Coronary Plaque Morphology and the Anti-Inflammatory Impact of Atorvastatin: a Multi-Center FDG-PET/CT Study

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ABSTRACT

**Background:** Non-obstructive coronary plaques manifesting higher-risk morphology (HRM) associate with an increased risk of adverse clinical cardiovascular events. We sought to test the hypothesis that statins have a greater anti-inflammatory effect within coronary plaques containing HRM.

**Methods:** In this prospective multicenter study, 55 subjects with or at high risk for atherosclerosis underwent $^{18}$F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging at baseline and after 12 weeks of treatment with atorvastatin. Coronary arterial inflammation (FDG uptake, expressed as target-to-background ratio [TBR]) was assessed in the left main coronary artery (LMCA). While blinded to the PET findings, contrast-enhanced CT angiography (CTA) was performed to characterize the presence of HRM (defined as non-calcified or partially-calcified plaques) in the LMCA.

**Results:** Arterial inflammation (TBR) was higher in LMCA segments with- vs. without- HRM (mean ± SEM: 1.95±0.43 vs. 1.67±0.32, LMCA with- vs. without HRM, p=0.04). Moreover, atorvastatin treatment for 12 weeks reduced TBR more in LMCA segments with- vs without- HRM (12 week-baseline ΔTBR [95% CI]: -0.18 [-0.35, -0.004] vs. 0.09 [-0.06, 0.26], p=0.02). Furthermore, this relationship between coronary plaque morphology and change in LMCA inflammatory activity remained significant after adjusting for baseline LDL and statin dose ($\beta$=-0.27, p=0.038).
**Conclusions:** In this first study to evaluate the impact of statins on coronary inflammation, we observed that the anti-inflammatory impact of statins is substantially greater within coronary plaques that contain higher-risk morphological features. These findings suggest an additional mechanism by which statins disproportionately benefit individuals with more advanced atherosclerotic disease.

**Key Words:** carotid, coronary artery, FDG-PET, inflammation, statins
Short Commentary

Atherosclerotic disease is distributed inhomogeneously within the arterial wall. The presence of non-obstructive plaques, in particular, those with higher risk morphology (HRM) is associated with an increased risk of atherothrombosis. We tested the hypothesis that the anti-inflammatory effect of statins is greatest within left main coronary artery (LMCA) plaques containing HRM. Herein, we provide an initial observation that statin therapy results in a reduction in LMCA inflammation. Further, we show in both coronary and extra-coronary arteries that the anti-inflammatory impact of statins is substantially greater within plaques that contain HRM. Together, the findings suggest an additional mechanism by which statins may disproportionately benefit individuals with more advanced atherosclerotic disease.

ABBREVIATIONS

CT = computed tomography
CTA = CT angiography
CRP = C-reactive protein
FDG-PET = 18F-fluorodeoxyglucose-positron emission tomography
HDL = high-density lipoprotein
LDL = low-density lipoprotein
LMCA = Left main coronary artery
MMP = matrix metalloproteinase
PCP/NCP = partially calcified plaque / non-calcified plaque

SUV = standardized uptake value

TBR = target-to-background ratio
INTRODUCTION

It is well-accepted that the presence of non-obstructive atherosclerotic plaques, particularly those with high-risk morphological (HRM) features, is associated with an increased risk of future cardiovascular disease events \(^1,2\). This observation has led to proposals to use data on non-obstructive plaque characteristics (if available) to alter the thresholds for prescribing lipid-lowering drugs for primary prevention \(^3,4\). A related and yet unresolved question is whether the anti-atherosclerotic benefits of statins may be differentially imparted depending on the severity of the underlying atherosclerotic process. This question is of substantial importance, since an association between atherosclerotic disease morphology and statin efficacy would provide a second reason to consider structural disease characteristics when deciding on primary prevention therapy.

Atherosclerosis is a systemic inflammatory condition \(^5\); the anti-inflammatory actions of statins is one of its most important beneficial effects on atherosclerosis \(^6\). Arterial imaging using 18-fluorodeoxy glucose positron emission tomography and computed tomography (FDG-PET/CT) is used to reproducibly measure atherosclerotic inflammation \(^7-10\). Atherosclerotic FDG uptake can be quantified non-invasively, and significantly correlates with systemic inflammatory biomarkers \(^11\), and macrophage infiltration as well as inflammatory cell gene expression within the arterial wall \(^12,13\). Further, it provides an independent marker of risk for future atherothrombotic events \(^14,15\), and is modifiable by statin therapy \(^9,16\). The majority of FDG-PET imaging studies have focused on extra-coronary vessels \(^7,10,17\). However, successful evaluation of coronary FDG uptake has been reported previously \(^18\), and has recently focused on the left
main coronary artery (LMCA) segment, which does not have an epicardial course and thus, lends itself to measurement of FDG uptake 19.

We hypothesized that atherosclerotic inflammation is greatest within LMCA manifesting higher-risk morphological features (HRM). Accordingly, in this prospective treatment study, we tested the hypothesis that the anti-inflammatory actions of atorvastatin are greatest in LMCA with-(vs. without) HRM.

**METHODS**

**Study design**

This study is part of a larger randomized double-blinded trial (www.clinicaltrials.gov, NCT00703261) that was conducted at 10 U.S. centers to investigate the impact of atorvastatin therapy on arterial wall inflammation. The study complies with the Declaration of Helsinki. The protocol was reviewed and approved by each center’s Institutional Review Board (IRB) and all participants provided written informed consent prior to any study procedures. Analysis of FDG uptake in the LMCA, carotid arteries and aorta was performed prior to un-blinding of the data. In the current study, we used CT angiography (CTA) images and performed a blinded analysis of plaque composition in carotids and coronary arteries, and additionally assessed the relationship between FDG uptake vs. high-risk plaque morphology. Permission was received from the Partners Healthcare IRB to perform these additional analyses on the anonymized images. The primary endpoint of the study, evaluating the effect of statin therapy on large vessel inflammatory activity (assessed by FDG PET/CT) was previously reported 9.
Patients

One hundred and sixty three subjects were initially screened and 83 subjects (78% men, median age 59 year, range 37-78 years) underwent baseline FDG-PET/CT imaging. Criteria for inclusion were individuals 30 to 80 years old with documentation or history of any one of the following: 1) coronary artery disease, 2) carotid artery disease, 3) cerebrovascular disease, 4) peripheral arterial disease (ankle-brachial index ≥0.5 and ≤0.9), 5) type 2 diabetes mellitus, or 6) BMI 30 to 40 kg/m², or waist circumference >102 cm in men and >88 cm in women. Subjects were excluded if they had a history of: 1) type 1 diabetes mellitus, 2) significant cardiovascular event or intervention within 12 weeks of screening, 3) significant heart failure (i.e. NYHA Class III or IV), 4) hepatobiliary disease, 5) chronic systemic inflammatory condition (such as rheumatoid arthritis or psoriasis), or 6) chronic infection. In addition, eligible subjects were required to have LDL-C ≥60 mg/dL and triglyceride level <350 mg/dL, and were required to be statin naïve or taking no more than low-dose statins (defined as: atorvastatin ≤10 mg, simvastatin ≤20 mg, rosuvastatin ≤5 mg, pravastatin ≤40 mg, or fluvastatin ≤40 mg).

After the initial clinical screening, subjects underwent baseline imaging with FDG-PET/CT. Since the study was originally designed to evaluate the effect of statin treatment on arterial wall inflammation, subjects without evidence of arterial inflammation (i.e. only subjects with TBR ≥1.6 in either the aorta or carotids were included) at baseline were excluded prior to randomization, resulting in the exclusion of approximately 10% of the initially screened population. Follow-up FDG-PET/CT images were obtained after 12 weeks of atorvastatin therapy.
**FDG-PET/CT imaging**

FDG-PET/CT imaging was performed using previously reported approaches \(^9\). Briefly, \(^{18}\)F-FDG was administered intravenously (approximately 10 mCi for a 70 kg patient) after an overnight fast, and imaging was performed 90 minutes after FDG injection using a hybrid PET/CT scanner (Seimens Biograph 64 or similar). To suppress myocardial FDG uptake, subjects were instructed to consume a low-carbohydrate, high-fat diet starting with the dinner meal (or 5 pm, whichever comes first), the evening before the day of FDG-PET/CT imaging, to suppress myocardial FDG uptake. An attenuation correction CT scan using 140 kVp was performed followed by PET imaging of the neck and chest, with 15 min acquisitions per bed position. The reconstruction of attenuation-corrected images was performed using ordered subset expectation–maximization algorithm. All patients had a blood sugar concentration of <200 mg/dl at the time of imaging.

**Measurement of coronary artery FDG uptake**

PET/CT images were analyzed using previously detailed methods \(^{18,19}\). Investigators were blinded to the clinical history and temporal sequence of the images. Subsequently, the datasets (week 0 and 12 images) were batch analyzed after co-registration of PET and CT images (Leonardo TrueD, Siemens Forchheim, Germany). Maximum standardized uptake value (SUV) of FDG was measured in LMCA by placing 4 regions of interest (ROI) at the: LMCA ostium, 5 and 10 mm distal to the ostium, and LMCA bifurcation. The measurements from those LMCA locations were averaged to produce mean of maximum LMCA SUV. Care was taken to avoid the spill-over activity from the myocardium, as performed in a prior study by our group \(^{18}\). The fact that coronary artery activity measurements were limited to the LMCA, a non-epicardial segment
of the coronary tree, facilitated the avoidance of myocardial activity. Target-to-background ratios (TBR) were derived from the ratio of the arterial SUV to background venous blood SUV from the superior vena cava. In addition, FDG uptake was measured in the aorta and carotids using previously described methods.9

Measurement of Arterial Inflammation the Aorta and Carotids

FDG uptake (TBR) was evaluated in three extra-coronary arterial locations (right and left carotid and aorta). The extra-coronary artery with the highest FDG uptake at baseline was identified as the index vessel, as previously described9. The mean TBR of the index vessel was defined as the average of the maximum TBR activity for all of the axial segments that compose the index vessel.

CT Angiography

Coronary CTA, to assess coronary artery plaque morphology, was performed in helical mode on multi-detector CT scanners with 64 or more slices. Imaging parameters included rotation time of 420ms or less, tube current of ~750-850 mAs (effective) and voltage of 120 kVp. Image acquisition characteristics were slice thicknesses of 0.75 mm and pitch of 0.2-0.4. Iopamidol 300mg/ml or similar was used as an intravenous contrast agent and infused at 5-6 ml/sec. Immediately following coronary CT angiography, the table was repositioned for acquisition of carotid images. Settings for carotid CT scanning were: pitch 2.8, rotation time of 500ms or less, tube current of ~180-300 mA and voltage of 120 kVp.

Assessment of atherosclerotic plaque morphology in the coronary arteries
Evaluation of the CTA images was performed while blinded to PET data and clinical information. Plaque morphology was assessed in the LMCA. HRM plaques in the LMCA were identified by presence of non- or partially-calcified plaques as described in prior studies\textsuperscript{20, 21}. An analysis examining morphological features of atherosclerotic plaques in the entire coronary arterial tree and carotid circulation was also performed (please refer to the supplement Table S1 and Figure S1, respectively).

**Assessment of blood biomarkers**

C-reactive protein (CRP) and matrix metalloproteinase-3 (MMP-3) concentrations were obtained at baseline and 12 weeks. Serum biomarker analyses were performed in batches.

**Statistical analysis**

Descriptive data are presented as mean ± standard deviation (SD) for continuous normally distributed variables, median (interquartile range [IQR]) for continuous non-normally distributed data, and frequency with proportions for nominal variables as appropriate. Independent samples t-test was used for cross-sectional comparison of normally distributed continuous variables. Mann-Whitney U test was employed for the similar analyses of continuous variables without normal distribution (such as CRP). A linear regression model was fitted to adjust for potential confounding factors on the effects of statin therapy in reduction of FDG uptake (TBR). The potential confounders for adjustment were selected based on the prior studies or clinical relevance. In the linear regression model to adjust for baseline LM TBR, we used tertiles of baseline TBR. adjustment for Fisher’s exact test was performed for comparison of dichotomous variables. Pearson correlation coefficient (R) was used to assess correlations between continuous variables once normal distribution was verified and Spearman ρ was reported as correlation.
coefficient for non-normally distributed variables. Two-tailed probability values are reported and statistical significance is defined as $P<0.05$. All statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY).

RESULTS
Baseline characteristics of study subjects are detailed in Table 1. Seventy-one subjects completed the 12-week treatment period. In 68 of those subjects, PET/CT image quality was sufficient to analyze FDG uptake in the LMCA and extra-coronary vessels (i.e. aorta, carotids). Fifty-five subjects provided adequate quality coronary CTA images to assess plaque morphology in the LMCA and carotid arteries (Figure 1).

Left main coronary arteries containing high-risk plaque morphological features have greater arterial wall inflammation
LMCA inflammation (TBR) was higher in LMCA with- vs. without HRM, as non- or partially-calcified plaque in LMCA, ([mean ± SE] 1.95±0.43 vs. 1.67±0.32, $p=0.043$, Figure 2 and Figure 3). A similar relationship between plaque morphology (as determined by CTA) and arterial inflammation (as determined by FDG-PET/CT) was seen in the carotid arteries (see supplement Figure S1).

Statins reduce left main coronary artery inflammation, an effect more pronounced within advanced coronary lesions
We evaluated the impact of statin therapy on LMCA and observed that after 12 weeks of statin therapy, FDG uptake was reduced in LMCA with- but not without- HRM (12 week-baseline change in TBR [95% CI]: -0.18 [-0.35, -0.004], vs. 0.09 [-0.06, 0.26], $p=0.02$; Figure 4). This relationship remained significant in a multivariate model after adjusting for pre-study statin use
and statin dose after randomization (β= -0.286, p= 0.02). The relationship remained statistically significant after adjusting for baseline TBR (β= -0.26, p= 0.04). Additionally, the relationship between LMCA plaque morphology and change in LMCA inflammation (TBR) after atorvastatin remained significant after adjusting for BMI (β= -0.27, p=0.02), and after adjusting for baseline LDL and statin dose (β= -0.27, p=0.038).

**Association between imaging measures and serum biomarkers**

For the comparison between blood biomarkers and coronary plaques, we assessed plaque morphology across the entire coronary tree (see supplement). Because of the relative abundance of plaques across the entire coronary tree, we were able to employ a more stringent definition of HRM, in this case, plaques with both positive remodeling and low attenuation (double-positives). At baseline, CRP was significantly higher in subjects with- vs. without HRM within the entire coronary arterial tree (median [IQR] = 3.6 mg/L [1.0-4.8] vs. 1.3 [0.6-2.5], p=0.01). We did not observe significant association between CRP concentrations and LMCA inflammation (TBR), though we observed a correlation between serum MMP-3 and LMCA inflammation (TBR) (ρ=0.31, p=0.04; R=0.42, p=0.004).

**Left main coronary artery inflammation correlates with inflammation in extra-coronary arteries**

At baseline, LMCA inflammation (TBR) correlated with inflammation (TBR) in the: aorta (r=0.6, p<0.001), carotid (r=0.32, p=0.04) and index vessel (r=0.49, p=0.001, Figure 5A). Likewise, in response to 12 weeks of atorvastatin treatment, changes in LMCA inflammation (TBR) correlated with changes in extra-coronary arterial inflammation (ΔAorta TBR vs.
**ΔLMCA TBR:** $r=0.51$, $p=0.001$; **ΔIndex vessel TBR vs. ΔLMCA TBR:** $r=0.33$, $p=0.04$, (Figure 5B).

**Higher extra-coronary arterial inflammation is associated with presence of higher-risk coronary structural features**

Furthermore, the TBR (inflammation) in the aorta was associated with the presence of HRM coronary plaque features (by CTA) such that subjects with higher aortic TBR ($\geq$median) exhibited a higher frequency of higher-risk structural plaque features throughout the coronary tree (44% vs. 13%, $p=0.02$) (Figure 6).

**DISCUSSION**

This first study examining the impact of statins on coronary artery inflammation yielded several novel observations. First, we provide initial evidence, in the coronary circulation, that coronary artery FDG accumulation, a marker of atherosclerotic inflammation, associates with higher-risk morphological features (HRM). Second, we demonstrate that statins result in a reduction in coronary inflammation, primarily in atherosclerotic plaques manifesting HRM. Furthermore, we demonstrate that statin-induced therapeutic modulation of extra-coronary artery FDG uptake parallels changes in coronary arterial FDG uptake. Together, these findings highlight the systemic nature of atherosclerotic arterial inflammation and also suggest that statin therapy may have its greatest impact on more advanced atherosclerotic disease.

The key finding of this study is the observation that the anti-inflammatory effect of statins is seen primarily within more advanced lesions. The association between plaque morphology and statin effect was evident in both the coronary and extra-coronary circulation, and remained robust after correcting for potential confounders such as baseline TBR, pre-study statin use, LDL
concentration and statin dose. Accordingly, the findings of this study provide additional support for the hypothesis that assessment of atherosclerosis, including arterial wall inflammatory activity, might help identify individuals that would derive the greatest benefit from statin therapy (even among individuals already deemed to be at increased risk using traditional risk calculators)²²,²³. This assertion is conceptually in-line with findings from the Multi-Ethnic Study of Atherosclerosis (MESA) study, where among individuals eligible for primary prevention, the majority of CHD and CVD events occurred in those with CAC scores >100²². From that, the authors suggested that preventative therapies should be preferentially prescribed to individuals with imaging evidence of more advanced atherosclerotic disease.

Similarly, Emami et al., recently demonstrated that the presence of non-obstructive atherosclerotic plaques is associated with an increased risk of future ASCVD events, and that incorporating information on non-obstructive CAD results in more accurate allocation of statin therapy. Our findings add an important additional consideration, by indicating that the underlying plaque morphology may additionally impact the local efficacy of statins. Together, these findings suggest that available imaging data might be useful for guiding treatment decisions regarding the use of statins or newer anti-atherosclerotic approaches, especially in cases where there may be relative equipoise when deciding on primary prevention. Given the likely emergence of a number of new pharmacological tools (such as novel lipid lowering drugs and anti-inflammatory drugs) with which to reduce the risk of incident atherothrombotic events, the medical community will likely experience a greater need to better-allocate those new treatments, a paradigm that is in-line with the contemporary emphasis on precision medicine²⁴.
In this study, we also tested the hypothesis that atherosclerotic inflammatory activity (represented as FDG uptake in LMCA) is highest in coronary plaques with HRM. While the relationship between HRM and inflammation has been previously reported for the carotids,\textsuperscript{25,26} the current study is the first to extend that observation to the coronary circulation. This observation provides further validation of FDG-PET/CT imaging as a tool to characterize proximal coronary atherosclerosis, in so far that it demonstrates that coronary FDG uptake (by PET) associates with high-risk structural features that are identified using an orthogonal technique (CTA).

Further, we investigated the relationship between inflammation in coronary and extra-coronary vessels. In this evaluation, we observed several important associations. First, we found that individuals with higher extra-coronary arterial inflammation had greater coronary inflammation, and were also more likely to have coronary plaques containing high-risk structural features. Furthermore, we observed that the anti-inflammatory actions of statins was similarly manifested in the extra-coronary and coronary circulation. These observations provide additional confidence that the data derived by looking at the large arteries (which are much more amenable to imaging), provide important insights into the coronary atherosclerotic milieu (where the atherothrombotic events of greatest concern originate). The data also provide additional insights as to why imaging of the aorta with FDG-PET/CT functions as an independent marker of risk of future CV events\textsuperscript{14,15}.

Lastly, we studied the relationship between both plaque morphology and inflammation with established serum pro-inflammatory biomarkers, MMP-3 and CRP. MMP-3 has been shown to correlate with inflammation (FDG uptake) in the aorta\textsuperscript{11}, and here, we replicate that finding, but further demonstrate that this relationship extends to the coronary artery as well. Similar to other
groups, we show a significant association between CRP and higher-risk coronary plaque features. Collectively, our findings emphasize the systemic nature of atherosclerosis and arterial inflammation by providing insights on the biological links between resident plaques in both large and small arteries, and circulating pro-inflammatory markers.

Limitations

Of the patients enrolled in the larger randomized-controlled prospective study, this study was limited to only those patients with evaluable CTA images and thus, limits the generalizability of the results. In this subset of patients, a smaller proportion had CT evidence of high-risk plaques, and perhaps may have limited our ability to detect a consistent relationship with CRP and MMP-3. It’s also worth noting that analyses were not sufficiently powered to assess the impact of statin dose (high-dose vs. low-dose) on LCMA.

In addition, coronary CTA was performed at a single timepoint, thereby precluding longitudinal assessment of changes or stability of coronary plaques at 12 weeks (after treatment). However, the reduction in both the coronary and extra-coronary artery FDG signal, which has been validated histopathologically as an inflammatory marker, suggests that the underlying inflammation-mediated higher-risk plaque features may have been favorably modified. Although the image analyses in our study were pre-specified prior to initiation of any study procedures, future studies are warranted to confirm our findings.

Conclusions

In summary, we show, for the first time, that statin therapy results in reduction in coronary inflammation, and that the anti-inflammatory impact of statins is substantially greater within
morphologically more advanced coronary plaques. Collectively, these findings suggest one potential mechanism by which statins may disproportionately benefit individuals with more advanced atherosclerotic disease.

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Disclosures

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FIGURE LEGENDS

Figure 1: Study Flow
Out of 163 subjects who were initially screened, 83 subjects underwent baseline FDG-PET/CT scan followed by statin treatment with atorvastatin. Follow-up FDG-PET scan was performed after 12 weeks of statin therapy. Seventy-one subjects completed the study and 68 had evaluable PET/CT images. Thereafter, an independent reader analyzed 55 evaluable coronary and carotid CTA images while blinded to PET data.

Abbreviations: CT, computed tomography; CTA, computed tomography angiography; FDG, $^{18}$F-flurodeoxyglucose; PET, positron emission tomography.

Figure 2: Association between high-risk plaque morphology and FDG uptake in LMCA
LMCA inflammation (TBR) in the index vessel was significantly higher in subjects with vs. without HRM (NCP/PCP) in the underlying coronary segment as detected by coronary CTA. Error bars represent SEM.

Abbreviations: CTA, computed tomography angiography; FDG, $^{18}$F-flurodeoxyglucose; HRM, high-risk morphology; LMCA, left main coronary artery; NCP, non-calcified plaque; PCP, partially-calcified plaque; TBR, target-to-background ratio.

Figure 3: Focal FDG uptake in patient with high-risk plaque morphology in the left main coronary artery
Fused PET/CT image showing intense and focal FDG uptake in the LMCA, in orthogonal images (A and B), corresponding MIP reconstructed CTA image of LMCA with non-calcified plaque (arrow) (C), and axial CTA showing a cross-sectional view (D) of an additional plaque in
the RCA manifesting positive remodeling and low attenuation \((arrow)\) in the same subject.

Abbreviations: CTA, computed tomography angiography; FDG, \(^{18}\)F-flurodeoxyglucose; HRM, high-risk morphology; LMCA, left main coronary artery; MIP, maximum intensity projection; NCP, non-calcified plaque; PET, positron emission tomography.

**Figure 4: Statin therapy results in a greater reduction of FDG uptake in LMCA with high-risk morphology**

Changes in LMCA TBR after 12 weeks of statin therapy were more pronounced in arteries with HRM in coronary CTA. Error bars represent SEM.

Abbreviations: CTA, computed tomography angiography; HRM, high-risk morphology; LMCA, left main coronary artery; TBR, target-to-background ratio.

**Figure 5: Extra-coronary arterial FDG uptake parallels left main coronary artery FDG uptake**

Index vessel FDG uptake (TBR) at baseline (A), and changes over the 12 week treatment period (B) significantly correlated with baseline LMCA TBR and changes in LMCA TBR, respectively.

Abbreviations: FDG, \(^{18}\)F-flurodeoxyglucose; LMCA, left main coronary artery; TBR, target-to-background ratio.

**Figure 6: Extra-coronary arterial inflammation associates with coronary structural features**
The PET/CT-derived inflammatory signal in the ascending aorta (TBR) was associated with presence of high-risk coronary plaque features by CTA such that subjects with higher aortic TBR (≥median) had increased frequency of high-risk plaque features (positive remodeling or low-attenuation plaque without dense calcification) in the entire coronary tree (43.5% vs. 13%, p=0.02)

Abbreviations: CT, computed tomography; CTA, computed tomography angiography; PET, positron emission tomography; TBR, target-to-background ratio.
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Values are presented as mean ± SD or n (%)