



Review

Cardiac monitoring in HER2-positive patients on trastuzumab treatment: A review and implications for clinical practice



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ABSTRACT

Trastuzumab prolongs progression-free and overall survival in patients with human epidermal growth factor receptor 2 (HER2) positive breast cancer. However, trastuzumab treatment is hampered by cardiotoxicity, defined as a left ventricular ejection fraction (LVEF) decline with a reported incidence ranging from 3 to 27% depending on variable factors. Early identification of patients at increased risk of trastuzumab-induced myocardial damage is of great importance to prevent deterioration to irreversible cardiotoxicity. Although current cardiac monitoring with multi gated acquisition (MUGA) scanning and/or conventional 2D-echocardiography (2DE) have a high availability, their reproducibility are modest, and more sensitive and reliable techniques are needed such as 3D-echocardiography (3DE) and speckle tracking echocardiography (STE). But which other diagnostic imaging modalities are available for patients before and during trastuzumab treatment? In addition, what is the optimal frequency and duration of cardiac monitoring? At last, which biomarker monitoring strategies are currently available for the identification of cardiotoxicity in patients treated with trastuzumab?

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1. Introduction

About 20% [1] of breast tumors show overexpression of human epidermal growth factor receptor 2 (HER2), which is caused by amplification of the HER2-oncogene [2]. HER2 is a transmembrane receptor with an intra- and extracellular domain which plays an important role in normal growth and in the development of various tissues [3,4]. In HER2-overexpressing breast tumors, HER2 is often the main driver through which rapid growth occurs resulting in a poor prognosis [5,6].

Trastuzumab is a humanized monoclonal antibody targeting the extracellular domain of HER2. After binding to the extracellular domain of HER2, trastuzumab inhibits the intracellular tyrosine kinase activity and thereby inhibiting the proliferation of HER2-positive breast cancers resulting in cell death. Therefore, trastuzumab is highly effective in patients with HER2-overexpressing breast cancer. Large randomized phase 3 trials showed that addition of one year of trastuzumab treatment to adjuvant chemotherapy impressively improves overall survival by 24–33% in these patients [7,8]. Likewise, addition of trastuzumab to chemotherapy in first line setting for advanced breast cancer increases the overall survival by 5–8 months [8,9] and even up to 15 months when combined with pertuzumab and docetaxel in first line relapse setting [10].

HER2 is also physiologically expressed on myocytes. Although HER2 is not overexpressed on myocytes, trastuzumab treatment is associated with an increased risk of a decrease in left ventricular ejection fraction (LVEF) which can lead to clinically manifest heart failure. Risk factors for trastuzumab-induced cardiotoxicity are older age (>65 years), hypertension, diabetes mellitus, obesity (BMI >30 kg/m²), previous anthracycline exposure, short time between anthracycline treatment and anti-HER2 treatment, previous radiation therapy and compromised cardiac function before treatment [11–15]. Because of the impressive prognostic impact of trastuzumab treatment, a sizeable number of patients who survive HER2-positive breast cancer due to trastuzumab are at risk for developing cardiotoxicity. Hence, strategies to monitor and prevent long-term disabling cardiotoxicity are of utmost importance.

Although trastuzumab-induced cardiotoxicity is believed to be reversible, some reports suggest that in about 50% it is only partly reversible and in 12–29% it is even irreversible [16–19]. It should be mentioned that these patients in these reports were all pre-treated with anthracyclines, which is a known cause of irreversible cardiotoxicity [20]. Early detection of trastuzumab-derived cardiotoxicity might prevent both reversible and possibly irreversible effects on the heart function [21], because early discontinuation of trastuzumab and/or early implementation of cardio-protective therapies positively impact cardiac outcome [22,23]. Importantly, most patients successfully restart trastuzumab treatment after transient LVEF impairment as it has been shown that trastuzumab does not induce permanent myocyte apoptosis as opposed to anthracyclines that induce cardiomyocyte apoptosis via oxidative stress and free radical formation [24,25]. However, recent studies in human cardiac cell cultures and in mice indicate that trastuzumab can induce myocyte apoptosis leading to irreversible cardiotoxicity

[26–28].

The exact mechanism of trastuzumab-induced cardiotoxicity is still unknown. Some studies show that trastuzumab inhibits cardiomyocyte repair by blocking neuregulin-1 and the HER2 downstream pathway which is required for cardiac repair, especially after anthracycline treatment [29,30]. Another study showed that trastuzumab inhibits topoisomerase IIB, similar to anthracycline, leading to increased reactive oxygen species formation and sequential apoptosis [31]. More research is needed to clearly understand the mechanism of trastuzumab-induced cardiotoxicity.

Thus, monitoring of LVEF during trastuzumab is important. However, current cardiac monitoring techniques have some important limitations. First, LVEF measurements vary between the different techniques used in clinical practice and the reproducibility of many techniques are questionable. Second, LVEF reflects the functional status of the left ventricle (LV) and a LVEF decline is only observed once functional impairment already has occurred. Third, the LVEF is preload and afterload dependence and can substantially change based on different loading conditions [32]. Therefore, for the early detection of injured myocardial cells more sensitive diagnostic tools are required.

In this review, we present an overview and critical appraisal of the state-of-the-art with respect to the role, frequency and duration of cardiac imaging and biomarker monitoring strategies in trastuzumab-treated HER2-positive breast cancer patients.

1.1. What is the incidence of cardiotoxicity of trastuzumab?

The incidence of cardiotoxicity due to trastuzumab treatment varies according to the definition used, whether or not trastuzumab is combined with anthracyclines (sequential or concomitant) and/or other HER2-blocking agents such as pertuzumab and lapatinib which have similar to lower risk of cardiotoxicity (Table 1), treatment duration, and type of imaging technique used. Most trials use the definition of cardiotoxicity related to cancer therapeutics defined by the European Society of Cardiology (ESC) as a decrease in LVEF of >10%-points to a value below 50% [33]. However, consensus on the definition for cardiotoxicity is missing. In this review, the term cardiotoxicity refers to myocardial damage related to anticancer pharmacological therapies.

Trastuzumab monotherapy in adjuvant setting has a relatively low incidence of trastuzumab-related cardiotoxicity of 3–7%, however when given concomitantly with doxorubicin and cyclophosphamide the reported incidence of cardiotoxicity can increase up to 27% in clinical trials [34]. This seems due to cumulative toxicity of simultaneous administration of these agents as the repair of oxidative stress induced by anthracycline is hampered by trastuzumab blocking the HER2 downstream pathway that is required for cardiac repair [39]. Interestingly, concomitant use of trastuzumab and epirubicin appears to be far less cardiotoxic [40,41], resulting in an increased use even in the neo-adjuvant setting. Although both agents are anthracyclines, it remains unknown why epirubicin, a 4'-epimer of doxorubicin, is less cardiotoxic [42].

An important issue to address is whether these incidence rates

Table 1
Incidence of cardiotoxicity varying per chemotherapeutic and definition used.

Exposed chemotherapeutic	Incidence	Cardiotoxicity definition used:
Trastuzumab monotherapy [34]	3–7%	CREC criteria: 1. Cardiomyopathy characterized by a decrease in cardiac LVEF global or severe in the septum 2. Symptoms of CHF 3. Associated sign of CHF, including S3 gallop, tachycardia or both 4. Symptomatic decline in LVEF >5% to an LVEF <55% or an asymptomatic LVEF decline of >10% to an LVEF <55%.
Trastuzumab with previous anthracycline: epirubicin [117]	4%	CHF
Trastuzumab with previous anthracycline: doxorubicin [34]	13%	CREC criteria as mentioned above.
Trastuzumab, epirubicin and cyclophosphamide [118]	5%	Symptomatic heart failure NYHA class III or IV associated with an absolute decrease in LVEF of more than 10% points to less than 50%
Trastuzumab, doxorubicin and cyclophosphamide [34]	27%	CREC criteria as mentioned above.
Trastuzumab + HER2 inhibitor: pertuzumab [119]	4%	LVEF of less than 50% and a decrease of more than 10% from baseline
Trastuzumab + intracellular HER2-kinase inhibitor: lapatinib [120]	3%	LVEF of less than 50% and a decrease of more than 10% from baseline or congestive heart failure or myocardial ischemia

Abbreviations: CREC, Cardiac Review and Evaluation Committee; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; NYHA, New York Heart Association; HER, human epidermal growth factor receptor.

are similar to those among older patients (aged >70 years), patients with comorbidities and with a history of cardiac disease or heart failure who are excluded in most clinical trials. Population based, retrospective studies indicate that the rates and impact of trastuzumab-induced cardiotoxicity might be higher in 'real world' patients than mentioned in clinical trials [43]. For example, the 5-year cumulative incidence of cardiotoxicity in older patients (aged >75 years) treated with anthracycline and trastuzumab was 40.7% compared to incidence of 27% found in a clinical trial [34,44]. Therefore, the incidence rates of these selected patients from prospective clinical trials cannot be unconditionally extrapolated to 'real world' patients.

2. Which diagnostic imaging modalities are currently available for patients on trastuzumab treatment?

2.1. MUGA scan

Multi gated acquisition (MUGA) scanning is a frequently used

imaging modality for evaluation of LVEF evolution during chemotherapy and trastuzumab therapy. MUGA scanning is a minimal-invasive nuclear imaging technique using ^{99m}Tc -erythrocyte labeling. It is capable to measure systolic-diastolic changes in radioactivity within the LV to calculate the blood flow leaving the LV, i.e. the LVEF. This method has a high availability and few technical limitations as it can be done in all patients without limitations due to obesity, poor acoustic windows or presence of cardiac devices such as pacemakers or defibrillators (see Table 2) [45]. Nevertheless, major limitations of measuring the LVEF with MUGA scans are the questionable accuracy, modest reproducibility, cumulative radiation exposure of serial monitoring, and its limited information on structural cardiac dysfunction [46]. The accuracy of MUGA scans remains dubious as contemporary MUGA scans are performed with a large-field-of-view, two head system gamma cameras that do not allow optimal patient positioning [47]. In addition, assessment of the LVEF with MUGA scans has shown to have large inter- and intra-observer variations and varies between hospital centers and software packages computer processing

Table 2
Various imaging techniques for the detection of cardiotoxicity.

Imaging technique	Advantages	Limitations
Echocardiography • Two-dimensional	Wide availability Lack of radiation exposure Cost-effective Assessment of myocardial structures	High inter-observer variability Dependent on image quality Insensitive to detect small LVEF changes
• Three-dimensional	High accuracy in detecting small LVEF changes High reproducibility compared to 2DE Lack of radiation exposure Cost-effective Assessment of myocardial structures	Dependent on image quality and operator experience Low availability in cancer centers
Speckle tracking echocardiography	GLS for subclinical identification of cardiotoxicity Relatively low angle dependence Same advantages as echocardiography	Inter-vendor variability Technical requirements Dependent on image quality Low temporal resolution Different results due to different algorithms
Cardiac magnetic resonance	High accuracy High reproducibility Assessment of myocardial structures/myocardial fibrosis Helps identifying the cause of cardiotoxicity	Limited availability High costs Low temporal resolution Patients adaptation (claustrophobia, breath hold and long acquisition times)
MUGA scanning	Low radiation exposure Availability Few technical limitations	Limited in patients with metallic prosthetics High cumulative radiation exposure Limited informative on cardiac structures Lower accuracy

Abbreviations: LVEF, left ventricular ejection fraction; MUGA, multi-gated acquisition scan.

systems, where in the latter the variation can be 5.1 LVEF %-points [48,49].

Besides this, the radiation exposure from a single MUGA scan is approximately 10 mSv per scan, which is three times the average yearly background radiation [46]. Thus, serial monitoring of the LVEF results in an unacceptable high cumulative exposure, while most breast cancer patients already have an increased radiation exposure due to other imaging modalities used for staging of the breast cancer. Fortunately, new 3D MUGA cameras allow obtaining the LVEF with less than 2 mSv [50], but these cameras are not yet implemented in daily clinical practice.

2.2. Echocardiography, ultrasound of the heart

Cardiac evaluation before, during and after trastuzumab treatment can also be performed with conventional echocardiography. Advantages of echocardiography over MUGA are its lack of radiation exposure and the possibility to assess the complete cardiac structure. Disadvantages of echocardiography are the high inter-observer variability, dependency on image quality, insensitivity to detect small LVEF changes and false positive rate of cardiotoxicity of 3.6% [51].

Three-dimensional echocardiography (3DE) has a better accuracy in detecting LVEF below the lower limit of normal and a better reproducibility than the conventional two-dimensional echocardiography (2DE) biplane Simpson method [52,53]. However, applicability of 3DE in the oncologic setting is limited, because it remains dependent on availability in the different hospitals, requires adequate image quality (more so than 2DE) and operator experience (Table 2).

3. Which new diagnostic imaging modalities are available for patients on trastuzumab treatment?

3.1. Speckle tracking echocardiography

A sensitive and promising diagnostic modality is the so-called strain imaging with speckle tracking echocardiography (STE) [47]. Dedicated STE software is capable to track the movement of speckles, which are tracking points that are placed automatically on the LV wall in the conventional 2D-echocardiographic images and reflect the movement of the different segments of the heart [54]. Additionally, STE can also be applied in 3DE and CMR, which is currently not frequently observed in clinical practice [55].

Strain is a method for measuring regional or global myocardial deformation, i.e. the proportional change in dimension of the heart in relation to the original dimension of the heart. Consequently, strain measurement with STE is capable to quantify myocardial function regionally, and to identify subtle and subclinical LV dysfunction. New parameters for myocardial function assessment emerged with the introducing of STE, including global longitudinal strain (GLS), global circumferential strain (GCS) and global radial strain (GRS). The GLS reflects the longitudinal contraction of the myocardium, and thus represents the global left ventricular function [56,57]. The GCS reflects the circumferential contraction of the myocardium and is expressed as a negative percentage value, likewise as the GLS, as the myocardium shortens during contraction. Finally, the GRS reflects the radial contraction of the myocardium, i.e. the lengthening of the myocardium and is expressed as a positive percentage. In the general population, GLS has a better prognostic value than 2DE-LVEF to predict major adverse cardiac events including hospitalisation due to heart failure and cardiac death during an average follow-up of 27 months [58].

In patients with HER2-positive breast cancer treated with anthracyclines and trastuzumab an GLS decline from baseline

measured with STE precedes an LVEF decline measured with 2DE [59–62]. The systematic review of Thavendiranathan et al. demonstrated that an early relative reduction in GLS of $\geq 10\%$ during therapy is very likely to be indicative for cardiotoxicity defined as an LVEF decline of $\geq 5\%$ to an LVEF $< 55\%$ or symptomatic heart failure [63]. In addition, the expert consensus document of the American Society of Echocardiography (ASE) and European Association for Cardiovascular Imaging (EACVI) suggests that a relative change in GLS $> 15\%$ from baseline is likely to indicate of clinically meaningful cardiotoxicity [47]. Likewise, a recent meta-analysis showed that the absolute GLS cutoff values, ranging from -21% to -14% , can be useful to stratify patients at high risk of developing cardiotoxicity which is important in patients without baseline cardiac imaging [64]. Although a reduction in GLS is correlated with an reduction in LVEF [59–62], little is known about the predictive value of an impaired GLS on long-term cardiotoxicity, the optimal GLS cutoff value and the development of an impaired GLS to symptomatic heart failure. Importantly, STE has some disadvantages including the need for high-resolution image quality and the insufficient standardization of measurements by different echocardiographic vendors resulting in non-comparative results [33].

Thus, the role of speckle tracking echocardiography in early detection of subclinical cardiotoxicity in the oncologic setting seems promising. However, these findings should be validated in larger prospective multicenter studies. The results of the SUCCOUR trial, which is a currently ongoing randomized controlled trial that randomly allocates patients on cardiotoxic cancer treatment to an GLS-guided treatment strategy or LVEF-guided treatment strategy, are urgently awaited in this respect [65].

3.2. Cardiac MRI

Cardiac magnetic resonance (CMR) imaging is often considered the gold standard for evaluation of the cardiac structure and cardiac function. Besides quantification of cardiac dysfunction, CMR provides insight in its likely cause, as it provides information about the cardiac structure and myocardial fibrosis because of its high resolution [66]. Other advantages of CMR are its high reproducibility and accuracy. The major limitations of CMR however, are its high costs and therefore limited availability, the reason why CMR is currently not used for serial monitoring of the LVEF.

3.3. Comparison of imaging modalities and summary

LVEF assessments with MUGA scanning, echocardiography and CMR show poor correlation [67]. Discordance between MUGA and CMR in measuring the LVEF particularly occurred in small left ventricles, small hearts and hearts with a history of atrial fibrillation [68]. Furthermore, 2DE is suggested to overestimate the mean LVEF with 5% and has a lower sensitivity in detecting LVEF values less than 50% compared to CMR [69]. Possible false-positive results due to measuring the LVEF with echocardiography or MUGA cannot be excluded. In contrast to conventional 2DE, 2D-STE is highly correlated with CMR in measuring the LVEF [70]. Comparisons of 2D-STE with 3D-STE showed that 3D-STE had lower inter- and intra-observer variability [71]. Therefore, it is recommended to use the same monitoring modality for baseline and follow-up LVEF assessments [33,72].

Concluding, not 2DE or MUGA scanning but 3DE seems most suitable for cardiac monitoring of patients on trastuzumab due to the high reproducibility, high accuracy and the ability to assess the complete cardiac structure. In addition, strain measurement with STE seems promising to detect myocardial damage in an early stage compared to LVEF measurement.

4. What is the optimal frequency and duration of cardiac monitoring for patients on trastuzumab?

Another important question for clinicians who treat patients with trastuzumab is: what is the optimal frequency and duration of cardiac monitoring? The US Food and Drug Administration (FDA) label of trastuzumab recommends, based on protocols in clinical trials, LVEF monitoring prior to initiation of trastuzumab and every 3 months during and upon completion of adjuvant trastuzumab treatment. After completion of 1 year trastuzumab in the adjuvant setting, LVEF monitoring every 6 months for at least 2 years is recommended. If trastuzumab is withheld for significant LV cardiac dysfunction, cardiac monitoring should occur monthly. These recommendations have been adopted into clinical practical guidelines by the European Society of Medical Oncology (ESMO) [73], European Society of Cardiology (ESC) [33] and American Society of Clinical Oncology (ASCO) [11]. The ESC differentiates between low risk patients (normal baseline echocardiogram and no clinical risk factors) for whom cardiac monitoring every 3 months is advised and high risk patients (abnormal baseline echocardiography and clinical risk factors) for whom even more frequent cardiac monitoring is advised. Interestingly, it should be noted that the ASCO recommends cardiac monitoring 6–12 months after completion of therapy in high risk patients. Lastly, the ESMO recommends cardiac monitoring infrequently in the absence of symptoms during trastuzumab for advanced breast cancer. As these guidelines are mainly based on expert consensus rather than trial data and as they have not been prospectively validated, the optimal frequency of cardiac monitoring during trastuzumab therapy has not been established yet.

Table 3 gives an overview of frequency and duration of cardiac monitoring during and after trastuzumab treatment in current literature. In cohort studies, cardiac monitoring was most often performed every 3–4 months in the first year of trastuzumab treatment for early-stage breast cancer. However, after discontinuation of trastuzumab for early-stage breast cancer, cardiac monitoring was only observed in a few studies (4 out of the 13). During trastuzumab treatment for advanced-stage disease, cardiac monitoring was performed every 3–8 months up until 2 years of trastuzumab treatment. After 2 years of trastuzumab treatment, cardiac monitoring was only observed in 1 study [74]. In addition, in randomized controlled trials, cardiac monitoring was performed every 3–6 months during the first year of trastuzumab treatment or even 2 years in some studies [9,10,75,76]. After discontinuation of trastuzumab, cardiac monitoring was performed in the majority of the studies (10 out of the 16), which was not often observed in the cohort studies. Studies investigating cardiac monitoring after discontinuation of trastuzumab showed a low cumulative incidence of cardiotoxicity, defined as LVEF decline >10%-points from baseline to LVEF <50% or <55% or New York Heart Association (NYHA) class III or IV, of 0.5–5.8% [19,77,78]. However, conflicting results are found regarding the development of heart failure 2 years after starting trastuzumab. An 2-fold increased risk of late heart failure of trastuzumab compared to chemotherapy alone has been found in one study [79], whereas other studies did not find excess risk of late heart failure after trastuzumab discontinuation [80,81]. Concluding, cardiac monitoring, predominantly with echocardiography or MUGA, occurs most often every 3 months during trastuzumab treatment for early-stage breast cancer, and more infrequently during trastuzumab treatment for advanced-stage breast cancer. Based on current knowledge, the additional value of frequent cardiac monitoring after discontinuation of trastuzumab has not been confirmed. It would be reasonable to consider a less frequent schedule or omission of monitoring after discontinuation of trastuzumab.

5. What is the role of cardiac biomarkers in detecting cardiotoxicity?

5.1. Troponin

Cardiac troponin regulates the contractile element actin and myosin. It is a protein with three subunits: T, I and C. Troponin I and troponin T are exclusively present in myocardial cells, whereas troponin C is also present in slow-twitch skeletal muscles [101]. Elevated cardiac troponin is indicative of myocardial damage due to for instance acute coronary syndrome or acute myocarditis [102,103]. Therefore, it can be expected that myocardial damage due to trastuzumab therapy can lead to increased troponin levels [104].

Studies measuring conventional troponin showed conflicting results (Table 4). Some studies, in which patients received anthracycline and trastuzumab, demonstrate a relationship between increased troponin values during trastuzumab treatment and an LVEF decline [105,106]. In particular, patients with increased troponin values after anthracycline treatment had higher risk of developing cardiotoxicity than those with stable (low) values [107]. However, most studies did not demonstrate this relationship in patients with trastuzumab-based chemotherapy [108–113]. One of these studies concluded that elevation of troponin preceded changes in LVEF, but not particularly predicted clinical cardiac dysfunction [112]. The most likely explanation for the conflicting results is the timing of conventional troponin measurement [114] and the preceding treatment with anthracyclines [107,115,116].

However, the studies that used high-sensitivity (hs) troponin assays demonstrated a relationship between increased hs-troponin values and LVEF [59,60,116,117]. It is plausible that hs-troponin assays have a better range for detection of cardiac dysfunction in patients treated with trastuzumab than conventional troponin assays. Lastly, sex-specific cut-off values of troponin assays have to be taken into account [121].

5.2. NT-proBNP

The N-terminal fragment of the pro-hormone brain natriuretic peptide (BNP), NT-proBNP, is the inactive N-terminal fragment of the biologically active hormone BNP and is secreted by myocytes in response to increased cardiac transmural pressure. NT-proBNP has shown to be useful as a diagnostic and prognostic indicator of heart failure in multiple clinical settings, as summarized in the systematic review by Santaguida et al. [122].

Increased NT-proBNP values have been associated with cardiotoxicity in patients treated with anthracyclines [118,123,124]. Interestingly, another study demonstrated that in patients treated with anthracyclines and trastuzumab the risk of LVEF decline increased by almost 30% for each 10 ng/dL increase in NT-proBNP during trastuzumab treatment [117]. However, elevated NT-proBNP values are also seen in patients receiving trastuzumab with a normal LVEF [125]. Furthermore, not every study demonstrated an association between NT-proBNP and cardiotoxicity during anthracycline and trastuzumab (Table 4) [59,60,106,111,113,119]. This is possibly due to the wide biological variation (analytical and intra-individual) of natriuretic peptides levels due to secretory burst and rapid turnover [126].

5.3. CRP

C-reactive protein (CRP) is a marker of inflammation which plays a role in atherosclerosis and acute coronary syndrome [127,128]. It has also been demonstrated to be of prognostic value in patients with chronic heart failure [129]. Therefore, it could be

Table 3

Overview of studies in which cardiotoxicity was monitored during and after trastuzumab treatment.

Study	N	Stage	Treatment	Cardiac monitoring modality	During trastuzumab treatment						Monthly interval	After trastuzumab			Cardiotoxicity incidence	Definition of cardiotoxicity	Additional remarks
					Baseline	0–3 months	3–6 months	6–12 months	1–2 years	>2 years		0–3 months	3–6 months	>6 months			
Cohort																	
Tarantini (2012) [82]	499	Early	AC + Tax + T	Echo	+	+	+	+	NA	NA	3	–	–	–	27%	LVEF decline >10% or <50% or heart failure	
Piotrowski (2012) [83]	253	Early	AC + Tax + T	2DE	+	+	+	+	NA	NA	3	+	+		21%	LVEF decline >15%, or >10% to <50% or signs of heart failure	
Cochet (2011) [84]	118	Early	AC + Tax + T	Radionuclide angiography	+	+	+	+	NA	NA	3	–	–	–	15%	Asymptomatic LVEF decline >10%	
Dent (2012) [85]	48	Early	AC + T	Echo and MUGA	+	+	+	+	NA	NA	3	–	–	–	59%	LVEF decline ≥10 or heart failure	Repeat monitoring as clinically indicated
Matos (2016) [86]	92	Early	AC + T	2DE	+	–	+	+	NA	NA	4	–	–	–	21%	LVEF decline >10% or signs of heart failure	
Seferina (2016) [87]	230	Early	AC + Tax + T	Unknown	+	+	+	+	NA	NA	3	–	–	–	13%	LVEF decline >10% to <50%	
Visser (2016) [88]	171	Early	Chemo + T	MUGA	+	+	+	+	NA	NA	3	–	+	+	NA	NA	
Chavez (2015) [89]	2203	Early	Chemo + T	Echo or MUGA	76% ^a	53% ^a	40% ^a	30% ^a	NA	NA	4(43%) ^a	+	+	–	NA	NA	
Lidbrink (2019) [90]	3733	Early	AC + Tax + T	Echo, MUGA, CMR or other	+	+	+		NA	NA	3	–	+	+	3%	Symptomatic heart failure	Until 2 years after stop T
Grazziotin (2017) [91]	109	Early/advanced	AC + Tax + T	Echo	+	+	+	+	–	–	3–4	–	–	–	53%	LVEF decline >10% or <50% or heart failure	Frequency depending on physicians
Sun (2016) [74]	105	Early/advanced	AC + T	Echo	+	+	+	+	+	+	3				NA	NA	
Davis (2016) [92]	43	Early/advanced	AC + Tax + T	Echo	+	–	–	+-	+-	–	8	–	–	–	18%	CREC criteria (Table 1)	
Extra (2010) [93]	623	Advanced	AC + T	Unknown	+	+/-	+/-	+/-	+	–	No	–	–	–	3%	Heart failure	
RCT																	
Perez (2008) [78]	2148	Early	AC + P	Echo or MUGA	+	+	+	+	NA	NA	3	+	+	–	3%	Cardiac event assessed by 3 cardiologists	
Suter (2007) [94]	3386	Early	AC + P + T	Echo or MUGA	+	+	+	+	NA	NA	6	+	+	+	7%	LVEF decline >10% to <50%	
Romond (2005) [7]	3351	Early	AC + P	Echo or MUGA	+	+	+	+	NA	NA	NA	–	–	–	4%	NYHA III/IV heart failure after 3 years	
Joensuu (2009) [72]	232	Early	AC + P + T	(Isotope) echo	+	–	+	–	NA	NA	NA	–	–	+	1%	Heart failure	Up to 5 years after start T
Tan-Chiu (2005) [19]	2043	Early	Tax + FEC + T	V + FEC + T	+	–	+	+	NA	NA	NA	–	+	–	4%	NYHA III/IV heart failure after 3 years	Repeat monitoring as clinically indicated
Piccart-Gebhart (2005) [95]	5081	Early	AC + P + T	MUGA scan	+	+	+	+	NA	NA	6	–	+	+	1%	Symptomatic heart failure	Up to 5 years after start T
Cameron (2017) [77]	5102	Early	AC + T	Echo or MUGA	+	+	+	+	NA	NA	6	–	+	+	1%	NYHA III/IV and LVEF decline >10% to <50%	3 years after start T annually to 10 years
Gianni (2010) [96]	235	Early	AC + Tax + T	Echo or MUGA, + ECG	+	–	–	–	NA	NA	NA	+	–	–	2%	NYHA III/IV heart failure	
Slamon (2011) [97]	3222	Early	ACT-T + T	Echo ^b or MUGA	+	+	–	+	NA	NA	NA	–	–	+	19%	Heart failure and LVEF decline >10%	Up to 5 years after start of T
Swain (2015) [10]	808	Advanced	Pe + T + Tax	TCH	+	+	+	+	+	+	3	+	+	+	6%	LVEF decline >10% to <50%	Up to 1.5 year after stop of T
	296	Advanced	T + Tax	Echo or MUGA	+	+	+	+	+	+	1	+	–	–	7%	LVEF decline <20%	

Blackwell (2010) [75]			AC + Tax + T T + L														
Marty (2005) [9]	186	Advanced	AC + T T + Tax	Echo or MUGA	+	+	+	+	+	+	3	–	–	–	2%	Symptomatic heart failure	
Von Minckwitz (2009) [98]	156	Advanced	T T + C	Echo	+	–	–	–	–	–	NA	–	–	–	5%	NYHA class III/IV heart failure	Repeat monitoring as clinically indicated
Gasparini (2007) [99]	123	Advanced	T T + P	Echo or MUGA	+	+	+	+	–	–	3	–	–	–	0%	Symptomatic heart failure	
Kaufman (2009) [76]	207	Advanced	T T + A	Unknown	–	+	+	+	+	–	2 months	–	–	–	14%	Cardiac events: heart failure, LVEF decline or discontinuation of T	
Müller (2018) [100]	19	Advanced	T	Echo or MUGA	–	–	–	–	–	–	No				0%	NYHA class II-IV	Monitoring as clinically indicated

Abbreviations: AC, anthracycline + cyclophosphamide; T, trastuzumab; Tax, taxanes; P, paclitaxel; D, doxorubicin; V, vinorelbine; FEC, fluorouracil, epirubicin, docetaxel; Pe, pertuzumab; ACT-T, doxorubicin, cyclophosphamide followed by docetaxel; TCH, doxetaxel, carboplatin and trastuzumab; L, lapatinib; C, capecitabine; A, anastrozole; Echo, echocardiography; MUGA, multi-gated acquisition scan; CMR, cardiac magnetic resonance imaging; NA, not applicable; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; CREC, Cardiac Review and Evaluation Committee; NYHA, New York Heart Association.

^a Adherence rate of cardiac monitoring.

^b Echocardiography is preferred cardiac monitoring method, same method is advised. + cardiac monitoring performed, - monitoring not performed.

Table 4
(Cardiac) biomarkers for identification of cardiotoxicity.

Type cardiac biomarker	Study	Number of patients	Chemotherapy	Time point(s) indicative of cardiotoxicity	Detection of cardiotoxicity?	Definition cardiotoxicity:
Troponin T	Fallah-rad (2011) [108]	42	AC + T	12 months after initiation of T treatment	–	Absolute LVEF decline > 10% from baseline to <55% with symptoms of heart failure
	Ponde (2018) [109]	280	T + L	Baseline 2 and 18 weeks after initiation of T treatment	–	Symptomatic heart failure NYHA class III or IV, or cardiac death and secondary cardiac events were asymptomatic or symptomatic absolute LVEF decline <50% and >10%-points
	Goel (2019) [113]	217	AC + T	Baseline, after AC and every 3 months during T	–	Absolute LVEF decline >15% from baseline, or absolute LVEF decline >10%–50%.
Troponin I	Cardinale (2004) [107]	703	AC + Tax + C	Soon after chemotherapy and 1 month after chemotherapy	+	Death with cardiac cause Acute pulmonary edema Overt heart failure Asymptomatic LVEF reduction ≥ 25% Arrhythmias and conduction disturbances requiring a pacemaker Absolute LVEF decline
	Cardinale (2002) [115]	211	High dose chemotherapy	After high dose chemotherapy	+	
	Onitilo (2012) [110]	54	T	Baseline vs. every 3 weeks during 1 year T treatment	–	Absolute LVEF decline ≥15% from baseline or an LVEF<50%
	Cardinale (2010) [105]	251	AC + T	Baseline vs. during T treatment	+	Absolute LVEF decline >10% from baseline to <50%
	Ky (2014) [106]	78	AC + T	Baseline vs. 3 months after initiation of AC	+	CREC definition of cardiotoxicity
	Putt (2015) [111]	78	AC + Tax + T	Baseline vs. every 3 months–15 months after start treatment	–	CREC definition of cardiotoxicity
		59	AC + L + T		–	Maximal absolute LVEF decline (max LVEF –min LVEF/min LVEF) and congestive heart failure

(continued on next page)

Table 4 (continued)

Type cardiac biomarker	Study	Number of patients	Chemotherapy	Time point(s) indicative of cardiotoxicity	Detection of cardiotoxicity?	Definition cardiotoxicity:
	Morris (2011) [112]			Maximum levels of: Baseline, 2 months after start AC, 3 months after start AC		
Hs-Troponin T	Kitayama (2017) [116]	40	AC + T	Baseline vs. during AC and/or T treatment	+	Absolute LVEF decline >10% from baseline, symptomatic cardiac failure, acute coronary syndrome or arrhythmias
	Zardavas (2017) [117]	452	AC + T	Baseline	+	Absolute LVEF decline of >10% from baseline to <50%
Hs-Troponin I	Sawaya (2011) [60]	43	AC + T	Baseline vs. completion of AC treatment	+	Absolute LVEF decline of ≥5% to <55% with symptoms of heart failure or an asymptomatic absolute LVEF decline ≥10% to <55%
	Sawaya (2012) [59]	81	AC + Tax + T	At completion of AC treatment	+	Absolute LVEF decline of ≥5% to <55% with symptoms of heart failure or an asymptomatic absolute LVEF decline ≥10% to <55%
	Zardavas (2017) [117]	452	AC + T	Baseline	+	Absolute LVEF decline of >10% from baseline to <50%
NT-proBNP	Romano (2011) [118]	71	AC + Tax + T	Baseline vs. highest value during chemotherapy	+	Absolute LVEF decline ≥20% and/or increase in LV end systolic volume ≥15% from baseline at 3, 6 and 12 months;
	Zardavas (2017) [117]	452	AC + T	Baseline vs. highest value during T treatment	+	Absolute LVEF decline of >10% from baseline to <50%
	Ponde (2018) [109]	280	L + T	Baseline 2 and 18 weeks after initiation of T treatment	–	Symptomatic heart failure NYHA class III or IV, or cardiac death and secondary cardiac events were asymptomatic or symptomatic absolute LVEF decline <50% and >10%-points
	Ky (2014) [106]	78	AC + T	Baseline vs. 3 months after initiation of AC	–	CREC definition of cardiotoxicity
	Sawaya (2011) [60]	43	AC + T	3 months after initiation of AC Baseline vs. 3 months after initiation of AC treatment	–	Absolute LVEF decline of ≥5% to <55% with symptoms of heart failure or an asymptomatic absolute LVEF decline ≥10% to <55%
	Putt (2015) [111]	78	AC + Tax + T	Baseline vs. every 3 months–15 months after start T	–	CREC definition of cardiotoxicity
	Sawaya (2012) [59]	81	AC + Tax + T	Baseline vs. during 1 year follow-up	–	Absolute LVEF decline of ≥5% to <55% with symptoms of heart failure or an asymptomatic absolute LVEF decline ≥10% to <55%
	Fallah-rad (2011) [108]	42	AC + T	12 months after initiation of T treatment	–	Absolute LVEF decline >10% to <55% with symptoms of congestive heart failure.
	Bouwter (2019) [119]	135	AC + T	Baseline vs. during Treatment	–	Absolute LVEF decline >10% and/or LVEF <45%
	Goel (2019) [113]	217	AC + T	Baseline, after AC and every 3 months during T	–	Absolute LVEF decline >15% from baseline, or absolute LVEF decline >10%–50%.
hs-CRP	Putt (2015) [111]	78	AC + Tax + T	Baseline vs. every 3 months–15 months after start T	–	CREC definition of cardiotoxicity
	Onitilo (2012) [110]	54	T	Maximum values from baseline and every 3 weeks during 1 year T	+	Absolute LVEF decline ≥15% from baseline or an LVEF <50%
	Ky (2014) [106]	78	AC + T	Baseline vs. 3 months after initiation of AC	–	CREC definition of cardiotoxicity
CRP	Fallah-rad (2011) [108]	42	AC + T	12 months after initiation of T treatment	–	Absolute LVEF decline >10% to <55% with symptoms of congestive heart failure.
	Morris (2011) [112]	59	AC + L + T	Baseline	–	Maximal absolute LVEF decline (max LVEF –min LVEF/min LVEF) and congestive heart failure
MPO	Ky (2014) [106]	78	AC + T	Baseline vs. 3 months after initiation of AC	+	CREC definition of cardiotoxicity
	Putt (2015) [111]	78	AC + Tax + T	Baseline vs. every 3 months–15 months after start T	+	CREC definition of cardiotoxicity
IgE	Beer (2016) [120]	7	AC + T	Baseline	+	Absolute LVEF decline ≥10 from baseline to <50%
ST2	Sawaya (2012) [59]	81	AC + T	Baseline vs. during 1 year follow-up	–	Absolute LVEF decline of ≥5% to <55% with symptoms of heart failure or an asymptomatic absolute LVEF decline ≥10% to <55%

Abbreviations: AC, anthracycline + cyclophosphamide; T, trastuzumab; L, lapatinib; Tax, taxanes; C, carboplatin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CREC, Cardiac Review and Evaluation Committee.

hypothesized that inflammation could also have a role in trastuzumab-induced cardiotoxicity.

A small study of 54 breast cancer patients undergoing trastuzumab therapy revealed that normal hs-CRP values may be associated with low risk of developing a LVEF decline, thus suggesting that hs-CRP might have a high negative predictive value (Table 4). However, multiple other studies could not demonstrate this relationship [108,111,112].

5.4. MPO

Myeloperoxidase (MPO) is a pro-inflammatory enzyme secreted by polymorph nuclear neutrophils that is involved in lipid peroxidation and released in periods of oxidative stress [130,131]. MPO is associated with increased risk of cardiac problems such as coronary artery disease and heart failure exacerbations [132,133]. The potential pathophysiological mechanisms of cardiotoxicity due to anthracyclines or trastuzumab involves oxidative stress [134]. Therefore, it is biologically plausible that elevated MPO after anthracycline and trastuzumab therapy can be associated with cardiotoxicity.

The study of Ky et al. demonstrated that 1 standard deviation increase in MPO during anthracycline treatment in patients with early-staged breast cancer was associated with a 34% increased risk of subsequent cardiotoxicity [106]. In addition, another study found that increases in MPO were associated with cardiotoxicity during anthracycline and trastuzumab treatment [111].

5.5. IgE

Immunoglobulin E (IgE) is involved in the immune defense against parasitic diseases and in the pathogenesis of allergic diseases. IgE is synthesized by plasma cells and the expression is controlled by two CD4⁺ T-helper cells: Th1 and Th2 which have counter-regulatory effects. It is known that the immune system is involved in maintaining myocardial homeostasis in patients with heart failure as it influences myocyte hypertrophy and myocyte loss through apoptosis [135]. The precise role of the immune system in trastuzumab-induced cardiotoxicity is yet unknown.

The study of Beer et al. showed that high baseline IgE levels were associated with a lower risk of cardiotoxicity in patients treated with anthracyclines and trastuzumab [120]. This suggests that the immune system may be a potential mediator in cardiotoxicity caused by anthracyclines or trastuzumab. An interesting finding which needs further investigation.

5.6. ST2

Suppressor of tumorigenicity 2 (ST2) is a member of the interleukin 1 receptor family. It has a transmembrane (ST2L) and a soluble (sST2) form [136]. As sST2 concentrations reflect cardiovascular stress and myocardial fibrosis, it has become a relative new prognostic biomarker in both acute and chronic heart failure [137,138]. Combination of ST2 with other cardiac biomarkers may improve the prognostic ability of each individual biomarker in predicting myocardial damage [139]. The 2017 American College of Cardiology/American Heart Association recommends ST2 in addition to NT-proBNP as biomarker of myocardial fibrosis or injury for additive risk stratification [140]. In a small study of 81 patients treated with anthracyclines and trastuzumab, ST2 levels did not change during anthracycline and trastuzumab treatment and measurement of ST2 at completion of anthracyclines did not predict subsequent development of cardiotoxicity [59].

5.7. Summary of different biomarkers

Measuring cardiac biomarkers may also be a potential diagnostic tool for early identification of cardiotoxicity. In theory, biomarker monitoring strategies are less expensive, less time-consuming for the patient, easier to perform and may possibly detect myocardial damage at an earlier stage than imaging strategies. However, early identification of patients at high risk for cardiotoxicity with cardiac biomarkers remains questionable and the reason why routine assessment of cardiac biomarkers has not yet been adopted in daily practice. Taken together, measurement of (a combination of) MPO and hs-troponin seems most promising in detecting cardiotoxicity in patients treated with anthracyclines and trastuzumab. The utility of ST2 and IgE in detecting cardiotoxicity in these patients has to be additionally studied in order to be incorporated into clinical practice. Further research is required to determine the optimal (combination of) biomarker(s), timing of biomarker analysis and the optimal intervention based on these biomarker results.

6. Summary

Concluding, trastuzumab treatment prolongs progression-free and overall survival in patients with HER2-positive breast cancer, but is hampered by cardiotoxicity. Identification of patients at increased risk of trastuzumab-induced cardiotoxicity is of great importance to prevent deterioration to irreversible cardiotoxicity. Nowadays, 3DE seems most suitable for cardiac monitoring of patients treated with trastuzumab due to the high reproducibility, high accuracy, the ability to assess the complete cardiac structure and the possibility to measure strain. Strain measurement with STE seems promising to detect myocardial damage in an early stage compared to LVEF measurement. However, high quality images and certain technical requirements are needed to perform STE. In addition to STE, early signs of myocardial damage could possibly be detected by measuring cardiac biomarkers of which (a combination of) MPO and hs-troponin are most promising. The optimal frequency of cardiac monitoring during trastuzumab therapy has not been established yet. Literature indicates that averagely cardiac monitoring occurs every 3 months during trastuzumab for early-stage breast cancer and more infrequently during trastuzumab for advanced-stage breast cancer. The additional value of frequent cardiac monitoring after discontinuation of trastuzumab has not been confirmed. To validate the role, frequency and duration of STE and certain cardiac biomarkers in clinical practice more and larger studies with clearly defined endpoints in a homogeneous population are urgently awaited.

Ethical approval

Ethical approval was not required for this review.

Declaration of competing interest

All authors indicate no financial relationships.

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