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Statins and Left Ventricular Ejection Fraction Following Doxorubicin Treatment

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Abstract

BACKGROUND—Statins taken for cardiovascular indications by patients with breast cancer and lymphoma during doxorubicin treatment may attenuate left ventricular ejection fraction (LVEF) decline, but the effect of statins on LVEF among patients with no cardiovascular indications is unknown.

METHODS—A double-blind, placebo-controlled, 24-month randomized trial of 40 mg of atorvastatin per day administered to patients with breast cancer and lymphoma receiving doxorubicin was conducted within the National Cancer Institute Community Oncology Research Program across 31 sites in the United States. At pretreatment and then 6 and 24 months after initiating doxorubicin, we assessed left ventricular (LV) volumes, strain, mass, and LVEF through cardiac magnetic resonance imaging, along with cognitive function and serum markers of inflammation. The primary outcome was the difference in 24-month LVEF between placebo and treatment groups, adjusted for pretreatment LVEF.

RESULTS—A total of 279 participants were enrolled in the trial. Participants had a mean (±SD) age of 49±12 years; 92% were women; and 83% were White. The mean (±SD) LVEF values were 61.7±5.5% before treatment and 57.4±6.8% at 24 months in the placebo group and 62.6±6.4% before treatment and 57.7±5.6% at 24 months in the atorvastatin group. On the basis of a multiple imputed data set for missing data and adjusted for each individual's pretreatment LVEF, 24-month declines in LVEF averaged 3.3±0.6 percentage points and 3.2±0.7 percentage points, for those randomly assigned to placebo versus statins, respectively (P=0.93). Across both treatment arms, similar percentages of individuals experienced changes of more than 10 percentage points in LVEF, LV strain, LV mass, cognition, and inflammation biomarkers, including among those with greater than 90% drug compliance.

CONCLUSIONS—In patients with breast cancer and lymphoma with no existing indication for statin therapy, prospective statin administration did not affect LVEF declines 2 years after doxorubicin. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01988571.)

Introduction

Heart failure related to left ventricular (LV) dysfunction is associated with high morbidity and mortality for individuals receiving doxorubicin-based chemotherapy for breast cancer or lymphoma.[1–3] Additional data suggest that patients receiving 3-hydroxy-3-methylglutarylcoenzyme-A reductase inhibitors, or statins, for primary or secondary prevention of cardiovascular events exhibit higher left ventricular ejection fraction (LVEF) measures several years after doxorubicin as opposed to those not receiving statins.[4,5] However, it is unknown whether the prospective administration of statins to individuals without a cardiovascular indication would attenuate declines in LVEF during or 2 years after completion of doxorubicin treatment for breast cancer or lymphoma.

Accordingly, we conducted a multicenter, double-blind, randomized, placebo-controlled trial of 40 mg of atorvastatin per day administered to patients receiving doxorubicin for breast cancer or lymphoma, and we assessed pretreatment and 24 months posttreatment measures of LVEF.

Methods

TRIAL POPULATION AND DESIGN

This trial was implemented through the Wake Forest National Cancer Institute Community Oncology Research Program (NCORP) Research Base and was approved by the National Cancer Institute Division of Cancer Prevention and Control; the National Heart, Lung, and Blood Institute; and the institutional review board of the Wake Forest School of Medicine. All participants provided witnessed and written informed consent. The trial (WF-98213) was registered with ClinicalTrials.gov (NCT01988571). Additional information is available in the Supplementary Appendix and Protocol provided with the full text of this article at evidence.nejm.org.

Participants were enrolled across 31 community and academic cancer centers participating in the Wake Forest NCORP Research Base, Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN), and Alliance for Clinical Trials networks and included patients 21 years of age or older scheduled to receive doxorubicin for treatment of stage I to III breast cancer or stage I to IV lymphoma with an expected survival of more than 2 years. Exclusions for participation included an indication to receive a statin for primary or secondary prevention of cardiovascular disease (e.g., diabetes, hyperlipidemia, an American College of Cardiology/American Heart Association 10-year cardiovascular event risk >7.5%),[6] concurrent use of a CYP3A4 inhibitor, a clinical precancer treatment measurement of LVEF below 55%, pregnancy or breastfeeding, a contraindication to receipt of a statin, or an inability to undergo a cardiovascular magnetic resonance (CMR) imaging examination (e.g., severe claustrophobia or intraorbital ferrous metal). Consenting individuals were randomly assigned in a 1:1 double-blind fashion to receive a daily dose of 40 mg of atorvastatin (manufactured by Greenstone, Inc., and distributed by Biologics, Inc.) or placebo for at least 24 to 27 months. Participants were stratified on the basis of cancer type (breast cancer or lymphoma), age (older than or younger than 52 years), and total planned doxorubicin equivalent dosing (≥225 or ≤225 mg/m^2) and were instructed to begin the drug 48 hours before receipt of their first dose of doxorubicin. To determine patients' adherence with the agent, a medication diary and instructions for its use were provided to participants by staff, and returned bottle pill counts were performed at 6 and 24 months.

Demographic data, including height and weight, were collected, and each participant was scheduled for trial visits before receipt of doxorubicin (pretreatment visit) and then 6, 12, 18, and 24 months after random assignment (Fig. 1). At the pretreatment, 6-month, and 24-month visits, the following were assessed: participant cardiac morphometric and hemodynamic data to include LV volumes, strain, ejection fraction, and mass by CMR[7]; neurocognitive function[8]; serum measures of lipoproteins, glucose, liver function, creatine kinase, systemic inflammation, and evaluation of the renin-aldosterone axis; and review of participant diaries related to trial drug compliance. Cancer treatment data, including the cumulative doses of treatment agents, cardioactive medication, and type/stage of cancer, were also recorded at each visit.

CMR AND COGNITION

Participants underwent CMR imaging with a standard set of acquisition parameters across a range of 1.5- and 3.0-Tesla scanners from General Electric (Milwaukee), Philips (Amsterdam), and Siemens (Erlangen, Germany). Circumferential strain and other LV measures were obtained through previously published methods using cine white blood steady-state free precession techniques with a 256×128 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.[9,10] All images were analyzed by readers blinded to all identifiers in an unpaired blinded read. Heart rate (in beats per minute) and systolic and diastolic blood pressure (in millimeters of mercury) were also measured during CMR imaging.

Because of a previous warning issued by the Food and Drug Administration indicating that statin administration could potentially be associated with memory decline, we included a cognitive assessment as part of our secondary analyses. At pretreatment, 6 months, and 24 months, cognition was assessed through the Hopkins Verbal Learning Test–Revised (HVLT-R), a neuropsychological test that measures verbal learning and memory.[8] Scores from HVLT-R range from 0 to 36, with a score of 36 reflecting 100% recollection of tested words and a score difference of 0.5 or higher indicating a clinically significant change.[8]

OUTCOMES

The primary outcome was the difference in 24-month LVEF between placebo and treatment groups, adjusted for pretreatment LVEF. Secondary outcomes included 24-month left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LV global circumferential strain (GCS), adjusted for pretreatment values.

STATISTICAL ANALYSIS

Because of the previously documented reproducibility of CMR measures among patients treated for cancer, CMR imaging was chosen to assess LVEDV, LVESV, GCS, and LVEF.[9,10] This trial was designed to have 80% power to detect a 2.8-percentage-point LVEF difference between groups after adjusting for pretreatment LVEF. This threshold was chosen because a less than 3-percentage-point decrease in LVEF (e.g., from 60 to 57%) would have little clinical relevance.[11] Counts and percentages are reported for all categorical variables, and means (±SDs) are reported for all continuous variables. The primary assessment of LVEF was performed with a pretreatment-adjusted linear model (i.e., analysis of covariance [ANCOVA]). The 24-month LVEF was modeled as the primary outcome with treatment group included as the main effect of interest, adjusted for pretreatment LVEF. We followed an identical modeling framework for all secondary continuous outcomes recorded over time. A significant treatment effect with respect to 24-month outcome was based on a P value less than 0.05 for the main treatment effect. In addition, we fit a longitudinal linear mixed model to assess the change in LVEF over time, and we specifically compared the change in LVEF from 0 to 6 months with the overall change to 24 months and with the change from 6 to 24 months.

In a secondary analysis of LVEF, we created binary endpoint variables based on whether a patient had a less than 5-percentage-point decline in LVEF, a greater than 10-percentage-point decline in LVEF, and a composite outcome based on whether a patient had a greater than 10-percentage-point decline to an absolute LVEF value of less than 50%. We analyzed each of the binary end points through robust Poisson regression (using SEs), allowing us to interpret results in terms of risk ratios,[12] with pretreatment LVEF included as a confounding variable and treatment group included as a main effect. Results for these secondary analyses were interpreted in terms of risk ratios.

We assumed missing data to be missing at random and used multiple imputation by chained equations to impute missing data.[13] Our primary analysis was performed using multiple imputed data with results presented from the pooled estimates. As a sensitivity analysis, we first performed our primary analysis (ANCOVA) using complete case data. In addition, we modeled our complete case data using a linear mixed model with LVEF as a continuous outcome, with treatment group and visit included as fixed effects and random intercepts by patient. Under this modeling framework, a significant treatment-by-visit interaction would indicate a significant treatment effect. All statistical analyses were performed in R statistical software version 4.10.[14]

Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals (CIs). The widths of the CIs were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

Results

We recruited and randomly assigned 279 patients to the placebo (n=140) or the atorvastatin (n=139) arm of this trial. At 6 and 24 months, 248 (126 placebo vs. 122 statin) and 205 (105 placebo vs. 100 statin) patients, respectively, underwent testing (Fig. 1). At pretreatment, 6 months, and 24 months, 209, 207, and 176 measurements of our primary outcome (LVEF) were obtained, resulting in 70 patients (25.1%), 72 patients (25.8%), and 103 patients (35.8%) with missing data, respectively. Demographic data for the patients in this trial are presented in Table 1. The mean (±SD) patient age in the statin and placebo groups was 48.5±12.5 and 49.4±11.5 years, respectively. Mean body-mass index (BMI) was slightly higher in the placebo group (31.0±7.4) than in the statin group (29.0±6.4). The majority of patients (238 [85.3%]) had received a diagnosis of breast cancer, with the remaining patients having lymphoma (Table S1 in the Supplementary Appendix); 256 patients (91.8%) were female (Table 1). Overall, the demographics of this trial demonstrate a representative population of those receiving doxorubicin for breast cancer or lymphoma (Table S2). Reasons for participant discontinuation of the trial in the placebo and statin arms can be found in Table S3. Data from both arms reported the same top three discontinuation reasons: withdrawal of consent, inability to comply with the daily receipt of the trial drug, and a feeling of being overwhelmed.

Of those enrolled, 42.7% of patients came from academic centers and 57.3% came from community hospitals. Prospective data on participants' resting heart rate, systolic and diastolic systemic arterial pressure, LVEDV, LVESV, LV stroke volume, LV mass, and serum chemistry are reported across all three visits in Table 2.

The primary finding in this trial showed similar mean 24-month LVEF for the placebo and statin arms. After multiple imputation for missing data and adjusting for pretreatment LVEF, patients taking either placebo or atorvastatin had a mean 24-month LVEF of 58.2±0.7% and 58.2±0.6%, respectively. The estimated mean difference in 24-month LVEF between the placebo and atorvastatin groups was −0.08 percentage points (95% CI, −1.83 to 1.67; P=0.93). Secondary analyses did not show differences in LVEDV indexed for body surface area or (i) (95% CI for difference between treatment groups at 24 months, −2.7 to 2.8 ml/m^2) and LVESV (95% CI, −1.9 to 2.0 ml/m^2), both indexed for body surface area, or circumferential strain (95% CI, −1.3 to 2.0 σ) (Fig. S1) between groups.

On the basis of a multiple imputed data set for missing data and adjusted for each individual's pretreatment LVEF, 24-month declines in LVEF averaged 3.3±0.6 percentage points and 3.2±0.7 percentage points, respectively, for those randomly assigned to placebo versus statins (P=0.93). In both treatment groups, we observed similar decreases in LVEF from pretreatment to 6 months after initiating doxorubicin as estimated from a linear mixed model of the imputed data, with an estimated change in LVEF from pretreatment to 6 months of −4.0 percentage points (95% CI, −5.46 to −2.52) in the statin group and −3.1 percentage points (95% CI, −4.59 to −1.65) in the placebo group (Fig. 2). Between 6 and 24 months, we observed changes of 0.40 percentage points (95% CI, −1.12 to 1.93) in the treatment group and 0.17 percentage points (95% CI, −1.33 to 1.67) in the placebo group. The administration of statin therapy also did not attenuate decline in LVEF regardless of whether patients had breast cancer or lymphoma, with a difference in 24-month LVEF of 0.26 percentage points (95% CI, −3.82 to 4.34) between patients with lymphoma and breast cancer taking a statin. Among those receiving assessments of LVEF pretreatment and 24 months after initiating doxorubicin, 66 and 31 individuals experienced greater than 5- and 10-percentage-point declines in LVEF, respectively. Across the trial, 11 individuals (4 in the statin group and 7 in the placebo group, respectively) experienced LVEF declines to absolute values below 50%.

In a sensitivity analysis, we modeled the relative risk of LVEF decline as defined by a more than 5-percentage-point drop in LVEF from pretreatment, adjusting for race, use of cardioactive drugs, BMI, systemic arterial pressure, smoking status, and patient age. We observed no significant associations between these patient factors and the relative risk of 24-month LVEF decline, with CIs for the relative risk of each effect containing 1; effects estimates in terms of risk ratios and 95% CIs from this logistic regression model are presented in Figure 3.

Patients receiving statins experienced a decline of 25.7±4.2 and 26.4±3.9 mg/dl in total cholesterol and low-density lipoprotein, respectively, compared with changes of 4.3±3.9 and −1.8±3.7 mg/dl in the placebo group (Table 2). Individuals experiencing greater declines in serum lipoproteins, regardless of random assignment to statins versus placebo, did not

experience differences in declines in LVEF relative to those without greater than 10% changes in serum lipoproteins, with the difference in 24-month LVEF between those with a greater than 10% lipoprotein decline and those without being 0.01 percentage points (95% CI, −2.03 to 2.05 mg/dl) (Table 2). We did not observe significant associations between changes in LVEF and serum markers of inflammation and renin across all three trial visits throughout the trial (Table 2).

Patients receiving atorvastatin did not experience differences in total recall assessed through the HVLT-R throughout the trial, compared with patients in the placebo arm. We observed a difference between the placebo and statin groups of −0.99 at 24 months (95% CI, −2.29 to 0.54). We also did not find a difference in the results of the HVLT-R in younger or older women, with total recall scores of 27.46±0.49 and 26.55±0.54, respectively (difference of 0.91; 95% CI, −0.32 to 2.14).

In a sensitivity analysis, we did not find any substantial differences with respect to changes within the treatment group between our imputed and nonimputed analyses. A pretreatment imbalance in BMI and weight between treatment groups led us to test BMI or just the weight measurement in all fitted linear models as a confounding variable in all data analyzed. Neither analysis showed that BMI affected treatment.

In a post hoc analysis, we assessed the relationship between LVEDV change and LVESV change with LVEF change. The correlation between 24-month LVEDV change and 24-month LVESV change was 0.66. We refit our primary model for 24-month LVEF change along with 24-month LVEDV change and 24-month LVESV change included as main effects in two separate models. Changes in 24-month LVESV were significantly associated with 24-month LVEF change, such that every point increase in LV end-systolic volume from pretreatment to 24 months was associated with a 0.16-percentage-point decrease in 24-month LVEF (95% CI, 0.06 to 0.26); however, LVEDV change was not associated with 24-month LVEF change. During the trial, 15 reportable serious adverse events (SAEs; grade 4 and 5 events) occurred, with 6 in the atorvastatin group and 9 in the placebo group. There were no definitive, probable, or possible reportable SAEs associated with the trial drug. Of these 15 reportable events, 3 resulted in deaths that were determined to be unrelated to the trial drug. Reportable SAEs are listed in Table S4.

Discussion

Our data do not provide evidence that statin use affects LVEF decline in patients with cancer who received doxorubicin but do not otherwise have an indication to receive a statin for primary or secondary prevention of a cardiovascular event. Approximately one in six to one in seven of these patients experienced a greater than 10-percentage-point decline in LVEF regardless of whether they received 40 mg of atorvastatin or placebo each day during and for the full 24 months after initiating cancer treatment. Although LVEF declined significantly in both groups from pretreatment to 6 months, LVEF at 6 months did not differ significantly from LVEF at 24 months. Results of this multicenter trial were consistent with differences in other single-center LVEF studies of individuals receiving doxorubicin for treatment of cancer.[8,15,16] LVEF decline also occurred in patients who were

90% compliant with their trial drug. Finally, the addition of 40 mg of atorvastatin per day did not affect memory (measured by HVLT-R), serum markers of systemic inflammation (C-reactive protein, interleukin-6, and tumor necrosis factor-α), or serum hormones of the renin-angiotensin-aldosterone axis.

Prior observational studies have suggested an association between statin use and higher postcancer treatment (including doxorubicin treatment for adjuvant breast cancer) measurements of LVEF relative to no statin use.[4,5,17–20] We did not observe preservation of LVEF at 6 or 24 months after initiating doxorubicin in this randomized clinical trial that included patients without an indication to receive a statin for primary or secondary prevention of a cardiac event. In addition, we did not observe differences in LVEF decline among subgroups of patients including those with hypertension, smoking, or advanced age or among individuals receiving additional cardioprotective drugs (e.g., angiotensin-converting enzyme inhibitors) for treatment of hypertension.

The data showed that, despite random assignment, individuals not receiving atorvastatin had higher body weights and exhibited greater BMI values relative to individuals receiving atorvastatin. To account for differences in body size, all LV function data were indexed for body surface area, and a sensitivity analysis was performed. Both assessments indicate similar results in LVEF change between groups regardless of BMI or weight.

In this trial, we also observed a deterioration in LV myocardial circumferential strain. This deterioration was experienced in both groups of patients and occurred in individuals who concomitantly experienced an increase in LVESV and a decline in LVEF. These results suggest that the receipt of atorvastatin did not impact changes in LV circumferential strain 6 or 24 months after initiating doxorubicin.

Our data demonstrate that individuals experienced declines in LVEF concomitant with an increase in LVESV regardless of receipt of atorvastatin 40 mg per day. As a result, the etiology of the decline in LVEF appears to be related to the impact of doxorubicin on LVESV as opposed to a decrement in LV preload that would manifest as a decrease in LVEDV.[16]

The U.S. Food and Drug Administration previously issued a warning regarding the potential association of statin administration and memory decline.[21] In addition, doxorubicin may affect memory.[22] We serially assessed verbal memory throughout the trial using the HVLT-R. Although our trial was not powered for this end point, neither the statin nor the placebo patient group experienced significant differences in HVLT-R results during their first 2 years of treatment.

Lower levels of serum cholesterol and markers of systemic inflammation occurred in patients receiving statin therapy versus placebo. This finding indicates a high likelihood of patients adhering to the trial drug regimen, because atorvastatin can lower low-density lipoprotein and has pleiotropic anti-inflammatory effects.[23] We did not observe differences in LVEF declines among patients who experienced greater declines in serum low-density lipoprotein or markers of systemic inflammation.

There are limitations to our trial. First, several participants either withdrew or were noncompliant with their trial drug because of feeling overwhelmed by the many tests and hospital visits related to their cancer treatment. Although most participant withdrawals were attributable to a feeling of being overwhelmed, more detailed information about withdrawals is included in Table S3. Importantly, however, we had sufficient power to detect small changes in LVEF even when taking into account the potential reduction in the effective sample size due to patient withdrawal or noncompliance. This is possible because of the relatively high reproducibility and low variance of the CMR outcome measures. Of note, the LVEF decline in patients was not appreciably different between groups on the basis of patient trial drug compliance levels (>90% compliance threshold; Table S5). Second, we did not assess progression of coronary arteriosclerosis using coronary arterial computed tomography. Third, participants initiated statin therapy 24 to 48 hours before their first dose of doxorubicin. As a result, we are uncertain as to whether the initiation of statins at an earlier time point for more extended periods of time (similar to taking statins for primary or secondary cardiovascular event prevention) would reduce declines in LVEF in the years after doxorubicin receipt.

In summary, the administration of atorvastatin 40 mg per day to individuals who otherwise did not have a primary or secondary indication for prevention of cardiovascular events did not affect declines in LVEF or circumferential strain 6 and 24 months after initiating doxorubicin in patients with breast cancer or lymphoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

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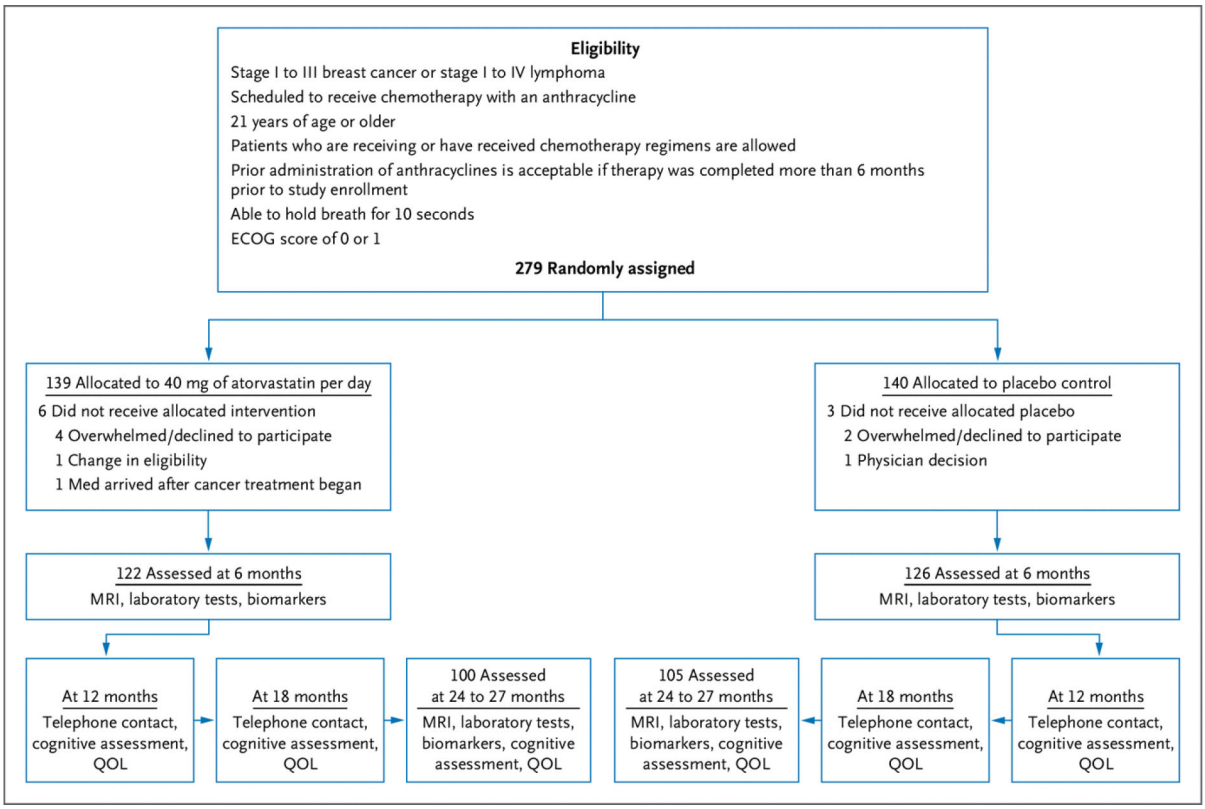

Figure 1. Trial Design.

The eligibility criteria and random assignment of participants to the placebo or atorvastatin (40 mg per day) arm is shown. The number of patients at the pretreatment, 6-month, and 24-month time points after cancer treatment initiation is indicated. Information on measurements (e.g., magnetic resonance imaging [MRI], serum biomarkers, and cognition tests) is shown at the pretreatment and 6-, 12-, 18-, and 24-month time points. Reasons for withdrawal are listed at the random assignment step. ECOG denotes Eastern Cooperative Oncology Group (scores range from 0 5 no impairment to 5 for death); and QOL, quality of life.

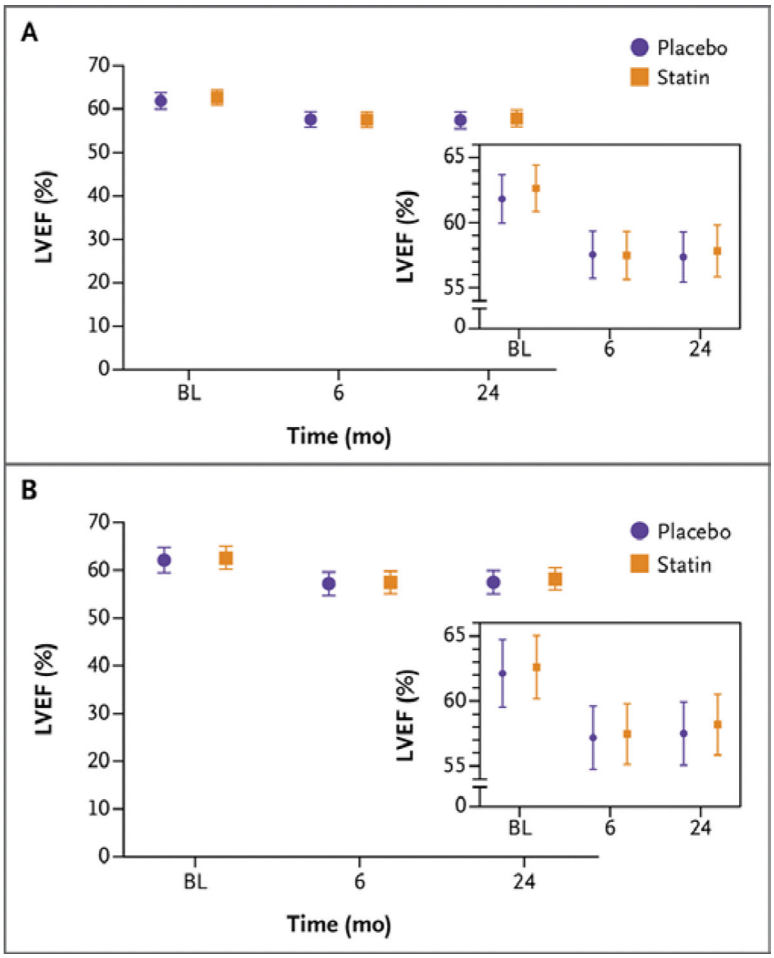

Figure 2. Measures of Left Ventricular Ejection Fraction.

Differences in left ventricular ejection fraction (LVEF) are shown for individuals who were randomly assigned to statins (squares) or placebo (circles) (Panel A) or who were 90% compliant with the patient-reported daily consumption of their drug throughout the 24 months of participating in the trial (Panel B). The pretreatment, 6-month, and 24-month time points after doxorubicin initiation (x-axis) show the estimated mean LVEF and 95% confidence interval as estimated from the longitudinal linear mixed model (y-axis). BL denotes baseline.

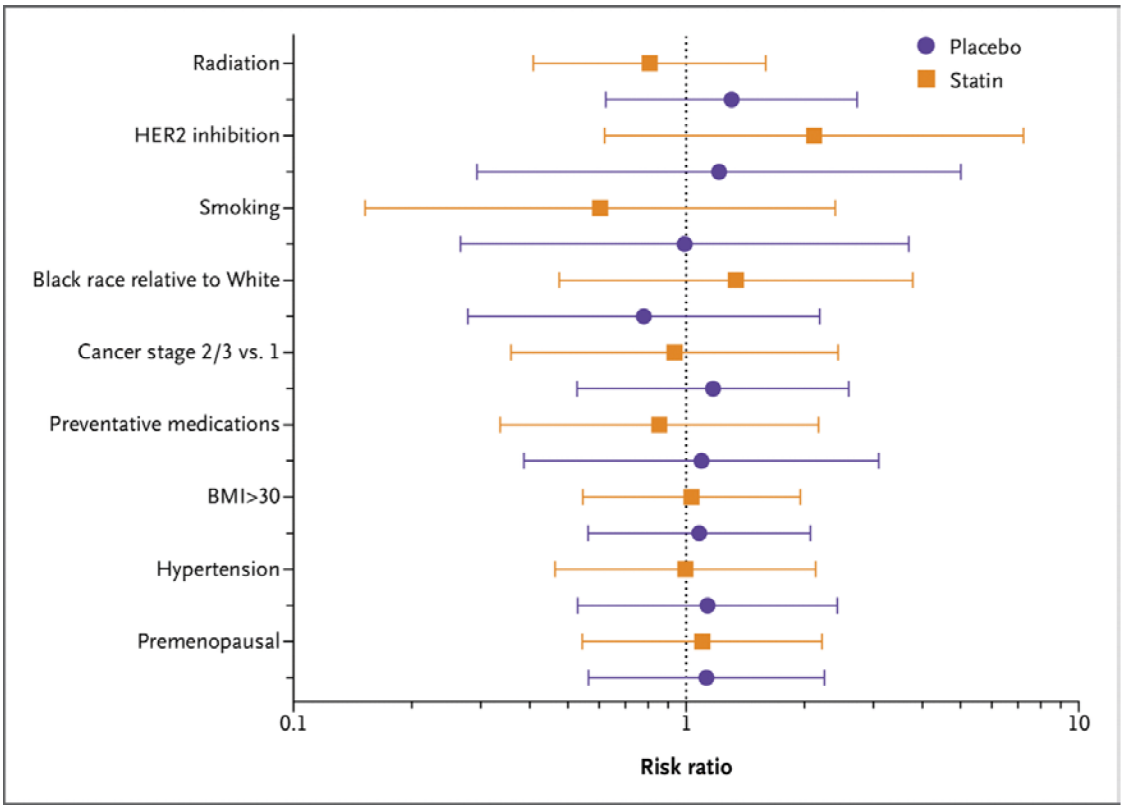

Figure 3. Subgroup Analyses Regarding Left Ventricular Ejection Fraction Decline.

Risk ratios and corresponding 95% CIs for greater than 5-percentage-point declines in left ventricular ejection fraction over 24 months estimated from a multivariable model are shown. The y-axis shows the statin (squares) or placebo (circles) arm when categorized by radiation treatment, human epidermal growth factor receptor 2 (HER2) inhibition treatment, smoking status, Black versus White race identified by patient report, cancer stage, preventative medications, body-mass index (BMI), hypertension status, and menopause status.

Table 1.

Patient Demographics, Radiation, and Drug Exposure.*

Characteristic	Statin (n = 139)	Placebo (n = 140)
Age — yr		
Mean (±SD)	48.5±12.5	49.4±11.5
Median (minimum, maximum)	50.0 (22.0, 76.0)	49.0 (23.0, 78.0)
Female sex — no. of patients (%)	129 (92.8)	127 (90.7)
Race — no. of patients (%)		
Asian	2 (1.4)	1 (0.7)
Black	16 (11.5)	22 (15.7)
Native Hawaiian/Pacific Islander	4 (2.9)	0 (0)
Native American/Alaskan	1 (0.7)	1 (0.7)
Unknown	1 (0.7)	0 (0)
White	115 (82.7)	116 (82.9)
Height — cm		
Mean (±SD)	165.5±7.5	166.6±8.4
Median (minimum, maximum)	165.1 (152.4, 189.0)	165.1 (149.9, 195.6)
Weight — kg		
Mean (±SD)	79.4±18.9	85.8±20.6
Median (minimum, maximum)	77.2 (47.6, 143.0)	82.6 (49.1, 157.0)
Body-mass index†		
Mean (±SD)	29.0±6.4	31.0±7.4
Median (minimum, maximum)	28.2 (17.6, 49.6)	30.0 (19.5, 55.8)
Received radiation before trial — no. of patients (%)	78 (56.1)	82 (58.6)
HER2 inhibitor taken before trial — no. of patients (%)	4 (2.9)	7 (5.0)
Taking cardioprotective medications (e.g., β blocker, calcium channel blocker, ARB, or ACE inhibitor) before trial — no. of patients (%)	20 (14.4)	28 (20.0)
Cumulative anthracycline dose — mg/m^2, median (minimum, maximum)	240 (8, 307)	240 (60, 480)

*The widths of the CIs have not been adjusted for multiplicity and cannot be used to infer treatment effects. ACE denotes angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and HER2, human epidermal growth factor receptor 2.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2.

Participant Measures and Laboratory Values Taken across All Three Visits.

	Mean (±SD)					
	Pretreatment Visit		6 mo after Treatment Initiation		24 mo after Treatment Initiation	
Measure and Value	**Statin (n = 139)**	**Placebo (n = 140)**	**Statin (n = 122)**	**Placebo (n = 126)**	**Statin (n = 100)**	**Placebo (n = 105)**
Participant Measures						
Resting heart rate (bpm)	77±13	79±12	81±15	81±12	77±14	77±13
Systolic blood pressure (mm Hg)	124±17	128±18	121±17	125±17	124±16	127±17
Diastolic blood pressure (mm Hg)	75±11	79±13	74±9	77±16	75±12	76±11
End-diastolic volume (ml)	129±30	135±36	129±30	131±34	126±30	133±34
End-systolic volume (ml)	49±15	52±17	55±17	56±17	54±16	57±19
Stroke volume (ml)	81±20	83±22	74±18	75±21	73±18	76±20
Left ventricular mass (g)	90±22	94±23	88±20	91±22	86±20	88±22
Left ventricular mass index (g/m^2)	47±8	47±9	47±7	46±9	45±8	44.9±9
Laboratory Values						
Cholesterol (mg/dl)	192±41	195±32	156±38	200±31	172±42	196±36
Triglycerides (mg/dl)	112±52	127±92	110±52	142 ±72	117±59	124±84
Low-density lipoprotein (mg/dl)	111±29	112±26	75±32	116±29	89±38	110±34
High-density lipoprotein (mg/dl)	59±18	57±14	60±18	56±16	59±16	61±17
Glucose (mg/dl)	91.6±14.9	91.3±10.3	95.6±16.8	99.1±25.9	96.7±19.0	97.0±17.8
Total bilirubin (mg/dl)	0.5±0.3	0.4±0.2	0.4±0.3	0.4±0.2	0.5±0.4	0.4±0.3
Alanine aminotransferase (IU/l)	21.7±14.7	21.2±12.0	25.7±13.0	25.1±14.1	23.5±14.6	20.7±11.1
Aspartate aminotransferase (IU/l)	21.2±10.9	20.2±8.6	23.9±7.8	23.5±8.9	23.5±9.08	21.5±9.0
Creatinine kinase (mg/dl)	80.4±48.6	74.7±49.1	90.6±80.1	73.4±40.5	133±236	101±62.9
Thyroid-stimulating hormone (mIU/l)	1.82±1.1	2.01±1.5	1.94±2.2	1.95±2.2	3.08±7.9	2.94±3.0
Troponin (ng/ml)	0.03±0.2	0.01±0.0	0.03±0.1	0.03±0.1	0.01±0.0	0.02±0.1
C-reactive protein (mg/l)	7.2±20.1	9.0±16.7	3.9±13.7	4.9±8.0	4.6±9.7	3.7±3.9
Interleukin-6 (pg/ml)	5.33±9.6	4.90±9.2	3.19±3.8	3.62±5.0	3.85±7.7	3.36±3.2
Tumor necrosis factor-α (pg/ml)	1.46±1.3	1.73±2.4	1.07±0.5	1.23±0.5	1.23±0.6	1.20±0.5
Renin (ng/ml/hr)	2.15±3.5	2.45±5.5	1.60±1.8	2.79±7.4	1.49±2.1	1.90±4.2
Aldosterone (ng/dl)	8.63±10.5	6.87±7.6	8.76±13.8	9.36±8.4	7.58±5.5	8.25±6.6