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Treatment-Resistant Depression and Mortality after Acute Coronary Syndrome

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Abstract

Depression is a risk factor for morbidity and mortality in patients with coronary heart disease (CHD), especially following acute coronary syndrome (ACS). Evidence from recent clinical trials suggests that treatment-resistant depression may be associated with a particularly high risk of mortality or cardiac morbidity in post-ACS patients. This manuscript reviews this evidence, and considers possible explanations for this relationship. Directions for future research are also considered, with particular emphasis on efforts to elucidate the underlying mechanisms and to develop more efficacious treatments for depression in patients with CHD.

Depression is a risk factor for morbidity and mortality in coronary heart disease (CHD). A meta-analysis of 22 studies found that major depression more than doubles the risk of mortality after an acute myocardial infarction (MI).(1) There has been less research on the prognostic importance of depression after hospitalization for unstable angina, but in one study, depression increased the risk of nonfatal MI or cardiac death more than four fold after an episode of unstable angina.(2) Thus, depression is a significant risk factor in both forms of acute coronary syndrome (ACS).

It has been clear for some time that the risk of mortality is not uniformly high among depressed ACS patients, but little progress has been made in differentiating between high- and low-risk forms of post-ACS depression. However, converging evidence from several recent studies suggests the possibility that *treatment-resistant major depression* may be a distinctly high-risk form of depression in post-ACS patients.

Treatment-Resistant Depression

Treatment resistance has been defined in a variety of ways in the depression literature.(3) Failure to respond to a single trial of monotherapy is the most inclusive definition, Thase and Rush's five-stage model(4) is the most restrictive, and failure to respond to two or more monotherapies is one of the most common. About 50% of depressed patients have an adequate response to antidepressant therapy, and about 15% have a partial response, but between 20 and 35% are classified as nonresponders.(5) In addition, some patients actually become more severely depressed after the initiation of treatment. Thus, there is a wide range of responses to treatment of depression, extending from full remission to partial response, nonresponse, or deterioration.

Various approaches for overcoming treatment resistance have been tried, including sequential, combination, and augmentation therapies. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is the largest effort to date to identify effective

strategies for treating refractory depression under conditions similar to those encountered in clinical practice.(6) Over 4,000 outpatients with nonpsychotic unipolar depression were enrolled in STAR*D. Many of them had psychiatric or medical comorbidities. All of the participants were initially treated with citalopram and given a higher dose (55 mg/day) for a longer duration (12 weeks) than is usually provided in routine care. Remission of depression was defined as a score of ≤ 7 on the 17-item Hamilton Depression Rating Scale (HAM-D) or ≤ 5 on the 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR). Response was defined as a $\geq 50\%$ reduction in the QIDS-SR score.

Two popular strategies for treating the STAR*D nonresponders were tested: switching to a different antidepressant, or augmenting citalopram with a second drug or with cognitive therapy. About 25% of the citalopram nonresponders remitted after switching to a second antidepressant.(7) A slightly higher percentage remitted after augmentation of citalopram with bupropion.(7;8) Thus, about 50% of the participants remitted, either during the initial citalopram-only phase or during the switching or augmentation phase. Another 20% responded but did not fully remit. Over 30% did not fully remit even after trying two additional antidepressants or cognitive therapy, for a total of up to four treatments. Those who did respond to either the third or fourth treatment had a high relapse rate.(9) Antidepressant trials often produce more favorable outcomes than these, but most of them exclude patients with psychiatric or medical comorbidities such as heart disease. Although the STAR*D findings are encouraging, they suggest that a substantial minority of patients fail to remit, or respond only partially, even to state-of-the-art treatment for depression. Even prior to STAR*D, it was known that between 20% and 30% of depressed patients fail to respond even to multiple agents.(5;10;11)

Cardiac Events and Treatment-Resistant Depression: ENRICH D

The Enhancing Recovery in Coronary Heart Disease (ENRICH D) study was a multicenter, randomized, controlled clinical trial designed to determine whether treating depression and low perceived social support reduces the risk of recurrent infarction and death after an acute MI.(12) Patients with major or minor depression, and/or low perceived social support, were randomly assigned to usual care (UC) or an intervention (Tx) that provided up to 6 months of cognitive behavior therapy (CBT). In addition, sertraline was given for up to one year to patients in the intervention arm who either had severe depression (HAM-D-17 score >25) at enrollment, or who did not improve at least 50% on the Beck Depression Inventory (BDI) after 6 sessions of CBT. Among the depressed patients, 6-month mean BDI change scores were -8.6 ± 9.2 and -5.8 ± 8.1 in the Tx and UC arms, respectively. However, there was no between-group difference in reinfarction-free survival during a median of 29 months of follow-up.(13)

However, among Tx patients with major depression, the nonresponders had a higher risk of late mortality (i.e., death occurring ≥ 6 months after the acute MI) compared to responders. (14) Patients whose depression worsened by ≥ 10 BDI points despite treatment were 1.6 times more likely to die in the ensuing months than were those who merely failed to improve (i.e., no or minimal change in BDI score), and 2.5 times as likely to die as those who improved by ten or more points on the BDI. These effects were independent of the baseline BDI score, antidepressant use, and established predictors of post-MI mortality, including LVEF, age, and prior history of MI. Curiously, although there was a strong relationship between change in depression and late mortality in the Tx arm, the relationship was not significant in the UC arm (See Figure 1). Although fewer subjects in the Tx (15%) than the UC (26%) arm failed to show any improvement in BDI score from baseline to six months (defined as a 6-month BDI score that was equal to or higher than the baseline BDI),

the mortality rate among non-improvers was higher in the Tx arm (21%) than in the UC arm (10%) of the trial.

The Tx patients who failed to improve did so despite receiving 6 months of aggressive treatment. However, only about 15% of the UC patients received any form of non-study treatment for their depression during the first six months. Even fewer of the UC patients who failed to improve had received any depression treatment. Some of them might not have remitted even if they had been treated, but others might have responded very well to treatment had it been provided. Although the subgroup sample sizes were small and the effect was not significant, there was a stronger relationship between treatment nonresponse and late mortality among Tx patients who received both sertraline and CBT than those who received only CBT. Similarly, among UC patients who took non-study antidepressants, there was a two-fold difference in mortality between those with the best and worst treatment responses.⁽¹⁴⁾ Relatively few UC patients were treated, and the effect was not statistically significant. Nevertheless, these findings suggest that exposure to the ENRICHD intervention identified patients with a high-risk subtype of depression, i.e., depression that does not respond to standard antidepressant therapy.

Cardiac Events and Treatment-Resistant Depression: Other Clinical Trials

There is evidence from other clinical trials supporting this conclusion. The Myocardial Infarction and Depression Intervention Trial (MIND-IT) compared 24 weeks of UC vs mirtazapine vs placebo, followed by open-label citalopram for treatment nonresponders.⁽¹⁵⁾ Like ENRICHD, the MIND-IT trial failed to demonstrate the superiority of the study interventions over UC with respect to cardiac event-free survival during an average of 27 months of follow-up.⁽¹⁵⁾

In a recent secondary analysis, de Jonge et al.⁽¹⁶⁾ classified Tx patients in MIND-IT as responders (≥ 50% improvement on the HAM-D at 24 weeks) or nonresponders (<50%). They compared these two subgroups to UC patients who did not receive any treatment for depression. The 18-month incidence of cardiac events was 26% in Tx nonresponders, 11% in untreated controls, and 7% in responders ($p < .001$). These findings are strikingly similar to the ENRICHD outcomes. Also like ENRICHD, the MIND-IT findings could not be explained by between-group differences in the initial severity of medical illness. Specifically, MIND-IT responders and nonresponders did not differ in age, left ventricular ejection fraction (LVEF), Killip class, the Charlson Comorbidity Index, or in the prevalence of diabetes, cerebrovascular disease, peripheral vascular disease, hypercholesterolemia, smoking, or prior revascularization.

The Montreal Heart Attack Readjustment Trial (MHART) tested the efficacy of a 12-month, home-based nursing intervention targeting emotional distress in post MI-patients.⁽¹⁷⁾ Although depression per-se was not the primary target of the intervention, over 1/3 of the Tx patients had clinically significant depression (BDI >10) at baseline. Like MIND-IT and ENRICHD, the MHART intervention also failed to improve post-MI survival.

A 5-year follow-up of the UC arm of MHART showed that improvement in depression after one year was associated with lower cardiac mortality only in patients who had mild depression at baseline.⁽¹⁸⁾ There was no relationship between change in depression and subsequent mortality among patients who had moderate to severe depression at baseline, the very patients who may be considered for treatment in clinical settings.

This report did not include comparable analyses of the outcomes within the Tx arm. In unpublished analyses, however, the MHART investigators found a relationship between BDI change from baseline to 3 months and 5-year survival in the Tx ($p < .0001$) but not in the

UC arm ($p=.98$) (Frasure-Smith, personal communication, 2004). Only 6% of the patients in the Tx arm who were in the highest quintile of improvement on the BDI died within the first year, compared to 17% of patients in the lowest quintile. Thus, there is a striking similarity between the MHART and ENRICHD findings.

The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) was designed to determine the safety and efficacy of sertraline in patients with a recent ACS. At the completion of the trial, the sertraline and placebo arms did not differ on the HAM-D in the overall sample. However, there was a statistically significant difference in HAM-D outcomes in the subgroup with severe, recurrent major depression. There was also a trend toward fewer cardiac events in the sertraline arm.(19)

The SADHART investigators recently completed a long-term follow-up (median 6.6 years) of the trial participants. They found a significant relationship between improvement in depression during the 24 weeks of treatment and survival in both the sertraline and placebo arms, even after adjusting for other mortality risk factors (Glassman, personal communication, 2008). Using the Clinical Global Impression (CGI) scale to measure improvement in depression following treatment, they found that the patients in both the placebo and sertraline groups with the most improvement ($n=130$) had the lowest rate of mortality (11.5%). For those with moderate improvement ($n=80$), 22.5% died; and for those whose depression minimally improved, worsened, or stayed the same following treatment ($n=148$), 28.4% died during follow-up ($p=0.001$).

Unlike ENRICHD and M-HART, the control group in the SADHART trial also showed a relationship between improvement in depression and survival. However, a placebo condition and a usual care or no-treatment control group are not equivalent. A review of the efficacy data reported for placebo controlled antidepressant trials found that the average HAM-D difference between drug and placebo groups is just 2 points (range, 0.89 to 3.21).(20;21) Although the placebo is pharmacologically inert, the clinical management that is provided to a patient in a double-blinded study is often perceived as supportive and beneficial. Simply meeting with patients to discuss their depression symptoms, encouraging them to take the pills as prescribed and to return for the next scheduled visit, may be therapeutic. For example, in a study of 248 patients with CHD, Lespérance et al. found greater depression improvement in patients who received only clinical management compared to those who received clinical management plus interpersonal psychotherapy (IPT), a recognized treatment for depression in psychiatric patients.(22)

The relationship between treatment-resistant depression and cardiac mortality and morbidity extends beyond traditional treatments for depression. Milani and Lavie(23) studied 522 CHD patients in a cardiac rehabilitation aerobic exercise program. The participants were assessed for depression symptoms before and after the program. A comparison group ($n=179$) was assessed at baseline but not at follow-up. The mortality rate among the depressed patients who completed the training but who remained depressed was significantly higher (22%) than that of the nondepressed participants (5%) and of the initially depressed patients whose mood improved following the exercise program (8%; $p=.0004$). Thus, patients whose depression did not respond to exercise training had a 3–4 fold higher risk of dying than depression responders and nondepressed patients. Exercise training can therefore be added to the list of depression interventions, including sertraline, mirtazapine, citalopram, cognitive behavior therapy, and stress management, in which nonresponse is associated with an increased risk of mortality.

Milani and Lavie's(23) findings are consistent with our hypotheses. However, they do not reveal whether patients with persistent, *untreated* depression (a subgroup which includes

both potential treatment responders and potential nonresponders) are also at increased risk for mortality because they did not assess depression in the comparison patients during follow-up.

Taken together, these findings, especially those from the ENRICHD, MIND-IT, SADHART, and MHART clinical trials, suggest that unsuccessful treatment of depression after hospitalization for ACS identifies a high-risk patient subgroup. This may help to explain the failure of ENRICHD and the other clinical trials to improve survival. Although depression may have improved slightly more on average in the patients who received the intervention than in those who received usual care, the patients who were at the highest risk for cardiac events did not improve despite treatment, and they were at higher risk for cardiac events after treatment than were the responders. Because the participants in these trials were randomly assigned to treatment or control conditions, patients with potentially treatment-resistant depression were probably equally distributed between the groups. In the usual care groups, in which most patients did not receive any non-study treatment for depression, the potential nonresponders cannot be easily distinguished from potential responders who were simply never treated.

Clinical Characteristics of Depression Treatment Nonresponders

What are the characteristics of patients who do not respond well to standard treatments for depression? There have been many efforts to identify predictors of poor response to treatment in medically well, depressed psychiatric patients. Misdiagnosis, suboptimal treatment, intolerance to the side effects of the drug, and poor adherence to the treatment regimen are clearly responsible for poor response to antidepressant treatments in many cases.(24;25) Some psychiatric comorbidities, especially cognitive dysfunction, substance abuse, anxiety disorders, and personality disorders also negatively affect depression treatment outcome in patients with unipolar major depression.(26;27) Having specific medical comorbidities, such as thyroid dysfunction and rheumatoid arthritis, diminish antidepressant efficacy(24;25), but merely having one or more chronic medical illnesses is not reliably associated with a poorer response. Long duration of the present episode has consistently been a strong predictor of a poor response(10;11;24;25), as has a family history of depression.(27) Except for psychosis, the clinical characteristics of the depressive episode do not consistently predict treatment response.(24)

The explanation for why depression that is unresponsive to treatment is associated with a greater risk for cardiac-related morbidity and mortality is not immediately apparent. However, a number of biological markers that have been shown to predict poor response to depression treatment in psychiatric patients have also been identified as risk markers for cardiac events. These have also been suggested as possible mechanisms underlying the effect of depression on mortality in patients with CHD.

Inflammatory Markers and Depression Treatment Resistance

Elevated inflammatory markers consistent with an acute phase immunological response(28–33), HPA axis and ANS dysregulation(34–37), low thyroid hormone levels(37), and low plasma levels of omega-3 free fatty acids(38), have all been associated with poor response to a variety of antidepressants. In separate studies, they have also been identified as risk factors for cardiac morbidity and mortality.

Several sleep abnormalities which have cardiovascular effects have also been linked to antidepressant treatment resistance, including poor subjective sleep quality, abnormal sleep architecture, especially shortened REM latency(39), and both central and obstructive sleep apnea.(40) Poor sleep quality(41), sleep apnea(42), subclinical hypothyroidism(43;44), and

low plasma levels of omega-3 FFAs(45) have also been associated with alterations in autonomic nervous system (ANS) activity and/or elevated inflammatory markers, suggesting possible connections to other cardiac risk markers and depression treatment resistance.

Few studies have examined relationships between cardiac risk factors and treatment-resistant depression in patients with CHD. Shimbo and his colleagues(31) classified patients with a recent ACS into two groups: those having no depressive symptoms (≤ 4 on the BDI), and those with at least mild depression (BDI ≥ 10). They found that elevated C-reactive protein (CRP) at baseline tended ($p=.10$) to be more common in patients who remained depressed after three months (95%) than in those whose depression improved (79%) or in those who were never depressed (73%). At 3 months, CRP was elevated in 71%, 54%, and 31% of each respective group. This was a natural history study, and many of the depressed patients presumably did not receive any depression treatment. For the patients who did receive treatment, we would expect to see larger differences between the groups, with higher CRP at baseline in true treatment nonresponders, and improvement in CRP and other risk markers in patients whose depression improved with treatment.

Vascular Depression

It is possible that patients with CHD who do not respond to depression treatment have a qualitatively different form of depression than patients whose depression improves with treatment. Cerebrovascular comorbidity is common in elderly patients with advanced CHD, and there is evidence that some cases of late-onset depression may be caused or exacerbated by cerebrovascular disease, a condition referred to as “vascular depression.”(46) Neuroimaging studies of first-episode depressions occurring late in life have found evidence of structural and functional brain abnormalities in some of these patients.(47)

Although the patients in ENRICHD or MIND-IT did not undergo neuroimaging studies, there was little evidence in either study to support overt or subclinical cerebrovascular disease as an explanation for poor response to treatment. Contrary to what would have been expected if patients with cerebrovascular depression had comprised a large proportion of the nonresponders, the ENRICHD study revealed no differences between the improved and unimproved groups in age at enrollment, history of hypertension or stroke, age at time of the initial depressive episode (mid-thirties, on average), the number of prior major depression episodes, the duration of the current episode, or the proportion of patients with a family history of depression. Nevertheless, the possible contribution of subclinical cerebrovascular disease to non-response in these studies cannot be ruled out. Similarly, all of the trials reviewed here, especially ENRICHD, SADHART, and MIND-IT, controlled for predictors of cardiac mortality and morbidity, and the ENRICHD therapists’ ratings of their patients’ physical ability to participate in the intervention during the course of treatment did not differ between treatment responders and nonresponders, but it remains possible that a deterioration in cardiac function that was not predicted by the conventional risk factors was responsible for the patients’ poor response to treatment and subsequent death.

Initial vs. Recurrent Major Depressive Episode

Another series of secondary analyses of clinical trials of depression treatment and survival following ACS have focused on whether the depressive episode was either the first ever or a recurrent episode, and whether it preceded or followed the acute cardiac event. Most of these studies have found that first depressive episodes and those that begin after the index cardiac event are more predictive of mortality and morbidity than are episodes that are recurrent and/or that precede the onset of the MI.(48–52) For example, participants in the ENRICHD clinical trial with a first episode of major depression had poorer survival (18.4% all-cause mortality) than those with recurrent major depression (11.8%), and both groups

had significantly poorer survival than did nondepressed controls (3.4% all-cause mortality). Moreover, Glassman et al.(53), found that patients with either recurrent major depression or a depressive episode whose onset preceded an acute coronary syndrome, responded better to sertraline than did those with an initial episode of depression or whose episode began after the acute event. Lespérance et al.(22) reported a similar finding for citalopram in patients with medically stable coronary artery disease. Thus, the findings of treatment response and survival may be linked to whether the depression is a recurrent or an initial episode of major depression. However, no relationship between improvement in BDI scores and recurrent vs. first depression was observed in a recent analysis of the ENRICH clinical trial.(48) Nevertheless, the relationship between response to depression treatment, depression history, and survival deserves more careful study.

Future Directions

Although of obvious importance to the field of psychiatry, remarkably little is known about the biology of treatment-resistant depression. There is, however, growing interest in identification of the genes associated with the treatment mechanisms, response, or tolerance to antidepressants.(54–57) Some of the genetic factors identified through pharmacogenetic research, such as the serotonin transporter gene polymorphism(54;56), may also have a role in promoting coronary disease.(58) This area clearly needs further study.

Most studies of treatment-resistant depression have focused primarily on pharmacological treatments, although some of the same factors that predict poor response to antidepressants have also been associated with poor response to psychotherapy.(59) However, a better understanding of the factors predicting poor response to psychotherapy is also needed. Furthermore, there are few depression treatment studies of any type in patients with CHD. Factors associated with treatment resistance may differ in this subgroup of depressed patients. For the purpose of improving medical outcomes following ACS, more research focusing on depressed patients with CHD is also needed.

If specific cardiac risk markers are found to predict treatment resistance in patients with CHD, it might be possible to improve depression and possibly even survival in these patients by aggressively treating the cardiovascular risk factors, or by choosing depression treatments that also modify these risk factors. Research on this question could provide a direction for developing new antidepressants or other depression treatment strategies for these patients. For example, if subclinical hypothyroidism is found to be commonly associated with depression treatment resistance in patients with CHD, then patients with low levels of thyroid hormone who do not respond to depression treatment could receive T3 augmentation of standard antidepressants. If elevated inflammatory markers are associated with treatment resistance in CHD patients, for example, then patients who do not respond to antidepressants could be tried on an anti-inflammatory drug or on specific cytokine antagonists along with standard depression treatment.

What should practitioners do in the mean time? Nonresponse to depression treatment should be considered a cardiac risk marker in patients with coronary disease. These patients should be followed more closely and perhaps be given more aggressive cardiological care than might otherwise seem warranted. Every effort should be made to intervene in all other modifiable risk factors, and to treat all comorbid medical disorders to the extent possible. More aggressive treatment for depression may also be warranted, but further research is needed to develop more effective ways to treat depression in patients with CHD who do not respond to first-line interventions.

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Figure 1.
ENRICHD: Covariate-Adjusted Change in BDI & Post 6 month Mortality by Treatment Group