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PRIMER IN CARDIO-ONCOLOGY

Cardiovascular Toxicity of Antibody-Drug Conjugates in Breast Cancer

Current Evidence and Evolving Considerations: *JACC: CardioOncology* Primer

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Antibody-drug conjugates (ADCs) are a newer class of targeted cancer therapies composed of a monoclonal antibody linked to a cytotoxic payload, designed to deliver cancer therapy directly to cancer cells. ADCs have rapidly transformed the therapeutic landscape of breast cancer. Trastuzumab emtansine (T-DM1), approved in 2013 by the US Food and Drug Administration (FDA) for metastatic human epidermal growth factor-2 (HER2)-positive disease, was the first ADC for this indication. Since then, additional ADCs have been approved across metastatic breast cancer and are increasingly being evaluated for curative-intent.[1] As ADC use expands into early-stage disease, defining and mitigating cardiovascular toxicity are critical. In addition, combination strategies may further amplify cardiovascular risk.

The current primer reviews mechanisms of cardiovascular injury, summarizes observed toxicities, and highlights risk factors, mitigation strategies, and future directions.

MECHANISMS OF CARDIOVASCULAR TOXICITY

Each component of an ADC, the antibody, linker, and cytotoxic payload, can independently contribute to cardiovascular toxicity (**Figure 1**). Among these, HER2-directed antibodies are among the most well-established drivers in breast oncology. HER2 receptors are expressed on cardiomyocytes, in which they regulate cell growth, homeostasis, and oxidative stress. Disruption of HER2 signaling is associated with both reversible and irreversible cardiovascular toxicity, most commonly left ventricular systolic dysfunction.[2] Fc-mediated off-target effects may contribute to ADC toxicity; although described for noncardiac effects (eg, thrombocytopenia with T-DM1), their role in cardiotoxicity remains less defined.

Linker and payload properties of an ADC can independently influence cardiovascular risk, although this relationship is interdependent, as the

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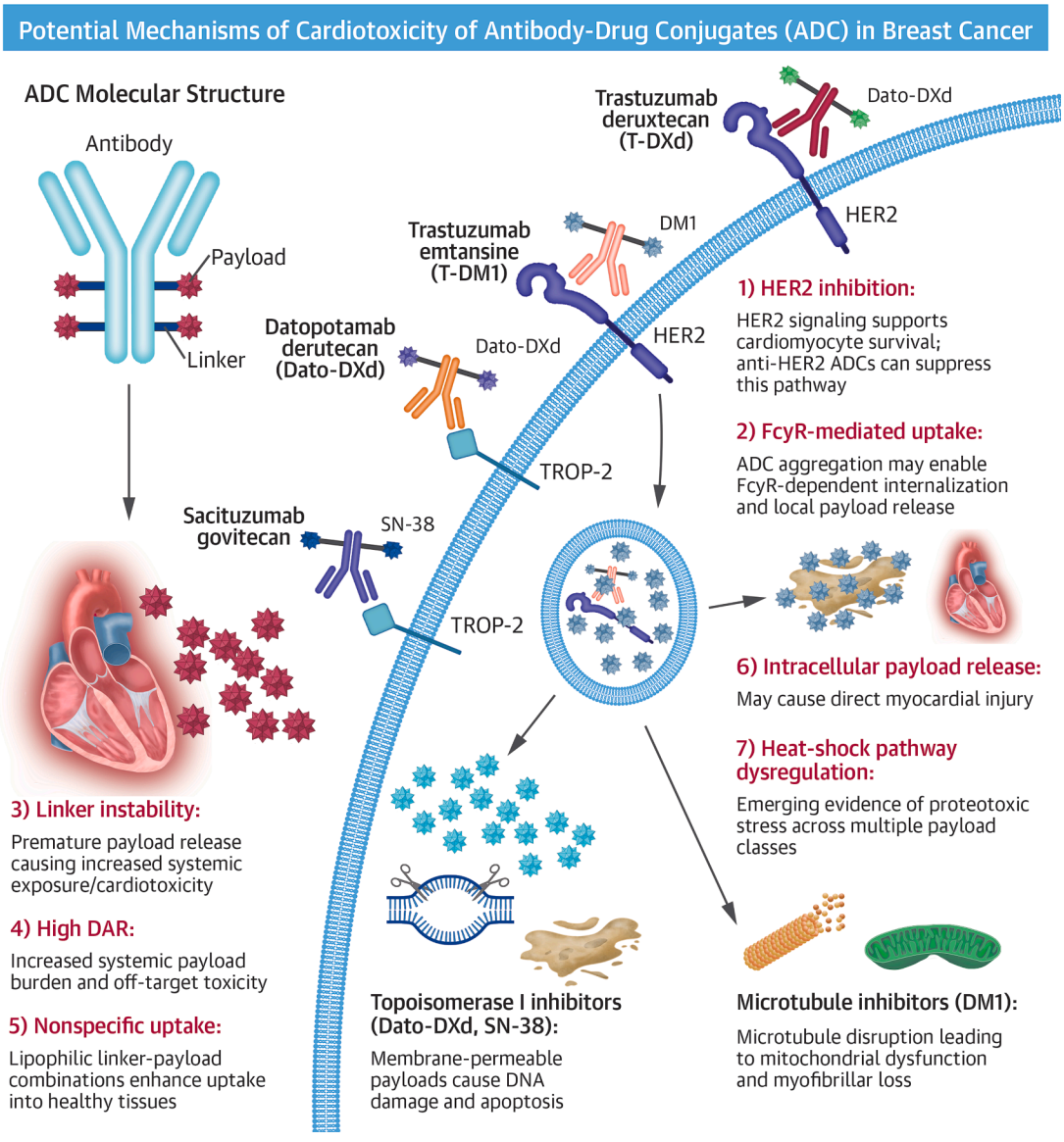
FIGURE 1 Schematic of ADCs and Proposed Mechanisms of Cardiotoxicity



Antibody-drug conjugates (ADCs) comprise a monoclonal antibody linked to a cytotoxic payload via a chemical linker. Cardiotoxicity may result from: (1) human epidermal growth factor-2 (HER2) pathway inhibition impairing cardiomyocyte survival; (2) Fc gamma receptor (FcγR)-mediated uptake and immune activation; (3) linker instability causing premature payload release; (4) high drug-to-antibody ratio (DAR) increasing off-target toxicity; (5) nonspecific tissue uptake; (6) intracellular payload release causing direct injury (payload-specific effects include microtubule disruption [eg, DM1] and topoisomerase I inhibition [eg, deruxtecan, SN-38], leading to mitochondrial dysfunction, DNA damage, apoptosis, and potential bystander effects); and (7) heat shock pathway disregulation. Representative ADCs include trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), datopotamab deruxtecan (Dato-DXd), and sacituzumab govitecan (SG). DXd = deruxtecan; LVEF = left ventricular ejection fraction; TROP-2 = trophoblast cell surface antigen 2.

linking technology can affect payload exposure. Some ADCs incorporate cleavable linkers (eg, hydrazone, disulfide, tetrapeptide) that can be cleaved independent of antigen internalization, are less stable in circulation, and may permit premature payload release.[3] As such, they can increase off-target effects but enable the "bystander effect" in which released payload diffuses to kill neighboring antigen-negative tumor cells. For example, trastuzumab deruxtecan (T-DXd), which has a cleavable linker, shows activity in HER2-positive tumors as well as in HER2-low and HER2-ultra-low tumors. In contrast, noncleavable linkers (eg, thioether or maleimidocaproyl) require intracellular processing for payload release, limiting off-target toxicity but also reducing bystander activity. In addition, linker properties affect the drug-to-antibody ratio (DAR), which influences systemic payload exposure.

The cytotoxic payload of an ADC may also contribute to cardiotoxicity, depending on its mechanism of action. In contrast to the predominantly reversible, functional consequence of HER2 pathway inhibition on cardiomyocytes, the cytotoxic payload may contribute an element of direct myocyte injury whose clinical significance remains incompletely characterized. Antimicrotubule agents can be associated with ischemia in their free form, although this appears attenuated in ADC constructs. Topoisomerase I inhibitor payloads do not seem to be intrinsically associated with cardiotoxicity across ADCs; however, T-DXd retains cardiovascular risk likely attributable to its HER2-directed antibody backbone. In contrast, other topoisomerase I ADCs (eg, datopotamab deruxtecan [Dato-DXd], sacituzumab govitecan [SG]) are associated with relatively low cardiovascular risk, with rare reports of arrhythmias and related events.

OBSERVED CARDIOVASCULAR TOXICITY

Despite variability in how cardiovascular adverse events (AEs) have been defined across trials, most HER2-antibody-based therapies have been associated with cardiotoxicity. The cardiotoxicity of HER2-directed ADCs varies by agent and treatment population (**Table 1**). The phase 3 EMILIA (A Study of Trastuzumab Emtansine Versus Capecitabine + Lapatinib in Participants With HER2-positive Locally Advanced or Metastatic Breast Cancer) (NCT00829166) trial compared T-DM1 vs capecitabine plus lapatinib in patients with HER2-positive locally advanced/metastatic breast cancer and incorporated a composite cardiovascular endpoint. Left ventricular ejection fraction (LVEF) changes were similar in both arms, with one grade 3 LVEF event in the T-DM1 group. In the phase 3 KATHERINE (A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy) (NCT01772472) trial of T-DM1 vs trastuzumab in early-stage HER2-positive breast cancer with residual disease after neoadjuvant therapy, there were fewer adjudicated cardiac events in the T-DM1 arm (0.1%) compared with the trastuzumab arm (0.6%), with only 5 cardiovascular events overall.

T-DXd differs from T-DM1 in DAR, payload, mechanism of action, and linker design. These differences result in greater systemic payload exposure and may influence off-target toxicity profiles, including cardiovascular effects. The reported incidence of T-DXd-associated LVEF decline has varied across the DESTINY-Breast studies, likely reflecting differences in patient populations, treatment setting (early vs late), and line of therapy. The DESTINY-Breast01 (NCT03248492) and DESTINY-Breast03 (NCT03529110) trials included patients with metastatic HER2-positive breast cancer and reported LVEF decreases of 1.6% and 2.3%, respectively. Higher rates of LVEF decline were reported in the metastatic HER2-low and HER2-ultra-low populations included in DESTINY-Breast04 (NCT03734029) (13.4% LVEF decrease grade 2 or greater) and DESTINY-Breast06 (NCT04494425) (8.1% left ventricular dysfunction). The DESTINY-Breast12 (NCT04739761) trial evaluated patients with HER2-positive metastatic breast cancer with and without brain metastases and reported high rates of LVEF decrease at 10.8% to 11.8% for patients without and with brain metastases. Of note, T-DXd-associated cardiotoxicity was reported inconsistently across the DESTINY-Breast trials (eg, LVEF decline vs a composite term "LV dysfunction"), contributing to variability in reported cardiovascular AE rates.

In early-stage HER2-positive breast cancer, T-DXd is now FDA approved in both the neoadjuvant setting (before surgery, DESTINY-Breast11 [NCT05113251]) as well as the adjuvant setting (after surgery, DESTINY-Breast05 [NCT04622319]). In DESTINY-Breast11, two participants were noted to have a decrease in LVEF (0.7%) with T-DXd vs four participants (1.3%) with T-DXd plus taxane with trastuzumab and pertuzumab, with one grade 3 event. In DESTINY-Breast05, participants received 14 cycles of T-DXd or T-DM1 adjuvantly; decreased LVEF occurred in 2.9% and 1.7% of participants receiving T-DXd or T-DM1, respectively.

TABLE 1 Cardiac Events Observed With Antibody-Drug Conjugates in Breast Cancer

Agent	Payload	Linker	DAR	Trials	LVEF Decrease/Cardiotoxicity[a]	Other CV Toxicities
T-DM1	DM1, microtubule inhibitor	Thioether Noncleavable	4:1	Early stage (HER2+)		Pooled analysis found that cardiac arrhythmia occurred in 0.7% and cardiac ischemia in 0.1%[7]
				KATHERINE (N = 1,486)	0.1% adjudicated cardiac events (T-DM1) vs 0.6% trastuzumab	
				Metastatic (HER2+)		
				EMILIA (N = 991)	1 G3 LVEF event (T-DM1)	
T-DXd	DXd, TOPO1i	Tetrapeptide Cleavable	8:1	Early stage (HER2+)		A meta-analysis estimated the pooled incidence of QTc prolongation at 7.8% across T-DXd breast cancer studies[10]
				DB-11 (N = 927)	LV dysfunction 0.7% (T-DXd) LV dysfunction 1.3% (T-DXd + THP) LV dysfunction 6.1% (ddAC-THP)	
				DB-05 (N = 1,635)	LVEF dysfunction 2.9% (T-DXd) vs 1.7% (T-DM1)	
				Metastatic (HER2+, HER2–, low and ultra-low)		
				DB-01 (N = 184)	LVEF decrease 1.6% (T-DXd) (phase 2, no comparator arm)	
				DB-03 (N = 524)	LVEF decrease 2.3% (T-DXd) LVEF decrease 0.4% (T-DM1)	
				DB-04 (N = 557)	LVEF decrease 11.9% (grade 2) 1.5% (G3) (T-DXd) LVEF decrease 5.8% (Grade 2) 0% (Grade 3) (physician's choice)	
				DB-06 (N = 866)	LV dysfunction 8.1% (T-DXd) LV dysfunction 3.8% (chemotherapy)	
				DB-09 (NCT04784715) (N = 1,157)	LV dysfunction 11% (T-DXd + P) LV dysfunction 7.1% (THP)	
				DB-12 (N = 504)	LVEF decrease 10.8%-11.8% (T-DXd) (11.8% with BMs, 10.8% without BMs)	
SG	SN-38, TOPO1i	Hydrolyzable Cleavable	8:1	Metastatic (HR+, TNBC)		No other cardiac events reported
				ASCENT (N = 529)	No cardiac events reported	
				ASCENT-03 (NCT05382299) (N = 558)		
				ASCENT-04 (N = 443)	1 reported case of grade ≥3 pericarditis in SG plus pembrolizumab	
				TROPICS-02 (N = 543)	No cardiac events reported	
Dato-DXd	DXd, TOPO1i	Tetrapeptide Cleavable	4:1	Metastatic (HR+, TNBC)		No other cardiac events reported
				TROPION-Breast01 (N = 732)	No cardiac events reported	
				TROPION-Breast02 (N = 644)		

[a]Definitions of cardiotoxicity vary between trials to include left ventricular (LV) dysfunction, left ventricular ejection fraction (LVEF) dysfunction, and LVEF decrease as noted within the table.

BMs = brain metastases; CV = cardiovascular; DAR = drug-to-antibody ratio; Dato-DXd = datopotamab deruxtecan; DB = DESTINY-Breast; ddAC-THP = doxorubicin, cyclophosphamide, taxane, trastuzumab, pertuzumab; DM1 = mertansine; DXd = deruxtecan; G3 = grade 3; HER2 = human epidermal growth factor-2; P = pertuzumab; SG = sacituzumab govitecan; SN-38 = 7-ethyl-10-hydroxycamptothecin; T-DM1 = trastuzumab emtansine; T-DXd = trastuzumab deruxtecan; THP = taxane, trastuzumab, pertuzumab; TNBC = triple-negative breast cancer; TOPO1i = topoisomerase 1 inhibitor.

Patients with preexisting cardiovascular disease were frequently excluded from these trials, potentially limiting generalizability and underestimating event rates. Real-world data sets offer some insight but can be limited by incomplete data, underrepresentation of vulnerable populations, and selection and confounding biases, supporting the need for prospective cohort studies to fully understand the cardiovascular impact of these agents. In addition to the direct cardiotoxic effects, T-DXd has been associated with interstitial lung disease requiring prolonged corticosteroid therapy; the cardiovascular implications of this ADC-related steroid exposure and of interstitial lung disease itself have not been systematically studied.

Newer ADCs entering breast cancer treatment include SG and Dato-DXd. SG uses a trophoblast cell surface antigen 2 target, cleavable linker, and 7-ethyl-10-hydroxycamptothecin topoisomerase I inhibitor payload; Dato-DXd also targets trophoblast cell surface antigen 2 but has a topoisomerase I inhibitor DXd payload (the same payload as T-DXd) and lower DAR

compared with T-DXd. SG was studied in patients with metastatic triple-negative breast cancer (TNBC) and metastatic hormone receptor-positive, HER2-negative breast cancer in the phase 3 ASCENT (NCT02574455) and TROPICS-02 (NCT03901339) clinical trials, respectively. No cardiac AEs were reported in these studies.

One of the most common AEs associated with SG is diarrhea. Electrolyte disturbances and volume depletion associated with SG-related diarrhea may represent indirect risks for cardiovascular events and warrant clinical awareness.

Dato-DXd was also studied in patients with metastatic hormone receptor-positive, HER2-negative breast cancer, and metastatic TNBC in the phase 3 TROPION-Breast01 (NCT05104866) and TROPION-Breast02 (NCT05374512) trials, respectively. Neither trial reported concerning cardiac safety signals. The phase 3 ASCENT-04 (NCT05382286) trial evaluated SG with pembrolizumab in first-line programmed cell death ligand 1-positive (combined positive score ≥10) metastatic TNBC. In this study, there were no observed immune checkpoint inhibitor-induced cardiotoxicities in the control chemotherapy plus pembrolizumab arm and one reported case of grade ≥3 pericarditis in the SG plus pembrolizumab arm. Given the established cardiovascular immune-related AEs associated with immune checkpoint inhibitors, continued safety evaluation of ADC/immune checkpoint inhibitor combinations is warranted. In contrast to HER2-directed ADC trials, these studies used less stringent cardiac eligibility criteria. Because trial populations are typically healthier than real-world patients, ongoing safety surveillance will be essential to fully define cardiovascular risk.

Cross-trial comparison is further limited by variation in prior anthracycline exposure, an established risk factor for HER2-directed cardiotoxicity. It is reported inconsistently across trials, ranging from 61% in EMILIA and >76% in KATHERINE to 50% in the adjuvant DESTINY-Breast05 trial, reflecting declining anthracycline use in contemporary HER2-positive regimens. By contrast, exposure remained high (approximately 81%-83%) in the triple-negative ASCENT trial, in which no cardiac events were reported with SG, supporting that the HER2-directed antibody backbone, rather than prior anthracycline exposure alone, is the principal driver of the cardiac signal observed with HER2-directed ADCs. Several other trials reporting cardiac events did not report this proportion.

Emerging ADCs in breast cancer, including sacituzumab tirumotecan and patritumab deruxtecan, use novel antibody, linker, and payload designs. Additional data are needed to characterize cardiotoxicity, particularly in higher risk populations that are often underrepresented in clinical trials. Real-world evidence and prospective cohort studies may again fill this knowledge gap.

RISK FACTORS FOR CARDIOVASCULAR TOXICITY

Early, albeit limited, information on real-world risk factors for cardiovascular toxicity from ADC therapy in breast cancer is emerging. In a review of 15,276 ADC-related AEs in breast cancer reported to the FDA Adverse Event Reporting System from 2019 to 2023, cardiac AEs accounted for 1,410 (9.2%).[4] In this cohort, those with cardiovascular AEs were older than those with noncardiovascular AEs (mean age: 58.7 vs 55.5 years; $P < 0.0001$). Median time to cardiovascular AE was 116 days from treatment initiation, with >80% occurring within 352 days. This was longer than the 86 days observed across all tumor types.

For the HER2-directed therapies, risk factors for on-target, off-tumor cardiovascular AEs associated with this class of therapy are well established. These include exposure to anthracyclines, low/abnormal baseline LVEF, preexisting cardiac disease, and/or hypertension.[5,6] Data specific to HER2-directed ADCs, largely from clinical trial populations, have mirrored this experience; for instance, a pooled analysis of patients who received T-DM1 on a clinical trial found that age, baseline LVEF, and dual-HER2 blockade were independent risk factors for cardiac events on multivariate analysis.[7] Notably, although cardiometabolic conditions such as dyslipidemia and diabetes mellitus have been recorded, prospective data are needed to more fully elucidate how dyslipidemia, insulin resistance, and obesity affect cardiovascular toxicity in this setting.

CARDIOVASCULAR MANAGEMENT STRATEGIES

Evidence guiding cardiovascular surveillance during ADC therapy remains limited and differs between HER2-directed and non-HER2-directed ADCs. For HER2-directed ADCs, including T-DM1 and T-DXd, monitoring is largely extrapolated from trastuzumab experience, with serial LVEF assessment recommended, particularly in high-risk patients. Emerging data suggest less frequent surveillance may be appropriate in carefully selected, low-risk patients, although this has not been prospectively validated in ADC-specific populations.[8] Management of HER2-

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HIGHLIGHTS

- As ADC use in breast cancer expands, understanding cardiovascular toxicity becomes increasingly critical, particularly in curative-intent settings.
- Antibody, linker, and payload components each contribute to cardiotoxicity risk, with HER2-directed antibodies as the dominant driver.
- T-DXd shows higher, more variable LVEF decline rates than T-DM1, whereas trophoblast cell surface antigen 2–directed ADCs exhibit limited cardiac signal.
- Prospective studies, pragmatic trials, and real-world evidence hold promise to maximize the therapeutic benefits of ADCs while minimizing cardiovascular harm.

directed ADC-associated cardiac dysfunction similarly follows guideline-directed heart failure therapy. Prospective cardio-oncology studies, such as SAFE-HEaRt (NCT01904903), show that HER2-targeted therapies, including T-DM1, can often be continued safely in patients with mildly reduced LVEF under neurohormonal blockade and close surveillance.[9]

In contrast, non-HER2-directed ADCs, such as SG and Dato-DXd, lack established cardiac monitoring paradigms. Although overt systolic dysfunction appears rare, observational and pharmacovigilance data suggest a broader spectrum of cardiovascular events, including arrhythmias, thromboembolic events, and inflammatory syndromes. Evidence-based management strategies for these toxicities remain undefined, and current practice is largely empirical. Although further study is warranted, a multidisciplinary approach involving cardio-oncology and breast oncology is needed to set surveillance intervals tailored to each patient's cardiovascular risk.

Observational pharmacovigilance data across ADCs raise the hypothesis that inflammatory mechanisms may contribute to some cardiovascular events, with dexamethasone exposure potentially mitigating select toxicities[4]; causal relationships remain unproven, however. Dexamethasone, commonly used for antiemetic prophylaxis with T-DXd and other therapies, has anti-inflammatory properties that could attenuate ADC-induced myocardial stress, although steroid-associated metabolic effects such as hyperglycemia may counterbalance such benefit. Further investigation is needed to clarify whether corticosteroids meaningfully modify ADC-associated cardiovascular toxicity.

FUTURE DIRECTIONS

Despite the growing clinical experience with ADCs in breast cancer, substantial knowledge gaps remain. Real-world data on cardiovascular toxicity are still limited, particularly for patients underrepresented in clinical trials, including older adults and those with preexisting cardiovascular disease. Long-term cardiac sequelae are incompletely characterized, an issue of increasing importance as ADCs move into curative-intent settings in which survivorship horizons are long. In addition, the cardiovascular safety of emerging combination strategies requires systematic evaluation, as overlapping or synergistic toxicities may alter risk profiles. The optimal cardiac monitoring paradigms for ADCs, particularly those with non-HER2 targets, also remain uncertain. Promising areas of research include novel biomarkers for early detection, utilization of artificial intelligence and machine learning for risk prediction, optimizing ADC engineering to minimize toxicity, and novel cardioprotective strategies. Prospective studies and pragmatic clinical trials, complemented by real-world evidence, are needed to define evidence-based strategies for cardiotoxicity surveillance, cardioprotective strategies, and short- and long-term cardiovascular disease prevention that maximize the therapeutic benefits of ADCs while minimizing cardiovascular harm.

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