JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 14, 2019

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Screening and Management of Depression in Patients With Cardiovascular Disease

JACC State-of-the-Art Review

Manish K. Jha, MD,[a] Arman Qamar, MD,[b,c] Muthiah Vaduganathan, MD, MPH,[d] Dennis S. Charney, MD,[a,e] James W. Murrough, MD, PhD[a]

JACC JOURNAL CME/MOC/ECME

This article has been selected as the month's *JACC* CME/MOC/ECME activity, available online at http://www.acc.org/jacc-journals-cme by selecting the *JACC* Journals CME/MOC/ECME tab.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 Medical Knowledge MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Screening and Management of Depression in Patients With Cardiovascular Disease: *JACC* State-of-the-Art Review will be accredited by the European Board for Accreditation in Cardiology (EBAC) for 1 hour of External CME credits. Each participant should claim only those hours of credit that have actually been spent in the educational activity. The Accreditation Council for Continuing Medical Education (ACCME) and the European Board for Accreditation in Cardiology (EBAC) have recognized each other's accreditation systems as substantially equivalent. Apply for credit through the post-course evaluation. While offering the credits noted above, this program is not intended to provide extensive training or certification in the field.

Method of Participation and Receipt of CME/MOC/ECME Certificate

To obtain credit for *JACC* CME/MOC/ECME, you must:

1. Be an ACC member or *JACC* subscriber.
2. Carefully read the CME/MOC/ECME-designated article available online and in this issue of the *Journal*.
3. Answer the post-test questions. A passing score of at least 70% must be achieved to obtain credit.
4. Complete a brief evaluation.
5. Claim your CME/MOC/ECME credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

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.

CME/MOC/ECME Editor Disclosure: *JACC* CME/MOC/ECME Editor Ragavendra R. Baliga, MD, FACC, has reported that he has no financial relationships or interests to disclose.

Author Disclosures: Dr. Jha has received contract research grants from Janssen Research and Acadia Pharmaceuticals. Dr. Qamar is supported by the National Heart, Lung, and Blood Institute T32 postdoctoral training grant (T32HL007604) and the American Heart Association Strategically Focused Research Network in Vascular Disease grant (18SFRN3390085). Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541); and has served on advisory boards for AstraZeneca, Bayer AG, and Baxter Healthcare. Dr. Charney has the following patents: U.S. 9,592,207, Intranasal Administration of Ketamine to Treat Depression (issued March 14, 2017), U.S. 9,539,220, Methods for Treating Suicidal Ideation (issued January 10, 2017), and U.S. 8,785,500, Intranasal Administration of Ketamine to Treat Depression (issued July 22, 2014), all licensed to Janssen Pharmaceuticals; WO 2016/049234, Systems and Methods for Treating a Psychiatric Disorder licensed to

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Depression 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; [b]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [c]Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [d]Heart & Vascular Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and the [e]Office of the Dean, Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Jha has received contract

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.01.041

Click Therapeutics; U.S. Serial No. 14/783,686 and related foreign patent applications, Ketamine as a Rapid Treatment for Post-Traumatic Stress Disorder (PTSD) (pending); U.S. Serial No. 14/889,746 and related foreign patent applications, Intranasal Neuropeptide Y (NPY) for the Treatment of Mood and Anxiety Disorders (pending); WO 2016/172672, Method of Reducing Risk of Suicidal Ideations with Combined Ketamine/Lithium Therapy (pending); and U.S. Serial No. 15/379,013 and U.S. Serial No. 15/417,689, Intranasal Administration of Ketamine to Treat Depression (continuation patent applications in the same patent family as issued U.S. Patents 8,785,500 and U.S. 9,539,220 and U.S. 9,592,207, pending). Dr. Murrough has provided consultation services in the past 5 years to FSV7, Boehringer Ingelheim, Sage Therapeutics, Novartis, Allergan, Fortress Biotech, Janssen Research and Development, Genentech, MedAvante-Prophase, and Global Medical 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).

Medium of Participation: Print (article only); online (article and quiz).

CME/MOC/ECME Term of Approval

Issue Date: April 16, 2019
Expiration Date: April 15, 2020

---

research grants from Janssen Research and Acadia Pharmaceuticals. Dr. Qamar is supported by the National Heart, Lung, and Blood Institute T32 postdoctoral training grant (T32HL007604) and the American Heart Association Strategically Focused Research Network in Vascular Disease grant (18SFRN3390085). Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst (NIH/NCATS Award UL 1TR002541); and has served on advisory boards for AstraZeneca, Bayer AG, and Baxter Healthcare. Dr. Charney has the following patents: U.S. 9,592,207, Intranasal Administration of Ketamine to Treat Depression (issued March 14, 2017), U.S. 9,539,220, Methods for Treating Suicidal Ideation (issued January 10, 2017), and U.S. 8,785,500, Intranasal Administration of Ketamine to Treat Depression (issued July 22, 2014), all licensed to Janssen Pharmaceuticals; WO 2016/049234, Systems and Methods for Treating a Psychiatric Disorder licensed to Click Therapeutics; U.S. Serial No. 14/783,686 and related foreign patent applications, Ketamine as a Rapid Treatment for Post-Traumatic Stress Disorder (PTSD) (pending); U.S. Serial No. 14/889,746 and related foreign patent applications, Intranasal Neuropeptide Y (NPY) for the Treatment of Mood and Anxiety Disorders (pending); WO 2016/172672, Method of Reducing Risk of Suicidal Ideations with Combined Ketamine/Lithium Therapy (pending); and U.S. Serial No. 15/379,013 and U.S. Serial No. 15/417,689, Intranasal Administration of Ketamine to Treat Depression (continuation patent applications in the same patent family as issued U.S. Patents 8,785,500 and U.S. 9,539,220 and U.S. 9,592,207, pending). Dr. Murrough has provided consultation services in the past 5 years to FSV7, Boehringer Ingelheim, Sage Therapeutics, Novartis, Allergan, Fortress Biotech, Janssen Research and Development, Genentech, MedAvante-Prophase, and Global Medical 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).

Manuscript received November 18, 2018; revised manuscript received January 2, 2019, accepted January 2, 2019.

Screening and Management of Depression in Patients With Cardiovascular Disease

JACC State-of-the-Art Review

Manish K. Jha, MD,[a] Arman Qamar, MD,[b,c] Muthiah Vaduganathan, MD, MPH,[d] Dennis S. Charney, MD,[a,e] James W. Murrough, MD, PhD[a]

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)

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 lifestyle 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.

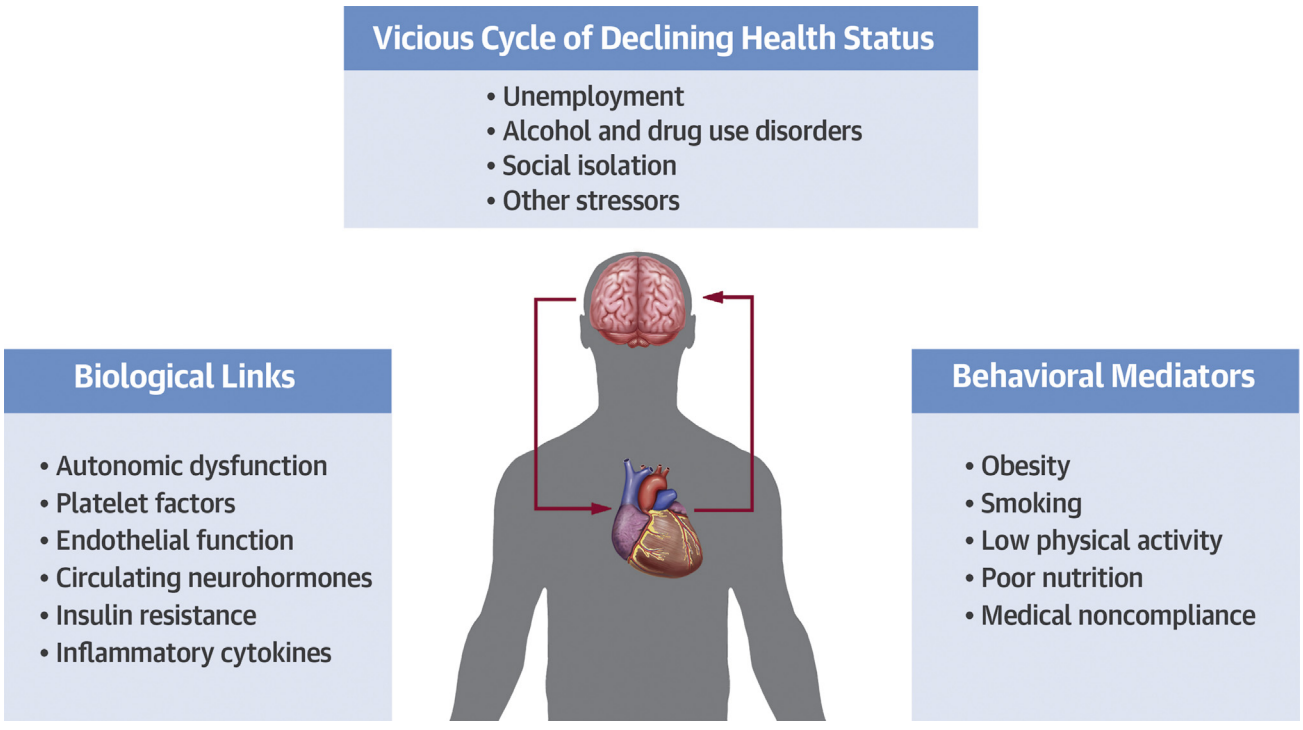
BIOLOGICAL LINKS BETWEEN DEPRESSION AND CVD

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-1β and -6, tumor necrosis factor-alpha, 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).

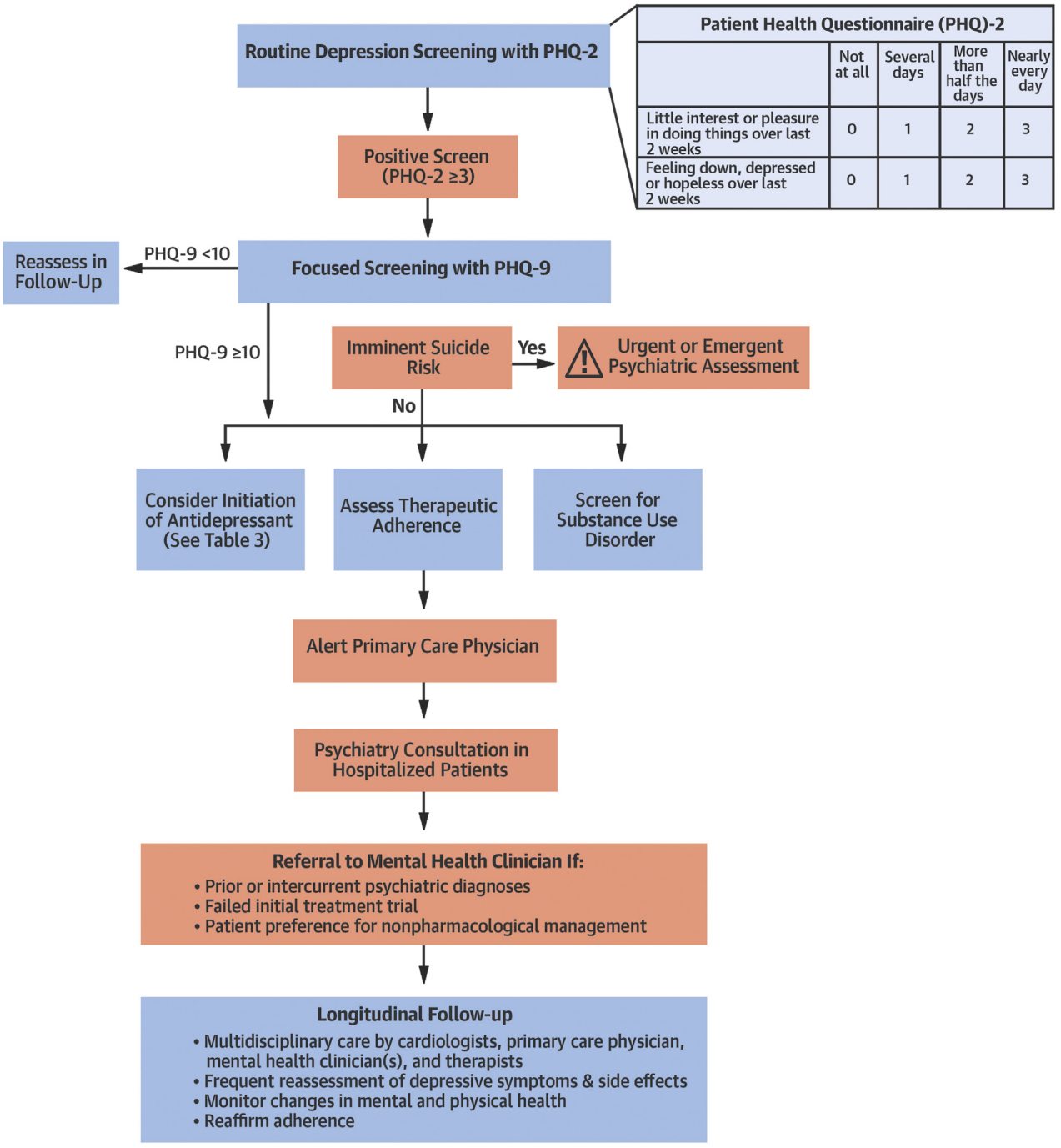
WHAT ARE THE TOOLS FOR DEPRESSION SCREENING? The PHQ-2 is a self-report questionnaire that is commonly used for screening of depression (8,74). The 2 items (sad mood and anhedonia) of this scale are rated from 0 to 3 with total score ranging from 0 to 6 (74). Positive screen on PHQ-2 has been defined 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**



Patient Health Questionnaire (PHQ)-2

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things over last 2 weeks	0	1	2	3
Feeling down, depressed or hopeless over last 2 weeks	0	1	2	3

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. **S**leep disturbance **I**nterest (diminished) **G**uilt or feeling worthless **E**nergy (loss) **C**oncentration difficulties or indecisiveness **A**ppetite abnormality or weight change **P**sychomotor retardation or agitation **S**uicide 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

Risk Factors Associated with Suicidality

- Active plans for suicide
- Active intent or preoccupation with self-harm
- History of suicide attempts
- Hopelessness
- Social withdrawal
- Intense distress related to recent loss/trauma
- Recent increase in substance/alcohol use
- Rage or extreme anger
- Dramatic/rapid changes in mood
- Worsening anxiety, insomnia, agitation, or irritability

Triage Pathway for Actively Suicidal Patients from Cardiovascular Settings

- Urgent/emergent psychiatric evaluation
- Arrange transfer to ER/mental health facility
- Engage law-enforcement per local laws
- Develop safety plan:
  - Triggers or warning signs
  - Coping strategies
  - Contacts for safety
  - Limit access to dangerous materials
  - Information for urgent/emergency care

Presence of high-risk factors in patients endorsing suicidal ideation may necessitate urgent or emergent psychiatric interventions. Triage pathways are provided based on availability of resources at the cardiology services and in the community. ER = emergency room.

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 ENRICHD 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 ENRICHD 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

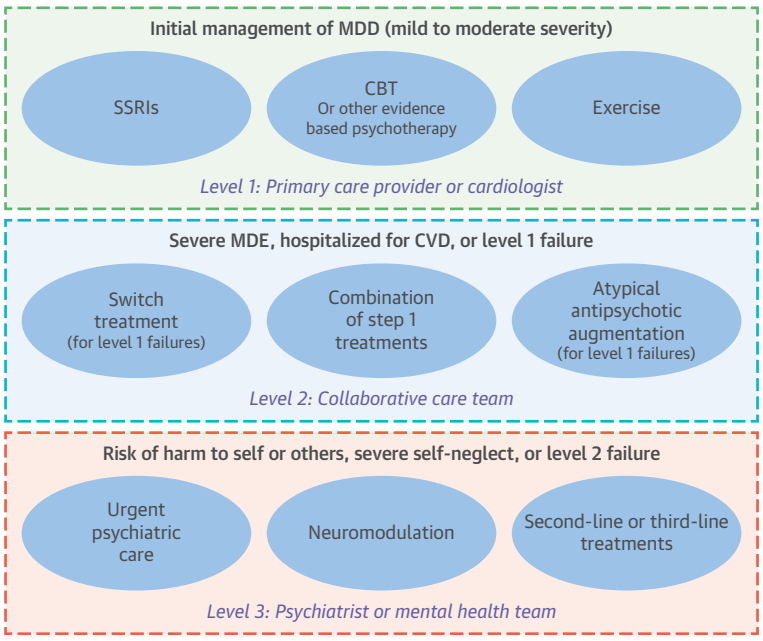
CVD = cardiovascular disease; SGA = second-generation antipsychotic; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

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. Antidepressant 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: "*F*lu-like symptoms, *I*nsomnia, *N*ausea, *I*mbalance, *S*ensory disturbances, and *H*yperarousal (anxiety/agitation)" (120). These symptoms are most common with paroxetine and least common with fluoxetine among SSRIs (120). Additionally, SGAs (quetiapine, olanzapine, aripiprazole, and brexpiprazole) 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 maybe 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.

REFERENCES

1. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211–59.

2. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry 2018;75:336–46.

3. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2017;16:163–80.

4. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.

5. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: Results from the national comorbidity survey replication (NCS-R). JAMA 2003;289:3095–105.

6. Huffman JC, Smith FA, Blais MA, Beiser ME, Januzzi JL, Fricchione GL. Recognition and treatment of depression and anxiety in patients with

acute myocardial infarction. Am J Cardiol 2006;98:319–24.

7. Siu AL, for the U.S. Preventive Services Task Force. Screening for depression in adults: U.S. Preventive Services Task Force recommendation statement. JAMA 2016;315:380–7.

8. Lichtman JH, Bigger JT Jr., Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation 2008;118:1768–75.

9. Bhattacharjee S, Goldstone L, Vadiei N, Lee JK, Burke W. Depression screening patterns, predictors, and trends among adults without a depression diagnosis in ambulatory settings in the United States. Psychiatr Serv 2018;69:1098–100.

10. Berkman LF, Blumenthal J, Burg M, et al. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. JAMA 2003;289:3106–16.

11. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.

12. Kim J, Stewart R, Lee Y, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. JAMA 2018;320:350–8.

13. Ziegelstein RC. Depression in patients recovering from a myocardial infarction. JAMA 2001;286:1621–7.

14. Thombs BD, Bass EB, Ford DE, et al. Prevalence of depression in survivors of acute myocardial infarction. Gen Intern Med 2006;21:30–8.

15. 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;358:1766–71.

16. Grenon SM, Hiramoto J, Smolderen KG, Vittinghoff E, Whooley MA, Cohen BE. Association between depression and peripheral artery disease: insights from the heart and soul study. J Am Heart Assoc 2012;1:e002667.

17. McDermott MM, Greenland P, Guralnik JM, et al. Depressive symptoms and lower extremity functioning in men and women with peripheral arterial disease. J Gen Intern Med 2003;18:461–7.

18. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 2006;48:1527–37.

19. Freedland KE, Rich MW, Skala JA, Carney RM, Davila-Roman VG, Jaffe AS. Prevalence of depression in hospitalized patients with congestive heart failure. Psychosom Med 2003;65:119–28.

20. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87:488–93.

21. Bilge AK, Ozben B, Demircan S, Cinar M, Yilmaz E, Adalet K. Depression and anxiety status of patients with implantable cardioverter defibrillator and precipitating factors. Pacing Clin Electrophysiol 2006;29:619–26.

22. Kamphuis HC, de Leeuw JR, Derksen R, Hauer RN, Winnubst JA. Implantable cardioverter defibrillator recipients: quality of life in recipients with and without ICD shock delivery: a prospective study. Europace 2003;5:381–9.

23. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. Circulation 1996;93:1976–80.

24. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int J Geriatr Psychiatry 2007;22:613–26.

25. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. Gen Hosp Psychiatry 2011;33:203–16.

26. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J 2006;27:2763–74.

27. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995;91:999–1005.

28. Bush DE, Ziegelstein RC, Tayback M, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. Am J Cardiol 2001;88:337–41.

29. Carney RM, Blumenthal JA, Freedland KE, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. Psychosom Med 2004;66:466–74.

30. Saur CD, Granger BB, Muhlbaier LH, et al. Depressive symptoms and outcome of coronary artery bypass grafting. Am J Crit Care 2001;10:4–10.

31. Smolderen KG, Safley DM, House JA, Spertus JA, Marso SP. Percutaneous transluminal angioplasty: association between depressive symptoms and diminished health status benefits. Vasc Med 2011;16:260–6.

32. Cherr GS, Wang J, Zimmerman PM, Dosluoglu HH. Depression is associated with worse patency and recurrent leg symptoms after lower extremity revascularization. J Vasc Surg 2007;45:744–50.

33. Cherr GS, Zimmerman PM, Wang J, Dosluoglu HH. Patients with depression are at increased risk for secondary cardiovascular events after lower extremity revascularization. J Gen Intern Med 2008;23:629–34.

34. Frasure-Smith N, Lesperance F, Habra M, et al. Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure. Circulation 2009;120:134–40. 3p following 140.

35. Jiang W, Alexander J, Christopher E, et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. Arch Intern Med 2001;161:1849–56.

36. Sherwood A, Blumenthal JA, Trivedi R, et al. Relationship of depression to death or hospitalization in patients with heart failure. Arch Intern Med 2007;167:367–73.

37. Jani BD, Mair FS, Roger VL, Weston SA, Jiang R, Chamberlain AM. Comorbid Depression and Heart Failure: A Community Cohort Study. PloS One 2016;11:e0158570.

38. Himelhoch S, Weller WE, Wu AW, Anderson GF, Cooper LA. Chronic medical illness, depression, and use of acute medical services among Medicare beneficiaries. Med Care 2004;42:512–21.

39. Muller-Tasch T, Peters-Klimm F, Schellberg D, et al. Depression is a major determinant of quality of life in patients with chronic systolic heart failure in general practice. J Card Fail 2007;13:818–24.

40. Dunbar SB, Clark PC, Quinn C, Gary RA, Kaslow NJ. Family influences on heart failure self-care and outcomes. J Cardiovasc Nurs 2008;23:258–65.

41. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. Arch Intern Med 2005;165:2508–13.

42. Sin NL, Kumar AD, Gehi AK, Whooley MA. Direction of Association Between Depressive Symptoms and Lifestyle Behaviors in Patients with Coronary Heart Disease: the Heart and Soul Study. Ann Behav Med 2016;50:523–32.

43. Tang HY, Sayers SL, Weissinger G, Riegel B. The role of depression in medication adherence among heart failure patients. Clin Nurs Res 2014;23:231–44.

44. Stapelberg NJ, Neumann DL, Shum DH, McConnell H, Hamilton-Craig I. A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease. Aust N Z J Psychiatry 2011;45:351–69.

45. Blumenthal JA, Babyak MA, Carney RM, et al. Exercise, depression, and mortality after myocardial infarction in the ENRICHD Trial. Med Sci Sports Exerc 2004;36:746–55.

46. Dhar AK, Barton DA. Depression and the link with cardiovascular disease. Front Psychiatry 2016;7:33.

47. Kaye DM, Lefkovits J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. J Am Coll Cardiol 1995;26:1257–63.

48. Pitzalis MV, Iacoviello M, Todarello O, et al. Depression but not anxiety influences the

autonomic control of heart rate after myocardial infarction. Am Heart J 2001;141:765–71.

49. Wong ML, Kling MA, Munson PJ, et al. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. Proc Natl Acad Sci U S A 2000;97:325–30.

50. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 2002;90:1279–83.

51. Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006;49:837–45.

52. Pan A, Ye X, Franco OH, et al. Insulin resistance and depressive symptoms in middle-aged and elderly Chinese: findings from the Nutrition and Health of Aging Population in China Study. J Affect Disord 2008;109:75–82.

53. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. Am J Psychiatry 1996;153:1313–7.

54. Williams MS. Platelets and depression in cardiovascular disease: a brief review of the current literature. World J Psychiatry 2012;2:114–23.

55. Musselman DL, Marzec UM, Manatunga A, et al. Platelet reactivity in depressed patients treated with paroxetine: preliminary findings. Arch Gen Psychiatry 2000;57:875–82.

56. Post-Myocardial Infarction Depression Clinical Practice Guideline Panel. AAFP guideline for the detection and management of post-myocardial infarction depression. Ann Fam Med 2009;7:71–9.

57. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–200.

58. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

59. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the american heart association. Circulation 2011;123:1243–62.

60. Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2015;132:965–86.

61. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–81.

62. Borowsky SJ, Rubenstein LV, Meredith LS, Camp P, Jackson-Triche M, Wells KB. Who is at risk of nondetection of mental health problems in primary care? J Gen Intern Med 2000;15:381–8.

63. Waldman SV, Blumenthal JA, Babyak MA, et al. Ethnic differences in the treatment of depression in patients with ischemic heart disease. Am Heart J 2009;157:77–83.

64. Davis KAS, Sudlow CLM, Hotopf M. Can mental health diagnoses in administrative data be used for research? A systematic review of the accuracy of routinely collected diagnoses. BMC Psychiatry 2016;16:263.

65. Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and delay in initial treatment contact after first onset of mental disorders in the national comorbidity survey replication. Arch Gen Psychiatry 2005;62:603–13.

66. Wong J, Motulsky A, Abrahamowicz M, Eguale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. BMJ 2017;356.

67. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. National Ambulatory Medical Care Survey: 2015 state and national summary tables. Available at: https://www.cdc.gov/nchs/data/ahcd/namcs_summary/2015_namcs_web_tables.pdf. Accessed August 24, 2018.

68. Bureau of Health Workforce Health Resources and Services Administration (HRSA), U.S. Department of Health & Human Services. Third quarter of fiscal year 2018 designated HPSA Quarterly Summary as of June 30, 2018. Available at: https://ersrs.hrsa.gov/ReportServer?/HGDW_Reports/BCD_HPSA/BCD_HPSA_SCR50_Qtr_Smry_HTML&rc:Toolbar=false. Accessed August 24, 2018.

69. Ziegelstein RC, Thombs BD, Coyne JC, de Jonge P. Routine screening for depression in patients with coronary heart disease: never mind. J Am Coll Cardiol 2009;54:886–90.

70. Thombs BD, Roseman M, Coyne JC, et al. Does evidence support the American Heart Association's recommendation to screen patients for depression in cardiovascular care? An updated systematic review. PloS One 2013;8:e52654.

71. Blumenthal JA, O'Connor C. No laughing matter. J Am Coll Cardiol 2010;55:836.

72. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163:28–40.

73. Jha MK, Minhajuddin A, South C, Rush AJ, Trivedi MH. Worsening anxiety, irritability, insomnia, or panic predicts poorer antidepressant treatment outcomes: clinical utility and validation of the Concise Associated Symptom Tracking (CAST) Scale. Int J Neuropsychopharmacol 2018;21:325–32.

74. Kroenke K, Spitzer RL, Janet BWW. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 2003;41:1284–92.

75. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. Ann Fam Med 2010;8:348–53.

76. Spitzer RL, Kroenke K, Williams JW, for the Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of prime-md: The PHQ primary care study. JAMA 1999;282:1737–44.

77. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.

78. Spitzer RL, Williams JW, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care: The prime-md 1000 study. JAMA 1994;272:1749–56.

79. Arroll B, Khin N, Kerse N. Screening for depression in primary care with two verbally asked questions: cross sectional study. BMJ 2003;327:1144–6.

80. Elderon L, Smolderen KG, Na B, Whooley MA. Accuracy and prognostic value of American Heart Association: recommended depression screening in patients with coronary heart disease: data from the Heart and Soul Study. Circ Cardiovasc Qual Outcomes 2011;4:533–40.

81. Haddad M, Walters P, Phillips R, et al. Detecting depression in patients with coronary heart disease: a diagnostic evaluation of the PHQ-9 and HADS-D in primary care, findings from the UPBEAT-UK Study. PloS One 2013;8:e78493.

82. McGuire AW, Eastwood J-A, Macabasco-O'Connell A, Hays RD, Doering LV. Depression screening: utility of the patient health questionnaire in patients with acute coronary syndrome. Am J Crit Care 2013;22:12–9.

83. Schalet BD, Pilkonis PA, Yu L, et al. Clinical validity of PROMIS Depression, Anxiety, and Anger across diverse clinical samples. J Clin Epidemiol 2016;73:119–27.

84. Kahalnik F, Sanchez K, Faria A, et al. Improving the identification and treatment of depression in low-income primary care clinics: a qualitative study of providers in the VitalSign6 program. Int J Qual Health Care 2019;31:57–63.

85. Redelmeier DA, Kraus NC. Patterns in patient access and utilization of online medical records: analysis of MyChart. J Med Internet Res 2018;20:e43.

86. Lofthus DM, Gadgil JY, de Lemos JA. Overriding concerns: the role of electronic medical record-based best practice alerts in reducing

unnecessary laboratory testing. Clin Chem 2015;61:456–8.

87. Forkmann T, Vehren T, Boecker M, Norra C, Wirtz M, Gauggel S. Sensitivity and specificity of the Beck Depression Inventory in cardiologic inpatients: How useful is the conventional cut-off score? J Psychosom Res 2009;67:347–52.

88. Strik JJ, Honig A, Lousberg R, Denollet J. Sensitivity and specificity of observer and self-report questionnaires in major and minor depression following myocardial infarction. Psychosomatics 2001;42:423–8.

89. Tesio V, Marra S, Molinaro S, Torta R, Gaita F, Castelli L. Screening of depression in cardiology: a study on 617 cardiovascular patients. Int J Cardiol 2017;245:49–51.

90. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, DC: American Psychiatric Pub, 2013.

91. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR* D): rationale and design. Control Clin Trials 2004;25:119–42.

92. Raison CL, Borisov AS, Broadwell SD, et al. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J Clin Psychiatry 2005;66:41–8.

93. Lehmann M, Kohlmann S, Gierk B, Murray AM, Lowe B. Suicidal ideation in patients with coronary heart disease and hypertension: baseline results from the DEPSCREEN-INFO clinical trial. Clin Psychol Psychother 2018;25:754–64.

94. Bolton JM, Gunnell D, Turecki G. Suicide risk assessment and intervention in people with mental illness. BMJ 2015;351.

95. Bekelman DB, Plomondon ME, Carey EP, et al. Primary results of the Patient-Centered Disease Management (PCDM) for Heart Failure Study: a randomized clinical trial. JAMA Intern Med 2015;175:725–32.

96. Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Rubin EH. Cognitive behavior therapy for depression and self-care in heart failure patients: a randomized clinical Trial. JAMA Intern Med 2015;175:1773–82.

97. Pina IL, Di Palo KE, Ventura HO. Psychopharmacology and cardiovascular Disease. J Am Coll Cardiol 2018;71:2346–59.

98. Zuidersma M, Conradi HJ, van Melle JP, Ormel J, de Jonge P. Depression treatment after myocardial infarction and long-term risk of subsequent cardiovascular events and mortality: a randomized controlled trial. J Psychosom Res 2013;74:25–30.

99. Strik JJ, Honig A, Lousberg R, et al. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. Psychosom Med 2000;62:783–9.

100. Chocron S, Vandel P, Durst C, et al. Antidepressant therapy in patients undergoing coronary artery bypass grafting: the MOTIV-CABG trial. Ann Thorac Surg 2013;95:1609–18.

101. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. J Am Coll Cardiol 2010;56:692–9.

102. Angermann CE, Gelbrich G, Stork S, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: The MOOD-HF Randomized Clinical Trial. JAMA 2016;315:2683–93.

103. Freedland KE, Skala JA, Carney RM, et al. Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. Arch Gen Psychiatry 2009;66:387–96.

104. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: results from the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study. J Am Coll Cardiol 2012;60:1053–63.

105. Blumenthal JA, Babyak MA, O'Connor C, et al. Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-Action randomized trial. JAMA 2012;308:465–74.

106. Milani RV, Lavie CJ. Impact of cardiac rehabilitation on depression and its associated mortality. Am J Medicine 2007;120:799–806.

107. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane systematic review and meta-analysis. J Am Coll Cardiol 2016;67:1–12.

108. Milani RV, Lavie CJ, Mehra MR, Ventura HO. Impact of exercise training and depression on survival in heart failure due to coronary heart disease. Am J Cardiol 2011;107:64–8.

109. Sangster J, Furber S, Allman-Farinelli M, et al. Effectiveness of a pedometer-based telephone coaching program on weight and physical activity for people referred to a cardiac rehabilitation program: a randomized controlled trial. J Cardiopulm Rehabil Prev 2015;35:124–9.

110. Rouleau CR, King-Shier KM, Tomfohr-Madsen LM, et al. The evaluation of a brief motivational intervention to promote intention to participate in cardiac rehabilitation: a randomized controlled trial. Patient Educ Couns 2018;101:1914–23.

111. Davidson KW, Bigger JT, Burg MM, et al. Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: CODIACS vanguard randomized controlled trial. JAMA Intern Med 2013;173:997–1004.

112. Davidson KW, Rieckmann N, Clemow L, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. A Arch Intern Med 2010;170:600–8.

113. Lesperance F, Frasure-Smith N, Koszycki D, et al. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. JAMA 2007;297:367–79.

114. Huffman JC, Mastromauro CA, Beach SR, et al. Collaborative care for depression and anxiety disorders in patients with recent cardiac events: the Management of Sadness and Anxiety in Cardiology (MOSAIC) randomized clinical trial. JAMA Intern Med 2014;174:927–35.

115. Huffman JC, Mastromauro CA, Sowden G, Fricchione GL, Healy BC, Januzzi JL. Impact of a depression care management program for hospitalized cardiac patients. Circ Cardiovasc Qual Outcomes 2011;4:198–205.

116. Rollman BL, Belnap BH, LeMenager MS, et al. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. JAMA 2009;302:2095–103.

117. Carney RM, Freedland KE, Steinmeyer BC, Rubin EH, Ewald G. Collaborative care for depression symptoms in an outpatient cardiology setting: a randomized clinical trial. Int J Cardiol 2016;219:164–71.

118. Maslej MM, Bolker BM, Russell MJ, et al. The mortality and myocardial effects of antidepressants are moderated by preexisting cardiovascular disease: a meta-analysis. Psychother Psychosom 2017;86:268–82.

119. O'Connor CM, Jiang W, Kuchibhatla M, et al. Antidepressant use, depression, and survival in patients with heart failure. Arch Intern Med 2008;168:2232–7.

120. Jha MK, Rush AJ, Trivedi MH. When discontinuing SSRI antidepressants is a challenge: Management tips. Am J Psychiatry 2018;175:1176–84.

121. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 2009;360:225–35.

122. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015;14:119–36.

123. Feinstein RE, Blumenfield M, Orlowski B, Frishman WH, Ovanessian S. A national survey of cardiovascular physicians' beliefs and clinical care practices when diagnosing and treating depression in patients with cardiovascular disease. Cardiol Rev 2006;14:164–9.

124. Gaynes BN, Rush AJ, Trivedi MH, et al. Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. J Gen Intern Med 2008;23:551–60.

125. Suissa K, Lariviere J, Eisenberg MJ, et al. Efficacy and safety of smoking cessation interventions in patients with cardiovascular disease: a network meta-analysis of randomized controlled trials. Circ Cardiovasc Qual Outcomes 2017;10.

126. Mohamed S, Johnson GR, Chen P, et al. Effect of antidepressant switching vs augmentation on remission among patients with major depressive disorder unresponsive to antidepressant treatment: The vast-d randomized clinical trial. JAMA 2017;318:132–45.

127. Bambauer KZ, Locke SE, Aupont O, Mullan MG, McLaughlin TJ. Using the Hospital Anxiety and Depression Scale to screen for depression in cardiac patients. Gen Hosp Psychiatry 2005;27:275–84.

128. Bunevicius A, Staniute M, Brozaitiene J, Bunevicius R. Diagnostic accuracy of self-rating scales for screening of depression in coronary artery disease patients. J Psychosom Res 2012;72:22–5.

129. Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry 2008;65:62–71.

130. Huffman JC, Doughty CT, Januzzi JL, Pirl WF, Smith FA, Fricchione GL. Screening for major depression in post-myocardial infarction patients: operating characteristics of the Beck Depression Inventory-II. Int J Psychiatry Med 2010;40:187–97.

131. Low GD, Hubley AM. Screening for depression after cardiac events using the Beck Depression Inventory-II and the Geriatric Depression Scale. Social Indicators Research 2006;82:527.

KEY WORDS antidepressant treatment, cardiovascular disease, depression, screening

Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.