Depression and cardiovascular disease: a pharmacoepidemiologic perspective

by

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Abstract

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Depressive disorder and cardiovascular disease comprise the two health conditions with higher burden in public health. It is known that individuals suffering from chronic illness are more likely to suffer psychological disturbances. In both cases treatment relies mostly on pharmacological interventions. Neuro-physiological and psychosocial links have been proposed to explain the interaction between depression and cardiovascular conditions.

Our aim was to study the association between depression and cardiovascular disease from a pharmacoepidemiologic perspective, namely the likelihood for the treatment of depression to be associated with the treatment of cardiovascular disease, and the factors affecting this association.

The study was comprised of two stages: a) a systematic review of available literature on the association of antidepressant drugs use with cardiovascular therapy; b) a cross-sectional study where treatment with antidepressant drugs was considered the outcome of interest, evaluating the effect of selected determinants including concomitant use of cardiovascular treatment.

The systematic literature review consisted of a search on MEDLINE, EMBASE and PsycINFO databases using pre-specified keywords. 4 publications were included in the review out of 1008 citations initially retrieved. The published evidence reveals a small number of studies and inconclusive results. Predominantly the authors suggest a

strong influence by factors, such as gender and intensity of contact with the healthcare system.

A cross-sectional study was conducted based on self-reported information on drug use, collected through interviews from a cohort of adults residents the city of Porto, Portugal. The data about the drugs used regularly in the year previous to the interview were then coded and classified according to the ATC classification system. Gender, age, marital status, educational attainment, employment situation and medical history were also collected. Of the 1852 individuals participating in the study, 1016 completed the Beck Depression Inventory and were asked the number of medical visits during the preceding 12 months.

In the complete cohort, the prevalence of antidepressants use was 7.0% (95%CI: 5.8, 8.2) and depression was reported by 4.3% (95%CI: 3.4, 5.3) of the participants. Although antidepressant use was associated with female gender, some age strata, divorced/widowed marital status and cardiovascular drug use in the univariate analysis, after adjusting for demographic and social factors, using unconditional logistic regression, the association with cardiovascular drug use dissipated. The only factors remaining positive were female gender and self-reported depression.

In a second analysis, those participants with a BDI≥10 or had reported using at least one antidepressant drug, were classified as depressed and were included in the sub-analysis to assess the likelihood of antidepressant use among depressed patients adjusting for age and gender together with number of medical visits and cardiovascular drug use. Female gender (OR=2.72; 95%CI: 1.20, 6.15) and a greater number of medical visits in the previous year [OR=3.88 (95%CI: 1.55, 9.75) for 2-5 visits, and OR=11.40 (95%CI: 3.92, 33.14) for 6-11 visits, compared to 0-1 visits] had a statistically significant association with antidepressant use in patients classified as depressed.

The results of this study are in line with the results from previous research and allow us to conclude that the use of antidepressants is not likely to be associated with concomitant use of cardiovascular therapies. The apparent association may be the result of parallel chronic conditions and intense contact with the health care system.

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List of acronyms

ATC	Anatomical Therapeutic Classification
AD	Antidepressant
BDI	Beck Depression Inventory
CAD	Coronary Artery Disease
CI	Confidence Interval
CV	Cardiovascular
CYP450	Cytochrome P450
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders
DUS	Drug Utilisation Study
ENRICHD	Enhancing Recovery in Coronary Heart Disease Patients
ESEMED	European Study of the Epidemiology of Mental Disorders
HMG-CoA redutase	3-hydroxy-3-methylglutaryl-CoA reductase
ICD-9	International Classification of Diseases (Ninth revision)
INFARMED	Instituto Nacional da Farmácia e do Medicamento
MHART	Montreal Heart Attack Readjustment Trial
MMSE	Mini Mental State Examination
MOI	Monoamine Oxidase Inhibitor
OTC	Over-the-counter
SADHART	Sertraline AntiDepressant Heart Attack Trial
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
WHO	World Health Organisation

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1. Background

Depressive disorders and cardiovascular disease are the two leading causes of disability worldwide.(1) Pharmacological therapy is the most frequent intervention applied in the prevention and treatment of disease.(2) Understanding the determinants that influence the use of medicines allows for the optimisation of benefits and minimisation of risks for the patient and reduces squander of resources. Scientific evidence about the interaction mechanisms between these two medical conditions, their aetiology and treatments, is paramount to make high quality recommendations and sound decisions to improve public health.

1.1. Drug utilisation studies

The object of drug utilisation studies is defined by the World Health Organisation (WHO) as being "the marketing, distribution, prescription and use of medications in a society, with a special emphasis on the consequences and results in terms of health, economy and society".(3) In accordance with this definition, drug utilisation studies are not exclusively focused on the clinical aspects that determine prescription or dispensing, but are also concentrated on the ways that drug utilisation is associated with beneficial or adverse effects.(4) The scientific discipline supporting drug utilisation studies is pharmacoepidemiology and produces evidence in various areas including: populational patterns of utilisation, quality of therapy and effect size of drug use, both in terms of benefit and harm.(3)
One of the aims of studying drug utilisation is to describe the factors that influence the distribution, selection/prescription, dispensing and utilisation of medicines, while remaining mindful of their impact on patients' health. In essence, these are epidemiological studies with focus on the rational utilisation of medicines.(4, 3)

The most common sources of data for drug utilisation studies reside in large administrative databases belonging to healthcare providers (hospital and claims databases), regulatory agencies (such as the INFARMED) and medicine distribution networks including pharmacy records. Useful data is also collected at the clinic level either continuously or exceptionally for specific studies. Apart from these sources of data, information can be collected directly from patients.(3) Conflicts between data

obtained from different sources, in terms of validity and accuracy of the information on the use of medicines, is a real problem that is far from being resolved.(5, 6)

1.2. Depression

Depression is an important public health challenge affecting large sections of the population. It generates a high burden to the patient and worsens the prognosis of concomitant illnesses. The direct and indirect costs associated with the condition are high. Even though, it is frequently considered the *"hypertension of mental illness in primary care – common, often undiagnosed and not appropriately treated"*.(7)

1.2.1. Definition

Depression refers to a condition which is part of a spectrum of psychiatric illnesses called mood disorders. These disorders commonly encompass mood change as the psychopathological feature.

The main characteristics of depressive disorder are absence of initiative and lack of positive affluence associated with low mood, markedly distinct from common sadness. Other features are loss of interest in or content with the experiences of daily life (anhedonia) and poor concentration and deteriorated self-esteem.(8) The patient may present typical psychomotor retardation (slowing of mental and motor activity) and restlessness. Anxiety and irritability are often present. In terms of cognition, the patient is often afflicted by thoughts of guilt and self-blame for events in the past, feelings of failure in everything they do, and anticipation of failure or personal catastrophes in the future. The most serious consequence through severe stages of depressive disorder is suicide, often with forewarning of suicidal ideation, planning and/or attempt.(8)

"Physical" symptoms of the disease include disturbance of sleep, mood swings during the day, appetite and weight loss, constipation, decreased libido and, in women, amenorrhoea. In severe depression these symptoms are more frequent and intense.(8)

The distinction of depression from other mood disorders and between mild and severe forms is based on three main dimensions: the aetiology; the symptoms and the course of the disease.

Course

The onset of depression can occur at any age, the average being between 20 and 30 years old. The recurrence of depressive episodes is variable, some people have isolated crises with gaps of many years, others develop clusters of episodes and a third group develop increasingly frequent crises with age.(9) Some individuals experience anxiety, phobias and panic attacks before the onset of depression, others however develop fulminant disease rapidly. For many patients depression is a chronic condition with a long history of relapses and recurrences.(10)

In approximately 30% of the cases the condition ends completely after the first episode. Although it is common to characterise depression as a transient distress with a time limited course of 6 months on average, recent studies revealed that up to 66% of patients with depression still have significant symptoms one year after diagnosis.(11, 12)

The condition significantly reduces multiple aspects of quality of life, both directly(13) and indirectly, when associated with an increased risk for disability in older depressed patients.(14) Furthermore, when depression is secondary or occurs parallel to other illnesses, it amplifies the symptoms, determines higher mortality rates and worse outcomes.(15)

1.2.2. Aetiology

Depression is a medical condition recognized for over 3000 years. Hippocrates coined the term “melancholia” to describe its presumed origin, the “black bile”. In the centuries ahead depression was predominantly identified with religious beliefs , “evil spirits” and “God’s reprimands”. Remains of these popular superstitions were carried to the modern day and are responsible for the stigma associated with mental diseases in contrast with physical illnesses.(16)

Despite the numerous possible symptom profiles in depression, it is accepted that they all result from common underlying abnormalities in neuronal transmission in various regions of the brain.(12)

In the 1960s, the discovery of the first neurotransmitters and the effect of substances capable of inhibiting their reuptake gave rise to the monoamine theory. According to

this interpretation, the pathophisiology of depression was a deficiency in monoamines, including serotonine (5-HT) and norepinephrine, in the presynaptic gap.(17) However this theory was later disproved since a few doses of antidepressants bring the concentration of synaptic neurotransmitters back to normal levels, although the effect in the depressive symptoms take several weeks to be noticed.(17) The monoamine model was later substituted by the receptor dysregulation theory. This approach encompasses a potential effect of the antidepressants, not only in the monoamine reuptake but also in the configuration of postsynaptic receptors and cellular pathways, including gene expression, in the neurons. This theory apparently explains the 2-6 week delay of effect of antidepressant therapy.(17) Findings from genetic studies describe the depressive response to stress as being more common among people with a variant of the gene encoding the serotonin transporter (5-HTT), the target of the serotonin-reuptake inhibitors drugs.(12)
An alternative etiological path for depression emerges from endocrine abnormalities. This line of research is centered in findings from Cushing's syndrome, Addison's disease, post-partum and post-menopausal depression. Serum cortisol is increased in almost half of all depressive patients, but the raise is not specific to depression. The increase in cortisol has been suggested as resulting from life long exposure to stress. The higher concentrations are suspected to interfere with the normal activity of 5-HT in the brain.(8) There have also been results suggesting that depression is associated with encephalic constitution and anatomy.(18, 19)

The most recent theories depict depression as a result from the interaction between a) stressful events and b) "constitutional factors", the latter related with the genetic constitution (biochemical, endocrine, psychological) together with early age experiences.(8)

In conclusion, genes and stress are hypothesized to modify the neuronal processes.(12) Although, none of the theories in isolation have gained unconditional acceptance. It is acknowledged that depression has a complex multifactorial aetiology, which is highly dependent on the individual's vulnerability, on their circumstances and on the way that the various factors interact.(11)

1.2.3. Diagnosis

The accurate diagnosis of depression is based on a thorough medical history, assessment of mental state, relevant physical examinations and investigations, and cohabitants' descriptions. The diagnosis follows objective criteria such as those published by the American Psychiatric Association in the "The Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV)(9).

Major depressive disorder

Acording to those standards, major depressive disorder requires 5 of the 9 following symptoms (criteria) to be present during the same two-week period:

- Depressed mood or feeling of hopelessness (A1)
- Loss of interest or pleasure (A2)
- Weight change (A3)
- Insomnia or hypersomnia (A4)
- Psychomotor retardation or agitation (A5)
- Decreased energy and fatigue (A6)
- Feelings of worthlessness and guilt (A7)
- Thinking impairment or difficulty making decisions (A8)
- Thoughts of death and suicide with or without attempt (A9)

It also requires change from previous functioning status with a degree of functional impairment and/or distress, and exclusion of other potential causes (e.g. drug abuse) or life events that may be responsible for the symptoms (e.g. bereavement).(9)

The DSM-IV criteria distinguishes major depression from Mood Disorder Due to a General Medical Condition. In this case the mood disturbance is a direct consequence of a specific medical condition (e.g. brain tumor, multiple sclerosis, myocardial infarction).(9)

Mild depressive disorder

The classification of mild or minor depression requires depressed mood or loss of interest and/or pleasure during most of the day, nearly every day for two weeks, with

a cumulative number of two to four depressive symptoms, and excluding previous medical history of major depressive disorder.

In general, for a diagnosis of depression, the clinical psychiatric assessment should reveal at least two weeks of depressed mood, loss of interest, or diminished sense of pleasure plus four of the seven other features. Objectively the other features include weight change of 5 percent or more in one month, persistent change of appetite, insomnia or hypersomnia in most days, alteration of psychomotor state, tiredness, expressions of guilt and worthless, low concentration and deteriorated decision making, and suicidal ideation or attempt.

In order to aid the clinicians with the complex task of detecting and establishing a differential diagnosis for depression, two main strategies have been developed, namely a) simple mnemonics and b) questionnaires (scale/score instruments).

The most common mnemonic for the assessment of depression is called the

SIG E CAPS + Mood(20) referring to:

S Sleep (insomnia or hypersomnia)
I Interests (diminished interest in or pleasure from activities)
G Guilt (excessive or inappropriate guilt; feelings of worthlessness)
E Energy (loss of energy or fatigue)
C Concentration (diminished concentration or indecisiveness)
A Appetite (decrease or increase in appetite; weight loss or gain)
P Psychomotor (retardation or agitation)
S Suicide (recurrent thoughts of death, suicidal ideation or suicide attempt)
+ Mood

The questionnaires for assessment of depressive symptoms are designed for self-reporting or health professional interview.
One example of a self-reporting tool is the PHQ-9, a nine item questionnaire intended to be filled-out in the waiting room before a medical visit. A score above the threshold alerts the health professional for the need of clinical assessment.(10)
Other rating scales available to assess depression are the Hamilton Rating Scale(21) for Depression and the Beck Depression Inventory(22).

In a meta-analysis to evaluate the impact of screening instruments when compared with medical examination (case note entries of depression), Gilbody et al. found that the case-finding questionnaires had a borderline effect (RR=1.38; 95%CI: 1.04, 1.83) in improving the recognition of depression.(23)

Additionally, a study evaluated seven questionnaires and found that a two-question instrument had 96% sensitivity and 57% specificity for depression, much similar to the other longer and more complex instruments.(24) The two questions were:

- *During the past month, have you often been bothered by feeling down, depressed, or hopeless?*
- *During the past month, have you often been bothered by little interest or pleasure in doing things?*

In terms of detecting the risk of suicide in a depressed patient, the most accepted strategy is direct simple questioning, for example(10):

- *Do you ever think of hurting yourself or taking your own life?*
- *Do you currently have a plan?*
- *What is the plan?*

In the diagnosis of depression with the patient, it is important to enpahsize the clinical (biological) aspects of the disease. Some patients may perceive the diagnosis as a personality flaw or individual weakness.(10)

Although depression is a frequent illness at all levels of health care, it is poorly recognised and frequently missed. It has been estimated that 30% to 50% of all cases of depression in the general population are not detected by a medical professional.(25, 14, 24). Some authors explain the extent of undiagnosed depression by the lack of attention and misconceptions about what constitutes depression.(24) This may result from lack of adequate training to recognize depressive symptoms, busy schedules in the clinical setting and ultimately because they are not familiar with how to best treat the condition.(24)

Often, both the patient and the physician, tend to focus their diagnosis and treatment preferentially on somatic symptoms.(26) Complaints are frequently ambiguous including fatigue, “blahs”, headache, malaise, sexual dysfunction, abdominal discomfort and diffused pain. People from specific cultural/ethnic groups and older patients are more likely to report symptoms of depression using somatic descriptors.(17, 9) An example is the use of “nerves” and headaches by Latino and Mediterranean cultures in contrast with persistent weakness or “imbalance” often reported in Asian cultures. Middle Eastern cultures may complain of “problems of the heart”.(27, 17) Concerns of embarrassment may also restrain patients to disclose their depressive mood to the physician. As revealed by a general population survey, 60% (n=1203) of those inquired reported feeling embarrassed if needing to consult their general practitioner because of depression.(28)

In the elderly, depression is often wrongly accepted as an integral aspect of aging.(14) There is also sparse evidence on the treatment of depression in the elderly due to a lack of published studies examining the efficacy of antidepressants in this population.(29)

Studies have found that more than 50% of patients with depressive and anxiety disorders state initially somatic complaints. Other studies have shown that an increase number of visits to the primary care clinics and hospitalizations precede the diagnosis of depression and that the reasons for the visits are often ambiguous “functional” symptoms, vague aches and pains with no evident physical cause and increased tension or anxiety.(26, 12) The medical context of the disorder presented by the patient may influence the diagnosis of depression. For some doctors, depressive symptoms are accepted as part of the overall painful or chronic condition such as arthritis, diabetes or hypertension. By focusing the treatment strategy on the physical illness the physician may expect to improve the depressive mood.(15)

Some concomitant diseases are particular strong camouflages of depressive symptoms. Heart failure, for example, is associated with fatigue, malaise and insomnia, common symptoms of depression.(24) Other conditions that often masquerade depressive symptoms range from myocardial infarction, cerebrovascular

accident, Parkinson's and Alzheimer's disease, epilepsy, hypothyroidism, chronic pain syndromes, among many others.(30)

Ultimately, patients deliberately avoid to disclose emotional distress to health professionals worrying of being stigmatized with a mental disease label or because they assume the symptoms are part of some other medical illness.(24)

Case finding in epidemiological research

In epidemiological research of depression, the case-finding strategies are diverse and the choice of instruments have a high impact on the results.(31, 23) A study in 460 inpatients found a 2 fold difference in the estimate of major depression prevalence (from 10 % to 21%) depending on the diagnostic scheme used. The potential for bias is increased in the presence of concomitant illness because most depression scales do not take symptom overlap into account (24) this being particularly limiting when studying elderly populations with multiple diseases.(32)

The self-rating inventories are very sensitive, identifying most patients with major depression. On the other hand they have high rates of false positives, misclassifying other primary disorders as depression. When comparing four studies using self-rating scales with those that used structured psychiatric interviews, Katon et al. found a difference of 12-25% to 5-10% respectively, in the prevalence estimates among outpatients.(26)

There has been some discussion regarding the factors behind a marked time trend in the detection of depressive disorders over the 80s and 90s. Some authors consider the introduction of newer antidepressant therapies, particularly the SSRIs as a main factor. Aggressive pharmaceutical industry advertisement together with public health efforts and better screening instruments are also responsible for the increased detection and treatment.(33) Others argue that the increased diagnosis and treatment are associated with better management of the disease at the primary health care level, with more non-psychiatrists being confident to diagnose and treat depression.(34)

1.2.4. Epidemiology

In 1997, the Global Burden of Disease Study positioned depression in fourth place of the leading causes of early death and disability worldwide. In Western countries, depressive disorder was only topped by ischemic heart disease.(1) It was also the second most common chronic condition after hypertension. The same report predicted that depression would take the second place in the rank of disease burden by the year 2020.(1) More recently, the 2002 World Health Report reported that major depressive disorder accounted for 4.4 percent of the overall disease burden, a similar role to the one played by ischemic heart disease and diarrhoeal disease worldwide.(12)

Depression is present in approximately 5% of the entire population, in 5 to 13% of all outpatients and over 15% of all inpatients at any one point in time.(10, 26, 12) Studies in medically ill patients report prevalence's of depression as high as 40%.(35)

Kessler et al. reported a 16.2% (95%CI: 15.1, 17.3) life-time prevalence of major depression in the US population, based on a cross-sectional household face-to-face survey of 9 090 adults, using the DSM-IV criteria. The same study estimated a 12-month prevalence of 6.6% (95%CI: 5.9, 7.3) for the same condition.(36)

One European study that involved adults (18-64 years) from five countries estimated the prevalence of depressive disorders to be 8.6% (95%CI: 7.0, 10.4).(37) Lepine et al.(38) reported a prevalence of depression of 17% in the community, and Alonso et al. reported consistent figures resulting from the *European Study of the Epidemiology of Mental Disorders* (ESEMED) study with a 12-month prevalence of 3.9% (95%CI: 3.6, 4.2) and life time prevalence of 12.8% (95%CI: 12.2, 13.4) for major depression.(39)

In regards to mortality, a recent meta-analysis estimates a relative risk of 1.81 (95%CI: 1.58, 2.07) for mortality not only in major depression but also in patients with sub-clinical presentations.(14)

In Portugal, a prevalence study based in a health care centre, which included a total of 260 adults between 35 and 65 years of age, obtained an estimated prevalence of 33%

presenting with "any depressive perturbation" and 13% presenting objective criteria for the diagnosis of a "major depressive episode". Of these cases, only 36% had been diagnosed with depressive disorders (of which only 46% of the individuals who satisfied the criteria for a major depressive episode had been diagnosed).(40)

Economic burden

Direct costs imputed to depression originate from higher utilization of healthcare resources by depressed patients when compared with non-depressed. Depressed patients make more visits to physicians and have more medical investigations(26) and more frequent hospitalisations(25) than patients without depression.

Indirect costs are associated with the adverse effects of depression on work and productivity. Workers with depression report significantly more health related lost productivity time (LPT) than those without depression. A study in the US, estimated an excess of 31 billion dollars per year in losses associated with LPT in depressed workers.(41)

Overall, the direct and indirect annual costs attributed to depressive disorders by Rappa et al., in 2001, of 44 billion dollars and Katon et al., in 2005, of 81.5 billion dollars, reflect the high economic impact of depression in various sectors.

1.2.5. Risk factors

Several risk factors for depression have been identified, these include age, gender, previous history of depression, genetics and family history of depression, specific types of personality and loss of active life or major role, social support and socioeconomic circumstances.(11, 20) Depression is also associated with chronic medical conditions with risk varying on the type of illness.(15, 42)

Age

Incidence of depression increases with age reaching 17 per 1000 person-years between the ages of 70-79 and up to 44 per 1000 person-years from 79-85.(32) Depression in the elderly is recognized as a major public health concern.(15) Though,

it has not been possible to isolate the effect of age alone due to the correlated increase of comorbidity, which also constitutes a risk factor.(14)
Some authors go as far as to consider depression in late life a defined medical entity with distinguishing features from depression in early age. Kraepelin (1896) distinguished late life depression from manic-depressive disorders by calling it "involutional melancholia". The distinctive characteristics are the late life onset, high frequency of fear and hypochondriacal delusions, long course and poor outcome with high incidence of cognitive deterioration.(32)

Gender

Gender influences the risk, clinical presentation and response to treatment of depression. In Western countries the prevalence of depression is 2-3% in men and 4-9% in women. The lifetime risk also differs between genders with 1 in 10 men affected comparing to 1 in 4 women.(8) The underlying cause of this difference is not yet established.(17, 8) It is often described that women are more likely to have atypical symptoms of depression such as hypersomnia and hyperalgia. Although women are more likely to attempt suicide, men are more likely to kill themselves.(17)

Genetics

Well defined genetic anomalies have not yet been identified to determine the hereditary component of depression, but both major depression and bipolar disorders are clearly hereditary.(12)

Chronic medical conditions

The course of depressive disorders is often parallel to other chronic conditions. (15) In geriatric patients the most common precipitating factor for depression is the stress associated with physical illness.(26) Kessler et al. (2003) estimated that among 9090 adults in the Unites States, most prevalent cases of major depression (72.1%) and 12-months prevalent (78.5%) had a comorbidity. The depressive disorder was rarely primary.(36) Some causal theories indicate that physical diseases, such as diabetes, cardiac disease, hypo- and hyperthyroidism, influenza, among others, can significantly increase the risk of depressive disorders.(11)

Other risk factors include urban population when compared to rural areas; lack of social support, particularly in people living alone; loss of functioning, of particular importance in disabilitating conditions; loss of major life role, for example in retirement; socioeconomic status, with higher prevalence in people in adverse socioeconomic conditions.(8) Medicines and drugs of abuse (e.g. alcohol, heroin) have also been identified as increasing the risk for depression.

1.2.6. Treatment

The treatment of depression is necessary and recommended to improve patients' quality of life. The treatment is organised in three main stages with the objective of controlling the depressive symptoms and ultimately achieving complete recovery. The first stage is the acute phase treatment to alleviate the symptoms of depression. In the second phase, a stable treatment program is implemented together with monitoring of progressive improvements towards cure. The third phase, or maintenance phase, is particular to patients at risk of recurrence and aims to protect from further episodes.(8)

The attitude of patients towards treatment of depression may influence the quality of care. A survey of the general population in the United Kingdom reported that 85% (n=1704) of people accepted counselling to be an effective treatment for depression. Many subjects (78%; n=1563) viewed antidepressants as addictive.(28)

Non-pharmacological treatments

There is large number of alternatives when it comes to treatment of depression. Life-style changes, psychotherapy, electroconvulsive and antidepressant drugs.

Increasing physical activity in leisure-time has a positive effect on depressive symptoms.(14) Additionally, psychological treatments such as cognitive behavioural therapy (CBT), inter-personal therapy (IPT) and brief focal analytic psychotherapy are effective treatments for depression, but are under-used.(14) Drugs in combination with psychotherapy is an option often used to treat depression.(43)

Electroconvulsive therapy (ECT) consists of stimulating the brain with low intensity electric current. The therapeutic efficacy of ECT is often claimed to be superior to antidepressants. The mortality rate of 2-4% of treated patients is mostly due to cardiac complications. Other adverse effects are memory problems and falls.(14) Emerging

treatments, such as rapid transcranial magnetic stimulation and vagal nerve stimulation, may become important alternatives in the future.(16)

Antidepressant drugs

History of antidepressants *[adapted from Rappa et al. (2001)]*(16)

The treatment of depression by means of psychopharmacology began approximately two centuries ago during the apogee of psychiatric institutionalization.

The early 1900s are marked by an interest of medical research into the fields of surgery anaesthetics, cardiology and physiology. Depression and its treatment was not a high priority.

Bromide was used in the XIX century to treat anxiety and induce sedation. The toxic effects of long-term use caused the therapy to be abandoned. During the same century more sedative agents were developed, including the first barbiturates, urethane and sulfonal, to name a few. Cocaine and caffeine were discovered in South America and were rapidly revealed in Western medicine as the first stimulants. Not long after, cocaine was used in anesthetic, nasal congestion and investigated for its euophoria effects. In 1886 it was incorporated in coca-cola and subsequently withdrawn in 1903. Over the next decades the overuse of cocaine together with a rise in abuse of opium motivated regulation and further restrictions to the availability of these substances.

Ephedrine, in its herbal form, had been used in chinese medicine to treat depression for many milenia when the first amphetamine was synthetised in late XIX century. Initially amphetamines were studied for their bronchodilation and sympathomimetic properties, only later the effect on the central nervous system was found, namely producing euphoria, relief of fatigue, improved motor performace and anorexia. Around the 1930s, amphetamines were used in the treatment of mental disorders including depression; apparently effective in the treatment of the acute phase but their actions temporarily decreased over time with chronic treatment.

The 30s also saw the rise of a stimulant drink called “Lithiated Lemon-Lime Soda”, now considered the first significant populational antidepressant exposure. The name was later symplified to 7UP and Lithium was part of the formulation until the 1940s.

Electroconvulsive shock therapy, insulin shock therapy and lobotomy were emerging treatments for different types of mental disorders. Their use was common practice until the development of antidepressants in the 1950s.

In the 1940s, iminodibenzyl derivatives were being studied for antihistamine agents. Molecules with less antihistmine potency were abandoned until researchers in Switzerland reexamined them and tested one, a promazine analogue, in 100 depressed patients. In 1957 imipramine was marketed as the first tryciclic antidepressant (TCA). Although imipramine was the first developed drug for depression, antidepressant activity of medicines had been observed earlier in the 50s. The tuberculosis epidemic forced large numbers of patients to be secluded in "sanatoria" for long-term treatment. Depression was therefore a common comorbidity in patients with tuberculosis. Isoniazid and iproniazid were the two predominant therapies for tuberculosis in 1951 and 1952. It was then sugested that iproniazid, but not isoniazid, improved patients depressive status. It was discovered that the drug inhibited an enzyme, the monoamine oxidase. Iproniazid was marketed in the US in 1958 as an antidepressant and later withdrawn due to hepatic toxicity, and substituted by isocaboxazid, a less toxic monoamine oxidase inhibitor (MAOI).
Only about a decade later, research brought to light two important chemicals: noradrenaline, in 1965, and serotonin, in 1969. These new compounds were then investigated to address what was considered the deficiency of these two neurotransmiters in the central nervous system. Fluoxetine was the first of a new class of antidepressant drugs, the selective serotonin reuptake inhibitors (SSRIs), in 1974.

Between the 1970s and the 1990s, more antidepressant substances were discovered. These include trazodone (1975), citalopram (1977), sertraline (1983), paroxetine (1990), and venlafaxine (1981). There are currently over 20 different antidepressant substances available in the therapeutic arsenal.

Mechanism of action

Antidepressant drugs act generally through increasing the neurotransmitters activity in the synaptic space. Three main mechanisms are used: a) the increased release of neurotransmitters, b) the inhibition of their degradation by enzyme blocking, and c) the specific or non-specific reuptake inhibition of neurotransmitters released to the synaptic gap.(12)

TCAs

Tricyclic antidepressants work by inhibiting norepinephrine and serotonin reuptake by the synaptic nerve terminals which leads to an increased density of monoamines in the synapses. Because their mechanism of action is non-specific, TCAs also antagonize various other neurotransmitter receptors such as serotonergic, a-adrenergic, histamine, and muscarinic receptors inducing a wide range of side effects including dry mouth, blurred vision, constipation and urinary retention, cognitive disturbances and potential distubance of heart rate and rhythm. TCAs toxicity is of most concern in cases of accidental or intentional overdose.(43) The most important representatives of this therapeutic class are: imipramine, amitriptyline, desipramine, nortriptyline, protriptyline, and doxepin.

SSRIs

Selective serotonin reuptake inhibitors (SSRIs) specifically target the serotonin transporter (SERT) inhibiting serotonin reuptake from the synaptic clef. The selectivity of the mode of action grants the SSRIs a more beneficial safety profile with fewer anticholinergic effects, including cardiac side effects, than TCAs. (43) The commonly reported toxicity of the SSRIs are insomnia, somnolence, nausea, and sexual dysfuntion. Most side effects reduce over the first month of therapy. 60% of patients treated will develop sexual dysfuntion and this is the adverse effect least likely to resolve. Significant representatives of the class are: fluoxetine, citalopram, paroxetine, fluvoxamine, and sertraline.

Other antidepressants

Monoamine oxidase inhibitors (MAOIs) act by selectively inhibiting the monoamine oxidase enzyme (MAO) responsible for the degradation of the monoamines released in the synaptic space. The most significant side effects include hypertension, seizures, respiratory depression, and central nervous system depression.(17) Therapy with MAOIs also require a tyramine-restricted diet to prevent severe drug induced toxicity.

Nefazodone and mirtazapine are classified as receptor modulators. Mirtazapine enhances the release of norepinephrine by selective blocking of two adrenergic autoreceptors as well as serotonin 5-HT_{2A} and 5-HT_3 and histamine H_1 receptors. Its

efficacy is similar to that of tricyclic antidepressants and SSRIs, and it is less likely to have sexual and sleep-related side effects.(12)
Nefazodone, blocks the 5-HT_{2A} serotonin receptor and serotonin reuptake. It has an antidepressant efficacy similar to that of SSRIs but with a lower likelihood of sexual-dysfunction and sleep-related side effects.(12)

Dual-action antidepressants, serotonin-norepinephrine reuptake inhibitors block monoamine transporters more selectively than TCAs with a more favourable cardiac effect profile.(12) Venlafaxine, milnacipran and duloxetine are part of this group.

The newer antidepressants have not shown greater efficacy, demostrated in clinical trials, than the TCAs, and none seem to have greater effectiveness in "real world" clinical use. The development of newer agents was accompanied by an improved safety profile. Although older drugs are still available in the market, the prescribing trend is for agents with lower risk of adverse effects.

About half of moderate-to-severe newly diagnosed episodes of depression improve with the first antidepressant treatment(12) and 80% will respond to at least one antidepressant. 40% of treated patients will recover at 6 weeks , 60% will have recovered by 12 weeks, and 80% at 6 months of therapy.(10, 44)
When selecting an antidepressant for a specific patient, it is important to take into consideration the points suggested in the *STEPS* acronym, namely: Safety, Tolerability, Efficacy, Price and Simplicity.(7, 20)

Antidepressant therapy is contraindicated in patients with a medical history of maniac episodes, since the therapy can trigger the condition. Complex depressive syndromes with concomitant mental illness are usually referred to specialised psychiatric care.(10)

Close monitoring in the initial phase of therapy allows for prompt intervention in case of aggravation of the symptoms or intolerable side-effects. The effect of the medication is likely to be noticed from 2 to 4 weeks into the treatment.(10) If the symptoms respond positively to a medication plan, the therapy shall be maintained for

6 months to prevent relapses, but patients with lifetime recurrent episodes should be medicated for at least 2 years.(10, 12)

TCAs are often first choice in the treatment of depression but the SSRIs have emerged to become the most used antidepressants due to their better tolerability and higher rates of adherence.(20, 12)

1.2.7. Antidepressant drugs utilization

Egberts et al. reported, in 1997,(45) a prevalence of antidepressant use in the Dutch population of 2.2% to 4.1%, almost twice more frequent in women, with no association with age, but a marked association with health care utilization. A study to assess the frequency of use of psychoactive medication using 1 777 street interviews, in the city of Buenos Aires, estimated a 3% prevalence of antidepressant exposure during the preceding year, and identified gender as a significand determinant. No association was found with educational attainment or socioeconomic status.(46)

In Spain an increasing utilisation of antidepressants followed the introduction of the SSRIs in the 80s, with an increment of populational exposure of 247%, from 2.7DDD/1000 habitants/day in 1985 to 9.3DDD/1000 habitants/day in 1994.(47) In Italy, a more recent study involving over 140 000 individuals showed a 20% increase in antidepressant use from 5.08% (95%CI: 4.97, 5.20) in 2003 to 6.00% (95%CI: 5.88, 6.13) in 2004.(48)

A study produced by INFARMED to evaluate the impact of legislative changes on the reimbursement of antidepressant agents revealed an increase in their use. Between 1995 and 2001 the number of packages dispensed raised by 102.8%, corresponding to an increased financial burden to the National Health System of 308.4%.(49)

Large observational studies carried out in the United States estimated that between half and one third of all depressed patients receive treatment for the condition,(26, 36, 16) and among those treated for major depressive disorder, only one fourth receive the best available intervention.(36) Another study reports a proportion of minimal adequate treatment in 63% of depressed patients in the 12 months preceding the survey.(24) In Finland, Laukkala et al. reported treatment of major depressive

episode, during the previous 12 months, in 13% of the cases identified using the DSM criteria. Regular use of any other medication, visit to psychiatric services, prolonged sick leave and smoking were associated with antidepressant treatment.(50)
The findings of the *ESEMED* study revealed that only 21.2% of the participants with a diagnosis of a major depressive disorder for greater than 12 months, received antidepressant treatment.(51) On the other hand, with respect to the effectiveness of healthcare, mortality in depressed individuals is estimated to be 20% at two years after diagnosis and depression remains prevalent in 40%.(11)

Conflicting information on the quality of prescription, dispensing and rational use of antidepressant therapies fuels an ongoing debate. On one side, there is the potential *medicalisation* of health conditions with more appropriate non-pharmacological treatments available,(52) yet on the other side, there is the potential sub-diagnosis of clinically important depressive disorders.(51)
Despite the increasing number of guidelines issued to prescribers on the best use of antidepressants, the patterns of use diverge greatly from the recommendations, having, in some parts, TCAs being more prescribed to treat pain and trazadone being used in sleep disorders more frequently than for psychiatric indications, for example.(53)

The need to study the epidemiology of depressive disorders in depth in Portugal, in order to define evidence-based therapeutic protocols is highlighted by Gusmão et al.(54), especially given the expected load that this pathology has on the health system.

1.3. Cardiovascular disease

The progressive aging of the population together with the development of more efficient treatments that grant higher rates of survival after acute cardiovascular events have jointly contributed to a pandemic of chronic cardiovascular disease.(55)

The impact of this trend in the health care systems is high and difficult to predict. A study involving health care centers in 44 countries (Reduction of Atherothrombosis

for Continued Health (REACH) Registry) involving 68 236 between 2003-2004, found that 1 in 7 patients diagnosed with atherosclerosis at index date suffered a major cardiovascular episode or was subject to revascularization during the first year of follow-up.(55)

1.3.1. Definition and types

Cardiovascular disease encompasses a variety of health problems that affect the heart and blood vessels. This wide ranging classification includes atherosclerosis, coronary ischemia (ischemic heart disease), valvular disease and arrhythmias, cardiac insufficiency, hypertension and arterial hypotension, cerebrovascular disease and other diseases of the peripheral blood vessels. The genesis of cardiovascular disease is complex and multifactorial. Genetic conditioning interacts with lifestyle factors such as diet, smoking habits and physical exercise, generating a syndromatic condition essentially characterised by resistance in blood circulation. This results, in turn, in an acute and continuous deficiency of nutrients and oxygen in the specific tissues such as the heart muscle or the brain. We feel that a thorough description of cardiovascular disease falls out of the scope of this thesis, therefore we include a brief summary of the most significant features.

Hypertension

Hypertension is characterised by an abnormaly increased sustained pressure inside the blood vessels. The objective criteria for diagnosis of high blood pressure has changed over the years, but according to recent widely accepted consensus guidelines(56) it is considered positive if, after two consecutive measurments of blood pressure in two distinct days, systolic blood pressure is higher than 140 mmHg or diastolic blood pressure above 90 mmHg.

The complications resulting from hypertension spread across all the cardiovascular disease spectrum. Blood pressure increases the risk for heart disease and stroke two to three fold, and is potentiated by the presence of concomitant cardiovascular risk factors.(57)

Hypercholesterolemia

Lipoproteins are essential compounds to the normal functioning of the human physiology playing a major role in the dynamics of lipids and cholesterol. They are

responsible for the transportation of the lipids in the serum. The high concentration of lipoproteins, and cholesterol derivates in general, is identified as a modifiable risk factor for cardiovascular disease. Early prophylactic treatment of hypercholesterolemia has been shown to reduce cardiovascular mortality and morbidity.(58)

Ischemic heart disease / Coronary syndromes

Ischemic heart disease, also called coronary syndrome - acute or chronic, results from the total or partial blockage of an artery in the heart precipitating a degree of ischemia and subsequent complications. The syndrome includes clinical entities such as angina, myocardial infarction and other coronary thrombotic causes of sudden death. In the majority of the cases, the occlusion is caused by fragments of atherosclerotic formations that are released into the blood stream.(59) These conditions are the most frequent cause of death in Western countries and are resposible for aproximately one quarter of all cause mortality.(60)

Cerebrovascular disease includes two main types of pathologies: a) those resulting from infarction of arteries or veins and, b) haemorrhagic episodes resulting from the rupture of blood vessels, both occurring in the brain. The diagnosis is based on computed tomography scanning or magnetic resonance image techniques. The consequences for the patient depend on the extension of the resulting lesion. Stroke is the third most frequent cause of death after ischemic heart disease and cancer.(61)

Heart failure is a syndrome in which a reduction in left ventricular function causes pathophysiology that results in characteristic symptoms and exercise limitation. It can result from a wide variety of cardiovascular disorders: anything that puts an excessive demand on the heart for a prolonged period can lead to myocardial failure. Alternatively, degeneration of the myocardium muscle, such as an infarction or ischemia can lead to heart dysfunction and trigger the onset of the clinical syndrome.(62) Patients with heart failure present a number of symptoms; the most common are breathlessness, fatigue, intolerance to exercise and retention of fluids. The diagnosis is confirmed by echocardiography.(63)

Other diseases within the scope of cardiovascular conditions include: atherosclerosis, cardiac dysrhythmias, hypotension, embolism and phlebitis.

1.3.2. Epidemiology

Cardiovascular disease constitutes the most frequent cause of death in the so-called developed world, and it is estimated that by 2020 cardiovascular disease will become the principal cause of death and incapacity worldwide.(64, 65) Within the Portuguese population, cardiovascular disease is the primary cause of death corresponding to 39% of the deaths occurring in 1999.(66)

In a populational study in people 16 years or older hypertension was estimated to be present in 19% of men and 20% of women. In a different study aproximately 25% of men and 20% of women between the ages of 40 and 59 had blood pressure with criteria for hypertension in the United Kingdom. In older age, hypertension can reach a prevalence of 65% in those above 80 years old.(57)

The number of patients with chronic heart failure is on the rise, affecting 1-3% of the adult population and up to 10% in the elderly. The incidence of the condition increases with age which is expected to have a proportional growth, accompanying the aging population. In the future, heart failure may consume 1.5-2.5% of the total health resources with high levels of hospitalisation.(67) The increased rate of survival to a myocardial infarction also contributes to the increase in heart failure as a sequel.(24) The life-time risk of developing heart failure is 20%. Hospital re-admission in the 6 months after onset is 25-50%. Mortality is estimated as high as 25% after 1 year, reaching 59% for men and 45% for women by 5 years after diagnosis.(62)

Information available on the incidence and prevalence of cardiovascular disease in Portugal is limited and studies that evaluate the impact of these diseases to public health are rare. One cross-sectional study presents a prevalence of self-reported arterial hypertension in all ages of 18.2% (95%CI: 16.8, 19.8) (68). In another study, in adults with 39 years of age or more, the prevalence obtained was 57.1% (69). With respects to myocardial infarction, a study based on information collected from the

"Médicos Sentinela" (Sentinel Doctors) network between 1990-1998 estimated an annual mean incidence of 53.7/100 000 habitants.(70)

1.3.3. Risk factors

The Framingham Study together with several other longitudinal populational studies in late 90s gave the necessary insight into the cardiovascular risk factors that have strengthened the treatment and prevention of cardiovascular disease.(55)

Age

Age is one of the most significant cardiovascular risk factors. The cumulative nature of the aggressions to the cardiovascular system throughout ones' life together with the normal degradation of the physiological regulatory mechanisms (kidney and heart) and loss of arterial elasticity, result in a well defined correlation between cardiovascular incidence and age.

Gender

The homogeneity across genders of traditionally accepted coronary risk factors derived from large epidemiological studies have been subject to skepticism due to their failure to predict the cardiovascular risk in women as accurately as in men.(71) In coronary heart disease, the prevalence in male over female follows a 2:1 ratio in younger ages, though this difference disappears in older ages. Gender is also associated with differences in clinical manifestations and response to treatment of coronary heart disease. (72)

Genetics

Family history of cardiovascular disease is associated with higher risk of developing various cardiovascular conditions. More than 250 genes have been identified as potentially related to the susceptibility for coronary artery disease alone.(72) Although, the correlates within families can be confounded by lifestyles carried forward within families. The genetic tendency for cardiovascular disease may not be capable of developing the condition without environmental triggers.(57)

Diet and life-style

Environmental risk factors for cardiovascular disease include diet (obesity, alcohol consumption, salt), child development, psychosocial stress and physical activity.
A diet rich in saturated lipids, high content of salt and low content of vegetables and fruit are strong causes of obesity and are at the root cause of dyslipidaemia and insulin resistance. Therefore, directly or indirectly, associated with higher risk of cardiovascular disease. Moderate consumption of alcohol has a protective effect, though heavy drinkers are at higher risk.

Psychosocial stress, including adverse socio-economic conditions, are also considered independent predictors of cardiovascular disease. Continuous pressure over the sympathetic nervous system, caused by stress, may be involved in the dysfunction of artery lumen regulation.

Sedentary life-styles, either due to physical impairment or optional inactive daily activities, are know to be associated with long term risk of cardiovascular disease.

1.3.4. Treatment

Prophylaxis and treatment of cardiovascular disease aims to prolong life expectancy and to improve functioning and quality of life.

Although the most effective method of primary prevention is based on educating the public about healthy lifestyles, pharmacological therapy is the most used strategy to diminish pre-diagnosis risks and used as treatment after diagnosis. Therapeutic interventions are multifaceted, ranging from agents which modify plasma lipid profiles, to anti-platelet agents, antihypertensives and antiarrhythmics, among others. (11, 73, 74)

The preventive use of statins (HMG-CoA redutase inhibitors)(58) has reduced the risk of acute coronary syndromes among individuals at high risk of major coronary events. Since their introduction into the market, statins' use has been steadily growing with increased prevalence of treatment in earlier ages.(75) Due to the potential beneficial

impact in public health simvastatin has been made available over-the-counter in several countries.(76)

In the United States, 14% of all prescribed and OTC medicines used by adults are indicated for hypertension.(77)

According to a study undertaken by the *Observatório do Medicamento e dos Produtos de Saúde do Instituto Nacional da Farmácia e do Medicamento* (INFARMED), 264 doses.habitant.day (DHD) of antihypertensives were dispensed (sold) in Portugal during 2001. A DHD, in the context of the study, represents the approximate populational exposure to a specific medication or class of medications, corresponding to the Daily Defined Dose (DDD) per 1000 habitants per day. The report refers to an additional increase in the utilisation of antihypertensives of 65.5% between 1995 and 2001.(66) A second study from the same Institute, utilising an apparently similar methodology applied to the years 1999 to 2003 resulted in findings that did not, however, coincide with the results from the study between 1999 and 2001.(78) The results of the latter study estimate an increase of 28% in the Daily Defined Dose per 1000 habitants per day (DHD) between 1999 and 2003, from 183 DHD to 234 DHD respectively. Information concerning the populational exposure to cardiovascular drugs in Portugal from all other classes of cardiovascular therapy is almost inexistent and the drug utilisation data is mainly reviewed from the perspective of financial management.

1.4. Depression and Cardiovascular disease

Chronic medical conditions are intimately associated with depressive symptoms and development of major depressive disorder. (79, 42) When occurring in parallel with chronic medical conditions, depression augments the symptoms and deteriorates the prognosis as well as the adherence to treatment regimens.(15)

Cumulative evidence shows that depression is a risk factor for the development of cerebrovascular and coronary artery diseases in hitherto fit individuals. Moreover it constitutes a risk factor for the occurrence of adverse outcomes in patients with a

history of coronary heart disease (10) and worsens the prognosis and death rates for patients with cardiovascular disease in general.(80, 32, 81, 82)

The *causal pathways* through which depression may interact with cardiovascular disease include that:

a) depression results from vascular disease, potentially through cerebral degeneration;
b) depression has a direct effect on the regulation of the cardiovascular system;
c) depression and cardiovascular disease have common underlying aetiological mechanisms
d) all aforementioned pathways may coexist.

Although artists and cultural heritage have been, for endless times, warning of the sequels of feelings of *heartbreak*, the first scientific record of the relation between depression and cardiovascular disease is attributed to Malzberg, in 1937. Malzbeg observed that sudden death of cardiovascular causes was six times higher than expected, in depressed patients that had been chronically institutionalised. His findings are still relevant nowadays given that the estimates were *clean* of somatic antidepressant treatment.(82) Four decades elapsed before the analysis of the Danish National Registries by Weeke, in the 1970s, estimated a higher risk for cardiovascular disease in patients with severe forms of depression in the general population. At the time, the suspicion was allocated to the emerging antidepressant agents. Strong up-to-date evidence linking depression with ischemic heart disease emerged more recently from a group of large, longitudinal, community-based prospective studies with an average follow-up of 11.3 years (from 4-37 years) conducted in North America and Europe.(83)

Diagnosis of depression in cardiovascular disease

Depression and cardiovascular disease are usually managed at primary health care level together with other chronic conditions.(15) Several studies have found that health professionals commonly overlook the depressive symptoms leaving a high proportion of patients with cardiovascular disease untreated.(84, 85) The diagnosis of depression in patients with cardiovascular disease may be challenging, for the reasons

previously presented regarding the diagnosis of depression in the general population plus additional factors specific to the coexistence of cardiovascular disease. It is believed that less than 25% of major depressive cases with coexistent cardiovascular disease are diagnosed and about half of these receive treatment.(84)

Fatigue, one of the most common symptoms in primary care, and sleep disturbances are common to depression and heart failure. Other common symptoms are weight change and cognitive and sleep disturbances.(86)

It may be assumed that depression is an integral part of cardiovascular disease and lastly physicians may be worried about the potential side-effects of antidepressants in patients with cardiovascular disease.(20)

The choice of treatment for depression in patients with ischemic cardiac disease is largely based on the safety profile of the available therapeutic agents.(87) Due to their adverse cardiac safety profile TCAs are contraindicated in patients with most cardiovascular conditions, particularly in heart disease.(35) Monoamine oxidase inhibitors are recommended only as second line treatment when depression is refractory to other medications.(44, 35) The most recommended treatment for depression in patients with cardiovascular disease are SSRIs and some of the newer antidepressants depending on specific treatment objectives.(88, 12)

Follow-up and close monitoring of therapeutic effect and patient's adherence is critical in the treatment of depression in patients with cardiovascular disease.(10)

1.4.1. Cardiovascular disease as a risk factor for depression

Depression resulting from cardiovascular disease, specifically cerebrovascular deterioration, has been hypothesised in older age.(32) It has been proposed that cerebral atherosclerosis of small vessels is responsible for subcortical brain lesions causing disruptions to the thalamo-cortical axis. A second explanation involves prolonged atherosclerosis induced inflammatory response in the brain. This cytokine-mediated stimulation would lead to neuronal toxicity and consequent reduced monoamine activity.(32)

The prevalence of depression in people with cardiovascular disease is in the main higher than in the general population. Patients with heart failure are estimated to have a prevalence between 11% and 25% of depression when in primary care and up to 70% while hospitalised.(24) Prevalence estimates of approximately 20%, for depressive symptoms which meet diagnostic criteria, are reported in patients that survive a myocardial infarction (10, 30, 20) raising to over 30% during hospitalization due to acute coronary episodes.(81)

1.4.2. Depression as a risk factor for cardiovascular disease

Depression is widely accepted as an independent risk factor for cardiovascular disease.(89, 80) Depression has been included in the group of modifiable factors to reduce the risk of myocardial infarction, along with diabetes, smoking and hypertension.(10, 90)

The presence of depression in patients with cardiac conditions constitutes an additional risk for mortality.(83) Depression is also a predictor of development of heart failure and is 4-5 times more common among patients with the condition. (24)

Depressed patients who suffered a myocardial infarction, are 3.5 times more likely to die in the 6 months following the event than those not depressed after the event.(91, 20, 92) In cohort studies with long follow up the risk of myocardial infarction remained high up to 10 years after the first depressive episode.(32)

In terms of the seven main epidemiological criteria for depression to be considered a cardiovascular risk factor, depression fulfils the requirements on 4 criteria: “strength” of association, “consistency”, “dose-response” effect and “predictability”. The criteria “specificity” and “biological plausibility” have been fed by emerging results from research exploring some of the explanatory physiological mechanisms. The less supported criteria is “response to treatment” where evidence from clinical trials have not been conclusive.(7, 17)

Despite the accumulated evidence, some authors consider the association between depression and cardiovascular risk highly confounded by the severity of the condition and the timing of onset of depression (93) and some found no relation with increased cardiovascular mortality(94).

1.4.3. Mechanism of depression - cardiovascular disease

The mechanisms connecting the association between depression and cardiovascular disease are not completely understood but they can be grouped as biological or behavioural. The biological factors include alterations to cardiac rhythm, increased platelet activation, high serum levels of catecholamines and serotonin, inflammation, serum cholesterol and toxicity of tricyclic antidepressants. The behavioural factors are related to mental stress, poor diet, low levels of physical exercise, non-adherence to medicinal therapy, weak social support and, in general, to unhealthy lifestyles.(10)

1.4.3.1. Neuroendocrine pathways

The biological causal mechanisms rely on a cascade of neuroendocrine connections that link depression to cardiovascular disease in a multiaxial way. Evidence suggests that hyperactivity at the hypothalamic-pituitary-adrenal (HPA) axis and increased sympathomedular activity may stimulate inflammatory response with high cytokine levels, activation of platelet aggregation and subsequent vascular damage. Serum fatty acids are also suggested to be involved.

Hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal (HPA) system constitutes the individual's mechanism to cope with stress. In situations of stress the hypothalamus signals the pituitary gland to release corticotrophin. The features of hyperactivity of the HPA system in mental disease, including depression, are well documented. A basal over-reactivity of the HPA axis generates a cascade of neurohormonal responses including the release of corticosteroids and subsequent induction of hypercholesterolemia, hypertrigliceridemia and activation of vasopressin resulting in hypertension and aggression to the arteries' inner epithelium, aggravating or stimulating atherosclerosis and cardiovascular episodes.(95)

Autonomic function

Heart rate variability (HRV) reflects the amplitude in the sinus rhythm interval (R-R) and is dependent on the equilibrium between sympathetic and parasympathetic systems.

Healthy people have a high degree of heart rate variability. However, individuals with coronary heart disease have a reduced variability and therefore a higher risk of sudden cardiac arrest and death. A predominance of sympathetic over parasympathetic tone can also determine a lower HRV and lower limits for onset of ventricular arrhythmia.(96) Increased sympathetic tone is found in depressed patients together with arrhythmogenic features (tachycardia, fibrillation, bradicardia) suggesting a potential mechanism amplifying the risk of cardiac death through arrhythmia.(97)

Immune response (cytokines)

Inflammatory response is an important haemostasis and tissue repair mechanism. However, when disproportionate or prolonged for a long time, the oxidative and protein upregulation processes cause tissue injury, including the inner layer of blood vessels. Depressed patients have been found to have higher plasma levels of acute-phase response biomarkers namely cytokines.(98) The cytokine-mediated model suggests that sustained sub-clinical levels of inflammatory mediators promote or aggravate the development of atherosclerosis and associated cardiovascular disorders. On the other hand, some patients treated with immunotherapy agents (interferon, tumour necrosis factors and interleukins) for cancer or viruses have developed depressed mood and other symptoms not associated with the baseline condition.(24) Additionally, statins have an antiinflammatory effect which would explain, to some extent, a double protective effect, one cardiovascular and one reducing the inflamatory link with depression.(81)

Platelet activation

Platelet activation induces thrombogenicity which results in coagulation/thrombosis, arterial constriction and vessel occlusion.(99)

Low serotonin activity has been a central feature in depressed patients and a target for treatment. In addition to its role in neurotransmission, serotonin is also responsible for platelet aggregation and vasoconstriction.

Untreated depressed patients have been found to present an increased density of platelar serotonin receptors HT_{2A}. After treatment with paroxetine these patients reveal a decrease in thrombotic activity with lower levels of coagulation biomarkers.(87) Therefore, serotonin upregulated platelet activation may be responsible for increased thrombosis and ischemic events.

Serum lipid profile

Tiemeier et al.(100) found that a relationship existed between the blood lipid profile, a cardiovascular disease risk factor, and the incidence of depression in a population sample of adults of or over 60 years of age. In two other studies in the same population (*Rotterdam study*) a significant correlation was reported between the loss of elasticity of the arterial wall and depressive symptoms (OR=1.24, 95%CI: 1.01, 1.52) (101), as well as an equally significant association between the presence of atherosclerosis and depression.(102)

Serum cholesterol, on the other hand, has been associated with low response to antidepressant therapy and increased risk of violent suicide (32) but the results are contentious. In this context, low intake of essential fatty acids has also been hypothesised as another biological link. Omega-3 fatty acids raise HDL concentration and decrease triglycerides playing a protective role in cardiovascular disease. Neurons' membranes are constituted mostly by lipid structures. Thus, abnormal concentrations of essential fatty acids may have an influence in the dynamic of neurotransmission and consequently in the aetiology of depression. (32)

1.4.3.2. Psychosocial factors

In terms of behavioural and social links between depression and cardiovascular disease, both are highly associated with illness-promoting lifestyles, such as smoking, poor diet, and high levels of stress. Concomitant depression in chronic disease is often responsible for a reduction in self-care and monitoring i.e. medication non-adherence, augmented alcohol consumption, sedentarism and weight gain.(26)

Lifestyle change

Physical exercise, diet change, smoking reduction and other behaviour changes to reduce cardiovascular risks are often prescribed after myocardial infarction, stroke or diagnosis of other cardiovascular conditions. Studies have found that depressed

patients are 40% less likely to stop smoking and more likely to abandon exercise programs.(103, 82)

Non-adherence to drugs

Increased mortality and morbidity are expected in those patients with irregular adherence to preventive medications.(90) In heart failure, for example, treatment regimens include over 5 drugs.(63)

Depressed patients have feelings of hopelessness, tend to isolate themselves dissociating from support and care, and present reduced concentration and or cognitive disturbances. All the previously enumerated features are related with non-adherence to medication regimens by depressed patients in the general population.(85) Adherence to preventive aspirin therapy has been estimated to be 45% in patients with depression compared with 69% in non-depressed patients.(104) Rieckmann et al. also found a dose-response association between the severity of depressive symptoms and the level of non-compliance.(105) In a study including 940 participants, non-adherence to cardiovascular medication was persistent after adjustment for demographic features, social support and severity of the cardiovascular disease.(90) Katon et al. reported higher adherence to comorbid medications in treated depressed patients compared with non-treated.(106)

Social Support

Lack of social support has an adverse influence on the course of depression, cardiac disease, stroke, renal disease to name a few.(24) The influence may be channelled through third factors such as treatment compliance and sedentary lifestyle, for example.

1.4.3.3. Adverse drug reactions

One additional possible link between depression and cardiovascular disease is the potential for some medications to cause depressive symptoms or increase cardiovascular risk. We have looked at the literature regarding cardiovascular drugs associated with depressive symptoms and antidepressant drugs associated with increased cardiovascular adverse reactions.

Depression as adverse drug reaction

Patients treated with corticosteroids, opioid derivates and benzodiazepine may show depressive symptoms.(10)

Starting in the late 1960s, beta-blocker agents were suspected of being associated with onset or aggravation of depression. The suspicion, although based on low methodological quality studies, restricted the use of this medication in many patients that suffered a myocardial infarction and were diagnosed with depression.(92) Ko et al. performed a meta-analysis of 15 randomized controlled trials of beta-blockers to find that, though the drugs were associated with symptoms of fatigue and sexual dysfunction, no statistically significant association was found with depression.(107) Rathma et al. studied the association between depression and cardiovascular drugs (calcium channel blocker, beta-blocker and ACE inhibitors) in diabetic patients and found no association.(25)

Sporadic reports have also reported depression associated with angiotensin converting enzyme inhibitors, calcium channel antagonists and methyldopa.(43)

The natural history of cardiovascular disease, as presented before, may lead to depressive symptoms. In the face of newly identified depression health professionals are likely to be *confounded by indication* and wrongly impute the cardiovascular therapy as the cause.

Cardiovascular disease as an adverse drug reaction to antidepressants

The most significant link between antidepressant therapy and cardiovascular disease resides in the arrhythmogenic effect of the tricyclic antidepressants (TCAs). However, specific safety features of other antidepressants may be relevant in the context of managing cardiovascular risk, such as weight gain, thrombosis, raised blood pressure.

The average annual mortality rate estimated to antidepressant toxicity (excluding overdose) is 1/3000 treated patients. This estimate is higher for TCAs (1/1750 treated patients for one year) and lower for SSRIs (1/100 000 patients treated for one year).(43)

In the late 1980s, a series of trials (Cardiac arrhythmia suppression trials - CAST) was designed to test the hypothesis that suppression of post-myocardial infarction ventricular irritability would reduce cardiac mortality. To that end, patients were randomized to placebo or three antiarrhytmic drugs. The trials were interrupted when a 2-3 fold increased mortality was detected for 2 of the 3 antiarrhythmic drugs and these drugs are now contraindicated in patients with previous myocardial infarction.(108)
All current available TCAs have anticholinergic and class I antiarrhythmic effects, and the potential associated adverse reaction, dry mouth, blurred vision, constipation, urinary retention, memory impairment and tachycardia. Moreover TCAs acelerate heart rate or cause orthostatic hypotension in up to 20% of patients treated.(108, 82) Significant risk for cardiac death was worse in case of overdose, which is more frequent in depressed patients.(43)

Even though tricyclic antidepressants are effective against depression, their safety profile and the emergence of less cardiotoxic alternatives, make them contraindicated in patients with cardiovascular disease.(109)

SSRIs are safer alternatives in terms of cardiac effects, namely their neutral effect on heart rate or rhythm and safety during overdose.(108) SSRIs have been associated with alterations to the serum lipid constitution raising the levels of low-density lipoproteins.(110)

Newer antidepressant drugs have not been extensively studied in patients with underlying cardiovascular disease. Several safety aspects have been reported that are relevant in this context. Weight gain is a potential side effect of mirtazapine and paroxetine. Raised blood pressure is also associated with venlafaxine(7) and bupropion(108, 20)

Drug-drug interactions

Drug-drug interactions between cardiovascular drugs and antidepressant drugs may also have an effect on worsening the prognosis or modifying the treatment outcome. The two main interaction mechanisms are the ones involving the enzymes of the cytochrome P450 (CYP450) and plasma protein binding.(43)

SSRIs are CYP450 inhibitors, this effect may change the pharmacokinetics of drugs such as warfarin and digoxin as well as beta-blockers, statins, antihypertensives (losartan, valsartan, irbesartan), for example.(20, 104)

Fluoxetine, sertraline, paroxetine and fluvoxamine are known to bind extensively to plasma proteins potentially displacing other drugs that compete for the same protein.(43)

1.4.3.4. Cardiovascular outcomes of depression treatment

Assuming that depression activates physiological mechanisms, appropriate treatment of depression would be expected to have a positive impact on the cardiovascular disease prognosis, supposing the drug toxicity to be minimal. For example, it has been speculated that SSRIs may improve cardiovascular outcomes by reducing platelet activation through serotonin modulation.(108, 88)

Three trials have been conducted to test the hypothesis, namely, the Montreal Heart Attack Readjustment Trial (MHART), the Sertraline AntiDepressant Heart Attack Trial (SADHART) and the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD).

The SADHART trial, involving 369 participants, showed sertraline to be safe, in the trial conditions, for the treatment of depression in patients with ischemic heart disease. No difference was found between the sertraline and placebo groups in respect to cardiac mortality at 24 weeks.(111)

In the MHART trial the results were even more astonishing. The intervention arm, randomized to psychosocial support, had worse outcomes from the recovering post-Myocardial Infarction program than the arm on placebo. The investigators justify the results due to the potential disruption of the program in the natural process of coping with the event, paradoxically increasing the stress of the participants in the program constantly reminded them of the event.(83)

The results of the ENRICHD trial are somehow similar. Cognitive-behavioural therapy was found to be effective in the treatment of depression, but the effect on cardiovascular mortality and morbidity was not significant at 29 months average follow up.(112) *A posteriori* secondary analyses of the participants in the trial suggest the use of SSRIs to be associated with a 40% death and myocardial infarction reduction.(10)

The evidence from these trials is inconclusive due, in part, to the small sample and lack of statistical power to detect differences in objective cardiovascular outcome. However, even if no effect is seen in the cardiovascular outcomes, the appropriate treatment of depression would improve depressive symptom and patients' quality of life.

In summing up, the association between depression and cardiovascular disease has been shown to be significant, dose-dependent, compatible in temporality and independent from conventional cardiovascular risk factors. The direction and specificity of the multiple proposed causal mechanisms remains theoretical. The evidence, mostly originating from observational studies, has the potential to be confounded.

2. Aim

The aim of this study is to estimate the effect that the treatment of cardiovascular disease has on the use of antidepressant drugs.

3. Systematic literature review

3.1. Specific objective

The objectives of the systematic literature review were to compile and analyse current knowledge on the association between the treatment of depression and cardiovascular disease.

3.2. Methods

The MEDLINE, EMBASE and PsycINFO reference databases were searched without date limits (last search in 02-2007). Potential relevant articles were systematically searched using the key concepts:
[(Disease **OR** Therapy) **AND** cardiovascular] **AND** [(Disease **OR** Therapy) **AND** depression]

Reports of systematic reviews and meta-analysis, clinical trials, cross-sectional studies, case-control studies and cohorts, written in portuguese, english or spanish were eligible for inclusion. A full description of the search strategy is included in Appendix 1.
The selection and review of the publications was made by the principal investigator. Additional references were selected from bibliographies of selected papers or from identified review papers.

3.3. Results

From the 1008 unique citations retrieved, 79 were considered after title and abstract review. Of these, 26 full papers were not accessible. Of the 53 reviewed, 4 papers that reported on the association between antidepressant therapy and cardiovascular disease/treatment were included.

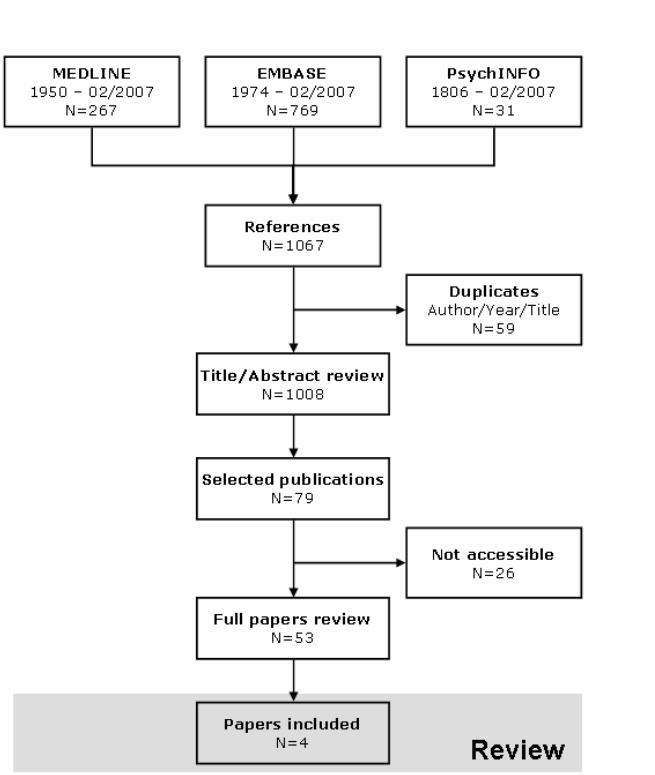


Fig. 1 - Systematic literature review flowchart

In a follow-up study involving 7 983 adults aged 55 years or older, Egberts et al.(45) investigated the prevalence of antidepressant use among various chronic medical conditions. Overall a higher prevalence of antidepressant use was found in patients with chronic disease. The results show a significant relative risk (RR) for using antidepressants in patients with history of stroke (RR=2.2; 95%CI: 1.0, 3.9), but no association was found with hypertension (RR=1.0; 95%CI: 0.8, 1.3) or history of myocardial infarction (RR=1.1; 95%CI: 0.8, 1.6). The authors also report that the choice of antidepressant drug was not influenced by the type of chronic condition.

A cross-sectional study conducted by Heckman et al.(86) based on medication chart review of 1 223 residents of elderly homes identified 245 (20%) heart failure patients. In this study, those receiving appropriate ACE-inhibitor therapy were less likely to have been prescribed an antidepressant drug (OR=0.11; 95%CI: 0.02, 0.76). The authors also report absence of an association between use of antidepressants and any specific class of cardiovascular drugs including beta-blockers.

Kuzuya et al.(29) investigated the rate of polypharmacy and its determinants in the oldest elderly using the data collected from 632 men and 1 243 women participants in the Nagoya Longitudinal Study for Frail Elderly (≥65 years). The results of the study revealed a lower probability for the older patients (≥85 years) with depression and medical history of cardiovascular disease to receive antidepressant therapy (OR=0.48; 95%CI: 0.23, 0.97).

Harman et al.(15) assessed the impact of four chronic medical conditions (diabetes, hypertension, arthritis and heart disease) on the probability of adequate depression treatment (recognition, treatment and guideline concordance). The analysis was based on 468 patients with depression identified from a sample of 6 594 aged 65 years or older. Higher likelihood of antidepressant treatment (appropriate or not-appropriate) was observed for patients with hypertension (OR=2.33; 95%CI: 1.38, 3.95) but hypertensive patients were not more likely to receive appropriate treatment (OR=1.38; 95%CI: 0.80, 2.40) comparing with patients with other chronic conditions. Patients with heart disease had no difference in propensity for any antidepressant treatment (OR=0.97; 95%CI: 0.55, 1.70) or appropriate treatment (OR=0.89; 95%CI: 0.47, 1.68).

The results emerging from the literature reviewed are inconclusive regarding the association between antidepressant drug use and cardiovascular disease and treatment. Some of the authors identify gender, socioeconomic factors and intensity of contact with the healthcare system as possible determinants. To our knowledge, no study has assessed the association between antidepressant treatment and cardiovascular therapy across all adult ages in the community, taking into account the potential interfering factors.

4. Cross-sectional study

4.1. Specific objective

The objectives of this study are: a) to characterise the association between antidepressant therapy and the utilisation of cardiovascular medication, and b) to identify the correlates of treatment of depression, in a cohort of adult residents of an urban region.

4.2. Methods

Study population

Adults (18 years or older) living in the city of Porto (Portugal) were identified through random-digit-dialling and invited to participate in a cross-sectional community-based study. The rationale and details of the recruitment process and ethics have been described elsewhere.(113-115) All participants provided informed consent and confidentiality was maintained throughout the study.

Data collection

Data was collected by means of a structured questionnaire administered in face-to-face interviews by trained research staff. The interviews took place between October 1995 and December 2003.

Sociodemographic information was obtained for age, sex, marital status, educational achievement and current occupation. Marital status was classified into three groups: married; single/never married; divorced/separated/widowed. Education was stratified by: 4 years or less; 5 to 11 years; and 12 or more complete school years. Occupation/employment status was defined as *white-collar; blue-collar;* or unemployed/retired. The intensity of health-care utilization was assessed by the number of medical visits in the previous 12 months and classified into those with 0-1 visits; 2-5; 6-11; and 12 or more visits.

Data on the use of medicines was collected in free-text format by asking the patient:

Do you take medicines regularly (medicines taken in the last year)?

If yes, which ones?

Participants were also instructed to bring their current medication to the study appointment.

Self-reported drugs' names (and health products) were entered in a database using the brand or generic name as reported, and were later classified using the Anatomical Therapeutic Chemical (ATC) terminology.(116) The identification and ATC classification was undertaken by a pharmacist and independently verified by a second pharmacist. The cases with disagreement were resolved through consensus or otherwise classified as void.

Users of antidepressants were classified as those participants reporting at least one drug from within the ATC therapeutic classes "N06A - Antidepressants" or "N06CA - Antidepressants in combination".(116)

Participants were classified as users of cardiovascular drugs if they reported using one or more drugs from the ATC anatomical class "C – Cardiovascular system" or the therapeutic class "B01 –Antithrombotic agents".

Medical history and health status were assessed using an **open-ended question**,

Do you currently have any disease that demands regular medical care, i.e. treatments, clinical analyses or consultations?

If yes, which ones?

and **disease specific questions** for depression, angina, myocardial infarction, cardiac arrhythmia, heart failure, other cardiac disorders, stroke, among others. The question read:

Has a physician ever diagnosed you with ….?

If yes, how long ago?

The free text answers were classified using the International Classification of Diseases, Ninth Revision (ICD-9), codes.

Depression - case definition

Cases of depression were considered those with one of the following ICD-9 codes:

296.2	*Major depressive disorder, single episode*
296.3	*Major depressive disorder, recurrent episode*
298.0	*Reactive depressive psychosis*
300.4	*Dysthymic disorder*

311 Depression NOS

309.0-309.1 Adjustment reaction with depressive symptoms

or a diagnosis of depression during the previous year in the depression specific question.

Additionally, a sub-sample of patients responded to the 21-item Beck Depression Inventory (BDI).(22, 117) The BDI is a widely used self-reporting instrument to assess the intensity of depressive symptoms covering most of the DSM-IV categories for major depressive episode. Scores of 10 or higher indicate at least mild to moderate symptoms of depression.(83, 94) The threshold of 10 was chosen because similar studies have found effects on cariovascular risk at this level of depressive symptoms.(84)

Cardiovascular disease – case definition

Cases of cardiovascular disease were considered as any participant with a positive answer to at least one cardiovascular disease-specific question, regardless of how long before the diagnosis had been made, or one ICD-9 code within the following list:

272.0 Pure hypercholesterolemia
272.1 Pure hyperglyceridemia
272.2 Mixed hyperlipidemia
272.3 Hyperchylomicronemia
272.4 Other and unspecified hyperlipidemia
401-405 Hypertensive disease
410-414 Ischemic heart disease
427 Cardiac dysrhythmias
428 Heart failure
429.2 Cardiovascular disease, unspecified
429.9 Heart disease, unspecified
430-438 Cerebrovascular disease
440 Atherosclerosis
444 Arterial embolism and thrombosis
445 Atheroembolism
451 Phlebitis and thrombophlebitis

453 *Other embolism and thrombosis*

458 *Hypotension*

Inclusion/exclusion criteria

Patients aged 65 or older with a score below 24 in the Mini-Mental State Examination(118) were excluded from the study due to the potential for unreliable self-reported information. Patients for whom at least one self-reported medication verbatim was ambiguous, hampering the identification of the drug, were also excluded to avoid case misclassification.

Analyses

Two analyses were performed: **the first** investigating the use of antidepressants as the outcome of interest, and **a second** one, that incorporated the BDI score, examining the treatment of depressive symptoms as the outcome of interest. Both followed similar statistical approaches.

Differences in characteristics between antidepressant users and non-users, and treated versus non-treated depression, were compared using the Pearson chi-square test. Unconditional multiple logistic regression was conducted to obtain adjusted odds ratios to examine the cross-sectional association between antidepressant drug use (outcome) and cardiovascular drug use (primary predictor) taking into consideration sociodemographic characteristics (gender, age, marital status, education, employment) and self-reported diagnosis of depression (*analysis 1*).

In the secondary analysis (*analysis 2*), using logistic regression, the likelihood of treated depression was adjusted for gender and age, indicator variables for cardiovascular drug use plus a variable for the number of medical visits in the previous year. The defined outcome of interest was treatement of depression. The BDI respondents with scores of 10 or higher were aggregated with the BDI respondents under antidepressant treatment and were classified as “treated depression” if they had reported the use of an antidepressant; or “not treated” if, although having a score over the threshold, they have not used an antidepressant drug.

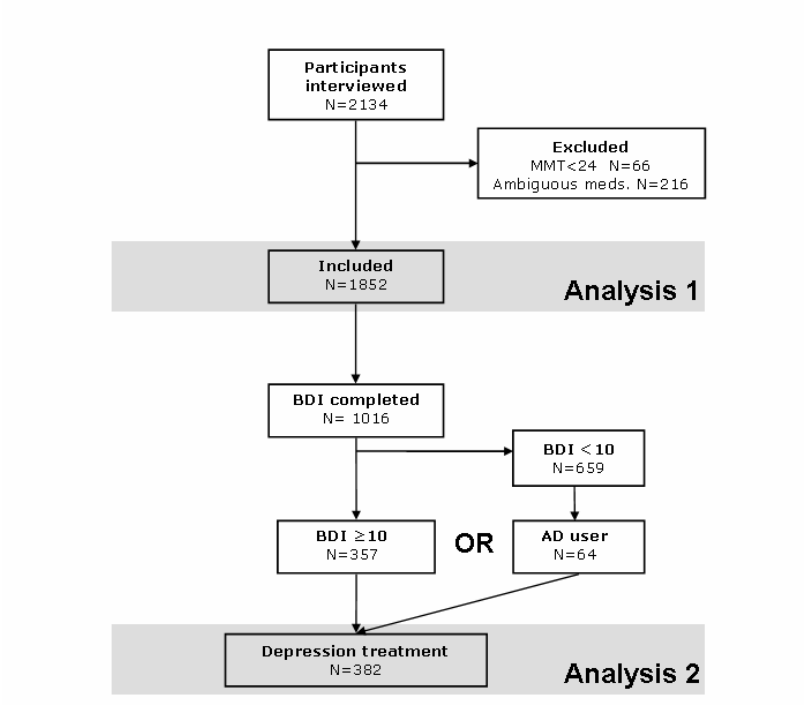
To determine whether a statistical association existed we reported odds ratios (ORs) with confidence intervals (CIs). All statistical comparisons were 2-sided, and a value of $p \leq 0.05$ was considered statistically significant.

Statistical analyses were conducted using the statistical packages SPSS version 14.0® and R version 2.4.1(package: epitools)(119, 120).

4.3. Results

Of the 2 134 participants interviewed a total of 1 852 met the study inclusion criteria. Figure 2 represents the study participants' flowchart. Approximately 60.1% of the sample was female, and an average age of 52.6 years. (Table 1)

The second stage of analysis (analysis2) included 357 participants with BDI≥10 and 64 users of antidepressants.



MMT = Mini-Mental State Examination; Ambiguous meds. = Ambiguous self-reported medication; BDI = Beck Depression Inventory; AD = antidepressant drug

Fig. 2 – Participants flowchart

4.3.1. Analysis 1

Of the 1852 participants, 1010 (54.5 %) reported having taken regularly, at least, one drug during the year previous to the interview date. Table 2 shows the distribution of the drugs by ATC anatomical class. The categories with higher prevalence of utilization, within those taking medicines regularly, were cardiovascular (60.2%), nervous system (52.1%) and alimentary tract and metabolism (44.9%).

129 participants reported the use of at least one antidepressant drug corresponding to a prevalence of 7.0 % (95%CI: 5.8, 8.2). The most prevalent therapeutic class among the users of antidepressants were SSRIs with a proportion of 46.5%, followed by "other antidepressants" (34.1%), which included the newer agents (Table 3).

Regarding cardiovascular drugs, 617 patients were classified as users, 33.3% of the entire cohort. Among the cardiovascular medicines used, ACE-inhibitors (41.7%) were the most frequent. 160 patients (25.9% of those taking CV drugs) were users of serum lipid reducing agents, 144 (23.3%) diuretics and 125 (20.3%) cardiac therapy. The proportion of antidepressant users among therapeutic classes of cardiovascular drugs were not homogeneous, suggesting a higher prevalence of antidepressant use among the patients taking peripheral vasodilatators, vasoprotectives and beta-blocking agents, but the small number of occurrences in each strata does not allow for robust inference (Table 4).

Depression was reported by 4.3% (95%CI: 3.4, 5.3) of the participants (Table 1) and cardiovascular disease by 1028 participants (55.5%). Dyslipidaemia (62.5%) and hypertension (53.4%) were the two most frequent self reported cardiovascular conditions. The proportion of antidepressant utilization among the various categories of cardiovascular disease was apparently homogeneous. (Table 5)

Table 1 presents the results of the unadjusted estimates of odds ratios (OR) and adjusted OR for the factors taken into account in the analysis.

According to the unadjusted estimates comparing antidepressant users with non-users, women are almost 4 times more likely to use antidepressants than men (OR=3.67;

95%CI: 2.28, 5.92). Participants 40 years of age or older show a significant (or borderline significance) association with utilization of antidepressants, stronger for the age band 50-59 (OR=1.26; 95%CI: 1.26, 13.63). Regarding the indicator variables for social support, divorced/widowed marital status was associated with a high probability of antidepressant use comparing with participants that were married (OR=1.56; 95%CI: 1.02, 2.39). No difference was found between single/never married and those married. Educational achievement and employment status were not associated with a differential use of antidepressants. The univariate correlation between self reported depression and antidepressant use was strong and statistically significant (OR=48.90, 95%CI: 28.86, 82.88).

Users of cardiovascular medication were 64% more likely to be antidepressant users when compared with those not using cardiovascular drugs in unadjusted analysis, (OR=1.64; 95%CI: 1.14, 2.36).

After adjusting for gender, age, marital status, education, employment situation and self reported depression, the main predictor of interest, cardiovascular drug use, lost statistical association (OR=1.32; 95%CI: 0.80, 2.16) with the use of antidepressants. Out of all the other factors included in the regression, gender (OR=2.92; 95%CI: 1.70, 5.02) and self-reported depression (OR=46.18; 95%CI: 26.35, 80.95) maintained a statistically significant association with antidepressant use.

Table 1. Characteristics of the participants by antidepressant utilization in the previous year, and determinants for use of antidepressants.

Determinants	Antidepressant use			Odds Ratio (95% CI)	
	Did not use (n= 1723) n (row %)	Used (n= 129) n (row %)	Total (n=1852) n (col. %)	Unadjusted OR	Adjusted OR†
Sex					
Male	718 (97.2)	21 (2.8)	739 (39.9)	1	1
Female	1005 (90.3)	108 (9.7)	1113 (60.1)	3.67 (2.28-5.92)	2.92 (1.70-5.02)
				$X^2_1 = 32.3$*	
Age (years)					
18-29	135 (97.8)	3 (2.2)	138 (7.5)	1	1
30-39	184 (93.9)	12 (6.1)	196 (10.6)	2.93 (0.81-10.60)	2.25 (0.49-10.28)
40-49	413 (92.8)	32 (7.2)	445 (24.0)	3.49 (1.05-11.57)	2.81 (0.66-11.88)
50-59	413 (91.6)	38 (8.4)	451 (24.4)	4.14 (1.26-13.63)	2.53 (0.59-10.80)
60-69	334 (92.8)	26 (7.2)	360 (19.4)	3.50 (1.04-11.77)	3.34 (0.75-14.94)
≥70	244 (93.1)	18 (6.9)	262 (14.1)	3.31 (0.96-11.47)	3.15 (0.66-14.99)
				$X^2_5 = 6.66$	
Marital status					
Married	1214 (93.3)	87 (6.7)	1301 (70.2)	1	1
Single / Never married	223 (95.7)	10 (4.3)	233 (12.6)	0.63 (0.32-1.22)	0.77 (0.34-1.76)
Divorced/Widowed	286 (89.9)	32 (10.1)	318 (17.2)	1.56 (1.02-2.39)	0.98 (0.57-1.69)
				$X^2_2 = 7.43$*	
Education (years)					
≤4	647 (91.6)	59 (8.4)	706 (38.1)	1	1
5-11	535 (93.7)	36 (6.3)	571 (30.8)	0.74 (0.48-1.13)	0.83 (0.48-1.43)
≥12	541 (94.1)	34 (5.9)	575 (31.1)	0.69 (0.45-1.07)	0.84 (0.44-1.61)
				$X^2_2 = 3.48$	
Employment status					
White-collar	685 (93.6)	47 (6.4)	732 (39.5)	1	1
Blue-collar	286 (94.4)	17 (5.6)	303 (16.4)	0.87 (0.49-1.53)	0.65 (0.30-1.40)
Unemployed/Retired	752 (92.0)	65 (8.0)	817 (44.1)	1.26 (0.85-1.86)	0.84 (0.45-1.58)
				$X^2_2 = 2.43$	
Depression					
Not depressed	1698 (95.8)	75 (4.2)	1773 (95.7)	1	1
Depressed	25 (31.6)	54 (68.4)	79 (4.3)	48.90 (28.86-82.88)	46.18 (26.35-80.95)
				$X^2_1 = 479.90$*	
Cardiovascular drug use‡					
No	1163 (94.2)	72 (5.8)	1235 (66.7)	1	1
Yes	560 (90.8)	57 (9.2)	617 (33.3)	1.64 (1.14-2.36)	1.32 (0.80-2.16)
				$X^2_1 = 7.38$*	
Constant					0.01

* Chi-square statistically significant at α=0.05; †Adjusted for all variables in the table, ‡*Cardiovascular drug* includes ATC: B01.

Table 2. All-drug utilisation by ATC anatomical class and antidepressant use.

		Antidepressant use		Total
		Did not use	Used	
		Count (row %)	Count (row %)	Count (col. %)
Did not use drugs		-	-	842 (45.5)
Used drug(s) (ATC anatomical class)	ALIMENTARY TRACT AND METABOLISM	*387 (85.4)*	*66 (14.6)*	*453 (44.9)*
	BLOOD AND BLOOD FORMING ORGANS	*33 (80.5)*	*8 (19.5)*	*41 (4.1)*
	CARDIOVASCULAR SYSTEM	*551 (90.6)*	*57 (9.4)*	*608 (60.2)*
	DERMATOLOGICALS	*6 (100.0)*	-	*6 (0.6)*
	GENITO URINARY AND SEX HORMONES	*72 (93.5)*	*5 (6.5)*	*77 (7.6)*
	SYSTEMIC HORMONAL PREP, EXCL SEX HORM. AND INSULINS	*82 (85.4)*	*14 (14.6)*	*96 (9.5)*
	ANTIINFECTIVES FOR SYSTEMIC USE	*18 (85.7)*	*3 (14.3)*	*21 (2.1)*
	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	*8 (100.0)*	-	*8 (0.8)*
	MUSKULO-SKELETAL SYSTEM	*141 (86.5)*	*22 (13.5)*	*163 (16.1)*
	NERVOUS SYSTEM	*397 (75.5)*	*129 (24.5)*	*526 (52.1)*
	RESPIRATORY SYSTEM	*77 (96.3)*	*3 (3.8)*	*80 (7.9)*
	SENSORY ORGANS	*14 (93.3)*	*1 (6.7)*	*15 (1.5)*
	VARIOUS	*1 (100.0)*	-	*1 (0.1)*
	ATC NOT APPLICABLE*	*6 (100.0)*	-	*6 (0.6)*
Subtotal		-	-	1010 (54.5)
Total				1852 (100.0)

**ATC Not applicable* corresponds to nutritional supplements incorporating multiple vitamins, minerals and well defined substances that are not listed in the ATC classification.

Table 3. Antidepressant drug use by ATC therapeutic class.

		Total
		Count (col. %)
Did not use AD*		1723 (93.0)
AD class (ATC)	NON SELECTIVE MONOAMINE REUPTAKE INHIBITORS	*34 (26.4)*
	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	*60 (46.5)*
	MONOAMINE OXIDASE A INHIBITORS	*1 (0.8)*
	OTHER ANTIDEPRESSANTS	*44 (34.1)*
Subtotal		129 (7.0)
Total		1852 (100.0)

*AD=Antidepressant drug

Table 4. Cardiovascular drug use by therapeutic class and antidepressant drug use.

		Antidepressant use		Total
		Did not use	Used	
		Count (row %)	Count (row %)	Count (col. %)
Did not use CV drugs*		1163 (94.2)	72 (3.8)	1235 (66.7)
Used CV drugs				
Therapeutic class (ATC)	ANTITHROMBOTIC AGENTS	*105 (96.3)*	*4 (3.7)*	*109 (17.7)*
	CARDIAC THERAPY	*115 (92.0)*	*10 (8.0)*	*125 (20.3)*
	ANTIHYPERTENSIVES	*4 (100.0)*	-	*4 (0.6)*
	DIURETICS	*126 (87.5)*	*18 (12.5)*	*144 (23.3)*
	PERIPHERAL VASODILATORS	*36 (80.0)*	*9 (20.0)*	*45 (7.3)*
	VASOPROTECTIVES	*66 (84.6)*	*12 (15.4)*	*78 (12.6)*
	BETA BLOCKING AGENTS	*70 (85.4)*	*12 (14.6)*	*82 (13.3)*
	CALCIUM CHANNEL BLOCKERS	*101 (91.0)*	*10 (9.0)*	*111 (18.0)*
	AGENTS ACTING ON THE RENNIN-ANGIOTENSIN SYSTEM	*239 (93.0)*	*18 (7.0)*	*257 (41.7)*
	SERUM LIPID REDUCING AGENTS	*145 (90.6)*	*15 (9.4)*	*160 (25.9)*
Subtotal		560 (90.8)	57 (9.2)	617 (33.3)
Total				1852 (100.0)

*CV (cardiovascular) drugs includes ATC: B01

Table 5. Frequency of self-reported cardiovascular disease by type.

		Antidepressant use		Total
		Did not use	Used	
		Count (row %)	Count (row %)	Count (col. %)
No CV* disease		777 (94.3)	47 *(5.7)*	824 (44.5)
CV disease	Hypertension	*502 (91.4)*	*47 (8.6)*	*549 (53.4)*
	Dyslipidaemia	*590 (91.8)*	*53 (8.2)*	*643 (62.5)*
	Ischaemic heart disease	*96 (92.3)*	*8 (7.7)*	*104 (10.1)*
	Heart failure	*17 (94.4)*	*1 (5.6)*	*18 (1.8)*
	Cerebrovascular disease	*43 (93.5)*	*3 (6.5)*	*46 (4.5)*
	Other CV disease	*221 (87.0)*	*33 (13.0)*	*254 (24.7)*
Subtotal		946 (92.0)	82 (8.0)	1028 (55.5)
Total				1852 (100.0)

CV=cardiovascular

4.3.2. Analysis 2

The analysis 2 was based on the data collected from the sub-sample of 1016 patients that completed the BDI. This sub-sample did not differ significantly from the original participants in regards to age and gender distributions. In terms of agreement between the BDI classification and self reported depression, of the 37 cases of self reported depression in the sub/sample, merely 2 were misclassified as non-depressed according to the joint criteria of BDI $\geq$10 with antidepressant use. Of the 382 participants classified as depressed, 64 (16.8%; 95%CI: 13.1, 20.9) were considered treated (users of antidepressant).

Table 6 presents the results of the unadjusted and adjusted analysis 2.
Unadjusted analysis identified female gender (OR=2.72, 95%CI: 1.20, 6.15) and higher number of medical visits in the previous year as significantly associated with treatment. The average number of medical visits was shown to be statistically different between the treated and untreated groups ($p<0.05$ in Mann-Whitney test). Age and use of cardiovascular drugs were not associated with the likelihood of antidepressant treatment.

4 cases were excluded from the adjusted analysis because of missing information on the number of medical visits.
After adjustment, the magnitude of the association was barely affected. Females were more likely than men to have treated depression (OR=2.72; 95%CI: 1.20, 6.15). No association was present between treatment of depression and age or cardiovascular drug use.

The association between number of medical visits and treatment of depression remained significantly positive. Compared to patients having 0-1 encounters with medical care, patients with 2-5 visits were 4 times more likely to be treated for depression (OR=3.88; 95%CI: 1.55, 9.75), increasing to 12 times more likely in those patients with 6-11 visits (OR=11.40; 95%CI: 3.92, 33.14) and 6-fold more likely in those reporting 12 visits or more (OR=5.87; 95%CI: 1.75, 19.60).

Table 6. Treatment of depressive symptoms by patients' characteristics, presence of cardiovascular drug use and number of medical visits.

Determinants	Treatment of depression (BDI≥10 or AD use)		Odds Ratio (95% CI)	
	Not Treated (n= 318) Count (%)	Treated (n= 64) Count (%)	Unadjusted OR	Adjusted OR†
Sex				
Male	89 (91.8)	8 (8.2)	1	1
Female	229 (80.4)	56 (19.6)	2.72 (1.25-5.94)	2.72 (1.20-6.15)
			$X^2_1 = 6.74$*	
Age (years)				
18-39	41 (87.2)	6 (12.8)	1	1
40-69	154 (81.9)	34 (18.1)	1.51 (0.59-3.84)	1.31 (0.48-3.56)
≥70	123 (83.7)	24 (16.3)	1.33 (0.51-3.49)	1.27 (0.42-3.82)
			$X^2_2 = 0.79$	
Medical visits (past 12 m) ‡ (4 missing values)				
0-1	104 (94.5)	6 (5.5)	1	1
2-5	162 (83.1)	33 (16.9)	3.53 (1.43-8.72)	3.88 (1.55-9.75)
6-11	28 (63.6)	16 (36.4)	9.90 (3.55-27.66)	11.40 (3.92-33.14)
≥12	22 (75.9)	7 (24.1)	5.52 (1.69-18.01)	5.87 (1.75-19.60)
Missing	2	2	$X^2_3 = 23.7$*	
Median (IQR)	2 (1-4)	4 (2-6)	p<0.01§	
Cardiovascular drug use				
No	177 (83.1)	36 (16.9)	1	1
Yes	141 (83.4)	28 (16.6)	0.98 (0.57-1.68)	0.64 (0.33-1.22)
			$X^2_1 = 0.01$	
Constant				0.02

* Chi-square statistically significant at α=0.05

† Adjusted for all variables in the table

‡ Valid percentages out of 1833 cases

§ Mann-Whitney test for the number of medical visits as a continuous variable

‖ Cardiovascular drugs includes ATC: B01

5. Discussion

The prevalence of self-reported depression observed in this study was largely in the range of estimates from population-based studies (10, 39, 12) but not as high as the study by Goncalves et al. in one health care center in Portugal(40) who estimated a prevalence of depressive symptoms of aproximately 40%. Moreover, the relatively higher prevalence of antidepressant use in women comparing to men was, in this study, slightly higher than previous estimates(45), though within the same magnitude. The diverse criteria and methodologies used to classify depressive symptoms and diagnose depression may be responsible for the variation in incidence and prevalence estimates and hamper potential comparisons between studies.

Age was not found to be a significant determinant of antidepressant use in this study. Although depression is known to be more prevalent with increasing age, prescribers may avoid antidepressant therapy in the elderly to reduce the risk of adverse drug reaction and drug-drug interactions.(29)

The association between the use of cardiovascular drugs and antidepressants, although statistically significant in the univariate analysis, was dissipated in the presence of demographic characteristics in the multivariate regression analysis. This seems to be consistent with findings from Egberts et al.(45). The association between the use of these two therapies may result from correlated factors such as comorbidity related with increased age and lifestyle risk factors.

Patients with depression are known to visit the physician more frequently than patients with similar health conditions other than depression. (25, 26) On the other hand, depressed patients may have a higher necessity to use health resources.(24) The strong and, apparently, “dose-related” association between the number of medical visits and the use of antidepressant drugs may have two main causal paths: a) depression causes, by itself, a higher demand for health care, or b) chronic comorbidity functions as an effect modifier, i.e., on one side, it is associated with the onset of depressive symptoms and, on the other, increases the health care requirements.

The model of “competing demands” may be useful to understand the dynamics of depression in the presence of concomitant health conditions. Some authors have reported that the presence of competing demands poses a deteriorating effect in the care of depression at the primary care level.(15, 121)
Two scenarios are possible, a) the role of the chronic condition may be to bring the patients closer to the health care provider, causing a higher number of visits, for example, and as a result the physician will be more likely to detect the depressive symptoms and initiate antidepressant therapy. Alternatively, b) the chronic disease may absorb most of the physician’s attention and energy reducing the probability for diagnosis and treatment of the concomitant depression.(122, 123)

This study has certain limitations which include treatment assumptions, self-reported information on medication and diagnosis and selection bias.
Although depression is the main indication for prescribing antidepressant drugs, panic disorder, neuropathic pain and sleep disturbances are also being treated with antidepressant drugs. This constitutes a potential for misclassification bias where all users of antidepressants were classified as depressed. Baseline depression was not possible to determine with clinical accuracy, additionally the prescription of antidepressant drugs is only one of the available treatments for depression, as presented in the background section. Data was not collected regarding other non-pharmacological treatments, which could have had an effect on the BDI index and therefore potential for misclassification of patients with depression.

Due to the lack of statistical power to include all possible illnesses in the analyses, we have assumed that the likelihood of missclassification with respect to comorbidity was the same among strata. This may not be always valid due to correlations between some of these conditions, such as, diabetes and coronary heart disease.

The validity and agreement between various sources of information on individuals’ drug use is a contentious theme. The agreement between prescription data, at the physician level, with dispensed information, at the pharmacy level, and the patient self-reported use is poor.(124, 125) In relying on self-reported information we have assumed that its validity was no worse than the alternative sources.(126)

Ultimately, when studying depression and antidepressant drug use, the “inverse care law” is highly relevant, i.e. those patients most at risk are least likely to receive treatment.(127) Intrinsically severe depression is characterised by lack of interest and involvement. Thus, patients in more severe depressive states may have been less likely to accept voluntarily participating in the study when contacted by phone.

In this study we identified female gender and the number of medical visits as the factors associated with increased likelihood for utilization of antidepressant drugs regardless of the use of cardiovascular drugs, age, marital status, education or employment situation.

6. Conclusions

Based on the results of this study it is possible to conclude that the use of antidepressants is not likely to be associated with concomitant use of cardiovascular therapies.

Patients with depression that report a more intense contact with the health care system were found to be more likely to be receiving antidepressant therapy. The methodology employed in this study does not allow us to establish the direction of the causal association, if depression, or underlying causes, increases the demand for health care resources or if the closer contact with health care poses greater probability of diagnosis and treatment of depression. Further longitudinal studies, based on inception cohorts of patients with newly diagnosed cardiovascular disease and long-enough follow up, may elucidate the natural history of depression in cardiovascular disease improving the efficiency of care.

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Appendices

Appendix 1.Systematic literature review – search strings

Appendix 2. List of questions from interview/questionnaire

Appendix 1. Systematic literature review – search strings

MEDLINE (using DialogStar)

1	depression
2	depressive ADJ disorder
3	Depressive-Disorder-CO#.DE. OR Depressive-Disorder-DI#.DE. OR Depressive-Disorder-DT#.DE. OR Depressive-Disorder-EP#.DE. OR Depressive-Disorder-ET#.DE. OR Depressive-Disorder-TH#.DE.
4	1 OR 2 OR 3
5	antidepress$
6	Antidepressive-Agents#.DE.
7	5 OR 6
8	4 AND 7
9	cardiovascular
10	myocardial ADJ (ischemi$ OR inchaemi$)
11	coronary
12	infarct$
13	(ischemic OR ischaemic) ADJ heart ADJ disease
14	(heart OR cardiac) ADJ failure
17	hypertension OR blood ADJ pressure
18	hyperlipidaemi$ OR hyperlipidemi$
19	Cardiovascular-Diseases-CO#.DE. OR Cardiovascular-Diseases-DI#.DE. OR Cardiovascular-Diseases-DT#.DE. OR Cardiovascular-Diseases-EP#.DE. OR Cardiovascular-Diseases-ET#.DE. OR Cardiovascular-Diseases-TH#.DE.
20	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 17 OR 18 OR 19
21	Cardiovascular-Agents#.DE.
22	20 AND 21
23	8 AND 22
24	LG=EN OR LG=SP OR LG=PT
25	23 AND 24

EMBASE (using DialogStar)

1	depression.TI,AB.
2	(depressive ADJ disorder).TI,AB.
3	Depression#.W..DE.
4	1 OR 2 OR 3
5	cardiovascular.TI,AB.
6	coronary.TI,AB.
7	(infarct OR infarction).TI,AB.
8	myocardial.TI,AB.
9	((ischaemic OR ischemic) ADJ heart ADJ disease).TI,AB.
10	((heart OR cardiac) ADJ failure).TI,AB.
11	(hypertension OR blood ADJ pressure).TI,AB.
12	(hyperlipidaemi$ OR hyperlipidemi$).TI,AB.
13	5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
14	Antidepressant-Agent#.DE.
15	4 AND 14
16	Cardiovascular-Agent#.DE.
17	13 AND 16
18	15 AND 17
19	LG=EN OR LG=SP OR LG=PT
20	18 AND 19

PsychINFO (using DialogStar)

1	depression.TI,AB.
2	(depressive ADJ disorder).TI,AB.
3	1 OR 2
4	cardiovascular.TI,AB.
5	coronary.TI,AB.
6	(infarct OR infarction).TI,AB.
7	myocardial.TI,AB.
8	((ischaemic OR ischemic) ADJ heart ADJ disease).TI,AB.
9	((heart OR cardiac) ADJ failure).TI,AB.
10	(hypertension OR blood ADJ pressure).TI,AB.
11	(hyperlipidaemi$ OR hyperlipidemi$).TI,AB.
12	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13	Drugs.W..DE.
14	3 AND 12 AND 13

Appendix 2. List of questions from interview/questionnaire

Number	Description
ID	Número de identificação do questionário
1	Sexo
2	Data de nascimento
3	Idade
5	Estado marital
6	Anos completos de escolaridade
7	Profissão
8	Actividade actual
18	Mediu a pressão arterial nos últimos 12 meses
19	Fez análises sanguíneas nos últimos 12 meses
20	Nos últimos 12 meses quantas vezes consultou um médico
21	Nos últimos 12 meses quantas vezes consultou um dentista
22	Tem actualmente alguma diseasegue obriga a cuidados médicos
22.1.a	Se Sim, quais
22.1.b	Se Sim, quais
22.1.c	Se Sim, quais
23.1	Alguma vez um médico lhe diagnosticou Depression?
23.1.a	Há quanto tempo
23.2	Alguma vez um médico lhe diagnosticou angina de peito
23.2.a	Há quanto tempo
23.3	Alguma vez um médico lhe diagnosticou enfarte do miocardio
23.3.a	Há quanto tempo
23.4	Alguma vez um médico lhe diagnosticou acidente vascular cerebral
23.4.a	Há quanto tempo
23.5	Alguma vez um médico lhe diagnosticou arritmia
23.5.a	Há quanto tempo
23.6	Alguma vez um médico lhe diagnosticou insuficiência cardíaca
23.6.a	Há quanto tempo
23.7	Alguma vez um médico lhe diagnosticou outra diseasecardíaca
23.7.a	Há quanto tempo
25	Tem dislipidemia
25.a	Se sim, desde que idade
25.1a	Que tipo de tratamento faz ou fez (actual)
25.1b	Que tipo de tratamento faz ou fez (actual)
25.1c	Que tipo de tratamento faz ou fez (actual)

25.2a	Desde
25.2b	Desde
25.2c	Desde
25.3	Tx inicial
26	É hipertenso
26.a	Se sim, desde que idade
26.1a	Que tipo de tratamento faz ou fez (actual)
26.1b	Que tipo de tratamento faz ou fez (actual)
26.1c	Que tipo de tratamento faz ou fez (actual)
26.2a	Desde
26.2b	Desde
26.2c	Desde
26.3	Tx inicial
27	É Diabético
27.a	Se sim, desde que idade
27.b	De que tipo
27.1.a	Que tipo de tratamento faz ou fez (actual)
27.1.b	Que tipo de tratamento faz ou fez (actual)
27.1.c	Que tipo de tratamento faz ou fez (actual)
27.1.d	Que tipo de tratamento faz ou fez (actual)
27.2.a	Desde
27.2.b	Desde
27.2.c	Desde
27.2.d	Desde
27.3	Tx inicial
37	Toma habitualmente medicamentos
37a1	Se sim quais
37a2	Se sim quais
37a3	Se sim quais
37a4	Se sim quais
37a5	Se sim quais
37a6	Se sim quais
37a7	Se sim quais
37a8	Se sim quais
37a9	Se sim quais
37a10	Se sim quais
37a11	Se sim quais
47	Toma ou tomou contraceptivos orais
47.1.a	Se sim, durante quanto tempo tomou

47.1.b	Qual
50	Classificação do *Mini-mental state examination*
80	Data da entrevista
84.2	Peso actual
85.2	Altura actual
86.2	Perímetro cinta
89.1	Pressão arterial sistólica
89.2	Pressão arterial diastólica
97	Evidência de lesão isquémica electrocardiográfica
98	Data da colheita
103	Colesterol total
104	LDL
105	HDL
106	Triglicerídeos