Analysis of fatal adverse drug events recorded in several Italian emergency departments (the MEREAFaPS study)

Internal and Emergency Medicine
https://doi.org/10.1007/s11739-020-02521-x

EM - ORIGINAL

Analysis of fatal adverse drug events recorded in several Italian emergency departments (the MEREAFaPS study)

Silvia Pagani[1] · Niccolò Lombardi[2] · Giada Crescioli[2] · Giuditta Violetta Vighi[3] · Giulia Spada[3] · Isabella Romoli[3] · Paola Andreetta[1] · Annalisa Capuano[4] · Eleonora Marrazzo[5] · Anna Marra[6] · Olivia Leoni[7] · Alfredo Vannacci[2] · Mauro Venegoni[1,8] · Giuseppe Danilo Vighi[1] on behalf of The MEREAFaPS Study group

Received: 3 April 2020 / Accepted: 28 September 2020

Abstract
Fatal Adverse Events (FADEs) are a major public health problem, and some FADEs could be preventable. The aim of the present study is to describe the frequency, the drugs involved and the preventability in the FADEs collected through the MEREAFaPS Study between 2012 and 2018. All cases including the outcome "death" have been examined. We excluded cases with vaccine-related ADEs, overdose or suicide, and ADEs occurred during the hospitalisation. Two trained assessors evaluated all cases fulfilling the inclusion criteria. ADEs' preventability was evaluated applying the Schumock and Thornton algorithm. During the study period, we observed 429 cases of death, 92 of which were excluded. The remaining 337 cases involved 187 women and 150 men, with a mean age of 79 and of 77 years, respectively. For each report, the suspected drugs and concomitant ones were 1.26 and 4.20, respectively. Anticoagulants and antiplatelet agents account for more than 40% of FADE cases and the most frequent reactions are haemorrhages (37.5%). The 25% of the FADEs were preventable. This study confirms that FADEs are still a relevant clinical occurrence, and are often caused by widely used old drugs associated with adverse events. The death of one in four patients was preventable. Further efforts should be done to improve the appropriateness of the therapy, especially in older patients who are treated with anticoagulants.

Keywords Adverse drug reaction · Pharmacovigilance · Drug safety · Medication error · Appropriateness of drug use

Background

Adverse Drug Events (ADEs) are an important cause of drug-related Emergency Department (ED) visits [1–5], and many of these are preventable [6, 7]. Among them, fatal adverse drug events (FADEs) are a major public health problem, both for the burden of pain, suffering, death and for the economic costs [8–13].

In 1970, Girdwood and colleagues [14] published the first analysis of FADEs collected in the United Kingdom from 1963 to 1969. In those years, the underreporting was very high and reliable data on the prescriptions of medications were lacking. Nevertheless, authors highlighted the risk of

S. Pagani, N. Lombardi and G. Crescioli authors contributed equally.

✉ Silvia Pagani
silvia.pagani@asst-vimercate.it

1 Department of Medicine, ASST Vimercate, Via Santi Cosma e Damiano 10, 20871 Vimercate, MB, Italy

2 Department of Neurosciences, Psychology, Drug Research and Child Health, Section of Pharmacology and Toxicology, University of Florence, Florence, Italy

3 Hospital Pharmacy, ASST Vimercate, Vimercate, Italy

4 Section of Pharmacology "L. Donatelli", Department of Experimental Medicine, Campania Regional Centre for Pharmacovigilance and Pharmacoepidemiology, University of Campania "Luigi Vanvitelli", Naples, Italy

5 Piedmont Regional Centre for Pharmacovigilance, Turin, Italy

6 Hospital Pharmacy, "Sant'Anna" University Hospital, Ferrara, Italy

7 Lombardy Regional Centre for Pharmacovigilance, Milan, Italy

8 Department of Health Sciences, University of Verona, Verona, Italy

Published online: 04 January 2021

some classes of drugs like analgesics. In 1979, Bottinger published the 10-year report of FADEs at the Swedish ADR Committee [15], followed in 1991 by the report of Danish FADEs [16]. In Bottinger's study, anti-inflammatory drugs were responsible for 20% of the FADEs, followed by oral hypoglycaemic and oral contraceptives. The Danish study was the first one comparing the FADEs with the number of prescriptions. In 1998, Lazarou reported that the overall incidence of serious ADEs was 6.7% and of FADEs was 0.3% among hospitalized patients [1]. This study estimated that 106,000 (95% IC 76,000–137,000) hospitalised patients experienced a FADE, making FADEs between the fourth and sixth leading cause of death in the United States. The first report on Italian FADEs was published in 2008 [17], with data retrieved from the National Pharmacovigilance database, considering only spontaneous ADE reports. The drugs most frequently involved in FADEs caused serious skin or systemic allergic events and were characterized by a high prevalence of use. Ceftriaxone, ticlopidine and nimesulide were associated with the highest number of fatalities (this reflects the huge use of these drugs in Italy in that period).

A meta-analysis of prospective studies focused on FADEs estimated a mean prevalence of fatal events of 0.2%, with a higher prevalence of studies performed within internal medicine wards, intensive care units and neonatal/paediatric wards [18]. Despite the large variability in the results, due to patients' and involved hospitals' characteristics, the percentage of preventable FADEs was still high, even if some authors report a decreasing trend [19].

The MEREAFaPS Study (Monitoraggio Epidemiologico delle Reazioni Avverse da Farmaci in Pronto Soccorso, Epidemiological Monitoring of Adverse Drug Reactions and Events leading to Emergency Department) is a national multicentre active pharmacovigilance project aimed at collecting ADEs as cause of ED visits since 2006. This is an on-going initiative which collects all ADEs leading to ED visits in 94 EDs belonging to general hospitals distributed through the national territory in five Italian Regions: Lombardy and Piedmont (north), Tuscany and Emilia-Romagna (centre), and Campania (south) [20–22]. The EDs involved in this study allowed us to reach a good and widespread coverage of the Italian population [23].

Based on data retrieved through the MEREAFaPS Study, we analysed all FADEs [21], with the aim of describing their frequency, pharmacological characteristics and preventability.

Methods

We conducted an observational study on fatal adverse event reports collected between January 1, 2012 and December 31, 2018. Data were retrieved from the MEREAFAPS Study database. We selected and analysed all cases in which "death" was reported as an ADE's outcome.

In the MEREAFAPS Study, on the basis of the Italian pharmacovigilance legislation [24], through the specific report form, ED trained monitors recorded: (1) patients' demographic characteristics (age, gender, ethnic group); (2) patients' clinical status on ED visit; (3) suspected and concomitant medications, depending on the monitor judgment of the relationship drug-event (for each one, administration route, therapy duration, dosages, and therapeutic indication, were recorded); (4) ADE description; (5) exitus description (i.e., clinical course, and, if reported, laboratory and imaging examinations).

A suspect drug is a drug which is considered to be associated with the adverse event. A concomitant drug is a drug used by the patient at the time of the adverse event. Suspected and concomitant medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

Patients who developed a FADE after being admitted to the ED or hospital, those who reported a vaccine-related ADE, and cases of overdose or suicide were excluded. FADEs description according to diagnosis and symptoms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and organized by System Organ Class (SOC) and Preferred Term (PT) [25].

A multidisciplinary team composed of experts in internal medicine, clinical pharmacology, toxicology, and epidemiology performed a clinical evaluation of cases included in the analysis, to assess the causality relationship between the suspected medications and their related ADEs with the Naranjo's algorithm [26]. Moreover, two trained assessors independently evaluated each FADE report to establish if the suspected drug caused or contributed to the patient's death. In case of discrepancy, cases were discussed together by two assessors to reach an agreement. To avoid a subjective evaluation, the preventability was evaluated using the Schumock and Thornton algorithm [27]. This is a tool with several questions to evaluate the predictability of ADEs. The criteria were established for assessing the preventability of ADRs.

For each case, we also calculated the Charlson Comorbidity Index (CCI) [28], using data of concomitant diseases and concomitant medications as a proxy of patient's comorbidities.

For each suspected agent, the rate of FADEs was calculated dividing the total number of deaths collected during the study period by total ADE reports in MEREAFaPS Study database. Although all ADEs were recorded for each ED, data on the total number of ED visits (i.e., those not related to an ADE) were not always available for the ED monitors. In the MEREAFaPS Study, these data were complete for Lombardy region only, so we calculated and

reported the rate of total deaths over the number of total ED visits for this region (supplementary material).

Descriptive statistics were used to summarize data. Categorical data were reported as frequencies and percentages and compared using the chi-square test, whereas continuous data were reported as mean values and standard deviation (SD) and compared with *t* test. Logistic regression analyses were used to estimate the reporting odds ratios (RORs) with 95% confidence intervals (CIs) of ADE-related "death", considering the most frequently reported suspected medications [29]. Due to the observational nature of the study, no sample size calculations were undertaken. All analyses were undertaken using STATA version 14.

Results

During the study period, the MEREAFaPS Study database collected a total of 57,988 ADE reports, of which 429 (0.73%) reported the outcome "death". After the clinical evaluation performed by two trained assessors, 337 (0.58%) ADE reports met the inclusion criteria. Ninety-two fatal cases were excluded for the following reasons: 57 (61.9%) cases were diagnosed during hospital stay; 5 (5.4%) cases concerned intentional drug overdose, or drug abuse, or self-poisoning; 10 (10.9%) cases were not clinically associable with the outcome "death"; 3 (3.3%) cases reported a vaccine as suspected drug; 17 (18.5%) cases were marked by a classification error.

Patients' characteristics are shown in Table 1. Females were more represented than males ($n=187$, 55.5% vs. $n=150$, 44.5%), mean age was higher for women (79 vs. 77; p value 0.037), and 89% ($n=300$) of cases were observed in subjects aged more than 65 years old. The mean number of suspected drugs was 1.3 (SD: ± 0.60), whereas the mean number of concomitant drugs was 5.0 (SD: ± 2.64), with a range from 0 to 16. Overall, the mean CCI was 2.7 (SD: ± 2.05), 2.9 and 2.5 for males and females (p value 0.086), respectively.

During the study period, the frequency of FADEs in comparison with the total ADEs varied between 0.42% and 0.79%; 82 cases (24.3%) were considered preventable (range from 14.5% to 37.2%) (Table 2). The reasons of preventability were: use of drug out of the pharmacologic range ($n=58$, 70.7%), generally oral anti vitamin K antagonists (VKAs) over the therapeutic range; lack in drug monitoring ($n=24$, 29.3%); negative drug–drug interaction ($n=5$); lack in preventive measures ($n=5$); inappropriate drug use ($n=4$); and lack of patient's compliance ($n=2$). The total is more than 82 due to the coexistence of multiple factors.

Anticoagulants were the most frequently reported suspected class ($n=172$, 40.7%), followed by antiplatelet agents ($n=75$, 17.7%), antineoplastic drugs ($n=75$, 17.7%), hypoglycaemic ($n=27$, 6.4%) and antibiotics ($n=15$, 3.6%). The most frequently reported suspected drugs were: warfarin ($n=95$, 22.5%), acetylsalicylic acid ($n=53$, 12.5%), metformin ($n=21$, 5%), dabigatran ($n=20$, 4.7%), enoxaparin ($n=14$, 3.3%), acenocoumarol ($n=11$, 2.6%), digoxin ($n=11$, 2.6%), rivaroxaban ($n=10$, 2.4%), ticlopidine

Table 1 Characteristics of the study population

	Total No. 337 (%)	Males No. 150 (%)	Females No. 187 (%)	*p* value
Age classes (years)				
18–64	37 (11.0)	19 (12.7)	18 (9.6)	0.460
65–74	55 (16.3)	30 (20.0)	25 (13.4)	0.293
75–84	148 (43.9)	67 (44.7)	81 (43.3)	0.869
> 85	97 (28.8)	34 (22.6)	63 (33.7)	0.024
Mean age (± SD) overall	78.3 (10.9)	77.0 (10.4)	79.5 (11.3)	0.037
Median	80	79	81	
Suspected drugs				
Mean number of suspected drugs (± SD)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)	0.816
Range	1–4	1–4	1–4	
Concomitant drugs				
Mean number of concomitant drugs (± SD)	5.0 (2.6)	5.2 (2.7)	4.9 (2.6)	0.356
Range	0–16	0–16	0–11	
Median	5	5	5	
Comorbidity				
Mean Charlson's comorbidity index (± SD)	2.7 (2.1)	2.9 (2.2)	2.5 (1.9)	0.086
Range	0–9	0–9	0–9	

No number, *SD* standard deviation

Table 2 FADEs rate and preventability

Year	Total ADEs	Total FADEs	Rate (%)	Not preventable FADEs No. (% in row)	Preventability not assessable* No. (% in row)	Preventable FADEs No. (% in row)
2012	8,483	55	0.65	42 (76.4)	5 (9.1)	8 (14.5)
2013	13,472	79	0.59	50 (63.3)	5 (6.3)	24 (30.4)
2014	11,563	59	0.51	44 (74.6)	3 (5.1)	12 (20.3)
2015	7,645	61	0.79	47 (77.0)	3 (4.9)	11 (18.1)
2016	3,863	21	0.54	15 (71.4)	0 (0.0)	6 (28.6)
2017	4,661	27	0.58	15 (55.6)	4 (14.8)	8 (29.6)
2018	8,301	35	0.42	20 (57.1)	2 (5.7)	13 (37.2)
Total	57,988	337	0.58	233 (69.1)	22 (6.5)	82 (24.3)

ADEs adverse drug events, *FADEs* fatal adverse drug events, *No* number

*Not enough information

($n = 10$, 2.4%), clopidogrel ($n = 8$, 1.9%) (Table 3). Overall, the first ten suspected substances accounted for 59.8% of FADEs, and the majority of them were anticoagulants or antiplatelet agents. Among the most frequently reported substances, all drugs except clopidogrel showed a statistically significant association to FADEs, in particular dabigatran for anticoagulants (ROR 8.84, 95% CI 5.89–14.00), digoxin (ROR 6.25, 95% CI 3.40–11.50), metformin (ROR 5.89, 95% CI 3.77–9.20), ticlopidine and acetylsalicylic acid for antiplatelet agents (ROR 4.71, 95% CI 2.49–8.89 and ROR 2.88, 95% CI 2.16–3.85, respectively).

Oral anticoagulants were involved in 146 cases (43% of deaths). In particular, 106 FADEs were associated with VKAs and 38 to direct oral anticoagulants (DOACs) (Table 4). Patients with a FADE related to oral anticoagulants had a mean age of 81 years, were administered with a mean number of 5.09 concomitant drugs, and were associated with a mean CCI of 2.09. Between VKA and DOAC users, no substantial differences for age, gender, number of concomitant drugs, and CCI were found. The preventability, calculated with the Shumock algorithm, was 42% for VKA-related cases and 7% for DOAC-related ones (data not shown). The total number of deaths observed for VKAs and DOACs changed during the study period, accordingly with the prescriptive changes observed in Italy (2012–2018). In 2013, FADEs associated to VKAs and DOACs were 29 versus 2, respectively, while in 2017, more cases for DOACs (10) than VKAs (8) were observed (supplementary material).

The majority of FADEs were related to: cerebral haemorrhage ($n = 114$, 16.9%), coma ($n = 33$, 4.9%), lactic acidosis ($n = 17$, 2.5%), and subarachnoid haemorrhage ($n = 14$, 2.1%) (Table 5). Notably, haemorrhagic FADEs (reported as preferred term, PT) represented 37.5% of the total ADEs analysed.

Table 3 The ten most frequently reported suspected drugs and their reporting odds ratio (ROR) of FADEs

Suspected drug	ATC class	Total FADEs No. 423 (%)	Total not fatal ADEs No. 72,941 (%)	ROR (CI 95%)
Warfarin	B01AA03	95 (22.5)	6,995 (9.6)	2.73 (2.17–3.44)
Acetylsalicylic acid	B01AC06	53 (12.5)	3,455 (4.7)	2.88 (2.16–3.85)
Metformin	A10BA02	21 (5.0)	641 (0.9)	5.89 (3.77–9.20)
Dabigatran etexilate	B01AE07	20 (4.7)	407 (0.6)	8.84 (5.89–14.00)
Enoxaparin	B01AB05	14 (3.3)	488 (0.7)	5.08 (2.96–8.72)
Acenocoumarol	B01AA07	11 (2.6)	691 (0.9)	2.79 (1.53–5.10)
Digoxin	C01AA05	11 (2.6)	310 (0.4)	6.25 (3.40–11.50)
Rivaroxaban	B01AX06	10 (2.4)	398 (0.6)	4.41 (2.33–8.89)
Ticlopidine	B01AC05	10 (2.4)	373 (0.5)	4.71 (2.49–8.89)
Clopidogrel	B01AC04	8 (1.9)	856 (1.2)	4.62 (0.80–3.27)

ATC anatomical therapeutic and chemical classification, *ADEs* adverse drug events, *CI* confidence interval, *FADEs* fatal adverse drug events, *ROR* reporting odds ratio

Table 4 FADEs associated with oral anticoagulants

	Total VKAs-related FADEs No. 106 (%)	Total DOACs-related FADEs No. 38 (%)	*p* value
Gender			
Males	53 (50.0)	20 (52.6)	0.781
Females	53 (50.0)	18 (47.4)	
Age classes (years)			
18–64	4 (3.8)	1 (2.6)	0.743
65–74	10 (9.4)	4 (10.6)	0.845
75–84	58 (54.7)	17 (44.7)	0.292
> 85	34 (32.1)	16 (42.1)	0.267
Age (mean ± SD)			
Mean age (± SD)	80.97 ± 8.66	82.05 ± 6.36	0.483
Median	81	83.5	
Comorbidities			
Mean Charlson's comorbidity index (± SD)	2.05 ± 1.56	2.11 ± 1.57	0.845
Concomitant drugs			
Mean number of concomitant drugs (± SD)	5.09 ± 2.49	4.06 ± 2.00	0.282
Median	5	4	

DOACs direct oral anticoagulants, *FADEs* fatal adverse drug events, *No* number, *SD* standard deviation, *VKAs* vitamin K antagonists

Table 5 Twenty most frequently reported preferred terms (PTs)

Preferred term	PT code	Total FADEs No. 676 (%)
Cerebral haemorrhage	10008111	114 (16.9)
Coma	10010071	33 (4.9)
Lactic acidosis	10023676	17 (2.5)
Subarachnoid haemorrhage	10042316	14 (2.1)
Septic shock	10040070	13 (1.9)
Haemorrhagic shock	10049771	13 (1.9)
Melena	10027141	13 (1.9)
Anaemia	10002034	13 (1.9)
Dyspnoea	10013968	12 (1.8)
Toxicity to various agents	10070863	11 (1.6)
Subdural hematoma	10042361	10 (1.5)
Febrile neutropenia	10016288	10 (1.5)
Thrombocytopenia	10043554	9 (1.3)
Increase of the normalized international ratio	10022595	9 (1.3)
Cardiac arrest	10007515	8 (1.2)
Hemiplegia	10019468	8 (1.2)
Rectal haemorrhage	10038063	8 (1.2)
Neutropenia	10029354	8 (1.2)
Acute renal failure	10038436	8 (1.2)
Hypotension	10021097	7 (1.0)

Discussion

This study aimed at describing the frequency and the drugs involved in FADEs recorded in the EDs participating in the MEREAFAPS Study. This is the first nationwide pharmacovigilance study on FADEs, conducted with an "active" approach, for a long period of observation and in a representative number of Italian EDs. In this study, the frequency of FADEs was around 2% of the total adverse events, and the subjects most represented were women, elders (aged ≥ 65 years), exposed to a mean of 5 concomitant drugs and with a mean CCI of 2.69. One-hundred-and-seventy-four patients (51.6%) had a FADE related to a haemorrhagic event, due to anticoagulant and/or antiplatelet treatment.

Several studies have been published on ED admissions due to ADEs [2, 11, 30] but evidence on fatal cases is still limited [9]. A meta-analysis on mortality due to ADEs identified 49 studies in which hospital mortality ranged from 0.01% to 0.44% [18]. The high variability in mortality was attributed to the differences observed in terms of population (i.e., paediatric or elderly patients), hospital settings (i.e., emergency services, intensive care units, internal medicine, and oncology) and to small sample size. Only three studies included a total of 40,000 patients and the rate between FADEs and ADEs leading to hospitalisation ranged from 0.04 to 0.19, respectively. The analysis conducted on data of the Lombardy Region (supplementary material) showed that the rate of ED visits for ADEs (3.6%) was comparable to the evidence provided by Bouvy's meta-analysis (4.6%) [31]. During the study period, a slight reduction in the frequency of FADEs/year was observed (from 0.8% in 2012 to 0.5% in 2018). This evidence is comparable to the decrease of fatalities associated to ADEs in a recently published study [19].

Moreover, several studies demonstrated an association between polypharmacy and an increased risk of ADEs [8, 29, 30], including FADEs, and that CCI could be considered as an independent predictor of ADEs [31–33]. In particular, our data showed that CCI was higher in males than in females, as reported previously for FADEs by Angamo et al. [37]. These data describe the real-world clinical practice in elderly patients, who can be exposed to potentially inappropriate medication, if a regular therapeutic reconciliation is not done [34, 35, 36]. This evidence was suggested by the presence of some representative cases, such as anticoagulants prescribed to a patient with serious cognitive impairment or to one with limited self-sufficiency, and antiplatelet agents and/or anticoagulants prescribed to patients with poly-pathologies. As we showed in a previous study, lack of mandatory laboratory tests, underestimation of patient's

prodromal symptoms, polypharmacy and potentially dangerous drug–drug interactions represent factors that have influenced the occurrence of ADEs [39].

In our study, the classes of drugs most frequently involved in FADEs were anticoagulants and antiplatelet agents. This explains why haemorrhages, especially cerebral, were the reactions most frequently observed in FADEs. The meta-analysis on FADEs did not describe the drug most frequently involved, and only few of the included studies examined the frequency of anticoagulants in FADEs [11]. In recent years, anticoagulant therapy has been increasingly prescribed (especially DOACs) due to safety data from Randomized Clinical Trials (RCTs) [40]. Nevertheless, the effectiveness of anticoagulants, particularly of DOACs, needs the appropriateness of the prescription, with frequent controls of blood count and renal function, giving adequate information to patients whom anticoagulants are prescribed. Since 2017, in Italy, the prescription of DOACs is higher than VKAs, and in 2018 accounted for 2/3 of the total prescriptions of oral anticoagulants [38]. In Italian EDs, cerebral haemorrhages represented more than 20% of FADEs, confirming data described by Pedros and colleagues [11], followed by gastrointestinal haemorrhages, lactic acidosis and systemic pathologies. On the contrary, in our data, the number of cases with renal failure was low.

Finally, our study showed that the number of potentially preventable cases is high and represents about a quarter of fatal cases. As the majority of FADEs are associated with anticoagulants, antiplatelet agents and metformin, the need for a more appropriate prescription and adequate patient information is mandatory for these drugs [41].

Limitations and strengths

Our study presents some limitations. First, the study includes all cases of FADEs managed at the ED. However, patients that died at home or while being transported to the hospital were not included. Moreover, the retrospective nature of the study may have induced an underestimation of FADEs if the clinicians did not recognize the causal association between the suspected drug and the fatality. Third, although this is an active pharmacovigilance study, we cannot exclude a quote of underreporting. Nevertheless, this issue affects FADEs reporting to a minimal extent. Similarly, data on the number and type of drugs taken by patients might have been influenced by monitors' accuracy and quality of reporting. Finally, we cannot exclude an underestimation of the percentage of preventable events, lower than that of other studies [7], in which medical records were available, due to possible lacking of data in the ADEs report forms [42], which are usually less complete. The number of concomitant medications could be underestimated too, as the doctor's availability and the patient's condition do not always allow clinicians to collect an accurate pharmacological history in the emergency department.

Despite these limitations, our study has several strengths. The cases described in our study come from 94 EDs, located in cities or in the countryside of 5 regions, from North to South of Italy. Therefore, the sample reproduces, with good approximation, the national distribution of FADEs, and its results are quite generalizable. The high number of ADE reports collected during the study period (over 55,000) increases the reliability of these results.

Conclusion

After 50 years of pharmacovigilance, FADEs continue to be an important problem of public health and the rate of preventability remains relatively high.

Anticoagulants, antiplatelet agents and hypoglycaemic drugs are associated with more than half of the FADEs and hemorrhagic events, especially cerebral haemorrhage, are the most frequently reported adverse events. Our evidence could help both healthcare professionals and patients to improve their awareness of drug use, especially those associated to fatal events.

Acknowledgements Members of the MEREAFaPS Study group who provided patient data for this study: Maria Luisa Aiezza (Naples), Alessandra Bettiol (Florence), Daria Bettoni (Brescia), Corrado Blandizzi (Pisa), Roberto Bonaiuti (Florence), Valentina Borsi (Florence), Annalisa Capuano (Naples), Errica Cecchi (Prato), Irma Convertino (Pisa), Giada Crescioli (Florence), Martina Del Lungo (Florence), Cristina Di Mauro (Naples), Gabriella Farina (Milan), Sara Ferraro (Pisa), Annamaria Fucile (Naples), Elena Galfrascoli (Milan), Elisabetta Geninatti (Turin), Linda Giovannetti (Florence), Luca Leonardi (Pisa), Rosa Liccardo (Naples), Niccolò Lombardi (Florence), Anna Marra (Ferrara), Eleonora Marrazzo (Turin), Giovanna Monina (Gallarate), Alessandro Mugelli (Florence), Silvia Pagani (Vimercate), Maria Parrilli (Florence), Concetta Rafaniello (Naples), Francesco Rossi (Naples), Marco Rossi (Siena), Stefania Rostan (Naples), Marco Ruocco (Vimercate), Marita Sironi (Vimercate), Giulia Spada (Vimercate), Liberata Sportiello (Naples), Marco Tuccori (Pisa), Alfredo Vannacci (Florence), Mauro Venegoni (Vimercate), Giuditta Violetta Vighi (Vimercate), Giuseppe Danilo Vighi (Vimercate).

Author contributions Study design was contributed by P, L, C and V, with assistance from the rest of the authors. P took the lead in data analysis, assisted by A, L and C. Data interpretation was performed by P, L, C, V and V, with assistance from the other authors. The manuscript was written primarily by P, L, C and V, with assistance from the other authors, and revised by C, V and V. All authors approved the final version of the manuscript.

Funding Mereafaps Study was funded by a research grant from the AIFA (the Italian Medicines Agency), Rome, Italy, Fondi Regionali per la Farmacovigilanza. Giunta Regionale della Lombardia, Delibera n° 2112 del 11/07/2014. The funder of the study had no role in the collection, analysis and interpretation of data, nor in the writing of the report, nor in the decision to submit the article for publication.

Compliance with ethical standards

Conflicts of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval The MEREAFaPS Study was approved in 2006 by the local institutional ethics committee of the coordinating centre, Niguarda Ca' Granda Hospital, according to the legal requirements concerning observational studies [20].

Informed consent Due to the retrospective nature of the present study and data anonymization, patient's consent to participate was not required.

References

1. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of adverse drug reactions in hospitalized patients: a meta- analysis of prospective studies. J Am Med Assoc 279:1200–1205
2. Oscanoa TJ, Lizaraso F, Carvajal A (2017) Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol 73(6):759–770
3. Hamed R, Mefteh S, Jouini S, Saïdi K, Chtourou D, Maaref A et al (2017) Drug-adverse related events in emergency department : epidemiological, clinical profile and prognosis. Tunis Med 95(1):53–59
4. Wu T-Y, Jen M-H, Bottle A, Molokhia M, Aylin P, Bell D, et al. (2010) Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009. J R Soc Med [cited 2019 Nov 4] ;103(6):239–50. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20513902
5. Lombardi N, Crescioli G, Bettiol A, Marconi E, Vitiello A, Bonaiuti R, et al. (2018) Characterization of serious adverse drug reactions as cause of emergency department visit in children: a 5-years active pharmacovigilance study. BMC Pharmacol Toxicol [cited 2019 Nov 19]; 19(1):16. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29661234
6. Ahern F, Sahm LJ, Lynch D, McCarthy S (2014) Determining the frequency and preventability of adverse drug reaction-related admissions to an Irish university hospital: a cross-sectional study. Emerg Med J 31(1):24–29
7. Patel NS, Patel TK, Patel PB, Naik VN, Tripathi CB (2017) Hospitalizations due to preventable adverse reactions-a systematic review. Eur J Clin Pharmacol [cited 2019 Oct 28]; 73(4):385–98. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27913837
8. Pardo Cabello AJ, Del Pozo Gavilán E, Gómez Jiménez FJ, Mota Rodríguez C, Luna Del Castillo J de D, Puche Cañas E (2016). Drug-related mortality among inpatients: a retrospective observational study. Eur J Clin Pharmacol [cited 2019 Oct 28]; 72(6):731–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26896941
9. Wester K, Jönsson AK, Spigset O, Druid H, Hägg S (2008) Incidence of fatal adverse drug reactions: a population based study. Br J Clin Pharmacol 65(4):573–579
10. Mouton JP, Mehta U, Parrish AG, Wilson DPK, Stewart A, Njuguna CW, et al. (2015) Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. Br J Clin Pharmacol [cited 2019 Oct 28]; 80(4):818–26. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25475751
11. Pedrós C, Formiga F, Corbella X, Arnau JM (2016) Adverse drug reactions leading to urgent hospital admission in an elderly population: prevalence and main features. Eur J Clin Pharmacol 72(2):219–226
12. van der Hooft CS, Sturkenboom MCJM, van Grootheest K, Kingma HJ, Stricker BHC (2016). Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. Drug Saf [cited 2019 Oct 28]; 29(2):161–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16454543
13. Cabello AJP, Contreras LGG, Gamero MVM, Jiménez FJG, Cañas EP (2009) Prevalence of fatal adverse drug reactions in hospitalized patients. Int J Clin Pharmacol Ther 47(10):596–602
14. Girdwood RH (1974) Death after taking medicaments. Br Med J 1(5906):501–504
15. Böttiger LE, Furhoff AK, Holmberg L (1979) Fatal reactions to drugs. A 10-year material from the Swedish adverse drug reaction committee. Acta Med Scand [cited 2019 Oct 28]; 205(6):451–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/452938
16. Kromann-Andersen H, Andersen M, Andersen HO, Juul P (1991) Fatal adverse drug reactions reported in Denmark 1968–1988. Int J Risk Saf Med 2(6):305–319
17. Leone R, Sottosanti L, Luisa Iorio M, Santuccio C, Conforti A, Sabatini V et al (2008) Drug-related deaths: an analysis of the Italian spontaneous reporting database. Drug Saf 31(8):703–713
18. Patel TK, Patel PB (2018) Mortality among patients due to adverse drug reactions that lead to hospitalization: a meta-analysis. Eur J Clin Pharmacol 74:819–832
19. Lapatto-Reiniluoto O, Patinen L, Niemi M, Backman JT, Neuvonen PJ (2015) Drug-related inadvertent deaths in a university hospital: a declining trend. Basic Clin Pharmacol Toxicol 117:421–426
20. Perrone V, Conti V, Venegoni M, Scotto S, Degli Esposti L, Sangiorgi D, et al. (2015) Seriousness, preventability, and burden impact of reported adverse drug reactions in Lombardy emergency departments: a retrospective 2-year characterization. Clinicoecon Outcomes Res [cited 2019 Oct 28]; 6:505–14. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25506231
21. Lombardi N, Crescioli G, Bettiol A, Tuccori M, Bonaiuti R, Mugelli A, et al. Italian emergency department visits and hospitalisations for outpatients' adverse drug events: 12-year active pharmacovigilance surveillance (the MEREAFaPS Study). Front Pharmacol
22. Lombardi N, Bettiol A, Crescioli G, Ravaldi C, Bonaiuti R, Venegoni M, et al. Risk of hospitalisation associated with benzodiazepines and z-drugs in Italy: a nationwide multicentre study in emergency departments. Intern Emerg Med
23. BILANCIO DEMOGRAFICO NAZIONALE ANNO (2018) https://www.istat.it/it/files//2019/07/Statistica-report-Bilancio-demografico-2018.pdf. Last access 4.2.2020 [cited 2020 Jan 23]. Available from: https://www.istat.it/it/files//2019/07/Statistica-report-Bilancio-demografico-2018.pdf
24. Mazzitello C, Esposito S, De Francesco AE, Capuano A, Russo E, De Sarro G (2013) Pharmacovigilance in Italy: an overview. J Pharmacol Pharmacother [cited 2019 Nov 19]; 4 (Suppl 1):S20–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24347976
25. Lombardi N, Crescioli G, Bettiol A, Tuccori M, Rossi M, Bonaiuti R, et al. (2019) Vaccines safety in children and in general population: a pharmacovigilance study on adverse events following anti-infective vaccination in Italy. Front Pharmacol [cited 2019 Dec 3]; 10:948. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31543816
26. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30(2):239–245
27. Schumock GT, Thornton JP (1992) Focusing on the preventability of adverse drug reactions. Hospital Pharm 27:538

28. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
29. Rothman KJ, Lanes S, Sacks ST. (2004) The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf [cited 2020 Feb 24]; 13(8):519–23. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15317031
30. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS (2016) US emergency department visits for outpatient adverse drug events, 2013–2014. JAMA J Am Med Assoc 316:20
31. Bouvy JC, De Bruin ML, Koopmanschap MA (2015) Epidemiology of adverse drug reactions in europe: a review of recent observational studies drug safety. Springer Int Publ 38:437–453
32. Chan, M. Nicklason, F. Vial JH (2019). Adverse drug events as a cause of hospital admission in the elderly: PubMed: NCBI [cited 2019 Oct 29]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/?term=CHAN+M%2C+NICKLASON+F
33. Nguyen JK, Fouts MM, Kotabe SE, Lo E (2006) Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. Am J Geriatr Pharmacother 4(1):36–41
34. Onder G, Pedone C, Landi F, Cesari M, Della Vedova C, Bernabei R, et al. (2002) Adverse drug reactions as cause of hospital admissions: results from the Italian group of pharmacoepidemiology in the elderly (GIFA). J Am Geriatr Soc [cited 2020 Feb 25]; 50(12):1962–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12473007
35. Sikdar KC, Dowden J, Alaghehbandan R, MacDonald D, Peter P, Gadag V (2012) Adverse drug reactions in elderly hospitalized patients: a 12-year population-based retrospective cohort study. Ann Pharmacother 46(7–8):960–971
36. Obreli-Neto PR, Nobili A, De Oliveira Baldoni A, Guidoni CM, De Lyra DP, Pilger D, et al. (2012) Adverse drug reactions caused by drug-drug interactions in elderly outpatients: a prospective cohort study. Eur J Clin Pharmacol [cited 2020 Feb 25]; 68(12):1667–76. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22644345
37. Angamo MT, Chalmers L, Curtain CM, Yilma D, Bereznicki L (2018) Mortality from adverse drug reaction-related hospitalizations in south-west Ethiopia: a cross-sectional study. J Clin Pharm Ther [cited 2020 Feb 25]; 43(6):790–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29722039
38. Kessler C, Ward MJ, McNaughton CD (2016) Reducing adverse drug events: the need to rethink outpatient prescribing. JAMA J Am Med Assoc 316:2092–2093
39. Spada G, Vighi G V., Pagani S, Vighi GD, Venegoni M, Ruocco M (2020) What are the characteristics of patients experiencing adverse drug reactions to oral anticogulants and how can such reactions be prevented? Curr Drug Saf [cited 2020 Feb 27]; 15(1):38–44. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31580253
40. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS (2016) US emergency department visits for outpatient adverse drug events, 2013–2014. JAMA J Am Med Assoc 316(20):2115–2125
41. Hedna K, Hakkarainen KM, Gyllensten H, Jönsson AK, Petzold M, Hägg S (2015) Potentially inappropriate prescribing and adverse drug reactions in the elderly: a population-based study. Eur J Clin Pharmacol [cited 2019 Nov 5]; 71(12):1525–33. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26407684
42. Liu BA, Knowles SR, Mittmann N, Einarson T, Shear NH (2001) Reporting of fatal adverse drug reactions. Can J Clin Pharmacol [cited 2019 Oct 29]; 8(2):84–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11493936