# High-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta blocker therapy to prevent anthracycline cardiotoxicity: the Cardiac CARE RCT

Peter Henriksen,[1*] Morag MacLean,[2] Marek Atter,[2] Steff Lewis[2] and Aryelly Rodriguez,[2] on behalf of the Cardiac CARE Investigators

[1]Edinburgh Heart Centre, NHS Lothian Western General Hospital, Edinburgh, UK
[2]Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, NINE Edinburgh BioQuarter, Edinburgh, UK

[*]Corresponding author phenrik1@ed.ac.uk

Published August 2024
DOI: 10.3310/APTU2400

## Scientific summary

High-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta blocker therapy to prevent anthracycline cardiotoxicity: the Cardiac CARE RCT

Efficacy and Mechanism Evaluation 2024; Vol. 11: No. 12
DOI: 10.3310/APTU2400

NIHR Journals Library www.journalslibrary.nihr.ac.uk

# Scientific summary

## Background

Anthracycline chemotherapy has been shown to reduce the chances of cancer recurrence and death in individuals diagnosed with breast cancer and non-Hodgkin lymphoma. Anthracyclines can also cause damage to the heart muscle, potentially leading to left ventricular systolic dysfunction and cardiac failure. As cancer survival rates improve, there is growing concern about the long-term impact of chemotherapy-related cardiac toxicity.

Previous studies have revealed that approximately 5% of patients treated with high doses of anthracycline experience cardiac failure, with the prevalence rising to 10% among those aged > 65 years. The progression from initial heart muscle injury during chemotherapy to the development of left ventricular systolic dysfunction and subsequent clinical heart failure remains poorly understood. Thankfully, the severity and incidence of cardiotoxicity have decreased with the implementation of modern chemotherapy protocols that use lower cumulative doses of anthracycline.

To mitigate the risk of systolic dysfunction in patients receiving anthracyclines, recent clinical trials have investigated the use of medications commonly employed in heart failure treatment. A recent meta-analysis of 17 trials involving patients receiving anthracycline-based chemotherapy and randomised to neurohormonal blockade showed a mean 4-percentage-point higher left ventricular ejection fraction (LVEF) in the blockade group, along with a non-significant trend towards fewer clinical events. However, the studies in this meta-analysis have their limitations. First, therapy was prescribed to all patients, resulting in significant overtreatment as most patients do not develop cardiotoxicity. Second, the medications used targeted either the renin-angiotensin system or the sympathetic nervous system (B-adrenoreceptor blocker), even though the strongest evidence supports combined therapy with these medications for the treatment of left ventricular systolic dysfunction.

With modern advancements in cancer care, lower rates of cardiotoxicity are being achieved. Consequently, future trials should focus on interventions for patients who are at the highest risk of developing cardiotoxicity. Addressing the limitations of previous studies, the Cardiac CARE trial (registered as EudraCT 2017-000896-99 and ISRCTN24439460) aimed to select patients who demonstrated the most evidence of anthracycline-induced myocardial injury and randomise them into a combination treatment of candesartan and carvedilol.

## Objectives

The primary goals of the Cardiac CARE trial were twofold: first, to investigate whether high-sensitivity plasma cardiac troponin I (cTnI) monitoring can identify patients who are at risk of developing left ventricular systolic dysfunction after undergoing anthracycline chemotherapy, and, second, to determine if cTnI-guided treatment with candesartan and carvedilol can prevent the development of left systolic ventricular dysfunction. By achieving these objectives, Cardiac CARE trial findings would have immediate practical implications for clinical practice by testing a straightforward monitoring and intervention pathway that could easily be implemented within cancer treatment centres. The primary end point of the study was to measure the change in left ventricular ejection fraction using cardiac magnetic resonance imaging conducted 6 months after the final dose of anthracycline chemotherapy. The first secondary end point and main secondary objective were to establish the specificity of high-sensitivity cardiac troponin I (hs-cTnI) monitoring for cardiotoxicity by assessing the change in left ventricular ejection fraction in the low-risk non-randomised group. Additional secondary end points included evaluating hs-cTnI concentrations, conducting further cardiac magnetic resonance imaging

measurements to assess the efficacy of candesartan and carvedilol treatment, and determining the specificity of hs-cTnI monitoring for cardiotoxicity. The study summarised clinically relevant thresholds for grading anthracycline cardiotoxicity based on treatment, but no formal statistical testing was performed due to inadequate power and the risk of testing multiple hypotheses simultaneously.

## Methods

The study was conducted in accordance with the Declaration of Helsinki and received approval from the South East Scotland Research Ethics Committee (17/ES/0071). It followed a prospective, randomised, open-label, blinded end-point design. All patients received standard of care and underwent cardiac magnetic resonance imaging before and 6 months after completing anthracycline chemotherapy. Patients with high sensitivity plasma cTnI concentrations in the upper tertile during chemotherapy were randomly assigned in a 1 : 1 ratio to receive either standard of care alone or standard of care along with combined candesartan and carvedilol therapy. Patients aged ≥18 years who were starting anthracycline treatment for adjuvant or neo-adjuvant therapy of breast cancer or non-Hodgkin lymphoma were eligible to participate. To focus on the dose-dependent nature of anthracycline cardiotoxicity and considering the lower incidence observed in recent studies, only patients scheduled to receive a cumulative dose of at least 300 mg/m$^2$ of epirubicin or 150 mg/m$^2$ of doxorubicin over three, four or six cycles of treatment were approached. In comparison, the Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) study included 60% of patients receiving low-dose anthracycline (cumulative epirubicin dose ≤ 240 mg/m$^2$), and around 20% of them also received trastuzumab. Cardiac CARE excluded patients with HER2-positive disease scheduled for trastuzumab treatment. Although studying the outcomes of patients receiving anthracycline followed by trastuzumab is clinically relevant, it would require a larger study to account for the effects of two agents with interacting but distinct mechanisms of myocardial injury and potentially reversible changes in left ventricular ejection fraction occurring over an additional 15 months of trastuzumab administration. Plasma hs-cTnI concentrations were measured before and during chemotherapy to identify patients at high risk. The thresholds for randomisation were based on findings from a pilot study that identified patients with high sensitivity plasma cTnI concentrations in the upper tertile on completion of anthracycline chemotherapy.

Patients were randomised using a web-based service to ensure allocation concealment and avoid bias. Randomisation was performed between the standard of care alone and the standard of care plus combined candesartan and carvedilol (cardioprotection) therapy groups. Patients assigned to the treatment intervention started with 8 mg of candesartan once daily, with dosage increases of at least 3 days to reach 16 mg and 32 mg once daily. Simultaneously, carvedilol was initiated at 6.25 mg twice daily and increased to 12.5 mg and 25 mg twice daily. The medications were dispensed on the day of randomisation and continued until patients completed the study or withdrew from participation. Adherence to medication was recorded through dose titration clinics and in patient diaries. Patients with plasma hs-cTnI concentrations below the randomisation threshold remained on standard of care alone. Health utility, measured with the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) questionnaire, was assessed at chemotherapy cycle 1 by a research nurse and approximately every 9 weeks until the completion of the study (a total of five times).

## Sample size and statistical analysis

The Cardiac CARE trial aimed to enrol at least 168 patients from various regional cancer centres in the UK. It was estimated that approximately one-third of the enrolled patients ($n$ = 56) would develop high-sensitivity plasma cTnI concentrations that met the criteria for high risk based on the Cardiac CARE pilot study. We assumed that this threshold would select all patients at risk of experiencing a ≥ 5%-point reduction in left ventricular ejection fraction, which may be associated with long-term clinical outcomes.

The randomisation was set at a 1 : 1 ratio between the treatment arm and standard care. Treatment allocation employed dynamic randomisation, with minimisation of group imbalances in prognostic factors, including age (≥ 65 or < 65 years), baseline LVEF (≥ 60% or < 60%) and planned cumulative epirubicin equivalent dose (300 or > 300 mg/m$^2$). To detect a difference of 5 percentage points between groups (standard deviation 5) with 90% power at a significance level of = 0.05, we needed to randomise 23 patients per group. Accounting for an estimated 17% missing data, the sample size requirement increased to 28 patients per group, resulting in a total randomised trial size of 56 patients. Since one-third of enrolled patients were expected to be randomised, the total enrolment needed to be at least 168 patients. To assess the specificity of the plasma hs-cTnI assay for left ventricular systolic dysfunction in non-randomised patients, we aimed to demonstrate that there was no change in left ventricular ejection fraction percentage (with equivalence limits of ± 2%). To achieve this, we needed complete paired magnetic resonance imaging scans from 68 non-randomised patients for a paired *t*-test with two-sided *p*-value of 0.05, 90% power, and a standard deviation of differences of 5%.

## Results

Between 4 October 2017 and 30 June 2021, 175 patients were enrolled. Fifty-seven (32.6%) of patients were randomised. Twenty-nine were allocated to cardioprotection, with two patients in this group not completing the final follow-up magnetic resonance imaging (MRI) scan. Twenty-eight were allocated to standard care, with one patient not completing the final follow-up MRI scan. Within the remaining 118 non-randomised group, 21 patients did not complete the final follow-up magnetic resonance imaging scan. Twenty patients (68.9%) were adherent to cardioprotection treatment at 6 months. Two patients (6.9%) randomised to cardioprotection did not receive medication owing to illness at the time of randomisation. Adverse events were more common in cardioprotection than in the standard care groups (71.4% and 10.3%, respectively). Seven (24.1%) participants stopped both cardioprotection drugs within 2 months owing to symptoms.

The mean (standard deviation) patient age in the non-randomised, cardioprotection and standard care groups was 52.1 (11.0) years, 54 (14.1) years and 53.5 (13.3) years, respectively. Mean mass (standard deviation) was higher in the standard care group (82.5 kg; 6.7 kg) than in the cardioprotection (70.7 kg; 16.5 kg) and non-randomised groups (76.6 kg; 6.5 kg); 71.2% of patients had received a diagnosis of breast cancer. Non-Hodgkin lymphoma patients were more frequently randomised than breast cancer patients, making up 43.9% of the randomised and 21.2% of the non-randomised groups. Cardiovascular risk markers and concomitant cardiovascular medication prescription were uncommon across all three groups. Hypertension and coronary disease were more common in the standard care group (14.3% and 7.1%, respectively) than in the non-randomised (8.5% and 3%) and cardioprotection groups (6.9% and 0%). The mean anthracycline dose was higher in the cardioprotection (469 mg/m$^2$) and standard care groups (479 mg/m$^2$) than in the non-randomised group (424 mg/m$^2$). Radiotherapy was more commonly prescribed in the non-randomised group (71.2%) than in the cardioprotection (57.1%) and standard care groups (53.6%). Patients randomised to cardioprotection or standard care had a mean (standard deviation) LVEF 6 months after completion of anthracycline chemotherapy of 65.7% (6.6%) and 64.9% (5.9%), respectively. After adjustment, the estimated mean difference in 6-month LVEF between the cardioprotection and standard care groups was −0.4% points [95% confidence interval (CI) −3.6 to 2.8 points; $p$ = 0.82].

We examined the per-protocol primary efficacy outcome between the randomised groups in a post hoc sensitivity analysis. When only 19 cardioprotection patients who were adherent to treatment were included, there was no change in the primary outcome. The estimated mean difference in the change in 6-month LVEF between the cardioprotection and standard care groups was −0.7 percentage points (95% CI −4.3 to 2.9 percentage points; $p$ = 0.70).

In non-randomised patients, the baseline and 6-month LVEF (standard deviation) were 69.3% (5.7%) and 66.4% (6.3%), respectively. The estimated mean difference was 2.9 percentage points (95% CI 1.45 to 4.28 percentage points; $p = 0.92$). The main secondary objective of demonstrating zero-percentage-point change with equivalence of ± 2% was not met. Secondary analysis identified a difference between cardioprotection and standard care groups in adjusted left ventricular end-diastolic volume indexed for body surface area of 6.0 ml/m$^2$ (95% CI 0.6 to 11.4 ml/m$^2$; $p = 0.03$). There was no difference between the groups in global longitudinal and circumferential strain, left ventricular mass or left atrial area. hs-cTnI concentrations were higher in the randomised groups. The adjusted change in hs-cTnI concentration from baseline to 2 months in the cardioprotection and standard care groups was 27.3 ng/l (7.4 ng/l) and 28.8 ng/l (8.8 ng/l) [estimated mean (standard error)]. The estimated mean difference was −1.6 ng/l (95% CI −17.6 to 14.4 ng/l; $p = 0.85$). No cardiovascular deaths or new atrial fibrillation were recorded during the trial. One patient in the standard care treatment group developed congestive cardiac failure. This patient received heart failure treatment including candesartan and their ejection fraction was seen to have recovered on the 6-month cardiac MRI scan. No patients met the criteria for asymptomatic cancer therapy-related cardiac dysfunction (CTRCD) of a 10-percentage-point LVEF fall and fall to an absolute LVEF below 50%. Similarly, the CTRCD criterion of > 15% fall in global longitudinal strain was uncommon across the groups. Chronic myocardial injury 2 months after completion of chemotherapy was not uncommon and was similar in the non-randomised (32.1%) and cardioprotection (35.7%) groups. The proportion with chronic myocardial injury was higher (60%) in the standard care treatment group. Any recording of high hs-cTnI concentration was confined to randomised groups.

## Conclusions

We found no evidence of cardioprotection effect with combined candesartan and carvedilol. This combination was associated with side effects, and discontinuation of therapy was not uncommon. Our findings do not support the European Society Guidelines that give a class II recommendation to use of either an angiotensin blocker or B-blockers for high-risk anthracycline-treated patients.

Furthermore, the small decline in LVEF at 6 months in all groups together with the low levels of other cardiotoxicity measures cast doubt over whether any form of broadly administered cardioprotection therapy is required for these patients.

The recently published European Society of Cardio-Oncology Guidelines provide a class I recommendation for the use of cTn monitoring in anthracycline patients at high risk of cardiotoxicity. The Cardiac CARE trial findings raise doubt about whether this monitoring strategy is helpful when patients with both low- and high-risk hs-cTnI concentration profiles developed small reductions in left ventricular ejection fraction. Although the pathological link between cTn as a biomarker of anthracycline myocardial injury is clear, we found no evidence that elevated concentrations strongly predict cardiotoxicity, inform disease management or improve care when added to current treatment pathways. Further analysis of the data will establish the correlation between hs-cTnI concentrations and change in LVEF and global longitudinal strain. We will also examine whether there is a threshold hs-cTnI concentration below which patients do not develop a decline in LVEF.

An LVEF decline of 4.3% at 6 months after chemotherapy may not have immediate clinical implications for an individual patient. Applied across a population, this magnitude of LVEF decline is likely to confer a generalised increased risk of future cardiac dysfunction and heart failure. Future research should be directed at understanding the factors determining the evolution of cardiac dysfunction with monitoring and longer-term follow-up studies.

## Trial registration

This trial is registered as ISRCTN24439460 and EudraCT 2017-000896-99.

## Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (NIHR award ref: 15/48/20) and is published in full in *Efficacy and Mechanism Evaluation*; Vol. 11, No. 12. See the NIHR Funding and Awards website for further award information.

# Efficacy and Mechanism Evaluation

ISSN 2050-4373 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

*Efficacy and Mechanism Evaluation* (EME) was launched in 2014 and is indexed by Europe PMC, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and NCBI Bookshelf.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme.

**Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal**
Manuscripts are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

## EME programme

The Efficacy and Mechanism Evaluation (EME) programme funds ambitious studies evaluating interventions that have the potential to make a step-change in the promotion of health, treatment of disease and improvement of rehabilitation or long-term care. Within these studies, EME supports research to improve the understanding of the mechanisms of both diseases and treatments.

The programme supports translational research into a wide range of new or repurposed interventions. These may include diagnostic or prognostic tests and decision-making tools, therapeutics or psychological treatments, medical devices, and public health initiatives delivered in the NHS.

The EME programme supports clinical trials and studies with other robust designs, which test the efficacy of interventions, and which may use clinical or well-validated surrogate outcomes. It only supports studies in humans and where there is adequate proof of concept. The programme encourages hypothesis-driven mechanistic studies, integrated within the efficacy study, that explore the mechanisms of action of the intervention or the disease, the cause of differing responses, or improve the understanding of adverse effects. It funds similar mechanistic studies linked to studies funded by any NIHR programme.

The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

## This article

The research reported in this issue of the journal was funded by the EME programme as award number 15/48/20. The contractual start date was in April 2017. The draft manuscript began editorial review in December 2022 and was accepted for publication in September 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, the EME programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the EME programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.



Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).