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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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 HER2-targeting 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

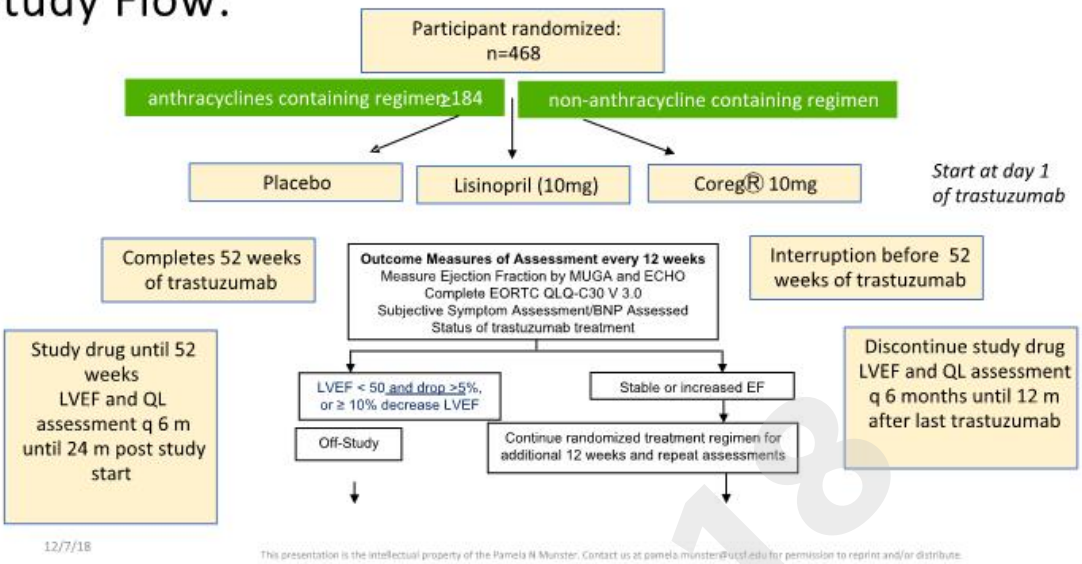
Secondary Endpoints

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

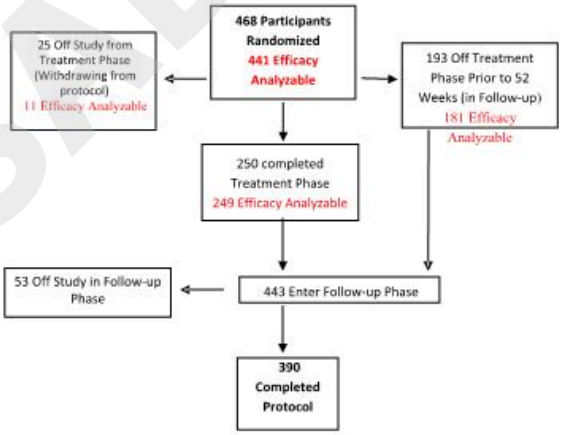
Major Eligibility Criteria

- **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

Study Flow:



Consort diagram



193 Off Treatment Phase Prior to 52 Weeks *(Continuing to Follow-up, 181 Efficacy Analyzable)*

8: Became ineligible due to prohibited concomitant medications
86: Decrease in cardiac function, i.e. drop in LVEF
5: Discontinuation of trastuzumab
8: Investigator decision - will complete follow-up visits
4: Non-compliant with study procedures - will complete follow-up visits
10: Other
26: Refusal to continue study therapy - will complete follow-up visits
19: Toxicity side effects complications related to related to disease and or disease treatment
27: Toxicity side effects complications related to study agent

Baseline characteristics

		By Treatment Group				By Strata	
		Carvedilol (N=156)	Lisinopril (N=158)	Placebo (N=154)	Combined (N=468)	Anthracycline (N=189)	No Anthracycline (N=279)
Age at Baseline (years)	Mean	52	51	51	51	**48***	**53***
	S.D.	11	11	10	11	**10**	**11**
Race/ Ethnicity (%)	His/Lat	6	10	10	9	9	9
	Black/ AA	3	9	10	7	5	9
	White	88	87	84	86	90	84
	Other	9	4	6	6	5	7
LVEF at Baseline (%)	Mean	63	63	62	63	62	63
	S.D.	7	6	6	6	6	6
BMI (kg/m^2)	Mean	28	28	29	28	28	29
	S.D.	6	7	6	6	6	6
BP Systolic (mmHg)	Mean	125	126	127	126	**120***	**130***
	S.D.	18	18	16	17	**15**	**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

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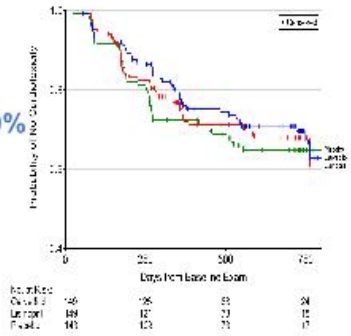
Results Summary

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

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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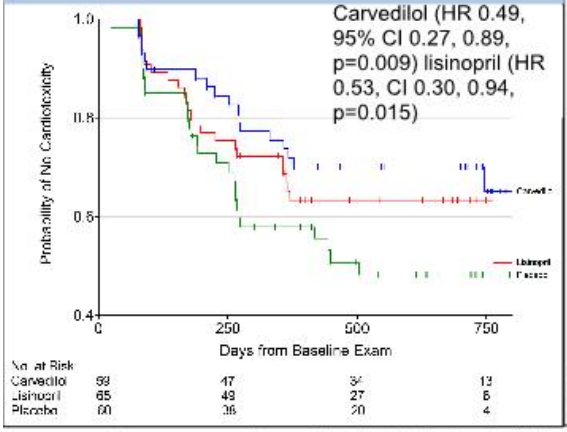
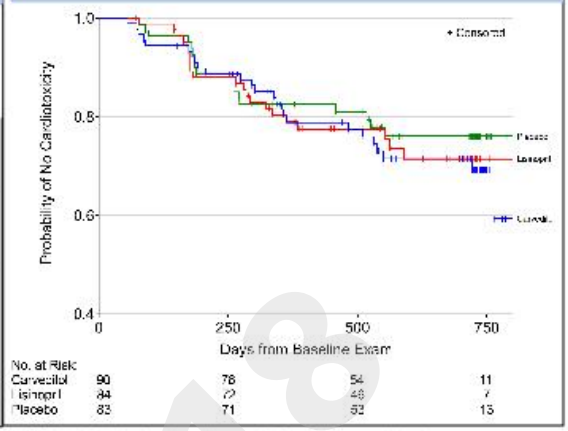
Cardiotoxicity free survival

anthracycline cohort



non-anthracycline cohort



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Interruption of trastuzumab for any reason

	Carvedilol			Lisinopril			Placebo			Active vs placebo
	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

		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%

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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Participating Institutions

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With Gratitude

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

UCSF University of California San Francisco

University of Kentucky

SunCoast

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

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