Antidepressant Use by Class: Association with Major Adverse Cardiac Events in Patients with Coronary Artery Disease

Sherry L. Grace^{a,b} Jose R. Medina-Inojosa^c Randal J. Thomas^c
Heather Krause^d Kristin S. Vickers-Douglas^e Brian A. Palmer^e
Francisco Lopez-Jimenez^c

^aCardiovascular Prevention and Rehabilitation Program, University Health Network, University of Toronto, Toronto, ON, Canada; ^bSchool of Kinesiology and Health Science, York University, Toronto, ON, Canada; ^cDivision of Preventive Cardiology, Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; ^dDatassist, Centre for Social Innovation, Toronto, ON, Canada; ^eDepartment of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA

Keywords

Depression · Coronary artery disease · Antidepressants · Mortality · Cardiac rehabilitation

Abstract

Background: To assess use of antidepressants by class in relation to cardiology practice recommendations, and the association of antidepressant use with the occurrence of major adverse cardiovascular events (MACE) including death. **Methods:** This is a historical cohort study of all patients who completed cardiac rehabilitation (CR) between 2002 and 2012 in a major CR center. Participants completed the Patient Health Questionnaire (PHQ-9) at the start and end of the program. A linkage system enabled ascertainment of antidepressant use and MACE through 2014. **Results:** There were 1,694 CR participants, 1,266 (74.7%) of whom completed the PHQ-9 after the program. Depressive symptoms decreased significantly from pre- (4.98 ± 5.20) to postprogram (3.57 ± 4.43) ($p < 0.001$). Overall, 433 (34.2%) participants

were on antidepressants, most often selective serotonin reuptake inhibitors (SSRI; $n = 299$; 23.6%). The proportion of days covered was approximately 70% for all 4 major antidepressant classes; discontinuation rates ranged from 37.3% for tricyclics to 53.2% for serotonin-norepinephrine reuptake inhibitors (SNRI). Antidepressant use was significantly associated with lower depressive symptoms after CR (before, 7.33 ± 5.94 vs. after, 4.69 ± 4.87 ; $p < 0.001$). After a median follow-up of 4.7 years, 264 (20.9%) participants had a MACE. After propensity matching based on pre-CR depressive symptoms among other variables, participants taking tricyclics had significantly more MACE than those not taking tricyclics (HR = 2.46; 95% CI 1.37–4.42), as well as those taking atypicals versus not (HR = 1.59; 95% CI 1.05–2.41) and those on SSRI (HR = 1.45; 95% CI 1.07–1.97). There was no increased risk with use of SNRI (HR = 0.89; 95% CI 0.43–1.82). **Conclusion:** The use of antidepressants was associated with lower depression, but the use of all antidepressants except SNRI was associated with more adverse events.

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Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide [1, 2] and depression is the second leading cause of disability worldwide [3]. The conditions are highly comorbid [4], with depression being approximately 3 times more common in patients after an acute myocardial infarction than in the general community [5]. It has been estimated that 30% of patients who have been hospitalized for a myocardial infarction experience increased depressive symptoms, and 15–20% suffer from major depression. Depression in patients who have CVD is associated with less adherence to secondary prevention treatments, poor health-related quality of life, and higher rates of adverse events, including mortality rates that are twice as high than those in patients without depression [6, 7].

Accordingly, the American Heart Association [8] recommends screening for depression in cardiac patients using the Patient Health Questionnaire (PHQ) [9]. Assessment of depressive symptoms [10, 11] is considered a core component of cardiac rehabilitation (CR) by many professional societies [12–15]. When depression is detected and formally diagnosed, the American Heart Association also recommends appropriate treatment with cognitive-behavioral therapy and/or antidepressants [8].

Given trial evidence of efficacy in reducing depression, and their presumed safety [16], selective serotonin reuptake inhibitors (SSRI) are the recommended antidepressant class for first-line pharmacologic therapy in CVD patients [17], and atypical antidepressants are recommended as second-line therapy. Serotonin-norepinephrine reuptake inhibitors (SNRI) are also recommended as second-line therapy; however they have not been studied in CVD patients [17]. Tricyclic antidepressants (TCA) are not recommended in many patients with CVD, particularly among those with coronary artery disease (CAD) or ventricular arrhythmias due to their documented arrhythmogenic effects [18]. Research in CVD populations has shown that use of pharmacologic antidepressant therapy is associated with moderate reductions in depression but does not necessarily reduce cardiovascular events or deaths in the context of comorbid depression [5, 16, 19–21]. However, no studies to our knowledge have examined the association between antidepressant class and long-term outcomes in CAD patients. There is also a paucity of data assessing current patterns of antidepressant use by class and current clinical practice recommendations, and patients' adherence.

Accordingly, the objectives of this study were to describe and assess in a cohort of CAD patients participating in CR: (1) antidepressant use by class in relation to clinical practice recommendations, (2) patients' adherence to pharmacologic antidepressant treatment, and (3) the association between antidepressant use by class and the occurrence of major adverse cardiovascular events (MACE) including death.

Materials and Methods

Design and Data Sources

This is an observational, community-based, retrospective cohort study. Patients with CAD who entered the Mayo Clinic CR program in Rochester, MN, USA, between 2002 and 2012 comprised the cohort. Clinical data from CR intake assessments were extracted. Patients were administered the PHQ-9 before and after the program.

Medication and MACE were ascertained through record linkage with the Rochester Epidemiology Project through to December 2014 [22]. This population-based record linkage system electronically stores the clinical information developed by the Mayo Clinic with that obtained by other community providers, the Olmsted Medical Group, and the affiliated Olmsted Community Hospital, that have provided research authorization to the state of Minnesota [23]. Follow-up data was complete for this cohort. The study protocol was approved by both the Mayo Clinic and the Olmsted Medical Center Institutional Review Board.

Setting

Residents of Rochester or Olmsted County, MN, USA, and the surrounding area are relatively distant from other large metropolitan health care institutions, and the Mayo Clinic CR program was the only CR program in the county during the study period. The outpatient CR program is 12 weeks in duration, and it is based on American Association of Cardiovascular and Pulmonary Rehabilitation guidelines [12]. All patients are encouraged to attend group stress management sessions; there, a video is presented which describes how stress affects the body, as well as techniques such as relaxation, exercise, and deep breathing. Patients are also provided videos to take home demonstrating relaxation, tai chi/qigong, and mindfulness-based approaches to stress management.

The PHQ-9 is administered routinely to all patients at CR intake and discharge assessments [9]. The staff discusses the results with the patients. Patients with pre-CR scores ≥ 10 are considered for referral to psychology; patients expressing suicidal ideation are provided an emergency consultation. Primary care and/or mental health providers may then prescribe pharmacotherapy or other treatments.

Participants

Inclusion criteria were: patients 18 years of age or older, with a documented diagnosis of CAD, who attended the CR program. CAD was defined as: (1) a previous myocardial infarction (ST or non-ST segment elevation), (2) stable or unstable angina, and/or (3) previous revascularization by either coronary artery bypass grafting or percutaneous coronary intervention. In order to facili-

tate outcome assessment, an additional inclusion criterion was that patients had to be residents of Olmsted County, MN, USA. Patients who did not complete the pre- or post-CR PHQ-9 were excluded. Thus, the included patients completed the CR program.

Measures

Most participant characteristics were obtained from the record linkage system. The date of CR intake was defined as the index date. The smoking history was obtained from the electronic medical record based on self-report to a healthcare provider.

Medications were also available through the record linkage system. Psychopharmacological medications were extracted from 2001 to the end of 2014. Variables were computed to categorize medication class. Antidepressant categories were 5-fold: SSRI, SNR, TCA, atypicals, and others (e.g., MAOI). Trazodone was included as an atypical herein, but it can also be considered a serotonin antagonist and reuptake inhibitor or tetracyclic. Other psychopharmacological medications were also categorized (e.g., benzodiazepines and antipsychotics). The proportion of days covered was also computed (i.e., proportion of days in the measurement period on which the participant had filled a prescription for the medication, which is an indicator of medication adherence) using a validated approach [24, 25].

Independent Variable

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression [9], recommended for administration in cardiac samples [8]. The tool assesses the criteria on which the diagnosis of depressive disorder is based [26]. Response options for each item range from 0 (not at all) to 3 (nearly every day). It yields both a provisional depression diagnosis and a severity score [9].

PHQ-9 total scores range from 0 to 27. Cut-off points of 5, 10, 15, and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively [27]. A single cut-off point is currently recommended at a score of 10 or greater (i.e., “elevated” symptoms), as this has a sensitivity for depression of 88%, a specificity of 88%, and a positive likelihood ratio of 7.1 [9]. The minimal clinically important difference used for the analysis was 5 points or greater [28]. Major depression is considered if 5 or more of the 9 depressive symptom criteria have been present on at least “more than half the days” (response option 2) in the past 2 weeks, and one of the symptoms is depressed mood or anhedonia.

Dependent Variables

MACE were ascertained using the record linkage system from the Rochester Epidemiology Project and included any of the following events: acute coronary syndrome (myocardial infarction [International Classification of Diseases-9, 410x] or unstable angina [International Classification of Diseases-9, 411x]), coronary revascularization (coronary artery bypass grafting [Current Procedural Terminology/International Classification of Diseases-9, 337700-337735/V45.81] or percutaneous coronary intervention [Current Procedural Terminology/International Classification of Diseases-9 2980-92982/V45.82]), ventricular arrhythmias that required in-hospital management (International Classification of Diseases-9 427x), [29] or death from any cause. Mortality information was obtained directly from the Rochester Epidemiology Project, which records the vital status from state vital statistics offices and the National Death Index [30].

All outcome information was followed passively through electronic ascertainment using diagnosis codes (an approach which has been validated) [22]. A physician-investigator/coauthor (J.R.M.-I.), who was blinded to baseline characteristics, reviewed a fraction of the records in the record linkage system to confirm the outcome and validate the research strategy. Additionally, a random 10% of the outcomes were reviewed in duplicate by a masked clinician expert/senior author (F.L.-J.) to ascertain interobserver agreement. It was within the excellent range ($\kappa = 0.89$).

Statistical Analyses

First, the differences in sociodemographic and clinical characteristics of participants who were retained after CR (i.e., completed the PHQ-9 after the program) versus those who did not complete the post-CR PHQ-9 were compared using *t* tests or a χ^2 test, as appropriate. Changes in depressive symptoms from pre- to post-CR were tested using a paired *t* test (continuous measure), and a χ^2 test (for severity categories). The association between depressive symptoms and antidepressant use was tested using *t* tests, both independent samples (at pre- and post-CR) and paired (change in depressive symptoms from pre- to post-CR by antidepressant use, including by class). The association between antidepressant adherence and depressive symptoms was tested with Pearson correlations, and the association between antidepressant adherence and MACE was tested with *t* tests.

The association between antidepressant use, overall and by class, and MACE was first tested at a bivariate level using χ^2 analyses. To adjust for confounders that may determine the likelihood of either being placed on an antidepressant or suffering from MACE, we used a propensity matching approach. Given the sample size herein, this is considered to be a more robust approach and provide a less-biased estimator than building a traditional multivariate regression model with confounders as predictors [31]. The nearest neighbor propensity score matching algorithm was applied, with a 2:1 matching ratio, using the following variables: age, sex, pre-CR depressive symptoms (i.e., PHQ-9 scores), BMI, hypertension, dyslipidemia, smoking status, previous percutaneous coronary intervention or bypass surgery or heart failure, comorbid stroke, lung disease, kidney disease, peripheral vascular disease, cancer, and diabetes. Kaplan-Meier curves and Cox regression models were created to test the association between a matched participant's use or nonuse of each antidepressant within each class, and the likelihood of MACE including death, in the propensity-matched samples. The log-rank test was used to test for differences in survival. $p < 0.05$ was considered statistically significant. These analyses were undertaken with the statistical package R 3.3.1.

Results

Respondent Characteristics

Overall, 1,694 patients initiated CR during the period of study, and 1,266 (74.7%) of these completed the follow-up PHQ-9 and comprised the sample. Their characteristics are shown in Table 1. As shown, the retained participants did not differ with regard to sociodemographic

Table 1. Participants' pre-CR clinical and sociodemographic characteristics by retention status

Characteristic	Lost to follow-up (<i>n</i> = 428; 25.3%)	Retained sample (<i>n</i> = 1,266; 74.7%)	Total (<i>n</i> = 1,694)
<i>Sociodemographic</i>			
Age, years	65.22±12.32	63.89±12.88	64.23±12.75
Female sex	124 (29.0)	413 (32.6)	537 (31.7)
White race	388 (90.7)	1,191 (94.1)	1,579 (93.2)
<i>Clinical</i>			
Cardiovascular history			
Percutaneous coronary intervention	251 (58.6)	715 (56.2)	966 (57.0)
Coronary artery bypass graft	110 (25.7)	325 (25.5)	435 (25.7)
Stroke	86 (20.1)	289 (22.8)	375 (22.1)
Heart failure	38 (8.9)	193 (15.2)	231 (13.6)**
Risk factors			
Dyslipidemia	394 (92.1)	1,175 (92.8)	1,569 (92.6)
Hypertension	302 (70.6)	936 (73.5)	1,238 (73.1)
Diabetes	191 (44.6)	633 (49.7)	824 (48.6)
Smoking (past or current)	152 (35.5)	556 (43.7)	708 (41.8)**
BMI	29.9±6.56	29.91±6.00	29.9±6.14
Comorbidities			
Peripheral vascular disease	121 (28.3)	443 (34.8)	564 (33.3)*
Chronic obstructive pulmonary disease	76 (17.8)	241 (18.9)	317 (18.7)
Cancer	72 (16.8)	237 (18.6)	309 (18.2)
Chronic kidney disease	22 (5.1)	110 (8.6)	132 (7.8)*
Psychological			
Depressive symptoms (PHQ-9)	3.37±4.13	4.98±5.19	4.67±5.09***
Antidepressant use	140 (32.7)	433 (34.2)	573 (33.8)***

Values are presented as means ± SD or numbers (%). CR, cardiac rehabilitation. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2. Depressive symptoms before and after CR

	Pre-CR	Post-CR	<i>p</i>
Total PHQ-9 score	4.98±5.19	3.57±4.43	<0.001 ^a
Depressive symptom severity			
Minimal (1–4)	758 (59.9)	907 (71.2)	<0.001 ^b
Mild (5–9)	284 (22.4)	234 (18.4)	
Moderate (10–14)	135 (10.7)	80 (6.8)	
Moderately severe (15–19)	54 (4.3)	30 (2.4)	
Severe (20–27)	31 (2.5)	15 (1.2)	
Diagnostic criteria ^c			
Major depression	67 (5.3)	24 (1.4)	<0.001 ^b
Other depressive disorder	24 (1.9)	67 (4.0)	<0.001 ^b

Values are presented as means ± SD or numbers (%). The total number of patients is 1,266. CR, cardiac rehabilitation; PHQ, Patient Health Questionnaire; SD, standard deviation. ^a Paired *t* test. ^b χ^2 test. ^c Provisional, based on PHQ-9 scoring.

characteristics from those who did not complete the follow-up PHQ-9, although they were more likely to have a history of several comorbidities and smoking. Moreover, the retained participants had significantly higher depressive symptoms before CR and were more likely to be taking any antidepressant than those who did not complete the follow-up assessment.

Depressive Symptoms

Mean depressive symptom scores, severity categorizations, and diagnoses based on the PHQ-9 scores before and after CR are shown in Table 2. As shown, most participants scored in the minimal range before and after CR. All depressive symptom indicators decreased significantly from between pre- and post-CR.

Overall, 220 out of 1,266 (17.4%) participants scored in the “elevated” range before CR (i.e., ≥ 10), and 125 out of 1,266 (9.9%) participants did so after the test. Participants were categorized based on scoring above or below

Table 3. Occurrence of MACE by antidepressant class (unadjusted)

	SSRI (<i>n</i> = 299; 23.6% ^a)	Atypicals (<i>n</i> = 179; 14.1% ^a)	TCA (<i>n</i> = 102; 8.1% ^a)	SNRI (<i>n</i> = 62; 4.9% ^a)	Total ^b (<i>n</i> = 1,266 ^c)
Percutaneous coronary intervention	56 (18.7)**	38 (21.2)**	25 (24.5)**	16 (25.8)**	177 (14.0)**
Angina	53 (17.7)***	29 (16.2)	20 (16.7)*	13 (20.1)*	152 (12.0)
Myocardial infarction	37 (12.4)**	17 (9.4)	14 (13.7)*	6 (9.7)	99 (7.8)*
Death	29 (9.7)	16 (8.9)	16 (15.7)**	7 (11.3)	96 (7.6)
Heart failure	28 (9.6)**	12 (6.7)	12 (11.8)*	7 (11.3)	78 (6.2)
Coronary artery bypass graft	19 (6.4)*	8 (4.5)	6 (5.9)	3 (4.8)	50 (3.9)*
Ventricular arrhythmia	5 (1.0)	4 (2.2)*, d	2 (2.0)	1 (1.6)	11 (0.9)
Any MACE, excluding death	105 (35.1 ^e)***	62 (34.6 ^e)**	38 (37.3 ^e)**	20 (32.3 ^e)	225 (17.8 ^e)***
Any MACE	122 (40.8 ^e)***	72 (40.2 ^e)**	46 (45.1 ^e)**	24 (38.7 ^e)	264 (20.9 ^e)***

χ^2 tests, * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ for the occurrence of MACE in those taking vs. not taking an antidepressant in that class. MACE, major adverse cardiovascular event; CR, cardiac rehabilitation; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants. ^a Percentages were calculated using the denominator of a total sample of 1,266. ^b Values reported in this column reflect the association of each MACE with the use of any antidepressant (i.e., many participants on ≥ 1). ^c Number of MACE overall reported in this column (i.e., on or not on an antidepressant). ^d Caution is warranted in overinterpreting this association, due to the small cell size. ^e Because many participants had more than 1 MACE, the numerator used to calculate the percentages was the number of participants on that class of antidepressant who had any MACE.

10 on the PHQ-9 both before and after CR. Results showed that 984 out of 1,266 (77.7%) remained subclinical (i.e. < 10) throughout CR, 115 out of 1,266 (9.1%) went from elevated to subclinical, 46 out of 1,266 (3.6%) went from subclinical to elevated, and 49 (3.9%) remained elevated.

Of the participants with elevated depressive symptoms before CR, their mean PHQ-9 score after CR was 7.30 ± 6.36 (SD). In most participants ($n = 983$; 77.6%) PHQ-9 scores did not change at follow-up, when using a cutoff of 5 as the minimal clinically important difference, but in 204 (16.1%) participants the scores decreased by at least 5 points and in 79 (6.2%) the scores increased by at least 5 points.

Antidepressant Use

Overall, 446 (35.2%) participants were taking any psychopharmacological medication at any point during the period of this study; 433 (34.2%) of them were on antidepressants, and 118 (9.3%) were taking more than 1 antidepressant, with a median of 2 drugs per patient.

The class of antidepressant used is shown in Table 3. Most participants taking antidepressants were on SSRI (most commonly citalopram [$n = 132$; 10.4%], sertraline [$n = 101$; 8.0%], and paroxetine [$n = 36$; 2.8%]), followed by atypical antidepressants (most commonly trazodone [$n = 106$; 8.4%], bupropion [$n = 72$; 5.7%], and mirtazapine [$n = 31$; 2.4%]), TCAs (most commonly amitriptyline [$n = 50$; 3.9%], nortriptyline [$n = 39$; 3.1%], and trimipramine [$n = 7$; 0.6%]), and SNRs (only venlafaxine [$n = 54$;

3.2%] and duloxetine [$n = 31$; 1.8%]). None of the participants was on any other class of antidepressant (e.g., MAOI). Other psychoactive medications participants were taking were: sedatives ($n = 63$; 5.0%; e.g., zolpidem, $n = 51$; 4.0%), benzodiazepines ($n = 67$; 5.3%; e.g., lorazepam, $n = 63$; 3.7%), antipsychotics ($n = 25$; 2.0%; e.g., quetiapine, $n = 22$; 1.3%; generally as combination therapy), stimulants ($n = 5$; 0.4%; e.g., modafinil, $n = 5$; 0.4%), and mood stabilizers (lithium, $n = 3$; 0.3%).

Participants were on their antidepressant for an average of 4.39 ± 3.19 years during the period of study, with an average of 71.1% of days covered. About half (46.6%) stopped taking their antidepressant during follow-up; 33 out of 62 (53.2%) stopped taking SNRI, 153 out of 299 (51.2%) stopped taking SSRI, 80 out of 179 (44.7%) stopped taking atypicals, and 38 out of 102 (37.3%) stopped taking TCA during the period of study. The degree of adherence to any class of antidepressants was not significantly associated with post-CR depressive symptoms (all $p < 0.05$).

Among the 220 participants with elevated PHQ-9 scores before CR, 202 (91.8%) were on any antidepressant medication, and this rate is higher than among those without elevated scores (188/1,046 [18.0%]; $p < 0.001$). Moreover, among participants on antidepressants, the mean pre-CR PHQ-9 score was 7.33 ± 5.94 , and post-CR scores were 4.69 ± 4.87 (paired $t = 6.17$, $p < 0.001$; Fig. 1). These scores were significantly higher than in partici-

Table 4. Cox regression models of major adverse coronary events including death likelihood by use of antidepressant class in propensity-matched patients

	Coefficient	HR	95% CI	z score	p	Wald
SSRI	0.37	1.45	1.07–1.97	2.36	0.018	5.58, $p = 0.018$
SNRI	−0.11	0.89	0.43–1.82	−0.30	0.762	0.09, $p = 0.760$
TCA	0.90	2.46	1.37–4.42	3.12	0.002	9.13, $p = 0.003$
Atypical	0.46	1.59	1.05–2.41	2.17	0.023	4.71, $p = 0.029$

SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Fig. 1. Depressive symptoms before and after cardiac rehabilitation by any antidepressant use. t test pre-CR, $p < 0.001$. Post-CR, $p < 0.001$; ANOVA 2 (antidepressant status) $\times$ 2 (time), $p < 0.001$. CR, cardiac rehabilitation; PHQ, Patient Health Questionnaire.

pants not on antidepressants both before (4.98 ± 5.20 , $p < 0.001$) and after CR (3.57 ± 4.43 , paired $t = 9.75$, $p < 0.001$). Participants taking any of the 4 classes of antidepressants experienced significant reductions in symptoms from pre- to post-program (all $p < 0.007$).

MACE and Their Associations with Depressive Symptoms and Antidepressant Use

Over a median follow-up of 4.7 ± 3.3 years, 264 (20.9%) participants had a MACE (Table 3). Many participants had more than 1 MACE, and these participants had a mean of 2.36 ± 1.24 MACEs (median = 2). Additionally, the median time to total mortality for the 96 participants who died was 4.4 ± 3.0 years after CR initiation.

Greater pre-CR depressive symptoms were significantly associated with the occurrence of MACEs ($t = 2.42$, $p < 0.02$), specifically percutaneous coronary intervention ($t = 2.86$, $p = 0.04$), myocardial infarction ($t = 2.42$, $p = 0.02$), heart failure ($t = 2.59$, $p = 0.01$), and death ($t = 2.88$, $p < 0.01$). Moreover, the number of MACE experienced by each participant was significantly associated with greater pre-CR depressive symptoms (Spearman $\rho = 0.06$, $p < 0.02$). As shown in Table 3, the use of antidepressants of any class was significantly associated with more MACE (shown in the most common individual antidepressants in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000486794).

Propensity matching was successful in balancing participant characteristics among those taking antidepressant of a specific class versus those not doing so (online suppl. Tables 2–5). Cox regression models testing the association between a matched participant's use or nonuse of each antidepressant class and the likelihood of MACE after CR are presented in Table 4. When considering different classes, the use of SSRI, TCA, and atypicals was associated with an increased risk of MACE, including death, while SNRI were not. The Kaplan-Meier median survival rate was 67.2, 60.0, 68.6, and 77.7%, respectively ($p < 0.01$). Kaplan-Meier curves displaying the time to MACE by use of each antidepressant class are shown in Figure 2.

Given the different mechanisms of action and adverse effect profiles of the individual antidepressants within classes, the most commonly used medications (more than 50 patients) were tested individually in the same manner against matched controls. No difference in MACE risk was observed for citalopram (SSRI), trazodone (atypical), sertraline (SSRI), bupropion (atypical), or venlafaxine (SNRI; $p < 0.05$), but it was found for amitriptyline (TCA; risk ratio = 2.51; 95% CI 2.03–3.74).

The proportion of days covered was significantly associated with the occurrence of any MACE in those taking SSRI ($74.6 \pm 11.9\%$ adherence in participants with any

Fig. 2. Kaplan-Meier curves displaying the time to major adverse cardiovascular events (MACE) by use of each antidepressant class: SSRI (**a**), SNRI (**b**), TCA (**c**), and atypical (**d**). SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin-norepinephrine reuptake inhibitors; TCA, tricyclic; HR, hazard ratio; CI, confidence interval.

MACE vs. $69.5 \pm 14.3\%$ adherence in participants with no MACE; $p = 0.02$), but not in those taking other antidepressant classes ($p < 0.05$). The proportion of days covered on any class was not significantly associated with death ($p < 0.05$).

Discussion

In this population-based cohort of CAD patients attending CR, it has been shown that depressive symptoms are common. The high prevalence of depressive symptoms is consistent with what is reported in the literature [5]. A significant proportion of patients used antidepres-

sants, which effectively lowered depressive symptoms, but in many instances this was associated with a higher incidence of MACE.

In this study, one third of CAD patients were on an antidepressant, and this rate is higher than what has been previously reported [32, 33]. In accordance with clinical recommendations for CAD patients with depression, most participants were on first-line recommended therapy, i.e., the SSRI citalopram and sertraline, or second-line therapies, i.e., atypicals [17]. However, some patients were taking antidepressants that have not been well studied in the CAD population (i.e., SNRI) or are not recommended for this population (i.e., TCA) [34]. Given that depression has been historically underrecognized and

undertreated, the overall results herein suggest that symptoms are being detected and managed in accordance with American Heart Association recommendations [35].

This is one of the only studies in the literature to our knowledge to report on long-term antidepressant adherence and outcomes in a cardiac population. Up to one half of the participants stopped taking an antidepressant during the period of study, but whether discontinuation was due to side effects, remission, or another reason cannot be ascertained. Adherence to therapy [36] and discontinuation rates were consistent with what has been described in psychiatric samples more broadly [34, 37, 38]. Discontinuation rates were highest and the proportion of days covered was lowest among those on SNRIs. Given that the results herein suggest that they may have a safer profile (see more below), the tolerance of these medications (particularly of side effects such as insomnia and gastrointestinal issues) [39, 40], warrants further study.

While antidepressant use was associated with reductions in depressive symptoms in the CR setting, the use of all classes except SNRIs was associated with poorer cardiovascular outcomes. While SNRI are considered as potential second-line therapy for CAD patients, they are understudied in this population [17, 34]. While few patients were on SNRI in the cohort and therefore the lack of an association could be due to low statistical power, the results did suggest fewer MACE in patients taking SNRI. Their safety profile was superior to that of the recommended first-line therapy of SSRI. However, there are some reports of adverse cardiac effects in geriatric samples taking venlafaxine XR, and therefore caution is warranted [41], but no increased risk of MACE with venlafaxine (whether it was IR or XR is not known) was observed in this study.

MACE were 1.5× more common in those taking SSRI or atypicals. Indeed, there has been some suggestion that SSRI may not be as safe as previously described [42–44]. Some of the drugs in this class are associated with QT issues and can increase bleeding. However, some other research has shown that SSRI may be associated with lower rehospitalization – an outcome we did not examine herein. Based on the fact that no increased risk of MACE was observed with the 2 most commonly prescribed SSRI, i.e., citalopram and sertraline, these results suggest that more research regarding individual SSRI may be needed, given recommendations to prescribe them as first-line agents [35].

The use of TCA in the cohort was associated with 2.5× higher rates of MACE, as has been shown in psychiatric patients without CAD [17, 34], and in patients with CAD assessing mortality only [42, 45]. To the best of our knowledge, this is the first study to show in a CAD population

an increased rate of MACE with the use of TCA, including fatal and nonfatal events. These results confirm recommendations not to prescribe TCA in CAD populations. Appropriately, rates of use were low, consistent with previous research [32, 33], and may have been in patients who were taking those medications before the index event, or were considered not to be early post-myocardial infarction or at risk of long QT, or suffered severe depression and were nonresponsive to SSRI. However, appropriateness cannot be ascertained with the available data.

No prior publication has directly compared the 4 major antidepressant classes and the rate of MACE in CAD patients – a comparison that will contribute to a better understanding of the current usage and safety of antidepressants in CAD patients. Results herein regarding poorer outcomes among CAD patients taking antidepressants are consistent with the limited literature in this area, which has been primarily collected in HF populations taking SSRI, examined effects on mortality only, and not always adjusted for depression [32, 33, 42, 45, 46], although results are not consistent with all of the literature [34, 47]. In the Heart and Soul Study, for example, CAD patients broadly were included, and only 2 classes of antidepressants were considered (SSRI and TCA). TCA (consistent with the findings herein) but not SSRI (consistent with our findings regarding citalopram and sertraline) were associated with increased mortality [45]. Rutledge et al. [48] undertook a meta-analysis of the effects of mental health treatments (a composite of psychotherapy and antidepressants) on MACE. It was shown that treatment of depression, by either/both of these strategies, was associated with significantly fewer MACE but there was no effect on total mortality. However, CR was associated with lower depression, MACE, and death rates. Finally, a recent meta-analysis including 11 studies of CAD patients showed no significant association of antidepressant use with mortality or MACE, but findings did suggest that different classes of antidepressants had differential impacts [34].

The results of our study failing to show a lower rate of MACE with use of antidepressant therapy add to the wealth of evidence failing to prove that pharmacologic therapy of depression has any effect on MACE [34, 35]. Because depression in CAD patients has consistently been shown to be associated with increase rates of MACE, the apparent lack of benefit rendered by antidepressants calls for additional research to elucidate this paradox. Because certain antidepressants (e.g., amitriptyline) are associated with increases in MACE, it is plausible that the beneficial effect of some medications is being masked by the negative

effect of others [34]. In future studies, researchers should be certain not to report MACE across antidepressant classes but rather consider them individually.

Caution is warranted when interpreting these results. First, the design was observational, and hence causal associations between the use of antidepressants and increased rates of MACE cannot be drawn, in spite of the propensity-matched analysis meant to reduce indication bias. Second, with regard to generalizability, our data are limited to a single center and to individuals with CAD attending CR who were primarily male. However, the CR center was the only one available in the region, and therefore findings should be fairly representative of patients who attend CR in general. The generalizability of the cohort more broadly has been established elsewhere [49].

Third, there was some retention bias in the sample, particularly that the analyzed cohort had higher depressive symptoms and a greater use of antidepressants than those who did not complete the PHQ-9 at both time points and were hence excluded. Fourth, with regard to measurement, there was no structured clinical interview. Therefore, no definitive diagnosis of depression can be inferred from the data. There was also no assessment of depression that coincided with the time of antidepressant treatment initiation or follow-up appointments. Fifth, the effects of use of multiple antidepressants and dose were not considered. In addition, due to propensity matching and the use of multiple antidepressants, a comparison between antidepressant classes could not be performed. Fi-

nally, while all CR participants were exposed to stress management, the use of psychotherapy, which is another evidence-based treatment for depression, was not ascertained in this group and therefore could not be considered in the analyses.

In conclusion, depressive symptoms and use of antidepressants are common in CR. Use of antidepressants is generally in accordance with clinical practice guideline recommendations. Use of antidepressants was associated with lower depressive symptoms, but often more adverse cardiac events. The safety profile of SNRI warrants further consideration.

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