

# Depression and Cardiovascular Disease

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The Cartesian notion that mind and body are two separate dualities has, thankfully, long been abandoned and it is now generally accepted that neurological function has physiologic effects on most bodily systems. It is not surprising that what we call "states of mind" (eg, depression and anxiety) have profound effects on cardiovascular biology and outcomes, and vice versa. In spite of the evidence linking depression and cardiovascular disease, physicians still pay insufficient attention to depression in women. While they may be careful in assessing other risk factors, such

as high cholesterol or hypertension, few systematically assess depression.

This article reviews evidence linking depression and cardiovascular morbidity and mortality in postmenopausal women, as well as the effects of hormone therapy (HT) on depression. It also summarizes the recommendations for screening and referral.

## Prevalence of Depression

Depression is two to three times more common in women than in men, and the prevalence of major depression ranges between 6% and 17%;<sup>1</sup> subclinical or mild to moderate depression may be more common. The Behavioral Risk Factor Surveillance System (BRFSS), a continuing telephone survey that uses random-digit dialing to assess health-

related information, reported that among adults ages 45 and older (n=129,499) the prevalence of lifetime diagnosis of depression was 16.3% and the prevalence of current depression was 8.4%.<sup>2</sup> In the Women's Health Initiative (WHI), current depression (as measured by being above a cut-point that has shown good sensitivity and specificity on a screening instrument) was more common in the younger postmenopausal women, with a prevalence of 14.1% among those 50-59, 10.0% among those 60-69 and 8.5% among those 70-79 years of age.<sup>3</sup> In the Framingham study approximately 11% were depressed (CES-D [a common epidemiologic screening instrument] score >16).<sup>4</sup> Depression is more common in African-American women and in Hispanic women than in white women, and its prevalence is lowest in Asian women.<sup>3</sup>

## Relation of Depression to CVD

The relation of depression to cardiovascular disease (CVD) has been amply demonstrated as a correlate of cardiovascular comorbidities, and as a precursor to and a consequence of cardiovascular events. There is a good deal of literature showing that depression is 2 to 3 times more common following a heart attack than in the general population. In the BRFSS, prevalence of current depression was twice as high among those who had had a stroke or myocardial infarction (MI).<sup>2</sup> Furthermore, prognosis is poorer among heart attack victims who are depressed.<sup>5,6</sup> There is, however, also accumulating

evidence that depressive symptoms, depressive mood or subclinical depression precede heart attacks or stroke.<sup>3,4,7</sup>

In the Systolic Hypertension in the Elderly Program, a randomized, placebo-controlled, double-blind clinical trial of antihypertensive therapy in men and women age 60 or older, increase in depressive symptoms over time, as measured by the CES-D, was associated with a significant and substantial excess risk of death and stroke or MI. Depression was an independent predictor of these events in both placebo and active drug groups, and the association was strongest as a risk factor for stroke among women.<sup>7</sup> The WHI showed that CVD events were about 40% higher in depressed women than in non-depressed women. Furthermore, in women with no history of CVD, baseline depression was associated with a 58% higher risk for CVD-related death.<sup>3</sup> Figure 1 shows crude event rates by depression status; with the exception of cancer, those rates are higher for those depressed than for those not depressed, indicating that depression is associated with cardiovascular endpoints and not with cancer. In the Framingham Study, among those who were younger than 65 years, those who were depressed had a 4-fold greater risk of developing stroke or a transient ischemic attack than did the participants who were not depressed, but there was no association between depression and stroke among those 65 years or older.<sup>4</sup>

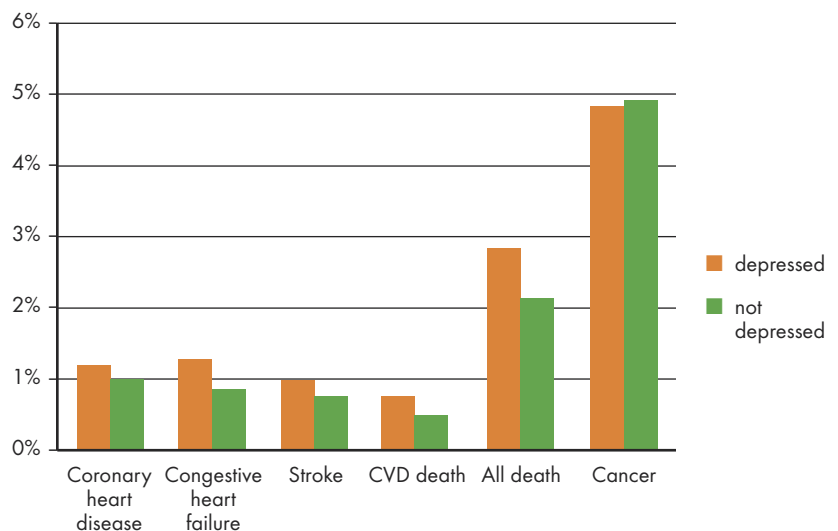
### Treatment of Depression and CVD

Unfortunately, there are no definitive studies indicating that treating depression will prevent cardiovascular events in women without established coronary heart disease (CHD). The only clinical trials of depression treatment were in patients who already had heart disease. Some studies have shown a beneficial effect in secondary

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prevention (ie, among those with established CHD). The Sertraline Antidepressant Heart Attack Randomized Trial of 369 patients showed no difference in the primary endpoint (left ventricular ejection fraction) between those who were on sertraline and those on placebo, but was underpowered to determine whether sertraline reduced MI or death. Nevertheless, when var-

ious endpoints were combined (death, MI, stroke, congestive heart failure and angina) those on sertraline had fewer of the composite events than those on placebo, albeit a non-statistically significant difference.<sup>8</sup> The larger (n=1,834 men and women) Enhancing Recovery in Coronary Heart Disease study<sup>9</sup> showed that cognitive behavioral therapy did not reduce MI or death, although it helped the depression. Patients who did not respond to cognitive behavioral therapy or who had severe depression were treated with antidepressants (less than 10% of the participants at baseline and about 20% by the end of follow-up). These patients had a significant (42%) reduction in death or recurrent MI as compared to the depressed patients not receiving antidepressants. This was not, however, a randomized trial of antidepressants, but rather an observational analysis within a randomized trial of cognitive therapy; it should, therefore, be cautiously interpreted.<sup>9</sup>



**Figure 1.** Women's Health Initiative findings: Percentage of depressed versus not depressed women experiencing cardiovascular events (unadjusted).\*

Current or History of Depression (n= 20,130); not depressed (n= 71,546)

\*Adapted from: Wassertheil-Smoller S, et al.<sup>3</sup>

## Depression and Hormone Replacement

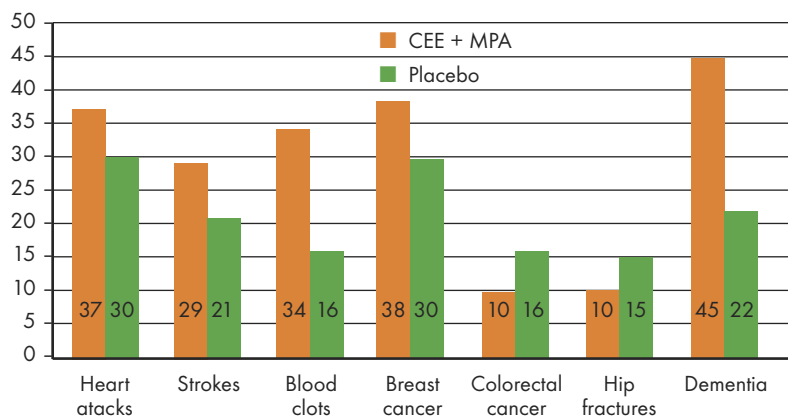
Menopause is associated with a range of vasomotor symptoms, sleep disturbances and mood swings. In the WHI clinical trial of estrogen plus progestin versus placebo (n= 16,608), about 12% of women reported moderate or severe vasomotor symptoms at baseline.<sup>10</sup> In the trial of estrogen alone versus placebo in hysterectomized women (n=10,739), about 17% reported such symptoms.<sup>11</sup> Thus, between 83% and 88% of postmenopausal women do not suffer from vasomotor symptoms or have only mild symptoms. While severe menopausal symptoms were not an exclusion criterion in these trials, it may be that women with severe symptoms chose not to participate since they did not wish to be randomized to placebo. Unfortunately, while other studies asked about symptom frequency, they did not assess severity or tolerability. In the Study of Women Across the Nation, 11% of women ages 40-52 reported 6 or more days of vasomotor symptoms in the previous 2 weeks; 29% reported 1-5 days and 60% reported no such symptoms. Women with more frequent symptoms tended to be less educated, with lower incomes, less likely to be working, less physically active, more likely to smoke, to be older, to be heavier and to have reported premenopausal symptoms. African-Americans reported the highest rate of symptoms of 6 or more days' duration and Asian women the lowest rate. The percent reporting frequent symptoms peaked in the early perimenopause (about 30%) to late perimenopause and stabilized by the late perimenopause-to-postmenopausal period.<sup>12</sup>

Many women turn to HT to relieve menopausal symptoms; indeed, HT does improve sleep problems and some vasomotor symptoms. However, HT in the form of estrogen plus prog-

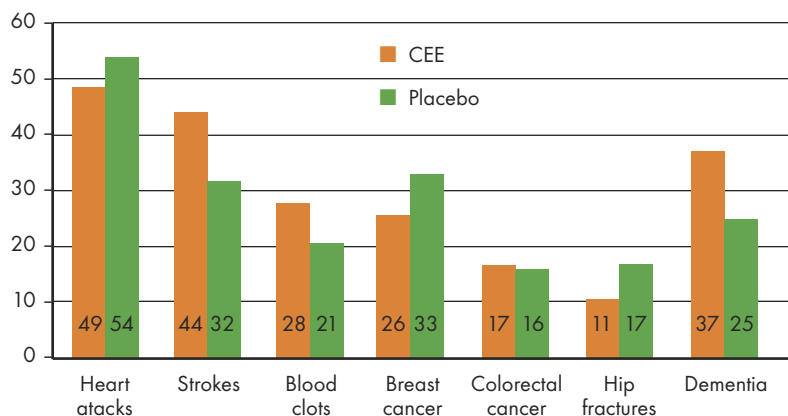
estin carries proven risks of breast cancer and heart disease, pulmonary embolism,<sup>13</sup> stroke,<sup>14</sup> and dementia (assessed in women over age 65)<sup>15</sup> and, while it protects against colorectal cancer and fractures, the overall health risks exceed benefits in healthy postmenopausal US women.<sup>13</sup> Fortunately, the increased risk of breast cancer associated with the use of estrogen plus progestin declines markedly soon after discontinuation of combined HT.<sup>16</sup>

Overall, the risk-benefit-ratio is somewhat better for women who have

had a hysterectomy and who are on estrogen alone than it is for women with a uterus who are on estrogen plus progestin. Estrogen alone in hysterectomized women increases the risk of stroke,<sup>17</sup> decreases the risk of hip fracture, and does not affect CHD incidence; there may also be a possible reduction in breast cancer risk, but this needs further investigation.<sup>18</sup> Estrogen alone also increases the risk of dementia or mild cognitive impairment (Figure 2).<sup>19</sup> These findings pertain to conjugated equine estrogens and



**Figure 2a.** Women's Health Initiative E+P (CEE + MPA) trial: Absolute (annualized) risk.\*  
Number of cases per 10,000 women per year



**Figure 2b.** Women's Health Initiative E-alone (CEE) trial: Absolute (annualized) risk.\*  
Number of cases per 10,000 women per year

\*Adapted from: Rossouw JE, et al,<sup>13</sup> Shumaker SA, et al,<sup>15</sup> Anderson GL, et al,<sup>18</sup> Shumaker SA, et al.<sup>19</sup>

medroxyprogesterone given in daily doses of 0.625 mg and 2.5 mg, respectively. The WHI prompted the FDA to add labeling stating that HT should be given in the lowest doses and for the shortest time to relieve postmenopausal symptoms. There are no conclusive clinical trials testing other preparations or lower dosages; however, in the absence of such evidence there is no reason to suspect that they would act differently from the most common oral preparations tested. The FDA labeling states, “In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.” Thus, in view of the overall undesirable effects of HT on important causes of morbidity and mortality, it is important to examine the effects of HT on depression and quality of life so that a woman may decide whether she wishes to take the health risks in the hopes of reaping quality-of-life benefits.

While it has been thought that HT may relieve depressive symptoms, the only large-scale clinical trials that could address this issue, the WHI hormone trials, have not shown such an effect. In the WHI study of the effects of estrogen plus progestin, depression (as assessed by an abbreviated version of the CES-D scale) showed small and similar changes in scores among women after 1 year of treatment with estrogen plus progestin or with placebo.<sup>20</sup> In the estrogen-only versus placebo trial among women with a hysterectomy, the results were similar.<sup>12</sup> In fact, of 13 sub-scales assessing quality of life there were small but statistically significant benefits in only three areas—sleep dis-

turbances, physical functioning and bodily pain—after 1 year on estrogen plus progestin, and these differences disappeared after 3 years. Women in the WHI were ages 50–79 (average age, 63) and it may be that in younger women in the perimenopausal period, HT does affect depression. However, in a WHI analysis of the younger women (ages 50–54 and, thus, closest to perimenopause) who reported moderate-to-severe vasomotor symptoms at baseline, estrogen plus progestin showed benefit with regard to sleep disturbances, but no significant improvements in any of the other health-related quality of life measures, including depression, even though there was relief of vasomotor symptoms.<sup>10</sup> For women on estrogen alone, a sleep benefit was seen at 1 year and no differences in any of the other measures. This suggests that HT has no significant effect on depression in postmenopausal women, even though it does substantially decrease hot flashes and night sweats.

### Depression after Discontinuing HT

Many women discontinue HT after a while and, in the year after the results of the WHI clinical trial of estrogen plus progestin were released, prescriptions of Prempro dropped by 66%.<sup>21</sup> What happens to menopausal symptoms after stopping HT? Are women permanently “cured” of such symptoms? Apparently not. It depends on the symptoms women had before starting HT. A year after the trial of the WHI estrogen-plus-progestin trial was stopped, women with a mean age of 69 years and an average of 5.7 years on HT were asked about their symptoms. The biggest determinant of symptoms after stopping HT was whether the women had symptoms before starting HT.<sup>22</sup> Women who had symptoms of depression before starting the study medications were about 4 times as likely to have symp-

toms after stopping either placebo or the hormone pills as those who had no such baseline symptoms. Nevertheless, among those with no prior depression, those who stopped the hormones had a small but significantly higher rate of depression symptoms (8.6%) than those who stopped placebo pills (5.6%). A similar, but non-significant, finding occurred among those who were initially depressed.

Overall, it appears that women who take hormones have no appreciable difference in most health-related quality-of-life measures (including perceptions of general health, physical or social functioning, energy or fatigue, mental health, depressive symptoms), although they report considerable relief of vasomotor symptoms. Estrogen, with or without a progestin, has a beneficial effect on sleep disturbances, and those on estrogen with progestin also experience improvement in bodily pain. After discontinuing hormones, women are likely to have the same symptoms they had before starting, meaning that the HT may just postpone symptom appearance.

### Conclusions: Recommendations and Guidelines

There are no official recommendations for screening patients who are free of CHD, but the American Heart Association (AHA) provides recommendations for patients with CHD.<sup>23</sup> In view of findings that show that depression is about 3 times more common after an MI than in the general population, physicians should be aware of the increased risk of depression and its consequences in patients who have had a cardiovascular event, and should routinely screen for depression in such patients. The AHA recommends the Patient Health Questionnaire (PHQ-2), which has two items that ask whether the person is feeling down or depressed and whether she exhibits little interest

or pleasure in doing things. If the answer is yes to either of these items, the full 9-item scale PHQ-9 should be administered (Table). The AHA recommends that if the PHQ-9 score is 10 or greater, or if the patient reports suicidal thoughts (question 9), the patient should be referred for professional diagnosis and management.

There are other brief screening instruments for depression that can also easily be used in clinicians' offices. Although treatment for depression in patients with CHD has not been shown to reduce cardiovascular events, depression has been associated with less adherence to preventive and treatment measures and, of course, results in a poorer quality of life. This underscores the importance of paying appropriate attention to such issues.

An important and unresolved question is whether generally healthy women who have no history of heart disease should be screened routinely by obstetrician-gynecologists or primary care physicians. There are no conclusive, or even suggestive, recommendations for this, but in postmenopausal women it would seem to be a good idea, if primarily for the reasons of improving quality of life, putting it in the context of the woman's physical complaints and enhancing her chances of adhering to prescribed therapy for numerous conditions. All too often physicians may dismiss an older woman's complaints as just that—complaints—rather than symptoms of depression, and pay scant attention to them. Not surprisingly, women anticipating such a reaction may be hesitant to complain when they should. Brief depression screening by gynecologists and primary care physicians may impel the physician to spend more time with the patient and assess whether she needs to be referred further. And it will serve as a reminder that there is no separation of mind and body. ■

**Table.** Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? Read each item carefully, and circle your response.				
	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thinking that you would be better off dead or that you want to hurt yourself in some way	0	1	2	3
Totals				

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*This article includes discussion of off-label use of medication.*

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