Published in final edited form as:
Eur J Cardiovasc Nurs. 2014 October ; 13(5): 444–450. doi:10.1177/1474515113507508.

Depressive Symptoms and Inflammatory Biomarkers in Patients with Heart Failure

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Abstract

Background—Inflammation may be a link between depressive symptoms and outcomes in patients with heart failure (HF). It is not clear whether inflammatory markers are independently related to depressive symptoms in this population.

Aim—To determine which inflammatory biomarkers are independently associated with depressive symptoms in HF.

Methods and Results—We analyzed data from 428 outpatients enrolled in a HF registry (32% female, 61 ± 12 years, 48% NYHA Class III/IV). Depressive symptoms were measured with the Beck Depression Inventory-II. Serum C-reactive protein (CRP), cytokines (interleukin [IL] 1RA, 2, 4, 6, 8, 10), tumor necrosis alpha, and soluble receptors sTNFR1 and sTNFR2 were measured with enzyme immunoassay. Multiple regressions were used to determine which biomarkers were associated with depressive symptoms controlling for demographics, HF severity, and clinical variables. Twenty-seven percent (n = 119) had depressive symptoms. CRP was related to depressive symptoms after controlling for age and gender, but no inflammatory biomarkers were associated with depressive symptoms after controlling for all variables in the model.

Conclusions—There was no relationship between inflammatory biomarkers and depressive symptoms. Our findings, in combination with prior researchers, suggest there is not a robust relationship between depressive symptoms and individual biomarkers of inflammation in HF.

Keywords

Inflammation; depression; heart failure; cytokines; cardiovascular

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There are no industry relationships to disclose.

The purpose of this study was to examine the relationship between depressive symptoms and inflammatory biomarkers in patients with heart failure (HF). Patients with HF frequently experience depressive symptoms that contribute to poor outcomes. One in five patients with HF has major depressive disorder[1], and an even higher proportion of patients—up to 50%—experience clinically significant depressive symptoms as assessed by self-report questionnaires.[2] Importantly, patients with HF and depressive symptoms are twice as likely to be re-hospitalized or die compared to patients with no depressive symptoms.[1]

Although a large body of research has provided evidence that depressive symptoms independently predict morbidity and mortality in patients with HF, the biobehavioral mechanisms underlying this relationship remain poorly understood. Researchers have proposed that inflammation may be a link between depressive symptoms and worse health outcomes in HF.[3] Patients with HF have high levels of inflammatory cytokines such as tumor necrosis factor-alpha (TNFα) and interleukin 6 (IL-6), which are independent predictors of HF exacerbations and HF-related death.[4–6] Clinical depression is also accompanied by an increase in proinflammatory cytokine levels. In 2009, Howren et al.[7] conducted a meta-analysis of 136 studies and found that higher levels of inflammatory C-reactive protein (CRP), IL-1, and IL-6 were associated with depression in both community and clinical samples, including patients with coronary artery disease.

Seven groups of researchers have examined levels of inflammation in patients with HF with and without depressive symptoms.[8–14] In the largest study on inflammation and depression in HF to date ($N = 517$), Johannson et al.[8] found that a combined measure of CRP and IL-6 was a positive predictor of depressive symptoms at baseline but a negative predictor of depressive symptoms at 18 months, after controlling for severity of HF. Other inflammatory biomarkers that have been associated with depression in patients with HF include TNFα,[12] soluble receptors sTNFR1[9] and sTNFR2,[10] and TNFα/IL-10.[11] However, four of these seven studies had sample sizes less than 40.[11–14] Furthermore, there has been little consistency between various researchers' findings. Therefore, we examined a panel of inflammatory biomarkers in a large sample of outpatients with HF with and without depressive symptoms.

Our specific aims were to 1) compare levels of inflammatory biomarkers between patients with depressive symptoms and without depressive symptoms, and 2) determine whether inflammatory biomarkers are independently related to depressive symptom levels before and after controlling for demographics, functional status, and clinical variables including body mass index. We hypothesized there would be an independent relationship between inflammatory biomarkers and depressive symptoms.

Methods

Design and Sample

This was a cross-sectional, secondary data analysis of data from the HF Quality of Life registry. A detailed summary of registry methods has been previously published.[15, 16] The present subset (N = 428) includes a convenience sample of outpatients from three registry studies who had baseline data on depressive symptoms and at least one inflammatory

biomarker. The purpose of the first study was to test the effects of biofeedback and cognitive therapy on HF outcomes (National Institutes of Health/National Institutes of Nursing Research R01NR 008567). The second study was a prospective study in which investigators evaluated mechanisms linking depression to worse outcomes in patients with HF. In the third study, investigators examined the effects of body mass index on survival in patients with HF. All three studies took place in the Southeastern United States.

All three studies selected for this data analysis used the same inclusion and exclusion criteria. Patients were eligible for inclusion if they had a diagnosis of chronic HF, preserved or non-preserved systolic function, taking stable medications for 3 months, and English-speaking. Patients were excluded for a myocardial infarction or unstable angina in the past 3 months, cognitive impairment, placement at a skilled nursing facility, or severe psychiatric impairment other than depression or anxiety.

As this was a secondary data analysis, the sample size for each of the biomarkers was different because we were limited by the data collected in each sub-study. For each of the sub-studies that were included in this data analysis, we consciously recruited samples that were very similar—each study had the same inclusion/exclusion criteria, and we have previously found that there are no significant differences in clinical or demographic variables from each of the sub-studies used in this data analysis.

Protocol

This investigation conforms to the principles outlined in the Declaration of Helsinki. Local institutional review boards approved the individual studies, and all patients provided written informed consent. Baseline assessments were conducted at General Clinical Research Centers. After completion of each study, data were de-identified and integrated into a single database. The review board at the first author's institution approved secondary data analysis with this dataset as an exempt protocol.

Measurement

Demographics and clinical variables—To completely describe the sample and obtain data on potential confounding variables, the following information was collected by patient interview and chart review: age, sex, race/ethnicity, marital status, education level, and time since diagnosis. The following clinical characteristics were collected by chart review: smoking status, ejection fraction, and medications. Height and weight were measured during the baseline visit. Data on comorbidites were collected by chart review and patient interview using the Charlson Comorbidity Index.[17, 18]

Depressive symptoms—Depressive symptoms were measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a 21-item questionnaire that assesses the presence and severity of depressive symptoms. A score of 14 or greater indicates the presence of clinically significant depressive symptoms. The reliability and validity of the BDI-II has been supported in both medical and non-medical populations.[19, 20]

Inflammatory biomarkers—Serum C-reactive protein (CRP), interleukins- (IL) 1 receptor antagonist (RA), 2, 4, 6, 8, and 10), TNFα, sTNFR1 and sTNFR2 were drawn by venipuncture at a standardized time of day and measured with enzyme-linked immunoassay. Blood was centrifuged within 30 minutes. Serum was placed in aliquotes and stored at −70°C until analyzed in the same General Clinical Research Center core laboratory. Samples were run in duplicate and the amount determined from standard curves using a 4-parameter curve fit. Any samples with intra-assay coefficient of variations >10% were rerun with subsequent acceptable coefficient of variations.

Functional status—New York Heart Association (NYHA) functional class is a subjective indicator of functional status and was determined by patient interview.[21] Patients were assigned a classification of I (ordinary physical activity causes no symptoms of fatigue, dyspnea, angina or palpitations), II (symptoms with ordinary physical activity), III (symptoms occur with less than ordinary physical activity) or IV (symptoms occur even at rest).

Covariates—Covariates included in the final regression model were age, gender, NYHA classification, chronic obstructive pulmonary disease (COPD), current smoking status, cholesterol lowering drugs, and body mass index. Age, sex, and body mass index were included as covariates because each of these variables are associated with inflammation. [7,22–23] The use of statin drugs can lower levels of CRP, TNFα, IL-1, and IL-6.[24] We did not have information on statin drugs, so we included cholesterol lowering drug use as a proxy measure for statin use. COPD and smoking status were included as confounders because of their bivariate associations with depressive symptoms. Finally, we included NYHA Class because worse functional status is associated with both inflammation[25] and depression.[26] We chose not to include antidepressants in the regression because antidepressants can serve as a proxy-measure for depressive symptoms, and the dependent variable in the regression was depressive symptoms.

Data Analysis

Data analysis was conducted using SPSS v. 20 (SPSS Inc, Chicago). All continuous biomarker data are reported as the median (25^{th} percentile, 75th percentile). Logarithmic transformations were used to transform CRP, sTNFR2, IL-1ra, IL-6, and IL-8. Log transformation did not result in a normal distribution for sTNFR1; instead, we used the formula $1/(x + .05)$. We compared between-group differences in circulating levels of the transformed data using independent *t*-tests. There were four biomarkers that could not be transformed adequately using any method (TNF-α, IL-2, IL-4, and IL-10). We used the non-parametric Mann Whitney U test to compare group differences in these biomarkers. Three biomarkers (IL-2, IL-4, and IL-10) had a few extreme outliers; for these biomarkers we excluded values outside the 95^{th}% in all analyses. Chi-square tests were used to compare the proportion of patients with and without depressive symptoms who had biomarker levels above the median and 75^{th} percentile.

Individual hierarchical multiple regressions were used to determine which biomarkers were associated with levels of depressive symptoms (the dependent variable) before and after

controlling for demographics, HF severity, and clinical variables. One biomarker was included in each regression model. BDI-II was the dependent variable, with independent variables entered as follows: Step 1, individual biomarker; Step 2, age and gender; Step 3, NYHA Class I/II or III/IV; and Step 4, COPD, cholesterol lowering agents, smoking status (current smoker: yes or no) and body mass index. An alpha of 0.05 was set a priori. For biomarkers that could not be transformed for parametric analysis (TNF-α, IL-2, IL-4, and IL-10), the median cut-point was used to create a categorical variable for high or low levels. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity.

Results

Sample characteristics

The final sample consisted of 436 outpatients with HF, one-third of whom were female. Most patients had stable HF—the median time since the last HF hospitalization was 24 months, and only 4% had been hospitalized in the past month. Approximately half of the sample was classified as NYHA functional class III or IV, and one-fourth of the patients were taking antidepressants. In Table 1, the baseline characteristics of the overall sample and patients with (n = 119) and without depressive symptoms (n = 317) were compared.

Patients with depressive symptoms were younger and had fewer years of education compared to patients without depressive symptoms. There was a higher percentage of patients with depressive symptoms who had NYHA class III or IV HF (69% vs. 39%, $p < .001$), were current smokers (28% vs. 16%, $p = .007$), and had a history of chronic obstructive pulmonary disease (23% vs. 13%, $p = .009$). Among patients with depressive symptoms, 43% were taking antidepressants, compared to 17% of patients without depressive symptoms ($p < .001$). Median time since last HF hospitalization was shorter in the patients with depressive symptoms (14 months vs. 30 months, $p = .001$).

Differences in biomarker levels between the two groups

Table 2 presents median biomarker levels for the overall sample and a comparison between patients with and without depressive symptoms. There were no significant differences in median levels of inflammatory biomarkers between the groups. There was a trend towards higher levels of CRP (median 3.67 [25^{th} percentile = 1.86, 75^{th} percentile = 9.27] vs. 2.71 [1.45, 6.12], $p = .071$) in patients with depressive symptoms. A higher proportion of patients with depressive symptoms had CRP values above the median (66% vs. 44%, $p = .014$), and there was a trend towards a higher proportion of patients with depressive symptoms who had sTNFR2 levels above the 75^{th} percentile (33% vs. 24%, $p = .06$).

Regression results

None of the inflammatory biomarkers were independently associated with depressive symptoms after controlling all the variables in the model (Table 3). In both the unadjusted analysis and after controlling for age and gender, CRP was associated with depressive symptoms ($p = .004$ and 07). However, after adjusting for NYHA class, CRP was no longer significant. Soluble receptors TNFR1 and 2 were significantly associated with depressive

symptoms during step 2 of the regression (p = .01 and .03), but were no longer significant after NYHA class was entered into the model.

Discussion

Surprisingly, we found that none of the inflammatory biomarkers were independently associated with depressive symptoms. Although there was a bivariate relationship between CRP and depressive symptoms, this relationship did not continue after controlling for functional class. At first glance, it appears that our results were not consistent with previous researchers' findings. However, 4 of the prior studies were limited by very small sample sizes. When our results are compared with the 3 studies with larger sample sizes, some similarities are noted.

Johannson et al[8] reported that higher levels of IL-6 and CRP during a HF hospitalization were positively associated with depressive symptoms at baseline (N = 517). Furthermore, high levels of IL-6 and CRP at baseline were associated with lower levels of depressive symptoms 18 months later. Although statistically significant, the relationships that they identified were very small—the standardized betas were 0.18 and −0.18, respectively. Our study differs from Johannson et al.'s in that we measured depressive symptoms and inflammation at one time point in stable outpatients, while they enrolled patients during a hospitalization and followed them prospectively. However, our negative study findings, along with Johannson et al.'s finding of only a small effect, suggest that the relationship between inflammation and depression is not as robust as some researchers have proposed.

In another large study, Moorman et al.[9] measured TNFα, sTNFR1, sTNFR2, CRP, IL-1β, IL-1ra, IL-6, IL-6r, IL-8, IL-10 in 129 outpatients with HF. Out of this panel of biomarkers, sTNFR1 was the only biomarker in which higher quartiles were independently associated with major depression and depressive symptoms, after controlling for age, gender, ejection fraction, systolic blood pressure, NYHA class, HF severity (Seattle HF model score), creatinine level, and spironolactone use. Depressive symptoms were not associated with any of the other inflammatory biomarkers. Interestingly, although Moorman et al. found that the highest quartile of sTNFR1 was a significant predictor of depressive symptoms compared to the lowest quartile of sTNFR1 after controlling for NYHA class (OR 3.5, p = .005) , it did not in our sample that was almost 3 times larger. The potential reasons for the disconnect between our findings and those of Moorman et al. are not clear. One might think that that we would find a significant relationship between CRP, sTNFR1, and sTNFR2 if we too entered these biomarkers as quartiles into the regression models. However, upon doing this in a post-hoc analysis, we still found no independent relationship between the biomarkers and depressive symptoms. Regardless, we did have one finding in common with Moorman et al. —we both found no evidence of a relationship between most markers of inflammation and depressive symptoms in patients with HF.

Similarly, Kupper et al.[10] measured TNF-α, IL-1ra, sTNFR1, sTNFR2, IL-6, CRP in 125 outpatients with HF. Out of this panel of biomarkers, sTNFR1 and IL-1Ra were the only ones independently and positively associated with cognitive-affective symptoms of depression, and sTNFR2 was the only marker positively associated with somatic-affective

depressive symptoms. However, although statistically significant, the size of these relationships were small (standardized beta = 0.20, 0.28, 0.21, respectively). When the data were examined prospectively, baseline cognitive-affective symptoms of depression—but not somatic-affective symptoms—were a positive predictor of sTNFR1 and sTNFR2 at 12 months, but again, the size of the relationships were small (standardized beta = 0.21, 0.25). Although we used the same instrument to measure depressive symptoms—the Beck Depression Inventory-II—our study differed from that of Kupper et al.'s in that we did not differentiate between cognitive-affective and somatic-affective symptoms of depression, and we chose to use depressive symptoms as our dependent variable rather than an independent variable. Yet still, our results shared a common link in that most markers of inflammation were not independently related to depressive symptoms.

Our study was not designed to determine whether inflammation is the mechanistic link between depressive symptoms and poor outcomes in patients with HF. However, based on our findings and results from prior investigators, it seems that levels of most inflammatory cytokines are not substantially higher in patients in patients with HF and depressive symptoms. Thus it is possible that inflammation may not be the major biological link between depressive symptoms and poor outcomes in HF. Prospective research studies are needed to evaluate the relationship between depressive symptoms, inflammation, and survival outcomes in patients with HF. Furthermore, we suggest researchers determine whether behavioral mechanisms, such as medication adherence, compose the major link between depressive symptoms and poor outcomes.

Limitations

Because this study was cross-sectional, we cannot determine causality. Furthermore, the pathophysiology of heart failure and inflammation are complex, thus it may be an oversimplification to use analytic strategies that only examine one biomarker at a time. Future research is needed to measure inflammation and depression prospectively in patients with HF, and to examine effects of the elevation of multiple inflammatory biomarkers. Our study was also limited by the use of self-report questionnaires to measure depressive symptoms. Future research would benefit from the use of both diagnostic interviews and depression questionnaires. In our study, we included patients with both preserved and non-preserved ejection fraction, as well as patients with NYHA Class I-IV, who may have different responses to depression. However, we also see this inclusion of the varying types and severity of HF as strength, because we are better able to generalize our findings to people with non-preserved and preserved systolic function HF, as well as to people with different levels of HF severity.

Conclusions

In conclusion, we found no independent relationships between inflammatory biomarkers and depressive symptoms at baseline. Our findings suggest there is not an independent relationship between depressive symptoms and single biomarkers of inflammation in this population. Additional research is needed to prospectively examine the relationship between depressive symptoms, inflammation, behavior, and survival in patients with HF, to determine the mechanistic link between depression and poor outcomes in this population.

Acknowledgments

Funding Sources: This research was supported by an American Association of Critical Care Nurses Phillips Medical Research award, an American Heart Association post-doctoral fellowship, the National Institutes of Health, National Institute of Nursing Research, K23 NR013480, R01 NR 008567, R01 NR 009280, the University of Kentucky General Clinical Research Center, M01RR02602, and the University of Kentucky College of Nursing Center for Biobehavioral Research on Self-Management, NINR, P20 NR 010679. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Nursing Research or the National Institutes of Health.

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Implications for Practice

- Depression levels are high in patients with heart failure
- HF patients with depression have shorter survival times
- Inflammation may be why there are worse outcomes in HF
- However, depression and inflammation were not related in this study
- Research is needed on the link between depression and outcomes

Table 1

Baseline Characteristics*

Characteristic	Overall sample N = 436	BDI-II < 14 n = 317	BDI-II ≥ 14 n = 119	*p* value†
Female, %	31.7	30	36	.22
Age	61.1 ± 11.6	62.6 ± 11.9	57.1 ± 9.8	<.001
Married, %	53	55	47	.16
Minority, %	22	24	18	.18
BDI-II	10.3 ± 8.3	6.2 ± 3.7	21.4 ± 7.2	<.001
Body Mass Index	31.4 ± 7.3	31 ± 7.2	32.5 ± 7.6	.07
NYHA functional class, %				
Class I	10	12	5	<.001
Class II	42	49	26	
Class III	39	33	53	
Class IV	9	6	16	
Ejection fraction (%)	35 ± 14	34.5 ± 14	36.3 ± 14.7	.26
Non-preserved systolic function (Ejection fraction < 40%)	36	35	39	.66
Ischemic HF etiology, %	49	50	46	.5
Education level (# years)	13.5 ± 3.4	13.9 ± 3.3	12.4 ± 3.3	<.001
Current smoker, %	19	16	28	.005
Months since diagnosed with HF (reported as median, 25th %, 75th %)	60 (24, 110)	60 (23, 112)	52 (24, 105)	.73
Months since hospitalized with HF (reported as median, 25th %, 75th %)	24 (6, 84)	30 (8, 107)	14 (4, 36)	.001
Comorbidities, %				
Diabetes	42	40	45	.35
Chronic obstructive pulmonary disease	15	13	23	.009
Implanted cardiac defibrillator	47	46	48	.78
Stroke	20	19	24	.32
Atrial fibrillation	43	43	44	.96
Medications, %				
Angiotensin Converting Enzyme inhibitor	70	72	65	.09
Angiotensin receptor blocker	17	16	20	.26
Digoxin	23	24	23	.84
Cholesterol lowering agent	71	71	71	.89
Diuretic	73	73	74	.81
Beta blocker	87	88	86	.61
Antidepressant	24	17	43	<.001

*Data are given as mean ± SD unless otherwise indicated

† *p* values were calculated using independent *t* tests for continuous variables, the Mann Whitney U test for non-parametric data (months since HF hospitalization and months since HF diagnosis), and the chi-square test of independence for categorical variables

Abbreviations: BDI-II = Beck Depression Inventory version II; NYHA = New York Heart Association; HF = heart failure

Table 2

Median biomarker levels*

Biomarker	Overall sample Median (25th%, 75th%)	Depressive symptoms		No depressive symptoms		*P* value
		N	Median	N	Median	
CRP† *n* = 271	2.95 (1.55, 7.08)	78	3.67 (1.86, 9.27)	193	2.71 (1.45, 6.12)	.071
sTNFR1‡ *n* = 428	1783 (1386, 2267)	118	1854 (1324, 2378)	310	1747 (1404, 2243)	.915
sTNFR2† *n* = 428	2948 (2267, 3854)	118	3207 (2266, 4179)	310	2884 (2266, 3750)	.270
TNF-α§ *n* = 191	3.23 (2.00, 8.59)	61	2.83 (1.91, 7.50)	130	3.82 (2.00, 9.48)	.216
IL-1ra† *n* = 177	217.50 (58.25, 730.50)	56	249 (51.5, 474)	121	182 (64, 809)	.826
IL-2§ *n* = 183	.98 (.12, 4.43)	59	.49 (.12, 3.30)	124	1.3 (.12, 4.55)	.327
IL-4§ *n* = 180	5.19 (.12, 42.8)	61	3.51 (.12, 27.7)	119	5.19 (.12, 41.6)	.920
IL-6† *n* = 192	8.96 (4.40, 26.85)	63	7.12 (4.28, 18.6)	129	11.2 (4.4, 29.9)	.086
IL-8† *n* = 192	10.6 (7.20, 15.95)	63	10.1 (6.85, 15.3)	129	10.6 (7.22, 16.5)	.918
IL-10§ *n* = 181	5.58 (10.23)	59	6.08 (1.73, 12.2)	122	5.19 (1.59, 9.22)	.316

*Median and 25th%, 75th% levels were reported using untransformed data for all biomarkers. To compare levels between depressive and non-depressive groups, independent t-tests were used to compare differences between transformed data, and Mann Whitney U tests were used to analyze non-parametric data (unable to be transformed).

†Logarithmic transformations were used to transform CRP, sTNFR2, IL-1ra, IL-6, and IL-8.

‡The formula 1/(x + .05) was used to transform sTNFR1.

§Four biomarkers could not be transformed adequately using any method (TNF-α, IL-2, IL-4, and IL-10).

Abbreviations: CRP = high sensitivity C-reactive protein, sTNFR = soluble tumor necrosis factor receptor, IL = interleukin,

Table 3

Beta Values of Individual Inflammatory Biomarkers from Hierarchical Multiple Regressions Predicting Depressive Symptoms*

	Unadjusted		Step 2†		Step 3‡		Step 4 (Final model)§	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
CRP (*n* = 271)	**.17**	**.004**	**.12**	**.047**	.10	.07	.10	.09
sTNFR1 (*n* = 428)	.03	.48	**.11**	**.03**	.06	.19	.06	.18
sTNFR2 (*n* = 428)	.08	.10	**.12**	**.01**	.08	.10	.08	.10
TNF-α (*n* =191)	−.01	.88	.001	.99	.02	.79	.02	.74
IL-1RA (*n* = 177)	−.05	.54	−.06	.4	−.09	.24	−.07	.35
IL-2 (*n* = 184)	−.06	.44	−.06	.39	−.10	.16	−.08	.10
IL-4 (*n* = 181)	−.02	.75	−.06	.45	−.05	.53	−.02	.81
IL-6 (*n* = 192)	−.12	.10	−.09	.21	−.10	.14	−.09	.20
IL-8 (*n* = 192)	−.02	.79	.01	.93	.00	.99	.02	.84
IL-10 (*n* = 182)	.09	.22	.09	.21	.10	.16	.12	.12

*Each biomarker was individually entered into a separate regression model predicting depressive symptoms (Total of 10 regression models). Logarithmic transformations were used to transform CRP, sTNFR2, IL-1ra, IL-6, and IL-8, the formula 1/(x + .05) was used to transform sTNFR1, and four biomarkers could not be transformed adequately using any method (TNF-α, IL-2, IL-4, and IL-10).

†Step 2 = Adjusted for biomarker, age, and gender;

‡Step 3 = adjusted for previous variables plus NYHA class divided into 2 groups (I/II and III/IV);

§Step 4 (Final model) = adjusted for previous variables plus cholesterol lowering agent, chronic obstructive pulmonary disease, current smoking status, and body mass index.

Abbreviations: CRP = high sensitivity C-reactive protein, sTNFR = soluble tumor necrosis factor receptor, TNF-α = tumor necrosis alpha, IL = interleukin