CV Strategies to Mitigate Cardiotoxicity Pharmacologic Therapy – Heart Failure Medications and Statins and For How Long

Ileana L. Piña, MD, MPH

Professor of Medicine and Epidemiology/Population Health
Albert Einstein College of Medicine
Associate Chief for Academic Affairs – Cardiology
Head Clinical Trials, Cardiology
Montefiore-Einstein Medical Center
Bronx, NY

Heart Failure due to Chemotherapeutic Agents: Issues

- Can patients at risk be identified prior to chemotherapy
- Can very early or incipient cardiomyopathy be identified
- Once identified, will biomarkers indicate severity or prognosis.
  - Used to guide therapy?
- Can HF therapy prevent the remodeling? HFpEF vs. HFrEF
  - Onset of symptoms
  - Cardiac mortality
- How is the HF treated?
  - Standard Guideline Directed Care?
    - *Where is the evidence?*
    - *If function improves, what to do with Rx?*
    - *What about statins and exercise*

Risk Factors

Can occur early (acute) or late > 1 year post chemoRx (most common)

Anthracycline

- Older age
- Female gender
- Hypertension and other risk fx for CVD
- Pre-existing cardiac disase
- Mediastinal radiation
- Cumulative anthracycline dose

Trastuzumab

- Adjuvant anthracyclines
- Older age
- Hypertension
- Diabetes
- CAD
- A fib
- Renal insufficiency

Nohria. ACC 2016

Non-invasive Imaging

- Echocardiography has been the traditional tool +-MUGA to detect LV dysfunction
  - Manifest or early?
- Global Longitudinal Strain and strain rate (GLS) assessed using automated 2D-speckle-tracking echocardiography (STE) --recent technique for detecting and quantifying subtle disturbances in (LV) systolic function. more reproducible than ejection fraction
- Strain rate and deceleration time to detect early diastolic filling.

Table 2 Recommended cardio-oncology echocardiogram protocol

Standard transthoracic echocardiography
- In accordance with ASE/EAE guidelines and IAC-Echo

2D strain imaging acquisition
- Apical three-, four-, and two-chamber views
  - Acquire ≥3 cardiac cycles
- Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
  - Frame rate between 40 and 90 frames/sec or ≥40% of HR
- Aortic VTI (aortic ejection time)

2D strain imaging analysis
- Quantify segmental and global strain (GLS)
- Display the segmental strain curves from apical views in a quad format
- Display the global strain in a bull's-eye plot

2D strain imaging pitfalls
- Ectopy
- Breathing translation

3D imaging acquisition
- Apical four-chamber full volume to assess LV volumes and LVEF calculation
- Single and multiple beats optimizing spatial and temporal resolution

Reporting
- Timing of echocardiography with respect to the IV infusion (number of days before or after)
- Vital signs (BP, HR)
- 3D LVEF/2D biplane Simpson's method
- GLS (echocardiography machine, software, and version used)
- In the absence of GLS, measurement of medial and lateral s′ and MAPSE
- RV: TAPSE, s′, FAC

Plana JC, Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after CancerTherapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27:911-39

Echo Guidelines

- A decreased LVEF at baseline or after anthracyclines is associated with higher rates of cardiac events on follow-up.
- Although it has been suggested that alterations in LV diastolic function (as evaluated by Doppler indices of mitral inflow and e′ by pulsed DTI) precede alterations in systolic function, the evidence does not support the role of these indices for the prediction of later CTRCD.

Detecting early

- Myocardial deformation (strain) can be measured using DTI or 2D STE. The latter is favored because of a lack of angle dependency.
- GLS is the optimal parameter of deformation for the early detection of subclinical LV dysfunction.
- Ideally, the measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements, a relative percentage reduction of GLS of <8% from baseline appears not to be meaningful, and those >15% from baseline are very likely to be abnormal.
- When applying STE for the longitudinal follow-up of patients with cancer, the same vendor-specific ultrasound machine should be used.

Noninvasive Cardiac Imaging

Patients with suspected or new-onset HF, or those presenting with acute decompensated HF, should undergo a chest x-ray to assess heart size and pulmonary congestion, and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patients' symptoms.

A 2-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function.

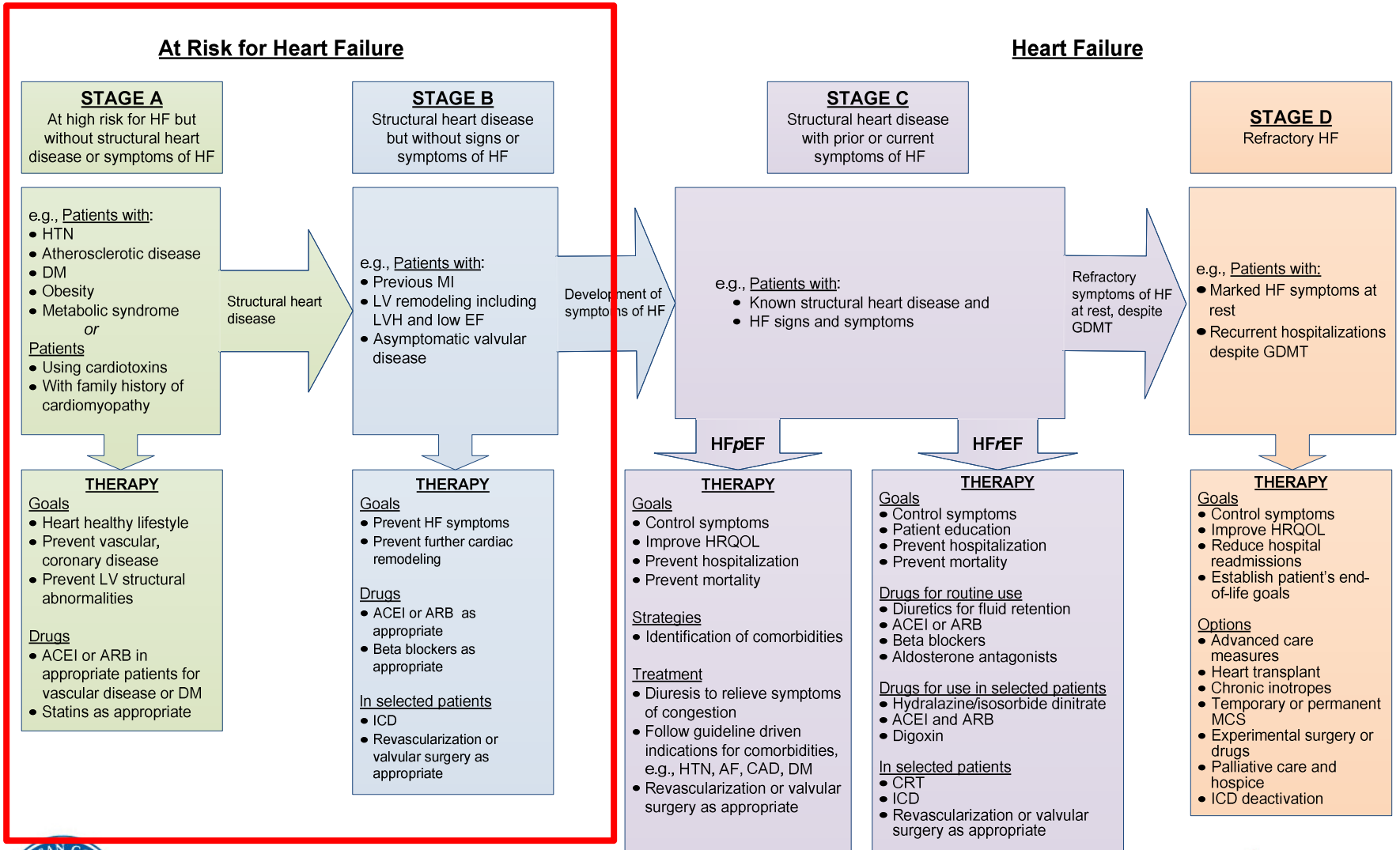
Repeat measurement of EF and measurement of the severity of structural remodeling are useful to provide information in patients with HF who have had a significant change in clinical status; who have experienced or recovered from a clinical event; or who have received treatment, including GDMT, that might have had a significant effect on cardiac function; or who may be candidates for device therapy.

Stage A

Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.

Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.

Stages, Phenotypes and Treatment of HF



(*Circulation*. 2006;114:2474-2481.)

Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

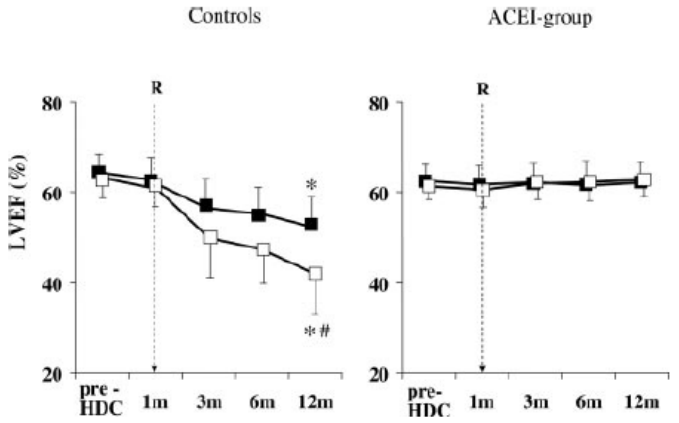
Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

TABLE 3. Echocardiographic Parameters During the Study Period

	Baseline	Randomization	3 mo	6 mo	12 mo	*P**
EDV, mL						
ACEI group	101.7±27.4	100.2±26.1	98.1±27.8	97.5±24.5	101.1±26.4	0.045
Control subjects	103.2±20.1	103.9±21.0	106.4±21.0	107.1±23.9	104.2±25.6	
ESV, mL						
ACEI group	38.6±10.8	38.7±10.4	37.3±10.9	37.4±10.3	38.5±11.2	<0.001
Control subjects	38.8±10.2	40.5±12.2	49.8±17.6	51.8±16.9	54.4±20.1†	
LVEF, %						
ACEI group	61.9±2.9	61.1±3.2	61.9±3.3	61.6±3.9	62.4±3.5	<0.001
Control subjects	62.8±3.4	61.8±4.3	54.2±8.1	51.9±7.9	48.3±9.3†	

TABLE 4. Cardiac Events in the Study Groups

	Total (n=114), n (%)	ACEI Group (n=56), n (%)	Control Subjects (n=58), n (%)	*P*
Sudden death	0 (0)	0 (0)	0 (0)	1.0*
Cardiac death	2 (2)	0 (0)	2 (3)	0.49*
Acute pulmonary edema	4 (3)	0 (0)	4 (7)	0.07*
Heart failure	14 (12)	0 (0)	14 (24)	<0.001
Arrhythmias requiring treatment	11 (10)	1 (2)	10 (17)	0.01
Cumulative events	31	1	30	<0.001

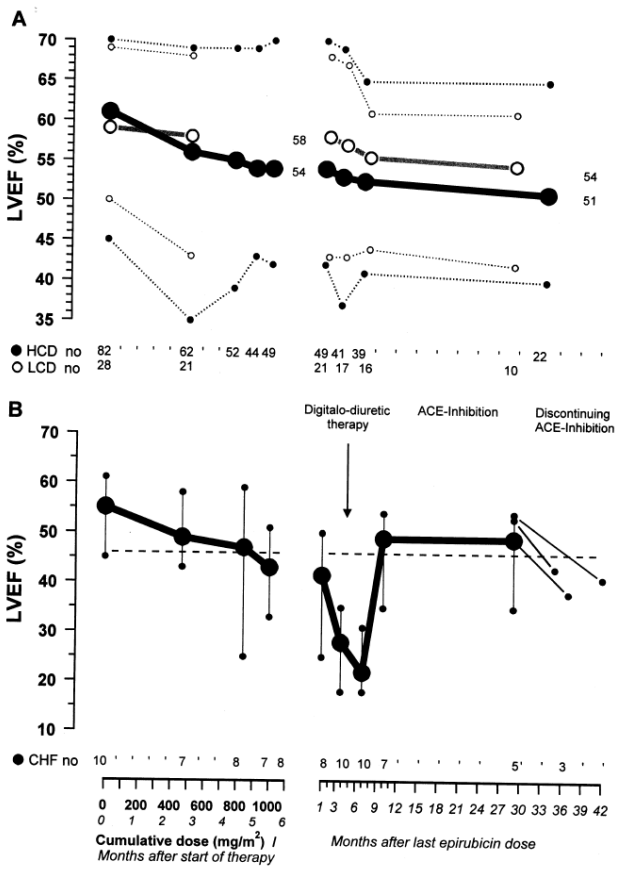


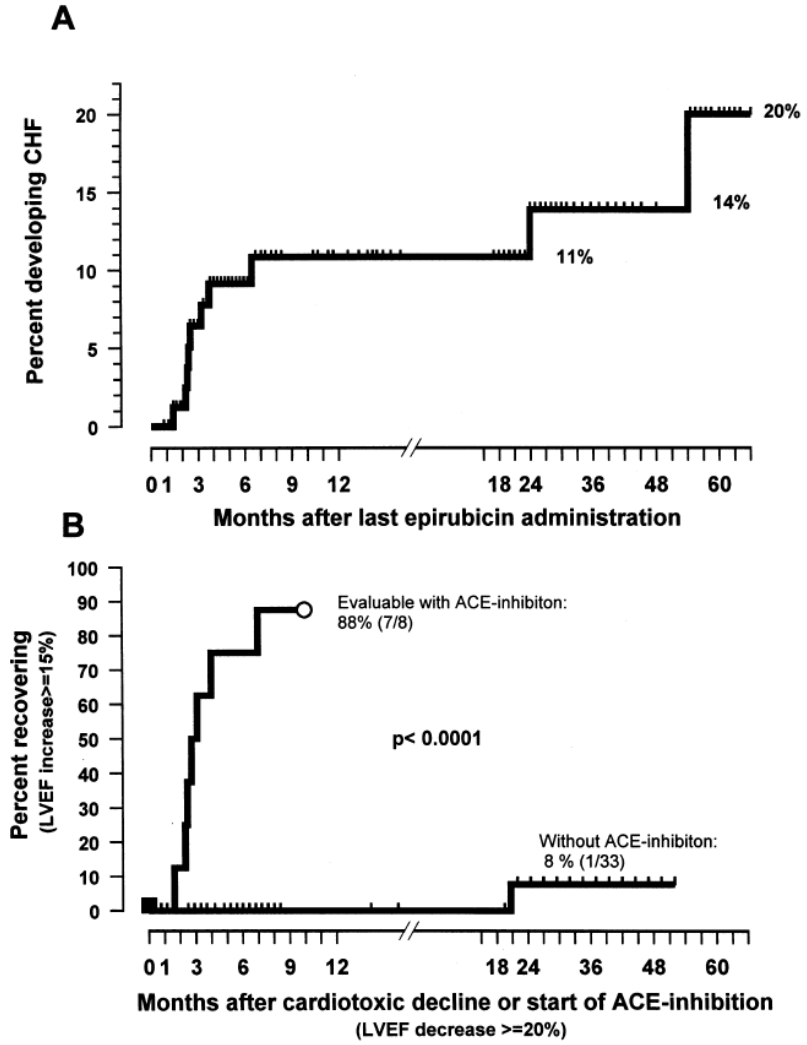
Original article

Annals of Oncology 13: 699–709, 2002
DOI: 10.1093/annonc/mdf132

Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients

B. V. Jensen[1]*, T. Skovsgaard[1] & S. L. Nielsen[2]





ACEI therapy: In Pediatric Cancer

Table 4. Left Ventricular End-Systolic Wall Stress Using a Piecewise Linear Model

Time Periods	No. of Observations in Model*	Enalapril Slope†	SE	Placebo Slope	SE	*P*
LVESWS year 1	261	−8.62	3.37	1.66	3.22	.036
LVESWS year 2 to end	781	−0.30	1.01	0.49	0.89	.560

NOTE. Adjusted for age at treatment, anthracycline dose, follow-up time, heart irradiation, and sex.
*Patients without postbaseline evaluations were excluded from analysis.
†Slope refers to the estimated change in LVESWS per year.

- **The reduction in LVESWS associated with enalapril was largely due to a reduction in endsystolic pressure.**
- **model -- the first-year reduction in end-systolic pressure in the enalapril group was 7.2 *vs.* 5.87mmHg in placebo group (*P* .0006).**
- **no significant difference end systolic posterior wall thickness over the length of the study.**

Silber JH et al. Enalapril to Prevent Cardiac Function Decline in Long-Term Survivors of Pediatric Cancer Exposed to Anthracyclines. J Clin Oncol 2004; 22:820-828

RCTs of Prophylactic Treatment With Neurohormonal Antagonists to Prevent Anthracycline- and Trastuzumab-Induced Cardiomyopathy

Positive Trials								
Kalay et al.[29]	Anthracycline	Nebivolol (5 mg)	27	18	6 months	Mean ejection fraction at 6 months	Echo	63.8 ± 3.9% vs. 57.5 ± 5.6%, p = 0.01
Bosch et al.[30]	Anthracycline	Enalapril (8.6 ± 5.9 mg) + Carvedilol (23.8 ± 17 mg)	45	45	6 months	Δ ejection fraction from baseline)	Echo; cardiac magnetic resonance imaging	-0.17 vs. -3.28, p = 0.04 0.36 vs. -3.04, p = 0.09
Kalay et al.[29]	Anthracycline	Carvedilol (12.5 mg)	25	25	5.2 ± 1.2 months	ejection fraction < 50%	Echo	RR: 0.2 (0.03-1.59)
Kanbabai et al.[31]	Anthracycline	Enalapril (17.94 ± 4.10 mg)	34	35	6 months	Δ ejection fraction from baseline @ 6 mths	Echo	0.55 vs. -13.3, p < 0.001
Cardinale et al.[32]	Anthracycline	Enalapril (16±6 mg)	56	58	12 months	↓ ejection fraction >10% from baseline and <50%	Echo	0 vs. 43%, p<0.001
Akpek et al.[33]	Anthracycline	Spironolactone (25 mg)	43	40	6 months	Δ ejection fraction from baseline @ 6 mths	Echo	67 ± 6.1→65.7 ± 7.4 vs. 67.7 ± 6.3→53.6 ± 6.8, p < 0.001
Gulati et al.[34]	Anthracycline ± Trastuzumab	Candesartan (32 mg)	60	60	10-61 weeks	Δ ejection fraction from baseline	Cardiac magnetic resonance imaging	-0.8 vs. -2.6%, p = 0.026

Negative Trials								
Gulati et al.[34]	Anthracycline ± Trastuzumab	Metoprolol (100 mg)	58	62	10-61 weeks	Δ ejection fraction from baseline	Cardiac magnetic resonance imaging	-1.6 vs. -1.8%, p=0.77
Georgakopoulos et al.[35]	Anthracycline	Metoprolol	40	42	31 months	HF	Clinical	1 vs. 3, p = not significant
Georgakopoulos et al.[35]	Anthracycline	Enalapril	40	43	31 months	HF	Clinical	2 vs. 3, p = not significant
Pituskin et al.[36]	Trastuzumab	Perindopril (8 mg)	33	30	12 months	Δ LV end diastolic volume index from baseline	Cardiac magnetic resonance imaging	7 vs. 4 ml/m^2, p = not significant
Pituskin et al.[36]	Trastuzumab	Bisoprolol (10 mg)	31	30	12 months	Δ LV end diastolic volume index from baseline	Cardiac magnetic resonance imaging	8 vs. 4 ml/m^2, p = not significant
Nakamae et al.[37]	Anthracycline	Valsartan (80 mg)	20	20	7 days	Δ ejection fraction from baseline @ 7 days	Echo	p = 0.07 vs. p = 0.07

A.Nohria. http://www.acc.org/latestincardiology/articles/2016/09/29/13/25/preventionofcardiomyopathyinpatientswithcancer?w_nav=Tab

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Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

Nihat Kalay, MD,* Emrullah Basar, MD,* Ibrahim Ozdogru, MD,* Ozlem Er, MD,† Yakup Cetinkaya, MD,* Ali Dogan, MD,* Tugrul Inanc, MD, Abdurrahman Oguzhan, MD,* Namik Kemal Eryol, MD,* Ramazan Topsakal, MD,* Ali Ergin, MD*

Table 1. Baseline Characteristics of Patients

	Carvedilol (n = 25)	Control (n = 25)	p Value
Age (yrs)	46.8 ± 14	49.0 ± 9.8	NS
Female (%)	88	84	NS
BMI (kg/m^2)	1.75 ± 12.7	1.71 ± 21.1	NS
Baseline LVEF (%)	70.6 ± 8.0	69.7 ± 7.3	NS
LVDd (mm)	47.7 ± 5.3	45.5 ± 4.8	NS
LVSd (mm)	31.4 ± 5.0	30.2 ± 4.7	NS
Type of cancer, n (%)			
Breast	18 (72)	16 (64)	NS
Lymphoma	4 (16)	5 (20)	NS
Other	3 (12)	4 (16)	NS
CT strategy, n (%)			
CEF/CAF	17 (68)	16 (64)	NS
CHOP/ABVD	4 (16)	4 (16)	NS
Other	4 (16)	5 (20)	NS
Total adriamycin dose (mg/m^2)	525.3	513.6	NS
Total epirubicin dose (mg/m^2)	787.9	770.4	NS
Number of cycles	6	6	
Control echocardiography time (months)	5.0 ± 1.1	5.4 ± 1.3	NS

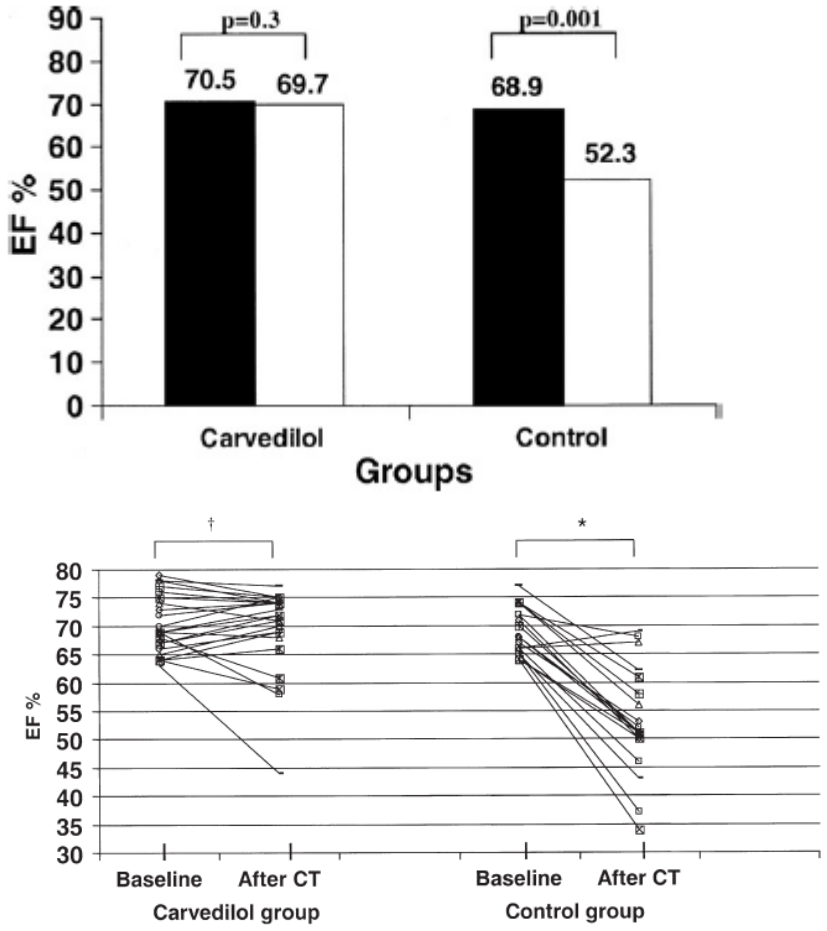

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Table 2. Results of Doppler Examination on Carvedilol Group

	Baseline	After CT	p Value
Peak E velocity (cm/s)	80.2 ± 18.4	70.5 ± 17.1	0.03*
Peak A velocity (cm/s)	75.1 ± 13.9	73.9 ± 14.3	0.79
E/A ratio	1.08 ± 0.2	0.98 ± 0.2	0.23
IVRT (ms)	64.3 ± 19.9	75.6 ± 17.8	0.1
IVCT (ms)	57.6 ± 19.6	72.3 ± 23.1	0.1

*$p < 0.05$ considered statistically significant. Data expressed as mean ± SD.
CT = chemotherapy; IVCT = isovolemic contraction time; IVRT = isovolumic relaxation time.

Table 3. Results of Doppler Examination on Control Group

	Baseline	After CT	p Value
Peak E velocity (cm/s)	69.8 ± 15.2	58.4 ± 17.9	0.019*
Peak A velocity (cm/s)	68.7 ± 13.0	68.0 ± 14.2	0.79
E/A ratio	1.03 ± 0.2	0.87 ± 0.2	0.02*
IVRT (ms)	72.7 ± 16.1	72.7 ± 2.0	0.9
IVCT (ms)	73.3 ± 18.7	78.8 ± 18.3	0.5

*$p < 0.05$ considered statistically significant. Data expressed as mean ± SD.
CT = chemotherapy; IVCT = isovolemic contraction time; IVRT = isovolemic relaxation time.

European Journal of Heart Failure (2015) **17**, 81–89
doi:10.1002/ejhf.196

Protective effects of spironolactone against anthracycline-induced cardiomyopathy

Mahmut Akpek[1]*, Ibrahim Ozdogru[1], Omer Sahin[1], Mevlude Inanc[2], Ali Dogan[1], Cevat Yazici[3], Veli Berk[2], Halit Karaca[2], Nihat Kalay[1], Abdurrahman Oguzhan[1], and Ali Ergin[1]

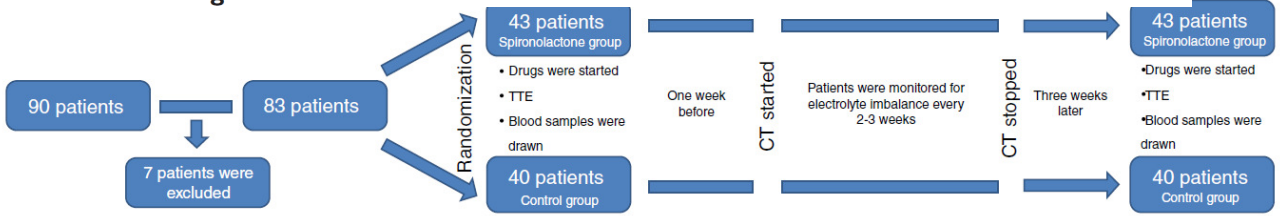
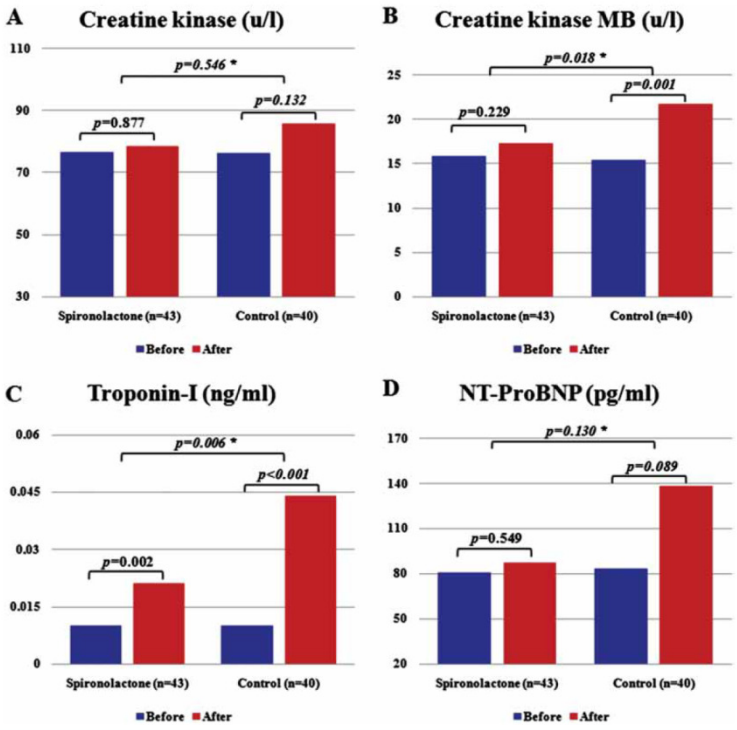


Figure 1 Study flow. CT, chemotherapy; TTE, transthoracic echocardiography.



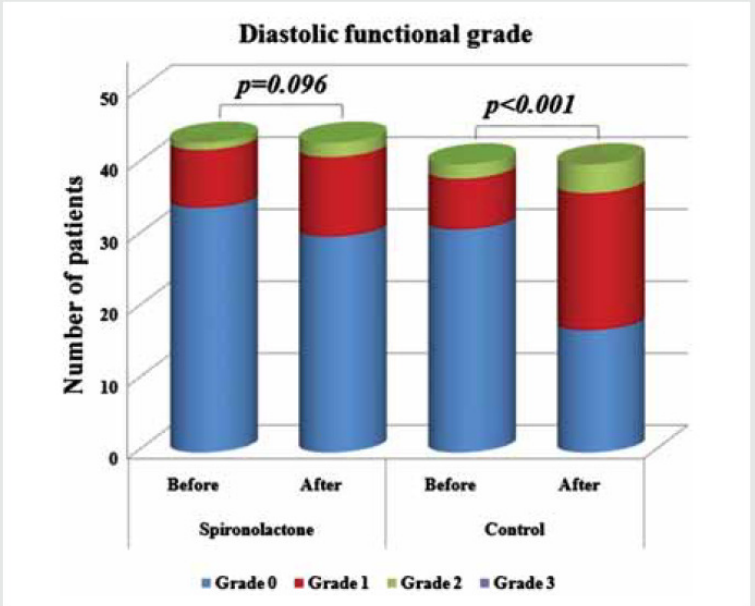


Figure 5 Changes in diastolic functional grade.

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Protective effects of spironolactone against anthracycline-induced cardiomyopathy

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Table 3 Cardiac and oxidative biomarkers

	Spironolactone group ($n = 43$)			Control group ($n = 40$)			
	Before	After	*P*-value	Before	After	*P*-value	*P*-value*
Creatine kinase (U/L)	74 (55–77)	69 (53–98)	0.877	70 (55–98)	87 (70–102)	0.132	0.546
Creatine kinase-MB (U/L)	15.8 ± 5.3	17.3 ± 6.0	0.229	15.4 ± 6.8	21.7 ± 9.5	0.001	0.018
Troponin-I (ng/mL)	0.010 (0.001–0.020)	0.015 (0.004–0.032)	0.002	0.010 (0.001–0.021)	0.026 (0.010–0.053)	<0.001	0.006
NT-proBNP (pg/mL)	71 (48–125)	85 (51–100)	0.549	70 (56–72)	100 (89–138)	0.089	0.130
TAC (μmol/L)	286.1 ± 44.7	275.4 ± 37.6	0.083	295.0 ± 47.5	250.4 ± 19.7	<0.001	0.001
TOC (μmol/L)	449.7 ± 222.5	487.0 ± 211.0	0.449	465.0 ± 256.4	594.8 ± 372.1	0.057	0.259
OSI	1.61 ± 0.80	1.79 ± 0.79	0.282	1.60 ± 0.90	2.37 ± 1.45	0.004	0.055

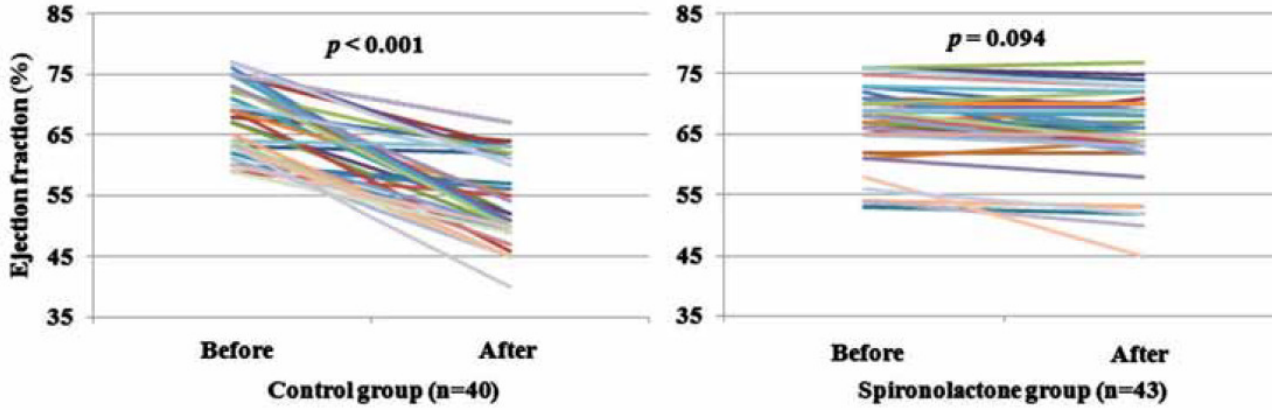
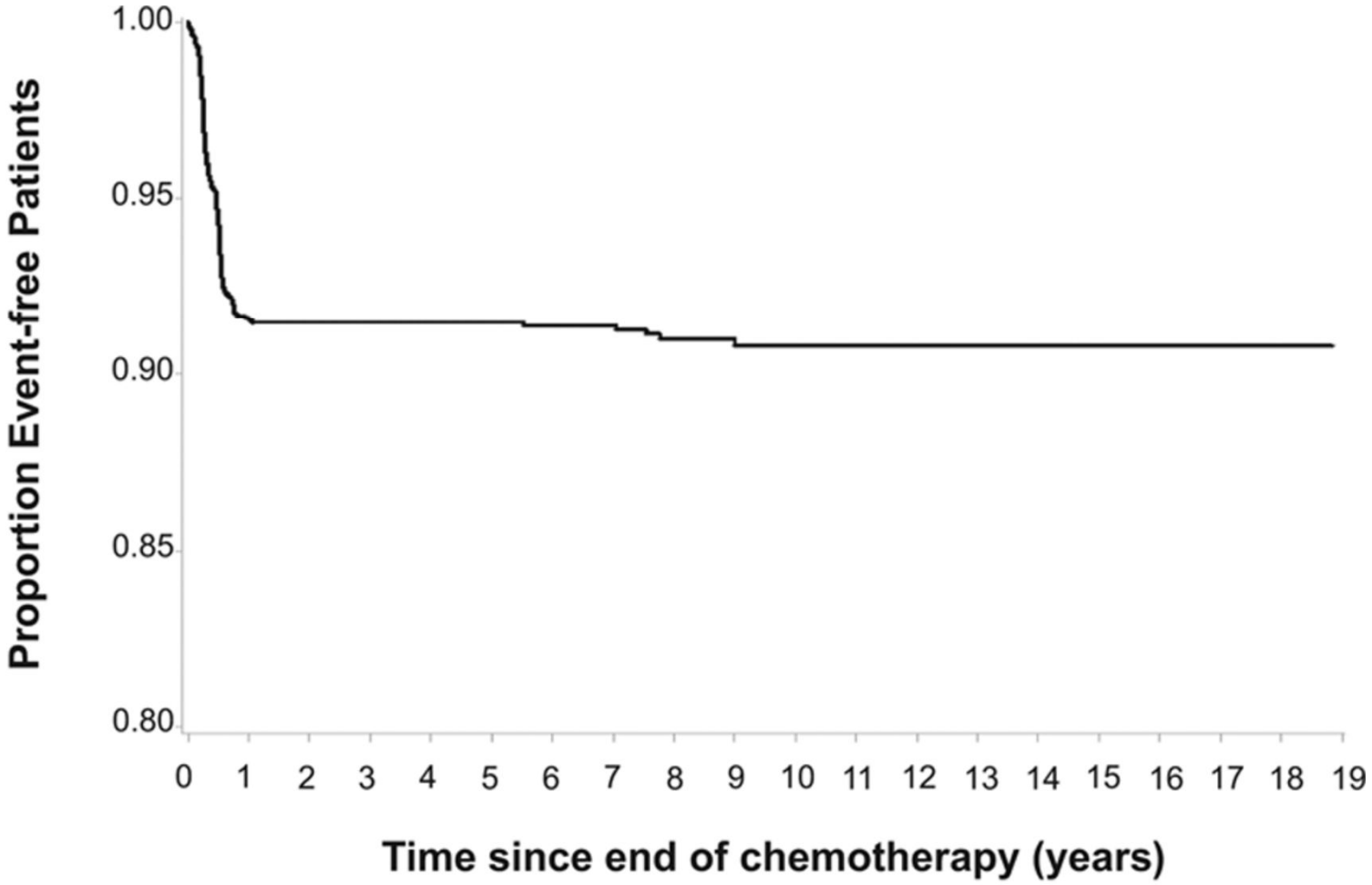


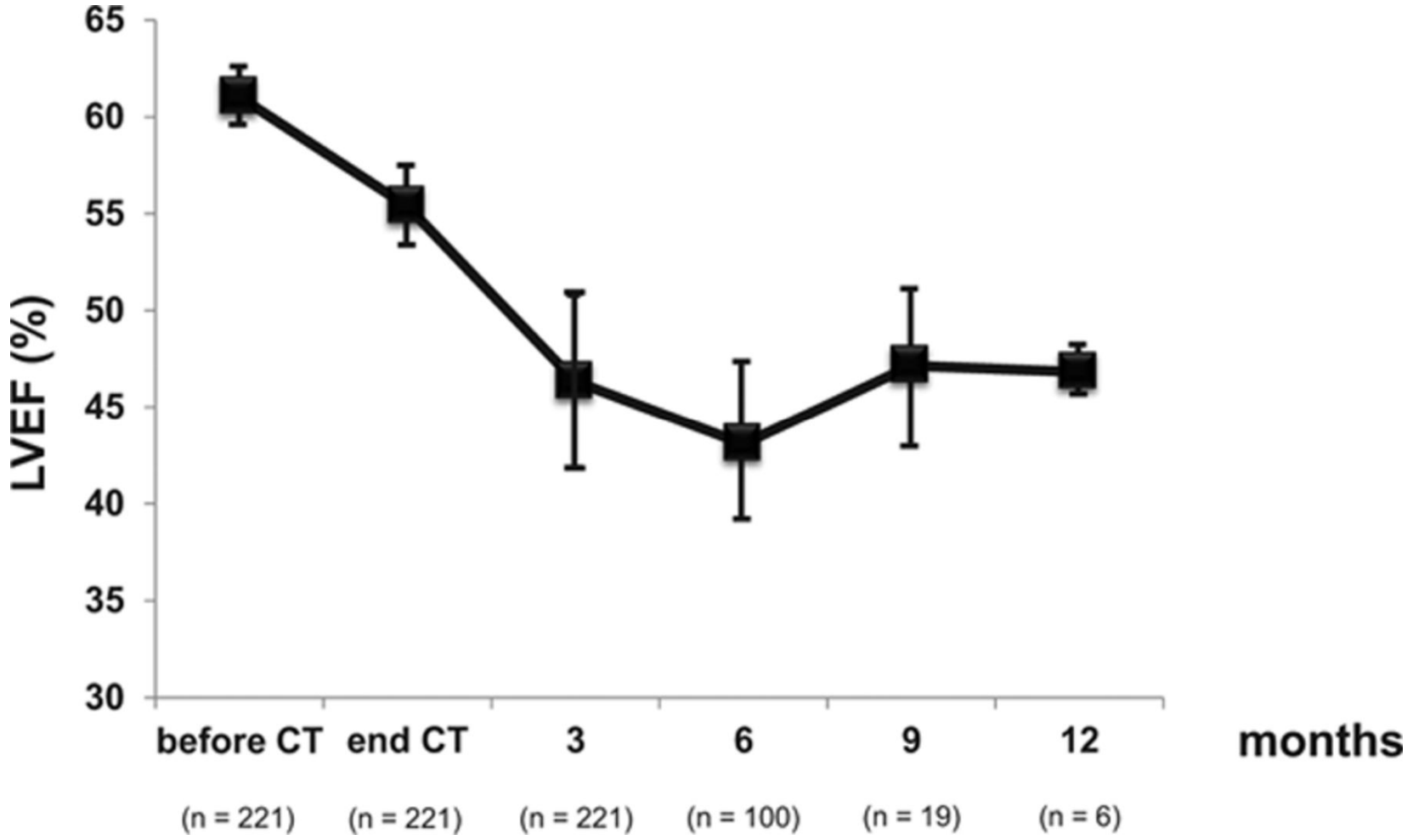
Figure 3 Individual systolic function data at baseline and after chemotherapy in the control and spironolactone groups.

Kaplan–Meier curve showing the cumulative incidence of cardiotoxicity in the study population.



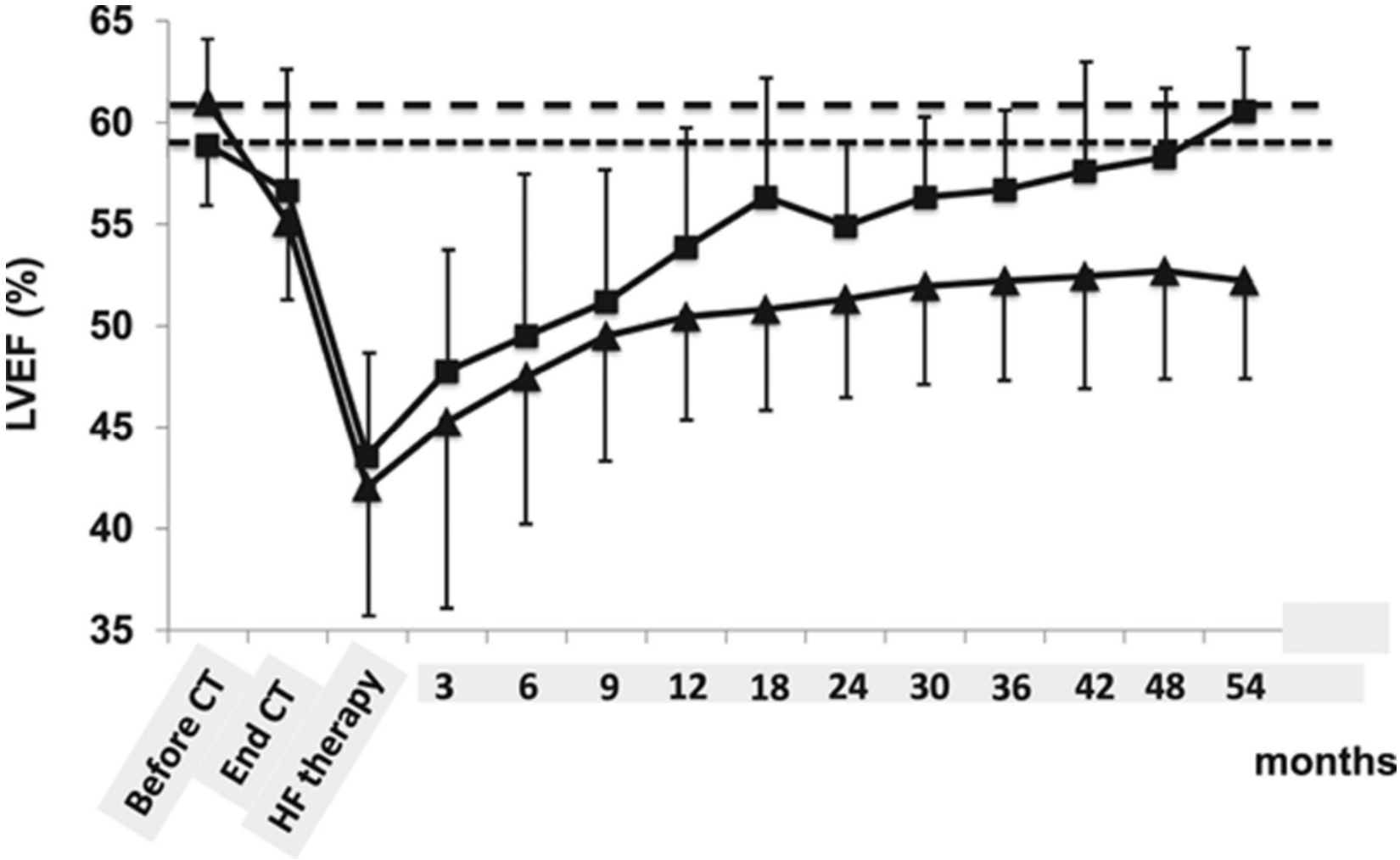
Daniela Cardinale et al. Circulation. 2015;131:1981-1988

Left ventricular ejection fraction (LVEF; mean±SD) behavior in patients developing cardiotoxicity in the first year, from baseline (before starting chemotherapy) to the initiation of heart failure therapy.



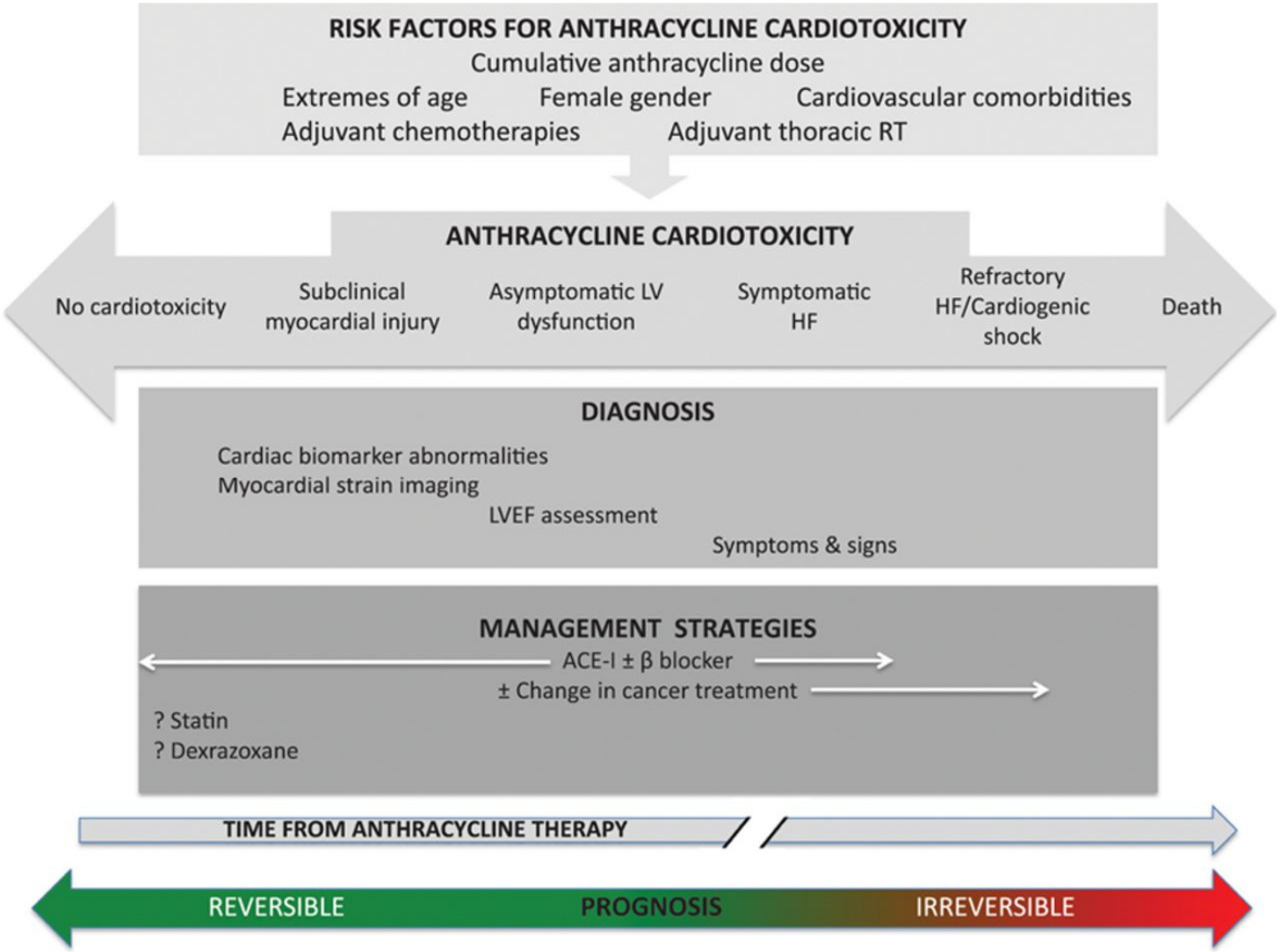
Daniela Cardinale et al. Circulation. 2015;131:1981-1988

Left ventricular ejection fraction (LVEF) in patients with cardiotoxicity and with partial (triangle) or full (square) recovery with heart failure therapy.



Daniela Cardinale et al. Circulation. 2015;131:1981-1988

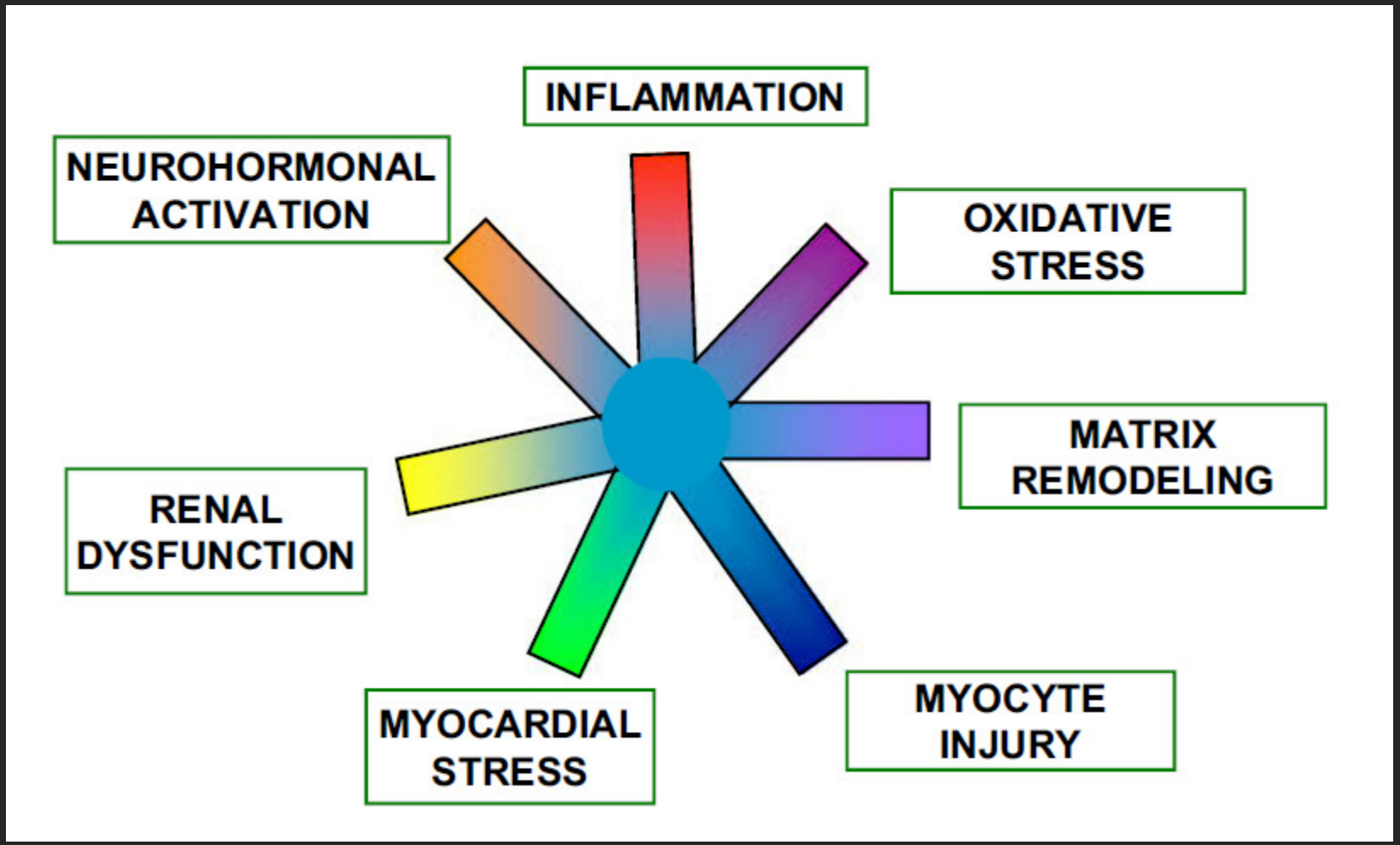
Continuum of anthracycline cardiotoxicity.



John D. Groarke, and Anju Nohria Circulation. 2015;131:1946-1949

American Heart Association.

Multimarker Risk Prediction



Braunwald, E. NEJM. 2008.
Braunwald, E. JACC HF. 2013.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404

Barbara L. Asselin, Meenakshi Devidas, Lu Chen, Vivian I. Franco, Jeanette Pullen, Michael J. Borowitz, Robert E. Hutchison, Yaddanapudi Ravindranath, Saro H. Armenian, Bruce M. Camitta, and Steven E. Lipshultz

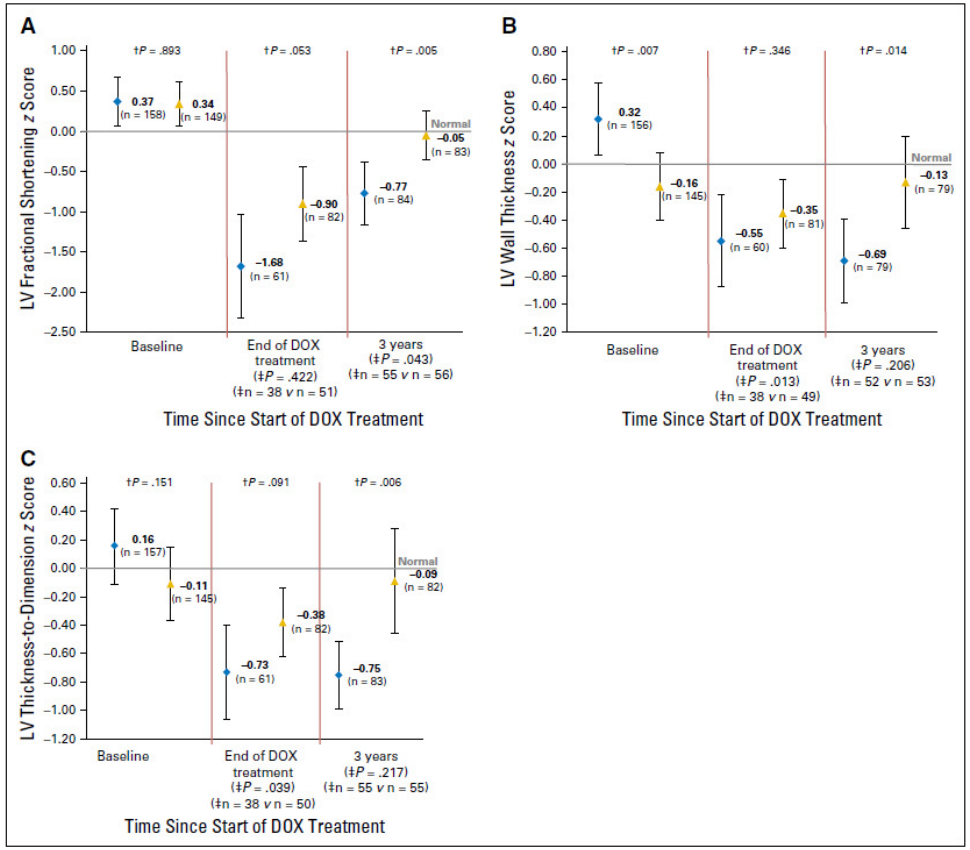
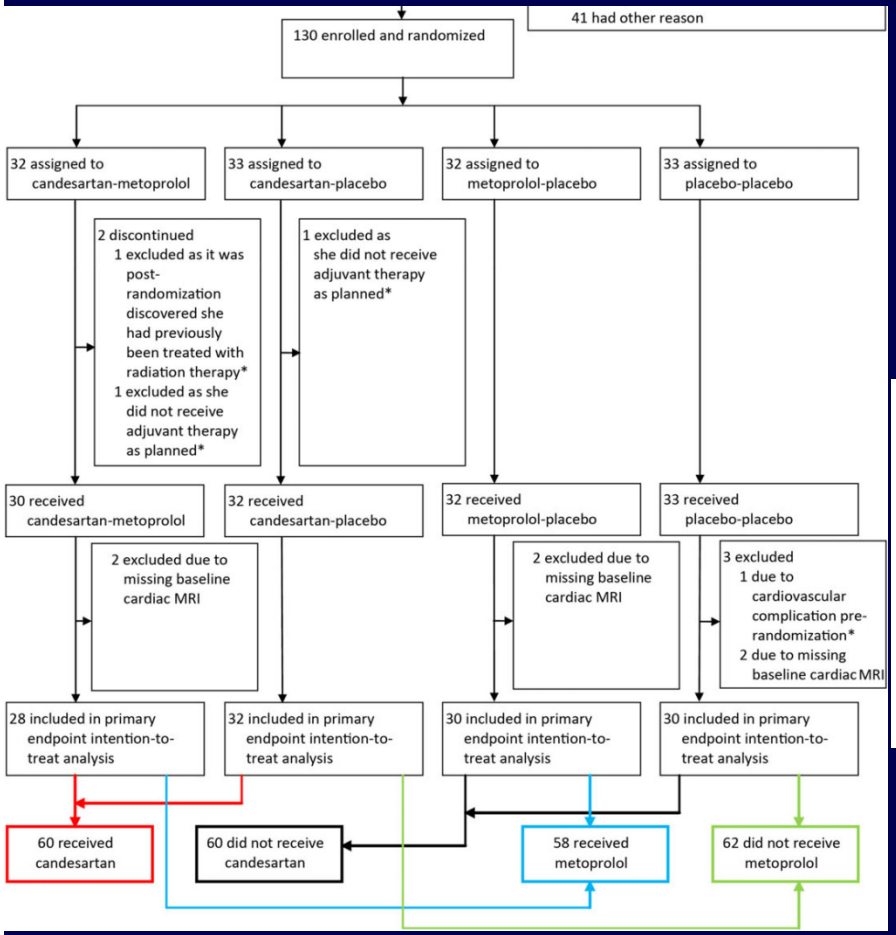


Fig 3. Estimated mean *z* scores by treatment group among 307 children with T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma at baseline (n = 307), at end of therapy (n = 143), and at 3 years (n = 167). Comparison of change from baseline at each time point is noted at the bottom of the figure. (A) LV fractional shortening. (B) LV wall thickness. (C) LV thickness-to-dimension ratio. Bars represent 95% CIs; blue diamond, standard treatment only (doxorubicin [DOX]); gold triangle, dexrazoxane plus standard treatment (DRZ + DOX). †*P* values comparing the two groups at each time point (baseline, end of DOX treatment, and 3 years). ‡*P* values for differences in change in mean *z* scores since baseline in DOX- versus DOX- + DRZ-treated patients, for those patients with values at baseline and a second time point. n indicates number of patients with paired studies in each treatment group. Only patients with paired baseline and end-of-therapy or 3-year *z* scores were included in these analyses.



European Heart Journal (2016) **37**, 1671–1680
doi:10.1093/eurheartj/ehw022

AHA FASTTRACK
CLINICAL RESEARCH

Heart failure/cardiomyopathy

Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol

Geeta Gulati[1,2†], Siri Lagethon Heck[1,2†], Anne Hansen Ree[3,4], Pavel Hoffmann[5], Jeanette Schulz-Menger[6,7], Morten W. Fagerland[8], Berit Gravdehaug[9], Florian von Knobelsdorff-Brenkenhoff[6], Åse Bratland[10], Tryggve H. Storås[11], Tor-Arne Hagve[4,12], Helge Røsjø[1,2], Kjetil Steine[1,2], Jürgen Geisler[3,4], and Torbjørn Omland[1,2*]

Table 2 Primary and secondary endpoints, estimated values from linear mixed models (intention-to-treat analysis)

	n	Baseline	EOS	Change from baseline to EOS	Between-group difference in change from baseline to EOS	*P*-value
LVEF						
No candesartan	60	63.2 (62.0, 64.4)	60.6 (59.4, 61.8)	−2.6 (−3.8, −1.5)	1.9 (0.2, 3.5)[a]	0.026
Candesartan	60	62.1 (61.0, 63.3)	61.4 (60.2, 62.6)	−0.8 (−1.9, 0.4)		
No metoprolol	62	62.8 (61.6, 64.0)	61.0 (59.8, 62.2)	−1.8 (−3.0, −0.7)	0.2 (−1.4, 1.9)	0.772
Metoprolol	58	62.5 (61.3, 63.7)	61.0 (59.8, 62.2)	−1.6 (−2.8, −0.4)		
RVEF						
No candesartan	60	61.3 (60.0, 62.5)	58.9 (57.6, 60.1)	−2.4 (−3.7, −1.1)	0.8 (−1.0, 2.6)	0.370
Candesartan	60	60.2 (59.0, 61.4)	58.7 (57.4, 59.9)	−1.6 (−2.8, −0.3)		
No metoprolol	62	60.4 (59.2, 61.6)	58.0 (56.8, 59.3)	−2.4 (−3.7, −1.1)	0.8 (−1.0, 2.6)	0.377
Metoprolol	58	61.1 (59.8, 62.3)	59.5 (58.3, 60.8)	−1.6 (−2.9, −0.3)		

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101–Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity

Edith Pituskin, John R. Mackey, Sheri Koshman, Davinder Jassal, Marshall Pitz, Mark J. Haykowsky, Joseph J. Pagano, Kelvin Chow, Richard B. Thompson, Larissa J. Vos, Sunita Ghosh, Gavin Y. Oudit, Justin A. Ezekowitz, and D. Jan Paterson

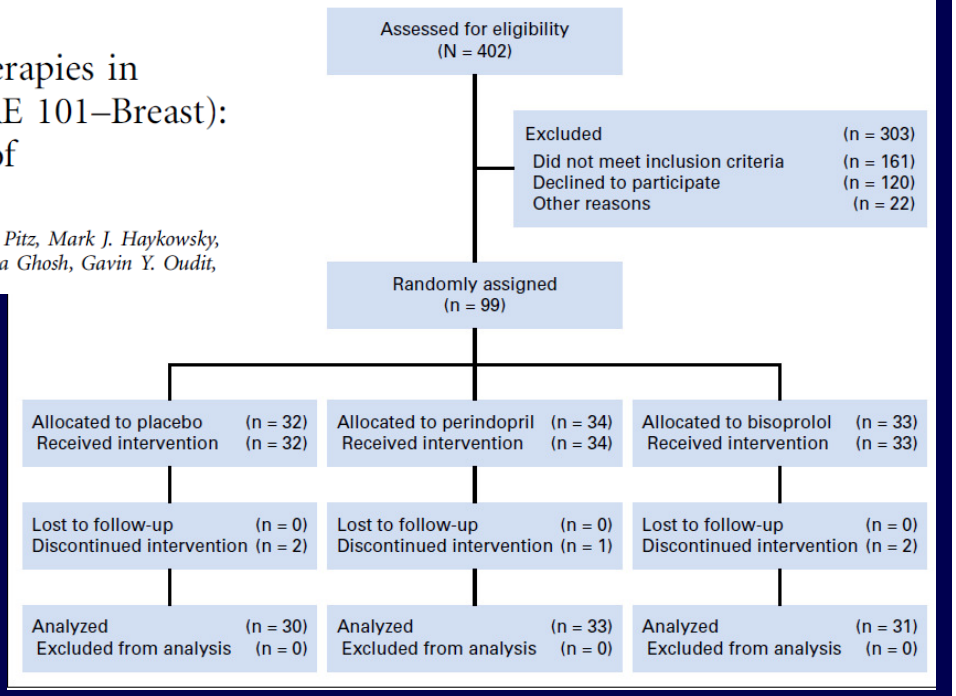


Table 3. Cardiac Magnetic Resonance Imaging Measures Throughout Trastuzumab Therapy

Measure	Placebo (n = 30)	Perindopril (n = 33)	Bisoprolol (n = 31)	ANOVA *P*
LVEDVi, mL/m^2				
Baseline	76 ± 13*	67 ± 14	69 ± 10	.01
Post–cycle 4	77 ± 10	71 ± 16†	76 ± 11†	.09
Change from baseline	+2 ± 9	+4 ± 9	+7 ± 8	.07
Post–cycle 17	79 ± 12	74 ± 16†	76 ± 14†	.27
Change from baseline	+4 ± 11	+7 ± 14	+8 ± 9	.36
LVEF, %				
Baseline	61 ± 5	62 ± 5	62 ± 4	.55
Post–cycle 4	54 ± 5*†	59 ± 6†	59 ± 4†	< .001
Change from baseline	−7 ± 5*	−4 ± 4	−4 ± 5	.01
Post–cycle 17	56 ± 4*†	59 ± 6†	61 ± 4	< .001
Change from baseline	−5 ± 5*	−3 ± 4	−1 ± 5	.001

Angiotensin II–Receptor Inhibition With Candesartan to Prevent Trastuzumab-Related Cardiotoxic Effects in Patients With Early Breast Cancer

A Randomized Clinical Trial

Annelies H. Boekhout, PhD; Jourik A. Gietema, MD, PhD; Bojana Milojkovic Kerklaan, PhD; Erik D. van Werkhoven, MSc; Renske Altena, MD, PhD; Aafke Honkoop, MD, PhD; Maartje Los, MD, PhD; Willem M. Smit, MD, PhD; Peter Nieboer, MD, PhD; Carolien H. Smorenburg, MD, PhD; Caroline M. P. W. Mandigers, MD, PhD; Agnes J. van der Wouw, MD, PhD; Lonneke Kessels, MD; Annette W. G. van der Velden, MD; Petronella B. Ottevanger, MD, PhD; Tineke Smilde, MD, PhD; Jaap de Boer, MD; Dirk J. van Veldhuisen, MD, PhD; Ido P. Kema, PhD; Elisabeth G. E. de Vries, MD, PhD; Jan H. M. Schellens, MD, PhD

JAMA Oncol. doi:10.1001/jamaoncol.2016.1726

Figure 1. Trial Enrollment Flowchart

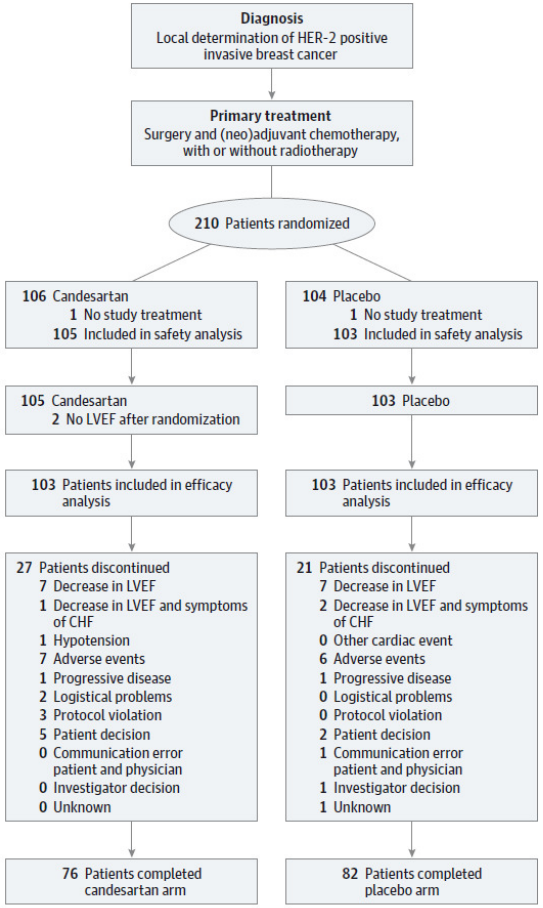
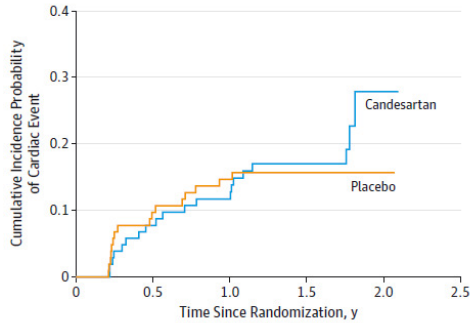


Figure 2. Kaplan-Meier Curve Showing the Cumulative Incidence of Cardiac Events

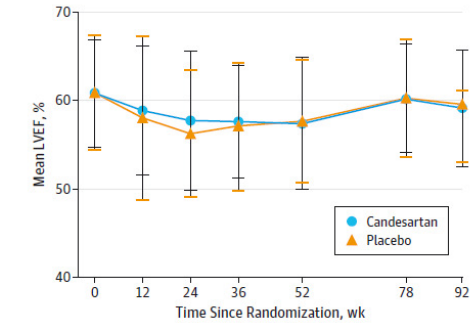


No. at risk

Candesartan	103	93	84	68	1	0
Placebo	103	92	85	83	4	0

Illustrated are the cumulative 2-year incidences of cardiac events for the patients assigned to receive candesartan and those assigned to the placebo group.

Figure 3. Mean (SD) Left Ventricular Ejection Fraction (LVEF) Over Study Follow-up Time



No. at risk

Candesartan	103	101	100	97	99	85	75
Placebo	103	101	102	96	95	88	84

Journal of the American College of Cardiology
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ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.07.067

Effect of Statin Therapy on the Risk for Incident Heart Failure in Patients With Breast Cancer Receiving Anthracycline Chemotherapy

An Observational Clinical Cohort Study

Sinziana Seicean, MD, MPH, PHD,*† Andreea Seicean, MPH,† Juan Carlos Plana, MD,* G. Thomas Budd, MD,* Thomas H. Marwick, MD, PHD, MPH*‡

Cleveland, Ohio; and Hobart, Tasmania, Australia

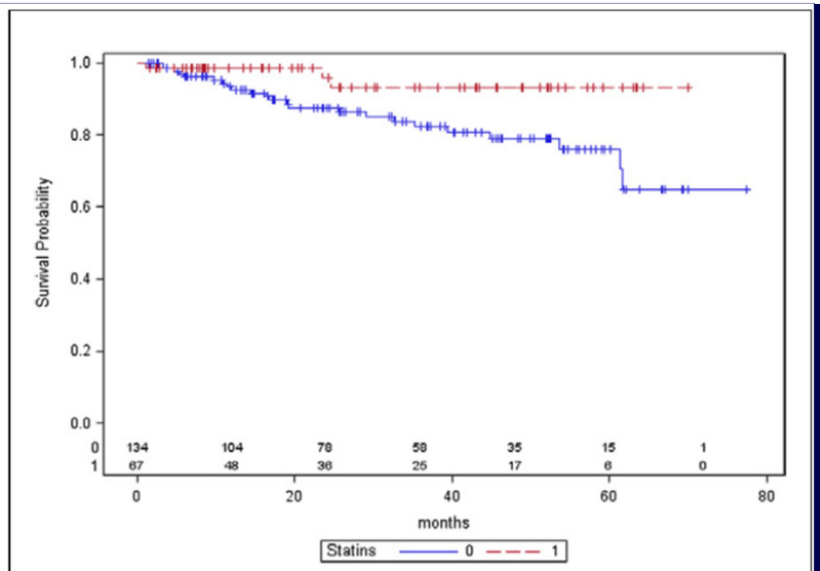

Figure 1 Heart Failure-Free Survival

These survival curves illustrate survival in statin **(red)** and non-statin **(blue)** treated groups. Figures above the abscissa relate to numbers of patients surviving without heart failure at each 12-month interval.

Journal of the American College of Cardiology
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Vol. 58, No. 9, 2011
ISSN 0735-1097/$36.00

CORRESPONDENCE

Research Correspondence

Efficiency of Atorvastatin in the Protection of Anthracycline-Induced Cardiomyopathy

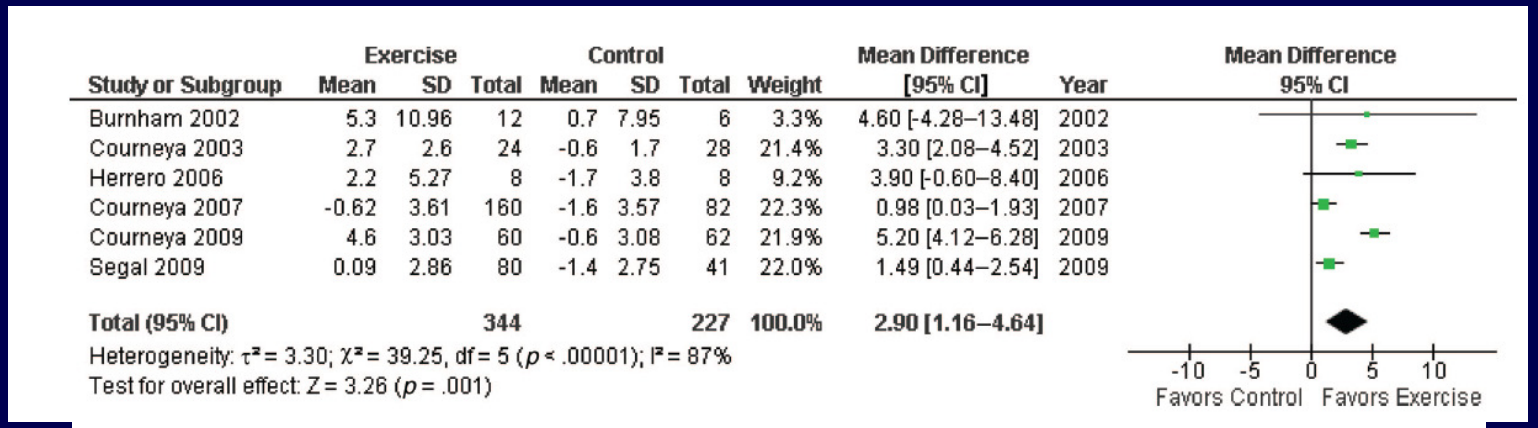
Table 1 Comparison of Echocardiographic Parameters in the Study Group Between Baseline and Follow-Up Values

	Statin Group (n = 20)	Control Group (n = 20)	p Value
LVEF (%)			
Baseline	61.3 ± 7.9	62.9 ± 7.0	
After 6 months	62.6 ± 9.3	55.0 ± 9.5	
Mean change	1.3 ± 3.8	−7.9 ± 8.0	<0.001
LVEDD (mm)			
Baseline	46.5 ± 7.2	47.2 ± 5.2	
After 6 months	46.3 ± 6.8	49.2 ± 6.2	
Mean change	−0.15 ± 4.0	2.0 ± 3.3	0.021
LVESD (mm)			
Baseline	30.9 ± 7.2	30.3 ± 5.4	
After 6 months	29.6 ± 6.1	32.3 ± 5.4	
Mean change	−1.35 ± 4.0	2.1 ± 1.8	<0.001

LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

Effect of Exercise Training on Peak Oxygen Consumption in Patients with Cancer: A Meta-Analysis.

Jones et al. ***The Oncologist*** 2011;16:112–120



Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference [95% CI]	Year
Burnham 2002	5.3	10.96	12	0.7	7.95	6	3.3%	4.60 [-4.28–13.48]	2002
Courneya 2003	2.7	2.6	24	-0.6	1.7	28	21.4%	3.30 [2.08–4.52]	2003
Herrero 2006	2.2	5.27	8	-1.7	3.8	8	9.2%	3.90 [-0.60–8.40]	2006
Courneya 2007	-0.62	3.61	160	-1.6	3.57	82	22.3%	0.98 [0.03–1.93]	2007
Courneya 2009	4.6	3.03	60	-0.6	3.08	62	21.9%	5.20 [4.12–6.28]	2009
Segal 2009	0.09	2.86	80	-1.4	2.75	41	22.0%	1.49 [0.44–2.54]	2009
Total (95% CI)			**344**			**227**	**100.0%**	**2.90 [1.16–4.64]**	

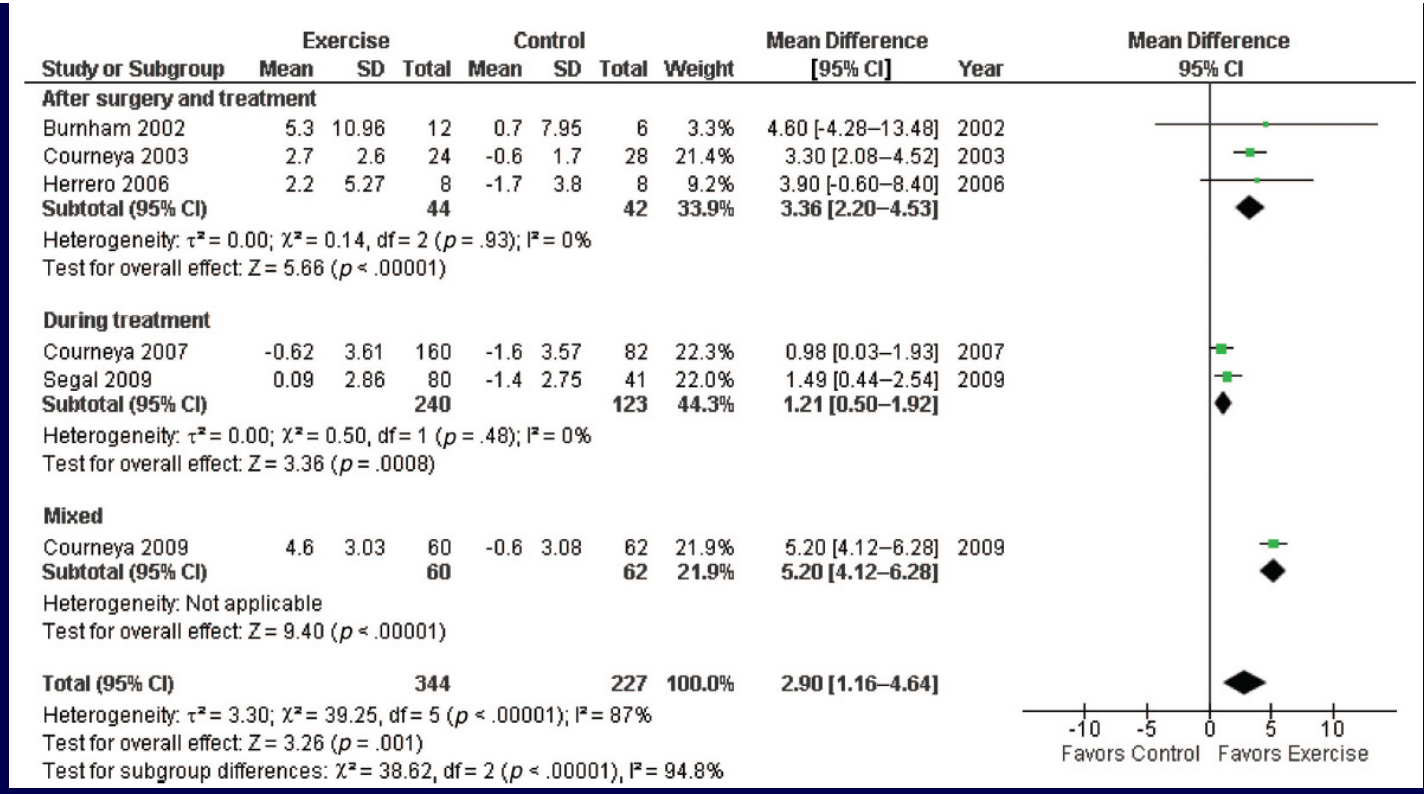
Heterogeneity: $\tau^2 = 3.30$; $\chi^2 = 39.25$, df = 5 ($p < .00001$); $I^2 = 87\%$

Test for overall effect: $Z = 3.26$ ($p = .001$)

Mean Difference 95% CI

-10 -5 0 5 10

Favors Control Favors Exercise



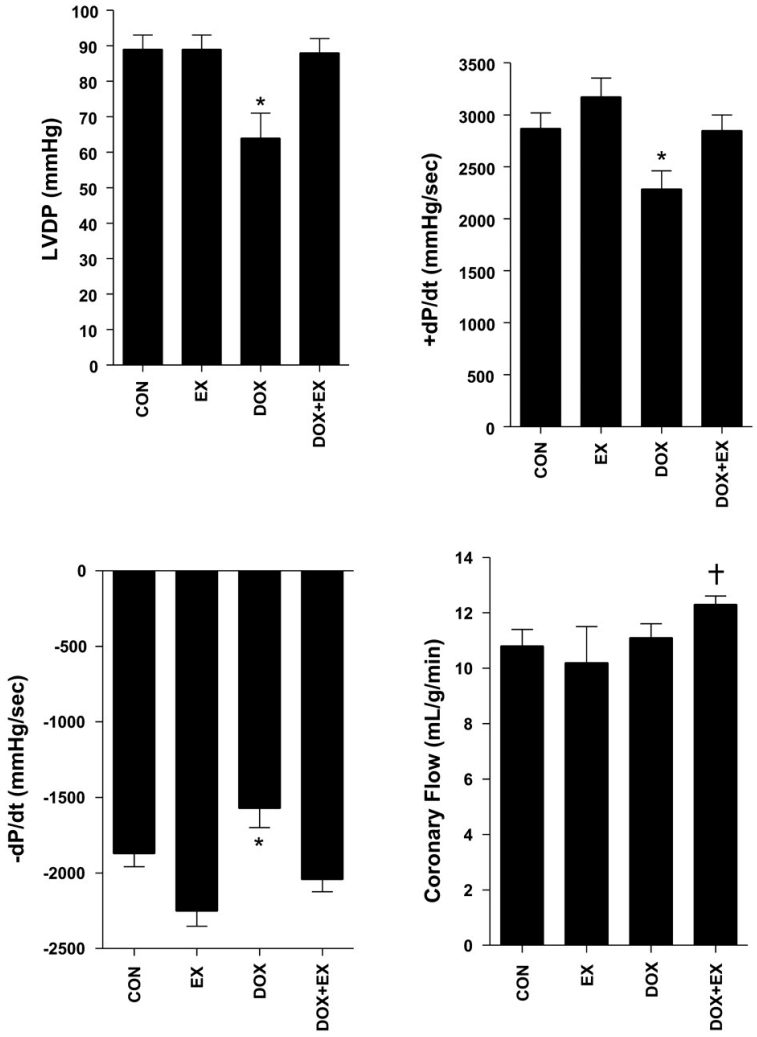
Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference [95% CI]	Year
After surgery and treatment									
Burnham 2002	5.3	10.96	12	0.7	7.95	6	3.3%	4.60 [-4.28–13.48]	2002
Courneya 2003	2.7	2.6	24	-0.6	1.7	28	21.4%	3.30 [2.08–4.52]	2003
Herrero 2006	2.2	5.27	8	-1.7	3.8	8	9.2%	3.90 [-0.60–8.40]	2006
Subtotal (95% CI)			**44**			**42**	**33.9%**	**3.36 [2.20–4.53]**	
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.14$, df = 2 ($p = .93$); $I^2 = 0\%$									
Test for overall effect: $Z = 5.66$ ($p < .00001$)									
During treatment									
Courneya 2007	-0.62	3.61	160	-1.6	3.57	82	22.3%	0.98 [0.03–1.93]	2007
Segal 2009	0.09	2.86	80	-1.4	2.75	41	22.0%	1.49 [0.44–2.54]	2009
Subtotal (95% CI)			**240**			**123**	**44.3%**	**1.21 [0.50–1.92]**	
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.50$, df = 1 ($p = .48$); $I^2 = 0\%$									
Test for overall effect: $Z = 3.36$ ($p = .0008$)									
Mixed									
Courneya 2009	4.6	3.03	60	-0.6	3.08	62	21.9%	5.20 [4.12–6.28]	2009
Subtotal (95% CI)			**60**			**62**	**21.9%**	**5.20 [4.12–6.28]**	
Heterogeneity: Not applicable									
Test for overall effect: $Z = 9.40$ ($p < .00001$)									
Total (95% CI)			**344**			**227**	**100.0%**	**2.90 [1.16–4.64]**	
Heterogeneity: $\tau^2 = 3.30$; $\chi^2 = 39.25$, df = 5 ($p < .00001$); $I^2 = 87\%$									
Test for overall effect: $Z = 3.26$ ($p = .001$)									
Test for subgroup differences: $\chi^2 = 38.62$, df = 2 ($p < .00001$), $I^2 = 94.8\%$									

Mean Difference 95% CI

-10 -5 0 5 10

Favors Control Favors Exercise

Effect of exercise training and Dox on cardiac function in hearts isolated from Con (n = 6), Dox (n = 8), Ex (n = 6), and Dox+Ex (n = 8) animals.



Adam J. Chicco et al. J Appl Physiol 2006;100:519-527

Journal of Applied Physiology

Exercise Cardioprotection From Doxorubicin

This study is currently recruiting participants. *Verified May 2015 by University of British Columbia*

Sponsor: University of British Columbia
Collaborator: British Columbia Cancer Agency
ClinicalTrials.gov Identifier: NCT02006979
First received: December 5, 2013
Last updated: May 27, 2015
Last verified: May 2015

ClinicalTrials.gov

Exercise to Prevent AnthrCycline-based Cardio-Toxicity Study (EXACT)

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2016 by Nova Scotia Health Authority

Sponsor: Nova Scotia Health Authority

ClinicalTrials.gov Identifier: NCT02471053

First received: May 11, 2015; Last updated: August 16, 2016

Last verified: August 2016

OptiTrain - Optimal Training Women With Breast Cancer (OptiTrain)

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2016 by Karolinska Institutet

Sponsor: Karolinska Institutet

ClinicalTrials.gov Identifier: NCT02522260

First received: June 9, 2015; Last updated: August 30, 2016

Last verified: August 2016

Peak VO_2 change at 3 months

Peak VO2 change at 3 months	Females Usual Care	Males Usual Care	Females Exercise	Males Exercise
N	229	668	290	682
Mean ± SD	0.15 ± 2.1	0.26 ± 2.6	0.88 ± 2.2	0.77 ± 2.7*
Median	0.20	0.20	0.80	0.60
(Min, Max)	(-6.9, 7.80)	(-11.6, 13.50)	(-10.7, 10.20)	(-8.90, 12.50)

*p=0.42;

Adherence: median men 80 min/wk (25th percentile, 75th percentile 41, 121); women were 70 min/wk (37, 108).

Represents 6.6% inc in women and 5.2% in men

Pina IL et al. : JACC Heart Failure Volume 2, Issue 2, 2014, 180–186

Adjusted Models: Hazard Ratios for Specified Effects among Males and Females, with Tests for Corresponding Interactions of Interest

Model Endpoint	Gender Interaction Effect	Estimated Effect in Females	Estimated Effect in Males	P-Value for Interaction
All-Cause Death/Hosp[1]	HR (95% CI): Exercise (vs. Control)	0.74 (0.59 - 0.92)	0.99 (0.86 - 1.13)	0.027
All Cause Death[2]	HR (95% CI): Exercise (vs. Control)	0.71 (0.43 - 1.15)	1.01 (0.79 - 1.28)	0.20
CV-Death/CV-Hosp[3]	HR (95% CI): Exercise (vs. Control)	0.79 (0.62 - 1.00)	0.96 (0.83 - 1.11)	0.17
CV-Death/HF-Hosp[4]	HR (95% CI): Exercise (vs. Control)	0.76 (0.55 - 1.05)	0.90 (0.75 - 1.10)	0.36
All-Cause Death/Hosp[1]	HR (95% CI): Non-White (vs. White)	1.01 (0.81 - 1.27)	1.25 (1.08 - 1.45)	0.11
All-Cause Death/Hosp[1]	HR (95% CI): Baseline PkVO2 (up to 20)	0.92 (0.90 - 0.95)	0.92 (0.90 - 0.94)	0.74

Pina IL et al. : JACC Heart Failure Volume 2, Issue 2, 2014, 180–186

European Heart Journal Advance Access published August 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Table 14 Summarizes the potential benefits of exercise during and/or after cancer treatment

Improvement of: • Cardiorespiratory and cardiovascular function • Body composition (preservation or increase in muscle mass, loss of fat mass) • Immune function • Chemotherapy completion rates • Muscle strength and flexibility • Body image, self-esteem and mood
Reduction in: • Number and severity of side effects including nausea, fatigue and pain • Reduction of hospitalization duration • Reduction of stress, depression and anxiety

Table 13 Strategies to reduce chemotherapy-induced cardiotoxicity[226–228,245–248]

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy drugs	Identify and treat cardiovascular risk factors
	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities
	Minimize cardiac irradiation
Anthracyclines and analogues	Limit cumulative dose (mg/m^2): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	β-blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	β-blockers

AHA SCIENTIFIC STATEMENT

Bozkurt et al. Circulation. 2016;134:e579–e646

Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies

A Scientific Statement From the American Heart Association

Key Management Strategies for Cardiomyopathy Related to Chemotherapeutic Agents

Treatment Recommendations With Strong Level of Consensus for Cardiomyopathy Related to Chemotherapeutic Agents

1. Patients treated with cardiotoxic chemotherapeutic agents should have cardiac functional assessment with LVEF measurement at baseline, after completing treatment, and while on treatment at regular intervals, or sooner if HF symptoms develop *(Level of Evidence B)*.
[128]
2. If test results indicate deterioration in cardiac function associated with cardiotoxic chemotherapy, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage
(Level of Evidence C).
3. Cancer patients with systolic HF should be treated with GDMT
(Level of Evidence B).

AHA SCIENTIFIC STATEMENT

Bozkurt et al. Circulation. 2016;134:e579–e646

Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies

A Scientific Statement From the American Heart Association

Recommendations With Moderate Level of Consensus for Cardiomyopathy Related to Chemotherapeutic Agents

1. Measurement of cardiac troponin is reasonable to identify patients at risk of cardiotoxicity with cancer therapy
   (Level of Evidence B).
2. In patients at high risk for cardiac toxicity, strategies such as administration of divided continuous infusions, liposome encapsulation, use of less cardiotoxic derivatives, or use of cardioprotective agents such as dexrazoxane in conjunction with treatment can be useful to reduce cardiotoxicity of doxorubicin chemotherapy
   (Level of Evidence B)

Recommendations With Uncertainty for Cardiomyopathy Related to Chemotherapeutic Agents

1. The usefulness of serial/repeated measurements of cardiac biomarkers for monitoring cardiotoxicity with cancer therapy is uncertain
   (Level of Evidence C).
2. Usefulness of β-blockers, ACE inhibitors, or ARBs for primary prevention of cardiac toxicity of chemotherapy is uncertain at this time
   (Level of Evidence B)

European Heart Journal
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Even when EF improves, What to do? Stop Rx?? Continue?

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

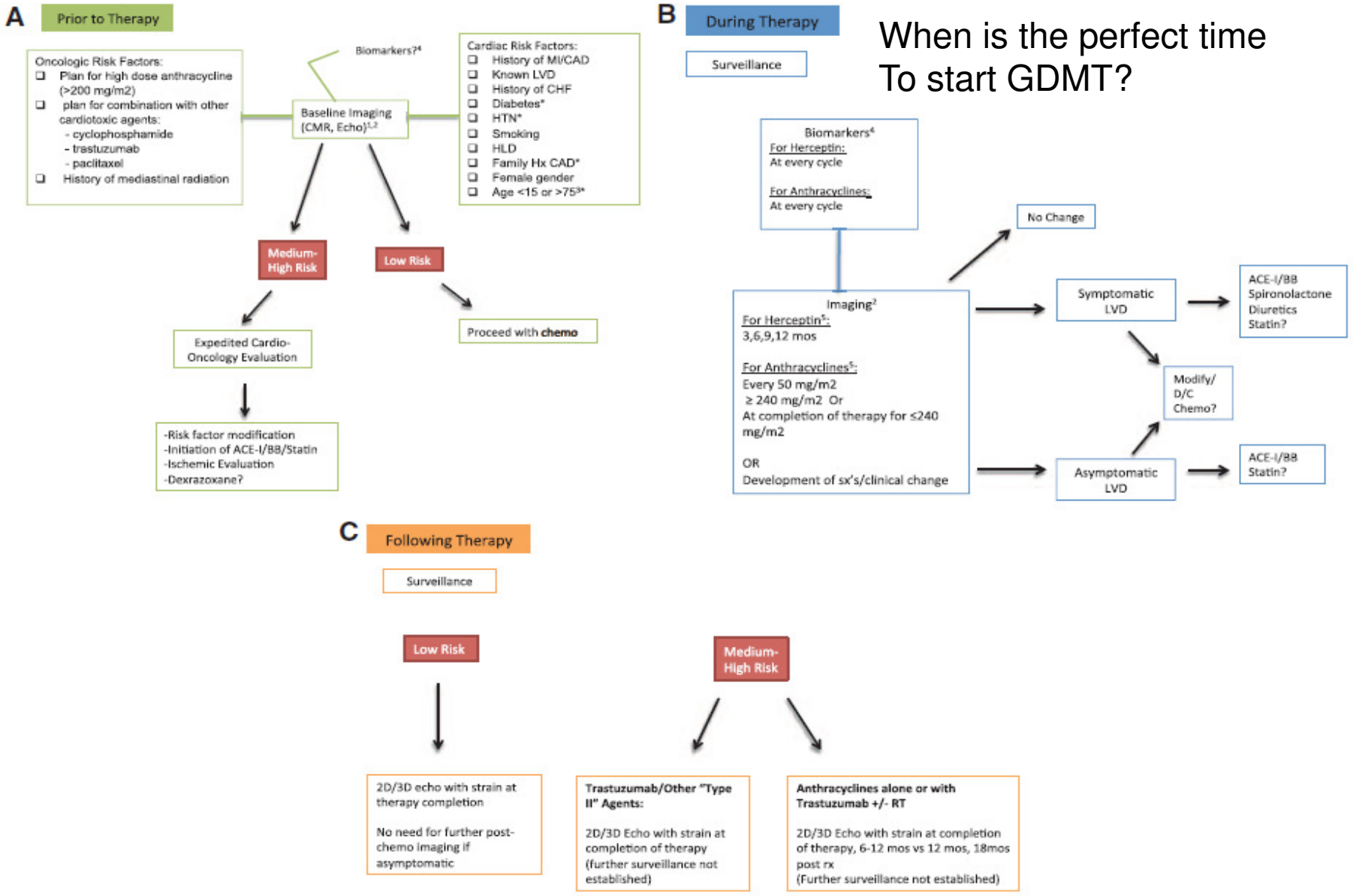
BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL

Cancer Therapy–Related Cardiac-Dysfunction and Heart Failure. Part 2: Prevention, Treatment, Guidelines, and Future Directions.

Hamo et al. *Circ Heart Fail*. 2016;9:e002843



When is the perfect time
To start GDMT?

Summary

- Heart failure associated with chemotherapy can be severe and include both elements of HFrEF and HFpEF
- Risk factor identification is critical prior to the initiation of chemo
- HF associated with chemotherapy can respond to GDMT
- GDMT may also be protective if administered with chemotherapy although the data are not consistent
- GDMT may reverse LV dysfunction previously thought non-reversible
- A panel of biomarkers may be predictive of cardiotoxicity and could serve as markers of improvement .
- Further research is needed in mREF patients whose LV function improves