2017 HFCT Annual Meeting "The Heart Failure Crosstalk"
June 16, 2017

Cardio-Oncology: Cardiologist's Perspective

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Agenda

- Introduction
- Mechanisms of cardiotoxicity
- Definition and Diagnosis
- Monitoring cardiotoxicity
- Management

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Introduction:

How important is cardio-oncology?

- Cancer-related death is one of the leading causes of death.
- Over the past few decades, mortality from cancer has decreased tremendously due to earlier diagnosis and novel treatments.
- Cardiac morbidity and mortality of cancer survivors has increased.
- Risk of death from cardiovascular causes exceeds that of tumor recurrence for many forms of cancer.

Cardio-Oncology

CV complications related to chemotherapy and radiation therapy

- Myocyte damage
- Left ventricular dysfunction and heart failure
- Thrombogenesis
- Ischemia and vasospasm
- Pericardial pathology
- Hypertension
- Conduction and rhythm disturbances

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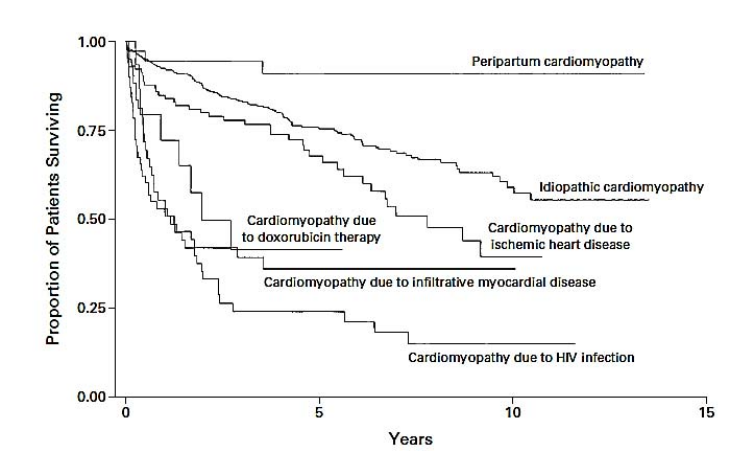
Long-Term Survival: Underlying Cause of Cardiomyopathy

3.5-fold increased mortality risk compared with idiopathic cardiomyopathy



Felker, GM. NEJM 2000

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Cancer Therapy Related to Cardiotoxicity

- **Cytotoxic chemotherapy**
  - **Anthracyclines:** doxorubicin, daunorubicin, epirubicin, and idarubicin
  - Alkylating agents: cyclophosphamide, ifosphamide, and melphalan
  - Microtubular Polymerization Inhibitors/Taxanes: paclitaxel and docetaxel
- **Molecular targeted therapy**
  - HER2-Targeted Cancer Therapies: Trastuzumab
  - VEGF Inhibitors: Tyrosine Kinase Inhibitors (sunitinib, sorafenib)
- **Chest and mediastinal irradiation**

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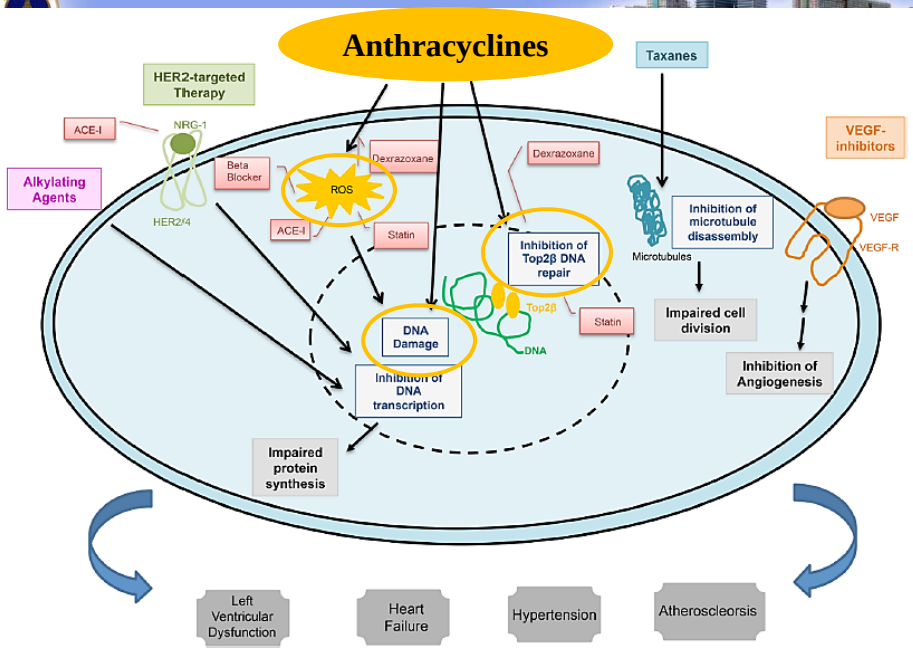

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Anthracyclines: Cardiotoxicity

- Association between cumulative dosing and cardiotoxicity:
  - Diastolic dysfunction: 200 mg/m^2
  - Systolic dysfunction: 400-600 mg/m^2
- LV dysfunction can occur at any dose:
  - 18.9% of patients receiving a doxorubicin dose of 240 mg/m^2 in combination with cyclophosphamide
- Risk factors: CVD risk factors, mediastinal irradiation, concomitant therapy with agents eg. cyclophosphamide, paclitaxel and trastuzumab

Int J Cardiol. 2010;144:3–15.;Br J Cancer. 2004;91:37–44.; Curr Cardiol Rev. 2011;7:214–20.

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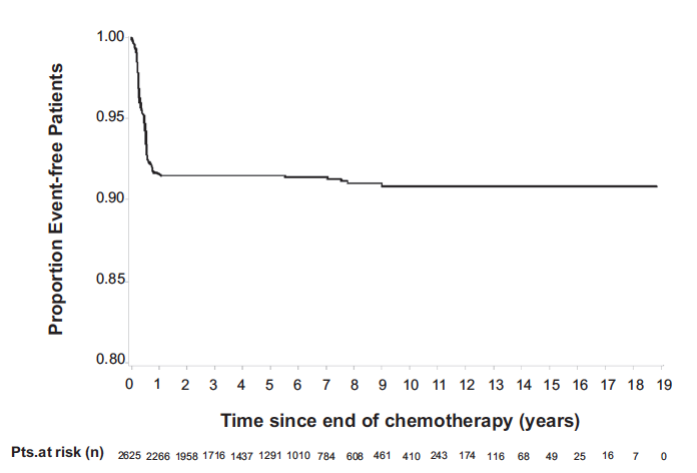
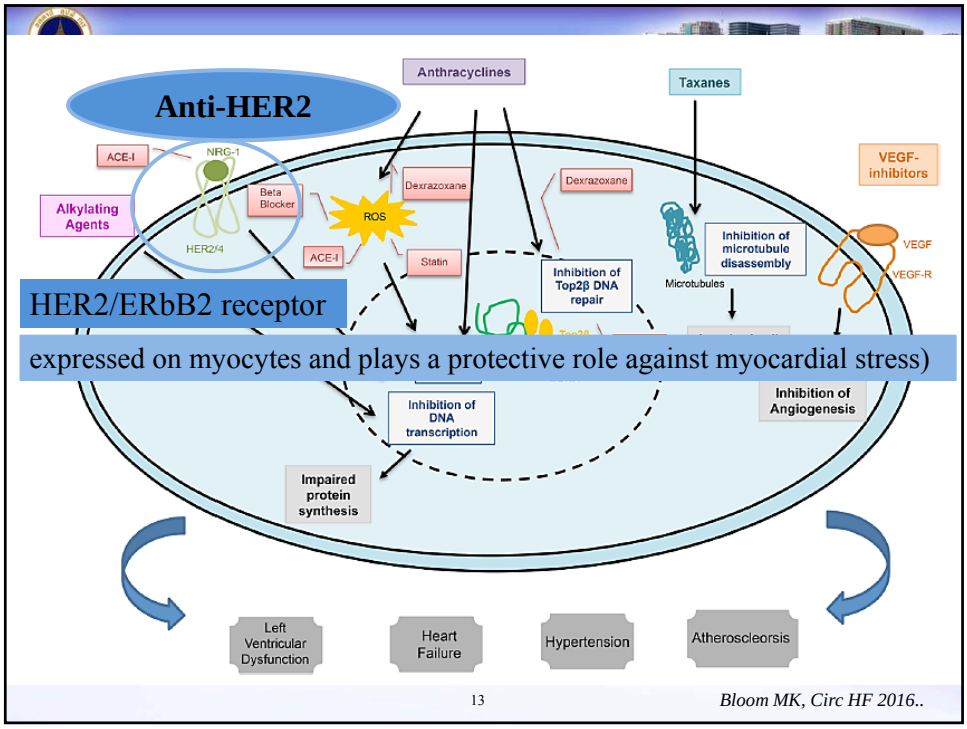
Cumulative incidence of AC related cardiotoxicity



Circulation. 2015;131:1981-1988.



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Trastuzumab (humanized anti-HER2 monoclonal antibody)

- Prevalence: adjuvant therapy to anthracycline based regimen
  - Heart failure:1.7-4.1%
  - LV dysfunction in 7.1-18.6% of

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J Clin Oncol. 2015;33:1136–1142.

CTRCD type I vs. type II

Table 1 Characteristics of type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

JASE 2014;27:911-39.

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Chest/Mediastinal Irradiation

- **Acute radiation myocarditis:** rare
- **Late to very later complications:**
  - Macrovascular complications
  - Microvascular complications
  - Endothelial injury: valvular dysfunction
  - Atherosclerosis
  - Fibrosis
  - Pericardial disease: constrictive pericarditis

Bloom MK, Circ HF 2016.

Chest/Mediastinal Irradiation
Late to very late complications

- In patients with breast cancer, received chest RT: Events occurred 5 years after initial exposure and continued through the third decade following exposure.

N Engl J Med. 2013;368:987–998..

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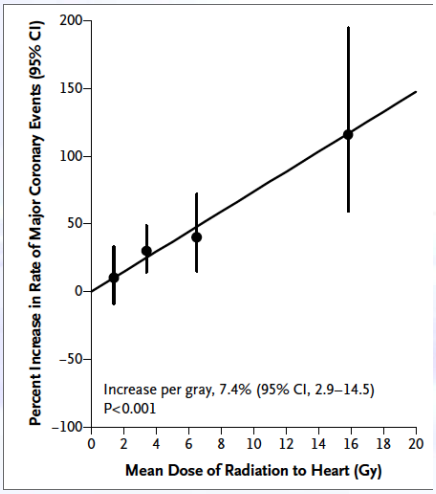
Linear increase in coronary events with radiation dose



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N Engl J Med. 2013;368:987–998..

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Chemotherapy related cardiac dysfunction (CTRCD)

No Specific Definition!

- Anthracycline cardiotoxicity: *US FDA 2015*
  - >20% decrease in LVEF when baseline LVEF is normal, or
  - >10% decrease when baseline LVEF is not normal
- Trastuzumab cardiotoxicity: *J Clin Oncol. 2002;20:1215–1221*
  - Asymptomatic decrease in LVEF of >10% to <55%, or
  - Decrease in LVEF of >5% to <55%, combined with symptoms of heart failure
- Decrease in LVEF >10 %, to a value < 53%

2014 ASE guideline. JASE 2014;27:911-39.

Chemotherapy related cardiac dysfunction: Diagnosis

- Clinical CTRCD:
  - LVEF measured by cardiac imaging:
  - **Echo, MUGA**, MRI, PET/MRI etc.
- Subclinical CTRCD:
  - **Global longitudinal strain**
  - **Serum troponin-I**

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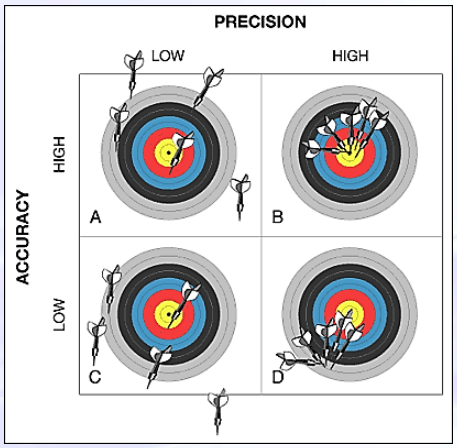


Inter-measurement variability

- Intra-observer variability
- Inter-observer variability
- Test-retest variability:
  - Temporal variability
  - Coefficient of variation

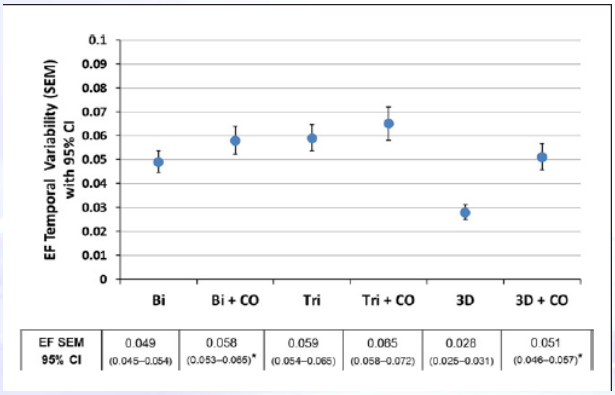
Temporal variability (Coefficient of variation; COV)

Method	EF COV (95% CI), %	EDV COV (95% CI), %	ESV COV (95% CI), %
Bi-Plane	7.4 (6.2 - 9.1)	16.2 (13.7 – 20.0)	22.0 (18.5-27.0)
Bi-Plane + Contrast	8.4 (7.0 – 10.5)*	16.0 (13.3 – 20.0)	23.6 (19.7 – 29.6)
Triplane	9.4 (7.9 – 11.5)	23.0 (19.4 – 28.2)*	26.2 (22.1 – 32.3)
Triplane + Contrast	9.4 (7.8 – 11.8)	20.1 (16.7 – 25.2)	23.6 (19.7 – 29.7)
3D	4.0 (3.3 – 4.9)	11.9 (10.0 – 14.7)	13.2 (11.1 – 16.2)
3D + Contrast	7.2 (6.0 - 9.1)*	16.6 (13.8 – 20.9)*	20.0 (16.5 – 25.1)*

Non-contrast 3D had the lowest temporal variability based on COV for EF, EDV, and ESV compared to all other methods ($p<0.01$ for all). *statistically different when compared to the respective non-contrast method ($p<0.05$).

JASE 2014;27:911-39.

Temporal variability of EF, EDV, ESV



Minimal detectable change in LVEF not attributable to variability: 5-6% with 3D TTE vs. 10-13% with 2D TTE

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JASE 2014;27:911-39.

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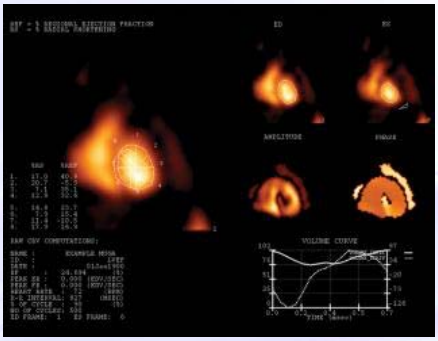
Multi-gated acquisition (MUGA) scan



- Advantages
  - Excellent reproducibility
  - Not dependent on acoustic windows
  - Historical outcome data
- Disadvantages:
  - Ionizing radiation
    5-10 mSv per scan
  - No additional info on pericardium, valves and RV

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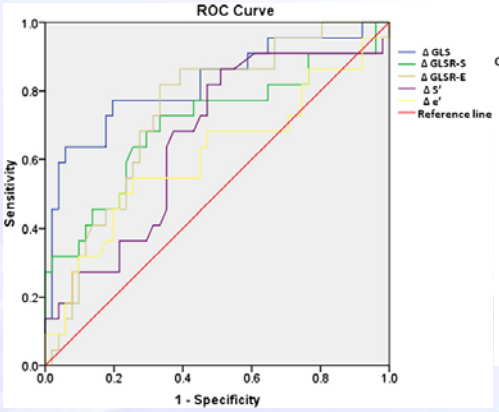
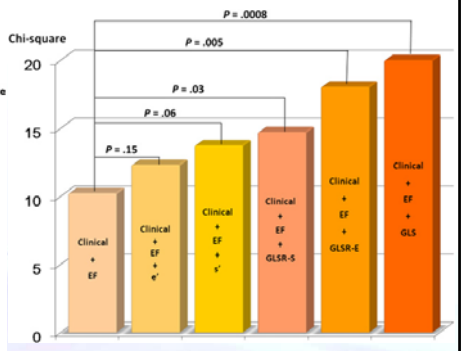
Table 3 Percent changes in echocardiographic parameters in 6 months within the groups

	No cardiotoxicity	Cardiotoxicity	*P*
GLS	0.2 ± 8.6	11.4 ± 9.8	<.001
GLSR-S	−0.2 ± 16.8	12.8 ± 19.4	.009
GLSR-E	5.1 ± 21.2	−11.9 ± 14.5	.002
s′	−5.0 ± 18.9	−17.0 ± 23.9	.04
e′	3.5 ± 37.1	−10.0 ± 28.7	.09
GCS	−1.0 ± 29.7	9.3 ± 27.4	.18
GRS	8.3 ± 48.5	−10.0 ± 39.3	.11

GCS, Global circumferential peak systolic strain; *GRS*, global radial peak systolic strain.

Negishi K, et al. JASE 2013;26:493-8.)





Change in GLS at 6 months: AUC = 0.84, p<0.001

Optimal cut point = 11% reduction (95% CI, 8.3%–14.6%) having sensitivity of 65% and specificity of 94%.

NRI 0.77 (95% CI, 0.33–1.22; P = .036)

IDI 18.6% (95% CI, 8.6–28.6; P = .0003).

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Negishi K, et al. JASE 2013;26:493-8.)

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2014 ASE guideline: GLS

Subclinical CTRCD:

- A relative percentage decrease of >15% compared with baseline, or
- Absolute value <19% if no baseline

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2014 JASE;27:911-39.

Strain imaging

Table 5 Effect of vendor age and gender on GLS

Vendor	Age group (y) 0–19	20–29	30–39	40–49	50–59	≥60	*P*
V1							
Overall	−22.1 ± 2.4	−21.2 ± 1.9	−21.1 ± 2.1	−21.4 ± 2.0	−21.0 ± 2.2	−20.3 ± 1.9	.0218
Male	−21.7 ± 3.1	−20.9 ± 1.9	−20.6 ± 1.9	−20.9 ± 1.8	−21.0 ± 1.9	−19.7 ± 1.4	.1982
Female	−22.4 ± 1.6	−22.3 ± 1.6	−22.8 ± 1.8	−22.6 ± 2.1	−23.3 ± 1.9	−20.9 ± 2.1	.0348
P (male vs female)	.4292	.0316	<.0001	.0178	.0029	.1381	
V2							
Overall	−19.9 ± 2.5	−19.0 ± 2.1	−19.5 ± 2.2	−18.2 ± 2.5	−17.6 ± 2.5	−16.7 ± 2.1	<.0001
Male	−19.4 ± 2.7	−18.8 ± 2.0	−19.1 ± 2.3	−17.9 ± 2.8	−16.9 ± 2.3	−15.8 ± 1.4	.0019
Female	−20.5 ± 2.2	−20.6 ± 2.3	−20.2 ± 2.0	−19.3 ± 0.9	−20.4 ± 1.5	−17.3 ± 2.3	.0002
P (male vs female)	.1349	.0248	.1083	.4316	.0294	.0928	
V3							
Overall	−21.4 ± 1.7	−20.2 ± 2.1	−20.4 ± 2.3	−19.4 ± 2.2	−18.5 ± 2.6	−17.8 ± 2.8	<.0001
Male	−21.6 ± 2.0	−20.2 ± 2.0	−20.4 ± 2.2	−19.8 ± 2.3	−18.7 ± 2.6	−16.3 ± 3.1	<.0001
Female	−21.2 ± 1.5	−20.2 ± 2.4	−20.4 ± 2.8	−18.7 ± 1.8	−18.3 ± 2.8	−18.6 ± 2.3	.0141
P (male vs female)	.6076	.9787	.9201	.1415	.7374	.0668	

V1, Vivid 7 or Vivid E9 (GE Healthcare); *V2*, iE33 (Philips Medical Systems); *V3*, Artida or Aplio (Toshiba Medical Systems).
Reproduced with permisssion from *Circulation Journal*.[166]

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JUSTICE study. Circ J 2012;76:2623-32.

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Chemotherapy related cardiac dysfunction: Diagnosis

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Cardiac biomarkers: Troponin-I

Screening:

- Absence of troponin elevation in patients receiving high-dose anthracyclines: High NPV for CTRCD
- Troponin I levels at completion of anthracycline treatment: predict of subsequent reduction in LVEF and cardiac events

Risk stratification, monitoring:

- Increased troponin I in patients receiving trastuzumab:
  - Decrease likelihood of LVEF recovery
  - Higher incidence of cardiac events

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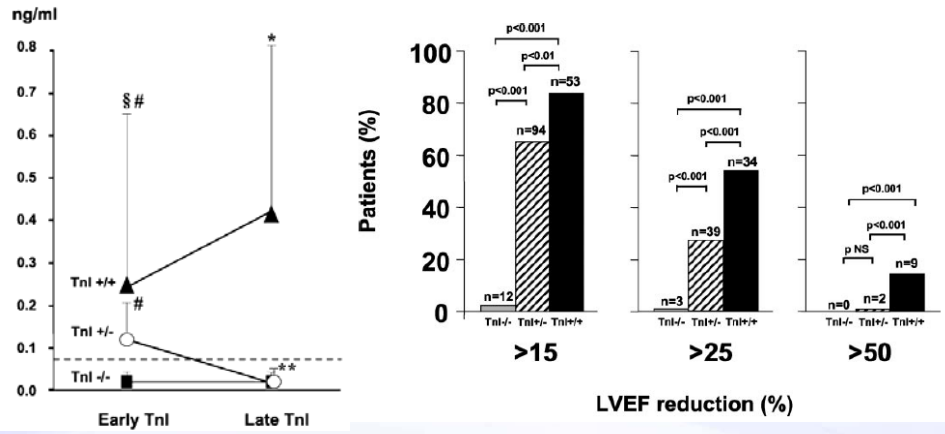
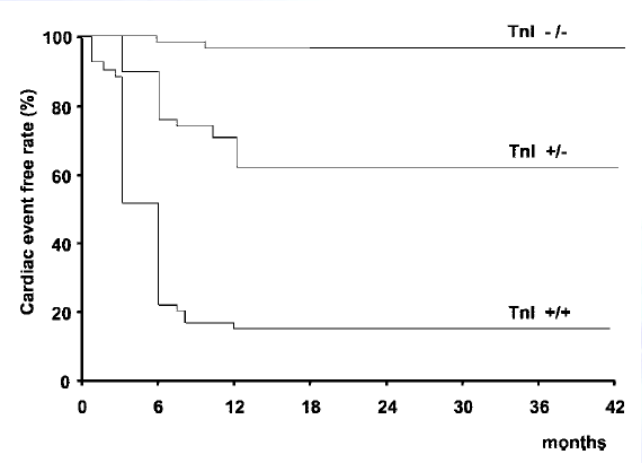
Predictive value of Troponin change: LVEF reduction



Circulation. 2004;109:2749-2754.

Predictive value of Troponin change: Cardiac event free rate



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Circulation. 2004;109:2749-2754.

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Cardiac biomarkers: Concerns

- No specific strategy:
  - Timing of measurement?:
    - How often, timing relative to chemo
    - When can we stop checking?
  - Optimal assays?
  - Use alone or in conjunction with cardiac imaging?

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Management

- Prevention strategy:
  - Primary prevention
  - Secondary prevention

Secondary prevention

- Standard neurohormonal blockade for heart failure management: ACEI/ARB, Beta-blocker, MRA?
  - Lack of large RCT

Secondary prevention: Asymptomatic LVD

Table 2. Treatment of ASLVD in Adult Patients with Cardiotoxic Chemotherapy

Reference	Type of Study	Patient Population an Cancer Therapy	N	Cardiac Treatment Modality	Timing of Initiation of Treatment	Mean Follow-Up	Results
Cardinale et al[34]	Prospective	201 patients with LVEF ≤45% due to anthracylcines	201	Enalapril up to 20 mg/d and coreg up to 50 mg /d; of note: mean dose enalapril 11 mg/d and coreg 14 mg/d	Rx initiated immediately after detection of ASLVD	Echo at baseline, every month for 3 mo, and every 3 mo during following 3 y, every 6 m thereafter Mean follow-up 36 mo	Primary EP: LVEF response to therapy Responders,* 42%; partial responders, 13%; nonresponders, 45% Responders showed lower rate of cum cardiac events than partial and nonresponders (5%, 31%, 29%, *P*<0.001)
Cardinale et al[35]	Prospective	Mix of cancer, non-Hodgkin's lymphoma Chemotherapy naive patients scheduled for anthracyclines (note excluded high-dose anthracycline or trastuzumab)	2625	Enalapril alone (before 1999) enalapril and β-blockers carvedilol or bisoprolol (after 1999)	Therapy promptly administered and uptitrated to maximal tolerated doses	Echo at baseline, every 3 mo during chemotherapy, at end of treatment (within 1 mo, every 3 mo during first year following chemotherapy, every 6 mo during the following 40 y, yearly afterward) Median follow-up 5.2 y	Anthracycline-induced cardiotoxicity occurred in 9% of adult treated patients (dose dependent; highest incidence in first year after completion of chemotherapy) Median time between last dose of anthracycline and development of cardiotoxicity was 3.5 mo, 98% of cases within the first-year follow-up 82% of patients recovered from cardiotoxicity (11% full recovery; 71% partial recovery)

ASLVD indicates asymptomatic left ventricular dysfunction; EP, end point; LVEF, and left ventricular ejection fraction.
*Responders had a significantly shorter time to initiation of therapy.

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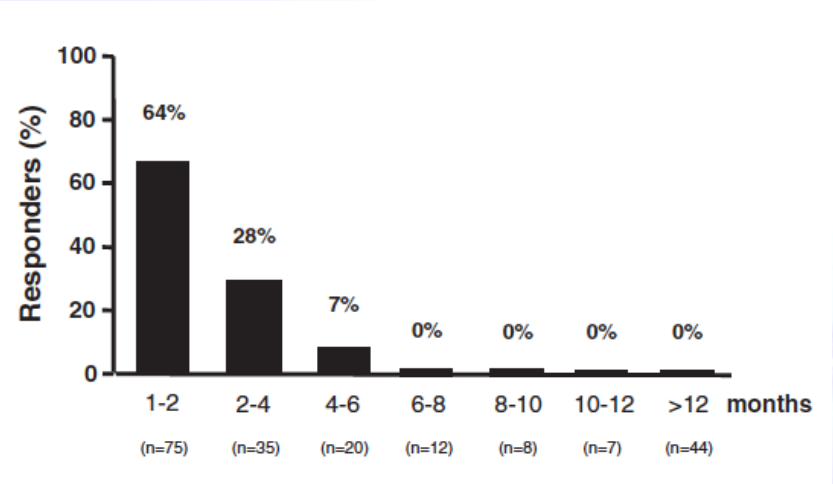
Percentage of Responders vs Time to start HF therapy



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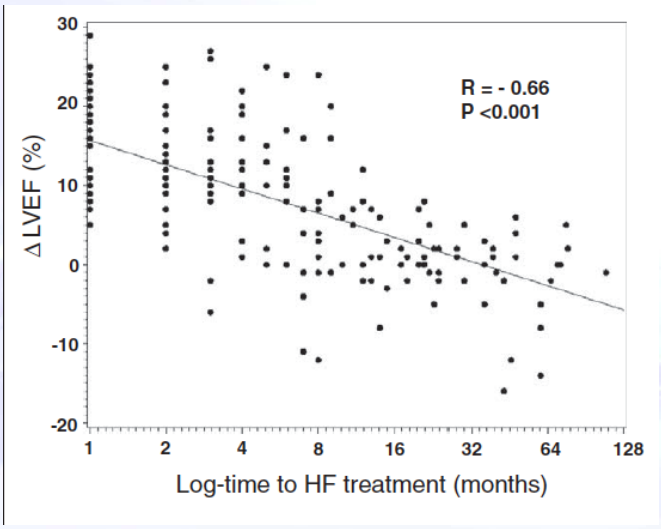
J Am Coll Cardiol 2010;55:213–20.

Percentage of LVEF change vs Time to start HF therapy



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J Am Coll Cardiol 2010;55:213–20.

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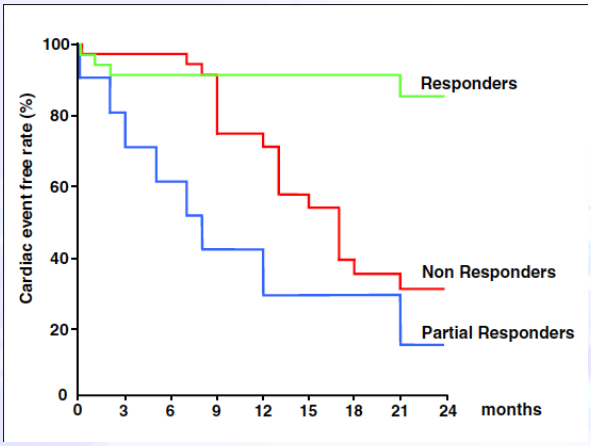
Cardiac event rate



Responders:
LVEF increased ≥ 50%

Partial responders:
LVEF increased ≥10% (absolute points) but <50%

Nonresponders:
LVEF increased <10% (absolute points) and <50%.

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J Am Coll Cardiol 2010;55:213–20.

Primary prevention

- Carvedilol and nebivolol started at initiation of anthracycline use: higher degree of LVEF preservation
- Use of β-blockers during treatment with trastuzumab and anthracyclines was associated with a lower incidence of HF over a 5-year period.
- Controversial results of benefit of ACEI on CTRTD

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