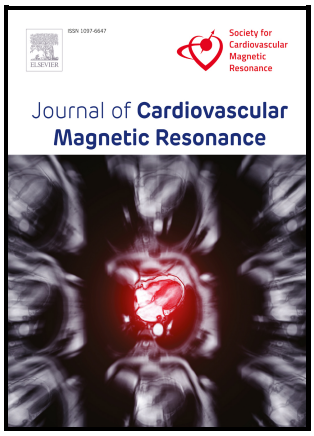

Atorvastatin and Left Atrial Function During Anthracycline-based Chemotherapy

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Title page

Title

Atorvastatin and Left Atrial Function During Anthracycline-based Chemotherapy

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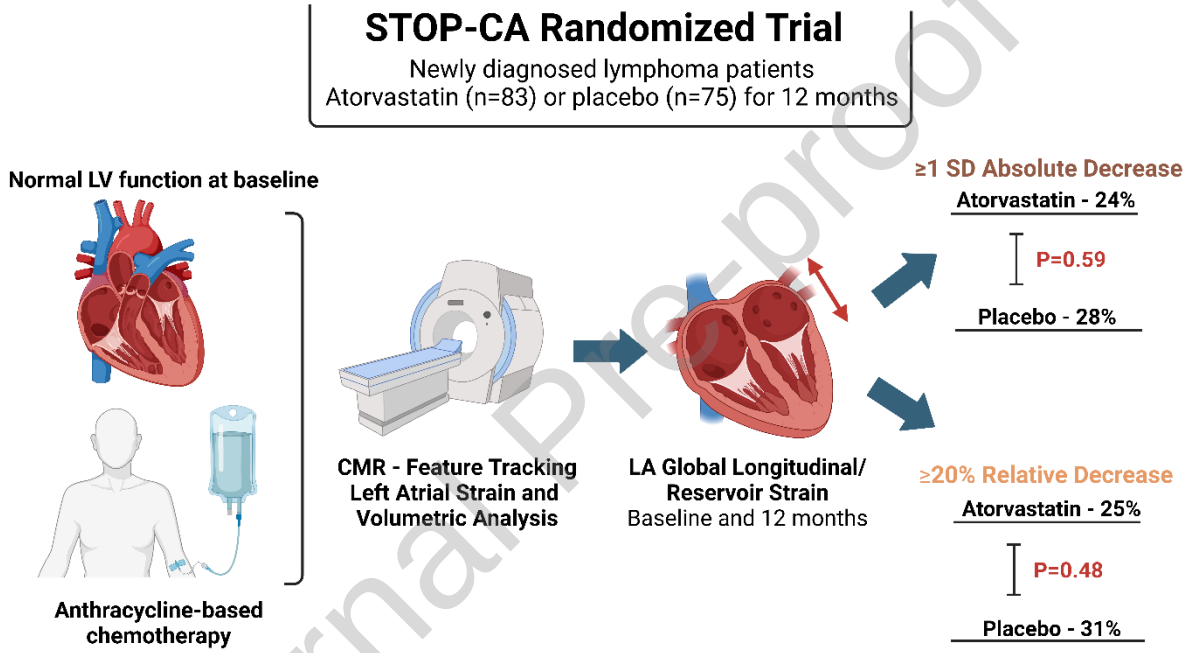
Graphical abstract



Keywords

Cardiac dysfunction, myocardial strain, feature tracking, cardiac magnetic resonance, cancer therapy-related cardiac dysfunction

Abstract

Background

Structural and functional abnormalities of the left atrium (LA) predict adverse outcomes such as heart failure and mortality in many patients with heart disease. However, the effect of

anthracyclines on LA structural and functional abnormalities remains incompletely characterized. Further, atorvastatin prevented the anthracycline-associated decline in the left ventricular ejection fraction; however, whether atorvastatin protects against anthracycline-associated impairment of LA structure and function is currently unknown.

Methods

In the STOP-CA randomized clinical trial, participants with lymphoma treated with anthracyclines were randomized to placebo (n=150) or atorvastatin (n=150) for 12 months. In post-hoc analyses, CMR-derived LA volumetric and functional measurements (reservoir [GLS], conduit, and booster strain) were measured at baseline and 12 months using feature tracking (FT). The primary endpoint was the difference in the proportion of participants with a ≥1 SD decrease in LA GLS between the atorvastatin and placebo groups. The secondary endpoint was a ≥20% relative decrease in LA GLS. Other exploratory endpoints included volume indices and emptying fractions.

Results

Of 300 participants, 158 (mean age 51±16 years, 48% female, 83 with atorvastatin) had paired CMR-derived LA strain and volumetric data at baseline and follow-up. Both groups had similar baseline characteristics and cancer treatment. All LA strain and volumetric measures were similar between the two groups at baseline. Among the placebo group, LA GLS decreased from baseline to follow-up (35.5±8.8 vs. 32.4±8.2%, p=0.007). A ≥1 SD absolute decrease in LA GLS (8.8% units) was observed among 24% with atorvastatin and 28% with placebo (p=0.59). Similarly, a ≥20% relative decrease in GLS was observed in 25% vs. 31% (p=0.48). Participants over 50 had an almost 10% (9.9%, 95% confidence interval: -18.75, -1.12) greater relative decrease in LA GLS with anthracyclines. There were no differences between cardiac hospitalization rates with a ≥1 SD absolute decrease (5% vs. 8%, p=0.72) in LA GLS at 24 months. Among other indices of LA structure and function, the LA total emptying fraction also decreased from baseline to follow-up, with no differences between groups at follow-up.

C**onclusion**

Atorvastatin did not attenuate the decline in CMR-derived LA GLS among lymphoma patients undergoing anthracycline-based chemotherapy.

(Clinical trial registration: NCT02943590; https://clinicaltrials.gov/study/NCT02943590)

Introduction

Anthracyclines are a standard chemotherapy drug used in the treatment of many malignancies, including breast cancer, lymphomas, and leukemias [1]. However, anthracyclines can impair cardiac function, leading to an increased risk of heart failure. Left atrial (LA) functional -

including strain - parameters are important predictors of heart failure and adverse events in a wide range of cardiac diseases [2–6].

To date, a few echocardiography-based studies have reported the effect of anthracyclines on LA function; however, no CMR-derived data are available. For example, among 136 breast cancer patients treated with anthracyclines and trastuzumab (+/- radiation therapy) who underwent serial imaging, echocardiography-derived LA reservoir strain improved diastolic dysfunction classification and was associated with subsequent cancer therapy-related cardiac dysfunction (CTRCD) [7]. Similarly, in a prospective cohort study of 128 HER2-negative breast cancer patients, LA reservoir and conduit strains by echocardiography were reduced after anthracycline treatment [8]. Finally, in a systematic review and meta-analysis, both reservoir and conduit strains were reduced post-anthracyclines [9].

With broader indications, such as accurate measurement of left ventricular ejection fraction (LVEF) in cases of uncertainty, quantification of myocardial fibrosis, and monitoring of LV global longitudinal strain, the number of cardio-oncology patients undergoing CMR is expected to increase [1]. By leveraging CMR to comprehensively characterize changes in LA structure and function due to cardiotoxic cancer therapy, the diagnostic efficacy of a single scan may be further enhanced. Therefore, the first goal of our study was to characterize the effect of anthracyclines on CMR-derived LA structure and function. Additionally, there is no data regarding whether interventions to protect the heart during anthracyline-based chemotherapy can attenuate the adverse anthracycline-associated effects on the LA. In the STOP-CA study, newly diagnosed lymphoma participants randomized to atorvastatin had lower odds of a significant decrease in LVEF and an increase in ECV compared to the placebo group [10,11]. Therefore, the second goal of this substudy of the STOP-CA trial was to test whether the use of atorvastatin was protective against LA functional and structural deterioration.

Methods

Trial Design

The STOP-CA randomized trial recruited 300 participants with newly diagnosed lymphoma across nine US and Canadian academic centers. All participants provided written informed consent prior to participation. Enrolment occurred between January 25, 2017, and September 10, 2021. Participants were randomized to atorvastatin (40 mg/day) or placebo in a 1:1 ratio for 12 months without a standard clinical indication for a statin. Detailed protocol information on the STOP-CA trial has been previously published [11]. The protocol was approved by the institutional review board or independent ethics committee at each participating center and adhered to the tenets of the Declaration of Helsinki.

CMR Methodology

CMR images were acquired using 1.5T and 3T scanners (Siemens Skyra, Prisma, Avanto, and GE Signa) as locally available at the trial sites. Long-axis cine sequences were acquired in two and four-chamber views using balanced steady-state free precession (b-SSFP) sequences. Typical sequence parameters are detailed in **Supplemental Table 1**. Semi-automatic endocardial contour detection with manual adjustment was performed with the QStrain (v2.0) application in Medis Suite (v2.0; Leiden, The Netherlands) with feature tracking (FT). Left atrial (LA) global longitudinal strain (GLS, as a measure of reservoir strain) was assessed at end-systole, conduit, and booster strains, strain rates, and total, active, and passive emptying fractions were calculated as previously described [3,12].
In brief, GLS or reservoir strain was measured at LV end-systole. Booster strain was determined in late diastole, before LA active contraction. Conduit strain was calculated as the difference between the reservoir and booster strain values. Strain values were averaged between two-chamber (2CH) and four-chamber (4CH) views.
LA volumes were determined using the biplane area-length method. The total emptying fraction was determined by the percentage change in LA volume from maximum (end-systole) to minimum (end-diastole) volumes. Passive emptying fraction was calculated as the volume change from maximum LA volume to the volume just before atrial contraction. Active emptying fraction was derived from the volume change during atrial contraction, from pre-atrial contraction volume to the minimum volume. **Supplemental Figure 1** depicts strain and volume concepts used for the calculations. Volumes were indexed to body surface area. All post-processing tasks were blinded by a fully licensed CMR reader (V.J., European Society of Cardiology license - level 3). Images and, consequently, participants with apparent foreshortening or planning flaws in either of the long-axis movies or arrhythmias preventing accurate strain measurements were excluded from the analyses (**Figure 1**).

Outcomes

Anthracycline-associated changes in CMR-derived LA functional and structural parameters were characterized in the placebo group. In treatment arm-adjusted analyses, possible demographic and clinical predictors of LA phasic strain values and changes were evaluated. Next, the effects of atorvastatin on LA GLS endpoints were assessed. First, testing a ≥1 SD decrease in LA GLS as a primary endpoint. Second, testing a ≥20% relative decrease in LA

GLS between baseline and 12-month follow-up as a secondary outcome, based on previous literature data reporting very good specificity (88%) and good sensitivity (71%) for subsequent LV dysfunction [13]. Associations between the change in LA GLS and LVEF and myocardial ECV were evaluated [10]. Finally, the proportions of participants meeting the LA strain endpoints and with an incident heart failure (HF) event or cardiac hospitalization for any cardiac reason (including high blood pressure, arrhythmias, myocardial infarction, or heart failure) were evaluated at 24 months.

Data Handling and Statistical Analysis

Descriptive statistics are indicated as means with standard deviations or medians with interquartile ranges (IQR). Categorical variables are denoted as counts and percentages. Fisher's exact test assessed the differences in proportions of the specified outcomes between the treatment groups. Differences in non-normal distribution continuous variables were evaluated with Wilcoxon rank-sum tests between the subgroups. Within-group differences in non-normal distribution continuous variables between baseline and follow-up were compared with the Wilcoxon signed-rank test. Two-sided statistical tests were used, and a P value less than 0.05 was considered significant. Multivariable linear regression analyses - adjusted for the treatment arm - were performed to assess the associations between the outcome variables and potential predictor demographic and clinical variables; 95% confidence intervals were included. All mean estimates reported below are adjusted for the treatment arm. Estimates for baseline and follow-up values are expressed as absolute percent (%) unit changes, whereas mean estimates for changes between baseline and follow-up are expressed as percentage relative changes. Pearson correlation was used to determine the correlation between normally distributed continuous variables. An intention-to-treat approach was applied irrespective of anthracycline protocol completion or study drug adherence. R version 4.3 (R Core Team) was used for all analyses performed by the Biostatistics Program at Dana-Farber Cancer Institute. The Office of Data Quality at Dana-Farber/Harvard Cancer Center oversaw clinical research auditing, subject registration, randomization, statistical analyses, data and safety monitoring, and quality control.

Results

Baseline Characteristics

Altogether, 158 participants [median age 53 years, interquartile range (IQR) 39-65; 48% female, n=83 (53%) randomized to atorvastatin] had CMR scans with appropriate quality at baseline and 12-month follow-up. Participants with poor image quality or a significant arrhythmia on either the two-chamber or four-chamber cines were excluded (**Figure 1**). The baseline characteristics of the atorvastatin and placebo groups were similar in demographics, type of lymphoma, relevant cardiac medications, cardiac risk factors, and cancer treatment regimen (**Table 1**). None of the participants had pre-existing atrial fibrillation in the presented subcohort. The comparison of baseline characteristics between those included in and excluded from LA functional analyses is presented in **Supplemental Table 2**.

The Effect of Anthracyclines on CMR-derived Left Atrial Strain and Function

In the placebo group (n=75, median age 52 years, IQR 38-62; 52% female), LA GLS (35.5±8.8% vs. 32.4±8.2%, p=0.007), conduit strain (21.4±8.1% vs. 19.4±7.0%, p=0.011), and total emptying fraction (68.0±8.6% vs. 65.2±8.9%, p=0.009) decreased between baseline and after anthracyclines (**Figure 2, Supplemental Table 3**). Additionally, pre-atrial-contraction volume indices (22.3±8.9 ml/m^2 vs. 24.2±10.3 ml/m^2, p=0.041) and minimal volume indices (12.8±6.2 ml/m^2 vs. 14.5±7.1 ml/m^2, p=0.009) significantly increased (**Figure 2, Supplemental Table 3**).

Associations Between Changes in Left Atrial Strain and Other Variables

Baseline LA GLS was associated with a -4.9% unit lower absolute value in participants over 50 (95% CI -7.29, -2.47, p<0.001). Moreover, a body mass index (BMI) ≥30 kg/m^2 was associated with a -5.3% lower baseline LA GLS (95% CI -9.03, -1.57; p=0.006; **Supplemental Figure 2**). At the 12-month follow-up, BMI ≥30 kg/m^2 and age >50 showed more negative estimates than at baseline (**Supplemental Figure 3**). Lastly, age >50 at randomization was associated with a 9.93% higher relative decrease (95% CI -18.75, -1.12, p=0.028) in LA GLS between baseline and follow-up (**Supplemental Figure 4**).
Baseline LA conduit strain showed an association with higher age (age at randomization >50: mean estimate -6.78% unit; 95% CI -8.97, -4.59; p<0.001) and higher BMI (BMI ≥25: mean estimate -3.27% unit; 95% CI -5.98, -0.55; p=0.019) were associated with lower baseline LA conduit strain values (**Supplemental Figure 5**). Follow-up LA conduit strain values showed associations of similar amplitude with higher age and BMI at 12-month follow-up (**Supplemental Figure 6**). There were no associations between demographic and clinical variables and relative change in LA conduit strain between baseline and 12-month follow-up (**Supplemental Figure 7**).
Baseline LA booster strain was associated with higher age (every 10-year increase at randomization: mean estimate 0.71%, 95% CI 0.24-1.18; p=0.003; >50 years: mean estimate 1.9% unit; 95% CI 0.35-3.45; p=0.017) and prevalent hypertension (mean estimate 3.91% unit; 95% CI 1.15-6.67; p=0.006, **Supplemental Figure 8**). There were no significant associations between demographic and clinical variables and the 12-month follow-up LA booster strain values (**Supplemental Figure 9**). However, age over 50 at randomization

(mean estimate -18.96%; 95% CI -33.98, -3.94; p=0.014) and hypertension (mean estimate: -36.61, 95% CI -63.41, -9.81; p=0.008) were associated with a greater relative decreases in LA booster strain between baseline and follow-up (**Supplemental Figure 10**).

Associations with Clinical Events, LV Ejection Fraction, and Myocardial Extracellular Volume Changes

Participants of this subcohort with 24-month follow-up data available had no clinical heart failure events with either a ≥1 SD absolute or a ≥20% relative decrease in LA GLS (total HF events: n=7/149, 5%). There were also no differences between cardiac hospitalization rates (total cardiac hospitalization events: n=10/139, 7%) with either ≥1 SD absolute (5% meeting the endpoint vs. 8% not meeting the endpoint, p=0.72) or a ≥20% relative decrease (5% meeting the endpoint vs. 8% not meeting the endpoint, p=0.72).
There was a very weak correlation between the change in LV EF and LA GLS (r=0.18, p=0.024). Follow-up LA conduit strain values showed modest associations with a ≥5% drop in LVEF (mean estimate -2.39% unit, 95% CI -4.66, -0.12; p=0.039; **Supplemental Figure 6**). However, when applying the primary outcome measure of the STOP-CA trial, a ≥10% drop in LVEF to a final value of <55%, there was no significant difference in the change in LA GLS between those meeting the trial's primary LVEF endpoint and those not meeting it (p=0.13). There was no correlation between the interval change in myocardial ECV and LA GLS (p=0.16), LA conduit strain (p=0.22), or LA booster strain (p=0.68) changes.

The Effect of Atorvastatin on Left Atrial Strain and Volume Indices

Baseline LA GLS was similar in the atorvastatin and placebo groups (33.6±6.9% vs. 35.5±8.8%, p=0.20) and remained comparable at 12-month follow-up (32.0±8.0% vs. 32.4±8.2%, p=0.60, **Table 2**). No significant difference was observed in the interval change in LA GLS between the groups (-1.6±8.7% atorvastatin vs. -3.1±8.8% placebo, p=0.54). The proportions of participants meeting the primary endpoint of a ≥1 SD (8.8% unit) decrease in LA GLS were also similar between groups (24% atorvastatin vs. 28% placebo, p=0.59). The endpoint of a relative decrease of ≥20% was similar between the two groups (25% atorvastatin vs. 31% placebo, p=0.48; **Table 2 and Graphical Abstract**).
Baseline LA conduit strain was statistically similar in the atorvastatin and placebo groups (19.7±7.1% vs. 21.4±8.1%, p=0.24) and remained comparable at 12-month follow-up (19.2±7.2% vs. 19.4±7.0%, p=0.60, **Table 2**). However, the LA conduit strain decreased between baseline and follow-up in the placebo group (21.4±8.1% vs. 19.4±7.0%, p=0.011, **Figure 2**, **Supplemental Table 3**). At the same time, there was no significant decrease in LA conduit strain with atorvastatin (19.7±7.1% vs. 19.2±7.2%, p=0.38, **Figure 2, Supplemental Table 3**). Strain rates decreased between baseline and follow-up within both groups; however, there was no difference in baseline and follow-up values, and interval changes between the atorvastatin and placebo groups (**Supplemental Tables 4 and 5**).
Baseline LA booster strain was similar in the atorvastatin and placebo groups (13.9±4.6% vs. 14.1±5.3%, p=0.92) and remained comparable at 12-month follow-up (12.8±4.3% vs. 13.0±4.5%, p=0.85, **Table 2**). All LA maximal, minimal, pre-atrial-contraction volume indices and total, active, and passive emptying fractions were similar at baseline and 12-

month follow-ups between the atorvastatin and placebo groups (**Supplemental Table 6**). However, there was an increase in the pre-atrial-contraction volume index in the placebo group at follow-up (22.3±8.9 ml/m^2 vs. 24.2±10.3 ml/m^2, p=0.041). At the same time, there was no significant change in the atorvastatin group (23.7±8.5 ml/m^2 vs. 24.7±9.4 ml/m^2, p=0.38, **Figure 2, Supplemental Table 3**).

Implications of Lymphoma Type

Subgroup analyses comparing the effect of anti-cancer treatment and atorvastatin in non-Hodgkin (NHL) and Hodgkin lymphoma (HL) were also performed. The cumulative anthracycline dose was significantly higher in the NHL subgroup (275±50 vs. 230±74 mg/m^2, p<0.001), while radiation treatment was similar (12% vs. 14%, p=0.78). There was no significant difference in the interval changes and the proportions of participants with a ≥1 SD decrease in LA GLS in either the atorvastatin or the placebo groups, between the NHL and HL subgroups (**Supplemental Table 7**).

Discussion

This substudy of a large prospective randomized trial reports on the impact of anthracyclines on CMR-derived LA structure and function, including strain parameters. LA structural and functional parameters are strongly associated with adverse clinical outcomes, such as heart failure. In the placebo group, there was a decrease in LA global longitudinal (reservoir) strain and conduit strain at 12 months after anthracycline therapy initiation compared to baseline. The relative decline in LA GLS and LA booster strain was more pronounced in patients over 50 years, as was the relative change in booster strain in participants with preexisting hypertension. Although this trial was not powered for clinical events, LA GLS was not associated with lower cardiac hospitalization rates at 24 months or a decline in LVEF. In STOP-CA, atorvastatin preserved the LVEF after anthracyclines; however, the adverse effect of anthracyclines on LA GLS was not attenuated by atorvastatin. To our knowledge, this is the first study to evaluate the impact of anthracyclines on CMR-derived LA functional and deformational parameters; the results indicate the need for ongoing efforts to ameliorate the detrimental effects of anthracyclines on the heart.

Left atrial strain and volumetric parameters have been associated with adverse non-cardiac and cardiac outcomes in various heart diseases, including myocardial infarction, atrial fibrillation, hypertrophic cardiomyopathy, and cardiotoxicity [3,9,14–20]. Data on LA structure and function change with anthracyclines are derived primarily from studies with echocardiography. Using echocardiography, reductions in LA emptying fractions and strain parameters due to anthracyclines have been reported [4,8,9,21,22]. However, the incidence of LA dysfunction with anthracyclines has not been extensively documented, and standard cut-off criteria have not been established. For example, a 3D echocardiography study with 80 diffuse large B-cell lymphoma patients assessed LV and LA function after four and six cycles of anthracyclines. This study reported a 71% sensitivity and 88% specificity for a >19.75%

relative decline after four cycles of anthracyclines in the LA reservoir strain to associate with a subsequent LVEF decline assessed after six cycles of anthracyclines [13]. In our cohort, albeit both evaluated at the same time point, 12 months after anthracycline initiation, this cut-off was not associated with LVEF decline. Similarly, a 3D echocardiography study with 61 large B-cell lymphoma patients suggested that the passive emptying function of the LA may deteriorate with an increased active emptying component, compensating for a preserved total emptying fraction as measured one day after chemotherapy completion [21]. In contrast, we found no significant differences in passive and active volumetric parameters in our control group. However, differences in study cohort demographics, imaging timing, cancer type, cumulative anthracycline dose, and cancer treatment regimens can contribute to the variation in reported outcomes with LA parameters. With improved access and technology, the number of CMR examinations carried out among cancer patients is expected to increase. Leveraging multiple aspects of functional and volumetric testing of the different chambers may contribute to our mechanistic understanding of cardiotoxicity and more accurate characterization of cardiac adverse effects in these groups of patients. Moreover, FT-CMR captures the entire atrial myocardium with high spatial resolution and no reliance on acoustic windows, yielding more reproducible biplane LA strain and exact volume measurements than speckle-tracking echocardiography—an important advantage in oncology patients whose chest-wall changes can compromise echo image quality [23,24]. Whether CMR-derived left atrial strain parameters may be helpful as surrogate criteria for identifying or tracking subclinical cardiotoxicity and protective interventions requires further work.

Previous data suggest that cancer patients above the age of 50, those who are overweight or have prevalent hypertension, may be at additional risk of cardiotoxicity due to anthracyclines. For example, in the STOP-CA trial, participants above the median age had a more significant decrease in the LVEF [11]. In this study, age >50 was associated with lower baseline and follow-up LA GLS values and a more pronounced relative decrease by 12 months. However, the latter was affected by a greater relative decline in the LA booster strain rather than in the conduit strain. A systematic review and meta-analysis found that a BMI $\geq$25 kg/m^2 was associated with a pooled odds ratio of 1.38 (95% CI 1.06-1.80) for cardiotoxicity in breast cancer patients treated with anthracyclines and trastuzumab [25]. While a lower baseline reservoir and conduit strain was associated with BMI $\geq$25 kg/m^2 in our cohort, we did not find a more pronounced temporal decline. In a systematic review with 7,488 anthracycline-treated patients, hypertension was associated with a 1.99 times higher odds ratio for subsequent cardiotoxicity [26]. In this study, pre-existing hypertension was associated with a pronounced relative decline in LA booster function. However, we did not find meaningful associations between LA function changes and LVEF and LA GLS. This suggests that patients at risk of a decline in LVEF only partially overlap (at least in time) with patients presenting with worsening LA functional parameters measured at 12 months after anthracycline initiation. Similarly, a recent study among breast cancer patients with serial imaging reported that only 22% of patients with subsequent CTRCD present with diastolic dysfunction (including LA reservoir strain as a criterion) before transitioning to a decreased systolic function phenotype secondary to cardiotoxicity [7]. Finally, we compared NHL and HL subgroups and found no significant difference between the effect of anti-cancer and atorvastatin therapy on LA GLS.

While the primary analyses of the STOP-CA trial reported a more pronounced decrease in LVEF with NHL, a difference in cardiotoxicity phenotype or cardioprotection was not found by measuring LA GLS [11].

In the STOP-CA study, atorvastatin preserved the LVEF and ECV after anthracyclines [10,11]. Here, atorvastatin did not attenuate the anthracycline-associated decline in LA GLS and most LA volumetric parameters. The lack of detection of a clinically significant protective effect of atorvastatin on LA function may have multiple reasons. In this study, there was only a weak association between changes in LA function and changes in the LVEF and no correlation with ECV changes, suggesting that the mechanism of injury/protection may differ for anthracycline-associated impairment in the LVEF, diffuse myocardial fibrosis, and the anthracycline-associated impairment in LA function. Mechanistically, the cardiotoxic effects of anthracyclines involve the cardiomyocytes directly, exerting a more pronounced effect on the dense, metabolically demanding LV myocardium than on the LA wall tissue, which has a substantially lower number of myocytes and is metabolically less active [27–30]. Thus, it is possible that statins do not completely attenuate the diastolic impairment of the LV and deterioration of LA function [31,32]. Alternatively, the left atrial findings may relate to the timing of imaging visits, earlier stages of cardiac dysfunction, or a different phenotype of cardiotoxicity, considering the weak correlation with LVEF changes. Different follow-up imaging or serial measurement timings with longer follow-up may provide more insight into the changes in CMR-derived LA parameters with anthracyclines and the effect of statins or other potentially cardioprotective interventions. In patients with anthracyclines and trastuzumab, the nadir in LA strain decline was observed between 6 and 12 months after therapy initiation [7]. Nevertheless, further work is needed to clarify the mechanistic reasons why atorvastatin appears protective against a decline in LV systolic function and prevents LV fibrosis, but does not preserve LA function [10,11,33].

Limitations

These results should be interpreted within the context of the study design. While this substudy of a randomized trial represents 53% (n=158/300) of the total cohort, the baseline characteristics of the two treatment arms remained similar. With that, a modest sample size and the low number of clinical events limited the statistical power of the analyses. The use of post-hoc endpoints in this substudy reflects the exploratory nature of secondary analyses. A single imaging time point may not have captured long-term effects of either anthracyclines or atorvastatin, and data with extended follow-up times and multiple imaging time points are necessary to elucidate cardiac sequelae beyond 12-24 months. All relevant previous investigations reported left atrial volumetric parameters using echocardiography and strain parameters via speckle-tracking echocardiography in anthracycline-treated patients, limiting direct comparison with CMR-derived results. The poor agreement between STE and CMR-derived LA strain requires cautious inter-modality interpretations [34]. However, structural and functional analyses of the LA showed reasonable accuracy and reproducibility with CMR [12,35]. A proportion of scans had to be excluded from the analyses due to poor image quality. However, LA-focused cine image planning may further improve accuracy and reduce exclusions due to image planning issues. Additionally, focused LA assessment may result in

faster acquisition and reduce the underestimation of LA volumes and the overestimation of reservoir strain [36].

Conclusion

CMR-derived LA strain parameters deteriorated 12 months after anthracycline therapy initiation in participants with newly diagnosed lymphoma, and the decline in the LA structure and function was observed more commonly among older patients and was only weakly associated with the changes in the LVEF. Atorvastatin did not attenuate the decline in LA GLS at 12 months, compared to placebo. As LA structural and functional decline can predict cardiovascular events, future work is needed to test alternative interventions to preserve LA structure and function in patients treated with anthracyclines.

List of Abbreviations

b-SSPF – balanced steady-state free precession

CTRCD – cancer therapy-related cardiac dysfunction

ECV – extracellular volume

FT – feature tracking

GLS – global longitudinal strain

HL – Hodgkin lymphoma

LA – left atrium

NHL – non-Hodgkin lymphoma

STE – speckle tracking echocardiography

Declarations

Disclosures

Dr Neilan reported receipt of personal fees for consulting from Bristol Myers Squibb; receipt of personal fees from Genentech, GSK, Roche, Sanofi; and receipt of grants from Bristol Myers Squibb and AstraZeneca. Dr. Januzzi has served as a board member for Imbria Pharmaceuticals, has received grant support from Abbott, Applied Therapeutics, HeartFlow, Innolife, and Roche Diagnostics, has received consulting income from Abbott, Beckman, Bristol Myers Squibb, Boehringer Ingelheim, JanaCare, Janssen, Novartis, Pfizer, Merck, Roche Diagnostics, and Siemens, and has participated in clinical endpoint committees/data

safety monitoring boards for Abbott, AbbVie, CVRx, Intercept, and Takeda. Dr. Neuberg has stock ownership in Madrigal Pharmaceuticals. Dr. Asnani receives royalties from patent #US20210163495A1 (Mass General Brigham), and sits on the Board of Directors for Corventum, Inc. The remaining authors have nothing to disclose.

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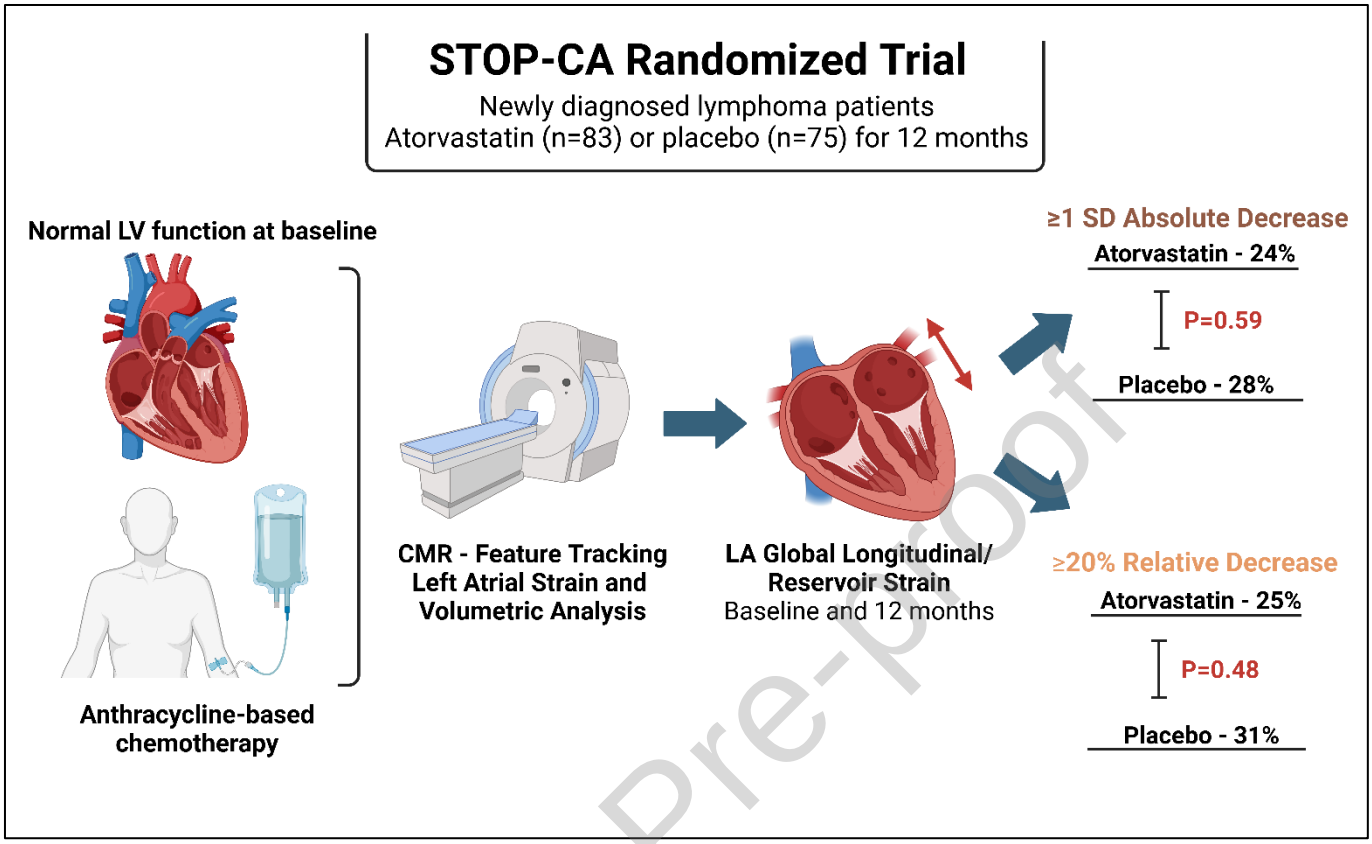
Data Availability Statement

We will make de-identified data available on reasonable request, provided it follows IRB and consent directions.

Graphical Abstract



Figures

Figure 1.

Study flowchart

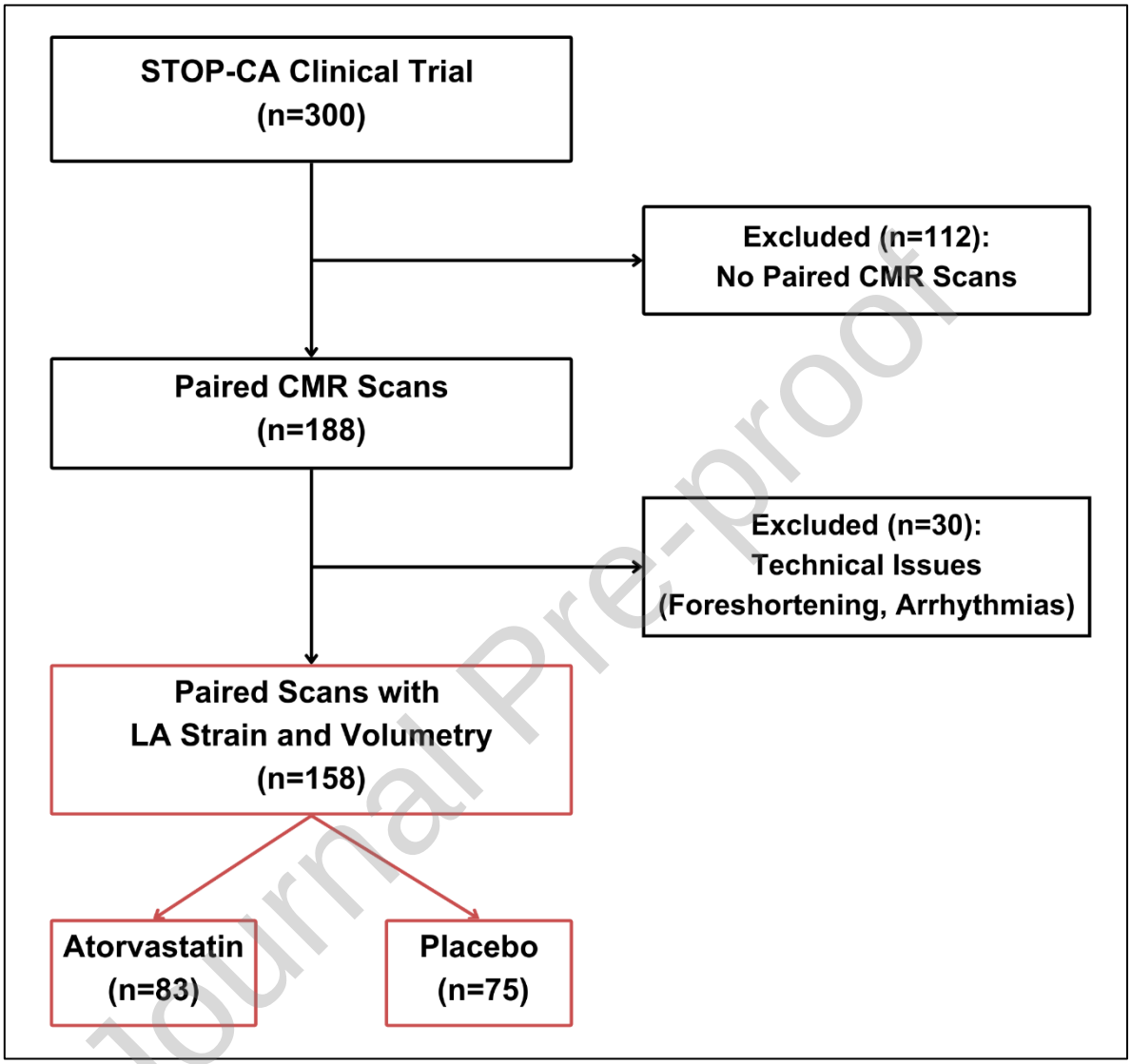
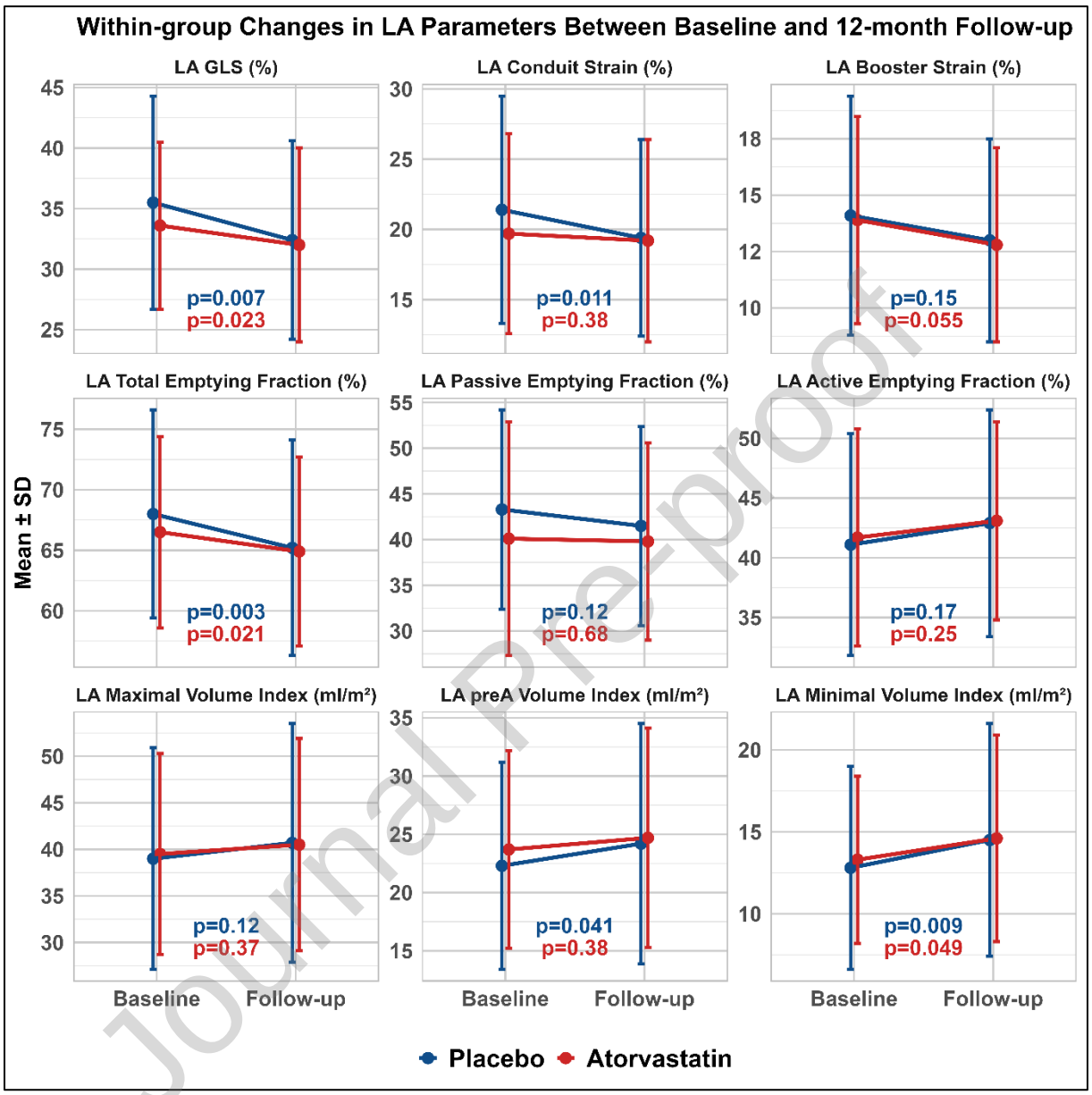


Figure 2.

Within-group changes in left atrial parameters between baseline and 12-month follow-up



Legend: P values (blue=placebo, red=atorvastatin) refer to changes between baseline and follow-up; within treatment groups. Numerical values are found in Supplemental Table 3. LA: left atrium, preA: pre-atrial-contraction, GLS: global longitudinal strain

Tables

Table 1.

Baseline characteristics of the left atrial CMR subcohort of the STOP-CA trial

		Treatment arm		
	Total n = 158 (%)	**Atorvastatin n = 83 (53)**	**Placebo n = 75 (47)**	**p-value**
Age at randomization, years				
Mean (SD)	51 (±16)	52 (±17)	51 (±15)	0.48[a]
Median [IQR]	53 [39 – 65]	55 [40 – 66]	52 [38 – 62]	
Sex				
Female	76 (48)	37 (45)	39 (52)	0.43[b]
Male	82 (52)	46 (55)	36 (48)	
Race				
White	145 (92)	77 (93)	68 (91)	0.38[b]
Black	2 (1)	2 (2)	-	
Asian	7 (4)	2 (2)	5 (7)	
Unknown	4 (3)	2 (2)	2 (3)	
Ethnicity				
Hispanic/Latino	12 (8)	9 (11)	3 (4)	0.18[b]
Non-Hispanic/Latino	140 (89)	72 (87)	68 (91)	
Unknown	6 (4)	2 (2)	4 (5)	
Body mass index, kg/m^2				
Mean (SD)	27.3 (±5.7)	27.2 (±5.4)	27.4 (±6.0)	0.98[a]
Median [IQR]	25.9 [23.6 - 29.9]	26.1 [23.7 - 30.0]	25.7 [23.4 - 29.8]	
Body mass index, WHO criteria				
Underweight, < 18.5	2 (1)	-	2 (3)	0.73[b]
Normal weight, ≥ 18.5	63 (40)	32 (39)	31 (41)	
Overweight, ≥ 25	55 (35)	31 (37)	24 (32)	
Obese, ≥ 30	23 (15)	12 (14)	11 (15)	
Severely Obese, ≥ 35	15 (9)	8 (10)	7 (9)	
Type of lymphoma				
B cell Lymphoma	115 (73)	59 (71)	56 (75)	0.91[b]
T cell Lymphoma	7 (4)	4 (5)	3 (4)	
Hodgkin Lymphoma	36 (23)	20 (24)	16 (21)	
ECOG Performance Status Scale				
Grade 0	130 (82)	66 (80)	64 (85)	0.80[b]
Grade 1	23 (15)	13 (16)	10 (13)	
Grade 2	3 (2)	2 (2)	1 (1)	

Grade 3	-	-	-	
Cardiac medications				
ARB, or ACE inhibitor				
No	148 (94)	76 (92)	72 (96)	0.50[b]
Yes	9 (6)	6 (7)	3 (4)	
Beta-blocker				
No	150 (95)	77 (93)	73 (97)	0.45[b]
Yes	7 (4)	5 (6)	2 (3)	
Aspirin				
No	149 (94)	78 (94)	71 (95)	> 0.99[b]
Yes	8 (5)	4 (5)	4 (5)	
Calcium channel blocker				
No	153 (97)	80 (96)	73 (97)	> 0.99[b]
Yes	4 (3)	2 (2)	2 (3)	
Other (e.g., diuretic, aldosterone antagonist)				
No	154 (97)	80 (96)	74 (99)	> 0.99[b]
Yes	3 (2)	2 (2)	1 (1)	
Cardiac Risk Factors				
Hypertension				
No	145 (92)	76 (92)	69 (92)	> 0.99[b]
Yes	13 (8)	7 (8)	6 (8)	
Smoking history				
No	121 (77)	63 (76)	58 (77)	> 0.99[b]
Yes	35 (22)	18 (22)	17 (23)	
Current smoker				
No	30 (19)	15 (18)	15 (20)	> 0.99[b]
Yes	5 (3)	3 (4)	2 (3)	
Sleep apnea				
No	150 (95)	81 (98)	69 (92)	0.15[b]
Yes	8 (5)	2 (2)	6 (8)	
Diabetes				
No	158 (100)	83 (100)	75 (100)	> 0.99[b]
Yes	-	-	-	
Cumulative anthracycline dose (mg/m^2)				
Mean (SD)	265.0 (±59.4)	265.8 (±60.2)	264.0 (±58.9)	0.28[a]
Median [IQR]	299.7 [240.2 - 300.3]	299.5 [260.6 - 300.0]	300.0 [214.4 - 301.3]	
Radiation treatment				
No	138 (87)	74 (89)	64 (85)	0.48[b]
Yes	20 (13)	9 (11)	11 (15)	
[a]Wilcoxon rank-sum test, [b]Fisher's test				

Table 2.

Comparison and changes in left atrial strain parameters at baseline and follow-up

		Treatment arm		
	Total n=158	**Atorvastatin n=83**	**Placebo n=75**	**p-value**
Left Atrial Global Longitudinal Strain (LA GLS)				
LA GLS - Baseline (%)				
Mean (±SD)	34.5 (±7.9)	33.6 (±6.9)	35.5 (±8.8)	0.20[a]
Median [IQR]	34.0 [29.2 - 39.5]	33.2 [28.9 - 38.8]	34.9 [29.2 - 41.3]	
LA GLS - 12 Months (%)				
Mean (±SD)	32.2 (±8.1)	32.0 (±8.0)	32.4 (±8.2)	0.60[a]
Median [IQR]	31.8 [26.6 - 37.8]	31.5 [26.2 - 37.2]	32.1 [27.7 - 38.3]	
LA GLS - Absolute Change (% unit)				
Mean (±SD)	-2.3 (±8.8)	-1.6 (±8.7)	-3.1 (±8.8)	0.54[a]
Median [IQR]	-2.4 [-8.8, 2.9]	-2.4 [-7.3, 2.6]	-2.4 [-9.9, 2.9]	
LA GLS – Absolute Decrease ≥1 SD (8.8% unit) [n (%)]				
No	117 (74)	63 (76)	54 (72)	0.59[b]
Yes	41 (26)	20 (24)	21 (28)	
LA GLS - Relative Decrease ≥20% [n (%)]				
No	114 (72)	62 (75)	52 (69)	0.48[b]
Yes	44 (28)	21 (25)	23 (31)	
Left Atrial Conduit Strain				
LA Conduit Strain – Baseline (%)				
Mean (±SD)	20.5 (±7.6)	19.7 (±7.1)	21.4 (±8.1)	0.24[a]
Median [IQR]	20.0 [14.1 - 25.8]	19.7 [13.7 - 25.2]	21.4 [16.1 - 25.9]	
LA Conduit Strain – 12 months (%)				
Mean (±SD)	19.3 (±7.1)	19.2 (±7.2)	19.4 (±7.0)	0.58[a]
Median [IQR]	18.8 [14.4 - 22.7]	17.9 [13.8 - 22.8]	19.6 [14.9 - 22.4]	
Left Atrial Booster Strain				
LA Booster Strain – Baseline (%)				
Mean (±SD)	14.0 (±4.9)	13.9 (±4.6)	14.1 (±5.3)	0.92[a]
Median [IQR]	13.9 [10.7 - 17.1]	13.7 [10.8 - 16.9]	14.0 [10.5 - 17.2]	
LA Booster Strain – 12 months (%)				
Mean (±SD)	12.9 (±4.4)	12.8 (±4.3)	13.0 (±4.5)	0.85[a]
Median [IQR]	12.8 [9.5 - 15.4]	12.9 [9.3 - 15.4]	12.5 [9.7 - 15.6]	
[a]Wilcoxon rank-sum test; [b]Fisher's test				

Declaration of Interest Statement

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr Neilan reported receipt of personal fees for consulting from Bristol Myers Squibb; receipt of personal fees from Genentech, GSK, Roche, Sanofi; and receipt of grants from Bristol Myers Squibb and AstraZeneca. Dr. Januzzi has served as a board member for Imbria Pharmaceuticals, has received grant support from Abbott, Applied Therapeutics, HeartFlow, Innolife, and Roche Diagnostics, has received consulting income from Abbott, Beckman, Bristol Myers Squibb, Boehringer Ingelheim, JanaCare, Janssen, Novartis, Pfizer, Merck, Roche Diagnostics, and