Carmen WS Chan

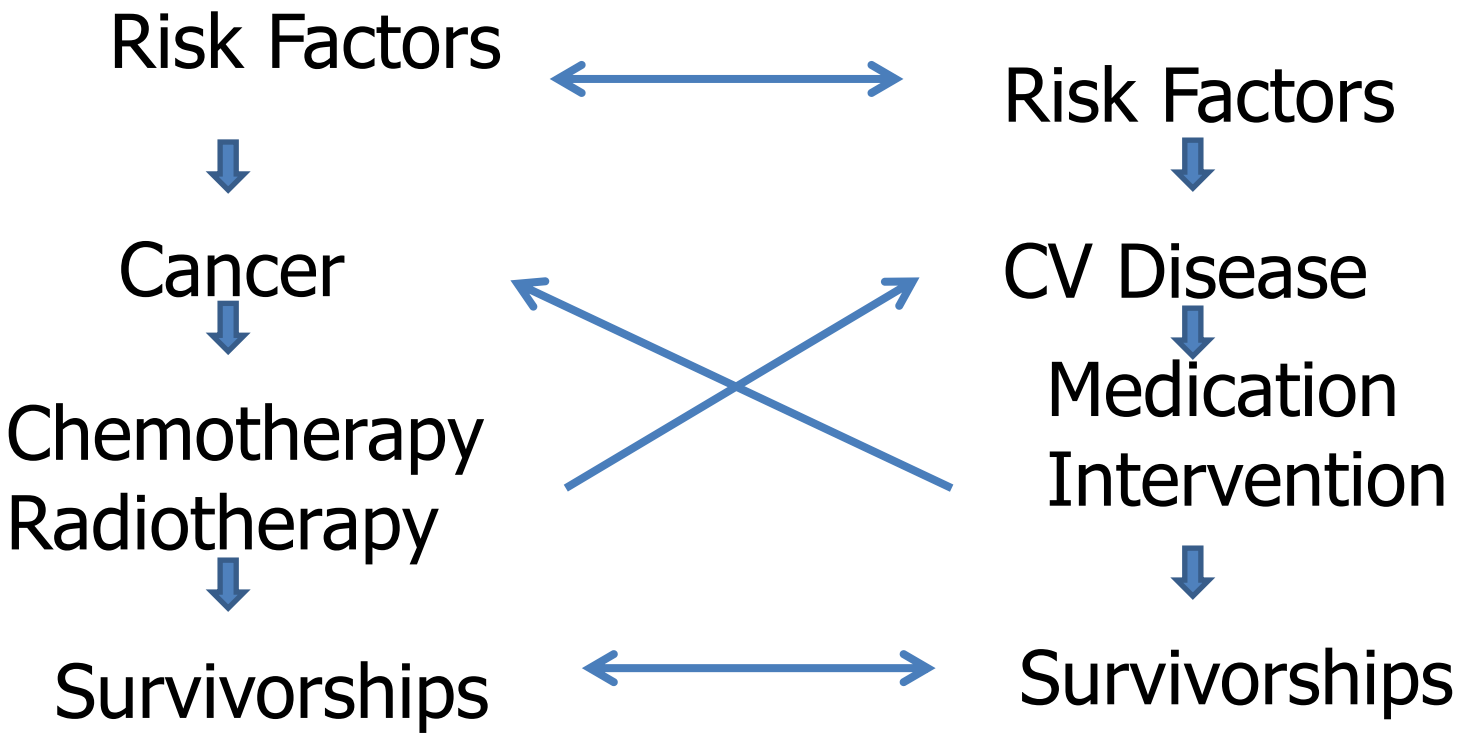
4 July 2020

Paediatric Cardiology Symposium,
Annual Scientific Meeting, Hong Kong College Of Cardiology

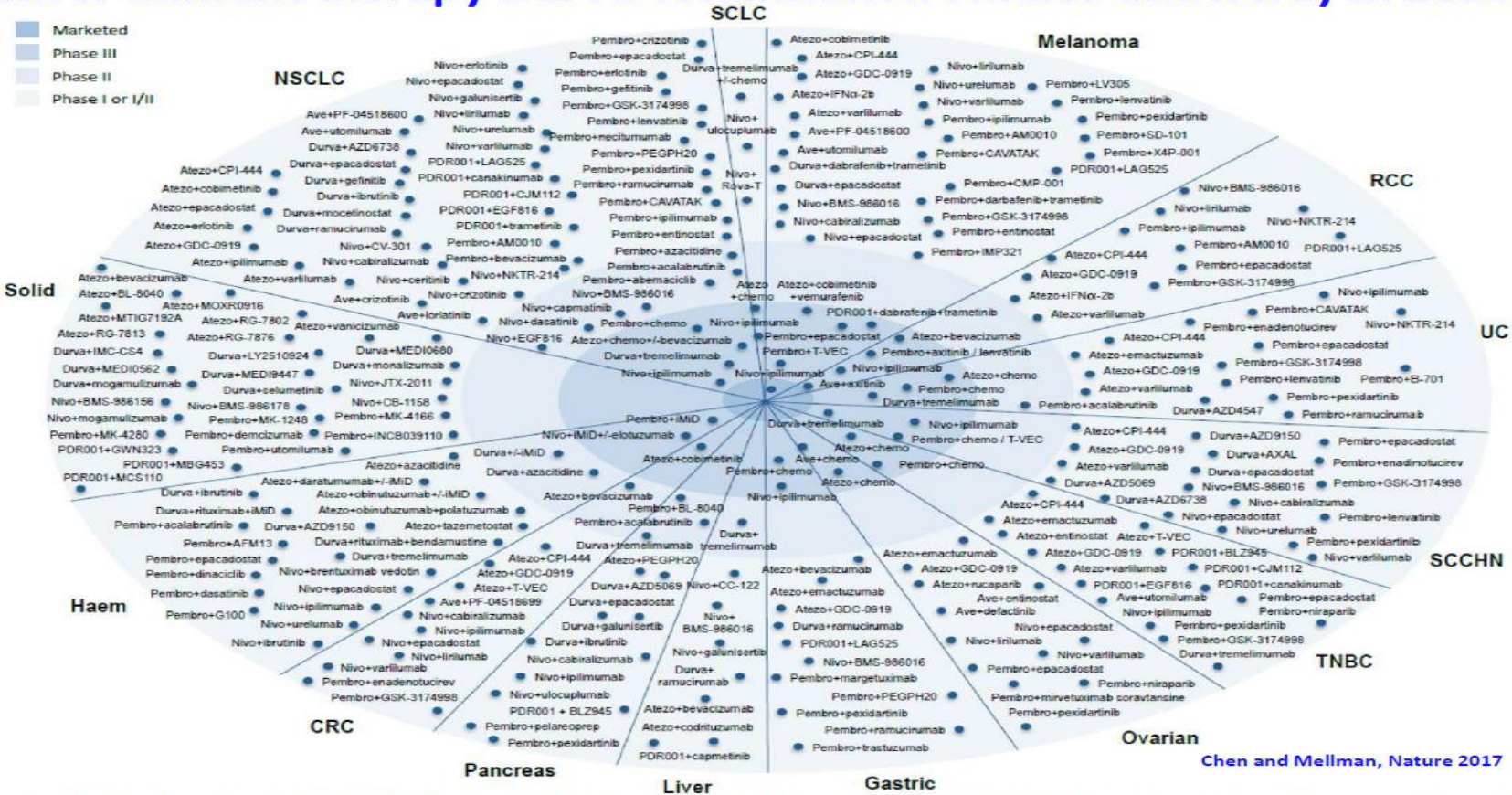
Scope

- Cardiovascular disease and Cancer are two leading causes of death worldwide
- Survival rates from cancer are improving
- Cardiovascular disease is a leading cause of morbidity and mortality in cancer survivors

Increasing Influence Among Cancer and Cardiovascular Disease

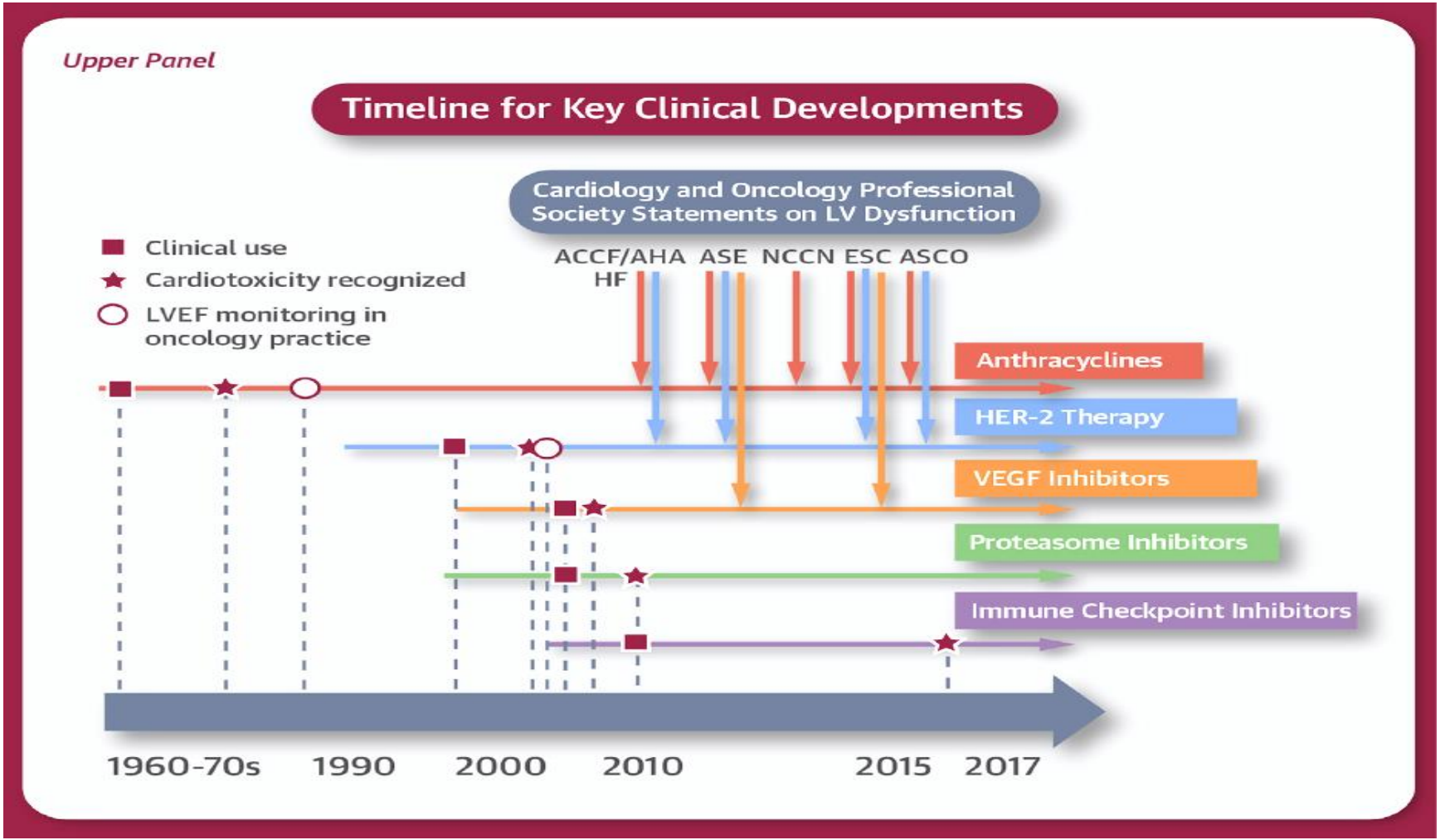


Cancer immunotherapy-based combination studies underway in 2016



A dramatic and unprecedented increase in clinical cancer immunotherapy combination studies (across Phase I, II and III trials) has occurred in recent years. The studies in this figure represent many of the current studies that include a PD-L1/PD-1 pathway inhibitor in combination with other immune modulators, targeted therapy, chemotherapy and/or radiation therapy. These studies are designed to characterize the efficacy, safety and biology related to combinability, synergy or antagonism associated with these combinations. Adapted from Vanessa Lucey of the Cancer Research Institute.

Upper Panel



Kenigsberg, B. et al. J Am Coll Cardiol HF. 2018;6(2):87-95.

Lower Panel

Current Clinical Practice of Stage A-D HF Related to Cancer Therapeutics

Cancer Therapeutics	Stage A Risk Stratification and Modification	Stage B Screening for LV Dysfunction	Stage C Symptomatic HF	Stage D Advanced HF
Anthracyclines	√	√	√	√
HER-2 Therapy	√	√	√	√
VEGF Inhibitors	√*	√*	√	O
Proteasome Inhibitors	O	O	√	O
Immune Checkpoint Inhibitors	O	O	√	O

√ Clinical data and/or guideline recommendations on LV dysfunction available

√* LVEF screening recommended by ASE and ESC but not ASCO guidelines

O Lack of data and guideline recommendations

Cardio-Oncology

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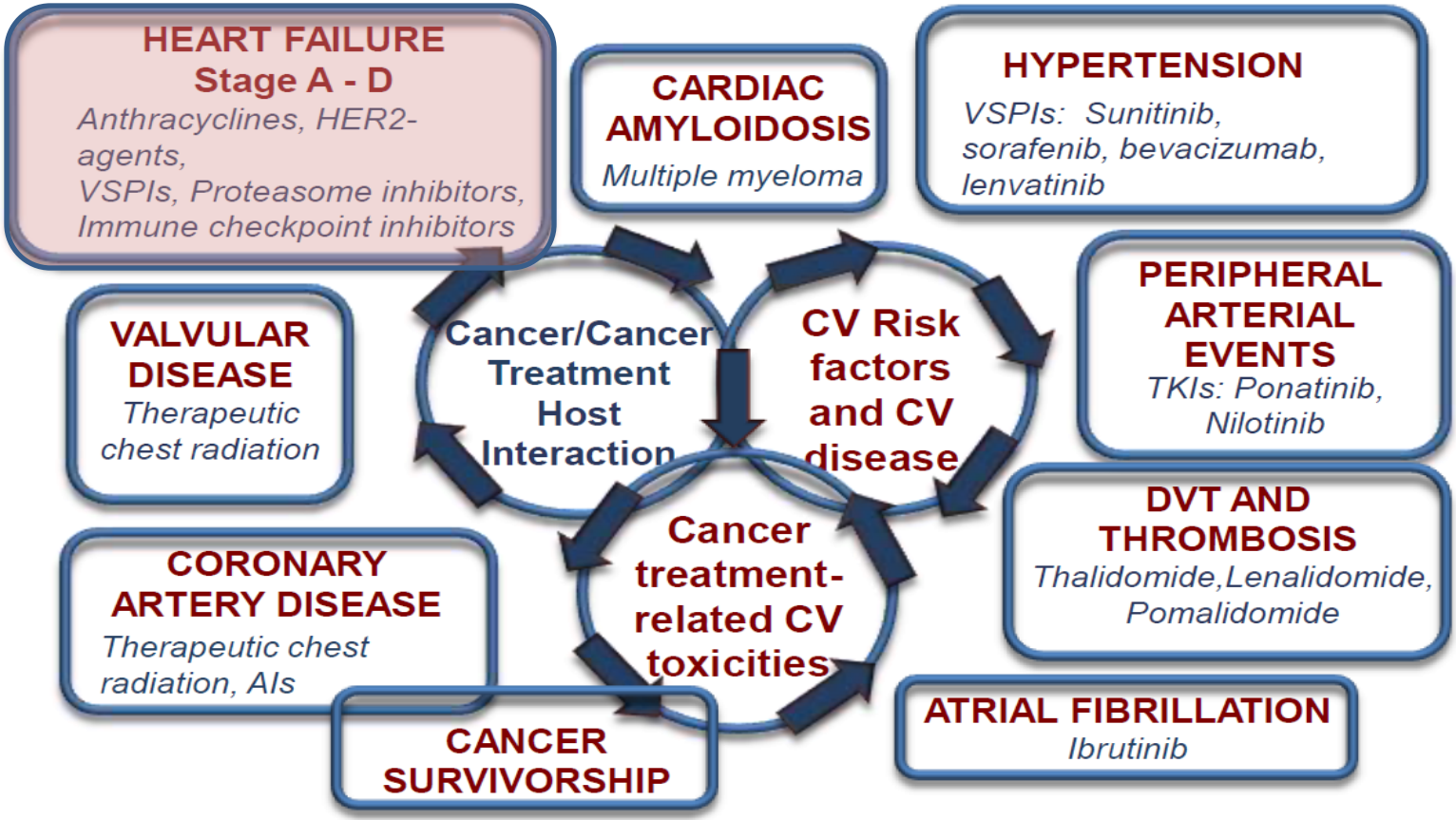
It is not only heart failure

Comprehensive CV Care in Real-Time Oncology World



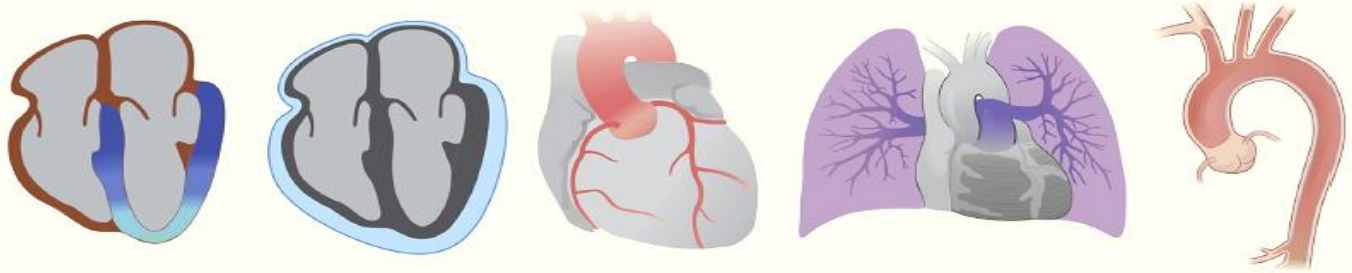
CARDIOVASCULAR COMPLICATIONS OF CANCER THERAPY

STAGES OF THE EVALUATION

Risk Stratification → Early Detection of Injury → Prediction of Recovery → Detection of Injury in the Survivor

CLINICAL CONDITIONS TO BE EVALUATED

LV Dysfunction | Pericardial Disease | CAD | Pulmonary Hypertension | Aortopathy

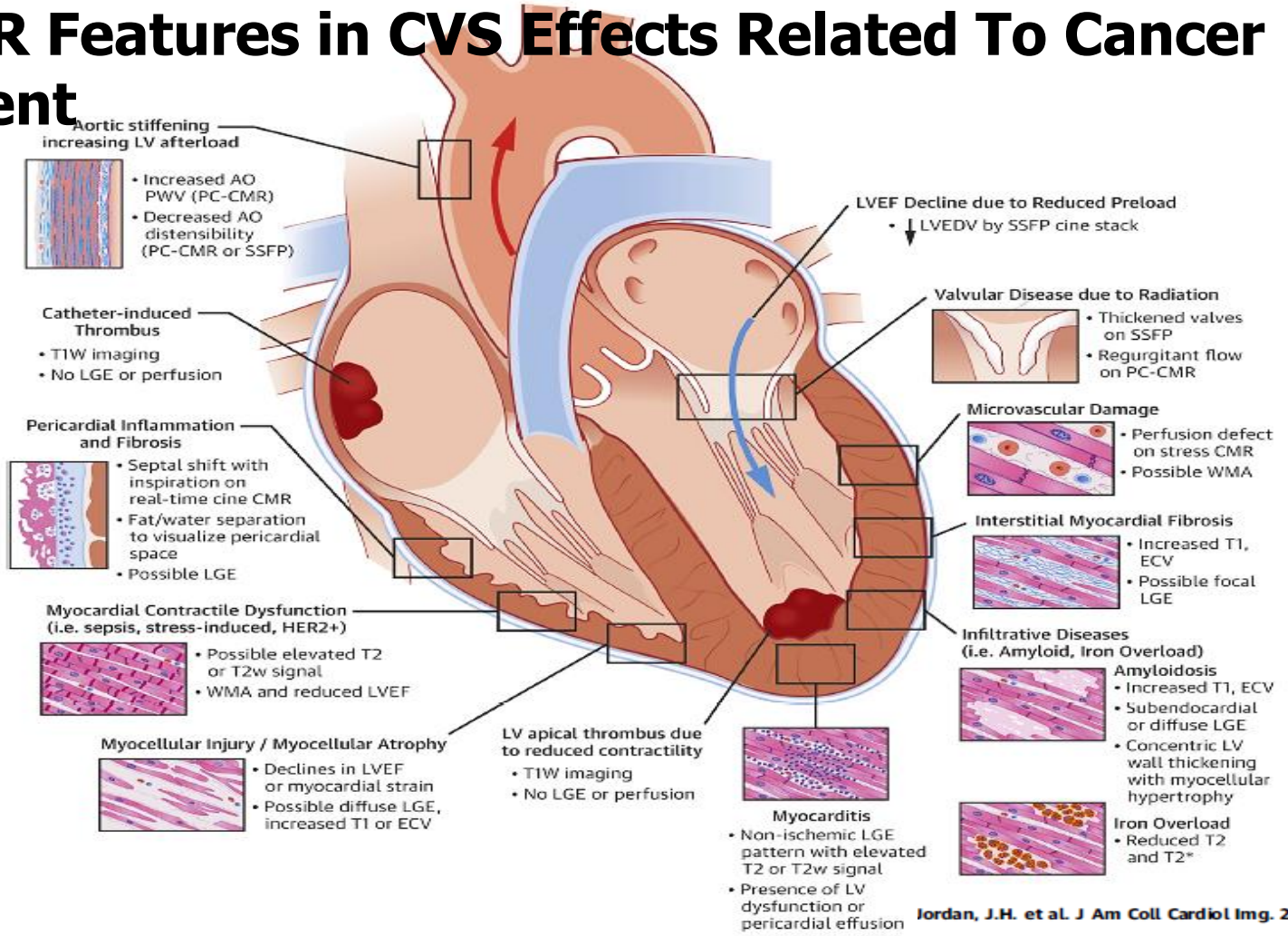


IMAGING MODALITIES ARMAMENTARIUM

ECHO | Nuclear/PET | Cardiac CT | CMR

Plana, J.C. et al. J Am Coll Cardiol Img. 2018;11(8):1173-86.

Key CMR Features in CVS Effects Related To Cancer Treatment

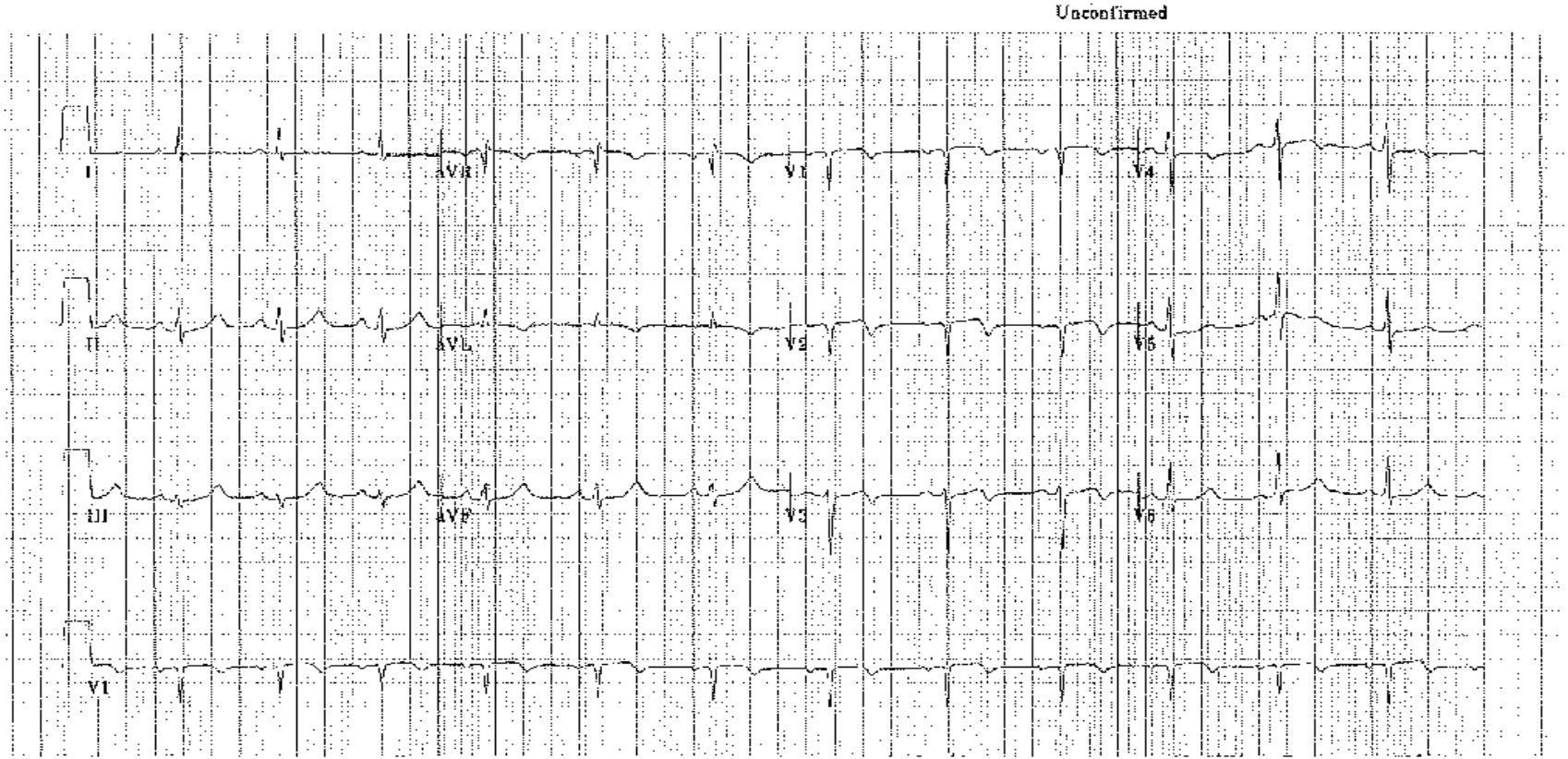


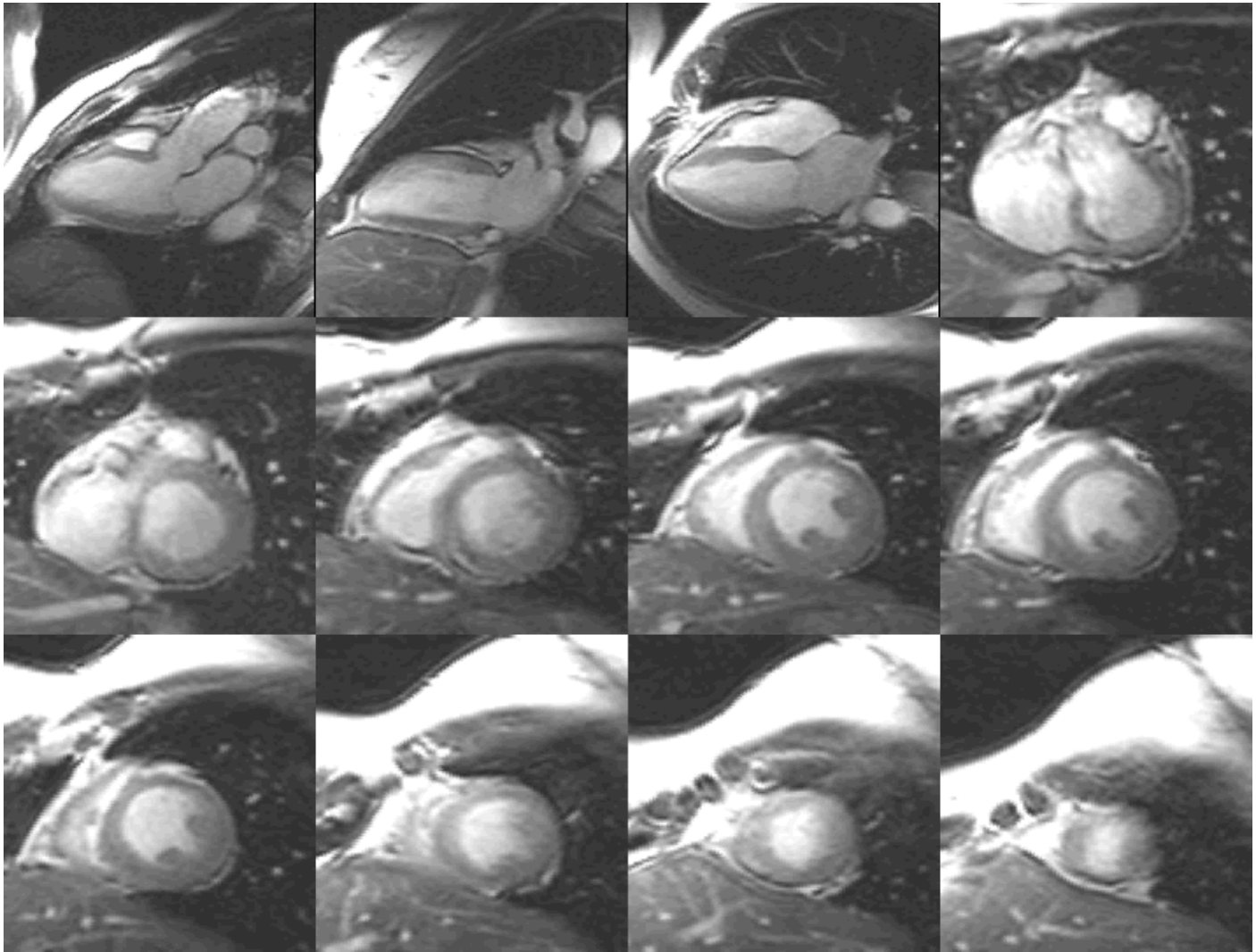
Jordan, J.H. et al. J Am Coll Cardiol Img. 2018;11(8):1150–72.

Example 1

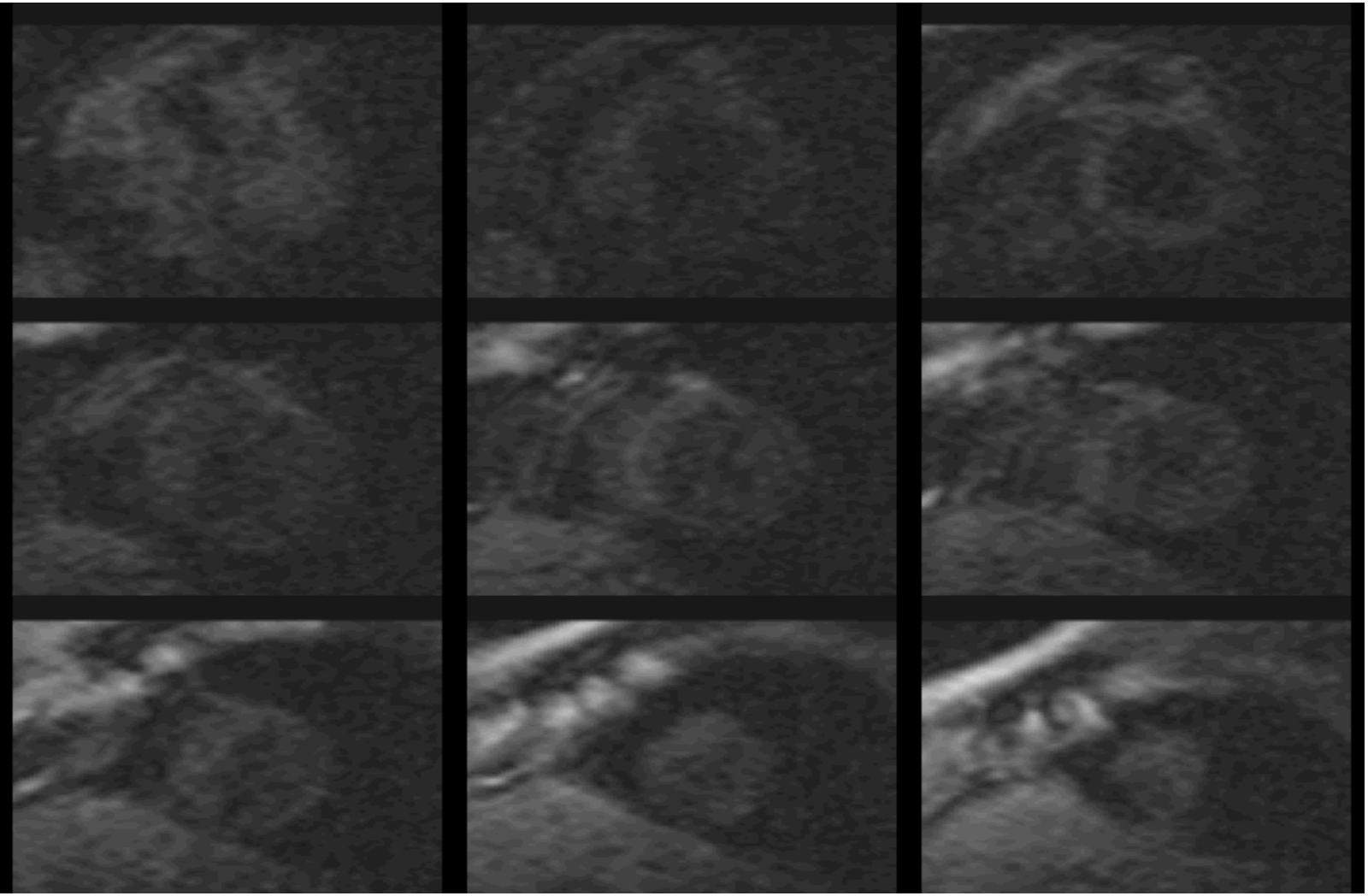
- 42 years old woman with history of CA breast presented with 1 week of progressive exertional chest pain
- HPI:
- Diagnosed in 2010, received left sided lumpectomy followed by radiation therapy
- No history of DM, HT or hyperlipidaemia
- No family history of IHD/CVA

ECG After Admission



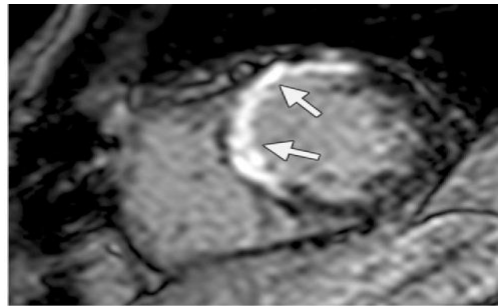


Myocardial Function Assessment



Adenosine Myocardial Perfusion Study

Late Gadolinium Enhancement Study



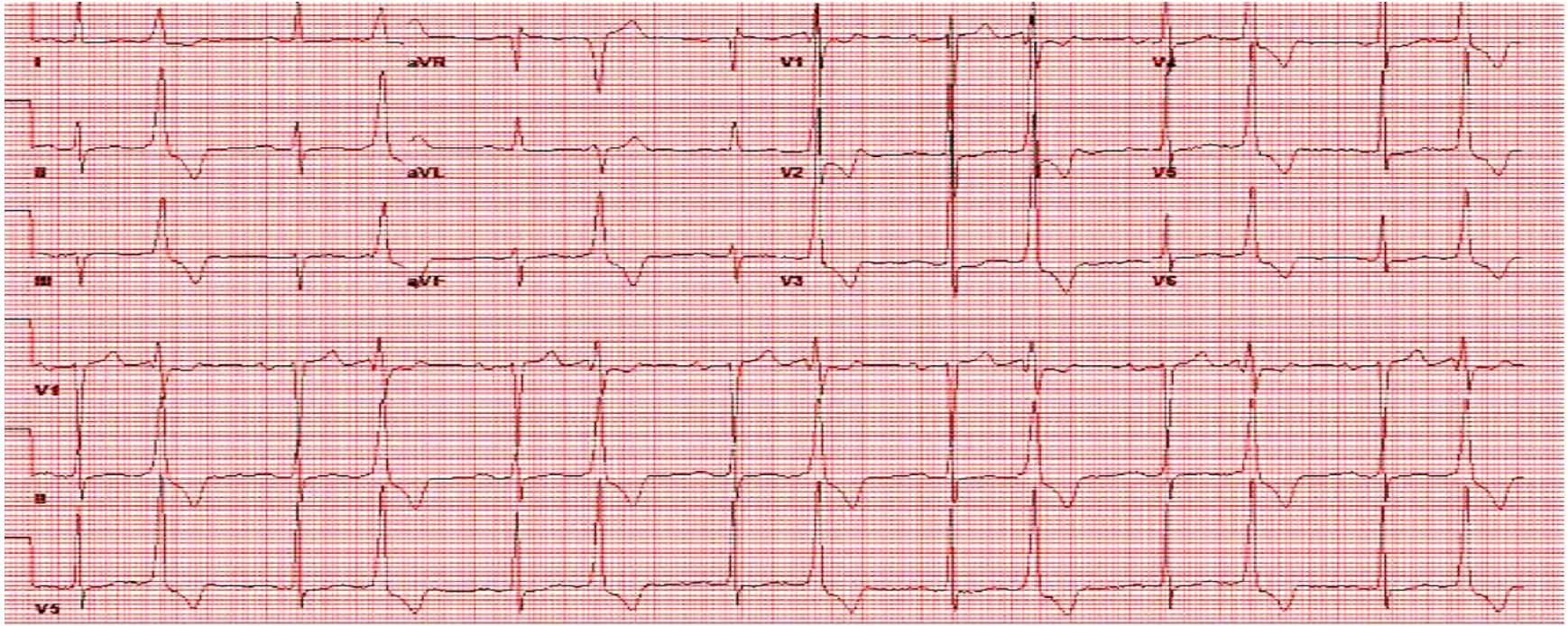
Subsequently…

- Angiogram showing severe proximal LAD disease
- IVUS confirmed marked stenosis with circumferential atherosclerosis without calcification
- PCI to proximal LAD was performed

Example 2

- 50 years old woman with metastatic CA stomach presented with 2 weeks of progressive SOB and rapid deterioration, hospitalized and intubated.
- HPI:
- Diagnosed in 2017, received FOLFOX for 9 months (Folinic acid, 5FU, Oxaliplatin)
- Put on Capecitabine, bevacizumab , atezolizumab in 2018
- ADL independent and working in office prior to this event, no previous cardiac history

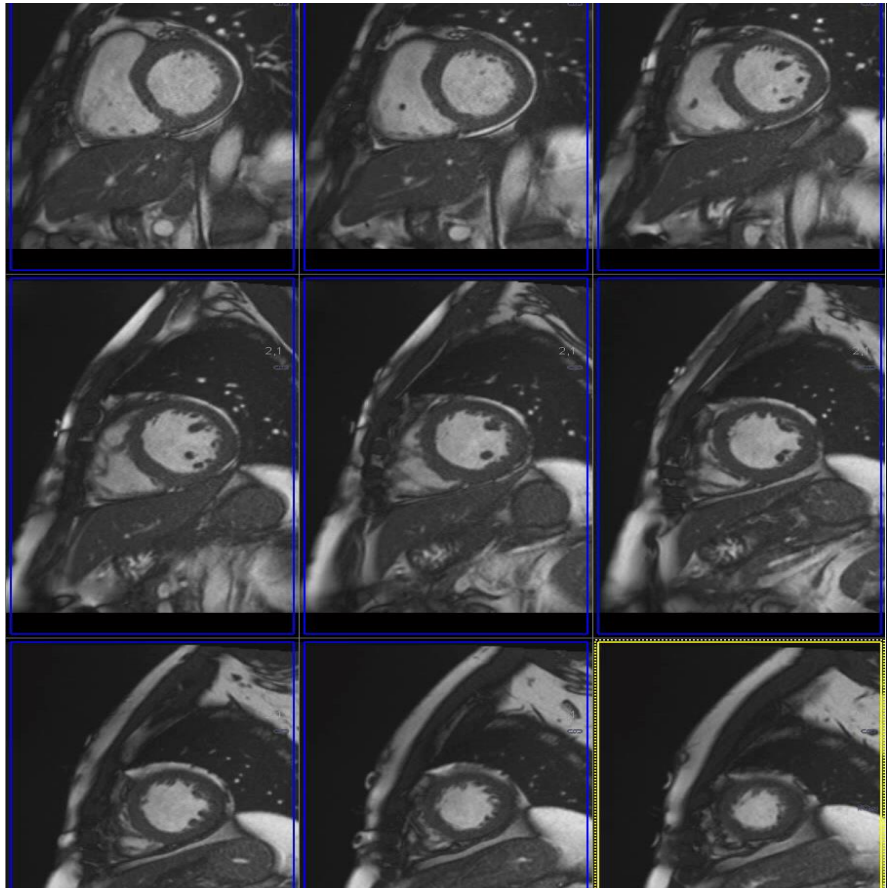
ECG After Admission



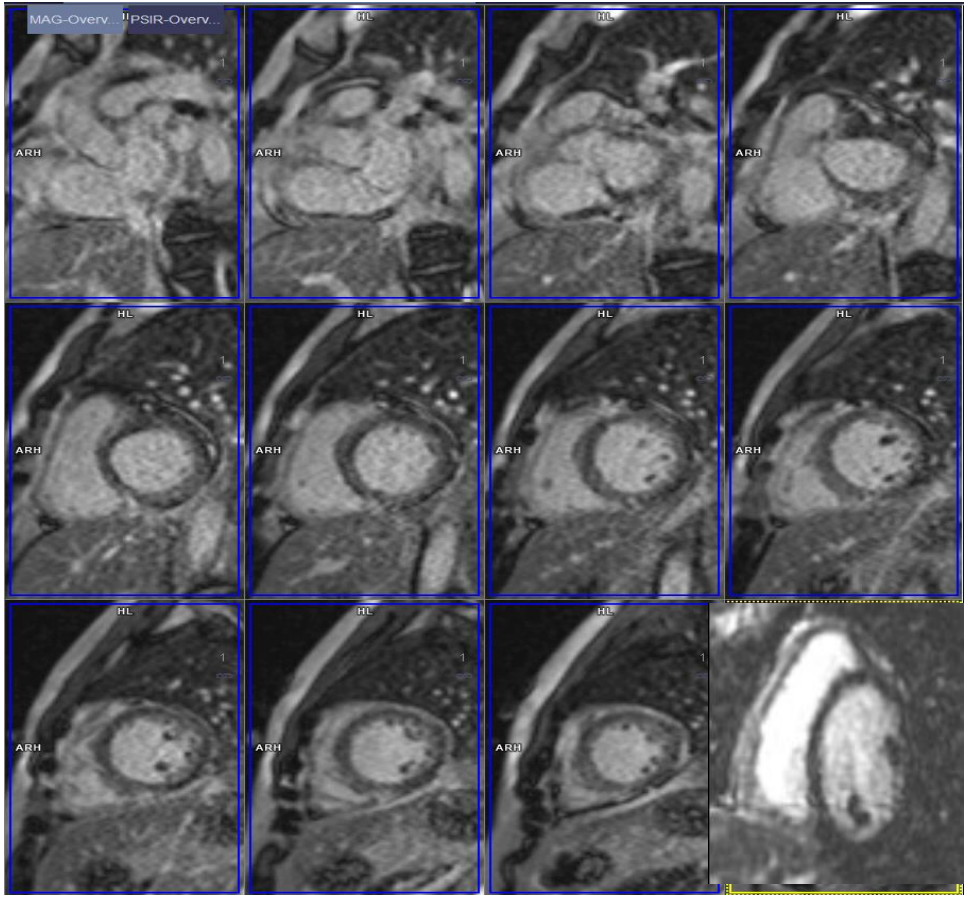
What is the potential cancer treatment related cardiac toxicity?

- Capecitabine (Xeloda)
  Oral preparation of 5FU- coronary spasm
- Bevacizumab(Avastin)
  Antibody to VEGF- Hypertension,
  LV dysfunction
- Atezolizumab (PD1-L antibody)
  Immune checkpoint inhibitor
  Possibility of inducing myocarditis

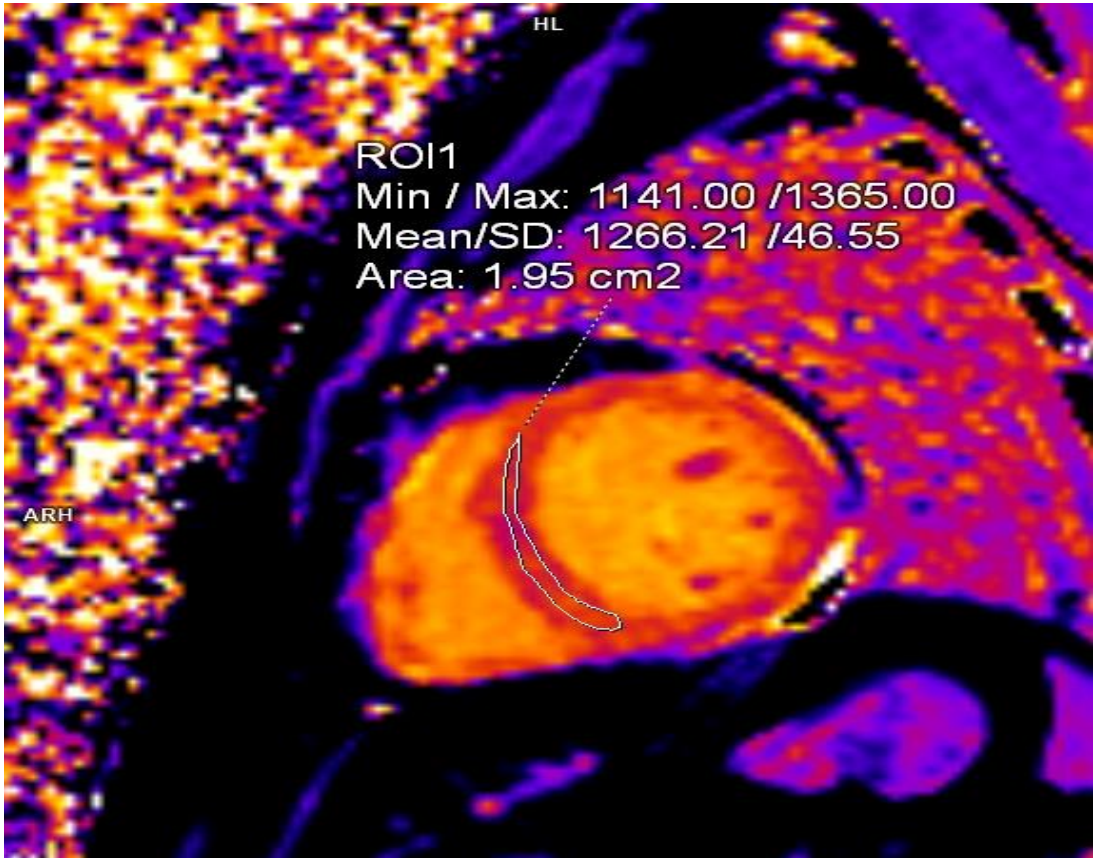
Function



Late Gadolinium



T1 Mapping



The T1 value of normal myocardium at :

1.5T is ranging from 950-1000 ms;
3T is ranging from 1100-1250ms

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

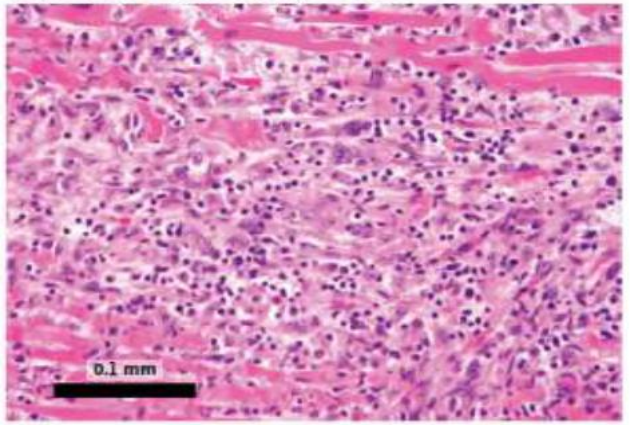
Fulminant Myocarditis with Combination Immune Checkpoint Blockade

.. Two cases of patients with metastatic melanoma presenting with rapid clinical deterioration, heart failure, preserved LVEF on the echo and arrhythmia (VT or complete heart block)..

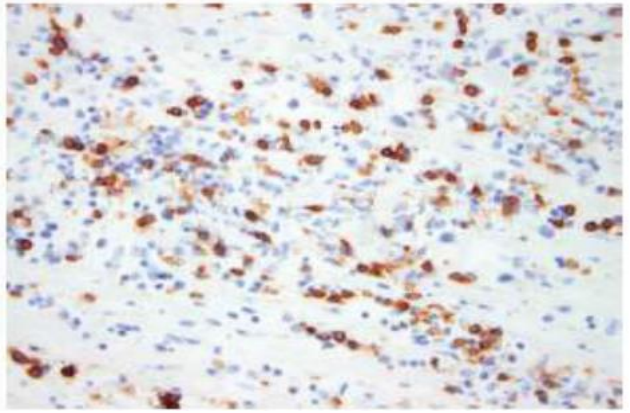
- **Ipilimumab (anti CTLA-4)**
- **Nivolumab (anti PD1)**
- **Incidence <1%**

Johnson DB ...Moslehi J. 2016 NEJM 375:1749

Lymphocytic Infiltration of the Myocardium



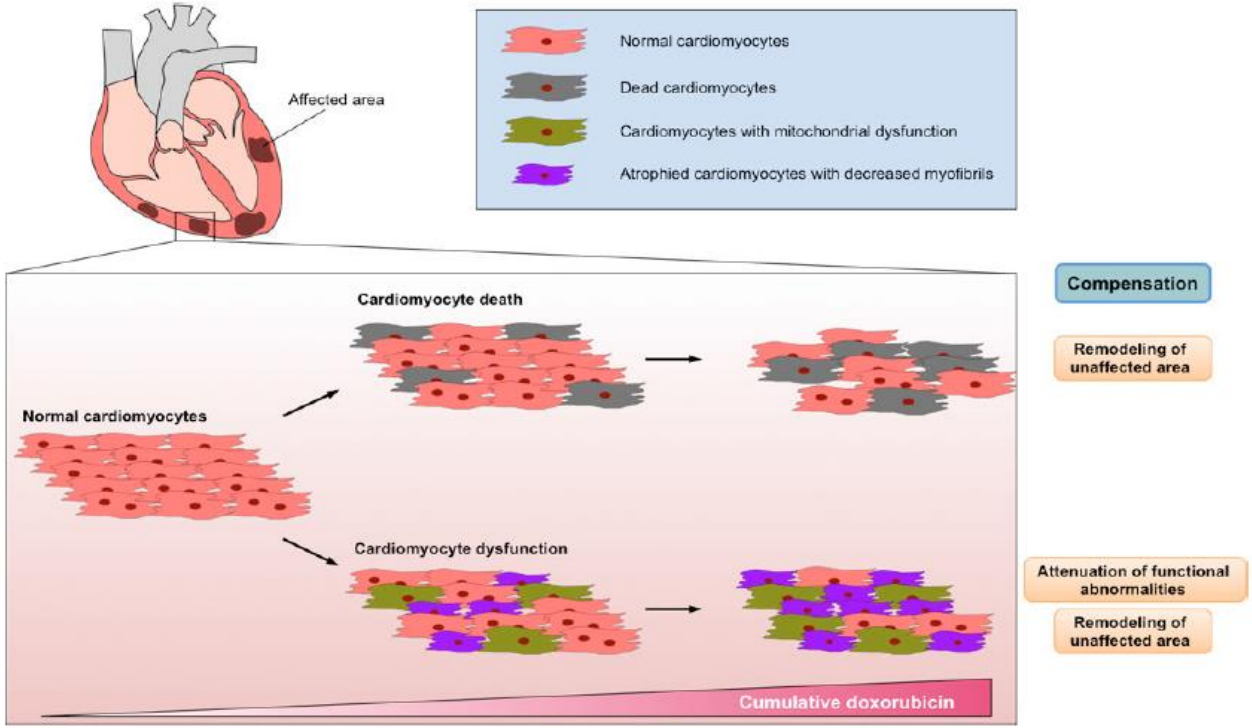
Infiltrate with CD8+ T Cells



Management

- High dose steroid was given and later tapered
- Put on standard anti-heart regime
- Amiodarone given for frequent ectopics
- Improving LVEF on subsequent assessment

What is happening to the myocytes and the cells in the myocardial extracellular space?



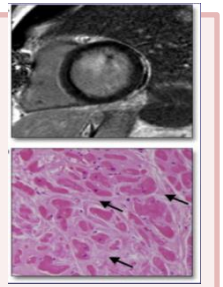
Inflammation
Fibrosis
Senescence
Cell injury
Cell death

Moslehi, Circulation 2017

Cardio-Oncology

Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors

Jennifer H. Jordan, PhD, MS; Sujethra Vasu, MD; Timothy M. Morgan, PhD; Ralph B. D'Agostino, Jr, PhD; Giselle C. Meléndez, MD; Craig A. Hamilton, PhD; Andrew E. Arai, MD; Songtao Liu, MD; Chia-Ying Liu, PhD; João A.C. Lima, MD; David A. Bluemke, MD, PhD; Gregory L. Burke, MD, MSc; W. Gregory Hundley, MD

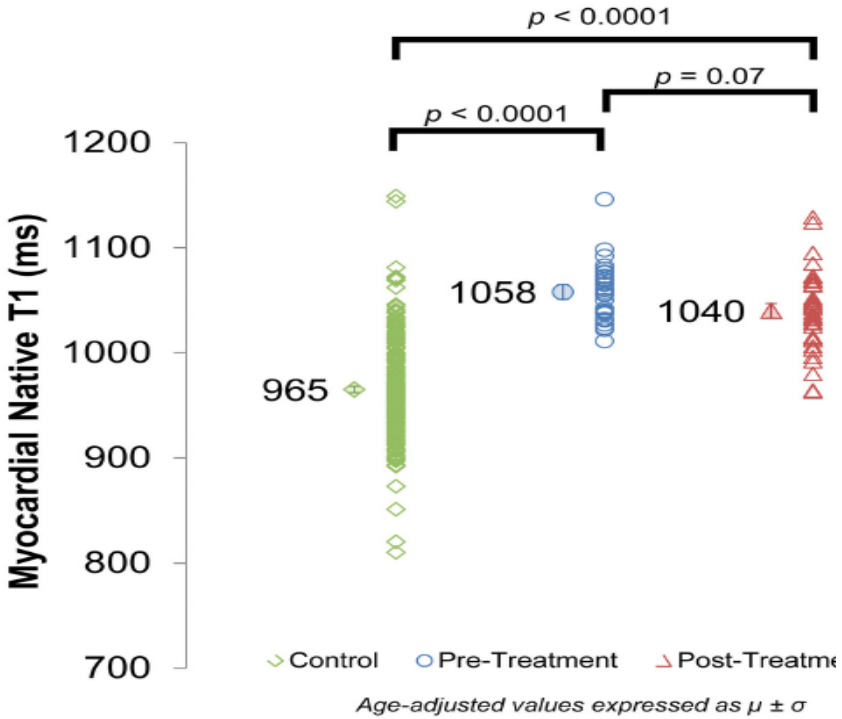


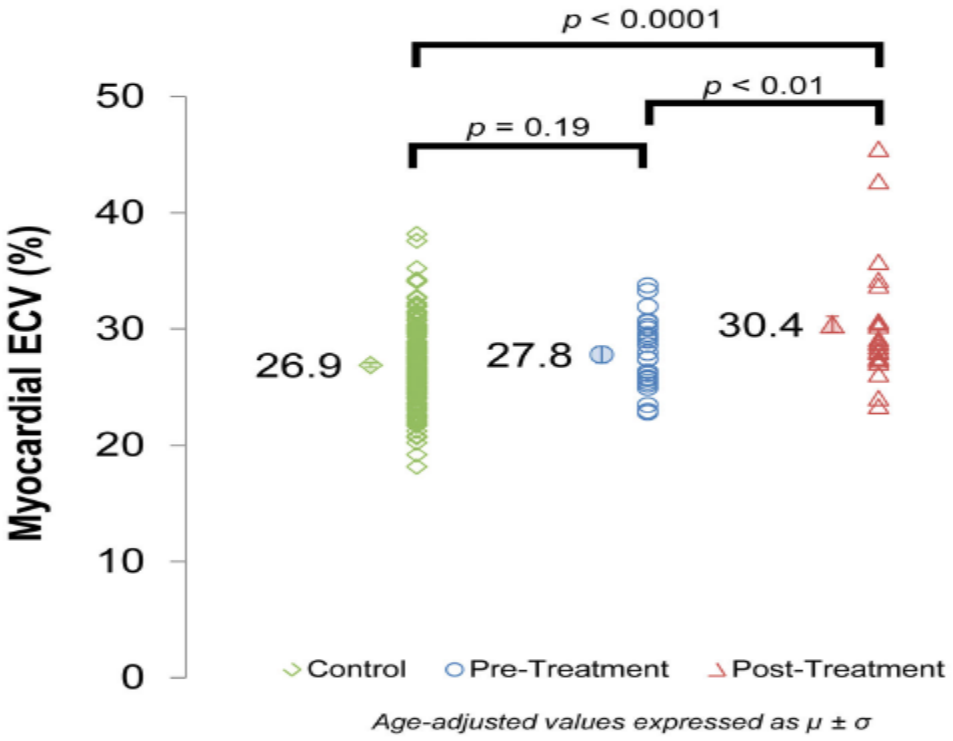
Study populations from northwest NC, southwest VA and east TN (N=310)

- **Pre Treatment Cancer Patients N=37**
- **Post Anthracycline Treatment Survivors N=37**
- **N=236 Normal Control**

Journal of Cardiovascular Magnetic Resonance Volume 18, Article number: 89 (2017)

Myocardial Fibrosis is elevated in Survivors in Post Treatment Group





Elevated Fibrosis Measured By CMR Persists Despite Accounting Other Risk Factors or Coexistence CV Comorbidities

Model	Covariates	ECV
Model 1	Group	$p < 0.0001$
Model 2	Group + Age, Race, Gender, Age*Gender	$p < 0.0001$
Model 3	Model 2 + Weight, Heart Rate, Systolic BP, CAD, DM, DysL, HTN	$p < 0.0001$
Model 4	Model 3 + LVEF, LV Mass Index	$p < 0.0001$

Journal of Cardiovascular Magnetic Resonance

RESEARCH Open Access

Diffuse myocardial fibrosis by T_1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling

Edythe B Tham[1,4*], Mark J Haykowsky[2], Kelvin Chow[3], Maria Spavor[1], Sachie Kaneko[1], Nee S Khoo[1], Joseph J Pagano[3], Andrew S Mackie[1] and Richard B Thompson[3]

Abstract

Background: The late cardiotoxic effects of anthracycline chemotherapy influence morbidity and mortality in the growing population of childhood cancer survivors. Even with lower anthracycline doses, evidence of adverse cardiac remodeling and reduced exercise capacity exist. We aim to examine the relationship between cardiac structure, function and cardiovascular magnetic resonance (CMR) tissue characteristics with chemotherapy dose and exercise capacity in childhood cancer survivors.

Methods: Thirty patients (15 ± 3 years), at least 2 years following anthracycline treatment, underwent CMR, echocardiography, and cardiopulmonary exercise testing (peak VO_2). CMR measured ventricular function, mass, T_1 and T_2 values, and myocardial extracellular volume fraction, ECV, a measure of diffuse fibrosis based on changes in

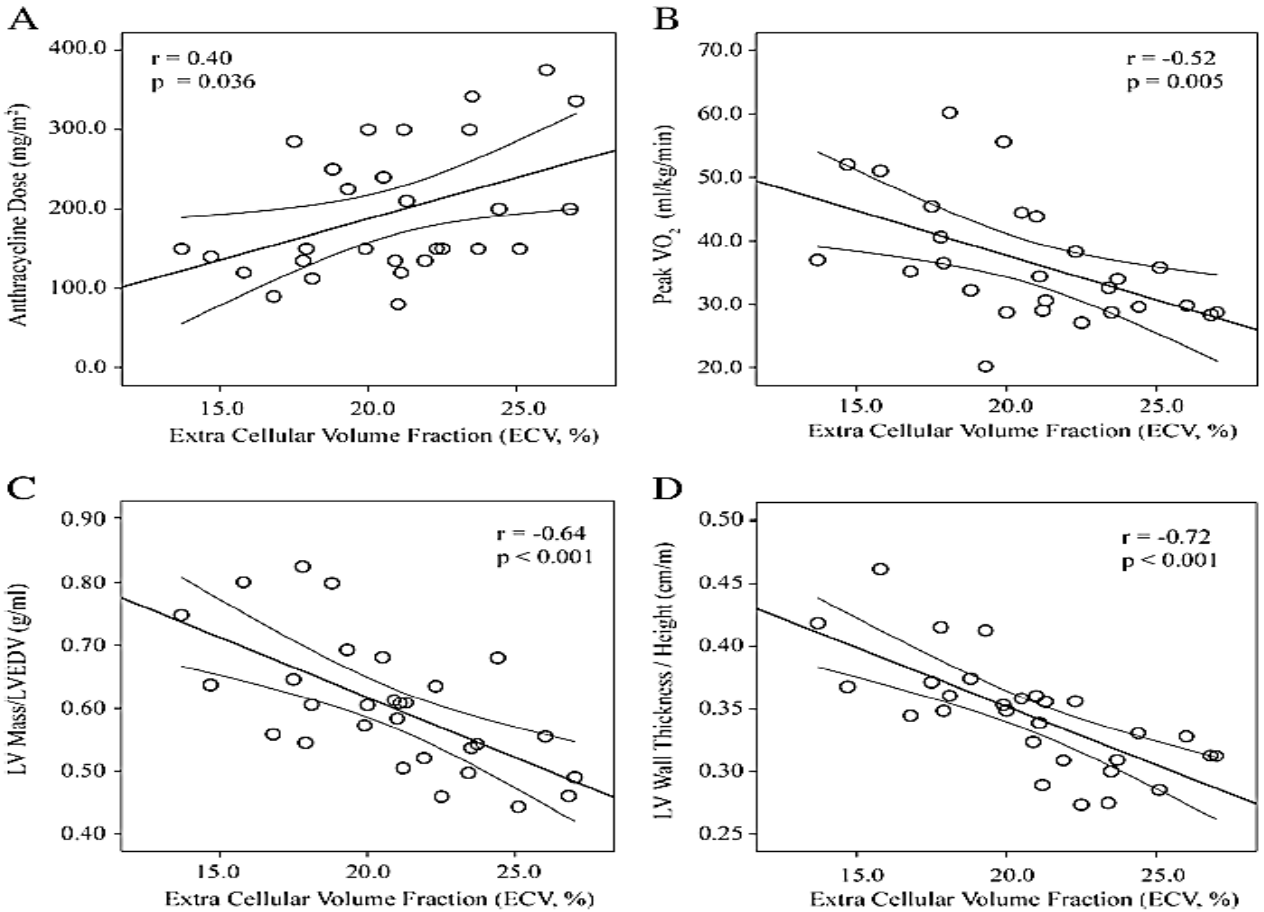


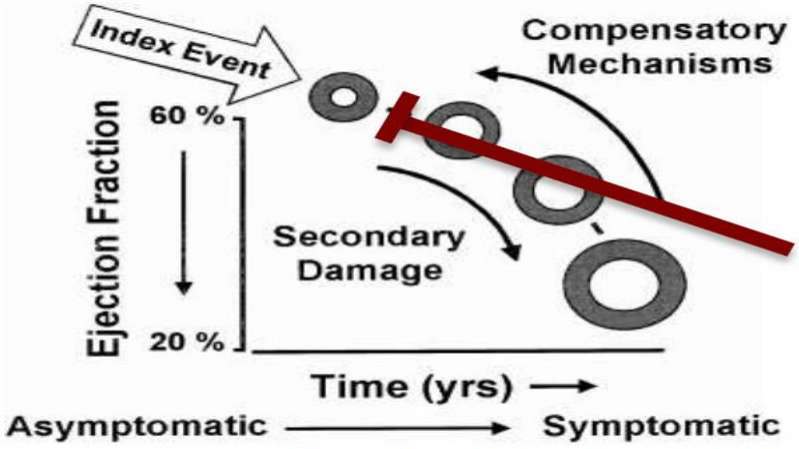
Figure 3 Correlation of extracellular volume fraction (ECV) with A) anthracycline dose, B) peak VO_2, C) left ventricular mass/LVEDV and D) LV wall thickness/height. Error bars show the 95% confidence interval.

Any Role of CMR In Primary Prevention?

Hypothesis

Can neurohormonal inhibition started with cancer treatment prevent LV dysfunction in patients receiving HER2 targeted therapies?

B Blocker, ACEI/ARB?



from Mann D Circ 1999;100:999

Beyond diagnosis…

PRADA

PRevention of cArdiac Dysfunction

- Study Population
  - All epirubicin, 22% trastuzumab
- Study design
  - 2x2, metoprolol and candesartan
- Primary Outcome
  - **Changes in LVEF by CMR at 10-64 weeks**
- Results
  - **Attenuation of LVEF decline with candesartan (order of 2-3%)**

Gulati G et al. Eur Heart J. 2016

MANTICORE

Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research

- Study Population
  - All trastuzumab, 12-33% anthracycline
- Study design
  - 1:1:1 bisoprolol, perindopril, placebo
- Primary Outcome
  - **Changes in LVEDVi by CMR at 1 year**
- Results
  - **Attenuation of LVEF decline with bisoprolol (order of 4%)**

Pituskin E et al. J Clin Oncol. 2016

Courtesy of Ana Barac MD, PhD, FACC

Conclusion

- With the advancement in the treatment, Cardio-oncology is an rapidly growing field
- New Cardiovascular challenges from those cancer patients are expected
- MRI plays important roles throughout the journey of cancer patients

Thank You