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Heart disease and depression: Don't ignore the relationship

ABSTRACT

Evidence is mounting that depression is a risk factor for the development of cardiovascular disease and portends a worse outcome in cardiac patients. Depression can be easily diagnosed and safely treated in cardiac patients, but it is undertreated.

KEY POINTS

After a myocardial infarction, the incidence of major depression is from 15% to 20%, and an additional 27% of patients develop minor depression.

Depression increases the risk of developing cardiovascular disease. It is also associated with higher rates of cardiac death and all-cause mortality.

Depression may contribute to cardiac disease through an overactive hypothalamic-pituitary-adrenocortical axis, platelet activation, and decreased heart rate variability.

Selective serotonin reuptake inhibitors (SSRIs) are the preferred medications, as they have little effect on blood pressure or cardiac conduction. However, physicians should be aware of significant drug interactions caused by inhibition of cytochrome P450 isoenzymes.

DEPRESSION seems to be a bona fide risk factor for coronary artery disease. Statistical associations exist between depression and the development of coronary disease, and the prognosis is worse for coronary patients with depression. Moreover, there are plausible physiologic mechanisms to explain the link.

Although we do not know if treating depression can improve one's coronary prognosis, it can certainly make the patient feel better. Yet, depression is undertreated in coronary patients.

This paper reviews the surprising association of depression with coronary artery disease and explains the possible mechanisms leading to major adverse cardiac events. It also discusses treatment options, including drug interactions and measures aimed at improving clinical outcomes in cardiac patients.

DEPRESSION IS COMMON

Depression affects 6% of men and 18% of women in the general population at any one time.¹ The lifetime risk is 20% to 25% for women and 7% to 12% for men.² In the medically ill, the prevalence of depression can be as high as 40%.³

The Global Burden of Disease Study⁴ ranked unipolar depression as the fourth leading cause of early death and disability worldwide. In developed countries, only ischemic heart disease confers a higher disease burden than depression.

DEPRESSION AS A RISK FACTOR FOR HEART DISEASE

Cardiovascular disease is the leading cause of death and disability in the United States,⁵ and

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†Dr. Franco has indicated that she is on the speakers' bureau of the Pfizer corporation.

TABLE 1

Depression as a risk factor for cardiac disease

AUTHORS	YEAR	NO. OF PATIENTS	FINDINGS*
Frasure-Smith et al ¹⁴	1993	222	Adjusted HR for death: 4.29
Anda et al ⁹	1993	2,832	Adjusted RR for cardiac death: 1.5
Ladwig et al ⁹²	1994	377 [†]	Unadjusted RR for follow-up angina: 3.12
Aromaa et al ⁹³	1994	5,355	RR for MI in men: 2.62 RR for MI in women: 1.90
Barefoot and Schroll ⁹⁴	1996	730	RR for MI: 1.71 RR for death: 1.59
Pratt et al ⁸	1996	1,551	OR for MI for history of dysphoria: 2.09 OR for MI for history of major depressive disorder: 4.54
Ford et al ⁹⁵	1998	1,190 [†]	RR for CHD: 2.12 RR for MI: 2.12
Ferketich et al ⁹⁶	2000	7,893	Adjusted RR for CHD in women: 1.73 Adjusted RR for CHD in men: 1.71 Adjusted RR for CHD death in men: 2.34
Ariyo et al ⁹⁷	2000	4,493	Adjusted HR for CHD: 1.15 Adjusted HR for MI: 1.14 (with every 5-unit increase in mean depression score)
Barefoot et al ¹⁶	2000	1,250	69% greater odds of cardiac death 78% greater odds of all-cause death
Penninx et al ¹⁸	2001	2,397	With cardiac disease: RR for cardiac death with major depression: 3.0 RR for cardiac death with minor depression: 1.6
		450	Without cardiac disease: RR for cardiac death with major depression: 3.9 RR for cardiac death with minor depression: 1.5

*HR = hazard ratio, OR = odds ratio, RR = relative risk, CHD = coronary heart disease, MI = myocardial infarction

[†]All men

Evidence is increasing that depression affects the incidence and outcome of coronary disease

evidence is increasing that depression affects its incidence and outcome (TABLE 1). (Other psychosocial stressors associated with coronary heart disease incidence and worse outcome include anxiety, hostility, hopelessness, social isolation, and lower socioeconomic status.⁶)

Incidence of cardiac events increased

Depression is a risk factor for both ischemic heart disease and myocardial infarction (MI).⁷ In two studies, subjects with no known cardiovascular disease at baseline were followed for

at least 12 years, and both studies reported that a history of depression was associated with an increased risk of both fatal and nonfatal ischemic heart disease.^{8,9}

Depression predicts a worse outcome

Depression is associated with a worse prognosis after an MI, whether the depression was evident before the attack or was diagnosed afterwards.

Many patients develop depression after an MI: the incidence of major depression is 15%



■ Depression and the heart: Pathways of cardiac events

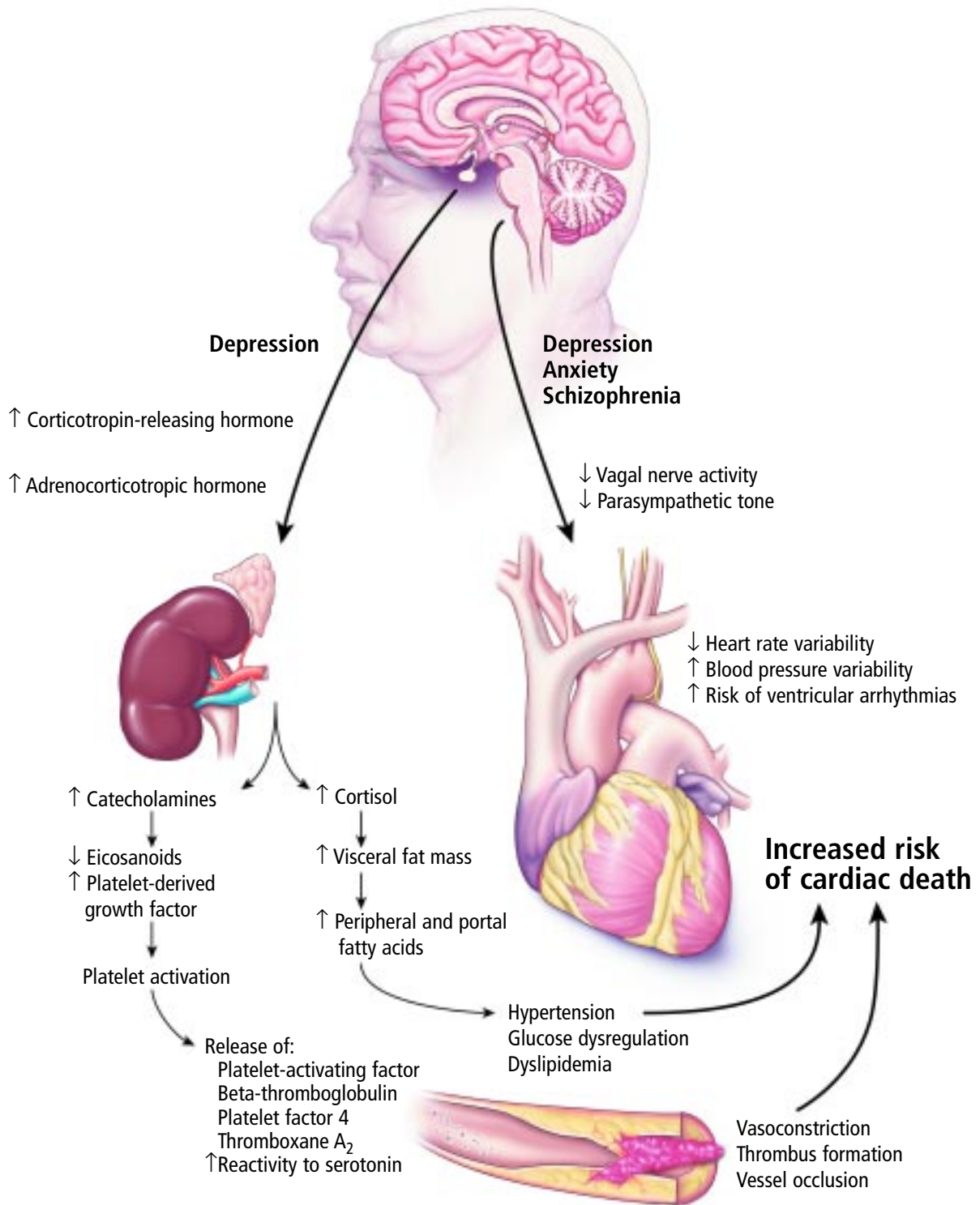


FIGURE 1

to 20%, and an additional 27% of patients develop minor depression.^{10–12}

Carney et al¹¹ reported that major depressive disorder was a better predictor of MI, coronary artery bypass grafting (CABG), angioplasty, or death in the 12 months following cardiac catheterization than was age, New York Heart Association class, cholesterol level, severity of coronary artery disease, left ventricular ejection fraction, smoking, sex, hypertension, ventricular arrhythmias, diabetes, or the use of beta-blockers, calcium channel blockers, diuretics, or nitroglycerin.

In a 16-year prospective study, those who were depressed at baseline had a higher mortality rate compared with nondepressed subjects following a major cardiac event.¹³ MI patients were three to four times more likely to die in the subsequent 6 months if they were depressed, as measured 1 week following the MI.¹⁴ In the same study, depression continued to be an independent risk factor for at least 18 months, after controlling for left ventricular dysfunction, prior MI, and age.¹⁵

Mortality risk seems to be higher for depressed patients in the long term as well. Barefoot and colleagues¹⁶ followed 1,250 patients with coronary artery disease for nearly 20 years after evaluating them with the Zung Self-Rating Depression Scale. Those who were moderately to severely depressed had an 85% greater risk of cardiac death over the next 5 to 10 years compared with nondepressed subjects, and a 72% greater risk of death thereafter.

Depression affects angina

Depression is also associated with a worse prognosis in patients with unstable angina, the condition that accounts for most coronary hospitalizations.

In a prospective study of 430 patients with unstable angina,¹⁷ depressed patients had a fourfold higher risk of cardiac death or nonfatal MI at 1 year. Depression was an important risk factor even after controlling for left ventricular function, extent of atherosclerosis, and baseline evidence of ischemia on electrocardiography.

Risk increases with depression severity

The more severe the depression, the greater

the risk of death following a cardiac event.^{8,16–18}

Penninx et al,¹⁸ in a 4-year study of 2,847 men and women, found that the risk for cardiac mortality increased with the severity of depression. Subjects with major depression and no known cardiac disease were nearly four times more likely to suffer cardiac death than nondepressed subjects, after adjustment for smoking, body mass index, stroke, diabetes, and cancer. Minor depression was associated with a 1.5 times increased risk.

This study examined cardiac risk in age-matched controls both with and without cardiovascular disease, and depression was associated with increased mortality in both groups.

Frasure-Smith et al¹⁵ detected an association between minor depression after MI and an eightfold increased risk of cardiac death. However, because many patients with minor depression eventually develop major depression, it is unclear whether minor depression by itself poses such a high risk or if it poses a risk only if it worsens.¹⁹

Depression affects prognosis after cardiac procedures

Depression is common after CABG: one study found that half of patients reported clinically meaningful depression up to 6 months after the procedure.²⁰

Scheier et al²¹ reported that patients with depressive symptoms had twice the risk of having a major cardiac event in the 6 months following CABG.

Connerney et al²² found patients with major depression undergoing CABG were more than twice as likely to die or be readmitted for cardiac causes in the year after discharge. Major depression was as strong a predictor of cardiac events as was low ejection fraction.

POSSIBLE MECHANISMS LINKING DEPRESSION WITH HEART DISEASE

A number of mechanisms have been suggested for the cardiovascular vulnerability seen in depression, including excess cortisol, increased platelet activation, and altered autonomic function (FIGURE 1).

Mortality risk is higher for depressed patients in the short and long term

Half of CABG patients reported depression 6 months later

Excess cortisol

In depressed patients, the hypothalamic-pituitary-adrenocortical axis may be hyperactive,²³ with increased concentrations of corticotropin-releasing hormone,²⁴ reduced function of the glucocorticoid receptors,²⁵ and higher plasma cortisol concentrations after dexamethasone suppression.²⁶

Corticosteroids mobilize free fatty acids, causing endothelial inflammation and excessive clotting, and are associated with hypertension, hypercholesterolemia, and glucose dysregulation.^{12,27} Increased circulating lipids and endothelial shearing stress can lead to vascular damage and plaque formation.²⁸

An active adrenal medulla may produce more of the catecholamines epinephrine and norepinephrine,²⁹ which can be measured in plasma or as metabolites in the urine.^{30,31} Depressed patients undergoing cold or orthostatic challenge have higher levels of plasma norepinephrine than nondepressed subjects.^{32,33}

Catecholamines may also enhance platelet activity by inhibiting eicosanoid synthesis and stimulating platelet-derived growth factor formation.³²

Increased platelet activation

Platelet activation may also lead to vascular damage and plaque formation.²⁷ Activated platelets release platelet factor 4 (PF-4), beta-thromboglobulin, thromboxane A₂, and platelet-activating factor, which results in thrombosis, vasoconstriction, and vessel occlusion.²⁴

Patients with depression have up-regulation of serotonin receptors on platelets and have fewer serotonin transporters.³⁴ Increased platelet reactivity to serotonin may promote platelet aggregation, coronary vasoconstriction, and progression of coronary artery disease.^{35,36}

Altered autonomic function

Patients with depression commonly show decreased variability in their heart rate, which has also been observed in patients with panic disorder and schizophrenia.^{37,38} Carney et al³⁹ found significantly lower measures of heart rate variability in depressed than in nondepressed patients following acute MI.

Heart rate variability is decreased when sympathetic innervation overrides parasympathetic influences via the vagus nerve, due to increased levels of circulating acetylcholine and catecholamines, as well as input from the cortex, brainstem, and hypothalamus.⁴⁰⁻⁴³

Decreased heart rate variability is associated with an increased risk of ventricular arrhythmias and sudden death.⁴⁴ It is also associated with greater variation in blood pressure, which is also more common in depressed patients^{45,46} and is another predictor of cardiac events.⁴⁷

We do not know whether depressed patients have an increased incidence of arrhythmias. However, mortality risk with post-MI depression was found to be greatest among patients with at least 10 premature ventricular contractions per hour.¹⁵

The Cardiac Arrhythmia Pilot Study (CAPS) found that depressive symptoms continued to predict increased cardiac events at 1 year, even after controlling for premature ventricular contractions or episodes of nonsustained ventricular tachycardia.⁴⁸

■ DIAGNOSING DEPRESSION

Even though depression is common, it often goes undiagnosed and undertreated in medical settings.⁴⁹⁻⁵¹

Many clinicians think that depression after an MI or CABG is merely a transient reaction to the event and does not deserve special attention. But, as we have seen, multiple studies have shown that depression contributes substantially to an increased risk of cardiac mortality. And even if the depression seen in heart disease is situational, its resolution is often prolonged and can be shortened with treatment.⁵²

Many patients with heart disease struggle with issues of dependence or loss of self-esteem and sometimes experience fear, frustration, or guilt from having led an illness-promoting lifestyle.

Are symptoms due to depression or medical illness?

Diagnosing depression after a cardiac event is particularly difficult, because many medical patients have somatic symptoms such as



TABLE 2

Diagnostic criteria for depression: Proposed changes for medically ill patients

Must be present

At least 2 weeks of depressed mood OR loss of interest in nearly all activities

Plus additional symptoms*

- Significant change in appetite or weight
- Insomnia or hypersomnia
- Fatigue or loss of energy
- Psychomotor agitation or slowing
- Feelings of worthlessness or inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide

FROM THE AMERICAN PSYCHIATRIC ASSOCIATION: DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FOURTH EDITION, TEXT REVISION. WASHINGTON, DC: AMERICAN PSYCHIATRIC ASSOCIATION; 2000.

Proposed modified additional symptom list for the medically ill†

- Anhedonia – loss of pleasure/enjoyment
- Unusual tearfulness
- Depressed appearance
- Social withdrawal
- Ruminating thoughts
- Hopelessness/helplessness
- Psychomotor agitation or slowing
- Feelings of worthlessness or inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide

*A total of five symptoms constitutes major depression; a total of two to four constitutes minor depression.

†Proposed by Cavanaugh⁵⁴ and Endicott⁵²

**Two questions
can identify
96% of patients
with depression**

fatigue and poor appetite,⁵³ which are also symptoms of depression.

To address this problem, Endicott,⁵² Cavanaugh,⁵⁴ and others have proposed additional symptoms to assess depression in the medically ill (TABLE 2).

Tools to aid diagnosis

Various screening tests can help to diagnose depression. The Beck Depression Inventory⁵⁵ and the Zung Depression Scale⁵⁶ are patient-rated and easily scored.

An alternative is a two-question test advocated by Whooley and Simon⁵⁷:

- In the past month, have you felt “down,” depressed, or hopeless?
- In the past month, have you had little pleasure or interest in doing things?

The test is 96% sensitive: almost all who are depressed answer yes to both questions.

However, because its specificity is only 57%, the clinician should obtain additional information to substantiate the diagnosis.

TREATING DEPRESSION IN CARDIAC PATIENTS

There is no good evidence that treating depression improves cardiac prognosis. Nonetheless, we recommend treating it, even if only to improve mood and quality of life.

Psychotherapy can be tried for mild depression. Only cognitive behavioral therapy and interpersonal psychotherapy have proven effective without medications, though this has not been specifically evaluated in cardiac patients.^{58,59} If the patient has not improved after several weeks, medication should be added.

We recommend antidepressant medica-

TABLE 3

Antidepressant medications to avoid in cardiac patients

MEDICATIONS	POTENTIAL DRAWBACKS
Tricyclic antidepressants (Contraindicated in patients with ischemic heart disease)	Tachycardia Prolonged PR, QRS, and QTc intervals Orthostatic hypotension Class 1A antiarrhythmic properties
Monoamine oxidase inhibitors (Avoided unless depression is refractory)	Orthostatic hypotension Dietary restrictions required to prevent hypertensive crises

tion for moderate to severe major depressive disorder. The clinician should see the patient several times over the subsequent 2 months to assess suicide potential and treatment outcome, or to refer the patient to a psychiatrist.

■ SSRIs HAVE BEST CARDIAC PROFILE

All approved antidepressants are effective, but their safety and tolerability vary.

Tricyclic antidepressants are contraindicated in patients with ischemic heart disease,^{60–64} and monoamine oxidase inhibitors are recommended only for depression refractory to other medications (TABLE 3).

Selective serotonin reuptake inhibitors (SSRIs) are preferred for patients with heart disease, because they have few cardiovascular side effects and can easily be initiated by primary care physicians. All SSRIs are similarly effective in improving depressive symptoms and quality of life.⁶⁵

The commonly used SSRIs—fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and citalopram (Celexa, Cipramil)—are not known to significantly affect blood pressure or cardiovascular conduction. However, bradycardia can occur, and some cases of syncope have been reported.^{66,67}

Fluvoxamine (Luvox), which is especially effective in obsessive-compulsive disorder, has recently been linked to intraventricular cardiac delay and prolonged QTc interval.⁶⁸

Fluoxetine has been studied specifically in patients with cardiovascular disease. Despite fairly large doses (average 60 mg/day), no orthostatic hypotension, arrhythmias, or

other cardiac conduction effects were noted, except for a 5-beat/minute decrease in heart rate.⁶⁹ Interestingly, improved ejection fraction was observed in patients with diminished ventricular conduction at baseline.

Paroxetine and the tricyclic antidepressant nortriptyline were also studied in patients with heart disease. Neither drug significantly affected blood pressure or conduction intervals, but nortriptyline was associated with other adverse cardiovascular effects.⁷⁰

Sertraline was studied in a preliminary open-label trial in 26 patients with major depression following an MI. Most patients improved over 16 weeks of treatment, with no alterations in blood pressure, ejection fraction, cardiac conduction, or arrhythmias induced.⁷¹

The multicenter, double-blind, placebo-controlled Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) confirmed sertraline's safety in the treatment of depression in heart patients after an acute event. Nearly 370 depressed patients post-MI or with unstable angina participated in a 2-week placebo run-in before being randomized to sertraline or placebo. Patients with a first episode of major depression improved on sertraline according to the Clinical Global Impression Improvement Scale but not on the Hamilton Depression Inventory. Those with recurrent major depressive disorder improved according to both instruments.⁷²

Monitor for SSRI-cardiac drug interactions

SSRIs are not completely benign and commonly have gastrointestinal and sexual side

Tricyclics are contraindicated in patients with ischemic heart disease

**TABLE 4****Some antidepressant drugs raise the levels of some cardiac drugs by inhibiting their metabolism**

DRUGS	INHIBITORY EFFECT ON SPECIFIC CYTOCHROME P450 ENZYMES				
	CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 3A4
Selective serotonin reuptake inhibitors*					
Citalopram (Celexa, others)	0 to +	0	0	0	0
Fluoxetine (Prozac)	0 to +	+++	++	++++	++
Fluvoxamine (Luvox)	++++	+++	++++	+	+++
Paroxetine (Paxil)	0 to +	0 to +	0 to +	++++	0 to +
Sertraline (Zoloft)	0 to +	++	+ to ++	++	++ to +++
Other antidepressants*					
Bupropion (Wellbutrin, others)	0	0	0	0	0
Mirtazapine (Remeron)	0	0	0	0	0
Nefazodone (Serzone)	0	0	0	+	++++
Venlafaxine (Effexor)	0	0	0	+	0
Tricyclic antidepressant*					
Nortriptyline (Pamelor)	0	0	0	0	0
Future agents*					
Escitalopram	0	0	0	0	0
R-Fluoxetine	?	?	?	?	?
Cardiac medications metabolized by P450 enzymes†	R-Warfarin Verapamil Propranolol	S-Warfarin Propranolol NSAIDs	S-Warfarin Propranolol NSAIDs	Beta-blockers Class 1C anti-arrhythmics‡	Calcium channel blockers§ Statins Steroids Lidocaine Quinidine Losartan

0 insignificant, + mild, ++++ potent

*Compiled from references 98–100

†Compiled from references 75, 101–104

‡Encainide, flecainide, and propafenone

§Diltiazem, disopyramide, amlodipine, felodipine, isradipine, nifedipine, nimodipine, nisoldipine, and verapamil

||Atorvastatin, lovastatin, pravastatin, and simvastatin

effects. They also interact with beta-blockers, warfarin, digoxin, and other medications by inhibiting the cytochrome P450 (CYP) isoenzymes (TABLE 4). Overall, their benefits outweigh the risks if they are monitored carefully.

SSRIs may help underlying cardiac disease

Although we primarily treat depression in the post-MI period to improve quality of life, SSRIs may also alter the pathophysiology responsible for the increase in cardiac mortality:

- Fluoxetine has been shown to significantly increase heart rate variability^{73,74}
- Paroxetine has been shown to reduce high levels of PF-4 and beta thromboglobulin, which are associated with increased platelet activation.⁷⁵

■ SECOND-LINE AGENTS

Other pharmacologic agents can be used if SSRIs fail.

Psychostimulants, such as methylpheni-

date (Ritalin), can be used to treat patients who do not improve with SSRIs and who have predominant symptoms of fatigue, apathy, or psychomotor retardation.⁷⁶ In medically ill patients, methylphenidate 2.5 mg in the morning and early afternoon can be started and the dosage increased as needed. A total daily dose of 20 mg is typically required.

At typical doses, cardiovascular side effects, including tachycardia, tachypnea, arrhythmias, and either hypertension or hypotension, are unusual but should be looked for. Stimulants may also increase warfarin levels and decrease the effectiveness of adrenergic blocking agents such as prazosin (Minipress), doxazosin (Cardura), and guanethidine (Ismelin).⁷⁷

Bupropion (Amfebutamone, Wellbutrin, Zyban) and venlafaxine (Effexor) have been associated with dose-related blood pressure elevations, although they rarely produce electrocardiographic changes and have not been reported to cause conduction delays or arrhythmias.^{78,79} They may be used as second-line agents in patients with well-controlled blood pressure.

Nefazodone (Serzone) may induce orthostatic hypotension and has recently been linked to liver failure.

■ OTHER TREATMENT CONSIDERATIONS

Ask about suicide

Clinicians are strongly advised to address expressions of hopelessness, worthlessness, or suicidal ideation. Never hesitate to ask about passive or active thoughts of suicide; it could be life-saving.

Refer severe cases to psychiatrists

Psychiatric referral is critical for patients experiencing treatment-refractory or severe depression with either significant functional

disability or suicidal thoughts.


Psychiatrists can fine-tune medications and provide psychotherapy, light therapy, or electroconvulsive therapy (ECT). ECT is generally reserved for patients requiring rapid resolution of symptoms or for whom two or more medications have failed. It is safe for cardiac patients who can tolerate general anesthesia.⁸⁰

Social support is also important

Patients with depression after an MI are at higher risk of poor quality-of-life outcomes than nondepressed patients⁸¹: they are less likely to return to work in the 6 months after their infarction,⁸² they are at increased risk for ensuing disability,⁸³ they use more medical services,⁸⁴ and they are less likely to comply with cardiac medications and lifestyle changes.⁸⁵

Social stress contributes to depression in medically ill patients, and hopelessness is an independent risk factor for lower survival in patients with heart disease.^{8,86}

Poor social support correlates with higher morbidity and mortality rates, independent of disease severity, in patients with heart disease,^{87–89} especially in younger patients.⁹⁰

The Enhancing Recovery in Coronary Heart Disease (ENRICH) trial, sponsored by The National Heart, Lung and Blood Institute, is a multicenter collaboration designed to evaluate the effects of psychosocial intervention on cardiovascular morbidity and mortality in post-MI patients displaying clinical depression or having little social support.⁹¹ Patients randomized to the psychosocial intervention receive individual and group cognitive-behavioral therapy. Medications are prescribed for patients with severe depression or those not improving with psychotherapy. Study results have not yet been published. 

Never
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■ REFERENCES

1. **Blazer DG.** Mood disorders: epidemiology. In: Sadock BJ, Sadock VA, editors. *Comprehensive Textbook of Psychiatry*, Seventh Edition. Philadelphia: Lippincott, Williams and Wilkins, 2000:1298–1308.
2. **Kay J.** *Psychiatry: Behavioral Science and Clinical Essentials*. Philadelphia: W.B. Saunders, 2000.
3. **Crum RM, Cooper-Patrick L, Ford DE.** Depressive symptoms among general medical patients: prevalence and one-year outcome. *Psychosom Med* 1994; 56:109–117.
4. **Murray CJ, Lopez AD.** Global mortality, disability and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; 349:1436–1442.
5. **American Heart Association.** *Heart Attack and Stroke Facts*. Dallas: American Heart Association, 1998.
6. **Rozanski A, Blumenthal JA, Kaplan J.** Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999; 99:2192–2217.
7. **Jiang W, Krishnan RR, O'Connor CM.** Depression and heart disease: evidence of a link, and its therapeutic implications. *CNS Drugs* 2002; 16:111–127.

8. **Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW.** Depression, psychotropic medication and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. *Circulation* 1996; 94:3123–3129.
9. **Anda R, Williamson D, Jones D, et al.** Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. *Epidemiology* 1993; 4:285–294.
10. **Schleifer SJ, Macari-Hinson MM, Coyle DA, et al.** The nature and course of depression following myocardial infarction. *Arch Intern Med* 1989; 149:1785–1789.
11. **Carney RM, Rich MW, Freedland KE, et al.** Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med* 1988; 50:627–633.
12. **Gold PW, Chrousos GP.** The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. *Proc Assoc Am Physicians* 1999; 111:22–34.
13. **Murphy JM, Monson RR, Olivier DC, Sobol AM, Leighton AH.** Affective disorders and mortality: a general population study. *Arch Gen Psychiatry* 1987; 44:473–480.
14. **Frasure-Smith N, Lesperance F, Talajic M.** Depression following myocardial infarction: impact on 6-month survival. *JAMA* 1993; 15:1819–1825.
15. **Frasure-Smith N, Lesperance F, Talajic M.** Depression and 18-month prognosis after myocardial infarction. *Circulation* 1995; 91:999–1005.
16. **Barefoot JC, Helms MJ, Mark DB, et al.** Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol* 1996; 78:613–617.
17. **Lesperance F, Frasure-Smith N, Juneau M, Theroux P.** Depression and 1-year prognosis in unstable angina. *Arch Intern Med* 2000; 160:1354–1360.
18. **Penninx BW, Beekman AT, Honig A, et al.** Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 2001; 58:221–227.
19. **Horwath E, Johnson J, Klerman GL, Weissman MM.** Depressive symptoms as relative and attributable risk factors for first-onset major depression. *Arch Gen Psychiatry* 1992; 49:817–823.
20. **Burker EJ, Blumenthal JA, Feldman M, et al.** Depression in male and female patients undergoing cardiac surgery. *Br J Clin Psychol* 1995; 34:119–128.
21. **Scheier MF, Matthews KA, Owens JF, et al.** Optimism and rehospitalization after coronary artery bypass graft surgery. *Arch Intern Med* 1999; 159:829–835.
22. **Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP.** Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet* 2001; 358:1766–1771.
23. **Nemeroff CB.** The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. *Mol Psychiatry* 1996; 1:336–342.
24. **Musselman DL, Evans DL, Nemeroff CB.** The relationship of depression to cardiovascular disease: epidemiology, biology and treatment. *Arch Gen Psychiatry* 1998; 55:580–592.
25. **Pariante CM, Miller AH.** Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry* 2001; 49:391–404.
26. **World Health Organization Collaborative Study.** The dexamethasone suppression test in depression. *Br J Psychiatry* 1987; 150:459–462.
27. **Malhotra S, Tesar GE, Franco K.** The relationship between depression and cardiovascular disorders. *Curr Psychiatry Rep* 2000; 2:241–246.
28. **Anfossi G, Trovati M.** Role of catecholamines in platelet function: pathophysiological and clinical significance. *Eur J Clin Invest* 1996; 26:353–370.
29. **Wilson JD, Foster DW, Kronenberg HM, Larsen PR.** *Williams Textbook of Endocrinology*, Ninth Edition. Philadelphia: W.B. Saunders; 1998.
30. **Roy A, Pickar D, De Jong J, Karoum F, Linnoila M.** Norepinephrine and its metabolites in cerebrospinal fluid, plasma and urine. Relationship to hypothalamic-pituitary-adrenal axis function in depression. *Arch Gen Psychiatry* 1988; 45:849–857.
31. **Roy A, Linnoila M, Karoum F, Pickar D.** Urinary-free cortisol in depressed patients and controls: relationship to urinary indices of noradrenergic function. *Psychol Med* 1988; 18:93–98.
32. **Roy A, Guthrie S, Pickar D, Linnoila M.** Plasma norepinephrine responses to cold challenge in depressed patients and normal controls. *Psychiatry Res* 1987; 21:161–168.
33. **Roy A, Pickar D, Linnoila M, Potter WZ.** Plasma norepinephrine level in affective disorders: relationship to melancholia. *Arch Gen Psychiatry* 1985; 42:1181–1185.
34. **Shimbo D, Child J, Davidson K, et al.** Exaggerated serotonin-mediated platelet reactivity as a possible link in depression and acute coronary syndromes. *Am J Cardiol* 2002; 89:331–333.
35. **Nemeroff CB, Knight DL, Franks J, Craighead WE, Krishnan KRR.** Further studies on platelet serotonin transporter binding in depression. *Am J Psychiatry* 1994; 151:1623–1625.
36. **Cerrito F, Lazzaro MP, Gaudio E, Arminio P, Aloisi G.** 5HT₂-receptors and serotonin release: their role in human platelet aggregation. *Life Sci* 1993; 53:209–215.
37. **Gorman JM, Sloan RP.** Heart rate variability in depressive and anxiety disorders. *Am Heart J* 2000; 140(suppl 4):77–83.
38. **Malaspina D, Dalack G, Leitman D.** Low heart rate variability is not caused by typical neuroleptics in schizophrenia patients. *CNS Spectrums* 2002; 7:53–57.
39. **Carney RM, Blumenthal JA, Stein PK, et al.** Depression, heart rate variability and acute myocardial infarction. *Circulation* 2001; 104:2024–2028.
40. **Braunwald E, Zipes DP, Libby P.** *Heart Disease: A Textbook of Cardiovascular Medicine*, Sixth Edition. Philadelphia: W.B. Saunders; 2001:89–90,1099–1100,1200.
41. **Klein E, Cnaani E, Harel T, Braun S, Ben-Haim SA.** Altered heart rate variability in panic disorder patients. *Biol Psychiatry* 1995; 37:18–24.
42. **American College of Cardiology Cardiovascular Technology Assessment Committee.** Heart rate variability for risk stratification of life-threatening arrhythmias. *J Am Coll Cardiol* 1993; 22:948–950.
43. **Cripps TR, Malik M, Farrell TG, Camm AJ.** Prognostic value of reduced heart rate variability after myocardial infarction: clinical evaluation of a new analysis method. *Br Heart J* 1991; 65:14–19.
44. **Van Ravenswaaij-Arts CM, Kollee LA, Hopman JC, Stoeltinga GB, van Geijn HP.** Heart rate variability. *Ann Intern Med* 1993; 118:436–447.
45. **Dalack GW, Roose SP.** Perspectives on the relationship between cardiovascular disease and affective disorder. *J Clin Psychiatry* 1990; 51(suppl):4–9.
46. **Viskin S, Belhassen B.** Noninvasive and invasive strategies for the prevention of sudden death after myocardial infarction: value, limitations and implications for therapy. *Drugs* 1992; 44:336–355.
47. **Sloan RP, Shapiro PA, Bagiella E, Myers MM, Gorman JM.** Cardiac autonomic control buffers blood pressure variability responses to challenge: a psychophysiological model of coronary artery disease. *Psychosom Med* 1999; 61:58–68.
48. **Ahern DK, Gorkin L, Anderson JL, et al.** Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). *Am J Cardiol* 1990; 66:59–62.
49. **Perez-Stable EJ, Miranda J, Munoz RF, Ying YW.** Depression in medical outpatients. Underrecognition and misdiagnosis. *Arch Intern Med* 1990; 150:1083–1088.
50. **Hirschfeld RM, Keller MB, Panico S, et al.** The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *JAMA* 1997; 277:333–340.
51. **Freedland KE, Lustman PJ, Carney RM, Hong BA.** Underdiagnosis of depression in patients with coronary artery disease: the role of nonspecific symptoms. *Int J Psychiatry Med* 1992; 3:221–229.
52. **Endicott J.** Measurement of depression in patients with cancer. *Cancer* 1984; 53(suppl 10):2243–2249.
53. **Freedland KE, Carney RM, Lustman PJ, Rich MW, Jaffe AS.** Major depression in coronary artery disease patients with versus without a prior history of depression. *Psychosom Med* 1992; 54:416–421.
54. **Cavanaugh S.** Depression in the medically ill: critical issues in diagnostic assessment. *Psychosomatics* 1995; 36:48–59.
55. **Beck AT, Ward CH, Mendelson M, et al.** An inventory of measuring depression. *Arch Gen Psychiatry* 1961; 4:53–63.
56. **Zung WWK.** A self-rating depression scale. *Arch Gen Psychiatry* 1965; 12:63–70.
57. **Whooley MA, Simon GE.** Managing depression in medical outpatients. *N Engl J Med* 2000; 343:1942–1948.



58. Swartz HA, Markowitz JC. Time-limited psychotherapy. In: Tasman A, Kay J, Lieberman J, editors. *Psychiatry*. Philadelphia: W.B. Saunders; 1997:1405–1417.
59. Thase ME, Wright JH. Cognitive and behavioral therapies. In: Tasman A, Kay J, Lieberman J, editors. *Psychiatry*. Philadelphia: W.B. Saunders; 1997:1418–1438.
60. CAST Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; 321:406–412.
61. CAST II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. *N Engl J Med* 1992; 327:227–233.
62. Bigger JT, Giardina EG, Perel JM, Kantor SJ, Glassman AH. Cardiac antiarrhythmic effect of imipramine hydrochloride. *N Engl J Med* 1977; 296:206–208.
63. Roose SP, Glassman AH, Dalack GW. Depression, heart disease and tricyclic antidepressants. *J Clin Psychiatry* 1989; 50(suppl 7):12–18.
64. Roose SP, Glassman AH, Siris SG, Walsh BT, Bruno RL, Wright LB. Comparison of imipramine and nortriptyline-induced orthostatic hypotension: a meaningful difference. *J Clin Psychopharmacol* 1981; 1:316–319.
65. Kroenke K, West SL, Swindle R, et al. Similar effectiveness of paroxetine, fluoxetine and sertraline in primary care: a randomized trial. *JAMA* 2001; 286:2947–2955.
66. Ellison JM, Milofsky JE, Ely E. Fluoxetine-induced bradycardia and syncope in two patients. *J Clin Psychiatry* 1990; 51:385–386.
67. Feder R. Bradycardia and syncope induced by fluoxetine. *J Clin Psychiatry* 1991; 52:139.
68. Rodriguez de la Torre B, Dreher J, Malevany I, et al. Serum levels and cardiovascular effects of tricyclic antidepressants and selective serotonin reuptake inhibitors in depressed patients. *Ther Drug Monit* 2001; 23:435–440.
69. Roose SP, Glassman AH, Attia E, Woodring S, Giardina EG, Bigger JT Jr. Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am J Psychiatry* 1998; 155:660–665.
70. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 1998; 279:287–291.
71. Shapiro PA, Lesperance F, Frasere-Smith N. An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (the SADHART Trial). *Sertraline Anti-Depressant Heart Attack Trial*. *Am Heart J* 1999; 137:1100–1106
72. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; 288:701–709.
73. Balogh S, Fitzpatrick DF, Hendricks SE, Paige SR. Increases in heart rate variability with successful treatment in patients with major depressive disorder. *Psychopharmacol Bull* 1993; 29:201–206.
74. Khaykin Y, Dorian P, Baker B, et al. Autonomic correlates of antidepressant treatment using heart-rate variability analysis. *Can J Psychiatry* 1998; 43:183–186.
75. Pollock BG, Laghrissi-Thode F, Wagner WR, et al. Increased platelet factor 4 and beta thromboglobulin in depressed patients with ischemic heart disease. Presented at the 34th annual meeting of the American College of Neuropsychopharmacology; Dec 11–14, 1995; San Juan, Puerto Rico.
76. DasGupta K. Treatment of depression in elderly patients: recent advances. *Arch Fam Med* 1998; 7:274–280.
77. Masand PS, Tesar GE. Use of stimulants in the medically ill. *Psychiatr Clin North Am* 1996; 19:515–547.
78. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG. Cardiovascular effects of bupropion in depressed patients with heart disease. *Am J Psychiatry* 1991; 148:512–516.
79. Feighner JP. Cardiovascular safety in depressed patients: focus on venlafaxine. *J Clin Psychiatry* 1995; 56:574–579.
80. Zielinski RJ, Roose SP, Devanand DP. Cardiovascular complications of ECT in depressed patients with cardiac disease. *Am J Psychiatry* 1993; 150:904–909.
81. Mayou RA, Gill D, Thompson DR, et al. Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med* 2000; 62:212–219.
82. Lloyd GG, Cawley RH. Distress or illness? A study of psychological symptoms after myocardial infarction. *Br J Psychiatry* 1983; 142:120–125.
83. Hlatky MA, Haney T, Barefoot JC, et al. Medical, psychological and social correlates of work disability among men with coronary artery disease. *Am J Cardiol* 1986; 58:911–915.
84. Frasere-Smith N, Lesperance F, Gravel G, et al. Depression and health-care costs during the first year following myocardial infarction. *J Psychosom Res* 2000; 48:471–478.
85. Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch Intern Med* 2000; 160:1818–1823.
86. Everson SA, Goldberg DE, Kaplan GA, et al. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. *Psychosom Med* 1996; 58:113–121.
87. Krishnan KR, George LK, Pieper CF, et al. Depression and social support in elderly patients with cardiac disease. *Am Heart J* 1998; 136:491–495.
88. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Psychosocial influences on mortality after myocardial infarction. *N Engl J Med* 1984; 311:552–559.
89. Orth-Gomer K, Unden AL, Edwards ME. Social isolation and mortality in ischemic heart disease: a 10-year follow-up study of 150 middle aged men. *Acta Med Scand* 1988; 224:205–215.
90. Barefoot JC, Brummett BH, Clapp-Channing NE, et al. Moderators of the effect of social support on depressive symptoms in cardiac patients. *Am J Cardiol* 2000; 86:438–442.
91. The ENRICH Investigators. Enhancing Recovery in Coronary Heart Disease (ENRICH) study intervention: rationale and design. *Psychosom Med* 2001; 63:747–755.
92. Ladwig KH, Roll G, Breithardt G, Budde T, Borggrefe M. Post-infarction depression and incomplete recovery 6 months after acute myocardial infarction. *Lancet* 1994; 343:20–23.
93. Aromaa A, Raitasalo R, Reunanen A, et al. Depression and cardiovascular disease. *Acta Psychiatr Scand Suppl* 1994; 377:77–82.
94. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation* 1996; 93:1976–1980.
95. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is a risk factor for coronary artery disease in men: the precursors study. *Arch Intern Med* 1998; 158:1422–1426.
96. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. *Arch Intern Med* 2000; 160:1261–1268.
97. Ariyo AA, Haan M, Tangen CM, et al. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. *Circulation* 2000 10; 102:1773–1779.
98. DeVane CL. Differential pharmacology of newer antidepressants. *J Clin Psychiatry* 1998; 59(suppl 20):85–93.
99. Owen JR, Nemeroff CB. New antidepressants and the cytochrome P450 system: focus on venlafaxine, nefazodone, and mirtazapine. *Depress Anxiety* 1998; 7(suppl 1):24–32.
100. Fait ML, Wise MG, Jachna JS, et al. Psychopharmacology. In: Wise MG, Rundell JR, eds. *The American Psychiatric Publishing Textbook of Consultation-Liaison Psychiatry*. Psychiatry in the Medically Ill. 2nd ed. Washington DC: American Psychiatric Publishing; 2002:939–988.
101. Nemeroff CB, DeVane LC, Pollock BG. Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 1996; 153:311–320.
102. Ereshefsky L, Dugan D. Review of the pharmacokinetics, pharmacogenetics, and drug interaction potential of antidepressants: focus on venlafaxine. *Depress Anxiety* 2000; 12(suppl 1):30–44.
103. Michalets LE. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 1998; 18:84–112.
104. Shader RI, von Moltke LL, Schmider J, Harmatz JS, Greenblatt DJ. The clinician and drug interactions—an update. *J Clin Psychopharmacol* 1996; 16:197–201.

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