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ORIGINAL RESEARCH

OUTCOMES AND QUALITY

TITAN Trial

A Randomized Controlled Trial of a Cardiac Rehabilitation Care Model in Breast Cancer

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ABSTRACT

BACKGROUND Cardiac rehabilitation (CR) modeled care is recommended for patients with breast cancer to mitigate risk of cardiotoxicity. However, the cardiovascular impact of CR-modeled interventions has not been studied.

OBJECTIVES The purpose of this study was to evaluate if a multidisciplinary model of CR reduces cardiotoxicity and improves cardiovascular risk in patients undergoing breast cancer treatment.

METHODS We randomly assigned patients with stage I to III breast cancer scheduled to receive anthracycline and/or trastuzumab-based chemotherapy to the CR intervention (n = 37) or usual care (n = 37). The intervention included guideline-directed management of cardiovascular risk factors, dietary counselling, and supervised exercise for 52 weeks. Cardiac magnetic resonance imaging, cardiopulmonary exercise testing, dual-energy x-ray absorptiometry, and serum biomarkers were acquired at baseline and 52 weeks.

RESULTS There was no difference in the primary outcome, left ventricular ejection fraction (LVEF), between groups at 52 weeks (61% ± 6%). Other markers of cardiotoxicity, including high-sensitivity troponin I and brain natriuretic peptide, were similar between groups. However, total cholesterol (5.2 ± 0.8 mmol/L to 4.7 ± 0.8 mmol/L, $P = 0.002$) and low-density lipoprotein (3.0 ± 0.7 mmol/L to 2.4 ± 0.7 mmol/L, $P < 0.001$) decreased in the intervention group at 52 weeks and were unchanged in usual care. In all patients, adverse cardiac and metabolic changes occurred over 52 weeks including reductions in LVEF, left ventricular mass, high-density lipoprotein, lean body mass, insulin-like growth factor-1, as well as increased triglycerides, whole-body and truncal fat mass (all $P < 0.050$).

CONCLUSIONS The CR-modeled intervention had no effect on LVEF or biomarkers of cardiotoxicity. Future lifestyle intervention trials in patients with breast cancer should consider targeting other risk factors associated with incident cardiovascular disease. (Multidisciplinary Team IntervenTion in CArdio-ONcology [TITAN Study] [TITAN]; NCT01621659) (JACC Adv 2023;2:100424) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BNP = brain natriuretic peptide

CR = cardiac rehabilitation

EBC = early-stage breast cancer

GLS = global longitudinal strain

HDL = high-density lipoprotein

IGF = insulin-like growth factor

LDL = low-density lipoprotein

LV = left ventricle

LVEF = left ventricular ejection fraction

MRI = magnetic resonance imaging

RCT = randomized controlled trial

VO_2peak = peak oxygen uptake

Systemic therapies for early-stage breast cancer (EBC) can have detrimental effects on cardiovascular function such that within 3 years of chemotherapy rates of heart failure are elevated 3-fold.[1] Further, peak oxygen uptake (VO_2peak), a strong predictor of cardiovascular disease and mortality[2] is consistently reduced in EBC[3] and linked to chemotherapy-related cardiotoxicity and mortality.[4,5] As a result, death from cardiovascular disease may exceed cancer-specific in many EBC survivors.[6]

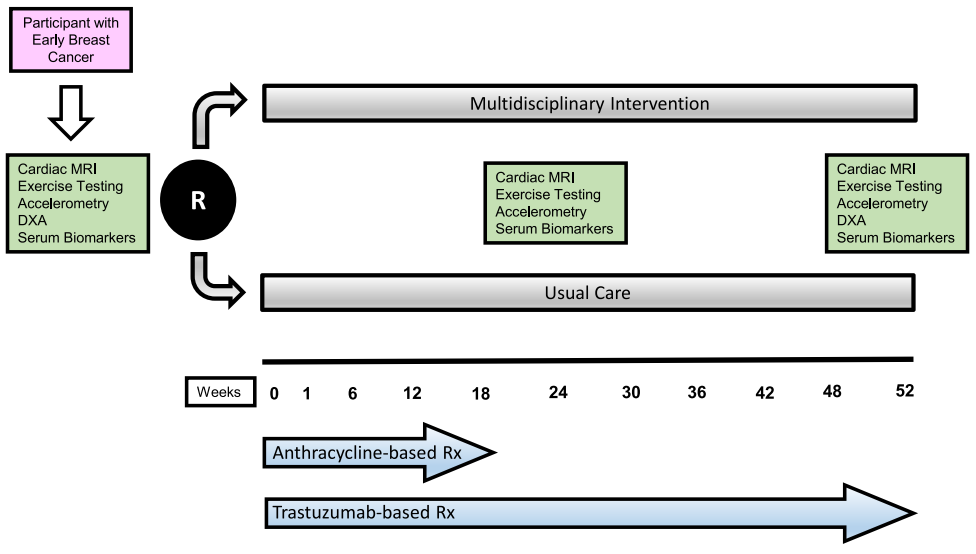
Routine cardiology care involves addressing modifiable cardiovascular risk factors including smoking cessation, physical inactivity and obesity in addition to guideline-based treatment of hypertension, dyslipidemia, and diabetes mellitus. Cardiac rehabilitation (CR) is a well-established multidisciplinary program targeting this risk profile and has been shown to reduce cardiac-specific mortality, improve medication adherence, and increase VO_2peak in patients with cardiovascular disease.[7] An American Heart Association scientific statement recommends similar programs for high-risk patients with cancer to prevent latent cardiovascular disease.[8] In this statement, high-risk was defined by: 1) patient factors including age ≥60 years, 2 or more cardiovascular risk factors and prior cardiac disease; 2) exposure to anthracycline and/or trastuzumab cancer treatment; and 3) the appearance of cardiac symptoms. To date, no randomized controlled trials (RCTs) have evaluated the impact of a CR intervention on cancer treatment-related cardiotoxicity.

We performed a RCT of a personalized CR-modeled intervention for patients with EBC initiating cardiotoxic systemic therapy. The primary aim was to evaluate the effect of the intervention on left ventricular ejection fraction (LVEF). Secondary objectives included determining effects on cardiovascular risk profile and overall fitness (VO_2peak, muscle strength, body composition).

METHODS

DESIGN. The study protocol has been previously reported.[9] Participants were randomly assigned 1:1 in parallel groups to the intervention or to usual care (NCT01621659) (**Figure 1**). Simple randomization was performed using a random number generator computer function with no stratification or blocks. Allocation concealment was achieved with sequentially numbered, opaque, sealed envelopes filled by independent research personnel. Randomization occurred following written informed consent, baseline magnetic resonance imaging (MRI) scan and

FIGURE 1 Study Design



The diagram indicates timing of assessments **(green)**, study interventions **(gray)**, and cancer treatments **(blue)**. DXA = dual x-ray absorptiometry; MRI = magnetic resonance imaging; R = randomization; Rx = treatment.

cardiopulmonary exercise testing. Blinding of participants was not possible; however, all outcome measures were acquired and/or analyzed by personnel blinded to group assignment. The Health Research Ethics Board of Alberta Cancer Committee provided ethical oversight (HREBA.CC-16-0637).

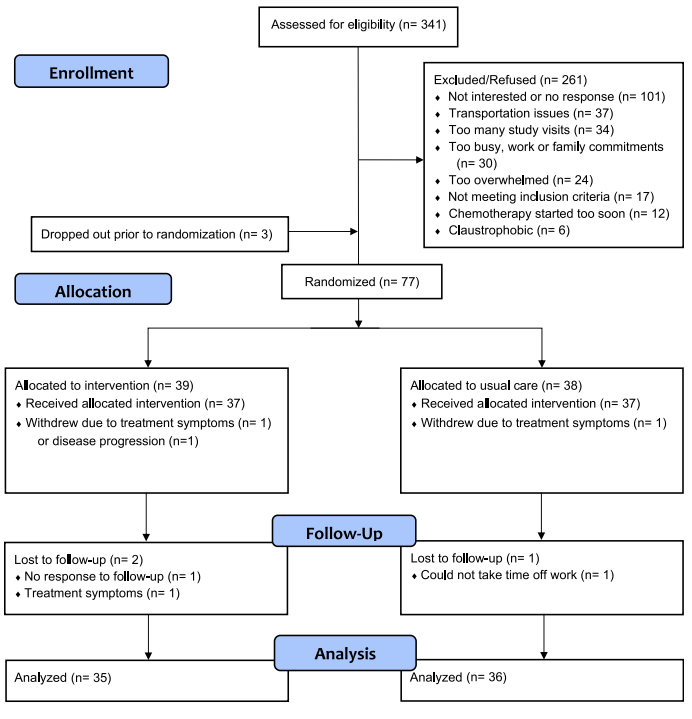
PARTICIPANTS. Potential participants were identified at tumor board review. Inclusion criteria were age >18 years, histologically-confirmed EBC (I-III), scheduled to receive trastuzumab and/or anthracycline-based chemotherapy and English-speaking. Patients were excluded for contraindications to MRI/exercise testing, previous heart failure, baseline LVEF <50%, or prior cardiotoxic treatment.

INTERVENTION. The intervention was a patient-directed, multidisciplinary assessment and care plan modeled on CR via risk factor management, exercise, and nutrition in addition to usual cancer care. Participants in the intervention group were offered the following components in an individualized manner for up to 52 weeks (see the Supplemental Appendix for additional details). Clinicians with cardio-oncology expertise (D.I.P., E.P.) assessed cardiovascular risk factors (blood pressure, lipid profile, glucose) and developed a guideline-based management plan.[10-12] An oncology-specialized registered dietitian developed a personalized nutritional diagnosis and recommendations, which could include modification to macronutrient ratios, caloric intake, or specific guidance (alcohol, sodium, sugar). Phone follow-up and dietary review was offered every 6 weeks. An exercise physiologist provided group-based, individualized supervised programming similar to CR, generally consisting of up to 2 sessions/wk of 60 to 90 minutes of moderate-intensity aerobic and resistance training. Progressions in intensity and duration and the inclusion of home-based exercise were implemented as tolerated. In order to mimic real-world CR implementation and reinforce our patient-centered approach, participants were encouraged to personalize their use of the offered dietary and exercise programming. Participants randomized to usual care received best supportive cancer care which allowed clinician or self-referral to allied health disciplines according to need.

OUTCOME MEASURES. The primary outcome was cardiac MRI-derived LVEF at 52 weeks. Secondary outcomes included cardiotoxicity at 52 weeks, defined as >10% absolute drop in LVEF from baseline to <53%[13]; temporal changes in left ventricular (LV) global longitudinal strain (GLS); circulating cardiac biomarkers (brain natriuretic peptide [BNP], high-sensitivity troponin I); cardiovascular risk factors (physical activity, blood pressure, lipid profile, glucose); and physical fitness (VO_2peak, muscular strength, body composition). Assessments were performed at baseline (prechemotherapy), 24 weeks (end of chemotherapy) and 52 weeks, with exception of body composition, blood pressure, and biomarkers which were not measured at 24 weeks (**Figure 1**).

Details of outcome assessments are provided (Supplemental Appendix) and are described briefly here. Ventricular volumes, ejection fraction, mass, and GLS were derived from cine imaging on cardiac MRI. VO_2peak was evaluated by cardiopulmonary exercise testing. We measured moderate-to-vigorous physical activity, sedentary time, and total energy expenditure over 5 days.[14] We assessed upper and lower body muscular strength via 1 repetition maximum of chest press and leg press, respectively.[15] Whole-body fat, lean mass, bone mineral content as well as truncal fat (a known cardiovascular risk factor),[16] was assessed with dual-absorptiometry x-ray. Finally, we analyzed circulating biomarkers associated with myocardial injury (high-sensitivity troponin I, BNP), metabolic risk (insulin-like growth factor (IGF)-1, random glucose, lipid profile), and cardiac remodeling (endothelin-1 and its precursor, big endothelin-1).

FIGURE 2 Study CONSORT Diagram



CONSORT = Consolidated Standards of Reporting Trials.

TABLE 1 Participant Baseline Characteristics

	All (N = 74)	Usual Care (n = 37)	Intervention (n = 37)
Age (y)	52 ± 10	52 ± 9	53 ± 10
Postmenopausal	45 (61%)	21 (57%)	24 (65%)
Body mass index (kg/m^2)	27.6 ± 6.2	27.8 ± 5.6	27.4 ± 6.8
Cardiovascular risk factors			
Hypertension	12 (16%)	9 (24%)	3 (8%)
Diabetes mellitus	5 (7%)	3 (8%)	2 (5%)
Hypercholesterolemia	5 (7%)	3 (8%)	2 (5%)
Current smoker	3 (4%)	3 (8%)	0
Previous smoker	19 (26%)	9 (24%)	10 (27%)
Overweight (25.0-29.9 kg/m^2)	28 (38%)	18 (49%)	10 (27%)
Obese (>30.0 kg/m^2)	19 (26%)	9 (24%)	10 (27%)
Total number of risk factors			
None	20 (27%)	8 (22%)	12 (32%)
1	29 (39%)	14 (38%)	15 (41%)
2	17 (23%)	9 (24%)	8 (22%)
3 or more	8 (11%)	6 (16%)	2 (5%)
Medication use			
ACEI/beta-blocker	13 (18%)	9 (24%)	4 (11%)
Oral hypoglycemic/insulin	5 (7%)	3 (8%)	2 (5%)
Statin	5 (7%)	2 (5%)	3 (8%)
Breast cancer stage			
I	18 (24%)	9 (24%)	9 (24%)
II	44 (59%)	24 (64%)	20 (54%)
III	12 (16%)	4 (11%)	8 (22%)
Receptor status			
Estrogen/progesterone positive	66 (89%)	33 (89%)	33 (89%)
HER2 positive	23 (31%)	12 (32%)	11 (30%)
Triple negative	4 (5%)	2 (5%)	2 (5%)
Chemotherapy regimen[a]			
Neoadjuvant	11 (15%)	7 (19%)	4 (11%)
None	1 (1%)	0	1
Anthracycline-containing	51 (69%)	26 (70%)	25 (68%)
Epirubicin dose (mg/m^2), median	300	300	300
Trastuzumab-containing	22 (30%)	11 (30%)	11 (30%)
Trastuzumab dose (mg/kg), median	104	104	104
Radiation therapy[b]			
Left-sided	33 (45%)	20 (54%)	13 (35%)
Right-sided	36 (49%)	15 (41%)	21 (57%)
None	6 (8%)	3 (8%)	3 (8%)

Values are mean ± SD or n (%). [a]Chemotherapy regimens included $FE_{100}C$ (n = 2), $FE_{100}C$>taxane (n = 46), $FE_{100}C$>DH (n = 1), TCH (n = 22), AC>taxane (n = 1), and TAC (n = 1). [b]Left mean radiotherapy dose 4,568 cGy (range 3,250-5,750 cGy), mean fractions 20 (range 16-25).

AC = doxorubicin, cyclophosphamide; ACEI = angiotensin-converting enzyme inhibitor; DH = docetaxel, trastuzumab; FE100C = fluorouracil, epirubicin (100), cyclophosphamide; HER2 = human epidermal growth factor receptor 2; TAC = docetaxel, doxorubicin, cyclophosphamide; TCH = docetaxel, carboplatin, trastuzumab.

POWER CALCULATION AND ANALYSIS. From our prior work, 52-week LVEF was estimated at 59% and 55% in the intervention and usual care groups respectively, with an SD of 6% for each.[17] Based on a 2-tailed significance level of 0.05, power of 0.80, and a 10% allowance for loss to follow-up, we recruited 80 patients. The primary outcome was evaluated by intention-to-treat analysis. Generalized linear mixed models were used to compare the change over time between groups for each continuous variable. Fixed effects included time (which was also a repeated factor), group and a group*time interaction, while participant was a random effect. For each model, we chose the distribution and link function that provided normally distributed residuals (determined by quantile-quantile plots) and/or the best model fit (Akaike Information Criterion). Fixed effects with $P \leq 0.05$ were investigated using pairwise contrasts between time points. We also conducted an exploratory analysis to examine potential underlying relationships between adverse changes in body composition across 52 weeks and concurrent changes in cardiac, metabolic, and physical activity metrics using Pearson correlations. A post hoc analysis was performed to compare the highest and lowest tertiles of adherence to each of the exercise, nutrition, and both interventions. After identifying that 5/37 usual care participants accessed the registered dietitian for counseling, we also performed post hoc as treated analysis to compare those participants attending ≥50% of prescribed dietary counseling sessions to those attending no sessions. We used SPSS version 26.0 (IBM Corp) for all analyses.

RESULTS

PARTICIPANTS. We enrolled 80 women with EBC from January 2015 to May 2018 (Consolidated Standards of Reporting Trials [CONSORT] diagram) (**Figure 2**). Three did not complete all baseline assessments due to cancer-related symptoms and were not randomized and 3 patients asked to withdraw due to noncardiac complications arising from cancer treatment or disease progression. Thus, 74 participants were available for analysis, 37 in each group. Groups had similar baseline clinical characteristics and treatments (**Table 1**), including relative dose intensities of cancer therapies (epirubicin, 1.0; trastuzumab, 0.97; docetaxel, 0.91). Intervention uptake was good in the intervention group including 81% receiving nutritional support and 70% participating in the exercise program (Supplemental Appendix, Supplemental Tables 1 and 2).

PRIMARY AND SECONDARY OUTCOMES. There was no difference in the primary outcome, LVEF at 52 weeks, between the CR intervention and usual care (61% ± 6% in each group) (**Table 2**). We did not identify any relationship between adherence to the diet or exercise intervention components and LVEF (Supplemental Table 3). In the overall cohort, LVEF was mildly decreased by 24 weeks (61% ± 6%, $P = 0.001$) and 52 weeks (61% ± 6%, $P = 0.001$)

relative to baseline (63% ± 6%). However, no cases of cardiotoxicity occurred in either group at either time point. Incidence of LVEF drop >10% was also very low, with a single case at 52 weeks and 2 cases at 24 weeks (all in the intervention group).

Similarly, there were no differences between groups over time in other biomarkers of cardiotoxicity including GLS and BNP (**Table 2**, Supplemental Table 4). High-sensitivity troponin I was higher in the usual care group at both baseline and 24 weeks compared to the intervention group. However, there were no group differences when analysis of covariance was used to compare the change with adjustment for baseline (24 weeks: $P = 0.42$; 52 weeks: $P = 0.28$). No differences existed between groups for any other cardiac MRI, circulating biomarker, or body composition metric. The only group differences were a significant reduction in total cholesterol (5.2 ± 0.8 mmol/L to 4.7 ± 0.8 mmol/L, $P = 0.002$) and low-density lipoprotein (LDL) (3.0 ± 0.7 mmol/L to 2.4 ± 0.7 mmol/L, $P < 0.01$) in the intervention group at 52 weeks, with no changes to cholesterol with usual care (**Table 3**). Importantly, there were no differences in physical activity and exercise performance measures between groups at any time point (Supplemental Table 5). Several adverse changes to cardiac and cardiometabolic phenotype occurred over time, regardless of group assignment and included an increase in total and trunk body fat percentage and reduction in IGF-1 (Supplemental Appendix, Supplemental Tables 4 to 7, Supplemental Figure 1).

TABLE 2 LV Function, Volumes, and Structure

	Usual Care (n = 37)	Intervention (n = 37)	Time*Group Interaction *P* Value	All (N = 74)	Time *P* Value
LV ejection fraction (%)			0.41		**<0.001**
Baseline	63 ± 6	62 ± 6		63 ± 6	
24 wk	61 ± 6	60 ± 6		61 ± 6[a]	
52 wk	61 ± 6	61 ± 6		61 ± 6[a]	
LV midwall GLS (%)			0.89		0.44
Baseline	−20.9 ± 2.5	−20.8 ± 2.4		−20.8 ± 2.7	
24 wk	−20.7 ± 3.0	−20.9 ± 2.4		−20.8 ± 2.6	
52 wk	−21.1 ± 2.3	−21.3 ± 2.7		−21.2 ± 2.5	
LV end-diastolic volume (mL/m^2)			0.45		**0.02**
Baseline	73 ± 15	72 ± 14		73 ± 14	
24 wk	72 ± 19	71 ± 16		72 ± 17	
52 wk	70 ± 14	67 ± 16		68 ± 15[a]	
LV end-systolic volume (mL/m^2)			0.12		**0.04**
Baseline	27 ± 7	28 ± 8		27 ± 8	
24 wk	29 ± 12	29 ± 9		29 ± 10[a]	
52 wk	27 ± 7	26 ± 8		27 ± 8[b]	
LV stroke volume (mL/m^2)			0.68		**0.001**
Baseline	46 ± 10	44 ± 8		45 ± 9	
24 wk	43 ± 9	43 ± 9		43 ± 9[a]	
52 wk	42 ± 9	41 ± 10		42 ± 9[a]	
LV mass (g/m^2)			0.29		**<0.001**
Baseline	54 ± 7	52 ± 5		54 ± 6	
24 wk	51 ± 9	49 ± 6		50 ± 7[a]	
52 wk	50 ± 7	47 ± 5		48 ± 6[a,b]	

Values are mean ± SD. Missing data: 24 weeks, n = 1 in intervention group; 52 weeks, n = 1 in usual care, n = 2 in intervention group **Bold** indicates statistically significant. [a]Different from baseline ($P \leq 0.05$). [b]Different from 24 weeks ($P \leq 0.05$).

GLS = global longitudinal strain; LV = left ventricle.

DISCUSSION

To our knowledge, this is the first RCT of a CR-based intervention for patients with EBC and comprehensive characterization of temporal changes in cardiovascular risk. While the intervention did not have an effect on LVEF or other biomarkers of cardiotoxicity, we observed 20% decrease in LDL and 10% decrease in total cholesterol, not attributable to new pharmacotherapy (**Central Illustration**). Adverse cardiometabolic changes characterized by whole-body and truncal fat accumulation, elevated triglycerides, and reduced high-density lipoprotein (HDL) and IGF-1 was observed in all participants.

LOW INCIDENCE OF LEFT VENTRICULAR DYSFUNCTION. Despite using cardiac MRI, the most sensitive imaging modality available, we observed negligible effects of cancer treatment on LVEF or GLS and no cases of cardiotoxicity. Potential explanations for the low incidence of cardiotoxicity in our study include conservative anthracycline dosing and infrequent use of sequential anthracycline-trastuzumab regimens. Notably, the median dose of epirubicin was 300 mg/m^2 (150 mg/m^2 doxorubicin equivalent),[18] significantly below the 240 mg/m^2 doxorubicin equivalent threshold associated with risk of cardiotoxicity.[13] According to the American Heart Association statement on mitigating cardiovascular risk in patients with cancer, 54 of 74 patients in our cohort (73%) met criteria for referral to cardio-oncology rehabilitation according to higher risk patient and treatment factors.[8] Therefore, it does not appear that patient selection played a role in the low incidence of cardiac dysfunction. The marginal effects of cancer therapy on LVEF in our cohort are comparable to other recent studies of patients with EBC receiving anthracyclines.[19,20] In fact, the low incidence of cardiac dysfunction associated with contemporary cancer regimens has led to questions regarding the utility of current cardioprotective strategies.[21] Moreover, traditional cardio-oncology guideline measures of a reduction in resting cardiac function may result in a failure to detect heart failure with

TABLE 3 Cardiovascular Risk Factors

	Usual Care (n = 37)	Intervention (n = 37)	Time*Group Interaction *P* Value	All (N = 74)	Time *P* Value
Systolic blood pressure (mm Hg)			0.03		NA
Baseline	132 ± 18	127 ± 15		129 ± 16	
52 wk	111 ± 16[a]	115 ± 15[a]		113 ± 15	
Diastolic blood pressure (mm Hg)			0.67		0.02
Baseline	73 ± 11	74 ± 9		73 (10)	
52 wk	70 ± 13	70 ± 10		70 ± 11[a]	
Random glucose (mmol/L)			0.81		0.88
Baseline	5.5 ± 1.0	5.5 ± 0.8		5.5 ± 0.9	
52 wk	5.7 ± 1.3	5.5 ± 1.2		5.6 ± 1.2	
Total cholesterol (mmol/L)			0.04		NA
Baseline	5.0 ± 1.1	5.2 ± 0.8		5.1 ± 1.0	
52 wk	5.0 ± 1.0	4.7 ± 0.8[a]		4.8 ± 0.9	
Triglycerides (mmol/L)			0.91		<0.001
Baseline	1.2 ± 0.5	1.3 ± 0.8		1.3 ± 0.7	
52 wk	1.7 ± 0.8	1.7 ± 1.0		1.7 ± 0.9[a]	
Low density lipoprotein (mmol/L)			0.02		NA
Baseline	2.9 ± 0.9	3.0 ± 0.7		2.9 ± 0.8	
52 wk	2.8 ± 0.8	2.4 ± 0.7[a]		2.6 ± 0.7	
High density lipoprotein (mmol/L)			0.92		0.002
Baseline	1.6 ± 0.5	1.6 ± 0.4		1.6 ± 0.5	
52 wk	1.4 ± 0.3	1.5 ± 0.3		1.5 ± 0.3[a]	
Total energy expenditure (kcal/d)			0.56		0.03
Baseline	1,956 ± 332	1,867 ± 287		1,911 ± 311	
24 wk	2,079 ± 336	1,888 ± 380		1,989 ± 367	
52 wk	2,042 ± 293	1,931 ± 275		1,992 ± 287[a]	
Moderate-to-vigorous physical activity (min/d)			0.54		0.02
Baseline	40 ± 54	26 ± 34		34 ± 39	
24 wk	57 ± 69	29 ± 38		38 ± 71	
52 wk	56 ± 57	35 ± 50		45 ± 55[a]	
Sedentary time (h/d)			0.94		0.04
Baseline	12.2 ± 3.5	11.2 ± 3.0		11.8 ± 3.1	
24 wk	11.0 ± 4.7	11.6 ± 3.5		11.5 ± 3.7	
52 wk	11.5 ± 2.6	11.0 ± 2.8		11.3 ± 2.7[a]	

Values are mean ± SD. [a]Different from baseline ($P \leq 0.05$).
NA = not applicable.

preserved ejection fraction which is more frequent in older breast cancer survivors.[22,23] Furthermore, we have recently shown that cancer survivors are also at significantly increased risk for nonheart failure related cardiovascular events including stroke and pulmonary embolism.[24]

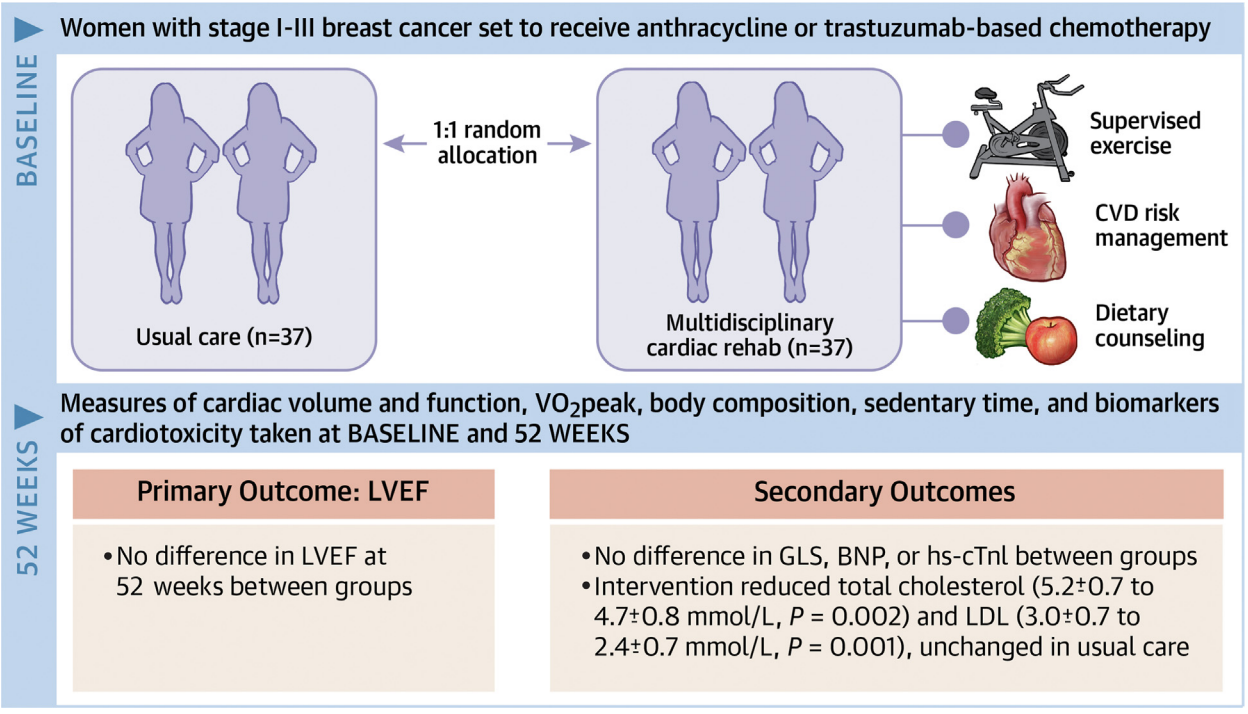
IMPACT OF EXERCISE-BASED INTERVENTIONS IN PATIENTS WITH EBC. Despite overwhelmingly positive preclinical evidence that aerobic exercise protects against anthracycline-mediated cardiotoxicity,[25] we found no effect of exercise training on cardiac function. While the average exercise stimulus in the intervention group may have been low, our adherence-based analysis also did not detect a difference between groups with high and low adherence to exercise (Supplemental Table 3). The lack of effect of our intervention on cardiac function is also congruent with recent exercise studies conducted during anthracycline or trastuzumab treatment for EBC that were smaller (n = 12-37 total), nonrandomized or noncontrolled.[25-29] Potential reasons for lack of translation of the cardioprotective effects of exercise include that animal models typically lack important host confounding variables (eg, cancer itself, cardiovascular risk factors) and that exercise adherence among laboratory animals far exceeds that which is feasible for humans during chemotherapy.[28-30]

We chose to make the exercise component of our intervention patient-directed to mimic real-world experience. Our 70% uptake of supervised exercise was similar to uptake of enrollment in other RCTs of exercise in patients with EBC and is greater than the <39% uptake of CR amongst women with cardiac diseases.[31-33] However, the exercise dose delivered in the current study is lower than that in prior exercise RCTs of EBC.[3,32,34] Nevertheless, in our overall cohort, fitness levels returned to baseline by 52 weeks while physical activity increased over the same time frame. Further, VO_2peak at baseline and post-treatment was ~40% higher in all of our patients compared to expected measures in EBC.[3] These observations suggest that our participants were highly motivated and well-supported throughout the study to develop and maintain habitual lifestyle modifications in the medium term.

Women in particular experience barriers to attend in-person programming (eg, lack of social support, family responsibilities[35]), further compounded by the recent impact of the COVID-19 pandemic. In view of these long-standing and contemporary barriers to in-person programming among women, telehealth and distance-based interventions are an important area of future research to reduce cardiovascular risk among EBC.[36] Despite these potential challenges, the intervention group participants who participated in the exercise intervention attended a median of 30 training sessions which favorably compares to CR attendance among patients with coronary artery disease.[37]

CHANGES IN CARDIOMETABOLIC PROFILE DURING CANCER THERAPY. While the incidence of LV dysfunction and cardiotoxicity were extremely low, we observed significant worsening of the cardiovascular metabolic profile in patients with EBC including increased whole-body and truncal fat, reduced HDL,

CENTRAL ILLUSTRATION **Overview of the Design and Main Findings From the TITAN Randomized Controlled Trial**



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Overview of the design and main findings from the TITAN randomized controlled trial including randomization to groups **(purple)**, study assessments **(blue)**, and primary and secondary outcomes **(red)**. BNP = brain natriuretic peptide; CVD = cardiovascular disease; GLS = global longitudinal strain; Hs-cTnI = high sensitivity cardiac troponin I; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; RCT = randomized control trial; TITAN = IntervenTion in cArdio-oNcology; VO_2peak = peak oxygen consumption.

increased triglycerides, and reduced IGF-1. IGF-1 is a major mediator of growth hormone action with low levels associated with higher risk of cardiovascular disease-related death, possibly through adverse effects on visceral adiposity and dyslipidemia.[38] In another study of patients with EBC, we reported that IGF-1 decreases and visceral and intermuscular fat increase during trastuzumab therapy and these 2 fat pools are elevated at ~1 year postanthracycline.[39,40] Others have shown that greater visceral fat at the time of EBC diagnosis predicts incident cardiac events and all-cause mortality.[41,42] Taken together, our data suggest that *fat accumulation* is a potentially critical and underappreciated contributor to overall cardiovascular risk after EBC treatment.

STUDY LIMITATIONS. As previously mentioned, the low incidence of cardiotoxicity may have impeded our ability to detect between-group differences on our primary outcome. Our study lacked early assessments (eg, 6 or 12 weeks) which may have reduced our ability to detect cardiotoxicity during the treatment period. However, other studies of anthracycline-related cardiotoxicity have not detected early LV dysfunction in patients with EBC.[20] Our study also lacks longer-term follow-up (eg, beyond 52 weeks) and is not powered for the evaluation of clinical outcomes. Given these limitations, the inclusion of more patients and more cardiac function assessments may have allowed the detection of a treatment effect from our intervention. Finally, future studies are needed to examine exercise cardiovascular and skeletal muscle function as resting measures of cardiotoxicity may not detect impaired ventricular-vascular coupling and reduced skeletal muscle reserve that occur during submaximal and peak exercise stress.

CONCLUSIONS

We report the first RCT of a CR-based intervention in patients with EBC receiving cardiotoxic systemic therapy with comprehensive characterization of cardiovascular function and risk profile. We did not find a substantial effect of this intervention on LV

function or on biomarkers of cardiotoxicity compared to usual cancer care. Future studies of lifestyle interventions should consider targeting other risk factors associated with incident cardiovascular disease.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A multidisciplinary CR-based intervention did not impact LVEF or other markers of cardiotoxicity in patients undergoing early breast cancer treatment; however, it was associated with modest reductions in LDL and total cholesterol when compared to usual care. Adverse metabolic changes were observed amongst all participants including increased whole-body and truncal adiposity, reduced HDL, elevated triglycerides and reduced IGF-1.

TRANSLATIONAL OUTLOOK: Future studies should consider lifestyle modifications targeted to improve cardiometabolic risk including body composition as a strategy to prevent incident cardiovascular disease in patients with breast cancer undergoing trastuzumab and/or anthracycline-based chemotherapy.

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APPENDIX For supplemental appendix, tables, and a figure, please see the online version of this paper.