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# Epidemiology and Management of Depression Following Coronary Heart Disease Diagnosis in Women

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**Abstract** Coronary heart disease (CHD) and depression are both highly prevalent in women. Importantly, depression is associated with significantly elevated morbidity and mortality in women with CHD. There are intriguing speculations about biological mechanisms underlying this association, such as endothelial dysfunction, subclinical atherosclerosis, inflammation, and autonomic dysregulation. Social and behavioral mechanisms, such as lack of social support and physical inactivity, have also been shown to play important roles. Unfortunately, many randomized clinical trials of counseling and pharmacologic interventions for depression in patients with CHD have failed to improve cardiovascular outcomes, and in fact have raised the possibility that interventions might be harmful in women. Several recent trials of new treatment strategies, however, have been more effective

in improving depressive symptoms and quality of life and deserve further investigation. In this review, we summarize recent findings with regards to the epidemiology, etiology, diagnosis, and management of depression in women diagnosed with CHD.

**Keywords** Depression · Women · Epidemiology · Management · Coronary heart disease

## Introduction

Despite advances in prevention and treatment, cardiovascular disease (CVD) remains the leading cause of death for women in the United States, accounting for >300,000 deaths per year [1]. Depression is common in patients with CHD: around 20% meet criteria for major depression, and up to 50% experience some depressive symptoms [2]. Furthermore, depression has been shown to be independently associated with significantly increased risk for recurrent cardiovascular events and mortality [2, 3]. Similar to the general population, women with CHD are much more likely to experience depression as compared to men, and it has been argued that this partly explains why women face increased risk of death after myocardial infarction (MI) [4]. Due to these considerations, depression screening and treatment for patients with CHD has been recommended by both the 2008 American Heart Association (AHA) Science Advisory on Depression and Heart Disease [5••] and the 2011 update of the AHA Practice Guidelines for Prevention of Cardiovascular Disease in Women [6]. To date, however, depression interventions have demonstrated only limited cardiovascular or mental health benefits in patients with CHD [7, 8••].

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Currently, the relationship between depression and cardiovascular risk remains an area of active investigation. In this review, we highlight recent literature on the prevalence and impact of depression in this patient population, the mechanisms that could potentially explain the elevated risk conferred by depression, as well as the ongoing debate on how best to diagnose and manage depression in women with CHD.

### Prevalence and Impact

The association between depression and increased risk for incident CHD events was confirmed by several large cohort studies, though there was mixed evidence on whether women might be at higher risk than men. Because there were considerable variations in these studies on how depressive symptoms were assessed, the specific instrument used for each will be briefly mentioned. Nabi et al. [9] reported that in a Finnish cohort of 23,282 young to middle-aged adults (59% women) with no prior CHD, presence of elevated depressive symptoms, defined as Beck Depression Inventory (BDI) score  $\geq 10$  (hazard ratio [HR] 1.47, 95% CI 1.08–1.99) or being prescribed anti-depressants, were independent risk factors for developing incident CHD (HR 1.72, 95% CI 1.06–2.77) [9]. Similarly, in a cohort of 2278 urban adults aged 60 years or older without prior cardiovascular disease (CVD), of which 71% were women, depressive symptoms as measured by the Center for Epidemiologic Depression Scale (CES-D) score  $\geq 16$  were associated with a nearly 50% increase in the risk of incident myocardial infarction (MI) or CHD death (relative risk [RR] 1.46, 95% CI 1.20–1.77) after adjustment for demographic and medical covariates [10]. In both studies, tests of interaction did not show any differences between men and women in the strength of association between depression and cardiac risk. In contrast, Shah et al. [11] found that in 7641 US adults (54% women) younger than 40 years of age, depression or a history of attempted suicide as assessed via the Diagnostic Interview Schedule was associated with increased risk of premature death from CVD and ischemic heart disease (IHD), with the effect size more pronounced in women compared to men (for CVD, HR 3.20, 95% CI 1.12–9.17 for women vs HR 2.37, 95% CI 0.85–6.58 for men; for IHD, HR 14.57, 95% CI 2.65–80.10 for women vs HR 3.52, 95% CI 1.05–11.76 for men). Although these results are intriguing, it should be noted that the absolute incidence of events were low in this study, resulting in wide confidence intervals [11].

Several studies have further refined our understanding of how depression adversely affects the prognosis of patients with CHD. The Heart and Soul Study followed 1017 patients (18% women) with stable CHD and reported that elevated depressive symptoms, defined as Patient Health Questionnaire (PHQ-9) score  $\geq 10$ , were associated with increased risk for subsequent cardiovascular events (HR 1.50, 95% CI 1.16–

1.95) [12•]. An innovative case–control study by Larsen et al. [13] using a large Finnish registry showed that patients after MI are at higher risk for suicide, the most extreme manifestation of depression. The risk was especially pronounced in those who had previous psychiatric illnesses (RR 64.05, 95% CI 13.36–307.06), but was also elevated in those who did not (RR 3.25, 95% CI 1.61–6.56) [13]. In this study, male and female patients had similar risk of suicide following MI. Further highlighting the complexity of the relationship between depression and outcomes in patients with CHD, another study examined whether the dynamic course of depressive symptoms following CHD diagnosis influences cardiac risk. In a cohort of 2325 patients (31% women) with stable CHD, Doering et al. [14] assessed persistent symptoms of depression and anxiety across a 3-month period using the Multiple Adjective Affect Checklist. The combination of both was present in 26% of participants, and was furthermore associated with increased mortality (odds ratio [OR] 2.35, 95% CI 1.23–4.47). Notably, women were also more likely to have combined persistent depression and anxiety symptoms (30.6% vs 24.2% for males,  $P=0.001$ ) [14]. These results are consistent with the emerging understanding that the relationship between depression and elevated cardiovascular risk may be modified by what is now termed “depression phenotypes” (eg, persistent depression or mixed depression/anxiety) [15•].

Finally, the potential increase in healthcare costs for women with depression and CHD was formally evaluated in the Women’s Ischemia Syndrome Evaluation Study. Accounting for both direct costs of healthcare utilization and indirect costs such as loss of productivity, those with depression (defined by either use of anti-depressants, self-reported depression treatment, or baseline BDI score  $\geq 10$ ) incurred annual costs that were on average \$1550 to \$3300 higher than those without depression [16]. Higher costs associated with depression were seen in women with and without angiographic evidence of CHD, though the association was only significant in the latter. These findings will be useful for cost-effectiveness evaluations of future depression interventions.

### Potential Mechanisms

A variety of biological, social, and behavioral mechanisms have been invoked to explain the association between depression and cardiovascular outcomes. The most relevant findings that apply to women with CHD and depression are summarized below.

#### Biological Mechanisms

As a whole, recent investigations of biological mechanisms underlying the relationship between depression and CHD risk tended to show negative or mixed results. Of the studies that

examined the role played by endothelial dysfunction, a meta-analysis by Cooper et al. [17] found that both clinical and subclinical depression was modestly associated with impaired flow-mediated dilatation ( $r=0.19$ , 95% CI 0.08–0.29). Women were well-represented in the individual studies, and the correlation was larger when restricted to studies of patients with CHD or CHD risk factors ( $r=0.29$ ). However, in another study of 434 urban subjects (55% women), depressive symptoms as measured by CES-D were not associated with serum markers of endothelial function, including e- and p-selectins and s-ICAM1 [18]. Similarly, recent studies have challenged the hypothesis that the risk associated with depression in women with CHD can be explained by inflammatory processes. In a cross-sectional study of 9258 subjects (54% women), Bjerkeset et al. [19] showed that depressive symptoms defined as Hospital Anxiety and Depression Scale (HADS-D) score  $\geq 8$  were associated with elevated C-reactive protein (CRP) in the unadjusted model (OR 1.28, 95% CI 1.10–1.49); however, this association disappeared after full adjustment for prior medical conditions and demographic and lifestyle covariates (OR 1.08, 95% CI 0.91–1.30) [19]. Negative findings were also reported by Amyre Morris et al. [20], who examined the relationship between depression defined as BDI score  $\geq 14$  and elevated CRP level in a cohort of 512 African American and white participants (61% women). In this study, the association between depressive symptoms and elevated CRP disappeared after adjusting for metabolic risk factors such as smoking status, waist circumference, systolic blood pressure, and cholesterol [20], suggesting that these traditional risk factors represent confounders of this relationship.

There were also mixed results with regards to the role played by autonomic dysfunction. Kop et al. [21] examined the relationship between measures of heart rate variability (HRV), depressive symptoms as assessed by CES-D, and cardiovascular mortality in a cohort of 907 participants (59% women) without prior CHD. Of the 11 HRV indices assessed, only one measure, daytime detrended fluctuation analysis, was associated with depression. In addition, although depressive symptoms were associated with increased cardiovascular mortality, addition of HRV and inflammatory markers to the model only attenuated the association modestly (12.7%) [21]. On the other hand, an elegant study by Way et al. [22] showed that a polymorphism in the promoter region of the serotonin transporter gene SLC6A4 influenced blood pressure and HRV in response to negative evaluations in healthy young adults. The effect was moderated by sex and was mainly seen in women [22]. This interesting finding will need to be replicated, and further studies will need to confirm whether SLC6A4 polymorphism and its downstream effect on autonomic function contribute to the relationship between depression and cardiovascular risk.

In contrast to the negative findings above, several studies demonstrated that subclinical atherosclerosis may explain

part of the association between depression and CHD risk. Pizzi et al. [23] followed a cohort of 391 subjects (51% women) with at least two CHD risk factors, and reported that depressive symptoms defined as BDI score  $\geq 10$  were independently associated with increased carotid intima-media thickening (CIMT) [23]. Similarly, Janssen et al. [24] assessed the progression of coronary artery calcification (CAC) in 346 middle-aged women with no prior CHD over an average of 2.3 years, showing that each standard deviation increase in CES-D carried a 25% increased risk of CAC progression. A study from Hamer et al. [25] followed 454 participants (46% women) from the Whitehall II cohort and found that persistent depressive symptoms, defined as General Health Questionnaire score  $\geq 4$  on at least two occasions, was associated with increased risk of having CAC  $> 0$  and  $\geq 100$  (OR 2.56, 95% CI 1.14–5.78 and OR 2.36, 95% CI 1.04–5.35, respectively). However, in analysis stratified by sex, this relationship was significant only in men, which the authors attribute to decreased power due to the lower prevalence of CAC in the women studied [25]. To assess the direction of causality between depression and atherosclerosis, Newson et al. [26] analyzed data from 3564 participants (56% female) enrolled in the Rotterdam study. They found that baseline atherosclerosis, measured through CAC, CIMT, aortic calcification, and ankle-brachial index, did not predict incident depression [26]. As the authors note, this result argues against atherosclerosis as a cause of depression, but is consistent with either depression leading to an increase in cardiovascular risk or with both depression and CHD being associated with other shared risk factors.

Two other studies that investigated novel mechanisms linking depression and CHD in women deserve mentioning. Hoen et al. [27] reported from the Heart and Soul Study that in patients with CHD, shorter telomere length at baseline, thought to be a potential marker for lifetime burden of oxidative stress, was associated with depression. In a cohort of 243 men and 139 women who had myocardial infarction, Whang et al. [28] reported that BDI score  $\geq 10$  was associated with significantly longer corrected QT interval in women ( $435.4 \pm 26.6$  ms vs  $408.6 \pm 24.3$  ms) but not in men. The authors suggest that this may help explain the known increased risk of sudden death and ventricular arrhythmia in women with depression [28]. These findings will need to be confirmed in other cohorts, but offer intriguing insights into other potential biological mechanisms that may be involved in the association between depression and cardiovascular risk in women with CHD.

#### Social and Behavioral Mechanisms

Recently, considerable progress was made in our understanding of potential social and behavioral mechanisms that link depression to CHD risk. In the Heart and Soul Study, it

was shown that physical inactivity and smoking status explained much of the association between depression and recurrent cardiovascular events in patients with established CHD [12•]. A similar finding was reported by Win et al. [29], who followed 5888 elderly participants (58% female) of the Cardiovascular Health Study over an average of 10.3 years. In this study, a low level of physical activity predicted depression defined as CES-D score  $\geq 8$ ; furthermore, although both depression and low level of physical activity were associated with increased cardiovascular mortality, after adding physical activity to the model the log hazard ratio for depression was reduced by 28% [29]. Our group examined the relationship between physical inactivity, depressive symptoms, and subsequent cardiovascular events or mortality in 4676 participants (40% women) with prior CHD in the Reasons for Geographic and Racial Differences in Stroke Study and found a similar 21% reduction in the association between depressive symptoms and clinical events after accounting for physical inactivity (Ye et al., submitted). Taken together, it appears that physical inactivity is a powerful risk marker in this population, and whether interventions that encourage exercise uptake in depressed patients with CHD may be of benefit warrants further investigation.

Several other studies reported on differential risks conveyed through component domains of depressive symptoms in patients with CHD, highlighting the heterogeneity and prognostic significance of possible depression phenotypes [15•]. In a cohort of 453 patients hospitalized for acute coronary syndromes (ACS), of which 42% were women, we found that anhedonia (the loss of pleasure or interest and one of the two cardinal symptoms of depression) assessed by structured interview was a stronger predictor of death or recurrent MI (HR 1.58, 95% CI 1.16–2.14) than the presence of depressed mood (the other cardinal symptom of depression) or major depressive episodes [30]. Another report from the Heart and Soul Study by Hoen et al. [31] showed that after full adjustment, only somatic symptoms, such as fatigue and difficulty sleeping, were associated with increased risk for cardiovascular events (HR 1.14, 95% CI 1.05–1.24, for each somatic symptom) in patients with prior CHD, whereas cognitive symptoms such as depressed mood were not. This finding was corroborated by a retrospective analysis of 2442 (44% women) participants with depression or low perceived social support enrolled in the Enhancing Recovery in Coronary Heart Disease (ENRICH) trial, which showed that at 12 months after the index MI, somatic symptoms but not cognitive symptoms assessed by BDI were independently associated with all-cause and cardiovascular mortality (HR 1.43, 95% CI 1.13–1.81 and HR 1.60, 95% CI 1.17–2.18, respectively) [32]. As Hoen et al. [31] note, it is possible that physical inactivity is related to the presence of somatic symptoms, thereby driving an increase in cardiovascular risk.

There were also two reports that focused on increased social vulnerabilities experienced by women with CHD and comorbid depression. A study by Leifheit-Limson et al. [33] showed that in a cohort of 2411 patients (33% women) hospitalized for MI, low perceived social support was associated with significantly lower quality of life, physical functioning, and increased depressive symptoms. In sex-stratified analysis, the effect was seen only in women and not in men [33]. Similarly, in a cross-sectional study of 1951 patients (35% women) with CHD and depressive symptoms measured by the Multiple Adjective Affect Checklist, Doering et al. [34] found that compared with men, women were more likely to be single, to be unemployed, to have lower level of education, and to perceive lower control over health. These findings suggest that the increased social vulnerabilities faced by women with CHD and comorbid depression may represent another mechanism by which depression increases cardiovascular risk in this patient population.

## Diagnosis and Screening

As mentioned previously, depression screening has been recommended for patients with CHD in both the 2008 AHA Science Advisory on Depression and Heart Disease [5••] and the 2011 update of the AHA Practice Guidelines for Prevention of Cardiovascular Disease in Women [6]. The AHA Advisory recommends administering a standard depression screening questionnaire to patients with CHD, with referral for those who screen positive to a professional qualified to diagnose and manage depression. It is suggested that the brief 2-item Patient Health Questionnaire (Table 1) be used as the initial step, to be followed by the full 9-item questionnaire if the initial screen is positive (Table 2), with the acknowledgement that any standardized, valid depression questionnaire can be used in substitution [5••]. The validity of the AHA Advisory algorithm (Fig. 1) is supported by a study from Elderon et al. [35] that evaluated the algorithm's performance in the Heart and Soul Study, and showed that the algorithm was highly specific (0.91, 95% CI 0.89–0.93) though not sensitive (0.52, 95% CI 0.46–0.59). Furthermore, after multivariate adjustment, those who screened positive had elevated risk of adverse cardiovascular events (HR 1.41, 95% CI 1.10–1.81) [35].

Since the release of the AHA Advisory, several studies have examined implementation of depression screening programs in patients with CHD. One study by Shemesh et al. [36•] screened 1008 patients (~38% women) with CHD using the algorithm suggested by the AHA Advisory and found that 12% of those screened endorsed suicidal ideation as assessed by question 9 on the PHQ-9; 121 patients had to be interviewed immediately for safety, and after further evaluation by a psychiatrist, 4 patients (0.45%) required

**Table 1** 2-item Patient Health Questionnaire (PHQ-2)\*, for initial depression screening in patients with CHD

Over the past 2 weeks, how often have you been bothered by any of the following problems?

- (1) Little interest or pleasure in doing things.
- (2) Feeling down, depressed, or hopeless.

\*Answering “yes” to either question is considered screening positive, and indicates need for further screening with PHQ-9, or for referral for professional evaluation for depression diagnosis and treatment

(Adapted from Kroenke et al. [44]; with permission.)

hospitalization for suicidal intent [36•]. The study demonstrates a clear need of any screening program to put in place appropriate and timely referral mechanisms for high-risk patients. An interesting study by Smolderen et al. [37] evaluated a single-center initiative mandating the nursing staff to screen depression in patients hospitalized with MI using the AHA Advisory algorithm. The performance of the initiative was compared with depression assessment conducted separately through a large registry of which the center was a member. Despite the initiative, 135 (26.8%) of 503 eligible patients were not screened, and the proportion of women in the unscreened group was significantly higher than those in the screened group (36.3% vs 26.6%,  $P=0.04$ ). Furthermore, of patients who were identified as having depression in the registry, only 38.3% were recognized through the screening initiative [37]. The authors' experiences suggest that future efforts to implement depression screening programs in patients with CHD will need to address the optimal mode of screening and potential barriers in subgroups such as women.

Despite the AHA recommendations, however, the important issue of which instrument is the most suitable for

depression assessment in patients with CHD remains unresolved. Vieweg et al. [38] points out in a recent review that the various depression instruments used in cardiovascular studies are highly heterogeneous and are derived from different patient populations. They were also frequently applied in settings that do not match those from which they were developed and were scored using different cutoff values depending on the study. This heterogeneity limits comparison and generalizability of findings in this area [38], and the diagnostic validity and clinical applicability of different depression instruments will need to be investigated further.

## Management

A recently released Cochrane review summarized the existing literature on pharmacologic and psychological interventions for depression in patients with CHD, concluding that in general, interventions of either kind had no beneficial effects on cardiovascular events or mortality, though there may be a modest improvement in psychosocial dimensions of quality of life assessment [8••]. The psychological interventions employed in the studies reviewed were Cognitive Behavioral Therapy, Psychodynamic Psychotherapy, Interpersonal Psychotherapy, and Non-directive Supportive Therapy and Counseling. Various commonly used antidepressants, particularly SSRIs, were considered in studies of pharmacologic interventions. A reduction in hospitalizations was seen for pharmacologic intervention, but was primarily driven by results from a single study, the Sertraline Antidepressant Heart Attack Randomized Trial, which compared sertraline with placebo [39]. The Cochrane review was not able to assess whether depression interventions had differential effects on men and women. However, it

**Table 2** Patient Health Questionnaire-9 (PHQ-9)\* scale for depression screening

Over the past 2 weeks, how often have you been bothered by any of the following problems?

- (1) Little interest or pleasure in doing things.
- (2) Feeling down, depressed, or hopeless.
- (3) Trouble falling asleep, staying asleep, or sleeping too much.
- (4) Feeling tired or having little energy.
- (5) Poor appetite or overeating.
- (6) Feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down.
- (7) Trouble concentrating on things such as reading the newspaper or watching television.
- (8) Moving or speaking so slowly that other people would have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual.
- (9) Thinking that you would be better off dead or that you want to hurt yourself in some way.

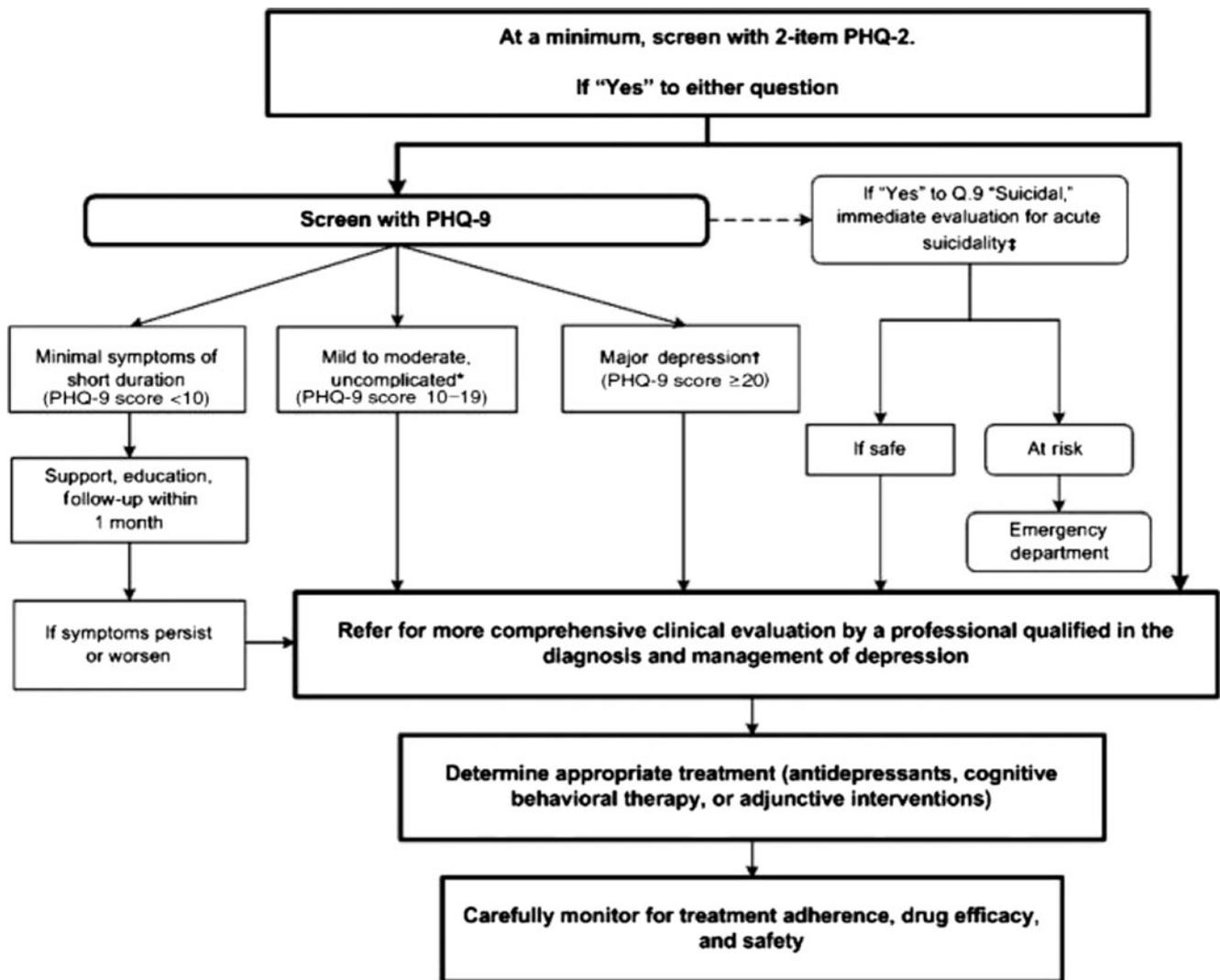
\*For each question, “not at all” is scored as 0; “several days” as 1; “more than half of the days” as 2; and “nearly every day as 3”. Scores for all items are summed to obtain total score for depression severity

(Adapted from Kroenke et al. [44]; with permission.)

should be noted that in both the ENRICH trial, which compared cognitive behavioral therapy with sertraline versus usual care for severely depressed patients with CHD, and the Montreal Heart Attack Readjustment Trial, which evaluated home-based treatment of psychological stress versus usual care, a trend towards increased MI or death with intervention was seen in women only [7, 40]. These two trials were among the largest conducted examining depression treatment for CHD patients, and their findings point to the need for careful assessment of the unique risk profiles of women with CHD and comorbid depression that

may lead them to respond adversely to standardized depression interventions.

Despite these negative findings, there were also several recent trials of innovative depression treatment approaches that seem promising. A large, primary care-based randomized clinical trial by Katon et al. [41•] evaluated the effect of collaborative care—a team-based approach that combined self-care support with pharmacotherapy and emphasized individualized goal setting—in patients with depression and either diabetes or CHD. The study enrolled 214 participants (52% women) and showed that after a 12-month



**Fig. 1** Recommendation for depression screening from the 2008 American Heart Association Science Advisory on Depression and Heart Disease. *Asterisk* indicates meets diagnostic criteria for major depression, has a Patient Health Questionnaire (PHQ)-9 score of 10–19, has had no more than 1 or 2 prior episodes of depression, and screens negative for bipolar disorder, suicidality, significant substance abuse, or other major psychiatric problems. *Dagger* indicates meets the diagnostic criteria for major depression and 1) has a PHQ-9 score  $\geq 20$ ; or 2) has had 3 or more prior depressive

episodes; or 3) screens positive for bipolar disorder, suicidality, significant substance abuse, or other major psychiatric problem. *Double dagger* indicates that if “Yes” to Q.9 “suicidal,” immediately evaluate for acute suicidality. If safe, refer for more comprehensive clinical evaluation; if at risk for suicide, escort the patient to the emergency department. (Reprinted from Lichtman JH, Bigger JT, Blumenthal JA, et al. [5••]. Depression and Coronary Heart Disease. *Circulation*. 2008;118(17):1768–75; with permission.)

period, those who received intervention had significantly improved depressive symptoms measured by the Symptom Checklist-20 (difference, -0.40, 95% CI -0.56 to -0.26) as well as improved control of hypertension, hyperlipidemia, and diabetes [41]. A similar study of collaborative care by Huffman et al. [42] enrolled 175 patients with depression (51% women) who were hospitalized for MI, arrhythmia, or heart failure and found that compared with the usual care arm, the intervention arm showed improved depressive symptoms assessed by PHQ-9 at 12 weeks as well as the number and severity of cardiac symptoms at 6 months. However, no difference was seen in the number of cardiac readmissions, and the effect of intervention on depressive symptoms diminished after the end of the intervention period [42]. Similarly, our group recently reported findings from the Coronary Psychosocial Evaluation Studies Randomized Trial, which randomized 157 patients (54% women) with persistent depressive symptoms following hospitalization for ACS to usual care or an intervention comprised of patient-preference driven problem solving therapy and/or pharmacotherapy. At the end of the 6-month intervention period, patients randomized to intervention had significantly larger decrease in BDI score (difference, -1.9 points, 95% CI -3.8 to -0.1) as well as decreased number of cardiac events including death and recurrent ACS [43]. However, the effect of intervention on cardiac events disappeared at 18-months of follow-up, with analysis showing a significant group-time interaction that suggested a “delayed risk” phenomenon after the intervention ended (HR for intervention arm for the entire follow-up period 0.94, 95% CI 0.44–2.04; HR for 6-month treatment period 0.27, 95% CI 0.07–0.98; HR for after treatment period ended 4.07, 95% CI 0.84–19.73;  $P=0.005$  for interaction) (Ye et al., submitted). We hypothesize that depression may need to be treated as a chronic disease, and that providing depression treatment for short periods of time, and then withdrawing it, may not be an appropriate strategy for those with persistent depression.

Taken together, these results indicate that larger trials are needed to detect whether these stepped depression interventions can improve quality of life and reduce the excess cardiac risk in patients with CHD and comorbid depression. An adequate number of women will need to be enrolled to better delineate sex-specific risks and differences in response to intervention compared to men. Furthermore, our experience suggests that the optimal timing and intensity of depression treatment will need to be considered carefully, and it may be that ongoing treatment is needed for the benefit to persist, consistent with a conceptual model of depression as a chronic illness. In the meantime, given the absence of definitive data, it is reasonable to offer continued psychological and/or pharmacologic treatment of depression in patients with CHD based on individual preference, an approach that has been shown to be associated with high

patient satisfaction and significant depression improvement [30, 43].

## Conclusions

In this review, we summarized recent findings on the high prevalence of depression in women with CHD and its association with increased risk for adverse cardiovascular events and mortality. A number of studies suggested that this association may be explained in part by biological mechanisms such as endothelial dysfunction, subclinical atherosclerosis, inflammation, and autonomic dysregulation, though the current data suggest that they do not explain the majority of the association. In contrast, social and behavioral mechanisms such as physical inactivity and decreased level of social support are increasingly being shown to play an important role in the relationship between depression and cardiovascular risk, particularly in women. Despite recommendations for universal screening of depression in patients with CHD, implementation of screening guidelines remains a challenge, and screening may be less likely to occur in women as compared to men. Unfortunately, psychological and pharmacologic interventions of depression in patients with CHD have thus far shown only limited benefit with regards to cardiac outcomes, though new models of collaborative, personalized care hold promise. Future research is needed to clarify the mechanisms that underlie sex-specific differences in depression and cardiovascular risk and to identify effective strategies of depression management that also reduce cardiovascular morbidity and mortality.

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