





A randomized community-based trial of an angiotensin converting enzyme inhibitor, lisinopril or a beta blocker, carvedilol for the prevention of cardiotoxicity in patients with early stage HER2-positive breast cancer receiving adjuvant trastuzumab.

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NCI 3U10CA081920SunCoast CCOP Research Base at the University of South Florida,







Disclosures

no conflicts for any authors



Rationale for Study

Trastuzumab is a highly effective therapy for HER2

 positive breast cancer.

- Cardiac side effects require frequent monitoring resulting in dose interruptions and discontinuation of trastuzumab.
- Prevention of chemotherapy-induced cardiotoxicity by prophylactic use of angiotensin converting enzyme (ACE) inhibitors and beta blockers (BB) has been suggested in small studies.

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Challenges and Potential Confounders

...wide ranging reports of cardiotoxicity associated with HER2targeting regimens in a community-based practice

...evolving changes in practice patterns and preferred (neo)adjuvant regimens by geographic areas and clinical settings

....influence of regimen selection by perceived or actual underlying cardiac risk factors in patients with HER2-positive tumors



Study Design and Endpoints

Design:

- · Randomized, double-blind, placebo-controlled, multicenter community-based clinical trial in patients with early stage HER2 positive breast cancer receiving trastuzumab
- Stratified for patients with or without use of anthracyclines (≥184) in the regimen
- · Intervention (carvedilol, lisinopril or placebo) from day 1 of trastuzumab for 52 weeks
- · Cardiotoxicity defined as an absolute decrease in left ventricular ejection fraction (LVEF) of 10% or at least a 5% decrease for LVEF <50%

Endpoints:

Primary Endpoints:

· rates of cardiotoxicity during the 52 weeks of treatment with trastuzumab and in the year after completion of trastuzumab

Secondary Endpoints

- · toxicity, tolerability
- · quality of life
- brain natriuretic peptide (BNP), troponins

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Major Eligibility Criteria

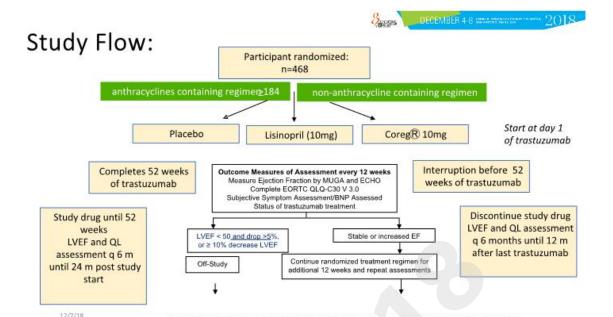


Inclusion:

- · Early stage HER2-positive breast cancer with planned 1-year treatment with trastuzumab
- · Adjuvant or neoadjuvant cytotoxic therapy
- · Age ≥18 year
- LVEF ≥50 % by ECHO or MUGA
- Systolic blood pressure ≥90 mmHg
- Pulse ≥ 60 beats/m
- · Ability to give consent and adhere to protocol

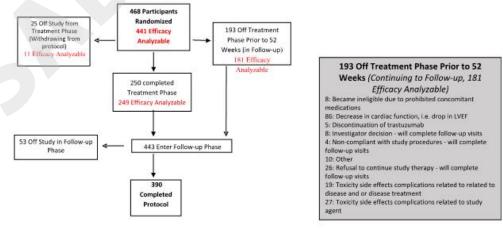
Exclusion:

- · Prior trastuzumab, prior anthracyclines
- · Current treatment with beta blockers or ACE inhibitors
- · Angioedema
- · Known allergy or intolerance to either lisinopril or carvedilol
- · Known present or past cardiac disease (myocardial infarction, arrhythmias, myocarditis, heart failure)
- · History of bronchospasm or interfering lung disease





Consort diagram



				By Treat	ment Grou	By Strata		
			Carvedilol (N=156)	Lisinopril (N=158)	Placebo (N=154)	Combined (N=468)	Anthracycline (N=189)	No Anthracycline (N=279)
Baseline characteristics	Age at Baseline (years)	Mean S.D.	52 11	51 11	51 10	51 11	48* 10	53* 11
	Race/ Ethnicity (%)	His/Lat Black/ AA White Other	6 3 88 9	10 9 87 4	10 10 84 6	9 7 86 6	9 5 90 5	9 9 84 7
	LVEF at Baseline (%)	Mean S.D.	63 7	63 6	62 6	63 6	62 6	63 6
	BMI (kg/m²)	Mean S.D.	28 6	28 7	29 6	28 6	28 6	29 6
	BP Systolic (mmHg)	Mean S.D.	125 18	126 18	127 16	126 17	120* 15	130* 17
	Known Diabetes (%)		2.56	1.27	3.23	2.35	2.12	2.51
	Known hyper- cholesterolemia (%)		7.69	8.23	9.10	8.33	7.94	8.60



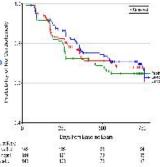


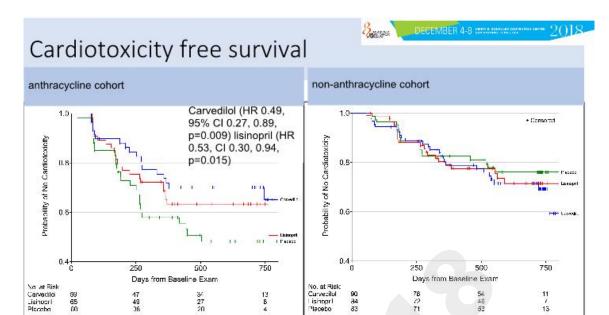
Results Summary

- · 468 patients enrolled, 127 sites
 - · 189 patients in the anthracycline cohort and 279 in the non-anthracycline

Entire group

- · Cardiotoxicity: Similar for all cohorts: Placebo: 32% vs Carvedilol: 29% vs Lisinopril: 30% (p=0.270 and p=0.358)
- · Cardiotoxicity free survival: comparable HR 0.71; 95% CI (0.47, 1.07) for carvedilol (p=0.052) HR 0.74; 95% CI (0.48, 1.12) for lisinopril (p=0.076)





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Interruption of trastuzumab for any reason

, 	Carvedilol			Lisinopril		Placebo			Active vs placebo	
S	N	n	%	N	n	%	N	n	%	P- value
Entire cohort	156	24	15.4	156	27	17.3	152	40	26.3	0.01
No anthracyclines	95	12	12.6	91	12	13.2	90	15	16.7	0.40
Anthracyclines	61	12	19.7	65	15	23.0	62	25	40.3	0.007

Toxicity by intervention



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		Carvedilol N=156		Lisinopril N=158		Placebo N=154	
Fatigue		18%		26%*		16%	
	Grade 1		9%		10%		8%
	Grade 2		7%		13%		5%
	Grade 3		2%		3%		3%
Dizziness		10%		20%*		11%	
	Grade 1		8%		16%		8%
	Grade 2		1%		3%		2%
	Grade 3		1%		1%		1%
Headache		6%		8%*		3%	
	Grade 1		3%		6%		1.5%
	Grade 2		3%		2%		1.5%
Cough		7%		11%*		4%	
	Grade 1		6%		6%		3%
	Grade 2		1%		5%		0.5%
	Grade 3		0%		0%		0.5%
Hypotension		4%		13%**		3%	
	Grade 1		3%		4%		1%
	Grade 2		1%		6%		2%
	Grade 3		0%		3%		0%

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Conclusions and Relevance

- Cardiotoxicity-free survival was longer in both carvedilol or lisinopril than on placebo in the anthracycline containing regimens.
- · No differences were seen in the non-anthracycline containing regimen

In patients with HER2-positive breast cancer treated with trastuzumab and anthracyclines, the addition of lisinopril or carvedilol should be considered.

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With Gratitude

To all patients, families, friends, advocates and health care providers









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Effects on global health status, Blood pressure and BNP

	Carvedilol	Lisinopril	Placebo	P _{C-P}	P _{L-P}	P _{Active-P}
Entire Cohort EORTC Global Health Status Blood Pressure-Systolic -Diastolic BNP*	Effect (%) n	Effect (%) n	Effect (%) n			
	2 (17) 129 -0.9 (15.9) 143 -1.2 (11.4) 143 -19 (35) 135	1 (23) 128 -6.8 (16.3) 138 -4.7 (11.4) 138 -13 (24) 131	5 (21) 111 -1.1 (16.0) 136 -0.7 (9.9) 136 -16 (34) 123	0.338 0.675 0.160 0.068	0.318 <0.001 0.001 0.410	0.265 0.019 0.269 0.129
Non-anthracycline EORTC Global Health Status Blood Pressure-Systolic -Diastolic BNP*	Effect (%) n	Effect (%) n	Effect (%) n			
	-2 (21) 76 -3.0 (16.6) 87 -0.8 (10.5) 87 -23 (40) 84	-3 (21) 69 -9.8 (16.3) 76 -6.8 (10.7) 76 -15 (25) 74	2 (19) 66 -3.9 (16.7) 78 -2.7 (9.0) 78 -16 (36) 72	0.351 0.847 0.361 0.239	0.446 0.006 0.006 0.657	0.333 0.087 0.270 0.355
Anthracycline	Effect (%) n	Effect (%) n	Effect (%) n			
EORTC Global Health Status Blood Pressure-Systolic -Diastolic BNP*	8 (20) 53 2.1 (14.2) 56 4.3 (12.0) 56 -11 (23) 51 This presenta	5 (24) 59 -3.0 (15.7) 62 -2.0 (11.8) 62 -10 (22) 57	9 (23) 45 2.6 (14.3) 58 1.9 (20.6) 58 -16 (31) 51	0.692 0.658 0.289 0.099	0.526 0.017 0.058 0.378	0.560 0.104 0.644 0.146