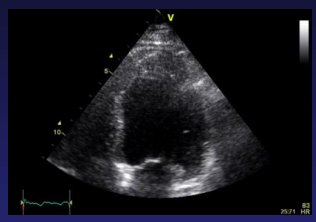
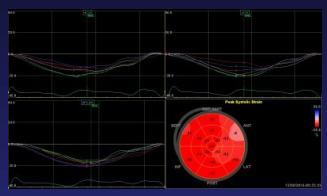
# Cardio-oncology: Basics and Knowing When You Need an Echo





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## No Disclosures

- Acknowledgement: Nausheen Akhter, MD, Director of the cardio-oncology program at Northwestern

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# Introduction

- The number of cancer therapies have significantly increased
- Cancer survival has improved
- A number of cancer therapies have cardiotoxic effects

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# Cardiotoxic Syndromes Associated with Chemo

Agents associated with LV dysfunction

- Anthracylines
- Mitoxanthrone
- Cyclophosphamide
- Trastuzumab
- Ifosfamide
- All-trans retinoic acid

Agents associated with ischemia

- 5-FU
- Cisplatin
- Capecitabine (Xeloda)
- IL-2

Yeh et al. Circulation 2004

Agents associated with hypertension

- Bevacizumab (Avastin)
- Cisplatin
- IL-2

Agents associated with Other toxic effects

- Tamponade or endomyocardial fibrosis (Busulfan)
- Hemorrhagic Myocarditis (Cyclophosphamide)
- Bradycardia (Taxol, Thalidomide)
- Raynaud's (Vinblastine)
- Autonomic neurop (Vincristine)
- Long QT (Arsenic trioxide)
- Pulm fibrosis (Bleo)

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# Angiogenesis Inhibitors

- Angiogenesis is a key factor for tumor growth and survival.
- Angiogenesis inhibitors have shown to improve outcomes in various malignancies
- Tumor growth suppression achieved by:
  - **Direct inhibition of VEGF ligand's ability to target receptor (bevacizumab, ramucirumab, aflibercept)**
  - **Small molecules that inhibit tyrosine kinases (sunitinib, sorafenib, pazopanid, vandetanib, vatalanib, cobazantinib, axitinib, regorafenib)**

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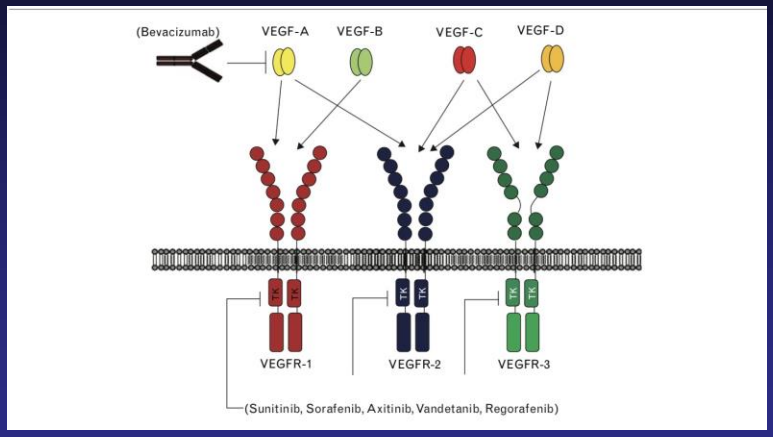
# Mechanisms of Action of Angiogenic Inhibitors




Maurea N et. J Cardiovasc Med 2016;17(suppl):e-19-e26

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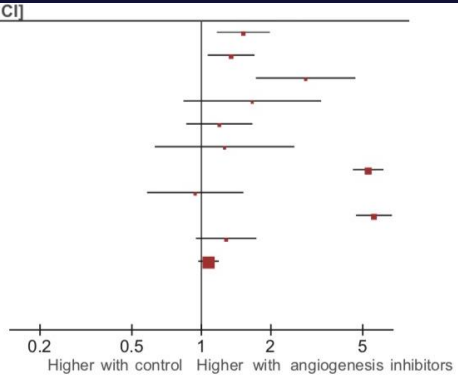
# Odds ratio for adverse cardiac events due to angiogenesis inhibitors

| Toxicity | Odds Ratio [95% CI] |
|---|---|
| Arterial thromboembolism | 1.52 [1.17, 1.98] |
| Cardiac dysfunction | 1.35 [1.06, 1.70] |
| Cardiac ischemia | 2.83 [1.72, 4.65] |
| Congestive Heart Failure | 1.66 [0.84, 3.30] |
| Deep vein thrombosis | 1.20 [0.86, 1.66] |
| Fatal cardiovascular events | 1.26 [0.63, 2.53] |
| Hypertension | 5.28 [4.53, 6.15] |
| Pulmonary embolism | 0.94 [0.58, 1.52] |
| Severe hypertension | 5.59 [4.67, 6.69] |
| Unspecified thromboembolism | 1.28 [0.95, 1.73] |
| Unspecified venous thromboembolism | 1.07 [0.97, 1.19] |




Abdel-Qadir H et al. Cancer Treatment Reviews 20178;53:120-127.

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EXPERT CONSENSUS STATEMENT

## Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marielle Scherrer-Crosbie, MD, PhD, FASE, Javier Ganame, MD, PhD, FASE, Igal A. Sebag, MD, FASE, Deborah A. Agler, RCT, RDCS, FASE, Luigi P. Badano, MD, PhD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, PhD, FESC, Joseph Carver, MD, Manuel Cerqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott D. Flamm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andreia Magalhães, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector R. Villarraga, MD, FASE, and Patrizio Lancellotti, MD, PhD, FESC, *Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, District of Columbia; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Quebec, Canada; Chicago, Illinois; Oslo, Norway; Liege, Belgium; New York, New York; Lisbon, Portugal; Hobart, Australia; Rochester, Minnesota*

J Am Soc Echocardiogr 2014;27:911-39.

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# CTRCD Defined

- CTRCD (Cancer Therapeutics-Related Cardiac Dysfunction)
  - **Decrease in LVEF > 10% to a value < 53%**

**Reversible**: to within 5 % points of baseline

**Partially reversible**: improved by ≥10 % points from the nadir but remaining >5 % points below baseline

**Irreversible**: improved by < 10 % points from the nadir and remaining > 5 % points below baseline

Plana, JC et al. JASE 2014; 27: 911-39

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# CTRCD

| TYPE 1 | TYPE 2 |
|---|---|
| • Anthracycline-induced | • Non-ANT agents |
| • Dose-related | • Not dose related |
| • Irreversible damage | • Generally reversible myocardial dysfunction |
| • Early treatment with HF therapy can prevent LV remodeling/EF decline | • No apparent ultrastructural abnormalities |

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# Type 1 CTRCD

| Drug | Toxic Dose Range | Cardiac Toxicity | % |
|---|---|---|---|
| Doxorubicin | >450 mg/m2 | LVD | 3 – 12% |
| Epirubicin | >720 mg/m2 | | 0.9 – 3.3% |
| Paclitaxel | Conventional dose | LVD | 5 – 15% |
| Docetaxel | | HF | 2 – 8% |
| Cyclophosphamide | >150 mg/kg | HF 1-10 d after 1st dose | 7-28% |
| Ifosfamide | | HF | 10-30% |

Oreto et al. JASE 2012

Giuseppe et al. Progress in Cardiovascular Disease 53 (2010) 94 – 104.

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# Type 2 CTRCD

| Drug | Cardiac Toxicity | % |
|---|---|---|
| Trastuzumab | LVD<br>With concurrent anthracycline | 2 – 10%<br>27% |
| Lapatinib | Asymptomatic cardiac events, reversible LVD | 1% |
| Sunitinib | LVD<br>Hypotension | 10-30% |
| Bevacizumab | LVD | 2-3% |

Giuseppe et al. Progress in Cardiovascular Disease 53 (2010) 94 – 104. , Oreto et al. JASE 2012

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## Which echo measures can you use to predict CTRCD?

LV EF (2D/3D)

Diastology

Tissue Doppler Imaging (s')

MAPSE

Myocardial Deformation Imaging

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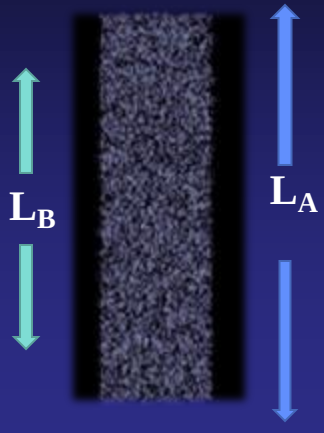
## Strain Imaging

**Strain = % change in length of the myocardium during relaxation and contraction**




$$\text{Strain} = \frac{L_B - L_A}{L_A} = \frac{\Delta L}{L_A}$$

$L_A$ = Myocardial length at end diastole
$L_B$ = Myocardial length at end systole

Courtesy of Ben Freed, MD

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# Anthracyclines

- Cardiac damage thought to occur by:
  - **Production of free radicals**
  - **Free radicals are highly toxic and react with lipids, proteins and nucleic acids**
  - **Results in lipid peroxidation, depletion of sulfhydryl-containing peptides, and damage to DNA.**
  - **Cardiac myocytes have low levels of free radical scavenging systems**

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# Anthracycline Toxicity: Acute, Subacute, Chronic

- Acute – 1st week of therapy
  - **< 1% of pts immediately after infusion**
  - **Transient, reversible decrease in LVEF**
  - **Improves with discontinuation**
- Subacute onset – 1st year of therapy
  - **1.6 % to 2.1 % of patients**
  - **Dose-related decrease in LVEF, irreversible**
  - **Can progress to clinical HF**
- Chronic or late onset > 1 year after therapy
  - **1.6 % to 5% of patients**
  - **Can be triggered by a secondary insult, generally irreversible**

Giuseppe et al. Progress in Cardiovascular Disease 53 (2010) 94 – 104.

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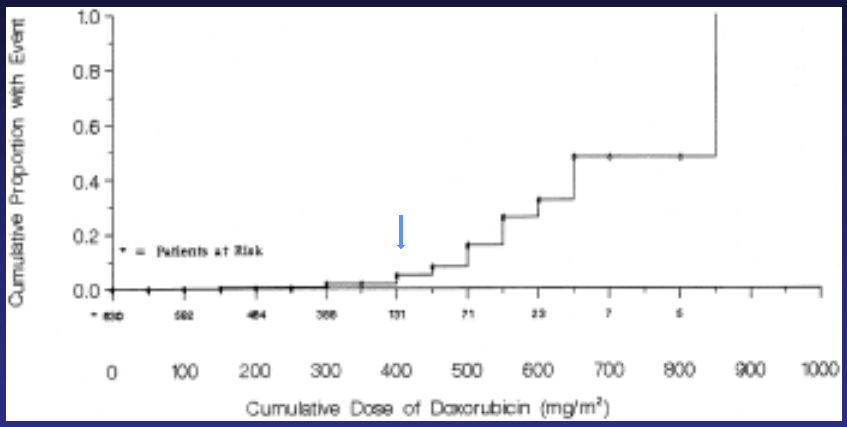
# Dose-related ANT Toxicity




Swain et al. Cancer (2003).

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# Anthracycline Cardiotoxicity: Risk Factors

- Cumulative dose
- Method of administration: IV bolus administration, higher single dose, dose dense therapy
- Baseline low EF
- Older age
- Prior or concomitant RT
- Concomitant cardiotoxic chemotherapy
  - **Trastuzumab**

Giuseppe et al. Progress in Cardiovascular Disease 53 (2010) 94 - 104

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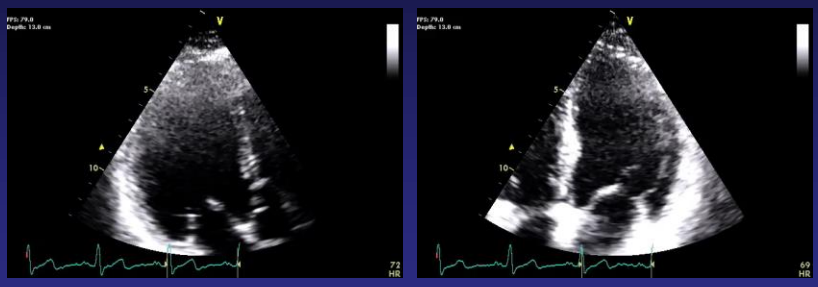
## 48 yo M with h/o LCX infarct diagnosed with DLBCL who presents for baseline echo prior to undergoing doxorubicin-based chemotherapy.

**Baseline EF = 49%**



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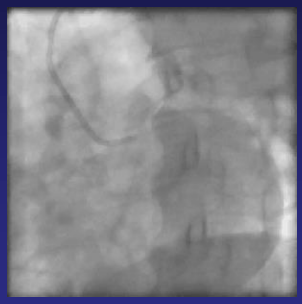
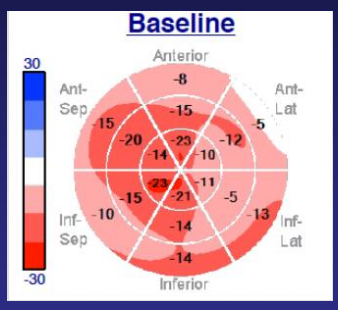
## 48 yo M with h/o LCX infarct diagnosed with DLBCL who presents for baseline echo prior to undergoing doxorubicin-based chemotherapy.

**Baseline Bull's Eye with LCX infarct, GLS: - 13.9%**



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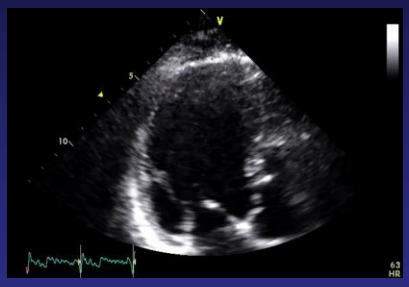
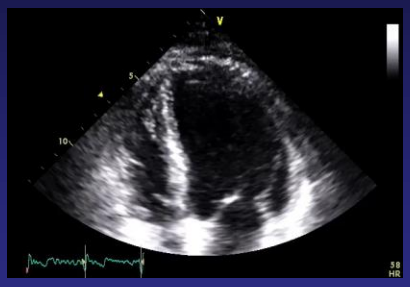
## 48 yo M with h/o LCX infarct and DLBCL s/p CHOP chemotherapy (total doxorubicin dose 300 mg/m$^2$) presents for post-chemo echo.

**Post Chemo EF = 33%**





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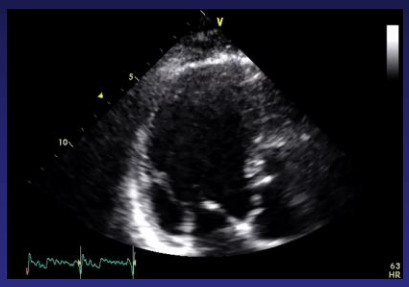
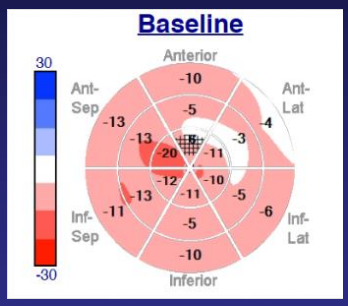
## 48 yo M with h/o LCX infarct and DLBCL s/p CHOP chemotherapy (total doxorubicin dose 300 mg/m$^2$) presents for post-chemo echo.

**Post Chemo GLS: - 9.6%**



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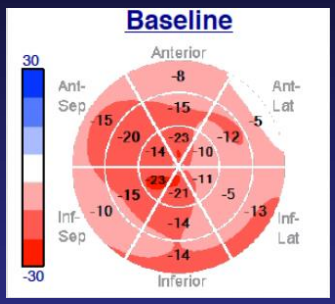
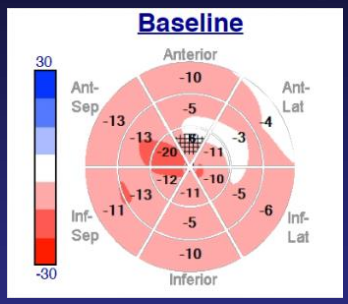
**Pre-CHOP Chemotherapy**




EF = 49%
GLS = -13.9%

**Post CHOP Chemotherapy**




EF = 33%
GLS = -9.6%

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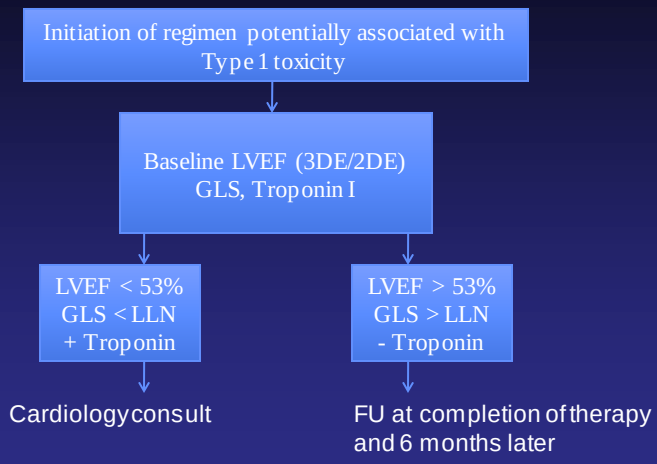
# Integrated Approach




Plana, JC et al. JASE 2014; 27: 911-39

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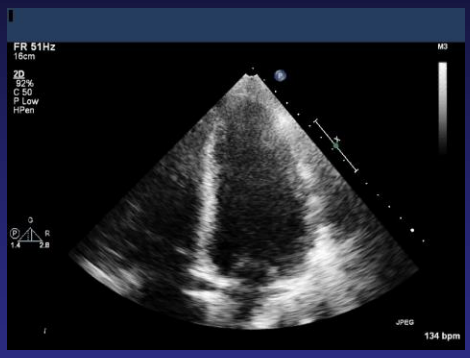
**25 yo male with newly dx AML s/p 7+3 chemotherapy, septic in ICU, had a normal baseline echo.**

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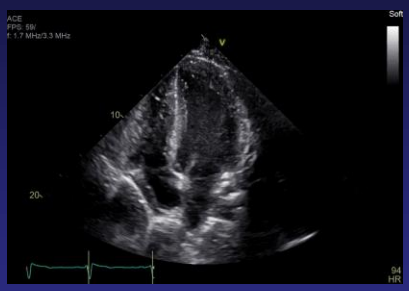
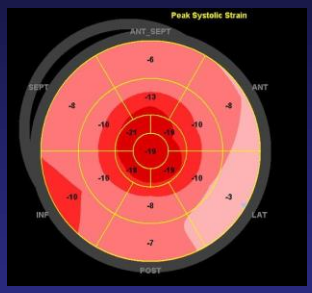
# 10 days later

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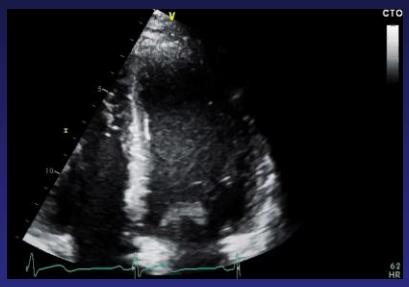
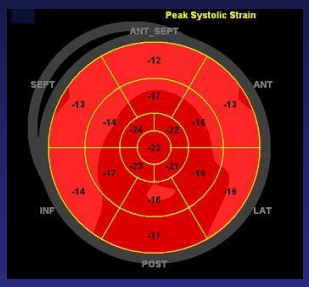
# 3 weeks later

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# Trastuzumab

- Human epithelial growth factor 2 (HER-2) is over expressed in approx 20% breast cancer pts
- Amplifications of HER-2 associated with decreased survival and increased recurrence
- Trastuzumab (Herceptin) is a humanized HER-2 monoclonal antibody FDA approved in 1998

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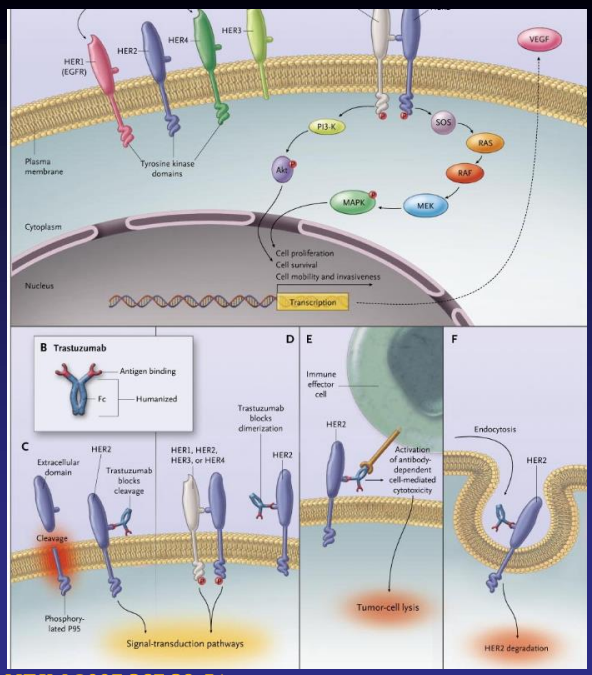


Hudis m CA et al. NEJM 2007;367:39-51

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# Trastuzumab Cardiac Toxicity

- Mechanism not fully understood
- Directly related to HER-2 receptor blockade
- HER-2 receptors expressed on myocytes for protection from cardiotoxins and for embryonic cardiac development.
- Inhibition of HER-2 receptor blocks ErbB2 signaling that is responsible for growth, repair and survival of myocytes
- Suppression of HER-2 gene in mice resulted in DCM

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## Herceptin Adjuvent Trial (HERA): Cardiac Events

| | Trastuzumab (n = 1,678) | Observation (n = 1,708) |
|---|---|---|
| Cardiac death | 0 (0%) | 1 (0.6%) |
| Severe CHF (not including cardiac death) | 10 (0.6%) | 0 (0%) |
| Symptomatic CHF (including severe CHF, not including cardiac death) | 36 (2.15%) | 2 (0.12%) |
| Confirmed significant LVEF drop (asymptomatic or mildly symptomatic) | 51 (3.04%) | 9 (0.53%) |
| Any type of cardiac end point (at least one occurrence of cardiac adverse events above) | 61 (3.64%) | 10 (0.59%) |
| At least one significant LVEF drop | 118 (7.03%) | 35 (2.05%) |

Suter TM et al. J Clin Onc 2007;25:3859-3865

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## Cardiac Monitoring Based on Initial Traztuzumab Trials

- LVEF at baseline, following completion of chemo (usually Adria, Cyclophos)
- LVEF at 3, 6, +/-9, 12, 18 months from initiation of chemo
- Metastatic disease: Infrequent monitoring in absence of symptoms

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# Trending Strain For Prognostication

- 81 women with HER 2+ disease were prospectively studied, 37 who had also received concurrent ANT.
- 30% of patient had a decrease in GLS at 6 months who *later* developed cardiotoxicity.
- Strongest predictor of cardiotoxicity was change in GLS of 11%, sensitivity 65% specificity 94%.
- Compared to baseline strain measurements, "reductions of strain of <8% appear not to be meaningful, and those >15% are very likely to be abnormal."

Negishi et al. J Am Soc Echocardiogr 2013; 26: 493-8

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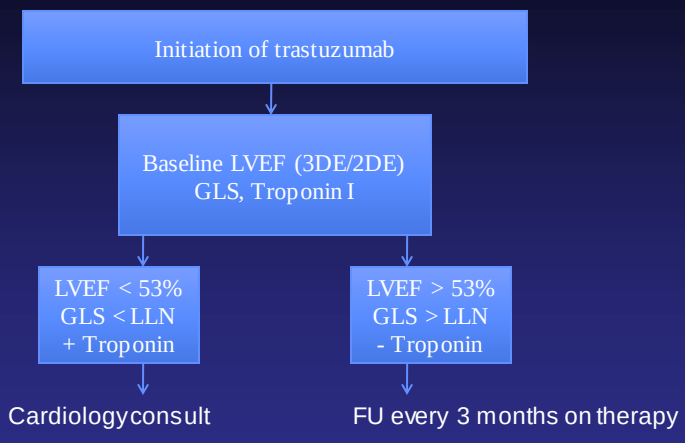
# Integrated Approach




Plana, JC et al. JASE 2014; 27: 911-39

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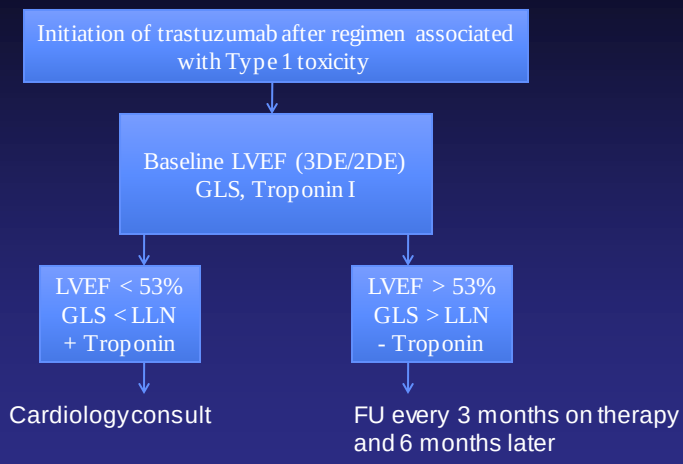
# Integrated Approach

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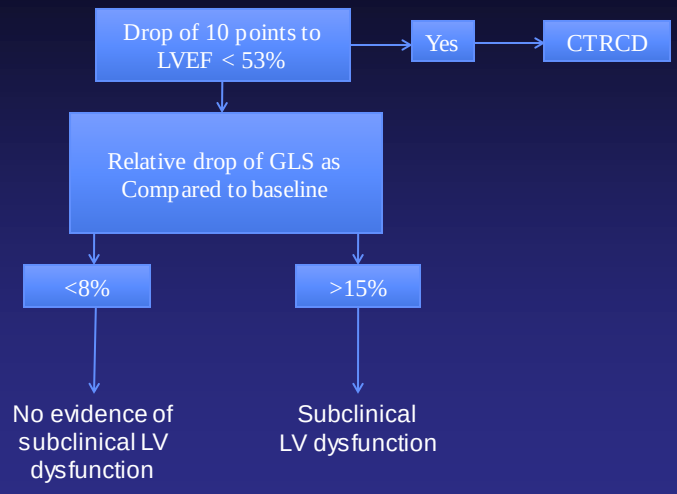
# Integrated Approach




Plana, JC et al. JASE 2014; 27: 911-39

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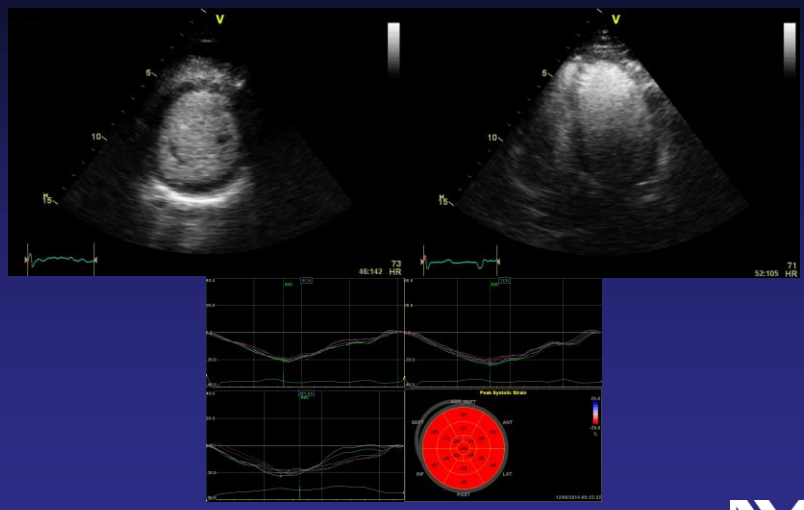
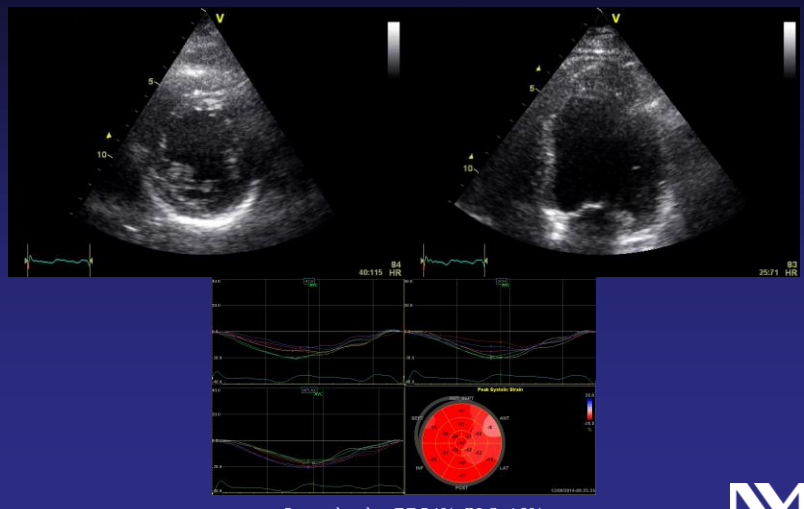
## 55 yo female with HTN, HER2 + breast cancer s/p AC-TH, on maintenance trastuzumab.



Baseline echo, EF 60%, GLS -21%

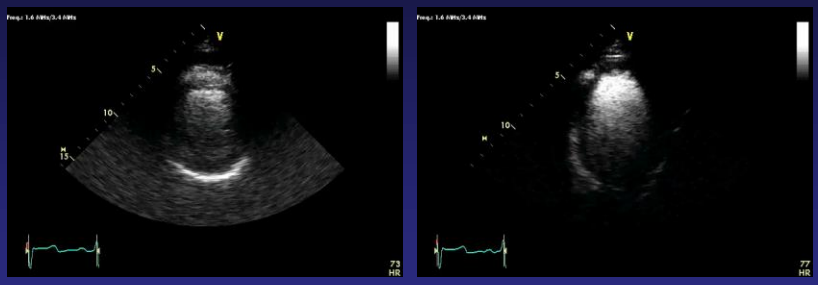


## 55 yo female with HTN, HER2 + breast cancer s/p AC-TH, on maintenance trastuzumab. 3 month surveillance echo…



3 month echo, EF 54%, GLS -16%

**55 yo female with HTN, HER2 + breast cancer s/p AC-TH, on maintenance trastuzumab. 6 month surveillance echo…**



6 month echo, EF 40%

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# Late Cardiac Effects

- Anthracyclines can manifest cardiotoxicity late in life, especially when used in pediatric pts
- Risk of adverse effects of chest radiation increases with time

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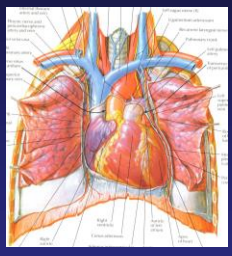
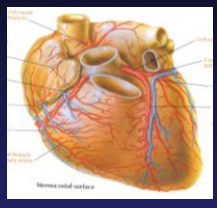
# Sites of Cardiac Involvement

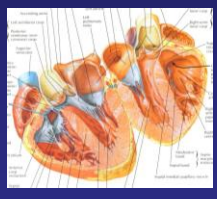
Coronary Artery Disease



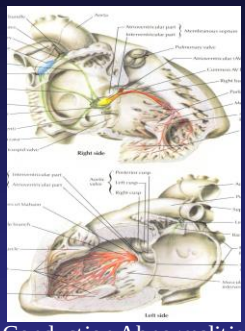
Pericardial Disease



Myocardial Dysfunction



Valvular Heart Disease



Conduction Abnormalities

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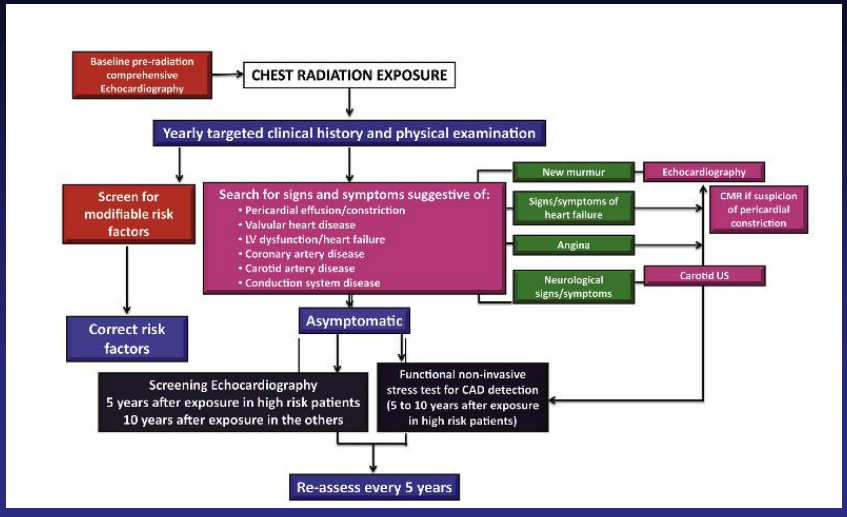
# EACVI/ASE Recommended Algorithm for Patient Management Following XRT




J Am Soc Echocardiogr 2013;26:1013-32

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# Summary

- Variety of cancer drugs are now available and have improved cancer survival
- Several agents have cardiotoxic effects
- Echo is the primary imaging modality to follow patients at baseline, during treatment and long term
- Toxicity is agent-specific. Imaging and clinical followup is specific to the disease and agents used for treatment

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# Thank You

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