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CHAPTER 10

Cardiac Toxicity of HER-2 Targeted Regimens

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INTRODUCTION

The advent of anti-HER2 cancer therapies has heralded significantly improved survival rates along with decreased recurrence in breast cancer and is being increasingly used in other malignancies, including gastrointestinal tumors. However, a known effect that has been well documented is the onset of cardiomyopathy during treatment, which may potentially alter or delay critical treatment to these patients. This chapter reviews the proposed mechanisms of HER2-related cardiotoxicity, its incidence in major cancer trials and in the postapproval era—much of it related to trastuzumab—and proposed cardioprotective and surveillance strategies to potentially reduce the risk of developing cardiotoxicity.

PROPOSED MECHANISM OF HER2 CARDIOTOXICITY

In recent American and European cardiology society Expert Consensus statements, Cancer therapeutics–related cardiac dysfunction (CTRCD) is defined as a decline in left ventricular ejection fraction (LVEF) of >10% to a value of <53% and confirmed on repeat study after 2–3 weeks.[1] A "multiple-hit hypothesis" has been proposed as a potential explanation for the development of cardiotoxicity. This hypothesis states that patients with breast cancer, who are already at a higher risk of cardiovascular disease due to overlapping risk factors, develop subclinical or clinical cardiotoxicity due to subsequent serial or concurrent injury from various chemotherapeutics as well as maladaptive lifestyle changes during chemotherapy (Fig. 10.1).[2] Cardiac injury is generally classified into two types: Type I, as seen with anthracycline-induced cardiotoxicity, and Type II, caused by trastuzumab and other similar agents. This classification is likely an oversimplification and does not account for many complex mechanistic effects of both traditional and novel chemotherapeutic agents; however, it provides a useful framework by highlighting some of the key differences in the pathophysiology, histologic appearance,[3] and prognosis of cardiotoxicity due to different chemotherapeutic agents (Table 10.1).

Although cardiotoxicity was recognized as a complication from trastuzumab more than a decade ago, the mechanism of cardiac injury remains unclear. The epidermal growth factor receptors (HER, EGFR, or ErbB) constitute a family of cell-surface receptor tyrosine kinases, which are essential to normal cell function, growth, and survival. A number of different receptors exist in the human body, including HER1 (EGFR), HER2 (erbB2), HER3 (erbB3), and HER4 (erbB4). Trastuzumab binds the HER2/erbB2 and has antineoplastic effects in tumors that overexpress those receptors.

Studies in animal models provide insight into the importance of HER/erbB receptors for cardiac development, maintenance of cardiac function, and enactment of compensatory mechanisms in the setting of cardiac stress. Mice with absence of erbB2/HER2 die in utero during embryogenesis secondary to abnormal cardiac development and loss of ventricular trabeculae.[4] Similar findings have also been reported for the erbB4 receptor.[5] In contrast, mice that are deficient in cardiac HER2/erbB2 have normal cardiac structure at birth; however, over several subsequent months, they demonstrate progressive ventricular dilation, reduced contractility, impaired relaxation, and overexpression of molecular markers of hypertrophy, all consistent with cardiomyopathy.[6,7] These mice hearts also demonstrate impaired compensatory and survival mechanisms in the setting of stressors and are more vulnerable to anthracycline toxicity. Similarly, mice

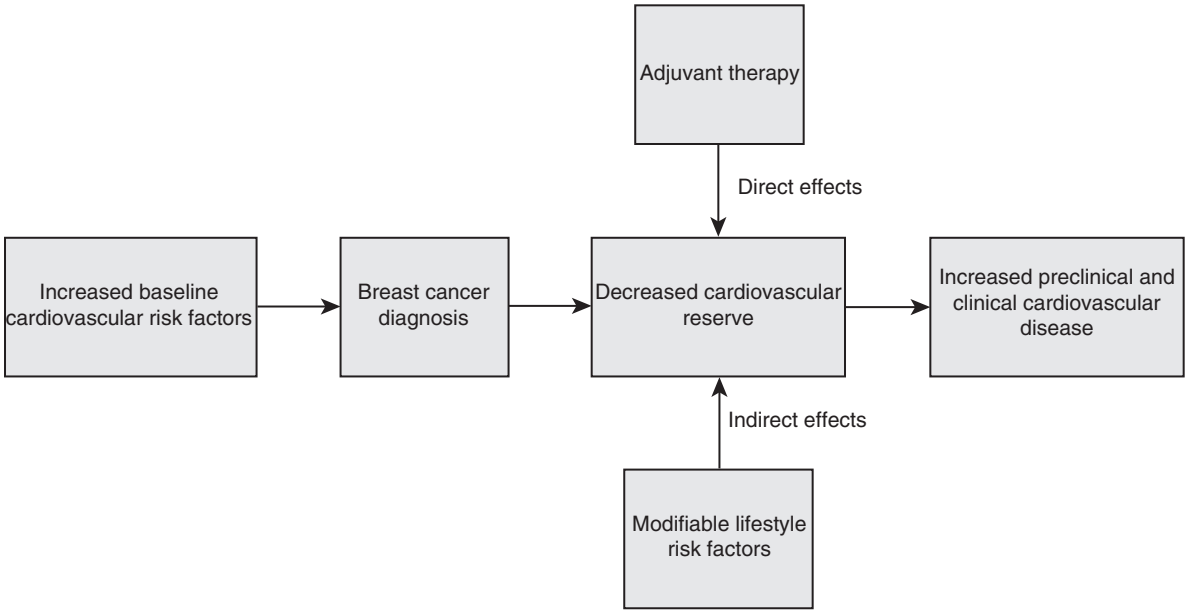


FIG. 10.1 Multiple-Hit Hypothesis for the Development of Cardiotoxicity. Flow Diagram. (Adapted from Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol*. 2007;50:1435–1441.)

TABLE 10.1
Characteristics of Type I and Type II Cardiotoxicity

	Type I	Type II
Characteristic agent	Doxorubicin, daunorubicin, epirubicin	Trastuzumab, lapatinib
Dose effect	Dose dependent	Not dose dependent
Ultrastructural abnormalities	Vacuoles, myofibrillar disarray, myocyte necrosis	No apparent abnormalities
Reversibility	Permanent myocyte injury	Largely reversible
Prognosis	Variable, may stabilize after treatment	Good
Effect of rechallenge	High likelihood of recurrent cardiac dysfunction which may be progressive	Generally well tolerated

deficient in erbB4 are born with normal ventricular walls. They subsequently develop ventricular cavity dilation, reduced contractility, abnormal conduction systems and have reduced life expectancy.[8]

Human studies also indicate that HER2 signaling may be an important part of cardiac response and compensatory mechanisms in the setting of stress. One study looked at patients with HER2-negative tumors who were treated with anthracycline therapy. Radioactively labeled ^{111}In trastuzumab was infused after anthracycline treatment, and 50% (5/10) of patients showed cardiac uptake of trastuzumab. There was no uptake in the control group of patients with chronic heart failure.[9] In addition, chronic heart failure, a disease characterized by chronic activation of compensatory mechanisms and the sympathetic nervous system in response to cardiac stress eventually leading to myocardial destruction and disease progression, is associated with elevated HER2 levels. Higher HER2 levels also correlate with lower LVEF and higher New York Heart Association (NYHA) functional class.[10]

In conclusion, HER/erbB receptors appear to be essential for normal cardiac function and survival mechanisms in the setting of cardiac stressors. Patients

treated with anthracyclines have increased trastuzumab binding, suggesting that upregulation of HER/erbB receptors may be an important compensatory mechanism to anthracycline toxicity. The fact that trastuzumab cardiotoxicity is largely seen in combination or following anthracycline administration supports the idea that trastuzumab acts as a modifier to anthracycline-induced cardiotoxicity[9] (Fig. 10.2). Nonetheless, it remains unclear whether trastuzumab simply acts as a modifier to anthracycline-induced cardiotoxicity or if it independently impairs normal cardiac function as well.

CLINICAL TRIALS AND INCIDENCE OF HER2 CARDIOTOXICITY

Clinical Incidence

Based on a metaanalysis of eight randomized-controlled trials (RCTs) of trastuzumab therapy, the overall incidence of congestive heart failure (CHF) is 2.5%, with a relative risk of 5.11[12] at a median follow up of 18–65 months. The definition of CHF varied among the trials and included the following: (1) determined to be symptomatic by a cardiologist with a decrease in LVEF ≥10% to <50%, (2) NYHA class III/IV either with or without a decrease in LVEF ≥10% from baseline to <50%, (3) heart failure grades 3 or 4, or (4) definition was not reported (Table 10.2).[12] These eight RCTs included 11,991 women with early breast cancer with a median age of 49 years (range 22–80 years). They concluded that if 1000 low-risk women are treated with conventional therapy (including anthracyclines), 900 would survive and 5 would experience CHF. With trastuzumab treatment, 933 would survive but 26 would experience CHF, although this cardiotoxicity is often reversible. Compared with development of CHF, the incidence of LVEF reduction was higher with 11.2% of patients showing left ventricular (LV) systolic dysfunction; however, there was substantial variation among studies in the definition of LVEF reduction.[12] The majority of patients included in the eight RCTs were also treated with anthracyclines. In the BCIRG 006 trial, there was one arm randomized to treatment with

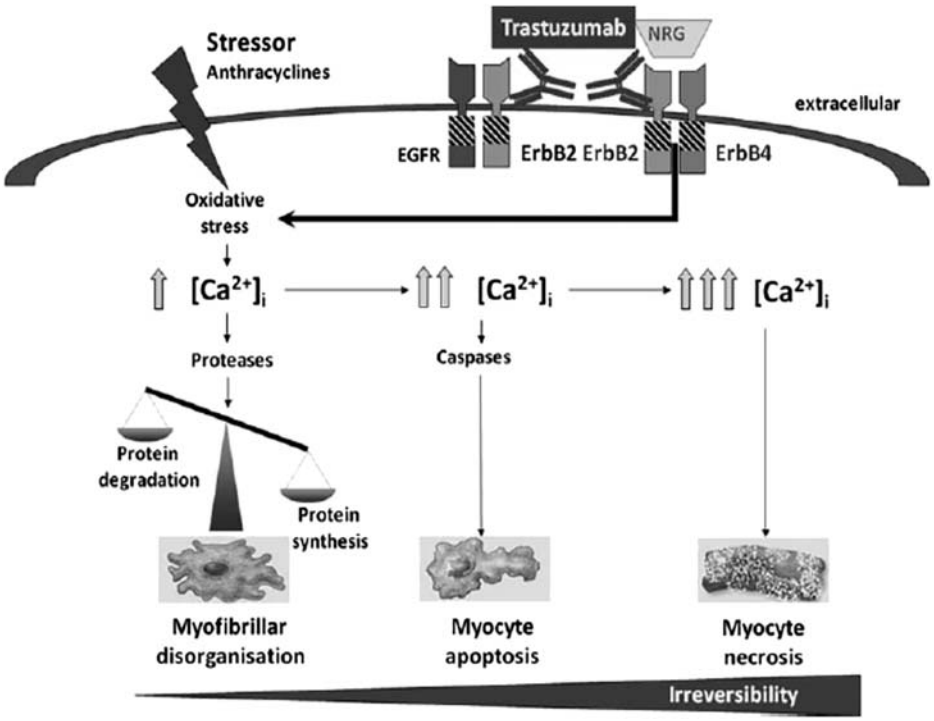


FIG. 10.2 Interplay of Anthracycline and Trastuzumab Cardiotoxicity. Trastuzumab Blocks the ErbB2-ErbB4 Repair Mechanism Enabling Anthracycline-Induced Oxidative Stress to Cause Cardiomyocyte Injury and Necrosis. (Reproduced from Tocchetti CG, Ragone G, Coppola C, et al. Detection, monitoring, and management of trastuzumab-induced left ventricular dysfunction: an actual challenge. *Eur J Heart Fail*. 2012;14:130–137 with permission.)

TABLE 10.2
Different Classification Schemes for Cardiac Toxicity and Heart Failure

Classification System	Severity				
	Low		Intermediate		High
ONCOLOGY DERIVED					
LV systolic dysfunction (CTCAE, version 4.03)	–	–	Symptomatic as a result of a drop in EF; responsive to intervention	Refractory or poorly controlled HF owing to EF drop; intervention such as LVAD, vasopressor support, or heart transplantation indicated	Death
Heart failure (CTCAE, version 4.03)	Asymptomatic with abnormal biomarkers or imaging	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Decreased ejection fraction (CTCAE, version 4.03)	–	Resting EF 40%–50%; 10%–19% drop from baseline	Resting EF 20%–39%; >20% drop from baseline	Resting EF <20%	–
Cardiac review and evaluation committee	Any of the four criteria confirms cardiac dysfunction: cardiomyopathy, reduced LVEF (global or more severe in the septum); symptoms of HF; signs associated with HF (S3 gallop and/or tachycardia); and decrease in LVEF from baseline ≥5% to <55% with accompanying signs or symptoms of HF or decline in LVEF ≥10% to <55% without accompanying signs of symptoms of HF				-
CARDIOLOGY DERIVED					
Heart failure stage (ACC/AHA)	Stage A, at risk (e.g., patients receiving cardiotoxic medications but without structural heart disease or symptoms)	Stage B, structural heart disease (hypertrophy, low EF, valve disease)	Stage C, structural heart disease with prior or current symptoms	Stage D, refractory HF requiring specialized interventions	–
NYHA symptom classification	Grade I, no limitations of activity		Grade II, mild limitation of activity; grade III, marked limitation of activity	Grade IV, confined to bed or chair	–

CTCAE, common terminology criteria for adverse events; *EF*, ejection fraction; *HF*, heart failure; *IV*, intravenous; *LV*, left ventricular; *LVAD*, left ventricular assist device; *LVEF*, left ventricular ejection fraction.

Adapted from Khouri MG, Douglas PS, Mackey JR, et al. Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues. *Circulation*. 2012;126:2749–2763.

docetaxel, carboplatin, and trastuzumab without anthracyclines; this group of patients notably had the lowest incidence of cardiotoxicity (0.4%).[13]

Data from clinical trials may not reflect the incidence of cardiotoxicity in community practice, however. One population-based, retrospective cohort study of 12,500 women, which sought to show the real-world rates of cardiotoxicity, showed that the incidence may be higher than reported in the clinical trials. The risk of heart failure or cardiomyopathy in patients treated with trastuzumab with or without anthracyclines was 6.2% at 1 year following therapy and increased to 20.1% at 5 years.[14] The difference in incidence of cardiotoxicity is likely multifactorial, both due to different outcome definitions, concomitant usage of anthracyclines, as well as different age and comorbidity profiles of patients treated in the community.

Incidence of trastuzumab-induced cardiotoxicity (TIC) in breast cancer patients with metastatic disease may be higher than those with early disease; however, this has been less well defined. The pivotal trastuzumab studies H0649g, H0650g, and H0648g retrospectively noted an incidence of symptomatic heart failure of 8.5%, 2.6%, and 8.8%, respectively, in patients with HER2-positive metastatic breast cancer.[15] Another study looking at patients with HER2-positive metastatic breast cancer with progressive disease despite one to two cytotoxic chemotherapy regimens and who received recombinant humanized anti-HER2 antibody reported an incidence of cardiotoxicity of 4.7% (10/213 patients).[16]

Most of the cardiotoxicity appears to occur during or shortly after trastuzumab administration. In the B31 trial, for example, at 7 years, the incidence of cardiac events was 4.0% (37/947) in patients treated with trastuzumab versus 1.3% in the control group. Only 2 of the 37 events occurred after 2 years of follow-up.[17] A retrospective cohort study from the Ontario Cancer Registry that looked at 19,074 women with breast cancer showed that the risk of cardiotoxicity was much higher during the initial 1.5 years after treatment compared with patients receiving conventional chemotherapy (hazard ratio 5.77, CI 4.38−7.62, $P < .001$). However, the cardiotoxicity risks were not significantly different in the trastuzumab and control arms after 1.5 years (hazard ratio 0.87, CI 0.57−1.33, $P = .53$).[18]

Risk Factors

Risk factors which have thus far been associated with developing cardiotoxicity include anthracycline use,[15] previous administration of anthracyclines,[15] age[17] (≥50 years,[15] ≥60 years[19]), black race,[20] NYHA >II before enrollment,[15] higher cancer stage,[18] being on antihypertensive medications,[17,19] and low LVEF[21] (or less than 55% but above the lower limit of normal[19] and marginally normal LVEF 50%−54%[17]). Obesity and being overweight have also been shown to be associated with increased risk of cardiotoxicity (BMI >25[21]) in patients receiving anthracyclines or anthracyclines and trastuzumab,[21,22] although this risk factor is less accepted due to concerns regarding the methodology of the data interpretation.[23] Increased number of comorbidities[18,20] appear to increase risk of cardiotoxicity, and these include hyperlipidemia,[15] diabetes,[18,20] coronary artery disease,[20] stroke or transient ischemic attack,[20] hypertension,[20] renal failure,[20] atrial fibrillation/flutter.[20] Radiation therapy has not been found to be an independent risk factor for TIC.[17,24] Longer duration of trastuzumab (defined as >6 months) is associated with a significant increase in CHF; however, it is nonetheless associated with improved overall survival in patients with early breast cancer.[12]

Prior anthracycline administration appears to be the biggest risk factor for TIC by far.[15,24] One study looking at patients with HER2-positive metastatic breast cancer showed that trastuzumab alone has a risk of 3.6% versus 28% for anthracyclines in combination with trastuzumab. The risk for anthracyclines only was about 9.6%.[15] A population-based, retrospective cohort study of 12,500 women treated across 14 nonprofit research centers showed considerable variation in cardiotoxicity between patients who did and did not receive anthracyclines in addition to trastuzumab. The adjusted hazard ratio for patients with trastuzumab without anthracyclines was 4.12, 95% CI = 2.30 to 7.42, whereas the adjusted HR for patients with trastuzumab and anthracyclines was 7.19, 95% CI = 5.00 to 10.35.[14] Sequential and concurrent administration of anthracycline and trastuzumab are associated with a similar increase in risk of CHF.[12]

Age appears to be a big risk factor as well. A retrospective study looking at heart failure and cardiomyopathy incidence in breast cancer patients found that the event rate increased with age, such that patients who got anthracyclines and trastuzumab had an event rate as follows: <55 years old 7.5%, 55−64 years old 11.4%, 65−74 years old 35.6%, ≥75 years 40.7%.[14]

A risk score was developed to predict which patients with nonmetastatic breast cancer are at high risk of developing cardiotoxicity including heart failure and cardiomyopathy using the surveillance, epidemiology, and end result medicare dataset (Fig. 10.3). Based on a cohort of 1664 women with mean age 73.6 ± 5.3,

Risk Factor	Hazard Ratio (95% Confidence Interval)	Regression Coefficient	*P* Value	Points Assigned
Adjuvant therapy				
Anthracycline chemotherapy	1.93 (1.11 to 3.36)	0.66	0.020	2
Non-anthracycline chemotherapy	1.64 (0.99 to 2.73)	0.50	0.055	2
No identified chemotherapy	Reference	Reference		
Age category, y				
67 to 74	Reference	Reference		
75 to 79	1.36 (0.92 to 2.01)	0.31	0.125	1
80 to 94	2.04 (1.29 to 3.24)	0.71	0.003	2
Cardiovascular conditions and risk factors				
Coronary artery disease	2.16 (1.21 to 3.86)	0.77	0.009	2
Atrial fibrillation/flutter	1.69 (0.98 to 2.91)	0.53	0.058	2
Diabetes mellitus	1.50 (1.03 to 2.18)	0.41	0.034	1
Hypertension	1.44 (0.99 to 2.08)	0.36	0.054	1
Renal failure	1.99 (0.96 to 4.14)	0.69	0.065	2

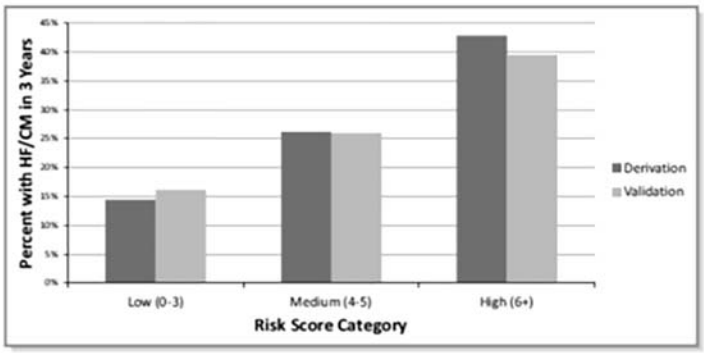


FIG. 10.3 Risk Prediction Model for Development of Heart Failure (HF) and Cardiomyopathy (CM) After Trastuzumab Therapy. (Reproduced from Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Heart Assoc*. 2014;3 with permission.)

predominantly Caucasian, they created a risk score of low (0−3 points), medium (4−5 points), and high (≥6 points). The risk factors included were anthracycline chemotherapy (2 points), nonanthracycline chemotherapy (2 points), age 75−79 (1 point), age 80−94 (2 points), coronary artery disease (2 points), atrial fibrillation/flutter (2 points), diabetes mellitus (1 point), hypertension (1 point), renal failure (2 points). The 3 year rates of heart failure and cardiomyopathy were 16.2%, 26.0%, and 39.5%, respectively.[25]

Cardiac Recovery

TIC has been shown to be a predominantly reversible disease in numerous studies. In the pivotal trials evaluating the effects of trastuzumab for the treatment of HER2-positive metastatic breast cancer, the majority of patients with symptomatic cardiac dysfunction who were started on medical therapy (78%, or 32/41 patients) had significant improvement. The majority (68%, or 28/41 patients) also continued to receive trastuzumab, and of those, 75% (21/28 patient) showed improvement in cardiac symptoms nonetheless. For patients who stopped trastuzumab therapy, 85% (11/13 patients) showed improvement.[15] Patients with cardiac dysfunction were treated with diuretics (78%), angiotensin-converting enzyme inhibitors (ACEi, 58%), cardiac glycosides (58%), and other inotropic agents (10%). β-blockers use and nitrates

were not quantified, although some patients did use those medications as well.[24]

A retrospective study at the University of Texas MD Anderson Cancer Center also suggests that there is typical reversibility seen with TIC.[26] They identified 38 patients with HER2-positive breast cancer treated at their institution who were suspected of having TIC based on either a drop in LVEF and/or development of CHF. Almost all, 92% (35/38), of the patients had a normal LVEF before initiation of trastuzumab (mean 61% ± 13). The mean LVEF decreased to 43% ± 16 at a median of 4.5 months. The majority of patients (97% or 37/38) discontinued therapy. Eighty-four percent of patients (31/37) were treated with medications for cardiac dysfunction including ACE-I and β-blockers. The mean LVEF improved to 55% ± 11 after about 1.5 months. More than half of these patients (66% or 25/38) were re-challenged with trastuzumab after stabilization of symptoms and LVEF while being on maximal medical therapy with ACE-I and β-blockers. LV reduction and/or heart failure symptoms were only seen in three patients (12%), while the majority (88% or 22/25 of patients) did not have any recurrence of heart failure.[26]

Two other RCTs (B31[17] and HERA[21]) showed similar findings. In the B31 study, over 50% of patients had LVEF recovery (58% or 21/36) and 92% (33/36) of patients were asymptomatic at ≥6 months.[17] In the HERA trial, of the patients with symptomatic CHF, 67% (24/36) recovered the LVEF within 151 days (median), and 69% (35/51) of patients who had an LVEF drop recovered in 191 days on average (median).[21]

A multitude of data shows that TIC is reversible in the majority of cases. However long-term data looking at patients who are >10 years out from trastuzumab are lacking.

CARDIOTOXICITY OF OTHER HER2 BLOCKING AGENTS

Other HER2 signaling pathway inhibitors are used in breast cancer either in place of or in combination with trastuzumab to strengthen the antineoplastic effect. In general, the incidence of cardiotoxicity associated with these agents is similar to or less than that seen with trastuzumab.

Monoclonal Antibodies: Trastuzumab Emtansine and Pertuzumab

Ado-trastuzumab emtansine (T-DM1) is an antibody drug conjugate consisting of trastuzumab, a thioether linker, and the antimitotic agent maytansine. When T-DM1 is administered following anthracycline-based chemotherapy in patients with early-stage HER2-positive breast cancer, cardiac event rate appears low. One study reported a 2.7% incidence of asymptomatic reduction in LVEF (≥10% from baseline to <50%).[27] Prior treatment with trastuzumab does not appear to significantly increase the rate of T-DM1-associated cardiotoxicity. Two studies that looked at patients with advanced HER2-positive breast cancer who had prior treatment with trastuzumab showed low rate of cardiac adverse events. In one study, there were no instances of LVEF decline to ≤45% or symptomatic congestive heart,[28] whereas in the second study, the rate of LVEF reduction to below 50% and ≥15% from baseline occurred in 8/481 patients (or 1.7%).[29]

A comparison of trastuzumab versus T-DM1 shows that the rate of cardiotoxicity is similar between the two drugs. In a phase II, multicenter study, patient with HER2-positive breast cancer, which was either locally advanced and unresectable or metastatic, 4.4% (or 3/67 patients) treated with T-DM1 experienced an asymptomatic decline in LVEF compared with 4.3% (or 3/70 patients) treated with trastuzumab and docetaxel.[30] No patients experienced symptomatic CHF in either arm.

Pertuzumab is a monoclonal antibody that targets the HER2 receptor but binds to a different epitope than trastuzumab; therefore, using a trastuzumab and pertuzumab combination can potentially cause a synergistic effect on tumor inhibition. This combination was initially tested in a multicenter phase II, single-arm study in patients with advanced HER2-positive breast cancer who experienced progression of disease during prior trastuzumab therapy. These patients received a combination of both trastuzumab and pertuzumab with 24.2% of patients showing an objective response to treatment regarding their cancer progression. Overall, the cardiac events were rare with only 4.5% (or 3/66 patients) developing an asymptomatic decline in LVEF to ≥10% and <50%.[31] Pertuzumab was subsequently tested in a randomized, double-blind, placebo-controlled trial which compared pertuzumab/trastuzumab/docetaxel to placebo/trastuzumab/docetaxel in patients as a first-line treatment. LV systolic dysfunction of ≥10% to below 50% was actually more common in the placebo group: 3.8% of patients in the pertuzumab arm (including all grades of dysfunction) versus 6.6% of patients in the placebo arm. Symptomatic LV systolic dysfunction was low, occurring in 1.0% of patients in the pertuzumab arm versus 1.8% of patients in the placebo group.[32]

Most recently, patients with node-positive or high-risk node-negative HER2-positive breast cancer were randomized to receive pertuzumab with standard chemotherapy and trastuzumab for 1 year in a multicenter, double-blind, placebo-controlled trial and showed even lower rates of cardiotoxicity. Pertuzumab did portend a slightly worse rate of cardiotoxicity with 17 patients (or 0.7%) experiencing a primary cardiac event (NYHA class III or IV heart failure or LVEF drop >10% and below 50%) with a median follow up of 45.4 months. The placebo group had an event rate of 0.3%.[33]

Tyrosine Kinase Inhibitors: Lapatinib, Afatinib, and Neratinib

Several tyrosine kinase inhibitors (TKIs) that block different parts of the HER2 signaling pathway also have therapeutic benefit in patients with breast cancer. The best studied is lapatinib, a small molecule and reversible inhibitor of HER2 and ErbB1 tyrosine kinase. Lapatinib has been evaluated as treatment for patients with HER2-positive breast cancer who have progression despite treatment with anthracyclines, taxane, and trastuzumab. Patients randomized to receive lapatinib and capecitabine had very few cardiac events (2.6% or 4/155 patients), all of which were asymptomatic.[34] A Mayo pooled analysis of patients who received lapatinib for a number of different cancers across 44 clinical studies including 10% healthy volunteers showed that the rate of cardiac events was also low (1.6% or 60/3689). The majority of patients with LVEF decline showed recovery in systolic function, and the recovery seemed similar between patients who discontinued lapatinib and those who did not.[35]

Combination HER2 blocking therapy does not appear to significantly increase cardiotoxicity with respect to monotherapy. Lapatinib and trastuzumab result in cardiotoxicity rates similar to those reported for trastuzumab alone (Table 10.3). One study showed that in patients with HER2-positive breast cancer with progression despite trastuzumab, patients treated with lapatinib and trastuzumab had a cardiac event rate of 3.4%. The group who received lapatinib alone in this study had an event rate of 1.4%.[38] A metaanalysis of six trials was done to look at the rates of cardiac events in dual HER2 therapy (pertuzumab and trastuzumab or trastuzumab and lapatinib) versus monotherapy (either lapatinib, trastuzumab, or pertuzumab). The overall odds ratio of developing CHF or decline in LVEF was not significantly different between dual and monotherapy.[39]

Two TKIs of HER2/ErbB2 with irreversible inhibition include afatinib and neratinib. Both TKIs have been studied as therapy in patients with HER2-positive breast cancer who had already been treated with trastuzumab, and both showed minimal to no significant cardiotoxicity. Afatinib was studied in a phase III, open-label study of 508 patients with two treatment arms: afatinib and vinorelbine versus trastuzumab and vinorelbine. Only one patient in the afatinib arm had a decline in ejection fraction (EF) (0.3% compared with 1.8% in the trastuzumab arm), and no patient developed CHF.[40] Neratinib was studied in a phase III multicenter trial of patients with early-stage HER2-positive breast cancer who completed trastuzumab therapy were randomized to receive neratinib versus placebo for a year. Neratinib improved invasive disease-free survival and showed minimal cardiotoxicity with only 1% of patients in both arms showing a decrease in LVEF at a 2 year follow-up.[41]

DETECTION OF CARDIOTOXICITY

Several diagnostic modalities have been investigated over the years to detect cardiac dysfunction from chemotherapeutic agents. Assessment of LV structure and function, which is central to the diagnosis of cardiotoxicity,[1] can be evaluated using multiple different imaging modalities including multigated cardiac blood pool acquisition (MUGA), cardiac magnetic resonance imaging (CMR), and transthoracic echocardiography (TTE). The advantages and disadvantages of the different modalities are described in the following section (Table 10.4).

Multigated Cardiac Blood Pool Acquisition

A MUGA study is performed by using a radiotracer to label a patient's red blood cell pool and detecting a change in counts of the tracer as the blood circulates through the heart. The LVEF is calculated based on the principle that the changes in count density are proportional to the changes in the LV volumes. MUGA scans are highly accurate, reproducible, and reliable, making them a very useful tool to assess LVEF; however, valvular and pericardial functions are not assessed. In addition, due to ongoing radiation exposure for baseline and follow-up assessments, risks and benefits of this technique should be weighed.

Cardiac Magnetic Resonance Imaging

CMR imaging is considered the gold standard of noninvasive assessment of ventricular volumes and systolic function. It can also be used to assess other cardiac

TABLE 10.3
Cardiotoxicity Induced by Trastuzumab in Five Randomized Controlled Trials

Trial	NCCTG N9831[19]	NSABP B31[17]	BCIRG 006[13]	HERA[36]	FinHer[37]
Number of patients	1944	2119	3222	3401	Total 1010, HER2+ 232
Age	49 years (median)	49 years (mean)	Majority of patients were <50 years	49 ± 10 years (median)	50.9 (25.5–65.8) years (median)
Breast cancer	HER2+, and node+ or high-risk node-invasive cancer	HER2+ and node+ primary breast cancer	HER2+, and node+ or high-risk node-cancer	HER2+ early-stage cancer	HER2+ or HER2-, and node+ or high-risk node-cancer
Follow-up time	3.75 years	87 months (median)	65 months (median)	3.6 years	62 months
Treatment arms	1. AC >paclitaxel 2. AC ->paclitaxel >trastuzumab 3. AC >paclitaxel + trastuzumab >trastuzumab	1. AC + paclitaxel 2. AC + paclitaxel + trastuzumab	1. AC >docetaxel 2. AC >docetaxel >trastuzumab 3. Docetaxel + carboplatin >trastuzumab	1. Standard (neo)adjuvant chemotherapy[a] ± radiotherapy >observation 2. Standard (neo)adjuvant chemotherapy[a] ± radiotherapy >1 year of trastuzumab 3. Standard (neo)adjuvant chemotherapy[a] ± radiotherapy >2 years of trastuzumab	1. Docetaxel >FEC >no trastuzumab 2. Docetaxel >FEC >trastuzumab 3. Vinorelbine >FEC >no trastuzumab 4. Vinorelbine >FEC >trastuzumab
Definition of cardiac events	Symptomatic CHF Definite cardiac death Probable cardiac death	CHF (dyspnea + drop in LVEF) Definite cardiac death Probable cardiac death	CHF	Cardiac death Severe (Class III–VI) CHF Symptomatic CHF LVEF reduction ≥10% and <50%	LVEF decrease >20% Symptomatic heart failure Myocardial infarction
Total cardiac event rate based on treatment arm	1) 0.3% 2) 2.8% 3) 3.3%	1) 1.3% 2) 4.0%	1. 0.7% 2. 2.0% 3. 0.4%	1. 0.7% 2. 4.3% Data not available	1&3. 7.8% 2&4. 12.2%
Cardiac imaging modality	MUGA Echocardiography	MUGA	MUGA Echocardiography	MUGA Echocardiography	Isotope cardiography Echocardiography
Cardiac improvement	"Majority" of patients improved	LVEF recovered to ≥50% in 57% of patients	Asymptomatic reduction in LVEF persisted in 33%	Acute recovery[b] occurred in 80.8% of patients within a median of 6.4 mos	–

AC, doxorubicin + cyclophosphamide; *BCIRG*, Breast Cancer International Research Group; *CHF*, congestive heart failure; *FEC*, flourourail + epirubicin + cyclophosphamide; *FinHer*, Finland Herceptin trial; *HERA*, Herceptin adjuvant trial; *LVEF*, left ventricular ejection fraction; *MUGA*, multigated cardiac blood pool acquisition; *NCCTG*, North Central Cancer Treatment Group; *NSABP*, National Surgical Adjuvant Breast and Bowel Project.

[a]94% of chemotherapy was anthracycline based.

[b]Acute recovery is defined as two or more sequential normal LVEFs.

TABLE 10.4
Imaging Modalities Currently Used to Evaluate Cardiotoxicity

Modality	Pros	Cons
MUGA	Reproducibility	Involves radiation
	Accuracy	Not able to evaluate other cardiac structures
CMR	Accuracy	Not easily available at all centers
	Can evaluate other cardiac structures	Higher costs
	Can evaluate myocardial perfusion, viability, and fibrosis	
TTE (2D/3D)	Easy accessibility	Not as accurate in evaluating LVEF when compared with MUGA and CMR and can miss small changes in LV contractility (use of contrast is recommended in 2D images if two contiguous segments are not well visualized in apical views)
	Portability	
	No radiation	
	Can evaluate other cardiac structures and pulmonary hypertension	
	Can use speckle tracking to evaluate for subclinical markers such as myocardial deformation	

2D, two-dimensional imaging; *3D*, three-dimensional imaging; *CMR*, cardiac magnetic resonance imaging; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *MUGA*: multigated cardiac blood pool acquisition; *TTE*, transthoracic echocardiogram.

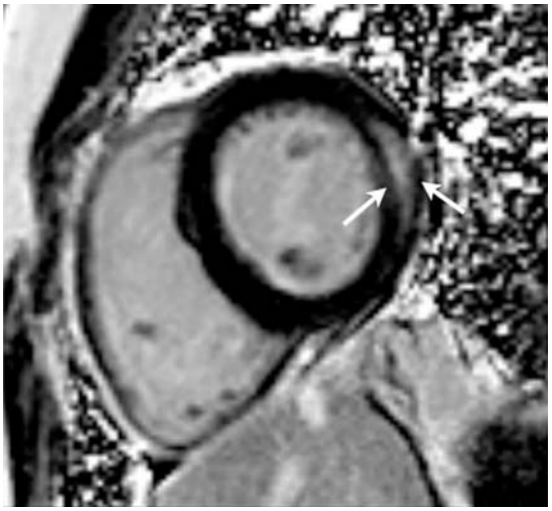


FIG. 10.4 Cardiac magnetic Resonance Imaging Demonstrates a Short Axis View of the Left and Right Ventricles, With a Short Axis Phase-Sensitive Reconstructed Inversion Recovery-True Fast Imaging With Steady-State Procession Image Through the Midventricle at the Level of the Papillary Muscle, Demonstrating mid-myocardial Delayed Enhancement (*arrows*) in the Lateral Wall of a Patient Who Developed Trastuzumab-Induced Cardiotoxicity. (Reproduced from Fallah-Rad N1, Walker JR, Wassef A, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol*. 2011;57:2263–2270 with permission.)

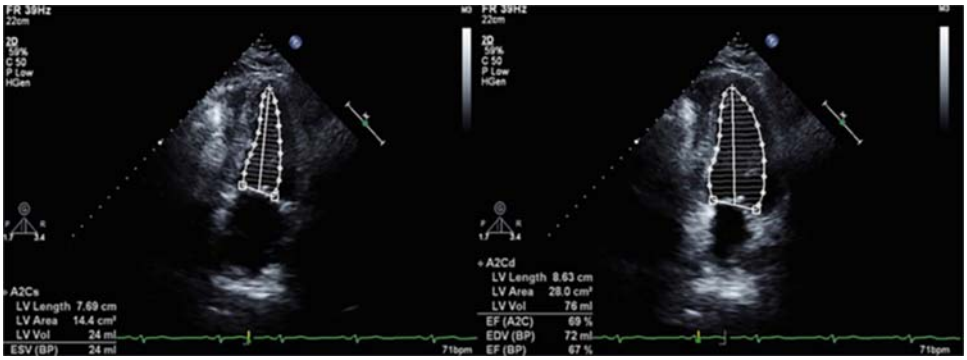
chambers, valves, myocardium, and the pericardium. It is useful in evaluating myocardial perfusion, viability, and fibrosis in certain circumstances as well. Its utility is restricted by a lack of widespread availability and higher costs than other noninvasive imaging. In addition to an LVEF decrease as a sign of cardiotoxicity, presence of delayed enhancement of the midlateral wall after treatment with trastuzumab has also been noted in smaller studies[42] (Fig. 10.4).

Transthoracic Echocardiography

Echocardiography is the most common imaging modality used to detect cardiac dysfunction before, during, and after treatment (Fig. 10.5). Benefits of echocardiography include easy accessibility, portability, low cost, and no radiation exposure. Besides an assessment of LV systolic and diastolic function, it allows for assessment of the right ventricle, valvular dysfunction, pericardial diseases, and pulmonary hypertension.

Assessment of LVEF by three-dimensional echocardiography (3DE) is usually recommended if available in a given laboratory. For a two-dimensional (2DE) LVEF assessment, biplane Simpson's method using apical two- and four-chamber measurements is commonly used. A wall motion score index is also recommended as part of the LV function assessment. A conventional assessment of diastolic function is usually recommended, although diastolic parameters have not yet shown to be prognostic of CTRCD.[1]

Panel A



Panel B

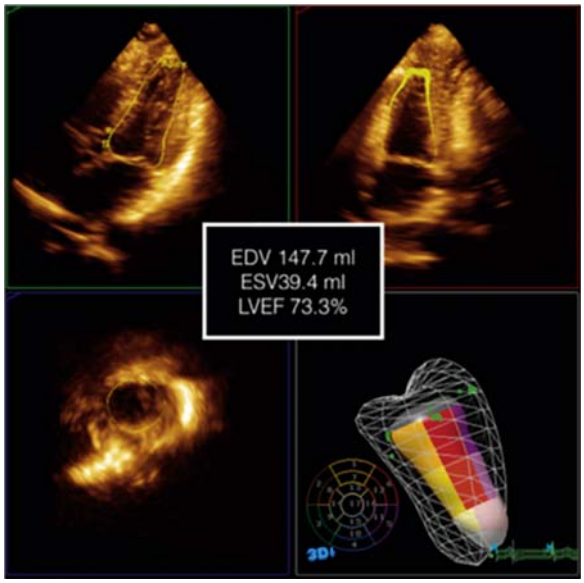


FIG. 10.5 Example of 2D and 3D Echocardiography With Measurement of the LVEF by the Modified Simpsons Biplanar Quantification Method With the Left Ventricular Endocardial Border Traced in End-Systole and End-Diastole to Create Disks Forming a Cylinder **(Panel A)** and 3D Dimensional Assessment. *LV*, left ventricular; *LVEF*, left ventricular ejection fraction. (Reproduced from Garg V, Vorobiof G. Echocardiography and alternative cardiac imaging strategies for long-term cardiotoxicity surveillance of cancer survivors treated with chemotherapy and/or radiation exposure. *Curr Oncol Rep*. 2016;18:52 with permission.)

DETECTION OF SUBCLINICAL CARDIOTOXICITY

Several studies have looked at subclinical markers that may help predict eventual reduction in LVEF in patients, and can be used to help identify patients at risk of developing cardiotoxicity, and help tailor their treatment before significant heart failure develops. These include changes in myocardial deformation (or strain imaging) as well as several serum biomarkers.

Strain Imaging

Newer markers of subclinical cardiotoxicity include assessment of myocardial deformation or stretch by using tissue-Doppler imaging (TDI) and speckle tracking (2D and 3D STE) strain measurements (Fig. 10.6). The strain (a measurement of total deformation during a cardiac cycle expressed as a percentage of its initial length) and strain rate (rate of change in deformation) can be measured in longitudinal, radial, and

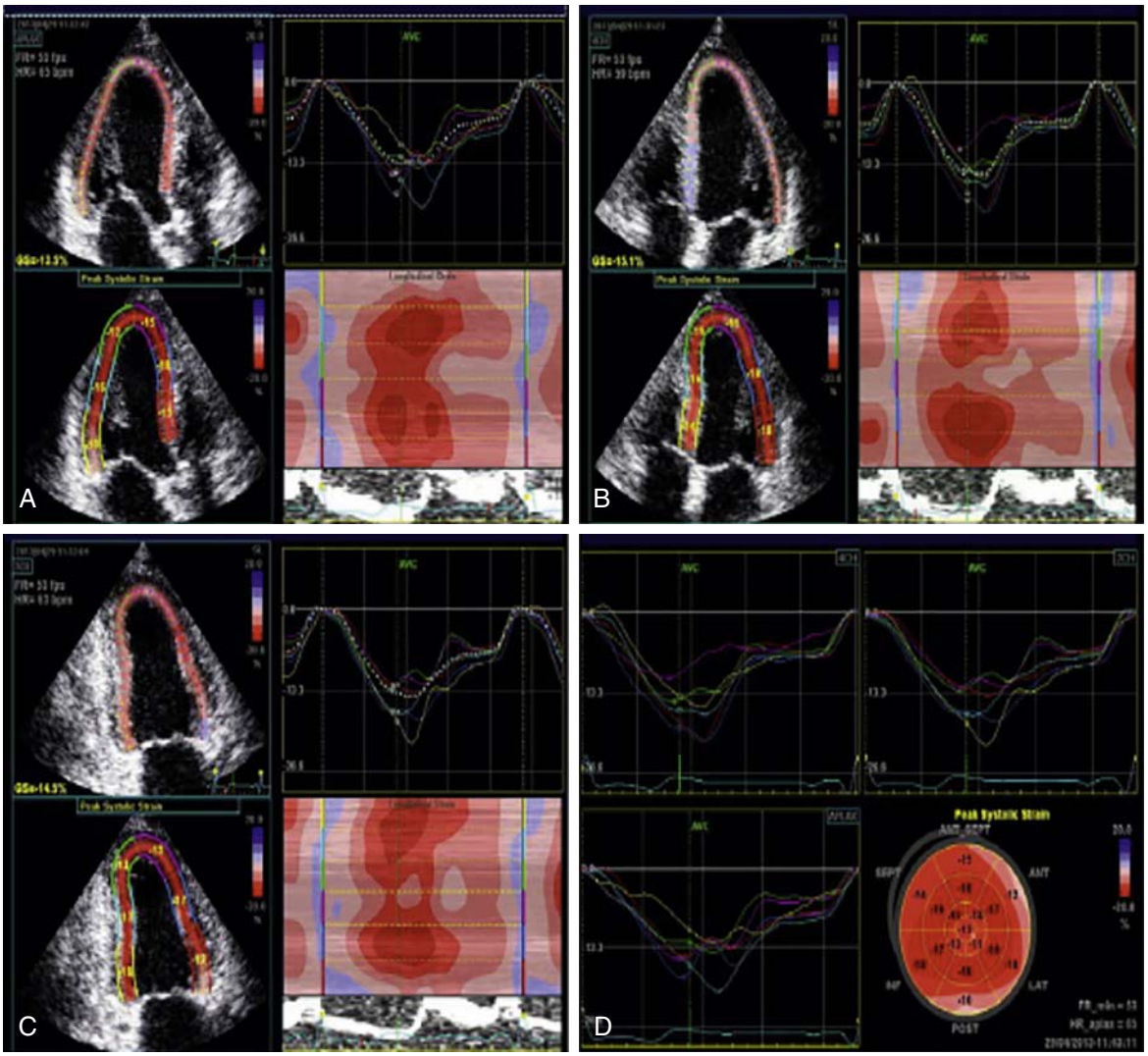


FIG. 10.6 Example of Speckle Tracking Echocardiographic Images Assessing Myocardial Strain. Images Are Obtained in the Apical Long Axis View **(Panel A)**, Four Chamber View **(Panel B)**, and Two Chamber View **(Panel C)** With Strain Curves and "Bull's Eye" Plot **(Panel D)** in a Patient With Breast Cancer Who Developed Left Ventricular Dysfunction After Doxorubicin and Trastuzumab Administration. Each Segment Has a Numeric and Color-Coded Strain Value, With Cardiac Dysfunction Presenting With Regional Abnormalities. (Reproduced from Plana JC, Galderisi M, Barac S, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27:911–939 with permission.)

circumferential directions (Fig. 10.6). A 2D global systolic longitudinal strain (GLS) reduction of 9%–19% has been the most consistent and reliable measurement in studies suggestive of acute myocardial changes either during or immediately following anthracycline therapy.[45] When using TDI-based strain, a reduction of 9%–20% in the longitudinal strain rate of the basal intraventricular septum is suggestive of acute myocardial injury due to anthracycline use.[45] A fall in GLS of 10%–15% by STE has been correlated to the later

TABLE 10.5
Biomarkers and Trastuzumab-Induced Cardiotoxicity

Study	Biomarker	Timing	Chemotherapy	Outcomes	Correlation With Outcomes
Cardinale et al.[46]	Troponin I	Before and after each cycle	Trastuzumab	LVEF decrease >10% and below 50%	Positive
Fallah-Rad et al.[43]	Troponin T NT-proBNP	Baseline, and every 3 months for 1 year	Trastuzumab	LVEF decrease ≥10% and below 55% with signs/symptoms of CHF	Neutral
Morris et al.[47]	Troponin I	Baseline, every 2 wks, and 6, 9, and 18 months	Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, lapatinib	LVEF decrease >10% and below 55%, congestive heart failure	Negative
Sawaya et al.[48]	Troponin I NT-proBNP	Baseline, and 3 and 6 months during therapy	Anthracyclines, trastuzumab	LVEF decrease ≥5% and below 55% with symptoms of heart failure, an asymptomatic LVEF decrease of ≥10% to below 55%	Troponin: positive NTproBNP: negative
Ky et al.[49]	Troponin I NT-proBNP MPO	Baseline, and 3 and 6 months during therapy	Doxorubicin, trastuzumab	LVEF decrease ≥5% and below 55% with symptoms of heart failure, an asymptomatic LVEF decrease of ≥10% to below 55%	Troponin: positive NT-proBNP: negative MPO: positive
Putt et al.[50]	Troponin I NT-proBNP MPO GDF-15 PlGF	Baseline, and every 3 months for 15 months	Doxorubicin, trastuzumab	LVEF decrease ≥5% and below 55% with symptoms of heart failure, an asymptomatic LVEF decrease of ≥10% to below 55%	Troponin: negative NT-proBNP: negative MPO: positive GDF-15: positive PlGF: positive
Sandri et al.[51]	NT-proBNP	Baseline and after each cycle	High-dose chemotherapy	LVEF and diastolic parameters	Positive
Sawaya et al.[52]	Troponin I NT-proBNP	Baseline, and every 3 months for 15 months	Anthracyclines, taxanes, trastuzumab	LVEF decrease ≥5% and below 55% with symptoms of heart failure, an asymptomatic LVEF decrease of ≥10% to below 55%	Troponin: positive NTproBNP: negative
Grover et al. [53]	Troponin T	Baseline, and 1 and 4 months after therapy	Doxorubicin or epirubicin, trastuzumab	LV/RV structure and function on CMR	Negative
Zardavas et al.[54]	Troponin I and T	Baseline, week 13, 25, 52 month 18, 24, 30, 36, every unscheduled LVEF assessment	Trastuzumab	NYHA class III/IV symptoms, LVEF decrease >10% and below 50%, death due to cardiac cause	Positive

CHF, congestive heart failure; *CMR*, cardiac magnetic resonance imaging; *LVEF*, left ventricular ejection fraction; *MPO*, myeloperoxidase; *NT-proBNP*, N-terminal prohormone of brain natriuretic peptide.
Adapted from Shah KS, Yang EH, Maisel AS, Fonarow GC. The role of biomarkers in detection of cardio-toxicity. *Curr Oncol Rep*. 2017;19:42.

development of cardiotoxicity including both symptomatic and asymptomatic reduction in LVEF, whereas changes in global radial strain and global circumferential strain have not been found to be predictive.[45] Per the consensus statement by the American Society of Echocardiography released in 2014, a decrease in GLS >15% in patients with no significant change in LV function suggests subclinical LV dysfunction.[1]

Cardiac Biomarkers

Several studies have looked at multiple serum biomarkers at baseline, during, and post chemotherapy to evaluate their utility in signaling a risk of developing cardiotoxicity (Table 10.5). An elevation in troponin, a marker of myocardial injury, appears to correlate with development of cardiotoxicity. In one of the largest studies enrolling 703 patients with cancer and varying chemotherapy regimens, cardiac troponins were measured immediately after chemotherapy and 1 month later. Patients with increases in troponin ($\geq$0.08 ng/mL) early on or with persistently elevated levels had an increased risk of adverse cardiac events (cardiac death, acute pulmonary edema, heart failure, LVEF reduction by $\geq$25% or life-threatening arrhythmia) and increased severity of CTRCD.[57] Cardinale et al. also studied 251 breast cancer patients who underwent therapy, particularly with trastuzumab and measured troponin I (Tn-I) levels before and after each cycle. Patients with increased levels of troponin were noted to have more adverse cardiac events and low chance of recovery of systolic function.[46]

Myeloperoxidase (MPO), a peptide secreted by leukocytes and a prooxidant linked to atherogenesis, may be a useful biomarker of subclinical cardiotoxicity.[49,50] Ky et al.[49] looked at 8 biomarkers including Tn-I, high-sensitivity C-reactive protein, N-terminal prohormone brain natriuretic peptide (pro NT-BNP), growth differentiation factor, MPO, placental growth factor, soluble fms-like TKI, and galectin in 78 breast cancer patients undergoing treatment with doxorubicin and trastuzumab. A greater risk of cardiotoxicity was associated with early increases in Tn-I, MPO, and a combination of the two markers.[49]

Natriuretic peptides are commonly used as markers of myocardial stretch and pressure overload, and they have an important role in the diagnosis and management of heart failure. However, the few studies that have evaluated NT-proBNP use in trastuzumab have not found it to be a reliable predictor of subsequent CTRCD (Table 10.5).[58]

SURVEILLANCE OF TRASTUZUMAB CARDIOTOXICITY

According to the AHA/ACC guidelines on heart failure, an asymptomatic decline in LV function (AHA stage B) or a symptomatic decline (AHA stage C/D) is a progressive disorder that is associated with reduced mortality.[59] Given the significant event rate of both asymptomatic and symptomatic decline in LV function in the major trastuzumab trials (Table 10.3), the product label emulates clinical trial design and dictates the need and frequency of routine cardiac monitoring while undergoing therapy with trastuzumab. Early identification of cardiac dysfunction can lead to implementation of cardiac therapies at each AHA stage of heart failure that help reduce cardiovascular mortality.[59]

The frequency of this surveillance has come under scrutiny because of concerns that the clinical trial event rate of LV dysfunction is low in anthracycline-free regimens, TIC can be reversible without the use of medications, lack of evidence-based guidelines and prospective studies validating frequent testing, and concerns of rising healthcare costs.[60] However, clinical trials typically enroll younger and healthier subjects while often excluding patients with preexisting cardiac conditions and risk factors. Clinical trial data therefore likely significantly underestimate the real-world rate of symptomatic and asymptomatic LV dysfunction in patients treated with trastuzumab.[14] Based on the incidence of TIC in clinical trials and real-world TIC, several national and international societies have created guidelines based on expert consensus opinions, which will be reviewed below.

Prechemotherapy Surveillance

All major society guidelines agree that the first opportunity to offer surveillance for cardiotoxicity is before the onset of any cancer therapeutics. Similar to a preoperative evaluation, the American Society of Clinical Oncology (ASCO) strongly recommends that any patient with an active cardiac complaint or symptom should undergo further evaluation and referral to a cardiologist.[61]

Pretreatment assessment recommendations extend to asymptomatic patients who are about to receive cytotoxic chemotherapy (Fig. 10.7). The European Society of Medical Oncology (ESMO), ASCO, and the UK National Cancer Research Institute recommend a cardiac-focused medical history, physical examination, 12-lead ECG looking for arrhythmias and markers of LV structural damage, and a baseline measurement of LVEF for all patients with HER2-positive breast

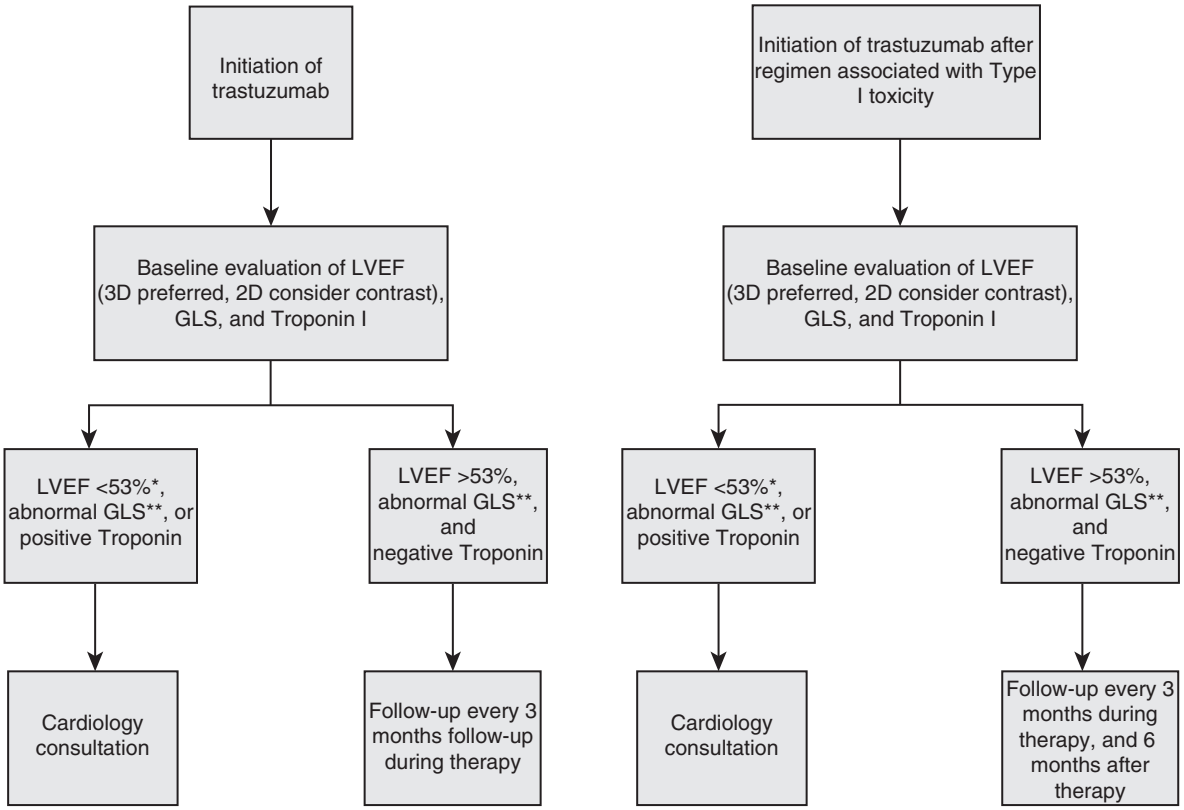


FIG. 10.7 2014 American Society of Echocardiography/European Association of Cardiovascular Imaging Expert Consensus of Multimodality Imaging of Adult Patients During and After Cancer Therapy in Regard to Monitoring of Cardiotoxicity Related to Trastuzumab (Type II Toxicity). *GLS*, global longitudinal strain; *LVEF*, left ventricular ejection fraction. *Consider confirming with cardiac MRI; **Normal values vary based on vendor, gender, and age. (Adapted from Figs. 14 and 15 from Plana JC, Galderisi M, Barac S, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27:911–939 with permission.)

cancer.[61–63] Similar recommendations regarding baseline assessment of LVEF are mirrored by a joint statement by the American Society of Nuclear Cardiology (ASNC), the European Society of Cardiology (ESC), and the American Society of Echocardiography (ASE) with the European Association of Cardiovascular Imaging (EACVI).[1,64,65] Baseline assessment would allow clinicians to differentiate whether a subsequent decline in LVEF is due to cancer therapy versus preexisting LV dysfunction.

ESMO and ASCO use additional criteria based on the chemotherapy regimen and cardiac risk factors to identify high-risk individuals who would benefit from a baseline LVEF assessment. This includes high-dose anthracycline (>/=250 mg/m^2 doxorubicin, >/=600 mg/m^2 epirubicin), high-dose radiotherapy (>/=30 Gy where the heart is in the treatment field), low-dose anthracycline in combination with low-dose radiotherapy, low-dose anthracycline and two cardiac risk factors, therapy with trastuzumab alone and two cardiac risk factors, low-dose anthracycline followed by trastuzumab, age >/=60 years at cancer treatment, and/or known compromised cardiac function (such as lower limit of normal EF, history of myocardial

infarction, or moderate or greater valvular heart disease).[61,63] The ASE/EACVI writing group use traditional cardiovascular risk factors such as age, gender, hypertension, hyperlipidemia, and family history of premature coronary artery disease to classify if a patient is high risk.[1] ASCO expands cardiac risk factors to also include smoking, diabetes, and obesity.[61] These traditional cardiac risk factors increase the risk of developing ischemic heart disease and other cardiomyopathies that may leave cardiac myocytes even more vulnerable to stress from cytotoxic chemotherapy.

Although most guidelines identify risk factors for TIC as a method to target routine cardiac surveillance, the Canadian Trastuzumab Working Group (CAN) recommends using certain risk factors as exclusion criteria from treatment with trastuzumab. Patients with existing heart failure or LVEF <50%, or both, should be excluded from receiving trastuzumab, unless their risk of disease recurrence is very high. They go on to recommend that patients with ischemic heart disease, valve dysfunction, or an LVEF at the lower limit of normal/mildly abnormal (EF 50%–55%) before trastuzumab therapy require special consideration. These recommendations are based on clinical trial data and may change as more real-world data are published (Table 10.2).[66]

Surveillance During Chemotherapy

After careful selection of patients into the adjuvant trastuzumab therapy pathway, all society guidelines consistently recommend routine surveillance of LVEF while on trastuzumab for 1 year (Table 10.6).[1,61–63,65,66] This recommendation originates from earlier clinical trials when anthracycline and trastuzumab were administered concurrently and the rate of symptomatic heart failure was up to 27%.[67] Subsequent adjuvant trials used strict cardiac monitoring and interruption of trastuzumab therapy based on changes in LVEF and saw a sharp decline in rate of severe heart failure (<1%).[21] Based on these trial designs and observations, different societies have developed surveillance protocols of LVEF during trastuzumab therapy and recommendations on adjustment of therapy based on the LVEF (Fig. 10.8). Frequent surveillance is used to identify early dysfunction of the heart so that cardiac medications can be initiated, which have been shown to aid in recovery of LVEF and prevent recurrent decline when trastuzumab is resumed.[26]

Patients should undergo routine surveillance for LV dysfunction before initiation of anthracycline and at the completion of its course and again 6 months after that. If patients are to receive more than 240 mg/m^2 of doxorubicin or its equivalent, then an assessment of LVEF is needed before each additional dose of 50 mg/m^2. Once anthracycline is completed and/or before initiation of trastuzumab, a repeat LVEF assessment is recommended. This is repeated at 3-month intervals through the course of the therapy[52] and again at 6 months after completion of therapy. In addition, ESC and the NCRI agree that if a patient is at low risk for TIC during adjuvant therapy, LVEF assessment can be performed every 4 months (instead of 3 months).[62,65]

In regard to patients with metastatic disease who receive trastuzumab indefinitely, ESMO and ASCO agree that after baseline imaging, the frequency of cardiac imaging be determined by symptoms and/or clinical judgment. The NCRI recommends testing at baseline, 4 months, 8 months and then leaves further testing to the discretion of the physician.[61,63]

Postchemotherapy Surveillance

Once adjuvant cancer therapy is complete, ASCO and ESMO recommend a repeat echocardiogram between 6 and 12 months in higher risk patients, although this recommendation is directed primarily with patients with a history of anthracycline exposure. Beyond 1 year, there are no recommendations to support further testing.[1,63]

Surveillance With Biomarkers and Strain Imaging

In addition to assessment of LVEF, the ASE/EACVI recommends assessment of troponins and GLS at the same time LVEF surveillance is performed. ASE/EACVI/ESC recommend using an absolute change of >15% in GLS as well as a positive troponin as supportive indices of TIC to help aid in clinical decision-making regarding cessation of therapy.[1,65] Given TIC is not dose dependent and has a variable time of onset, measurement of troponin with every cycle of trastuzumab may be considered in high-risk patients.[49,68] The ASE/EACVI recommends using CMR as a confirmatory imaging modality when discontinuation of chemotherapy secondary to TIC is being considered. CAN and ASNC prefer MUGA over echocardiogram for routine surveillance because of its increased sensitivity in picking up a change in LVEF of 10%.[64,66] Whichever imaging modality is ultimately chosen, all guideline committees agree that using the same imaging modality, machine, operator, and calculation algorithms for each subsequent study is important[1,62] (Table 10.4). A general flow diagram for assessment of cardiotoxicity is shown in Figs. 10.7 and 10.8.

TABLE 10.6
Recommendations for Surveillance for Cardiac Dysfunction According to Major Societies

Society	Modality of Choice	Frequency of Monitoring
American Society of Clinical Oncology (ASCO)	1. Echocardiography: MUGA or MRI if echocardiography is not available, with MRI preferred over MUGA 2. Strain imaging and biomarkers (BNP, troponin) could be considered in conjunction with routine echocardiography	Frequency of surveillance should be determined by the provider based on patient's clinical characteristics
American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI)	1. Echocardiography, ideally incorporating three-dimensional imaging and GLS 2. Consider measuring high-sensitivity troponin in conjunction with imaging	Every 3 months during therapy
European Society for Medical Oncology (ESMO)	1. Echocardiography or MUGA 2. May consider MRI as an alternative	Baseline, every 3, 6, 9, 12, and 18 months after initiation of treatment For patients with metastatic disease, obtain baseline measurement and only repeat if patient develops symptoms of HF
European Society of Cardiology (ESC)	1. Echocardiography including 3-dimensional assessment of LVEF and GLS 2. MUGA and MRI may be considered as alterantives	Baseline, every 3 months during therapy and once after completion
Canadian Cardiovascular Society (CCS)	1. Echocardiography including 3-dimensional imaging and strain, MUGA and MRI as alternatives 2. Consider concomitant measurement of biomarkers (BNP, troponin)	No specific recommendation
Trastuzumab labeling	1. Echocardiography or MUGA	Baseline (immediately preceding initiation of trastuzumab), every 3 months during or upon completion of therapy, and at every 6 months for at least 2 years following completion of therapy

BNP, B-type/brain natriuretic peptide; *GLS*, global longitudinal strain; *LVEF*, left ventricular ejection fraction; *MRI*, magnetic resonance imaging; *MUGA*, multigated acquisition.
Adapted from Florido R, Smith KL, Cuomo KK, Russell SD. Cardiotoxicity from human epidermal growth factor Receptor-2 (HER2) targeted therapies. *J Am Heart Assoc*. 2017;6.

PREVENTION AND TREATMENT STRATEGIES

Primary Prevention

It is unknown whether cardioactive therapies can prevent TIC. Few studies have evaluated therapies that may prevent the development of TIC (Table 10.7), and of those, the majority included patients who were also treated with anthracyclines. The PRADA trial,[70] for example, included patients with breast cancer who were treated with anthracycline therapy and trastuzumab. Patients were started on candesartan (ACE-i) and metoprolol succinate (β-blocker) before

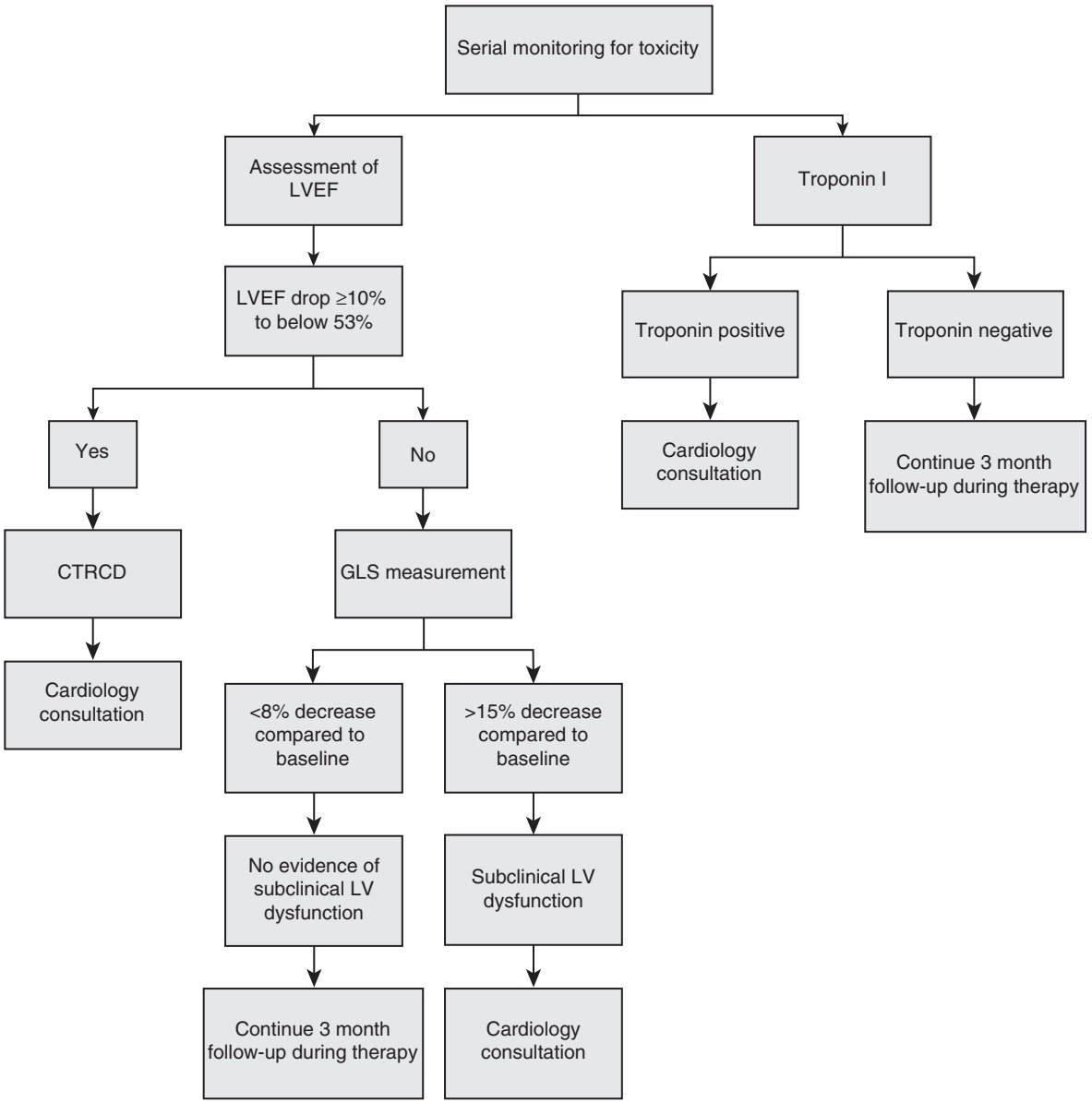


FIG. 10.8 Surveillance Algorithm From 2014 American Society of Echocardiography/European Association of Cardiovascular Imaging Expert Consensus of Multimodality Imaging of Adult Patients During and After Cancer Therapy in Regard to General Monitoring of Cardiotoxicity. *CTRCD*, cancer therapeutics-related cardiac dysfunction; *GLS*, global longitudinal strain; *LVEF*, left ventricular ejection fraction. (Adapted from Figs. 16 and 17 from Plana JC, Galderisi M, Barac S, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27: 911–939.)

TABLE 10.7
Prevention and Treatment of Trastuzumab-Induced Cardiotoxicity

	Study Type	Chemotherapy	Cardiac Therapy	Design and Medication	Patients	Duration	Primary Outcome	Results
PRIMARY PREVENTION								
Gulati et al.[70]	RCT	FEC, taxanes, trastuzumab	ACEi, β-blocker	2 × 2 factorial: candesartan, metoprolol vs. placebo	120	10–61 weeks	LVEF on CMR	Candesartan protective against LVEF reduction, no benefit with metoprolol
Pituskin et al.[71]	RCT	Trastuzumab	β-blocker	Perindopril, bisoprolol, placebo 1:1:1	94	347–356 days	LV remodeling (change in LVEDV on CMR)	Perindopril and bisoprolol did not prevent LV remodeling; however, they independently predicted stable LVEF
Seicean et al.[72]	Observational	Athracyclines, trastuzumab	β-blocker	1:2 propensity matched β-blocker vs. no β-blocker	318	3.2 ± 2.0 years	HF event	Continuous β-blocker use was associated with lower risk of HF events
Seicean et al.[73]	Observational	Anthracyclines, trastuzumab	Statin	2:1 propensity matched statin vs. no statin	201	2.6 ± 1.7 years	New-onset HF	Statin group had lower risk of new-onset HF
Boekhout et al.[74]	RCT	Trastuzumab	ACEi	Candesartan vs. placebo	210	78 weeks	LVEF	No significant difference in cardiac events in the candesartan group
SECONDARY PREVENTION								
Negishi et al.[75]	Observational	Anthracyclines ± trastuzumab, trastuzumab alone	β-blocker	Patients with GLS reduction ≥11% after therapy (average 7 ± 7 mos), β-blockers vs. no β-blocker	52	6 months	GLS	β-blocker use was associated with improvement in GLS

ACEi, Angiotensin converting enzyme inhibitor; *CMR*, cardiac magnetic resonance imaging; *FEC*, 5-fluorouracil, epirubicin, cyclophosphamide; *GLS*, global longitudinal strain; *HF*, heart failure; *LV*, left ventricle; *LVEDV*, left ventricular end diastolic volume; *LVEF*, left ventricular ejection fraction; *RCT*, randomized controlled trial.
Adapted from Pun SC, Neilan TG. Cardioprotective interventions: where are we? *J Am Coll Cardiol*. 2016.

chemotherapy. They found that patients who were treated with candesartan had a lower incidence of reduction in LVEF; no benefit was seen with β-blockers. However a more recent RCT by Boekhout et al. did not show a benefit in cardiac events in patients treated with candesartan for 78 weeks.[74] The MANTICORE trial[71] specifically evaluated the benefit of β-blocker use during trastuzumab treatment only. In that study, β-blockers were effective at preventing decline in LVEF; however, they did not prevent LV remodeling as measured by the change in the LV end-diastolic volume index. Lipid lowering treatment with statin may also provide protection from development of heart failure. One observational study found that patients undergoing chemotherapy with anthracycline and/or trastuzumab who were treated with a statin had a lower incidence of heart failure than propensity-matched control patients.[73] Until larger randomized controlled trials are done and there are established guidelines, initiation of cardioactive medications before trastuzumab should be based on patient's cardiovascular risk factors as well as administration of other cardiotoxic agents such as anthracyclines.

Secondary Prevention

For patients who develop TIC, the consensus among different societies is to temporary withdraw trastuzumab therapy and allow for a drug holiday with reassessment of risks and benefits after several weeks.[58,76] One possible algorithm proposed by ESMO for deciding to withdraw therapy based on LVEF evaluation is shown in Fig. 10.9.[64] Whether cessation of therapy is in fact necessary after development of cardiotoxicity is currently under investigation.[77] The early trastuzumab studies showed that the majority of patients had cardiac recovery even with continuation of therapy.[15] For those patients with evidence of cardiac damage including asymptomatic or symptomatic LVEF drop $\geq$10% or $\leq$50%, have a relative change in GLS of $\geq$15%, or positive troponins, initiation of cardioactive medications should be considered. Only one trial has looked at using β-blockers in patients who have evidence of abnormal GLS after chemotherapy. Patients who had a drop in GLS $\geq$11% with chemotherapy and were subsequently treated with β-blockers had improvement in GLS compared with patients without β-blocker therapy.[75] For patients with sustained TIC, ACC/AHA guideline–directed medical therapy for heart failure should be initiated by a cardiology specialist.[59] This includes initiation of an ACEi and β-blocker therapy.

Ultimately, larger studies with longer follow-up are needed to assess the optimal prevention and treatment strategies for patients undergoing chemotherapy with trastuzumab.

FUTURE AVENUES

Although there has been progress made in strategies aimed at potentially detecting and treating subclinical and clinical TIC, many of these studies are limited by small patient numbers, single institutional experience, and retrospective analyses of cardiotoxicity. As such, there remain a number of issues that require further investigation (Table 10.8). In addition, in many phase I/II trials analyzing the efficacy of anti-HER2 therapies, patients with preexisting cardiovascular risk factors and other comorbidities may be excluded, and thus the cardiotoxic impact of these therapies in "real-world" patients may be underestimated.

Given the recent increases in clinical trials examining the prevalence, detection, and treatment of chemotherapy-induced cardiotoxicity, the multidisciplinary field of cardio-oncology has gained international traction and interest among both fields of cardiovascular disease and hematology-oncology. One of the primary objectives of this field is to understand the mechanistic overlap between the effects of cancer treatments and cardiovascular disease, as well as to provide proactive clinical care and develop cardioprotective strategies to allow cancer patients to safely continue their treatment. Because of a theoretical higher risk of developing LV dysfunction in breast cancer patients with preexisting cardiovascular risk factors, which likely are present in older patients afflicted with breast cancer, cardio-oncology programs have evolved to assist patients, their oncology providers, and support staff with risk stratification of cardiotoxicity, initiation of cardioprotective therapy in selected patients, and provision of recommended strategies of short- and long-term surveillance of cardiotoxicity based on recent literature. The goal is to provide more consistent, streamlined avenues of care of cardioprotective therapies for patients at risk or those with cardiotoxicity to allow for the continuation of oncology treatments. Ongoing discussions with

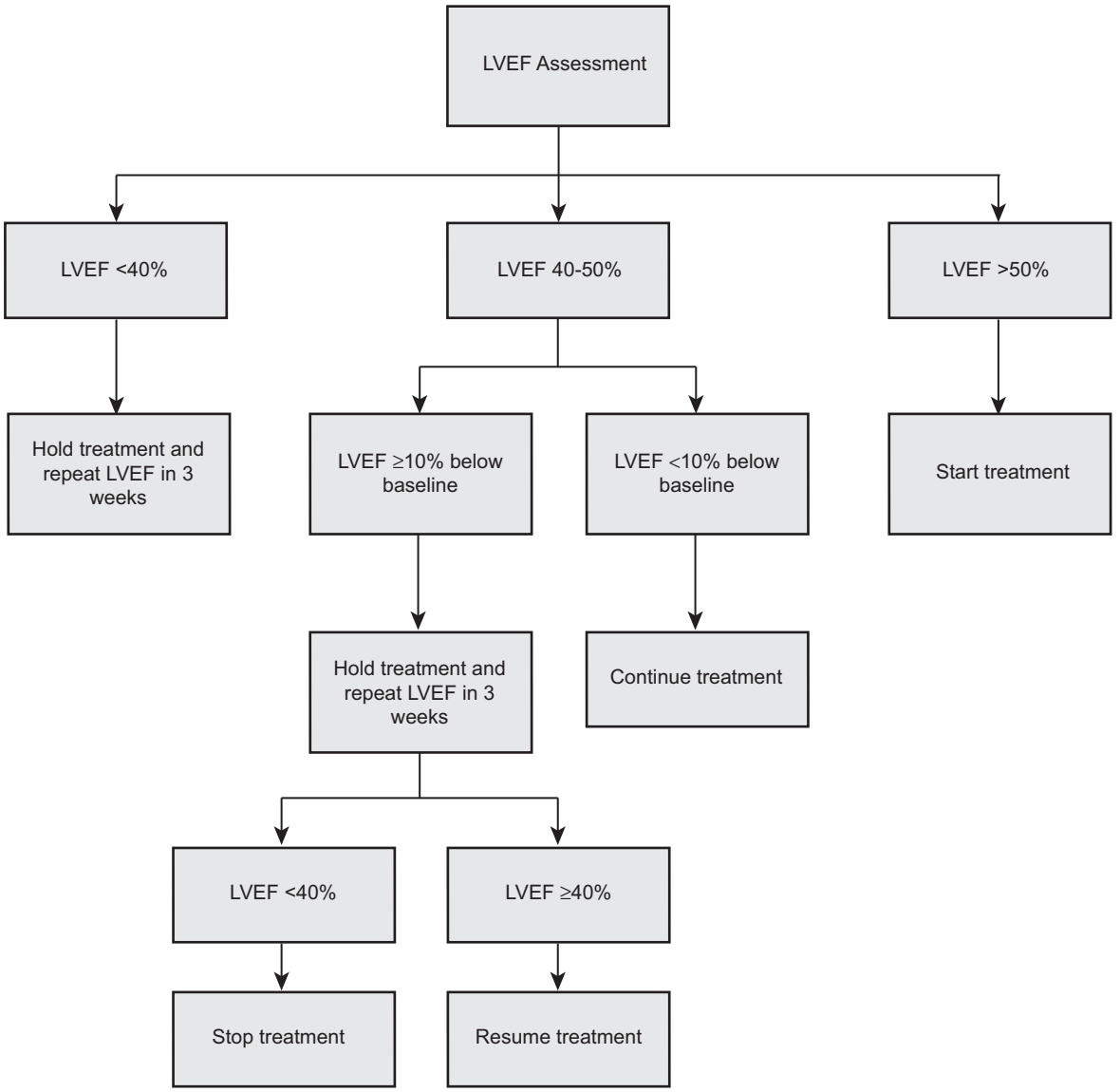


FIG. 10.9 Recommendations From the American Society of Nuclear Cardiology 2016 Information Statement for Altering Trastuzumab Therapy Based on Evaluation of Left Ventricular Ejection Fraction (LVEF). (Adapted from Russell RR, Alexander J, Jain D, et al. The role and clinical effectiveness of multimodality imaging in the management of cardiac complications of cancer and cancer therapy. *J Nucl Cardiol*. 2016;23:856–884.)

the patient's oncology team with the risks and benefits of continuing or changing treatment in patients who have experienced cardiotoxicity is critical for the patient to receive optimal oncologic and cardiovascular care.[78] However, further data and trials are needed to explore the impact on both cancer and cardiac outcomes in patients who receive cardio-oncology care in this nascent field.

Ongoing clinical trials are being designed and employed to further understand the natural course of

TABLE 10.8
Topics Requiring Further Investigation in Anti HER2-Related Cardiotoxicity

- Long-term cardiotoxicity surveillance in cancer survivors who have received anthracyclines and trastuzumab
- Cardiovascular and cancer outcomes, via establishment of national/international registries in cancer patients, who develop cardiotoxicity during trastuzumab treatment but continue chemotherapy with close cardiac monitoring and treatment
- Long-term cardiovascular outcomes in cancer survivors who develop cardiotoxicity during treatment with near complete recovery, or whose cardiac function does not recover with medical therapy
- Impact of cardio-oncology multidisciplinary care in cancer patients at risk for cardiotoxicity
- Role of pharmacologic/nonpharmacologic interventions during treatment in reducing risk of cardiotoxicity (i.e., exercise therapy, statin)
- Impact of prophylactic cardioprotective therapies (i.e., β-blockers, angiotensin converting enzyme inhibitors) in patients deemed to be high risk for cardiotoxicity before initiating anti-HER2 therapies
- Impact of early implementation of cardioprotective therapies with detection of subclinical cardiotoxicity (i.e., abnormal strain measurements with normal left ventricular function)
- Validation of risk prediction models that identify patients at highest risk for trastuzumab-induced cardiotoxicity

TIC and how interventional strategies can potentially reduce the risk of developing cardiotoxicity during treatment (Table 10.9). In regard to pharmacologic interventions, a prospective, multicenter, randomized, phase II placebo-controlled clinical trial cosponsored by the University of South Florida and the National Cancer Institute is evaluating the effects of an ACE-I (lisinopril) and β-blocker (carvedilol phosphate—extended release) on TIC with a target accrual of 468 patients (NCT01009918).[83] In patients who have experienced suspected TIC (LVEF ≥40% and 50%) while on treatment, the SAFE-HEaRt trial (NCT01904903) is looking at cardiac outcomes in this patient population with close cardiac monitoring and treatment with continued chemotherapy treatment.[77] While primarily focused on anthracyline-based regimens in breast cancer treatment along with trastuzumab, the SAFE trial (NCT2236806) is a randomized phase III, four-arm, single-blind, placebo-controlled study aiming to look at the effects of bisoprolol, ramipril, or both drugs on subclinical cardiotoxicity by speckle tracking on TTE.[79] The STOP trial (NCT02674204) is a randomized, placebo-controlled trial analyzing the effects of statin usage (atorvastatin) on subclinical cardiotoxicity by cardiac MRI in patients being treated with trastuzumab.[80] The CARDAPAC study (NCT02433067) is a phase II multicenter randomized trial of 112 HER2 breast cancer patients undergoing adjuvant treatment with trastuzumab, which is looking at the impact of a 3-month supervised exercise program with moderate and high intensity activity on cardiotoxicity (defined as a decrease of LVEF under 50%, or an absolute drop of LVEF 10% at baseline and at 3 months).[86] In regard to patients also receiving radiation therapy, a study is being conducted looking at breathhold techniques during treatments to reduce cardiac toxicity, as demonstrated by cardiac MRI at 12 months (NCT02052102).[87] Finally, from an imaging perspective, a double-blinded, prospective observational study is being conducted comparing cardiac MRI with MUGA scans in patients receiving trastuzumab in regard to LVEF assessment and LV volumes, and also comparing serial biomarker levels with changes in cardiac structure and function.[82]

Although ongoing efforts on an international scale are providing invaluable insight into the incidence and historical course of TIC, continued challenges remain in determining the most optimal surveillance frequency for cardiotoxicity, as well as interventional strategies. As anti-HER2 treatments, traditional and newer agent, continue to extend into treatments of malignancies other than breast cancer, the importance of continuing these research efforts remain paramount. With the increase in multidisciplinary collaborations within the field of cardio-oncology and raised awareness and vigilance of TIC—in addition to overall cardiovascular risk stratification and modification in breast cancer patients—patients hopefully can continue potentially lifesaving treatments for their cancer with earlier detection and treatment of subclinical cardiotoxicity, with the aim of living their lives with significantly less cardiac and oncologic short- and long-term comorbidity and mortality (Fig. 10.10).[88]

TABLE 10.9
Current Clinical Trials Investigating Surveillance, Detection, and Treatment of Trastuzumab-Induced Cardiotoxicity

Trial Name or PI	Clinical Trials ID	Sponsor	Study Type	Population	Intervention	Target Enrollment	Start/ Completion Date	Cardiac Assessment
SAFE[79]	NCT02236806	Azienda Ospedaliero-Universitaria Careggi, Florene, Italy	Phase III/ randomized, placebo-controlled/drug prevention	Nonmetastatic primary invasive BC	Bisoprolol, ramipril, placebo	480	July 2015/ November 2017	Biomarkers (TnI, NT-pro-NP), TTE
STOP[80]	NCT02674204	Cedars-Sinai Medical Center, Los Angeles, CA, USA	Randomized, placebo-controlled/drug intervention	Stage 1–3 HER positive BC undergoing treatment with trastuzumab +/−AC	Atorvastatin, placebo	90	May 2016/ October 2019	CMR with global circumferential strain
Yu, et al.[81]	NCT02615054	Memorial Sloan Kettering Cancer Center, New York, NY, USA	Prospective observational/ imaging	Primary invasive BC >/=2 years with and without cardiotoxicity	TTE with speckle tracking, CPET	55	November 2015/ November 2018	TTE with speckle tracking, CPET
Brezden-Masley, et al.[82]	NCT01022086	St. Michael's Hospital, Toronto, Canada	Prospective observational/ imaging	Invasive HER2 positive BC, planned treatment with trastuzumab	CMR, biomarker testing	50	November 2009/ December 2019	CMR, biomarkers (BNP, TnI, TGF B1, PINP, PIIINP, CITP)
Guglin, et al.[83]	NCT01009918	University of South Florida, Tampa, FL, USA	Phase II/ prospective randomized, placebo-controlled/drug prevention	HER2 positive BC undergoing trastuzumab +/− pertuzumab	Lisinopril, carvedilol phosphate extended-release, placebo	468	March 2010/ July 2017	TTE or MUGA, biomarkers (BNP, TnI)
Yu, et al.[84]	NCT02177175	Memorial Sloan Kettering Cancer Center, New York, NY, USA	Phase II/ prospective randomized placebo-controlled/drug prevention/ imaging	Nonmetastatic primary invasive HER2-positive BC undergoing AC and anti-HER2 treatment	Carvedilol, placebo (intervention), TTE with speckle tracking (imaging)	82	June 2014/ June 2018	TTE with speckle tracking
OTT 15–05[85]	NCT02696707	Ottawa Hospital Research Institute, Ottawa, Canada	Prospective, randomized/ imaging surveillance	Early-stage HER2 positive BC with planned trastuzumab therapy	TTE or MUGA q3 months vs. q4 months	200	June 2016/ March 2018	TTE or MUGA

Continued

TABLE 10.9
Current Clinical Trials Investigating Surveillance, Detection, and Treatment of Trastuzumab-Induced Cardiotoxicity—cont'd

Trial Name or PI	Clinical Trials ID	Sponsor	Study Type	Population	Intervention	Target Enrollment	Start/ Completion Date	Cardiac Assessment
SAFE-HEaRt[77]	NCT01904903	Washington Heart Center, Washington DC, USA	Prospective, open label/ treatment	Stage 1-IV HER2-positive BC with LVEF>/ = 40% and <50% on TTE receiving anti-HER2 treatment	Serial TTEs, cardiac treatment with β-blockers and ACE-I during chemotherapy	30	August 2013/ August 2018	TTE with speckle tracking and biomarkers (TnI, hsTnT)
CARDAPAC[86]	NCT02433067	University of Franche-Comte, Doubs, France	Prospective open label/ intervention with exercise	Nonmetastatic HER2-positive BC undergoing trastuzumab monotherapy	Control arm: standard oncologic care Interventional arm: physical activity intervention 3X/week	117	April 2015/ April 2018	TTE, measurements of body composition, muscle function, metabolic/ hormonal/ inflammatory responses, quality of life
COBC	NCT02571894	Karolina University Hospital, Stockholm, Sweden	Prospective, randomized open label/ intervention	Newly diagnosed BC eligible for neoadjuvant/ adjuvant chemotherapy, +/- trastuzumab	Observational arm: standard oncologic care. Interventional arm: serial TTEs with speckle tracking and biomarkers (hesitant, BNP)	320	July 2014/ February 2019	Serial TTEs with speckle tracking and biomarkers (hs-TnT, BNP)
Joseph et al.	NCT02052102	AHS Cancer Control, Alberta, Canada	Prospective, open label/ intervention with radiation breathing techniques	Left-sided BC who is a candidate to adjuvant RT with prior history of AC/trastuzumab	Impact on cardiotoxicity of DIBH versus FB	63	October 2014/March 2017	Functional CMR and biomarker (BNP, PIIINP, CITP)

AC, anthracycline; *ACE-I*, angiotensin converting enzyme inhibitor; *BC*, breast cancer; *BNP*, B-type natriuretic peptide; *CITP*, carboxy-terminal telopeptide of collagen type 1; *CMR*, cardiac magnetic resonance imaging; *CPET*, cardiopulmonary exercise testing; *DIBH*, deep inspiration breathhold; *FB*, free breathing; *HER2*, human epidermal growth receptor factor 2; *hsTnT*, high-sensitivity troponin-T; *LVEF*, left ventricular ejection fraction; *MUGA*, mitigated acquisition scan; *PI*, principal investigator; *PIIINP*, amino-terminal propeptide of procollagen type III; *PINP*, amino-terminal propeptide of procollagen type I; *RT*, radiotherapy; *TnI*, troponin I; *TTE*, transthoracic echocardiography.

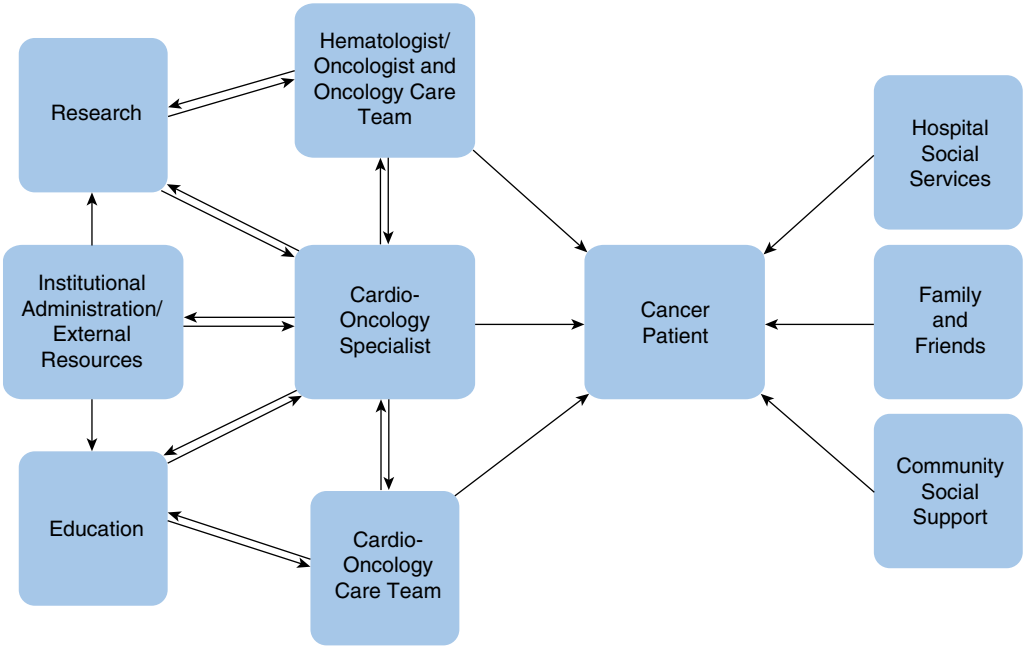


FIG. 10.10 Proposed Cardio-Oncology Multidisciplinary Care Team Model. (Reproduced from Okwuosa TM, Barac A. Buregoning cardio-oncology programs: challenges and opportunities for early career cardiologists/ faculty directors. *J Am Coll Cardiol*. 2015;66:1193–1197 with permission.)

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