# C. Depression and Cardiovascular Disease

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## Introduction

Mounting evidence of a relationship between depression and cardiovascular disease exists.[1–3] This brief report summarizes evidence for this relationship and describes two possible mechanisms for the relationship.

Although many risk factors for coronary artery disease – genetic factors, diabetes, hypertension, clotting abnormalities, hyperlipidemia, smoking and obesity – have been recognized for many years, the role depression or depressed affect plays has only recently gained attention.

In this paper, we explore: research studies supporting the increased rate of depression in ischemic heart disease; the concept that depression or depressed or negative affect is a risk factor for morbidity/mortality following myocardial infarction; and whether depression or depressed affect is a risk factor for the development of coronary artery disease.[2]

In a groundbreaking study in 1995, Frasure-Smith and colleagues measured multiple variables at the time of a myocardial infarct and identified those associated with mortality. Major depression, smoking status or whether an individual received thrombolysis was not associated with mortality at 18 months. Previous myocardial infarction (MI) and a Beck depression inventory of >10 were highly associated with mortality (previous MI [CI, 1.9–17] and elevated Beck depression inventory (CI, 2.4–25). This work has recently been replicated[4, 5] and has been extended beyond myocardiac infarction to include studies of patients following valve replacement[6, 7] or coronary artery bypass grafting.[8] Lesperance et al and Frasure-Smith and Lesperance extended the finding of a relationship between depressive symptoms and MI, demonstrating increased risk of mortality with each increase in score on the Beck Depression Inventory.

Other types of studies have been conducted, such as the Northwick Park Heart Study. This study included 1,408 White males, between the ages of 40 and 64. At the time of enrollment, none of the subjects had suffered from a MI. Psychological state was measured by the Crown-Crisp Experiential Index (CCEI). One of the major components of this index is obsessionality. While systolic blood pressure had the largest impact on the likelihood of fatal ischemic heart disease (28% and relative risk [RR] of 8.7–46.8), the obsessionality factor also significantly contributed to the increased risk (20% and RR, 20–37.3).[3]

Another way of looking at the relationship between depression and cardiovascular disease is to examine hospitalized cardiac-risk patients diagnosed with major depression. Pratt et al looked at the Baltimore cohort of a national epidemiological sample to determine the role of major depression in MI risk, as well as to examine possible role of psychotropic medications in risk. The study participants included 64 with MI and 1,551 without heart disease. The odds ratio for MI in patients with depression was highly significant at 4.54. The use of tricyclic antidepressants (then the standard of care for depression) was not associated with the risk of myocardial infarction risk.[16]

The relationship was also supported by the Johns Hopkins Precursors Study.[9] This study was a prospective, longitudinal study of 1,190 medical students with a 40-year followup. The cumulative incidence of clinical depression was 12%. Men developing depression drank more coffee than those who did not, but did not differ in terms of baseline blood pressure, serum cholesterol levels, smoking status, physical activity, obesity or

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family history of coronary artery disease. In multivariate analysis, the men who reported clinical depression were at significantly greater risk for subsequent coronary artery disease (RR, 2.12; CI, 1.24–3.63) and myocardial infarction (RR, 2.12; CI, 1.1–4.06). The increased risk associated with clinical depression was present even for myocardial infarctions occurring 10 years after the onset of the first depressive episode (RR, 2.1; CI, 1.1–4.0). The authors concluded that clinical depression appears to be an independent risk factor for incident coronary arterial disease (CAD) for several decades after the onset of the clinical depression.

Not all studies have confirmed the association between depression and increased cardiac mortality.[10] Differences in methodology, particularly when the depression is diagnosed (before the MI, in the hospital during the MI, or several weeks after the MI) all lead to different results. In addition, it appears that negative or depressed affects are more powerful predictors of the relationship than are operationalized diagnoses of major depression.

What factors might mediate the relationship? At least two possible mechanisms have been proposed that might provide the pathophysiological link between depression and the rate of increased cardiac mortality. The two, which are not mutually exclusive, are exaggerated platelet reactivity,[11,12] and reduced heart rate variability.[13,14]

Patients with major depression have been found to have increased activation of the thrombotic pathway, in particular, exaggerated platelet reactivity.[11,12] Selective serotonin reuptake inhibitors, currently the most widely used antidepressants, appear to unstick the sticky platelets, at least *in vitro*. In one study, the selective serotonin re-uptake inhibitor sertraline led to significantly decreased measures of platelet activation compared with placebo treated patients.[15]

Beat-to-beat heart rate variability reflects a balance between vagal tone and sympathetic activity. Altered heart rate variability has been reported in both psychiatric disorders such as panic disorder and major depression[14] and in patients with cardiovascular disease.[13] Some psychotropic medications, such at tricyclic antidepressants, decrease heart rate variability and might lead to sudden cardiac death, while serotonin drugs have the opposite effect.[14]

## CONCLUSIONS

In summary, diagnosis of major depression or dimensional measures of depressed mood or negative affect is a risk factor for cardiovascular disease. Major depression or depressive symptoms are risk factors for poor outcome following cardiac events. Major depression is associated with several defects in the clotting cascade (increasing the likelihood of thrombus formation). Treatment with selective serotonin reuptake inhibitors, such as sertraline, reverses many depression-associated effects on the clotting cascade. Finally, altered heart rate variability might increase the chance of fatal arrhythmias.

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