Chapter 4

Troponin and (NT-pro)BNP as predictors for the occurrence of cardiac dysfunction during or after breast cancer treatment: a systematic review

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Submitted
Abstract

Purpose
To date, monitoring of cardiac function after cardiotoxic chemotherapy relied on imaging techniques. The aim of this review was to evaluate association between the biomarkers troponin and (NT-pro)BNP and cardiac dysfunction in adult women treated for breast cancer.

Patients and methods
PubMed and Embase were systematically searched. Studies that evaluated the association between troponin, (NT-pro)BNP during cardiotoxic therapy and cardiac dysfunction during and after treatment using echocardiography, magnetic resonance imaging, or multigated acquisition scans were included. Random effect models were applied to pool odds ratios (ORs).

Results
12 out of 691 identified studies were included, evaluating 742 women. Median follow-up ranged from 0–14 months. The weighted prevalence of cardiac dysfunction was 17.8% (range 0%–47%). Increased troponin or (NT-pro)BNP levels during treatment were not associated with cardiac dysfunction (OR 3.14, 95%CI 0.73–13.50 and 2.07, 95% CI 0.50-8.59, respectively).

Conclusion
There is insufficient evidence that either troponin or (NT-pro)BNP is associated with cardiac dysfunction during or after chemotherapy or radiotherapy for breast cancer. Studies with longer follow-up periods are needed to evaluate the predictive value of these biomarkers for cardiac dysfunction.
Introduction
Each year approximately 1.7 million women are diagnosed with breast cancer worldwide, making it the most common type of cancer among women.¹ Fortunately, due to advances in treatment and early detection, survival rates have increased by 25% to a 10-years survival of 75%.⁸, ¹⁰, ¹¹, ¹³, ¹¹⁷ Most women now receive chemotherapy, radiotherapy, or both.¹⁵-¹⁸ However, these therapies are associated with increased cardiovascular morbidity and mortality, which may present many years after treatment.⁷³-⁷⁵ On the one hand, after chemotherapy (mainly anthracyclines) and targeted therapy (trastuzumab) women have been shown to develop congestive heart failure significantly earlier than women who did not receive those therapies.³⁴-³⁷, ¹¹⁸ On the other hand, women who received radiotherapy have been shown to be at risk of cardiomyopathy and ischemic heart disease due to vascular damage.⁵²

Cardiac dysfunction due to chemotherapy and/or radiotherapy for breast cancer may lead to congestive heart failure or cardiomyopathy at any stage from during treatment to more than 10 years after treatment has ended.³⁵, ⁴⁶ The type of cardiac damage that occurs during initial treatment seems reversible, at least in the short term, possibly because agents like trastuzumab simply block the repair mechanism of the heart while being taken.⁶⁴ By contrast, cardiac dysfunction that becomes clinically apparent during long-term follow-up is usually irreversible and is probably caused by oxidative stress and free radical damage to the cardiac muscle during chemotherapy and radiation treatment.⁶⁴

Given the increasing number of long-term survivors of breast cancer, physicians should be aware of these potential irreversible effects on cardiac function. Indeed, early detection of cardiac dysfunction is important because timely treatment might prevent further deterioration.¹¹⁹-¹²¹ However, early detection is difficult because cardiac damage and dysfunction can be asymptomatic, or can manifest with non-specific symptoms like fatigue.³⁹ To date, monitoring of cardiac dysfunction has relied on echocardiography, magnetic resonance imaging (MRI), and multigated acquisition (MUGA) scanning.¹²² In contrast to these costly and labor intensive methods biomarkers troponin, brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are widely available. Troponin assays are commonly used in the diagnosis of acute myocardial infarction¹²³, while BNP and NT-proBNP are routinely used to screen for heart failure.¹²⁴, ¹²⁵ To date, experimental research has shown that exposure to anthracycline chemotherapy causes a dose-dependent reduction in cardiomyocyte contractility that correlates with the release of the cardiac-specific biomarker
troponin T. Furthermore, several studies have found that increased levels of BNP and NT-proBNP are negatively correlated with the left ventricular ejection fraction (LVEF) in patients receiving cardiotoxic treatments for breast cancer.

Given that troponin, BNP or NT-proBNP levels may increase due to the cardiotoxic effects of chemotherapy and radiotherapy, they may be used as biomarkers to identify patients with cardiac damage after breast cancer treatment who might be at increased risk for cardiac dysfunction. In this systematic literature review and meta-analysis, we evaluated the association between increased value of the biomarkers troponin, BNP, NT-proBNP and the occurrence of cardiac dysfunction during or after chemotherapy and/or radiotherapy for breast cancer. In this study, (NT-pro)BNP is used to refer to studies of either BNP or NT-proBNP and troponin to studies of either Troponin I or T.

Material & Methods

Box 1 Search strategy

Design, selection criteria and data extraction

Searches were performed of the PubMed and Embase databases from inception to October 2016. The study was performed and is reported according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The research protocol is available at the PROSPERO register [ID: CRD42014007195]. Search terms were based on MeSH terms and text related to breast cancer, troponin, (NT-pro)BNP, and cardiac dysfunction (Box 1). We also searched the reference lists of the included review articles and studies. Independently, three reviewers analyzed and identified studies for eligibility and extracted the relevant data (LMB, CvdV, and DB). Two reviewers assessed the methodological quality of the included articles (LMB and DB). Disagreements were resolved by consensus or arbitration with a third, independent reviewer (MYB or AJB).

For inclusion, studies were required to have a study population of women aged ≥18 years who were treated with cardiotoxic therapies (anthracyclines, taxanes, trastuzumab, or radiotherapy) for breast cancer, with no restrictions to care setting.
Studies had to address the target condition of cardiac dysfunction during or after treatment, assessed by echocardiography, MRI, or MUGA. The studies had to include measurements of troponin or (NT-pro)BNP at time of treatment. Data collection had to be prospective. We included studies with survivors of other types of cancer if separate analyses had been done for survivors of breast cancer.

Using a structured predefined data extraction form, we extracted information on the following: care setting, follow-up time, participants (age, diagnosis, and type of breast cancer treatment), drop-out rates (including the details), information about troponin and (NT-pro)BNP measurements (type, index tests, cutoff values, and measurement time points), and details of cardiac dysfunction measurements and outcomes (definitions of cardiac dysfunction as assessed by echocardiography, MRI, and MUGA and time of assessment (during or after treatment)).

Definitions
A positive biomarker was defined as one or more measurements above the cut-off value as used by the authors of the original study at the measurement points as depicted in table 1. For evaluating the occurrence of cardiac dysfunction the definition of the included study was followed (table 1). The treatment period was defined as the period from start of treatment until the end of cardio toxic treatment.

Quality assessment
To assess the methodological quality of the included articles, we used a checklist based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (Table 2). Listed items were divided into five categories: general, study population, type of breast cancer treatment, measured biomarkers, and outcome. Items could be answered “yes (1 point),” “no (0 points),” “cannot determine (CD),” “not applicable (NA),” and “not reported (NR).” The item was ignored if the outcome was marked NA, or grouped under “no” if marked NR or CD. The summary score of each study was then calculated and expressed as a percentage that was categorized into one of four categories: poor (0%–25%), fair (25%–50%), good (50%–75%), or excellent (75%–100%).

Analysis
For each study, the occurrence of cardiac dysfunction was calculated as a percentage of the total sample of women treated for breast cancer, weighted by study size. The relation between a biomarker test above the cut-off value and the occurrence of
cardiac dysfunction was evaluated by estimating odds ratio’s (ORs) and 95% confidence intervals (95% CIs). To meta-analyze the estimated results, Mantel–Haenszel random effects models were applied to calculate pooled estimates of the ORs. Overall statistical heterogeneity was tested by I² tests. Results were presented stratified by moment of outcome assessment (during treatment only vs. during or after treatment) in forest plots. Potential sources of heterogeneity were evaluated. For outliers (identified by “eyeballing”), we evaluated whether bias or specific study characteristics could explain the results. All analyses were conducted using Review Manager (version 5.3. Copenhagen, The Cochrane Collaboration, 2014).

Results
Study characteristics and participants
The search yielded 691 unique studies (Figure 1), of which 12 met our inclusion criteria. These studies comprised 742 patients in total (range 9–251) with a mean age varying from 46 to 62 years (Table 1). In all but one study, patients received anthracyclines. In nine studies, all patients received trastuzumab, in one study only 20% of patients received trastuzumab treatment. Eight studies comprised women who also received (neo)adjuvant radiotherapy. Two studies excluded patients who had previously received chemotherapy or radiotherapy. In three studies, patients had received these therapies before baseline measurement in three studies. The other studies did not mention whether prior treatment was an exclusion criteria.

The two reviewers initially agreed upon 75% of the items in the methodological quality list. The mean overall quality score for all included studies was 65% (range 38%–88%). Three studies scored excellent, seven studies scored good, and two were of fair quality (Table 2). The most prevalent shortcomings were in reporting the participation rate of eligible persons and similarity of exposed and unexposed populations. Sample sizes were frequently not justified. Furthermore, blinding for the exposure state was a frequently occurring source of potential bias, as was appropriateness of analysis, and statistical adjustment for confounding variables.
Figure 2 Flow diagram for study inclusion

- Records identified through database searching (n = 870)
- Additional records identified through other sources (n = 0)
- Records after duplicates removed (n = 691)
- Records screened (n = 691)
  - Records excluded based on title and abstract (n = 485)
  - No full text available (n = 91)
  - Full-text articles assessed for eligibility (n = 115)
    - Studies included in quantitative synthesis (meta-analysis) (n = 12)
      - Full-text articles excluded
        - No reference standard (n = 13)
        - No index test (n = 24)
        - No separate analysis for breast cancer patients (n = 10)
        - No analysis relating biomarker and cardiac function (n = 10)
        - No information on prognostic value available (n = 4)
        - Unable to construct a 2 × 2 table (n = 31)
        - No prognostic research (n = 11)
Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Setting</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallah-Rad, 2011</td>
<td>Prospective cohort study</td>
<td>consecutive diagnosed BC patients with HER2 overexpression at University hospital Canada</td>
<td>Epirubicin (88%), Doxorubicin (12%), Trastuzumab (100%), Radiotherapy (98%)</td>
</tr>
<tr>
<td>Katsurada, 2014</td>
<td>Prospective cohort study</td>
<td>Breast cancer women at medical university hospital</td>
<td>Anthracyclines (100%), Taxanes (100%), Trastuzumab (100%) Radiotherapy (63%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition of Cardiotoxicity</th>
<th>Outcome Measure</th>
<th>Measuring points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in LVEF of at least 10% below 55% with accompanying signs or symptoms of CHF, necessitating discontinuation of the drug</td>
<td>ECHO</td>
<td>same time points as biomarkers for ECHO, and at baseline and 12 mo. for MRI</td>
</tr>
<tr>
<td>hsTnT &gt; 5.5 pg/mL</td>
<td>Measuring points for biomarker: baseline, and every 3 mo. until the end of trastuzumab at 15 mo.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Eligible</th>
<th>Included</th>
<th>Mean age</th>
<th>Follow-up duration after treatment</th>
<th>Lost to follow-up: not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female patients who received adjuvant trastuzumab in the setting of HER2 overexpressing BC</td>
<td>-</td>
<td>Unknown</td>
<td>E</td>
<td>42</td>
<td>47 ± 9 y</td>
<td>0 mo.</td>
<td></td>
</tr>
<tr>
<td>Eligible N = 42</td>
<td>Included</td>
<td>E</td>
<td>20</td>
<td>10</td>
<td>0 mo.</td>
<td>not reported</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Troponin</th>
<th>Measuring points for cardiotoxicity: baseline, and every 3 mo. until the end of trastuzumab at 15 mo.</th>
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</thead>
<tbody>
<tr>
<td>NT-pro BNP</td>
<td>Cutoff value: NT-pro BNP &gt; 35 pmol/l</td>
</tr>
<tr>
<td>Measuring points for biomarker: Baseline (before starting treatment with anthracyclines), before, and at 3, 6, 9, and 12 mo. after starting trastuzumab</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting and Treatment</th>
<th>Outcome</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: Breast cancer women at medical university hospital</td>
<td>ECHO</td>
<td>NT-pro BNP</td>
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<td>Treatment: Anthracyclines (100%), Taxanes (100%), Trastuzumab (100%) Radiotherapy (63%)</td>
<td>Measuring points for biomarker: baseline, and every 3 mo. until the end of trastuzumab at 15 mo.</td>
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<tr>
<th>NT-pro BNP</th>
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<tr>
<td>Measuring points for biornarker: Baseline, and every 3 mo. until the end of trastuzumab at 15 mo.</td>
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<tr>
<td>HER2-positive breast cancer and scheduled to receive adjuvant chemotherapy including anthracyclines, taxanes and trastuzumab</td>
<td>-</td>
<td>Unknown</td>
<td>E</td>
<td>20</td>
<td>0 mo.</td>
<td>not reported</td>
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| Included | E | 20 | |

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**Ky, 2013**

**Setting:** Consecutive patients newly diagnosed with BC at a university hospital in Japan

**BC Treatment:**
- Doxorubicin (88%)
- Epirubicin (12%)
- Taxanes (100%)
- Trastuzumab (100%)
- Radiotherapy (60%)

**Inclusion:**
- Patients ≥18 y of age
- Newly diagnosed with human epidermal growth factor receptor 2-overexpressing BC and scheduled to receive adjuvant therapy including anthracyclines, taxanes, and trastuzumab

**Exclusion:**
- Patients who had a baseline LVEF <50%

**Eligible:** N = 99
**Included:** N = 81
**Mean age:** 50 ± 10 y

**Follow-up duration after treatment:** 0 mo.

**Cardiomyopathy with decreased LVEF, a reduction of LVEF of LVEF >5% to <55% with symptoms of heart failure or an asymptomatic reduction of LVEF ≥10% to <55% (CREC)**

**TnI**

**Cutoff value:** >0.03 ng/mL

**NT-pro BNP**

**Cutoff value:** >125 pg/mL

**Measuring points for biomarker:** Baseline, and after 3 and 6 mo.

**BNP**

**Cutoff:** > 100 pg/mL

**Measuring points for biomarker:** Baseline (before treatment with trastuzumab); 3 months, 6 months, and 12 months after diagnosis

**ECHO**

**Measuring points for cardiototoxicity:** Baseline (before any therapy), after anthracyclines (3 mo.), 6,9,12 and 15 mo. after baseline

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**Nakano, 2016**

**Setting:** Consecutive newly diagnosed HER2 overexpressive BC at university hospital Japan

**BC treatment:**
- Anthracyclines (66.7%)
- Taxanes (33.3%)
- Trastuzumab (100%)
- Radiotherapy (55.6%)

**Inclusion:**
- Newly diagnosed with HER 2-overexpressing BC

**Exclusion:**
- Artificial pacemaker implantation, chronic arrhythmia such as atrial fibrillation, chronic kidney disease (eGFR <30mL/min/1.73m²), metastatic cancer

**Eligible:** N = unknown
**Included:** N = 16 (included in analysis 9)
**Mean age:** 62.3 ± 12.6 years

**Follow-up duration after treatment:** unknown

**Lost to follow-up:** 7

**LVEF < 55%**

**TnI**

**Cutoff value:** >0.3 ng/mL

**BNP**

**Cutoff:** > 100 pg/mL

**Measuring points for biomarker:** Baseline (before treatment with trastuzumab); 3 months, 6 months, and 12 months after diagnosis

**ECHO/MRI**

**Measuring points for cardiototoxicity:** Baseline (before treatment with trastuzumab); 3 months, 6 months, and 12 months after diagnosis
**Onitilo, 2012** 137

**Setting:** newly diagnosed primary BC patients at a cancer clinic in the USA

**BC treatment:**
- Anthracyclines (44%)
- Taxanes (85%)
- Trastuzumab (100%)
- Radiotherapy (37%)

**Inclusion:**
- Female patients aged >18 y
- First diagnosis of HER2-positive primary BC (stages 1–3)
- Deemed eligible for trastuzumab adjuvant therapy

**Exclusion:**
- missing laboratory values or insufficient testing for LVEF

**Measuring points for cardiotoxicity:**
Baseline, after 4 cycles and after completion of treatment both MUGA and ECHO

**BNP**

**Cutoff:** ≥200 pg/mL

**Measuring points for biomarker:**
- Baseline (before treatment)
- every 3 wk during treatment, up to 12 mo.

**cTnI**

**Cutoff value:** ≥0.1 ng/mL

**Measuring points for biomarker:**
- Baseline (before treatment)
- every 3 wk during treatment, up to 12 mo.

**Decrease in ejection fraction of 15% or more from baseline or to a value below 50%**

**Severe heart failure (Common toxicity criteria grade 3; NYHA functional class II to IV)**

**Follow-up duration after treatment:** 0 mo.
**Lost to follow-up:** 0

**Mean age:** 55.41 y (patients with a normal LVEF) and 59.58 y (patients with a decreased LVEF)

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**Perik, 2006** 136

**Setting:** Patients at the University hospital Groningen (Netherlands)

**BC treatment:**
- Epirubicin (40%)
- Doxorubicin (67%)
- Paclitaxel (100%)
- Trastuzumab (100%)

**Inclusion:**
- Age ≥18 y, diagnosed with HER2-positive metastatic or locally advanced BC, suitable for treatment with paclitaxel and trastuzumab, and an Eastern Cooperative Oncology Group performance status of 0 to 2.

**Exclusion:**
- Treatment with any investigational drug within 30 days before the start of the study, radiotherapy within 4 wk of enrollment, serious uncontrolled CNS metastases, LVEF <40% on MUGA, or symptomatic heart failure NYHA functional class III or IV. Patients

**TnI**

**Cutoff value:** >500,000 ng/mL

**Measuring points for biomarker:**
- before, at 1 and 7 days after the first trastuzumab infusion, and at the end of each cycle

**NT-pro BNP**

**Cutoff value:** 125 ng/L

**Measuring points for biomarker:**
- before, at 1 and 7 days after the first trastuzumab infusion, and at the end of each cycle

**Decrease in ejection fraction of 15% or more from baseline or to a value below 50%**

**Severe heart failure (Common toxicity criteria grade 3; NYHA functional class II to IV)**

**Follow-up duration after treatment:** 0 mo.
**Lost to follow-up:** 0

**Mean age:** 55.41 y (patients with a normal LVEF) and 59.58 y (patients with a decreased LVEF)

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- before, at 1 and 7 days after the first trastuzumab infusion, and at the end of each cycle

**Decrease in ejection fraction of 15% or more from baseline or to a value below 50%**

**Severe heart failure (Common toxicity criteria grade 3; NYHA functional class II to IV)**

**Follow-up duration after treatment:** 0 mo.
**Lost to follow-up:** 0

**Mean age:** 55.41 y (patients with a normal LVEF) and 59.58 y (patients with a decreased LVEF)
abnormal laboratory tests (neutrophil count <1.5 × 10⁹/L, platelets <100 × 10⁹/L, serum total bilirubin >1.5 × ULN, an ALT or AST more than 2.5 × ULN (>5.0 × ULN in case of liver metastases), alkaline phosphatase more than 2.5 × ULN (>4.0 × ULN in case of liver or bone metastases), or serum creatinine more than 1.5 × ULN).

Eligible patients: N = 17
Included patients: N = 15
Mean age: 52.4 y

Follow-up duration after treatment: 0 mo.
Lost to follow-up: 2 (both due to oncological reasons)

<table>
<thead>
<tr>
<th>Yu, 2016</th>
<th>Prospective cohort study</th>
<th>Setting: Metastatic breast cancer patients at a cancer centre in the USA</th>
<th>Inclusion: HER2-positive breast cancer with metastatic disease, age ≥18 y, an Eastern Cooperative Oncology Group performance status of 0 to 1, measurable or nonmeasurable disease, zero to one prior treatment, adequate organ function, baseline LVEF of ≥50% or ≥50% or ≥16% by echo within 4 weeks before enrollment</th>
<th>Cutoff value: &gt;0.06 ng/mL</th>
<th>cTnI Cutoff: &gt; 100 pg/mL</th>
<th>Measuring points for biomarker: At baseline, and every other cycle for up to 6 time points (12,18,24,30 weeks)</th>
<th>Measuring points for cardiotoxicity: At baseline and every three months thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BC treatment: Anthracyclines (0%)</td>
<td>Taxanes (100%)</td>
<td>Trastuzumab (100%)</td>
<td>Radiotherapy (7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cardinal e, 2010

Prospective cohort study

Setting: Consecutive diagnosed BC patients at a cancer center in Italy

BC treatment:
- Epirubicin (31%)
- Doxorubicin (48%)
- Taxanes (7%)
- Trastuzumab (100%)
- Radiotherapy (35%)

Inclusion: Women with BC undergoing trastuzumab therapy (early-stage and advanced or metastatic BC, with HER2 overexpression)

Exclusion: Age <18 y or >75 y, ischemic and valvular heart disease, LVEF <55% before treatment, severe hypertension, life expectancy ≤12 wk, or abnormal renal or hepatic functions.

Eligible patients: $N = \text{unknown}

Included patients: $N = 251$

Mean age: $50 \pm 10$ y

Follow-up duration after treatment: median 14 mo. (range 1–79 mo.)

Lost to follow-up: 66 (62 died of oncologic reason)

LVEF decrease of cTnI >10 units from baseline, associated with a decline below the normal limit of 50%

Cutoff value: >0.08 ng/ml

Measuring points for biomarker: TnI before and soon after each trastuzumab cycle (each patient and each cardiology check after completion of the therapy)

Measuring points for cardiotoxicity:
- Baseline (before trastuzumab treatment), every 3 mo.
- During trastuzumab treatment, every 3 mo. during the first year after discontinuation, and every 6 mo.
- Thereafter (in case of loss to follow-up or oncologic death, last evaluation = final measurement)

uncontrolled ventricular arrhythmias, prior pertuzumab, grade ≥ 2 neuropathy

Eligible: $N = \text{unknown}

Included: $N = 69$

Median age: 53 (range 26-84)

Follow-up duration after treatment: median 21 months (range 2-38); treatment duration 30 weeks

Lost to follow-up: 2
### Erdim, 2009 [44]

**Setting:** BC patients at the University hospital Turkey

**BC treatment:**
- **Epirubicin (100%)**

**Inclusion:** patients treated with epirubicin-containing adjuvant chemotherapy for stage 2 or 3 BC who have undergone either modified radical mastectomy or breast-saving surgery.

**Exclusion:**
- Patients with metastasis, ischemic or valvular heart disease, any type of cardiomyopathy, heart failure, baseline LVEF <50%, and uncontrolled hypertension.

**Eligible patients:** $N =$ unknown

**Included patients:** $N = 45$

**Mean age:** 48 ± 8 y

**Follow-up duration after treatment:** 12 mo.

**Lost to follow-up:** 4 (2 due to oncological reasons)

**Final LVEF cTnT**
- $<50\%$ or an absolute drop of $>10\%$ng/mL

**Cutoff value:** $>0.01$ ng/mL

**Measuring points for biomarker:**
- Before and 72 hours after each cycle of chemotherapy
  (each patient 4–6 cycles)

**Inclusion:**
- Patients treated with epirubicin-containing adjuvant chemotherapy for stage 2 or 3 BC who have undergone either modified radical mastectomy or breast-saving surgery.

**Exclusion:**
- Patients with metastasis, ischemic or valvular heart disease, any type of cardiomyopathy, heart failure, baseline LVEF <50%, and uncontrolled hypertension.

**Eligible patients:** $N =$ unknown

**Included patients:** $N = 45$

**Mean age:** 48 ± 8 y

**Follow-up duration after treatment:** 12 mo.

**Lost to follow-up:** 4 (2 due to oncological reasons)

### Erven, 2012 [42]

**Setting:** Consecutive patients diagnosed with BC at the University hospital Belgium

**BC treatment:**
- **Epirubicin (91%)**
- **Doxorubicin (4%)**
- **Pegylated liposomal doxorubicin (5%)**
- **Taxanes (100%)**
- **Trastuzumab (20%)**
- **Radiotherapy (100%)**

**Inclusion:** Patients with histologically proven early BC requiring adjuvant RT, and fulfilling the following criteria: prior surgery (lumpectomy or mastectomy with or without axillary dissection) and prior adjuvant anthracycline- and taxane-based chemotherapy.

**Exclusion:** Prior RT with inclusion of the heart in the RT fields; history of serious cardiac illness, including congestive heart failure or cardiomyopathy; and poor echogenicity.

**Eligible patients:** $N = 75$

**Included patients:** $N = 56$

**Mean age:** right sided BC: 52 ± 7 y

**Left-sided BC:** 54 ± 8 y

**Follow-up duration after treatment:** 14 mo.

**Lost to follow-up:** unclear, samples available for 56 out of 75 patients

**Significant decrease in conventional parameters for systolic or diastolic function or strain**
- **TnI**

**Cutoff value:** >0.13 ng/mL

**Measuring points for biomarker:**
- First and last day of radiotherapy

**Measuring points for cardiotoxicity:**
- Before radiotherapy, immediately after radiotherapy, 8 and 12 mo. after radiotherapy

**Setting:** Consecutive patients diagnosed with BC at the University hospital Belgium

**BC treatment:**
- **Epirubicin (91%)**
- **Doxorubicin (4%)**
- **Pegylated liposomal doxorubicin (5%)**
- **Taxanes (100%)**
- **Trastuzumab (20%)**
- **Radiotherapy (100%)**

**Prospective cohort study**

**Prospective cohort study**
<table>
<thead>
<tr>
<th>Morris, 2011</th>
<th>Prospective cohort study</th>
<th>Setting: newly diagnosed primary BC patients at a cancer clinic in the USA</th>
<th>Inclusion: early BC which overexpressed HER-2/neu, regardless of nodal status or tumor size. ECG and normal LVEF by MUGA (≥50%). Exclusion: Patients with serious medical illnesses including unstable angina, myocardial infarction, and CHF. An absolute neutrophil count &lt;1000/µL; platelet count &lt;100,000/ µL; abnormal bilirubin and transaminases &gt;2.5 × ULN. Patients treated with CYP3A4 inducers/inhibitors and/or treatment with drugs that may prolong the QTc. Patients with grade 3 QTc. Eligible: N = Unknown Included: N = 95 Median age: 46 (range 28–73) Follow-up duration after treatment: 4 mo. Lost to follow-up: (46 stopped treatment)</th>
<th>Symptomat ic or asymptomatic decline in LVEF &gt;10% to &lt;50%</th>
<th>TnI</th>
<th>Cutoff value: “Detectable” i.e., ≥0.06 ng/mL and ≥0.04 ng/mL</th>
<th>Measuring points for biomarker: Every 2 wk during treatment</th>
<th>MUGA</th>
<th>Measuring points for cardiotoxicity: Baseline (before start treatment), at 2, 6, 9, and 18 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nistico, 2007</td>
<td>Prospective cohort study</td>
<td>Setting: women with chemotherapy-naive metastatic BC at a general hospital in Italy</td>
<td>Inclusion: patients affected by HER-2-negative advanced/metastatic BC, not previously treated Exclusion: patients younger than 18 and older than 75 y -having a history of cardiovascular disease, drug-uncontrolled systemic hypertension, LVEF &lt;50% or chronic renal failure Eligible: N = Unknown Included: N = 20 Median age: 56 y (range 34–75 y) Follow-up duration after treatment: 14 mo. (24 wk treatment; median follow-up of 20 mo.) Lost to follow-up: 0</td>
<td>Abnormal LVEF or diastolic dysfunction cTnT</td>
<td>Cutoff value: ≥0.1 U/l</td>
<td>Measuring points for biomarker: Immediately before and 4 h after chemotherapy administration</td>
<td>ECHO/MUGA</td>
<td>Measuring points for cardiotoxicity: Baseline (immediately before the first cycle of chemotherapy) and after the 8th, 16th, and 24th (last) administration of chemotherapy. Every 3 mo. thereafter and MUGA if LVEF decreased &gt;20%</td>
<td></td>
</tr>
</tbody>
</table>

---
Abbreviations Table 1: BC, breast cancer; BMI, BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAD, coronary artery disease; CHF, congestive heart failure; CNS, central nervous system; CREC, Cardiac Review and Evaluation Committee; ECG, electrocardiogram; ECHO, echocardiography; Hs CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; NYHA, New York Heart Association; RT, radiotherapy; ULN, upper limit of normal; TnI, troponin I; TnT, troponin T

Table 2 Quality assessment

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>General</td>
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</tr>
<tr>
<td>1. Was the research question or objective in this paper clearly stated?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>No</td>
<td>Y</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>And was it in concordance to our research question?</td>
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<tr>
<td>Study population/patients</td>
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<tr>
<td>2. Was the study population clearly specified and defined? (At least mentioned: age of patients; type of cancer therapy given, time since cancer therapy, and setting)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>No</td>
<td>Y</td>
<td>No</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>3. Was the participation rate of eligible persons at least 50%?</td>
<td>NR</td>
<td>Y</td>
<td>No</td>
<td>CD</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>CD</td>
<td>NR</td>
</tr>
<tr>
<td>4. Were all the subjects selected or recruited from the same or similar populations? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?</td>
<td>CD</td>
<td>Y</td>
<td>Y</td>
<td>CD</td>
<td>Y</td>
<td>CD</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>5. Were sample size justification, power description, or variance and effect estimates provided?</td>
<td>No</td>
<td>Y</td>
<td>NR</td>
<td>Y</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>6. Was loss to follow-up after baseline 20% or less?</td>
<td>NR</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>No</td>
<td>Y</td>
<td>No</td>
<td>No</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Exposure to cardiotoxic treatment</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7. Where details of treatment described? (At least mentioned: cumulative dose of chemotherapy, type of chemotherapy, radiation therapy, left/right sided radiation therapy, and trastuzumab treatment.)</td>
<td>Y</td>
<td>Y</td>
<td>No</td>
<td>Y</td>
<td>Y</td>
<td>CD</td>
<td>No</td>
<td>No</td>
<td>Y</td>
<td>No</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Prognostic markers</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>8. For the analyses in this paper, were the biomarkers (troponin and/or (NT-pro)BNP) measured prior to the outcome being measured?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>
9. Was the prognostic marker assessed more than once over time?  
|   | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

10. Were the prognostic markers (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?  
|   | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

**Outcome**

11. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? Follow-up was at least until the end of treatment with cardiotoxic therapies (anthracyclines, taxanes, trastuzumab, and radiotherapy).  
|   | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |

12. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?  
|   | Y | Y | No | Y | Y | CD | No | CD | Y | CD | CD | Y |

13. Was the outcome assessed more than once over time?  
|   | Y | Y | Y | Y | Y | No | Y | Y | Y | Y | Y | Y |

14. Were the outcome assessors blinded to the biomarker status of participants?  
|   | NR | Y | Y | NR | Y | NR | NR | Y | Y | NR | NR | NR |

15. Was appropriate analytic analysis performed and presented? Hazard ratio/Odds ratio?  
|   | No | Y | Y | No | Y | No | NA | No | No | No | NA | No |

16. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? (Corrected/stratified for cumulative dose of chemotherapy/trastuzumab, or left-sided radiation.)  
|   | No | No | Y | NA | Y | No | CD | No | NA | No | NA | No |

17. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? (age for [NT-pro]BNP, cumulative dose chemo/Herceptin/radiation, left-sided radiation, age at time of diagnosis, multivariate model.)  
|   | NA | No | CD | NA | Y | NA | NA | NA | NA | NA | NA | NA |

**Total score**

|   | + | ++ | ++ | ++ | -/+ | + | + | -/+ | + | + |

CD, cannot determine; NA, not applicable; NR, not reported; [NT-pro]BNP: brain natriuretic peptide (BNP) or the N-terminal of BNP (NT-proBNP); Y, yes; poor (-), faire (-/+), good (+), excellent (++)
Prognostic value of troponin
In all 12 included studies, troponin was evaluated as a biomarker to evaluate the occurrence of cardiac dysfunction: troponin I in eight studies and troponin T in four studies (Table 1). The median prevalence of troponin levels above the cut-off value was 14% (range 0%–67%), which did not vary by of the type (I or T) or of the cut-off value used. The weighted prevalence of cardiac dysfunction was 17.8% (range 0%–47%), and was independent of the method by which it was assessed (echocardiography, MUGA, or MRI). In three smaller studies, no cardiac dysfunction was observed.\textsuperscript{140,142,143} Median follow-up periods in the 12 included studies ranged from 0 to 14 months.

The pooled OR for cardiac dysfunction in patients with elevated troponin was 3.14 (95% CI 0.73–13.50) when compared with the odds for patients with normal troponin levels; however, the $I^2$ was 85%, indicating statistically significant heterogeneity (Figure 2). Due to the small number of studies, no subgroup analysis was performed by follow-up duration. One study was identified as an outlier.\textsuperscript{134} The heterogeneity decreased to 46% after it was excluded, and the pooled OR decreased to 1.72 (95%CI 0.66–4.45). This outlier study of Cardinale and coworkers was the largest study ($n = 251$) with the longest follow-up after end of trastuzumab therapy (median 14 and range 1–79 months)\textsuperscript{134}, and showed an association between troponin and cardiotoxicity (OR 33.34, 95%CI 13.29–78.71). This study did not differ from the other included studies by the type of breast cancer treatment, cutoff value of the biomarker, choice of reference standards, prevalence of cardiac dysfunction, or bias in our quality assessment.

Two studies\textsuperscript{134,139} reported Hazard Ratios, indicating that cardiac dysfunction typically manifested significantly earlier after a positive troponin test result compared with a negative troponin test result (HR 1.36, 95% CI 1.07–1.73; HR 17.6, 95% CI 8.85–35; respectively).
Figure 2 All studies investigating troponin as a prognostic biomarker for the occurrence of cardiac dysfunction following cardiotoxic therapies for breast cancer

<table>
<thead>
<tr>
<th>Outcome assessed only during treatment</th>
<th>Events</th>
<th>Total</th>
<th>Incidence (%)</th>
<th>FU*</th>
<th>Measurement Biomarker</th>
<th>OR (95% CI)</th>
<th>HR (95% CI)</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallah-Rad 2011 (40)</td>
<td>0</td>
<td>0</td>
<td>32</td>
<td>5</td>
<td>3 weeks after AC &amp; during trastuzumab</td>
<td>N.E.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Katsurada 2014 (46)</td>
<td>7</td>
<td>9</td>
<td>10</td>
<td>0</td>
<td>During AC and during trastuzumab</td>
<td>14 (1.54-127.23)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ky 2013 (44)</td>
<td>11</td>
<td>26</td>
<td>52</td>
<td>0</td>
<td>Just after AC &amp; during trastuzumab</td>
<td>2.44 (0.89-6.72)</td>
<td>1.36 (1.07-1.73)</td>
<td></td>
</tr>
<tr>
<td>Nakano 2016 (46)</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>During AC and during trastuzumab</td>
<td>N.E.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Onitillo 2012 (42)</td>
<td>0</td>
<td>14</td>
<td>49</td>
<td>0</td>
<td>Unclear, probably during trastuzumab</td>
<td>N.E.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Perik 2006 (41)</td>
<td>0</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>During trastuzumab &amp; paclitaxel</td>
<td>0.05 (0.00-25.00)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome during and after treatment</th>
<th>Events</th>
<th>Total</th>
<th>Incidence (%)</th>
<th>FU*</th>
<th>Measurement Biomarker</th>
<th>OR (95% CI)</th>
<th>HR (95% CI)</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardinale 2010 (39)</td>
<td>26</td>
<td>36</td>
<td>215</td>
<td>4</td>
<td>Unclear, during follow-up</td>
<td>33.34 (13.29-78.71)</td>
<td>17.6 (8.85-35)</td>
<td></td>
</tr>
<tr>
<td>Erdtmann 2009 (49)</td>
<td>9</td>
<td>26</td>
<td>4</td>
<td>15</td>
<td>First and last day of RT</td>
<td>1.46 (0.36-5.91)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Enver 2012 (47)</td>
<td>0</td>
<td>0</td>
<td>56</td>
<td>0</td>
<td>During AC and during trastuzumab</td>
<td>N.E.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Morris 2011 (50)</td>
<td>6</td>
<td>64</td>
<td>31</td>
<td>12</td>
<td>Before and after AC</td>
<td>0.43 (0.13-1.47)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Nistico 2007 (48)</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>Before and after AC</td>
<td>N.E.</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Yu 2016 (38)</td>
<td>0</td>
<td>3</td>
<td>64</td>
<td>3</td>
<td>During trastuzumab</td>
<td>3.57 (0.14-89.53)</td>
<td>-</td>
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</tr>
</tbody>
</table>

Total heterogeneity: $\tau^2=2.93$; $\chi^2=39.03$, df=6 ($P=0.0001$); $I^2=85$

Test for overall effect: $Z=1.54$ ($P=0.12$)

**Prognostic value of NT-pro BNP**

Seven studies, which included 279 patients in total, investigated (NT-pro)BNP as a biomarker for predicting cardiac dysfunction in patients receiving cardiotoxic breast cancer therapies. NT-proBNP was used in four studies\(^ {135, 136, 139, 141}\) and BNP was used in three\(^ {133, 137, 140}\). One study used a cutoff value of 297 pg/mL\(^ {135}\), another did not mention the cutoff used\(^ {141}\), and the remainder used cutoff values of 100–200 pg/mL\(^ {133, 136, 137, 139, 140}\). In six studies, patients were followed until the end of treatment, but one study\(^ {133}\) had a longer follow-up period (Table 1). The weighted prevalence of cardiac dysfunction was 21.7% (range 3%–47%) in these seven studies. Ten cardiotoxicity events were observed in the study by Fallah-Rad, but there were no NT-proBNP levels above the cut-off value.\(^ {135}\) Unfortunately, two studies lacked key information: Ky et. al. did not present the number of events for women with increased and normal NT-
proBNP levels separately, while Katsurada et al. did not present either the numbers of women with increased NT-proBNP levels or the cutoff levels used. The pooled OR for cardiac dysfunction in patients with elevated (NT-pro)BNP was 2.07 (95% CI 0.50-8.59) (figure 3). Heterogeneity was low (I²=0%). No subgroup analyses were performed due to the low number of studies. Finally, although one study estimated the time to occurrence of cardiac dysfunction during treatment, it failed to show any association with a positive (NT-pro)BNP (HR: 0.89; 95% CI: 0.59–1.35).

**Figure 3** All studies investigating (NT-pro)BNP as a prognostic biomarker for the occurrence of cardiac dysfunction following cardiotoxic therapies for breast cancer

<table>
<thead>
<tr>
<th>Outcome assessed only during treatment</th>
<th>Increased (NT-pro)BNP</th>
<th>Normal (NT-pro)BNP</th>
<th>Prevalence/Incidence (%)</th>
<th>FU</th>
<th>Measurement Biomarker</th>
<th>OR (95% CI)</th>
<th>NR (95% CI)</th>
<th>Odds Ratio for OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falken-Rud 2015 (40)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>31.30%</td>
<td>0 weeks after AC &amp; during trastuzumab</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Katsurada 2014 (46)</td>
<td>NR†</td>
<td>NR†</td>
<td>NR†</td>
<td>47.4%</td>
<td>During AC and during trastuzumab</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ky 2013 (66)</td>
<td>NR†</td>
<td>NR†</td>
<td>NR†</td>
<td>25.50%</td>
<td>90 days after AC &amp; during trastuzumab</td>
<td>-</td>
<td>0.89 (0.55-1.35)</td>
<td>-</td>
</tr>
<tr>
<td>Nakano 2016 (43)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00%</td>
<td>During AC and during trastuzumab</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Onofrio 2012 (42)</td>
<td>2</td>
<td>9</td>
<td>12</td>
<td>28.6%</td>
<td>Unknown; probably during trastuzumab</td>
<td>1.29 (0.23-8.66)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renk 2006 (41)</td>
<td>4</td>
<td>32</td>
<td>0</td>
<td>3.7%</td>
<td>During trastuzumab &amp; paclitaxel</td>
<td>9.71 (3.15-33.75)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vu 2015 (8)</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>3%</td>
<td>During trastuzumab &amp; paclitaxel</td>
<td>5.28 (0.39-138.21)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.07 (0.50-8.59)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a FU (follow-up) is defined as the median number of months after the end of treatment; † NR: Not reported in the article; (NT-pro)BNP: brain natriuretic peptide (BNP) or the N-terminal of BNP (NT-pro)BNP

**Discussion**

To our knowledge, this is the first systematic review evaluating the association of commonly available cardiac biomarkers with cardiac dysfunction in women treated for breast cancer. We found a prevalence of 17.4% (range 0-47.4%) for cardiac dysfunction in women treated for breast cancer. This is high in comparison to prevalence reported in women without a history of breast cancer. In a recent study examining cardiac dysfunction in 350 women who survived breast cancer and 350 women without cancer, cardiac dysfunction was defined as a LVEF<54%. In this study prevalences of 15.3% and 7% respectively, were reported.

In this review, we found insufficient evidence of an association between troponin or (NT-pro)BNP measured during treatment and cardiac dysfunction. When time to occurrence of cardiac dysfunction was taken into account, cardiac dysfunction
manifested earlier in women with positive troponin results during treatment than in women with normal troponin results. However, there were few events and confidence intervals were wide. Because of the small number of studies, small number of patients, and short follow-up durations, the results should be interpreted with caution.

In the included studies, the prevalence of raised troponin levels (median 14%, range 0%–67%) was remarkably high when compared with the prevalence in the general population (2.5%). Because the release of troponin is related to cell apoptosis and reduced cardiac muscle contractility, increased levels may indicate damage to the cardiac muscle during treatment that could lead to cardiac dysfunction. However, in this meta-analysis we did not show a statistically significant relationship between increased troponin levels and cardiac dysfunction, possibly due to the short follow-up of the included studies. (NT-pro)BNP has been associated with increased wall tension in the heart. Given that (NT-pro)BNP levels were increased in 0%–80% of the women in the included studies, it is possible that increased wall tension is present without resulting in clinically demonstrable cardiac dysfunction.

Specific biomarker kinetics might have influenced the results. In the included studies, a positive troponin or (NT-pro)BNP was defined as the presence of at least one increased measurement. However, in the study by Cardinale et al., it was reported that troponin was prognostic for a reduction in LVEF and poor cardiac outcome in patients with persistent (>1 month) increased troponin values. While a single increased value might be either due to reversible damage or to measurement error, a more prolonged elevation may be associated with irreversible cardiomyocyte damage. It is possible that the rate of troponin increase during treatment, or the relative increase in troponin from baseline to the end of treatment, has more prognostic value. For (NT-pro)BNP, only persistently increased levels during treatment or a lower cutoff point might be associated with cardiac dysfunction.

All included studies measured LVEF as primary endpoint for cardiotoxicity, even though a decreased LVEF is a late sign because of the significant functional reserve of the heart. It could be that women with increased troponin or (NT-pro)BNP levels had pre-clinical cardiac dysfunction for which the used imaging techniques (echocardiography, MRI, or MUGA) were insufficiently sensitive. Strain measurements that are currently in development may be able to detect dysfunction caused by damage from cardiotoxic therapies at an earlier stage.

Not all possible risk factors for cardiac dysfunction were considered in the included studies. Factors that may also be considered are the cumulative anthracycline
dose, smoking, and other cardiovascular risk factors. The included studies gave insufficient information for adjusted analysis. Therefore the lack of an association found, should be interpreted with caution.

**Strengths and limitations**
A strength of this systematic review was the extensive literature search, which minimized the risk of missing relevant publications. To avoid missing studies, we did not use a prognostic filter to identify prognostic studies only. In addition, no relation was observed between quality and the prognostic value of either biomarker. However, there were some important limitations. To date, for example, it has proven difficult to standardize LVEF thresholds, and the classification for cardiotoxicity remains a topic of debate. In this review, differences in the definitions of cardiac dysfunction between studies used were revealed. This may have led to under- or overestimation of the prognostic value of the biomarkers. Unfortunately, we also could not investigate the effect of different cardiotoxic treatments on the association between biomarker levels and cardiotoxicity, because this was not analyzed in the included studies. Furthermore, we could not perform a separate analysis of women with either chemotherapy or radiotherapy as most studies included only women with both treatments. Thus, we cannot comment specifically on the value of the cardiac biomarkers in predicting the occurrence of radiation-induced heart disease. Furthermore, the ORs calculated in eight of the studies did not take renal disease into account, while another four studies excluded patients with renal disease. This is especially important because moderate reductions in the estimated glomerular filtration rate can increase serum troponin or (NT-pro)BNP levels.

**Conclusion**
Recognition of cardiac dysfunction is difficult in women treated for breast cancer, not least because symptoms may overlap with other late symptoms of cancer. Therefore, it is important to know who will develop cardiac dysfunction in the long-term. Based on current evidence, this review and analysis showed that the occurrence of cardiac dysfunction cannot be predicted by troponin or (NT-pro)BNP. However, because of the small number of studies, small number of patients, and short follow-up durations, the results should be interpreted with caution. Given the multifactorial nature of cardiovascular disease, it seems only prudent to include additional risk factors in any clinical prediction model. Moving forward, more robust studies with both serial measures and lower thresholds of biomarkers, as well as longer follow-up of cardiac
function, are needed to evaluate the predictive value of these markers in a clinical prediction model.

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