Depression as a Risk Factor for Coronary Artery Disease: Evidence, Mechanisms, and Treatment

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Objective: The present paper reviews the evidence that depression is a risk factor for the development and progression of coronary artery disease (CAD). **Methods:** MEDLINE searches and reviews of bibliographies were used to identify relevant articles. Articles were clustered by theme: depression as a risk factor, biobehavioral mechanisms, and treatment outcome studies. **Results:** Depression confers a relative risk between 1.5 and 2.0 for the onset of CAD in healthy individuals, whereas depression in patients with existing CAD confers a relative risk between 1.5 and 2.5 for cardiac morbidity and mortality. A number of plausible biobehavioral mechanisms linking depression and CAD have been identified, including treatment adherence, lifestyle factors, traditional risk factors, alterations in autonomic nervous system (ANS) and hypothalamic pituitary adrenal (HPA) axis functioning, platelet activation, and inflammation. **Conclusion:** There is substantial evidence for a relationship between depression and adverse clinical outcomes. However, despite the availability of effective therapies for depression, there is a paucity of data to support the efficacy of these interventions to improve clinical outcomes for depressed CAD patients. Randomized clinical trials are needed to further evaluate the value of treating depression in CAD patients to improve survival and reduce morbidity. **Key words:** depression, coronary artery disease, physiological mechanisms, behavioral mechanisms, randomized clinical trials.

AMI = acute myocardial infarction; **ANS** = autonomic nervous system; **BDI** = Beck Depression Inventory; **CABG** = coronary artery bypass graft; **CAD** = coronary artery disease; **CBT** = cognitive behavior therapy; **CES-D** = Center for Epidemiological Studies Depression Questionnaire; **CHD** = coronary heart disease; **CHF** = congestive heart failure; **DIS** = Diagnostic Interview Schedule; **ENRICHD** = Enhancing Recovery in Coronary Heart Disease; **HBP** = high blood pressure; **HPA** = hypothalamic pituitary adrenal; **HRV** = heart rate variability; **IHD** = ischemic heart disease; **MDD** = major depressive disorder; **SNS** = sympathetic nervous system; **SSRI** = selective serotonin reuptake inhibitor.

Over the past century, coronary artery disease (CAD) has been the primary killer of both men and women in the United States (1). Psychosocial factors have long been implicated in the etiology and progression of CAD (2). Recent research suggests that depression is a particularly robust psychosocial predictor of CAD onset and progression (3–6). This paper reviews evidence for depression as a risk factor and summarizes treatment strategies to improve prognosis in depressed CAD patients.

Articles for the primary review of depression as a risk factor were identified with MEDLINE (1966 to 2003) and PsychINFO (1872 to 2003) searches using the terms "prognosis," "risk factors," "depression," "depressive disorder," "major depression," "coronary disease," "myocardial infarction," "coronary artery bypass," and "congestive heart failure." The searches were limited to studies using human subjects and available in English-language. Reference sections of relevant articles were used to identify additional studies that had not been identified by the database searches. Studies that measured depression at baseline including both measures of depressive symptoms and clinical depression, had longitudinal or case-control designs, and included "hard" endpoints like death or cardiac events were included in the primary review.

EMPIRICAL EVIDENCE FOR DEPRESSION AS A RISK FACTOR FOR CAD

Cross-sectional Studies

Preliminary evidence to support a relationship between depression and CAD has been provided by numerous cross-sectional studies of CAD patients. These studies have documented a disproportionately high prevalence of depression in CAD patients relative to the general population. Point prevalence estimates for the population at large range from 4 to 7% (7,8). By comparison, point prevalences range from 14% to as high as 47% in CAD patients, with higher rates recorded most often in patients with unstable angina or in patients awaiting coronary artery bypass graft (CABG) surgery (9–21). When DSM criteria are used to establish diagnosis, estimates of the prevalence of depression in CAD patients tend to be lower at 15 to 20% (9,11,12,15,17). The high prevalence of depression in CAD patients suggests that depression may contribute to the development of CAD, but evidence from these cross-sectional studies may be confounded by selection factors and other potential sources of bias. Therefore, prospective studies have been conducted to determine if depressed individuals are more likely to develop CAD and its complications.

Prospective Studies With Population Samples and Case-Control Studies

As highlighted in Table 1, these studies reveal that the presence of depression in individuals without CAD most consistently confers an approximately 1.5-fold to 2.0-fold adjusted relative risk for the subsequent development of CAD (22–30). Pennix et al (29) followed 2397 patients who were free of CAD at baseline for 4 years. Those with a diagnosis of major depressive disorder (MDD) were 3.9 times more likely to die of cardiac causes compared with those without depression at baseline, even after controlling for disease severity and other risk factors.

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TABLE 1. Studies Assessing Depression and the Initial Onset of CAD in Initially Healthy Individuals

Author	*N*	Follow-up Time	Endpoint(s)	Adjusted Relative Risk
Anda et al (22)	2832	Mean = 12.4 yr	Fatal IHD Nonfatal IHD	RR = 1.5 1.6
Barefoot et al (23)	730	27 yr	MI	RR = 1.71
Ford et al (24)	1190	40 yr	CHD events; MI	RR = 1.7 2.12
Mendes de Leon et al (30)	2812	10 yr	CHD deaths Diagnosis of CHD	NS
Hippisley-Cox et al (25)	327 with IHD matched to 897 controls without IHD	Not specified	Diagnosis of IHD	NS for women OR = 2.75 for men
Ariyo et al (26)	4493	6 yr	CHD	HR = 1.15
Ferketich et al (27)	7893	10 yr	Diagnosis of CHD CHD mortality	Women: CHD RR = 1.73, CHD mortality NS; Men: CHD RR = 1.71, CHD mortality 2.34
Pennix et al (29)	2397 ages 55–85 yr	4 yr	Cardiac mortality	RR = 3.9
Aromaa et al (28)	5355	6.6 yr	CAD	Women: RR = 2.59; Men: RR = 3.45 (controlling for age only)

Although most studies have reported greater risk for depressed patients, a few have reported mixed or negative findings or small effect sizes. Ariyo et al (26) followed 4493 patients free of cardiovascular disease at baseline for 6 years. Depression (as measured by the 10-item CES-D) was a statistically significant predictor of CHD diagnosis, but the effect size was relatively small, with a hazard ratio of 1.15 for a 5-point increase in the 10-item scale.

Other studies have suggested that the relation between depression and clinical outcomes may not be consistent across certain subgroups (25,27). For example, Hippisley-Cox et al (25) conducted a population-based case-control study of 327 subjects free of CAD matched with 897 controls without CAD and found that depression did not put woman at risk for subsequent diagnosis of CAD. In contrast, depression at baseline put men at 2.75 times greater risk for subsequent diagnosis of IHD. The negative findings notwithstanding, a recent meta-analytic review of the literature concluded that depression is an independent risk factor for CAD with an overall risk ratio of 1.64 (after controlling for a likely publication bias) (31).

Prospective Studies With CAD Samples

Depression also has been shown to be predictive of outcomes in CAD patients. A large number of studies have measured depression in CAD patients using clinical interviews and/or questionnaires and followed them over time to assess the extent to which depression predicts clinical outcomes. Table 2 summarizes the relation of depression and "hard" clinical endpoints such as death or MI.

Stable CAD and Prognosis

Studies of patients with stable CAD have reported significant associations of depression and clinical outcomes. Carney et al (9) followed 52 patients for 12 months after catheterization and found that a diagnosis of MDD was associated with an adjusted risk ratio of 2.2. Barefoot et al (32) assessed 1250 patients with documented CAD using the Zung Self-Report Depression Scale at the time of diagnostic coronary angiography and followed patients for up to 19.4 years. Results showed that patients with moderate to severe depression were at 69% greater risk for cardiac death and 78% greater risk for all-cause death (32).

AMI and Prognosis

A number of studies have assessed the relationship of depression and CAD outcomes in patients hospitalized for acute myocardial infarction (AMI; Table 2). These studies suggest that the presence of depression during or shortly after hospitalization confers 2 to 3 times the risk for mortality or nonfatal cardiac events (11,33–39). Frasure-Smith et al (34) followed 896 patients with a recent AMI for 1 year. The presence of elevated depressive symptoms on the Beck Depression Inventory (BDI) was a significant predictor of cardiac mortality after controlling for other multivariate predictors of mortality (OR = 3.29 for women; 3.05 for men). Although there have been some null findings in this area (40–44), most have been from small studies with limited follow-up or inadequate assessment of depression (5). For example, Jenkinson et al (40) followed 1376 patients hospitalized for MI for 3 years and reported no association between depression at the time of hospitalization and all-cause mortality. Although the large sample size was a strength of the study, one possible explanation for the null finding was that depression was assessed using a nonvalidated scale consisting of only 3 items related to depression. Lane et al (42–44) followed 288 patients hospitalized for AMI for up to 1 year and also found that depression (assessed by the BDI) was not related to cardiac or all-cause mortality at 4 months or 1 year, nor was it related to cardiac events at 1 year. However, a notable limitation of this series of studies is the small sample size and event rate, which can yield highly unstable estimates

TABLE 2. Studies Assessing the Effect of Depression on Outcomes in CAD Samples

Author	N/# Events	Patients	Follow-up Time	Endpoint(s)	Adjusted Relative Risk
Carney et al (9)	52/22 cardiac	CAD	12 months	Cardiac event	RR = 2.2
Barefoot et al (32)	1250/N/A	CAD	0–19.4 yr	Cardiac and all-cause mortality	Cardiac mortality RR = 1.7; all-cause mortality RR = 1.8
Jiang et al (17)	374/61 deaths	CHF	12 months	All-cause mortality	OR = 2.23
Murberg et al (58)	119/22 cardiac deaths	CHF	2 yr	Cardiac mortality	HR = 1.9
Frasure-Smith et al (11)	222/12 deaths	MI	6 months	Cardiac mortality	DIS:HR = 4.29
Frasure-Smith et al (33)	222/21 deaths		18 months	Cardiac mortality	DIS NS; BDI OR = 6.64
Frasure-Smith et al (34)	896/39 deaths	MI	1 yr	Cardiac mortality	Men OR = 3.05; Women OR = 3.29
Frasure-Smith et al (35)	896/155 deaths		5 yr	Cardiac mortality	HR = 3.13–3.17
Lane et al (42)	288/25 deaths	MI	4 months	Cardiac or all-cause mortality	NS
Lane et al (43)	288/82 deaths		1 yr	Cardiac or all-cause mortality	NS
Lane et al (44)	288/31 deaths		1 yr	CHD events	NS
Ahern et al (36)	265/N/A	MI	Varying	Mortality; Cardiac arrest	RR = 1.38
Jenkinson et al (40)	1376/247 deaths	MI	3 yr	All-cause mortality	NS
Ladwig et al (41)	560/12 deaths; 17 arrythmic	MI	6 months	Cardiac death; Arrhythmic event	NS
Welin et al (37)	275/167 deaths	MI	10 yr	Coronary mortality	RR = 3.16
Bush et al (38)	144/17 deaths	MI	4 months	Mortality	RR = 3.5
Horsten et al (39)	292/81 deaths	Acute CHD event (MI or Angina)	5 yr	Death or cardiac event	RR = 1.9
Lesperance et al (14)	430/16 deaths; 28	Unstable angina	1 yr	Cardiac death or MI	OR = 6.73
Connerney et al (15)	309/8 deaths; 42	CABG	1 yr	Cardiac event; mortality	Cardiac events, RR = 2.3; mortality NS; BDI NS
Baker et al (20)	158/6 deaths	CABG	Median = 24 months	Mortality	OR = 6.24
Saur et al (47)	416/N/A	CABG	1 yr	Mortality	NS
Blumenthal et al (50)	817/122 deaths	CABG	Mean = 5.2 yr	Mortality	Moderate-severe depression HR = 2.84; persistent depression HR = 2.33
Burg et al (49)	89/7 deaths	CABG	2 yr	Cardiovascular mortality	OR = 23.16

N/A = not available.

(45). Women are at higher risk for mortality after MI (46) and have higher rates of depression than men. Frasure-Smith et al (35) investigated the possibility that the increased risk for women is due higher rates of depression or gender differences in the impact of depression on clinical events. They failed to find any evidence in support of these possibilities. However with only 290 patients (133 women) and 42 deaths, the study may have had inadequate power to detect any gender effects.

CABG Surgery and Prognosis

CABG surgery is a common surgical intervention for CAD patients, and depression rates are known to be particularly high in CABG patients both before and immediately after surgery (15,18–21,47,48). However, there are very few prospective studies of patients undergoing CABG surgery (15,20,47,49,50). Connerney et al (15) followed 309 CABG patients for 1 year after surgery. Compared with nondepressed patients, depressed patients (as assessed by the DIS) were more than twice as likely to have a cardiac event within 12 months after surgery but were not at higher risk for mortality within the first year. In a larger sample of 817 CABG patients followed for up to 12 years (mean = 5.2 years), Blumenthal et al (50) assessed the effect of depression on mortality after CABG surgery. Depression was assessed both at baseline and 6 months after surgery. Results indicated that moderate to severe depression (CES-D scores $\geq$ 27) on the day before surgery as well as depression that persisted from baseline to 6 months after surgery (CES-D scores $\geq$ 16) were independently associated with 2-fold to 3-fold increased risk of mortality.

Although women are at increased risk compared with men for poor outcomes after surgery (15,51,52) and may be more likely to be depressed before and after cardiac surgery (18,53–55), there is no evidence that depression places women at greater risk compared with men. It is more likely that increased medical comorbidities might place women at greater risk for depression and adverse clinical outcomes. Women are more likely to have other features putting them at risk for poorer outcome, such as decreased functionality, older age at the time of surgery (55), increased angina, more severe hypertension and diabetes (56,57), and smaller coronary artery diameter (52,58).

CHF and Prognosis

Although only a subset of patients with congestive heart failure (CHF) have underlying CAD, both Jiang et al (17) and Murberg et al (59) have reported that depression in patients with CHF is associated with reduced life expectancy. Murberg et al followed 119 patients with CHF for 24 months. Depressed mood, as assessed by the Zung Self-Rating Depression Scale, was associated with a significant hazard ratio of 1.9 for predicting cardiac mortality.

BIOBEHAVIORAL MECHANISMS

As depicted in Figure 1, a number of plausible biobehavioral mechanisms have been hypothesized to underlie the relationship between depression and CAD: treatment adherence; lifestyle factors such as smoking, heavy alcohol use, and physical inactivity; traditional risk factors including hypertension, diabetes, and insulin resistance; changes in platelet reactivity; dysregulation of the autonomic nervous system and hypothalamic pituitary adrenal (HPA) axis; and alterations in the immune response/inflammation. However, much of the existing evidence for the mechanisms that underlie the relationship between depression and CAD is derived from cross-sectional studies. Few prospective studies have been conducted to date.

Treatment Adherence

Many studies have shown that depression predicts poor adherence to prescribed regimens. In a recent meta-analysis, Di Matteo et al (60) concluded that depression puts patients with a variety of medical problems at twice the risk for nonadherence with prescribed therapies, including patients with CAD (61–64). Nonadherence to recommended lifestyle changes and medication regimes itself is associated with decreased survival for CAD patients (65–67), suggesting that adherence may be a mechanism linking depression and CAD outcomes.

Lifestyle Factors: Smoking, Alcohol Consumption, and Physical Activity

Smoking and physical inactivity are important risk factors for CAD and are often targets for the prevention and treatment (68). Although many studies have shown that low to moderate levels of alcohol consumption actually confer a protective effect for CAD, the highest levels of alcohol consumption put

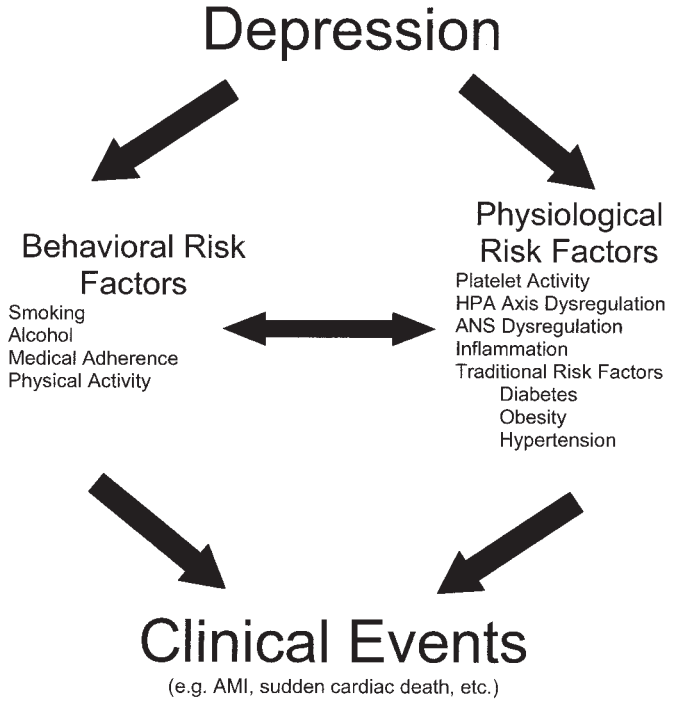

Figure 1. Biobehavioral model for the relationship between depression and CAD clinical events.

patients, especially women, at risk for increased mortality (69,70). Depression is associated with increased rates of smoking in CAD patients (71) and may lower the success of smoking cessation programs (72). Depression also is associated with increased alcohol use and physical inactivity (73). Cross-sectional and longitudinal studies have shown that active persons are less depressed compared with their sedentary counterparts and that inactive persons who become active are less likely to become depressed (73–80). Furthermore, there is evidence that depression may potentiate other risk factors. For example, in a case control study Panagiotakos et al (75) demonstrated that depression, especially when accompanied by alcohol use, physical inactivity and/or smoking, was associated with increased risk for the development of CAD.

Traditional Risk Factors and the Metabolic Syndrome

The American Heart Association has recently classified obesity as a major modifiable risk factor for CAD and has called for more research and interventions in this area (81). Furthermore, obesity tends to cluster with several other risk factors for CAD including diabetes, hypertension, and hyperlipidemia. Together, these risk factors have been described as the "metabolic syndrome," which has been shown to contribute to both the onset and progression of CAD (82–84). Diabetes and obesity in particular have been linked to depression (85,86).

Platelet Activity

Platelet activity is an important factor in the development of atherosclerosis, acute coronary syndromes, and thrombosis, and anti-platelet medications have been used as secondary prevention for CAD (87,88). In addition, increased platelet reactivity has been associated in cross-sectional studies with higher levels of depression in healthy (89,90) and CAD populations (91). The role of serotonin in both platelet function (92) and depression (93) also provides suggestive evidence linking platelet activity and depression.

Hypothalamic Pituitary Adrenal (HPA) Axis

Alteration of the functioning of the HPA axis is another possible mechanism of action (6,94). A number of studies have demonstrated that depression is associated with imbalances in HPA axis functioning. Depressed patients tend to exhibit higher basal cortisol levels (95,96) and nonsuppression of endogenous cortisol secretion after dexamethasone administration, providing an overall picture of impaired feedback and consequent HPA axis hyperactivity in depression (97,98). However, current research highlights the variability in HPA axis functioning within depressed samples and suggests that HPA axis functioning in depression is best described as dysregulated (95,99,100). HPA axis dysregulation is related to many cardiovascular disease risk factors such as truncal obesity, hypercholesterolemia, hypertriglyceridemia, increased blood pressure, and elevated heart rate (101,102).

Autonomic Nervous System

ANS dysregulation has been implicated in CAD. Hyperactivity of the SNS has been linked to HBP (103) and other risk factors for CAD mortality such as decreased HRV, decreased vagal tone, and reduced heart rate recovery (104–106). SNS activation may elicit coronary vessel constriction in CAD patients, resulting in myocardial ischemia (107,108). Abnormal ANS functioning has also been shown in depressed patients. Conflicting evidence suggests that depression is not associated simply with global increases or decreases in ANS activity, but it may be better conceptualized by ANS dysregulation (109–112). The link between depression and impaired ANS function has been demonstrated in CAD populations. For example, several cross-sectional studies have shown depressed patients with CAD to have decreased HRV (113–116). Reduced baroreflex cardiac control (another measure of ANS activity) also has been shown to correlate with depressive symptom severity in CAD patients (117).

Inflammation

Emerging evidence suggests that alterations in immune functioning and inflammation may contribute to the development and clinical manifestations of CAD. The body's inflammatory response to chronic hypercholesterolemia and hypertension may contribute to atherosclerosis as damage to the arterial lining occurs over time (118). For example, Ridker et al (119) showed that patients who were initially disease free but who developed peripheral arterial disease over 5 years differed from controls in having higher levels of C-reactive protein after controlling for other risk factors. There is also evidence from both population and CAD samples that increased inflammation is associated with depression (90,120,121) and with other CAD risk factors such as the metabolic syndrome (122,123). Thus, some preliminary evidence exists to show that inflammation may mediate the relation between depression and CAD.

INTERVENTIONS

There are currently several empirically validated treatments for depression. However, to our knowledge, there have been only two completed clinical trials treating depression in cardiac patients (124,125), and no clinical trials with nonCAD populations have examined CAD outcomes.

Psychosocial Interventions

Psychosocial interventions (including individual or group psychotherapy, support, stress reduction) have been used as treatments for depression in CAD patients. The aim of these interventions is to reduce psychological distress, which in theory would ultimately improve clinical outcomes. Methodological limitations of many of the existing studies in this area include lack of a control group (126), "soft" endpoints (127–129), and small sample sizes (130,133). There have been several studies of psychosocial interventions for a general (nondepressed) cardiac population (130–139). For example, in the M-HART trial (139) 1376 patients with a recent MI

were randomly assigned to 12 months of a psychosocial nursing intervention or usual care. The intervention consisted of monthly phone monitoring by an untrained person. Patients who reported high levels of distress were visited in their homes by a nurse. Twelve-month follow-up data indicated that the intervention did not protect against re-infarction or cardiac or all-cause mortality. Furthermore, there were no significant reductions in symptoms of depression or anxiety as a result of the intervention. Similarly, Jones and West (133) randomized 2328 patients with a recent AMI to usual care or seven 2-hour sessions of a psychosocial intervention that included group and individual psychotherapy, relaxation training, and stress management. Twelve-month follow-up data revealed that the intervention did not decrease the risk for mortality or re-infarction. However, the intervention was not successful in decreasing symptoms of depression, which may account for the lack of effect.

Despite these negative studies, other studies have shown improved psychosocial function and health outcomes (135,137,140,141). For example, in the Ischemic Heart Disease Life Stress Monitoring Program (135), 461 men with a recent AMI were randomly assigned to usual care or a psychosocial intervention identical to the intervention used later in the M-HART trial. At 1-year follow-up, patients in the intervention group had greater reductions in distress and decreased mortality. In the Myocardial Ischemia Intervention Trial (141), 136 patients with documented CAD and recent exercise-induced ischemia were assigned to usual care, exercise training, or a psychosocial stress management intervention. The psychosocial intervention resulted in reductions in general distress and hostility relative to control. Furthermore, patients who took part in the psychosocial intervention showed reduced ischemia and were less likely to suffer a cardiac event over a mean follow-up time of 38 months. Indeed, the benefits appeared to persist for up to 5 years among patients receiving stress management training, and the clinical benefits were also associated with significant changes in medical expenses (142). Considering these studies together, a recent meta-analytic review concluded that psychosocial interventions increase quality of life and improve clinical outcomes (143).

There are several empirically validated therapies for MDD, including behavior therapy, interpersonal therapy, and cognitive therapy (144). Until recently, none have been applied to a clinically depressed CAD population. The recently completed ENRICHD study (125,145) is the first clinical trail to include patients with clinical depression. On the basis of evidence that both low social support and depression confer a risk for poorer clinical outcomes, patients with an MI within 1 month who also had a diagnosis of MDD, minor depression with a history of MDD, dysthymia, or low social support were randomly assigned to usual care or a psychosocial intervention. The psychosocial intervention consisted of 6 sessions to 6 months of individual CBT, group therapy (when feasible), and concomitant treatment with antidepressant medication for severe or persistent depression.

Initial results of the ENRICHD trial indicate that the intervention was associated with statistically significant improvements in depression and low social support compared with usual care. However, the CBT intervention was not effective in reducing rates of mortality or recurrent cardiac events in the overall sample or in a sub-sample including only patients with depression. At 3-year follow-up, 24.4% of the patients in the treatment group had either died or had another heart attack, compared with 24.2% in the usual care group. Furthermore, there was a trend approaching statistical significance showing that the intervention may actually have had a detrimental effect on female patients (125). The relatively modest between-group differences (ie, the treatment group showed a 57% reduction in HAM-D scores, the usual care group showed a 47% reduction) might have been a factor that contributed to the negative findings, although the magnitude of change in depression was comparable to that seen with trials of antidepressant medication.

Antidepressant Medication

There are several classes of antidepressant medications that have been shown to be effective in treating depression (146). The SSRI class of antidepressants is currently considered the safest to use with CAD patients, in contrast with the tricyclics, which may alter heart rate and rhythm (143,144). The recently completed SADHART trial compared the effects of sertraline and placebo for 24 weeks in MDD patients with unstable angina or recent MI (124). Initial follow-up data extending to the time the treatment ended suggested that SSRI treatment did not adversely affect cardiac function and was considered to be safe for most patients. However, as was the case in the ENRICHD trial, improvements in depression were rather modest. In subsequent analyses, it was found that patients with at least 1 prior episode of depression or more severe depression showed consistent improvement in depression relative to control, suggesting that treatment with SSRIs is a good option for this subset of depressed CAD patients. Although SADHART was not powered to detect a treatment effect on mortality and a composite measure of "hard" and "soft" outcomes was used, there was a tendency for the patients treated with sertraline to have fewer serious adverse events (death or rehospitalization for MI, CHF, stroke, or angina) than those receiving placebo. The ENRICHD trial also found that treatment with antidepressant medication improved prognosis for MI patients. Patients who were treated with antidepressants (regardless of randomization assignment to the intervention or usual care) were at decreased risk for death and reinfarction compared with those who did not take antidepressants (125). In addition to reducing symptoms of depression, SSRIs have anticoagulation attributes, which may be effective in reducing risk for cardiac events in susceptible patients with CAD (147–149).

Exercise

Exercise is a particularly promising treatment for depression in CAD patients. In a recent meta-analysis, Jolliffe et al

(150) reported an overall mortality odds ratio of 0.69 for exercise interventions representing a 31% decrease in the odds of cardiac mortality. In addition, there is preliminary evidence, mostly from noncontrolled trials, that exercise is an effective treatment for depression (74,151). In one of the better-controlled studies in this area (152), depressed adult patients with MDD were randomized to treatment with exercise, antidepressant medication, or both. Exercise was shown to be about as effective as antidepressant medication in treating depression by the end of the 16-week treatment. Moreover, patients who continued to exercise were less likely to relapse after 10 months (153). Studies of CAD patients (again primarily noncontrolled trials) suggest that exercise may be a viable treatment for depression in this population as well (50,132,154–160). In one of the few controlled studies in this area, Stern et al (132) randomized 106 male patients with a recent AMI and elevated depression, anxiety, or low fitness to 12 weeks of exercise training, group therapy, or a usual care control group. At 1-year follow-up, both the counseling and the exercise group showed improvements in depression relative to control. However, only the exercise group showed improved health outcomes. The evidence that exercise affects both depression and CAD outcomes suggests that exercise is a promising intervention for depression in this population, perhaps because is it able to directly target both depression and CAD risk factors. Indeed, many of the proposed physiological mechanisms linking depression and CAD outcomes, such as alterations in ANS (161–163) and HPA axis functioning (6,94,98,99,164–167), insulin resistance (168), and inflammation (169), are likely to be directly targeted by exercise.

CONCLUSIONS/FUTURE DIRECTIONS

Recent evidence suggests that depression is a significant and independent risk factor for CAD in both healthy and CAD populations, with a relative risk of about 2.0. It is possible that depression is merely a marker of a broader phenomenon, such as negative affect, or is tapping a related psychosocial risk factor, such as vital exhaustion (170), decreased social support (37), personality factors (171,172), anger expression (173), hostility (174), negative emotions (175,176), and anxiety (177). However, studies that have been able to compare the unique predictive value of these related constructs have suggested that depression and negative affect are the factors that emerge as most predictive of increased risk (175,176) and thus warrant closer clinical attention and further study.

Research on potential mechanisms suggests that there are several plausible biobehavioral mechanisms for which preliminary support exists, including treatment adherence, lifestyle factors, traditional risk factors including the metabolic syndrome, platelet reactivity, ANS and HPA axis dysregulation, and inflammation. Future work may work toward identifying genetic factors that increase risk for both depression and CAD. For example, recent evidence points to the role of a polymorphism in the promoter region of the serotonin transporter gene in predisposing patients to depression after stressful life events (178). Other work has investigated the possibility that this polymorphism is common to both altered serotonergic function and cardiovascular reactivity to stress (179). A study of monozygotic and dizygotic twins has provided further evidence for a genetic risk factor common to both depression and heart disease (180).

In a recent editorial, Frasure-Smith and Lesperance (181) suggested that depression is a risk factor in search of a treatment. Indeed, it is clear that depression is an important risk factor for CAD patients, yet the question remains how to best to treat it. The results of the ENRICHD trial indicate that CBT is not effective in reducing rates of mortality or cardiac events in MI patients. However, it is possible that other psychosocial interventions may prove to be effective. On the other hand, the SADHART trial and ENRICHD trial both have provided suggestive evidence that treatment with SSRIs improves prognosis for depressed CAD patients. Larger randomized clinical trials of SSRIs are needed to further evaluate the potential of this treatment. In addition, exercise training is emerging as a promising intervention, as there is mounting evidence that it is an effective treatment for depression and affects a wide array of risk factors linking depression and CAD. Future trials are warranted to address the potential of exercise as an intervention.

Further research on patient-treatment match and the timing of treatment also may improve treatment efficacy. For example, the ENRICHD trial was designed to intervene with depression detected shortly after an AMI. In retrospect, this may not be the optimal time to assess and intervene with depression as the chance of detecting an adjustment disorder or transient depressed mood is high (181). Existing evidence suggests that more severe or chronic depression detected at this time puts patients at higher risk and is most likely to respond to treatment (32,49,124). However, some patients may be unwilling to address psychological issues at the time of surgery or AMI and may be more amenable to medication or exercise at that time. The SADHART and ENRICHD trials both reported statistically significant changes in depression, but the effect sizes may not have been clinically meaningful, suggesting the need to increase the efficacy of depression interventions for CAD patients. Although it is not possible at this point to recommend treatment for depression to reduce cardiac risk, depression is common in this population and certainly warrants treatment due to quality of life concerns alone.

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