Depression and Cardiovascular Disease: The Need for Improved Case Definition

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ABSTRACT:
Depression and cardiovascular disease are two of the leading causes of disability worldwide. Depression is an independent risk factor for the development of coronary heart disease and has been shown to be a negative prognostic indicator when it is present following acute coronary syndrome. Despite these clear associations the underlying mechanism(s) linking these disorders remains unknown. The challenge in elucidating pathophysiological mechanisms may lie in the heterogeneity of patients that meet the criteria for depression. Improved and measurement of depressive symptoms may lead to refined case definition in future research.

Key words: Depression, cardiovascular disease, comorbidity

Individuals with psychiatric disorders are well known to have an increased risk of morbidity and mortality as compared with the general population. Numerous factors likely contribute to this increased mortality, including suicide, sedentary lifestyle, poor diet, substance abuse, and poor access to adequate preventative health care (1). Epidemiological studies, however, point to a higher association between psychiatric disorders and cardiovascular disease than in the general population. This association remains poorly understood, and the strength of the association varies depending on which psychiatric population is being studied.

Depression and cardiovascular disease are two of the leading causes of isability worldwide according to the World Health Organization. In middle- to high-income countries, unipolar depression and cardiovascular disease represent the number one and number two causes, respectively, of disability-adjusted years lost (DALYs). Together they represent over 10% of the total burden of DALYs, and their impact on healthcare systems and society is significant. Understanding the interaction of these two disorders, therefore, remains an important area of research.

Depression has been identified both as an independent risk factor for the development of cardiovascular disease, and as a negative prognostic indicator in individuals with known cardiovascular disease (2). Many studies cite a two- to three-fold increase in risk for negative outcomes in patients with acute coronary syndromes and depressive symptoms (3). In 2008, the American Heart Association issued a scientific advisory (4) outlining recommendations for the screening, referral, and treatment of depression in patients with cardiovascular disease. This advisory further emphasized the clinical light the impact that comorbid depressive symptoms can have on cardiovascular outcomes. Despite the recognition of the role of depressive...
symptoms in poorer cardiovascular outcomes, there is insufficient evidence in the literature that treatment of depressive symptoms alters cardiovascular outcomes.

In the SADHART study, Glassman et al. (5) evaluated the safety and efficacy of the use of sertraline on patients admitted to hospital for recent myocardial infarction or unstable angina with major depression. Although they were able to demonstrate that the use of sertraline was safe in this population, there were not statistically significant decreases in Hamilton Depression (HAM-D) scores in sertraline-treated patients as compared to placebo. Subgroup analysis did demonstrate that patients with a previous history of depression showed a statistically significant response to sertraline. When they compared the incidence of severe cardiovascular events in the sertraline-treated group (14.5%) versus the placebo group (22.4%) they were unable to find statistical significance. So although sertraline was effective in treating depressive symptoms in a recurrent depression sub-group post myocardial infarct, they were unable to show an impact between groups in cardiovascular outcomes.

The ENRICHD study (6) compared a cognitive behavioural therapy (CBT) intervention in patients admitted with acute myocardial infarction who fulfilled criteria for major or minor depression or low perceived social support as compared to a usual care group. A total of 2,481 subjects were randomized to either the CBT intervention or usual care group. Within the intervention group, if patients had scores on the Hamilton Rating Scale for Depression (HAM-D) greater than 24 or failed to have a 50% reduction in Beck Depression Inventory (BDI) scores after five weeks of intervention, they were referred for consideration of antidepressant add-on treatment (sertraline>other SSRIs>nortriptyline). Antidepressant use reached 20.6% and 28% in the usual care and intervention groups respectively. Although the intervention in this study decreased depressive symptoms and improved social support as compared to the usual care group, it did not affect the primary end points of death and non-fatal myocardial infarction. The trend was again to see a reduction in reinfarction and mortality in patients on antidepressant therapy. The authors, however, concluded that given their design study this finding may have been related to a pharmacodynamic effect of SSRIs, such as platelet inhibition, rather than to an improvement in depressive symptoms.

Honig et al. (7) opted to study the effects of a dual acting antidepressant, mirtazapine, to evaluate its safety and efficacy in depressed patients post-myocardial infarction. Ninety-one patients who met criteria for major or minor depressive disorder were randomized to either placebo or mirtazapine treatment and were followed for 24 weeks. Using a last observation carried forward model, the authors did not find a statistically significant difference in mirtazapine versus placebo in either the acute phase (8 weeks) or the entire treatment phase (24 weeks) using the primary measure of reduction in HAM-D score. Statistical significance was, however, found when the authors compared the efficacy of mirtazapine on the secondary outcome measures of scores on the BDI, the depression subscale of the Symptom Checklist 90 (dSCL-90) and the Clinical Global Impression (CGI). Mirtazapine was also shown to be safe in this post-myocardial infarction population, although, as in the SADHART study, medications were not prescribed until 3 months after the incident event. The authors speculate that including major and minor depression may have influenced the statistical significance of their findings on their primary outcome measure. This reflects one of the major limitations in most of the depression and cardiovascular literature, which is that the operational and inclusion criteria for defining and measuring depression and depressive symptoms are inconsistent. It is plausible that the rating scales used as outcome measures are distinct in how they identify and track depressive symptoms post acute coronary syndrome.

There is some debate as to why depressive symptoms post-myocardial infarction do not respond to antidepressant therapy or psychological intervention as expected when compared to a “healthy” depression population. There seems to be some distinction in response between patients with a previous history of major depressive disorder and patients who develop incident depressive symptoms post myocardial infarction (8). Similarly, the failure to show that treating depressive symptoms improves cardiovascular outcomes promotes reflection on the etiology and biologic underpinnings of these depressive symptoms. One of the challenges in studying underlying pathophysiologic mechanisms lies in the inherent heterogeneity of subjects who meet the DSM-IV criteria for major depressive disorder. Patients meeting the criteria for depression often have a wide variance in symptom severity and symptom expression that likely represents important sub-types.
Furthermore, the presence of co-morbid syndromes such as anxiety may play a significant role. The literature linking anxiety spectrum disorders and phobic anxiety to adverse cardiovascular outcomes is almost as extensive as that of depression (9). Does this mean that each separate psychiatric diagnosis that has been linked to the development or progression of cardiovascular disease is operating via a mutually exclusive mechanism?

More recent studies have begun to try to identify the key component(s) of depressive symptoms that confer(s) the cardiotoxic effect(s) (10). The worldwide genome project has led to much excitement in trying to identify candidate genes for a number of psychiatric disorders. In a review article, Hasler et al. (11) describe a number of potential phenotypes of depression and potential biomarkers that may lead to the discovery of endophenotypes that may aid researchers in refining criteria for the complex syndrome that is presently termed depression.

In this vein, two recent studies have begun to identify important elements or symptoms of depression that are more clearly identified with negative cardiovascular outcomes. Hoen et al. (12) looked at the relationship between cognitive and somatic depressive symptoms and cardiovascular outcomes in outpatients with stable coronary heart disease. The 9-item Patient Health Questionnaire was administered to 1,019 patients with stable heart disease to determine the presence and severity of depressive symptoms as outlined in the DSM-IV. Depressive symptoms categorized as primarily cognitive were depressed mood, lack of interest, worthlessness, concentration difficulties and suicidal ideation. Depressive symptoms categorized as somatic were challenges with appetite, sleeping difficulties, psychomotor changes and fatigue. Patients were followed with annual phone calls to determine if there were any deaths or hospitalizations for “heart trouble”. Chart reviews were conducted for any patient with an adverse cardiovascular event. The outcome measures were cardiovascular events including heart failure, myocardial infarction, stroke, transient ischemic attack or death. In age-adjusted analyses both somatic and cognitive symptoms were associated with an increased risk for cardiovascular events (21% and 12% respectively). Once this data was adjusted for confounding variables the cognitive sum score did not significantly predict cardiovascular events. The somatic symptoms of sleeping difficulties, fatigue and appetite problems were, however, independently predictive of cardiovascular events after adjustment for age, sex, diabetes, history of myocardial infarction, history of heart failure, left ventricular ejection fraction, body mass index, smoking and use of cardioprotective agents. It may be argued that in patients with coronary heart disease somatic symptoms such as fatigue, sleeping difficulties and psychomotor slowing merely reflect an increased severity of heart disease at baseline. The authors attempted to correct for this by using a stable outpatient population and correcting for confounding factors. They argue that a focus on treatment of the somatic symptoms identified may lead to improved cardiovascular outcomes. The authors, however, acknowledge that a further understanding of how the mechanisms of sleep disturbance, changes in appetite and psychomotor abnormalities lead to worsening cardiovascular prognosis is crucial for the design of future trials.

Davidson et al. (10) used an observational cohort study design to determine if one of two core diagnostic criteria of depression, i.e. depressed mood or anhedonia, predicts one-year medical outcomes for patients with acute coronary syndromes. They looked at 453 consecutive patients with an acute coronary syndrome admitted to one of three hospitals. Patients underwent a semi-structured interview to determine criteria for a major depressive episode, and the BDI was used to assess depressed mood and anhedonia. Using these measures, 48 patients met the criteria for major depressive disorder, 108 were rated as having depressed mood and 77 were rated as having anhedonia. The primary end point of the study was either the first occurrence of a major adverse cardiac event or all-cause mortality at twelve months. Both depressed mood and anhedonia predicted major adverse cardiac events and all-cause mortality in an age-adjusted model, however, only anhedonia remained as a significant predictor for adverse cardiovascular outcome after adjusting for age, sex and medical covariates. Anhedonia remained a significant predictor after adjusting for major depressive disorder and severity of depressive symptoms.

It is postulated that depressed mood and anhedonia (13) may represent distinct biologic pathophysiologies, and therefore may help distinguish whether one entity is more predictive in cardiovascular disease. Anhedonia in particular has some overlap with somatic symptoms.
including sleep, appetite, weight gain, satisfaction and libido. Hasler et al. (11) describe anhedonia as more closely associated with catecholaminergic dysfunction as opposed to serotonergic dysfunction, which is linked more closely to depressed mood. The identification of correlations between anhedonia and the somatic symptoms of depression may also allow for further study into their mechanisms. Linking the identification of sub-types of depression with potential biological markers such as platelet reactivity (14,15), heart rate variability (16), REM sleep patterns (11) and endothelial function (17) may lead to a further understanding of the complex relationship between depressive symptoms and cardiovascular disease.

There is a wealth of published studies looking at both etiologic and prognostic factors as they relate to depression and cardiovascular disease. Unfortunately many of these studies have significant methodological differences, and measures of diagnosis and outcome vary immensely, such that conclusions are difficult to make. It is important to continue to try and refine our case definition and develop improved measures that will allow us to focus on the common mechanisms that underlie the relationships between cardiovascular disease, depression and psychiatric pathology in general.

References:


