Latent Effects of Chemotherapy & Radiation on the Heart

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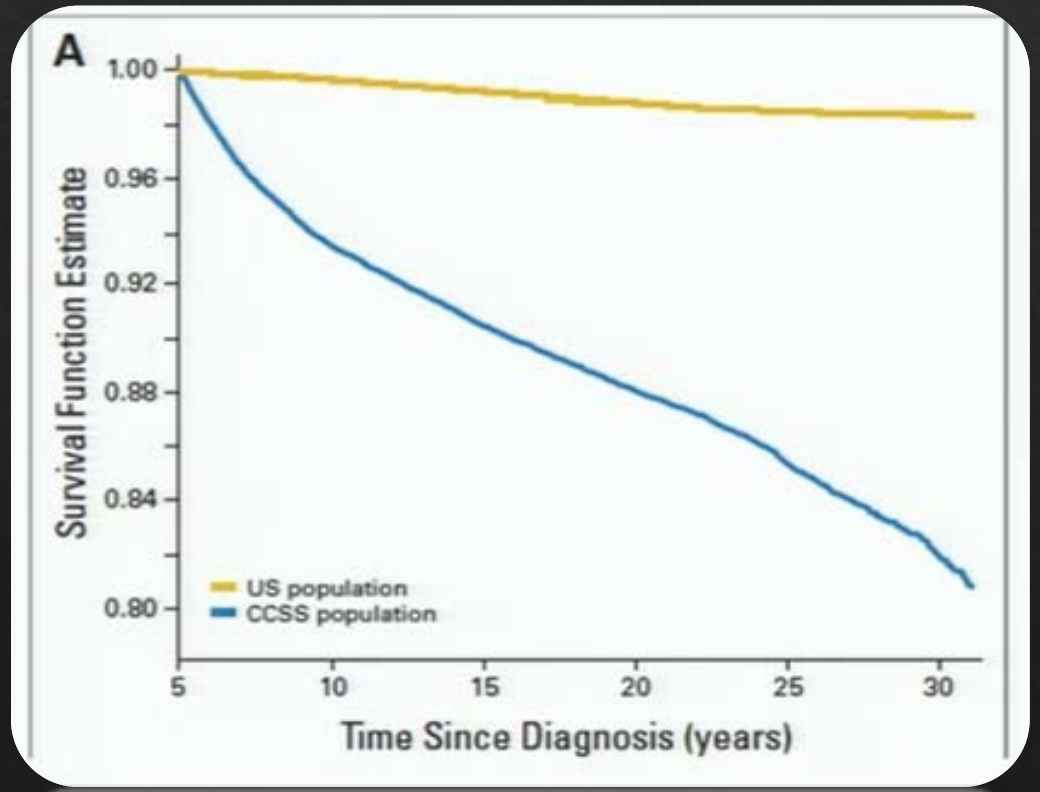
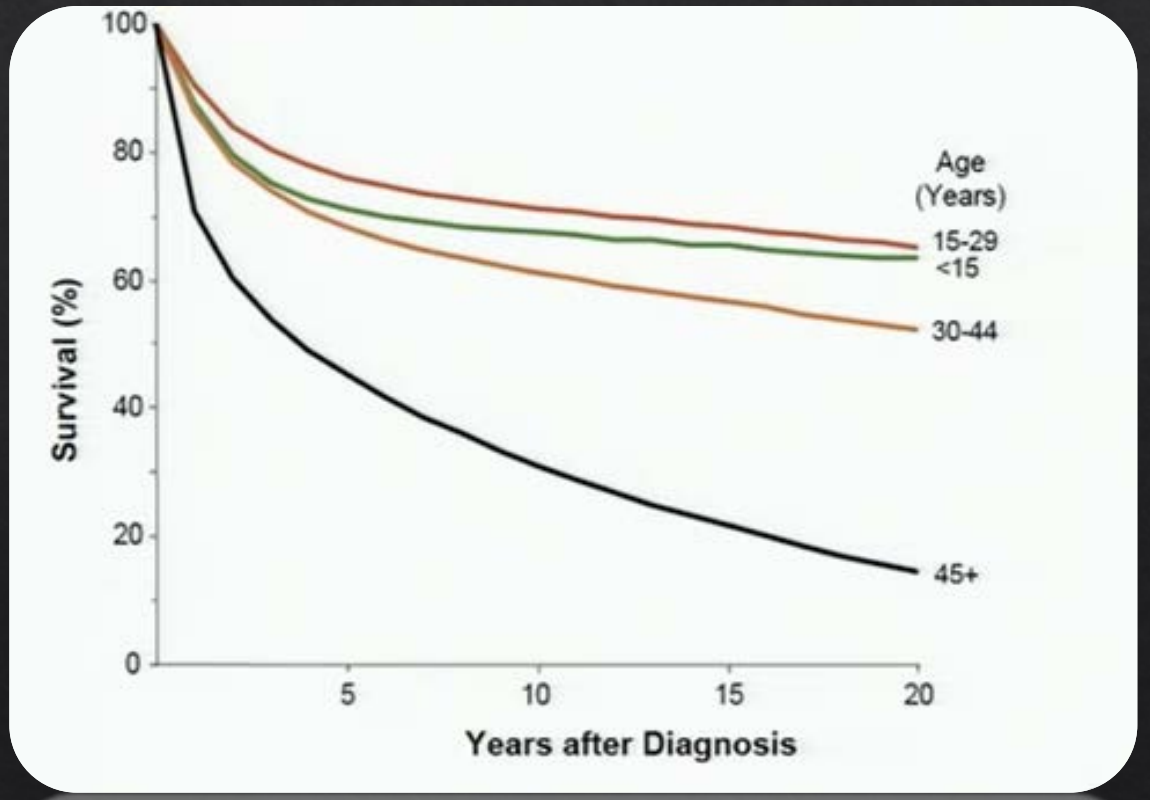
Cancer Survivorship, What Do We Know?

Cancer Survival in Children

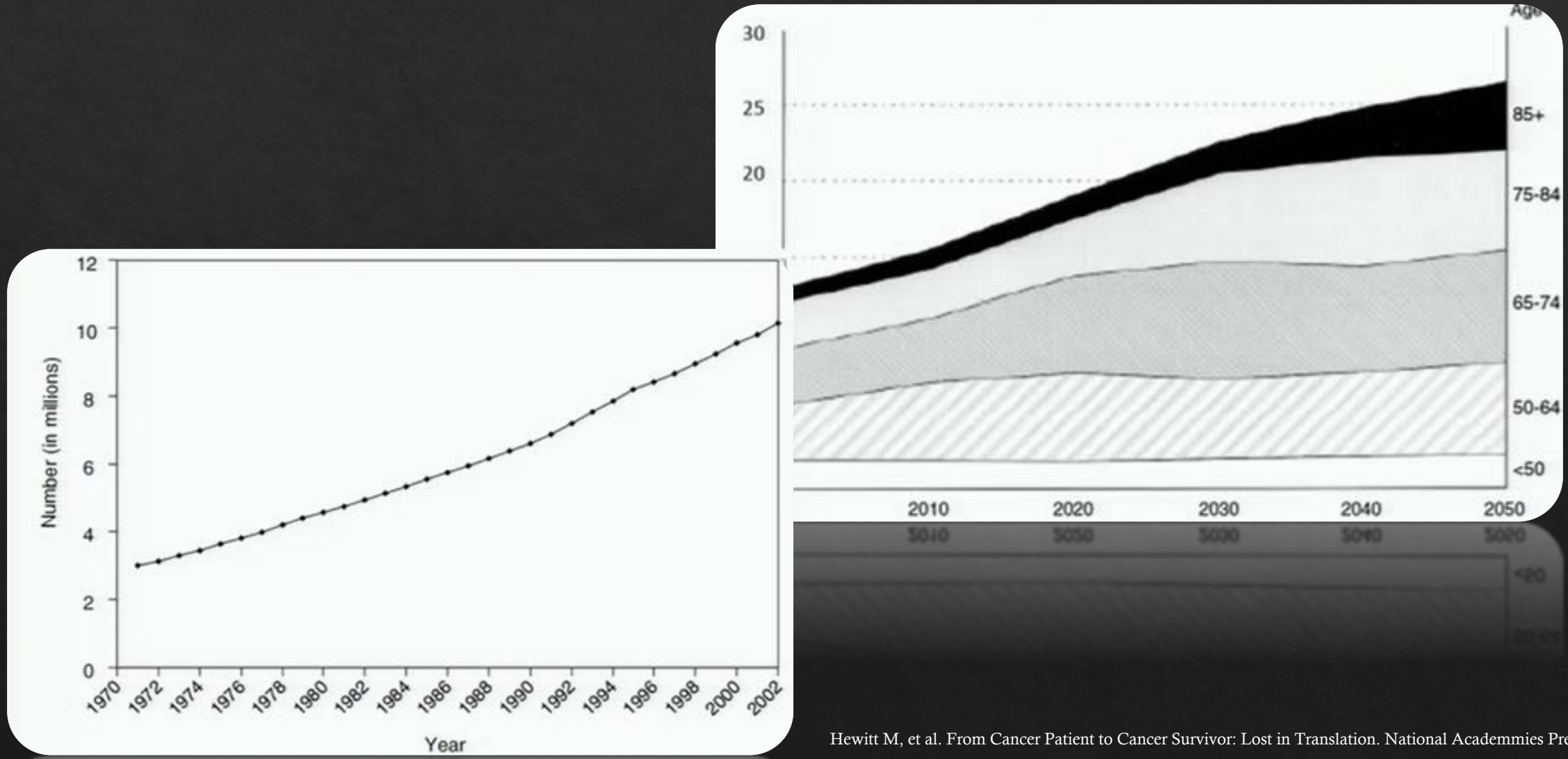


Cancer Survival in Young adults



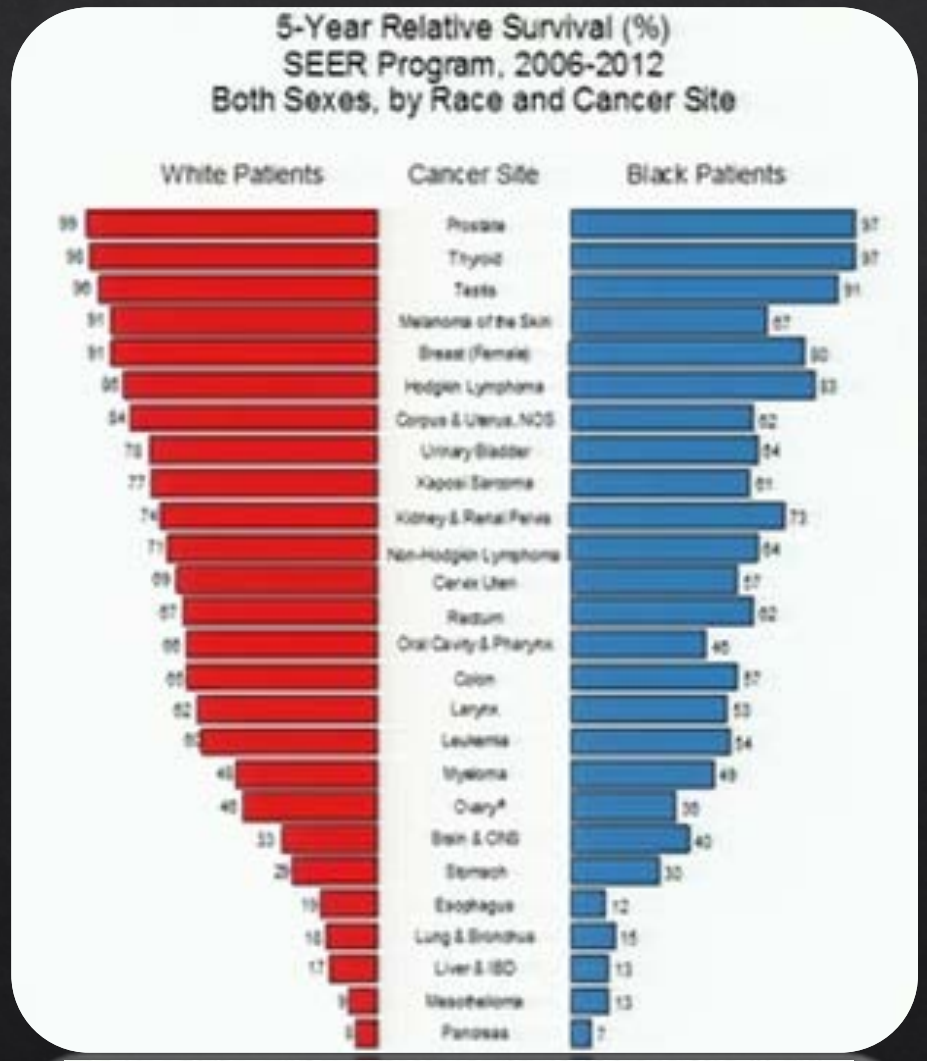
Armstrong, J. Clin Oncol. 2009 May
Bleyer, National Cancer Institute, 2006

Cancer Survivorship on the Rise

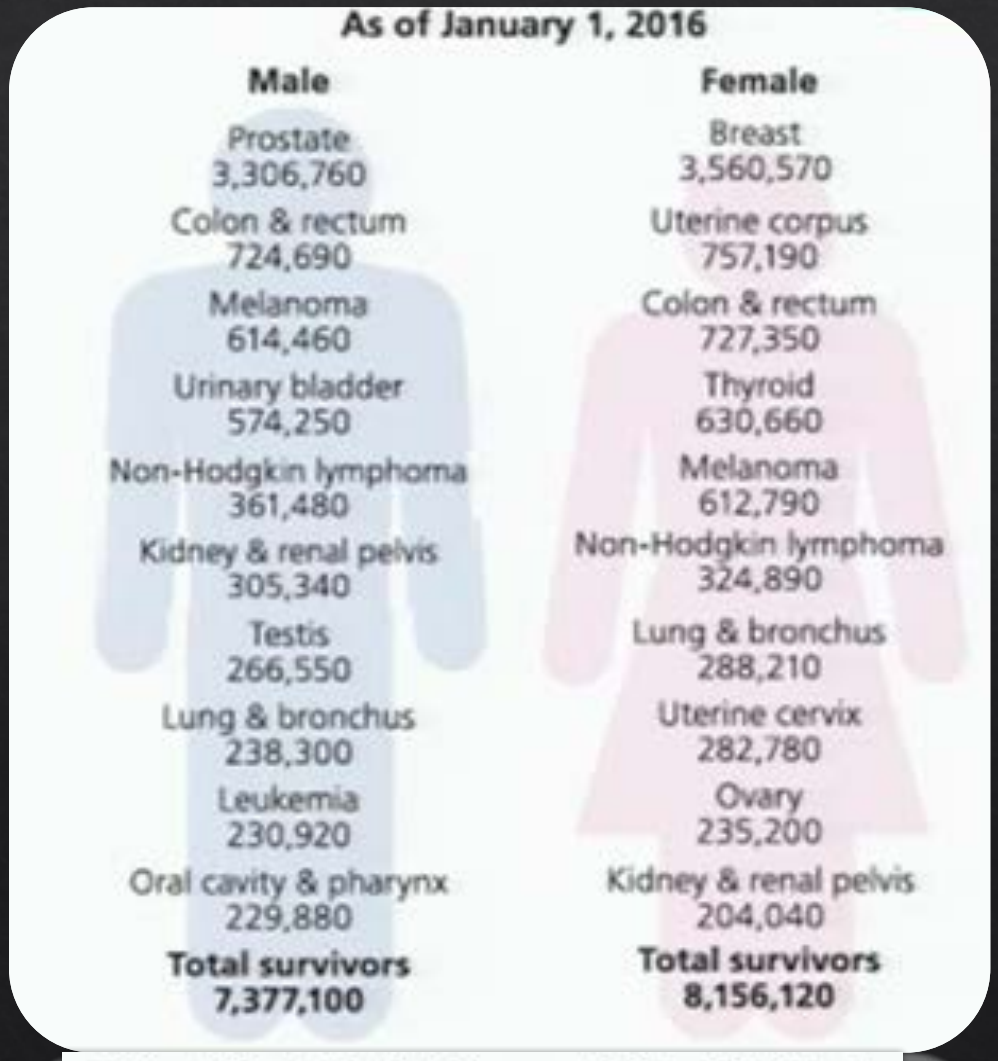


Hewitt M, et al. From Cancer Patient to Cancer Survivor: Lost in Translation. National Academmies Press

Cancer Type Specific Survival

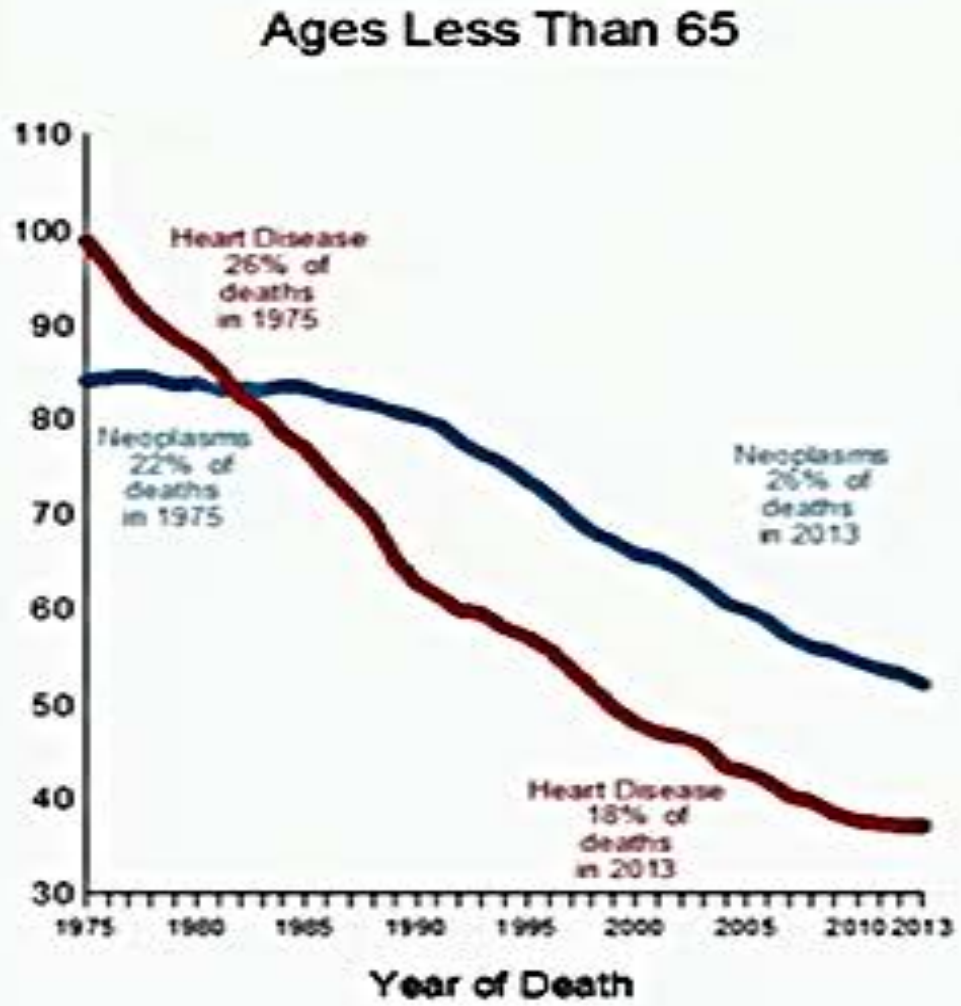


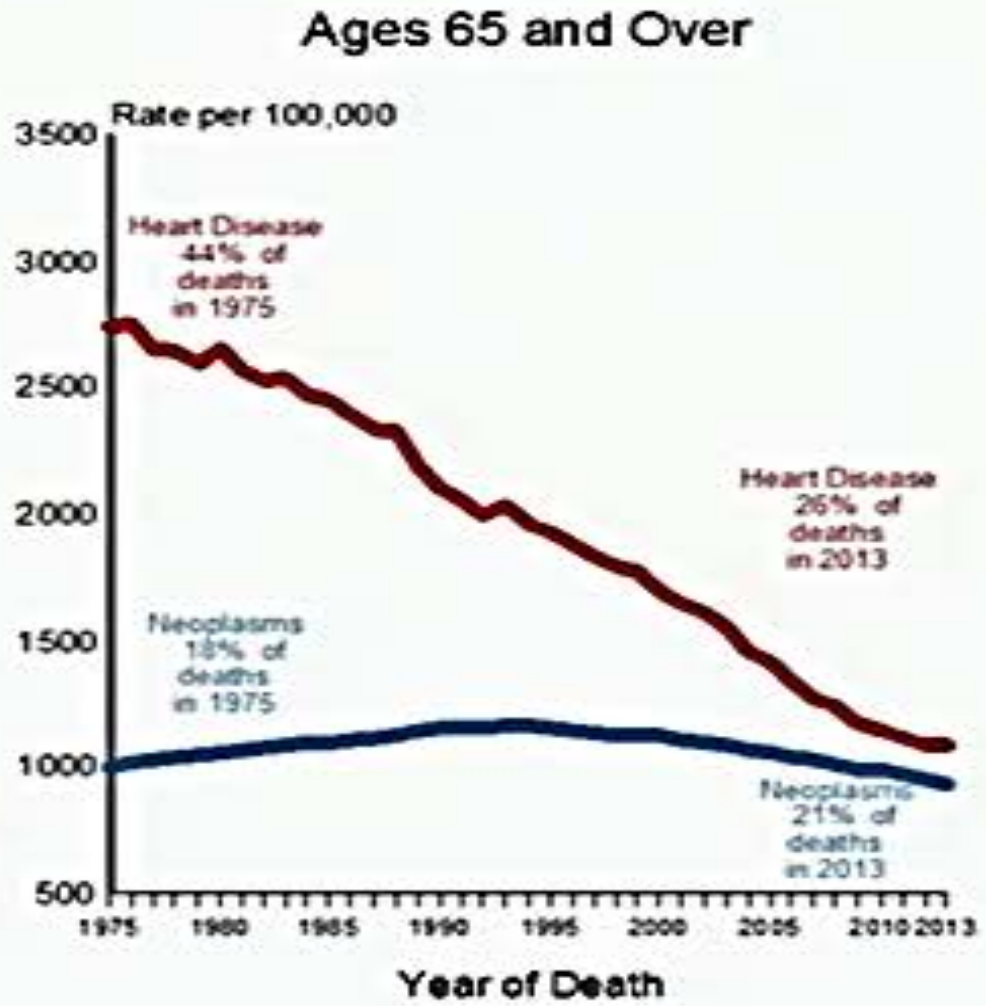
http://seer.cancer.gov/csr/1975_2013



Miller KD, et al. CA Cancer J Clin. 2016 Jul

Us Death Rates, 1975-2013
Heart Disease compared to Neoplasms, by age at death

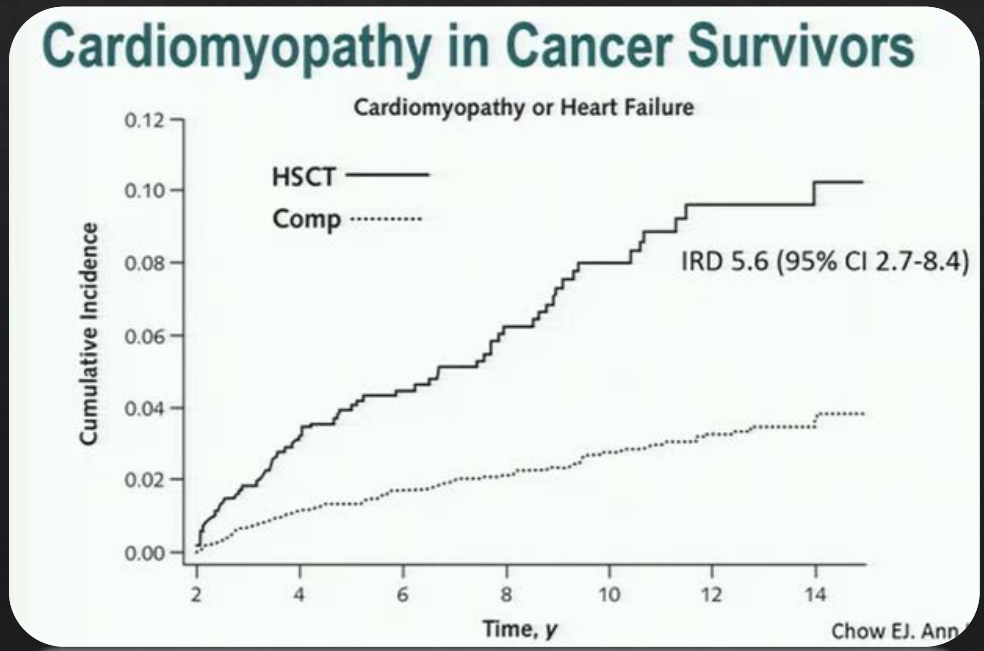




http://seer.cancer.gov/csr/1975_2013

Mortality Rates

- Mortality from Breast Cancer vs. Cardiovascular Mortality:
  - 44.5% vs. 24% for age >65
  - 49.9% vs. 16.3%
- Composite Risk of Ischemic Heart Disease, Heart failure, and Stroke:
  - Multiple Myeloma: 1.70 (95% CI 1.31-2.21)
  - Lung Cancer: 1.58 (95% CI 1.30-1.90)
  - Non-Hodgkin Lymphoma: 1.41 (95% 1.20-1.65)
  - Breast Cancer : 0.89 (95% CI 0.84-0.95)



Colzani, J Clin Oncol.2011 Oct
Abdel-Qadir, JAMA Cardiol.2017 JAN
American SH, et al. J Clin Oncol. 2016 Apr
Chow EJ, Ann Intern Med. 2011 JUL

CARDIO-TOXICTY: Definition

	Definition	Modality of Measurement	Chemotherapy Agents	Comments
Alexander et al.	***Mild: Decline in LVEF > 10% Moderate: Decline in LVEF > 15% to final LVEF < 45% Severe: congestive HF***	Multigated acquisition (MUGA) scan	Anthracycline	
Schwartz et al.	***Decline in LVEF > 10% to final LVEF < 50%***	MUGA scan	Anthracycline	
Cardiac Review and Evaluation Committee	***1. Cardiomyopathy characterized by a decrease in LVEF globally or more severe in the septum 2. Sign and symptoms of HF 3. Decline of EF ≥5% to final ejection fraction < 55% with symptoms of congestive HF 4. Asymptomatic decline of LVEF ≥ 10% to final ejection fraction < 55%***	MUGA scan and echocardiogram	Trastuzumab +/- Anthracycline	
Common Terminology Criteria for Adverse Events, version 4.03 (HF, left ventricular dysfunction)		Not defined	N/A	Other definitions included such as troponin and clinical HF
American Society of Echocardiography and European Association of Cardiovascular Imaging	***≥10% decline in LVEF to final LVEF < 53%*** (suggests repeat imaging)	Echocardiography; two-dimensional (2D) and three-dimensional (3D) contrast, cardiac magnetic resonance imaging, MUGA scan	N/A	***First guideline to include global longitudinal strain >15%***

Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. N Engl J Med 1979;300:278-83.
23.Schwartz RG, McKenzie WB, Alexander J, et al. Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med 1987;82:1109-18.
24.Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215-21.
Common Terminology Criteria for Adverse Events (CTCAE) (U.S Department of Health and Human Services website). 2010. Available at: http://evs.nci.nih.gov/ftp1/CTCAE. Accessed February 2016.

Chemotherapy Associated with Drop In Systolic Function

HER-2 related CHF/cardiomyopathy

Trastuzumab

27% NYHA 3-4 with anthracycline/cyclophosphamide
(Slamon. N Engl J Med 2001)

4.1% NYHA 3-4 adjuvent therapy after anthracycline
(Romond. N Engl J Med 2005)

0.4% CHF & 9.4% cardiomyopathy without anthracycline
(Slamon. N Engl J Med 2011)

Monocional antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7–3	++
Trastuzumab (Herceptin) (20–28)	2–28	++
Proteasome inhibitor		
Bortezomib (Velcade) (10,17)	2–5	++
Small molecule tyrosine kinase inhibitors		
Dasatinib (Sprycel) (10)	2–4	++
Imatinib mesylate (Gleevec) (34,35)	0.5–1.7	+
Lapatinib (Tykerb) (32)	1.5–2.2	+
Sunitinib (Sutent) (36,37)	2.7–11	+++

Table 1 Chemotherapy Associated With Left Ventricular Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3–26*	+++
Epirubicin (Ellence) (10)	0.9–3.3	++
Idarubicin (Idamycin PFS) (8)	5–18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11–13)	7–28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clolar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3–8	++
Monocional antibody-based tyrosine kinase inhibitors		
Bevacizumab (Avastin) (10,18,19)	1.7–3	++
Trastuzumab (Herceptin) (20–28)	2–28	++
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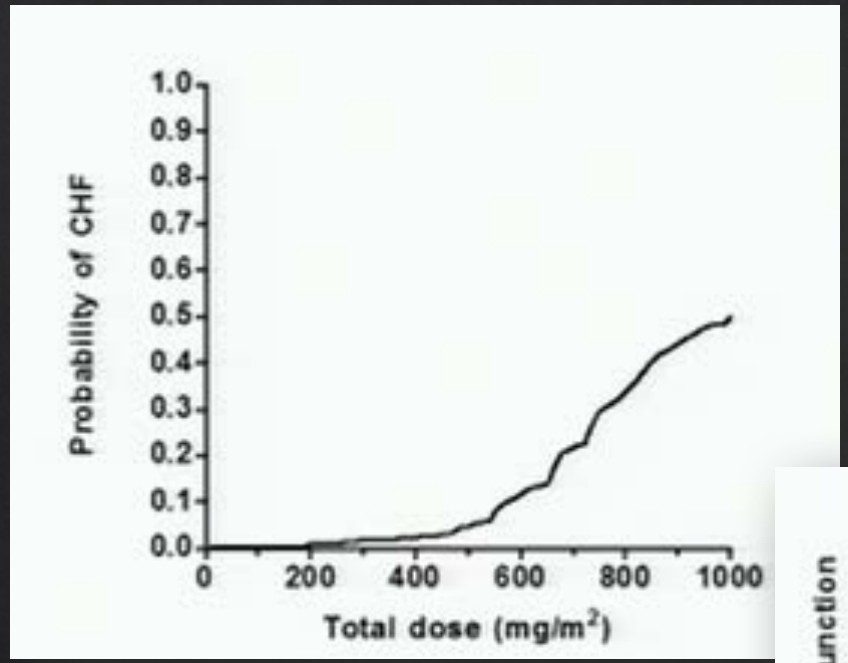
Sunitinib (Sutent) (36,37)	2.7–11	+++

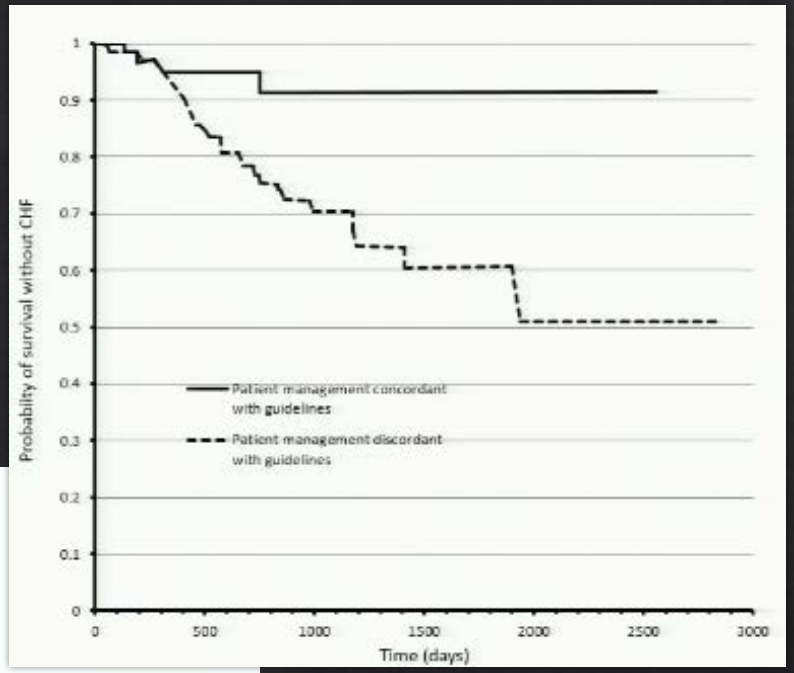
Yeh. J Am Coll Cardiol.2009 Jun 16

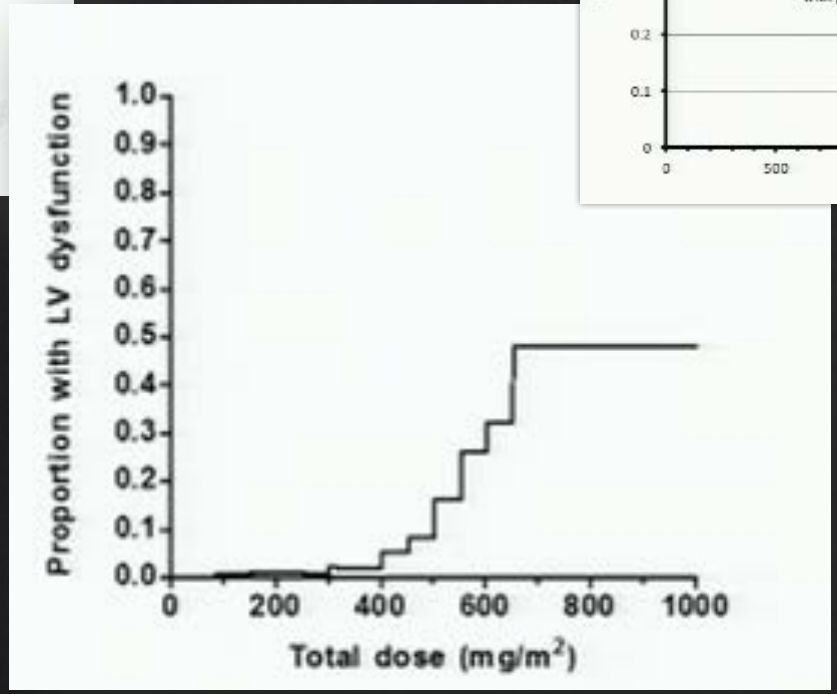
Risk Factors for Cardiotoxicity

- Anthracyclines:
  - Cause a dose-dependent cardiotoxicity that ranges from subtle changes in myocardial strain or biomarkers to overt left ventricular (LV) systolic dysfunction and clinical HF most studies identify increased oxidative stress and inhibition of topoisomerase 2 as the two major mechanisms involved in mediating myocardial cell death and apoptosis.
  - Risk factors for anthracycline cardiotoxicity include:
    - cumulative dose
    - concurrent mediastinal radiation
    - extremes of age
    - female gender
    - cardiac risk factors or pre-existing cardiovascular disease

Historical Perspective on Anthracycline Toxicity

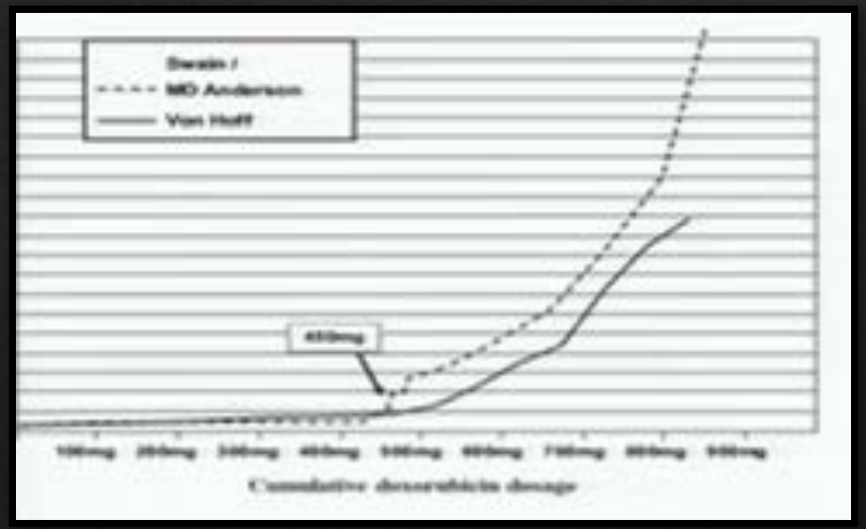


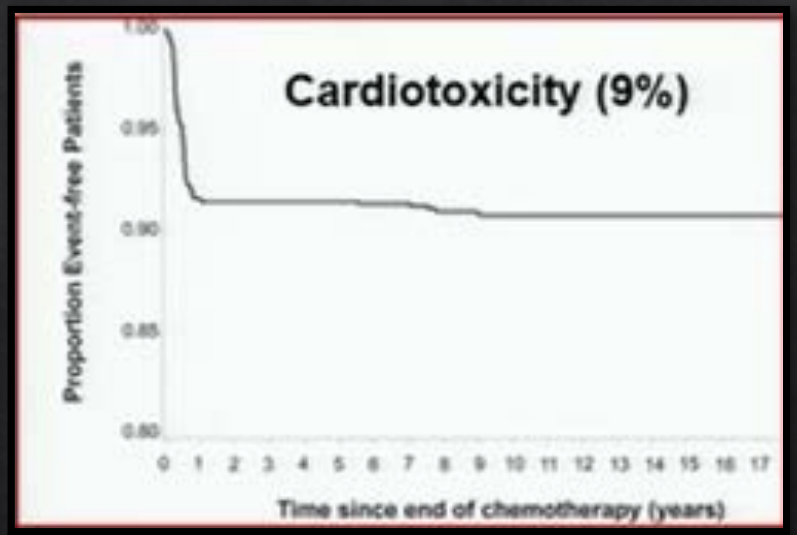


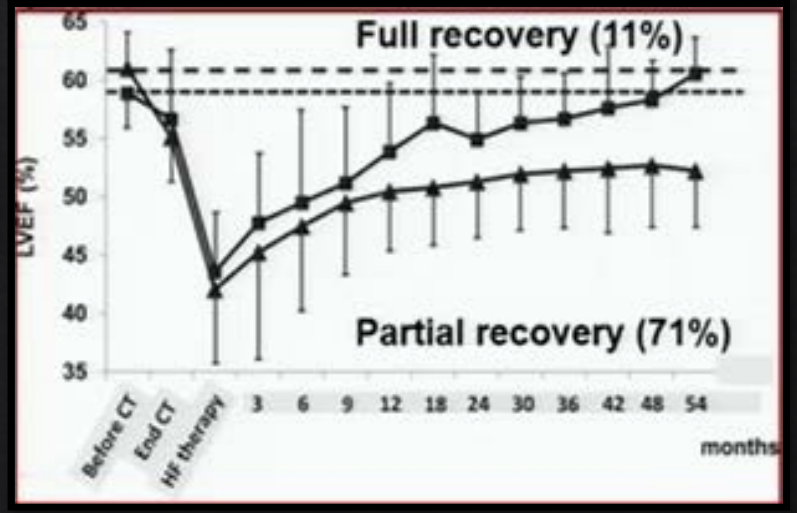


Schwartz et al. Am J Med (1987) 82:1109
Von Hoff et al. Ann Int Med 91:710,1979
Swain tet al. Cancer 97:2869,2003

Anthracycline Cardio-toxicity Occurs Earlier, but Potentially Reversible







- LVEF assessed in 2,625 patients receiving anthracyclines over a median follow up of 5.2 years
- 98% of cases within first year post Chemotherapy completion
- Cardio-toxicity defined: reduction in EF by 10% and <50%
- Partial recovery: Increase by>5% & increase to >50%
- Full recovery: Return to baseline EF

Schwartz et al. Am J Med (1987) 82:1109
Von Hoff et al. Ann Int Med 91:710,1979
Swain tet al. Cancer 97:2869,2003
Heart Failure Clin 2011
NEJM 1998; 330

Strategies to Reduce Risk of Cardiotoxicity

- No threshold anthracycline dose below which cardiotoxicity does not occur
- Cumulative lifetime anthracycline dose : *450-550 mg/m^2 doxorubicin or 800-1000 mg/m 2 epirubicin*
- A recent meta-analysis of 7 studies showed a significantly lower rate of clinical HF with an anthracycline infusion duration ≥ 6 hours compared with shorter infusion durations (relative Risk [RR] 0.27; 95% confidence interval [CI], 0.09-0.81)
  - Prolonged infusions, rather than bolus administration, to reduce anthracycline cardiotoxicity remain controversial due to the increased risk of extravasation and tissue necrosis.
- Compared with conventional doxorubicin, liposomal doxorubicin has been shown to reduce the incidence of both asymptomatic and symptomatic cardiomyopathy (odds ratio = 0.46; 95% CI, 0.23-0.92; p = 0.03) without reducing progression-free or overall survival
  - The routine use of liposomal doxorubicin has been limited by increased skin toxicity (hand-foot syndrome) and higher cost
- Mitoxantrone and Epirubicin are also believed to be less cardiotoxic than conventional doxorubicin → no prospective or systematic trials comparing the cardiac effects of these agents.

Risk Factors for Cardiotoxicity

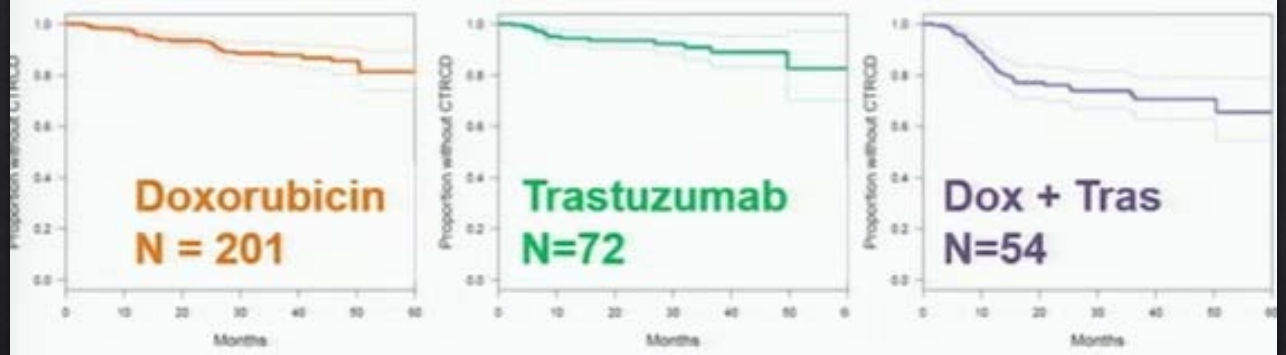
- Trastuzumab:
  - prevents activation of *ErbB2-4 receptors*, thus disrupting cellular repair pathways, and promotes myocardial dysfunction rather than cell death.
  - Risk Factors for Trastuzumab cardiotoxicity include:
    - Adjuvant anthracyclines
    - Increasing age
    - Hypertension
    - Diabetes
    - coronary artery disease
    - atrial fibrillation
    - chronic renal insufficiency

Trastuzumab Trials in metastatic HER2+ Breast Cancer

Cardiotoxicity	trastuzumab + AC	AC
Cardiac dysfunction %	28	10
NYHA III/IV CHF, %	19	3

Slamon et al. NEJM. 2001;344:783 *Seidman A et al. 2002. J Clin Oncol : 20:1215*

Cardiac Dysfunction in Breast Cancer: Penn CCT Cohort Study (N = 327)



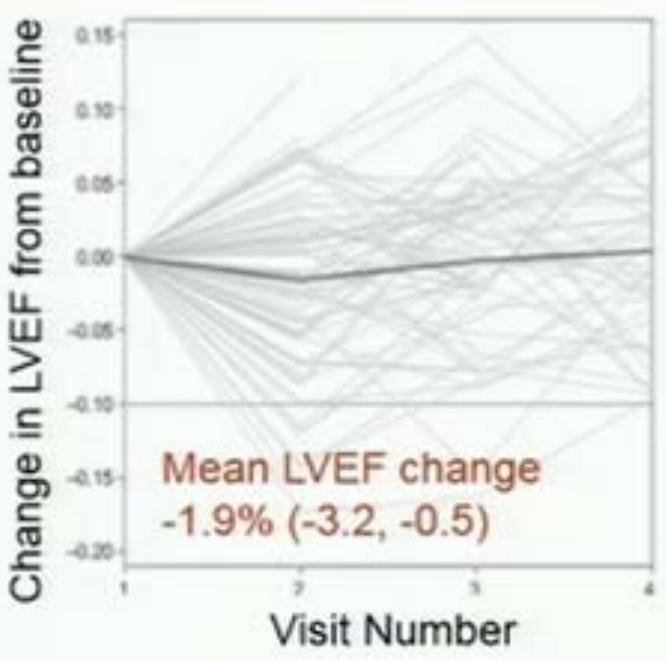
Median Time to Dysfunction in Months (IQR)		
14.8 (7.4, 26.2)	6.9 (5.4, 8.9)	7.7 (5.2, 11.2)
Total Followup Time in Months (Median, IQR)		
18.1 (6.6, 39.4)	14.2 (9.4, 30.3)	28.6 (10.2, 52.3)

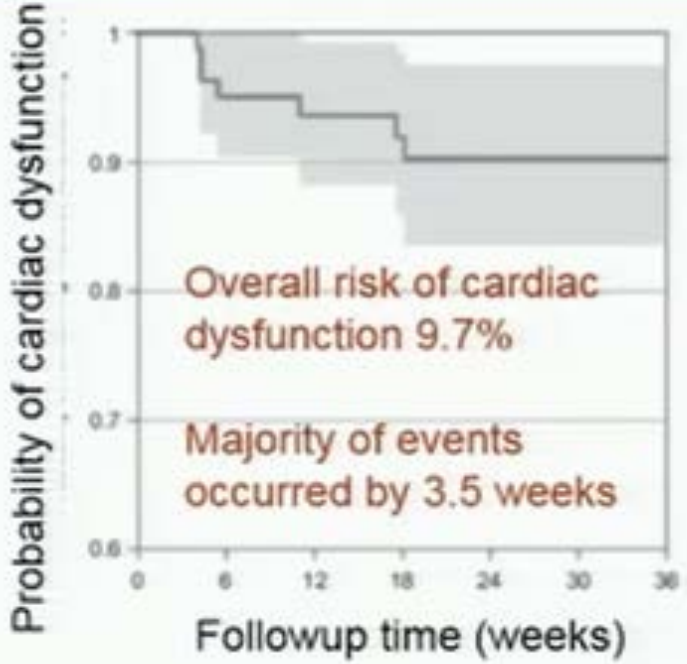
Median LVEF at dysfunction ~43% (IQR 39%,45%)

Finkelman...Ky. In process

Prospective Evaluation of Sunitinib-Induced Cardiotoxicity in Patients with Metastatic Renal Cell Carcinoma

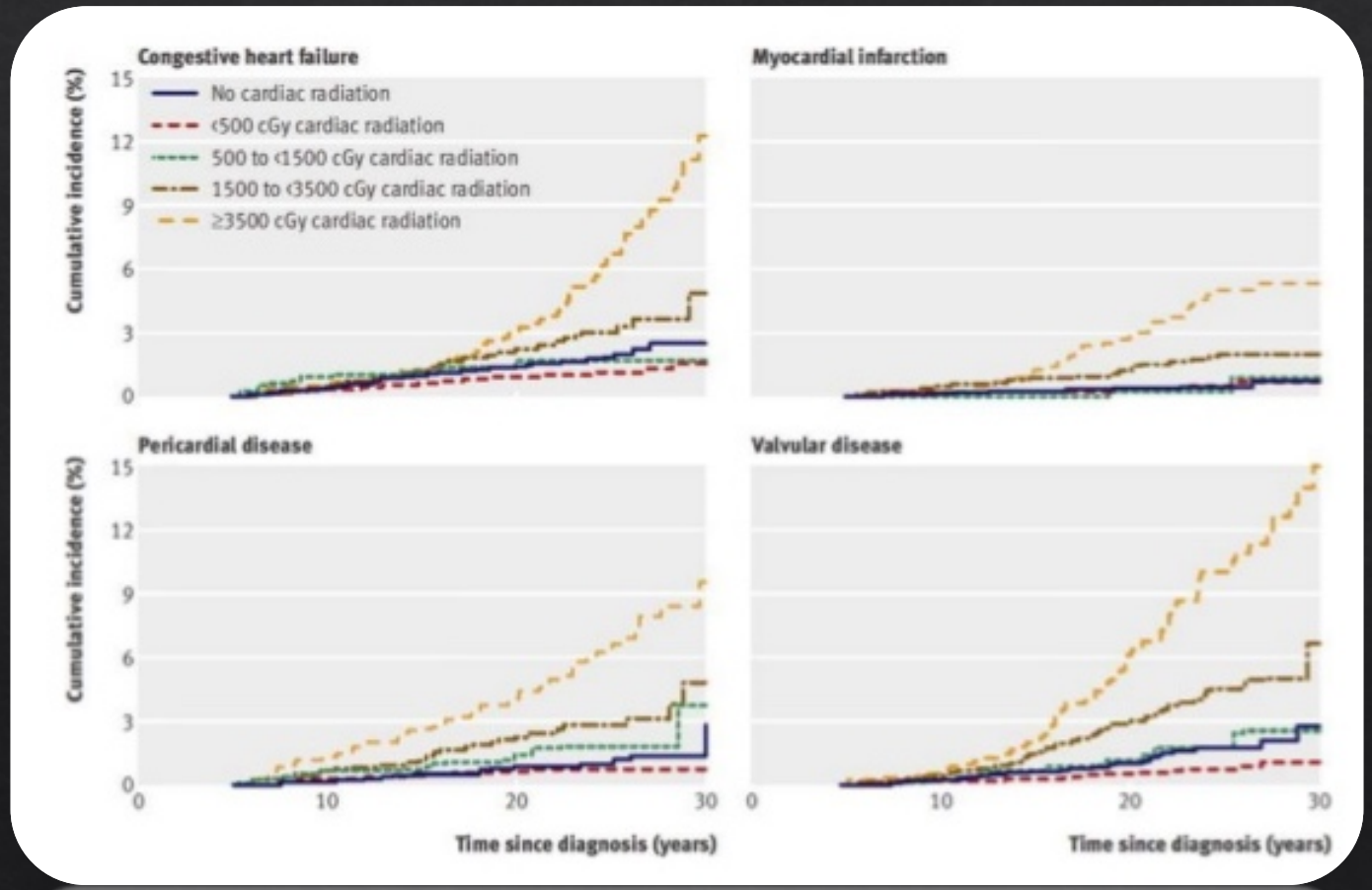
Vivek Narayan[1,2], Stephen Keefe[1,2], Naomi Haas[1,2], Le Wang[3], Igor Puzanov[4], Mary Putt[3], Anna Catino[5], James Fang[5], Neeraj Agarwal[6], David Hyman[7], Amanda M. Smith[7], Brian S. Finkelman[3], Hari K. Narayan[8], Steven Ewer[9], Chantal ElAmm[10], Daniel Lenihan[11], and Bonnie Ky[2,3,7]



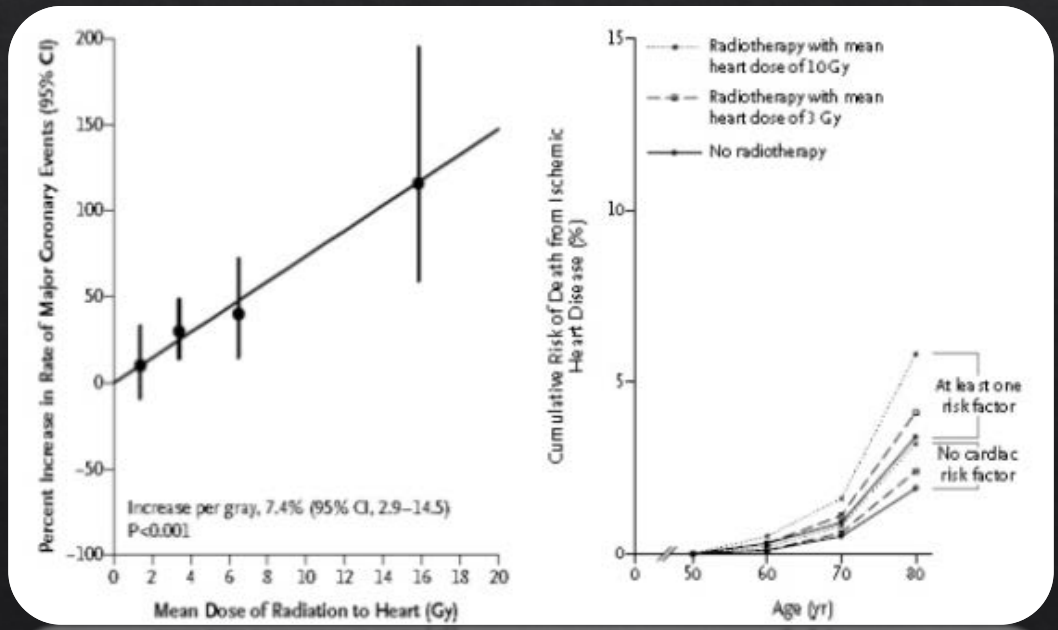


Narayan., Ky. Clin Cancer Res. 2017.

Radiation therapy



Childhood Cancer Experience



Breast Cancer Survivors

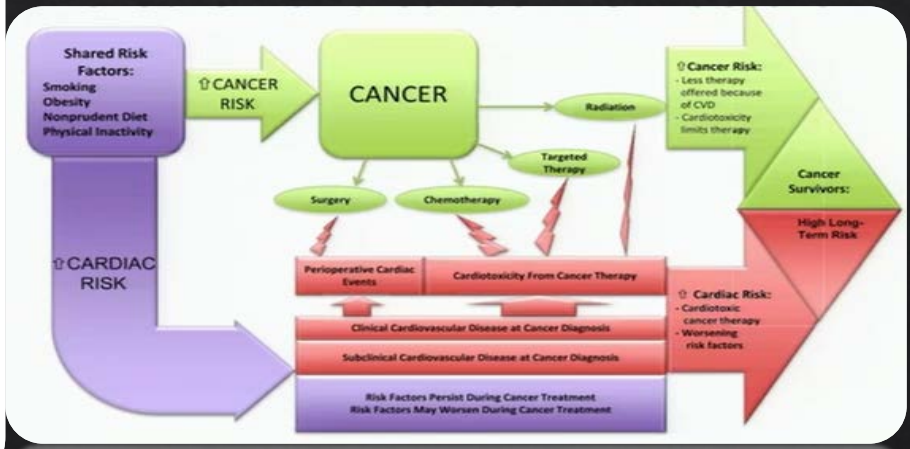
Mulrooney et al, BMJ 2009
Darby et al, NEJM 2013

ACC/AHA CLASSIFICATIONS OF HEART FAILURE AND STAGES

Table 4. Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications

ACCF/AHA Stages of HF[38]		NYHA Functional Classification[46]	
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.



Johnson. Can J Cardiol. 2016 Jul

ACC/AHA CLASSIFICATIONS OF HEART FAILURE AND STAGES

Table 3. Definitions of HF*r*EF and HF*p*EF

Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HF*r*EF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HF*p*EF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF*p*EF.
b. HF*p*EF, improved	>40	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

EF indicates ejection fraction; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; and HF*r*EF, heart failure with reduced ejection fraction.

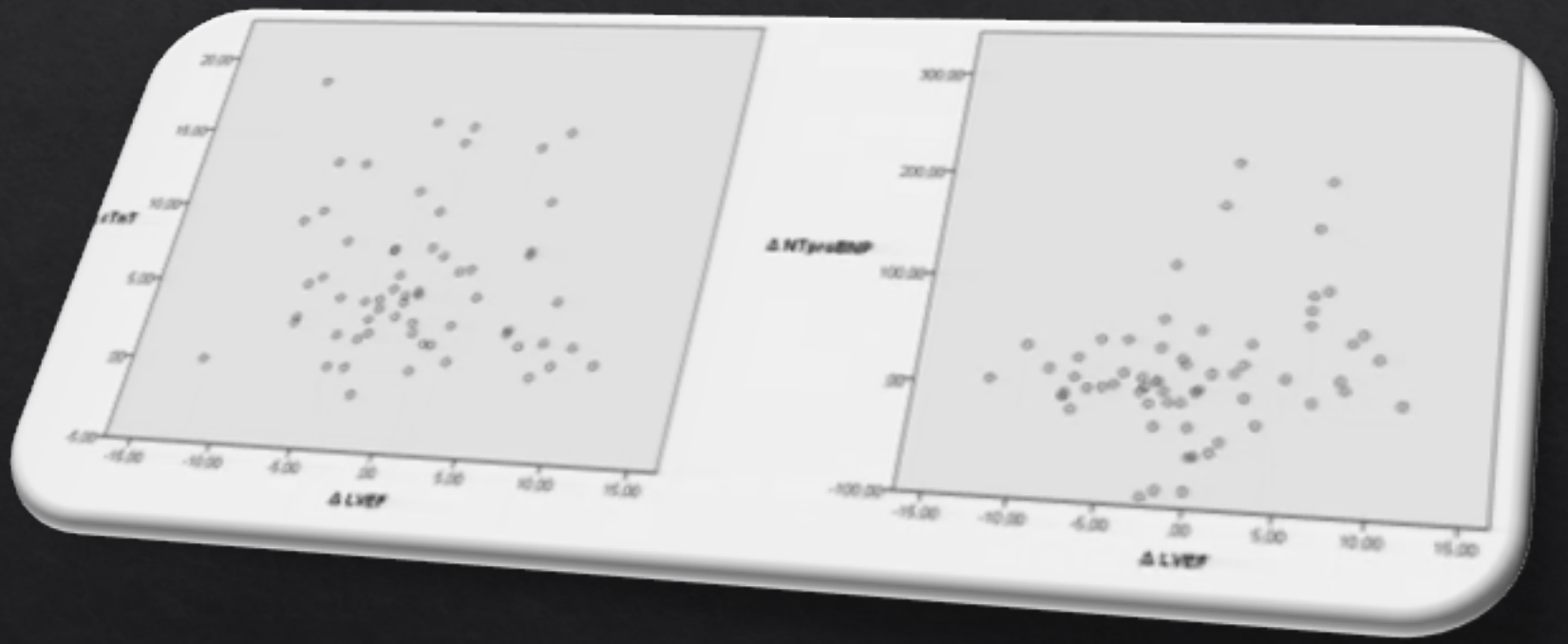
Table 4. Co

ACCF/AHA Stage		
A	At high	
B	Structu	
C	Structu	
D	Refractory HF requiring specialized interventions	IV Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

ACCF indicates American College of Cardiology Foundation; AHA, American Heart Association; HF, heart failure; and NYHA, New York Heart Association.

Johnson. Can J Cardiol. 2016 Jul

Biomarkers and LV Function in PRADA



Routine Surveillance, How Often & For How Long?

Guideline	Who?	How Often
ASE *Plana, et al. JASE. 2014.*	• Anthracyclines • Anti-HER2 therapies • VEGF Inhibitors • Proteasome inhibitors	• Repeat 2-3 weeks after abnormal study • 6 months after therapy completed • Annual assessment with imaging as per provider
ESC *Zamorano, et al. EHJ. 2016.*	• Cardiotoxic therapies (Broadly defined)†	• LVEF before and periodically during • Repeat 2-3 weeks after abnormal study
	• Survivors	• Periodic screening
ASCO *Armenian, et al. JCO. 2016.*	• Asymptomatic, high risk DURING treatment*	• Routine surveillance, frequency determined by provider
	• Those with signs/symptoms concerning for dysfunction	
ASCO *Armenian, et al. JCO. 2016.*	• Asymptomatic, high risk AFTER treatment	• 6 to 12 months after therapy completion
	• Those with signs/symptoms concerning for dysfunction	

* High risk = high dose anthracyclines, high dose radiotherapy; multiple CV risk factors, older age, compromised CV function; sequential therapy (anthracyclines + radiation or trastuzumab)
† Cardiotoxic therapies = anthracyclines, alkylating agents, antimetabolites, antimicrotubules, monoclonal antibodies, TKIs, proteasome inhibitors, misc

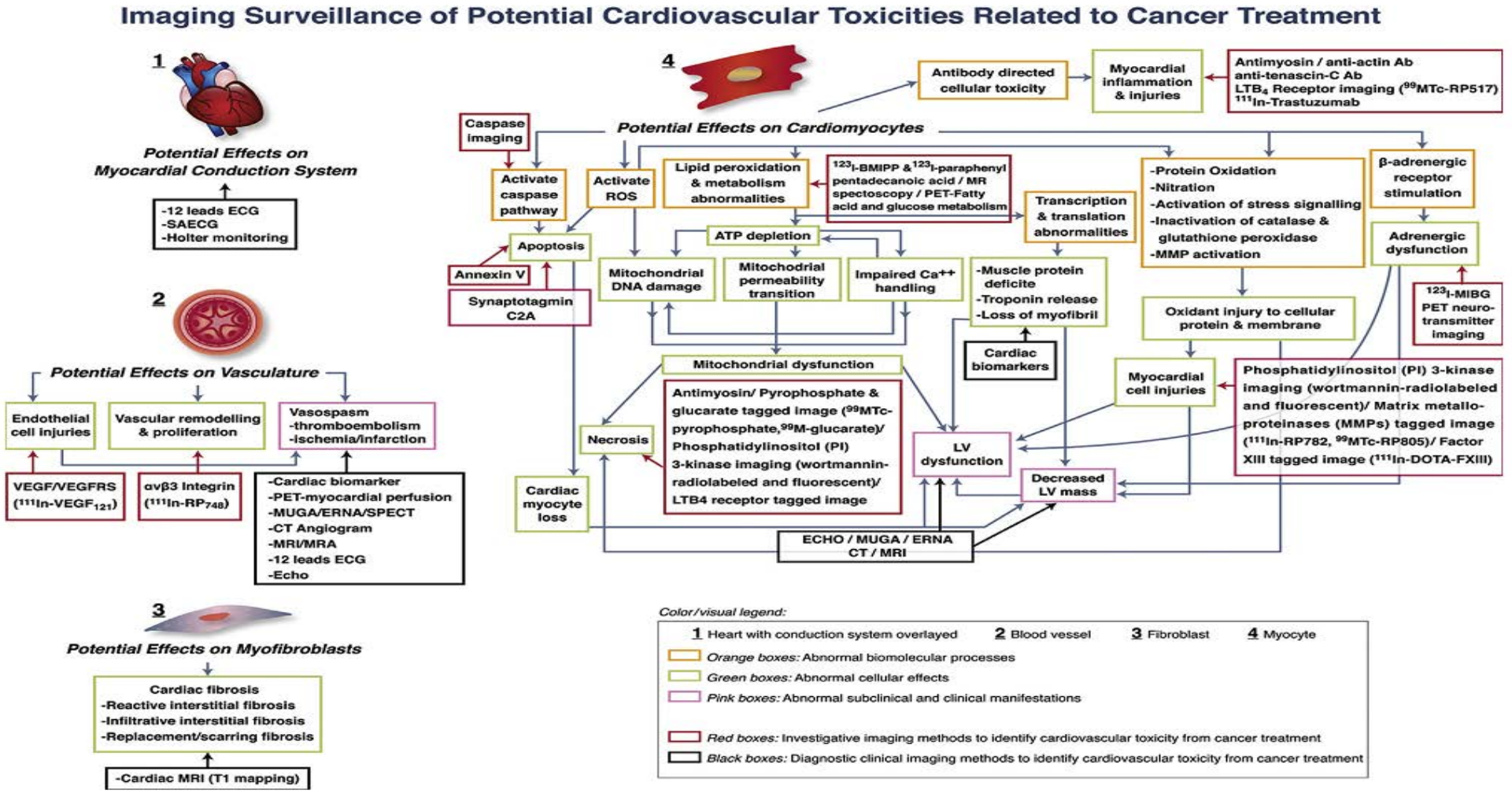


FIGURE 4 **Imaging Techniques in Clinical Use and in Development**

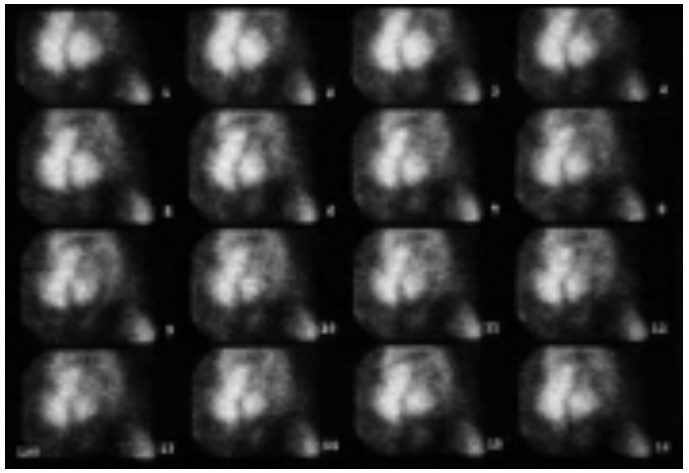
Opportunities for utilizing existing **(black boxes)** and developmental **(red boxes)** noninvasive imaging technologies for identifying processes associated with myocellular, myofibroblast, myocardial conduction, and vascular injuries associated with the administration of cancer therapies that may adversely impact the cardiovascular (CV) system. As shown, existing technologies identify mainly clinically evident manifestations of CV injury, whereas developmental technologies may facilitate assessment of biomolecular pathways that precede end-organ damage. Ab = antibody; CT = computed tomography; ERNA = equilibrium radionuclide angiography; LV = left ventricular; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography; MUGA = multigated acquisition scanning; PET = positron emission tomography.

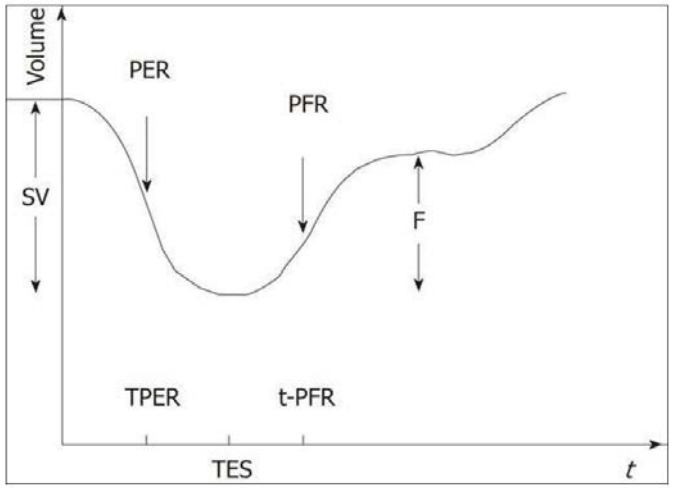
Kongbundansuk et al. JACC Imaging 2014

Nuclear Imaging In Cardio-Oncology

Equilibrium Radionuclide Ventriculography (ERNV)

- Can calculate systolic function
- Can evaluate for diastolic dysfunction
- Can assess RV function
- Most validated for screening and follow up for chemotherapeutic agents





Evaluation of diastolic dysfunction

- Need high temporal resolution with at least 32 frames per cardiac cycle for reliability of measurement
  - PEAK FILLING RATE (PFR): Normal = >2.5 (elderly) – 3.0 (young) EDV/sec
  - The time to PFR (tPFR): Normal < 180 milliseconds
  - The relative contribution of atrial filling to LV filling ratio of the atrial peak to the peak of the rapid filling phase on the first derivative curve (ratio of less than 1:4 are normal but may increase with aging)

Guidelines for Monitoring Doxorubicin (Adriamycin) Therapy with Serial Resting RNA

- LVEF > 50% at baseline:
  - Baseline MUGA within first 100 mg/m^2 in all patients
  - Next MUGA at 250 - 300 mg/m^2
  - Next MUGA at 450 mg/m^2 or 400 mg/m^2 if high risk: cyclophosphamide, heart disease, mediastinal radiation, abnormal ECG
  - Next MUGA prior to each dose > 450 mg/m^2
  - Discontinue therapy if LVEF decreases > 10% from baseline *AND* reaches < 50%

Schwartz RG et al. American J. Med. 82: 1109-1118, 1987

Guidelines for Monitoring Doxorubicin (Adriamycin) Therapy with Serial Resting RNA

- *LVEF < 50%* at baseline:
  - Baseline MUGA within first 100 mg/m^2 in all patients
  - *Serial MUGA prior to each subsequent dose*
  - Discontinue therapy if LVEF *decreases > 10% from baseline*

  OR reaches LVEF < 30%

Schwartz RG et al. American J. Med. 82: 1109-1118, 1987

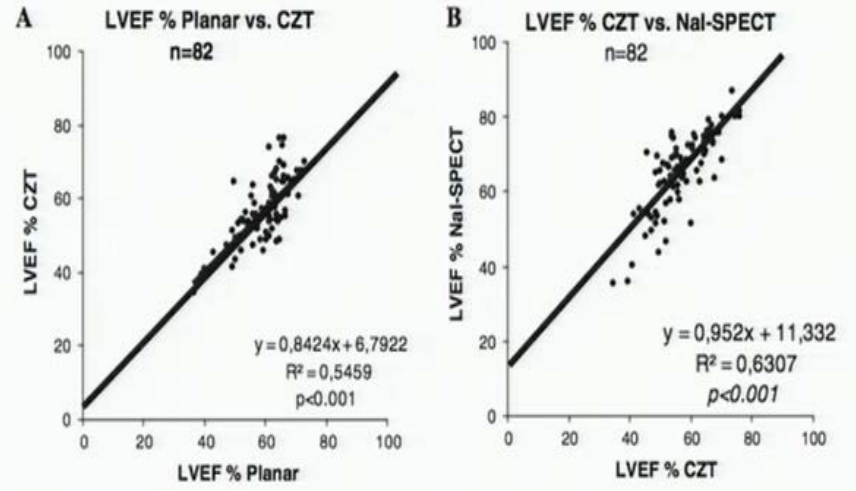
Reliability and accuracy (why ERNA is the preferred Method for follow up)

- Diagnostic Accuracy of ERNV
  - Excellent correlation with LVG with calculated LVEF (r = 0.93)
  - Point-by-point LV volume curve
  - Excellent LVEF precision
  - Robust automated computer processing (90% correlation with manual analysis)
  - *repeat acquisitions (3.7% variability)*
  - *repeat processing (2% variability)*
  - *Excellent intra-observer agreement (1.4% variability)*
  - *Excellent inter-observer agreement (1.6% variability)*

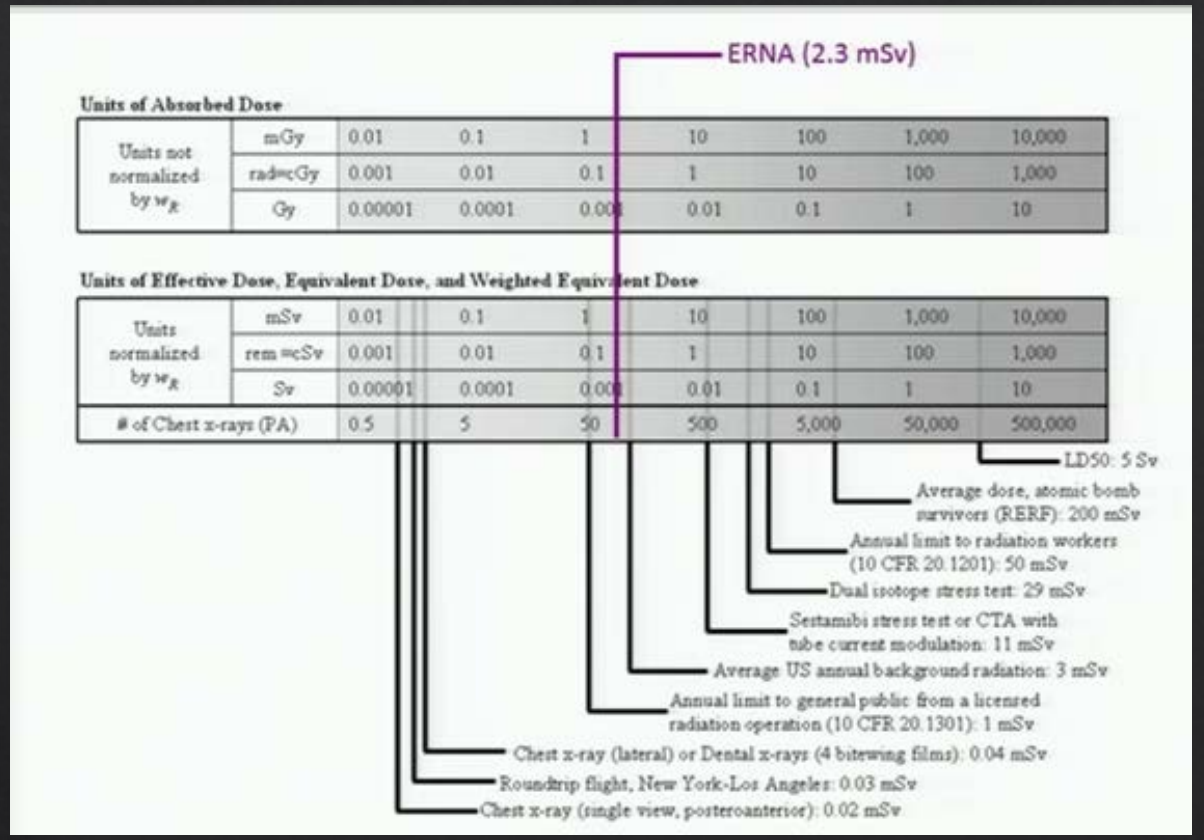
1. Burrow RD, Circulation 1977; 56:1024-1028
2. Folland ED, J Nucl Med 1977; 18: 1159-1166
3. Ashburn WL, Prog Cardiovasc Dis 1978; 20:267-284
4. Shen AC, Am J Pathol 1972; 67:441-452
5. Christian PE, J Nucl Med 1985; 26:775-782
6. Wackers FJ, Am J Cardiol 979; 43:1159-1166

Can We Decrease Radiation Exposure?

Assessment of LV function with CZT cameras



Jensen *et al. J Nucl Cardiol* (2014) **21**: 384



Einstein et al. Circ 116:1290,2007

MIBG Imaging and Potential applications

- Meta-iodoben-benzyl-guanidine (MIBG) is a quanethidine analog that shares type I adrenergic neuroreceptor uptake storage and release mechanisms with norepinephrine

- ***123I-MIBG*** : heart-to-mediastinum count ratio **(H/M ratio)** of 123I-MIBG uptake & 4 hour post injection washout rates utilized in heart failure or anthracycline-based chemotherapy (decrease in H/M ratio correlated with a higher cumulative dose of anthracycline)

- Decreases of MIBG uptake may be seen up to 10 years → severe anthracycline-induced cardiomyopathy (regardless LV function recovery) → suggest myocardial cell injury and adrenergic dysfunction from destruction of adrenergic nerve tissue

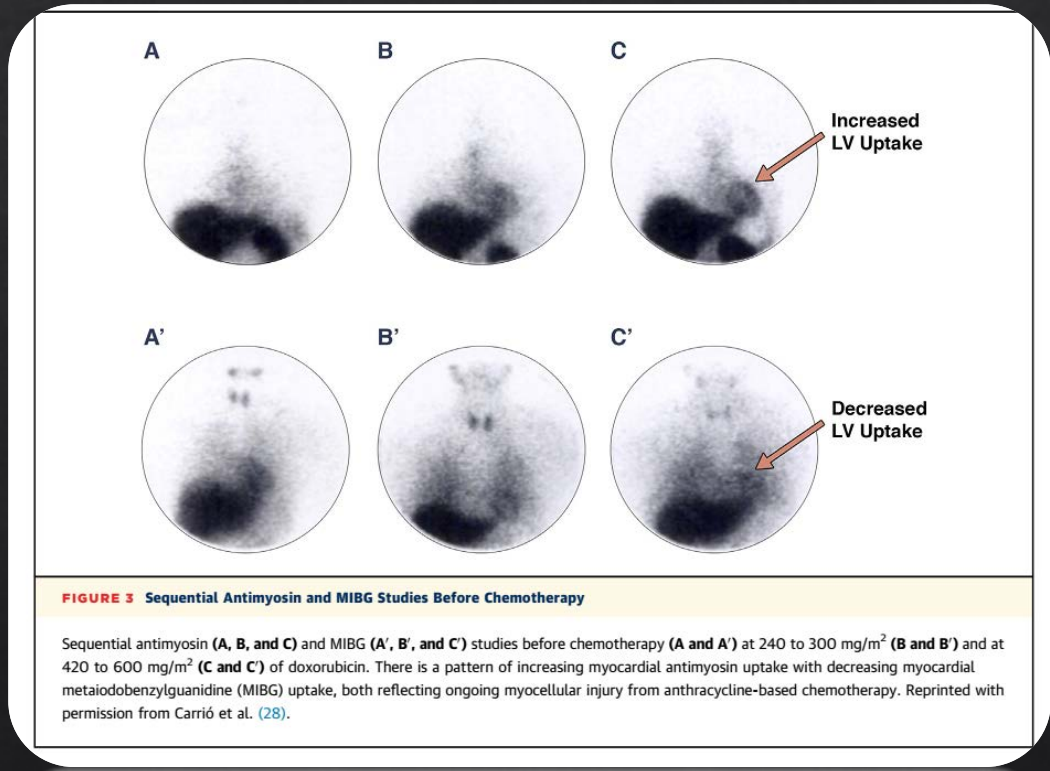
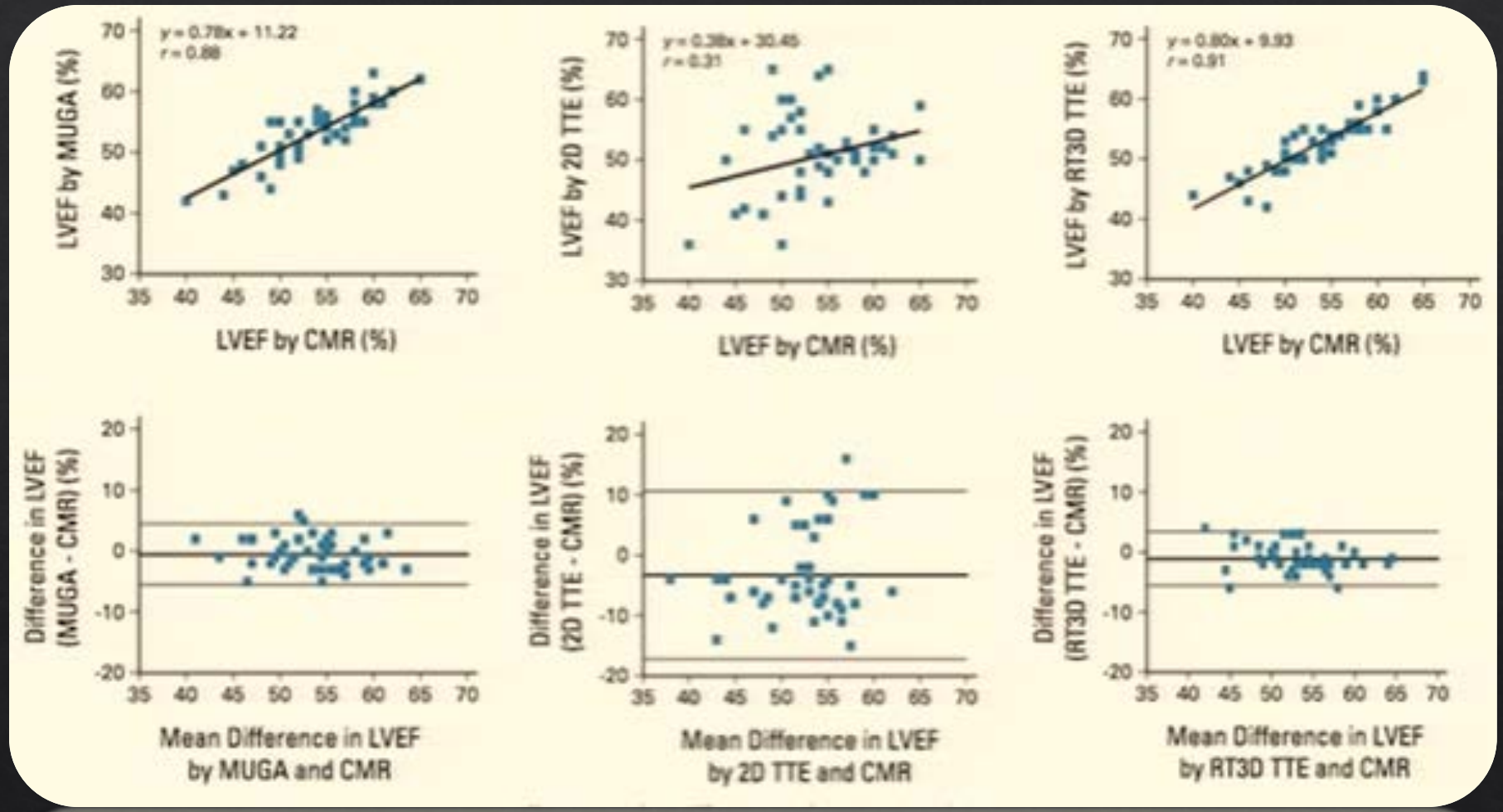


FIGURE 3 Sequential Antimyosin and MIBG Studies Before Chemotherapy

Sequential antimyosin **(A, B, and C)** and MIBG **(A′, B′, and C′)** studies before chemotherapy **(A and A′)** at 240 to 300 mg/m^2 **(B and B′)** and at 420 to 600 mg/m^2 **(C and C′)** of doxorubicin. There is a pattern of increasing myocardial antimyosin uptake with decreasing myocardial metaiodobenzylguanidine (MIBG) uptake, both reflecting ongoing myocellular injury from anthracycline-based chemotherapy. Reprinted with permission from Carrió et al. (28).

Kongbundansuk et al. JACC Imaging 2014

Multi-Imaging Modality Correlation

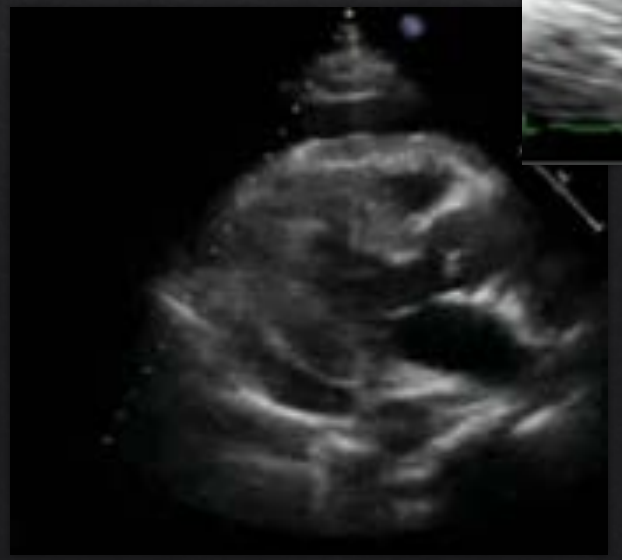


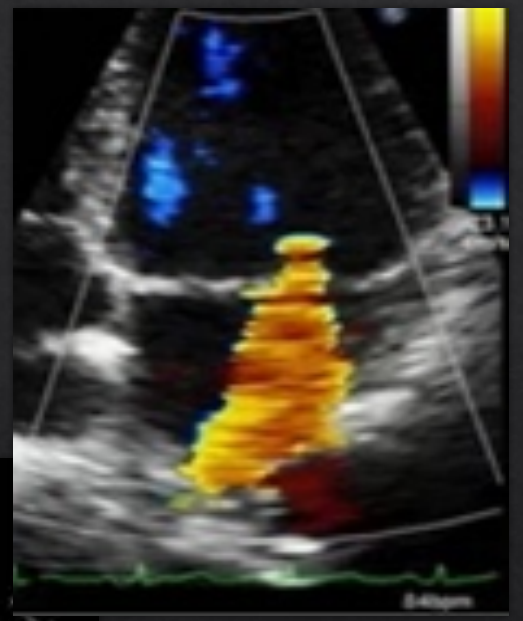
Walker et al. J Clin Oncol 28:3429,2010

Echocardiography with 3D EF and Global Longitudinal Strain

Structural Heart Disease in Echocardiography

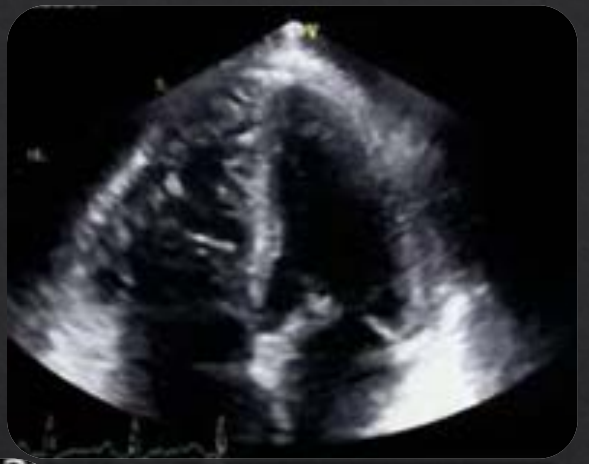
- Valvular pathology with stenosis or regurgitation (aortic and mitral) from remodeling or radiation
- Tumor expansion :
  - Metastatic tumors >Primary (Lung, renal Cell, Melanoma and Mesothelioma)
  - Pericarditis/Pericardial effusion : Mets vs. radiation
- Pulmonary hypertension with RV dysfunction
  - Dasatinib, carfilzomib
  - Malignancies

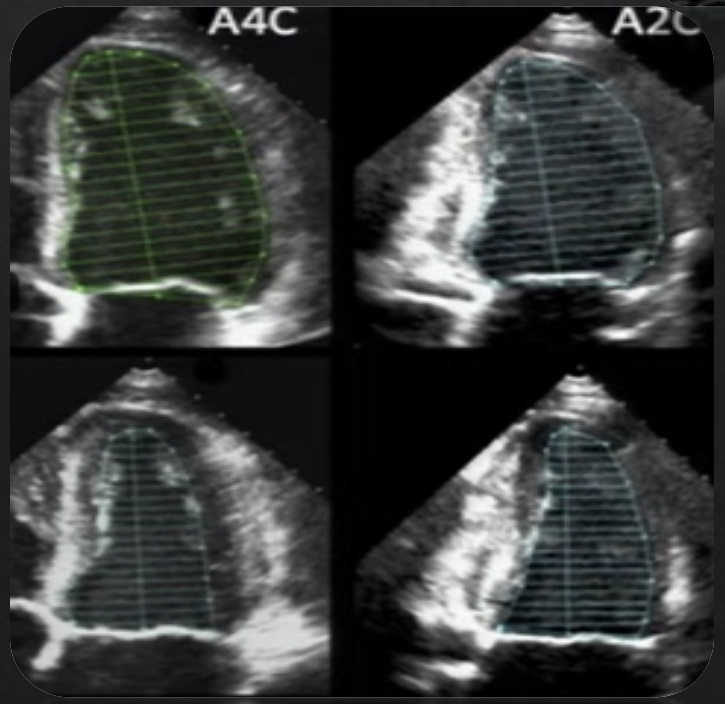




Early Detection and Screening With Echocardiography

- LV Assessment 2D vs. 3D echocardiography:
- Modified Biplane Simpson's Technique:
  - Range 53% - 73% with wide variation
  - ***Inter- & Intra-observer variability of 8-9%***
- 3D EF: automated and reproducible with ***0.6% variability***





Thavendiranathan P, et al. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: Application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013;61:77–84

Early Detection and Screening With Echocardiography

Table 3 Early Predictors of Cardiotoxicity

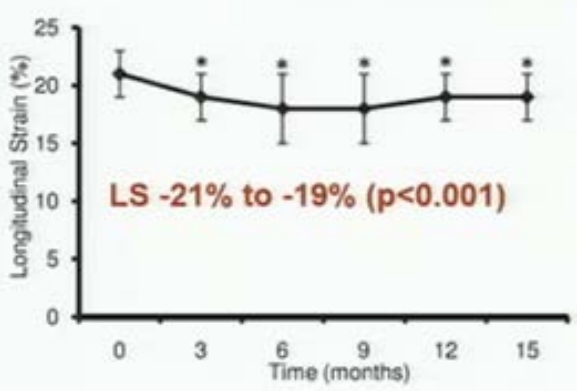
Studies/First Author (Ref. #)	Sensitivity	Specificity	PPV	NPV
Fallah-Rad et al. (44)*				
2% absolute (10.1% relative) decrease in LS	79%	82%	60%	92%
0.8% decrease in RS	86%	81%	60%	95%
Sawaya et al. (41)†				
10% decrease in GLS	78%	79%	50%	93%
Elevated hsTnI	67%	82%	50%	90%
10% decrease in GLS and elevated hsTnI	55%	97%	83%	89%
10% decrease in GLS or elevated hsTnI	89%	65%	40%	97%
Sawaya et al. (40)†				
GLS <19%	74%	73%	53%	87%
hsTnI >30 pg/ml	48%	73%	44%	77%
LS <19% and usTnI >30 pg/ml	35%	93%	67%	77%
LS <19% or usTnI >30 pg/ml	87%	53%	43%	91%

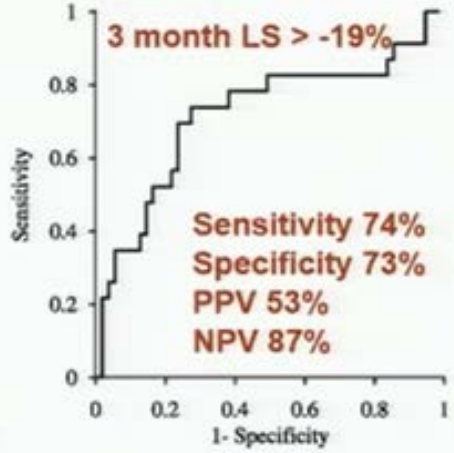
Thavendiranathan P, et al. JACC: 63:2751-68

Longitudinal Strain in Risk Assessment

Assessment of Echocardiography and Biomarkers for the Extended Prediction of Cardiotoxicity in Patients Treated With Anthracyclines, Taxanes, and Trastuzumab

Heloisa Sawaya, MD, PhD; Igal A. Sebag, MD; Juan Carlos Plana, MD; James L. Januzzi, MD; Bonnie Ky, MD, MSCE; Timothy C. Tan, MBBS, PhD; Victor Cohen, MD; Jose Banchs, MD; Joseph R. Carver, MD; Susan E. Wiegers, MD; Randolph P. Martin, MD; Michael H. Picard, MD; Robert E. Gerszten, MD; Elkan F. Halpern, PhD; Jonathan Passeri, MD; Irene Kuter, MD; Marielle Scherrer-Crosbie, MD, PhD





Cardiotoxicity defined as a reduction of EF ≥5% to <55% with HF or an asymptomatic reduction of EF ≥10% to <55%.

Sawaya, et al. Circ CV Imaging. 2012.

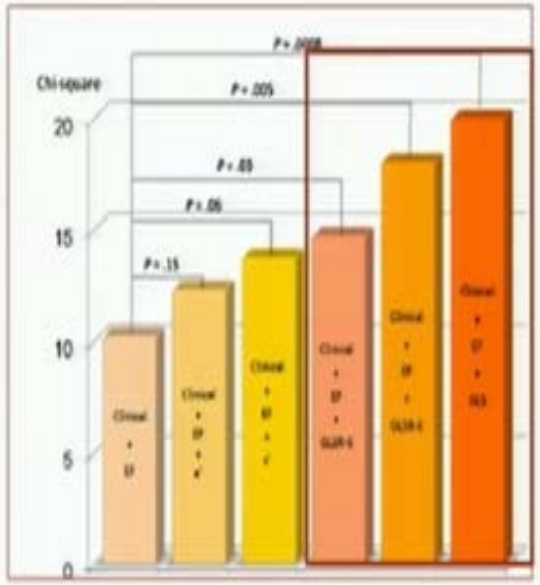
Independent and Incremental Value of Deformation Indices for Prediction of Trastuzumab-Induced Cardiotoxicity

Kazuaki Negishi, MD, PhD, Tomoko Negishi, MD, James L. Hare, MBBS, PhD, Brian A. Haluska, PhD, Juan Carlos Plana, MD, and Thomas H. Marwick, MBBS, PhD, MPH, *Cleveland, Ohio; Brisbane and Hobart, Australia*

- 81 breast cancer patients with at least 3 echocardiograms
- GLS and systolic and diastolic strain rate of incremental utility
  - 11% reduction in GLS had sensitivity 65%; specificity 94%

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 ± 46.5	−10.0 ± 39.3	.11



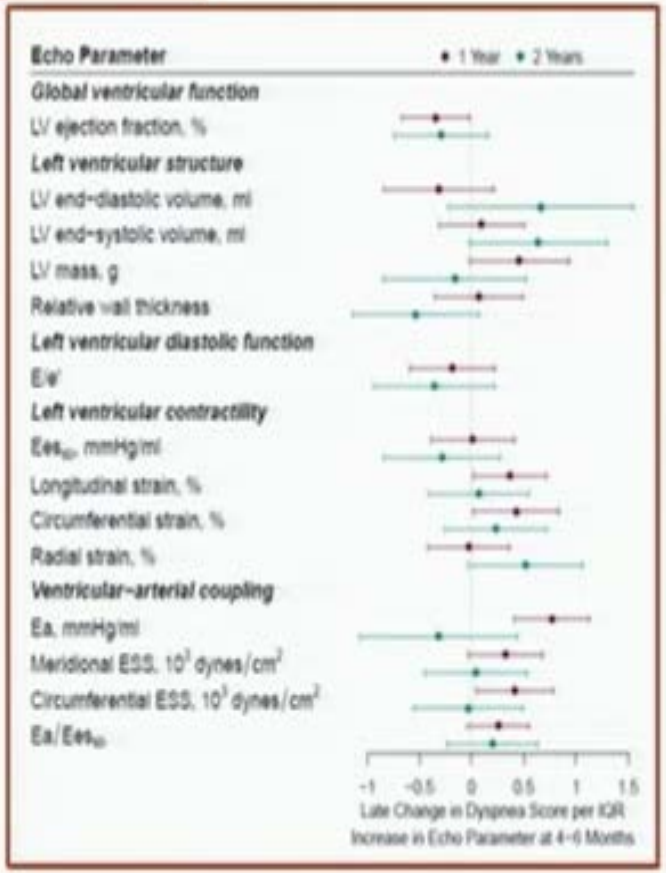
Negishi, et al. JASE. 2013.

ORIGINAL RESEARCH ARTICLE

Detailed Echocardiographic Phenotyping in Breast Cancer Patients

Associations With Ejection Fraction Decline, Recovery, and Heart Failure Symptoms Over 3 Years of Follow-Up

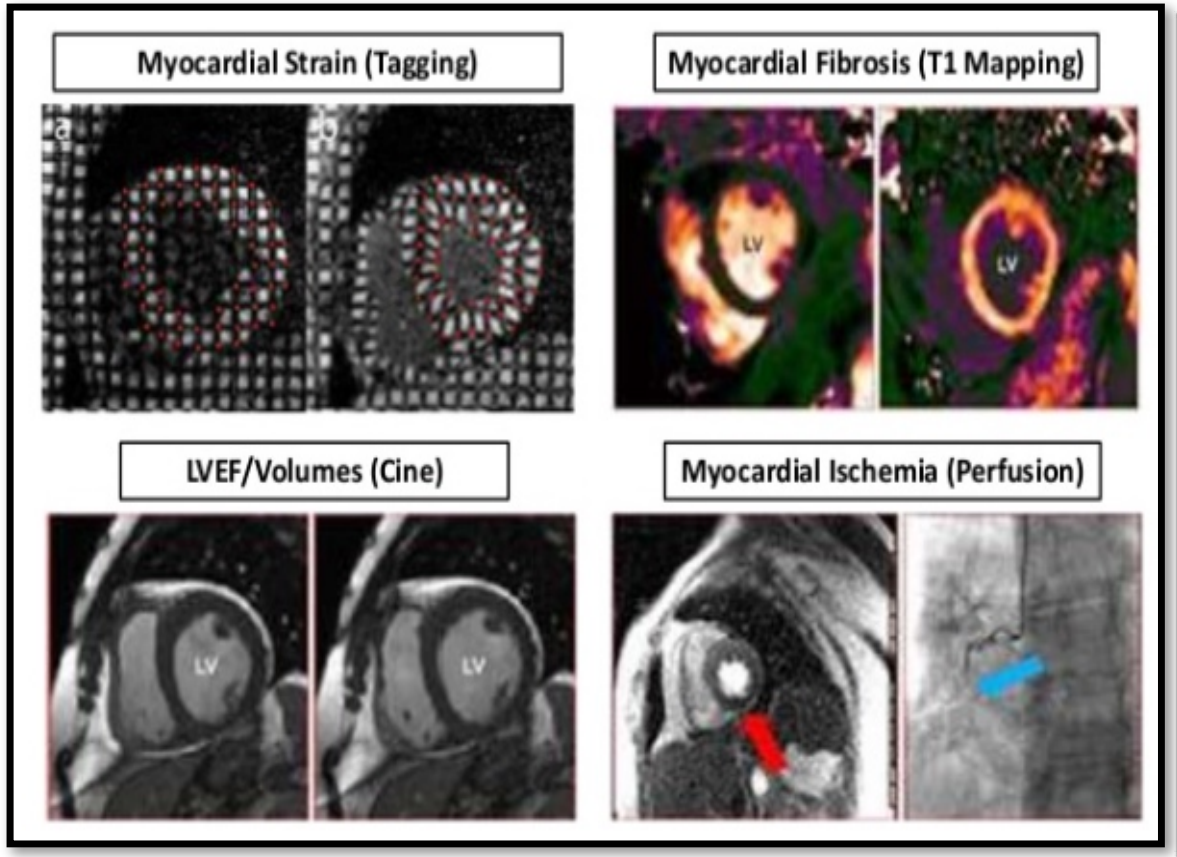
- 277 participants with breast cancer, treated with doxorubicin and/or trastuzumab
- Early changes in volumes, longitudinal & circumferential strain, arterial load (Ea), and Ea/Ees_{sb} are associated with subsequent LVEF declines and with cardiac symptoms

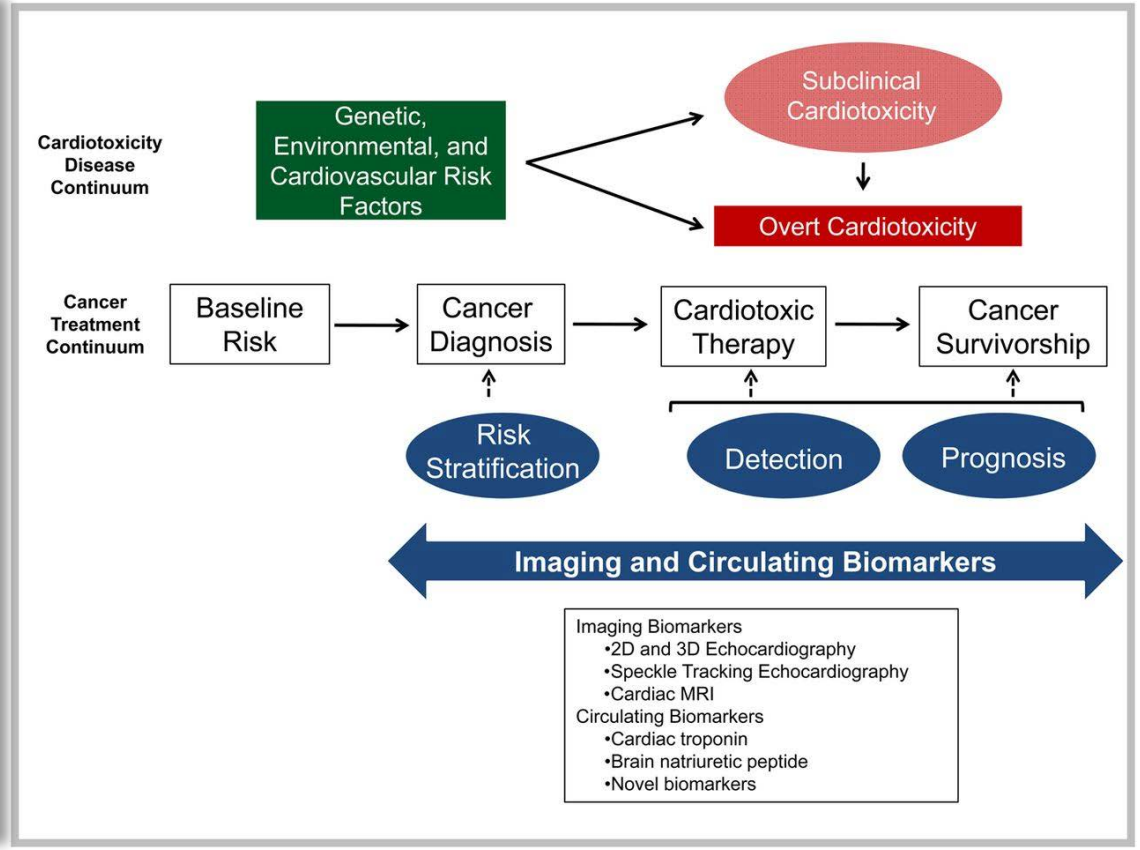


Narayan, Finkelman...Ky. Circulation. 2017

Cardiac Magnetic Resonance Imaging

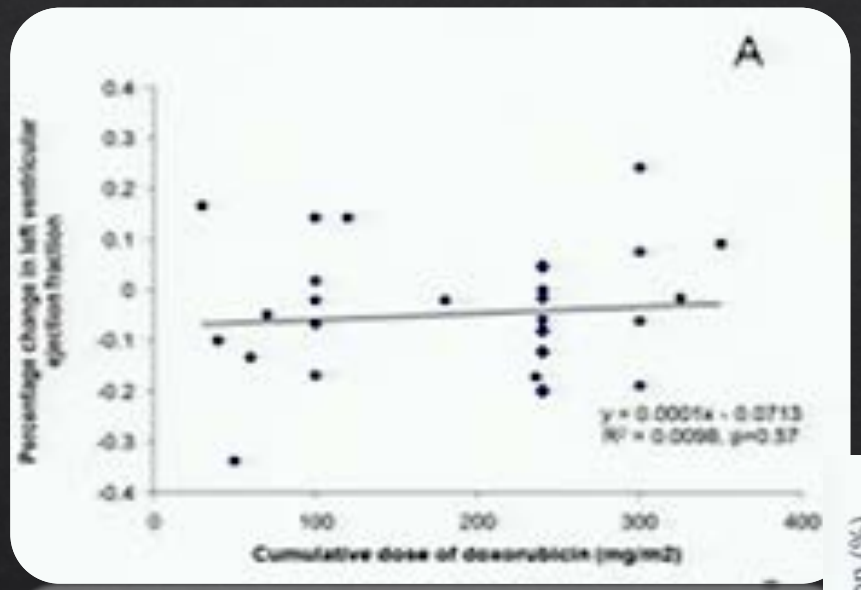
Chemotherapy and CMR

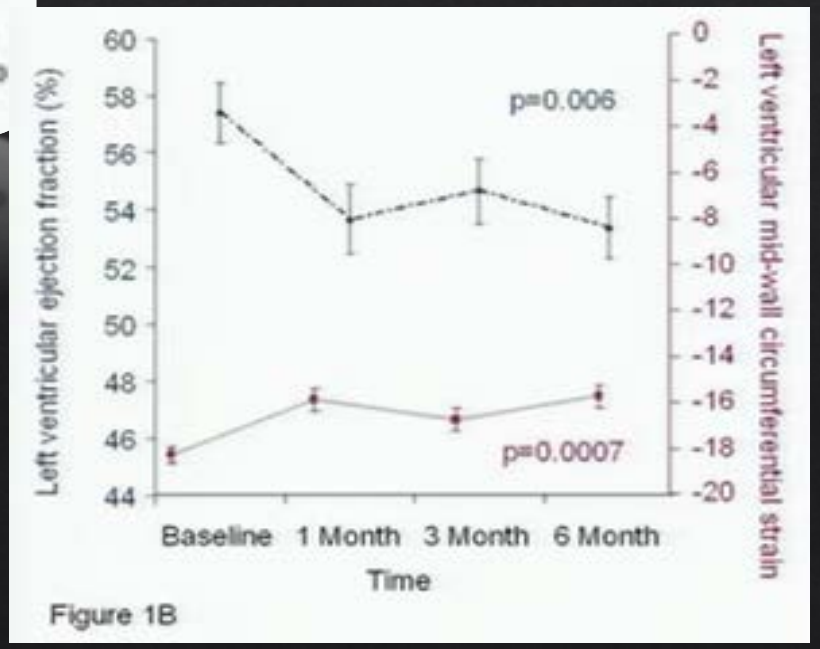




Hundley, et al J Cardiovasc MR 2013
Drafts, et al., JACC Imaging 2012

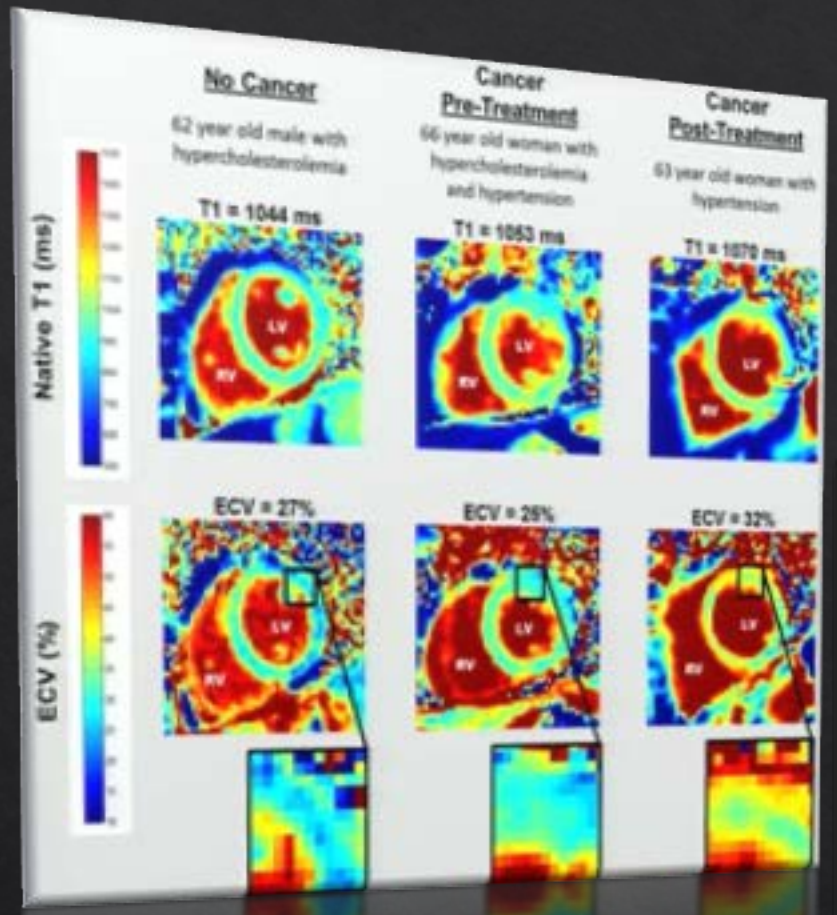
Anthracyclines Based Chemotherapy and Strain on CMR

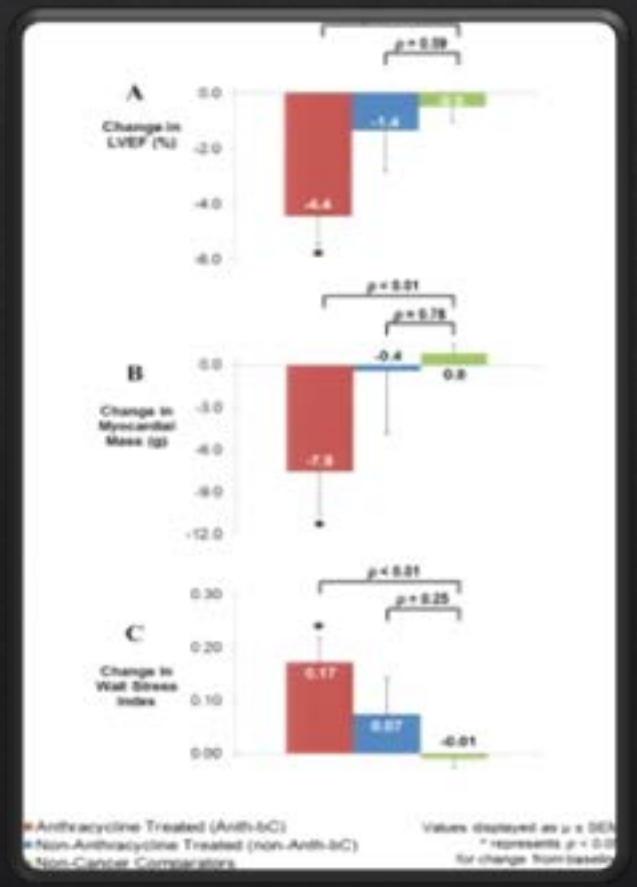


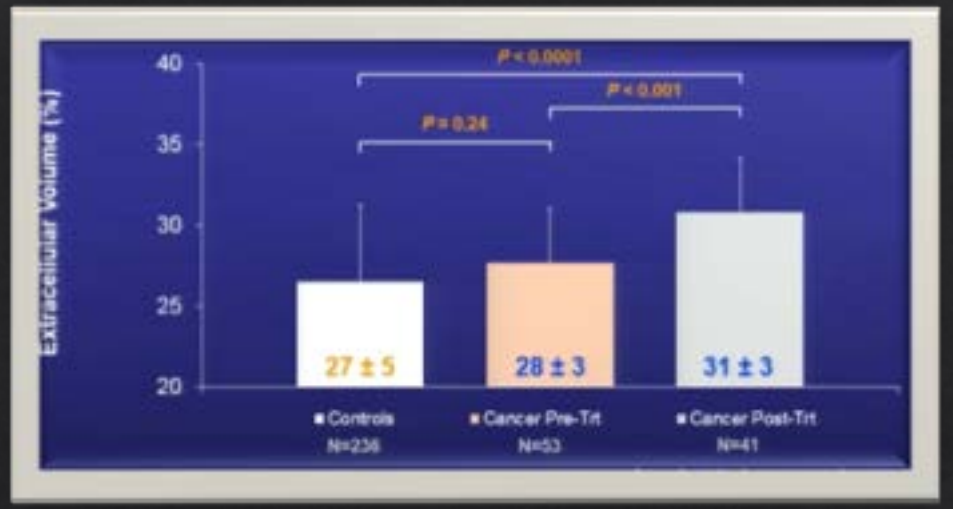


- Independent of:
  - Gender/Age or Race
  - Type of Cancer
  - Chemotherapy dose
  - Cardiovascular co-morbidities

Drafts, et al., JACC Imaging 2012

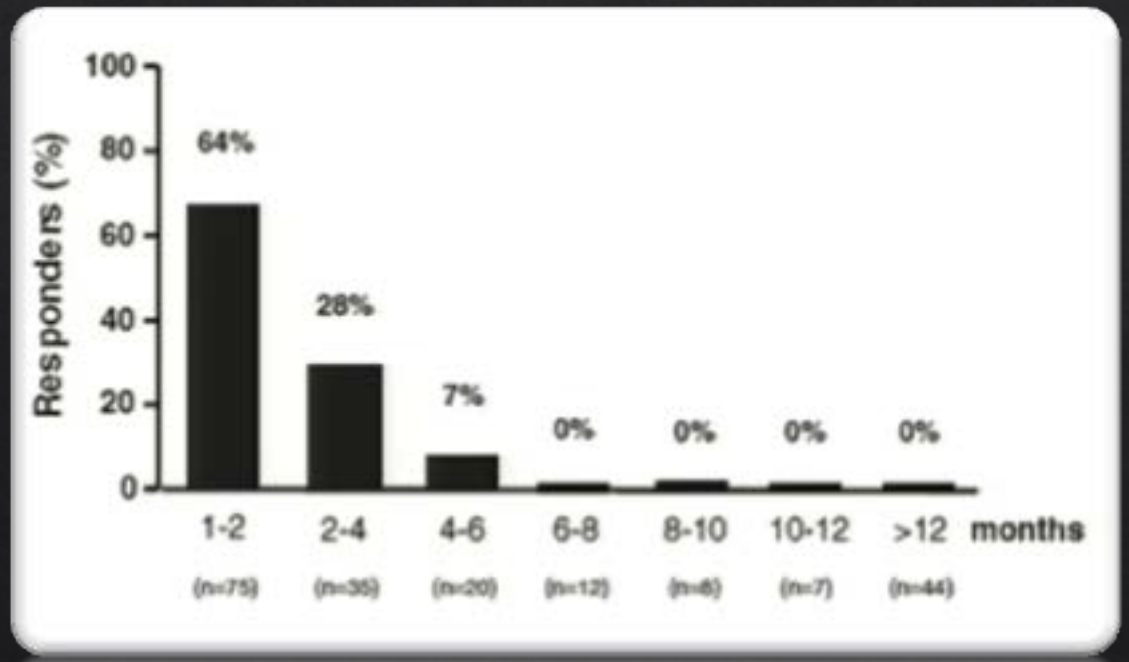






Jordan, et al., Circulation Imaging 2016

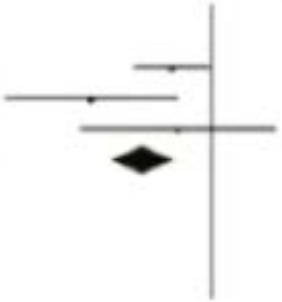
Detection to Intervention



1.1.4 Angiotensin antagonist vs control						
Bosch -2 2013	3	45	11	45	3.9%	0.27 [0.08, 0.91]
Cardinale 2006	0	56	25	58	8.8%	0.02 [0.00, 0.33]
Nakamae 2005	0	20	1	20	0.5%	0.33 [0.01, 7.72]
Subtotal (95% CI)		121		123	13.2%	0.11 [0.04, 0.29]
Total events	3		37			

Heterogeneity: $Chi^2 = 4.20$, $df = 2$ ($P = 0.12$); $I^2 = 52\%$

Test for overall effect: $Z = 4.34$ ($P < 0.0001$)



30% event rate in the control arm

89% Relative Risk Reduction

Number Needed to Treat: 3.6

Cardinale D, et al. Circ 2006

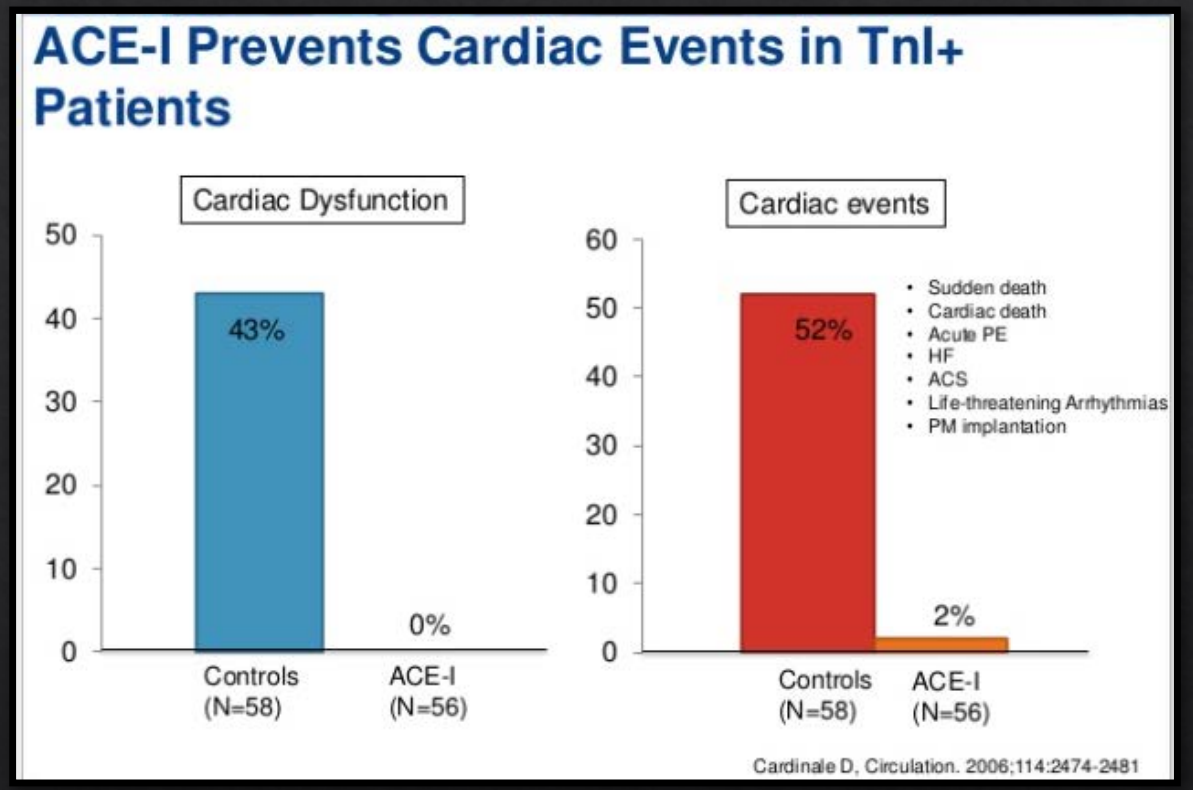
Kalam, et al.. European Journal of Cancer 2013

Strategies to Reduce Risk of Cardiotoxicity

- ***Dexrazoxane (Zinecard ®)***
- potent intracellular chelating agent that interferes with ***iron-mediated oxygen free radical generation***
- In a meta-analysis of *5 randomized clinical trials (RCTs)* of anthracyclines ± dexrazoxane, use of dexrazoxane reduced the incidence of both asymptomatic and symptomatic cardiomyopathy (RR 0.29; 95% CI, 0.2-0.4; $p < 0.00001$)
- Reduced Cardiomyopathy incidence of cardiotoxicity even when administered after receipt of 300 mg/m^2 of anthracyclines
- Widespread use of dexrazoxane has been limited by concerns:
  - Reduced tumor response rates in one breast cancer trial
  - Perceived increase in the risk of secondary hematologic malignancies in children
  - **Meta-analyses** reveal that there is no difference in oncologic response rates or oncologic survival between patients treated with or without dexrazoxane
  - RCT of dexrazoxane added to anthracycline-based chemotherapy in children with T-cell acute lymphoblastic leukemia or lymphoblastic non-Hodgkin lymphoma did not show a significant increase in secondary malignancies with dexrazoxane
- Currently approved only in the United States for use in adult patients with metastatic breast cancer who have received ≥ 300 mg/m^2 and need additional anthracycline therapy

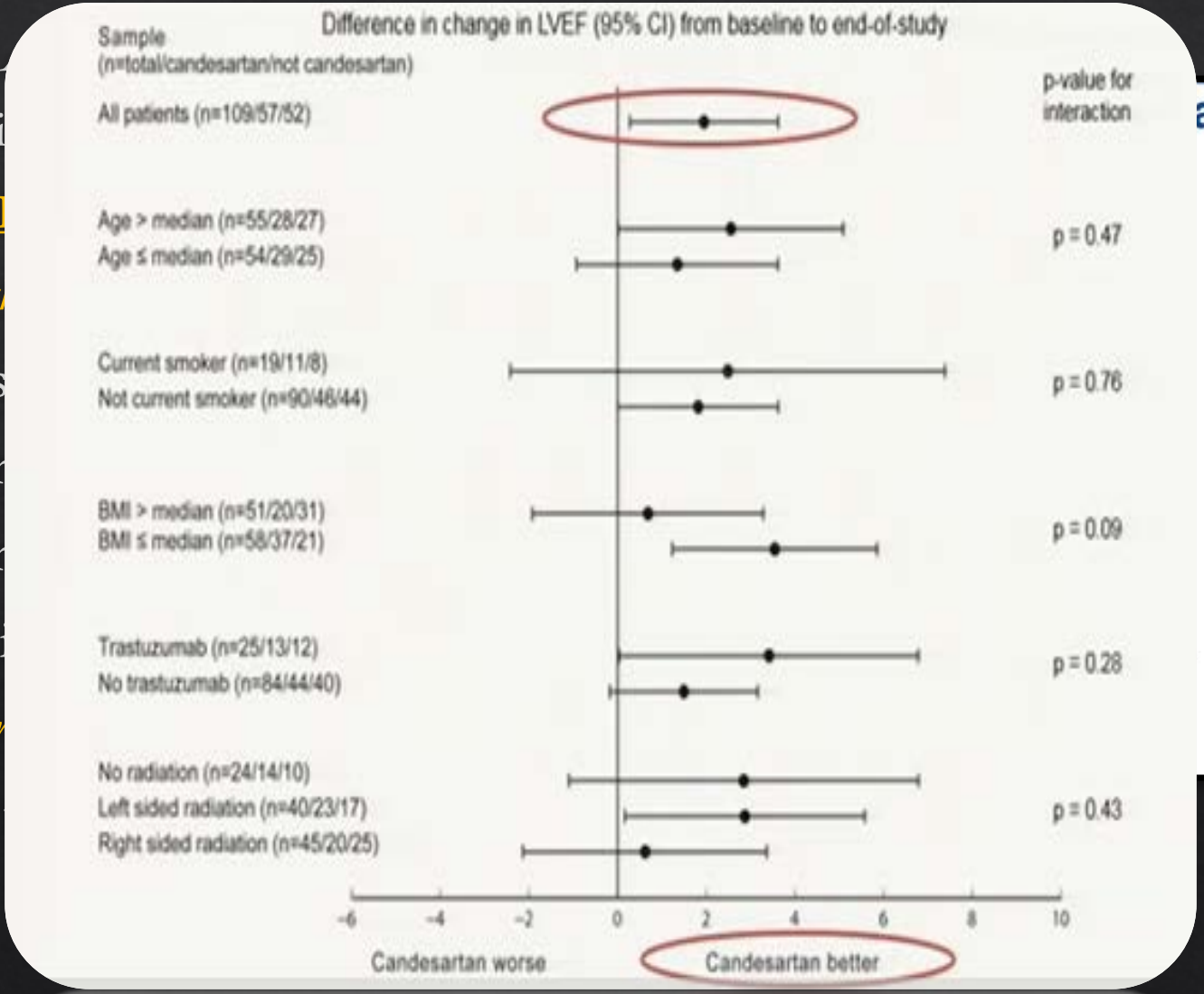
Strategies to Reduce Risk of Cardiotoxicity

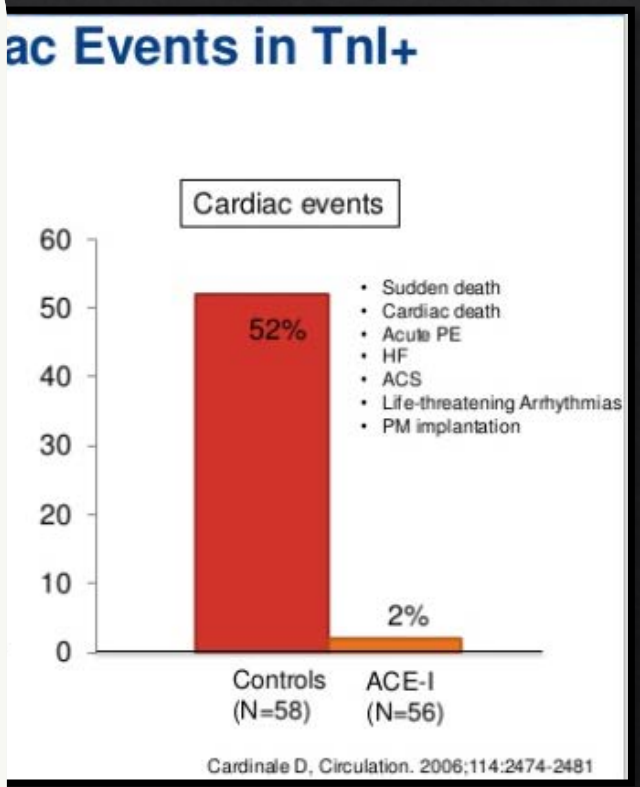
- *Cardioprotective Agents*
  - Several pre-clinical studies suggesting that **angiotensin II and endothelin I** are involved in mediating *anthracycline cardiotoxicity*
  - Several RCTs evaluating the role of neurohormonal antagonists → prophylactic neurohormonal blockade in patients exposed to anthracyclines or trastuzumab is associated with a *smaller decrement in LV ejection fraction*
  - *underpowered* to detect a difference in clinical HF events



Strategies to Reduce Risk of Cardiotoxicity

- *Cardioprotective*
  - Several pre-cli
    angiotensin II
    mediating *anti*
  - Several RCTs
    neurohormon
    neurohormon
    to anthracycli
    with a *smaller*
  - *underpowered*
    HF events





Strategies to Reduce Risk of Cardiotoxicity

- In animals exposed to anthracyclines:
  - ***Beta-1 → cardiotoxic***
  - ***Beta-2 activation → cardioprotective***
- Carvedilol and nebivolol that have additional antioxidant properties, have been shown to attenuate the *histopathologic* changes seen in anthracycline-mediated cardiomyopathy & ***Reduce decrement in EF & BNP***
- **Upregulation of beta receptors** in breast cancer cells is associated with *growth and Metastasis*
- *Beta-blockers downregulate* beta receptors and in some studies reduce metastasis

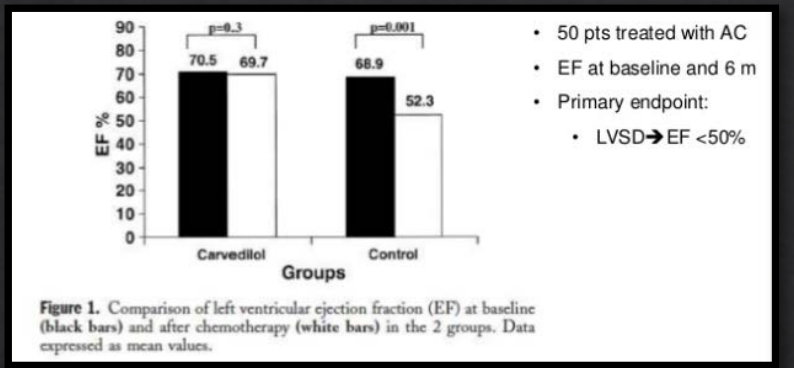
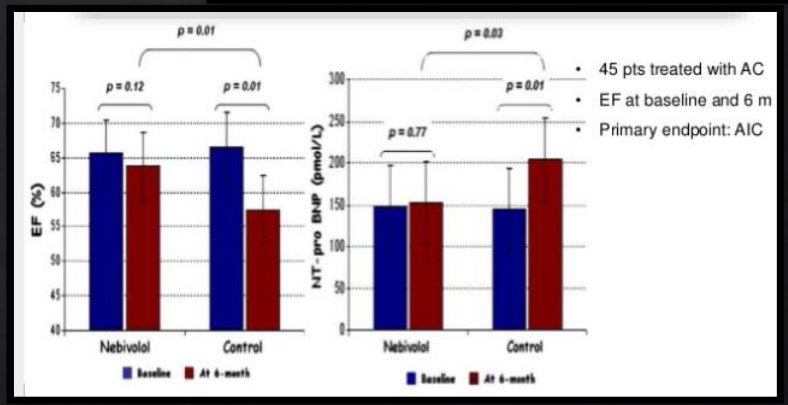
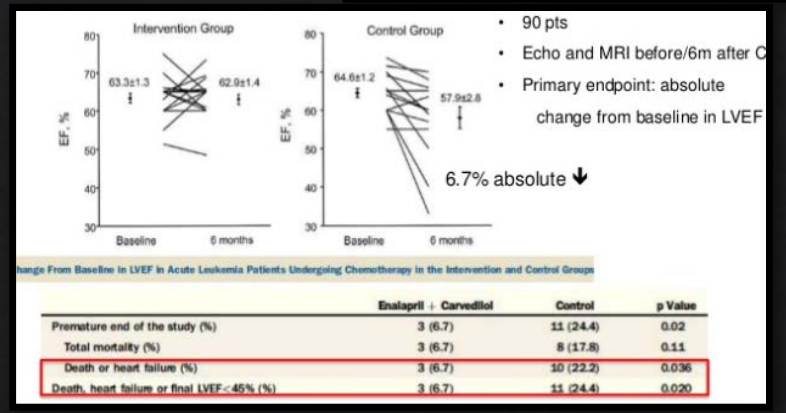


Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline **(black bars)** and after chemotherapy **(white bars)** in the 2 groups. Data expressed as mean values.





hange From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45% (%)	3 (6.7)	11 (24.4)	0.020

Kaya et al, int J Card 2013
Bauch at al, JACC 2013
Kalay et al., JACC 2006

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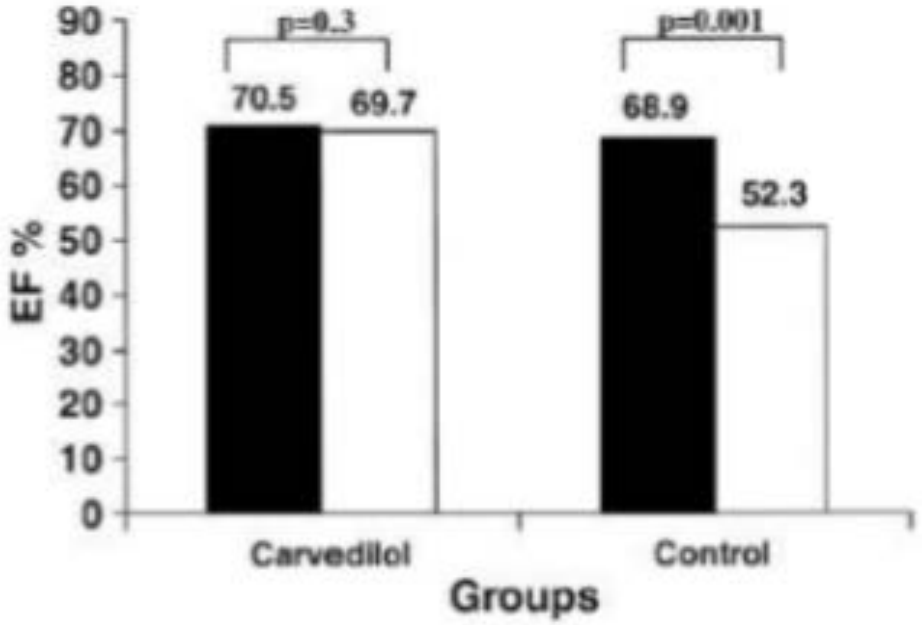
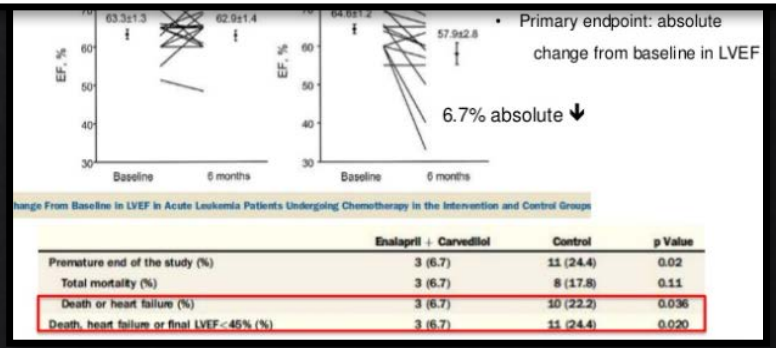


Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline (**black bars**) and after chemotherapy (**white bars**) in the 2 groups. Data expressed as mean values.

- 50 pts treated with AC
- EF at baseline and 6 m
- Primary endpoint:
  - LVSD→ EF <50%



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Kaya et al, int J Card 2013
Bauch at al, JACC 2013
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Strategies to Reduce Risk of Cardiotoxicity

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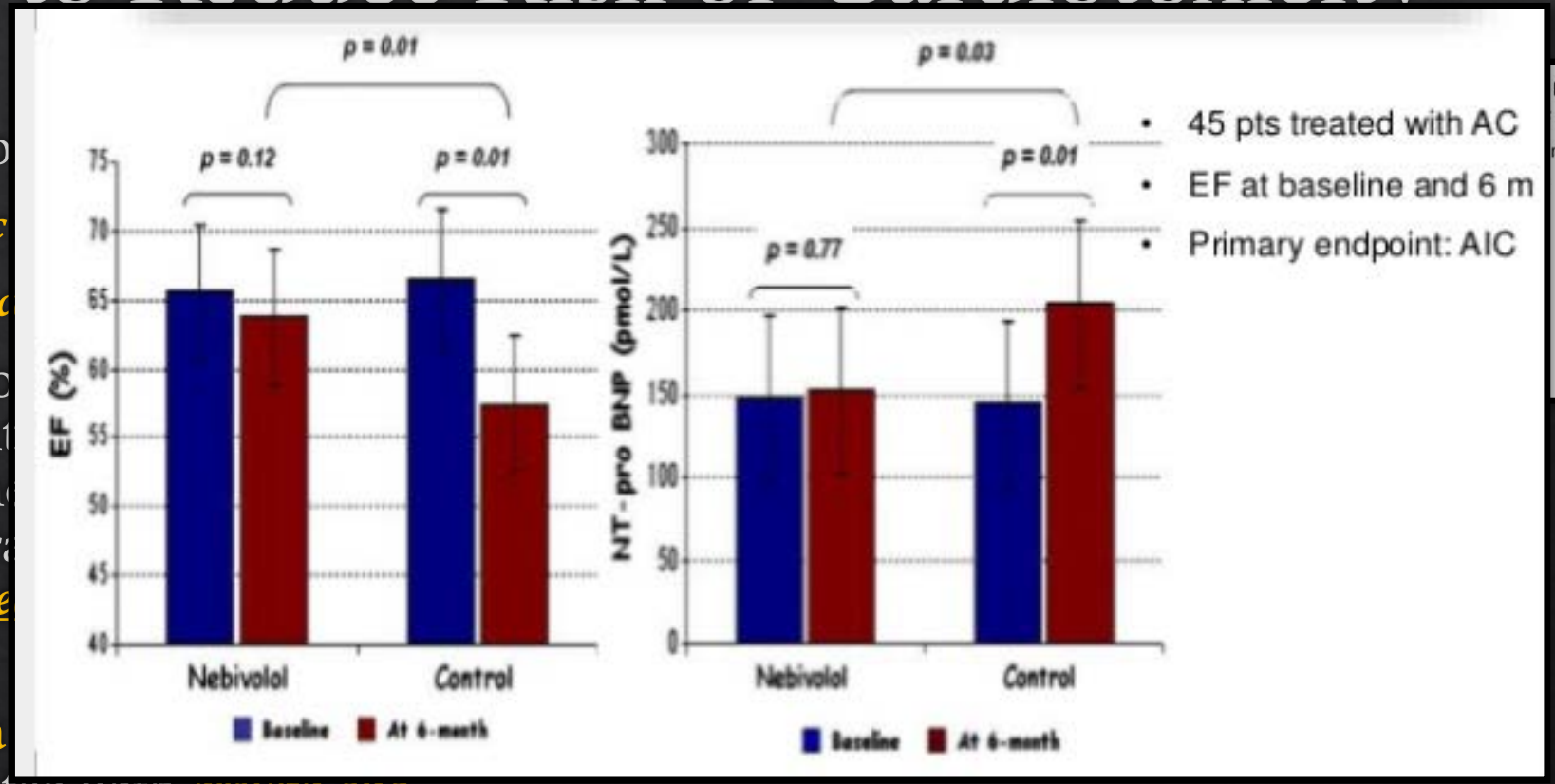
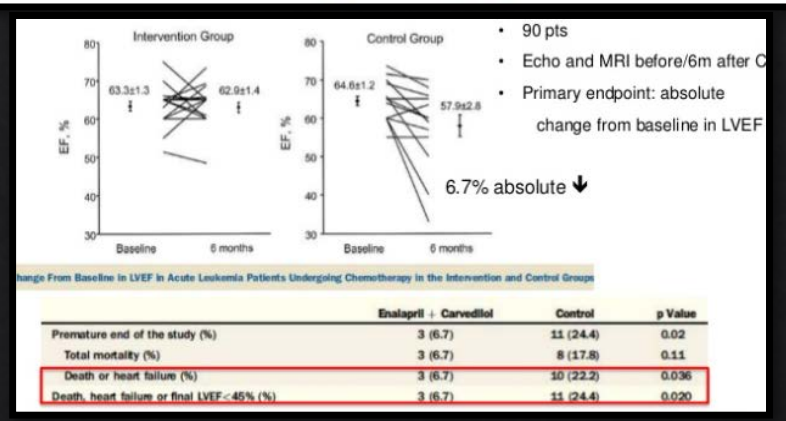


pts treated with AC
at baseline and 6 m
mary endpoint:
LVSD→EF <50%



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Kaya et al, int J Card 2013
Bauch at al, JACC 2013
Kalay et al., JACC 2006

Strategies to Reduce Risk of Cardiotoxicity

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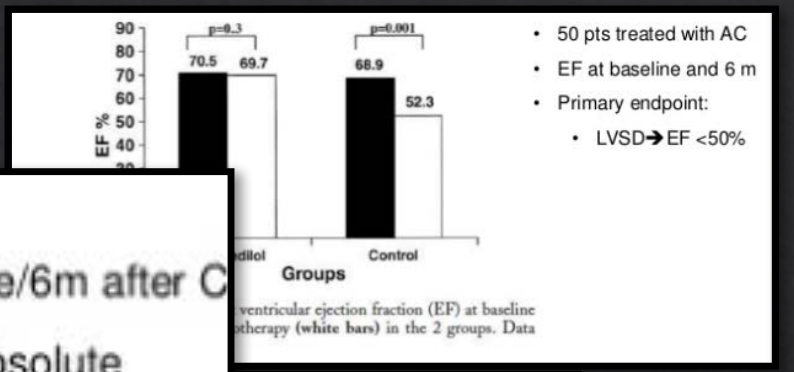
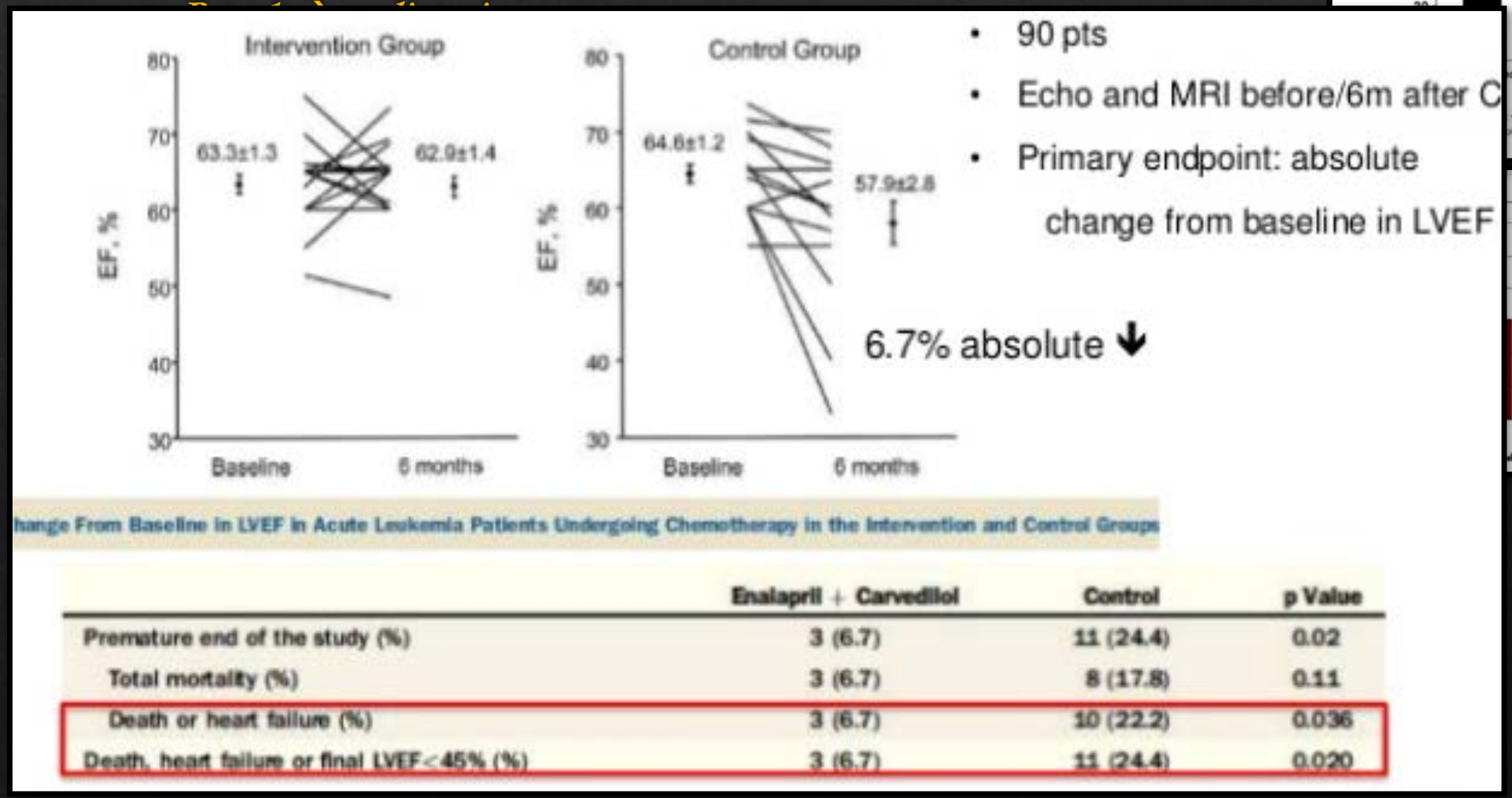
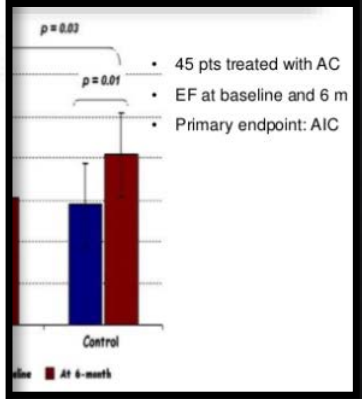






hange From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45% (%)	3 (6.7)	11 (24.4)	0.020

Strategies to Reduce Risk of Cardiotoxicity

- In animals exposed to anthracyclines:
  - ***Beta-1 → cardiotoxic***
  - ***Beta-2 activation → cardioprotective***
- Carvedilol and nebivolol that have additional antioxidant properties, have been shown to attenuate the *histopathologic* changes seen in anthracycline-mediated cardiomyopathy & ***Reduce decrement in EF & BNP***
- **Upregulation of beta receptors** in breast cancer cells is associated with *growth and Metastasis*
- ***Beta-blockers downregulate*** beta receptors and in some studies reduce metastasis

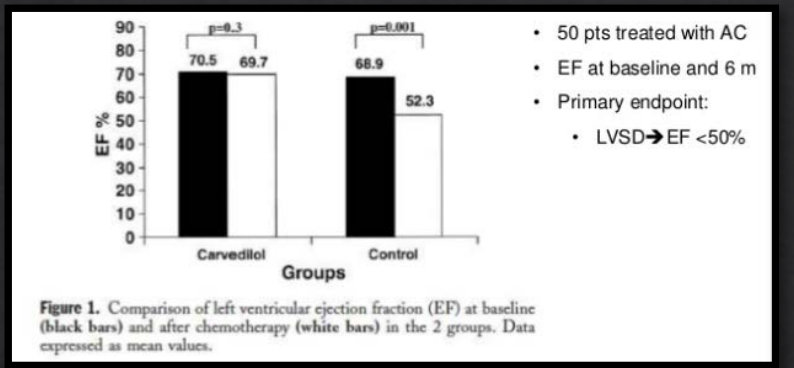
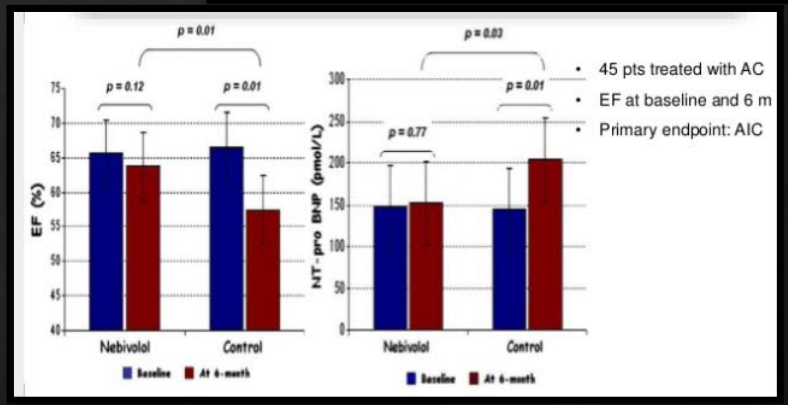
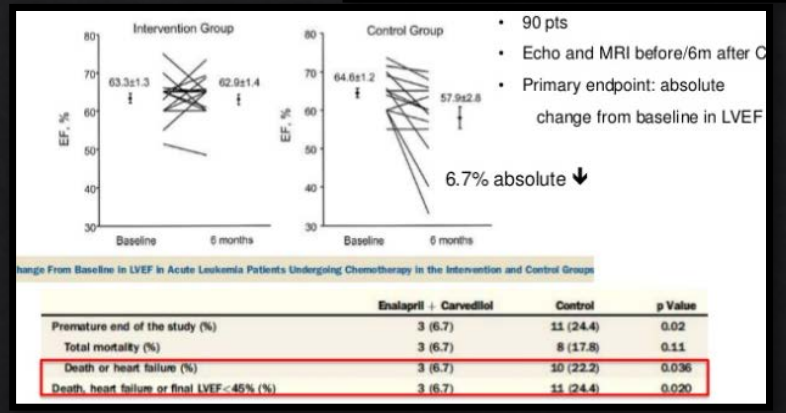


Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline (**black bars**) and after chemotherapy (**white bars**) in the 2 groups. Data expressed as mean values.





Change From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45% (%)	3 (6.7)	11 (24.4)	0.020

Kaya et al, int J Card 2013
Bauch at al, JACC 2013
Kalay et al., JACC 2006

Strategies to Reduce Risk of Cardiotoxicity

Parameter	HR	p-value	95% Confidence Interval	
			Lower	Upper
BCSS				
Tumour size	1.985	0.004	1.248	3.159
Tumour grade	1.904	<0.001	1.435	2.526
Tumour stage	1.565	<0.001	1.218	2.011
beta-blocker treatment	0.291	0.007	0.119	0.715
DM				
Tumour size	1.916	0.005	1.221	3.005
Tumour grade	1.519	0.002	1.171	1.971
Tumour stage	1.624	<0.001	1.270	2.076
beta-blocker treatment	0.430	0.031	0.200	0.926

Table 4: The effect of beta-blocker treatment on breast cancer specific survival (BCSS) and distant metastasis (DM) formation was compared with tumour size, grade and stage to determine the relative risk (Hazard Ratios (HR)) in BC patients.

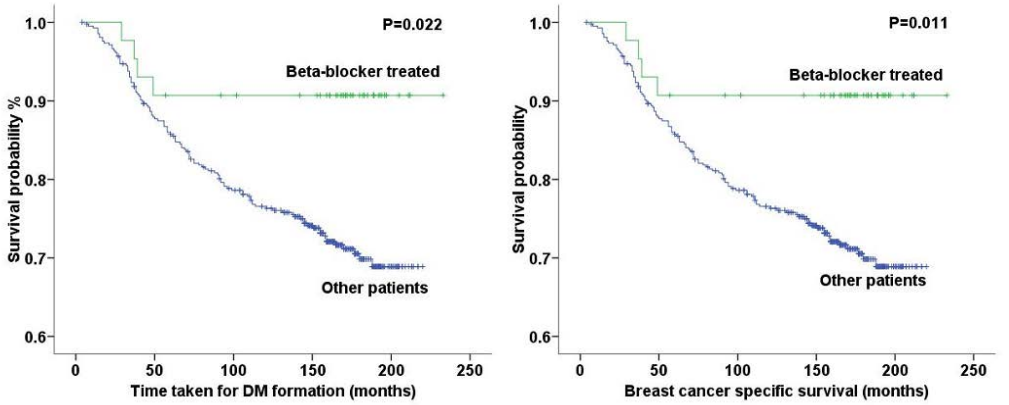


Figure 1a: Hypertensive BC patients therapeutically treated with beta-blockers showed significantly (p=0.022) longer times before acquiring metastases compared to non-treated patients.
Figure 1b. Hypertensive BC patients receiving beta-blocker therapy showed significantly (p=0.011) improved 10 year survival rates compared to non-treated patients.

MANTICORE 101-Breast

- Bisoprolol or perindopril or placebo on MRI indices of LV remodeling and serum biomarkers in 159 women with HER2+ early breast cancer

NCT01009918

- Phase II study on the effect of Carvedilol and lisinopril vs placebo on LVEF at 52 weeks in 468 women with HER2+ early breast cancer

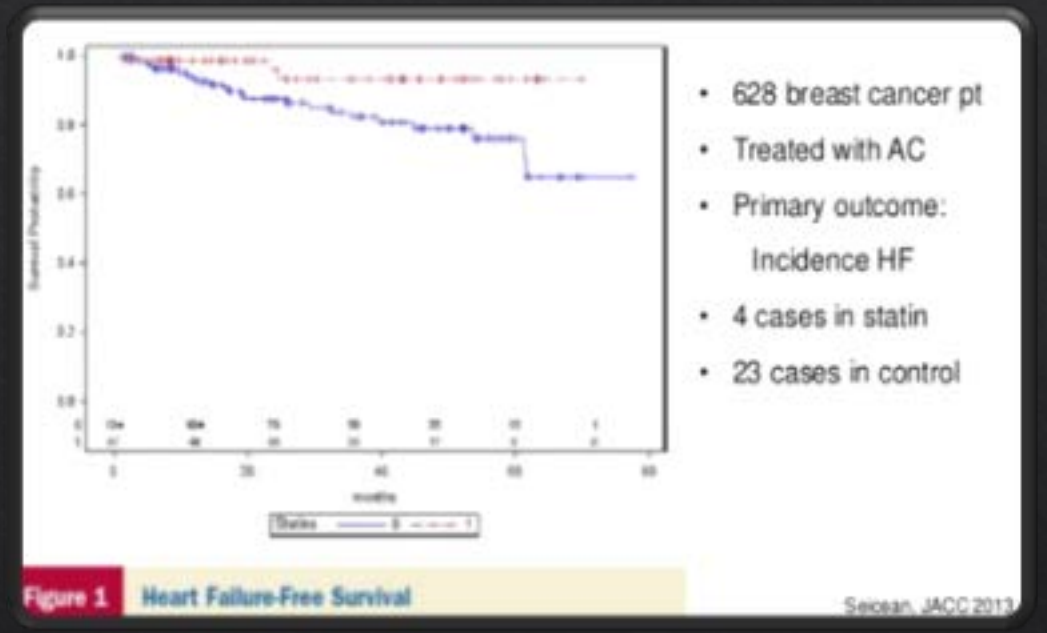
Heart Failure Trials

Trial	Rx	Total	Non-African Americans (%)	African Americans	African Americans (%)
V-HeFT I + II1	ISDN/HYD, Enalapril	1419	1024	395	28
SOLVD[2]	Enalapril	2569	2175	394	15
US Carvedilol[3]	Carvedilol	1094	877	217	20
COPERNICUS[4]	Carvedilol	2289	2168	121	5
BEST[5]	Bucindolol	2708	2081	627	23
MERIT-HF[6]	Metoprolol	3991	3783	208	5
EPHESUS[7]	Eplerenone	6632	6558	74	1
Val-HeFT[8]	Valsartan	5010	4666	344	7
VALIANT9	Valsartan, Valsartan/Captopril	14703	14296	407	3
CHARM[10]	Candesartan	3023	2897	126	4
A-HeFT[11]	ISDN/HYD	1050		1050	100
	TOTAL	44,488	40,525	3,963	7

1. Carson P et al. J Card Fail. 1999;5:178-187; 2. Hall WD. Ethn Dis. 1999;9:333-340; 3. Yancy CW et al. N Engl J Med. 2001;344:1358-1365;
4. Packer M et al. N Engl J Med. 2001;344:1651-1658; 5. BEST Investigators. N Engl J Med. 2001;344:1659-1667; 6. MERIT-HF study group. Lancet. 1999;353:2001-2007; 7. Pitt B et al. N Engl J Med. 2003;348:1309-1321; 8. Cohn JN. N Engl J Med. 2001;345:1667-1675; 9. Pfeffer MA et al. N Engl J Med. 2003;349:1893-1906; 10. Yusuf S et al. Lancet. 2003;362:777-781.

Strategies to Reduce Risk of Cardiotoxicity

- ***Statins***
  - *Pleotropic effects by decreasing oxidative stress and inflammation*
  - *In a propensity-matched analysis, women with newly diagnosed breast cancer on concomitant statins during anthracycline-based chemotherapy compared to 134 non-statin treated controls*
    - Statin treatment: significantly lower risk of HF hospitalizations (hazard ratio 0.3; 95% CI, 0.1-0.9; p = 0.03)
  - *Another small study evaluated LV function using CMR in patients receiving anthracycline-based chemotherapy: Statin arm experienced no decline in LV function at 6 months as compared to non statin arm (from 57.5 ± 1.4% to 52.4 ± 1.2%, p = 0.0003) after anthracycline treatment*
  - *A RCT of 40 patients undergoing anthracycline treatment compared 6 months of prophylactic **atorvastatin (40 mg daily)** to placebo → statin therapy resulted in a smaller decline in mean **LV ejection fraction (1.3 ± 3.8% vs. - 7.9 ± 8.0%, p < 0.001) and a lesser increase in mean LV end-systolic (p < 0.001) and end-diastolic (p = 0.02)** dimensions compared with placebo*



Current Efforts Towards Local Comprehensive Cardio-Oncology Program

Cardio-Oncology Centers

Pulse
Heart Institute

Echocardiography Request Form
Cardio-Oncology

Phone: 253-572-7320
Fax: 253-627-3191

Patient Name:	**DOB:**
Requesting Physician:	Fax #:
Insurance Name:	Policy #:
Authorization #:	**Date range for auth:**

- 93306 – Echo, transthoracic, **with** spectral Doppler and color flow Doppler
- 93307 – Echo, transthoracic, **without** spectral and color flow Doppler
- 93312 – Echo, transesophageal
- 93308 – Echo, transthoracic, follow-up or limited

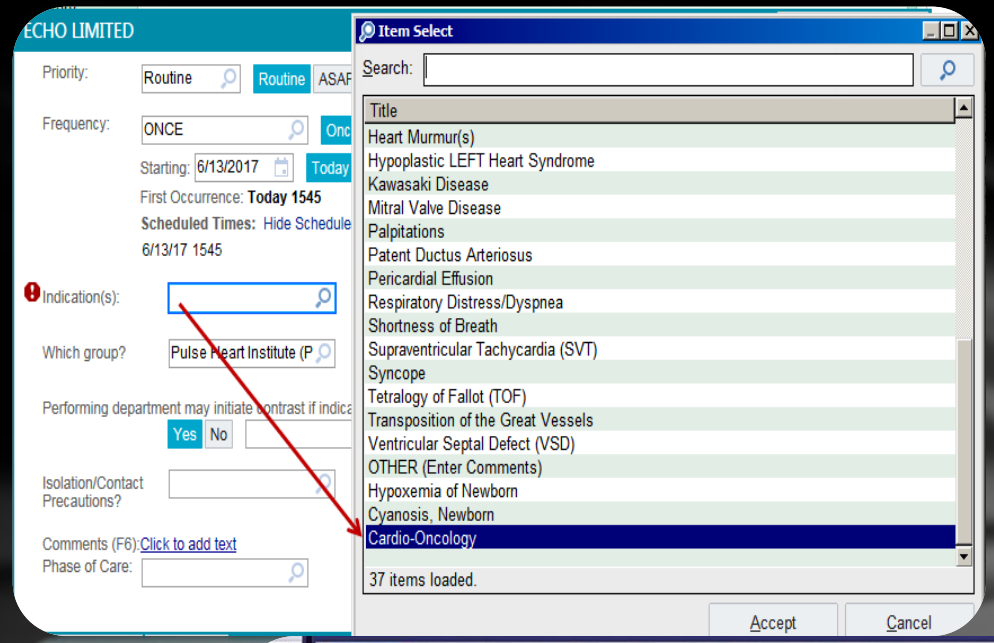
Please indicate any **additional** studies to be performed

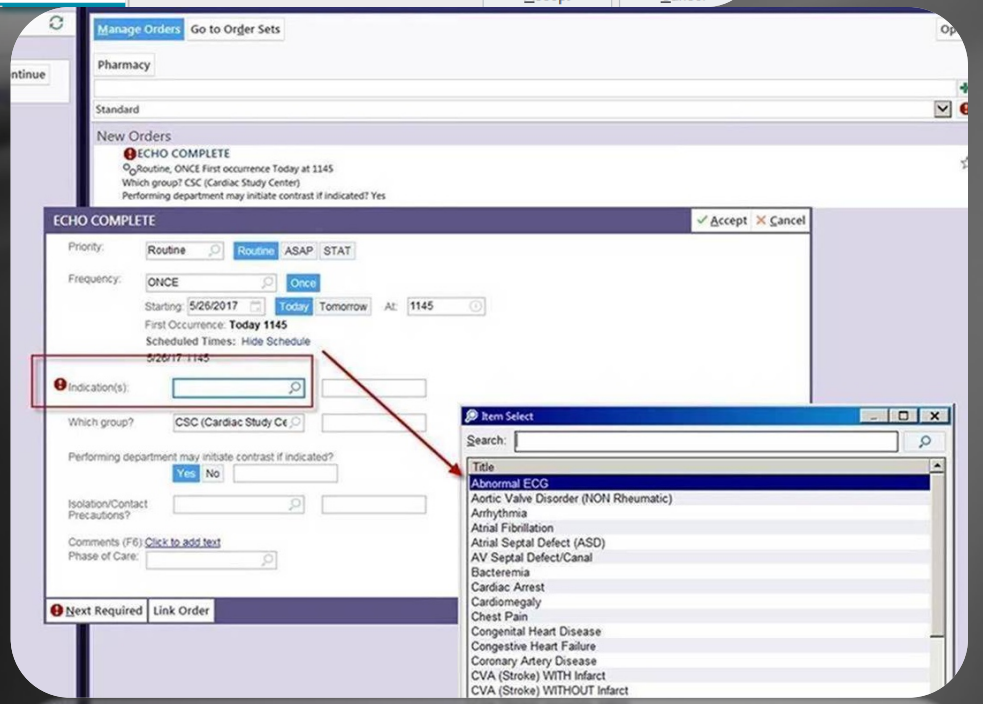
- 93320 – Doppler spectral
- 93325 – Color flow Doppler
- 93352 – Contrast
- 76376 – 3D, **without** post processing on independent station
- 0399T – Myocardial strain imaging

Indication(s)

Current chemotherapy
- Z79.810 selective estrogen receptor modulators
- Z79.811 aromatase inhibitors
- Z79.818 other agents affecting estrogen
- Z79.899 other drug therapy

Completed therapy
- Z92.21 antineoplastic
- Z92.22 monoclonal
- Z92.23 estrogen
- Z92.25 immunosuppression
- Z92.29 other drug therapy
- Z92.3 irradiation





For initial Copies of Form contact Camille Labbs: 253-572-7320, ext: 3049

Latent Effects of Chemotherapy & Radiation on the Heart

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