

REVIEW

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Cardiotoxicity of monoclonal antibody-based therapies in breast cancer: a contemporary narrative review

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Abstract

Monoclonal antibody-based therapies have substantially improved outcomes in breast cancer, particularly through HER2-directed treatment strategies, but have also introduced important cardiovascular toxicities that require careful recognition and management. This narrative review summarizes current evidence on cardiotoxicity associated with monoclonal antibody therapies used in breast cancer, with emphasis on HER2-targeted antibodies, antibody-drug conjugates, and selected immune checkpoint inhibitors. Trastuzumab remains the best-characterized monoclonal antibody associated with cancer therapy-related cardiac dysfunction, most commonly presenting as left ventricular systolic dysfunction, particularly in patients previously exposed to anthracyclines or with baseline cardiovascular risk factors. Pertuzumab and currently available antibody-drug conjugates have not shown a major increase in cardiotoxic risk beyond that observed with established HER2-directed therapy, although long-term data remain limited for some newer agents. Immune checkpoint inhibitors are less commonly associated with cardiovascular toxicity, but may rarely cause severe immune-mediated complications, particularly myocarditis and also non-immune mediated toxicity such as cardiac dysfunction. Contemporary evaluation of cardiotoxicity increasingly relies on an integrated cardio-oncology framework incorporating left ventricular ejection fraction, global longitudinal strain, and cardiac biomarkers, with growing recognition of subclinical dysfunction and right ventricular involvement. Current management strategies emphasize baseline cardiovascular risk assessment, risk-adapted surveillance, early initiation of heart failure therapy when indicated, and individualized multidisciplinary decision-making regarding continuation of anticancer treatment, including permissive cardiotoxicity in selected patients. As the use of monoclonal antibody therapies continues to expand, optimizing the balance between oncologic efficacy and cardiovascular safety remains a central goal of modern breast cancer care.

Highlights

- Monoclonal antibody-based therapy improves survival but poses unique cardiac risks.
- Trastuzumab cardiotoxicity differs mechanistically from that of anthracyclines.
- Antibody–drug conjugates have lower cardiotoxicity, but long-term data are limited.

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- Early detection and cardio-oncology collaboration optimize patient safety.

Keywords Breast cancer, Monoclonal antibody, Antibody–drug conjugate, Cardiotoxicity

Introduction

Breast cancer is the most frequently diagnosed malignancy among women. In 2022, there were an estimated 2.3 million new cases, accounting for 11.6% of all cancers globally. It represented nearly one in four cancer diagnoses in women and was also the leading cause of female cancer deaths in 112 countries [5]. While the incidence of age-standardized breast cancer has increased worldwide, mortality rates have been decreasing in the same period in many countries with high or very high human development indices [79].

The improvement in effective therapeutic options for the management of breast cancer has led to an increased number of breast cancer survivors, who can experience long-term toxicities from cancer treatments [81]. Currently, there are approximately 4.1 million breast cancer survivors in the United States alone [72]. An increasing share is made up of long-term survivors: in the USA, the 5 year survival rate of breast cancer (all stages) increased from 79% (1984–1986) to 91% (2008–2014) [46].

Despite the substantial clinical benefit of targeted therapies in breast cancer, cardiotoxicity remains a relevant concern, with potential implications for treatment adherence and long-term outcomes [47]. In this context, the objective of this narrative review is to provide a contemporary synthesis of the evidence on cardiotoxicity associated with monoclonal antibody (mAb)-based therapies in breast cancer.

Methodology

This study was conducted as a narrative review of the available evidence on cardiotoxicity associated with mAb-based therapies used in breast cancer, including mAbs, antibody drug conjugates (ADC) and selected immune checkpoint inhibitors (ICI). A literature search was performed in PubMed/MEDLINE, Embase, Scopus, and Web of Science, complemented by publicly available documents from the FDA and EMA, as well as relevant clinical practice guidelines from the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society of Cardiology (ESC). The search included combinations of keywords and controlled vocabulary related to breast cancer, cardiotoxicity, monoclonal antibodies, HER2-targeted therapy, ADC, and ICIs, as well as the international nonproprietary names of the main agents used in current breast cancer treatment. Studies published up to September 2025 were considered.

Eligible sources included randomized clinical trials, prospective and retrospective observational studies, systematic reviews, meta-analyses, narrative reviews, clinical practice guidelines, consensus statements, and regulatory reports addressing cardiovascular safety in patients with breast cancer receiving mAb-based therapies. For older agents such as trastuzumab and pertuzumab, priority was given to pivotal trials, major meta-analyses, and cardio-oncology guideline documents. For newer agents, including some ADC and ICI, evidence was supplemented with regulatory data and more recent early-phase or post-approval reports when long-term cardiovascular data were limited.

Sources were selected for inclusion if they were written in English and provided information relevant to the incidence, mechanisms, manifestations, risk factors, monitoring, prevention, or management of cardiotoxicity in the context of breast cancer treatment. Publications focused exclusively on non-breast malignancies, non-antibody therapies without direct relevance to the review question, preclinical studies without clear translational relevance, duplicate reports, and abstracts lacking sufficient methodological or outcome detail were excluded from the main narrative synthesis, although highly relevant background references were occasionally retained for contextual discussion.

Screening and selection were performed in a pragmatic narrative-review framework rather than through a formal systematic-review process. Titles and abstracts were initially reviewed for relevance, followed by full-text assessment of potentially eligible sources. When multiple publications addressed the same topic, preference was given to the most informative, methodologically robust, and clinically relevant sources. In total, 426 records were screened, and 81 sources were included in the final narrative synthesis.

As a narrative review, this work was not designed to provide a quantitative pooled estimate of cardiotoxicity incidence and remains subject to selection bias. However, efforts were made to improve breadth and balance by using multiple bibliographic databases, guideline sources, and regulatory documents, and by prioritizing higher-level evidence whenever available.

MABs used in breast cancer treatment

Breast cancer is most often managed with a combination of treatment modalities, including surgery, radiotherapy and systemic drug therapy. The latter has been transformed by mAbs which have produced substantial gains

in survival, particularly for patients with human epidermal growth factor receptor positive (HER2+) [11, 21, 70] and triple-negative breast cancer (TNBC) [63]. Moreover, their increasing use has revealed a new challenge: cardiovascular toxicity. Understanding the mechanisms by which different classes of targeted agents contribute to cardiotoxicity is essential for optimizing long-term outcomes (Table 1).

Drug-based systemic therapy for breast cancer is largely determined by the molecular classification of the cancer, which is commonly grouped into four categories on the basis of hormone receptor (HR) expression: estrogen receptor positive (ER+); progesterone receptor positive (PR+); HER2+; and TNBC, which is characterized by the lack of expression of any of the previously mentioned receptors [22, 65].

MAbs have played an important and growing role in the treatment of breast cancer, most prominently in the group of HER2+breast cancers, where trastuzumab was approved at the end of the last millennium. HER2+ tumors represent one of the most aggressive subtypes of breast cancer, but their prognosis has improved dramatically in the past two decades since the development of HER2-targeted therapy. Before the arrival of trastuzumab, HER2+breast cancer was associated with a poor outcome. While metastatic HER2+breast cancer is still considered not curable, its increasing survival time has often led to chronic disease [17, 20, 73]. In early HER2+breast cancer, the addition of trastuzumab to chemotherapy in adjuvant therapy increased disease-free survival from 67.1% to 85.3% within a 4-year observation period [59]. Adding pertuzumab to trastuzumab and chemotherapy in the adjuvant setting for lymph node-positive patients increased overall survival (OS) at 10 years to 91.6% [39].

In patients with metastatic HER2+breast cancer, the addition of trastuzumab to chemotherapy increased the median OS from 20.3 months to 25.4 months [19]. The addition of pertuzumab to trastuzumab and chemotherapy further increased the median OS to 56.5 months vs 40.8 months with trastuzumab+chemotherapy [68]. ADCs have provided the chance for extended OS even for patients in second line treatment after progression on trastuzumab therapy, in the case of T-DXd with a median OS of 52.6 months vs 42.7 months with T-DM1 [10, 33].

MAbs were introduced for the treatment of ER+/PR+ and TNBCs only in 2019, indicating significant advancements in therapeutic options [66]. However, pembrolizumab, which has been used in TNBC since 2020, has a longer history in other solid tumors and was first approved for the treatment of melanoma in 2014 [78]. The toxicity of pembrolizumab could therefore be observed over a longer period. The same applies for atezolizumab, although the breast cancer indication has been withdrawn in the USA [60].

MAbs are normally used in combination with a chemotherapy backbone, which varies on the basis of the specific tumor type. This group can include taxanes, platinum-based therapies and anthracyclines. ADCs are typically not combined with chemotherapy, as they carry a chemotherapeutic agent linked to the antibody. However, these therapies are often used in patients who have previously undergone therapies that include chemotherapy [22].

Definitions and clinical criteria of cardiotoxicity

Definitions of cardiotoxicity in breast cancer have evolved considerably over time. In major trastuzumab clinical trials, cardiotoxicity was primarily defined using left ventricular ejection fraction (LVEF)-based criteria,

Table 1 mAbs and ADCs approved for breast cancer and cardiotoxicity profiles

Drug	Type	FDA/EMA Approval	Breast Cancer Indication	Setting	Combination
Trastuzumab	Anti-HER2 mAb	1998	HER2+	Neo- adjuvant, adjuvant, metastatic	Monotherapy or with chemotherapy
Pertuzumab	Anti-HER2 mAb	2012	HER2+	Neo- adjuvant, adjuvant, metastatic	Always with trastuzumab+ chemotherapy
Metastatic	Anti-HER2 mAb	2020 (FDA only)	HER2+	3rd line metastatic	Chemotherapy
T-DM1 (trastuzumab emtansine)	ADC	2013	HER2+	Adjuvant, metastatic	Monotherapy
T-DXd (trastuzumab deruxtecan)	ADC	2019	HER2+	Adjuvant, metastatic	Monotherapy
Datopotamab deruxtecan	ADC	2025	HR+	Metastatic after ET+ chemo	Monotherapy
Sacituzumab govitecan	ADC	2020	TNBC, HR+ (advanced)	Metastatic	Monotherapy
Pembrolizumab	Check- point inhibitor (PD-1)	2020 (BC)	TNBC (PD-L1 +, high-risk early-stage)	Neo- adjuvant, adjuvant, metastatic	Monotherapy or with chemotherapy
Atezolizumab	Check- point inhibitor (PD-L1)	2019 (BC: EMA only)	TNBC (PD-L1 +)	Metastatic (EMA only)	With nab- paclitaxel

Abbreviations ADC Antibody- drug conjugate, BC Breast cancer, EMA European Medicines Agency, HER2+ =Human epidermal growth factor receptor 2 positive, HR+ Hormone receptor positive, mAb Monoclonal antibody, PD-1 Programmed Death-1, PD-L1 Programmed death-ligand 1, TNBC Triple negative breast cancer. Sources: FDA, EMA

usually including symptomatic congestive heart failure (CHF) and/or an absolute decline in LVEF. Common historical definitions included: (i) cardiomyopathy characterized by a decrease in LVEF that was either global or more severe in the septum; (ii) symptoms of CHF; (iii) associated signs of CHF, including but not limited to S3 gallop, tachycardia, or both; and (iv) a decline in LVEF of at least 5% to <55% with accompanying signs or symptoms of CHF, or a decline in LVEF of at least 10% to <55% without accompanying signs or symptoms. A simpler and frequently used trial-based definition has also been an absolute decrease in LVEF of at least 10% to a value below 55% [38]. However, these historical criteria were heterogeneous and relied predominantly on overt changes in systolic function, which may underestimate earlier or subclinical myocardial injury. This heterogeneity in trial-based definitions, together with differences in monitoring strategies and patient populations, has made it difficult to compare cardiotoxicity rates and prognostic implications reliably across studies. Importantly, grouping asymptomatic ventricular dysfunction and symptomatic heart failure under the same umbrella term may obscure clinically meaningful differences in severity, reversibility, and management.

The contemporary reference standard in cardio-oncology is the universal definition of cancer therapy-related cardiac dysfunction (CTRCD) proposed by the Heart Failure Association (HFA) of the ESC in collaboration with the International Cardio-Oncology Society (IC-OS) [25]. This framework expands the definition of cardiotoxicity beyond LVEF alone by integrating imaging and biomarker parameters, particularly global longitudinal strain (GLS) and cardiac biomarkers, thereby allowing earlier recognition of subclinical dysfunction. According to this classification, severe CTRCD is defined as a new reduction in LVEF to <40%. Moderate CTRCD is defined as either a new reduction in LVEF by ≥ 10 percentage points to an LVEF of 40%–49%, or a new reduction in LVEF by <10 percentage points to an LVEF of 40%–49% accompanied by either a relative decline in GLS of >15% from baseline or a rise in cardiac biomarkers. Mild CTRCD is defined by an LVEF $\geq 50\%$ associated with a relative GLS decline of >15% from baseline and/or a rise in cardiac biomarkers indicative of myocardial injury or stress [25].

Future clinical trials and observational studies should preferentially adopt this contemporary standardized definition to improve consistency, comparability, and clinical interpretability of cardiotoxicity outcomes.

Cardiac biomarkers are increasingly used as adjuncts to imaging in the surveillance of cancer therapy-related cardiac dysfunction. While troponin is generally considered a marker of myocardial injury, natriuretic peptides, particularly B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), may

provide complementary information regarding myocardial stress and early ventricular dysfunction. In the setting of trastuzumab-related cardiotoxicity, natriuretic peptides may be especially useful because they may rise in association with developing functional impairment and, in some settings, appear more sensitive than troponin for identifying early cardiotoxicity. Nevertheless, biomarker interpretation should be integrated with echocardiographic parameters, particularly LVEF and GLS, as well as the overall clinical context, rather than being used as standalone markers of cardiotoxicity [12, 58].

Although cancer therapy-related cardiac dysfunction has historically been assessed primarily through LVEF, growing evidence indicates that the right ventricle (RV) may also be affected and deserves specific attention in cardio-oncology. According to a recent scientific statement from HFA of the ESC and the ESC Council of Cardio-Oncology, the right heart may be impaired in patients with cancer through multiple mechanisms, including direct myocardial toxicity, pulmonary vascular changes, thromboembolic disease, increased afterload, cancer treatment-related lung injury, and ventricular interdependence. RV dysfunction is clinically relevant because it may contribute to symptoms, functional limitation, and adverse cardiovascular outcomes, yet it is often underrecognized in routine oncologic surveillance [29]. In patients receiving HER2-directed therapy, emerging evidence suggests that RV dysfunction may occur alongside or even before overt changes in conventional left ventricular (LV) parameters. In a prospective study, Keramida *et al.* [30] demonstrated longitudinal changes in RV deformation mechanics during trastuzumab therapy, suggesting that RV strain may identify early subclinical myocardial impairment. Likewise, Mazzutti *et al.* [44] reported alterations in RV function during trastuzumab treatment for breast cancer. Together, these findings support a more comprehensive biventricular approach to cardio-oncology surveillance, particularly in patients receiving potentially cardiotoxic anti-HER2 therapies.

Cardiovascular toxicity in patients with breast cancer is mechanistically heterogeneous. The traditional type I/II/III framework has historically been used to distinguish anthracycline-related irreversible myocardial injury (type I) from the generally more reversible dysfunction associated with anti-HER2 therapies (type II), and type III referred to myocarditis typically caused by ICIs. This model is increasingly recognized as an oversimplification. Contemporary cardio-oncology recognizes that cancer therapy-related cardiovascular toxicity may result from multiple and sometimes overlapping mechanisms, including direct myocardial injury, disruption of cardiomyocyte survival pathways, inflammatory myocardial damage, vascular dysfunction, arrhythmias, and hemodynamic effects. ICIs, for example, are more commonly

associated with inflammatory cardiotoxicity such as myocarditis, whereas anti-HER2 therapies are classically linked to noninflammatory myocardial dysfunction, although overlap may occur [81]. Reversibility should therefore not be assumed solely on the basis of historical mechanistic classification (Table 2).

Mechanisms and manifestations of mAb-induced cardiotoxicity in breast cancer

In the following sections, we summarize the main cardiotoxic manifestations and proposed mechanisms associated with each mAbs therapy used in breast cancer.

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that binds to the extracellular juxtamembrane domain (domain IV) of HER2, thereby inhibiting receptor activation and downstream signaling pathways involved in cell proliferation and survival [26]. Although this antitumor effect is central to its efficacy, HER2 is also expressed in adult cardiomyocytes, where it plays an important role in growth, repair, and survival signaling [15]. This explains why blockade of HER2 may adversely affect myocardial homeostasis.

This profile differs from anthracycline-related cardiotoxicity, which has classically been associated with direct structural myocardial injury and increased autophagy, although overlap may occur in patients exposed to both agents [18, 38]. This distinction is clinically relevant because prior anthracycline exposure substantially increases the risk of trastuzumab-related cardiac dysfunction.

Clinical, imaging, and biomarker studies further suggest that trastuzumab-related cardiotoxicity may extend beyond an isolated decline in LVEF. In an analysis of breast cancer patients treated with trastuzumab with different chemotherapy backbones, treatment was associated with impaired cardiac function, early myocardial inflammation, and deleterious cardiometabolic changes, including increased noncardiac body mass

and body fat depots [31]. Trastuzumab-mediated cardiotoxicity was characterized by concurrent LV and RV dysfunction, reversible myocardial inflammation, and transient cardiac edema [31]. In the same study, trastuzumab increased biomarkers related to myocardial stress (growth differentiation factor-15, GDF-15) and myocardial proteolysis (matrix metalloproteinase-2,MMP-2), but not high-sensitivity Troponin (hsTn), whereas hsTn was increased in patients previously exposed to anthracyclines, again supporting biological differences between trastuzumab- and anthracycline-related cardiotoxicity [31].

Clinically, an estimated 1% to 4% of patients treated with trastuzumab develop overt heart failure (HF), whereas approximately 10% experience asymptomatic reduction in LVEF. When trastuzumab is combined with anthracyclines, the incidence of cardiotoxicity may be substantially higher, reaching up to 34% in some reports [27, 43]. Overall, trastuzumab remains the best-characterized mAb associated with CTRCD in breast cancer, particularly in patients with prior anthracycline exposure or baseline cardiovascular risk factors.

Pertuzumab

Pertuzumab is a fully humanized mAb directed against HER2 and is used in combination with trastuzumab or a trastuzumab-containing ADC in HER2+ breast cancer [7]. Available evidence suggests that pertuzumab has a relatively favorable cardiac safety profile and does not substantially increase cardiotoxic risk beyond that already associated with trastuzumab-containing regimens.

Although the precise mechanisms underlying pertuzumab-related cardiotoxicity remain less well defined, preclinical data suggest that pertuzumab may have less impact on cardiomyocyte survival pathways than trastuzumab.

Clinical findings are somewhat heterogeneous. A meta-analysis of eight studies comparing pertuzumab plus trastuzumab and chemotherapy with trastuzumab

Table 2 Historical trial-based definitions of cardiotoxicity and contemporary ESC/HFA/IC-OS classification of CTRCD

Framework	Main criteria	Key limitation/implication
Historical trastuzumab trial-based definitions	LVEF decline, symptomatic CHF, signs of CHF	Heterogeneous criteria across studies; mainly detects overt dysfunction
Simplified trial-based definition	Absolute LVEF decline ≥ 10% to <55%	Does not capture subclinical dysfunction
ESC/HFA/IC-OS 2022	Classifies adverse effects according to (i) cardiac dysfunction (cardiomyopathy/ heart failure), (ii) myocarditis, (iii) vascular toxicity, (iv) hypertension and (v) arrhythmias and QTc prolongation Each of these groups has specific criteria defining mild, moderate, severe and very severe	Standardized classification based on consensus definitions

Abbreviations: ESC European Society of Cardiology, HFA Heart Failure Association, IC-OS International Cardio-Oncology Society, CTRCD Classification of cancer therapy-related cardiac dysfunction [25, 38]

and chemotherapy reported no increase in the risk of asymptomatic or minimally symptomatic left ventricular dysfunction (LVD) with the addition of pertuzumab. In the same analysis, however, the risk of symptomatic HF was significantly increased [1]. This apparent discrepancy should be interpreted cautiously. First, the absolute number of HF events was very low, with 4 cases per 1,000 patients in the trastuzumab plus chemotherapy (or trastuzumab-emtansine) group versus 8 cases per 1,000 patients in the pertuzumab-containing group, corresponding to only 48 events overall (0.6%). Second, asymptomatic LVD and clinical HF are distinct endpoints and may not change in parallel, particularly when event counts are small. Third, incomplete information on concomitant chemotherapy in some studies limits interpretation, especially because background cardiac risk may be influenced by prior or concurrent exposure to other potentially cardiotoxic agents [1].

These findings should also be viewed in the context of earlier larger studies, which reported a low absolute incidence of symptomatic cardiac events with pertuzumab-containing regimens [64, 69]. More recent real-world data in the neoadjuvant setting did not show any increase in cardiotoxicity when pertuzumab was added to trastuzumab and chemotherapy [6]. Similarly, long-term safety follow-up with a median follow-up of 74 months revealed no increase in cardiac events with the addition of pertuzumab, and changes in LVEF over time were similar between groups [14]. Overall, current evidence suggests that pertuzumab does not substantially increase cardiotoxicity beyond the background risk associated with HER2-directed therapy.

Margetuximab

Margetuximab is a HER2-targeted mAb with a modified Fc region designed to enhance immune-mediated anti-tumor activity against HER2+ breast cancer cells [23]. It has been approved in combination with chemotherapy for pretreated metastatic HER2+ breast cancer. In clinical studies, margetuximab improved progression free survival (PFS) compared with trastuzumab, although no significant improvement in OS was demonstrated [61, 62].

From a cardiovascular perspective, available evidence suggests a low rate of cardiotoxicity. In the phase III trial, the proportion of patients experiencing a reduction in LVEF was identical in the margetuximab and trastuzumab arms (2.3% in both groups) [81]. Importantly, this population consisted of patients with pretreated metastatic HER2+ breast cancer and prior exposure to anti-HER2 therapy. Overall, current evidence does not suggest a major excess cardiac risk with margetuximab compared with trastuzumab, although clinical experience remains limited.

T-DM1 (trastuzumab emtansine)

T-DM1 is an ADC in which trastuzumab is linked to the microtubule toxin DM1, a derivative of maytansine. The trastuzumab moiety allows targeted delivery of the cytotoxic complex to cells expressing the HER2 receptor via receptor-mediated endocytosis. The incidence of T-DM1-induced cardiac dysfunction is low, regardless of prior anthracycline therapy. In a pooled analysis, only 2.4% of patients experienced grade 1/2 drops in the LVEF, and 0.71% experienced grade 3/4 drops or congestive heart failure, although 63.4% of the studied population was previously treated with anthracyclines [35, 56].

In clinical studies, T-DM1 showed a lower incidence of LVEF decline rates than comparator regimens containing trastuzumab plus different chemotherapy backbones or pertuzumab and trastuzumab plus taxane [16]. The incidence of LVEF or cardiotoxicity in general was between 0.3% and 1.7% for T-DM1 in key phase III trials [34, 53, 75, 76].

All of these clinical data suggest that T-DM1 is less cardiotoxic than trastuzumab is. Although the antibody molecule is the same, this ADC may have different effects on cardiomyocytes [35].

T-DXd (trastuzumab deruxtecan)

T-DXd is an ADC with a topoisomerase I inhibitor as its cytotoxic payload. Available data suggest a low frequency of clinically significant cardiotoxicity, with grade 3 or higher cardiac events reported in only 0.5% of patients in clinical studies. By contrast, interstitial lung disease (ILD) has emerged as the main safety concern in phase II trials [16].

A systematic review and single-arm meta-analysis reported an incidence of LVEF decrease of 1.95% and QT interval prolongation of 7.77% with T-DXd [67]. Overall, no major cardiotoxic signal has emerged with T-DXd to date, although longer follow-up and broader real-world experience remain necessary.

Datopotamab deruxtecan

Datopotamab deruxtecan is a trophoblast cell-surface antigen 2 (Trop-2)-directed ADC with a topoisomerase I inhibitor payload. It was approved in the US and the EU in 2025 for patients with unresectable or metastatic HR+/HER2-negative breast cancer previously treated with endocrine-based therapy and chemotherapy. No significant cardiovascular toxicity was reported in the available studies [2, 3].

Sacituzumab govitecan

Sacituzumab govitecan is a Trop-2-directed ADC approved for pretreated metastatic TNBC and HR+/HER2-negative breast cancer. In the approval trials, no significant cardiovascular toxicity was reported [81].

Overall, currently available evidence does not suggest a major cardiotoxic signal with sacituzumab govitecan, although longer-term and post-marketing data remain important.

Immune checkpoint inhibitors (Pembrolizumab, Atezolizumab, Dostarlimab)

ICI are mAbs used in selected breast cancer settings, particularly TNBC. Pembrolizumab targets PD-1, whereas atezolizumab targets PD-L1. Atezolizumab’s indication for breast cancer was withdrawn in the US but remains valid in the EU [24]. Dostarlimab, another ICI, may be used in later treatment lines for MSI-H/dMMR solid tumors, including breast cancer [22, 51].

ICIs have become increasingly relevant in the treatment of selected patients with breast cancer and their cardiovascular toxicity deserves specific consideration. ICI-related cardiotoxicity includes both inflammatory and non-inflammatory phenotypes. The best recognized form is myocarditis, a rare but potentially fulminant immune-mediated complication associated with high mortality. Proposed mechanisms include dysregulated T-cell activation and loss of immune tolerance, leading to myocardial inflammation. Clinical presentation ranges from asymptomatic troponin elevation to chest pain, dyspnea, arrhythmias, conduction abnormalities, acute heart failure, cardiogenic shock, and sudden death. Because of its severity, early diagnosis and prompt treatment with interruption of ICI therapy and initiation of immunosuppression are critical.

In addition to myocarditis, ICIs may also be associated with non-inflammatory LVD, characterized by new LV systolic impairment with or without heart failure symptoms, but without clear evidence of acute myocardial inflammation. This entity remains less well defined, and

its pathophysiology may involve indirect immune-mediated injury, cytokine effects, endothelial dysfunction, or unmasking of pre-existing susceptibility. Distinguishing myocarditis from non-inflammatory LVD is clinically important because these entities may differ in presentation, prognosis, and management. While myocarditis carries a high risk of severe cardiovascular events and death, non-inflammatory LV dysfunction appears to be a more heterogeneous and potentially underrecognized phenotype requiring further investigation [49, 71] (Table 3).

Risk factors for cardiotoxicity during mAb treatment in patients with breast cancer

The advent of mAbs in the treatment of breast cancer has provided important benefits for patients. In a follow-up publication of a large Phase 3 trial, 37% of patients had already reached 8 years of OS [70]. These long survival times mean that the risk of cardiotoxicity needs to be managed from the beginning to avoid treatment-related cardiac diseases becoming limiting factors for quality of life or even survival. Early identification and prompt treatment of subclinical cardiotoxicity may improve the cardiologic prognosis of these patients and may allow oncologists to avoid withdrawal of systemic therapy [50]. The Cancer Care Pathways recommend that patients have a baseline cardiovascular toxicity assessment at the time of cancer diagnosis. Patients at low risk would follow standard surveillance during treatment and an annual cardiovascular assessment, starting from 1 year after the completion of therapy. Patients at moderate or high risk should be referred to a cardiologist at the beginning of cancer therapy and undergo regular assessment after the completion of therapy [42].

Risk factors for trastuzumab-induced cardiotoxicity have been studied by different groups, but the results

Table 3 Mechanisms of action and cardiotoxicity associated with monoclonal antibodies in breast cancer

Drug	Molecular Target/Mechanism	Type of Cardiotoxicity	Reversibility	Key Notes
Trastuzumab	HER2 extracellular domain IV	LVEF ↓, CHF (1–4%)	Usually, reversible	↑ risk with anthracyclines; ROS accumulation, impaired PI3K-Akt signaling
Pertuzumab	HER2 domain II, blocks HER2/HER3 dimerization	Mild LVEF ↓; HF rare	Reversible	Less ROS/autophagy effect than trastuzumab
Targeted therapies				
Margetuximab	Fc-engineered anti-HER2	Similar to trastuzumab	Reversible	No OS benefit over trastuzumab
T-DM1	HER2-directed ADC with DM1 payload	LVEF ↓ < 2%	Reversible	Safer cardiac profile vs trastuzumab
T-DXd	HER2-directed ADC with topoisomerase I inhibitor	LVEF ↓ ~ 2%; QT prolongation	Reversible	ILD main concern
Sacituzumab govitecan	Trop-2 ADC	None relevant	—	No cardiotoxic signal
Immunotherapy				
Pembrolizumab	PD-1 inhibitor	Myocarditis, pericarditis	Potentially severe	Immune-mediated
Atezolizumab	PD-L1 inhibitor	Myocarditis, pericarditis	Potentially severe	Immune-mediated

Abbreviations: ADC Antibody–drug conjugate, CHF Congestive heart failure, DM1 Maytansine derivative 1, Fc Fragment crystallizable region, HER2/3 Human epidermal growth factor receptor 2/3, ILD Interstitial lung disease, LVEF Left ventricular ejection fraction, OS Overall survival, PD-1 Programmed Death-1, PD-L1 Programmed death-ligand 1, PI3K-Akt Phosphatidylinositol 3-kinase (PI3K)/Protein Kinase B (Akt), ROS Reactive oxygen species, Trop 2 Trophoblast cell-surface antigen 2 [1–3, 16, 18, 26, 31, 35, 38, 56, 67, 71, 81]

have sometimes been inconsistent. Advanced age, hypertension, diabetes mellitus, previous anthracycline use, reduced baseline LVEF and existing coronary disease have been associated with increased risk but not hyperlipidemia [27, 32, 48, 54].

Exploratory studies suggest that selected HER2-related single nucleotide polymorphisms may influence susceptibility to treatment-related cardiotoxicity. In particular, the HER2 655 Ile/Val polymorphism has been associated with increased risk, whereas the HER2 1170 Pro/Ala polymorphism has been associated with reduced risk. In addition, several cardiomyopathy-related genetic variants have been proposed as potential modifiers of cardiotoxicity risk in patients receiving trastuzumab and chemotherapy. However, these findings remain investigational and do not currently support routine clinical genetic testing [40].

An association between trastuzumab-induced chemotherapy-related cardiotoxicity and the altered expression profile (i.e., upregulation or downregulation) of several genes, as determined via RNA sequencing, has also been reported [77].

Although trastuzumab-related cardiotoxicity has traditionally been considered more reversible than anthracycline-induced myocardial injury, recovery is not universal. In particular, prior anthracycline exposure appears to modify both the risk and the reversibility of subsequent trastuzumab-related LVD. Cardinale and colleagues showed that a substantial proportion of patients treated with trastuzumab after anthracyclines did not experience full recovery of left ventricular systolic function, underscoring that this form of cardiotoxicity may not be as benign or uniformly reversible as previously assumed [8].

This has important practical implications. The 2022 ESC cardio-oncology guidelines emphasize early recognition of cancer therapy-related cardiac dysfunction, integration of imaging and biomarkers, and prompt initiation of heart failure therapy when indicated, particularly in higher-risk patients. In this context, patients with prior anthracycline exposure, baseline cardiovascular risk factors, or early evidence of ventricular dysfunction may

particularly benefit from close cardio-oncology follow-up and optimization of heart failure treatment (Table 4).

Prevention and treatment of antibody-induced cardiotoxicity

Prevention and management of cardiotoxicity associated with monoclonal antibody-based therapies should be individualized according to baseline cardiovascular risk, the severity of CTRCD, and the expected oncologic benefit of treatment. In breast cancer, most available evidence on preventive and therapeutic strategies derives from patients receiving anthracyclines and/or trastuzumab rather than from studies focused specifically on pertuzumab or newer ADCs.

Among neurohormonal strategies, angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blockers (ARB) and beta blockers (BB) have shown potential benefit in reducing or attenuating decline in LVEF during trastuzumab-containing treatment, although the magnitude and consistency of benefit remain variable across studies. In the randomized MANTICORE trial, perindopril and bisoprolol did not prevent the primary endpoint of left ventricular remodeling, but both were associated with less decline in LVEF compared with placebo during trastuzumab-based therapy [55]. Other studies have also suggested a possible protective effect of neurohormonal blockade, although results have not been uniform, likely owing to differences in study design, baseline cardiovascular risk, concomitant anthracycline exposure, sample size, and cardiotoxicity definitions [52]. More recently, meta-analytic evidence has supported a modest overall cardioprotective effect of ACEi, ARBs, and beta-blockers in patients receiving anthracyclines and/or trastuzumab, while also highlighting the limited certainty and heterogeneity of the available data [37]. Accordingly, the role of these agents in trastuzumab-related cardiotoxicity should not be considered absent, but rather modest, context-dependent, and better supported in higher-risk populations.

The 2022 ESC cardio-oncology guidelines recommend that anti-HER2 therapy may be continued in patients

Table 4 Risk factors for cardiotoxicity in patients treated with monoclonal antibodies

Risk Factor	Evidence of Association	Comments
Advanced age	Consistently reported	Higher vulnerability to LVEF decline
Hypertension	Strong association	Especially with trastuzumab
Diabetes mellitus	Reported in multiple cohorts	Synergistic with other CV risks
Previous anthracycline use	Major risk	Up to 34% cardiotoxicity with trastuzumab + anthracycline
Reduced baseline LVEF	Predictive of symptomatic HF	Should guide monitoring
Coronary artery disease	Reported in several studies	Additive effect
Genetic polymorphisms (HER2 Ile/Val 655, HER2 Pro/Ala 1170)	Emerging evidence	May predict susceptibility

Abbreviations: CV Cardiovascular, HF Heart failure, Ile Isoleucine, LVEF Left ventricular ejection fraction, Pro Proline, Val Valine
Source: [8] Cardinale et al., 2010 ; [27] Jawa et al., 2016 ; [32] Koulaouzidis et al., 2021 ; [40] Lunardi et al., 2022 ; [48] Nadarajah et al., 2019

with asymptomatic mild CTRCD and in selected patients with asymptomatic moderate CTRCD with LVEF 40%–49%, provided that cardiology-guided management and close surveillance are in place; by contrast, therapy interruption is generally recommended for symptomatic moderate-to-severe CTRCD or asymptomatic CTRCD with LVEF <40%. Once dysfunction is established, heart failure therapy, including ACEi/ARB and BB, should be initiated promptly when indicated. At present, evidence specifically addressing prevention or treatment during therapy with pertuzumab or newer ADC remains limited, and recommendations in these settings are largely extrapolated from trastuzumab-based experience and contemporary cardio-oncology guidelines.

The concept of permissive cardiotoxicity, formally introduced by Porter et al., refers to the deliberate continuation of effective anticancer therapy despite mild cancer therapy-related cardiac dysfunction when the anticipated oncologic benefit outweighs the cardiovascular risk, provided that patients are managed with close cardio-oncology supervision and appropriate heart failure therapy [57]. In HER2+ breast cancer, this approach is supported mainly by the prospective SAFE-HEaRt and SCHOLAR studies, which showed that selected patients with mild left ventricular dysfunction could often continue HER2-targeted therapy safely under structured monitoring and treatment [36, 41]. These data suggest that mild asymptomatic cardiac dysfunction should not necessarily mandate automatic interruption of HER2-directed therapy.

In daily clinical practice, permissive cardiotoxicity is most applicable to carefully selected patients with mild or asymptomatic CTRCD, preserved clinical stability, and substantial expected oncologic benefit from continuing HER2-directed therapy. It should be implemented within a multidisciplinary cardio-oncology framework, with close follow-up using serial clinical assessment, echocardiography, and, when appropriate, biomarkers. By contrast, this strategy is generally not appropriate for patients with symptomatic HF, progressive ventricular dysfunction, or severe CTRCD.

Several studies and meta-analyses have shown that patients receiving statins during cancer treatment have a lower incidence of cardiotoxicity and are more likely to maintain LVEF during the follow-up period, suggesting that statins have the potential to mitigate the cardiotoxic effects of anthracyclines and trastuzumab. This may be related to the antioxidant and anti-inflammatory properties of rosuvastatin combined with its ability to induce STAT-3 expression and preserve the morphology of cardiomyocytes [28, 38].

Despite major progress in the characterization of cardiotoxicity associated with monoclonal antibody-based therapies, several important uncertainties remain. Much of the available evidence derives from clinical trials with

selected populations, standardized surveillance, and strict eligibility criteria, which may underestimate the burden and complexity of cardiotoxicity seen in routine practice. In contrast, real-world cohorts often include older patients, greater comorbidity burden, prior anthracycline exposure, and less uniform cardiac monitoring, which may influence both the reported incidence and clinical consequences of CTRCD.

Important unmet needs include better risk stratification for patients receiving anti-HER2 therapy, clearer definitions and endpoints for cardiotoxicity across studies, more robust evidence for prevention and treatment in the setting of newer ADC and ICI, and improved understanding of the long-term cardiovascular effects of these agents. Future research should also clarify how best to integrate biomarkers, deformation imaging, and cardio-oncology follow-up strategies into routine practice without compromising oncologic efficacy (Fig. 1).

Future perspectives

Future directions in the field should focus on improving diagnostic strategies for the early identification and characterization of cardiovascular toxicities, as well as developing more effective treatment algorithms to prevent their onset or mitigate their clinical consequences. Advances in cardiac imaging are particularly promising, with the emerging field of radiomics—leading mathematical algorithms and artificial intelligence to extract high-dimensional data from imaging—offering novel opportunities for risk stratification and early detection [9, 80]. Serum cardiac biomarkers such as NT-proBNP and troponin are currently used in clinical practice, but their specific value in monitoring antibody-induced cardiotoxicity remains uncertain. In parallel, microRNAs have shown potential as sensitive biomarkers for chemotherapy-related cardiotoxicity, and specific miRNA panels may, in the future, allow tailored detection of myocardial injury associated with distinct anticancer agents [77].

Promising data are emerging concerning the use of sodium-glucose cotransporter-2 inhibitors (SGLT2is). They have been shown to significantly reduce heart failure hospitalizations and all-cause mortality in cancer patients treated with cardiotoxic therapies, whereas benefits are clearest in breast cancer patients receiving anthracycline-based chemotherapy, but a direct effect on trastuzumab-induced cardiotoxicity has not been clearly established [4]. The mechanisms involved in cardioprotection are mainly their natriuretic and glycosuric effects. However, their ability to reduce oxidative stress and enhance autophagy may be interesting in the context of trastuzumab [13, 74].

From a therapeutic perspective, the recognition that mitochondrial dysfunction and impaired cardiac energy metabolism are central to trastuzumab-induced cardiotoxicity has stimulated interest in metabolic modulators.

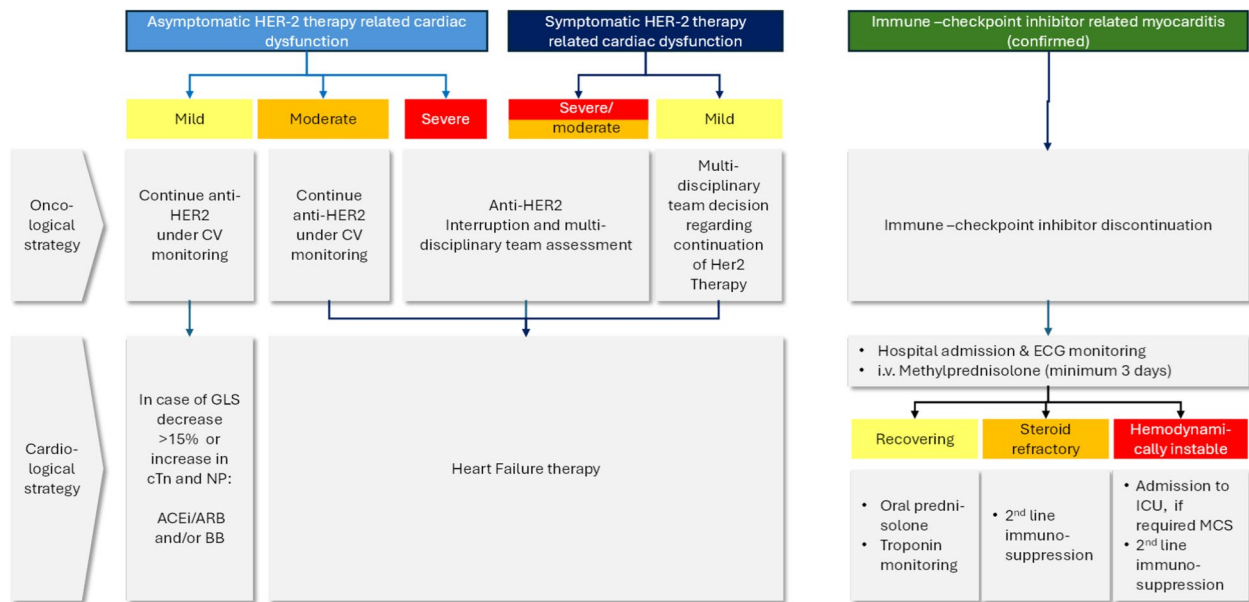


Fig. 1 Algorithm for the management of HER-2 mAb- and ICI-based cardiovascular toxicity. Adapted from the 2022 ESC Guidelines [42]. Abbreviations: ACEi=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; BB=beta blocker; CV=cardiovascular; cTn=cardiac troponin; ECG=electrocardiogram; GLS=global longitudinal strain; ICU=intensive care unit; MCS=mechanical circulatory support; NP=natriuretic peptide

Agonists of AMP-activated protein kinase (AMPK), including metformin, have been shown to improve mitochondrial function and may provide cardio protection against both ischemic injury and trastuzumab-related dysfunction [38]. Antioxidant strategies also represent a promising avenue, as they may attenuate the oxidative stress induced by HER2-targeted therapies and thereby mitigate downstream myocardial damage. Several pre-clinical studies support this hypothesis, although clinical validation is still needed [45].

Together, these diagnostic and therapeutic innovations highlight the importance of integrating precision medicine approaches into cardio-oncology. By combining advanced imaging, molecular biomarkers, and novel cardioprotective agents, future strategies have the potential to minimize cardiotoxicity without compromising the oncologic efficacy of life-saving therapies.

Limitations

While this review provides a comprehensive overview of the current literature on this topic, it has certain limitations that must be acknowledged. First, as a narrative rather than a systematic review, it is subject to selection bias despite efforts to perform a comprehensive literature search across multiple databases and regulatory sources. The heterogeneity of the available studies further complicates interpretation, as clinical trials, observational cohorts, and regulatory reports vary widely in design, patient populations, follow-up duration, and definitions of cardiotoxicity. In addition, long-term data on newer agents such as ADCs and ICIs remain limited, making it

difficult to draw firm conclusions about their cardiotoxicity risk. These limitations should be taken into account when the findings are interpreted.

Conclusion

Monoclonal antibody-based therapies have substantially improved outcomes in breast cancer, making the recognition and management of cardiotoxicity increasingly important in contemporary practice. Among these agents, trastuzumab remains the best-characterized cause of treatment-related cardiac dysfunction, whereas pertuzumab and ADCs have not shown a clear increase in cardiotoxic risk beyond that already associated with HER2-directed therapy. Immune checkpoint inhibitors, although less commonly associated with cardiovascular events, may cause severe immune-mediated toxicity, particularly myocarditis.

In clinical practice, the priority is early identification of cardiac dysfunction through risk-adapted surveillance and multidisciplinary management, particularly in patients with baseline cardiovascular risk factors. Contemporary cardio-oncology strategies increasingly emphasize continuation of effective anticancer therapy whenever feasible, supported by close monitoring and individualized cardiological management.

Future research should refine risk stratification, improve the role of biomarkers and deformation imaging in early detection, and better define preventive and management strategies for newer antibody-based therapies. A multidisciplinary approach remains essential to preserve both oncologic efficacy and cardiovascular health in long-term breast cancer survivors.

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Authors' contributions

Ana Cláudia Aparecida Santos Nussbaum: Conceptualization, Methodology, Investigation, Writing – Original Draft Marcelo Antonini: Methodology, Writing – Review & Editing André Mattar: Methodology, Writing – Review & Editing Fernando Bacal: Writing – Review & Editing, Supervision Juliana Monte Real: Writing – Review & Editing, Supervision.

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