The Influence of Anxiety and Depression on Outcomes of Patients With Coronary Artery Disease

James L. Januzzi, Jr, MD; Theodore A. Stern, MD; Richard C. Pasternak, MD; Roman W. DeSanctis, MD

For years, patients with cardiac disease have been thought to exhibit characteristic emotional features. However, the modern understanding of the relationship between affective disorders and the heart may be traced to the mid-19th century, with the publication of Williams’ seminal text regarding “nervous and sympathetic palpitations of the heart.” This was followed through the late 1800s by numerous works that described the concept of neurologically based, or “neurasthenic,” cardiac disorders. In the 20th century, large advances occurred in the area of mood-related issues that pertained to coronary artery disease (CAD) and sudden cardiac death (SCD). In his 1910 Lumleian lecture, Sir William Osler described his typical patient with angina pectoris as “a man whose engine is always set full speed ahead” and further noted his patients with cardiac disease to be “worriers.” The Menningers, in early psychoanalytic studies, described a characteristic tendency to suppress anger among patients with CAD, as did Helen Flanders Dunbar, a pioneer of psychosomatic medicine. More recently, Stewart Wolf, in his 1969 lecture “Psychosocial Forces in Myocardial Infarction and Sudden Death,” commented on a phenomenon of “joyless striving” among his patients with heart disease.

The results of work conducted in the 20th century suggested that several psychosocial risk factors contribute to the development of cardiovascular disease and influence the course of those who have it. These risk factors included anger, hostility, social isolation, stress, anxiety, and depression. Similar strong associations were thought to exist between cardiovascular disease and personality traits (eg, the so-called type A or type D personalities).

Characterized by aggressivity, hostility, and a chronic sense of urgency, the type A personality disorder (TAPD) represents the most extensively investigated psychobehavioral variable relating to cardiac disease. It was first implicated as a possible risk factor for CAD in the prospective Western Collaborative Group Study, which suggested a 2-fold increase in risk for CAD among patients exhibiting type A behavior patterns. While other prospective and cross-sectional studies of patients with type A behavior appeared to confirm this increase in risk of cardiovascular disease, the results of subsequent large-scale trials, including the Multiple Risk Factor Intervention Trial (MRFIT) and others, not only contradicted this finding but also suggested a possible salutary effect of TAPD on post-myocardial infarction (MI) prognosis. The reason for these contradictory findings is unclear, but they may be explained by an improved coping ability among patients with type A behavior or by more effective post-MI lifestyle modifications made by these patients. Additionally, the deleterious effects of “toxic” subcomponents of type A behavior (eg, hostility, anger, and depression) may explain the increased risk without the need to invoke the consequences of a specific personality structure.

The evolution in the understanding of TAPD illustrates the difficulty in clearly elucidating the effects of pure syndromes of affect or personality, as several disorders (eg, depression and social isolation)
The early data regarding affective disorders and heart disease far exceed the scope of this review, we will focus our discussion on 2 disorders that are particularly common among patients with cardiac disease: anxiety and depression. We will review the effects of these disorders on the genesis of cardiac illness, specifically CAD and SCD, and the marked impact of affective disorders on prognosis following MI, including death and recurrent ischemic events. Several possible pathophysiological mechanisms that underlie this negative effect on prognosis are considered, as are possible treatment modalities for these patients. Finally, future directions for investigation are identified.

ANXIETY AND DEPRESSION: THEIR RELATIONSHIP TO THE GENESIS OF CAD AND SCD

The early data regarding affective disorders and the development of cardiac disease are difficult to interpret for several reasons. Many studies were secondary analyses of previously gathered population-based data; they were not designed as prospective studies of psychiatric conditions. Additional problems included a lack of consistent term definition, inadequate controls for comorbid psychiatric and medical illnesses, and the use of different tests for psychiatric assessment. Moreover, since the care and outcome of patients with CAD have changed dramatically in recent years, the applicability of data from older studies (many of which were conducted more than 30 years ago) is questionable today. Nonetheless, numerous population-based studies suggest a causative link between anxiety and depression and the development of heart disease (Table 1 and Table 2).

The results of several early retrospective studies suggested a high risk for cardiovascular complications from anxiety syndromes. These findings were subsequently confirmed in several high-quality prospective studies. Kawachi and coworkers noted a 3-fold increased risk for fatal CAD (primarily confined to a 6-fold increase for SCD) and nonfatal MI among male health professionals exhibiting high levels of phobic anxiety, identified by elevated scores on the Crown-Crisp anxiety index. Additionally, there was a clear gradient of risk, with the highest rates of death occurring among the patients with the highest anxiety scores.

Similar findings were demonstrated in the Normative Aging Study, which documented a 3- to 6-fold increased risk for MI and SCD among highly anxious patients. In addition to the marked increase in risk for SCD engendered by anxiety, 2 specific subtypes of anxiety (panic disorder and worry) were also linked with a significantly increased risk for MI when compared with unaffected controls (Table 1).

Depression has been linked in several studies to the development of CAD (Table 2). In one angiographic study, the prevalence of depression in patients with asymptomatic angiographically proven CAD was 18%, as compared with a 4.9% prevalence in the community. The recently reported Johns Hopkins Precursor Study suggested a compelling link between depression and the development of heart disease and demonstrated a highly significant 2-fold augmentation in risk in a more than 40-year follow-up among male physicians as compared with controls. Other studies suggested an increased risk for CAD not only in patients with major depression but also in those with depressive symptoms and dysphoria. Furthermore, in these studies, the magnitude of risk seemed to follow a graded effect, with increasing risk for CAD among patients with more severe depression.

In recent years, research has focused on the interaction between emotional disorders and established structural heart disease, especially with regard to patients following an acute coronary syndrome (ACS). Anxiety and depression occur more often among patients with unstable angina as well as those with acute MI and have marked effects on long-term prognosis.

### Table 1. Selected Studies of Anxiety and Related Syndromes and the Development of Heart Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Factor</th>
<th>End Point(s)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coryell et al.34</td>
<td>Panic disorder</td>
<td>Death (Not reported)</td>
<td>2.0 (Not reported)</td>
</tr>
<tr>
<td>Haines et al.35</td>
<td>Phobic anxiety</td>
<td>Death</td>
<td>3.8 (1.6-8.6)</td>
</tr>
<tr>
<td>Weissman et al.36</td>
<td>Panic disorder</td>
<td>MI</td>
<td>1.3 (0.6-2.5)</td>
</tr>
<tr>
<td>Kawachi et al.37</td>
<td>Phobic anxiety</td>
<td>MI</td>
<td>4.5 (1.7-12.3)</td>
</tr>
<tr>
<td>Kawachi et al.38</td>
<td>Anxiety</td>
<td>Sudden death</td>
<td>6.1 (2.4-15.7)</td>
</tr>
<tr>
<td>Kubzansky et al.39</td>
<td>Worry</td>
<td>MI</td>
<td>0.9 (0.5-1.8)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; MI, myocardial infarction; and CHD, coronary heart disease.

### Table 2. Selected Studies Regarding Anxiety and Established Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Factor</th>
<th>End Point(s)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anda et al.30</td>
<td>Depressive symptoms</td>
<td>MI and nonfatal MI</td>
<td>1.5 (1.0-2.3)</td>
</tr>
<tr>
<td>Aromaa et al.31</td>
<td>Depressive symptoms</td>
<td>MI</td>
<td>3.5 (1.8-6.8)</td>
</tr>
<tr>
<td>Pratt et al.32</td>
<td>Major depression</td>
<td>MI</td>
<td>4.5 (1.7-12.4)†</td>
</tr>
<tr>
<td>Barefoot and Schroll33</td>
<td>Depressive symptoms</td>
<td>MI</td>
<td>1.7 (1.2-2.3)</td>
</tr>
<tr>
<td>Ford et al.34</td>
<td>Depressive symptoms</td>
<td>MI</td>
<td>2.1 (1.2-4.1)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; and MI, myocardial infarction.
†For symptoms of dysphoria: RR, 2.1 (95% CI, 1.2-3.7).
ANXIETY AND ESTABLISHED HEART DISEASE

Anxiety is exceptionally common in patients with ACS, with an in-hospital incidence approaching 50% among patients in the coronary care unit. Furthermore, the vast majority of these patients go undiagnosed and undertreated or are not treated at all.

Anxiety may cause a variety of physiological responses; several studies suggest that anxiety exerts a significant acute and chronic influence on outcomes following ACS (Table 3). In 1995, Frasure-Smith and colleagues demonstrated a compelling 2.5-fold increase in risk for ischemic complications resulting from anxiety following MI, while a substudy from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial suggested that patients with acute MI and a high level of in-hospital anxiety (assessed via the Brief Symptom Inventory) had an almost 5-fold increase in risk for recurrent ischemia, reinfarction, or death compared with patients with MI without high levels of anxiety. In fact, this study suggested that early in-hospital anxiety following MI was one of the best predictors for in-hospital complications.

The mechanism by which anxiety influences outcome in ischemic heart disease remains largely unknown. As many of the adverse effects of anxiety seem to be related to SCD, attention has been given to abnormalities of cardiac rhythm as an explanation. An increased incidence of electrocardiographic (ECG) QT interval prolongation has been demonstrated among patients with anxiety, which may reflect a proclivity toward ventricular arrhythmia. Additionally, patients with anxiety have been shown consistently to have evidence of abnormalities in the balance of the autonomic nervous system, characterized by sympathetic nervous system up-regulation, with excessive catecholamine production. Furthermore, impaired vagal control, manifest as an impaired baroreflex response and a decrease in heart rate variability (HRV; a reduction in the SD of normal relative risk intervals as assessed by continuous ambulatory ECG monitoring), has been noted in patients with anxiety. Impairment of the baroreflex response and decreased HRV are each thought to be sensitive markers for abnormalities in autonomic cardiovascular regulation and are independent risk factors for SCD.

Some of the cardiac effects of anxiety are thought to be due to an exaggerated sensitivity to exogenous stress, which itself has been shown to have profound effects on the heart. Clinically, the effect of mental stress on established ischemic heart disease has been demonstrated in several studies; each documented significant stress-related increases in the risk for recurrent ischemia, MI, or death. Experimentally, stress (acute, subacute, or chronic) has been shown to provoke myocardial ischemia via numerous mechanisms in patients with CAD. Vasomotor abnormalities of atherosclerotic epicardial coronary arteries and the cardiac microcirculation have been noted in patients with CAD subjected to mental stress. Additionally, patients with anxiety and CAD often exhibit an exaggerated systemic response to stress, characterized by an abnormally increased production of catecholamines, which can result in increased myocardial oxygen demand due to elevations in heart rate, blood pressure, and the rate of ventricular contraction. Finally, abnormalities of thrombosis and hemostasis, including increases in platelet aggregability and alterations in the fibrinolytic system (possibly as a consequence of elevated plasminogen activator inhibitor 1 levels) have been noted in patients subjected to chronic stress. The clinical significance of these findings remains speculative.

In addition to the biological risks engendered by anxiety, the additive effects of adverse behavioral risk factors (eg, excessive nicotine and perhaps caffeine) in anxious patients are not to be underestimated. Furthermore, since anxiety frequently coexists with depression, some have argued that the higher mortality in anxious patients may be due to the presence of depression rather than anxiety per se.

DEPRESSION AND ESTABLISHED HEART DISEASE

Convincing evidence for a close connection between the mind and the heart comes from the studies of depression following MI (Table 4). Up to 25% of patients have severe, often recurrent major depression following acute MI, while 65% of patients after MI manifest symptoms diagnostic of either major or minor depression, the incidence and severity of which are not explainable by central nervous system adverse effects of cardiovascular drugs (eg, β-blockers or lipid-lowering agents).

The diagnostic criteria for major depression are determined by the presence of depressed mood and at least 4 of the following (to qualify for a diagnosis of major depression, symptoms must be present for at least 2 weeks):

- Changes in sleep pattern (increased or decreased).
- Decreased interest.
- Changes in appetite (increased or decreased) with or without weight gain or loss.

### Table 3. Selected Studies Regarding Anxiety and Established Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Factor</th>
<th>End Point(s)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frasure-Smith et al</td>
<td>Anxiety</td>
<td>Fatal and nonfatal MI, UAP</td>
<td>2.5 (1.6-5.6)</td>
</tr>
<tr>
<td>Moser and Dracup</td>
<td>Anxiety</td>
<td>Death, MI, VT/VF, UAP</td>
<td>4.9 (2.1-12.2)</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>Anxiety</td>
<td>Death</td>
<td>1.06 (Not reported)</td>
</tr>
<tr>
<td>Denollet and Brutsaert</td>
<td>Anxiety</td>
<td>Death, MI, UAP</td>
<td>3.9 (1.2-9.6)</td>
</tr>
<tr>
<td>Herrmann et al</td>
<td>Anxiety</td>
<td>Mortality</td>
<td>2.5 (1.4-4.4)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; MI, myocardial infarction; UAP, unstable angina pectoris; VT, ventricular tachycardia; and VF, ventricular fibrillation.

©2000 American Medical Association. All rights reserved.
• Suicidal ideation or thoughts of death.
• Decreased concentration ability.
• Feelings of guilt or preoccupation of thought.
• Decreased energy.
• Psychomotor agitation or retardation.

The impact of major depression on patients after MI is far reaching. For instance, the Medical Outcomes Study70,71 showed that depression causes as much disruption in daily functioning as do most chronic medical conditions, including heart disease itself. Furthermore, depression and heart disease seem to have independent additive adverse effects on functioning, well-being, and mortality. The combination of advanced CAD and depression causes almost twice the social impairment caused by either condition alone.70,71 In addition, depressed patients after MI are more likely to report being more anxious or stressed than their counterparts without depression.72

The evidence that depression affects post-MI prognosis is growing. Those with post-MI depression are at increased risk for subsequent cardiac events, including reinfarction and rehospitalization, as compared with patients after MI without depression.22,23,73 More importantly, Frasure-Smith et al22 found compelling evidence that depression (detected with the Diagnostic Interview Schedule35) was associated with a more than 4-fold increased risk of mortality during the first 6 months following acute MI (Figure), while depressive symptoms (as assessed with the Beck Depression Inventory51) were associated with an almost 8-fold increase in cardiac mortality during 18 months of follow-up.23 These findings remained significant when adjusted for relevant covariates, including left ventricular dysfunction, tobacco use, or history of MI.22,23 In fact, depression was a more powerful, independent predictor of mortality than any of these more traditional measures of risk stratification. Furthermore, the combination of depression and greater than 10 premature ventricular contractions per hour imparted an almost 30-fold increase in the risk for cardiac death.23 Similar findings were reported by Barefoot and coworkers,19 who noted a 69% increase in the risk for cardiac death in a heterogeneous group of patients with CAD and moderate to severe depression during a median follow-up of 15.2 years. Preliminary work from Frasure-Smith and associates23 suggests that depression has a similar impact on prognosis in patients with unstable angina pectoris.

The mechanism by which depression increases morbidity and mortality in these patients is unclear. Patients with depression have baseline elevations in circulating catecholamines and demonstrate an exaggerated response to exogenous stress with abnormally brisk production of catecholamines.53,60,64 Both of these elements of abnormal catecholamine metabolism likely have significant effects on heart rate, blood pressure, cardiac rhythm, and myocardial oxygen consumption. Finally, increases in platelet aggregability have been documented in depressed patients with CAD.52,74 Together or independently, these effects may increase the risk for ischemia and activate unstable coronary syndromes.

Efforts have been made to determine the relationship between depression and cardiac rhythm disturbances,73,74 Population analyses suggest that a major factor contributing to the increased long-term risk associated with depression is likely an increased incidence of sudden death from abnormalities of cardiac rhythm.23,76-78 Impaired baroreflex responses and decreased HRVs have also been documented in patients with depression.79,80 Since the long-term prognosis of patients with heart disease and major depression is poorest in those patients with greater than 10 premature ventricular contractions per hour,23 it is probable that an enhanced susceptibility to arrhythmia exists. Indeed, an increased incidence of significant ventricular tachyarrhythmias has been observed in depressed patients with CAD compared with controls.73,76 The explanation for this phenomenon remains unknown. However, the association between depression and decreased HRVs, leading to a relatively proarrhythmic state, has been invoked.80 Furthermore, the increased levels of catecholamines noted in depressed patients with CAD may lower the threshold for ventricular tachycardia or fibrillation.82-85

In addition to the biological risks, depressed patients have behavioral issues that may negatively influence their long-term prognosis. These include decreased adherence to prescribed medications and cardioprotective therapies48 and a lower likelihood of undertaking car-

Table 4. Selected Studies Regarding Depression and Established Ischemic Heart Disease*

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Factor</th>
<th>End Point(s)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carney et al47</td>
<td>Depression</td>
<td>Death, MI, PTCA, CABG</td>
<td>2.5 (Not reported)</td>
</tr>
<tr>
<td>Frasure-Smith et al48</td>
<td>Depression</td>
<td>Fatal and nonfatal MI, UAP</td>
<td>3.6 (1.3-10.1)†</td>
</tr>
<tr>
<td>Barefoot et al23</td>
<td>Depression</td>
<td>Cardiac death, total mortality</td>
<td>P = .002 for cardiac death, P = .001 for total mortality</td>
</tr>
<tr>
<td>Denollet and Brutsaert27</td>
<td>Depressive symptoms</td>
<td>Cardiac death, MI</td>
<td>4.3 (1.4-13.3)†</td>
</tr>
<tr>
<td>Frasure-Smith et al48</td>
<td>Depressive symptoms</td>
<td>Cardiac death</td>
<td>3.3 (1.0-10.59)‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.05 (1.29-7.17)§</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; and UAP, unstable angina pectoris.
†For depressive symptoms: RR, 7.8 (95% CI, 2.4-25.3).
‡Female patients.
§Male patients.
TREATMENT OF ANXIETY AND DEPRESSION IN PATIENTS WITH CARDIAC DISEASE

The psychological benefits of treatment for anxiety and depression in the setting of heart disease seem clear. Conversely, the cardiovascular benefits of controlling these states are unproven; only recently have investigations shown that anxiety states may affect cardiovascular risk. In patients with coronary artery disease, anxiety is associated with adverse outcomes. The need for treatment for anxiety remains underappreciated, however, by the National Heart, Lung, and Blood Institute currently in the enrollment phase. This study proposes to test the hypothesis that pharmacological interventions, with or without psychotherapy, for patients with acute cardiac disease and depression and/or social isolation will reduce morbidity and mortality in these patients. Results from this trial are not anticipated for several years.

Stress Reduction Techniques

Early data from the Ischemic Heart Disease Life Stress Monitoring Program suggested that the increased cardiovascular risk associated with stress could be reduced to control levels with aggressive stress reduction techniques. These data were confirmed by Blumenthal et al, who demonstrated a 74% reduction in combined end points of death, MI, and revascularization among a small group of patients with stress and hostility, managed with group instruction and stress reduction techniques. However, these optimistic results were not reproduced by the Montreal Heart Attack Readjustment Trial (M-HART), a recent, large, home-based, nurse-administered, stress reduction program after MI. In the latter study, outcomes were not improved, and there appeared to be a surprising trend toward increased mortality among female patients. The reasons for this unusual finding remain unclear. The intervention itself was minimal; it may have been insufficient to have a sustained effect on more profound anxiety states. Preliminary results from a substudy of M-HART suggested a salutary treatment effect, with morbidity and mortality both decreased, among patients responding to the home-based program (identified via serial administration of the General Health Questionnaire-20). Those who did not respond had no evidence of benefit. Thus, individualized psychosocial intervention may have the potential to modify prognosis. However, at present, the benefits of interventions to reduce anxiety or stress states for the prognosis following MI remain unclear.

Drug Therapy for Affective Disorders

Benzodiazepines, such as alprazolam, clonazepam, diazepam, and lorazepam, are safe and effective drugs for the treatment of anxiety in patients with CAD, with or without comorbid depression. Their rapid onset of action and relatively favorable adverse-effect profile make benzodiazepines particularly useful for the acute treatment of anxious patients in the cardiac care unit. Long-term use of benzodiazepines for anxiety is often complicated by issues of dependence. Furthermore, depression by itself is not considered an indication for benzodiazepine monotherapy, usually requiring the addition of an antidepressant.

Prior to the introduction of selective serotonin reuptake inhibitors (SSRIs), the psychopharmacologic treatment for patients with affective disorder and stable cardiovascular illness relied on tricyclic antidepressants (TCAs), such as amitriptyline, imipramine, nortriptyline, desipramine, and doxepin. Drugs from this class have several adverse effects that complicate their use in patients with cardiac disease. Tricyclic antidepressants cause...
orthostatic hypotension, which may result in hemodynamic instability, especially in those patients with conduction system disease and congestive heart failure. They may potentiate the effects of vasoconstrictor medications. Furthermore, TCAs possess significant anticholinergic effects, having numerous drug-drug interactions, and can cause abnormalities of cardiac conduction. Additionally, TCAs may increase the risk for proarrhythmia because of their intrinsic quinidine-like qualities. For these reasons, TCA treatment in the first 2 months following MI has often been avoided. This same period is when major depression often develops and when the effects of depression on morbidity and mortality appear to be the greatest.

Other non-TCA anxiolytic and antidepressant agents are available, but few data are available regarding their use in patients with heart disease. Included among these are trazodone hydrochloride, nefazodone hydrochloride, and mirtazapine. These drugs cause adverse effects, including sedation, hypotension, and (in the case of trazodone) a rare risk of priapism in male patients. Bupropion hydrochloride (a relatively stimulating antidepressant) has been shown to be effective for assisting in smoking cessation, independent of potential drug-drug interactions (especially with warfarin sodium) have been raised. The SSRIs are as effective as TCAs for the treatment of depression and panic disorder, are generally well tolerated, and are associated with a lower incidence of both serious cardiac events and discontinuation rates. Although tachyarrhythmias and bradycardia have been reported in patients taking SSRIs, important disturbances of cardiac rhythm are very infrequent. An augmented coronary artery vasospastic response following angioplasty has been noted in laboratory animals treated with fluoxetine, while myocardial ischemia has been rarely observed following abrupt discontinuation of SSRIs. Nevertheless, the risk of adverse cardiovascular effects appears to be extremely low, for example, with an incidence of cardiovascular events for fluoxetine reported as low as 0.0003%. Recent data suggest that sertraline may have a modest antiplatelet effect, likely mediated via this agent's effect on platelet serotonin metabolism. Whether this action has any bearing on the risk of thrombosis remains unclear.

Despite the apparently benign adverse-effect profile possessed by SSRIs, little research exists regarding their benefit in patients with acute cardiac disease. The Sertraline Antidepressant Heart Randomized Trial (SADHART) is a large-scale, multicenter, double-blind, randomized study of the safety and efficacy of sertraline therapy in patients with acute cardiac disease and is currently in the enrollment phase. Since it will be many more years before meaningful data will be available, the use of antidepressants in patients with cardiac disease requires consideration of the possible risks vs the presumed benefits associated with treatment.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT), the most effective therapy for severe, drug-resistant depression, has profound effects on cardiovascular function. It may alter heart rate and

Cardiac Rehabilitation and Affective Disorders

In addition to its salutary effects on lipids, weight loss, and exercise tolerance, cardiovascular rehabilitation improves self-image, provides emotional support, reduces levels of depression, improves quality-of-life scores, and reduces mortality by approximately 25%. These beneficial effects of cardiac rehabilitation extend equally to various high-risk patient groups (such as elderly patients and those with diabetes mellitus) who tend to become depressed more often than do others following major cardiac events.

As the average length of stay for patients with ACS continues to decrease, opportunities for the identification of symptoms or signs of incipient anxiety or depression commensurately drop. Cardiovascular rehabilitation programs offer an attractive conduit through which patients following ACS may be identified for these symptoms or signs of affective disease, additionally allowing for initiation of potential interventions if indicated. This addition of specific psychosocial screening and interventions (eg, CBT) to car-
diac rehabilitation (so-called comprehensive cardiovascular rehabilitation) appears to be a cost-effective method for the identification and treatment of anxiety and depression following major cardiac events. Such comprehensive cardiovascular rehabilitation programs may further decrease psychological distress, improve coping skills, and reduce some biological risk factors, such as social isolation and tobacco use.

Tempering the positive qualities of cardiovascular rehabilitation is the fact that only a small percentage of eligible patients ever get referred, despite national guidelines from the Agency for Health Care Policy and Research (AHCPR) encouraging such referral. The reason for the underutilization of cardiac rehabilitation is unclear, though inadequate physician referral as well as resistance from some third-party payers may explain at least some of the poor referral statistics. Finally, some evidence shows that specific psychosocial interventions added to conventional cardiac rehabilitation may not afford additional benefits in terms of mortality or morbidity, though these discordant findings might be because of ineffective interventions in the negative studies. Nonetheless, some have questioned the routine addition of post-MI psychosocial interventions to cardiac rehabilitation.

**SUMMARY**

A fundamental paradox has existed in the area of psychosocial risk factors and CAD for some time: while investigators and theorists have pursued the underlying role of these factors in the development and exacerbation of CAD and SCD, most clinicians have generally considered such psychosocial characteristics to be a consequence of cardiac disease. There is strong epidemiologic evidence, however, that psychological factors, notably anxiety and depression, have effects on the development of CAD and the precipitation of SCD. These psychosocial risk factors exert a profoundly negative effect on quality of life and adversely influence outcomes of ischemic heart disease from many standpoints, including recurrent hospitalization, an increased incidence of ischemic events, and higher mortality.

Anxiety is prevalent among patients with acute cardiac illness and triples the risk for all-cause mortality following MI, almost doubles the risk for reinfarction over 5 years, and increases the risk for SCD by a factor of 6.

The incidence of major depression in patients with acute cardiac illness is approximately 25%. Independent of classic prognostic markers, major depression following MI has a devastating effect on both the quality of life and the adherence to therapies and quadruples the risk for mortality. In patients after MI with ventricular irritability, depressive symptoms substantially increase the risk for cardiac death.

The mechanism by which these psychological states exert these deleterious effects is unclear, but possible causes include heightened activation of the sympathetic nervous system, diminished parasympathetic activity, alterations in coagulation and fibrinolysis, and reduced compliance with treatment programs.

Although there is much information concerning the adverse effects of these psychological states in patients with CAD, there are few data as to whether treatment is effective in improving the incidence of morbidity and mortality. Knowledge about the benefits of specific therapy for affective disorders in patients with CAD will likely be enhanced by the ENRICHD and SADHART trials. However, relatively safe therapies, such as benzodiazepines for anxiety or SSRIs for depression or CBT for both, are now available. Given the exceptionally negative effects that these common disorders exert on the quality of life in patients with CAD, sufficient data now exist to support more aggressive screening for psychosocial risk factors and the institution of appropriate therapies. Cardiovascular rehabilitation programs appear to be an excellent way to achieve this goal.

Much more information is needed to understand the impact of psychosocial background on the increased risk of mortality and morbidity in patients with cardiac disease and to better delineate the mechanism(s) of increased risk engendered by affective disorders, especially with regard to their biological effects, including abnormalities of endothelial function, atherosclerotic plaque integrity, and changes in thrombosis or hemostasis, as well as their electrophysiologic effects. Clearer delineation of neural-cardiac anatomic relation is critical to better understand the upstream mediators of the increased cardiac risk of psychosocial factors. Clinically, further investigation regarding methods for the identification of those at greatest risk from psychosocial factors is required, as is a method for selecting those most in need of intervention, as well as which intervention to use. Interdisciplinary integration among basic scientists and clinicians will be necessary to make this a reality.

Accepted for publication November 4, 1999.

This study was supported in part by a grant from the Charles A. Dana Foundation, New York, NY. Dr Januzzi is supported by the Clinical Scholar Fund of the Massachusetts General Hospital, Boston.

Corresponding author: Roman W. DeSanctis, MD, Department of Medicine, Cardiac Unit, Ambulatory Care Center, Suite 467, Massachusetts General Hospital, Boston, MA 02114.

**REFERENCES**


70. Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpa-
71. Wells KB, Steward A, Hays RD, et al. The func-
tioning and well-being of depressed patients: re-
sults from the Medical Outcomes Study. JAMA. 1989;262:914-919.
72. Lloyd GG, Cawley RH. Distress or illness? a study of psychosocial symptoms after myocardial in-
73. Schleifer SJ, Macari MM, Slater W, Kahn M, Zuck-
er H, Gorini R. Predictors of outcome after myocardial infarction: role of depression. Cir-
charge. 1974;2:2-10.
74. Musselman DL, Evans DL, Nemeroff CB. The rel-
ationship of depression to cardiovascular dis-
75. Fellick MJ, Ahern DK, Gorkin L, et al. Relation of psychosocial and stress reactivity variables to
76. Carney RM, Freedland KE, Rich MW, Smith LJ, Jaffe AS. Ventricular tachycardia and psychiat-
77. Ladwig KH, Kieser M, Konig J, Breithardt G, Borg-
greffe M. Affective disorders and survival after myocardial infarction: results from the Post-
78. Rosenman RH, Brand RJ, Sholtz RI, Friedman M. Multivariate prediction of coronary heart dis-
ease during 8.5 year followup of the Western Col-
79. Rechlin T, Weiss M, Aspitzer A, Kascika H. Are affective disorders associated with alterations of
heart rate variability? J Affect Disord. 1994;32:
271-275.
reduced heart rate variability in coronary artery
81. Watkins LL, Grossman P, Association of depre-
sion with reduced baroreflex cardiac control in
82. Hjemdahl P, Larsson PT, Wallen NH. Effects of stress on the sympathetic block on platelet function. Cir-
cculation. 1991;84(suppl I):VI44-VI61.
83. Schwartz PJ, Sloweid NG, Brown AM. Effects of unilateral cardiac sympathetic denervation on the
84. Kikis RB, Burgess MJ, Abildskov JA, Influence
of sympathetic tone on ventricular fibrillation
85. Podrid PJ, Fuchs T, Candinis R. Role of the symp-
pathetic nervous system in the genesis of vent-
man JR, editors. The MGH Guide to Psychi-
ary Care in Primary Care. New York, NY: McGraw-
87. Williams RB, Litman AB. Psychosocial factors: role in cardiac risk and treatment strategies. Car-
88. Brennan A. Efficacy of cardiac rehabilitation: Z
89. O’Meara PB, Martin A, Greenland J, Bernstein L, Allan R. A controlled trial of a behavioral and
educational intervention following coronary ar-
90. Bennett P, Carroll D. Cognitive-behavioral inter-
ventions in cardiac rehabilitation. J Psychosom
distress on rehospitalizations in cardiac re-
habilitation patients. Psychosomatics. 1989:39:
134-143.
92. Dafna W, Huston P. Current trends in card-
93. Linden W, Stoessel C, Maurice J, Psychosocial inter-
156:745-752.
94. Schneiderman N. Enhancing Recovery in Coro-
nary Heart Disease (ENERCHD) Patients. Beth-
esda, Md: National Heart, Lung, and Blood Insti-
management and exercise training in cardiac pa-
 tients with myocardial ischemia: effects on prog-
nosis and evaluation of mechanisms. Arch Intern
96. Cossette S, Frasure-Smith N, Lesperance F, Impact
of improving psychological distress in post-MI patients [abstract]. Presented at: Ameri-
can Psychosomatic Society Meeting; March 18,
1999; Vancouver, British Columbia.
97. Tese GA. Cardiovascular side effects of psychot-
ropic agents. In: Stern TA, Herman JB, Flavin PL, eds. The MGH Guide to Psychi-
ary Care in Primary Care. New York, NY: McGraw-
98. Boyer W, Chernow B, Lake CR. Psychopharma-
cology in the intensive care unit. Psychiatr Clin
99. Glassman AH. The newer antidepressant drugs and
their cardiovascular effects. Psychopha-
100. Sheline YI, Freedland KE, Carney RM. How safe
are serotonin reuptake inhibitors for inhibi-
tion in patients with coronary heart disease? Am
101. Warrington SJ, Padgham C, Lader M. The car-
diovascular effects of antidepressants. Psychol
102. Stern TA. The management of depression and
anxiety following myocardial infarction. Mt Si-
103. Hunt RD, Sachs DPL, Glover ED, et al. A com-
parison of sustained-release propranolol and pla-
337:1195-1202.
104. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Rela-
tionship of improved psychological distress to psychophar-
macological intervention: 10-year results of a comprehensive reha-
 bilitation programme. Eur Heart J. 1993;14:831-
833.
105. Burgess AW, Lerner DJ, D’Agostino RB, Vokos-
as PS, Hartman CR, Gaccione P. A random-
ized control trial of cardiac rehabilitation. Soc
106. Milani RV, Lavie CJ, Cassidy MM. Effects of car-
diac rehabilitation and exercise training pro-
gerations of ECT in depressed patients with cardiac
107. Mayou R. Rehabilitation after heart attack. BMJ.
108. Benoliel J, Brutsaert DL. Enhancing emotional
well-being by comprehensive rehabilita-
tion with coronary heart disease. Eur Heart J. 1995;
16:1070-1078.
109. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA.
Cardiac rehabilitation after myocardial infarc-
tion: combined experience of randomized clin-
110. Lavie CJ, Milani RV. Effect of cardiac rehabili-
tation and exercise training programs in pa-
tients > or = 75 years of age. Am J Cardiol. 1996;
78:675-677.
111. Lavie CJ, Milani RV. Benefits of cardiac rehabili-
tation and exercise training in elderly women. Am
112. Milani RV, Lavie CJ. Behavioral differences and
effects of cardiac rehabilitation in diabetic pa-
tients following cardiac events. Am J Med. 1996;
100:517-523.
113. Jones DA, West RR. Psychological rehabilita-
tion after myocardial infarction: multicentre ran-
domised controlled trial. BMJ. 1996;313:1517-
1521.
114. Wenger NK, Froelicher ES, Smith LK, et al. Car-
diac Rehabilitation, Clinical Guideline No. 17.
Bethesda, Md: Agency for Health Care Policy and
Research, National Heart, Lung, and Blood In-
stitute, Public Health Service, Department of
Health and Human Services; October 1995. Publica-
tion AHCPR 96-0672.