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Antidepressants and the risk of cardiovascular diseases

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Abstract

Depression is considered an important public health issue. Nowadays, about 300 million people are affected by depressive disorders and a quarter of them just in Europe. Antidepressant (AD) treatment like tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or newer atypical antidepressants (NAAs) seems to be the most appropriate therapy in order to treat depressive symptoms.

In the first study, a synthesis of the available scientific literature was performed on the possible association between use of AD and cardiovascular diseases (CVD). A search of published observational studies was carried out using terms directly related with cardiovascular and antidepressive field. In addition, the quality of the included studies, the heterogeneity among them as well as the presence of publication bias was evaluated.

The second part of the thesis regards the studies conducted within the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) project, where data from different regional healthcare utilization databases involved in the Italian Group for Appropriate Drug Prescription in the Elderly (I-GrADE) was used. The project is focused on the evaluation of inappropriate prescribing in a population of elderly hospitalized with a diagnosis of CVD. In the second study, nested-case control studies were applied for the evaluation of the role of AD respect to the occurrence of CVD, among the elderly population. Sensitivity analyses were performed, like a Monte Carlo Sensitivity Analysis (MCSA), which quantified the potential bias introduced by a particular confounder (smoking factor) and by changing the length of AD exposure's window.

In the third study, the acute effect of AD treatment was evaluated respect to the onset of arrhythmia. The cohort selection was restricted to the new AD users who did not developed a previous event of arrhythmia. Nested case-control and case-crossover studies were applied and estimates were adjusted for drug prescriptions and hospitalizations. Sensitivity analyses were performed by using different criteria to define the outcome of interest or by changing length of AD exposure's window.

In the fourth study, we focused on the role of AD medication respect to mortality. The possible link between adherence to AD and increased or decreased risk of mortality was tested among the elderly cohort. The selection was restricted to elderly who were all AD users and started AD therapy since cohort recruitment. A Cox model was applied and the combined levels of adherence to AD and co-treatments were evaluated during observation time. Estimates were adjusted for

several variables such as the polypharmacy. Then, sensitivity analyses were performed on the basis of AD coverage's definition.

The results of the meta-analysis showed a significant increased risk of cerebrovascular disease and acute heart failure respectively for SSRIs and TCA users. Then, these results were confirmed by the observational studies performed within the AIFA Project. A positive relation was found between AD exposure and CVD in a cohort of elderly patients already affected by a CVD, in particular a proarrhythmic effect of AD exposure was revealed by our estimates. Finally, adherence to AD treatment was associated with a decreased risk of death by considering different levels of adherence to co-treatments assumed during the observation time.

In conclusion, these studies showed that the use of AD could increase the risk of several CV disease, therefore, physicians need to carefully monitor their patients to ensure a correct assumption of the drugs and concurrently try to prevent the onset of CV outcomes. Since any potential increased risk may result in a considerable impact, the risk effect estimates provided by these studies may support both clinical practices and regulatory activities.

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INTRODUCTION

Depression

General description

Nowadays, the importance of psychiatric disorders continues to increase especially by providing health and socio-economic consequences all over the world. There are several types of depressive disorders, and in general, depression could be defined as:

"sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, tiredness, and poor concentration" [1, 2]

Depression is a widespread disorder with more than 300 million people affected equal to 4.4% of the total population. The World Health Organization (WHO) confirms that depression is one of the major causes of disability and will be the most common disease among mental illnesses in 2020 [3]. Non-fatal losses in health and functioning could be estimated by Years Lived with Disability (YLD), and in 2015 depressive disorders were ranked as its first contributor in 7.5% of all YLD [4].

Depression could affect almost one out of 15 adults (6.7%) every year and one out of six people (16.6%) will experience depressive syndrome during their life.

In general, depression could affect any person regardless of age, even though often begins in adulthood [5].

At its worst, depression could lead to suicide, 800,000 people die every year and unfortunately is the second cause of death in people between 15 and 29 ages [1].

Forms of depression

The two currently accepted diagnostic systems for mental disorders are the International Classification of Diseases (ICD) generated by the World Health Organization (WHO) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) elaborated by the American Psychiatric Association. The two diagnostic systems, which classify the mental disorders, were developed respectively in the 1950s and early 1960s [6].

Both systems may identify the various forms of depression, through a different classification in order to characterize depressive disorders. ICD-10 requires the presence of a minimum number of symptoms for 2 weeks or more, while for DSM-5 at least 5 key symptoms should be present for 2 weeks and may be associated "with clinically significant distress or impairment in social or occupational functioning" to identify depressive disorder [6].

These two methods of classification, DSM-5 and ICD-10, have specified a certain threshold related to the severity of the disease, concerning duration, course and subtype of depressive disorders.

The classification of interest was organized depending on the severity of depressive disorders, which was based on the number of symptoms and their duration associated with depressive disorder [7].

Low severity and duration of depressive episodes could anticipate a greater likelihood of improvement whereas great severity, chronicity and number of previous depressive episodes may increase the risk of subsequent relapse.

The categorization into minor, persistent and severe appears to be implemented without the consideration of some aspects such as duration [8]. However, these factors should be carefully evaluated because depression may cause social problems and other psychiatric conditions, such as psychiatric disorders and physical comorbidity [9].

To define the "degree" of depression, the forms and the course of the depressive disorders should be taken into account. Indeed, there are several forms of depressive disorders, such as persistent, perinatal, psychotic, seasonal and bipolar disorder [10].

Moreover, for the likelihood of relapse/recurrence, the course of the depressive disorder should be considered in treatment's implications, like the number of depressive events and the interval among them. Indeed, subjects may be characterized by a different number and length of time among episodes [7].

Clinicians are often required to take a decision about AD treatment - for example, treat or not based on a symptom severity ratings (for example, a PHQ-9 score alone). Patient Health Questionnaire-9 (PHQ-9) is a short self-administered tool specifically developed for the monitoring of depression [11], which is a reliable and valid measure of depression severity [12]. Indeed, PHQ-9 is composed by nine items that correspond to the symptoms of major depression according to DSM-classification. Then, the severity of depression may be classified according to the scores obtained by PHQ-9 [13] into mild or minimal depressive symptoms, moderate depressive symptoms (or minor depression), moderately severe major depression, severe major depression. However, PHQ-9 which counts individual symptoms, should not be used to determine the presence or absence of a depressive disorder [7].

Risk factors

Depending on mild, moderate or severe intensity, depression may become an important health condition that could seriously influence ordinary work and social activities [1]. People with depression may experience the following symptoms: change in appetite, disturbed sleep cycle, loss of energy and concentration, suicidal instinct or self-harm [14].

Age, gender, social isolation, presence of chronic diseases (like cancer, diabetes or heart disease), disability or abnormal sleep cycle are characteristics potentially associated with a higher risk of developing depression [5, 15, 16].

Moreover, the personal or the family history of depression, the use of comedications (e.g. antihypertensive, lipid modifying, other CV agents and antidiabetics), the presence of chronic health condition (such as osteoarthritis, hypertension, heart disease, diabetes mellitus), are factors that characterize the elderly population and may influence the subsequent development of depressive disorders.However, elderly may not receive adequate treatment, as they could not understand the importance of appropriate treatments.

Moreover, individual features, such as thoughts, emotions, behavior and interactions, various factors (social, cultural, political, environmental) and economic aspects, may influence the onset of psychiatric disorders [17]. There could be a link between mental and physical health, which could lead to the onset of disability, which is extended to multiple developmental areas like cognitive functioning and adaptative behavior [17], and to the reduction of the productivity [18].

Depression is widespread in poor countries where people are more likely to suffer from it. In poor countries, between 76% and 85% of people with psychiatric disorders are not treated for their disorder while the percentage varies between 35% and 50% in developed countries [17].

Biological aspects

Various biological and genetic aspects may be related with depressive syndrome [5].

The activity of certain genes would directly control the brain changes recorded in depression. Some genes, characterized by lower expression in depressed individuals, could be related with synapse function. GATA 1 protein-transcription factor is significantly more expressed in some cerebral areas of subjects with depressive disorders and the turn off of neural circuits could be regulated by the activity of this single transcription factor [19].

Moreover, dysfunction within the medial prefrontal cortex and circuits connected with cortical and limbic structures may take part to the onset of mood disorders [20, 21].

Thus, some cerebral portions are implicated in mood state-regulation, and these differences may locate areas where physiological activity changes. Other abnormalities are discovered in orbital and medial prefrontal cortex areas, such as reductions of cortex volume [22].

Two global scientific consortia, ENIGMA (Enhancing Neuro Imaging Genetics through Meta-Analysis) [23] and CHARGE (Cohorts for Hearth and Aging Research in Genomic Epidemiology) [24], showed a correlation between variations in an individual's genetic code and the size of certain brain structures. Variations of the genetic information could be related with intracranial volume changes [25] and certain genetic variations region, which are employed in the regulation of gene expression during development and that could be linked with the onset of depressive disorders [26].

Moreover, some genes, that seem to confer risk for psychiatric disorders (schizophrenia, bipolar disorder, and depression), may interact through pathways involved in i) epigenetic mechanism that regulates the switching on-or-off of genes in response to environment and experience, ii) the communication between brain cells and iii) susceptibility to psychological stress and mood disorders through the action of the immune system [27].

At last, depressed subjects may exhibit various features derived by an inflammatory response, as increased expression of pro-inflammatory cytokines [28, 29].

Brain networks should be identified, specifically those involved in the regulation of the various aspects of mental function and dysfunction, such as cognition, emotion and social behavior in order to develop biomarkers and new pharmacological and genetic tools, which may modulate the signaling pathways and circuits damaged by mental illnesses. An answer could be offered by the elaboration of biomarkers, that may be useful to predict the onset of certain illnesses in individuals at risk. This should be the first step for the elaboration of an effective intervention, by taking in

consideration the individual's diagnosis and characteristics. Biomarkers could represent an important tool to identify subgroups of individuals who share common characteristics in terms of diagnostic categories [30].

Preventive programs and therapies for depressive syndrome

Depression is often related to incorrect lifestyle, which significantly affects the onset of depressive disorders. For this reason, these aspects should be taken into account to assess the appropriate treatment of depressive symptoms.

Preventive programmes may decrease depressive syndrome, both in children and adults.

- ✓ WHO's Mental Health Action Plan 2013-2020, endorsed by the World Health Assembly in 2013, focuses attention on mental health in achieving health for all people. The Programme aims to support countries for the increase of services for people with psychiatric disorders. The Programme asserts that proper care, psychological and drugs therapy could be an ideal treatment for people with depression, schizophrenia and epilepsy [31].
- ✓ World Health Day provided useful information about the development of a depressive disorder. The campaign was dedicated to giving information about the underestimated problem of depression and the related multidisciplinary care approach (or psychotherapeutic therapy and pharmacological treatment) [32].
- ✓ European Depression Day, focused on information about depression and mood disorders. There could be a large interval between the diagnosis and the onset of symptoms. Moreover, a considerable role is assumed by social stigma concerning mental illness, which is related to economic, physical, emotional and social aspects [33].

Health-care providers may offer many different psychotherapeutic or pharmaceuticals interventions or a combination of both.

The first includes behavioral activation, cognitive behavioral therapy (CBT), interpersonal psychotherapy, or problem-solving treatment combined with the AD therapy. Different methods of treatment include (a) individual and/or group face-to-face psychological treatments organized by professionals and therapists, as well as (b) self-help psychological treatment. Psychotherapy (or "talk therapy") could also be an effective therapy, through the education of new point of views that involve thought, behavior and habits [10]. Psychotherapy may involve a singular individual or a group therapy where people with similar illnesses may participate. Depending on the severity of depressive syndrome, treatment could take a few weeks or much longer. In many cases,

significant improvement may result in 10 to 15 sessions [34]. Psychotherapy is often adopted as an initial treatment for mild depression. Psychotherapy is considered a useful support to understand severity and persistence of depression and how to proceed with a drug therapy [35], although some older adults prefer psychotherapy session compared to pharmacological treatments [10].

Cognitive-behavioral therapy (CBT) is a behavioral approach that attempts to support people with psychological problems through the change of distorted thinking and behaviors [34]. This "interpersonal therapy" could be considered as a useful tool dedicated to the improvement of life's quality [10]. Moreover, the combined treatment of medication and CBT has been demonstrated to be preferable therapy for achieving remission sooner [36], especially among elderly [37]. On the contrary, some studies have demonstrated a similar response among subjects who were treated with one type of therapy, AD or CBT [38], as well as the combination of the AD therapy.

However, if depressive symptoms are severe or there are other chronic diseases, drugs therapy or the combination with psychotherapy may be a better choice [10].
If medications are not able to reduce depressive symptoms, then electroconvulsive therapy (ECT) or a brain stimulation therapy may be an option to provide relief in people with severe depression [17, 34, 39].
ECT is a medical treatment most commonly used among people with severe depression who do not respond to therapies [39]. Certain treatments are still in their experimental stage. Types of brain stimulation therapies, which are recently used to treat medicine-resistant depression, include repetitive transcranial magnetic stimulation and vagus nerve stimulation [39].
AD treatment is generally prescribed for the treatment of depression, although this kind of therapy could be prescribed to treat other diseases, such as panic-agoraphobia disorder, obsessive-compulsive disorder, social phobia, anxiety disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, borderline personality disorder, eating disorder and obesity, chronic fatigue syndrome, cessation from smoking, therapy related to addictive behavior.

Antidepressant treatment

The Italian report edited by Medicines Utilisation Monitoring Centre (OsMed) in 2015 reported that the prevalence of AD treatment was 6.1% on the total of population beneficiary of National Health Service (NHS) (6.3% North, 6.4% Centre, 5.7% South). Prevalence of AD therapy was higher in female (8.3% respect to 3.9% in male) and increased with age (2.7% among subjects aged less than 45 years, 6.4% 45-65 years, 9.6% 65-75 years and 13.7% for people aged more than 75 years). The prevalence was higher, +1.1%, in 2015 compared to 2014.

The percentage of subjects adherent to the AD treatment was 39.6% (+0.7% in 2015 compared to 2014). Adherence level was lower in the Centre respect to the North and South (37.4%, 40.0%, 38.0%) and among male subjects (38.8% respect to 40.0% in female individuals). The increase of age is associated with a better adherence (34.2% among subjects with less than 45 years, 38.5% for 46-65 years, 42.0% for 66-75 years, 43.3% for individuals with more than 75 years) and an higher percentage was found among individuals who already used AD compared to new users (50.6% vs 17.2%). Excluding occasional AD users, the percentage of adherent patients to AD treatment in 2015 was 51.6%. The adherence level was 37.4%, by excluding subjects affected by other psychiatric diseases.

In 2015 pharmaceutical spending related to mental illnesses was placed at the fifth place, shared for 41.5% by NHS, 43.1% directly by residents and 15.3% by public healthcare structure. The analysis of pharmacoutilization registered a constant increase about the use of drugs related to mental illnesses. In particular, SSRIs and antiepileptics were at first place in terms of pharmaceutical spending among drugs for mental illnesses [16].

As confirmed by Organisation for Economic Co-operation and Development, the increase of pharmaceutical spending should be considered a strategy for the management of chronic diseases, the prevention of complications and the reduction of health resources' use.

In the last years, an increase in drug use has been registered, likely explained by the increase of population aging and chronic diseases (cancer, diabetes, depression) and by the availability of new medicines and changes regarding drugs prescriptions [40].

Categories of antidepressants

There are different types of drugs used to treat depressive symptoms: Tricyclic Antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs), Newer Atypical Antidepressants (NAAs) [41]. The primary action of the AD therapy is dedicated to mood-elevating effect, whose mechanisms are different depending on the patterns of neurotransmission regulation.

The AD treatment could be considered as an effective treatment for severe depression although these medications are not accounted as a first line to treat mild depressive symptoms. However, there could be possible adverse effects associated with AD treatment, in terms of individual preferences, proficiency and/or use of a certain therapy [17].

TCAs were introduced in the 1950s, with imipramine as first (Kuhn, 1958) [42]. TCAs could cause numerous side effects which may contraindicate their use, oblige to the suspension of their treatment and compromise AD adherence at the beginning and in the middle of the treatment. The most common side effects may be related to the anticholinergic properties, such as dry mouth, constipation, sleep disturbance, cognitive disorders and confusional states [41]. Other side effects may implicate cardiovascular system, such as tachycardia, orthostatic hypotension with the risk of falls, especially in elderly, retardation of intracardiac conduction and increased repolarization period with the risk of bradyarrhythmias or other cardiovascular problems in predisposed patients [41, 43]. Furthermore, adverse events could involve nervous system, such as tremor, or high risk of convulsive seizures in predisposed subjects [41, 44]. Moreover, TCAs could inhibit the reuptake of monoamine neurotransmitters into the presynaptic neuron and enhance noradrenergic and serotonergic neurotransmission. TCAs overdose facilitates an increase of mortality and morbidity, such as suicidal intentions.

For this reason, new ADs have been developed such as SSRIs and newer classes of AD [45].

SSRIs inhibit the reuptake of serotonin into the presynaptic neuron and some of these AD are able to block the reuptake of noradrenaline and/or dopamine to a lesser extent. This class of AD may be safer in overdose than TCAs or NAAs. SSRIs could cause significant adverse effects, such as nausea, headache, diarrhea, anxiety/restlessness and insomnia [41, 46] at the initial stages of therapy. In general, these effects are dose-dependent and tend to disappear after the first days or weeks of treatment [46]. Increased appetite and weight during SSRI treatment are revealed by some studies [47], but other studies showed opposite findings [48]. Considering toxicity and adverse effects, SSRIs are better tolerated compared to TCAs, due to less toxicity and lower lethality regarding overdose [49-51].

Moreover, NAAs may cause adverse events such as dry mouth, nausea, or cardiovascular problem like the increase in blood pressure [41].

The combination of the AD therapy is an important tool in clinical practice. A combination of serotonergic and noradrenergic drugs could be translated into a “dual action” while combined serotonergic drugs with different mechanisms of action could increase serotonergic neurotransmission, and likely develop serotonin syndrome. Thus, AD combination could be additive, but in certain cases this could be toxic [52].

Phases of antidepressant treatment

The AD treatment may be subdivided into 3 phases: an acute treatment phase to achieve remission of symptoms, a continuation phase to prevent recurrence of the same episode of illness (relapse), and a maintenance phase to prevent future episodes (recurrence) [53].

As terminology related to AD treatment, "*relapse*" could be defined as the onset of symptoms immediately after therapy interruption, proving a too short therapy duration [54], without the presence of depressive symptoms or remission [53]. While "*recurrence*" could be understood as a recurrent onset of depressive symptoms after a certain period, without medication assumption and/or nearly without symptoms [54]. With an increase of depressive episodes, the risk of recurrence could increase [55].

Two or four weeks are usually required to relieve AD effects such as sleep, appetite and concentration improvement [5]. Moreover, response to the AD treatment could be complete, partial or unsatisfactory, likely caused by low compliance level, severity or type of depressive event [56]. AD medication should be maintained for at least six months after the improvement of the condition since relapses could happen if treatment duration is shorter. Among people at high risk, a longer-duration of the therapy could be requested to reduce the onset of episodes [34].

Sometimes people tend to interrupt AD assumption due to apparent beneficial effects. However, AD treatment should not be abruptly stopped because this could cause withdrawal symptoms or lead to a relapse. A treatment interruption should be controlled by clinicians, usually after a course of 6 to 12 months with a slow decrease of AD dose assumption [10]. WHO recommends avoiding interruption in the 9 -12 months after recovery among depressed adults who have already started AD treatment [57]. Higher rates of relapse after AD treatment's discontinuation has been registered in elderly compared with young people [58] while a progression of AD treatment could be efficacious to prevent relapse or recurrence in elderly [59]. Indeed, a remission of depressive symptoms has been detected to be equal to 31 % after 14 weeks and 65 % at six months [60]. Furthermore, an average rate of relapse was 41 % for patients who switched to placebo, compared to 18 % for individuals who continued AD treatment [61].

Thus, it is important to obtain an early diagnosis and a suitable pharmacological treatment, not only for resolving the acute episode, but also to prevent relapse and enhance the quality of life.

The terminology and definitions used to characterize adherence to AD varied considerably. This lack of standardization is a common and well-documented problem in adherence research, and debate still exists on the appropriate terminologies to describe patients' medication-taking behavior [62]. WHO defines adherence as the adherence to a therapy, which better corresponds to

the recomendations of a healthcare provider. WHO has gathered together five aspects associated with adherence/non-adherence like information about subject, depressive disorder, treatment, socioeconomic and health system related [63].

Moreover, poor adherence could be correlated with various factors, like treatment complexity, lack of disease severity's consideration, inadequate follow-up, cognitive impairment and depression [64]. Poor adherence to AD treatment is common and results in increased disability and costs. This could be considered as the main cause of therapy's ineffectiveness, associated with a certain amount of healthcare intervention, morbidity and mortality.

Antidepressants and Cardiovascular diseases

Role of Antidepressants

In 2004, U.S. Food and Drug Administration (FDA) stated a public warning about a possible increase in the risk of suicidal thoughts or behavior in children and adolescent users of SSRIs therapy. FDA asserts that young people taking AD should be controlled especially in the first weeks of treatment, in order to monitor these eventual adverse events. In 2006, the warning was extended up to age 25. Moreover, an additional "black box" was introduced in the presence of major depressive disorder [35].

A strong relation among AD treatment and cardiovascular diseases (CVD) seems to exist. Moreover, it should be evidenced that CVD is included among the main causes of deaths for non-communicable diseases [65].

Several studies found that TCAs could increase heart rate, cause orthostatic hypotension, reduce intraventricular cardiac conduction and be characterized by antiarrhythmic and proarrhythmic cardiac activity [66-68]. TCAs are characterized by anticholinergic and adrenergic properties [69, 70], and they could inhibit sodium and potassium channels, which are responsible for the QT interval prolongation, or time between the Q and the T wave of the electrical conduction system [71]. For this reason, TCAs may be contraindicated for subjects affected by heart diseases [72].

Nowadays, SSRIs have replaced TCAs treatment due to their better safety profile, for this reason, SSRIs should be chosen as first-line treatment. SSRIs act on the reuptake of serotonin neurotransmitter which is mostly synthesized by the enterochromaffin cells in the gut and transported by dense granules contained in platelets [73], by compromising their hemostasis process [74, 75]. SSRIs' action potentially causes an abnormal platelet aggregation and increases the risk of bleeding [52, 75-87], such as hemorrhagic stroke [84, 87, 88]. However, the effect of SSRIs could be protective for thrombotic events. In addition, the SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) trial showed that sertraline (SSRI) in myocardial infarction (MI)/unstable angina patients could significantly improve depressive symptoms [89] while in depressed patients with chronic heart failure (HF) may improve cardiac outcome [90]. Furthermore, the CREATE (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy Trial) trial revealed as a combination of psychotherapy with citalopram (SSRI) could be considered as a better treatment for the initial acute phase of depression among patients with coronary artery disease [91] as well as ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) trial reported how a combination of CBT and SSRI treatment could reduce

depressive symptoms in MI patients [92]. At last, SSRIs could cause vasoconstriction in cerebral arteries, which may lead to ischemic stroke [93]. However, some studies found no increased cardiovascular risk considering SSRIs users [94-97] such as MIND-IT (Myocardial Infarction and Depression Intervention Trial) study, which was inconclusive respect to the effects of AD treatment on cardiac outcomes [98].

NAAs operate on multiple neuronal systems which could give a greater advantage compared to SSRIs treatment [99], such as the modulation of both serotonin and norepinephrine transmission [99-101]. Some AD belonging to NAAs' category appear capable to block cardiac channel conductance, like TCAs, and to stimulate cardiac activity [102]. In particular, venlafaxine was associated with increased blood pressure and reduced heart rate variability [103] while an increase of weight and body fat mass was related to mirtazapine. In general, NAAs' category was less studied compared to TCAs or SSRIs [71].
In adults or elderly, depression could co-occur with other diseases like diabetes, cancer, CV disease and psychiatric disorders [104]. A combination of depression and chronic diseases ideally causes worsening health state compared with the presence of each one separately [105]. Specifically, considerable relations among depression, cardiovascular morbidity and mortality were identified [106-114], especially in subjects already affected by CVD [89, 115-120].

Furthermore, few studies did not evidence an increase in suicide/suicidal thought or attempts among AD users [121, 122], while several studies have reported an increased risk of inducing suicidal thought and attempts, especially in young people [123-127]. However, the specific role of AD and depression could be difficult to evaluate because both seem to be associated with the risk of suicide. In addition, the risk of postpartum hemorrhage related with AD use appears to be modest, but statistically significant and clinically relevant, given that this complication is one of the major causes of maternal mortality and morbidity [128]. At last, AD medication was associated to falls, as reported in "Fall Risk Increasing Drugs" list of the most prescribed drugs related to falls [129].

Eventually, once clinicians prescribe AD, they should take into consideration additional chronic physical health problem, side effects caused by AD treatment and possible interactions with other medications [130].

OBJECTIVE

The objective of this thesis is the study of the association between AD treatment and risk of CVD or mortality. Several studies were performed to achieve this objective.

First, a synthesis of the available scientific literature was performed. I) A meta-analysis was realized on the basis of observational studies published up to October 2015 and concerning the association between use of AD and the onset of CV diseases. We hypothesized that AD could play an important role in the onset of CV events.

Then, one indicator of the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) project, based on appropriateness of drugs among elderly previously affected by CV events, was developed. Data from different regional healthcare utilization databases within the Italian Group for Appropriate Drug Prescription in the Elderly (I-GrADE) program was used. Participating healthcare territorial units were three Regions (Lazio, Lombardy, Tuscany) and two Local Health Units (Caserta, Treviso) and the elderly cohort was followed until 2012-2014 or data availability across participating healthcare territorial units.

II) The role of AD treatment was verified in the recurrence of CVD, through nested case-control studies.

III) The effect of AD treatment was evaluated on the onset of arrhythmia, by the application of nested-case control and case-crossover studies.

IV) The strength of better adherence to AD was considered respect to the risk of mortality, taking into account the presence of co-treatments during the observation time, through a Cox model.

METHODS

Meta-analysis

A meta-analysis is a statistical analysis that combines the results of multiple scientific studies regarding the same research topic. The aim of this analysis is to aggregate the results of single studies obtaining a pooled estimate as close as possible to the true underlying unknown parameter common to all studies. This process allows obtaining conclusive results from potentially contrasting evidence derived from the individual studies and more precise point estimates with an increased power compared with the individual studies, which could be characterized by a small sample size. However, in performing a meta-analysis, it is crucial to be careful in the study selection, data extraction and bias assessment (e.g. publication bias).

Meta-analysis is performed on well-formulated research questions such as the potential relationship between therapy and outcome, the research outcome, the treatment or intervention, the population of interest and the type of studies that you are looking for (observational studies or randomized clinical trials) [131].

Next step concerns literature review that is the identification of all published and unpublished literature, uncompleted research reports and eventually work in progress. A complete search literature aims to obtain all possible literature related to that research topic. It is, therefore needed to identify a set of terms' combination useful to retrieve all the suitable papers in the scientific papers search engines such as PubMed. Selection criteria should be established as the principal aim, common inclusion criteria regard the language constraints, unrelated issue, not reported the estimate of treatment and outcome association or not adequate comparator [131].

From the considered studies, items that need to be collected include general characteristics (author, year, source of publication, information about the populations and related features), research design, treatment, effect size and the related measures of variability, controlled variables or adjustments.

Once this information is collected, it is possible to calculate the pooled estimate of the effect sizes obtained from the individual studies that could be risk ratios, odds ratios, or risk differences for event data, differences in means for continuous data, or hazard ratios for survival time data. Different methods are available to obtain the summary estimates, the most common is the inverse variance weighting if no between studies heterogeneity is expected and the DerSimonian and Laird method when between-study heterogeneity is considered.

Fixed-effects model

Fixed-effects model is used in absence of between studies heterogeneity, that is, when all included studies provide the estimate of the same underlying unknown parameter.

This model considers the estimate Y_i related to each study, derived from a normal distribution with a common mean θ or central parameter of interest, and variance of the summary statistic s_i^2=var (Y_i). Each Y_i is assumed to be normally distributed as N (θ, s_i^2) for i=independent studies, assuming s_i^2 already known. According to this model, each estimate is considered as an independent estimate of the unknown parameter θ and the only source of uncertainty is considered the variability within each study. The pooled estimate or the average treatment effect could be generalized to populations with identical characteristics and study effects [132, 133].

Inverse variance method

Inverse variance method could be adopted to pool binary or continuous data. The effect size, Y_i (log odds ratio, log relative risk, risk difference, difference in means or standardised mean difference from the *i*th study) could be combined to give a summary statistics through weighted average from each study

$$\theta_{IV} = \frac{\sum_{i=1}^{n} w_i * Y_i}{\sum_{i=1}^{n} w_i}$$

where n is the number of studies included in the meta-analysis, Y_i are the study-specific estimates (transformed if needed) and w_i are the weights.

Weights are calculated by the reciprocals of the variances of the study estimates

$$w_i = \frac{1}{var(Y_i)}$$

More weight is assigned to larger studies, characterized by smaller standard errors, as opposed to smaller studies, which have larger standard errors. The standard error of the pooled treatment effect θ_{IV} is obtained by

$$SE(\theta_{IV}) = \frac{1}{\sqrt{\sum_{i=1}^{n} w_i}}$$

Thus, the average estimate is a weighted mean, considering the weight as the inverse of the estimate's variance, of the estimated effects derived by each study [132, 133].

Test of homogeneity

Fixed effects-models is based on homogeneity assumption among included studies, tested as the distance between the estimated effects of each study and the average fixed effect pooled estimate. The null and the alternative hypothesis are the following

$$H_0: \theta = \theta_1 = \theta_2 \ldots = \theta_k$$

$$H_1: \text{at least one different } \theta_i$$

The heterogeneity statistic consists into

$$Q = \sum_{i=1}^{n} w_i * (Y_i - \theta_{IV})^2 \sim \chi^2_{n-1}$$

If Q is greater than the 100 (1-α) percentile of the χ^2_{n-1} distribution, then the hypothesis H_0 could be rejected. Studies could be based on populations characterized by different features, thus a hypothetical homogeneous population may be obtained through stratification for certain covariates [132, 133].

Random-effects model

In presence of between-study heterogeneity, it is assumed that all included studies provide the estimate of a different underlying unknown parameter. In this case, the study-specific effect estimate Y_i, that may be considered as a random draw from a normal distribution with mean θ_i, and variance, s_i^2

$$Y_i | \theta_i, s_i^2 \sim N(\theta_i, s_i^2)$$

Furthermore, each study-specific parameter, θ_i, is assumed to be obtained from a normal distribution with mean θ and variance τ^2

$$\theta i | \theta, \tau^2 \sim N(\theta, \tau^2)$$

where τ2 represents the variance of the distribution of the parameters and could be interpreted as the between-study variance.

In random-effect model, the standard error could be greater, CI wider and its p-value larger (or less likely to be statistically significant) compared to the fixed effects estimate [132, 133].

DerSimonian and Laird random effects models

To obtain a pooled estimate which is able to take into account the presence of heterogeneity, the between study variance τ^2 need to be quantified. DerSimonian and Laird estimate of τ^2 results from

$$\tau^2 = \frac{Q-(n-1)}{\Sigma wi - (\Sigma \frac{w_i^2}{\Sigma w_i})}$$

where Q is the value of the statistic obtained from the homogeneity test, n-1 are the degrees of freedom of the statistics and w_i represents the inverse of variance estimate obtained from each study.

The pooled estimate is the obtained as

$$\theta_{DL} = \frac{\sum_{i=1}^{n} w_i' * Y_i}{\sum_{i=1}^{n} w_i'}$$

but in this case, the weights are calculated as

$$w_i' = \frac{1}{var(Y_i) + \tau^2}$$

considering both within and between study variability.

The standard error of the pooled estimate obtained with the DerSimonian and Laird method is

$$SE(\theta_{DL}) = \frac{1}{\sqrt{\sum_{i=1}^{n} w_i'}}$$

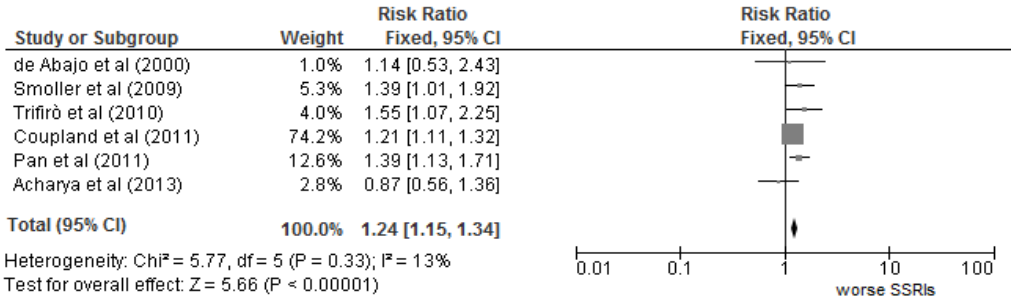
In comparison, random effects models assign more weight to smaller studies compared to fixed effect models. When τ^2 tends to the null, weights could be equivalent to those obtained by the inverse variance method.

Thus, if individual estimates of the considered studies are heterogeneous, the precision of the average treatment effect could be smaller. Heterogeneity could derive by the difference in the

study design as the considered population, treatment, outcome definition, statistical analyses or adjustments applied [132, 133].

Forest plot

The results of a meta-analysis are usually reported through a graphical representation called forest plot (as observed in the figure [134]). The vertical line represents the value "one" of the RR. This graphical display reports each study, that will be represented as a box whose area will be proportional to its weight (in terms of number of events and sample size), and the correspondent confidence interval. Through CI overlap, it should be possible to relieve the significance of each study, or when their IC does not cross the vertical line. Then, the black diamond at the bottom of the vertical line represents the summary estimate, where the center corresponds to the point estimate while its width to the CI [131, 135].



Inconsistency index

Another approach that is used to quantify heterogeneity among studies is called inconsistency index. This measure provides information about the presence of heterogeneity, evaluated through a percentage, which is obtained by $I^2 = 100\% \times (Q\text{-}df)/Q$, with Cochran's homogeneity statistic (Q) and the degrees of freedom (df). The I^2 index represents the proportion of the overall variability explained by the between studies heterogeneity.The range of this index is contained between 0% and 100% where 0% indicates an absence of heterogeneity while a greater value indicates a presence of heterogeneity among studies.

After calculating the pooled estimate, it is important to assess the presence of potential bias that could affect the pooled estimate and in case of presence of between-study heterogeneity, several analyses may be conducted to assess the potential sources of variability [131, 135].

Subgroup analysis

In the presence of heterogeneity, a subgroup analysis could be realized performing a stratification of the study-specific estimates according to study characteristics which are potential sources of heterogeneity and calculating the pooled estimate within each stratum. Stratification of studies could be an important tool to investigate the source of heterogeneity [135].

Influence analysis

A particular sensitivity analysis, or influence analysis, could be performed to verify the robustness of the summary estimated. By omitting one study at a time, it will be possible to evaluate which studies could influence the results. Moreover, this analysis allows the identification of potential outliers whose estimate is particularly distant from the summary estimate calculated on the remaining n-1 studies [131, 136].

Publication bias

A possible bias that could affect a meta-analysis is the publication bias, which consists in the tendency to include selected types of studies, for example those reporting significant results. In this case, the pooled estimate could be biased. A scatter diagram or funnel plot is usually adopted to evidence the presence of publication bias. The vertical line represents some measure of study size or another measure of precision, the horizontal line reports the study-specific estimate (such as RR reported on the log scale) and a dashed line will be equal to the pooled estimate. Each study will be represented as a singular point on the graph. Thus, in the absence of publication bias, the scatter of points will be symmetrical and similar to an inverted funnel [131, 133, 136].

Inappropriateness and AIFA indicators

An important aspect that should be controlled regards the use of additional drugs without precise information about their safety and efficacy, especially in elderly already users of other drugs.
The aging process is defined as physiological and functional changes that could deteriorate the correct mechanisms of protection and increase vulnerability to external attacks. Elderly considered as a fragile population, are characterized by differences on absorption and metabolism of drugs and about the potential drug to drug interactions [41, 52]. In general, elderly are characterized by several chronic diseases and comorbidities which are indicated to several drug prescriptions, considered as a possible cause of drug to drug interactions and adverse events [137]. A portion of the elderly population could develop depressive disorders and in order to treat this syndrome, drug interactions need to be minimized [138], as well as a correct balance between risks and benefits of treatments [139].
Nowadays, there are not so many clinical studies which investigate the efficacy and/or tolerability of several drugs assumed by elderly affected by polypathology. For this reason, elderly could be exposed to a greater risk in terms of polytherapies, drug interactions or therapeutic errors.

In general, inappropriateness is defined as the prescriptions that are not directly related to that specific disease, that could increase the risk of adverse events, or omission of drug prescriptions [140, 141]. Moreover, examples of inappropriateness include overprescription of medicines (polypharmacy), inappropriate dosages prescription or poor adherence to prescribed medications. Prescription inappropriateness is one of the most important problems in the field of healthcare assistance, explained by the increase of adverse reactions, hospitalization, death and economic causes [142].
New indicators related to inappropriateness question have been developed by the Geriatrics Working Group (GWG) AIFA (geriatrics, pharmacologists and epidemiologists) for a better evaluation about the quality of life and health of elderly. Inappropriateness about the prescription of drugs regarding treatment's chronic diseases or interaction among different molecules could be dangerous and provoke an increase in the risk of adverse events. This project funded by the AIFA regards the study about the inappropriateness of several drugs, specifically in a cohort of elderly or subjects with more than 65 years, characterized by a previous CV hospitalization (HF, cerebrovascular disease, arrhythmia, ischemic heart disease). This program involves the participation of five Italian healthcare territorial units participating to the so-called I-GrADE.

Participating healthcare territorial units are three Regions (Lazio, Lombardy, Tuscany) and two Local Health Units (Caserta, Treviso).

One of the objectives of AIFA involves the promotion, the safety and the appropriate use of drugs in order to ameliorate the standard of healthcare assistance. Poor quality of drugs prescription could be a cause of adverse events, hospitalization and mortality as described by several studies. For this reason, several indicators have been developed in order to measure the quality of drugs prescriptions among the elderly Italian population (12.301.537 subjects as reported by Istat for 2011).

Data of all reimbursable drugs by the National Health Service, obtained from the OsMed, have been analyzed.

First of all, a review of available scientific literature on PubMed, with the keywords "drugs", "elderly", "quality's indicators", in MeSH database (Medical Subject Headings), published up to September 2011, selected 275 articles, including non-English papers and letters to the editor, comments, review articles, editorials and observational studies. After a further selection on the basis of clinical relevance for elderly and availability of clinical data, the GWG group selected the final indicators.

Data sources and setting

The data used for the present study were retrieved from the healthcare utilization databases of the five Italian healthcare territorial units participating to the I-GrADE program, with the aim of assessing the appropriateness of outpatient drug prescriptions in the Italian elderly discharged from the hospital for CVD.

The information of about 21 million beneficiaries residing in these areas, accounting for nearly 35% of the Italian population, were recorded in the corresponding databases.

The National Health Service (NHS) provides universal coverage for most healthcare services to the entire Italian population. This service is administered through an automated system of databases recording the use of healthcare services, including: (1) an archive of residents who receive NHS assistance (the whole resident population), inclusive of demographic and administrative data (e.g. age, gender), other than the dates in which the individual started and stopped the condition of NHS beneficiary (i.e. from birth/immigration to death/emigration); (2) a database on hospital discharge records including information about primary diagnosis and up to five co-existing conditions and procedures coded according to the International Classification of Diseases, Clinical Modification 9th revision (ICD-9 CM); (3) a drug prescription database providing information on all outpatient drug prescriptions reimbursed by the NHS and coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The use of a unique personal identification code allows for the record linkage of all databases. In order to preserve privacy, the original identification code was replaced with its digest that is the image of the code through a cryptographic hash function. Data were drawn out from databases by means of standardized queries, which were defined and tested according to the study protocol.

Population

The target population consisted in all beneficiaries of the NHS residing in the territorial units collaborating in the project aged 65 years or older. From this population, individuals hospitalized for CVD were selected between 2008 - 2010 and the date of the last hospital discharge during this period was defined as the date of cohort entry. CVD at cohort entry was defined as a hospitalization with primary or secondary diagnosis of HF (ICD-9 codes 428.*, 402.01, 402.11, 402.91), cerebrovascular disease (ICD-9 codes 430.*-438.*), arrhythmia (ICD-9 codes 427.*, 785.0) or ischemic heart disease (ICD-9 codes 410.*-414.*).

Patients were excluded from the cohort if in the two years before the date of cohort entry, i) received at least an antineoplastic prescription (ATC code L) or were hospitalized for cancer (ICD-9 codes 140.*-239.*) to exclude patients with very severe clinical conditions and ii) were not covered by the NHS assistance to ensure to have enough information for the wash-out period. Moreover, patients with less than 6 months of follow-up were excluded from the analyses.

In the third study, we also excluded subjects who in the previous two years had at least one record of antiarrhythmic drug prescription or hospitalization for arrhythmia. Then, individuals who received AD drug prescriptions in the previous two years were not considered, such as for the fourth study. Moreover, in the fourth study, individuals who received at least one prescription of AD within one year after the index hospitalization, were considered eligible to enter the cohort. In the fourth study, the exclusion criteria were considered for the three previous years to cohort entry.

In the second and third study, the first CV hospital admission occurred during observation time was defined as the index hospitalization, while in the fourth study the date of death was considered as the index date.

The patients included in the final cohort were followed from the cohort entry date until the earliest of the following events: the outcome (the first hospital admission for CVD or date of death), death, emigration, onset of cancer or the end of follow-up defined for each unit by the end of data availability (Caserta 31/12/2012; Lazio 30/06/2011; Lombardy 30/11/2012; Treviso 31/12/2014; Tuscany 31/12/2012).

STUDY DESIGNS

Cohort studies

A commonly used epidemiologic study design is the cohort design. This study design is used to assess the incidence of a disease under study and to evaluate the relationship between a certain exposure and the outcome of interest, in particular when the exposure is rare. This design implies the selection of a sample of the study population (a cohort) sharing a defined characteristic, disease-free at study entry. The subjects included in the cohort are, then, followed for a certain time period. During this time frame, the outcome occurrence is evaluated. The end of follow-up period is defined as the earliest occurrence among date of outcome occurrence and the dates of death, migration, end of data availability [143, 144]. The analysis could be realized when the question of interest is clear and correctly formulated, considering the nature of the outcome or measure of disease occurrence, the nature of the exposure term and the variables of interest [145].

The choice of the cohort depends on the hypothesis under investigation. Moreover, factors that need to be considered in the analysis involve characteristics of individuals and the exposure, its duration and intensity [143]. Two groups of subjects are selected, namely exposed and unexposed to a certain factor, usually a disease risk factor, and the incidence of the disease is compared between both groups. The incidence of the disease in the exposed group could be compared with that of a group of unexposed subjects (e.g. smoker vs non-smokers) or with a group of subjects with a different level of exposure (e.g. heavy smokers vs light smokers). Exposed and unexposed groups should share various characteristics with respect to the distribution of all factors that could be associated with the outcome of interest, not considering the exposure under investigation. Moreover, exposure could be evaluated as time independent or time dependent [146]. Time-independent exposure is defined without taking into account its variability during time and it is usually measured at cohort entry, while the time-dependent exposure is measured during follow-up at the different time point to allow the assessment of the exposure modification during follow-up. However, if exposure changes over time, the use of time fixed exposure may introduce bias in the association estimate [146].

The advantages of cohort studies application regard the evaluation of multiple outcomes after a single exposure as well as the possibility to evaluate rare exposures. Then, these studies could assess the temporal relationship between exposure and onset of disease and allow to directly

measure the presence of the disease among exposed and unexposed group. However, cohort studies are not ideal to be employed if there are rare outcomes or events, which take a long time to develop. The problem could be overcome with the selection of a highly exposed group of people as the study population.

Nested case-control design

For the evaluation of AD treatment and the onset of CVD, two different designs have been applied: the nested case-control design and the case-crossover design. The nested case-control design could answer to the question "Why them?" (or why these subjects were chosen as cases compared to other individuals who did not?) while the case-crossover design may answer to the question "Why now?" (or why these subjects become cases on that day compared to the previous days? [147]).

The idea of case-control analysis was introduced in 1977 [143]. The nested case-control design could be defined as prospective observation of the cohort and a retrospective investigation of exposure before the manifestation of the event of interest. The use of nested case-control design implies three steps.

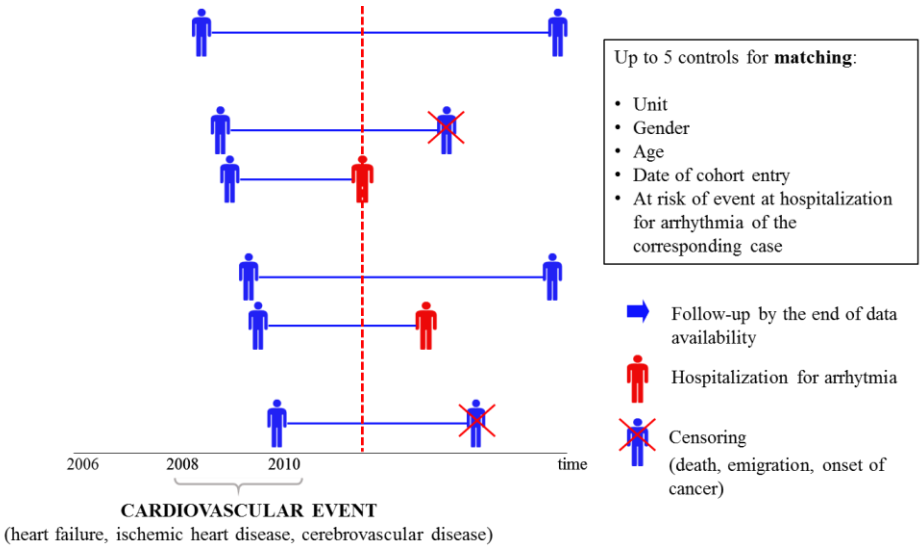
In the first step, the cohort of subjects characterized by certain conditions (i.e. CVD hospitalization) is defined and these individuals are then followed from the cohort entry date.

The second step regards the identification of cases, subjects who showed the event during observation time.

The third step, concerns for each case, a specified number of controls who are selected among the members of the cohort, still at risk of event at the time of the failure of the correspondent case. It is common to find five controls who are matched with each case, as confirmed by nested case-control literature. In this way, each case is matched with a certain number of controls, obtaining the so-called "risk set". Another important aspect of this design regards time-matching, whether controls are matched to cases on age, date of entry into the cohort, length of time in the cohort, or a combination of these measures. Moreover, a control may become a case later in time as well as the same cohort member could be selected more than one time as a control. Once the cases and matched controls are selected, the exposure is assessed at cohort entry or retrospectively in a time period equal for cases and matched control.

Several advantages characterize the nested case-control design. First, controls are part of the same population of cases. Second, this type of studies is relatively inexpensive to be performed and limited time for the elaboration of the analysis is required. Third, data on exposure are previously collected respect to diagnosis of disease, thus eliminating the possible introduction of recall bias [148]. Fourth, the matching among controls and the correspondent case allows obtaining several risk-sets approximately homogenous among themselves. Comparisons are more believable because controls result to be more similar to the correspondent case [149]. Moreover, matching is

used for the controlling of the confounding variables, like age, gender, age at cohort entry. In this case, it will not be possible to evaluate the effect of these variables, because matching could completely remove the bias potentially introduced by these confounding variables.



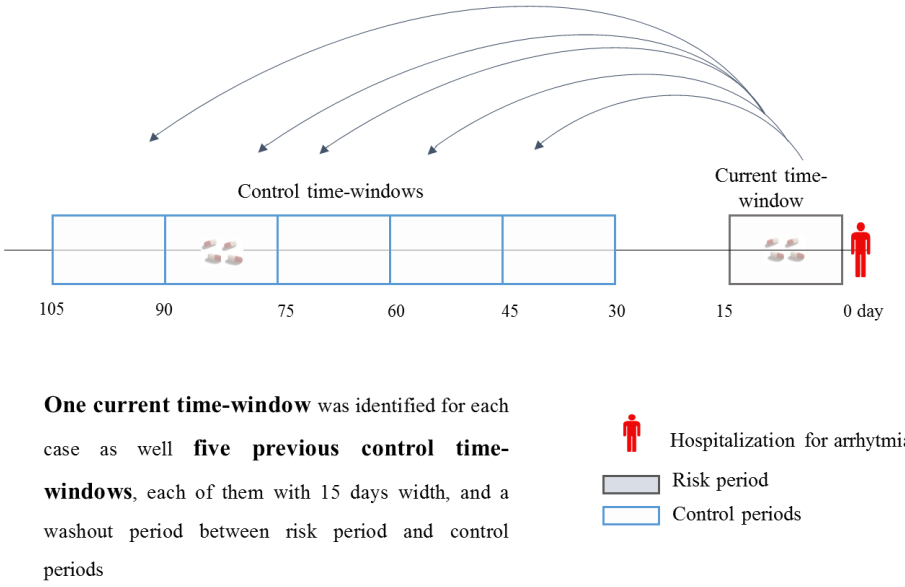
Above there is a graphical example of the nested case-control study. A certain number of controls are selected and matched with a case (e.g. hospitalized for arrhythmia), if they are still at risk of event at the time of the failure of the correspondent case, by obtaining the so-called “risk set”.

Case-Crossover Design

The case-crossover study design was first proposed in 1991 by Maclure [150]. The case-crossover design is a case-only design where the analysis is restricted to cases or subjects who experienced at least an event during the observation time.

The case-crossover study design was developed in order to assess the relationship between transient exposure and acute outcomes, considering the case as his own control. Difference in exposure rates before an event (case) with those at different time points in the history of the same individual (controls) are used to estimate the association between exposure and outcome.

This design requires strong assumptions, such as the transient exposure having a stable prevalence over time or the same opportunity to be exposed or not during the control and the risk period. Indeed, bias could be introduced in the presence of trends in exposure among the source population. If the risk period is more covered by exposure than the control period [151], this will influence the association among the drug treatment with the onset of the acute outcome, generating a noncausal association [152, 153]. The advantages of the design regard the choice of the controls which is limited to the cases, so reducing the selection bias and the control of unmeasured time-invariant confounding which do not change over time [154], or factors which are not recorded in healthcare databases [151]. However, case-crossover studies are not able to account for time-varying confounders that may not be captured by the administrative database and this could introduce bias in the estimates. Then in case-crossover design, the evaluation of exposure will be dependent on the distribution over time of drug prescriptions as well as by the choice of the window's length.



One current time-window was identified for each case as well **five previous control time-windows**, each of them with 15 days width, and a washout period between risk period and control periods

Above there is a graphical illustration of the case-crossover study, where the time window correspondent to the risk period of the case (e.g. hospitalized for arrhythmia) is used to analyze the drug exposure compared to five control periods. A major number of control periods could be chosen in order to increase the precision of the estimates and the power of the study.

For the evaluation of AD treatment and the onset of CVD, both nested case-control design and the case-crossover design were applied.

STATISTICAL ANALYSIS

Conditional Logistic Regression Model

Conditional logistic regression could be applied to estimate the parameters β in a stratified logistic regression model and it is usually used in nested case-control studies where a case is matched to 1 or more controls. Each stratum is composed by n_1 cases and n_0 controls and we could suppose to know the values $x_1,...,x_n$ of the exposure for the $n= n_1 + n_0$ subjects, without knowing which of the values are associated with the cases and which with the controls. The conditional probability of the observed data could be written as a product of terms

$$\frac{\prod_{j=1}^{n1} exp\ (\sum_{k=1}^{K} \beta_k x_{jk})}{\sum_{|} \prod_{j=1}^{n1} exp\ (\sum_{k=1}^{K} \beta_k x_{1jk})}$$

where | included the $\binom{n}{n1}$ number of possibility to assign the definition of case to a certain individual n_{1k} subjects among the n_k subjects. For the kth stratum, the conditional likelihood could be translated into the probability of the observed data conditional on the stratum total and the total number of cases observed.

In the case of a single binary exposure variable x, which is defined as x=0 for unexposed and x=1 for exposed, it is possible to calculate the total number of exposed in the stratum.

The conditional likelihood is obtained for a case-control study involving cases, controls and the conditioning event being the n observed exposure histories. If strata contain a great number of cases and controls, it is not possible to perform the calculation, thus the conditional approach is restricted to matched case-control design or by applying a stratification in order to avoid biased estimates.

Considering a particular design where each case is matched to one or more controls, the number of controls could be a fixed number M or could vary among the sets. With $x_{i0}= (x_{i01},...,x_{i0k})$, the exposure vector for the case could be identified as well as by $x_{ij}= (x_{ij1},..,x_{ijk})$, the exposure vector for the j^{th} control is identified within the i^{th} stratum ($j=1,..M_i$), where x_{ijk} represents the value of the k^{th} exposure variable for the case (j=0) or for the j^{th} control in the i^{th} matched set. The conditional likelihood could be written as [143]

$$\prod_{i=1}^{1} \frac{exp\left(\sum_{k=1}^{K} \beta_k x_{i0k}\right)}{\sum_{j=0}^{Mi} exp\left(\sum_{k=1}^{K} \beta_k x_{ijk}\right)} = \prod_{i=1}^{1} \frac{1}{1 + \sum_{j=1}^{Mi} exp\left(\sum_{k=1}^{K} \beta_k (x_{ijk} - x_{i0k})\right)}$$

If the x are matching variables and they have the same value for each member of a matched set, their contribution to the likelihood is zero and the correspondent β may not be evaluated. Indeed, matched analysis could not analyze the parameter related to the matching variables. Moreover, if a case and matched controls are characterized by common covariates, then the stratum will not "participate" to the estimation of the coefficients for any value of β. In particular, each covariate should be associated with a different value of at least one control compared to the correspondent case otherwise the stratum will not give additional information for that coefficient. It is possible to obtain the Odds ratios (ORs) of the association between exposure and outcome as $OR = e^{\beta}$. This measure of association evaluates how much the outcome is more frequent or not among exposed subjects (x=1) compared with unexposed (x=0). For example, the OR for the association between AD use and risk of arrhythmia is equal to 2, it indicates that the risk of arrhythmia is twice as likely to occur among subjects who are exposed to AD therapy compared to unexposed individuals [155].

Cox proportional hazard model

Survival analysis include various steps for the analysis of an outcome of interest, which regards time-to-event, or time until the occurrence of a certain event, where "time" could mean years, months, weeks or days of survival or the age of an individual when an event happens while "event" could mean the outcome of interest. Thus, survival refers to the survival of a subject up to a certain time period, like the occurrence of an event during observation time.

In any survival analysis, it is important to evaluate the presence of censored observations, which may occur when the individual: i) is not affected by the event before the study ends, ii) is lost to follow-up during the observation time, iii) withdraws from the study because of death, the event of interest or other reasons (like adverse events subsequent to drug treatment). The observation time of all individuals is usually right censored, because the exact survival time is not known, giving an observed survival time which is shorter than the true survival time. In general, censored subjects should be representative of all the subjects of the study who remained at risk at time t. However, bias may be introduced in the case of nonindependent censorship, for example when individuals are censored due to the occurrence of adverse events. These subjects will not be representative of the remaining cohort because they are more vulnerable to the occurrence of adverse events.

In general, if the hazard function is constant with time, i.e., $h(t)=\lambda$ for some specific value λ, the survival function could be obtained as follows $S(t)=e^{-\lambda t}$.

The relationship between S(t) and h(t) could be written as

$$S(t) = \exp[-\int_0^t h(u)du]$$

and

$$h(t) = -[\frac{\frac{dS(t)}{dt}}{S(t)}]$$

The first formula indicates the survival function S(t) in term of an integral which includes the hazard function or the exponential of the negative integral of the hazard function between integration limits of 0 and t. The survival function gives the probability that a random variable for an individual's survival time could exceed the specified time. The second formula shows how the hazard function could be evaluated in terms of derivative involving the survivor function, or equals to minus the derivative of S(t) compared to t divided by S(t). Thus, the hazard function provides

the instantaneous potential per unit time for the occurrence of the event considering the survival up to time t.

In 1972, Cox [156] introduced a regression technique suitable to model time to event data, namely the Cox proportional hazard model, commonly used in the analysis of data deriving from cohort studies.

The Cox proportional hazard model is usually reported as a formula referred to hazard model or

$$h(t, X) = h_0(t) e^{\sum_{i=1}^{p} \beta_i X_i}$$

as an expression of the hazard model at time t for a subject with certain explanatory variables denoted by X or a "vector" of variables modeled to predict an individual's hazard, through the multiplication of two terms. The first corresponds to the baseline hazard function h0(t) while the second concerns the exponential expression to the linear combination of the explanatory X variables. The assumption of the proportional hazard model is that i) censoring is not informative, ii) the ratio between the hazard function is constant over and iii) there should be a linear relationship between the log hazard and each covariate. If the variables' vector is time-dependent, the model will not satisfy the proportional hazard assumption. Moreover, the second term should never give negative estimated hazard, but it should range between zero and plus infinity [157]. Although the baseline hazard part of the formula is an unspecified function, the Cox model could be applied to estimate the vector of explanatory variables of interest or the exponential part of the model. Indeed, the measure of interest or the hazard ratio could be calculated without the specification of the baseline hazard function.

The estimates of the parameters included in the Cox formula are called maximum likelihood (ML) estimates $\hat{\beta} i$. As observed in the logistic regression model, the ML estimates of the Cox model parameters are obtained by maximizing a likelihood function, noted as L. The likelihood function is a mathematical expression, and represents the joint probability to observe certain data as a function of the unknown parameters considered in the model or L(β).

The likelihood of the Cox model is called partial likelihood function because it considers the probabilities of those subjects who exhibit the event, and not evaluating the probabilities of individuals who are censored. However, if a subject is censored after a certain f-th failure time, the individual will be included in the risk set to evaluate the partial likelihood at that f-th failure time. The partial likelihood is evaluated on the basis of the product of several likelihoods, for each

k failure times. L_f elaborates the likelihood of failing at each f-th failure time, considering survival up to this time [157]. The set of subjects at risk at the j-th failure time is called as "risk set" which could change or become smaller when the failure time increases.

$$L = L_1 \, x \, L_2 \, x \, L_3 \, x \, \ldots x \, L_k = \prod_{j=1}^{k} L_j$$

with k= number of failure times

Then, the likelihood function could be maximized through its natural log and the process of maximization continues with the partial derivatives of the log of L respect to each parameter of the model, and subsequently by solving a system of equations.

The hazard ratio (HR) is defined as the ratio between the hazard of an individual h(t,X*) respect to the hazard of another one h(t, X), where X* and X are referred to the set of predictors of the two compared individuals.

$$\widehat{HR} = \frac{\hat{h}\,(t, X^*)}{\hat{h}\,(t, X)} = \frac{\hat{h}_0(t) e^{\sum_{i=1}^{p} \hat{\beta}_i X_i^*}}{\hat{h}_0(t) e^{\sum_{i=1}^{p} \hat{\beta}_i X_i}} = e^{\sum_{i=1}^{p} \hat{\beta}_{i(} X_i^* - X_i)}$$

Thus, $\widehat{HR} > 1$ when $\hat{h}\,(t, X^*) > \hat{h}\,(t, X)$, means that the group with the larger hazard are related with X^* or the comparison group, while the group with the smaller hazard is associated with X or the treatment group. At last, the hazard ratio formula will be the exponential of the sum of each β_i "hat" times the difference between the two set of explanatory variables [157].

Thus, the exponential expression for the HR should correspond to a constant value, which does not depend on time and respects the proportional hazards assumption.

METHODS FOR BIAS CONTROL

Monte Carlo Sensitivity Analysis

Considering observational studies, the association between exposure and outcome could be influenced by the presence of measured and unmeasured confounders. In particular, the issue of unmeasured confounders is particularly relevant when the data sources are the HCU databases that lack of several clinical and lifestyle information such as BMI, smoking status, socioeconomic status, that could influence the exposure-outcome relationship under study. A confounding factor is a variable associated with both exposure and outcome [158] that influences the observed association measure. Thus, some additional analyses, called sensitivity analyses, were proposed to estimate the impact of unmeasured risk factor (confounder) on the results [158, 159]. The idea of sensitivity analysis and external adjustment for confounding by dichotomous variables was firstly introduced by Cornfield et al [160]. Sensitivity analysis (SA) is a useful approach to evaluate the real association between exposure and event, considering the presence of confounders [161]. For example in our study, for the evaluation of the association between AD exposure and the onset of CVD, we considered as an unmeasured confounder, the smoking status, whose information is not included in the administrative database.

It is first necessary to quantify the bias introduced in the exposure-outcome estimate caused by the omission of the unmeasured confounder. We could consider that the observed association measure, for example the relative risk (RR), called Apparent Relative risk (ARR), of the relationship between exposure and outcome is given be the true RR (RRed) and a certain bias introduced by the unmeasured confounder (Bias) as follows

$$ARR=RR_{ed} \times Bias$$

ARR corresponds to the relative risk adjusted for all measured confounders, excluding the unmeasured confounders. However, if measured and unmeasured confounders are correlated, this means that residual confounding caused by unmeasured factors will be reduced or partially adjusted [158].

The bias factor depends on the prevalence of the confounder among exposed and unexposed subjects, and on the degree of association between the unmeasured confounder and event (RR_{ce}).

Considering a dichotomous exposure and a categorical confounding variable, the bias factor may be quantified as follows.

$$Bias = \frac{\sum_{i=1}^{k} p_{1ci} * RR_{cie}}{\sum_{i=1}^{k} p_{0ci} * RR_{cie}}$$

where k represents the number of levels of the unmeasured confounders, p_{1ci} the proportion of subjects affected by the level of the confounder among the exposed, p_{0ci} the proportion of subjects affected by the level of the confounder among the unexposed and RR_{cid} the association measure between the confounder and the event under study.

This formula includes a weighted average regarding the effect of the confounder on the onset of the event among exposed subjects' strata compared to the weighted average among unexposed subjects' strata.

Therefore, it is possible to calculate the unmeasured confounder adjusted RR as

$$RR_{adj} = \frac{ARR}{Bias}$$

To account the uncertainty of external information, which are used to perform a SA and to evaluate the variability of the unmeasured confounder adjusted RR, a Monte Carlo procedure was added to the ordinary SA. SA method was extended to a Monte Carlo Sensitivity Analysis (MCSA), introduced by Steenland and Greenland [159]. MCSA compares a number of randomly sampled confounding scenarios to repeatedly estimate the bias factor and to quantify the robustness of the main analysis in the presence of unmeasured confounders. A simplicistic assumption regards the independence among measured and unmeasured confounders respect to exposure status, otherwise if they are associated, the bias will be overestimated [162].

First of all, it is necessary a prior assignment distribution of i) the different proportion of the confounder among the exposure's level, ii) the measure of association between confounder and event and iii) the measure of association between exposure and event, which is estimated by the main study. Each time a bias factor is constructed and then used to adjust the observed RR. Then, a normal approximation of their logit form needs to be assessed. The sampled logit is converted back to the proportions using the conversion formula: $1/(1+e^{-logit})$, obtaining $P\bar{e}c=1-Pec$ and $P\bar{ec}=1-P\bar{e}c$ [159]. The mean, the 2.5th and 97.5th percentiles of such distribution will be

considered respectively as the new-confounder-adjusted measure of association and corresponding 95% CIs [163]. Thus, MCSA provides a distribution of the association between exposure and outcome which depends on the input distributions. When the prior information is less precise, the bias distribution will lead to wider intervals [159].

The main difficulty of MCSA approach, for the adjustment of an unmeasured confounder at a time, regards the identification of the prevalence data regarding the confounder level among exposed and unexposed, which is obtained by validation study or more easily by scientific literature, through the identification of a comparable study about population definition and categories of exposure.

At last, the analysis of unmeasured confounders should be accounted to reduce the risk of bias, especially considering epidemiological or health research.

New user design

In a new-user design, patients who start a certain therapy with the study medication are selected [164, 165]. The identification of new users is based on the same time period of exposure during which the therapy may cause the outcome.

There are several advantages related to the new user design. First, it could eliminate the immortal time bias, because exposed person-time starts at the beginning of the therapy, which is identified after the exclusion of subjects who already received that treatment in the previous years [164, 166]. Consequently, the selection of new users may reduce the bias otherwise introduced if prevalent users are considered in the analysis, such as i) due to the fact that prevalent users may be less susceptible to the onset of the event [166]; ii) the modification of eventual disease risk factors' levels during drug treatment; iii) a better adherence to therapy. Second, new user design could identify effects which occur shortly after the initiation of the therapy compared to studies that include prevalent users [166], which mostly under-represent events happened immediately after the start of the therapy [164].

On the other hand, some limitations could be found in the application of new user design. First, the limited time of observation could reduce the possibility to check a decrease in the risk of disease. Second, differences in the estimates could be due to the indication used to define incident users. For example, newly marketed drugs, which are analyzed in the study, may have produced distorted results compared to drugs already introduced in the market and under study that could be better tolerated by patients. Third, new user design focuses the analysis on patients at the initial stage of the therapy or with a lower degree of disease severity, so reducing the power in terms of generalizability to the entire community setting. Restriction to incident users could reduce the sample size of the study and the precision of the final estimates [166]. Thus, large source populations like healthcare utilization databases may be needed to identify new users [167] or a multi-site study could be required to analyze a sufficient number of events of interest [166].

OTHER EVALUATIONS

Polypharmacy

Polypharmacy is a term introduced for the first time by the medical literature more than 150 years ago [168] and WHO defined it as “the administration of many drugs at the same time of an excessive number of drugs” [169]. Among elderly, polypharmacy or multiple medications [144] is considered appropriate in the presence of concomitant pathologies, like chronic pathologies [170], or in complex medical situations, otherwise the medications could be inappropriately prescribed [171]. Sometimes the term “polypharmacy” is confused with the concept of inappropriate prescription [172] and for this reason criteria that may define “potentially inappropriate” drugs were introduced [173-175].

In general, polypharmacy seems to be associated with multiple diseases (such as diabetes mellitus, CVD and respiratory diseases [176, 177]) and may be typical of elderly patients [176, 178, 179]. With aging, physiological changes of metabolism may occur, caused by modification of pharmacokinetic and pharmacodynamic parameters [180-182], and difficulty to follow a complex treatment regimen, due to a decline in cognitive abilities [183, 184]. Thus, clinicians should consider the state of old people which means their age, the number and type of drugs assumed, the presence of chronic disease and eventual adverse events during their hospitalization [182].
There are different thresholds to define polypharmacy. In general, the “more than 5 medications” threshold could be denominated as “non-polypharmacy” [185] or “oligopharmacy” [186] while the “more than 10 medications” threshold may correspond to “hyperpolypharmacy” [187] or “excessive multi-medication” [179, 188, 189].

Strategies to reduce the level of polypharmacy could involve the development of new therapies, the increase in the use of preventive strategies and medical guidelines, in order to improve the quality of care for elderly patients [190, 191]. Moreover, prescriptions of drugs should be better adapted depending on the range of ages [184].

RESULTS

I Study

Use of antidepressants and the risk of cardiovascular disease: a meta-analysis

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Abstract

Purpose: To systematically review studies quantifying the associations between antidepressants (ADs) use and the risk of cardiovascular (CV) outcomes.

Methods: Medline, searched to October 2015 for full text articles in English. Prospective cohort and case-control studies were admitted they investigated the relationship between current use of ADs as a whole, Tricyclic Antidepressants (TCAs) or Selective Serotonin Reuptake Inhibitors (SSRIs), and the onset CV events. Summary Relative Risks (RRs) with confidence intervals (CIs) were calculated using random-effects or fixed-effects models.

Results: A total of 100,067 incident cases of CV outcomes who met inclusion criteria were identified from 22 observational studies. Compared with no users of ADs, use of SSRIs was associated with an increased risk of cerebrovascular disease (RRs, 1.24; 95% CI, 1.15 to 1.34) while the use of TCA was associated with an increased risk of acute heart disease (RRs, 1.29; 95% CI, 1.09 to 1.54).

Conclusions: Weak and inconclusive evidence for the effect of SSRIs and TCAs on the risk of selected CV outcomes was obtained from this meta-analysis. We need high quality studies for throw light upon this issue. Weak evidence should not be accepted as a basis for definite conclusions that determine clinical practice.

Key words: Depression; Antidepressants; Tricyclic Antidepressants; Selective Serotonin Reuptake Inhibitors; Stroke; Cardiovascular Disease; Cerebrovascular Disease

Introduction

Due to its high worldwide prevalence, depression is a serious public health concern. Currently, it is estimated to affect over 350 million people worldwide and a quarter of the European population [192]. Adequate treatment of depression must be considered as a compelling public health intervention to reduce the burden of avoidable morbidity, disability, and mortality.

Antidepressant Drugs (ADs), developed since 1950s to treat depressive symptoms, are nowadays widely available with several treatment options. Tricyclic Antidepressants (TCAs), and Selective Serotonin Reuptake Inhibitors (SSRIs), are the most commonly prescribed ADs. Despite their similar effectiveness, however, SSRIs have in part replaced TCAs since their better tolerability [193].

In particular, TCAs have shown to be related with systemic inflammation which may lead to an increased risk of cardiovascular (CV) disease [71, 194-201] and, in particular, MI [194, 197, 201, 202], ventricular arrhythmia [194, 195, 203-205] and fatal cardiac events [206]. On the other hand, although SSRIs may reduce the risk of thrombotic events, their antiplatelet action and arterial vasoconstriction may increase the risk of stroke [88, 93]. However, the role of ADs in the onset of CV disease is still controversial, since inconsistent findings have been reported [94, 95, 200, 207-211].

It should be empathized that ADs are among the most commonly prescribed drugs worldwide [212] and CV disease is the first leading cause of mortality [213]. Therefore, effort aimed at elucidating the role of ADs on the onset of CV disease has major implications for public health. With these premises, and to provide a synthesis of the available scientific literature on this issue, we performed a meta-analysis of observational studies concerning the association between use of ADs and the onset of CV diseases. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed for designing and reporting the current investigation [214].

Materials and methods

Search strategy and study selection

We carried out a MEDLINE search for observational studies published up to October 2015 which investigated the association between use of ADs and CV disease. The following keywords and/or corresponding MeSH terms were used: ("TCAs + single active ingredients" OR "SSRIs + single active ingredients" OR "antidepressant") AND "cardiovascular disease subtypes" ("ischemic heart disease" OR "cerebrovascular disease" OR "other forms of heart disease"). Reviews and meta-analyses reference list published on this issue were hand-checked to identify additional relevant publications [88, 93, 200]. Search was limited to studies published in the English language.

Cohort and case-control studies were included if: (a) they reported as exposure current use of ADs as a whole, TCAs and/or SSRIs; use of other antidepressants was not considered in this meta-analysis; (b) the exposure was contrasted with no use of any ADs; other comparators (i.e. studies contrasting SSRIs vs TCAs users) were no considered in this meta-analysis; (c) CV events (including stroke, transient ischemic attack, ischemic and/or haemorrhagic stroke, myocardial infarction, ischemic heart disease, coronary heart disease and sudden death) were the outcomes of interest; studies investigating CV events as a whole were no considered in this meta-analysis; (d) they reported crude or adjusted estimates of the association between exposure and outcome (that is, relative risk, odds ratio, hazard or rate ratio, and the corresponding 95% confidence interval) or sufficient data to calculate them. When data were published more than once, the most recent and complete publication was considered. Papers which did not report original findings (i.e., letters, case report, systematic review and meta-analysis) were excluded. Two readers (AB and LS), independently determined the eligibility of each article for inclusion. Discrepancies between readers were resolved in conference.

Data collection and quality assessment

The same readers subsequently evaluated several characteristics of each included study (design, country, publication year, exposure of interest, investigated outcomes, adjustment and stratification variables, number of cases, relative risk (*RR*), or other association measures, and the corresponding 95% confidence interval (CI) or p-value) and scored the quality of the eligible studies according to the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized study in meta-analysis [215]. High-quality studies were defined as a score 6 or more of 9 total points.

Statistical analysis

The summary relative risk measuring the strength of the association between use of ADs as a whole, or TCAs or SSRIs, each contrasted with no use of ADs, and the risk of a given CV outcome was calculated, the latter being (1) acute heart disease, including coronary heart disease, acute myocardial infarction, ischemic heart disease, and sudden death; (2) cerebrovascular disease, including stroke and transient ischemic attack; (3) haemorrhagic stroke; and (4) ischemic stroke. Estimates were summarized if at least three studies reported the exposure-outcome association of interest. Where possible, we pooled adjusted estimates from the original studies; otherwise we used raw data and computed unadjusted summary relative risk.

Heterogeneity between study-specific estimates was tested using chi-square statistics [216] and measured with the I^2 index (a measure of the percentage variation across the studies caused by heterogeneity) [135]. We pooled the original estimates by fitting both fixed-effects and DerSimonian & Laird random-effects model [217]. When a significant heterogeneity was found, the results from the random-effects model were presented.

Publication bias was evaluated through funnel plot visual analysis and the Egger's test [218]. Finally, in order to identify to what extent the results were influenced by a single study, an influence analysis was conducted by omitting one study at a time.

All tests were considered significant statistically, for p-values less than 0.05. The analyses and the correspondent graphical visualization of forest and funnel plots were respectively performed by using RevMan Version 5.1 (Nordic Cochrane Center) and STATA Software Program Version 9 (STATA, College Station, TX).

Results

Fig. 1 shows the flow diagram for the study inclusion. Based on title and abstract, 1,058 papers were identified. We excluded 717 of them because they were unrelated to the issue according to title and/or abstract, 180 because they were no written in English, and further 144 because they did not satisfy the inclusion criteria. After the review of the references of other meta-analyses on this issue, 10 additional papers were included in our study. The remaining 22 studies met the inclusion criteria [94, 95, 97, 193, 194, 197, 211, 219-233] and were considered for the analysis. **Table 1** shows the main characteristics of the included studies. They were 10 cohort- and 12 case-control investigations together including 100,067 incident cases of CV outcomes, and specifically investigating acute heart disease (16 studies), cerebrovascular disease (6 studies) and/or ischemic and haemorrhagic stroke (3 studies). Only few studies (1 or 2) reported estimates on other CV outcomes (i.e., angina, arrhythmias and heart failure); therefore, they were not suitable for the calculation of the summary estimates. Twenty of the 22 included studies had NOS scores of 6 or greater and were so assigned to the category of high quality studies (**Supplementary Table S2-S3**).

Antidepressants as a whole

Fig. 2 shows the investigated effects of ADs on the risk of acute heart disease. Overall, 5 studies and 65,331 cases were included. However, because the study from Whang et al [233] reported separate estimates for myocardial infarction, coronary heart disease and sudden death, summary relative risks pooled 7 effects. Among these, 6 found increased risks, 4 of them being significant. The summary *RR*, however, did not reach significance 1.35 (95% CI, 0.90 to 2.02). Between-study heterogeneity was significant and numerically relevant (I^2 = 92%). There was no evidence of publication bias (**Supplementary Fig. S1**). However, that the summary effect was strongly influenced from the study of Surtees et al [231], being the summary RR (1.67; 1.27 to 2.19) strongly modified when omitting it (**Supplementary Table S1**).

Selective Serotonin Reuptake Inhibitors

The investigated effects of SSRIs on the risk of acute heart disease (83,765 cases, 14 studies), cerebrovascular disease (9,754 cases, 6 studies), haemorrhagic stroke (1,054 cases, 3 studies) and ischaemic stroke (4,281 cases, 3 studies) are shown in **Fig. 3**. There was no evidence that SSRI users were at higher risk of developing acute heart disease, but significant and numerically relevant (I^2 = 85%) between-study heterogeneity was observed. In addition, there was evidence of publication bias for the considered association being either strongly asymmetric the funnel plot (**Supplementary Fig. S1**) and significant the corresponding Egger's test (p = 0.010).

Almost all the individual studies reported increasing cerebrovascular *RRs*, the summary effect being 1.24 (1.15 to 1.34). The corresponding estimates for haemorrhagic and ischaemic stroke were respectively 1.29 (0.92 to 1.81) and 1.15 (0.98 to 1.36). There was no evidence of between-study heterogeneity for cerebrovascular outcomes. However, influence analysis showed that the effect for haemorrhagic stroke was strongly influenced from the study of Bak et al [219], being the summary RR (1.63; 1.03 to 2.59) strongly modified when omitting it (**Supplementary Table S1**).

Tricyclic Antidepressants

The investigated effects of TCAs on the risk of acute heart disease (70,416 cases, 9 studies), and cerebrovascular disease (8,656 cases, 4 studies) are shown in **Fig. 4**. There was no evidence that TCA users were at higher risk of developing cerebrovascular disease. Conversely, almost all the individual studies reported increased relative risks of acute heart disease, the summary random-effect being 1.29 (1.09 to 1.54). Between-study heterogeneity was significant and numerically relevant (I^2 = 73%). There was no evidence of publication bias (**Supplementary Fig. S1**), nor of influence of any individual study (**Supplementary Table S1**) for any of the investigated effects of TCAs.

Discussion

The current meta-analysis suggests that use of antidepressant agents may increase the risk of developing selected CV outcomes. The observed relationship appears clinically relevant since we estimated that use of SSRIs was associated with a 24% significant increase in the risk of cerebrovascular outcomes compared with no treatment with antidepressant agents. Analogously, 29% increased risk of acute heart disease was found for using TCAs. These relationships were consistently found for almost all the included original studies, most of them reported estimates adjusted for potentially confounding variables and almost all were high quality studies. However, the strength of evidence was reduced for some of the observed findings. Indeed, between study heterogeneity was always observed for the effects of ADs (as a whole, as well as SSRIs and TCAs) on acute heart disease. Moreover, there was evidence for selective inclusion of studies reporting higher harmful effect of SSRIs on the risk of acute heart disease, e.g. of publication bias, as well as of selective exclusion of "grey literature" (e.g. PhD theses, conference abstracts, no English papers). On the other hand, there was also evidence for excessive influence of an individual study

on the summary relationship between SSRIs and haemorrhagic stroke [219], being a 63% significant increase in the risk when omitting it.

It has long been established that depression itself increases the risk of cardiovascular disease through poor health behaviours (i.e., smoking, physical inactivity, poor diet, lack of medication compliance [234]), obesity [235] and other major comorbidities, such as diabetes [236] and hypertension [237]. Most of the studies included in our meta-analysis reported adjusted estimates for these risk factors, so that their contribution in explaining the reported findings should be reasonably limited.

Depression has well known immunological/inflammation effects [238-240] and correlates with abnormalities in the autonomic nervous system, enhanced platelet reactivity, endothelial dysfunction and increased thrombus formation [241-243]. Because all these factors are implicated in the onset of CV outcomes, it is not surprising that our meta-analysis offers some (weak and no significant) evidence that treatment with ADs had higher risk of developing CV outcomes than patients who did not use of any ADs. However, given that our main findings clearly show difference in the actions of SSRIs and TCAs on the development of CV outcomes, we speculate that the observed effects are in fact the average of two underlying indistinguishable actions, that is the effect of depression *per se* and the specific mechanism of action of the individual antidepressants.

Treatment with SSRIs has been associated with bleeding complications [77, 78], likely due to the impaired haemostatic response. It is thus a major concern whether SSRIs increase the risk of haemorrhagic stroke. Inconsistently with another meta-analysis [244], our summary estimates did not found evidence of increased risk of brain haemorrhage associated with SSRIs. Furthermore, two out of three studies included in our meta-analysis which investigated this issue [219, 227], did not found differences in the action of SSRIs on the risk of haemorrhagic and ischaemic stroke.

Finally, although it is conceivable that SSRIs might reduce the risk of thrombus formation so reducing the risk of ischaemic heart and cerebral outcomes [219], we did not found evidence of beneficial effect of SSRIs on the risk of both ischaemic stroke and acute heart disease. However, we can speculate that weaknesses in our summarized effects of SSRIs are really related to the expected (1) increased risk of haemorrhagic stroke when omitting the largest (and less extensively adjusted) study among those included; (2) risk reduction of acute heart disease when accounting for publication bias.

Tricyclic antidepressants have been classified as class I antiarrhythmic drugs, a group of medications that have been associated with an increased risk of sudden death [245]. They have also been shown to increase heart rate and reduce heart rate variability [246]. In line with another meta-analysis [247], our study found increased risk of acute heart disease associated with use of TCAs.

As all meta-analyses of observational studies, our results have some limitations which mainly reflect the sources of systematic uncertainty of the observational studies included in the meta-analysis. For example, we included studies reporting estimates unadjusted (or weakly adjusted) for the known risk factors of CV outcomes [193, 231]. This likely explains most of the observed between study heterogeneity. For example, the relative risks of acute heart disease associated with use of ADs ranged from 0.21 to 5.40 respectively reported from unadjusted [231] or only weakly adjusted [228] estimates. The definition of the considered CV outcomes was not identical between studies in this meta-analysis, which may introduce systematic uncertainty in our findings. Specific drugs within the classes of ADs, as well as their duration of use, dose, substitution within the class, and pattern of starting and stopping were not considered in our meta-analysis due to the dearth of available data.

In conclusion, our meta-analysis shows some weak and inconclusive evidence for the effect of using SSRIs and TCAs respectively on the risk of cerebrovascular and acute heart outcomes. High quality studies investigating the complex interactions between depression, antidepressant treatment and CV outcomes are urgently required. Weak evidence should not be accepted as a basis for definite conclusions that determine clinical practice.

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Conflict of interest

GC received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry for University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as member of Advisory Board from Roche.

Author’s contributions

GC generated the study idea and wrote the final manuscript. AB and LS contributed to study search and selection; AB carried out the statistical analyses. All authors edited the manuscript and approved the final version.

Table 1 Chronological summary of literature on antidepressants and risk of selected cardiovascular outcomes, and their main characteristics

First author publication year, country [reference]	Design	Gender	Outcome	No. cases	Exposure	RR (95% CI)	Controlled variables/ notes
MacDonald 1996, Scotland [226]	Case-control	MW	MI	166	SSRIs	1.26 (0.63 to 2.51)	Adjusted estimates: variables not listed in the article
					TCAs	1.02 (0.70 to 1.48)	
			AG	301	SSRIs	1.36 (0.83 to 2.22)	
					TCAs	0.95 (0.70 to 1.27)	
			HF	43	SSRIs	0.56 (0.12 to 2.68)	
					TCAs	1.28 (0.71 to 2.30)	
			AR	130	SSRIs	1.61 (0.87 to 2.97)	
					TCAs	0.75 (0.50 to 1.14)	
Penttinen 1996, Finland [228]	Case-control	M	MI	83	ADs	5.40 (1.80 to 16.10)	Age; sociodemographics; smoking
Cohen 2000, US [94]	Cohort	MW	MI	207	ADs	2.20 (1.30 to 3.70)	Age; gender; psychological distress; cardiovascular risk factors; diabetes; hyperlipidaemia – obesity; hospital admission for other cause; other drugs use and number of medications
					TCAs	2.80 (1.60 to 4.70)	
					SSRIs	1.10 (0.30 to 4.30)	
de Abajo 2000, UK [224]	Case-control	MW	S	65	SSRIs	1.14 (0.53 to 2.43)	Age; sex; calendar year; smoking; BMI; hypertension-hypercholesterolemia; hospital admission for other cause; use of other drugs and number of medications
Meier 2001, UK [95]	Case-control	MW	MI	3,315	SSRIs	0.90 (0.50 to 1.80)	Age; sex; smoking; BMI
Sauer 2001, US [97]	Case-control	MW	MI	653	SSRIs	0.35 (0.18 to 0.68)	Age; gender; sociodemographics; life style; chronic medical conditions; smoking; BMI; hypertension-hypercholesterolemia;

							diabetes; number of GP visits; use of other drugs and number of medications
Bak 2002, Denmark [219]	Case-control	MW	HS	659	SSRIs	1.00 (0.60 to 1.60)	Age; gender; calendar year; use of other drugs and number of medications
			IS	2,717	SSRIs	1.10 (0.90 to 1.40)	
Schlienger 2004, UK [211]	Case-control	MW	MI	8,688	SSRIs	0.63 (0.43 to 0.91)	Smoking; BMI; cardiovascular risk factors; hypertension, hypercholesterolemia; diabetes; number of GP visits; use of other drugs and number of medications
Tata 2005, UK [193]	Case-control	MW	MI	63,512	ADs	1.43 (1.40 to 1.47)	Unadjusted estimates
					SSRIs	1.49 (1.43 to 1.56)	
					TCAs	1.41 (1.37 to 1.45)	
Chen 2008, US [221]	Case-control	MW	S	1,086	ADs	1.43 (1.21 to 1.69)	Age; gender; calendar year; psychological distress; alcohol and related illness; hypertension, hypercholesterolemia; cardiovascular risk factors; diabetes; other drugs use and number of medications; overdose-substance abuse
Surtees 2008, UK [231]	Cohort	MW	IHD	274	ADs	0.21 (0.12 to 0.35)	Unadjusted estimates
Blanchette 2009, US [220]	Cohort	MW	MI	n.a.	SSRIs	1.85 (1.13 to 3.04)	Age; gender; sociodemographics; psychological distress; socioeconomics; smoking; BMI; diabetes; calendar year; severity of depression
Smoller 2009, US [230]	Cohort	W	MI/CHD	1,703	TCAs	1.05 (0.68 to 1.62)	BMI; severity of depression; cardiovascular risk factors; diabetes; propensity score; hospital admission for other cause; use of other drugs and number of medications
					SSRIs	0.88 (0.62 to 1.24)	
			S	1,451	TCAs	1.27 (0.80 to 2.00)	
					SSRIs	1.39 (1.00 to 1.91)	
			IS	1,026	SSRIs	1.21 (0.80 to 1.83)	
			HS	271	SSRIs	2.12 (1.10 to 4.07)	
	Cohort	W	MI	814	ADs	1.21 (0.96 to 1.53)	

Whang 2009, US [233]			SD	99	ADs	3.34 (2.03 to 5.50)	Age; life style; chronic medical conditions; smoking; alcohol and related illness; BMI; hyperlipidaemia- obesity; hypertension, hypercholesterolemia; diabetes; calendar year; use of other drugs and number of medications; menopausal status
			CHD	342	ADs	1.07 (0.75 to 1.53)	
Rosenberg 2010, US [229]	Cohort	MW	CHD	147	TCAs	2.10 (1.09 to 4.06)	Age; gender; psychological distress; calendar year; use of other drugs and number of medications; Framingham risk score
					SSRIs	1.33 (0.49 to 3.64)	
Trifirò 2010, The Netherlands [232]	Case-control	MW	S	996	TCAs	1.18 (0.73 to 1.91)	Age; gender; calendar year; chronic medical conditions; hypertension, hypercholesterolemia; cardiovascular risk factors; hospital admission for other cause; use of other drugs and number of medications; opioids
					SSRIs	1.55 (1.07 to 2.25)	
Coupland 2011, UK [222]	Cohort	MW	MI	2,350	TCAs	1.09 (0.96 to 1.23)	Age; gender; smoking; cardiovascular risk factors; hypertension, hypercholesterolemia; diabetes; calendar year; severity of depression; depression before age 65; townsend deprivation score; other diseases-hospitalisation; use of other drugs and number of medications
					SSRIs	1.15 (1.04 to 1.27)	
			S	5,303	TCAs	1.05 (0.95 to 1.17)	
					SSRIs	1.21 (1.11 to 1.32)	
Coupland 2011, UK [223]	Cohort	MW	SD	84	TCAs	1.36 (0.73 to 2.53)	Age; gender; smoking; cardiovascular risk factors; hypertension, hypercholesterolemia; diabetes; calendar year; severity of depression; depression before age 65; townsend deprivation score; other diseases-hospitalisation; use of other drugs and number of medications
					SSRIs	1.21 (0.70 to 2.07)	
Hamer 2011, Scotland [197]	Cohort	MW	CHD	968	TCAs	1.24 (0.87 to 1.75)	Age; gender; life style; psychological distress; socioeconomics; marital status; smoking; alcohol and related illness; BMI; cardiovascular interventions; hypertension, hypercholesterolemia
					SSRIs	0.81 (0.49 to 1.33)	
Kimmel 2011, UK [225]	Case-control	MW	MI	693	SSRIs	0.77 (0.57 to 1.03)	Age; gender; chronic medical conditions; hypertension, hypercholesterolemia; cardiovascular risk factors; diabetes; hospital admission for other cause; use of other drugs and number of medications
Pan 2011, US [227]	Cohort	W	S	1,033	ADs	1.30 (1.08 to 1.55)	Age; sociodemographics; life style; chronic medical conditions; marital status; smoking; alcohol and related illness; BMI; hypertension, hypercholesterolemia; diabetes; cardiovascular risk factors; hospital admission for other cause; use of other drugs and number of medications; menopausal status
					SSRIs	1.39 (1.13 to 1.72)	
			HS	124	ADs	1.19 (0.69 to 2.06)	
					SSRIs	1.25 (0.65 to 2.41)	

			IS	538	ADs	1.23 (0.95 to 1.58)	
					SSRIs	1.23 (0.90 to 1.67)	
Acharya 2013, US [194]	Case-control	MW	CHD	n.a.	TCAs	0.79 (0.32 to 1.91)	Age; gender; sociodemographics; psychological distress; smoking; cardiovascular risk factors; diabetes; Framingham risk score, BMI, hypertension, hypercholesterolemia; hospital admission for other cause; use of other drugs and number of medications
					SSRIs	1.14 (0.76 to 1.71)	
			TIA	n.a.	TCAs	0.75 (0.26 to 2.10)	
					SSRIs	0.87 (0.56 to 1.36)	
			HF	n.a.	TCAs	1.13 (0.32 to 4.03)	
					SSRIs	0.86 (0.44 to 1.70)	

M: Men; W: Women

MI: Myocardial Infarction; IHD: Ischaemic Heart Disease; CHD: Coronary Heart Disease; S: Stroke; HS: Haemorrhagic Stroke; IS: Ischemic Stroke; TIA: Transitory Ischemic Attack; AG: Angina; HF: Heart Failure; AR: Arrhythmia; SD: Sudden Death

ADs: Antidepressants; SSRIs: Selective Serotonin Reuptake Inhibitors; TCA: Tricyclic Antidepressants

n.a.: not available

Fig. 1 Flow-chart of inclusion and exclusion criteria

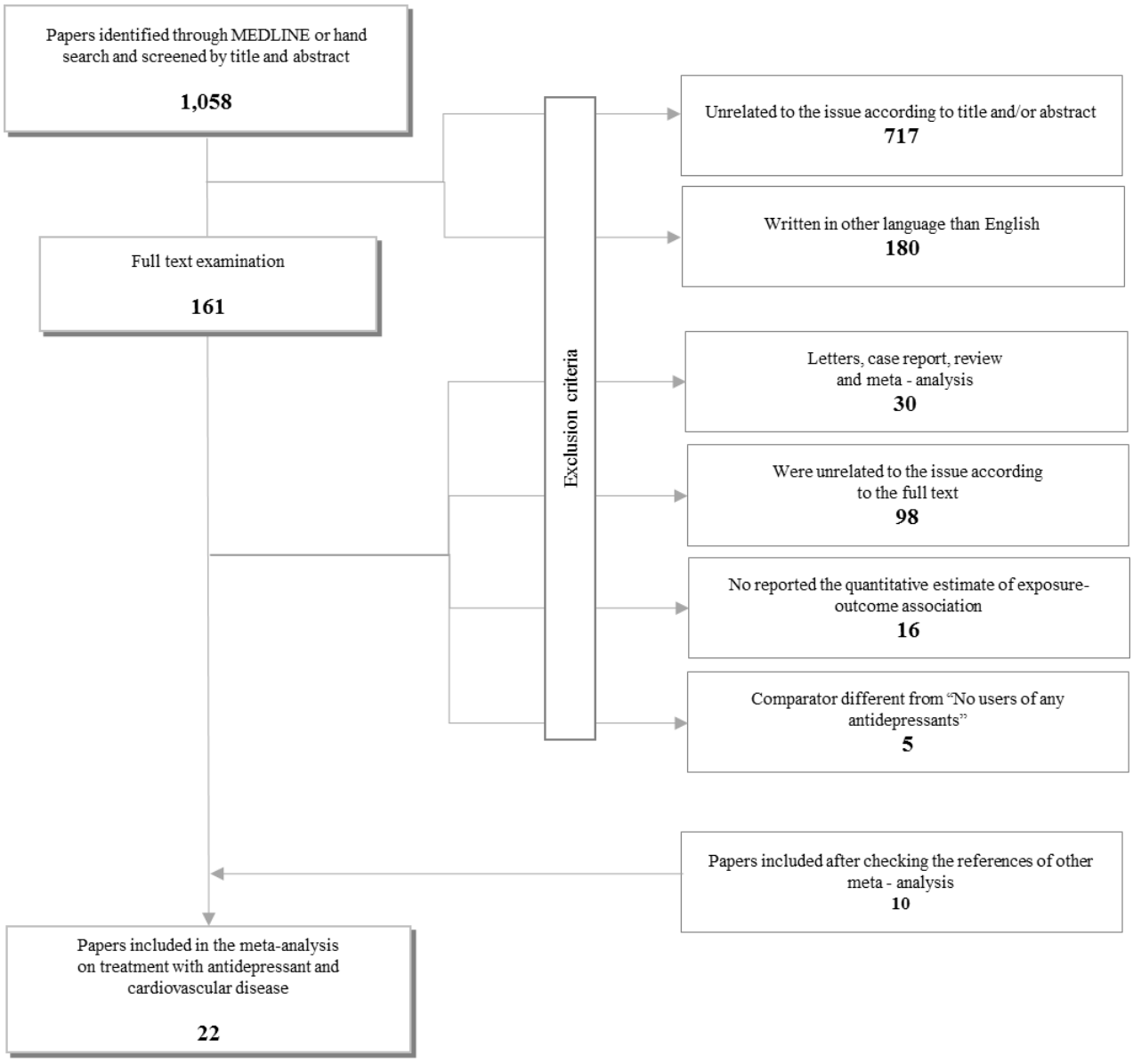
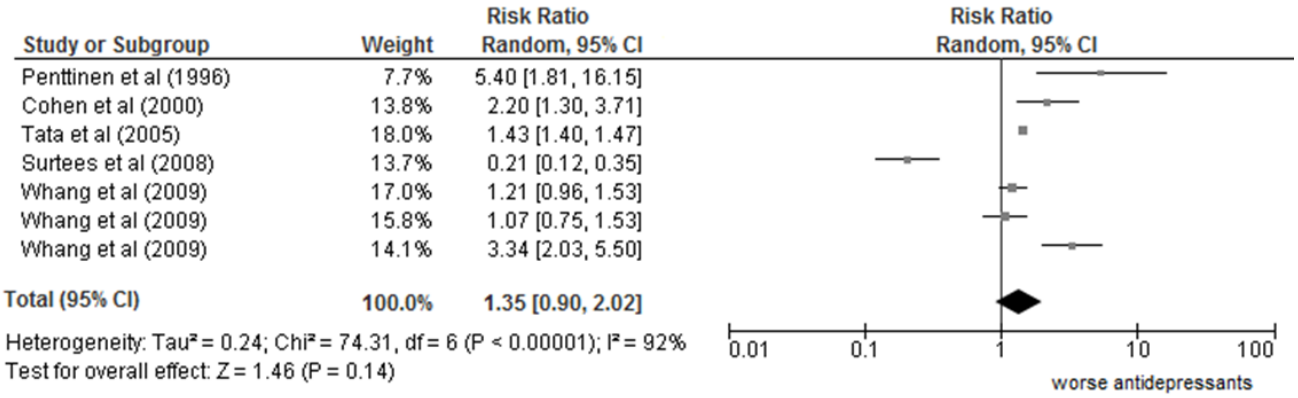
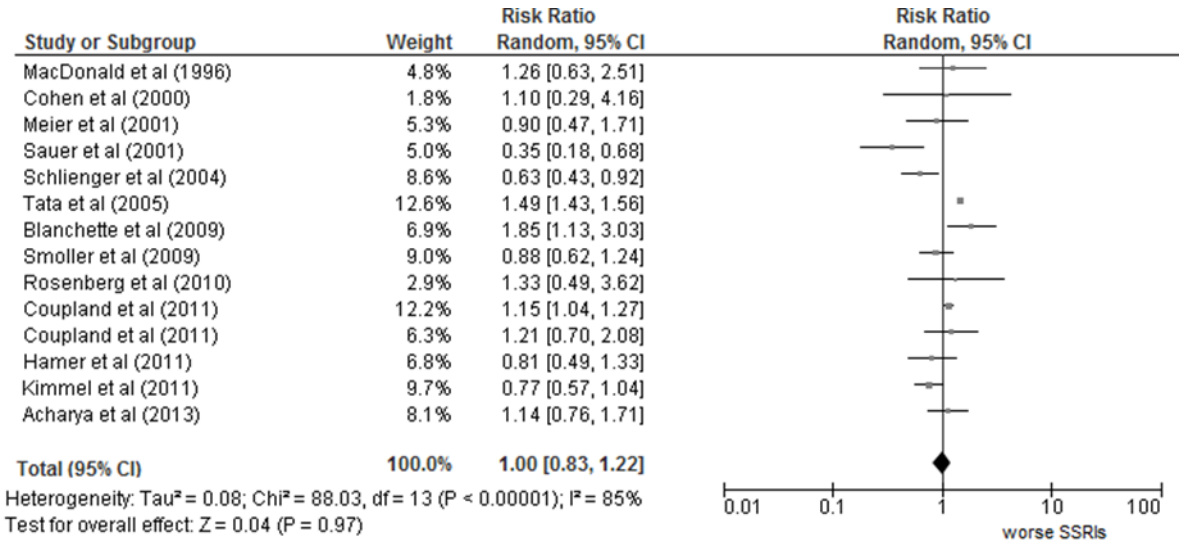


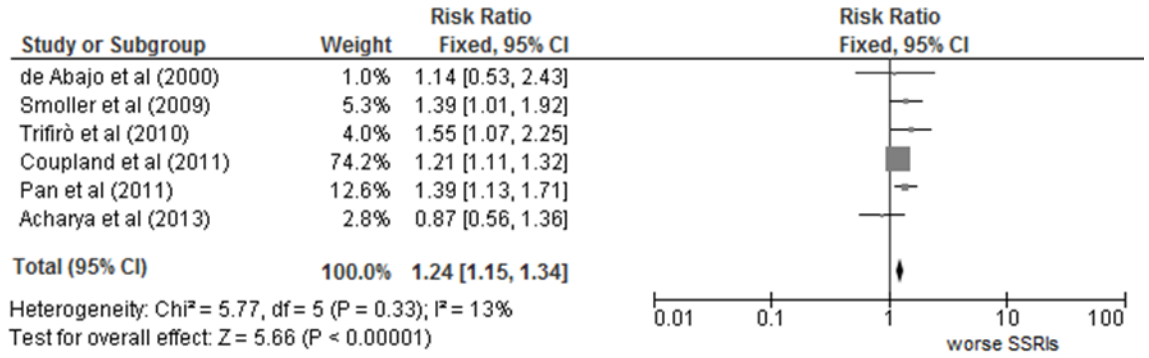
Fig. 2 Forest plots of study-specific and summary relative risks for the association between use of Antidepressant Drugs and Acute heart disease (including coronary heart disease, acute myocardial infarction, ischemic heart disease, and sudden death)

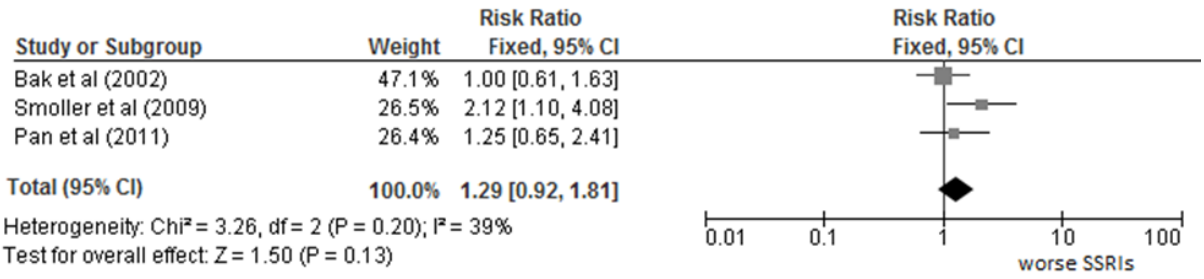


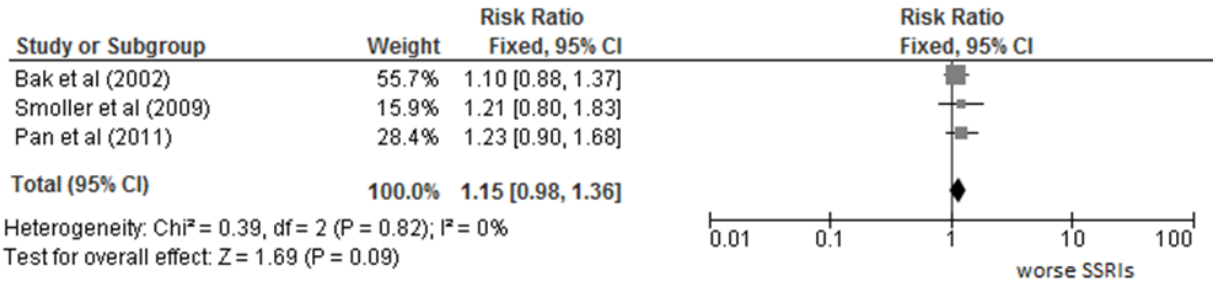
Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; *p*-values are from testing for heterogeneity between study-specific estimates. Abbreviations: CI, confidence interval; RR, relative risk

Fig. 3 Forest plots of study-specific and summary relative risks for the association between use of Selective Serotonin Reuptake Inhibitors and Acute heart disease (including coronary heart disease, acute myocardial infarction, ischemic heart disease, and sudden death), Cerebrovascular disease (including stroke and transient ischemic attack), haemorrhagic stroke and ischemic stroke



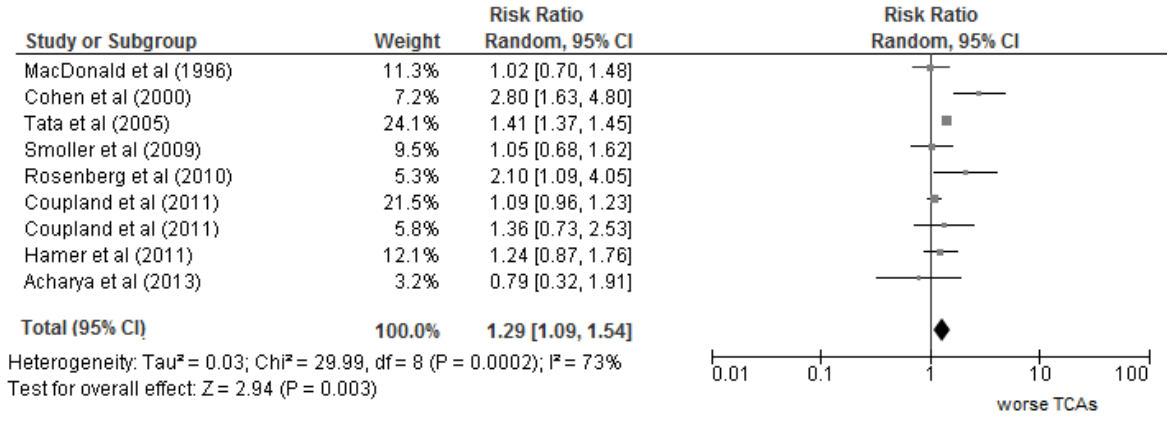


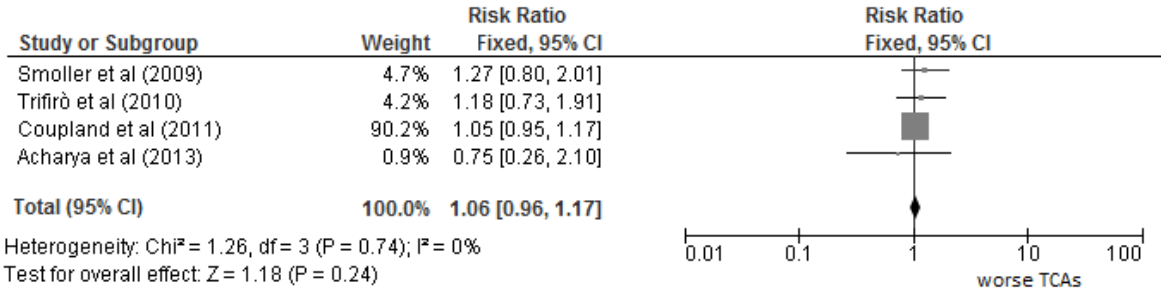




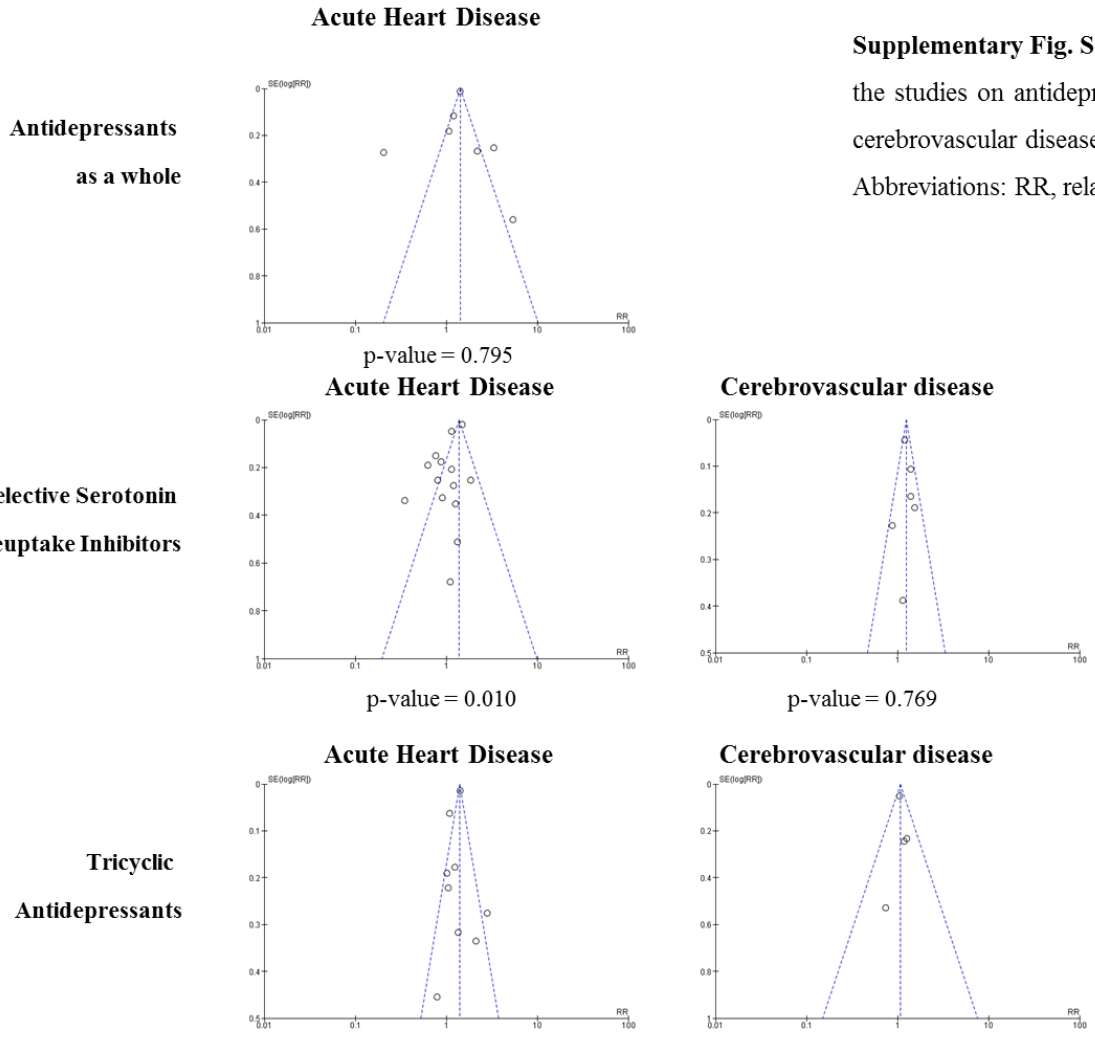
Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; *p*-values are from testing for heterogeneity between study-specific estimates. Abbreviations: CI, confidence interval; RR, relative risk

Fig. 4 Forest plots of study-specific and summary relative risk estimates for the association between use of Tricyclic Antidepressants and Acute heart disease (including coronary heart disease, acute myocardial infarction, ischemic heart disease, and sudden death) and Cerebrovascular disease (including stroke and transient ischemic attack)





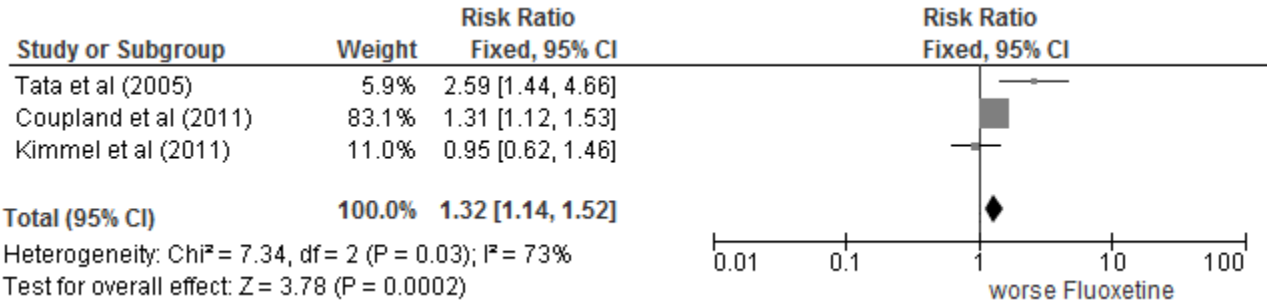
Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; *p*-values are from testing for heterogeneity between study-specific estimates. Abbreviations: CI, confidence interval; RR, relative risk



Supplementary Fig. S1 Begg's funnel plot and Egger's test p-value for publication bias in the studies on antidepressant treatment associated with the onset of cardiovascular and cerebrovascular disease

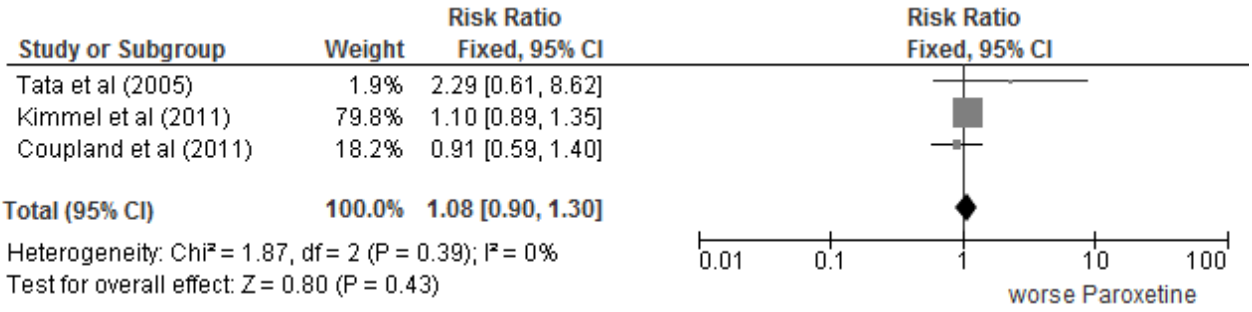
Abbreviations: RR, relative risk; SE, standard error

Supplementary Figure S2 Forest plots of study-specific and summary relative risks for the association between use of Fluoxetine (SSRIs Antidepressant) and Myocardial Infarction



Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; *p*-values are from testing for heterogeneity between study-specific estimates. Abbreviations: CI, confidence interval; RR, relative risk

Supplementary Figure S3 Forest plots of study-specific and summary relative risks for the association between use of Paroxetine (SSRIs Antidepressant) and Myocardial Infarction



Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, that is, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with corresponding 95% CIs; *p*-values are from testing for heterogeneity between study-specific estimates. Abbreviations: CI, confidence interval; RR, relative risk

Supplementary Table S1 Influence analysis investigating the summary relative risk of selected CV outcomes associated with use of antidepressants by omitting one study at a time among those contributing the estimates reported in Figures 2-4

Antidepressants and Acute Heart Disease

Omitted study (First author, publication year [reference]	Summary RR (95% CI)	Heterogeneity	
		p-value	I^2
Penttinen et al (1996) [228]	1.20 (0.80 to 1.82)	<0.001	93%
Cohen et al (2000) [94]	1.25 (0.80 to 1.96)	<0.001	93%
Tata et al (2005) [193]	1.40 (0.71 to 2.76)	<0.001	93%
Surtees et al (2008) [231]	1.67 (1.27 to 2.19)	<0.001	79%
Whang et al (2009) myocardial infarction [233]	1.42 (0.88 to 2.30)	<0.001	93%
Whang et al (2009) coronary heart disease [233]	1.42 (0.80 to 2.53)	<0.001	93%
Whang et al (2009) sudden death [233]	1.16 (0.76 to 1.78)	<0.001	92%

Selective Serotonin Reuptake Inhibitors and Acute Heart Disease

Omitted study (First author, publication year [reference]	Summary RR (95% CI)	Heterogeneity	
		p-value	I^2
MacDonald et al (1996) [226]	0.99 (0.81 to 1.21)	<0.001	86%
Cohen et al (2000) [94]	1.00 (0.82 to 1.22)	<0.001	86%
Meier et al (2001) [95]	1.01 (0.83 to 1.23)	<0.001	86%
Sauer et al (2001) [97]	1.06 (0.89 to 1.28)	<0.001	83%
Schlienger et al (2004) [211]	1.05 (0.87 to 1.27)	<0.001	83%
Tata et al (2005) [193]	0.95 (0.78 to 1.15)	0.001	64%
Blanchette et al (2009) [220]	0.96 (0.78 to 1.17)	<0.001	86%
Smoller et al (2009) [230]	1.02 (0.83 to 1.24)	<0.001	85%
Rosenberg et al (2010) [229]	1.00 (0.82 to 1.21)	<0.001	86%
Coupland et al (2011) [222]	0.98 (0.75 to 1.27)	<0.001	84%
Coupland et al (2011) [223]	0.99 (0.81 to 1.21)	<0.001	86%
Hamer et al (2011) [197]	1.02 (0.84 to 1.24)	<0.001	86%
Kimmel et al (2011) [225]	1.04 (0.85 to 1.26)	<0.001	84%
Acharya et al (2013) [194]	0.99 (0.81 to 1.22)	<0.001	86%

Selective Serotonin Reuptake Inhibitors and Cerebrovascular Disease

Omitted study (First author, publication year [reference]	Summary RR (95% CI)	Heterogeneity	
		p-value	I^2
De Abajo et al (2000) [224]	1.24 (1.15 to 1.34)	0.221	0%
Smoller et al (2009) [230]	1.23 (1.14 to 1.33)	0.260	24%
Trifirò et al (2010) [232]	1.23 (1.14 to 1.33)	0.362	8%
Coupland et al (2011) [222]	1.33 (1.15 to 1.55)	0.339	12%
Pan et al (2011) [227]	1.22 (1.13 to 1.32)	0.344	11%
Acharya et al (2013) [194]	1.25 (1.16 to 1.35)	0.512	30%

Selective Serotonin Reuptake Inhibitors and Haemorrhagic stroke

Omitted study (First author, publication year [reference]	Summary RR (95% CI)	Heterogeneity	
		p-value	I^2
Bak et al (2002) [219]	1.63 (1.03 to 2.59)	0.263	20%
Smoller et al (2009) [230]	1.08 (0.73 to 1.60)	0.593	0%
Pan et al (2011) [227]	1.31 (0.89 to 1.94)	0.072	69%

Selective Serotonin Reuptake Inhibitors and Ischaemic stroke

Omitted study (First author, publication year [reference]	Summary RR (95% CI)	Heterogeneity	
		p-value	I^2
Bak et al (2002) [219]	1.22 (0.96 to 1.57)	0.950	0%
Smoller et al (2009) [230]	1.14 (0.95 to 1.37)	0.564	0%
Pan et al (2011) [227]	1.12 (0.93 to 1.37)	0.690	0%

Tricyclic Antidepressants and Acute Heart Disease

Omitted study (First author, publication year [reference]	Summary RR (95% CI)	Heterogeneity	
		p-value	I^2
MacDonald et al (1996) [226]	1.33 (1.11 to 1.60)	<0.001	74%
Cohen et al (2000) [94]	1.22 (1.04 to 1.44)	0.001	70%
Tata et al (2005) [193]	1.28 (1.02 to 1.59)	0.024	57%
Smoller et al (2009) [230]	1.32 (1.10 to 1.59)	<0.001	75%
Rosenberg et al (2010) [229]	1.26 (1.06 to 1.50)	<0.001	75%
Coupland et al (2011) [222]	1.36 (1.12 to 1.65)	0.044	52%
Coupland et al (2011) [223]	1.29 (1.08 to 1.55)	<0.001	77%
Hamer et al (2011) [197]	1.30 (1.08 to 1.58)	<0.001	76%
Acharya et al (2013) [194]	1.32 (1.11 to 1.57)	<0.001	75%

Tricyclic Antidepressants and Cerebrovascular Disease

Omitted study (First author, publication year [reference]	Summary RR (95% CI)	Heterogeneity	
		p-value	I^2
Smoller et al (2009) [230]	1.05 (0.95 to 1.16)	0.725	0%
Trifirò et al (2010) [232]	1.06 (0.96 to 1.17)	0.587	0%
Coupland et al (2011) [222]	1.17 (0.85 to 1.61)	0.654	0%
Acharya et al (2013) [194]	1.07 (0.96 to 1.18)	0.666	0%

Supplementary Table S2 NOS for assessment of Quality of Included studies: Case-Control Studies

[1] Maximum 4 stars awarded for case-definition, representativeness of the cases, selection of controls, definition of controls

[2] Maximum 2 stars awarded for comparability of cases and controls on the basis of the design or analysis; considering the most important factors (age, gender, smoking, BMI) and additional factors (cardiovascular risk factors, cardiovascular intervention, hypertension-hypercholesterolemia)

[3] Maximum 3 stars awarded for ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate

[4] Studies receiving at least 6 points were considered high quality; a maximum of 9 points could be awarded

Study	**SELECTION[1]**				**COMPARABILITY[2]**		**EXPOSURE[3]**			**Total[4]**
MacDonald 1996, Scotland [226]	*	*			*			*		4
Penttinen 1996, Finland [228]	*	*	*	*	*		*	*		7
de Abajo 2000, UK [224]	*	*	*	*	*	*	*	*		8
Meier 2001, UK [95]	*	*	*	*	*		*	*		7
Sauer 2001, US [97]	*	*	*	*	*	*	*	*	*	9
Bak 2002, Denmark [219]	*	*	*	*	*		*	*		7
Schlienger 2004, UK [211]	*	*	*	*	*	*	*	*		8
Tata 2005, UK [193]	*	*	*	*			*	*		6
Chen 2008, US [221]	*	*	*	*	*	*	*	*		8
Trifirò 2010, The Netherlands [232]	*	*	*	*	*	*	*	*		8
Kimmel 2011, UK [225]	*	*	*	*	*	*	*	*		8
Acharya 2013, US [194]	*	*		*	*	*	*	*		7

Supplementary Table S3 NOS for assessment of Quality of Included studies: Cohort Studies

[1] Maximum 4 stars awarded for representativeness of the exposed cohort, selection of the non exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study

[2] Maximum 2 stars awarded for comparability of cohorts on the basis of the design or analysis- considering the most important factors (age, gender, smoking, BMI) and additional factors (cardiovascular risk factors, cardiovascular intervention, hypertension-hypercholesterolemia)- and assessment of outcome

[3] Maximum 3 stars awarded for follow-up length, adequacy of follow-up of cohorts

[4] Studies receiving at least 6 points were considered high quality; a maximum of 9 points could be awarded

Study	**SELECTION[1]**				**COMPARABILITY[2]**		**OUTCOME[3]**			**Total[4]**
Cohen 2000, US [94]	*		*	*	*	*	*	*	*	8
Surtees 2008, UK [231]	*			*			*	*	*	5
Blanchette 2009, US [220]	*	*	*	*	*		*	*	*	8
Whang 2009, US [233]	*			*	*	*	*	*	*	7
Rosenberg 2010, US [229]	*	*	*	*	*		*	*	*	8
Coupland 2011, UK [222]	*	*	*	*	*	*	*	*	*	9
Coupland 2011, UK [223]	*	*	*	*	*	*	*	*	*	9
Hamer 2011, Scotland [197]	*		*	*	*	*	*	*	*	8
Smoller 2009, US [230]	*	*	*	*	*	*	*	*	*	9
Pan 2011, US [227]	*	*		*	*	*	*	*	*	8

Supplementary Table S4 MOOSE checklist for Meta-analyses of Observational Studies

Item N.	Recommendation	Reported on Page N.
Reporting of background should include		
1	Problem definition	2-3
2	Hypothesis statement	3
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	3
5	Type of study designs used	3-4
6	Study population	3-4
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	4
9	Effort to include all available studies, including contact with authors	4-5
10	Databases and registries searched	4
11	Search software used, name and version, including special features used (eg, explosion)	5
12	Use of hand searching (eg, reference lists of obtained articles)	4-5
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	4
15	Method of handling abstracts and unpublished studies	4
16	Description of any contact with authors	N/A
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4-5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4-5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	4-5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	4-5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
22	Assessment of heterogeneity	5-6

23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5-6
24	Provision of appropriate tables and graphics	Fig. 1-4 Table 1 Suppl. Fig. S1-S2-S3 Suppl. Table S1-S3
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig. 2-4
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Suppl. Table S2-S3
28	Indication of statistical uncertainty of findings	Fig. 2-4 7-8
Reporting of discussion should include		
29	Quantitative assessment of bias (eg. Publication bias)	9-10
30	Justification for exclusion (eg. Exclusion of non-English language citations)	9
31	Assessment of quality of included studies	9
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	9-11
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	10
34	Guidelines for future research	12
35	Disclosure of funding source	12

II Study

Antidepressants and the risk of cardiovascular disease in elderly affected by a previous cardiovascular disease:

a real-life investigation from Italy

Running head: Antidepressants use and risk of cardiovascular disease among elderly affected by a previous cardiovascular disease

Word count: 2,880

Number of tables: 3

Number of tables (supplementary material): 1

Number of figures: 3

Abstract

Aim: To assess the possible relation between antidepressant drugs (ADs) by estimating the risk of hospitalization for cardiovascular disease associated with use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and newer atypical ADs (NAAs) among elderly with previous cardiovascular (CV) events.

Methods: A nested case-control study was conducted among subjects aged ≥ 65 years from five Italian healthcare territorial units who were discharged for cardiovascular outcomes in the years 2008-2010. The cohort was composed by 344,747 individuals and of these 97,739 patients experienced hospital admission for cardiovascular disease (myocardial infarction, arrhythmia, stroke, heart failure) during follow-up and were included as cases. The risk of cardiovascular disease associated with AD past or current use was modelled by fitting conditional logistic regression. Up to five controls were randomly selected and matched to each case by territorial unit of recruitment, gender, age at cohort entry, date of cohort entry and index date. A set of sensitivity analyses was performed to account the effect of systematic uncertainty.

Results: Past AD users and current users of SSRIs and NAAs were at increased risk of cardiovascular disease with nested case-control odds ratios (OR) of 1.12 (95% confidence interval, CI: 1.09 to 1.14), 1.21 (1.17 to 1.25) and 1.26 (1.21 to 1.32). An increased risk of arrhythmia, acute myocardial infarction and heart failure was associated with past and current (SSRIs and NAAs) AD use. Analysis of the effect of AD use depending on period of assumption (before or during follow-up), emphasized the acute effect on cardiovascular risk.

Conclusions: Evidence that past and current (SSRIs and NAAs) AD use is associated to an increased risk of cardiovascular disease among elderly with CV disease was consistently supplied by several sensitivity analyses.

Key words: Cardiovascular disease, Antidepressants, Tricyclic antidepressants, Selective serotonin reuptake inhibitors, Healthcare utilization databases

Introduction

Depression is a common disease characterized by low mood and aversion to activity affecting people's behavior thoughts and feelings [248]. The disease represents an important public-health issue because of its relatively high prevalence (2%-15% lifetime) and associated disability [105].

In particular, depression is a common symptom in the elderly population. The prevalence of major depression varies from 4.6 to 9.3%, while the prevalence of less severe depressive disorders from 4.5 to 37.4% in patients ages 75 years or older [249]. In the 1950s the first antidepressants (ADs) were developed to relieve depressive symptoms, namely the the tricyclic antidepressants (TCAs). In the subsequent years, the selective serotonin reuptake-inhibitors (SSRIs) and selective nonadrenaline re-uptake inhibitors entered the pharmaceutical market extending the indication of these drug class to both depressive and anxiety disorders. Since SSRIs tend to be better tolerated, they are frequently administered to elderly to treat depression [250]. However, it is important to underline that this specific population is frequently affected by several comorbidities and treated with polypharmacy making it prone to drug-drug and drug-disease interaction [251]. Moreover, the aging process induce changing in the pharmacokinetics and pharmacodynamics of the drugs due to a reduction in the function of different organ system leading to a potential increase risk of adverse drug reactions even for drugs with a proven safety profile in the general population, such as ADs [252]. In the elderly, the use of AD was related with an increased risk of hyponatraemia [222, 253, 254], falls and fractures [222, 255, 256], all cause mortality and cardiovascular (CV) diseases [197, 222, 230].

In elderly patients with an impaired cardiovascular profile the AD use may lead to an increased risk of cardiovascular disease recurrence [250].

The aim of this study is to verify the role of antidepressant treatment in the recurrence of cardiovascular disease in a cohort of elderly with a previous hospital discharge for cardiovascular

disease using the data from different regional healthcare utilization databases within the I-GrADE project. The project, supported by the Italian medicine Agency, aims to assess the potential inappropriate prescribing in patients aged 65 years or older affected by cardiovascular disease.

Methods

Setting

The data used for the present study were retrieved from the healthcare utilization databases of the five Italian healthcare territorial units participating in the I-GrADE project namely three Regions (Lazio, Lombardy, Tuscany) and 2 Local Health Units (Caserta, Treviso). The information of about 21 million beneficiaries residing in these areas, accounting for nearly 35% of the whole Italian population, were recorded in the corresponding databases.

In Italy, the whole population is covered by National Health Service (NHS) that has been associated with an automated system of databases recording the use of healthcare services including: (i) an archive of NHS beneficiaries (which almost completely reflects the resident population), inclusive of demographic and administrative data; (ii) a hospital discharge database, reporting all discharge diagnoses released from public or private hospitals; and (iii) an outpatient drug prescriptions database, reporting all dispensations of drugs reimbursable by the NHS.

Cohort and Follow - up

The target population consisted in all beneficiaries of the NHS residing in the territorial units collaborating in the project aged 65 years or older. From this population, we selected the subjects hospitalized for cardiovascular disease between 2008 - 2010 and the date of the last hospital discharge during this period was defined as the date of cohort entry. CVD at cohort entry was defined as a hospitalization with primary or secondary diagnosis of heart failure (ICD-9 codes

428.*, 402.01, 402.11, 402.91), cerebrovascular disease (ICD-9 codes 430.*-438.*), arrhythmia (ICD-9 codes 427.*, 785.0) and ischemic heart disease (ICD-9 codes 410.*-414.*).

Patients were excluded from the cohort if in the two years before the date of cohort entry, i) received at least an antineoplastic prescription (ATC code L) or were hospitalized for cancer (ICD-9 codes 140.*-239.*) to exclude patients with very severe clinical conditions and ii) were not covered by the NHS assistance to ensure to have enough information for the wash-out period. Moreover, patients with less than 6 months of follow-up were excluded from the analyses.

The patients included in the final cohort were followed from the cohort entry date until the earliest of the following events: the first hospital admission for cardiovascular disease (outcome), death, emigration, onset of cancer or the end of follow-up defined for each unit by the end of data availability (Caserta 31/12/2012; Lazio 30/06/2011; Lombardy 30/11/2012; Treviso 31/12/2014; Tuscany 31/12/2012).

Cases and controls

Cases were the members of the cohort who were hospitalized for cardiovascular disease specifically for acute myocardial infarction (AMI, ICD-9 code 410.*), cardiac arrhythmia (ICD-9 codes 427.*, 785.0), stroke (ICD-9 codes 430.*-435.*) or heart failure (ICD-9 codes 428.*, 402.01, 402.11, 402.91) during follow - up. The date of the earliest hospital admission occurred during follow-up was defined as the index date. Up to five controls were randomly selected and matched to each case by territorial unit of recruitment, gender, age at cohort entry, date of cohort entry and index date.

Exposure

All prescription of ADs (SSRIs, ATC code: N06AB, TCAs ATC: N06AA and newer atypical antidepressants NAAs ATC: N06AX) dispensed to cases and controls during follow-up were

identified. AD exposure was categorized into mutually exclusive groups as current, past, and no use. A patient was defined as current user if the last prescription of ADs was dispensed within 30 days period before index date, while past users were those whose last prescription was dispensed later than 31 days before the index date. Patients with no ADs prescriptions during follow-up were considered as no users.

Current users were further classified according to specific class of ADs (SSRIs, TCAs, NAAs). To evaluate effect of the period of use (before or after cohort entry), the use of AD was also classified as: no use, baseline use only, use during follow-up only and use in both periods.

Covariates

Several potential confounder of the association of interest were assessed at cohort entry and during follow-up. Some covariates were measured both in the 2 years before cohort entry date (baseline) and during follow-up, in particular: use of cardiovascular drugs (antiarrhythmic, digoxin and nitrates, ATC codes C01B, C01AA05 and C01DA), antidiabetics (ATC codes A10), antihypertensive drugs (ATC codes C02, C03, C07, C08, C09) and lipid-lowering drugs (ATC codes C10), hospitalization for diabetes mellitus (ICD-9 code 250.*), hypertension and hyperlipidemia (ICD-9 codes 401.*, 272.0 and 272.4). Additional variables considered as potential confounders were: previous use of ADs, type of CVD at cohort entry and the Charlson comorbidity index [257]. The Charlson comorbidity index was categorized as 0, 1 or >1.

Data analysis

The χ^2 test, or its version for the trend, was used, when appropriate, to compare cases and controls according to the selected covariates and exposure. A conditional logistic regression model was used to estimate the odds ratio (OR) and corresponding 95% confidence interval (95%CI) for the association between current and past use of the specific classes of ADs considering no antidepressant users as reference. The same model was applied considering as exposure the time-

period of AD use. Estimates were adjusted for the selected covariates, at baseline and during follow-up. The association between period of use and CVD risk was also evaluated. The analyses were performed by considering both CV disease overall and specific cardiovascular outcomes (arrhythmia, AMI, heart failure, stroke). All analyses were performed using the Statistical Analysis System software version 9.4 (SAS Institute, Cary, NC, USA). For all tested hypotheses, two-tailed p-values less than 0.05 were considered statistically significant.

Sensitivity Analyses

To verify the robustness of our findings respect to the definition of current use and to the potential presence of unmeasured confounders, we performed a sensitivity analysis. Regarding the first issue, in the sensitivity analysis, the length of the current widow was set to 15-day and 45-days before the index date.

Further, because smoking may be an important confounder of the association of interest but it is not measured in the healthcare utilization databases, we quantified the potential bias of the confounder using the Monte-Carlo sensitivity analysis [258]. 4 scenarios were created varying the expected proportion of smokers among patients treated or not treated with ADs and the strength of the association between smoking and CV disease risk. The prevalence of smokers among elderly AD users was set to 12% and 24% while among elderly non users of ADs to 10.5% and 17% [220, 259]. In addition, we assumed that smokers had a 2-fold [260] or 3-fold [261] higher risk of cardiovascular diseases compared to no smokers [163].

Results

Patients

Figure 1 shows the flow chart of the exclusion criteria. We identified 680,381 subjects aged 65 years or older who were hospitalized for cardiovascular disease between the 1/1/2008 and the 31/12/2010. We excluded 103,599 patients with signs of cancer (hospitalization for cancer or prescription of antineoplastic prescription) in the two years before the cohort entry date. Further 33,600 subjects were excluded because were registered in the database from less than two years. After the exclusion of patients with less than six months of follow-up, the final cohort comprised of 344,747 subjects. This cohort generated 97,739 cases of CV disease and were matched to 486,316 controls.

The characteristics of the cases and matched controls are summarized in Table 1. During current period, compared to controls, a higher percentage of cases was exposed to antidepressant treatment. Compared to controls, cases seem to have a worse clinical profile defined by a significantly higher proportion of cardiovascular hospital discharge after recruitment, Charlson score greater than one, use of cardiovascular drugs (including antiarrhythmic, digoxin and nitrates), comorbidities, in particular diabetes and hypertension both at baseline and during follow–up.

Moreover, cases were more frequently hospitalized for a cardiovascular disease and treated with antidepressants than controls before cohort entry.

Use of antidepressants and the risk of cardiovascular disease

Table 2 reports the association between current use of SSRIs, TCAs and NAAs or past use of any antidepressant, and the risk of cardiovascular hospitalization. An increased risk of CV disease was found among current users of SSRIs (OR 1.21, 95% CI 1.17-1.25) and NAAs (OR 1.26, 95% CI

1.21-1.32) and past users (OR 1.12, 95% CI, 1.09 – 1.14), while a no increased risk was found for TCAs users.

The results of these analyses regarding the association between specific ADs classes use and the risk of specific outcomes are reported in Figure 2.The number of cases of arrhythmia, heart failure, stroke and AMI registered during follow-up are respectively 58.791, 57.054, 32.968 and 13.424.

As shown by Figure 2 current use of SSRIs seems to increase the risk of stroke (OR 1.27, 95% CI 1.21 – 1.35), heart failure (OR 1.30, 95% CI 1.25 – 1.36) and arrhythmia (OR 1.17, 95% CI 1.11 – 1.22) but not the risk of AMI. Similar results were obtained for current users of NAAs. No association was conversely observed between current use of TCAs and risk of each cardiovascular event.

The results of the analyses regarding the association between period of AD use and CV disease are reported in Table 3. Considering no use of ADs as reference, a positive association was verified both during follow-up period, OR 1.17 (CI 95%, 1.14 – 1.20) and in both periods OR 1.09 (CI 95%, 1.07 – 1.12).

Sensitivity Analyses

As shown in Supplementary Table 1, the association estimates did not substantially change varying the length of the time window used to define the current use for SSRIs and NAAs treatments (panel a, b, c) The only exception was observed for TCAs current exposure considering a length of the time window of 15 days where a significant positive association was detected (OR 1.22 95% CI 1.16 – 1.30).

Figure 3 shows the CV relative risks of cardiovascular diseases associated with the current treatment with ADs (regardless the class of drug) after adjustment for smoking factor through the application of the Monte Carlo sensitivity analysis. As expected, estimates adjusted for the

unmeasured confounder showed a lower association than unadjusted estimates. The difference become more evident as the relation confounder-exposure became greater.

Discussion

The present observational study evaluated the relationship between AD treatment and the risk of cardiovascular disease among elderly with previous cardiovascular disease. The findings of this analysis shows that current use of SSRIs and NAAs medications significantly increased the risk of cardiovascular disease as well as past use of any ADs compared to no use. When AD use was categorized according to use before or during follow-up, it has been noticed that only the use during follow-up increased the risk of CV disease. This emphasized the acute effect of antidepressant treatment on cardiovascular risk, especially shortly before the index date.

Specifically, for stroke, heart failure and arrhythmia a significant increased risk was noticed for current use SSRIs and NAAs assumption but not for TCAs. No antidepressant drug was associated with AMI hospitalization The sensitivity analysis performed varying the time window (15, 30 or 45 days) showed that our findings were robust except for TCAs treatment. Further, our results were not substantially modified after the adjustment for smoking performed using the Monte Carlo sensitivity analysis approach.

In line with other studies, our findings showed an increased risk of arrhythmia associated with use of SSRIs [262] and of stroke among elderly users of NAAs [222] and SSRIs [79, 222, 232]. To the best of our knowledge, this is the first study suggesting a potential increased risk of heart failure among current users of SSRIs and NAAs.

It must be noticed that both depression and AD treatment are involved in the increase of CV risk. Depression may cause abnormalities in the sympathoadrenal system, the autonomic nervous system, and platelet function leading to an increased cardiovascular risk [97], while different mechanisms of action may explain the effect of AD treatment depending on the class of drug considered [99].

In particular, SSRIs inhibit the serotonin transporter protein and the uptake of serotonin into platelets whose functionality will be impaired [232, 263], leading to a decrease in platelet concentration and consequently to impaired aggregation and prolonged bleeding times [78, 263, 264]. Moreover, the use of SSRIs, on one hand could have a cardioprotective effect due to the inhibition of platelet aggregation [263, 264], while on the other hand, serotonin release may promote vasoconstriction in cerebral arteries increasing the risk of ischemic stroke [93].

TCAs either inhibit norepinephrine reuptake or inhibit both norepinephrine and serotonin reuptake [99]. The effects of TCAs on cardiac tissue are similar to class I antiarrhythmic medications [72] but their effect on the heart could contraindicate use for patients with irregular heartbeats [99], particularly, their use might be problematic in depressed patients with a wide range of CVD problems [72]. Furthermore, TCAs may block parasympathetic nervous system activity, as well as fast sodium [250] that could prolong intraventricular conduction [43] and affect the activity of potassium channels [265], prolonging the QT interval [266] which is associated with an increased risk of sudden death and cardiovascular death. Therefore, TCAs due to anticholinergic properties could cause the heart rate reduction which is a known risk factor for cardiovascular diseases [71, 204].

At last, NAAs have multiple direct effects on neuronal systems, including norepinephrine [71, 267], that could lead to ischemia, chest pain, hypertension, and arrhythmias [268].

This study has several strengths. First, the investigation was based on a large unselected population from three Italian regions and two ASL, allowing to obtain precise and generalizable results. Moreover, it permitted to study not only the effect of the ADs on the onset of CV disease overall but also for stroke, acute myocardial infarction, arrhythmia and heart failure separately. Second, the drug prescription database provided highly quality data because pharmacists are required to report prescriptions in detail to obtain reimbursement, and incorrect reports about the dispensed

drugs have legal consequences [269]. Third, this study is focused on a specific target population of elderly affected by CV diseases which is not frequently involved in randomized clinical trials providing further insight of drug effect in the frail population. Fourth, two sensitivity analyses were performed to verify the robustness of the main analysis' results with respect to the definition of current period and the presence of unmeasured confounders through Monte Carlo sensitivity analysis. The results of these analyses confirmed the increased risk of CV disease due to an acute exposure to ADs.

Several limitations of the study need to be acknowledged. First of all, because of privacy regulations, hospital records were not available for review to verify the accuracy of the reported diagnosis. Although the quality of the data available in the healthcare utilization databases is high [270], due to a lack of evidence, misclassification of the outcome cannot be completely excluded in our setting. Finally, since the allocation to AD treatment was not randomized, the results may be affected by confounding. However, the reported estimates were adjusted for a large number of potential confounders, including comedications, comorbidities and Charlson score, therefore a very low effect of residual confounders is expected. Residual confounding may be due to socioeconomic and lifestyle factors, that can not be ruled out because not available in the administrative databases.

In summary, the potential risks and benefits of different ADs need careful consideration when these drugs are prescribed to older people, taking into account the severity of depression, the socio-economic and demographic characteristics of individuals, and the development of adverse effects.

Table 1. Characteristics of the 97,739 cases hospitalized for cardiovascular disease and the corresponding 486,316 controls

	Cases (n=97,739)	**Controls (n=486,316)**	**p-value**
Age, Mean (SD)	79.53 ± 7.1	79.44 ± 7.0	mv
Male gender	48,049 (49.2%)	238,938 (49.1%)	mv
Recency of antidepressants			
No use	73,497 (75.2%)	374,718 (77.0%)	<.0001
Past	15,516 (15.8%)	73,655 (15.1%)	
Current[†]			
SSRIs	5,507 (5.6%)	24,028 (4.9%)	
TCAs	289 (0.3%)	1,478 (0.3%)	
NAAs	2,930 (3.0%)	12,437 (2.6%)	
Diagnosis at index hospitalization			
Heart failure	23,752 (24.3%)	72,059 (14.8%)	<.0001
Cerebrovascular disease	26,102 (26.7%)	172,300 (35.4%)	<.0001
Ischaemic heart disease	26,359 (27.0%)	154,272 (31.7%)	<.0001
Arrhythmia	21,526 (22.0%)	87,685 (18.0%)	<.0001
Charlson comorbidity index			
0	16,641 (17.0%)	101,983 (21.0%)	<.0001
1	36,873 (37.7%)	209,609 (43.1%)	
>1	44,225 (45.2%)	174,724 (35.9%)	
Previous comorbidities and co-treatments			
CV disease	20,685 (21.2%)	72,364 (14.9%)	<.0001
Diabetes[*]	28,798 (29.5%)	116,050 (23.9%)	<.0001
Hypertension[*]	88,829 (90.9%)	419,057 (86.2%)	<.0001
Hyperlipidemia[*]	37,292 (38.1%)	181,349 (37.3%)	<.0001
Antiarrhythmic	15,294 (15.6%)	51,390 (10.6%)	<.0001
Digoxin	15,218 (15.6%)	44,126 (9.1%)	<.0001
Nitrates	29,185 (29.9%)	118,035 (24.3%)	<.0001
Antidepressants	21,568 (22.1%)	104,721 (21.5%)	.0002
Comorbidities and co-treatments during follow-up			
Diabetes[*]	30,165 (30.9%)	112,573 (23.1%)	<.0001
Hypertension[*]	91,869 (94.0%)	439,722 (88.4%)	<.0001

Hyperlipidemia*	43,673 (43.7%)	220,360 (45.3%)	<.0001
Antiarrhythmic	17,591 (18.0%)	62,279 (12.8%)	<.0001
Digoxin	16,735 (17.1%)	47,860 (9.8%)	<.0001
Nitrates	33,222 (34.0%)	131,864 (27.1%)	<.0001

*At least one hospitalization or prescription medication for the treatment of the disease

MV matching variables; SSRIs: Selective serotonin reuptake inhibitor; TCAs: Tricyclic antidepressants; NAAs: Newer atypical antidepressants

† Exposure time-window of 30 days

Table 2. Nested case-control odds ratios of cardiovascular hospitalization associated with past and current use of antidepressants, Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAa) and Newer Atypical Antidepressants (NAAs)

	OR[†]	**95% CI**
Recency of antidepressants		
No use	1.00	Ref.
Past	1.12	(1.09 to 1.14)
Current, SSRIs[††]	1.21	(1.17 to 1.25)
Current, TCAs[††]	1.08	(0.95 to 1.23)
Current, NAAs [††]	1.26	(1.21 to 1.32)
Charlson comorbidity index		
0	1.00	Ref.
1	1.23	(1.20 to 1.26)
>1	1.52	(1.48 to 1.56)
Previous co-treatments and comorbidities		
Antidepressants	0.95	(0.93 to 0.97)
CV disease	1.39	(1.36 to 1.42)
Diagnosis of cohort entry		
Ischemic heart	1.03	(1.01 to 1.05)
Arrhythmia	1.60	(1.56 to 1.64)
Heart failure	1.72	(1.69 to 1.76)
Comorbidity and drugs during follow-up		
Diabetes[*]	1.31	(1.29 to 1.33)
Hypertension[*]	1.63	(1.59 to 1.68)
Hyperlipidemia[*]	0.90	(0.89 to 0.92)
Antiarrhythmic	1.36	(1.33 to 1.39)
Digoxin	1.54	(1.51 to 1.57)
Nitrates	1.30	(1.28 to 1.32)

*At least one hospitalization or prescription medication for the treatment of the disease

[†] Odds ratios estimated with conditional logistic regression model. Please see Method section for the corresponding ICD-9 and ATC codes

[††] Exposure time-window of 30 days

Table 3. Evaluation of the relationship between antidepressant assumption and the relative period of administration, at baseline and/or follow-up

	OR[†]	**95% CI**
No use	1.00	Ref.
Antidepressant use at baseline	0.98	(0.95 to 1.00)
Antidepressant use during follow up	1.17	(1.14 to 1.20)
Antidepressant use during both periods	1.09	(1.07 to 1.12)

[†] Odds ratios estimated with conditional logistic regression model for the nested case-control design. Estimates were adjusted for covariates measured at baseline and during follow-up. Please see Table 1 for the complete list of covariates, and Method section for the corresponding ICD-9 and ATC codes

Figure 1. Study flow diagram

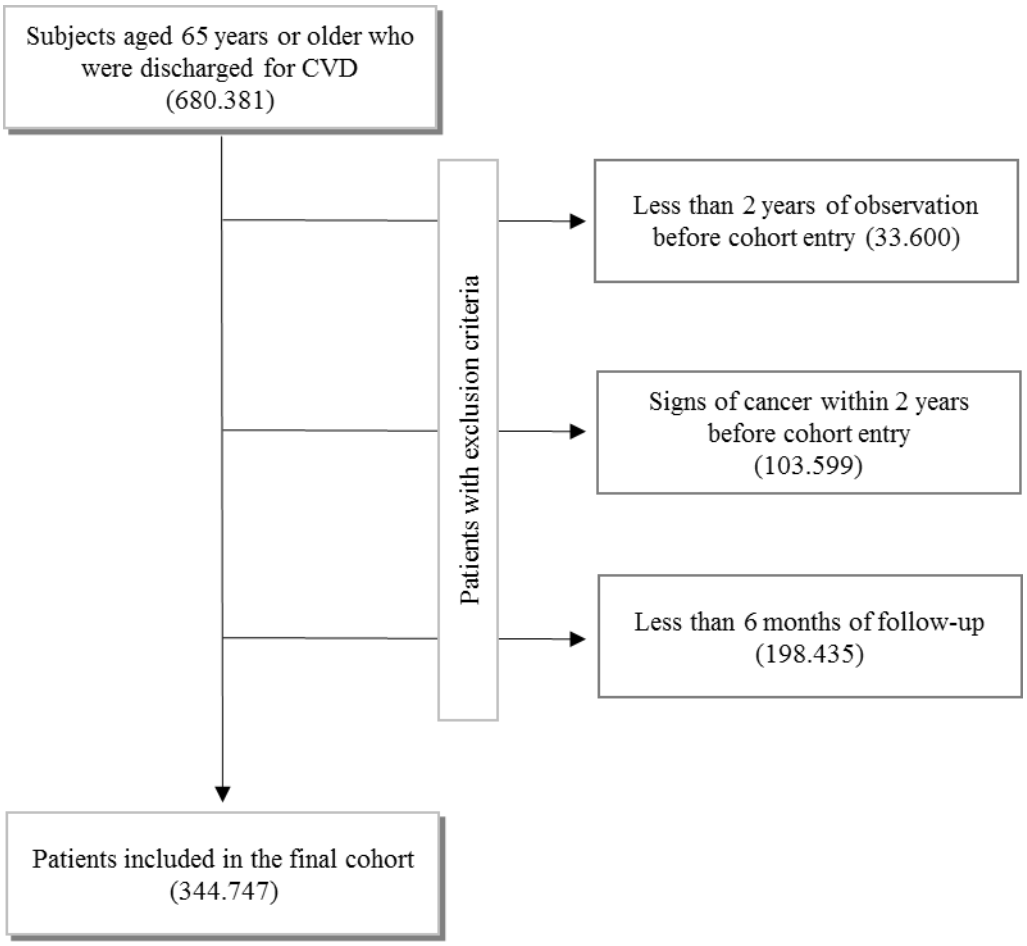
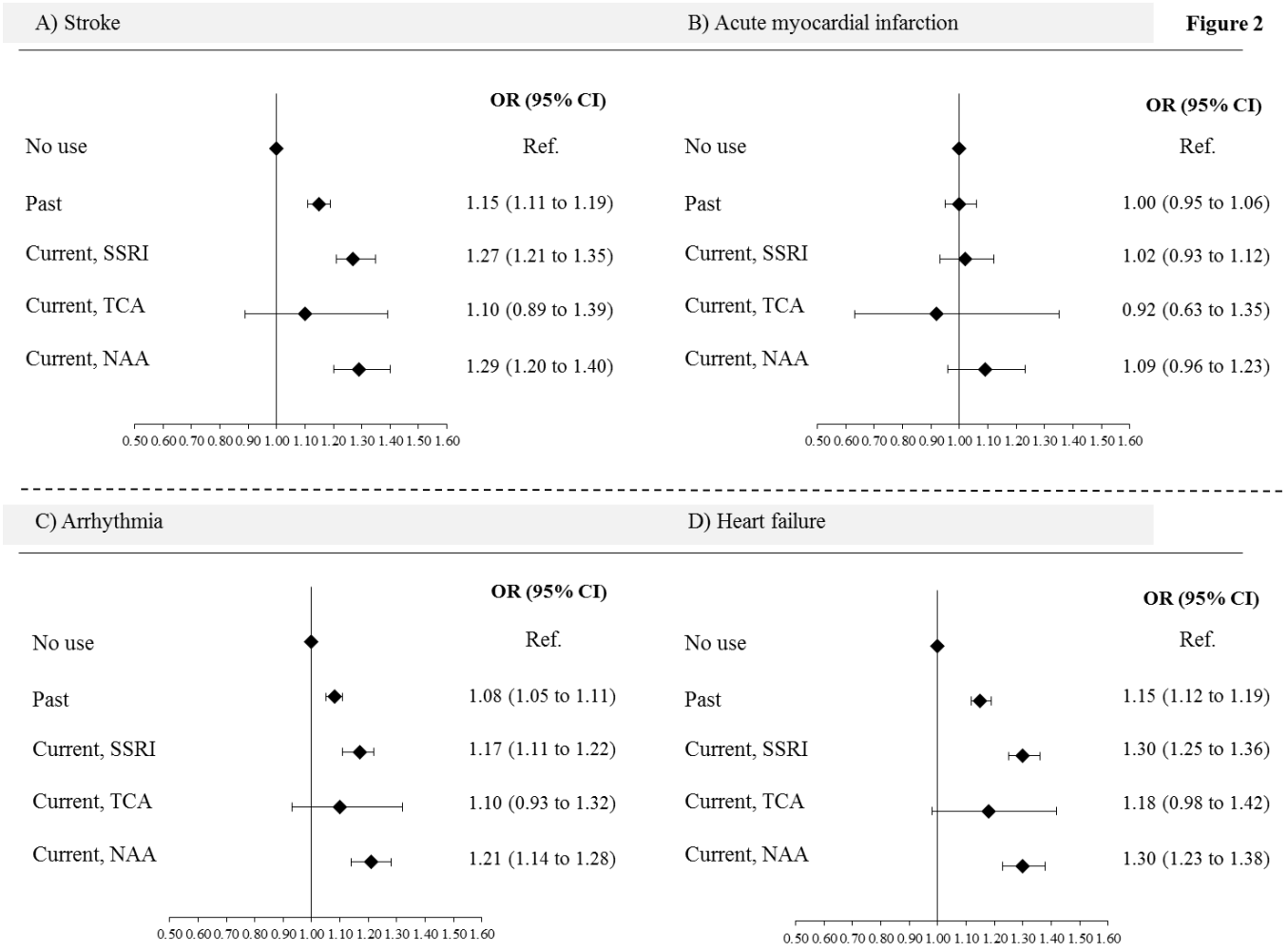
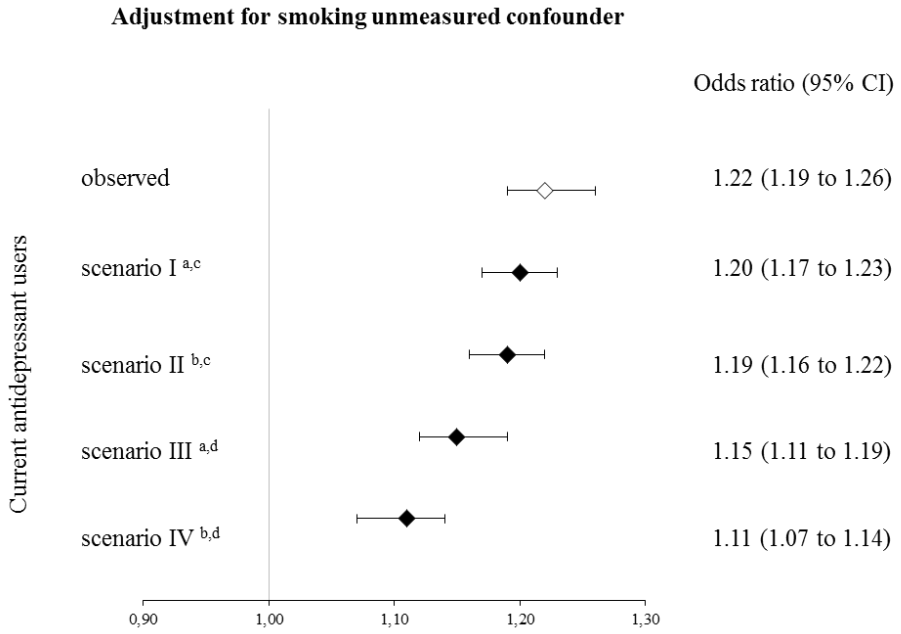


Figure 2. Nested case-control, ORs (and corresponding 95% confidence intervals, CI) of the relationship between current use of Selective Serotonin Reuptake Inhibitor (SSRIs), Tricyclic Antidepressants (TCAs) and Newer Atypical Antidepressants (NAAs) and the risk of cardiovascular hospitalization (stroke, acute myocardial infarction, arrhythmia, heart failure)



Footnote: Odds ratios estimated with conditional logistic regression model. Estimates were adjusted for covariates measured at baseline and during follow-up. Please see Table 1 for the complete list of covariates, and Method section for the corresponding ICD-9 and ATC codes

Figure 3. Forest plot comparing odds ratios (and corresponding 95% CIs) of cardiovascular outcomes associated with current antidepressant assumption, after adjustment for smoking unmeasured confounder, as verified by the literature. Adjustments were performed by means of Monte-Carlo sensitivity analysis considering differences in the smoking factor between current antidepressant users and 4 scenarios imposing that ln(RR) linearly increases with an increasing slope across the categories of the confounder (see text).



a) Relation confounder – outcome — HR 2.00 (95% CI, 1.59 - 1.25) [260]

b) Relation confounder – outcome — HR 2.98 (95%CI, 2.47 - 3.60) [261]

c) Relation confounder – exposure — 12% smokers and users of antidepressants in elderly population
10.5% smokers and no users of antidepressants in elderly population [220]

d) Relation confounder – exposure — 24% smokers and users of antidepressants in elderly population
17% smokers and no users of antidepressants in elderly population [259]

Supplementary Table S1. Sensitivity analyses considering different time window to define current users as a) 15, b) 30, c) 45 days before the index date

a) Time-window: 15 days	**OR**[†]	**95% CI**
Recency of antidepressants		
No use	1.00	Ref.
Past	1.13	(1.11 to 1.15)
Current, SSRIs	1.25	(1.20 to 1.30)
Current, TCAs	1.22	(1.16 to 1.30)
Current, NAAs	1.22	(1.16 to 1.30)
b) Time window: 30 days	**OR**	**95% CI**
Recency of antidepressants		
No use	1.00	Ref.
Past	1.12	(1.09 to 1.14)
Current, SSRIs	1.21	(1.17 to 1.25)
Current, TCAs	1.08	(0.95 to 1.23)
Current, NAAs	1.26	(1.21 to 1.32)
c) Time-window: 45 days	**OR**	**95% CI**
Recency of antidepressants		
No use	1.00	Ref.
Past	1.10	(1.08 to 1.13)
Current, SSRIs	1.21	(1.17 to 1.24)
Current, TCAs	1.11	(0.99 to 1.25)
Current, NAAs	1.26	(1.21 to 1.31)

[†] Odds ratios estimated with conditional logistic regression model for the nested case-control design. Estimates were adjusted for covariates measured at baseline and during follow-up. Please see Table 1 for the complete list of covariates, and Method section for the corresponding ICD-9 and ATC codes

III Study

Antidepressants and the risk of arrhythmia in elderly affected by a previous cardiovascular disease:

a real-life investigation from Italy

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Abstract

Purpose: To fill existing knowledge gaps on the safety of antidepressant drugs (ADs) by estimating the risk of hospitalization for arrhythmia associated with use of selective serotonin reuptake inhibitors (SSRIs) and newer atypical ADs (NAAs) among elderly with previous cardiovascular (CV) events.

Methods: The cohort was composed by 199,569 individuals aged ≥ 65 years from five Italian healthcare territorial units who were discharged for cardiovascular outcomes in the years 2008-2010. The 17,277 patients who experienced hospital admission for arrhythmia during follow-up were included as cases. Odds of current AD use among cases (i.e., 14 days before hospital admission) was compared with (i) odds of current use of 1:5 matched controls (between-patients case-control) and with (ii) odds of previous use during 1:5 matched control periods (within-patient case-crossover). The risk of arrhythmia associated with AD current use was modelled fitting a conditional logistic regression. A set of sensitivity analyses were performed to account for sources of systematic uncertainty.

Results: Current users of SSRIs and NAAs were at increased risk of arrhythmia with case-control odds ratios (OR) of 1.37 (95% confidence interval, CI: 1.18 to 1.58) and 1.41 (1.16 to 1.71), and case-crossover OR of 1.48 (1.20 to 1.81) and 1.72 (1.31 to 2.27). An increased risk of arrhythmia was associated with current use of trazodone (NAA) consistently in case-control and case-crossover designs.

Conclusions: Evidence that current use of SSRIs and NAAs is associated to an increased risk of arrhythmia among elderly with CV disease was consistently supplied by two observational approaches.

Key words: Arrhythmia, Antidepressants, Tricyclic antidepressants, Selective serotonin reuptake inhibitors, Newer atypical antidepressants, Nested case-control study, Case-crossover study, Database

Introduction

Due to the high prevalence [192], particularly among elderly people [271], depression is considered a major health problem worldwide. Adequate treatment of depression must be considered as a compelling intervention to reduce the burden of avoidable morbidity, disability, and mortality.

Since 1950s, different types of Antidepressant Drugs (ADs) have been developed to treat depressive symptoms. Nowadays several treatment options are available, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and newer atypical antidepressants (NAAs), among others.

Over many years, a number of different ADs have been associated with an increased risk of cardiovascular (CV) disease [88, 134] and, in particular, with the occurrence of arrhythmia [102]. TCAs, SSRIs (particularly citalopram, fluoxetine, and paroxetine), and NAAs (particularly venlafaxine), are known to prolong QT interval on the electrocardiogram [272-274]. Because QT interval prolongation can lead to arrhythmias including potentially fatal torsades de pointes [275], the relationship between use of ADs and onset of arrhythmia represents a topic of high clinical relevance [276]. In spite of this, few studies have specifically assessed the risk of arrhythmia associated with specific AD molecules [277]. Moreover, an urgent clinical question concerns the effect of ADs on the occurrence of arrhythmia among elderly patients with established CVD.

To address these knowledge gaps, we investigated the association between current use of ADs as a whole, ADs classes (TCAs, SSRIs and NAAs) and individual ADs agents, on the risk of hospitalization for arrhythmia among elderly with previous CV events.

Methods

Data sources and setting

The data used for the present study were retrieved from the healthcare utilization databases of five Italian healthcare territorial units participating to the so-called I-GrADE (Italian Group for Appropriate Drug Prescription in the Elderly) program, funded by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), with the aim of assessing the appropriateness of outpatient drug prescriptions in the Italian elderly discharged from hospital for cardiovascular (CV) disease.

Participating healthcare territorial units were three Regions (Lazio, Lombardy, Tuscany) and two Local Health Units (Caserta, Treviso). Data from about 21 million beneficiaries residing in these areas (accounting for nearly 35% of the Italian population) were recorded in the corresponding databases.

The National Health Service (NHS) provides universal coverage for most healthcare services to the entire Italian population. This service is administered through different databases including: (1) an archive of residents who receive NHS assistance (the whole resident population), reporting demographic and administrative data (e.g. age, gender), other than the dates in which the individual started and stopped the condition of NHS beneficiary (i.e. from birth/immigration to death/emigration); (2) a database on hospital discharge records including information about primary diagnosis and up to five co-existing conditions and procedures coded according to the International Classification of Diseases, Clinical Modification 9th revision (ICD-9 CM); (3) a drug prescription database providing information on all outpatient drug prescriptions reimbursed by the NHS and coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The use of a unique identification code allows for the record linkage of all databases. In order to preserve privacy, the original identification code was replaced with its digest that is the image of the code through a cryptographic hash function. Data were drawn out from databases by means of standardized queries, which were defined and tested according to the study protocol.

ICD-9 CM and ATC codes used for drawing records and fields from databases are respectively reported in **Supplementary Tables S1 and S2**.

Cohort selection, follow-up and outcome

Beneficiaries of the NHS who during 2008-2010 were (i) resident in the participating healthcare territorial units, (ii) aged 65 years or older, (iii) hospitalized for selected CV disease (heart failure, cerebrovascular disease or ischaemic heart disease), and (iv) discharged alive from the index hospitalization, were considered eligible to enter the cohort. The first CV hospital admission occurred during this period was defined as the index hospitalization and the date of the corresponding discharge as the cohort entry.

Subjects were excluded if they had less than two years of look-back period prior to the cohort entry and at least six months of follow-up, to ensure enough time of observation respectively back (for baseline covariates assessment) and forwards (for adequate potential exposure to the drugs of interest). Furthermore, subjects were excluded if, during two-year before the cohort entry, had at least one record of (i) antineoplastic agent or hospitalization for cancer, to exclude patients with high frailty, (ii) antiarrhythmic drug prescription or hospitalization for arrhythmia, to ensure the observation of only incident cases of arrhythmia during follow-up, (iii) AD drug prescription, to exclude patients who started AD therapy before the cohort entry.

The remaining individuals included in the study cohort accumulated person-years of follow-up starting from the cohort entry until the occurrence of one of the following events, whichever came first the study outcome (hospital admission for arrhythmia), or censoring for death, emigration, onset of cancer or the end of study period. As there were differences in data availability across participating healthcare territorial units, the study period ended at December 31, 2011 for Lazio, December 31, 2012 for Lombardy, Tuscany and Caserta and December 31, 2014 for Treviso.

The primary outcome was the first hospitalization with cardiac dysrhythmias as the main reason of hospital admission identified during follow-up. Although cardiac dysrhythmias encompasse a wide range of clinical outcomes, from a simple tachycardia until a fatal ventricular arrhythmia, power concern suggested of collapsing the observed outcomes in a unique category of cardiac dysrhythmias. However, as below specified, ventricular arrhythmias were also considered as alternative outcome.

Selecting cases and controls within the cohort members

A subset of cohort members were included into the analyses according to a nested case-control design. Cases were patients who experienced the hospitalization for cardiac dysrhythmia during follow-up and the first date of admission was considered as index date. Each case was matched to up to five controls randomly selected from the same risk-set of the corresponding case (i.e., among cohort members still at risk of experiencing the outcome). Matching was performed within each participating healthcare territorial unit according to gender, age at cohort entry (± 3 year), and date of cohort entry (± 7 days).

Selecting current and referent periods within the follow-up

Selected time-windows were investigated within the follow-up period. One current time-window was identified for each case and control as that corresponding to 15 days before the index date. Five referent periods preceding the current time-window, each of them with the same 15 days width of the latter, were identified for each case. In addition, with the aim of avoiding a carryover effect, a washout period of 15 days was left between the current time-window and the most recent referent period.

Use of antidepressants and covariates

All ADs dispensed during follow-up were identified. Cases and controls were considered "current AD users" whether an AD agent was dispensed at least once during the current time-window, "past

AD users" were those subjects with at least an AD prescription later than the current time-window and “no AD-users” otherwise. Analogously, ADs use and no-use were investigated during the referent periods for each case.

For each case and control, several covariates were assessed during observation time. Among these, baseline characteristics (i.e., those recorded within two years before the date of cohort entry) included the main diagnosis at index hospitalization (heart failure, cerebrovascular disease or ischaemic heart disease), previous CV hospitalizations, selected co-treatments (digoxin, nitrates, antihypertensive, lipid-lowering agents and antidiabetics) and hospital admissions with diagnosis of diabetes mellitus, hypertension and hyperlipidaemia, and the Charlson comorbidity index (categorized as 0, 1, or ≥ 2) [257]. Features measured during follow-up included the use of antihypertensive, lipid-lowering agents and antidiabetics, as well as of drugs known or suspected to induce arrhythmias [278-287]. Arrhythmogenic drugs are listed in **Supplementary Table S2** and included antiepileptic, antiparkinsonian, psycholeptics, antihypertensive, antidiabetics, antineoplastic, antibiotics, antihistaminic and respiratory drugs.

Data analysis

Two approaches were used for assessing potential pro-arrhythmic effect of current use of ADs (as a whole), of specific ADs classes (i.e., TCAs, SSRIs and NAAs) and of the ten most prescribed individual ADs.

One, according to the nested case-control design, current use of ADs was compared among cases and controls, by allowing a between-patients comparison. A conditional logistic regression model for 1:5 matched data were used to estimate the case-control odds ratio (OR), and 95% confidence interval (CI), of arrhythmia associated with current use vs. current no-use of ADs. Estimates were unadjusted and adjusted for the above listed covariates measured at baseline, during follow-up, or both.

Two, according to the case-crossover design, use of ADs during current and referent periods were compared within each included case. By comparing cases to themselves at different points in time, the case-crossover approach automatically controls for between-person confounding by constant characteristics, e.g. confounding by chronic indication [288]. A conditional logistic regression model for 1:5 matched data was again used to estimate the case-crossover OR, and 95% CI, of hospital admission for arrhythmia associated with current vs. referent use of ADs. Estimates were unadjusted and adjusted for the above listed covariates measured during follow-up.

Heterogeneity of both case-control and case-crossover ORs between the classes of investigated ADs, as well as between individual ADs, was assessed by means of Cochran's Q statistics [289].

Sensitivity analyses

To verify the robustness of our findings, the following sets of sensitivity analyses were performed. First, we verified if our estimates were influenced by the exclusion of subjects who already used ADs during two years before the cohort entry. A larger cohort including prevalent AD users was selected and all analyses above described were performed. Two, the effect of three different ways to ascertain arrhythmia was assessed. In the first one, a limited and specific set of ICD-9 CM codes for ventricular arrhythmias was used. In a second one, we considered as cases those subjects who during follow-up had hospitalization for arrhythmia (as in the main analysis) or a first dispensation of an antiarrhythmic agent, whatever occurred firstly. In the third one, we defined as cases those subjects hospitalized for arrhythmia and who subsequently received an antiarrhythmic prescription. Finally, we verified if our estimates were affected by the adopted criteria for defining the current time-window by considering as current users those patients who received ADs within 30 days before the index date, rather than 15 days as in the main analysis.

All analyses were performed using the Statistical Analysis System software version 9.4 (SAS Institute, Cary, NC, USA). For all tested hypotheses, two-tailed p-values < 0.05 were considered statistically significant.

Results

Patients

The process of selection of the study cohort is described in **Figure 1**. The 199,569 subjects included into the study cohort accumulated 559,406 person-years of observation (on average 2.8 years per patient) and generated 17,277 first hospital admissions for arrhythmia, included as cases in the subsequent analyses. Cases were matched to 85,432 controls.

Selected characteristics of cases and matched controls are compared in **Table 1**. At baseline, mean age was about 79 years and 55% of patients were men. More cases than controls currently used ADs, while no evidence of heterogeneous distribution in the use of specific ADs during the current period was observed. Compared to controls, cases were more often diagnosed for heart failure than for cerebrovascular and ischaemic heart diseases. With few exceptions, comorbidities and co-treatments were significantly more frequent amongst cases than controls both at baseline and during follow-up.

Use of antidepressants and the risk of arrhythmia

The effect of current use of ADs on the risk of arrhythmia is shown in **Figure 2**. Compared with no-users, current users of whatever AD agent, as well as of SSRIs or NAAs alone, exhibited an increased risk of arrhythmia, consistently with both case-control and case-crossover estimates. The case-control ORs were directionally similar for current use of TCAs although without achieving statistical significance, the risk excess being however annulled for the case-crossover estimate. It

is worth observing that: (i) unadjusted estimates did not substantially differ from the adjusted ones, so suggesting weak confounding effect of the considered covariates; (ii) excepting that for TCAs, case-control and case-crossover estimates did not substantially differ, suggesting that between-person confounding by unmeasured constant characteristics only weakly affected case-control estimates; (iii) there was no evidence that the three compared classes of ADs had heterogeneous pro-arrhythmic effect for both case-control (p=0.935) and case-crossover (p=0.405) designs.

Both cardiovascular disease at index hospitalization, and healthcare territorial unit where cohort members were recruited, did not significantly affect case-control estimates (**Supplementary Tables S3 and S4**).

The effect of the ten most prescribed ADs and the risk of arrhythmia is shown in **Figure 3**. Compared with no-users, current use of trazodone exhibited increased risks of arrhythmia consistently with both case-control and case-crossover estimates. Evidence was inconsistent for escitalopram, mirtazapine (only case-control) and citalopram, paroxetine and venlafaxine (only case-crossover). Our study does not offer evidence that current use of sertraline, amitriptyline, duloxetine and fluoxetine may increase the risk of arrhythmia. Finally, there was evidence that individual ADs had heterogeneous pro-arrhythmic effect according to case-crossover design (p=0.040), but not case-control one (p=0.498).

Sensitivity analyses

Table 2 shows that our main results were directionally confirmed by: (i) including into the cohort prevalent AD users (i.e., by increasing the number of cohort members from 199,569 incident users to 274,523 prevalent users); (ii) extending the outcome detection to the first dispensation of an antiarrhythmic agent (i.e., by increasing the number of patients experiencing the outcome from 17,277 to 20,048); (iii) limiting the outcome to hospitalizations for arrhythmia followed by antiarrhythmic prescriptions (i.e., by reducing the number of events to 3,780); (iv) limiting the

outcome ascertainment to a more specific set codes suggestive of ventricular arrhythmias (i.e., by reducing the number of patients experiencing the outcome to 3,030); (v) prolonging the width of the current time-window to 30 days (i.e., increasing the number of current ADs users from 437 to 715).

Discussion

In this large population-based study of elderly patients formerly experiencing a hospital admission for a major CV event, we found that current users of SSRIs and NAAs were at increased risk for developing arrhythmia, the risk being from 37% to 72% higher than that of patients who did not currently use ADs. In particular, our study offer consistent evidence that trazodone (an AD belonging to the NAAs class) may increase the risk of developing arrhythmia of almost 50% - 90% respectively according to the case-control and case-crossover designs. Because of inconsistence between estimators, the proarrhythmic potential of individual SSRIs (escitalopram, citalopram and paroxetine) and NAAs (mirtazapine and venlafaxine) was more uncertain from our study. Finally, likely because our study was underpowered for studying the effect of more rarely prescribed medications, we did not found evidence of proarrhythmic potential of TCAs as a class, as well as individual ADs belonging to the classes of SSRIs (sertraline and fluoxetine), NAAs (duloxetine) and TCAs (amitriptyline).

Comparison with available evidence

Our findings are consistent with previous studies showing increased risk of arrhythmia associated with use of SSRIs [262], as well as increased incidence of ventricular arrhythmia and/or sudden cardiac death among users of SSRIs as a whole [290], sertraline [291] and citalopram [292, 293].

To the best of our knowledge, this is the first study suggesting a possible increased risk of arrhythmia among current users of selected NAAs.

Plausibility

One possible contributing factor to the increased risk of arrhythmia is the strength of different ADs to interfere with cardiac repolarization [294], which may cause QT prolongation on electrocardiogram (ECG) and possibly cardiac ventricular arrhythmia [295]. These effects have been described for (i) TCAs, through their ability to inhibit both neuronal re-uptake of noradrenaline and serotonin, as well as potassium and fast sodium channels [250, 265]; (ii) SSRIs, through the block of rapid potassium delayed rectifier current [296, 297] and the disruption of the hERG protein expression [297]; and (iii) NAAs, through enhanced concentrations of a wide range of central neurotransmitters, including norepinephrine [267]. Taken together, these mechanisms may potentially trigger clinical manifestations arrhythmia, especially in susceptible patients [294]. Additionally, since the proarrhythmic mechanism of drugs depends by their chemical structure [298], the risk of clinical arrhythmia is expected to be heterogeneous among individual ADs. However, except for duloxetine, the ten ADs most prescribed in our setting were listed on the Arizona Center for Education and Research on Therapeutics [299].

Strengths and weaknesses

The present study is unique in several respects. One, the investigation was based on data from a very large unselected population, which was made possible because in Italy a cost-free healthcare system involves virtually all citizens. Two, the drug prescription database provides highly accurate data, because report of prescriptions by the pharmacies is essential for reimbursement, and incorrect report about the dispensed drugs has legal consequences [269]. Three, selection bias from no-response and measurement bias from differential recall cannot be assumed for interpreting our

findings because all eligible patients were included and use of ADs was recorded before the outcome occurred. Four, following the new-user paradigm [165], patients already treated with antidepressants before the index hospital admission were excluded, so reducing the potential biases for the inclusion of those patients. Five, remarkable between-estimates consistency was usually observed irrespectively whether current use of ADs experienced by an individual case was compared to (i) current use of ADs experienced by five matched controls (case-control design), or (ii) use of ADs experienced by the individual case during five matched referent periods (case-crossover design). Doubtless, this result strengthens the robustness of our findings. Finally, a number of sensitivity analyses also gave robustness to our findings.

Our study has a number of potential limitations. One, generalizability of our findings is limited to the persons aged 65 years or older experiencing a major CV event. Two, notwithstanding the large sample size, our study was underpowered for appreciate the effect of less prescribed drugs (particularly TCAs). For example, by accepting a 0.05 two-sided first type error and requiring a 80% power, we estimate that our study was able to detect as significant ORs of 1.2, 1.3 and 1.8 associated with current use of SSRIs, NAAs and TCAs respectively.

Three, as electrocardiograms were not available in our data sources, and proxies of arrhythmia onset were used, outcome misclassification might affect our estimates. We relied on hospital diagnostic codes for capturing patients experiencing arrhythmia. Codes used to identify patients experiencing the primary study outcome, they showed high positive predictive values as reported by a systematic review [300]. However, it should be mentioned that the relationship of interest was confirmed when patients experiencing arrhythmia were captured from a subset of diagnostic codes, as well as from new dispensing of antiarrhythmic agents. In particular, the use of more specific diagnostic codes, minimizing the bias of the outcome misclassification on the association measure [270], makes our corresponding estimates particularly reliable. Finally, as it seems highly

unlikely that errors in diagnostic codes could differently affect patients according to their use of ADs.

Four, evaluation of ADs use was based on pharmacy-dispensing information. This method assumes that prescription corresponds to medication use, which may not be invariably true. Although data on dispensing history have shown to be consistent with other adherence measures [301], medication dispensing as a measure of drug use remains a source of uncertainty of our estimates.

Five, as depressive symptoms could be confused with those of other neuropsychiatric syndromes, as hypoactive delirium [302], antidepressants, in particular trazodone, may have been prescribed for conditions different from depression, e.g. neuropsychiatric diseases [303]. This however, does not modify our main conclusion about the positive association between the considered drugs and the onset of arrhythmia in elderly patients with previous CV event.

Finally, as for any observational study, residual confounding cannot be fully eliminated. In the current application, an important portion of the association between current use of ADs and onset of arrhythmia observed by adopting the between-patients comparison (i.e., the case-control design) might be due to depression per se, rather than its drug therapy. In fact, as major depression after myocardial infarction is a significant predictor of subsequent CV events, including arrhythmias and sudden cardiac death [304-306], we might speculate that the significant higher prevalence of AD users among patients who experience arrhythmia with respect to those who did not experience it, may be explained by higher prevalence of depressive symptoms. However, this is unlikely to be the only explanation of our findings because, as above reported, remarkable consistency of estimates was usually observed when the within-patients comparison (i.e., the case-crossover design) was adopted. As confounders that remain constant within individuals are implicitly controlled by this approach, we speculate that the estimated proarrhythmic effects unlikely might

be due to depression per se. There are several possible explanations for the observed association between current use of ADs and risk of arrhythmia. For example, although we tried to control for the action of known proarrhythmic drugs (e.g., use of antihistamines, gastrointestinal prokinetic agents, antiemetics, other psychotropic drugs, among others [307]), the action of over-the-counter dispensations, as well as drugs interaction cannot be excluded. However, it seems unlikely that these factors may differentially confound the effect of the considered ADs.

Conclusions

This large population-based study offers evidence that the most frequently used ADs are associated with an increased risk of arrhythmia among elderly with previous CV hospital admission, and that the magnitude of the arrhythmogenic effect varies among individual drugs. Since any potential increased risk may result in a considerable impact, the risk effect estimates provided by this study may support both clinical practices and regulatory activities.

Competing interests

Conflict of interests. EL received research support from the Italian Agency of Drug (AIFA).

AM received research support from the Italian Agency of Drug (AIFA), the Italian Ministry for University and Research (MIUR), Gilead, and Menarini. In the last two years he received personal fees as speaker/consultant from Menarini Group, IBSA, Molteni, Angelini and Pfizer Alliance. None of these is related to this study.

GT leads an academic pharmacoepidemiology team which runs project that are sponsored by pharmaceutical companies and that are not related to the topic of the paper.

GC received research support from European Community (EC), European Medicine Agency (EMA), Italian Agency of Drug (AIFA), and Italian Ministry of Health, and of University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as member of Advisory Board from Roche. None of these is related to this study. All other authors declare that they have no conflict of interest.

Contributors

GC generated the study idea and wrote the final manuscript. AB performed all statistical analyses. All Authors abstracted the data, authorized their utilization, and contributed to their interpretation and to the final manuscript by approving the final version.

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Table 1. Characteristics of 17,277 cases hospitalized for arrhythmia and the corresponding 85,432 controls

	Cases	Controls	p-value
Age, Mean (SD)	79.6 (7.1)	79.5 (7.0)	mv
Male gender	9,514 (55.1%)	47,080 (55.1%)	mv
Antidepressants			
No use	14,760 (85.4%)	73,967 (86.6%)	<0.0001
Past use	2,080 (12.1%)	9,941 (11.6%)	
Current use	437 (2.5%)	1,524 (1.8%)	
Antidepressants during the current time-window †			
SSRIs	270 (1.6%)	965 (1.1%)	0.7596
TCAs	14 (0.1%)	41 (0.1%)	
NAAs	153 (0.9%)	518 (0.6%)	
Diagnosis at index hospitalization			
Heart failure	5,037 (29.1%)	13,417 (15.7%)	<0.0001
Cerebrovascular disease	5,505 (31.9%)	36,244 (42.4%)	<0.0001
Ischaemic heart disease	6,735 (39.0%)	35,771 (41.9%)	<0.0001
Charlson comorbidity index			
0	1,747 (10.1%)	11,129 (13.0%)	<0.0001
1	7,014 (40.6%)	39,673 (46.4%)	
≥2	8,516 (49.3%)	34,630 (40.5%)	
Previous comorbidities and co-treatments ††			
Cardiovascular disease	2,729 (15.8%)	10,564 (12.4%)	<0.0001
Diabetes	5,519 (31.9%)	23,046 (27.0%)	<0.0001
Hypertension	15,539 (89.9%)	72,044 (84.3%)	<0.0001
Hyperlipidaemia	7,128 (41.3%)	34,398 (40.3%)	0.0154
Digoxin	1,940 (11.2%)	3,718 (4.3%)	<0.0001
Nitrates	5,628 (32.6%)	22,339 (26.1%)	<0.0001
Co-treatments during follow up ††			
Antidiabetics	5,963 (34.5%)	23,271 (27.2%)	<0.0001
Antihypertensive	16,270 (94.2%)	76,064 (89.0%)	<0.0001
Lipid-lowering drugs	8,917 (51.6%)	46,640 (54.6%)	<0.0001
Antiepileptics	1,414 (8.2%)	5,754 (6.7%)	<0.0001
Antiparkinsonian	270 (1.6%)	1,227 (1.4%)	0.2102
Psycholeptics	554 (3.2%)	2,122 (2.5%)	<0.0001
Digoxin	2,471 (14.3%)	3,925 (4.6%)	<0.0001
Nitrates	7,325 (42.4%)	27,843 (32.6%)	<0.0001
Respiratory drugs	5,372 (31.1%)	16,992 (19.9%)	<0.0001
Antihistamines:			

Phenothiazine derivatives	14 (0.1%)	64 (0.1%)	0.7624
Piperazine derivatives	814 (4.7%)	3,043 (3.6%)	<0.0001
Other antihistamines for systemic use	759 (4.4%)	3,026 (3.5%)	<0.0001
Antibacterials for systemic use:			
Tetracyclines	206 (1.2%)	727 (0.8%)	<0.0001
Beta-Lactam antibacterials, Penicillins	5,523 (32.0%)	21,025 (24.6%)	<0.0001
Other Beta-Lactam antibacterials	4,139 (24.0%)	14,019 (16.4%)	<0.0001
Sulfonamides and Trimethoprim	514 (3.0%)	1,845 (2.2%)	<0.0001
Macrolides, Lincosamides and Streptogramins	3,200 (18.5%)	11,763 (13.8%)	<0.0001
Aminoglycoside antibacterials	208 (1.2%)	689 (0.8%)	<0.0001
Quinolone antibacterials	6,907 (40.0%)	24,162 (28.3%)	<0.0001

MV matching variables; SSRIs: Selective serotonin reuptake inhibitor; TCAs: Tricyclic antidepressants; NAAs: Newer Atypical ADs

† Exposure time-window of 15 days

†† Please see **Supplementary Tables S1 and S2** for ICD-9 and ATC codes used for defining comorbidities and co-treatments measured at baseline (i.e. in the two years before the entry date) and during follow-up

Table 2. Influence of varying criteria of exposure and outcome definitions on nested, case-control and case-crossover odds ratios of arrhythmia associated with current use of antidepressants as a whole (ADs), Selective Serotonin Reuptake Inhibitor (SSRIs), Tricyclic Antidepressants (TCAs) and Newer Atypical Antidepressants (NAAs)

	Antidepressant class	Nested, case-control †	Case-crossover †
Inclusion of prevalent users	ADs	1.07 (1.00 to 1.15)	1.08 (0.95 to 1.22)
	TCAs	1.16 (0.84 to 1.60)	0.98 (0.61 to 1.59)
	SSRIs	1.04 (0.95 to 1.14)	1.04 (0.91 to 1.18)
	NAAs	1.11 (0.99 to 1.25)	1.13 (0.95 to 1.34)
Extending criteria for outcome detection ††	ADs	1.21 (1.08 to 1.35)	1.50 (1.22 to 1.85)
	TCAs	1.78 (1.01 to 3.15)	1.05 (0.43 to 2.60)
	SSRIs	1.18 (1.03 to 1.36)	1.42 (1.17 to 1.74)
	NAAs	1.22 (1.01 to 1.47)	1.54 (1.18 to 2.02)
Restricting criteria for outcome detection§	ADs	1.32 (1.01 to 1.72)	1.15 (0.71 to 1.86)
	TCAs	1.58 (0.31 to 8.01)	1.06 (0.18 to 6.17)
	SSRIs	1.27 (0.90 to 1.77)	1.08 (0.75 to 1.56)
	NAAs	1.39 (0.89 to 2.17)	1.80 (1.09 to 2.98)
Restricting criteria for outcome definition #	ADs	1.48 (1.15 to 1.92)	1.55 (0.95 to 2.52)
	TCAs	1.97 (0.46 to 8.47)	1.68 (0.25 to 11.25)
	SSRIs	1.58 (1.15 to 2.18)	2.29 (1.40 to 3.73)
	NAAs	1.27 (0.81 to 1.99)	1.84 (0.93 to 3.64)
Lengthening exposure time-window ##	ADs	1.23 (1.13 to 1.34)	1.32 (1.09 to 1.60)
	TCAs	1.49 (0.93 to 2.40)	0.67 (0.30 to 1.48)
	SSRIs	1.19 (1.07 to 1.33)	1.58 (1.31 to 1.91)
	NAAs	1.28 (1.10 to 1.48)	1.90 (1.49 to 2.41)

† Odds ratios estimated with conditional logistic regression model. For the nested case-control design, estimates were adjusted for covariates measured at baseline and during follow-up; for the case-crossover design, estimates were adjusted for covariates measured during follow-up. Please see **Table 1** for the complete list of covariates, and **Supplementary Tables S1 and S2** for the corresponding ICD-9 and ATC codes

†† Outcome detection: hospital admission with main diagnosis of arrhythmia or prescription of an antiarrhythmic agent, whichever came first. Please see Supplementary Table S2 for ATC codes of antiarrhythmic agents

§Outcome detection: hospital admission with main diagnosis of arrhythmia subsequently followed by antiarrhythmic prescription

[#] Outcome definition: hospital admission with main diagnosis of ventricular arrhythmia. Please see **Supplementary Table S1** for ICD-9 codes of ventricular arrhythmia
[##] Exposure time-window of 30 days

Figure 1. Study flow diagram

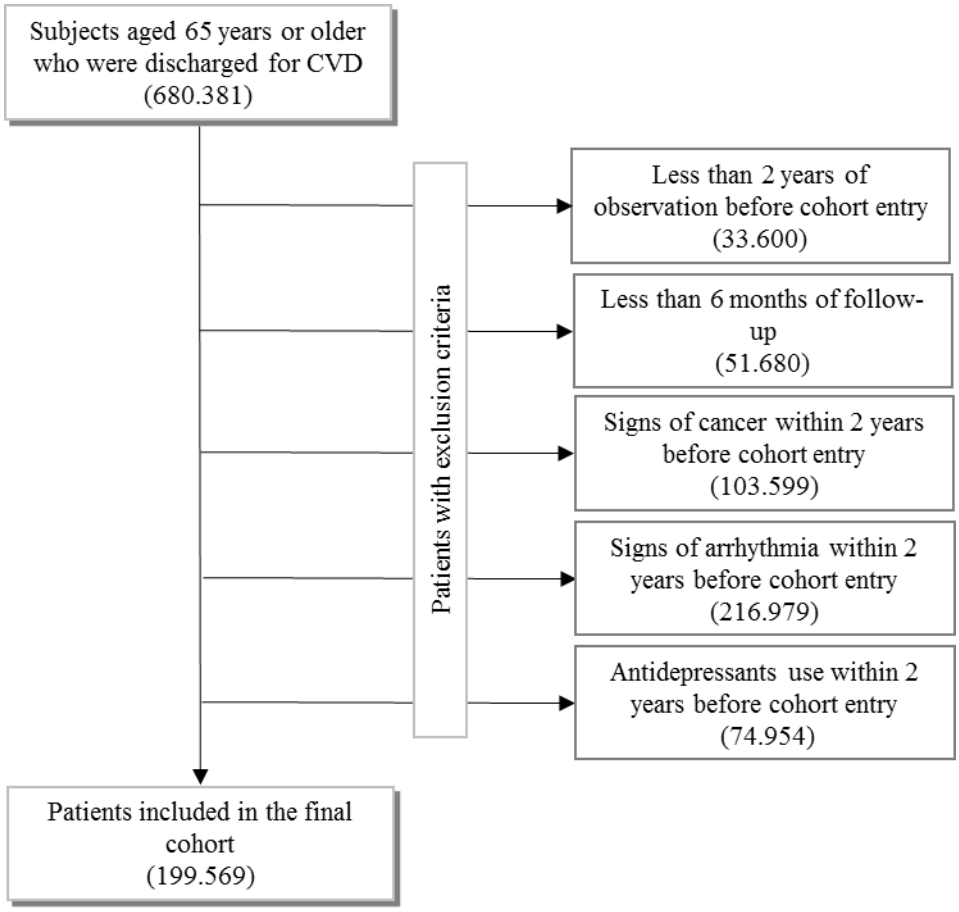
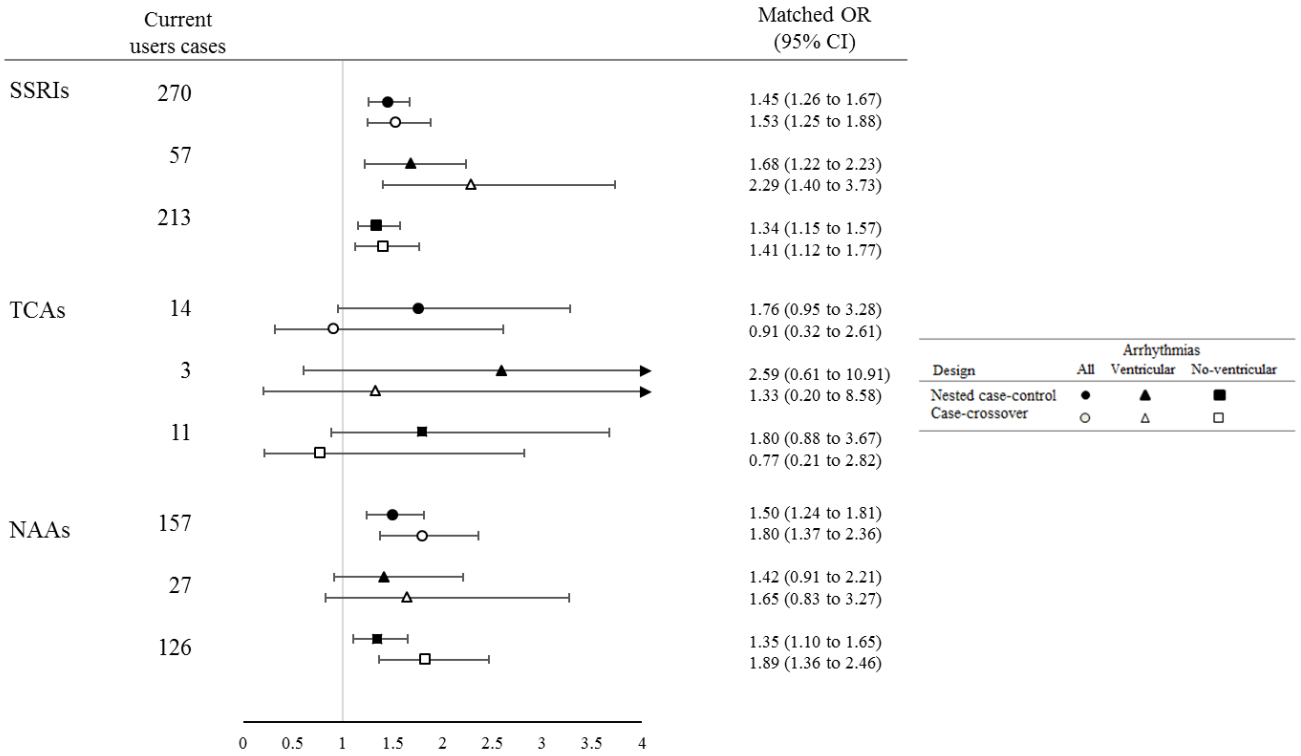
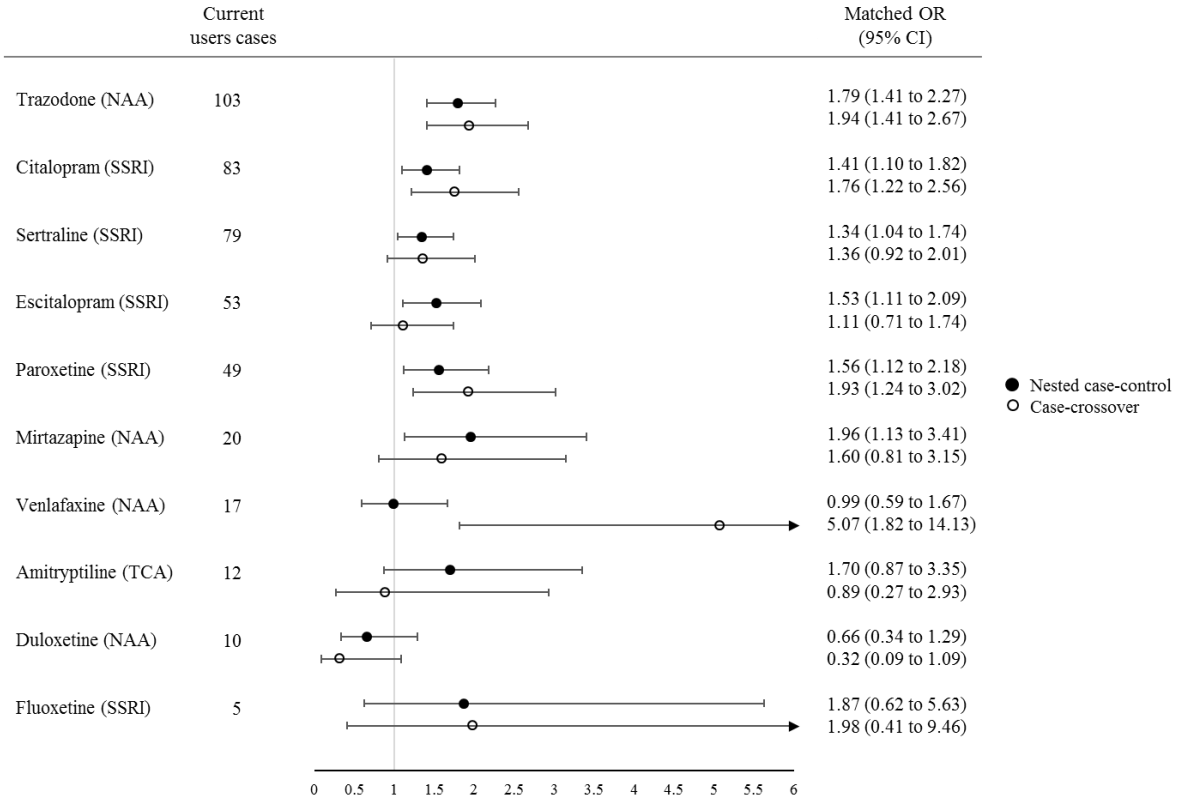


Figure 2. Nested case-control and case-crossover, ORs (and corresponding 95% confidence intervals, CI) of the relationship between current use of Selective Serotonin Reuptake Inhibitor (SSRIs), Tricyclic Antidepressants (TCAs) and Newer Atypical Antidepressants (NAAs) and the risk of hospitalization for arrhythmia



Footnote: Odds ratios estimated with conditional logistic regression model. For the nested case-control design, estimates were adjusted for covariates measured at baseline and during follow-up; for the case-crossover design, estimates were adjusted for covariates measured during follow-up. Please see **Table 1** for the complete list of covariates, and **Supplementary Tables S1 and S2** for the corresponding ICD-9 and ATC codes

Figure 3. Nested case-control and case-crossover odds ratios, ORs (and corresponding 95% confidence intervals, CI) of the relationship between current use of individual Selective Serotonin Reuptake Inhibitor (SSRIs), Tricyclic Antidepressants (TCAs) and Newer Atypical Antidepressants (NAAs), and hospitalization for arrhythmia



Footnote: Odds ratios estimated with conditional logistic regression model. For the nested case-control design, estimates were adjusted for covariates measured at baseline and during follow-up; for the case-crossover design, estimates were adjusted for covariates measured during follow-up. Please see **Table 1** for the complete list of covariates, and **Supplementary Tables S1 and S2** for the corresponding ICD-9 and ATC codes

Supplementary material

Table S1. Diagnostic codes used for the study purpose (ICD-9 CM classification)

Arrhythmia
- 427.* (Cardiac dysrhythmias)
  - 427.0 (Paroxysmal supraventricular tachycardia)
  - 427.1 (Paroxysmal ventricular tachycardia)
  - 427.2 (Paroxysmal tachycardia, unspecified)
  - 427.3 (Atrial fibrillation and flutter)
  - 427.4 (Ventricular fibrillation and flutter)
  - 427.5 (Cardiac arrest)
  - 427.6 (Premature beats)
  - 427.8 (Other specified cardiac dysrhythmias)
  - 427.9 (Cardiac dysrhythmia, unspecified)
- 785.0 (Tachycardia unspecified)

Ventricular arrhythmia
- 427.1 (Paroxysmal ventricular tachycardia)
- 427.4 (Ventricular fibrillation and flutter)
- 427.5 (Cardiac arrest)
- 427.69 (Other premature beats (ventricular premature beats, contractions, or systoles))

Heart failure
- 428.*, 402.01, 402.11, 402.91

Cerebrovascular disease
- 430.*-438.*

Ischaemic heart disease
- 410.*-414.*

Neoplasms
- 140.*-239.* (Malignancies)

Diabetes
- 250.* (Diabetes mellitus)

Hypertension
- 401.* (Hypertension)

Hyperlipidaemia
- 272.0, 272.4 (Hyperlipidaemia)

Table S2. Anatomical, Therapeutic and Chemical codes of drugs used for the study purpose

Antidepressants
- N06AA (Tricyclic antidepressants)
  - N06AA02 (Imipramine)
  - N06AA04 (Clomipramine)
  - N06AA06 (Trimipramine)
  - N06AA09 (Amitriptyline)
  - N06AA10 (Nortriptyline)
- N06AB (Selective serotonin reuptake inhibitors)
  - N06AB03 (Fluoxetine)
  - N06AB04 (Citalopram)
  - N06AB05 (Paroxetine)
  - N06AB06 (Sertraline)
  - N06AB08 (Fluvoxamine)
  - N06AB10 (Escitalopram)
- N06AX (Newer atypical antidepressants)
  - N06AX03 (Mianserin)
  - N06AX05 (Trazodone)
  - N06AX11 (Mirtazapine)
  - N06AX12 (Bupropion)
  - N06AX16 (Venlafaxine)
  - N06AX18 (Reboxetine)
  - N06AX21 (Duloxetine)

Antiarrhythmics
- C01BA01 (Quinidine)
- C01BA03 (Disopyramide)
- C01BB02 (Mexiletine)
- C01BC03 (Propafenone)
- C01BC04 (Flecainide)
- C01BD01 (Amiodarone)
- C01BD07 (Dronedarone)

Antineoplastics and immunomodulating agents
- L

Antidiabetics
- A10

Antihypertensive agents
- C02 (Antihypertensive)
- C03 (Diuretics)
- C07 (Beta blocking agents)
- C08 (Calcium channel blockers)
- C09 (Agents acting on the Renin-Angiotensin System)

Lipid-modifying agents
- C10

Other CV agents
C01AA05 (Digoxin)
C01DA (Nitrates)

Antiepileptic
N03

Antiparkinsonian
N04

Psycholeptics
N05

Antibiotics
J01A Tetracyclines
J01C Beta-lactam antibacterials, Penicillins
J01D Other beta-lactam antibacterials
J01E Sulfonamides and Trimethoprim
J01F Macrolides, Lincosamides and Streptogramins
J01G Aminoglycoside antibacterials
J01M Quinolone antibacterials

Antihistaminic
R06AD Phenothiazine derivatives
R06AE Piperazine derivatives
R06AX Other antihistamines for systemic use

Respiratory drugs
R03 Drugs for obstructive airway diseases

Table S3. Nested case-control design, stratification according to cardiovascular disease at index hospitalization

	AD class	Cerebrovascular disease		Heart failure		Ischemic heart disase		*Homogeneity test p-value*
		OR	**95% IC**	**OR**	**95% IC**	**OR**	**95% IC**	
All arrhythmias	ADs	1.26	(1.06 to 1.49)	1.32	(1.05 to 1.67)	1.56	(1.27 to 1.93)	0.2882
	TCAs	1.18	(0.45 to 3.05)	0.97	(0.20 to 4.59)	4.13	(1.34 to 12.69)	0.1792
	SSRIs	1.36	(1.11 to 1.68)	1.23	(0.92 to 1.64)	1.45	(1.10 to 1.90)	0.7168
	NAAs	1.09	(0.81 to 1.46)	1.57	(1.06 to 2.33)	1.63	(1.16 to 2.29)	0.1520

Footnote: Odds ratios estimated with conditional logistic regression model. Estimates were adjusted for covariates measured at baseline and during follow-up. Please see **Table 1** for the complete list of covariates, and **Supplementary Tables S1 and S2** for the corresponding ICD-9 and ATC codes

Table S4. Nested case-control design, stratification according to the Italian healthcare territorial unit

	AD class	Caserta		Lazio		Lombardy		Tuscany		Treviso		*Homogeneity test p-value*
		OR	**95% IC**	**OR**	**95% IC**	**OR**	**95% IC**	**OR**	**95% IC**	**OR**	**95% IC**	
	ADs	0.97	(0.49 to 1.92)	1.55	(1.12 to 2.15)	1.36	(1.15 to 1.61)	1.42	(1.18 to 1.71)	1.37	(0.64 to 2.93)	0.8067
All	TCAs	n.a.		1.46	(0.16 to 13.39)	2.17	(0.94 to 5.00)	0.97	(0.31 to 3.02)	n.a.		0.5330
arrhythmias	SSRIs	1.18	(0.54 to 2.60)	1.77	(1.21 to 2.58)	1.32	(1.07 to 1.63)	1.35	(1.05 to 1.73)	1.27	(0.53 to 3.05)	0.7268
	NAAs	0.71	(0.20 to 2.59)	1.09	(0.56 to 2.11)	1.36	(1.01 to 1.84)	1.56	(1.18 to 2.08)	1.72	(0.39 to 7.54)	0.6818

Footnote: Odds ratios estimated with conditional logistic regression model. Estimates were adjusted for covariates measured at baseline and during follow-up. Please see **Table 1** for the complete list of covariates, and **Supplementary Tables S1 and S2** for the corresponding ICD-9 and ATC codes

IV Study

Adherence to antidepressants and risk of mortality in elderly patients with cardiovascular disease

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Abstract

PURPOSE. Conflicting findings from studies evaluating the association between use of antidepressant drugs and mortality have been reported. We tested the hypothesis that better adherence to antidepressant therapy may reduce the risk of death.

METHODS. The cohort, which comprised 29,845 individuals aged ≥ 65 years from several Italian health units and newly treated with antidepressant drugs after hospital discharge with a diagnosis for cardiovascular disease during 2008–2010, was followed from the first prescription until the end of data availability (i.e. 2012-2014, depending on the local database). During this period, information on medications prescription renewals of antidepressants and other medications, and deaths for any cause (outcome), was recorded. Proportional hazards models were fitted for estimating the association between better adherence to antidepressants (i.e., cumulative time-dependent antidepressant covering ≥75%, as contrasted with covering <75%) and outcome, after adjusting and stratifying for several covariates.

RESULTS. Patients with better adherence to antidepressants had reduced risk of death of 9% (95% confidence interval, 3% to 14%). Patients who did not use other medicaments during follow-up, had reduced risk of death associated with better adherence to antidepressant of 21% (-1% to 38%), 14% (7% to 20%), 20% (13% to 26%) and 13% (7% to 19%) for no users of antihypertensive, lipid-lowering agents, other cardiovascular drugs and antidiabetics, respectively.

CONCLUSIONS. Better adherence to antidepressants is associated with reduced all-cause mortality, mainly in patients who did not use other pharmacologic treatments. Enhancing adherent behaviour among elderly with cardiovascular disease, might offer important benefits in reducing their mortality.

KEY WORDS. Adherence; Antidepressants; Cardiovascular disease; Mortality

Key points

- The role of adherence to antidepressant respect to the risk of mortality is still controversial, since few studies have specifically assessed this relationship among elderly patients with established CVD.
- The better adherence to antidepressant may decrease the risk of mortality, mainly among elderly patients who did not use comedications.
- The findings provided by this study may result in a considerable public health impact and may support both clinical practices and regulatory activities.

1 Introduction

Due to its high worldwide prevalence, depression is a serious public health concern. Currently, it is estimated to affect over 350 million people worldwide and up to a quarter of the European population [192]. One in five older people experience anxiety and/or depression with prevalence increasing with age [308]. Anxiety and depression prevalence is reported to be high among people with co-morbid long-term conditions [105]. Although prevalence of depression among patients with cardiovascular disease (CVD) varies according to the specific disease processes and assessment method [309], around 50% of patients experience major or minor depression at least once in the course of experiencing CVD [310].

Adequate treatment of depression must be considered as a compelling public health intervention to reduce the burden of avoidable morbidity, disability and mortality. Antidepressant Drugs (ADs), developed since 1950s to treat depressive symptoms, are nowadays widely available with several treatment options [134].

Poor adherence to ADs is commonly reported among people who are prescribed ADs [311-314], including patients with CVD [120, 210, 315]. On the other hand, conflicting results have been reported from studies addressing the relationship between adherence to ADs and mortality among CVD patients [315, 316]. Differences in study design, often its methodological shortcomings with variable impact (e.g., the inclusion of prevalent users of ADs and poor information about adherence to other medications), likely explain most of these conflicting results.

To address these knowledge gaps, we tested the hypothesis that a better adherence to ADs may reduce the risk of death among older people (i.e. more than 65 years) with CVD. The study is a part of an Italian project funded by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) which supported the Italian Group for Appropriate Drug prescription in the Elderly (I-GrADE) for assessing the appropriateness of outpatient drug prescriptions in the Italian elderly discharged from hospital for CVD.

2 Methods

2.1 Data sources and setting

The data used for the present study were retrieved from the healthcare utilization databases of five Italian healthcare territorial units participating to the I-GrADE project, namely three Regions (Lazio, Lombardy, Tuscany) and two Local Health Units (Caserta, Treviso). Data from about 21 million beneficiaries residing in these areas (accounting for nearly 35% of the Italian population) were recorded in the corresponding databases.

The National Health Service (NHS) provides universal coverage for most healthcare services to the entire Italian population. This service is administered through different databases including: (i) an archive of residents who receive NHS assistance (i.e. the whole resident population), including demographic and administrative data (e.g. age, gender), as well as start and end dates of the condition

of NHS beneficiary (i.e. from birth/immigration to death/emigration); (ii) a database on hospital discharge records including information about primary diagnosis and up to five co-existing conditions and procedures coded according to the International Classification of Diseases, Clinical Modification 9th revision (ICD-9 CM); (iii) a drug prescription database providing information on all outpatient drug prescriptions reimbursed by the NHS and coded according to the Anatomical Therapeutic Chemical (ATC) classification system. The use of a unique person identification code allows for the record linkage of all databases. In order to preserve privacy, the original identification code was replaced with its digest that is the image of the code through a cryptographic hash function. Data were drawn out from databases by means of standardized queries, which were defined and tested according to the study protocol.

ICD-9 CM and ATC codes used for drawing records and fields from databases are respectively reported in Supplementary Tables S1 and S2.

2.2 Cohort selection, follow-up and outcome

Beneficiaries of the NHS who during 2008-2010 (i) were residents in the participating healthcare territorial units and beneficiaries of the NHS; (ii) were over 65 years of age; (iii) were hospitalized at least once for selected CVD (heart failure, cerebrovascular disease, ischaemic heart disease or arrhythmia); (iv) were discharged alive from the first occurred CV hospital admission (i.e., the index hospitalization); (v) received at least one prescription of ADs within one year after the index hospitalization, were considered eligible to enter the cohort. Following the user-only paradigm, subjects who did not use ADs were also excluded, so reducing the potential for confounding by indication (e.g., due to uncontrolled differences in baseline risk between AD users and no-users) [317].

Subjects were excluded if they had less than three years of look-back time prior to the first AD prescription and at least six months of follow-up after. The former criterion was applied to ensure

enough observation time to identify baseline covariates and the latter to ensure enough observation time to assess drug utilisation (including adherence) and the occurrence of death. Subjects were also excluded if during three years prior the first AD prescription, they (i) had at least one record of antineoplastic and immunomodulating agents or hospitalization for cancer, so excluding those patients who had high physical frailty and therefore a high baseline risk of death; (ii) were already in treatment for depression, so reducing the potential for the selective inclusion of those patients who kept therapy (i.e., a new-user design was adopted from our study) [165].

The remaining patients included in the study cohort accumulated person-years of follow-up starting from the cohort entry (i.e., the first prescription of ADs occurred within a year after the date of discharge from the index hospitalization) until the occurrence of death for any cause (study outcome), emigration, or the end of study period. As there were differences in data availability across databases of the participating healthcare territorial units, the study period ended at December 31, 2011 for Lazio, December 31, 2012 for Lombardy, Tuscany and Caserta and December 31, 2014 for Treviso.

Because we had no information about drug prescriptions for inpatients, with the aim to assess the potential impact of the so-called immeasurable time bias, i.e. the differential misclassification due to unmeasured drug exposure during hospitalizations [318], we did not account for the follow-up time corresponding to any hospitalization event plus 10 days after hospital discharge.

2.3 Adherence to antidepressants

All ADs dispensed to cohort members during follow-up were identified. The period covered by a prescription was calculated from the number of posologic units in the dispensed canisters, assuming a treatment schedule of one posologic unit per day [319]. For overlapping prescriptions, the individual was assumed to have refilled and completed the first prescription before starting the second. Consecutively refilled prescriptions were assigned to a unique therapeutic cycle if a drug overlapped or was prescribed within a grace period (i.e., 30 days following the end of the latest dispensation in

the main analysis), and the entire period between the two consecutive prescriptions was assumed covered by drug availability. Conversely, i.e., if a given prescription was not renewed within the grace period, the patient was assumed to have stopped treatment at that point, and the period between the two prescriptions was considered uncovered by drug availability. Adherence was assessed as the cumulative number of days coverered by AD prescriptions divided by the number of days of patient follow-up, a masure referred to as "proportion of days covered" (PDC) [320]. In the main analysis, we classified cohort members according whether PDC was <75% or ≥75%, denoting they as poorly and highly adherent patients respectively.

2.4 Covariates

Cohort members were assessed for several covariates. Among these, baseline characteristics included age, gender, class of antidepressant firstly prescribed (i.e., selective serotonin reuptake inhibitor, tricyclic antidepressants, newer atypical antidepressants, or a fixed combination of two ADs), main diagnosis at index hospitalization (heart failure, cerebrovascular disease, ischaemic heart disease or arrhythmia), comorbidities and comedications. The Charlson comorbidity score [257] was calculated via the diagnostic information provided by the inpatient charts within the 3 years before the first AD prescription, and categorized as 0, 1 or ≥2. Selected co-treatments dispensed in the year before the first AD prescription included antiarrhythmic, antithrombotic, antihypertensive, lipid modifying, other CV and antidiabetic agents, drugs for obstructive airway diseases and thyroid therapy, and antiepileptic, antiparkinsonian, psycholeptics, and psychoanaleptics (excluding antidepressants). Looking at the year prior the first AD prescription, a polypharmacy score was developed by categorizing the highest number of drugs with different 5-digit ATC codes dispensed in a day as 0, 1-4, 5-9, and ≥10 prescriptions [321].

Finally, the use of antihypertensive, lipid modifying, other CV agents and antidiabetics was evaluated during follow-up. Adherence to each of these medications was calculated among users of them with

the same criteria above described for ADs. Cohort members were so classified in poorly and highly adherent with PDC <75% and ≥75%.

2.5 Data analysis

Individual-level data retrieved from local databases of the participating healthcare territorial units were firstly gathered into a pooled dataset that was used for data analysis. Chi-square, its version for the trend, and t-test were used where appropriate to test for differences between cohort members who highly or poorly adhered to therapy with ADs.

The Cox proportional hazard regression model was used to estimate the hazard ratio (HR) and its 95% confidence interval (CI), for the association between adherence to ADs and the risk of death. Adjustments were always made for the above listed covariates measured at baseline and during follow-up. The joint action of antidepressants and other medications on the risk of death, was assessed including dummy variables obtained by combination of AD adherence with three categories for each comedications (no users and two levels of adherence). As use and adherence to drugs may change over time, assessment of its effect requires consideration of its cumulative and varying nature. This was done by fitting the Cox model expressing use and adherence categories as time-dependent covariates. Models were separately fitted according to strata of CV diagnosis at index hospitalization.

To check whether our estimates were affected by the adopted criteria for measuring adherence to ADs, two sensitivity analyses were performed. One, other than a 30-day grace period allowed for assigning two consecutive prescriptions to a unique therapeutic cycle, alternative lengths of 20 and 40 days were adopted. Two, other than the 75% PDC value for defining trade-off between poorly and highly adherent patients, more permissive (70%) and more restrictive (80%) trade-offs were adopted.

All analyses were performed using the Statistical Analysis System Software (version 9.2; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

3 Results

3.1 Patients

The process of selection of the study cohort is reported in Figure 1. The 29,845 patients included into the final cohort accumulated 79,260 person-years (PYs) (on average 2.7 years per patient) and generated 7,882 deaths, mortality rate being 99.4 every 1,000 PYs.

Among the 29,845 cohort members, only 5,959 (20%) adhered to ADs during follow-up. Table 1 shows that, compared to highly adherent, patients who were poorly adherent to AD treatment during follow-up were older, initially treated on monotherapy with tricyclic antidepressants or newer atypical antidepressants and showed a slightly better clinical profile according to the Charlson comorbidity score. At the same time, poorly adherent patients received more co-treatments (according to the polypharmacy score assessed during the year prior the first AD prescription). Conversely, during follow-up, these patients were poorly treated with comedications (except CV drugs) than individuals who highly adhered to ADs.

3.2 Adherence to antidepressant drug therapy and risk of death

Figure 2 shows that, compared to poorly adherent, highly adherent patients had reduced risk of death ranging from 9% (95% CI, 3% to 14%) to 16% (11% to 21%) respectively according whether estimates were adjusted for comedications during follow-up, or they were obtained regardless them. There was statistical evidence that AD adherence was associated with reduced mortality among cohort members who had main diagnosis of cerebrovascular disease at index hospitalization. The effect of adherence to ADs among patients affected by ischemic heart disease, arrhythmia and heart failure, although directionally similar, was weaker and did not reach statistical significance.

Figure 3 shows that, although adherence to ADs increased survival in all categories of use and adherence to comedications, its action decreased from patients who did not use them (being the

reduced mortality associated with adherence to ADs respectively 21% for users of antihypertensive agents, 14% for users of lipid modifying agents, 20% for users of other CV agents and 13% for users of antidiabetics agents), to users with good adherence (8%, 1%, 7% and 6%).

3.3 Sensitivity analyses

Our main findings substantially did not change by varying criteria for calculating adherence to ADs. In fact, mortality was reduced of 19% (14% to 24%) and 15% (10% to 19%) by respectively allowing 20 and 40 days grace period between two dispensings. Moreover, mortality was reduced of 14% (9% to 19%) and 21% (16% to 25%) by defining highly adherent those patients who had PDC≥70% and PDC≥80% respectively.

4 Discussion

Our study based on "real-world" data on almost 30,000 elderly people who started AD treatment after hospital discharge for CV outcome, provides further evidence that the more adherent is the use of AD, the greater is the reduction in mortality risk. In particular, we observed that compared with patients at poor adherence, those with better adherence had a significant 9% reduction in the risk of death. In addition, as a novel and original message, our study showed that better adherence to antidepressant drug therapy exerted its protective action mainly among patients who did not use other selected medications, rather than among those who used them with better adherence.

Our findings may shed light on the clinically important question of whether the detrimental effect of suboptimal treatment with ADs in patients suffering of major CVD, might be indeed the consequence of decreasing adherence to other life-saving medications such as cardiovascular drugs compared with no depressed patients [322, 323], as suggested by preliminary reports of small-scale studies [324, 325]. Specifically, it was not clear whether the association between poor adherence to ADs and

mortality is the result of depression itself rather than the degree of adherence (confounding by indication) and/or whether this association is confounded by poor adherence to non-AD life saving medications. The first issue was addressed by empolying a user-only design [317] i.e., patients who did not use ADs after experiencing CV hospitalization were excluded, thus reducing the possibility of confounding the effect of AD medication with its indication (depressive symptoms). In this way, it is not unexpected that our findings are consistent with other with other studies showing that poor adherence to ADs reduced survival in general population [326], as well as in CV patients [315, 316]. On the contrary, the increased mortality observed in patients who used ADs with respect to those who did not use them [197, 327-329], may be explained by the action of depression in worsening prognosis of CV patients [330].

The second issue, and perhaps the more important one, concerns the potential confounding of the association between poor adherence to ADs and mortality by non-use of or poor adherence to other important medications known to reduce mortality [331]. This finding suggests that better adherence to ADs ensures greater survival among patients who did not receive pharmacologic treatment for lowering blood pressure, cholesterol or glycaemia, or for treating angina, heart failure, atrial fibrillation or other arrhythmias. In these patients, better adherence to ADs could be a marker of a healthy adherer effect, that is, that such patients are more mindful of health-related behaviours (e.g., physical activity, healthy diet and smoking cessation) [316, 332]. On the contrary, patients who receive pharmacologic treatment with the considered comedications, take less advantage from adherence to ADs, likely because antidepressants poorly affect the prognosis in these patients. Of course, this hypothesis needs to be tested in future studies.

At least other two results of our study deserve to be mentioned. One, in line with previous studies [314, 333], we observed that almost one in five patients kept good adherence to ADs after a mean time of nearly 3 years of follow-up from starting therapy. It adds to the previous results, however, the fact that the cohort was generated by adopting a new-user design [165], i.e., patients who already

used ADs before experiencing CV hospitalization were excluded. This makes our data less susceptible to bias arising from the selection of those patients who survived their initial therapy with ADs before experiencing index CV hospitalization. Two, the beneficial effect of ADs on mortality was mainly exerted among patients who had previous hospital admission for cerebrovascular disease compared to the other cardiovascular diseases studied. As post-stroke depression occurs in 31% stroke survivals [334] and was found to be associated with increased mortality [335-338], patients experiencing stroke could gain more benefit from adherence to AD than other CV patients.

Our study has several key strengths. One, the investigation was based on a large unselected population, which was made possible because in Italy a universal healthcare assistance is provided to virtually all citizens. Two, the drug prescription database provided highly accurate data, because pharmacists are required to report prescriptions in detail in order to obtain reimbursement, and incorrect reports about the dispensed drugs have legal consequences [269]. Three, participants were identified at the time of their initial antidepressant drug therapy, and only patients who had used ADs were included, having "new-user" and "user- only" approaches demonstrated to reduce the potential for confounding by indication and to avoid underscertainment of events occurring soon after therapy begins [165, 317]. Finally, we found that changing criteria employed for exposure definitions in terms of adherence and grace period did not affect our estimates, thus confirming the robustness of our findings.

However, our study has also limitations. First, data on the indications for AD therapy associated with the need for antidepressant therapy, as well as on cause of death (e.g., deaths due to CVD, suicide, or other cause) were not available in our database. Two, adherence with treatment was derived from drug dispensings. This is a widely used method to estimate adherence to treatment in large populations [339], which requires, however, the assumption that, in the case of the present study, the number of dispensed posologic units actually corresponds to the number of days of drug use [340]. Three, the period covered by a prescription was calculated assuming a treatment schedule of one

posologic unit per day. However, recommendation of posologic units may be variable considering their dosage and depending by the needs of patients. Four, the 2.7-years follow-up maybe not long enough for assessing mortality as an outcome measure. Finally, given the observational nature of the data used for this study, caution is necessary in making inferences regarding causality since the possible differential distribution of unmeasured patients' characteristics across the exposure groups (eg. smoking, obesity, physical inactivity, unhealthy diet) might have confounded the observed association.

5 Conclusions

The present study suggests that among elderly starting antidepressant drug therapy after hospital admission for cerebrovascular outcomes, and perhaps for other major CVD, survival was higher among highly adherent subjects to ADs. Survival was increased up to 20% among patients who were not treated with cardiovascular drugs. Poor adherence to ADs in these patients could be a marker of unhealthy behaviours that by themselves may explain the excess of mortality. Thus, improving adherence in elderly with CVD represents a public health concern. Further studies are needed to better clarify mechanisms underlying the association between depression, antidepressant drug therapy and mortality in frail patients.

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Conflicts of interests

EL received research support from the Italian Agency of Drug (AIFA). AM received research support from the Italian Agency of Drug (AIFA), the Italian Ministry for University and Research (MIUR), Gilead, and Menarini. In the last two years he received personal fees as speaker/consultant from Menarini Group, IBSA, Molteni, Angelini and Pfizer Alliance. GC received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry for University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as member of Advisory Board from Roche. AC received support for participation at pharmacological meetings (SIF) and honoraria as member of Advisory board on biological drugs.

Other authors declare that they have no conflict of interest to disclose.

Table 1. Selected characteristics of the 29,845 patients included into the final cohort according to their adherence to therapy with antidepressant agents. I-GrADE program, Italy, 2008-2014

	Poor adherent[1] (n =23,886)	Highly adherent[1] (n =5,959)	p-value[2]
At baseline			
Age in years: mean (SD)	79.1 (7.2)	77.9 (6.7)	<0.0001
Women	13,486 (56%)	3,437 (58%)	0.0897
First antidepressant pharmacotherapy			
SSRIs	17,587 (74%)	5,279 (89%)	<0.0001
TCAs	1,756 (7%)	139 (2%)	<0.0001
NAAs	8,719 (36%)	1,810 (30%)	<0.0001
Fixed dose combination	1,811 (8%)	1,263 (21%)	<0.0001
Diagnosis at index hospitalization			
Heart failure	3,595 (15%)	653 (11%)	<0.0001
Cerebrovascular disease	10,354 (43%)	3,325 (56%)	
Ischaemic heart disease	5,918 (25%)	1,181 (20%)	
Arrhythmia	4,019 (17%)	800 (13%)	
Charlson comorbidity score[3]			
0	3,281 (14%)	602 (10%)	<0.0001
1	9,828 (41.1%)	2,654 (44.5%)	
≥2	10,777 (44.9%)	2,703 (45.5%)	
Comedications[4]			
Antiarrhythmic agents	3,581 (15%)	781 (13%)	0.0005
Antithrombotic agents	19,125 (81%)	4,520 (78%)	<0.0001
Antihypertensive agents	21,105 (90%)	5,210 (90%)	0.5477
Lipid modifying agents	9,705 (41%)	9,397 (41%)	0.8883
Other CV agents	8,309 (35%)	1,750 (30%)	<0.0001
Antidiabetic agents	5,577 (24%)	1,353 (23%)	0.4420
Antihemorrhagics agents	301 (1%)	43 (1%)	0.0006
Drugs for obstructive airway diseases	5,744 (24%)	1,259 (22%)	<0.0001
Drugs for thyroid therapy	1,222 (5%)	271 (5%)	0.0920
Antiepileptic agents	2,013 (9%)	510 (9%)	0.6274
Antiparkinsonian agents	514 (2%)	114 (2%)	0.2823
Psycholeptics	744 (3%)	155 (3%)	0.0467
Psychoanaleptics	232 (1%)	55 (1%)	0.7710
Polypharmacy score[5]			
0-4	7,083 (29.6%)	2,043 (34.3%)	<0.0001
5-9	13,568 (56.8%)	3,211 (53.9%)	
≥10	3,235 (13.5%)	705 (11.8%)	
Comedications during follow-up			
Antihypertensive agents			
No users	1,718 (7%)	353 (6%)	<0.0001
Users with PDC<75%[1]	9,198 (38%)	1,648 (28%)	

Users with PDC≥75%[1]	12,970 (54%)	3,958 (66%)	
Lipid modifying agents			
No users	12,479 (52%)	2,945 (49%)	<0.0001
Users with PDC<75%[1]	8,482 (35%)	1,965 (33%)	
Users with PDC≥75%[1]	2,925 (12%)	1,049 (18%)	
Other CV agents			
No users	14,507 (61%)	3,914 (66%)	0.0048
Users with PDC<75%[1]	6,246 (26%)	1,144 (19%)	
Users with PDC≥75%[1]	3,133 (13%)	901 (15%)	
Antidiabetics			
No users	17,521 (73%)	4,341 (73%)	0.0416
Users with PDC<75%[1]	4,632 (19%)	1,108 (19%)	
Users with PDC≥75%[1]	1,733 (7%)	510 (9%)	

List of abbreviations: SD: Standard Deviation, PDC: proportion of days covered, SSRIs: Selective Serotonin Reuptake Inhibitor, TCAs: Tricyclic Antidepressants; NAAs: Newer Atypical Antidepressants

[1] Adherence was assessed as the cumulative number of days during which medication was available divided by the number of days of follow-up, a quantity referred to as "proportion of days covered" (PDC). Cohort members were classified according whether PDC was <75% or ≥75%, denoting they as poorly and highly adherent patients respectively

[2] According to t-test (age), chi square (gender, diagnosis at index hospitalization and comedications during follow-up) or its version for the trend (categories of polypharmacy and Charlson comorbidity scores). Comedication use and no use during follow-up, as well as PDC<75% and ≥75% among comedication users, were separately tested

[3] Measuring the extension of comorbidity in the three years prior the first AD prescription

[4] Counting patients who used selected comedications during the year prior the first AD prescription

[5] Measuring the highest number of drugs with different 5-digit ATC codes dispensed in a day during the year prior the first AD prescription

Figure 1. Study flow diagram

List of abbreviations: CVD Cardiovascular Disease, ADs Antidepressants

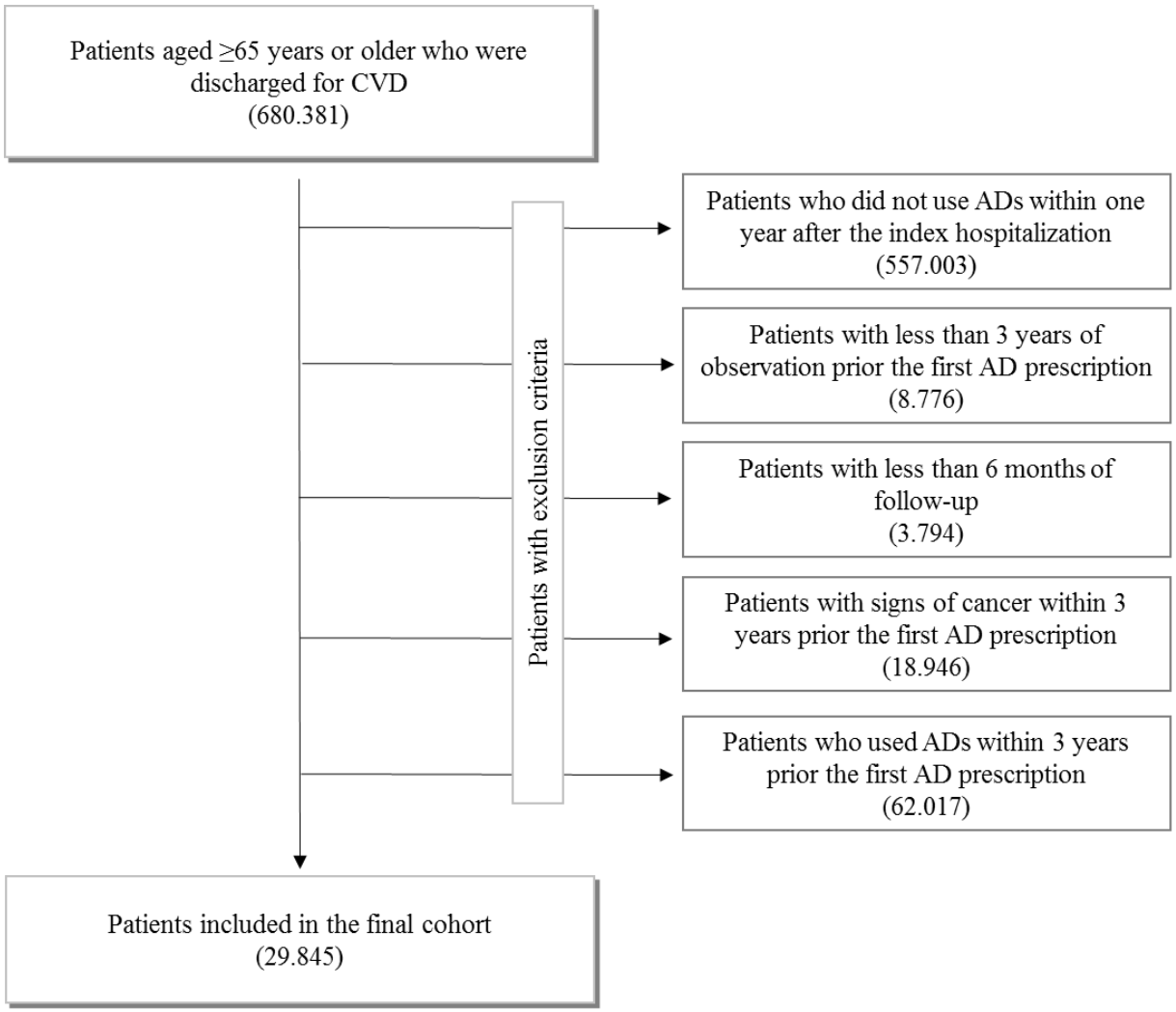
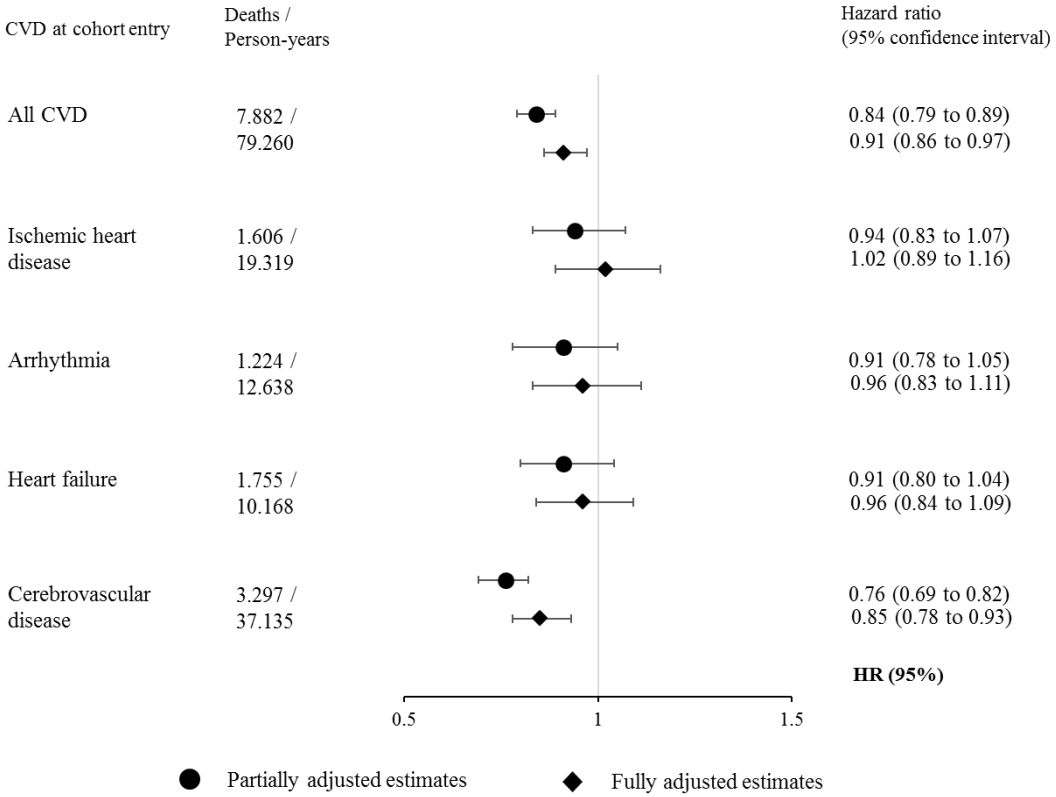


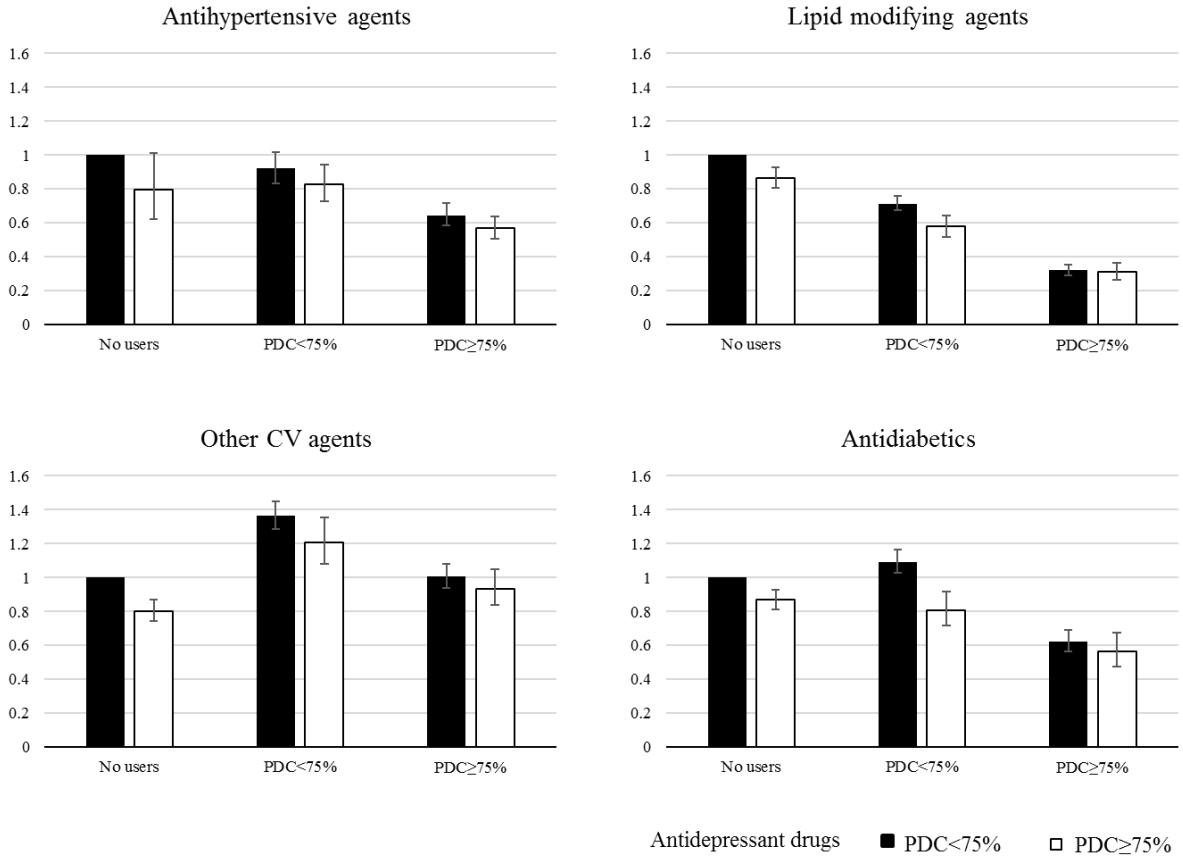
Figure 2. Forest plot showing the effect of adherence to antidepressant drug therapy on the risk of death in the entire cohort and according to specific cardiovascular disease diagnosed at index hospitalization. I-GrADE program, Italy, 2008-2014



List of abbreviations: CVD Cardiovascular Disease

Adherence to therapy with antidepressants was assessed as the cumulative number of days during which the medication was available divided by the number of days of follow-up, a quantity referred to as "proportion of days covered" (PDC). Cohort members were classified according whether PDC was <75% or ≥75%, denoting they as no-poorly and highly adherent patients respectively. Hazard ratios, and 95% confidence, estimated with Cox proportional hazard models. Estimates were partially adjusted (only for baseline covariates, i.e., gender, age, diagnosis at index hospitalization, class of antidepressant firstly employed, Charlson comorbidity score and polypharmacy score) and fully adjusted (also for comedication with selected CV drugs during follow-up)

Figure 3. Combined action of use of antidepressant and other selected drugs during follow-up on the risk of death. I-GrADE program, Italy, 2008-2014



List of abbreviations: PDC Proportion of Days Covered

Adherence was assessed as the cumulative number of days during which medication was available divided by the number of days of follow-up, a quantity referred to as "proportion of days covered" (PDC). Cohort members who used the considered drugs were classified according whether PDC was <75% or ≥75%, denoting they as poorly and highly adherent patients respectively. Hazard ratios, and 95% confidence, estimated with Cox proportional hazard models. Estimates were adjusted for baseline covariates (i.e., gender, age, diagnosis at index hospitalization, class of antidepressant firstly employed, Charlson comorbidity score and polypharmacy score)

Supplementary Table S1. Diagnostic codes used for the study purpose (ICD-9 CM classification)

Arrhythmia
427.* (Cardiac dysrhythmias)
785.0 (Tachycardia unspecified)

Heart failure
428.*, 402.01, 402.11, 402.91

Cerebrovascular disease
430.*-438.*

Ischaemic heart disease
410.*-414.*

Neoplasms
140.*-239.* (Malignancies)

Supplementary Table S2. Anatomical, Therapeutic and Chemical codes of drugs used for the study purpose

Antidepressants
- N06AA (Tricyclic antidepressants)
  - N06AA01 (Desipramine)
  - N06AA02 (Imipramine)
  - N06AA04 (Clomipramine)
  - N06AA06 (Trimipramine)
  - N06AA09 (Amitriptyline)
  - N06AA10 (Nortriptyline)
- N06AB (Selective serotonin reuptake inhibitors)
  - N06AB03 (Fluoxetine)
  - N06AB04 (Citalopram)
  - N06AB05 (Paroxetine)
  - N06AB06 (Sertraline)
  - N06AB08 (Fluvoxamine)
  - N06AB10 (Escitalopram)
- N06AX (Newer atypical antidepressants)
  - N06AX03 (Mianserin)
  - N06AX05 (Trazodone)
  - N06AX11 (Mirtazapine)
  - N06AX12 (Bupropion)
  - N06AX16 (Venlafaxine)
  - N06AX18 (Reboxetine)
  - N06AX21 (Duloxetine)

Antidiabetics
- A10

Antithrombotic agents
- B01

Antihemorrhagics
- B02

Antiarrhythmics
- C01B

Other CV agents
- C01AA05 (Digoxin)
- C01DA (Nitrates)

Antihypertensive agents
- C02 (Antihypertensive)
- C03 (Diuretics)
- C07 (Beta blocking agents)
- C08 (Calcium channel blockers)
- C09 (Agents acting on the Renin-Angiotensin System)

Lipid-modifying agents
- C10

Thyroid therapy
H03

Antineoplastics and immunomodulating agents
L

Antiepileptic
N03

Antiparkinsonian
N04

Psycholeptics
N05

Psychoanaleptics
N06 (excluding N06A Antidepressants)

Respiratory drugs
R03 Drugs for obstructive airway diseases

DISCUSSION

The aim of this thesis regards the evaluation of the effect of AD treatment on the occurrence of CVD or overall mortality. First, the meta-analysis gave us information about which type of association may exist between AD and the CVD outcome. We found a significant increased in the risk of cerebrovascular outcomes related to SSRI exposure while of acute heart disease associated with the use of TCAs.

After that, we performed several observational studies using the healthcare utilization database of the units participating in the AIFA Project to evaluate the relationship between AD use and risk of CVD, like arrhythmia, and mortality. The results of the second study confirmed the findings already observed in the meta-analysis about the relation between acute exposure to SSRIs or NAAs and CVD, in particular stroke, HF and arrhythmia, as confirmed by the application of several sensitivity analyses.

In the third study, we evaluated the effect of AD respect to arrhythmia. In general, AD use may act on several mechanisms linked to the onset of arrhythmias such as the QT interval prolongation or the block of cardiac potassium channels. In particular, TCAs that are classified as class I antiarrhythmic drugs, may be associated with the increased heart rate, as well as certain AD agents belonging to SSRIs and NAAs category. Thus, a proarrhythmic power of AD was revealed by our estimates which were also adjusted for drugs with known or suspected proarrhythmic effect.

Finally, in the fourth study, we evaluated whether adherence to AD treatment was associated with the risk of death. We found that a decreased risk of death was associated with a high adherence to AD alone and in combination with high adherence to antidiabetics, other CV agents, lipid-lowering drugs and antihypertensives assumed during the observation time.

It should be taken into account that patients, previously affected by CVD, could be characterized by a greater vascular vulnerability and, among them, the prevalence of depression may be high [341]. Thus, the presence of depressive disorder/AD treatment could be directly or partly involved with the recurrence of CVD in those patients. Various factors may be related with the occurrence of CVD among depressed patients, such as inflammation, endothelial dysfunction and platelet function, that could be impaired by the block of neurotransmitter's transporter, like SSRIs [341, 342]. Indeed depressed subjects seem to be affected by abnormal endothelium that, in response to inflammatory stimuli (such as tumor necrosis factor alpha), could highly express adhesion molecules on endothelium, although changes of anti-inflammatory levels seem to be controlled by AD treatment [342].

Furthermore, chronic illness could play an important role in the onset of depressive disorders among elderly, whose symptoms may be similar and thus not be recognizable. The presence of multiple and chronic illness could greatly impact the state of mental health and may influence the progression and treatment of the disease. In addition, eventual side effects and drug interactions, due to common pathway shared by treatments, could increase the risk of additional adverse events and mortality [343]. Moreover, the benefit may not be associated with multiple drug treatment in presence of chronic conditions [343], known as multidrug therapy problem.

The strength of the meta-analysis regards the more precise pooled estimates compared to those reported by single studies. Moreover, it is characterized by a major power to detect effects than individual studies. Limitations for the meta-analysis concern: i) high heterogeneity between study heterogeneity to highly variable pooled estimates; ii) lack of homogeneity in the definition of the AD treatment or CVD categorization and the selection of the population among studies and iii) the presence of differences in the variables used to adjust the study-specific estimates.

The studies, conducted within the AIFA project, have several strengths. Firstly, the analyses were based on a large unselected population, which was made possible by the use of data retrieved from the healthcare utilization databases. Second, data are provided on an elderly population who is less likely to participate in clinical trials, allowing a better understanding of drug's effects on this stratum of the population. Third, the drug prescription database provided accurate data, because pharmacists are required to report prescriptions in detail in order to obtain reimbursement, therefore exposure misclassification should be minimal or absent. Limitations of these studies concern the absence of clinical information such as electrocardiogram data or information about the depressive diagnosis. The performed studies do not lead to evaluate if the recurrence of CVD is associated with depression itself, AD use or both. However, AD use seems to play a role in the CVD onset as shown in Study II (Table 3) where only patients currently using AD have an increased risk of CVD, while no increased risk was found among those who stopped the treatment. Furthermore, the study on the relationship between AD use and mortality, it was conducted under the assumption that drug prescription corresponds with drug assumption leading to potential exposure misclassification.

Finally, the presence of unmeasured confounders could have biased the estimates. However, after the application of case-only designs and the Monte Carlo Sensitivity Analysis for the adjustment of the unmeasured confounder, the main results were not strongly modified suggesting a small effect of the potential residual confounding.

For the treatment of depressive disorders, the importance of AD treatment should be highlighted for the improvement of the quality of life. Clinicians should monitor depressed patients during AD therapy in order to avoid adverse events or related diseases, eventually caused by AD treatment. Moreover, it could be interesting to characterize a clinical profile about the occurrence of depressive symptoms among elderly patients affected by CVD as well as the onset of CVD among depressed elderly patients, by considering the presence and severity of depressive symptoms and vascular risk factors.

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