Supplemental Online Content

Neilan TG, Quinaglia T, Onoue T, et al. Atorvastatin for anthracycline-associated cardiac dysfunction. *JAMA.* Published August 8, 2023. doi:10.1001/jama.2023.11887

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eAppendix. Supplementary Methods

Study Design

This was a randomized double-blind, placebo-controlled clinical trial. Patients were treated with atorvastatin or placebo for 12 months.

Primary Objective

To determine whether atorvastatin resulted in a significant reduction in the proportion of patients with cardiac dysfunction over 12 months among patients with lymphoma treated with anthracyclines, defined as a reduction of ≥10 percentage points in LVEF to <55%.

Participant Selection

Inclusion criteria

- ≥ 18 years of age
- All patients with newly diagnosed lymphoma
- Scheduled to receive anthracycline-based chemotherapy

Exclusion criteria

- Statin use or statin use indicated based on guidelines. Statin use indicated based on the guidelines was defined as one of the following:
    - Patients with a prior atherosclerotic cardiovascular event.
    - No prior atherosclerotic cardiovascular event but with an LDL-C of ≥ 190 mg/dl
    - No prior atherosclerotic cardiovascular event, LDL-C 70-189 mg/dl, age 40-75 years and diabetes mellitus
    - No prior atherosclerotic cardiovascular event, age 40-75, no diabetes mellitus, and an 10 year predicted risk of ≥7.5%.
- Pregnancy or breastfeeding
- Unable to provide informed consent
- Unexplained persistent (>48h) elevation of transaminases (>3 times upper limits of normal)
- Concomitant use of oral cyclosporine
- Contraindication to a CMR (metallic object, severe claustrophobia, pacemaker, vascular clip)

Definition of Heart Failure[1]

- Incident heart failure at 24 months was an exploratory endpoint: An incident heart failure event will be defined as an event that meets criteria for (1) symptoms, (2) evidence, **and** (3) treatment in a participant **without** a history of acute decompensated heart failure in the 30-day period prior to randomization.

- Symptom criteria for incident heart failure:

  The participant exhibits documented new or worsening symptoms due to HF on presentation, including *at least one* of the following:

  i. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)

  ii. Decreased exercise tolerance

  iii. Fatigue

  iv. Other symptoms of worsened end-organ perfusion or volume overload (as determined by the medical judgement of the investigator)

- Evidence criteria for incident heart failure:

  The participant has objective evidence of new or worsening heart failure, consisting of *at least two* physical examination findings or one physical examination finding and *at least one* laboratory or imaging criterion.

- Physical examination criteria:

  i. Physical examination findings considered to be due to heart failure to include:

  ii. Peripheral edema

  iii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)

  iv. Pulmonary rales/crackles/crepitations

  v. Increased jugular venous pressure and/or hepatojugular reflux

  vi. S_3 gallop

  vii. Clinically significant or rapid weight gain thought to be related to fluid retention

- Laboratory or Radiology criteria:

  i. Increased B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (defined as BNP >500 pg/ml or NT-proBNP >2,000 pg/ml).

  ii. Radiological (CXR or CT) evidence of pulmonary congestion

  iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)) *Or:*

  iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m2))

- Treatment criteria for incident heart failure: The participant receives *at least one* of the following treatments specifically for heart failure:
    i. Initiation of intravenous diuretic (even a single dose) or vasoactive agent (e.g., inotrope, vasopressor, vasodilator)
    ii. Mechanical or surgical intervention, including:
        - Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
        - Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

Treatment Plan

Treatment regimen

Atorvastatin (or placebo) was given at a dose of 40 mg once a day. Treatment was administered on an outpatient basis.

Pre-Treatment Criteria

At baseline, a non-fasting lipid panel, measurements of CBC, potassium, renal function and AST and ALT were obtained. Beta-HCG testing was obtained in women between 18 and 55 years of age.

On study Laboratory Values

Visits at one, three, six month and 12 months included measurement of a basic metabolic profile, a blood count, and AST and ALT. At three months, a non-fasting lipid profile was added.

Agent Administration

The drug was taken by mouth, once a day for the entire study. The research pharmacy at each site supplied atorvastatin or placebo to participants via direct home delivery. Participants were contacted within 24 hours of drug shipment and instructed to take the study drug starting the night before the first cycle of chemotherapy and continue study drug for 12 months. If the period between randomization and the first cycle of chemotherapy was too short, then the participants were handed their study drug at their study visit. Atorvastatin and placebo were prepared and packaged identically to maintain blinding.

Criteria for Taking a Participant off Protocol Therapy

Duration of therapy was 12 months. In the absence of treatment delays due to adverse event(s), treatment was continued for 12 months or until one of the following criteria applied:

- Intercurrent illness that prevented further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrated an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decided to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Adverse Events of Interest

Risks of statin therapy: Particpants were randomized to either placebo or atorvastatin as part of the proposed protocol. The reported risks of atorvastatin therapy include statin myopathy, rhabdomyolyis, renal failure as a result of rhabdomyolysis, and hepatotoxicity.

Muscle toxicity: In statin clinical trials, the reported incidence of myopathy is low (0.1%) and data from a large meta-analysis (with 246,955 patients) of patients taking statins has been reported the incidence of myopathy to be similar to control. Another compilation of randomized controlled statin trials revealed that among 83,858 patients randomly assigned to receive either statin treatment or placebo, there were 49 cases of myositis and 7 cases of rhabdomyolyis in the statin groups, compared with 44 cases of myositis and 5 cases of rhabdomyolyis in the placebo groups. The risk of skeletal muscle effects such as myopathy and rhabdomyolyis increases in a dose-dependent manner with advanced age (≥65 years old) and renal impairment.

Hepatotoxicity: Based on guidelines, a modest elevation in transaminases to less than 3 times the upper limits of normal was not be considered a contra-indication to inclusion in the study. The incidence of elevated liver biochemical tests is increased to 1% of patients on statins. The majority of liver abnormalities occur within the first 3 months of therapy. Fulminant hepatic failure from statin therapy, without the presence of rhabdomyolyis and renal failure, is rare.

Dosing delays and modifications.

Treatment was temporarily suspended if the liver function tests (LFTs) elevated by more than 3 times normal. The LFTs were rechecked within 1 week and treatment was reinstated provided the LFTs returned to normal. LFTs were remeasured after treatment reinstatement and treatment was indefinitely suspended if another elevation was noted. The patients with side effects were not excluded from the protocol. If the participant developed myalgia, the study drug was temporarily withheld (1 week) and a creatinine kinase (CK) was measured. If the CK was normal, then the study drug was reintroduced, and discontinued if myalgia persisted.

Study drug adherence

To determine adherence with the study drug, a medication diary and instructions for its use were provided to participants and a monthly pill count was performed and recorded by study staff. Adherence was defined as greater than 75% compliance confirmed using both methods. In situations where the data from the pill count and the medication diary were not consistent, the participant was contacted to resolve.

Duration of Follow Up

The primary study endpoint was the proportion of participants with a reduction in the LVEF at 12 months. An exploratory outcome was the rates of incident heart failure at 24 months. At the time of this analyses, 24 month follow-up was not available among all participants. Participants removed from protocol therapy for unacceptable adverse event(s) were followed until resolution or stabilization of the adverse event.

Imaging Protocols
Image Analysis: End point assessments were blinded to treatment assignment and the timing of the study. MRI measures of the LVEF were performed on anonymized images in a core laboratory at CIRC. Echocardiographic measures of LVEF were performed on anonymized two-dimensional images in a core laboratory at the University of Pennsylvania.

MRI Protocol: Cardiac MRI imaging was performed with a standard set of acquisition parameters using a standardized protocol using scanners from Siemens (Erlangen, Germany). Short axis cine images covering the entire ventricles were obtained using steady-state free precession techniques with a standard 256 x 128 matrix, a 40-cm field of view, a 10-ms repetition time, a 4-ms echo time, a 20-degree flip angle, an 8-mm thick slice with a 2-mm gap, and a 40-ms temporal resolution. The LV measures were obtained from the cine images using standard MRI post-processing software (Medis Suite 3.2, Medis, Leiden, the Netherlands).[12]

Echocardiography Protocol: The echocardiograms were acquired on commercially available equipment (Philips, Andover MA, GE, Milwaukee, WI) using a standardized protocol. Apical four and two chamber views were used to trace the left ventricular endocardium. The LVEF was measured using a modified Simpson's method.

Data Safety Monitoring
The DSMB (list of participants provided page 7) met once a year to review data safety. In parallel, the Dana Farber/Harvard Cancer Center (DF/HCC) Data and Safety Monitoring Committee (DSMC) reviewed and monitored toxicity and accrual data from this study. The committee was composed of clinical specialists with experience in oncology and who have no direct relationship with the study.

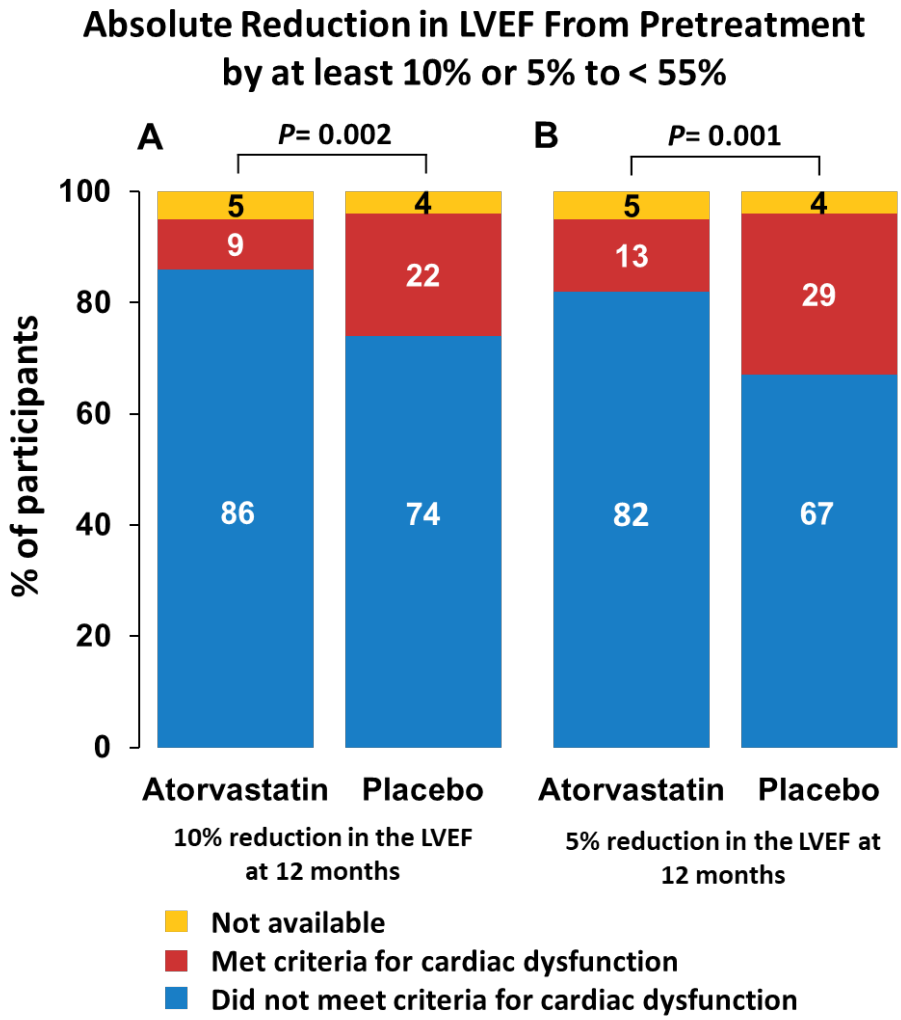
Randomization Process
Within the Dana-Farber/Harvard Cancer Center, randomized comparative studies are conducted in a manner such that for a blinded randomization, the individual assigning study treatment is not a member of the study team but is from the office for the Office of Data Quality (ODQ). Central randomization with a permuted blocks algorithm, with block size of 4, was performed according to an algorithm provided by the statistician. Randomized treatment assignment was delivered to the research pharmacy at the site in an unblinded fashion, and pharmacy dispensed blinded study drug. The study team were blinded to study group assignment.

Pharmacy
The research pharmacy at each site supplied atorvastatin or placebo to participants via direct home delivery. Participants were contacted within 24 hours of drug shipment and instructed to take the study drug starting the night before the first cycle of chemotherapy and continue study drug for 12 months. If the period between randomization and the first cycle of chemotherapy was too short, then the participants were handed their study drug at their study visit. Atorvastatin and placebo were prepared and packaged identically to maintain blinding.
Sample Size Considerations

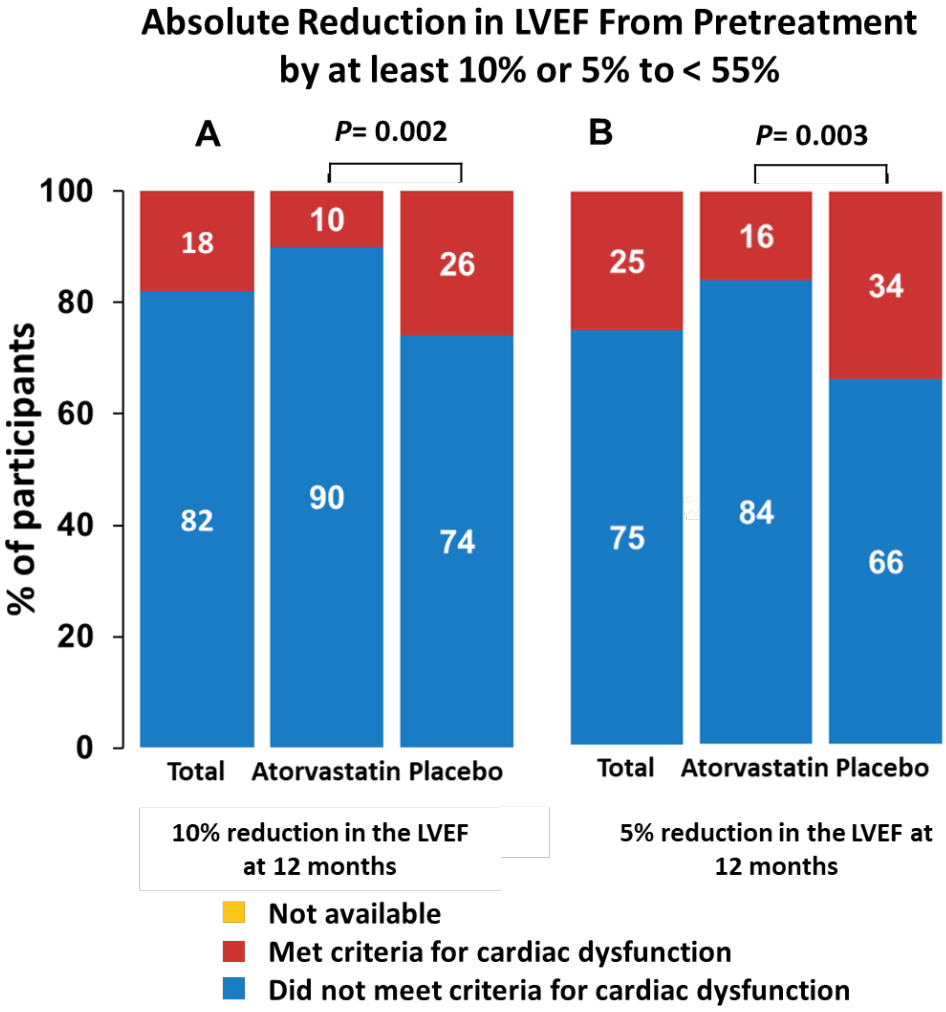
Assumptions: The Study anticipated that 20% of the patients in the placebo group would achieve the primary end-point. This assumption was based on prior literature; specifically, Limat *et al.* performed a prospective study where they enrolled patients similar to those proposed in this study (lymphoma receiving anthracycline-based chemotherapy) and performed a baseline measurement of LVEF and a measurement at 1 year.[2] Their primary end-point was a more stringent cut-off than recommended by guidelines or being used in this study, a decrease of >15% in LVEF. They found that 20% of their population had a reduction of >15% in LVEF. Using CMR, two studies have tested the percentage of patients with a significant reduction in LVEF after anthracyclines. In a prospective observational study, Drafts and colleagues found that 26% of patients decreased their LVEF to <50%,[3] and in a prospective randomized study, Bosch and colleagues found that up to 33% of patients decreased their LVEF to <55%.[4] This study assumed that 5% of patients treated with atorvastatin would reach the primary endpoint. In the single small, randomized study which also used 40 mg of atorvastatin with 20 subjects in each arm, there was no decrease in LVEF after anthracyclines among patients on statins.

The base case assumptions were as follows: 20% of the placebo group and 5% of the statin treatment group would meet the primary endpoint and the study would enroll 300 patients meeting all inclusion and exclusion criteria. From these, the study anticipated a drop-out rate of approximately 10% due to a one-year mortality of ≈5-6% and atorvastatin related side-effects in 4-5% of patients. The remaining 270 patients would provide us with a >90% power to detect a 15% difference in the proportions of those achieving the primary end-point at a one-sided significance level of 0.05. The study would have a 70% power if the difference in the percentage reaching the primary end-point between groups falled as low as 10%.

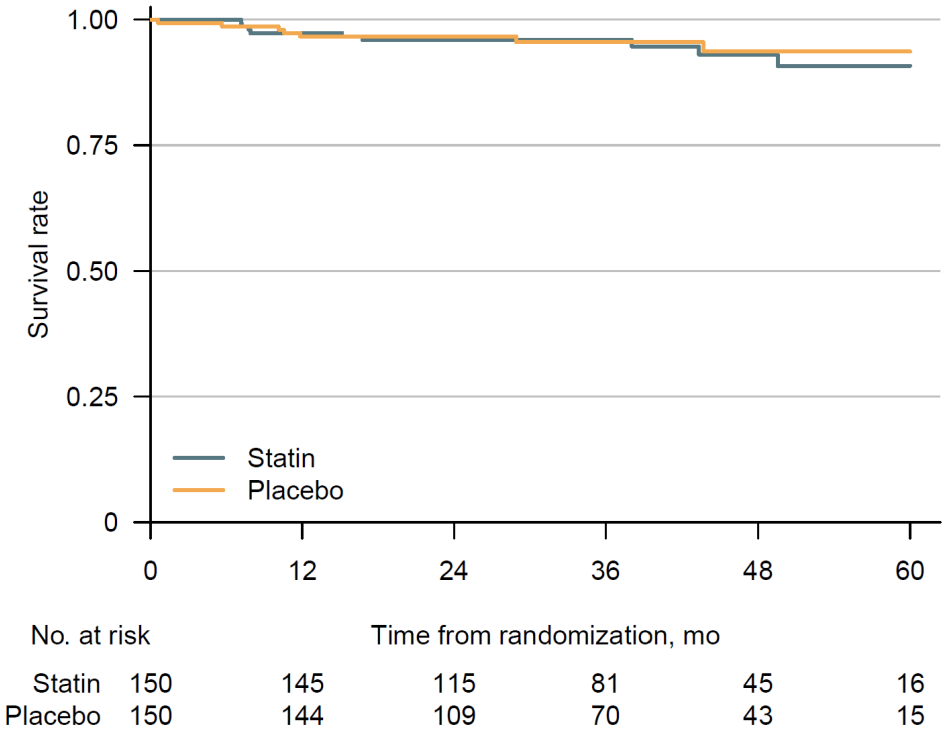
eFigure 1. Effect of Atorvastatin or Placebo on the Cardiac Dysfunction After Anthracyclines. The figure shows the rate of the primary (A) and secondary (B) endpoint in the two groups. Also shown are the percentage of patients, in each group, who did not have 12-month follow-up, 5% of the atorvastatin group and 4% of the placebo group. The rate of the primary end point, a ≥ 10% reduction in the LVEF from pretreatment to less than 55%, was 9% in the atorvastatin group and 22% in the placebo group (A). The rate of the secondary end point, a ≥ 5% reduction in the LVEF from pretreatment to less than 55%, was 13% in the atorvastatin group and 29% in the placebo group (B).



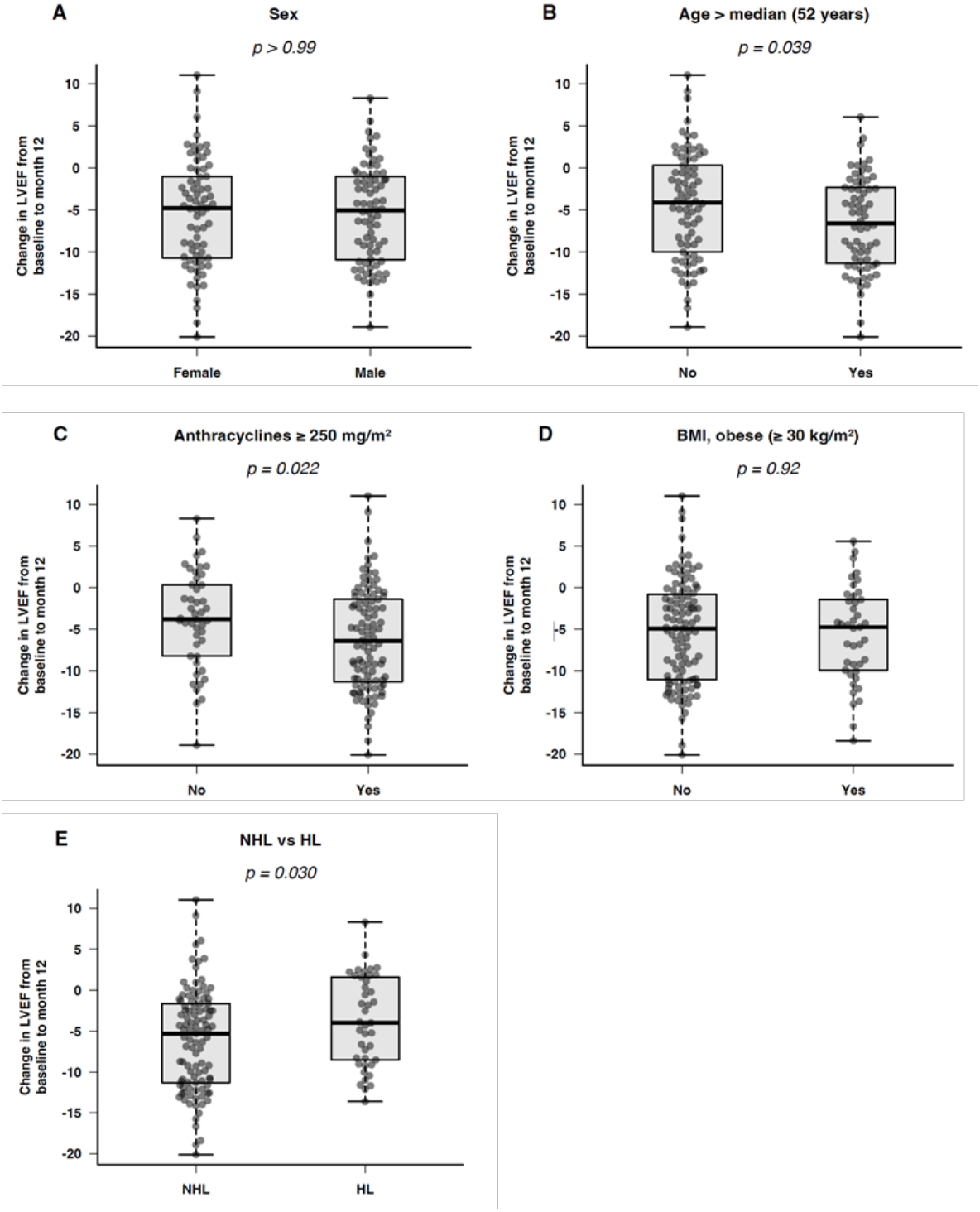
eFigure 2. Reduction in the LVEF Only Among Patients With a Cardiac MRI-Derived LVEF at 12 Months. The figure shows the rate of the primary (A) and secondary (B) endpoint among the combined cohort and by study group assignment. Overall, 77% of the the available follow-up was with a cardiac MRI. The rate of the primary end point, a ≥10% reduction in the LVEF from pretreatment to less than 55%, was 10% in the atorvastatin group and 26% in the placebo group (A). The rate of the secondary end point among those with MRI follow-up only, a ≥5% reduction in the LVEF from pretreatment to less than 55%, was 16% in the atorvastatin group and 34% in the placebo group (B).



eFigure 3. Kaplan-Meier Estimates of Overall Survival. The median follow-up for participants in the study was 37.5 months (39.8 months and 35.1 months, for statin and placebo, respectively). There were 17 deaths in the entire group over that follow-up period. There was no difference in overall survival between those randomized to placebo or atorvastatin (*P*= .67)



eFigure 4. Change in LVEF From Baseline to Follow-up Among Participants Who Were Treated With Placebo by Pre-specified Categories. There was a greater deline in the LVEF among participants who were older than the median age, who were treated with a higher anthracycline dose and those with non-Hodgkins lymphoma. A: Sex. B: Age > median. C: Cumulative anthracycline dose (doxorubicin equivalents) of >250 mg/m^2. D: BMI (≥30 kg/m^2). E: non-Hodgkin lymphoma (NHL) vs Hodgkin lymphoma (HL).



eTable 1. Cancer Treatment Regimens

		Treatment Arm	
Number (%)[a]			
	Total n=300	**Atorvastatin n=150**	**Placebo n=150**
ABVD	74 (25)	34 (23)	40 (27)
CHOP	8 (3)	4 (3)	4 (3)
CHOP-R	162 (54)	76 (51)	86 (57)
EPOCH	8 (3)	7 (5)	1 (1)
EPOCH-R	18 (6)	12 (8)	6 (4)
EPOCH-R DA	10 (3)	6 (4)	4 (3)
Other	20 (7)	11 (7)	9 (6)

[a] *participants may have started one regime and then transitioned to another and thus could have been listed as having received more than one cancer treatment regimen. ABVD = Adriamycin-Bleomycin-Vinblastine-Dacarbazine regimen, CHOP = Cyclophosphamide-hydroxydaunorubicin-Oncovin-Prednisone regimen, CHOP-R = Cyclophosphamide- hydroxydaunorubicin-Oncovin-Prednisone-Rituximab regime, EPOCH = Etoposide-Prednisone-Oncovin-Cyclophosphamide-Hydroxydaunorubicin regimen, EPOCH-R = Etoposide-Prednisone-Oncovin-Cyclophosphamide-Hydroxydaunorubicin-Rituximab regimen, EPOCH-R DA = Etoposide-Prednisone-Oncovin-Cyclophosphamide-Hydroxydaunorubicin-Rituximab regimen (Dose Adjusted)*

eTable 2. Patient Demographics, Cancer Characteristics, Drug Exposure, Cancer Treatments by Group and by Study Drug Adherence

	No		Yes	
Characteristics	**Atorvastatin (n=12)**	**Placebo (n=15)**	**Atorvastatin (n=138)**	**Placebo (n=135)**
Compliance				
▪ **No**	12	15	-	-
▪ **Yes**	-	-	138	135
Age — years				
▪ **Mean (SD)**	49 (16)	51 (20)	50 (17)	49 (16)
▪ **Median (minimum, maximum)**	52 (23 - 71)	51 (24 - 78)	51 (20 - 91)	52 (20 - 83)
Sex — no. of patients (%)				
▪ **Female**	5 (42)	8 (53)	63 (46)	66 (49)
▪ **Males**	7 (58)	7 (47)	75 (54)	69 (51)
Race — no. of patients (%)				
▪ **Asian**	-	-	4 (3)	7 (5)
▪ **Black**	-	2 (13)	5 (4)	2 (1)
▪ **White**	11 (92)	13 (87)	124 (90)	118 (87)
▪ **Unknown**	1 (8)	-	5 (4)	8 (6)
Ethnicity — no. of patients (%)				
▪ **Hispanic/Latino**	2 (17)	1 (7)	9 (7)	7 (5)
▪ **Non-Hispanic/Latino**	10 (83)	14 (93)	125 (91)	122 (90)
▪ **Unknown**	-	-	4 (3)	6 (4)
Body-mass index				
▪ **Mean (SD)**	31 (6)	28 (8)	28 (6)	28 (6)
▪ **Median (minimum, maximum)**	30 (21 - 42)	26 (18 - 50)	27 (14 - 52)	27 (17 - 45)
Body mass index, (kg/m^2) WHO criteria				
▪ **Underweight, < 18.5**	-	1 (7)	2 (1)	5 (4)
▪ **Normal weight, ≥ 18.5**	1 (8)	5 (33)	47 (34)	46 (34)
▪ **Overweight, ≥ 25**	5 (42)	3 (20)	51 (37)	48 (36)
▪ **Obese, ≥ 30**	3 (25)	5 (33)	22 (16)	22 (16)
▪ **Severely Obese, ≥ 35**	3 (25)	1 (7)	16 (12)	14 (10)
Type of lymphoma — no. of patients (%)				
▪ **T-cell**	-	1 (7)	9 (7)	4 (3)
▪ **B-cell**	10 (83)	8 (53)	94 (68)	94 (70)
▪ **Hodgkin**	2 (17)	6 (40)	35 (25)	37 (27)
ECOG Performance Status Scale				
▪ **Grade 0**	10 (83)	6 (40)	102 (74)	98 (73)
▪ **Grade 1**	2 (17)	7 (47)	27 (20)	29 (21)
▪ **Grade 2**	-	-	4 (3)	7 (5)
▪ **Grade 3**	-	-	1 (1)	1 (1)
▪ **Unknown**	-	2 (13)	4 (3)	-

ECOG = Eastern Cooperative Oncology Group

Characteristics	No		Yes	
	Atorvastatin (n=12)	Placebo (n=15)	Atorvastatin (n=138)	Placebo (n=135)
Cardiac medications — no. of patients (%)				
▪ **ARB, or ACE inhibitor**	1 (8)	3 (20)	6 (4)	7 (5)
▪ **Beta-blocker**	-	1 (7)	7 (5)	2 (1)
▪ **Aspirin**	1 (8)	1 (7)	9 (7)	5 (4)
▪ **Calcium channel blocker**	-	-	4 (3)	4 (3)
▪ **Other (e.g., diuretic, aldosterone antagonist)**	-	2 (13)	3 (2)	1 (1)
Cardiac Risk Factors — no. of patients (%)				
▪ **Hypertension**	-	3 (20)	14 (10)	17 (13)
▪ **Smoking history**	4 (33)	5 (33)	25 (18)	27 (20)
○ **Current**	-	2 (13)	6 (4)	6 (4)
▪ **Sleep apnea**	1 (8)	-	3 (2)	7 (5)
Cumulative anthracycline dose (mg/m^{2,} doxorubicin equivalents)				
▪ **Mean (SD)**	246 (69)	234 (81)	270 (56)	262 (59)
▪ **Median (minimum, maximum)**	284 (102 - 304)	295 (50 - 303)	300 (100 - 308)	300 (99 - 312)
Radiation treatment[a] — no. of patients (%)				
▪ **No**	12 (100)	13 (87)	126 (91)	116 (86)
▪ **Yes**	-	2 (13)	12 (9)	19 (14)

ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, [a] 4 participants had radiation treatment that involved the cardiac silhouette.

eTable 3. Participants With Cardiac MRI at Pretreatment and Follow-up

eTable S3. Participants with cardiac MRI at pretreatment and follow-up.			
	Treatment Arm		
Number (%)			
Total	Atorvastatin	Placebo	*P* Value
Baseline			
237 (79)	117 (78)	120 (80)	0.78
Follow-up[a]			
219 (77)	112 (79)	107 (74)	0.27

[a] *Proportion of the 286 participants with 12-month follow-up*

eTable 4. Participant Demographics, Cancer Characteristics, Drug Exposure, Radiation, and LVEF Change by Primary Outcome

	Primary outcome	
Characteristics	No	Yes
	n = 240 (80)	n = 46 (15)
Age at randomization, years		
• **Mean (SD)**	49 (17)	52 (15)
Sex		
• **Female**	115 (48)	19 (41)
• **Male**	125 (52)	27 (59)
Race		
• **White**	215 (90)	40 (87)
• **Asian**	7 (3)	4 (9)
• **Black**	5 (2)	1 (2)
• **Unknown**	13 (5)	1 (2)
Ethnicity		
• **Hispanic/Latino**	13 (5)	4 (9)
Body mass index, kg/m2		
• **Mean (SD)**	27.81 (6.23)	26.96 (5.29)
Body mass index, WHO criteria		
• **Underweight, < 18.5**	7 (3)	1 (2)
• **Normal weight, ≥ 18.5**	81 (34)	14 (30)
• **Overweight, ≥ 25**	79 (33)	23 (50)
• **Obese, ≥ 30**	43 (18)	5 (11)
• **Severely Obese, ≥ 35**	30 (12)	3 (7)
Type of lymphoma		
• **B cell Lymphoma**	157 (65)	38 (83)
• **Hodgkins Lymphoma**	73 (30)	5 (11)
• **T cell Lymphoma**	10 (4)	3 (7)
ECOG Performance Status Scale		
• **Grade 0**	178 (74)	31 (67)
• **Grade 1**	48 (20)	13 (28)
• **Grade 2**	9 (4)	2 (4)
• **Grade 3**	1 (0)	-
Cardiac medications		
ARB, or ACE inhibitor		
• **Yes**	13 (5)	2 (4)
Beta-blocker		

• **Yes**	8 (3)	1 (2)
Aspirin		
• **Yes**	14 (6)	2 (4)
Calcium channel blocker		
• **Yes**	4 (2)	3 (7)
Other (e.g., diuretic, aldosterone antagonist)		
• **Yes**	2 (1)	3 (7)
Cardiac Risk Factors		
Hypertension		
• **Yes**	25 (10)	6 (13)
Smoking history		
• **Yes**	53 (22)	5 (11)
Sleep apnea		
• **No**	234 (98)	41 (89)
• **Yes**	6 (2)	5 (11)
Cumulative anthracycline dose (mg/m2)		
• **Mean (SD)**	262 (61)	276 (47)
Radiation treatment		
• **Yes**	29 (12)	4 (9)
Compliance		
• **No**	15 (6)	5 (11)
LVEF change from baseline to 12 months.		
• **Mean (SD)**	-3.0 (4.7)	-14.0 (3.9)

eTable 5. Participant Non-imaging Measures and Laboratory Values Across Study Visits

	Means (95% CI)							
	Pretreatment Visit		3 months after treatment initiation		6 months after treatment initiation		12 months after treatment initiation	
Measure and Value	**Statin**	**Placebo**	**Statin**	**Placebo**	**Statin**	**Placebo**	**Statin**	**Placebo**
▪ Resting heart rate (bpm)	80.2 (56.7 - 111.6)	80.8 (58.0 - 116.1)	82.7 (56.0 - 117.3)	81.2 (59.7 - 114.3)	81.0 (63.0 - 116.6)	82.4 (60.2 - 109.8)	76.0 (55.0 - 100.0)	76.7 (54.6 - 110.4)
Missing (n %)	-	-	-	1 (1)	13 (9)	19 (13)	8 (5)	6 (4)
▪ Systolic blood pressure (mmHg)	127.0 (96.6 - 163.3)	124.5 (99.0 - 157.3)	121.5 (98.0 - 151.3)	122.3 (99.0 - 152.0)	121.4 (95.4 - 147.0)	123.6 (98.5 - 151.8)	123.6 (101.6 - 155.4)	123.5 (102.3 - 151.3)
Missing (n %)	-	-	-	2 (1)	13 (9)	19 (13)	8 (5)	6 (4)
▪ Diastolic blood pressure (mmHg)	74.9 (55.7 - 100.3)	74.0 (54.7 - 93.0)	71.3 (56.0 - 89.3)	72.1 (55.7 - 90.3)	71.4 (55.4 - 87.0)	73.1 (55.2 - 90.2)	74.3 (58.0 - 93.4)	74.2 (58.6 - 95.0)
Missing (n %)	-	-	-	2 (1)	13 (9)	19 (13)	8 (5)	6 (4)
▪ Weight (pounds)	179.7 (103.5 - 268.9)	178.0 (109.9 - 276.1)	179.8 (106.7 - 281.3)	177.5 (112.6 - 279.4)	179.2 (100.0 - 282.2)	179.2 (113.2 - 281.8)	179.8 (106.0 - 269.4)	183.2 (115.6 - 294.3)
Missing (n %)	-	-	-	1 (1)	13 (9)	19 (13)	8 (5)	6 (4)
Laboratory Values								
▪ Alanine aminotransferase (IU/l)	21.9 (6.7 - 64.1)	22.9 (6.0 - 80.8)	30.6 (10.0 - 78.4)	28.3 (8.7 - 72.3)	27.0 (10.0 - 64.2)	24.0 (9.0 - 73.5)	23.7 (10.6 - 50.0)	23.9 (8.0 - 60.4)
Missing (n %)	-	-	1 (1)	3 (2)	14 (9)	20 (13)	8 (5)	6 (4)
▪ Aspartate aminotransferase (IU/l)	22.9 (9.0 - 60.6)	22.6 (10.7 - 55.9)	26.1 (11.7 - 77.4)	23.8 (11.0 - 55.3)	26.8 (13.4 - 57.8)	25.0 (12.0 - 50.5)	23.4 (13.0 - 41.8)	23.2 (11.0 - 44.7)
Missing (n %)	-	-	1 (1)	3 (2)	14 (9)	20 (13)	8 (5)	6 (4)
▪ Cholesterol[a] (mg/dl)	175.7 (100.7 - 257.8)	177.3 (102.0 - 261.3)	138.4 (82.9 - 258.4)	188.4 (134.0 - 246.0)	165.6 (112.0 - 242.2)	190.2 (153.2 - 238.9)	169.5 (92.9 - 262.2)	192.8 (135.9 - 263.0)
Missing (n %)	-	-	4 (3)	6 (4)				
▪ Triglycerides[a] (mg/dl)	124.9 (43.9 - 349.5)	131.8 (41.8 - 319.0)	137.5 (49.2 - 415.2)	160.4 (54.3 - 324.6)	96.3 (51.8 - 141.7)	131.8 (51.3 - 219.8)	138.3 (47.0 - 336.6)	140.4 (47.0 - 329.0)
Missing (n %)	-	-	4 (3)	6 (4)				

eTable 5. Continued

Measure and Value	Pretreatment Visit		3 months after treatment initiation		6 months after treatment initiation		12 months after treatment initiation	
	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo
▪ Low-density lipoprotein * (mg/dl)	103.9 (51.4 - 173.6)	103.6 (40.5 - 169.4)	66.1 (21.6 - 165.0)	110.0 (58.0 - 171.0)	85.0 (35.6 - 162.0)	100.0 (42.1 - 137.7)	86.3 (33.3 - 169.2)	108.6 (62.7 - 164.1)
Missing (n %)	-	-	4 (3)	6 (4)				
▪ High-density lipoprotein * (mg/dl)	48.0 (15.2 - 79.7)	49.0 (12.0 - 81.1)	46.9 (25.4 - 76.2)	47.1 (30.0 - 73.9)	61.2 (37.5 - 86.2)	58.0 (47.5 - 74.3)	57.4 (27.0 - 94.5)	57.3 (31.0 - 99.1)
Missing (n %)	-	-	4 (3)	6 (4)				
▪ Sodium (mmol/liter)	139.1 (133.7 - 143.3)	139.2 (131.7 - 145.0)	140.1 (135.0 - 144.4)	139.8 (134.0 - 145.0)	139.8 (133.4 - 145.0)	140.1 (133.2 - 145.0)	140.0 (132.2 - 146.4)	140.1 (134.0 - 146.9)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)
▪ Potassium (mmol/liter)	4.1 (3.5 - 4.8)	4.2 (3.5 - 4.8)	4.0 (3.4 - 4.5)	4.1 (3.4 - 4.9)	4.1 (3.3 - 5.0)	4.2 (3.3 - 5.1)	4.2 (3.3 - 5.0)	4.2 (3.3 - 4.9)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)
▪ Urea nitrogen (mg/dl)	15.6 (8.0 - 29.3)	16.7 (7.0 - 51.4)	14.3 (6.6 - 24.0)	14.8 (6.0 - 26.0)	15.2 (6.0 - 26.2)	15.9 (7.2 - 27.0)	16.2 (7.6 - 27.0)	15.6 (7.4 - 25.6)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)
▪ Creatinine (mg/dl)	0.9 (0.5 - 1.3)	0.9 (0.6 - 1.4)	0.8 (0.5 - 1.2)	0.8 (0.5 - 1.4)	0.9 (0.6 - 1.3)	0.9 (0.5 - 1.3)	0.9 (0.6 - 1.3)	0.9 (0.6 - 1.3)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)
▪ Glucose (mg/dl)	104.0 (76.7 - 165.0)	101.1 (74.0 - 164.3)	111.1 (75.0 - 211.9)	107.9 (71.5 - 195.5)	103.7 (71.1 - 147.5)	103.1 (78.0 - 154.5)	101.6 (77.2 - 154.0)	99.5 (76.7 - 136.9)
Missing (n %)	-	-	4 (3)	6 (4)	14 (9)	23 (15)	8 (5)	6 (4)
▪ White cell count (per µl)	7.5 (2.7 - 14.5)	7.4 (3.0 - 15.0)	5.8 (1.5 - 14.8)	5.5 (2.0 - 13.2)	5.6 (1.6 - 12.4)	6.1 (2.3 - 15.2)	6.0 (2.4 - 11.8)	6.1 (2.9 - 11.4)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)
▪ Hemoglobin (g/dl)	13.1 (9.4 - 16.0)	13.0 (8.9 - 16.0)	11.5 (7.6 - 14.4)	11.4 (8.3 - 14.2)	12.6 (9.5 - 15.3)	12.5 (8.7 - 15.3)	13.5 (11.0 - 16.1)	13.5 (10.1 - 15.8)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)
▪ Hematocrit (%)	39.2 (28.7 - 47.2)	38.7 (27.9 - 47.0)	34.1 (22.9 - 42.6)	33.9 (24.0 - 41.4)	37.7 (29.2 - 45.0)	37.3 (26.2 - 44.9)	39.9 (31.2 - 47.0)	40.2 (30.6 - 46.8)
Missing (n %)	**-**	**-**	**4 (3)**	**6 (4)**	**13 (9)**	**22 (15)**	**8 (5)**	**6 (4)**

eTable 5. Continued

	Pretreatment Visit		3 months after treatment initiation		6 months after treatment initiation		12 months after treatment initiation	
	Statin	**Placebo**	**Statin**	**Placebo**	**Statin**	**Placebo**	**Statin**	**Placebo**
Hemoglobin (g/dl)	13.1 (9.4 - 16.0)	13.0 (8.9 - 16.0)	11.5 (7.6 - 14.4)	11.4 (8.3 - 14.2)	12.6 (9.5 - 15.3)	12.5 (8.7 - 15.3)	13.5 (11.0 - 16.1)	13.5 (10.1 - 15.8)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)
Hematocrit (%)	39.2 (28.7 - 47.2)	38.7 (27.9 - 47.0)	34.1 (22.9 - 42.6)	33.9 (24.0 - 41.4)	37.7 (29.2 - 45.0)	37.3 (26.2 - 44.9)	39.9 (31.2 - 47.0)	40.2 (30.6 - 46.8)
Missing (n %)	**-**	**-**	**4 (3)**	**6 (4)**	**13 (9)**	**22 (15)**	**8 (5)**	**6 (4)**
▪ Platelet count (per µl)	269.8 (116.1 - 468.5)	266.9 (110.7 - 485.1)	242.4 (63.8 - 432.8)	270.8 (94.6 - 533.0)	218.2 (56.4 - 427.4)	216.0 (77.6 - 354.0)	216.7 (94.6 - 348.3)	219.3 (92.1 - 349.9)
Missing (n %)	-	-	4 (3)	6 (4)	13 (9)	22 (15)	8 (5)	6 (4)

[a] Lipid values were measured at pre-treatment and 3 months.

eTable 6. Participant Cardiac MRI Measures Across Study Visits

	Pretreatment visit				12 months after Treatment Initiation		
Mean (SD)							
		Treatment arm			Treatment arm		
Measure and Value	Combined	Atorvastatin	Placebo	*P* Value	Atorvastatin	Placebo	*P* Value
Left ventricle							
▪ **End-diastolic volume (ml)**	157 (40)	154 (36)	161 (43)	.36	163 (40)	163 (41)	>0.99
▪ **End-systolic volume (ml)**	61 (20)	59 (17.5)	62 (23)	.53	66 (22)	68 (22)	.31
▪ **Stroke volume (ml)**	97 (22)	95 (21)	99 (24)	.23	98 (21)	95 (24)	.46
▪ **Ejection fraction (%)**	63 (4.6)	62.9 (4.5)	62.5 (4.9)	.56	58.8 (5.9)	57.1(5.4)	.03
▪ **Cardiac output (L)**	7.0 (1.7)	6.9 (1.6)	7.1 (1.8)	.37	6.7 (1.7)	6.4 (1.7)	.38
▪ **Left ventricular mass (g)**	97 (24)	96 (24)	98 (24)	.37	97 (23)	97 (24)	.80
Right ventricle							
▪ **End-diastolic volume (ml)**	164 (43)	160 (42)	167 (44)	.34	163 (45)	165 (46)	.78
▪ **End-systolic volume (ml)**	72 (24)	70 (23)	73 (26)	.49	70 (28)	71 (27)	.75
▪ **Ejection fraction (%)**	59 (5.9)	57 (5.7)	57 (6.1)	.93	58 (7.5)	58 (7.1)	.76

eTable 7. Adverse Events of Special Interest Across Study Visits

eTable S7. Adverse events of interest occurring during study

		Treatment Arm		
	Total	**Statin**	**Placebo**	***P* value**
Muscle Pain				
	49 (16)	28 (19)	21 (14)	0.35
Elevated AST/ALT				
	51 (17)	27 (18)	24 (16)	0.76
Myositis				
No	-	-	-	> 0.99
Renal Failure				
No	6 (2)	2 (1)	4 (3)	0.68

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