Title

Rationale and design of the Cardiac CARE trial: A randomized trial of troponin-guided neurohormonal blockade for the prevention of anthracycline cardiotoxicity.

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Abstract

Background: Anthracyclines are effective cytotoxic drugs used in the treatment of breast cancer and lymphoma but are associated with myocardial injury, left ventricular dysfunction and heart failure. Anthracycline-induced cardiotoxicity is highly variable in severity and without a proven therapeutic intervention. Beta-adrenergic receptor blockers and renin-angiotensin-system inhibitor therapies have been associated with modest cardioprotective effects in unselected patients.

Methods:

The Cardiac CARE trial is a multicentre prospective randomized open label blinded endpoint trial of combination beta-adrenergic receptor blocker and renin-angiotensin-system inhibitor therapy in patients with breast cancer and non-Hodgkin lymphoma receiving anthracycline chemotherapy that is associated with myocardial injury. Patients at higher risk of cardiotoxicity with plasma high sensitivity cardiac troponin I concentrations in the upper tertile at the end of chemotherapy are randomized to standard of care plus combination candesartan and carvedilol therapy or standard of care alone. All patients undergo cardiac magnetic resonance imaging before and 6 months after anthracycline treatment. The primary endpoint is the change in left ventricular ejection fraction at 6 months after chemotherapy. In low-risk non-randomized patients, left ventricular ejection fraction before and 6 months after anthracycline will be compared to define the specificity of the high-sensitivity cardiac troponin I assay for identifying low-risk participants who do not develop left ventricular systolic dysfunction.

Discussion: Cardiac CARE will examine whether cardiac biomarker monitoring identifies patients at risk of left ventricular dysfunction following anthracycline chemotherapy and whether troponin-guided treatment with combination candesartan

and carvedilol therapy prevents the development of left ventricular dysfunction in these high-risk patients.

Non-standard Abbreviations and Acronyms

hs-cTnI high sensitivity cardiac troponin I

PRADA Prevention of cardiac dysfunction during adjuvant breast cancer therapy

ICOS-ONE International CardioOncology Society One

CECCY Carvedilol for prevention of chemotherapy related cardiotoxicity

EuroQoL European quality of life scale

GLS Global longitudinal strain

GCS Global circumferential strain

Keywords

Anthracycline, left ventricular dysfunction, cardiac troponin, breast cancer, non-Hodgkin lymphoma, cardiac magnetic resonance imaging

Commentary

What is new?

- Cancer survivors face risk from anthracycline related cardiac dysfunction despite reduced toxicity with modern protocols.
- Trials of potentially cardioprotective therapies should focus on the smaller group patients at highest risk of anthracycline cardiotoxicity.

What are the clinical implications?

- On treatment cardiac high sensitivity troponin I concentrations correlate with cumulative anthracycline dose and predict left ventricular dysfunction.

- The Cardiac Care trial will use on treatment troponin I to identify high risk patients for randomization to cardioprotection using neurohormonal blockade with combined rapid titration of candesartan and carvedilol.

Introduction

Anthracyclines are widely used cytotoxic drugs that reduce the risk of relapse and death in patients with breast cancer and non-Hodgkin lymphoma. They also cause myocardial injury which can lead to left ventricular systolic dysfunction and heart failure. Concern about the late impact of treatment related cardiac toxicity has increased with improved cancer-free survival. Cohort follow-up studies from patients receiving high doses of doxorubicin in the 1980s and early 1990s indicate that 5% of all treated patients develop symptomatic heart failure and the prevalence is up to 10% in those aged over 65 years[1]. The progression from heart muscle injury occurring at the time of chemotherapy to the development of left ventricular systolic dysfunction and subsequent clinical heart failure is poorly understood.

In a prospective evaluation of 2625 cancer patients (74% women; 51% breast cancer and 28% non-Hodgkin lymphoma), the incidence of cardiotoxicity was 9% with 98% of cases developing in the first year. Cardiotoxicity was defined as an absolute reduction in left ventricular ejection fraction of more than 10% or an overall left ventricular ejection fraction of less than 50%. The median time elapsed from the final dose of anthracycline chemotherapy until the development of cardiotoxicity was 3.5 months.[2] The magnitude and rate of cardiotoxicity have fallen with modern chemotherapy protocols which frequently employ a smaller cumulative anthracycline dose. A recent meta-analysis of 660 patients assigned to placebo in randomized controlled trials identified a mean decline in left ventricular ejection fraction of 5.4% (95% confidence interval 3.5-7.3%) 6 months after completion of anthracycline chemotherapy.[3]

Set against the challenge of an event rate that varies according to different treatment protocols and timing of measurements, recent clinical trials have investigated whether administration of medications established in the treatment of heart failure can prevent systolic dysfunction in patients receiving anthracyclines.[4, 5]

These studies are limited by prescribing therapy to all patients resulting in substantial over-treatment as most patients do not develop cardiotoxicity. They have also used treatments that either block the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) or the sympathetic nervous system (beta-adrenoreceptor blocker) but not the combination which has the most robust evidence base for improving function and survival in patients with left ventricular systolic dysfunction.[6] Omland has recently highlighted the positive impact of modern cancer care delivering lower cardiotoxicity rates and the consequent need for future trials to focus effective interventions on the highest risk patients.[6] The Cardiac CARE Trial (EudraCT 2017-000896-99, ISRCTN24439460) will address these limitations of earlier studies by selecting patients with the greatest evidence of anthracycline-induced myocardial injury and randomizing them to combination candesartan and carvedilol treatment.

Guidelines for monitoring and identification of anthracycline-induced cardiotoxicity

Imaging

International guidelines recognise the challenge of variable patient susceptibility to anthracycline cardiotoxicity.[7] Extremes of age, cumulative anthracycline dose and underlying cardiac disorders such as hypertension, pre-existing cardiomyopathy and

valve disease are established risk factors. Baseline evaluation of cardiac function is recommended to provide a reference point and exclude hitherto unidentified disease.[7, 8] Recommendations for further monitoring are based on expert consensus and indicate additional evaluation of cardiac function during and following completion of anthracycline chemotherapy depending on cumulative dose and plans for further cardiotoxic therapy. However, cardiac imaging conducted too soon after completion of anthracycline chemotherapy may miss the nadir of the fall in left ventricular ejection fraction. Indeed, immediate post-treatment scanning (within 1 month) may have contributed to the smaller than expected fall in left ventricular ejection fraction observed in the control group of the prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA) study. Here, patients with breast cancer receiving anthracycline with or without trastuzumab were randomized to treatment with the candesartan or metoprolol. Overall decline in left ventricular ejection fraction on cardiac magnetic resonance was only 2.6% (95% confidence interval 1.5-3.8%) in the placebo group.[4]

Cardiotoxicity monitoring guidelines recognise the potential for late changes in cardiac function and advocate additional serial cardiac imaging monitoring in high risk and pediatric populations. The uptake of late monitoring with cardiac imaging is variable and there are cost implications associated with the follow-up of large populations of cancer survivors. UK patients receiving the anthracycline regimes studied in the Cardiac CARE trial routinely receive risk factor assessment and cardiac imaging prior to treatment together with follow up cardiac imaging conducted at a variable interval between 6 to 12 months following completion of chemotherapy. Better methods to identify most patients who are at low risk of cardiotoxicity and do

not require close follow up are required.

Humoral Biomarkers

Cardiac troponin I and T are markers of myocardial injury, and plasma concentrations have been used to detect early anthracycline-induced cardiomyocyte toxicity.[9] High-sensitivity cardiac troponin assays can accurately quantify low plasma concentrations below the 99th centile upper reference limit. These lower concentrations contain important prognostic information that can identify individuals at heightened risk and increased mortality.[10] We have previously shown that plasma cardiac troponin I concentrations exhibit an anthracycline dose-dependent increase in patients with breast cancer.[11] More than a third of patients developed biochemical evidence of sustained myocardial injury with plasma troponin concentrations above the 99th centile upper reference limit. Early changes in this marker accurately predicted final concentrations at the end of chemotherapy suggesting that it represents a patient-specific marker of on-treatment myocardial injury.

Monitoring of cardiac troponin concentration during anthracycline therapy has been advocated in guidelines and adopted widely into clinical protocols despite having no broad mandate from randomized trials.[7, 8, 12] Furthermore, the reference 99th centile upper reference limit concentration and lowest concentration at which a 10% coefficient of variation is obtained varies considerably between vendor specific platforms for both contemporary and current high-sensitivity cardiac troponin I and troponin T assays preventing meaningful comparison of recorded concentrations and thresholds for intervention between studies and protocols using different assay platforms.[13]

A recent meta-analysis confirmed that increased plasma cardiac troponin concentrations during or after anthracycline treatment are associated with a 7-fold increase in the likelihood of developing left ventricular systolic dysfunction as well as a 93% negative predictive value for concentrations below the 99th centile.[14] More than three quarters of patients in this meta-analysis had cardiac troponin concentrations quantified with contemporary (non-high-sensitivity) assays. It is worth noting that the chemotherapy dose and consequent magnitude of myocardial injury recorded with cardiac troponin quantification were both greater in many of the earlier studies included in this meta-analysis.[9, 15] The International CardioOncology Society-One (ICOS-ONE) multicentre trial randomised patients treated with anthracycline to enalapril either up-front or triggered by an elevated cardiac troponin determined by either a traditional or high-sensitivity assay.[16] There was no placebo group and change in cardiac function was reported as development of cardiotoxicity defined on surveillance echocardiography out to one year after chemotherapy as an absolute reduction in left ventricular ejection fraction of more than 10% and an overall left ventricular ejection fraction of less than 50%. This categorical definition of cardiotoxicity using echocardiography will not record smaller but potentially clinically important changes in left ventricular ejection fraction following chemotherapy. There was no difference in outcome between treatment approaches, but the most striking finding was the low rate of cardiotoxicity; only 3 cases in the 273 trial participants and no episodes of congestive cardiac failure or cardiovascular death.

It remains unknown whether the introduction of cardioprotective medicines based solely on changes in high-sensitivity cardiac troponin concentrations has an effect

upon the development of left ventricular dysfunction or heart failure. N-terminal pro B-type natriuretic peptide (NT-pro BNP) quantification has been proposed to anticipate late development of heart failure in anthracycline treated patients.[7] NT-pro BNP may be considered a marker of myocardial stretch and there are no data to support a role for monitoring and detection of early, on treatment anthracycline related myocardial injury.

The UK centres participating in Cardiac CARE do not routinely monitor cardiac troponin or NT-pro BNP concentrations during anthracycline chemotherapy.

Prevention of anthracycline cardiotoxicity

Current guidelines recommend active management of modifiable cardiovascular risk factors and promotion of a healthy lifestyle including exercise where possible in order to minimise the risk of developing cardiotoxicity.[7, 8, 12] It is assumed that any medication targeted at preventing cardiotoxicity must be introduced before or during chemotherapy. The treatment must be well tolerated by patients undergoing concurrent chemotherapy and have no impact on the efficacy of anticancer therapy. In the absence of a method to identify the minority (< 10%) of patients who will develop cardiotoxicity, randomised controlled trials of preventive medication are faced with the problems of unnecessarily treating the vast majority of patients who will not develop cardiotoxicity, and for those who do develop cardiotoxicity, the potential beneficial effects will be diluted and may pass undetected because of the neutral effects on the majority of those randomised.

Prevention of cardiotoxicity with neurohumoral blockade

Combined renin-angiotensin system inhibition and beta-adrenoreceptor blockade has been demonstrated to have major morbidity and mortality benefits in patients with heart failure and reduced ejection fraction across a broad range of etiologies, including chemotherapy-related heart muscle disease. The benefits of these therapies extend to asymptomatic left ventricular systolic dysfunction, the most common manifestation of anthracycline cardiotoxicity. Enalapril reduces death and hospitalization for heart failure in patients with asymptomatic left ventricular dysfunction[17] and the combination of carvedilol with an ACE inhibitor reduces all-cause mortality in patients with left ventricular dysfunction following acute myocardial infarction.[18]

In contrast to their well-validated effects in the treatment of patients with established left ventricular systolic dysfunction, randomized controlled trials examining the potential for neurohormonal blockade in the prevention of anthracycline cardiotoxicity have had mixed outcomes. A recent meta-analysis examined 17 trials that included patients receiving anthracycline-based chemotherapy and were randomized to neurohormonal blockade. This demonstrated that those receiving neurohormonal blockade had a 4% higher left ventricular ejection fraction and a non-significant trend towards fewer clinical events.[19] However, many of the trials were single-centre and there was significant heterogeneity and evidence of publication bias. Of relevance to these smaller trials, participant inclusion and randomization were not stratified to include patients at elevated risk for cardiotoxicity, and the trials frequently examined single therapeutic agents. It remains unclear whether a more potent treatment effect has, therefore, been diluted by the inclusion of lower risk patients with exposure to single and heterogeneous treatments.

Dexrazoxane

Dexrazoxane has proven protective activity against anthracycline-induced cardiotoxicity. It prevents a decline in left ventricular ejection fraction and reduces cardiac troponin release[20] by binding to myocardial topoisomerase 2β to induce a conformational change that prevents anthracycline binding. Prior concern about reduced anticancer efficacy of anthracyclines and a signal for excess secondary malignancies with dexrazoxane has led to its restricted use.[21] More recent reviews have questioned the evidence for secondary malignancies and have called for a review of the guidelines to recommend more widespread application.[22] Current guidelines advocate selective use of dexrazoxane only in patients receiving high-dose anthracycline regimes and where treatment is necessary in patients with established cardiomyopathy.[7, 8]

The Cardiac CARE Trial

The objectives of the Cardiac CARE trial are to determine whether high-sensitivity plasma cardiac troponin monitoring identifies patients at risk of left ventricular systolic dysfunction following anthracycline chemotherapy and whether cardiac troponin-guided treatment with candesartan and carvedilol prevents the development of left systolic ventricular dysfunction. In meeting these objectives, the Cardiac CARE trial findings will have immediate relevance to clinical practice through testing a simple monitoring and threshold guided intervention pathway that can be readily contained and delivered within cancer treatment centres.

Study Design

Additional data and the full study protocol are available from the corresponding author upon reasonable request. The study has been conducted in accordance with the Declaration of Helsinki and with research ethics committee approval (South East Scotland Research Ethics Committee 17/ES/0071).

The trial has a prospective, randomized, open-label, blinded endpoint (PROBE) design. All patients will receive standard of care and undergo cardiac magnetic resonance before and 6 months after completion of anthracycline chemotherapy. Participants exhibiting upper tertile high-sensitivity plasma cardiac troponin concentrations during chemotherapy will be randomized 1:1 to standard of care alone or standard of care plus combined candesartan and carvedilol therapy.

Rationale for choice of trial intervention

Candesartan has an established role in the treatment of patients with left ventricular dysfunction and in the PRADA study demonstrated a protective effect on left ventricular ejection fraction in this patient population.[4] The avoidance of cough as a side effect is considered an advantage of angiotensin receptor blockade (candesartan) over ACE inhbition in this immunocompromised cancer population. The target dose and dose titration schedule for candesartan were identical for Cardiac CARE and PRADA. Carvedilol has been tested previously in a similar population of anthracycline treated breast cancer patients (Carvedilol for prevention of chemotherapy-related cardiotoxicity; The CECCY Trial).[5] There was no difference in the primary cardiotoxicity endpoint compared to placebo. Carvedilol treatment was associated with lower circulating cTnI concentrations and less diastolic dysfunction. For Cardiac CARE the target carvedilol dose of 25 mg BD is the same but the

interval between dose titration is much shorter at 3 days compared to 3 weeks in the CECCY Trial. The key difference in approach between the Cardiac CARE trial and previous cardioprotection studies is to focus maximum neurohormonal blockade on high risk patients with co-prescription of candesartan and carvedilol rather than a single agent.

Study population

The main inclusion and exclusion criteria for Cardiac CARE are listed in supplementary Table 1. Patients aged ≥18 years commencing anthracycline for adjuvant or neo-adjuvant treatment of breast cancer or non-Hodgkin lymphoma will be invited to participate. Anthracycline cardiotoxicity is dose dependent and, recognizing the lower incidence of anthracycline-induced cardiotoxicity observed in recent studies, only patients scheduled for ≥300 mg/m^2 cumulative dose epirubicin or ≥150 mg/m^2 cumulative dose doxorubicin over 3, 4 or 6 cycles of treatment will be approached. By comparison, 60% of participants in the PRADA study received low-dose anthracycline (cumulative epirubicin dose ≤240 mg/m^2).[4] Around 20% of PRADA patients also received trastuzumab. Patients with HER-2 positive disease scheduled for trastuzumab are excluded in Cardiac CARE. Although studying the outcomes of patients receiving anthracycline followed by trastuzumab is clinically relevant, to do so would require a larger study to account for the effects of two agents with interacting but different mechanisms of myocardial injury and potentially reversible changes in left ventricular ejection fraction occurring over an additional 15 months of trastuzumab administration.

Trial intervention

The study flow is illustrated in Figure 1. Participants will have high-sensitivity plasma cardiac troponin I concentrations quantified before and during chemotherapy. Participants identified as high risk according to on treatment high-sensitivity plasma cardiac troponin I concentrations (defined as ≥ 5 ng/L at cycle 2 or ≥ 23 ng/L at cycles 3 to 6) will be randomised to the trial intervention. These concentration thresholds for randomisation are illustrated in Figure 2 and are based upon findings from a pilot study of patients who exhibited high-sensitivity plasma cardiac troponin concentrations in the upper tertile at the completion of anthracycline chemotherapy.[11] Patients will be randomised using a web-based service to avoid bias and ensure allocation concealment. Randomisation will be to either standard of care alone or to standard of care plus combined candesartan and carvedilol therapy. Participants allocated to the treatment intervention will have candesartan started at 8 mg once daily and increased at a minimum of 3-day intervals to 16 mg and 32 mg once daily. The carvedilol will be initiated simultaneously at 6.25 mg twice daily and increased to 12.5 mg twice daily and 25 mg twice daily. These drugs will be dispensed on the day of randomisation and will continue until completion or withdrawal from the study. Medication adherence will be recorded from the dose titration clinic and patient diaries. Participants with plasma cardiac troponin concentrations below the threshold for randomisation will remain on standard of care only.

Criteria for discontinuing or modifying allocated interventions

Following the introduction of candesartan, estimated glomerular filtration rate and serum creatinine concentration will be monitored at each dose titration clinic. A

decrease in estimated glomerular filtration rate of up to 25% from baseline or an increase in serum creatinine concentration of up to 30% will be accepted. Participants exhibiting changes in renal function from baseline within these limits will have further dose increases at the clinical team's discretion or remain on established doses. Participants exhibiting changes in renal function beyond these thresholds or an estimated glomerular filtration rate of <45 mL/min/1.73 m^2 will have candesartan discontinued. Participants unable to reach target dose because of symptomatic or asymptomatic hypotension (systolic blood pressure <90 mmHg) or bradycardia (heart rate <50 bpm) will continue in the study on maximal tolerated doses.

Study assessments

Cardiac magnetic resonance imaging

All participants will undergo cardiac magnetic resonance at baseline and 6 months after the final dose of anthracycline. This period is likely to capture the maximal fall in left ventricular ejection fraction.[2] Cardiac magnetic resonance imaging and left ventricular ejection fraction measurements will be conducted by dedicated research imaging facilities at each site and results will be immediately available to inform ongoing participant management. Cardiac magnetic resonance imaging measurements for the primary and secondary trial endpoints will be performed by an Image Analysis Core laboratory (Edinburgh Imaging University of Edinburgh). Analysts will be independent to the research team and blinded to treatment allocation.

High-sensitivity cardiac troponin I quantification

In our pilot study, we found that, compared with measurements from pre-chemotherapy blood, plasma high-sensitivity cardiac troponin concentrations measured 24 h after chemotherapy were 33% lower[11]. Plasma high-sensitivity cardiac troponin concentration will therefore be quantified on blood taken prior to each anthracycline cycle to best reflect the degree of ongoing myocardial injury. Plasma high-sensitivity cardiac troponin I concentrations will be quantified using the ARCHITECT$_{STAT}$ or ALINITY hs-cTn I assay (Abbott Laboratories, Chicago, IL, USA) during each 3-week chemotherapy cycle. Additional blood samples for quantification of ongoing myocardial injury will be taken at 3 weeks following chemotherapy in participants receiving only 3 or 4 cycles of anthracycline. All participants will with have plasma high-sensitivity cardiac troponin I concentrations recorded at 2, 4 and 6 months following completion of anthracycline chemotherapy. Blood samples will be taken at the General Practitioner's surgery or according to participant preference by the oncology research nurse at the regional cancer center.

Health economic assessment

Health utility (preference-based quality of life) will be measured using the European Quality of Life Scale (EuroQoL) EQ-5D-5L questionnaire administered at chemotherapy cycle 1 by a research nurse then approximately every 9 weeks until study completion (5 times).

Outcomes and endpoints

The primary endpoint will be change in left ventricular ejection fraction on cardiac magnetic resonance conducted 6 months after final anthracycline dose. The first secondary endpoint and main secondary objective is to establish the specificity of

high-sensitivity cardiac troponin monitoring for cardiotoxicity by measuring change in left ventricular ejection fraction in the low-risk non-randomised group.

The primary and secondary endpoints are listed in supplementary Table 2. The secondary endpoints further examine high-sensitivity cardiac troponin I concentrations and additional cardiac magnetic resonance imaging measurements for efficacy of candesartan and carvedilol treatment and specificity of high-sensitivity cardiac troponin I monitoring for cardiotoxicity. The following clinically relevant thresholds for grading anthracycline cardiotoxicity will be summarised by treatment but no formal statistical testing will be performed: i) chronic myocardial injury defined as persistent elevations of high-sensitivity cardiac troponin I above the sex-specific 99th centile at 2 months; ii) any high-sensitivity cardiac troponin concentration > 80 ng/L during or after treatment; iii) fall in left ventricular ejection fraction of ≥ 10 percentage points and a drop in ejection fraction below 50%; iv) any fall in left ventricular ejection fraction below 50%; v) any fall in left ventricular ejection fraction below 40%; vi) a 15 % increase in left ventricular global longitudinal strain (GLS) or global circumferential strain (GCS) on 6-month post-anthracycline cardiac magnetic resonance imaging. No statistical analyses has been planned for these outcomes to avoid simultaneously testing multiple hypotheses with inadequate power.

Sample size and statistical analysis

Cardiac CARE will aim to recruit at least 168 patients from several UK regional cancer centers. It was estimated that one third of enrolled patients (n=56) will develop high-sensitivity plasma cardiac troponin concentrations defined as 'high risk' from the Cardiac CARE pilot study. We have assumed that this threshold will select

all participants at risk of developing a ≥ 5 percentage point reduction in left ventricular ejection fraction that may be associated with longer-term clinical outcomes.[23] Randomization will be 1:1 into treatment arm or standard care. Treatment will be allocated by dynamic randomization, with minimization of group imbalances in prognostic factors:[24] (i) age; ≥65 or <65 years, (ii) baseline left

ventricular ejection fraction ≥60% or <60%, (iii) planned cumulative epirubicin

equivalent dose 300 mg/m2 or >300 mg/ m2.

We will need to randomize 23 participants per group to detect a difference of 5 percentage points between groups (standard deviation 5), at 90% power, p=0.05. Allowing for 17% missing data brings this to 28, and a total randomized trial size of 56. A third of participants in the group initially enrolled are expected to be randomized, so the total enrolled will be at least 168.

To assess the specificity of the plasma high-sensitivity cardiac troponin I assay for left ventricular systolic dysfunction in non-randomized participants, we wish to show that there is zero left ventricular ejection fraction % change (with equivalence limits of ±2%). Using a paired t-test to test for a zero change, using two- sided p=0.05, 90% power and a standard deviation of differences of 5%, we need complete paired magnetic resonance imaging scans in 68 non-randomized participants.

Current status

Recruitment commenced in September 2017. Although there has been disruption to research activity across all nine United Kingdom sites resulting from the Covid-19 pandemic, target recruitment was completed in July 2021 with randomizations and

study follow up scheduled to continue until May 2022.

Discussion

Despite recognising the clinical problem of cardiotoxicity associated with anthracycline chemotherapy and the availability of cardiac biomarker and imaging surveillance to detect myocardial injury, current guidelines do not have an agreed approach to prevent the development of early left ventricular systolic dysfunction and late heart failure in patients treated with anthracyclines. Modern chemotherapy protocols are associated with less cardiotoxicity[3] and a selective approach with preventive pharmacological intervention based on the patient's risk of developing cardiotoxicity is preferred. There is a clear parallel with primary prevention of coronary heart and stroke disease delivering treatments that must be tolerated well and are targeted based on risk.

The Cardiac CARE Trial has two key objectives. First, it will assess whether high-sensitivity cardiac troponin I concentrations can identify patients receiving anthracycline who develop cardiotoxicity and be used to select patients for combined angiotensin receptor blocker and beta-adrenergic receptor blocker therapy to prevent cardiotoxicity. Second, it will evaluate whether high-sensitivity cardiac troponin I concentration monitoring is specific for cardiotoxicity by identifying a low-risk group of anthracycline treated patients who do not develop reduced left ventricular ejection fraction following treatment. Previous studies examining neurohormonal blockade in anthracycline cardiotoxicity can be criticized for taking a non-selective approach to treatment randomization and using only one component of neurohormonal blockade despite the evidence that combined interventions confer greater myocardial protection in patients with established left ventricular systolic dysfunction. We have outlined here how the Cardiac CARE Trial design addresses these concerns by

using the most sensitive and specific biomarker of myocardial injury and a combined therapeutic approach to the prevention and treatment of left ventricular systolic dysfunction.

The primary endpoint of 6-month change in left ventricular ejection fraction in Cardiac CARE will be quantified with cardiac magnetic resonance. This is the most precise measure of cardiac function and provides additional measures of systolic volume, extracellular volume and cardiac strain that will inform early mechanisms and potentially more subtle forms of chemotherapy-induced cardiac muscle injury. Cardiac magnetic resonance allows detection of smaller changes in left ventricular ejection fraction and will maximise our ability to detect changes in cardiac performance and anticipated small effect sizes.

Some limitations are to be acknowledged. First, the non-blind design may introduce bias. This will be mitigated by the PROBE design and prevent major bias on the measurement of the endpoint variables. Second, the trial is not powered to examine differences in clinical endpoints. Change in left ventricular ejection fraction 6 months after completing anthracycline chemotherapy is the blinded surrogate endpoint for Cardiac CARE. The relationship between asymptomatic decline in left ventricular ejection fraction and subsequent development of heart failure is poorly understood but asymptomatic left ventricular systolic dysfunction is associated with increased risk of future congestive cardiac failure and death.[25] Left ventricular ejection fraction is a potent prognostic indicator in patients with heart failure and changes resulting from therapy or disease progression are closely associated with outcomes.[26]

Results from Cardiac CARE will inform the use of troponin-stratified cardioprotection in patients receiving anthracycline-based chemotherapy. The data obtained will also be invaluable for the design of future larger studies evaluating biomarker-based interventions, including longer and pragmatic follow-up for clinical events. Stratified and evidence-based cardioprotective interventions are urgently required to prevent the development of heart failure in the rapidly growing population of cancer survivors.

Disclaimer

Disclosures

None

Supplemental Materials

Tables S1-2

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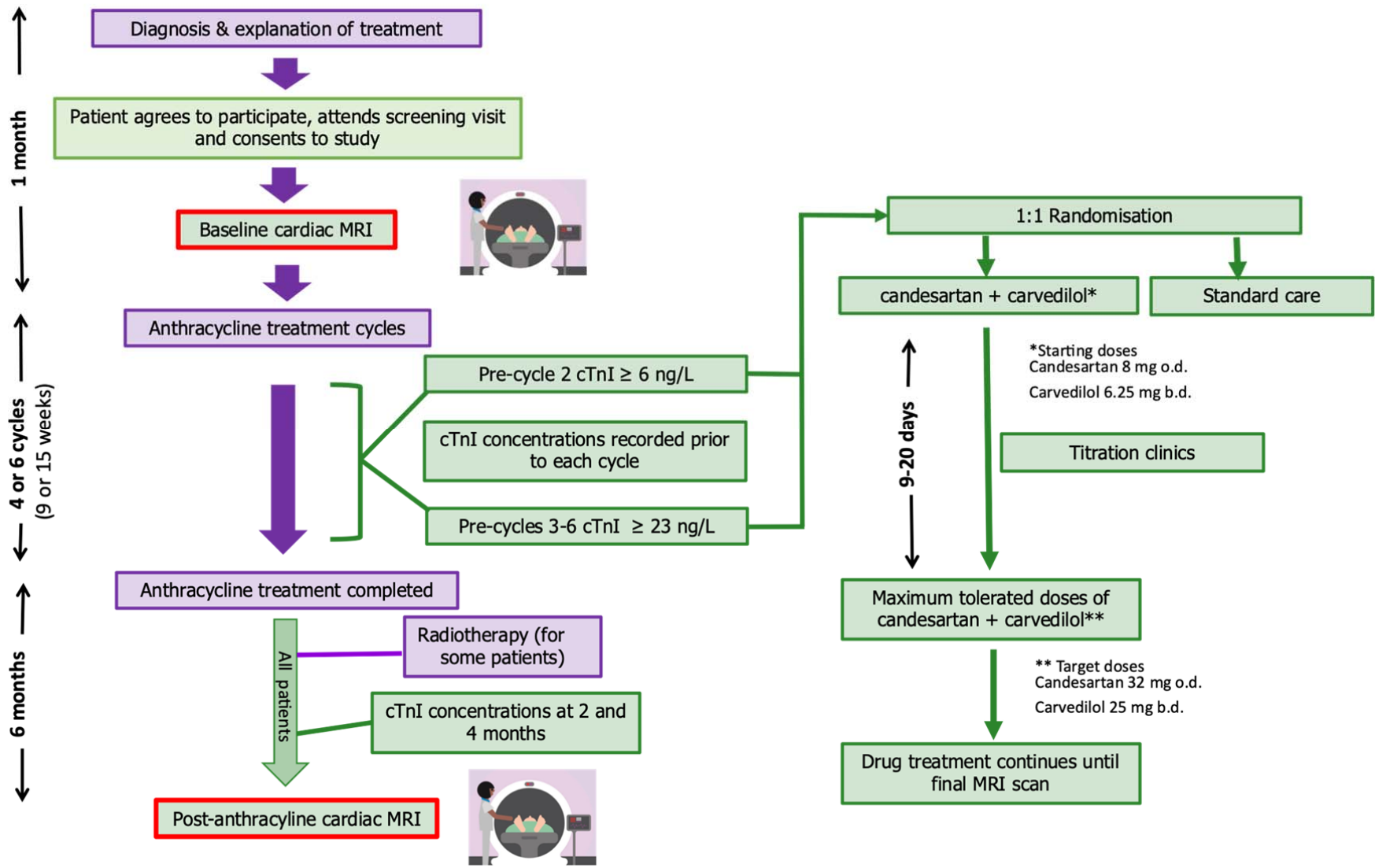
Left column (timeline):

- 1 month
- 4 or 6 cycles (9 or 15 weeks)
- 6 months

Flowchart (left branch):

Diagnosis & explanation of treatment

↓

Patient agrees to participate, attends screening visit and consents to study

↓

Baseline cardiac MRI

↓

Anthracycline treatment cycles

↓

- Pre-cycle 2 cTnI ≥ 6 ng/L
- cTnI concentrations recorded prior to each cycle
- Pre-cycles 3-6 cTnI ≥ 23 ng/L

↓

Anthracycline treatment completed

↓ (All patients)

- Radiotherapy (for some patients)
- cTnI concentrations at 2 and 4 months

↓

Post-anthracycline cardiac MRI

Flowchart (right branch):

1:1 Randomisation

↓

- candesartan + carvedilol*
- Standard care

9-20 days

*Starting doses
Candesartan 8 mg o.d.
Carvedilol 6.25 mg b.d.

Titration clinics

↓

Maximum tolerated doses of candesartan + carvedilol**

** Target doses
Candesartan 32 mg o.d.
Carvedilol 25 mg b.d.

↓

Drug treatment continues until final MRI scan

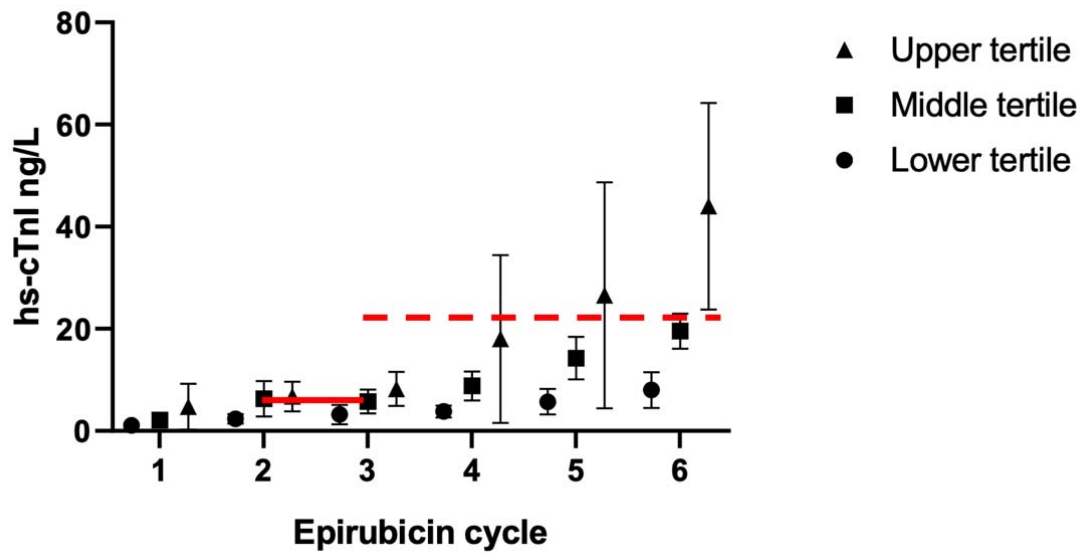**Figure 1:** Study flow for the Cardiac CARE Trial. cTnI: high sensitivity cardiac troponin I

Figure 2. Randomization thresholds for high-sensitivity cardiac troponin I (hs-cTnI) concentrations in the Cardiac CARE Trial superimposed on a high-sensitivity cardiac troponin I tertile plot for breast cancer patients receiving six cycles of epirubicin (cumulative dose 400 mg/m^2). Plot of high-sensitivity cardiac troponin I concentration (median and interquartile range) tertiles according to concentration before sixth treatment cycle (modified from Tzolos et al[11]). solid line, 5 ng/L; cycle 2, broken line, 23 ng/L; cycles 3-6.