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Statin Effects on Myocardial Fibrosis Markers in People Living with HIV

Christopher deFilippi[1], **Robert Christenson**[2], **Jessica Joyce**[3], **Elli A. Park**[3], **Ashley Wu**[3], **Kathleen V. Fitch**[3], **Sara E. Looby**[3], **Michael T. Lu**[4], **Udo Hoffmann**[4], **Steven K. Grinspoon**[3], and **Janet Lo**[3]

[1]Inova Heart and Vascular Institute, Falls Church, Virginia [2]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland [3]Department of Medicine, Endocrine Division, Program in Nutritional Metabolism, Massachusetts General Hospital, Boston, USA [4]Department of Radiology, Cardiovascular Imaging Section, Massachusetts General Hospital, Boston, USA

Abstract

Background—In observational studies, HIV patients have higher levels of soluble ST2 (sST2), galectin-3, growth differentiation factor-15 (GDF-15) than non-HIV controls. As statins exert pleiotropic immunomodulatory effects that may affect markers of myocardial fibrosis, the objective of the current study is to determine if biomarkers of myocardial fibrosis reflecting subclinical pathology may be modified by statin therapy in patients with HIV.

Setting and Methods—40 HIV+ men and women participated in a single center 12-month randomized, double-blind placebo controlled trial of atorvastatin 40mg qd vs. placebo. At baseline and 12-months sST2, GDF-15, galectin-3, were measured.

Results—The changes in sST2 were −0.310 [−4.195,2.075] vs. 1.163 [0.624, 4.715]ng/mL, median[IQR] atorvastatin vs. placebo (p=0.04). The change in sST2 was significantly related to changes in monocyte activation markers sCD14 (r=0.63, p<0.0001) and MCP (r=0.52, p=0.0009), markers of generalized inflammation hs-IL-6 (r=0.58, p=0.0002), oxLDL (r=0.49, p=0.002), and GDF-15 (r=0.54, p=0.0008).

Conclusion—sST2, a member of the IL-1 receptor family and a marker of fibrosis and inflammation increases over time among HIV patients and this increase is attenuated by statin therapy in HIV. This effect may relate to immunomodulatory mechanisms of statins.

Clinical Trial Registration—The trial is registered on http://clinicaltrials.gov registry number: (NCT00965185).

Keywords

HIV; soluble ST2 (sST2); growth differentiation factor-15 (GDF-15); coronary artery disease; statin

Corresponding Author: Janet Lo, M.D., M.MSc, Massachusetts General Hospital, LON-203, 55 Fruit Street, Boston, MA USA 02114, (p) 617-724-3425, (f) 617-724-8998, jlo@mgh.harvard.edu.
Alternate Corresponding Author: Steven K Grinspoon, M.D., Massachusetts General Hospital, LON-207, 55 Fruit Street, Boston, MA USA 02114, (p) 617-724-9109, (f) 617-724-8998, sgrinspoon@mgh.harvard.edu

INTRODUCTION

Patients living with HIV (PLHIV) have an increased risk of myocardial infarction, heart failure and heightened inflammation[1–4]. We have previously shown that PLHIV have higher soluble ST2 (sST2), and galectin-3 than non-HIV controls[5]. sST2, thought to be a soluble decoy receptor to its cell membrane bound counterpart has been associated with atherosclerosis, fibrosis, inflammation, and immune activation possibly through inhibiting ST2/interleukin-33 (IL-33) signaling[6–9]. Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor-β (TGF-β) superfamily, is secreted in the heart in response to ischemia and pressure overload[10–12] with levels measured in blood predicting cardiac events and mortality in the general population[13]. Both GDF-15 and sST2 were found to be elevated and associated with mortality in PLHIV[14]. Galectin-3, a marker of inflammation and cardiac fibrosis, has been shown to predict incident heart failure and increased LV mass in the Framingham Offspring and Framingham Heart studies[15]. Statin therapy, a potent lipid lowering therapy, also significantly reduces measures of inflammation independent of low-density lipoprotein (LDL) lowering[16]. Statins in animal models can inhibit cardiac fibrosis independent of LDL cholesterol lowering thought to be mediated through Rho kinases (ROCKs) inhibition. ROCK mediated effects are thought to be responsible for several of the pleotropic effects of statins including limiting cardiac fibrosis, hypertrophy and pathologic remodeling in response to adverse stimuli such as angiotensin II[17]. In PLHIV, who have a greater burden of cardiac fibrosis than age and risk factor matched controls[18], the influence of high potency statin therapy on these markers could provide important insights into the potential clinical effects of statin therapy.

METHODS

Study Design

This study was a single center 12-month randomized, double-blind, placebo-controlled clinical trial of atorvastatin vs. placebo, showing effects on coronary plaque volume as previously reported[19]. However, markers of fibrosis were not assessed previously nor are these results available from other statin studies in HIV. HIV-infected subjects 18 to 60 years of age, on stable antiretroviral therapy (ART) with no changes in ART regimen in the preceding six months, and LDL-cholesterol between 70–130 mg/dL (not meeting clinical guidelines criteria at the time for statin therapy) were enrolled. Exclusion criteria were prior history of CVD, evidence of subclinical obstructive ASCVD, defined by presence of one or more plaques on CCTA with significant stenosis (>50% left main stenosis or >70% stenosis in any major vessel), concurrent use of a statin, AST or ALT three times greater than the upper limit of normal and/or treatment for active liver disease, renal disease and/or creatinine >1.5 mg/dL, as well as other criteria as previously described[19]. Patients were randomized in 1:1 ratio to either atorvastatin (starting at dose of 20 mg per day and escalating to 40 mg per day at three months visit if study drug was well-tolerated) or placebo groups. All subjects received standardized lifestyle counseling based on National Cholesterol Education Program (NCEP) guidelines. All participants provided written

informed consent and the study was approved by the MGH institutional IRB. The trial is registered on ClinicalTrials.gov (NCT00965185).

For the current analysis, we measured markers of myocardial fibrosis with inflammatory mechanisms (sST2, galectin-3 and GDF-15) previously found to be elevated in HIV that we hypothesized may be reduced by statin therapy. Secondarily, we sought to assess whether baseline and changes in sST2, galectin-3 and GDF-15 related to baseline and changes in circulating markers of inflammation and oxidized LDL.

Biomarker Assessments

The following soluble protein biomarkers were measured at baseline and at 12-months for this analysis: sST2, for adverse cardiac remodeling and tissue fibrosis; galectin-3, for fibrosis and inflammation; and GDF-15. ELISA measurements for the following biomarkers were performed in strict accordance with manufacturer instructions: sST2 (Critical Diagnostics, San Diego, CA, USA); galectin-3 (BG-Medicine, Waltham, MA, USA); GDF-15 (R&D Systems, Minneapolis, MN). For sST2, the assay measurement range was 3.1 to 200.0 ng/mL; the inter-assay CVs ranged from 8.9% to 7.3% at values between 20 ng/mL and 79.0 ng/mL. The Galectin-3 assay's measurement range is 0.96 to 130 ng/mL; inter-assay CVs ranged from <10% to 15% at values between 6 ng/mL and 70 ng/mL. For GDF-15, typical interassay imprecision is 6.0% at 225 pg/mL GDF-15 and 5.6% at 900 pg/mL. All laboratory assessments were obtained after a 12 hour fast and other analytes were measured as previously reported[19, 20].

Statistical Analysis

Comparisons between the two groups (atorvastatin vs. placebo) were performed using Student t test for normally-distributed continuous variables and Wilcoxon rank sum test if the distribution was non-normal. To assess changes within each group, paired t-test or Wilcoxon signed rank test was performed, depending on normality of distribution. Pearson correlation coefficient was used to assess relationships of sST2, Galectin-3, GDF-15 with other parameters. Two-tailed probability values are reported, and statistical significance was assumed when $p < .05$. Means and standard deviations (SD) are reported to describe changes in continuous variables with normal distribution; otherwise, medians and interquartile ranges (IQR) are used. For analysis of GDF-15, two outliers based on the Dixon criteria were excluded. All statistical analyses were performed using SAS JMP version 11 (SAS Institute, Cary, North Carolina).

RESULTS

Characteristics of the Participants at Baseline

Eighty-one HIV-infected participants underwent screening for this study. 40 participants were randomized to atorvastatin or placebo. Demographic, clinical characteristics, lipids, immunologic and systemic inflammatory markers of these 40 study participants have previously been described and are also shown in Supplemental Table. Participants were all on antiretroviral therapy and most patients had undetectable viremia with similar immunological and virological indices between groups. At baseline, there were no

significant differences in cardiac immunologic, inflammatory or cardiac biomarkers between the groups (Supplemental Table and Table 1). After randomization, 1 out of 21 patients in the placebo group and 2 out of 19 in the statin group discontinued and did not have a 12-month evaluation.

Changes in cardiac biomarkers in the atorvastatin group vs. placebo

Changes in sST2 were −0.3 ng/mL (IQR −4.2 to 2.1) with atorvastatin vs. an increase of 1.2 ng/mL (0.6 to 4.7) with placebo (p=0.04 for comparison of change between groups) (Table 1 and Figure). Atorvastatin tended to lower GDF-15 with a change in GDF-15 of −19 ± 425 pg/mL with atorvastatin vs. a 262 ±507 pg/mL increase with placebo, but this did not reach statistical significance (p=0.08 for comparison of change between groups) (Table 1). In contrast, galectin-3 did not change significantly between groups with atorvastatin vs. placebo treatment.

Correlation with changes in cardiac biomarker levels

In all patients, the change in sST2 positively correlated with changes in monocyte activation markers sCD14 (r=0.63, p<0.0001) and MCP-1 (r=0.52, p=0.0009), hsIL-6 (r=0.58, p=0.0002), oxLDL (r=0.49, p=0.002), % CD14+CD16+ monocytes (r=0.46, p=0.03), and change in GDF-15 (r=0.54, p=0.0008), whereas, the change in GDF-15 was positively correlated with changes in galectin-3 (r=0.51, p=0.002), MCP-1 (r=0.42, p=0.01), sCD14 (r=0.45, p=0.007), hsIL-6 (r=0.47, p=0.005), and change in %CD14+CD16+ monocytes (r=0.52, p=0.02).

DISCUSSION

In the current analysis, we found sST2 increased significantly more in the placebo treated patients than atorvastatin-treated PLHIV, suggesting a potential effect of statins to mitigate ongoing fibrosis in this population. We also demonstrate that overall changes in sST2 is related to changes in monocyte activation markers.

Cardiac fibrosis is increased in HIV patients[18]. Statin therapy is being increasingly contemplated for PLHIV, due to effect on subclinical atherosclerotic disease, but little is known regarding effects of statin therapy on markers of cardiac fibrosis in HIV. One marker of importance in this regard is sST2. sST2 has been shown to be higher in PLHIV compared to non-infected individuals[5, 21]. Furthermore, sST2 has also been shown to be associated with cardiovascular dysfunction and strongly predictive all-cause mortality in patients living with HIV[14]. In the general population sST2 predicts cardiovascular events and all-cause mortality[13], and also predicts worse clinical outcomes in patients after acute myocardial infarction[22] and in patients with chronic heart failure[23].

ST2 is an interleukin-1 family receptor involved in inflammatory and immune responses[8]. The *ST2* gene encodes for two isoforms of the ST2 protein: transmembrane ST2L, which is primarily expressed on dendritic cells, mast cells, macrophages, and T helper cells, and secreted soluble ST2 (sST2)[6]. The functional ligand of ST2 is interleukin-33 (IL-33), which has a variety of biological functions including its role as an alarmin which responds to cellular stress and infection[24]. IL-33 is released by myocardial endothelial cells and gut

epithelial cells, and signals via binding to the ST2 receptor to mediate both proinflammatory and anti-inflammatory mechanisms,[25–27]. IL-33/ST2 signaling has been shown to reduce the development of atherosclerosis in mice, presumably through the induction of a Th1-to-Th2 shift and the production of antioxidized low-density lipoprotein (ox-LDL) and IL-5 antibodies[6]. Decreased production of ox-LDL antibodies may result from elevated sST2 levels, which would limit IL-33/ST2 signaling and elevate oxLDL, offering a possible explanation for the positive correlation we observed between sST2 and ox-LDL.

IL-33 signaling also has demonstrated antifibrotic effects in the myocardium, however endothelial cell production of IL-33 in response to myocardial pressure overload can induce a systemic inflammatory state[25]. IL-33/ST2 signaling is controlled by sST2, which acts as a decoy receptor to limit IL-33 activity, preventing the myocardial and vascular protective benefits of IL-33[25]. As such, elevated sST2 levels are associated with adverse prognosis in CVD and have been identified as a biomarker in heart disease, fibrosis, atherosclerosis, and inflammation[8]. IL-33 signaling via ST2 activates T cells and promotes Th2 lymphocyte responses, and has been shown to activate alternatively activated macrophages in ST2 deficient mice[28, 29]. The role of IL-33/ST2 signaling in monocyte and macrophage activation suggests that increased sST2 would result in increased inflammation.

The effect of statin therapy on IL-33/ST2 signaling has not yet been clearly elucidated, though previous studies have demonstrated that treatment of human umbilical vein endothelial cells (HUVEC) with statins affects expression of IL-33 and ST2 mRNA expression. DNA microarray studies have shown that atorvastatin and pitavastatin decrease ST2 mRNA expression[30]. These data suggest that statin therapy may directly affect the expression of IL-33 and ST2s[31].

We demonstrated that the change in sST2 related significantly to the change hs-IL6 as well as to changes in MCP-1, sCD14 with statin therapy, further confirming the relationships between sST2 and markers of monocyte activation consistent with the known role of IL-33/ST2 signaling in monocyte and macrophage activation. Furthermore, change in sST2 related to the change in oxidized LDL. It is uncertain whether statins' effects on lowering oxidized LDL may potentially mediate the reduction in sST2, however these relationships suggest that statins may reduce sST2 via direct anti-inflammatory effects on immune cells and possibly also via lowering of oxidized LDL. Given the prior strong association of sST2 with diastolic dysfunction and increased mortality in PLHIV prospective studies of statins such as the pitavastatin in the randomized trial to prevent vascular events in HIV (REPRIEVE, NCT02344290) will provide the opportunity to determine if a statin mediated decrease in sST2 is independently associated with a reduced incidence of heart failure and death as well as non-fatal ASCVD.

Another well-validated cardiac biomarker assessed in the current study is GDF-15, which we found to increase significantly over time in the placebo group but not in the atorvastatin group. GDF-15, also known as MIC-1, PTGF-β, PDF, PLAB, NAG-1, and PL74 is a member of the transforming growth factor-β (TGF-β) superfamily[10] that is expressed in the heart and other tissues in response to pro-inflammatory cytokines and cardiovascular stress-

related stimuli[10–12]. Though the exact mechanisms are unclear, these effects appear to be mediated via Akt- and SMAD2/3-related signaling pathways[11, 12].

Levels of GDF-15 have been shown to correlate with cardiovascular mortality, and all-cause mortality in the general population[32–34]. In the Framingham heart study, both GDF-15 and sST2 were found to be predictive of death, heart failure, and major cardiac events[13]. Though GDF-15 is increased in settings of inflammation and cardiovascular injury, Bonaca et al. found no significant difference in the effect of high dose vs. low dose statin therapy on GDF-15 levels in the PROVE-IT TIMI 22 trial[35]. Their null findings may be because both groups had received statin therapy so it would be harder to detect a difference. Although we did not find a significant decrease in GDF-15 with atorvastatin in our study either, our data suggest that statin therapy may help to prevent increases in GDF-15 in the HIV population which has increased GDF-15 at baseline. To our knowledge, no prior studies have examined the effects of statins on GDF-15 compared to placebo in HIV.

Only one prior study has assessed GDF-15 in HIV-infected participants. In that prospective cohort study, GDF-15 levels were elevated in HIV patients compared to controls, were associated with pulmonary hypertension and independently predicted all-cause mortality in the HIV group[14]. In our study, we demonstrated an increase in GDF-15 in the placebo group over 1 year and showed that atorvastatin tended to lower GDF-15 compared to placebos. GDF-15 may be induced by LPS in intestinal myofibroblasts[36, 37]. Further research is needed to determine if GDF-15 is increased in HIV by similar mechanisms.

In our study, we observed significant correlations between change in GDF-15 and markers of immune activation and inflammation, suggesting that GDF-15 may act primarily via immune and inflammatory pathways.[38]. In addition, we found the changes in GDF-15 and sST2 to be positively correlated. This finding is consistent with other studies[13, 39, 40] and suggests that GDF-15 and sST2 may act via a common biological pathway.

This study has limitations, including its small size. Despite this, results from this randomized placebo-controlled trial are informative regarding potential effects of statins on myocardial fibrosis in HIV, which may be modulated by effects on immune pathways. Data from our randomized trial suggest for the first time that statin therapy may prevent ongoing progression of fibrosis as indicated by sST2 in PLHIV and thus help to preserve the cardioprotective mechanisms of the IL-33/ST2 signaling system. Statin therapy may also help to prevent the progression of rise in GDF-15. Further larger studies are now needed to confirm these findings and ultimately determine if such changes relate to improved measurements of cardiac fibrosis, inflammation and events and whether PLHIV with higher sST2 or GDF-15 should be targeted for such studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DISCLOSURES

Unrelated to this study, Dr. deFilippi has received research support and consulted for Roche Diagnostics. He also consults for Alere, Ortho Diagnostics, Metanomics, and Siemens healthcare diagnostics; serves on an endpoint committee for Radiometer and Qunitiles; and receives royalties from UpToDate. Dr. Lo has served as consultant for Gilead Sciences. Dr. Hoffmann received grant support from Siemens Healthcare and HeartFlow Inc., unrelated to this manuscript. Dr. Grinspoon has consulted with Navidea and Theratechnologies, and received grant support from Gilead, KOWA Pharmaceuticals, and Theratechnologies, unrelated to this manuscript.

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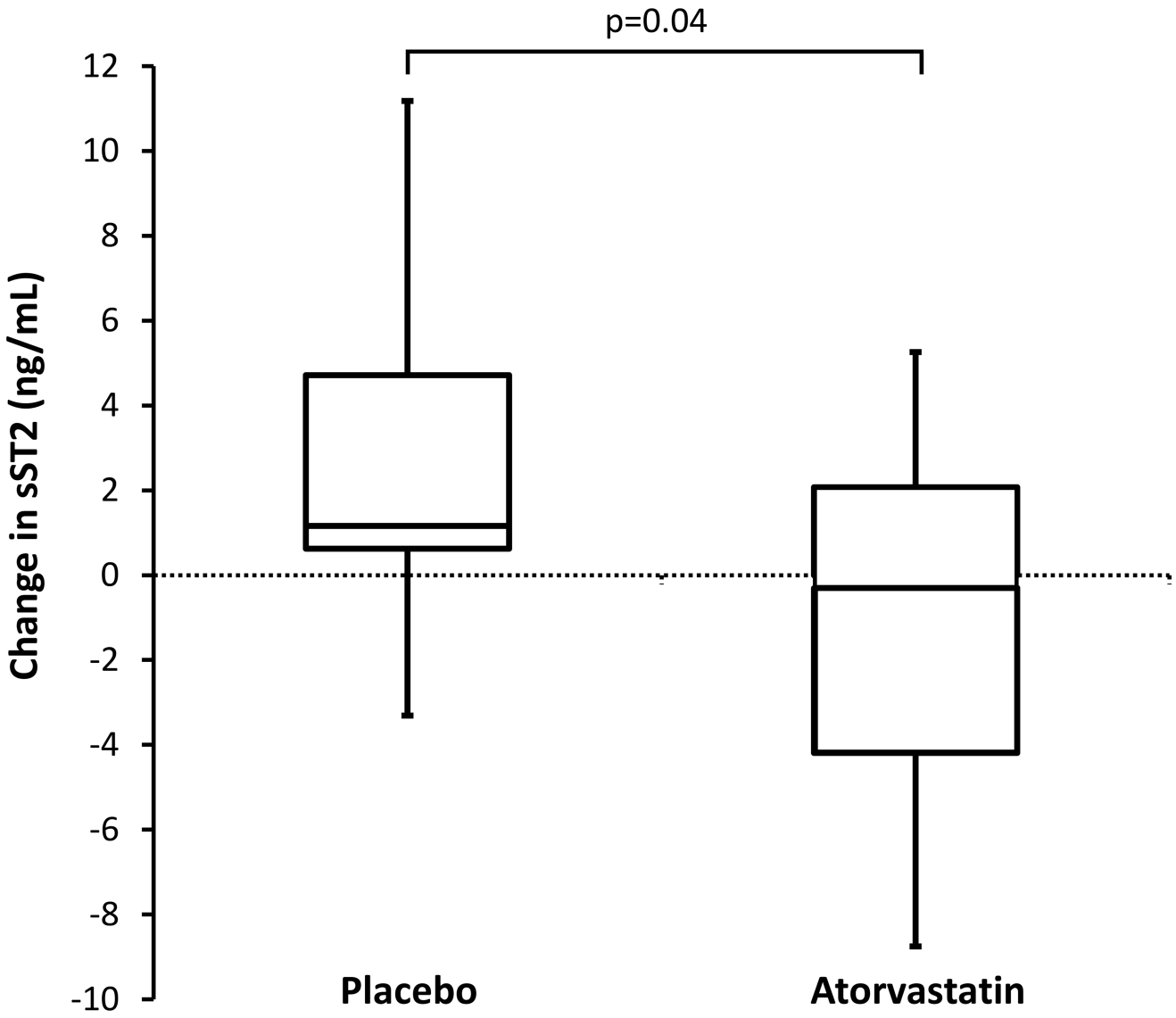

FIGURE.

Bolded line inside box denotes median and top of box denotes 75th centile and lower end of box denotes 25th centile. Ends of whiskers denote 90th and 10th centile.

Table 1

Lipids, Inflammatory Parameters, and Cardiac Biomarkers

	Baseline Placebo (n=21)	Baseline Atorvastatin (n=19)	Between Group P-value	12-month Placebo (n=20)	12-month Atorvastatin (n=17)	Within Group (Placebo) P-value	Within Group (Atorvastatin) P-value	Change Placebo (n=20)	Change Atorvastatin (n=17)	Between Group P-value
Lipids										
Total cholesterol (mg/dL)	192 ± 27	199 ± 38	0.52	198 ± 29	153 ± 29	0.30	<0.0001	5 ± 20	−47 ± 23	<0.0001
HDL-Cholesterol (mg/dL)	51 ± 15	52 ± 19	0.84	49 ± 15	55 ± 17	0.54	0.70	−2 ± 11	1 ± 10	0.48
Direct LDL-Cholesterol (mg/dL)	125 ± 32	124 ± 37	0.93	137 ± 30	86 ± 30	0.03	<0.0001	11 ± 21	−38 ± 29	<0.0001
Triglycerides (mg/dL)	113 (92 to 136)	120 (97 to 204)	0.39	117 (86 to 176)	110 (81 to 134)	0.93	0.49	8 (−41 to 34)	−9 (−41 to 39)	0.64
Oxidized LDL (U/L)	63.5 ± 13.1 (n=21)	62.2 ± 15.9 (n=18)	0.78	67.7 ± 19.2 (n=21) *	47.2 ± 11.3 (n=18) *	0.24	<0.0001	4.2 ± 15.8 (n=21) *	−14.9 ± 10.1 (n=18) *	<0.0001
Inflammatory Parameters	(n=21)	(n=19)								
C-reactive protein (mg/L)	1.1 (0.4 to 2.4)	0.8 (0.3 to 1.9)	0.36	1.5 (0.5 to 3.2)	0.5 (0.3 to 1.2)	0.26	0.27	0.2 (−0.1 to 1.5)	−0.1 (−1.1 to 0.2)	0.07
Interleukin-6 (ng/L)	0.8 (0.5 to 1.2)	0.6 (0.4 to 1.6)	0.75	1.0 (0.5 to 1.8)	0.8 (0.6 to 1.1)	0.44	0.93	0.1 (−0.2 to 0.4)	0.2 (−0.8 to 0.3)	0.77
sCD14 (ng/mL)	1953 (350 to 2400)	2100 (1088 to 2552)	0.48	1848 (475 to 2652)	1064 (509 to 2466)	0.31	0.26	125 (−238 to 495)	−162 (−780 to 201)	0.15
Cardiac Biomarkers	(n=20)	(n=17)								
Galectin-3 (ng/ml)	11.8 (10.3 to 15.2) (n=19)	13.2 (10.4 to 15.4)	0.63	13.9 (10.2 to 15.3)	12.5 (11.0 to 16.9)	0.26	0.43	0.5 (−1.1 to 1.8) (n=19)	0.2 (−1.5 to 3.2)	0.97
sST2 (ng/ml)	24.7 (20.4 to 30.9)	27.7 (20.4 to 36.2)	0.49	26.9 (21.4 to 31.1)	27.0 (20.0 to 31.8)	0.02	0.55	1.2 (0.6 to 4.7)	−0.3 (−4.2 to 2.1)	0.04
GDF-15 (pg/ml)	2221 ± 2458 (n=19)	1357 ± 836 (n=16)	0.16	2482 ± 2372 (n=19)	1339 ± 602 (n=16)	0.04	0.86	262 ± 507 (n=19)	−19 ± 425 (n=16)	0.08

Data reported as mean ± standard deviation or median (IQR).

* Serum from last visit prior to study discontinuation used for 12-month oxidized LDL

Within group changes assessed by paired t-test for normally distributed variables or by Wilcoxon signed rank test as nonparametric version of paired t-test for non-normally distributed variables. Between group differences assessed by Student's t-test for normally distributed variables or by Wilcoxon rank sum test for non-normally distributed variables.