All-cause mortality and antipsychotic use among elderly persons with high baseline cardiovascular and cerebrovascular risk: a multi-center

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
https://doi.org/10.1080/17425255.2019.1561860

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ORIGINAL RESEARCH

All-cause mortality and antipsychotic use among elderly persons with high baseline cardiovascular and cerebrovascular risk: a multi-center retrospective cohort study in Italy

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ABSTRACT

Background: Little is known about the comparative risk of death with atypical or conventional antipsychotics (APs) among persons with cardiovascular or cerebrovascular disease (CCD).

Research design and methods: A cohort study was conducted using five Italian claims databases. New atypical AP users with CCD aged ≥65 (reference) were matched to new conventional AP users. Mortality per 100 person-years (PYs) and hazard ratios (HR), estimated using Cox models, were reported. Incidence and risk of death were estimated for persons having drug–drug interactions. Outcome occurrence was evaluated 180 days after AP initiation.

Results: Overall 24,711 and 27,051 elderly new conventional and atypical AP users were identified. The mortality rate was 51.3 and 38.5 deaths per 100 PYs for conventional and atypical AP users. Mortality risk was 1.33 (95%CI: 1.27–1.39) for conventional APs. There was no increased mortality risk with single drug–drug interactions (DDIs) vs. no DDI. AP users with ≥1 DDI had a 29% higher mortality risk compared to no DDI in the first 90 days of treatment (HR: 1.29 (95% CI: 1.00–1.67)).

Conclusions: Conventional APs had a higher risk of death than atypical APs among elderly persons with CCD. Having ≥1 DDI was associated with an increased risk of death.

ARTICLE HISTORY
Received 9 October 2018
Accepted 17 December 2018

KEYWORDS
Antipsychotics; elderly; mortality; cohort study; drug interactions

1. Introduction

Antipsychotic drugs (APs) are a large group of central nervous system drugs with indications related to psychotic symptoms. They can be broadly divided into two classes, conventional and atypical drugs. Conventional drugs were marketed before atypical drugs and are known for their marked extrapyramidal symptoms [1]. Atypical drugs are less likely to cause extrapyramidal symptoms compared with the older agents but may cause sedation, weight gain and changes in metabolism [2].

APs of both classes are commonly prescribed among elderly persons for several reasons. Elderly persons with cognitive impairment or dementia may engage in challenging or difficult behavior such as agitation, aggression or wandering. As a result, they may be prescribed APs, although their efficacy is limited [3]. APs may also be prescribed for their sedating effects in such situations [4]. Another scenario in which APs may be prescribed includes delirium, which in the elderly may be a symptom of pneumonia [5] or other conditions. Although information on the exact indication of antipsychotic use among elderly persons in Italy is scarce, it has been shown that these drugs are widely used, especially among dementia patients [6]. In Europe, antipsychotic use in patients with dementia is often off-label, as only risperidone is indicated for the short-term (<6 weeks) management of aggression in such population. Several observational studies have reported an increased risk of all-cause mortality associated with antipsychotic use [7–9]. The risk of all-cause mortality among elderly persons appears to be high for both conventional and atypical APs [7,10–12].

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There is currently a paucity of evidence on the safety of antipsychotics among persons with the pre-existing cardiovascular or cerebrovascular disease, although these diseases are frequent comorbidities in the elderly population and among the top 10 causes of death worldwide [13]. The benefit–risk ratio of antipsychotic use among elderly persons with a known cerebrovascular or cardiovascular disease is very likely to lean towards a greater risk than benefit. However, it is important to investigate the antipsychotic safety in this population because it is likely that antipsychotics are nevertheless used among these patients. To our knowledge, there is no recent study on the risk of all-cause mortality among elderly antipsychotic users in Italy, although a small number of observational studies conducted a decade or more ago evaluated the risk of all-cause mortality with these drugs among elderly persons with dementia [11,14,15]. However, these studies are limited by confounding by indication, as the safety of antipsychotic use is compared to non-exposure to antipsychotics. Any effects of antipsychotics on safety are therefore likely to be driven by the underlying indication (severity of non-cognitive symptoms of dementia present among antipsychotic users, which is likely to be absent among non-users who may have less severe symptoms) [16]. This, in addition to the high prevalence of antipsychotic use among elderly persons in Italy compared to other countries [6], highlights the pressing need to evaluate antipsychotic drug safety in persons with a history of cerebrovascular and cardiovascular morbidity.

Another potentially important issue among antipsychotic users with a high baseline risk of mortality concerns the presence of drug–drug interactions (DDIs), i.e., interactions between antipsychotics and other drugs, and whether they alter the risks associated with antipsychotic use. A nationwide study carried out in Italy in 2011 showed that polypharmacy was very common since 1.3 million persons (11.3% of the persons included in the study) were taking 10 or more drugs [17]. Although there are not many studies describing drug interactions among elderly community-dwelling persons in Italy, a study conducted within a catchment area in Lombardy reported that 16% of the catchment area population had a DDI [18]. Two other Italian observational studies confirmed that elderly persons were more likely to have a DDI than younger persons [19,20]. None of these studies focused on antipsychotic DDIs in the elderly, however. To our knowledge, there are no studies investigating how antipsychotic DDIs may alter the risk of all-cause mortality among antipsychotic users in Italy.

The aim of the present study was therefore to investigate the comparative risk of all-cause mortality associated with atypical vs. conventional antipsychotic use in a high-risk elderly population and to explore the effect of antipsychotic DDIs on mortality in this population.

2. Patients and methods

2.1. Data source

The claims databases of Lombardy, Tuscany and Lazio regions and the Local Health Units (LHU) of Caserta and Treviso in Italy were used to conduct this study. The present study was conducted as part of the I-GrADE project on drug use and safety among Italian elderly persons, funded by the Italian Drug Agency (AIFA) [21–27]. Each database contains a demographic registry, an out-patient pharmacy claims database, a hospital discharge diagnosis database and a database containing medical procedures performed among hospital in-patients. Data from different databases can be linked at a patient level using an encrypted patient identifier. Drug information in the pharmacy claims is recorded using the Anatomical and Therapeutic Chemical (ATC) codes as well as the Italian marketing authorization code, while hospital discharge diagnoses and procedures are registered using the ninth edition of the International Classification of Diseases, with Clinical Modification (ICD-9 CM).

2.2. Cohort definition and study design

Data for the present retrospective cohort study were extracted from 2008 to 2010 in Lazio region, from 2002 to 2011 in Lombardy region, from 2005 to 2011 in Tuscany region, from 2008 to 2011 in Caserta LHU and from 2008 to 2013 in Treviso LHU. All elderly patients (≥65 years) initiating an antipsychotic therapy after a hospital discharge for a cerebrovascular or cardiovascular event (i.e. arrhythmia, heart failure, ischemic heart disease, and stroke), were identified (see Table A1 for details). The first hospitalization for a cerebrovascular or cardiovascular event during the study period was defined as the index hospitalization. Cohort entry was defined as the first antipsychotic dispensing, identified from the pharmacy claims, following the index hospitalization. A new-user design was implemented, whereby patients with less than six months of database history before cohort entry, as well as those patients receiving an antipsychotic dispensing within six months before cohort entry, were excluded. Patients with a history of cancer any time prior to cohort entry were also excluded.

2.3. Exposure

Patients were categorized into two mutually exclusive exposure groups based on the antipsychotic drug received at cohort entry as atypical or conventional antipsychotic users (see Table A2 for a list of antipsychotics and classification). Patients receiving more than one antipsychotic at cohort entry were excluded.

New antipsychotic users exposed to drugs potentially interacting with antipsychotics in the 90 days prior to cohort entry were considered to be exposed to a DDI. Drugs interacting with APs were identified and grouped by type of adverse drug reaction, based on their pharmacological mechanism of action [28]. Interactions were classified according to the risk of adverse drug reaction (ADR) potentially resulting from the concomitant exposure to antipsychotic and other interacting drugs: QT interval prolongation, neutropenia, sedation, anticholinergic effects, hypotension or falls, seizures, and metabolic effects (Table A3). This approach was used to categorize DDIs for the following reasons: 1) it is easier to interpret the frequency of DDIs in a clinically meaningful way when they are grouped by specific ADR rather than listing the frequency of DDIs for single drugs or drug classes with no information on why may be harmful; 2) grouping DDIs by specific ADR risk lends a greater coherence to analysis of their impact on the

risk of death, as patients are clustered by exposure to DDIs with a similar type of risk. This method has been used previously to study the frequency and safety of AP-related DDIs in elderly populations although the impact of the single DDI groups on mortality could not be investigated as the number of exposed persons was too low [29].

2.4. Covariates

Demographic information including age and sex were identified for each patient any time prior to cohort entry using hospital admission claims and disease-specific pharmacy claims. The following comorbidities were identified: anxiety, bipolar disease, delirium, dementia, depression, non-schizophrenia psychosis, schizophrenia, cerebrovascular and cardiovascular diseases such as hypertension, ischemic heart disease, stroke, arrhythmia, congestive heart failure, cardiac valve disorders, venous thrombo-embolism, peripheral arterial disease, and other conditions including diabetes mellitus, epilepsy, hip fracture, chronic obstructive pulmonary disease (COPD), osteoporosis, Parkinson's disease and pneumonia.

With regards to concomitant drug use, pharmacy claims for the following drugs were identified: digoxin, non-steroidal anti-inflammatory drugs (NSAIDs), drugs for peptic ulcers, low-dose aspirin, antithrombotic drugs, antibacterial drugs, organic nitrates, anti-hypertensives, antidyslipidemic drugs corticosteroids, and the number of individual active compounds. Concomitant drugs were identified from the drug dispensing registry within three months prior to cohort entry.

2.5. Outcome

The outcome of the study was all-cause mortality within 180 days of antipsychotic initiation. Date of death is recorded for all persons in Italian claims databases and is reliable as recording this information is mandatory by law. Cause of death is however not reported.

2.6. Statistical analysis

Baseline patient characteristics were described at cohort entry in terms of demographics, comorbidities, and concomitant drug use. All baseline covariates were used to estimate the conditional probability of being treated with conventional versus atypical antipsychotics, thus creating a propensity score (PS), using a multivariate logistic regression model. Each conventional antipsychotic user was then PS-matched to one atypical antipsychotic user, using a nearest neighbor matching algorithm with a caliper equal to 0.2 times the logit of the standard deviation of the PS [30]. Imbalances between the two study groups were assessed through standardized mean differences for binary and continuous covariates. Equipoise was considered to be reached when the between-group comparison of covariates had a mean standardized difference of <0.1 [31].

An intention-to-treat approach was used whereby patients were followed for a maximum of 180 days until the end of the study period, disenrollment from the database, death or 180 days of accumulated follow-up, whichever came first. This approach has the advantage of limiting immeasurable time bias [32]. The 180-day window has been used previously to investigate the mortality associated with antipsychotics, with the rationale that the average duration of clinical trials identifying the risk of death in elderly antipsychotic users was 180 days [7]. This period is therefore held to be sufficient for the outcome to occur. A Kaplan-Maier curve was plotted to describe the 180 days cumulative survival probability in users of conventional compared to atypical antipsychotics.

The mortality rate per 100 person-years (PYs) was calculated to provide an absolute measure of risk. Crude and adjusted hazard ratios (HR) of mortality in users of atypical compared to conventional antipsychotics, along with 95% confidence intervals, were calculated using Cox proportional hazards models. Analyses were then stratified by sex, age groups, the presence of dementia, and cardiovascular disease or cerebrovascular disease, all of which were evaluated at cohort entry. A sensitivity analysis was carried out by restricting follow-up duration to 90 days and extending it to 365 days. To explore the robustness of our findings, a rule-out sensitivity analysis was performed. This analysis, also known as target-adjustment sensitivity analysis, estimates the magnitude of confounding required to entirely account for study findings and has been described in greater detail elsewhere [33].

The frequency of drug–drug interactions was reported by ADR type group. All-cause mortality per 100 PYs and the risk of death in unmatched users of antipsychotics exposed to DDIs was assessed at 180 days after cohort entry. The absence of interactions was considered as the reference category. To avoid exposure misclassification due to our inability of capturing drug use during hospitalizations, those patients entering the cohort after less than 90 days after the index hospitalization discharge date were excluded from the analysis. HRs of all-cause mortality were then estimated using Cox proportional hazards models. Analyses were adjusted for all covariates evaluated at baseline. A sensitivity analysis was carried out, restricting the calculation of relative and absolute risk of death with DDIs occurring to the 90 days following the cohort entry.

3. Results

Overall, 1,365,679 elderly patients with a hospital discharge for cerebrovascular or cardiovascular disease were identified in the study period, of whom 86,976 (6.4%) had a pharmacy claim for an antipsychotic after hospital discharge (Figure 1). After applying inclusion and exclusion criteria, 75,399 (86.7% of all antipsychotic users) new antipsychotic users were included in the final study cohort. Of these, 24,711 (47.7%) and 27,051 (52.3%) patients were treated with conventional and atypical antipsychotics, respectively (Table 1). The most frequently used conventional antipsychotics were haloperidol, chlorpromazine, and periciazine (64.2%, 17.0% and 4.3% of conventional antipsychotic users, respectively), while the most frequently used atypical antipsychotics were quetiapine, clotiapine and risperidone (52.5%, 16.9% and 11.5% of atypical antipsychotic users, respectively). Almost a third of unmatched atypical antipsychotic users had dementia (n = 8,010; 29.6%),

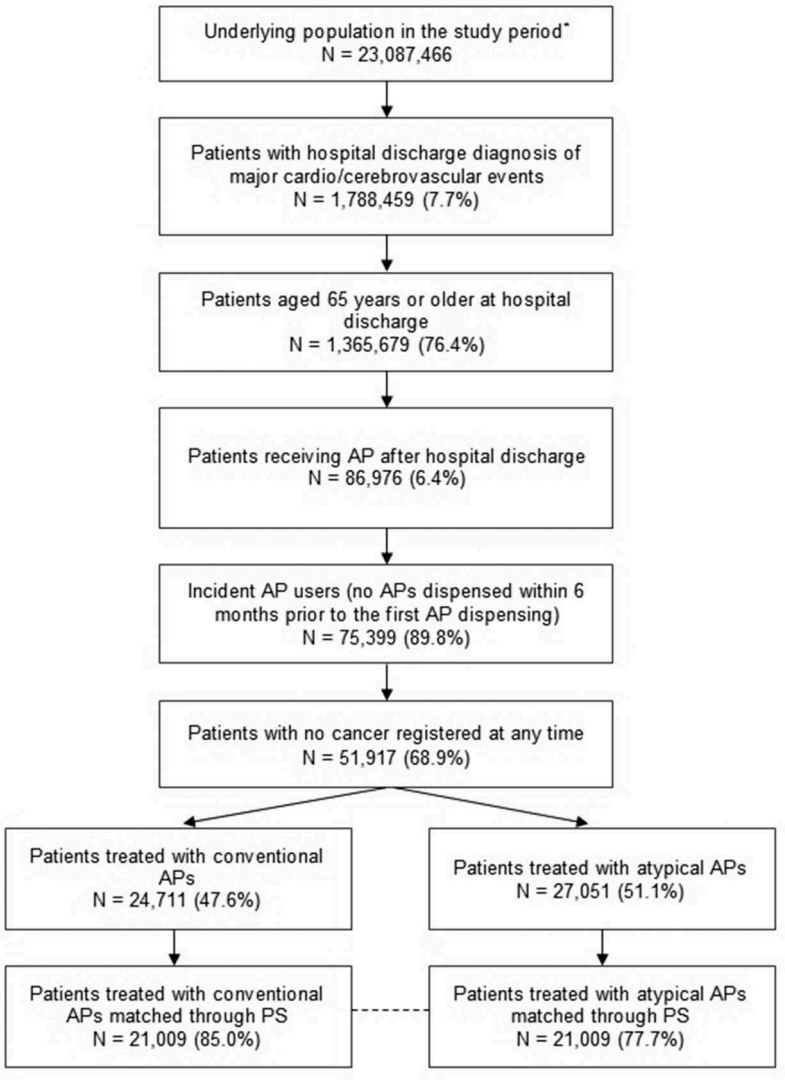

Figure 1. Flowchart showing how the study cohort was identified.

*Lazio region: 2008–2010; Lombardy region: 2002–2011; Tuscany region 2005–2011; Caserta Local Health Unit: 2008–2011; Treviso Local Health Unit: 2008–2013. APs: antipsychotics; PS: propensity score.

while fewer conventional antipsychotic users had dementia (n = 4,723; 19.1%).

The mean age of conventional and atypical antipsychotic users was approximately 82 years, with a higher proportion of females (60%) than males in both groups. Before PS-matching, users of atypical antipsychotics had a higher burden of psychiatric conditions such as bipolar disease, delirium, dementia, depression, non-schizophrenic psychosis, and Parkinson's disease, compared to conventional antipsychotic users. Conversely, users of conventional antipsychotics had a higher burden of cardio- and cerebrovascular diseases such as congestive heart failure, ischemic heart disease, and valve disorders. After PS-matching, users of atypical and conventional antipsychotics were comparable in terms of all measured covariates (Table 1). The PS distribution in the cohort before and after matching is shown in Figure A1.

The 180-day survival curve in PS-matched patients (Figure 2) showed a statistically significant higher mortality rate among users of conventional antipsychotics compared to atypical antipsychotics (p-value from log-rank test < 0.001). The Cox regression analysis showed a statistically significant 33% increased risk of death among conventional antipsychotic users compared to atypical antipsychotic users at 180 days (HR: 1.33 (95%CI: 1.27–1.39); the mortality rate was also higher among conventional antipsychotic users (51.3 deaths per 100 PYs) as compared to atypical antipsychotic users (38.5 deaths per 100 PYs) (Table 2). The mortality rate increased over time with increasing age (from 16.8 to 24.4 deaths per 100 PYs in atypical antipsychotics and conventional antipsychotics, respectively, aged 65–75 years, to 61.1 and 73.9 deaths per 100 PYs in atypical antipsychotics and conventional APs, respectively, aged over 85 years). The relative risk of death, however, decreased with age (HR: 1.44 (95%CI: 1.23–1.68) among persons aged 65–75 and (HR: 1.20 (95%CI: 1.13–1.28)) among those aged 85 and over). Stratified analyses showed the risk of all-cause mortality in users of atypical versus conventional antipsychotics to be similar in patients with and without dementia. Stratification of analyses by cardiovascular rather

Table 1. Patient characteristics at cohort entry before and after propensity score matching.

	Before matching			After matching		
	Atypical APs N = 27,051 (%)	Conventional APs N = 24,711 (%)	SMD	Atypical APs N = 21,009 (%)	Conventional APs N = 21,009 (%)	SMD
Mean age ± SD	81.8 ± 7.1	83.6 ± 7.3	0.026	82.5 ± 7.1	82.9 ± 7.2	0.006
Males	11,095 (41.0)	9,585 (38.8)	0.032	8,444 (40.2)	8,319 (39.6)	0.009
Psychiatric or mental health conditions*						
Anxiety	741 (2.7)	506 (2.0)	0.032	506 (2.4)	481 (2.3)	0.006
Bipolar disease	2,821 (10.4)	2,046 (8.3)	0.052	2016 (9.6)	1,873 (8.9)	0.017
Delirium	1,858 (6.9)	1,155 (4.7)	0.067	1,218 (5.8)	1,107 (5.3)	0.016
Dementia	8,010 (29.6)	4,723 (19.1)	0.174	5,040 (24.0)	4,563 (21.7)	0.038
Depression	17,172 (63.5)	14,785 (59.8)	0.053	13,063 (62.2)	12,773 (60.8)	0.020
Non-schizophrenic psychosis	1,828 (6.8)	999 (4.0)	0.085	1,098 (5.2)	966 (4.6)	0.021
Schizophrenia	518 (1.9)	330 (1.3)	0.032	368 (1.8)	308 (1.5)	0.016
Cardio/cerebrovascular disease*						
Arrhythmia	11,413 (42.2)	11,120 (45.0)	0.040	9,059 (43.1)	9,274 (44.1)	0.015
Congestive heart failure	7,449 (27.5)	8,506 (34.4)	0.106	6,321 (30.1)	6,664 (31.7)	0.025
Ischemic heart disease	9,927 (36.7)	10,194 (41.3)	0.066	8,062 (38.4)	8,320 (39.6)	0.018
Stroke	9,374 (34.7)	8,448 (34.2)	0.007	7,298 (34.7)	7,246 (34.5)	0.004
Diabetes	7,475 (27.6)	7,426 (30.1)	0.038	6,093 (29.0)	6,178 (29.4)	0.006
Hypertension	25,239 (93.3)	23,465 (95.0)	0.050	19,775 (94.1)	19,842 (94.4)	0.010
Peripheral arterial disease	1,797 (6.6)	1,986 (8.0)	0.038	1,514 (7.2)	1,560 (7.4)	0.006
Valve disorders	1,862 (6.9)	2,010 (8.1)	0.034	1,525 (7.3)	1,610 (7.7)	0.011
Venous thrombosis embolism	224 (0.8)	279 (1.1)	0.022	204 (1.0)	207 (1.0)	0.001
Other conditions*						
COPD	4,243 (15.7)	4,671 (18.9)	0.060	3,581 (17.0)	3,708 (17.6)	0.011
Osteoporosis	1,143 (4.2)	1,126 (4.6)	0.011	925 (4.4)	904 (4.3)	0.003
Parkinson's disease	3,250 (12.0)	2,136 (8.6)	0.078	2,205 (10.5)	1,999 (9.5)	0.023
Epilepsy	828 (3.1)	701 (2.8)	0.009	621 (3.0)	622 (3.0)	0.000
Hip fracture	2,630 (9.7)	3,014 (12.2)	0.056	2,251 (10.7)	2,311 (11.0)	0.006
Pneumonia	943 (3.5)	842 (3.4)	0.003	749 (3.6)	704 (3.4)	0.008
Concomitant drugs^						
Digoxin	2,939 (10.9)	3,486 (14.1)	0.069	2,503 (11.9)	2,696 (12.8)	0.020
NSAIDs	2,445 (9.0)	3,043 (12.3)	0.075	2,103 (10.0)	2,289 (10.9)	0.020
Low dosage aspirin	8,080 (29.9)	8,440 (34.2)	0.065	6,802 (32.4)	6,784 (32.3)	0.001
Antibacterials	7,848 (29.0)	8,881 (35.9)	0.105	6,626 (31.5)	6,848 (32.6)	0.016
Anti-thrombotics	13,037 (48.2)	13,283 (53.8)	0.079	10,912 (51.9)	10,804 (51.4)	0.007
Drugs for peptic ulcers	9,478 (35.0)	10,945 (44.3)	0.134	8,404 (40.0)	8,439 (40.2)	0.002
Organic nitrates	6,048 (22.4)	6,122 (24.8)	0.040	4,889 (23.3)	5,077 (24.2)	0.015
Corticosteroids	1,438 (5.3)	2,518 (10.2)	0.129	1,359 (6.5)	1,534 (7.3)	0.023
Antihypertensives	19,402 (71.7)	18,562 (75.1)	0.054	15,390 (73.3)	15,543 (74.0)	0.012
Anti-dyslipidemic drugs	5,255 (19.4)	4,415 (17.9)	0.028	4,044 (19.2)	3,955 (18.8)	0.008
Mean N. concomitant drugs ± SD	5.1 ± 3.6	6.0 ± 3.9	0.224	5.5 ± 3.7	5.6 ± 3.6	0.031

*comorbidities were evaluated at any time prior to cohort entry; ^concomitant drugs were evaluated within 3 months prior to cohort entry. APs: antipsychotics; COPD: chronic obstructive pulmonary disease; SD: standard deviation; SMD: standardized mean differences; NSAIDs: Non-steroidal anti-inflammatory drugs.

than cerebrovascular diseases confirms results from the main analysis, suggested a high risk of death for conventional antipsychotic users compared to atypical antipsychotics. The mortality rate was very similar among these two groups. Sensitivity analyses at 90 and 365 days showed that the increased risk of death in users of atypical antipsychotics remained consistent, with the risk decreasing slightly on expanding the time window from an HR of 1.42 (95%CI: 1.34–1.50) at 3 months to an HR of 1.25 (95%CI: 1.21–1.30) at 365 days (Table A4). A rule-out sensitivity analysis showed that in order to move the observed HR to the null, a potential residual confounding should be associated with a three-fold increased odds of exposure to atypical versus conventional antipsychotic, and with at least 3 or 5 fold increased risk of death, assuming the hypothesized confounder to have a prevalence of, respectively, 50% and 10% in the study cohort (Figure 3).

Analyses on DDIs showed that interactions causing sedation and QT prolongations were the most frequent interactions with APs, occurring in 3,083 (7.4%) and 2,564 (6.2%) patients, respectively (Table 3). A total of 482 (1.2%) of antipsychotic users had more than one interaction during the observation period, although most of antipsychotic users (n = 34,988; 84.0%) had no antipsychotic–related interaction. Adjusted HRs did not suggest any increased risk of all-cause mortality in patients exposed to single DDIs at 180 days. However, sensitivity analyses restricted to 3 months showed that patients exposed to more than one interacting drug class had a 29% higher risk of death compared to persons not exposed to any antipsychotic DDIs (adjusted HR: 1.29, 95%CI 1.00–1.67) (Table A5).

4. Discussion

Antipsychotics were not commonly prescribed to elderly persons with the cardio- or cerebrovascular disease after being hospitalized, as only 6.4% had a pharmacy claim for antipsychotics. The main finding from this study is that conventional antipsychotic use in elderly persons with a history of cardiovascular or cerebrovascular events is associated with a 33% increased risk of all-cause mortality during the first 180 days of treatment when compared with atypical antipsychotics. Several other studies suggest increased all-cause mortality associated with conventional antipsychotics [9–12] compared

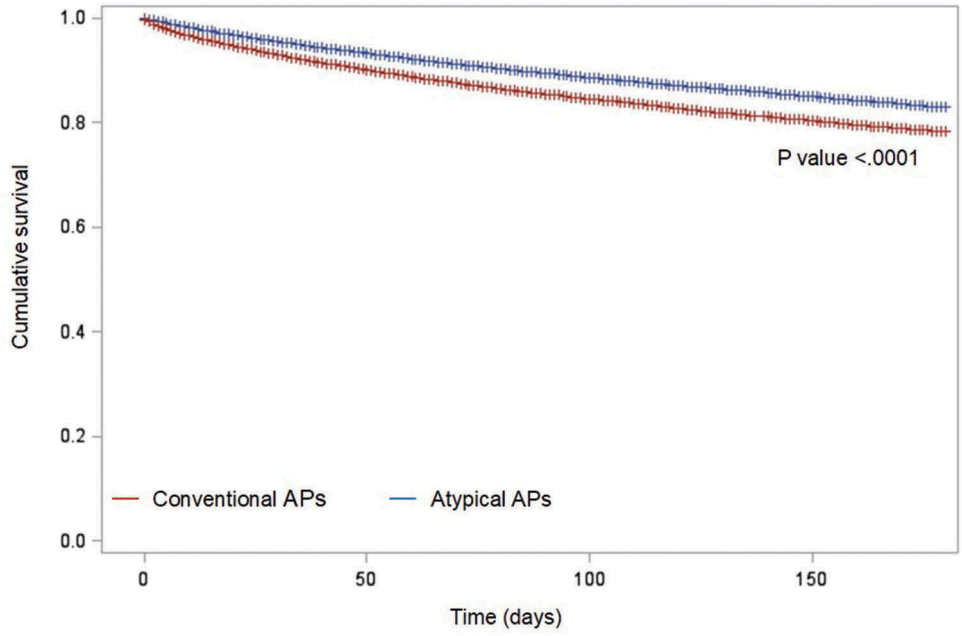

Figure 2. Time to event (all-cause mortality) in users of conventional versus atypical antipsychotics.
The blue line refers to atypical antipsychotic use and the red line refers to conventional antipsychotic use. APs: antipsychotics.

Table 2. Hazard ratios of all-cause mortality in users of conventional compared to atypical antipsychotics overall and stratified by sex, age classes, the presence of dementia and the presence of cardiovascular and cerebrovascular diseases.

Subgroups	Antipsychotic class	Patients	PYs	Deaths	Incidence per 100 PYs	HR (95%CI)
All patients	Atypical	21,009	3,303,957	3,482	38.5	1.00 (Reference)
	Conventional	21,009	3,172,993	4,454	51.3	1.33 (1.27–1.39)
Sex						
Males	Atypical	8,444	1,307,420	1,579	44.1	1.00 (Reference)
	Conventional	8,319	1,226,492	2,017	60.1	1.35 (1.27–1.44)
Females	Atypical	12,565	1,996,537	1,903	34.8	1.00 (Reference)
	Conventional	12,690	1,946,501	2,437	45.7	1.31 (1.23–1.39)
Age classes						
65–75	Atypical	3,653	615,240	283	16.8	1.00 (Reference)
	Conventional	3,518	574,577	381	24.2	1.44 (1.23–1.68)
76–85	Atypical	9,912	1,595,757	1,372	31.4	1.00 (Reference)
	Conventional	9,441	1,458,421	1,767	44.3	1.40 (1.31–1.51)
>85	Atypical	7,444	1,092,960	1,827	61.1	1.00 (Reference)
	Conventional	8,050	1,139,995	2,306	73.9	1.20 (1.13–1.28)
Dementia						
Yes	Atypical	5,040	794,936	845	38.8	1.00 (Reference)
	Conventional	4,563	692,043	1,022	53.9	1.38 (1.26–1.52)
No	Atypical	15,969	2,509,021	2,637	38.4	1.00 (Reference)
	Conventional	16,446	2,480,950	3,432	50.5	1.31 (1.25–1.38)
Cardio-cerebrovascular disease						
Cardiovascular*	Atypical	14,792	2,290,391	2,705	43.1	1.00 (Reference)
	Conventional	15,177	2,252,334	3,520	57.1	1.32 (1.25–1.38)
Cerebrovascular**	Atypical	13,491	2,129,309	2,192	37.6	1.00 (Reference)
	Conventional	13,434	2,048,562	2,722	48.5	1.29 (1.22–1.36)

*Cardiovascular disease includes: arrhythmia, heart failure and ischemic heart disease; **Cerebrovascular disease refers to stroke. CI: confidence intervals; HR: hazard ratio; PYs: person-years.

to atypical antipsychotics in elderly persons in general and in patients with dementia specifically. The risk of all-cause death associated with atypical antipsychotics only emerges in comparison with non-exposure to antipsychotics [11,12,34]. However, the latter comparison suffers from confounding by indication, since persons prescribed antipsychotics for dementia are likely to have poorer overall health, potentially due to more severe dementia symptoms, than their non-exposed counterparts, and therefore a lower baseline life expectancy. Dementia was the most commonly recorded diagnosis that may potentially be an indication for antipsychotic use. Nevertheless, dementia may be under-reported in Italian claims data as it is a chronic rather than the acute condition. The high mortality rate observed for users of both antipsychotic classes is attributable to the high baseline risk of death in the study population, as this is made up of patients who were hospitalized for cardiovascular or cerebrovascular events and were then treated with antipsychotics. The risk of death

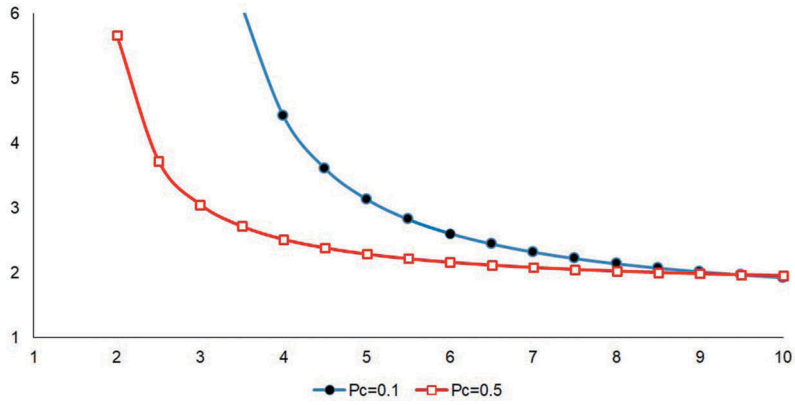

Figure 3. Rule-out sensitivity analysis.

The red line refers to a confounder prevalence of 50% and the blue line refers to a confounder prevalence of 10% in the study cohort.

Table 3. Hazard ratios of all-cause mortality in the first 180 days of follow-up in patients exposed to drugs potentially interacting with antipsychotics as grouped by ADR type group.

Effect	Patients N = 41,763 (%)	PYs	Deaths	Incidence rate per 100 PYs	Crude HR	Adjusted* HR (95% CI)
No interaction	34,988 (84.0)	14,806	6,145	41.5	1.00	1.00 (Reference)
Sedation	3,083 (7.4)	1,301	512	39.3	0.95	1.10 (1.00–1.22)
QT prolongation	2,564 (6.2)	1,021	631	61.8	1.48	1.04 (0.95–1.13)
Others	486 (1.2)	206	83	40.3	0.93	1.01 (0.76–1.35)
More than one	482 (1.2)	202	91	45.0	1.09	1.23 (0.99–1.53)

Abbreviations: CI: confidence intervals; HR: hazard ratios; PYs: person-years. **Note**: Classes of interactions with less than 5% of users were included in a separate category.

reported in the present study must, therefore, be interpreted in light of the population characteristics, and as such, is unlikely to not be generalizable to other, healthier populations. The present study also found that the risk of death with conventional antipsychotics compared to atypical ones decreased with increasing age. Our interpretation of this finding is that conventional antipsychotic may be prescribed more cautiously among older adults, thus leading to a lower risk of death.

Another interesting finding of this study concerns the low proportion of persons found to have antipsychotic-related drug interactions. Although antipsychotic users were concomitantly prescribed on average six drugs, over 80% of patients were not exposed to any drug potentially interacting with antipsychotics. Indeed, although a recent review reported that the prevalence of drug interactions among elderly persons in a primary care setting ranges from 25% to 100%, antipsychotics were not reported to be common sources of interactions [35]. The most common antipsychotic drug interaction pairs were those associated with sedation and QT prolongation, which were present in roughly 7% and 6% of the cohort, respectively. A multi-center retrospective study in cognitively impaired nursing home patients using similar DDI groupings also found that antipsychotic-related DDIs leading to QT interval prolongation and sedation were common, but reported that DDIs leading to hypotension and falls were the most common causes accounting for a third of all DDI groups in a cohort of 604 patients [29]. In the present study, DDIs related to fall and hypotension were identified in only 268 patients (0.6%). The difference between the two studies may be attributable to the difference in the study setting. The main analysis in the present paper concerning the risk of death associated with DDIs within 180 days of antipsychotic initiation in the present study is in line with the main analysis by Liperoti et al., who also did not find a strong association between more than one interaction and mortality. In the present study, the risk of death with more than one DDI emerged when restricting the analysis to 90 days of antipsychotic initiation, suggesting a 29% increased risk of death, although the risk estimate was borderline significant (HR: 1.29 (95% CI: 1.00–1.67)). It is likely that among persons prescribed antipsychotics with multimorbidity, the effect of antipsychotic drug interactions is overshadowed by the effect of other potential risk factors, such as increasing frailty due to disease burden. Indeed, a similar effect was seen for increasing age, where the relative risk of death with antipsychotic use decreased with increasing age. This is likely due to the comparatively smaller role of antipsychotic risk compared to other factors, such as multimorbidity and frailty. Several antipsychotics already have a baseline risk of both sedation and QT prolongation, as has been reported by several observational studies [36]. Antipsychotic-induced sedation has been implicated as a risk factor for other antipsychotic-related effects such as aspiration pneumonia [37] and falls, although the evidence for the latter is less consolidated [38]. Compared to not having a drug interaction, the individual interactions did not appear to increase the risk of mortality.

As mentioned above, antipsychotic drugs can be used for several reasons in the elderly, such as old-age schizophrenia, mood disorders, and non-cognitive symptoms of dementia [39] as well as potentially mistakenly prescribed for

pneumonia-induced delirium [5]. In Europe, the prescription rate of antipsychotics, in particular, was quite high in the elderly compared to younger persons and increased with age [40]. Although antipsychotics are widely prescribed among elderly persons in Italy, in the European comparison by Oteri et al., antipsychotics were more commonly prescribed to elderly persons in Germany and the Netherlands, with Italy being the country with the third highest use [40].

The potential over-use of APs among elderly persons is a concern for several reasons. There is a wide array of known potential ADRs [36] to which elderly persons may be more susceptible due to age-related changes in pharmacokinetics and pharmacodynamics [41]. Polypharmacy is another issue which may increase the risk of ADRs and increase the risk of a potential DDI [14]. Furthermore, some aspects of elderly health status, such as being a resident of a nursing home, may alter the risk of mortality, as shown in a large observational cohort study [42]. Several observational studies have explored different definitions of frailty, including in relation to drug safety. However, accounting for frailty when studying antipsychotic safety among elderly persons is very challenging due to issues such as unmeasured or poorly measured aspects of frailty or selective reporting of such items [42] as well as potential drug discontinuation in response to increasing levels of frailty and poorer health. An example of this concerns a recent study investigating the risk of mortality stratified by frailty levels, which reported the paradoxical finding of a higher risk for less frail persons compared to frailer ones [43].

While the potentially harmful effects of DDIs are widely acknowledged, evaluating the clinical impact of DDIs is very challenging. Such difficulties arise from unmeasured and to a certain extent, unmeasurable, true adherence in observational studies and all other studies where it is assumed that patients take the medication they are prescribed or dispensed. Other challenges concern potentially missing information such as over-the-counter drugs and medicinal supplements. A 'simple' solution to reducing both the risk of ADRs with antipsychotic use as well as with potentially harmful DDIs may be deprescribing. Deprescribing is a relatively new concept concerning the practice of reviewing medication use and stopping treatment if a drug is not clearly indicated or beneficial, appropriate or in line with global goals of patient care [44]. Frank et al. write that barriers to deprescribing may, however, be significant, such as prescriber reluctance to discontinue medications prescribed by other physicians, as well as patient beliefs that deprescribing may constitute under-treatment. Irrespective of deprescribing, it is important to review patient medications in view of whether there is a clear clinical need for them and whether the risks exceed the benefits. Another practice that could potentially improve patient safety in elderly persons for drugs deemed necessary is using the lowest effective dose for appropriate periods.

It is important to remember that the burden of ADRs, whether those due to APs, DDIs related to APs or other drugs, does not only have a clinical nature but also an economic one. Preventable ADRs, such as those caused by drugs which may be deemed inappropriate either because they are not clearly indicated or because they are used inappropriately (e.g. at a high dose, for long periods, concomitantly with interacting drugs, etc.) lead to costs which are preventable. According to a recent systematic review, the costs related to preventable ADRs are not uniformly estimated across different studies, as a result, it is difficult to extrapolate the costs associated with AP-related ADRs per patient, per drug or per setting [45]. The cost of preventable AP-related ADRS, and of AP-related DDIs in particular, would, however, be useful information that could serve as an additional persuasive argument for the safer use of antipsychotics, particularly addressed to health-care providers.

This study has several strengths as well as limitations. Firstly, the present study draws from a large sample of approximately 25% of the general population in Italy. The nature of the data, i.e., claims data, ensures that prescribing and other health-care information is representative of routine clinical practice. Furthermore, the use of an active comparator reduces the effect of confounding by indication while the use of a new-user study design ensures that time-varying risks commence at the same time for all patients, preserving the temporality of outcome assessment [46]. Further strengths concern the identification of the outcome, all-cause mortality, which is reliably recorded and identifiable in Italian claims data. The use of all-cause mortality as an outcome circumvents the problem of competing risks in survival analysis [47]. On the other hand, this approach precluded analysis of specific causes of mortality. Several sensitivity analyses confirmed the robustness of study findings. However, this study also has some limitations. The classification of antipsychotics used, i.e., considering antipsychotics atypical or conventional, is widely used and for this reason, was adopted. Nevertheless, this classification has received criticism as it may be more relevant to classify antipsychotics based on their pharmacological properties and chemical structures [48].

It was not possible to account for the severity of the underlying cardiovascular or cerebrovascular disease. However, the rule out-sensitivity analysis showed that it is unlikely that the measured effects are mainly because of residual confounding. It is possible that exposure misclassification occurred if patients who are dispensed antipsychotics do not take them. However, it is unlikely that this exposure misclassification is differential among users of conventional and atypical antipsychotics. Furthermore, antipsychotic switching and adherence were not considered in the present study design; this may affect the outcome but is also unlikely to be differential in the comparison between atypical and conventional antipsychotics, moving the observed effects toward the null. In addition, information on drug dose was not available, so it was not possible to evaluate the dose-effect response. Finally, only DDIs related to antipsychotic use were considered. It is, however, possible that other DDIs were present; these were not considered, although all analyses are adjusted for concomitant drug use.

5. Conclusions

Conventional antipsychotics were associated with a 33% higher risk of death at 180 days after the start of antipsychotic use, compared to atypical APs, in a cohort of elderly persons with pre-existing cerebrovascular or cardiovascular disease. Antipsychotic-related DDIs were not common among these patients, but more

than one DDI was associated with an increased risk of death within 90 days of antipsychotic initiation, thus highlighting the importance that physicians should be aware of prescribing concomitant medications which may interact with antipsychotics.

Author contributions

G Trifiro' conceived the study. F Giorgianni, J Sultana, and G Trifirò designed the study. F Giorgianni carried out data analysis. F Giorgianni, Janet Sultana, and G Trifiro' interpreted the results. F Rea, E Lucenteforte, J Sultana, N Lombardi, A Mugelli, A Vannacci, G Roberto, R Liperoti, U Kirchmayer, C Vitale, A Chinellato and G Corrao wrote and/or critically revised the manuscript.

Funding

The study was funded by the Italian Medicines Agency (project AIFA-FARM9LBBBL).

Data availability statement

The dataset used to carry out the present study is not available in a public repository.

Declaration of interest

G Trifiro' coordinates an MSc programme for which his department has received funding from Baxter, Celgene, ABC pharmaceuticals, Amgen, MSD, Shire, Teva pharmaceuticals, unrelated to this study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Ethics approval

This study was approved by the Ethic Committee of the '"Azienda Ospedaliera Universitaria di Careggi"', Florence, Italy, on 26 March, 2012; Protocol Number: 2012/0012643.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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