ACC.24

# PROACT: Can we prevent chemotherapy-related heart damage in patients with breast cancer and lymphoma?


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# Disclosures

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# Preventing cardiac damage in patients treated for breast cancer and lymphoma: a phase 3 Randomised, Open label, blinded endpoint superiority trial of enalapril to prevent Anthracycline-induced CardioToxicity

**Registration:** Clinicaltrials.org: NCT03265574

https://research.ncl.ac.uk/proact/

# Background

- Anthracyclines are widely used in cancer treatment
- Anthracycline cardiotoxicity is dose dependent and associated with myocardial injury
- Prevention of cardiotoxicity is key to reducing the life-long impact of cancer treatment in the increasing population of cancer survivors
- The absence of myocardial injury during or immediately after anthracycline treatment has a high negative predictive value for clinical cardiotoxicity
- ACE inhibitors may be protective against anthracycline toxicity
- **Aim:** To establish the effectiveness of the ACE inhibitor enalapril in the prevention of anthracycline cardiotoxicity in patients with breast cancer and non-Hodgkin lymphoma (NHL)

# Key design features of PROACT

- Multi-center randomized controlled trial
- Blinded end point analysis at core laboratories (PROBE design)
- Enriched population receiving high dose anthracyclines (≥300mg/m$^2$ doxorubicin-equivalent)
- Fair test of enalapril - aimed to titrate to 10mg bd
- End points consistent with current understanding of anthracycline cardiotoxicity
  - Now enshrined in ESC Cardio-oncology guideline (2022)

# Blinded, Core lab assessed end points

## Primary end point:

- Myocardial injury defined as cTnT ≥14ng/L

## Secondary end points:

- Myocardial Injury defined as cTnI >26.2ng/L
- Left ventricular global longitudinal strain (LV GLS) >15% relative decline from baseline
- Left ventricular ejection fraction (LVEF) >10% absolute decline from baseline

hs Trop I
BHF Cardiovascular Biomarker Lab,
University of Edinburgh

hs Trop T
Royal Victoria Infirmary,
Newcastle Upon Tyne

Echocardiographic Core lab
The James Cook University Hospital,
Middlesbrough

## Inclusion

Adult patients due to receive 6 cycles (≥ 300mg/m$^2$ doxorubicin-equivalent) of anthracycline chemotherapy

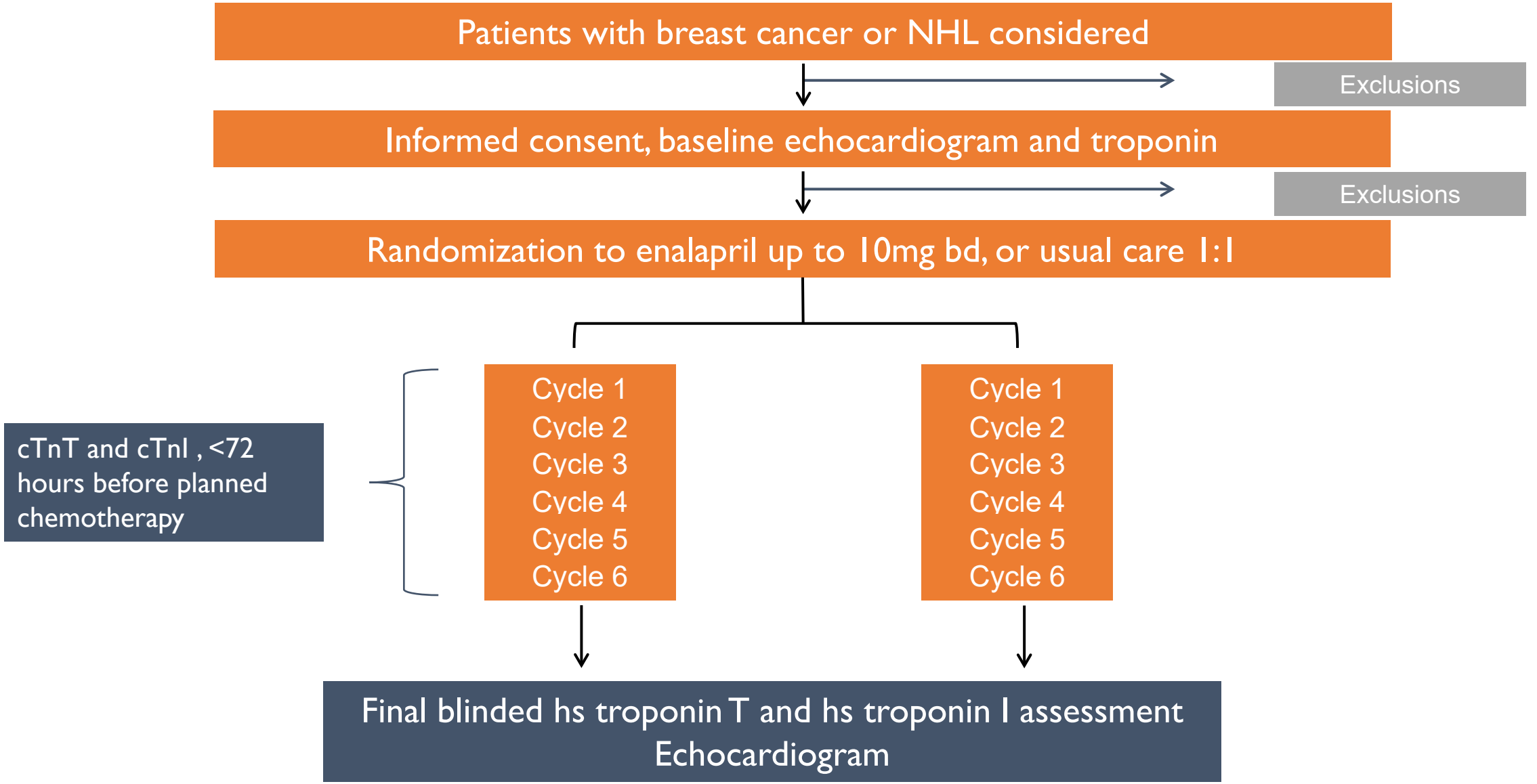
- **EC 90** (432mg/m$^2$ doxorubicin-equivalent)
- **FEC 75** (360mg/m$^2$ doxorubicin-equivalent)
- **R-CHOP** (300mg/m$^2$ doxorubicin-equivalent)

## Key exclusion

- Myocardial injury at baseline
- LVEF <50% on echo
- Contraindications to enalapril
- Already taking agents acting on RAAS

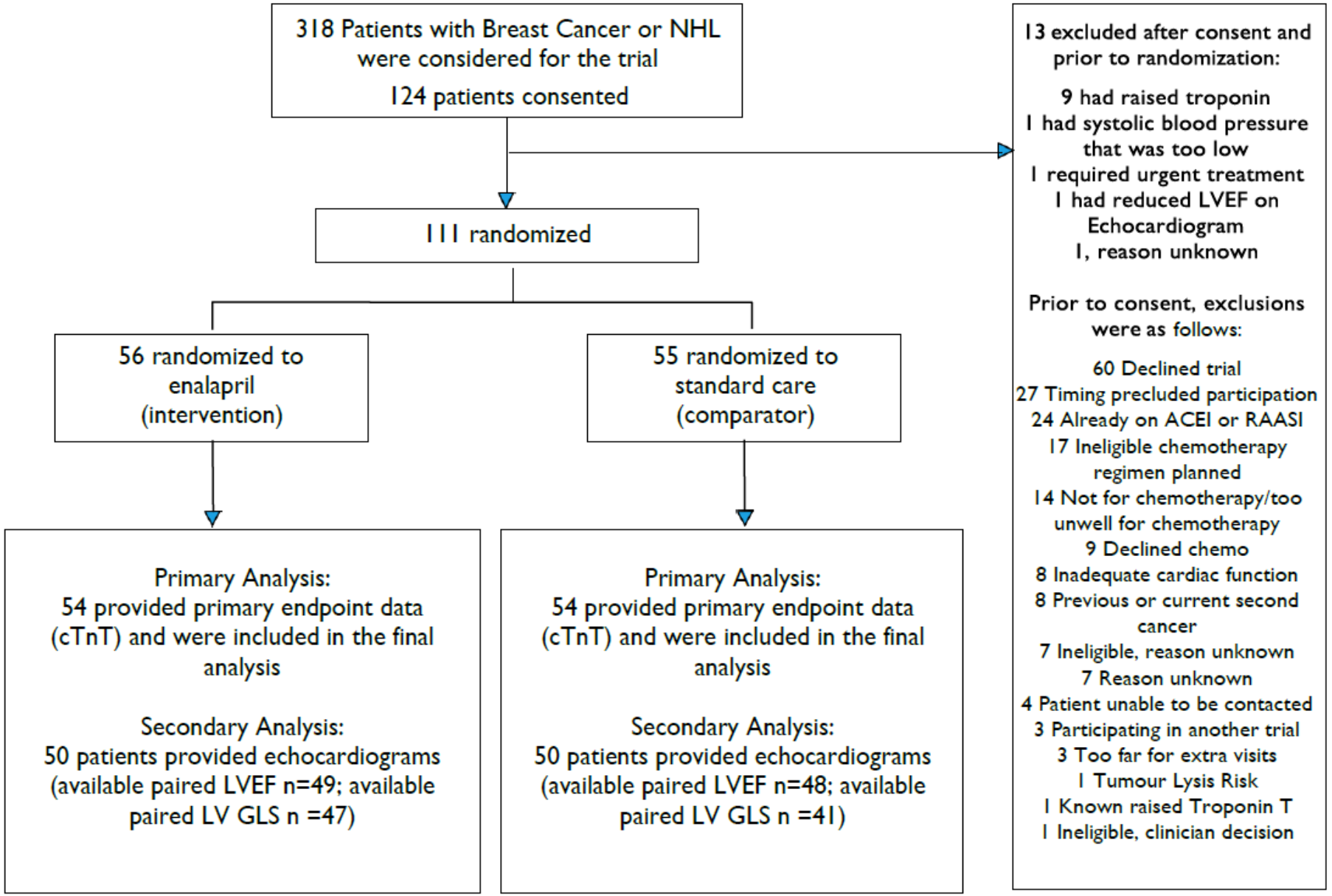
# Power calculation

- Based on pilot data (FEC 75) and consultation with oncology, cardiology and two patient groups
- Assumption that 47% of patients would exhibit myocardial injury
- For enalapril to be considered effective, the myocardial injury would be reduced to 20% of patients
- At **90%** power, **140** patients would be needed (plus attrition)
- Due to complex recruitment challenges, including COVID 19, the power was reduced to **80%**, and a **minimum of 106 patients** (plus attrition) was required with the same assumptions


Patients with breast cancer or NHL considered
Exclusions
Informed consent, baseline echocardiogram and troponin
Exclusions
Randomization to enalapril up to 10mg bd, or usual care 1:1
cTnT and cTnI , <72 hours before planned chemotherapy
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6
Final blinded hs troponin T and hs troponin I assessment
Echocardiogram

- North Tyneside General Hospital, Northumbria
- Freeman Hospital, Newcastle upon Tyne
- Sunderland Royal Hospital, Sunderland
- County Durham and Darlington
- University Hospital of North Tees, Stockton
- The James Cook University Hospital, Middlesbrough
- Castle Hill Hospital, Hull
- Blackpool Victoria Hospital, Blackpool
- Clatterbridge Hospital, Liverpool
- Weston Park Hospital, Sheffield
- Royal Berkshire Hospital, Reading
- Kent and Canterbury Hospital, Canterbury
- Derriford Hospital, Plymouth

Recruitment: October 2017 to March 2023


318 Patients with Breast Cancer or NHL were considered for the trial
124 patients consented
111 randomized
56 randomized to enalapril (intervention)
55 randomized to standard care (comparator)
Primary Analysis:
54 provided primary endpoint data (cTnT) and were included in the final analysis
Secondary Analysis:
50 patients provided echocardiograms (available paired LVEF n=49; available paired LV GLS n =47)
Primary Analysis:
54 provided primary endpoint data (cTnT) and were included in the final analysis
Secondary Analysis:
50 patients provided echocardiograms (available paired LVEF n=48; available paired LV GLS n =41)
13 excluded after consent and prior to randomization:
9 had raised troponin
1 had systolic blood pressure that was too low
1 required urgent treatment
1 had reduced LVEF on Echocardiogram
1, reason unknown
Prior to consent, exclusions were as follows:
60 Declined trial
27 Timing precluded participation
24 Already on ACEI or RAASI
17 Ineligible chemotherapy regimen planned
14 Not for chemotherapy/too unwell for chemotherapy
9 Declined chemo
8 Inadequate cardiac function
8 Previous or current second cancer
7 Ineligible, reason unknown
7 Reason unknown
4 Patient unable to be contacted
3 Participating in another trial
3 Too far for extra visits
1 Tumour Lysis Risk
1 Known raised Troponin T
1 Ineligible, clinician decision

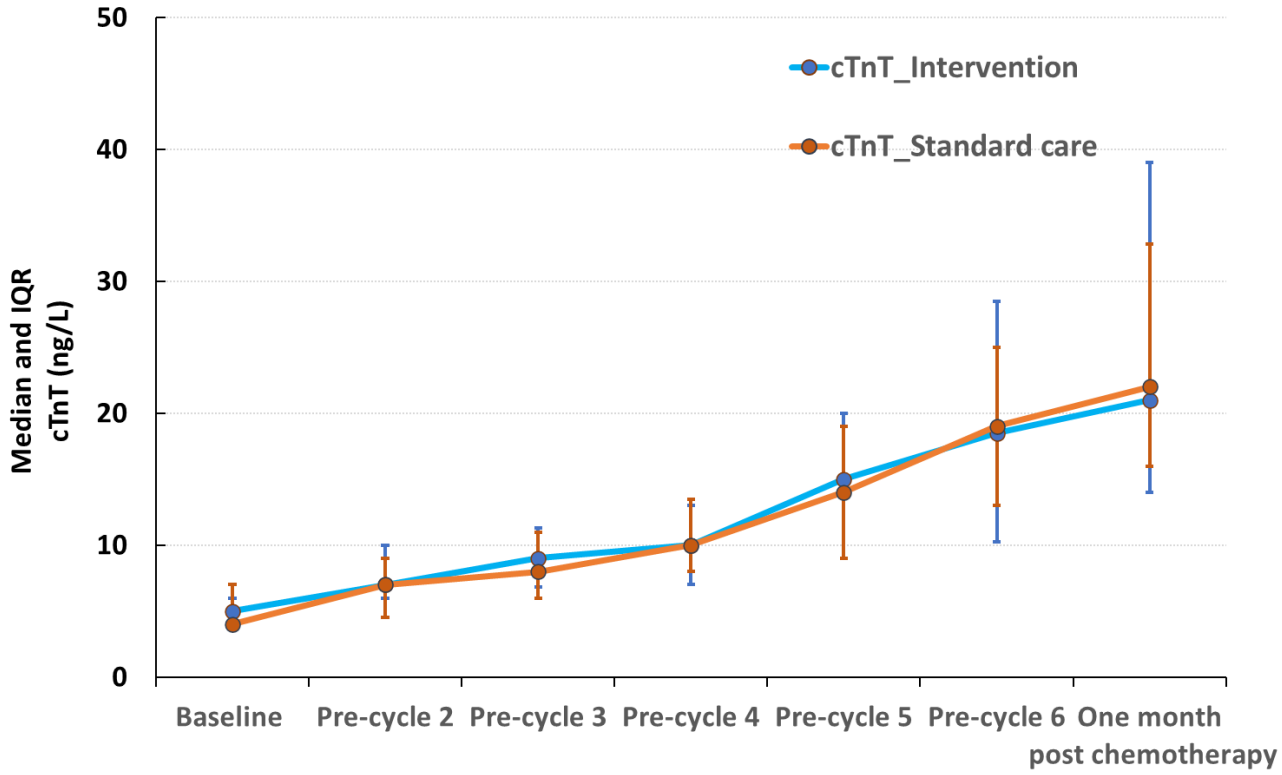
# Key findings

- Average age: 58 years old
- Predominantly white British, >75% female population
- Breast cancer 62% NHL 38%
- Chemotherapy regimens well balanced
- Received chemotherapy dose was **328mg/m² doxorubicin–equivalent**
- Enalapril titrated to 20mg in >75% of patients, **mean 17.7mg**

| Characteristics | | Enalapril (n = 56) | Standard care (n = 55) |
|---|---|---|---|
| **Demographic** | | | |
| **Age at randomization, mean (SD)** | | 58 (11) | 58 (12) |
| **Female, no. (%)** | | 45 (80.4) | 41 (74.5) |
| **Ethnicity** | White | 55 (98.2) | 52 (94.5) |
| | Non white | 1 (1.8) | 3 (5.5) |
| **Body Mass Index, mean (SD)** | | 28.3 (4.8) | 28.2 (5.5) |
| **Clinical history, no (%)** | | | |
| **Breast cancer** | | 35 (62.5) | 34 (61.8) |
| **Non-Hodgkin Lymphoma** | | 21 (37.5) | 21 (38.2) |
| **NYHA functional class** | | | |
| | I | 48 (85.7) | 48 (88.9) |
| | II | 8 (14.3) | 6 (11.1) |
| **ECOG performance status scale** | | | |
| | Grade 0 | 49 (87.5) | 48 (87.3) |
| | Grade 1 | 6 (10.7) | 7 (12.7) |
| | Grade 2 | 1 (1.8) | 0 (0.0) |
| **Coronary Heart Disease** | | 2 (3.6) | 2 (3.6) |
| **Diabetes** | | 5 (8.9) | 3 (5.5) |
| **Hypertension** | | 12 (21.4) | 5 (9.1) |
| **Current or ex-smoker** | | 29 (51.7) | 18 (32.7) |
| **Chemotherapy regimen, No (%)** | | | |
| | FEC75 | 8 (14.3) | 9 (16.4) |
| | EC90 | 27 (48.2) | 25 (45.5) |
| | (R-)CHOP | 21 (37.5) | 21 (38.2) |

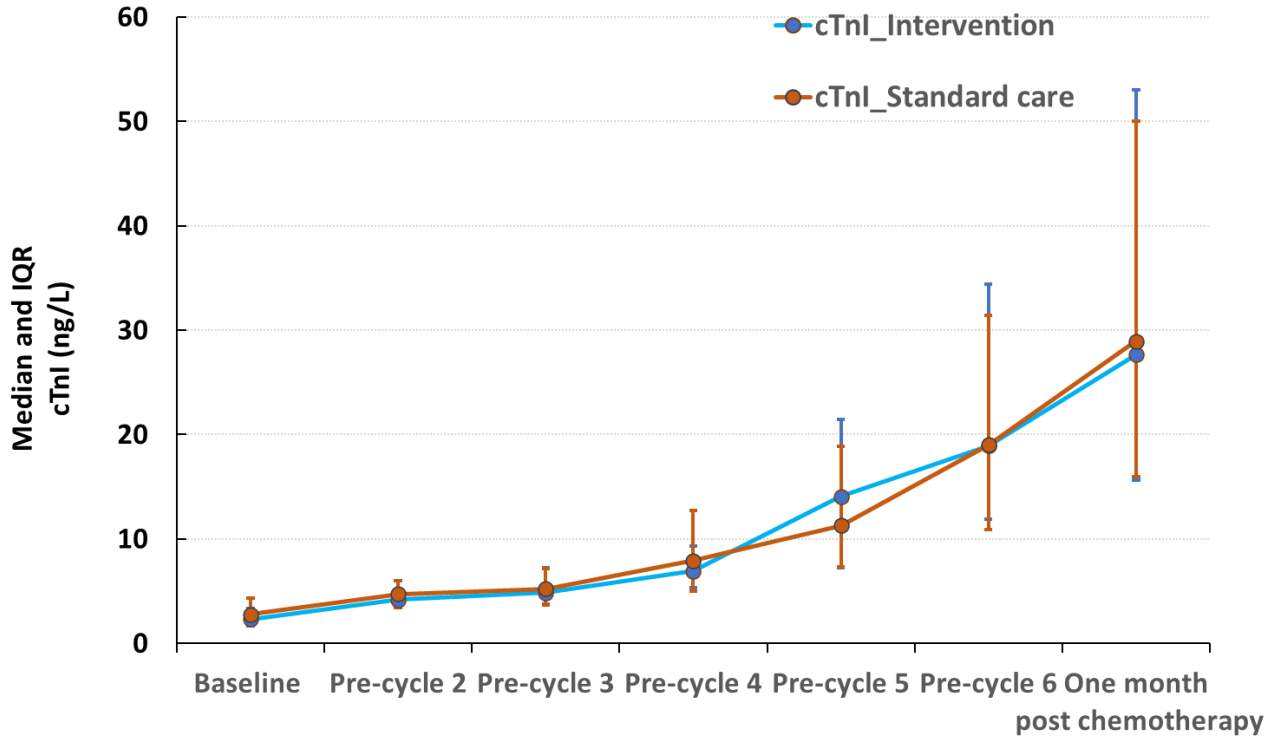
# Troponin T: primary endpoint

| Indicator | Groups | Total n/N (%) | Adjusted Odds Ratio (95% CI) | P value |
|---|---|---|---|---|
| cTnT | Enalapril | **42/54 (78)** | **0.65 (0.23-1.78)** | **0.405** |
| | Standard care | **45/54 (83)** | | |

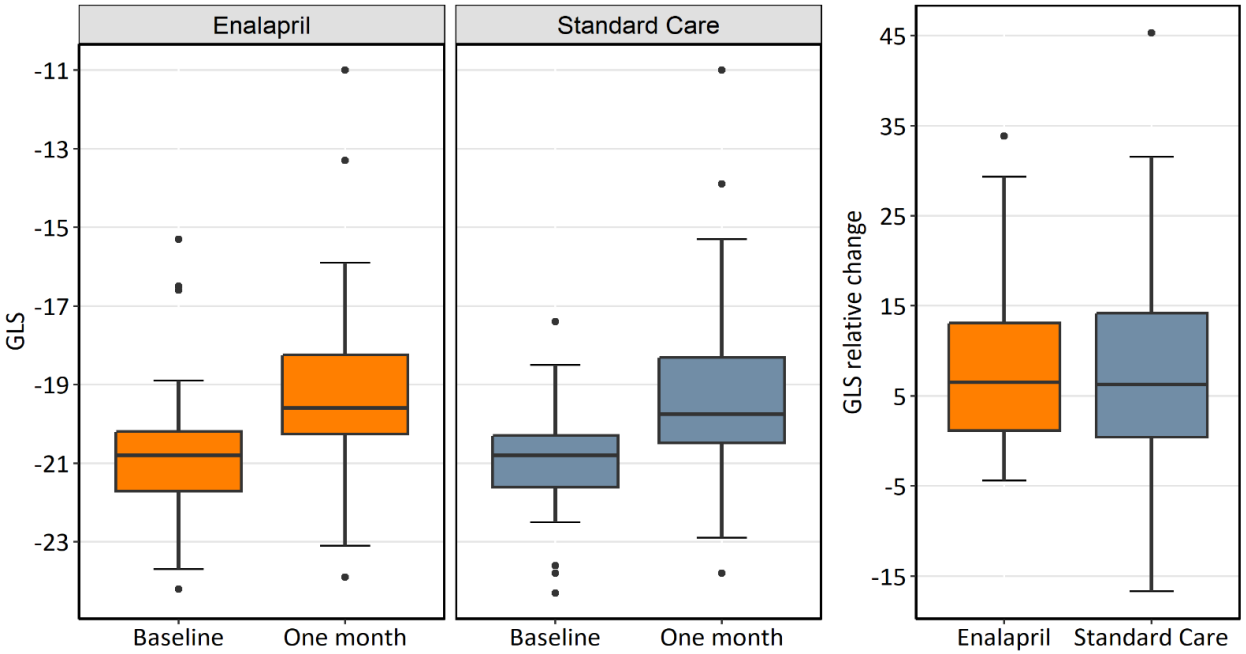


# Troponin I: secondary endpoint

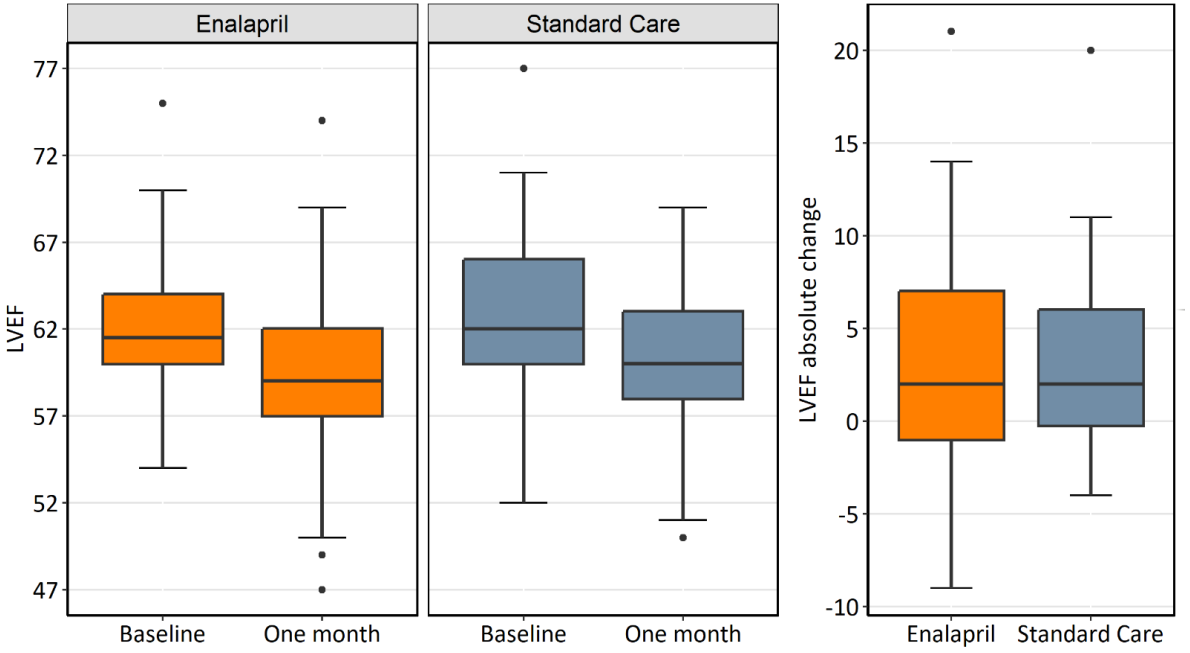
| Indicator | Groups | Total n/N (%) | Adjusted Odds Ratio (95% CI) | P value |
|---|---|---|---|---|
| cTnI | Enalapril | **25/53 (47)** | **1.10 (0.50-2.38)** | **0.819** |
| | Standard care | **24/53 (45)** | | |



# Cardiac function: LV GLS




# Cardiac function: LV EF




| Indicator | Groups | Total n/N (%) | Adjusted Odds Ratio (95% CI) | p |
|---|---|---|---|---|
| **LV GLS** | Enalapril | 10/47 (21) | 0.95 (0.33-2.74) | 0.921 |
| | Standard care | 9/41 (22) | | |

| Indicator | Groups | Total n/N (%) | Adjusted Odds Ratio (95% CI) | p |
|---|---|---|---|---|
| **LVEF** | Enalapril | 2/49 (4) | 4.89 (0.40-674.62 | 0.236 |
| | Standard care | 0/48 (0) | | |

# Key findings

- **81%** of patients had myocardial injury on cardiac troponin T criteria
- **46%** of patients had myocardial injury on cardiac troponin I criteria
- Cardiac troponin T and cardiac troponin I did not give equivalent results

- **21%** had a >15% relative decrease in LV GLS
- **2%** had a >10% reduction in LV EF to <50%

- Enalapril did not affect myocardial injury or cardiac function outcomes

# Limitations

- Open label
- Challenging recruitment
  - Included NHL patients
  - Power 90% to 80% during COVID 19 pandemic
- Echocardiographic assessment at an early post chemotherapy stage – further clinical and echo follow up is on going

# Conclusion

Adding enalapril to standard care was not superior to standard care alone in the prevention of cardiotoxicity in patients receiving high-dose anthracycline based chemotherapy

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Cardiovascular Unit

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- Core lab teams

- Trial Steering Committee
  - Chairs:

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    Dr Colette Jackson
- Independent Data Monitoring Committee
  - Chair: Dr Alex Lyon
- Sponsor: South Tees NHS Foundation Trust

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