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Is There a High-Risk Subtype of Depression in Patients with Coronary Heart Disease?

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Abstract

Depression is a risk factor for cardiac morbidity and mortality in patients with coronary heart disease, especially in those with a recent history of acute coronary syndrome. To improve risk stratification and treatment planning, it would be useful to identify the characteristics or subtypes of depression that are associated with the highest risk of cardiac events. This paper reviews the evidence concerning several putative depression subtypes and symptom patterns that may be associated with a high risk of morbidity and mortality in cardiac patients, including single-episode major depressive disorder, depression that emerges after a cardiac event, somatic symptoms of depression, and treatment-resistant depression.

Keywords

Coronary disease; Coronary heart disease; Subtype; High risk; Depression; Depressive disorder; Major depressive disorder; Treatment-resistant depression; Myocardial infarction; Mortality; Myocardial ischemia

Introduction

Depression is an established risk factor for morbidity and mortality in patients with coronary heart disease (CHD), especially in those with a recent history of acute coronary syndrome (ACS) [1–4]. However, some studies have failed to find this relationship. It is conceivable that the positive findings have been due to chance, that publication bias has selectively filtered more negative than positive findings out of the literature, or that depression is merely an epiphenomenon of relatively severe cardiac illness. However, three meta-analyses suggest that depression is a robust predictor of mortality and morbidity in patients with CHD [2–4], and most of the positive studies have adjusted for mortality risk factors, including indicators of the severity of cardiac disease.

Nevertheless, the inconsistency of this literature deserves consideration. One of the possible reasons for the divergent findings is that there have been differences among studies with regard to how depression has been defined and measured [1]. However, findings have differed even among studies that have relied on similar definitions of and methods of assessing depression [5, 6].

Another potential explanation is that some, but not all, depressed cardiac patients are at high risk of morbidity and mortality. If there is a high-risk subtype of depression, and if it is underrepresented in some studies and overrepresented in others, this could help explain the divergent findings. Identification of the high-risk subtype, if it actually exists, would clarify

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the status of depression as a cardiac risk factor and enable researchers and clinicians to focus on screening and treating the patients for whom depression poses the most serious health hazard. It would also facilitate the characterization of the biobehavioral pathways through which depression increases the risk of mortality. This in turn would redirect research efforts toward developing treatments that could attenuate or block these risk mechanisms. This paper reviews the current evidence concerning several putative depression subtypes and symptom patterns that may be associated with a high risk of morbidity and mortality in cardiac patients.

Single-Episode Versus Recurrent Major Depressive Disorder

The longitudinal course of major depressive disorder (MDD) was one of the first moderators of the effect of depression on cardiac outcomes to be investigated. Among patients who are diagnosed with MDD shortly after ACS, some are experiencing major depression for the first time in their lives, whereas others are having a recurrent episode. Among the latter, there are differences in the age at onset of the first episode and in the number of lifetime episodes. Many individuals start having major depressive episodes years or even decades before they are diagnosed with coronary disease. The question this poses is whether information about the lifetime course of depression adds anything to the prognostic value of current depression in patients with recent ACS.

Lespérance and colleagues [7] were the first to address this question. In a study of 222 patients with a recent history of acute myocardial infarction (MI), they found an 18-month post-MI mortality rate of 40% in patients with recurrent major depression, compared with 10% in patients with single-episode major depression. This finding fit with an expectation that many of us hold—that more exposure to a risk factor over a longer period of time should place patients at greater risk. An individual who has just started smoking, for example, is at lower risk of developing coronary artery disease than someone who has smoked for 30 years. Similarly, a patient who is depressed following an acute MI and who has experienced multiple episodes of major depression over the preceding 30 years should be at higher risk than a patient who is depressed for the first time. Perhaps for this reason, this finding went unchallenged for many years, despite the fact that the study was based on relatively few patients and end points and that the analysis was post hoc and not adjusted for possible confounders. However, larger, more recent studies have not supported this finding [8–12].

Grace et al. [11] were the first to report, in a study of 750 post-MI patients, that although current depression (Beck Depression Inventory [BDI] score ≥10) was a significant predictor of all-cause mortality, the risk was limited to patients who had never been depressed before. Thus, single-episode depression predicted survival, but recurrent depression did not. In a study of 468 patients with a recent acute MI, de Jonge and colleagues [8] also found that only those patients who were depressed for the first time were at increased risk of the combined end point of cardiovascular mortality or hospitalization. Similar findings have been reported by Dickens et al. [9], Goodman et al. [10], and Spijkerman et al. [12].

Dickens and colleagues [9] initially found that depression did not predict cardiac outcomes in their study of 588 post-MI patients. They subsequently reported that the subgroup of patients who were depressed and/or anxious (Hospital Anxiety and Depression Scale score >17) 12 months after the MI and who had denied ever being depressed before the acute event were at increased risk of cardiovascular mortality during the follow-up period [9]. This raises the possibility that other studies that failed to find that depression increases the risk of cardiac morbidity and mortality may have enrolled a high proportion of patients with recurrent depression.

Our group conducted a subgroup analysis of data from the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial [13]. This analysis included a larger sample of depressed patients and had more statistical power to detect differences in survival than did any of the earlier studies. It compared the 29-month post-MI survival rates of 370 patients with an initial episode of MDD, 550 with recurrent MDD, and 408 who were free of depression but who were otherwise medically eligible for the clinical trial [14•]. After adjusting for medical and demographic predictors of all-cause mortality, the baseline BDI score, and the use of selective serotonin reuptake inhibitor antidepressants, patients with a single episode of MDD had poorer survival (all-cause mortality, 18.4%) than those with recurrent MDD (11.8%; hazard ratio [HR], 1.4 [95% CI, 1.0–2.0]; P=0.05). This difference was not the result of more severe heart disease at index, poorer response to depression treatment, or a higher risk of cerebrovascular disease or "vascular depression" in patients with single-episode MDD. Also, despite this difference, both the single-episode (HR, 3.1 [95% CI, 1.6–6.1]; P=0.001) and the recurrent MDD (HR, 2.2 [95% CI, 1.1–4.4]; P=0.03) subgroups had significantly higher all-cause mortality rates than did the nondepressed patients (3.4%). In short, both depressed subgroups were at increased risk, but the single-episode subgroup was at the highest risk.

Some studies, however, have failed to replicate this finding. A study by Parker and colleagues [15] suggested that the timing of the depressive episode relative to the acute event determines risk status, not whether it is the patient's first depressive episode. They found that the patients who became depressed after an MI were at higher risk of cardiac events (death or ACS readmission) than those whose depressive episode began before the event. Grace et al. [11] and de Jonge et al. [8] also found that depressive episodes that begin after ACS increase the risk of future cardiac events. However, unlike the Grace et al. [11] and de Jonge et al. [8] studies, the risk in the Parker et al. [15] study was present in patients who were depressed after the event, regardless of whether it was the individual's first episode or a recurrent one.

In a recent secondary analysis of data from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), neither single-episode MDD nor onset of a major depressive episode after an MI were associated with higher mortality risks than those conferred by recurrent MDD or by pre-MI onset of depression [16]. SADHART did not include a nondepressed comparison group, so it was not possible to determine which subgroups were at higher risk than patients who had never been depressed.

There are methodologic differences among these studies, including in the definition and assessment of depression, end points (all-cause mortality, cardiovascular-related mortality, combined end point of cardiac events), and timing of the assessment of depression relative to the index cardiac event. However, none of these differences seem to explain the contradictory findings. This may be due in part to the fact that the subgroups of interest are not mutually exclusive. For example, many patients who become depressed after ACS are experiencing their first-ever depressive episode. Furthermore, it can be difficult to obtain a reliable lifetime depression history from a depressed middle-aged or older adult, particularly when the history is taken in the wake of a potentially life-threatening medical crisis [17, 18], and middle-aged and older men in particular may be reluctant to admit to past or present depressive episodes. Thus, it is possible that differences in depression history ascertainment may at least partially explain some of the variation in the findings. In a thorough review of this literature, Zuidersma and colleagues [19•] concluded that there is not yet sufficient evidence to characterize either single-episode MDD or major depressive episodes with a post-ACS onset as high-risk subtypes.

Patterns of Depressive Symptoms

There is evidence of a dose–response relationship between depression severity and cardiac risk [16, 20, 21]. Cardiac patients with as few as two or three symptoms of depression are at elevated risk of cardiac morbidity and mortality, and more symptoms yield greater risk. Common features of depression include dysfunctional cognitions such as hopelessness, somatic symptoms such as disturbed sleep, and mood disturbances such as sadness and irritability. Depression is a polythetic syndrome; consequently, many different combinations of symptoms meet the *DSM-IV-TR* criteria for a major depressive episode [22]. This creates the possibility that typical patterns of depressive symptoms may differ across different populations of depressed patients.

Are the symptoms of depression in patients with heart disease different from those reported by depressed but otherwise medically healthy psychiatric patients? A secondary analysis of data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a multicenter trial in which more than 4,000 outpatients were treated for major depression, showed that patients with heart disease were more likely than other patients to have a family history of depression and to report symptoms of sympathetic nervous system arousal, including tremors; blurred vision; tinnitus; increased sweating; cardiac symptoms such as palpitations, dyspnea, and chest pain; and early-morning insomnia, but not fatigue or other symptoms of depression. Patients with heart disease also had a higher prevalence of comorbid panic disorder than patients without heart disease, but they did not differ in the rate of other Axis I psychiatric disorders [23].

Martens and colleagues [24] compared symptoms reported by depressed psychiatric patients with those reported by cardiac patients who were depressed following an MI, and found that cognitive and affective symptoms of depression were reported more frequently by the former than the latter patients. However, the psychiatric patients were being treated for depression at a psychiatric clinic, whereas the patients with CHD were identified as being depressed by researchers who were conducting an observational study of post-MI depression. Contextual differences such as these may influence patients' symptom-reporting behavior independent of any actual differences in the phenomenology of depression. It is also possible that patients who seek treatment for depression tend to have different symptom profiles than depressed patients who do not seek treatment.

In a recent series of studies, somatic symptoms of depression, including disturbed sleep and fatigue, were better predictors of cardiac events in patients with CHD than were cognitive symptoms of depression [25–32]. In a group of patients with a recent MI, de Jonge and colleagues [25] found that a cluster of somatic/affective, but not cognitive/affective depression symptoms predicted cardiac events after adjusting for relevant covariates. Others have reported similar results in women undergoing coronary angiography [28], patients with documented medically stable CHD [27], and patients with chronic heart failure [31]. In patients with no clinical evidence of heart disease, somatic, but not cognitive symptoms of depression have predicted subclinical atherosclerotic progression [33]. It is possible that somatic symptoms predict cardiac events because they reflect the severity of the underlying heart disease, but these studies adjusted for various indices of heart disease severity. Thus, patients with predominantly somatic symptoms may have a cardiotoxic subtype of depression. However, several other studies do not support this finding.

Barefoot et al. [34] reported that only negative affect predicted survival in patients with angiographically diagnosed coronary artery disease when included in a model with somatic and other depression symptoms. However, some studies have reported that cognitive and somatic symptoms predict cardiac events [35, 36], whereas others have reported that

cognitive, but not somatic symptoms predict cardiac events [37–39]. Interestingly, all three studies of patients undergoing revascularization found that only cognitive symptoms predicted events. On the other hand, none of the post-MI or post-ACS studies found only cognitive symptoms to be predictive of cardiac events. Two studies found that both cognitive and somatic symptoms were associated with an increased risk in post-MI patients, and five found only somatic symptoms predicted a greater risk of cardiac events.

We previously pointed out the methodologic differences among these studies, as well as potential confounders that may at least partially explain the inconsistency of the results [40]. For example, somatic symptoms were more frequent and more severe in some of these studies and therefore may have been confounded with the overall severity of depression. Perhaps the most problematic methodologic issue is variation in the methods used to classify symptoms. There are two general approaches for classifying symptoms: reliance on the "face validity" of the items and reliance on principal components or factor analysis. Different factor analyses often produce different factors because of differences in the samples, analytic procedures, and decision rules used to include or exclude items from factors. Some investigators retain only the items that load highly on one and only one factor, whereas other researchers count the same item as both a somatic and cognitive symptom if it loads highly on both factors. In addition, scales formed by factor analytic methods often differ from scales formed on the basis of face validity. For example, in both the de Jonge et al. [25] and Martens et al. [29] studies, the BDI "dissatisfaction" item loaded higher on the "somatic/affective" factor (0.69 and 0.72, respectively) than on the "cognitive" factor (0.49 and 0.38, respectively). Dissatisfaction is usually considered to be a cognitive item on the basis of face validity. Similarly, in the de Jonge et al. [25] study, the "indecisiveness" item had the second highest loading on the "somatic/affective," but it would be called a cognitive symptom if categorized based on its face validity.

The diversity of depression measures and methods of classifying symptoms have made this literature very difficult to evaluate. In a previous review of this literature, we argued that it would be premature to conclude that distinctly high cardiac risks can be attributed to any individual depression symptom or set of symptoms [40]. Nevertheless, we believe that this is a promising line of research. Future analyses should adjust for the potentially confounding effects of differences in the frequency and severity of the different types of symptoms, as well as for the effects of the overall burden of depression. Studies relying on factor analytic techniques should use a common set of rules for identifying and classifying cognitive and somatic symptoms and consider reporting both factor analytic and face valid methods in the same study. This would facilitate comparisons among studies and make it easier to determine the extent to which the findings result from differences in methodology. Less reliance on exploratory factor analysis and a greater emphasis on confirmatory factor analysis [41] would also help. Finally, it may not make sense to evaluate two highly correlated factors, such as cognitive and somatic depression symptoms, in the same statistical model due to multicollinearity [42]. Evaluating them separately could yield more consistent findings across studies.

Chronic, Persistent, and Treatment-Resistant Forms of Depression

A recent meta-analysis found that when depression is assessed within 2 weeks after ACS, it is less predictive of cardiac events than when it is assessed more than 2 weeks after the event [2]. This might be due to the prognostic insignificance of transient depressive symptoms that resolve as soon as the patient recovers from the ACS.

A recent study found that of the patients who were depressed after ACS, only those with persistent symptoms, as defined by an elevated BDI score both at baseline and at 12-month

follow-up, were at risk of adverse cardiac outcomes. Patients with transient depressive symptoms were not at increased risk [43]. Interestingly, patients with transient depression actually had higher BDI scores at baseline than did the persistent cases. Although not all studies have found that patients with persistent depression are at higher risk [44], one form of persistent depression that has been consistently found to be a predictor of cardiac mortality following ACS is depression that has failed to respond to one or more conventional treatments.

In the ENRICHD trial, 2,481 patients with major or minor depression and/or low perceived social support were randomly assigned to usual care or an intervention. The intervention provided up to 6 months of cognitive-behavioral therapy and sertraline for up to 1 year for patients who had severe depression (Hamilton Depression Rating Scale [HAM-D]-17 score >25) at baseline or who did not improve at least 50% on the BDI after 6 sessions of cognitive-behavioral therapy. Six-month mean BDI change scores were −8.6±9.2 among the depressed patients in the intervention group and −5.8±8.1 among those in the usual care group. However, there was no between-group difference in event-free survival over 29 months [13].

Among the depressed patients in the ENRICHD intervention arm, treatment nonresponders had a higher risk of death after 6 months of treatment than did the responders [45]. Patients whose BDI score increased by 10 or more points after 6 months of treatment were 1.6 times more likely to die during the follow-up compared with patients whose BDI scores did not change, and 2.5 times more likely to die than those whose BDI score decreased by 10 or more points. These effects were found after adjusting for baseline BDI score, age, antidepressant use, and major predictors of post-MI mortality, including left ventricular ejection fraction and a prior MI. Although there was a positive relationship between a change in depression and late mortality in the intervention arm, there was no such relationship in the usual care arm. More than 80% of the usual care patients received no treatment for depression. Among those who did receive treatment, usually in the form of an antidepressant, there was a twofold difference in mortality between those with the best and those with the worst response to treatment. However, because relatively few patients in the usual care group received treatment for depression, this difference was not statistically significant.

ENRICHD is the only clinical trial conducted to date that may have been adequately powered to determine whether treating depression improves survival after an MI, but there have been other clinical trials of depression treatment in post-MI or post-ACS patients. The Myocardial Infarction and Depression Intervention Trial (MIND-IT), a study from The Netherlands of 331 depressed post-MI patients, compared 24 weeks of usual care to a complicated treatment regimen that included mirtazapine or placebo followed by open-label citalopram for nonresponders, or a choice of other antidepressants or psychotherapy [46]. MIND-IT also investigated the effect of treatment on event-free survival. Like the ENRICHD trial, MIND-IT found no difference between the intervention and usual care groups in cardiac event–free survival during an average of 27 months of follow-up [46].

In a secondary MIND-IT analysis, de Jonge et al. [47] classified patients who received the intervention as responders (≥50% improvement on the HAM-D at 24 weeks) or nonresponders (<50% change in HAM-D score), and compared these two groups with patients who received no treatment for depression. After 18 months of follow-up, 26% of the nonresponders, 7% of responders, and 11% of the untreated controls had experienced a cardiac event ($P<0.001$). The treatment responders and nonresponders did not differ in age, left ventricular ejection fraction, Killip class, prior revascularization, the Charlson

Comorbidity Index, or in the prevalence of specific comorbid conditions (eg, diabetes, cerebrovascular disease, peripheral vascular disease, or hypercholesterolemia).

In the SADHART trial, no difference was noted in depression outcomes between the sertraline and placebo arms. However, treatment did have a statistically significant effect on HAM-D outcomes in the subgroup of patients who had severe, recurrent major depression [48]. The SADHART investigators also reported the results of a long-term follow-up (median, 6.6 years) of the trial participants [49]. They found a significant relationship between improvement in depression following treatment and survival in both the sertraline and placebo groups after adjusting for other major risk factors for mortality. The patients in both the placebo and sertraline groups with the most improvement (n=130) had the lowest rate of mortality (11.5%). Among the patients whose depression improved moderately (n=80), 22.5% died. In contrast, of those whose depression improved minimally or not at all (n=148), 28.4% died during the follow-up period (P=0.001).

Milani and Lavie [50] reported the results of an exercise training program in 522 CHD patients enrolled in cardiac rehabilitation. Depression was assessed before and after the exercise program. After completion of the exercise training, the mortality rate among the depressed patients who remained depressed was significantly higher (22%) than that of the nondepressed participants (5%) and the patients who had an improvement in depression symptoms following the exercise program (8%; P=0.0004). In short, patients whose depression did not respond to exercise training had a threefold to fourfold higher risk of dying than depression responders and nondepressed patients.

Thus, the association between improvement in depression and improvement in post-ACS survival seems to be robust as well as independent of the type of treatment for depression. However, residual confounding cannot be ruled out. Whether the failure to respond to treatment identifies a qualitatively different form of depression that is associated with a higher risk of mortality, or whether it is simply remaining depressed that places patients at high risk is not clear from these studies. In ENRICHD, improvement in depression decreased the risk of mortality, but only in patients who received an intervention, not in the untreated usual care patients. This seems to support the possibility that it is poor response to treatment, and not persistent depression per se, that predicts cardiac events and mortality. On the other hand, the SADHART trial found that improvement in depression lowered the risk of mortality in the intervention and placebo groups. However, patients in most drug trials, including SADHART, receive clinical management, which in itself can be therapeutic. Neither MIND-IT nor the Milani and Lavie [50] exercise study assessed depression after the intervention period in patients who did not receive treatment. Thus, this issue remains to be resolved.

Too few clinical trials have been conducted to resolve this issue, and more are needed. Identifying patients who are treatment resistant, and testing hypotheses regarding high-risk depression subtypes (eg, vascular depression or depression with elevated inflammatory markers) should advance our knowledge in this area.

Conclusions

Convincing evidence does not yet exist that any particular depression subtype or set of depression symptoms defines a group at especially high risk of cardiac morbidity and mortality. There are several promising lines of research, however, including studies of the clinical characteristics of high-risk depression reviewed in this article. In addition, other studies have attempted to identify the biobehavioral mediators of the relationship between depression and cardiac events, such as elevated proinflammatory and procoagulant activity

and autonomic nervous system dysfunction [1], that are present in some, but not all patients with depression. Some of these studies may also help clarify the relationships between cardiac outcomes and clinical characteristics of depression reviewed in this paper (eg, by examining whether inflammatory markers are elevated in patients who do not respond to depression treatment). All these efforts should be encouraged. We have known for some time that depression is a risk factor for cardiac events, including mortality. Identifying those depressed patients at the highest risk would greatly assist in risk stratification and in the design of appropriate treatments to improve survival in these patients.

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