The Brokenhearted: Cardiovascular Disease and Depression

Lead Article
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Cardiovascular disease and depression: caring for the brokenhearted

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Over the last decades, the association between depression and cardiovascular disease has received a lot of attention. The effect of depression has been studied along two separate lines of research: both as a risk factor for the onset of cardiovascular disease in initially healthy persons (showing markedly increased mortality rates), and as a risk factor for cardiovascular disease progression in patients with already manifest disease, particularly coronary artery disease (showing both that the prevalence of depression is increased in coronary artery disease patients, and that depression is a risk factor for cardiac events in patients with coronary artery disease). By now it is thus well established that depression is a risk factor for the onset and progression of cardiovascular disease, but intervention studies have failed to show that treating depression can counter these effects. Pertinent issues in this field of research include the question whether the association between depression and heart disease is causal, what the underlying mechanisms are that explain the association (the two pathophysiological mechanisms that have attracted most of the attention are altered autonomic nervous system activity and inflammatory processes), how clinicians should best deal with depressed heart disease patients, and whether the association is unique with respect to depression, or should be extended to different forms of psychological distress.

Coronary heart disease (CHD) and depression are the two strongest contributors to the global burden of disease.1 There has been a tremendous increase in research on the comorbidity of the two disorders over the last decades. This research has shown that: (i) depression is a risk factor for cardiovascular disease; (ii) cardiovascular disease is a risk factor for depression; and (iii) depression in patients with established cardiovascular disease is a risk factor for cardiovascular disease progression. Although much progress has been made due to the involvement of many dedicated scientists, several issues remain unsolved and return in the literature in different disguise:

• Is the association between depression and heart disease causal, i.e., is depression a cardiotoxic disorder?
• What are the underlying mechanisms that may explain the association between depression and cardiovascular disease?
• How should clinicians best deal with depressed heart disease patients?
• Is the association between heart disease and depression unique with respect to depression, or does it apply to different forms of psychological distress?

In this Lead Article, I will introduce the topic and summarize findings with respect to the nature of the association between depression and cardiovascular disease, and refer to pertinent literature when needed. In three subsequent articles, my colleagues will discuss the three remaining issues in more detail. Mark Hamer will explain the biobehavioral mechanisms underlying the association;2 Johan Denollet will describe the Type D personality as an alternative source of psychological distress,3 and Ian M. Kronish, David J. Krupka, and Karina W. Davidson will elaborate on treatment issues regarding depressed heart disease patients.4

Keywords: cardiovascular disease; coronary artery disease; depression; prognosis; risk factor; self-report questionnaire; stress; treatment
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INTRODUCTION TO THE CONCEPT OF DEPRESSION

The concept of depression goes back to the ancient Greek physicians, and has been described ever since, in only slightly different shapes. Several issues related to the concept of depression have been quite stable as well, and include the distinction between normality and sickness, the interplay and relative importance of preexisting vulnerability (personality) versus stressor (life event), and a debate on the need for treatment.\textsuperscript{5,6}

Although the concept of depression has prevailed through the ages, its explicit operationalization took a huge leap with the development of the Feighner criteria. This development took place in the late 60s to the early 70s and represented a major transition in psychiatric nosology\textsuperscript{7} as it laid the basis for the Research Diagnostic Criteria (RDC) and the \textit{Diagnostic and Statistical Manual of Mental Disorders (DSM)}—the current psychiatric diagnostic system. As a result of this development, psychiatry had moved toward a discipline in which diagnosis became central. Depression is nowadays defined as one of the mood disorders in DSM-IV.\textsuperscript{8} Major depressive disorder (MDD) is the single most important single disorder in terms of prevalence and severity, characterized by one or more episodes of depressed mood and loss of interest according to a scoring of the following symptoms (\textit{Table I}).\textsuperscript{5}

To be diagnosed with MDD, individuals have to experience at least one of the symptoms from Category 1 and at least three symptoms from Category 2, for a total of at least 5 out of 9 symptoms. These symptoms must be present for most of the day, nearly every day, for at least 2 weeks. MDD is thus operationalized as a syndrome, of which the exact appearance may vary among individuals. In research settings, the presence of depression is detected by one of the three following methods: (i) self-report questionnaires (eg, BDI [Beck Depression Inventory]),\textsuperscript{9} HADS [Hospital Anxiety and Depression Score],\textsuperscript{10} PHQ-9 [Patient Health Questionnaire],\textsuperscript{11} IDS [Inventory of Depressive Symptomatology]\textsuperscript{12}; (ii) psychiatric interviews, conducted either by laypersons (eg, CIDI [Composite International Diagnostic Interview],\textsuperscript{13} MINI [MINI-International Neuropsychiatric Interview]\textsuperscript{14}), or by clinicians (eg, mini-SCAN [Schedules for Clinical Assessment in Neuropsychiatry]\textsuperscript{15}); and (iii) clinical diagnoses derived from medical files. While the psychiatric interviews are largely following the DSM-IV criteria for depression, self-report questionnaires mostly do not follow these criteria (with the exception of the PHQ-9). It should be noted that, although each of these methods have limitations of their own, \textit{if the goal is to determine the presence of depression according to DSM-IV criteria}, the psychiatric interviews will probably give the most valid estimates. Self-report questionnaires generally result in an overestimation of the prevalence of depression, while data from medical files or registries will generally result in underestimations.

In recent years, there has been considerable debate on the lack of evaluation of the DSM-IV depression construct, stressing the need to identify etiologically meaningful subtypes of depression.\textsuperscript{16-19} There is, in contrast to for instance heart disease, no gold standard to determine the presence of depression in a given individual. Diagnosis cannot be on the basis of a biomarker, but has to rely in part on the subjective reporting of symptoms by an individual. A problem associ-
**PREVALENCE AND CONSEQUENCES OF DEPRESSION**

Several large-scale studies on individuals in the general population using psychiatric interview data, have confirmed that DSM-IV defined depression is a prevalent disorder. Estimates of the prevalence of depression in the general population are mostly around 5% 12-month prevalence. Recent studies have revealed that depression is one of the leading causes of disability in the world. Not only quality of life is substantially affected in depressed individuals, with effects at least equal to or perhaps even greater than most of the somatic diseases, but also somatic morbidity and mortality rates are considerably increased in individuals suffering from this condition. Projections of disability-adjusted life years of the next decades have even suggested that depression will become the most important contributor to the global burden of disease, with effects that even go beyond major diseases such as ischemic heart disease and the cancers.

The reasons for this expectation include the high prevalence of depression, its relatively early onset compared with the major somatic diseases, and its often chronic course. While the risk of recurrence of depression is already substantial in persons after their first episode (ie, about 20% per year), this risk steadily increases as a function of the number of previous episodes.

Specific attention has been directed to the putative cardiotoxic effects associated with depression. In a carefully conducted study of elderly subjects living in the community, Penninx and colleagues demonstrated that depression was associated with an increased cardiac mortality rate in subjects without cardiac disease at baseline. After controlling for several confounding variables, including age, smoking status, and body mass index, 3- to 4-fold increased cardiac mortality rates were reported. In a meta-analysis, Van der Kooij and colleagues showed that in initially healthy individuals, depression was prospectively associated with an approximate 50% increased rate of cardiovascular disease, including coronary artery disease and cerebrovascular disease. While these results apply to the putative consequences of depression of initially healthy persons, most attention has been directed to depression in patients with already manifest heart disease, and particularly coronary artery disease. Yet it is important to note that this reflects two separate lines of research: depression as a risk factor for the onset of cardiovascular disease, and as a risk factor for cardiovascular disease progression.

**DSM-IV criteria for Major Depressive Episode**

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

**Category 1:**
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective report or observation made by others).

**Category 2:**
3. Significant weight loss when not dieting or weight gain, or a decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either subjective report or observation made by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

To be counted as symptoms, they need to cause clinically significant distress or impairment in functioning and are not the direct physiological effects of a substance or general medical condition, and are not better accounted for by bereavement.

**Table I. DSM-IV criteria for major depressive episode.**

DEPRESSION IN PATIENTS
WITH CORONARY ARTERY DISEASE

Several studies have indicated that the prevalence of depression is increased in coronary artery disease patients. Thoms and colleagues performed a systematic review and found 8 studies in which a psychiatric interview was used to detect the presence of depression in myocardial infarction (MI) patients. Approximately 20% of MI patients were found to be affected by depression, and this prevalence was relatively comparable across the studies. It should be noted that the figure of 20% refers to prevalent cases of depression. Yet, several studies have indicated that approximately half of the depressed MI patients are incident cases of depression, ie, with a first-ever depressive episode that started after the myocardial infarction. This is of particular interest as some studies have suggested that these incident post-MI depressions may have different etiology and consequences than depressions that preceded the onset of MI, although findings have not been entirely consistent (eg, 40-42).

Carney and colleagues were among the first to study the consequences of depression in the context of acute coronary syndrome and identified depression as a risk factor for cardiac events in patients with coronary artery disease. In similar vein, Frasure-Smith and colleagues showed an increased risk of mortality in depressed MI patients. To date, a large body of literature, summarized in several meta-analyses, has confirmed that depressed patients with established heart disease have an increased rate of adverse cardiovascular outcomes. In the most recent and comprehensive meta-analysis, summarizing >25 years of research, Meijer and colleagues conclude that post-MI depression is associated with an approximately twofold increased rate of all-cause mortality, cardiac mortality, and onset of new cardiac events (such as a new MI). Despite the growth and relative consistency of results in this area of research, debates on the interpretation of findings have continued, focusing on the extent to which the association can be interpreted as representing causal effects of depression on cardiac disease progression. Two issues are central in this discussion: confounding by disease severity and overlap between psychosocial factors.

CONFOUNDR BY
CARDIAC DISEASE SEVERITY

There is substantial disagreement on the possible confounding of the apparent cardiotoxic effects of depression by MI severity and its consequences. The previously described observation that MDD is present in 20% of post-MI patients, while the prevalence of depression over the past 12 months in the general population is only 5%, seems to suggest that MI is a risk factor for depression and thus that reverse causality may be present (ie, heart disease leading to depression). However, it should be noted that an increased prevalence of depression is not necessarily a reflection of physiological changes that accompany the (acute) heart disease. Instead, it is quite possible that it is due to the fact that a MI, for many individuals, represents a significant psychological stressor capable of triggering depression through psychological mechanisms. Still, if a considerable level of confounding by MI severity is present, it is conceivable that specific physiological processes that surround an acute coronary syndrome (eg, inflammatory processes) might contribute to the etiology of post-MI, arguably resulting in different treatment options for post-MI depression. Evidence for the possibility of confounding can be seen in the association between left ventricular ejection fraction (LVEF) and post-MI depression. LVEF is an important determinant of cardiac disease severity in the post-MI setting, and reflects the adequacy of pump function of the heart. In a sample of almost 2000 MI patients, Van Melle and colleagues observed a dose-response association between LVEF and post-MI depression. LVEF is an important determinant of cardiac disease severity in the post-MI setting, and reflects the adequacy of pump function of the heart. In a sample of almost 2000 MI patients, Van Melle and colleagues observed a dose-response association between LVEF and post-MI depression. Evidence for the possibility of confounding can be seen in the association between left ventricular ejection fraction (LVEF) and post-MI depression. LVEF is an important determinant of cardiac disease severity in the post-MI setting, and reflects the adequacy of pump function of the heart. In a sample of almost 2000 MI patients, Van Melle and colleagues observed a dose-response association between LVEF and post-MI depression. Still, an association between disease severity factors and depression does not necessarily imply that the association between depression and cardiac prognosis is confounded. Confounding implies that, when cardiac disease severity is added to a prediction model for cardiac prognosis, the association between depression and prognosis is attenuated. Using data from a systematic review, Nicholson and colleagues concluded that almost half of the variance in the prognostic association between depression and cardiac prognosis was explained away when LVEF was added to the prediction model. However, in the most recent account of the literature, the meta-analysis by Meijer and colleagues, this level of attenuation was estimated to be around 20% when using appropriate statistics, based on eight studies in which an appropriate adjustment for MI severity was made. Also, in patients with stable coronary artery disease, the level of attenuation by LVEF was estimated to be 19%.
Confounding may also occur by complaints attributable to the MI or somatic comorbidities such as diabetes or heart failure. Symptoms such as pain or physical limitations, that can be seen as mere consequences of these comorbidities, might even be falsely counted as symptoms of depression. Although the DSM-IV diagnosis requires symptoms not to be “…the direct physiological effects of a substance or general medical condition,” it is often difficult to ascertain the etiology of each symptom, and interviewers (perhaps more specifically laypersons) may be overinclusive in attributing those symptoms to depression where in fact they would be the consequence of somatic comorbid conditions. Unfortunately, there has not been much research on the etiology of specific symptoms of depression based on interview data. In one of the exceptional studies, Irvine and colleagues tested for the confounding effects of fatigue, and found that the effects attributed to depression largely disappeared. 53

HEtEROGENEITY OF DEPRESSION IN HEART DISEASE PATIENTS

Several studies using self-reported data suggest that some symptoms of depression may be more strongly related to cardiac disease parameters than others. These studies have mainly used the BDI. The BDI is among the most frequently used self-report instruments for depression, designed according to the cognitive theory of depression. 54-57 In this theory, depression was conceptualized as a complex consisting of cognitive, somatic, and affective symptoms. In empirical evaluations of the structure of the BDI, depressive symptoms are often clustered within two separate dimensions: a somatic symptom dimension, dominated by symptoms like fatigue, sleep, and inability to work, and a cognitive dimension mainly reflecting feelings like shame, guilt and low self-esteem. This distinction has been reported in various populations. 58,59

Watkins and colleagues showed that in post-MI patients the BDI score was correlated with the Charlson comorbidity index, in which the number of somatic diseases is scored. 60 Of interest, the authors found that only the somatic symptoms of depression, such as fatigue, sleeping difficulties, and working difficulties, were associated, whereas the cognitive symptoms were not. This finding has led others to further study this heterogeneity. 61-62 Specifically with respect to the putative cardiotoxic aspects of depression. In one study, Martens and colleagues showed that depression observed in heart disease patients may be different in symptomatology than in patients that are found in psychiatric settings. 62 Especially, cognitive symptoms of depression, such as shame or guilt feelings, were found to be less prevalent in cardiac patients, suggesting that in heart disease patients the stressor (eg, a cardiac event) may be a more important etiological factor in depression than the presence of a preexisting cognitive vulnerability (eg, negative self-image). Interestingly, in a series of studies, it was demonstrated that there are prognostic differences between somatic and cognitive depressive symptoms. While cognitive symptoms are found not to be related to cardiac prognosis, somatic symptoms are predictive of cardiovascular mortality and cardiac events, even after somatic health status has been controlled for. 63 These findings have been replicated in samples of post-MI patients, 64-66 and in patients with chronic heart failure, 67 although an opposite finding in coronary heart failure was also reported. 68

In a recent essay, Frasure-Smith and Lespérance portrayed the present status and future directions of research regarding depression and cardiac risk, making a comparison between depression and Type A behavior, characterized by high levels of competition and hostility. 69 In 1981, a review stated that Type A behavior was associated with an increased risk of CHD. However, soon after this statement, contradictory evidence began to appear and today Type A research is scarce. Frasure-Smith and Lespérance concluded that, “only time will tell whether depression will follow in the footsteps of Type A behavior, or whether the efforts at isolating and treating its most cardiotoxic elements or behavioral and pathophysiological pathways will succeed.” Future research will hopefully help to pinpoint the precise nature of the harmful aspects of depression, as well as the mechanistic pathways that link depression to CHD progression. Deconstructing depression in order to pinpoint its exact cardiotoxicity is bound to be the next phase in this area of research. 70

A MODEL THAT INTEGRATES INCONSISTENT FINDINGS IN THE ASSOCIATION BETWEEN DEPRESSION AND HEART DISEASE

Both in general psychiatry and in the field of cardiac psychiatry/psychology, the phenotypical heterogeneity of depression is currently subjected to debate (eg, 71-73). Lux and Kendler, 74 distinguished between cognitive and neurovegetative symptoms and found that cognitive symptoms were associated with several clinical characteristics, including higher neuroticism and lower introversion scores, longer depression duration,
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and more chronicity. Combining these findings with the abovementioned work on post-MI depression, we presented an integrative dynamic model to describe the association between depression and progression of CHD. This model has been built upon three hypotheses: (i) depression in CHD patients consists of mixtures of two types of depression, denoted as cognitive and somatic depression (Table II and Figure 1); (ii) depression, when it persists, can become a causal factor in disease progression, and (iii) the pathways mediating the effects of depression vary from largely behavioral with respect to cognitive depression, to physiological with respect to somatic depression. This model summarizes the differential predictive properties in cardiotoxicity of a somatic and a cognitive depression symptom dimension, but it may well extend to healthy populations because even in the general population a generic effect of depression on mortality is found.

This model explains some apparently unrelated bodies of literature and some inconsistent findings. For instance, the somatic subtype of depression links very well with the concept of vital exhaustion that was developed by Appels and colleagues. Vital exhaustion is characterized by feelings of fatigue, irritability, and demoralization, and has also been associated with adverse clinical outcome. In EXIT (Exhaustion Intervention Trial), treatment of vital exhaustion resulted in improvements in fatigue, but not in cardiovascular prognosis. Also, it accounts for the possibility that some depressions that occur in the context of heart disease may have an etiology that is intertwined with the heart disease itself, whereas other forms of depression are relatively independent of the heart disease (Figure 2).

Table II. Prototypical symptoms of the cognitive and somatic subtypes of depression.

<table>
<thead>
<tr>
<th>Cognitive subtype</th>
<th>Somatic subtype</th>
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<tbody>
<tr>
<td>Depressed mood</td>
<td>Fatigability</td>
</tr>
<tr>
<td>Lack of interest</td>
<td>Psychomotor agitation/retardation</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>Work difficulty</td>
</tr>
<tr>
<td>Negative feelings/</td>
<td></td>
</tr>
<tr>
<td>cognitions about self</td>
<td>Sleep problems</td>
</tr>
<tr>
<td>• Self-dislike</td>
<td>(mostly more sleep)</td>
</tr>
<tr>
<td>• Sense of failure</td>
<td>Aches and pains</td>
</tr>
<tr>
<td>• Self accusations</td>
<td>Appetite disturbance</td>
</tr>
<tr>
<td>• Self-criticism and blame</td>
<td>(mostly increased appetite)</td>
</tr>
<tr>
<td>Guilt</td>
<td>Weight disturbance</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>(mostly weight gain)</td>
</tr>
<tr>
<td>Future pessimism</td>
<td>Depressed mood</td>
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HOW DO THE EFFECTS OF DEPRESSION RELATE TO THOSE OF OTHER PSYCHOSOCIAL FACTORS?

Depression is seldom a phenomenon that occurs in isolation. Often, patients who are depressed suffer from multiple, related psychosocial problems, which in turn may be related to cardiac disease progression. While researchers have tended to evaluate the putative effects of depression by analyzing a single psychological construct at a time, the increased risk of cardiac events may well extend to patients with symptoms of negative affect other than depression. Several candidate psychosocial risk factors have been investigated, although rarely simultaneously.
Anxiety is an interesting factor in this respect, as depression and anxiety are highly comorbid disorders, and symptoms of depression and anxiety frequently co-occur in heart disease patients. Several studies have reported symptoms of anxiety to be predictive of subsequent cardiac events and mortality post-MI, independently of established biomedical risk factors, which recently have been summarized in a meta-analysis. In this meta-analysis, it was found that anxious MI patients had a 36% increased risk of adverse cardiac events. The extent to which these findings are attributable to depression, or conversely, the extent to which the results with respect to depression are attributable to anxiety, is not known to date.

A second risk factor is Type D personality, which differs from depression in that it includes social inhibition apart from negative affectivity, and is conceptualized as a trait rather than a state. Type D personality has been associated with vulnerability to emotional distress and an increased risk for adverse clinical events in CHD patients. Consequently, personality may comprise a general disposition that acts as an underlying variable promoting both depression and CHD risk.

In several papers, a distinction between Type D personality and depression was supported. In the article by Johan Denollet, in this issue, the conceptual basis of Type D personality is discussed as well as a summary of studies evaluating its predictive value in heart disease patients.

Other possible psychosocial factors of interest to take into account in the association between depression and cardiovascular disease include anger and hostility. These factors are associated with more mixed findings and a recent meta-analysis suggests relatively small effect sizes in CHD patients. Given this level of risk, hostility and anger do not seem to be major cardiac risk factors. Further research is needed to identify psychological risk indicators in patients with heart disease, as well as how they operate in concert. For a more detailed discussion on this topic, see Suls and Bunde.

MECHANISMS UNDERLYING THE ASSOCIATION BETWEEN DEPRESSION AND HEART DISEASE

Several physiological and behavioral mechanisms have been proposed to explain the cardiotoxic properties of depression (Table III, page 94). Two physiological mechanisms have attracted most of the attention, namely, altered autonomic nervous system activity and inflammatory processes. It should be noted that in order to qualify as mediator and explain the cardiotoxic properties, these factors should be related to depression and to heart disease (progression), and attenuate the effects of depression on heart disease outcomes.

Altered autonomic nervous system (ANS) activity is characterized by sympathetic overactivity and/or parasympathetic withdrawal. Heart rate variability (HRV) is a noninvasive marker of ANS activation of the heart,
and reduced HRV is an important risk factor for cardiac mortality. Several studies have associated depression with reduced HRV in heart disease patients. It should be noted, however, that most of these studies have been cross-sectional and were not entirely fit to look into the issue of mediation. In one of the exceptions, however, it was found that HRV partially mediated the effect of depression on survival after acute MI.97 This was subsequently contradicted by a second study in which low HRV was not associated with depression, and consequently did not mediate the effect of depression on adverse cardiac events.98 Of interest, a differential association of somatic and cognitive depressive symptoms with HRV was also found, in which somatic depressive symptoms were associated with lower HRV, while cognitive depressive symptoms were not.99 These results suggest that perhaps individual symptoms of depression may have a differential association with HRV, and that HRV may mediate the effects of only some of the depressive symptoms but not others.

Higher levels of inflammatory markers, including C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α have consistently been found in heart disease patients.100 These elevations impose an increased risk of adverse cardiac outcome. Depression has also been associated with increased levels of inflammation (ie, CRP and IL-6) in CHD patients.101 Whether the effects of depression are mediated by inflammation has only been examined in a single study, and it was found that the increased risk of adverse cardiac events could only be partly explained by CRP, with a level of attenuation of about 10%.52 In a subsequent analysis on the same sample, it was reported that there is more evidence that depression leads to elevated levels of inflammatory markers than reversibly, although the effects were rather small and only present when depression persisted over a period of several years.102 Of interest, proinflammatory induced depression is also referred to as “sickness-behavior,” in which somatic, flu-like symptoms of depression such as fatigue, decreased appetite, and psychomotor retardation become dominant.103 This provides an additional potential explanation for a differential association between specific symptoms of depression and inflammation as these flu-like symptoms are rather similar to the somatic component of the depression concept. Among the other physiological factors, platelet aggregation,104 hypothalamus-pituitary-adrenal axis function,105 and serotonin metabolism106 have been suggested. However, research addressing these factors has been relatively limited and dominated by research designs in which no appropriate test for mediation could be conducted. In addition, several behavioral mechanisms have been proposed, though remarkably fewer studies have evaluated these possible pathways than the physiological ones.107-112 Examples of the behavioral factors that have been proposed include reduced adherence (either to medication or other treatment regimens), reduced access to medical care in the presence of depression, and inability to modify lifestyle factors such as smoking, unhealthy diet, and physical inactivity. It is unlikely that any single physiological or behavioral mechanism will fully explain the prospec- tive association between depression and cardiac outcome. Moreover, it is unlikely that the effects of different symptoms of depression can be explained by the same mediators. This will be an important avenue of research in the next years. A thorough discussion of the variety of the potential physiological and behavioral mediators of the cardiotoxic properties of depression will be given in the paper by Hamer et al.2

### Table III.
Mechanisms through which depression may lead to cardiac events.

<table>
<thead>
<tr>
<th>Physiological mechanisms</th>
<th>Behavioral mechanisms</th>
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<tbody>
<tr>
<td>Lower heart rate variability (HRV) reflecting altered cardiac autonomic tone</td>
<td>Cigarette smoking and hypertension</td>
</tr>
<tr>
<td>Inflammatory processes</td>
<td>Nonadherence to cardiac prevention and treatment regimens</td>
</tr>
<tr>
<td>Increased platelet aggregation</td>
<td>Dietary factors</td>
</tr>
<tr>
<td>Enhanced activity of the hypothalamic pituitary axis</td>
<td>Lack of exercise</td>
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<tr>
<td>Increased whole blood serotonin</td>
<td>Poor social support</td>
</tr>
<tr>
<td>Lower omega-3 fatty acid levels</td>
<td></td>
</tr>
<tr>
<td>Antidepressant cardiotoxicity</td>
<td></td>
</tr>
<tr>
<td>Increased catecholamine levels</td>
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</table>

TREATMENT OPTIONS FOR DEPRESSION IN HEART DISEASE PATIENTS

Given the potential cardiotoxic properties of depression and the availability of depression treatments, several studies have been conducted over the years in which depression was targeted in heart disease patients order to improve cardiovascular prognosis. It should be noted that to date no studies exist in which depression was targeted in healthy individuals in order to prevent the onset of heart disease. There are many available guidelines for the treatment of depression in which psychotherapy, antidepressant drugs, and combinations of the two are generally considered as the most important first steps in the treatment of depression. A large body of evidence has demonstrated that both forms of treatment are moderately effective in terms of reducing depressive symptomatology. Recently, however, it has been argued that the efficacy of antidepressive drugs has been overestimated due to publication bias.113,114

In heart disease patients, the evaluation of treatment options can be described according to two phases in which studies took place. A more detailed description of how clinicians can best deal with depressed heart disease patients is given in the subsequent chapter by Kronish and colleagues.4

Phase 1: Psychological treatments with rather poor study design

Many early studies have evaluated the effectiveness of various forms of psychological treatments in heart disease patients, such as relaxation therapy, patient education, and stress management, summarized in several meta-analyses.115,116 A review by Rees and colleagues117 indicated that small reductions in depression are associated with treatment, but no significant effects of psychological interventions on all-cause or cardiac mortality have been observed. Linden and colleagues examined various forms of psychological treatment of cardiac patients,116 and found mortality benefits due to psychotherapy in men only. However, there were several problems associated with the studies included in this meta-analysis. Notably, there was significant heterogeneity in terms of the nature of the interventions, eg, stress management, versus meditation, versus cognitive-behavioral therapy, and individual versus group therapy. Similarly, some trials evaluated psychological treatment as a single intervention, while others evaluated the treatment as part of a comprehensive cardiac rehabilitation program. Also, some patients received the intervention post-MI while others received it post-surgery, and some studies also included patients with chronic CHD and angina. Several studies did not evaluate the effects of depression-specific treatment in the population of CHD patients with comorbid depressive disorder, but evaluated the effects in the population of CHD patients with comorbid anxiety, depression, composite psychological outcomes, and others (stress and Type A behavior). Overall, although suggesting efficacy in terms of psychological and cardiac outcomes, this phase of intervention studies has not produced definitive evidence for or against the effects of depression treatment and was followed by a wave of studies with better design.

Phase 2: Depression treatment and the effect on depression and cardiac outcome

Despite the prevalence of depression and its association with negative cardiac prognosis, only a limited number of adequately powered pharmacological and behavioral randomized controlled trials have been performed in CHD patients with comorbid depressive disorder. Overall, treating depressive patients has served two goals: evaluating the effects on depression per se and the effects on cardiovascular outcomes.

SADHART (Sertraline AntiDepressant Heart Attack Randomized Trial) is the largest RCT evaluating anti-depressant medication use for depressed patients with unstable ischemic heart disease.118 The authors reported that sertraline was associated with relatively minor improvements in depression compared with placebo. Second, CREATE (the Canadian Cardiac Randomized Evaluation of Antidepressant and psycho-Therapy Efficacy trial) evaluated whether two forms of depression treatment would improve depression in CHD patients.119 In CREATE, citalopram was compared with placebo, and short-term interpersonal psychotherapy combined with clinical management was compared with clinical management alone in depressed patients with coronary artery disease. The authors reported a small effect of citalopram in comparison with placebo, but there was no demonstrable benefit of psychological treatment over clinical management alone. MIND-IT (Myocardial INfarction and Depression–Intervention Trial) evaluated whether antidepressive treatment for post-MI depression improved long-term depression status and cardiovascular prognosis.120 The study was an effectiveness rather than an efficacy study, and compared the effects of an active, multicomponent treatment strategy with usual care. Patients with
a post-MI depressive episode were randomized to intervention (ie, antidepressive treatment) or care as usual. First-choice treatment consisted of placebo-controlled treatment with mirtazapine. In case of refusal or nonresponse, treatment with citalopram was offered. Both treatment arms were followed for end points, which included cardiac death or hospital admission for documented nonfatal myocardial infarction, myocardial infarction, coronary revascularization, heart failure or ventricular tachycardia. Antidepressive treatment was slightly more effective than placebo after 8 weeks of treatment, but no long-term effects on depression or cardiac outcomes were observed. The ENRICHD trial (ENhancing Recovery in Coronary Heart Disease) determined whether cognitive behavioral therapy (CBT), plus sertraline in case of insufficient response, was more effective than usual care following MI. This study found that CBT did improve depression, although only modestly. However, the authors reported no effects on the composite end point of all-cause mortality and nonfatal-MI over 2 years.

Since then, several researchers have suggested cardiac benefits for patients receiving antidepressive treatment in secondary analyses of the abovementioned studies. For instance, in the ENRICHD trial it was found that the prescription of serotonin reuptake inhibitors was associated with 40% reductions in both recurrent MI and death. In addition, several studies suggest that unsuccessful treatment of depression was associated with a high cardiac risk, and that response to antidepressive treatment was associated with fewer subsequent cardiac events. However, these findings must be interpreted with caution as they do not represent randomized comparisons.

In a systematic review by Thombs and colleagues in which the effects of depression treatment on depressive symptoms and cardiac outcomes were summarized, it was concluded that depression treatment has only minor effects in terms of reducing depressive symptoms (effect size: 0.20-0.38; r²: 1%-4%), and no effect on cardiac outcomes. These effects on depression outcomes are highly comparable to estimates of the effects of depression treatment in unselected patient samples and suggest that improvements in the efficacy of depression treatment are badly needed. These improvements might lie in novel treatments per se, but it is far more reasonable to expect that improvements may be made by a better targeting of intervention to the “staging and profiling” of depression in which already existing interventions are adjusted to subtypes of depression.

**STAGING AND PROFILING OF DEPRESSION**

The fact that randomized comparisons did not show positive effects of depression treatment on cardiac prognosis has led several researchers to believe that depression does not have a causal effect on cardiac disease progression. An alternative explanation however, lies in the observation that depression is a heterogeneous condition. It is quite possible that subtypes of depression exist that are cardiotoxic while others are not, and that some types may respond to treatment while others do not. It is therefore important to identify patients who are at the highest risk for adverse cardiac outcome. Several subtypes of depression may be of importance in this respect. Recently, several studies have reported interesting subgroup analyses and reanalyses of existing epidemiological studies and clinical trials. In this context, the concepts of staging and profiling are useful referring to a conception of depression as a disorder in which different stages and different symptom constellations can be detected for which different interventions are indicated. The most promising intervention strategies for depression in which this is integrated are stepped care (ie, the level of depression care depends on the stage of the disease) and collaborative care (ie, interventions from different care specialists are integrated involving some level of care coordination. They will be described in more detail in the paper by Kronish and colleagues.

**DISCUSSION**

Depression and CHD are the two strongest contributors to the global burden of disease. Despite considerable efforts, several issues remain unresolved, with regard to the precise nature of the harmful CHD effects, the mechanistic pathways that link depression to CHD, the implementation of depression screening in CHD patients, and the best treatment for CHD patients with depression. The bidirectional relationship between CHD and depression thus continues to represent a major challenge in health care. The field of depression and CHD has expanded enormously over the last two decades, but continues to be faced with these unresolved issues.

For clinical care, an important unresolved issue is whether patients with heart disease should be routinely screened for depression in clinical practice. There is an ongoing debate considering the benefits of depression screening in patients with cardiovascular disease. Recently, the American Heart Association science ad-
visory recommended screening all post-MI patients for depression at regular intervals during the post-MI period, including during hospitalization, using a standardized depression symptoms checklist, and treat identified depression aggressively to improve not only the depression, but also cardiac prognosis. This recommendation was based on the high prevalence of depression in CHD and on the association of depression with poor cardiovascular prognosis, but a careful review of benefits and harms of routine depression screening was not performed. In contrast, in a systematic review by Thombs and colleagues, routine screening was discouraged, because there is a lack of evidence that depression screening in patients with cardiovascular disease produces better outcomes. So far, no study has actually evaluated whether screening for depression in patients with CHD improves access to depression care and thereby cardiac outcomes.

An important issue that lies at the heart of this issue is the relative inefficacy of current treatments of depression. It is quite possible that new care models need to be developed that are not based on monotherapy, but instead based on stepped care and interdisciplinary collaborations. In addition, the etiology of depression and the possible mechanisms by which depression may lead to cardiac events are still poorly understood, hampering the development of effective interventions that might prevent these effects. Clarification of how depression may lead to adverse cardiac outcome can only be achieved by prospective research designs that carefully document depression, while simultaneously monitoring possible mediators and CHD outcomes. Perhaps such studies should focus particularly on behavioral instead of physiological pathways as they appear to be relatively understudied.

There is strong recent evidence that lifestyle and physical exercise represent important pathways between depression and CHD outcomes in stable CHD patients. Physical exercise could therefore be an important and effective component of rehabilitation programs in future trials. Health care–related behavior in general may be a relevant target for intervention in depressed MI patients. Interventions focused on health care–related behavior could be implemented in collaborative care models for depressed patients. Collaborative care is based on the principle of structured care involving a greater role of nonmedical specialists to augment primary care. According to a recent meta-analysis, collaborative care is more effective than standard care in improving depression outcomes in the short and long terms. Perhaps in depressed CHD patients, collaborative care can serve two goals simultaneously: treatment of depression and enhancement of cardiac aftercare. Hopefully, future studies will help to pinpoint the mechanistic pathways that link depression to CHD progression. However, it is also quite possible that these mechanistic pathways may differ for different symptoms and stages of depression.

With respect to subtyping depression based on the symptomatology of depression, the distinction between somatic and cognitive depressive symptoms seems to be the most promising to date. Several studies showed that there is a consistent association between adverse cardiac outcome and somatic/affective, but not cognitive/affective symptoms of depression. Perhaps depression treatment trials in CHD patients have primarily targeted the cognitive symptoms of depression, and their inability to demonstrate reductions in cardiovascular morbidity and mortality may be partly attributable to undertreatment of the somatic features of depression. Although treating cognitive depressive symptoms is of importance, it may not directly result in improved cardiovascular outcome. The results from studies focusing on somatic and cognitive depressive symptoms indicate the need for future research directed at identifying the underlying pathophysiological processes by which somatic depressive symptoms contribute to prognosis in CHD patients. In addition, various interventions must be tested in order to alleviate the associated risk. Acknowledging the etiological heterogeneity in cognitive versus somatic symptoms of depression may help moving the field ahead.

Perhaps standard depression treatments are ineffective for somatic depressions because of their atypical etiology and underlying physiology. In order to prevent the cardiotoxic effects of depression, treatments must lead to significant improvement in CHD risk factors in order to normalize atherosclerosis and CHD-associated abnormalities. This might include factors like inflammation and reduced heart rate variation, both of which might be addressed by interventions that are not yet specifically known as antidepressant therapies.

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The Brokenhearted: Cardiovascular Disease and Depression

Expert Answers to Three Key Questions

1. What are the mechanisms underlying the association between depression and cardiovascular disease?
   
   M. Hamer

2. Depression and distressed (Type D) personality: what is their impact on cardiovascular outcomes?
   
   J. Denollet

3. How should we treat depression in patients with cardiovascular disease?
   
   I. M. Kronish, D. J. Krupka, K. W. Davidson
What are the mechanisms underlying the association between depression and cardiovascular disease?

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Numerous intermediate mechanisms might explain the link between depression and cardiovascular disease (CVD). The mechanisms can be broadly divided into two groups, encompassing (1) health behaviors, such as physical activity and smoking; and (2) psychobiological processes, such as inflammation, cardiac autonomic regulation, and dysfunction of major stress axis. At present the underlying pathways linking depression and CVD are incompletely understood, which is partly due to a reliance on observational studies and lack of good quality controlled trial data. A better understanding of these mechanisms will help to develop targeted treatments that reduce depression and improve cardiovascular prognosis.

The link between depression and CVD has been identified as an important public health issue. Evidence from prospective cohort studies is compelling and has consistently demonstrated an association between depressive symptoms and future risk of CVD in both initially healthy samples and cardiac patient, with effect sizes that are comparable to conventional risk factors such as hypertension, obesity, and smoking. The value of treating depression using a range of modalities has therefore been an area of considerable interest and intense debate in clinical and research work in CVD. In order for treatment to be successful it is essential to understand the pathways that might explain the associations between depression and disease. The underlying pathways linking depression and CVD are incompletely understood, which is partly due to methodological limitations and lack of controlled trial data. At present, the evidence base is largely limited to findings from observational population studies and small psychophysiological experiments. Population studies enable large numbers of participants to be followed over time for hard clinical endpoints although causal links cannot be established. Acute psychophysiological stress testing involves the assessment of individual differences in biological responses to standardized stressors that can be related to psychosocial risk factors, thus is a useful technique to investigate underlying mechanisms.

The aim of this paper is to discuss the potential pathways linking depression and CVD, based on the available evidence. The mechanisms can be broadly divided into two groups (Figure 1, page 108), encompassing: (i) health behaviors and (ii) psychobiological processes, although these groupings are arbitrary and should not be treated as mutually exclusive.

**HEALTH BEHAVIOR**

Behavior is closely linked with both mental and physical health. The behavioral pathways that might explain associations between depression...
 Mechanisms underlying the association between depression and CVD - Hamer

For example, among 1017 outpatients with stable coronary disease from the Heart and Soul study, those reporting depressive symptoms at baseline were at 50% increased risk of a secondary CVD event during 4.8 years of follow-up. 

Table I. Association between depression and CVD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Exposure and outcome</th>
<th>% Explained by physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamphuis et al.,4 2007</td>
<td>Healthy European elderly men (n=909)</td>
<td>Zung Self-Rating Depression Scale; CVD death, 10-y follow-up</td>
<td>9%</td>
</tr>
<tr>
<td>Hamer et al.,5 2008</td>
<td>Healthy general UK population (n=6576)</td>
<td>GHQ-12; CVD events, 7.2-y follow-up</td>
<td>22%</td>
</tr>
<tr>
<td>Whooley et al.,6 2008</td>
<td>Cardiac patients (n=1017)</td>
<td>PHQ-9; Recurrent CVD, 4.8-y follow-up</td>
<td>31%</td>
</tr>
<tr>
<td>Hamer et al.,7 2011</td>
<td>UK elderly population (n=1007)</td>
<td>GDS-15; CVD death, 9.2-y follow-up</td>
<td>25% (12.5% activity; 12.5% function)</td>
</tr>
<tr>
<td>Win et al.,8 2011</td>
<td>Healthy general US population (n=5888)</td>
<td>CES-D; CVD death, 10.3-y follow-up</td>
<td>26%</td>
</tr>
</tbody>
</table>

Table 1. Summary of results from epidemiological studies exploring the extent to which physical activity behavior explains the association between depression and CVD.

Abbreviations: CES-D, Center for Epidemiological Studies Depression scale; CVD, cardiovascular disease; GDS-15, Geriatric Depression Scale; GHQ-12, General Health Questionnaire; PHQ-9, Patient Health Questionnaire.
ioral intervention trials to date, consisting of 2481 myocardial infarction (MI) patients suffering from depression and low perceived social support, treatment with cognitive behavior therapy had no effect on event-free survival after 29 months of follow up despite significant improvement in depression and perceived social support. However, in a secondary analysis of the ENRICH cohort (ENhancing Recovery In Coronary Heart Disease), self-reported exercise in the 6 months following myocardial infarction was associated with a more than 50% reduction in the risk of subsequent death.

Physical inactivity not only carries cardiovascular health risks, but is also important in predicting the onset of physical decline in older adults and partly explains the link between depression and disability. Thus, physical decline, together with perceived barriers toward physical activity, such as fear and negative experiences, low self-efficacy, and lack of knowledge, may partly explain the increased risk of physical inactivity among participants with depressive symptoms. However, impaired executive function, with reduced ability to handle, process, and retain new information may also partly explain why depressed patients are less likely to adhere to treatments and lifestyle modification.

Factors that precipitate the onset of depression, such as acute life events, poor social networks, and various types of chronic adversity such as work stress, are also associated with poor health behavior such as unhealthy diets and smoking. Smoking is often used as a form of self-medication to deal with the symptoms of stress and depression, although it is also a potent risk factor for CVD. Further research is, however, required to establish whether physical inactivity, alcohol abuse, and smoking are more accurately conceived of as a set of depressogenic behaviors or representative of the behavioral phenotype of individuals genetically predisposed to depression.

**PSYCHOBIOLOGICAL MECHANISMS**

Depressive symptoms correlate with several pathophysiological risk markers including sympathetic nervous system hyperactivity, disturbances in hypothalamic-pituitary-adrenal (HPA) function, chronic systemic inflammation, hemostasis, and altered metabolic and cardiac autonomic control. The existing evidence suggests that these pathways explain a modest amount of the association between depression and CVD. For example, in recent studies, adiposity and metabolic syndrome appeared to partly mediate the association between depression and subclinical atherosclerosis.

Markers of systemic inflammation, such as C-reactive protein and interleukin-6, explained approximately 17% of the association between depression and CVD events in women with suspected coronary ischemia. Autonomic dysfunction and inflammation contributed only 12.7% to the increased CVD mortality risk associated with depression in the Cardiovascular Health Study. In other studies, various inflammatory markers did not, however, explain any of the association between depressive symptoms and risk of CVD. Thus there is clearly a need for further research in this area. Nevertheless, experimental research underlines the effects of acute psychosocial stress on inflammatory responses and these responses may be amplified by the presence of chronic psychosocial stress and depressive symptoms. Acute stress has also been shown to activate nuclear factor kappa B in peripheral blood mononuclear cells and gene expression and protein production of several inflammatory cytokines are dependent on stimulation of the sympathetic nervous system.

One of the reasons for inconsistency in this area is that inflammatory processes might have more relevance in clinical populations. In particular, new-onset depression in acute coronary syndrome (ACS) might be qualitatively distinct from depression in healthy populations. ACS patients developing new-onset depression (post-ACS depression with no prior history of depression) are at particularly high risk of poor prognosis and recurrent events. An ACS is associated with large acute inflammatory responses that are predictive of poor cardiac outcomes. Thus, depression and poor prognosis in ACS patients appear to share a common inflammatory pathology that might underlie the somatic symptoms often observed.

Disturbances in the major stress axis—the sympathetic nervous system and HPA system—is a plausible mechanism in explaining the depression—CVD association. Depression is associated with alterations in hormone and catecholamine circadian rhythms and heightened sympathetic activation to stressors. An increased prevalence of carotid plaque found in chronically stressed spousal caregivers of Alzheimer’s disease was partly explained by prolonged sympathoadrenal arousal to acute stress, although this has not been confirmed in other studies. An increased secretion and reactivity of cortisol together with an altered feedback inhibition are the most widely observed HPA abnormalities in depression. HPA axis hyperactivity is a marker of glucocorticoid resistance, implying ineffective action of glucocorticoid hormones on target tissues, which could lead to immune activation and the associated in-
creases in inflammatory markers. Several population studies have demonstrated associations between disturbed HPA function and CVD. Dekker et al.\textsuperscript{37} observed an association between total cortisol exposure while awake, and higher carotid plaque scores in a sample of older adults, while another study showed a greater presence of coronary artery calcium (CAC) in younger participants with a flatter diurnal cortisol decline across the day.\textsuperscript{38} In a cross-sectional study containing healthy participants from a subsample of the Whitehall II cohort, we recently demonstrated an association between heightened cortisol reactivity to mental stress and subclinical coronary disease as indexed by CAC (Figure 2).\textsuperscript{39}

Also, in the main Whitehall II study, a flatter slope in cortisol levels across the day was associated with an increased risk in CVD mortality in British civil servants,\textsuperscript{40} and elevated 24-hour urinary cortisol was associated with CVD death in the and recurrent CVD events in coronary patients.\textsuperscript{6} The ambiguity might be related to the strong diurnal nature of cortisol secretion (peaking after awakening and steadily declining across the day) that can heavily influence the results. Therefore, single measures of cortisol might not be appropriate to capture the dynamic nature of HPA activity. In addition, there is marked variability in diurnal cortisol patterns within individuals across different days,\textsuperscript{47} thus suggesting that repeated sampling is required to obtain the most robust measure of chronic HPA activity. The findings from clinical patient groups are also mixed. Low serum cortisol levels were shown to predict death following myocardial infarction\textsuperscript{48} and reduced cortisol stress responses in patients with stable coronary artery disease have also been observed\textsuperscript{49} In contrast, elevated fasting cortisol was associated with risk of future cardiac events in patients with chronic heart failure,\textsuperscript{50,51} Thus, taken together it has been difficult to establish the importance of various psychobiological processes that might underlie the association between depression and CVD. However, this issue might be partly due to the difficulties in obtaining accurate measures of chronic exposure for many of the described biomarkers.

**DISCUSSION AND CONCLUSIONS**

Attempts to evaluate the effects of treating depression on CVD prognosis in coronary patients has shown modest improvement in depressive symptoms, but no improvement in cardiac outcomes.\textsuperscript{52} One of the reasons for these findings may be the heterogeneity of depression as a syndrome. Emerging data are beginning to demonstrate the importance of somatic symptoms of depression (e.g., loss of appetite, disturbed sleep, fatigue), which have a relatively higher prevalence than cognitive symptoms and are more strongly associated with CVD prognosis.\textsuperscript{53} This raises the possibility that to improve CVD outcomes, interventions for depression should be specifically directed at somatic symptoms. Cognitive depressive symptoms, such as feelings of worthlessness and suicidal ideation, have been specific targets for intervention in psychotherapy, while physical activity interventions, for example, may specifically improve somatic

Figure 2. Mental stress, cortisol, and coronary atherosclerosis. Participants with heightened cortisol responses to mental stress are more likely to have underlying coronary atherosclerosis, signified by coronary artery calcium (CAC) scores above 100 (data adapted from Hamer et al\textsuperscript{39}). An increased secretion and reactivity of cortisol together with an altered feedback inhibition are the most widely observed HPA abnormalities in depression, and may be an important mechanism in explaining increased CVD risk.

Abbreviations: CVD, cardiovascular disease; HPA, hypothalamic-pituitary axis.
Indeed, disturbed sleep might itself be seen as a possible mechanism given that there is accumulating evidence on the link between sleep quantity and quality with CVD. In addition, biological processes appear to be differentially associated with specific depressive symptoms, both cardiac autonomic regulation and inflammatory markers are more strongly related to somatic symptoms.

Our understanding of the mechanisms is also hampered by methodological limitations. For example, a clear limitation of the existing epidemiological work is that most studies are unable to provide a robust test of mediation because the potential mediating variables are usually measured at the same point in time as the assessment of depression, thus making it difficult to determine the temporal nature of the association. Indeed, the association of depressive symptoms with intermediate risk factors for CVD might be bidirectional in that depression not only causes disturbances in behavior and pathophysiological markers, but vice versa. For example, there appears to be a bidirectional association between depressive symptoms and inflammatory markers, which suggests depression not only causes inflammation, but that inflammation can also cause depression. Physical activity appears to be protective against the development of depression and stress-related illness, although individuals with mental illness are less likely to undertake any activity. Residual confounding is also a particularly relevant issue in this research area.

Several factors that relate to depression, including functional disability, cognitive impairment, and self-rated health all predict mortality in the elderly population, and previous studies have attempted to disentangle these associations. In the Cardiovascular Health Study containing 5201 participants aged 65 years and older, depression was independently associated with mortality after adjustment for a wide range of sociodemographic and objective physical health variables. In other studies the association between depression and mortality is substantially diluted or disappears when self-assessments of perceived health, self-reported functional status, and other indicators of subjective well-being are included as covariates. This might suggest that depressive symptoms partly reflect motivational and affective factors that are measured by other self-report constructs and therefore the effects will be shared and diluted. Nevertheless, the extent to which depressive symptoms reflect preclinical disease is a major concern, and despite extensive statistical adjustments it is impossible to rule out unknown indicators of underlying disease or that depression and CVD are the products of common causes, such as genetics.

In summary, numerous intermediate mechanisms might explain the link between depression and CVD, ranging from behavioral to biological risk factors. It is, however, vitally important that the relative contribution of behavioral and pathophysiological processes in accounting for the depression-CVD link be reliably established. Taken together, the currently available data from epidemiological studies suggest varying contributions of different processes, which might differ according to the population (clinical vs healthy). Nevertheless, regardless of the characteristics of the study sample, behavioral pathways (especially physical activity and smoking) appear to be most relevant (Figure 3). Whether this reflects a measurement issue, in that chronic exposure is easier to capture for behavioral variables than psychobiological markers, is presently unclear. Given the very different treatment modalities that follow from a greater emphasis on either class of process, eg, behavior change and pharmacotherapy, these data would help establish priorities for the allocation of health care and research resources.

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Figure 3. Relative contributions of behavioral and psychobiological processes in explaining the association between depression and CVD.
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Depression and distressed (Type D) personality: what is their impact on cardiovascular outcomes?

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Depression and distressed (Type D) personality represent complementary perspectives on behavioral risk factors in cardiovascular patients. Type D refers to the combination of the negative affectivity and social inhibition personality traits, and highlights the chronic nature of emotional distress in some patients. Evidence from studies that compared Type D personality and depression indicates that both constructs are related, yet distinct prognostic risk factors for clinical events and poor patient-reported outcomes in cardiac patients. The increase in risk associated with Type D personality withstands adjustment for depression, and the evidence that Type D personality is associated with a higher prevalence of depressive symptoms in cardiac patients is robust. Assessment of Type D personality may enhance our understanding of the role of behavioral factors in cardiovascular patients.

Keywords: cardiovascular disease; coronary artery disease; depression; emotion; prognosis; risk factor; Type D personality

In the past two decades, depression has been studied extensively as a risk factor for cardiovascular disease. However, other negative emotional conditions such as anxiety and anger may also promote cardiovascular disorders, including coronary artery disease (CAD). More specifically, evidence indicates that general emotional distress—a broad, distress factor that is shared across personality construct is defined as: “The Type D (distressed) personality profile refers to a general propensity to psychological distress that is characterized by the combination of negative affectivity and social inhibition.”

As indicated in the paper describing Type D assessment, the Type D personality construct is based on a hierarchical model (Figure 1).

At the lowest level of personality organization, negative affectivity is represented by the facet scales dysphoria (NA1), anxious apprehension (NA2), and irritability (NA3). Negative affectivity refers to the tendency to experience negative emotions across time and situations. At the lowest level, social inhibition is represented by the facet scales social discomfort (SI1), reticence (SI2), and lack of social poise (SI3). Social inhibition refers to the tendency to inhibit the expression of emotions and behavior in social interaction. At the intermediate level, negative
affectivity and social inhibition can be assessed in their own right as continuous personality dimensions. At the highest, superordinate level, the overall Type D personality construct refers to the combination of high negative affectivity and high social inhibition.

Type D personality can be assessed in a standardized way with the 14-item Type D Scale or DS14. The DS14 comprises two 7-item subscales that measure the two components of the Type D construct at the intermediate- and low-order levels. Both the negative affectivity subscale (e.g., I am often in a bad mood, I often feel unhappy) and the inhibition subscale (e.g., I am a closed kind of person, I am inhibited in social interactions) are internally consistent (Cronbach’s α = 0.88 and 0.86, respectively), and have good construct validity. Using a cutoff score ≥10 on both these DS14 subscales, 4 patients are classified as Type D if they have an elevated score on both Type D components. On the basis of this classification, the prevalence of Type D personality has been estimated to range between 20% to 40%, across different manifestations of cardiovascular conditions. Recently, cross-cultural analysis of the DS14 measure of Type D in 6222 patients with ischemic heart disease from the International Heart-QoL Project confirmed the validity of the hierarchical Type D model (Figure 1) in 21 different countries around the world. 5

Meta-analytic research of prospective studies suggests that Type D personality may be associated with a 2- to 3-fold increased risk of poor health outcomes, such as cardiac death or myocardial infarction (MI) among patients with established cardiovascular disease. 3,6 Type D personality has also been associated with important patient-reported outcomes. Following an MI, Type D patients experience more cardiopulmonary symptoms, 7 and believe that their condition will be less responsive to treatment, 7 than non-Type D patients. Meta-analytic research confirmed that Type D was associated with a 2-fold increased odds for impaired physical health status and a 2.5-fold increased odds for impaired mental health status. 8

**FOCUS ON DEPRESSION AND TYPE D PERSONALITY**

The Type D personality construct was designed to enhance the early identification of patients who may be at risk for chronic emotional distress. Patients may go in and out of depressive episodes, but there are underlying vulnerability factors that may predispose cardiac patients to depression or other forms of emotional distress. The Type D profile is more stable than depressive episodes, and highlights the chronic nature of emotional vulnerability to distress in some individuals. Accordingly, Type D personality has been associated with an increased vulnerability for depression in the general population. 9,10

The main purpose of this review was to summarize the evidence of studies that compared Type D personality and depression as potential prognostic risk markers in patients with cardiovascular disorders. It should be clear from the outset that this does not imply that depression and Type D represent antonymous perspectives on emotional distress in cardiovascular populations. Nor does this imply that one perspective would be necessarily better than the other perspective in explaining or predicting cardiovascular events. As discussed previously, 3 both constructs represent complementary perspectives on the importance of behavioral factors in patients with a cardiovascular condition.

In the following paragraphs, the comparison of Type D personality and depression in cardiovascular research will focus on three selected issues: (i) the risk of adverse health outcomes and associated biological risk markers 11-26; (ii) the risk of poor patient-reported outcomes 27-37, and (iii) the risk of depression associated with Type D personality 38-47.

**TYPE D PERSONALITY, DEPRESSION, AND CARDIOVASCULAR EVENTS**

A number of studies have focused on the independent prognostic power of Type D personality as compared to depression, and on the association of Type D and depression with biological mechanisms as potential pathways of the link between emotional distress and cardiovascular events (Table I). 11-26 Ten of the 16 studies that reported on the relationship between Type D personality, depression and adverse health outcomes or biological risk markers included patients with established CAD, 11-20 three studies included patients with heart failure 21-23 and three studies included patients with cardiac arrhythmia 24-26.

Regarding health outcomes, some studies used all-cause mortality as an end point. In 1996, we reported that Type D independently predicted all-cause mortality in patients with CAD, whereas depressive symptoms...
## Table I. Type D personality, depression, and health outcomes/biological factors.

<table>
<thead>
<tr>
<th>Study (1st author)</th>
<th>Scale</th>
<th>Study population</th>
<th>Findings on Type D personality and depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study (1st author)</strong></td>
<td><strong>Scale</strong></td>
<td><strong>Study population</strong></td>
<td><strong>Findings on Type D personality and depression</strong></td>
</tr>
<tr>
<td>de Jonge, 2007</td>
<td>CIDI</td>
<td>1205 Post-MI patients</td>
<td>Type D was not confounded by disease severity, whereas depressive disorder was clearly associated with left ventricular dysfunction</td>
</tr>
<tr>
<td>Denollet, 1996</td>
<td>MBHI</td>
<td>303 Patients with CAD</td>
<td>Type D independently predicted cardiac death, whereas depressive symptoms were no longer significant in the multivariable model</td>
</tr>
<tr>
<td>Denollet, 1998</td>
<td>MBHI</td>
<td>87 Post-MI patients</td>
<td>Type D independently predicted the end point of cardiac death/MI, whereas depressive symptoms were not significant in the multivariable model</td>
</tr>
<tr>
<td>Denollet, 2000</td>
<td>HPPQ</td>
<td>319 Patients with CAD</td>
<td>Type D independently predicted the end point of cardiac death/MI, whereas depressive symptoms were not significant in the multivariable model</td>
</tr>
<tr>
<td>Denollet, 2006</td>
<td>HADS</td>
<td>875 Patients with CAD</td>
<td>Type D independently predicted major adverse cardiac events; depressive symptoms were not significantly associated with cardiac events</td>
</tr>
<tr>
<td>Denollet, 2008</td>
<td>BDI</td>
<td>337 Post-MI patients</td>
<td>After adjustment for depressive symptoms, Type D remained an independent predictor of major adverse cardiac events</td>
</tr>
<tr>
<td>Grande, 2011</td>
<td>HADS</td>
<td>977 Cardiac patients</td>
<td>Both Type D personality and depressive symptoms failed to predict all-cause mortality in multivariable analyses</td>
</tr>
<tr>
<td>Martens, 2010</td>
<td>HAM-D</td>
<td>473 Post-MI patients</td>
<td>Type D independently predicted the end point of cardiac death/MI, after adjustment for clinical assessment of depression severity</td>
</tr>
<tr>
<td>Molloy, 2008</td>
<td>BDI</td>
<td>70 Patients with CAD</td>
<td>Type D predicted higher cortisol levels, whereas depressive symptoms were not significantly associated with cortisol levels</td>
</tr>
<tr>
<td>Whitehead, 2007</td>
<td>BDI</td>
<td>72 Patients with CAD</td>
<td>Type D was associated with an increased cortisol waking response, adjusting for depressive symptoms at baseline</td>
</tr>
<tr>
<td>Coyne, 2011</td>
<td>BDI</td>
<td>706 Patients with CHF</td>
<td>Both Type D personality and depressive symptoms failed to predict all-cause mortality in multivariable analyses</td>
</tr>
<tr>
<td>Kupper, 2009</td>
<td>BDI</td>
<td>122 Patients with CHF</td>
<td>Type D was associated with oxidative stress, but depressive symptoms were not related to oxidative stress</td>
</tr>
<tr>
<td>Pelle, 2010</td>
<td>SAD4</td>
<td>641 Patients with CHF</td>
<td>Both Type D personality and depression/anxiety symptoms failed to predict all-cause or cardiac mortality in multivariable analyses</td>
</tr>
<tr>
<td>Lange, 2007</td>
<td>HADS</td>
<td>54 Patients with AF</td>
<td>Depressive symptoms predicted atrial fibrillation, whereas Type D was not associated with atrial fibrillation</td>
</tr>
<tr>
<td>Pedersen, 2010</td>
<td>ICDC</td>
<td>371 Patients with an ICD</td>
<td>Type D was associated with an increased risk of all-cause mortality, adjusting for ICD concerns as marker of disease-related emotional distress</td>
</tr>
<tr>
<td>van den Broek, 2009</td>
<td>BDI</td>
<td>391 Patients with an ICD</td>
<td>Anxious Type D patients were at increased risk of ventricular arrhythmias in the first year of ICD therapy; depression not related to arrhythmia</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; BDI, Beck Depression Inventory; CAD, coronary artery disease; CHF, chronic heart failure; CIDI, Composite International Diagnostic Interview; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression rating scale; HPPQ, Heart Patients Psychological Questionnaire; ICD, implantable cardioverter defibrillator; ICDC, ICD patient Concerns questionnaire; IHD, ischemic heart disease; MBHI, Millon Behavioral Health Inventory; MI, myocardial infarction; SAD4, Symptoms of mixed Anxiety-Depression index.
were no longer significant in the multivariable model. However, more recently we also reported that both Type D personality and symptoms of depression/anxiety failed to predict all-cause mortality in a study of patients with heart failure, and another recent study in patients with heart failure confirmed that both Type D personality and depressive symptoms failed to predict all-cause mortality in multivariable analyses. In addition, a study in a heterogeneous sample of cardiac patients with substantial somatic comorbidity found that Type D personality and depressive symptoms failed to predict all-cause mortality in multivariable analyses. In contrast, another study in patients with an implantable cardioverter defibrillator (ICD) reported that Type D personality did predict an increased risk of all-cause mortality, adjusting for ICD concerns as a marker of disease-related emotional distress.

Hence, Type D personality predicted all-cause mortality in patients with CAD or ICD, but both Type D or depression may have less power to predict all-cause mortality in patients with heart failure or in patients that are compromised by comorbid conditions. These findings suggest that the prognostic importance of psychological factors may be dependent upon the nature and severity of cardiac and other medical disorders. Regarding the effect of disease severity on psychological status, a large study of 1205 post-MI patients showed that left ventricular dysfunction may partly explain the incidence of depression, in contrast,

<table>
<thead>
<tr>
<th>Study (1st author)</th>
<th>Scale</th>
<th>Study population</th>
<th>Findings on Type D personality and depression</th>
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</thead>
<tbody>
<tr>
<td>Al-Ruzzeh,27 2005</td>
<td>HADS</td>
<td>437 Patients after CABG</td>
<td>Type D independently predicted poor health status at 1 year following CABG; depressive symptoms were not associated with health status</td>
</tr>
<tr>
<td>Mols,28 2010</td>
<td>BDI</td>
<td>501 Post-MI patients</td>
<td>Type D independently predicted poor health status and unstable angina 2 months post-MI, after adjustment for depressive symptoms</td>
</tr>
<tr>
<td>Pelle,29 2008</td>
<td>HADS</td>
<td>368 Patients with CAD</td>
<td>Type D independently predicted poor health status pre- and post-cardiac rehabilitation, after adjustment for depressive symptoms</td>
</tr>
<tr>
<td>Spindler,30 2007</td>
<td>HADS</td>
<td>167 Patients with CAD</td>
<td>Type D independently predicted the persistence of anxiety symptoms, after adjustment for depressive symptoms</td>
</tr>
<tr>
<td>van Gestel,31 2007</td>
<td>HADS</td>
<td>416 Patients with CAD</td>
<td>Type D independently predicted increased levels of anxiety symptoms, after adjustment for depressive symptoms</td>
</tr>
<tr>
<td>Wikman,32 2008</td>
<td>BDI</td>
<td>213 Patients with ACS</td>
<td>Type D was associated with posttraumatic stress, but was no longer significantly associated after adjustment for depressive symptoms</td>
</tr>
<tr>
<td>Schiffer,33 2008</td>
<td>BDI</td>
<td>166 Patients with CHF</td>
<td>Type D independently predicted poor health status, also after adjustment for depressive symptoms</td>
</tr>
<tr>
<td>Schiffer,34 2008</td>
<td>BDI</td>
<td>149 Patients with CHF</td>
<td>Type D independently predicted clinically assessed severity of anxiety severity; depressive symptoms did not predict anxiety severity</td>
</tr>
<tr>
<td>Smith,35 2007</td>
<td>BDI</td>
<td>136 Patients with CHF</td>
<td>Type D independently predicted more symptoms of general fatigue, after adjustment for depressive symptoms</td>
</tr>
<tr>
<td>Son,36 2012</td>
<td>HADS</td>
<td>114 Patients with AF</td>
<td>Type D was independently associated with poor health-related quality of life, adjusting for depressive symptoms</td>
</tr>
<tr>
<td>Versteeg,37 2012</td>
<td>HADS</td>
<td>272 Patients with ICD</td>
<td>Type D and depressive symptoms were both independently associated with poor device acceptance following ICD implantation</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndromes; BDI, Beck Depression Inventory; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, chronic heart failure; HADS, Hospital Anxiety and Depression Scale; HRQoL, Health-Related Quality of Life; MI, myocardial infarction.

Table II. Type D personality, depression, and patient-reported outcomes.
Type D personality was not associated with severity of systolic dysfunction. This finding suggests that depression may be more liable to reversed causality (disease causing depression) than Type D, but more research is needed to address this issue.

Clinical evidence in patients with CAD showed that Type D personality independently predicted the combined end point of cardiac death or (recurrent) MI, as well as the prevalence of nonsustained ventricular tachycardia. Two studies in patients with CAD showed that Type D personality also independently predicted the combined end point of major adverse cardiac events, including death, MI, and coronary revascularization. Depressive symptoms, however, were not significantly associated with adverse cardiac events in these two studies. After adjustment for other negative emotional conditions, such as anxiety or perceived stress, Type D personality has also emerged as an independent predictor of prognosis in patients with CAD. In addition, Type D personality has been shown to predict major adverse cardiovascular events in CAD patients who underwent invasive cardiac interventions such as percutaneous coronary intervention or cardiac surgery.

A number of studies investigated biological mechanisms as a potential pathway that may explain the link between emotional distress and poor prognosis in cardiac patients. Two studies in patients with CAD examined the stress hormone cortisol as such a potential pathway. These authors showed that Type D was associated with an increased cortisol awakening response and predicted higher daytime cortisol levels, whereas depressive symptoms were not significantly associated with cortisol. Accordingly, a study in patients with heart failure reported that Type D personality was associated with increased oxidative stress levels, whereas depressive symptoms were not related to oxidative stress. Research on biological mechanisms in patients with cardiac arrhythmia yielded mixed findings. In a study of patients with atrial fibrillation, self-reported depression, but not Type D, was associated with atrial fibrillation. Another study of patients with ICD found that depression was not related to arrhythmia, but that anxious Type D patients were at significantly increased risk of ventricular arrhythmias in the first year of ICD therapy.

**TYPE D PERSONALITY, DEPRESSION, AND PATIENT-REPORTED OUTCOMES**

Given the emerging importance of perceived health status and quality of life in cardiovascular research and practice, this review also focused on the role of Type D personality and depression regarding these patient-reported outcomes (Table II). Six of the 11 studies that reported on the relationship between Type D personality, depression, and patient-reported outcomes included patients with established CAD. Three studies included patients with heart failure, and two studies included patients with cardiac arrhythmia. In patients with CAD, Type D personality independently predicted patient reports of unstable angina and poor health status 2 months post-MI, after adjustment for depressive symptoms. This adverse effect of Type D personality on health status in patients with CAD seems to persist following invasive and noninvasive treatment. Type D personality, but not depression, was significantly associated with poor health status 1 year following coronary bypass surgery. In a clinical trial of cardiac rehabilitation among patients with CAD, Type D personality independently predicted an increased risk of poor health status both pre- and post-rehabilitation, after adjustment for depressive symptoms.

Type D has also been related to these outcomes in patients with cardiac arrhythmia. In patients with atrial fibrillation, Type D personality was independently associated with poor health-related quality of life, controlling depressive symptoms. In another study, Type D personality and depressive symptoms were significant independent correlates of poor device acceptance in patients with an ICD.

Research has also examined the role of Type D and depression as vulnerability factors for anxiety-related mental health problems. Among patients with an acute coronary syndrome, Type D personality was associated with posttraumatic stress symptoms at follow-up, but adjustment for depressive symptoms attenuated this association.

Two studies in patients with CAD found that Type D personality predicted the prevalence of increased post-MI.
The evidence that Type D personality is associated with a higher prevalence of depressive symptoms in cardiac patients is robust. In a study of patients with CAD who were free from depression at baseline, Type D personality predicted the onset of new depressive symptoms at 1 year following invasive treatment with percutaneous coronary intervention. Two studies examined Type D as a vulnerability factor for depressive symptoms in a combined sample of patients with either CAD or chronic heart failure. In the first study, Type D personality predicted depressive symptoms at 1 year follow-up, after adjustment for baseline levels of depression. In this study, it was Type D personality, but not disease severity that emerged as a vulnerability factor for depressive symptoms. In the second study, Type D remained a significant independent associate of depressive symptoms in adjusted analyses.

Type D is also related to the persistence of depressive symptoms in cardiac patients. Type D personality predicted the persistence of depressive symptoms in patients with an acute coronary syndrome and in post-MI patients, even after adjustment for depressive symptoms at baseline or the history of depression. Type D personality also independently predicted persistent depression after ICD implantation. Moreover, recent findings from a German study showed that Type D personality was an even stronger predictor for persistent depression in cardiac patients than depression at baseline.

Although Type D personality can be considered a vulnerability factor for depression and both constructs are related to some degree, conceptual differences and clinical evidence indicate that Type D personality and depression represent two distinct forms of emotional distress (Table III). From a conceptual point of view, Type D personality not only focuses on depressive affect or dysphoria, but also on the general distress shared across negative emotions. Accordingly, the hierarchical model of the negative affectivity component of Type D also includes the low-order traits anxious apprehension and irritability. Furthermore, the Type D hierarchical model holds that social inhibition should also be considered as a broad, stable trait that may modulate the effect of negative emotions.

Clinical evidence confirms that depression and Type D are only partly overlapping. In fact, most coronary patients with a Type D personality do not cross the diagnostic threshold for clinical depression. One study found that only one third (55/156) of distressed CAD patients had both Type D personality and increased levels of depressive symptoms, whereas 28% had Type D only and 37% had depression only.

This was confirmed in a study of 1205 post-MI patients, showing that only 1 out of 4 patients who were distressed in the year following MI met criteria for both Type D and depression (n=90/340); the majority of distressed post-MI patients had only one form of distress, but not the other. Moreover, evidence suggests that the assessment of Type D personality in post-MI patients is not confounded by changes in depressive symptoms over time. Finally, psychometric evidence using factor analytic research in a sample of patients with CAD or CHF clearly showed that the negative affectivity and social inhibition components of the Type D construct loaded on distinctly different dimensions than standard depressive symptoms.
Overall, the findings presented above suggest that Type D personality may help to identify psychologically vulnerable patients with a cardiovascular condition who tend to experience feelings of depression. This link between Type D and increased vulnerability for depression is not limited to cardiovascular populations, but has also been observed in other medical populations and in the general population.\(^9,10\)

Importantly, Type D is also related to the prevalence of suicidal ideation, even after adjustment for depressive symptoms.\(^51\)

**TYPE D PERSONALITY AND PATHWAYS OF DISEASE**

A number of Type D studies investigated several mechanisms as potential pathways that may explain the link between personality and cardiovascular events. There is some evidence to suggest that Type D personality may be associated with cardiovascular events through behavioral pathways. Type D has been associated with an unhealthy lifestyle such as lack of physical activity\(^9,52\) or an unhealthy diet\(^53\). In addition, individuals with a Type D personality profile are more vulnerable to stress across situations\(^48\) and are more likely to use disengagement or other maladaptive coping strategies in the face of stress.\(^54,55\)

Regarding coping with a medical condition, Denollet et al.\(^56,57\) discussed the role of Type D personality in depression and cardiovascular outcomes. They observed differences in psychological distress among patients with Type D personality compared to those without. The table below summarizes the findings from these studies:

<table>
<thead>
<tr>
<th>Study (1st author)</th>
<th>Scale</th>
<th>Study population</th>
<th>Onset and prevalence of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pedersen, 38 2006</td>
<td>HADS</td>
<td>542 Patients with CAD</td>
<td>In patients who were free from depression at study enrollment, Type D predicted the onset of depressive symptoms at 1 year following PCI</td>
</tr>
<tr>
<td>Smith, 39 2008</td>
<td>MQ-D</td>
<td>506 Patients CAD or CHF</td>
<td>Type D independently predicted depressive symptoms at 1 year follow-up, after adjustment for baseline levels of depressive symptoms</td>
</tr>
<tr>
<td>Spindler, 40 2009</td>
<td>HADS</td>
<td>707 Patients CAD or CHF</td>
<td>Type D remained a significant independent associate of depressive symptoms in adjusted analyses</td>
</tr>
<tr>
<td>Doyle, 41 2011</td>
<td>HADS</td>
<td>375 Patients with ACS</td>
<td>Type D independently predicted the persistence of depressive symptoms, adjusting for baseline depression</td>
</tr>
<tr>
<td>Martens, 42 2008</td>
<td>BDI</td>
<td>287 Post-MI patients</td>
<td>Type D independently predicted the persistence of depressive symptoms, adjusting for history of depressive disorder</td>
</tr>
<tr>
<td>Pedersen, 43 2011</td>
<td>HADS</td>
<td>386 Patients with ICD</td>
<td>Type D independently predicted persistence of depressive symptoms at 3 months following ICD implantation</td>
</tr>
<tr>
<td>Romppel, 44 2012</td>
<td>HADS</td>
<td>679 Cardiac patients</td>
<td>Type D was an even stronger predictor for the persistence of depressive symptoms, than depression at baseline</td>
</tr>
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<table>
<thead>
<tr>
<th>Study (1st author)</th>
<th>Scale</th>
<th>Study population</th>
<th>Persistence of depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denollet, 16 2008</td>
<td>BDI</td>
<td>337 Patients with CAD</td>
<td>Of the 156 distressed patients, 28% (n=43) were Type D and 37% (n=58) had depression; only 35% (n=55) had both forms of emotional distress</td>
</tr>
<tr>
<td>Denollet, 45 2009</td>
<td>CIDI</td>
<td>1205 Post-MI patients</td>
<td>Of the 340 distressed patients, 39% (n=134) were Type D and 34% (n=116) had depression; only 27% (n=90) had both forms of distress</td>
</tr>
<tr>
<td>Martens, 46 2007</td>
<td>BDI</td>
<td>475 Post-MI patients</td>
<td>The assessment of Type D classification was not confounded by changes in depressive symptoms over time</td>
</tr>
<tr>
<td>Pelle, 47 2009</td>
<td>BDI</td>
<td>565 Patients CAD or CHF</td>
<td>Type D traits and depressive symptoms loaded on distinctly different dimensions in factor analytical research</td>
</tr>
</tbody>
</table>

**Table III. Type D personality and vulnerability for depression.**

BDI, Beck Depression Inventory; CAD, coronary artery disease; CHF, chronic heart failure; CIDI, Composite International Diagnostic Interview; HADS, Hospital Anxiety and Depression Scale; MQ-D, depression subscale of the Maastricht Questionnaire; MI, myocardial infarction.
condition, Type D has been shown to predict poor medication adherence in post-MI patients. Similarly, Type D has been related to poor adherence to continuous positive airway pressure treatment of obstructive sleep apnea.

As noted above, several studies showed that Type D is also associated with a number of biological pathways, also after adjustment for depression. These mechanisms included increased cortisol levels, oxidative stress and risk of ventricular arrhythmia. A number of these biological mechanisms have also been documented in healthy Type D individuals, suggesting that these associations cannot be explained away by the confounding effect of underlying cardiovascular disease. In experimental research with healthy individuals, Type D has been related to greater cortisol reactivity to stress, as well as higher cardiovascular stress reactivity, including increased heart rate, blood pressure, and cardiac output.

Autonomic dysregulation can also be inferred in healthy Type D individuals on the basis of their higher resting heart rate as compared with non-Type Ds. Type D has been related to reduced heart rate recovery in patients with heart failure.

Other studies found that Type D was associated with inflammatory dysregulation. Type D has been related to higher concentration of C-reactive protein in healthy adults and in patients with atrial fibrillation. Other research showed that Type D personality was associated with increased plasma levels of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) and its soluble receptors 1 and 2 in heart failure patients. Finally, the number of bone-marrow derived endothelial progenitor cells that play a role in maintaining vascular integrity were reduced by more than 50% in Type D patients with heart failure.

**CLINICAL RESEARCH AND PRACTICE**

The evidence that has been summarized here clearly supports the notion that Type D personality and depression are related, yet distinct, risk factors for adverse health outcomes in patients. Among other things, this paper provides evidence showing that the increase in prognostic risk associated with Type D personality withstands adjustment for depression. Of course, the findings of this review should be put into perspective in view of the large number of depression measures that were used in these studies. Most studies used self-report measures of depressive symptoms such as the Beck Depression Inventory, Hospital Anxiety and Depression Scale, or other self-report measures. Clinical depression was assessed with the Composite International Diagnostic Interview (CIDI) or Hamilton Depression rating scale in 3 studies.

Some have argued that Type D does not have meaningful implications in terms of intervention because it refers to personality traits that may be less likely to change. Others have argued that it is plausible that cardiac patients with a Type D personality may learn new strategies to reduce their level of general distress; in other words, they are not “doomed” because they have this personality profile. Behavioral interventions like stress management training, relaxation training, social skills training, or psychotherapy could have the potential to reduce stress levels in Type D patients and improve the way they deal with their emotions in social interactions. However, clinical research still needs to examine the extent to which behavioral or psychopharmacological intervention may also alter the risk of Type D patients for adverse cardiac events. Currently, there are a number of ongoing clinical trials that are investigating the effect of intervention in patients with Type D personality.

In terms of invasive cardiac interventions, there is some evidence to suggest that Type D personality may have an adverse effect on the outcome of these interventions. Research in the Netherlands suggests that Type D personality may be related to an increased risk of death or MI in CAD patients who were treated with percutaneous coronary artery stenting. In a British study, Type D personality was associated with a significantly impaired patient-reported health status at 1 year following coronary artery bypass surgery, and in a Hungarian study, Type D predicted an increased risk of adverse cardiovascular events at five following cardiac surgery. Finally, Type D personality also independently predicted an increased risk in all-cause mortality, life-threatening ventricular arrhythmia, increased symptom levels of anxiety, and poor device acceptance in cardiac patients who were treated invasively with an ICD implantation.

In addition to the prevailing focus on depression as a behavioral risk marker in the cardiovascular literature, the Type D construct highlights the importance of also considering more chronic, subclinical forms of psychological distress that may affect the clinical course of some cardiac patients. Patients may differ substantially in their vulnerability to psychological distress, which implies that we need to have a differentiated view at the way different psychological factors combine as determinants of cardiovascular and...
patient-reported outcomes. Accumulating evidence suggests that CAD patients who have a Type D personality profile may be particularly prone to the adverse health effects of general distress, although this association is less obvious in patients with heart failure.

In conclusion, Type D personality refers to a more covert, chronic form of emotional distress that only partly overlaps with depression and that has incremental prognostic and explanatory value as compared with depression or with other personality trait ratings. The present summary article showed that the general propensity to distress, as defined by the Type D construct, may have a substantial effect on cardiovascular outcomes, irrespective of measures of depression. This is not to say that one approach is better than the other. Rather, both approaches to distress and heart disease represent complementary perspectives that may benefit cardiovascular research and practice. Unfortunately, individual differences in Type D personality are often ignored in risk stratification and estimates of the vulnerability for depression or other emotional disorders among patients with a cardiovascular condition. The DS14 is a brief, easy-to-use measure of Type D personality that has been shown to have a high degree of cross-cultural validity. By using this scale in future research, we can examine whether accounting for individual differences in Type D personality would enhance a more personalized approach to cardiac care.

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How should we treat depression in patients with cardiovascular disease?

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Among patients with cardiovascular disease (CVD), depression is highly prevalent and is associated with worse cardiovascular prognosis and lower quality of life. Treatments for depression in CVD patients produce modest, but clinically significant, reductions in depressive symptoms and show promise for improving cardiovascular prognosis. While tricyclics should generally be avoided, antidepressants from multiple other classes appear to be safe in cardiac patients. A strategy of engaging patients in choosing medications or psychotherapy and then intensifying treatment to therapeutic goal appears to be more effective at reducing depression than single-mode interventions. Recommendations for screening all CVD patients for depression may be premature given increased costs associated with screening and gaps in knowledge about the risk-benefit ratio of depression treatment in mild and moderately depressed patients.

Patients with cardiovascular disease (CVD) have a twofold increased risk of depression compared with patients without heart disease. Additionally, the presence of depression in CVD patients is associated with increased mortality, cardiac events, and health care costs, as well as lower quality of life and adherence to recommended treatments. Given the high impact of comorbid depression on medical, quality of life, and societal outcomes in patients with CVD, a growing body of research has assessed the effectiveness of depression interventions in these patients. While a tantalizing goal of depression treatment is the possibility that it might improve cardiovascular prognosis, the remission of depression, alone, is a worthy goal of depression treatment as depression is a major contributor to lower quality of life and increased health care costs in CVD patients.

Before evaluating the effectiveness of depression treatments in CVD patients, it is important to consider why treatment of depression in such patients may differ from treatment of depression in the general population. First, there is heightened concern regarding the possibility of cardiotoxic effects of some depression treatments. Second, if the depressive symptoms are in reaction to the stressful medical event (e.g., an adjustment disorder in reaction to the CVD event), then the symptoms are likely to spontaneously remit without screening and treatment. Third, the acceptability of a

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<tr>
<td>CAST</td>
<td>Cardiac Arrhythmia Suppression Trial</td>
</tr>
<tr>
<td>COPES</td>
<td>Coronary Psychosocial Evaluation Study</td>
</tr>
<tr>
<td>CREATE</td>
<td>Canadian Cardiac Randomized Evaluation of Antidepressant and psychoTherapy Efficacy</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>ENRICHD</td>
<td>ENhanced Recovery In Coronary Heart Disease patients [trial]</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>MIND-IT</td>
<td>Myocardial INFarction and Depression–Intervention Trial</td>
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<tr>
<td>SADHART</td>
<td>Sertraline AntiDepressant Heart Attack Randomized Trial</td>
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<tr>
<td>SSRI</td>
<td>serotonin-specific reuptake inhibitor</td>
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psychiatric treatment may differ in patients for whom CVD is the primary disease. Fourth, although mild subsyndromal symptoms of depression have been associated with worse prognosis in CVD patients, it is not clear whether standard depression treatments will benefit CVD patients with milder depressive symptom burden. With these considerations in mind, below we review the evidence behind single-modality and combined interventions involving pharmacotherapy, psychotherapy, or other approaches to treating depression in CVD patients (Table I, page 128).³⁸

**ANTIDEPRESSANT MEDICATIONS**

Concern about the safety of antidepressant medications in cardiac patients emerged from the experience gained from CAST (Cardiac Arrhythmia Suppression Trial) in which increased mortality was reported in post–myocardial infarction (MI) patients treated with Class 1 antiarrhythmics. Because tricyclic antidepressants belong to the group of Class 1a antiarrhythmics, tricyclic antidepressants are presumed to be unsafe for use in depressed patients with ischemic heart disease.³ Subsequent to CAST, investigators have carefully explored the safety and benefits of newer-generation antidepressants in CVD patients.

The first large-scale trial carefully assessing the safety of serotoninn-specific reuptake inhibitors (SSRIs) in CVD patients was SADHART (Sertraline AntiDepressant Heart Attack Randomized Trial) in which sertraline was used in the treatment of major depression in patients with acute myocardial infarction or unstable angina.⁴ In this study, 369 participants with major depressive disorder after MI were randomized to sertraline or placebo. The primary outcome was change in left ventricular ejection fraction (LVEF) at 4 months. SADHART also assessed the effectiveness of sertraline at reducing depressive symptoms. Sertraline was found to have short-term safety with respect to LVEF as well as safety for secondary outcomes including blood pressure and ECG characteristics.

Although sertraline demonstrated short-term safety, it did not significantly reduce depression symptoms in the overall sample according to the primary depression rating scale. This study, however, was not powered to detect differences in depression symptoms. Subsequent trials have assessed the effectiveness of other antidepressants in CVD patients. Antidepressants tested include citalopram CREATE (Canadian Cardiac Randomized Evaluation of Antidepressant and psychoTherapy Efficacy)⁵ and mirtazepine MIND-IT (Myocardial Infarction and Depression–Intervention Trial).⁶ and of these two, only citalopram resulted in a clear reduction in depression symptoms and increase in depression remission. A Cochrane meta-analysis of antidepressant trials showed that, overall, antidepressants produce a small, but clinically significant reduction in depression symptoms and result in reduced rehospitalizations for combined cardiac and noncardiac diagnoses.⁷

The Cochrane meta-analysis also examined the effect of antidepressants in depressed CVD patients on cardiac outcomes and all-cause mortality. The meta-analysis showed that although antidepressants were associated with lower odds of mortality and recurrent cardiac events, the confidence intervals for these comparisons crossed 1 such that they did not reach the predefined significance level.⁷ A separate meta-analysis that only included trials of SSRI antidepressants concluded that SSRI use was associated with a significant decrease in CVD readmission (risk ratio, 0.63; 95% CI, 0.46 to 0.86) and mortality rates (risk ratio, 0.56; 95% CI, 0.35 to 0.88).⁸ This meta-analysis, however, included data from nonrandomized samples.

**PSYCHOTHERAPY**

The largest study of depression treatment in CVD patients is the ENRICHD (ENHanced Recovery In Coronary Heart Disease patients) trial.⁹ This study randomized 2500 post–myocardial infarction (MI) patients and tested whether enhanced treatment of depression with cognitive behavioral therapy (augmented by sertraline for treatment nonresponders) could improve both depression and event-free survival. While the intervention significantly decreased depressive symptoms, there were no significant differences in all-cause mortality or MI recurrence between the intervention and usual care arms. Subgroup analysis showed that while there was a trend toward benefit in men, there was a nearly significant P-value for harm in women (P<0.03 for the interaction between arms and gender for MI recurrence/death). Post-hoc adjustment for age and Charlson comorbidity index attenuated the interaction considerably (P<0.20), but there is no other sufficiently-powered trial to determine if this was a chance finding, or if some harm might accrue to female MI patients provided with psychological depression treatment. While the results of ENRICHD were a disappointment to experts in the field of behavioral cardiology, commentators noted that: (i) the cognitive behavioral therapy treatment yielded only modest improvements in depression with an effect size of 0.31 (typically considered a “small” effect size), and (ii) usual depression care resulted
Table 1. Summary of key trials of depression treatment in patients with cardiovascular disease.
in greater improvements than expected, possibly because some of the depressed cases had adjustment disorder that spontaneously remitted, and possibly because participation in the trial led to greater awareness of depression and this improved usual depression care.

Researchers have subsequently tested other psychological treatments for depression including interpersonal psychotherapy and supportive stress management. These approaches overall resulted in small benefits in improving depression on the same order of magnitude as pharmacologic based interventions. No trial of psychological intervention, alone, has yet been associated with a reduction in cardiovascular outcomes or mortality, but as mentioned above, only one has had a sufficient number of patients to actually test this properly.

There are a few examples of head-to-head comparisons between different types of psychological interventions or between psychological and pharmacologic interventions for depression treatment in CVD patients (Figure 1).

The CREATE trial (Canadian Cardiac Randomized Evaluation of Antidepressant and psychoTherapy Efficacy) involved a full factorial design with four arms: citalopram + interpersonal psychotherapy, citalopram + clinical management, placebo + interpersonal psychotherapy, and placebo + clinical management. In this trial, citalopram outperformed interpersonal psychotherapy in reducing depression in patients with stable coronary artery disease. Freedland et al compared cognitive behavioral therapy with stress management in post–coronary artery bypass graft (CABG) patients and found cognitive behavioral therapy more effective.

**COMBINED APPROACHES**

In mental health and primary care settings, evidence suggests that combinations of psychotherapy and antidepressants are better than either treatment modality alone. Furthermore, many patients hold preferences for one mode of mental health treatment over another. For example, while some patients have heightened concerns about side effects of antidepressant medications, others are skeptical of the potential for benefitting from psychotherapy or may lack the time and financial resources to attend multiple psychotherapy appointments. Accordingly, in an effort to develop more potent depression interventions, cardiovascular researchers have tested enhanced depression care interventions in which patients choose their initial treatment modality and then are followed by mental health specialists who intensify or “step-up” treatment when depression symptoms are not remitting. This patient-preference, stepped-care approach resulted in a larger depression treatment effect size in one trial of post–acute coronary syndrome (ACS) patients ([COPES] Coronary Psychosocial Evaluation Study, effect size 0.59). Participants in the intervention group of this study were all given access to problem-solving psychotherapy at no cost. Notably, the COPES intervention also resulted in a borderline significant short-term reduction in recurrent cardiovascular events ($P=0.05$).

**OTHER TREATMENTS**

Exercise is effective at treating depression in the general population. Accordingly, trials are under way.
The role of β-blockers

Historically, there have been concerns that β-blockers, a mainstay of secondary prevention in post-MI patients, cause or exacerbate depressive symptoms. β-Blockers can be associated with adverse side effects, including fatigue and, in some cases, sexual dysfunction. However, rigorously conducted, placebo-controlled, studies have since disproven the conventional wisdom that β-blockers worsen overall depressive symptoms. While this does not preclude the possibility that certain individuals are susceptible to rare depressogenic side effects of β-blockers, this class of drug should not be denied to depressed patients for this reason. Instead, careful attention should be paid to ensuring that depressed patients are using all available evidence-based risk-reducing pharmacologic treatments since these patients are at elevated risk for cardiac events.

UNANSWERED QUESTIONS

Who are the optimal patients to target for enhanced depression treatment?

Existing trials of depression treatments have used a heterogeneous set of eligibility criteria, both in terms of the nature of CVD (acute versus stable) and with respect to the severity and timing of depression symptoms. Elevated depressive symptoms frequently remit without treatment after hospitalization for ACS. Hence, targeting depression treatments at persistent, rather than remittent, depressed patients may lead to greater relative benefits. Further, in noncardiac populations, there is evidence that antidepressant medications are only effective in patients with severe depressive symptoms. Hence, while even mild depressive symptoms confer increased risk in CVD patients, novel interventions may be needed to reduce this type of milder depression in CVD patients. Depression is a heterogeneous condition comprised of both somatic and psychological symptoms. There are data demonstrating that patients with anhedonic (lack interest or pleasure in doing things), but not depressive, symptoms have increased risk for poor cardiac outcomes. Hence, targeting anhedonic depression may be more effective at improving cardiovascular prognosis. Finally, some studies have shown that patients with first onset of depression after acute coronary events are at especially high risk for poor subsequent prognosis. This may represent an important group of depressed CVD patients to target in future studies.

Should all CVD patients be screened for depression?

Despite the extensive epidemiology connecting depression and poor prognosis in CVD patients, recent surveys have shown that many cardiologists are unaware of the epidemiology associating depression and CVD and even fewer screen or treat depression. Accordingly, several professional societies including the American Association of Family Physicians and multiple European societies of cardiovascular disease prevention have published guidelines for the management of depression in CVD patients and, in 2008, the American Heart Association (AHA) published a science advisory recommending routine screening for depression in CVD patients. This AHA publication led to considerable controversy by leaders in the field.

On the one hand, proponents argued that depression screening when tied to depression care management programs is already evidence-based for primary care and
can be assessed with as few as two questions. Proponents further argued that depression treatments appear to be safe and similarly effective at reducing depression in CVD patients as compared with the general population, and may potentially improve prognosis. Others, however, are concerned that there is insufficient information to recommend depression screening. Many patients identified through screening will have mild symptoms that are unlikely to benefit from current treatments and may spontaneously remit. Further, while depression treatments appear to be safe, there was a trend toward harm from psychological treatment among women in ENRICHD, and the long-term consequences of newer-generation antidepressants in CVD patients remain poorly understood. Those opposed to universal screening point out that while screening may be brief, the consequences of screening may consume significant health care resources with unclear benefits.

SUMMARY AND RECOMMENDATIONS FOR TREATING DEPRESSION IN CVD PATIENTS

A variety of depression treatments are effective in depressed CVD patients. Although there is a need to develop more potent depression interventions for CVD patients, the effect size of such treatments with respect to reducing depression is similar in CVD patients as compared with the general population (Figure 2). Other than one trial for which the effect of the intervention on prognosis was a secondary outcome, depression treatment has not thus far been proven to offset the risk of depression on cardiovascular prognosis. However, only one trial of depression treatment has been adequately powered to assess this outcome, and when analyzed together, depression interventions show promise for being able to not only reduce depression, but reduce major adverse cardiac events and mortality as well (Figure 3). Accordingly, there is a need for additional trials of our most potent depression interventions in CVD patients.

Figure 2. The effect sizes of pharmacotherapy for depression are similar in trials of patients with cardiovascular disease as compared to the general population. The estimate for the effect size of antidepressants in the general population is based on a systematic review of 125 published and unpublished trials.

Figure 3. Comparison of effect sizes of depression treatments on cardiovascular outcomes and/or all-cause mortality in patients with cardiovascular disease.

Abbreviations: CBT, cognitive behavioral therapy; IPT, interpersonal psychotherapy; PST, problem-solving therapy. Acronyms of studies: see Box on page 126.
Clinicians can also consider screening all CVD patients for depression; however, current evidence has not verified that this is a cost-effective approach. Structured depression assessment tools like the Patient Health Questionnaire-9 (PHQ-9), comprised of 9 items that ask about the frequency of symptoms used to diagnose depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) classification system, can be useful supplements to clinical interviews. In addition, serial measurements of depression severity using such tools can be helpful for tracking the effectiveness of depression treatments. Patients with minimal symptoms can be observed with a plan to re-assess symptoms at a later date. In contrast, patients with severe symptoms or at risk for suicide should be urgently assessed by a mental health specialist. Patients with mild-to-moderate symptoms should be educated about treatment options and should then be asked for their preferred approach. Unless patients have severe symptoms or are at risk for suicide, observation with scheduled follow-up remains a reasonable option, as depression symptoms may spontaneously remit especially if they developed after acute coronary events. Clinicians will benefit by being informed as to the availability and affordability of treatment options in their health care system, especially nonpharmacologic ones. Ideally, clinicians will have identified mental health specialists or collaborative care managers with expertise in managing patients with comorbid depression and CVD. With patient preferences in mind, patients can then be referred to appropriate specialists and/or antidepressants can be initiated by the treating provider. Close collaboration with mental health specialists or other members of the treatment team will be important to ensure that depression treatment is optimized. Clinicians should be cautioned that these recommendations are opinion-based, and not evidence-based, as neither a depression screening or CVD outcome randomized trial has been performed yet to directly inform clinical practice.

Other than ensuring that depressed patients are receiving appropriate depression treatment, clinicians should pay special attention to risk factor control and to adherence problems. The use of nonjudgmental language during adherence assessments, and possibly validated adherence assessment tools such as the Morisky Medication Adherence Questionnaire, may facilitate more accurate adherence assessments.

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Heart and Literature

HEART OF MYTH – HEART OF SCIENCE

Part I

Harriet Martineau’s cardiac symptoms: a Victorian case history

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This article explores the history and meanings of the heart and its diseases as aspects of the histories of science and emotion. Analyzing the twofold meanings of the heart as both bodily object and cultural symbol, it explores the reasons for the apparent conflict in meanings of the heart of science and the heart of emotion in Western medical culture since the 19th century. In Part I, a case study of the writer, economist, and philosopher Harriet Martineau is used to demonstrate and trace that conflict, while Part II highlights the manifold meanings of the heart both in the past and in the present.

A radical transition in medical theory took place between the late 19th and early 20th centuries, as the heart was divorced by science from the status of cultural symbol and center of cognitive faculties (attributes it had been invested with since the dawn of time by most civilizations), to become a bodily organ with a mere pump function.

Through a case study of one particular woman—Harriet Martineau, a writer, economist, philosopher, and early feminist—I will explore the ways the heart in general, and the diseased heart in particular, became the site for a series of conflicts about identity, illness, and gendered sensibility in Victorian England. After considering Martineau’s claims that she suffered from heart disease, a narrative of weakness and invalidity that has often been reproduced by literary historians without reference to the medical testimony, I will examine the response of her doctors, and consider that response against the backdrop of increased medicalization, professionalization, and objectification of cardiac medicine. I will show that Martineau’s claims of heart disease were deliberately constructed in order to avoid what was, to her, a far worse diagnosis.

HARRIET MARTINEAU: WRITER, PHILOSOPHER, AND JOURNALIST

Harriet Martineau (1802-1876) was born in Norwich to a textile manufacturer of Huguenot descent. A sickly child, she suffered from anosmia and grew deaf at the age of 20. In 1821, she started writing articles for a Unitarian journal, the Monthly Repository. Left with very little means at the age of 24 after the death of her father, she started a career in writing, becoming a successful author and prolific journalist, writing extensively for the daily and weekly press. After spending two years in the United States (1834-1836), she became a staunch advocate of abolitionism. After early works on religion (Unitarianism) and morals, she turned to political economy and sociological themes, both factual and in the form of novels.
She befriended John Stuart Mill, Thomas Malthus, George Eliot, Elizabeth Barrett Browning, Thomas Carlyle, Florence Nightingale, Charlotte Brontë, and Charles Darwin, among many others belonging to the intellectual elite of her time. She embraced philosophical atheism, feminism, and Malthusianism. An admirer of Auguste Comte, the founder of sociology and positivism (which holds that only knowledge based on experimentation is valid), she translated his *Philosophie Positive*. In 1839, her health deteriorated and she became an invalid. Recovering in 1844, she claimed that mesmerism had healed her, and published the *Letters on the Laws of Man’s Social Nature*, which raised much controversy because of its agnostic content and support of mesmerism. In 1855, Martineau’s health deteriorated again, a state she ascribed to heart disease. Believing she was close to death, she started working on her autobiography—though she lived on another 20 years, producing a steady stream of articles, studies, and novels.

**SELF-DIAGNOSIS: “A HEART TOO FEEBLE FOR ITS WORK”**

To Martineau and her circle, heart disease signified something other than weakness and invalidity. In the cultural and emotional world of the 19th-century literary elite, heart disease was a sign of immense creativity and sensitivity. While heart disease itself might feature very differently in the imaginations of cardiac specialists and patients then, definitions of cardiac pathology also differed, depending both on the means by which the assessment was made, and on the interpretative lens being used.

In her *Autobiography*, published posthumously in 1877, Harriet Martineau complained that she had been suffering from unusual heart symptoms. She detailed how she:

> Had been kept awake for some little time at night by odd sensations at the heart, followed by hurried and difficult breathing... the disturbance on lying down increased, night by night. There was a creaking sensation at the heart (the beating of which was no longer to be felt externally), and, after the...
creek, there was an intermission, and then
a throb. When this had gone on for a few min-
utes, breathing became perturbed and dif-
cult, and I lay till two, three, or four o’clock,
struggling for breath. When this process
began to spread back into the evening, and
then forward into the morning, I was con-
vinced that there was something seriously
wrong.  

The words used by Martineau sketch
out rather accurately the symptoms of
cardiac disease as illustrated in medi-
cal treatises of the time. In particular,
the shortness of breath, the creaking
sound, the worsening at night or when
lying down, all were commonplace
symptoms for congestion of the heart
accompanied by shortness of breath,
or dyspnea. Immediately after experi-
encing these symptoms, Martineau
began to write to her friends to tell
them of her decline. She became, in
her words, “convinced” that there was
“something seriously wrong” with her
heart, a conviction that was apparent-
ly proved correct when she received
a terminal diagnosis from Peter Mere
Latham and Sir Thomas Watson, two
of the country’s most eminent cardiac
specialists. At the age of 53, Marti-neau’s heart had become simply “too
feeble for its work.”

Although she lived until 1876, Marti-neau recorded her subsequent death in
a self-penned obituary that was tagged
to the Daily News’ introduction to
Martineau’s Autobiography in 1876.

Her disease was deterioration and en-
largement of the heart, the fatal character
of which was discovered in January, 1855.
She declined throughout that and subse-
quent years, and died.

It is clear that in preparing herself, and
her readers, for her death, heart dis-
ease became the logical end point of
Martineau’s life. Martineau suffered
years of chronic ill-health, and her in-
structive narrative on how best to care
for an invalid—entitled Life in the
Sickroom—has become a well-read
piece of Victorian self-fashioning. Yet,
 despite an extensive historiography
on Martineau and on Life in the Sick-
room, there has been no systematic
analysis of Martineau’s status as a
heart disease patient, or the reasons
why cardiac disease might have pro-
vided Martineau with a valid vehicle
for self-fashioning.

THE CARDIOLOGISTS’
DIAGNOSIS:
PETER LATHAM

Situating Martineau’s case in the con-
text of contemporary medical and
literary attitudes toward the heart,
emotions, and disease, I would like to
suggest that in self-identifying with
cardiac disease, Martineau appropri-
ated medical authority. This is a differ-
ent matter from disagreeing with her
physicians’ diagnosis on the basis of
her own “lived experience,” a charac-
teristic that historians have often as-
sociated with Martineau’s varied af-
fections. Martineau did not claim to

know something more than her physicians; she harnessed their authority in order to declare herself a heart disease patient. Her physicians were also the most respected authorities available. Along with Latham (“Heart Latham” as he was known), Watson was nationally recognized as a key cardiac specialist. In 1859, Watson was also appointed physician extraordinary to the Queen, and he served as President of the Royal College of Physicians from 1862. His Lectures on the Principles and Practice of Physic was published between 1840 and 1842, and it was the chief English textbook of medicine for the next thirty years.5

Peter Mere Latham was contacted by several of Martineau’s literary friends when they began to experience the symptoms of cardiac disease—the propensity of which I will come back to later in this paper. Among those friends were Thomas Arnold, the educational reformer who died suddenly of angina pectoris, and his son Matthew Arnold, the poet. Those “odd sensations” about her breast became followed by periods of difficult breathing and even—when reading in the daytime—some apparently connected difficulties with her vision.6 When Martineau began to experience this “hurried and difficult breathing,” and a “creaking sensation of the heart,” she contacted Latham, reporting to friends that she was fully prepared, even eager, to take on whatever diagnosis might emerge, recording how “that honest and excellent physician knew beforehand that I desired to know the exact truth, and he fulfilled my wish.”7

As was usual for the period, Martineau initially became involved with Latham through a correspondence relationship, and many of Latham’s letters to Martineau survive. I can find no trace of Martineau’s own letters to Latham. These may have been casualties of another aspect of Martineau’s self-fashioning. In 1843, she ordered all her correspondents to destroy her letters to them, upon pain that she would never write to them again.8

In his first letter to Martineau, dated 12 January 1855, Latham was evidently responding to her described symptoms of breathlessness at night and when lying down, but also to a more general account of her health and habits that she had given him. He advised that “the effect of the remedy often serv[ing] to interpret the disease”—Latham advised that she take a “very mild opiate (1/8 of a grain), in combination with ammonia.” This very common aid to pain relief was recommended taken with water every six hours for the space of a week. During this time, Latham cautioned, Martineau was to ensure that she was not constipated, that she took moderate exercise, and drank a little wine.

On 18 January, less than a week later, Latham wrote again to Martineau. Her symptoms had apparently worsened since his previous correspondence. Latham was reluctant to “strike any hard blows in the dark,” so instructed her to “give up altogether” the treatment that he had previously recommended. “From what your letter of today tells me of your present condition it will not be safe for me to venture further upon your treatment without seeing you.” Yet Latham instructed Martineau not to visit him, advising against travel to London “in this cruel weather.”12

Soon after her receipt of this letter, Martineau arrived in London, staying at the lodgings of John Chapman, physician and editor of the Westminster Review.13 Her rationale for this choice of lodgings was explicit: she “felt it so probable that I might die in the night” that she refused to go to the house of her “nearest friends, or of any aged or delicate hostess.” At the Chapman’s residence, “all possible care would be taken of me without risk to anyone.”14 It was at these lodgings that Latham had first visited Martineau on the day after she arrived in London.

Martineau later described that examination to her friend, Maria Weston Chapman. Martineau had met Chapman, a prolific American abolitionist, during a visit to Boston in 1835. Chapman was requested by Martineau to conclude the final part of Martineau’s
Autobiography after her death. Chapman agreed, and the result was the Memorials, appended to the third volume of the Autobiography. This contribution was explicitly influenced by the letter she received from Martineau on 24 January 1855. In it, Martineau revealed that “the first man for heart complaints” had just “made a long examination [of Martineau’s chest] by auscultation.” He “did not attempt to conceal the nature and extent of the mischief”:

From his being unable to feel the pulsation of the heart in any direction, while it is audible over a large surface, he believes that the organ is extremely feeble in structure. — “too weak for its work”—and very greatly enlarged.

With expressed regret, therefore, Martineau informed her friend she was “mortally ill,” having suffered some months from “what now turns out to be organic disease of the heart.” The disease being increased by “the anxiety and fatigue of the autumn,” there was no knowing how much longer Martineau had to live.

THE CARDIOLOGIST’S DIAGNOSIS: THOMAS WATSON

According to Martineau’s Autobiography, and to at least one of Martineau’s biographers, Latham urged her to consult another physician who was then acting as his locum. One week later, on 31 January 1855, Martineau did pay a visit to the physician, Thomas Watson. Martineau reported the outcome of this meeting in her Autobiography. She recalled how Watson’s opinion:

Formed on examination, without prior information from Dr Latham or from me, was the same as Dr Latham’s. Indeed the case seems to be as plain as can well be. It appears that the substance of the heart is deteriorated, so that “it is too feeble for its work”; there is more or less dilatation, and the organ is very much enlarged.

Even before Martineau left London, she found herself subject to “the sinking fits which are characteristic of the disease.” It was “perfectly understood by us all that the alternative lies between death at any hour in one of these sinking fits, or by dropsy, if I live for the disease to run its course.” Although she had been anticipating this prognosis before seeing Latham or Watson, Martineau found herself “rather surprised that it caused so little emotion in me.” She went out immediately to visit a friend, “to tell her the result of Dr Latham’s visit, and I also told a cousin who had been my friend since our school days.” While dressing for dinner, Martineau recalled, she experienced “a momentary thrill of something like painful emotion… not at all because I was going to die, but at the thought that I should never feel health again.” Martineau subsequently informed her family of her impending demise, and rewrote her will.

From this time on, Martineau lived as a woman dying from organic heart disease. She took on that mantle with little trepidation, describing herself—after years of ill health—as “more than ready… even joyful in the prospect of sudden departure.” She put all “her affairs” in order “as soon as Dr Latham’s warning was given,” and was quite prepared to die.

In her contribution to Martineau’s Autobiography, Chapman recalled how, a year after this damning diagnosis, Martineau was still regularly, and publicly, “subjected to very severe suffering”:

The frequent recurring of suspense of the heart’s action was very alarming. Her recovery from each attack seemed at the time as doubtful as resuscitation after drowning. “Really and truly,” said her friend Lord Houghton, who was accidentally present at one of these sudden seizures, “one may use St Paul’s words, ‘she dies daily.’”

THE DISPUTE UNFOLDS

Martineau’s reporting of her heart disease seemed uncontroversial. And yet it does not quite sit with the available evidence. If we turn to the letters written by Latham between 1855 and 1857, the period when the physician was apparently treating Martineau for her fatal cardiac complaint, we find no mention made of any diagnosis of heart disease. Instead, Latham repeatedly recommends the use of opium, to relieve Martineau’s discomfort. The remainder of his advice concerned her experience of persistent “neuralgic” pains (which Latham believed to be a side effect of the opium, or else symptomatic of actual disease elsewhere...
in the body). And while he makes reference in one instance to her “weak” heart, it is in the context of her age, her overall health, and an apparently related dysfunction—of which, more later.

In 19th-century medical theory, the transmission of symptoms from one part of the body to another was perfectly commonplace. In part this was a nervous characteristic meaning that symptoms could be transferred via the nerves from one site in the body to another because of the role of the brain and central nervous system. In Martineau’s case, Latham believed that an abdominal tumor was to blame. When he examined her abdomen some months earlier in London he had found it “enlarged and hard,” symptomatic, he believed, of an extensive “tumor.” This seemed to have been growing so steadily that it began to fill her entire abdomen. Latham was not the only doctor to suggest Martineau had a tumor.

Martineau consulted Thomas Watson when he was working as Latham’s locum. In her Autobiography, Martineau had said that Watson, like Latham, believed her to suffer from fatal heart disease. And yet, again, Watson’s own record tells a different story. With reference to notes taken at the time of the consultation, Watson, recalled in an article to the BMJ after Martineau’s death that Martineau had complained to him of “intermissions of the beats and subsequent boundings of the heart, felt by her very disagreeably, with flutterings and bumps.” Under examination by auscultation, Watson found the “pulsations of the heart noisy, and audible over a large portion of the chest, but there were no murmurs attending its action, nor any other evidence of organic disease.” According to Watson’s established register of symptoms, then, Martineau’s cardiac sensations were not unusual. And while Martineau told friends that Watson declared her to be suffering from an enlarged and dilated heart, one which was “too feeble for its work,” Watson denied this claim. He reportedly told Martineau that her heart was in the condition that one would expect in a 52-year-old woman. At the age of 63, he had said to her, he had “sufficient experience [himself] of these disagreeable flutterings and intermissions of the heart and pulse, lasting sometimes for days together.” Had he believed she had any “flaws in the
mechanism of the heart” that needed “careful management,” then he would have advised her, or a member of her family as a matter of urgency. Yet “in Mrs Martineau’s case there was no such obvious rift, and I, therefore, affirmed to her that her life was in no immediate danger.” He believed, moreover, that she would have received “a similar opinion from Dr Latham, than whom no physician at that date was more competent to form a correct judgment about affections of the heart.” 27 Watson believed that Martineau was unwilling to receive his diagnosis, however, and his response draws attention to the tension that existed in the therapeutic encounter: the patient “plainly distrusted, or rather she disbelieved, my reassurances, looking upon them, I fancy, as well-meant and amiable attempts to soothe and tranquilize a doomed patient.” 28

If Watson did not diagnose Martineau with heart disease, what was his opinion as to her condition? He believed her to be suffering from “a large pear-shaped indolent tumor, reaching as high as the lower part of the epigastrium.” 29 Martineau’s brother in law, Thomas Greenhow, had earlier reached a similar conclusion — indeed he published a very private account of her symptoms that she found humiliating. On the basis of postmortem evidence, Martineau’s ovarian cyst was seen to have forced her stomach into the thoracic cavity, arching the diaphragm and impeding the action of the heart and lungs. 30 So we have a medically sanctioned and mechanistic explanation for the physical symptoms experienced by Martineau. The tumor, removed from her dead body and paraded in front of medical students (one hopes not too gleefully), provided concrete evidence that the physicians got it right.

THE PUBLIC FACE OF A HUMILIATING DISEASE

In presenting the public face of her mysterious illness as heart disease, then, might Harriet Martineau have attempted to participate in its cultural cachet, to demonstrate further the emotional sensitivity exhibited through her fictional writing and in her Autobiography? She would certainly have been well versed in the dual rhetoric of sensitivity and cardiac dysfunction at a time when literary and medical discussions of cardiac characteristics drew from and influenced one another. 31 On a personal level, moreover, Martineau’s extensive literary and social connections connected her to several fellow sufferers and literary figures — one of her closest friends being Mary Arnold, Thomas Arnold’s widow — for whom the experience of heart disease loomed large. Perhaps even most

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Interestingly, this network focused on the connections between these members of the literary élite and Peter Mere Latham, the foremost cardiac specialist in Victorian culture. Along with Thomas Arnold and his son Matthew, Latham treated the writer Christina Rossetti, whose likely heart disease seems to have been historiographically subsumed by her diagnosis of cancer. Moreover, a disproportionate number of Martineau's female correspondents and literary associates also suffered from cardiac symptoms, including Elizabeth Barrett Browning, Elizabeth Gaskell (who died of a heart attack aged only 55), Mary Carpenter (educationalist and associate of Harriet's brother James Martineau), the suffragist and philanthropist Ann Sykes Swaine, and the playwright Mary Russell Mitford.

In one exchange between Barrett Browning and Martineau, Winter records, the two intellectual women debated the relationship between creativity and nervous tension, the desire to create, or to produce (and the complex feelings that that desire produced within a suffering individual), being incomprehensible to physicians. It was pointless, Martineau observed, for them to forbid “all excitement & intellectual labor, as if one could hush one’s mind, as you put your dog to sleep.” And while it would be better for Barrett that her “pulses” remained “in order,” disorder was often necessary for the creative process: Barrett would not recover while she was “keeping a burning and thrilling weight of poetry on [the] heart and brain.”

Why, then, given the lack of status given to heart disease by the medical profession—as a sign of physical or emotional weakness, especially in women, and as a sign of neurosis, did Martineau self-identify with cardiac disease? Part of the answer lies in the even more derogatory status of gynecological disease. After all Martineau did privately acknowledge a “tumor” to be the source of her ill health. We know that Martineau described herself as humiliated by the publicization of her tumor by her brother-in-law. On a political level too, to admit publicly to a tumor would have meant that Martineau succumbed to a “female malady” at a time when women were increasingly reduced to their biology, and gynecological specialization was proving one more means by which the male medical profession dominated and excluded female (and lay) knowledge. Consider, for instance, the statement of Sir Charles Mansfield Clarke, who examined Martineau during her illness: “For a physician to treat women with any reference to her own perception of her illness was like expecting to remove [round worms] from the anus by making application to the nostrils.”

Martineau had very good reason, then, not to be enamored of the medical profession.

Part II of ‘Heart of Myth – Heart of Science—Exploring the symbols, fantasy, and ideology of the heart: Victorians, Romantics, and Homo scientifícus’ will appear in the next issue of Dialogues in Cardiovascular Medicine.

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2. For a broader discussion of Martineau’s case, see Fay Bound Alberti, Matters of the Heart: History, Medicine, Emotion (Oxford, UK: Oxford University Press; 2010).


5. Anka Ryall.


10. “Battley’s Laudanum” or “Battley’s Sedative Solution” was a sedative composed of opium dissolved in alcohol.

11. Harriet Martineau, Special Collections, Birmingham University Library, HM 539.

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12. Letter from Latham to Martineau dated January 18 1855, HM540, Special Collections, Birmingham University Library.

13. Martineau was a regular contributor to the Westminster Review from the 1830s.


24. Sir Thomas Watson, Correspondence. British Medical Journal, 8 July, 1876, p 64.


31. On the interactions between writers and physicians, see Blair, Victorian Poetry, introduction and chapter 1.

32. See Blair, Victorian Poetry, p 35.


34. Martineau and Barrett Browning, cited in Winter. Mesmerized, p 236.

35. See Cooter, Dichotomy and Denial.

On the gendering of Martineau’s illness see Diana Postlethwaite, Mothering and Mesmerism in the Life of Harriet Martineau, Signs, 14 (1989), pp 583-609, esp. p 588; Bohrer, Harriet Martineau, p 22.

The Brokenhearted: Cardiovascular Disease and Depression

Summaries of Ten Seminal Papers

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1. Depression and cardiac mortality: results from a community-based longitudinal study
B. W. Penninx and others. Arch Gen Psychiatry. 2001

2. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis
J. P. van Melle and others. Psychosom Med. 2004

3. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions
J. Suls and J. Bunde. Psychol Bull. 2005

4. Prevalence of depression in survivors of acute myocardial infarction: review of the evidence
B. D. Thombs and others. J Gen Intern Med. 2006

5. Depression as an aetiologic and prognostic factor in coronary heart disease...

6. Depression screening and patient outcomes in cardiovascular care: a systematic review
B. D. Thombs and others. JAMA. 2008

7. Depression and coronary heart disease: recommendations for screening, referral, and treatment

8. Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients...
P. de Jonge and others. Neurosci Biobehav Rev. 2010

9. Depression and cardiac risk: present status and future directions
N. Frasure-Smith and F. Lespérance. Heart. 2010

10. Unipolar depression and the progression of coronary artery disease; toward an integrative model

Selection of seminal papers by Peter de Jonge, PhD
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Highlights of the years by Ian Mudway, MD
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Penninx and colleagues evaluated the cardiac effects of depression in a sample of mostly men aged 55-85 years, living in the community. After baseline assessment for depression, subjects were followed up for 5 years for onset of cardiovascular disease (CVD) and cardiac mortality. The presence of depression was determined using the Center of Epidemiological Studies Depression Scale (CES-D), assessing self-reported symptoms, and the Diagnostic Interview Schedule (DIS), which is an interview-based method that approaches the diagnostic criteria of the DSM. The authors distinguished between minor depression (self-reported symptoms not fulfilling diagnostic criteria) and major depression (self-reported symptoms fulfilling diagnostic criteria), which made it possible to evaluate a “dose-response”–like association with the outcome of interest.

Depression at baseline was associated with an increased risk of CVD and cardiac mortality, and particularly those with major depression. An important strength of this study was that analysis excluded all participants with CVD at baseline. Moreover, many of the potentially confounding factors were included in the prediction models, including body mass index, smoking, blood pressure, and somatic comorbidity. Although some attenuation took place, this was relatively minor, suggesting that the effects of depression were relatively independent. Remarkably, results were highly comparable with and without CVD at baseline, and when using either cardiac mortality in general or ischemic heart disease mortality as outcome of interest. Furthermore, a gradual increase in mortality risk was observed when using the CES-D score as a continuous variable.

Several randomized controlled trials have since been conducted in patients with a recent myocardial infarction and comorbid depressive disorder (eg, ENRICHD and MIND-IT), which unfortunately were not successful in reducing cardiac event rates. No such studies have been performed in CVD–free subjects or subjects with subclinical levels of CVD. First of all, the lower cardiac event rates in these populations would result in enormous sample sizes needed to obtain sufficient power to address this question. Second, recruitment of patients with established CVD may be easier than the detection of subjects with subclinical levels of CVD.

The question how depression may result in increased cardiac mortality rates remains relatively open. Although many physiological and behavioral mechanisms have been proposed, it is unlikely that a single mechanism is involved. Recently, Penninx and colleagues have started a new project building on the results of this paper, suggesting telomere shortening as the mediating mechanism through which depression exerts its cardiotoxic properties. Telomeres are simple repetitive sequences (TTAGGG) at the ends of eukaryotic chromosomes protecting cells from genomic instability during mitotic cell proliferation. Telomeres progressively shorten with each mitotic division due to the limiting nature of linear DNA replication mechanisms. After a critical degree of telomere shortening, cells lose the ability to replicate and may cease dividing (senescence) or undergo programmed cell death. Telomere shortening has been shown to be associated with age-related morbidity and mortality and with depression, and may therefore explain the depression/CVD link.

This study evoked a lot of attention, partly as most of the studies evaluating the potential effects of depression on CVD progression included patients with CVD at baseline. In contrast, by starting with initially healthy subjects, the issue of confounding by CVD severity is less important, although subclinical levels of CVD, particularly atherosclerosis may still play a role. The authors speculated that prevention and treatment of depression were perhaps an effective way to reduce the risk for fatal cardiac events.
Depression after myocardial infarction (MI) is more prevalent than in the general population. Several studies suggest that depression is a risk factor for cardiovascular morbidity and mortality, but others could not confirm this. The present article presents a meta-analysis on the association of depression after MI with new cardiovascular events and mortality.

Eligible studies concerned MI patients in whom depression was determined within 3 months after the MI using either validated questionnaires or a standardized psychiatric interview, and cardiovascular prognosis was prospectively compared between depressed and nondepressed patients. Data were then converted and pooled.

Major depression was present in 5%-47% of MI patients, and elevated depressive symptoms were present in 8%-47%. Twenty-two prospective studies comparing cardiovascular prognosis between depressed and nondepressed MI patients were identified, comprising 6367 MI patients. Nine studies reported on all-cause mortality. The pooled odds ratio for all-cause mortality associated with depression was 2.38. Nine studies reported on cardiovascular mortality. The pooled odds ratio associated with depression was 2.59. Nine studies reported on cardiovascular events. The pooled odds ratio associated with depression was 1.95. Of the 12 studies that made adjustments for potential confounders, 11 showed multivariate odds ratios that were smaller than univariate odds ratios. The risk of all-cause and cardiovascular mortality was not influenced by the way depression was assessed (ie, questionnaire vs psychiatric interview), or the duration of the follow-up period (ie, longer or shorter than 6 months), but the association was more pronounced in older studies than in the more recent studies. Funnel plots and Egger tests revealed some evidence for publication bias for studies evaluating cardiovascular mortality, but not for all-cause mortality and cardiovascular events.

Depression after MI was associated with a 2-2.5 times increased risk of new cardiovascular events and mortality. The less profound effect in later studies may be due to improvements in cardiovascular care. The finding that the magnitude of the association is not influenced by the way depression is assessed (ie, questionnaire or psychiatric interview) may have important clinical implications for the identification of MI patients with poor prognosis, since questionnaires are easier, faster, and cheaper than psychiatric interviews. The finding that in 11 out of 12 studies the multivariate odds ratios were smaller than the univariate odds ratios suggests that the effect of depression on cardiovascular prognosis may be partly dependent on other factors. Because this meta-analysis shows results from bivariate analysis and not multivariate analysis, the possibility of confounding factors (such as cardiac disease severity) that reduce the strength of the association between post-MI depression and cardiovascular prognosis cannot be ruled out. Potential mechanisms include behavioral mechanisms (ie, diminished compliance, smoking, unhealthy diet, inactivity), physiological mechanisms (ie, increased sympathetic nervous system activity, increased platelet activation, changes in the immune system and hypothalamic-pituitary-adrenocortical system), and deficits in quality of medical care (ie, less coronary revascularization procedures, and less prescription of important cardiac medications). These findings underscore the importance of intervention trials evaluating the effects of depression treatment on cardiovascular prognosis. However, caution is warranted since the included studies were all observational, and the observed effects of depression were smaller in those studies in which adjustments for cardiac disease severity were made.

Dutch filmmaker Theo van Gogh is stabbed and shot dead in Amsterdam; on its release computer game “Halo 2” takes more 125 million US dollars making it the largest opening day in entertainment history; and the United States lifts a 23-year travel ban against Libya.
In this extensive review of the literature, the authors evaluate the role of three affective dispositions in coronary artery disease, namely depression, anxiety, and anger-hostility. They draw attention to the problem that these negative dispositions are overlapping or at least correlated, which complicates the interpretation when these dispositions are evaluated in isolation.

With respect to depression, the authors found that it was associated with an increased risk of cardiac outcomes. This was observed both in healthy populations and in populations with known heart disease, but more consistently in the first. With respect to anxiety, markedly fewer studies were identified, but the pattern was similar with cardiotoxic effects of anxiety observed particularly in healthy populations. With respect to the various aspects of anger, less convincing evidence was found for effects on cardiac outcomes. If any, this was observed only in healthy populations.

The authors introduce the term negative affectivity as a higher order construct subsuming the three psychological risk factors described in this review. Negative affectivity is defined as a general disposition to experience negative feelings of anxiety, sadness, guilt, irritability among others and represents a more stable personality trait that may be responsible for the observed effects of anxiety, depression and anger. Suls and Bunde go on to argue that there are several ways of how negative affectivity may result in an increased cardiac risk. Negative affectivity is associated with several traditional risk factors for cardiovascular disease, but also with adverse health behaviors and physiological factors that may explain its cardiotoxic properties. They conclude with a conceptual analysis of the overlap between depression, anxiety, and anger, and the implications this overlap may have for clinical care and research on the cardiotoxic properties of negative emotions. As such, the review offers a framework for future research in this field, extending the work on negative emotions to personality as well.

Overlap between aspects of negative affectivity is problematic as it raises some important issues related to validity. To assess symptoms of negative affect, researchers have to rely on self-report data in the absence of objective measures. There is no golden standard for assessing the presence of, eg, depression, and it is possible that a depressed person rates him- or herself as being relatively hostile, as a result of the state of depression where the person is in. Or vice versa, because a patient is hostile, he or she may not share symptoms of depression with the researcher or clinician. Also, in contrast to, eg, an acute myocardial infarction in which an objectively measureable process is going on, depression is a term that was coined based on consensus rather than empirical data. It is unlikely that depression reflects a single process, but instead is a disorder with a “multifactorial etiology.” In fact, the concept does not differ so much from the concept “quality of life,” except that depression is somehow considered to be a disorder, which suggests some kind of homogeneous etiology. Although on the one hand, subjectively assessed self-reported symptoms remain crucial in determining the presence of depression, these kind of data may not result in progress with respect to etiology, because the minds of patients may not behave like the theoretical models designed by scientists. On the other hand, relying on biomarkers only to determine the presence of depression will not do sufficient justice to the patient (even if someone does not feel depressed, he or she may then be diagnosed as being depressed), but also our understanding of the functions of the biomarkers that may be involved in depression may still be too limited in order to make them useful for clinical practice.

Nobel Laureate Hans Bethe, discoverer of stellar fusion and an outspoken critic nuclear proliferation, dies, aged 98 years; former chess world champion Garry Kasparov retires; and structures resembling red blood cells are identified in a fossilized bone from *Tyrannosaurus rex*.
Increasing attention has been paid to depression in patients with cardiovascular disease (CVD). Depression has been reported to be highly prevalent in patients with CVD in individual studies. In addition, numerous studies have reported an association between depression and cardiovascular events and mortality following myocardial infarction (MI). However, there are also studies which did not find this association when other predictors of mortality were taken into account. Furthermore, symptoms common to both depression and CVD can be confounding factors in this relationship. Symptoms characteristically associated with depression may also occur as a normal reaction to the MI or the hospitalization itself, for example fatigue and sleep problems. This might complicate the diagnosis of depression.

The authors assessed the prevalence of a diagnosis of major depression and that of clinically significant symptoms of depression among patients hospitalized for acute MI. They also looked at the relationship between assessment modality (eg, clinical interview versus self-report) and reported prevalence. Further, they wanted to assess how symptoms of depression evolve over time.

The authors systematically searched the literature and included 24 articles on patients during their hospitalization for acute MI. Eight studies used a structured clinical interview and major depression was identified in 19.8% of these patients. Seventeen studies used a validated questionnaire and found prevalence rates of clinically significant depressive symptoms ranging from 10% to 47%. However, results for different instruments varied substantially. Six studies using the Beck Depression Inventory-I (BDI-I), with a cutoff of ≥10 to indicate mild-to-moderate symptoms of depression, found a prevalence of 31.1%. In four studies that used a score of ≥8 on the HADS, the prevalence of depressive symptoms was 15.5%.

So, the prevalence of depression appeared to be considerably higher in MI patients compared with the general population, where the prevalence of major depression is estimated to be 5%. However, differences were found between the instruments. The prevalence of depression using a structured clinical interview was higher than the prevalence of depression using the HADS, and lower than the reported prevalence using the BDI-I. These differences are probably the result of somatic symptoms included in the structured interview and the BDI-I. Somatic symptoms used to diagnose depression can be difficult to distinguish from symptoms secondary to CVD. The DSM-IV states that symptoms “accounted for by a general medical condition” should not be counted toward a diagnosis of major depression. However, the cause of symptoms is almost never clear, leaving it to the judgment of the interviewer. The HADS does not include any questions about somatic symptoms, but 7 of the 21 items on the BDI-I do (eg, fatigue, weight loss, insomnia, and loss of appetite) without reference to the cause. It is therefore not surprising that the reported prevalence of depression using the BDI-I was higher than the prevalence using the HADS and a structured clinical interview.

Only four studies assessed how symptoms of depression evolve following hospitalization. In these studies, depression persisted in about half to two thirds of the initially depressed patients in the first 1 to 12 months after discharge. To conclude, depression is common and persistent in patients hospitalized for acute MI. However, the discrepancies between measurements reflect some of the challenges in evaluating depression among these patients. In later work by Thombs and colleagues, this issue of heterogeneity between studies and how it affects study results has been explored in more detail.

Four years after defaulting on its debt, Argentina repays the International Monetary Fund; international music events take place to mark the 250th anniversary of Mozart’s birth; and Evo Morales becomes the first indigenous American President of Bolivia.
Numerous studies have shown an association between depression and the development and progression of coronary heart disease (CHD). This led to randomized controlled trials evaluating whether treatment of depression could improve cardiac prognosis following myocardial infarction (MI). These studies showed an improvement in depressive symptoms, but no improvement in cardiac prognosis. This prompts the question whether depression is a true causal risk factor of CHD or whether this relationship is confounded by other factors.

This meta-analysis had three objectives. The first was to quantify the effect of depression on CHD etiology and prognosis, as patients at high risk for CHD or more severe CHD might be more likely to report depressive symptoms and coronary risk factors, and severity of CHD might confound the relationship between depression and CHD. The second objective was to assess the contribution of confounding by coronary risk factors in etiological and prognostic studies and disease severity in prognostic studies. The third was to examine whether the association between depression and CHD was affected by timing of the depression assessment (e.g., following acute MI or prior to undergoing angioplasty).

In the first part of the meta-analysis, 21 studies on the potential effect of depression on development of CHD were included. Subjects who were depressed at baseline were at an 80% increased risk of CHD. However, studies for which only unadjusted results were present had a lower effect estimate compared with unadjusted results from studies that also reported adjusted results. In the studies that reported an adjusted effect, the effect estimate was reduced by 12%. However, these studies did not adjust for all potential confounders. Because of these factors, the true association between depression and development of CHD is probably weaker.

There were 34 prognostic studies included in the second part of the meta-analysis. Depression was associated with an 80% increased risk of worse prognosis, highly similar to the estimate of the effect of depression in the first part. However, only 11 studies adjusted for severity of CHD, and these had a significantly lower effect estimate. Therefore, the independent effect of depression predicting cardiovascular prognosis is probably lower. Adjustment for measures of cardiac disease severity, and especially left ventricular ejection fraction (LVEF) had a large effect on the effect size in the studies that reported both unadjusted and adjusted results. Finally, the effect of depression on adverse outcomes was stronger after acute MI than in patients with angioplasty or coronary artery bypass grafting.

To conclude, although significant associations were found between depression and CHD, it is unsure whether depression is a causal risk factor of CHD. There are several biases in the literature, including publication bias, biased availability of adjustments, and incomplete adjustments for conventional risk factors and disease severity. It is unclear whether depression truly causes CHD or whether reverse causality plays a role in the sense that patients with more severe disease are more likely to report depressive symptoms. Also, the effect of depression on prognosis was stronger in patients with an acute cardiac event than in those with stable heart disease. This finding supports the reverse causation argument because the effect of cardiac disease on reporting of depressive symptoms, especially somatic symptoms like fatigue and problems sleeping, is probably more prominent in acutely ill patients. Future studies should assess the topic of reverse causality in detail. However, it should not be forgotten that depression is highly prevalent in patients with CHD and that it is worth treating, irrespective of a causal association with CHD.

Russia defeats Argentina 3-2 to win the 2006 Tennis Davis Cup; the Nobel Peace Prize is awarded to Bangladeshi economist Muhammad Yunus and his Grameen Bank; and South Korean diplomat Ban Ki-moon is sworn in as UN Secretary-General.
Depression screening and patient outcomes in cardiovascular care: a systematic review


*JAMA*. 2008;300(18):2161-2171

The present article is a systematic review of the literature evaluating whether empirical evidence supports recommendations for systematic screening in cardiovascular disease (CVD) care settings. Three Key Questions were defined:

1. What is the accuracy of screening instruments for depression in CVD care populations?
2. Is treatment for depression in CVD care patients effective in improving depression and cardiovascular outcomes?
3. Is systematic screening for depression more effective than usual care in identifying patients with depression, facilitating treatment of depression, reducing depressive symptoms, and improving cardiac outcomes?

Eligible articles were identified and included if they concerned CVD patients and if they compared a depression screening instrument with a diagnostic tool for depression (Key Question 1), or if they compared the effects of depression treatment on depression or cardiac outcomes with placebo or usual care in a randomized controlled trial (Key Question 2), or if they evaluated the effect of depression screening on depression identification and treatment rates, depression or cardiac outcomes (Key Question 3).

For Key Question 1, eleven articles were identified, which showed that depression screening tools are reasonably accurate in CVD patients (median sensitivity: 84%, median specificity: 79%). For Key Question 2, six randomized controlled trials were identified that evaluated the effects of depression treatment in CVD patients, including pharmacological treatment (fluoxetine, citalopram, sertraline, and mirtazapine) and nonpharmacological treatment (cognitive behavioral therapy and interpersonal psychotherapy). Their results showed only modest improvements in depression associated with depression treatment. Effect sizes of drug treatment trials were modestly positive (0.20-0.38, explaining 1%-4% of the variance in depression change scores). None of the trials found depression treatment to improve cardiovascular outcomes. For Key Question 3, no articles or studies were identified evaluating potential benefits or harms of depression screening in CVD patients.

It is concluded that it is unknown whether depression screening is of benefit to patients with cardiovascular disease. Although screening tools seem reasonably accurate, depression treatments only modestly improved depression and did not improve cardiovascular outcomes.

Because of the high false-positive rates of screening tools, a follow-up clinical interview would be necessary to establish a diagnosis of major depression, which would consume substantial resources. If antidepressant therapies are prescribed by cardiologists based on a screening tool alone, then potentially dangerous overtreatment and mislabeling could occur. No study evaluated potential harms like these, related to screening or treatment. In non–mental health settings, screening results in a modest increase in recognition of depression by clinicians, but does not improve depression outcomes. No study evaluated this in cardiovascular care settings, but there is little reason to believe that the situation would be better there. The authors introduce collaborative care as a potential solution that may improve both short- and longer-term depression outcomes, but this should be evaluated in future studies.

Because of these gaps in our knowledge, the present review concludes that there is no evidence for or against the recommendations that depression screening should be part of standard care in patients with cardiovascular disease. Although there is no evidence to support routine depression screening in cardiovascular care settings, physicians should be aware that depression is a life-threatening and disabling condition and that these patients should be provided appropriate treatment, referral, or both.

French rally driver Sébastien Loeb wins his fifth consecutive World Rally Championship for Citroën; a series of coordinated terrorist attacks take place in Mumbai leaving 164 people dead; and New Zealand defeats Australia’s 34-20 to win the 2008 Rugby League World Cup.
Robust evidence shows that depression is associated with cardiovascular morbidity and mortality, even after adjustment for cardiac disease severity and other potential confounders. This is a dose-response relationship with more severe depression associated with earlier and more severe cardiac events. Several biological and behavioral mechanisms are proposed to underlie the increased risk associated with depression. Compared with nondepressed CHD patients, depressed CHD patients have higher levels of biomarkers predicting cardiac events and atherosclerosis, reduced heart rate variability, hypothalamic-pituitary-adrenal axis dysfunction, increased platelet activation, impaired vascular function, and an increased inflammatory response. In addition, depressed CHD patients have worse diet, less physical activity, smoking, social isolation, chronic life stress, decreased adherence to medications, noncompliance with medical treatment regimens, poorer risk-factor modification, less participation in cardiac rehabilitation, higher health care utilization and costs, and reduced quality of life. Therefore, it is argued that it is important to screen for and treat depression in cardiovascular care settings.

The authors propose a model in which CHD patients are administered the 2-item Patient Health Questionnaire (PHQ-2). If the answer is “yes” to at least one of the items, the PHQ-9 is administered. The PHQ-9 is a brief depression screening instrument, easily administered and reasonably accurate for the detection of major depression in CHD patients. For patients scoring below the threshold (<10), a subsequent visit is advised to evaluate whether symptoms persist or increase. Patients scoring 10 or higher should be referred for a more comprehensive clinical evaluation by a professional qualified to evaluate the presence of other mental disorders associated with adverse outcomes (eg, anxiety), and to determine a suitable individualized treatment plan.

Depression treatments that should be considered include antidepressant drugs, cognitive behavioral therapy, and physical activity. The selective serotonin reuptake inhibitors (SSRIs) sertraline and citalopram have been found to be safe for CHD patients and moderately effective in improving depression in those with moderate, severe, and recurrent depression. In a nonrandomized comparison, treatment with an SSRI in depressed myocardial infarction (MI) patients reduced the risk of death or recurrent MI by 42%. SSRI treatment is relatively inexpensive and may improve medication adherence in MI patients. Sertraline and citalopram are the first-line antidepressant drugs in CHD patients. Patients who previously tolerated and responded well to another antidepressant may resume taking that agent instead. However, tricyclic antidepressants and monoamine oxidase inhibitors are contraindicated because of their cardiotoxic side effects. Patients who initiated pharmacological treatment should be monitored closely during the first 2 months and regularly thereafter for suicidal risk, medication compliance, adverse effects, and drug interactions. Patients who do not tolerate or prefer pharmacological treatment can be offered cognitive behavioral therapy. In addition, patients with moderate-to-severe depression may respond better to the combination of pharmacological treatment and cognitive behavioral therapy. One randomized controlled trial in depressed MI patients found remission of moderate-to-severe depression associated with at least 12 to 16 sessions of cognitive behavioral therapy over 12 weeks. Finally, aerobic exercise and cardiac rehabilitation can reduce depressive symptoms in addition to improving cardiovascular outcomes. Cardiologists should therefore encourage depressed CHD patients to participate in cardiac rehabilitation and exercise programs.

Osamu Shimomura, Martin Chalfie, and Roger Y. Tsien are awarded the 2008 Nobel Prize in Chemistry for their discovery and development of the green fluorescent protein; the Man Booker Prize is won by Indian novelist Aravind Adiga for his first book “The White Tiger”; and India launches unmanned lunar probe Chandrayaan-1

 depression and coronary heart disease: recommendations for screening, referral, and treatment

J. H. Lichtman, J. T. Bigger Jr, J. A. Blumenthal, et al; American Heart Association; American Psychiatric Association

Circulation. 2008;118(17):1768-1675
In this recent review, De Jonge and colleagues discuss and evaluate the empirical support for the role in the depression–heart disease link of several of the proposed psychophysiological biomarkers (heart rate variability, inflammation, platelet function, hypothalamus pituitary-adrenal axis, serotonin, and polyunsaturated fatty acids). These biomarkers have been associated both with depression and with the onset or progression of heart disease.

Heart rate variability (HRV) is a marker of autonomic nervous system activity of the heart. Two studies have evaluated whether HRV mediates the effects of depression on cardiovascular mortality. One was positive and one was negative. Inflammatory processes, such as leukocyte recruitment and cytokine expression, are involved in several stages of the atherosclerotic process. Moreover, inflammatory markers are associated with depression, particularly with what has been referred to as “sickness behavior”—a flu-like state that includes feelings of fatigue and psychomotor retardation. There are indications that the association between depression and cardiac disease progression is partly mediated by inflammation. With respect to the other mechanisms, some indirect evidence is available that supports their possible involvement, but no studies are present in which a formal test for mediation was performed.

The authors of the review then stress the point that, as both depression and heart disease are complex and heterogeneous diseases, it is unlikely that their association can be explained by a single psychophysiological marker. Instead, a network of effects in which several markers operate in concert, mutually influencing each other, is far more likely. Several of the possible interrelations between biomarkers are discussed, and it is concluded that only a few attempts have been made in which multiple biomarkers have been assessed in a single dataset allowing to test for such a network of effects. Moreover, it is stated that although most attention in the depression-heart disease literature has been directed to biomarkers, behavioral factors comprise perhaps more powerful candidate mediators, including non-adherence to cardiac aftercare and lifestyle factors such as poor diet, smoking and limited physical exercise. In one study, in which several biomarkers and behavioral factors were evaluated together with respect to their potential of mediating the association between depressive symptoms and cardiac prognosis in patients with stable coronary artery disease, it was found that lifestyle factors explained about 50% of the observed effects of depression. Physical exercise alone already accounted for more than 30% of the effects. In contrast, of the biomarkers included, only inflammation (assessed with CRP) attenuated the association significantly (by about 10%).

Another point stressed by the authors was that the association between depression and heart disease may not be the same for all individual depression symptoms and that individual symptoms may differ in their level of cardiotoxicity, with somatic symptoms (fatigue, sleeping problems, psychomotor retardation or agitation) playing a more important role than cognitive symptoms (shame, guilt, low self-esteem). Moreover, the link with biomarkers may also be differential. For instance, inflammatory-based sickness behavior seems far more similar to somatic depression than to cognitive depression. Likewise, HRV has been found to be associated with somatic, but not cognitive symptoms of depression. This distinction in symptoms may be relevant in optimizing antidepressant treatment in the future, but may also be of interest in our further understanding of the depression–heart disease link.

Sofia Coppola’s film “Somewhere” wins the Golden Lion for best film at the 67th Venice International Film Festival; Belgium tennis player Kim Clijsters wins her second successive US Open championship; and the United States wins the 2010 Basketball World Championship, defeating Turkey 81-64 in the final
Depression and cardiac risk: present status and future directions

N. Frasure-Smith, F. Lespérance

*Heart*. 2010;96(3):173-176

Frasure-Smith and Lespérance, who were among the pioneers in this field, portray the present status and future directions of research regarding depression and cardiac risk. A large body of literature has confirmed that depressive patients with established heart disease have an increased risk of suffering adverse cardiovascular events, with current estimates finding that depression is associated with a twofold increased rate of mortality and cardiac events. However, despite the relative consistency of results, debates on the interpretation of findings have continued.

Without question, depression is related to the prognosis of patients with established CHD. However, whether the association between depression and heart disease is causal remains debated. A major problem with depression as a risk factor for cardiac disease is the extent to which depression may reflect (subclinical) cardiac disease. Although studies in patients with existing CHD extensively controlled for reliable measured covariates, it is impossible to rule out the possibility that depression reflects some unknown indicator of disease severity or progression. The treatment of depression in CHD patients has drawn a lot of attention, especially because it has the potential to evaluate the extent to which the association between depression and cardiovascular prognosis is causal. However, despite the prevalence of depression and its association with negative cardiac prognosis, only few pharmacological and behavioral randomized controlled trials have been performed in CHD patients with comorbid depressive disorder. Overall, depression treatment in CHD patients had only minor effects in terms of reducing depressive symptoms, which did not lead to enhanced survival. Therefore, caution is warranted when speaking about depression as a causal risk factor.

There are two recent trends in research on depression and CHD. The first line of research considers depression as a heterogeneous condition. It is possible that some types are cardiotoxic, while others are not and some types may respond to treatment while others do not. Several subtypes of depression may be important in this respect. Several studies have reported interesting subgroup analyses and reanalyses of existing epidemiologic studies and clinical trials in order to dismantle the depression concept. Another line of research assumes that depression is causally linked to CHD, and is attempting to determine the pathophysiological mechanisms, including depression-related changes in autonomic balance, platelet reactivity, and inflammation. So far, there is no consensus on which line of research is clinically most relevant.

Frasure-Smith and Lespérance compared depression and type A behavior, characterized by high levels of competition and hostility. In 1981, a review stated that Type A behavior was associated with an increased risk of CHD. However, soon after contradictory evidence emerged and today Type A research is scarce. Frasure-Smith and Lespérance concluded that, “only time will tell whether depression will follow in the footsteps of Type A behavior, or whether the efforts at isolating and treating its most cardiotoxic elements or behavioral and pathophysiological pathways will succeed.” Future research will hopefully pinpoint the exact nature of the harmful aspects of depression, as well as the mechanistic pathways that link depression to CHD progression. Increasing the number of strong interdisciplinary research and clinical partnerships could be of great importance in this respect. Meanwhile, it is important to realize that treating depression in itself is a relevant goal due to its association with quality of life. The CREATE trial (Canadian Cardiac Randomized Evaluation of Antidepressant and psychoTherapy Efficacy), in which Lespérance and colleagues compared several treatment options in depressive coronary artery disease patients, used no cardiovascular end points as outcome.

2010

The *Lancet* retracts the paper alleging a link between the MMR vaccine and autism; and British fashion designer Alexander McQueen commits suicide, aged 40
Based on the existing literature, the authors elaborate on the difficulty of reaching causal interpretations in the association between depression and heart disease progression. First, the point is made that although many studies have demonstrated that depression is an etiological and prognostic marker of coronary artery disease (CAD), there is reason to doubt whether this represents a causal association. This doubt is based on three points: prognostic studies have insufficiently controlled for potential confounders, the possibility of reverse causality is not ruled out, and randomized controlled trials in which the effects of depression treatment on cardiac prognosis were evaluated were negative or inconclusive. In this paper, the authors present a model to explain the interrelations between CAD, and depression, resting on three hypotheses:

1. Depressive symptoms are explained by a distinction between cognitive and somatic symptoms. It is argued that these symptom dimensions may stem from different etiological pathways, and joining these two prototypical forms of depression may blur findings with respect to etiology. The etiology of cognitive depression is characterized by a combination of a psychological vulnerability and the experience of stressful life events. The etiology of somatic depression is less clear and the literature is less consistent, but it is suggested to be caused by inflammatory processes, deregulated hypothalamic-pituitary-adrenal axis functioning, or autonomic nervous system activity.

2. The nature and course of depression determine its relation with CAD progression. Evidence for this hypothesis is found in the literature suggesting that somatic depressive symptoms are more cardiotoxic than cognitive depressive symptoms, and that particularly persistence of depression is associated with an increased risk of adverse events. When depression persists in patients with CAD, it may shift from a risk marker to a causal risk factor. Particularly chronic somatic depressions are thought to be cardiotoxic.

3. Behavioral mechanisms can best explain the effects of depression on CAD progression. Most of the literature on possible mediators between depression and cardiovascular disease is about physiological parameters. It is argued that the role of behavioral factors mediating the effects of depression may be much stronger, including less optimal cardiac care for depressed individuals, higher rates of non-adherence and dropout from cardiac rehabilitation, and limited physical exercise.

The model is trying to explain several inconsistent findings in the literature, such as the failure of randomized controlled depression trials to affect cardiovascular outcomes. According to the model, this lack of effect is due to the preponderance of somatic depression which may be more resistant to depression treatment, and the lack of cardiotoxic properties of cognitive, nonpersistent depression. The model may also help in the debate regarding routine screening for depression in patients with CAD. By acknowledging the etiological and phenomenological heterogeneity of depression, a more nuanced position can be taken. However, it is also acknowledged that this is still work in progress and that more pieces of the puzzle have yet to come. The most effective way of improving cardiac prognosis by targeting depression, it is argued, will be by applying interventions that are beneficial both for depression and heart disease itself, such as promoting a healthy lifestyle.

American actor Peter Falk, best known for his role as Lieutenant Columbo, dies; and two new elements are added to the periodic table, flerovium, atomic number 114 and livermorium, 116
The Brokenhearted: Cardiovascular Disease and Depression

Bibliography of One Hundred Key Papers

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