Obstructive Sleep Apnea/Hypopnea Syndrome and Poor Response to Sertraline in Patients With Coronary Heart Disease

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ABSTRACT

Objective: Evidence from several clinical trials in patients with coronary heart disease suggests that depression that does not respond to treatment is associated with a particularly high risk of adverse cardiac outcomes. The purpose of this study was to determine whether obstructive sleep apnea/hypopnea syndrome (OSAHS) is associated with a poor response to antidepressant medication in patients with coronary heart disease.

Method: This was a secondary analysis of data from a randomized, double-blind, placebo-controlled clinical trial of omega-3 fatty-acid augmentation of sertraline for depression in patients with coronary heart disease. Patients with documented coronary heart disease were recruited between May 2005 and December 2008 from cardiology practices in St Louis, Missouri, and through cardiac diagnostic laboratories affiliated with Washington University School of Medicine, St Louis, Missouri. One hundred five patients (mean age = 58 years) with coronary heart disease and current major depressive disorder (*DSM-IV*) were randomized to receive sertraline plus either omega-3 or placebo for 10 weeks. Cyclical heart-rate patterns associated with OSAHS were detected via ambulatory electrocardiography prior to treatment. Symptoms of depression were measured at baseline and follow-up with the Beck Depression Inventory-II (BDI-II) and the 17-item Hamilton Depression Rating Scale (HDRS-17). The primary endpoint was the BDI-II score at 10 weeks.

Results: Thirty of the 105 patients (29%) were classified as having probable moderate to severe OSAHS on the basis of nighttime heart-rate patterns. These OSAHS patients had significantly higher scores on both the BDI-II ($t = -2.78$, $P = .01$) and the HDRS-17 ($t = -2.33$, $P = .02$) at follow-up as compared to the reference group. Adjustment for baseline depression score, treatment arm (omega-3 vs placebo), body mass index, and inflammatory markers did not change the results. Patients with OSAHS reported higher item scores at follow-up on all depressive symptoms measured with the BDI-II compared to those without OSAHS.

Conclusions: Obstructive sleep apnea/hypopnea syndrome is associated with a relatively poor response to sertraline treatment for depression. Future research should determine the contribution of OSAHS to the increased risk of adverse cardiac outcome associated with treatment-resistant depression.

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Depression is associated with morbidity and mortality in patients with coronary heart disease.[1,2] Randomized controlled trials focusing on the effects of antidepressant treatment on depression and cardiac outcome have found modest effects on depressive symptoms but no effect on cardiac outcome.[3,4] Secondary analyses of these studies have shown that patients who did not respond to the antidepressant treatment were at increased risk of adverse cardiac events.[5,6] Therefore, depression that does not respond to treatment may be associated with a particularly high risk of mortality or cardiac morbidity in patients with coronary heart disease.[7] There are no well-established risk factors for nonresponse to antidepressant treatment in patients with coronary heart disease.[6,7] Obstructive sleep apnea/hypopnea syndrome (OSAHS) has been linked to treatment-resistant depression in depressed psychiatric patients.[8–10] However, this link has not yet been investigated in patients with coronary heart disease.

Obstructive sleep apnea/hypopnea syndrome is a chronic, sleep-related breathing disorder characterized by recurrent complete blockage (apnea) or partial blockage (hypopnea) of the upper airway. Obstructive sleep apnea/hypopnea syndrome is a potent trigger of nocturnal myocardial ischemia and dysrhythmias characteristic of cardiac sympathetic predominance and is associated with low heart-rate variability. Consequently, OSAHS is a significant risk factor for acute myocardial infarction and sudden cardiac death in patients with coronary heart disease.[11–14] Obstructive sleep apnea/hypopnea syndrome is common in patients with coronary heart disease, with an estimated prevalence of 30%–50%.[15–17] Despite its high prevalence and associated risk for cardiac events, OSAHS is seldom identified or treated in patients with coronary heart disease.[18]

Obstructive sleep apnea/hypopnea syndrome is usually diagnosed by polysomnography at a sleep medicine laboratory. However, Guilleminault et al[19] observed that OSAHS can also be identified from a cyclical heart-rate pattern that begins with a slowing in heart rate, sometimes leading to bradycardia, shortly after the onset of the apneic episode. The heart rate then shifts abruptly to tachycardia with the resumption of breathing and concludes with a return to baseline if there is a sufficiently long interval of normal breathing before the next apneic episode.[19] Previous studies have reported a correlation of $r = 0.96$ between the frequency of apneic events associated with an O_2 desaturation of ≥ 3% during polysomnography and the frequency of this heart-rate pattern on simultaneous electrocardiography.[20] The characteristic pattern can be detected in ambulatory electrocardiography data and has been shown to be a moderately to highly sensitive and specific test, with or without oximetry, for moderate to severe OSAHS.[20,21]

The purpose of this study was to test the hypothesis that the presence of OSAHS, as identified from the cyclical heart-rate pattern, is associated with a poor response to antidepressant treatment.

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Clinical Points

- Depression and obstructive sleep apnea/hypopnea syndrome (OSAHS) are both associated with cardiac mortality in patients with heart disease.
- Both depression and OSAHS are very common in patients with heart disease.
- Untreated OSAHS is associated with a poor response to sertraline treatment in patients with heart disease and major depression.

METHOD

Subjects and Study Design

This question of whether OSAHS is associated with poor response to antidepressant treatment was examined in a secondary analysis of data collected for a randomized, double-blind, placebo-controlled clinical trial (clinicaltrials.gov Identifier: NCT00116857) of omega-3 augmentation of sertraline for depression in patients with coronary heart disease. The clinical trial found no effects of omega-3 augmentation on depression outcomes.[22]

Patients with documented coronary heart disease were recruited between May 2005 and December 2008 from cardiology practices in St Louis, Missouri, and through cardiac diagnostic laboratories affiliated with Washington University School of Medicine, St Louis, Missouri. Patients were excluded if they (1) had cognitive impairment, comorbid psychiatric disorders, psychosis, a high risk of suicide, or current substance abuse; (2) had an acute coronary syndrome within the previous 2 months, a left ventricular ejection fraction < 30%, advanced malignancy, or were physically unable to participate; (3) were taking an antidepressant, anticonvulsant, lithium, or omega-3 supplements; (4) had a known sensitivity to sertraline or omega-3; or (5) refused to participate or were disqualified by their physician from participating in the study. Those who met *DSM-IV* criteria for a current major depressive episode on the basis of a structured depression interview,[23] scored ≥ 16 on the Beck Depression Inventory-II (BDI-II),[24] and met none of the exclusion criteria were enrolled in the trial. Written informed consent was obtained from all study participants. The study was approved by the Human Research Protection Office at Washington University, St Louis, Missouri.

After a 2-week run-in phase, patients who continued to meet the depression criteria and who were not excluded for other reasons were fitted with an ambulatory electrocardiography monitor for a 24-hour recording. Following baseline assessments, patients were randomized to receive 50 mg per day of sertraline plus either 2 capsules per day of omega-3 fatty acid ethyl esters (930 mg of eicosapentaenoic acid [EPA] and 750 mg of docosahexaenoic acid [DHA]) or 2 capsules per day of corn-oil placebo for 10 weeks. Compliance with both the sertraline and the omega-3 or placebo capsules was checked weekly by pill counts and by asking the participant to confirm that all pills that had been removed were actually taken as prescribed.

At baseline and 10 weeks, 40 mL of blood was drawn. Red-blood-cell membrane EPA + DHA was measured pretreatment and posttreatment by capillary gas chromatography and expressed as a percentage of the total red-blood-cell fatty acids (ie, the Omega-3 Index).[25] High-sensitivity C-reactive protein and interleukin-6 were measured by standard techniques. Further details on the design and methods of this study can be found elsewhere.[22]

Ambulatory Electrocardiography Recording

The Holter electrocardiography recordings were scanned at the Heart Rate Variability Laboratory at Washington University, St Louis, Missouri, with Cardioscan Holter (version 52a; DMS Holter, Stateside, Nevada) or MARS Holter (version 7.01; GE Medical Systems, Milwaukee, Wisconsin) scanning software. A continuous stream of instantaneous, accurately annotated (beat-to-beat) interbeat intervals was extracted from the electrocardiograms, and heart-rate tacho grams (plots of instantaneous heart rate vs time) were produced. Only validated normal-to-normal interbeat intervals were used to produce the tachograms. The cyclical heart-rate pattern criteria required a series of at least 3 abrupt tachycardias, each lasting > 10 seconds, followed by a return to baseline and occurring > 30 seconds and < 90 seconds apart.[20] This pattern was identified by applying the algorithm developed at the Washington University School of Medicine, St Louis, Missouri.[20] In a recent study using this method, the presence of these heart-rate patterns had a sensitivity of 98% and a positive predictive value of > 92% for identifying patients with moderate to severe OSAHS, defined as ≥ 30 episodes of apneas and/or hypopneas per hour of sleep as determined from polysomnography.[26] Patients with at least 2 consecutive hours of the cyclic variation of heart-rate pattern during sleep were classified as having OSAHS. These classifications were confirmed by visual inspection.

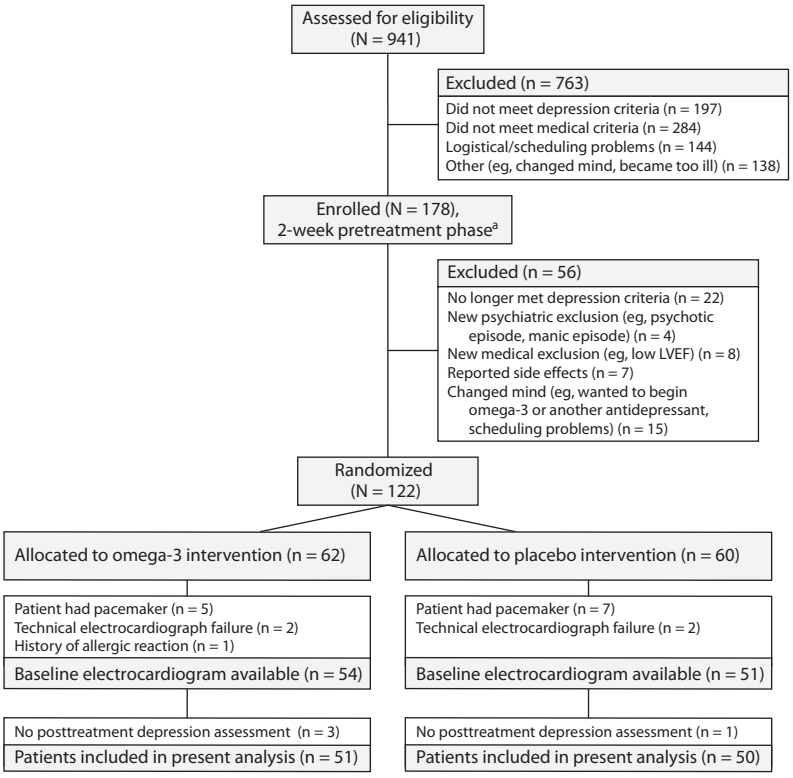
Assessment of Depressive Symptoms

Symptoms of depression were measured at baseline and follow-up with the BDI-II and the 17-item Hamilton Depression Rating Scale (HDRS-17). The BDI-II is a 21-item depression symptom questionnaire with scores ranging from 0 to 63. The HDRS-17 is an interview-based measure of depression symptom severity. Both are widely used for assessing depression outcomes and have established reliability and validity.[27,28] The primary endpoint was the BDI-II score at 10 weeks, consistent with the primary outcome of the clinical trial.[22] The HDRS-17 score at 10 weeks was used as a secondary outcome.

Statistical Analysis

χ^2 tests and analyses of variance were used to test for differences in demographic, psychiatric, and medical characteristics and in treatment adherence between patients with versus without OSAHS. Analysis-of-covariance models adjusting for baseline depression scores and treatment

Figure 1. Study Flowchart: Investigation of Association Between Obstructive Sleep Apnea/Hypopnea Syndrome and Poor Response to Antidepressant Treatment in Patients With Coronary Heart Disease



[a]Participants received 25 mg of sertraline plus 2 placebo capsules daily.
Abbreviation: LVEF = left ventricular ejection fraction.

assignment (omega-3 augmentation or placebo) were used to compare patients with versus without OSAHS on week-10 BDI-II and HDRS-17 scores. The interaction between OSAHS and treatment assignment was tested to determine whether the hypothesized effect of OSAHS on the response to sertraline depends on the presence or absence of omega-3 augmentation. In secondary analysis-of-covariance models, we tested the possible confounding effects of body mass index, high-sensitivity C-reactive protein, and interleukin-6, as obesity and inflammation have been associated with poor treatment response to antidepressant treatment.[29,30] Cohen *d* was calculated for the OSAHS versus non-OSAHS group difference in BDI-II scores at follow-up. To explore whether the difference in the depression outcome might be explained by nonspecific symptoms such as fatigue, analysis of variance was used to identify differences in individual depressive symptoms at 10 weeks on the BDI-II in patients with versus without OSAHS.

All statistical tests were 2-tailed, with $P < .05$ denoting significance. The software used for all statistical analyses was SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 122 patients enrolled and randomized in the clinical trial, 12 patients did not undergo 24-hour Holter monitoring because they had a pacemaker, and 1 additional patient could not be monitored due to a history of allergic reaction to the electrocardiography lead adhesive. Of those who underwent monitoring, heart rate could not be measured in 4 patients due to equipment failures. Thus, 105 patients had usable electrocardiography data at baseline (Figure 1).

Baseline Characteristics

Consistent with the findings of previous studies of patients with coronary heart disease,[15,16] the prevalence of OSAHS was high in this sample. Thirty of the 105 patients (29%) were classified as having OSAHS on the basis of heart-rate patterns during self-reported sleep. Table 1 compares the demographic and medical characteristics of the patients with versus without OSAHS. Patients with OSAHS had a higher body mass index and higher high-sensitivity C-reactive protein levels than those without OSAHS. There were no differences in the severity or duration of the present depressive episode, history of depression, or history of depression treatment.

Posttreatment (10-week) Outcomes

Four participants did not complete the posttreatment depression assessment. As shown in Table 2, treatment adherence did not differ between patients with and without OSAHS. After 10 weeks of treatment, patients with OSAHS had a mean score of 19.0 (SD = 11.0) on the BDI-II. The mean score of the comparison group was 13.0 (SD = 9.2). Patients with OSAHS had significantly higher BDI-II ($t = -2.78$, $P = .01$) and HDRS-17 ($t = -2.33$, $P = .02$) scores compared to patients without OSAHS. These results remained significant for both the BDI-II ($t = -2.49$, $P = .01$) and the HDRS-17 ($t = -2.03$, $P = .04$) after controlling for baseline depression score and treatment group (omega-3 or placebo). The interaction between OSAHS and treatment group provided no evidence that the association between depression and OSAHS differed by group at follow up (BDI-II: $F = 3.30$, $P = .07$; HDRS-17: $F = 0.09$, $P = .77$). Further adjustment for body mass index, high-sensitivity C-reactive protein, and interleukin-6 did not affect the association between OSAHS and treatment response to sertraline (Table 2). The standardized effect (Cohen *d*) of OSAHS was 0.62 for the BDI-II follow-up score after controlling for baseline depression, treatment group, body mass index, and high-sensitivity C-reactive protein.

Individual Depressive Symptoms

Compared to patients without OSAHS, those with OSAHS reported higher item scores on all depressive symptoms measured at follow-up with the BDI-II. The difference

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Table 1. Baseline Demographic and Medical Characteristics of Patients With Versus Without Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) (N = 105)

Characteristic	OSAHS Present (n = 30)	OSAHS Absent (n = 75)	*P* Value
Treatment assignment, omega-3, n (%)	17 (56.7)	37 (49.3)	.50
Age, mean (SD), y	58.7 (9.9)	58.4 (8.8)	.89
Sex, female, n (%)	8 (26.7)	28 (37.3)	.30
Race, white, n (%)	22 (73.3)	65 (86.7)	.10
Education, > 12 years, n (%)	20 (66.7)	48 (64.0)	.80
Body mass index, mean (SD)	37.0 (9.3)	31.6 (5.8)	< .001
Smoking, n (%)	9 (30.0)	15 (20.0)	.27
Hypertension, n (%)	24 (80.0)	57 (76.0)	.66
Diabetes, n (%)	13 (43.3)	26 (34.7)	.41
History of myocardial infarction/acute coronary syndrome, n (%)	17 (56.7)	44 (58.7)	.85
History of coronary artery bypass graft, n (%)	14 (46.7)	22 (29.3)	.09
History of percutaneous transluminal coronary angioplasty, n (%)	17 (56.7)	49 (65.3)	.41
New York Heart Association classification, n (%)			.24
No chronic heart failure	17 (56.7)	51 (68.0)	
Class I	3 (10.0)	7 (9.3)	
Class II	6 (20.0)	15 (20.0)	
Class III	3 (10.0)	1 (1.3)	
Class IV	1 (3.3)	1 (1.3)	
Total cholesterol, mean (SD), mg/dL	173.3 (42.8)	170.4 (42.9)	.76
High-density lipoprotein cholesterol, mean (SD), mg/dL	43.3 (16.1)	44.6 (12.6)	.69
Triglycerides, fasting, mean (SD), mg/dL	205.6 (159.7)	174.4 (104.8)	.25
High-sensitivity C-reactive protein, mean (SD), mg/L	7.8 (7.3)	5.0 (5.8)	.04
Interleukin-6, mean (SD), pg/mL	3.9 (3.1)	3.0 (2.4)	.12
Medication use, n (%)			
Aspirin	21 (70.0)	63 (84.0)	.11
Calcium channel blockers	12 (40.0)	22 (29.3)	.29
β-Blockers	22 (73.3)	61 (81.3)	.36
Ace inhibitors	17 (56.7)	34 (45.3)	.29
Statins	20 (66.7)	59 (78.7)	.20
Depression			
History of major depression, n (%)	20 (66.7)	48 (64.0)	.93
Duration of current depressive episode, mean (SD), mo	13.7 (18.4)	13.4 (17.1)	.93
History of depression treatment, n (%)	19 (63.3)	46 (61.3)	.85
Heart rate and frequency (daytime)			
Very low frequency (natural logarithm), mean (SD)	6.9 (0.73)	6.7 (0.91)	.34
Heart rate, mean (SD), beats per minute	74.2 (10.0)	75.1 (11.2)	.71

was significant for appetite disturbance ($P = .002$), decreased appetite ($P = .04$), irritability ($P = .01$), crying ($P = .048$), agitation ($P = .01$), sleep disturbance ($P = .03$), insomnia ($P = .02$), feelings of past failure ($P = .04$), guilt ($P = .03$), self-dislike ($P = .02$), and worthlessness ($P = .04$).

DISCUSSION

The results of the study show that moderate to severe OSAHS, based on heart-rate patterns during sleep, is associated with poor treatment response to sertraline in depressed patients with coronary heart disease. After 10 weeks, the mean score on the BDI-II was 6 points higher for patients with OSAHS compared to patients without OSAHS. This difference could not be attributed to a difference in treatment adherence. The association between OSAHS and treatment response to sertraline remained significant after adjustment for baseline depression severity and treatment group. In addition, body mass index and inflammatory markers did not account for the relationship between OSAHS and treatment response. The patients with OSAHS reported significantly higher scores on a variety of depressive symptoms at follow-up, including symptoms that are not directly related to OSAHS, such as self-dislike, feelings of past failure, guilt, and worthlessness. Thus, the difference in depression outcome was not explained solely by symptoms that are also associated with OSAHS, such as sleep problems or fatigue.

This study raises the possibility that resistance to antidepressant medication might be caused in some cases by undiagnosed OSAHS. The fact that OSAHS is an independent risk factor for cardiac mortality and morbidity could help to explain the adverse cardiovascular outcomes that have been associated in previous studies with treatment-resistant depression. However, OSAHS is also a risk factor for depression,[31] and OSAHS and depression might interact to further increase the risk for cardiac events. There are multiple possible pathways through which depression may lead to adverse outcomes in patients with OSAHS. There is evidence that depression is associated with a diminished hypercapnic ventilatory response.[32–34] In patients with OSAHS and comorbid depression, apneic episodes could be prolonged and could produce greater O_2 desaturation, thereby increasing the risk for cardiac events. Consistent with this possibility, we recently found that depression is associated with prolonged episodes of apnea in patients with OSAHS.[35] Further research is needed to confirm these findings. Additional physiologic mechanisms associated with both OSAHS and depression that could lead to more adverse cardiac outcomes include low heart-rate variability,[36] inflammatory processes, endothelial dysfunction, oxidative stress, platelet aggregation, and metabolic dysfunction.[14,18,37,38]

Although OSAHS is a common risk factor for further morbidity and mortality in patients with heart disease, it is seldom diagnosed or treated.[18] A recent review[18] concluded that patients with cardiovascular disease should be routinely screened for OSAHS. Although polysomnography is the gold standard for diagnosing OSAHS, a medical history and physical examination with validated questionnaires and nighttime electrocardiogram patterns can be used to screen for the disorder.[14] Obstructive sleep apnea/hypopnea syndrome can be effectively treated by continuous positive airway pressure, which prevents upper airway occlusion during sleep.[39] Continuous positive airway pressure has also been shown to lower blood pressure, attenuate signs of early atherosclerosis, and, in patients with heart failure, improve cardiac function.[40] Since depression that does not respond to standard antidepressant treatment may be associated with a particularly high risk of adverse medical outcomes in

Table 2. Characteristics at 10-Week Follow-Up in Patients With Versus Without Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) (N = 101)

Measure	OSAHS Present (n = 30), Mean (SD)	OSAHS Absent (n = 71),[a] Mean (SD)	*P* Value
Beck Depression Inventory-II			
Baseline score	30.0 (9.0)	28.2 (9.0)	.35
Follow-up score at 10 weeks	19.0 (11.0)	13.0 (9.2)	.01
Adjusted for baseline	18.4 (9.1)	13.3 (9.1)	.01
Adjusted for baseline and treatment group	18.3 (9.2)	13.3 (9.1)	.01
Adjusted for baseline, treatment group, and body mass index[b]	19.0 (9.4)	13.2 (9.2)	.01
Adjusted for baseline, treatment group, body mass index, and high-sensitivity C-reactive protein[c]	19.5 (9.3)	13.8 (9.1)	.01
Adjusted for baseline, treatment group, body mass index, and interleukin-6[d]	19.3 (9.2)	13.2 (9.0)	.01
17-Item Hamilton Depression Rating Scale			
Baseline score	21.2 (6.7)	20.0 (4.8)	.30
Follow-up score at 10 weeks	11.6 (7.4)	8.4 (5.8)	.02
Adjusted for baseline	11.3 (5.9)	8.6 (5.9)	.04
Adjusted for baseline and treatment group	11.3 (6.0)	8.6 (6.0)	.04
Adjusted for baseline, treatment group, and body mass index[b]	11.7 (6.2)	8.5 (6.1)	.03
Adjusted for baseline, treatment group, body mass index, and high-sensitivity C-reactive protein[c]	12.0 (6.2)	9.1 (6.1)	.04
Adjusted for baseline, treatment group, body mass index, and interleukin-6[d]	11.9 (6.2)	8.6 (6.1)	.02
Omega-3 Index (percentage of EPA + DHA in red blood cells)			
Baseline score	4.8 (1.5)	4.6 (1.5)	.46
Follow-up score	6.5 (2.2)	5.9 (2.1)	.26
Cumulative treatment adherence (percentage of days pill removed)			
Omega-3/placebo	96.7 (5.4)	97.8 (2.8)	.20
Sertraline	98.5 (2.6)	98.9 (2.2)	.50

[a]Four participants without obstructive sleep apnea/hypopnea syndrome were lost to follow-up.
[b]Body mass index value was missing for 1 participant.
[c]High-sensitivity C-reactive protein measurement was missing for 7 participants.
[d]Interleukin-6 measurement was missing for 1 participant.
Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid.

patients with heart disease,[7] OSAHS is a factor that should be taken into account in future depression treatment trials.

This study has some limitations. First, we assessed the presence of OSAHS with electrocardiography recordings, although polysomnography is the gold standard for diagnosing OSAHS. However, nighttime electrocardiography patterns can be used to screen for the disorder,[14] and previous research has shown that the electrocardiography pattern detected in this study is a reliable and valid method for detecting moderate to severe OSAHS.[20] In addition, patients diagnosed with OSAHS by the heart-rate pattern had a higher body mass index and higher high-sensitivity C-reactive protein levels (both of which are associated with OSAHS) than patients without OSAHS. Since the cyclical patterns of heart rate are most prominent in patients with moderate to severe OSAHS, it is possible that patients with mild but clinically significant OSAHS were not recognized. Moderate to severe OSAHS is consistent with an apnea-hypopnea index corresponding to > 30 apneas and hypopneas per hour of sleep, but results from the Sleep Heart Health Study[41] suggest that even an apnea-hypopnea index as low as 5 is associated with an increased risk of cardiovascular events.

The study also had a relatively small sample size. However, similar to prior studies of patients with coronary heart disease, the prevalence of previously undetected OSAHS was high in this group of patients. Furthermore, this study was based on a secondary analysis of a randomized controlled trial to evaluate the effect of omega-3 augmentation of sertraline for the treatment of depression in patients with coronary heart disease. The participants were treated with a single antidepressant medication at a relatively modest dose. Better outcomes might have been achieved if the participants had been given a higher dose of sertraline or another antidepressant. However, previous studies have found little additional improvement in response rates with higher dosages of sertraline (100–200 mg/d), despite a significant increase in side effects.[42,43] Future research should assess the association between OSAHS and treatment response to standard antidepressant medications using additional antidepressants and formal definitions of treatment resistance.[44]

In summary, this study showed that a heart-rate pattern consistent with OSAHS is associated with poor treatment response to sertraline in patients with coronary heart disease. This association is not explained by differences in body mass index, high-sensitivity C-reactive protein, or interleukin-6, or by nonspecific symptoms common to both OSAHS and depression. Future research should determine the contribution of OSAHS to the increased risks associated with depression and investigate the association of OSAHS with poor response to antidepressant treatment. Additionally, studies are needed to identify better treatments for depression in the presence of OSAHS, especially in patients with heart disease.

Drug names: lithium (Lithobid and others), omega-3-acid ethyl esters (Lovaza), sertraline (Zoloft and others).

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Author contributions: All the authors had access to study data and participated in writing the article.

Potential conflicts of interest: **Dr Carney** or a member of his family owns stock in Pfizer. **Mss Roest** and **Meyer**; **Drs Stein**, **Freedland**, **de Jonge**, and **Rubin**; and **Mr Steinmeyer** report no conflicts of interest relative to this article.

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