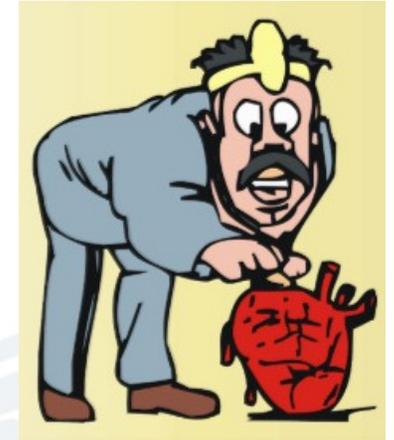




# Breast Cancer Treatment and Cardiovascular Risk



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# Objectives

- To understand breast cancer treatment paradigm and breast cancer therapies with potential cardiovascular toxicity
- To identify and manage cardiovascular risk in breast cancer patients prior to and during cancer therapy



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# ARS Question 1

A 67 years old woman with hypertension, diabetes and breast cancer metastatic to the bone presents with LE edema and progressive DOE. Her medications include losartan, metformin She is receiving trastuzumab/pertuzumab as part of her cancer therapy. The most likely cause of her symptoms is:

- A. Ischemic cardiomyopathy related to diabetes and history of prior radiation
- B. Inhibition of neuregulin/ErbB2/HER2 signaling in cardiomyocytes
- C. Cancer treatment-induced worsening of hypertension and hypertensive cardiomyopathy
- D. Tumor progression



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- D. Tumor progression



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# ARS Question 2

A 40 years-old woman with history of Hodgkin's lymphoma treated with anthracycline-based chemotherapy has a new diagnosis of Stage II HER2 positive breast cancer. She is referred for evaluation of mildly reduced LVEF of 45%. The best next step in her management is:

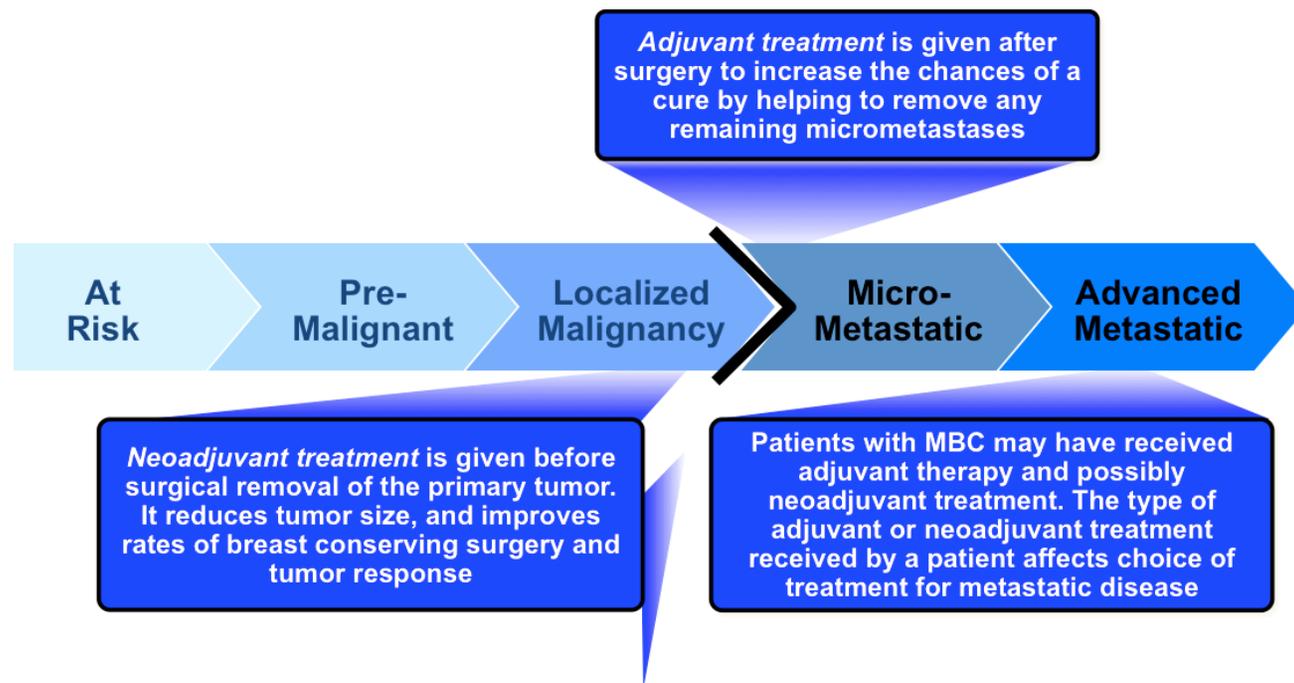
- A. Repeat echocardiogram with GLS, if strain is normal she may initiate trastuzumab
- B. Obtain cardiac MR
- C. Initiate beta-blockers and ACE-inhibitors/ARBs
- D. Discuss with the oncologist that her cardiac function is likely irreversibly reduced in light of prior anthracycline-based therapy and she should not initiate HER2 targeted tx

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# Breast Cancer Treatment Paradigm



# Multidisciplinary approach to treatment of breast cancer

- Surgery
  - Definitive surgery (and reconstruction)
- Systemic Therapy
  - Chemotherapy
  - Targeted therapy (e.g. trastuzumab, pertuzumab, T-DM1)
  - Endocrine therapy (tamoxifen, aromatase inhibitors)
- Radiation therapy
  - Cardioprotective techniques

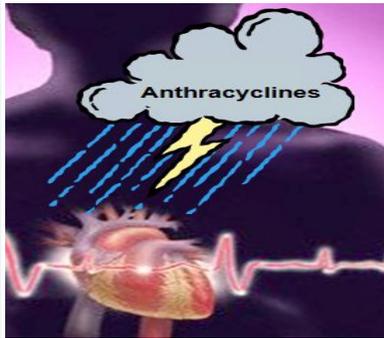


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# Cardiotoxicity of Chemotherapy Drugs in Breast Cancer

**Table 1** Systemic cancer drugs with important cardiovascular side effects; selected indications

	Class/drug	Selected indications	Important CV side effects
Cytostatic chemotherapeutics	Anthracyclines/analogue	Lymphoma	Cardiac dysfunction/heart failure
	Doxorubicin	Leukaemia	
	Daunorubicin	Breast cancer	
	Epirubicin	Ovarian cancer	
	Mitoxantrone	Sarcoma	
		Leukaemia	Coronary spasms/ischaemia
	Pyrimidine analogues	Multiple sclerosis	
	Fluorouracil (5-FU)	Colorectal cancer	
	Capecitabine	Breast cancer	
	Alkylating agents	Breast cancer	
Cyclophosphamide	Genitourinary cancer		
	Cisplatin	Breast cancer	Thrombosis
Antimicrotubule agents	Colorectal cancer		
	Paclitaxel		Bradycardia



Suter and Ewer. Eur Heart Journal, 2013



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# Cardiotoxicity of Targeted agents in Breast Cancer

**Table 1** Systemic cancer drugs with important cardiovascular side effects; selected indications

	Class/drug	Selected indications	Important CV side effects
Signalling inhibitors	Anti-HER2 Trastuzumab Lapatinib	Breast cancer Gastric cancer	Cardiac dysfunction
	Angiogenesis inhibitors/anti-VEGF Bevacizumab Sunitinib Sorafenib	Gastrointestinal cancer Renal cell carcinoma Hepatocellular carcinoma	Hypertension Endovascular damage
Trastuzumab Pertuzumab	BCR-ABL inhibitors Imatinib	Leukaemia	Oedema, cardiac dysfunction (rare)
	Dasatinib Nilotinib	Gastric cancer	QTc prolongation

Suter et al. Eur Heart Journal, 2013



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# Case # 1: Mrs. H.R.

- 61 y.o post-menopausal women with self-detected mass left breast
- Dx: infiltrating ductal carcinoma
- Lumpectomy and sentinel lymph node biopsy
- Pathology: 2.1 cm (T2), 1/2 lymph nodes positive (N1)
- ER+/PR+/HER2-
- Seen by oncology who recommends adjuvant systemic chemotherapy followed by radiation and endocrine therapy



# Past Medical History

- Mild asthma in the past
- Hypertension
- Type II DM
- No ETOH; non-smoker
- Does not exercise regularly but reasonably active in household activities during the day



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# Systemic Chemotherapy Options

- **dd AC-T:** Adriamycin/cyclophosphamide Q2 wks x 4;  
paclitaxel Q2 wks x 4
- **AC-wT:** Adriamycin/cyclophosphamide Q 3 wks x 4;  
paclitaxel QW x 12
- **FEC-D:** 5FU/epirubicin/cyclophosphamide Q3 wks x 3;  
docetaxel Q 3 wks x 3
- **TC:** Docetaxel/cyclophosphamide Q3 wks x 4

A: adriamycin: 60 mg/m<sup>2</sup>: E: epirubicin 100 mg/m<sup>2</sup>



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# Red Flags

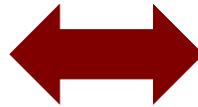
- What are the “red flags” that I should be looking for given a background history that might suggest higher risk of cardiotoxicity?
- How do we assess baseline cardiovascular risk factors in breast cancer patients?



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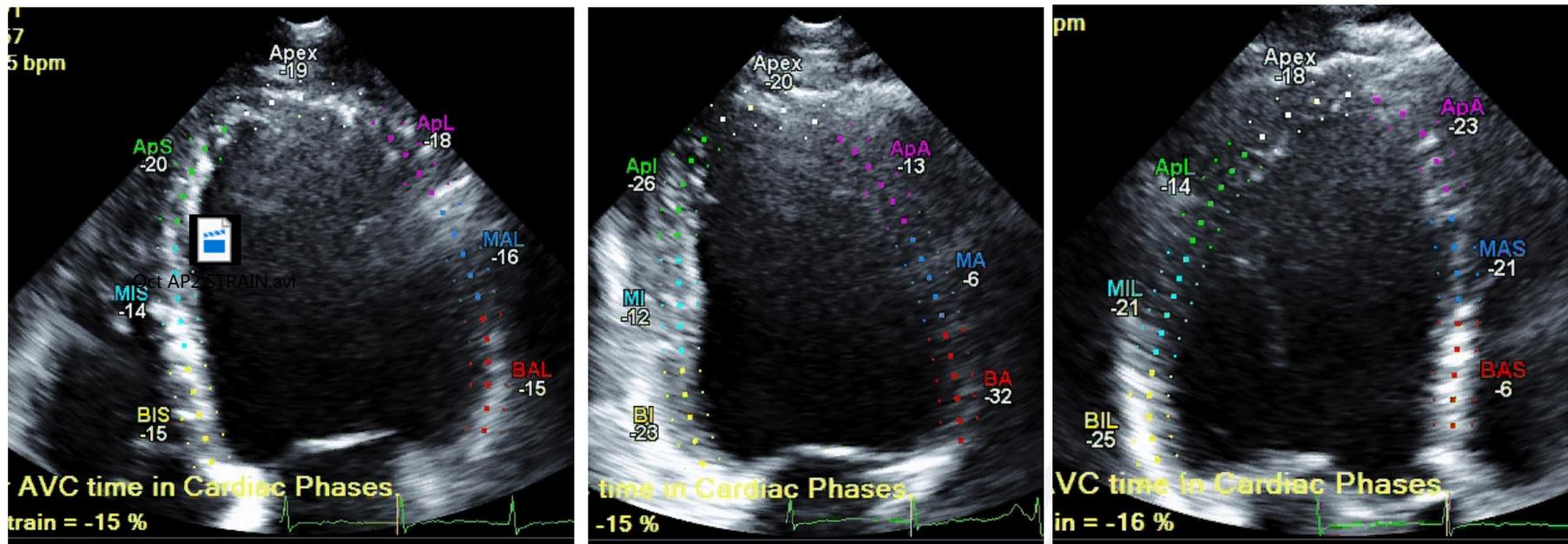
## Case # 1: Mrs. H.R. – Cardiology Visit

- Treatment associated risk
  - Cardiomyopathy (doxorubicin)
  - CAD (radiation)
  - Hyperlipidemia (AIs)
  - Decreased MVO<sub>2</sub>
- CV risk
  - Hypertension
  - Cholesterol
  - Diabetes
  - Physical Activity
- Ischemic symptoms?
- HF symptoms?



## Case # 1: Mrs. H.R. – Cardiology Visit

- 61 yo F, node + breast cancer, ER/PR+, HER2-
- Borderline hypertension; type II DM; non-smoker
- Physical exam: BP 170/90
- No JVD, normal S1 and S2, no murmurs, no edema
- Asymptomatic at lower levels of physical activity
- ECG: NSR, 89 bpm, mild LVH, normal intervals
- Echo



- LVEF 40%, GLS -15%
- Mildly dilated LV, mildly dilated LA
- Normal RV, No valvular abnormalities

## Case # 1: Mrs. H.R. –CMP evaluation

- Coronary CT
  - LAD: MLA, RCA: 30% mid, LCx:30% mid to distal
- Cardiac MR
  - Mildly dilated LV, LVEF 43%
  - Normal size RV
  - No LGE
- Laboratory
  - NTproBNP, TSH, iron, HIV, lipid panel



## Case # 1: Mrs. H.R. – CMP Treatment

- Therapy initiation (+ plan for titration)
  - Lisinopril 20 mg once daily
  - Carvedilol 6.25 mg twice daily
  - (Spironolactone 25mg)
  - Atorvastatin 40 mg
- **Cancer treatment discussion**
  - Is non-anthracycline regimen an option?
  - Any other strategy that can be considered?

## Q2 Preventative strategies to minimize risk prior to chemotherapy

- **Avoid or minimize** the use of potentially cardiotoxic therapies **if established alternatives** exist that would not compromise cancer-specific outcomes
- Chemotherapy options (non-anthracycline):
  - Docetaxel/cyclophosphamide (TC)
  - Cyclophosphamide/methotrexate/5FU (CMF)

Armenian SH et al. J Clin Oncol. 2016 Dec

[www.asco.org/cardiac-guideline](http://www.asco.org/cardiac-guideline)

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ASCO | GUIDELINES™

## Q2 Preventative strategies for minimizing risk during administration of chemotherapy

- Clinicians should screen for and **actively manage modifiable cardiovascular risk factors** (smoking, hypertension, diabetes, dyslipidemia, obesity) in all patients receiving potentially cardiotoxic treatments
- Clinicians may incorporate a number of strategies, including use of the
  - **cardioprotectant dexrazoxane,**
  - **or continuous infusion,**
  - **or liposomal formulation of doxorubicin**in patients planning to receive high-dose (e.g.  $\geq 250$  mg/m<sup>2</sup> doxorubicin,  $\geq 600$  mg/m<sup>2</sup> epirubicin) anthracyclines

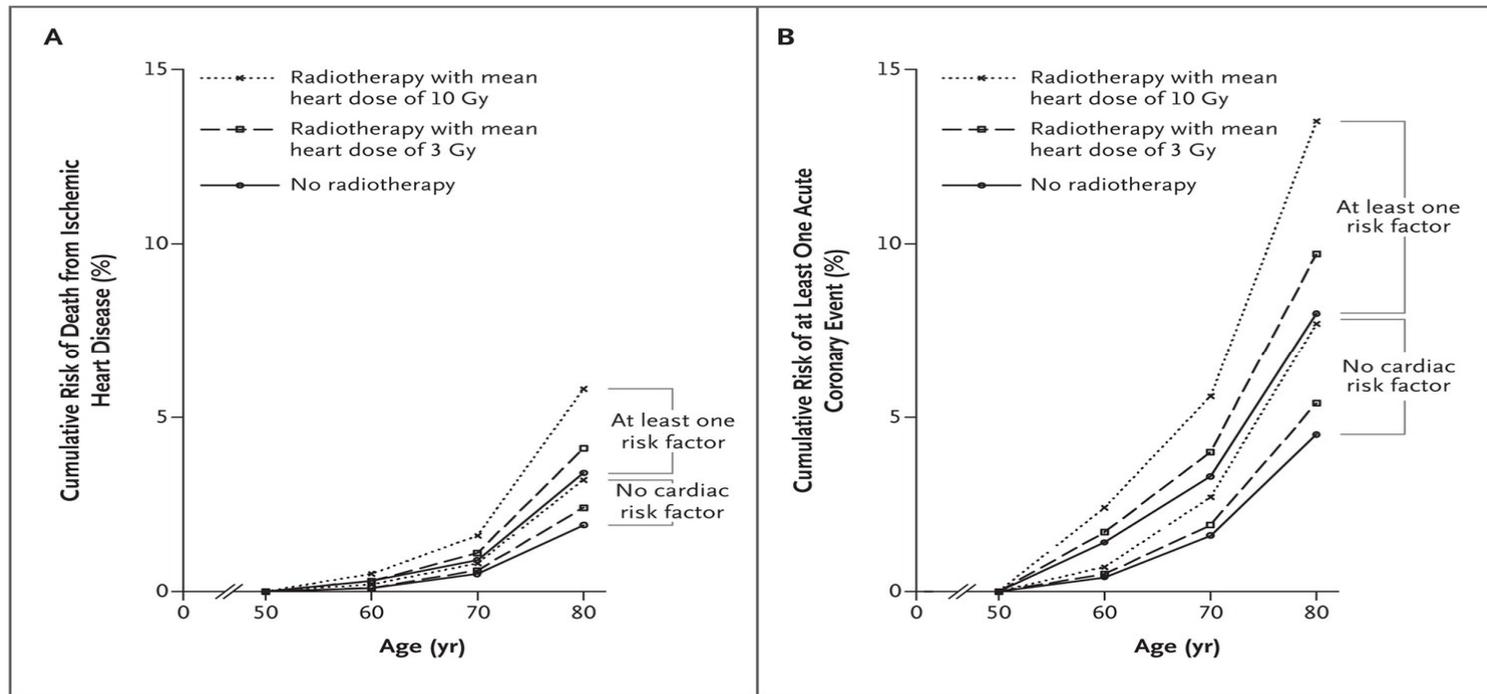
# Case # 1: Mrs. H.R.

- Decision to proceed with 4 cycles of TC chemotherapy
- Continues on lisinopril 40, carvedilol 12.5mg bid, spironolactone 25, and atorvastatin
  - Plan to repeat imaging based on symptoms
- She is now scheduled to receive adjuvant left breast radiation: Do you have any concerns?



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# Cumulative Risks of Death from Ischemic Heart Disease and of at Least One Acute Coronary Event



Darby SC et al. N Engl J Med 2013;368:987-998.

# Preventative strategies to minimize risk during the administration of cancer therapy

For patients who require mediastinal RT that might impact cardiac function, clinicians should select lower radiation doses when clinically appropriate, and use more precise or tailored radiation fields with exclusion of as much of the heart as possible.

These goals can be accomplished through use of **advanced techniques** including:

- **Deep inspiration breath-holding** for patients with mediastinal tumors or breast cancer in which the heart might be exposed
- **Intensity modulated radiation** therapy that varies the radiation energy while treatment is delivered in order to precisely contour the desired radiation distribution and avoid normal tissues

## Case# 2: Mrs. H.P.

- 36 y.o. woman with mammogram detected mass
- Biopsy: infiltrating ductal carcinoma
- Mastectomy with tissue expander and SLN biopsy
- Pathology: T1 (1.5 cm) N1 (1/2) LN +; grade 2 ductal carcinoma
- ER +/PR-/HER2+
- Seen by oncologists who recommend chemotherapy, trastuzumab, hormonal and radiation therapy



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# Past Medical History and Exam

- Borderline elevated cholesterol
- Normal weight, no hypertension or diabetes
- Active lifestyle: runs 1-2 times a week, no symptoms
- BP 135/70 mmHg, HR 60
- Normal exam, healing left breast scar
- Baseline echocardiogram
  - Normal LV function, LVEF 60 %



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# Systemic Chemotherapy Options

- **dd AC-T:** AC Q2 wks x 4 P Q2 wks x 4 + H\*
- **AC-wT:** AC Q 3 wks x 4; P QW x 12 + H\*
- **FEC-D:** FEC Q3 wks x 3; D Q 3 wks x 3 + H\*
- **TC:** DC Q3 wks x 4 + H\*
- **wT:** weekly P x 12 + H\*

\* Trastuzumab qw or q 3w x 1 year

A: adriamycin; C: cyclophosphamide; P: paclitaxel; D: docetaxel  
H: trastuzumab



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## Case # 2 – Mrs. H. P.

- She completes AC chemotherapy and starts paclitaxel concurrent with trastuzumab (T + H)
- Echocardiogram after 3 months of H
  - Mild global hypokinesis, LVEF=45-50%
  - Mildly reduced compared to prior Echo (LVEF by biplane Simpsons 46%)
- Patient asymptomatic; normal BP
- Her oncologists decides to hold her treatment and refers her to cardiology

# Questions

- What are the current guidelines for cardiac monitoring for patients receiving trastuzumab?
- What do the guidelines recommend with regards to holding/stopping trastuzumab?
- What strategies can we use to facilitate completion of cancer therapy?



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# Management of Trastuzumab Therapy

Canadian Consensus Guidelines: Discontinue if symptomatic.

Management of trastuzumab therapy in adjuvant breast cancer patients with asymptomatic decreases in LVEF (Mackey et al 2008):

Relationship of LVEF to Lower Limit of Normal (LLN)	Trastuzumab dose modification		
	based on asymptomatic LVEF decrease from baseline		
	≤ 10 percentage points	10-15 percentage points	≥ 15 percentage points
Within facility's normal limits	Continue	Continue	<b>Hold</b> and repeat MUGA/ECHO after 4 weeks
1-5% below LLN	Continue <sup>1</sup>	<b>Hold</b> and repeat MUGA/ECHO after 4 weeks <sup>1, 2</sup>	<b>Hold</b> and repeat MUGA/ECHO after 4 weeks <sup>2, 3</sup>
≥ 6% below LLN	Continue and repeat MUGA/ECHO after 4 weeks <sup>3</sup>	<b>Hold</b> and repeat MUGA/ECHO after 4 weeks <sup>2, 3</sup>	<b>Hold</b> and repeat MUGA/ECHO after 4 weeks <sup>2, 3</sup>

<sup>1</sup> Consider cardiac assessment and starting ACEI therapy

<sup>2</sup> After 2 holds, consider permanent trastuzumab discontinuation

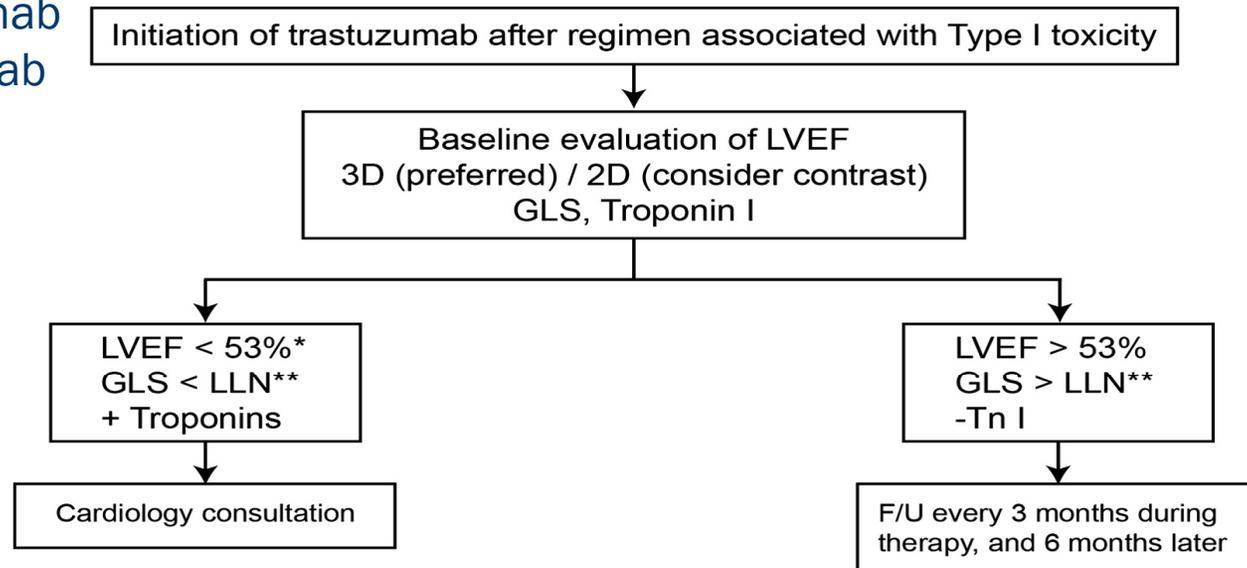
<sup>3</sup> Start ACEI therapy and refer to cardiologist

Mackey et. al Current Oncology, 2008 Jan: 15(1): 24-35



# Monitoring of Cardiac Function During HER2 Therapy

- Trastuzumab
- Pertuzumab
- T-DM1



\* Consider confirmation with CMR.

\*\* LLN = Lower limit of normal. Please refer to Table 5 for normal GLS values based on vendor, gender and age.

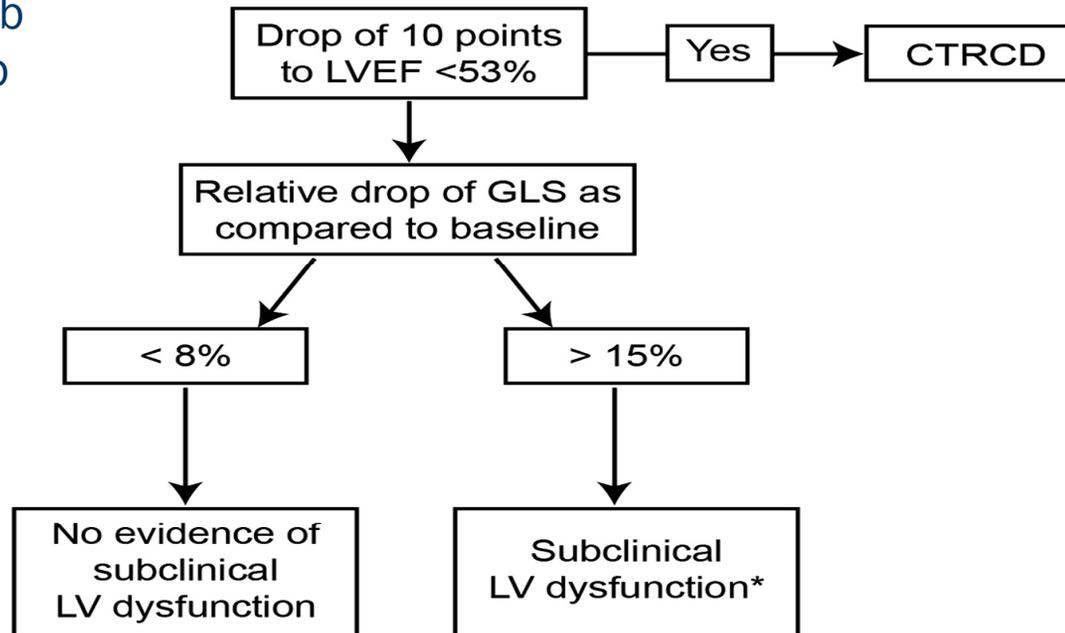
Plana JC et al. JASE 2014 27, 911-939



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# Monitoring of Cardiac Function During HER2 Therapy

- Trastuzumab
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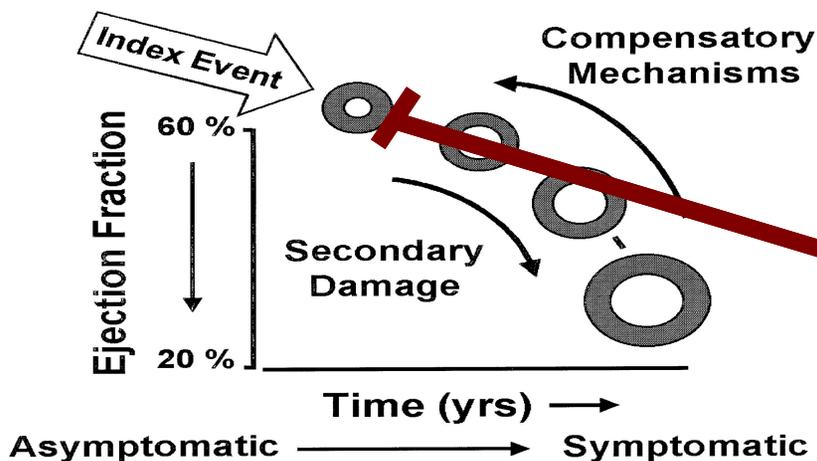
\* The data supporting the initiation of cardioprotection for the treatment of subclinical LV dysfunction is limited.

Plana JC et al. JASE 2014 27, 911-939



# Primary Prevention of Cardiac Dysfunction?

Can we use neurohormonal inhibition to prevent LV dysfunction in patients receiving HER2 therapies?



from Mann D Circ 1999;100:999

- ✓ **PRADA** (Gulati G et al. Eur Heart J. 2016, 37(21):1671)
- ✓ **MANTICORE 101-Breast** (Pituskin E et al. J Clin Oncol. Nov 2016)

# MANTICORE

vs

# PRADA

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

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

## Case # 2: Mrs. H.P

- Trastuzumab held, lisinopril 10mg daily started
- Repeat echo in 3 weeks: LVEF 50-55 %
- She resumes trastuzumab with subsequent echocardiograms showing stable LVEF
- Her oncologist now recommends aromatase inhibitor, letrozole 2.5 mg/d x 5 years
- Do you have any concerns?



## Cardiovascular Disease After Aromatase Inhibitor Use

### Tamoxifen vs Aromatase Inhibitors (AIs) in postmenopausal women

- Epidemiology studies: inconclusive data
- AIs: unfavorable effects on cholesterol profile
- No elevated risk of cardiac ischemia and stroke
  - JAMA Oncol. 2016; 2(12): 1590
- Could statins mitigate the effect ?

#### Key Points

**Question** What is the long-term effect of aromatase inhibitors (AIs) on cardiovascular disease risk in breast cancer survivors?

**Findings** In this retrospective cohort study of 13 273 women with 72 886 person-years of follow-up, AI-only users had a similar risk of cardiac ischemia and stroke as tamoxifen-only users.

**Meaning** The risk of cardiac ischemia and stroke was not elevated in AI-only users compared with tamoxifen-only users, providing reassurance that AIs may not increase the risk of the most fatal cardiovascular events.

JAMA Oncol. 2016; 2(12): 1590



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# Conclusion

- **Comprehensive CV Risk assessment** prior and during treatment of breast cancer
  - Impacts systemic chemotherapy choice
  - Holds promise to improve CV & breast cancer outcomes
- **LVEF assessment and monitoring**
  - Prior to systemic therapy for patients who are at increased risk for cardiotoxicity
  - During therapy in patients on HER2 targeted therapies
  - After therapy based on risk and symptoms



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**Additional Slides**

A pilot study evaluating cardiac SAFETY of HER2 targeted therapy in patients with HER2 positive breast cancer and mildly reduced LV function (SAFE-HEaRt)

### **Eligibility criteria**

- HER2+ breast cancer stage I-IV
- LVEF  $\geq 40\%$  and  $< 50\%$
- Tx with trastuzumab, trastuzumab + pertuzumab or T-DM1
- No HF in last 12 months nor current HF
- No concomitant use of anthracyclines in the last 50 days

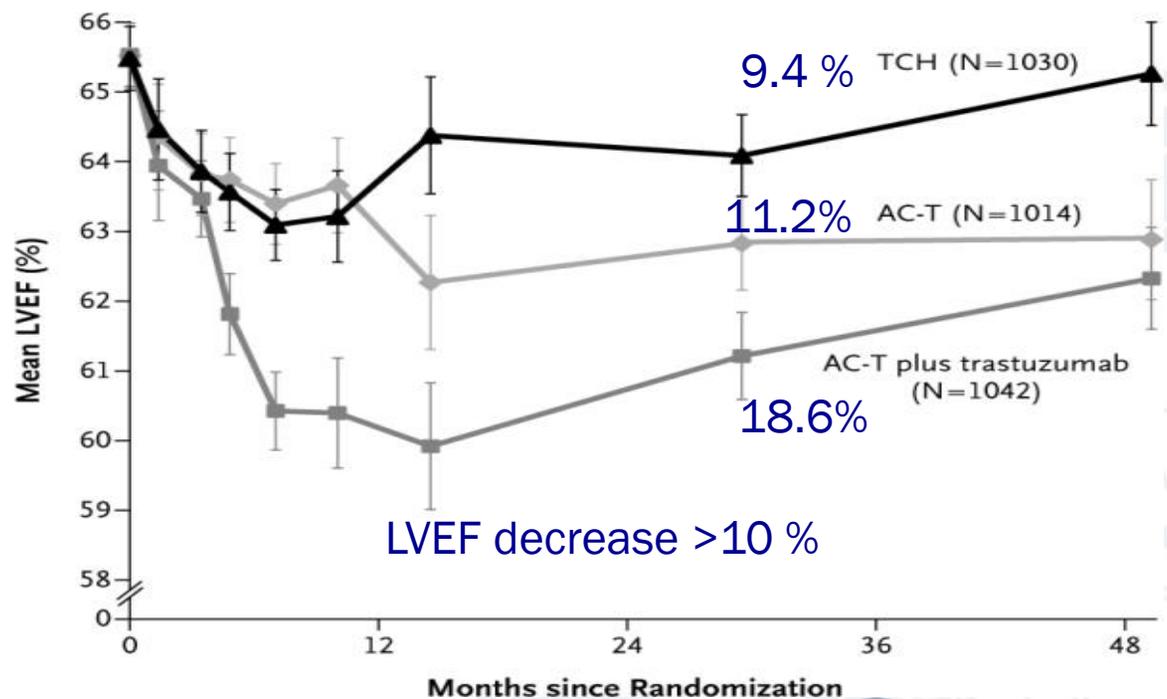
ClinicalTrials.gov Identifier: NCT01904903



# Successes and Challenges of Cardiac Screening in Adjuvant HER2+ Breast Cancer Trials

## BCIRG-006

- 7 LVEF measurements
- Symptomatic HF
  - AC-T 0.7%
  - AC-TH 2%
  - TCH 0.4%



Slamon D et al. N Engl J Med. 2011 365(14):1273



# Q1 Which cancer patients are at increased risk for developing cardiac dysfunction?

Cancer patients who meet any of the following criteria should be considered at increased risk for developing cardiac dysfunction.

- **High dose anthracycline** (e.g.  $\geq 250$  mg/m<sup>2</sup> doxorubicin,  $\geq 600$  mg/m<sup>2</sup> epirubicin)
- **Lower dose anthracycline** (e.g.  $< 250$  mg/m<sup>2</sup> doxorubicin,  $< 600$  mg/m<sup>2</sup> epirubicin) in combination with lower dose radiotherapy ( $< 30$  Gy) where the heart is in the treatment field

## Q1 Which cancer patients are at increased risk for developing cardiac dysfunction?

- Treatment with **lower dose anthracycline** (e.g. <250 mg/m<sup>2</sup> doxorubicin, <600 mg/m<sup>2</sup> epirubicin) or trastuzumab alone, and presence of **any of the following risk factors**:
  - **Multiple (≥2) cardiovascular risk factors**, including: smoking, hypertension, diabetes, dyslipidemia, obesity during or after completion of therapy
  - **Older (≥60 years) age** at cancer treatment
  - **Compromised cardiac function** (e.g. borderline low LVEF [50-55%], history of myocardial infarction, ≥moderate valvular heart disease) at any time prior to or during treatment