ASSOCIATION AMONG DEPRESSIVE SYMPTOM CHANGES, PSYCHOPHARMACOLOGIC THERAPY AND OUTCOMES IN CARDIAC REHABILITATION PARTICIPANTS

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ABSTRACT

Cardiovascular diseases (CVDs) and depression are the leading causes of mortality and disability worldwide, respectively; they are highly comorbid such that depression is 3 times more common in patients after an acute MI than the general population. 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 without depression. Patients prescribed antidepressants are often not monitored and screening is controversial, therefore identification and therapeutic response is suboptimal. This thesis is a secondary analysis of post-cardiac rehabilitation patients that explored the intersection of cardiac events and antidepressant use; specifically, the effects of medical history, depression status and antidepressant use on the likelihood of having major adverse cardiac events over a 10 year follow-up period. Antidepressant use was found to have a larger positive effect on depression status vs patients not on antidepressants; most patients were taking an SSRI as per guidelines and the degree of medication adherence was not associated with depressive symptoms. However, TCAs were most often associated with death outcomes, while SSRIs were significantly associated with non-lethal cardiac outcomes. A review of antidepressant use by class in this population may be warranted.

DEDICATION

I would like to dedicate this thesis to my family, who helped me through the late nights and the hard work. You have both taught me that *amare et sapere vix deo conceditur.*. Mom, you have been the motivation for me to reach for the stars. I'm not there yet, but I'm on my way. Dad, you were always my safe place and believed in me when I didn't believe in myself. You saw potential in me when I couldn't find it within myself, and I will always remember you for that. Jordan, you were there to give me a break from talking about the "T" word- I really needed that from time to time! This is also for extended family; my grandparents who passed before me and those still here- I hope you're proud of me. Also, my dog Belle, who would sit with me as I looked at databases and wrote manuscripts throughout my two year degree, reminding me that I always had a friend nearby.

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INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide(Go et al., 2013; Yusuf, Reddy, Ounpuu, & Anand, 2001), and depression is the leading cause of disability worldwide(Mathers, Colin, Stevens, Gretchen, Mascarenhas, 2009), accordingly, they are highly comorbid (Thombs et al., 2005). Specifically, depression is approximately 3 times more common in patients after an acute myocardial infarction than in the general community (Ruo B, Rumsfeld JS, Hlatky MA, Liu H, Browner WS, 2009). It has been estimated that 30% of patients who have been hospitalized for a myocardial infarction experience elevated depressive symptoms, and 15-20% suffer from major depression (Geggel L, 2015; Halaris, 2009); this is at least 3 times the incidence of non-CVD patients, whose overall rate of depression is 3-5% globally (Milani & Lavie, 2007) . Women experience twice the rates of depression as men (Shanmugasegaram, Russell, Kovacs, Stewart, & Grace, 2012). 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 without depression (K. W. Davidson et al., 2010).

Accordingly, the American Heart Association (Goff et al., 2014; Judith H Lichtman et al., 2008) recommends screening for depression in cardiac patients using the Patient Health Questionnaire (PHQ)(K Kroenke, Spitzer, & Williams, 2001). Cardiac rehabilitation (CR), which is a comprehensive outpatient program of secondary prevention and lifestyle counseling (Lett et al., 2004), includes assessment of depressive symptoms (Herridge, Stimler, Southard, & King, 2005; Rutledge, Redwine, Linke, & Mills, 2013). Indeed, psychological health is considered a core component of CR by many learned societies (AACVPR, 2013; Bjarnason-Wehrens et al., 2010; Buckley et al., 2013; Haddadzadeh, Maiya, Shad, Mirbolouk, & Padma Kumar, 2011; Paul Dendale, Patrick Doherty, Dan Gaita, Stefan Höfer, Hannah McGee, Miguel Mendes, Josef Niebauer & Massimo F Piepoli, Ugo Corrà, Stamatis Adamopoulos, Werner Benzer, Birna Bjarnason-Wehrens, 2014). A recent meta-analysis established

there are moderate-sized reductions of depression with CR participation (Rutledge et al., 2013). These reductions could be attributed to screening and detection (leading to referral for diagnosis, and where positive use of evidence-based therapies such as antidepressants and psychotherapy), social support, psychosocial education (e.g., stress management), the mood-enhancing effects of exercise (Samartzis et al., 2013), or more likely a combination of these components of CR. Studies also suggest that CR participation may attenuate the excess mortality associated with depressive symptoms (C J Lavie, Morshedi-Meibodi, & Milani, 2008).

While depressive symptom reductions are observed in CR trials, in the "real-world", most CR programs have insufficient mental health care capacity to meet required services for many patients (Cahill, M.C., Bilanovic, A., Kelly, S., Bacon, S., & Grace, 2015). Where treatment is accessed, patients are more often prescribed antidepressants than offered psychotherapy, due again to issues of capacity. However, patients prescribed antidepressants are often not monitored, such that therapeutic response is not optimized. Moreover, previous research has reported continued use of a class of antidepressants known as tricyclics (Grace, Leung, & Stewart, 2008) despite their contraindication in this population, due to arrhythmogenic effects (Bradley SM, 2015). Therefore, based on the inconsistency of identification of depression among cardiac patients, as well as the poorer health outcomes attributed to depressed patients, this thesis will explore many facets of depression screening, treatment, and benefits in cardiac patients, including the use of antidepressants in patients assessed for depression during CR, the effects of medical history, comorbid conditions, depression status and antidepressant use on the likelihood of having major adverse cardiac events, over a 10 year follow-up period.

Literature Review

Cardiovascular Disease and Its Burden

Cardiovascular diseases (CVDs) are conditions that involve partial or complete blockage of blood vessels which can lead to a heart attack or stroke. An estimated 1.6 million Canadians are living with heart

disease or the effects of a stroke; 1.3 million Canadians are living with heart disease alone (Hazinski et al., 2015). Globally, incidence of CVDs is rising; in 2010, an estimated 111.7 million individuals (1.62% of the global population) had angina due to ischemic heart disease, as reported by the Global Burden of Disease Study (Turk-Adawi, Sarrafzadegan, & Grace, 2014). Once a patient has CVD, the risk of recurrent cardiac events has been estimated at 34.9%, and is even higher in certain groups. For example, in cardiac patients with comorbid kidney disease, the risk nearly doubles, to 65.5% (Weiner et al., 2004).

Depression

Depression is a mood disorder, characterized by a depressed mood and combination of other symptoms such as weight change, sleep disturbance, insomnia, fatigue, feelings of guilt, worthlessness, and/or hopelessness. The symptoms may appear in different degrees in individuals, such that they have "the blues". Even mild symptoms can be hazardous in the context of CVD (Vieweg, Hasnain, Lesnefsky, & Pandurangi, 2011).

However, for the diagnosis of depression to be met, according to The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (APA, 2013) five of nine symptoms (examples above) must be present, and at least one of the five must be the cardinal features of 'depressed mood' or 'loss of interest or pleasure'. All must be judged to be significant by an experienced clinician in terms of severity, duration, abnormality, distress and impairment (i.e., social and occupational functioning) during a structured clinical interview for a diagnosis to be made. The ICD-10 (World Health Organization, 1992) criteria for Major Depressive Disorder (code F33) diagnosis are based on a number of characteristics, defined as a disorder characterized by melancholic feelings of grief or unhappiness: a melancholy feeling of sadness and despair; a mental condition marked by ongoing feelings of sadness, despair, loss of energy, and difficulty dealing with normal daily life; feelings of worthlessness and hopelessness, loss of pleasure in activities, changes in eating or sleeping habits, and thoughts of death or suicide.

Regardless of whether the DSM-V or ICD-10 criteria are used, depression is diagnosed using a semi-structured interview that determines the length of time mood disturbance was present, the severity of the disorder, and whether suicidal ideation is present at the time of assessment (Ceccarini et al., 2014). For research purposes, often a validated depressive symptom scale is administered, which has pre-specified thresholds for probable depression diagnosis; no diagnosis can be made however without a structured diagnostic interview by a registered healthcare professional (i.e., clinical psychologist or psychiatrist).

Burden of Depression

Globally, approximately 20% of CVD patients have depressive symptom levels similar to those meeting criteria for Major Depressive Disorder (Thombs et al., 2005). In the general population, rates of depression are roughly one-quarter to one-third less prevalent, with estimates around 3-5% (Cohen, Edmondson, & Kronish, 2015). Here in Canada, the rates of depression in the general population are similar to those globally at 3-5%; in cardiac patients, those rates increase to almost one-third of CVD patients (Marzolini, Leung, Alter, Wu, & Grace, 2013).

Globally, incidence of comorbid depression and CVD are rising, such that the World Health Organization (WHO) predict that by the year 2020, both CVD and depression will be the two major causes of disability-adjusted life years (Reddy, 2010). Depression and CVD are so commonly linked, and so closely associated with poorer cardiac outcomes, the American Heart Association issued a 2014 Scientific Statement recommending that depression be elevated to the status of a risk factor in acute coronary syndrome survivors (Hazinski et al., 2015).

Effect of Comorbid Depression in CVD Patients

Individuals with both CVD and depression have greater functional declines, impaired quality of life, and increased morbidity and mortality compared to patients with either CVD or depression alone. An

estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths (P. M. Davidson et al., 2016). In patients with CVD, mortality is twice as high in patients with comorbid depression compared to those who do not (van Melle et al., 2008). From an economic standpoint, the increased morbidity and mortality cause an increased burden on the health care system, creating an increased demand for resources caused by increased visits to emergency departments, decreased bed availability, and higher amounts of surgical and pharmacological intervention over the life span of the patient (Barth, Härter, Paul, & Bengel, 2005). Therefore, it is important to detect and address depression in CVD patients from both a health and economic standpoint.

Mechanisms Linking Depression and CVD

Depression and CVDs are linked by both behavioural and biological mechanisms. With regard to the former, certain behaviors in depressed patients contribute to the progression of coronary disease. These include poor diet, lack of exercise, poor medication adherence, and tobacco use (Huffman et al., 2014). Psychosocially, depressed CVD patients have decreased ability to deal with life stressors, and a smaller support network (Berkman et al., 2003). This constellation of behavioural and psychological symptoms causes an individual to be more likely to display sedentary behavior, poor coping skills, unhealthy dietary habits, and decreased ability for tobacco use or alcohol cessation(WHO, 2000).

On a physiological level, depression is linked to CVD by a number of factors. Compared with nondepressed individuals, depressed patients with CVD often have higher levels of biomarkers found to predict cardiac events or promote atherosclerosis (Huffman et al., 2016; C J Lavie et al., 2008). Although not always consistent, several studies in depressed patients with coronary artery disease have reported reduced heart rate variability (suggesting increased sympathetic activity and/or reduced vagal activity), evidence of hypothalamic-pituitary-adrenal axis dysfunction, increased plasma platelet factor and alpha-thromboglobulin (suggesting enhanced platelet activation),impaired vascular function, and increased C-

reactive protein, interleukin-6, intercellular adhesion molecule-1, and fibrinogen levels (suggesting increased innate inflammatory response) (Zhang, 2015).

Treatment Of Depression In CVD

The major evidence-based therapies for depression are psychotherapy and antidepressant medications. These have been tested and shown efficacious in CVD patients as well. With regard to psychotherapy, the most effective form for depression has consistent been cognitive behavioral therapy (Berkman et al., 2003; Hare, Toukhsati, Johansson, & Jaarsma, 2014). Cognitive behavioral therapy (CBT) is a type of talking therapy (psychotherapy) that assumes that maladaptive thinking patterns cause maladaptive behavior and "negative" emotions. Maladaptive behavior, in this context, is behavior that is counterproductive or interferes with everyday living. The treatment focuses on changing an individual's thoughts (cognitive patterns) in order to change his or her behavior and emotional state (Sniehotta et al., 2005). Trials of CBT in CVD patients have shown moderate reductions in depressive symptoms can be achieved, as first demonstrated in the ENRICHD trial (Berkman et al., 2003). Other forms of psychotherapy have been infrequently tested in CVD patients. A trial of interpersonal psychotherapy (IPT) showed no beneficial effect (Lespérance et al., 2007); problem-solving therapy, on the other hand, has recently shown considerable promise (K. W. Davidson et al., 2013).

Furthermore, a large Cochrane review from 2011 focusing on the seminal work on depression and cardiac disease has found that though evidence-based treatments are efficacious for depression, they may not act to necessarily resolve all of the patients' change in psychomotor or emotional functioning, including deficits in motivation, memory, and cognition. Residual effects from the depression may still be present, quality of life increases were inconclusive, and most strikingly, there was no improvement with respect to cardiac events and cardiac hospitalizations even in patients with the greatest reductions in depressive symptoms (Baumeister, Hutter, & Bengel, 2011).

While antidepressant therapy will be considered in more detail below, many patients with moderate to severe depression may respond better to the combination of an antidepressant and psychotherapy (combination therapy) than to either treatment alone (Hare et al., 2014). In clinical practice, the duration and frequency can be customized by the treating therapist to meet the individual needs of the patient; some patients may prefer and do well with a less intensive regimen. Moreover, many therapeutic trials for depressed CVD patients have been applying stepped, collaborative care approaches (K. W. Davidson et al., 2013; Huffman et al., 2014). These treatments have been associated with moderately improved depression scores and better cardiac prognosis, though depression treatments have not been found to account for all of the increased risk of cardiac events in CVD patients (J. H. Lichtman et al., 2014).

Antidepressants

Due to greater accessibility, pharmacotherapy is often the mainstay of the medical management of Major Depressive Disorder. Table 1 lists the major classes of antidepressants, along with examples of medications in each class, along with clinical recommendations for CVD patients. These are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Each are described in turn, below.

In the 1980s, pharmacologic treatment was limited to TCAs and MAOIs; both TCAs and MAOIs are referred to as traditional or first-generation antidepressants. These drugs are often accompanied by multiple side effects that many patients find intolerable; e.g., TCAs tend to cause anticholinergic effects including dry mouth and eyes, urinary hesitancy, and sometimes fluid retention and constipation; MAOIs have the potential to produce hypertensive crisis if taken along with certain foods or dietary supplements containing excessive amounts of tyramine (MacGillivray et al., 2003). Thus, first-generation antidepressants are no longer agents of choice in many circumstances (Stephen Waring, 2010).

After the 1980s, newer treatments were developed, including SSRIs, SNRIs, and other second-generation drugs. The first of the second-generation drugs was introduced to the US market in 1985, when bupropion (a so-called "atypical") was approved for the treatment of major depressive disorders. In 1987, the US Food and Drug Administration (FDA) approved the first SSRI, fluoxetine. Since then, five other SSRIs have been introduced: sertraline (1991), paroxetine (1992), citalopram (1999), fluvoxamine (2000), and escitalopram (2002). The SNRIs were first introduced to the market in 1993 with the approval of venlafaxine. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), was approved for the treatment of major depressive disorder in 2004 (Khawaja, Westermeyer, Gajwani, & Feinstein, 2009; Stephen Waring, 2010).

The mechanism of action of most second-generation antidepressants is poorly understood. In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. The SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) act by selectively inhibiting the reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) at the presynaptic neuronal membrane. The SNRIs (desvenlafaxine, venlafaxine) are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as an SNRI and other times as an atypical, is believed to enhance central noradrenergic and serotonergic activity as a 5-HT2 and 5-HT3 receptor antagonist. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine. Preclinical studies of duloxetine suggest that it is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake (Knadler, Lobo, Chappell, & Bergstrom, 2011).

Effects of Antidepressants on Symptom Reduction and Clinical Outcomes in CVD Patients

There have been 9 major trials of depression treatment in CVD patients; of which 6 administered antidepressants. Each of the later trials is described below, with a particular focus on the effects on MACEs including death.

In 2007, a Canadian Randomized Clinical Trial titled Cardiac Randomized Evaluation of Antidepressant and Therapy Efficacy (CREATE) was conducted via St. Michael's Hospital in Toronto (Lespérance et al., 2007). The study was a randomized, controlled, 12-week, parallel-group trial conducted May 1, 2002, to March 20, 2006, among 284 patients with CAD from 9 Canadian academic centers. All patients met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for diagnosis of major depression of 4 weeks' duration or longer and had baseline 24-item Hamilton Depression Rating Scale (HAM-D) scores of 20 or higher. The study looked at depressed patients with coronary artery disease in a 2 x 2 design (that is, Citalopram (SSRI) vs placebo compared to IPT vs placebo). The rationale behind using IPT in comparison to CBT as the form of psychotherapy offered was that IPT for depression is a form of psychotherapy that focuses on the relationships between a person and significant others. It is based on the idea that humans, as social beings, have their personal relationships at the center of psychological problems. This aspect of IPT would have addressed the realities of living with CAD for the patients involved, and emphasized the contribution of a social network to psychosocial components of depression. Also, IPT's incorporation of social networks would have mitigated the effect of social isolation on patients; lack of social support had previously been linked to increased morbidity and mortality for patients. The results demonstrated that citalopram was superior to placebo in reducing 12-week HAM-D scores (mean difference, 3.3 points; 96.7% confidence interval [CI], 0.80-5.85; P = .005), with a small to medium effect size of 0.33. Mean HAM-D response (52.8% vs 40.1%; P = .03) and remission rates (35.9% vs 22.5%; P = .01) and the reduction in Beck Depression Inventory (BDI-II) scores (difference, 3.6 points; 98.3% CI, 0.58-6.64; P = .005; effect size = 0.33) also favored citalopram. There was no evidence of a benefit of IPT over clinical management, with the mean HAM-D difference favoring clinical management (-2.26 points; 96.7% CI, -4.78 to 0.27; P = .06; effect size, 0.23). The difference on the BDI-II did not favor clinical management (1.13 points; 98.3% CI, -1.90 to 4.16; P = .37; effect size = 0.11). To conclude, the authors found that based on the results,

citalopram or sertraline plus clinical management should be considered as a first-step treatment for patients with CAD and major depression instead of IPT or other psychosocial skills management techniques.

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study was a multicenter randomized clinical trial of 2,481 post-MI patients (ENRICHD Investigators, 2001). Subjects met criteria DSM-IV criteria for major depression, minor depression with history of major depression, or met certain criteria on a social support instrument. The primary endpoint was cardiovascular mortality and non-fatal recurrent MI. Intervention involved 6 group sessions of cognitive behavioral therapy over 6 months, followed by open group membership, with SSRI use also allowed for unremitting or severe depression in both groups. The intervention did not increase event-free survival after 29 months (75.8% vs 75.9%). Also no differences in mortality or infarction in any of the subgroups (e.g. those isolated and depressed). There were, however, significant improvements in depression and social support among intervention participants. Though some benefits were seen, lack of benefits across all outcomes may be due to improvements in depression and social support that also occurred in the usual care group, as well as high SSRI use in both groups. Though the trial demonstrated that a combination of short-term individual CBT and a selective serotonin reuptake inhibitor , when needed, was significantly better than usual care (referral to a psychologist after a brief screening on-site, followed by antidepressant therapy as required) at reducing depressive symptoms over 6 months in depressed or socially isolated myocardial infarction patients, the effect size was small. The study ultimately failed to show that the ENRICHD treatment protocol was better than usual care in preventing all-cause mortality and recurrent myocardial infarctions. A follow-up, post-hoc analysis demonstrated positive changes (per 1 point increase) in somatic depressive symptoms (HR: 0.95; 95% CI: 0.92–0.98; p =0.001) but not in cognitive depressive symptoms (HR: 0.98; 95% CI: 0.96–1.01; p =0.19) were related to a reduced risk of recurrent MI and mortality after adjustment for baseline depression scores. After controlling for demographic and

clinical variables, the association between changes in somatic depressive symptoms and event-free survival remained significant in the intervention arm (HR: 0.93; 95% CI: 0.88–0.98; *p* =0.01) only (Roest et al., 2013).

The Sertraline Anti-Depressant Heart Attack Randomized Trial (SADHART) was a randomized controlled trial examining pharmacological treatment versus placebo in 369 patients with either unstable angina or myocardial infarction and comorbid major depressive disorder (Glassman et al., 2002). The trial was double-blind and placebo-controlled, and patients received either sertraline (an SSRI) or a placebo for 16 weeks after all patients were given a placebo for the initial two weeks. The analysis divided the patients to examine a more severely depressed subgroup with higher Hamilton Depression Inventory (HAM-D) scale scores at baseline, and with history of 2 or more recurrent major depressive disorder episodes. The primary (safety) outcome measure was change from baseline in left ventricular ejection fraction; secondary measures included surrogate cardiac measures and cardiovascular adverse events, as well as scores on the HAM-D scale and Clinical Global Impression Improvement scale (CGI-I) in the total randomized sample. Among all patients, a repeated-measures analysis found sertraline to be significantly superior to placebo on the CGI-I scale measured over 24 weeks, but not on the HAM-D scale, which was obtained over 16 weeks. In the 2 recurrent depression groups, sertraline was significantly superior to placebo on both the CGI and HAM-D measures. In all groups, responder status using the standard criteria of CGI-I score of 1 or 2 (very much or much improved) was achieved at end point by significantly more patients treated with sertraline than with placebo. However, there was no difference between groups on endpoint measure of number of urgent cardiac events in the sertraline-treated group versus the placebo group.

The Myocardial Infarction and Depression Intervention Trial (MIND-IT) was conducted in 2007 as a prospective multicenter study, where 2177 MI patients were evaluated for depressive disorder during the first year post-MI (Honig et al., 2007). Ninety-one patients who met the DSM-IV criteria for major or

minor depressive disorder were randomized to a 24-week, double-blind, placebo-controlled trial. The antidepressant studied in this trial was Mirtazapine, a noradrenergic and specific serotonergic antidepressant that is used primarily in the treatment of depression. It is also commonly used as an anxiolytic, hypnotic, antiemetic and appetite stimulant. In terms of structure, mirtazapine can also be classified as a tetracyclic antidepressant (TeCA), which leads to this drug being classified as either an atypical antidepressant as well as, occasionally, a TCA (though it is only structurally-related to the TCA family). The primary outcome was reduction in depressive symptomatology on the 17-item Hamilton-Depression Rating Scale (Ham-D), and secondary outcomes were the BDI-II and depression subscale of the Symptom Check List 90 items (dSCL-90) as well as the Clinical Global Impression scale. The trial found that, using the "last observation carried forward" method, mirtazapine did not show to be superior to placebo on the Ham-D, but did on the BDI, dSCL-90, and CGI scales over the acute treatment phase of 8 weeks (*n* = 91). Using mixed models analysis over the entire 24 weeks of treatment (*n* = 40), they found a significant difference favoring mirtazapine to placebo on the Ham-D, BDI, and CGI, but on the dSCL-90, this difference was not significant. In conclusion, the authors demonstrated efficacy of mirtazapine on primary and secondary depression measures, and established that mirtazapine seems to be safe in the treatment of post-MI depression.

The Montreal Heart Attack Readjustment Trial (M-HART) was a randomised, controlled trial to assess whether psychological distress screening-related improvement in cardiac prognosis for men and women recovering from MI, as reported in previous literature, could be replicated using a screening program (Frasure-Smith, 1995). This study examined whether the program would reduce 1-year cardiac mortality for women and men. This trial consisted of 1376 post-MI patients (903 men, 473 women) assigned to the intervention program (n=692) or usual care (n=684) for 1 year. All patients completed a baseline interview that included assessment of depression and anxiety. Survivors were also interviewed at 1 year. Unfortunately, the program had no overall survival impact. Preplanned analyses showed

higher cardiac (9·4 *vs* 5·0%, p=0·064) and all-cause mortality (10·3 *vs* 5·4%, p=0·051) among women in the intervention group. There was no evidence of either benefit or harm among men (cardiac mortality 2·4 *vs* 2·5%, p=0·94; all-cause mortality 3·1 *vs* 3·1%, p=0·93). Therefore, the program's impact on depression and anxiety among survivors was small. The authors concluded that the results do not warrant the routine implementation of programs that involve psychological-distress screening and home nursing intervention for patients recovering from MI. The poorer overall outcome for women, and the possible harmful impact of the intervention on women, underline the need for further research and the inclusion of adequate numbers of women in future post-MI trials. Women are usually underserved in the CR community as there have been barriers to access to care; women are more likely to feel responsible for continuing to support their family members, even though they require individualized treatment. They are also less likely to adopt a "goal-driven" attitude towards fitness and lifestyle goals emphasized during CR, which may end up favoring outcomes for men instead of women.

In 2013, the Centralized, Stepped, Patient Preference–Based Treatment for Patients With Post–Acute Coronary Syndrome Depression (CODIACS) trial was published (K. W. Davidson et al., 2013), to provide evidence regarding conflicting reports concerning whether depression can be successfully managed after acute coronary syndrome (ACS) and whether it can be cost-effective. The trial design was a multicenter randomized controlled trial; patients were recruited from 2 private and 5 academic ambulatory centers across the United States. A total of 150 patients with elevated depressive symptoms (Beck Depression Inventory [BDI] score ≥10) 2 to 6 months after an ACS, recruited between March 18, 2010, and January 9, 2012. Patients were randomized to 6 months of centralized depression care (patient preference for problem-solving treatment given via telephone or the Internet, pharmacotherapy, both, or neither), stepped every 6 to 8 weeks (active treatment group; n = 73), or to locally determined depression care after physician notification about the patient's depressive symptoms (usual care group; n = 77). The change in depressive symptoms during 6 months and total health care

costs were evaluated, and the results determined that depressive symptoms decreased significantly more in the active treatment group than in the usual care group (differential change between groups, −3.5 BDI points; 95% CI, −6.1 to −0.7; P = .01). Although mental health care estimated costs were higher for active treatment than for usual care, overall health care estimated costs were not significantly different (difference adjusting for confounding, −$325; 95% CI, −$2639 to $1989; P = .78). The authors concluded that for patients with post-ACS depression, active treatment had a substantial beneficial effect on depressive symptoms and that this kind of depression care is feasible, effective, and may be cost-neutral within 6 months.

In 2010, the Coronary Psychosocial Evaluation Studies Randomized Controlled Trial (COPES) was launched to examine depressed patients with acute coronary syndrome (ACS) (defined as stable or unstable angina, urgent hospitalizations and revascularization) and their satisfaction levels with depression care (K. W. Davidson et al., 2010). A 3-month observation period to identify patients with ACS and persistent depressive symptoms was followed by a 6-month randomized controlled trial. From January 1, 2005, through February 29, 2008, 237 patients with ACS from 5 hospitals were enrolled, including 157 persistently depressed patients randomized to intervention (initial patient preference for problem-solving therapy and/or pharmacotherapy, then a stepped-care approach involving 80 patients) or usual care (77 patients) and 80 non-depressed patients who underwent observational evaluation, as a secondary control to the usual care group. The primary outcome was patient satisfaction with depression care. Secondary outcomes were depressive symptom changes (assessed with the Beck Depression Inventory), major adverse cardiac events, and death. At the end of the trial, the proportion of patients who were satisfied with their depression care was higher in the intervention group (54% of 80) than in the usual care group (19% of 77) (odds ratio, 5.4; 95% confidence interval [CI], 2.2-12.9 [P < .001]). The Beck Depression Inventory score decreased significantly more (t(155) = 2.85 [P = .005]) for intervention patients (change, -5.7; 95% CI, -7.6 to -3.8; df = 155) than for usual care patients (change, -

1.9; 95% CI, -3.8 to -0.1; df = 155); and the depression effect size was 0.59 of the standard deviation. At the end of the trial, 3 intervention patients and 10 usual care patients had experienced major adverse cardiac events (MACEs) (4% and 13%, respectively; [P = .047]), as well as 5 nondepressed patients (6%) for the intervention vs nondepressed cohort, [P = .49]). The authors concluded that improved depression care for patients with ACS was associated with greater satisfaction, a greater reduction in depressive symptoms, and an encouraging improvement in prognosis.

Another Randomized Controlled Trial (RCT), a study design which randomizes patients to either usual care (or placebo) compared to a treatment group without the participants knowing which group to which they belong, to look at psychosocial intervention in the management of secondary cardiovascular disease was titled The Secondary Prevention in Uppsala Primary Health Care Project (SUPRIM) (Gulliksson et al., 2007). The aim was to look at cognitive behavioural therapy and measure its effects on cardiovascular disease recurrence, given that psychosocial factors are independently associated with increased risk of cardiovascular disease. The study included 362 women and men (75 years or younger) who were discharged from the hospital after a coronary heart disease event within the past year. Patients were randomized to receive traditional care (reference group, 170 patients) or traditional care plus a CBT program (intervention group, 192 patients), focusing on stress management, with 20 two-hour sessions during 1 year. Median attendance at each CBT session was 85%. Outcome variables were all-cause mortality, hospital admission for recurrent CVD, and recurrent acute myocardial infarction. During a mean 94 months of follow-up, the intervention group had a 41% lower rate of fatal and nonfatal first recurrent CVD events (hazard ratio [95% confidence interval], 0.59 [0.42-0.83]; P = .002), 45% fewer recurrent acute myocardial infarctions (0.55 [0.36-0.85]; P = .007), and a nonsignificant 28% lower all-cause mortality (0.72 [0.40-1.30]; P = .28) than the reference group after adjustment for other outcome-affecting variables. In the CBT group there was a strong dose-response effect between intervention group attendance and outcome. During the first 2 years of follow-up, there were no

significant group differences in traditional risk factors. The investigators concluded that CBT intervention decreases the risk of recurrent CVD and recurrent acute myocardial infarction, which may have implications for secondary preventive programs in patients with coronary heart disease.

A recent RCT, The Management of Sadness and Anxiety in Cardiology (MOSAIC) Randomized Clinical Trial (MOSAIC) was published in 2014, looking at interventions for depression and anxiety associated with adverse cardiovascular outcomes in patients with recent acute cardiac events, given that there has been minimal study of collaborative care management models for mental health disorders in high-risk cardiac inpatients, and none have simultaneously managed depression and anxiety disorders (Huffman et al., 2014). This study aimed at determining the impact of a low-intensity CC intervention for depression, generalized anxiety disorder, and panic disorder among patients hospitalized for an acute cardiac illness. The design was a single-blind randomized clinical trial, with study assessors blind to group assignment, from September 2010 through July 2013 of 183 patients admitted to inpatient cardiac units in an urban academic general hospital for acute coronary syndrome, arrhythmia, or heart failure and found to have clinical depression, generalized anxiety disorder, or panic disorder on structured assessment. Participants were randomized to 24 weeks of a low-intensity telephone-based multicomponent CC intervention targeting depression and anxiety disorders (n = 92) or to enhanced usual care (serial notification of primary medical providers; n = 91). The CC intervention used a social work care manager to coordinate assessment and stepped care of psychiatric conditions and to provide support and therapeutic interventions as appropriate. The primary outcome measure was improvement in mental health–related quality of life (Short Form-12 Mental Component Score [SF-12 MCS]) at 24 weeks, compared between groups using a random-effects model in an intent-to-treat analysis. Patients randomized to CC had significantly greater estimated mean improvements in SF-12 MCS at 24 weeks (11.21 points [from 34.21 to 45.42] in the CC group vs 5.53 points [from 36.30 to 41.83] in the control group; estimated mean difference, 5.68 points [95% CI, 2.14-9.22]; P = .002; effect size, 0.61). Patients

receiving CC also had significant improvements in depressive symptoms and general functioning, and higher rates of treatment of a mental health disorder; anxiety scores, rates of disorder response, and adherence did not differ between groups. The study evaluated the use of a CC model and found that their telephone-based, low-intensity model to concurrently manage cardiac patients with depression and/or anxiety disorders was effective for improving mental health–related quality of life in a 24-week trial.

All of the studies summarized above give a wealth of information concerning depression in the CVD community: that all-inclusive screening, while effective, may not be worth the added cost and time required to screen every patient; that antidepressants are usually found to be more effective than either placebo or usual care, and that finally, though both antidepressants and psychosocial therapy (usually CBT) have been found to decrease depression and improve secondary outcomes and relapse events, it remains to be seen how much of an effect is conferred by the treatment, and how much either spontaneously resolves as the patient feels better, or how much benefit is conferred by attending a CR program model, which includes exercise as a core component.

Observational Data on the Effects of Antidepressant Use in CVD Patients – Morbidity and Mortality

As seen above, effects of psychosocial interventions on depression symptoms in patients with CVD have been modest and prone to confounding effects- furthermore, effects on morbidity and mortality have only been explored in recent trials. A meta-analysis of 36 studies involving 12,851 patients showed only a slight reduction in non-fatal MI and no reduction in cardiac mortality; however, many studies often had a negligible improvement in depression (Anderson & Taylor, 2014). However, in the CR setting, a meta-analysis of 23 randomized trials showed all-cause mortality to be 28% lower in those trials that included psychosocial interventions compared to those who did not (van Melle et al., 2008), but reduction in mortality seen only in those who effectively reduced psychological distress. Many of the

studies looking at mortality and morbidity rates in cardiac patients on antidepressants have been observational in nature; these are described in turn, below:

In 2014, researchers looked at antidepressants, autonomic function, and mortality in patients with coronary heart disease (Zimmermann-Viehoff, Kuehl, Danker-Hopfe, Whooley, & Otte, 2014). The data used was from a larger study titled the Heart & Soul Study. This study aimed to examine whether the use of TCAs or SSRIs was associated with mortality in patients with coronary heart disease, and to determine whether this association is mediated by autonomic function. A total of 956 patients with coronary heart disease were followed for a mean duration of 7.2 years. Autonomic function was assessed as heart rate variability, and plasma and 24-h urinary norepinephrine. Of 956 patients, 44 (4.6%) used TCAs, 89 (9.3%) used SSRI, and 823 (86.1%) did not use antidepressants. At baseline, TCA users exhibited lower heart rate variability and higher norepinephrine levels compared with SSRI users and antidepressant non-users. At the end of the observational period, 52.3% of the TCA users had died compared with 38.2% in the SSRI group and 37.3% in the control group. The adjusted hazard ratio (HR) for TCA use compared with non-use was 1.74 [95% confidence interval (CI) 1.12-2.69, p = 0.01]. Further adjustment for measures of autonomic function reduced the association between TCA use and mortality (HR = 1.27, 95% CI 0.67-2.43, p = 0.47). SSRI use was not associated with mortality (HR = 1.15, 95% CI 0.81-1.64, p = 0.44). The authors concluded that the use of TCA was associated with increased mortality. This association was at least partially mediated by differences in autonomic function; however, the findings suggest that TCAs should be avoided in patients with coronary heart disease.

In 2011, The Danish Heart Failure Clinics Network funded a study to look at whether pharmacologically treated depression was associated with increased mortality risk in systolic heart failure patients (O'Connor et al., 2010). Patients (n=3346) with systolic heart failure (left ventricular ejection fraction≤0.45) and primarily New York Heart Association (NYHA) classes II–III (78%) were recruited from a clinical database used in 20 heart failure clinics in Denmark. The association between

pharmacologically treated depression identified by at least one prescription of an antidepressant and mortality risk was evaluated. Follow-up time was 540 days (range: 30–1600 days), and 539 patients died over the time span. For 243 patients (7%) an antidepressant had been prescribed at least once. In a Cox Proportional Hazard Model, pharmacologically treated depression was associated with a 49% increased mortality risk (Hazard ratio: 1.49, 95% confidence interval: 1.03–2.16) after adjustment for traditional confounders. Three months after the baseline visit in the heart failure clinic, these patients received lower doses of beta-blockers than patients without antidepressant therapy (p=0.006). Female sex (p<0.001) and NYHA classes III–IV (p=0.007) were associated with the prescription of an antidepressant. Their results suggest that pharmacologically treated depression is associated with a 49% increased mortality risk, and that these high-risk patients receive lower doses of beta-blockers than patients with no antidepressant therapy.

Another study, from 2013, looked at whether depression and the use of antidepressants were related to long-term mortality in heart failure (Diez-Quevedo et al., 2013). Heart failure outpatients (n=1017) from a specialized tertiary unit in Spain were studied for a median follow-up of 5.4 years. Depressive symptoms were assessed using an abbreviated version of the geriatric depression scale. Survival rates during the study period (August 2001 until December 2010) and hazard ratios (HR) for mortality were adjusted by several demographic and clinical variables. Depressive symptoms were detected in 302 patients (29.7%) at baseline and 222 (21.8%) during follow-up; 304 patients (29.9%) received at least one prescription of antidepressants, mainly selective serotonin reuptake inhibitors (92.8%); 441 patients (43.4%) died. In a multivariate Cox proportional hazard model, depression was associated with an increased all-cause (HR, 1.39; 95% CI, 1.15-1.68), but not cardiovascular, mortality risk after adjustment for several demographic and clinical confounders. The use of any antidepressant was not independently associated with mortality (HR, 0.89; 95% CI, 0.71-1.13), but benzodiazepines showed a protective role (HR, 0.70; 95% CI, 0.57-0.87). On the contrary, fluoxetine prescriptions, but not

duration of fluoxetine treatment, were associated with increased mortality (HR, 1.66; 95% CI, 1.13-2.44). The authors concluded that depressive symptoms are associated with long-term mortality, but the use of antidepressants and benzodiazepines is safe regarding survival in HF patients, although further research is needed considering individual antidepressants separately.

Another study used data from the SADHART (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial mentioned above. Researchers tested the hypothesis that heart failure patients treated with sertraline would have lower depression scores and fewer cardiovascular events compared with placebo, given that depression is common among heart failure patients and is associated with increased hospitalization and mortality (Glassman et al., 2002). The SADHART trial was a randomized, double-blind, placebo-controlled trial of sertraline 50 to 200 mg/day versus matching placebo for 12 weeks. All participants also received nurse-facilitated support. Eligible patients were age 45 years or older with HF (left ventricular ejection fraction ≤45%, New York Heart Association functional class II to IV) and clinical depression (Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition criteria for current major depressive disorder). Primary end points were change in depression severity (Hamilton Depression Rating Scale total score) and composite cardiovascular status at 12 weeks. A total of 469 patients were randomized (n = 234 sertraline, n = 235 placebo). The mean ± SE change from baseline to 12 weeks in the Hamilton Depression Rating Scale total score was −7.1 ± 0.5 (sertraline) and −6.8 ± 0.5 (placebo) ($p < 0.001$ from baseline, $p = 0.89$ between groups, mean change between groups −0.4; 95% confidence interval: −1.7 to 0.92). The proportions whose composite cardiovascular score worsened, improved, or was unchanged were 29.9%, 40.6%, and 29.5%, respectively, in the sertraline group and 31.1%, 43.8%, and 25.1%, respectively, in the placebo group ($p = 0.78$). The authors concluded that sertraline was safe in patients with significant HF. However, treatment with sertraline compared with placebo did not provide greater reduction in depression or improved cardiovascular status among patients with HF and depression.

The final study that will be examined regarding antidepressant use and cardiovascular-related morbidity and mortality is one completed in 2009, predicated on the literature that indicated treatment with antidepressants may improve survival in cardiac patients (Fosbol et al., 2009). Guidelines recommend use of SSRIs; but knowledge of the prognostic effect of different classes of antidepressants is sparse. The authors studied 99,335 patients surviving first hospitalization for heart failure from 1997 to 2005. Use of medication and antidepressants (divided into tricyclic antidepressants (TCA) and SSRI) was determined by prescription claims. Risk of overall and cardiovascular death associated with antidepressants, heart failure medication and co-administration of these two drug-classes was estimated by Cox proportional hazard analyses. Propensity adjusted models were performed as sensitivity analysis. In the study period there were 53,988 deaths of which 83.0% were from cardiovascular causes (median follow-up 1.9 years). Use of beta-blockers was associated with decreased risk of cardiovascular death (hazard ratio (HR)=0.77, 95% confidence interval (CI): 0.75-0.79). Antidepressants were prescribed to 19,411 patients, and both TCA and SSRI were associated with increased risk of overall and cardiovascular death (TCA: HR=1.33, CI: 1.26-1.40 and HR=1.25, CI: 1.17-1.32 and SSRI: HR=1.37, CI: 1.34-1.40 and HR=1.34, CI: 1.30-1.38, respectively). Co-administration of SSRI and beta-blockers was associated with a higher risk of overall and cardiovascular death compared with co-administration of beta-blockers and TCA (p for interaction <0.01). The authors concluded that use of antidepressants in patients with heart failure was associated with worse prognosis. Co-administration of SSRIs and beta-blockers was associated with increased risk of overall death and cardiovascular death compared with co-administration of TCAs and beta-blockers. To further clarify the interaction of SSRIs and beta-blockers (beta-blockers being commonly used in HF patients), clinical trials testing the optimal antidepressant strategy in HF patients are warranted. Though TCAs are contraindicated, there may be certain cases, such as with co-administration of beta-blockers, where TCA implementation may be

beneficial. However, this is currently based on limited evidence and would require much more testing before implementation could be undertaken.

Each of these studies has examined the effects of taking antidepressants on future MACEs. None of the studies have found the antidepressant treatments to be completely effective regarding MACE prevention; however, the utility of antidepressants is limited due to individual and environmental factors which may affect how well the antidepressant is working, as well as the side effect profile on an individual level. For patients for whom the antidepressants worked, certain studies seem to indicate that there is no reduction in morbidity and mortality compared to antidepressant non-users (Glassman et al., 2002; O'Connor et al., 2010); still other studies show that antidepressants have a relatively small advantage over non-use (Zimmermann-Viehoff et al., 2014); and finally, that certain classes of antidepressants may be associated with increased cardiac events (Fosbol et al., 2009). TCAs have been repeatedly shown to be cardiotoxic (Fosbol et al., 2009; Stephen Waring, 2010); however, co-administration with beta-blockers seems to decrease their lethality, as demonstrated in the 2009 study by Fosbol et al. At this point, antidepressants seem to generally be safe for cardiac patients, and this is true only for the SSRIs, as none of the other classes have been tested adequately, and TCAs may actually be harmful and thus, are contraindicated in this population. Interestingly, though SSRIs have been demonstrated to be relatively safe in cardiovascular patients, fluoxetine in particular has been associated with worse outcomes compared to other SSRIs (Diez-Quevedo et al., 2013). Future research is needed to further examine the major classes of antidepressants, as well as look at antidepressants individually for their effects on mortality and morbidity in cardiac populations.

Since guidelines for depression treatment in CVD patients have been created by many organizations, certain meta-analyses have recently been undertaken to determine if the guidelines can be improved, and what recommendations should be made, given the current body of literature on the subject. A large meta-analysis in 2013 completed by Thombs, et al., looked at whether or not the current American

Heart Association's guidelines for mandatory depression screening in cardiac patients should be revised in light of conflicting research. Depression treatment with antidepressants or psychotherapy generated modest symptom reductions among post-myocardial infarction (post-MI) and stable CHD patients (N = 6; effect size = 0.20–0.38), but antidepressants did not improve symptoms more than placebo in 2 heart failure trials (Diez-Quevedo et al., 2013; Taylor & Frasure-Smith, 1995). Depression treatment did not improve cardiac outcomes. The conclusion was that, given the modest evidence for non-heart failure cardiac patients, depression treatment only improved outcomes modestly; in heart failure patients, this benefit was negated. Since effects of treating depression are so small, the recommendation was that the American Heart Association's guidelines should be changed to reflect current literature, and the lack of evidence regarding the subject of depression screening (Thombs et al., 2013).

Another meta-analysis from 2013 performed by Rutledge, et al. , attempted to quantify the efficacy of mental health treatments- both pharmacological and psychotherapeutic- and cardiac rehabilitation treatments for improving event risk and depression in patients with coronary heart disease . The authors found that among patients with CVD, mental health treatments and CR may each reduce depression and CVD events, but only CR is effective in reducing total mortality. The results support a continued role for mental health treatments and a larger role for mental health professionals in CR.

As shown in both observational trials and meta-analyses, the research on antidepressant use and its utility in reducing excess mortality in depressed cardiac patients has shown modest benefit. Exacerbating the issue is that trials are often underpowered; observational studies looking at morbidity and mortality in depressed cardiovascular patients are often secondary analyses, and hence limited. Differences in antidepressants and classes may affect morbidity and mortality; however, the effects have been indistinguishable through current data. The randomized, controlled trials have, as yet, not focused entirely on cardiac events and mortality, and the observational data seems to indicate that antidepressant use can be associated with higher depression and increased incidence of MACEs.

Data on the use of antidepressants in patients with coronary heart disease are limited. With regard to choice of agent, SSRIs are the recommended class in CVD. The SSRIS sertraline and citalopram specifically are the first-line antidepressant drugs for patients with CVD. They are generally well-tolerated, effective and safe to use in patients with CHD when appropriate precautions are taken. Sertraline is safe post-MI and considered the drug of choice in these patients. Citalopram is associated with dose-dependent QT interval prolongation and is contra-indicated in patients with known QT interval prolongation. It is also cautioned in patients at higher risk of developing Torsades de Pointes (Lichtman et al., 2008).

SNRIs, due to being understudied in CVD patients, are not recommended as first-line therapy; however, their use is not necessarily contraindicated. Research suggests using SNRIs with caution, and that monitoring and follow-up are required for cardiac patients on this class of medications (Khawaja et al., 2009; Roest et al., 2013).

TCAs are best avoided in patients with CHD and are contraindicated in patients who have had a recent MI. TCAs are viewed as highly cardiotoxic in overdose and may therefore worsen outcome in CHD patients. Mirtazapine (an SNRI) is a suitable alternative in CHD if SSRIs cannot be used but it should be used with caution. There is evidence of safety post-MI (Stephen Waring, 2010; Taylor & Frasure-Smith, 1995).

Patients with recurrent depression who previously tolerated and responded well to another antidepressant may resume taking that agent instead, unless it is now contraindicated. For example, TCAs and MAOIs are contraindicated for many patients with heart disease because of their cardiotoxic side effects (Waring, 2010).

Antidepressant Initiation and Monitoring

When pharmacological treatment is initiated, patients should be observed closely for the first 2 months and regularly thereafter to monitor suicidal risk, ensure medication compliance, and detect and manage adverse effects. Approximately 15% to 25% of patients stop their antidepressants during the first 6 months of treatment because of adverse effects or lack of efficacy (Grace et al., 2008; Khawaja, Westermeyer, Gajwani, & Feinstein, 2009).

Initially, a starting dose should be prescribed and titrated, where necessary, up to the recognised minimum effective dose. SSRIs, mirtazapine and venlafaxine (SNRI), and atypicals moclobemide and reboxetine are often effective at the starting dose and titration may be unnecessary. Lower starting doses should be considered for patients with CVD. General principles in cardiac disease are that polypharmacy should be avoided where possible, particularly with drugs likely to affect cardiac rate and electrolyte balance, to be aware of QT prolongation is and to be careful with drugs likely to increase QT interval; to avoid drugs that are specifically contraindicated, and finally, to avoid rapid escalation while monitoring the patient closely (Zemrak & Kenna, 2008).

Although antidepressant use has been associated with both increased and decreased cardiac risk in some epidemiological studies, randomized clinical trials have demonstrated that 2 selective serotonin reuptake inhibitor antidepressants, sertraline and citalopram, are safe for patients with CVD and effective for reducing moderate, severe, or recurrent depression (Glassman et al., 2002; Honig et al., 2007; Lespérance et al., 2007; Samartzis et al., 2013). Nonrandomized, post-hoc analysis of the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study revealed that patients treated with an SSRI, whether assigned to receive cognitive behavioral therapy or usual care, had a 42% reduction in death or recurrent MI as compared with the depressed patients not receiving an antidepressant (Roest et al., 2013). Given that SSRI treatment soon after acute MI appears safe, is relatively inexpensive, and may be effective for post-acute-MI depression, it may be a viable option for these patients. Not only does treatment improve mood and quality of life, but studies have shown that

depression interferes with compliance, and treatment of depressive symptoms may improve medication adherence in patients after acute MI (Khawaja et al., 2009).

Sertraline and citalopram are the first-line recommended antidepressant drugs for patients with cardiovascular disease. Patients with recurrent depression who previously tolerated and responded well to another antidepressant may resume taking that agent instead, unless it is now contraindicated. For example, TCAs and MAOIs are contraindicated for many patients with heart disease because of their cardiotoxic side effects (Waring, 2010).

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Many anti-depressants have poor adherence rates due to adverse effects. Though side-effect profiles vary from class to class of antidepressants, in general, weight gain, tiredness, poor concentration and decreased sexual function are main reasons why patients discontinue their medications, often without the advice of their doctor (Vanderkooy, Kennedy, & Bagby, 2002).

Depressive symptom reduction should be assessed after antidepressant initiation. Non-response at two to six weeks is a good predictor of overall non-response to a specific agent. If patients do not respond, a new agent may be tried. When switching antidepressants, a different SSRI or a better tolerated newer-generation antidepressant should be tried, followed if necessary by a trial of an antidepressant from a different class (Czarny et al., 2011; Stephen Waring, 2010).

When changing from one antidepressant to another, consideration should be given to the possibility of discontinuation reactions, potential loss of antidepressant effect, and the risks of

concomitant therapy. Cross-tapering is one method of switching, whereby the dose of the ineffective or poorly-tolerated medicine is slowly reduced while the new medicine is slowly introduced. Sometimes, cross-tapering is not necessary or advisable. Concomitant use of some antidepressants is contraindicated and a drug-free interval may be required after cessation to avoid clinically significant interactions (Czarny et al., 2011; Stephen Waring, 2010; Yekehtaz, Farokhnia, & Akhondzadeh, 2013).

Potential interactions with the SSRIs should be taken into account when prescribing in CHD. Recommendations are for people with depression who also have a chronic physical health problem to consider using sertraline as this has a lower propensity for interactions. Venlafaxine, an SNRI, is contraindicated in patients with an identified high risk of a serious cardiac ventricular arrhythmia or with uncontrolled hypertension. It should be used with caution in established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent MI). Venlafaxine is associated with a greater risk of death from overdose compared with other equally effective antidepressants (Waring, 2010).

Patients can be on antidepressants for long periods of time. Certain schools of thought indicate that as long as the patient has no trouble continuing the medication, and there are no adverse health effects due to the drug, that patients may be on antidepressants indefinitely (Czarny et al., 2011; K. W. Davidson et al., 2006; Zemrak & Kenna, 2008). Alternately, certain providers ascribe to the view that patients should be discontinued from antidepressants after no more than a few years of treatment, though this view is in the minority. Patients may be switched from one antidepressant to another due to side effects or improved efficacy, or antidepressants may be discontinued all together. When discontinuing an antidepressant, there is usually a taper period of 2-4 weeks; the dose is initially given at half strength for the first half of the taper, and then at quarter strength for the remainder of the taper period. If another antidepressant is to be initiated, preferred technique is to taper off of the first medication and taper on to the second. However, some clinicians will, in cases of severe depression,

abruptly discontinue the first medication and start the new one, though this method is not preferred (MacGillivray et al., 2003).

Rates of Use of Antidepressants in CVD Patients

A 2011 meta-analysis on rates of use of antidepressants was published by Czarny, et al., whose objective was to assess rates of antidepressant use or prescription to patients within a year of an acute coronary syndrome or cardiac hospitalization (Czarny et al., 2011). PubMed, PsycINFO, and CINAHL databases were searched; a total of 24 articles were included. The majority were from North America and Europe, and most utilized chart review or self-report to assess antidepressant use or prescription. Although there was substantial heterogeneity in results, overall rates of antidepressant use or prescription increased from less than 5% prior to 1995 to 10–15% after 2000. In general, studies from North America reported substantially higher rates than studies from Europe, approximately 5% higher among studies that used chart or self-report data. The authors concluded that antidepressant use or prescription has increased considerably, and that by 2005 approximately 10% to 15% of ACS patients were prescribed or using one of these drugs (Czarny et al., 2011).

Slightly lower values were found in an earlier, population-based study cross-sectional time series analysis in which antidepressant prescription data were obtained for elderly Ontarians from 1993 to 2002 who had experienced an MI, as well as for controls with no history of MI (Benazon, N. , Mamdani, M., Coyne, J., 2005). Since there had been a substantial increase in the prescribing of antidepressants on a population basis and in particular serotonin reuptake inhibitors (SSRIs), the authors examined how the prescribing of antidepressants to patients post–myocardial infarction (MI) changed in the decade 1993 to 2002, including the proportion accounted for by TCAs. Results were found that indicated that post-MI patients were more likely to receive an antidepressant relative to controls, with an overall odds ratio (OR) of 1.34; 95% confidence interval (CI), 1.29–1.38. However, with adjustment for the number of

medications received, post-MI patients were 20% less likely to receive an antidepressant relative to controls, adjusted OR = 0.81; 95% CI, 0.78–0.84. The proportion of antidepressants prescribed to post-MI patients accounted for by TCAs decreased, but the proportion of post-MI patients receiving a TCA remained stable at approximately 6%. In general, the conclusion states that increases in the prescription of antidepressants, and in particular SSRIs, to post-MI patients reflect general population trends- rather than being specifically due to treating post-MI depression.

Screening and Diagnosis of Depression in CVD Patients

Given the risks associated with depression in the context of CVD, screening is important, so depression can be identified and diagnosed. Screening refers to a strategy used in a population to identify the possible presence of an as-yet-undiagnosed disease in individuals without signs or symptoms. Diagnosis refers to the process of identifying the cause or disease process that matches the patient's symptoms. Screening for depression may aid in identification of depression, which can be difficult in those who have CVD, due to the CVD itself causing some cardinal depressive symptoms (e.g., sleep disturbance, social role impairment related to hospitalizations) (Gilbody, Sheldon, & House, 2008).

Several professional associations have published recommendations regarding depression screening in cardiac (or chronic disease) patients. Table 2 lists the main associations and their screening recommendations, with associated screening tool where screening is indeed recommended. Arguably, the most influential guidelines appear to be those issued by the American Heart Association. As shown, recommendations for screening (or for instrument, as discussed below) are not consistent (P. Tully, 2015). Indeed, some have suggested that there is no evidence to support screening in the context of CVD (Thombs et al., 2013; Ziegelstein, Thombs, Coyne, & de Jonge, 2009). Currently, research is underway to determine whether the screening in accordance with the AHA protocol is related to justifiably improved prognosis for those patients whose depression is identified and treated (K. W. Davidson, 2015).

With regard to recommended screening tool, the Patient Health Questionnaire-9 (PHQ-9) is now commonly accepted as the most sensitive and specific of all of the brief depression screeners (Hazinski et al., 2015; Smith et al., 2011). In the clinical setting, tools are required to be brief so that they can be easily administered by clinicians, easily scored, and are not too time-consuming. Clinicians often do not have a lot of time with their patients, especially in the primary care setting, and so the brevity of the screening tool is essential to whether the clinician would be more likely to administer it. Other screening tools, such as the Beck Depression Inventory (BDI) are associated with high sensitivity but slightly lower specificity (Kourkoveli et al., 2015). Other tests, such as the older PRIME-MD (the precursor to the PHQ), the Hamilton Depression Inventory (HAM-D), and Cognitive Behavioural Assessment Hospital Form (CBA-H), are no longer commonly-used, and the HADS (Hospital Anxiety and Depression Scale) is currently not recommended as an accurate screening tool (Ceccarini et al., 2014; Hare et al., 2014; P. J. Tully et al., 2015).

Indeed, the PHQ is considered one of the most reliable screening tools for depression, based on both sensitivity and specificity. The Patient Health Questionnaire (PHQ-2) (Ceccarini et al., 2014; Kurt Kroenke, Spitzer, & Williams, 2003) should first be administered (Appendix A, items 1-2). If the answer is "yes" to either or both questions, it is recommended that all 9 PHQ items (Appendix A, all items) be asked (K Kroenke et al., 2001).

The PHQ-9 is a brief depression screening instrument (Appendix).Most patients are able to complete it without assistance in 5 minutes or less. It yields both a provisional depression diagnosis (i.e., structured clinical interview required for formal diagnosis) and a severity score that can be used for treatment response monitoring. The PHQ-9 has been shown to have reasonable sensitivity and specificity for patients with CHD- PHQ-9 score ≥10 has a sensitivity of 88% and a specificity of 88% for major depression. PHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively. If patients screen as moderate to severe (- PHQ-9 score ≥10), they

should be referred to a psychiatrist for treatment initiation, or treatment may be initiated through the primary care physician, if preferred.

Current evidence indicates that only approximately half of cardiovascular physicians are aware of CVD in their patients, and roughly a third report that they treat depression in their patients; of those, about 70% do not use a validated screening tool (Feinstein, Blumenfield, Orlowski, Frishman, & Ovanessian, 2006), and not all patients who are recognized as depressed are treated (Barth et al.). Therefore, CR is an important setting for screening of depression. Indeed the major CR associations recommend screening for depression (see Table 2).

Cardiac Rehabilitation

CR is an outpatient chronic disease management program. These programs offer comprehensive secondary prevention strategies; patients are often seen for a couple of visits per week over several months. It is delivered by an interprofessional team, which may include a social worker or psychologist. Physical activity is a core component, and has beneficial effects on depressive symptoms (Scholz, Knoll, Sniehotta, & Schwarzer, 2006). Patients receive social support from health care providers and peers. Stress management is another core component, and often includes training in relaxation techniques which can also ameliorate depression. Finally, guidelines state that patients should be screened for depression in these programs (Herridge et al., 2005).

Since sedentary behavior is considered a risk factor for depression, it stands to reason that it also may contribute to depression- and that is exactly what studies have demonstrated (Hughes, Mutrie, & Macintyre, 2007; Samartzis et al., 2013). Fortunately, attendance in CR programs has therefore been demonstrated to have a mild reduction in exercise symptoms, and since exercise is a vital component of the CR model, exercise, independent of other CR components, has been proven to be efficacious at treating depression (Milani, Lavie, & Cassidy, 1996). Mechanisms of action revolve largely around up-regulation of dopamine (which, in depression, is in lowered concentrations in the nucleus accumbens

and limbic system, resulting in both dampened emotions and autonomic dysregulation). Increasing exercise via upregulation of dopamine ligand-gated receptor channels allows dopamine to remain in the intracellular synapse for a longer duration, thereby increasing its effects on the body. Similar mechanisms have been examined for serotonin and epinephrine; however, the greatest current challenge is that depression does not involve uniform neurotransmitter dampening within the synapse; instead, smaller areas are mediated by highly specific types of neurotransmitter receptors, receptor densities may fluctuate, and increasing dopamine and serotonin in certain areas of the brain may promote depressive symptoms (Dunlop et al., 2007). The complexity of the neuro-architecture is such that any of the evidence based treatments that work by specific physiological modulation, such as exercise, may address some aspects of depression very well, yet address others poorly (Lambert, Johansson, Ågren, & Friberg, 2000). However, due to its efficacy, though mild, exercise should be considered a first line recommendation in patients still within the acute grieving stage, which can be expected to recede 6-8 months post-event, or for very low levels of depression that can be managed by exercise alone.

Though the benefits of CR are its positive association with lowered depression (Milani & Lavie, 2007), oftentimes, adherence to CR programs is low (Blanchard et al., 2003). Depressed patients are doubly disadvantaged because depression can cause a lack of motivation on top of the main mood component; this makes going to participate in physical activity much harder to achieve. For patients who do complete CR, reductions in morbidity and mortality remain low, though risk factors tend to decrease dramatically as a result of finishing the CR program, much of which can be determined to be a product of the CR itself and not any associated antidepressant use, as noted above.

The guidelines set forth by the American Association of Cardiovascular Prevention and Rehabilitation includes recommendations for depression. They are to: initially, identify psychological distress as indicated by clinically significant levels of depression using interview and/or standardized

measurement tools (PHQ-9, BDI) and offer individual and/or small group education and counseling on adjustment to heart disease, stress management, and health-related lifestyle change. When possible, include family members, domestic partners, and/or significant others in these sessions, teach and support self-help strategies, and finally, arrange for ongoing management if important psychosocial issues are present.

Though screening is definitely important in identifying depressed individuals and referring them to appropriate treatment, it has yet to be determined whether mandatory screening is worth the expense to the healthcare system, and whether there is a risk of over-diagnosis of depression, leading to false-positive results and unnecessary treatments. However, research on screening is scarce: no RCTs have been conducted to determine whether screening is taking place, or whether it is effective. A current study looked at five journals, 3 of which determined that screening is taking place in the CR setting ranging from one-third to over two-thirds of individuals entering CR. Of those being screened, the remaining two papers determined that there was no significant difference in depression scores at follow-up between patients with higher rates of screening (Cahill, M.C., Bilanovic, A., Kelly, S., Bacon, S., & Grace, 2015).

Depression following major cardiac events is associated with higher mortality, so it has been surmised this can be reduced through CR and exercise training. Researchers evaluated the impact of CR on depression and its associated mortality in coronary patients by evaluating 522 consecutive coronary patients (381 men, 141 women; aged 64+/-10 years) enrolled in CR from January 2000 to July 2005 and a control group of 179 patients not completing rehabilitation. Prevalence of depressive symptoms decreased 63% following rehabilitation, from 17% to 6% (P <.0001). Depressed patients following rehabilitation had an over 4-fold higher mortality than nondepressed patients (22% vs 5%, P=.0004). Depressed patients who completed rehabilitation had a 73% lower mortality (8% vs 30%; P=.0005) compared with control depressed subjects who did not complete rehabilitation. Reductions in

depressive symptoms and its associated mortality were related to improvements in fitness; however, similar reductions were noted in those with either modest or marked increases in exercise capacity (Milani & Lavie, 2007). Follow-up studies by the same researchers led them to conclude that in patients following major coronary events, CR is associated with both reductions in depressive symptoms and the excess mortality associated with it. Moreover, only mild improvements in levels of fitness appear to be needed to produce these benefits on depressive symptoms and its associated mortality (C J Lavie et al., 2008; Carl J Lavie et al., 2015).

A study by Gordon, et al. determined whether patients who take antidepressants derived the same benefits from CR in terms of improvements in multiple risk factors (Gordon et al., 2013). A cohort of 26,957 CR patients constituted the study population, who were stratified into 3 cohorts (i.e., nondepressed, depressed unmedicated, and depressed medicated) at baseline according to a self-reported history of depression and the current use of antidepressants. Of these patients, 2,147 (41.5%) were taking antidepressants. Patients in the nondepressed cohort (49.4% completion) were more likely ($p < 0.001$) to complete the entire CR program than patients in the depressed unmedicated (44.5% completion) or depressed medicated (43.5% completion) cohorts. Patients in all 3 cohorts who completed the exit assessment in their CR program showed significant improvement in multiple risk factors. Additionally, the magnitude of improvement in blood pressure, serum lipids and lipoproteins, fasting glucose, weight, and body mass index was similar ($p > 0.05$) in patients taking antidepressants and those who were not. This study is therefore the first to demonstrate that antidepressants do not offset the average magnitude of improvement in multiple atherosclerotic risk factors that occurs with completion of a CR program (Gordon et al., 2013). This study underscores the benefits to cardiac patients that CR can provide, and that antidepressant therapy may not be accountable for much of the improvement that is seen from initiation to CR exit. However, exactly how much benefit CR provides to

the patient in terms of relief of depressive symptoms and decreased associated morbidity and mortality is still unclear.

Though depression is being recognized and treated in the CR setting, treatment modalities are far from ideal. While antidepressants have shown to be effective at relieving depression, but slightly less effective in decreasing the morbidity and mortality associated with cardiovascular disease, they are still the treatment of choice for many clinicians, especially in the primary care setting, where specialized knowledge of cardiology may be lacking (Khawaja et al., 2009). Antidepressants that patients were taking before entering a CR program are often just carried forward unless a specialist is aware of the contraindication of TCAs, or to switch from a less efficacious antidepressant (many of the atypicals) to an SSRI. Depression treatment with pharmacological agents, then, can result in conflicting modalities as research has not yet been clear as to which antidepressants are both efficacious and well-tolerated by the cardiac population. SSRIs certainly seem to be the best option, for now, but the literature is still scarce and relatively few studies have even looked at the administration of other classes of antidepressants (SNRIs, atypicals) to determine their suitability in this population (Benazon, Nili R., 2005; Mamdani, M, Coyne, M, 2005; Judith H Lichtman et al., 2008; Zimmermann-Viehoff et al., 2014). Complicating the picture is that the percentage of patients on antidepressants while in CR is not known, and is usually estimated based on the percentage of patients with moderate-severe depression while in CR; a figure that is approximately 15-30% .However, psychopharmacological agents are not the only choice for treatment. Psychotherapy is an option, and of the RCTs that have been conducted, CBT seems to be the modality of choice. Whether other types of psychotherapy work as well as CBT in cardiac patients can still be considered up for debate; very few studies have even looked at the effectiveness of different types of psychotherapy for depression in cardiac populations (Koszycki, Lafontaine, Frasure-Smith, Swenson, & Lespérance, 2004; Lespérance et al., 2007).

Since the literature on the three main types of depression treatment in cardiac settings (psychotherapy, pharmacotherapy, and CR) is mixed, and in some cases nonexistent, it is difficult at this time to draw firm conclusions on the effects on antidepressant use in CR patients that exhibit depressive symptoms. Furthermore, it is difficult to elucidate the effects of the CR program itself- exercise, additional social supports, and referrals for psychotherapy- compared to the effects of the antidepressants, on a number of domains: mood, risk factors for secondary cardiac events, the occurrence of further events, and mortality rates in the years following CR completion.

Objectives

The objectives of this thesis will be to describe and assess in a large cohort of CR participants: (1) changes in depressive symptoms from pre to post-program; (2) class of antidepressants used, in relation to evidence and clinical practice recommendations, (3) antidepressant adherence (i.e., proportion of days covered and cessation rates), (4) the association between depressive symptoms and antidepressant use, and (5) the association between antidepressant use, by class, and the occurrence of major adverse coronary events (MACEs) including death.

Since studies in this area, both RCTs and observational, have shown mixed effects on cardiac morbidity and mortality from depression treatments, whether psychopharmacotherapy is an effective treatment, and if so, which medication classes should be used. Gaps in the literature exist to determine which medications are the most efficacious in terms of both reducing depressive symptoms as well as the mortality and morbidity caused by depression, while still remaining safe in cardiac patients. This thesis, by way of the objectives outlined above, will examine antidepressant use, both by class and individually, and its effects on the number of MACEs experienced by patients over a 10 year post-CR follow-up period. Lastly, it will be only study in the literature to our knowledge to report on long term antidepressant adherence and outcomes in a cardiac population , as no studies to our knowledge have

examined the association between antidepressant use, across all the major, currently-used classes, and outcomes in CAD patients; this is particularly notable for including cardiac events , as most studies to date look at mortality only. The results of this paper will add more evidence to current literature on the effects that antidepressants may have on cardiovascular events, and the increased amount of concrete evidence regarding antidepressants and their role in treating depression in CVD patients along with their potential effectiveness against CVD-related outcomes may affect treatment recommendations and inform current guidelines on depression treatment in cardiac patients.

METHODS

DESIGN AND DATA SOURCES

This was an observational and prospective cohort study, undertaken as secondary analysis. Patients with CVD who entered the Mayo Clinic CR program in Rochester, Minnesota between the years of 2002 and 2012 will comprise the cohort. Clinical data from CR intake assessments were extracted. Patients were administered the PHQ-9 pre and post-program.

Medication and MACEs were ascertained through record linkage with the Rochester Epidemiology Project through to December 2014. This Project is a population-based record linkage system which 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(Melton, 1996). The study protocol was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Board.

SETTING

Residents of Rochester or Olmsted County, Minnesota, and the surrounding area are relatively distant from other large metropolitan health care institutions, and hence, the Mayo Clinic CR program serves most cardiac patients. The outpatient CR program is 12 weeks in duration, and patients attend three times per week for a total of 36 sessions. The program was based on the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines ("Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs, 5th Edition," n.d.).

Each CR session is approximately 60 minutes, of which 40 minutes is exercise time. All patients attend group stress management sessions; here, a video is presented which describes how stress affects the body, and techniques such as relaxation, exercise and deep breathing. Patients are also provided videos to take home addressing relaxation, tai chi/qigong, and mindfulness-based approaches to stress management.

The PHQ-9 (K Kroenke et al., 2001) is administered routinely to all patients at CR intake and discharge assessments. Staff discusses abnormal results with patients. Patients with pre-CR scores >5 are considered for referral to psychiatry; patients expressing suicidal ideation are provided an emergency consult. Psychiatrists may then prescribe pharmacotherapy or other treatments.

PARTICIPANTS

Inclusion criteria were patients 18 years of age or older, with a documented diagnosis of CVD, 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 CABG or PCI. In order to facilitate outcome assessment, an additional inclusion criterion was that patients were to be residents of Olmsted County, Minnesota. Patients who did not complete the post-CR PHQ-9 were excluded.

MEASURES

Most participant characteristics were obtained from the record linkage system. Clinical characteristics to be extracted include CR referral indication, comorbidities and cardiac risk factors. Sociodemographic characteristics will include ethnicity, age, and sex. Smoking history was obtained from the electronic medical record, based on self-report to a healthcare provider. The date of CR intake was recorded.

Medications were also available through the record linkage system. Psychiatric medications were extracted from 2001 to the end of 2014. Variables were computed to specify medication class (e.g., anti-depressant categories were five-fold: Selective Serotonin Re-uptake Inhibitors [SSRIs], Serotonin-Norepinephrine Re-uptake Inhibitors [SNRIs], TCAs, atypicals, and others [MAOIs]; other psychiatric medications [e.g., benzodiazepines, antipsychotics]). Proportion of days covered will also be computed (i.e., proportion of days in the measurement period the participant had filled a prescription for the medication, which is an indicator of medication adherence)(Ho, Bryson, & Rumsfeld, 2009), and whether the patients initiated the medication before, during or after CR.

Independent Variable

The PHQ-9 (Appendix A) is a multi-purpose instrument for screening, diagnosing, monitoring and measuring the severity of depression (K Kroenke et al., 2001), recommended for administration in cardiac samples (Judith H Lichtman et al., 2008). The tool assesses the criteria on which the diagnosis of depressive disorder is based (American Psychiatric Association, 1994). Response options for each item range from 0 “not at all” to 3 “nearly every day”, with greater scores reflective of greater symptomatology. It yields both a provisional depression diagnosis and a severity score (K Kroenke et al., 2001).

Major depression is considered if 5 or more of the 9 depressive symptom criteria have been present 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. Question 9 screens for the presence and duration of suicidal ideation and counts if present at all, regardless of frequency. A follow-up, non-scored question screens and assigns weight to the degree to which depressive symptoms have affected the patient's functioning.

PHQ-9 total scores range from 0 to 27. Cut-points of 5, 10, 15, and 20 represent the thresholds for mild, moderate, moderately severe, and severe depression, respectively (Gilbody et al., 2008). A single cut-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 (K Kroenke et al., 2001). The minimal clinically important difference (MCID) to be used for the analysis were 5 points or greater, as described by Lowe et al.(Lowe B, Unutzer J, Callahan CM, Perkins AJ, 2004).

Dependent Variables

Subsequent clinical events were ascertained using the record linkage system from the Rochester Epidemiology Project. MACEs included any of the following events: acute coronary syndrome (myocardial infarction [ICD-9, 410.x] or unstable angina [ICD-9, 411.x), coronary revascularization (Coronary Artery Bypass Graft [CABG; CPT/ICD-9 337700-337735/V45.81] surgery or Percutaneous Coronary Intervention [PCI; CPT/ICD-92980-92982/V45.82]), ventricular arrhythmias that required in-hospital management (ICD-9 427.X), or death from any cause. Mortality information was obtained directly from the REP, which records vital status from state vital statistics offices and the National Death Index. (St Sauver et al., 2012)

All outcome information were followed passively, through electronic ascertainment using diagnosis codes. A physician-investigator / co-author (JMI), who were blinded to baseline characteristics, will review 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 clinician expert / senior author (FLJ), with excellent inter-observer agreement.

STATISTICAL ANALYSES

First, the differences in sociodemographic and clinical characteristics of participants who were retained post-CR (i.e., completed PHQ-9 post-program) versus lost to follow-up were compared using t-tests or chi-square, as appropriate. To test the first objective, a descriptive examination of depressive symptoms pre and post-CR were performed in the retained sample, and a paired t-test were run. To test the second objective, anti-depressants use were described, and these were coded by class (i.e., SSRIs, SNRIs, TCAs, and atypicals). Further calculations include specifying whether antidepressants were used during CR specifically. To test the third objective, adherence to these antidepressants were operationalized by proportion of days covered. To test the fourth objective, associations between depressive symptoms and antidepressant use were calculated using t-tests, both independent samples and paired.

To test the last objective, Kaplan-Meier curves were generated, though hazard time was used instead of survival time to represent risk of MACE due to the possibility of multiple MACEs occurring. Finally, adjustment for covariates across the time-dependent model was computed via a Cox regression analysis, which tests the association between depressive symptom change and antidepressant use (independent variables) on MACE hazard risk, while adjusting for clinical characteristics which were significantly different between retained patients versus those lost to follow-up.

RESULTS

Respondent Characteristics

Overall, 1964 patients initiated CR during the period of study, of which 1266 (74.7%) completed the follow-up PHQ-9 and comprised the sample. Their characteristics are shown in Table 1. As shown, retained participants did not differ with regard to sociodemographic characteristics from those lost to

follow-up. However, retained participants were significantly more likely to be referred to CR for peripheral vascular disease, stroke, and heart failure, more often smoked, and had chronic kidney disease than those lost to follow-up. Moreover, retained participants had significantly lower depressive symptoms pre-CR and were more likely to be taking any anti-depressant than those lost to follow-up.

DEPRESSIVE SYMPTOMS- OBJECTIVE ONE

Mean depressive symptom scores, severity categorizations and provisional diagnoses based on the PHQ-9 scores pre and post-CR are shown in Table 2, as per objective one. As shown, most participants scored in the minimal range pre and post-CR. Women had significantly higher depressive symptom scores pre-CR (mean ± standard deviation=5.41±5.29 females vs 4.78±5.14 males, p=0.04), though not post (3.74±4.47 vs 3.49±4.40, p=0.35). All depressive symptom indicators decreased significantly from pre to post-program.

Overall, 220/1266 (17.4%) participants scored in the "elevated" range pre-CR (i.e. >10), and 125/1266 (9.9%) at post-test. Participants were categorized based on scoring above or below 10 on the PHQ-9 both pre and post-CR. Results showed that 984/1266 (77.7%) remained subclinical throughout CR, 115/1266 (9.1%) went from elevated to subclinical, 46/1266 (3.6%) went from subclinical to elevated, and 49 (3.9%) remained elevated.

Of participants with elevated depressive symptoms pre-CR, their mean PHQ-9 score post-CR was 7.30±6.36. Overall, 983 (77.6%) participants' PHQ-9 scores did not change either higher or lower than the MCID of 5 from pre to post-CR, but for 204 (16.1%) participants their scores decreased at least 5 or more, and for 79 (6.2%) their scores increased at least 5 or more.

ANTIDEPRESSANT USE- OBJECTIVE TWO

Overall, 446 (35.2%) participants were taking any psycho-pharmacological medication, with 278/446 (62.3%) taking more than one (mean 2.70±0.97 medications/patient; median=2). Significantly more women than men were on antidepressants (n=162, 39.3% women vs. n=271, 31.6% men, p<0.01).

Class of antidepressant used is shown in Table 3, as per objective 2. As shown, most participants were on SSRIs (most commonly citalopram 132 [10.4%], sertraline 101 [8.0%], and paroxetine 36 [2.8%]), followed by atypical antidepressants (most commonly trazodone 106 [8.4%], bupropion 72 [5.7%], and mirtazapine 31 [2.4%]), TCAs (most commonly amitriptyline 50 [3.9%], nortriptyline 39 [3.1%]; and trimipramine 7 [0.6%]), and SNRIs (only venlafaxine 54 [3.2%], and duloxetine 31 [1.8%]). No participants were on any other class of antidepressant (e.g., monoamine oxidase inhibitors). 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%), stimulants (n=5, 0.4%; e.g., modafinil n=5, 0.4%), and mood stabilizers (lithium n=3, 0.3%).

MEDICATION ADHERENCE- OBJECTIVE THREE

Participants were on their antidepressant for an average of 4.39±3.19 years during the period of study (objective 3). Of those taking the major classes of antidepressants, 33/62 (53.2%) stopped taking SNRIs, 153/299 (51.2%) stopped taking SSRIs, 80/179 (44.7%) stopped taking atypicals, and 38/102 (37.3%) stopped taking TCAs during the period of study. With regard to proportion of days covered, participants were most adherent to atypicals (72.4%), followed by TCAs (71.8%), SSRIs (71.7%), and finally SNRIs (68.5%). Degree of adherence to any class of anti-depressants was not significantly associated with post-CR depressive symptoms (all p>0.05).

DEPRESSION SYMPTOMS AND ANTIDEPRESSANT USE- OBJECTIVE FOUR

With regard to objective four, among the 220/1266 (17.4%) participants with elevated PHQ-9 scores pre-CR, 202/220 (91.8%) were on any antidepressant medication during CR, and this was significantly greater than among those without elevated scores (188/1046 [18.0%]; p<0.001). Moreover, among participants on any antidepressant during CR, their mean pre-CR PHQ-9 scores were 7.33±5.94, and post-CR scores were 4.69±4.87 (paired t=6.17, p<0.001; Figure 1). These scores were significantly higher than participants not on antidepressants both pre (4.98±5.20, p<0.001) and post-CR (3.57±4.43, paired t= 9.75, p<0.001).

MACES, AND THEIR ASSOCIATIONS WITH DEPRESSIVE SYMPTOMS AND ANTIDEPRESSANT USE

Overall, there were 264 patients who had any MACE. MACEs are shown in Table 3; as shown in the total column, one-fifth of participants had a MACE, and this was most frequently PCI, followed by angina and myocardial infarction. Moreover, 151/329 (45.9%) had more than one MACE, and these participants had a mean of 2.36±1.24 MACEs (median=2). The mean time to the first MACE from CR initiation was 392.21±421.74 days. For participants who died, the mean time to mortality was 457.29±467.71 days.

Greater pre-CR depressive symptoms were significantly associated with the occurrence of MACEs, 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 MACEs was significantly and positively associated with greater pre-CR depressive symptoms (r=0.10, p<0.01).

Proportion of days covered on any antidepressant class was not significantly associated with occurrence of any MACEs (all p>0.05), except for in those taking SSRIs (74.62±11.91% adherence in participants with any MACE vs 69.57±14.32% adherence in participants having no MACEs, p=0.02). Proportion of days covered on any class was not significantly associated with death (all p>0.05).

With regard to the final objective, occurrence of any MACE including death was significantly higher in participants taking any antidepressant at any time point (n=168/433, 38.8%) than participants

not taking an antidepressant (n=223/833, 26.8%; p<0.001). As shown in Table 3, use of antidepressants of any class was significantly associated with more MACEs. PCI in particular was more frequent among participants taking an antidepressant of any class when compared to participants not taking antidepressants from that class. Death was significantly more common among participants taking TCAs than those not taking TCAs. The number of ventricular arrhythmias was low, and hence results should be interpreted with caution. Myocardial infarction and heart failure were more common in participants taking SSRIs, and the highest proportion of MACEs overall occurred in participants taking this class of antidepressants. Overall, participants taking SNRIs had the least MACEs. There were no antidepressants used associated with significantly fewer MACEs.

Table 4 displays the Cox regression model of factors associated with time to first MACE. The overall model, which adjusted for depressive symptoms, was significant ($\chi 2=25.49$, $p<0.01$). As shown, over and above history of peripheral vascular disease and heart failure, use of TCAs was significantly related to greater MACE hazard. No other antidepressants were associated with MACEs in the adjusted model. A Kaplan-Meier survival curve displaying time to MACE by use of TCAs is shown in Figure 2.

Discussion

In a population-based cohort, this study has shown that participation in CR is associated with significant reductions in depressive symptoms, and these are clinically-significant reductions among those with elevated symptoms. Approximately one-third of cardiac patients were on an antidepressant, with almost half of these patients starting an antidepressant during CR. Most participants were taking the recommended class of antidepressants; but some patients were taking antidepressants which have not been well-studied in the CVD population (i.e., SNRIs), and unfortunately even which are often contraindicated in this population (i.e., TCAs). Patients were on their antidepressants for an average of four years, and took their medication about three-quarters of the time. One-third to one-half of

participants stopped taking an antidepressant during the period of study, depending on the class. While antidepressant use was associated with reductions in depressive symptoms, unfortunately use of TCAs specifically was associated with poorer cardiovascular outcomes, including death. MACEs occurred 93% sooner among patients on a TCA.

Almost one-fifth of CR participants had elevated depressive symptoms, which is consistent with what is reported in the literature. Use of antidepressants in this cohort (approximately one-third) was much higher however, than what has previously been reported in the literature (10-15%)(Thombs et al., 2005)(Czarny et al., 2011; Grace et al., 2008), although the review by Czarny et al. noted higher rates in the United States (from where this cohort stems), and increasing rates over time. Given depression has been historically under-recognized and treated, the results herein suggest symptoms are being detected and managed in accordance with the AHA recommendations (Lichtman et al., 2008); although there may be a trend toward over-prescribing (i.e., rates of use 10% higher than the average burden of depression of 20% in this population, and two-thirds taking more than one antidepressant [although combination augmentation strategies can increase remission]) (Moret, 2005). Adherence to therapy (Nwokeji et al., 2012), and discontinuation rates were consistent with what has been described in the literature (Geddes et al., 2003). This is one of the only studies in the literature to our knowledge to report on antidepressant adherence indicators in a cardiac population.

In accordance with clinical recommendations for CVD patients with depression, most participants were on first-line recommended therapy, namely SSRIs, or second-line therapies, namely atypicals (Bradley et al., 2015). While SNRIs are considered as potential second-line therapy for CVD patients, they are unstudied in this population (Bradley et al., 2015). While few patients were on SNRIs in the cohort and therefore lack of association could be due to low power, the results did suggest few MACEs in patients taking SNRIs. In fact, their safety profile was superior to the recommended first-line

therapy of SSRIs. Indeed, there has been some suggestion that SSRIs may not be as safe as previously described (Fosbol et al., 2009; Pacher & Kecskemeti, 2004).

While patients were given antidepressants and their treatment appeared to be managed in accordance with recommendations, the depression-mitigating effects of the patients' CR program, especially the exercise component, cannot be ignored. Since patients were assessed for depression at CR intake and exit, there was a roughly 3-month period during which patients were on a regimen of exercise and possibly antidepressants. A mean decrease of PHQ-9 scores from 4.98 to 3.57 during CR was observed overall; the decrease is relatively modest and may be attributable to increased exercise accompanying the CR program. However, looking at patients with "severe" depression, the proportion was more than halved from 2.5% of the depressed population to only 1.2%. Severe and refractory depression does not respond well to exercise-only therapies (Cooney et al., 2013; Mota-Pereira et al., 2011), so it is unlikely that the entirety of the reduction in depressive symptoms could be explained by exercise in CR. However, for the mild-to-moderately depressed cardiac patients, exercise may well be a useful intervention in lowering their depressive symptoms, and may have played a small role in depressive symptom improvement over the course of their CR program.

Use of TCAs in the cohort was associated with MACEs, as has been established in the literature (Bradley et al., 2015). Appropriately, rates of use were low, consistent with previous research (Zimmermann-Viehoff et al., 2014), and may have been in patients who were not early post-myocardial infarction or at risk of long QT, or who suffered severe depression and were non-responsive to SSRIs (i.e,. appropriateness cannot be ascertained from the data at hand). For patients who were on TCAs prior to CVD diagnosis, clinicians can taper the TCA, and either wait until it is finished, or slowly introduce an SSRI during the taper (British Columbia Public Health, 2013).

The mechanisms by which antidepressant classes may cause MACEs should be considered. TCAs have been well-established to cause arrhythmogenic events; most commonly, sinus tachycardia, brachial tachycardia, atrial fibrillation, and intraventricular conduction deficits. For this reason, the arrhythmia caused by TCAs is often severe in consequence (Fasoli & Glauser, 1981). Cardiac abnormalities are well known and understood with TCAs; essentially, TCAs are known to cause blockage of sodium through ion-gated channels responsible for the entire action potential and refractory period of a heartbeat. The increased extracellular sodium then causes hyperpolarization of the extracellular matrix, making an action potential less likely to occur with a given amount of positive ions inside the cell. The elongation of this timeframe, where sodium ions are slowly entering the cell but are somewhat blocked, is known as the QT interval and is the refractory period between action potential cycles (Pacher & Kecskemeti, 2004). Mechanism-wise, drug interactions may exacerbate certain conditions; for example, fluoxetine's long half-life is increased in heart failure patients, and bupropion causes increased blood pressure. Both of these medications end up elongating the QT interval and patients should be monitored closely for signs of MI.

None of the other antidepressant classes examined in this thesis has so far been associated with cardiotoxicity; however, a large number of non-fatal cardiac events were associated with SSRI usage (Table 3). No literature seems to discuss cardiac events in non-overdose cases (except Selective Serotonin Toxicity in overdose; the release of Serotonin through the CNS where it is mainly stored and potentially affecting QT intervals). In usual dose, risk of QT appears to be understudied in the literature. One study found that by electrocardiography, QT prolongation appears to be linked to SSRI use, and is similar to that seen in patients on TCAs; the main difference being the length of the QT prolongation as it is longer in patients on TCAs (Açikalin et al., 2010). In addition, citalopram, due to its increased risk of serotonin toxicity, is associated with dose-dependent QT interval prolongation and is contra-indicated in

patients with known QT interval prolongation or congenital long QT syndrome, according to the Canadian Network of Mood and Anxiety Disorders (Ramasubbu et al., 2012).

Results herein regarding poorer outcomes among CVD patients taking antidepressants are consistent with previous literature (which has been primarily in HF populations taking SSRIs) (Diez-Quevedo et al., 2013; Veien et al., 2011), although results are not consistent with all literature (Diez-Quevedo et al., 2013; Fosbol et al., 2009). For instance, the results herein are contrary to the findings by Connor et al., that the association between SSRI use and mortality was mitigated by depressive symptoms (Grace et al., 2008; MacGillivray et al., 2003; O'Connor et al., 2008); while our model adjusted for depressive symptoms, they were not significant. This incongruence could be explained by the fact that all patients in the current study participated in CR, which is associated with lower depression (Rutledge et al., 2013). In the Heart and Soul study, CVD patients more broadly were included (not just HF) as in the current study, and 2 classes of antidepressants were considered (not just SSRIs, but also TCAs). Similar to the findings herein, TCAs but not SSRIs were associated with increased mortality (Zimmermann-Viehoff et al., 2014). We could find no studies comparing MACEs in cardiac patients across each of the 4 of the major antidepressant classes, and hence again this study represents an important contribution to the literature. However, Rutledge et al. undertook a review of the effects of mental health treatments (a composite of psychotherapy and antidepressants) versus CR on MACEs(Rutledge et al., 2013). In his work, it was shown that treatment of depression, by any of these strategies including CR, was associated with significantly fewer MACEs. Again, in the current study we did not observe lower MACEs with use of any antidepressant class. The inconsistency between these findings is likely due to the capacity herein to focus on individual antidepressant classes, and the lack of consideration of psychotherapy.

Mechanisms

Lastly, it is worth mentioning that in all of the literature that currently exists regarding antidepressants, cardiac patients, CR, and MACEs, the commonalities appear to be that depression is an independent predictor of mortality and morbidity, that CR decreases depression symptoms by its multifaceted approach, and that a new strategy to look at this problem may be needed in order to elucidate the effects of specific factors (like antidepressants) on MACE events in cardiac patients, while considering the effects of confounders. So far, there has been no model that has been able to do that well. This study may be the first in the area to take a microscopic approach to a macroscopic system; looking at a large, complex issue made up of many sub-issues, and focusing only on a few small, specific factors that would be relevant to the gap in the literature that requires further study. A diagram is presented in Appendix D which displays the potential pathways from depression to CVD events in cardiac patients. Conceptually, these factors are so integrally related that the best course of action may be to untangle them from a very basic level; here we have decided to look at the pathway mediated by antidepressants and how pharmacotherapy might change CVD outcomes in a CR population.

Limitations

Caution is warranted in interpreting the results. First, with regard to design, this study lacked a control group who was not exposed to CR, and therefore history and maturation effects will not be able to be ruled out. Second, the design was observational, and hence causal conclusions were not able to be drawn. Third, as a secondary analysis, it was not be powered specifically for the current analysis.

Fourth, with regard to generalizability, it must be conceded it was limited as the data stems from a single center. However, the CR center is the only one available in the region, and therefore findings should be fairly representative of patients who attend CR in general. It is unknown how generalizable the results are to cardiac patients more broadly; however there are systematic referral processes in place at the Mayo Clinic for those with insurance coverage.

Fifth, there was some retention bias in the sample particularly that retained patients had less depressive symptoms and use of anti-depressants than those lost to follow-up. Sixth, with regard to measurement, there was no structured clinical interview. Therefore, no definitive diagnosis of depression can be inferred from the data. Seventh, multiple comparisons were undertaken to assess the associations between antidepressant classes and specific MACEs, and therefore some of the associations observed may be spurious. Finally, while all CR participants were exposed to stress management, use of psychotherapy, which is another evidence-based treatment for depression, was not known and therefore cannot be considered in the analyses. It is not captured at the Mayo Clinic CR program.

Conclusions

In summary, depression is successfully detected and managed in the CR setting, with patients generally being prescribed antidepressants in accordance with clinical practice guideline recommendations, and use of combination/augmentation strategies to optimize symptom reduction. Use of antidepressants was associated with lower depression, but often more adverse events. While not associated with MACEs in the adjusted model, the safety profile of SNRIs warrants further consideration; emerging evidence may warrant changes to prescribing recommendations in this population. Further research is also needed on approaches and impact of tapering CVD patients off TCAs.

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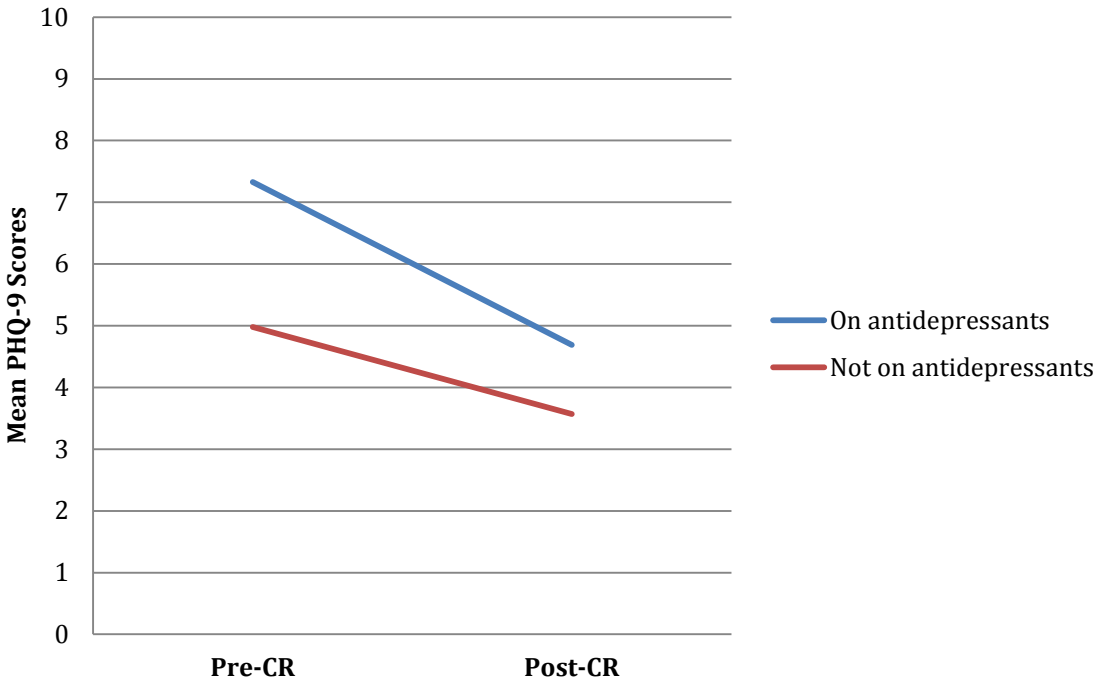
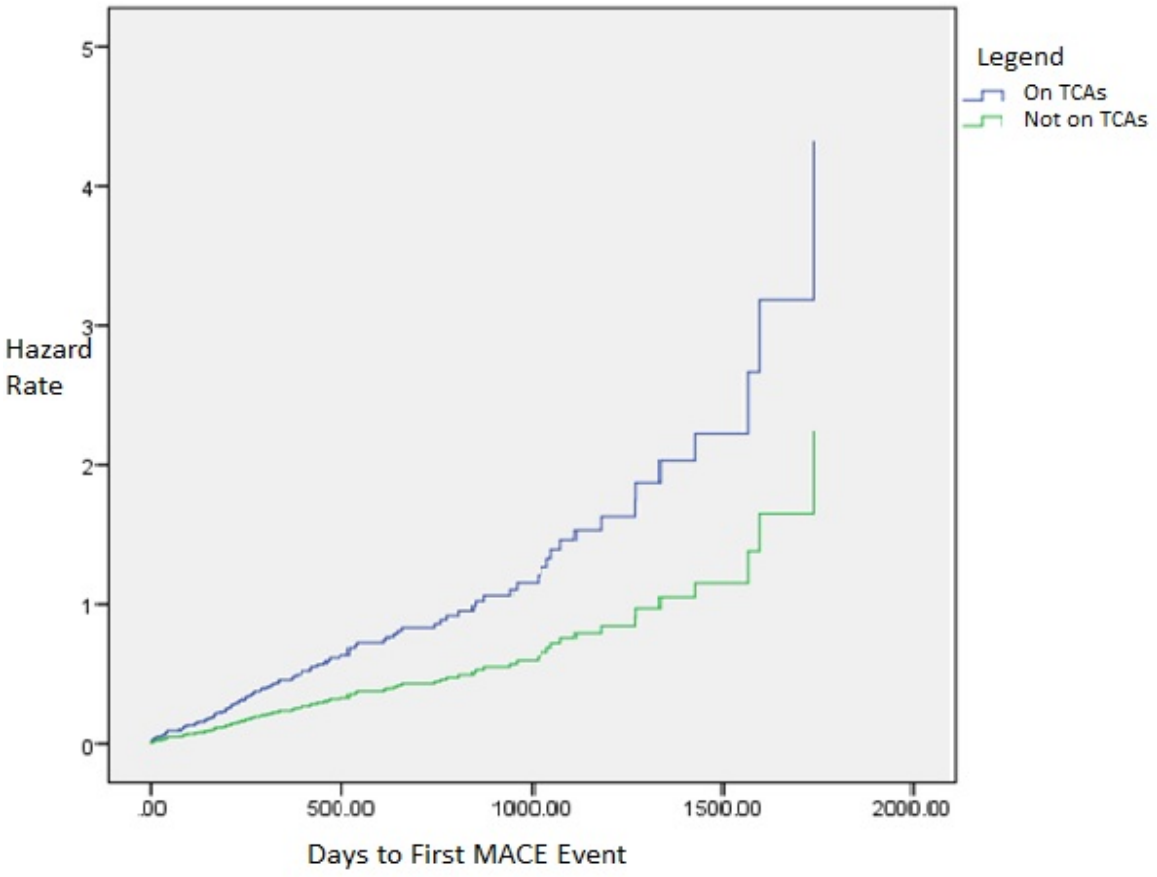
FIGURE 1. DEPRESSIVE SYMPTOMS PRE AND POST-CARDIAC REHABILITATION BY ANY ANTIDEPRESSANT USE.



Notes: t-test pre-CR p=<0.001; post-CR p=<0.001; ANOVA 2 (antidepressant status) x 2 (time), p<0.001.
PHQ=Patient Health Questionnaire; CR=cardiac rehabilitation.

FIGURE 2: KAPLAN-MEIER HAZARD RATES OF DEVELOPING ANY MAJOR ADVERSE CORONARY EVENT BY TRICYCLIC ANTIDEPRESSANT USE



TCA= Tricyclic antidepressants

TABLE 1. PARTICIPANTS' PRE-CR CLINICAL AND SOCIODEMOGRAPHIC CHARACTERISTICS BY RETENTION STATUS.

Characteristic	**Lost to Follow-Up n=428 (25.3%)**	**Retained Sample n=1266 (74.7%)**	**Total N=1694**
Sociodemographic			
Age, years (mean±SD)	65.22±12.32	63.89±12.88	64.23±12.75
Sex, (% female)	103 (24.1)	444 (33.3)	537 (31.7)
Race / ethnicity, (% white)	388 (90.7)	1191 (94.1)	1579 (93.2)
Clinical (% yes)			
Cardiovascular Indication			
Percutaneous Coronary Intervention	251 (58.6)	715 (56.2)	966 (57.0)
Peripheral Vascular Disease	121 (28.3)	443 (34.8)	564 (33.3)**
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)	1175 (92.8)	1569 (92.6)
Hypertension	302 (70.6)	936 (73.5)	1238 (73.1)
Diabetes	191 (44.6)	633 (49.7)	824 (48.6)
Smoking History	152 (35.5)	556 (43.7)	708 (41.8)**
Body Mass Index (mean±SD)	29.9±6.56	35.25±5.54	33.9±6.24
Comorbidities			
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 (mean± SD)	5.06±5.29	3.37±4.13	4.67±5.09***
Antidepressant Use (% yes)	140 (32.7)	433 (34.2)	573 (33.8)***

SD = standard deviation.
*p<.05; **p<.01; ***p<.001

Table 2. Depressive Symptoms pre and post-Cardiac Rehabilitation, N=1266.

	Pre-CR	**Post-CR**	**p**
Total PHQ-9 Score (mean±SD)	4.98±5.19	3.57±4.43	<.001*
Depressive Symptom Severity, n (%)			
Minimal (1-4)	758 (59.9)	907 (71.2)	<.001*
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‡, n (%)			
Major Depression	67 (5.3)	24 (1.4)	<.001*
Other Depressive disorder	24 (1.9)	67 (4.0)	<.001†

*paired t-test; †chi-square; ‡provisional based on PHQ-9 scoring.

CR=cardiac rehabilitation; SD=standard deviation; PHQ=Patient Health Questionnaire

TABLE 3. OCCURRENCE OF MAJOR ADVERSE CORONARY EVENTS BY ANTIDEPRESSANT CLASS.

	SSRIs n=299 (23.6%)	Atypical n=179 (14.1%)	TCAs n=102 (8.1%)	SNRI n=62 (4.9%)	**Total‡** N=1266§
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)*†	2 (2.0)	1 (1.6)	11 (0.9)
Any MACE, excluding death	105 (31.8)***	62 (18.8)**	38 (11.5)**	20 (6.1)	225 (17.8)***
Any MACE	122 (31.2)***	72 (18.4)**	46 (11.8)**	24 (6.1)	264 (20.9)***

Chi-square tests *p<.05; **p<.01; ***p<.001.

CR= Cardiac Rehabilitation; SSRI= Selective Serotonin Reuptake Inhibitors; TCAs= Tricyclic antidepressants; SNRIs= Serotonin Norepinephrine Reuptake Inhibitors.

†caution is warranted in over-interpreting this association, due to the small cell size.

‡*reported in this column reflect association of each MACE with use of any antidepressant (i.e., many participants on ≥1).

§number of MACEs overall.

TABLE 4. COX REGRESSION MODEL OF FACTORS ASSOCIATED WITH OCCURRENCE OF ANY MAJOR ADVERSE CORONARY EVENT INCLUDING DEATH

				95% CIs	
	Wald	p	Hazard Ratio	Lower	Upper
Peripheral Vascular Disease	4.74	.03	1.64	1.05	2.57
Stroke	0.32	.57	1.14	0.72	1.81
Heart Failure	6.10	.01	2.13	1.17	3.87
Chronic Kidney Disease	0.92	.34	1.43	0.69	2.97
History of Smoking	0.22	.64	1.11	0.73	1.67
Pre-CR depressive symptoms	0.30	.58	1.01	0.97	1.05
Tricyclic antidepressants	4.75	.03	1.93	1.07	3.49
Selective Serotonin Reuptake Inhibitors	1.26	.26	1.32	0.81	2.13
Serotonin-Norepinephrine Reuptake Inhibitors	1.75	.19	2.28	0.67	7.71
Atypical antidepressants	2.14	.14	1.42	0.89	2.29

CR= Cardiac Rehabilitation, CI=confidence interval.

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

(Use "✔" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

APPENDIX B- ANTIDEPRESSANT RECOMMENDATIONS IN CVD PATIENTS BY CLASS

Antidepressant Class	**Examples**	**Recommendations in CVD Patients**
SSRIs	Citalopram, Escitalopram,	Yes; first-line agents
SNRIs	Duloxetine, Venlafaxine	Yes; second-line only
Atypicals	Mirtazapine, Bupropion, Trazodone	Yes; second-line or adjunct
TCAs	Amitriptyline, Pretriptyline	No
MAOIs	Rasagiline, Isocarboxazid	No

SSRI= selective serotonin reuptake inhibitor; SNRI= serotonin-norepinephrine reuptake inhibitor; TCA= tricyclic antidepressants; MAOI= monoamine oxidase inhibitor.

(Yekehtaz et al., 2013)

APPENDIX C- DEPRESSION SCREENING TOOLS RECOMMENDED BY VARIOUS ASSOCIATIONS

Association	Screening Tool Recommendations	Citation
American Heart Association	PHQ-9 (Kroenke et al., 2001)*	(Judith H Lichtman et al., 2008)
American Association of Cardiovascular Rehabilitation and Prevention	BDI-2 (Ceccarini et al., 2014), PHQ-9	(Herridge et al., 2005)
National Heart Lung and Blood Institute	BDI-2, BDI-9 (Ceccarini et al., 2014)	(National Heart Lung and Blood Institute, 2016)
British Association for Cardiovascular Prevention and Rehabilitation	Screening recommended with appropriate tool (unspecified)	(Buckley et al., 2013)
International Collaboration in Cardiovascular Prevention and Rehabilitation	Screening recommended with appropriate tool (unspecified)	(Grace et al., 2013, 2016)
Irish Association of Cardiac Rehabilitation	No tool recommended	(Mccreery et al., 2013)
Canadian Association of Cardiovascular Prevention and Rehabilitation	PHQ-2	(CACPR, 2016)
European Society	No tool recommended	(Perk, De Backer, Gohlke, Graham, & Reiner,

of Cardiology		2012)
Australian Cardiovascular Health and Rehabilitation Association	Screening recommended with appropriate tool (unspecified)	(Woodruffe et al., 2014)

***Both the first instance of a screening tool has been cited, as well as each of the depression screening guidelines for cardiac patients.**

APPENDIX D- FROM DEPRESSION TO MACE IN CARDIAC PATIENTS: CONCEPTUAL DIAGRAM