Flowchart: identification of cases.

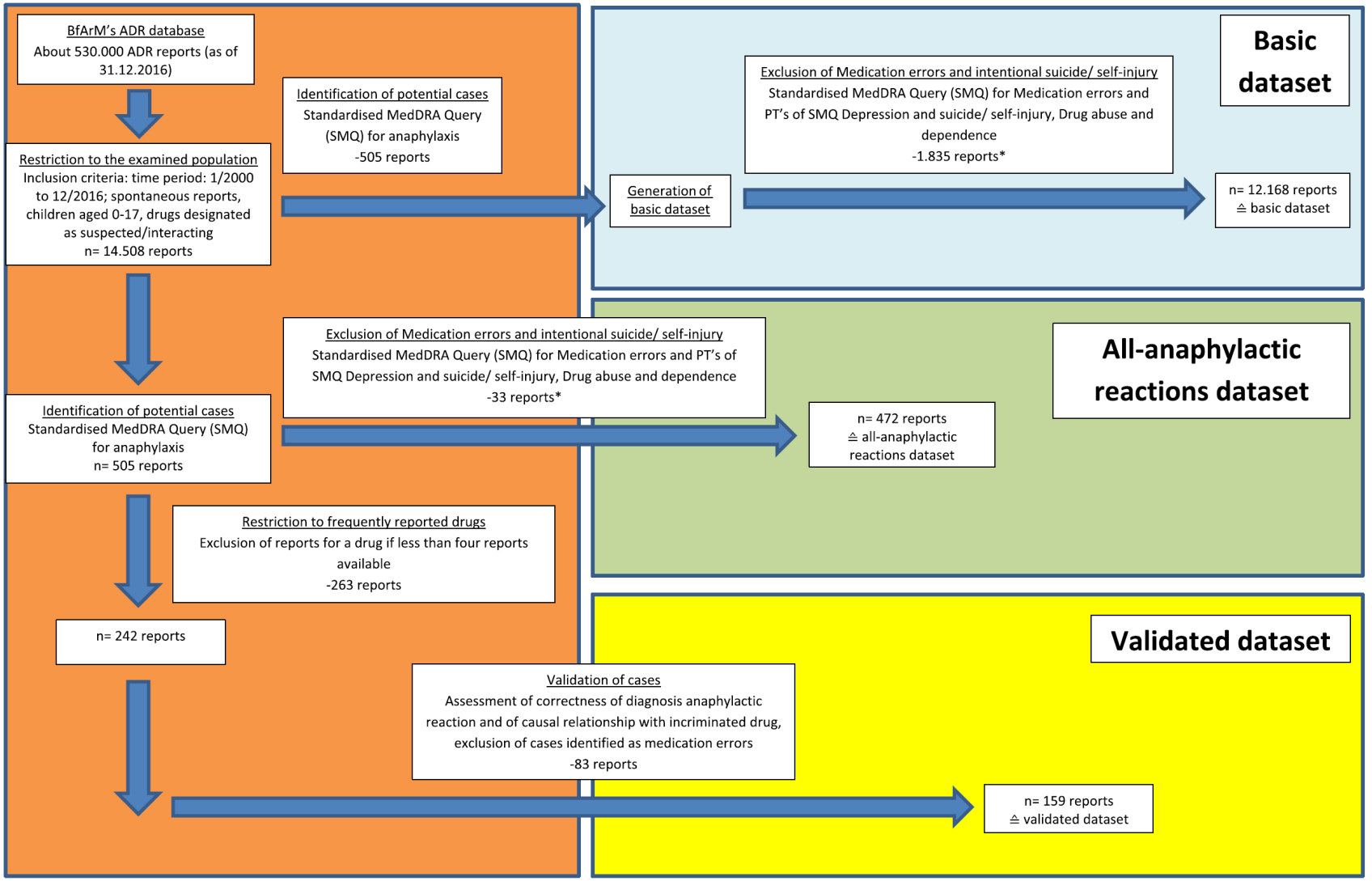


Figure Legend

Figure 1) Flow chart depicting the process of identification, selection, and validation of spontaneous reports of anaphylactic reactions contained in BfArM's ADR database and description of the three datasets

*Since cases in which the ADR resulted from a medication error had been deleted from the validated cases, such reports (medication errors or intentional overdose (e.g. suicide)) were also excluded in the other two datasets by applying respective SMQs. The reasoning for this approach was that usually in these cases inappropriate doses are administered resulting in a higher risk for ADRs.

Quality of validated cases

The completeness of data in the validated cases was assessed according to a published score (28). Calculation of the score was modified as it was not computed for every reported drug-ADR pair (in case more than one ADR had been reported) and then aggregated to an average, to yield an overall score for the corresponding report. Instead, since our analysis focussed on anaphylactic reactions, the calculation of the score referred only to the diagnosis anaphylactic reaction. A completeness score of 0.89 [0.81-0.95] was calculated (> 0.8 well-documented according to (28)). Most data in the variable *dose* (30.8 % of reports) was missing.

Generation and comparison of additional datasets

In order to address the lack of a control group we generated a reference group ("basic dataset") containing all other ADR reports on children 0-17 years excluding the 505 cases identified by the SMQ "anaphylactic reaction" (n= 12,168 reports). In addition, we created the "all-anaphylactic reactions" dataset in order to examine whether differences between the basic dataset and the validated dataset might have resulted from the validation process or from restriction to reports with drugs reported in more than 3 cases. This dataset was based on the 505 identified anaphylactic reaction cases and finally resulted in 472 reports. The same predefined inclusion and exclusion criteria of cases were applied for both datasets.

The three datasets were compared with regard to basic characteristics, incriminated drugs, and the seriousness criteria based on the legal (not clinical) definition, i.e. outcome of the ADR is *fatal*, *life-threatening* or leads to (prolonged) *hospitalization*, persistent or significant *disabilities* or *congenital anomalies*/*birth defects* (29).

Analysis of the validated cases

Any analysis was based on the information provided in the complete report including narrative and follow-ups.

Cases were classified with regard to increasing severity (grade I-IV) according to a national guideline (3). Grade I reactions, for example, are characterized by cutaneous and subjectively perceived general symptoms only, whereas grade IV refers to cardiovascular and/or respiratory arrest (unclassifiable cases are denoted as NOS).

Cases were also analyzed concerning reported symptoms by analyzing assigned preferred terms (26) and associated factors like atopy/allergy. Atopy is an individual susceptibility usually occurring in childhood to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens. These individuals can develop allergic asthma, allergic rhinoconjunctivitis, or atopic dermatitis (1). No published algorithm to diagnose atopy was found. Hence, an individual was designated as atopic if either atopy or one of the following conditions was reported: atopic dermatitis/asthma/pollinosis, a total IgE >100 kU/L or IgE slightly elevated. A patient was designated as allergic if allergy (NOS or specified) was reported.

The classification “drug administered before” referred to the previous administration of drugs with the same active ingredient except in cases where excipients were also co-suspected (e.g. coloring agents or flavors). The classification “drug not tolerated before” referred to the occurrence of hypersensitivity-like symptoms after previous administration.

Statistical analysis

The descriptive analysis was carried out with means (+/- SD) (for age, estimated yearly increase, drugs per report) and frequency distributions with percentages (all other results). Due to unequal variances Welch’s t-test was performed to compare mean ages between drug subgroups and the remaining validated cases. For differences in frequency distributions between the two anaphylactic reactions datasets and the basic dataset, and in the validated dataset between drug subgroups and the remaining cases (without the respective drug subgroup) the chi-square test was applied (in case of < 6 cases: Fisher’s exact test).

The study has been approved by the local ethics committee (009/17).

Results

Comparison of datasets

Table 1) shows the characteristics of the three datasets. The number of reports in the basic dataset increased by an average of 36 reports per year whereas the annual number of validated cases remained stable with an average proportion of 1.4 % (range: 0.7-2.2 %) per year. The validated cases in comparison to the basic dataset more often reported the seriousness criteria *life-threatening* (23.3 % vs. 5.8 %) or *hospitalization* (45.3 % vs. 30.0 %) but less often *death* (0.6 % vs. 3.5 %).

Female gender was more frequently reported in the validated than in the basic dataset (51.6 % vs. 43.4 %). Gender differences were also noted depending on the drug administered (e.g. MRI contrast media (female gender) 73.7 % vs. 49.1 %).

The drug classes most frequently suspected in the validated cases were less often reported in the basic dataset (antibiotics 30.2 % vs. 11 %, analgesics/antipyretics 22.0 % vs 5.6 %; p-values <0.001).

Intravenous administration was clearly more often reported in the validated compared to the basic dataset (38.4 % versus 6.7 %; p= <0.001, based on the number of suspected drugs) and differed depending on drug class.

For most parameters, larger (but similar) differences were observed between the validated and the basic dataset, than between the all-anaphylactic and the basic dataset. However, the number of cases that reported the seriousness criterion *death* was larger in the all-anaphylactic (6.1 %) than in the validated dataset (0.6 %).

Table 1. Characterization of the three datasets.

	Spontaneous reports from 2000-2016 without medication errors and intentional overdose age: 0-17 years		
Criteria	basic dataset† (without anaphylactic reaction cases) (n= 12,168 cases)	all-anaphylactic reactions dataset (determined by SMQ‡) (n= 472 cases)	validated dataset (n= 159 cases)
Estimated yearly increase (in cases +/- SD)	y= 36.875 [+/- 110.9]	y= 0.0625 [+/- 7.7]	y= 0.0625 [+/- 5.4]
Number of suspected/ interacting drugs§	16,777	576	164
Drugs per report (+/- SD)	1.4 [0.4- 2.4]	1.2 [0.5- 1.9]	1.0 [0.8- 1.2]
Primary source Physician Consumer/non HCP¶	 61.1 % (n= 7,437) 8.9 % (n= 1,084)	 67.4 % (n= 318) 8.7 % (n= 41)	 71.1 % (n= 113) 5.7 % (n= 9)
Serious ‖ Hospitalization Life-threatening Death	82.5 % (n= 10,041) 30.0 % (n= 3,647) 5.8 % (n= 710) 3.5 % (n= 426)	87.5 % (n= 413) 41.9 % (n= 198) 22.0 % (n= 104) 6.1 % (n= 29) ††	88.0 % (n= 140) 45.3 % (n= 72) 23.3 % (n= 37) 0.6 % (n=1)
Mean age [years +/- SD]	8.2 [2.0-14.4]	10.0 [4.4-15.6]	8.9 [3.5-14.3]
Male Female Unknown	50.2 % (n= 6,106) 43.4 % (n= 5,278) 6.4 % (n= 784)	48.7 % (n= 230) 50.0 % (n= 236) 1.3 % (n= 6)	48.4 % (n= 77) 51.6 % (n=82)
Administration route‡‡ Intravenous Oral Rectal Unknown	 6.7 % (n= 1,121) 38.9 % (n= 6,519) 0.8 % (n= 139) 21.2 % (n= 3,555)	 25.0 % (n=144)* 39.9 % (n= 230) 3.3 % (n= 19) 19.4 % (n= 112)	 38.4 % (n= 63)* 39.6 % (n= 65) 4.3 % (n= 7) 12.8 % (n= 21)
Analgesics (n02) §§ and ibuprofen¶¶	687 cases (5.6 %)	56 cases (11.9 %)*	35 cases (22.0 %)*
Mean age (years +/- SD)	6.9 [0.7-13.1]	9.1 [4.2-14.0]	7.9 [3.2-12.6]

Female Male Unknown	40.8 % (n= 280) 52.0 % (n= 357) 7.3 % (n= 50)	33.9 % (n= 19) 66.1 % (n= 37)	34.3 % (n=12) 65.7 % (n= 23)
Antibiotics (j01) §§ Mean age (years +/- SD) Female Male Unknown	1,336 cases (11.0 %) 8.2 [2.2-14.2] 48.1 % (n= 643) 48.1 % (n= 643) 3.7 % (n= 50)	89 cases (18.9 %)* 9.7 [4.0-15.4] 52.8 % (n= 47) 47.2 % (n= 42)	48 cases (30.2 %)* 8.8 [3.4-14.2] 54.2 % (n= 26) 45.8 % (n= 22)
Iron Mean age (years +/- SD) Female Male Unknown	40 cases (0.3 %) 8.2 [1.6-14.8] 60.0 % (n= 24) 25.0 % (n= 10) 15.0 % (n= 6)	9 cases (1.9 %)* 15.1 [11.3-18.9] 77.8 % (n= 7) 22.2 % (n= 2)	7 cases (4.4 %)* 14.7 [10.4-19.0] 71.4 % (n= 5) 28.6 % (n= 2)
Alglucosidase Mean age (years +/- SD) Female Male Unknown	35 cases (0.3 %) 2.7 [-1.9-7.3] 51.4 % (n= 18) 37.1 % (n= 13) 11.4 % (n= 4)	12 cases (2.5 %)* 3.3 [0.4-6.2] 33.3 % (n= 4) 66.7 % (n= 8)	12 cases (7.5 %)* 3.3 [0.4-6.2] 33.3 % (n= 4) 66.7 % (n= 8)
MRI (v08c) §§ Mean age (years +/- SD) Female Male Unknown	57 cases (0.5 %) 12.0 [7.7-16.3] 49.1 % (n= 28) 47.4 % (n=27) 3.5 % (n= 2)	25 cases (5.3 %)* 12.1 [7.3-16.9] 72.0 % (n= 18) 28.0 % (n= 7)	19 cases (11.9 %)* 11.5 [6.4-16.6] 73.7 % (n= 14) 26.3 % (n= 5)
Atracurium Mean age (years +/- SD) Female Male	3 cases (0.02 %) 11.7 [9.4-14.0] 0 % 100.0 % (n= 3)	5 cases (1.1 %)* 9.4 [3.0-15.8] 20.0 % (n= 1) 80.0 % (n= 4)	5 cases (3.1 %)* 9.4 [3.0-15.8] 20.0 % (n= 1) 80.0 % (n= 4)

*Chi²-test/Fischer's exact test; $p < 0.001$. Further information for calculation of p-values is included in the section Methods (statistical analysis).

†serving as a reference

‡Standardized MedDRA Querry (SMQ). The dataset "all-anaphylactic reactions" includes all identified anaphylactic reactions by application of the respective SMQ. The 159 validated cases (= validated dataset) are also included in this dataset.

§In some cases more than one drug is reported as suspected. Therefore, the number of reported drugs exceeds the number of reports.

¶There are also other primary sources besides physicians or consumer/non-HCPs. Thus the percentages do not yield 100%.

‖The “seriousness” assessment may not reflect the clinical severity of the reaction since they refer to the legal definition of the Medicinal Products Act: An adverse drug reaction (ADR) is considered serious when the ADR results in *death*, is *life-threatening*, requires in-patient *hospitalization* or prolongation of existing hospitalization, results in persistent or significant *disability* or incapacity, or is a *congenital anomaly/birth defect*. One case may contain more than one of these criteria.

††29 cases with the seriousness criterion "death" were determined; 14 of these cases were assessed within the validation process leading to the exclusion of 13 cases. The remaining 15 cases were excluded due to the criterion "drug was not reported more than three times".

‡‡Frequency distributions of administration routes refer to the total number of drugs per dataset.

§§First the reported suspected/interacting drug subgroups of the validated dataset were identified. Then, respective ATC codes were assigned to the identified drug subgroups. Subsequently, their ATC codes were applied for the stratification of drug subgroups in the other two datasets. Stratification with the suspected/interacting drugs by their active ingredient name only (without application of their ATC code) yielded similar results.

¶¶Ibuprofen is assigned to more than one ATC class. Thus, not all cases could be retrieved by ATC code N02 (analgesics) and ibuprofen was identified by its active ingredient name.

Legend table 1)

In Table 1) the three generated datasets with their basic characteristics (e.g. yearly increase, number of drugs, primary sources), their number of reports, and their proportional ratio in the respective dataset are depicted.

Analysis of validated cases

Demographic parameters

The mean age of validated cases was 8.9 years (SD= 5.4) (table 2). Slightly more reports were found for preschoolers (≥3 - ≤6 years; 28.9 %) and adolescents (≥16 - ≤17 years; 17.6 %). Drug-related age and gender differences were observed, e.g. mean age: iron (14.7 years); gender: MRI contrast media (14 females vs. 5 males). These gender differences were also observed in the stratified age groups (female 0-5 years: 38.2 %; female 13-17 years: 62.7 %).

Table 2. Characterization of validated cases of anaphylactic reactions.

	All validated cases (n=159)†	Cases attributed to antibiotics n=48 (30.2 %)	Cases attributed to analgesics/ antipyretics n=35 (22.0 %)	Cases attributed to MRI contrast media n=19 (11.9 %)	Cases attributed to alglucosidase (enzymes)‡ n=12 (7.5 %)	Cases attributed to iron n=7 (4.4 %)	Cases attributed to atracurium n=5 (3.1 %)	All other cases n=36 (22.6 %)
Serious§ Hospitalization Life-threatening	88.1 % (140/159) 45.3 % (72/159) 23.3 % (37/159)	75.0 % (36/48) 43.8 % (21/48) 31.3 % (15/48)	100.0 % (35/35) 62.9 % (22/35) 22.9 % (8/35)	84.2 % (16/19) 42.1 % (8/19) 5.3 % (1/19)	100.0 % (12/12) 25.0 % (3/12) 8.3 % (1/12)	85.7 % (6/7) 14.3 % (1/7) 14.3 % (1/7)	100.0 % (5/5) 40.0 % (2/5) 60.0 % (3/5)	91.7 % (33/36) 44.4 % (16/36) 27.8 % (10/36)
Mean Age [years +/- SD]	8.9 [3.5-14.3] ¶	8.8 [3.4-14.2] Cefaclor 5.8 [1.7-9.9]*	7.9 [3.2-12.6] Ibuprofen 7.3 [2.8-11.8]*	11.5 [6.4-16.6]*	3.3 [0.4-6.2]*	14.7 [10.4-19.0]*	9.4 [3.0-15.8]	9.6 [4.3-14.9]
Female Male	51.6 % (82/159) 48.4% (77/159)	54.2 % (26/48) 45.8 % (22/48)	34.3 %* (12/35; 75.0 % (9/12) ibu-profen) 65.7 % (23/35; 91.3 % (21/23) ibuprofen)	73.0 % (14/19) 26.3 % (5/19)	33.3 % (4/12) 66.7 % (8/12)	71.4 % (5/7) 28.6 % (2/7)	20,0 % (1/5) 80,0 % (4/5)	61.1% (22/36) 38.9 % (14/36)
Intravenous administration‖	39.6 % (63/159)	20.8 %* (10/48)	0 %	78.9 %* (15/19)	100.0 % (12/12)	85.7 %* (6/7)	80.0 % (4/5)	44.4 % (16/36)
Drug administered before N= information contained =yes/no; (†† T=tolerated; NT=not tolerated; NA= unknown)	n= 78 No= 15.1 % (24/159) Yes= 34.0 % (54/159) T= 44.4 % (24/54) NT= 40.1 % (22/54) NA= 14.8 % (8/54)	n= 19 No= 12.5 % (6/48) Yes= 27.1 % (13/48) T= 61.5 % (8/13) NT= 30.8 % (4/13) NA= 7.7 % (1/13)	n= 21 No= 2.9 % (1/35) Yes= 85.7 % (20/35) T = 55.0 % (11/20) NT= 40.0 % (8/20) NA= 5.0 % (1/20)	n= 9 No= 42.1 % (8/19) Yes= 5.3 % (1/19) T= 100.0 % (1/1) NT= 0 % NA= 0 %	n= 12 No= 0 % Yes= 100 % (12/12) T= 8.3 % (1/12) NT= 50.0 % (6/12) NA= 41.7 % (5/12)	n= 3 No= 28.6 % (2/7) Yes= 14.3 % (1/7) T= 100.0 % (1/1) NT= 0 % NA= 0 %	n= 1 No= 0 % Yes= 20.0 % (1/5) T= 0 % NT= 100.0 % (1/1) NA= 0 %	n= 16 No= 19.4 % (7/36) Yes= 25.0 % (9/36) T= 22.2 % (2/9) NT= 66.7 % (6/9) NA= 11.1 % (1/9)

*Chi²-test/Fischer's exact test; $p < 0.05$. Further information on calculation of p-values is included in the section Methods (statistical analysis).

†159 case reports contained 164 suspected drugs. Cases with more than one drug were counted in each drug class. However, they were not counted twice if they belonged to the same drug class. Therefore, the sum of cases of all drug subgroups exceeds 159 cases.

‡12 case reports for alglucosidase. Among these 12 cases there was one patient accounting for 5 cases (each at a different date). In these cases there was no evidence that the reactions occurred in context with a desensitization procedure.

§The "seriousness" assessment may not reflect the clinical severity of the reaction since they refer to the legal definition of the Medicinal Products Act: An adverse drug reaction (ADR) is considered serious when the ADR results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. One case may contain more than one of these criteria.

¶ one case with age unknown

‖Since this table refers to the number of cases (n=159), the calculation of percentages is also based on the number of cases per drug subgroup. The respective figures relating to the number of incriminated drugs (n=164) are: all validated cases: 38.4 % (63/164), antibiotics: 20.4 % (10/49), analgesics/antipyretics: 0 %, MRI: 78.9 % (15/19), alglucosidase 100 % (12/12), iron: 85.7 % (6/7), atracurium: 80.0 % (4/5), all other cases 44.4 % (16/36)

†† the relative distributions if a "drug was tolerated"/"not tolerated" or "tolerated is unknown after previous administration" refer to the number reporting "drug administered before". The 13.8 % (22/159) cases which reported previous hypersensitivity to the administered drug included repeated re-administration (four times) in one patient (assigned to the drug subgroup alglucosidase). 11.3 % (18/159) of cases remained if these four reports were excluded.

Legend table 2)

Table 2) shows the validated cases (n= 159; validated dataset) stratified by drug class and seriousness criteria, age and gender, proportion of intravenous administration, and drug-specific history.

In 48 antibiotic cases 49 antibiotics (one case with cefotaxime and cefixim) were reported. One case reporting cefaclor and ibuprofen as suspected drugs was also counted for the drugs class analgesics.

In 35 analgesic cases 36 analgesics (one case with ibuprofen and metamizole) were reported. One case reporting cefaclor and ibuprofen as suspected drugs was also counted for the drug class antibiotics. One report included metamizole and metoclopramide as suspected drugs and was therefore also counted in the group “all other cases”.

One of the 5 atracurium reports included atracurium and propofol as suspected drugs and, thus, was also counted in the group "all other cases".

In 36 “all other cases” atracurium and propofol were reported as suspected drugs and, hence, were also counted for atracurium. One report included metamizole and metoclopramide as suspected drugs and was therefore also counted in the group analgesics.

Classification and description of anaphylactic reactions

10.1 % of the validated cases were classified as grade I, 67.3 % as grade II, 17.0 % as grade III, and 0.6 % as grade IV. Grade I/II (moderate; 77.4 %) and grade III/IV (severe; 17.6 %) cases were pooled for subanalysis. More severe than moderate reactions were only reported in atracurium cases (table 3).

Table 3. Classification of anaphylactic reactions.

	All cases of anaphylactic reactions (n=159)†	Cases attributed to antibiotics n=48 (30.2 %)	Cases attributed to analgesics/ antipyretics n=35 (22.0 %)	Cases attributed to MRI contrast media n=19 (11.9 %)	Cases attributed to alglucosidase n=12 (7.5 %)‡	Cases attributed to iron n=7 (4.4 %)	Cases attributed to atracurium (muscle relaxants) n=5 (3.1 %)	All other cases n=36 (22.6 %)
Anaphylactic reaction grades I-II (n=123)	77.4 % of cases (123/159)	66.7 % (32/48)*	80.0 % (28/35)	89.5 % (17/19)	91.7 % (11/12)	85.7 % (6/7)	0 % (0/5)	83.3 % (30/36)
Anaphylactic reaction grades III-IV (n=28)	17.6 % of cases (28/159)	22.9 % (11/48)	17.1 % (6/35)	10.5 % (2/19)	8.3 % (1/12)	14.3 % (1/7)	80.0 % (4/5)*	13.9 % (5/36)
Anaphylactic reaction NOS (n=8)	5.0 % of cases (8/159)	10.4 % (5/48)	2.9 % (1/35)	0 % (0/19)	0 % (0/12)	0 % (0/7)	20.0 % (1/5)	2.8 % (1/36)

In n= 8 cases the anaphylactic reaction was classified as NOS (not otherwise specified). Only 1/159 (0.6%) of cases (atracurium) had a fatal outcome.

*Chi²-test/Fischer's exact test; $p < 0.05$. Further information on the calculation of p-values is included in Methods (statistical analysis).

†159 case reports contained 164 suspected drugs. Cases with more than one drug were counted in each drug class. However, they were not counted twice if they belonged to the same drug class.

‡12 case reports for alglucosidase. Among these 12 cases there was one patient accounting for 5 cases (each at a different date). In these cases there was no evidence that the reactions occurred in context with a desensitization procedure.

Legend table 3)

Table 3) shows the stratification of the validated cases (n= 159; validated dataset) by drug class and assigned grade of anaphylactic reaction (moderate (grade I/II), severe (grade III/IV), classification not possible (NOS)).

The most frequently reported symptom was dyspnea (35.8 %; 57/159 cases) followed by urticaria (33.3 %; 53/159). Differences were noted for analgesics/antipyretics (urticaria: 40.0 %) and for atracurium cases (anaphylactic shock: 60.0 %) (table 4). Urticaria (43.6 %) was the leading symptom reported for the age class 0-5 years whereas this was dyspnoea for age classes 6-12 (32.7 %) and 13-17 years (33.3 %) (data not shown).

Table 4. Distribution of designated allergy/atopy and reported symptoms according to suspected underlying pathophysiology

	Validated dataset (n=159)†	Cases attributed to antibiotics n=48 (30.2 %)	Cases attributed to iron n=7 (4.4 %)	Cases attributed to analgesics/ antipyretics n=35 (22.0 %)	Cases attributed to atracurium n=5 (3.1 %)	Cases attributed to MRI contrast media n=19 (11.9 %)	Cases attributed to alglucosidase (enzymes)‡ n=12 (7.5 %)
Suspected pathophysiology according to literature (5,35, 38-43)		immune-mediated§	non-immune mediated	non-immune mediated ¶	immune or non-immune mediated	immune or non-immune mediated	immune (IgE) or non-immune mediated
Allergy/ atopy‖	25.2 % (40/159)	14.6 %* (7/48)	14.3 % (1/7)	42.9 %* (15/35)	20.0 % (1/5)	31.6 % (6/19)	0 %
Reported symptoms††	35.8 % dyspnoea (57/159) 33.3 % urticaria (53/159) 22.0 % rash (35/159)	50.0 %* dyspnoea (24/48) 31.3 % urticaria (15/48) 27.1 % rash (13/48)	42.9 % dyspnoea (3/7) 42.9 % urticaria (3/7)	40.0 % urticaria (14/35) 31.4 % anaphylactic reaction (11/35) 31.4 %* angioedema (11/35)	60.0 %* anaphylactic shock (3/5) 40.0 %* bronchospasm (2/5)	42.1 % dyspnoea (8/19) 31.6 %* erythema (6/19) 31.6 %* cough (6/19)	58.3 %* rash (7/12) 50.0 % urticaria (6/12) 50.0 %* vomiting (6/12)

Non-immune mediated reactions cover different pathomechanisms, like NSAID-induced inhibition of COX enzymes (5,35,38), complement activation by intravenously administered iron (39), direct degranulation of mast cells in non-IgE-mediated hypersensitivity reactions induced by MRI contrast media (40,41) or by neuromuscular blocking agents like atracurium (38,43).

*Chi²-test/Fischer's exact test; $p < 0.05$. Further information on the calculation of p-values is included in Methods (statistical analysis).

†159 case reports contained 164 suspected drugs. Cases with more than one drug were counted in each drug class. However, they were not counted twice if they belonged to the same drug class.

‡12 case reports for alglucosidase. Among these 12 cases there was one patient accounting for 5 cases (each at a different date). In these cases there was no evidence that the reactions occurred in context with a desensitization procedure.

§This group also contained four fluoroquinolone cases. Both immune-mediated and non-immune-mediated reactions have been described for fluoroquinolones. The first is reported as being more common (38).

¶Five subtypes of NSAID-induced hypersensitivity reactions have been proposed (35), including non-immune mediated and immune-mediated reactions. In one publication it is assumed that non-immune mediated cases account for more than 75% of cases (38).

‖cases with patients designated as atopic (n=22) or allergic (n=29) were pooled for subgroup analysis (see section Results). Not mentioned does not exclude allergic/atopic condition.

††reported symptoms by analyzing the assigned preferred terms. The diagnosis "anaphylactic reaction" is based on specific symptoms reported. Some symptoms may be reported more often than others. In some cases only the diagnosis "anaphylactic reaction" is reported.

Legend table 4)

In Table 4) the validated cases (n= 159; validated dataset) are stratified according to drug class, the reported underlying allergic/ atopic conditions, the assumed underlying pathophysiological mechanisms, and the three most frequently reported symptoms.

Atopy/allergy

Only 15.1 % respectively 27.7 % of the cases yielded information on atopy (24/159) and allergy (44/159). 13.8 % (22/159) of the cases were designated as atopic and allergy was determined in 18.2 % (29/159) of the cases. In 23/29 of the allergy cases, specific information about the allergen was provided (pollen/house dust mites/animals (n=13), food (nuts, milk, eggs etc.; n=9), antibiotics (n=2), and hymenoptera (n=1) (some patients reported more than one allergen). Histamine intolerance was reported in one case. For subgroup analysis, the atopy cases (n= 22) and allergy cases (n= 29) were pooled (altogether 40 cases, since 11 cases reported atopy as well as allergy). This was considered reasonable since the reported allergens are common in immediate-type allergic reactions (e.g. allergic rhinoconjunctivitis) which is also a characteristic of atopy.

32 (26.0 %) of the pooled atopy/allergy cases were classified as grade I/II (n= 123) and n=6 (21.4 %) as grade III/IV (n= 28) reactions (2 cases NOS).

The largest number of reports designated as atopic/allergic was observed in the analgesics/antipyretics drug class (42.9 %; 15/35; $p < 0.05$), followed by MRI contrast media (31.6 %; 6/19) (table 4); whereas, only 14.6 % (7/48; $p < 0.05$) of the antibiotic cases were designated as atopic/allergic.

Drug-related findings

Table 5) shows the ten drugs most frequently assessed as causal inducers.

Table 5. The ten drugs most frequently assessed as causal inducers among the 159 cases † of the validated dataset.

Ranking	Drug substance	Drug class
1.	ibuprofen (n= 30)	analgesics
2.	cefaclor (n= 13)	antibiotics
3.	alglucosidase (n= 12)	alglucosidase
4.	gadobutrol (n =9)	MRI
5.	azithromycin (n =5)	antibiotics

5.	cefuroxime (n= 5)	antibiotics
5.	etoposide (n= 5)	other
5.	atracurium (n = 5)	atracurium
5.	gadopentetate (n= 5)	MRI
5.	gadoteric acid (n= 5)	MRI

†: 159 cases with 164 incriminated drugs

Ibuprofen ranked first with 18.9 % (30/159; 85.7 % (30/35) of analgesic/antipyretic cases) and was observed more frequently in males (21 vs. 9; $p < 0.05$) and ages 0-12 years (86.7 %). In 56.7 % (17/30) of the reports the drug had been administered orally. 41.2 % (7/17) of the oral formulations contained flavors (e.g. strawberry). Allergy/atopy was stated in 43.3 % (13/30) of the reports.

Cefaclor ranked second and accounted for 52.0 % (13/25) of the reports attributed to cephalosporins and for 27.1 % (13/48) of the antibiotic cases. 46.2 % (6/13) of these cases reported the seriousness criterion *life-threatening* (compared to 23.3 % of all cases). Age stratified analysis showed a larger number of reports for the ages 0-12 (92.3 %) and no gender differences were observed. None of the cefaclor cases reported allergy or atopy.

3/5 atracurium cases (rank 5) were classified as anaphylactic reactions grade III (1 grade IV (*fatal* outcome), 1 NOS); 4/5 of these cases were in males.

4/7 iron-related cases referred to ferric carboxymaltose (intravenous; rank 6), and one case each to ferric gluconate (intravenous), ferric dextran (intravenous) and ferric sulfate (oral). In all cases the reaction occurred within 30 minutes.

Four cases of anaphylactic reaction after intravenous corticosteroid therapy with asthma as comorbidity (rank 6) were identified.

Another four cases reported anaphylactic reactions (3/4 grade II, 1/4 NOS) after topical application of an ointment with the ingredients methyl nicotinate and symphytum officinale (rank 6).

In 15.1 % (24/159) of the reports, the drug had never been taken previously (table 2). In 34.0 % (54/159) of the cases the drug had been given previously (not tolerated before: 40.7 % (22/54) (33.3 % if excluding repeated re-administration in one person); tolerated before: 44.4 % (24/54); unknown: 8/54). Cases reporting “not tolerated before” (13.8% of *all* cases (22/159) or 11.3% (18/159) if excluding repeated re-administration in one person) were more often designated as severe (grade III/IV 22.7 % vs. 8.3 %), *life-threatening* (36.4 % vs. 20.8 %), *serious* (100 % vs. 83.3 %) than cases reporting “drug never used before”.

Discussion

The present study analyzed 159 validated cases of drug-induced anaphylactic reactions in children and compared this dataset to a reference (basic dataset) containing all ADR reports excluding anaphylactic reactions.

Comparison of datasets

The drugs most frequently suspected in the validated dataset compared to the basic dataset were antibiotics (30.2 % vs. 11.0 %), analgesics/antipyretics (22.0 % vs. 5.6 %), and MRI contrast media (11.9 % vs. 0.5 %). Hence, these may play a prominent role in drug-induced anaphylactic reactions in children as also reported in literature (5,13,30,31). Different drug-exposure rates may also account for this finding. However, in Germany analgesics and antiinfectives ranked only fourth and eighth in this respect (32).

Intravenous administration was reported more frequently in the validated compared to the basic dataset (38.4 % versus 6.7 %). Hence, intravenous administration may entail a higher risk for anaphylactic reactions as also reported in other investigations (14); alternatively, drugs with a higher risk may be more likely to be given intravenously.

In contrast to the basic dataset, the average number of cases reporting anaphylactic reactions did not increase in the past 16 years (validated dataset). Although this finding is reassuring, it cannot be concluded whether it also applies in real life due to the limitations of the spontaneous reporting system.

The reports of anaphylactic reactions appeared to be more severe based on the legally defined criteria of seriousness *life-threatening*, *hospitalization*, but were astonishingly less frequently reported as *fatal* (0.6 % (validated) vs. 3.5 % (basic)). This particular finding may however result from the validation since *fatal* outcome was even higher (6.1 %) in the all-anaphylactic-reaction dataset (not-validated).

The differences between the validated and the basic dataset were mostly similar but larger than between the all-anaphylactic and the basic datasets. Therefore, the dis-

cussed differences between the basic and the validated dataset are unlikely to have resulted from the validation process. On the other hand, validation improves data quality, as could be seen with regard to the outcome *fatal*.

Analysis of the validated dataset

Consistent with literature (32-34), we observed no obvious gender-predominance over all validated cases (51.6 % female vs. 48.4 % male). Likewise, gender-related drug exposure in Germany from 2003 to 2006 for children reported similar figures (53.1 % females; 48.7 % males) (32). However, we did observe a gender-predominance for certain drugs (e.g. female gender: iron). Since literature only reports a significant gender difference in drug exposure for drugs related to the urogenital system/sexual hormones (contraceptives) (32), the observed differences could be due to chance or unknown factors.

Largely in accordance with a recent study (12), the majority of anaphylactic reactions was classified as moderate (77.4 %; grade I/II). Likewise, only 1/159 cases reported a *fatal* outcome. Although others reported similar findings (11), fear of legal consequences might have discouraged reporting.

Dyspnea was the leading reported symptom (35.8 %) over all validated cases whereas urticaria (40.0 %) ranked first in analgesics/antipyretics-induced cases. Regarding the differentiation of NSAID-induced hypersensitivity (35), this finding could reflect a higher proportion of the “NSAID-induced urticaria/angioedema” type or the “NSAID-exacerbated cutaneous disease” type in our cases. Children aged 0-5 years more often reported urticaria and vomiting than older age classes. In contrast, decreased blood pressure was more frequent in adolescents (13-17; data not shown) as also reported by others (11).

About one quarter of the cases was designated as atopic/allergic; similar results were reported in other studies (8,36). Although preferential underreporting cannot be excluded, atopy was not confirmed as a risk factor for severe reactions in our study, which is also in accordance with literature (12,15,18,37).

Atopic patients are immunoglobulin E antibody high responders (1). We found a lower percentage (14.6 %) of patients reporting atopy/allergy in "antibiotics cases" with assumed preferential immune-mediated pathophysiology (according to literature (5)). On the other hand, in the "analgesics/antipyretics cases" with assumed preferential non-immune-mediated pathophysiology (according to literature (5,35,38-43)) a higher percentage (42.9 %) was observed. No significant association with atopy for beta-lactam allergy in children (44,45) was found in other studies either. Instead, varying associations of atopy with different phenotypes of NSAID-induced hypersensitivity have been described, suggesting that atopy may predispose to selected forms of NSAID hypersensitivity (46). However, in one study in patients of all ages no differences were found (14). Therefore, our findings could also be due to chance or varying documentation.

Ibuprofen accounted for nearly every fifth of all incriminated drugs (18.9 %; 30/164) and nearly every fourth in the age groups 0-5 and 6-12 (data not shown). No matching exposure data are available. However, ibuprofen passed paracetamol in terms of exposure in 2007 and accounted for 76 % of all analgesics prescribed to children within the statutory insurance system in Germany in 2013 (47). Over-the-counter sales may further increase this exposure. Nevertheless, if the large number of reports is seen in context with the large exposure we arrive at a more reassuring scenario.

Cefaclor accounted for 27.1 % (13/48) of cases attributed to antibiotics and nearly every second (46.2 %; 6/13) was designated as *life-threatening*. Cefaclor accounted for 10.4 % of all antibiotics prescribed to children (0-15 years) in Germany in 2004 and for 18.6 % in 2013. In contrast, amoxicillin accounted for only 4 reports (none designated as *life-threatening*) although it was the most frequently prescribed antibiotic for children in Germany in 2013 (28.7 % of all antibiotics); this ratio has remained relatively stable since 2004 (47). However, due to the limitations of the spontaneous reporting system we cannot determine whether this finding reflects drug-preferential reporting, different potentials of these drugs to induce anaphylactic reactions, or other reasons.

All five atracurium cases were designated as *serious* (one *fatal*). It remains unclear whether atracurium is associated with more severe anaphylactic reactions or whether severe anaphylactic reactions occurring under anesthesia are more likely to be noticed/reported. The latter would also apply to other drugs used in anesthesia which was

not seen in our analysis. Nevertheless, our finding could also reflect different exposure rates. An analysis in France (48) also reported a higher ratio of grade III/IV hypersensitivity reactions for neuro-muscular blocking agents.

In 13.8 % of the cases (11.3 % if excluding reported re-administration in one person), previous hypersensitivity to the drug had been reported and these reactions appeared to be more severe than cases designated as “drug never used before”. Hence, serious anaphylactic reactions might have been avoided in about every seventh case if taking the patient's history had included previous hypersensitivity reactions and this factor had been considered prior to treatment. Concerning the 22/54 (40.7 %) cases where previous administration had been tolerated, sensitization could have occurred in the immune-mediated cases. Finally, we cannot rule out that there may have been cases for which no alternative medication was available.

The strengths of the spontaneous reporting system encompass the large number of potential cases, the inclusion of vulnerable patient populations (e.g. children), and the possibility to detect very rare/long latency ADRs. Its limitations include underreporting, preferential and stimulated reporting, a varying degree of documentation in the reports, and the impossibility to calculate ADR frequencies due to lack of exposure data (49). Hence, epidemiological studies not based on spontaneous data are usually required to further investigate the signals observed.

In conclusion, a heterogeneous clinical phenotype with differences in associated factors was observed, suggesting different underlying mechanisms triggered by the different drug groups. Future studies may thus focus on defined drug groups. Exploration of larger databases like EudraVigilance could be helpful in order to gain access to further of such cases.

Acknowledgments

This project received funding from the Federal Institute for Drugs and Medical Devices (BfArM) own resources and the Institute for Medical Biometry, Informatics, and Epidemiology (IMBIE), University Hospital of Bonn (V-16703/68502/2016-2020).

The authors would like to thank the ADR database research team of BfArM's pharmacovigilance division for their excellent support.

References

1. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunology 2004; 113(5): 832-6.

2. Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. World Allergy Organ J. 2011; 4(2): 13-37.

3. Ring J, Beyer K, Biedermann T, et al. Leitlinie zu Akuttherapie und Management der Anaphylaxie. Allergo J Int 2014; 23: 96-112.

4. Montañez MI, Mayorga C, Bogas G, et al. Epidemiology, Mechanisms, and Diagnosis of Drug-Induced Anaphylaxis. Front Immunol 2017; 8: 614.

5. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol 2011; 71(5): 684-700.

6. Hoffer V, Scheuerman O, Marcus N, et al. Anaphylaxis in Israel: experience with 92 hospitalized children. Pediatr Allergy Immunol 2011; 22(2): 172-7.

7. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. Allergy 2005; 60(4): 443-51.

8. Dinakar C. Anaphylaxis in Children: Current Understanding and Key Issues in Diagnosis and Treatment. Curr Allergy and Asthma Rep 2012; 12(6): 641-9.

9. Orhan F, Canitez Y, Bakirtas A, et al. Anaphylaxis in Turkish children: a multi-centre, retrospective, case study. Clin Exp Allergy 2011; 41(12): 1767-76.

10. West SL, D'Aloisio AA, Ringel-Kulka T, Waller AE, Clayton Bordley W. Population-based drug-related anaphylaxis in children and adolescents captured by South Carolina Emergency Room Hospital Discharge Database (SCERHDD) (2000–2002). Pharmacoepidemiol Drug Saf 2007; 16(12): 1255-67.

11. Xing Y, Zhang H, Sun S. et al. Clinical features and treatment of pediatric patients with drug-induced anaphylaxis: a study based on pharmacovigilance data. Eur J Pediatr 2018;177:145-54.

12. Cavkaytar O, Karaatmaca B, Cetinkaya PG et al. Characteristics of drug-induced anaphylaxis in children and adolescents. Allergy Asthma Proc 2017; 38: e56-63.

13. Ribeiro-Vaz I, Marques J, Demoly P, Polónia J, Gomes E. Drug-induced anaphylaxis: a decade review of reporting to the Portuguese Pharmacovigilance Authority. Eur J ClinPharmacol 2013; 69(3): 673-81.

14. Faria E, Rodrigues-Cernadas J, Gaspar A, et al. Drug-induced anaphylaxis survey in Portuguese Allergy Departments. J Investig Allergol Clin Immunol 2014; 24(1): 40-8.

15. Jares EJ, Sanchez-Borges M, Cardona-Villa R, et al. Multinational experience with hypersensitivity drug reactions in Latin America. Ann Allergy Asthma Immunol 2014; 113(3): 282-9.

16. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: A population-based study. J Allergy and Clin Immunol 1999; 104(2): 452-6.

17. Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. Ann Allergy Asthma Immunol 2006; 97(1): 39-43.

18. Banerji A, Rudders S, Clark S, Wei W, Long AA, Camargo CA Jr. Retrospective study of drug-induced anaphylaxis treated in the emergency department or hospital: patient characteristics, management, and 1-year follow-up. J Allergy Clin Immunol Pract 2014; 2(1): 46-51.

19. Simons FER, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J 2015; 8(1): 32.

20. Sachs B, Fischer-Barth W, Erdmann S, Merk HF, Seebeck J. Anaphylaxis and toxic epidermal necrolysis or Stevens-Johnson syndrome after nonmucosal topical drug application: fact or fiction? Allergy 2007; 62(8): 877-83.

21. Sachs B, Riegel S, Seebeck J, et al. Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. Drug Saf 2006; 29(11): 1087-100.

22. Federal Institute for Drugs and Medical Devices (BfArM). http://www.bfarm.de/EN/Home/home_node.html.

23. Paul-Ehrlich-Institut (PEI). http://www.pei.de/EN/home/node.html.

24. Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG). Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 5 des Gesetzes vom 4. Mai 2017 (BGBl. I S. 1050) geändert worden ist.

25. German Institute of Medical Documentation and Information (DIMDI): Anatomical Therapeutic Chemical (ATC) classification system.
http://www.dimdi.de/static/en/amg/atcddd/index.htm.

26. Medical Dictionary for Regulatory Activities(MedDRA). https://www.meddra.org/how-to-use/support-documentation/english

27. Edwards IR and Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356(9237): 1255-9.

28. Bergvall T, Norén GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Saf 2014; 37(1): 65-77.

29. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 4). 2017.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143294.pdf

30. Renaudin JM, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin DA. Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. Allergy 2013; 68(7): 929-37.

31. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med 2001; 161(1): 15-21.

32. Knopf H. Arzneimittelanwendung bei Kindern und Jugendlichen. Bundesgesundheitsbl - Gesundheitsforsch-Gesundheitsschutz 2007; 50: 863-70.

33. Ensina LF, de Lacerda AE, de Andrade DM, Machado L, Camelo-Nunes I, Solé D. Drug-induced anaphylaxis in children: nonsteroidal anti-inflammatory drugs and drug provocation test. J Allergy Clin Immunol Pract 2014; 2(6): 825.

34. Liew WK, Williamson E, Tang MLK. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol 2009; 123(2): 434-42.

35. Kowalski ML, Makowska JS, Blanca M, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis, and management: review of the EAACI/ENDA and GA2LEN/HANNA. Allergy 2011; 66(7): 818-29.

36. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. J Allergy Clin Immunol 2004; 113(3): 536-42.

37. Aun MV, Blanca M, Garro LS, et al. Nonsteroidal Anti-Inflammatory Drugs are Major Causes of Drug-Induced Anaphylaxis. J Allergy Clin Immunol 2014; 2(4): 414-20.

38. Dona I, Barrionuevo E, Blanca-Lopez N, et al., Trends in hypersensitivity drug reactions: more drugs, more response patterns, more heterogeneity. J Investig Allergol Clin Immunol 2014; 24(3): 143-53.

39. Szebeni J, Fishbane S, Hedenus M, et al. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. Br J Pharmacol 2015; 172(21): 5025-36.

40. Fok JS, Smith WB. Hypersensitivity reactions to gadolinium-based contrast agents. Curr Opin Allergy Clin Immunol 2017; 17(4): 241-246.

41. Carr TF. Pathophysiology of Immediate Reactions to Injectable Gadolinium-based Contrast Agents. Top Magn Reson Imaging 2016; 25(6): 265-268.

42. El-Gharbawy AH, Mackey J, DeArmey S, et al. An individually, modified approach to desensitize infants and young children with Pompe disease, and significant reations to alglucisodase alfa infusions. Mol Genet Metab 2011; 104(0): 118-22.

43. McNeil B, Pundir P, Meeker S et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. Nature 2015; 519(7542): 237-41.

44. Ponvert C, Le Clainche L, de Blic J, Le Bourgeois M, Scheinmann P, Paupe J. Allergy to beta-lactam antibiotics in children. Pediatrics 1999; 104: e45.

45. Ponvert C, Perrin Y, Bados-Albiero A, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. Pediatric Allergy and Immunology 2011; 22: 411–8.

46. Quiralte J, Blanco C, Delgado J, et al. Challenge-based clinical patterns of 223 spanish patients with nonsteroidal anti-inflammatory-drug-induced-reactions. J Investig Allergol Clin Immunol 2007; 17(3): 182-8.

47. Kapellen T, Telschow C, Zawinell A. Trends bei der Verordnung von Arzneimitteln bei Kindern und Jugendlichen. In: Klauber J, Günster C, Gerste B, Robra B-P, Schmacke N (editors). Versorgungsreport 2015/2016. Schwerpunkt: Kinder und Jugendliche. Stuttgart: Schattauer 2015, pages 71-88.
https://www.wido.de/themenbereiche/versorgungsanalysen/vsreport/versorgungs-report-2015-160.html

48. Reitter M, Petitpain N, Latarche C, et al. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. Allergy 2014; 69(7): 954-9.

49. Hazell L, Shakir SAW. Under-Reporting of Adverse Drug Reactions. Drug Safety 2006; 29(5): 385-9.

Appendix D

Dubrall D, Schmid M, Stingl JC, Sachs B. Angioedemas associated with renin-angiotensin system blocking drugs: Comparative analysis of spontaneous adverse drug reaction reports. PLoS One 2020; 15(3): e0230632.

Full Title:

Angioedemas associated with renin-angiotensin system blocking drugs: Comparative analysis of spontaneous adverse drug reaction reports

Short Title: Angioedemas associated with renin-angiotensin system blocking drugs

Authors' full names:

Diana Dubrall[1,2], Matthias Schmid[1], Julia Stingl[3], Bernhardt Sachs[2,4]

Authors' institutional affiliations including city and country

1) Institute for Medical Biometry, Informatics and Epidemiology, (IMBIE), University Hospital of Bonn, Bonn, North Rhine-Westphalia, Germany

2) Federal Institute for Drugs and Medical Devices (BfArM), Research Division, Bonn, North Rhine-Westphalia, Germany

3) Intitute of Clinical Pharmacology, University Hospital of the RWTH Aachen, Aachen, North Rhine-Westphalia, Germany

4) Department for Dermatology and Allergy, University Hospital of the RWTH Aachen, Aachen, North Rhine-Westphalia, Germany

Disclaimer

The information and views set out in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Federal Institute for Drugs and Medical Devices.

Abstract

Introduction: Angioedema is a subcutaneous swelling typically affecting the face, larynx or pharynx. It is a known adverse drug reaction (ADR) of ACE inhibitors (ACEi), angiotensin-II-receptor blockers (ARBs) and aliskiren (renin inhibitor). Several studies have reported pathophysiological mechanisms and risk factors of ACEi-associated angioedemas, whereas little is known for ARBs and aliskiren. The aim of the study was to analyze comparatively ACEi versus ARBs and aliskiren angioedema reports contained in the European ADR database EudraVigilance with regard to reported risk factors and clinical phenotypes.

Methods: All spontaneous angioedema reports received between 01/2010-06/2017 reporting either an ACEi, ARB, or aliskiren as "suspected/interacting" drug were identified using the Standardized MedDRA Query "angioedema (narrow)". In order to perform a comparative analysis, odds ratios (ORs) were calculated for angioedema reports of ACEi (n= 3.194) versus ARBs (n= 687) and aliskiren (n= 162).

Results: More patients with a history of allergy were included in angioedema reports of ARBs (6.8 %) and aliskiren (13.6 %) versus ACEi (4.3 %). "Urticaria" as an ADR was reported more frequently in angioedema reports of ARBs (18.5 %) and aliskiren (9.0 %) versus ACEi (5.0 %). ACEi-associated angioedemas were more often designated as "life-threatening" compared to ARBs (OR 2.2 [1.6-2.9]) and aliskiren-associated angioedemas (OR 14.2 (3.5-57.4). Concomitant therapy with mTOR inhibitors (OR 4.3 [1.0-17.9]) and fibrinolytics (OR 7.8 [1.1-57.2]) was reported more often in ACEi versus ARBs angioedema reports.

Conclusion: The reported clinical phenotypes differed between ACEi versus ARBs and aliskiren angioedema reports. Differences between the patient populations as observed in our study or differences with regard to underlying pathomechanisms could account for this finding. Due to the methodological limitations of spontaneous reporting systems, we cannot draw a firm conclusion in this regard. Hence, further research is necessary to confirm our observation and elucidate the underyling causes.

Introduction

Angioedema is a deep dermal, subcutaneous swelling that typically affects the face, lips, tongue, larynx or pharynx [1, 2]. It may be life-threatening [1, 3, 4], especially when the airways are involved. Angioedema is a known adverse drug reaction (ADR) for drugs acting on the renin-angiotensin system (RAS) with varying incidences for the individual drug classes.

For instance, about 0.1 to 0.7 % of patients treated with angiotensin-converting enzyme inhibitors (ACEi) develop angioedema [3, 5]. In two-thirds of the patients, ACEi angioedemas occurred within the first three months of treatment [6-8]. A multicenter study in the USA [9] estimated that 30 % of all emergency department visits due to angioedema are ACEi-associated.

The assumed underlying pathomechanism of ACEi-associated angioedema is the accumulation of bradykinin through inhibition of ACE (angiotensin converting enzyme). ACE is the mainly responsible enzyme for the degradation of bradykinin [10]. If other bradykinin degrading enzymes cannot compensate for this inhibition due to functional relevant genetic variants or environmental factors [11-13], the bradykinin concentration may rise and favor the development of angioedema [2, 14-15].

Environmental factors that are reported to increase the risk of angioedema occurrence include co-medications such as acetylsalicyclic acid or non-steroidal anti-inflammatory drugs (NSAID), immunosuppressive agents used in transplant patients, DPPIV inhibitors (DPPIVi), fibrinolytics and estrogens [14, 16, 17, 18]. In addition, female gender (relative risk RR: 1.45, 95 %-CI: 0.82–0.95) [5, 19] and smoking have been identified as risk factors for ACEi-associated angioedemas (hazard ratio [HR]: 2.7, 95 %-CI: 1.1–7.0) [20, 21].

Concerning the genetic association, on a more general basis, Afro-American descent is described to increase the risk ([RR]: 3.88, 95 %-KI: 2.99–4.95) [1, 5, 19, 20]. On a more detailed level, genetic variants that affect the ACEi gene function or the bradykinin receptors, as well as genes involved in fibrinolytic and coagulation or immune response

and inflammatory pathways have been identified as risk factors. However, the results of these genetic associations were not strong and have not been replicated, so far [22].

The angioedema incidence for angiotensin-receptor blockers (ARBs) is reported to be lower [8, 23], than for ACEi. For aliskiren (renin inhibitor) lower [23] and equal angioedema incidences [8, 24] are reported compared to ACEi.

ARBs, as well as aliskiren, do not interact with ACE directly [25, 24, 26] and should therefore not affect bradykinin levels through this pathway. For ARBs and aliskiren the pathophysiology causing an angioedema is not fully understood [26, 27]. To date, literature is inconsistent as to whether ARBs, and/or aliskiren can be used as an alternative treatment after ACEi-associated angioedema occurred [27-29].

ACEi therapy is recommended as one of the first-line treatments for hypertension and heart failure in national and international guidelines [30, 31]. Therefore, the worldwide number of patients exposed to ACEi is huge [9]. In Germany, an enormous increase of ACEi prescriptions has been observed over the past few years [32]. A national study evaluated that ACEi was the drug class most frequently taken in 2008-2011, with a significantly higher use in males than females [33]. In contrast, ARBs and aliskiren are prescribed much less frequently than ACEi. However, ARB prescriptions have increased during the time frame of our analysis (2000-2016) [32].

To the best of our knowledge, this is the first retrospective comparative analysis of angioedema reports associated with ACEi, ARBs and aliskiren performed in the European adverse drug reaction database EudraVigilance (analyzing tool: EVDAS) of the European Medicine Agency (EMA) [34] and the national ADR database of the Federal Institute for Drugs and Medical Devices (BfArM) [35] in Germany. The first aim of the present study was to analyze whether there are characteristics more often reported in ACEi, ARBs and aliskiren angioedema reports compared to their respective controls. The second aim was to analyze whether there are differences between ARBs and aliskiren versus ACEi angioedema reports concerning the reported characteristics and clinical phenotypes. The third aim was to analyze the differences between the high-level analyses in **EVDAS** covering the entire European Economic Area (EEA) versus the analysis of national validated cases of **BfArM's ADR-database**.

This topic is highly relevant due to the high and increasing number of patients exposed to RASi which may lead to an increase of potentially life-threatening angioedemas.

Materials and Methods

1.) *BfArM's ADR-database* and *EVDAS*

Physicians in Germany are obliged by their professional conduct code to report ADRs to their professional councils. These forward the reports to either the Federal institute for Drugs and Medical Devices (BfArM) [35] (responsible for chemically defined drugs) or the Paul-Ehrlich-Institut (PEI) [36] (responsible for monoclonal antibodies, vaccines etc.), as described elsewhere [37, 38]. Physicians may also have reported directly to marketing authorization holders. All reports received up until 22/11/2017 were stored in one of the two national **ADR-databases** in accordance with the responsibilities of the aforementioned competent authorities and forwarded to **EudraVigilance**, the database of the European Medicines Agency (EMA) [39]. However, on 22/11/2017 both national **ADR-databases** were closed and since then marketing authorization holders as well as the national competent authorities report serious and non-serious ADRs directly to the EMA [39].

In the presented study we performed two separate analyses. The analysis covering the entire European Economic Area (EEA) was performed in **EVDAS**. **EVDAS** is the interface for analyzing ADR reports in **EudraVigilance** [40]. The analysis of the national ADR reports (originating from Germany) was performed in a validated dataset (see 2.2.1.) of **BfArM's ADR-database**.

In **BfArM's ADR-database**, drugs are coded in accordance with the Drug Dictionary of the World Health Organization (WHO) [41] and the Anatomical Therapeutic Chemical (ATC) classification system [42]. In **EVDAS**, drugs are coded in accordance with the EudraVigilance medicinal product dictionary (XEVMPD or Article 57 database) [43]. ADRs are coded in accordance with the terminology of the Medical Dictionary for Regulatory Activities (MedDRA) [44] in both databases. The MedDRA terminology includes five different hierarchical levels for coding, and thus for the analysis of the ADRs reported. The highest level of the MedDRA terminology enables an analysis of aggregated data (coarse-grained data) with lowest specificity. In contrast, the lowest level of the MedDRA terminology enables a finer-grained analysis with highest specificity. The most specific level is designated as "Lowest Level Term (LLT)" and represents the ADR/s reported in

clinical practice. Each LLT belongs to one preferred term (PT). Each PT summarizes the LLTs and describes the symptom, investigation or disease diagnosis. These PTs are assigned to the High Level Terms (HLTs) and High Level Group Terms (HLGTs) based on their anatomy, pathology, physiology, etiology or function. The HLGTs are assigned to the System Organ classes (SOCs). The SOCs represent the anatomical areas in which the ADR occurs and are, thus, the aggregated level of analysis.

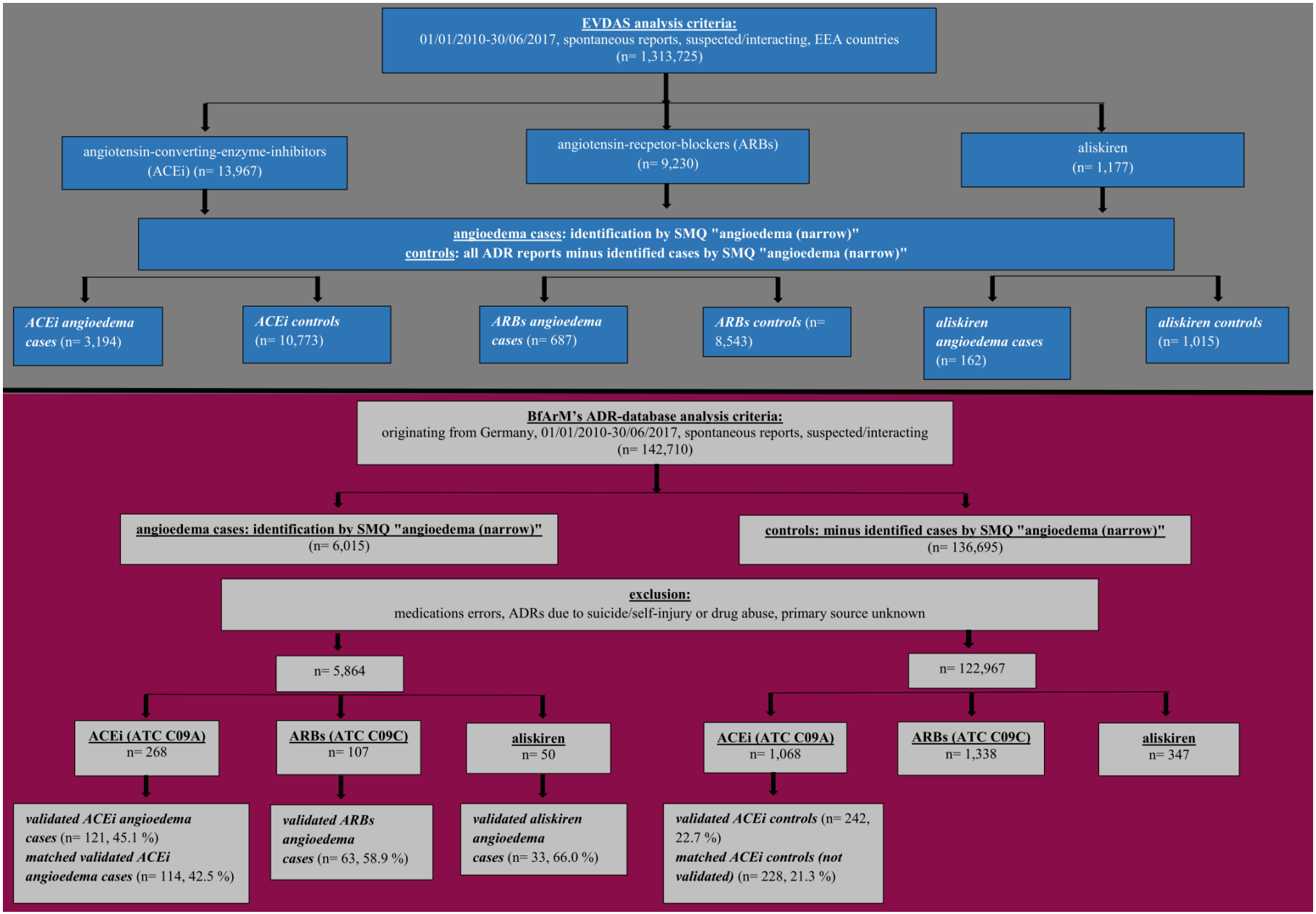
2.) Identification of cases in *EVDAS* and *BfArM's ADR-database*

2.1) *EVDAS*

In **EVDAS**, all spontaneous ADR reports registered between 01/2010 and 06/2017 within the EEA were identified in which either an ACEi, ARB or aliskiren was reported as a "suspected/interacting" drug monosubstance (query date: 17/12/2018) (Fig 1)). For each RASi, the angioedema cases were extracted by application of the standardized MedDRA Query (SMQ) "angioedema (narrow)" [45]. A SMQ is a validated standard set of specific and less specific MedDRA terms at the PT level that facilitates the retrieval of MedDRA coded data. In order to identify specific or specific and less specific terms, one can choose among a narrow and a broad search strategy. These differ in their specificity and sensitivity. Narrow searches are used to identify symptoms that are highly likely to represent the condition of interest. In contrast, broad searches also include symptoms and signs with little or no interest on closer inspection. For the present analysis we chose the narrow search in order to identify ADRs that are more likely representative for angioedemas.

In addition, for each drug class a dataset of controls was generated consisting of all other ADR reports excluding *angioedema cases*.

Fig 1. Flowchart: identification of cases. Fig 1 represents the number of cases identified for *ACEi*, *ARBs* and *aliskiren angioedema cases* and their respective *controls* in **EVDAS** and **BfArM's ADR-database.**


EVDAS analysis criteria:
01/01/2010-30/06/2017, spontaneous reports, suspected/interacting, EEA countries
(n= 1,313,725)
angiotensin-converting-enzyme-inhibitors (ACEi) (n= 13,967)
angiotensin-recpetor-blockers (ARBs) (n= 9,230)
aliskiren (n= 1,177)
angioedema cases: identification by SMQ "angioedema (narrow)"
controls: all ADR reports minus identified cases by SMQ "angioedema (narrow)"
ACEi angioedema cases (n= 3,194)
ACEi controls (n= 10,773)
ARBs angioedema cases (n= 687)
ARBs controls (n= 8,543)
aliskiren angioedema cases (n= 162)
aliskiren controls (n= 1,015)
BfArM's ADR-database analysis criteria:
originating from Germany, 01/01/2010-30/06/2017, spontaneous reports, suspected/interacting
(n= 142,710)
angioedema cases: identification by SMQ "angioedema (narrow)" (n= 6,015)
controls: minus identified cases by SMQ "angioedema (narrow)" (n= 136,695)
exclusion:
medications errors, ADRs due to suicide/self-injury or drug abuse, primary source unknown
n= 5,864
n= 122,967
ACEi (ATC C09A) n= 268
ARBs (ATC C09C) n= 107
aliskiren n= 50
ACEi (ATC C09A) n= 1,068
ARBs (ATC C09C) n= 1,338
aliskiren n= 347
validated ACEi angioedema cases (n= 121, 45.1 %) matched validated ACEi angioedema cases (n= 114, 42.5 %)
validated ARBs angioedema cases (n= 63, 58.9 %)
validated aliskiren angioedema cases (n= 33, 66.0 %)
validated ACEi controls (n= 242, 22.7 %) matched ACEi controls (not validated) (n= 228, 21.3 %)

2.2) *BfArM's ADR-database*

For the analysis in **BfARM's ADR-database** the same research strategy as applied in **EVDAS** was used for the identification of *ACEi, ARBs and aliskiren angioedema cases*. Deviating from the **EVDAS** analysis, we restricted our dataset to ADRs that occurred in association with the intended drug use. Therefore, we excluded all ADR reports in which a medication error or drug intake due to intentional suicidal/self-injury behaviors was described by application of respective SMQs. Furthermore, we excluded ADR reports with unknown sender.

2.2.1) *BfArM's ADR-database*: validation of angioedema cases

In order to strengthen the results of the high-level **EVDAS** analysis and to broaden the analysis with information provided in more detail in the case narratives (e.g. treatment of angioedema), an assessment of each individual RASi angioedema report with German origin was performed by the author DD. The causal relationship with the reported "suspected/interacting" RASi was assessed according to WHO criteria [46]. Those reports for which the causal relationship was assessed as at least "possible" were subjected to further analysis. Additionally, the correctness of the diagnosis "angioedema" was assessed. Therefore, all angioedema cases were reviewed in detail to confirm that swellings/oedemas of the head areas (e.g. lips, face), the respiratory tract (e.g. tongue, pharynx), the intestinal tract or genitals were reported. Some reports only provided the diagnosis "angioedema". These reports were only considered for further analysis if angioedema treatment was in accordance with medical practice and led to symptom relief or if a physician reported the diagnosis "angioedema" based on the assumption of existing medical expertise. We excluded all reports in which the angioedema was more likely induced by other causes, e.g. heart failure, tooth extractions. Reports that could not be unambiguously assigned with regard to causality or the correctness of the diagnosis were discussed together by the authors DD and BS prior to the final assignment.

2.2.2) *BfArM's ADR-database*: generation of validated ACEi controls

In order to establish a dataset of *validated ACEi controls* in a 2:1 ratio to the *validated ACEi angioedema cases* (n= 121), a random sample of the identified *ACEi controls* (n= 1,068) was selected. This random sample was assessed with regard to the causal relationship as described above until 242 *validated ACEi controls* were available. The ADRs reported most often in the *validated ACEi controls* were "cough" (17.8 %), "acute kidney injury" (9.9 %), "dizziness" (9.1 %), "nausea" (5.0 %) and "hyperkaliaemia" (4.5 %).

Additionally a 1:2 matching by age and gender of *validated ACEi angioedema cases* to *ACEi controls* (not validated, n= 1,068) was performed in order to confirm the observed results between *validated ACEi angioedema cases* versus *validated controls*. In seven *validated ACEi angioedema cases*, the age or gender of the patient was missing. Thus, the datasets of *matched validated ACEi angioedema cases* and *controls* include 114 and 228 cases.

2.2.3) *BfArM's ADR-database*: documentation quality of validated cases

Finally, the quality (completeness of reports) of all *validated angioedema cases* and the *validated ACEi controls* was assessed according to a published score (vigiGrade) [47]. The calculation of the score was modified as it was computed for the reported diagnosis "angioedema", only [48].

3.) *EVDAS* and *BfArM's ADR-database*: analysis of angioedema cases and controls

In both databases, all identified angioedema cases and controls were analyzed with regard to the reported patient demographics, smoking habits, comorbidities, administered ACEi (for reports of ACEi), ARBs (for reports of ARBs), comedications and the reported seriousness criteria. Gender-stratified analyses were performed in *ACEi angioedema cases*.

Comparative analyses were conducted between *ACEi, ARBs, aliskiren angioedema cases* versus their respective *controls*, and between *ACEi angioedema cases* versus *ARBs* and *aliskiren angioedema cases*, separately.

All analyses in **EVDAS** were computer-based without individual assessment of the cases. Smoking, allergic conditions and comorbidities were identified by summarizing appropriate preferred terms [44] or by application of appropriate SMQs [45].

Any analysis in **BfArM's ADR-database** was based on the information provided in the complete report including narrative and follow-ups.

The classes of comedications were formed in accordance with the ATC-code [42]. Therefore, all drugs co-reported to the "suspected/interacting" RASi were assessed as concomitant, regardless of whether they had been reported as "suspected", "interacting" or "concomitant". Furthermore, the analysis of comedications was restricted to the drugs most frequently reported and/or reported in literature to potentiate the risk of angioedema occurrence when used concomitantly with ACEi (e.g. (DPPIVi or mammalian target of rapamycin (mTOR) inhibitors (mTORi)) [16, 17, 18].

According to the legal definition, an ADR is considered serious if it led to "death", was "life-threatening", required or prolonged "hospitalization", resulted in persistent or significant "disabilities" and/or was a "congenital anomaly/birth defect" [38]. Hence, this classification of seriousness of the ADR report may differ from the clinical severity of the ADR.

The number of reports per anatomical area affected by the angioedema was analyzed in **EVDAS** for all three RASi, and for *ACEi angioedema cases* with concurrent mTORi, firbinolytics, and DPPIVi therapy. It should be pointed out that mTORi, fibrinolytics and DPPIVi themselves are also associated with angioedemas.

In order to investigate angioedemas that are probably related to the respective RASi, the analysis was restricted to reports in which only the respective RASi was reported as "suspected" (exclusion of cases in which other drugs had been reported as co-suspected). Hence, 77.3 % (2,469/3,194) of *ACEi,* 71.5 % (491/687) of *ARBs* and 82.7 % (134/162) of *aliskiren angioedema cases* remained.

Concerning these remaining cases, in 54.9 % (1,355/2,469) of *ACEi,* 41.8 % (205/491) of *ARBs* and 32.8 % (44/134) of *aliskiren angioedema cases*, only the diagnosis "angioedema" was reported. Since information about the affected anatomical areas may be reported in the narratives of the cases, the same analysis was repeated in the analysis of **BfArM's ADR-database.** Further on, in these validated cases a stratified analysis of anatomical areas affected by the angioedema was conducted.

The aforementioned analyses were also conducted for sacubitril/valsartan. Due to the limited number of cases, the results were not included in the manuscript (S1 File).

3.2) *BfArM's ADR-database* analysis

3.2.1.) Number of ADR reports in relation to the number of assumed ACEi-exposed inhabitants/males/females

The number of assumed ACEi-exposed inhabitants/males/females was estimated based on the number of inhabitants/males/females per year [49] multiplied by the proportional share of ACEi exposure in the German population (DEGS1) [33]. The average and its standard deviation (+/-SD) of the number of angioedema and ADR reports (total) divided by the number of assumed ACEi-exposed inhabitants/males/females for the six years was calculated. The results are presented as the number of ADR reports per 1 million assumed ACEi-exposed inhabitants/males/females. Unfortunately, the proportional share of ARBs and aliskiren exposure in the German population was not reported in DEGS1. Thus, this calculation could not be performed for ARBs and aliskiren.

3.2.2.) Number of ADR reports in relation to the number of drug prescriptions

Annually published prescription data (Drug Prescription Reports 2011-2017) [32] were used to summarize the number of drug prescriptions (in million DDD) for ACEi, ARBs and aliskiren monosubstances for the years 2010-2016 in Germany. Hence, the time frame of **BfArM's ADR-database** analysis had to be adapted to 01/2010-12/2016. The average (+/-SD) of the number of angioedema and ADR reports (total) divided by the

number of drug prescriptions for the six years was calculated. The drug prescription reports contain the number of drug prescriptions in defined daily doses (DDD) [32]. However, the DDD may deviate from the administered or prescribed dose to a varying extent depending on the individual drug [50]. Therefore, angioedema incidence rates observed in a meta-analysis of clinical trials are also described in the legend of Fig 2 and depicted in S7 Table [23].

3.2.3) Additional analysis: time-to-onset and treatment of angioedema

Both "time-to-onset" (i.e. time point of first intake of the suspected drug to time point of first onset of the ADR) and the treatment of the angioedema, including its clinical response, are often described in more detail in the narratives of the ADR reports. Hence, these analyses were only performed in validated cases.

4.) Statistical analysis

Mean and median were calculated for the age of the patients and frequency distribution for all other variables. Odds ratios (ORs) and the 95 % confidence interval (CI) were calculated in order to assess differences in the frequency distributions between the compared groups.

A logistic regression analysis was performed for each comparison of *angioedema cases* versus controls, and *ACEi angioedema cases* versus *ARBs* and *aliskiren angioedema cases* as outcome variable and all other variables (if possible) as covariates. Diabetes was not included as a variable in the logistic regression model to avoid overlaps with the variable "antidiabetics". The same applies to the variables "death", "life-threatening", "hospitalization" and "disabling" with regard to the variable "serious" (the definition "serious" includes all of the aforementioned variables). Results obtained from logistic regression are reported in terms of OR with 95 % CI. In logistic regression analysis, the age of the patients was stratified in patients 65 years and older versus patients younger than 65 years.

In **BfArM's ADR-database** analysis, a sensitivity analysis by multiple imputation using the MICE package for R version 3.5.2 was performed for comparison of *validated ACEi angioedema cases* and *validated ACEi controls*, since 22 cases were incomplete (gender was unknown in two cases, age was unknown in 21 cases, both variables were missing in one case).

The ADR reports are included in the databases in a pseudonymized form. In accordance with the formal requirements, the reporting of ADRs in the post-marketing setting does not require any consent from the patient affected by the ADR. The study had been approved by the local ethics committee of the Medical Faculty of Bonn (009/17). Since the closure of BfArM's ADR-database, public access to the restricted set of data elements is no longer available. Due to data privacy requirements, it is not possible to make the complete individual case report available to the readership [51]. Researchers and/or readers who are interested can perform the same analysis in the ADR database EudraVigilance of the EMA (public access: http://www.adrreports.eu/en/index.html). However, different levels of access are granted for different stakeholders [52]. Nevertheless, even with the lowest level of access an analysis of aggregated data is possible.

Results

1.) Summary of reported characteristics in RASi angioedema cases and controls

1.1) *EVDAS* analysis

The age and gender distribution of *ACEi angioedema* cases and *controls* was almost equal (Table 1). Histories of "allergy" (OR 1.8 [1.4-2.3]), "previous/recurrent angioedema" (OR 36.8 [18.5-73.3]) or "urticaria" (OR 3.5 [1.4-8.4]) and "asthma" (OR 1.7 [1.2-2.3]) were reported more often in *ACEi angioedema cases* than in controls. In contrast, "renal disorders" (OR 0.6 [0.5-0.8]) were reported more frequently in *ACEi controls*. Enalapril (OR 1.9 [1.6-2.3]) and lisinopril (OR 2.0 [1.6-2.5]) had been administered more often in *ACEi angioedema cases* than in controls. Likewise, mTORi (OR 8.9 [4.9-16.4]) and fibrinolytics (mostly alteplase) (OR 16.3 [7.5-35.1]) had been used as concomitant medication more frequently in *ACEi angioedema cases* than in *controls*.

Gender-stratified analysis of *ACEi angioedema* cases revealed that a previous history of "allergy" (OR 2.3 [1.6-3.4], "urticaria" (OR 3.0 [1.0-9.2]), "asthma" (OR 1.8 [1.1-3.1]), "thyroid disorders" (OR 5.6 [3.1-10.0]) as well as concurrent use of diuretics (OR 1.5 [1.2-1.8]) and analgesics (OR 1.3 [1.1-1.7]) was more often reported for females than for males (S2 Table). In contrast, being a smoker (OR 0.3 [0.2-0.6]) and having a history of "previous/recurrent angioedema" (OR 0.5 [0.3-0.7]), "renal disorders" (OR 0.5 [0.4-0.8]) and concurrent treatment with a calcium antagonist (OR 0.8 [0.6-0.9]) and acetylsalicyclic acid (OR0.6 [0.5-0.8]) were more frequently reported for males than for females.

ACEi angioedema cases were more frequently designated as "serious" and "life-threatening" than *ACEi controls* (Table 1). Half of the *ACEi angioedema case* (50.7 %) either led to or prolonged "hospitalization".

Almost the same observations (but with different frequencies as seen in *ACEi angioedema cases*) were noted for *ARBs* and *aliskiren angioedema cases* with regard to reported "allergy", "previous/recurrent angioedema" and comorbidities when compared to their controls (S3 Table). More females in *aliskiren angioedema cases* (OR 1.5 [1.0-2.2]), a higher concomitant drug use of DPPIVi in *ARBs* (OR 1.8 [1.1-3.1]) and *aliskiren*

angioedema cases (OR 1.6 [0.5-5.2]) as well as concurrent ACEi use in *ARBs angioedema cases* (OR 2.2 [1.6-3.0]) were observed compared to their respective controls.

Table 1. *EVDAS* analysis: reported characteristics in *ACEi angioedema cases* and *ACEi controls* and comparative analysis of *ACEi angioedema cases* versus *ARBs* and *aliskiren angioedema cases*.

***EVDAS* analysis**	**Characteristics *ACEi angioedema cases* and *ACEi controls***		***ACEi angioedema cases* versus *ACEi controls***		***ACEi angioedema cases* versus *ARBs angioedema cases*** [k]		***ACEi angioedema cases* versus *aliskiren angioedema cases*** [l]	
	***ACEi angioedema cases* (n= 3,194; 22.9 %)**	***ACEi controls* (n= 10,773; 77.1 %)**	**unadj. OR [+/- 95 % CI]**	**logistic regression OR [+/- 95 % CI]**	**unadj. OR [+/- 95 % CI]**	**logistic regression OR [+/- 95 % CI]**	**unadj. OR [+/- 95 % CI]**	**logistic regression OR [+/- 95 % CI]**
patient demographics								
mean age (median) [years] [a]	66.8 (68.0)	67.1 (69.0)	-	1.0 [0.9-1.1]	-	1.0 [0.9-1.2]	-	1.1 [0.7-1.6]
female	47.2 % (1,506)	48.6 % (5,239)	0.9 [0.9-1.0]	1.0 [0.9-1.1]	0.6 [0.5-0.8]*	0.7 [0.6-0.9]*	0.5 [0.4-0.8]*	0.6 [0.4-0.9]*
male	50.6 % (1,617)	49.4 % (5,323)						
unknown	2.2 % (71)	2.0 % (211)						
patients history								
smoker [b]	2.1 % (66)	2.4 % (255)	0.9 [0.7-1.1]	0.8 [0.6-1.1]	1.0 [0.6-1.9]	0.8 [0.4-1.5]	1.6 [0.4-6.7]	1.3 [0.3-5.7]
allergy [c]	4.3 % (137)	2.1 % (228)	2.1 [1.7-2.6]*	1.8 [1.4-2.3]*	0.6 [0.4-0.9]*	0.8 [0.5-1.1]	0.3 [0.5-0.2]*	0.4 [0.2-0.8]*
urticaria	0.5 % (17)	0.1 % (9)	6.4 [2.8-14.4]*	3.5 [1.4-8.4]*	0.5 [0.2-1.2]	0.5 [0.2-1.3]	-	-
angioedema [d]	4.0 % (129)	0.1 % (9)	50.3 [25.6-99.1]*	36.8 [18.5-73.3]*	1.1 [0.7-1.9]	1.1 [0.7-1.8]	1.0 [0.4-2.4]	1.4 [0.5-3.8]

comorbidities [e]								
renal disorders	4.5 % (144)	6.4 % (694)	0.7 [0.6-0.8]*	0.6 [0.5-0.8]*	2.5 [1.4-4.5]*	1.9 [1.1-3.5]*	1.2 [0.5-2.7]	0.9 [0.2-2.2]
diabetes	10.2 % (325)	11.2 % (1,206)	0.9 [0.8-1.0]	-	1.4 [1.0-1.9]	-	0.9 [0.5-1.4]	-
asthma	2.3 % (74)	1.3 % (137)	1.8 [1.4-2.4]*	1.7 [1.2-2.3]*	0.9 [0.5-1.6]	0.9 [0.5-1.7]	0.4 [0.2-0.9]*	0.5 [0.2-1.1]
malignant tumors	4.0 % (127)	4.3 % (462)	0.9 [0.8-1.1]	0.9 [0.7-1.1]	1.4 [0.8-2.2]	1.1 [0.7-1.8]	1.6 [0.6-4.3]	1.8 [0.5-5.9]
thyroid disorders	2.6 % (82)	2.8 % (306)	0.9 [0.7-1.2]	0.9 [0.7-1.2]	0.8 [0.5-1.3]	0.8 [0.5-1.3]	0.6 [0.3-1.2]	0.6 [0.3-1.5]
administered ACEi [f]								
ramipril	37.4 % (1,195)	45.3 % (4,884)	0.7 [0.7-0.8]*	1.2 [1.0-1.4]	-	-	-	-
enalapril	28.2 % (902)	21.8 % (2,346)	1.4 [1.3-1.5]*	1.9 [1.6-2.3]*	-	-	-	-
perindopril	16.1 % (514)	15.6 % (1,676)	1.0 [0.9-1.2]	1.4 [1.2-1.7]*	-	-	-	-
lisinopril	13.1 % (419)	10.2 % (1,096)	1.3 [1.2-1.5]*	2.0 [1.6-2.5]*	-	-	-	-
comedication [g]								
β-blockers	22.7 % (725)	30.3 % (3,259)	0.7 [0.6-0.7]*	0.8 [0.7-0.9]*	1.4 [1.1-1.7]*	1.1 [0.9-1.4]	1.3 [0.9-2.0]	1.1 [0.7-1.9]
diuretics	21.9 % (700)	34.5 % (3,715)	0.5 [0.5-0.6]*	0.5 [0.4-0.6]*	1.2 [0.9-1.4]	1.0 [0.8-1.2]	0.9 [0.6-1.3]	0.8 [0.5-1.2]
calcium antagonists	17.5 % (558)	16.9 % (1,817)	1.0 [0.9-1.2]	1.1 [1.0-1.2]	1.4 [1.1-1.9]*	1.1 [0.8-1.4]	0.6 [0.4-0.8]	0.4 [0.3-0.6]*
ARBs	4.0 % (127)	4.8 % (518)	0.8 [0.7-1.0]	0.8 [0.7-1.0]	-	-	-	-

acetylsalicyclic acid	19.9 % (636)	20.7 % (2,235)	0.9 [0.9-1.0]	1.1 [1.0-1.2]	2.0 [1.5-2.5]*	1.4 [1.1-1.8]*	1.6 [1.0-2.5]	1.5 [0.9-2.6]
analgesics [h]	11.4 % (365)	13.6 % (1,469)	0.8 [0.7-0.9]*	0.8 [0.7-0.9]*	1.3 [1.0-1.8]*	1.1 [0.8-1.6]	1.9 [1.0-3.6]	2.6 [1.2-5.7]*
antidiabetics [i]	10.1 % (322)	12.8 % (1,376)	0.8 [0.7-0.9]*	0.8 [0.7-0.9]*	1.0 [0.7-1.3]	1.2[0.9-1.8]	1.2 [0.7-2.0]	1.6 [0.8-3.2]
DPPIVi	2.1 % (67)	2.2 % (232)	1.0 [0.7-1.3]	0.9 [0.6-1.2]	0.7 [0.4-1.1]	0.5 [0.3-0.9]*	0.5 [0.2-1.3]	0.6 [0.2-1.8]
mTORi	1.3 % (42)	0.2 % (18)	8.0 [4.6-13.8]*	8.9 [4.9-16.4]*	4.3 [1.0-17.9]	2.8 [0.7-12.0]	-	-
fibrinolytics	1.2 % (38)	0.1 % (9)	14.4 [7.0-29.8]*	16.3 [7.5-35.1]*	7.8 [1.1-57.2]*	-	-	-
seriousness criteria [j]								
serious	88.8 % (2,836)	73.9 % (7,965)	2.8 [2.5-3.1]*	3.3 [2.9-3.7]*	1.8 [1.5-2.3]*	1.8 [1.4-2.3]*	0.3 [0.1-0.6]*	0.3 [0.1-0.9]*
death	1.6 % (52)	2.7 % (288)	0.6 [0.4-0.8]*	-	2.7 [1.0-7.4]	-	0.6 [0.2-1.8]	-
life-threatening	15.5 % (496)	5.9 % (632)	2.9 [2.6-3.3]*	-	2.2 [1.6-2.9]*	-	14.2 [3.5-57.4]*	-
hospitalization	50.7 % (1,619)	45.6 % (4,909)	1.2 [1.1-1.3]*	-	2.3 [1.9-2.8]*	-	5.4 [3.5-8.3]*	-
disabling	0.8 % (27)	2.4 % (262)	0.3 [0.2-0.5]*	-	0.3 [0.2-0.5]*	-	0.7 [0.2-2.8]	-

*OR=1 is not included; OR > 1 reported more often in *ACEi angioedema cases*; OR < 1 reported more often in *ACEi controls*, *ARBs angioedema cases*, *alisiren angioedema cases*

[a] age unknown: *ACEi angioedema cases*: 179 cases (5.4 % of cases), *ACEi controls*: 717 cases (6.7 % of cases).

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] urticaria was analyzed based on the HLT "urticarias". The term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] suitable hierarchical levels of the MedDRA terminology were chosen for analysis of the reported patients' comorbidities. The term "renal disorders" was identified using the SMQs "acute renal failure" and "chronic kidney disease"; "diabetes": SMQ "hyperglycaemia/new onset diabetes mellitus"; "asthma": SMQ "asthma/bronchospasm"; "malignant tumors": SMQ "malignant tumours"; "thyroid disorders": SMQ "thyroid dysfunction".

[f] the four ACEi monosubstances most frequently reported as "suspected/interacting" are tabulated. The relative number of ADR reports specifying one of the remaining ACEi (not listed) as "suspected/interacting" was lower than 2 %. One ADR report may contain more than one ACEi as "suspected/interacting" drug substance. Thus, the number of reported ACEi exceeds that of the ADR reports.

[g] the analysis of the most frequently reported and most relevant comedications refers to monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the "suspected/interacting" ACEi were assessed as concomitant, regardless of whether they had been reported as "suspected", "interacting" or "concomitant".

[h] deviating from the ATC-code, the analysis concerning "analgesics" also includes ADR reports in which ibuprofen and/or diclofenac were listed as suspected/interacting or concomitant drug. We excluded ADR reports in which acetylsalicyclic acid was listed as suspected/interacting or concomitant drug. The number of ADR reports in which acetylsalicyclic acid was used concurrently were analyzed separately.

[i] deviating from the ATC-code, we excluded ADR reports in which a DPPIVi was listed as suspected/interacting or concomitant drug in the analysis concerning "diabetics". The number of ADR reports in which DPPIVi was used concurrently was analyzed separately.

[j] one ADR report may yield information about more than one seriousness criterion, therefore, the number of reported seriousness criteria exceeds that of the ADR reports.

[k] 44 cases which were included in *ACEi angioedema cases* and *ARBs angioedema cases* were excluded.

[l] 6 cases which were included in *ACEi angioedema cases* and *aliskiren angioedema cases* were excluded.

Table 1 shows the absolute and relative number of reports for the reported demographic parameters, comorbidities, comedications and seriousness criteria of *ACEi angioedema cases* and ACEi *controls* and the calculated unadjusted and adjusted odds ratios of *ACEi angioedema cases* versus *ACEi controls*, versus *ARBs angioedema cases* and versus *aliskiren angioedema cases*. The raw data of the *ARBs* and *aliskiren angioedema cases* as well as their unadjusted and adjusted odds ratio compared to their *controls* are presented in S3 Table.

1.2) *BfArM's ADR-database* analysis

Slightly more males (53.7 % versus females 43.4 %) were included in the *validated ACEi angioedema cases* versus *validated ACEi controls* of **BfArM's ADR-database** analysis (Table 2). However, after relating the number of ACEi angioedema reports to the assumed ACEi-exposed inhabitants/males/females (DEGS1) [33], ACEi-associated angioedema cases referred 1.5 times more often to females than to males (S4 Table).

In contrast to the **EVDAS** analysis, more smokers (OR 4.8 [2.0-11.4]) and patients with concurrent calcium antagonist intake (OR 2.1 [1.1-4.0]) were among the *validated ACEi angioedema cases* compared to *validated ACEi controls* (unadjusted Odds Ratios, Table 2). However, only smoking (p-value: 0.043) remained statistically significantly after sensitivity analysis with multiple imputation. Concurrent intake of diuretics was reported statistically significantly more often in *validated ACEi controls* after logistic regression and multiple imputation (p-value: 0.023).

The reporting of smoking (OR 4.3 [1.8-9.9]) remained statistically significantly more often, and concurrent intake of diuretics (OR 0.4 [0.3-0.8]) remained reported statistically significantly less often in *matched validated ACEi angioedema cases* versus *ACEi controls (not validated)* after 1:2 matching by age and gender (S5 Table).

Furthermore, compared to the **EVDAS** analysis (i) "allergy" and "asthma" were not reported statistically significantly more frequently in the *validated ACEi angioedema cases*, (ii) "renal disorders" was not reported more frequently in *validated ACEi controls*, (iii) ramipril was much more frequently reported as "suspected/interacting" ACEi, in general.

Table 2. *BfArM's ADR-database* analysis: characteristics of *validated ACEi angioedema cases* and *validated ACEi controls*.

***BfArM's ADR-database* analysis**	***characteristics of validated ACEi angioedema cases and validated controls***		***validated ACEi angioedema cases* versus *validated ACEi controls***			
	***validated ACEi angioedema cases* (n= 121)**	***validated ACEi controls* (n= 242)**	**unadj. OR [+/- 95 % CI]**	**logistic regression OR [+/- 95 % CI]**	**logistic regression p-values**	**logistic regression + imputation (MICE) p-values**
completeness score [a]	0.74 [0.65-0.82]	0.71 [0.65-0.77]	-	-	-	-
patient demographics [b]						
mean age (median) [years]	64.5 (68)	63.5 (65)	- -	1.5 [0.9-2.7]´	0.121	0.099
female	46.3 % (56)	55.8 % (135)	0.7 [0.4-1.0]	0.9 [0.5-1.5]	0.569	0.665
male	53.7 % (65)	43.4 % (105)				
smoking and drinking habits, allergic conditions						
smoker [c]	14.0 % (17)	3.3 % (8)	4.8 [2.0-11.4]*	2.7 [1.0-7.6]	0.058	0.043*
alcohol consumption [d]	9.1 % (11)	2.5 % (6)	3.9 [1.4-10.9]*	2.9 [0.8-10.4]	0.098	0.088
allergy [e]	12.4 % (15)	10.3 % (25)	1.2 [0.6-2.4]	1.0 [0.5 -2.3]	0.942	0.988
angioedema [f]	24.0 % (29)	-	-	-	-	-
comorbidities [g]						

renal disorders	9.9 % (12)	8.7 % (21)	1.2 [0.5-2.4]	1.0 [0.4-2.3]	0.953	0.749
diabetes	15.7 % (19)	13.2 % (32)	1.2 [0.7-2.3]	1.1 [0.5-2.2]	0.892	0.951
asthma/COPD	9.1 % (11)	6.2 % (15)	1.5 [0.7-3.4]	1.8 [0.7-4.8]	0.253	0.231
administered ACEi [h]						
ramipril	67.8 % (82)	75.2 % (182)	0.7 [0.4-1.1]	1.4 [0.4-5.0]	0.620	0.997
enalapril	16.5 % (20)	12.4 % (30)	1.4 [0.8-2.6]	1.4 [0.4-5.8]	0.607	0.822
lisinopril	10.7 % (13)	9.1 % (22)	1.2 [0.6-2.5]	1.5 [0.4-6.7]	0.563	0.770
comedication [i]						
β-Blocker	28.1 % (34)	23.1 % (56)	1.3 [0.8-2.1]	1.6 [0.8-3.0]	0.165	0.275
diuretics	13.2 % (16)	17.4 % (42)	0.7 [0.4-1.4]	0.4 [0.2-0.8]*	0.023*	0.023*
calcium antago-nists	17.4 % (21)	9.1 % (22)	2.1 [1.1-4.0]*	1.6 [0.7-3.3]	0.248	0.181
NSAID	21.5 % (26)	19.8 % (48)	1.1 [0.6-1.9]	0.5 [0.3-1.0]	0.057	0.083
everolimus	5.8 % (7)	0.0 % (0)	-	-	-	-
alteplase	0.8 % (1)	0.0 % (0)	-	-	-	-
seriousness criteria [j]						
serious	89.3 % (108)	53.7 % (130)	7.2 [3.8-13.4]*	7.7 [3.9-15.1]*	< 0.001*	< 0.001*
death	3.3 %	1.2 %	2.7 [0.6-12.4]	-	-	-

	(4)	(3)				
life-threatening	28.9 %	5.0 %	2.8 [1.6-4.8]*	-	-	-
	(35)	(12)				
hospitalization	49.6 %	28.5 %	2.5 [1.6-3.9]*	-	-	-
	(60)	(69)				
disabling	0.8 %	5.0 %	0.2 [0.0-1.2]	-	-	-
	(1)	(12)				

*OR = 1 is not included; OR > 1 reported more often in *validated ACEi angioedema cases*; OR < 1 reported more often in *validated ACEi controls*

[a] in cases and controls, most data referring to the variable "time to onset" was incomplete or missing. The calculation of the completeness score is described in the Methods section: 2.2.3. **BfArM's ADR-database**: documentation quality of validated cases.

[b] *validated ACEi angioedema cases*: age unknown in 21 reports, gender unknown in 2 reports.

[c] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[d] information about the amount of alcohol consumed (daily/weekly) was rare and may not have been reported. It was not possible to classify the cases in patients with a high or moderate alcohol consumption due to inaccurate information. Therefore, all cases in which any alcohol consumption was reported were counted, independent of the amount.

[e] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[f] the term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[g] refers to renal disorders, diabetes, asthma/COPD (chronic obstructive pulmonary disease) reported in the patients' history or as a drug indication term for the used comedication.

[h] the three ACEi monosubstances most frequently reported as "suspected/interacting" are tabulated. The remaining ACEi (not listed) were reported fewer than 5 times.

[i] the analysis of the most frequently reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the "suspected/interacting" ACEi were counted as "concomitant", regardless of whether they were reported as "suspected", "interacting" or "concomitant".

[j] One ADR report may yield information about more than one seriousness criterion, therefore, the number of reported seriousness criteria exceeds that of the ADR reports.

Table 2 shows the absolute and relative number of reports and the calculated unadjusted and adjusted odds ratios for the reported demographic parameters, comorbidities, comedications, and seriousness criteria of *validated ACEi angioedema cases* and *controls* originating from Germany. Since there were 21 cases with missing data in the variables age and/or gender, multiple imputation methods were applied.

2.) Comparative analysis of angioedema cases: ACEi versus ARBs and aliskiren

2.1.) *EVDAS* analysis

Comparative analysis of angioedema cases between *ACEi* versus *ARBs* and *aliskiren* (each separately) revealed more females in *ARBs* (OR 0.7 [0.6-0.9]) and *aliskiren* cases (OR 0.6 [0.4-0.9]) than in *ACEi* cases (Table 1). In contrast, concurrent intake of acetylsalicyclic acid, analgesics, mTORi and fibrinolytics was more frequently reported in *ACEi* versus *ARBs* and *aliskiren angioedema cases.* A higher proportion of allergic patients was included in *ARBs* (6.8 %) and *aliskiren* (13. 6 %) *angioedema cases*, as well as patients with a history of urticaria in *ARBs angioedema cases* (0.9 %) compared to *ACEi angioedema cases* (allergy: 4.3 %, urticaria: 0.5 %) (Table 1, S3 Table). *ACEi angioedema cases* were classified as "life-threatening" (15.5 %) and led to or prolonged "hospitalization" (50.7 %) the most frequently compared to the others.

2.2) *BfArM's ADR-database* analysis

2.2.1. Patient populations

Regarding the relevant information included in the calculation of the completeness score, the highest score was calculated for *ACEi angioedema cases* (0.74 [0.65-0.82]), followed by *ARBs* (0.67 [0.54-0.80]) and *aliskiren ,*(0.68 [0.49-0.88]) *angioedema cases* (Table 2 and S6 Table).

In general, the proportion of allergic patients and patients with previous/recurrent angioedema in *validated ACEi* (12.4 %, 24.0 %)*, ARBs* (19.0 %, 11.1 %) and *aliskiren angioedema* cases (24.2 %, 35.4 %) was much higher than in the **EVDAS** analysis (ACEi: 4.3 % & 4.0 %, ARBs: 6.8 % & 4.5 %, aliskiren: 13.6 % & 4.9 %) (Table 1, S3 Table). More patients with allergies were included in *validated ARBs* and *aliskiren angioedema cases* and more patients with a history of previous/recurrent angioedema in the *validated aliskiren angioedema cases* compared to the *validated ACEi angioedema cases*.

In eight (12.7 %) of the *validated ARBs angioedema cases*, a history of prior ACEi therapy was reported. Reasons for discontinuing the previous ACEi therapy were "cough" (four times), "allergy" (once) and "angioedema" (once). In two cases, information was not available (NA).

In thirteen (39.4 %) of the *validated aliskiren angioedema cases*, a history of prior ACEi and/or ARBs therapy was reported. As a reason for the discontinuation of the prior ACEi/ ARBs therapy, "angioedema" was reported seven times and "cough" twice. In four cases no information was available (NA).

2.2.2. Number of ADR reports in relation to the number of drug prescriptions

The number of angioedema reports per 1,000 million drug prescriptions (in DDD) was higher for *ARBs* (10 angioedema reports) and *aliskiren* (154 angioedema reports) than for *ACEi* (8 angioedema reports) (Fig 2). Regarding the reported drug substances, the highest reporting rate (i.e. the number of ARD reports per 1,000 million drug prescriptions in DDD) compared to the other *ACEi/ ARBs* was found for lisinopril (13 angioedema reports) and valsartan (16 angioedema reports).

Fig 2. Number of *ACEi*, *ARBs*, and *aliskiren angioedema cases* per 1,000 Mio drug prescriptions in DDD (2010-2016).

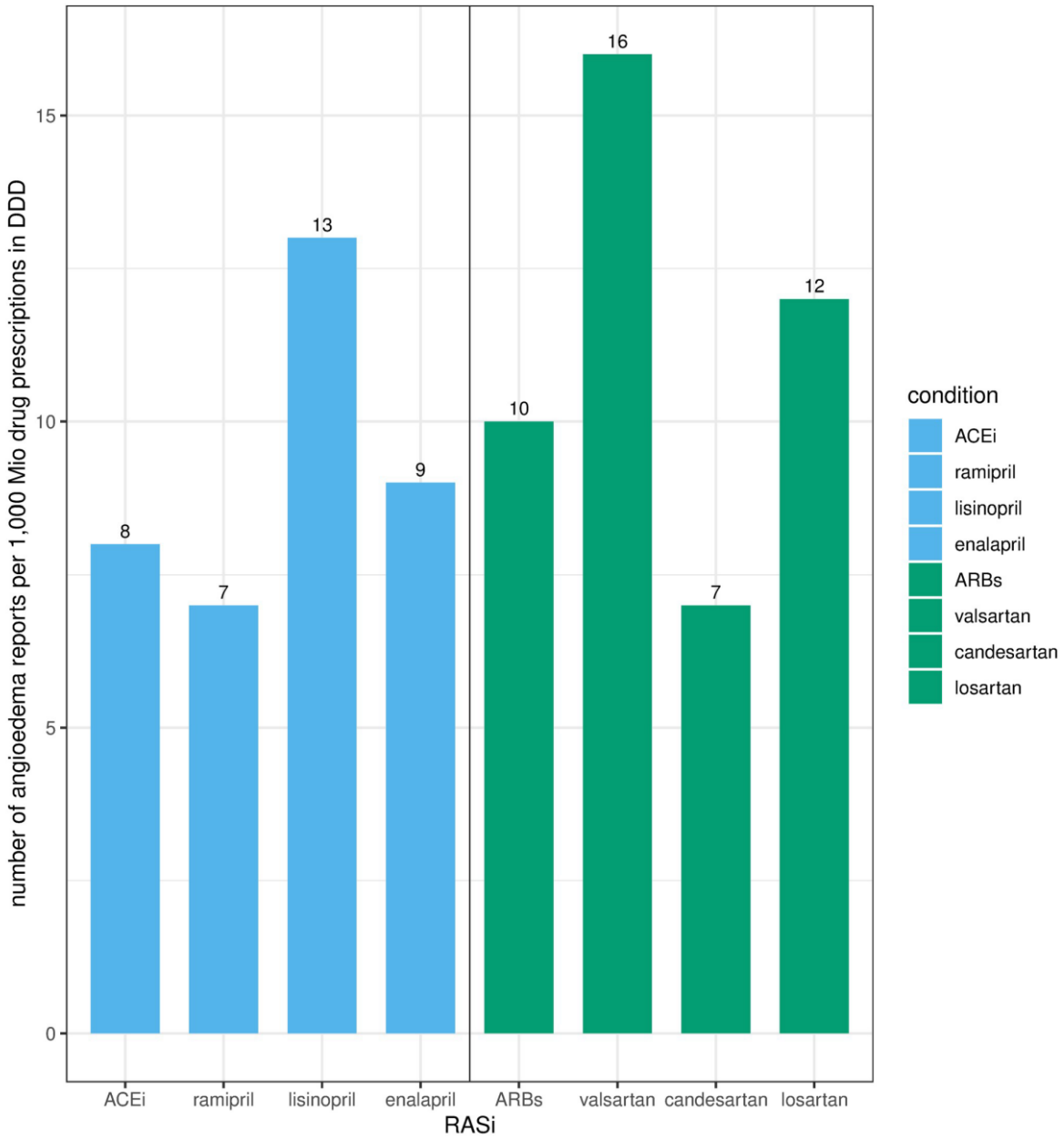


Fig 2 shows the number of angioedema reports per 1,000 Mio drug prescriptions in DDD for ACEi, and ARBs. For aliskiren, 154 angioedema reports per 1,000 Mio drug prescriptions were calculated. The number is not depicted in Fig 2 in order to make the difference between the respective drug substances of ACEi and ARBs clearer. The complete presentation of the number of cases and the number of drug prescriptions used for the

calculation of the number of angioedema reports per 1,000 Mio drug prescriptions in DDD is contained in S7 Table. Our result deviates from existing literature. With regard to a meta-analysis of randomized trials for renin-angiotensin system inhibitors associated angioedemas, the incidences for ACEi were 0.30 % for ARBs 0.11 % and for aliskiren 0.13 % [23]. The limitations of spontaneous reporting systems have to be considered.

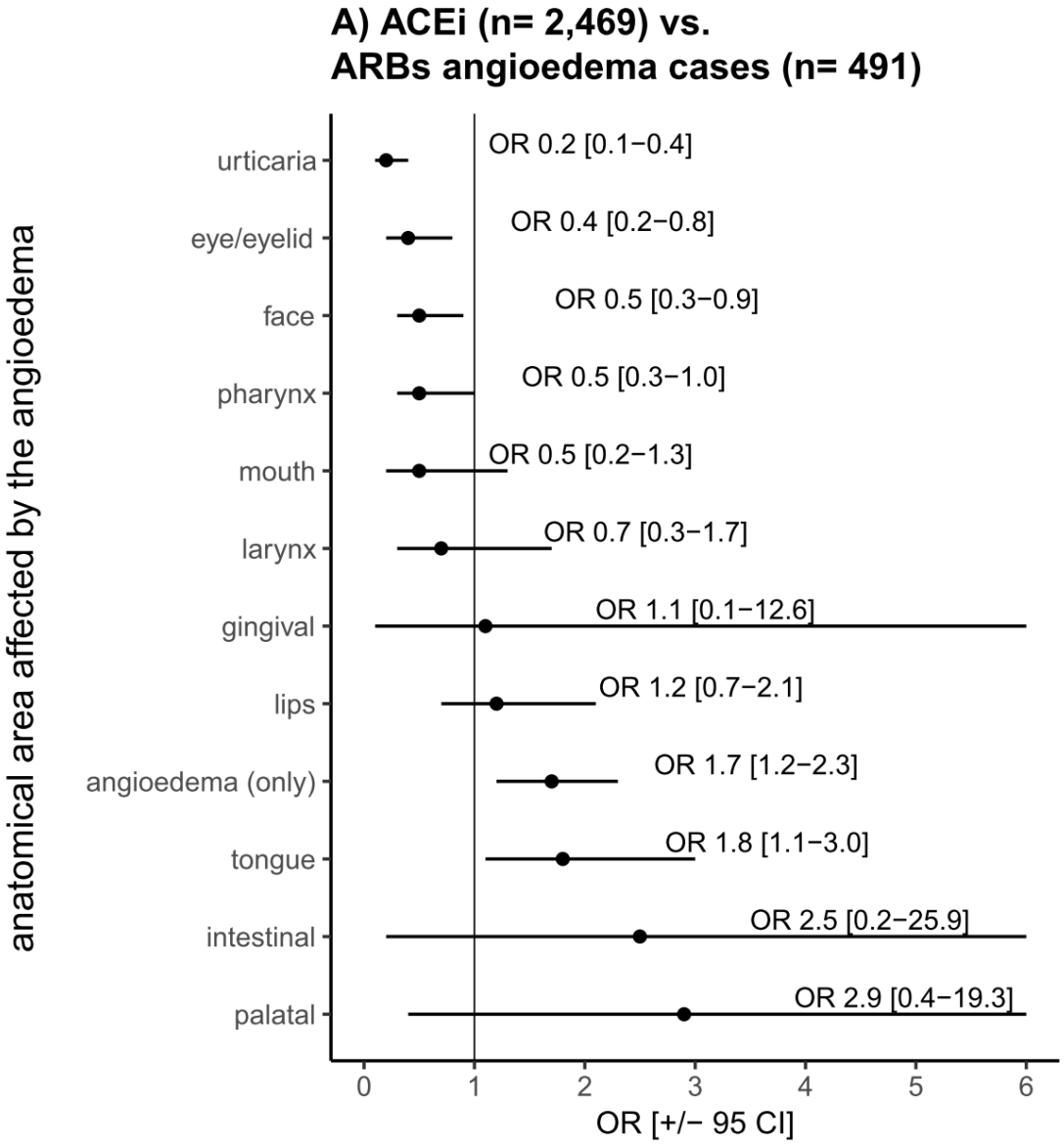
3.) Reported clinical phenotype

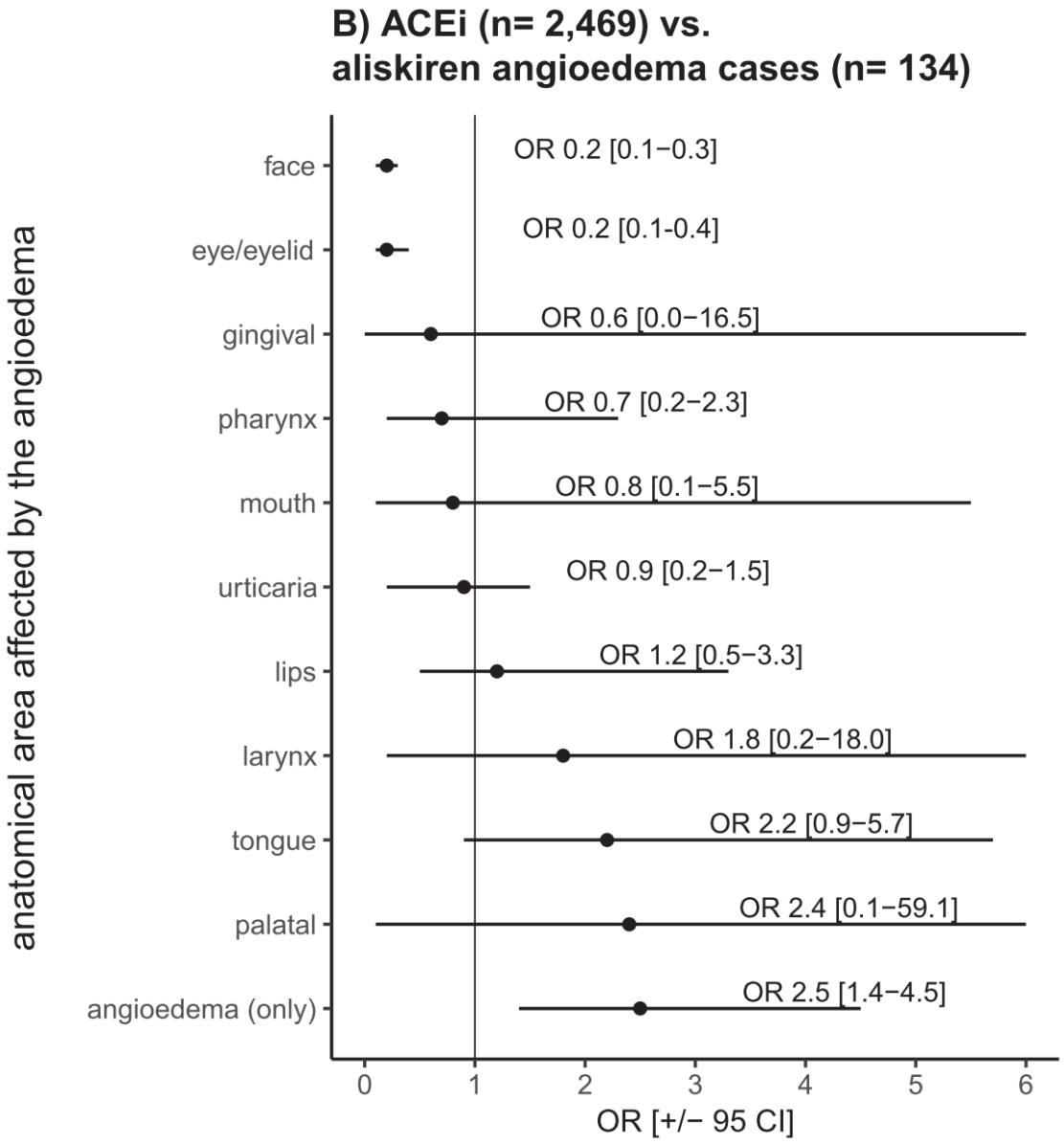
3.1) *EVDAS* analysis

In *ACEi angioedema cases*, the "tongue" (19.4 %) was mostly involved and more frequently reported in *ACEi* versus *ARBs* and *aliskiren angioedema cases* (Fig 3). In contrast, "face" and "eye/eyelid" were reported more frequently as affected anatomical areas in *ARBs* and *aliskiren angioedema cases* than in *ACEi angioedema cases*. In *ARBs* and *aliskiren angioedema cases,* "urticaria" (18.5 %, 9.0 %) and/or "pruritus" (9.2 %, 13.4 %) were reported more often as attendant symptoms than in *ACEi angioedema cases* ("urticaria": 5.0 %, "pruritus": 3.1 %). Additionally, "peripheral swellings/oedemas" were more frequently reported in *aliskiren* (23.1 %) compared to *ACEi* (1.2 %) and *ARBs* (2.6 %) *angioedema cases*.

In a stratified analysis of *ACEi angioedema cases* with concurrent use of mTORi (n= 42) or fibrinolytics (n= 38), the "tongue" was most often involved (31.0 %, 31.6 %) and more often involved than in the whole dataset (19.4 %). Interestingly, none of these cases reported "urticaria" or "pruritus" (S8 Table).

Fig 3. *EVDAS* analysis: reported anatomical area affected by the angioedema according to SMQ "angioedema (narrow)" of the MedDRA terminology.





*OR = 1 not included. OR > 1 more often reported in *ACEi angioedema cases*; OR < 1 more often reported in *ARBs* or *aliskiren angioedema cases.*

Fig 3 shows the calculated odds ratios with Bonferroni adjusted confidence intervals for the reported anatomical areas affected by the angioedema according to the SMQ "angioedema (narrow)" for *ACEi angioedema cases* versus *ARBs* and *aliskiren angioedema cases*. Therefore, only cases in which the respective RASi was reported as the "suspected" drug were included. For calculation of the odds ratios, the *ACEi angioedema cases* served as a reference. The number of ADR reports describing the same anatomical area e.g. "tongue oedema" and "swollen tongue" were merged into one group (here: tongue). In some of the reports, only the diagnosis "angioedema" was coded (designated as “only diagnosis angioedema”). One ADR report can contain more than one reported anatomical area affected by the angioedema. Therefore, the number of reported anatomical areas affected by the angioedema exceeds that of the ADR reports. Please note that some of the confidence intervals are not displayed completely.

3.2) *BfArM's ADR-database* analysis

In 15.7 % of *validated ACEi angioedema cases*, only the summarized diagnosis "angioedema" was reported. As well as in **EVDAS**, the "tongue" was mostly involved in the *validated ACEi angioedema cases* (41.3 %) (Table 3) in the **BfArM's ADR-database***.* In general, the proportion of reports yielding information about the anatomical area affected by the angioedema was much higher in **BfArM's ADR-database** compared to the **EVDAS** analysis.

With regard to the stratified analysis, patients in whom the "eye/eyelid" was involved were younger, more often females (77.8 %) and the reports were less often designated as "serious". Additionally, "allergy" and "pruritus" as attendant symptoms were mentioned in one third of these reports. Patients in whom the "cheek", "pharynx", "glottis" or "neck/throat" were affected were more often males and the reaction was described more often as "serious". "Urticaria" and "pruritus" did not occur in patients in whom the "tongue" and the "pharynx" were involved.

A higher proportion of "face" and "eye/eyelid" involvement was also observed in *validated ARBs* (34.9 %, 12.7 %) and *aliskiren* (39.4 %, 12.1 %) *angioedema cases* versus v*alidated ACEi angioedema cases* (20.6 %, 7.4 %) (Table 3 and S6 Table). The same applies for "pruritus" and "urticaria" (*validated ARBs angioedema cases*: 15.9 %, 12.7 %, *validated aliskiren angioedema cases*: 15.2 %, 9.1 %, *validated ACEi angioedema cases*: 5.0 %, 3.3 %).

Table 3. *BfArM's ADR-database* analysis: stratified analysis of anatomical areas affected by ACEi-associated angioedemas

	tongue [a] 41.3 % (n= 50)	**lips [a] 28.1 % (n= 34)**	**face [a] 20.6 % (n= 25)**	**pharynx [a] 13.2 % (n= 16)**	**neck/ throat [a] 12.4 % (n= 15)**	**cheek [a] 10.7 % (n= 13)**	**glottis [a] 9.1 % (n= 11)**	**eye/ eyelid [a] 7.4 % (n= 9)**
patient demographics								
mean age (median) [years]	66.0 (70)	64.9 (68.5)	65.7 (69)	66.6 (68.5)	66.1 (69)	65.4 (69)	65 (67)	57.8 (61)
female	46.0 % (23)	32.4 % (11)	64.0 % (16)	31.3 % (5)	40.0 % (6)	30.8 % (4)	36.4 % (4)	77.8 % (7)
male	54.0 % (27)	67.6 % (23)	36.0 % (9)	68.8 % (11)	60.0 % (9)	69.2 % (9)	63.6 % (7)	22.2 % (2)
smoking habits, allergic conditions								
smoker [b]	26.0 % (13)	5.9 % (2)	12.0 % (3)	12.5 % (2)	13.3 % (2)	7.7 % (1)	36.4 % (4)	11.1 % (1)
allergy [c]	8.0 % (4)	20.6 % (7)	16.0 % (4)	6.3 % (1)	13.3 % (2)	7.7 % (1)	0.0 % (0)	33.3 % (3)
angioedema [d]	16.0 % (32)	44.1 % (15)	32.0 % (8)	18.8 % (3)	33.3 % (5)	30.8 % (4)	45.5 % (5)	44.4 % (4)
asthma/COPD [e]	10.0 % (5)	14.7 % (5)	8.0 % (2)	6.3 % (1)	6.7 % (1)	7.7 % (1)	0.0 % (0)	22.2 % (2)
comedication								

everolimus	8.0 % (4)	8.8 % (3)	16.0 % (4)	6.3 % (1)	0.0 % (0)	15.4 % (2)	0.0 % (0)	11.1 % (1)
alteplase	2.0 % (1)	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)
reported attendant reactions								
urticaria [f]	0.0 % (0)	8.8 % (3)	4.0 % (1)	0.0 % (0)	0.0 % (0)	0.0 % (0)	18.2 % (1)	0.0 % (0)
pruritus [h]	0.0 % (0)	14.7 % (5)	16.0 % (4)	0.0 % (0)	6.7 % (1)	7.7 % (1)	0.0 % (0)	33.3 % (3)
seriousness criteria [i]								
serious	92.0 % (46)	91.2 % (31)	92.0 % (23)	100.0 % (16)	93.3 % (14)	92.3 % (12)	100.0 % (11)	77.8 % (7)
death	6.0 % (3)	2.9 % (1)	0.0 % (0)	12.5 % (2)	13.3 % (2)	0.0 % (0)	18.2 % (1)	0.0 % (0)
life-threatening	48.0 % (24)	8.8 % (3)	32.0 % (8)	43.8 % (7)	46.7 % (7)	23.1 % (3)	54.5 % (6)	11.1 % (1)
hospitalization	54.0 % (27)	32.4 % (11)	40.0 % (10)	68.8 % (11)	60.0 % (9)	30.8 % (4)	63.6 % (7)	11.1 % (1)

[a] one report can yield information about more than one anatomical area affected by the angioedema. Therefore, the total number of areas affected by the angioedema exceeds that of the ADR reports.

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] the term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] the term "asthma/COPD" refers to asthma/COPD (chronic obstructive pulmonary disease) reported in the patients' history or as a drug indication for one of the drugs used concomitantly.

[f] the term "urticaria" summarizes urticarias coded in the SMQ "angioedema (narrow)" reported as adverse drug reaction.

[h] the term "pruritus" summarizes PTs that included pruritus independent of the anatomical area affected by the ADR.

[i] one ADR report may yield information about more than one seriousness criterion. Thus, the number of reported seriousness criteria exceeds that of the ADR reports.

Table 3 shows the relative and absolute number of ADR reports of the stratified anatomical areas affected by ACEi-associated angioedemas. For each anatomical area affected by the angioedema, patient demographics, smoking habits and comorbidities, comedications, attendant symptoms and the seriousness criteria of the reports were analyzed. The information about anatomical areas affected by the angioedema was retrieved from the reported ADRs and the narratives of the angioedema reports.

4.) *BfArM's ADR-database* analysis: time-to-onset of angioedema reactions

In 76.9 % of *validated ACEi,* 58.7 % of *validated ARBs*, and 57.6 % of *validated aliskiren angioedema cases* data on the "time-to-onset" variable was available (Fig 4). Compared to *ACEi* (33.3 %) a higher proportion of *validated ARBs* (70.3 %) and *aliskiren* (84.2 %) *angioedema cases* reported that the angioedema occurred during the first month of therapy. In contrast, the reactions occurred after the first year in a much higher proportion in *validated ACEi angioedema cases* 46.2 % compared to ARBs (13.5 %) and aliskiren (0.0 %).

Fig 4. BfArM's ADR-database analysis: "time-to-onset" analysis of the angioedema reaction.

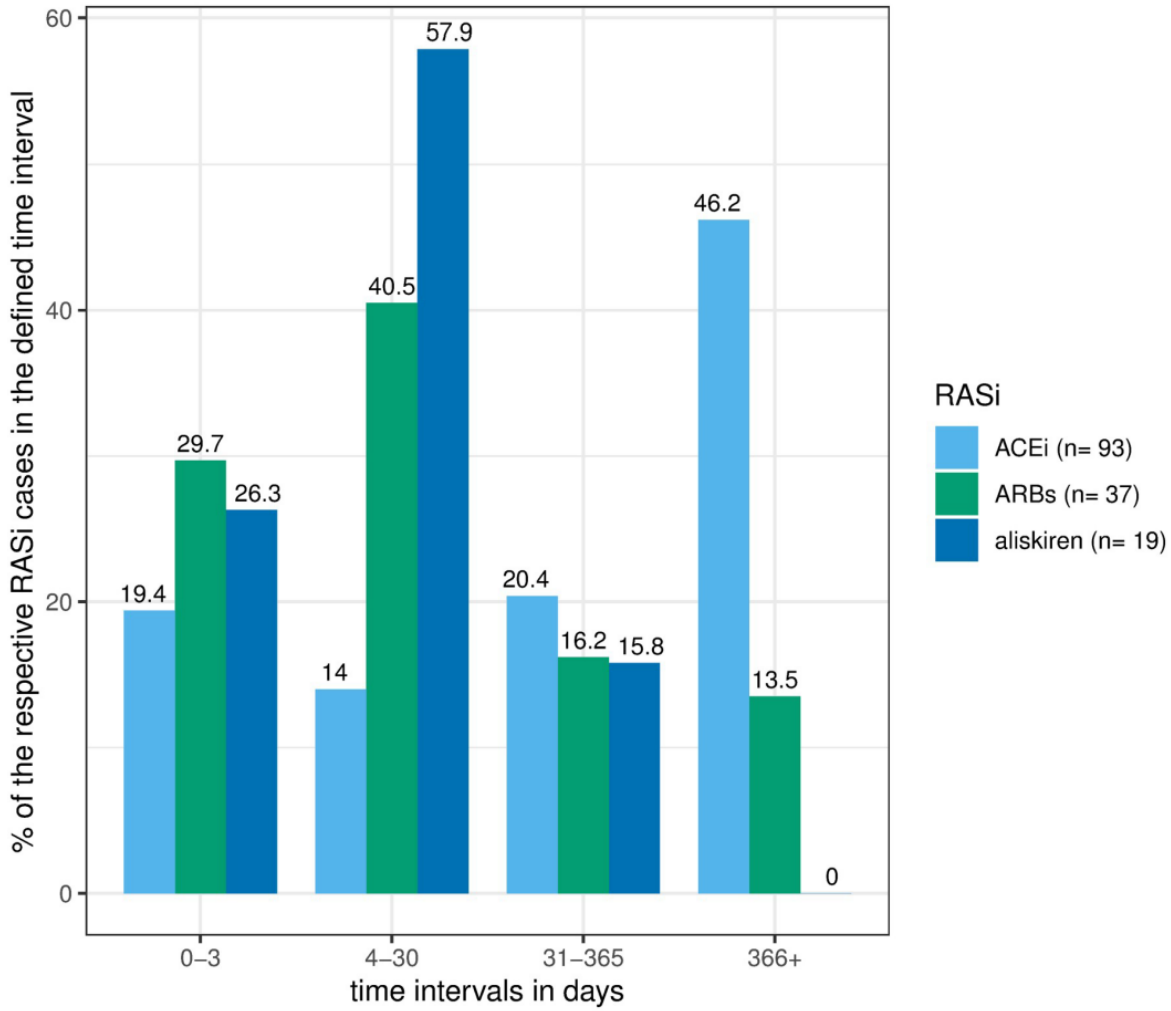


Fig 4 shows the "time-to-onset" analysis of validated ACEi, ARBs, and aliskiren-associated angioedemas. In this figure only cases providing information on the "time-to-onset" were included.

5.) *BfArM's ADR-database* analysis: treatment of angioedema

Information about the treatment of angioedemas was available in 64.4 % of the *validated ACEi angioedema cases* (S9 Table). Most of the patients were treated with antihistamines and/or steroids, only (60.3 %, n= 47). Of the patients treated with antihistamines and/or steroids, 15 had a rapid and 13 a slow regression of symptoms (19 cases: not assessable). Circulation stabilizing drugs (12.8 %, n= 10) were used additionally to antihistamines and/or steroids (n= 9) or alone (n= 1) and led to a rapid regression in two patients and a slow regression in seven patients (in one patient not assessable). A medical intervention (e.g. intubation) was performed in 16.7 % (n= 13) of the cases. C1-esterase inhibitors were used in 10.3 % (n= 8) of the cases (n= 6 rapid regression, n= 1 slow regression, n= 1 unknown). Icatibant was administered in 5.1 % of the cases and in one case additional fresh frozen plasma was administered. Both treatments led to a rapid regression of symptoms in all patients.

In 79.3 % of the *validated ACEi angioedema cases*, information about "action taken with regard to the administered ACEi" was available. "Drug withdrawn" was reported in 92.7 % of these cases.

Treatment was only rarely reported for ARBs (30.2 % of cases) and aliskiren (18.2 % of cases)-associated angioedemas. In those cases in which information about angioedema treatment was available, antihistamines and/or steroids were used. "Drug withdrawn" was reported in 86.7 % (39/45) of *ARBs*, and 96.0 % (24/25) of *aliskiren angioedema cases* (related to the number of reports that included information about action taken with regard to the administered drug).

Discussion

To the best of our knowledge, the present study represents the first retrospective analysis of angioedema reports associated with RASi covering the entire EEA performed in **EVDAS**. To strengthen the significance of this analysis, an additional analysis of validated cases originating from Germany was performed in **BfArM's ADR-database**.

Many studies have been published in which associated factors of ACEi-induced angioedemas were analyzed. However, only a few investigated associated factors of ARBs and aliskiren-associated angioedemas. In our analysis, already known associations of ACEi angioedemas were found and some of them were also observed for ARBs and aliskiren angioedemas (e.g. "previous/recurrent angioedema"). Differences were noted between ACEi, ARBs and aliskiren with regard to the reported seriousness criteria (ACEi-associated angioedemas were more "serious"), the reporting rates (higher rates for ARBs and aliskiren) and the clinical phenotypes ("urticaria" reported more often for ARBs and aliskiren-associated angioedemas). The analysis performed in **EVDAS** and **BfArM's ADR-database** showed similarities (e.g. clinical phenotypes) but also differences (e.g. smoking habits).

Patient demographics and gender-stratified analysis

Female gender has been reported by other authors [1, 5, 19, 53] as a risk factor for developing an ACEi-associated angioedema. In our analysis, ACEi-associated angioedemas occurred 1.5 times more often in females than in males when the *validated ACEi angioedema cases* were put in relation to the number of assumed ACEi-exposed patients [33]. Regardless of any patient-related exposure data (which were not available for aliskiren in DEGS1), more females were included in *aliskiren angioedema cases* compared to their controls. In order to make conclusive statements, gender-related drug exposure with aliskiren has to be considered.

Gender-stratified analysis showed that the association with smoking was more pronounced in males than in females whereas it was the opposite regarding allergic conditions. This finding possibly reflects gender-specific diseases or behaviors [54, 55]. A

previous German health study diagnosed more females as being allergic (35.8 %) and/or asthmatic (9.9 %) than males (24.1 % allergic, 7.3 % asthmatic), while surveys investigating smoking behavior reported more male than female smokers [54, 55].

Allergic conditions, comorbidities and reported seriousness criteria

A pre-existing history of urticaria and angioedema, as well as allergic and asthmatic conditions were reported more often in all of the three *RASi angioedema cases* compared to their *controls*. Seasonal allergies [19] and previous angioedemas [11] are also described as associated factors in ACEi angioedemas in literature.

In all three controls of the **EVDAS** analysis, more patients with a history of renal disorders were involved compared to their respective cases. This was not observed in the analysis of validated **BfArM** cases. However, this finding in the **EVDAS** analysis most likely reflects an association with the ADRs reported in the controls (e.g. acute kidney injury) and should therefore not be interpreted as a protective factor for RASi-associated angioedema [19]. It has to be noted that our analysis of renal disorders did not differentiate between acute and chronic kidney disease, which are substantially different clinical entities. This was the case because a proper assignment to one of the used SMQs was not possible since both SMQs have some preferred terms in common resulting in an overlap [45].

ACEi-associated angioedemas were most often designated as "life-threatening" and most often led to or prolonged "hospitalization" compared to ARBs and aliskiren. In this regard, Toh et al. [8] also discussed a more serious course of ACEi-associated angioedemas compared to ARBs and aliskiren.

Reported smoking habits, comedications and clinical phenotypes in relation to the assumed pathophysiological mechanism of interaction

With regard to pathophysiology, one can roughly distinguish between histamine-mediated and bradykinin-mediated angioedemas [2, 12]. The following section offers a

brief discussion of the differences between the clinical phenotypes of histamine-mediated and bradykinin-mediated angioedemas and the mechanism of interaction with some comedications in relation to the results of our analysis.

Both histamine and bradykinin can induce vasodilatation and increased vascular permeability leading to angioedema [12]. Histamine is either released from mast cells and/or basophils in context with an allergic, immunoglobuline E (IgE) mediated reaction or via non-immunological mechanisms [56]. Histamine-mediated reactions typically present with urticaria and pruritus [2, 12, 57] and respond to antihistamines [57, 58]. Bradykinin-mediated angioedema result from an interference in or inbalance of the bradykinin degradation pathway [2, 11, 12]. This may occur due to a hereditary defect or through external factors (e.g. ACEi). In contrast to histamine-mediated angioedemas, bradykinin-mediated angioedemas dot not usually present with "urticaria" and "pruritus".

When ACE is blocked, e.g. by ACEi, bradykinin can be degraded by alternative enzymes such as DPPIV and/or neutral endopeptidase (NEP). A decreased level of DPPIV activity was measured in patients during ACEi-associated angioedema attacks [59]. Therefore, drugs and/or comorbidities that have an impact on bradykinin levels by blocking or reducing DPPIV activity may influence the occurrence of angioedemas [59, 60].

Smoking has been described as a risk factor for ACEi-associated angioedemas [21, 59] and is assumed to lead to a reduced DPPIV activity [13, 60]. In our analysis, this was only observed for the comparison of *validated ACEi angioedema cases* with *validated ACEi controls* (p-value: 0.043) (**BfArM's ADR-database)**. An underreporting of smoking habits in **EVDAS** may be one possible explanation that this finding was not observed in **EVDAS**.

In our analysis, exposure to fibrinolytics (e.g. tissue plasminogen activators (tPA)) was 16.5 fold higher in *ACEi angioedema cases* versus their *controls*. Angioedema is described to occur in 1.7 [61] -7.9 % [62] of all cerebral vascular accident patients treated with tissue plasminogen activators (tPA) and is reported to occur more frequently when ACEi is taken concomitantly [61, 62, 63]. The increased risk of angioedema may result from neuronal damages leading to an upregulation of bradykinin-receptors-B2, and/or the increased production of bradykinin induced by tPA [62, 63].

mTORi therapy was reported about 9.2 times more often in the *ACEi angioedema cases* versus their *controls* and about 4.3 times more often versus *ARBs angioedema cases*. A greater number of angioedema events per 100 treatment years was estimated in kidney transplant patients treated with mTORi with combined ACEi therapy (3.8) than with combined ARBs therapy (0.5) [64]. The DPPIV activity in patients with renal transplants is generally expected to be lower [61, 65]. Additionally, the DPPIV activity in cultured endothelial cells was decreased by up to 60.0 % when treated with sirolimus [65].

However, in our analysis the number of cases with concurrent mTORi and fibrinolytics use in *ARBs* and *aliskiren angioedema cases* was rather low or no cases were available. Either, those drugs potentiate the angioedema risk only when combined with ACEi, or the combined therapies with ARBs and aliskiren are too seldom to be observed in our analysis.

Interestingly, in none of the *ACEi angioedema cases* with concurrent fibrinolytics or mTORi therapy "urticaria" and/or "pruritus" was mentioned. Hence, a bradykinin-mediated angioedema appears plausible as also described in literature [62, 63, 64, 65]. For both, the "tongue" was the anatomical area most often affected by the angioedema. In the stratified analysis, none of the validated cases in which the "tongue" was involved presented with "urticaria" or "pruritus" as attendant symptoms. Hence, based on our observations one may speculate whether involvement of the "tongue" could be more often associated with bradykinin-mediated angioedemas.

With regard to diabetes, some studies reported that ACEi-associated angioedemas occurred less frequently in patients with diabetes [5, 19, 65]. Byrd et al. reported a less frequent occurrence of ACEi- and NEP-associated angioedemas in ACE treated patients with diabetes and measured a higher DPPIV actitvity in ACEi treated diabetic patients compared to ACEi treated non-diabetic patients [13]. In line with these findings, in our analysis the proportion of patients taking any antidiabetic drugs (interpreted as patients with diabetes) excluding DPPIV inhibitors was slightly lower in all RASi angioedema cases versus RASi controls in the **EVDAS** analysis. However, patients concomitantly treated with DPPIV inhibitors may have an increased risk of developing ACEi-associated angioedemas potentiated by the inhibition of the enzyme DPPIV [11, 66]. In our analysis, a higher DPPIV inhibitor use compared to the respective controls was observed in *ARBs*

and *aliskiren angioedema cases* only. In literature, conflicting data exists whether the combined therapy of DPPIV inhibitors and ARBs may potentiate the occurrence of angioedemas [66, 67].

Concerning the anatomical areas affected by the angioedema, a higher proportion of "face" and/or "eye/eyelid" involvement was reported in *ARBs* and *aliskiren angioedema cases* compared to *ACEi angioedema cases.* The same applies to "urticaria" and "pruritus", as well as to "peripheral swellings/oedemas". Others reported that angioedemas that involved the "eye" are significantly more often histamine-mediated angioedemas [53] while peripheral swellings are more frequently observed in bradykinin-mediated angioedemas [53, 57]. Likewise, the proportion of reported "allergy" in the patients' history and "pruritus" as an ADR was highest in the stratified analysis of the validated cases in which the "eye/eyelid" was involved (small sample size: n= 9). Slightly more "peripheral swellings" caused by aliskiren vs. ARBs and ACEi were also described in literature [24]. However, "peripheral swellings/oedemas" may also be a symptom of target diseases for which the ACEi or ARB is taken (e.g. heart failure).

It should be noted, though, that inaccuracies in reporting like the use of "face" as an umbrella term, or reporting only the diagnoses "angioedema" might have impacted the results. However, the results from **EVDAS** were confirmed in our full-text analysis of the *validated RASi angioedema cases* (**BfArM's ADR-database**).

Antihistamines and glucocorticoids are used as standard therapy to treat angioedemas in German emergency departments [58]. Theoretically, both should only be effective in histamine-mediated angioedemas [10]. C1-inhbitors, fresh frozen plasma and icatibant are not approved for the treatment of drug-induced angioedemas. They may be used off-label and should lead to a clinical response in hereditary and bradykinin-mediated angioedemas. In our analysis of validated angioedema cases, C1 inhibitors, fresh frozen plasma and icatibant were only used to treat ACEi-associated angioedemas. Antihistamines and glucocorticoids were most frequently used to treat ACEi-associated angioedemas, but did not lead to any improvement in almost half of the *validated ACEi angioedema cases* (where information regarding the clinical response was available). How-

ever, a clear allocation of whether the angioedema was histamine-mediated or bradykinin-mediated is still not possible based on the treatment success of the applied therapy, since angioedema can also regress spontaneously [56]. Medical interventions (e.g. intubations) were only reported in ACEi-associated angioedemas. This reflects the more serious course of ACEi-associated angioedemas in our cases [8]. In general, information about the treatment of ARBs and aliskiren-associated angioedemas was rare, and if available, showed that antihistamines and/or glucocorticoids were used.

ARBs and aliskiren-associated angioedemas occurred more often within the first month of therapy, whereas 46.2 % of ACEi-associated angioedemas occurred even after one year of therapy. The occurrence of ACEi-associated angioedemas after several years of ACEi therapy is known [16, 68]. In contrast, this is not described in literature for ARBs and aliskiren-associated angioedemas.

In summary, one may speculate that there is a higher proportion of histamine-mediated angioedemas in *ARBs* and *aliskiren angioedema cases*, based on the observed differences of clinical phenotypes, treatment response and "time-to-onset" of angioedema reactions. However, this cannot be concluded with certainty based on our results, since (among others) laboratory investigations are lacking. The differences observed could also have been influenced by differences between the involved patient populations, e.g. more patients with allergies, and/or previous/recurrent angioedemas as well as ADRs, with previous drug therapies being included in *ARBs* and *aliskiren angioedema cases*.

BfArM's ADR-database **analysis: administered drug classes and drug substances in relation to the number of drug prescriptions**

As described above, angioedema incidences associated with ACEi use are reported to be higher than that of ARBs [8]. Regarding aliskiren-associated angioedemas, conflicting incidences have been published [8, 23, 24].

In our analysis, the largest number of angioedema reports in relation to the number of drug prescriptions in 1,000 million DDD was calculated for aliskiren (154 reports) followed by ARBs (10 reports) and ACEi (8 reports). However, it is possible that ACEi-

associated angioedemas may be reported less frequently than those associated with ARBs and aliskiren, since physicians tend to report known or expected ADRs less [69]. In contrast, unexpected ADRs (potentially aliskiren, ARBs-associated angioedemas) as well as ADRs associated with novel drug therapies are more likely to be reported [69]. With regard to the proportion of angioedema reports in relation to all ADR reports, we observed the highest proportion for ACEi (20.3 %) and the lowest (7.6 %) for ARBs (S7 Table).

Regardless of any exposure data, ramipril (67.8 %) was the ACEi and valsartan (33.3 %) the ARB most often reported. This finding is in line with ramipril being the ACEi with the largest exposure in Germany [32]. However, in the context of the number of drug prescriptions, slightly more angioedema reports were calculated for lisinopril (13 reports) and enalapril (9 reports) than for ramipril (7 reports). A higher angioedema incidence for lisinopril or enalapril has not previously been described. However, these marginal differences may more likely be coincidental.

In the **EVDAS** analysis, losartan was the ARB reported the most in *ARBs angioedema cases* and more often reported in *ARBs angioedema cases* versus *controls* (OR 1.7 [1.4-2.1]). This is in line with data reported in literature. Toh et al. suspected a higher angioedema incidence for losartan than for other ARBs with an incidence of 2.28 (1.84-2.79) per 1,000 person-years [8]. However, losartan ranked only third in **BfArM's ADR-database** analysis, and in relation to the number of drug prescriptions, higher reporting rates were calculated for irbesartan (18 reports), valsartan (16 reports) and telmisartan (13 reports).

EVDAS analysis versus *BfArM's ADR-database* analysis

Some of the analyses undertaken in both databases yielded the same results. However, as in the analysis of clinical phenotypes, the proportion of cases in the subgroups mostly increased in the full-text analysis performed in **BfArM's ADR-database**. Ramipril and smoking were reported more often in *validated ACEi angioedema cases* of **BfArM's ADR-database** compared to the **EVDAS** analysis. Differences in prescribing behavior (e.g., ramipril being the ACEi most frequently prescribed in Germany) and reporting be-

havior regarding life-style factors such as smoking among the EEA countries may account for these discrepancies. In summary, the high-level analysis seems to be sufficient to predict the direction of the results.

Strengths and limitations of the analysis

The major strengths of this analysis are the huge number of ADR reports collected over a long period of time in a diverse study population, as well as the case validation, which mainly supports the results of the high-level evaluation performed in EVDAS. One limitation is the lack of matching exposure data. Data from the German drug prescription reports are not patient-related and represent the number of drug prescriptions in defined daily doses only, which may differ from the actually prescribed and/or administered dose [32]. Additionally, not all ADRs that occur are reported and the proportion of this underreporting [70] is unknown. Additionally, the underreporting may differ depending on the drug administered and the nature of the ADR experienced. As a consequence of these both limitations, exact incidences and prevalences cannot be calculated, which also applies to our results. To address this limitation, we set the number of ACEi reports in relation to the number of assumed drug-exposed inhabitants. This allows for an estimation of the dimension but should not be misunderstood as exact prevalences and/or incidences. Unfortunately, patient-related data about ARBs and aliskiren use in the German population was not available [33], Therefore the calculation could not be carried out for ARBs and aliskiren. Furthermore, the quality of the analysis depends on the information provided in each ADR report and may differ between patient populations and countries.

Conclusion

Some of the risk factors already known for ACEi angioedemas were confirmed in our analysis and were also seen in ARBs and aliskiren-associated angioedemas. Differences between ACEi vs. ARBs and aliskiren regarding the reported clinical phenotypes, the "time-to-onset" and the treatment of angioedemas and their response to the treat-

ment, but also between the patient populations involved were observed. However, it needs to be clarified if the observed differences reflect different pathophysiologies or if differences between the patient populations involved may account for these findings. Due to the limitations of analysis in spontaneous report databases, further research, is needed to complement our data.

Acknowledgement

The authors would like to thank the ADR database research team of BfArM's pharmacovigilance division for their excellent support.

References

1. Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. Immunol Allergy Clin North Am. 2006; 26(4): 725-37.

2. Sachs B, Meier T, Nöthen MM, Stieber C, Stingl J. Drug-induced angioedema; Focus on bradykinin. Hautarzt. 2018; 69(4): 298-305.

3. Bas M. The Angiotensin-Converting-Enzyme-Induced Angioedema. Immunol Allergy Clin North Am. 2017; 37(1): 183-200.

4. Stauber T, Confino-Cohen R, Goldberg A. Life-threatening angioedema induced by angiotensin-converting enzyme inhibitors: characteristics and risk factors. Am J Rhinol Allergy. 2014; 28(1): 54-8.

5. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension. 2008; 51(6): 1624-30.

6. Beltrami L, Zingale LC, Carugo S, Cicardi M. Angiotensin-converting enzyme inhibitor-related angioedema: how to deal with it. Expert Opin Drug Saf. 2006; 5(5): 643-9.

7. Campo P, Fernandez TD, Canto G, Mayorga C. Angioedema induced by angiotensin-converting enzyme inhibitors Curr Opin in Allergy Clin Immunol. 2013; 13(4): 337-44.

8. Toh S, Reichmann ME, Houston M, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med. 2012; 172(20): 1582-9.

9. Banerji A, Clark S, Blanda M, LoVecchio F, Synder B, Camargo CA Jr.. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department.Ann Allerg Asthma Immunol. 2008; 100(4): 327-32.

10. Bas M, Greve J, Strassen U, Khosravani F, Hoffmann TK, Kojda G. Angioedema induced by cardiovascular drugs: new players join old friends. Allergy. 2015; 70(10): 1196-200.

11. Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. Clin Exp Allergy. 2010; 40(1): 50-61.

12. Kaplan AP. Drug-induced angioedema. Journal of Angioedema. 2011; 1(2): 14-22.

13. Byrd JB, Touzin K, Sile S, Gainer JV, Yu C, Nadeau J, et al. Dipeptidyl Peptidase IV in Angiotensin-Converting Enzyme Inhibitor–Associated Angioedema. Hypertension. 2008; 51(1): 141-7.

14. Campbell DJ. The Kallikrein–Kinin System In Humans. Clin Exp Pharmacol Physiol. 2001; 28(12): 1060-5.

15. Nussberger, J, Cugno M, Amstutz C, Cicarci M, Pellacani A, Agostina A. Plasma bradykinin in angio-oedema. The Lancet. 1998; 351(9117): 1693-7.

16. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor-induced angioedema: A review of the literature. J Clin Hypertens. 2017; 19: 1377-82.

17. Gallagher PE, Li P, Lenhart JR, Chappell MC, Brosnihan KB. Estrogen Regulation of Angiotensin-Converting Enzyme mRNA. Hypertension. 1999; 33(1): 323-8.

18. Lin SY, Tang SC, Tsai LK, Yeh SJ, Hsiao YJ, Chen YW, et al. Orolingual angioedema after alteplase therapy of acute ischaemic stroke: incidence and risk of prior angiotensin-converting enzyme inhibitor use. Eur J Neurol. 2014; 21(10): 1285-91.

19. Kostis JB, Kim HJ, Rusnak J, Casale T, Kaplan A, Corren J, et al. Incidence and characteristics of angioedema associated with enalapril. Arch Intern Med. 2005; 165(14): 1637-42.

20. Bezalel S, Mahlab-Guri K, Asher I, Werner B, Sthoeger ZM. Angiotensin-converting enzyme inhibitor-induced angioedema. Am J Med. 2015; 128(2): 120-5.

21. Morimoto T, Gandhi TK, Fiskio JM, Seger AC, SO JW, Cook EF, et al. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract. 2004; 10(4): 499-509.

22. Liau Y, Chua I, Kennedy MA, Maggo S. Pharmacogenetics of angiotensin-converting enzyme inhibitor-induced angioedema. Clin Exp Allergy. 2019; 49(2): 142-54.

23. Makani H, Messerli F, Romero J, Wever-Pinzon O, Korniyenko A, Berrios R, et al. Meta-Analysis of Randomized Trials of Angioedema as an Adverse Event of Renin–Angiotensin System Inhibitors. Am J Cardiol. 2012; 110(3): 383-91.

24. Withe WB, Bresalier R, Kaplan A, Palmer BF, Riddell RH, Lesogor A, et al. Safety and Tolerability of the Direct Renin Inhibitor Aliskiren: A Pooled Analysis of Clinical Experience in More Than 12,000 Patients With Hypertension. The Journal of Clinical Hypertension, 2010. 12(10): 765-775.

25. Burnier M, Brunner HR. Angiotensin II receptor antagonists. The Lancet. 2000; 355(9204): 637-45.

26. Joseph K, Tholanikunnel TE, Kaplan AP. In vitro comparison of bradykinin degradation by aliskiren, a renin inhibitor, and an inhibitor of angiotensin-converting-enzyme. J Renin Angiotensin Aldosterone Sys. 2015; 16(2): 321-7.

27. Sica DA, Black HR. Angioedema in heart failure: occurrence with ACE inhibitors and safety of angiotensin receptor blocker therapy. Congest Heart Fail. 2002; 8(6): 334-41.

28. van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema attributed to the use of losartan. Arch Intern Med. 1998; 158(18): 2063-5.

29. Cicardi M, Zingale LC, BergamaschiniL, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med, 2004. 164(8): 910-3.

30. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. ESC/ESH Arterial Hypertension (Management of) Guidelines: ESC Clinical Practice Guidelines. European Heart Journal, 2018. 39: 3021-3104.

31. Kovell LC, Ahmed HM, Misra S, Whelton SP, Prokopowicz GP, Blumenthal RS, et al. US Hypertension Management Guidelines: A Review of the Recent Past and Recommendations for the Future. Journal of the American Heart Association, 2015. 4(12):

32. Schwabe U, Paffrath D, Ludwig WD, Klauber J. Arzneiverordnungsreport 2017. Berlin Heidelberg: Springer Verlag Berlin-Heidelberg; 2017.

33. Knopf H, Grams D. Arzneimittelanwendung von Erwachsenen in Deutschland – Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsbl, 2013. 56(5): 868-877.

34. European Medicines Agency. EudraVigilance: https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance

35. Federal Institute for Drugs and Medical Devices (BfArM). http://www.bfarm.de/EN/Home/home_node.html

36. Paul-Ehrlich-Institut (PEI). http://www.pei.de/EN/home/node.html

37. Dubrall D, Schmid M, Alešik E, Paeschke N, Stingl J, Sachs B. Frequent Adverse Drug Reactions, and Medication Groups under Suspicion. Dtsch Arztebl Int. 2018; 115(23): 393-400

38. Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz -AMG). Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 5 des Gesetzes vom 4. Mai 2017 (BGBl. I S. 1050) geändert worden ist.

39. Federal Institute for Drugs and Medical Devices. European Database on Adverse Drug Reaction Reports: https://www.bfarm.de/EN/Drugs/vigilance/ReportingRisks/uawDB/_node.html;jsessionid=1BB26673C3179E94EDEDF2652336A714.1_cid319.

40. European Medicines Agency. EudraVigilance system overview. https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-system-overview

41.WHO Collaborating Centre for Drug Statistics Methodology: Anatomical Therapeutical Chemical (ATC) Classification. https://www.whocc.no/atc_ddd_index/. Accessed: 13 December 2018.

42. German Institute of Medical Documentation and Information (DIMDI). ATC-Clissification. https://www.dimdi.de/dynamic/en/drugs/atc-classification/index.html

43. European Medicines Agency. EudraVigilance User Manual: Individual Case Safety Report form: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/eudravigilance-user-manual-individual-case-safety-report-form-version-11_en.pdf. Version 1.1. 22 January 2018.

44. MedDRA: Medical Dictionary for Regulatory Activities. Introductory Guide MedDRA Version 21.0. https://www.meddra.org/sites/default/files/guidance/file/intguide_21_0_english.pdf. Accessed: March 2018.

45. MedDRA: Medical Dictionary for Regulatory Activities. Introductory Guide for Stanardised MedDRA Queries (SMQs) Version 16.0. https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_16_0_english.pdf. Accessed March 2013.

46. Edwards R, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000; 356(9237): 1255-1259.

47. Bergvall T, Noren GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Saf. 2014; 37(1): 65-77.

48. Sachs B, Dubrall D, Fischer-Barth W, Schmid M, Stingl J. Drug-induced anaphylactic reactions in children: A retrospective analysis of 159 validated spontaneous reports. Pharmacoepidemiol Drug Saf, 2019. 1-12.

49. Statistische Bundesamt. Bevölkerung: https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Bevoelkerung/Bevoelkerungsstand/Tabellen_/lrbev01.html%20D_STATIS

50. Grimmsmann T, Himmel W. Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes? Eur J Clin Pharmacol, 2011. 67: 847-854.

51. European Medicines Agency. EudraVigilance: security principles and responsibilities.

https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-security-principles-responsibilities

52. European Medicines Agency. Access to EudraVigilance data. https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data.

53. Bindke G, Schorling K, Wieczorek D, Kapp A, Wedi B. Genderaspekte bei Angioödemen. Der Hautarzt. 2019; 70: 92.

54. Langen U, Schmitz R, Steppuhn H. Prevalence of allergic diseases in Germany. Results of the German Health Interview and Examination Survey for Adults (DEGS1). Bundesgesundheitsbl. 2013; 56(5-6): 698-706

55. Zeiher J, Kuntz B, Lange C. Rauchen bei Erwachsenen in Deutschland. Journal of Health Monitoring. 2017; 2(2): 59-65.

56. Navinés-Ferrer A, Serrano-Candelas E, Lafuente A, Muñoz-Cano R, Martín M, Gastaminza G. MRGPRX2-mediated mast cell response to drugs used in perioperative procedures and anaesthesia. Sci Rep 8, 11628 (2018).

57. Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. Int J Emerg Med. 2017; 10(1): 15.

58. Hahn J, Nordmann M, Hoffmann TK, et al. Ulmer Notfallalgorithmus: Therapie von Medikamenten-induzierten, Bradykinin vermittelten Angioödemen. Laryngo Thino Otol. 2018; 97: 6.

59. Lefebvre J, Murphey LJ, Hartert TV, Jiao Shan R, Simmons WH, Brown NJ. Dipeptidyl peptidase IV activity in patients with ACE-inhibitor associated angioedema. Hypertension. 2002; 39 (2): 460-464.

60. Byrd JB, Shreevatsa A, Putlur P, et al. Dipeptidyl peptidase IV deficiency increases suspectibility to angiotensin-converting enzyme inhibitor-induced peritracheal edema. J Allergy Clin Immunol. 2007; 120(2): 403-408.

61. Engelter ST, Fluri F, Buitrago-Téllez C, et al. Life-threatening orolingual angioedema during thrombolysis in acute ischemic stroke. J Neurol. 2005; 252 (10): 1167-1170.

62. Hurford R, Rezvani S, Kreimei M, et al. Incidence, predictors and clinical characteristics of orolingual angio-oedema complicating thrombolysis with tissue plasminogen activator for ischaemic stroke. J Neurol Neurosurg Psychiatry. 2015; 86(5): 520-523.

63. Hill MD, Lye T, Moss H, et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology. 2003; 60(9): 1525-1527.

64. Duerr M, Glander P, Diekmann F, Dragun D, Neumayer HH, Budde K. Increased incidence of angioedema with ACE inhibitors in combination with mTOR inhibitors in kidney transplant recipients. Clin J Am Soc Nephrol. 2010; 5(4): 703-708.

65. Byrd JB, Woodard-Grice A, Stone E, et al. Association of angiotensin-converting enzyme inhibitor-associated angioedema with transplant and immunosuppressant use. Allergy. 2010; 65: 1381-1387.

66. Brown NJ, Byiers S, Carr D, Maldonado M, Warner BA. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. Hypertension. 2009; 54(3): 516-523.

67. Skalli S, Wion-Barbot N, Baudrant M, Lablanche S, Benhamou PY, Halimi S. Angio-oedema induced by dual dipeptidyl peptidase inhibitor and angiotensin II receptor blocker: a first case report. Diabetic Medicine. 2010; 27: 485-488.

68. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology and Incidence of ACE Inhibitor Angioedema Utilizing a Large Electronic Health Record. J Allergy Clin Immunol Pract. 2017; 5(3): 744-749.

69. Hasford J, Goettler M, Munter KH, Müller-Oerlinghausen B. Physicians‘ knowledge and atiitudes regarding the spontaenous reporting system for adverse drug reactions. Journal of Clinical Epidemiology. 2002; 55: 945-950.

70. Hazell L, Shakir SA. Under-Reporting of Adverse Drug Reactions. Drug Saf. 2006; 29(5): 385-396.

S1 Document. *EVDAS* analysis: sacubitril/valsartan-associated angioedemas.

Introduction

For sacubitril/valsartan, the angioedema incidence was estimated to be as frequent as for ACEi [1]. The combination product sacubitril/valsartan is an angiotensin receptor and neprilysin inhibitor which acts through the simultaneous inhibition of angiotensin-II-receptors and the inhibition of neprilysin. Neprilysin is also involved in bradykinin degradation [1, 2]. Hence, an increase in bradykinin concentration may be caused by the inhibition of neprilysin through sacubitril. So far, only a few studies have investigated sacubitril/valsartan-associated angioedemas. Therefore, in order to complete the performed analysis of angioedemas associated with drugs acting on the renin-angiotensinsystem, we also analyzed the characteristics, associated factors and clinical phenotypes reported in ADR reports of angioedema associated with the use of sacubitril/valsartan and compared them to their respective controls. In addition, we compared *sacubitril/valsartan angioedema cases* to *ACEi angioedema cases*.

Methods

1) Identification of sacubitril/valsartan angioedema cases

In EVDAS all spontaneous ADR reports registered between 1/2010 -06/2017 within the EEA in which the combination product sacubitril/valsartan was reported as "suspected/interacting" drug were identified (n= 1,429) (query date: 17/12/2018). The angioedema cases were extracted by application of the standardized MedDRA Query (SMQ) "angioedema (narrow)" (n=114) [3]. In order to determine whether there are factors reported more often in *sacubitril/valsartan angioedema cases* we compared them to a group of *controls* consisting of all other sacubitril/valsartan-associated ADR reports excluding *angioedema cases* (n= 1,315).

Analysis of *sacubitril/valsartan angioedema cases* originating from Germany was performed in EVDAS (n= 23) since the number of reports varied widely between BfArM's

ADR-database and EVDAS (more reports in EVDAS). This may be explained by a delayed reporting of ADRs after closure of BfArM's ADR-database (22.11.2017). A case validation of all *sacubitril/valsartan angioedema cases* originating from Germany was performed. A more detailed description of the validation process can be found in section 2.2.1) of the manuscript. After case validation, 19 cases (70.4 %) of *sacubitril/valsartan angioedema cases* originating from Germany remained.

2) Analysis of angioedema cases and controls

The identified *sacubitril/valsartan angioedema cases* and *controls* were analyzed with regard to reported patient demographics, smoking habits, comorbidities, comedications and the reported seriousness criteria. Comparative analyses were conducted among *sacubitril/valsartan angioedema cases* vs. their *controls* and among *ACEi angioedema cases* vs*. sacubitril/valsartan angioedema cases*. Sacubitril/valsartan was approved in 2016. Hence, the number of sacubitril/valsartan angioedema and ADR (total) reports per 1,000 drug prescriptions in million DDD [4] was calculated based only on the year 2016.

In order to analyze the clinical phenotype, the reports were restricted to those in which only the combination product sacubitril/valsartan was reported as "suspected" which was the case in 92.1 % (n= 105/114) of the European *sacubitril/valsartan angioedema cases*. The diagnosis "angioedema" was only coded in 47.6 % (50/105) of the remaining cases. Hence, to confirm the observed results of the high-level analysis of European *sacubitril/valsartan angioedema cases*, the same analysis was repeated in the full-text analysis of the validated German cases. In the full-text analysis, information about the "time-to-onset" of the angioedema reaction was also retrieved.

Results

1) EVDAS analysis: reported characteristics in sacubitril/valsartan angioedema cases and sacubitril/valsartan controls

Patients involved in *sacubitril/valsartan angioedema cases* were more often females (OR 1.9 [1.1-3.2]) and younger (OR 0.5 [0.3-0.8]) (patients older than or equal to 65

were coded as 1 and patients younger than 65 coded as 0 in the logistic regression analysis) than patients involved in *sacubitril/valsartan controls*. "Allergy" (OR 10.2 [2.8-37.2]), a history of "previous/recurrent angioedema" (3.5 % of cases vs. none of the controls) as well as concurrent ACEi intake (OR 2.6 [1.2-6.0]) were more often reported in *sacubitril/valsartan angioedema cases* vs. *controls*. Although *sacubitril/valsartan angioedema cases* were designated as "serious" slightly more often than their *controls* (OR 1.3 [0.5-3.3]), fatal outcome ("death") was much more frequently reported in *sacubitril/valsartan controls* (OR unadjusted 0.2 [0.1-0.6]). The same applies for "life-threatening" (OR unadjusted 0.7 [0.2-1.9]).

Table 1) EVDAS analysis: reported characteristics in *sacubitril/valsartan angioedema cases* and *sacubitril/valsartan controls*

	sacubitril/valsartan angioedema cases **(n= 114; 7.9 %)**	***sacubitril/valsartan controls*** **(n= 1,315; 92.1 %)**	**unadjusted OR [+/- 95 % CI]**	**logistic regression OR [+/- 95 % CI]**
patient demographics				
mean age (median) [years] [a]	66.2 (66.5)	70.3 (71.0)	-	0.5 [0.3-0.8]*
female	30.7 % (35)	21.7 % (285)	1.5 [1.0-2.3]	1.9 [1.1-3.2]*
male	66.7 % (76)	71.4 % (939)		
unknown	2.6 % (3)	6.9 % (91)		
life style factors, allergic conditions				
smoker [b]	3.5 % (4)	3.0 % (40)	1.2 [0.4-3.3]	1.0 [0.3-3.4]
allergy [c]	4.4 % (5)	0.8 % (10)	6.0 [2.0-17.8]*	10.2 [2.8-37.2]*
history of skin and subcutaneous disorders [d]				
skin/subcutaneous disorders	4.4 % (5)	1.1 % (15)	4.0 [1.4-11.1]*	5.5 [1.5-19.8]*
urticaria	-	-	-	-
angioedema	3.5 % (4)	-	-	-
comorbidities [e]				
renal disease	4.4 % (5)	14.3 % (188)	0.3 [0.1-0.7]*	0.2 [0.1-0.7]*
diabetes	9.6 % (11)	14.8 % (194)	0.6 [0.3-1.2]	-
asthma	1.8 % (2)	0.6 % (8)	2.9 [0.6-13.9]	1.2 [0.1-12.3]
malignant tumors	2.6 % (3)	3.0 % (39)	0.9 [0.3-2.9]	0.9 [0.2-4.3]

thyroid disorders	0.9 % (1)	2.4 % (32)	0.4 [0.0-2.6]	-
comedication [f]				
β-blockers	26.3 % (30)	29.6 % (389)	0.9 [0.6-1.3]	1.1 [0.5-2.5]
diuretics	34.2 % (39)	39.8 % 523)	0.8 [0.5-1.2]	0.6 [0.3-1.2]
calcium antagonists	3.5 % (4)	1.7 % (23)	2.0 [0.7-6.0]	3.0 [0.8-11.8]
ACEi	8.8 % (10)	4.4 % (58)	2.1 [1.0-4.2]	2.6 [1.2-6.0]*
acetylsalicyclic acid	13.2 % (15)	12.1 % (159)	1.1 [0.6-1.9]	0.9 [0.4-1.9]
analgesics [g]	2.6 % (3)	3.7 % (48)	0.7 [0.2-2.3]	0.2 [0.0-1.8]
antidiabetics [h]	6.1 % (7)	7.8 % (102)	0.8 [0.4-1.7]	1.0 [0.4-2.7]
DPPIVi	0.9 % (1)	1.7 % (22)	0.5 [0.1-3.9]	-
mTORi	-	-	-	-
fibrinolytics	-	-	-	-
seriousness criteria [i]				
serious	92.1 % (105)	89.4 % (1,175)	1.4 [0.7-2.8]	1.3 [0.5-3.3]
death	4.4 % (5)	15.6 % (205)	0.2 [0.1-0.6]*	-
life-threatening	3.5 % (4)	5.0 % (66)	0.7 [0.2-1.9]	-
hospitalization	26.3 % (30)	41.2 % (542)	0.5 [0.3-0.8]*	-
disabling	-	1.4 % (18)	-	-

*OR=1 is not included; OR > 1 reported more often in *sacubitril/valsartan angioedema cases*; OR < 1 reported more often in *sacubitril/valsartan controls*

[a] age unknown: *sacubitril/valsartan angioedema cases*: 41 cases (36.0 % of cases), *sacubitril/valsartan controls*: 527 cases (40.1 % of cases).

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] skin and subcutaneous tissue disorders were analyzed based on the SOC "skin and subcutaneous tissue disorders", urticaria based on the HLT "urticarias". The term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] suitable hierarchical levels of the MedDRA terminology were chosen for analysis of the reported patients' comorbidities. The term "renal disorders" was identified using the SMQ's "acute renal failure" and "chronic kidney disease"; "diabetes": SMQ "hyperglycaemia/new onset diabetes mellitus"; "asthma": SMQ "asthma/bronchospasm"; "malignant tumors": SMQ "malignant tumours"; "thyroid disorders": SMQ "thyroid dysfunction".

[f] the analysis of the most frequently reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the "suspected/interacting" ACEi were counted as concomitant, regardless of whether they were reported as "suspected", "interacting" or "concomitant".

[g] deviating from the ATC-code, the analysis concerning "analgesics" also includes ADR reports in which ibuprofen and/or diclofenac were listed suspected/interacting or concomitant drug. We excluded ADR reports in which acetylsalicyclic acid was listed as suspected/interacting or concomitant drug. The number of ADR reports in which acetylsalicyclic acid was used concurrently were analyzed separately.

[h] deviating from the ATC-code, we excluded ADR reports in which a DPPIVi was listed as suspected/interacting or concomitant drug in the analysis concerning "diabetics". The number of ADR reports in which DPPIVi was used concurrently was analyzed separately.

[i] one ADR report may yield information about more than one seriousness criterion, therefore, the number of reported seriousness criteria exceeds that of the ADR reports.

Table 1) shows the absolute and relative number of reports and the calculated unadjusted and adjusted odds ratios for the reported demographic parameters, comorbidities, comedications and seriousness criteria of *sacubitril/valsartan angioedema cases* and *controls* of the European Economic Area (EEA).

2) EVDAS analysis: characteristics of validated sacubitril/valsartan angioedema cases

Concerning the calculated completeness score, the *sacubitril/valsartan angioedema cases* were "poorly documented" (Score: 0.50 [0.28-0.73]) compared to *ACEi*, *ARBs* and *aliskiren angioedema cases*. Unfortunately, the number of reports regarding the investigated variables of interest were too small to make any valid statements.

Table 2) EVDAS analysis: characteristics of *validated ARBs, aliskiren and sacubitril/valsartan angioedema cases*

	***validated sacubitril/valsartan angioedema cases* (n= 19)**
completeness score	0.50 [0.28-0.73]
patient demographics	
mean age (median)	65.4 (72.5)
female	6 (31.6 %)
male	13 (68.4 %)
unknown	0 (0.0 %)
smoking habits and comorbidities	
smoking [b]	-
allergy [c]	-
angioedema [d]	1 (5.3 %)
renal disorders [e]	2 (10.5 %)
diabetes [e]	-
asthma [e]	-
comedication [f]	
β-blockers	5 (26.3 %)
diuretics	5 (26.3 %)
calcium antagonists	1 (5.3 %)
NSAID	3 (15.8 %)
everolimus	-
alteplase	-
ACEi	-
ARBs	-
seriousness criteria [g]	
serious	19 (100.0 %)
death	2 (10.5 %)
life-threatening	-
hospitalization	2 (10.5 %)

[a] age unknown: *validated sacubitril/valsartan angioedema cases*: 9 cases (47.4 % of cases).

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] the term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] refers to the respective comorbidity reported in the patients' history or as a drug indication term for the used comedication.

[f] the analysis of the most frequently reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the respective "suspected/interacting" drug substance were counted as concomitant, regardless of whether they were reported as "suspected", "interacting" or "concomitant".

[g] one ADR report may yield information about more than one seriousness criterion, therefore, the number of reported seriousness criteria exceeds that of the ADR reports.

Table 2) shows the absolute and relative number of the reported characteristics of *validated sacubitril/valsartan angioedema cases*.

3) EVDAS analysis: comparative analysis of ACEi angioedema cases* vs. *sacubitril/valsartan angioedema cases.

More females (OR 1.7 [1.0-2.9]) were included in *sacubitril/valsartan angioedema cases* compared to *ACEi angioedema cases*. Intake of calcium antagonists (OR 9.3 [2.3-38.5]) and analgesics (OR 11.1 [1.5-80.8]) was more frequently reported in *sacubitril/valsartan angioedema cases* vs. *ACEi angioedema cases*. *ACEi angioedema cases* were about 10 times (OR 9.9 [2.4-40.2]) more often designated as "life-threatening" and led to "hospitalization" more than 3 times (OR 3.3 [2.1-5.2]) more often than *sacubitril/valsartan angioedema cases*.

Table 3) EVDAS analysis: comparative analysis of *ACEi angioedema cases* vs. *sacubitril/valsartan angioedema cases*.

	OR (unadj.) [+/- 95 % CI] *ACEi angioedema cases* vs. *sacubitril/valsartan angioedema cases* (4 cases excluded [a])	**logistic regression *ACEi angioedema cases* vs. *sacubitril/valsartan angioedema cases* (4 cases excluded [a])**
patient demographics		
age > 65 years	-	1.1 [0.7-1.9]
female	1.9 [1.3-2.9]*	1.7 [1.0-2.9]*
smoking habits, allergic conditions and history of skin disorders		
smoker [b]	1.1 [0.3-4.6]	1.1 [0.2-5.1]
allergy [c]	0.9 [0.4-2.3]	0.4 [0.2-1.1]
urticaria [d]	-	-
angioedema [e]	1.5 [0.5-4.8]	1.1 [0.3-3.6]
comorbidities [f]		
renal disorders	1.0 [0.4-2.5]	0.9 [0.3-2.6]
diabetes	1.0 [0.5-1.9]	-
asthma	1.3 [0.3-5.3]	-
malignant tumors	1.5 [0.5-4.7]	1.3 [0.3-5.6]
thyroid disorders	2.9 [0.4-20.9]	-
comedication [g]		
β-blockers	0.9 [0.6-1.3]	0.6 [0.3-1.1]
diuretics	0.6 [0.4-0.8]	0.3 [0.2-0.5]*
calcium antagonists	7.5 [2.4-23.9]*	9.3 [2.3-38.5]*
acetylsalicyclic acid	1.7 [1.0-3.0]	1.7 [0.9-3.4]
analgesics [h]	4.6 [1.5-14.6]*	11.1 [1.5-80.8]*
antidiabetics [i]	1.8 [0.9-3.7]	1.3 [0.5-3.1]
DPPIVi	2.3 [0.3-17.0]	-
mTORi	-	-
fibrinolytics	-	-
seriousness criteria [j]		
serious	0.7 [0.4-1.4]	0.8 [0.3-1.9]

death	0.3 [0.1-0.9]*	-
life-threatening	9.9 [2.4-40.2]*	-
hospitalization	3.3 [2.1-5.2]*	-
disabling	-	-

*OR=1 is not included; OR > 1 reported more often in *sacubitril/valsartan angioedema cases*; OR < 1 reported more often in *sacubitril/valsartan controls*

[a] cases which were included in both of the opposing angioedema groups were excluded.

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] the term "urticaria" was analyzed based on the HLT "urticarias".

[e] the term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[f] suitable hierarchical levels of the MedDRA terminology were chosen for the analysis of the reported patients' comorbidities. The term "renal disorders" was identified using the SMQ's "acute renal failure" and "chronic kidney disease"; "diabetes": SMQ "hyperglycaemia/new onset diabetes mellitus"; "asthma": SMQ "asthma/bronchospasm"; "malignant tumors": SMQ "malignant tumours"; "thyroid disorders": SMQ "thyroid dysfunction".

[g] the analysis of the most frequently reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the "suspected/interacting" RASi were counted as concomitant, regardless of whether they were reported as "suspected", "interacting" or "concomitant".

[h] deviating from the ATC-code, the analysis concerning "analgesics" also includes ADR reports in which ibuprofen and/or diclofenac were listed suspected/interacting or concomitant drug. We excluded ADR reports in which acetylsalicyclic acid was listed as suspected/interacting or concomitant drug. The number of ADR reports in which acetylsalicyclic acid was used concurrently were analyzed separately.

[i] deviating from the ATC-code, we excluded ADR reports in which a DPPIVi was listed as suspected/interacting or concomitant drug in the analysis concerning "diabetics". The number of ADR reports in which DPPIVi was used concurrently was analyzed separately.

[j] one ADR report may yield information about more than one seriousness criterion, therefore, the number of reported seriousness criteria exceeds that of the ADR reports.

Table 3) shows the calculated unadjusted and adjusted odds ratios of the comparative analysis of *ACEi angioedema cases* vs. *sacubitril/valsartan angioedema cases*.

4) EVDAS analysis: Number of sacubitril/valsartan angioedema cases in relation to the number of drug prescriptions in Germany (2016)

The number of *sacubitril/valsartan angioedema cases* in relation to the number of drug prescriptions was higher than for *ACEi, ARBs* and *aliskiren angioedema cases*.

Table 4) Number of *sacubitril/valsartan angioedema cases* and their total number of ADR reports in relation to the number of drug prescriptions in Germany (2016).

RASi	number of angi-oedema reports[a] (% of all ADR reports for sacubi-tril/valsartan)	number of all ADR reports [a]	number of drug prescriptions in Mio DDD [b]	number of angi-oedema re-ports/number of drug prescrip-tions in 1,000 Mio DDD (2016)
sacubitril/ valsartan	23 (8.0 %)	289	3,7	6,216

[a] all identified cases (not validated) originating from Germany in EVDAS of the year 2016.

[b] number of drug prescriptions for the combination product sacubitril/valsartan for the year 2016 [4].

Table 4) shows the absolute and relative number of *sacubitril/valsartan angioedema cases* and their total number of ADR reports as well as their relation to the number of drug prescriptions in 1,000 Mio DDD.

5) EVDAS analysis: reported anatomical area affected by the angioedema

Regarding the clinical phenotypes the "eye/eyelid" (OR 0.2 [0.1-0.4]) was more often affected in sacubitril/valsartan-associated angioedemas compared to ACEi-associated angioedemas. "Urticaria" (9.5 % (n= 10)) as well as "pruritus" (15.2 % (n= 16)) and additional "peripheral swellings/oedemas" (10.5 % (n= 11)) as attendant symptoms were more often reported in *sacubitril/valsartan angioedema cases* compared to *ACEi angioedema cases* (5.0 % (n= 123), 3.1 % (n= 76), 1.2 % (n= 29)).

Table 5) EVDAS analysis: reported anatomical area affected by the angioedema and angioedema types according to SMQ "angioedema (narrow)" of the MedDRA terminology.

rank	***sacubitril/valsartan angioedema cases*** **(n=105)**
1.	angioedema (multiple reactions 75.2 %, n=79) (only 47.6 %, n=50, OR: 1.3 [0.7-2.5])
2.	face (17.1 %, n=18) OR: 0.4 [0.2-1.0]
3.	lips (12.4 %, n=13) OR: 0.9 [0.3-2.3] eye/eyelid (12.4 %, n=13) OR: 0.2 [0.1-0.4]*
4.	urticaria (9.5 %, n=10) OR: 0.5 [0.2-1.5]
5.	tongue (8.6 %, n=9) OR: 2.6 [0.8-7.9]
6.	larynx (6.7 %, n=) OR: 0.4 [0.1-1.4]
7.	mouth (4.8 %, n=5) OR: 0.4 [0.1-1.7]
8.	pharynx (2.9 %, n=3) OR: 1.5 [0.2-9.7]

*OR does not include 1. OR > 1 more often reported in *ACEi angioedema cases*; OR < 1 more often reported in *sacubitril/valsartan angioedema cases.*

Table 5) shows the absolute and relative number of ADR reports for the reported anatomical area affected by the angioedema and angioedema types according to the SMQ "angioedema (narrow)" of the MedDRA terminology, in which the combination product sacubitril/valsartan was reported as "suspected", only. For each anatomical area affected by the angioedema or angioedema type, odds ratios with Bonferroni adjusted confidence intervals were calculated. The *ACEi angioedema cases* served as a reference for the calculation of odds ratios. The number of ADR reports that described the same ana-

tomical area e.g. "tongue oedema" and "swollen tongue" were merged. In some reports only the diagnosis "angioedema" was coded, whereas in some others the term "angioedema" was coded additionally (defined as "angioedema multiple reactions").

6) EVDAS analysis: analysis of the "time-to-onset" of sacubitril/valsartan-associated angioedemas

Only nine of 19 *validated sacubitril/valsartan cases* included information about the "time-to-onset" of the angioedema reaction. In 66.7 % (6/9) of these cases the angioedema occurred within the first 30 days of therapy. In the remaining three cases (33.3 % (3/9)) the reaction occurred within the first year of the therapy.

Figure 1) EVDAS analysis: "time-to-onset" analysis of the angioedema reaction.

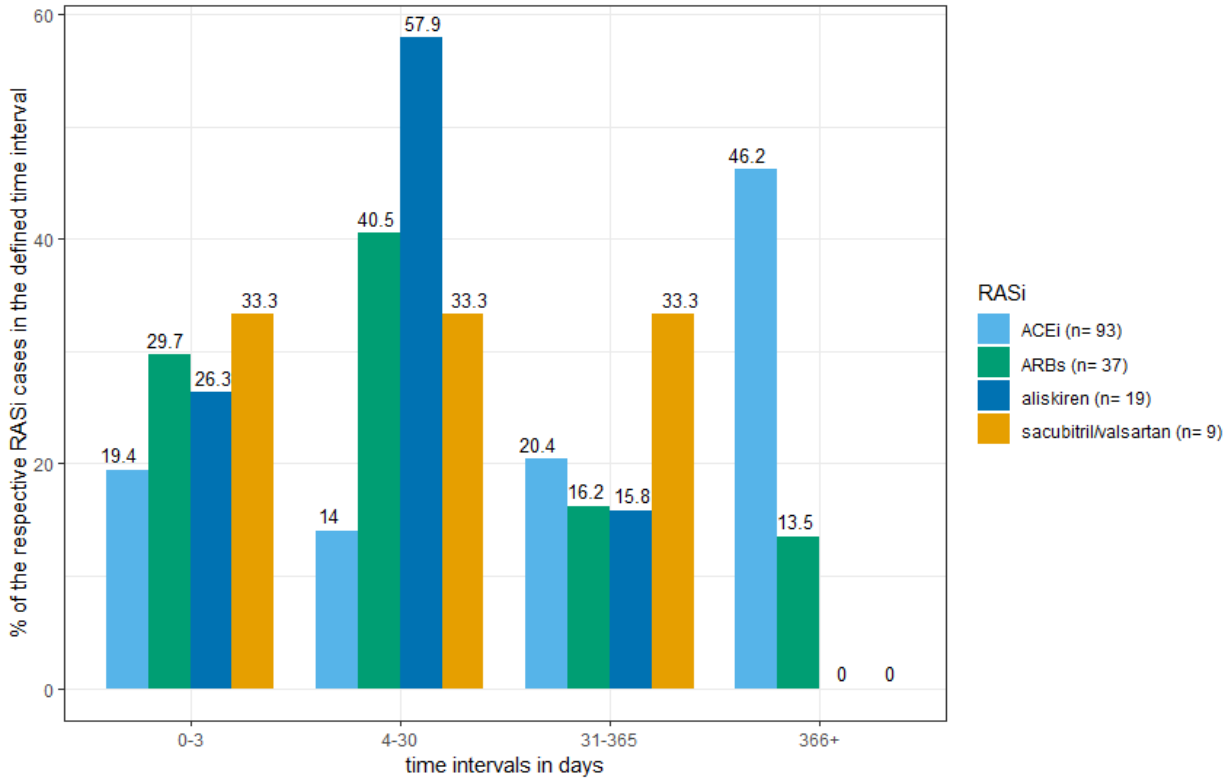


Figure 1 shows the "time-to-onset" analysis of validated sacubitril/valsartan-associated angioedemas compared to validated ACEi, ARBs and aliskiren-associated angioedemas. Only the cases with information provided on the "time-to-onset" were included.

Discussion

It seems that some of the reported characteristics like "allergy" and "previous/recurrent angioedema" have a tendency to occur more frequently in *sacubitril/valsartan angioedema cases* compared to their *controls*. However, the case numbers are too small to make a conclusive statement. The same applies to the clinical phenotype and the "time-to-onset" of the angioedema reaction.

According to the calculated completeness score, it seems that the *sacubitril/valsartan angioedema cases* are generally not well documented and are even more poorly documented than *ACEi*, *ARBs* and *aliskiren angioedema cases*. This could also explain the small number of cases regarding the investigated variables of interest. Possibly, the variables of interest were not reported at all.

A higher number of angioedema reports per 1,000 drug prescriptions in million DDD was calculated for sacubitril/valsartan compared to ACEi, ARBs and aliskiren. Sacubitril/valsartan was approved in 2016. Hence, a reporting bias has to be considered. As already mentioned in the discussion of the manuscript, a previous German study investigating ADR reporting behaviors concluded that ADRs related to novel drug therapies are likely to be reported more often than ADRs related to well-known drug therapies [5].

Conclusion

The data regarding sacubitril/valsartan-associated angioedemas were insufficient to make any valid statements. Further research with a larger number of cases and/or better documented cases or with other complementary methodological approaches is needed.

References

[1] Shi V, Senni M, Streefkerk H, Modgill V, Zhou W, Kaplan A. Angioedema in heart failure patients treated with sacubitril/valsartan (LCZ696) or enalapril in the PARADIGM-HF study. Int J Cardiol. 2018; 264: 118-23.

[2] Hoover T, Lippmann M, Grouzmann E, Marceau F, Herscu P. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. Clin Exp Allergy. 2010; 40(1): 50-61.

[3] MedDRA: Medical Dictionary for Regulatory Activities. Introductory Guide for Standardised MedDRA Queries (SMQs) Version 16.0. https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_16_0_english.pdf. Accessed March 2013.

[4] Schwabe U, Paffrath D, Ludwig WD, Klauber J. Arzneiverordnungsreport 2017. Berlin Heidelberg: Springer Verlag Berlin-Heidelberg; 2017.

[5] Hasford J, Goettler M, Munter KH, Müller-Oerlinghausen B. Physicians‘ knowledge and atiitudes regarding the spontaenous reporting system for adverse drug reactions. Journal of Clinical Epidemiology. 2002; 55: 945-950.

S2 Table. *EVDAS* analysis: gender-stratified analysis of reported characteristics in *ACEi angioedema cases*.

female vs. male	***ACEi angioedema cases: females* (n= 1,506; 47.2 %)**	***ACEi angioedema cases: males* (n= 1,617; 50.6 %)**	**unadj. OR [+/- 95 % CI]**	**logistic regression OR [+/- 95 % CI]**
patient demographics				
mean age (median) [yeas] [a]	67.1 (69)	66.6 (68)	-	0.9 [0.8-1.1]
smoking habits, allergic conditions				
smoker [b]	1.1 % (17)	3.0 % (49)	0.4 [0.2-0.6]	0.3 [0.2-0.6]*
allergy [c]	6.0 % (89)	2.8 % (46)	2.1 [1.5-3.1]*	2.3 [1.6-3.4]*
history of skin and subcutaneous disorders				
urticaria	0.8 % (12)	0.3 % (5)	2.6 [0.9-7.4]*	3.0 [1.0-9.2]*
angioedema [d]	2.8 % (42)	5.3 % (86)	0.5 [0.4-0.7]*	0.5 [0.3-0.7]*
***comorbidities* [e]**				
renal disorders	3.3 % (50)	5.7 % (92)	0.6 [0.4-0.8]*	0.5 [0.4-0.8]*
diabetes	9.4 % (142)	11.3 % (182)	0.8 [0.7-1.0]	-
asthma	3.3 % (49)	1.5 % (25)	2.1 [1.3-3.5]*	1.8 [1.1-3.1]*
malignant tumors	3.9 % (58)	4.3 % (69)	0.9 [0.8-1.3]	0.9 [0.6-1.3]
thyroid disorders	4.4 % (66)	0.9 % (16)	4.6 [2.6-8.0]	5.6 [3.1-10.0]*
***administered ACEi* [f]**				
ramipril	35.7 % (538)	38.7 % (626)	0.9 [0.8-1.0]	1.0 [0.7-1.4]
enalapril	28.3 % (426)	28.6 % (463)	1.0 [0.8-1.1]	1.0 [0.7-1.4]
perindopril	16.3 % (245)	15.8 % (256)	1.0 [0.9-1.2]	1.1 [0.9-1.3]
lisinopril	14.7 % (221)	11.5 % (186)	1.3 [1.1-1.6]*	1.4 [0.9-2.0]
***comedication* [g]**				
β-blockers	22.1 % (333)	23.8 % (384)	0.9 [0.8-1.1]	1.0 [0.8-1.2]
diuretics	24.4 % (368)	19.8 % (320)	1.3 [1.1-1.6]*	1.5 [1.2-1.8]*
calcium antagonists	15.7 % (236)	19.3 % (312)	0.8 [0.6-0.9]*	0.8 [0.6-0.9]*
ARBs	3.9 % (58)	4.1 % (67)	0.9 [0.6-1.3]	0.9 [0.6-1.3]
acetylsalicyclic acid	16.7 % (251)	23.2 % (375)	0.7 [0.6-0.8]*	0.6 [0.5-0.8]*

analgesics [h]	13.2 % (198)	9.8 % (159)	1.4 [1.1-1.7]*	1.3 [1.1-1.7]*
antidiabetics [i]	10.2 % (153)	10.2 % (165)	1.0 [0.8-1.3]	1.0 [0.8-1.3]
DPPIVi	1.9 % (29)	2.3 % (37)	0.8 [0.5-1.4]	0.9 [0.5-1.5]
mTORi	1.0 % (15)	1.7 % (27)	0.6 [0.3-1.1]	0.8 [0.4-1.5]
fibrinolytics	1.3 % (20)	1.1 % (18)	1.2 [0.6-2.3]	1.1 [0.5-2.2]
seriousness criteria [j]				
serious	87.1 % (1312)	90.0 % (1,456)	0.7 [0.6-0.9]*	0.7 [0.6-0.9]*
death	1.1 % (16)	2.0 % (33)	0.5 [0.3-0.9]*	-
life-threatening	15.1 % (228)	15.9 % (257)	0.9 [0.8-1.1]	-
hospitalization	50.3 % (758)	51.7 % (836)	0.9 [0.8-1.1]	-
disabling	1.0 % (15)	0.7 % (12)	1.3 [0.6-2.9]	-

* OR=1 is not included; OR > 1 reported more often in females; OR < 1 reported more often in males.

[a] age unknown: *ACEi angioedema cases*: 179 cases (5.4 % of cases), *ACEi controls*: 717 cases (6.7 % of cases).

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] skin and subcutaneous tissue disorders were analyzed based on the SOC "skin and subcutaneous tissue disorders", urticaria based on the HLT "urticarias". The term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] suitable hierarchical levels of the MedDRA terminology were chosen for analysis of the reported patients' comorbidities. The term "renal disorders" was identified using the SMQs "acute renal failure" and "chronic kidney disease"; "diabetes": SMQ "hyperglycaemia/new onset diabetes mellitus"; "asthma": SMQ "asthma/bronchospasm"; "malignant tumors": SMQ "malignant tumours"; "thyroid disorders": SMQ "thyroid dysfunction".

[f] the four ACEi monosubstances most frequently reported as "suspected/interacting" are tabulated. The relative number of ADR reports specifying one of the other ACEi (not listed) as "suspected/interacting" was lower than 2 %. One ADR report may contain more than one ACEi as "suspected/interacting" drug substance. Thus, the number of reported ACEi exceeds that of the ADR reports.

[g] the analysis of the most frequently reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the "suspected/interacting" ACEi were counted as concomitant, regardless of whether they were reported as "suspected", "interacting" or "concomitant".

[h] deviating from the ATC-code, the analysis concerning "analgesics" also includes ADR reports in which ibuprofen and/or diclofenac were listed as suspected/interacting or concomitant drug. We excluded ADR reports in which acetylsalicyclic acid was listed as suspected/interacting or concomitant drug. The number of ADR reports in which acetylsalicyclic acid was used concurrently were analyzed separately.

[i] deviating from the ATC-code, we excluded ADR reports in which a DPPIVi was listed as suspected/interacting or concomitant drug in the analysis concerning "diabetics". The number of ADR reports in which DPPIVi was used concurrently was analyzed separately.

[j] one ADR report may yield information about more than one seriousness criterion. Thus, the number of reported seriousness criteria exceeds that of the ADR reports.

S2 Table shows the absolute and relative number of reports and the calculated unadjusted and adjusted odds ratios of females versus males for the reported demographic parameters, comorbidities, comedications and seriousness criteria of the gender-stratified *ACEi angioedema cases* of the European Economic Area (EEA).

S3 Table. *EVDAS* analysis: reported characteristics in *ARBs* and *aliskiren angioedema cases* and *ARBs* and *aliskiren controls*.

***EVDAS* analysis**	**characteristics of *ARBs angioedema cases* and *ARBs controls***		***ARBs angioedema cases* versus *ARBs controls***		**characteristics of *aliskiren angioedema cases* and *aliskiren controls***		***aliskiren angioedema cases* versus *aliskiren controls***	
	ARBs angioedema cases (n= 687; 7.4 %)	*ARBs controls* (n= 8,543 92.6 %)	unadj. OR [+/- 95 % CI]	logistic regression OR [+/- 95 % CI]	*aliskiren angioedema cases* (n= 162; 13.8 %)	*aliskiren controls* (n= 1,015; 86.2 %)	unadj. OR [+/- 95 % CI]	logistic regression OR [+/- 95 % CI]
patient demographics								
mean age (median) [years] [a]	65.5 (67.0)	67.3 (69.0)	-	0.9 [0.7-1.0]	64.7 (68.0)	67.6 (70.0)	-	1.0 [0.6-1.5]
female	57.1 % (392)	54.0 % (4,615)	1.1 [1.0-1.3]	1.1 [0.9-1.3]	61.1 % (99)	47.7 % (484)	1.8 [1.3-2.5]*	1.5 [1.0-2.2]
male	40.2 % (276)	42.5 % (3,633)			35.8 % (58)	49.8 % (505)		
unknown	2.8 % (19)	3.5 % (295)			3.1 % (5)	2.6 % (26)		
smoking habits, allergic conditions								
smoker [b]	2.0 % (14)	1.7 % (143)	1.2 [0.7-2.1]	1.3 [0.7-2.3]	1.2 % (2)	2.5 % (25)	0.5 [0.1-2.1]	0.6 [0.1-2.8]
allergy [c]	6.8 % (47)	2.6 % (224)	2.7 [2.0-3.8]*	1.5 [1.0-2.3]*	13.6 % (22)	3.3% (33)	4.7 [2.7-8.3]*	3.5 [1.7-7.2]*
***history of skin and subcutaneous tissue disorders* [d]**								
skin/subcutaneous	7.0 % (48)	2.0 % (173)	3.6 [2.6-5.1]*	-	6.2 % (10)	2.3 % (23)	2.8 [1.3-6.1]*	1.3 [0.5-3.4]

disorders								
urticaria	0.9 % (6)	0.1 % (8)	9.4 [3.3-27.2]*	4.8 [1.5-15.7]*	-	-	-	-
angioedema	4.5 % (31)	0.1 % (11)	36.7 [18.3-73.3]*	22.7 [10.6-48.3]*	4.9 % (8)	0.1 % (1)	52.7 [6.5-424.1]*	-
comorbidities [e]								
renal disease	2.0 % (14)	5.7 % (492)	0.3 [0.2-0.6]*	0.4 [0.2-0.6]*	4.9 % (6)	15.3 % (116)	0.3 [0.1-0.7]*	0.4 [0.2-1.0]
diabetes	7.6 % (52)	9.4 % (807)	0.8 [0.6-1.1]	-	12.3 % (20)	18.6 % (189)	0.6 [0.4-1.0]	-
asthma	2.9 % (20)	1.6 % (133)	1.9 [1.2-3.1]*	1.3 [0.8-2.4]	4.9 % (8)	1.3 % (13)	4.0 [1.6-9.8]*	5.0 [1.7-14.8]*
malignant tumors	2.9 % (20)	4.5 % (386)	0.6 [0.4-1.0]	0.6 [0.4-1.0]	2.5 % (4)	3.6 % (37)	0.7 [0.2-1.9]	0.5 [0.1-1.9]
thyroid disorders	3.3 % (23)	3.0 % (259)	1.1 [0.7-1.7]	1.2 [0.7-2.0]	4.3 % (7)	2.2 % (22)	2.0 [0.9-4.9]	2.8 [1.0-7.9]
administered ARBs [f]								
losartan	25.8 % (177)	19.1 % (1,633)	1.5 [1.2-1.8]*	1.7 [1.4-2.1]*	-	-	-	-
candesartan	24.9 % (171)	21.0 % (1,792)	1.2 [1.0-1.5]	1.7 [1.3-2.1]*	-	-	-	-
valsartan	22.4 % 154)	21.7 % (1,855)	1.0 [0.9-1.3]	1.4 [1.1-1.8]*	-	-	-	-
comedication [g]								
β-blockers	18.5 % (127)	23.5 % (2,010)	0.7 [0.6-0.9]*	0.8 [0.7-1.0]	18.5 % (30)	30.0 % (304)	0.5 [0.3-0.8]*	0.7 [0.4-1.2]
diuretics	20.4 % (140)	29.0 % (2,481)	0.6 [0.5-0.8]*	0.6 [0.5-0.7]*	23.5 % (38)	37.2 % (378)	0.5 [0.4-0.8]*	0.6 [0.4-1.0]
calcium antagonists	15.4 % 106)	16.9 % (1,443)	0.9 [0.7-1.1]	0.9 [0.7-1.1]	28.4 % (46)	28.2 % (286)	1.0 [0.7-1.5]	1.5 [0.9-2.4]
ACEi	10.2 % (70)	4.6 % (397)	2.3 [1.8-3.0]*	2.2 [1.6-3.0]*	11.1 % (18)	17.8 % (181)	0.6 [0.3-1.0]	0.6 [0.3-1.2]

ARBs	-	-	-	-	11.7 % (19)	22.7 % (230)	0.5 [0.3-0.7]*	0.5 [0.3-1.0]
acetylsalicy-clic acid	12.1 % (83)	13.8 % (1,176)	0.9 [0.7-1.1]	1.1 [0.9-1.5]	14.8 % (24)	13.5 % (137)	1.1 [0.7-1.8]	1.8 [1.0-3.2]
analgesics [h]	8.6 % (59)	10.7 % (913)	0.8 [0.6-1.0]	0.7 [0.5-1.0]*	6.2 % (10)	7.1 % (72)	0.9 [0.4-1.7]	0.5 [0.2-1.2]
antidiabetics [i]	7.0 % (48)	9.4 % (803)	0.7 [0.5-1.0]	0.8 [0.5-1.1]	7.4 % (12)	13.6 % (138)	0.5 [0.3-0.9]*	0.6 [0.3-1.2]
DPPIVi	2.9 % (20)	1.7 % (142)	1.8 [1.1-2.9]*	1.8 [1.1-3.1]*	3.7 % (6)	2.0 % (20)	1.9 [0.8-4.8]	1.6 [0.5-5.2]
mTORi	0.3 % (2)	0.2 % (16)	1.6 [0.4-6.8]	2.3 [0.5-10.6]	-	0.1 % (1)	-	-
fibrinolytics	0.1 % (1)	-	-	-	-	-	-	-
seriousness criteria [j]								
serious	81.7 % (561)	71.4 % (6,102)	1.8 [1.5-2.2]*	1.8 [1.5-2.3]*	96.9 % (157)	91.8 % (932)	2.8 [1.1-7.0]*	3.1 [1.2-7.9]*
death	0.6 % (4)	2.5 % (215)	0.2 [0.1-0.6]*	-	2.5 % (4)	4.9 % (50)	0.5 [0.2-1.4]	-
life-threatening	8.6 % (59)	4.9 % (419)	1.8 [1.4-2.4]*	-	1.2 % (2)	6.1 % (62)	0.2 [0.0-0.8]*	-
hospitaliza-tion	32.0 % (220)	38.8 % (3,315)	0.7 [0.6-0.9]*	-	16.7 % (27)	37.1 % (377)	0.3 [0.2-0.5]*	-
disabling	2.9 % (20)	2.6 % (218)	1.1 [0.7-1.8]	-	1.2 % (2)	1.9 % (19)	0.7 [0.2-2.8]	-

*OR=1 is not included; OR > 1 reported more often in *ARBs* or *alsikiren angioedema cases*; OR < 1 reported more often in *ARBs* or *aliskiren controls*

[a] age unknown: *ARBs angioedema cases*: 88 cases (12.8 % of cases), *ARBs controls*: 1,276 cases (14.9 % of cases), *aliskiren angioedema cases*: 37 cases (22.8 % of cases), *aliskiren controls*: 242 cases (23.8 % of cases).

[b] only current smoking at the time of the reported ADR was counted. Former smokers were classified as non-smokers.

[C] the term "allergy" summarizes allergic and hypersensitivity reactions reported in the history of the patient.

[d] skin and subcutaneous tissue disorders were analyzed based on the SOC "skin and subcutaneous tissue disorders", urticaria based on the HLT "urticarias". The term "angioedema" summarizes previous angioedema or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] suitable hierarchical levels of the MedDRA terminology were chosen for the analysis of the reported patients' comorbidities. The term "renal disorders" was identified using the SMQs "acute renal failure" and "chronic kidney disease"; "diabetes": SMQ "hyperglycaemia/new onset diabetes mellitus"; "asthma": SMQ "asthma/bronchospasm"; "malignant tumors": SMQ "malignant tumours"; "thyroid disorders": SMQ "thyroid dysfunction".

[f] the three ARB monosubstances most frequently reported as "suspected/interacting" are tabulated. One ADR report may contain more than one ARB as "suspected/interacting" drug substance. Thus, the number of reported ARBs exceeds that of the ADR reports.

[g] the analysis of the most frequently reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the "suspected/interacting" ARBs were counted as concomitant, regardless of whether they were reported as "suspected", "interacting" or "concomitant".

[h] deviating from the ATC-code, the analysis concerning "analgesics" also includes ADR reports in which ibuprofen and/or diclofenac were listed as suspected/interacting or concomitant drug. We excluded ADR reports in which acetylsalicyclic acid was listed as suspected/interacting or concomitant drug. The number of ADR reports in which acetylsalicyclic acid was used concurrently were analyzed separately.

[i] deviating from the ATC-code, we excluded ADR reports in which a DPPIVi was listed as suspected/interacting or concomitant drug in the analysis concerning "diabetics". The number of ADR reports in which DPPIVi was used concurrently was analyzed separately.

[j] one ADR report may yield information about more than one seriousness criterion, therefore, the number of reported seriousness criteria exceeds that of the ADR reports.

S3 Table shows the absolute and relative number of reports and the calculated unadjusted and adjusted odds ratios for the reported demographic parameters, comorbidities, comedications and seriousness criteria of *ARBs* and *alsikiren angioedema cases* versus their respective *controls* of the European Economic Area (EEA).

S4 Table. Mean number of angioedema and ADR reports (total) in relation to the number of assumed ACEi-exposed inhabitants/males/females.

	mean number of angioedema reports [a] per 1 million assumed ACEi-exposed inhabitants/males/females	**mean number of controls (ADR reports [a] without angioedema reports) per 1 million assumed ACEi-exposed inhabitants/males/females**	**mean number of ADR reports (total) [a] per 1 million assumed ACEi-exposed inhabitants/males/females**
total	3 angioedema reports	10 controls	13 ADR reports (total)
male	2 angioedema reports	8 controls	10 ADR reports (total)
female	3 angioedema reports	12 controls	14 ADR reports (total)

[a] the calculation of the mean number of angioedema reports, controls (ADR reports without angioedema reports) and ADR reports (total) per 1 million ACEi-exposed inhabitants/males/females was restricted to the years 2010-2016. This was the case since the ADR reports were analyzed for only half of the year 2017 (analysis criteria 01/01/2010-30/06/2017).

S4 Table shows the calculated mean number of angioedema and ADR reports in relation to the assumed number of ACEi-exposed inhabitants/males/females per 1 million assumed ACEI-exposed inhabitants/males/females in Germany. The number of inhabitants per year was extracted from the GENESIS database [50] and multiplied by the proportional share of ACEi exposure in the German population published in DEGS1 [33]. A proportion of about 17.5 % of German adults, 19.0 % of German adult males, and 16.0 % of German adult females taking an ACEi were extracted from the published graphic in DEGS1.

S5 Table. *BfArM's ADR-database* analysis: characteristics of *matched validated ACEi angioedema cases* and *ACEi controls (not validated)*.

	***matched validated ACEi angioedema cases* (n= 114)[a]**	***matched ACEi controls (not validated)* (n= 228)**	**unadj. OR [+/- 95 % CI)**
patient demographics			
mean age (median) [years]	64.5 (68)	64.5 (67.5)	-
female/male	51 (44.7 %) / 63 (55.3 %)	102 (44.7 %) / 126 (55.3 %)	-
smoking habits, allergic conditions			
smoking [b]	17 (14.9 %)	9 (3.9 %)	4.3 [1.8-9.9]*
allergy [c]	14 (12.3 %)	16 (7.0 %)	1.9 [0.9-3.9]
history of skin and subcutaneous tissue disorders			
skin/subcutaneous disorders	8 (7.0 %)	7 (3.1 %)	-
urticaria	1 (0.9 %)	0 (0.0 %)	-
angioedema [d]	26 (22.8 %)	0 (0.0 %)	-
comorbidities [e]			
renal disorders	12 (10.5 %)	20 (8.8 %)	1.2 [0.6-2.6]
diabetes	19 (16.7 %)	45 (19.7 %)	0.8 [0.5-1.5]
asthma	5 (4.4 %)	4 (1.8 %)	2.6 [0.7-9.8]
malignant tumors	6 (5.3 %)	13 (5.7 %)	0.9 [0.3-2.5]
thyroid disorders	11 (9.6 %)	15 (6.6 %)	1.5 [0.7-3.4]
comedication [f]			
β-blockers	34 (29.8 %)	71 (31.1 %)	0.9 [0.6-1.5]
diuretics	15 (13.1 %)	59 (25.9 %)	0.4 [0.2-0.8]*
calcium antagonists	19 (16.7 %)	37 (16.2 %)	1.0 [0.6-1.9]
acetylsalicyclic acid	23 (20.2 %)	43 (18.9 %)	1.1 [0.6-1.9]
NSAID	4 (3.5 %)	10 (4.4 %)	0.8 [0.2-2.6]
diabetics	15 (13.1 %)	37 (16.2 %)	0.8 [0.4-1.5]
everolimus	6 (5.3 %)	0 (0.0 %)	-
alteplase	1	0	-

	(0.9 %)	(0.0 %)	
seriousness criteria [g]			
serious	101 (88.6 %)	161 (70.6 %)	3.2 [1.7-6.2]*
death	4 (3.5 %)	4 (1.8 %)	2.0 [0.5-8.3]
life-threatening	33 (28.9 %)	25 (11.0 %)	3.3 [1.9-5.9]*
hospitalization	58 (50.9 %)	81 (35.5 %)	1.9 [1.2-3.0]*

*OR=1 is not included; OR > 1 reported more often in *matched validated ACEi angioedema cases*; OR < 1 reported more often in *matched ACEi controls (not validated)*

[a] in 7 of the *validated ACEi angioedema cases* neither age or gender (or both) were reported, hence 114 cases remained. The 1:2 matching by age and gender to the *ACEi controls (not validated)* was only performed for the cases in which age and gender were reported.

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] the term "angioedema" summarizes previous angioedema, or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] refers to the respective comorbidity reported in the patients' history or as a drug indication tem for the used comedication.

[f] the analysis of the most reported and most relevant comedications is based on mono-substances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the "suspected/interacting" ACEi were counted as concomitant, irrespective if they were reported as "suspected", "interacting", or "concomitant".

[g] one ADR report may inform about more than one seriousness criterion. Thus, the number of reported seriousness criteria exceeds the number of ADR reports.

S5 Table shows the absolute and relative number of reports and the calculated unadjusted odds ratios for the reported demographic parameters, comorbidities, comedications, and seriousness criteria of the *matched validated ACEi angioedema cases* and *matched ACEi controls (not validated)*.

S6 Table. *BfArM's ADR-database* analysis: characteristics of *validated ARBs* and *aliskiren angioedema cases*.

	***validated ARBs angioedema cases* (n= 63)**	***validated aliskiren angioedema cases* (n= 33)**
completeness score	0.67 [0.54-0.80]	0.68 [0.49-0.88]
patient demographics		
mean age (median) [years]	66.2 (69)	62.1 (66)
female	45 (71.4 %)	21 (63.6 %)
male	17 (27.0 %)	11 (33.3 %)
unknown	1 (1.6 %)	1 (3.0 %)
smoking habits and comorbidities		
smoking [b]	2 (3.2 %)	1 (3.0 %)
allergy [c]	12 (19.0 %)	8 (24.2 %)
angioedema [d]	7 (11.1 %)	12 (36.4 %)
renal disorders [e]	-	2 (6.1 %)
diabetes [e]	3 (4.8 %)	7 (21.2 %)
asthma [e]	2 (3.2 %)	1 (3.0 %)
comedication [f]		
β-blockers	11 (17.5 %)	7 (21.2 %)
diuretics	8 (12.7 %)	7 (21.2 %)
calcium antagonists	10 (15.9 %)	7 (21.2 %)
NSAID	3 (4.8 %)	1 (3.0 %)
everolimus	-	-
alteplase	-	-
ACEi	-	5 (15.2 %)
ARBs	-	3 (9.1 %)
seriousness criteria [g]		

serious	57 (90.5 %)	161 70.6 %)
death	-	4 (1.8 %)
life-threatening	3 (4.8 %)	25 (11.0 %)
hospitalization	15 (23.8 %)	81 (35.5 %)
anatomical area affected by the angioedema [h]		
tongue	13 (20.6 %)	5 (15.2 %)
lips	13 (20.6 %)	8 (24.4 %)
face	22 (34.9 %)	13 (39.4 %)
pharynx	4 (6.3 %)	2 (6.1 %)
larynx	3 (4.8 %)	1 (3.0 %
eye/eyelid	8 (12.7 %)	4 (12.1 %)
throat	8 (12.7 %)	3 (9.1 %)
urticaria	8 (12.7 %)	3 (9.1 %)
reported attendant reactions [i]		
pruritus	10 (15.9 %)	5 (15.2 %)
peripheral swellings/oedemas	1 (1.6 %)	4 (12.1 %)
prior history of ACEi and/or ARBs use		
ACEi and/or ARBs use	8 (12.7 %)	13 (39.4 %)
withdrawn due to "cough"	4/8 (50.0 %)	2/13 (15.4 %)
withdrawn due to "allergy"	1/8 (12.5 %)	-
withdrawn due to "angioedema"	1/8 (12.5 %)	7/13 (53.8 %)
reason for withdrawn "NA"	2/8 (25.0 %)	4/13 (30.8 %)

[a] age unknown: *validated ARBs angioedema cases*: 21 cases (33.3 % of cases), *validated aliskiren angioedema cases*: 13 cases (39.4 % of cases).

[b] refers to current smoking at the time of the reported ADR. Former smokers were classified as non-smokers.

[c] the term "allergy" refers to a reported allergy and the occurrence of any allergic and hypersensitivity reactions reported in the history of the patient.

[d] the term "angioedema" summarizes previous angioedema, or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] refers to the respective comorbidity reported in the patients' history or as a drug indication tem for the used comedication.

[f] the analysis of the most reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported to the respective "suspected/interacting" drug substance were counted as concomitant, irrespective if they were reported as "suspected", "interacting", or "concomitant".

[g] one ADR report may inform about more than one seriousness criterion. Thus, the number of reported seriousness criteria exceeds the number of ADR reports.

[h] one ADR report may inform about more than one anatomical area affected of the angioedema. Thus, the number of reported anatomical areas affected of the angioedema exceeds the number of ADR reports.

[i] one ADR report may inform about more than one attendant symptom. Thus, the number of reported attendant symptoms exceeds the number of ADR reports.

S6 Table shows the absolute and relative number of the reported characteristics of the *validated ARBs* and *aliskiren angioedema cases*.

S7 Table. Number of *ACEi, ARBs, and aliskiren angioedema cases* and their total number of ADR reports in relation to the number of drug prescriptions in Germany (2010-2016).

RASi	number of angioedema reports [a] (% of all ADR reports of the respective drug substance)	number of all ADR reports [a]	number of drug prescriptions in Mio DDD [b]	number of angioedema reports /number of drug prescriptions in 1,000 Mio DDD	mean administered dose (median) [mg] [c]	defined daily dose (DDD) [mg] [d]	administered dose/ DDD ratio	number of angioedema reports/number of drug prescriptions in 1,000 Mio of the administered dose	meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors [e]
ACEi	253 (20.3 %)	1246	32382,4	8	-	-	-	-	0.30 %
ramipril	181 (20.2 %)	896	25846,8	7	6.0 (5.0)	2.5	2.4 (2)	17	-
lisinopril	28 (25.9 %)	108	2199,3	13	15.8 (15.0)	10.0	1.6 (1.5)	20	-
enalapril	33 (17.4 %)	190	3741,1	9	11.7 (5.0)	10.0	1.2 (0.5)	10	-
ACEi + everolimus	10 (90.9 %)	11 [f]	11,9 [g]	840	-	-	-	-	-
ARBs	103 (7.6 %)	1361	10550,7	10	-	-	-	-	0.11 %
valsartan	48 (10.5 %)	455	3089,2	16	126.6 (160.0)	80.0	1.6 (2.0)	25	-
candesartan	32 (6.8 %)	469	4720,3	7	17.1 (16.0)	8.0	2.1 (2.0)	14	-
losartan	10 (8.0 %)	125	868,6	12	75.0 (75.0)	50.0	1.5 (1.5)	17	-
aliskiren	50 (12.7 %)	394	267,6	154	204.0 (150.0)	150.0	1.4 (1.0)	252	0.13 %

[a] all identified cases (not validated) in **BfArM's ADR-database** analysis of the time period 01/2010-12/2016.

[b] cumulative number of drug prescriptions (monosubstances) for the years 2010-2016 [34].

[c] all angioedema reports including reports from 2017. The administered reported dose was analyzed during the validation process based on the complete report (including narratives; see material and methods).

[d] definition of ATC-code and the respective DDD of ACEi, ARBs and aliskiren monosubstances [41, 42].

[e] the incidences were taken from a meta-analysis of randomized trials performed by Makani et al. [23].

[f] number of ACEi reports with concomitant use of everolimus.

[g] number of drug prescriptions for everolimus [34].

S7 Table shows the absolute and relative number of *ACEi, ARBs and aliskiren angioedema cases* and their total number of ADR reports in the time periode 01/2010-12/2016 as well as their relation to the number of drug prescriptions in 1,000 Mio DDD. Additionally, the number of angioedema reports per drug prescriptions fitted to the administered dose versus defined daily dose (DDD) ratio was calculated.

S8 Table. *EVDAS* analysis: reported characteristics in *ACEi angioedema cases* with concurrent mTORi, fibrinolytics, or DPPIVi use.

	***ACEi angioedema cases* with mTORi as concomitant drug (n= 42; 1.3 %)**	***ACEi angioedema cases* with fibrino-lytics as concomi-tant drug (n= 38; 1.2 %)**	***ACEi angioedema cases* with DPPIVi as concomitant drug (n= 67; 2.1 %)**
patient demographics			
mean age (median) [years] [a]	62.6 (62)	71.6 (74)	68.3 (67)
female	35.7 % (15)	52.6 % (20)	43.3 % (29)
male	64.3 % (27)	47.4 % (18)	55.2 % (37)
unknown	0.0 % (0)	0.0 % (0)	1.5 % (1)
smoking habits, allergic conditions			
smoker [b]	2.3 % (1)	5.3 % (2)	3.0 % (2)
allergy [c]	0.0 % (0)	0.0 % (0)	4.5 % (3)
history of skin and subcutaneous disorders			
urticaria	0.0 % (0)	0.0 % (0)	1.5 % (1)
angioedema [d]	7.1 % (3)	2.6 % (1)	9.0 % (6)
comorbidities [e]			
renal disorders	31.0 % (13)	0.0 % (0)	6.0 % (4)
diabetes	11.9 % (5)	36.8 % (14)	61.2 % (41)
asthma	0.0 % (0)	2.6 % (1)	3.0 % (2)
malignant tumors	28.6 % (12)	2.6 % (1)	9.0 % (6)
thyroid disorders	4.7 % (2)	13.2 % (5)	4.5 % (3)
administered ACEi [f]			
ramipril	57.1 % (24)	18.4 % (7)	50.8 % (34)
enalapril	14.3 % (6)	26.3 % (10)	16.4 % (11)
perindopril	11.9 % (5)	26.3 % (10)	20.9 % (14)
lisinopril	11.9 % (5)	10.5 % (4)	10.5 % (7)
comedication [g]			
β-blockers	31.0 % (13)	34.2 % (13)	29.9 % (20)
diuretics	26.2 % (11)	26.3 % (10)	35.8 % (24)

calcium antagonists	7.1 % (3)	18.4 % (7)	17.9 % (12)
ARBs	0.0 % (0)	2.6 % (1)	3.0 % (2)
acetylsalicyclic acid	23.8 % (10)	18.4 % (7)	37.3 % (25)
analgesics [h]	2.4 % (1)	5.3 % (2)	16.4 % (11)
antidiabetics [i]	9.5 % (4)	31.6 % (12)	0.0 % (0)
DPPIVi	0.0 % (0)	2.6 % (1)	-
mTORi	-	0.0 % (0)	0.0 % (0)
fibrinolytics	0.0 % (0)	-	1.5 % (1)
seriousness criteria [j]			
serious	92.9 % (39)	86.8 % (33)	98.5 % (66)
death	4.8 % (2)	2.6 % (1)	6.0 % (4)
life-threatening	9.5 % (4)	50.0 % (19)	22.4 % (15)
hospitalization	59.5 % (25)	26.3 % (10)	67.2 % (45)
disabling	0.0 % (0)	0.0 % (0)	0.0 % (0)
anatomical area affected by the angioedema [k]			
angioedema	69.0 % (29)	71.1 % (27)	83.6 % (56)
tongue	31.0 % (13)	31.6 % (12)	20.9 % (14)
lips	4.8 % (2)	10.5 % (4)	4.5 % (3)
face	21.4 % (9)	2.6 % (1)	9.0 % (6)
pharynx	9.5 % (4)	5.3 % (2)	1.5 % (1)
larynx	2.4 % (1)	2.6 % (1)	4.5 % (3)
palatal	0.0 % (0)	0.0 % (0)	0.0 % (0)
mouth	4.8 % (2)	0.0 % (0)	1.5 % (1)
eye/eyelid	0.0 % (0)	0.0 % (0)	1.5 % (1)
urticaria	0.0 % (0)	0.0 % (0)	10.4 % (7)
reported attendant reactions [l]			
dyspnoea	11.9 % (5)	15.8 % (6)	10.4 % (7)
pruritus	-	-	1.5 %

			(1)
hypersensitivity	-	2.6 % (1)	3.0 % (2)
dysphagia	2.4 % (1)	-	1.5 % (1)
rash	-	-	-
erythema	2.4 % (1)	-	1.5 % (1)

[a] age unknown: *ACEi angioedema cases* with concomitant mTORi therapy: 3 cases (7.1 % of cases), *ACEi angioedema cases* with concomitant fibrinolytics therapy: 2 cases (5.3 % of cases), *ACEi angioedema cases* with concomitant DPPIVi therapy: 6 cases (9.0 % of cases).

[b] current smoking at the time of the reported ADR was count, only. Former smokers were classified as non-smokers.

[c] the term "allergy" summarizes allergic and hypersensitivity reactions reported in the history of the patient.

[d] skin and subcutaneous tissue disorders were analyzed based on the SOC "skin and subcutaneous tissue disorders", urticaria based on the HLT "urticarias". The term "angioedema" summarizes previous angioedema, or swellings coded in the SMQ "angioedema (narrow)" reported in the history of the patient.

[e] suitable hierarchical levels of the MedDRA terminology were chosen for the analysis of the reported patients' comorbidities. The term "renal disorders" was identified using the SMQs "acute renal failure" and "chronic kidney disease"; "diabetes": SMQ "hyperglycaemia/new onset diabetes mellitus"; "asthma": SMQ "asthma/bronchospasm"; "malignant tumors": SMQ "malignant tumours"; "thyroid disorders": SMQ "thyroid dysfunction".

[f] tabulated are the four ACEi monosubstances reported as "suspected/interacting" most frequently (of all cases). One ADR report may contain more than one ACEi as "suspected/interacting" drug substance. Thus, the number of reported ACEi exceeds the number of ADR reports.

[g] the analysis of the most frequently reported and most relevant comedications is based on monosubstances and combination products of the tabulated drug substances and/or drug classes and corresponds to the ATC classification. All drugs co-reported in *ACEi angioedema cases* with concurrent mTORi, fibrinolytics or DPPIVi use were counted as concomitant, regardless of whether they were reported as "suspected", "interacting" or "concomitant".

[h] deviating from the ATC-code, the analysis concerning "analgesics" also includes ADR reports in which ibuprofen and/or diclofenac were listed as suspected/interacting or concomitant drug. We excluded ADR reports in which acetylsalicyclic acid was listed as suspected/interacting or concomitant drug. The number of ADR reports in which acetylsalicyclic acid was used concurrently were analyzed separately.

[i] deviating from the ATC-code, we excluded ADR reports in which a DPPIVi was listed as suspected/interacting or concomitant drug in the analysis concerning "diabetics". The number of ADR reports in which DPPIVi was used concurrently was analyzed separately.

[j] one ADR report may yield information about more than one seriousness criterion. Thus, the number of reported seriousness criteria exceeds that of the ADR reports.

[k] one ADR report may yield information about more than one anatomical area affected of the angioedema. Thus, the number of reported anatomical areas affected of the angioedema exceeds that of the ADR reports.

[l] one ADR report may yield information about more than one attendant symptom. Thus, the number of reported attendant symptoms exceeds that of the ADR reports.

S8 Table shows the absolute and relative number of reports for the reported demographic parameters, comorbidities, comedications, and seriousness criteria, anatomical areas affected by the angioedema, and attendant symptoms of *ACEi angioedema cases* with concurrent mTORi, fibrinolytics or DPPIVi use of the European Economic Area (EEA).

S9 Table. *BfArM's ADR-database* analysis: reported treatment of ACEi-associated angioedema.

reported angioedema treatment	***validated ACEi angioedema cases* (n= 78; 64.4 %)**
Antihistamine and/or steroids	60.3 % (47/78)
additional cooling	4.3 % (2/47)
antihistamines only	8.5 % (4/47)
steroids only	38.3 % (18/47)
rapid regression of symptoms	31.9 % (15/47)
slow regression of symptoms	27.7 % (13/47)
regression was not assessable or not available	40.4 % (19/47)
circulation stabilizing drugs	12.8 % (10/78)
additional with antihistamines/steroids	90% (9/10)
circulation stabilizing drugs only	10 % (1/10)
rapid regression of symptoms	20 % (2/10)
slow regression of symptoms	70 % (7/10)
regression was not assessable or not available	10 % (1/10)
medical intervention	16.7 % (13/78)
additional with other medications	53.8 % (7/13)
medical intervention only	46.2 % (6/13)
intubation	61.5% (8/13)
conitotomy	15.4 % (2/13)
tracheotomy	15.4 % (2/13)
laryngeal tube	7.7 % (1/13)
C1-esterase inhibitors	10.3 % (8/78)
additional with antihistamines/steroids	75.0 % (6/8)
C1-esterase inhibitors only	25.0 % (2/8)
rapid regression of symptoms	75 % (6/8)
slow regression of symptoms	12.5 % (1/8)
regression was not assessable or not available	12.5 % (1/8)
icatibant	5.1 % (4/78)
additional with antihistamines/steroids	50.0 % (2/4)
icatibant only	50.0 % (2/4)
rapid regression of symptoms	100.0 % (4/4)
slow regression of symptoms	-
fresh frozen plasma	1.3 % (1/78)
additional with antihistamines/steroids	100.0 % (1/1)
rapid regression of symptoms	100.0 % (1/1)
slow regression of symptoms	-

S9 Table shows the absolute and relative number of the reported angioedema treatments in the *validated ACEi angioedema cases*.

Appendix E

Dubrall D, Schmid M, Alešik E, Paeschke N, Stingl J, Sachs B. In Reply: Frequent Adverse Drug Reactions, and Medication Groups under Suspicion. Dtsch Arztebl Int 2018; 115(41): 682.

Sachs B, Stingl J, Paeschke N, Dubrall D, Schmid M. Forschung im Bereich der unerwünschten Arzneimittelwirkungen. Bulletin zur Arzneimittelsicherheit 2017; 1: 29-32.