REVIEW

# The Role of Cardiac Biomarkers in Early Detection of Cardiotoxicity in Breast Cancer Treated with Trastuzumab in the Adjuvant Setting: A Systematic Review

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## Abstract:

Trastuzumab, a humanized monoclonal antibody against the extracellular domain of human epidermal growth factor receptor 2 (HER-2) prolongs disease-free survival (DFS) and overall survival (OS) in patients with early-stage breast cancer (BC). Although it is generally well tolerated, it has been associated with cardiotoxicity, mainly manifest as a reduction of left-ventricular ejection fraction (LVEF), especially if the patient has received anthracyclines.

It is generally known that a drop in LVEF has limited diagnostic ability. Therefore, the identification of serum biomarkers of cardiotoxicity, able to detect damage at an earlier phase, has become ideal.

Troponins (conventional and high-sensitive), natriuretic peptides, reactive C protein (CRP), myeloperoxidase (MPO), etc are molecular markers which have been assessed to determine their role in the detection of treatment induced cardiotoxicity (CTIC) with controversial results.

Objective: This systematic review will synthesize available evidence assessing the role of different serum biomarkers in early prediction of cardiotoxicity in BC patients treated with adjuvant trastuzumab.

Methods/Design: A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Distinct scientific databases such as Google Scholar, Pubmed, EBSCOhost, and PsycINFO were searched to aid in the investigation of the research problem.

Randomized clinical trials (RCT) and observational studies of patients with early BC receiving adjuvant trastuzumab were eligible for inclusion. Two investigators have independently evaluated those studies and used standardized data extraction templates to collect data on the study and patients' characteristics.

Results: Eleven articles were selected, one RCT and ten observational studies. The most studied biomarker was N-terminal-pro-brain natriuretic peptide (NT-proBNP) followed by troponins. Findings showed that NT-proBNP was not predictive of CTIC while conflictive results were seen with troponins.

One study showed a predictive role of high-sensitive (hs) CRP and another found a relationship with the levels of MPO.

Conclusion: Biomarkers offer a unique potential to improve the effectiveness and safety of trastuzumab through timely detection of CTIC and prompt initiation of appropriate treatment. Troponins I and T have shown a predictive role in early detection of CTIC but further research would be needed to enable more insight and improve the overall patient outcome

## Introduction

Breast cancer (BC) is the most frequent cancer in women. Significant improvements in its detection and treatment have led to improvements in disease free survival (DFS) and overall survival (OS) (1). However, reduction in cardiac function during treatment with drugs such as anthracyclines and trastuzumab prompt treatment interruptions placing patients at higher risks of recurrence (1). Although the BC International Group (BCIRG 006) trial showed a tendency to better DFS with a regimen containing anthracyclines and trastuzumab in Her-2 positive BC, when compared to a regimen without anthracyclines, this was not statistically significant and it came with a higher risk of cardiotoxicity. The group treated with anthracyclines and trastuzumab, had five times as many cases of congestive heart failure (CHF) as the group without anthracyclines (2% versus 0.4%) and this was statistically significant (2).

Anthracyclines and trastuzumab may independently produce cardiomyopathy. Moreover, the use of sequential trastuzumab may interfere with the repair of anthracyclines cardiac damage. As such, concurrent or sequential treatment with anthracyclines and trastuzumab have higher risks of cardiac issues (3). Nevertheless, the American Society for Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines recommend the use of sequential treatment, with anthracyclines followed by trastuzumab in high risk BC patients (4-6)

Therefore, early detection of cardiotoxicity may be a useful strategy by enabling early initiation of cardioprotective measures including medications. Currently, the standard method for detection of cardiotoxicity have involved serial determination of LVEF. But this is a parameter that when reduced is late evidence of myocardial damage, reducing the possibility of recovery(7).

It is in this area of need that cardiac biomarkers have shown potential in the detection of early treatment induced cardiotoxicity (CTIC) (8,9).

Several studies have suggested that elevations in conventional troponins (cTns) are frequent in patients who received anthracyclines and/or trastuzumab and that these elevations predict the development of CTIC. However, the results have been inconsistent between studies mainly due to different study designs and the lack of standardized reference ranges (8,9).

Nonetheless, recent ESMO guidelines recommend their use for high-risk patients and those receiving high doses of cardiotoxic treatments such as anthracyclines(10).

There are many studies of cardiac biomarkers in patients receiving antineoplastic therapies in a range of settings, mostly that of advanced disease. However, not many studies have focused solely on adjuvant treatment for patients with Her-2 positive BC. Therefore, this systematic review has been undertaken to identify the utility of the most used serum biomarkers to detect CTIC in patients receiving adjuvant sequential therapy with anthracyclines and trastuzumab.

## Material and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11).

This study was performed in accordance with an established protocol.

### Eligibility and exclusion criteria

We included randomised and non-randomised studies carried out in patients with early Her-2 positive BC, who received adjuvant trastuzumab and contained serial measurements of cardiac biomarkers and serial LVEF monitoring by echocardiograms.

Studies were ineligible if those included metastatic or advanced cases or any patients whose trastuzumab was used as neoadjuvant, case reports, articles presented only as an abstract and not fully published, regimens containing other targeting drugs in addition to trastuzumab.

### Literature search strategy

A systematic literature review was conducted to identify studies published between 2010 and 2019. Bibliographic searches were carried out on databases of Google Scholar, Pubmed, MEDLINE, Trip Medical, EMBASE/EBSCOhost, CINAHL, ClinicalKey, BMJ Journals, Cochrane Library and PsycINFO using the following terms: BC, early BC, breast neoplasms, Her-2 positive, cardiac biomarkers, biomarkers, cardiac dysfunction, cardiac event, early detection.

To obtain the required outcome comprehensively, a series of keywords combinations was used as well: {role/use of + cardiac biomarkers + early detection of cardiotoxicity + early BC HER- 2 positive + treatment with trastuzumab}.

Article selection was based on the examination of cardiac biomarkers used to predict/detect early cardiotoxicity during the administration of adjuvant trastuzumab.

## Selection of studies

Initially a thorough search was carried out with the help of Sian Hudson, Bournemouth, UK: East Dorset Library and Knowledge Service. Two authors independently screened all the retrieved articles for eligibility through the examination of the title and abstracts to determine relevance with the subject. All duplicates were removed as well as editorials, commentaries and reviews or articles referring to cancers other than breast or referring to cases where the aim of the treatment was not adjuvant.

The full text of potentially eligible articles was assessed again by two different authors independently. In case of disagreement, the final decision was made by discussion and consensus.

All excluded articles were recorded and reasons for exclusion explained.

## Data extraction

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Data extraction was also made by the same two authors independently and the following data were collected from each article: (a) study characteristics (year, country of publication, study design, sample size, type of biomarkers measured, definition of cardiac event); (b) characteristics of the study population (age, previous anthracyclines exposure, other cardiac risk factors present at baseline); (c) the evolution of the different biomarkers in the whole population and the differences in both populations, those who developed cardiotoxicity and those that did not.

Outcome extraction included the relationship between the increase in biomarkers and the development of trastuzumab-related cardiac dysfunction defined as a significant reduction in LVEF.

## Quality assessment

The quality of the studies was assessed using the already published Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses and the Cochrane collaboration modified tool for assessing risk of bias for RCTs (12,13).

Quality appraisal was performed by two researchers and the disagreements resolved through consensus. Studies were classified as good, fair or poor (13).

## Results

### Search results

The systematic review process yielded 1572 Studies that seemed relevant to this review. Seventy-six additional records were also identified.

The selected articles were then analysed for any duplicates, leading to the removal of 1357 articles. The remaining articles were screened to eliminate the ones that had no conformity to the topic, publication issues, lack of proper participant selection, and design issues. The screening process led to the elimination of 173 articles (Figure 1).

142 articles then underwent eligibility test to examine it they met the inclusion and exclusion criteria and an additional 131 were eliminated. Thus, only 11 articles met the threshold set for the systematic review, one randomized clinical trial (RCT) and 10 prospective observational studies.
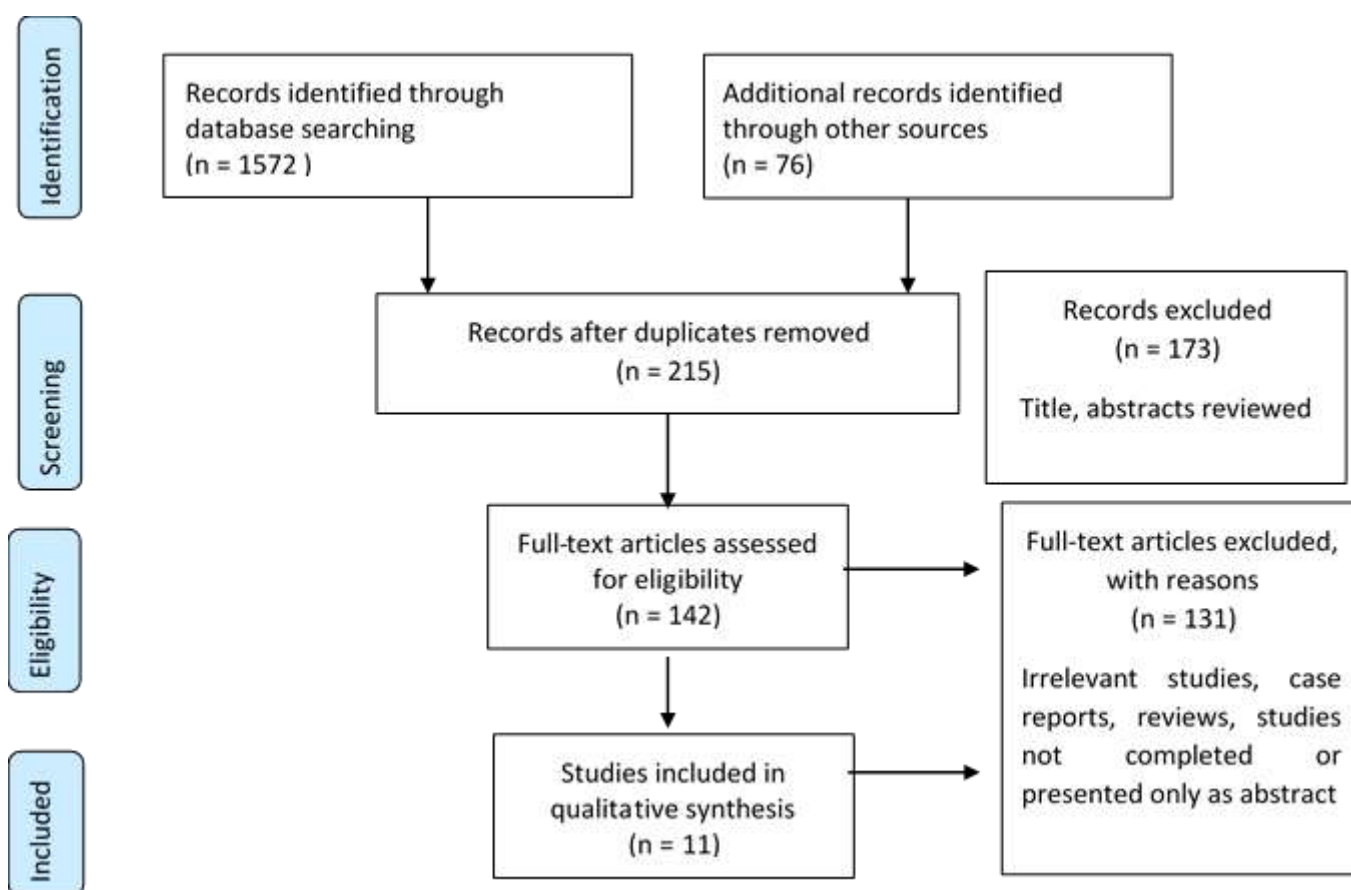


Figure 1: Flowchart of Publications Selection Process

*Quality assessment*

This was carried out as described in the methods section. All the studies included were categorised as good based on the Newcastle-Ottawa-Scale scores for the quality assessment of including studies (Table 1).

Table 1: Quality assessment of the studies included

| Studies included | Selection | Comparability | Outcome | Total of stars | Quality Rate |
|---|---|---|---|---|---|
| Fallah-Rad et al 2011 | *** | * | *** | 7 | Good |
| Sawaya et al 2011 | *** | * | ** | 6 | Good |
| Sawaya et al 2012 | *** | * | ** | 6 | Good |
| Onitilo et al 2012 | *** | * | ** | 6 | Good |
| Katsurada et al 2014 | *** | * | *** | 7 | Good |
| Ky et al 2014 | *** | * | ** | 6 | Good |
| Putt et al 2015 | *** | * | ** | 6 | Good |
| Zardavas et al 2017 | **** | * | *** | 8 | Good |
| El-Sherbeny et al 2018 | *** | * | *** | 7 | Good |
| Matos et al 2016 | *** | * | *** | 7 | Good |
| Goel et al 2019 | *** | * | ** | 6 | Good |

Newcastle-Ottawa-Scale scores for the quality assessment of including studies.

*Studies and patients' characteristics*

Studies and patients' characteristics are included on Table 2. The majority of the studies included are observational studies with only one RCT.

The studies were carried out in different countries with most of them being multicentre. All were prospective in design.

The median follow-up period ranged from 6 to 15months. The number of participating women with early BC HER-2 positive in each study varied from 20 to 533 with a total number of women included of 1212 patients. The total population age range was from 24 to 77 years, although El-Sherbeny et al only included patients from 30 to 60 years.

1117 patients had received anthracyclines before trastuzumab (92.16%) and 205 developed CTIC (16.91%).

*Cardiac risk factors*

Not all the studies included reported cardiac risk factors. Hypertension was not reported in one study, likewise for Diabetes Mellitus (DM) and hyperlipidemia.

Smoking was not reported in 3 of the studies and the presence of coronary artery disease (CAD) was not included in 7 of the studies.

These data are summarised in table 3.

Table 2: Characteristics of the included studies

| Study | Study design | Country | Evaluables pts /total | Treatment | Biomarkers assessed | Age (mean/SD; median /range) | Definition CTIC | Centres |
|---|---|---|---|---|---|---|---|---|
| Fallah-Rad et al 2011 | O | Canada | 42/42 | 88% FEC 12% AC All P+H3w | TnT CRP NT-proBNP | 47+/-9 | Decline LVEF ≥10% to below 55% + signs/symptoms CHF | S |
| Sawaya et al 2011 | O | US | 43/45 | 86% A 8.8% E 95% Tax All H | hsTnI NT-proBNP | 49*+/-10 | CREC | M |
| Sawaya et al 2012 | O | US | 81/81 | 88% A 12% E All P+H | usTnI NT-proBNP ST2 | 50+/-10 | CREC | M |
| Onitilo et al 2012 | O | United Kingdom | 49/54 | 44% A 85% Tax All H | BNP hsCRP TnI | 54.9* | Decline LVEF ≥15% from baseline or to <50% | S |
| Katsurada et al 2014 | O | Japan | 19/20 | AC or FEC → P+H | hsTnT hsTnI NT-proBNP hsCRP | 49*+/-9 | CREC | S |
| Ky et al 2014 | O | US | 78/78 | AC→P+ H3w | usTnI NT-proBNP CRP others | 50 (42-56.8) | CREC | M |
| Putt et al 2015 | O | US | 78/78 | A → P+H | hsTNI NT-proBNP MPO and others | 49+/-10 | CREC | M |
| Zardavas et al 2017 | RCT | Europe, Australia, Brazil, US | 452/533 | Anthra 66.2% Anthra+ P 27.9% All H | TnI TnT NT-proBNP | 51(24-74) | Symptomatic CHF + significant decline LVEF (NYHA III, IV) Decline LVEF asymptomatic or mildly symptomatic (NYHA I, II) Analysis only for secondary end-point | M |
| El-Sherbeny et al 2018 | O | US | 61/61 | AC → P+Hw | NT-proBNP | 47.4+/-9.1 | Decline LVEF ≥10% to below 55% with/ without signs/symptoms of CHF | S |
| Matos et al 2016 | O | Slovenia | 92/93 | 10.9% A 39.1% E 89% P All H 3w | NT-proBNP | Mean 53.6 (35-75) | Clinical signs/symptom CHF or a decline in | S |

| | | | | | | | LVEF ≥10% if no symptoms | |
|---|---|---|---|---|---|---|---|---|
| Goel et al 2019 | O | US, Australia | 217/222 | 37% AC 63% E All P+H (85% 3w; 15% w) | TnT NT-proBNP | Median52 (28–77) | NYHA class III or IV CHF or asymptomatic decrease LVEF >15% or symptomatic decrease LVEF >10% to absolute value <50%. | M |

O – observational study, A – doxorubicin, E – epirubicin, AC – doxorubicin/cyclophosphamide, P – paclitaxel, H – Trastuzumab, Tax – taxanes (either docetaxel or P), anthra – anthracyclines (either A or E), FEC – fluorouracil/E/cyclophosphamide), w – weekly, 3w – 3 weekly, S – single centre; M – multicenter, CREC - Cardiac Review and Evaluation Committee, NYHA – New York Heart Association

Table 3: Patients cardiovascular risk factors

| Studies | Evaluables pts | Hypertension | DM | Hyperlipidemia | Smoking | Family history of CAD | Impact on CTIC |
|---|---|---|---|---|---|---|---|
| Fallah-Rad et al 2011 | 42 | 5 | 6 | 15 | 4 | 7 | NS |
| Sawaya et al 2011 | 43 | 12 | 8 | 1 | 6 | NR | NS |
| Sawaya et al 2012 | 81 | 26 | 1 | 18 | 6 | NR | NS |
| Onitilo et al 2012 | 49 | 17 | 6 | 17 | 31 | 5 | |
| Katsurada et al 2014 | 19 | 2 | 0 | 4 | 6 | 1 | |
| Ky et al 2014 | 78 | 21 | 1 | 18 | NR | NR | |
| Putt et al 2015 | 78 | 21 | 1 | 18 | NR | NR | |
| Zardavas et al 2017 | 452 | NR | NR | NR | 48 | NR | |
| El-Sherbeny et al 2018 | 61 | 22 | 7 | 15 | 5 | NR | |
| Matos et al 2016 | 92 | 27 | 4 | 9 | NR | NR | |
| Goel et al 2019 | 217 | 40 | 11 | 35 | 86 | 46 | |

Table 4: Studies according to biomarker

| Biomarker | Number of studies | Number of patients |
|---|---|---|
| NT-proBNP | 10 | 1163 |
| TnT | 3 | 711 |
| TnI | 2 | 501 |
| hsTnT | 1 | 19 |
| hsTnI | 3 | 140 |
| usTnI | 2 | 159 |
| CRP | 2 | 120 |
| BNP | 1 | 49 |
| hsCRP | 2 | 68 |

All the studies assessed biomarkers serially before initiation of trastuzumab and generally every three months while on treatment (Table 5 and 6).

Table 5: Determination of biomarkers timing

| Study | Before chemotherapy | Completion of anthra (at 3m)/before Trastuzumab | Every 3 months | Total period |
|---|---|---|---|---|
| Fallah-Rad et al 2011 | X | X | X | 12m |
| Sawaya et al 2011 | X | X | At 6m | 6m |
| Sawaya et al 2012 | X | X | X | 15m |
| Onitilo et al 2012 | X (in 24) | X | 3 weeks | 12m |
| Katsurada et al 2014 | X | X | X | 15m |
| Ky et al 2014 | X | X | X | 15m |
| Putt et al 2015 | X | X | X | 15m |
| Matos et al 2016 | No | X | 4, 8, 12 | 12m |
| Zardavas et al 2017 | no | X | 3, 6, 12, 18, 24, 30, 36m | |
| El-Sherbeny et al 2018 | X | X | X | 15m |
| Goel et al 2019 | X | X | No further analyses included | 12m |

X – done, anthra – anthracyclines (either A or E)

Table 6: Studies and results

| Studies | CTIC per study definition | Biomarker results | Biomarker predictive | Positive study |
|---|---|---|---|---|
| Fallah-Rad et al 2011 | 10/42 (24%) | No changes | _ | No |
| Sawaya et al 2011 | 9/43 (21%) | Elevation of hsTnI after AC predictive of CTIC | hsTnI | Yes |
| Sawaya et al 2012 | 26/81 /(32%) | Elevated usTnI after AC predictive if combined with peak systolic longitudinal myocardial strain | usTnI | Yes |
| Onitilo et al 2012 | 14/49 (28.6%) | hsCRP predictive | hsCRP | Yes |
| Katsurada et al 2014 | 9/19 (47.36%) | hs-TnT at 3 and 6m predictive | hsTnT | Yes |
| Ky et al 2014 | 23/78 (24%) | Elevation usTnI at 3m associated with CTIC | usTnI | Yes |
| Putt et al 2015 | 23/78 (29%) | MPO associated with CTIC | MPO | Yes |
| Zardavas et al 2017 | 33/452 (7.3%) | TnT and TnI predict CTIC | TnT, TnI | Yes |
| El-Sherbeny et al 2018 | 18/61 (29.5%) | NT-proBNP did not predict | _ | No |
| Matos et al 2016 | 22 (23.9%) | NT-proBNP did not predict | _ | No |
| Goel et al 2019 | 18 (8.3%) | Biomarkers did not predict | _ | No |

## *CTIC: definitions used*

The definitions of CTIC are heterogeneous and those are included in table 7. All the studies used at least echocardiography as a tool to serially evaluate LVEF.

Five studies used the CREC (Cardiac Review and Evaluation Committee) definition for the end point.

The majority of the studies considered a significant decline of LVEF as a reduction of ≥10% to < 55% or <50% regardless of symptoms/signs of CHF.

Table 7: CTIC definitions

| Author/year publication | Cardiopathy as per study definition | Definition CTIC | Reduction of LVEF | Symptoms/Signs of CHF | N symptoms/signs |
|---|---|---|---|---|---|
| Fallah-Rad et al 2011 | 10/42 (24%) | Decline LVEF ≥10% to below 55% + signs/symptoms CHF | ≥10% to < 55% | Yes | 10 |
| Sawaya et al 2011 | 9/43 (21%) | CREC | ≥ 5% to < 55% | Yes | 9 |
|  |  |  | ≥10% to < 55% | No |  |
| Sawaya et al 2012 | 26/81 /(32%) | CREC | ≥ 5% to < 55% | Yes | 26 |
|  |  |  | ≥10% to < 55% | No |  |
| Onitilo et al 2012 | 14/49 (28.6%) | Decline LVEF ≥15% from baseline or to <50% | ≥15 Or to < 50% | not needed | 14 |
| Katsurada et al 2014 | 9/19 (47.36%) | CREC | ≥ 5% to < 55% | Yes | 9 |
|  |  |  | ≥10% to < 55% | No |  |
| Ky et al 2014 | 23/78 (24%) | CREC | ≥ 5% to < 55% | Yes | 23 |
|  |  |  | ≥10% to < 55% | No |  |
| Putt et al 2015 | 23/78 (29%) | CREC | ≥ 5% to < 55% | Yes | 23 |
|  |  |  | ≥10% to < 55% | No |  |
|  |  |  | Def alternative ≥10% to < 50% | No |  |
| Zardavas et al 2017 | 33/452 (7.3%) | Symptomatic CHF + significant decline LVEF (NYHA III, IV) Decline LVEF asymptomatic or mildly symptomatic (NYHA I, II) Analysis only for secondary end-point | regardless | Yes | 3 |
|  |  |  | ≥10% to < 50% | No/mild | 30 |
| El-Sherbeny et al 2018 | 18/61 (29.5%) | Decline LVEF ≥10% to below 55% with/ without signs/symptoms of CHF |  | not needed | 18 |
| Matos et al 2016 | 22/92 (23.9%) | Clinical signs/symptom CHF or a decline in LVEF ≥10% if no symptoms | regardless | Yes | 0 |
|  |  |  | ≥10% | No | 22 |
| Goel et al 2019 | 18/217 (8.3%) | NYHA class III or IV CHF or asymptomatic decrease LVEF >15% or symptomatic decrease LVEF >10% to absolute value <50%. | regardless | Yes | 18 |
|  |  |  | >15% | No |  |
|  |  |  | >10% to <50% | No |  |

CREC – Cardiac Review and Evaluation Committee, NYHA – New York Heart Association

Five of the studies included in this systematic review defined CTIC following the CREC as a reduction in LVEF of ≥10% to < 55% without symptoms of heart failure (CHF) or a decline of LVEF ≥ 5% to < 55% with symptoms/signs of CHF.

Other studies considered a reduction in LVEF of 10% to ≥15 or any reduction <50% with or without symptoms/signs of CHF or patients showing symptoms or signs of CHF regardless the LVEF.

### Incidence of CTIC

The overall incidence of cardiotoxicity was 12.0% with 95% confidence interval (CI) of 11.3% to 12.9%. A total of 205 patients (out of 1212 patients) experienced CTIC; unfortunately, only a few studies reported how many patients developed symptoms/signs of CHF or how many were asymptomatic (i.e., a decline in LVEF without any signs or symptoms of CHF).

None of the patients died due to cardiac toxicities associated to trastuzumab (follow up period 3-15 months).

### Biomarkers determinations

Again, we can see a significant heterogeneity in terms of the threshold values for abnormality in different studies as shown in tables 8 and 9 and also in the assays used to make the determinations.

Table 8: Determination of biomarkers

| Author/year publication | Biomarker determination |
| --- | --- |
| Fallah-Rad et al 2011 | TnT levels - third-generation Roche Elecsys assay (Roche Diagnostics, Inc., Indianapolis, Indiana). CRP levels - Immage 800 (Beckman Coulter, Brea, California) antigen-antibody precipitant rate reaction. NTpro-BNP levels - electrochemiluminescence sandwich immunoassay (Elecsys ProBNP, Roche Diagnostics) Roche 2010 system. |
| Sawaya et al 2011 | Dimension Vista 500 Intelligent Laboratory System (Siemens Healthcare Diagnostics, Deerfield, Illinois), using a 1-step, homogenous, sandwich chemiluminescent immunoassay based on LOCI technology (Siemens Healthcare Diagnostics, Deerfield, Illinois). |
| Sawaya et al 2012 | Troponin I - research-phase highly sensitive assay based on LOCI technology and run on a Dimension Vista 1500 System (Siemens Healthcare Diagnostics, Deerfield, IL). NT-proBNP - Dimension Vista 500 Intelligent Laboratory System (Siemens Healthcare Diagnostics). ST2 - research use only assay (Presage ST2, Critical Diagnostics, San Diego, CA) on an automated enzyme linked–immunosorbent assay platform. |
| Onitilo et al 2012 | BNP - Triage_ BNP Test (Inverness Medical, Princeton, NJ) hs-CRP - latex-enhanced nephelometry TnI Dimension Vista assay (Siemens Healthcare Diagnostics, Deerfield, IL) |
| Katsurada et al 2014 | hs-TnT, hs-CRP and NTproBNP – electrochemiluminescence immunoassay, latex-enhanced nephelometry, and an electrochemiluminescence sandwich immunoassay (Roche Diagnostics, Mannheim, Germany). hs-TnI - chemiluminescence sandwich immunoassay according to the manufacturer's instructions (Siemens Medical Solution Diagnostics, Tarrytown NY, USA) |
| Ky et al 2014 | usTnI and NT-proBNP - Dimension Vista 500 Intelligent Laboratory System (Siemens Healthcare Diagnostics, Deerfield, Illinois) using a 1-step, homogeneous, sandwich chemiluminescent pre-commercial immunoassay on the basis of Loci technology. hsCRP - Architect immunoassay (Abbott Laboratories, Abbott Park, Illinois). |
| Putt et al 2015 | hs-TnI - research prototype assay NT-proBNP - Dimension Vista 500 Intelligent Laboratory System (Siemens Healthcare Diagnostics); hsCRP - Architect immunoassay (Abbott Laboratories) |
| Zardavas et al 2017 | TnI - ADVIA Centaur XP platform (Siemens Healthcare Diagnostics, Tarrytown, NY) using the cTnI Ultra (Tnl-Ultra) assay TnT – hsTnT - Elecsys platform (Roche Diagnostics, Manheim, Germany) Cobas E411 NT-proBNP - Elecsys NT-proBNP assay on the Elecsys platform. |
| El-Sherbeny et al 2018 | NT-proBNP levels - Human NT-proBNP, ELISA Kit Catalog No: E0485 h (EIAab Science Co.Ltd). |
| Matos et al 2016 | NT-proBNP - electrochemiluminescence immunoassay (ECLIA) on Cobas e411 analyser (Roche Diagnostics GmbH, Mannheim, Germany). |

## *CTIC and biomarkers*

Biomarkers evaluated covered different molecules: troponins (TnT, hsTnT, TnI, usTnI, hsTnI), CRP, BNP, NT-proBNP and MPO.

The most commonly studied biomarker was NT-proBNP followed by TnT.

### CRP, hsCRP

Four studies evaluated CRP and hsCRP with variable results again.

When CRP was measured, no changes were detected. However, when a more sensitive test was carried out (hsCRP), one of the studies showed this to be a predictive factor, while the other did not show any significance.

Ky et al 2014, only reported variations between baseline and visit 2 (both before trastuzumab starts), which unfortunately is not representative of CTIC but related to anthracyclines toxicity, which may have an impact on future CTIC.

Goel et al 2019, only assessed data as well from the first two visits making difficult to draw any conclusions as to the role of biomarkers in predicting CTIC.

Onitilo et al 2012, on the other hand, reported that hsCRP is predictive of CTIC.

### MPO

Finally, Putt et al 2015, were the only authors assessing this marker and they reported this to be associated with CTIC.

### NT-proBNP

Ten studies assessed NT-proBNP but none of them proved this to be a significant predictor of. Goel et al 2019 reported that although early changes in NT-proBNP levels were statistically linked to the development of CTIC, this association did not pass the multivariate analyses.

### TnI, usTnI, hsTnI

The TnI assays were highly variable. One study assessed conventional TnI while 2 studies measured usTnI and another two studies evaluated hsTnI.

Conventional TnI was found predictive of CTIC if an increase level was detected at 3 months or what it is the same, before trastuzumab (Zardavas et al, 2017).

When considering usTnI, Sawaya et al 2012 and Ky et al 2014 found that when elevated at the end of the anthracyclines (again before trastuzumab), this could predict CTIC.

When assessing hsTnI, Sawaya et al 2011 showed that an elevation before trastuzumab is related to the development of CTIC at 6 months.

### TnT, hsTnT

Three studies assessed the conventional form of TnT whereas one evaluated hsTnT.

These found variable results. Zardavas et al 2017 concluded that the conventional TnT will predict TIC if elevated before trastuzumab.

In contrast, Fallah-Rad et al 2011, did not find any significant relationship, same to Goel et al 2019.

Katsurada et al 2014 who assessed hsTnT reported a predictive role when elevated at 3 and at 6 months.

Table 9: Biomarkers threshold for abnormality

| Studies | TnT | hsTnT | TnI | BNP | hsCRP | CRP | NT-proBNP | hsTnI | usTnI |
|---|---|---|---|---|---|---|---|---|---|
| Fallah-Rad et al 2011 | ≥0.01 g/l | | | | | ≥8 mg/l | ≥35pmol/l | | |
| Zardavas et al 2017 | 14 ng/L | | 40ng/L | | | | ? | | |
| Goel et al 2019 | ≥3 ng/l. | | | | | | ? | | |
| Katsurada et al 2014 | | ≥14pg/mL | | | ? | | ? | ≥40pg/mL | |
| Onitilo et al 2012 | | | 0.1ng/mL | 200pg/mL | 3 mg/L | | | | |
| Sawaya et al 2011 | | | | | | | ≥125pg/ml. | >0.015μg/L | |
| Ky et al 2014 | | | | | | ? | ? | | ? |
| Sawaya et al 2012 | | | | | | | >125pg/mL | | >30 pg/mL |
| Putt et al 2015 | | | | | | | ? | 3 ng/L | |
| El-Sherbeny et al | | | | | | | ? | | |
| Matos et al 2016 | | | | | | | ? | | |

## *Discussion*

Researchers have long endeavoured  to identify a reliable biomarker(s) predictive of CTIC. Many studies have assessed  changes in biomarker levels after being exposed to cancer treatment, aiming at exploring whether those changes could identify patients at high risk of CTIC or detect early CTIC.

Reductions in cardiac function can lead to treatment delays and interruptions in the short term, and mortality in the long term, especially in patients with other cardiovascular risk factors (1).

Cardio-specific biomarkers are proteins released into the bloodstream by injury to heart cells. Conventional Tn and natriuretic peptides (BNP, NT-proBNP) are the most widely studied within this group.

Cardiac Tn are released after cardiomyocyte damage induced by different mechanisms such as ischemia, oxidative stress  caused by anthracyclines, inflammation or apoptosis. (1,2)

Anthracyclines' induced CTIC has been reported in up to  6% of cases as being clinically relevant and in a further 18% of subclinical CTIC. This is dose dependent with higher severity  with higher doses. (14)

In addition, anthracyclines have a synergistic effect with radiation and trastuzumab in terms of CTIC(15).

This systematic review  focuses only on those cases of adjuvant sequential treatment with anthracyclines and trastuzumab.

There are two different patterns of CTIC linked to trastuzumab depending on the timing of anthracyclines administration. In patients receiving only trastuzumab, CTIC is not dose dependent and is reversible with cardioprotection therapy and stopping trastuzumab.  After cardiac recovery, a re-challenge is generally well tolerated(16).

However, in patients treated concurrently with anthracyclines or sequentially after, CTIC and symptomatic CHF can appear in 28% and 27% of patients, respectively (17,18).

The risk of CTIC reduces with longer intervals between both treatments, with an incidence of 4.3% with intervals longer than 90 days (19).

In this scenario the use of biomarkers able to evidence subclinical CTIC would be of extreme importance, not only because it will allow physicians to promptly initiate cardiac treatment but also to make the more informed decisions about treatment duration.

Tn are the best characterised biomarkers to assess anthracycline's induced cardiotoxicity. There are two Tn biomarkers, TnT and TnI and two different assays to check them, the old assays and the modern high-sensitive assays (20).

The prediction of CTIC seems to be less accurate with cTnT (21) compared with cTnI.

TnI is elevated in 14% of patients treated with trastuzumab monotherapy ,in around 33% by anthracyclines (although this proportion increased with the cumulative dosage) and the combination of anthracyclines and trastuzumab produce elevations in 21-24% of patients (22-26).

In those patients with elevation of TnI, the pattern of release is associated with the risk of LV dysfunction (22,23).

As such, early elevations after the anthracycline administration (27) and persistent high figures after completing anthracyclines are predictive of CTIC (28).

These two findings  were demonstrated by ¬¬¬¬Sawaya et al  in two different studies in patients receiving sequential anthracyclines and trastuzumab. Those who showed persistent elevation of cTnI/usTnI at the completion of anthracyclines and at 3 months, had higher chances of developing CTIC (24,26).

Baseline levels, on the contrary, do not seem to serve as  predictors. However, Kitayama et al reported that for hs-cTn baseline values along with levels throughout treatment should be collected to gain reliability. These authors found that an hs-TnT increase from baseline to the highest value was significantly greater  in patients with CTIC and the integration value had 100% sensitivity and specificity with a cut-off at 0.070 ng months/mL (29).

Some authors went even further and showed that cTnI elevations were associated with persistent LVEF reductions while normal levels were linked with a transient decline at 3 months and complete recovery at 7 months (22).

Indeed, Cardinale et al showed that recovery of LVEF in patients receiving trastuzumab, was more frequent in those patients who had normal TnI levels than in those with elevated figures (100 vs 35%).¬

In line with these findings, the absence of detectable cTnI early and one month after anthracyclines meant low risk of CTIC (1%) (23) and Cardinale et al have suggested the same predictive role for the elevation of cTnI for those receiving trastuzumab, (30) indicating that this biomarker might be relevant at the time of stratifying patient's risk.

Asub study of the HERA trial found that the elevation of cTnI and cTnT at the end of anthracyclines predicts CTIC as expected, but the contribution of sequential trastuzumab on this risk remained unclear (31). However, it appears that anthracyclines might increase the myocardial susceptibility to injury when combined with trastuzumab (32,33).

Recent studies confirmed that by using high-sensitivity assays, cTn elevations are even more frequent. However, the link between serial changes in hs-TnI and CTIC is not consistent (24,26,30,34-37).

Ky et al found a relation between early elevated levels of usTnI with CTIC but again it is not clear if those findings are  related to anthracyclines, trastuzumab or the combination of both (36).

The role of cTnT in the prediction of CTIC is less certain . However, Katsurada et al showed that elevated levels of hs-TnT at 6 months had 78%

sensitivity and 80% specificity for predicting CTIC at 15 months mindful they only included 19 patients (38).

Grover et al claimed that cTnT was a good marker of CTIC progression (39). Significant early functional changes were detected by cardiac MRI and these continued for 12 months. These accompanied significant changes in cTnT and CRP.

In contrast with these, other studies could not find any relation between the elevations of hsTnI and cTnT respectively and CTIC (37,38).

Putt et al found a substantial increase in hsTnI levels at 3 months which persisted at 15 months even though they could not determine if this was a good marker for CTIC perhaps due to data missing in a large fraction of patients (38). These authors hypothesized that the elevation of hsTnI might evidence damages predisposing to CTIC.

Other studies have reported increased levels of hs-TnT after anthracyclines whereas no elevations were seen with trastuzumab. They suggested that this may help identify patients at risk, especially when receiving trastuzumab sequentially, enabling early pre-emptive cardioprotective treatments or therapy modifications(40).

Theoretically, the ideal biomarker should detect early CTIC and should overcome the shortcomings linked with cardiac imaging. The biomarkers are not subjected to operator variability and interpretation. However, some authors could not find a predictive role for these biomarkers in isolation but when combined with other biomarkers or peak systolic myocardial strain (41).

For example, a study assessing hs-cTnT in patients with non-Hodgkin lymphoma suggested that combining this with two-dimensional speckle tracking echocardiography increases the sensitivity to detect late-onset CTIC in those patients who received anthracyclines (42). Similar observations were made by Sawaya et al(34).

The wide diversity in all these results is readily explained by the fact that different studies include different patient populations, utilised different assays to measure biomarkers, variable thresholds, sample sizes, different sample collection timings and variable CTIC definitions (43,44).

Theoretically, hs-Tns will increase the chances of early detection of cardiac damage. Nevertheless, other studies have shown an important role of elevated conventional cTn in early detection of myocardial damage due to chemotherapy (26,45).

## Natriuretic peptides

Another biomarker to have been assessed are the natriuretic peptides which mark cardiac volume and pressure overload. Their role is clear in acute and chronic CHF (26) however, their use in predicting CTIC is less clear (24,29).

It is known that trastuzumab may induce ventricle wall stress, which could release NT-proBNP and this could be detected prior to an LVEF decline.

Studies investigating the link between NT-proBNP and CTIC in BC patients have been inconclusive (24,32,34,36,37,46-48).

Two large prospective studies showed increased NT-proBNP levels in BC patients with CTIC (32,46), but other studies did not (24,34,36,37,47,48).

These studies are constrained by a low incidence of LVEF declines, or predominant focus on anthracyclines instead of trastuzumab(46).

Bouwer et al concluded that NT-proBNP cannot be used as a marker for trastuzumab-induced CTIC but showed that those patients showing a reduction in LVEF during anthracyclines, are high risk for further CTIC with trastuzumab.

Low figures of BNP/NT-proBNP have shown a high negative predictive value while high levels indicate CHF. However, these levels may not be as reliable as expected in advanced age, renal dysfunction or obesity.

Cutoff values for acute CHF have been established as <30-50pg/ml of BNP and <300pg/ml of NT-proBNP (49,50) but the exact figures to predict CTIC are still unknown.

Lenihan et al reported that among patients receiving anthracyclines who developed cardiac events, at least 1 BNP value was elevated at >100 pg/mL before the cardiac event, supporting the role of this biomarker as predictive of anthracyclines CTIC (51).

Others have found that baseline levels of NT-proBNP and LVEF decline during anthracyclines, were independently associated with CTIC. They even showed that for every 10 pmol/l elevation, LVEF declined by around 4% (46).

Consistent with this, Demissei et al showed that doubling the levels of NT-proBNP was linked to a 0.7% decline in LVEF at each subsequent visit. When those changes were classified by treatment regimen, it was reported that in those receiving anthracycline with trastuzumab, for each NT-proBNP doubling an up to 1.3% decline in LVEF was seen. And in those only on trastuzumab, NT-proBNP levels significantly declined in the first 6 months (52).

Authors advocated that BNP/NT-proBNP should be added to the basal cardiac risk factors as may help predict CTIC and they even suggested thresholds of 150 ng/L or 300 ng/L respectively to identify groups with high risk of developing CTIC (2 to 3-folds) especially in patients treated with the anthracyclines.

Our systematic review has found ten studies measuring NT-proBNP and one checking BNP. None of them showed these biomarkers to be predictive for CTIC in adjuvant BC patients with sequential treatment. Only Goel et al found that early changes in NT-proBNP levels were statistically correlated with CTIC, but this association did not pass the multivariate analyses (40).

Also the HERA sub study reported higher levels of NT-proBNP following anthracyclines and before trastuzumab. However, due to the lack of a definitive elevation threshold, they could not conclude any predictive role (32).

Romano et al found that NT-proBNP increased in all patients 24h after the initiation of chemotherapy. Moreover, patients with normal heart function showed normal or transiently high NT-proBNP. However, the levels persisted higher in patients with progressively worse heart function during treatment and at 3-, 6- and 12-month follow-up (46).

Similar results were reported by others showing that persistently high levels of NT-proBNP after having high dose of chemotherapy, is linked to the development of CTIC. (53)

In any case, the predictive value of these biomarkers is not definitively confirmed as prior studies mainly focused on the changes during a short time, mostly limited to the time of active therapy.

Urun et al have shown that a higher level of NT-proBNP is associated with CTIC even in patients with preserved baseline LVEF (36) whereas De Iuliis et al reported that NT-proBNP was significantly elevated at multiple time points after the completion of chemotherapy but there was no significant change in LVEF (54).

Perik et al found that baseline levels of NT-proBNP were higher in patients who develop CHF but this study included only 17 patients and all metastatic BC (55).

Grover et al observed NT-proBNP was worse than cTnT as a marker of CTIC progression (39).

They found that although CTIC occurred within 4 months, NT-proBNP did not change from baseline to that time. The levels of the natriuretic peptide stayed elevated at one year after stopping the chemotherapy.

Of note the kinetics of BNP/NT-proBNP and cTn release in CTIC remain unknown.

Ponde et al have suggested that only those treated with anthracyclines showed significant changes in circulating NTproBNP (as with cTn levels) (47).

### Other biomarkers

Other biomarkers such as MPO have been assessed but again results are inconsistent. Initially it was considered an attractive biomarker, as the central mechanism for anthracyclines induced CTIC is the oxidative stress, and some small studies have reported that higher levels of MPO during the treatment are associated with a higher risk of CTIC with anthracyclines followed by trastuzumab (36,37).

Ky et al found that among 78 BC patients receiving doxorubicin and trastuzumab, an early increase in MPO levels from baseline to 3 months was associated with a higher risk of CTIC during the 15-month period of treatment (36).

Putt et al in a later study showed that increases in MPO beyond 3 months of chemotherapy still remained predictive of increased CTIC risk over the period of treatment(37).

Recently, Demissei et al showed that elevations of MPO as well as baseline levels are linked to a higher risk of CTIC in patients treated with anthracyclines followed by trastuzumab (52).

Another studied biomarker is C-reactive protein (CRP) which is an acute phase reactant, involved in both anti-inflammatory and pro-inflammatory responses. It has been used as a marker of risk for cardiovascular disease since the 1960s. High-sensitivity CRP (hsCRP) is more accurate than routine CRP when measuring baseline levels (56).

Four studies included in this systematic review assessed CRP (two studies) and hsCRP (two studies). Only Onitilo et al suggested that abnormal hs-CRP has a high sensitivity (92.9 %) and negative predictive value (94.4 %) for reduced LVEF, although the specificity is low. These authors concluded that this could be a good biomarker to include on standard practice (49).

## Limitations

This systematic review found eleven studies that apply to BC patients receiving adjuvant trastuzumab. The review is limited by the heterogeneity between studies with respect to sample sizes, sample collection timing, definition of CTIC, limits of detection of assays utilised, interval times between

anthracyclines and trastuzumab, the lack of a positive threshold or the use of different thresholds of positivity and the low number of cardiac events (27,28).

Recently, Demissei et al (not included in this review as the study recruited metastatic patients as well) have reported the results of a prospective cohort of 323 patients treated with anthracyclines and/or trastuzumab followed over a maximum of 3.7 years with serial echocardiograms (52).

These authors found early elevations in all biomarkers with anthracyclines and reported that hs-cTnT levels >14 ng/L at anthracycline completion were linked to a 2-fold increased CTIC risk. Elevations of NT-proBNP and MPO were also associated with CTIC in the whole cohort but mostly with sequential anthracycline and trastuzumab.

## Conclusion

Circulating serum biomarkers are attractive tools to apply in early detection of CTIC, but no single determination seems to be perfect.

Based on the results of our systematic review, noting its limitations, it seems that

(a) elevations in TnI, hs-TnI, usTnI at completion of anthracyclines or early during trastuzumab seem to be associated with CTIC in patients receiving sequential anthracyclines and trastuzumab.

(b) For a long time, it has been known that the prediction of CTIC is less accurate with cTnT compared with cTnI. However, Zardavas et al showed for the first time, that cTnT elevations seem to be associated with CTIC within those patients receiving sequential anthracyclines followed by trastuzumab (32).

(c) Elevated levels of hs-cTnT specifically at the time of completion of anthracyclines and at 6 months seem to predict future CTIC.

(d) Elevation of MPO throughout the course of adjuvant anthracyclines and sequential trastuzumab are associated with CTIC.

(e) Elevations of NT-proBNP/BNP do not seem to be associated with CTIC in this population although the small size and small number of cardiac events in these studies limit the statistical power to conclude/exclude a predictive role.

(f) A multimodality strategy incorporating several biomarkers with cardiac imaging might provide higher value in detecting patients at high risk of CTIC.

In summary, there is a clear need for novel biomarkers able to detect myocardial damage earlier than Tn and also for standard strategies for cardio protection. With the new anti-Her-2 therapies currently used in adjuvant settings, well-designed prospective trials with statistical power and long-term follow-up are mandatory to assess these issues and to give clinicians the proper answers to manage this population.

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