EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Cardio-Oncology: A Path Towards Bigger and Bolder Cancer Care

Anant Mandawat, MD FACC
Director, Cardio-Oncology Center of Excellence
Winship Cancer Institute
Heart & Vascular Center
Emory University School of Medicine

Debates and Didactics in Hematology and Oncology
Sea Island, GA
July 26, 2024

Winship Cardio-Oncology:
To lead in collaborative cardiac care for patients with cancer

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

Disclosures

Grants/Research Support:

- Pfizer
- Myovent
- Prostate Cancer Foundation
- National Comprehensive Cancer Network
- Morningside Center for Innovation

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

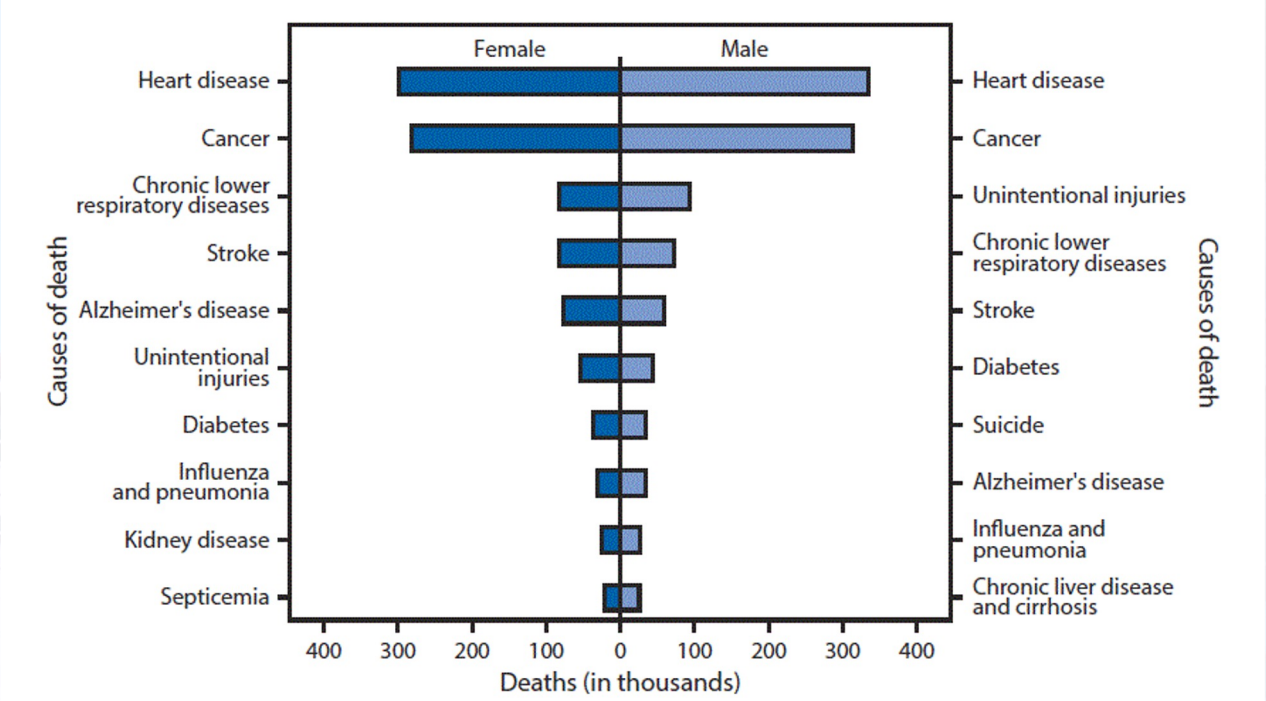
Objectives

- Describe the epidemiology of cardiac disease and cancer
- Develop a clinical framework to approach Cardio-Oncology
- Understand risk stratification in Cardio-Oncology
  Ex. Anthracyclines
  - Clinical tools
  - Strain imaging

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

The Epidemiology of Cancer & Cardiac Disease

Top 10 Causes of Death in the US

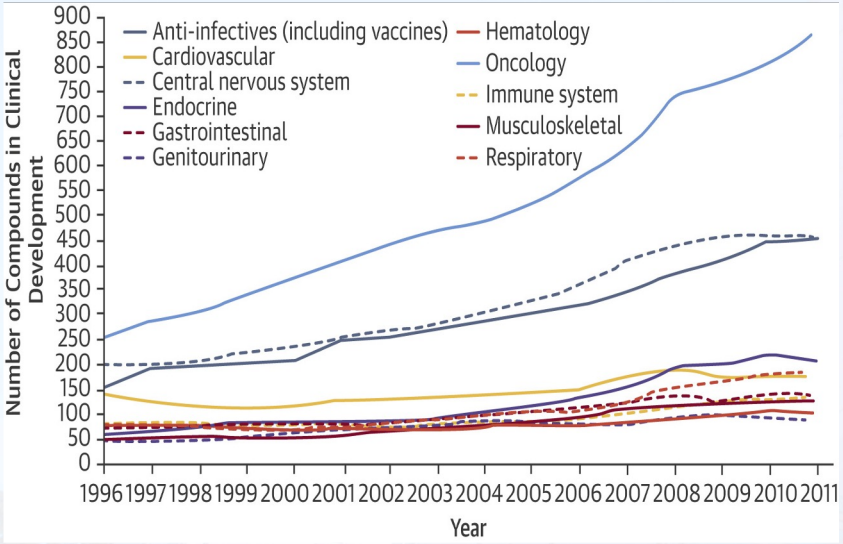


QuickStats: Number of Deaths from 10 Leading Causes, by Sex — National Vital Statistics System, United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66:413. DOI: http://dx.doi.org/10.15585/mmwr.mm6615a8External

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

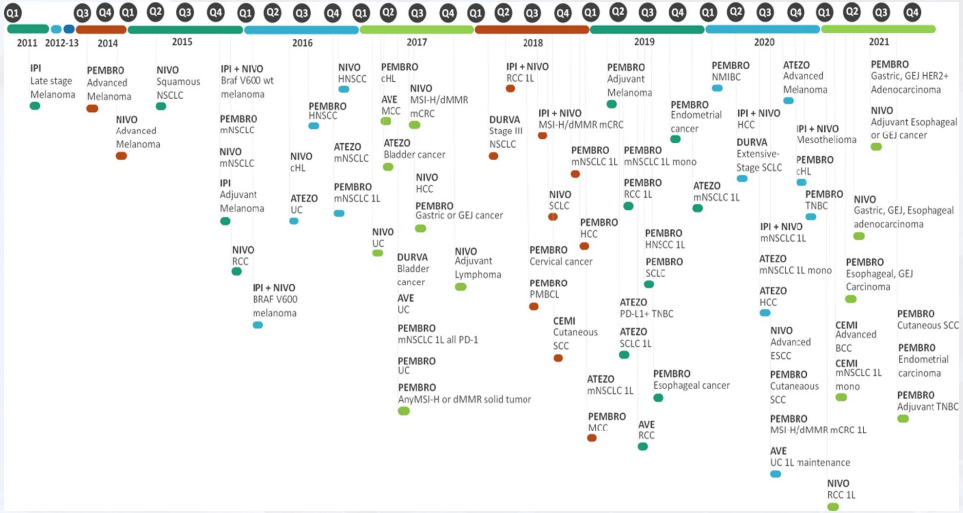
Increase in cancer therapies over time

Innovative phase I-III compounds



N Fordyce et. al, *JACC* 2015

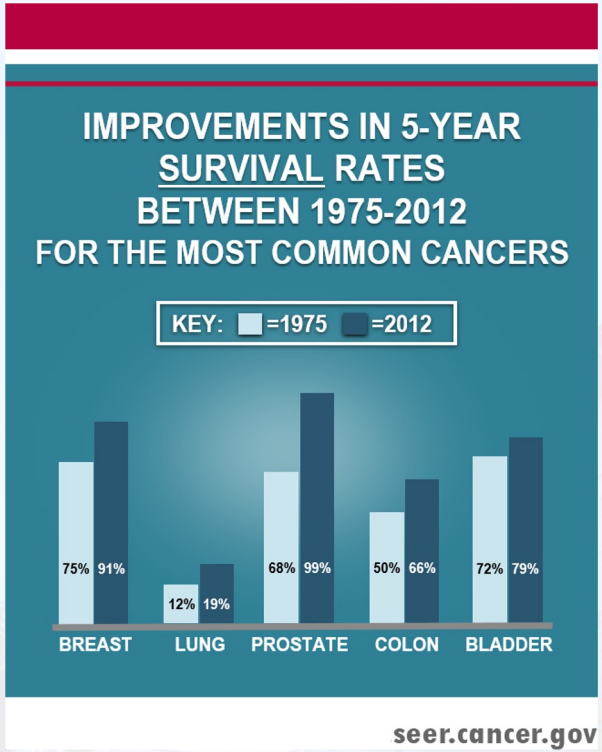
Expansion of immunotherapy indications

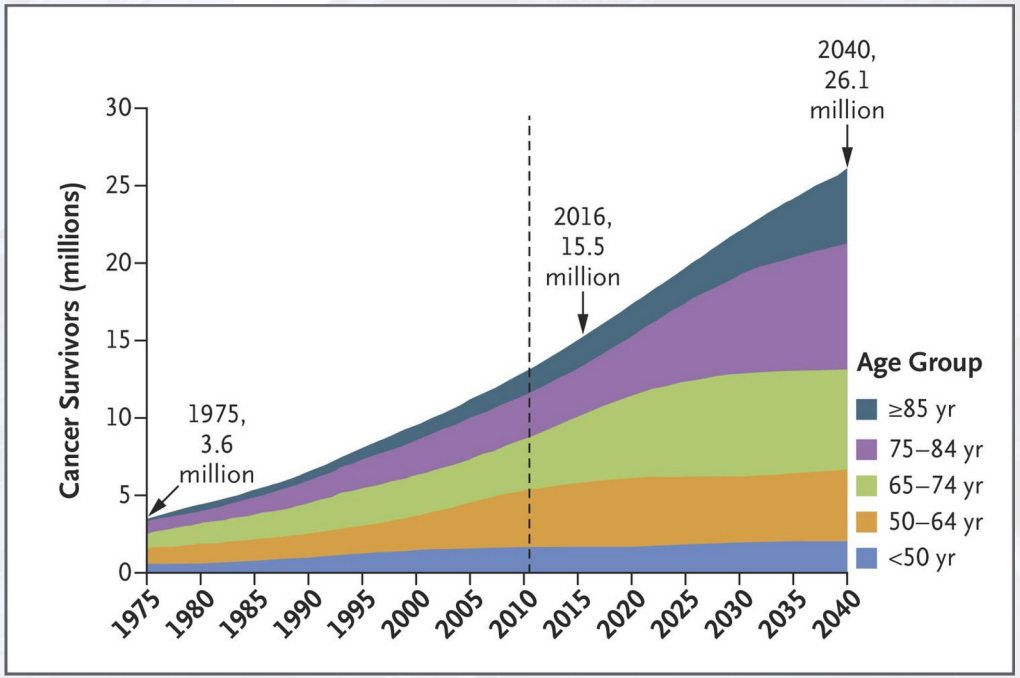


Maritaz et. al, *Journal of Hematology & Oncology*, 2022

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Improvement in Cancer Outcomes

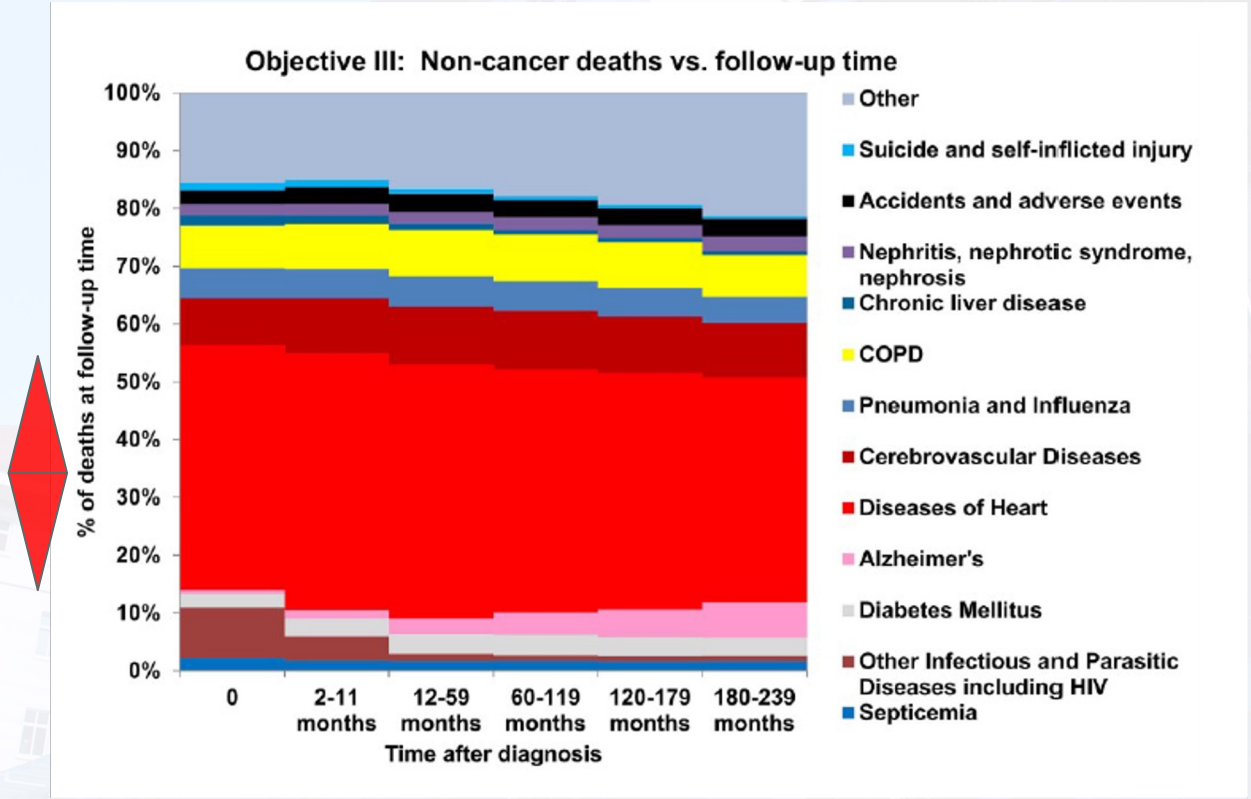




CL Shapiro. N Engl J Med 2018;379:2438-2450.

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Top Non-Cancer Causes of Death in Cancer Patients

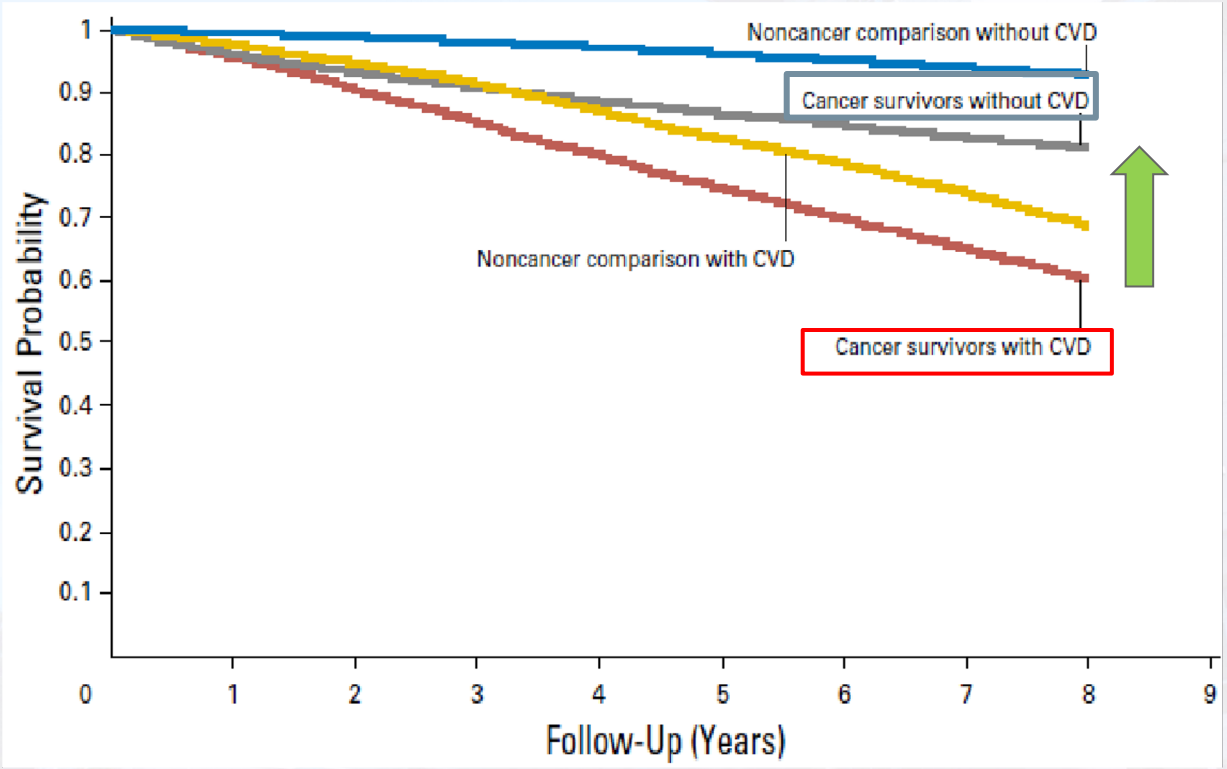


Zaorsky et al. *Ann Oncol* 2017

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Survival of Patients with Cancer & CVD

All Cancer Survivors



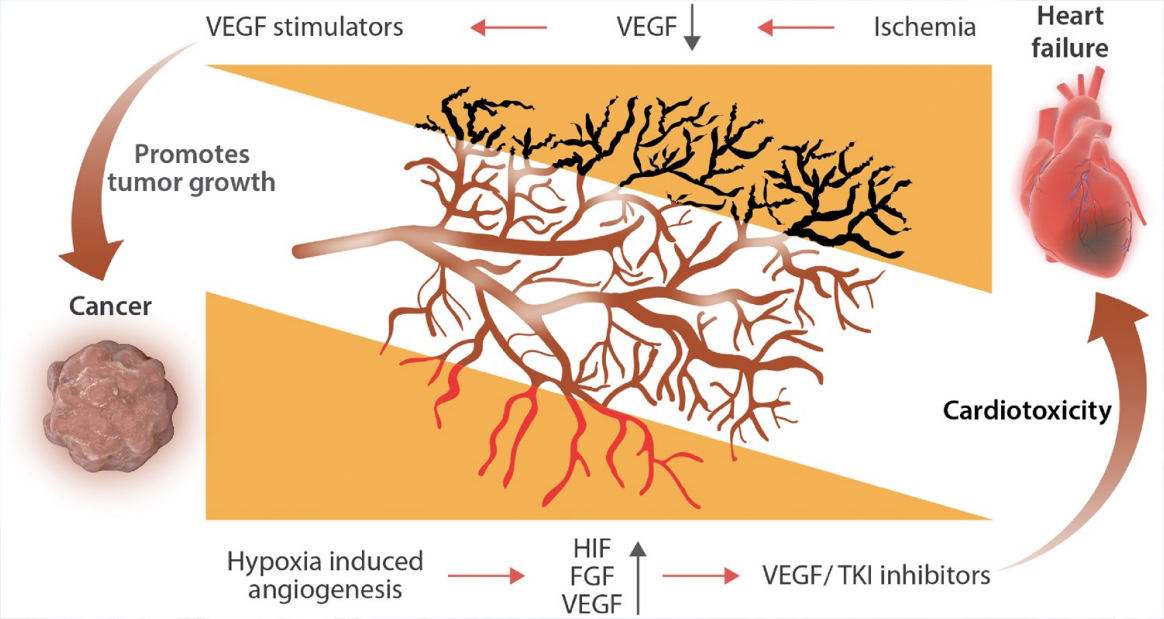
- >36k cancer survivors Kaiser Permanente-SEER
- Cancer survivors with CVD have worst survival out of any group
- Goal is to move them up the curve to improve outcomes

Armenian, et al. *JCO*, 2016

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Framework to Approach Cardio-Oncology

Competing Therapeutic Dynamic of Cancer and CVD



Meijers et. al, *Cardiovascular Research*, 2019

- In cancer treatment, the goal is to starve/target/destroy malignant cells
- In heart disease, the goal is to heal/nourish/protect cardiac myocytes
- Ex. VEGF inhibitor

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Overview of Cardiotoxicity

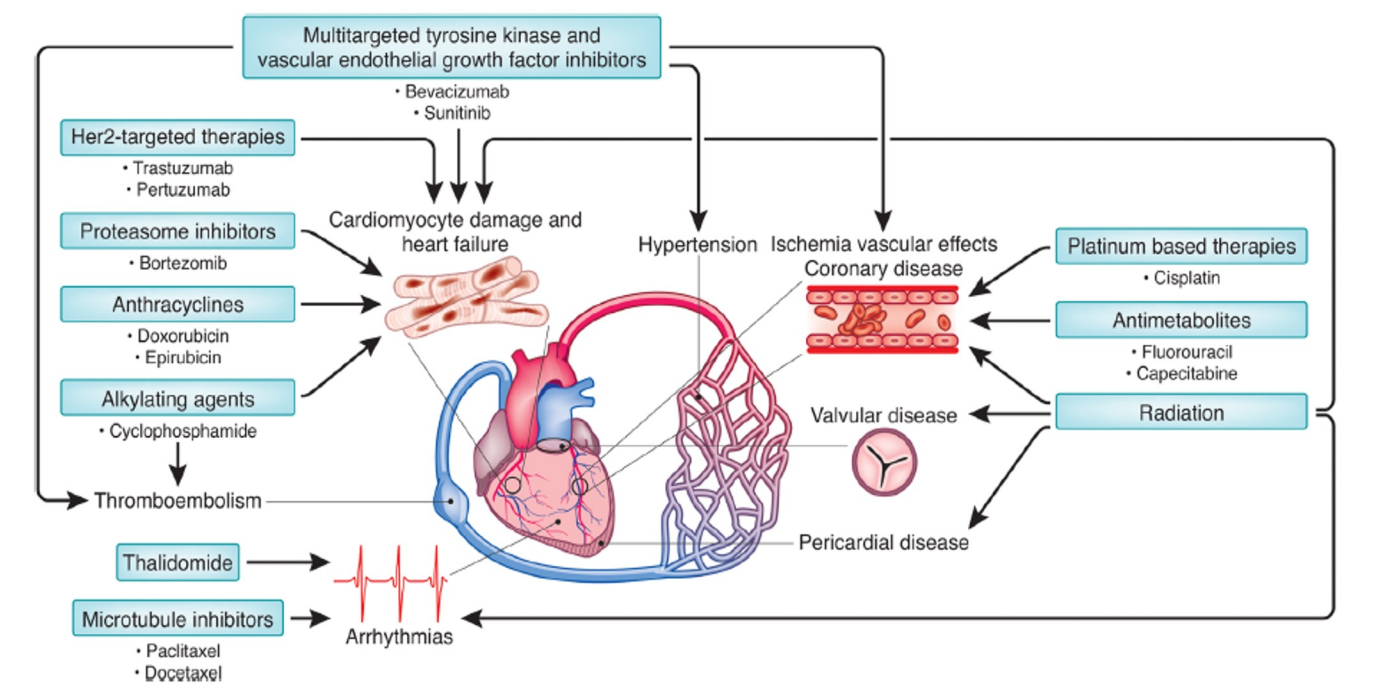


Figure 1. An overview of the cardiovascular side effects of chemotherapy and radiation.

- Broad Spectrum
- Acute & chronic
- Team-based approach

Adapted from Lenneman C, et al. *Circ Res*, 2016

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

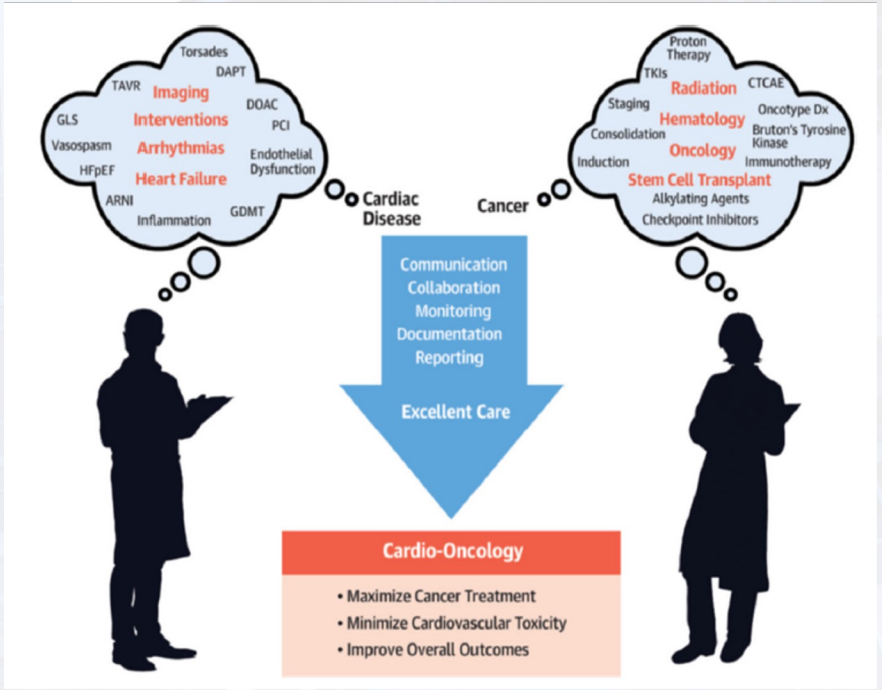
Implications of Cardiac Toxicity in Cancer Patients

- Interruption, or discontinuation of cancer therapy
- Physical morbidity & mortality of CVD
- Psychological impact of an additional severe comorbidity
- Disqualification from oncology clinical trials

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Cardio-Oncology: A Path Towards Bigger & Bolder Cancer Care

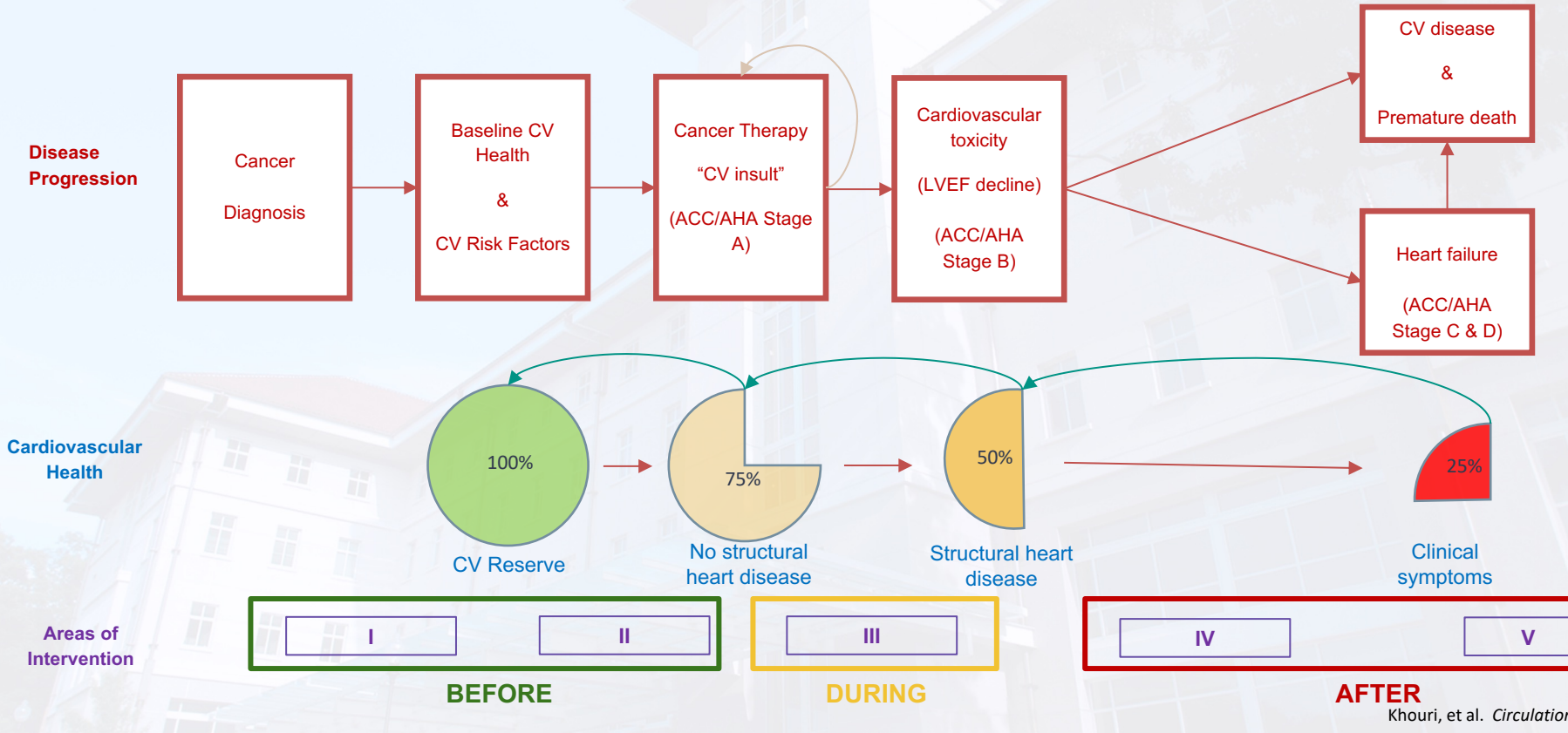
- Many cancer therapeutics are associated with **cardiovascular complications**
- Cardiovascular disease can be a **rate-limiting step** that **excludes** patients from optimal treatment and clinical trials
- Collaboration between cardiologists and oncologists can result in **bigger** and **bolder** treatment options



Adusumalli et al. J Cardiovasc. Trans. Res, 2020

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Integrated Approach of CVD & Cancer



Khouri, et al. *Circulation* 2012

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

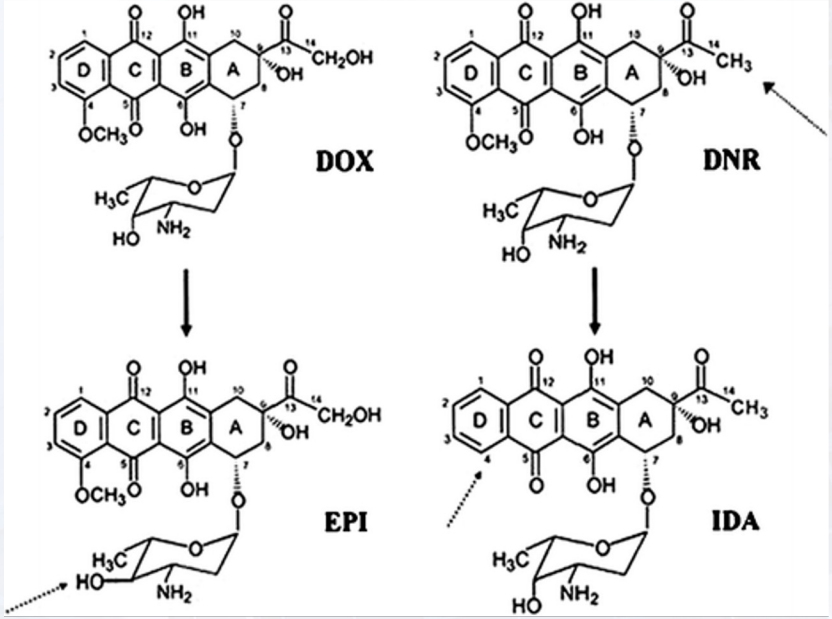
Risk Stratification in Cardio-Oncology

Case Example: Anthracyclines

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Anthracycline Experience

- Doxorubicin discovered from the fungi *Streptomyces peucetius*
- Functions by inhibition of topoisomerase I and II
- Used in clinical oncology starting in 1960s
- Effective in treating a variety of cancers
  - World Health Organization's list of essential medicines



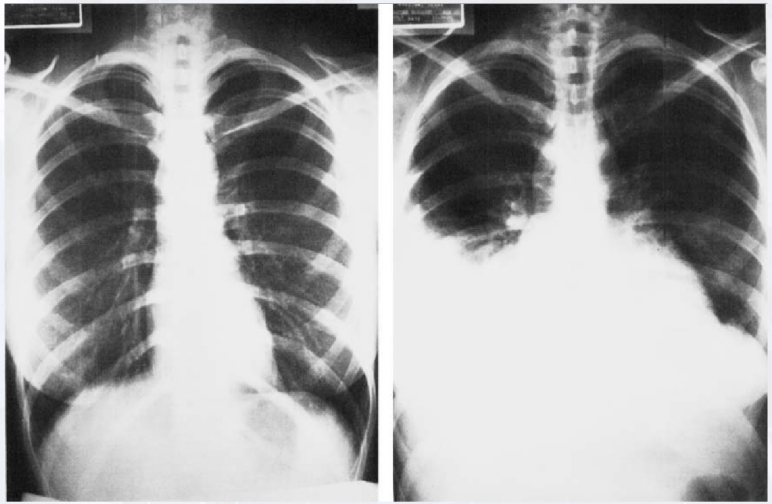
McGowan et. al, *Cardiovascular Drugs and Therapy*, 2017
Dhingra et. al, *Cardio-Oncology: Principles, Prevention, Management*, 2017

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

A CLINICOPATHOLOGIC ANALYSIS OF ADRIAMYCIN CARDIOTOXICITY

EDWARD A. LEFRAK, MD,* JAN PIŤHA, MD, PHD,†
SIDNEY ROSENHEIM, MD‡ AND JEFFREY A. GOTTLIEB, MD§

- Reviewed 399 patients at Baylor & MD Anderson treated with Adriamycin
- Found 11 cases of Adriamycin-induced cardiotoxicity
- Only 1 case of toxicity when dose <550 mg/m2. Recommendation to limit dose to 550 mg/m2

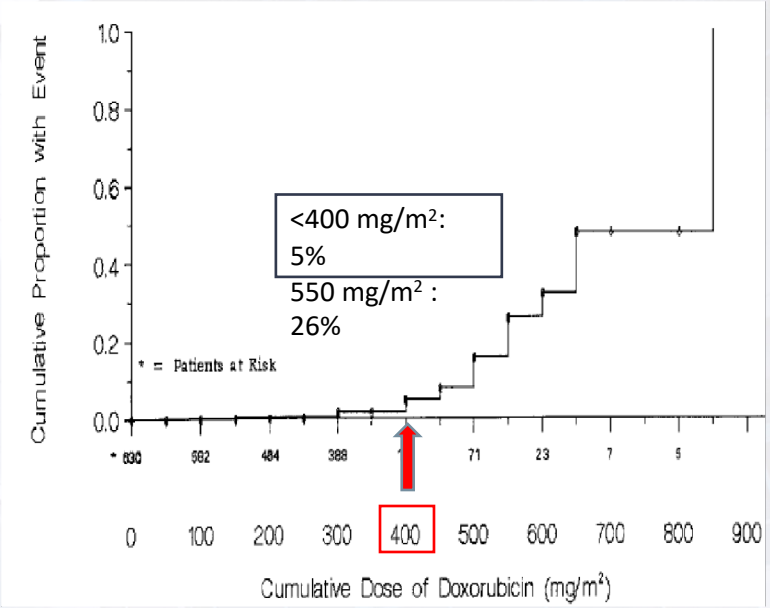


Lefrak et al., *Cancer*, 1973

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Anthracycline Cardiotoxicity: Threshold Lowered

- TTE was not widely available in 1970s, 550 mg/m2 cutoff based on clinical symptoms
- Swain in 2003 studied the rate of heart failure using TTEs in 630 patients with breast and lung cancer who received doxorubicin
- Doxorubicin related HF occured at a lower dose of 400mg/m2 and with greater frequency than previously thought from the 1970s

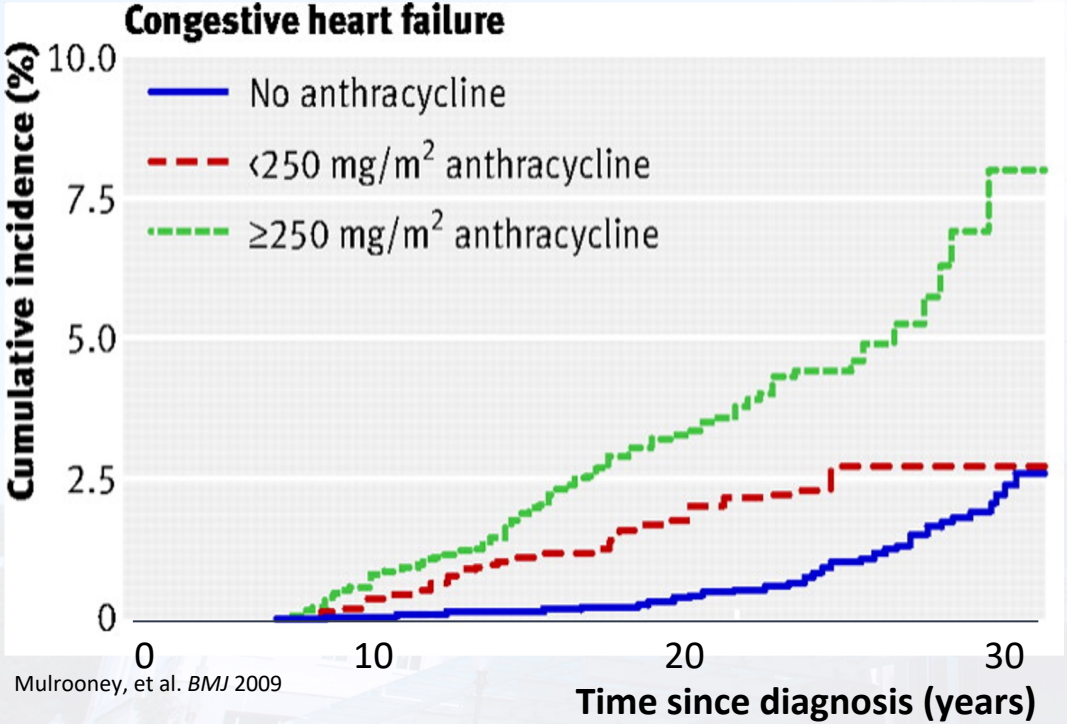


Swain, et al. *Cancer* 2003

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Even lower threshold for cardiac toxicity

Childhood Cancer Experience

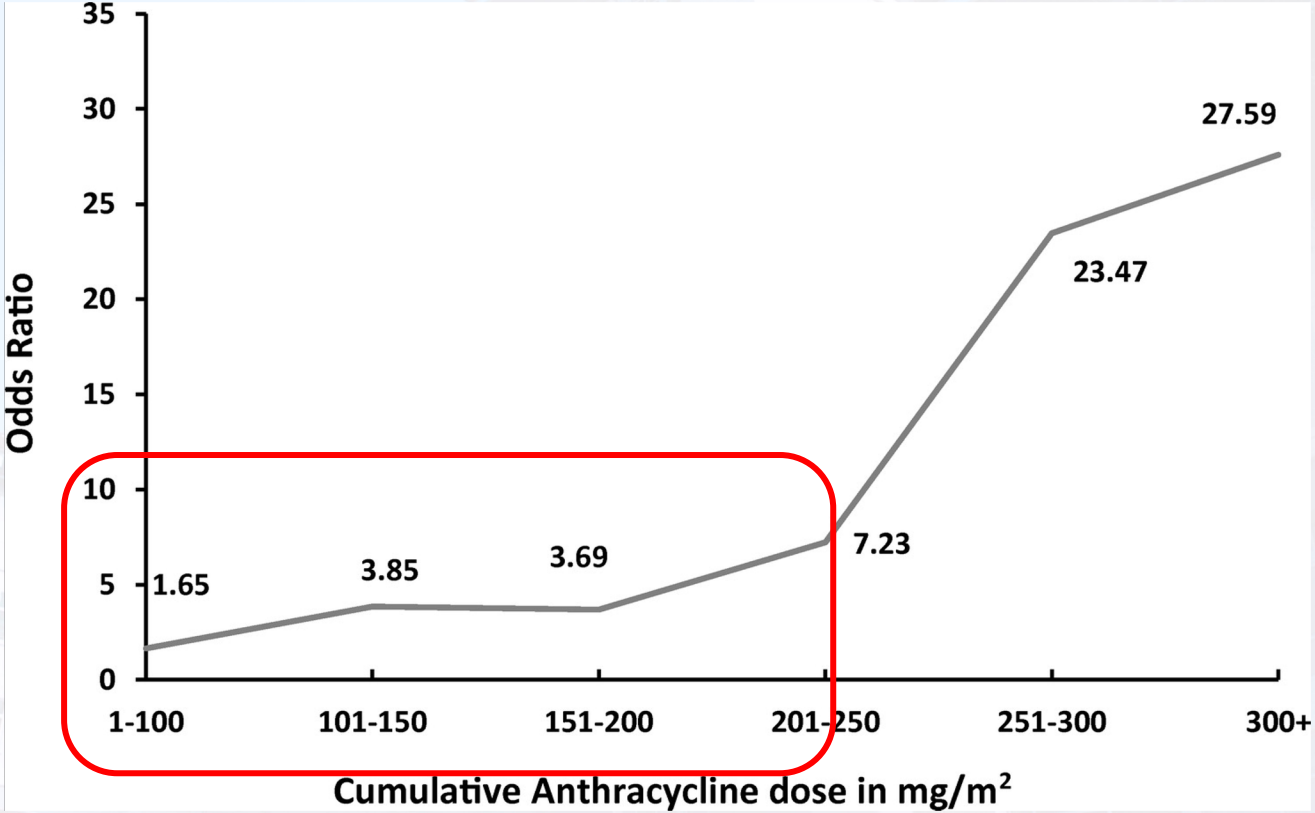


Mulrooney, et al. *BMJ* 2009

- 14k survivors of childhood cancer
- With longer follow up, the threshold for cardiac toxicity was even lower at 250 mg/m2
- Solidified a theme for anthracyclines that cumulative dose, even at small doses, can cause cardiac damage

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

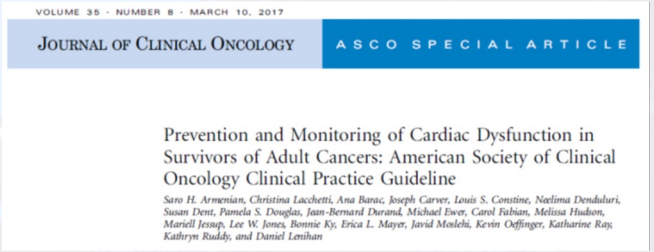
Anthracycline Cardiotoxicity Risk



Armenian & Bhatia, *ASCO edbook*, 2018

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Increased Risk for Developing Cardiotoxicity



- High dose anthracyclines (>=250mg/m2 doxorubicin; >=600mg/m2 epirubicin)
- High dose (>30 Gy) radiotherapy (RT) with heart in treatment field
- Lower dose anthracyclines (eg. <250 mg/m2 doxorubicin) with lower dose RT (<30 Gy) and heart in treatment field
- Treatment with lower dose anthracyclines (eg <250mg/m2 doxorubicin) with trastuzumab sequentially
- Lower dose anthracycline (eg. <250mg/m2 doxorubicin) or trastuzumab alone, and any of the following:
    - Multiple (>=2) CV risk factors: smoking, HTN, diabetes, dyslipidemia, obesity
    - Older age (>=60 y) age
    - Compromised CV function (e.g. borderline low LVEF (50-55%), history of MI, moderate valvular disease

Armenian et. al, *JCO*, 2018

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

HFA-ICOS Cardio-Oncology Risk Calculator

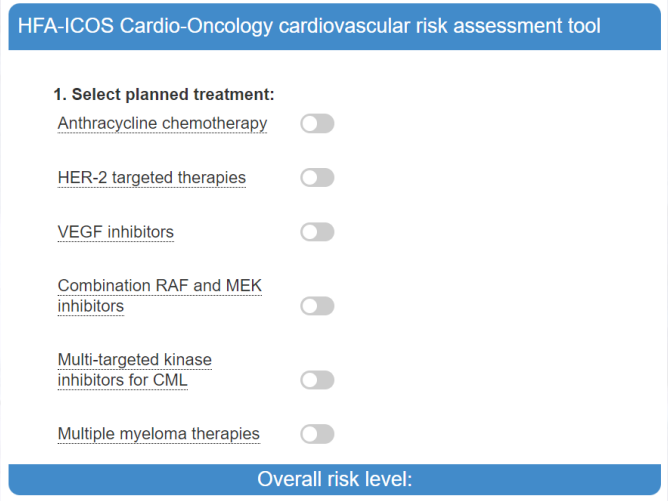
ESC European Society of Cardiology
European Heart Journal - Cardiovascular Imaging (2022) 23, e333–e465 https://doi.org/10.1093/ehjci/jeac106
ESC GUIDELINES

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS)

Table 2 Baseline cardiovascular risk stratification proforma for anthracycline chemotherapy

Risk factor	Score	Level of evidence
Previous cardiovascular disease		
Heart failure or cardiomyopathy	Very high	B
Severe valvular heart disease	High	C
Myocardial infarction or previous coronary revascularisation (PCI or CABG)	High	C
Stable angina	High	C
Baseline LVEF <50%	High	B
Borderline LVEF 50–54%	Medium[2]	C
Cardiac biomarkers (where available)		
Elevated baseline troponin[a]	Medium[1]	C
Elevated baseline BNP or NT-proBNP[a]	Medium[1]	C
Demographic and cardiovascular risk factors		
Age ≥80 years	High	B
Age 65–79 years	Medium[2]	B
Hypertension[b]	Medium[1]	B
Diabetes mellitus[c]	Medium[1]	C
Chronic kidney disease[d]	Medium[1]	C
Previous cardiotoxic cancer treatment		
Previous anthracycline exposure	High	B
Prior radiotherapy to left chest or mediastinum	High	C
Previous non-anthracycline-based chemotherapy	Medium[1]	C
Lifestyle risk factors		
Current smoker or significant smoking history	Medium[1]	C
Obesity (BMI >30 kg/m^2)	Medium[1]	C
Risk level		

Lyon et. al, EJHF, 2022

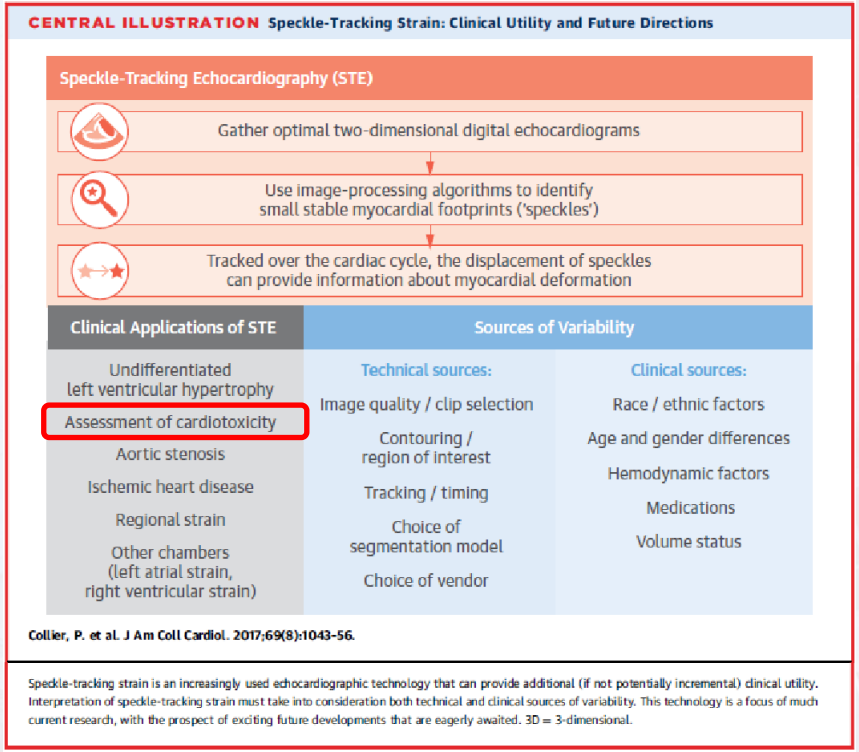


https://www.cancercalc.com/hfa-icos_cardio_oncology_risk_assessment.php

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

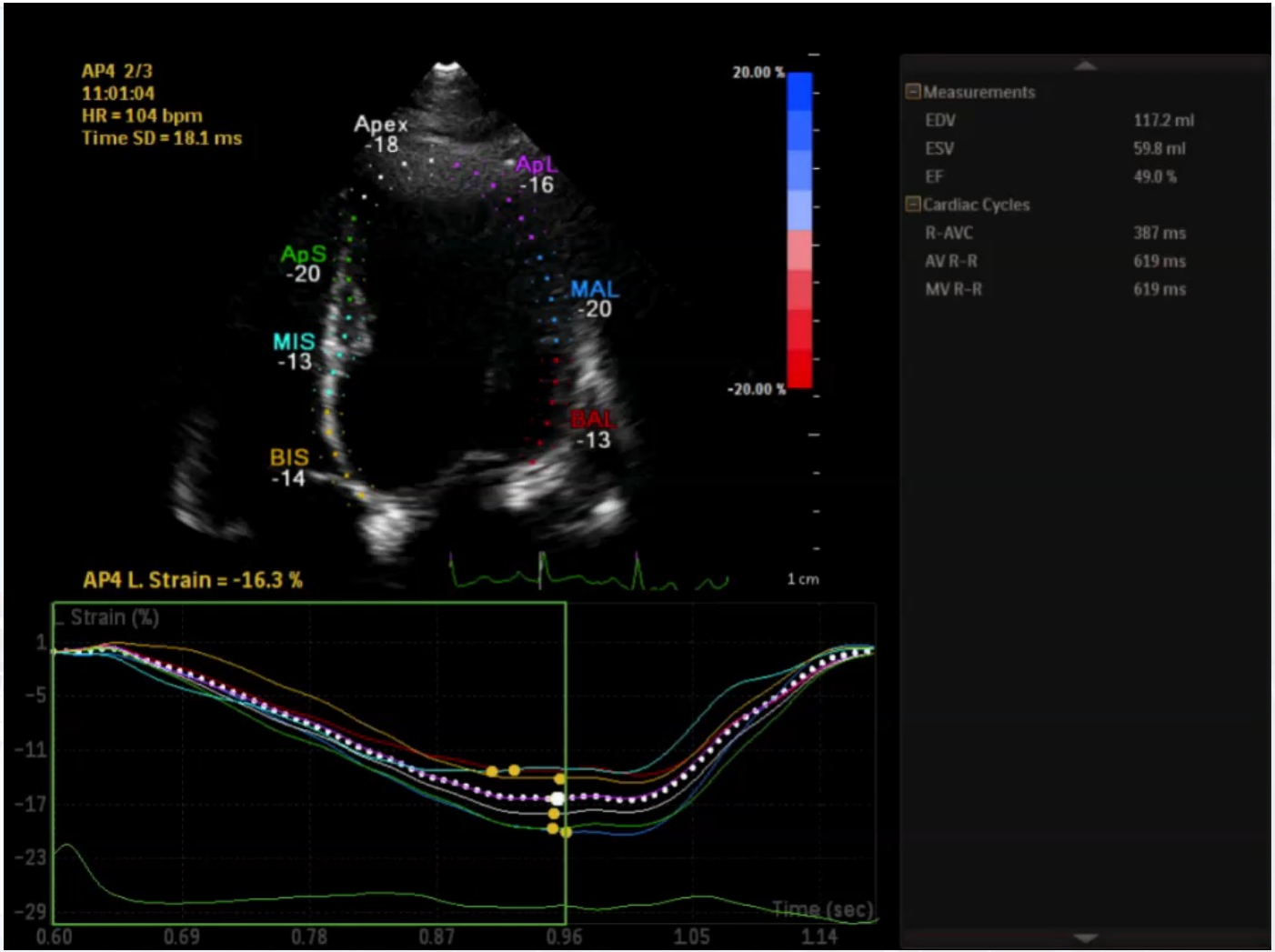
Myocardial Strain Imaging

- Early warning system for detecting cardiotoxicity that is more sensitive than ejection fraction
- Myocardial segments are tracked throughout the cardiac cycle for a change in size or deformation. The deformation values are averaged to generate the global longitudinal strain or GLS
- The higher the absolute number of GLS, the better the LV function i.e. -18% > -12%



Collier et. al, *JACC*, 2017

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

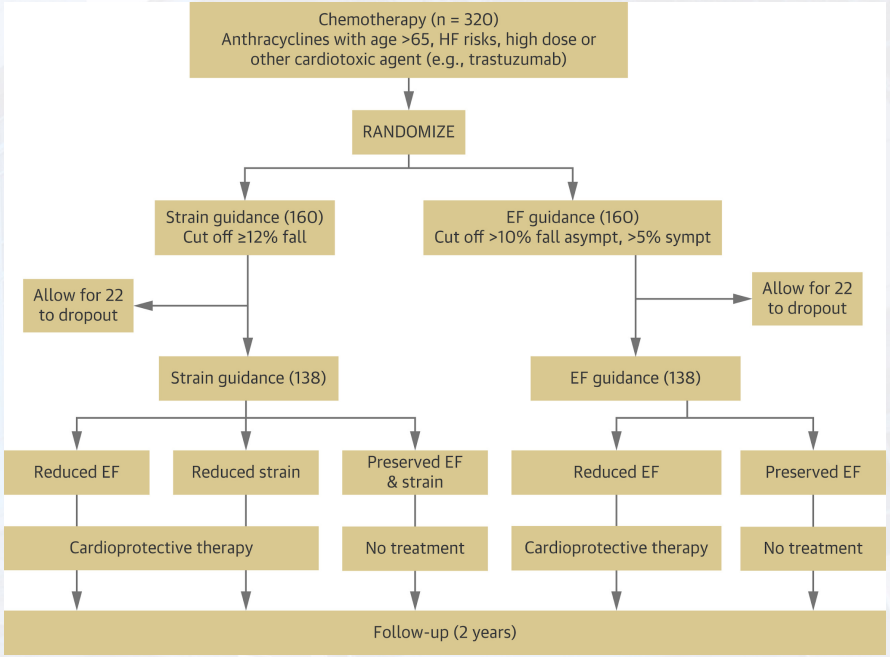


EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

SUCCOUR Trial

(Strain sUrveillance of Chemotherapy for improving Cardiovascular Outcomes)

- **Question:** Is GLS-guided initiation of cardioprotective medications better than LVEF-guided initiation?
- **Design:** International multicenter prospective randomized trial of 331 anthracycline treated patients . Median follow up 1 year
- In the GLS arm, less patients had cancer therapy related cardiac dysfunction (CTCRD) compared to LVEF arm, (6% vs. 14%, p=0.02);
- Among those with cardiotoxicity, GLS arm had a higher LVEF at follow up compared to the LVEF arm (9% vs. 3%, p=0.03)

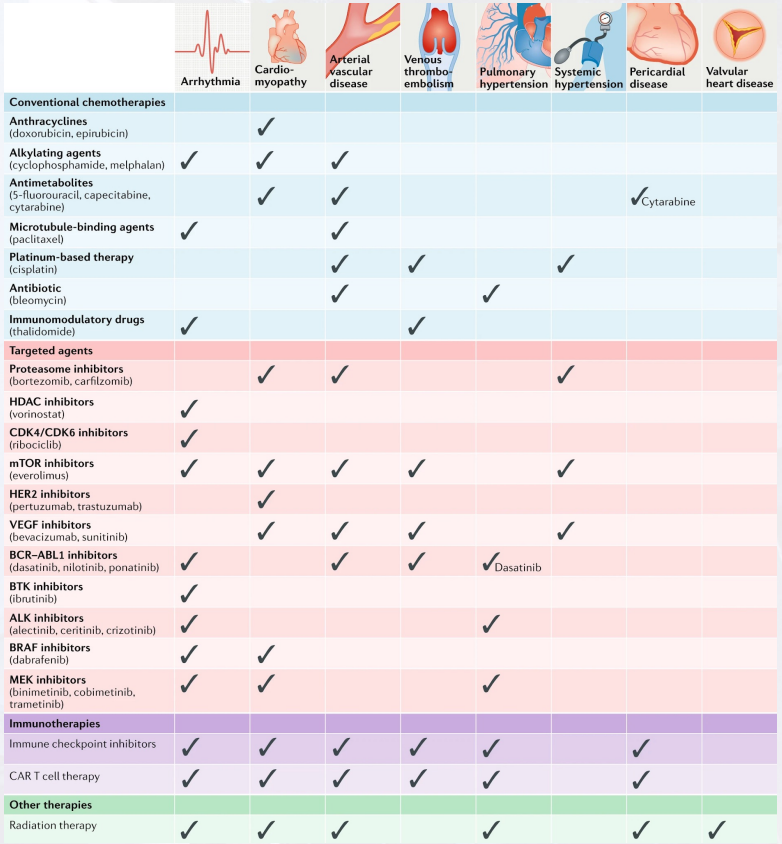


Negishi et al, *JACC Cardiovac Imaging*, 2018
Thavendiranathan et al, *JACC*, 2021

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

Conclusions

- Cardiovascular disease is a leading cause of morbidity & mortality in cancer patients
- There is a competing therpeutic dynamic between cancer treatment and cardiac health, highlighting the need for collaboration to deliver bigger and bolder cancer care and improve outcomes
- Risk stratification, using clinical tools and strain imaging, can identify high-risk patients who would benefit from cardio-oncology care



	Arrhythmia	Cardio-myopathy	Arterial vascular disease	Venous thrombo-embolism	Pulmonary hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Conventional chemotherapies								
Anthracyclines (doxorubicin, epirubicin)		✓						
Alkylating agents (cyclophosphamide, melphalan)	✓	✓	✓					
Antimetabolites (5-fluorouracil, capecitabine, cytarabine)		✓	✓				✓Cytarabine	
Microtubule-binding agents (paclitaxel)	✓		✓					
Platinum-based therapy (cisplatin)			✓	✓		✓		
Antibiotic (bleomycin)			✓		✓			
Immunomodulatory drugs (thalidomide)	✓			✓				
Targeted agents								
Proteasome inhibitors (bortezomib, carfilzomib)		✓	✓			✓		
HDAC inhibitors (vorinostat)	✓							
CDK4/CDK6 inhibitors (ribociclib)	✓							
mTOR inhibitors (everolimus)	✓	✓	✓	✓		✓		
HER2 inhibitors (pertuzumab, trastuzumab)		✓						
VEGF inhibitors (bevacizumab, sunitinib)		✓	✓	✓		✓		
BCR–ABL1 inhibitors (dasatinib, nilotinib, ponatinib)	✓		✓	✓	✓Dasatinib			
BTK inhibitors (ibrutinib)	✓							
ALK inhibitors (alectinib, ceritinib, crizotinib)	✓				✓			
BRAF inhibitors (dabrafenib)	✓	✓						
MEK inhibitors (binimetinib, cobimetinib, trametinib)	✓	✓			✓			
Immunotherapies								
Immune checkpoint inhibitors	✓	✓	✓	✓	✓		✓	
CAR T cell therapy	✓	✓	✓	✓	✓		✓	
Other therapies								
Radiation therapy	✓	✓	✓		✓		✓	✓

Herrmann, *Nat Rev Card*, 2020