Cardiac Monitoring in Patients Receiving HER2-Directed Therapy: A Meta-Analysis and Cost-Effectiveness Analysis

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BACKGROUND & OBJECTIVES

- HER2-directed therapies (e.g., trastuzumab, T-DM1, T-DXd) improve survival in HER2-positive breast cancer but have been associated with cardiotoxicity - particularly reduced left ventricular ejection fraction (LVEF).
- Guidelines recommend echocardiography every 3 months during treatment, regardless of patient's cardiovascular risk.

Objectives

1. **To estimate the incidence of cardiotoxicity across HER2-directed agents (meta-analysis).**
2. **To evaluate the cost-effectiveness of alternative echocardiogram monitoring strategies in the early and metastatic settings.**

METHODS

Systematic review & meta-analysis: (MEDLINE/Embase/Cochrane to 2024)**:**

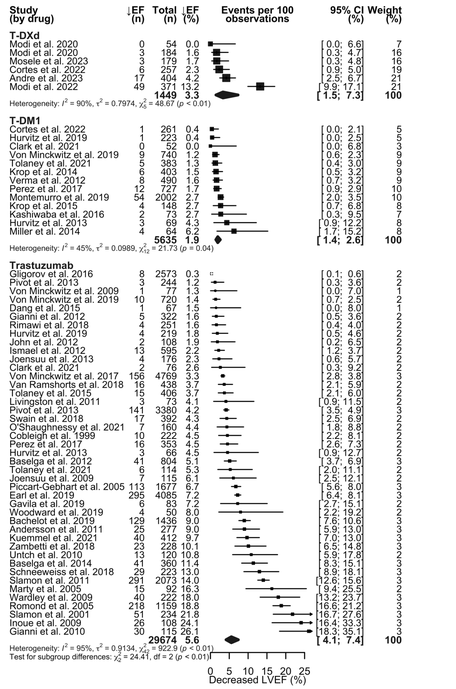
- **55 studies (25 early-stage; 30 metastatic);** >36,000 patients.
- **Regimens:** trastuzumab (n≈29.5k), T-DM1 (n≈5.5k), and T-DXd (n≈1.5k).
- **Outcomes:** LVEF decline, grade ≥3 cardiotoxicity.
- Random-effects models with heterogeneity assessment (Cochran's Q, I^2).

Cost-effectiveness Model:

- Decision-analytic model across HER-2 agents comparing echocardiogram monitoring strategies:
  - ✓For early stage: (1) baseline only (ICER reference, "base"); (2) baseline + at month 6 ("@6m"); (3) baseline + every 6 months ("q6m"); (4) baseline + every 3 months ("q3m").
  - ✓For metastatic: (1) baseline only (ICER reference, "base"); (2) baseline + every 12 months ("q12m"); baseline + every 6 months ("q6m"); baseline + every 3 months ("q3m").
- Early-stage and metastatic settings are modeled separately.
- Outcomes: costs (US$), QALYs, and ICERs at a willingness-to-pay of $120,000/QALY based on AHA recommendations.
- Sensitivity analyses based on screening start age: 45, 55, or 65.

RESULTS

Figure 1. Forest plot of cardiotoxicity risk by regimen



- Pooled cardiotoxicity with trastuzumab was low; T-DM1 and T-DXd were associated with substantially lower risks, particularly for grade ≥3 events (Figures 1 and 2).
- Between-study heterogeneity was present, especially for trastuzumab, partly due to differences in how reduced LVEF was reported (CTCAE grading versus absolute cut-offs) (Figure 1).

Figure 2. Grade ≥3 cardiotoxicity by regimen

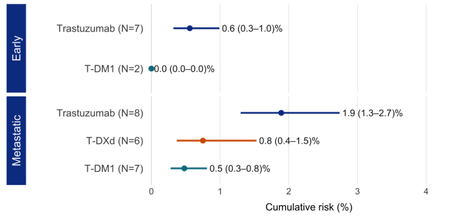
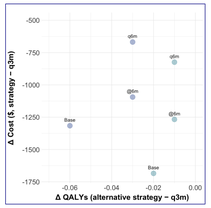
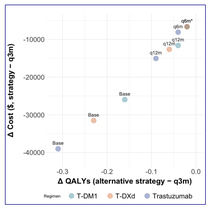


Figure 3. Alternative screening strategies vs standard of care

3a. Early (Δ Cost vs Δ QALY)
Alternative strategies vs standard of care (q3m)

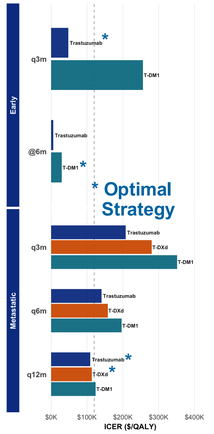


3b. Metastatic (Δ Cost vs Δ QALY)
Alternative strategies vs standard of care (q3m)



The * in q6m is due to the overwriting of T-DXd and T-DM1 with similar values.

3c. ICER per strategy
Only if defined (not dominated or reference)



Dashed line represents an ICER of $120,000/QALY.

Table 1. Optimal echocardiogram screening strategies by regimen

Stage	Regimen	Screening Strategy (begins at age 55)	Echocardiograms (N, median) Total	Δ	Life-years (years) Total	Δ	QALYs (years) Discounted*	Δ	Costs ($) Discounted*	Δ	ICER ($/QALY)
Early	Trastuzumab (HF risk 0.37%/mo)	Standard of care (q3m)	5	–	27.66	–	14.69	–	$198,849	–	**47,500**
		Baseline + at six months (@6m)	2	-3	27.78	−0.01	14.75	−0.01	$199,041	-$1,267	**29,600**
	T-DM1 (HF risk 0.11%/mo)	Standard of care (q3m)	5	–	27.79	–	14.76	–	$200,308	–	256,200
Metastatic		Baseline + every 12 months (q12m)	5	-12	6.01	−0.15	3.52	−0.09	$463,641	-$15,058	**108,900**
	Trastuzumab (HF risk 0.29%/mo)	Standard of care (q3m)	17	–	6.16	–	3.61	–	$478,699	–	207,700
		Baseline Only (base)	1	-17	6.20	−0.30	3.62	−0.16	$476,835	-$25,965	**Reference*****
	T-DM1 (HF risk 0.11%/mo)	Standard of care (q3m)	18	–	6.50	–	3.78	–	$502,800	–	351,100
		Baseline + every 12 months (q12m)	5	-12	6.20	−0.10	3.62	−0.06	$476,333	-$12,656	**113,100**
	T-DXd (HF risk 0.20%/mo)	Standard of care (q3m)	17	–	6.30	–	3.68	–	$488,989	–	280,300

This table compares the standard of care with the model-identified optimal strategy (in blue). * Discount rate 3%/yr. ** ICER reference.

- At a $120,000/QALY threshold, model-selected strategies generally favored LESS frequent monitoring than 3-monthly standard-of-care (Figure 3a and 3b, table 1).
- For many patients—especially those on T-DM1 or T-DXd and in the metastatic setting—baseline ± annual monitoring was often cost-effective (Figures 3c and 3d, table 1).

CONCLUSIONS

This meta-analysis of >36,000 patients revealed that HER2-directed therapy carries a low risk of severe cardiotoxicity. T-DM1 and T-DXd were associated with lower rates than trastuzumab; however, this may reflect bias, given that the initial studies with trastuzumab had a higher incidence for cardiotoxicity and that patients who tolerate trastuzumab may be able to tolerate subsequent HER2-directed therapies.

This analysis shows that echocardiography every 3 months is unlikely to be cost-effective for patients with standard cardiovascular risk. The optimal frequency of echocardiograms depends on the drug being used and the setting (screening strategy column table 1). A risk-adapted, regimen-specific approach may improve value while maintaining safety.

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