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

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on behalf of the Cardiac CARE Investigators*



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Abstract

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

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Background: Anthracycline-induced cardiotoxicity has a variable incidence, and the development of left ventricular dysfunction is preceded by rises in plasma cardiac troponin concentrations. Beta-adrenergic receptor blocker and renin-angiotensin-system inhibitor therapies have been associated with modest cardioprotective effects in unselected patients receiving anthracycline chemotherapy.

Methods: In a multicentre prospective randomised open-label blinded end-point trial, patients with breast cancer and non-Hodgkin lymphoma receiving anthracycline chemotherapy underwent plasma high-sensitivity cardiac troponin concentration monitoring and cardiac magnetic resonance imaging before and 6 months after anthracycline treatment. Randomised controlled trial – patients at high risk of cardiotoxicity (plasma cardiac troponin I concentrations in the upper tertile during chemotherapy) were randomised to standard care plus cardioprotection (combination carvedilol and candesartan therapy) or standard care alone. The primary end point was 6-month change in left ventricular ejection fraction. Prognostic cohort study – in low-risk non-randomised patients with plasma cardiac troponin I concentrations in the lower two tertiles, we hypothesised the absence of a 6-month change in left ventricular ejection fraction ($\pm 2\%$).

Results: Between October 2017 and June 2021, 175 patients (mean age 53 years; 87% female; 71% breast cancer) were recruited. Patients randomised to cardioprotection ($n = 29$) or standard care ($n = 28$) had mean left ventricular ejection fractions of $65.7 \pm 6.6\%$ and $64.9 \pm 5.9\%$, respectively, at 6 months. Twenty patients (68.9%) were adherent to cardioprotection therapy at 6 months. Adverse events were more commonly reported in the cardioprotection group, with 71.4% of patients having at least one adverse event compared with 12.7% non-randomised and 10.3% standard care patients. After adjusting for age, pre-treatment left ventricular ejection fraction and planned anthracycline dose, the estimated mean percentage-point difference in 6-month left ventricular ejection fraction between the cardioprotection and standard care groups was -0.4% (95% confidence interval -3.59 to 2.85% ; $p = 0.82$). In low-risk non-randomised patients, baseline and 6-month left ventricular ejection fractions were $69.3 \pm 5.7\%$ and $66.4 \pm 6.3\%$, respectively (estimated mean difference 2.9% , 95% confidence interval 1.45 to 4.28% ; $p = 0.92$, not equivalent). The main secondary objective of demonstrating zero percentage-point change with equivalence of $\pm 2\%$ was not met.

Conclusions: Combination candesartan and carvedilol therapy had no demonstrable cardioprotective effect in patients receiving anthracycline-based chemotherapy with high-risk on-treatment plasma cardiac troponin I concentrations. Low-risk non-randomised patients had similar modest declines in left ventricular ejection fraction, suggesting that the clinical utility of routine cardiac troponin monitoring

remains undefined. The modest short-term declines in left ventricular ejection fraction suggest that early cardioprotection therapy has a limited role in patients receiving anthracycline-based chemotherapy.

Limitations: Treatment effect might have been influenced by several patients stopping cardioprotection treatment within 2 months of randomisation. Across all groups, reduction in left ventricular ejection fraction was lower than expected and patients with high-risk cardiac troponin I concentrations did not exhibit a greater fall in left ventricular ejection fraction than low-risk patients. These factors, together with the trial being powered to detect a 5-percentage-point change in left ventricular ejection fraction, mean that a small treatment effect was not excluded.

Future work: Future work should aim to understand the transition from small changes in cardiac function, 6 months after completion of anthracycline chemotherapy, to the late development of heart failure in this population.

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

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Report Supplementary Material 2 Trial statistical analysis plan

Report Supplementary Material 3 Trial health economics analysis plan

Supplementary material can be found on the NIHR Journals Library report page (<https://doi.org/10.3310/APTU2400>).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

Glossary

hs-cTnl cardiac troponin I concentration quantified using the ARCHITECTSTAT or ALINITY high-sensitivity cardiac troponin I assay (Abbott Laboratories, Chicago, IL, USA).

List of abbreviations

ACEi	angiotensin-converting enzyme inhibitor	HER2	human epidermal growth factor receptor-2
AE	adverse event	HRU	healthcare resource use
ARB	angiotensin II type I receptor antagonist (e.g. candesartan)	HSUV	health state utility value
B-blocker	B-adrenoceptor blocker	ICER	incremental cost-effectiveness ratio
Cardiac CARE	High-Sensitivity Cardiac Troponin I-Guided Combination Angiotensin Receptor Blockade and Beta Blocker Therapy to Prevent Cardiac Toxicity in Cancer Patients Receiving Anthracycline Chemotherapy	IMP	investigational medicinal product
CECCY	Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity	LAA	left atrial area
CI	confidence interval	LVEDV	left ventricular end-diastolic volume
CTIMP	Clinical Trial of Investigational Medicinal Product	LVEF	left ventricular ejection fraction
CTRCD	cancer-therapy related cardiac dysfunction	LVEF%	left ventricular ejection fraction (expressed as a percentage)
cTnl	cardiac troponin I	LVM	left ventricular mass
ECTU	Edinburgh Clinical Trials Unit	MRI	magnetic resonance imaging
eGFR	estimated glomerular filtration rate	NHL	non-Hodgkin lymphoma
EQ-5D	EuroQol-5 Dimensions	PRADA	Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy
EQ-5D-5L	EuroQol-5 Dimensions, five-level version	PROBE	prospective randomised open-label blinded end point
GCS	global circumferential strain	PROM	patient-reported outcome measure
GLS	global longitudinal strain	QALY	quality-adjusted life-year
		RCT	randomised controlled trial
		SAE	serious adverse event
		SD	standard deviation
		VAS	Visual Analogue Scale

Plain language summary

The improved survival for patients with cancer is in part down to chemotherapy drugs called anthracyclines. This medication can cause the unwanted side effect of heart muscle pump injury in a minority of patients. Cancer survivors have increased rates of heart problems, including heart muscle pump failure.

Research questions

The Cardiac CARE trial tested whether tablet medications called angiotensin receptor blockers and B-blockers, taken together (cardioprotection therapy), can prevent heart muscle injury related to chemotherapy. Doctors treat heart pump failure using these medications. We examined whether a blood test called high sensitivity cardiac troponin I can detect very slight heart muscle injury and predict future problems with heart pump failure.

What we did

In the trial, only patients with increased levels of the troponin blood test marker were treated with cardioprotection therapy. Breast and blood cancer patients receiving anthracycline treatment were approached to take part. After giving consent they had a detailed scan of their heart prior to starting and 6 months after completing anthracycline chemotherapy. Patients receiving anthracycline had blood taken routinely 2 or 3 days before each treatment. Cardiac troponin levels were measured in these blood samples, and patients with an increased level were allocated at random to treatment with cardioprotection therapy or to normal care.

Research findings

We found no evidence that cardioprotection therapy prevented decline in heart function in anthracycline-treated patients with elevated cardiac troponin levels. Patients with no increased troponin level had a similar decline in heart function. It was reassuring that the reduction in heart muscle function following anthracycline chemotherapy was small. We believe the results show that cardioprotection therapy is not effective and may not be required for most patients.

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/m² of epirubicin or 150 mg/m² 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/m²), 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 $\geq 5\%$ -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 ($\geq 60\%$ or $< 60\%$) and planned cumulative epirubicin equivalent dose (300 or > 300 mg/m²). To detect a difference of 5 percentage points between groups (standard deviation 5) with 90% power at a significance level of $\alpha = 0.05$, 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 $\pm 2\%$). 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/m²) and standard care groups (479 mg/m²) than in the non-randomised group (424 mg/m²). 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 $\pm 2\%$ 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/m² (95% CI 0.6 to 11.4 ml/m²; $p = 0.03$). 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

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Chapter 1 Introduction

Background

Anthracyclines (doxorubicin and epirubicin) are used to treat a wide range of cancers, including breast cancer and lymphoma. Anthracycline administration is associated with dose-related cardiomyocyte injury and left ventricular dysfunction and heart failure leading to death.¹⁻³ Follow-up studies of breast cancer and lymphoma survivors demonstrate excessive cardiac events, including early and late development of heart failure. Prognosis from heart failure is poor.⁴ The progression from heart muscle injury at the time of chemotherapy to development of clinical heart failure is not understood, and no preventive treatments are available.

Monitoring and identification of anthracycline-induced cardiotoxicity

Imaging

International guidelines recognise the challenge of variable patient susceptibility to anthracycline cardiotoxicity.⁵ 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. Recommendations for further monitoring are based on expert consensus and indicate additional evaluation of cardiac function during and following the completion of anthracycline chemotherapy depending on cumulative dose and plans for further cardiotoxic therapy.^{5,6} However, cardiac imaging conducted too soon after the completion of anthracycline chemotherapy may miss the nadir of the fall in left ventricular ejection fraction (LVEF). Indeed, immediate post-treatment scanning (within 1 month) might have been a factor in the smaller-than-expected fall in LVEF 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 randomised to treatment with candesartan or metoprolol. Overall decline in LVEF on cardiac magnetic resonance was only 2.6% [95% confidence interval (CI) 1.5% to 3.8%] in the placebo group.⁷ Cardiotoxicity monitoring guidelines recognise the potential for late changes in cardiac function and advocate additional serial cardiac imaging monitoring in high-risk and paediatric 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 (High-Sensitivity Cardiac Troponin I-Guided Combination Angiotensin Receptor Blockade and Beta Blocker Therapy to Prevent Cardiac Toxicity in Cancer Patients Receiving Anthracycline Chemotherapy) trial routinely receive risk factor assessment and cardiac imaging before treatment together with follow-up cardiac imaging conducted at a variable interval of between 6 and 12 months following the completion of chemotherapy. Better methods are required to identify most patients who are at low risk of cardiotoxicity and do not require close follow-up.

Humoral biomarkers

Cardiac troponin (cTn) I and T are markers of myocardial injury, and plasma concentrations have been used to detect early anthracycline-induced cardiomyocyte toxicity.⁸ High-sensitivity cTn (hs-cTn) 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 increased risk of cardiovascular events and death.⁹ In pilot work for the Cardiac CARE trial, we demonstrated that plasma cardiac troponin I (cTnI) concentrations exhibit an anthracycline dose-dependent increase in patients with breast cancer.¹⁰ More than one-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 this represents a patient-specific marker of on-treatment myocardial injury. Monitoring of cTn concentration

during anthracycline therapy has been advocated in guidelines and adopted widely into clinical protocols despite having no broad mandate from randomised trials.^{11,12} 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 hs-cTnI and troponin T assays, preventing a 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 cTn concentrations during or after anthracycline treatment are associated with a sevenfold 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 cTn concentrations quantified with contemporary (non-high sensitivity) assays. It is worth noting that both the chemotherapy dose and the consequent magnitude of myocardial injury recorded with cTn quantification were greater in many of the earlier studies included in this meta-analysis.^{15,16}

N-terminal pro-B-type natriuretic peptide quantification has been proposed to anticipate late development of heart failure in anthracycline-treated patients.⁵ N-terminal pro-B-type natriuretic peptide 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 myocardial injury. The UK centres participating in Cardiac CARE do not routinely monitor cTn or N-terminal pro-B-type natriuretic peptide concentrations during treatment with anthracycline chemotherapy.

Existing research

Previous trials have investigated whether the administration of medications established for the treatment of heart failure can prevent systolic dysfunction in patients receiving chemotherapy. These studies are limited by (1) prescribing therapy to all patients resulting in substantial overtreatment and (2) using either an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II type I receptor antagonist (ARB) or a B-blocker rather than co-prescription, which has the most robust evidence base for improving function and survival among patients with left ventricular systolic dysfunction.¹⁷

The combination of inhibiting the renin-angiotensin system and blocking β -adrenoreceptors has shown significant benefits in reducing morbidity and mortality in heart failure patients with reduced ejection fraction, including those with chemotherapy-related heart muscle disease. These therapies have also proven effective for asymptomatic left ventricular systolic dysfunction, the most common form of anthracycline cardiotoxicity. For instance, enalapril has been shown to decrease the risk of death and hospitalisation for heart failure in patients with asymptomatic left ventricular dysfunction.¹⁸ Additionally, the combination of carvedilol and an ACE inhibitor has been found to reduce overall mortality in patients with left ventricular dysfunction following acute myocardial infarction.¹⁹ However, randomised controlled trials (RCTs) investigating the potential of neurohormonal blockade for preventing anthracycline cardiotoxicity have yielded mixed results.

In the PRADA study, breast cancer patients receiving anthracycline treatment, with or without trastuzumab, were randomly assigned to receive the ARB candesartan, the beta-blocker metoprolol, or a placebo.⁷ Whereas candesartan showed protection against myocardial dysfunction measured by LVEF on cardiac magnetic resonance imaging (MRI), metoprolol did not demonstrate the same effect. The decline in LVEF immediately after chemotherapy was 2.6 percentage points in the placebo group compared with 0.8 percentage points in those receiving candesartan ($p = 0.021$). However, in a subsequent extended follow-up study, a small decline in LVEF persisted, but there was no significant difference between the treatment groups.²⁰

A recent meta-analysis²¹ of 17 trials involving patients receiving anthracycline-based chemotherapy and randomised to neurohormonal blockade showed a 4% higher LVEF in the blockade group, along with a non-significant trend towards fewer clinical events. However, these trials were often single-centre,

exhibited significant heterogeneity and displayed evidence of publication bias. Moreover, patient inclusion and randomisation did not take into account stratification for elevated risk of cardiotoxicity, and the trials frequently examined single therapeutic agents. Therefore, it remains unclear whether the potential treatment effect was diluted by including lower-risk patients exposed to different treatments.

The International Cardio oncology Society-One (ICOS-ONE) multicentre trial²² focused on patients treated with anthracycline and randomised them to receive enalapril either upfront or triggered by elevated cardiac troponin levels measured using either a traditional or a high-sensitivity assay. The trial lacked a placebo group, and changes in cardiac function were evaluated based on the development of cardiotoxicity defined by a decrease in LVEF of > 10% and an overall LVEF of < 50% on surveillance echocardiography up to 1 year after chemotherapy. This categorical definition of cardiotoxicity using echocardiography may not capture smaller yet clinically significant changes in LVEF following chemotherapy. The study found no significant difference between the two treatment approaches, but the most notable observation was the low rate of cardiotoxicity, with only three cases among the 273 patients in the trial and no instances of congestive heart failure or cardiovascular death. It remains uncertain whether initiating cardioprotective medications solely based on changes in high-sensitivity cTn concentrations affects the development of left ventricular dysfunction or heart failure.

Rationale for choice of intervention

Candesartan has an established role in the treatment of patients with left ventricular dysfunction, and in the PRADA study it demonstrated an early protective effect on LVEF in this patient population.⁷ The avoidance of cough as a side effect is considered an advantage of angiotensin receptor blockade (candesartan) over ACE inhibition in this immunocompromised cancer population. The target dose and dose titration schedule for candesartan were identical in Cardiac CARE and the PRADA study. Carvedilol was tested previously in a similar population of anthracycline-treated breast cancer patients in the Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity (CECCY) trial.²³ There was no difference in the primary cardiotoxicity end point compared with placebo. Carvedilol treatment was associated with lower circulating cTnI concentrations and less diastolic dysfunction. In the Cardiac CARE trial, the target carvedilol dose of 25 mg twice-daily was the same but the interval between dose titration was much shorter, at 3 days compared with 3 weeks in the CECCY trial. The key difference in approach between the Cardiac CARE trial and previous cardioprotection studies is the focus in the former on maximum neurohormonal blockade on high-risk patients with coprescription of candesartan and carvedilol rather than a single agent.

Risks

Candesartan (ARB) and carvedilol (B-blocker) are widely used in the NHS with an established safety profile and cost-efficacy. No toxicity was reported in the PRADA study, which examined ARB and B-blocker combination in an identical study population to ours. ARBs and B-blockers are in widespread use for hypertension and other serious conditions including heart failure and following myocardial infarction. Patients in the study who were randomised to cardioprotection had their renal function and blood pressure monitored at dose titration clinics supervised by oncology research nurses. We followed a dose titration protocol used in the PRADA study. B-blockers may exacerbate psoriasis and asthma. Common side effects include lethargy and cold peripheries. For these reasons we believed that identifying an at-risk population of breast cancer and non-Hodgkin lymphoma (NHL) patients to target cardioprotection and closer monitoring was key.

Benefits

The long-term follow-up of breast cancer and NHL survivors demonstrates an increase in late cardiac events among this population, including symptomatic heart failure.¹ Clinical studies that record cardiac events during the period of chemotherapy therefore underestimate the magnitude of the problem. Improved survival has led to the recognition of the late impact of cardiac disease related to breast cancer therapies, and consensus statements from the European Society of Cardiology highlight the need for improved monitoring and preventive treatment.^{5,12} Current clinical protocols for cardiotoxicity monitoring are suboptimal, aiming to identify cardiac muscle dysfunction after it has become

established. Cardiotoxicity is identified by assessing cardiac function, using imaging to measure ejection fraction with echocardiography or radionuclide scans. By demonstrating that early cardiac injury can be detected with a high-sensitivity cardiac troponin I (hs-cTnI) assay, it will be possible to screen out a population of low-risk patients who do not exhibit elevation of this marker during chemotherapy and so do not require surveillance imaging.

Rationale for study

In this study, we used surveillance with high-sensitivity hs-cTnI blood testing in patients receiving cardiotoxic systemic therapy to identify early muscle injury, enabling targeted protective treatment with ARB and B-blocker. Our group's prospective cohort studies including 6304 patients presenting to hospital with suspected acute coronary syndrome and 155 patients with moderate to severe aortic stenosis have confirmed that low cTnI concentrations (< 5 ng/l) are associated with low risk of future cardiac events.^{9,24} In two independent validation cohorts of patients presenting with suspected acute coronary syndrome, we demonstrated that cTnI concentrations of < 5 ng/l had a negative predictive value of 99.4% for myocardial infarction or death at 30 days.⁹ We further demonstrated that using the high sensitivity cTnI assay to define a gender-specific upper reference limit (99th centile: ≥ 16 ng/l for women and ≥ 34 ng/l for men) in patients presenting with chest pain identifies a population of women at increased risk of cardiac events who would be missed using older contemporary cTnI assays.²⁵ Our pilot study for the Cardiac CARE trial in anthracycline-treated breast cancer patients demonstrated an increase in hs-cTnI concentrations with progressive cycles of treatment, with many patients developing circulating concentrations of > 16 ng/l.¹⁰ There is a continuum of heart muscle injury, and the PRADA study illustrated the potential for cardiac MRI to detect smaller, less severe changes in left ventricular function in these patients.²⁶ To capture patients with lesser degrees of cardiac dysfunction, we selected a hs-cTnI concentration threshold that randomised at least 33% of patients recruited into the study. Patients with hs-cTnI concentrations above the threshold were randomised to receive candesartan and carvedilol or to continue with routine clinical care.

Our research examined the clinical efficacy of ARB and B-blockade in preventing the development of heart muscle failure in breast cancer and NHL patients receiving anthracycline-containing chemotherapy. These treatments have an established role in the treatment of patients with left ventricular dysfunction. ARB and B-blockade have an additive treatment effect, and a strong treatment response has been demonstrated in patients with different heart failure aetiologies, including chemotherapy-related heart muscle disease. Response to ARB and B-blockade includes improved survival, improved symptoms and recovery of LVEF. LVEF is a potent prognostic indicator of heart failure,^{27,28} and changes resulting from therapy or disease progression are closely associated with outcomes.^{29,30} All patients had LVEF monitored with serial cardiac MRI scans. Cardiac MRI is the most precise measure of cardiac function^{31,32} and provides additional measures of systolic volume and cardiac strain that will inform early mechanisms of chemotherapy-induced cardiac muscle injury. We therefore chose change in LVEF recorded 6 months following completion of anthracycline chemotherapy as the primary end point and surrogate marker of future heart failure events. The hypothesis was that carvedilol and candesartan will prevent the development of cardiac dysfunction in at-risk patients identified by elevated plasma hs-cTnI concentrations. Additional outcomes included treatment effect on ongoing cardiac injury (persistence of cTnI elevation), death and heart failure (definition is provided in version 11.0 of the protocol; link to publication is in [Additional information](#)) and a provisional health economic analysis of this selective intervention strategy to prevent chemotherapy-related heart failure.

The event rate was low in the PRADA study, with an average LVEF decline of only 2.6 (95% CI 1.5 to 3.8) percentage points in the placebo group.⁷ Sixty per cent of patients received low-dose anthracycline (cumulative epirubicin dose of 240 mg/m²). Around 20% of patients also received trastuzumab, and the final MRI scan was conducted variably according to the end of adjuvant therapy: either immediately following 4–5 months' treatment with anthracycline or at 15 months following treatment with anthracycline and trastuzumab. We set out to ensure a higher event rate by (1) only approaching

patients scheduled for higher anthracycline doses (≥ 300 mg/m² cumulative dose of epirubicin) and (2) restricting randomisation to high-risk patients identified by hs-cTnI elevation.

The hypothesis was that hs-cTnI monitoring would improve the detection of heart muscle injury compared with previous studies with the more insensitive contemporary assays. Increased concentrations of this plasma marker appear before the development of reduced left ventricular function and heart failure. Patients recruited into the study who exhibited a plasma hs-cTnI concentration above a threshold defined by our cTnI monitoring study were randomised to receive both carvedilol and candesartan (B-blocker and ARB) or to continue with standard care.

Our research plan was relevant to NHS cancer care pathways, recruiting patients receiving anthracycline and taking a precision medicine approach by targeting cardioprotective treatments only to at-risk patients.

Objectives

The study hypotheses were as follows:

1. The development of heart muscle failure measured by cardiac ejection fraction change in breast cancer and NHL patients receiving anthracycline will be prevented by carvedilol and candesartan.
2. All patients at risk of developing heart muscle failure will be detected by elevation of hs-cTnI on serial testing, validating the test as a simple screening tool for selecting patients for protective therapy and closer monitoring.

Primary objective

The primary objective was to determine whether known treatments for heart failure can prevent or reduce myocardial injury and the development of left ventricular systolic dysfunction.

Secondary objectives

The secondary objectives were to establish whether a novel highly sensitive plasma marker of myocardial injury can anticipate the development and monitor the progression of left ventricular systolic dysfunction.

Chapter 2 Methods

Trial design

We published an article examining the rationale for the Cardiac CARE trial design as well as the full protocol prior to the end of the study.³³

The study was a multicentre, prospective, randomised, open-label, blinded end-point (PROBE) RCT, with 1 : 1 individual randomisation to the treatment arm or standard care. Patients with troponin elevation were randomised. Non-randomised patients were allocated to receive standard care and were also followed up.

The clinical pathway for Cardiac CARE is illustrated in [Figure 1](#). After enrolling in the study and receiving a baseline MRI scan, patients had serial blood tests for hs-cTnI concentration performed prior to each cycle of anthracycline. Patients could be randomised at each cycle from cycle 2 to cycle 6 for those patients receiving 3–6 cycles of anthracycline. The anthracycline cycle/cTnI concentration thresholds for randomisation were anthracycline cycle 2, ≥ 5 ng/l; and anthracycline cycles 3–6, ≥ 23 ng/l.

Cardiac MRI results were made available to inform clinical care. Two analysts, independent of the research teams and blinded to scan sequence (pre- or post-anthracycline scan) and treatment, conducted cardiac MRI measurements for the primary and secondary outcomes in the Core Image Analysis laboratory (Edinburgh Imaging, University of Edinburgh) in accordance with the Society for Cardiovascular Magnetic Resonance guidelines on dedicated software (CVI42 version 5.14, Circle Cardiovascular Imaging). The Cardiac CARE Cardiovascular Magnetic Resonance imaging manual has been included as [Report Supplementary Material 1](#).

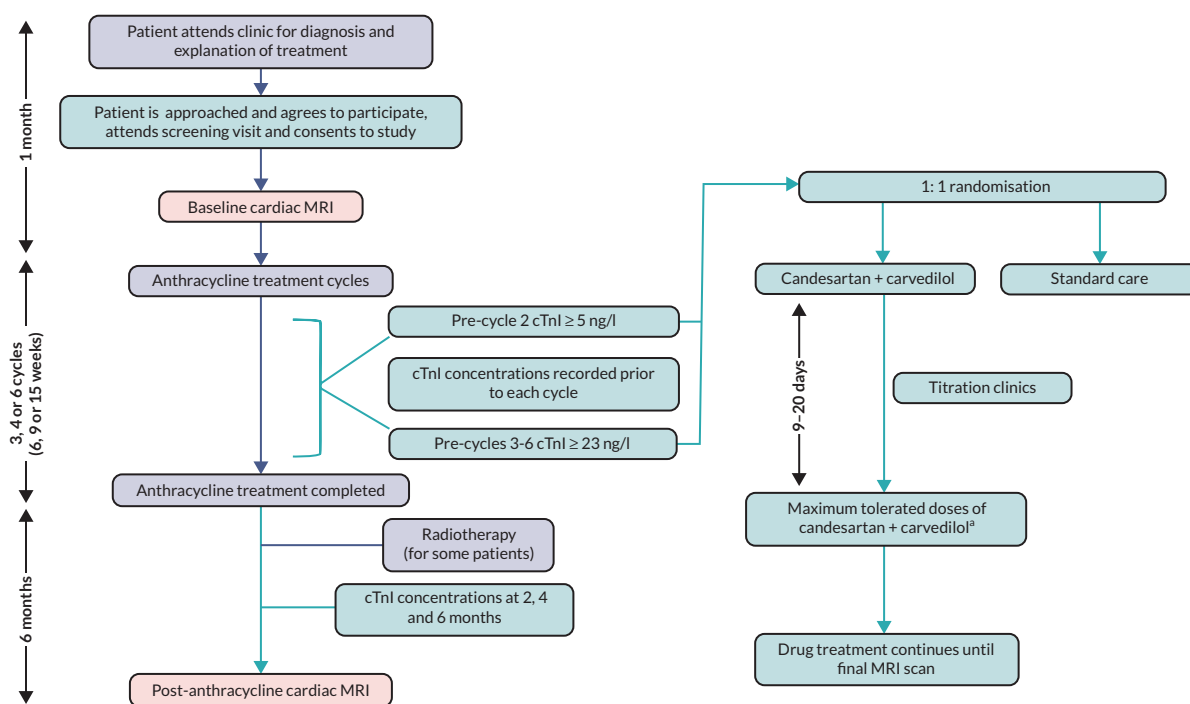


FIGURE 1 Clinical pathway for the Cardiac CARE trial. a, Target doses: candesartan 32 mg o.d.; carvedilol 25 mg b.d.

Changes to trial design

In 2018 the Trial Management Group made changes to the trial design to increase both recruitment and randomisation. Our co-applicants from the original application, the Breast Cancer Team in Leeds under Professor Chris Twelves, were projected to enrol up to one-third of patients for the study. The Leeds site did not open, and early recruitment from other sites indicated that we would need more sites and a broader population of eligible patients. Protocol version 6.0 (14 March 2018) included a major amendment to enrol patients with NHL who receive a similar anthracycline regime to breast cancer patients. A review of randomisation numbers in early 2018 indicated that < 30% of trial patients were being randomised. To increase randomisations, in protocol version 7.0 (8 August 2018), the threshold concentration was reduced from 6 ng/l to 5 ng/l at cycle 2 and randomisations were allowed at cycles 3, 4, 5 and 6 with a threshold of 23 ng/l (compared with just cycle 6).

A complete list of all protocol amendments can be found in [Appendix 2](#).

Participants

Patients aged ≥ 18 years commencing anthracycline for adjuvant or neo-adjuvant treatment of breast cancer or NHL were invited to participate in the study. Anthracycline cardiotoxicity is dose dependent, and only patients scheduled for ≥ 300 mg/m² cumulative dose of epirubicin (or equivalent) over 3, 4 or 6 cycles were approached. The sites recorded the patients approached on the sponsor subject pre-screening log.

The research study was explained by the consultant oncologist, haematologist or research nurse at the treatment planning clinic, and the patient was invited to participate. Patients were given information on the research study to take away after the diagnosis visit. They were contacted by telephone at least 24 hours after receiving the information, and if they agreed to take part they were invited to a screening visit where they were asked to provide consent. Full written consent was obtained by physicians on the research team, the research nurse or a deputy. If appropriate, the research nurse booked a MRI scan before anthracycline chemotherapy was started.

Patient eligibility was verified by a clinical trial physician after written informed consent was obtained. Confirmation of eligibility was recorded in patients' medical records.

Inclusion criteria

- Female or male aged ≥ 18 years.
- Histological diagnosis of invasive breast cancer or NHL.
- European Cooperative Oncology Group (ECOG) performance status 0–1.
- Planned to commence anthracycline-containing therapy.
- For adjuvant or neo-adjuvant treatment of breast cancer: breast cancer patients scheduled for ≥ 300 mg/m² cumulative dose of epirubicin or equivalent over 3, 4 or 6 cycles, or NHL patients planned to commence ≥ 3 cycles of CHOP or R-CHOP therapy containing ≥ 300 mg/m² epirubicin equivalent cumulative dose of anthracycline.
- A life expectancy of at least 12 months.
- LVEF of $\geq 50\%$ on baseline MRI.
- Systolic blood pressure (SBP) of ≥ 105 and ≤ 170 mmHg.
- An estimated glomerular filtration rate (eGFR) of > 45 ml/minute/1.73 m².
- Provided written consent to take part in the study.

Exclusion criteria

- Pregnancy or breastfeeding.
- Human epidermal growth factor receptor-2 (HER2) positive breast disease with planned trastuzumab therapy.
- Uncontrolled arterial hypertension defined as SBP on treatment of > 170 mmHg.
- Already taking B-blockers, ACEi or ARBs.
- Contraindication to ARBs (eGFR of ≤ 45 ml/minute/1.73 m², previous hypersensitivity, renal artery stenosis) or B-blockers (asthma, pathological heart block and pathological sinus bradycardia).
- Clinically proven intolerance to lactose monohydrate.
- A history of symptomatic heart failure.
- Contraindication to or inability to tolerate MRI scanning.
- Suspected poor drug compliance (suspected poor drug compliance and active alcohol or drug abuse was determined from history documented in the potential patient's medical notes).
- Active alcohol or drug abuse (suspected poor drug compliance and active alcohol or drug abuse was determined from history documented in the potential patient's medical notes).
- Previously treated with anthracyclines or trastuzumab.
- Uncontrolled concomitant serious illness, as determined by the investigator.
- Female or male aged < 18 years.
- Not provided written consent to take part in the study.
- Previously randomised into this trial.

Participant withdrawal from the trial

Patients were free to withdraw from the study at any point or a patient could be withdrawn by the investigator or responsible clinician. If withdrawal occurred, the primary reason for withdrawal was documented in the patient's case record form. The patient had the options of (1) allowing use of the data collected up until the time of withdrawal and allowing future access to central NHS registers for future record linkage; (2) allowing use of the data collected up until the time of withdrawal but not allowing future record linkage; and (3) not allowing use of the data already collected and having these data removed from final analysis.

Withdrawal from study treatment was distinguished from withdrawal from the study. Patients who were continuing with the study but had stopped taking the investigational medicinal product (IMP) were allowed to restart at the discretion of the supervising clinician. Patients could withdraw from some study procedures or study medication but remain in the trial without a change of status. Patients who had withdrawn from the study (i.e. change of status) were not permitted to restart the study.

Anthracycline cardiotoxicity is dose-dependent. Recent studies have confirmed that cardiotoxicity is negligible at low doses, and there was no benefit to patients of continuing in Cardiac CARE if they had a change in treatment plan and did not receive anthracycline as planned. Patients who for clinical reasons stopped anthracycline-containing chemotherapy before receiving their second dose of anthracycline were withdrawn from Cardiac CARE by the investigator.

Criteria for discontinuing or modifying study medications

An investigational product could be discontinued under the following circumstances:

1. at the request of the patient or if the patient withdraws from the study
2. by the investigator or the responsible clinician if this was felt to be in the best interests of the patient
3. on completion of the study.

Following the introduction of candesartan, eGFR and serum creatinine concentration were monitored at each dose titration clinic by the oncology research nurses. A decrease in eGFR of up to 25% from baseline or an increase in serum creatinine concentration of up to 30% was accepted. Patients exhibiting changes in renal function from baseline within these limits had further dose increases at the clinical team's discretion or remained on established doses. Patients exhibiting changes in renal function beyond these thresholds or an eGFR of $< 45 \text{ ml/minute/1.73 m}^2$ had candesartan discontinued. Patients unable to reach target dose because of symptomatic or asymptomatic hypotension (SBP of $< 90 \text{ mmHg}$) or bradycardia [heart rate (HR) of $< 50 \text{ beats per minute}$] continued in the study on maximal tolerated doses.

Study settings

The study recruited patients from UK regional cancer centres. All the cancer centres involved in the study had an established clinical trial infrastructure with oncology research nurses who were accustomed to co-ordinating the identification and recruitment of patients attending both the main and the satellite centres.

Interventions

This study compared standard care with standard care plus candesartan and carvedilol treatment.

Treatment arm

Standard care plus oral candesartan and carvedilol. Candesartan was started at 8 mg once-daily and increased at a minimum of 3-day intervals to 16 mg and 32 mg once-daily. Carvedilol was initiated simultaneously at 6.25 mg twice-daily and increased to 12.5 mg twice-daily and 25 mg twice-daily. The IMPs were dispensed as close as possible and ideally within 14 days of randomisation and continued until completion or withdrawal from the study. Drug prescription and dose titration visits in all sites were coordinated by oncology research nurses and supervised by oncologists.

Standard care

Standard care alone.

Outcomes

Primary outcome

Change in LVEF on cardiac MRI scan conducted 6 months after final anthracycline dose compared with baseline cardiac MRI scan conducted before anthracycline therapy compared between randomised groups.

Secondary outcomes: efficacy of candesartan and carvedilol treatment

The following biomarker, cardiac imaging and clinical end points were compared between randomised groups:

- hs-cTnI concentrations
 - hs-cTnI concentration change from baseline to 2 months following the completion of anthracycline chemotherapy.

- cardiac MRI
 - change in global longitudinal strain (GLS) and global circumferential strain (GCS) measured with feature tracking on cardiac MRI
 - change in left ventricular mass (LVM), left ventricular end-diastolic volume (LVEDV) and left atrial area (LAA).

Chapter 3 Clinical outcomes

- Cardiovascular death and heart failure. Heart failure was defined by the diagnosis of clinical (symptomatic) heart failure (see protocol version 11.0 for definition, links for which are in [Additional information](#)).
- HR and blood pressure at baseline and at 2 and 6 months following final dose of anthracycline.

The following clinically relevant thresholds for grading anthracycline cardiotoxicity were summarised by treatment but no formal statistical testing was performed.

hs-cTnI concentrations:

- Chronic myocardial injury defined as persistent elevations of hs-cTnI above the gender-specific 99th centile at 2 months. If the 2-month sample was not available, then hs-cTnI elevation above this threshold at any point beyond this was counted.
- Any hs-cTnI measurement of >80 ng/l during or after treatment. This concentration threshold measured with a contemporary assay has been used previously to define patients at risk of severe and early on-treatment cardiotoxicity.⁸

Change in LVEF:

- A fall in LVEF of 10% points AND a fall in ejection fraction < 50%.
- Any fall in LVEF < 50%.
- Any fall in LVEF < 40%.

Change in GLS and GCS myocardial strain:

- A > 15% fall in GLS or GCS on 6-month post-anthracycline cMRI.

Clinical outcomes:

- Death, cardiovascular death or heart failure. Heart failure was defined as the diagnosis of clinical (symptomatic) heart failure.

Specificity of hs-cTnI assay for cardiotoxicity

The trial aimed to identify patients at high risk of cardiotoxicity from early changes in hs-cTnI concentration on anthracycline treatment. The following comparisons were made within the low-risk non-randomised group. An additional exploratory comparison was made between the non-randomised and the high-risk randomised-to-standard-care groups.

Cardiac magnetic resonance imaging

Change in LVEF. This is the first secondary end point and main secondary objective. The aim was to demonstrate zero LVEF% change within the low-risk non-randomised group with equivalence limits of $\pm 2\%$:

- change in GLS and GCS
- change in LVM, left ventricular volume and LAA.

hs-cTnI concentrations

Compare baseline, final anthracycline cycle, 2, 4 and 6 months post anthracycline.

Health economics analysis

Health economics for all enrolled patients. Confirm the feasibility of data capture and assess the quality of data obtainable in this patient population. Provide information that can inform the design of further research including sample size calculation and/or value-of-information analysis.

Investigational medicinal product safety end points

The following were compared between the randomised groups:

- Hypotension: SBP of < 90 mmHg.
- Bradycardia: HR of < 50 bpm.
- Hyperkalaemia (K⁺ ≥ 5.0 mmol/l).
- Worsening renal function: decrease in eGFR of > 25% from baseline or an increase in creatinine of > 30% from baseline.
- Acute kidney injury: an eGFR drop to < 45 ml/minute/1.73 m².
- Fatigue grade of ≥ 2 using Common Terminology Criteria for Adverse Events (CTCAE) classification.
- New diagnosis of atrial fibrillation.

The protocol did not require all adverse events (AEs) to be recorded and reported in the eCRF. The safety assessments carried out for the trial and the pharmacovigilance reporting requirements are detailed in the protocol.

Changes to outcomes

No changes were made to the primary and main secondary outcomes during the study.

Sample size

A review of LVEF changes (measured by radioisotope scan) in 48 patients receiving adjuvant chemotherapy at Edinburgh Cancer Centre between 2010 and 2012 demonstrated that 15% sustained at least a 10-percentage-point change fall after anthracycline treatment and 31% exhibited the same magnitude of ejection fraction fall during trastuzumab treatment. Given the capacity of cardiac MRI to detect smaller changes in LVEF, we assumed that at least 20% of breast cancer patients receiving anthracycline chemotherapy would develop reduced LVEF. We planned to randomise at least 33% of patients using the hs-cTnI concentration threshold defined in the pilot study. We assumed that this threshold would select all patients developing meaningful reductions in LVEF. From these figures we would randomise 23 patients per group to detect a difference of 5 percentage points between the groups (standard deviation 5), at 90% power ($p = 0.05$).³⁴ A standard deviation of 5 was used in the PRADA study sample size calculation.³⁵ Allowing for 17% missing data (in line with PRADA) brings this to 28, and a total randomised trial size of 56. Thirty-three per cent of patients in the group initially enrolled were expected to be randomised, so the total enrolled was to be at least 168.

To assess the specificity of the plasma hs-cTnI assay for left ventricular systolic dysfunction in non-randomised patients, we wished to show that there is zero LVEF% change (with equivalence limits of $\pm 2\%$). Using a paired *t*-test to test for a zero change, using two-sided *p*-value of 0.05, 90% power and a standard deviation (SD) of differences of 5%, we needed complete paired MRI scans in 68 non-randomised patients.

Interim analyses and stopping guidelines

There was no planned interim analysis or stopping guideline.

Randomisation: sequence generation

After enrolment in the study and the baseline MRI scan, patients had serial blood tests for hs-cTnI concentration performed prior to each cycle of anthracycline. Patients could be randomised at any cycle with hs-cTnI concentration above the predetermined threshold from cycle 2 to cycle 6 for those patients receiving 3–6 cycles of anthracycline. The corresponding anthracycline cycle/hs-cTnI concentration thresholds for randomisation were:

- anthracycline cycle 2, ≥ 5 ng/l
- anthracycline cycles 3–6, ≥ 23 ng/l.

The allocation sequence was generated by Edinburgh Clinical Trials Unit (ECTU), using a web-based system to prevent bias. The study had a 1 : 1 randomised group design comparing standard care with standard care plus candesartan and carvedilol treatment in patients who exhibit elevated hs-cTnI concentrations during anthracycline treatment.

Randomisation: type

Patients were allocated to trial treatments using minimisation, with the following binary criteria:

- age ≥ 65 or < 65 years
- baseline LVEF of $\geq 60\%$ or $< 60\%$
- planned cumulative epirubicin equivalent (for doxorubicin the epirubicin equivalent is double, e.g. 300 mg/m² of doxorubicin is equivalent to 600 mg/m² of epirubicin) dose = 300 mg/m² or > 300 mg/m².

Patients were allocated to the allocation recommended by the minimisation algorithm 80% of the time, and to the opposite treatment group 20% of the time, with this choice decided randomly (with no restrictions or blocking).

Randomisation: allocation concealment mechanism

Randomisation allocation was not concealed from the patient or the clinical team.

Randomisation: implementation

The allocation sequence was generated by ECTU using a web-based system that communicated the randomisation result to the local randomising clinical team.

Following randomisation, the patient and the investigator were notified of the assigned treatment allocation.

Blinding

The study had a PROBE design and there was no blinding procedure. The image analysts at Edinburgh Imaging who performed the detailed MRI analysis were blinded to treatment allocation.

Similarity of interventions

Not relevant.

Statistical methods

Edinburgh Clinical Trials Unit statisticians were responsible for analysis of the study data. The full Cardiac CARE statistical analysis plan is included as [Report Supplementary Material 2](#).

The MRI scans from all sites were transferred to Edinburgh Imaging for detailed MRI analysis by two cardiac MRI analysts. The image analysts at Edinburgh Imaging were blinded to treatment allocation and were not involved with scanning or contact with patients. Edinburgh Imaging provided these data for the study database.

The primary analysis was change in LVEF on cardiac MRI 6 months following completion of anthracycline between randomised treatment groups, using linear regression, adjusted for age at consent, baseline LVEF and planned cumulative epirubicin equivalent dose. These were adjusted for binary fixed effects: age ≥ 65 or < 65 years; baseline LVEF $\geq 60\%$ or $< 60\%$; planned cumulative epirubicin equivalent dose = 300 mg/m^2 or $> 300 \text{ mg/m}^2$. Baseline LVEF was the finalised Edinburgh Imaging value. This was an intention-to-treat analysis, and treatment effect was expressed by a point mean difference estimate and its 95% CI. This approach was also used for the efficacy of candesartan and carvedilol treatment secondary outcomes from cardiac MRI and hs-cTnI concentrations at 2 months.

We endeavoured to keep missing values to a minimum, and the primary analysis was a complete-case analysis. If there were sufficient missing data to cause concern, multiple imputation was to be used as a sensitivity analysis, but the primary outcome did not have sufficient missing data to cause concern ($> 10\%$), and so multiple imputation was not necessary.

The specificity of the hs-cTnI assay for left ventricular dysfunction in non-randomised patients was assessed by calculating the mean of the within-person changes between patients' pre- and post-anthracycline MRI scans, plus its 95% CI at the end of the study. This CI was compared with the equivalence limits of $\pm 2\%$. Specificity was evaluated on all available non-randomised patients.

Other secondary outcomes were analysed appropriately: linear regression for continuous outcomes, logistic regression for binary outcomes and Cox proportional hazards for survival analysis, adjusted as for the primary analysis. A full statistical analysis plan was finalised before database lock.

Additional analyses

The statistical analysis plan included exploratory comparisons across all cardiotoxicity measures between the low-risk non-randomised group and the high-risk randomised-to-standard-care group. This analysis was performed to quantify the magnitude of hs-cTnI concentration increase in the randomised groups compared with non-randomised patients. The comparison of cardiac MRI measures of structure and function provided an indication of how effectively the trial protocol identified a population at increased risk of cardiotoxicity.

Co-enrolment

Patients were not to take part in other clinical trials of IMPs (or devices) until 2 weeks after they finished trial medication and/or final assessments, unless agreed otherwise in advance. This was to be considered

even if patients had finished the trial medication of another study but were still technically enrolled in that study for follow-up visits and so on.

Co-enrolment between Cardiac CARE and Clinical Trial of Investigational Medicinal Product (CTIMP) studies Add-Aspirin and MonarchE were agreed in writing between the sponsors and investigators for each study. Co-enrolment with other CTIMP studies was recorded in the eCRF. Participation in other research (e.g. non-CTIMP or observation studies) while taking part in this study was permissible and was recorded in the patient's medical records but not recorded in the eCRF.

Chapter 4 Results

Patient flow

[Figure 2](#) is the CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the Cardiac CARE trial.

Losses and exclusions

Between 4 October 2017 and 30 June 2021, 424 patients were approached across seven of the nine centres open for recruitment. One hundred and one (45.0%) of patients approached were consented. Sixteen patients from this group were subsequently excluded owing to exclusion criteria ($n = 14$) and the subsequent prescription of prohibited medication ($n = 2$). Fifty-seven (32.6%) of the remaining 175 patients were randomised. Twenty-nine were allocated to cardioprotection, with two patients in this group not completing the final follow-up MRI scan. Twenty-eight were allocated to standard care, with one patient not completing the final follow-up MRI scan. Within the remaining group of 118 non-randomised patients, 21 patients did not complete the final follow-up MRI scan. This included two deaths and 10 withdrawals from the study.

Recruitment

Cardiac CARE opened for patient recruitment across nine UK centres. Edinburgh opened on 4 October 2017, followed by Glasgow (5 December 2017), Velindre, Cardiff (9 May 2018), University Hospital Wales (20 September 2018), Oxford (25 February 2019), Mount Vernon (19 November 2019), Christie Hospital, Manchester (25 November 2019), Milton Keynes (18 December 2019) and New Victoria Hospital, Glasgow (21 March 2021). [Table 1](#) provides details about screening, recruitment and disposition across the nine centres. [Table 2](#) provides details of post-randomisation disposition by centre.

Baseline data

[Table 3](#) provides details of patient demographics and cancer treatment by randomised group.

Mean (SD) patient age in 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 (SD) was higher in the standard care group (82.5 kg; 16.7 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. NHL patients were more frequently randomised than breast cancer patients, making up 43.9% of randomised and 21.2% of 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%). Mean anthracycline dose was higher in the cardioprotection (469 mg/m²) and standard care group (479 mg/m²) than in the non-randomised group (424 mg/m²). Radiotherapy was more commonly prescribed in the non-randomised group (71.2%) than in the cardioprotection (57.1%) and standard care groups (53.6%).

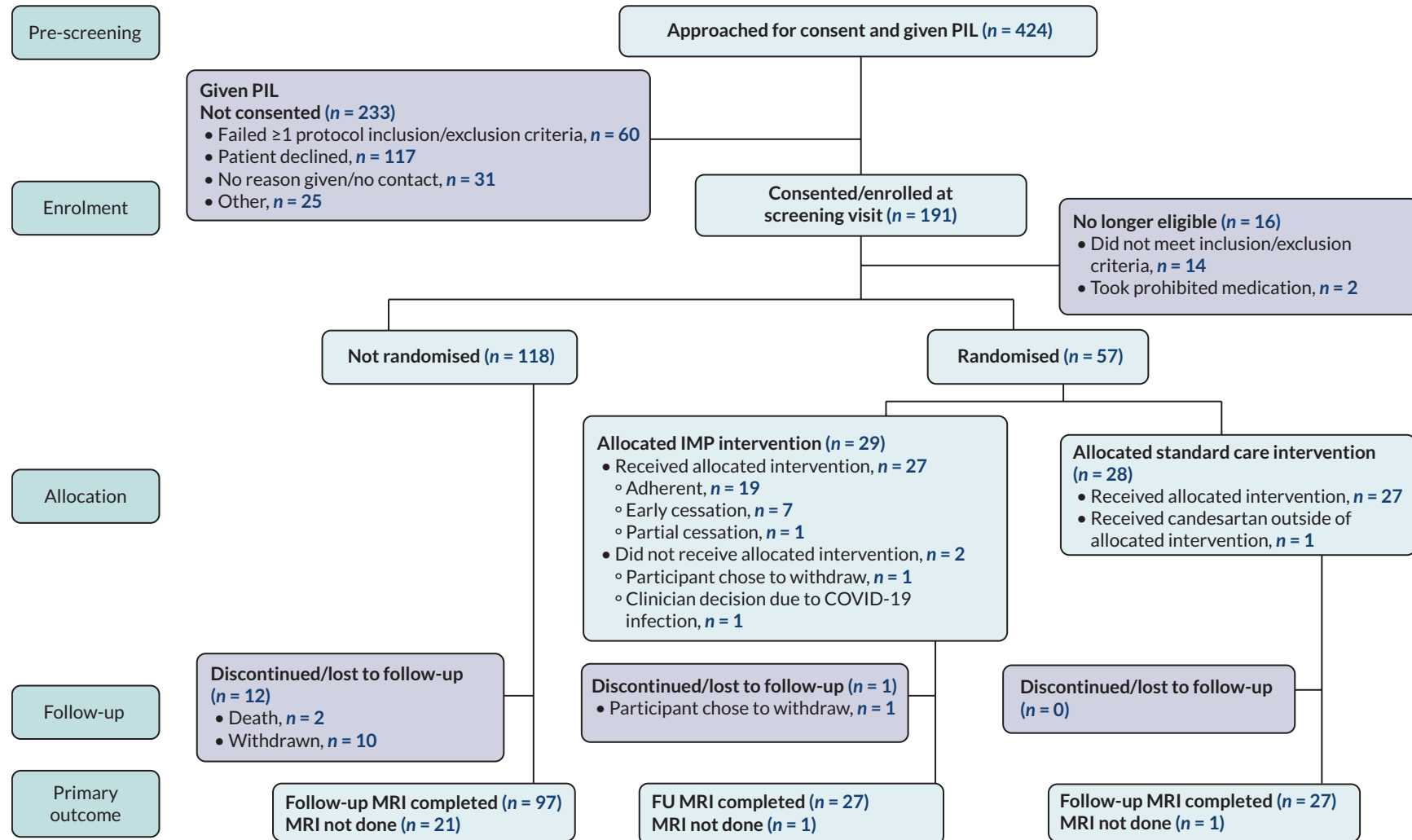


FIGURE 2 CONSORT flow diagram for the Cardiac CARE trial.

TABLE 1 Summary of screening and recruitment by centre

Centre	Start date	End date	Days recruiting	Screened	Consented	Eligible	Randomised
Christie	25 November 2019	30 June 2021	583	10 (2.4)	3 (1.6)	3 (1.7)	1 (1.8)
Edinburgh	4 October 2017	30 June 2021	1365	276 (65.1)	119 (62.3)	109 (61.6)	31 (54.4)
Glasgow	5 December 2017	30 June 2021	1303	67 (15.8)	36 (18.8)	34 (19.2)	9 (15.8)
Milton Keynes	18 December 2019	30 June 2021	560	0 (0.0)	-	-	-
Mount Vernon	19 November 2019	17 March 2020	119	2 (0.5)	2 (1.0)	2 (1.1)	-
New Victoria Hospital	21 March 2021	30 June 2021	101	0 (0.0)	-	-	-
Oxford	25 February 2019	30 June 2021	856	37 (8.7)	12 (6.3)	11 (6.2)	5 (8.8)
Velindre	9 May 2018	30 June 2021	1148	18 (4.2)	12 (6.3)	11 (6.2)	6 (10.5)
Wales	20 September 2018	30 June 2021	1014	14 (3.3)	7 (3.7)	7 (4.0)	5 (8.8)
All	4 October 2017	30 June 2021	1365	424 (100.0)	191 (100)	177 (100)	57 (100)

Note
Number of patients (percentage of patients in the trial).

TABLE 2 Post-randomisation disposition by centre

Centre	Non-randomised (n = 118)	Cardioprotection (n = 290)	Standard care (n = 28)	All randomised (n = 570)	All groups (n = 175)
Edinburgh	77 (65.3)	17 (58.6)	14 (50.0)	31 (54.4)	108 (61.7)
Glasgow	24 (20.3)	3 (10.3)	6 (21.4)	9 (15.8)	33 (18.9)
Velindre	5 (4.2)	4 (13.8)	2 (7.1)	6 (10.5)	11 (6.3)
University Hospital Wales	2 (1.7)	1 (3.4)	4 (14.3)	5 (8.8)	7 (4.0)
Oxford	6 (5.1)	4 (13.8)	1 (3.6)	5 (8.8)	11 (6.3)
Mount Vernon	2 (1.7)	0	0	0	2 (1.1)
Christie	2 (1.7)	0	1 (3.6)	1 (1.8)	3 (1.7)

Note
Number of patients (percentage of patients in the trial).

RESULTS

TABLE 3 Baseline demographics, radiation and anthracycline exposure

Characteristic	Non-randomised n = 118	Cardioprotection n = 29	Standard care n = 28
Age (years), mean (minimum, maximum)	52.1 (26–73)	54.0 (23–77)	53.5 (27–76)
Female sex, n (%)	107 (90.7)	23 (79.3)	22 (78.6)
Height (cm), mean (SD)	165.4 (7.9)	166 (8.1)	168 (8.4)
Weight (kg), mean (SD)	76.6 (16.5)	70.7 (15.0)	82.5 (16.7)
Cancer type, n (%)			
Breast	93 (78.8)	17 (58.6)	15 (53.6)
NHL	25 (21.2)	12 (41.4)	13 (46.4)
Risk markers for cardiovascular disease			
Smoker, n (%)			
Current	12 (10.2)	2 (6.9)	5 (17.9)
Ex for < 1 year	9 (7.6)	2 (6.9)	0
Ex for > 1 year	29 (24.6)	5 (17.2)	5 (17.9)
Never	68 (57.6)	20 (69)	18 (64.3)
Diabetes mellitus, n (%)			
Insulin dependent	3 (2.5)	0	0
Tablet controlled	1 (0.8)	0	0
Diet controlled	0	0	0
Hypertension, n (%)	10 (8.5)	2 (6.9)	4 (14.3)
Coronary disease, n (%)	2.5 (3)	0	2 (7.1)
Kidney disease, n (%)	0	0	0
Concomitant cardiovascular medications, ^a n (%)	9 (7.6)	2 (6.7)	6 (21)
Cancer therapy			
Cumulative anthracycline dose (mg/m ²)	424	469	479
Mean (Q1, Q3)	(300, 480)	(300, 600)	(330, 600)
3 cycles, n (%)	48 (40.7)	2 (6.9)	7 (25)
4 cycles, n (%)	35 (29.7)	14 (48.3)	14 (50)
6 cycles, n (%)	35 (29.7)	13 (44.8)	7 (25)
Radiotherapy, n (%)	79 (71.2)	16 (57.1)	15 (53.6)
Radiation target location, n (%)			
Left breast	36 (45.6)	7 (43.8)	5 (33.3)
Right breast	35 (44.3)	6 (37.5)	8 (53.3)
Both breasts	3 (3.8)	0	0
Outside chest/mediastinum ^b	5 (6.3)	3 (18.8)	2 (13.3)

^a Antihypertensive and angina medications including calcium channel blockers, thiazide and loop diuretics, nitrates and nicorandil.

^b NHL patients.

Numbers analysed

Fifty-four (94.7%) randomised and 97 (82.2%) non-randomised patients completed MRI scanning at 6 months for analysis of the respective primary and main secondary end points.

Outcomes and estimation

Prospective data on patients' LVEF, GLS, GCS, LVEDV, LVM, LAA, HR and systolic and diastolic systemic arterial pressure are given in [Table 4](#).

Primary end point

Patients randomised to cardioprotection or standard care had mean (SD) LVEF 6 months after completion of anthracycline chemotherapy of 65.7% (6.6%) and 64.9% (5.9%), respectively. Adjusted estimated mean change in primary end-point and secondary cardiac MRI measures are shown in [Table 5](#). After adjusting for age, pre-treatment LVEF and planned anthracycline dose, the estimated mean difference in 6-month LVEF between the cardioprotection and standard care groups was -0.4 percentage points (95% CI -3.6 to 2.8 percentage points; $p = 0.82$). The outcome was no different using a non-adjusted linear regression model (estimated mean difference 0.2 percentage points, 95% CI -3.1 to 3.4 percentage points; $p = 0.93$).

We examined the per-protocol primary efficacy outcome between randomised groups in a post hoc sensitivity analyses. 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; $p = 0.70$).

Main secondary end point

In non-randomised patients the baseline and 6-month LVEF (SD) were 69.3% (5.7%) and 66.4% (6.3%), respectively. The estimated mean difference was 2.9 percentage points (95% CI 1.4 to 4.3 percentage points; $p = 0.92$). The main secondary objective of demonstrating zero percentage-point change with equivalence of $\pm 2\%$ was not met.

Additional secondary end points

Secondary analysis (see [Table 5](#)) identified a difference between the cardioprotection and standard care groups in adjusted LV end-diastolic volume indexed for body surface area of 6.0 ml/m² (95% CI 0.6 to 11.4 ml/m²; $p = 0.03$). There was no difference between the groups for global longitudinal and circumferential strain, LVM or LAA.

hs-cTnI concentrations from baseline through chemotherapy to 6 months post chemotherapy are presented in [Table 6](#). hs-cTnI concentrations were higher in the randomised groups. Adjusted change in hs-cTnI concentration from baseline to 2 months in 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 (SE)]. The estimated mean difference was -1.6 ng/l (95% CI -17.6 to 14.4 ng/l; $p = 0.85$).

Additional analyses

Exploratory comparisons were conducted between the high-risk standard care group and the low-risk non-randomised group. [Figure 3](#) illustrates the increased average hs-cTnI concentrations from baseline to 6 months in the standard care group compared with the non-randomised group. Estimated mean difference in area-under-the-curve quantification of hs-cTnI concentrations from anthracycline treatment cycles 3–6 between groups are given in [Table 7](#). Patients in the non-randomised group had mean (SD) LVEF 6 months after completion of anthracycline chemotherapy of 66.4% (6.3%). The mean (SD) change in LVEF was -2.9% (6.1%) compared with -4.3% (4.4%) in the standard care group. The difference in LVEF decline between groups was not significant. Adjusted estimated mean difference

TABLE 4 Patients' cardiac MRI measures at baseline and 6 months post anthracycline

Patient measures (units)	Baseline, mean (SD)			6 months post-final anthracycline dose, mean (SD)			Change from baseline to 6 months, mean (SE)		
	Non-randomised (n = 118)	Cardioprotection (n = 29)	Standard care (n = 28)	Non-randomised (n = 97)	Cardioprotection (n = 27)	Standard care (n = 27)	Cardioprotection (n = 27)	Standard care (n = 27)	Non-adjusted mean difference (95% CI)
LVEF (%)	69.3 (5.7)	69.4 (7.4)	69.1 (6.1)	66.4 (6.3)	65.7 (6.6)	64.9 (5.9)	-4.2 (1.1)	-4.3 (1.1)	0.1 (-3.1 to 3.4)
GLS (%)	-17.1 (1.9)	-16.7 (2.7)	-16.1 (2.6)	-16.7 (1.8)	-16.2 (2.3)	-14.9 (2.0)	0.6 (0.5)	1.2 (0.5)	-0.6 (-1.9 to 0.7)
GCS (%)	-19.6 (2.3)	-18.9 (3.4)	-18.0 (3.1)	-19.1 (2.2)	-18.8 (2.8)	-18.3 (2.7)	0.0 (0.6)	0.3 (0.6)	-0.3 (-2.0 to 1.4)
LVM (g/m ²)	46.2 (8.4)	47.6 (12.1)	50.0 (8.2)	48.2 (8.0)	51.4 (11.2)	49.7 (7.4)	3.2 (1.9)	0.0 (1.9)	3.2 (-2.1 to 8.5)
LVEDV (ml/m ²)	62.5 (11.1)	63.4 (15.4)	63.9 (9.9)	63.6 (10.8)	69.4 (13.8)	64.1 (11.5)	5.6 (1.8)	0.2 (1.8)	5.4 (0.3 to 10.5)
LAA (cm ² /m ²)	11.6 (2.6)	11.9 (2.5)	11.4 (2.4)	11.7 (2.5)	11.9 (1.8)	10.8 (2.0)	0.0 (0.4)	-0.5 (0.4)	0.5 (-0.8 to 1.8)

Note

Non-adjusted estimated mean difference between randomised groups at 6 months.

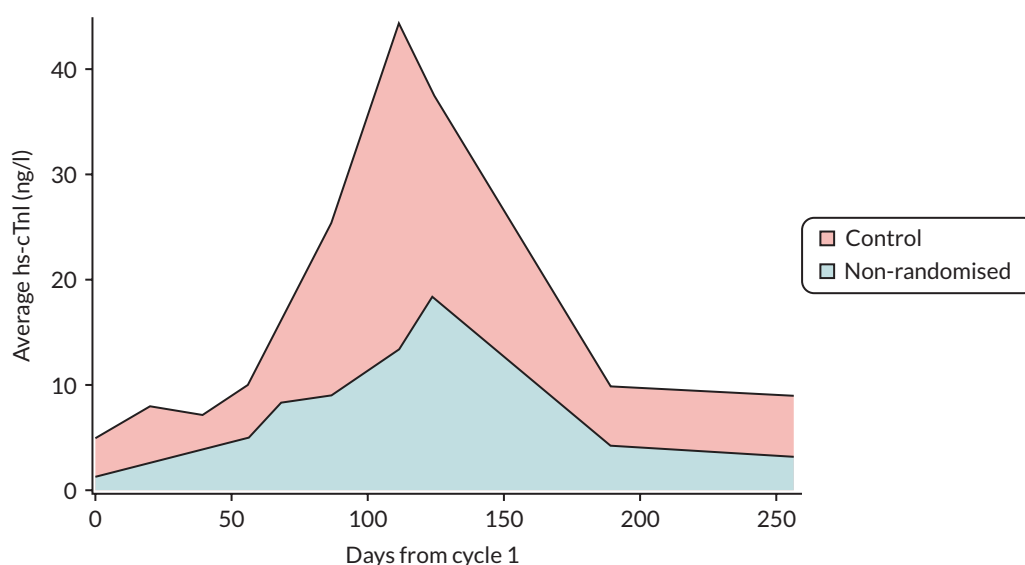
TABLE 5 Adjusted change in cardiac MRI measures from baseline to 6 months after final anthracycline dose

Patient measures (units)	Adjusted ^a estimated change from baseline to 6 months, mean (SE)		Estimated mean difference (95% CI)	p-value
	Cardioprotection (n = 27)	Standard care (n = 27)		
LVEF (%)	-1.3 (1.6)	-0.9 (1.9)	-0.4 (-3.6 to 2.8)	0.82
GLS (%)	0.1 (0.7)	0.5 (0.8)	-0.4 (-1.8 to 1.0)	0.59
GCS (%)	-2.0 (0.8)	-2.2 (1.0)	0.2 (-1.5 to 1.8)	0.84
LVM (g/m ²)	1.9 (2.8)	-1.9 (3.3)	3.8 (-1.9 to 9.4)	0.20
LVEDV (ml/m ²)	3.4 (2.7)	-2.6 (3.2)	6.0 (0.6 to 11.4)	0.03
LAA (cm ² /m ²)	0.4 (0.7)	0.1 (0.8)	0.3 (-1.0 to 1.6)	0.65

a Outcome adjusted for age at consent ≥ 65 or < 65 years, LVEF at baseline $\geq 60\%$ or $< 60\%$ and planned cumulative epirubicin equivalent dose as = 300 mg/m² or > 300 mg/m².

TABLE 6 Patients' cTnI concentrations [median ng/l (Q1, Q3)] taken across all visits from baseline to 6 months after final dose of anthracycline

	Non-randomised (n = 118)	Cardioprotection (n = 29)	Standard care (n = 28)
Baseline	0.5 (0.5, 2.0)	2 (1, 2)	2 (1, 4)
Cycle 2	2 (2, 3)	6 (5, 7.5)	7 (5, 9)
Cycle 3	3 (2, 4)	7 (5, 11)	6 (5, 8)
Cycle 4	4 (3, 6)	9 (7, 16)	9.0 (7, 12)
Cycle 5	8 (6, 12)	24 (11, 34)	22 (14, 34)
Cycle 6	12 (9, 18)	28.5 (18.5, 51.5)	36 (24.5, 59)
2 months	14 (7, 26)	13.5 (8.5, 36)	28 (13, 47)
4 months	3 (2, 5)	4.5 (3, 10.5)	6 (4, 10)
6 months	2 (2, 4)	3 (2, 9)	5 (3, 10.5)

**FIGURE 3** Increased average hs-cTnI concentrations from baseline to 6 months in the standard care group compared with the non-randomised group area under the curve.

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TABLE 7 Difference in hs-cTnI area-under-the-curve log concentrations between standard care and non-randomised groups at cycles 3, 4 and 6

hs-cTnI AUC log (n; standard care, n; non-randomised)	Estimated mean difference	95% CI	p-value
Cycle 3 (7, 32)	7.0	6.8 to 7.1	0.14
Cycle 4 (7, 46)	7.1	6.9 to 7.4	0.009
Cycle 6 (14, 32)	7.6	7.4 to 7.9	0.004

AUC, area under the curve.

TABLE 8 Exploratory analysis comparing differences in cardiac MRI measures at 6 months between non-randomised and standard care patients

Patient measures (units)	Adjusted ^a estimated change from baseline to 6 months, mean (SE)		Estimated mean difference (95% CI)	p-value
	Non-randomised (n = 97)	Standard care (n = 27)		
LVEF (%)	0.7 (1.6)	-0.6 (1.8)	-1.3 (-3.7 to 1.10)	0.29
GLS (%)	-1.0 (0.6)	-0.3 (0.6)	0.8 (-0.1 to 1.6)	0.10
GCS (%)	-0.8 (0.6)	-1.2 (0.7)	-0.4 (-1.3 to 0.6)	0.44
LVM (g/m ²)	1.2 (1.8)	-0.5 (2.0)	-1.7 (-4.5 to 9.4)	0.21
LVEDV (ml/m ²)	5.2 (2.7)	4.4 (3.1)	-0.8 (-5.0 to 3.4)	0.71
LAA (cm ² /m ²)	1.6 (0.7)	0.8 (0.8)	-0.9 (-2.0 to 0.2)	0.12

a Outcome adjusted for age at consent ≥ 65 or < 65 years, LVEF at baseline $\geq 60\%$ or $< 60\%$ and planned cumulative epirubicin equivalent dose as = 300 mg/m² or > 300 mg/m².

in 6-month LVEF and other cardiac MRI measures of cardiotoxicity between standard care and non-randomised groups are given in [Table 8](#). There was no difference in these measures between the groups.

Binary outcomes

Clinical end points and measures of cancer therapy-related cardiac dysfunction (CTRCD) are presented in [Table 9](#). There were no cardiovascular deaths or new atrial fibrillation 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 recovered on the 6-month cardiac MRI scan. No patients met the criteria for asymptomatic CTRCD of a 10-percentage-point LVEF fall and fall to an absolute LVEF below 50%. Similarly, the CTRCD criterion of $> 15\%$ fall in GLS was uncommon across groups. Chronic myocardial injury 2 months after the completion of chemotherapy was not uncommon and it 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.

Ancillary analyses

Clinical Trial of Investigational Medicinal Product adherence

Twenty patients (69%) were adherent to cardioprotection treatment, although one stopped candesartan within 2 months and continued with carvedilol alone. Two patients randomised to cardioprotection did not receive any medication owing to intercurrent illness and COVID-19 infection. A further seven (24%) stopped both cardioprotection drugs within 2 months owing to symptoms of light-headedness and dizziness, possibly related to low blood pressure.

TABLE 9 Patient clinical end points and measures of chemotherapy-related cardiac dysfunction

Outcome	Non-randomised (N=118), n (%)	Cardioprotection (N=29), n (%)	Standard care (N=28), n (%)
Cardiovascular death	0	0	0
Any new heart failure	0	0	1 (3.6)
Any new atrial fibrillation	0	0	0
Any $\geq 10\%$ point fall AND absolute LVEF fall below 50%	0	0	0
Any fall in LVEF below 50%	0	0	0
GLS fall of $> 15\%$	6 (6.5)	4 (14.8)	1 (3.7)
Chronic myocardial injury	34 (32.1)	10 (35.7)	15 (60)
Any hs-cTnI concentration of > 80 ng/l	0	3 (10.3)	5 (17.9)

Pulse and blood pressure

Pulse and blood pressure from baseline and across all visits after chemotherapy out to 6 months are reported in [Table 10](#). Blood pressure and HR were lower in the cardioprotection treatment group at 6 months. Post hoc analysis confirmed greater reduction in HR at 6 months in the cardioprotection group (estimated mean difference -11 bpm, 95% CI -18 to -4 bpm; $p = 0.003$). Although reductions were observed, there was no significant difference in SBP (-7 mmHg, 95% CI -17 to 2.0 mmHg; $p = 0.12$) and diastolic blood pressure (DBP, -6 mmHg, 95% CI -12 to 0.2 mmHg; $p = 0.06$) in the cardioprotection treatment group.

Harms

Safety end points related to cardioprotection therapy

Safety end points relevant to cardioprotection treatment were recorded for all groups. There was no protocol-defined hypotension or bradycardia at baseline or at 2, 4 and 6 months after chemotherapy.

Hyperkalaemia occurred in 10.3% of non-randomised patients. Hyperkalaemia was more common in the randomised groups: 20.7% of the cardioprotection group and 17.9% of the standard care group. Worsening renal function at any point beyond baseline occurred in 2.7%, 6.9% and 7.1% of the non-randomised, cardioprotection and standard care groups. Two patients in the non-randomised and none in the randomised groups developed acute kidney injury. Fatigue was reported by 12.1%, 3.4% and 25% of the non-randomised, cardioprotection and standard care groups.

Adverse event reporting

[Table 11](#) presents a summary of AE reporting. AEs were more commonly reported in the cardioprotection group, with 71.4% of patients having at least one AE compared with 12.7% non-randomised and 10.3% standard care patients. A total of 62.5% (20 out of 32) of AEs in the cardioprotection group were possibly related to CTIMP, with dizziness and syncope listed in 17 out of 20 possibly related AEs and hypotension, palpitation and venous thromboembolism listed for the remaining three AEs that had a possible causal link with the CTIMP.

TABLE 10 Patient HR, SBP and DBP at baseline and at 2, 4 and 6 months following completion of chemotherapy

Parameter (units)	Baseline, mean (SD)		2 months, mean (SD)		4 months, mean (SD)		6 months, mean (SD)	
	Cardioprotection	Standard care	Cardioprotection	Standard care	Cardioprotection	Standard care	Cardioprotection	Standard care
HR (bpm)	77 (12)	82 (13)	80 (12)	84 (14)	72 (11)	80 (10)	74 (9)	85 (13)
SBP (mmHg)	131 (17)	132 (18)	120 (22)	132 (17)	121 (14)	131 (18)	119 (17)	128 (15)
DBP (mmHg)	80 (12)	80 (11)	68 (11)	81 (9)	75 (9)	80 (9)	72 (11)	79 (9)

TABLE 11 Patient AE reporting

Category	Non-randomised (n = 118)	Cardioprotection (n = 28)	Standard care (n = 29)
AEs, n	18	32	3
Patients with at least one AE, n (%)	15 (12.7)	20 (71.4)	3 (10.3)
Serious AE, n (%)	11/18 (61.1)	12/32 (37.5)	2/3 (66.7)
AE possibly related to CTIMP, n (%)	1/18 (5.6)	20/32 (62.5)	0

Chapter 5 Health economics evaluations

Study question

The health economics study question, as outlined in the Cardiac CARE protocol, is the following: 'what are the important drivers of differences in costs and quality-adjusted life-years (QALYs) between standard care and hs-cTnI-guided cardioprotection?'

The study also aims to confirm the feasibility of data capture, assess data quality and provide insight into designing future cost-effectiveness research of hs-cTnI-guided cardioprotection.

Selection of alternatives

In the health economic analysis, costs and QALYs in the hs-cTnI-guided cardioprotection group ($n = 29$) are compared with those in the randomised standard care group ($n = 28$). The aim of the analysis is to estimate an incremental cost-effectiveness ratio (ICER) between the two groups within the study horizon, consistent with National Institute for Health and Care Excellence (NICE) guidelines, based on the assumption that costs and QALYs would not differ in patients who do not reach the hs-cTnI threshold for randomisation other than the basic cost of the assay.³⁶

Form of evaluation

The health economics analysis plan is included as [Report Supplementary Material 3](#). The evaluation takes the form of a within-trial economic analysis, in which costs and QALYs are calculated for each patient from trial healthcare resource use (HRU) and EQ-5D-5L data. Estimates of 6-month and 1-year mean costs and QALYs are calculated for each arm and used to estimate the ICER. Results are presented from NHS and societal perspectives in accordance with NICE guidelines.³⁶

Data collection

The methods of collecting data for the purposes of cost and QALY calculation in the within-trial economic analysis relied on case report forms and patient questionnaires; full details are given in [Appendix 1](#).

Allowance for uncertainty

In line with the objectives as a feasibility analysis, no modelling or sensitivity analysis was conducted as part of the current Cardiac CARE economic analysis. This was in part due to underpowered results for costs, life-years and QALYs limiting the utility of a modelling exercise to extrapolate these results.

Presentation of results

Quality of life (quality-adjusted life-year) analysis

[Table 12](#) shows the results of a linear regression, where 'beta' represents the difference in expected 6-month and 1-year QALYs gained by the intervention group (hs-cTnI-guided cardioprotection) compared with the randomised standard care group, controlling for baseline utility. The regression

model follows the methodology outlined by Manca.³⁷ [Table 13](#) shows the expected adjusted 6-month and 1-year QALYs for each arm as predicted by the regression model. The detailed methodology behind these calculations is given in [Appendix 1](#).

Cost analysis

[Table 14](#) shows the mean values and 95% CIs of NHS-perspective and societal-perspective costs for both randomised groups. Detailed cost and HRU breakdowns, as well as cost data for the whole Cardiac CARE patient population, can be found in [Appendix 1](#). The largest direct (NHS perspective) costs include the costs of inpatient stays, anthracycline therapy, radiotherapy and hospital doctor visits, with large differences between trial arms in each category.

Incremental cost-effectiveness ratio

Based on the study results, from the NHS perspective, hs-cTnI-guided cardioprotection has an ICER of £481,500 per QALY gained compared with standard care among patients marked as high risk by the troponin test with a time horizon of 1 year. From the societal perspective, however, hs-cTnI-guided cardioprotection 'dominates' standard care (i.e. the intervention's costs are lower while the QALY benefits are higher). However, the ICER estimates are limited by the fact that the QALY and cost estimates are not statistically significant.

TABLE 12 Regression results of 6-month and 1-year QALYs on randomisation arm, controlling for baseline health state utility

Characteristic	Beta	95% CI	p-value
Intervention			
6 months	0.01	-0.02 to 0.04	0.5
1 year	0.004	-0.10 to 0.11	>0.9

CI, confidence interval.

TABLE 13 Adjusted expected QALYs

	Standard care	Intervention
6 months	0.405 QALYs	0.414 QALYs
1 year	0.796 QALYs	0.800 QALYs

TABLE 14 Total costs

Perspective	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
NHS		
6 months	9142 (6906 to 11,377)	9074 (6658 to 11,491)
1 year	11,451 (8749 to 14,154)	13,378 (8873 to 17,882)
Societal		
6 months	14,428 (10,196 to 18,660)	11,403 (8055 to 14,752)
1 year	20,511 (13,019 to 28,004)	17,594 (12,162 to 23,026)

Health economics evaluation discussion

The within-trial analysis confirms the feasibility of capturing data that are suitable for a future clinical trial adequately powered for a cost-effectiveness end point. These data could also contribute to scenario analysis based on modelling to aid the understanding of how efficient cardiac protection strategies could be developed in the future.

The study could benefit from further research into the uncertainty surrounding specific estimates of the main drivers of cost-effectiveness, which would include longer-term survival and quality-of-life estimates as well as focused cost estimation on inpatient stays, anthracycline therapy, radiotherapy and hospital doctor visits. Full discussion and recommendations for future economic analysis of hs-cTnI-guided cardioprotection are presented in *Discussion* of the within-trial analysis in [Appendix 1](#).

Chapter 6 Discussion

We found no evidence that cardioprotection therapy with combined candesartan and carvedilol therapy prevents LVEF decline in breast cancer and NHL patients who exhibit elevated hs-cTnI concentrations during anthracycline chemotherapy. The LVEF decline observed in our multicentre study was smaller than that in previous studies using echocardiographic monitoring but similar to that in recent multicentre studies of similar patients using cardiac MRI.^{7,20} Moreover, LVEF decline was similar in low-risk non-randomised and high-risk randomised patient groups despite substantial differences in plasma cardiac troponin concentrations during anthracycline treatment. The implications of a small (< 5%) mean fall in ejection fraction across this population of cancer patients are uncertain. It is possible that a larger trial, randomising more patients, could have detected a small treatment effect with cardioprotection. Again, the long-term clinical benefit of such a small putative treatment effect on LVEF is uncertain.

The central hypothesis behind the Cardiac CARE trial design was that on treatment hs-cTnI concentrations would anticipate change in LVEF at 6 months. Overall, our findings question the benefits of early cardioprotection in patients with the highest levels of cardiac injury and indicate that the correlation between on-treatment cardiac troponin concentration and changes in 6-month LVEF and other cardiac is not strong.

In this trial we observed small deteriorations in both global and longitudinal strain across all groups. There was no difference in these early markers of ventricular dysfunction between randomised groups, and the cardiotoxicity threshold of > 15% relative fall in strain was uncommon at 6 months. To account for differences in body size, LVM, left ventricular end-diastolic volume and LAA data were indexed for body surface area. There was a small but significant increase in LVEDV in the cardioprotection group. This may reflect the impact of B-blockers slowing HR, with consequent increased filling and stroke volume.

In additional secondary analysis, cardioprotection therapy did not reduce hs-cTnI concentration change from baseline to 2 months post chemotherapy. We identified this time point to examine for treatment effect when hs-cTnI concentrations are still elevated after the completion of chemotherapy and patients randomised to cardioprotection will have received therapy for at least 2 months. High concentrations (any measurement of > 80 ng/l) were confined to randomised groups, and chronic myocardial injury, defined as a persistent elevation in hs-cTnI above the 99th centile upper reference limit at 2 months after chemotherapy, was not uncommon in all three groups. We believe that this is the first time this persistent signal of myocardial injury, present in 60% of the randomised to standard care group, has been demonstrated in a large population of patients receiving anthracycline cardiotoxicity.

Thirty-one per cent of patients stopped or did not start cardioprotection therapy within 2 months of randomisation. Symptoms possibly related to cardioprotection medication such as dizziness were frequently listed in AE reporting as the reason for early cessation. By contrast, the rate of non-adherence was lower in the PRADA study, with 7% of patients assigned to the combined metoprolol and candesartan therapy arm discontinuing medication.⁷ This higher level of adherence may reflect use of placebo control in PRADA. As in PRADA, we found no evidence for a signal of excess harm related to cardioprotection therapy in the safety end points. Indeed, fatigue was more common in the randomised-to-standard-care group. This result was unexpected, given that fatigue is a side effect commonly attributed to B-blockade.

Blood pressure and HR were lower in the cardioprotection group at 6 months. Fall in HR was significantly greater than in the standard care group. These observations are consistent with drug effect in the cardioprotection arm. Similarly, the per-protocol analysis examining only patients that were adherent to medication out to 6 months demonstrated no difference in the primary outcome, indicating

that lack of protection from cardiotoxicity was not caused by incomplete adherence. Our results are in accordance with recent RCTs investigating neurohormonal blockade in anthracycline-treated patients. The PRADA study found no difference in LVEF decline or cardiac troponin I concentrations with metoprolol or candesartan treatment on extended follow-up out to 23 months after commencing anthracycline chemotherapy.²⁶ Carvedilol had a neutral effect on LVEF decline in the CECCY trial, although secondary analysis revealed reduced cardiac troponin concentrations with treatment.²³

Limitations

There are limitations to our trial. Several patients discontinued cardioprotection medication within 2 months of randomisation and this might have had some influence on treatment effect. Despite excluding patients receiving low-dose anthracycline regimens and using hs-cTnI to select patients at risk of more substantial cardiotoxicity, the degrees of LVEF decline and cardiotoxicity were mild compared with those in studies completed over 10 years ago. One patient in the standard care arm developed acute heart failure during the trial. By 6 months this patient had an LVEF > 50%, and it is striking that no patients crossed the cardiotoxicity threshold of an LVEF decline < 50%. The trial was powered to detect a 5 percentage-point difference in LVEF between the randomised groups. There was no trend towards greater or less LVEF decline with cardioprotection, but a small treatment effect was not excluded. Finally, patients randomised to cardioprotection therapy received their first doses after at least one cycle of anthracycline. It is uncertain whether prescribing cardioprotection therapy earlier (as in PRADA and CECCY) would have altered the outcome.

Generalisability

Our findings have good external validity. We enrolled and consented 45% of 424 breast cancer and NHL patients presenting for anthracycline treatment to seven centres across England, Wales and Scotland. Patients can feel overwhelmed at the time of a cancer diagnosis, and 35% declined to participate. There were key exclusion criteria and patient groups who are not represented in this trial. We excluded low-dose anthracycline regimens because of the low risk of cardiotoxicity. The trial findings may not be applicable to children and patients receiving very high anthracycline doses or with established heart disease, who are particularly vulnerable to anthracycline cardiotoxicity. HER2-positive breast cancer patients were excluded. This group constitute up to 20% of those with breast cancers and go on to receive anti-HER2 therapy. Anti-HER2 treatment has established effects on LVEF decline and cardiotoxicity, and patients receiving anthracycline followed by anti-HER2 treatment are at increased cardiotoxicity risk.

Interpretation

hs-cTnI concentrations and risk of anthracycline cardiotoxicity

The hs-cTnI concentration thresholds used in the trial protocol failed to define true high- or low- risk populations in this study. Anthracycline chemotherapy was associated with LVEF decline in breast cancer and NHL patients 6 months after completion of chemotherapy. The degree of LVEF decline was smaller than expected in the randomised groups and not significantly greater than in the hypothesised low-risk, non-randomised group. This finding suggests that the correlation between on-treatment hs-cTnI concentrations and subsequent LVEF decline is not strong. That patients in the non-randomised group also had a detectable decline in LVEF indicates future risk of further deterioration.

Prevention of LVEF decline with cardioprotection therapy

We did not find evidence that combined candesartan and carvedilol therapy prevents LVEF reduction or reduces other markers of cardiotoxicity such as GLS and circulating hs-cTnI concentrations. However,

the mean deterioration in LVEF with chemotherapy was smaller than anticipated, and no participant's LVEF deteriorated by > 10% points and the randomised sample was not at higher risk. Therefore, a larger trial would be needed to detect the prevention of this smaller LVEF decline, or higher-risk participants would have to be recruited in future trials.

Impact of patient and public involvement on Cardiac CARE trial

Patients and public representatives were engaged from the start and several protocol design features were influenced by patient recommendations. Our lead patient representative and co-applicant was Professor Abigail Marks. Professor Marks has experience of treatment for early breast cancer including chemotherapy and monitoring for cardiac toxicity. It was helpful to have affirming comments from the patient and public involvement (PPI) committee of the National Institute for Health and Care Research (NIHR) Diagnostic Evaluation Cooperative and the national patient advocacy charity Independent Cancer Patients' Voice. Both groups recognised the concern that cancer patients have about cardiotoxicity from successful cancer treatment:

... I like the idea of having treatment that could provide protection against developing heart muscle problems. I also like the idea of being able to avoid a dose of radiation.

... an excellent study and good use of drugs which although do have side effects, these are well known and can in most cases be dealt with. I am a great fan for looking at using drugs differently – it is not only economic, but sensible.

Professor Marks participated in some Trial Steering Committee meetings but found attendance challenging owing to her own professional commitments. Difficulties and challenges during the study centred on problems opening sites and access to research infrastructure during the COVID-19 pandemic. Whenever patients were approached they were keen to participate and there was no strong need for PPI during the study.

We hosted a webinar with the Cardiac CARE patients 5 days after presenting the results at the European Society of Cardiology congress on 1 September 2022. Fifteen trial patients signed in to the webinar. The message that cardiotoxicity levels were low in the study is good news for patients and this was well received. Patients asked about ongoing cardiac follow-up in their respective centres and were interested in the possibility of further follow-up cardiac imaging studies. They appreciated the opportunity to learn about the trial results. Several noted that they had not been offered this opportunity in previous clinical trials. A key comment was that results communication about research scan results should be expedient even when the scan is not being conducted to inform patient care. Patients receiving cancer care are, naturally, concerned to receive results even if these confirm that no surprising or concerning findings have been made.

Chapter 7 Conclusions

The recently published European Society of Cardiology Cardio-Oncology guidelines provide a class I recommendation for the use of cTn monitoring in anthracycline patients at high risk of cardiotoxicity.¹² The Cardiac CARE trial findings raise doubt over whether this monitoring strategy is helpful when both patients with low-risk and patients with high-risk hs-cTnI concentration profiles developed small reductions in LVEF. 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 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 GLS. We will also examine whether there is a threshold hs-cTnI concentration below which patients do not develop a decline in LVEF.

We found no evidence of a 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 of Cardiology guidelines that give a class II recommendation for 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.

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 factors determining the evolution of cardiac dysfunction with monitoring and longer-term follow-up studies.

Additional information

Contributions of authors

Peter Henriksen (<https://orcid.org/0000-0003-4974-0344>) (Cardiology Consultant) was the chief investigator and site lead for Edinburgh and St John's Hospital, conceived and planned the study and acted as study lead. He led writing of the report and all aspects of study design, conduct and analysis and designed and led the training of research staff.

Morag MacLean (<https://orcid.org/0000-0002-4037-0247>) (Senior Trial Manager) provided expertise in study management, contributed to protocol design, provided staff training and supervision, was project manager and contributed to the writing of the report.

Marek Atter (<https://orcid.org/0000-0002-1628-7427>) (Health Economist) co-designed the health economics analysis, carried out the analysis of the health economics data and contributed to writing the report.

Steff Lewis (<https://orcid.org/0000-0003-1210-2314>) (Professor of Medical Statistics) was the trial statistician, co-designed the protocol, led the design of the statistical analysis plan, oversaw the statistical analyses and contributed to the writing of the report.

Aryelly Rodriguez (<https://orcid.org/0000-0002-1352-3922>) (Statistician) was a trial statistician and contributed to the development of the statistical analysis plan, undertook the statistical analyses and contributed to writing of the report.

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The full Cardiac CARE Investigator group are listed below.

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Trial Manager: Dr Morag MacLean.

Edinburgh Clinical Trials Unit: Anna Foster, Garry Milne, Lynsey Milne, Hannah Rickman and Michelle Stevens.

Edinburgh Imaging and clinical MRI reporting: Suzanne Ashford, David Brian, Annette Cooper, Russell Everett, Alexander Fletcher, Alan Japp, Tom MacGillivray, Alexandra Nicolae, Giorgos Papanastasiou, Scott Semple, Nick Spath and Michelle Williams.

Edinburgh Imaging Core Analysis: Shruti Josh and Trish Singh.

Other: The co-applicants, Professor Nicholas Mills and Professor Dave Newby, provided valuable input throughout the trial.

Governance

Throughout the study oversight was provided from the Trial Steering Committee, Data Monitoring and Ethics Committee, sponsor and patient advisory group. We sincerely thank the following members of the Trial Steering Committee for their support and guidance during the trial. Their contribution was invaluable. We also thank the members of the Data Monitoring and Ethics Committee, for their helpful contribution and scrutiny of the data. The trial management group also thank the Patient Advisory Group for their involvement. Their feedback and input was not only helpful for improving trial documentation but also for reinforcing that patients are at the heart of research and their contribution is essential. This study was co-sponsored by the University of Edinburgh and NHS Lothian, through the ACCORD office, the Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh, EH16 4TJ. The sponsor reference number is AC16148.

Trial Steering Committee

Chairperson: Professor Stephen Evans.

Members: Professor Abigail Marks, Professor Torbjørn Omland and Professor Russell Petty until he withdrew from the committee and was replaced by Dr Gordon Urquhart.

Data Monitoring Committee

Chairperson: Professor Helena Earl until her retirement, when the chair was taken by Dr C Mark Francis.

Members: Dr Ellen Copson, Dr Dominic Culligan and Ms Evie Gardner until her retirement, when she was replaced by Ms Helen Mossop.

Patient Advisory Group

Julie Croft, Heather Goodare, Ailsa Martin and Lesley Stephen.

Equality, diversity and inclusion

The patient population would only have been inclusive of patients who met the protocol-defined inclusion criteria. All patients who met the pre-screening criteria were eligible to be invited by site staff to participate in the Cardiac CARE trial. As NHS employees the site staff followed the NHS policy on equality, diversity and inclusion when approaching potential patients. The patient information leaflet and patient questionnaire were available in a large font for sight-impaired patients. Standard NHS translation resources were available to discuss the study and if necessary to discuss the PIS and consent with anyone who did not have English as their first language. Details of protected characteristics such as ethnicity or sexual orientation were not collected from patients. All oversight committees comprised men and women with a range of expertise. Individuals were recruited from across the UK and Norway. When vacancies became available in committees we sought out younger individuals to provide them with a development opportunity but also to provide a different perspective for our study. A PPI representative was a member of the Trial Steering Committee and a patient advisory group was convened and consulted for their input.

Reporting patient and public involvement

Two Patient Advisory Group (PAG) meetings were convened early in the trial to provide advice on study set-up and patient-facing documentation. The PAG supported the idea of keeping patients informed of the study progress. A patient newsletter was subsequently disseminated to patients. Further PAG meetings were disrupted by the COVID-19 pandemic; however, the group had already highlighted to us the importance of feeding back results to patients. This was backed up by the PPI representative on the Trial Steering Committee. Therefore, the chief investigator held a webinar to which patients were invited in order to share the study results. A lay summary has been posted on the clinical trials website and is open to the public. The link to the trial website was provided in the patient information leaflet.

Protocol

The study protocol is published on protocols.io: www.protocols.io/private/A47518A1A5A011EC9B000A58A9FEAC02

It is also available on the ECTU website: www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/ukcrc-studies/cardiac-care/cardiac-care-trial

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. *#datasaveslives* You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

Data-sharing statement

Patient data have been managed to safeguard the confidentiality of patients and is consistent with the terms of consent signed by patients. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review. Any data sharing approved would have to ensure patient confidentiality.

Ethics statement

Ethics approval was received for our research on 19 June 2017 from the East of Scotland Research Ethics Service. The Research Ethics Committee reference number is 17/ES/0071.

Information governance statement

Edinburgh Clinical Trials Unit, University of Edinburgh is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EUGDPR) 2016/679 under Data Protection legislation. ECTU is the data processor, ACCORD (joint sponsor consisting of the University of Edinburgh and NHS Lothian) are the data controller, and ECTU processes personal data in accordance with their instructions. You can find out how we handle personal data and

how to exercise your individual rights in the Cardiac CARE GDPR statement which can be found here: www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/ukcrc-studies/cardiac-care/cardiac-care-trial.

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Disclosure of interests

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Appendix 1 Health economic trial analysis

Introduction

The purpose of this document, as outlined in the health economics analysis plan (HEAP), is to present the results of the Cardiac CARE within-trial analysis, including estimates of quality-adjusted life-years (QALYs), total costs and HRU for each trial arm (cardioprotection vs. standard care for breast cancer and lymphoma patients with elevated cTnl).

Summary of key variables and population groups

Summaries are provided in [Tables 15](#) and [16](#).

Patient-reported outcome measure questionnaires

This section contains information about the observation period (in days) captured by the patient-reported outcome measures (PROMs). Baseline measurement was taken on day 1, corresponding to the first day of the first cycle of chemotherapy. Subsequent PROM measurements were conducted at the following time points:

- fourth cycle of chemotherapy
- post-anthracycline visit
- sixth cycle of chemotherapy
- follow-up (2 months)
- follow-up (4 months)
- follow-up (6 months).

The study period ended either on the date of the last available completed PROM form or on the day a patient's status changes (e.g. from active to deceased or withdrawn). The planned study period captured by the study period captured by the questionnaires consisted of up to 15 weeks of chemotherapy and 6 months of follow-up. The actual period captured and the number of questionnaires completed at each time point are summarised in [Tables 17](#) and [18](#).

TABLE 15 Patients by gender

Patient gender	All patients (%) (n = 191)	Not randomised (%) (n = 134)	Standard care (%) (n = 28)	Intervention (%) (n = 29)
Female	168 (88)	123 (92)	22 (79)	23 (79)
Male	23 (12)	11 (8)	6 (21)	6 (21)

TABLE 16 Patients by patient status

Patient status	All patients (n = 191) (%)	Not randomised (n = 134) (%)	Standard care (n = 28) (%)	Intervention (n = 29) (%)
Active	162 (85)	106 (79)	28 (100)	28 (97)
Deceased	2 (1)	2 (1)	0 (0)	0 (0)
Withdrawn	11 (6)	10 (7)	0 (0)	1 (3)
Screening failure	16 (8)	16 (12)	0 (0)	0 (0)

TABLE 17 Patient-reported outcome measure study period

	All patients (n = 191), mean (95% CI)	Standard care (n = 28), mean (95% CI)	Intervention (n = 29), mean (95% CI)
PROM study period (days)	273.95 (249.29 to 298.62)	269 (255.23 to 282.77)	308.07 (238.66 to 377.48)

TABLE 18 Patient-reported outcome measure responses (%)

All patients	Time point (n = 191) (%)	Not randomised (n = 134) (%)	Standard care (n = 28) (%)	Intervention (n = 29) (%)
Cycle 1 (baseline)	174 (91)	117 (87)	28 (100)	29 (100)
Cycle 4	117 (61)	81 (60)	21 (75)	15 (52)
Post-anthracycline visit	52 (27)	32 (24)	7 (25)	13 (45)
Cycle 6	61 (32)	34 (25)	14 (50)	13 (45)
Follow-up 2 months	167 (87)	111 (83)	28 (100)	28 (97)
Follow-up 4 months	164 (86)	108 (81)	28 (100)	28 (97)
Follow-up 6 months	162 (85)	106 (79)	28 (100)	28 (97)

Data cleaning and inspection

Revisions

Revisions to the study population are outlined in 'Analysis populations decision' version 1.0. The document stipulates, 'Patients 11,015 and 12,018 should be removed from all populations as these patients took prohibited medications before randomisation'.

Patient-reported outcome measure questionnaire errors

Patient 12,026 was removed from the QALY analysis due to two conflicting EQ-5D-5L observations recorded on the same day.

Health state utility and quality-adjusted life-years

The purpose of this section is to present 6-month and 1-year QALYs for each trial arm. QALYs are extrapolated from health state utility values (HSUVs), which in turn are derived from EQ-5D-5L profiles recorded in the PROM questionnaires.

Methods

The process of calculating 6-month and 1-year QALYs consists of the following steps and assumptions:

- collection of EQ-5D-5L data, which consists of five domains (see EuroQoL's EQ-5D-5L user guide):³⁸
 - mobility
 - anxiety/depression
 - pain/discomfort
 - usual activities
 - self-care.
- conversion of EQ-5D-5L data into HSUVs using the Crosswalk Index Value Calculator³⁹
- calculation of unadjusted and adjusted 6-month and 1-year QALYs using the area-under-the-curve outlined by Manca.⁴⁰

Obtaining utility values

Utility values are obtained by converting EQ-5D-5L observation sets into HSUVs using the Crosswalk Index Value Calculator (CIVC).³⁹ The CIVC provides a 'validated mapping function to derive utility values for the EQ-5D-5L from the existing EQ-5D (-3L)', which matches specific 5L profiles with 3L-derived HSUV values and is the preferred method of EQ-5D-5L analysis by the NICE reference case.³⁶

Calculating quality-adjusted life-years

Daily QALY fractions ($\frac{HSUV}{365.25}$) are calculated and summed for each patient from day 1 (first chemotherapy cycle) to the cut-off day based on the closest available utility observation; this ensures that calculations are consistent with the area-under-the-curve methodology. Furthermore, utility is set to 0 on and after the date of death and observations after the cut-off day (182 or 365) are ignored; utility between the last observation and the cut-off day is assumed not to change (last point carried forward). QALYs are calculated for each trial arm and summarised in [Table 19](#).

Adjusting quality-adjusted life-years

To estimate the difference in QALYs between trial arms, it is important to control for baseline utility. The regression adjustment methodology and justification used in this analysis are outlined by Manca.⁴⁰ The formula provided in the paper is as follows:

$$\beta_0 + \beta_1 \times t_i + \beta_2 \times Q_i^b \quad (1)$$

Where:

- i = patient ID
- β_0 = intercept
- β_1 = adjusted differential QALY after controlling for imbalance in the mean utility at baseline
- t_i = treatment arm dummy variable
- Q_i^b = patient-specific baseline utility

EuroQol-5 Dimensions utility versus Visual Analogue Scale

As part of the EQ-5D-5L instrument, the Cardiac CARE study collected patient-reported health state scores using a Visual Analogue Scale (VAS), with results ranging from 0 (worst health) to 100 (perfect health).

The key difference between utilities derived from EQ-5D data and VAS scores in this study hinges on VAS scores being derived from patients' subjective perceptions of health and quality of life (QoL), whereas EQ-5D utilities are based on general population preferences. Thus, the function of VAS is to provide 'an alternative way to elicit an individual's rating of their own overall current health'.³⁸

According to the NICE Reference Case, 'EQ-5D is the preferred measure of health-related quality of life in adults'.⁴¹ Therefore, VAS scores are not included in QALY calculations.

Results

EuroQol-5 Dimensions, five-level version profiles

[Figures 4–8](#) depict the distribution of responses across EQ-5D-5L health domains, categorised by trial arm and time point. Each figure shows the percentage of responses at each level of the domain, which range from 5 (extreme problems) to 1 (no problems). [Figures 4–8](#) show responses for 'usual activities', 'anxiety/depression', 'mobility', 'pain/discomfort' and 'self-care', respectively.

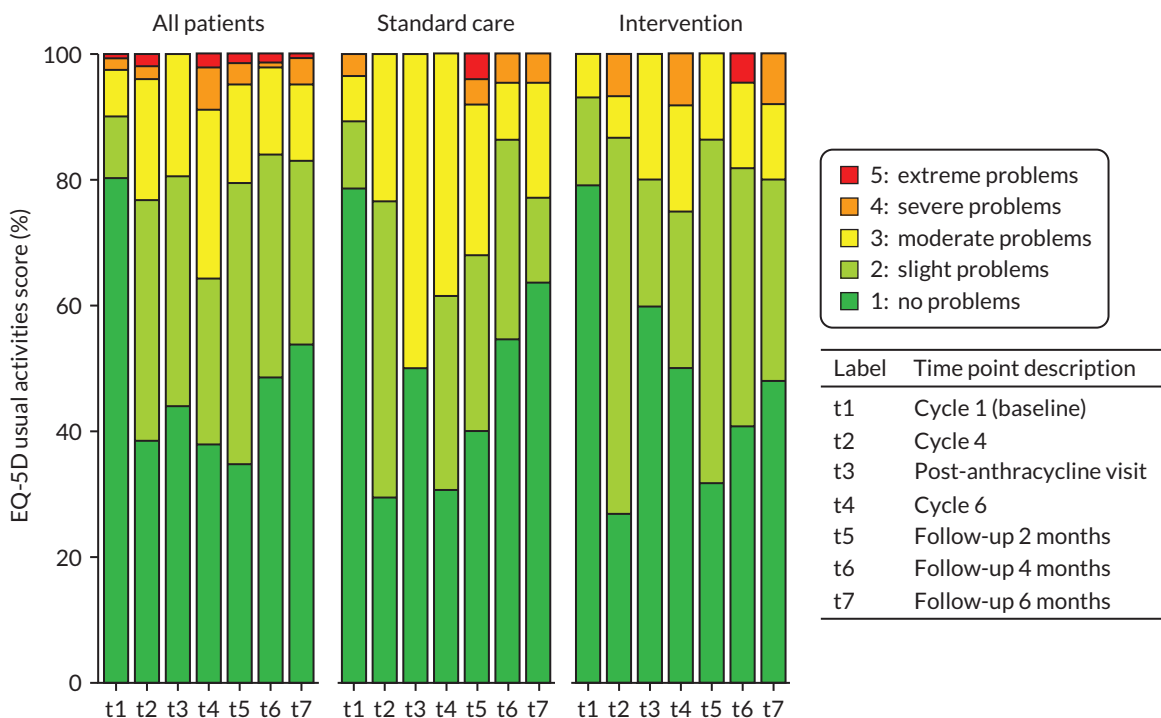


FIGURE 4 EuroQol-5 Dimensions, five-level version profiles – usual activities, by time point and trial arm.

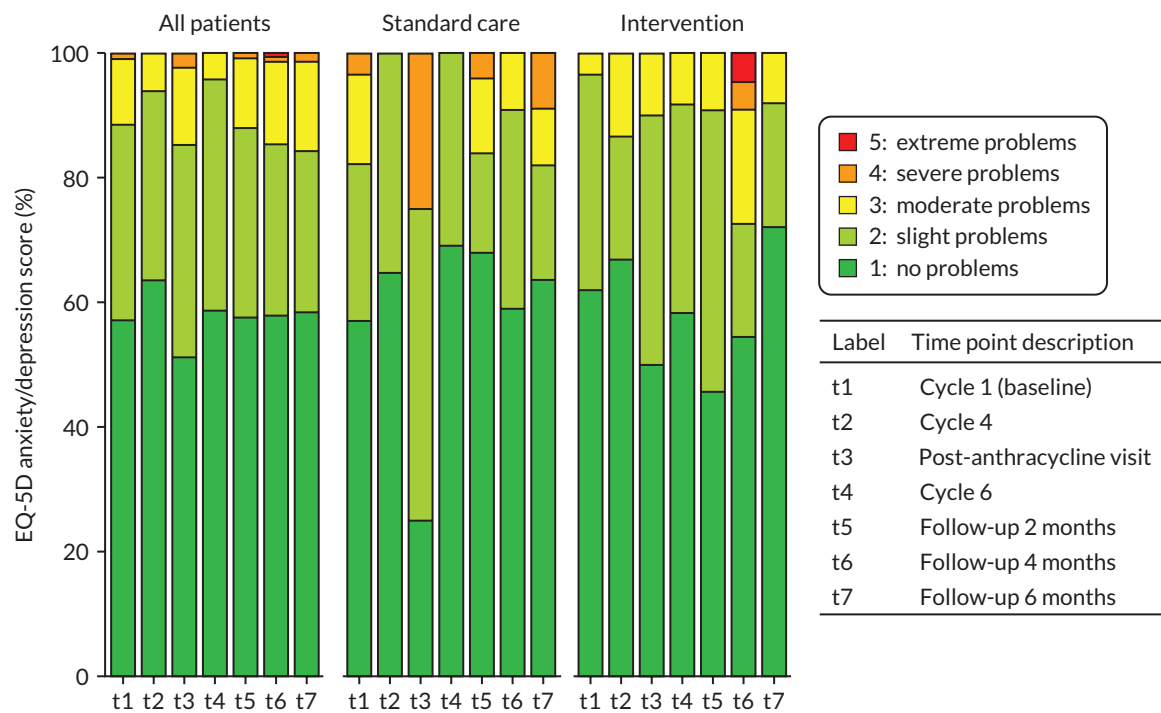


FIGURE 5 EuroQol-5 Dimensions, five-level version profiles – anxiety/depression, by time point and trial arm.

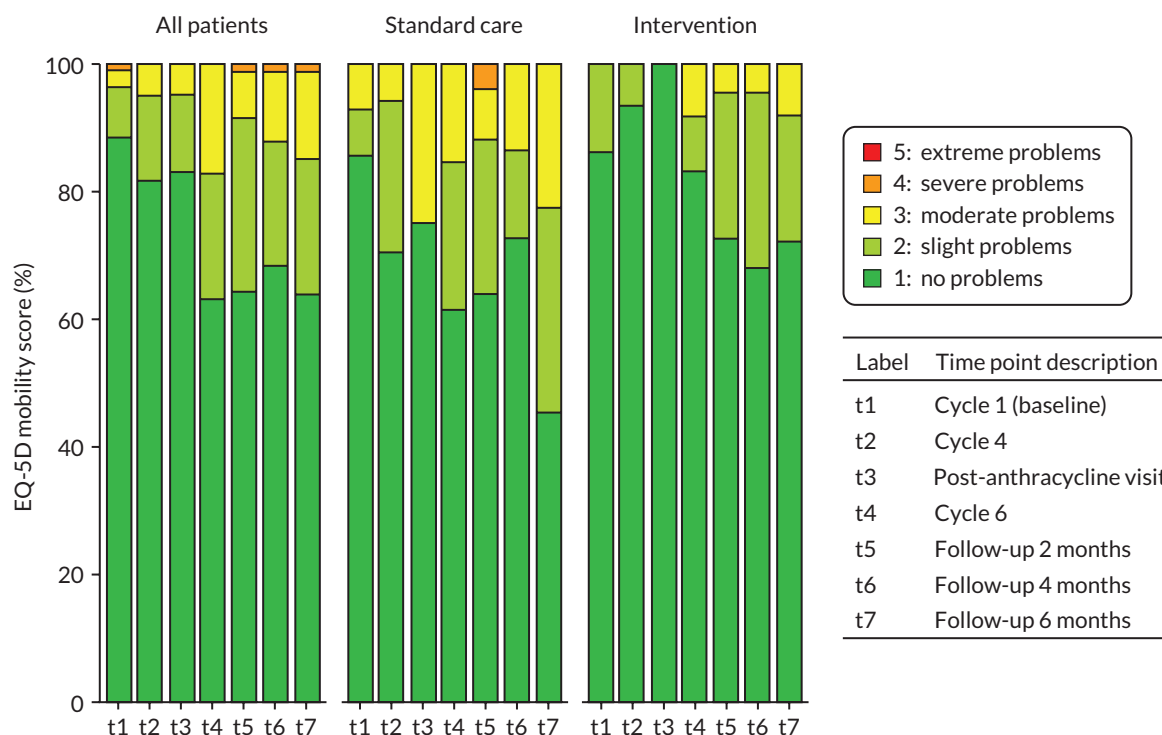


FIGURE 6 EuroQol-5 Dimensions, five-level version profiles – mobility, by time point and trial arm.

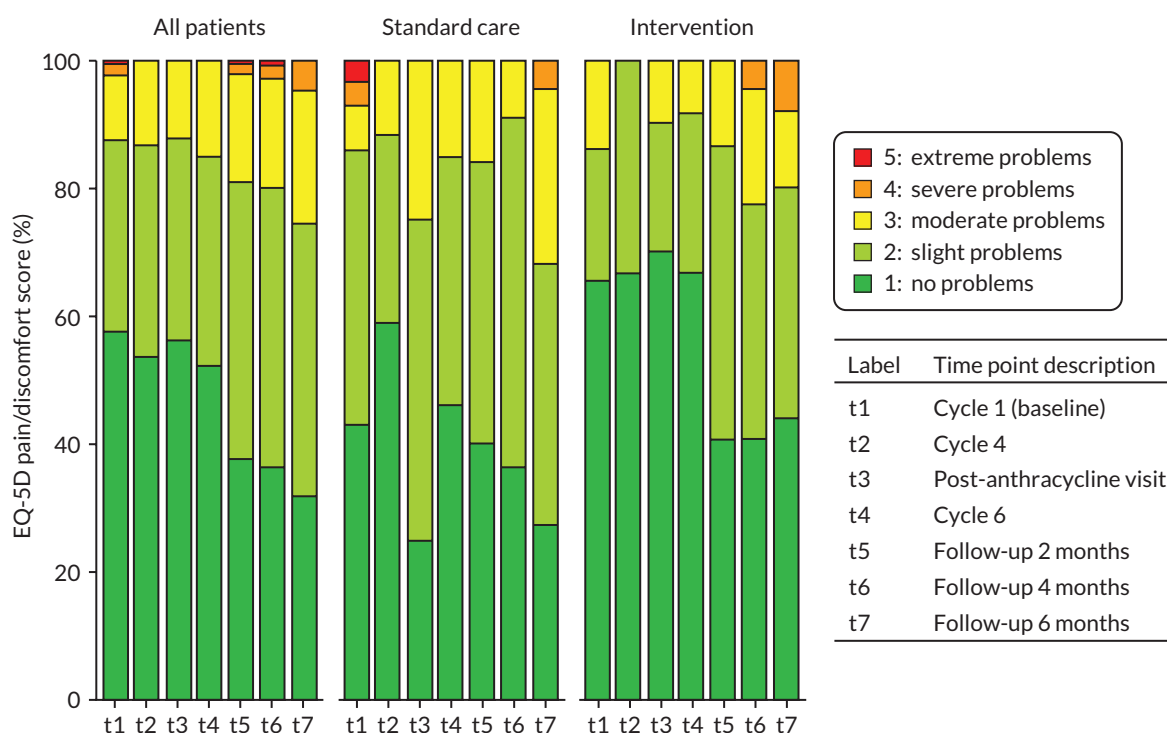


FIGURE 7 EuroQol-5 Dimensions, five-level version profiles – pain/discomfort, by time point and trial arm.

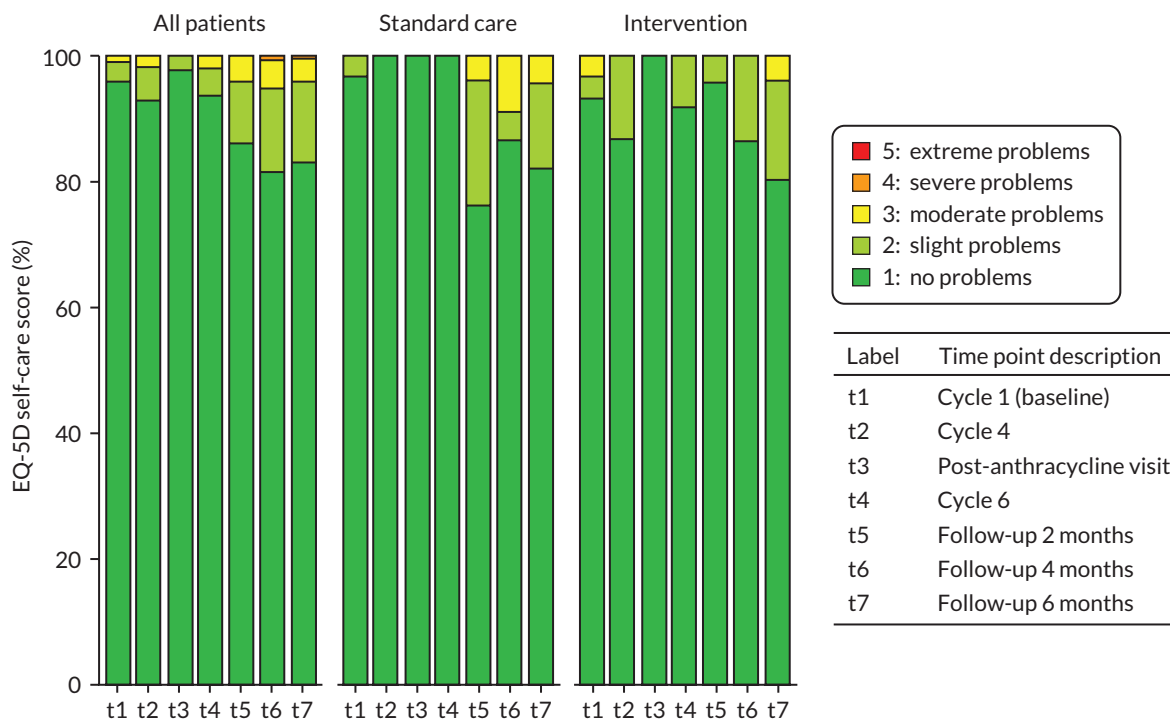


FIGURE 8 EuroQol-5 Dimensions, five-level version profiles – self-care, by time point and trial arm.

EuroQol-5 Dimensions health state utility

Figure 9 shows the mean HSUVs at each time point, stratified by randomisation group.

Visual Analogue Scale

Figure 10 shows the mean VAS scores at each time point, stratified by randomisation group.

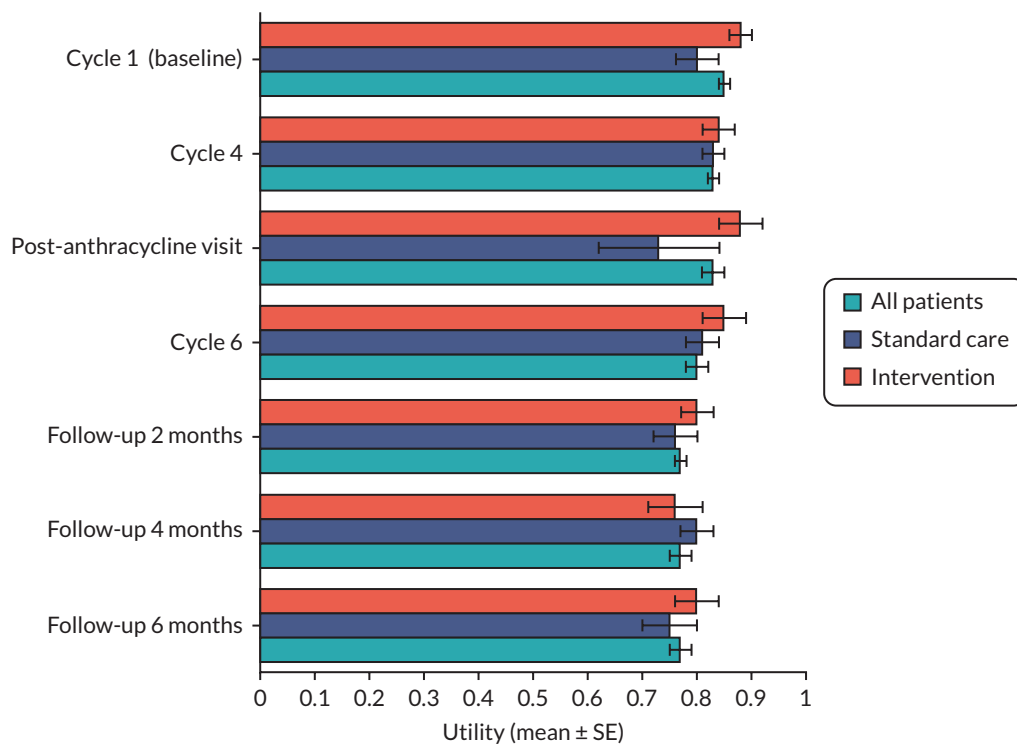


FIGURE 9 EQ-5D utility scores, by time point and trial arm.

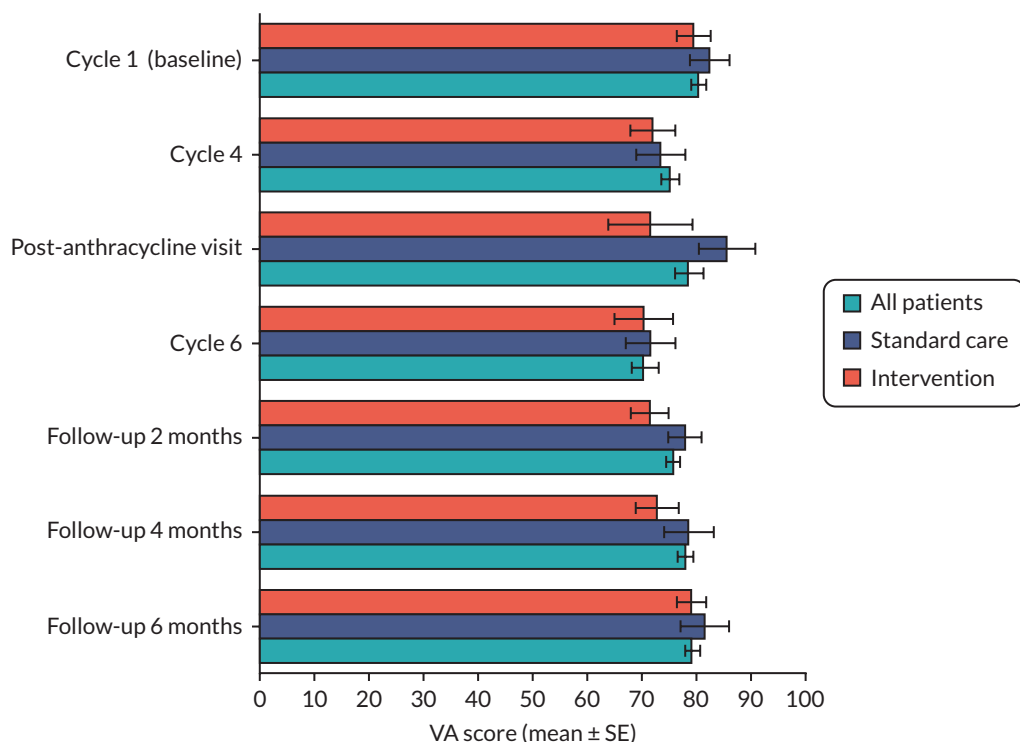


FIGURE 10 Visual Analogue Scale scores, by time point and trial arm.

Unadjusted quality-adjusted life-years

[Table 19](#) shows the unadjusted QALYs accumulated by each trial arm during the study period.

Adjusted quality-adjusted life-years

[Table 20](#) shows the regression coefficients, while [Table 21](#) shows estimates of expected adjusted QALYs for each trial arm predicted by the regression model (assuming mean baseline utility). *Intervention* denotes a binary variable [0 = standard care, 1 = intervention (candesartan and carvedilol)]. Baseline utility refers to utility derived from the PROM questionnaires collected during cycle 1 of chemotherapy.

The *p*-values in [Table 20](#) indicate that the results are not statistically significant. However, the results confirm the feasibility of data capture, a key objective outlined in the Cardiac CARE protocol.

Healthcare resource use

This section presents 6-month and 1-year costs of all HRU items recorded in the Cardiac CARE clinical trial, as well as differences in resource use patterns across trial arms.

Methods

Patient-reported outcome measure items

The Cardiac CARE PROM data include patient-reported resource use split into three categories: hospital based, community based and employment related. Each PROM observation contains a record of all resources used by a patient since their last questionnaire.

Six-month and 1-year costs for each item were calculated by multiplying the number of units used in the period of interest by the corresponding unit cost (see [Table 22](#)). For patients whose last PROM

TABLE 19 Unadjusted QALYs

	All patients (n = 191), mean (95% CI)	Standard care (n = 28), mean (95% CI)	Intervention (n = 29), mean (95% CI)
6 months	0.4 (0.39 to 0.42)	0.4 (0.37 to 0.42)	0.43 (0.41 to 0.45)
1 year	0.78 (0.75 to 0.81)	0.76 (0.67 to 0.85)	0.82 (0.75 to 0.89)

TABLE 20 Quality-adjusted life-year regression output

Characteristic		Beta	95% CI	p-value
Intervention	6 months	0.01	-0.02 to 0.04	0.5
	1 year	0.004	-0.10 to 0.11	>0.9

TABLE 21 Adjusted expected QALYs

	Standard care	Intervention
6 months	0.405	0.414
1 year	0.796	0.800

TABLE 22 Unit costs

Item	Unit	Cost (£, 2022)	Sources and assumptions
Anthracycline therapy (drug costs)	1 mg	0.24	Composed of the cost of 1 mg of epirubicin based on its 200 mg/100 ml vial (DHA026), as well as £0.07 worth of cyclophosphamide calculated based on its proportion of the EC100 chemotherapy regimen ⁴³
Anthracycline therapy (non-drug costs)	Cycle	587.03	Chemotherapy cycle delivery costs (£381.97), specialist nurse review (£190.59) and blood tests (£13.93) ⁴⁴
Bone scans	Scan	147.66	2020/21 NHS cost reference: nuclear bone scan of two or three phases, 19 years and over ⁴⁴
Breast cancer nurse telephone calls	Call	7.72	Assumed to be approximately equal to a nurse-led telephone triage with average time of 6.56 minutes ⁴⁵
Breast cancer nurse visits	Visit	90.49	2020/21 NHS cost reference: specialist nursing, cancer related, adult, face to face ⁴⁴
Cancer treatment helpline calls	Call	7.72	Assumed to be approximately equal to a nurse-led telephone triage with average time of 6.56 minutes ⁴⁵
Cancer treatment helpline visits	Visit	7.72	Assumed to be equal to the cost of a cancer treatment helpline call
Candesartan	1 mg	0.07	Derived from the drug tariff price of £1.01 for 7 candesartan cilexetil 2-mg tablets ⁴⁶
Cardiac MRIs	Scan	404.42	Obtained from NHS Lothian PLICS 2019/20 data ⁴⁷
Carvedilol	1 mg	0.01	Derived from the drug tariff price of £0.90 for 28 carvedilol 3.125-mg tablets ⁴⁸

TABLE 22 Unit costs (continued)

Item	Unit	Cost (£, 2022)	Sources and assumptions
Community physio-therapist clinic visits	Visit	118.88	2020/21 NHS cost reference: physiotherapy ⁴⁴
Community physio-therapist home visits	Visit	118.88	Assumed to be approximately equal to clinic visit
Community physio-therapist telephone calls	Call	8.79	Assumed to be approximately equal to the average cost per GP telephone consultation based on an average time of 5 minutes ⁴⁵
CT scans	Scan	98.90	2020/21 NHS cost reference: computerised tomography scan of one area, without contrast, 19 years and over ⁴⁴
cTnI test	1 test	5.53	CA\$10 (2016) converted to 2016 £4.89 using xe currency conversion tables from 1 January 2016 ^{49,50}
ECGs	Scan	61.21	Nurse-led rapid-access ECG clinic visit, obtained from NHS Lothian PLICS 2019/20 ⁴⁷
GP surgery clinic visits	Visit	39.75	GP per-patient contact lasting 9.22 minutes including direct care staff costs with qualification costs ⁴⁵
GP surgery home visits	Visit	39.75	Assumed to be approximately equal to clinic visit
GP surgery telephone calls	Call	8.79	Average cost per GP telephone consultation based on an assumed average time of 5 minutes ⁴⁵
Help support hours	Hour	12.70	Average hourly pay in 2018 (all ethnicities) ⁵¹
Helper days off	Day	75.69	Mean weekly paid hours worked by women multiplied by average hourly pay and divided by 5 (assumed five working days per week) ^{51,52}
Hospital doctor phone calls	Call	8.79	Assumed to be approximately equal to the average cost per GP telephone consultation based on an average time of 5 minutes ⁴⁵
Hospital doctor visits	Visit	217.22	2020/21 NHS cost reference: medical oncology ⁴⁴
Hospital nurse telephone calls	Call	7.72	Based on the cost of a nurse-led telephone triage with an average time of 6.56 minutes ⁴⁵
Hospital nurse visits	Visit	90.49	2020/21 NHS cost reference: specialist nursing, cancer related, adult, face to face ⁴⁴
Hospital physiotherapist telephone calls	Call	8.79	Assumed to be approximately equal to the average cost per GP telephone consultation based on an average time of 5 minutes ⁴⁵
Hospital physiotherapist visits	Visit	114	PSSRU 2021: physiotherapy, one-to-one session ⁴⁵
Inpatient days	Diem	704.05	Derived from average inpatient week cost in Scotland of £4702 ⁵³
Mammograms	Scan	8.79	Assumed to be approximately equal to X-ray costs ⁵⁴
Methylprednisolone	mg	0.06	Derived from NHS indicative price of £3.88 for 30 2-mg tablets ⁵⁵
NHS direct calls	Call	7.72	Assumed to be approximately equal to a nurse-led telephone triage with average time of 6.56 minutes ⁴⁵
NHS direct visits	Visit	7.72	Assumed to be approximately equal to the cost of a NHS Direct call
Nurse clinic visits	Visit	51.84	2020/21 NHS cost reference: district nurse, adult, face to face ⁴⁴
Nurse home visits	Visit	51.84	Assumed to be approximately equal to clinic visit

continued

TABLE 22 Unit costs (continued)

Item	Unit	Cost (£, 2022)	Sources and assumptions
Nurse telephone calls	Call	7.72	Nurse-led telephone triage based on an average time of 6.56 minutes ⁴⁵
Prednisolone	mg	0.03	Derived from NHS indicative price of 0.77 for 28 1-mg tablets ⁵⁶
Psychiatrist clinic visits	Visit	266.77	2020/21 NHS cost reference: liaison psychiatry ⁴⁴
Psychiatrist home visits	Visit	266.77	Assumed to be approximately equal to clinic visit
Psychiatrist telephone calls	Call	8.79	Assumed to be approximately equal to the average cost per GP telephone consultation based on an average time of 5 minutes ⁴⁵
Psychologist clinic visits	Visit	221.52	2020/21 NHS cost reference: clinical psychology ⁴⁴
Psychologist home visits	Visit	221.52	Assumed to be approximately equal to clinic visit
Psychologist telephone calls	Call	8.79	Assumed to be approximately equal to the average cost per GP telephone consultation based on an average time of 5 minutes ⁴⁵
Psychotherapist clinic visits	Visit	117.41	2020/21 NHS cost reference: psychotherapy ⁴⁴
Psychotherapist home visits	Visit	117.41	Assumed to be approximately equal to clinic visit
Psychotherapist telephone calls	Call	8.79	Assumed to be approximately equal to the average cost per GP telephone consultation based on an average time of 5 minutes ⁴⁵
Radiotherapy fraction	Fraction	217.25	2020/21 NHS cost reference: deliver a fraction of complex treatment on a megavoltage machine ⁴⁴
Radiotherapy preparation	Patient	1308.29	2020/21 NHS cost reference: preparation for complex conformal radiotherapy, with technical support ⁴⁴
Surgeon telephone calls	Call	8.79	Assumed to be approximately equal to the average cost per GP telephone consultation based on an average time of 5 minutes ⁴⁵
Surgeon visits	Visit	180.44	2020/21 NHS cost reference: general surgery ⁴⁴
Travel (miles driven)	Mile	0.13	Calculated from January 2021 Fuel Price Report and average UK MPG figure ^{41,57}
Ultrasounds	Scan	176.60	2020/21 NHS cost reference: ultrasound elastography ⁴⁴
X-rays	Scan	29.41	Freedom-of-information request to clinic ⁵⁴

MPG, miles per gallon.

observation fell prior to the 6-month or 1-year cut-off, imputation was conducted based on calculating the mean daily cost between the penultimate and final PROM date and assuming that it stayed constant until death or cut-off. All unit costs in [Table 22](#) were inflated to 2022 GBP using Consumer Price Index weights specific to medical goods published by the Office for National Statistics.⁴²

Limitation

Unscheduled hospital assessments were recorded as a binary variable instead of a continuous one, giving no information on the number of units used. Thus, the costs of unscheduled assessments were not captured in this analysis.

Candesartan and carvedilol

Candesartan and carvedilol costs were calculated by multiplying the cumulative dose taken of each drug during the study period (recorded in the Compliance SQL table) by its corresponding per-mg unit cost (see [Table 22](#)). For patients whose number of days prescribed exceeded the cut-off periods of 6 or 12 months, results were adjusted by the following formula, where *unadjusted cost* denotes the cost of the total dosage recorded over the study period:

$$\text{Adjusted cost} = \text{unadjusted cost} \times \frac{\text{Cut off days}}{\text{number of days prescribed}} \quad (2)$$

Anthracycline therapy

As outlined in the Cardiac CARE protocol version 11.0, patients underwent 3, 4 or 6 anthracycline therapy cycles lasting 6, 9 or 15 weeks. Since the chemotherapy treatment lasted no longer than 15 weeks, 1-year costs were equal to 6-month costs, as all costs were incurred within the first 6 months.

Based on chemotherapy cost calculators used in the OPTIMA trial,⁵⁸ all present calculations assumed:

- Patients followed the EC100 regimen for adjuvant and metastatic breast cancer, composed of epirubicin and cyclophosphamide – this assumption was based on expert advice.
- The *AnthracyclineDose* variable recorded in the SQL database corresponds to epirubicin (mg) but does not include cyclophosphamide.
- The cost of cyclophosphamide was calculated as a function of the epirubicin dosage, based on the proportion of cyclophosphamide in EC100 in the OPTIMA chemotherapy cost template.
- Per-cycle costs consist of:
 - delivery costs
 - specialist nurse review
 - blood tests.
- The supportive medications of EC100 are not included in the costs of anthracycline therapy; these were captured in the *Steroids* SQL table and calculated separately.

Steroids

Steroid dosage observations in the SQL database are recorded in one of two units:

- milligrams (*mg*)
- milligrams per metre squared (*m*²) (of surface area).

The conversion of *mg/m*² to *mg* assumes a surface area of 1.75 *m*² and a relative dose intensity of 0.92, based on the values in the OPTIMA chemotherapy cost template.⁵⁸

Radiotherapy

The radiotherapy costs consist of two elements:

1. radiotherapy preparation costs
2. radiotherapy fraction administration costs, multiplied by the number of administered treatments.

In the Cardiac CARE SQL database, dates of the first and last doses (fractions) are recorded for each patient who received radiotherapy, but the number of fractions itself is not recorded.

Radiotherapy cost calculations are based on an estimate of the number of patients' fractions, which assumes five fractions per week (on weekdays) between the dates of the first and last fractions recorded

in the database. The calculation's assumptions are based on treatments described in the Royal College of Radiologists' *Radiotherapy Dose Fractionation, Third Edition*, most of which involve five fractions per week.⁵⁹

For two patients, the period between the first and last fraction exceeded 2 months. These patients were assumed to have received 25 fractions, the maximum amount described in the RCR's document.

Limitations

The fraction administration costs could differ if patients' radiotherapy regimes diverge from the assumptions based on the RCR's document, for example by patients having received radiotherapy fractions:

- on an irregular basis
- at weekends
- more or less often than five times a week.

Perspectives

All HRU items were aggregated into totals and stratified into NHS perspective and non-NHS perspective costs. The societal perspective consists of the sum of costs in both categories. Each item was grouped according to the following guide:

*The NHS perspective includes treatment costs such as medicine costs, administration and monitoring, other health service resource use costs associated with the managing the disease (e.g. GP visits, hospital admissions), and costs of managing adverse events caused by treatment. It does not include patients' costs of obtaining care such as transportation, over-the-counter purchases, co-payments or time off work.*⁶⁰

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Regression

To assess the statistical significance of differences in total costs between trial arms, a simple linear regression of trial arm on costs was conducted.

Limitations

The model linear model is potentially sensitive to non-normally distributed cost data and confounding variables. In a future study, the model could be replaced with a multiple general linear model, as suggested by Barber and Thompson.⁶¹

Unit costs

Where possible, costs were sourced from a published paper or database (e.g. NHS reference costs). Where published data were lacking or judged as inapplicable or unrealistic during a review by the Cardiac CARE chief investigator, price weights were supplied by a NHS Lothian finance manager using internal and unpublished data. Where no suitable data were identified, unit costs were based on assumptions ([Table 22](#)). All costs are reported in 2022 GBP.

Summary of resource units used

[Table 23](#) summarises HRU units used per patient in each trial arm. [Figures 11–14](#) show the mean per-patient HRU units used within various resource categories, split by trial arm. [Figures 11–14](#) show on-site visits, home visits, telephone calls and scans, respectively. [Figures 15](#) and [16](#) are histograms that show the distribution of the number of chemotherapy cycles (see [Figure 15](#)) and radiotherapy fractions (see [Figure 16](#)) per patient in each trial arm.

TABLE 23 Units used

Units used	All patients (n = 191), mean (95% CI)	Standard care (n = 28), mean (95% CI)	Intervention (n = 29), mean (95% CI)
Bone scans	0.11 (0.06 to 0.16)	0.04 (-0.03 to 0.11)	0.07 (-0.02 to 0.16)
Breast cancer nurse telephone calls	1.07 (0.77 to 1.38)	0.68 (0.1 to 1.26)	0.52 (0.2 to 0.83)
Breast cancer nurse visits	0.85 (0.51 to 1.18)	0.61 (-0.01 to 1.22)	0.66 (0.14 to 1.17)
Cancer treatment helpline calls	1.47 (1.18 to 1.76)	1.54 (0.7 to 2.38)	1.38 (0.73 to 2.03)
Cancer treatment helpline visits	0.72 (0.48 to 0.96)	0.93 (0.2 to 1.66)	0.34 (-0.04 to 0.73)
Cardiac MRIs	0.6 (0.47 to 0.73)	0.5 (0.16 to 0.84)	0.9 (0.54 to 1.25)
Community physiotherapist clinic visits	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Community physiotherapist home visits	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Community physiotherapist telephone calls	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
CT scans	1.04 (0.8 to 1.28)	0.96 (0.49 to 1.44)	1.21 (0.77 to 1.65)
ECGs	0.63 (0.45 to 0.81)	0.68 (0.27 to 1.08)	0.76 (0.22 to 1.3)
GP surgery clinic visits	2.36 (1.91 to 2.81)	3.79 (2.15 to 5.42)	2.55 (1.35 to 3.75)
GP surgery home visits	0.05 (0.01 to 0.1)	0.18 (-0.05 to 0.41)	0 (0 to 0)
GP surgery telephone calls	1.61 (1.24 to 1.99)	2.11 (0.88 to 3.33)	2.17 (0.91 to 3.43)
Help support hours	45.97 (35.74 to 56.19)	101.32 (58.15 to 144.5)	42.05 (22.37 to 61.73)
Helper days off	20.09 (11.24 to 28.94)	22.84 (-2.73 to 48.41)	12.6 (-2.27 to 27.47)
Hospital doctor telephone calls	0.62 (0.43 to 0.81)	0.64 (0.29 to 1)	0.79 (0.18 to 1.4)
Hospital doctor visits	2.77 (2.25 to 3.29)	3.11 (2.02 to 4.19)	3.07 (1.83 to 4.31)
Hospital nurse telephone calls	0.61 (0.4 to 0.82)	0.61 (0.15 to 1.06)	0.72 (0.16 to 1.29)
Hospital nurse visits	2.59 (1.57 to 3.61)	3.07 (0.67 to 5.48)	4.69 (-0.75 to 10.13)
Hospital physiotherapist telephone calls	0.08 (0.03 to 0.14)	0 (0 to 0)	0.07 (-0.02 to 0.16)
Hospital physiotherapist visits	0.31 (0.17 to 0.44)	0.5 (-0.02 to 1.02)	0.48 (0.1 to 0.87)
Inpatient days	3.62 (2.6 to 4.64)	3.79 (1.52 to 6.05)	5.03 (1.86 to 8.21)
Mammograms	0.41 (0.28 to 0.55)	0.36 (< 0.01 to 0.71)	0.45 (0.05 to 0.84)
NHS direct calls	0.09 (0.03 to 0.15)	0.11 (-0.01 to 0.22)	0.03 (-0.03 to 0.1)
NHS direct visits	0.08 (0.01 to 0.16)	0.11 (-0.01 to 0.22)	0.03 (-0.03 to 0.1)
Nurse clinic visits	3.44 (2.61 to 4.28)	5.39 (1.41 to 9.38)	3.45 (1.61 to 5.29)
Nurse home visits	0.49 (0.07 to 0.92)	0.25 (-0.24 to 0.74)	0.79 (-0.38 to 1.97)
Nurse telephone calls	0.2 (0.07 to 0.32)	0.21 (<0.01 to 0.42)	0.1 (-0.1 to 0.31)
Patient days off	216.53 (175.35 to 257.71)	236.68 (139.43 to 333.92)	228.52 (88.78 to 368.25)
Psychiatrist clinic visits	0.04 (-0.01 to 0.08)	0.04 (-0.03 to 0.11)	0.14 (-0.13 to 0.41)
Psychiatrist home visits	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Psychiatrist telephone calls	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

continued

TABLE 23 Units used (continued)

Units used	All patients (n = 191), mean (95% CI)	Standard care (n = 28), mean (95% CI)	Intervention (n = 29), mean (95% CI)
Psychologist clinic visits	0.1 (-0.01 to 0.21)	0.32 (-0.24 to 0.88)	0.14 (-0.02 to 0.3)
Psychologist home visits	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Psychologist telephone calls	0.03 (<0.01 to 0.05)	0.07 (-0.07 to 0.21)	0 (0 to 0)
Psychotherapist clinic visits	0.11 (-0.06 to 0.27)	0.64 (-0.48 to 1.77)	0.03 (-0.03 to 0.1)
Psychotherapist home visits	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Psychotherapist telephone calls	0.01 (-0.01 to 0.03)	0 (0 to 0)	0 (0 to 0)
Surgeon telephone calls	0.1 (0.01 to 0.18)	0.04 (-0.03 to 0.11)	0.03 (-0.03 to 0.1)
Surgeon visits	0.75 (0.55 to 0.94)	0.75 (0.17 to 1.33)	0.52 (0.12 to 0.91)
Travel (miles driven)	242.88 (181.12 to 304.64)	132 (65.53 to 198.48)	347.07 (185.61 to 508.53)
Ultrasounds	0.66 (0.49 to 0.83)	0.54 (0.14 to 0.93)	0.86 (0.41 to 1.32)
X-rays	6.1 (-4.49 to 16.69)	1.04 (0.42 to 1.65)	0.93 (0.53 to 1.33)

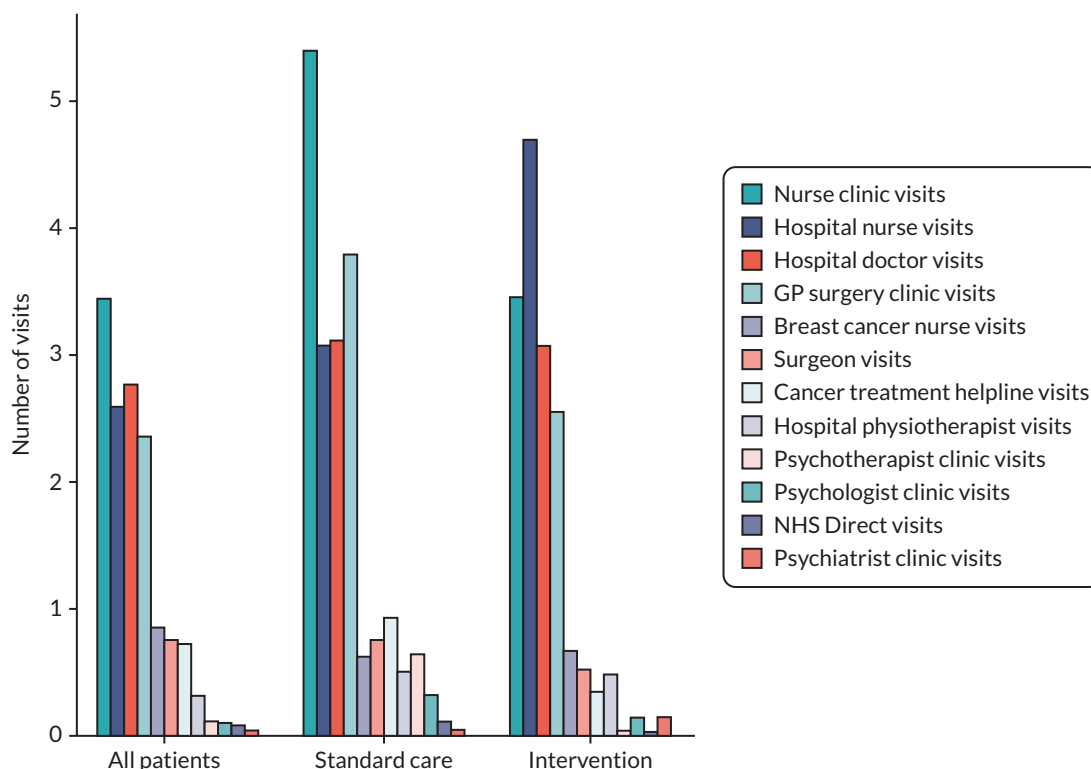


FIGURE 11 Mean clinic/on-site visits per patient during the study period, by trial arm.

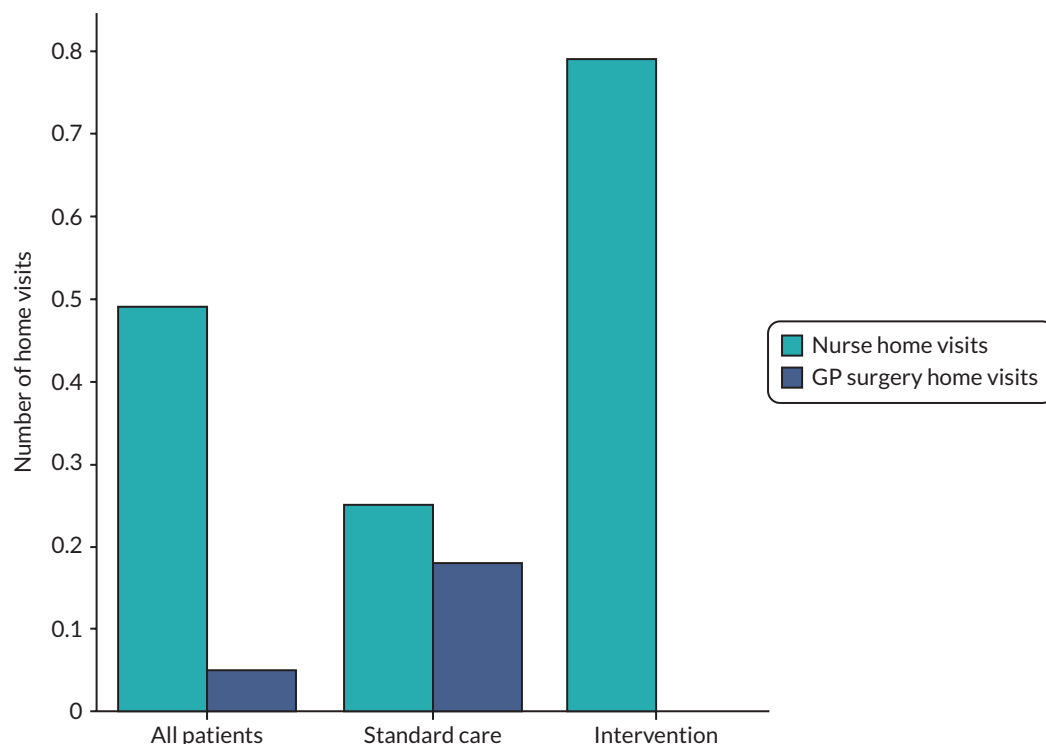


FIGURE 12 Mean home visits per patient during the study period, by trial arm.

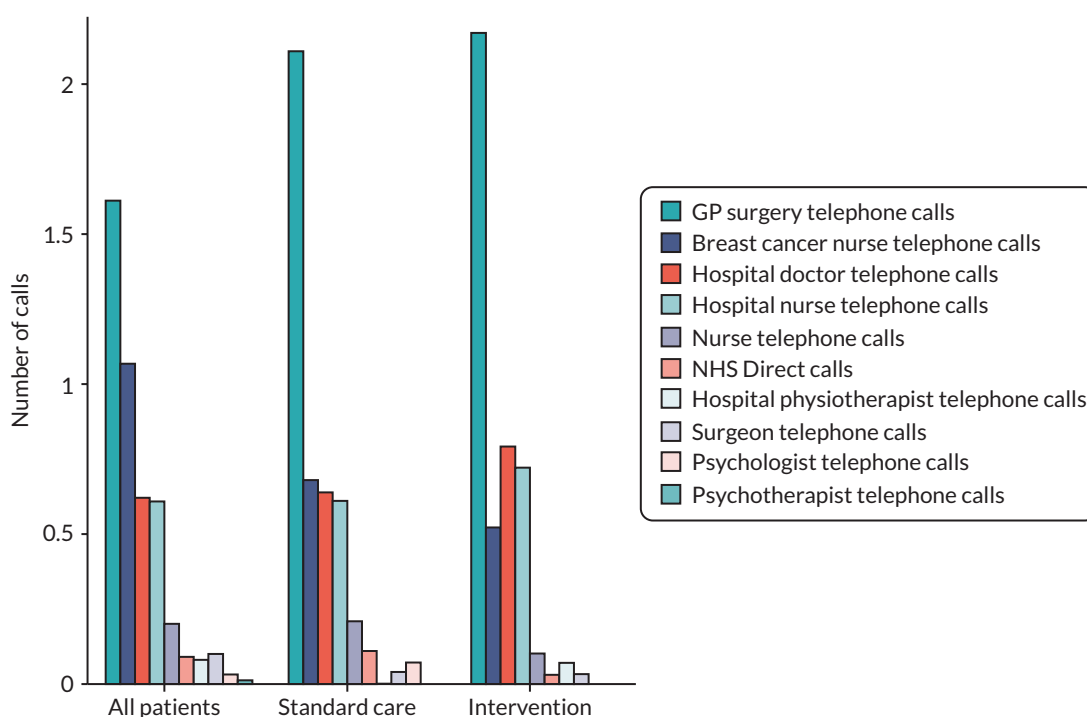


FIGURE 13 Mean telephone calls per patient during the study period, by trial arm.

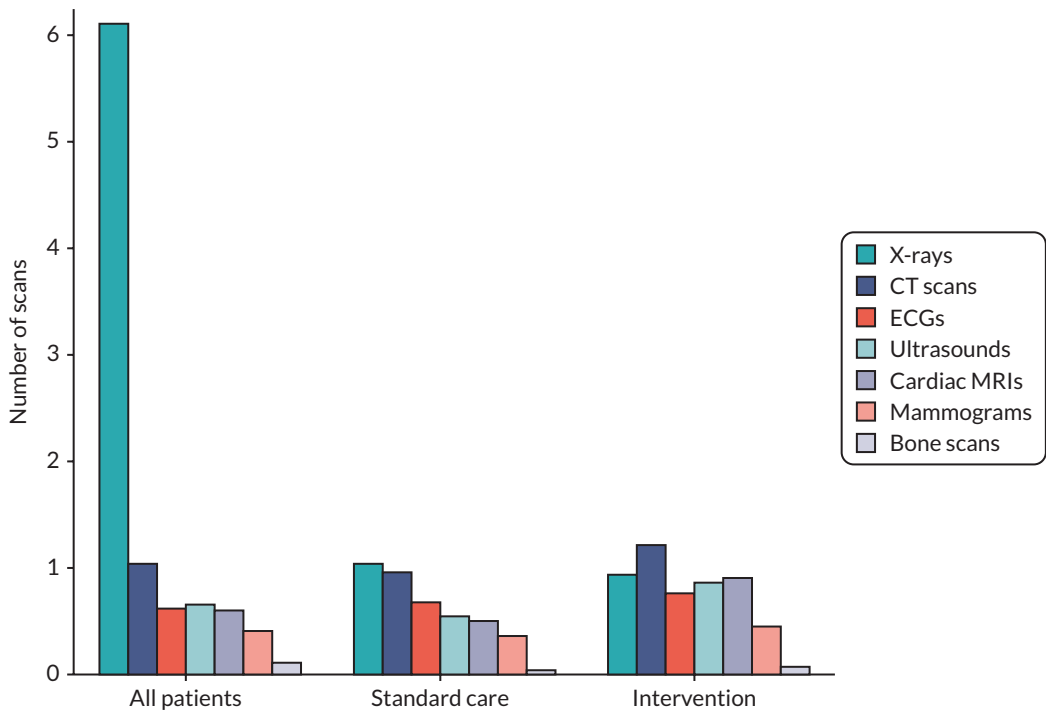


FIGURE 14 Mean scans per patient during the study period, by trial arm.

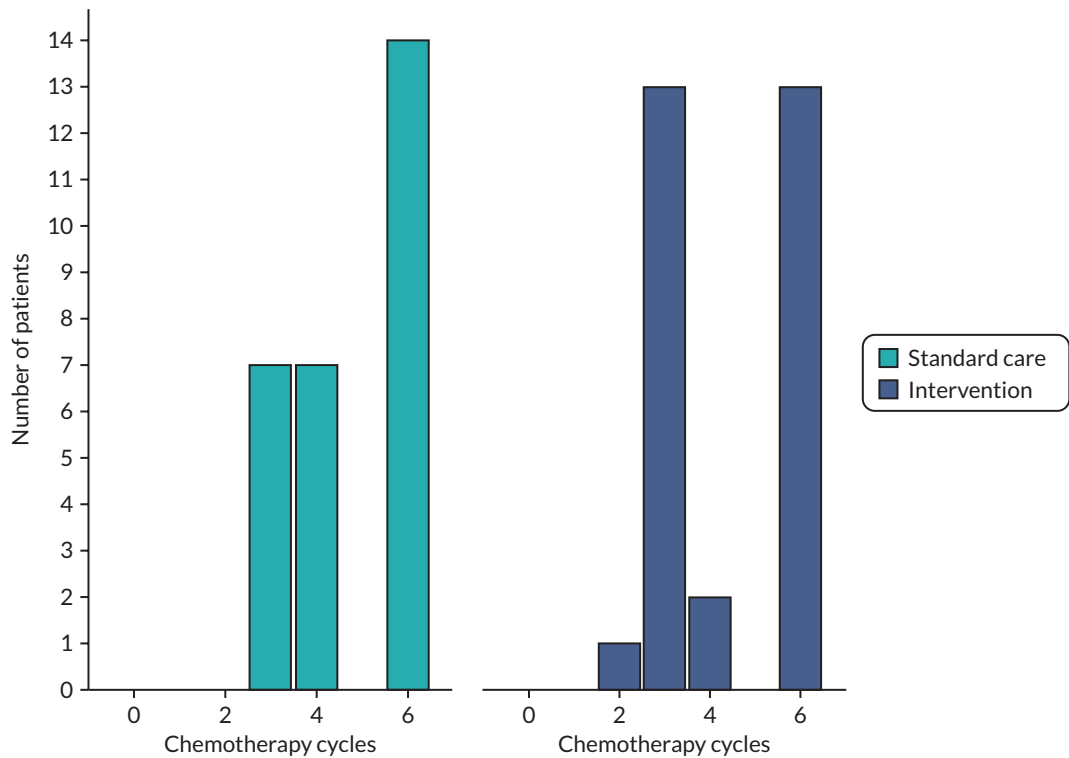


FIGURE 15 Histogram of chemotherapy cycles per patient, by trial arm.

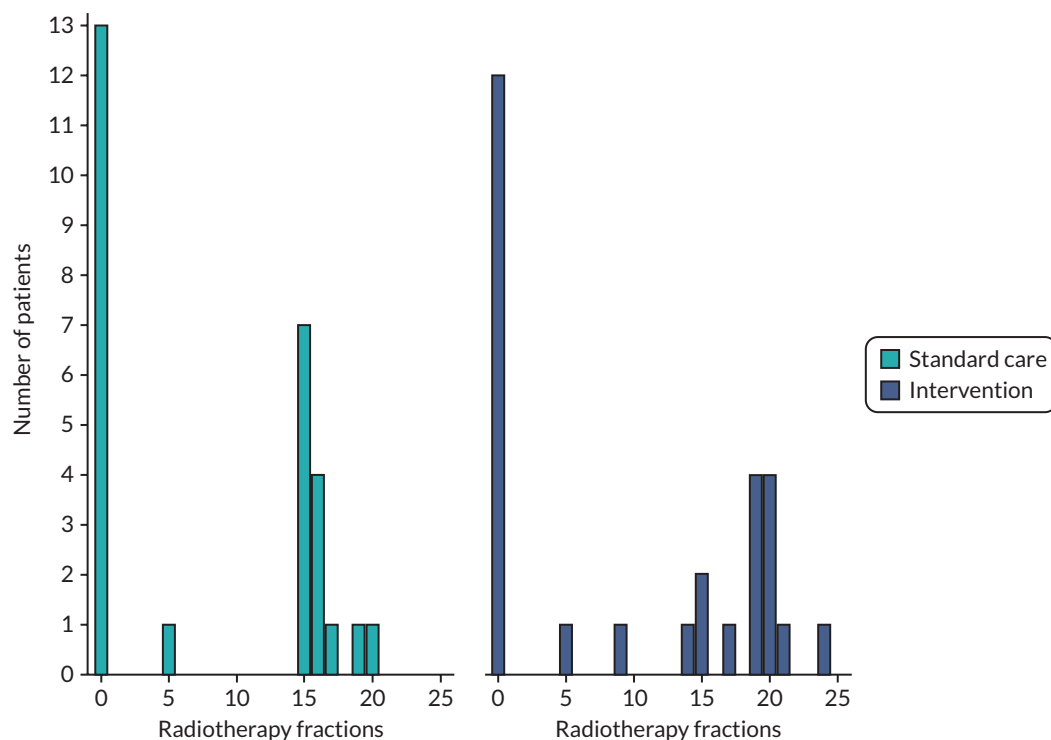


FIGURE 16 Histogram of radiotherapy fractions per patient, by trial arm.

Results

This section summarises the 6-month and 1-year costs of all HRU items included in this analysis, as well as total costs and regression outputs. [Table 24](#) summarises the costs of all HRU items recorded in the PROM questionnaires incurred by patients in each trial arm, categorised by resource types that include hospital-based, community care and employment-related (productivity loss) costs. Costs of the trial drugs (candesartan and carvedilol) are presented in [Table 25](#). Chemotherapy costs are presented in [Table 26](#). Costs of concomitant medications (steroids) are presented in [Table 27](#). Radiotherapy costs are presented in [Table 28](#). A summary of total costs by trial arm is presented in [Table 29](#).

Healthcare resource use item costs

Total costs

Total costs are summarised in [Table 29](#). [Figure 17](#) shows a breakdown of the largest components of the total costs for each trial arm.

Regression

In the regression analysis, *Intervention* is a binary variable where 0 represents standard care and 1 represents the intervention. Thus, the coefficient (Beta) shows the estimated difference in the mean total NHS-perspective per-patient costs (2021 GBP) between the intervention and standard care arms.

[Table 30](#) shows that 6-month costs are estimated to be £67 lower for the intervention arm than the standard care arm by the regression model, while 1-year costs are estimated to be £1926 higher.

TABLE 24 Patient-reported outcome measure HRU costs

Cost type	Item	Time point	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
Hospital	Bone scans	6 months	17 (7 to 27)	0 (0 to 0)	7 (-4 to 17)
		1 year	33 (13 to 53)	17 (-16 to 50)	22 (-12 to 56)
	Breast cancer nurse telephone calls	6 months	8 (5 to 11)	3 (< 1 to 7)	2 (<1 to 3)
		1 year	16 (10 to 22)	8 (1 to 16)	8 (3 to 14)
	Breast cancer nurse visits	6 months	68 (44 to 92)	46 (1 to 90)	51 (7 to 96)
		1 year	121 (76 to 166)	5 (-8 to 157)	73 (13 to 133)
	Cancer treatment helpline calls	6 months	13 (10 to 15)	12 (5 to 18)	11 (6 to 16)
		1 year	14 (11 to 18)	12 (5 to 18)	11 (6 to 16)
	Cancer treatment helpline visits	6 months	6 (4 to 8)	7 (1 to 12)	2 (<1 to 5)
		1 year	7 (5 to 10)	7 (2 to 13)	3 (<1 to 6)
	Cardiac MRIs	6 months	172 (126 to 218)	140 (32 to 249)	160 (81 to 239)
		1 year	409 (317 to 500)	335 (110 to 560)	430 (257 to 604)
	CT scans	6 months	84 (66 to 101)	76 (27 to 125)	90 (55 to 125)
		1 year	146 (116 to 176)	133 (76 to 189)	155 (93 to 217)
	ECGs	6 months	35 (25 to 45)	38 (14 to 61)	33 (10 to 56)
		1 year	55 (38 to 72)	46 (18 to 75)	59 (8 to 111)
	Hospital doctor telephone calls	6 months	5 (3 to 6)	4 (1 to 7)	5 (1 to 9)
		1 year	8 (5 to 10)	7 (3 to 11)	7 (1 to 13)
	Hospital doctor visits	6 months	528 (436 to 619)	601 (379 to 824)	523 (328 to 719)
		1 year	973 (700 to 1247)	763 (513 to 1013)	850 (435 to 1266)
	Hospital nurse telephone calls	6 months	5 (3 to 6)	4 (1 to 7)	5 (1 to 10)
		1 year	6 (4 to 8)	5 (1 to 9)	5 (1 to 10)
	Hospital nurse visits	6 months	209 (141 to 277)	237 (38 to 435)	271 (18 to 524)
		1 year	317 (185 to 448)	330 (103 to 557)	539 (-132 to 1210)
	Hospital physiotherapist telephone calls	6 months	0 (<1 to 1)	0 (0 to 0)	0 (0 to 0)
		1 year	2 (<1 to 3)	0 (0 to 0)	1 (-1 to 3)
	Hospital physiotherapist visits	6 months	29 (14 to 44)	57 (-2 to 116)	24 (<1 to 47)
		1 year	53 (30 to 76)	57 (-2 to 116)	84 (4 to 164)

TABLE 24 Patient-reported outcome measure HRU costs (continued)

Cost type	Item	Time point	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
	Inpatient days	6 months	2167 (1549 to 2785)	2450 (879 to 4021)	2422 (661 to 4183)
		1 year	3549 (2529 to 4569)	3097 (1312 to 4882)	4505 (1078 to 7933)
	Mammograms	6 months	4 (2 to 6)	3 (<1 to 5)	4 (<1 to 7)
		1 year	6 (3 to 9)	3 (<1 to 6)	5 (1 to 9)
	NHS Direct calls	6 months	1 (<1 to 1)	1 (<1 to 1)	<1 (<1 to 1)
		1 year	1 (<1 to 2)	2 (-1 to 4)	<1 (<1 to 1)
	NHS Direct visits	6 months	1 (<1 to 1)	1 (<1 to 1)	<1 (<1 to 1)
		1 year	1 (<1 to 2)	1 (<1 to 3)	<1 (<1 to 1)
	Surgeon telephone calls	6 months	1 (<1 to 1)	<1 (<1 to 1)	0 (0 to 0)
		1 year	1 (<1 to 3)	<1 (<1 to 1)	1 (-1 to 2)
	Surgeon visits	6 months	113 (82 to 144)	96 (20 to 171)	68 (15 to 120)
		1 year	242 (170 to 313)	194 (26 to 362)	176 (24 to 328)
	Ultrasounds	6 months	103 (75 to 132)	90 (24 to 157)	116 (40 to 192)
		1 year	157 (107 to 207)	95 (25 to 165)	189 (85 to 293)
	X-rays	6 months	194 (-153 to 540)	28 (11 to 44)	22 (12 to 32)
		1 year	205 (-141 to 552)	32 (12 to 51)	27 (15 to 39)
Employment	Help support hours	6 months	406 (298 to 514)	862 (422 to 1302)	347 (161 to 534)
		1 year	690 (499 to 881)	1192 (658 to 1725)	563 (270 to 856)
	Helper days off	6 months	1008 (571 to 1445)	1238 (-386 to 2861)	577 (-74 to 1228)
		1 year	2275 (1188 to 3363)	2773 (-499 to 6045)	1135 (-567 to 2837)
	Lost earnings	6 months	3306 (1243 to 5369)	3136 (1159 to 5113)	1336 (-156 to 2827)
		1 year	6753 (3902 to 9604)	5017 (1417 to 8617)	2410 (184 to 4635)
Community	Community physiotherapist clinic visits	6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
		1 year	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
	Community physiotherapist home visits	6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
		1 year	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

continued

TABLE 24 Patient-reported outcome measure HRU costs (continued)

Cost type	Item	Time point	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
	Community physiotherapist telephone calls	6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
		1 year	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
	GP surgery clinic visits	6 months	80 (63 to 98)	111 (54 to 169)	76 (32 to 120)
		1 year	155 (123 to 187)	215 (119 to 310)	139 (72 to 207)
	GP surgery home visits	6 months	3 (<1 to 6)	6 (-3 to 14)	0 (0 to 0)
		1 year	5 (-1 to 10)	7 (-2 to 16)	0 (0 to 0)
	GP surgery telephone calls	6 months	12 (9 to 15)	14 (5 to 23)	13 (4 to 23)
		1 year	23 (18 to 29)	25 (11 to 39)	28 (13 to 43)
	Nurse clinic visits	6 months	177 (131 to 223)	235 (28 to 442)	161 (68 to 254)
		1 year	256 (198 to 313)	318 (111 to 525)	219 (106 to 333)
	Nurse home visits	6 months	22 (2 to 42)	13 (-12 to 38)	24 (-5 to 54)
		1 year	33 (1 to 66)	13 (-12 to 38)	92 (-66 to 250)
	Nurse telephone calls	6 months	1 (<1 to 2)	1 (<1 to 2)	1 (-1 to 2)
		1 year	2 (1 to 4)	2 (<1 to 3)	1 (-1 to 2)
	Psychiatrist clinic visits	6 months	10 (-3 to 23)	10 (-9 to 28)	38 (-37 to 113)
		1 year	13 (-2 to 28)	10 (-9 to 28)	38 (-37 to 113)
	Psychiatrist home visits	6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
		1 year	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
	Psychiatrist telephone calls	6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
		1 year	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
	Psychologist clinic visits	6 months	15 (-2 to 31)	36 (-21 to 94)	13 (-5 to 30)
		1 year	35 (-8 to 78)	126 (-106 to 358)	24 (-10 to 58)
	Psychologist home visits	6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
		1 year	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
	Psychologist telephone calls	6 months	<1 (<1 to <1)	<1 (<1 to <1)	0 (0 to 0)
		1 year	1 (<1 to 2)	2 (-2 to 7)	0 (0 to 0)
	Psychotherapist clinic visits	6 months	11 (-6 to 27)	60 (42 to 162)	1 (-1 to 3)
		1 year	17 (-5 to 40)	75 (-56 to 207)	13 (-13 to 39)

TABLE 24 Patient-reported outcome measure HRU costs (continued)

Cost type	Item	Time point	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
	Psychotherapist home visits	6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
		1 year	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
	Psychotherapist telephone calls	6 months	<1 (<1 to <1)	0 (0 to 0)	0 (0 to 0)
		1 year	<1 (<1 to 1)	0 (0 to 0)	0 (0 to 0)
	Travel (miles driven)	6 months	29 (22 to 35)	13 (6 to 19)	37 (19 to 55)
		1 year	56 (38 to 74)	30 (9 to 51)	70 (33 to 106)
	Travel (parking)	6 months	2 (<1 to 5)	9 (-6 to 24)	<1 (<1 to 1)
		1 year	3 (<1 to 6)	11 (-6 to 28)	1 (<1 to 1)
	Travel (public transport)	6 months	26 (16 to 36)	29 (5 to 54)	31 (5 to 56)
		1 year	33 (21 to 45)	38 (6 to 69)	38 (10 to 67)

TABLE 25 Candesartan and carvedilol costs

		All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
Candesartan	6 months	158.08 (49.22 to 266.93)	0 (0 to 0)	1030.22 (401.56 to 1658.88)
	1 year	185.25 (54.34 to 316.16)	0 (0 to 0)	1207.34 (445.37 to 1969.32)
Carvedilol	6 months	226.03 (71.09 to 380.98)	0 (0 to 0)	1473.12 (579.52 to 2366.71)
	1 year	261.75 (80.39 to 443.11)	0 (0 to 0)	1705.86 (656.43 to 2755.29)

TABLE 26 Chemotherapy costs

Item	Time point	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
Anthracycline drugs	6 months	134 (126 to 142)	156 (144 to 167)	145 (121 to 168)
	1 year	134 (126 to 142)	156 (144 to 167)	145 (121 to 168)
Chemotherapy cycle delivery	6 months	2305 (2159 to 2450)	2788 (2501 to 3076)	2571 (2246 to 2896)
	1 year	2305 (2159 to 2450)	2788 (2501 to 3076)	2571 (2246 to 2896)
Total chemotherapy ^a	6 months	2439 (2287 to 2590)	2944 (2652 to 3236)	2716 (2381 to 3050)
	1 year	2439 (2287 to 2590)	2944 (2652 to 3236)	2716 (2381 to 3050)

^a Excluding concomitant medication (steroids), which are presented in Table 27.

TABLE 27 Concomitant medication (steroid) costs

	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
Prednisolone			
6 months	5.09 (2.59 to 7.60)	9.23 (1.10 to 17.37)	10.11 (1.02 to 19.20)
1 year	6.07 (3.39 to 8.74)	10.31 (2.22 to 18.41)	12.81 (2.66 to 22.97)
Methylprednisolone			
6 months	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
1 year	0.05 (-0.04 to 0.14)	0 (0 to 0)	0 (0 to 0)

TABLE 28 Radiotherapy costs

	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
6 months	1924 (1587 to 2261)	1810 (941 to 2678)	2077 (1138 to 3016)
1 year	2683 (2337 to 3030)	2485 (1593 to 3378)	2789 (1818 to 3761)

TABLE 29 Total costs

Cost type	Time point	All patients (n = 191), mean (£) (95% CI)	Standard care (n = 28), mean (£) (95% CI)	Intervention (n = 29), mean (£) (95% CI)
Total NHS-perspective costs ^a	6 months	8934 (8048 to 9820)	9142 (6906 to 11,377)	9074 (6658 to 11,491)
	1 year	12,550 (11,207 to 13,893)	11,451 (8749 to 14,154)	13,378 (8873 to 17,882)
Total non-NHS-perspective costs ^b	6 months	4777 (2645 to 6908)	5287 (2406 to 8168)	2329 (745 to 3913)
	1 year	9811 (6609 to 13,013)	9060 (3547 to 14,574)	4216 (1463 to 6969)
Total societal costs	6 months	13,711 (11,328 to 16,093)	14,428 (10,196 to 18,660)	11,403 (8055 to 14,752)
	1 year	22,361 (18,744 to 25,978)	20,511 (13,019 to 28,004)	17,594 (12,162 to 23,026)

a Includes all costs from [Tables 22–28](#), except for the below.

b Lost earnings, help support hours, helper days off, patient days off and travel costs (miles driven, parking and public transport).

Summary

The *p*-values in [Table 30](#) indicate that differences in costs between trial arms are underpowered for health economic analysis and not statistically significant. However, the HRU analysis confirms the feasibility of data capture and shows inpatient stays, anthracycline therapy and radiotherapy to be key drivers of NHS perspective costs in the Cardiac CARE study population.

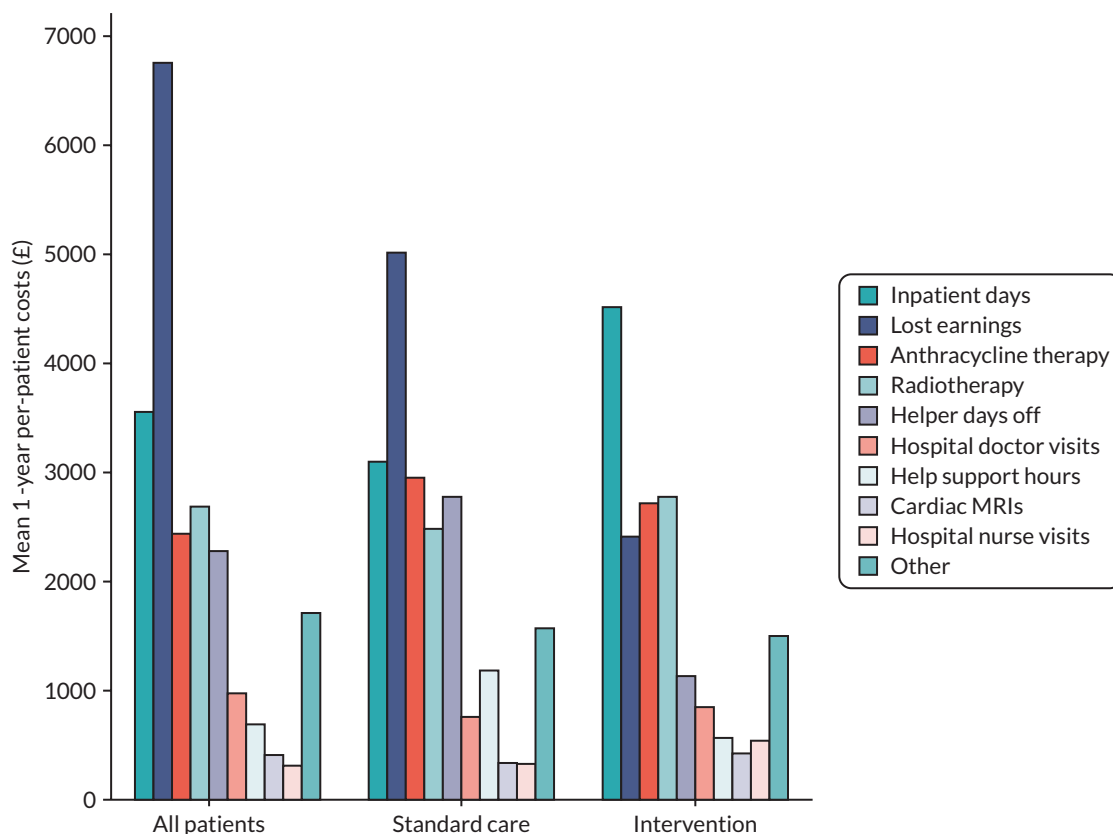


FIGURE 17 Mean 1-year HRU item cost breakdown, by trial arm.

TABLE 30 Total costs: regression output

Characteristic	Beta (£) (95% CI)	p-value
6 months	-67 (-£3434 to £3300)	> 0.9
Intervention 1 year	1926 (-£3447 to £7300)	0.5

Incremental cost-effectiveness ratio

The ICER is a 'ratio of the difference in the mean costs of a technology compared with the next best alternative to the differences in the mean outcomes'.³⁶ The formula for calculating the ICER for the candesartan and carvedilol intervention compared with standard care is:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{CI - CS}{EI - ES} \quad (3)$$

Where:

- C denotes total NHS perspective costs
- E denotes total QALYs
- I denotes the intervention arm (candesartan and carvedilol)
- S denotes the standard care arm.

Estimates of ΔE and ΔC are given by the β_1 regression coefficients for the intervention in [Tables 20](#) and [30](#), respectively, yielding a 1-year ICER of:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{\pounds 1926}{0.004 \text{ QALYs}} = \pounds 481,500/\text{QALY}$$

However, [Tables 20](#) and [30](#) also show that estimates of ΔE and ΔC are not statistically significant, yielding an inconclusive ICER result. Even if the results are indeed accurate and the ICER calculated in this section is a good approximation of the intervention's cost-utility, then it far exceeds the willingness-to-pay threshold (WTP) of £20,000–30,000 per QALY recommended by NICE.³⁶

Discussion

Patient-reported outcome measure period

As shown in [Table 17](#), the mean number of days tracked by PROM questionnaires (i.e. days between the first chemotherapy cycle and the last completed form) differs between trial arms: 269 days for standard care and 308.07 days for the intervention. Two patients in the intervention have over double the PROM days of the standard care arm's maximum length of 362 days. As the 95% CIs for PROM days overlap (see [Table 17](#)), this difference may be due to chance. A future study could further investigate differing PROM response patterns between randomisation groups, which could also explain discrepancies in response rates at different study time points (see [Table 18](#)).

EuroQol-5 Dimensions utility and Visual Analogue Scale

In [Figure 9](#), general population perception of health states (EQ-5D) is consistently higher for the intervention arm than for standard care across study time points, whereas the opposite is true for patient-perceived health state VAS scores in [Figure 10](#). In both figures, 95% CIs overlap, suggesting that the differences could be due to random variation. However, one possible explanation for this discrepancy could be the presence of more AEs or serious adverse events (SAEs) in the intervention group, which, although not captured by the EQ-5D, may be perceived as a reduction in life quality by patients themselves.

Nurse visits

[Figure 11](#) shows that, for patients in the standard care arm, the mean number of drop-in nurse clinic visits recorded over the study period (5.39) is greater than the mean number of hospital nurse visits (3.07). For the intervention arm, however, the opposite is true (3.45 drop-in nurse visits vs. 4.69 hospital nurse visits). However, as shown in [Table 23](#), the 95% CIs for mean estimates of hospital versus drop-in nurse visits overlap, so variation between visit types and trial arms could be due to randomness. Nevertheless, a future study could further investigate differences between trial arms of nursing resource requirements.

Patient-reported outcome measure questionnaire design and recommendations

Overall, the results of this analysis confirm data capture feasibility. However, several elements of the PROM questionnaire could be amended to simplify data collection and remove some of the limitations in the current analysis.

The PROM questionnaire data contains information on a wide variety of cost variables, many of which are associated with negligible costs (e.g. non-GP telephone calls). A more streamlined questionnaire could reduce the burden on patients and improve the data collection process.

Another challenge to calculating costs from the Cardiac CARE PROM data stems from unscheduled assessments being recorded as binary variables. To estimate the costs, a questionnaire should collect the number of assessments in addition to binary information on whether or not a given patient had an unscheduled assessment.

References

See [References](#).

Appendix 2 Protocol amendments

V1.0 (14 March 2017)	Initial submission to Research Ethics Committee
V2.0 (14 June 2017)	<ul style="list-style-type: none"> • updated wording in 5.6 withdrawal of study patients • removed wording from 6.3 dosing regime • removed references to IB in 10.4.3
V3.0 (28 August 2017)	<ul style="list-style-type: none"> • Updated study flow chart • Removed examples of inclusion criteria (Data Monitoring and Ethics Committee request) • Defined active drug or alcohol abuse (NIHR request) • Updated visit schedule tables and defined weekly timeline • Updated wording in 9.1 sample size calculation (Data Monitoring and Ethics Committee request) • Updated wording in 9.2 proposed analyses • Removed clinical pharmacologist from 11.3 Data Monitoring and Ethics Committee
V4.0 (28 September 2017)	<ul style="list-style-type: none"> • Added reference to trial website in section 14.2 publication
V5.0 (31 January 2018)	<ul style="list-style-type: none"> • Changed inclusion to include anthracycline = 300 mg/m² over 3, 4 or 6 cycles • Changed wording of co-enrolment agreement and co-enrolment recording in section 4.4 • Updated study flow chart • Added visit schedule for 3 cycles chemo (7.2.3) • Clarified in 10.3.2 that reportable SAE also recorded as AE
V6.0 (21 February 2018)	<ul style="list-style-type: none"> • Changed inclusion to include NHL patients scheduled for CHOP or R-CHOP • Updated reference to lymphoma patients throughout, including change of title • Updated section 5.5.1 randomisation minimisation • Updated section 9.2 proposed analyses • Updated section 10.3.2 to include infection and infusion-related reactions as an expected symptom of the underlying condition
V7.0 (8 October 2018)	<ul style="list-style-type: none"> • Updated section 4.2 inclusion criteria – clarification of NHL patient treatment regimes • Updated section 5.5.1 randomisation procedures – changed the cTnI threshold for randomisation at cycle 2 and included the opportunity to randomise at cycles 3, 4 and 5 • Updated section 5.6 withdrawal – included that patients no exposed to cardiotoxic levels of anthracycline can be withdrawn if participation is no longer in their best interest • Updated section 7.2 study assessments with the new randomisation schedule • Updated section 7.2.5 blood samples – cTnI concentration can be measured up to 1 week before chemotherapy visit • Updated section 10.6 reporting of SAEs – removed ambiguity and corrected the wording about SAE recording and reporting
V8.0 (19 June 2019)	<ul style="list-style-type: none"> • Updated section 5.5.2 treatment allocation – clarification of timing • Updated section 6.3 dosing regime – added confirmation that IMPs can be restarted • Visit schedule tables 7.2.1, 7.2.2 and 7.2.3 updated and table legends corrected – renal function bloods are not required for patients on standard care arm
V9.0 (29 April 2020)	<ul style="list-style-type: none"> • Updated section 6.3 – dosing regime – clarified time for renal function blood test and other minor changes • Added section 6.3.1 – provision of IMP – provision of IMP permitted by post • Updated 7.2.5 – blood samples during anthracycline therapy – amended to permit the Alinity assay • Updated 9.2 – proposed analyses – clarification of role of ECTU statisticians
V10.0 (17 May 2021)	<ul style="list-style-type: none"> • Updated section 2.2.2 – secondary end points – split the secondary end-point analysis into groupings: 1. Measurement of IMP efficacy, 2. specificity of high sensitivity cardiac troponin I for identifying patients at low risk of cardiotoxicity, 3. measures of IMP toxicity and 4. health economics analysis. The amendments clarify the additional analysis of cardiac MRI measures of myocardial injury including myocardial strain, LVM/volume and LAA
V11.0 (27 July 2021)	<ul style="list-style-type: none"> • Non-substantial amendment – correction of typos in section 2.2

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