A PILOT STUDY OF RISK-GUIDED CARDIOPROTECTION WITH CARVEDILOL IN BREAST CANCER PATIENTS TREATED WITH DOXORUBICIN AND/OR TRASTUZUMAB

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Investigational Product: Individually dosed Carvedilol (3.125mg - 25mg, twice daily)

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Initial version	v1 11/10/18	
Amended	v2 12/11/18	(response to stipulations from OCR IND group and IRB)
Amended	v3 01/23/19	(increase target enrollment, update Risk Score)
Amended	v4 09/10/19	(research echocardiogram at baseline)
Amended	v5 09/11/2020	(change to block randomization, identify targeted AEs)
Amended	v6 10/01/2021	(eligibility, AE attribution, SDOH)

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List of Abbreviations

AE**:** Adverse event
CCT: Cardiotoxicity of Cancer Therapy Cohort (IRB #811155 / UPCC 09110, Ky PI)
CTX: cardiotoxicity
CV: Cardiovascular
HF: Heart Failure
HR: Heart Rate
IDS: Penn Investigational Drug Service
LVEF: Left ventricular ejection fraction
TTE: Transthoracic Echocardiogram (Echo)
TNBC: Triple negative breast cancer
SBP: Systolic Blood Pressure

Study Summary

Title	A Pilot Study of Risk-Guided Cardioprotection with Carvedilol In Breast Cancer Patients Treated with Doxorubicin and/or Trastuzumab
Short Title	CCT-Guide Pilot
IRB# / UPCC#	832105 / 12118
Phase	Phase I
Methodology	Randomized, Open Label
Study Duration	3.5 years
Study Center	University of Pennsylvania Health System
Objectives	We will determine the feasibility and safety of a risk-guided cardioprotective treatment strategy with carvedilol, as compared to usual care, in breast cancer patients undergoing treatment with doxorubicin, trastuzumab (or trastuzumab-anns), or the combination.
Number of Subjects	We plan to enroll up to 110 patients for a target of 56 elevated risk patients
Main Inclusion and Exclusion Criteria	**Inclusion Criteria:** • Women ≥18 years old • Diagnosed with Stage I-III breast cancer and scheduled for treatment with doxorubicin and/or trastuzumab (or trastuzumab-anns) in the adjuvant or neo-adjuvant setting **Exclusion Criteria:** • Contraindication to carvedilol • Current therapy with beta blocker • Pregnant or breast feeding • Inability to provide consent
Investigational Product	Carvedilol initiated at 3.125mg twice daily and uptitrated as tolerated in a stepwise fashion to a maximum dose of 25mg twice daily or to a SBP of 110-120mmHg or HR of 50-55 beats per minute (bpm)
Duration of administration	12 months

Reference therapy	Patients will be stratified according to elevated or low CV risk, based upon a validated CV risk prediction score. Subjects in the elevated risk group will be randomized to open label, individually dosed carvedilol for 1 year vs usual care. Subjects in the low risk group will be assigned to usual care and followed prospectively (no prospective cardiovascular intervention).
Statistical Methodology	We will summarize the characteristics of all patients included in the study, overall, as well as stratified by study arm, cancer treatment, and baseline CV risk. An intent-to-treat approach will be used in all analyses. The primary analysis will examine the feasibility of the trial and the safety and tolerability of carvedilol.
Safety Evaluations	We will assess for adverse events using the CTCAE version 5.0; we will specifically evaluate for symptomatic hypotension (SBP<90mmHg), bradycardia (HR<50 bpm), and fatigue at all visits.
Data and Safety Monitoring Plan	The PI will be responsible for monitoring the data quality and the ongoing safety of subjects. The study will also be subject to monitoring by the Abramson Cancer Center Data Safety and Monitoring Committee.

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations. All episodes of noncompliance will be documented.

Introduction

1.1 Background and Relevant Literature

Highly effective cancer drugs, such as doxorubicin and trastuzumab (Herceptin®) are used widely and have led to critical survival gains. However, these agents carry a significant risk of cardiovascular (CV) morbidity and mortality in a growing cancer population of over 14 million individuals worldwide.[1] Doxorubicin-induced CV dysfunction occurs in approximately 10-15% of patients at 240mg/m^2.[2] Doxorubicin and trastuzumab in combination cause CV dysfunction in approximately 18-34% of individuals, and severe, symptomatic heart failure (HF) in 2-4%.[3] Moreover, cardiotoxicity (CTX) results in treatment interruptions, and potentially worse oncologic outcomes. It is critically important to advance our understanding of CTX risk; this need for robust risk stratification has been recognized as a high priority by the NIH, oncology and CV societies internationally.[3-5] This proposed study responds directly to these needs by defining "risk assessment strategies that can best identify subgroups that are most likely to receive the greatest benefit from pharmacologic approaches to prevent CTX during treatment."[4]

The prophylactic use of cardioprotective pharmacotherapies in *all* patients undergoing cancer therapy results in the unnecessary treatment of low-risk patients, and raises concerns over adherence, adverse effects, and patient quality of life/tolerability. As a result, cardioprotective agents are not routinely used in cancer patients. Better selection of patients for treatment through risk prediction models would maximize benefit and minimize risk. However, risk scores, while widely used in cardiology and oncology,[6-11] have not yet been applied to cardio-oncology. In this proposed study, we leverage the critical insights gained in R01 HL118018, focused on understanding individual patient risk and the functional and biologic perturbations secondary to cardiotoxic cancer therapy in the Penn Cardiotoxicity of Cancer Therapy (Penn CCT) longitudinal cohort study. We have developed and validated a simple, but robust risk score to predict CTX using readily obtained and highly accessible patient-level data at baseline. We have comprehensively defined the perturbations in CV function using detailed echocardiographic measures (diastolic function (E/e'); longitudinal and circumferential strain, ventricular arterial coupling) and CV biomarkers (high sensitivity TroponinT; NT-proBNP). Now, in this subsequent study, we propose to test a strategy of risk-guided cardioprotection. We will apply our risk model to breast cancer patients prior to cancer therapy; identify patients with elevated baseline CV risk; and randomize the elevated risk subgroup to prophylactic treatment with carvedilol (an established HF therapy that improves clinical outcomes, CV remodeling, and patient symptoms) versus usual care.[12-22] We will use echocardiographic and biomarker measures to determine the changes in CV function.

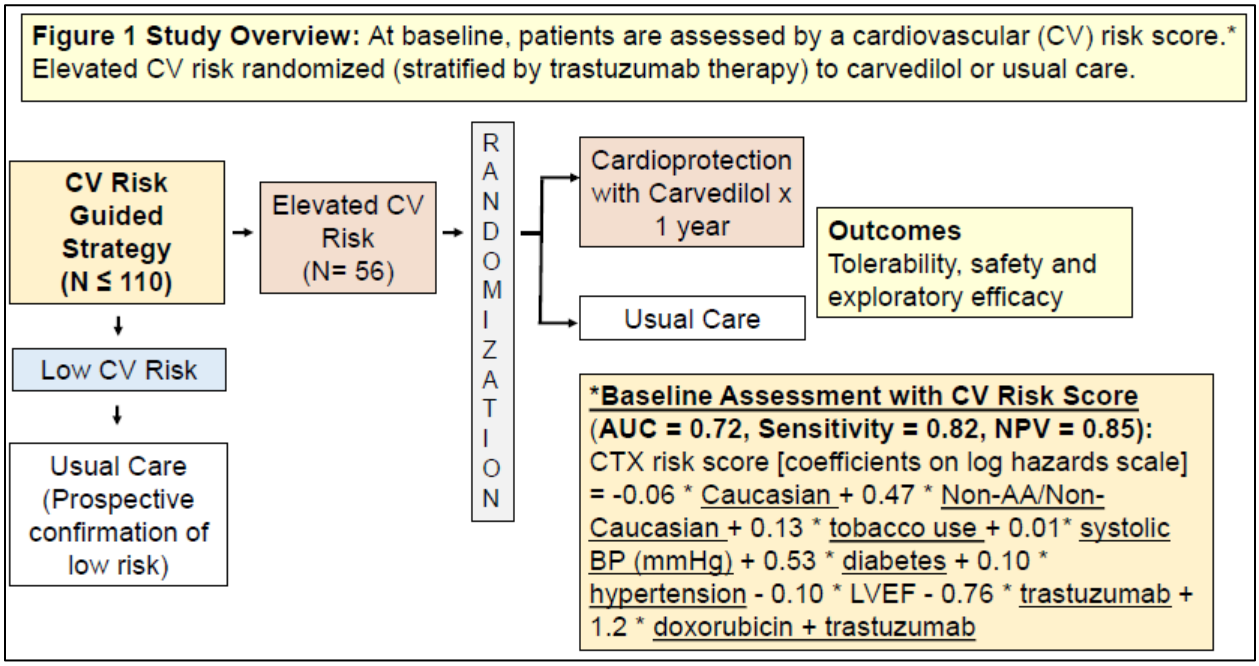
We are uniquely positioned to successfully execute this research, as one of the few centers in cardio-oncology in the US and internationally with detailed CV data obtained through the highly unique Penn CCT study (R01 HL118018, IRB #811155 / UPCC 09110). We have enrolled, rigorously phenotyped, and defined the biologic and functional perturbations in 571 breast cancer patients treated with doxorubicin and/or trastuzumab over a maximum follow-up of 7 years.

Our fundamental scientific premise is that there is a critical need to develop personalized strategies to identify and treat patients at risk for cancer therapy cardiotoxicity in the modern treatment era. Anthracyclines still play an important role in the current treatment of breast cancer, particularly those with high risk or triple negative breast cancer (TNBC).[23] Here, improvements in disease free survival with anthracycline containing regimens has clearly been demonstrated.[24] Trastuzumab is a humanized monoclonal antibody that disrupts ErbB2 (HER2/neu) signaling and has revolutionized the care of HER2+ breast cancer, but can result in clinically significant CTX. In breast cancer alone, over 3 million survivors are estimated to be at risk for cardiotoxicity (CTX).[27,28] In the long term, breast cancer survivors demonstrate

an increase in CV mortality that exceeds oncologic mortality.[29] Yet, robust strategies to identify patients who will suffer from CTX and who will derive the most benefit from prophylactic cardioprotective strategies still are not used in cardio-oncology.[30,31] Our ultimate goals are to ensure the safe delivery of necessary cancer therapies, by avoiding dose interruptions, delays, or early cessation of potentially life-saving treatment. Enhanced risk stratification would enable the early implementation of cardioprotective strategies when appropriate; prevent the interruption or cessation of potentially life-saving cancer therapies secondary to CTX; improve long-term CV health; and enable the maximum utilization of the most effective cancer therapies.

Risk scores have been used extensively in oncology and in cardiology to guide therapy, but not as of yet in cardio-oncology. Risk stratification through the identification of a clinical, biologic, or functional phenotype forms the basis of much of medical decision making, particularly in oncology and CV medicine. For example, the Gail model is a widely used breast cancer risk tool to inform the role of chemoprevention.[32] The risk of recurrence and choice of chemotherapy treatment are based upon integration of data for each individual data.[9-11] Decisions to treat with anticoagulation to prevent stroke in atrial fibrillation and to use lipid-lowering therapy for the prevention of CV disease are guided by risk prediction algorithms. These strategies are used in everyday clinical practice,[6,7] but have not yet been applied to cardio-oncology. This paradigm has the potential to directly and positively impact both CV and oncologic outcomes, and this proof-of-concept trial is a critically important step in determining the utility of risk-guided cardioprotection.

We plan to assess the feasibility and safety of a risk-guided cardioprotective treatment strategy with carvedilol, as compared to usual care, in breast cancer patients undergoing treatment with doxorubicin, trastuzumab, or the combination (Figure 1). Patients who will be treated with trastuzumab-anns (Kanjinti), which is a biosimilar to trastuzumab, will also be included. Our overarching hypothesis is that a risk-guided treatment strategy that initiates carvedilol in high risk patients prior to cancer therapy will result in a decreased incidence of CTX, as compared to usual care. For this pilot study, we propose to evaluate the feasibility of such a trial and safety of our intervention. Carvedilol will be administered in an open label fashion and compared to usual care.



1.2 Name and Description of the Investigational Product

Carvedilol (Coreg) is a safe, widely prescribed, guideline recommended, and FDA approved HF therapy with demonstrated benefits in CV outcomes (mortality, HF hospitalizations), remodeling (LVEF, longitudinal and circumferential strain, diastolic function), and patient symptoms.

Carvedilol phosphate (PCCID 2585) is an alpha/beta-adrenergic blocking agent indicated for the treatment of: (1) mild to severe chronic heart failure; (2) left-ventricular dysfunction following myocardial infarction in clinically stable patients; and (3) hypertension.

a. PHARMACOLOGY: carvedilol is a racemic mixture in which nonselective beta-adrenergic blocking activity is present in the S(-) enantiomer and alpha-1-adrenergic blocking activity in both the R(+) and S(-) enantiomers. It has no intrinsic sympathomimetic activity. Blocking beta-adrenergic activity causes vasodilation and a reduction in peripheral vascular resistance which results in a reduction in cardiac output, tachycardia, renin production, and reflex orthostatic tachycardia. Blocking alpha-adrenergic activity results in a reduction in standing blood pressure, more so than supine blood pressure. Vasodilation, increase in stroke volume reduction in pulmonary capillary wedge pressure, pulmonary artery pressure, heart rate, systemic vascular resistance and right arterial pressure may all contribute to the beneficial effects seen in congestive heart failure.

b. PHARMACOKINETICS:
   i. Absorption: Carvedilol is rapidly absorbed systemically and plasma concentrations achieved are correlated to the dose. It is extensively absorbed with a bioavailability of 25-30% due to first-pass metabolism. Food delays the rate but not the extent of absorption. Taking with food can minimize the effects of orthostatic hypotension. The onset and peak of antihypertensive effect are approximately 30 minutes and 1-2 hours respectively.
   ii. Distribution: Carvedilol is highly protein bound (>95%). There is substantial distribution into extravascular tissue with a steady state volume of distribution of 115L.
   iii. Metabolism: Carvedilol undergoes extensive hepatic metabolism primarily by cytochrome P450 (CYP) 2D6 and 2C9, with a minor contribution from CTP3A4, 2C19, 1A2, and 2E1 resulting in the formation of 3 active metabolites with beta receptor blocking activity. The metabolite 4-hydroxyphenyl is approximately 13 times more potent than the parent compound for beta-andrenergic blockade, however, concentrations of the metabolites are approximately one tenth that of the parent compound. The 3 active metabolites all exhibit weak vasodilatory activity. Plasma concentrations in the elderly and in those with cirrhotic liver disease are 4-7 times higher.
   iv. Elimination: Glucuronidated and sulfated secondary metabolites of carvedilol are excreted primarily through bile into the feces. Following oral administration, the mean systemic elimination half-life ranges from 7-10 hours.

1.2.1 Nonclinical Data

Animal models of doxorubicin CTX support a beneficial CV effect of carvedilol on oxidative stress, endothelial, and mitochondrial dysfunction,[33-35] which are central to the pathophysiology of anthracycline CTX.

1.2.2 Clinical Data to Date

Here, we detail the preliminary data that support the use of our risk model (CCT Risk Model) as well as the use of carvedilol to mitigate CV risk.

Preliminary Data Supporting the CCT Risk Model

Table 1: Baseline Risk Assessment – Model Variables: diabetes, hypertension, treatment, left ventricular ejection fraction (LVEF)

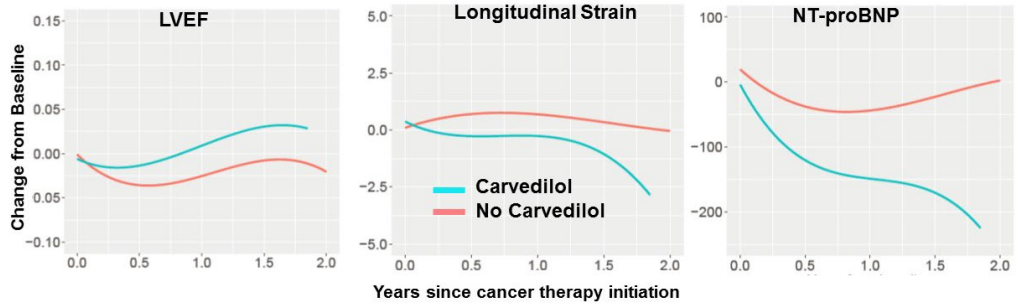
Study	Sensitivity	Specificity	NPV	Proportion Elevated Risk
Penn CCT (derivation cohort and study population)	**0.82**	**0.45**	**0.85**	**0.54**

Randomized clinical trials in cardio-oncology have evaluated the potential role for cardioprotection prophylaxis in "all comers," which we hypothesize has resulted in the observed lack of substantial CV benefit. We propose that the use of a risk guided strategy will identify those patients who may identify the greatest benefit and result in practice-changing guidelines. Our scientific premise is that a patient's clinical characteristics can be used to determine individual CTX risk with cancer therapy and to guide preventive strategies, and that carvedilol will mitigate CTX in elevated risk patients.

Our track record and results support the scientific premise and feasibility of this proposal. We have enrolled 625 patients since the initiation of the Penn CCT cohort study (IRB#811155 / UPCC 09110 / NCT01173341). We have developed an internally validated risk model for determination of risk at baseline (Table 1). The risk model was developed using LASSO applied to the Penn CCT cohort data, in order to identify the most important predictors for the binary outcome of CTX (consistently defined in all our work as an LVEF decline ≥10% to <50%) in the year after baseline. Model performance estimates in the Penn CCT cohort are based on leave-one-out cross-validation.

The CTX risk score [coefficients on log hazards scale] is as follows: -0.06 * **Caucasian race** (yes/no) + 0.47 * **Non-AA/Non-Caucasian race** (yes/no) +0.13 * **tobacco use** (yes/no**) +** 0.01* **systolic BP (mmHg)** + 0.53***diabetes** (yes/no) + 0.10* **hypertension** (yes/no) -0.10 * **LVEF** -0.76 * **trastuzumab** (yes/no) + 1.2 * **doxorubicin + trastuzumab** (yes/no). This score is comprised of a parsimonious set of measures that are readily accessible to clinical providers (oncologists, cardiologists), enhancing the applicability of our risk score to everyday use. Our risk model (**Table 1**) demonstrates an area under the curve (AUC) of 0.72 in Penn CCT. More important than the AUC, our model has favorable properties for a risk-guided treatment strategy. Our goal is to increase the likelihood of treatment of high risk patients while not withholding treatment due to false negative prediction. In particular, the model's risk threshold for "elevated risk" was selected to maximize the NPV, thus minimizing the risk of false negatives and ensuring that the majority of high risk patients are treated, given the burden of CTX (**Table 1**). Defining a predicted probability of CTX >4.6% as elevated risk results in an estimation that 54% of patients will be designated as elevated risk at baseline. This pre-specified elevated risk threshold correctly identifies 82% of patients experiencing CTX (i.e. sensitivity) and yields a NPV of 85%. As a result, the PPV is 12% in the Penn CCT cohort; this PPV is ~2.1 times greater than the observed CTX rate in the cohort at 1 year. Given the biosimilarity of trastuzumab and trastuzumab-anns, the risk score for patients treated with trastuzumab-anns or trastuzumab-anns+doxorubicin will be calculated as if they were being treated with trastuzumab.

Figure 2: Effects of Carvedilol on Cardiac Function and Mechanics in Penn CCT Positive changes observed with LVEF and negative changes in longitudinal strain and NT-proBNP in carvedilol treated patients (blue) indicate beneficial changes.



Inclusion of baseline characteristics resulted in a model with the highest discriminative value. Addition of baseline imaging and biomarker measures did not provide value to our risk score and lessen the generalizability of our score. We propose that a simple risk score comprised of readily obtained clinical variables will facilitate its use.

Preliminary Data to Support the Use of Carvedilol

Carvedilol is an FDA approved HF therapy with improved CV outcomes (mortality, HF hospitalizations), remodeling (LVEF, longitudinal and circumferential strain, diastolic function), and symptoms. The studies by Guglin, Avila, Kalay (**Table 2**) each demonstrate a modest, potential benefit to carvedilol. We postulate that the modest effect sizes observed in these RCTs are related to the treatment of a low risk population with a low prevalence of CV risk factors. As an example, the Guglin study suggests that the subgroup receiving both doxorubicin+trastuzumab derived a benefit from carvedilol, compared to trastuzumab-only patients. Based on our risk model, patients receiving both doxorubicin and trastuzumab sequential therapy is associated with a 7-fold increased risk of CTX. A sub-analysis of our own Penn CCT cohort data support our hypothesis that carvedilol use attenuates the declines in LVEF, longitudinal strain, and NT-proBNP observed with exposure to cancer therapy (**Fig. 2**). Longitudinal trends suggest that in patients treated with carvedilol at baseline, there was a consistent attenuation of the adverse changes seen in the non-carvedilol treated group.

In cardio-oncology, clinical trials have suggested a benefit from carvedilol (**Table 2**). In contrast, the data indicating a benefit with Angiotensin II receptor blockers (ARBs) and Angiotensin-converting enzyme inhibitors (ACE-Is) have been less consistent, with some RCTs showing a very modest CV benefit on LVEF alone [44] and others demonstrating no effect on LVEF[43] and no effect on other indices of cardiac injury and stress.[48] In addition, a recent trial subanalysis suggested superiority of carvedilol over ACE-Is in patients receiving doxorubicin and trastuzumab (a variable in our risk model).[8] We propose that carvedilol is more mechanistically relevant to both the biologic and functional perturbations that occur secondary to doxorubicin and trastuzumab. Animal models of doxorubicin CTX support a beneficial CV effect of carvedilol on oxidative stress, endothelial, and mitochondrial dysfunction,[49-51] which are central to the pathophysiology of anthracycline CTX. Our preliminary data also support this (**Figure 2**). Variables in our risk model further support the use of carvedilol. The model includes cancer treatment, diabetes, and hypertension. Carvedilol targets each of these factors; it attenuates the LVEF declines observed with doxorubicin and trastuzumab, improves insulin sensitivity, and decreases blood pressure (BP).

Clinical trial data to date suggest that carvedilol can be used safely in cancer patients undergoing chemotherapy, but the beneficial effects may be limited to high risk patients. No serious adverse events were reported in any of these studies (**Table 2**). However, carvedilol currently is not standard of care because of the lack of definitive benefit to date. We postulate that the modest reported effects of carvedilol are secondary to the “one size fits all” approach and dilution of a detectable benefit of carvedilol given

inclusion of a low risk population. The Guglin study (**Table 2**) described no effect by carvedilol in all comers, but had a significant effect in the high risk treatment group comprised of patients receiving anthracyclines followed by trastuzumab (a variable in our risk prediction model). Other CTX risk factors have been underrepresented in carvedilol trials to date, making it unfeasible to definitively determine if there is role for carvedilol in high CTX risk patients in posthoc analyses. For example, only ~3% of carvedilol treated participants had a history of hypertension in the CECCY trial[9] (**Table 2**), a significant factor in our CTX risk prediction model, which also contrasts with a prevalence of 30-60% encountered in everyday care. The existing trial data support the need to identify and target a high risk population to test a targeted CV risk reduction strategy in cardio-oncology.

Table 2: Studies Investigating the Impact of Carvedilol in Cardio-Oncology

Reference	Design and Study Population	Results
Kalay, et al. JACC. 2006 [40]	Single blind, placebo controlled RCT of 50 breast, lymphoma or other cancer receiving anthracyclines; 12.5mg once daily of carvedilol versus placebo for 6 months (Population characteristics not noted)	No significant change in LVEF in carvedilol group; significant decline in control group from 68.9 to 52.3% at a mean of 5.2 1.2 months (p<0.001)
Avila, et al. JACC. 2018.[39]	Double-blind, RCT of 192 breast cancer patients receiving anthracyclines, comparing carvedilol (goal 25mg twice daily) vs placebo; Her2+ excluded; 6.3% HTN	No significant effect on clinical LVEF at 6 months; attenuation of TroponinI increases (p=0.003) and diastolic dysfunction (p=0.039) within 6 months of carvedilol initiation
Guglin, et al. ACC 2018 (Late Breaking Clinical Trial)	Double-blind, RCT of 468 breast cancer, patients receiving trastuzumab +/- anthracyclines comparing placebo, lisinopril, or carvedilol; only 4% of patients with HTN; 38% treated with doxorubicin + trastuzumab	No effect on rate of cardiotoxicity (LVEF decline>10%) across entire population (HR 0.71, 95% CI 0.47-1.07, p=0.052); however, in patients receiving anthracyclines and trastuzumab (n=189), carvedilol reduced the incidence of cardiotoxicity (HR 0.49, 95% CI 0.27, 0.89, p=0.009); Effect of carvedilol more pronounced than lisinopril (HR 0.53, 95% CI 0.39, 0.94, p=0.015)

1.3 Dose Rationale

Subjects in the elevated risk group who are randomized to risk-guided intervention will be initiated at 3.125mg carvedilol twice daily and uptitrated as tolerated, at visits occurring at 1 or 2, 3 or 4, and 6 weeks. Carvedilol will be uptitrated in a stepwise fashion to 6.25mg twice daily to 12.5mg twice daily to a maximum dose of 25 mg twice daily, or to a SBP of 110-120mmHg or HR of 50-55 bpm. If excessive and symptomatic hypotension (SBP <90mmHg) occurs, the dose will be decreased. This dosing is consistent with clinical practice for patients with heart failure or hypertension.

2 Study Objectives

This is a pilot study intended to assess the feasibility of the study design, and the safety of a risk-guided approach to carvedilol prescription in breast cancer patients undergoing treatment with doxorubicin, trastuzumab, or the combination.

2.1 Primary Objective

The primary aim of this pilot study is to determine feasibility and safety/tolerability. We will determine whether breast cancer patients can be enrolled, have their CTX risk calculated, randomized, retained and will comply with the study intervention (where applicable). Moreover, we will determine the safety and tolerability of carvedilol in this setting.

2.2 Secondary Objectives

The secondary objectives of the study are to (1) to prospectively validate our CTX risk score, (2) to explore the impact of a risk-guided cardioprotective treatment strategy with carvedilol, as compared to usual care, on measures of CV function and stress, derived from echocardiography and blood biomarkers, and on clinical heart failure, and (3) to determine the associations between individual and structural social determinants of health and CTX risk.

3 Investigational Plan

3.1 General Design

This is a single-center, randomized clinical trial, testing a method for calculating CTX risk score in breast cancer patients treated with doxorubicin and/or trastuzumab cancer therapy. Subjects who are identified as having elevated CTX risk will be randomized to individually-dosed, open-label carvedilol vs usual care. We will use a stratified block randomization according to trastuzumab therapy (yes/no) to ensure balance across treatment regimens, given the different durations of therapy across treatment groups. Subjects being treated with trastuzumab-anns will also be included; for the purposes of stratification and risk-score calculation, trastuzumab-anns will be considered equivalent to trastuzumab. Clinical, echocardiographic, and biomarker data will be collected on all patients at baseline and standardized time intervals during and after therapy at approximately 3, 6, 9, 12, and 24 months.

3.1.1 Screening, Risk Calculation, and Randomization

Subjects will be recruited from the Rena Rowan Breast Cancer Clinic. Subjects who will be newly beginning treatment with anthracyclines and/or trastuzumab therapy and who appear to meet eligibility criteria for this study will be identified by the study team via review of PennChart. The study team will contact the treating oncologist for permission to approach the subject. The study team will then contact the patient (either in person during a regularly scheduled visit at PCAM or over the phone) to assess whether subjects are interested and gather additional information about eligibility criteria if necessary. If interested, subjects will be scheduled for a screening visit. The visit will include consent; a medical history; an echocardiogram (if value of LVEF from pre-chemotherapy clinical echocardiogram is not documented in the EMR), pregnancy test (if applicable and none available in the medical record within 10 days). At the end of the screening visit, the study staff will schedule time for the PI to speak with the patient about their risk score and (if applicable) their treatment arm assignment.

A study investigator will review the data gathered during screening to determine eligibility. The study team will calculate CTX risk using a risk score calculation module in the study REDCap database. The CTX risk score [coefficients on log hazards scale] is as follows: -0.06 * Caucasian race (yes/no) + 0.47 * Non-AA/Non-Caucasian race (yes/no) +0.13 * tobacco use (yes/no) + 0.01* systolic BP (mmHg) + 0.53*diabetes (yes/no) + 0.10* hypertension (yes/no) -0.10 * LVEF -0.76 * trastuzumab (yes/no) + 1.2 * doxorubicin + trastuzumab (yes/no). High (or elevated) risk is defined as a predicted CTX risk > 4.6%. This threshold optimizes the sensitivity and NPV and helps ensure to that all high risk individuals are identified. For the purposes of risk-score calculation, trastuzumab-anns will be considered equivalent to trastuzumab, given the biosimilarity of the two agents.

The PI will inform the subject of their risk group (Low or Elevated), and provide counseling about this information. For subjects in the elevated risk group, the PI will randomize them using a stratified block randomization module (according to trastuzumab therapy, yes/no) built into the study REDCap database, and inform the subject of their treatment arm assignment (individually dosed carvedilol vs usual care). Blocks of 4 will be used for the randomization. In general, this conversation will take place during a scheduled phone call 1-2 days prior to the start of treatment; if necessary, it may be done over the phone or in person on the day of treatment.

All necessary variables for calculating baseline CTX risk will be available at the time of the screening visit. LVEF will be derived from the clinical echocardiogram report. Subjects will not be consented if this information is not available. In the unlikely event that CTX cannot be calculated for a consented patient (for example, if LVEF is not able to be derived due to poor echocardiographic windows), the subject will be considered a screen failure post-consent and will not be randomized.

3.1.2 Study Intervention Phase

Subjects in the elevated risk group randomized to carvedilol will be initiated at 3.125mg twice daily, starting the evening of first chemotherapy. This will be performed in an open label fashion. Dose will be uptitrated as tolerated at visits occurring at 1 or 2; 3 or 4; and 6 weeks. These visits will be timed to coincide with clinical visits to the greatest extent possible. Titration will occur in a stepwise fashion, to 6.25mg twice daily to 12.5mg twice daily to 25mg twice daily, or to a SBP of 110-120mmHg or to a HR of 50-55bpm. If adverse events such as excessive and symptomatic hypotension (SBP<90mmHg) occurs or significant bradycardia (HR <40bpm) occurs, the dose will be adjusted by the PI. The duration of the intervention will be 12 months. Adherence will be assessed by pill count and study diary, and by patient questionnaire (Hill-Bone Compliance scale). All other subjects will be treated according to usual care. There will be no placebo control given this is a Phase 1 safety/feasibility study. The low risk group will not receive a prospective intervention, but will be treated according to usual care.

All subjects will have study visits (including echo, blood draw, medical chart review, and questionnaire) at regular intervals during and after the intervention phase. The exact number and timing of visits is determined by cancer treatment regimen. We will perform a stratified block randomization to ensure balance across treatment regimens. Blocks of 4 will be used for the randomization.

3.1.3 *Follow Up Phase*

Subjects in the elevated risk group assigned to carvedilol will take the study medication for 12 months, after which they will be instructed to stop. Carvedilol can be safely discontinued without a need for stepwise down-titration. Subjects assigned to carvedilol will have a final AE assessment (based on chart review and phone conversation as needed) 30 days following the final dose of study medication. In the event that patients are hypertensive (SBP>140mmHg on multiple readings), they will be referred to their primary care doctor or cardiologist.

All subjects will have a final study visit approximately 2 years after the start of chemotherapy.

In addition, subjects in the doxorubicin and trastuzumab cancer treatment group will also have a visit at completion of 1 year of trastuzumab therapy (approximately 14 months after start of chemotherapy).

3.1.4 Allocation to Interventional Group

After enrollment, we will calculate CTX risk and classify subjects as low or elevated Risk. The risk model is as follows: -0.06 * Caucasian race (yes/no) + 0.47 * Non-AA/Non-Caucasian race (yes/no) +0.13 * tobacco use (yes/no) + 0.01* systolic BP (mmHg) + 0.53*diabetes (yes/no) + 0.10* hypertension (yes/no) - 0.10 * LVEF -0.76 * trastuzumab (yes/no) + 1.2 * doxorubicin + trastuzumab (yes/no). High risk is defined as a predicted CTX risk > 4.6%. We expect 54% of subjects to be classified as elevated risk. Elevated risk subjects will be randomized to treatment with carvedilol (individually dosed) vs usual care (no prospective cardiovascular intervention). Subjects classified as Low Risk will receive usual care. All subjects will be followed serially by blood, survey, and echocardiogram

A randomization module in REDCap, will be used to determine Elevated Risk subjects' assignment to one of two equal sized groups: Randomization will use a block, stratified design (blocks of 4) to determine assignment in the high risk group to individually dosed carvedilol vs usual care. Stratification will be based on cancer treatment group (trastuzumab yes/no) to ensure a balanced distribution across arms. For the

purposes of risk score calculation and stratification, trastuzumab-anns will be considered equivalent to trastuzumab.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoint for this pilot study is feasibility of the study, and safety and tolerability of carvedilol. We will track and examine the following:

1. Feasibility of recruitment (ratio of subjects screened to subjects identified as eligible)
2. Acceptability of the study (ratio of subjects consented to subjects approached)
3. Ability to screen and consent subjects, calculate CTX risk score, and randomize elevated risk subjects prior to start of chemotherapy
4. Safety and tolerability of carvedilol
    a. Rate and grade of adverse events overall, and specifically relating to hypotension, bradycardia, and fatigue in the Elevated Risk Group
    b. Rate of dose interruptions or delays of cancer therapy in the Elevated Risk Group
5. Compliance with the study intervention among elevated risk subjects randomized to carvedilol who (based on pill count and Hill-Bones Compliance Scale).

3.2.2 Secondary Study Endpoints

The secondary endpoints are:

1. Maximum decline in LVEF during the first year of treatment
2. Maximum decline in LVEF at 2 years
3. Echocardiography-derived functional changes (E/e', longitudinal and circumferential strain, or ventricular arterial coupling)
4. Biologic changes (high-sensitivity TroponinT, NT-proBNP)
5. Clinical heart failure

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

- Females
- ≥ 18 years old
- Diagnosed with breast cancer, with treatment plan to include therapy with anthracyclines and/or trastuzumab/trastuzmab-anns in the adjuvant or neoadjuvant setting
- Able to swallow tablets
- Study team is able to obtain all necessary information for calculating baseline CTX risk (including echocardiographic images for quantitation of LVEF) prior to enrollment
- Standard of care pre-chemotherapy measurement of LVEF by echocardiogram (patients with pre-chemo MUGA will be asked to come in for a research echocardiogram as part of screening)

4.2 Exclusion Criteria

- Known Stage IV breast cancer at enrollment
- Pregnant or breast feeding. Due to unknown risks and potential harm to the unborn fetus a negative pregnancy test (serum or urine) within 10 days prior to enrollment is required in women with child-bearing potential. Due to the potential nursing infant harm, women who are currently breast feeding are not eligible for this study.
- Contraindication to carvedilol
    - Baseline systolic blood pressure < 90mmHg (if multiple blood pressures are available in the medical record within 1 month prior to screening, the average SBP will be considered)

  - Baseline heart rate < 55 bpm consistent with severe bradycardia (if multiple resting heart rates are available in the medical record within 1 month prior to screening, the average heart rate will be considered)
  - Allergy to carvedilol
  - History of bronchial asthma or related bronchospastic conditions. If asthma is listed in the medical history or problem list in the EMR but the patient reports no current asthma diagnosis and there are no medical visits with a diagnosis of asthma in the preceding 12 months, the patient will be considered not to have asthma and will not be excluded.
  - Known history of sick sinus syndrome
  - Severe hepatic impairment, defined as serum bilirubin > 3.0x ULN, AST or ALT > 5.0 ULN within 28 days of enrollment
  - Second- or third-degree AV block, as determined by electrocardiogram
  - Severe bradycardia (unless permanent pacemaker is in place)
  - Patients in cardiogenic shock or decompensated heart failure requiring the use of IV inotropic therapy
  - Current use of
    - Bupropion (Wellbutrin)
    - Fluoxetine (Prozac)
    - Paroxetine (Paxil)
    - Quinidine (Quinidex)
    - Duloxetine (Cymbalta)
    - Digoxin
- Current treatment with beta blocker
- Unable to provide consent

Subjects currently on another antihypertensive agent (with the exception of beta blocker) may be enrolled, provided SBP > 100mmHg. If classified as elevated risk and randomized to intervention, carvedilol will be initiated in addition to current therapy.

This protocol does not exclude patients who are participating on other investigational studies. However, enrollment of such patients will only be done with the agreement of the principal investigator of the other study. Therapeutic trials will always take priority.

4.3 Subject Recruitment

Subjects will be recruited from the Rena Rowan Breast Cancer Center. Patients with Stage I-III breast cancer scheduled to receive doxorubicin and/or trastuzumab (or trastuzumab-anns) will be prescreened by a clinical research coordinator and their attending oncologist or nurse practitioner through PennChart review. Patients that may be eligible may be contacted by telephone or approached in clinic by their treating physician or research staff (with permission from their treating physician). Research staff or the treating physician will approach the patient to assess interest. If interested, the patient will be given a copy of the consent form to review. Informed consent will be obtained by a research coordinator or attending physician trained on the protocol.

Settings that involve subject interaction will be limited to the clinics and research facilities at Penn that will be used for this research study. When possible, the consent process will be done in a private room. If patients are unable to give consent, they will not be enrolled in this study.

4.4 Duration of Study Participation

Subjects will participate in the study for a total of 2 years, with the final study visit approximately 24 months after start of chemotherapy.

4.5 Total Number of Subjects

We plan to enroll 110 subjects, for a target of 56 subjects in the elevated risk group.

4.6 Vulnerable Populations:
Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Intervention
5.1 Description
We will dispense carvedilol in 6.25mg tablets.

5.2 Intervention Regimen
Subjects in the Elevated Risk Group randomized to intervention will be treated with open-label carvedilol. All other subjects in the Elevated and Low Risk groups will receive usual care.

Study drug will be initiated at 3.125mg twice daily starting the day of the first chemotherapy cycle, and uptitrated at visits occurring at 2, 3 or 4, and 6 weeks, in a stepwise fashion to 6.25mg twice daily, to 12.5mg twice daily, to a maximum dose of 25mg twice daily, or to a SBP of 110-120mmHg or HR of 50-55bpm.

Subjects will remain on study drug for 12 months.

5.3 Receipt
The IDS will purchase the active drug commercially. Upon receipt the drug will be logged into inventory and stored securely.

5.4 Storage
Medication will be stored at room temperature (20-25 Celsius, with excursions permitted in the range of 15-30 Celsius). In the IDS, tablets will be kept in the original manufacturer's container until transferred to a standard prescription bottle for dispensing to individual study subjects. Once dispensed, subjects should keep the tablets in the prescription bottle.

In the event that the study team has to store medication temporarily before it can be given to the subject, it will be stored at room temperature in a locked cabinet on a secured floor (11 South Tower, PCAM). Access to this cabinet is limited to authorized members of the study team.

5.5 Preparation and Packaging
Investigational product will be dispensed in tablet form, in standard prescription bottles labeled for the individual study subject. Preparation will follow traditional pharmacy practice, pursuant to a prescription.

The active tablets, as noted above, will be purchased commercially and not altered in any way.

5.6 Administration and Accountability
The study team will order study drug from Penn IDS to be picked up the day of study visit, or to be shipped directly to the patient. The study team will maintain investigational product logs at the subject level.

5.7 Subject Compliance Monitoring
Compliance will be assessed using pill count, drug diary, and patient questionnaire (see appendix). Compliance will be assessed at visits at 1 or 2, 3 or 4, and 6 weeks, while dose is being titrated. After this time, study diaries and pill counts will be reviewed at each visit while subject is on study medication. As part of each compliance assessment, patients will also be assessed using the Hill-Bone High Blood Pressure Compliance Scale.

Patients will be considered noncompliant if they received < 80% or >120% of the cumulative prescribed dose for any period during the titration phase (first 6 weeks), or for any two periods on stable dose. If a patient is noncompliant, the study team will re-instruct patients in correct administration of medicine, and

will counsel patient regarding importance of taking study drug as instructed. If a patient is noncompliant during the titration phase, the dose will not be titrated until patient has been compliant for at least 2 weeks.

In the event of significant and repeated non-compliance (defined as 3 or more missed study visits, or repeated instances (3 or more) with study medication noncompliance as described above), a patient may be withdrawn from treatment at the PI's discretion.

5.7.1 Return or Destruction of Investigational Product

At the end of the year-long intervention, if the study team instructs the patient to stop taking study medication early, or if patient withdraws from treatment, the study team will collect all remaining study drug from the patient and perform a final compliance assessment. The investigational product will then be returned to Penn IDS for destruction.

6 Study Procedures

The exact number and timing of visits and duration of intervention will vary depending on which cancer therapy regimen patients are prescribed by the treating oncologist, their risk group, and their arm assignment.

There are some timepoints that will apply to all subjects:

- Screening, consent, and risk score calculation will take place prior to start of chemotherapy. This may be done the day of first chemotherapy.
- The baseline visit will take place during infusion on the first day of chemotherapy
- Subjects will have a final study visit approximately 2 years after the start of chemotherapy

Subjects in the Elevated Risk Group who are randomized to treatment with carvedilol will have study activities at additional timepoints:

- Subjects will take first dose of carvedilol in the evening of the first day of chemotherapy
- Subjects will have Titration Visits at 1 or 2, 3 or 4, and 6 weeks; to the greatest extent possible, these will be done in combination with regularly scheduled clinic visits.
- Subjects will remain on study medication for 1 year (365 days).
- Subjects will have a final AE assessment (by phone or in person) approximately 30 days after final dose of study medication

All other study visits will occur according to the below guidelines:

- For subjects treated with doxorubicin and trastuzumab/trastuzumab-anns:
  - Study visits prior to and after doxorubicin
  - Study visits prior to and approximately every 3 months while on trastuzumab/trastuzumab-anns
  - Study visit after final trastuzumab/trastuzumab-anns treatment (or after completion of 1 year of trastuzumab/trastuzumab-anns therapy, if on indefinitely)
- For subjects treated with trastuzumab/trastuzumab-anns (no doxorubicin):
  - Study visits prior to and approximately every 3 months while on trastuzumab/trastuzumab-anns
  - Study visit after final trastuzumab/trastuzumab-anns treatment (or after completion of 1 year of trastuzumab/trastuzumab-anns therapy, if on indefinitely)
- For subjects treated with doxorubicin (no trastuzumab/trastuzumab-anns):
  - Visits prior to and after doxorubicin
  - Visits at approximately 5, 8, and 11 months following start of chemotherapy (to align with timing for doxorubicin + trastuzumab/trastuzumab-anns patients)

Table 3 describes what study activities will be completed at each type of visit.

Table 3: Study Activities By Visit Type

	Pre-screening contact	Screening[1]	Baseline[6]	Titration Visits[C]	Study Visits (Intervention Phase)	Final AE Assessment[C]	Study Visits (Follow-up Phase)
Assess Interest	X						
Give copy of consent form	X						
Schedule Screening	X						
Medical Record Review	X						
Consent		X					
Medical History		X					
Serum / Urine Pregnancy test		X[2]					
Eligibility		X					
Electrocardiogram		X[3]					
Clinical Data		X	X	X[C]	X	X[C]	X
CTX Risk Score		X					
Randomization[E]		X					
Symptoms Questionnaires			X		X		X
Family/Social History			X				
SDOH			X				
Research Blood Draw			X		X		X
Echocardiogram		X[4]	X[5]		X[7]		X[7]
Adverse Event Assessment			X	X[C]	X	X[C]	
Compliance Assessment				X[C]	X[C]	X[C]	

[1] May be done same day as baseline visit
[2] For women of reproductive potential when a negative pregnancy test is not available in the medical record within the prior 10 days
[3] If none available in the medical record within 28 days prior to enrollment
[4] As standard of care, all breast cancer patients have their LVEF checked prior to starting treatment with Anthracyclines or trastuzumab/trastuzumab-anns . This is typically a TTE, but in some cases, the oncologist will order a MUGA instead. If patient has a MUGA, or if value of LVEF by pre-chemo echo is not documented in the EMR the study will arrange for a research echocardiogram as part of screening.
[5] First day of chemotherapy
[6] If no research echo is needed as part of screening, and either the pre-chemo echo is not done at the HUP/PCAM echo lab or the pre-chemo echo does not include the necessary images for strain or 3D analyses, the research team may arrange for a research echocardiogram at baseline
[7] As standard of care, all breast cancer patients will have an echocardiogram approximately every 12 weeks during treatment with trastuzumab or trastuzumab-anns, and between being treated with Anthracyclines and with trastuzumab/trastuzumab-anns. The study team will obtain a copy of these standard of care echocardiograms and use them in place of a research echocardiogram at these time points.
[E] Subjects in the Elevated Risk Group only
[C] Subjects in the Elevated Risk Group who are randomized to carvedilol only

6.1 Screening, Calculation of CTX Risk Score, and Randomization

The screening visit may be done the same day as the baseline visit. Consent may be obtained prior to the screening visit, but will not be obtained until study staff has verified that all data necessary to calculate risk score (including clinical LVEF by echocardiogram) will be available at the screening visit.

- Consent – will be obtained by research coordinator or attending physician
- Medical history
- Electrocardiogram - if none available in EMR within 28 days prior to consent
- Echocardiogram - if patient had pre-chemo MUGA or if documentation of clinical LVEF by echocardiogram is not documented in the EMR
- Pregnancy test - if woman of reproductive potential and negative pregnancy test is not available in the medical record within the preceding 10 days, a serum or urine pregnancy test will be obtained

After the screening activities are complete, the PI (or appropriately trained and delegated attending co-I) will confirm eligibility and calculate CTX risk score. Subjects in the elevated risk group will be randomized using a stratified (trastuzumab/trastuzumab-anns yes/no) block randomization module in REDCap. For the purposes of risk score calculation and stratification, trastuzumab-anns will be considered equivalent to trastuzumab. The PI will speak with the patient (on the phone or in person) to notify her of her risk group and provide counseling as to what this means. The PI will also inform subjects in the Elevated Risk Group of their treatment assignment during this conversation.

6.2 Study Intervention Phase

6.2.1 Baseline Visit

The baseline visit will take place on the first day of chemotherapy, during infusion. At this visit, the following activities will be completed:

- Collect clinical data
- Symptoms Questionnaires and SDOH
- Research blood draw (16 mL)
- Family and Social History
- Research Echocardiogram - if the pre-chemo echocardiogram is not done at the Hospital of the University of Pennsylvania/Perelman Center for Advanced Medicine Echo Lab or the pre-chemo echo does not include the necessary images of for longitudinal and circumferential strain and 3D analysis of the left ventricle, the study will arrange for a research echocardiogram to capture these images and ensure that complete echo data is available for all patients at baseline. The research echocardiogram may be done at any time between consent and first infusion.
- Subjects in the Elevated Risk Group randomized to carvedilol will be given study medication and will be instructed to take first dose of study medication in the evening of the first day of chemotherapy

6.2.2 First Titration Visit (Week 1 or 2) - Elevated Risk Subjects Randomized to Carvedilol only

Subjects will be asked to come in after 2 weeks on study medication to check vitals (if vitals not available in the medical record for this time point). Study team will also assess for compliance and AEs/SAEs. Whenever possible, this will be combined with a clinic or infusion visit in the Perelman Center.

Dose will be increased to 6.25mg twice daily if <u>all</u> below conditions are met:

- SBP > 110mmHg (if multiple blood pressures available since last visit, average SBP will be considered);
- HR > 50bpm (if multiple heart rates available since last visit, average HR will be considered);
- No AEs/SAEs which are possibly, probably, or definitely related to the intervention are reported; and
- Compliance between 80% and 120% (inclusive)

If one or more of the above conditions is not met, PI will determine whether to continue at current dose, uptitrate to next dose level, or hold study drug.

6.2.3 Second Titration Visit (Week 3 or 4) - Elevated Risk Subjects Randomized to Carvedilol only

Subjects will be asked to come in after 3-4 weeks on study medication to check vitals (if vitals not available in the medical record for this time point). Study team will also assess for compliance and AEs/SAEs. Whenever possible, this will be combined with a clinic or infusion visit in the Perelman Center.

Dose will be increased to 12.5mg twice daily if <u>all</u> below conditions are met:

- SBP > 110mmHg (if multiple blood pressures available since last visit, average SBP will be considered);

- HR > 50bpm (if multiple heart rates available since last visit, average HR will be considered);
- No AEs/SAEs which are possibly, probably, or definitely related to the intervention are reported; and
- Compliance between 80% and 120%

If one or more of the above conditions is not met, the PI will determine whether to continue at current dose, titrate to next higher dose level, or titrate to next lower dose level.

6.2.4 Third Titration Visit (Week 6) – Elevated Risk Subjects Randomized to Carvedilol only

Subjects will be asked to come in after 6 weeks on study medication to check vitals (if vitals not available in the medical record for this time point). Study team will also assess for compliance and AEs/SAEs. Whenever possible, this will be combined with a clinic or infusion visit in the Perelman Center.

Dose will be increased to 25mg twice daily if all below conditions are met:

- SBP > 110mmHg (if multiple blood pressures available since last visit, average SBP will be considered);
- HR > 50bpm (if multiple heart rates available since last visit, average HR will be considered);
- No AEs/SAEs which are possibly, probably, or definitely related to the intervention are reported; and
- Compliance between 80% and 120%

If one or more of the above conditions is not met, the PI will determine whether to continue at current dose, titrate to next higher dose level, or titrate to next lower dose level.

6.2.5 Unscheduled Titration Visit

If excessive (SBP < 90mmHg) and symptomatic hypotension and/or excessive (HR < 40bpm) and symptomatic bradycardia occurs, the patient will be asked to come in for an unscheduled titration visit. At this visit, study team will check vitals, review compliance and AEs/SAEs.

The PI will determine whether to continue at current dose or titrate to next lower dose level, and will determine timing of next titration visit (1-3 weeks).

6.2.6 Study Visit (On Intervention)

In general, study visits will occur every 3 months for approximately one year. However, the exact timing of the study visits on intervention will depend on patients' treatment regimen. Visits should be completed within +/- 28 days of targeted time point.

For subjects in the doxorubicin and trastuzumab/trastuzumab-anns cancer treatment group, the visit between doxorubicin and trastuzumab/trastuzumab-anns should be completed after final treatment with doxorubicin and before first treatment with trastuzumab/trastuzumab-anns (or vice versa).

During Study Visits on intervention, the following study activities will be completed:

- Collect clinical data (including images from standard of care echocardiogram if done)
- Symptoms Questionnaires
- Research blood draw (12 mL)
- AE Assessment
- Compliance Assessment (for Elevated Risk Subjects randomized to carvedilol only)
- Research echocardiogram if no standard of care echocardiogram at this time point (typically this will only apply to doxorubicin subjects)

6.3 Follow Up Phase of the Study

6.3.1 Off-Intervention Follow-up - Elevated Risk Subjects Randomized to Carvedilol Only

A final AE assessment will be conducted 30-40 days following the final dose of study medication, for AEs/SAEs that occur within 30 days following final dose. This may be done over the phone or in person, and will also involve medical record review.

A final compliance assessment may also be done at this time point, if not already completed. In this case, subject will be asked to come to the Perelman Center.

6.3.2 Study Visit (Off Intervention)

The exact timing of these visits will depend on patients' treatment regimen. After the first year, all patients will undergo an additional visit at two years (post cancer therapy initiation). Visits should be completed within +/- 28 days of targeted time point.

Subjects in the doxorubicin + trastuzumab/trastuzumab-anns cancer treatment groups will also have an off intervention study visit at the end of trastuzumab/trastuzumab-anns therapy (approximately 14 months following start of chemotherapy).

For subjects in the trastuzumab/trastuzumab-anns cancer treatment group, the end of trastuzumab/trastuzumab-anns study visit will be completed after final dose of study medication whenever possible.

The following study activities will be completed at these visits:

- Collection of clinical data (including images from standard of care echocardiogram if done)
- Symptoms Questionnaires
- Research blood draw (12 mL)
- Research echocardiogram if no standard of care echocardiogram at time point (will apply to most subjects at 24 Month Visit)

6.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, or because of AEs/SAEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects assigned to intervention with carvedilol and who withdraw early will have one final visit to collect investigational product and to follow up regarding adverse events. Subjects may withdraw or be withdrawn from treatment, but continue to participate in the observational portion of the study.

6.4.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects assigned to intervention with carvedilol who withdraw consent to participate in the study during the study intervention will be seen for one final visit to collect the investigational product. During this visit they will be asked for permission to have the study team contact them approximately 30 days after their final dose of the study drug to assess for adverse events.

Subjects may be withdrawn from treatment, but choose to continue to participate in other study activities. In this case, subjects will continue study visits as if they were in the low risk group.

For subjects in the low risk group or elevated risk subjects assigned to usual care who withdraw, and for all subjects who withdraw during follow-up, there will be no final visit and no data will be collected following withdrawal.

7 Study Evaluations and Measurements

7.1 Clinical Covariates

Detailed clinical covariates will be obtained from questionnaires and medical record review including:

- Date of birth
- Height (baseline only)
- Weight (all visits when clinical data is collected)
- Any history of disease, and in particular history of cardiac disease (collected at baseline, and updated at each visit when clinical data is collected)
- Blood pressure and heart rate (all visits when clinical data is collected)
- Medication Use (all visits when clinical data is collected)
- Clinical lab results not drawn specifically for this study, including pregnancy test, metabolic panel, CBC and hem profile, BNP/proBNP/NTproBNP, Troponin I/Troponin T, and other cardiac biomarkers if drawn (all visits when clinical data is collected)
- Results of cardiovascular testing, including electrocardiogram, echocardiogram, MUGA, stress tests (all types), cardiac MRI, and cardiac catheterization (all visits which include either clinical data collection or AE assessment)
- BRCA status, if known (at baseline, updated at 2YFU visit)
- Stage and grade of cancer (at baseline)
- Cancer therapy (including surgery, chemotherapy, non-chemo systemic therapies, and radiotherapy) (at all visits where clinical data is collected)
- Details of hospitalizations and procedures (at all visits where clinical data is collected or AE assessment is performed)
- Family history of cancer and cardiac disease (at baseline)
- Tobacco use (at screening)

7.2 Vital Signs

Blood pressure and heart rate may be taken at the 1st, 2nd, and 3rd titration visits (if not available in the medical record). Blood pressure and heart rate will be taken at any unscheduled titration visits.
Blood pressure will be taken sitting after 5 minutes of rest. If patient reports symptoms of orthostatic hypotension, blood pressure may also be taken standing to evaluate for orthostatic vital signs.

7.3 Laboratory Evaluations

Blood samples will be obtained for research purposes at baseline and at all study visits. 16mL (4mL SST and 12 mL EDTA) will be obtained at baseline and 12mL (4mL SST and 8mL EDTA) at the subsequent visits. Samples will be immediately processed and from these samples, plasma, serum, and buffy coat will be banked for future use. This protocol encompasses the measurement of specific biomarkers, but the objective is also to include these samples in our biobank for future research in cardiotoxicity of cancer therapies and risk-guided interventions, and patients will be consented to have their blood used for the testing of additional novel biomarkers. Blood sampling for research purposes will occur in conjunction with clinical blood draws when possible. Blood sampling will be done in the usual fashion with standard phlebotomy precautions. These specimens will be banked for future use (see Attachment for Blood Processing Protocol).

All assays will be performed posthoc, in batches, to minimize the effects of confounding. These assays will be performed in the Translational Core Lab, in the lab of Dr. Ky in the Smilow Translational Research Center, or in the lab of collaborators. We plan on testing for hsTnT and NT-proBNP, as well as other cardiac biomarkers to be determined as knowledge advances.

7.4 Pregnancy Testing

If a pregnancy test is not available in the medical record within 10 days prior to enrollment, a serum or urine pregnancy test will be performed for subjects of reproductive potential (defined as having had menses at any time in the preceding 12 consecutive months) as part of the screening visit.

7.5 Other Evaluations, Measures

7.5.1 Transthoracic Echocardiogram:

Resting echocardiograms (Vivid E9 or E95, GE Healthcare) with conventional measures of systolic and diastolic function, in conjunction with posthoc quantitation of novel measures of strain and strain rate will be obtained at study visits when subjects do not have a standard of care, clinically ordered echocardiogram. In addition to the standard echocardiographic protocol used in clinical practice, we will obtain additional imaging, including a more comprehensive assessment of longitudinal and radial measures of cardiac function and contractility via ascertainment of myocardial velocities, strain, and strain rate using high frame rate 2D and color tissue Doppler which will be used for research purposes only. For strain imaging, views over 5 cardiac cycles will be obtained from the 2-, 3-, and 4-chamber LV apical views, as well as via the parasternal short and long axis. These additional research images will add approximately 10 minutes to the total acquisition time. Off-line strain analyses will be performed on the EchoPAC system (EchoPAC, GE Healthcare, and Milwaukee, WI) or Tomtec System (Cardiac Performance Analyses). Results of the echocardiogram, according to current clinical standards, will be conveyed to the patient and entered in the patient's chart. Any clinically relevant findings will also be conveyed to the treating provider. In particular, findings that represent a significant cardiac event (such as LVEF reduction to less than 50%) will be conveyed to the treating provider (see Attachment for Echo Protocol). At times, clinical echocardiograms may be obtained as part of standard clinical practice and these studies will be obtained and used for quantitative analysis.

All echocardiograms will be rigorously analyzed by the Penn Center for Quantitative Echocardiography (blinded to clinical characteristics, arm assignment, and treatment assignment). The echocardiographic characterization will generate a rich dataset of measures of systolic function (LVEF, longitudinal and circumferential strain), structure (volumes, mass), diastolic function (E/e'), and VA coupling (Ea/Ees, Ea).

7.5.2 LVEF for Calculation of Risk Score

A value for LVEF from the report of the pre-chemotherapy echocardiogram is required for calculation of the risk score. In general, this is documented in the EMR. If the echo report provides a range rather than a value (e.g. "LVEF 55-60%"), the mean will be used in the calculator, consistent with our practice in the Penn CCT Cohort. If no echo report is available in the medical record, an office note signed by attending physician or APP will be considered acceptable source documentation of LVEF, provided it specifies the study date, modality, and a value (or range) for LVEF.

In some cases, we may perform an echocardiogram at screening. This will only be done if the study team is not able to obtain documentation of pre-chemotherapy LVEF by echocardiography in time for patient to be enrolled on study. The PI will read the screening echo and document her clinical assessment of LVEF for use in the calculator. Results of this screening echocardiogram, based on current clinical standards, will be entered into the EMR and will be shared with the patient. Any significant findings, based on current clinical standards, will be reported to the treating provider.

In some cases, we may perform a research echocardiogram at baseline in order to ensure that baseline 3D and strain echo data is available for all patients. If clinical LVEF is available from both the clinical pre-chemo echo and the baseline research echo, the Risk Score will be calculated using the clinical pre-chemo LVEF. This is consistent with the derivation of the Risk Score.

A member of the study team will use a REDCap module to calculate CTX risk score using race, hypertension, tobacco use, diabetes, SBP, planned treatment, and LVEF from clinical echo report.

7.5.3 Electrocardiogram

An electrocardiogram (EKG) will be checked as part of screening. The study team will perform one if there is none available in the medical record within 28 days of enrollment. Any clinically significant findings will be shared with the patient and provider and recorded in the medical record.

7.5.4 Symptoms and Activity Questionnaires

At baseline and at each study visit (on and off Intervention), we will collect symptoms data from all patients based on the MD Anderson Symptoms Inventory – Heart Failure, FACIT Fatigue, FACIT Dyspnea on Exertion, and exercise data using the Godin Leisure Time Exercise Questionnaire. All questionnaires are standardized and validated instruments,[41-43] commonly used in cardio-oncology and oncology research, as well as in other disciplines.

7.5.5 SDOH Measures

Using the National Institute of Minority Health and Health Disparities' PhenX Measures for SDOH Collections, we will perform comprehensive phenotyping of individual (race and ethnicity, gender identity, sexual orientation, educational attainment, employment status, occupational prestige, annual family income, health insurance coverage, health literacy, food insecurity, language barrier, access to health services, access to health technology, discrimination and disparate health care quality) and structural (air quality, concentrated poverty, racial/ethnic residential segregation, community educational attainment, food environment and social vulnerability) SDOH. We will additionally collect data on distress using the National Comprehensive Cancer Network (NCCN) distress thermometer and problem list.[56] We will also collect data on financial distress based on a commonly used questionnaire developed by the National Health Interview Survey.[57] All measures of SDOH will be obtained at baseline, prior to the initiation of cancer therapy.

7.5.5.1 Individual SDOH

Table 4 presents the specific instruments and modes of administration for the collection of measures of individual SDOH. These encompass existent and widely established, validated and reliable instruments for the collection of measures of individual and structural SDOH developed by the National Institute of Minority Health and Health Disparities with the goal of establishing a "common currency" of measurement protocols to inform effective interventions to reduce health disparities (www.phenxtoolkit.org/collections/sdoh).[58-61] The individual SDOH questionnaires will be primarily collected using the paper and pencil method. Trained clinical research coordinators will administer the interviewer-administered questionnaires in a face-to-face interview. Participants will be asked to complete the self-administered questionnaires. To improve compliance, participants who prefer to complete the self-administered questionnaires at home will be given the option to complete questionnaires digitally via email survey. Any clinically actionable patient responses (e.g. evidence of significant distress) will be relayed to the clinical oncologist and the Abramson Cancer Center social work services for appropriate follow-up once the participant agrees to sharing of this information with the clinical team (oncology and social work).

Table 4: National Institute of Minority Health and Health Disparities PhenX Instruments for measurements of individual SDOH

Measures of Individual SDOH	Protocol/Instrument	Mode of Administration

Race and ethnicity	US Census Bureau, Census 2020, Questionnaire	Self-administered
Educational attainment	National Health and Nutrition Examination Survey	Self-administered
Employment status	Panel Study of Income Dynamics	Self-administered
Occupational prestige	American Community Survey and General Social Survey Codebook	Self-administered
Gender identity	All of Us Research Program Participant Provided Information	Self-administered
Sexual orientation	All of Us Research Program Participant Provided Information	Self-administered
Distress	National Comprehensive Cancer Network Distress Thermometer and problem list	Self-administered
Language barrier (English proficiency)	California Health Interview Survey 2018 Adult Questionnaire	Interviewer-administered
Annual family income	National Health Interview Survey Family Questionnaire	Interviewer-administered
Health insurance coverage	Health Reform Monitoring Survey	Interviewer-administered
Access to health services	National Health Interview Survey, Adult Access to Health Care and Utilization Module	Interviewer-administered
Health literacy	Short Assessment of Health Literacy-English Questionnaire	Interviewer-administered
Access to health technology	National Cancer Institute's Health Information National Trends Survey	Interviewer-administered
Discrimination	Major Experiences and Everyday Discrimination Scales	Interviewer-administered
Disparate health care quality	California Health Interview Survey 2018 Adult Questionnaire	Interviewer-administered
Food insecurity	Short form of U.S. Department of Agriculture Economic Research Food Security Survey	Interviewer-administered
Financial distress	National Health Interview Survey	Interviewer-administered

7.5.5.2 Structural SDOH

As part of the PhenX tool, and as developed by the National Institute of Minority Health and Health Disparities with the goal of establishing a "common currency" of measurement protocols to inform effective interventions to reduce health disparities (www.phenxtoolkit.org/collections/sdoh), structural SDOH measures will also be obtained from existent resources such as the 5-year American Community Survey estimates by geocoding participant's current address to local geographic area (e.g. county, census tract). Participant's current address will be extracted from medical records. Thus, there will be no additional participant burden for the collection of structural SDOH measures. **Table 5** summarizes the specific structural SDOH measures and resources that will be used for the collection of each measure.

Table 5: National Institute of Minority Health and Health Disparities PhenX Instruments for measurements of structural SDOH

Measures of Structural SDOH	Protocol/Instrument
Air quality	US Environmental Protection Agency Air Quality Index report
Concentrated poverty	5-year American Community Survey estimates
Racial/ethnic residential segregation	5-year American Community Survey estimates
Community educational attainment	5-year American Community Survey estimates
Food environment	US Department of Agriculture Economic Research Service Food Environment Atlas
Social vulnerability	Agency for Toxic Substances and Disease Registry

7.5.6 Drug Diary, Compliance, and Pill Count – Elevated Risk Subjects randomized to Carvedilol only

Subjects will be asked to maintain a drug diary to track doses that are taken/missed, and any symptoms that they experience while on study medication. To minimize confusion regarding individualized dosing, the study team will customize the drug diary for each patient, at each period during the study, and will give patient new drug diaries whenever the dose is changed or when a refill is provided. The drug diary template is attached.

The compliance of elevated risk subjects randomized to carvedilol will be assessed using the Hill-Bone Compliance Scale and pill count at each study visit. This is a widely used, standardized[44] scale which provides a method for clinicians to assess patients' self-reported compliance levels and to plan appropriate interventions.

8 Statistical Plan

8.1 Primary Endpoint

In order to assess the safety and tolerability of carvedilol, we will quantify the incidence of adverse events according to NCI CTCAE v5.0 and assess medication compliance.

8.2 Secondary Endpoints

One of our secondary outcomes of interest is maximum decline in LVEF during the first year of follow-up, as a continuous measure. This is a highly clinically relevant variable. The rationale for this endpoint is as follows: LVEF is a valid, reproducible, and highly clinically relevant measure of cardiac function and is a potent predictor of all-cause and CV mortality.[45] Multiple oncologic and CV treatment decisions are made based upon LVEF.[46]

Other secondary outcomes of interest include: maximum LVEF decline at 2 years; time to CTX (defined by a decline in LVEF of ≥ 10% to <50%); clinical HF (urgent or new office or ED visit or hospitalization with HF signs or symptoms); changes in functional measures (E/e'; longitudinal and circumferential strain, ventricular arterial coupling); changes in biologic measures (high sensitivity TroponinT; NT-proBNP); and safety and tolerability of carvedilol. We will also assess the frequency of cancer therapy dose interruptions due to CTX across both treatment groups. HF will be adjudicated by a cardiologist, according to standard definitions. HF symptoms include dyspnea, decreased exercise tolerance, and fatigue; signs of HF include worse end-organ perfusion or volume overload (peripheral edema, increased abdominal distension, pulmonary crackles/rales, increased jugular venous pressure or S3). Initiation of CV medications will be recorded at each study visit. Although our primary outcome assessment is at 1 year, we will explore all outcome measures, including maximum change in LVEF, at 2 years.

8.3 Sample Size and Power Determination

Sample size estimates are based on data from the Penn CCT Cohort. Our primary objective is to establish the safety and tolerability of carvedilol in the high risk population. We therefore base sample size estimates for this pilot study on the minimum number of patients needed to identify a statistically significant difference in safety outcomes between carvedilol and usual care arms. We plan a total enrolled sample of size up to 110 (consisting of high and low risk) and assume ~10% attrition. This targeted sample size yields a target of 56 high risk patients, of whom 50 are expected to have complete follow-up data. With a sample of size 50 and assuming an incidence of 3.1% for hypotension, the half-width of our 95% confidence interval for the incidence rate will be 4.8%. For all adverse events, assuming an incidence of 12%, we will be able to estimate the 95% CI for the incidence rate of all adverse events with a half-width of 9%. With 50 patients, we are powered to detect a 4.9% difference in LVEF between the two arms.

8.4 Statistical Methods

The first step in statistical analysis will involve summarizing the characteristics of all patients. We will use standard descriptive statistics (means, standard deviations (SD), medians, interquartile ranges for continuous variables, counts, proportions for categorical variables) and graphical methods to summarize the study characteristics overall, and stratified by study arm, cancer treatment (doxorubicin, trastuzumab/trastuzumab-anns, doxorubicin+trastuzumab/trastuzumab-anns), and by risk.

An intent-to-treat approach will be used in all analyses. The intent to treat population used for our primary statistical analyses will include all randomized high CV risk patients. We will use a 2-sided significance level of 0.05 in all our hypothesis tests. Unless noted, comparisons will report unadjusted p-values.

We will quantify the recruitment and retention rates, adherence rates (pill count, study diary, Hill Bone Compliance questionnaire), maximum tolerated dosages of carvedilol, and rates of adverse events (CTCAE v5). We will define these rates across the entire study population and in the elevated risk patients, specifically evaluating the effect of carvedilol compared to usual care. We will compare rates between the carvedilol and usual care arms using chi-squared tests. Block randomization within cancer treatment strata will help to ensure an equal distribution of treatment groups across arms; randomization will help to ensure baseline characteristics and CV risk are similarly distributed across arms. Blocks of 4 will be used to generate the randomization scheme.
Our secondary analyses will explore the effect of carvedilol on LVEF change; the incidence of CTX (LVEF decline ≥ 10% to <50%); clinical HF (urgent or new office or ED visit or hospitalization with HF signs or symptoms); frequency of treatment interruptions due to CTX in order to obtain effect size and variance estimates to inform the design of our subsequent Phase III RCT. We will also explore changes in the following intermediary measures: longitudinal and circumferential strain, E/e', VA coupling (Ea/Ees), hsTnT and NT-proBNP to understand if these measures can be used as surrogate outcomes in a subsequent RCT. We will use t-tests to compare continuous outcomes between carvedilol and usual care groups.[55-58]Analyses of time-to-event secondary outcomes (CTX, HF, treatment interruptions) will be conducted using log rank tests to compare treatment arms; patients will be censored at the time of death or last follow-up. As an exploratory analysis, we will use the same approach to assess the effect of carvedilol at 24 months.

As an additional analysis, we will compare the incidence of CTX occurring within the first year of follow-up between high risk (in the usual care arm) and low CV risk (observational group), given our additional objective is to prospectively validate the performance of our risk model and the ability of our model to successfully identify patients in need of treatment. We will also use our biomarker and imaging measures to define if there are dynamic changes in these markers in low risk individuals that can be used to further enhance the performance of our risk prediction model in future iterations. We will also ascertain our outcomes according to the varying degrees of CTX risk. We will use regression models estimated via generalized estimating equations including time, treatment, and their interaction to estimate and compare trends in CTX risk over time and treatment group.

8.4.1 Safety Analysis

Carvedilol is safe, widely prescribed and a guideline recommended HF therapy. We will ensure the safe administration of study drug in the elevated CV risk group with careful oversight by PI. At each study visit, we will assess for adverse events using the CTCAE criteria. At study completion we will report the number and proportion of patients experiencing adverse events, and specifically evaluate hypotension, bradycardia, and fatigue, as well as treatment delays related to CV events and fatigue by risk group and treatment arm. Adverse events will be reported according to relevant institutional policies and FDA requirements.

8.5 Subject Population(s) for Analysis

An intent to treat approach will be used in all analyses; the intent to treat population used for our primary statistical analyses will include all randomized high CV risk patients.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

For FDA regulated studies the FDA defines an adverse event as the following:

Adverse event means any untoward medical occurrence associated with the use if a drug in humans whether or not considered drug related.

9.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

For the purpose of this study, planned procedures and hospitalizations (such as for mastectomy) will not be considered to be AEs/SAEs. Events that occur to complicate and prolong such hospitalizations will be considered to be AEs/SAEs, as appropriate.

9.2 Recording of Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for defining and grading AEs/SAEs. We will record cardiovascular AEs (Table 4), expected AEs regardless of attribution, unexpected AEs which are at least possibly related to the study intervention, incidental findings from the research echocardiogram, and all AEs ending in death. Only events Grade 2 and higher will be recorded, unless resulting in hospitalization for ≥24 hrs.

Table 4: CTCAE v5 Cardiovascular Terms

Cardiac Disorders	Vascular Disorders	Other CV Related Terms
Aortic Valve Disease	Arterial thromboembolism	Cardiac troponin I increased
Asystole	Capillary leak syndrome	Cardiac troponin T increased
Atrial Fibrillation	Flushing	CPK increased
Atrial Flutter	Hematoma	Ejection fraction decreased
Atrioventricular Block	Hot flashes	Electrocardiogram QT corrected interval prolonged
Atrioventricular Block first degree	Hypertension	Electrocardiogram T wave abnormal
Cardiac Arrest	Hypotension	Localized edema
Chest pain – cardiac	Lymph leakage	Pulmonary hypertension
Conduction disorder	Lymphedema	
Cyanosis	Lymphocele	
Heart Failure	Peripheral ischemia	
Left Ventricular Systolic Dysfunction	Phlebitis	
Mitral Valve Disease	Superficial thrombophlebitis	
Mobitz (type) II atrioventricular block	Superior vena cava syndrome	
Mobitz type I	Thromboembolic event	
Myocardial Infarction	Vasculitis	
Myocarditis	Vascular disorders – other, specify	
Palpitations		
Paroxysmal atrial tachycardia		
Pericardial effusion		
Pericardial tamponade		
Pericarditis		
Pulmonary valve disease		
Restrictive cardiomyopathy		
Right Ventricular dysfunction		
Sick sinus syndrome		
Sinus bradycardia		
Sinus tachycardia		
Supraventricular tachycardia		
Tricuspid Valve disease		
Ventricular arrhythmia		
Ventricular fibrillation		
Ventricular tachycardia		
Cardiac disorders – other, specify		

At each contact with the subject during the intervention phase and for 30 days following the final dose of study medication, the investigator will seek information on adverse events by review of the medical record, specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the documentation, though should be grouped under one diagnosis.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the intervention period will be followed up to determine the final outcome. Any serious adverse event that occurs within 30 days following the final dose of study medication and is considered to be possibly related to the study intervention or study participation will be recorded and reported once the study team becomes aware of it.

Once the final AE Assessment is completed (approximately 30 days after final dose of study medication) the study team will no longer document expected events. All cardiovascular AEs (Table 4) and AEs related to study activities will continue to be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken, outcome, and the investigator's assessment of causality (relationship to study activity) and determination of severity will be included in the record.

9.2.1 Toxicity Grading of Potentially Expected Respiratory Disorders

For rales and status asthmaticus, use CTCAE Category, "Respiratory, other".

9.3 Relationship of AE to Study and Expectedness

The PI will be responsible for determining the relationship of an AE to the study intervention or study activities. Events will be classified as unrelated, possibly, probably, or definitely related. If an AE is not unrelated, the PI will also determine if the AE is expected (known adverse effect of carvedilol) or unexpected. Known adverse effects of carvedilol are listed in Table 4 (Section 12.1) and described in the consent form. Finally, the PI will characterize the event's relatedness to underlying conditions; events will be characterized as not related to underlying condition, related to condition studied, or related to other co-morbidity.

9.4 Reporting of Adverse Events and Unanticipated Problems

The investigators will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, including the FDA, Penn IRB, and the Abramson Cancer Center.

At a minimum, the below information will be provided at the time of the initial report

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

9.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report or new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator will ensure that all SAE are followed until either resolved or stable.

9.4.2 Investigator Reporting to Penn Entities

AE/SAEs will be reported to the Penn IRB in accordance with IRB policy (http://www.upenn.edu/IRB/mission-institutional-review-board-irb/reportable-events).

All events meeting the DOCM reporting requirements will also be entered into the PennCTMS AE/SAE form (http://www.ctsrmc.org/sae.php).

As much as possible, events will be reported as a diagnosis, not as a list of symptoms. Symptoms that led to the diagnosis will be included in the event description, but will not be reported as the actual event.

9.4.3 Investigator Reporting to the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND/ IDE safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- **Within 7 calendar days**
  Any study event that is all:
  - associated with the use of the study drug, and
  - unexpected, and
  - fatal or life-threatening,

- **Within 15 calendar days**
  Any study event that is:
  - associated with the use of the study drug, and
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Additional reporting requirements

Sponsors are also required to identify in IND/IDE safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process

Applicable events can be reported to the FDA using Form FDA3500A or in narrative format. The report must be sent to the correct division. Specific information that must be included in the reports can be found in 21 CFR 312.32 or in 21 CFR 812.150.

Reports should be submitted to the Center for Drug Evaluation and Research (CDER) at 1-800-FDA-1088

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration

5901-B Ammendale Rd
Beltsville, MD 20705-1266

9.5 Medical Monitoring

9.5.1 Data and Safety Monitoring Plan

The monitoring of a clinical trial is an essential element of study processes designed to ensure the protection of subjects' rights, the safety of subjects enrolled in the trial, and the integrity and quality of the resulting data. The study shall adhere to the requirements described in the protocol, the International Conference on Harmonization (ICH) and FDA Good Clinical Practices (GCP) and SOPs. In addition to PI oversight, the protocol will be subject to review and oversight be the Abramson Cancer Center Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) and Department of Operations, Compliance, and Monitoring.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Each subject will be assigned a unique identifier upon signing consent. Any information linking the subject to his or her subject ID will be maintained locally in a password protected shared-drive hosted on the UPHS network and managed by UPHS IS; access to this drive will be controlled by the PI.
Paper copies of study records (including Case Report Forms (CRFs) and source documents) will be stored in a locked cabinet accessible to the study team only.

Enrollment and adverse event data will be recorded in PennCTMS. All research data will be maintained in a HIPAA compliant study database on REDCap.

Blood samples will be identified by subject ID, visit number, and date collected.

Echocardiographic images and a clinical report of the echocardiogram will be generated and linked with the patient's EMR. Quantitated echocardiographic data will be labeled with the subject ID, visit number, and date of echocardiogram only and entered into the REDCap database.

10.3 Records Retention

All study records will be maintained as described above for the duration of the study and until the last banked specimen has been exhausted or for at least one year following the final study-related publication or for at least seven years after the close out of the study (whichever is latest). After this time, financial records, source documentation, and paper CRFs may be appropriately destroyed. All versions of the protocol and all signed consent form/HIPAA authorizations will be retained permanently, in keeping with the University of Pennsylvania Records Retention Schedule.

Records in PennCTMS will be retained according to PSOM/UPHS policy.

There may be future questions of interest related to the study of the cardiovascular effects of doxorubicin and/or trastuzumab/trastuzumab-anns and risk-guided cardioprotective strategies. The de-identified data or samples collected from this study may be shared with academic collaborators both within and across institutions. In so doing, they will help to answer questions of mutual interest that are related to the overall aims of this study. To that end, subjects will be asked to opt in to allow the future use of their data and future use of their remaining blood samples. If they agree, their blood samples or data may be kept (as described above) indefinitely.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The investigator will allocate adequate time for all monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the CTSRMC, IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

12 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

12.1 Risks

12.1.1 Risks of Carvedilol

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Table 4 lists adverse effects that have been reported with carvedilol.

Table 4: Adverse Effects of Carvedilol

Common, May be Serious *(> 20%)*	**Occasional, May be Serious** *(4-20%)*	**Rare and Serious** (≤ 3%)
Tiredness	Asthenia (weakness or lack of energy)	Syncope (fainting)
Dizziness	Edema (swelling)	Angina (chest pain)
	Bradycardia (low heart rate)	Atrioventricular Block
	Hypotension (low blood pressure)	Erythema multiforme
	Hypertension (high blood pressure)	Stevens-Johnson Syndrome
	Heart Failure	Toxic Epidermal Necrolysis
	Headache	Aplastic Anemia
	Diarrhea	Intraoperative Floppy Iris Syndrome
	Nausea	Visual Changes
	Vomiting	Status Asthmaticus (severe asthma)
	Hyperglycemia (low blood sugar)	
	Hypercholesterolemia (high cholesterol)	
	Arthralgia (joint pain)	
	Cough	

	Rales	

Reproductive risks: Pregnancy category C. Animal (rats and rabbits) reproduction studies have shown adverse events. There is no adequate data on the use of carvedilol in pregnant women. It is not known whether carvedilol is excreted in human milk and infant risk cannot be ruled out. Study will obtain a pregnancy test as part of screening (if subject is able to become pregnant and one is not available in the medical record). Subjects in the Elevated Risk Group assigned to intervention with carvedilol and who are of potential child-bearing status will be instructed to use adequate birth control and will be offered counseling on what this entails. Such subjects will be instructed to notify the study doctor immediately if they are or think they may be pregnant while on study drug. If a patient becomes pregnant while on carvedilol, patient will be taken off of study drug; if appropriate, the PI will coordinate transition to other antihypertensive regimen with patient's clinical care team.

Drug interactions: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on drug interactions. Due to potential drug interactions, a complete patient medication list will be reviewed and recorded prior to initiation and at all study visits. Investigational carvedilol will be recorded in subject's EMR at current dose. Subject will be given a wallet card with information on the study drug and potential drug interactions and study contact information (see Wallet Card attachment) to share with clinical care team.

The following drugs have been reported as inhibitors or inducers of CYP2D6 which is the major P450 enzyme that metabolizes carvedilol. Concomitant use of strong and clinically significant moderate inhibitors will not be allowed during the intervention phase for subjects in the elevated risk group who are randomized to carvedilol.

1. NOT ALLOWED DURING INTERVENTION

Strong CYPD6 Inhibitors:
- buproprion (Wellbutrin)
- fluozetine (Prozac)
- paroxetine (Paxil)
- quinidine (Quinidex)

Clinically Significant Moderate CYPD6 Inhibitor
- duloxetine (Cymbalta)

2. SHOULD BE AVOIDED DURING INTERVENTION

Other Moderate CYP2D6 Inhibitors:
- sertraline (Zoloft)
- terabinafine (Lamisil)

Weak CYPD6 Inhibitors:
- amiodarone (Cordarone)
- cimetidine (Tagamet)
- thioridazine (Mellaril)

3. WILL BE TRACKED DURING INTERVENTION

Other Possible CYP2D6 Inhibitors:
- celecoxib (Celebrex)
- chlorpheniramine*
- chloropromazine (Thorazine)
- citalopram (Celexa)
- clemastin (Tavist)*
- clomipramine (Anafranil)
- diphenhydramine (Benadryl)*
- doxepin (Sinequan)
- doxorubicin (Adriamycin)
- escitalopram (Lexapro)
- halotantrine (Halfan)
- haloperidol (Haldol)
- hydroxyzine (Vistraril, Atarax)*
- levomepromazine (Noxinan)
- lopinavir (Kaletra)
- methadone
- metoclopramide (Reglan)
- midodrine (ProAmantine)
- moclobemide (Aurorix, Manerix)
- ranitidine (Zantac)*
- ritonavir (Norvir)
- ticlopidine (Ticlid)
- tipranavir (Aptivus)
- tripelennamine (Pyribenzamine)
- other histamine H1 receptor antagonists**

Possible CPY2D6 Inducers
- dexamethasone (Decadron, Hexadrol)
- rifampin (Rifadin, Rimactane)

* available over the counter

**Examples: cetirizine (Zyrtec), dimenhydrinate (Drammamine), doxylamine (included in NyQuil), fexofenadine (Allegra), loratidine (Claritin), meclizine (Antivert, Drammamine), pheniramine (Avil)

Patients on strong or clinically significant CYPD6 inhibitors (1) will be excluded at screening. Patients in the elevated risk group randomized to carvedilol will be asked to notify the study team immediately if they are prescribed one of these drugs while taking study medication. When the study team becomes aware that patient has been prescribed one of the drugs in (1), the PI will be notified. The PI will contact treating provider to recommend possible alternatives prior to the patient's starting the new medication. If there is no clinically acceptable alternative to a drug in (1), patient will stop carvedilol. Patient will continue on study and complete all study visits.

If a subject is on a drug in (2) at screening and is in the elevated risk group randomized to carvedilol, the PI will contact the treating provider as soon after consent as possible to recommend possible alternatives. Patient may start study medication while this is occurring. If a subject in the elevated risk group randomized to carvedilol is prescribed a drug in (2) during the intervention, they are asked to notify the study team immediately. When the study team becomes aware that the patient has been prescribed one of the drugs in (2), the PI will be notified and will contact the treating provider to recommend possible alternatives. If there is no clinically acceptable alternative to a drug in (2), the subject will stop carvedilol. Patient will continue on study and complete all study visits.

Of note, detailed correspondence with oncology PharmD at Penn do not indicate that the interaction with doxorubicin is clinically relevant, and patients have been safely treated with these agents in combination, both in clinical practice and in randomized clinical trials (Kalay et al, Avila et al).[39,40] In addition, although both dexamethasone and diphenhydramine are commonly used in this population as pre-medication for chemotherapy, the potential interaction with carvedilol is not believed to be clinically significant. We do not intend to restrict concomitant use of either agent in subjects on study intervention.

Carvedilol may mask symptoms of hypoglycemia or worsen hyperglycemia. Subjects with diabetes in the elevated risk group assigned to the intervention arm will be reminded to follow-up with their PMD or endocrinologist on a regular basis and to notify them that they are on carvedilol.

12.1.2 Risk of Study Procedures

Echocardiography is a safe and non-invasive imaging modality. There are no serious risks associated with transthoracic echocardiography. The additional strain imaging acquired during this study poses no foreseeable serious risks to subjects. Strain imaging prolongs acquisition time by approximately 15 minutes, which does not pose any foreseeable serious risks to subjects. It is possible that subjects may experience mild, temporary discomfort from the ultrasound probe being pressed against the chest or from lying in the recumbent position for the duration of the study.

Blood draws: Participants in this study will undergo blood sampling for biomarker assessment. Blood may also be drawn as part of screening (if results are not available within the medical record).
Occasionally there are risks associated with blood draws such as bruising, swelling, black and blue marks, fainting and/or infection at the site. Subjects may also experience a decrease in hemoglobin and hematocrit (red blood cell number, called anemia) from having blood drawn frequently. To minimize discomfort and inconvenience, blood sampling will be combined with a routine clinical blood draw whenever possible. Approximately 16mL (1tbs) of blood will be collected at baseline for research purposes and approximately 12mL (2tsp) of blood will be collected at subsequent visits (see Table 3 for timepoints when blood will be collected). We do not propose collecting more that 50mL in an 8-week period for the purposes of this study.

Symptoms Survey: There are no medical risks associated with answering survey questions. However, a patient may become uncomfortable providing personal information. Any question that makes a patient uncomfortable can be skipped.

12.1.3 Other Risks of Participating in Study

Risks Related to CTX Risk Calculator: We plan to tell subjects to which risk group they belong based on our CTX risk calculator. For some patients, knowing this information may cause additional anxiety. Additionally, subjects in the elevated risk group assigned to usual care may experience anxiety related to the fact that they are not receiving the active intervention. The PI will provide counseling to all patients about how to interpret their risk score to help them manage this anxiety. Furthermore, all subjects (regardless of risk group or arm assignment) will receive the same prospective monitoring. The PI will contact patients with the results of any echo done for research purposes, and we will reassure patients throughout the study that if there are any clinically significant findings from study procedures, we will tell them and their care team.

The risk of incorrect assignment to the elevated risk group (a false positive from the CTX Risk Calculator) would result in the prescription of carvedilol or usual care. Thus, the risks are analogous to that of being on carvedilol (discussed in 12.1.1). A false negative from the CTX Risk Calculator would result in assignment to the current standard of care.

Genetic Information: Plasma, serum, and DNA from blood samples will be banked for future use. Blood samples banked from this study may be used as part of an exploratory analysis to help generate hypotheses as to if there are SNP variations that are associated with an increased risk of cardiotoxicity development, and if there are SNP variations that are associated with deriving greater benefit from cardioprotection with carvedilol. We will determine the most cost-effective approach to genotyping at the time of analysis as this technology continues to evolve.

One possible risk is the loss of confidentiality of genetic information. This research includes genetic testing. The researchers believe that the risks that a subject will be identified solely from genetic information are very small, but the risk may change in the future as new methods of tracing information are developed.

There can be a risk to knowing genetic information. New health information about inherited traits that might affect subjects or their blood relatives could be found during a research study. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to subjects and their families are very low. Samples will be coded and results of genetic testing will not be shared with subjects or entered into their medical record. A related possible risk is disclosure of genetic information that could lead to discrimination in insurance or employment. Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

Time: As a result of taking part in this study, patients may lose time at work or home and spend more time in the doctor's office than usual. As much as possible, study visits will be planned on days subjects will be at the Perelman Center for clinical care, and scheduled so as to minimize the "extra" time patients are asked to spend here.

Other: In addition, there may be other unforeseeable risks and inconveniences associated with participation in this study.

12.2 Benefits

There may be no direct benefit to being in this study.

This study may benefit future breast cancer patients by furthering efforts to better predict who is at risk for cardiotoxicity, and is an important first step in developing risk-guided cardioprotective strategies for cancer patients.

12.3 Risk Benefit Assessment
While this study does involve certain risks to subjects, the potential benefits derived from this study significantly outweigh the risks associated with this research.

12.4 Informed Consent Process / HIPAA Authorization
The study will use a combined Informed Consent and HIPAA Authorization Form.

After the subject has been identified by the oncologist, study staff will conduct a phone or in-person interview (script attached) to assess subject interest in the study and review exclusion criteria. If patient is interested and is found to be ineligible, study staff will describe the study in detail to make the patient aware of the procedures, intervention, and time commitment involved with the study. During or immediately following this conversation, the subject will be given a copy of the informed consent form to review (coordinator will email or mail to patient with permission, or will make arrangements to meet patient at next visit at Perelman Center). During this conversation, patients will be encouraged to discuss the study with their treating oncologist and with other providers, including primary care provider or cardiologist. Patients will be given the opportunity to ask study staff questions about the study during this conversation and in follow-up conversations. The will also be offered an opportunity to discuss the study with the PI on the phone or in person prior to the screening visit. If interested, patients will be given the option of scheduling the screening visit during this conversation. If they prefer to consider the study further before scheduling the screening visit, study staff will ask for permission to follow-up with the patient at a specified time to see if they would like to schedule the screening visit.

Written consent will be obtained by research coordinator or attending physician investigator in person, in a private exam or consult room. The person obtaining consent will review the details of the study with the patient, and will remind the patient that participation is voluntary and will not change the treatment they would otherwise receive. Person obtaining consent will ensure all questions regarding the study are answered to the patient's satisfaction. A copy of the signed consent form will be given to the patient. No study procedures will be completed until written consent is obtained. Typically, consent will be obtained at the screening visit. The person obtaining consent will document consent in the electronic medical record.

13 Study Finances

13.1 Funding Source
Funding for this project will come from R01 HL118018 and from departmental start-up funds. In addition, the study has been funded by an AHA grant, and is currently supported by an NHLBI R21. This pilot study is critical to the generation of preliminary data for a new R01 application.

13.2 Conflict of Interest
All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

13.3 Subject Stipends or Payments
In appreciation for their participation, subjects will receive $6 for each study visit. If visits occur on days when patients are not scheduled for infusion, we will also reimburse for parking. Payment will be made using the Greenphire ClinCard. Subjects will be given a FAQ on the Clincard (see attachments).

14 Publication Plan
Publication authorship will be based on the relative scientific contributions of the PI, co-Investigators, and key personnel and in accordance with policies of the University of Pennsylvania. Drafting and publication of manuscripts will be carried out in a collaborative manner and pre-defined authorship roles will be set so as to avoid conflicts and disagreements. The PI will review progress, address concerns, prioritize analysis plans, and discuss publications.

15 Attachments

- Subject drug diary template
- Blood Processing Protocol
- Echo Protocol
- Hill-Bone Compliance Scale
- MD Anderson Symptoms Inventory – Heart Failure
- FACIT Fatigue
- FACIT Dyspnea on Exertion
- Godin Leisure-Time Questionnaire
- Greenphire Clincard FAQ
- Wallet Card

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