

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Screening and Management of Depression in Patients With Cardiovascular Disease

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Manish K. Jha, MD,^a Arman Qamar, MD,^{b,c} Muthiah Vaduganathan, MD, MPH,^d Dennis S. Charney, MD,^{a,e} James W. Murroughs, MD, PhD^a



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CME/MOC/ECME Objective for This Article: Upon completion of this activity, the learner should be able to: 1) discuss the dynamic interplay between depression and cardiovascular disease; 2) implement screening methods to identify depression among patients with cardiovascular disease; and 3) select appropriate treatments and level of care in patients with cardiovascular disease who experience depression.

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From the ^aDepression and Anxiety Center for Discovery and Treatment, Department of Psychiatry, and Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York; ^bTIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ^cHarvard T.H. Chan School of Public Health, Boston, Massachusetts; ^dHeart & Vascular Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and the ^eOffice of the Dean, Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Jha has received contract

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Education (GME); has received research support from Avanir Pharmaceuticals; is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders; and the Icahn School of Medicine (employer of Dr. Murrough) is named on a patent and has entered into a licensing agreement and will receive payments related to the use of ketamine if it is approved for the treatment of depression (Dr. Murrough is not named on this patent and will not receive any payments).

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ABSTRACT

Depression is a common problem in patients with cardiovascular disease (CVD) and is associated with increased mortality, excess disability, greater health care expenditures, and reduced quality of life. Depression is present in 1 of 5 patients with coronary artery disease, peripheral artery disease, and heart failure. Depression complicates the optimal management of CVD by worsening cardiovascular risk factors and decreasing adherence to healthy lifestyles and evidence-based medical therapies. As such, standardized screening pathways for depression in patients with CVD offer the potential for early identification and optimal management of depression to improve health outcomes. Unfortunately, the burden of depression in patients with CVD is under-recognized; as a result, screening and management strategies targeting depression have been poorly implemented in patients with CVD. In this review, the authors discuss a practical approach for the screening and management of depression in patients with CVD. (J Am Coll Cardiol 2019;73:1827–45) © 2019 by the American College of Cardiology Foundation.

Major depressive disorder, commonly referred to simply as depression, affects 1 of 5 adults during their lifetime and is the second leading cause of disability in the United States (1,2). Depression is a major cause of morbidity and poor quality of life among patients with cardiovascular disease (CVD) (3) and is also considered an independent risk factor for major adverse cardiovascular events (4). Epidemiological studies suggest that fewer than 20% of individuals with depression are adequately treated (5). These rates are even lower in patients with CVD; in a study of those admitted to cardiac inpatient services, only 11% of patients with depression received adequate antidepressant therapy (6). To improve identification of patients with depression, the U.S. Preventive Services Task Force (USPSTF) recently issued recommendations to screen for depression in the general adult population while emphasizing that patients with CVD are at an increased risk of depression (7). Similar to these recommendations, the American Heart Association (AHA) issued an advisory in 2008 to screen all patients with coronary artery disease (CAD) for depression (8). However, the uptake of the USPSTF recommendations in clinical practice remains poor. While screening for depression has increased gradually since 2009, it is estimated that only 3% of patients in ambulatory care settings were screened for depression in 2015 (9). Standardized screening

pathways for depression in CVD patients offer the potential for early identification and improved management of both CVD and depression (10–12). In this review, we discuss a practical approach for the screening and management of depression in patients with CVD.

IMPACT OF DEPRESSION IN CVD

PREVALENCE OF DEPRESSION IN PATIENTS WITH CVD. Prevalence of depression varies according to the type and severity of CVD. Approximately 15% to 20% of patients with CAD have depression; up to two-thirds of patients with myocardial infarction (MI) develop depression either during index hospitalization or in follow-up (13). Compared with the general population, patients with MI are at 3-fold higher risk of depression (14). In a prospective cohort study examining the prevalence of depression in approximately 1,000 patients undergoing coronary artery bypass graft (CABG) surgery, 38% of patients met criteria for depression, with 26% having mild depression and 12% moderate-to-severe depression (15). Depression is also present in 20% of patients with peripheral artery disease (PAD) (16,17) and heart failure (18). Patients with New York Heart Association (NYHA) functional class IV have nearly 4-fold higher rates of depression compared with NYHA functional class I heart failure (18). A pooled analysis of 5 studies

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

CBT = cognitive behavioral therapy

CVD = cardiovascular disease

HAMD = Hamilton Rating Scale for Depression

PHQ = Patient Health Questionnaire

SGA = second generation antipsychotic

SNRI = serotonin-norepinephrine reuptake inhibitor

SSRI = selective serotonin reuptake inhibitor

USPSTF = U.S. Preventive Services Task Force

reported comorbid depression in 11%, 20%, 38%, and 42% of patients with NYHA functional class I, II, III, and IV heart failure, respectively. Younger patients with heart failure (19) and those requiring implantable-cardioverter defibrillator insertion (20) or who experience attendant implantable-cardioverter defibrillator firing (21,22) are particularly at risk for comorbid depression.

DEPRESSION AS A RISK FACTOR FOR CVD.

Depression is associated with increased risk of future CVD. Depression and psychosocial factors (perceived stress, low locus of control, and major life events) were associated with a 2.5- to 3.5-fold higher risk of CVD in a large international study of patients with MI (n = 15,152) and control subjects (n = 14,820) even after controlling for life-

style factors and other medical disorders (4). Presence of depression at baseline was associated with higher risk of MI (>70%) and all-cause mortality (>60%) in community dwelling adults over 27-year follow-up independent of age, sex, and other risk factors (23). A meta-analysis of 8 prospective cohort and case-control studies showed a 60% higher adjusted risk of incident CVD in patients with depression (24).

PROGNOSIS OF PATIENTS WITH CVD AND DEPRESSION.

Depression in patients with CVD is associated with poor prognosis. Presence of depression after MI is independently associated with a 2-fold to 4-fold higher risk of subsequent cardiovascular events (25–27). This risk is directly proportional to depression severity (28). Patients with depressive symptoms that are refractory to antidepressant treatment remain at an increased risk for subsequent cardiovascular events (29). Similarly, depression is associated with higher cardiovascular event rates after CABG (15,30) and in patients with PAD and heart failure. Patients with PAD and concomitant depression experience higher vascular complications, suboptimal functional improvement after lower extremity revascularization, and an increased need for revascularization than those without depression (31–33). Depression is associated with a 2-fold to 3-fold higher risk of death or rehospitalization within 3 to 12 months after hospitalization for heart failure (34–37). Furthermore, depression in patients with heart failure is associated with greater health care utilization (38), poor quality of life (39), and greater risk of social isolation, economic burden, and caregiver fatigue (40).

HIGHLIGHTS

- Depression is a common problem and is associated with increased mortality and reduced quality of life in patients with CVD.
- Depression complicates the optimal management of CVD by worsening cardiovascular risk factors and decreasing adherence to healthy lifestyles and evidence-based medical therapies.
- Standardized screening pathways for depression in patients with CVD offer the potential for early identification and optimal management of depression to improve health outcomes.

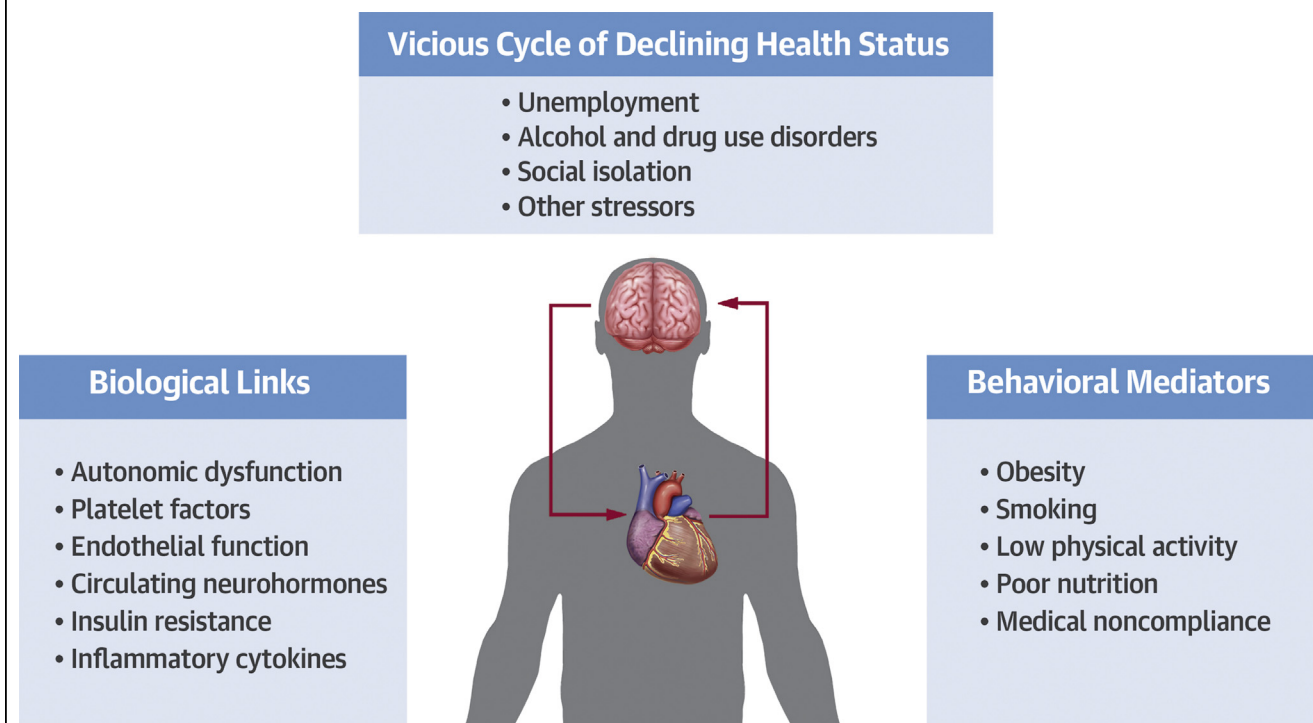
BIOLOGICAL LINKS BETWEEN DEPRESSION AND CVD

Several biological mechanisms have been proposed to explain the unfavorable prognosis of patients with CVD and depression, including lifestyle factors, autonomic dysfunction, neuroendocrine imbalance, inflammation, insulin resistance, and increased platelet reactivity (Figure 1). There is considerable functional overlap and interplay between these systems in regulating both cardiac and neuropsychiatric functioning.

LIFESTYLE FACTORS. Depression is associated with increased risk of nonadherence to cardioprotective medications and healthy lifestyle in patients with CVD (41,42). Furthermore, patients with depression may have less engagement in health behaviors that mitigate the risk of future cardiovascular events, such as physical activity, dietary modifications, smoking cessation, stress management, and substance abuse treatment (43,44), which may partially mediate the adverse cardiovascular health consequences of depression. Increased physical activity has been shown to improve depressive symptoms and improve cardiovascular outcomes (45).

AUTONOMIC DYSFUNCTION. Both depression and common forms of CVD are associated with autonomic dysfunction, which have the potential for increasing the risk for adverse cardiovascular events (46). As a result, depression is associated with resting tachycardia, reduced heart rate variability, and hypertension, which may underlie associated left ventricular hypertrophy, risk of ventricular arrhythmias, endothelial dysfunction, and myocardial supply/demand mismatch observed with depression (47,48).

FIGURE 1 Biological Mechanisms and Behavioral Mediators Linking Depression and Cardiovascular Disease



Depression and cardiovascular diseases share a variety of biological mechanisms and behavioral mediators as indicated by the **bidirectional arrows**. The **arrows** also represent the vicious cycle of declining health outcomes that may occur with depression in patients with cardiovascular disease due to worsening of lifestyle and socioeconomic factors.

NEUROENDOCRINE IMBALANCE. Hyperactivity of the hypothalamic-pituitary-adrenal axis is common in depression, and the ensuing hypercortisolemia may be a biological link with CVD and other chronic cardiometabolic conditions (49). High cortisol is associated with hypertension, premature atherosclerosis, prothrombotic effects, and heightened risk of diabetes mellitus.

INFLAMMATION. Patients with depression have higher levels of inflammatory cytokines, acute phase proteins, and adhesion molecules including interleukin-1 β and -6, tumor necrosis factor- α , and C-reactive protein (50), which may in turn be associated with cardiovascular events.

INSULIN RESISTANCE. The risk of cardiovascular events is higher in individuals with insulin resistance and diabetes mellitus (51), the incidence of which is significantly increased in depression. Depression may result in immune-mediated destruction of the pancreatic β -cells contributing to insulin resistance and diabetes mellitus, both of which are important risk factors for CVD (52). Insulin

resistance in depression may be related to lifestyle-related factors and mediated through visceral fat accumulation and central obesity from the chronic activation of the hypothalamic-pituitary-adrenal axis.

INCREASED PLATELET REACTIVITY. Enhanced platelet reactivity has been proposed as a potential mechanism for increased susceptibility to atherothrombosis in depression, as suggested by in vivo studies (53). Mechanisms for enhanced platelet reactivity in depression are comprised of augmented platelet thrombin response and an increased expression of platelet factors (54). Increased platelet aggregation in patients with depression has also been attributed to decreased endothelial nitric oxidase synthase activity. Additionally, exaggerated serotonin response, high platelet serotonin density, reduced serotonin transporter binding, and decreased platelet serotonin levels may also increase platelet reactivity in depression (54). Heightened platelet reactivity is attenuated with improvement in depressive symptoms (55).

TABLE 1 Select Recommendations for Screening of Depression in Cardiovascular Disease

Guideline (Year)	Population/Purpose	Summary
American Heart Association (2008)	Patients with coronary heart disease	All CAD patients should be screened at a minimum with PHQ-2 and those who answer "yes" to either question of PHQ-2 should be assessed further with PHQ-9. Those with PHQ-9 scores >10 or with an answer of "yes" to the ninth question assessing suicidal ideations, should be referred for further clinical evaluation.
U.S. Preventive Services Task Force (2016)	General adult populations	Adults age ≥18 years who receive care in practices with adequate systems for "accurate diagnosis, effective treatment, and appropriate follow-up after screening." Adults with chronic illnesses (such as CVD) are considered to be at increased risk of depression.
American Heart Association (2014)	Patients with ACS (myocardial infarction or unstable angina)	Depression in patients with ACS is associated with higher risk of all-cause and cardiac mortality as well as adverse outcomes including mortality or nonfatal cardiac events. The panel recommended that AHA and other organizations should include depression as a risk factor for poor prognosis after ACS. This report did not consider the clinical implications of depression screening.
American Academy of Family Physicians (2009)	Patients with myocardial infarction	Regular screening for depression using validated questionnaires at regular intervals during the post-myocardial infarction period, including during hospitalization.
American Heart Association (2011)	Women	Screening for depression is recommended as part of cardiovascular risk assessment as depression may indirectly affect the CVD risk through adherence to prevention therapies.
American Heart Association (2015)	Youth	Inclusion of depression and bipolar disorder in youth as tier II moderate-risk conditions that predispose to accelerated atherosclerosis and early CVD. Notably, depression is much more prevalent in this population compared with the other tier II moderate-risk conditions. Recommend diagnostic assessment instead of relying on measures of depressive symptom severity. Future studies are needed to understand the sex differences in the risk of CVD among youth with depression or bipolar disorder.
European Society of Cardiology (2016)	All adults at risk of cardiovascular disease	Assessment of depression and psychosocial factors with standardized methods recommended for use as risk modifiers of cardiovascular risk prediction.
European Society of Cardiology (2016)	Patients with heart failure	Depression is common in patients with heart failure and is associated with poor adherence and social isolation along with worse clinical status and poor prognosis. Routine screening of depression using a validated questionnaire is recommended as a good practice.

ACS = acute coronary syndrome; AHA = American Heart Association; CAD = coronary artery disease; CVD = cardiovascular disease; PHQ = Patient Health Questionnaire.

SCREENING FOR DEPRESSION IN CVD

CURRENT SCREENING GUIDELINES. According to the USPSTF guidelines, all adult patients with CVD are considered to be at an increased risk for depression and should be screened using validated questionnaires (7). The AHA recommends that all patients with CAD should be screened with at least the 2-item Patient Health Questionnaire (PHQ)-2. Those who screen positive on PHQ-2 should then be assessed with the 9-item PHQ-9 (8). Depression screening is recommended during hospitalization and at regular intervals throughout the post-MI period (56). The European Society of Cardiology guidelines provide similar routine screening recommendations in patients with heart failure (57,58). Screening of depression is also recommended for cardiovascular risk stratification in women (59) and in young patients (60), as well as to identify modifiable risk factors for patients in clinical practice who are at high risk of developing CVD (61) (Table 1).

PRACTICALITY OF ROUTINE SCREENING FOR DEPRESSION IN CVD. Routine systematic screening with validated self-report measures is needed for early and accurate identification of depression in CVD patients, as depression is often unrecognized or

inaccurately diagnosed in nonpsychiatric medical care settings (62). The burden of under-recognition and undertreatment of depression is likely to be higher in minority and underserved populations. For instance, although prevalence rates of depression were similar in white and black patients with CVD, black patients were >50% less likely to use antidepressant medications (63). More than 50% of patients with depression go unrecognized in medical settings, and the diagnosis of depression ascribed by clinicians has only a moderate level of agreement with gold-standard structured diagnostic evaluations (62,64). Median duration of delay in treatment initiation after initial contact with a health care provider for depression is 8 years (65), and this may be reduced with early and accurate identification of depression. Screening for diagnosis of depression may also help with reducing inappropriate or overprescription of antidepressant medications (66), which are the third most commonly prescribed class of medications (after analgesics and lipid-lowering therapies) in ambulatory care settings (67). Additionally, screening efforts can also help identify patients who have an established psychiatric/mental health provider but have failed to attain adequate symptom control.

Routine screening for depression requires minimal time and resources in hospital and ambulatory care

cardiovascular settings, but may require increased downstream support from mental health clinicians as depression is more frequently identified. As >35% of the U.S. population lives in a mental health profession-shortage area (68), patients who screen positive and are referred to mental health providers may not be able to access prompt services. Hence, Ziegelstein et al. (69) support increased education of CVD patients and their providers about depression and developing closer relationships between cardiologists and mental health providers, instead of a strategy of routinely screening for depression. While additional data are needed regarding the effects of routine screening of depression on cardiovascular outcomes (70), active engagement of cardiologists in screening for depression may not only reduce the stigma associated with depression, but also improve the quality of life of patients (71).

WHOM TO SCREEN FOR DEPRESSION? All adult patients, including those with acute or chronic CVD, should be screened for depression (7) (**Central Illustration**). Depression screening also may be conducted in younger patients for cardiovascular risk assessment (60). In patients with a history of depression, self-report assessments should assess for adequate symptomatic control (core depressive symptoms, as well as anxiety, irritability, mania, and/or panic), side effects burden, and adherence to prescribed antidepressants using the measurement-based care (MBC) approach (72,73).

WHAT ARE THE TOOLS FOR DEPRESSION SCREENING? The PHQ-2 is a self-report questionnaire that is commonly used for screening of depression (8,74). The 2 items (sad mood and anhedonia) of this scale are rated from 0 to 3 with total score ranging from 0 to 6 (74). Positive screen on PHQ-2 has been defined as total score ≥ 3 with a sensitivity of 83% and specificity of 92% for depression in patients seen in primary care settings (74). In a separate primary care sample, a PHQ ≥ 2 threshold had higher sensitivity (86%) and lower specificity (78%) for the diagnosis of depression than the threshold of PHQ-2 ≥ 3 (sensitivity 61% and specificity 92%) (75). The PHQ-9 more comprehensively assesses each of the 9 domains that define depression (76), and ranges from 0 to 27 (each item scored from 0 to 3). Scores of 0 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 to 27 on PHQ-9 are considered as minimal, mild, moderate, severe, and very severe symptom severity, respectively (77). When used as a screening instrument, PHQ-9 scores ≥ 10 had a sensitivity of 88% and specificity of 88% for major depression in primary care settings (77). A separate validation sample reported

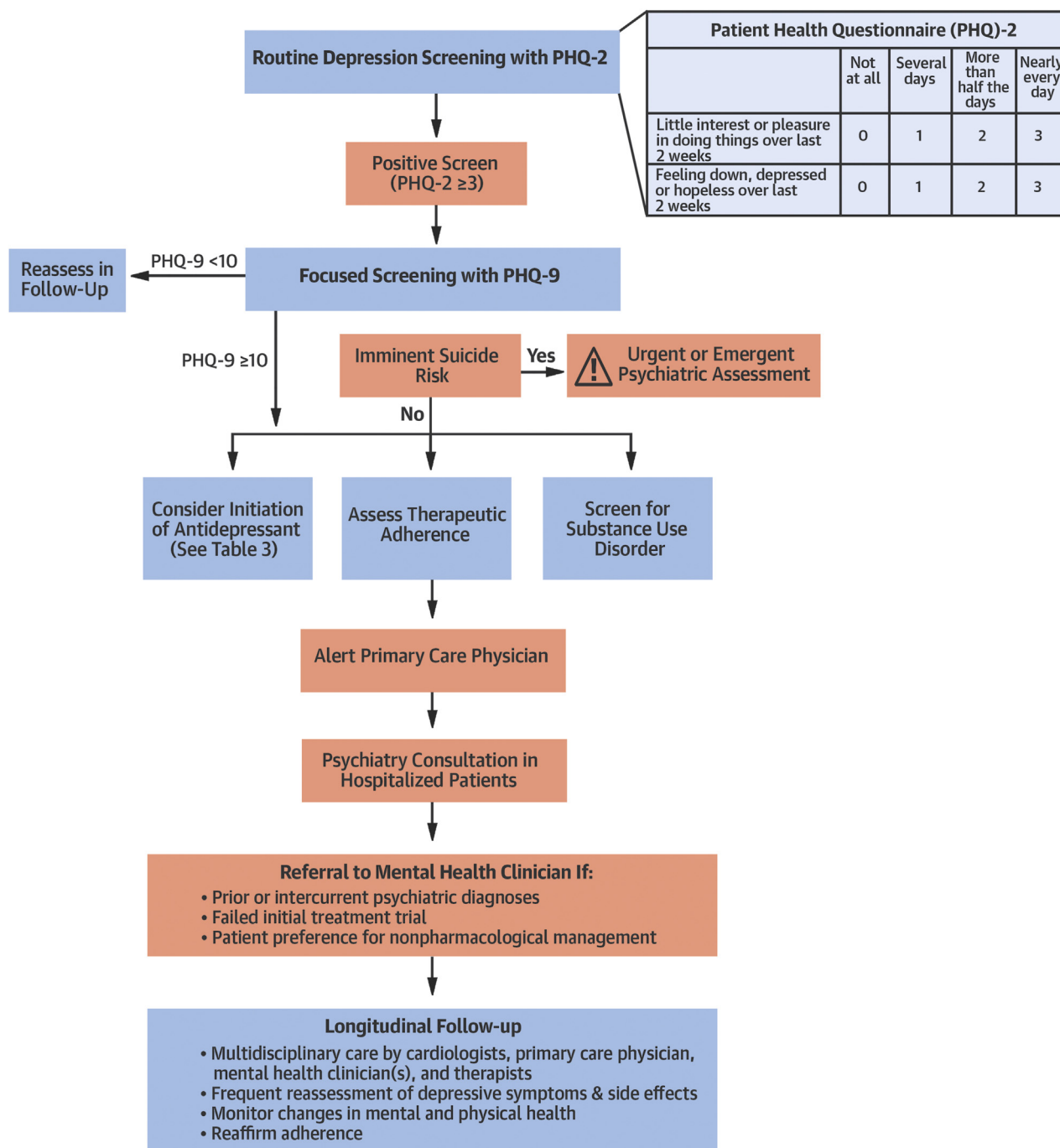
sensitivity and specificity of 74% and 91%, respectively, for the PHQ-9 ≥ 10 threshold (75).

The 2008 AHA guidelines recommend an earlier version of PHQ-2, which included yes/no options that can be verbally asked by physicians (78,79) as the first step followed by the full PHQ-9 for additional assessment. This 2-step algorithm (yes on either item of PHQ-2 Yes/No version and PHQ-9 ≥ 10) had low sensitivity (52%) but high specificity (91%) for detecting major depression in outpatients with CVD (80). Although standard screening tool cut-offs validated in general populations are currently endorsed, lower thresholds may be more applicable for patients with prevalent CVD. For instance, the optimal threshold for detection of major depression was PHQ-9 ≥ 8 (sensitivity 94% and specificity 84%) in outpatients with CAD (81), and PHQ-2 > 0 (sensitivity 95.6% and specificity 71.4%) and PHQ-9 ≥ 5 (sensitivity 95.6% and specificity 72.7%) (82) for inpatients with acute coronary syndromes (ACS).

Additional tools for screening of depression in patients with CVD are described in **Table 2**. The advantage of using these adjunctive tools over PHQ-2 is their use as baseline assessments of symptom severity to monitor subsequent improvement with antidepressant treatment. The Patient Reported Outcomes Measurement Information System (PROMIS) depression scale is publicly available and has been used to measure depressive symptom severity (83). However, its utility as a screening instrument and comparability with other established measures in patients with CVD have not been tested. Due to their ease of use, availability in multiple languages, and accessibility in the public domain, PHQ-2 and -9 appear to be the best tools currently available to screen for depression in patients with CVD.

HOW TO INTEGRATE DEPRESSION SCREENING IN CARDIOLOGY PRACTICES? The advances in health information technology that can incorporate self-report assessments in electronic health record systems can facilitate routine screening of depression in outpatient or inpatient settings (84,85). The 2-step PHQ-2 and -9 paradigm could be used where all patients are presented with PHQ-2; among those who screen positive, the questionnaire immediately expands to include the additional 7 items of PHQ-9 (84). To improve patient acceptability, cardiologists should discuss the importance of depression screening in patients with CVD prior to performing screening (84). Clinical decision support system tools such as “best practice alerts” (86) can be used to promote follow-up of positive depression screens or of those who may be at increased risk of suicide.

CENTRAL ILLUSTRATION Guideline-Supported Routine Depression Screening Pathway in Patients With Cardiovascular Disease



Jha, M.K. et al. J Am Coll Cardiol. 2019;73(14):1827-45.

Routine screening for depression using a 2-step process starting with the 2-item Patient Health Questionnaire (PHQ)-2 followed by focused screening with the 9-item PHQ-9 is recommended to minimize the burden on patients and systematically assess depressive symptoms, including suicidality (ninth item of PHQ-9). Management of those who screen positive for depression should incorporate a multidisciplinary team-based approach including primary care providers and mental health clinicians.

TABLE 2 Adjunctive Tools for Screening of Depression in Patients With CVD

Screening Tool	Cut-Off	Study Population	First Author (Ref. #)	Sample Size (n)	Sensitivity (%)	Specificity (%)
BDI	≥10	Cardiac inpatients	Forkmann et al. (87)	126	75.0	82.5
BDI	≥10	1-month post-MI	Strik et al. (88)	199	81.8	78.7
SCL-90	≥25	1-month post-MI	Strik et al. (88)	199	95.5	74.0
HAMD	≥15	1-month post-MI	Strik et al. (88)	206	86.4	93.2
HADS	≥13	1-month post-MI	Strik et al. (88)	179	90.0	84.3
HADS-D	≥4	1-month post-MI	Strik et al. (88)	179	85.0	74.8
HADS	≥13	Inpatients with ACS	Tesio et al. (89)	357	91.2	76.5
HADS	≥13	Inpatients with CAD	Tesio et al. (89)	260	84.4	80.9
HADS-D	≥4	Outpatients with CAD	Haddad et al. (81)	730	93.8	67.8
HADS-D	≥4	Recent ACS	Bambauer et al. (127)	79	96.0	25.0
HADS-D	≥4	Patients with CAD undergoing cardiac rehabilitation	Bunevicius et al. (128)	522	84.0	55.0
HADS	≥13	Patients with CAD undergoing cardiac rehabilitation	Bunevicius et al. (128)	522	82.0	75.0
BDI	≥14	Patients with CAD undergoing cardiac rehabilitation	Bunevicius et al. (128)	522	89.0	74.0
BDI	≥14	2 months post-ACS	Frasure-Smith et al. (129)	804	91.2	77.5
BDI	≥16	Patients with MI within 72 h of symptom onset	Huffman et al. (130)	131	88.2	92.1
BDI	≥10	2 weeks post-ACS	Low et al. (131)	119	100.0	75.0

BDI = Beck Depression Inventory; HAMD = Hamilton Rating Scale for Depression; HADS = Hospital Depression and Anxiety Scale; HADS-D = depression subscale of HADS; MI = myocardial infarction; SCL-90 = 90-item Symptom Check List (depression subscale); other abbreviations as in Table 1.

WHAT TO DO WITH A DEPRESSION SCREEN RESULT?

NEGATIVE SCREEN. Given variable sensitivity of depression screening instruments and the episodic nature of depression, a negative screen may not conclusively exclude the presence of depression. Rescreening for depression may be considered annually or on a more frequent basis in cases of stressful life events and/or changes in clinical condition, such as interval ACS and hospitalizations.

ADDITIONAL ASSESSMENTS FOR POSITIVE SCREEN. If the initial depression screen was performed with PHQ-2, full severity of depressive symptoms should be evaluated with PHQ-9 or other measures of depressive symptoms (8). Those who screen positive for depression should also be assessed for anxiety or substance use disorder (2) and other psychosocial risk factors that increase cardiovascular risk, including socioeconomic status, stressful life circumstance, social isolation, hostility/irritability, and other psychiatric disorders (61).

The specificity of depression screening questionnaires varies from 71% to 91% in patients with CVD (80,87–89). Thus, a positive screen for depression on a questionnaire should not be considered diagnostic of depression. Additionally, diagnosis of depression necessitates the exclusion of any lifetime manic or hypomanic episode as well as any other psychiatric or medical conditions that might account for these symptoms (90). Hence, additional diagnostic assessments with structured instruments or clinician

interviews guided by diagnostic checklist (91) should be conducted by the primary care or mental health providers working with the patient's cardiologist. Additionally, work-up is recommended to establish the diagnosis of depression by excluding other common psychiatric conditions (90), medical disorders (such as hypothyroidism, obstructive sleep apnea, and chronic fatigue syndrome) (90), or iatrogenic causes (such as interferon alpha [92]) (Table 3).

SUICIDE RISK ASSESSMENT. Among specific depressive symptoms, AHA emphasizes screening for the presence of suicidal ideation as measured by the ninth item of PHQ-9 (8). While AHA recommends immediate evaluation for acute suicidality, practical steps to follow-up on this recommendation were not provided (69). In a cross-sectional study of 1,976 patients with CVD, >14% reported suicidal ideation in the past 2 weeks (93). Although rapid evaluation of suicidality may be feasible in hospital settings, it may be considerably more challenging in the outpatient settings with limited access to mental health providers (68). Key factors to ascertain risk of suicide include the chronicity of symptoms to differentiate acute versus chronic risk, presence of passive (weary or tired of life, wishing to be dead, or feel better off dead than alive) versus active suicidal ideations (thinking about killing oneself or committing suicide), presence of any intent or plan to commit suicide, previous history of suicide attempt, presence of comorbid psychiatric disorders, and lack of protective factors (94). A simplified scheme for risk assessment is provided in Figure 2, which might

TABLE 3 Clinical Considerations for Initial Management of Patients With CVD Who Screen Positive for Depression

Clinical Consideration	Rationale	Rating Scales/Instruments
Self-reported assessments		
Anxiety	More than 75% of patients with depression have significant anxiety, which in turn is associated with worse antidepressant outcomes.	7-item Generalized Anxiety Disorder scale
Mania/hypomania	Patients with bipolar disorder who are currently depressed may screen positive with PHQ-2/PHQ-9.	Altman Self-Rated Mania Scale
Substance use	Patients with depression have 3× higher likelihood of drug use disorder.	Michigan Alcohol Screening Test, Drug Abuse Screening Test
Diagnostic assessment		
Major depressive episode per DSM-5	Presence of following 5 of 9 criterion symptoms (must include #1 or #2) during the same 2-week period nearly every day and represent change from previous functioning. 1. Sad/depressed mood 2. Anhedonia 3. Reduced/increased sleep 4. Reduced/increased weight or appetite 5. Poor concentration or impaired decision making 6. Fatigue or poor energy 7. Pessimism or excessive guilt 8. Psychomotor agitation/retardation 9. Suicidal ideations	Structured interviews or DSM-5 diagnostic checklist with recall of last 2 weeks. SIGECAPS mnemonic. Sleep disturbance Interest (diminished) Guilt or feeling worthless Energy (loss) Concentration difficulties or indecisiveness Appetite abnormality or weight change Psychomotor retardation or agitation Suicide or death (acts or thoughts of)
Rule out bipolar, psychotic, or other psychiatric disorder	Presence of MDE with any previous history of manic or hypomanic episode is diagnostic of bipolar disorder. Other primary psychiatric disorders as cause of MDE should be excluded.	Structured interview for lifetime manic/hypomanic episode, psychotic disorder, or other psychiatric disorders. Clinician use of DSM-5 diagnostic checklist for these disorders.
Exclude medical conditions	Hypothyroidism, obstructive sleep apnea, folate deficiency, anemia.	Laboratory tests.
Treatment initiation		
Pharmacotherapy	SSRIs are the first line of treatment due to favorable safety profile. MBC approach for improved outcomes.	Depression severity, side-effect rating, and adherence questionnaires at 2-week to 3-week intervals.
Psychotherapy	CBT has been shown to be effective in treatment of depression in patients with CVD.	Depression severity questionnaires every 2 to 3 weeks.
Exercise	Proven efficacious as treatment of CVD patients, especially those with heart failure.	Physical activity questionnaire.

CBT = cognitive behavioral therapy; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, fifth edition; MBC = measurement-based care; MDE = major depressive episode; other abbreviations as in Table 1.

be utilized if access to mental health clinicians is limited.

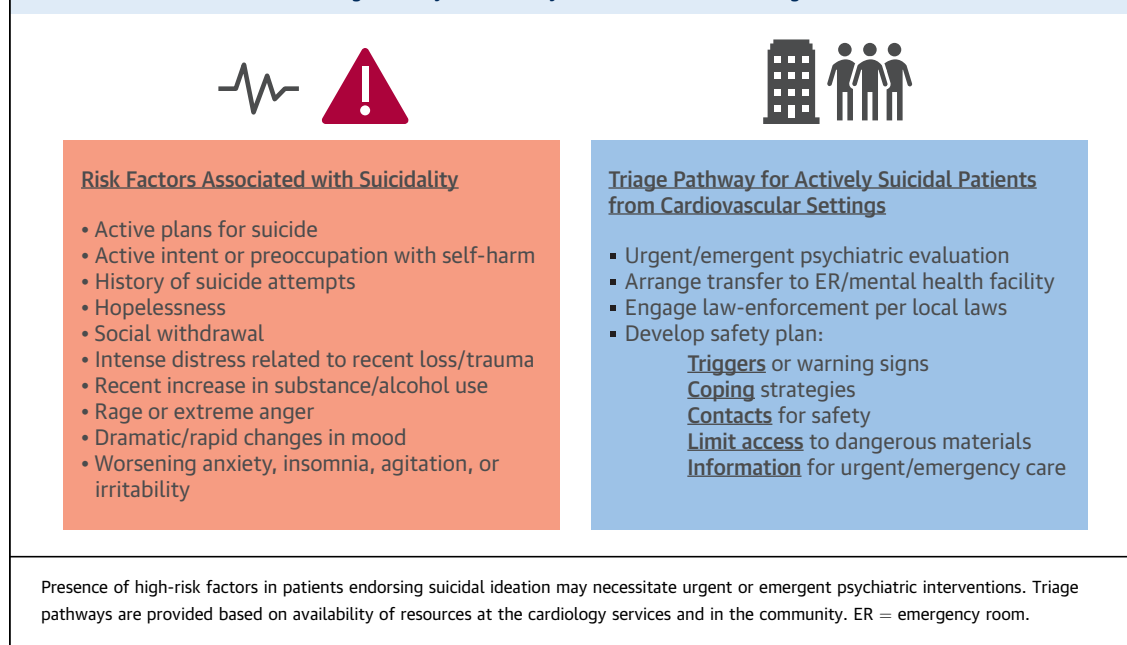
MANAGEMENT OF DEPRESSION IN PATIENTS WITH CVD

OVERVIEW. Antidepressant treatments, including pharmacotherapy, psychotherapy, and/or exercise, may relieve depressive symptoms and improve quality of life in patients with CVD (10–12,95,96). Medications that can either be used alone (selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], or other antidepressants) or to augment other therapies (such as second-generation antipsychotics [SGAs]) are listed in Table 4 (excluding tricyclic antidepressants or monoamine-oxidase inhibitors due to their unfavorable cardiovascular safety profile) (97).

EFFICACY OF PHARMACOTHERAPY. The SADHART (Sertraline Antidepressant Heart-Attack Randomized

Trial) randomized 369 patients with depression and recent ACS to either sertraline or placebo in a double-blind fashion for 24 weeks. Sertraline and placebo did not differ on changes in left ventricular ejection fraction (primary outcome), QT prolongation, and treatment-emergent increases in ventricular premature complexes. However, in the full randomized sample of this study, sertraline was superior to placebo in clinically-rated global improvement but not in reduction of Hamilton Rating Scale for Depression (HAMD) scores. In a prespecified subgroup of patients with any previous episodes of depression or with current severe depression (2 prior episodes plus HAMD ≥18), sertraline was superior to placebo in both clinically rated global improvement and reduction of HAMD scores (11). In a post hoc analysis of the ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) trial (n = 2,481), use of antidepressant medications, especially SSRIs, was associated with reduced risk of death or recurrent MI in patients

FIGURE 2 Risk Factors and Initial Triage Pathway for Suicidality in Cardiovascular Care Settings



with depression and low perceived social support after MI over 4-year follow-up (10). However, this beneficial effect was not based upon patients being randomized to antidepressant therapy; thus, the causal relationship between antidepressants and improved survival benefits in this study cannot be attributed to antidepressant therapy alone. The beneficial effects of SSRIs in patients with CVD were further supported in a recent trial with smaller sample ($n = 300$) but longer follow-up (median 8.1 years), escitalopram reduced major adverse cardiac events compared with placebo (40.9% vs. 53.6%) over 24 weeks after ACS (12). In another study of post-MI patients with depression ($n = 331$), any antidepressant treatment (pharmacotherapy or non-pharmacotherapy) was associated with lower rates of all-cause mortality (98). Longer-courses of antidepressant medications may be necessary in CVD patients, as suggested by a small study ($n = 54$), where fluoxetine had higher rates of response ($>50\%$ reduction in depressive symptoms) than placebo after 25 weeks but not after 9 weeks of treatment (99). Prolonged course (>6 months) of SSRI monotherapy is also effective in reducing depression severity and improving quality of life in post-CABG patients (100). Taken together, these data suggest that prolonged courses of antidepressant medications, especially SSRIs, may be effective in safely reducing the severity of depressive symptoms in post-ACS patients.

Utility of SSRIs in patients with heart failure is less established. In SADHART-CHF, sertraline did not

improve depression compared with placebo and did not increase adverse cardiovascular events (101). Similarly, compared with placebo, 18-month treatment with escitalopram did not reduce cardiovascular events or depressive symptom severity, but did carry an acceptable cardiovascular safety profile (102). **EFFICACY OF NONPHARMACOLOGICAL TREATMENTS.** Evidence-based psychotherapy, such as cognitive behavioral therapy (CBT), has been shown to be superior to usual care in reducing depressive symptom severity in patients with heart failure and depression (96). Similarly, CBT with or without antidepressant medication is effective in reducing depression severity in post-CABG patients (103). In a post hoc analysis of the ENRICH trial, reduction in depression severity was associated with improved survival only in those in the intervention arm (CBT plus antidepressant treatment) (29). Improved survival in the usual care arm was unrelated to change in depression severity.

Exercise is also an effective antidepressant therapy in patients with CVD and depression. In a randomized clinical trial, 4-month treatment with supervised group-aerobic exercise ($n = 37$) and sertraline ($n = 40$) were both superior to placebo ($n = 24$) in reducing severity of depressive symptoms (104). Exercise has also been shown to be effective in chronic heart failure ($n = 2,322$) in reducing composite death or any-cause hospitalization and self-rated depression severity after 3 and 12 months (105). In a secondary analysis of the ENRICH study, patients with depression who

TABLE 4 Pharmacotherapy for the Management of Depression in Patients With CVD

Drug	Daily Dose	Common Side-Effects	Cardiovascular Side-Effects and Drug Interactions
SSRIs			Class effects: Increased risk of bleeding, use with caution in patients on anticoagulants or aspirin, and potential for severe hyponatremia with thiazide diuretic agents
Fluoxetine	Initial: 20 mg Target: 20-80 mg	Abnormal dreams, abnormal ejaculation, anorexia, anxiety, diarrhea, dry mouth, dyspepsia, flu syndrome, impotence, insomnia, decreased libido, nausea, nervousness, pharyngitis, rash, sinusitis, somnolence, increased sweating, tremor	Vasodilatation and reduced metabolism of beta-blockers and certain antiarrhythmic agents (flecainide, lidocaine, mexiletine, and propafenone)
Citalopram	Initial: 20 mg Target: 20-40 mg	Dry mouth, nausea, somnolence, abnormal ejaculation, decreased libido, orgasmic disturbance	QTc prolongation, tachycardia, hypotension, postural hypotension, and reduced metabolism of beta-blockers and certain antiarrhythmic agents (flecainide, lidocaine, mexiletine, and propafenone)
Escitalopram	Initial: 10 mg Target: 10-20 mg	Insomnia, abnormal ejaculation, nausea, increased sweating, fatigue, somnolence, decreased libido, orgasmic disturbance	Hypertension, palpitation, and reduced metabolism of beta-blockers and certain antiarrhythmic agents (flecainide, lidocaine, mexiletine, and propafenone)
Paroxetine	Initial: 20 mg (immediate release), 25 mg (controlled release) Target: 20-50 mg (immediate release), 25.0-62.5 mg (controlled release)	Nausea, diarrhea, constipation, somnolence, insomnia, decreased libido, abnormal ejaculation, orgasmic disturbance	Reduced metabolism of CYP 1A2 substrates (clopidogrel, warfarin, mexiletine, propranolol, triamterene, and verapamil)
Sertraline	Initial: 50 mg Target: 50-200 mg	Nausea, diarrhea, dyspepsia, tremor, decreased appetite, increased sweating, abnormal ejaculation, decreased libido	Reduced metabolism of CYP 2D6 substrates at higher doses (flecainide, propafenone)
SNRIs			Class effects: Hypertension, tachycardia, increased risk of bleeding, use with caution in patients on anticoagulants or aspirin, and potential for hyponatremia with thiazide diuretic agents
Venlafaxine	Initial: 75 mg Target: 150-375 mg	Insomnia, nervousness, weight loss, nausea, abnormal ejaculation, abnormal dreams, increased sweating	Sustained hypertension at doses >300 mg/day, cholesterol elevation, and orthostatic hypotension
Desvenlafaxine	Initial: 50 mg Target: 50 mg	Nausea, dizziness, insomnia, increase sweating, constipation, somnolence, reduced appetite, anxiety, and sexual dysfunction	Cholesterol and triglyceride elevation, and orthostatic hypotension in patients ≥65 years of age
Duloxetine	Initial: 40-60 mg Target: 60-120 mg	Nausea, dry mouth, somnolence, fatigue, constipation, reduced appetite, increased sweating	Orthostatic hypotension and reduced metabolism of beta-blockers and certain anti-arrhythmic agents (flecainide, lidocaine, mexiletine, and propafenone)
Levomilnacipran	Initial: 20 mg Target: 40-120 mg	Nausea, constipation, increased sweating, vomiting, erectile dysfunction	Palpitations

Continued on the next page

reported adherence to regular physical exercise 6 months after acute MI had 38% to 52% lower rates of fatal events or nonfatal MI over 4 years compared with those nonadherent to regular exercise (45).

Cardiac rehabilitation after ACS is associated with both improvement in depressive symptoms and lower mortality. In a prospective observational study of 522 patients with recent ACS and depression, completion of cardiac rehabilitation was associated with a 73% lower mortality and 63% lower depressive symptoms compared with patients not completing rehabilitation (106). In a recent Cochrane review, exercise-based cardiac rehabilitation was superior to no-exercise controls in reducing cardiovascular mortality and rates of hospitalization and in improving quality of life in patients with CVD (107). Thus, cardiac

rehabilitation should be encouraged in patients with depression and CVD (108). As depression may prevent patients with CVD from initiating or continuing with cardiac rehabilitation, psychosocial interventions and coaching strategies using telephone and social media are being investigated to engage patients (109,110).

EFFICACY OF STEPPED-CARE OR COMBINATION APPROACHES. A stepped-care approach that utilizes initial treatment choice (pharmacotherapy and/or problem-solving psychotherapy) per patient preference with active changes in treatment every 6 to 8 weeks has been shown to reduce both the severity of depressive symptoms (111) and rates of major adverse cardiac events (112). In a study of patients with CAD (n = 284), 12-week treatment with

TABLE 4 Continued

Drug	Daily Dose	Common Side-Effects	Cardiovascular Side-Effects and Drug Interactions
Others			
Bupropion	Initial: 150 mg Target: 300-450 mg	Dry mouth, nausea, insomnia, dizziness, increased sweating	Palpitations, reduced metabolism of beta-blockers and certain antiarrhythmic agents (flecainide, lidocaine, mexiletine, and propafenone), and decreased plasma concentration of digoxin
Mirtazapine	Initial: 15 mg Target: 15-45 mg	Somnolence, weight gain, dizziness	Orthostatic hypotension, hypertension, enhanced activity of warfarin, and potential for hyponatremia with thiazide diuretic agents
Trazodone	Initial: 150 mg (1 time for extended release, divided for immediate release) Target: 150-375 mg (extended release), 300-500 mg (immediate release)	Somnolence, dizziness, blurred vision, constipation, priapism	Orthostatic hypotension, QTc prolongation, increased risk of bleeding, use with caution in patients on anticoagulants or aspirin, and increased level of digoxin
Nefazodone	Initial: 100 mg twice daily Target: 150-300 mg twice daily	Life-threatening hepatotoxicity, priapism, nausea, constipation, somnolence, dizziness, blurred vision	Orthostatic hypotension, sinus bradycardia, reduced metabolism of CYP3A4 substrates (apixaban, edoxaban, prasugrel, rivaroxaban, ticagrelor, amlodipine, diltiazem, felodipine, verapamil, atorvastatin, simvastatin), and increased levels of digoxin
Vilazodone	Initial: 10 mg Target: 40 mg (10 mg dose increment each week)	Diarrhea, nausea, vomiting, insomnia	Increased risk of bleeding, use with caution in patients on anticoagulants or aspirin
Vortioxetine	Initial: 10 mg Target: 10-20 mg	Nausea, vomiting, constipation	Increased risk of bleeding, use with caution in patients on anticoagulants or aspirin, and potential for severe hyponatremia with thiazide diuretic agents
SGAs			
Olanzapine	Initial: 5 mg Target: 5-20 mg	Weight gain, constipation, dizziness, dry mouth, somnolence, increased appetite	Hyperglycemia, QTc prolongation, hyperlipidemia, orthostatic hypotension, tachycardia, hypertension, and enhanced effect of antihypertensive drugs
Quetiapine	Initial: 50 mg Target: 150-300 mg	Somnolence, dry mouth, constipation, dizziness, increased appetite, dyspepsia, weight gain, fatigue, dysarthria, and nasal congestion	Hyperglycemia, hyperlipidemia, orthostatic hypotension, tachycardia, hypertension, and enhanced effect of antihypertensive drugs
Aripiprazole	Initial: 2.5 mg Target: 5-15 mg	Akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision	Dyslipidemia, orthostatic hypotension, bradycardia, palpitations, and enhanced effect of antihypertensive drugs by alpha adrenergic antagonism
Brexpiprazole	Initial: 0.5-1.0 mg Target: 2-3 mg	Weight gain, akathisia, increased cortisol, restlessness	Dyslipidemia and orthostatic hypotension
CVD = cardiovascular disease; SGA = second-generation antipsychotic; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.			

citalopram was superior to placebo in reducing depressive symptom severity, but the addition of interpersonal therapy over clinical management did not result in any significant improvement (113).

EFFICACY OF COLLABORATIVE CARE APPROACH.

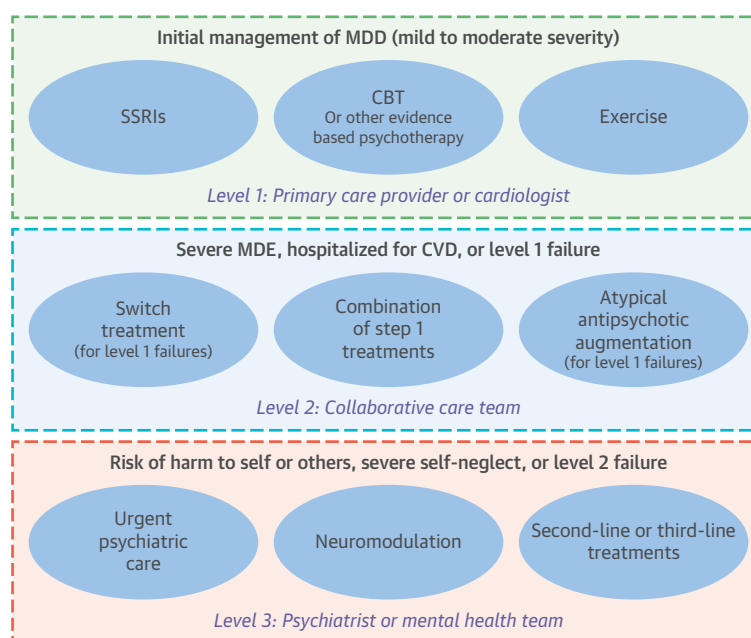
Involvement of support staff (such as care managers) to coordinate assessment and facilitate in-hospital collaborative care of depression and early post-discharge follow-up has been shown to significantly improve mental health outcomes and reduction in CVD-specific symptoms compared with usual care in CVD patients admitted to inpatient cardiac units (114,115) and in those with post-CABG depression (116). In a study of 392 patients with heart failure, the collaborative care approach was associated with fewer deaths in all patients and greater improvement in depression severity in those who screened positive

at the time of treatment initiation (95). In another study embedded within an academic center, although collaborative care was associated with lower all-cause mortality, there was no significant difference in depression outcomes between patients with CVD receiving collaborative care or usual care (117).

ADVERSE EFFECTS OF PHARMACOTHERAPY.

Anti-depressant medications may be associated with a wide range of cardiovascular adverse effects (Table 4) (97). The use of antidepressant medications in patients with CVD has not been associated with increased mortality, especially after controlling for the presence of depressive symptoms (97,118,119). All SSRIs cause some degree of QT-interval prolongation, with the risk being greatest with citalopram (97), prompting U.S. and European regulatory warnings in 2011 advising against the prescription of citalopram at

FIGURE 3 Sequenced Approach to Management of Depression in Patients with CVD



A sequenced treatment approach that considers the severity of illness and availability of resources is recommended for management of depression in patients with cardiovascular disease (CVD). While initial treatment with antidepressant medications (selective serotonin reuptake inhibitors [SSRIs]), psychotherapy (cognitive behavioral therapy [CBT]), or exercise can be started by primary care physicians or cardiologists, higher levels of care, including collaborative care team (level 2) or psychiatric experts (level 3), should be reserved for patients who are severely ill or who have failed treatments at lower levels of care. Neuromodulation includes treatments such as electroconvulsive therapy and repetitive transcranial magnetic stimulation. MDE = major depressive episode.

doses >40 mg/day. Use of SNRIs is associated with an increased risk of hypertension, especially at higher doses (97). All tricyclic antidepressants cause significant QT interval prolongation, increase the risk for ventricular arrhythmias, and should be avoided in patients with CVD (97). Similarly, trazodone and nefazodone should be avoided due to QT prolongation and risk for ventricular arrhythmias. Antidepressant medications are also subject to significant drug-drug interactions with medications commonly used to treat CVD (Table 4) (97). For instance, monoamine oxidase inhibitors should be avoided due to significant drug-drug interactions with certain cardiovascular therapies and increased risk of hypertension. Antidepressants, when discontinued, may cause withdrawal symptoms that are typically mild and can be remembered easily with the *FINISH* mnemonic: “Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (anxiety/agitation)” (120). These symptoms are most common with paroxetine and least common with fluoxetine among SSRIs (120). Additionally, SGAs (quetiapine, olanzapine, aripiprazole, and

brexipiprazole) are associated with a broad range of adverse cardiovascular effects, including stroke, sudden cardiac death, hypertension, QT prolongation, and orthostatic hypotension (121,122). Use of quetiapine and olanzapine are also associated with obesity and dyslipidemia, which can further increase cardiometabolic risk (122).

ROLE OF CARDIOLOGIST AND PRIMARY CARE PROVIDERS IN MANAGEMENT OF DEPRESSION.

Cardiologists may already be assessing and managing depression in their patients, as suggested by a national survey of 796 cardiologists (123); 55.5% felt comfortable with making a diagnosis of depression and 49.2% reported that they personally treat depression in their patients (123). Primary care providers may offer a vital link in initial management of antidepressant treatment in outpatients with CVD, especially in areas with limited mental health resources (68), as remission rates were identical in primary care clinics (n = 1,091; remission = 26.6%) and psychiatric care clinics (n = 1,785; remission = 28.0%) in a study of treatment-seeking depressed outpatients (124).

RECOMMENDATIONS. Pharmacotherapy with SSRIs or nonpharmacological treatments (such as CBT or exercise) may be considered as first-line treatment of depression in patients with ACS. In patients with heart failure, CBT and/or exercise may be preferred as utility of SSRIs is not well established. When indicated, use of SSRIs is preferred over SNRIs due to lower likelihood of hypertension and tachycardia (97). However, the role of SNRIs as antidepressant treatments has not been adequately examined in patients with CVD (97). While bupropion has been studied for its role in smoking cessation, it has not been studied as an antidepressant in nonsmokers with CVD (125). Similarly, while SGAs are effective in improving depression severity, their efficacy has not been studied systematically in patients with CVD (126).

A multidisciplinary approach should be considered for management of depression in patients with CVD. This approach may involve cardiologists working closely with primary care providers for the initial management of depression that is mild to moderate in severity. When available, care coordinators should facilitate management of depression using the collaborative care approach. Early referral to mental health specialists should be considered in the following circumstances: imminent risk of harm to self or others, hospitalized patients with CVD and depression, patient preference for nonpharmacological management, or outpatients with CVD who could not be adequately managed by their primary care physician, have treatment resistant depression, or have comorbid psychiatric disorders. A sequenced treatment approach is presented in **Figure 3** with recommendations to reassess levels of care at periodic intervals to ensure adequacy of treatment (111,112,114,116).

CONCLUSIONS

Depression represents a common comorbidity in patients with a broad range of cardiovascular conditions and identifies patients at heightened risk of short- and

long-term adverse cardiovascular events, excess health care expenditures, and adverse quality of life. Screening for depression utilizing standardized and guideline-supported simple questionnaires can be efficiently integrated into cardiovascular practices and should be routinely considered in patients with CVD. Although SSRIs are considered safe and effective first-line treatment for depression in most patients with CVD, nonpharmacological approaches may be more appropriate for patients with heart failure where the superiority of SSRIs is not well established. Clinicians should be mindful of polypharmacy, treatment adherence challenges, and potential for adverse drug-drug interactions in patients with depression and CVD. While studies of antidepressant treatments so far have focused on measures of depressive symptom severity or adverse cardiovascular events, future studies should also evaluate patient-centered outcomes such as quality of life and functional improvement. Future randomized clinical trials comparing different pharmacological and nonpharmacological approaches may further our understanding of personalized care plans for individual patients with CVD and depression. Cardiologists represent an important node of patient entry and identification in the multidisciplinary care model (involving primary care physicians, mental health clinicians, therapists, social workers, pharmacists, and care coordinators) in the comprehensive management of patients with depression. Similar to other chronic cardiometabolic conditions, depression has emerged as a prevalent, clinically important, and potentially modifiable risk factor of CVD.

ADDRESS FOR CORRESPONDENCE: Dr. James W. Murrough, Depression and Anxiety Center for Discovery and Treatment, Department of Psychiatry, and Department of Neuroscience, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1230, New York, New York 10029. E-mail: james.murrough@mssm.edu. Twitter: @IcahnDAC, @AqamarMD, @mvaduganathan, @JMurrough.

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