Identifying and Managing Cancer Treatment Cardiotoxicities in Patients Undergoing Therapy

Michel G. Khouri, MD

Associate Professor of Medicine

Division of Cardiology

Duke University Health System

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

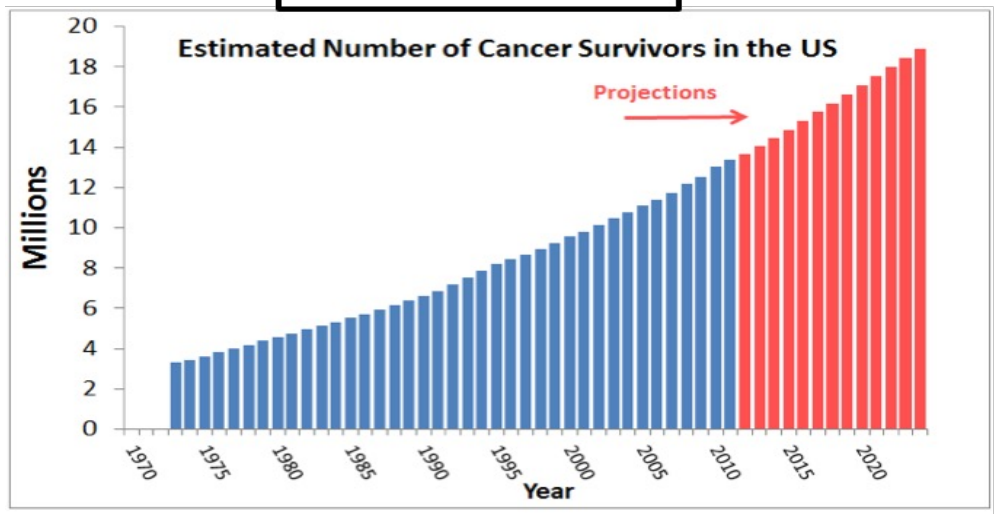
I have the following financial relationships to disclose:

- Consulting/advisory board: Pfizer, Eidos Therapeutics (BridgeBio) and Alnylam
- Research support: Pfizer, Alnylam Pharmaceuticals
- Speaker’s bureau: Alnylam Pharmaceuticals

Cardiovascular Risk for the Cancer Journey

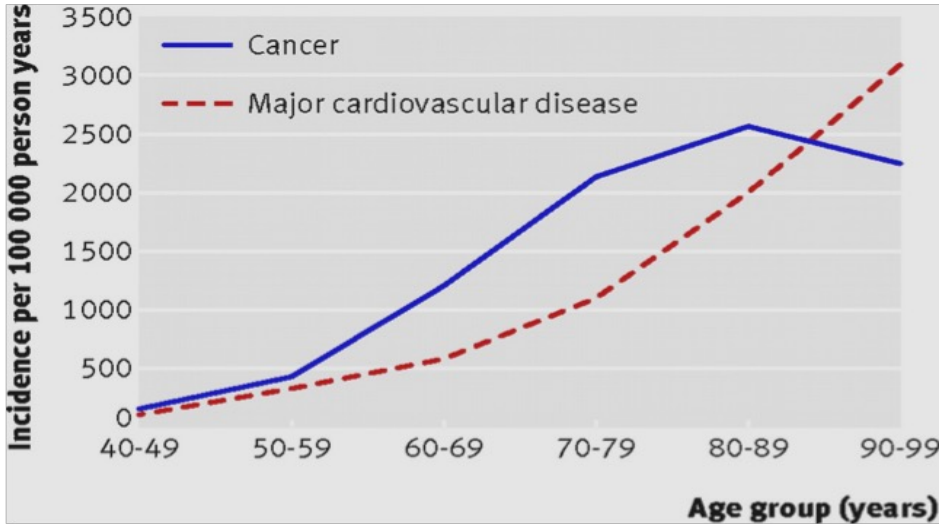
The Basis for Considering CV Risk in Cancer

Survival gains



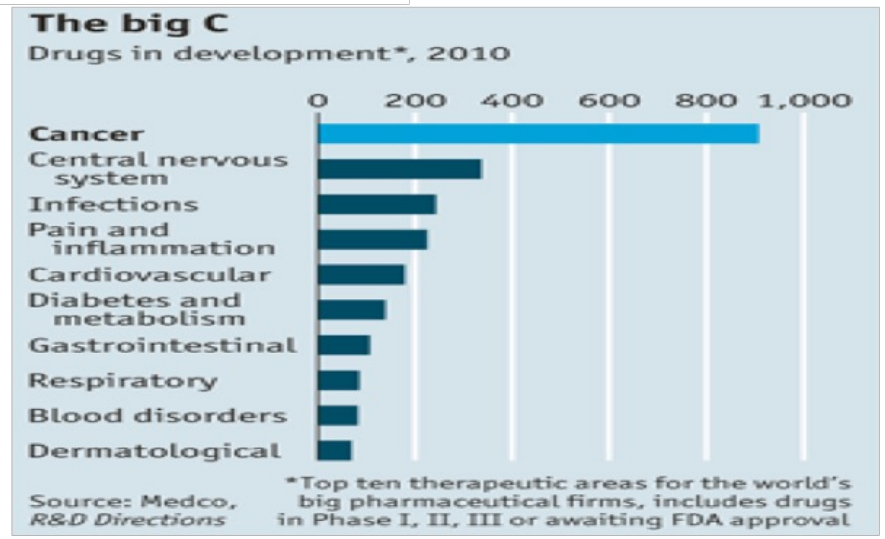
DeSantis CE et al. *CA Cancer J Clin*. 2014;64:252-271.

Cancer – CVD competing risks



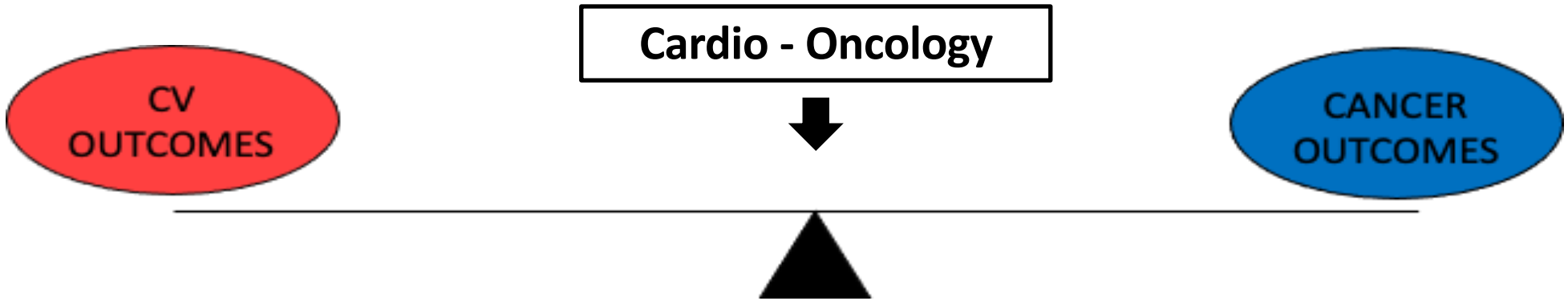
Driver JA et al. *BMJ*. 2008;337:a2467.

Cancer therapies ↑CV Risk

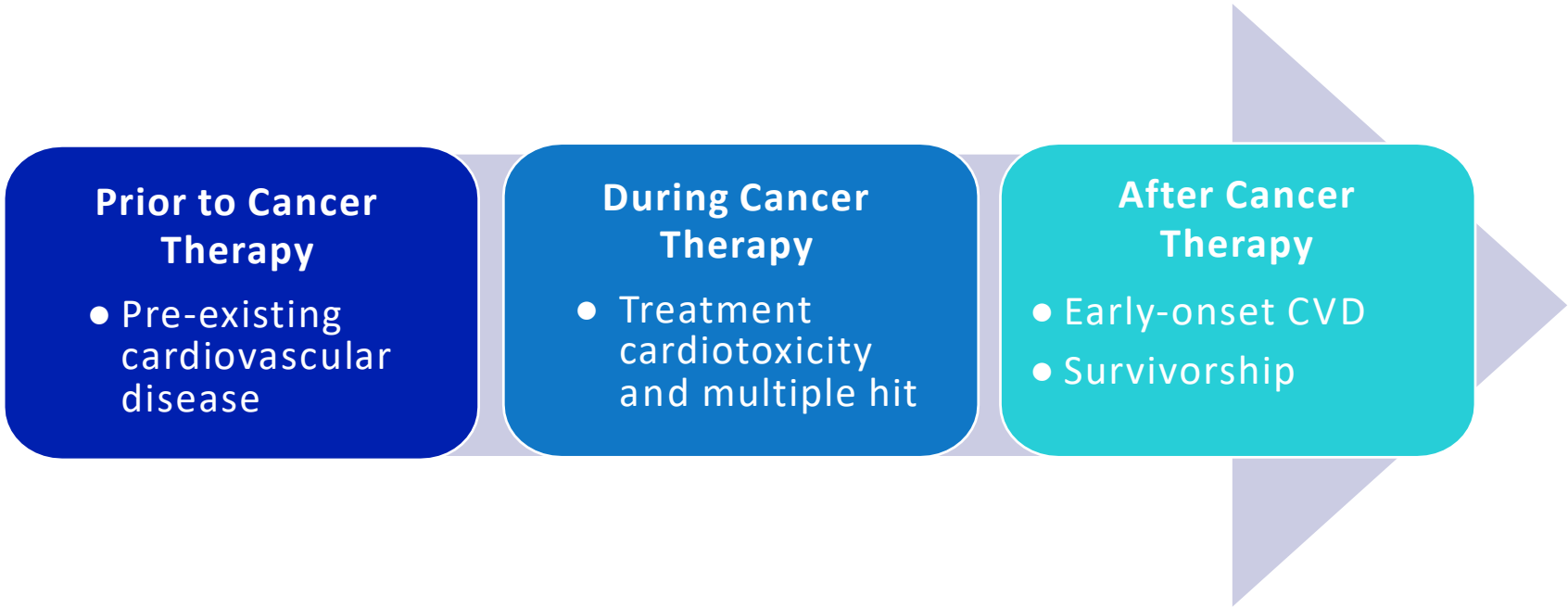


CVD=cardiovascular disease.

The Context: Balancing Cancer and CV Outcomes



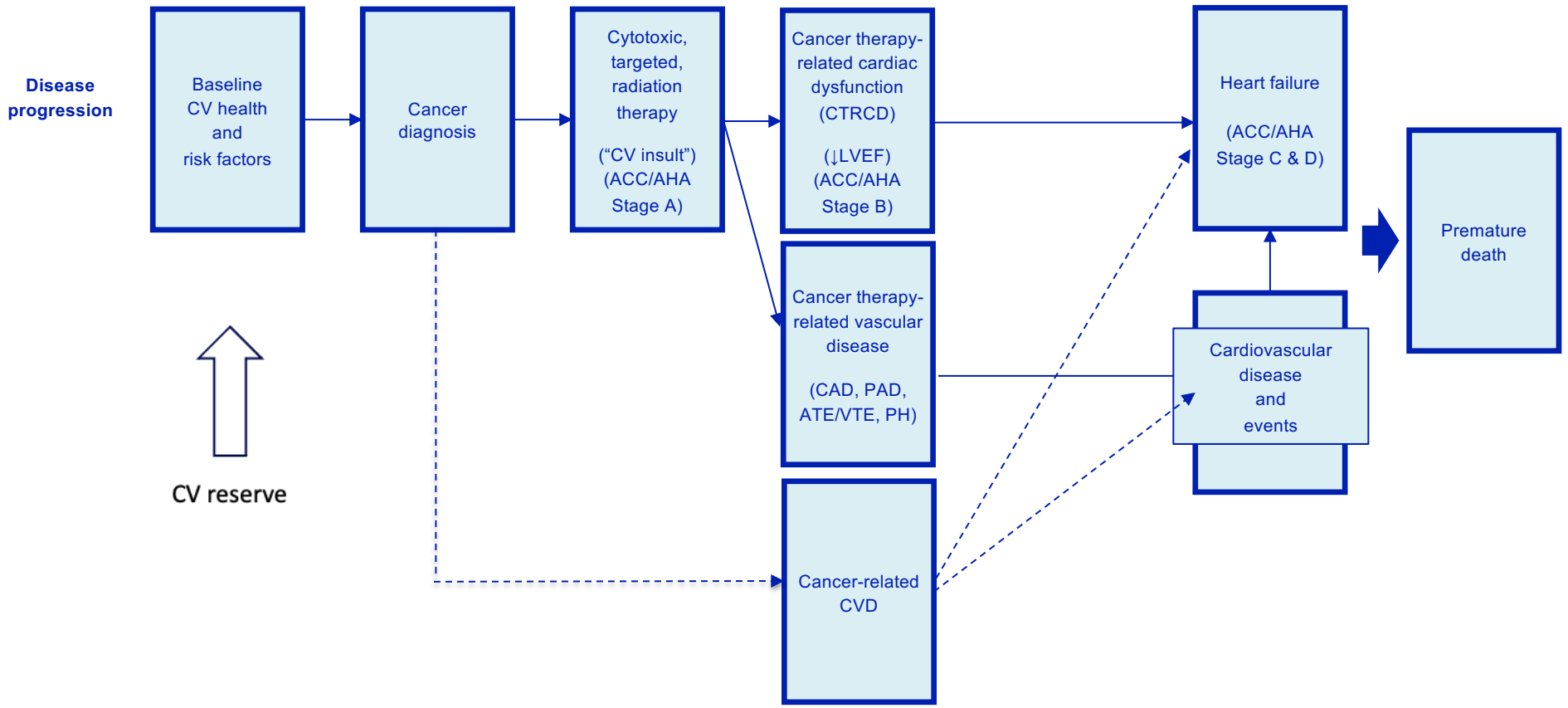
The Spectrum of CV Risk Considerations



Prior to Cancer Therapy

- Define the cardiovascular substrate

Defining the CV Substrate: Assessments of CV Reserve

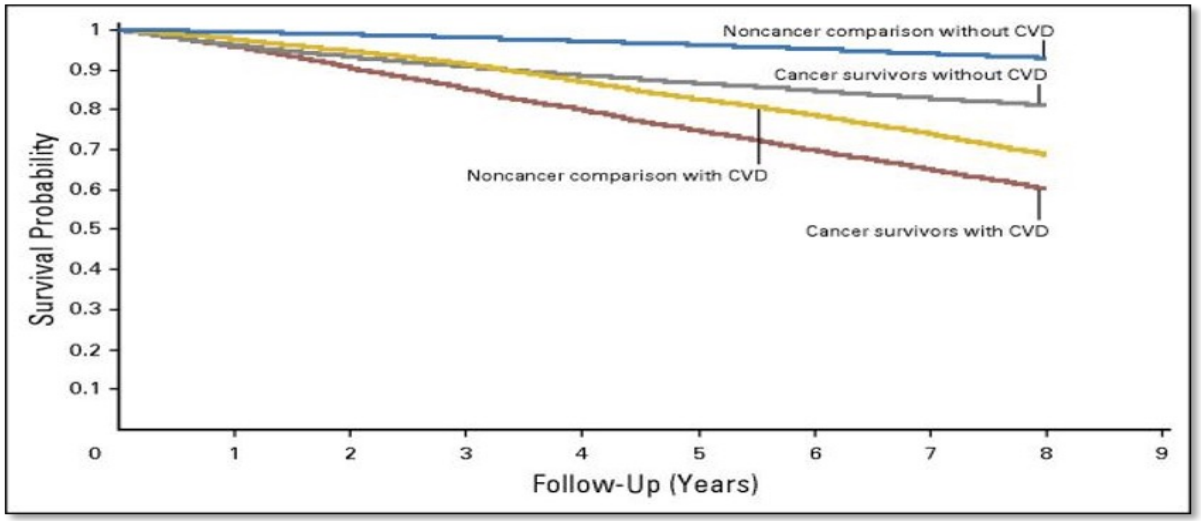


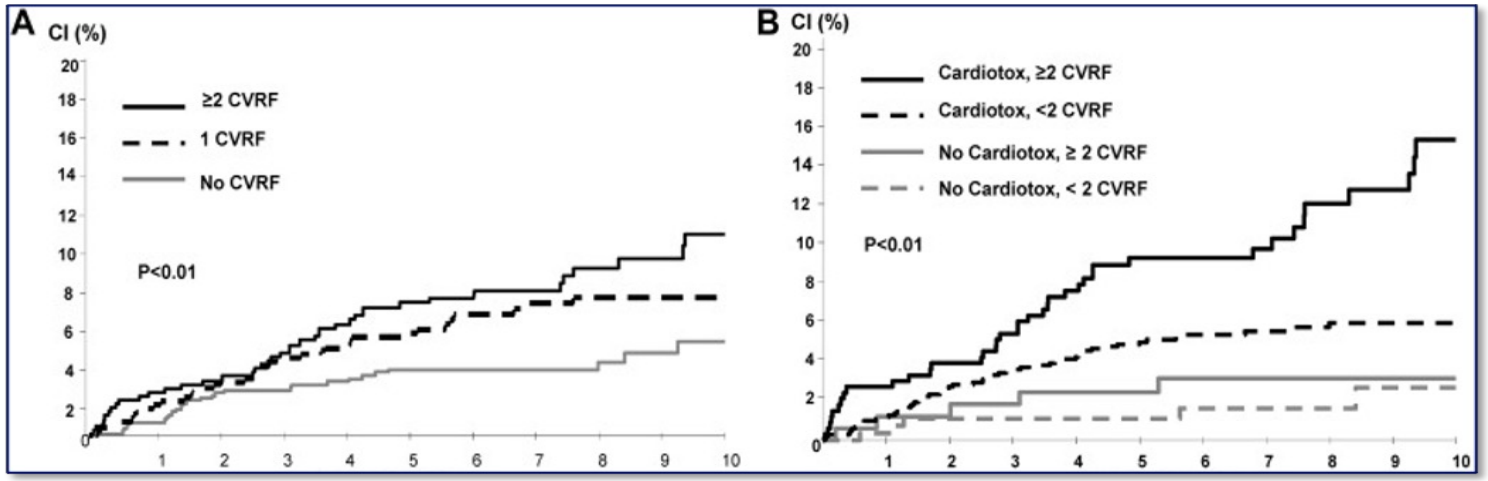
ACC=American College of Cardiology; AHA=American Heart Association; ATE=arterial thromboembolism; CAD=coronary artery disease; LVEF=left ventricular ejection fraction; PAD=peripheral artery disease; VTE=venous thromboembolism; PH=pulmonary hypertension.

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.

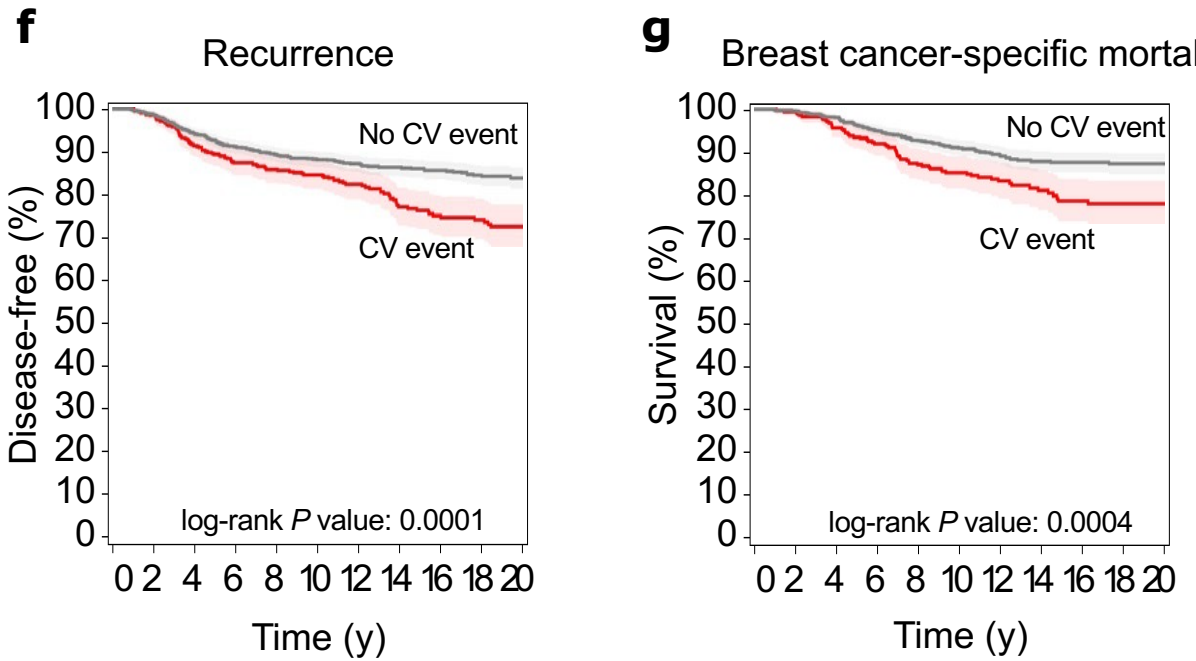
Existing CVD Can Worsen Cancer-specific Outcomes

nature medicine

LETTERS

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

Myocardial infarction accelerates breast cancer via innate immune reprogramming



	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.

Pre-Cancer Therapy: Guidance for CV Risk Stratification

Table 13 Strategies to reduce chemotherapy-induced cardiotoxicity[226–228,245–248]

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy drugs	Identify and treat cardiovascular risk factors
	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities
	Minimize cardiac irradiation
Anthracyclines and analogues	Limit cumulative dose (mg/m^2): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	β-blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	β-blockers

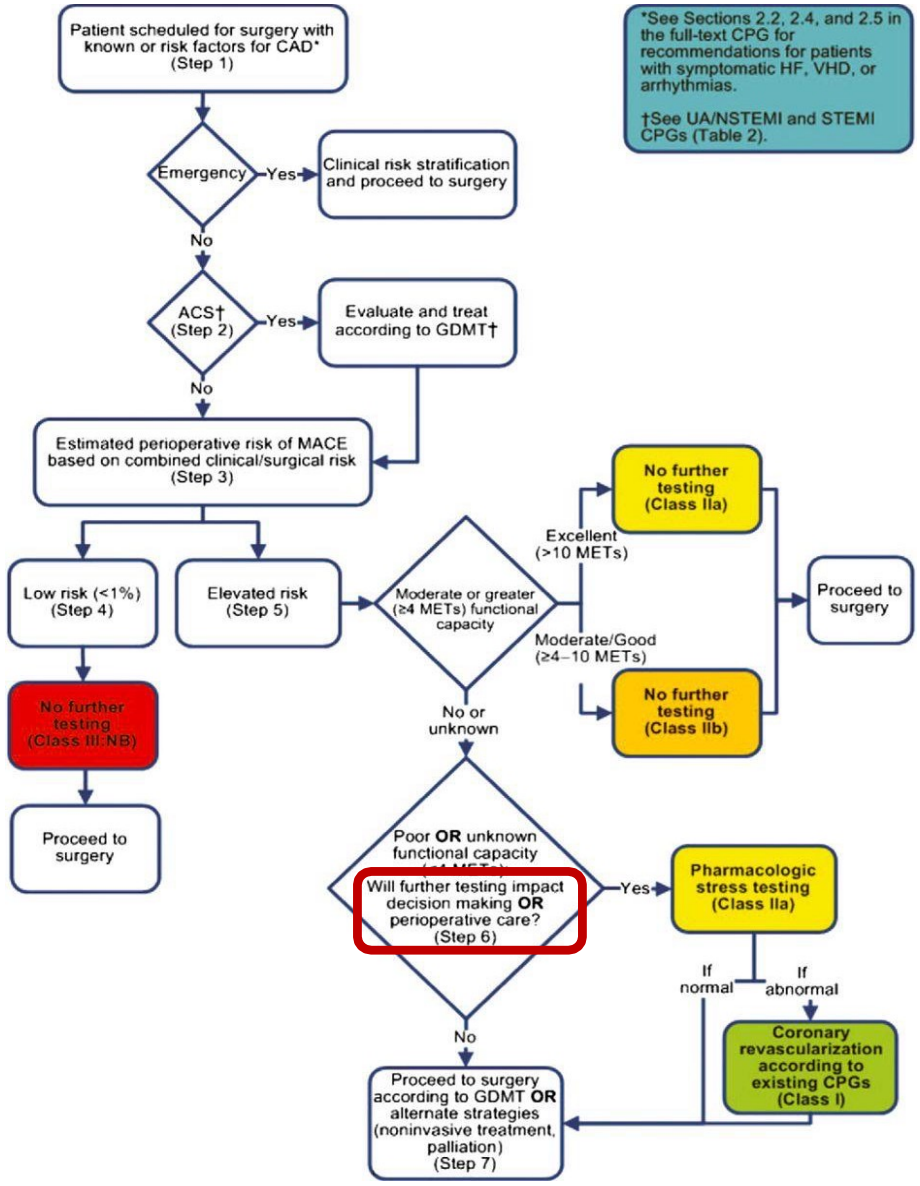
HF=heart failure; HTN=hypertension.

Zamorano JL et al. *Eur Heart J*. 2016;37:2768-2801.

European Society of Cardiology
2016 Position Paper

…25-page position paper contains
3 paragraphs (< ½ page) on pre-treatment risk stratification and risk reduction

Pre-Cancer Therapy: Guidance for CV Risk Stratification



Pre-surgical Risk Assessment

ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

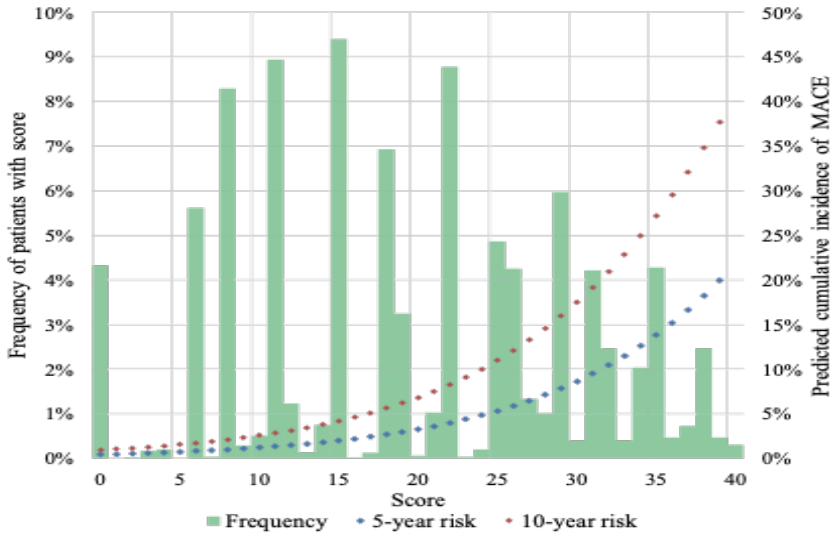
The approach to risk assessment prior to cancer surgery should follow the published guidelines. In general, stress testing is required only if functional quality is poor or unknown AND the results of testing will impact care. The risk of NOT doing surgery needs to be considered as well.

Fleisher LA et al. *J Am Coll Cardiol*. 2014;64:e77-e137.

Modeling Baseline CVD Risk: Breast Cancer Example

Table 2 **Risk score for prediction of major adverse cardiovascular events risk after breast cancer**

Select age category		Select past medical history	
<40 years	0	Heart failure	7
40–44 years	6	Atrial fibrillation	4
45–49 years	8	Peripheral vascular disease	4
50–54 years	11	Hypertension	4
55–59 years	15	Ischaemic heart disease	3
60–64 years	18	Diabetes	3
65–69 years	22	Chronic kidney disease	3
70–74 years	25	COPD	3
75–79 years	27	Cerebrovascular disease	2
≥80 years	31	Total score	



10-year MACE Risk:

<22 points = <7.5% (Low)

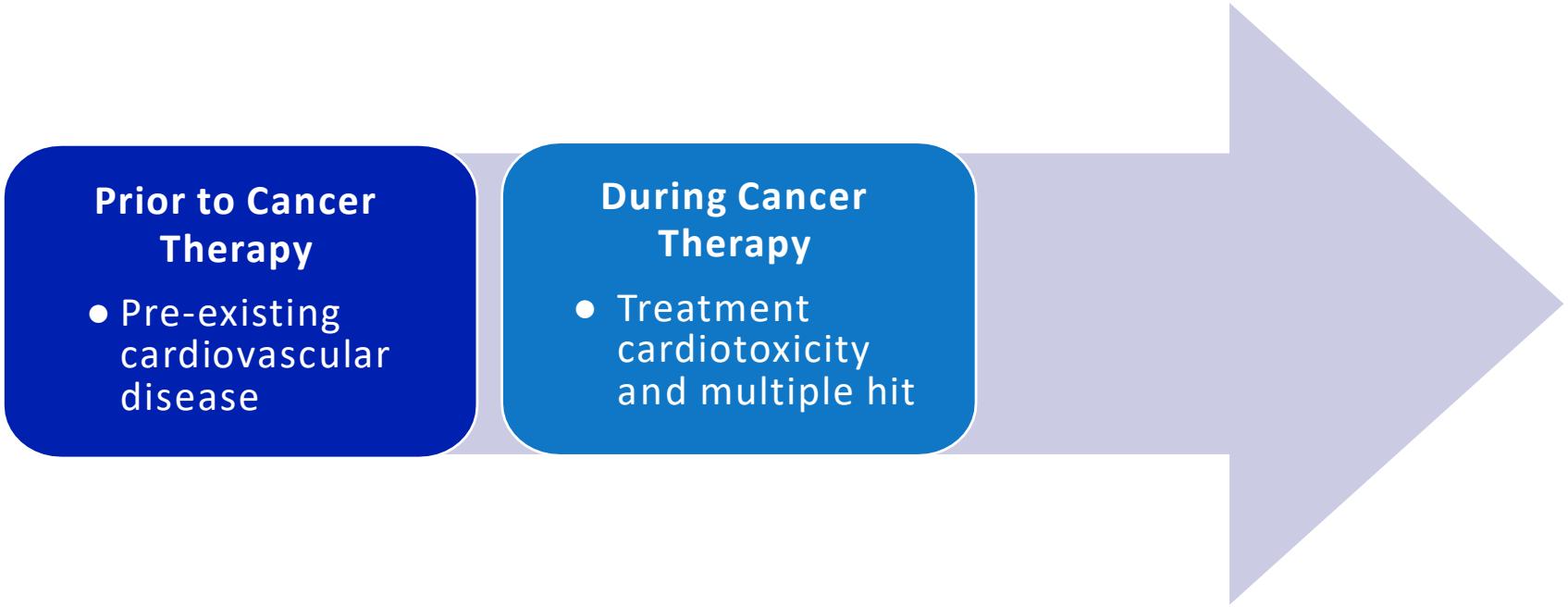
22-32 points = 7.5%-20% (Intermediate)

>32 points = >20% (High)

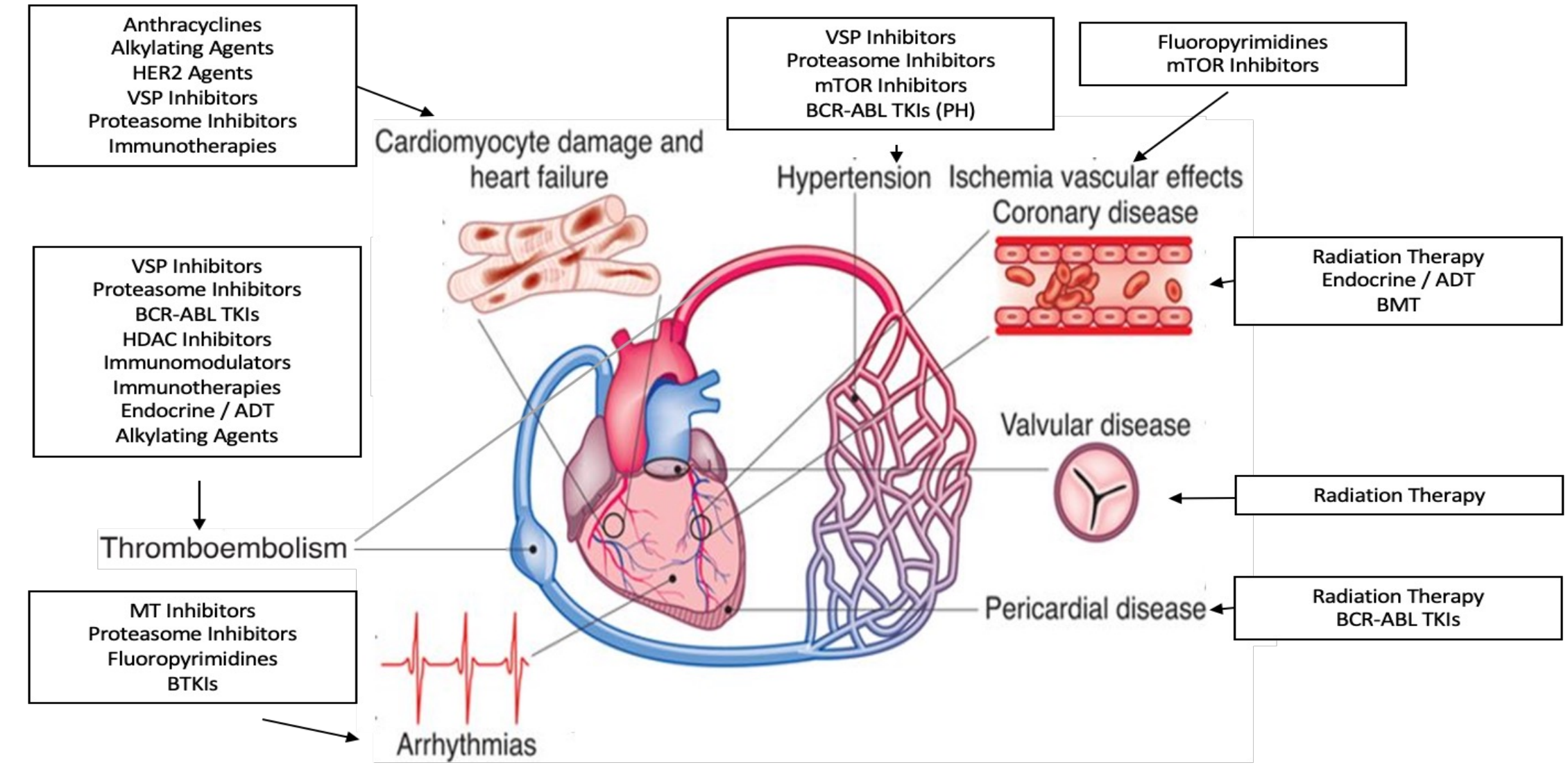
External validation is needed to realize the full potential of novel risk modeling…

MACE=major adverse cardiovascular events.

Abdel-Qadir H et al. *Eur Heart J*. 2019;40:3913-3920.


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

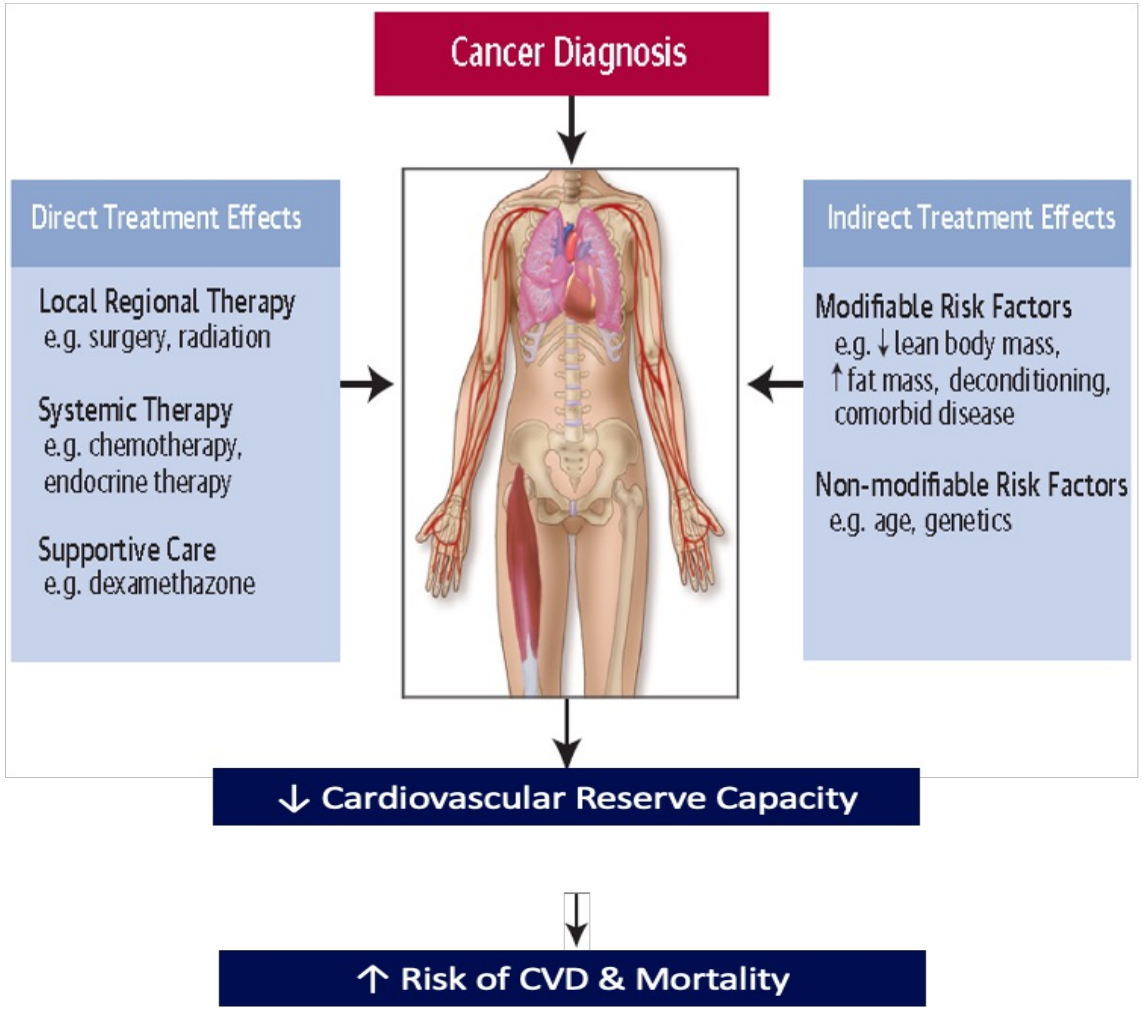
During Cancer Therapy: Spectrum of Treatment-related Cardiotoxicity

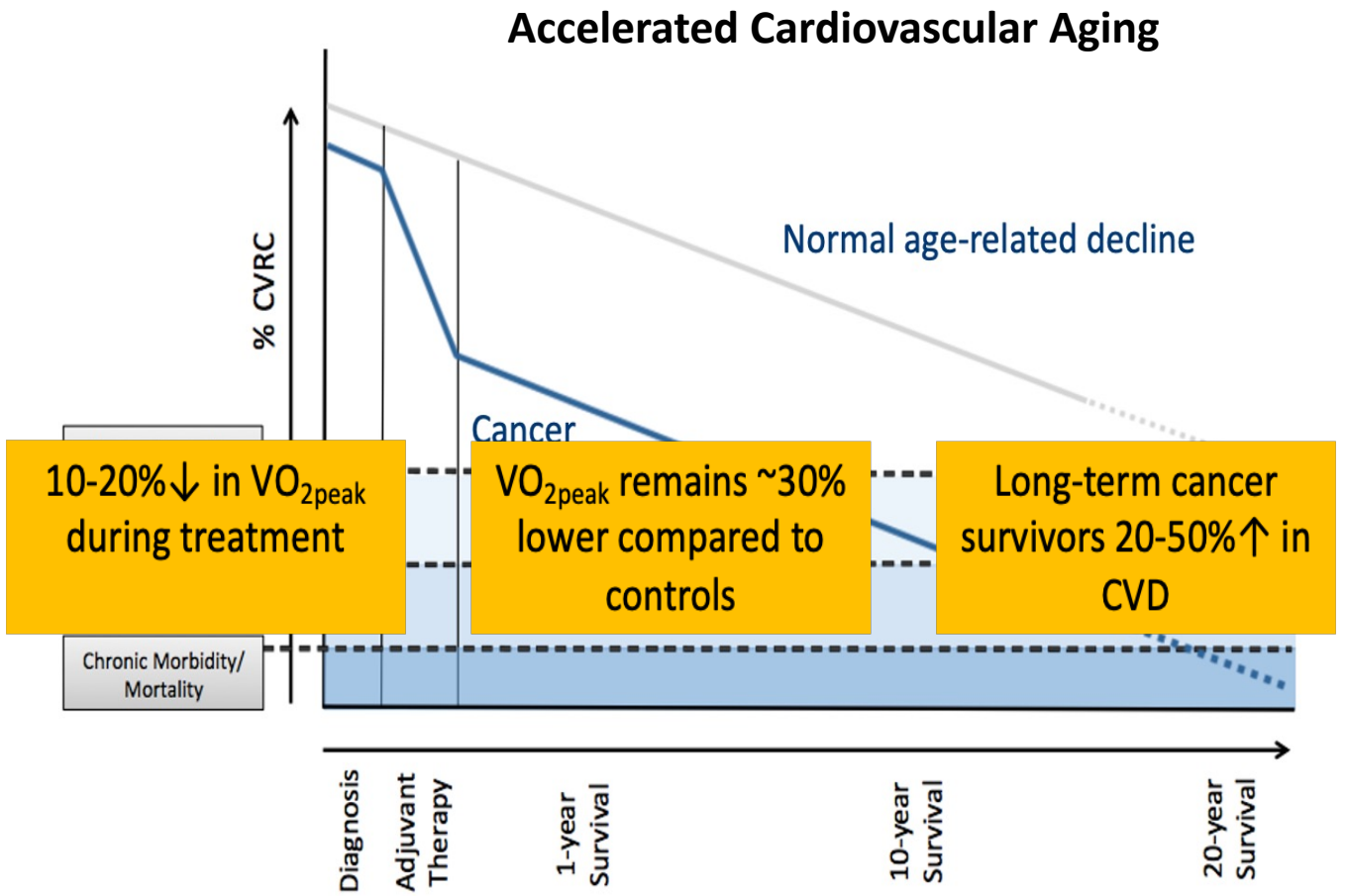


ADT=androgen deprivation therapy; BMT=bone marrow transplantation; HDAC=histone deacetylase; HER2=human epidermal growth factor receptor 2; MT=microtubule; mTOR=mammalian target of rapamycin; TKI=tyrosine kinase inhibitor; VSP=VEGF signaling pathway.

Adapted from Lenneman CG, Sawyer DB. *Circ Res*. 2016;118:1008-1020.

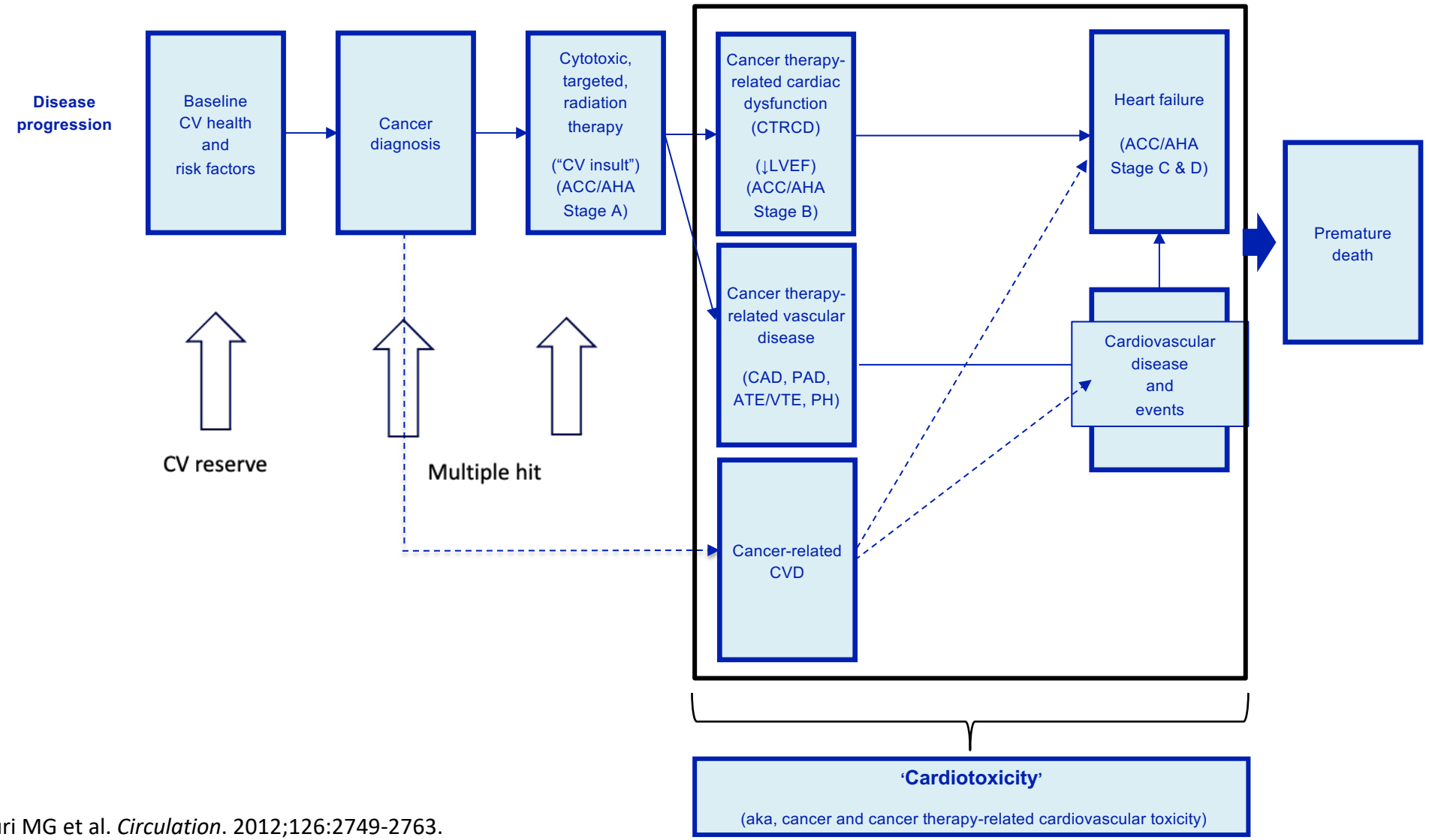
During Cancer Therapy: Multiple Hits to the CV System





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.

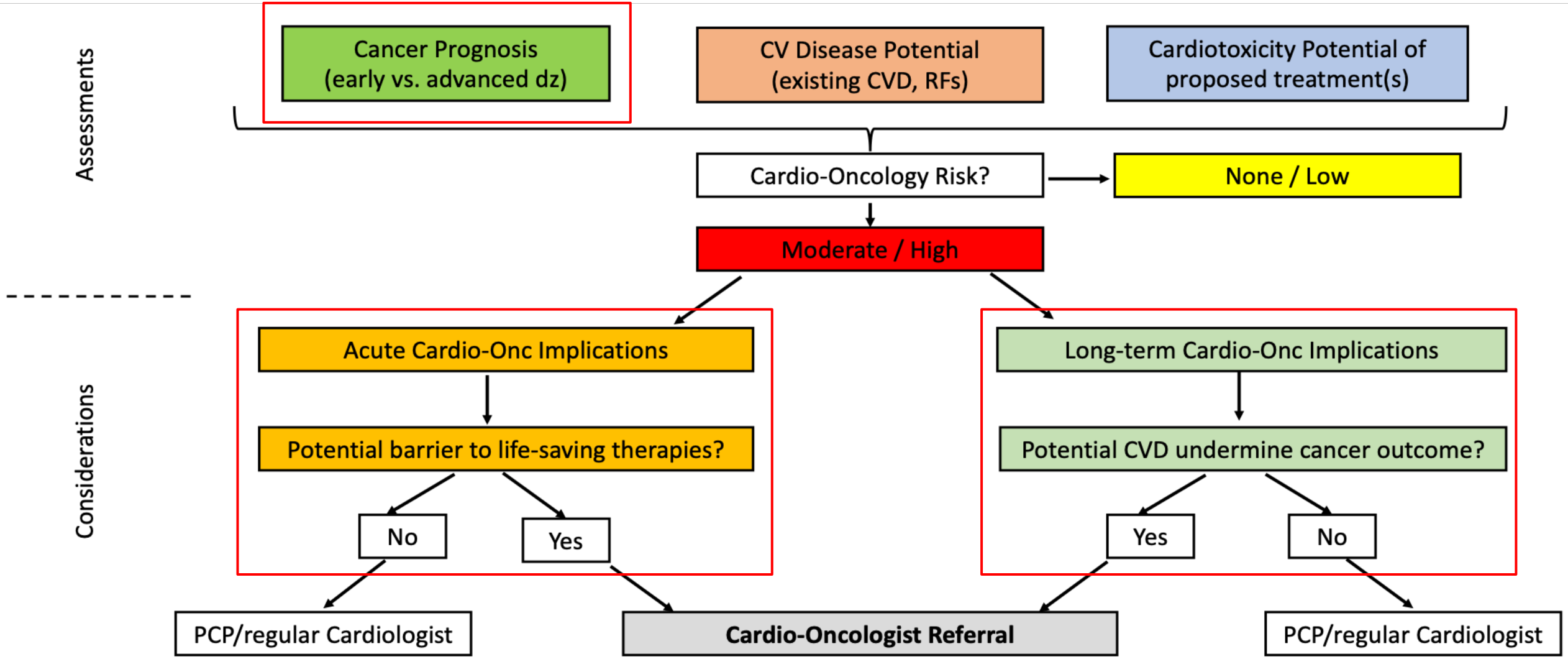
‘Cardiotoxicity’: A Spectrum of Risks, Outcomes, and Causes



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

The Context: Balancing Cancer and CV Outcomes

The importance of CV risk/disease has to be individualized to cancer status…



REFERENCE??

What can we do about cardiotoxicity?

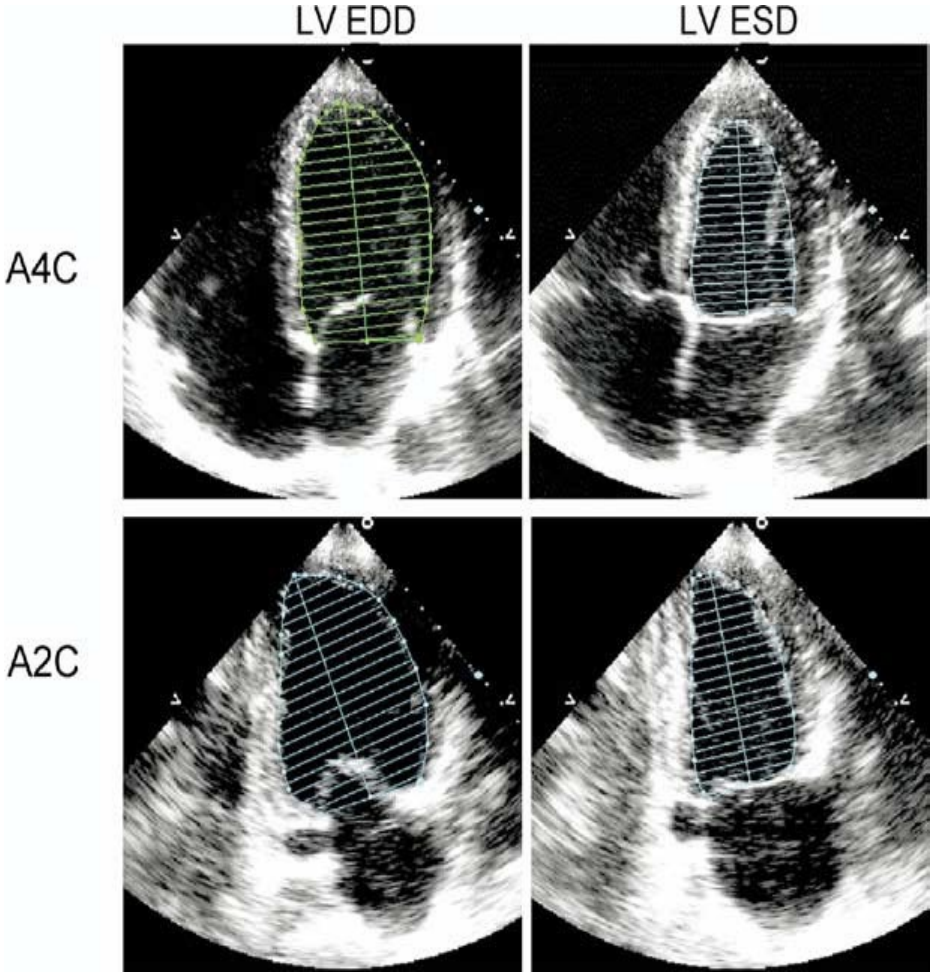
EARLY DETECTION

Modalities for Early Detection of CV Risk

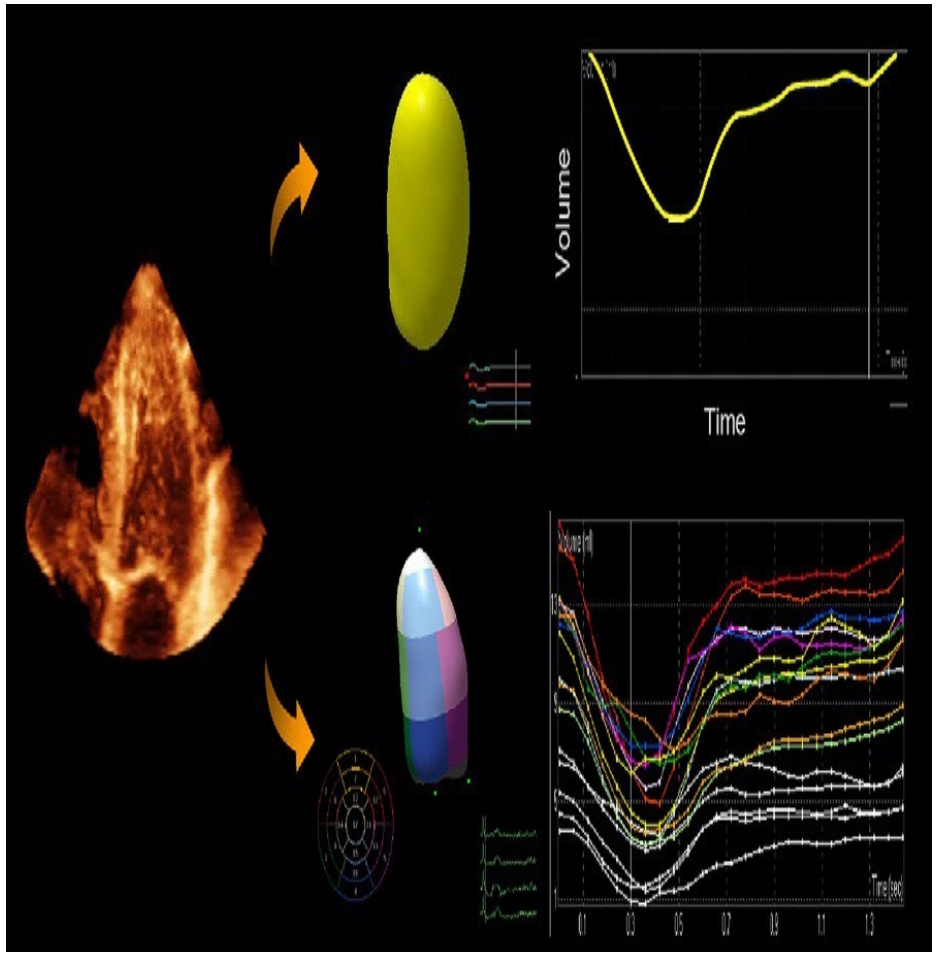
- Desirable features
  - Detects injury signal before LV impairment
  - Detects LV signal before symptoms
  - Highly predictive of clinically significant disease
  - Reproducible
  - Widely available
  - Noninvasive
  - Inexpensive
  - Actionable in guiding therapy

LV Ejection Fraction

2D Echo

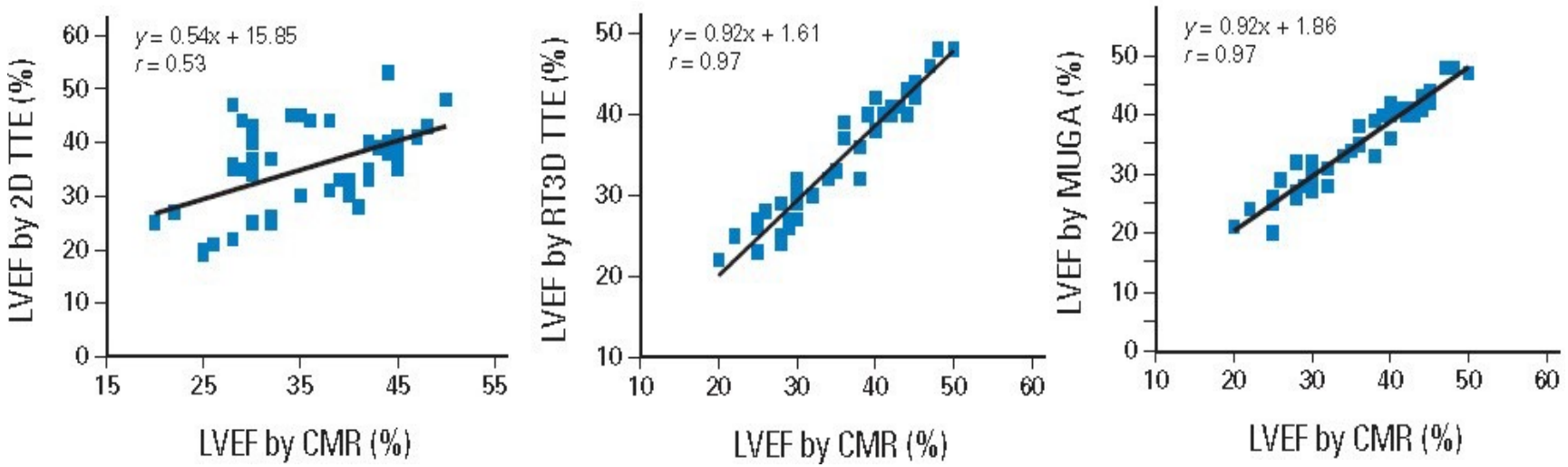


3D Echo

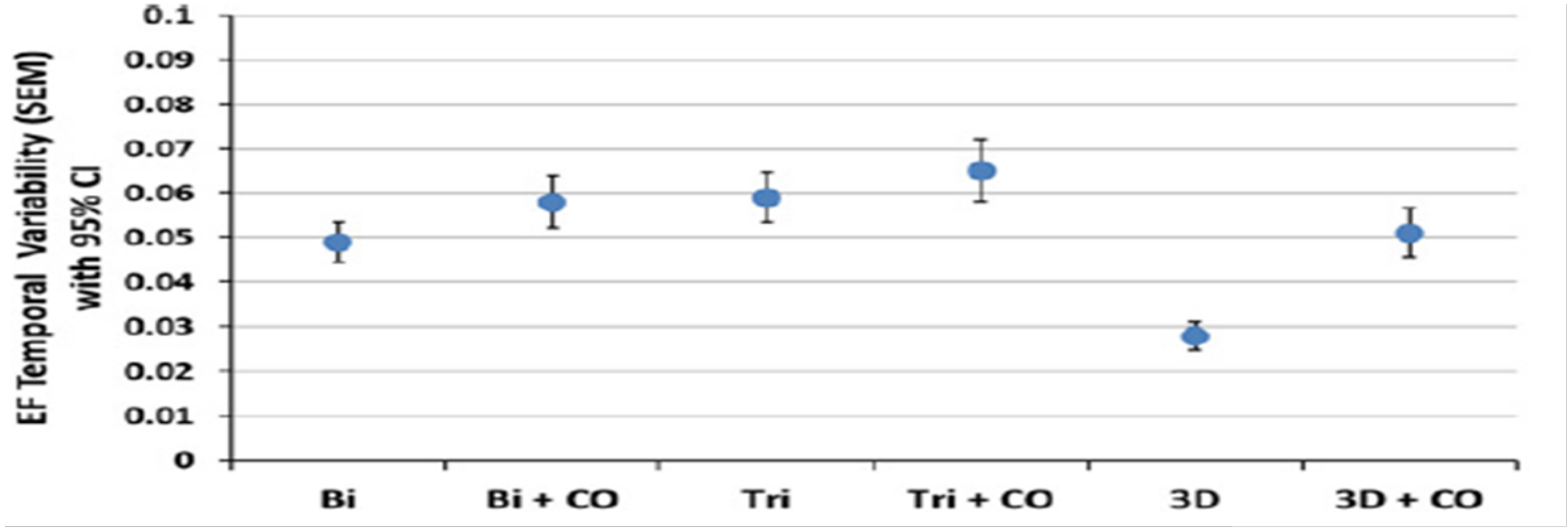


LVEF Sensitivity for Cardiotoxicity

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



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

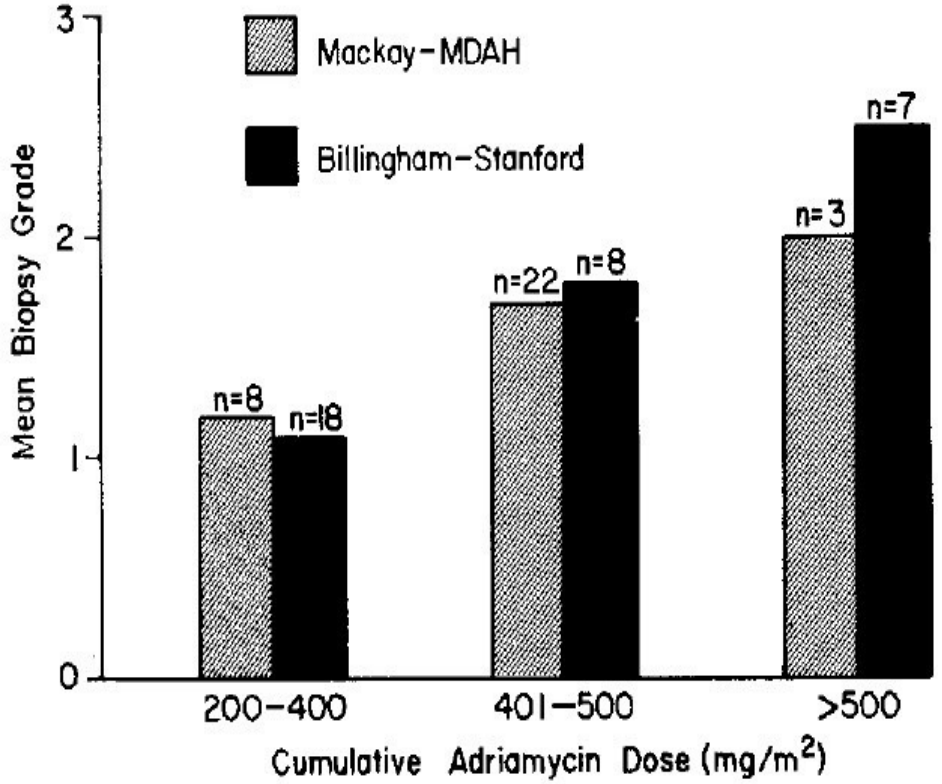


CMR=cardiovascular magnetic resonance; SEM=spatial error model; TTE=transthoracic echocardiogram.

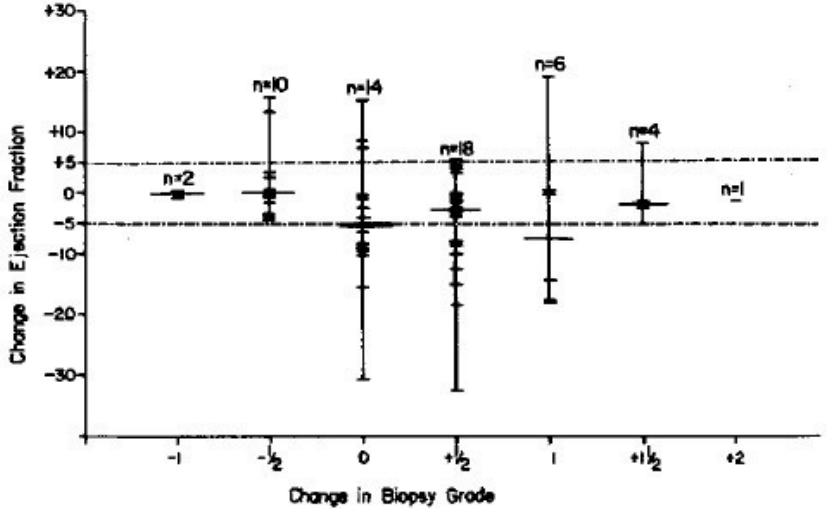
Thavendiranathan P et al. *J Am Coll Cardiol*. 2013;61:77-84.

LVEF Sensitivity for Cardiotoxicity

Discordance with Myocellular Injury



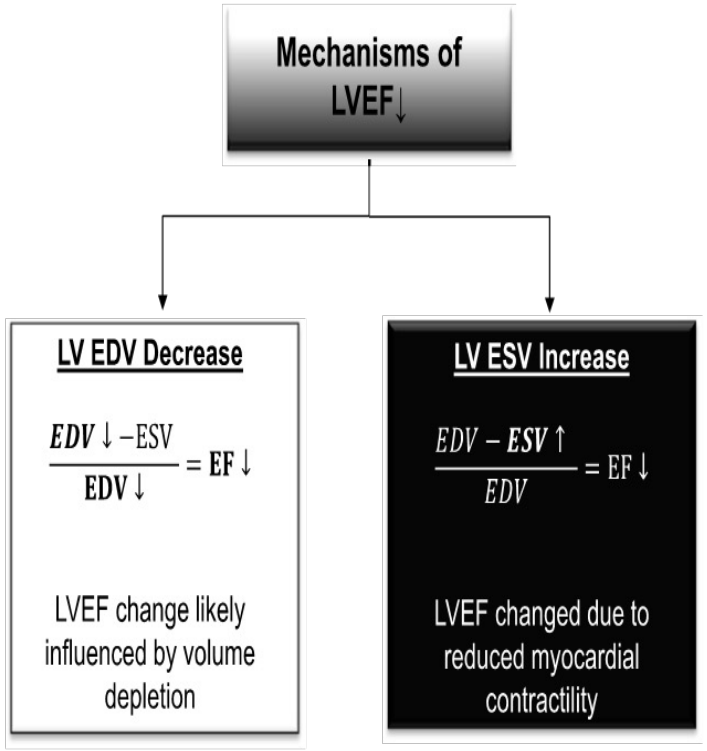
Biopsy Grade	Nuclear Scans (n = 173) No. Patients	Nuclear Scans (n = 173) Mean EF	Echocardiogram (n = 146) No. Patients	Echocardiogram (n = 146) Mean EF
0	16	63%	16	65%
0.5	50	66%	43	66%
1.0	55	62%	46	67%
1.5	21	58%	19	61%
2.0	20	61%	15	62%
3.0	11	61%	7	65%

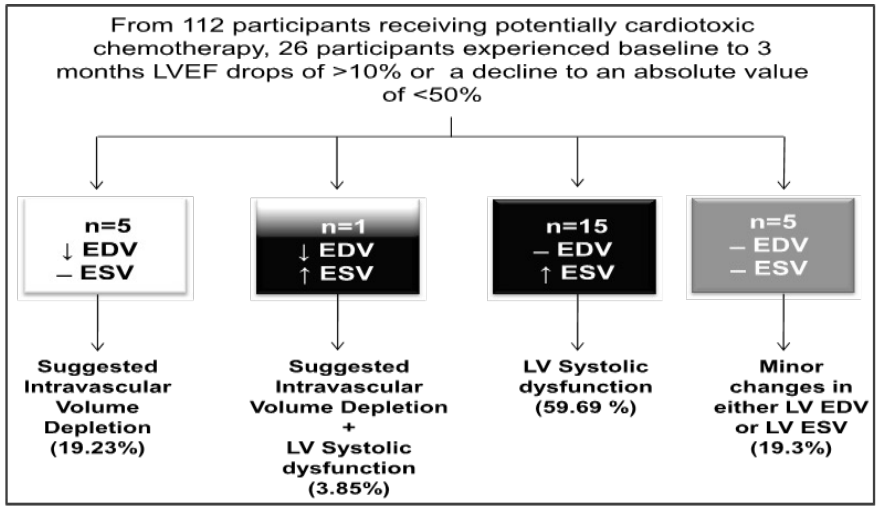


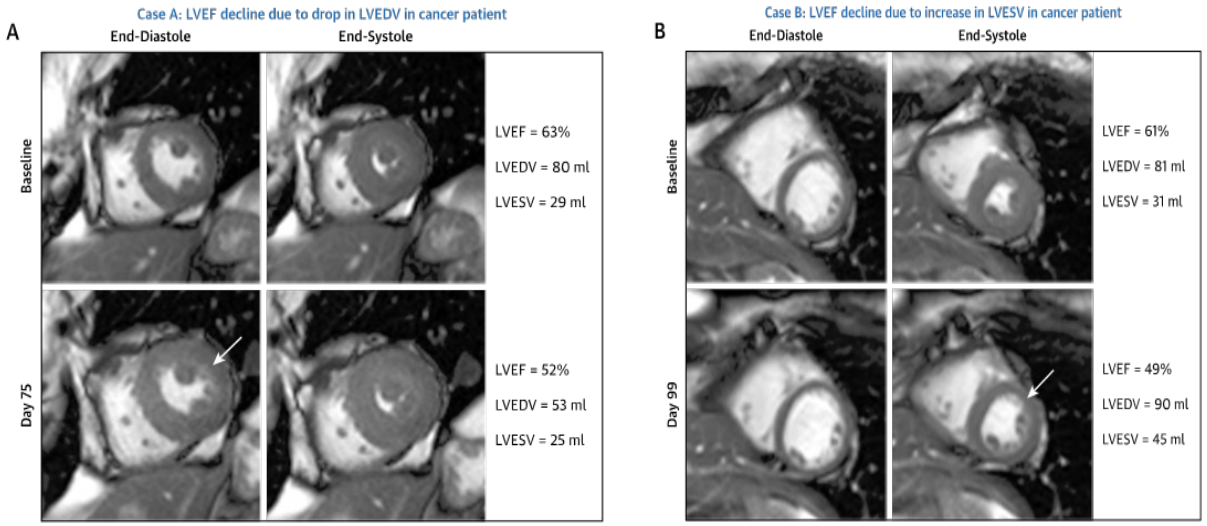
Ewer MS et al. *J Clin Oncol*. 1984;2:112-117.

LVEF Sensitivity for Cardiotoxicity

Susceptibility to Loading Conditions







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

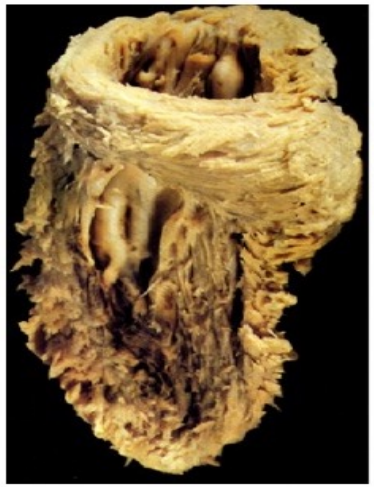
Meléndez GC et al. *Am J Cardiol*. 2017;119:1637-1642.

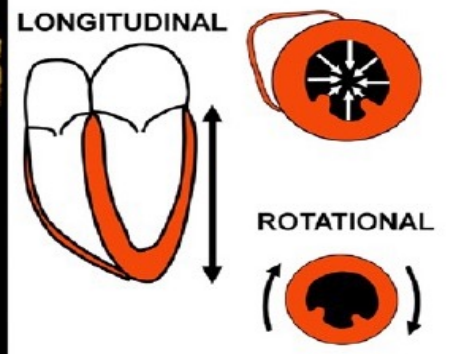
What can we do about cardiotoxicity?

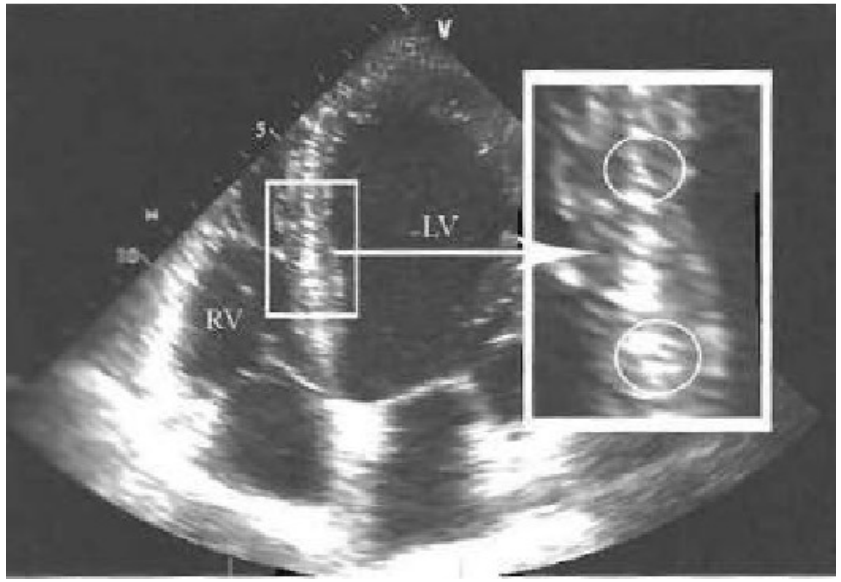
- ~~LVEF~~ - STRAIN

Advances in Imaging-based Screening

Speckle-tracking Strain Echocardiography







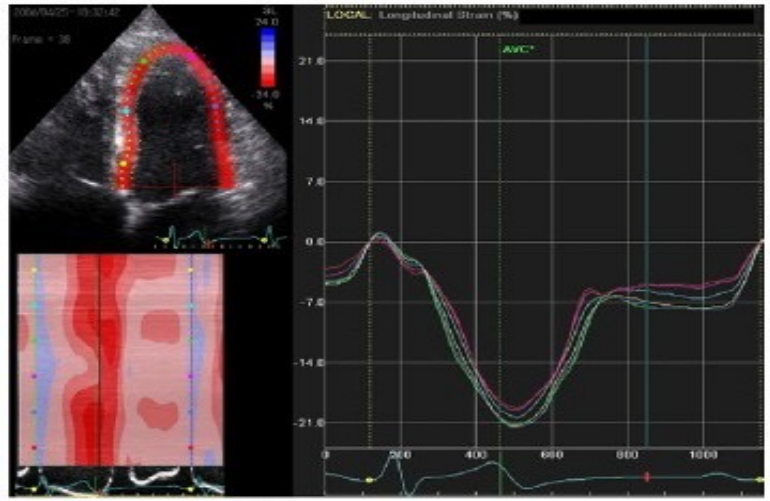
Strain Tissue deformation

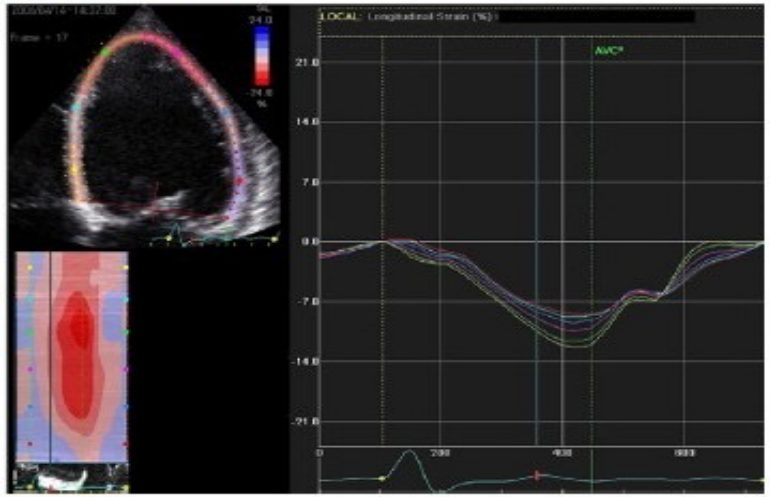
L_0 L_1

10 cm → 8 cm

-20%

Strain
% change from resting dimension



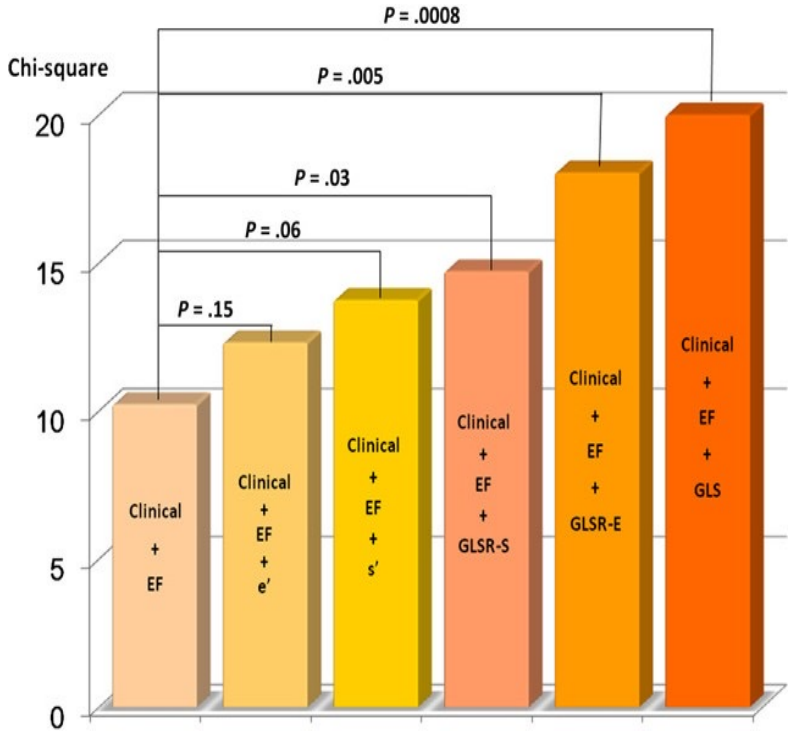


Gorcsan J, Tanaka H. *J Am Coll Cardiol*. 2011;58:1401-1413.

Advances in Imaging-based Screening

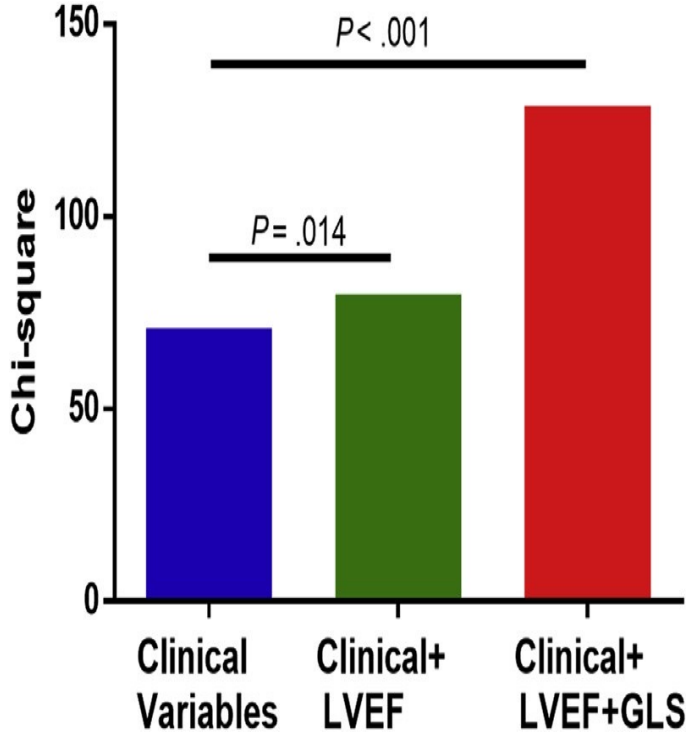
Traditional and Novel Parameters

CTRCD



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

Cardiac Events

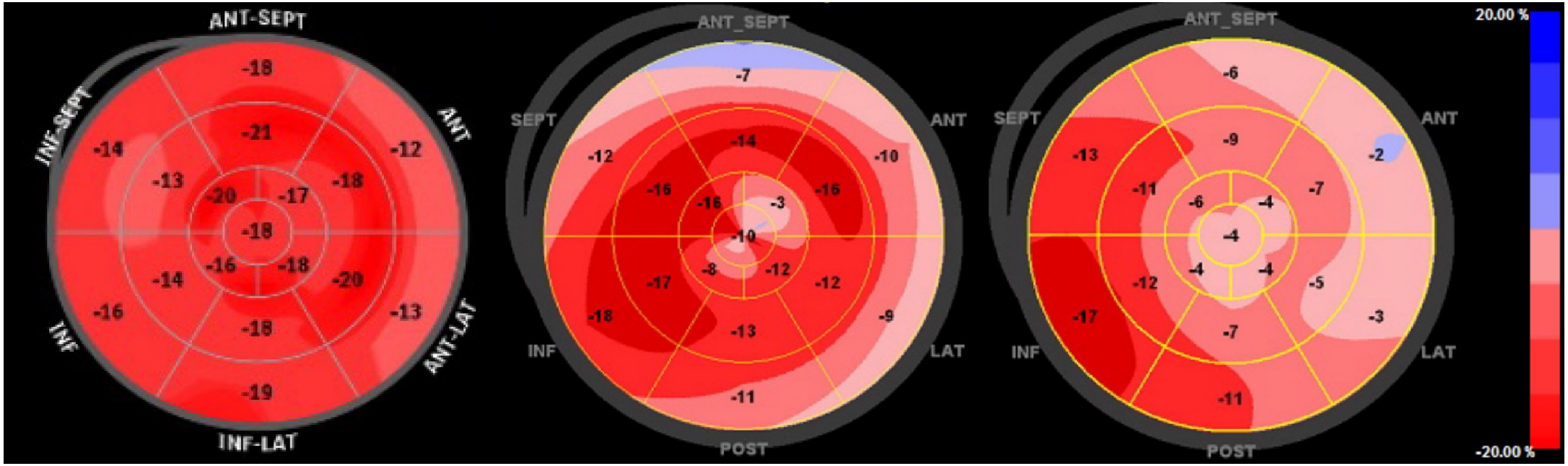


Ali MT et al. *J Am Soc Echocardiogr*. 2016;29:522-527.

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%

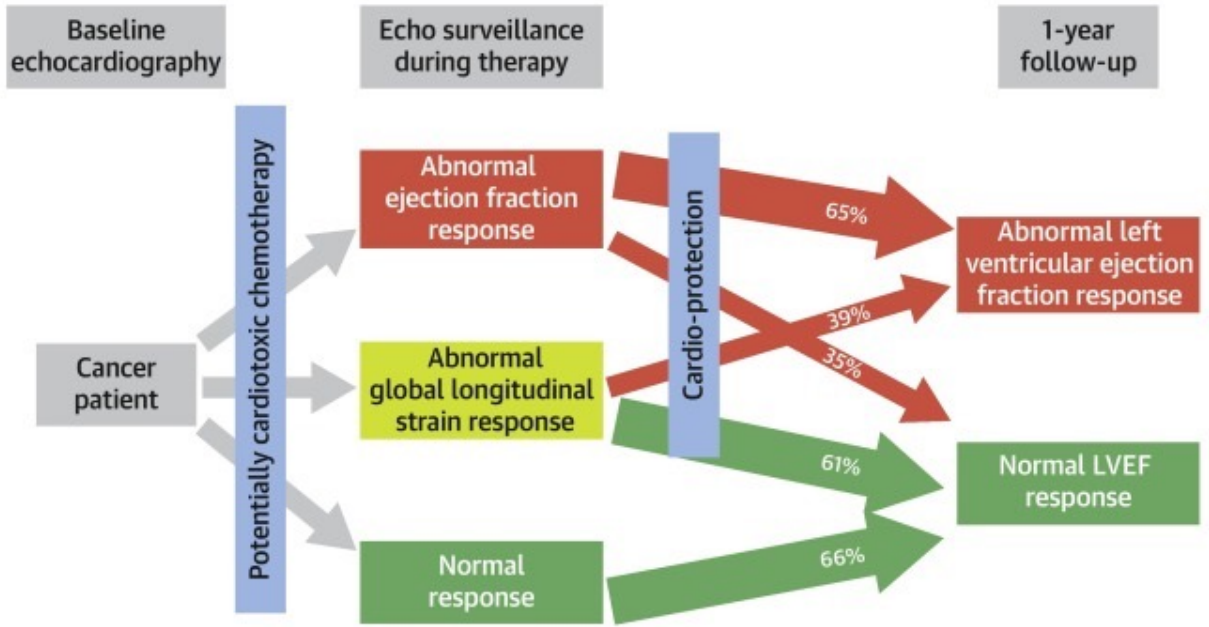
➡

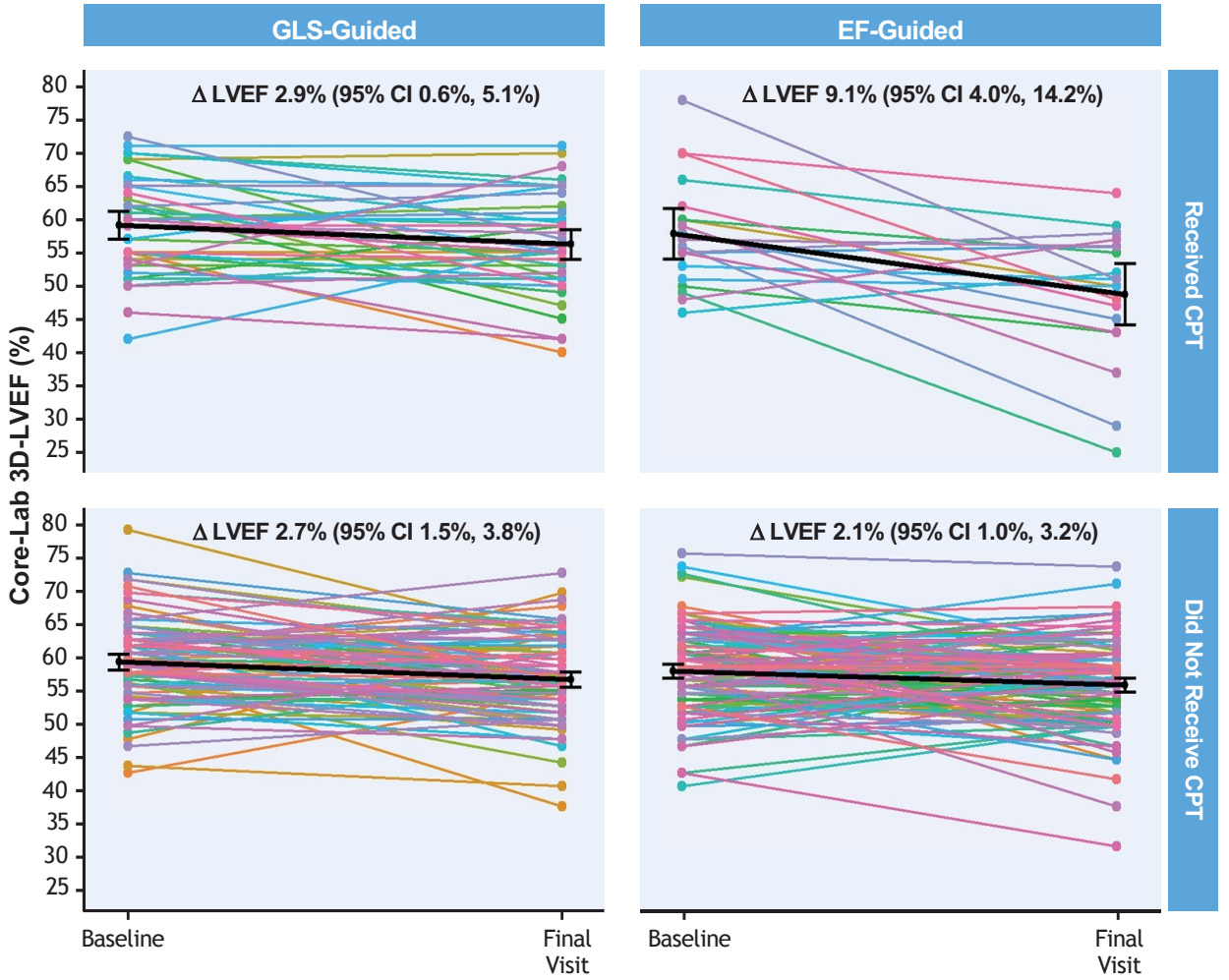
Trastuzumab x 5M Pertuzumab x 2M	
LVEF	29%
GLS	–7%

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.

Early Detection: Current State of Echo

- Current standard detection modalities in cardio-oncology (ie, resting LVEF) are insensitive for cardiotoxicity and may not be prognostic
- Emerging imaging modalities that assess myocardial deformation by echo have potential to improve early detection
- However, evidence with these modalities remains based on small, single-center studies
- Generalizability of novel echo modalities is uncertain
    - Reproducibility limitations across labs with rapidly evolving technologies and varying expertise
    - Universal, validated, meaningful cut points established in multi-center studies are needed
    - Feasible in single-lab environments with commitment to robust reproducibility and remediation processes

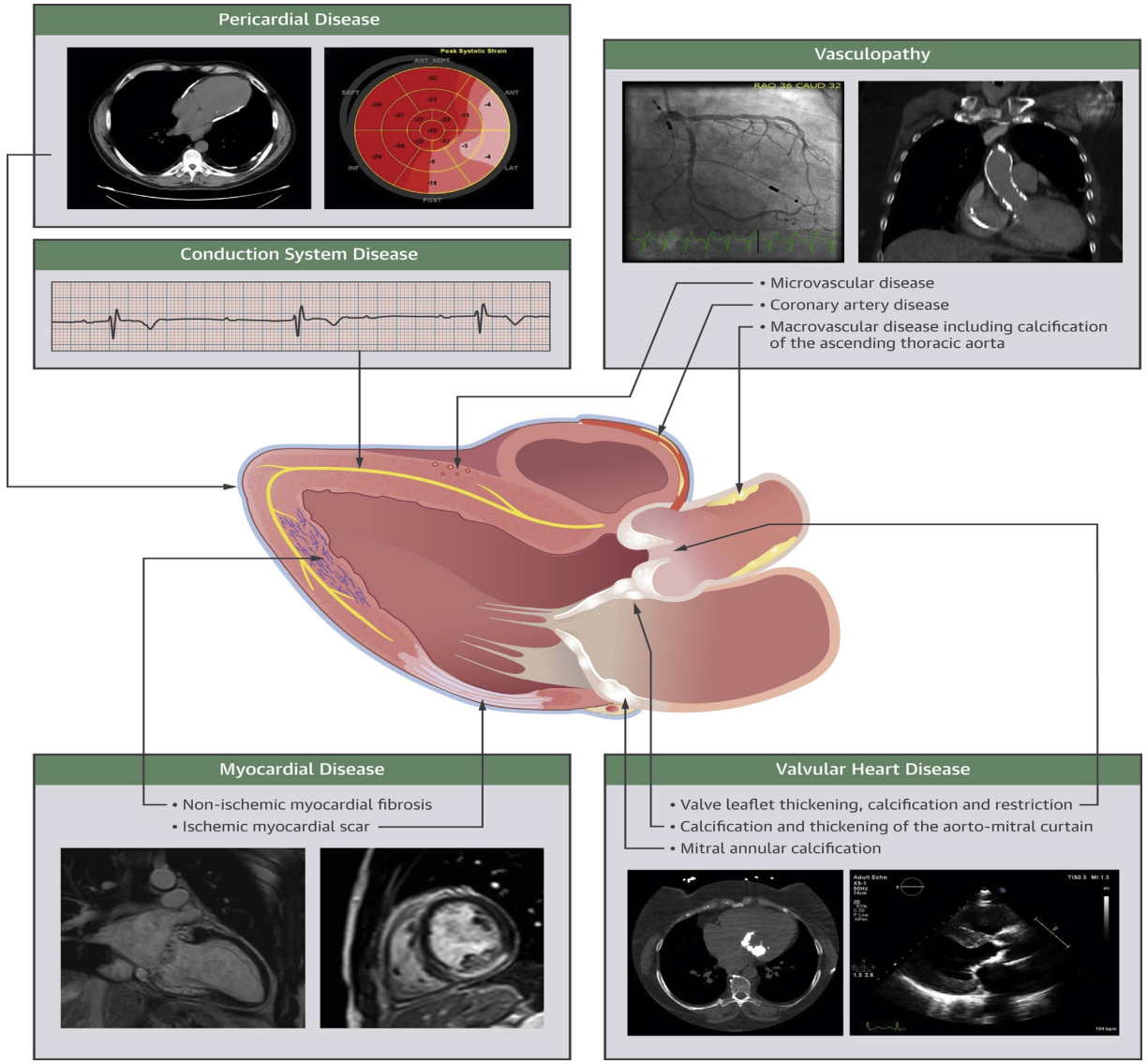
What can we do about cardiotoxicity?

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

Radiation-induced CV Disease: Multimodality Imaging Approach

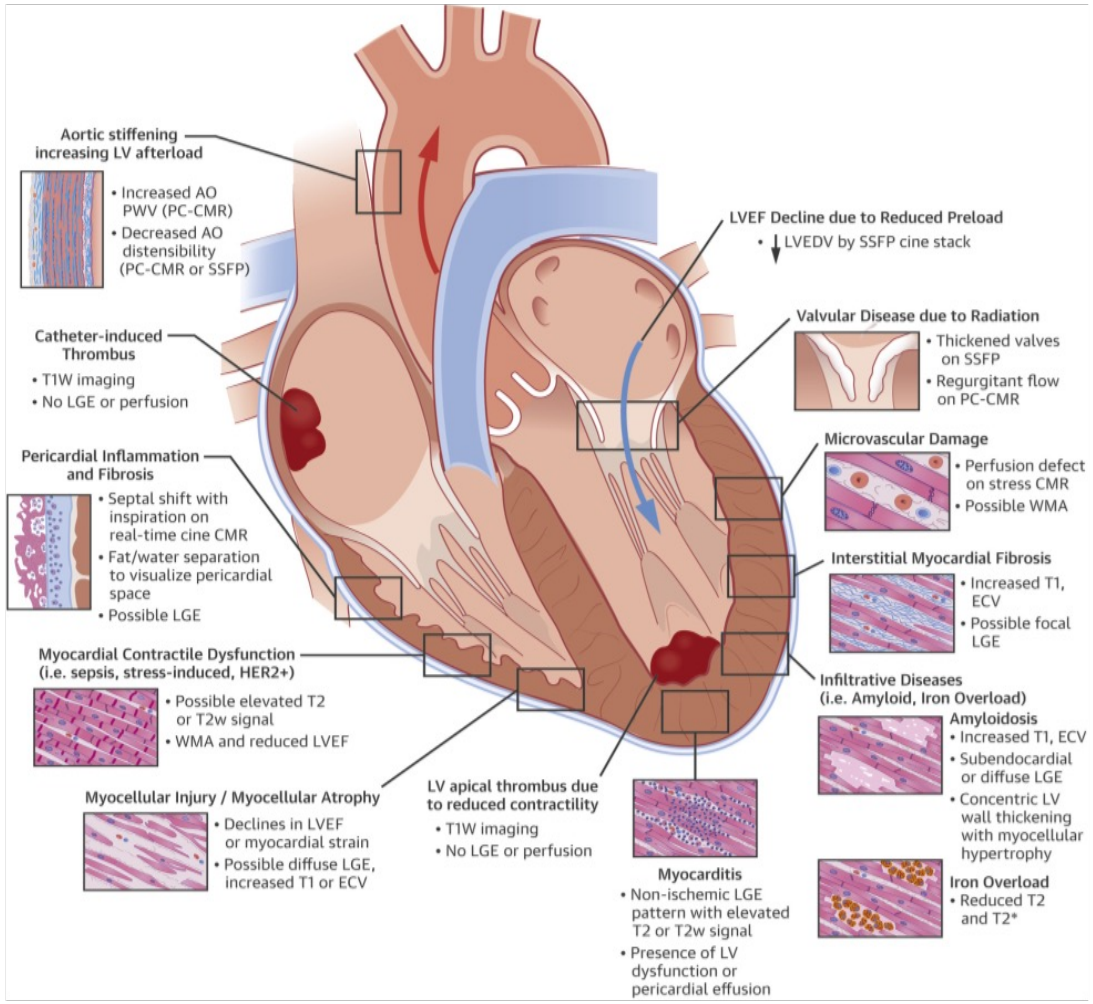
- Late manifestation occurring years-decades after treatment
- Results from diffuse interstitial fibrosis and collagen deposition
- Luminal narrowing of arteries and arterioles; accumulation of myofibroblasts and intimal proliferation
- Myocardial fibrosis, VHD (regurgitation or stenosis); CAD; pericardial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

VHD=valvular heart disease.

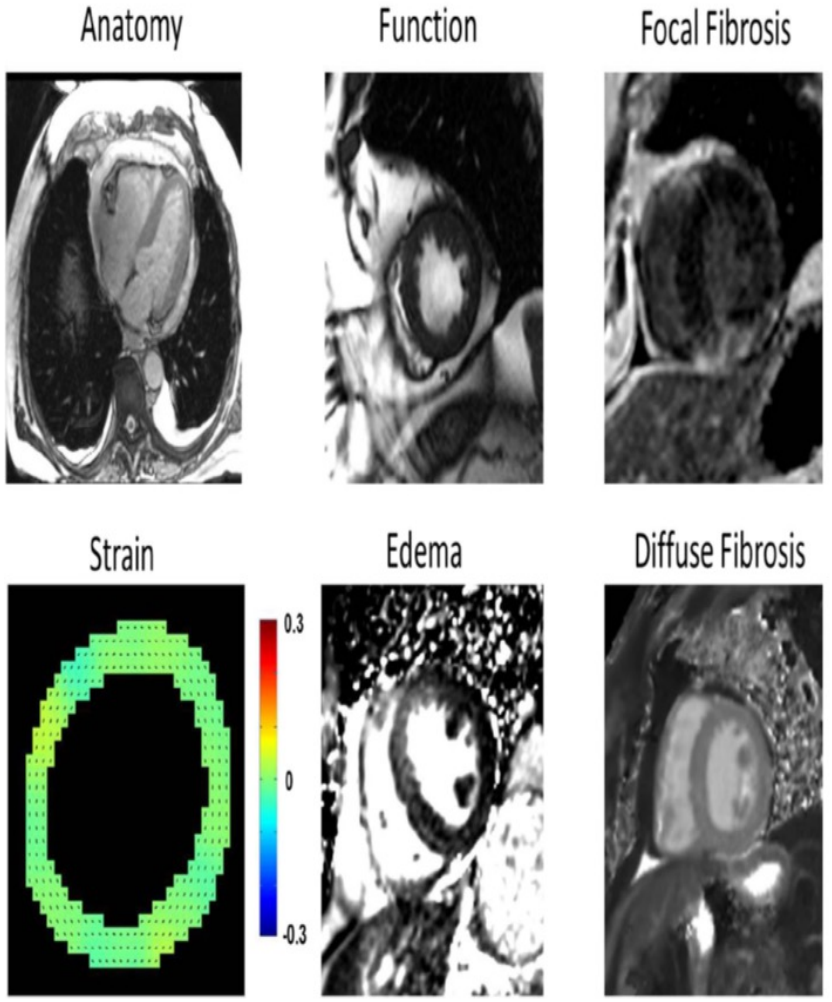


Desai MY et al. *JACC Cardiovasc Imaging*. 2018;11:1132-1149.

Cardiac Magnetic Resonance: Comprehensive Cardiovascular Evaluation

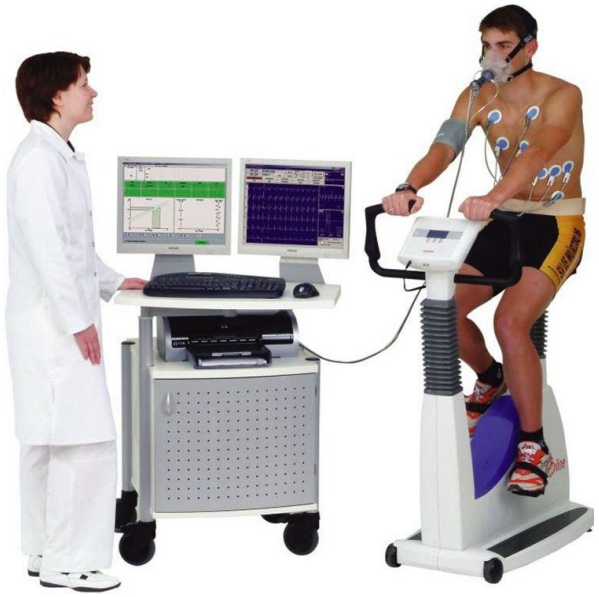


Jordan JH et al. *JACC Cardiovasc Imaging*. 2018;11:1150-1172.



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

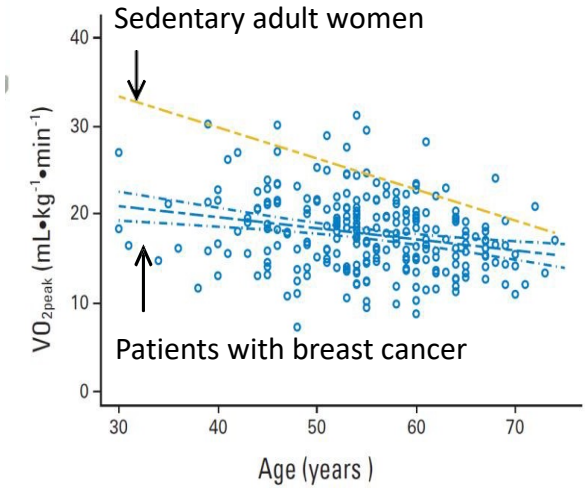
Physiologic Measures of CV Reserve: Exercise Testing



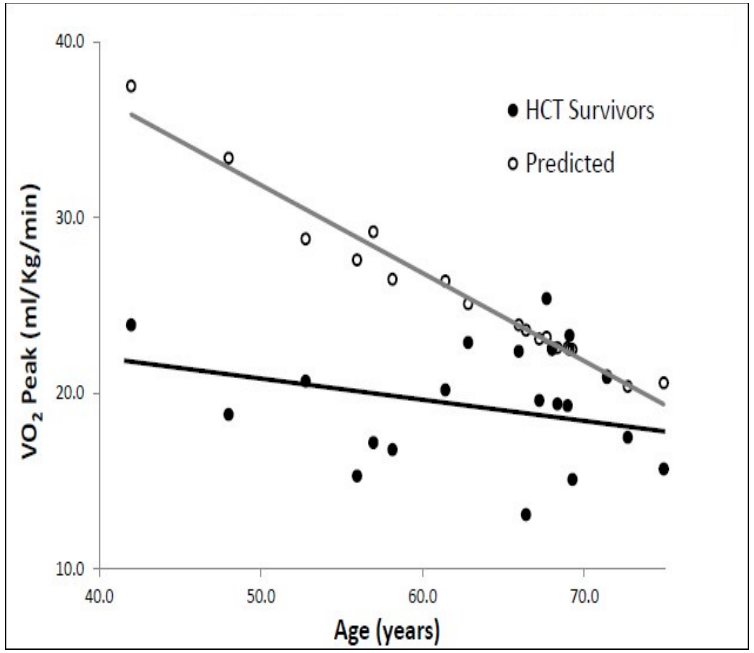
VO_{2peak}

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.

Multi-modality Imaging Approach for CV Risk in Cancer

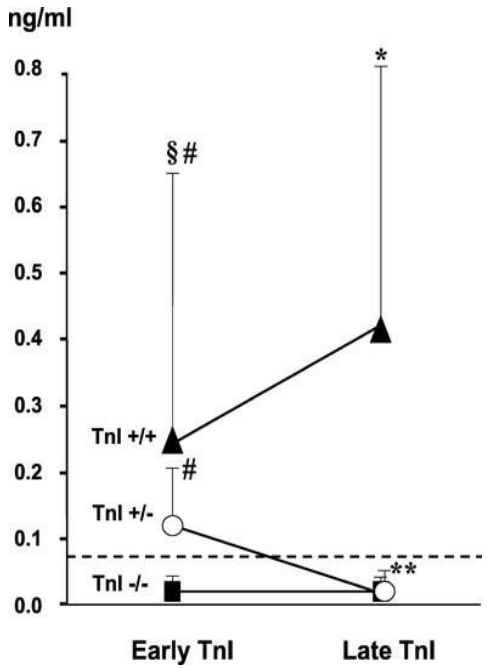
- Better characterizes the multi-level injury to the CV system from many cancer therapies
  - eg, processes (valvular or pericardial disease, myocellular injury, LV diastolic dysfunction, epicardial or microvascular CAD) that do not precipitate an early change in LV systolic function
- Accessibility and expertise are limitations to universal use
- Implementation should focus on institutional strengths

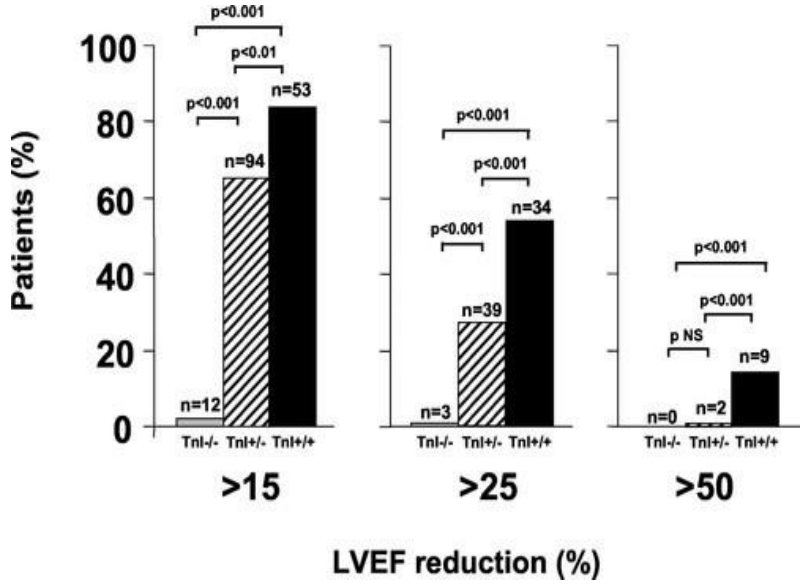
What else can we do about cardiotoxicity?

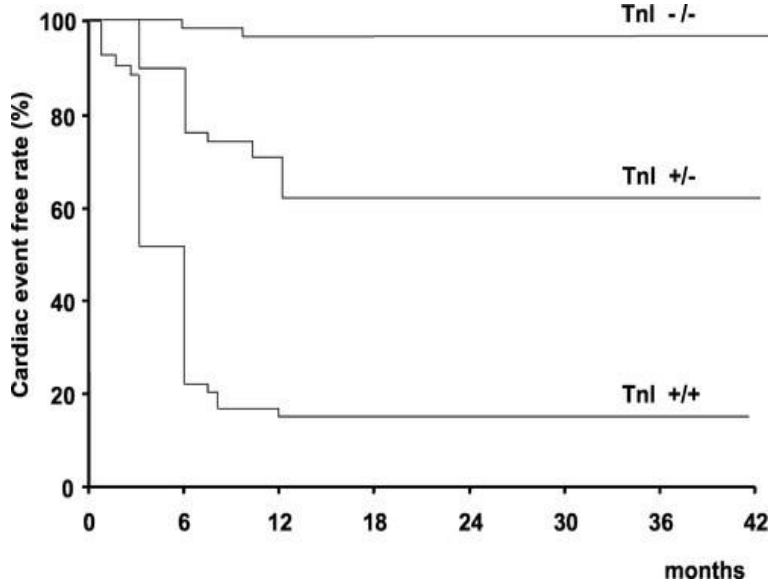
- ~~LVEF~~ - STRAIN?
- MULTI-MODALITY IMAGING?
- BLOOD BIOMARKERS

Blood Biomarkers

Elevated Troponin I After Anthracyclines Indicates Risk





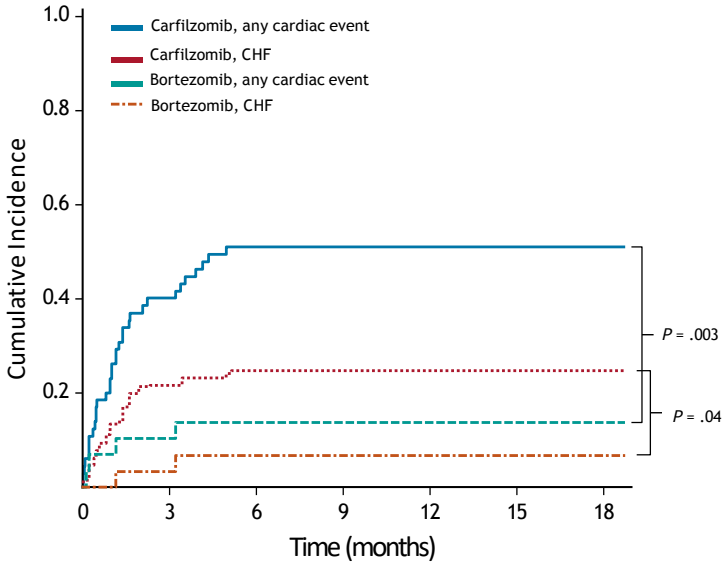


TnI=troponin I.

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

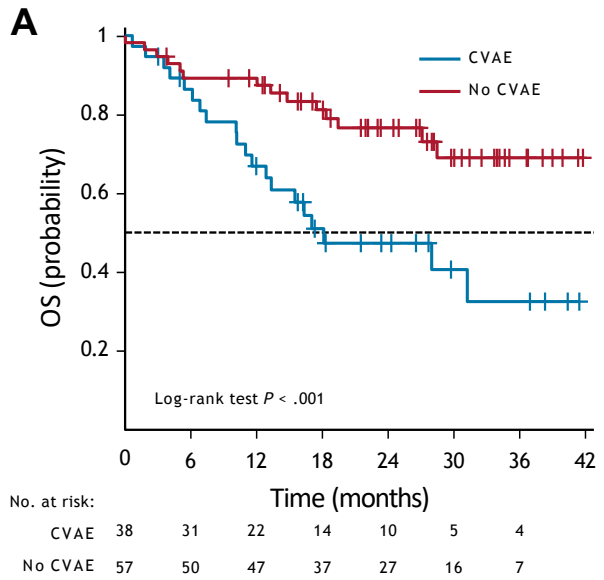
Blood Biomarkers

Elevated Natriuretic Peptides with Proteosome Inhibitors Indicate Risk



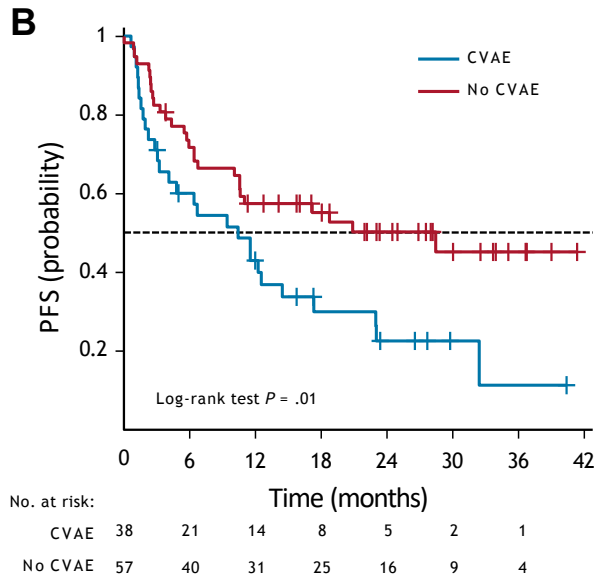
No. at risk:

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

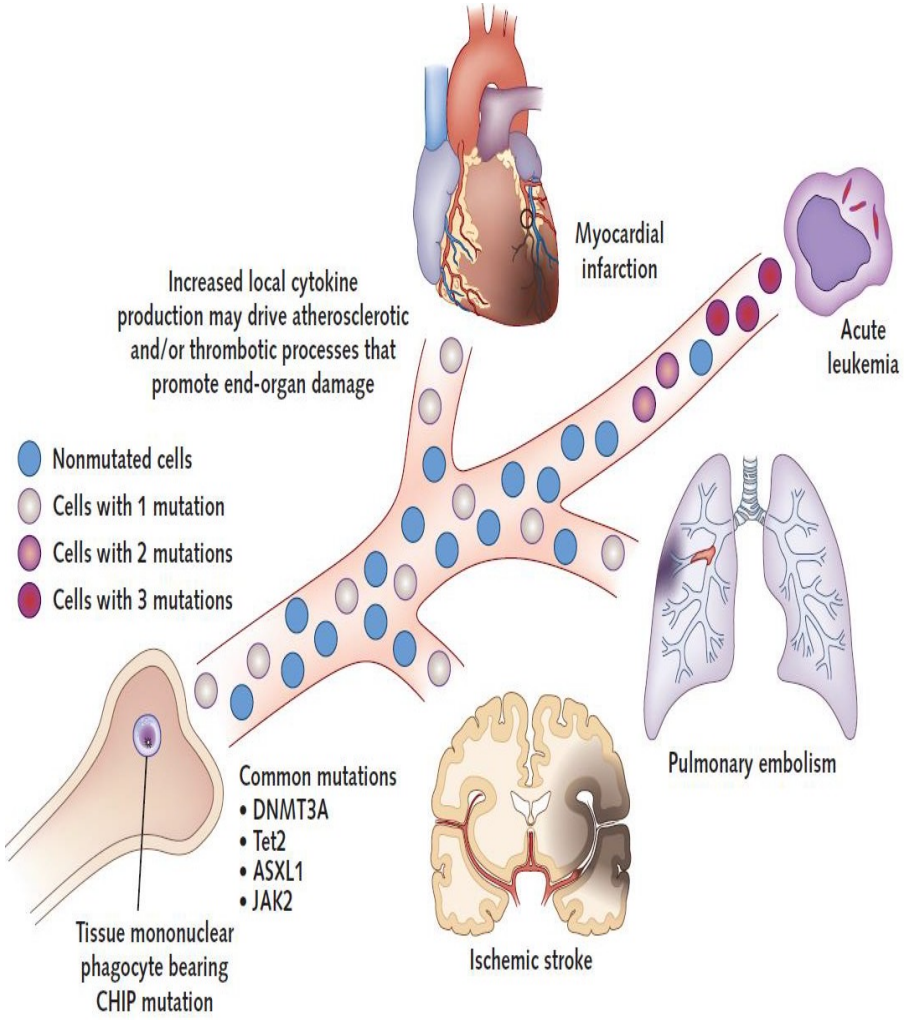
TABLE 4. Multivariable Competing Risk Analysis for Predictors of First CVAE

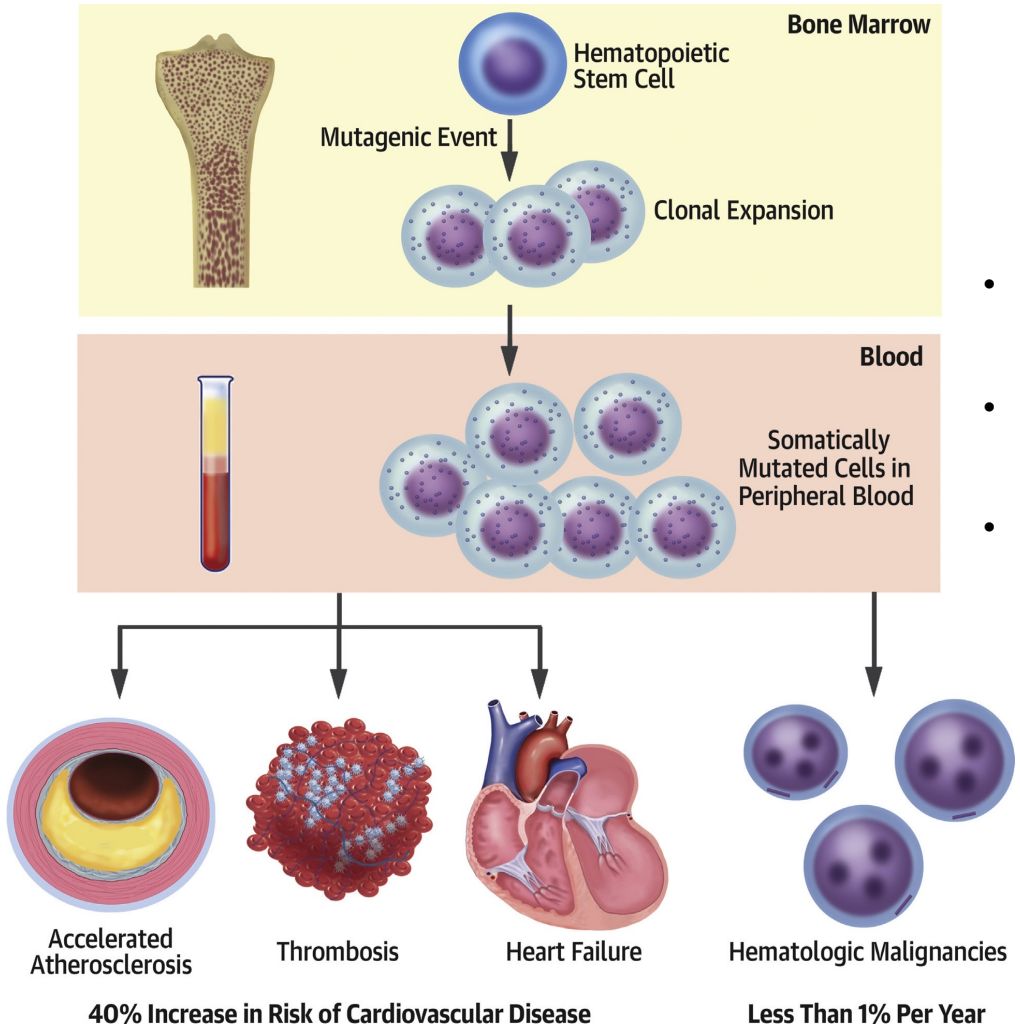
Effect	HR (95% CI)	P
Car lzomib v bortezomib	3.0 (1.1 to 8.4)	.04
Elevated baseline natriuretic peptide levels v normal levels	4.1 (2.1 to 8.1)	, .001
Normal baseline natriuretic peptide levels that became elevated mid– rst cycle of treatment v normal levels	9.5 (4.3 to 20.7)	, .001
# 1 traditional CV 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.

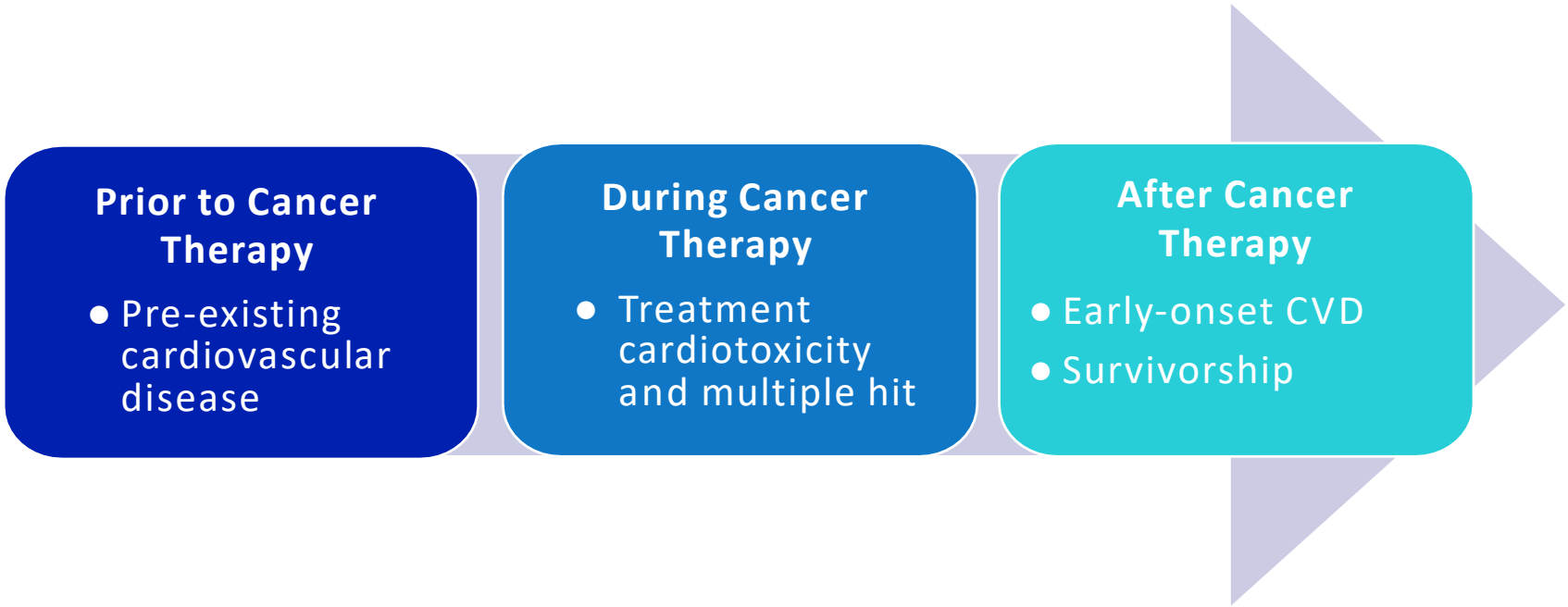
Blood Biomarkers: Clonal Hematopoiesis and CVD



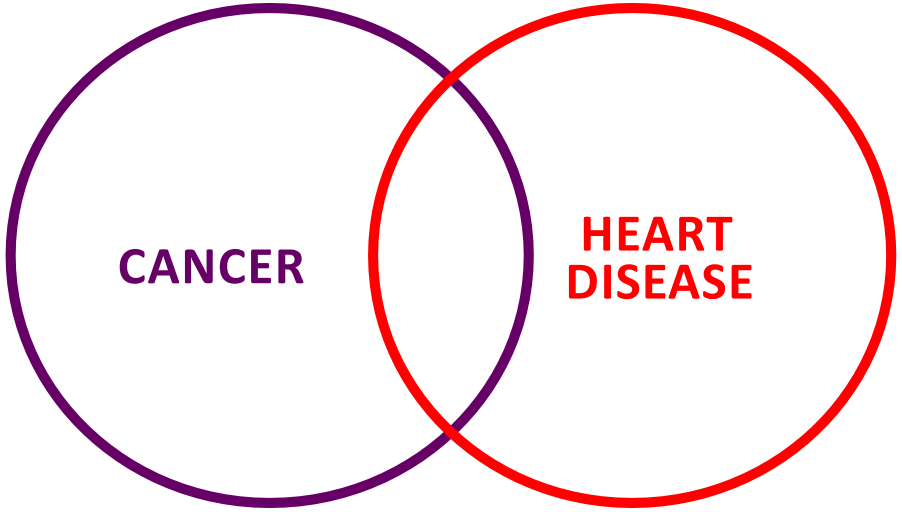


- We accumulate somatic mutations with age
- Common mutations (DNMT3A, TET2, ASXL1, JAK2)
- Increase in risk of hematologic cancer and CVD

Libby P et al. *J Am Coll Cardiol*. 2019;74:567-577.


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

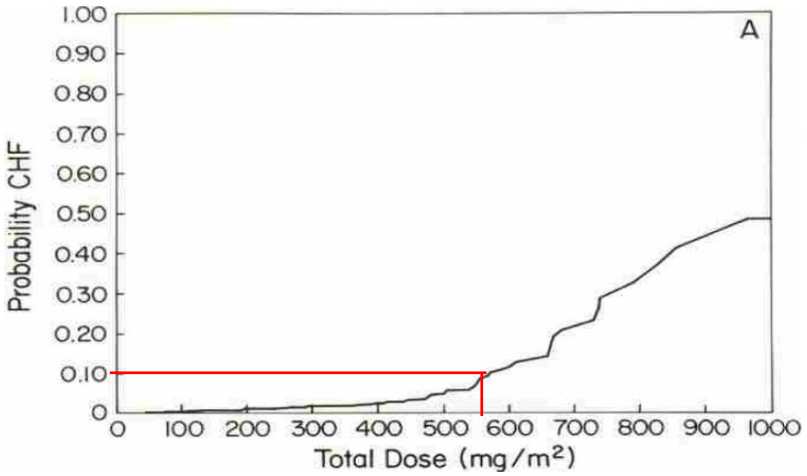


- Survivors have a 10 times higher risk for **coronary atherosclerosis**
- Survivors have a 15 times higher risk of **heart failure**
- Survivors have a 9.3 times the risk for **stroke**
- Risks are particularly high among survivors who had received **anthracycline drugs**, such as doxorubicin, or **high-dose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

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

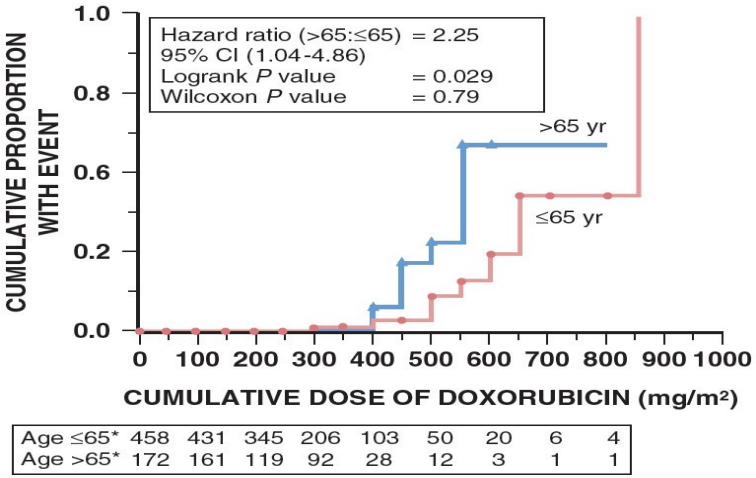
Early-onset Anthracycline Cardiomyopathy

Chart Review



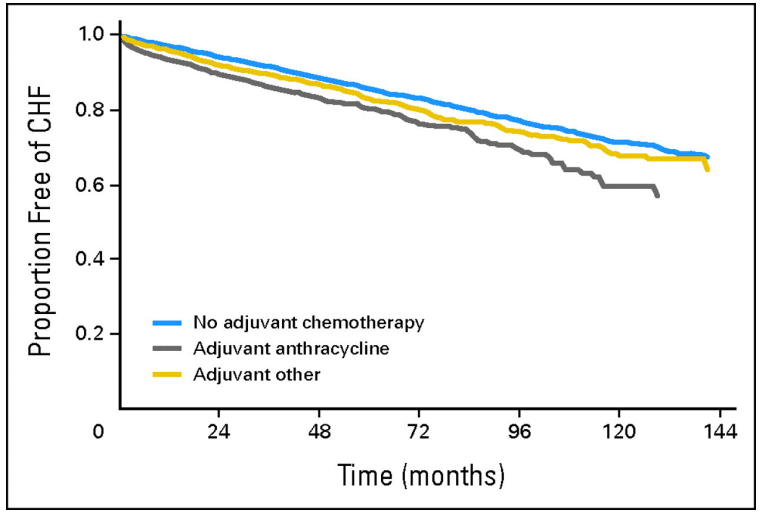
Von Hoff DD et al. *Ann Intern Med*. 1979;91:710-717.

Imaging



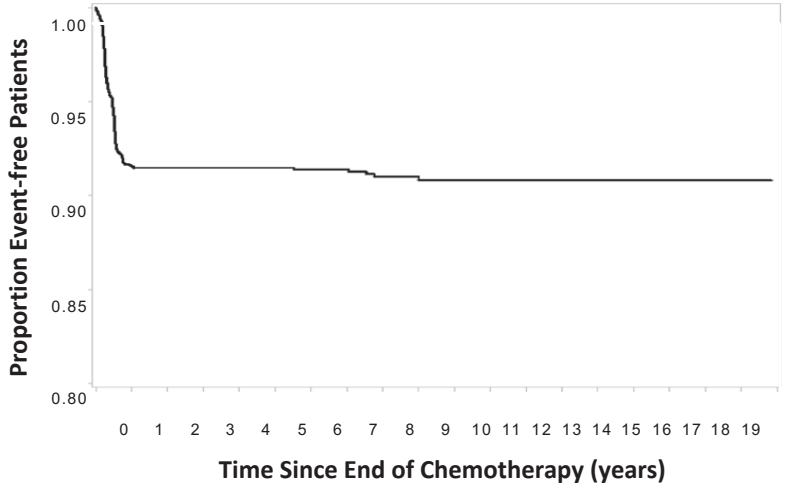
Swain SM et al. *Cancer* 2003;97:2869-2879.

Medicare SEER



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

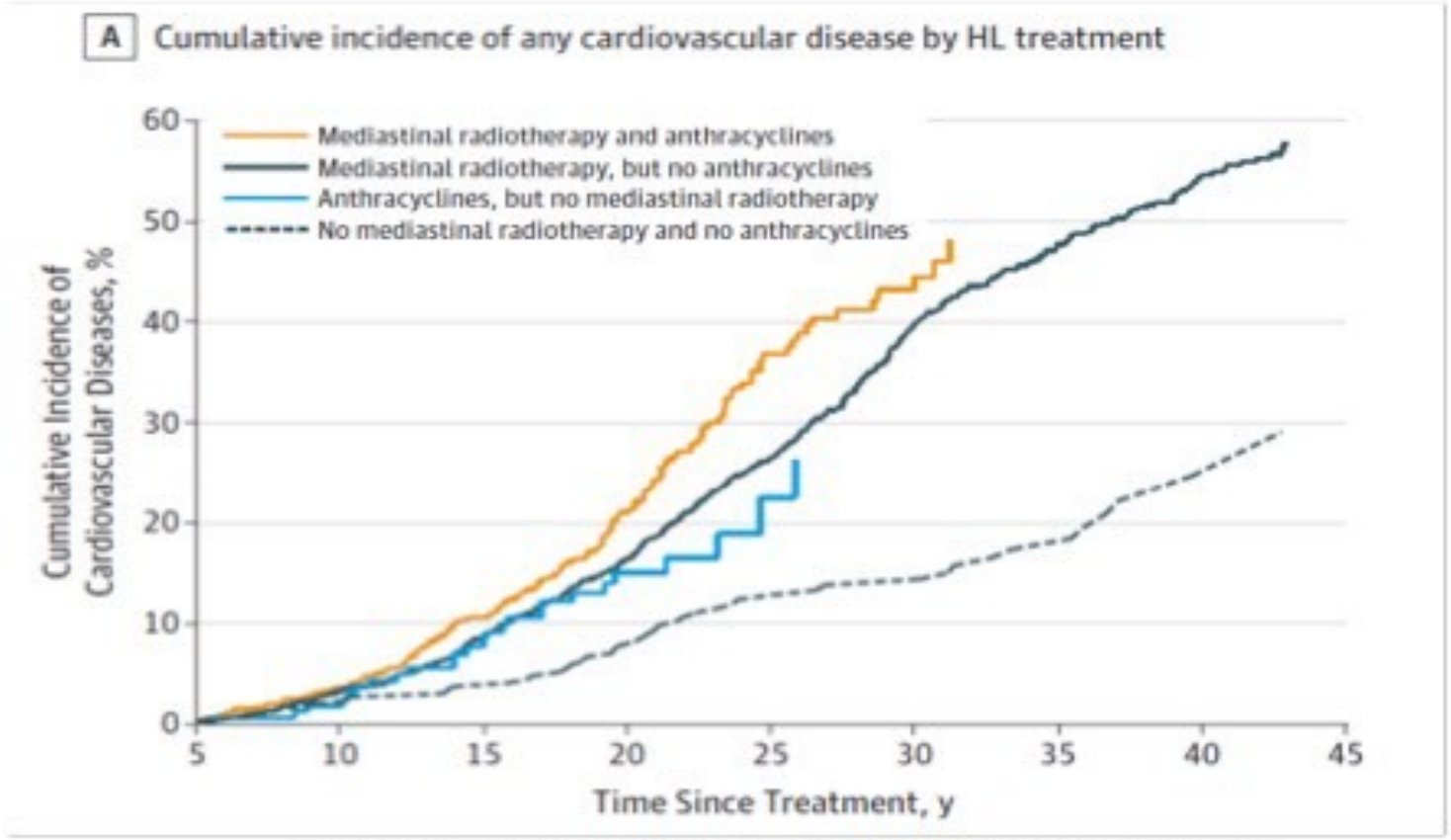
Timing



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

CV Disease in Cancer Survivorship

CV Disease After Hodgkin Treatment



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

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

CV Disease in Cancer Survivorship

VOLUME 25 · NUMBER 1 · JANUARY 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Screening for Coronary Artery Disease After Mediastinal Irradiation for Hodgkin's Disease

Paul A. Heidenreich, Ingela Schnittger, H. William Strauss, Randall H. Vagelos, Byron K. Lee, Carol S. Mariscal, David J. Tate, Sandra J. Horning, Richard T. Hoppe, and Steven L. Hancock

From the Department of Medicine, Division of Cardiology; Division of Medical Oncology; Department of Radiology,

ABSTRACT

In 972 Hodgkin's disease patients who received >= 35 Gy to the mediastinum, 53 of 345 deaths were attributed to heart disease

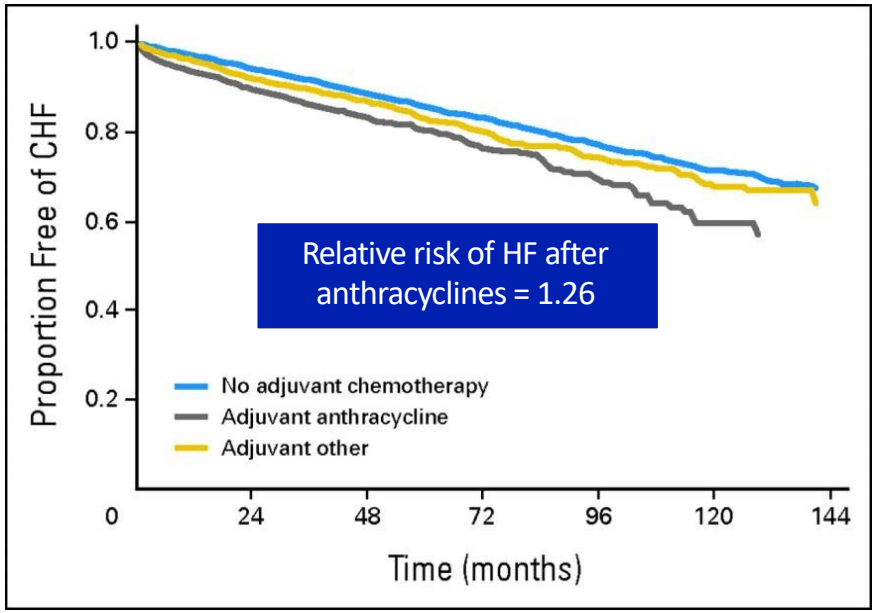
- Increased risks at all intervals after irradiation
- 27% of AMI deaths occurred before age 40 years of age
- 42% occurred within 10 years of Hodgkin's disease treatment

AMI=acute myocardial infarction.

Heidenreich PA et al. *J Clin Oncol*. 2007;25:43-49.

CV Disease in Cancer Survivorship

Heart Failure in Older Patients with Breast Cancer: Anthracyclines and Comorbidities Are Independent Risk Factors



Risk factors for HF

Charlson Comorbidity Score 1: HR 2.05
2: HR 3.62

Black race: HR 1.40
Trastuzumab: HR 1.46
Hypertension: HR 1.45
Diabetes: HR 1.74
CAD: HR 1.58

43,338 breast cancer survivors (66-80 years old) in Medicare SEER database. At 10 years, the risk of incident HF without chemotherapy 29%; with anthracycline-based chemotherapy 38%.

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

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