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Simona Monte, Alejandro Macchia, Marilena Romero, Antonio d'Ettoire, Rachele Giuliani, et al.. Antidepressants and cardiovascular outcomes in patients without known cardiovascular risk. *European Journal of Clinical Pharmacology*, 2009, 65 (11), pp.1131-1138. 10.1007/s00228-009-0692-x . hal-00534978

**HAL Id: hal-00534978**

**<https://hal.science/hal-00534978>**

Submitted on 11 Nov 2010

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# Antidepressants and cardiovascular outcomes in patients without known cardiovascular risk

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Received: 29 March 2009 / Accepted: 24 June 2009 / Published online: 14 July 2009  
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## Abstract

**Purpose** To identify a cohort of subjects without treatment for any cardiovascular risk and analyze the potential causative role of treatment for depression on the development of major cardiovascular outcomes during 2 years of follow-up.

**Methods** We carried out a record-linkage analysis of hospital discharge records, prescription databases and vital statistics for all consecutive patients aged 30 years or older in one Italian region during a 4-year period. Depression was defined in terms of exposure to at least three prescriptions of antidepressant drugs within 1 year. Patients had no history of treatment with cardiovascular or antidiabetic agents and had not been hospitalized with a diagnosis of any cardiovascular condition in the preceding year. Follow-up was extended up to 2 years or to time to occurrence of major outcomes defined as either all-cause mortality, hospitalization for any cardiovascular cause or chronic exposure to cardiovascular drugs (antihypertensive, statins, antidiabetics). The results are expressed hazard ratios (HRs) and 95% confidence intervals (CIs) within age categories (30–49, 50–59,  $\geq 60$  years).

**Results** A total of 105,573 persons without treated cardiovascular risk at baseline were identified, among whom 1,129

(1.1%) had been chronically exposed to antidepressant treatment. Treated depression determined an increased risk of all cause-mortality (HR 1.88, 95% CI 1.33–2.66,  $p < 0.001$ ) and of subsequent treatment with antidiabetic agents (HR 0.89, 95% CI 1.34–2.66,  $p < 0.001$ ), statins (HR 1.87, 95% CI 1.53–2.29,  $p < 0.001$ ) and antihypertensive drugs (HR 1.25, 95% CI 1.07–1.47,  $p = 0.006$ ).

**Conclusion** Among the general population without treated cardiovascular risk, pharmacologic treatment for depression was associated with an increase in all-cause mortality and major cardiovascular outcomes.

**Keywords** Cardiovascular risk · Depression · Epidemiology

## Introduction

Depression and heart disease are two common disorders that frequently coexist.

It is recognized that depression is a risk factor in patients with established cardiovascular disease (CVD), and independently predicts a worse cardiac outcome. Specifically, strong and consistent evidence has shown that depression is associated with increased mortality and coronary events in people with a history of coronary heart disease (CHD) [1, 2]. Depressive disorders have also been found to be independently related with poor clinical outcomes in patients with heart failure [3, 4].

In comparison, the potential role of depression in the development of cardiovascular problems is much more controversial. Although several studies have explored this association [5–14], the results have not been consistent, with some studies [5, 6, 8–11, 13, 14] suggesting that depression is associated with an increased risk of coronary events in patients without baseline heart disease and others

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showing a neutral effect [7, 12]. However, it is interesting to note that these studies recruited patients with an important burden of cardiovascular risk factors at baseline and overall recruited a limited number of patients (<30,000). Few data are available about the effect of treated depression on a population without any known/treated cardiovascular risk at baseline [15–17]. This probably is due to the inherent difficulty, in terms of time and investment of resources, of conducting a prospective study among the general population without any baseline cardiovascular treatment. In fact, a large sample size and a long period of observation would be necessary to find major events in this specific type of population.

In this perspective, the resource represented by record-linkage analysis of large databases, which has been increasingly recognized as a reliable tool to describe prospectively the history and to evaluate the outcomes of large cohorts representing the real context of care, seems to be very useful. Data sources, such as hospital discharge records, prescription databases and mortality statistics, and the reliability of record-linkage to produce epidemiological information have been validated and described elsewhere [18–21].

The aim of our study was to explore this specifically important problem in order to (1) identify a cohort of subjects without treated cardiovascular risk, (2) analyze the association between treated depression on the development of major cardiovascular outcomes and (3) evaluate if the effect of treated depression on relevant outcomes is different in different age groups.

## Methods

The databases including the detailed information on hospitalization, pharmacological treatments, death/life status of a population of 299,866 people aged  $\geq 30$  years from one local health authority (southern Italy) have been linked and used for this analysis.

### Data sources

Hospital discharge records include information on primary diagnoses and up to five coexisting conditions, performed procedures, date of admission, discharge and in-hospital death. All diagnoses are coded according to the International Classification of Disease, Ninth Revision (ICD-9 CM) [22].

The prescription database provides the community prescriptions reimbursed by the National Health System with drugs coded according to the Anatomical Therapeutic Chemical (ATC) Classification [23] and qualified with respect to dosages, date of first prescription and duration of exposure.

The Italian Civil Registry Database contains basic demographic information, including the vital status of each resident.

These three databases were linked anonymously using encrypted individual healthcare numbers in accordance with local laws for the treatment of personal data (privacy).

### Cohort definition

Between 1 January 2004 and 31 December 2004 (index year), 299,866 people aged 30 years or older, identified through the prescription database, were analyzed.

### *Assessment of the absence of previous cardiovascular disease*

For all patients, the databases were searched during a 12-month period preceding the index date to verify the absence of cardiovascular conditions, which was considered to be both a lack of previous hospitalization for any cardiovascular reason and no previous exposure to any kind of cardiovascular and antidiabetic treatment. The ICD-9 codes as well as the ATC codes used for this identification are listed in Table 1.

### *Identification of the index data*

For those patients who were exposed to antidepressants, index data were considered to be the date of the first prescription of these agents. Alternatively, for patients not exposed to antidepressants, the index data was considered the first prescription of any drug other than cardiovascular agents or those used in antidiabetic treatments.

### *Identification of depressed patients*

Depression was deemed present if the subjects had been chronically exposed to antidepressant drugs within the index year, i.e. they had filled three or more prescriptions.

The drugs used for the identification of depression were: selective serotonin-reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram); tricyclic antidepressants (TCAs; amitriptyline; clomipramine; imipramine; desipramine; nortriptyline); other antidepressants (reboxetine; venlafaxine; mirtazapine; mianserin; nefazodone; trazodone).

### *Outcome evaluation*

Patients were followed up from the index date up to 2 years or until the occurrence of events, if they did occur. The specific events considered were: overall mortality, prescriptions of any cardiovascular or antidiabetic drugs, hospital-

**Table 1** ATC and ICD-9 codes used for identification of cardiovascular diseases

Condition	Pattern prescription (ATC code)	Hospitalization associated diagnosis (ICD-9 code)
Cardiovascular and anti-diabetic drugs	C02, C03, C07, C08,C09, C10, A10	
Hospitalization for any cardiovascular reason	-	390–459
Cardiovascular procedures	-	35–39
Statins	C10AA	-
Diabetes	A10	-
Hypertension	C03AA03, C03BA04, C03BA10, C03BA11, C03CX01, C03EA01, C07AB03, C07AB04, C07AB05, C07AB08, C07AB12, C07AG01, C02AB, C02AC01, C08, C09AA, C09BA, C09CA, C09DA	
Malignancy	-	140.x–208.xx
COPD	R03	491.xx, 492.x, 493.xx, 496, 518.xx, 519.0

ATC, Anatomical Therapeutic Chemical classification; ICD-9, International Classification of Disease, Ninth Revision; COPD, chronic obstructive pulmonary disease

izations with cardiovascular diagnosis, the composite of either all causes of mortality, new prescriptions for cardiovascular reasons or cardiovascular procedures/hospitalization.

Information on death, cardiovascular events and procedures were obtained in the mortality statistics and hospital discharge records, respectively. All diagnoses were coded according to the ICD-9 (Table 1). Information on the exposure to cardiovascular treatments was obtained from the prescriptions' database, considering the drugs identifying underlying clinical conditions, such as statins and treatments for hypertension and diabetes, as previously described [18–21] and indicated in Table 1.

#### *Charlson index of comorbidities*

For all patients we calculated the value of the Charlson index of comorbidity [24, 25]. This index encompasses several medical conditions weighted by 1 to 6 points. A sum score can be tallied from the weighted conditions to yield the total score, which ranges from 0 to 37 points. The Charlson index of comorbidity has demonstrated excellent predictive validity in numerous studies. Because none of the patients in our study had previous known vascular disease or diabetes, we used the residual components of the index to calculate the total score.

#### *Identification of sub-cohorts*

The analysis of the cohort was carried out stratifying by age. Specifically, three subgroups of patients were identified: (1) subjects aged 30–49 years, for whom a high prevalence of depression and a low incidence, over the

specified time period, of events (mortality and clinical cardiovascular outcome) are to be expected; (2) middle-aged patients (50–59 years), characterized by a more significant rate of cardiovascular problems; (3) elderly patients ( $\geq 60$  years) for whom cardiovascular events become more frequent.

#### Statistical analysis

Baseline characteristics of patients were reported as percentages and mean  $\pm$  standard deviation (SD) and were compared with Pearson  $\chi^2$  and Mann-Whitney *U* test statistics for categorical and continuous variables, respectively.

The association of treated depression with the 2-year all-cause mortality, cardiovascular treatment, events and procedures was assessed using a Cox proportional hazards model, adjusted for age and sex and the value of the Charlson index. Survival curves were generated plotting the results of the Cox analysis.

Results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs) within age (30–49, 50–60, >61 years) categories.

A *p* values <0.05 was considered to be significant. All of the analyses were performed using SPSS ver. 10.0 (SPSS, Chicago, IL) and the SAS Statistical Package Release ver. 9.1 (SAS Institute, Cary, NC).

#### Results

We identified 105,573 persons without treated cardiovascular risk at baseline, with a mean age of  $49.2 \pm 13.3$  years.

Of these 1129 (1.1%) were exposed to chronic treatment for depression.

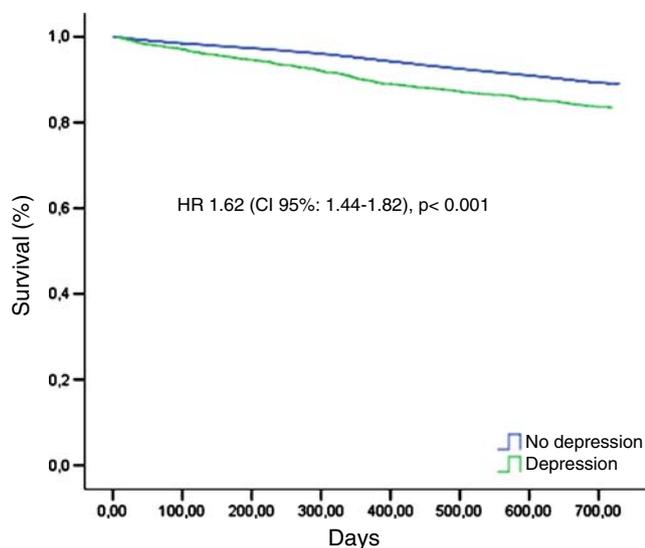
Subjects exposed to antidepressants were older ( $53.5 \pm 15.2$  years) than those not exposed ( $49.1 \pm 13.3$  years) ( $p < 0.001$ ). The use of antidepressants was more common among women than men (1.4 vs. 0.7%,  $p < 0.001$ ).

Most subjects (41.4%) were treated with SSRIs followed by TCAs (37.0%). Among subjects exposed to drugs for depression, 47.7, 19.0 and 33.3% were 30–49, 50–59 and  $\geq 60$  years old, respectively.

## Outcomes

The proportion of patients who present a composite of either death, need for any cardiovascular procedure/hospitalization or new cardiovascular medications was significantly higher among patients with treated depression than their counterparts without depression (HR 1.62, 95% CI 1.44–1.82,  $p < 0.001$ ) (Fig. 1, Table 2).

The proportion of patients that received new cardiovascular prescriptions during follow-up was significantly higher among subjects who had been previously exposed to antidepressants than among those who had not (16.5 vs. 8.6%,  $p < 0.001$ ) (Table 3). The adjusted risk of having a new prescription for cardiovascular drugs among patients previously treated with antidepressants was 1.38 (95% CI 1.20–1.60,  $p < 0.001$ ). Although this difference was present in all age categories, it did not reach a statistically significant value among the elderly patients ( $\geq 60$  years), probably reflecting the high incidence of new prescriptions



**Fig. 1** Survival free of cardiovascular disorder incidence (drug prescriptions, hospitalizations and death) among patients exposed and not exposed to antidepressants. HR Hazard ratio, CI confidence interval

for cardiovascular group drugs among patients who had not been previously been exposed to antidepressants (Table 3).

Specifically, Table 4 reports the type of prescriptions for the cardiovascular treatments among depressed and not depressed patients. Depression entailed an increased risk of receiving antidiabetic treatments (HR 1.89, 95% CI 1.34–2.66), statins (HR 1.87, 95% CI 1.53–2.29) and antihypertensive agents (HR 1.25, 95% CI 1.07–1.47) as compared with patients not previously exposed to antidepressants.

In all of the subgroups of the different age classes, there was an increased risk of receiving new treatments among patients exposed to antidepressants. This difference was particularly evident among the younger groups, probably also reflecting the high rate of prescriptions among elderly patients not exposed to antidepressant treatment.

As for the type of antidepressant used, we observed that the use of SSRIs and TCAs was independently associated with a 78% (HR 1.78, 95% CI 1.37–2.32) and 37% (HR 1.37, 95% CI 1.03–1.82) increase in the odds of receiving antihypertensive agents during follow-up. The prescription of other antidepressants did not appear to influence antihypertensive exposure.

The risk of treatment for diabetes increased (approx. twofold) only with exposure to SSRI (HR 2.09, 95% CI 1.15–3.79). We also found a significant statistically association between the use of all types of antidepressants and exposure to statins during follow-up (SSRIs: HR 2.06, 95% CI 1.5–2.9; TCAs: HR 2.20, 95% CI 1.58–3.05; others: HR 1.46, 95% CI 1.01–2.10).

A total of 884 (0.8%) patients died during the 2-year follow-up period; of these, 850 (0.8%) had not been exposed to antidepressants and 34 (3.0%) had been exposed (Table 2). The adjusted risk of death (HR) among patients exposed to antidepressant drugs was 1.88 (95% CI 1.33–2.66). Considering the population stratified by age, the analysis highlighted that there was an increased risk of all-cause mortality in all age categories but, as expected, only in elderly patients was a statistical significant difference reached (3.3 vs. 8.2%).

The same was true for the composite of cardiovascular hospitalizations and procedures (Table 2).

## Discussion

This analysis shows that there is a significant association between exposure to antidepressant agents and both an increased risk in all-cause mortality and a higher need of new prescriptions for cardiovascular drugs among patients without known/treated vascular disease at baseline and who were at very low cardiovascular risk.

Nearly 1% of the patients of our study cohort had been exposed to chronic treatment for depression. Although this

**Table 2** Composite outcome, all-cause mortality and major cardiovascular events among patients with and without depression

Outcomes	Events, <i>n</i> (%)		HR	95% CI	<i>p</i>
	No depression ( <i>n</i> = 104,444)	Depression ( <i>n</i> = 1129)			
Composite outcome <sup>a</sup>					
Total population ( <i>n</i> = 105,573)	12,255 (11.7)	291 (25.8)	1.62	1.44–1.82	<0.001
Age 30–49 years ( <i>n</i> = 60,976)	3,033 (5.0)	79 (14.7)	2.62	2.09–3.27	<0.001
Age 50–59 years ( <i>n</i> = 22,400)	3,379 (14.2)	58 (27.1)	1.68	1.30–2.18	<0.001
Age ≥60 years ( <i>n</i> = 22,197)	5,833 (26.8)	154 (41.0)	1.41	1.20–1.66	<0.001
All-cause mortality					
Total population ( <i>n</i> = 105,573)	850 (0.8)	34 (3.0)	1.88	1.33–2.66	<0.001
Age 30–49 years ( <i>n</i> = 60,976)	61 (0.1)	1 (0.2)	1.70	0.23–12.3	0.600
Age 50–59 years ( <i>n</i> = 22,400)	80 (0.4)	2 (0.9)	3.49	0.85–14.3	0.082
Age ≥60 years ( <i>n</i> = 22,197)	709 (3.3)	31 (8.2)	1.81	1.26–2.60	0.001
Hospitalizations with all cardiovascular events and procedures					
Total population ( <i>n</i> = 105,573)	2,129 (2.0)	39 (3.5)	1.35	0.98–1.85	0.066
Age 30–49 years ( <i>n</i> = 60,976)	781 (1.3)	10 (1.9)	1.24	0.66–2.31	0.501
Age 50–59 years ( <i>n</i> = 22,400)	523 (2.4)	4 (1.9)	0.74	0.28–1.98	0.549
Age ≥60 years ( <i>n</i> = 22,197)	825 (3.8)	25 (6.6)	1.63	1.09–2.43	0.016

Where appropriate, values are given as the number of patients with the percentage in parenthesis

<sup>a</sup> Composite outcome of either all-cause mortality, new cardiovascular or antidiabetic treatment and hospitalizations with all cardiovascular events and procedures

prevalence appears to be low, it agrees with the selective criteria used to identify patients (chronic treatment with antidepressants), and in this context, it is in line with known data reporting that depression is under-detected in up to 50% of all cases in primary care and that of these, 40–50% stop treatment after few weeks [26, 27].

#### Antidepressant use and need of new prescriptions for cardiovascular risk

In the general population setting of this study, our results show that pharmacologically treated depression was associated with an increased necessity for new prescriptions of cardiovascular and antidiabetic drugs during the follow-up period.

In particular, we found an 89% increased risk of beginning treatment for diabetes over the 2 years of follow-up in patients exposed to antidepressants. This risk was particularly relevant for the young population (30–60 years old). Very few studies have identified an independent increment in the risk of developing diabetes associated with the use of antidepressant medication [28], despite evidence suggesting that medications for the treatment of depression may have an impact on glucose tolerance. The DPP (Diabetes Prevention Program) [29] found a strong and statistically significant association between antidepressant use and diabetes. Our findings confirm and extend these observations to the general population. If future prospective research confirms an etiologic role for antidepressants in diabetes, efforts to

**Table 3** Proportion of patients who started on new cardiovascular or antidiabetic treatments among those previously exposed or not exposed to antidepressants

Cohort	Patients, <i>n</i> (%)		HR	95% CI	<i>p</i>
	No depression	Depression			
Total population <sup>a</sup>	8,970 (8.6%)	186 (16.5)	1.38	1.20–1.60	<0.001
Age 30–49 years	2,213 (3.7%)	55 (10.2)	2.39	1.83–3.12	<0.001
Age 50–59 years	2,205 (11.3%)	40 (18.7)	1.48	1.08–2.01	0.016
Age ≥60 years	4,252 (19.5)	91 (24.2)	1.15	0.93–1.42	0.185

Where appropriate, values are given as the number of patients with the percentage in parenthesis

<sup>a</sup> For the number of patients in the total population and in each age group, refer to Table 1

**Table 4** Type of cardiovascular treatments among patients with and without depression during follow-up

Cohort/cardiovascular treatment	No depression, <i>n</i> (%)	Depression, <i>n</i> (%)	HR	95% CI	<i>p</i>
Total population <sup>a</sup> , exposure to:					
Anti-hypertensives	7,931 (7.6)	153 (13.6)	1.25	1.07–1.47	0.005
Statins	3,554 (3.4)	96 (8.5%)	1.87	1.53–2.29	<0.001
Anti-diabetics	1,226 (1.2)	34 (3.0)	1.89	1.34–2.66	<0.001
Age 30–49 years, exposure to:					
Anti-hypertensives	1,880 (3.1)	43 (8.0)	2.17	1.61–2.94	<0.001
Statins	898 (1.5)	29 (5.4)	3.32	2.30–4.82	<0.001
Anti-diabetics	362 (0.6)	12 (2.2%)	3.03	1.70–5.40	<0.001
Age 50–59 years, exposure to:					
Anti-hypertensives	2,256 (10.2)	34 (15.9)	1.36	0.97–1.92	0.07
Statins	1,092 (4.9)	24 (11.2%)	2.05	1.37–3.08	<0.001
Anti-diabetics	317 (1.4)	8 (3.7)	2.35	1.16–4.74	0.02
Age ≥60 years, exposure to:					
Anti-hypertensives	3,795 (17.4)	76 (20.2)	1.05	0.84–1.32	0.65
Statins	1,564 (7.2)	43 (11.4)	1.55	1.14–2.11	0.004
Anti-diabetics	547 (2.5)	14 (3.7)	1.38	0.81–2.34	0.24

Where appropriate, values are given as the number of patients with the percentage in parenthesis

<sup>a</sup> For the number of patients in the total population and in each age group, refer to Table 1

minimize the potentially negative effects of these agents on glycemic control should be pursued.

Antidepressant agents were also independently associated to a 25% increase in the risk of beginning treatment for hypertension. Although the results of the studies examining the association between depression and hypertension are contradictory [15, 30–36], among our large study population, we found a significant association between these conditions. Our results are in accordance with the results of an epidemiological study of young adults without hypertension at baseline followed up for 5 years [15, 16].

Based on our results, it would appear that the exposure to anti-hypertensive drugs over 2 years of follow-up, in a relatively young population without any known/treated cardiovascular disease at baseline, could be a signal of subsequent development of coronary events. In fact, hypertension may be one of the mechanisms through which depression affects CHD [15] and ultimately mortality.

Particularly interesting is the result regarding the association between depression and the prescriptions of statins. We found that pharmacologically treated depressed patients had an increased risk of 87% of receiving a new prescription of statins during follow-up. Despite the fact that there is some published evidence reporting a significant relationship between depression and hypercholesterolemia [37], our study is among the first to report this association. Although the possible mechanisms of this association remain unknown, one possible explanation is in the fact that depressed individuals more often have deleterious health behaviors than non-depressed individuals, including

eating an unhealthy diet. Moreover, depression has been associated with dysregulation of the hypothalamic-pituitary-adrenal axis [38], which has also been implicated in the development of metabolic syndrome and CVD [39, 40].

In all age categories, patients treated with antidepressants had an increased risk of all-cause mortality, but only in the elderly did this difference, as expected, reach statistical significance. Our finding of an association between depression and all-cause mortality, in particular in patients aged ≥60 years is consistent with those of other studies indicating that depressive symptoms constitute a risk factor for mortality [41, 42], contributing to death primarily through pathways other than suicide [43]. Moreover, the aforementioned increased risk of developing new hypertension, hypercholesterolemia and diabetes could explain, at least partially, this increased risk of mortality. In fact, overall, there was a +35% increased risk of hospitalizations and procedures for cardiovascular reasons in the whole population, particularly among the elderly.

#### Strengths and limitations

The strength of this study is the specific methodology used that allowed us to identify a large cohort of patients without treated cardiovascular risk which, in turn, enabled us to study the effect of pharmacologically treated depression. It would be very difficult to set up a prospective study in a similar population because a very large number of patients and a long period of observation would be necessary. In

fact, in our analysis of 105,573 patients without a known cardiovascular risk, only 1129 were exposed to antidepressant treatment, and we observed these patients for over 2 years.

Our analysis has, however, a number of limitations that should be acknowledged.

The analysis is not intended to prove causality but to show associations between treated depression and major cardiovascular outcomes. Although the analysis does show an association between treated depression and major cardiovascular outcomes, we cannot definitely determine whether this effect is mediated by the condition of depression or whether it is related to the treatment for depression (pharmacologic side effect).

All of the analyses were corrected by age, sex and Charlson index as a proxy of comorbid conditions. Despite this approach to handling the data, which minimizes the ever-present and inherent problem of confounding by indication in this type of analysis, we cannot definitely rule out that some residual confounding could be still present.

Despite the consistency and magnitude of the associations, we cannot rule out that patients affected by depression could have a higher tendency to obtain drug prescriptions than other subjects.

The period of time available for the analysis was 4 years. Although this time window has been previously used by the authors and by other researchers, a longer period of observation was simply not available. Additionally, the prescription patterns used to identify some clinical conditions had inherent limitations due to the lack of validation.

Finally, although we attempted to identify a population without cardiovascular risk, we cannot be sure that lack of treatment is a proxy of lack of risk. However, the very low rate of events during the follow-up period revealed that lack of treatment was certainly a good indicator that the population selected was at very low cardiovascular risk.

In conclusion, this analysis suggests that pharmacologically treated depression is associated with an increased risk of beginning a new treatment for hypertension, diabetes and hypercholesterolemia. Furthermore, among patients with pharmacologically treated depression, there was an increase in all-cause mortality and hospitalizations and procedures for cardiovascular events. If antidepressants prove to be an independent risk for cardiovascular treatments and events, clinicians will need to take this into consideration when prescribing these agents.

**Acknowledgments** This work has been partially funded by the Rischio Assoluto Cardiovascolare–Epidemiologia (RIACE) Project, funded by the Agenzia Italiana del Farmaco (AIFA), Project FARM5T8T47.

## References

1. Van Melle JP, Jonge P, Spukerman TA et al (2004) Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 66:814–822
2. Barth J, Schumacher M, Herrmann-Lingen C (2004) Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 66:802–813
3. Macchia A, Monte S, Pellegrini F et al (2008) Depression worsens outcomes in elderly patients with heart failure: an analysis of 48, 117 patients in a community setting. *Eur J Heart Fail* 10(7):714–721
4. Rutledge T, Reis VA, Linke SE et al (2006) Depression in heart failure. A meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 48:1527–1537
5. Anda R, Williamson D, Jones D et al (1993) Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. *Epidemiology* 4:285–294
6. Aromaa A, Raitasalo R, Reunanen A et al (1994) Depression and cardiovascular diseases. *Acta Psychiatr Scand Suppl* 337:77–82
7. Vogt T, Pope C, Mullooly J et al (1994) Mental health status as a predictor of morbidity and mortality: a 15-year follow-up of members of a health maintenance organization. *Am J Public Health* 84:227–231
8. Pratt LA, Ford DE, Crum RM et al (1996) Depression, psychotropic medication, and risk of myocardial infarction. *Circulation* 94:3123–3129
9. Barefoot JC, Schroll M (1996) Symptoms of depression, acute myocardial infarction and total mortality in a community sample. *Circulation* 93:1976–1980
10. Sesso HD, Kawachi I, Vokonas PS et al (1998) Depression and the risk of coronary heart disease in the Normative Aging Study. *Am J Cardiol* 82:851–856
11. Ford DE, Mead LA, Chang PP et al (1998) Depression is a risk factor for coronary artery disease in men: the Precursors Study. *Arch Intern Med* 158:1422–1426
12. Penninx BWJH, Guralnik JM, de Leon CF Mendes et al (1998) Cardiovascular events and mortality in newly and chronically depressed persons >70 years of age. *Am J Cardiol* 81:988–994
13. Ferketich AK, Schwartzbaum JA, Frid DJ et al (2000) Depression as an antecedent to heart disease among women and men in the NHANES I study. *Arch Intern Med* 160:1260–1268
14. Beekman ATF, Deeg DJH, Van Limbeek J et al (1997) Criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D): results from a community-based sample of older subjects in the Netherlands. *Psychol Med* 27:231–235
15. Yan LL, Liu K, Matthews KA et al (2003) Psychosocial factors and risk of hypertension the coronary artery risk development in young adults (CARDIA) study. *JAMA* 290(16):2138–2148
16. Davidson K, Jonas BS, Dixon KE et al (2000) Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? *Arch Intern Med* 160:1495–1500
17. Knol MJ, Twisk JWR, Beekman ATF et al (2006) Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia* 49:837–845
18. Monte S, Macchia A, Pellegrini F et al (2006) Antithrombotic treatment is strongly underused despite reducing overall mortality among high-risk elderly patients hospitalized with atrial fibrillation. *Eur Heart J* 27:2217–2223
19. Macchia A, Monte S, Romero M et al (2007) The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. *Eur J Heart Failure* 9:942–948

20. D'Ettoire A (2005) ReClust: technical report. Available at: <http://easi.negrisud.it/software/reclust/index.html>
21. Macchia A, Monte S, Pellegrini F et al (2008) Omega-3 fatty acid supplementation reduce one-year risk of atrial fibrillation in patients hospitalized with myocardial infarction. *Eur J Clin Pharmacol* 64:627–634
22. National Center for Health Statistics (1998). International classification of diseases, 9th revision (clinical modification). Public Health Service, U.S. Department of Health and Human Services, Washington D.C.
23. WHO Collaborating Centre for Drug Statistics Methodology (2003). ATC Index with DDDs. World Health Organization, Oslo
24. Charlson ME, Pompei P, Ales KL et al (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40(5):373–383
25. D'Hoore W, Bouckaert A, Tilquin C (1996) The association of depression and painful physical symptoms—a review of the European literature. *J Clin Epidemiol* 49(12):1429–1433
26. Robinson WD, Geske AG, Layne AP et al (2005) Depression treatment in primary care. *J Am Board Fam Pract* 18:79–86
27. Garcia-Cebrian A, Gandhi P, Demyttenaere K et al (2006) The association of depression and painful physical symptoms—a review of the European literature. *Eur Psychiatry* 21(6):379–388
28. Knol MJ, Geerlings MI, Egberts ACG et al (2007) No increased incidence of diabetes in antidepressant users. *Int Clin Psychopharmacol* 22:382–386
29. Rubin RR, Ma Y, Maurer DG, Diabetes Prevention Program Research Group et al (2008) Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. *Diabetes Care* 31(3):420–426
30. Jonas BS, Franks P, Ingram DD (1997) Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic follow-up study. *Arch Fam Med* 6:43–49
31. Jonas BS, Lando JF (2000) Negative affect as a prospective risk factor for hypertension. *Psychosom Med* 62:188–196
32. Davidson K, Jonas BS, Dixon KE et al (2000) Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? *Arch Intern Med* 160:1495–1500
33. Markovitz JH, Matthews KA, Wing RR et al (1991) Psychological, biological and health behavior predictors of blood pressure changes in middleaged women. *J Hypertens* 9:399–406
34. Markovitz JH, Matthews KA, Kannel WB et al (1993) Psychological predictors of hypertension in the Framingham Study: is there tension in hypertension? *JAMA* 270:2439–2443
35. Jones-Webb R, Jacobs DR Jr, Flack JM et al (1996) Relationships between depressive symptoms, anxiety, alcohol consumption, and blood pressure: results from the CARDIA Study. *Alcohol Clin Exp Res* 20:420–427
36. Shinn EH, Poston WS, Kimball KT et al (2001) Blood pressure and symptoms of depression and anxiety: a prospective study. *Am J Hypertens* 14(7 pt 1):660–664
37. Kinder LS, Carnethon MR, Palaniappan PL (2004) Depression and the metabolic syndrome in young adults: findings from the third national health and nutrition examination survey. *Psychosom Med* 66:316–322
38. Rozanski A, Blumenthal JA, Kaplan J (1999) Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 99:2192–2217
39. Troxler RG, Sprague EA, Albanese RA et al (1977) The association of elevated plasma cortisol and early atherosclerosis as demonstrated by coronary angiography. *Atherosclerosis* 26:151–162
40. Brunner EJ, Hemingway H, Walker BR et al (2002) Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome. *Circulation* 106:2659–2665
41. Wulsin LR, Evans JC, Vasan RS et al (2005) Depressive symptoms, coronary heart disease, and overall mortality in the Framingham Heart Study. *Psychosom Med* 67:697–702
42. Ariyo AA, Haan M, Tangen CM et al (2000) Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. *Circulation* 102:1773–1779
43. Wulsin LR, Vaillant GE, Wells VE (1999) A systematic review of the mortality of depression. *Psychosom Med* 61:6–17