LV Dysfunction and Heart Failure Prior To, During and After Cancer Therapy

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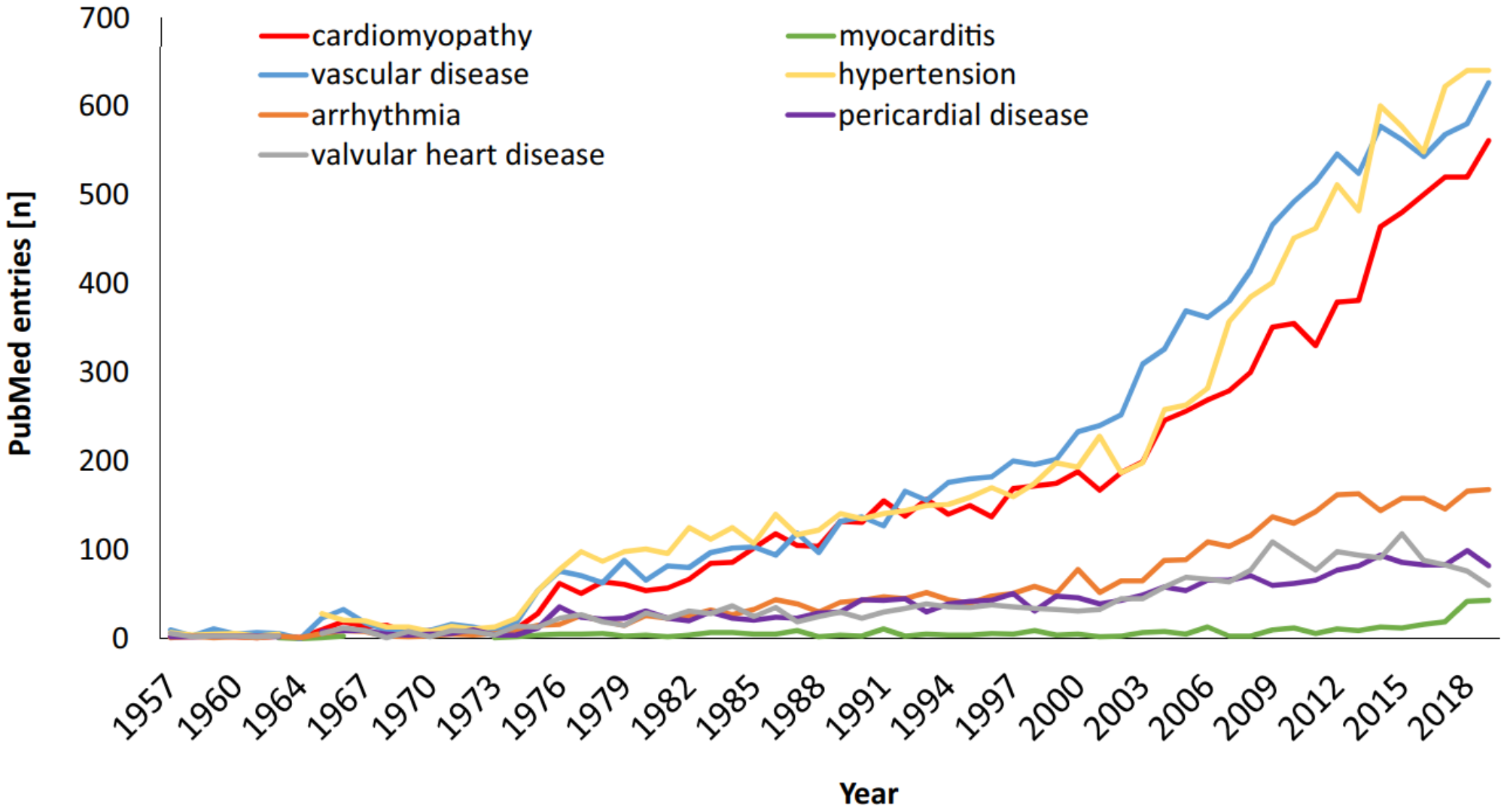
Objectives

- Review the data for cardioprotection during cancer treatment
- Discuss the concept of permissive cardiotoxicity
- Provide a snapshot of long-term concern in cancer survivors

Pubmed entries: CVD + Cancer



Herrmann J et al. Eur Heart J 2022 Jan

ICOS 2021 Consensus for CTCRD

Asymptomatic CTRCD (with or without additional biomarkers, LVEF values are based on 2D echo)	**Mild** •LVEF ≥50% •AND new relative decline in GLS by >15% from baseline •AND/OR new rise in cardiac biomarkers	**Moderate** •New LVEF reduction by ≥10% to an LVEF of 40-49% •New LVEF reduction by <10% to an LVEF of 40-49% •AND new relative decline in GLS by >15% from baseline •AND/OR new rise in cardiac biomarkers	**Severe** •New LVEF reduction to <40%	
Symptomatic CTRCD (with LVEF and supportive diagnostic biomarkers)	**Mild** •Mild HF symptoms, no intensification of therapy required	**Moderate** •Need for Outpatient intensification of diuretic and HF therapy	**Severe** •HF Hospitalization	**Very Severe** •Requiring inotropic support, mechanical circulatory support or consideration for transplantation

Modified from: Herrmann J et al. Eur Heart J 2022 Jan

HF Considerations in Cardio-oncology

HF Stage A

Prevention
- Who/When to refer
- Cardioprotection
- Surveillance

HF Stage B-C

Treatment of LVD/HF
- Medical therapy
- Cardiac resynchronization
- Permissive cardiotoxicity

HF Stage A-D

Long-term surveillance
- Survivorship
- Chronic systolic HF
- HFpEF
- Advanced HF therapies

Pre-Treatment

During Treatment

After Treatment

Table 28. Cancer Therapies Known to Be Associated With Cardiomyopathy

Class	Agent(s)	Cardiac Function Monitoring Often Performed in Clinical Practice	
		Pretherapy	Serial
Anthracyclines[55–57]	Doxorubicin, epirubicin	X	X
Alkylating agents[58–60]	Cyclophosphamide, ifosfamide, melphalan	X	
Antimicrotubule agents.[61,62]	Docetaxel		
Antimetabolites[63–72]	Fluorouracil, capecitabine, fludarabine, decitabine		
Anti-HER2 agents[73–76]	Trastuzumab, pertuzumab	X	X
Monoclonal antibodies[77]	Rituximab		
Tyrosine-kinase inhibitors[78–100]	Dabrafenib, dasatinib, lapatinib, pazopanib, ponatinib, sorafenib, trametinib, sunitinib, vandetanib, imatinib, vandetanib		
Immune checkpoint inhibitors[39,40,101]	Nivolumab, ipilimumab, pembrolizumab		
Protease inhibitors[102–106]	Bortezomib, carfilzomib		
Endocrine therapy[107–111]	Goserelin, leuprolide, flutamide, bicalutamide, nilutamide		
Chimeric antigen receptor T-cell therapy.[112,113]	Tisagenlecleucel, axicabtagene ciloleucel	X	
Hematopoietic stem cell transplantation[7,44,114–119]	Hematopoietic stem cell transplantation	X	
Radiation[7,44,114–119]	Chest		

Who/When to refer

1	B-NR	1. In patients who develop cancer therapy–related cardiomyopathy or HF, a multidisciplinary discussion involving the patient about the risk-benefit ratio of cancer therapy interruption, discontinuation, or continuation is recommended to improve management.[1,2]

Table 4 Heart Failure Association–International Cardio-Oncology Society baseline cardio stratification

Baseline CV toxicity risk factors	Anthracycline chemotherapy	HER2-targeted therapies	VEGF inhibitors	BCR-ABL inhibitors	Mu my therapies	inhibitors
Previous CVD						
HF/cardiomyopathy/ CTRCD	VH	VH	VH	H	VH	VH
Severe VHD	H	H	–	–	–	H
MI or PCI or CABG	H	H	VH	–	–	H
Stable angina	H	H	VH	–	–	H
Arterial vascular disease	–	–	VH	VH	VH	–
Abnormal ankle-brachial pressure index	–	–	–	H	–	–
PH	–	–	–	H	–	–
Arterial thrombosis with TKI	–	–	–	VH	–	–
Venous thrombosis (DVT/PE)	–	–	H	M2	VH	–
Arrhythmia[a]	–	M2	M2	M2	M2	M1
QTc ≥ 480 ms	–	–	H	H	–	–
450 ≤ QTc < 480 ms (men); 460 ≤ QTc < 480 ms (women)	–	–	M2	M2	–	–
Prior PI CV toxicity	–	–	–	–	VH	–
Prior IMiD CV toxicity	–	–	–	–	H	–
Cardiac imaging						
LVEF < 50%	H	H	H	H	H	H

2022 ESC Guidelines on cardio-oncology
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Case #1

- 46 year old woman without PMH diagnosed with R-sided IDC and DCIS, ER/PR neg, HER2 pos
- Planning for ddAC x4 cycles, then THP

Questions for the Panel

1) Would you recommend starting this patient on cardioprotection?
2) If yes, what would you start her on?

Recent RCT of cardioprotection during anthracycline therapy

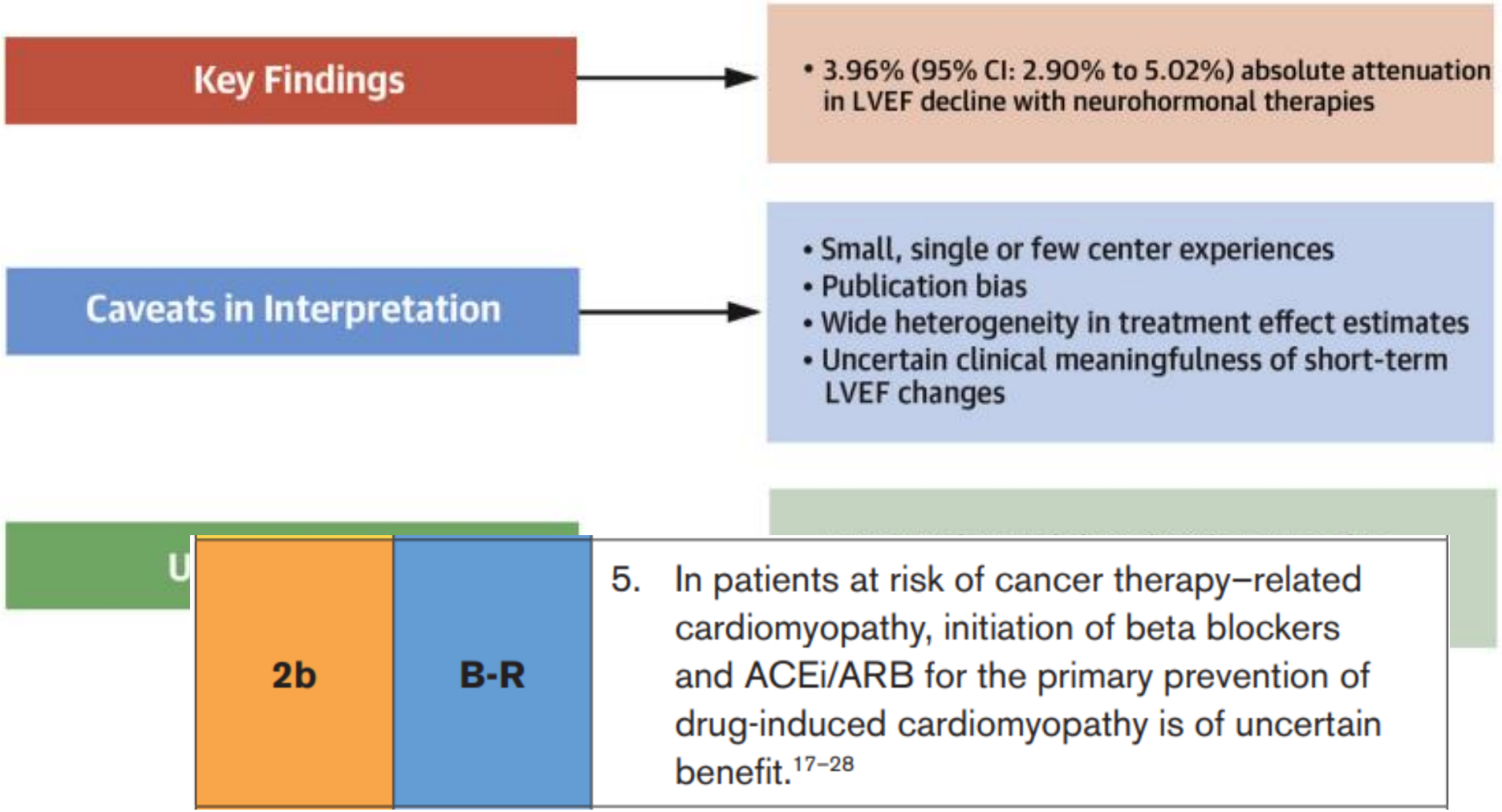
Trial	Trial Design	Trial Intervention	Imaging Method	N	Result of Primary Endpoint and Follow-Up Results	Result of Key Secondary Endpoints and Follow-Up Results
Pharmacologic intervention						
PRADA 	Randomized Placebo-controlled Double-blind 2 × 2 factorial	Metoprolol Candesartan / Metoprolol plus candesartan / Placebo	CMR	130 BC undergoing AC +/- Tras +/- RT	Primary trial: candesartan attenuated the reduction in LVEF Follow-up (median 23 mo): no difference in change in LVEF from baseline to extended follow-up in either treatment arm	Primary trial: metoprolol attenuated the rise in troponins Follow-up: no difference in change in troponins from baseline to extended follow-up in either treatment arm

Table modified from: Omland et al. JACC:CardioOnc 2022 Mar
Heck SL et al. Circulation 2021; 143

Avila SA et al. JACC 2018 May
Livi L et al. JAMA Oncol. 2021;7

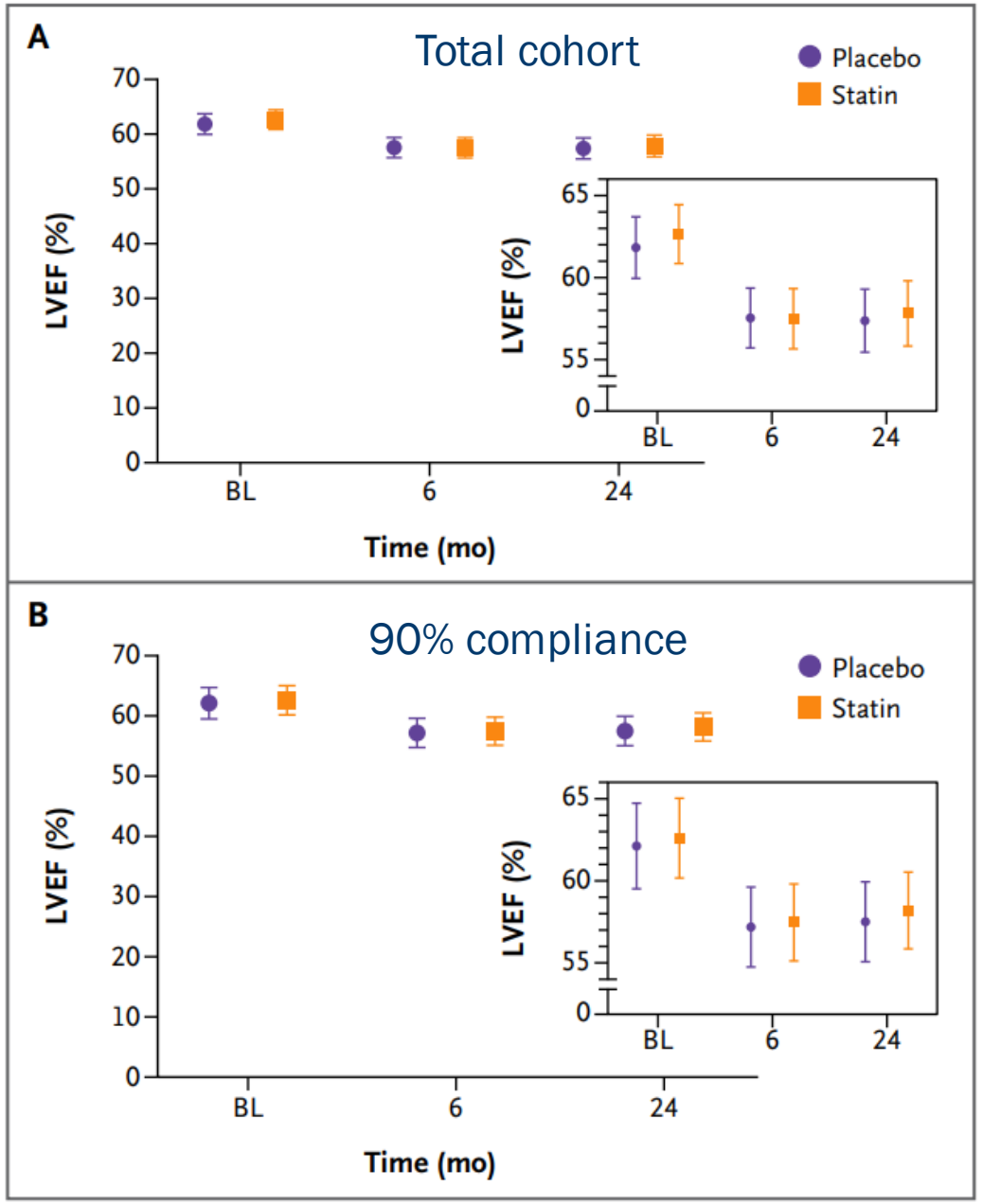
Meta-analysis of NH blockade

- Patients with cancer undergoing chemotherapy
- NH blockade (BB, ACEI/ARB, MRA)
- 17 RCT, 1984 participants



Statins – PREVENT

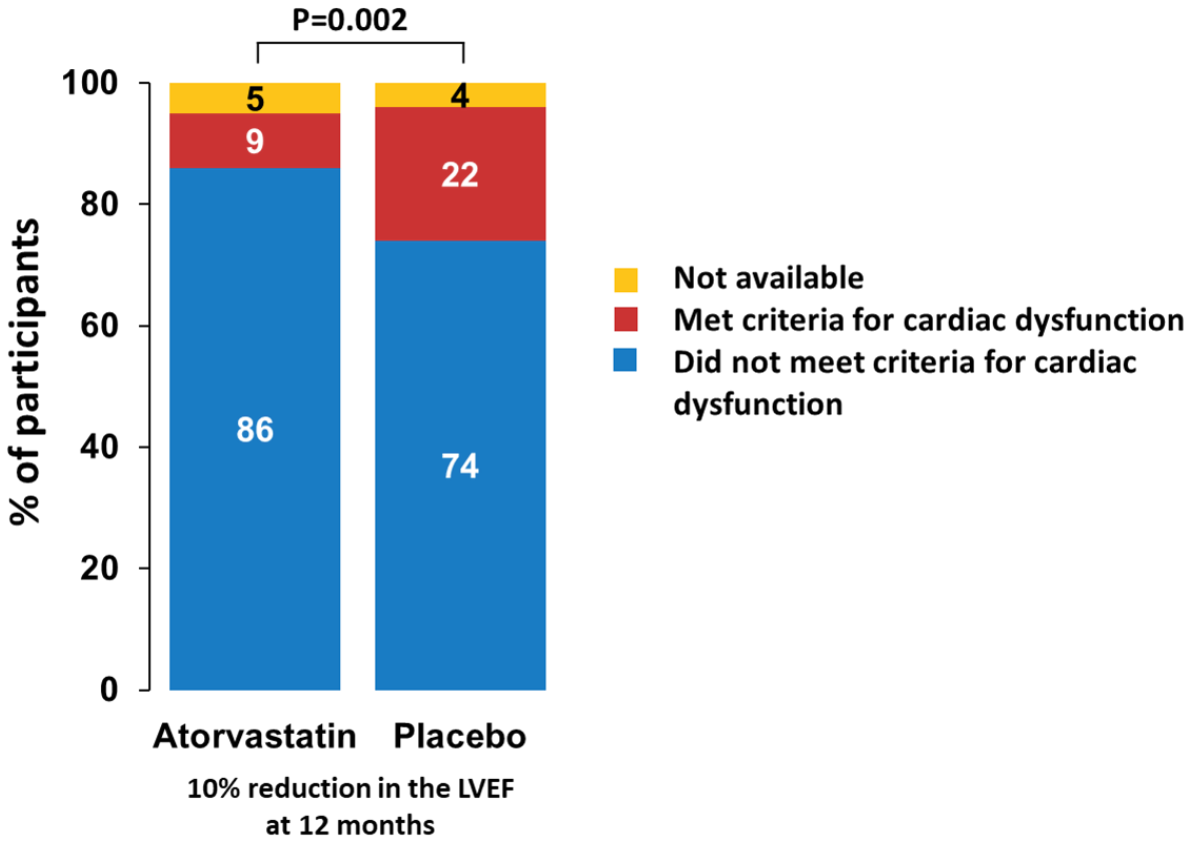
- 279 participants: Mean age 49 years, 92% women, 83% white
- Stage I-III BC or stage I-IV lymphoma scheduled to receive anthracyclines
- Randomized to atorvastatin 40 mg vs placebo (no indication for statin)
- Median anthracycline dose 240 mg/m2
- Primary endpoint: Difference in 24-month LVEF between groups by CMR



Hundley WG et al. NEJM Evid 2022; 1(9)

Statins: STOP-CA

- 300 participants: Mean age 50 years, 47% women, 89% white
- Hodgkin or non-Hodgkin lymphoma scheduled to receive anthracyclines
- Randomized to atorvastatin 40 mg vs placebo (no indication for statin)
- Median anthracycline dose 300 mg/m2
- Primary endpoint: Proportion with decline in LVEF ≥10% to <55%

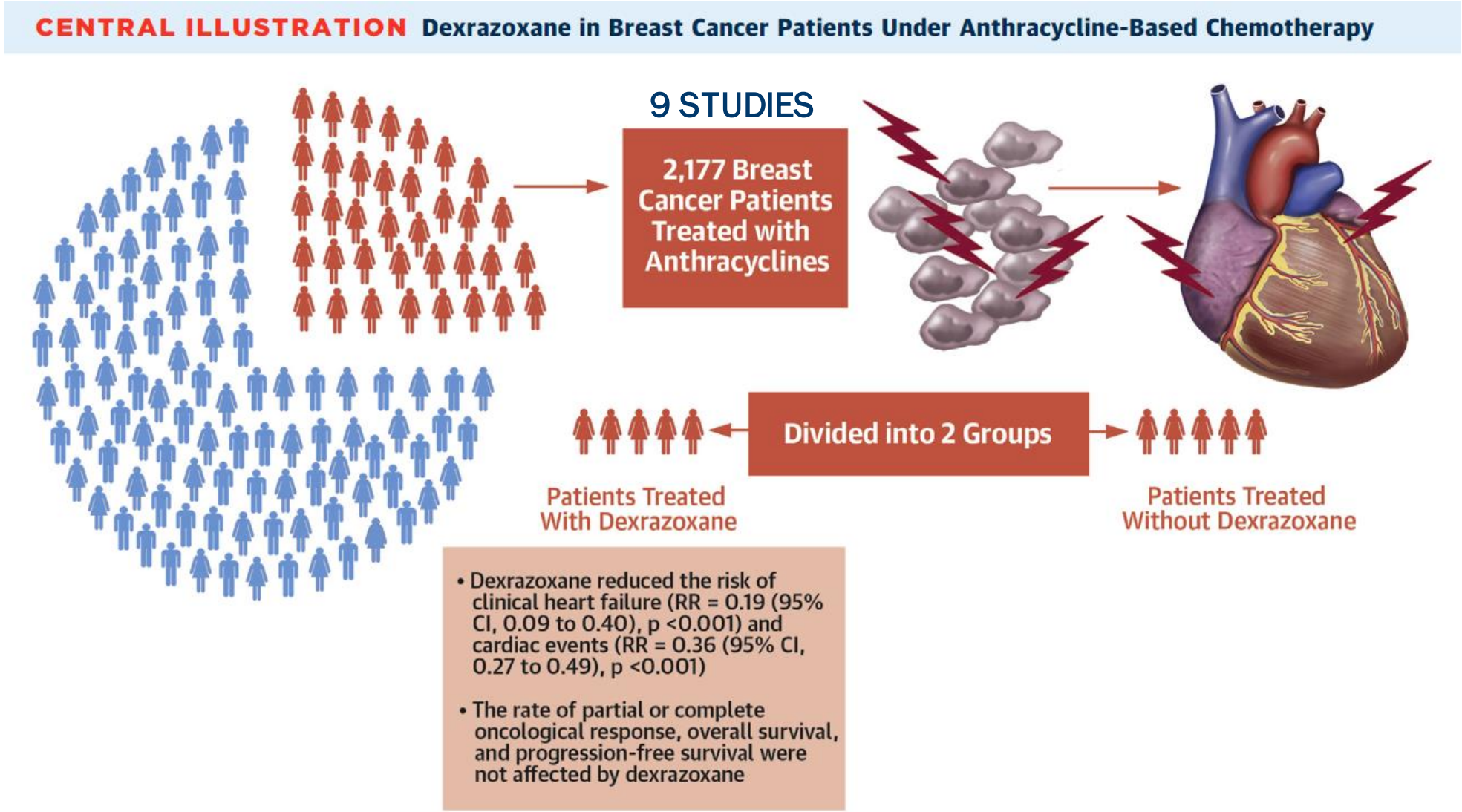


STOP-CA trial presented at ACC.23, slide courtesy of Tom Neilan

Do we need to target cardioprotection?

	PREVENT	STOP-CA
Age (mean)	49 years	50 years
Cancer type	85.6% Breast cancer 14.4% Lymphoma	Lymphoma
Anthracycline dose (median)	240 mg/m2	300 mg/m2
Primary endpoint	Difference in 24-month LVEF between placebo and treatment groups	Proportion of participants with an absolute decline in LVEF ≥10% from prior to chemo to <55% at 12 months

Meta-analysis of dexrazoxane in BC



Macedo AV et al. JACC: Cardio-oncology 2019 1(1)

Case #1

- s/p ddAC x4 cycles, then THP with drop in LVEF from baseline of 56% down to **LVEF of 38%**
- Completely asymptomatic

Questions for the Panel

1) What do you recommend doing with the HER2 directed therapy?
2) Would you start her on HF meds?

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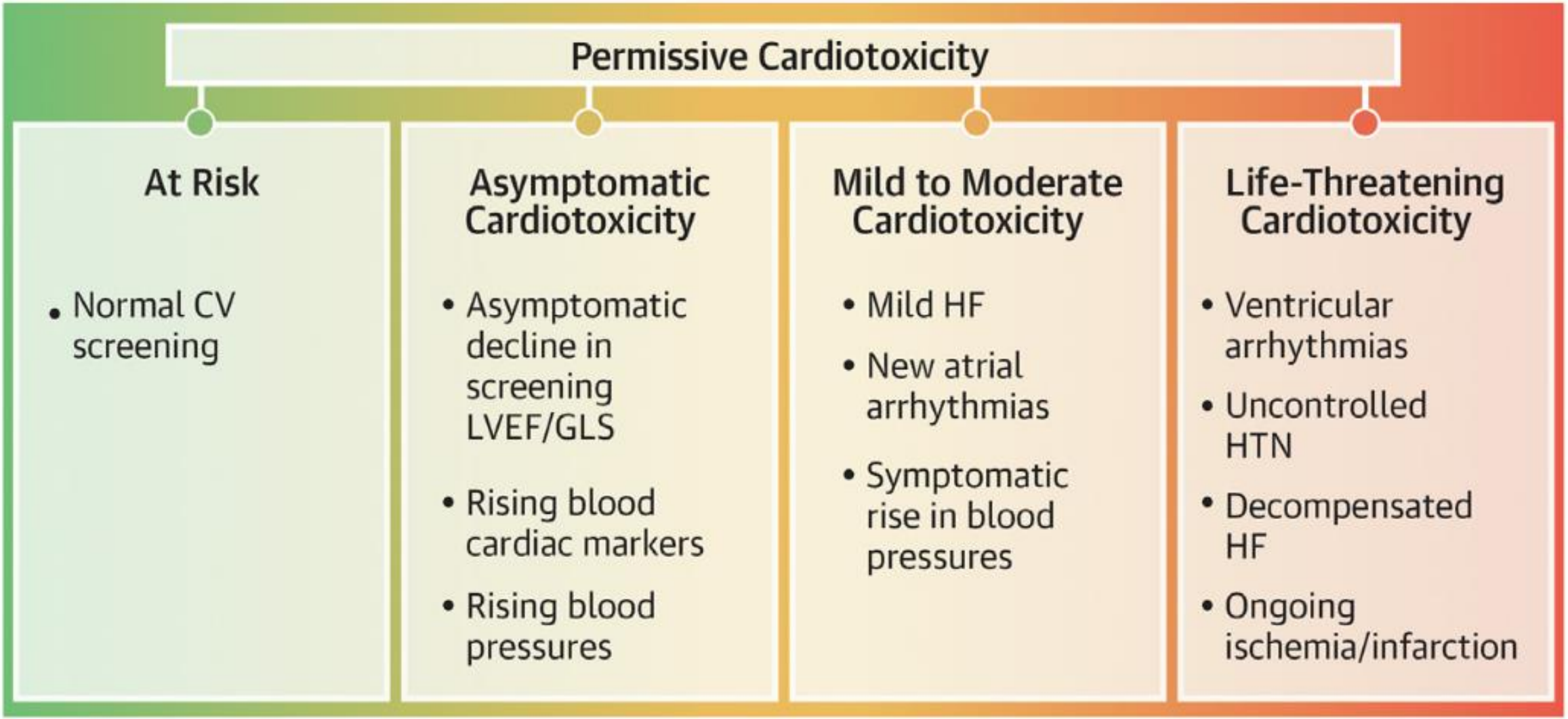
During Treatment

After Treatment

Permissive Cardiotoxicity



Porter C et al. JACC CardioOncol 2022 Sep 20

Permissive Cardiotoxicity

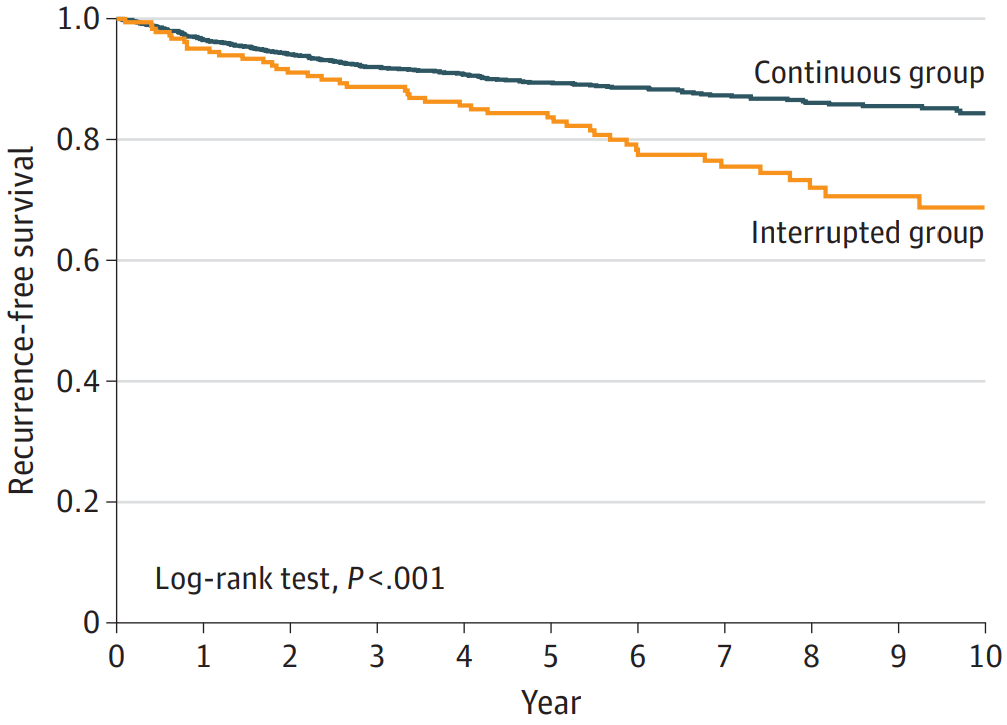
- HER2 directed therapy: LV dysfunction
- Anthracyclines: Asymptomatic decline in LVEF
- VEGF inhibitors: HTN and HF
- ICI’s: Low grade myocarditis

Porter C et al. JACC CardioOncol 2022 Sep 20

Dose interruption of trastuzumab

- 1396 HER2 positive BC at MSKCC from 2004-2013
- 13% had treatment interruption (67% for cardiotoxicity)
- Median follow-up of 6.0 years
- Dose interruption associated with higher rates of BC recurrence and death

Figure. Kaplan-Meier Plot of Recurrence-Free Survival According to Continuous vs Interrupted Trastuzumab



Copeland-Halperin RS et al. JAMA Oncol. 2020 Dec 1;6(12)

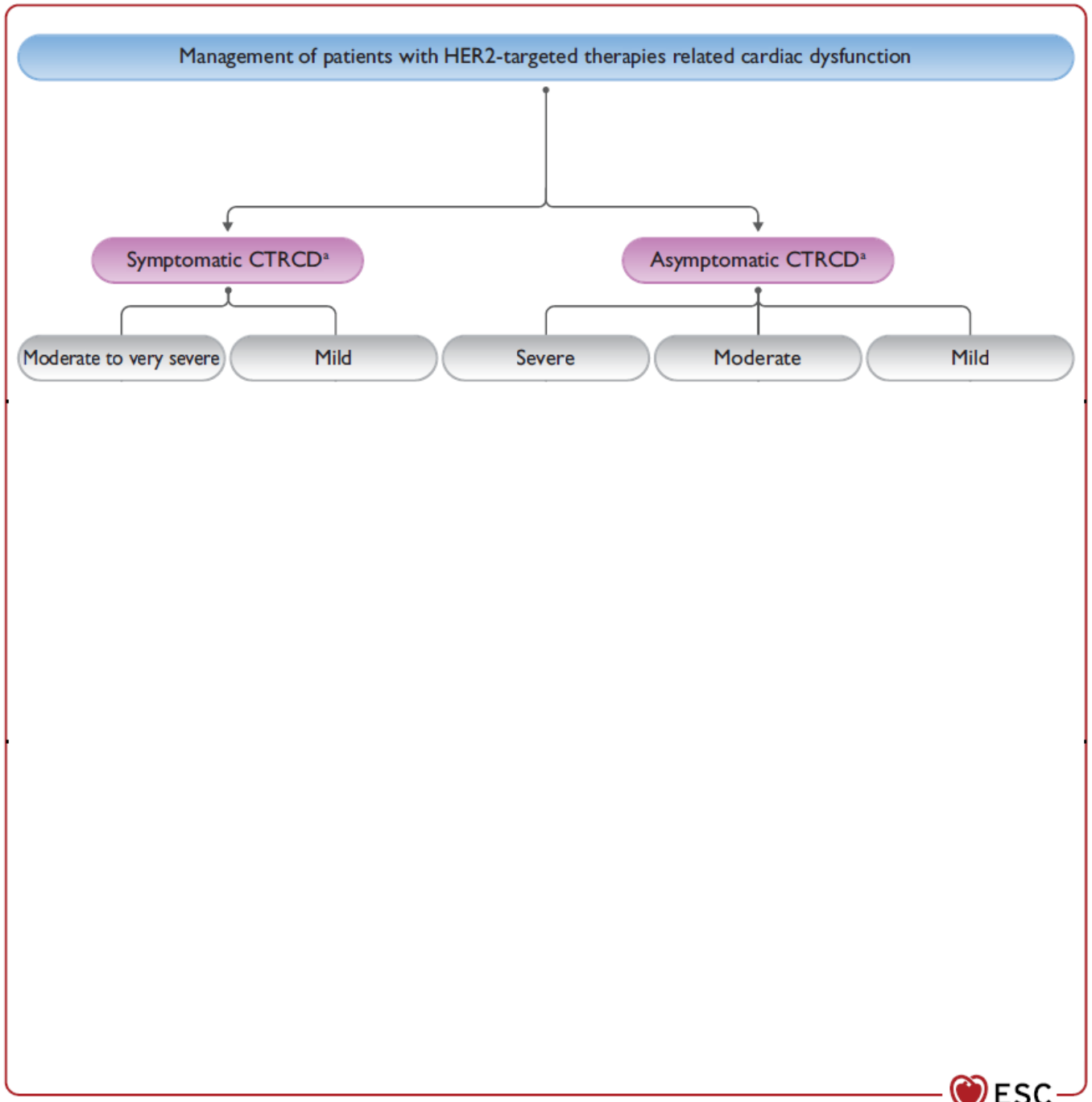
TABLE 5 Safety Trials for Trastuzumab if Left Ventricular Ejection Fraction Is Reduced

Trial	Trial Inclusion	Trial Intervention	Imaging Method	N	Primary Endpoint	Results
SAFE-HEART[49]	LVEF 40%-49% prior to study participation **Stage I-IV HER2+ BC and candidates for HER2 directed therapies**	Carvedilol and any angiotensin antagonist	Echocardiography	30	Patients completed planned HER2-targeted therapy without developing • Asymptomatic decline in LVEF of >10% from baseline and/or LVEF ≤35% or • Cardiac event, defined as ○ Symptomatic heart failure ○ Cardiac arrhythmia ○ Requiring intervention ○ Myocardial infarction ○ Sudden cardiac death	27 (90%) completed HER2-targeted therapies. 2 developed symptomatic heart failure 1 had asymptomatic LVEF decline to 32%
SCHOLAR[50]	LVEF 40%-54% or LVEF >54% and an absolute fall in LVEF of ≥15% from baseline **Phase I, single arm study of Stage I-III HER2+ BC on trastuzumab**	Angiotensin-converting enzyme inhibitor and beta-blocker	Echocardiography	20	Cardiac dose-limiting toxicity, defined as • Occurrence of any of the following ○ Cardiovascular death ○ LVEF <40% together with any heart failure symptoms ○ LVEF <35%	2 developed cardiac dose-limiting toxicity

SAFE-HEaRt = Cardiac Safety Study in Patients With HER2 + Breast Cancer; SCHOLAR = Safety of Continuing Chemotherapy in Overt Left Ventricular Dysfunction Using Antibodies to HER-2; other abbreviations as in Tables 1 and 3.

Table modified from: Omland et al. JACC:CardioOnc 2022 Mar
Leong DP et al. JACC CardioOncol 2019 Jul 17; 1(1)

Lynce F et al. Breast Cancer Res Treat 2019 Jun; 175(3)


Management of patients with HER2-targeted therapies related cardiac dysfunction
Symptomatic CTRCD[a]
Asymptomatic CTRCD[a]
Moderate to very severe
Mild
Severe
Moderate
Mild

Case #1: Treatment exposure

Cardiac Imaging	
MUGA baseline: LVEF 56%	Baseline; ddAC x4 cycles
MUGA post-AC: LVEF 56-59%	Taxol Trastuzumab/Pertuzumab
MUGA: LVEF 50-52%	RT (Proton therapy)
MUGA: LVEF 38-39%	Started ACEi and BB
Echo: LVEF 38%, GLS -12%	Held Trastuzumab/Pertuzumab
CMR after 1 month: LVEF 36%	Increased ACEi and BB, added MRA

Questions for the panel

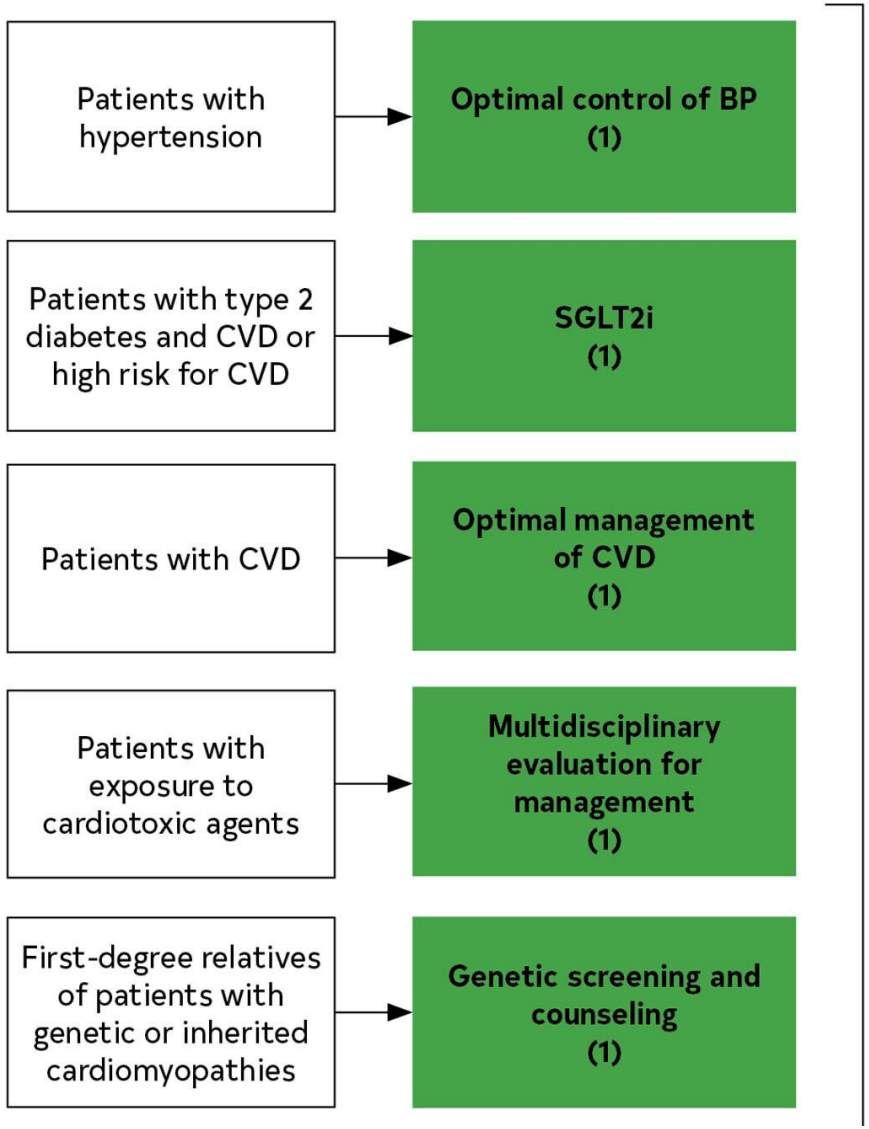
LVEF improves to 43%:

1) What would you do next regarding the HER2 directed therapy?

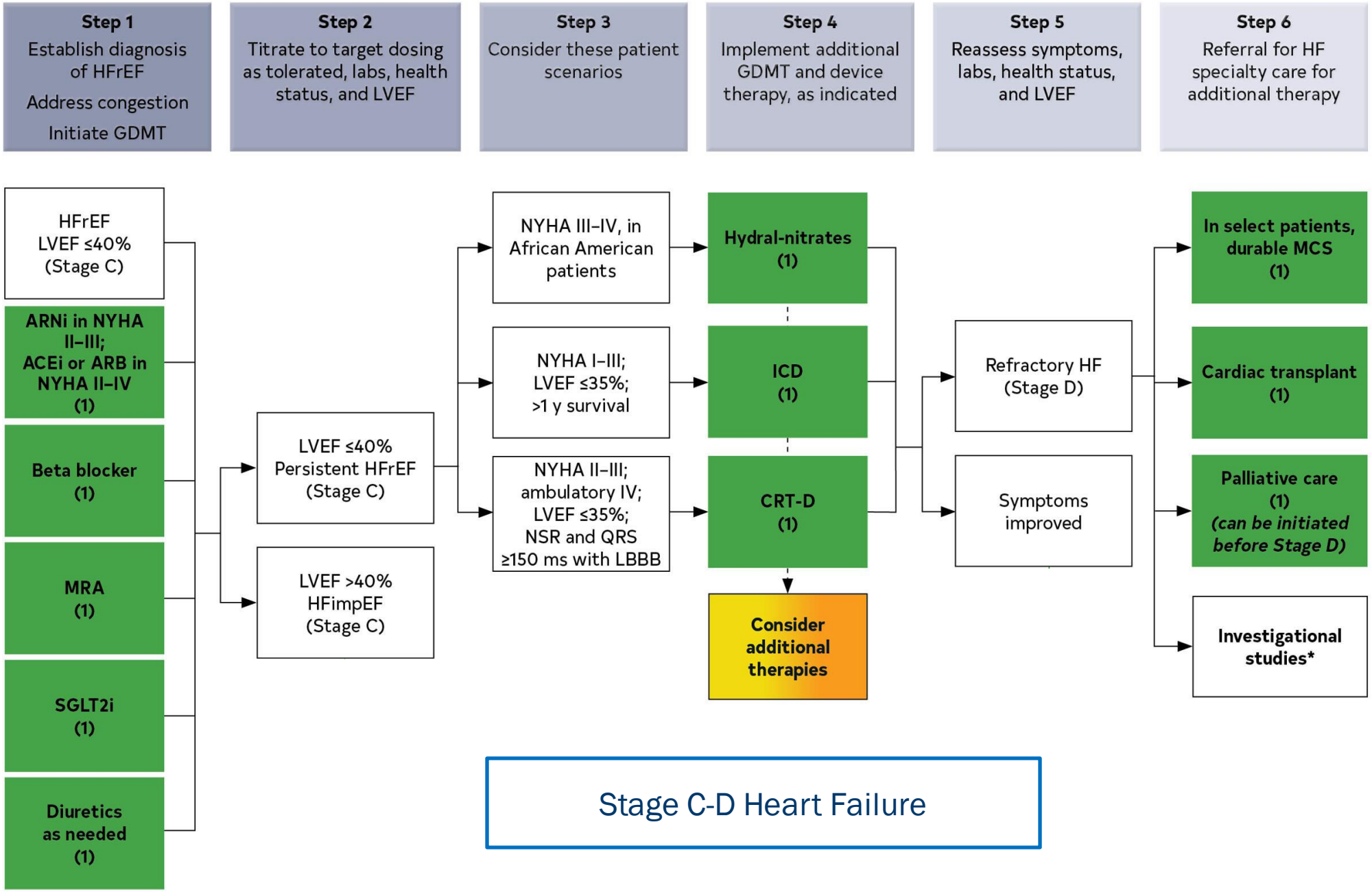
Case #1

- Repeat echo LVEF 43%, GLS -15.2%
- Continued HF GDMT, restarted HER2 directed therapy
- Completed treatment without clinical HF
- Post-treatment LVEF improved to 58%, GLS -18.2%

At risk for heart failure (Stage A)



Modified from: 2022 AHA/ACC/HFSA Heart Failure Guideline



Modified from: 2022 AHA/ACC/HFSA Heart Failure Guideline

CV Medications in Patients with Cancer

TABLE 1 Patient Characteristics

	All Patients (N = 320)	Patients Without History of Cancer (n = 251)	Patients With History of Cancer (n = 69)	p Value*
Age, yrs	65.3 ± 13.3	64.5 ± 13.4	68.2 ± 12.5	0.039
Male	207 (62.3)	163 (64.9)	38 (55.1)	0.160
BMI, kg/m^2	29.4 ± 6.9	29.3 ± 6.4	30.0 ± 8.5	0.444
Primary reason for admission				
ACS/CHD	218 (68.1)	178 (70.9)	40 (58.0)	0.057
Heart failure	61 (19.1)	40 (15.9)	21 (30.4)	0.009
Atrial fibrillation	9 (2.8)	6 (2.4)	3 (4.3)	0.411
Other	32 (10.0)	27 (10.8)	5 (7.2)	0.500
Past medical history				
Ischemic heart disease	287 (89.7)	227 (90.4)	61 (88.4)	0.396
Hypertension	148 (46.3)	112 (44.6)	36 (52.2)	0.278
Dyslipidemia	94 (29.4)	74 (29.5)	20 (29.0)	1.000
Diabetes	82 (25.6)	64 (25.5)	18 (26.1)	0.676
Heart failure	72 (22.5)	71 (28.3)	24 (34.8)	0.049
Atrial fibrillation	58 (18.1)	39 (15.5)	19 (27.5)	0.033
Stroke	31 (9.7)	23 (9.2)	9 (13.0)	0.611
Cardiovascular medication use				
Statins	244 (76.3)	200 (79.7)	44 (63.8)	0.010
ACE inhibitor/ARB	192 (60.0)	154 (61.4)	38 (55.1)	0.405
β-blockers	219 (68.4)	176 (70.1)	43 (62.3)	0.243
Antiplatelets	229 (71.6)	189 (75.3)	40 (58.0)	0.007
DOAC	47 (14.7)	36 (14.3)	11 (15.9)	0.705

Single center

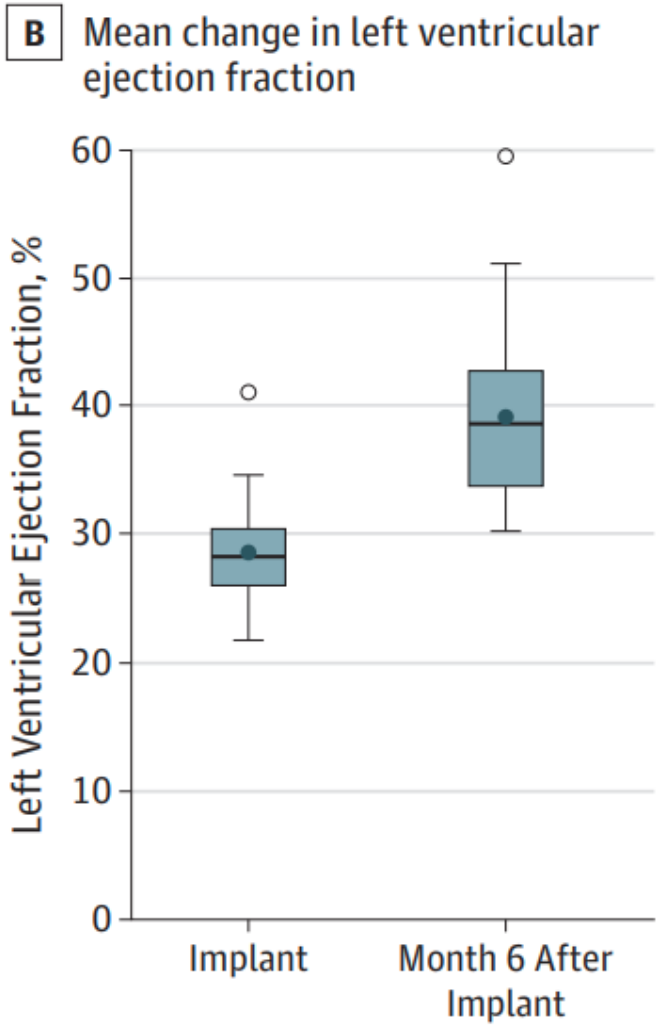
- 333 patients admitted between 2018-2019 at John Hunter Hospital
- Included patients with indication for cardioprotective medications

Untaru R et al. JACC CardioOncol. 2020 Jun 16

CRT in cardio-oncology patients

MADIT-CHIC study

- Prospective, cohort study of chemo-induced CMY
- Class I or II indication for CRT: LVEF ≤35%, NYHA II-IV and wide QRS (mean 152 ms)
- Enrolled 30, data on 26
- 73% breast cancer and 20% lymphoma/leukemia



Singh JP et al. JAMA 2019 Nov 12

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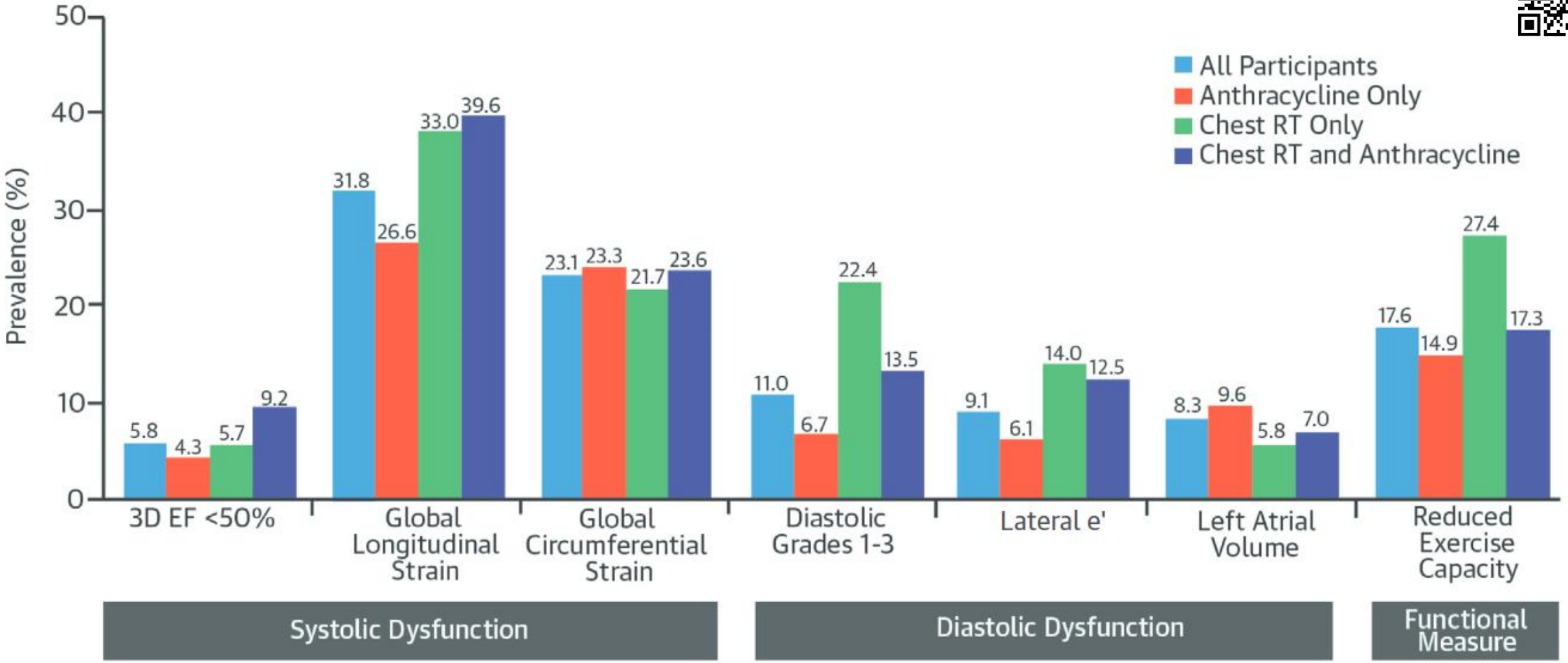
Pre-Treatment

During Treatment

After Treatment

Prevalence of cardiac dysfunction in adult 10-year survivors of childhood cancer



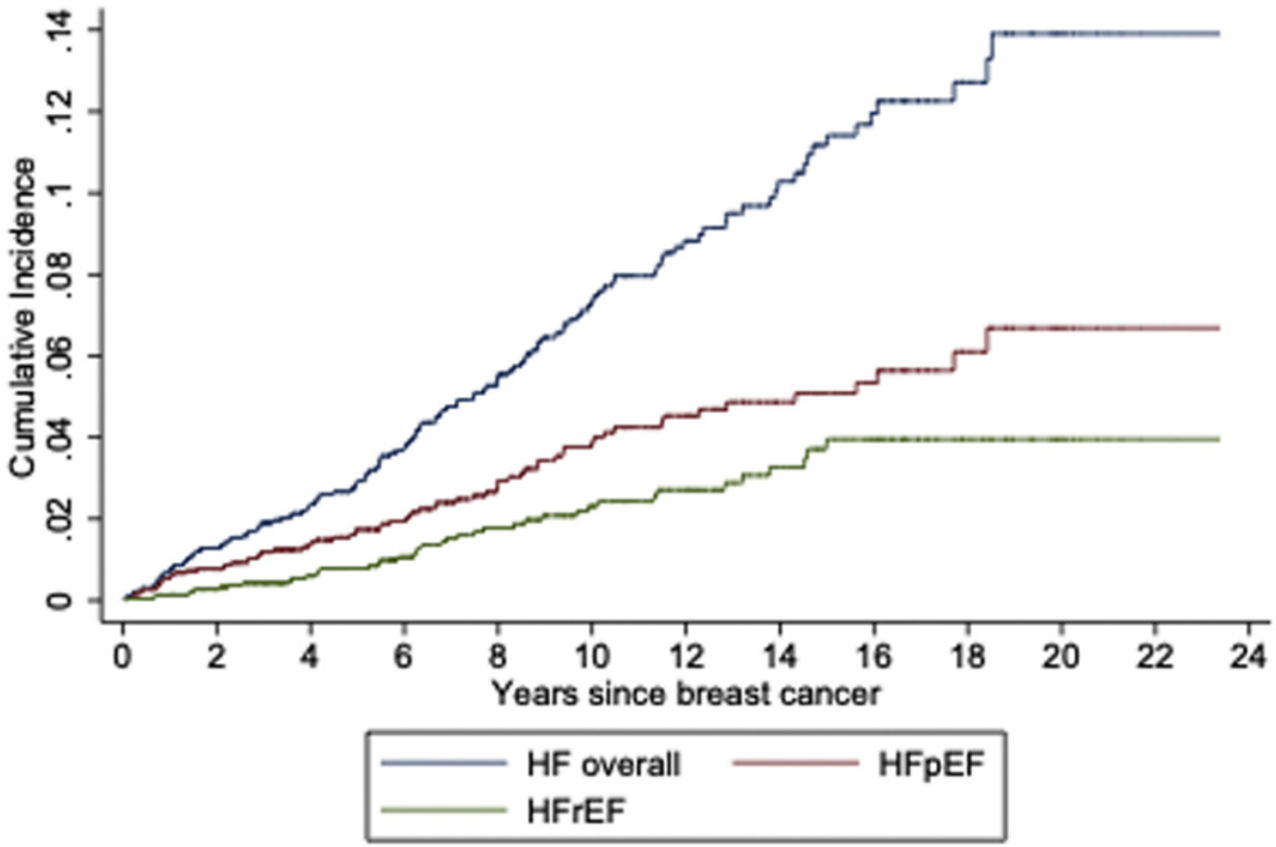
Armstrong GT et al. JACC 2015 Jun

Risk for HF in breast cancer survivors

Retrospective study

- Women's Health Initiative
- 2,272 postmenopausal BC survivors followed for physician adjudicated incident HF req admission
- 64.9% White, 28.6% Black
- Median follow-up 7.2 years

FIGURE 2 HF Hospitalizations After Breast Cancer



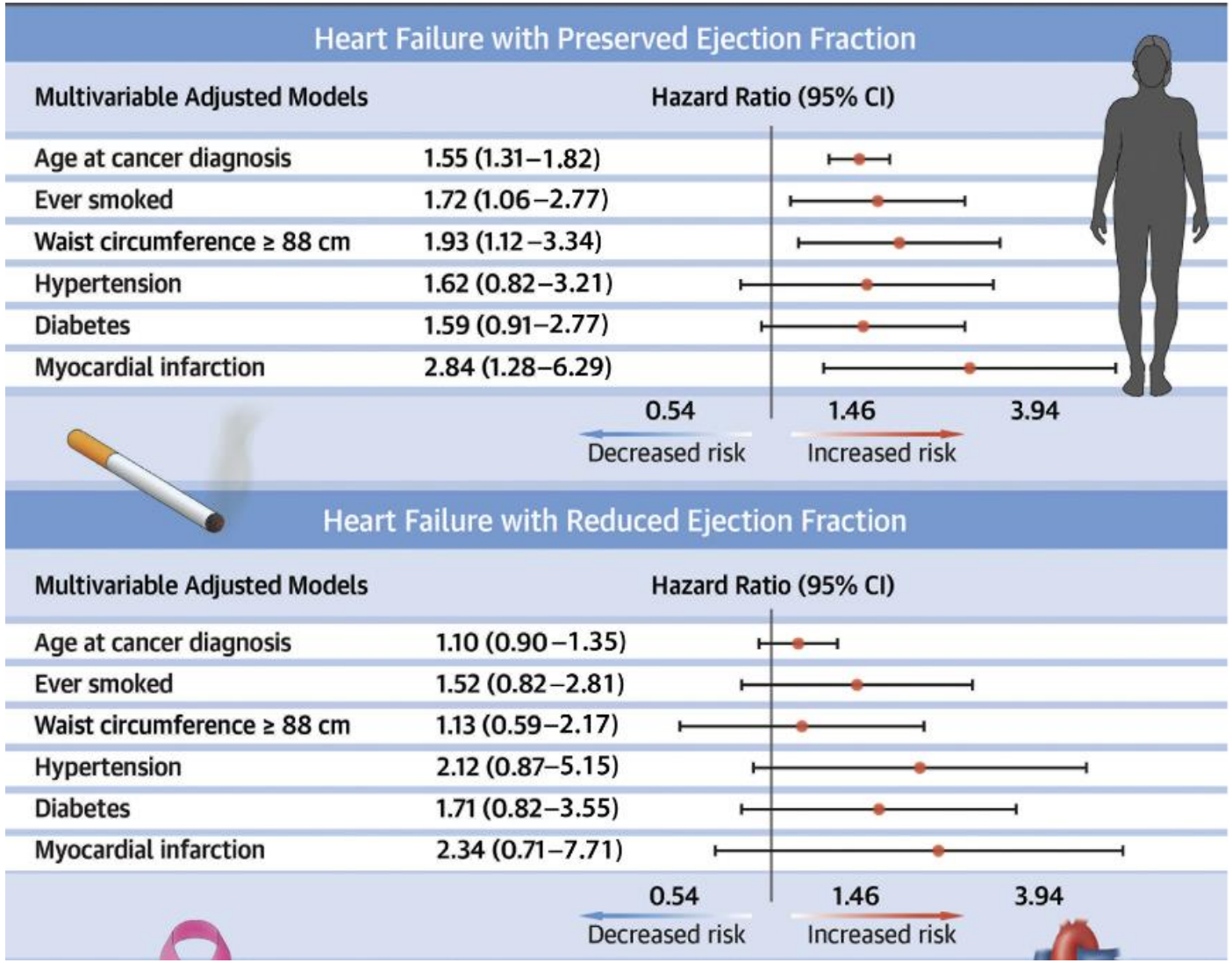
Reding KW et al. JACC: Cardio-oncology 2022 Mar

Risk for HF

- HFpEF 6.7%, HFrEF 4.0% at 7.2 years of follow-up
- Overall mortality compared to those without HF:

  HFpEF HR 5.7

  HFrEF HR 3.8



Reding KW et al. JACC: Cardio-oncology 2022 Mar

Balancing “healthy” and “sick” for AHFT

Sick enough to benefit?
Common Indications

- End-stage HF
- Advanced RCM
- Refractory severe angina
- Refractory VT

Healthy enough to do well?
Common contraindications

- Active infection
- **Current or recent cancer**
- Other end-organ dysfunction
- T2DM with end-organ damage
- Pulmonary hypertension
- Psychosocial barriers
- Severe obesity

Is LVAD an option in active cancer?

- 2 center study (Medstar + UW), 3:1 matching
- Cancer cohort: 27% female, 62 yrs

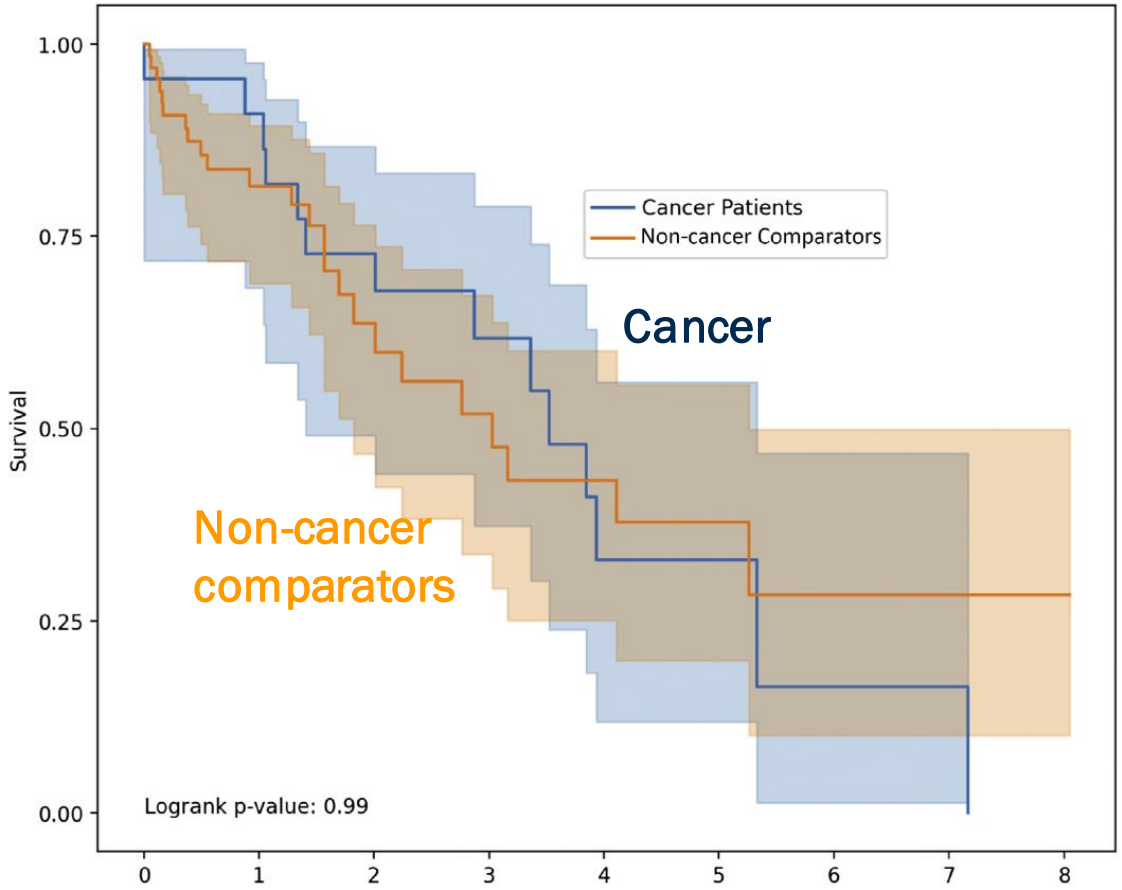


TABLE 2 Oncological Characteristics of Patients With Active Malignancy (N = 22)

Type of cancer	
Prostate	5 (23)
Renal	4 (18)
Hematologic malignancy	3 (14)
Breast	2 (9)
Lung	2 (9)
Bladder	2 (9)
Neuroendocrine tumor	2 (9)
Other	2 (9)
Median age at cancer diagnosis* (yrs)	61 (41-72)
Goal of therapy	
Curative	13 (59)
Palliative	6 (27)
No therapy	3 (14)
Type of cancer-directed therapy†	
Surgery	12 (55)
Systemic therapy	11 (50)
Radiation	5 (23)

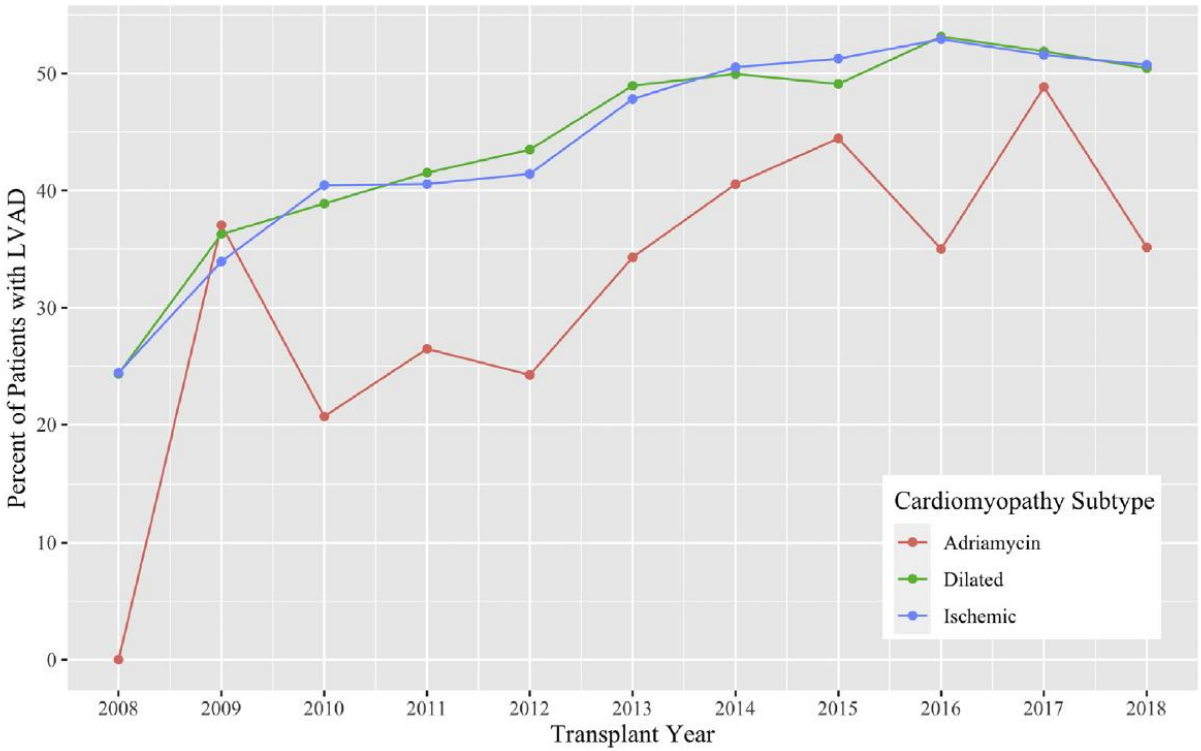
Schlam I et al. JACC CardioOncol 2021 Jun

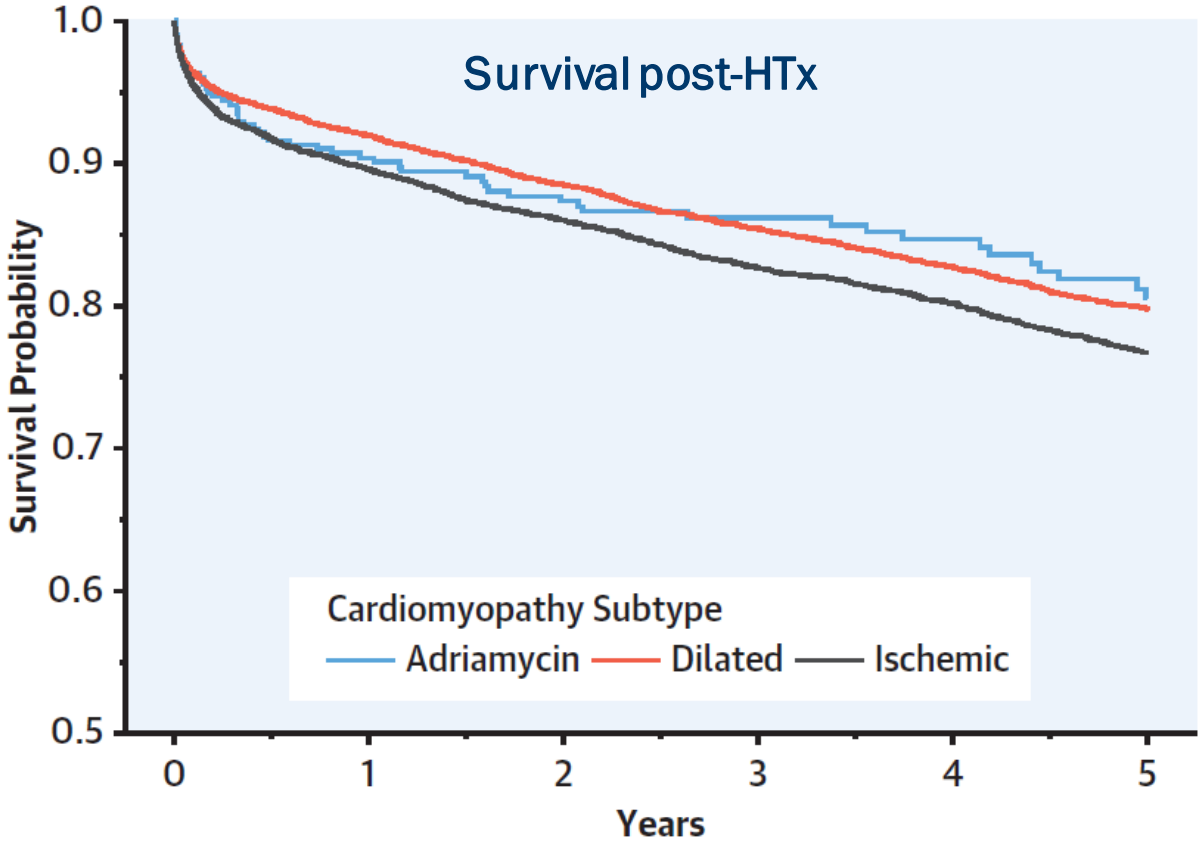
Heart transplant

- UNOS registry analysis 2008-2018
- Compared ACM, DCM and ICM
- 18,270 patients, 357 with ACM

- ACM were younger (51 yrs) more women (76%)

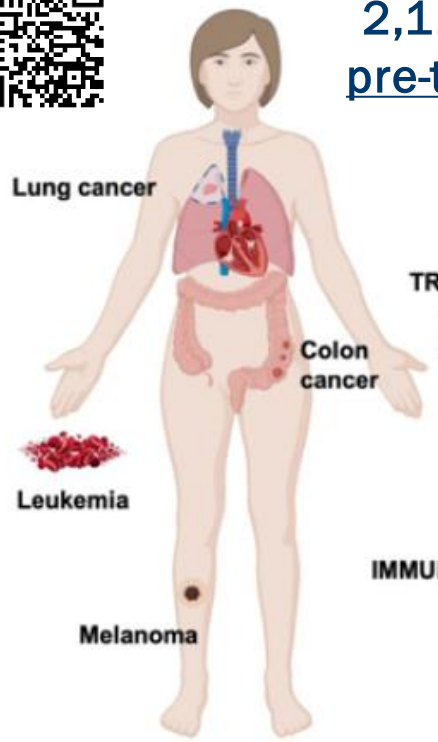
Percentage of patients with LVAD at time of HTx





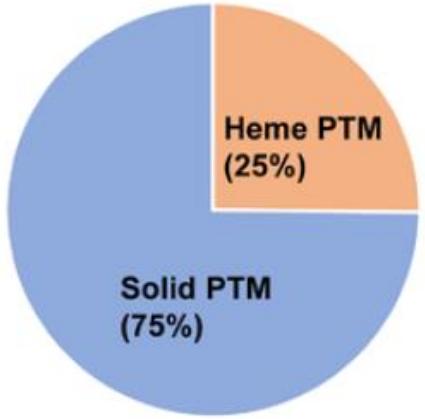
Ramu B et al. JACC Cardio-Onc 2021;3

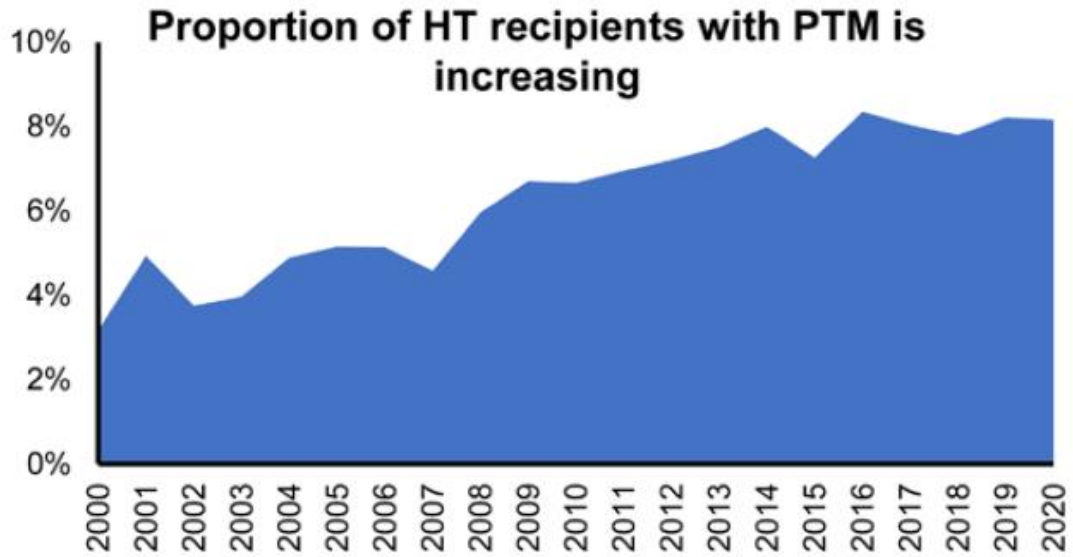
2,113 HTx Recipients (UNOS registry) with pre-transplant malignancy from 2010-2020

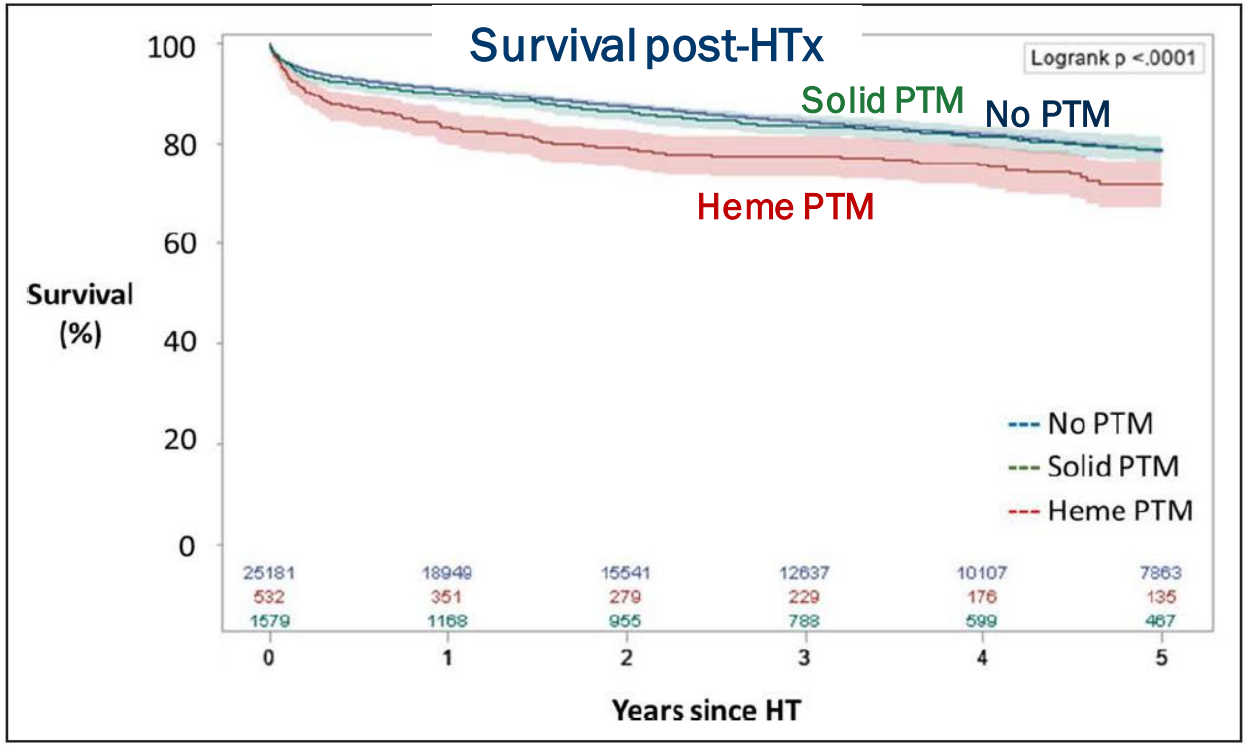


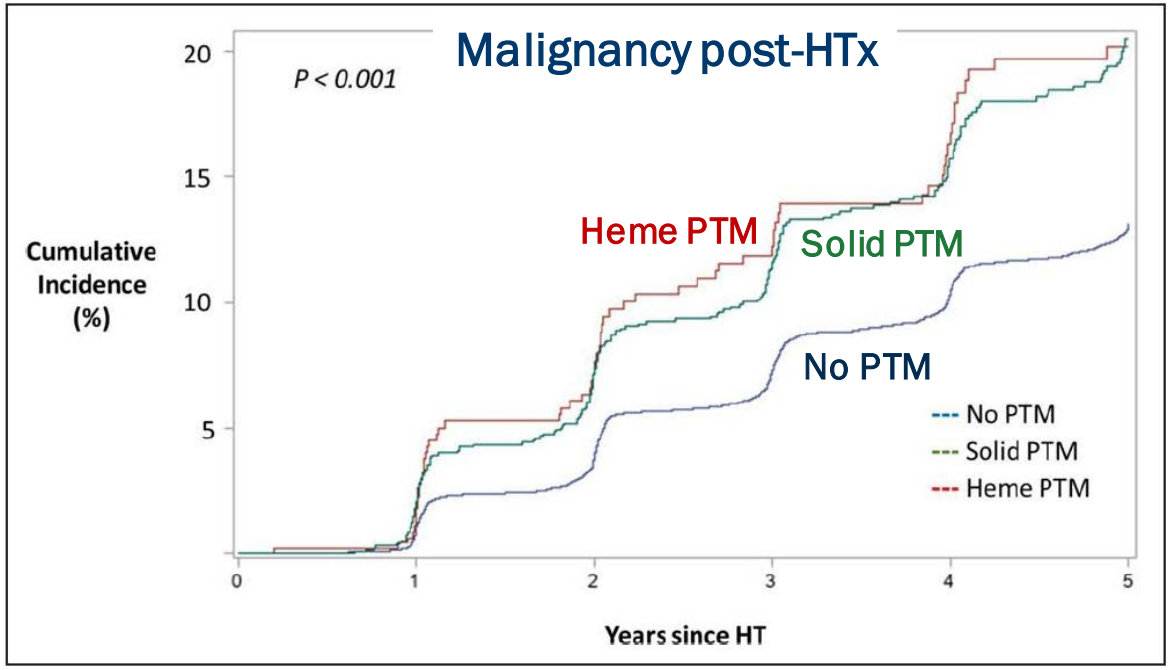
HEART TRANSPLANTATION

IMMUNOSUPPRESSION









Batra J et al. Circ Heart Fail. 2022 Jan 31

Take home points

What we know:

- LV dysfunction is not uncommon with cancer treatment
- We need to identify cardiotoxicity early and accurately
- Permissive cardiotoxicity may be safe in selected instances
- Long-term follow-up is needed as cancer survivors are at risk for HFpEF and HFrEF

What we don't know:

- Optimal cardioprotection strategy:
  - What patients should we target?
  - What is the optimal regimen?
  - Does it prevent clinical endpoints?
- What is the role of AHFT in patients with active or recent cancer?