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# Inflammation and treatment response to sertraline in patients with coronary heart disease and comorbid major depression

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## Abstract

**Objective—**Treatment-resistant depression has recently emerged as a marker of increased risk for morbidity and mortality in patients with coronary heart disease (CHD). Studies in depressed patients without CHD suggest that elevated markers of inflammation predict poor response to treatment. This may help to explain the increased risk of cardiac events associated with depression. We therefore studied the relationship between pre-treatment markers of inflammation and treatment response in patients with CHD and major depression.

**Methods—**This was a planned, secondary analysis of a clinical trial in which 122 patients with CHD and comorbid major depression were randomly assigned to 50mg of sertraline plus 2g/day omega-3 fatty acids or to 50mg of sertraline plus 2g/day corn oil placebo capsules for ten weeks. Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II). Blood samples were collected at baseline to determine levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). The primary outcome was the post-treatment BDI-II depression score.

**Results—**Baseline levels of hs-CRP, IL-6, and TNF-α were not associated with the 10-week post-treatment depression score (p=0.89, p=0.88, and p=0.31, respectively). Treatment responders (>50% reduction from baseline BDI-II score) did not differ from non-responders in either baseline hs-CRP, IL-6, or TNF-α (p=0.83, p=0.93, and p=0.24, respectively). Similarly, depression remitters (BDI-II ≤8 at post-treatment) did not differ from non-remitters on the three baseline inflammation markers.

**Conclusion—**These findings do not support the hypothesis that elevated baseline inflammatory markers predict poor response to sertraline in patients with CHD and major depression. The explanation for the increased risk of cardiac events associated with poor response to depression treatment remains unclear.



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**Trial Registration:** NCT00116857, www.clinicaltrials.gov.

### Keywords

depression; treatment response; inflammation; coronary heart disease

## Introduction

Depression is a risk factor for cardiovascular morbidity and mortality in patients with coronary heart disease (CHD) [1,2]. There has been growing interest in identifying the depression subtypes that carry the highest risk. Some evidence exists that patients with a first episode of depression and those whose depression began following a cardiac event, may be at especially high risk [3,4]. In addition, there is evidence that depression that does not respond to standard treatment may be a high-risk form of depression. Approximately 20 to 30% of depressed patients fail to respond even to multiple antidepressant treatments [5]. Secondary analyses of several randomized, controlled trials in patients with CHD showed that those who do not respond to depression treatment may be at a particularly high risk for mortality [5]. The explanation for this risk is unknown.

Inflammatory processes have been associated with the progression of coronary artery disease and with cardiac events, including myocardial infarction [6]. A recent meta-analysis found that increased levels of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6), are associated with depression, both with and without comorbid CHD [7]. Another meta-analysis showed that tumor necrosis factor alpha (TNF-α) was also increased in major depression [8].

In depressed patients without heart disease, high baseline levels of inflammatory markers have been associated with poor treatment response [9,10], although not all studies have found this [11]. In a study of patients with a recent acute coronary syndrome (ACS), those with persistent depression showed a trend towards higher baseline and follow-up CRP levels compared to remitted depressed patients [12]. No studies have examined the relationship between pre-treatment inflammation and treatment response in stable CHD patients with major depression. It is possible that elevated levels of inflammatory molecules may explain the increased risk of cardiac events in patients who do not respond well to antidepressant treatment.

The purpose of this study was to determine whether pretreatment levels of high-sensitivity CRP (hs-CRP), IL-6, and TNF-α, predict response to treatment with 50mg/day of sertraline in patients with CHD and comorbid major depression. We hypothesized that high levels of inflammatory markers are associated with poor response to depression treatment.

## Methods

### Participants and Study Design

This study was a planned, secondary analysis of data from a randomized, double-blind, placebo-controlled trial to determine whether omega-3 augmentation improves the efficacy of sertraline for the treatment of major depression in persons with CHD [13]. The study data provided no evidence that omega-3 augmentation increases the efficacy of sertraline for depression in patients with CHD [13]. The methods and results of the trial have been described previously [13].

Briefly, patients were recruited for this study between May, 2005 and December, 2008 from cardiology practices in St. Louis, Missouri, and from cardiac diagnostic laboratories affiliated with Washington University School of Medicine. Patients were eligible to

participate if they had documented CHD, met the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) criteria for a current major depressive episode, had a Beck Depression Inventory-II (BDI-II) score of ≥16, and still had a diagnosis of major depression following the two week pre-randomization phase of the study.

CHD was documented by ≥50% stenosis in ≥1 major coronary artery, a history of coronary revascularization, or hospitalization for an ACS at least 2 months prior to enrollment. Exclusion criteria were 1) cognitive impairment, comorbid major psychiatric disorders, psychosis, a high risk of suicide, or current substance abuse; 2) ACS or revascularization within the previous two months, a left ventricular ejection fraction (LVEF)<30%, a diagnosis of heart failure, advanced malignancy, or a physical impairment that would prevent participation; 3) ongoing use of an antidepressant, anticonvulsant, lithium, or omega-3 supplement; 4) sensitivity to sertraline or omega-3; and 5) physician or patient refusal. All participants gave written informed consent. The study was approved by the Human Research Protection Office at Washington University.

## Intervention

The participants were randomly assigned to the omega-3 or the placebo arm by a permuted block random allocation program (SAS Institute, Cary, NC). All participants were prescribed 50 mg/day of sertraline for 10 weeks. In addition to sertraline, the omega-3 group received 2 g/day omega-3 acid ethyl esters, containing 930 mg eicosapentaenoic acid (EPA) and 750 mg docosahexaenoic acid (DHA). The placebo group received sertraline plus 2 g/day placebo corn oil. The omega-3 fatty acids and corn oil were provided in two capsules each day for 10 weeks. The participants, research nurses, and investigators were blinded to treatment assignment during the trial. In order to assess medication adherence, participants were asked to return any unused pills and to confirm that the pills that were not returned had been taken as prescribed.

## Measurements

**Depression—**The 21-item BDI-II was administered weekly for 10 weeks, starting at baseline, to monitor changes in the severity of depression [14]. At baseline and at a 10-week post-treatment evaluation, interviewer-rated depression severity was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D) [15]. On both scales, higher scores reflect more severe depressive symptoms. Both instruments are widely used for assessing depression outcomes in clinical trials, and have established reliability and validity [14,15]. We defined treatment responders as participants who had a >50% reduction on the BDI-II from baseline. Patients with a post-treatment BDI-II score ≤8 were classified as depression remitters. The primary study outcome was the post-treatment BDI-II score. Secondary outcomes include the post-treatment HAM-D score, and the response and remission rates based on the BDI-II.

## Inflammation

Oral body temperature was measured at baseline in order to exclude patients with infectious diseases or other disorders that could cause a systemic increase in inflammatory markers. Blood samples were drawn at baseline and after 10 weeks of treatment to determine hs-CRP, IL-6, and TNF-α levels. Patients were asked to refrain from taking antihistamines, anti-platelet agents, and nonsteroidal anti-inflammatory agents including aspirin for 24 hours prior to the blood draws. The specimens were spun and frozen immediately.

hs-CRP was determined by an enhanced immunonephelometric assay on a BN II analyzer (Dade Behring; Newark, NJ). This assay can measure hs-CRP levels of less than 1 mg/dL with assay coefficients of variation below 10%. IL-6 and TNF-α were measured by high

sensitivity enzyme-linked immunosorbent assay (ELISA) (Quantikine HS, R&D Systems) according to the manufacturer's specifications.

### Statistical Analyses

Because of the possibility that omega-3 fatty acids might have affected the relationship between inflammation and depression outcome, we tested for interactions between treatment allocation and inflammatory markers in all analyses. If the interaction term was significant, the analysis was stratified by treatment group, otherwise, the analysis was conducted without stratification. A linear regression model was used to examine the relationship between baseline inflammation and post-treatment depression scores, adjusting for baseline depression scores and treatment allocation. Sensitivity analyses were conducted to determine whether the addition of age, sex, smoking status, aspirin and statins altered the association between baseline inflammation and depression outcome. Analysis of variance (ANOVA) was used to compare the baseline levels of inflammatory markers of the responders vs. non-responders and remitters vs. non-remitters. hs-CRP, IL-6, and TNF-α distributions were found to be positively skewed, and therefore natural logarithm-transformed values were analyzed for these variables. The Pearson correlation between change in inflammation from baseline to post-treatment and change in depression score from baseline to post-treatment was also calculated. The distributions of the changes in inflammatory levels were approximately normal. Hence, these raw values were analyzed without transformation. The two-tailed alpha level for significance was set at 0.05. SAS version 9.1 was used for all statistical analyses.

## Results

One hundred twenty-two patients (41 women, 34%) participated in the study. The mean age was 58 ± 9 years. All participants had body temperatures within the normal range on the day of the blood draw. Adherence to sertraline was >98%. Table II displays the pre- and post-treatment depression scores and levels of inflammatory markers. Seven participants did not complete the study. Reasons for discontinuation of participation were: withdrawal to try another antidepressant (n=2), refusal (n=2), insomnia or dizziness (n=2), and hospitalization because of worsening of a pre-existing medical condition (n=1). One hundred fifteen participants completed the study. Of these, baseline hs-CRP, IL-6, and TNF-α levels were measured in 106, 113, and 112 participants, respectively. Patients with missing baseline inflammatory markers or post-treatment depression score did not differ from those who had these data in age, sex or cardiovascular history.

### Baseline inflammatory markers and depression outcomes

No significant interactions were found between treatment allocation and any of the inflammatory markers. Thus, the analyses were performed without stratification. Table I presents the baseline characteristics of the study sample. After adjustment for the baseline BDI-II score and treatment allocation, baseline log-transformed hs-CRP, IL-6, and TNF-α levels were unrelated to the post-treatment BDI-II score (unstandardized regression coefficient (b)=0.10, 95% CI −1.25 – 1.44, p=0.89; b=0.21, 95% CI=−2.42 – 2.84, p=0.88,; and b=−2.94, 95% CI −8.66 - 2.77, p=0.31, respectively).

Similarly, baseline log-transformed hs-CRP, IL-6, and TNF-α levels remained unrelated to post-treatment HAM-D scores (b=0.21, 95% CI=−0.75 – 1.17, p=0.66; b=0.41, 95% CI −1.43 – 2.25, p=0.66; and b=0.28, 95% CI=−3.84 – 4.40, p=0.89, respectively) after adjustment for the baseline HAM-D score and treatment allocation. Adding age, sex, smoking, aspirin and statin use to the regression model only slightly altered the association between the inflammatory markers and treatment outcome (data not shown).

Table II displays the pre- and post-treatment depression scores and inflammatory marker measurements for the total group, and stratified by responders vs. non-responders and remitters vs. non-remitters. Fifty-seven (49.6%) of the 115 patients available at 10-week post-treatment were classified as responders after the 10 weeks of treatment with sertraline and omega-3 or corn oil capsules. The responders did not differ from the non-responders in baseline levels of log-transformed hs-CRP, IL-6 or TNF-α (p=0.83, p=0.93, and p=0.24 respectively). Thirty-three (28.7%) of the 115 patients available at post-treatment were classified as depression remitters. The remitters did not differ from the non-remitters in baseline levels of log-transformed hs-CRP, IL-6, or TNF-α (p=0.33, p=0.53, and p=0.82, respectively).

### Change in inflammatory markers and change in depression scores

Log-transformed levels of hs-CRP (p=0.004) and IL-6 (p=0.00l), but not TNF-α (p=0.19), were higher at ten weeks than at baseline. Change in hs-CRP was not correlated with change in BDI score (Pearson's r=0.08, p=0.42). However, change in hs-CRP was correlated with change in HAM-D score (r=0.20, p=0.04). Change in IL-6 was not correlated with either change in BDI or change in HAM-D score (r=0.10, p=0.31, and r=0.06, p=0.53, respectively). Likewise, change in TNF-alpha was not associated with either change in BDI score (r=0.08, p=0.38) or change in HAM-D score (r = −0.004, p=0.97).

## Discussion

Depression is related to increased cardiac morbidity and mortality in patients with CHD [1,2]. Patients with treatment-resistant depression may be at especially high risk of adverse cardiovascular outcomes, and it has been suggested that inflammation may help explain poor responsiveness to depression treatment [5]. However, in this study of patients with CHD and comorbid major depression, baseline levels of hs-CRP, IL-6, and TNF-α did not predict depressive symptoms following 10 weeks of treatment with sertraline. In addition, neither treatment response or depression remission was predicted by baseline levels of inflammation. Change in inflammatory markers did not correlate with change in the primary measure of depression, the BDI, although change in hs-CRP was weakly correlated (r = 0.20) with change in HAM-D scores.

A recent systematic review of the literature noted that antidepressant medications affect cytokine levels, and that this mechanism appears to influence treatment outcome in depression [16]. In our study, there was no evidence to suggest that baseline inflammation levels were associated with treatment response. This is consistent with the results of a small study (n=23) by Basterzi et al., wherein no difference in IL-6 levels was observed in depressed non-responders compared to responders to selective serotonin reuptake inhibitors [11]. In contrast, Lanquillon et al. observed significantly higher baseline release of IL-6 from peripheral mononuclear cells in non-responders compared to responders in a sample of depressed patients without heart disease [9]. However, as in our study, they found no difference in hsCRP between responders and non-responders [9]. Eller et al. found that higher levels of TNF-α were related to non-response to escitalopram [10]. We did not find an association between TNF-α and treatment non-response to sertraline.

There are several differences between our study and those previously reported, including participant characteristics, type of antidepressant treatment, type of inflammatory markers, and measurement procedures. CHD itself is characterized by inflammation [17], and this may have made it difficult to detect a relationship between inflammation and depression treatment response in this study population. Even among patients with CHD, however, higher levels of inflammatory markers have been reported in depressed compared to non-depressed patients [7]. The potential to detect a relationship between inflammation and

depression treatment outcomes may have also been limited by medication use in patients with CHD, since medications, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antiplatelet agents, statins, and antidiabetic agents, reduce levels of CRP and other inflammatory markers [18]. However, most patients in this study were on stable regimens of cardiac medications throughout the study. Exclusion of patients on these drugs would have limited the generalizability of the findings, since they are prescribed to almost all patients with CHD. Although studies differ in the inflammatory markers that are assessed, those in our study (hs-CRP, IL-6, and TNF-α) have been associated with major depression in meta-analyses [7,8], and have been reported as independent predictors of cardiovascular events [19,20].

Log-transformed hs-CRP and IL-6 levels actually increased from baseline to the ten week post-treatment assessment. This is likely due to the study enrollment criteria, and to subsequent medical events unrelated to participation in the study. Patients were eligible for enrollment only if they had been medically stable for at least two months and were free of recent acute illness or infection. Over the ten weeks of the trial, however, seven patients were hospitalized or seen in the emergency department for cardiac events (including MI, angioplasty, and an implanted defibrillator), and seven others were hospitalized for noncardiac causes (including injury from a fall, kidney stones, and a severe allergic reaction) [13]. In addition, some participants experienced colds, influenza, injuries, etc., over the course of the ten week trial. Any of these events may have resulted in higher levels of inflammation than those recorded at baseline.

Strengths of the present study include enrollment of patients with CHD and major depression, and the exclusion of patients with a known or suspected systemic infection. In addition, all patients received the same antidepressant, sertraline, and most patients adhered closely to the prescribed treatment regimen. Furthermore, this study included a larger sample of participants than the studies that have found significant relationships between inflammatory markers and depression outcome [9–11].

This study also had several limitations, including the use of data from a randomized controlled trial. However, although there is some evidence that omega-3 fatty acids have anti-inflammatory properties [21], we did not observe any significant interactions between allocation to omega-3 fatty acids or placebo and inflammation in relation to depression outcomes. Furthermore, all patients received identical dosages of sertraline. It is possible that some patients who were classified as non-responders in our study would have responded to a higher dose. However, previous studies have shown that higher doses only marginally increase the response rate while increasing adverse side-effects [22,23]. In addition, eight participants (7%) either did not complete the study or had no baseline inflammation markers. Although this is a small number, we cannot eliminate the possibility that inclusion of these participants would have affected the relationship between inflammation and depression. Furthermore, systemic inflammatory markers can be affected by fever, injuries, acute infections [24]. We measured body temperatures to exclude patients with fever, but we cannot completely rule out other factors that might have influenced the level of inflammation. In addition, the duration of the treatment was relatively brief. However, our intervention lasted longer than the treatment phase of the study by Lanquillon et al. which found a relationship between baseline inflammation level and treatment outcome [9]. Also, our study measured only proinflammatory markers. Anti-inflammatory cytokines may also be important determinants of depression treatment outcomes, although this has not been confirmed. Future studies should include both types of inflammatory markers. Finally, we lacked data on certain characteristics that could potentially moderate or confound the relationship between inflammatory markers and treatment outcome, including measures of the severity of CHD.

If inflammation does not explain treatment resistance in depressed CHD patients, what explanation does? Misdiagnosis, suboptimal treatment, intolerance to medication side effects, and poor adherence to the treatment regimen are clearly responsible in many cases for poor response to antidepressant treatments.[25,26] Cognitive dysfunction, substance abuse, anxiety disorders, personality disorders, and poor social support also negatively affect depression treatment outcome in depressed patients [27,28], and may also contribute to poor cardiac outcomes.

Further research is needed to investigate other possible explanations for the poor prognosis of patients with CHD and comorbid, treatment-resistant depression. This might lead to more efficacious interventions for depressed CHD patients who do not respond to standard treatments.

In summary, we found that baseline levels of hs-CRP, IL-6, and TNF-α were unrelated to treatment response following 10 weeks of treatment with sertraline in patients with CHD and comorbid major depression.

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**Table I**

Baseline characteristics of the study sample (N=122)

| | **Mean (SD) or n (%)** |
|---|---|
| Age (years) | 58.3 (8.9) |
| Omega-3 intervention arm | 62 (50.8%) |
| Female | 41 (33.6%) |
| Education > high school | 77 (63.1%) |
| Body Mass Index (kg/m$^2$) | 33.2 (7.3) |
| Cigarette smoker | |
| Never | 29 (23.8%) |
| Past only | 63 (51.6%) |
| Current | 30 (24.6%) |
| Hypertension | 94 (77.1%) |
| Diabetes | 44 (36.1%) |
| History of MI | 73 (59.8%) |
| History of CABG or PTCA | 101 (82.8%) |
| Baseline medications | |
| Aspirin | 98 (80.3%) |
| ACE inhibitors | 60 (49.2%) |
| Beta Blockers | 99 (81.1%) |
| Statins | 90 (73.8%) |
| Calcium channel blockers | 34 (27.9%) |
| Depression | |
| History of depression | 81 (68.6%) |
| Duration of current depressive episode (months) | 14.2 (17.2) |
| History of depression treatment | 76 (62.3%) |
| Generalized Anxiety Disorder | 42 (35.6%) |
| Hemoglobin (g/dL) | 13.9 (1.8) |
| Creatinine (mg/dL) | 0.96 (0.27) |
| LDL cholesterol (mg/dL) | 90.4 (36.7) |
| HDL cholesterol (mg/dL) | 43.2 (13.3) |
| Triglycerides (mg/dL) | 147 (107 - 223)* |

*median and interquartile range

**Table II**

Levels of depression and inflammation at baseline and at 10-week post-treatment for the total group and stratified by responders and remitters

| | Total group | | Responders | | Non-responders | | Remitters | | Non-remitters | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **N** | **Mean (SD)** |
| Baseline BDI-II score | 122 | 28.5 (8.9) | 57 | 28.9 (9.1) | 58 | 27.7 (8.9) | 33 | 26.1 (8.8) | 82 | 29.2 (8.9) |
| Post-treatment BDI-II score | 115 | 15.1 (9.8) | 57 | 8.1 (5.4) | 58 | 21.9 (8.3) | 33 | 4.5 (2.6) | 82 | 19.3 (8.3) |
| Baseline HAM-D score | 120 | 20.3 (5.3) | 56 | 19.9 (4.5) | 58 | 20.7 (6.1) | 33 | 19.1 (3.8) | 81 | 20.8 (5.8) |
| Post-treatment HAM-D score | 113 | 9.4 (6.6) | 56 | 5.7 (4.1) | 57 | 13.0 (6.5) | 32 | 4.4 (3.2) | 81 | 11.4 (6.5) |
| | **N** | **Median (IQR)** | **N** | **Median (IQR)** | **N** | **Median (IQR)** | **N** | **Median (IQR)** | **N** | **Median (IQR)** |
| Baseline hs-CRP level (mg/L)* | 113 | 3.9 (1.2–9.0) | 49 | 4.0 (1.1–9.7) | 57 | 3.9 (1.5–8.1) | 28 | 3.5 (1.0–7.3) | 78 | 4.0 (1.4–9.4) |
| Post-treatment hs-CRP level (mg/L)* | 107 | 4.8 (1.9–10.3) | 50 | 4.6 (1.8–12.6) | 57 | 4.8 (2.0–9.0) | 28 | 4.5 (1.3–10.1) | 79 | 4.8 (2.0–10.3) |
| Baseline IL-6 level (pg/mL)* | 113 | 2.5 (1.7–3.6) | 56 | 2.4 (1.7–4.2) | 57 | 2.6 (1.9–3.4) | 32 | 2.3 (1.8–3.7) | 81 | 2.5 (1.7–3.6) |
| Post-treatment IL-6 level (pg/mL)* | 113 | 3.1 (2.1–4.5) | 56 | 3.0 (2.2–4.6) | 57 | 3.1 (2.1–4.5) | 32 | 3.1 (2.2–4.3) | 81 | 3.0 (2.1–4.7) |
| Baseline TNF-α level (pg/mL)* | 112 | 1.3 (1.0–1.6) | 55 | 1.4 (1.1–1.6) | 57 | 1.2 (1.0–1.5) | 32 | 1.3 (1.1–1.5) | 80 | 1.3 (1.0–1.6) |
| Post-treatment TNF-α level (pg/mL)* | 113 | 1.3 (1.1–1.7) | 56 | 1.3 (1.1–1.7) | 57 | 1.3 (1.1–1.6) | 32 | 1.2 (1.1–1.7) | 81 | 1.3 (1.1–1.6) |

*back transformed levels

IQR = Interquartile range