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Long-term cardiac MRI follow up of MANTICORE (Multidisciplinary Approach to Novel Therapies in Cardio-Oncology REsearch)

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Abstract

Background This study investigates the long-term cardiac effects of trastuzumab-based chemotherapy in early breast cancer (EBC) survivors. We extend the original MANTICORE trial which showed that angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers (BB) could mitigate the decline in left ventricular (LV) ejection fraction (EF) during the first year of trastuzumab treatment.

Objectives We hypothesized that, over time, cardiac function would decline further and adverse changes in cardiac geometry would occur due to the aging of the population and prior treatment.

Methods The study enrolled 52 participants from the original MANTICORE trial cohort, with cardiac magnetic resonance (CMR) imaging conducted at a median of 6.5 years post randomization to treatment.

Results We found that, contrary to the hypothesis, participants maintained LV EF over the follow-up period. Specifically, the placebo group exhibited a recovery in LV EF to levels comparable with the treatment groups, suggesting no long-term differential impact on cardiac function. However, a significant reduction in LV mass was observed across all groups, the clinical implications of which remain unclear.

Conclusions The findings suggest that in a selected population receiving trastuzumab-based chemotherapy, extended cardiac imaging surveillance beyond one-year post-treatment may be unnecessary. We posit that the presence of HER2 overexpressing breast cancer influenced hypertrophic changes to cardiac geometry observed at baseline and one year, which resolved after completing HER2-blocking treatment. The study also highlights the need for further research to understand the significance of changes in cardiac geometry during and after breast cancer treatment.

Keywords HER2 therapy, Cancer survivorship, Health policy, Guidelines, Pharmacotherapy

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Background

Early breast cancer (EBC) remains the most common invasive cancer in North American women [1, 2]. With improvements in detection, systemic therapies and supportive care, long-term survival rates for early stage disease now approach 90% [3]. The discovery of the prognostic importance of human epidermal growth factor receptor 2 (HER2) amplification and overexpression where HER2 driven cancers were associated with pathologic high grade, early metastases and decreased overall survival [4], led to the development of anti-HER2 therapeutics. In the adjuvant setting, chemotherapy paired with trastuzumab significantly improves disease-free and overall survival [4, 5], but increases the risk of downstream cardiac toxicities. Relative risk of left ventricular (LV) dysfunction and heart failure (HF) in early survivorship are 5.1 and 1.8, respectively [6]. These effects contribute to the competing mortality risks from cardiovascular diseases (CVD) versus breast cancer recurrence [7, 8] observed as early as 3 years following treatment completion [8].

Current guidelines advise regular cardiac imaging during and 1 year following EBC treatment, but any subsequent cardiac imaging is at the discretion of the provider based on variable cardiovascular risk factors and treatment history [9]. The utility of extended surveillance is unknown due to the lack of long term, consistent surveillance studies in homogeneous populations receiving modern chemotherapy regimens. Moreover, after definitive treatment is complete, in many jurisdictions EBC patients are discharged to community provider surveillance where gaps in access and knowledge are prevalent [10, 11]. We previously conducted a randomized controlled trial of HF pharmacotherapy to prevent trastuzumab-related cardiotoxicity evaluated by cardiac MRI (Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research ([MANTICORE]) finding that LV ejection fraction (EF) decline can be prevented during the first year of treatment in HER2 overexpressing EBC [12, 13]. Cardiac magnetic resonance (CMR) remains the 'gold standard' in cardiac imaging with exceptional accuracy and reproducibility, permitting reduced sample sizes in clinical trials [14]. To characterize the longer-term cardiac effects of trastuzumab-based chemotherapy exposure, we used CMR to further study the participants of the original MANTICORE clinical trial. Given the long-term risk of HF in aging cancer survivors, we hypothesized that with increasing time from initial exposure to trastuzumab ± anthracyclines, LV adverse remodeling and dysfunction would occur.

Methods

Trial design

This cross-sectional study was conducted with approval of the University of Alberta Health Research Ethics Board Pro00063984. The parent trial has been previously reported [13]. In brief, we randomized 94 patients with HER2 overexpressing EBC receiving trastuzumab-based chemotherapy to perindopril, an angiotensin-converting enzyme inhibitor (ACEI), bisoprolol, a beta-blocker (BB), or placebo. At 1 year from trastuzumab initiation, we observed that both intervention arms attenuated decreases in LV EF on CMR and prevented interruptions in cancer therapy. Moreover, the study interventions were safe and well tolerated, with the majority of participants titrated to maximum clinically approved doses [13].

Participants

In this long-term follow-up study, enrolment was limited to the primary study site (Edmonton, Alberta Canada). 54 of the participants still alive agreed to participate with two scans being non-evaluable. Of the final 52 participants, 15, 16 and 21 had been randomized to placebo, perindopril and bisoprolol respectively in the parent study.

Methods

A health history was performed including cardiac medications initiated since MANTICORE study completion. Subjects underwent CMR using 1.5-T system (Aera, Siemens Healthcare, Erlangen, Germany) at a median of 6.5 years from the baseline scan. The same CMR imaging protocol as the original study was performed using end-inspiratory steady-state free precession cine imaging with retrospective ECG gating and reconstruction to 30 phases [13]. Core lab image analysis of these extended follow-up scans was performed using commercially available software (cvi42; Circle Cardiovascular Imaging Inc., Calgary, Canada; version 5.14.1) according to the Society of Cardiovascular Magnetic Resonance (SCMR) recommendations [15–17]. LV end-diastolic volume (EDV), LV end systolic volume (ESV), LV EF, and LV mass were calculated from a short axis stack of steady-state free precession cines by using a method of disks approach. Papillary muscles were included in the LV cavitary volume and excluded from LV mass. The primary outcome was the change in LV EF from baseline to extended follow-up. A secondary outcome measure was the prevalence of LV dysfunction at extended follow-up, defined as LV EF < 52% (CMR lower limit of normal for females according to the SCMR recommendations) [18].

Statistical methods

Continuous variables were expressed as mean ± standard deviation (SD) or median (Q1, Q3; categorical variables as counts [percentage]). Considering potential differences in variance and group size, comparisons between the randomized groups were performed using one-way Welch ANOVA, with post-hoc pair-wise comparisons performed using Games-Howell test. Repeated measures ANOVA was used to assess differences in changes over time of CMR characteristics between the randomization groups. Three time-points were included in the analysis: baseline, 1 year and extended follow-up. Assumption of sphericity for ANOVA was confirmed using Mauchly's test and univariable test results were reported. Multiple linear regression was used to explore the predictors of change in LV mass from baseline to extended follow-up, with predictors pre-specified based on known clinical relevance: age at baseline, randomization group, anthracycline therapy, left breast radiotherapy, and baseline LV mass.

Sample size and power calculations were not performed a priori for this long-term analysis of the original trial, as it involved follow-up data from participants who survived the initial trial period and agreed to undergo the extended follow-up CMR. However, after completing the analysis, a post hoc power calculation was conducted based on reasonable assumptions and demonstrated that the available sample size was adequate to detect the primary outcome with sufficient statistical power. To detect a clinically meaningful difference of 5% change in LV EF from baseline to extended follow-up between any two of the three randomization groups with a standard deviation of 8% using ANOVA, each of the three randomization groups would be required to have a minimum of 10 participants to achieve a statistical power of 80% at a two-tailed significance level of $\alpha = 0.05$. Statistical analyses were conducted using R version 4.3.1 and SPSS version 29, with p-value < 0.05 indicating statistical significance. Sample size calculations were performed using R package 'pwr'.

Results

Baseline characteristics of the study cohort and details of cancer therapy are shown in Table 1.. At the time of the extended follow-up, CMR participants were an average of 58.6 ± 8.6 years and a median of 6.5 years had elapsed since randomization (range 3.8 – 7.4 years). None reported cardiac symptoms and all were living independently with no physical limitations. No cardiac events in the intervening years were reported by any participant. Eighteen were still completing courses of tamoxifen or aromatase inhibitors. All received the intended relative dose intensity of trastuzumab, with no differences. Few cardiometabolic medications were initiated since primary study completion (Table 2).

Across the entire cohort, heart rate significantly decreased at the 1-year and extended follow-up CMR scans (-8 and -11 bpm), compared to baseline (Table 3). Regarding blood pressure, both systolic and diastolic blood pressure showed modest reduction at 1 year, followed by modest increase at the extended follow-up timepoint. Both LV EDV and LV ESV were significantly higher at 1 year vs baseline, then decreased towards baseline at extended follow-up while LV EF remained relatively stable at all 3 timepoints. Finally, LV mass was markedly decreased at extended follow-up from both baseline and 1-year scans.

When comparing randomization groups, there was no significant effect of randomization on changes in LV EDV, LV ESV, or LV mass (p-values for interaction between randomization and time = 0.75, 0.061, and 0.85) (Table 4). Randomization significantly affected changes in LV EF, where the placebo group showed significant decrease at 12 months and recovery to baseline values at follow up CMR. While the perindopril and bisoprolol groups showed stable LV EF at 12 months, both showed a statistically significant decline at 5 years, although the magnitude of the drop was modest (respective mean drop 4.0% and 2.6% vs baseline values) and within clinically acceptable limits. In the overall study cohort, 5 patients had an abnormal LV EF (< 52%) at time of extended follow-up, with no significant differences between randomization groups (2 in the placebo group, 2 in the perindopril group, and 1 in the bisoprolol group; $p = 0.60$). In a multivariable model for change in LV mass from baseline to extended follow-up, only a smaller baseline LV mass was significantly associated with a greater magnitude of change ($p < 0.001$; Table 5, Fig. 1). Traditional cardio-oncology risk factors including age, anthracycline-based regimen or left-sided radiotherapy had no influence.

Regarding non-participants, aside from recurrent disease or death, reasons for non-participation were loss to follow-up, did not express interest by returning the call and 1 with a metal implant. Participants lost to follow-up had moved to different provinces therefore their health record could not be viewed. Of those who remained in the province but did not participate, review of their records demonstrated no cardiac events or death from any cause with only one participant taking CVD medications (ramipril, rosuvastatin and metformin).

Discussion

The main finding of this study is that LV mass was significantly lower at extended follow-up compared to 1-year and baseline, however, contrary to our

Table 1 Patient characteristics and cancer treatment at baseline and extended follow-up

	Overall (*N* = 52)	Placebo (*N* = 15)	Perindopril (*N* = 16)	Bisoprolol (*N* = 21)	*p*-value
Age at baseline	52.4 ± 8.8	51.7 ± 8.0	51.6 ± 8.5	53.5 ± 9.8	0.76
Laterality (right vs left-sided)	24 (46%)	7 (47%)	6 (38%)	11 (52%)	0.67
Stage					0.50
1	20 (38%)	8 (53%)	7 (44%)	5 (24%)	
2	14 (27%)	3 (20%)	4 (25%)	7 (33%)	
3	18 (35%)	4 (27%)	5 (31%)	9 (43%)	
ER or PR positive	40 (77%)	13 (87%)	13 (81%)	14 (67%)	0.35
Coronary artery disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Arrhythmia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Peripheral vascular disease	1 (2%)	0 (0%)	0 (0%)	1 (5%)	0.999
Diabetes type 2	3 (6%)	0 (0%)	1 (6%)	2 (10%)	0.77
Dyslipidemia	2 (4%)	0 (0%)	1 (6%)	1 (5%)	0.999
Hypertension	2 (4%)	1 (7%)	1 (6%)	0 (0%)	0.51
Family history of premature cardiovascular disease					0.37
No	46 (88%)	15 (100%)	14 (88%)	17 (81%)	
Yes	4 (8%)	0 (0%)	2 (13%)	2 (10%)	
Unknown/adopted	2 (4%)	0 (0%)	0 (0%)	2 (10%)	
Alcohol use					0.78
None	13 (25%)	4 (27%)	4 (25%)	5 (24%)	
<1/day	37 (71%)	11 (73%)	12 (75%)	14 (67%)	
1-2/day	2 (4%)	0 (0%)	0 (0%)	2 (10%)	
Smoking history					0.84
Never	32 (62%)	8 (53%)	9 (56%)	15 (71%)	
Past	17 (33%)	6 (40%)	6 (38%)	5 (24%)	
Current	3 (6%)	1 (7%)	1 (6%)	1 (5%)	
Pack-year	0.0 (0.0, 9.3)	0.0 (0.0, 7.5)	0.0 (0.0, 11.3)	0.0 (0.0, 3.0)	0.48
Cancer treatment					
Trastuzumab relative dose intensity (%)*	102.6 (100.1, 106.5)	103.9 (101.0, 107.7)	103.1 (102.0, 106.6)	100.9 (98.8, 104.0)	0.14
Anthracyclines	7 (13%)	2 (13%)	3 (19%)	2 (10%)	0.87
Left radiotherapy	24 (46%)	8 (53%)	6 (38%)	10 (48%)	0.67

Values are mean ± SD or median (Q1, Q3), or number (column %)

* *Trastuzumab relative dose intensity is > 100% due to loading dose (8 mg/kg, 6 mg/kg maintenance)*

Table 2 Cardiac medications initiated since primary study completion

	Overall (*N* = 52)	Placebo (*N* = 15)	Perindopril (*N* = 16)	Bisoprolol (*N* = 21)	*p*-value
Beta blocker	2 (4%)	0 (0%)	1 (6%)	1 (5%)	0.999
ACEi /ARB	4 (8%)	1 (7%)	2 (13%)	1 (5%)	0.81
Diuretic	2 (4%)	0 (0%)	0 (0%)	2 (10%)	0.33
Diabetes treatment	1 (2%)	0 (0%)	0 (0%)	1 (5%)	0.999
Statin	4 (8%)	0 (0%)	2 (13%)	2 (10%)	0.54
Calcium channel blocker	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

Values are number (column %)

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 3 Change in vital signs and CMR characteristics over time, all participants

	Baseline	1 Year	Extended follow-up	Baseline-extended Followup	1 year -extended Followup	ANOVA p for time*
Vital signs						
Heart rate, bpm	76.6 ± 12.8	68.8 ± 13.8†	66.0 ± 12.6†	**< 0.001**	0.13	**< 0.001**
Systolic BP, mmHg	124.6 ± 12.7	118.6 ± 14.6†	127.6 ± 17.8‡	0.75	**< 0.001**	**< 0.001**
Diastolic BP, mmHg	74.8 ± 9.7	72.2 ± 11.2	79.0 ± 11.2‡	0.14	**0.003**	**0.002**
CMR measures						
LV EDV, mL	123.6 ± 25.1	137.7 ± 26.7†	123.0 ± 25.1‡	0.999	**< 0.001**	**< 0.001**
LV ESV, mL	47.4 ± 10.9	56.2 ± 14.5†	50.9 ± 12.6†‡	**0.021**	**< 0.001**	**< 0.001**
LV EF, %	61.6 ± 4.4	59.6 ± 5.4†	58.8 ± 5.3†	**< 0.001**	0.999	**< 0.001**
LV mass, g	91.6 ± 15.0	92.5 ± 14.5	65.7 ± 12.7†‡	**< 0.001**	**< 0.001**	**< 0.001**

Values are mean ± SD

BP: blood pressure; bpm: beats per minute; CMR: cardiac MRI; LV: left ventricle; EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume

All variables are complete in all patients with exception of the following at extended follow-up: missing SBP and DBP in 10 patients

* *p*-value from repeated measures ANOVA; † *p*-value < 0.05 versus baseline; ‡ *p*-value < 0.05 versus 1 year

Table 4 Comparison of the changes in CMR characteristics of LV by randomization groups

	Overall (*N* = 52)	Placebo (*N* = 15)	Perindopril (*N* = 16)	Bisoprolol (N = 21)	$p_{intercation}$*	p†
LV EF					**0.011**	
Baseline	61.6 ± 4.4	60.9 ± 4.4	62.4 ± 5.3	61.5 ± 3.8		0.64
1 year	59.6 ± 5.4	56.5 ± 5.1	60.0 ± 5.9	61.5 ± 4.4‖		**0.019**
Extended FU	58.8 ± 5.3	59.1 ± 4.9	58.4 ± 5.9	58.9 ± 5.2		0.94
Change from baseline to extended FU	-2.8 ± 4.6‡	-1.9 ± 4.1	-4.0 ± 4.6‡	-2.6 ± 4.8‡		0.42
Change from 1 year to extended FU	-0.8 ± 5.3	2.6 ± 5.4	-1.6 ± 3.8	-2.6 ± 5.3‖		**0.010**
LV EDV					0.75	
Baseline	123.6 ± 25.1	130.3 ± 30.4	117.3 ± 20.9	123.7 ± 23.8		0.36
12-month	137.7 ± 26.7	140.9 ± 24.7	135.1 ± 28.2	137.4 ± 27.8		0.84
Extended FU	123.0 ± 25.1	124.8 ± 23.2	120.8 ± 28.2	123.4 ± 24.9		0.91
Change from baseline to extended FU	-0.6 ± 18.2	-5.5 ± 26.6	3.6 ± 14.8	-0.3 ± 12.5		0.39
Change from 1 year to extended FU	-14.7 ± 19.0§	-16.1 ± 18.6§	-14.3 ± 22.0§	-14.0 ± 17.6§		0.94
LV ESV					0.061	
Baseline	47.4 ± 10.9	50.8 ± 12.8	44.2 ± 10.4	47.4 ± 9.6		0.25
1 year	56.2 ± 14.5	61.8 ± 14.6	54.8 ± 15.3	53.2 ± 13.2		0.19
Extended FU	50.9 ± 12.6	51.1 ± 11.0	50.9 ± 16.1	50.7 ± 11.1		0.999
Change from baseline to extended FU	3.5 ± 9.0‡	0.3 ± 10.2	6.8 ± 9.0‡	3.3 ± 7.5		0.13
Change from 1 year to extended FU	-5.3 ± 10.8§	-10.7 ± 12.0§	-3.8 ± 9.4	-2.5 ± 9.9		0.06
LV mass					0.85	
Baseline	91.6 ± 15.0	90.5 ± 16.1	92.3 ± 12.5	91.8 ± 16.4		0.95
1 year	92.5 ± 14.5	93.2 ± 15.3	92.1 ± 14.4	92.2 ± 14.6		0.97
Extended FU	65.7 ± 12.7	64.9 ± 14.3	67.0 ± 12.1	65.3 ± 12.4		0.89
Change from baseline to extended FU	-25.9 ± 8.9‡	-25.6 ± 8.9‡	-25.3 ± 9.6‡	-26.5 ± 8.8‡		0.92
Change from 1 year to extended FU	-26.7 ± 9.8§	-28.3 ± 11.4§	-25.1 ± 10.2§	-26.9 ± 8.6§		0.66

EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; FU: follow-up; LV: left ventricle; $p_{interacation}$: p-value for interaction between randomization group and time

* *p*-value from repeated measures ANOVA

† *p*-value for one-way ANOVA for comparison between randomization groups

‡ *p*-value < 0.05 versus baseline

§ *p*-value < 0.05 versus 1 year

‖ *p*-value < 0.05 versus placebo

Table 5 Multiple linear regression model for prediction of change in left ventricular mass from baseline to extended follow-up

Characteristic	*β* coefficient (95% CI)*	p
Randomization group		
Placebo	Reference group	
Perindopril	0.514 (-5.196–6.224)	0.86
Bisoprolol	-0.337 (-5.671–4.997)	0.90
Age at baseline, y	-0.118 (-0.377–0.140)	0.36
Anthracyclines	0.053 (-6.651–6.757)	0.99
Left breast radiotherapy	-2.451 (-7.041–2.138)	0.29
Baseline LV mass, g	-0.330 (-0.481-[-0.179])	**<0.001**

β: beta; CI: confidence interval; LV: left ventricle

* Values are β-coefficients with 95% CI in parenthesis

hypothesis LV EF was maintained at the extended follow-up timepoint. To the best of our knowledge, this is the longest follow up of a cardio-oncology interventional trial in a homogeneous HER2-overexpressisng breast cancer population. At a median follow-up of 6.5 years we observed increased LV EF in the placebo group to values comparable to the treatment groups, indicating recovery from the 12-month decline. Current American Society of Clinical Oncology guidelines have no surveillance recommendations for asymptomatic patients beyond 12 months of treatment completion [19] while European Society for Medical Oncology guidelines suggest cardiac assessment could be performed at 2 years post-treatment, influenced by the anthracycline dose administered [20]. The European Society of Cardiology advises that echocardiography be performed 1, 3 and 5 years after completion of cardiotoxic chemotherapy and consideration of every 5 years thereafter in asymptomatic, very high-risk adult survivors [21]. Our center uses anthracyclines infrequently in the HER2 overexpressing population, owing to the favorable risk to benefit ratio of the BCIRG006 docetaxel/carboplatin/trastuzumab combination [4, 22]. Left-sided radiotherapy did not influence our findings. Our province-wide electronic health record allowed us to verify that no selection bias existed between participants and non-participants. At the extended follow-up CMR, 5 participants had LV EF < 52%, with no significant differences between randomization groups and with only 3 having dropped LV EF to < 50%. Taken together, our results suggest that in many patients receiving trastuzumab-based chemotherapy, cardiac imaging beyond one year is not necessary [23].

Although our observations are reassuring from a cardiac performance perspective, we have previously shown that a cancer diagnosis conveys high risk of other cardiovascular events. Among 4,519,243 adults residing in Alberta Canada, a cancer diagnosis conveys HR of 1.33 for cardiovascular mortality, 1.01 for myocardial infarction, 1.44 for stroke, 1.62 for heart failure, and 3.43 for pulmonary embolism compared with participants without cancer [24]. Accordingly, lifelong screening for cardiovascular diseases among cancer survivors after treatment should be considered. To date, aside from obesity and smoking, baseline risk factors incorporated in CVD risk prediction models are relative or absolute contraindications for breast cancer chemotherapy [21, 25]. Nonetheless, all current guidelines advise ongoing management of risk factors and healthy lifestyle promotion, accepting that increased risk of CVD is persistent [20]. Our study participants had few risk factors at any timepoint and had ready access to care living in a province where health care and

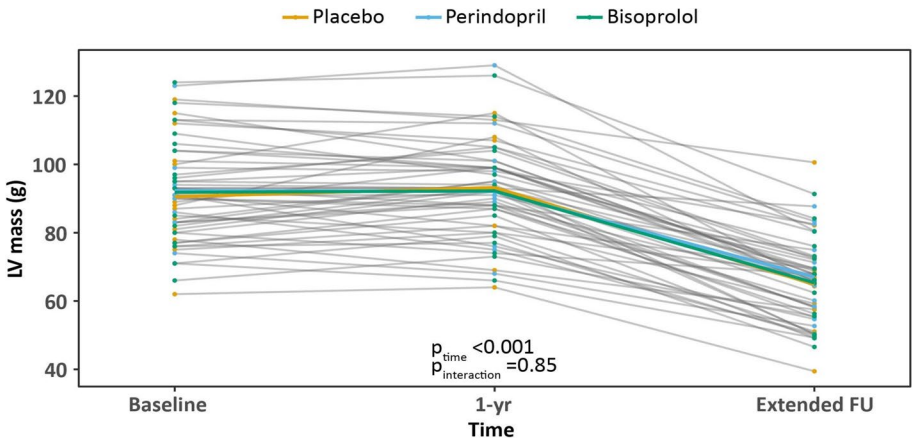

Fig. 1 Change in left ventricular mass assessed by CMR. FU: follow-up; LV: left ventricle; ptime: *p*-value for change in CMR parameter over time; pinteraction: p-value for interaction between randomization group and time

prescriptions are free of charge. Higher risk survivors living in other jurisdictions may warrant closer surveillance and regular, sensitive serial cardiac imaging.

At the 1-year scan we observed considerable enlargement of chamber volumes in all 3 randomization groups compared to baseline and normative values (normal values for LV EDV and ESV 112 ± 21 ml and 39 ± 12 ml for females) [18] despite normal mean LV EF. In a prior study of exercise to attenuate trastuzumab-related cardiac remodeling ($n = 17$) using CMR we observed LV EDV, LV ESV and LV mass increase despite training, whereas LVEF decreased from baseline to post-intervention (all p-values < 0.05). However, this study was short and only focused on the first 4 months of trastuzumab exposure. In our TITAN RCT examining the effect of one year of cardiac rehabilitation-modeled care in high risk breast cancer chemotherapy (anthracycline and/or trastuzumab-based) using CMR, LV geometry changes were minor and no significant differences were observed between the treatment arms [26]. In the PRADA study randomizing women receiving anthracycline chemotherapy (± trastuzumab) in a 2 × 2 design of candesartan or metoprolol [27], at 2 years the attenuating effect of candesartan on LV EF did not persist beyond the 1-year primary study outcome using CMR [28]. As the treatment/placebo arms were collapsed in the 2-year analysis (candesartan/placebo or metoprolol/placebo) it is difficult to interpret the findings but no significant changes were observed in LV EDV, LV ESV or LV mass [28]. CMR is the gold standard in imaging, thus used regularly in our research of cardiac and other physiology [12, 14, 29]. Taken together, this work represents our best and longest-term study of cardiac evolution during and after trastuzumab-based chemotherapy.

At the extended follow-up CMR we observed a marked reduction of LV mass in all randomization groups compared to both baseline and 1-year. Alongside our findings of normal LV EF in these survivors, the clinical significance of reduced LV mass is unknown. Although we did not study potential mechanism(s), it may be the result of sedentary deconditioning and concomitant decrease in LV mass [30]. However, recent interest has focused on the bidirectional relationship of cancer on the heart prior to cancer treatment, where the presence of cancer can affect cardiomyocytes and presence of cardiovascular diseases can stimulate tumor cell proliferation [31, 32]. We found that breast tumor cells secrete soluble factors including big endothelin-1 (ET-1) causing detrimental alterations in cardiomyocyte pathways inducing LV hypertrophy. Not only is ET-1 an important factor for the progression and metastasis of breast cancer, ET-1 is an established cardiomyocyte pro-hypertrophic factor. We showed that circulating ET-1 levels in early breast cancer patients were positively correlated with LV volume and mass [33, 34]. Given the dramatic decrease in LV mass at extended follow-up in all randomization groups compared to baseline and 1-year in this study, it is possible that their homogeneous HER2 overexpressing status played a particular role. Earlier work in transgenic models has demonstrated that increased erbB2 expression in the heart can induce a phenotype consistent with hypertrophic cardiomyopathy without heart failure [35]. Moreover, inhibiting his pathway may reverse this process. We posit that the presence of HER2 overexpressing breast cancer influenced hypertrophic changes to cardiac geometry observed at baseline and 1 year, which resolved after completing HER2-blocking treatment. This is also supported by our previous study of CMR-based phenotype in breast cancer and lymphoma patients prior to initiation of chemotherapy, compared to healthy volunteers [36]. Here, cancer patients exhibited significantly higher body surface area-indexed LV mass versus healthy age-matched controls. Future work should focus on the potential of breast cancer (and other cancer) subtypes to influence downstream cardiovascular effects, beyond simply the drugs or radiotherapy administered.

Limitations

We observed a total of 5 cardiotoxicity cases in our cohort. MANTICORE was conducted in a country where cancer survivors have ready access to health care and medication coverage. Our observations may not fully apply to survivors in other jurisdictions with varying access to surveillance and care.

The grant funds were not sufficient to collect and analyze blood biomarkers as performed in our parent study [12]. It is possible that such data could have identified those at risk of other cardiovascular diseases, as observed in our large provincial cohort [24]. Although our sample size is small by other comparators, CMR is a well-established and precise imaging method allowing greatly reduced sample sizes due to its accuracy [14] [37], Our sample size and power calculations were performed post hoc, rather than a priori. However, these calculations were based on reasonable assumptions rather than our observed study data and demonstrated that our small sample size was adequate to detect the differences between the three randomization groups with respect to the primary outcome of change in LV EF, with a statistical power of 80%.

We acknowledge the limitation that the core lab CMR image analysis of the baseline and short-term follow-up studies involving different observers and software (Syngo; Siemens Healthcare) versus the extended follow-up analysis (cvi42 software). This might have influenced some of our findings, especially LV mass that has been

reported by some studies to be more variable than other cine-based volume and EF measures [38, 39]. However, the magnitude of observed differences in LV mass from each of the baseline and 1-year follow-up to extended follow-up (mean difference 26–27 g) exceeds most of the reported wide 95% limits of intra- or inter-observer agreement in previous studies [38]. Additionally, one study assessing inter-vendor differences in LV volume, mass, and EF calculations, demonstrated that three different analysis platforms did not influence CMR metrics [40]. We excluded the papillary muscles from LV mass calculations which has been shown to improve reproducibility [41]. Finally, Alberta has the benefit of a province-wide CMR research team who have developed consistent core laboratory protocols for over a decade using different analysis software [42–44]. The value of high-quality training in CMR image analysis has been shown to significantly reduce intra- and inter-observer variability [39]. In other jurisdictions, lack of such a program could present a study limitation.

Conclusion

At extended follow-up after trastuzumab-based chemotherapy completion (median 6.5 years following cardio-protective treatment randomization) LV EF was normalized in this subset of MANTICORE study participants. LV EDV and LV ESV increased at 1 year and approached baseline levels at extended follow-up. At the latter time point, LV mass was markedly reduced from baseline and 1-year scans. Longer term surveillance may be warranted in some high-risk breast cancer populations. The significance of altered cardiac geometry along the breast cancer treatment and survivorship trajectory warrants further study.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
BB	Beta-blocker
CMR	Cardiac MRI
EBC	Early breast cancer
EDV	End-diastolic volume
EF	Ejection fraction
ESV	End-systolic volume
HER2	Human epidermal growth factor receptor 2
LV	Left ventricle
MANTICORE	Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research
SCMR	Society of Cardiovascular Magnetic Resonance

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40959-025-00313-w.

Supplementary Material 1.

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Authors' contributions

Authors' contributions: EP conceived of the study and design; EP, ES, DL were involved in the acquisition, analysis, interpretation of data; RBT and DIP were involved in the development of CMR protocol; EP, DL, MH, JRM and DIP developed or substantively revised the manuscript. All authors have approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted with approval of the University of Alberta Health Research Ethics Board Pro00063984.

Competing interests

The authors declare no competing interests.

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