Identifying and Managing Cancer Treatment Cardiotoxicities in Patients Undergoing Therapy

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Objectives

- Apply evidence-based approaches to identify and assess patients at risk for cardiotoxicity
- Discuss the use of clinical tools, imaging, and other tests to evaluate patients at risk for cardiotoxicity before, during, and after cancer treatment
- Employ multidisciplinary strategies to mitigate the risk for cardiotoxicity in cancer patients

Disclosures

I have the following financial relationships to disclose:

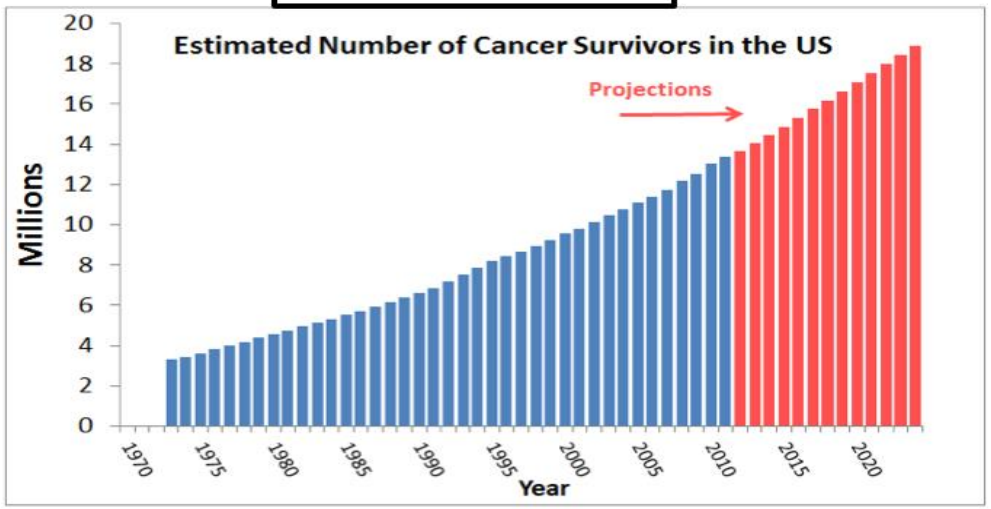
- Consulting/advisory board: Eidos Therapeutics (BridgeBio) and Alnylam Pharmaceuticals
- Research support (Institutional): Pfizer, Alnylam Pharmaceuticals, Eidos Therapeutics (BridgeBio), Ionis Therapeutics, Moleculin Biotech
- Speaker's bureau: Alnylam Pharmaceuticals
- Stock Shareholder: Springworks Therapeutics, Chimerix, Inc. (spouse)

None are relevant to the content of this presentation

Cardiovascular Risk for the Cancer Journey

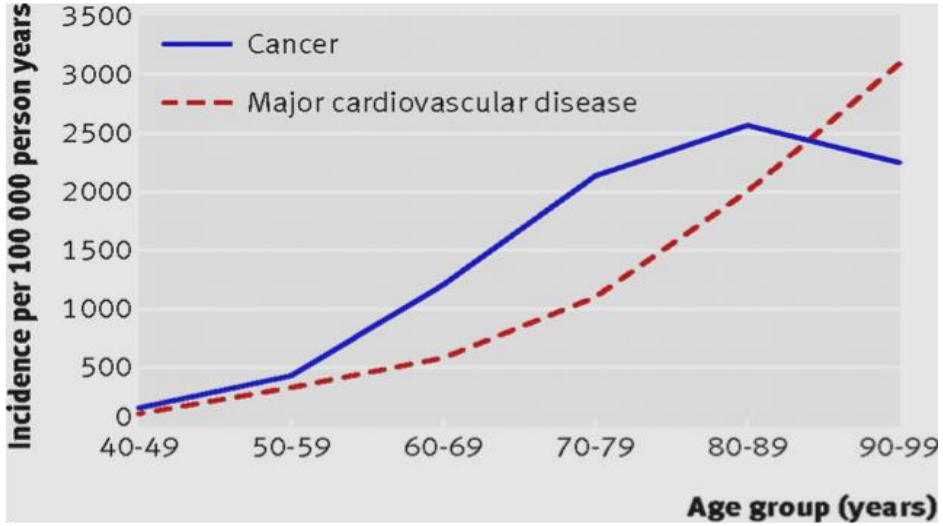
The Basis for Considering CV Risk in Cancer

Survival gains



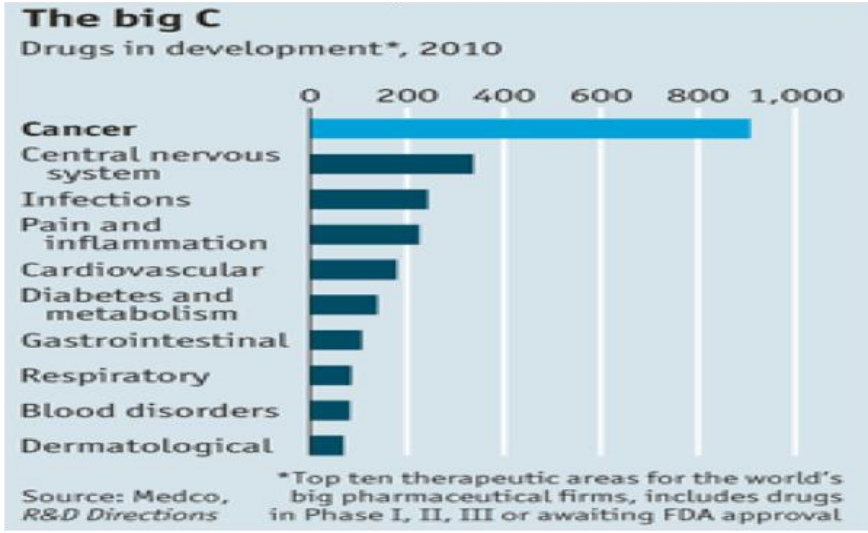
DeSantis CE et al. *CA Cancer J Clin*. 2014;64:252-271.

Cancer – CVD competing risks



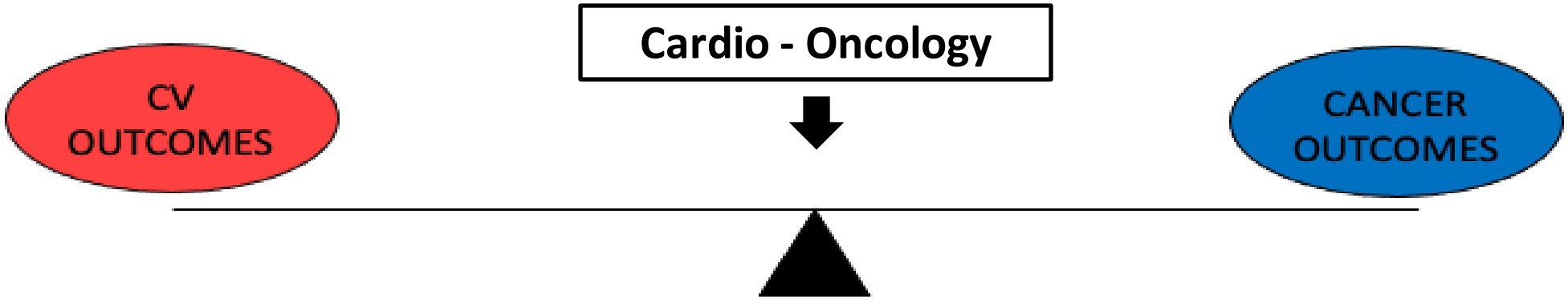
Driver JA et al. *BMJ*. 2008;337:a2467.

Cancer therapies ↑CV Risk

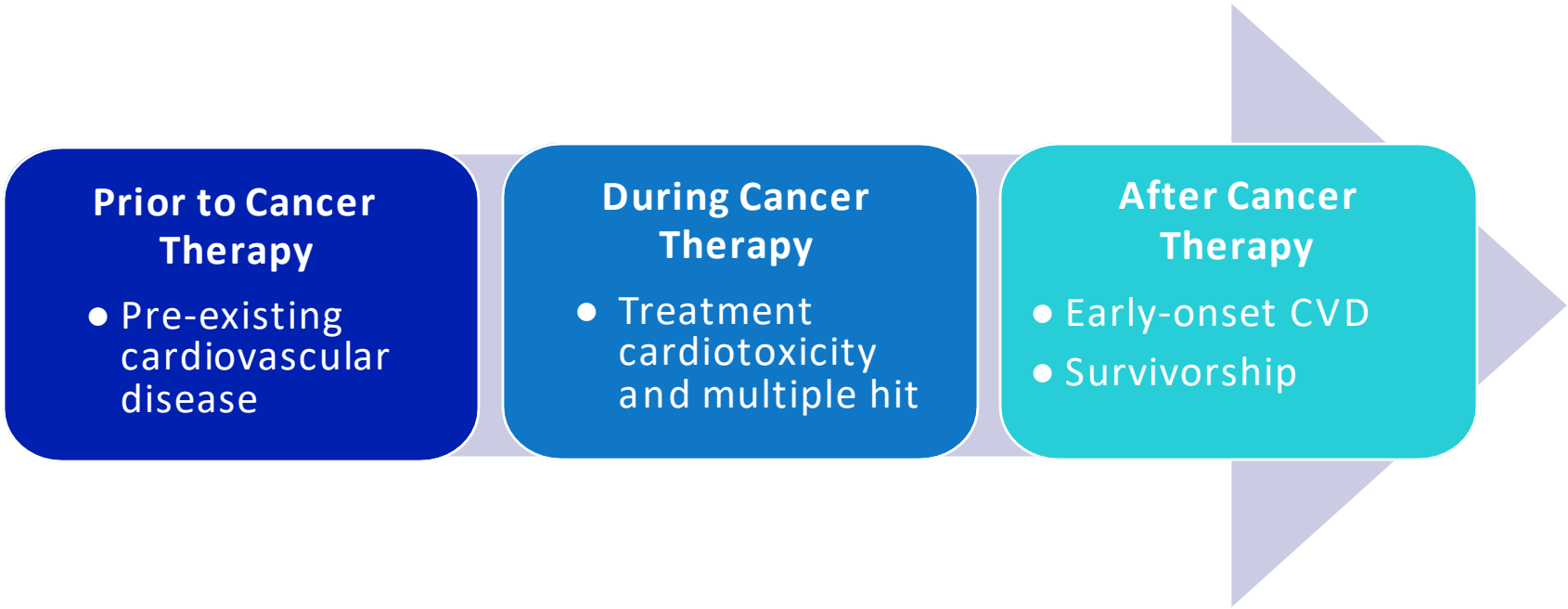


CVD=cardiovascular disease.

The Context: Balancing Cancer and CV Outcomes



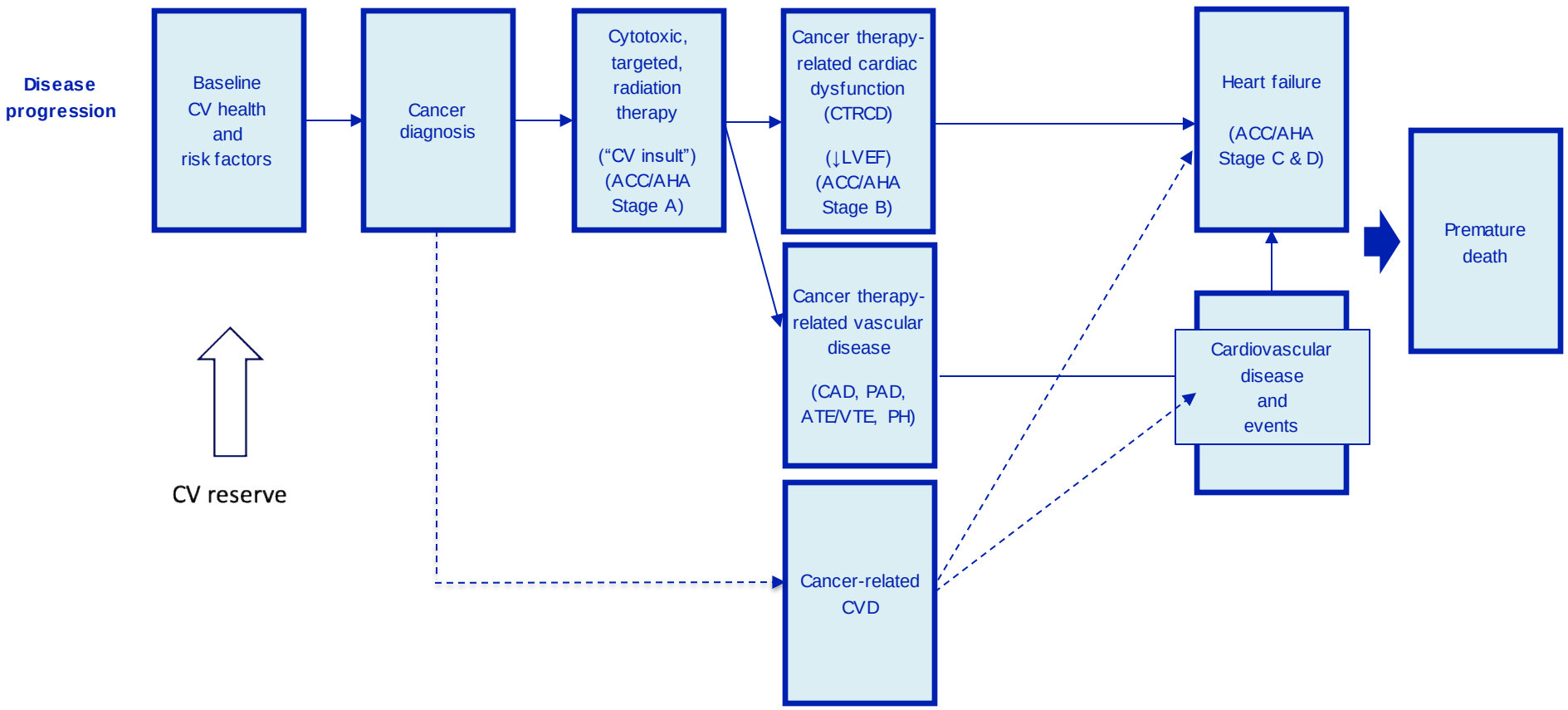
The Spectrum of CV Risk Considerations



Prior to Cancer Therapy

- Define the cardiovascular substrate

Defining the CV Substrate: Assessments of CV Reserve

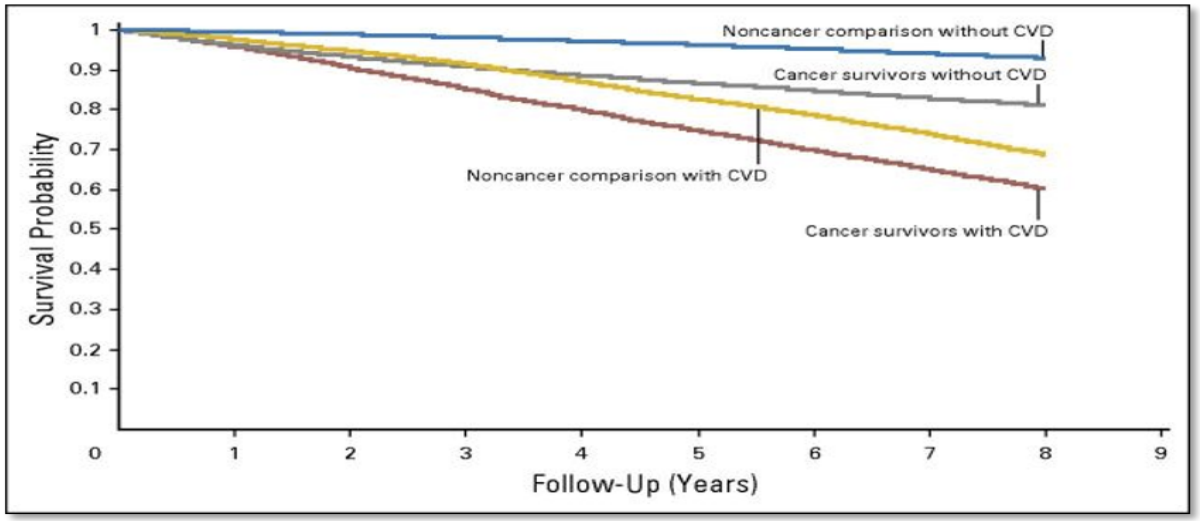


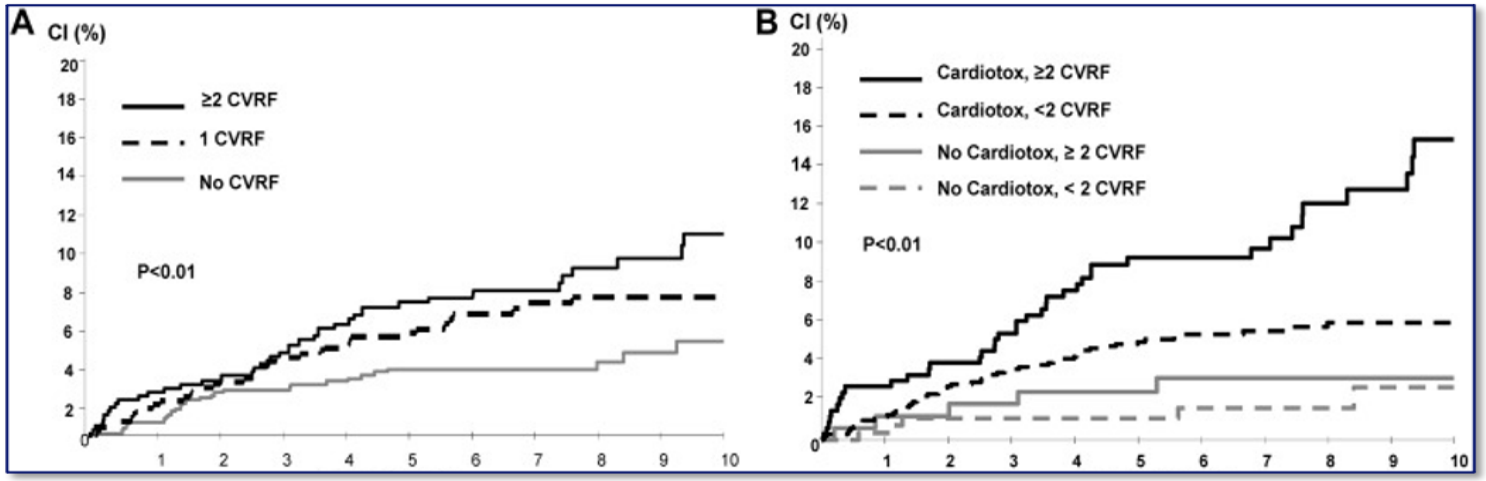
ACC=American College of Cardiology; AHA=American Heart Association; ATE=arterial thromboembolism; CAD=coronary artery disease; LVEF=left ventricular ejection fraction; PAD=peripheral artery disease; VTE=venous thromboembolism; PH=pulmonary hypertension.

Adapted from Khouri MG et al. *Circulation*. 2012;126:2749-2763.

Pre-Cancer Therapy: Importance of Baseline CV Disease

Presence of CVD is associated with worse outcomes in cancer survivors.





CVRF=cardiovascular risk factors.

Armenian SH et al. *Blood*. 2012;120:4505-4512.

Existing CVD Can Worsen Cancer-specific Outcomes

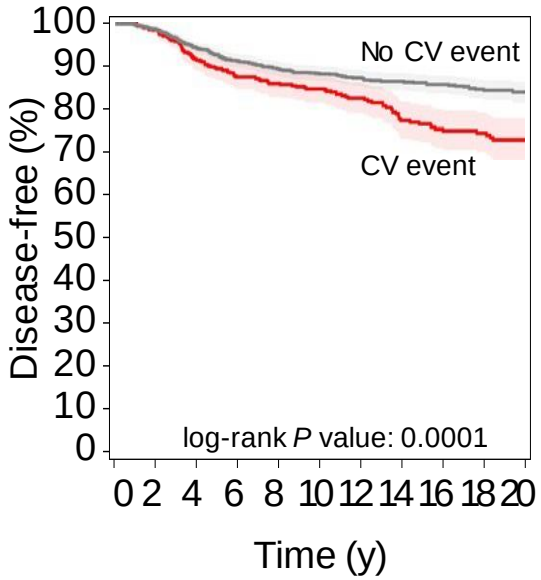
nature medicine

LETTERS

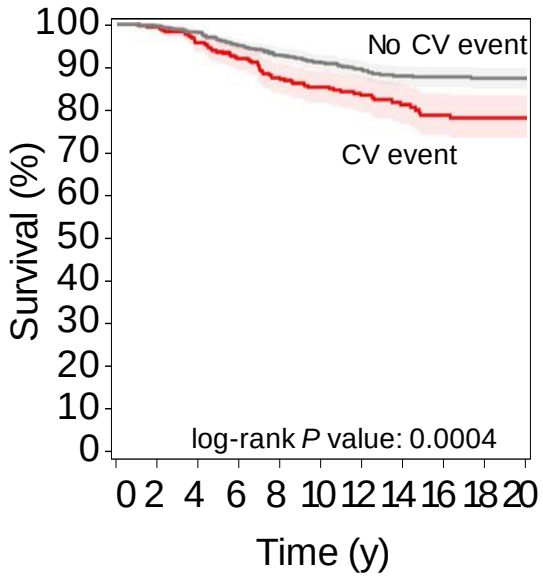
https://doi.org/10.1038/s41591-020-0964-7

Myocardial infarction accelerates breast cancer via innate immune reprogramming

f Recurrence

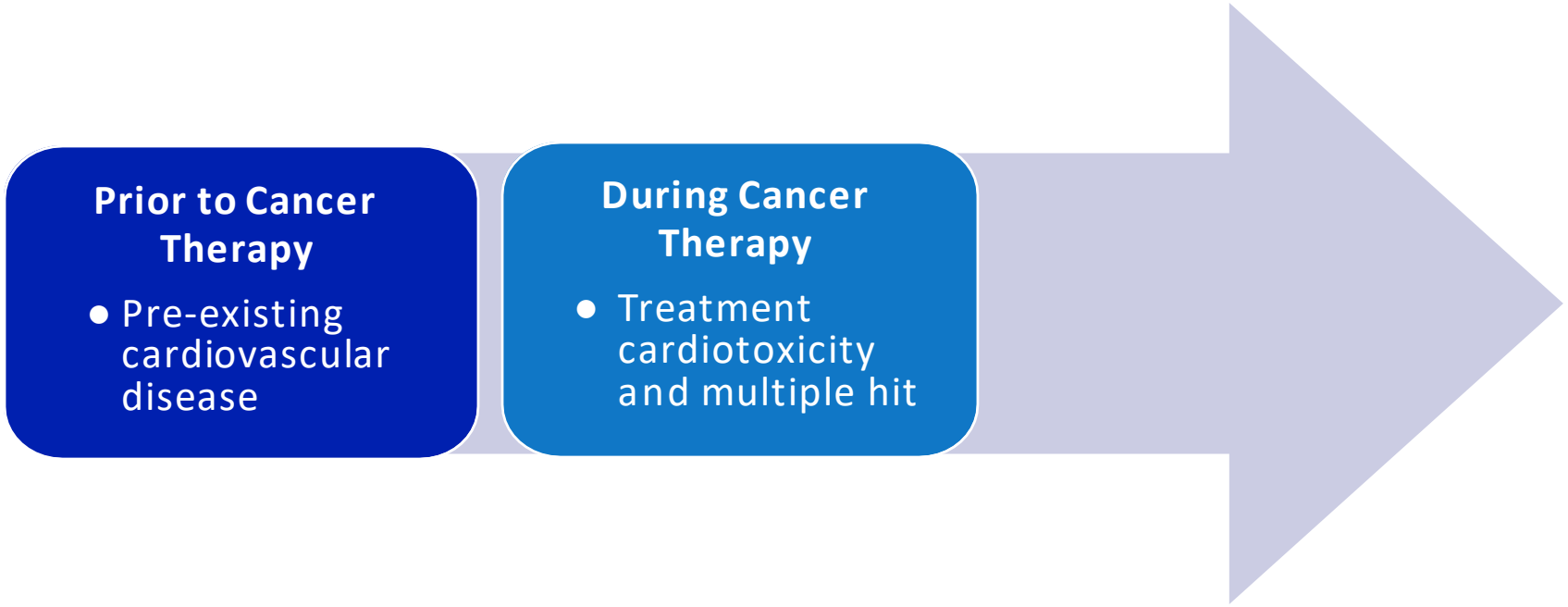


g Breast cancer-specific mortality

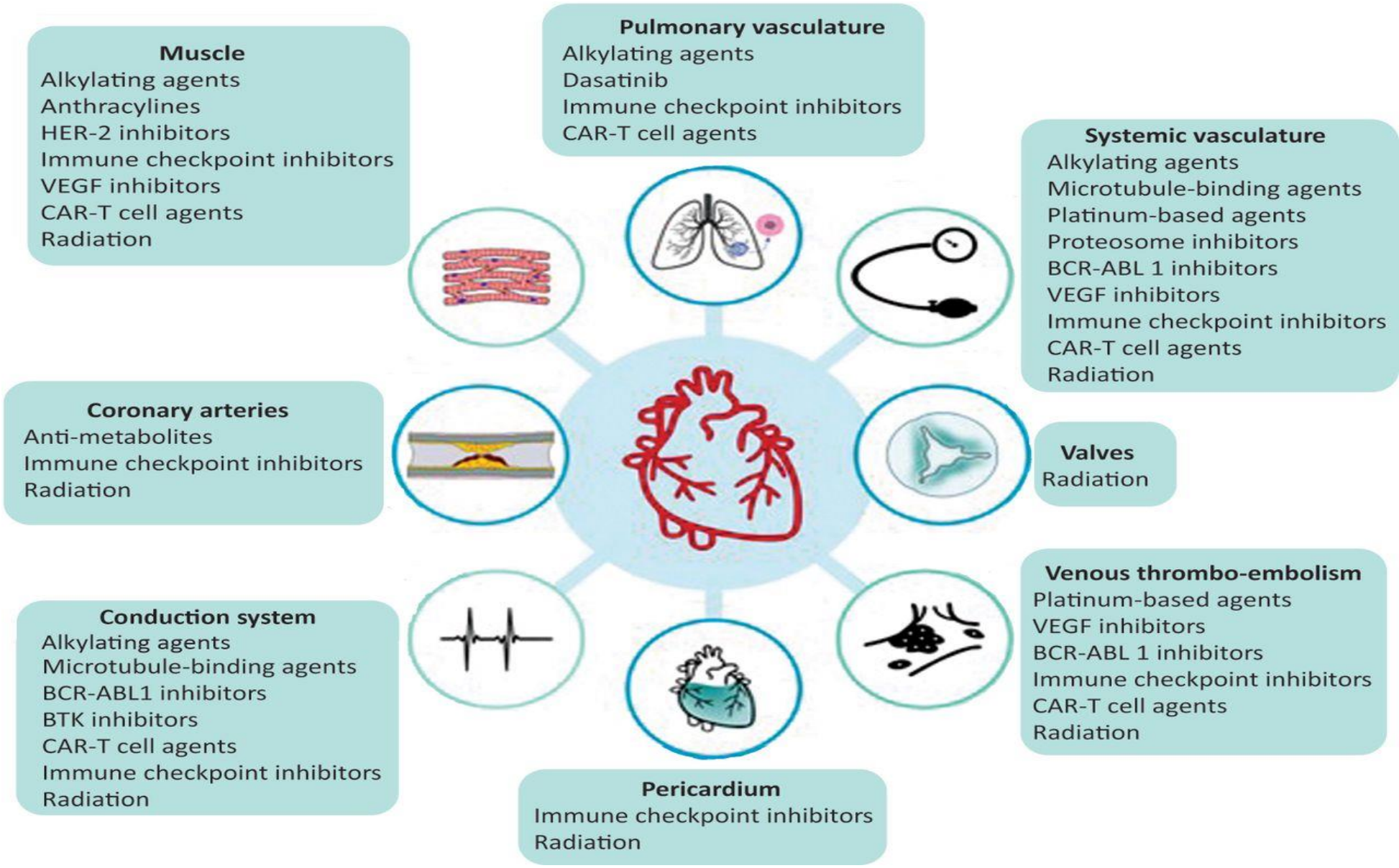


	Total	No. events	CV event-multivariable-adjusted HR (95% CI)	P_{trend}
Recurrence	1724	270	1.59 (1.23–2.05)	0.0004
Breast cancer-specific mortality	1544	168	1.60 (1.15–2.22)	0.0045

Koelwyn GJ et al. *Nat Med*. 2020;26:1452-1458.


Prior to Cancer Therapy
Pre-existing cardiovascular disease
During Cancer Therapy
Treatment cardiotoxicity and multiple hit

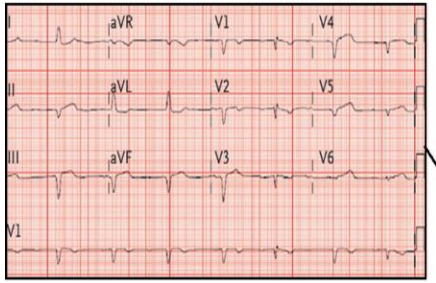
During Cancer Therapy: Spectrum of Treatment-related Cardiotoxicity



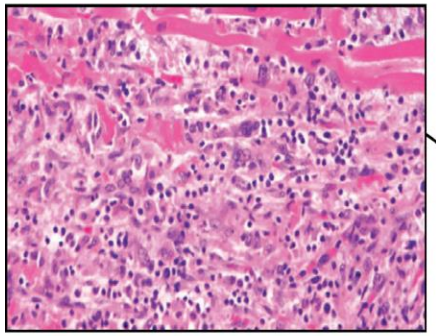
Ferreira VV et al. *ClinMed*. 2023; 23(1): 52-5.

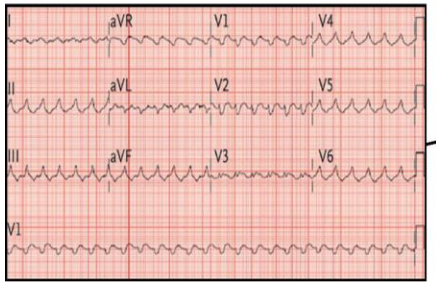
During Cancer Therapy: ICI CVAEs

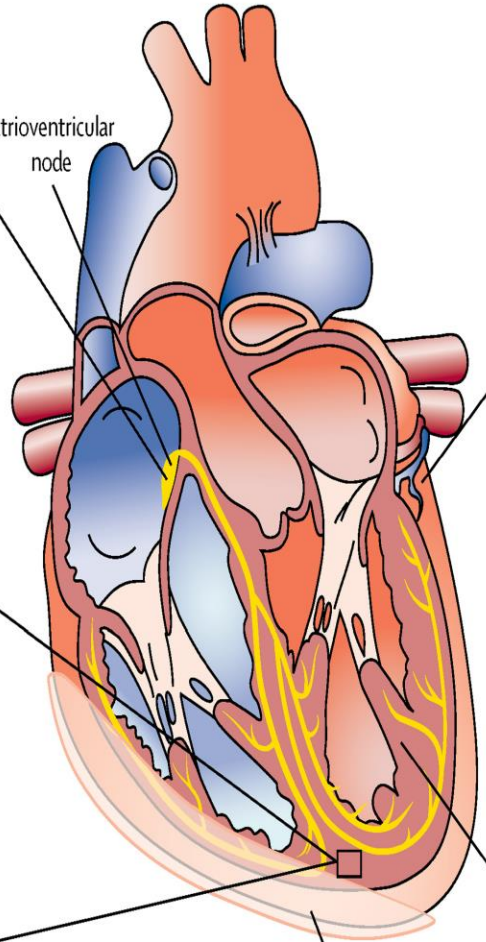
Conduction disease
- Atrioventricular block



Myocarditis
- Heart failure
- Ventricular arrhythmias





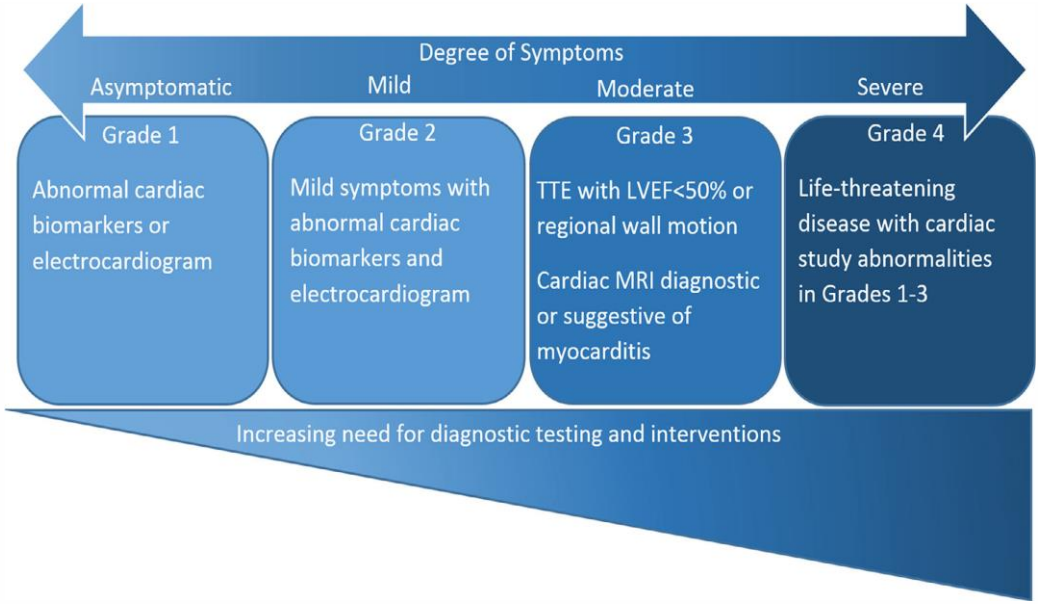


Coronary artery disease
- Atheriosclerotic plaque rupture
- Acute myocardial infarction
- Coronary vasculitis

Non-inflammatory left ventricular dysfunction
- Heart failure
- Takotsubo syndrome

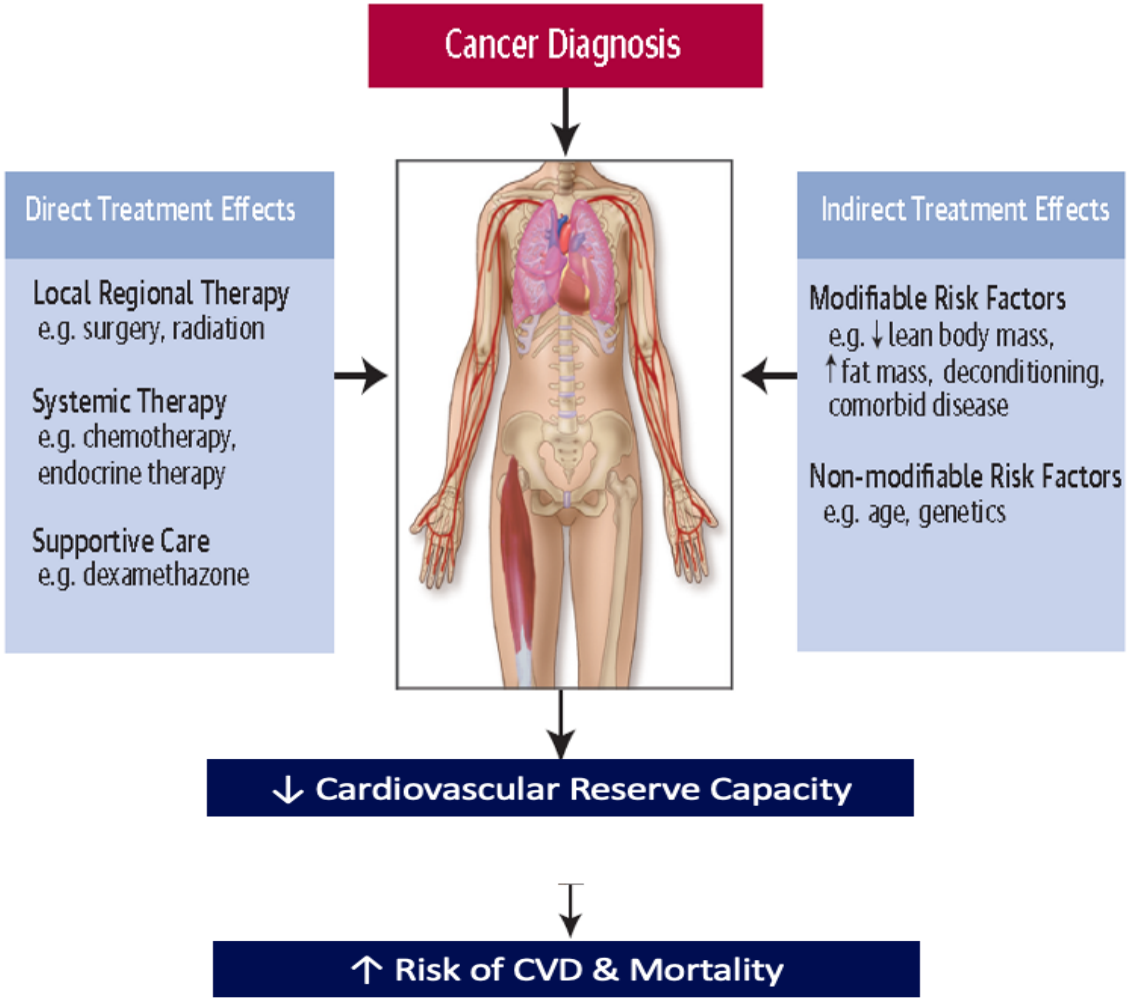
Lyon AR et al. *Lancet Oncol*. 2018; 19: E447-E458.

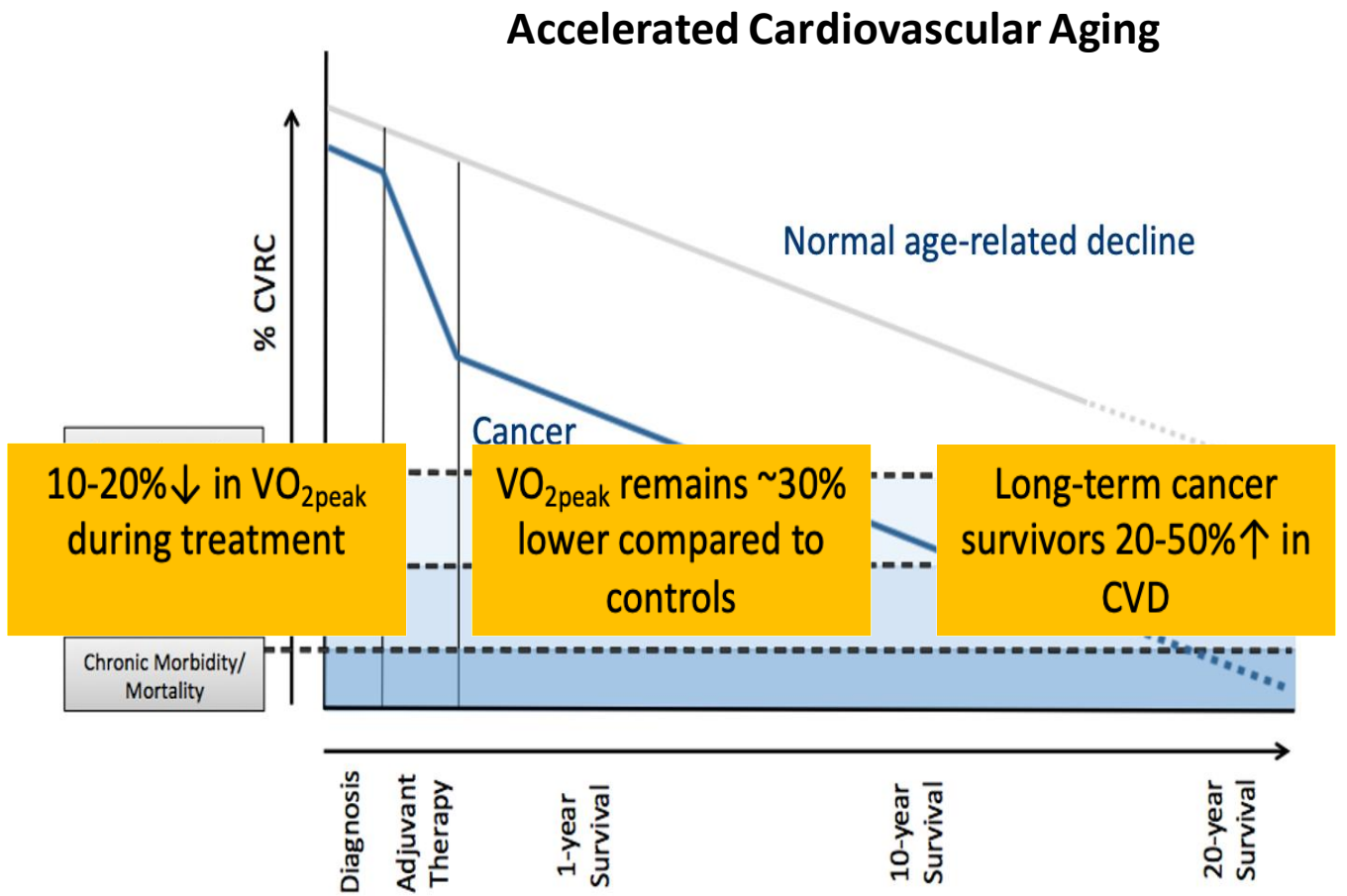
Spectrum of Myocarditis Presentations



Palaskas, et al. *JAHA* 2019

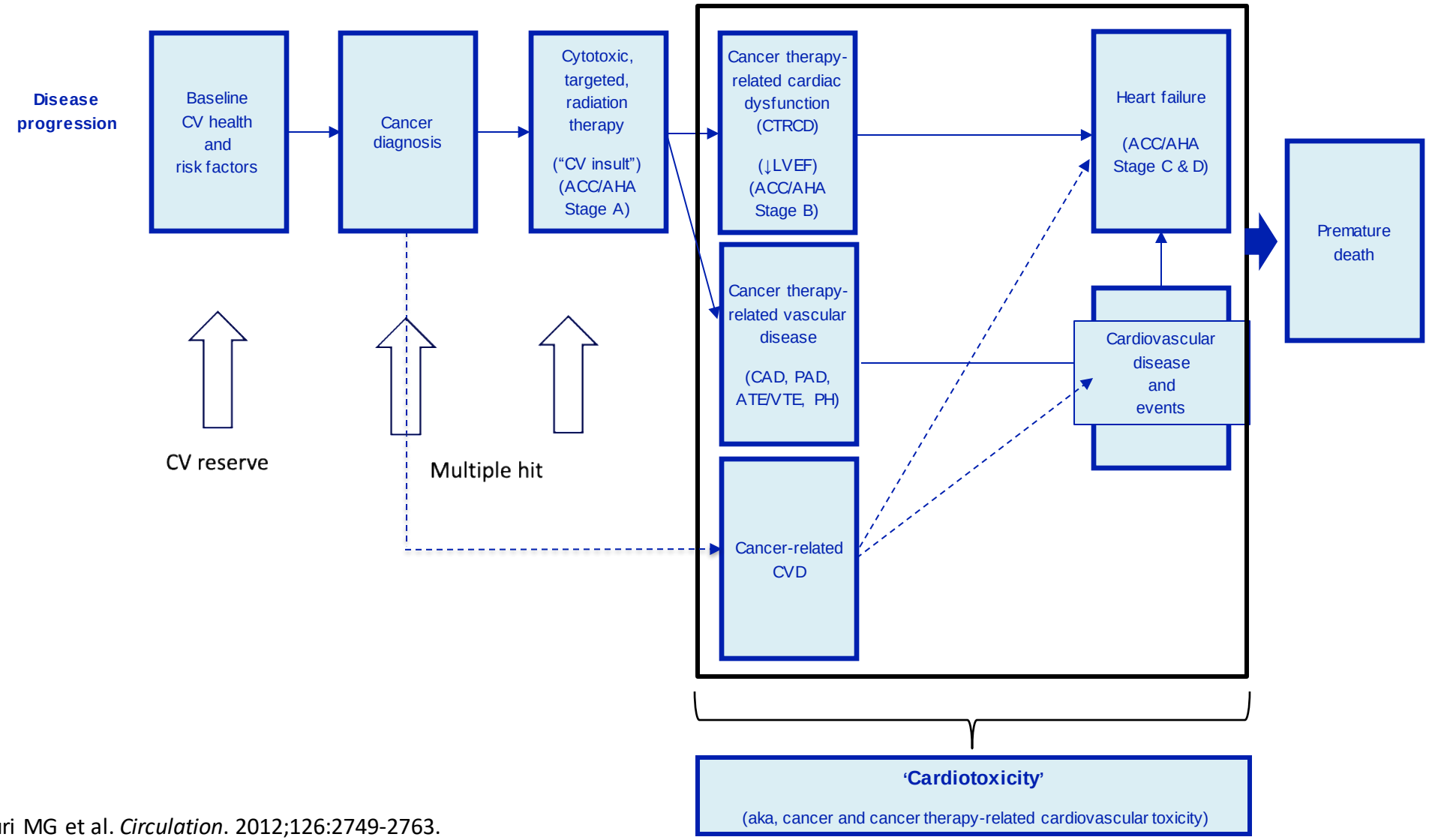
During Cancer Therapy: Multiple Hits to the CV System





Adapted from Armenian SH et al. *Heart Fail Clin*. 2017;13:337-345; Jones LW et al. *J Am Coll Cardiol*. 2007;80:1435-1441; Koelwyn GJ et al. *J Am Coll Cardiol*. 2014;64:1320-1322.

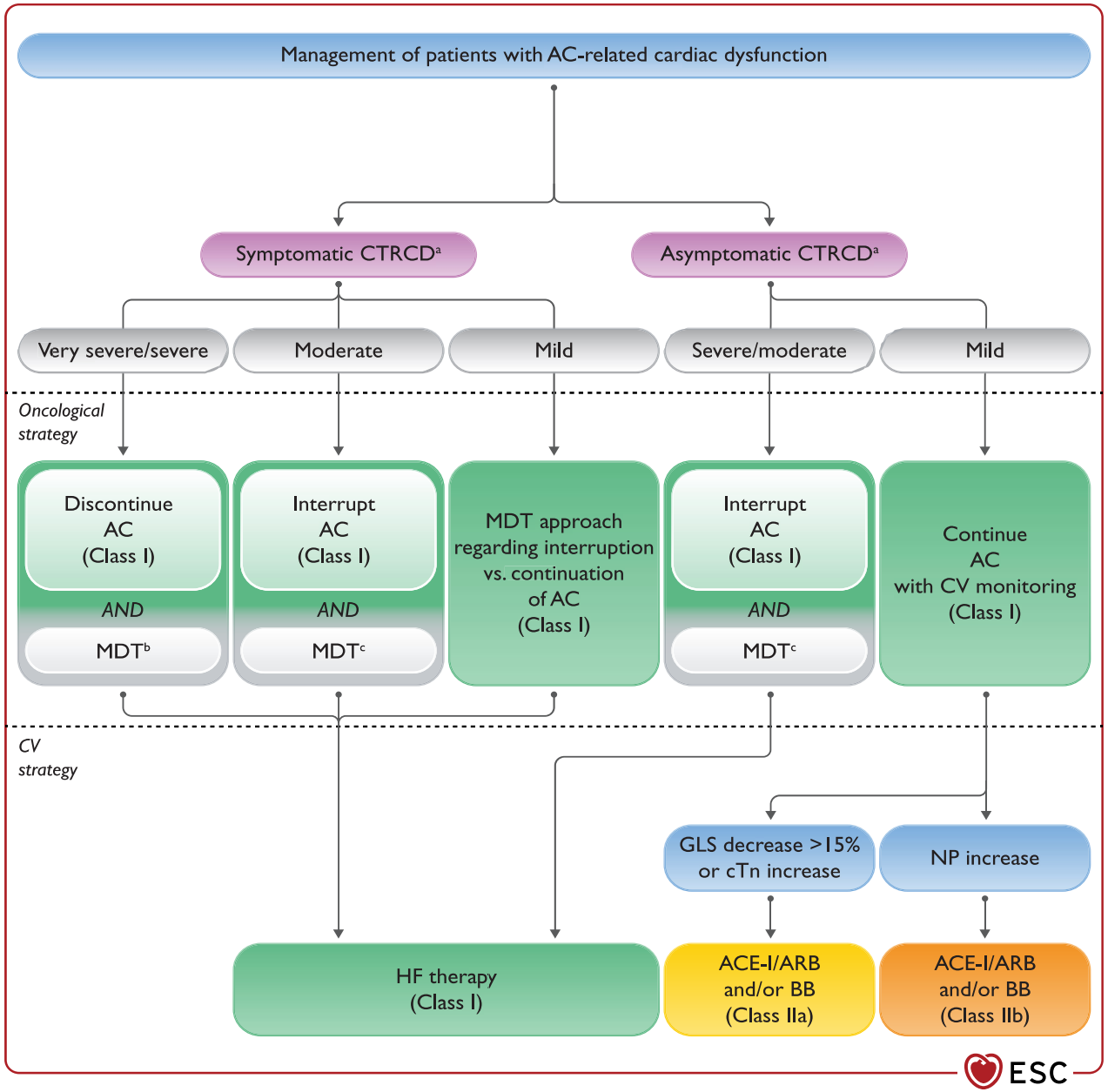
‘Cardiotoxicity’: A Spectrum of Risks, Outcomes, and Causes



Adapted from Khouri MG et al. *Circulation*. 2012;126:2749-2763.

Definitions and Significance of CTRCD

CTRCD		
Symptomatic CTRCD (HF)[a,b]	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to <40%
	Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% *OR* New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers[c]
	Mild	LVEF ≥ **50%** AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers[c]



Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

What can we do about cardiotoxicity?

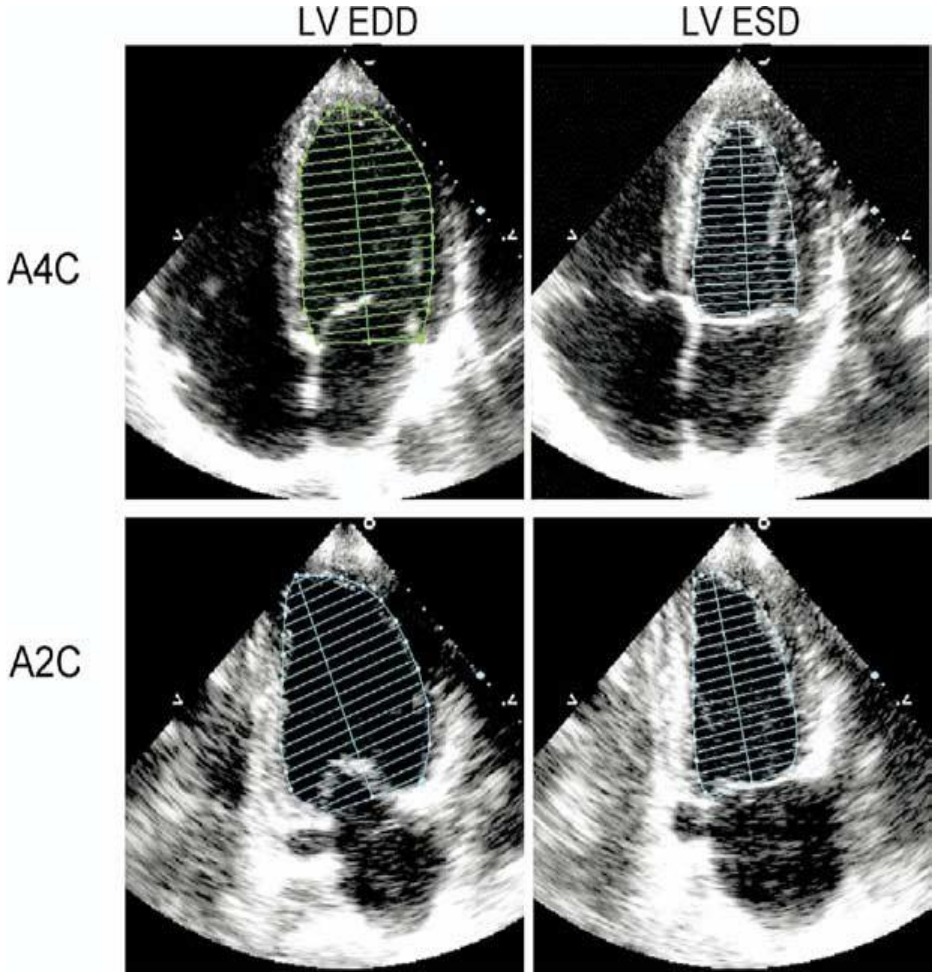
EARLY DETECTION

Modalities for Early Detection of CTRCD

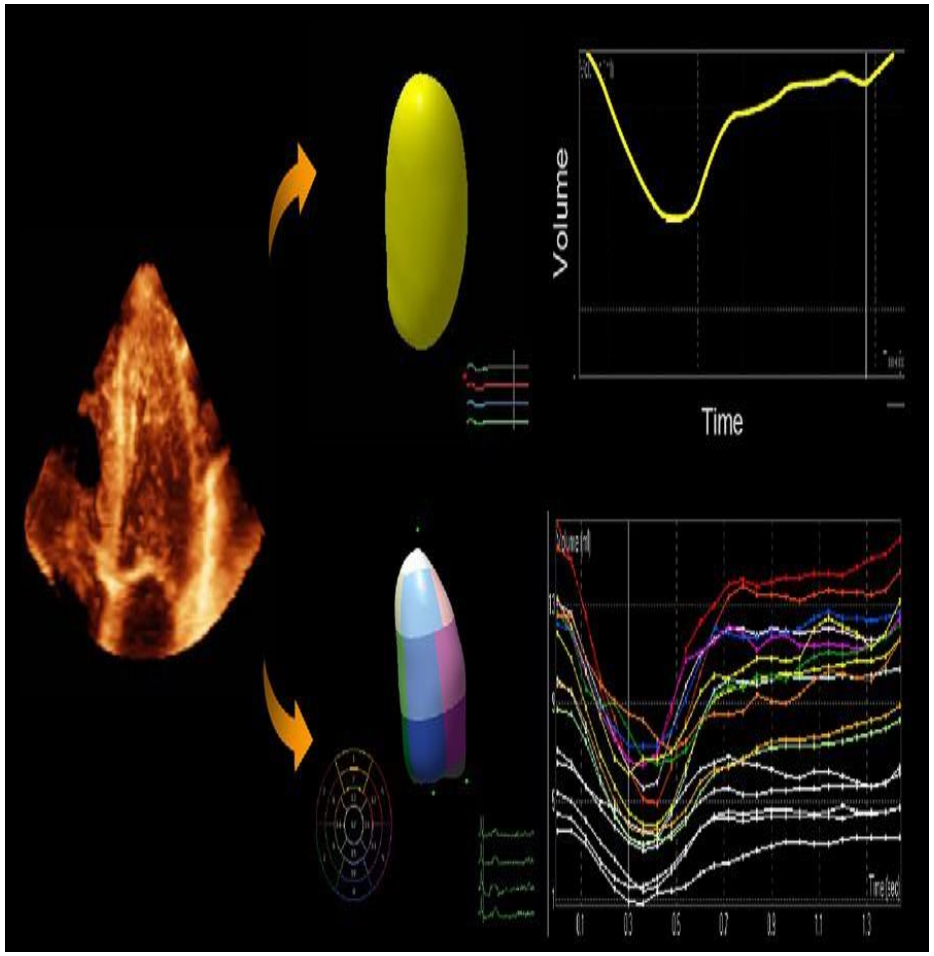
- Desirable features
  - Detects injury signal before LV impairment
  - Detects LV signal before symptoms
  - Highly predictive of clinically significant disease
  - Reproducible
  - Widely available
  - Noninvasive
  - Inexpensive
  - Actionable in guiding therapy

LV Ejection Fraction

2D Echo

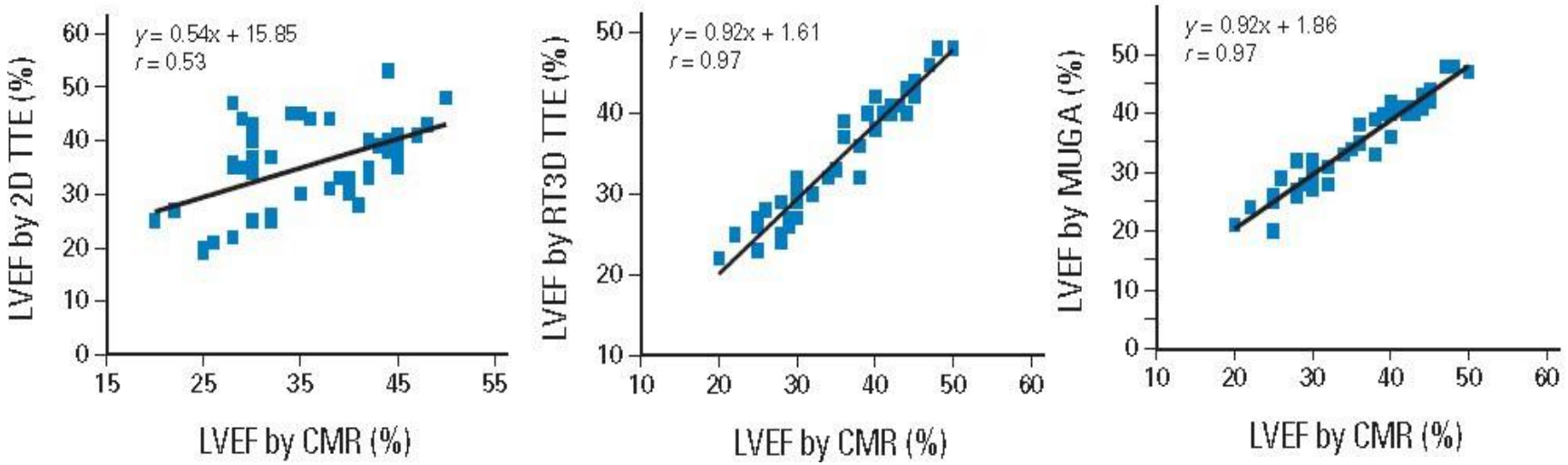


3D Echo

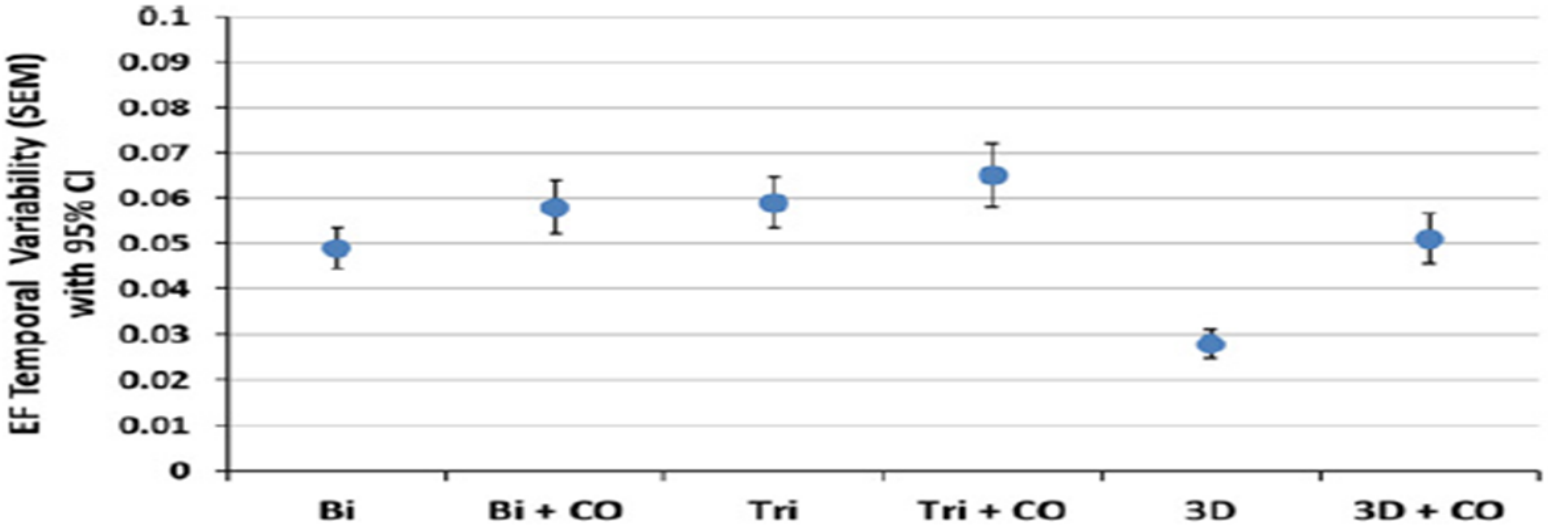


LVEF Sensitivity for Cardiotoxicity

Accuracy and Reproducibility: MRI vs Echo (2D, 3D) LVEF



Walker J et al. *J Clin Oncol*. 2010;28:3429-3436.

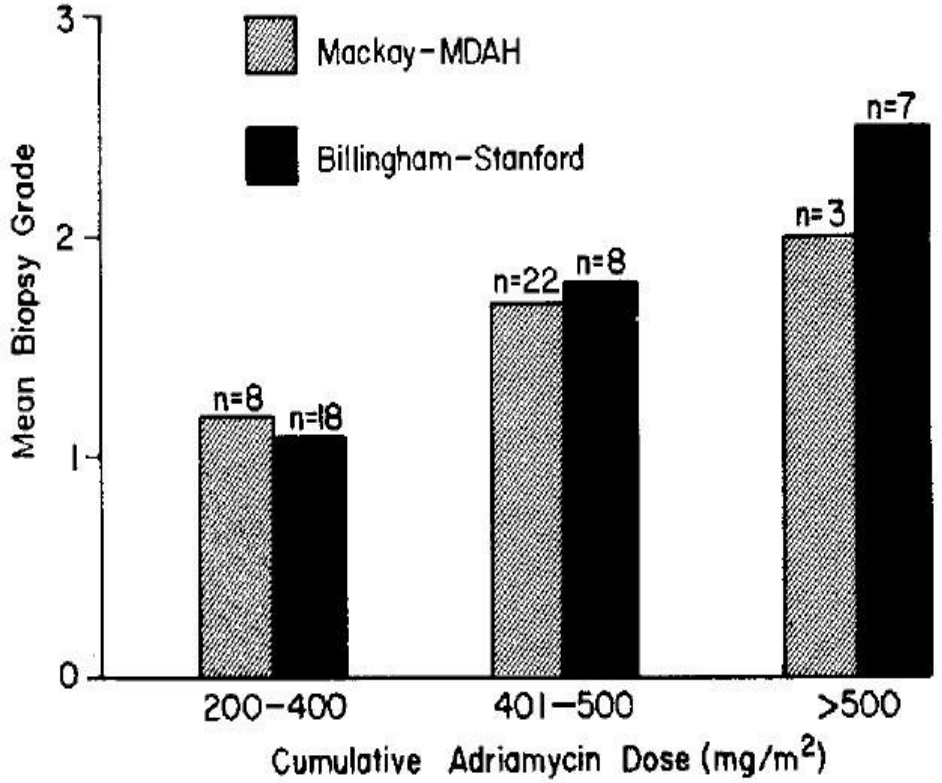


CMR=cardiovascular magnetic resonance; SEM=spatial error model; TTE=transthoracic echocardiogram.

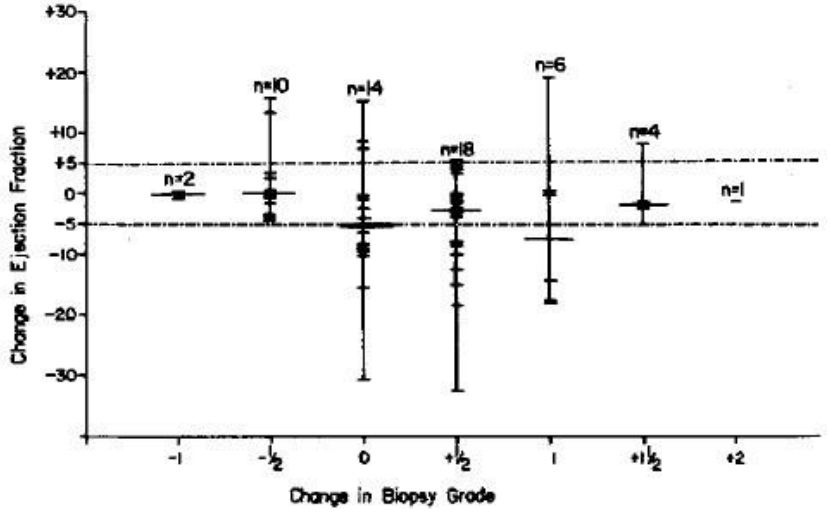
Thavendiranathan P et al. *J Am Coll Cardiol*. 2013;61:77-84.

LVEF Sensitivity for Cardiotoxicity

Discordance with Myocellular Injury



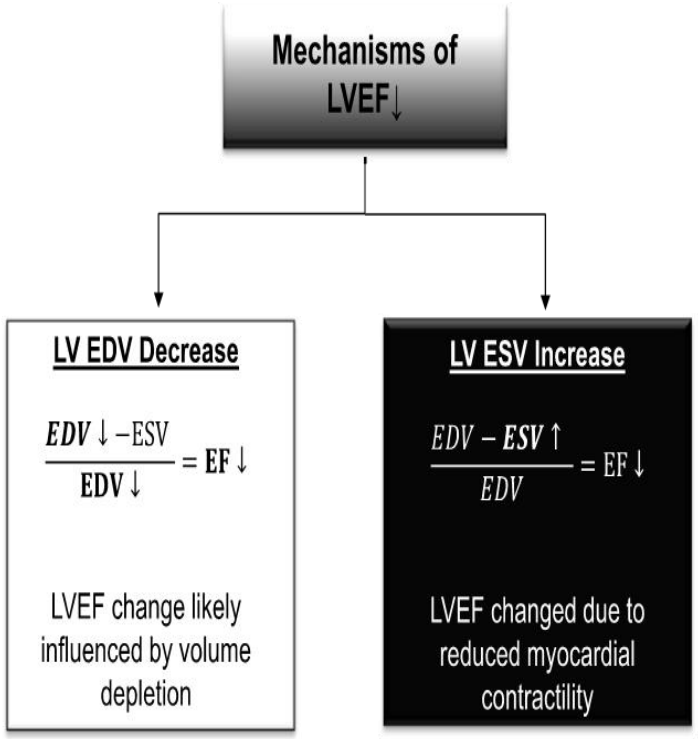
Biopsy Grade	Nuclear Scans (n = 173) No. Patients	Nuclear Scans (n = 173) Mean EF	Echocardiogram (n = 146) No. Patients	Echocardiogram (n = 146) Mean EF
0	16	63%	16	65%
0.5	50	66%	43	66%
1.0	55	62%	46	67%
1.5	21	58%	19	61%
2.0	20	61%	15	62%
3.0	11	61%	7	65%

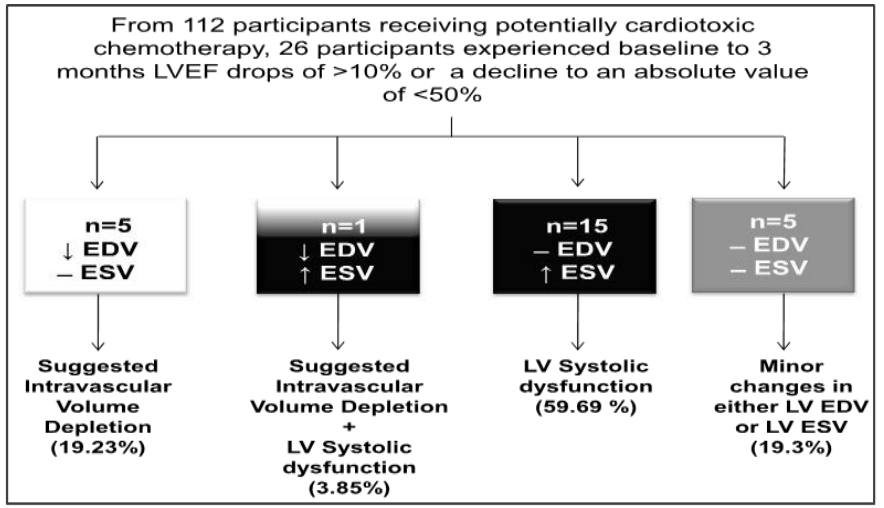


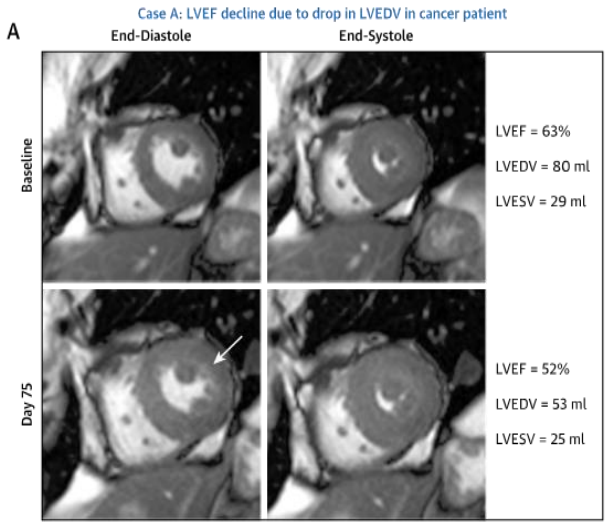
Ewer MS et al. *J Clin Oncol*. 1984;2:112-117.

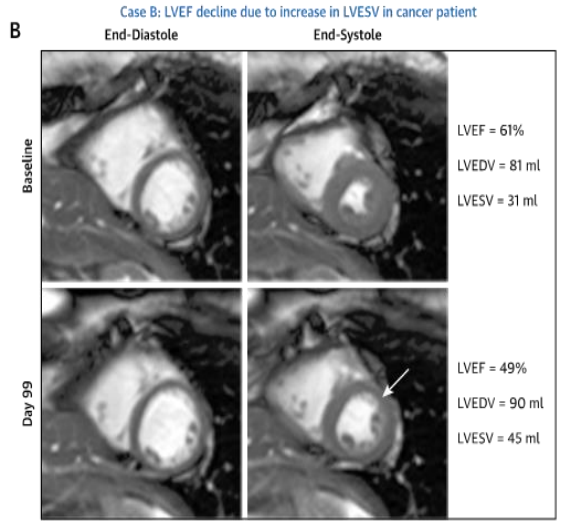
LVEF Sensitivity for Cardiotoxicity

Susceptibility to Loading Conditions









EDV=end-diastolic volume; ESV=end-systolic volume.

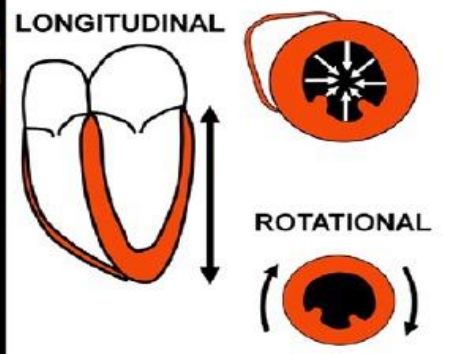
Meléndez GC et al. *Am J Cardiol*. 2017;119:1637-1642.

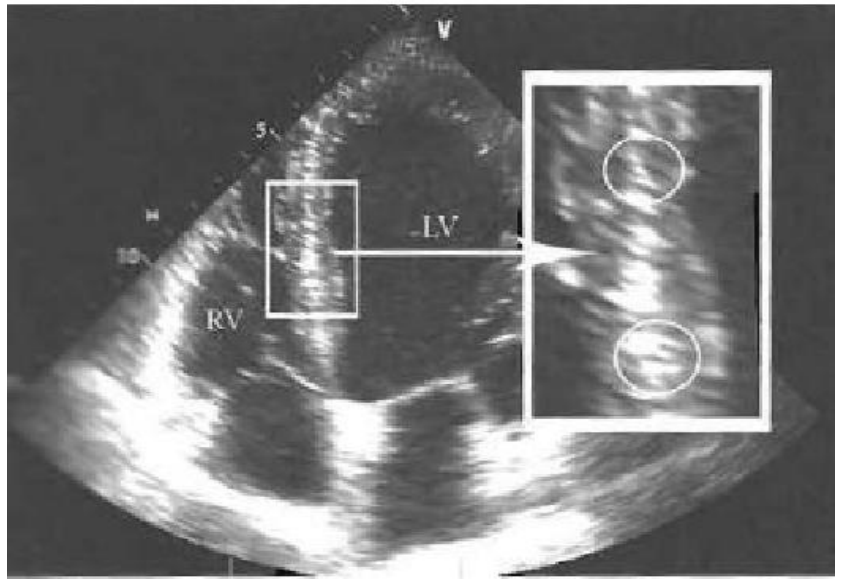
What can we do about cardiotoxicity?

- ~~LVEF~~ - STRAIN

Advances in Imaging-based Screening

Speckle-tracking Strain Echocardiography





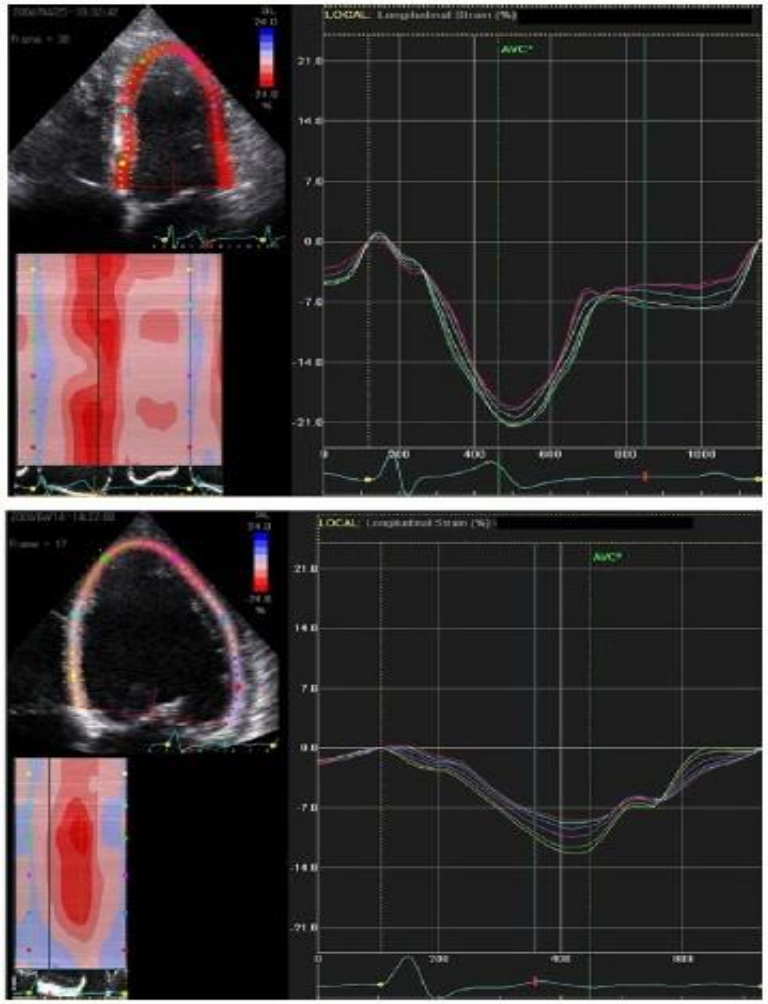
Strain Tissue deformation

L_0 L_1

10 cm → 8 cm

-20%

Strain
% change from resting dimension

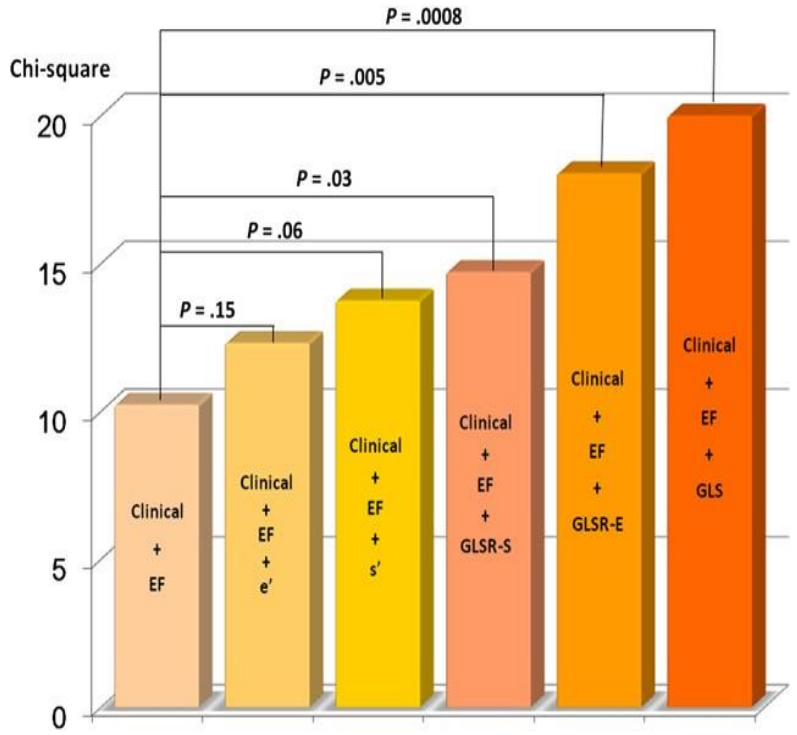


Gorcsan J, Tanaka H. *J Am Coll Cardiol*. 2011;58:1401-1413.

Advances in Imaging-based Screening

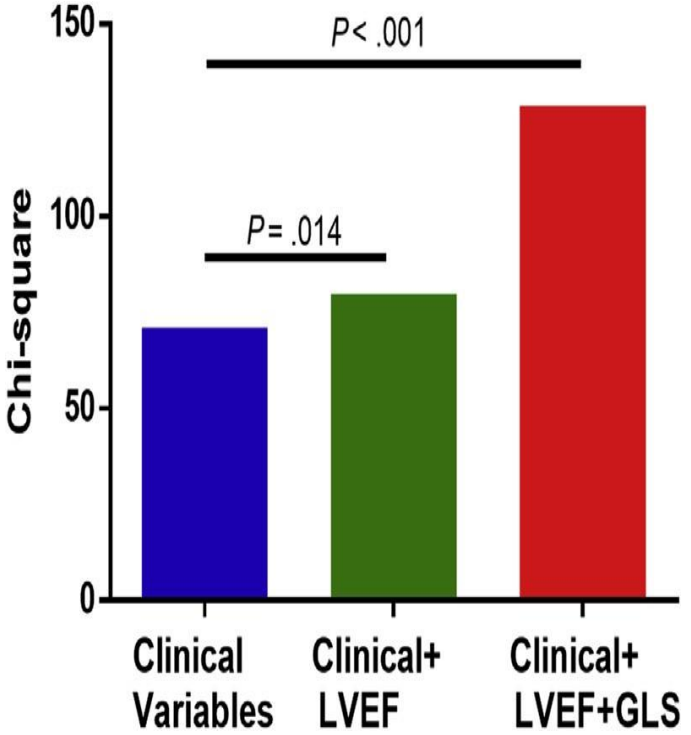
Traditional and Novel Parameters

CTRCD



Negishi K et al. *J Am Soc Echocardiogr*. 2013;26:493-498.

Cardiac Events

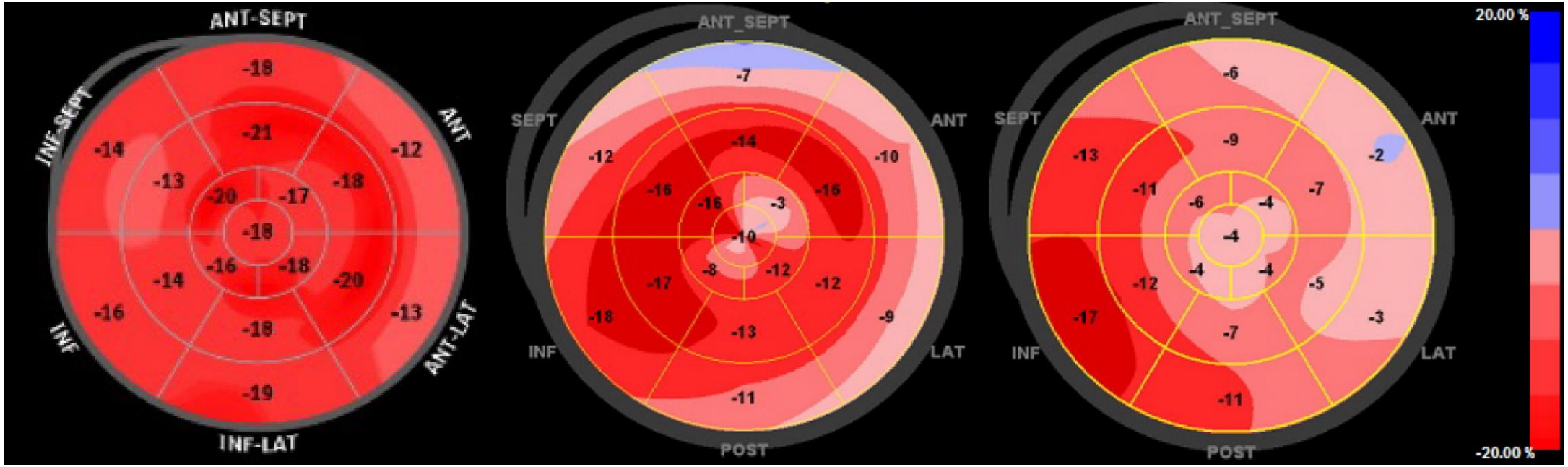


Ali MT et al. *J Am Soc Echocardiogr*. 2016;29:522-527.

GLS=global longitudinal peak systolic strain; GLSR-E=global longitudinal early diastolic strain rate; GLSR-S=GLS rate.

Early Detection

Longitudinal Strain vs 3D Echo LVEF



Post-TCPH Pre-Trastuzumab	
LVEF	54%
GLS	–17%

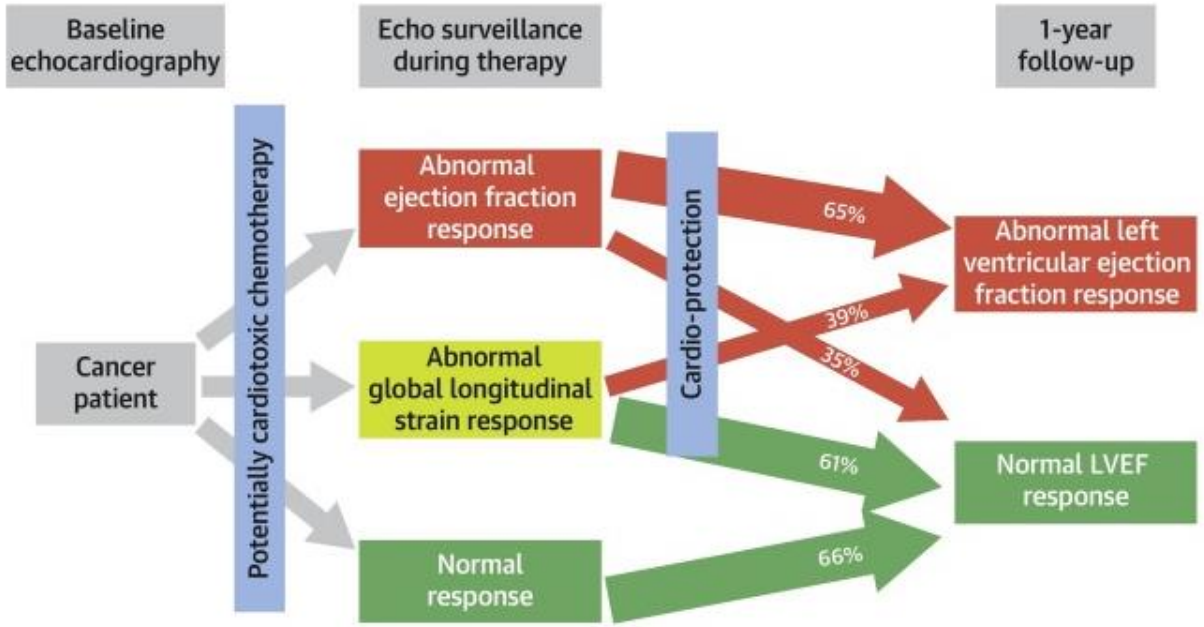
Trastuzumab x 3M Pre-Pertuzumab	
LVEF	53%
GLS	–11%

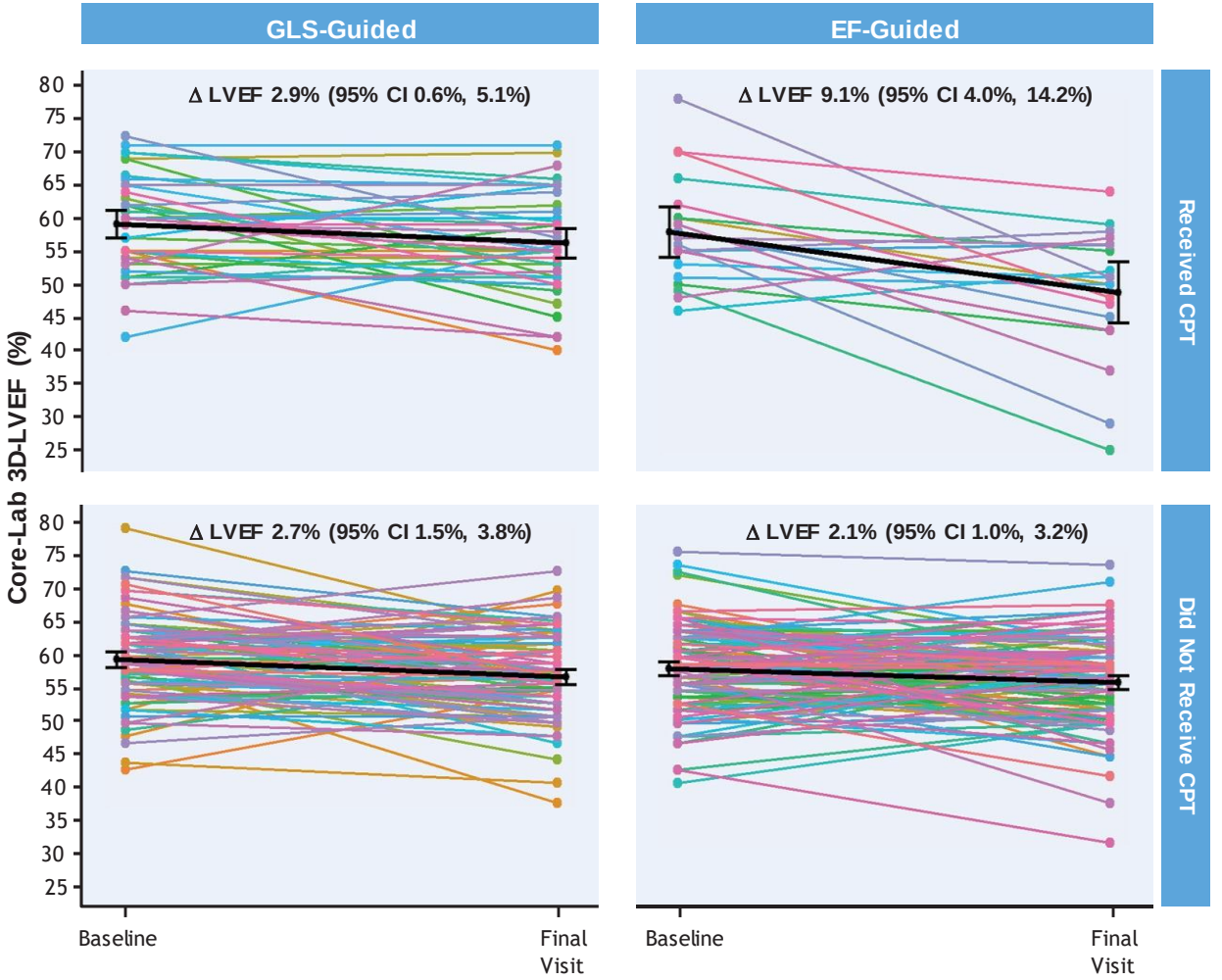
Trastuzumab x 5M Pertuzumab x 2M	
LVEF	29%
GLS	–7%

TCPH=docetaxel, carboplatin, trastuzumab, and pertuzumab.
REFERENCE??

Early Detection

Longitudinal Strain vs LVEF Surveillance: SUCCOUR Trial





CPT=cardioprotective therapy.

Thavendiranathan P et al. *J Am Coll Cardiol*. 2021;77:392-401.

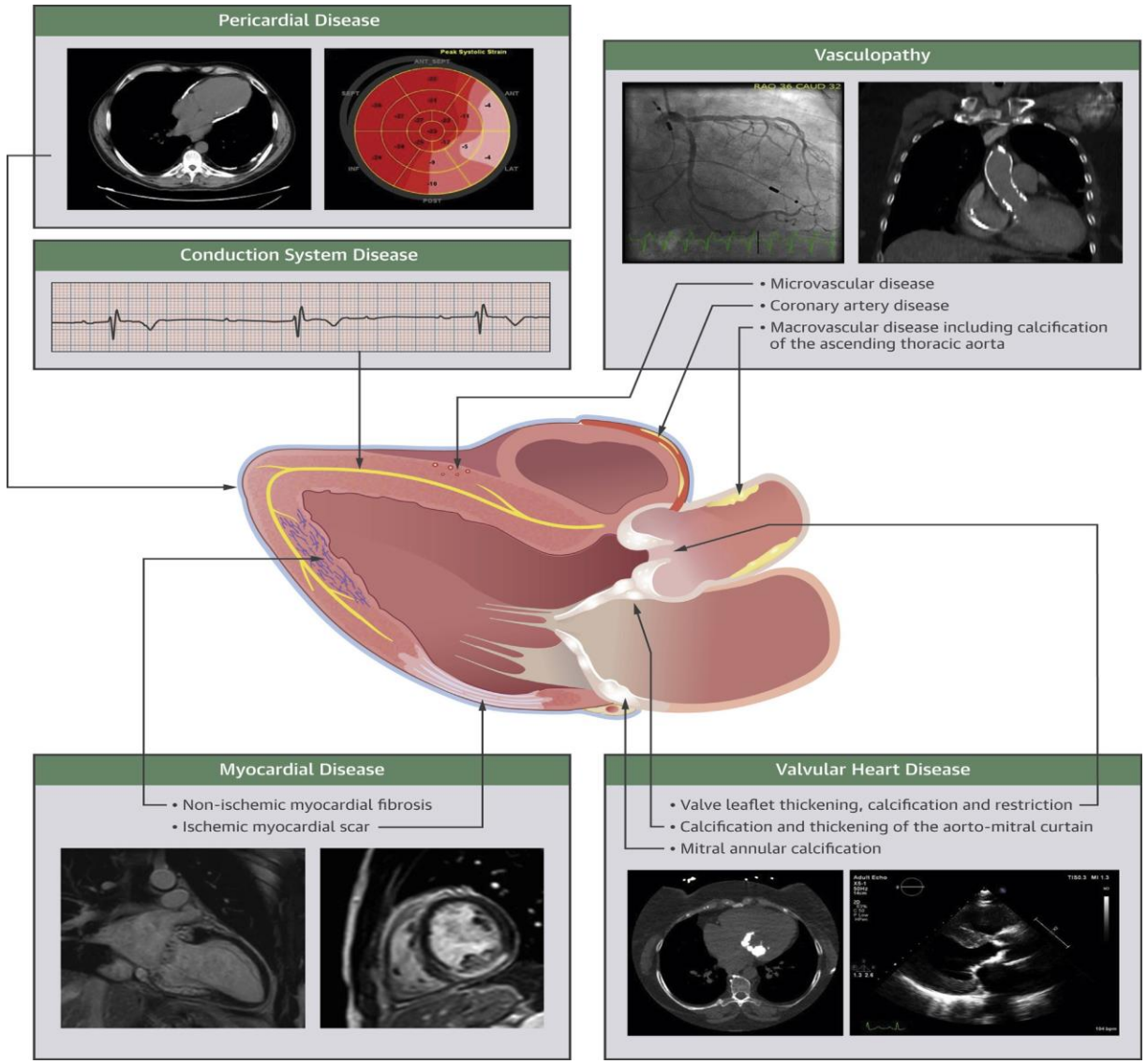
What can we do about cardiotoxicity?

- ~~LVEF~~ - STRAIN?
- MULTI-MODALITY IMAGING

Radiation-induced CV Disease: Multimodality Imaging Approach

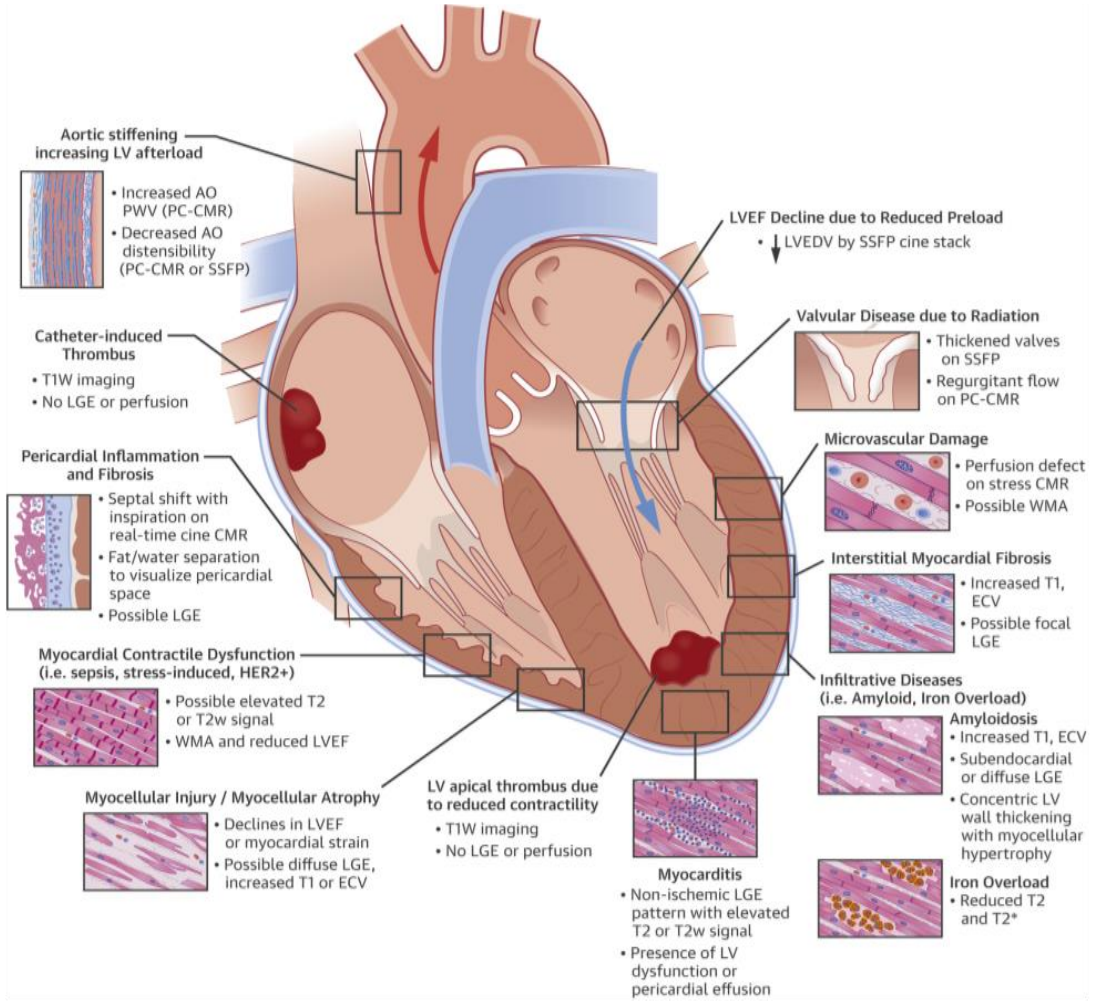
- Late manifestation occurring years-decades after treatment
- Results from diffuse interstitial fibrosis and collagen deposition
- Luminal narrowing of arteries and arterioles; accumulation of myofibroblasts and intimal proliferation
- Myocardial fibrosis, VHD (regurgitation or stenosis); CAD; pericardial disease and conduction system disease
- Often overlap of pathologies within individuals
- Non-specific symptoms: fatigue, dyspnea

VHD=valvular heart disease.

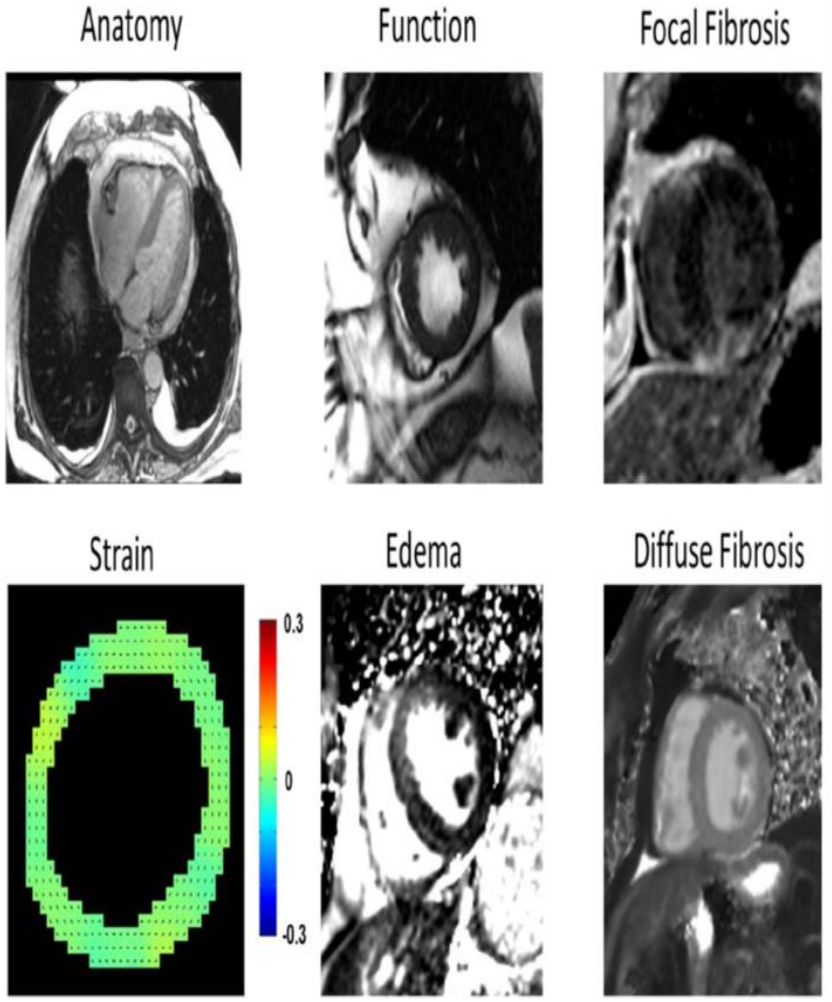


Desai MY et al. *JACC Cardiovasc Imaging*. 2018;11:1132-1149.

Cardiac Magnetic Resonance: Comprehensive Cardiovascular Evaluation



Jordan JH et al. *JACC Cardiovasc Imaging*. 2018;11:1150-1172.



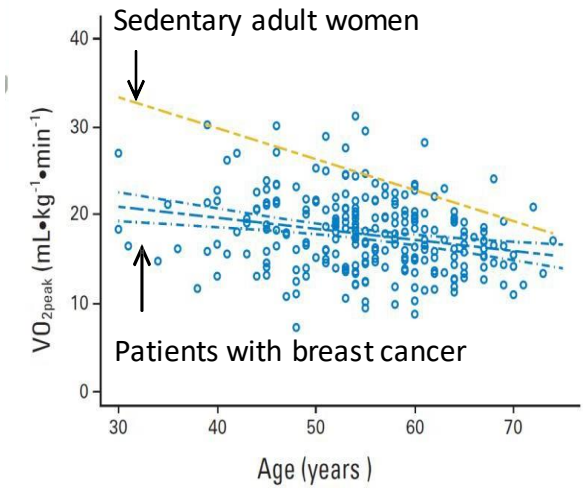
Löffler, Salerno M. *J Nucl Cardiol*. 2018;25:2148-2158.

Physiologic Measures of CV Reserve: Exercise Testing

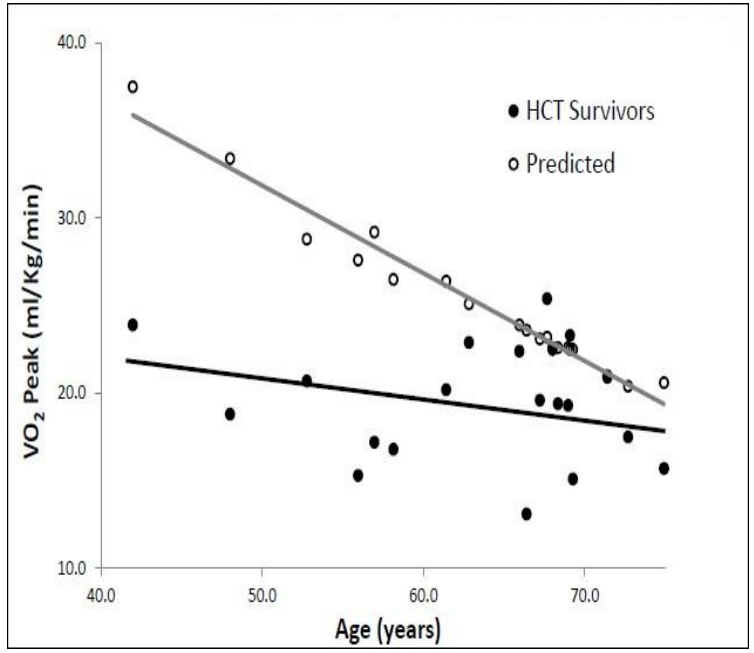
VO_{2peak}

Product of cardiac output and A-V oxygen difference

Inversely correlated with death from CV disease and all-cause mortality



Jones LW et al. *J Clin Oncol*. 2012;30:2530-2537.



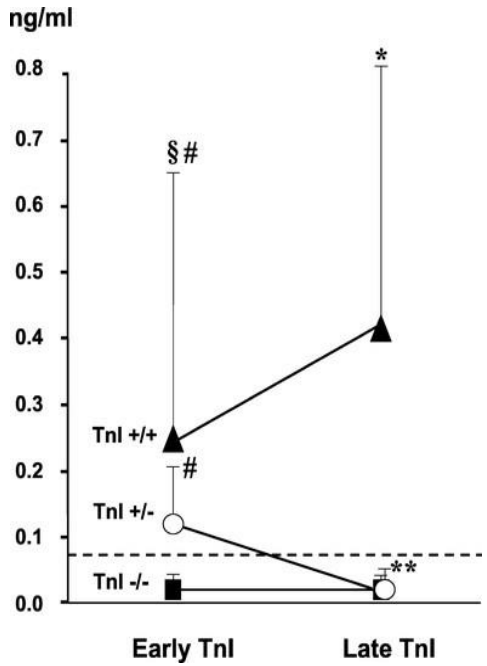
Armenian SH et al. *Biol Blood Marrow Transplant*. 2017;23:700-705.

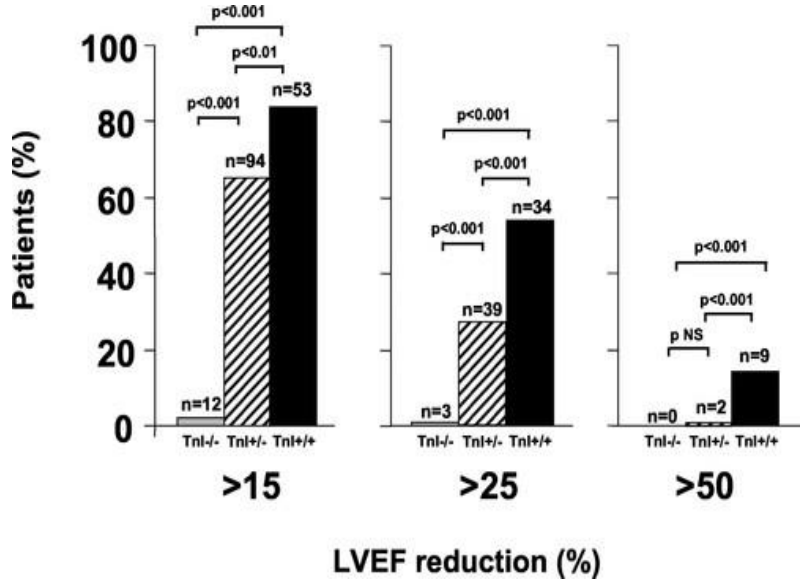
What else can we do about cardiotoxicity?

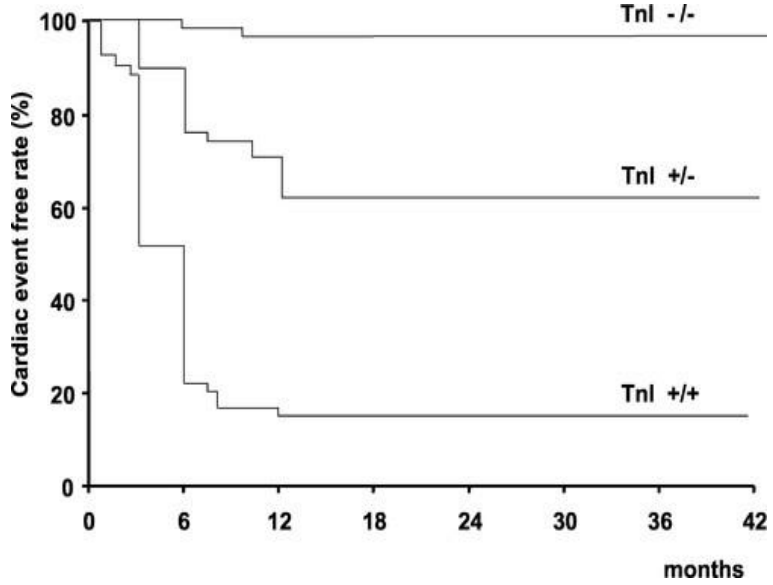
- ~~LVEF~~ - STRAIN?
- MULTI-MODALITY IMAGING?
- BLOOD BIOMARKERS

Blood Biomarkers

Elevated Troponin I After Anthracyclines Indicates Risk





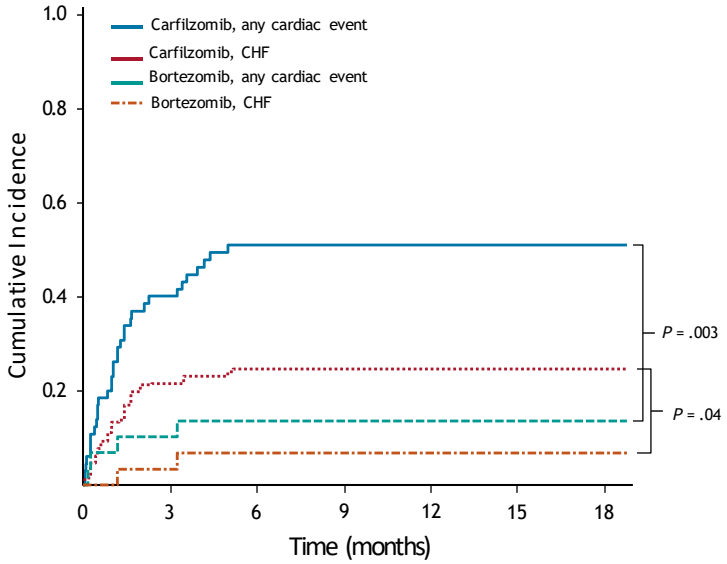


TnI=troponin I.

Cardinale D et al. *Circulation*. 2004;109:2749-2754.

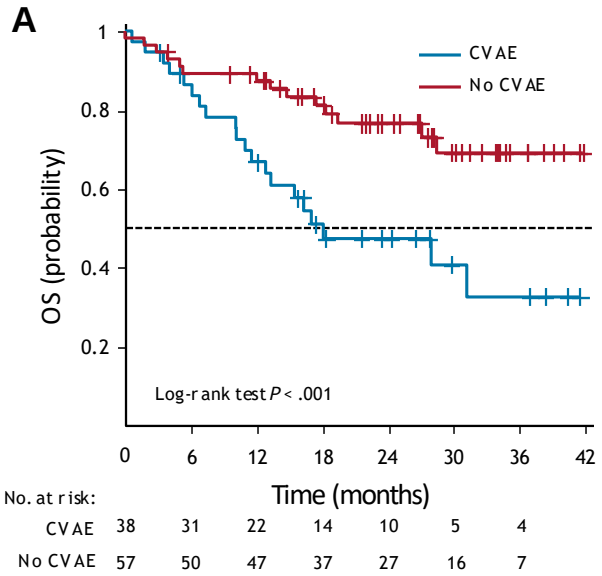
Blood Biomarkers

Elevated Natriuretic Peptides with Proteosome Inhibitors Indicate Risk



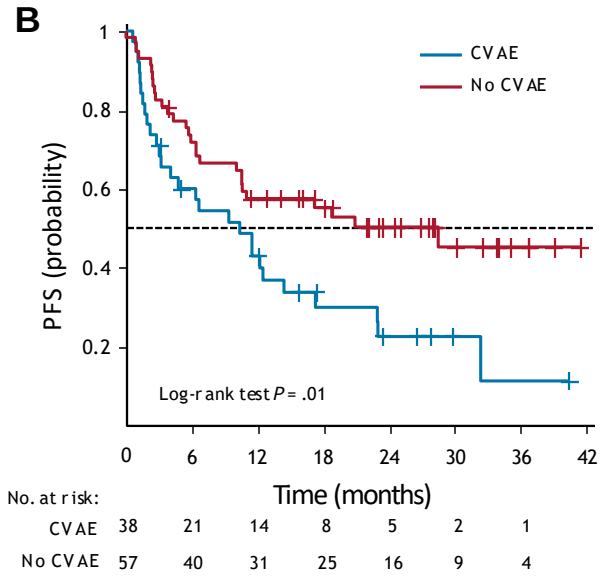
No. at risk:

Carfilzomib, any cardiac event	65	39	27	27	26	22	21
Carfilzomib, CHF	65	51	41	40	36	30	28
Bortezomib, any cardiac event	30	26	23	23	21	19	16
Bortezomib, CHF	30	29	26	26	22	20	17



No. at risk:

CVAE	38	31	22	14	10	5	4
No CVAE	57	50	47	37	27	16	7



No. at risk:

CVAE	38	21	14	8	5	2	1
No CVAE	57	40	31	25	16	9	4

TABLE 4. Multivariable Competing Risk Analysis for Predictors of First CVAE

Effect	HR (95% CI)	P
Car lzomib v bortezomib	3.0 (1.1 to 8.4)	.04
Elevated baseline natriuretic peptide levels v normal levels	4.1 (2.1 to 8.1)	, .001
Normal baseline natriuretic peptide levels that became elevated mid– rst cycle of treatment v normal levels	9.5 (4.3 to 20.7)	, .001
# 1 traditional CV risk factor v $ 2	0.5 (0.3 to 0.9)	.02
Time from myeloma diagnosis to enrollment in PROTECT	0.98 (0.6 to 1.5)	.9

CHF=congestive heart failure; CVAE=cardiovascular adverse event.

Cornell RF et al. *J Clin Oncol*. 2019;37:1946-1955.

Blood Biomarkers

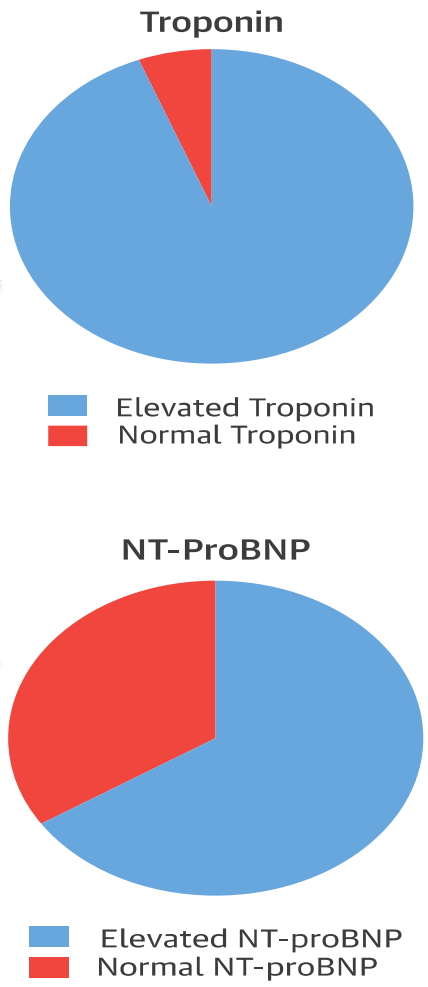
Elevated Troponin Predicts ICI Myocarditis

Laboratory

Troponin
- Preferably Troponin I
- Consider Troponin T, CK-MB, Total CK

Natriuretic Peptides
- NT-pro BNP
- BNP

Sensitivity



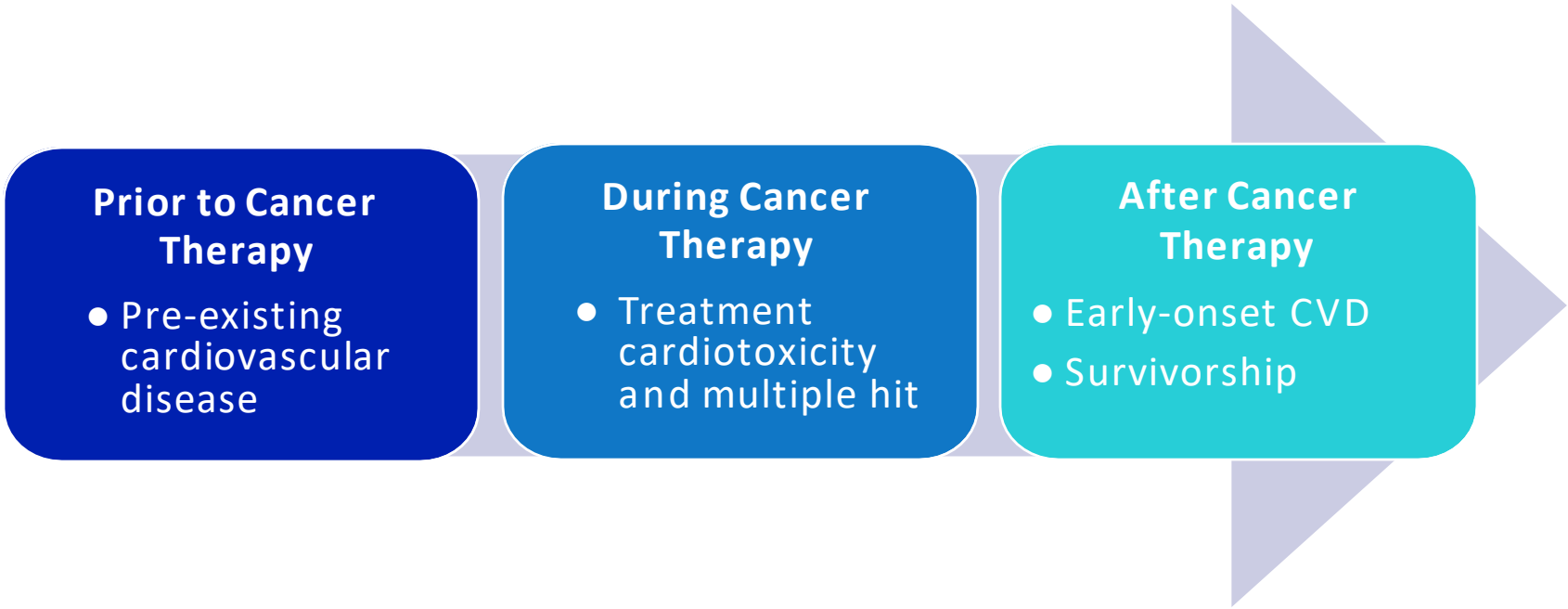
Mahmood, et al. *JACC* 2018
N = 35

Prediction

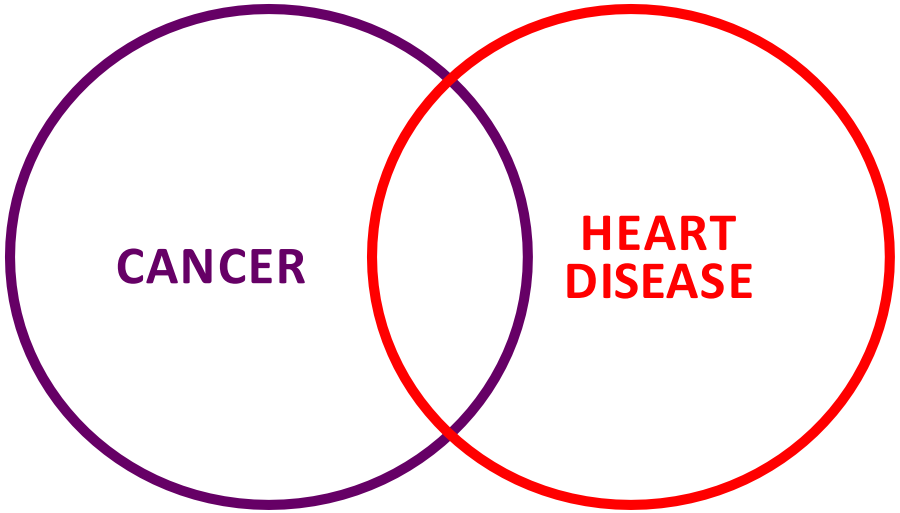
TABLE 6 Risk of MACE in Univariable and Multivariable Fine-Gray Hazard Model With Noncardiovascular Death as a Competing Event

	Univariable		Multivariable*	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age at start	0.98 (0.95-1.02)	0.44		
Female	0.92 (0.45-1.89)	0.82		
ICI	1.18 (0.57-2.43)	0.66	0.63 (0.29-1.35)	0.23
Nivolumab	1.16 (0.54-2.51)	0.70		
Pembrolizumab	1.14 (0.47-2.75)	0.77		
Atezolizumab	0.71 (0.17-3.03)	0.64		
Elevated troponin I (>0.01 ng/ml)	9.82 (4.91-19.66)	<0.001	7.27 (2.72-19.43)	<0.001
Initial troponin (in ng/ml)	1.01 (0.99-1.02)	0.54		
Peak troponin (in ng/ml)	1.01 (0.99-1.02)	0.20		
Elevated BNP (>100 pg/ml)	5.14 (2.36-11.20)	<0.001	2.65 (1.01-6.92)	0.047

Chitturi, et al. *JACC CO* 2019
N = 30


Prior to Cancer Therapy
Pre-existing cardiovascular disease
During Cancer Therapy
Treatment cardiotoxicity and multiple hit
After Cancer Therapy
Early-onset CVD
Survivorship

Cancer Increases Risk for Subsequent CV Disease

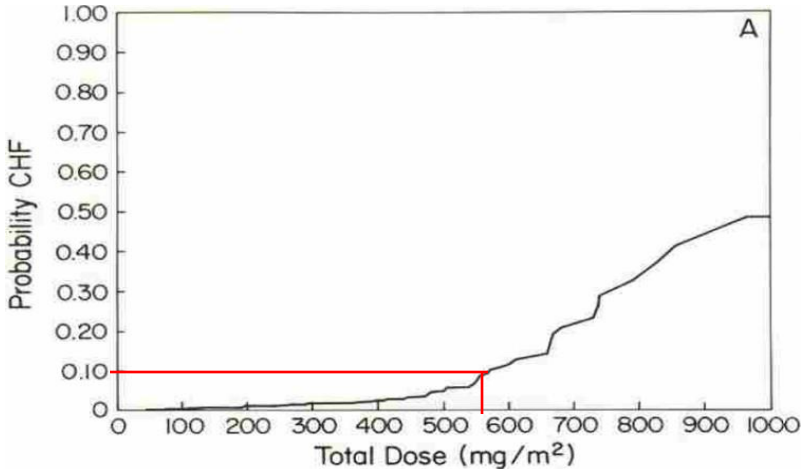


- Survivors have a 10 times higher risk for **coronary atherosclerosis**
- Survivors have a 15 times higher risk of **heart failure**
- Survivors have a 9.3 times the risk for **stroke**
- Risks are particularly high among survivors who had received **anthracycline drugs**, such as doxorubicin, or **high-dose radiation** therapy to the chest as part of their cancer treatment

Oeffinger KC et al. *N Engl J Med*. 2006;355:1572-1582.

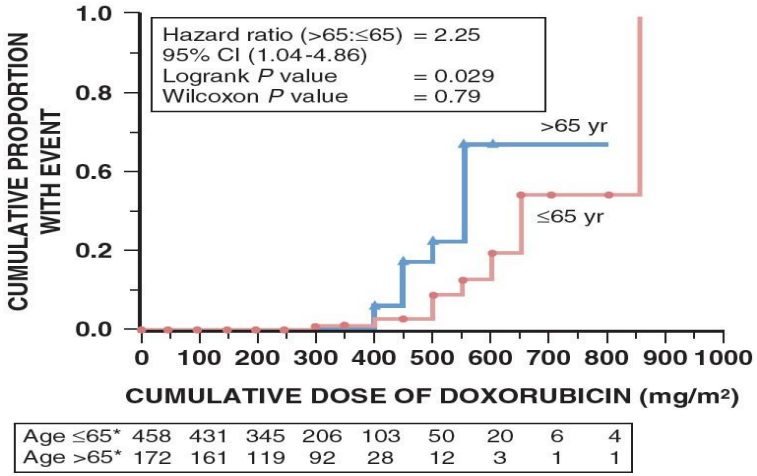
Early-onset Anthracycline Cardiomyopathy

Chart Review



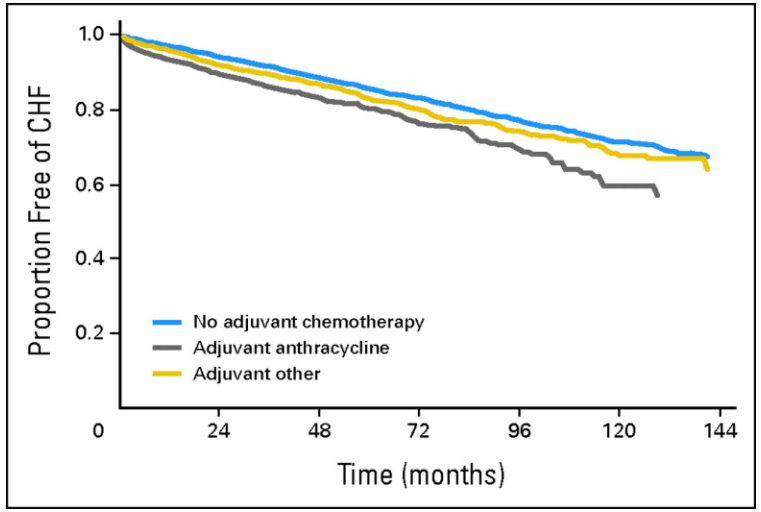
Von Hoff DD et al. *Ann Intern Med*. 1979;91:710-717.

Imaging



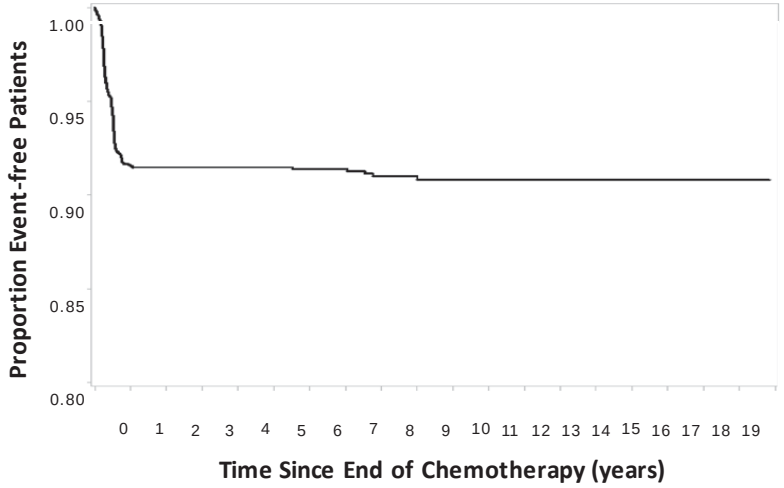
Swain SM et al. *Cancer* 2003;97:2869-2879.

Medicare SEER



Pinder MC et al. *J Clin Oncol*. 2007;25:3808-3815.

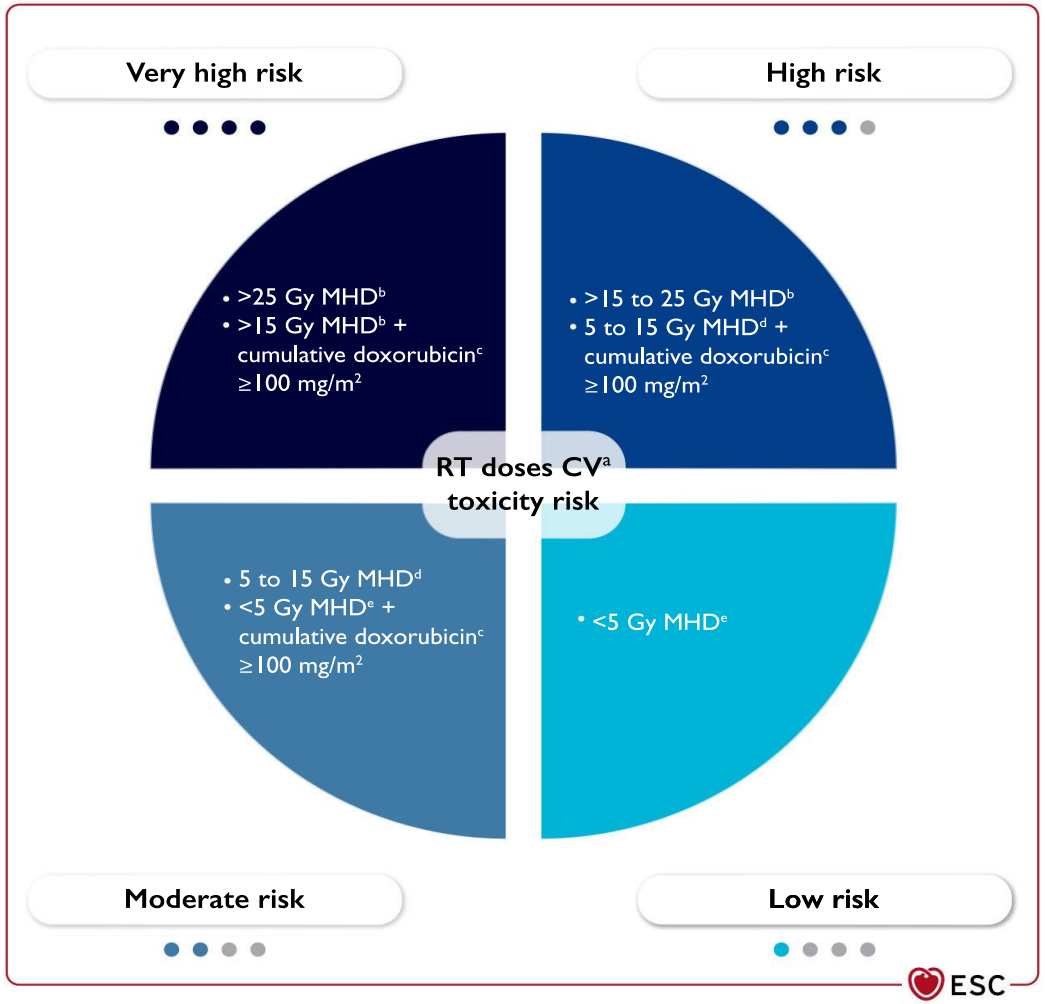
Timing

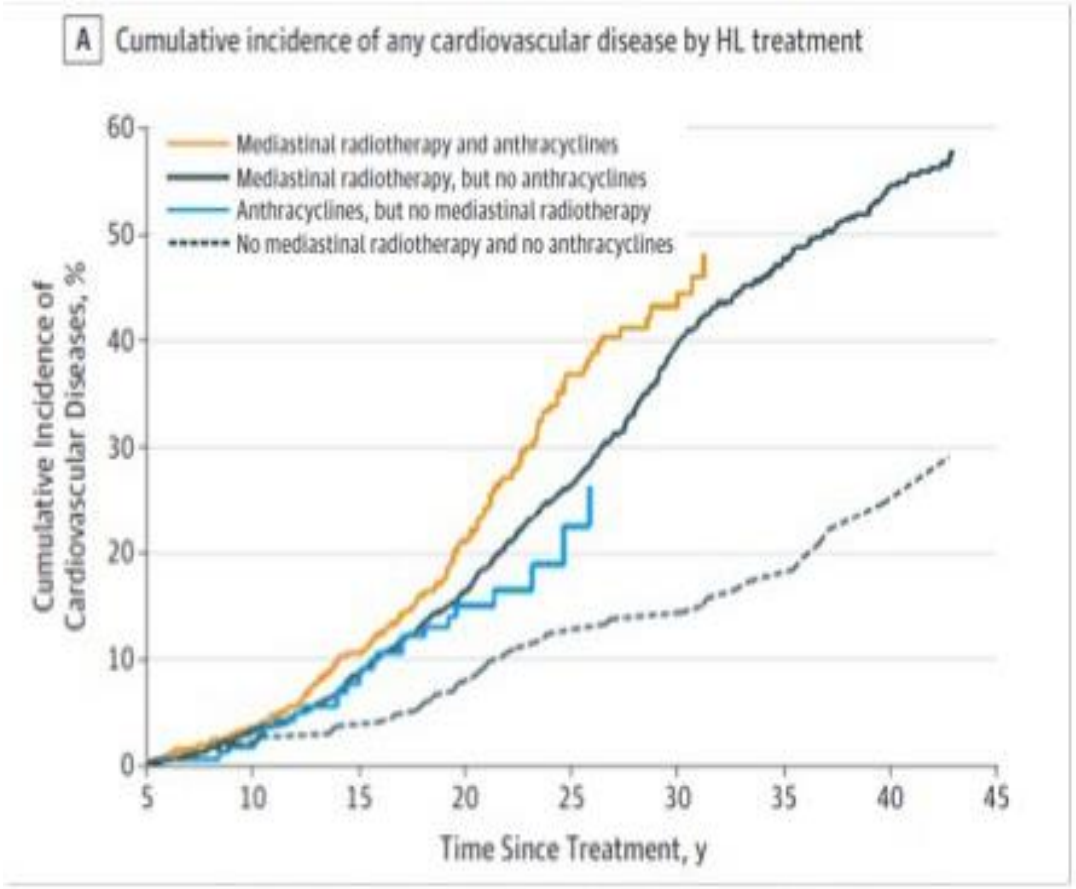


Cardinale D et al. *Circulation*. 2015;131:1981-1988.

CV Disease in Cancer Survivorship

CV Disease After Hodgkin's Treatment





2,524 HL survivors (81% radiation, 31% anthracyclines)
Median follow-up 20 years

Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

van Nimwegen FA et al. *JAMA Intern Med*. 2015;175:1007-1017.

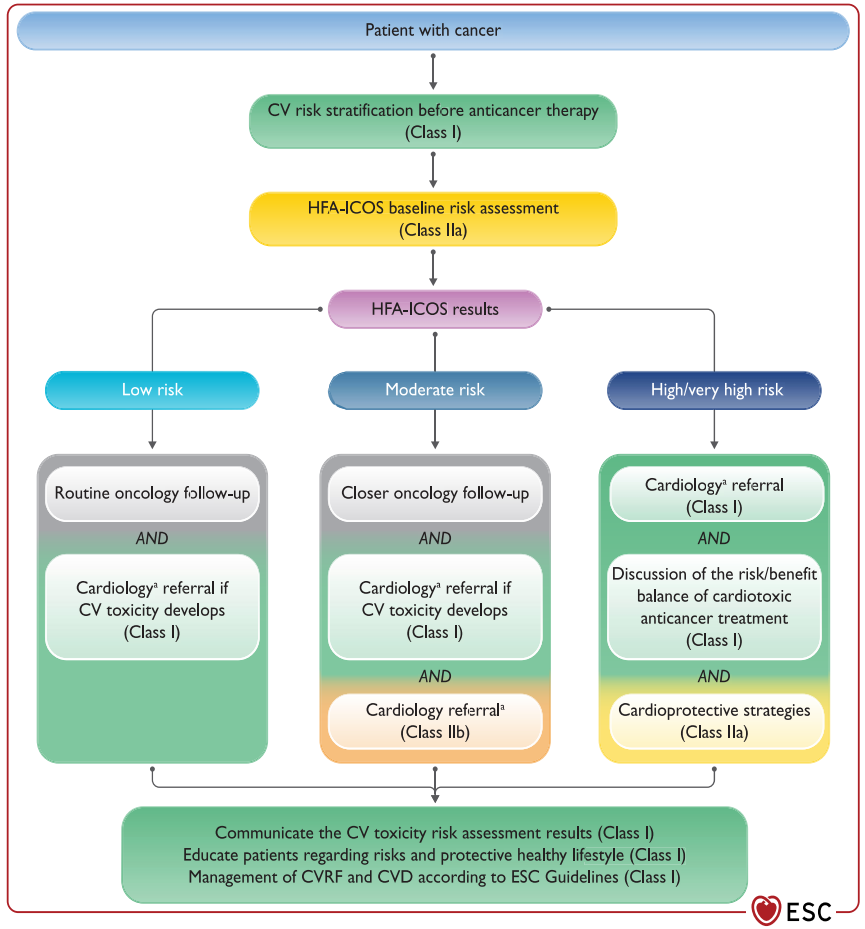
Conclusions

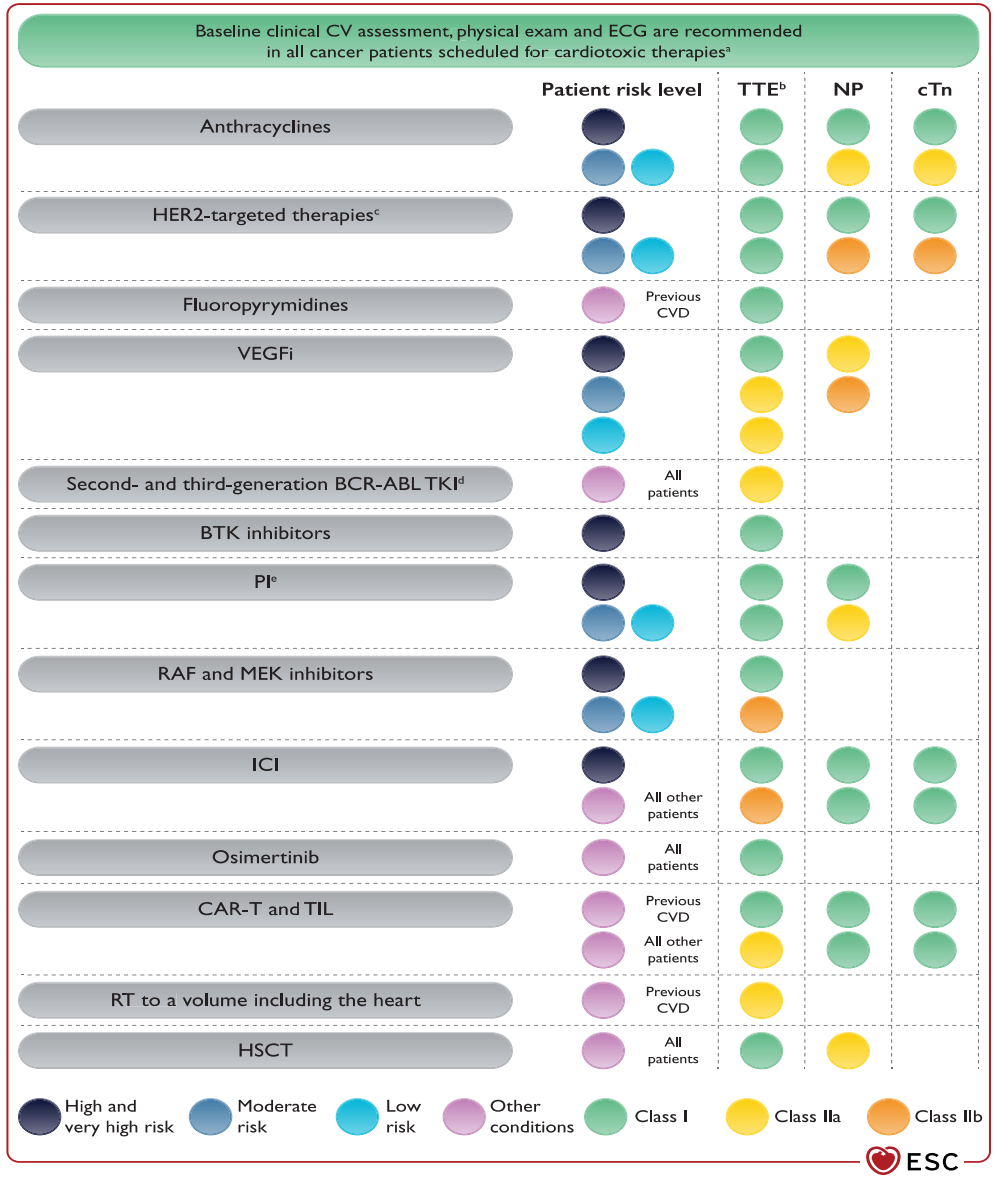
- Growing number of cancer patients and survivors are at risk for developing CVD which threatens to undermine successes of cancer-specific outcomes
- Longitudinal studies are needed to characterize CV disease in cancer patients
- Improving awareness for baseline CV risk factors is the key, first step for CV risk attenuation in cancer
- Cardiac imaging- and blood-based assessment are helpful
  - Accuracy and reproducibility are crucial
  - Optimal use and timing have yet to be defined
- Collaborative efforts are needed to translate observational studies into prevention research
- Evidence-based guidelines must also address the cost effectiveness of screening recommendations

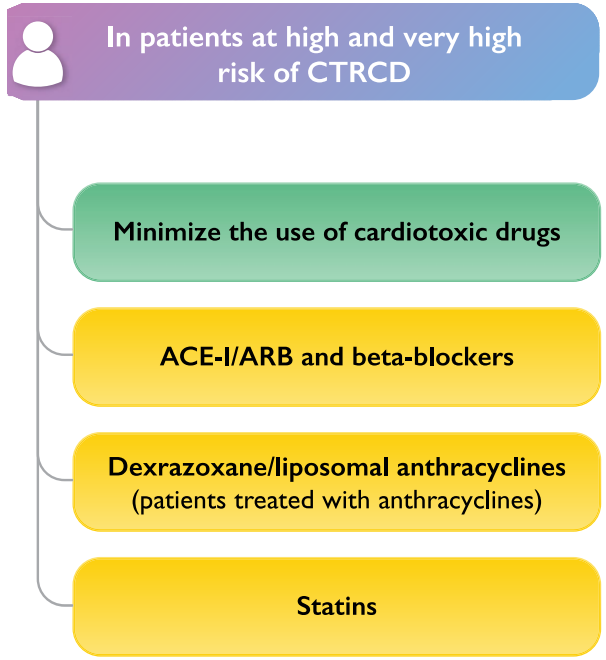
Thank You

Supplemental Resources
Cardio-Oncology Approaches

CV risk stratification and prevention



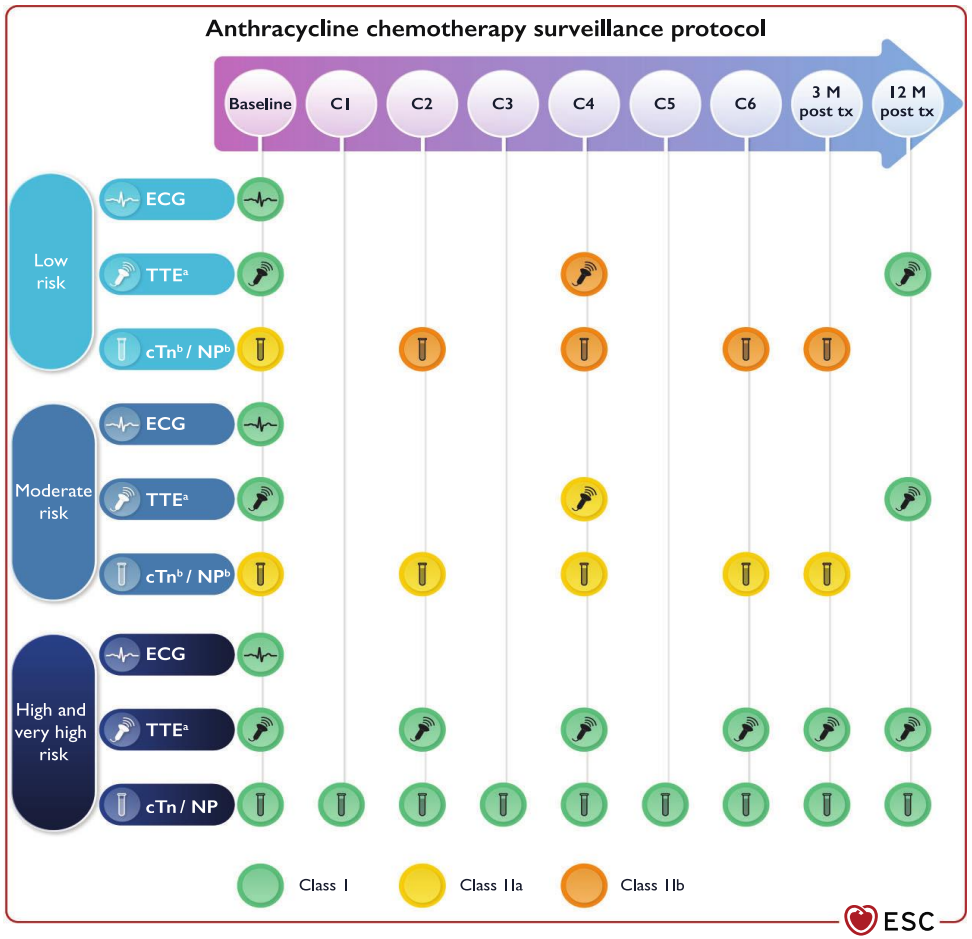


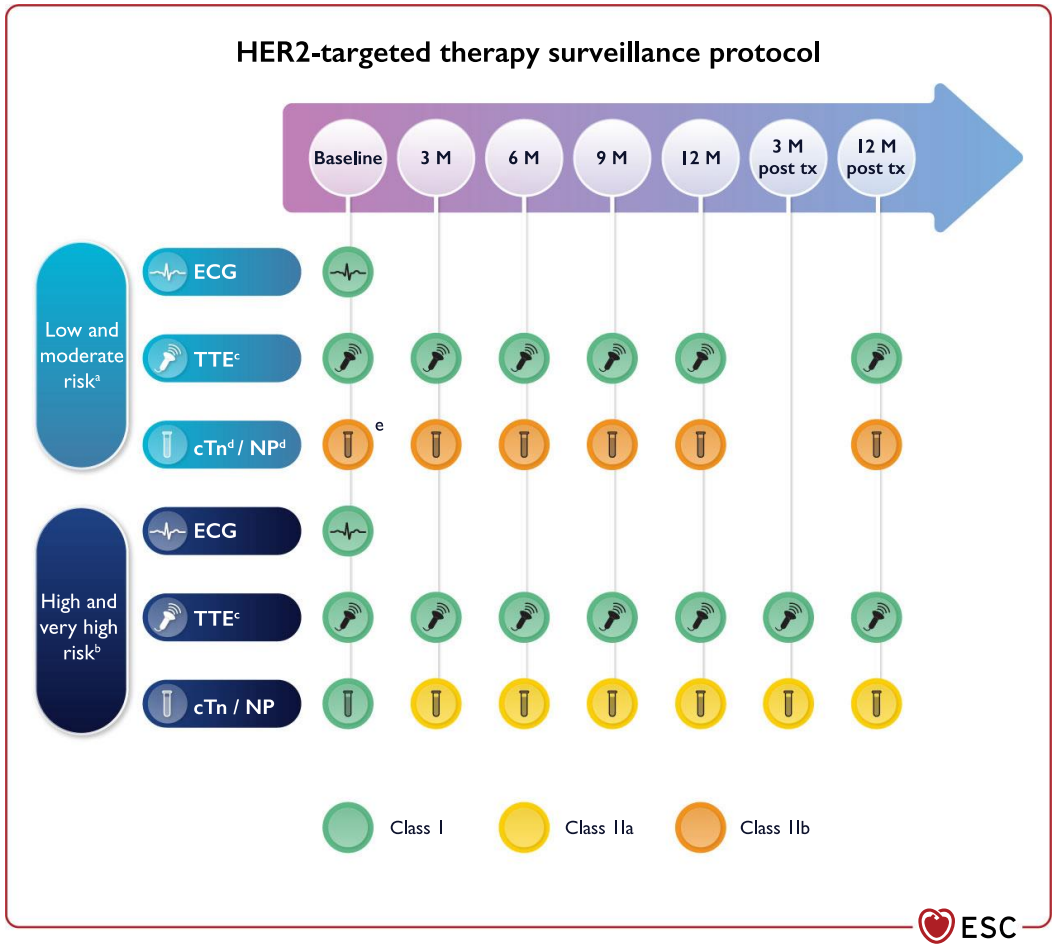


Class I Class IIa

Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

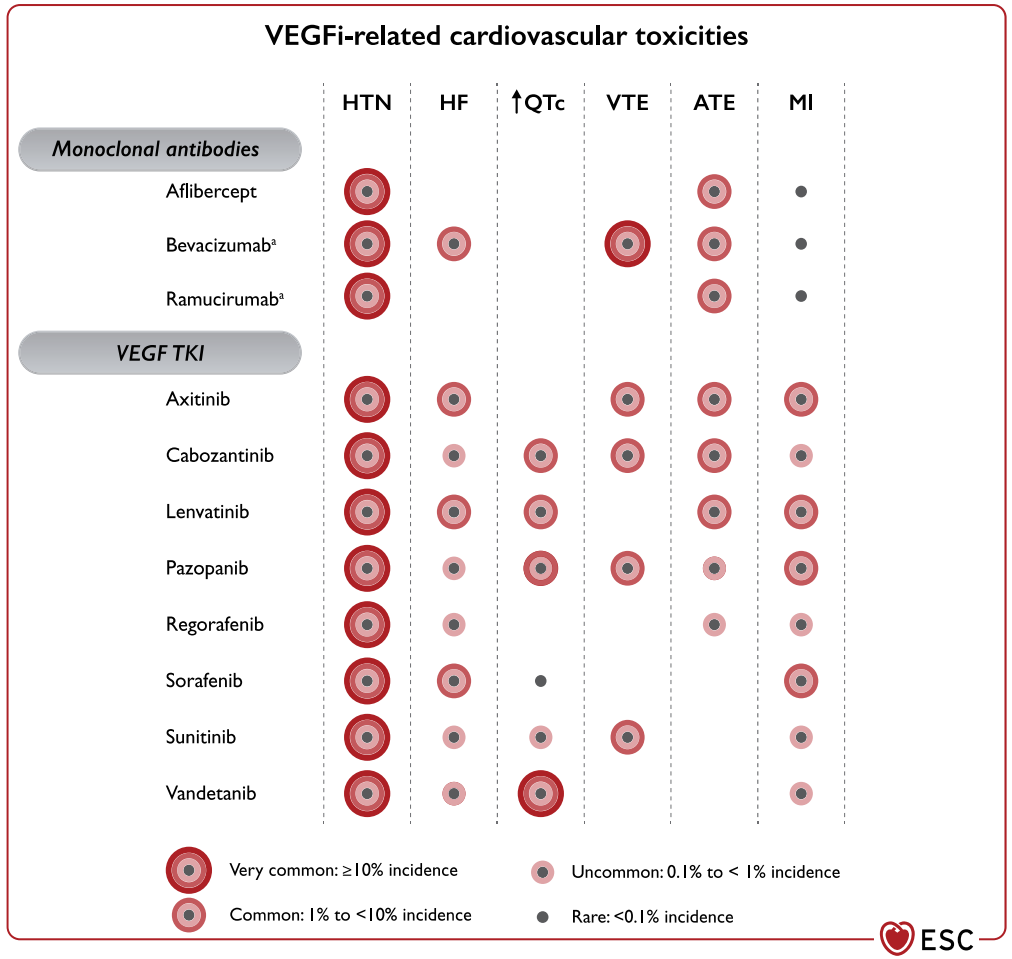
Anthracyclines and anti-HER2 therapies

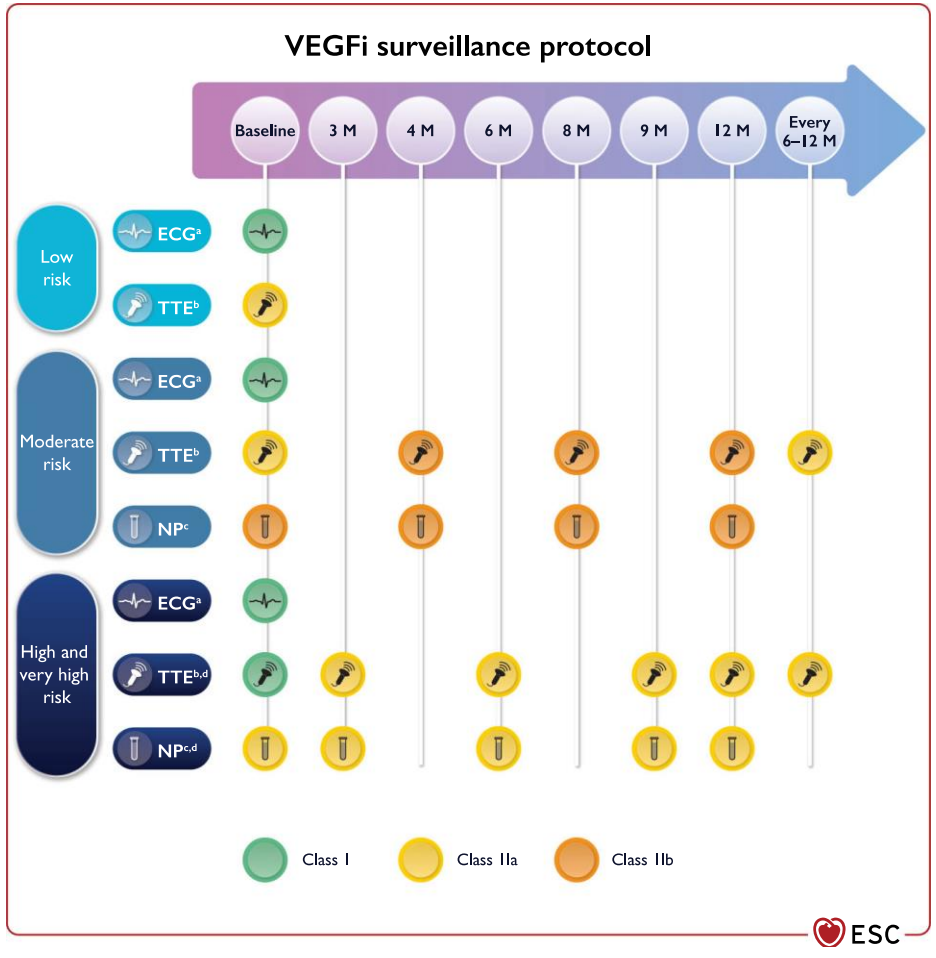




Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

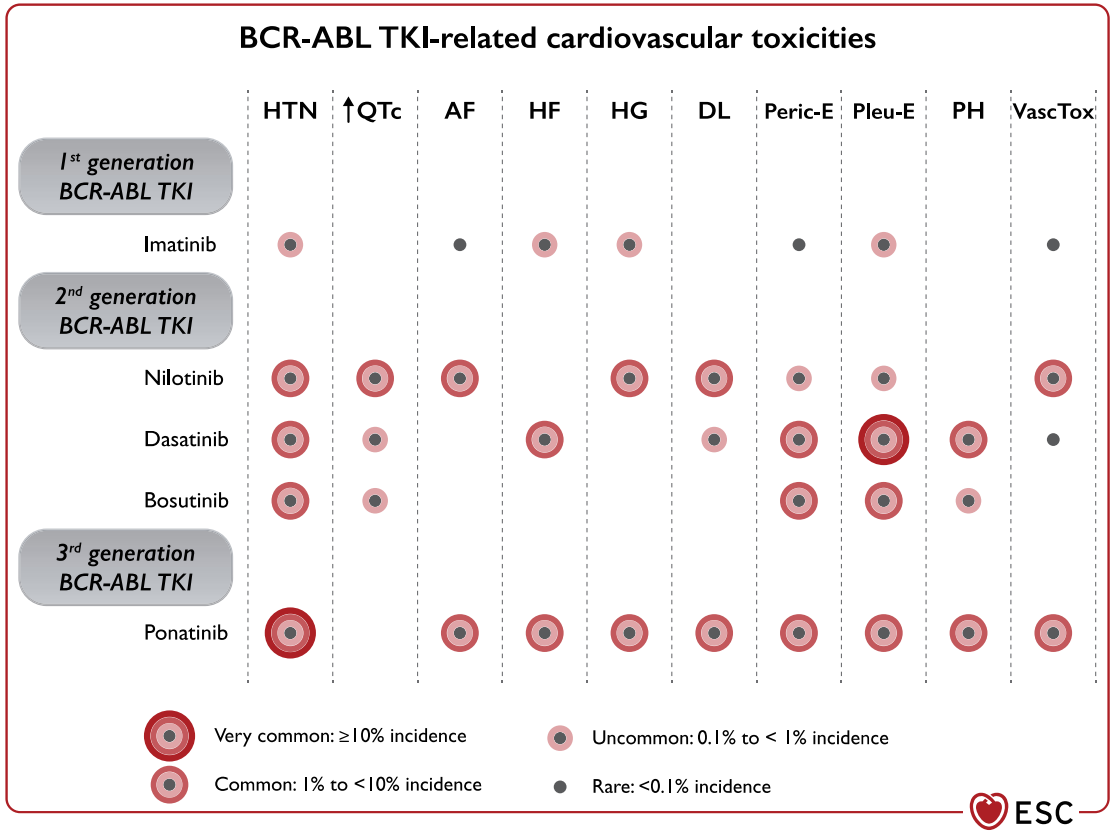
VEGF inhibitors

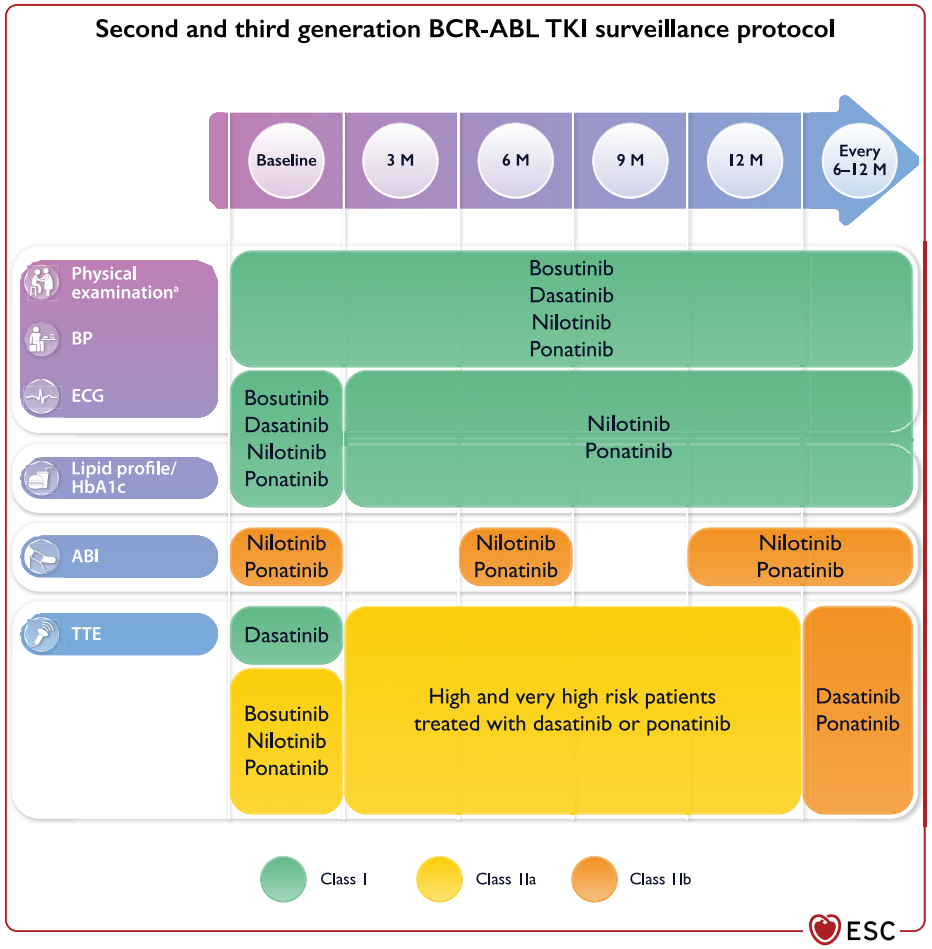




Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

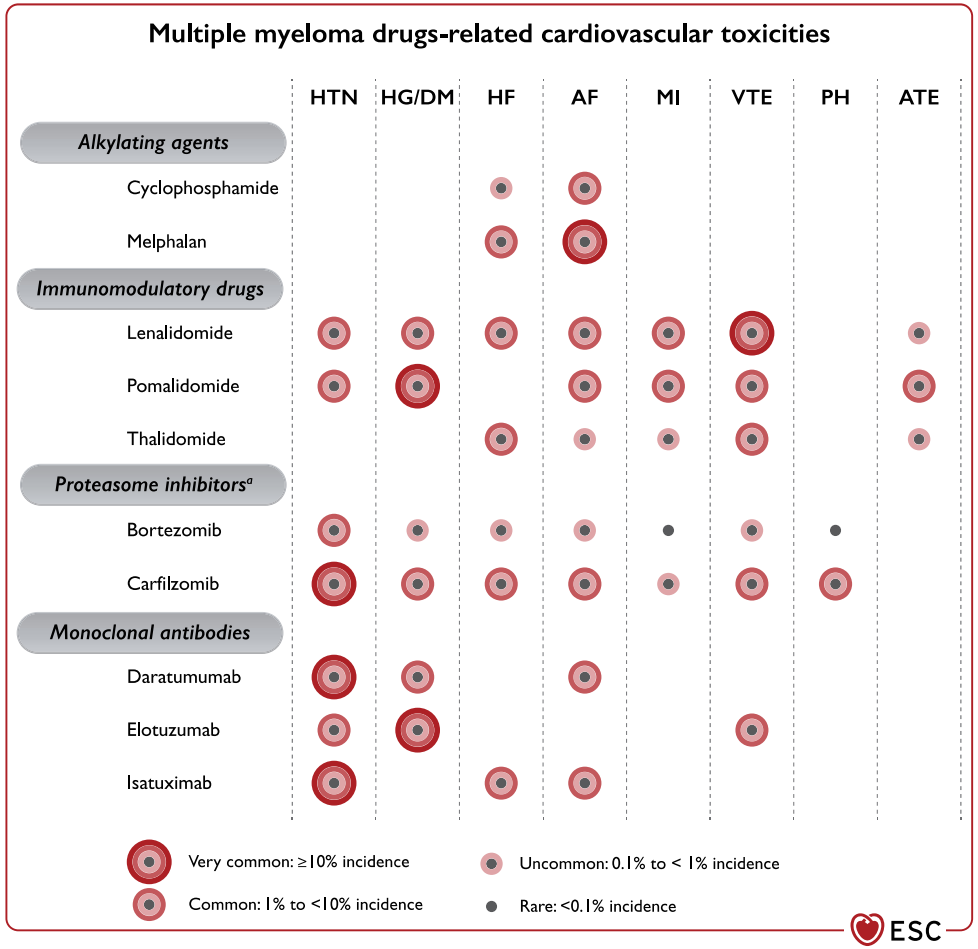
BCR-ABL TKIs

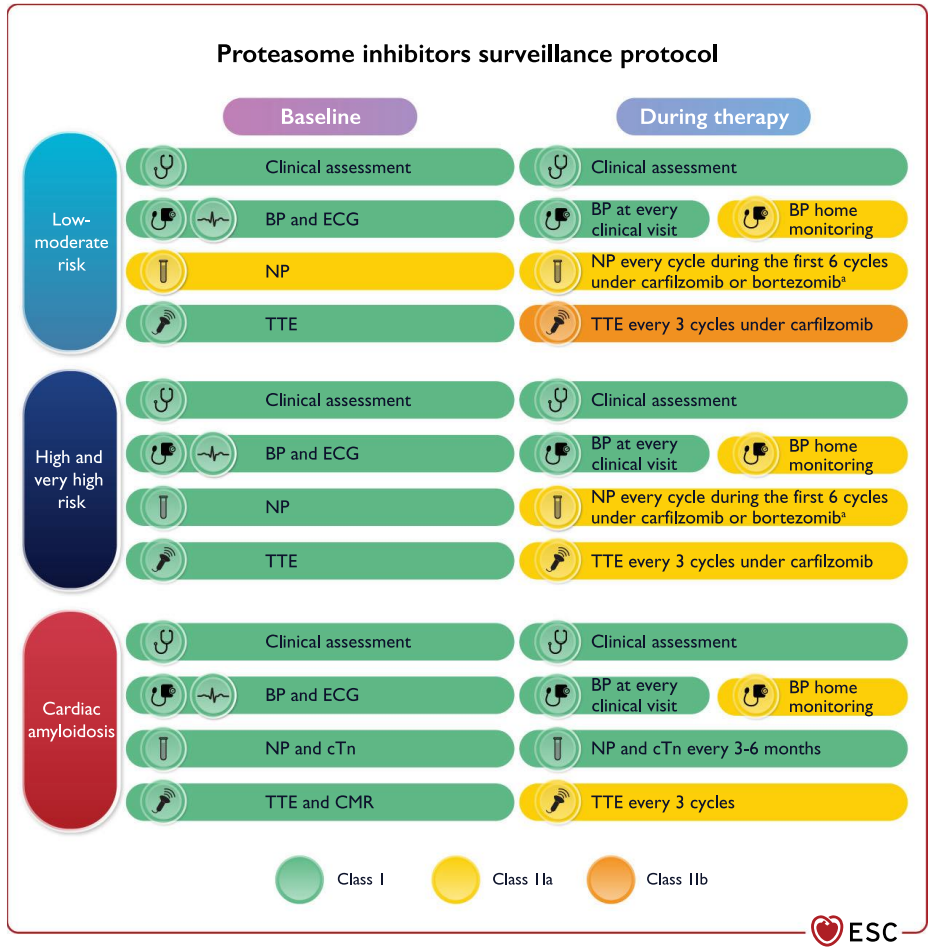




Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

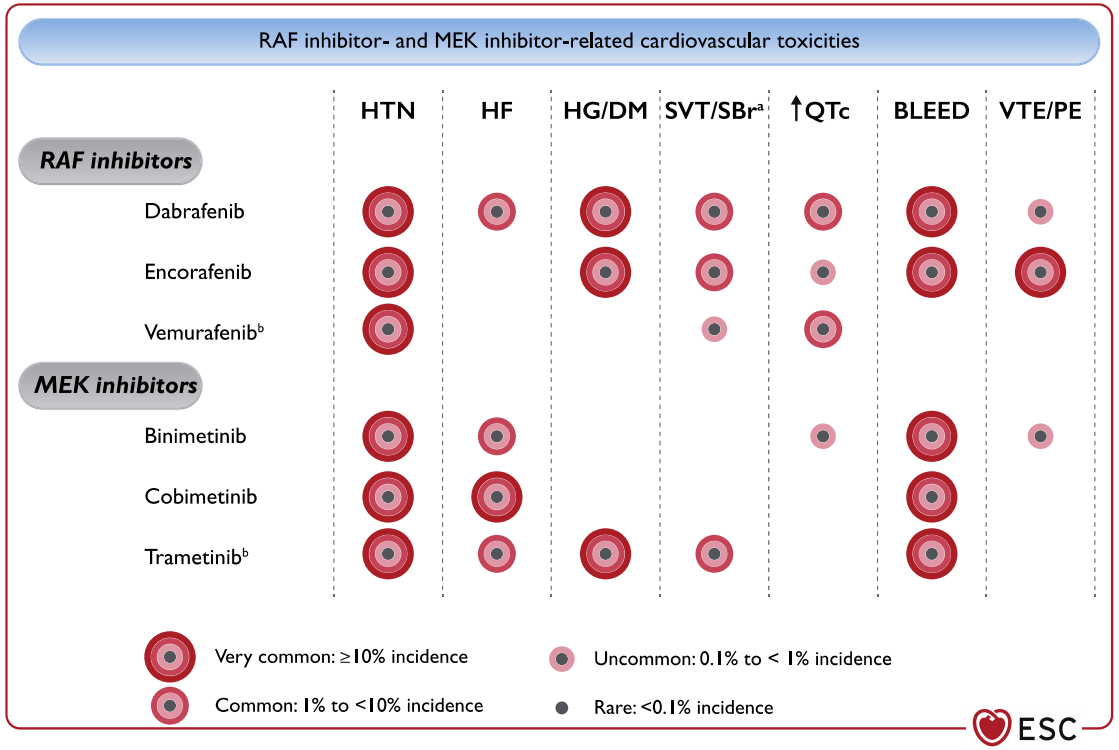
Proteosome Inhibitors

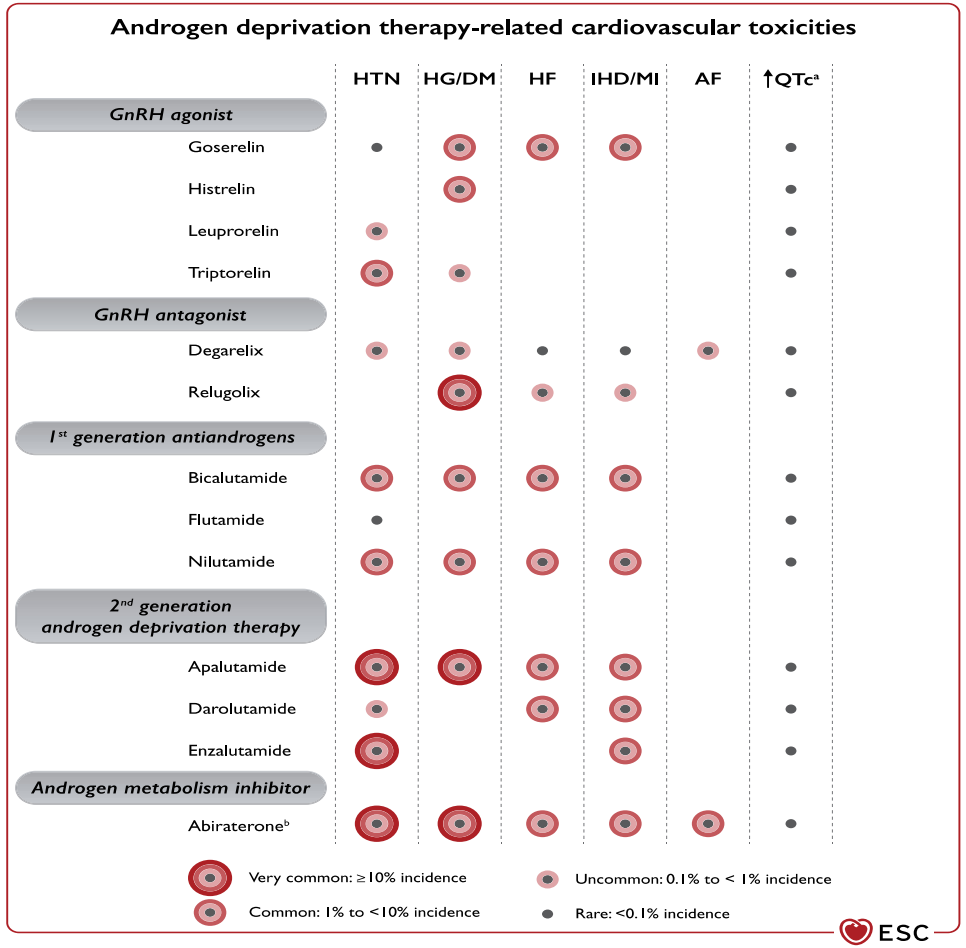




Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

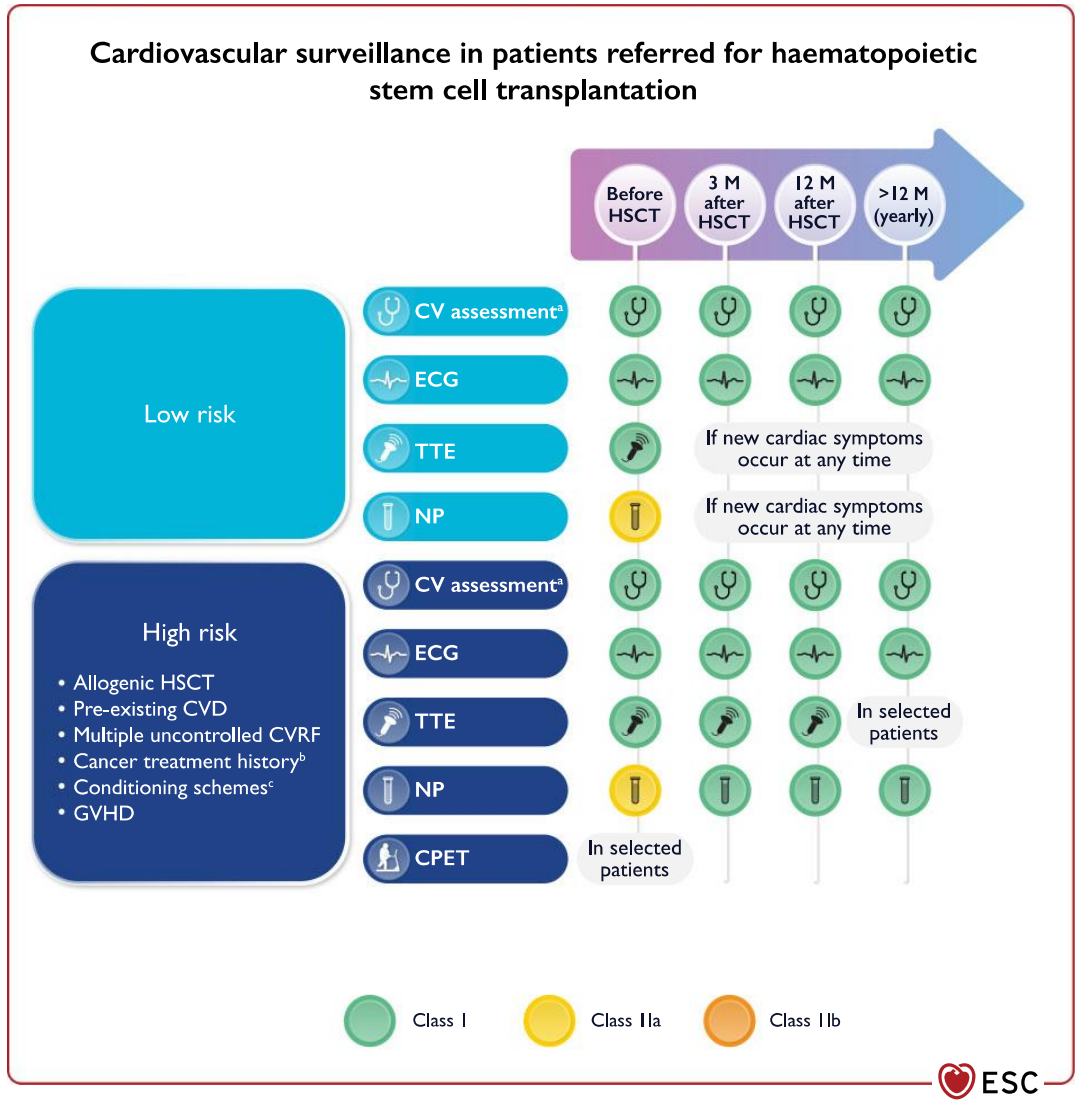
RAF-MEK inhibitors





Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.

HSCT Patients



Lyon AR et al. *Eur Heart J*. 2022; 43:4229-4361.