Relationship between antidepressant therapy and risk for cardiovascular events in patients with and without cardiovascular disease

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Abstract

Objective: The American Heart Association has endorsed depression as a cardiac risk factor and recommends screening as part of routine practice. This has been met with controversy due to inconsistencies in the data linking depression treatment to better cardiovascular outcomes. Our objective was to prospectively assess the association between depression treatment (defined as being prescribed antidepressant medication) and major adverse cardiovascular events (MACE) in patients referred for exercise stress tests.

Methods: 2385 consecutive patients presenting for myocardial perfusion exercise stress tests underwent a sociodemographic, medical, and psychiatric interview (PRIME-MD) and completed the Beck Depression Inventory (BDI). History of CVD and antidepressant use was self-reported and verified via chart review. Participants followed over an 8.8 year follow-up, and information regarding MACE incidence (including cardiac mortality, non-fatal myocardial infarction, revascularization procedures, cerebrovascular events) was obtained from provincial administrative databases.

Results: 8% (n=190) of the sample were taking antidepressants at baseline, 41% (n=916) had a history of CVD, and 38.7% (n=921) had depression according to the PRIME-MD or BDI. Antidepressant treatment was associated with a 30% reduced risk of MACE (HR=0.697; 95%CI=0.504-0.964; p=.029). A 46% reduction in risk was associated with antidepressant treatment among those without CVD (HR=0.542; 95%CI=0.299-0.981; p=.043). In depressed patients, a 33% reduction in risk of MACE associated with antidepressant use was seen (adjusted HR=0.674; 95%CI=0.440-1.033; p=.07).

Conclusions: Antidepressants may be cardio-protective among patients presenting for stress testing independent of risk factors including CVD and depression. Results support treating depression with antidepressants in this population to reduce risk of MACE.

Key words: Antidepressant treatment, Depression, cardiovascular disease, major adverse cardiovascular events

Introduction

Multiple studies have documented a disproportionately high rate of depressive symptomatology and clinical depression (i.e., major depressive disorder, MDD) among individuals with or at elevated risk for cardiovascular disease (CVD) (Barefoot et al., 2000; Carney et al., 1987; Frasure-Smith, Lesperance, & Talajic, 1993; Frasure-Smith, Lesperance, & Talajic, 1995b; Lane, Carroll, Ring, Beevers, & Lip, 2002; Steeds, Bickerton, Smith, & Muthusamy, 2004). Several reports have also linked depression to worse cardiovascular outcomes in both healthy and established populations, including an increased risk of major cardiovascular events, all-cause mortality, and poorer quality of life (Anda et al., 1993; Ariyo et al., 2000; Barefoot et al., 1996; Blumenthal et al., 2003; Burg, Benedetto, & Soufer, 2003; Frasure-Smith & Lesperance, 2005)

The amount and robustness of this data has recently lead the American Heart Association (AHA) to endorse depression as a cardiac risk factor, and now recommends depression screening as part of routine practice (Lichtman et al., 2014). Despite the compelling nature of this recommendation, it has been met with controversy due to a paucity of data linking depression treatment, including psychological and pharmacological-based treatments (Joynt & O'Connor, 2005) to better cardiovascular outcomes (Thombs et al., 2008; Thombs et al., 2013). Indeed, while there is evidence that depression screening can identify those *at risk* for worse cardiovascular outcomes (Elderon, Smolderen, Na, & Whooley, 2011), few studies have actually linked depression treatment to improved cardiovascular outcomes (Taylor et al., 2005). Further, among those that have, (Davidson et al., 2013; Katon et al., 2010) they did not assessed the role of antidepressants.

In this study, we prospectively assessed the association between depression treatment (defined as being prescribed antidepressant medication at baseline) and the occurrence of major adverse cardiovascular events (MACE) over an average of 8.8 years in patients undergoing

myocardial perfusion exercise stress tests, both in the entire sample and in those with and without evidence of CVD at baseline. As a secondary analysis, we also assessed the impact of antidepressant treatment in the subgroup of patients who had depression at baseline.

Methods

Participants

This is a sub-analysis of the Depression Effects on Coronary Artery Disease Events (DECADE) prospective observational Study, so the methods have been described elsewhere (Paine, Bacon, et al., 2016; Pelletier et al., 2015). Briefly, the sample included 2460 consecutive patients who presented to the Montreal Heart Institute (MHI) for diagnostic myocardial perfusion single photon emission computed tomography (SPECT) exercise stress testing between September 1998 and June 2002. All patients who were presenting for nuclear exercise stress tests who met inclusion criteria, were approached to participate, meaning our sample was not a randomly selected or a convenience sample. However, some patients were occasionally "missed" due to staffing limitations, likely at a rate estimated to be less than 5%, but this would have occurred at random. Patients were eligible if they were between the ages of 18 and 75, medically stable, and were fluent in English or French. Patients were excluded if they had a documented medical condition that conferred greater risk of illness morbidity than CVD (e.g., cancer); if they were inpatients at the time of their stress test; or if they were medically unstable (e.g., major cardiac event in the last 4 weeks). This protocol was approved by the MHI's ethics review board (ID: 07-965) and participants provided written, informed consent.

Study Procedure

Patients were approached after completing their exercise stress test. Patients underwent a medical history interview that included providing information about medications, followed by a structured psychiatric interview (PRIME-MD) (Spitzer et al., 1994), and completed the Beck

Depression Inventory (BDI). All medical diagnoses, procedures and events occurring during the period between recruitment and December 31st 2008 were obtained from Quebec's healthcare administrative databases (RAMQ and Medecho) which record all billable acts, visits and interventions in the province of Quebec. Official mortality data over the same period was obtained from the Institut de la statistique du Québec (ISQ), which records date of death and primary and secondary causes.

Baseline assessments

All participants underwent SPECT myocardial perfusion exercise stress testing (treadmill, Bruce protocol) according to standard procedures (Anagnostopoulos et al., 2004). Ischemia diagnoses were made by experienced Nuclear Medicine Physicians. Data regarding socio-demographics, health behaviors, clinical risk factors, history of CVD and medications were self-reported and verified via interview. History of CVD was defined as having had a previous MI, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or stroke.

Depression measures:

Depression was determined by assessing the presence of a depressive disorder (i.e., clinical depression) or the presence of clinically significant depressive symptoms. Depressive disorders (including major and minor depression, dysthymia, and bipolar disorder) were assessed at baseline using the Primary Care Evaluation of Mental Disorders (PRIME-MD)(Spitzer et al., 1994). This instrument was also used to assess the anxiety disorders (panic disorder, generalized anxiety disorder, 'other' anxiety disorder) for descriptive and adjustment purposes. The PRIME-MD is a brief, semi-structured psychiatric interview that was developed to identify the most common DSM-IV disorders seen in primary and tertiary care settings. Validation studies have reported a specificity of 88%, a sensitivity of 83%, and a kappa of .71 for the mood disorder module, which is comparable to longer interviews such as the Structured Clinical

Interview for DSM-IV (Spitzer, Kroenke, & Williams, 1999; Spitzer et al., 1994). An electronic version of the interview was administered by an experienced PhD-level psychology student and/or licensed clinical psychologist.

Depressive symptomatology was measured using the Beck Depression Inventory (BDI) (Beck & Steer, 1987; Beck, Steer, & Garbin, 1988), which is a 21-item self-report questionnaire that is one of the most commonly used instruments in studies assessing depression in CAD patients. It has excellent internal consistency (α = .90-.91) and high construct validity (r = .89) (Beck et al., 1988). BDI scores ≥ 10 are considered clinically significant (denoting mild depression (Moullec, Plourde, Lavoie, & Bacon, 2015)) and have been shown to be predictive of worse cardiovascular outcomes (Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002). A patient was classified as having depression if they met criteria for one or more mood disorders according to the PRIME-MD (which uses a diagnostic algorithm based on DSM-IV criteria) or had a score on the BDI ≥ 10, which has been shown to be clinically significant (Frasure-Smith, Lesperance, Juneau, Talajic, & Bourassa, 1999; Frasure-Smith, Lesperance, & Talajic, 1995a).

Follow-up outcome assessment

MACE was categorized according to the standard protocol published by the WHO (Luepker, Evans, McKeigue, & Reddy, 2004) and included: cardiac mortality, non-fatal MI, revascularization procedures, and cerebrovascular events. Cause of death was coded according to the ICD system. The primary reported cause of death was used to define cause of mortality. All International Classification of Disease (ICD)-9 (before April 1st 2006), ICD-10 (beginning April 1st 2006), Manuel des médecins omnipraticiens et spécialistes (for intervention procedures), and ISQ cause of death coding classifications used in the study have been previously reported (Pelletier et al., 2015).

Data reduction and statistical analyses

All data were analyzed using SAS Version 9.3 (SAS Institute, Cary, North Carolina, USA). Of the 2460 participants recruited, 75 were lost to follow-up due to missing data in the matching process (such as the absence of birth date) with the RAMQ databases, resulting in a final sample of 2385 patients. Rubin's rules (Rubin, 1987) were followed for our missing data analysis procedures, using multiple imputation (Barzi & Woodward, 2004) with missing at random (MAR) assumptions. Using the PROC MI method of multiple multivariate imputation in SAS, we independently analyzed 20 copies of the data. PROC MIANALYZE was used according to Harrell's guidelines (Harrell, 2001). One-way general linear models and χ^2 analyses were used to compare baseline sociodemographic and clinical characteristics.

Cox regression models were used to assess the main effect of antidepressant use on time to first MACE. The first occurrence of the outcome variable was taken as the event for analysis. Owing to the known association of the following variables with CVD outcomes (Rosengren et al., 2004), regression models were adjusted for the following a-priori defined covariates: baseline age, sex, smoking status, BMI, history of CVD (except for CVD stratified analyses), diabetes, hypertension, dyslipidemia, SPECT evidence of exercise-induced myocardial ischemia (on index stress test), baseline anxiety disorder (PRIME-MD), and baseline depression (except for depressed subgroup analyses).

Results

Sample characteristics

Sample characteristics are presented in Table 1. Briefly, the sample was 67% male, nearly 99% white, with a mean age of 56.8 [±8.5] years. A total of 41% had a history of CVD, 41% had ischemia on the index stress test, and 30% experienced a MACE during the follow-up (mean time to MACE=6.8 [±3.09] years). Out of the total sample of 2385 patients, only 8% (N=190)

were taking antidepressants at baseline, the majority of which (70%) were selective serotonin reuptake inhibitors (SSRI's). A total of 38.7% (n=921) of the sample had depression characterised by the presence of a depressive disorder (PRIME-MD) or a BDI score ≥10. In the patients who were identified as depressed (N=921), only 12.6% (N=116) were taking antidepressants. Only 14% (N=329) of our sample had major depression (per diagnosis/classification using the PRIME-MD), however out of those who were taking antidepressants (N=190) nearly 30% of those individuals had major depression. In the patients who were identified as having an anxiety disorder (n=475), 75 patients were taking an antidepressant, but only 11 patients with anxiety disorders only (i.e., no cormorbid depression) were taking antidepressants.

Sample characteristics presented as a function of antidepressant treatment at baseline are also presented in Table 1. Group differences were evident for certain characteristics: patients taking antidepressants were younger and less likely to be male. Conversely, in patients not taking antidepressants, there were significantly higher rates of cohabitating, current smokers, hyperlipidemia, beta-blocker use, aspirin use, and significantly higher resting systolic and diastolic blood pressure (*p's* <.05). Across the whole sample, rates of depressive and anxiety disorders were also higher in patients not taking antidepressants, but BDI score was higher in patients taking antidepressants (*p's* <.001).

Association between antidepressant use and risk of MACE in the whole sample

Unadjusted analyses examining the association between antidepressant use and MACE revealed a significant reduction in risk of 35% of MACE (HR=0.651; 95%CI = 0.474-0.896; *p* = .008). After adjustment for covariates including baseline depression, the use of antidepressants

was still associated with a significant 30% reduced risk of MACE over the follow-up (adjusted HR=0.697; 95%CI =0.504–0.964; *p*=.029) (see Table 2, figure 1).

Association between antidepressant use and risk of MACE in patients with vs. without CVD

There were also differences in MACE risk associated with antidepressant use as a function of CVD status in stratified analyses (see Table 3). In unadjusted analyses, patients without CVD had a 39.5% reduced risk of MACE that was marginally significant (HR = 0.605; 95%CI = 0.364 – 1.008; p = .054). Though risk estimates were in the same direction, there was no significant reduction in risk of MACE observed among those with CVD (HR = 0.715; 95%CI= 0.461 – 1.110; p=.135). After adjustment for covariates, the reduced risk of MACE associated with antidepressant use among patients without CVD was significant and increased to 46% (adjusted HR = 0.542; 95%CI = 0.299 – 0.981; *p* = .043); however, the risk of MACE associated with antidepressant use among those with CVD did not reach significance after covariate adjustment (adjusted HR = 0.690; 95%CI = 0.437 - 1.091; *p* = .113) (see figure 2).

Association between antidepressant use and risk of MACE in depressed patients

Among patients identified as depressed at baseline, only 12.6% (n=116) were taking antidepressants. In secondary subgroup analyses among depressed patients, results revealed a significant 37% reduction in risk of MACE associated with antidepressant use (HR = 0.629; 95%CI = 0.414-0.957; p=0.030). Though risk estimates were in the same direction, this became a non-significant trend after covariate adjustment (adjusted HR=0.674; 95%CI =0.440-1.033; *p*=.07) (see Table 4).

Sensitivity analyses

Supplementary analyses adjusting for depression using different definitions (i.e., major depression/minor depression and continuous BDI scores) revealed a similar pattern of results (data not shown). Additionally, supplementary analyses excluding anxiety disorders as a covariate (due to potential multicollinearity with depression) also revealed a similar pattern of results (data not shown). Finally, we conducted a sensitivity analysis including the four non a-priori defined covariates that were found to be significantly different between those taking and not taking anti-depressants at baseline (i.e., cohabitation and use of beta-blockers, lipid lowering medication, and aspirin), both in the whole sample and in those identified as depressed at baseline. These analyses also revealed a similar pattern of results, which can be found in supplementary content (Tables S1 and S2).

Discussion

We prospectively assessed the association between antidepressant depression treatment (defined as being prescribed antidepressant medication, primarily SSRI's) and occurrence of MACE in patients with and without CVD undergoing SPECT exercise stress tests, over an average 8.8 year follow up period. We observed a 30% reduction in 8-year risk of MACE among patients prescribed antidepressants after adjusting for several important covariates including age, sex, traditional risk factors, CVD history, and the presence of baseline anxiety and depressive disorders. This indicates that among patients with or at risk for CVD, antidepressants may be cardio-protective, irrespective of baseline depression status. Additionally, in stratified analyses, we observed a 46% reduction in risk associated with antidepressant use among those *without CVD* at baseline that was not observed among patients with a history of CVD. This suggests that the cardio-protective effects of antidepressant

treatment may be even stronger among patients early in the disease process, before the occurrence of any major cardiac events. Finally, we found a 37% reduced risk of MACE associated with antidepressant use in the subgroup of patients identified as depressed according to the PRIME-MD or BDI at baseline, which became a trend after full covariate adjustment. Given that risk estimates among depressed patients were consistent with those for entire sample suggests that this may have been due to reduced power given a lower sample size in subgroup analyses. Indeed, only 12.6% (n=116) of patients identified as depressed at baseline were taking antidepressants. This is noteworthy considering our definition of definition includes those who met diagnostic criteria for a depressive disorder according to the PRIME-MD and/or had a score of 10 or greater on the BDI. The reasons for such low rates of depression treatment are not known, but they are likely due to the fact that depression was not routinely assessed at our tertiary care cardiology hospital, so we were likely detecting either new or previously undiagnosed cases of depression. Nonetheless, despite the apparently low rates of antidepressant prescription among patients who were depressed, our overall pattern of results suggests that antidepressant treatment may be cardio-protective in this population, and particularly among those without established CVD. They also suggest that antidepressant use, and SSRI's in particular (which were the most commonly prescribed in our population) may also reduce the risk for subsequent cardiovascular events among depressed patients, which addresses a major gap in the literature.

Taken together, our findings are consistent with those of three other studies that observed significantly reduced risks of MI associated with SSRI-related antidepressant use (Kimmel et al., 2011; Noordam et al., 2016; Sauer, Berlin, & Kimmel, 2001). Our findings are also in line with trial results reported by Taylor et al., who found that antidepressant use was associated with a 43% reduction in risk of all-cause mortality and non-fatal MI among depressed post-MI patients in a secondary analysis of the ENRICHD Trial data (Taylor et al., 2005). Glassman et al. (2009)

showed a reduced risk of cardiac events in patients treated with sertraline, however this study did not show a decreased rate of cardiac mortality between sertraline and placebo (Glassman, Bigger, & Gaffney, 2009). Our results are inconsistent with the trial results of Zuidersma et al. (Zuidersma, Conradi, van Melle, Ormel, & De Jonge, 2012), neither of whom found a significant association between antidepressant therapy and future risk for cardiovascular events or mortality. There are several possible explanations for these disparate results: in Zuidersma et al.'s study, patients in the "treatment" group received both pharmacological and psychotherapies, which may act on cardiovascular outcomes in different ways. Further, the trial employed a "usual care" control group, 16% of which were receiving some form of treatment for depression and may have diluted group differences. Of note, they conducted a sensitivity analyses of all those receiving some form of depression treatment (in either group) and found a significant reduction in all-cause mortality (HR=0.52, 95% CI 0.28-0.97), which provides support for this hypothesis. Of note, their HR's were in the right direction (e.g., Zuidersma et al.'s mortality HR=0.74, 95% CI: 0.41 -1.33). Although our findings are observational, they do add to a body of literature supporting a potential protective effect of antidepressant use among patients with or at risk for CVD.

We were surprised to find that in our cohort, depression itself was not predictive of MACE when we adjusted for depression status in our analyses which demonstrated antidepressant use to be protective of MACE risk. The fact that the effect of antidepressants on risk of MACE was independent of depression status may seem counter-intuitive; however, it is likely that many of the patients taking antidepressants at baseline who were not depressed were in partial remission at the time of the baseline evaluation. This may have masked depression effects, because our baseline evaluation would have likely categorized remitted or partially remitted patients as non-depressed by failing to meet diagnostic or cut-off criteria. Since we did not collect data on psychiatric status prior to the entry into the study, we are unable to confirm this

hypothesis. However, the fact we observed a comparable reduction in risk of MACE in our subgroup of depressed patients suggests that antidepressants are indeed cardio-protective among depressed patients.

Mechanisms

Several studies have shown that antidepressants, particularly SSRI's, are associated with reduced platelet and blood serotonin levels (Schlienger & Meier, 2003; Wozniak, Toska, Saridi, & Mouzas, 2011), suggesting an inhibitory effect on platelet activation which may be protective for CVD. Given the vast majority (70%) of patients in our study were taking SSRI's provides support for this hypothesis. Further, depression is associated with an over-expression of C-reactive protein and pro-inflammatory cytokines (e.g., TNF-α, IFN-γ, IL-1 and IL-6) that stimulate central serotonin (5-HT) neurotransmission (Dinan, 2008), which has been linked to both MI and CVD (Wozniak et al., 2011). Thus, treatment of depression using antidepressants (and SSRI's in particular) may not only reverse or dampen the pro-inflammatory effects of depression but may also act directly on platelets, as mentioned above, to reduce CVD risk. In addition to direct pharmacological pathways, depression treatment may also improve many of the poor health behaviors that often accompany depression (e.g., increased smoking, poor dietary habits, greater physical inactivity, poor treatment adherence) (Lavoie & Fleet, 2000). While those on antidepressants at baseline had higher rates of current smoking and comparable BMI's as those not on antidepressants, the lack of follow-up data on these variables makes it impossible to know if treatment was successful at improving these risk factors. However, the size of our observed effects is comparable with other "behavioral" predictors of improved cardiovascular risk such as physical activity (Tambalis et al., 2016), dietary habits and alcohol intake, (Yusuf et al., 2004) all of which may be influenced by changes (improvements) in mood, which provides partial support for this hypothesis.

Finally, while unlikely, it is possible that patients who were taking antidepressants may have visited physicians more often, and as a result have received better overall health monitoring and treatment, independent of any specific effect of antidepressants. However, the fact we observed a cardio-protective effect associated with antidepressant use independent of depression status suggests that mechanisms are more likely to be pharmacological than behavioral.

Limitations and strengths

This study should be interpreted with caution in light of some limitations: First, this was not a randomized study of the effects of antidepressants on MACE, which would not have been ethical in a prospective observational study, so results should be interpreted with this in mind. Second, though we have data on what antidepressants patients were taking (primarily SSRI's), we do not have data on dose, length of treatment, or adherence (Sansone & Sansone, 2012). Thus, any potential beneficial physiological effects associated with antidepressant use (e.g., anti-platelet or anti-inflammatory) would only be expected to occur as long as patients were taking the medication. Similarly, we have no information on psychiatric history, or whether patients were receiving other forms of depression treatment (e.g., psychotherapy) at baseline or over the follow-up. However, this level of data collection is typical of large-scale epidemiological cohort studies in this area. Second, the lack of follow-up data on changes in health behaviors (that may have been mediators of our observed depression treatment effects) is a limitation. However, this is consistent with similarly designed studies with prolonged follow-up periods from baseline (e.g., (Glassman et al., 2009; Paine, Hinderliter, et al., 2016; Perez-Cornago et al., 2016; Tambalis et al., 2016)). We were also unable to obtain a more detailed measure of ischemia quantification to include information such as Duke Score or the magnitude/location of ischemia, which could be considered a limitation. Given the prospective nature of this study and lengthy follow-up, there may be concerns that antidepressant treatments have changed.

However, SSRI's were prescribed for the vast majority of patients in this study (70%) and remain the most common class of pharmacotherapy for depression to this day, so we are confident our results remain highly relevant (Nassan et al., 2016). Finally, this was a primarily male (67%) and white (99%) sample, and may therefore not be representative of the general population. However, the proportions of men and women in this study are consistent with referral statistics to nuclear exercise stress tests (Carney et al., 2003; Yusuf et al., 2004).

Despite the above limitations, this study has several notable strengths. To our knowledge, this is first study to date to examine the impact of antidepressant treatment on the prospective risk of MACE among patients with and at risk for CVD. The use of valid, reliable measures to assess depression (PRIME-MD and BDI) is another important strength. The large sample size (n=2460), consecutive recruitment, and the inclusion of both men and women increases the generalizability of the findings. We also linked antidepressant use to reduced risk for MACE after adjustment for several important covariates, including CVD history and the presence of anxiety and depressive disorders, which attest to the robustness of the findings. We used multiple imputation procedures to deal with missing data that increased the reliability and representativeness of our analyses. Finally, the relatively long follow-up period (8.8 years) and the use of objective administrative database data to measure cardiovascular outcomes are other important strengths.

Conclusion

Our findings indicate a potential cardio-protective effect of antidepressants on risk for MACE over an 8.8-year follow-up among patients presenting for exercise stress tests independent of traditional risk factors including baseline depression and CVD history. However, the cardio-protective effect of antidepressants was strongest among those without a history of CVD.

Finally, we found significantly reduced risk of MACE associated with antidepressant use in the subgroup of patients identified as depressed at baseline, which became a trend after full covariate adjustment. Though only a trend, risk reduction estimates for MACE in depressed patients (33%) were comparable to those observed in the whole sample (30%), suggesting antidepressant treatment may indeed reduce the risk for subsequent cardiovascular events among depressed patients, which addresses a major gap in the literature. Future studies, particularly RCT's, are encouraged to further examine the efficacy of depression treatment (pharmacological and psychotherapeutic) on cardiovascular outcomes, to further elucidate mechanisms of action.

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Table 1: Sample characteristics

	All	No Antidepressant Use (n=2195)	Antidepressant Use (n=190)	F/χ2	P	N missing
Demographics						
Age (years)	56.8(8.52)	56.9(8.56)	55.7(7.96)	3.71	.05	0†
Sex (% Male)	67.4(1610)	69.0(1511)	51.0(97)	25.1	<.001	2†
BMI (kg/m^2)	27.5(4.79)	27.6(4.75)	26.7(5.21)	2.11	.15	1570†
Race (% White)	98.7(2184)	98.6(2008)	100(175)	2.52	.11	177
Cohabiting (%)	71.0(953)	72.3(896)	54.9(56)	13.9	<.001	1048
Education (greater than 12 years; %)	58.2(781)	58.2(721)	58.8(60)	0.015	.90	1048
Psychiatric Status						
Any* Depression (%)	38.7(921)	36.7 (805)	61.0 (116)	43.57	<.001	9
PRIME-MD Depressive Disorder (%)	24.0(572)	22.4(491)	42.6(81)	39.2	<.001	8†
PRIME-MD Major Depression (%)	13.8(329)	12.5(273)	29.5(56)	43.28	<.001	8†
PRIME-MD Minor Depression (%)	9.19(219)	9.22(202)	8.95(17)	0.02	.90	8†
PRIME-MD Bipolar Disorder (%)	0.92(22)	0.59(13)	4.74(9)	33.26	< .001	7†
PRIME-MD Dysthymia (%)	6.29(150)	5.29(116)	17.9(34)	48.01	< .001	7†
PRIME-MD Anxiety Disorder (%)	20.0(476)	18.3(401)	39.5(75)	49.0	<.001	10†
BDI Score ≥ 10 (%)	29.5(707)	27.5(604)	54.2(103)	59.6	<.001	122
Mean BDI Score	8.05(7.25)	7.54(6.68)	13.7(10.4)	129.8	<.001	122†
Clinical Characteristics						
Current Smoker (%)	23.4(483)	22.7(431)	30.7(51)	7.40	.025	326†
Alcohol Heavy Consumption** (%)	6.0(81)	5.9(74)	6.8(7)	0.20	.90	1042†
CVD history (%)	41.4(916)	41.8(851)	36.6(64)	1.81	.18	178†
Diabetes (%)	10.8(238)	11.0(223)	8.6(15)	0.96	.33	179†
Hypertension (%)	43.5(961)	43.9(894)	38.3(67)	2.09	.15	179†
Hyperlipidemia (%)	59.2(1309)	60.0(1221)	50.3(88)	6.26	.01	178†
Stress Test Results						

Ischemia (%)	40.8(952)	41.1(881)	37.6(70)	0.85	.36	58†
Baseline HR (bpm)	66.4(12.1)	66.3(12.2)	68.0(11.1)	3.28	.07	56
Baseline SBP (mmHg)	135.7(20.3)	136.2(20.2)	130.6(21.1)	12.8	<.001	60
Baseline DBP (mmHg)	85.8(11.4)	86.0(11.4)	83.2(11.5)	11.0	<.001	60
Medications						
Ace Inhibitor (%)	16.9(372)	16.5(336)	20.6(36)	1.87	.17	182
Beta Block (%)	35.8(791)	36.5(742)	28.0(49)	5.10	.024	183
Diuretic (%)	7.52(166)	7.3(148)	10.3(18)	2.09	.15	182
Ca-Channel Blockers (%)	18.5(408)	18.5(377)	17.7(31)	0.07	.79	181
Lipid-Lowering Medication (%)	49.3(1088)	49.8(1013)	42.3(74)	3.67	.06	181
Anti-hypertension Medication Use (%)	55.3(1221)	55.7(1131)	51.4(90)	1.17	.28	182
Anti-ischemic Medication Use (%)	55.3(1219)	55.8(1132)	49.7(87)	2.41	.12	185
Aspirin (%)	55.9(1167)	53.7(1090)	44.0(77)	6.11	.013	185
Antidepressant Use (%)	8.0(190)	-	-	-	-	3†
Cardiovascular Outcomes						
Mean time to MACE (days)	6.84(3.09)	6.80(3.11)	7.20(2.87)	2.93	.09	1†
Incidence of MACE (%)	30.2(721)	28.5(680)	21.0(40)	8.13	.004	1†

Presented as Mean (SD) or % (n). *defined as any depressive disorder on the PRIME-MD or BDI ≥10); **alcohol consumption defined as greater than 3 drinks per day. † Variables included in the imputation procedure

Table 2. Unadjusted (top), adjusted for depression only (middle) and fully adjusted (bottom) association between antidepressant use and risk of MACE

	β-estimate	Hazard Ratio	95% Confidence Limits	p-value
Unadjusted				
Antidepressant use	-0.429	0.651	0.474-0.896	.008
Adjusted for depression only				
Antidepressant use	-0.435	0.648	0.470-0.892	.008
Depression*	0.025	1.025	0.880-1.194	.750
Fully adjusted				
Antidepressant use	-0.361	0.697	0.504–0.964	.029
Depression*	0.033	1.033	0.875–1.221	.699
Anxiety Disorder	0.174	1.189	0.971–1.456	.093
Sex	0.218	1.244	1.018–1.520	.033
CVD history	0.359	1.432	1.204–1.704	<.0001
Age	0.021	1.021	1.011–1.030	<.0001
Exercise-induced (SPECT) myocardial Ischemia	0.602	1.826	1.548–2.153	<.0001
Current smoking status	0.280	1.323	1.084–1.613	.006
Diabetes	0.218	1.244	0.995–1.554	.055
Hypertension	0.173	1.189	1.017–1.391	.030
Dyslipidemia	0.101	1.107	0.927–1.320	.261
BMI	-0.011	0.989	0.955–1.025	.532

Note: All variables coded as absent (0) or present (1), with the exception of BMI. * indicates depression diagnosis per PRIME-MD or BDI ≥ 10

Table 3. Association between antidepressant use and risk of MACE, stratified by CVD status (includes index stress test result).

Differences by CVD history	β-estimate	Hazard Ratio	95% Confidence Limits	p-value
No CVD history				
Unadjusted analysis				
Antidepressant use	-0.502	0.605	0.364 – 1.008	.054
Depression *	0.038	1.039	0.824 – 1.310	.749
Adjusted analysis				
Antidepressant use	-0.613	0.542	0.299 – 0.981	**.043**
Depression *	0.119	1.127	0.859 – 1.479	.390
CVD history				
Unadjusted analysis				
Antidepressant use	-0.336	0.715	0.461 – 1.110	.135
Depression *	0.026	1.027	0.832 – 1.268	.806
Adjusted analysis				
Antidepressant use	-0.371	0.690	0.437 – 1.091	.113
Depression *	-0.010	0.990	0.781 – 1.256	.936

*either depression diagnosis per PRIME-MD, or BDI score > 10. Adjusted analyses adjusted for anxiety disorder, age, exercise-induced SPECT Ischemia, current smoking status, presence of diabetes, hypertension, dyslipidemia, BMI, and sex, plus depression (shown).

Table 4.

Adjusted association between treatment of antidepressant use in depressed patients and risk of MACE (n=921)

	β-estimate	Hazard Ratio	95% Confidence Limits	p-value
Unadjusted analysis				
Antidepressant use	-0.463	0.629	0.414-0.957	.030
Adjusted analysis				
Antidepressant use	-0.394	0.674	0.440–1.033	.070
Anxiety Disorder	0.093	1.098	0.855–1.410	.465
Sex (male)	0.193	1.213	0.902–1.631	.201
CVD history	0.349	1.418	1.062–1.894	.018
Age	0.017	1.017	1.003–1.032	.021
Exercise-induced (SPECT) myocardial Ischemia	0.679	1.973	1.516–2.566	<.0001
Current smoking status	0.331	1.393	0.999–1.941	.050
Diabetes	0.347	1.415	1.008–1.987	.045
Hypertension	0.075	1.078	0.836–1.389	.564
Dyslipidemia	0.032	1.033	0.779–1.370	.823
BMI	-0.016	0.985	0.940–1.031	.498

Note: All variables coded as absent (0) or present (1), with the exception of BMI. Depression characterized as PRIME-MD or BDI ≥10. Depression with no treatment used as reference point

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Figure 1. Kaplan Meier survival curve for the use of anti-depressants on risk of MACE, for the whole sample. Solid line presents no anti-depressant use; dashed line indicates anti-depressant use

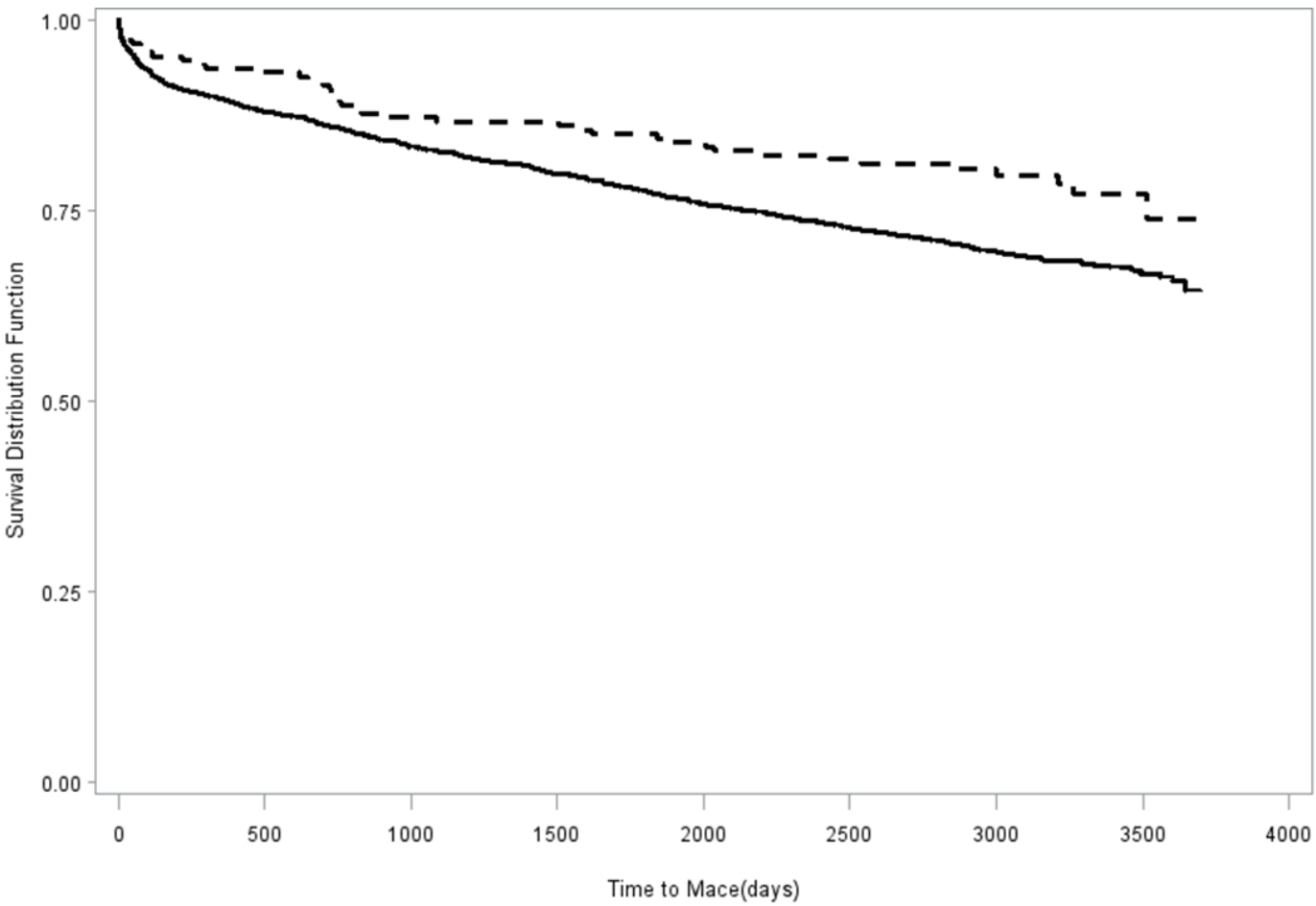

Figure 2. Kaplan Meier survival curve for the use of anti-depressants on risk of MACE, for patients without CAD history (top) and CAD history (bottom). Solid line presents no anti-depressant use; dashed line indicates anti-depressant use