Cardiotoxicity: The View of the Cardiologist

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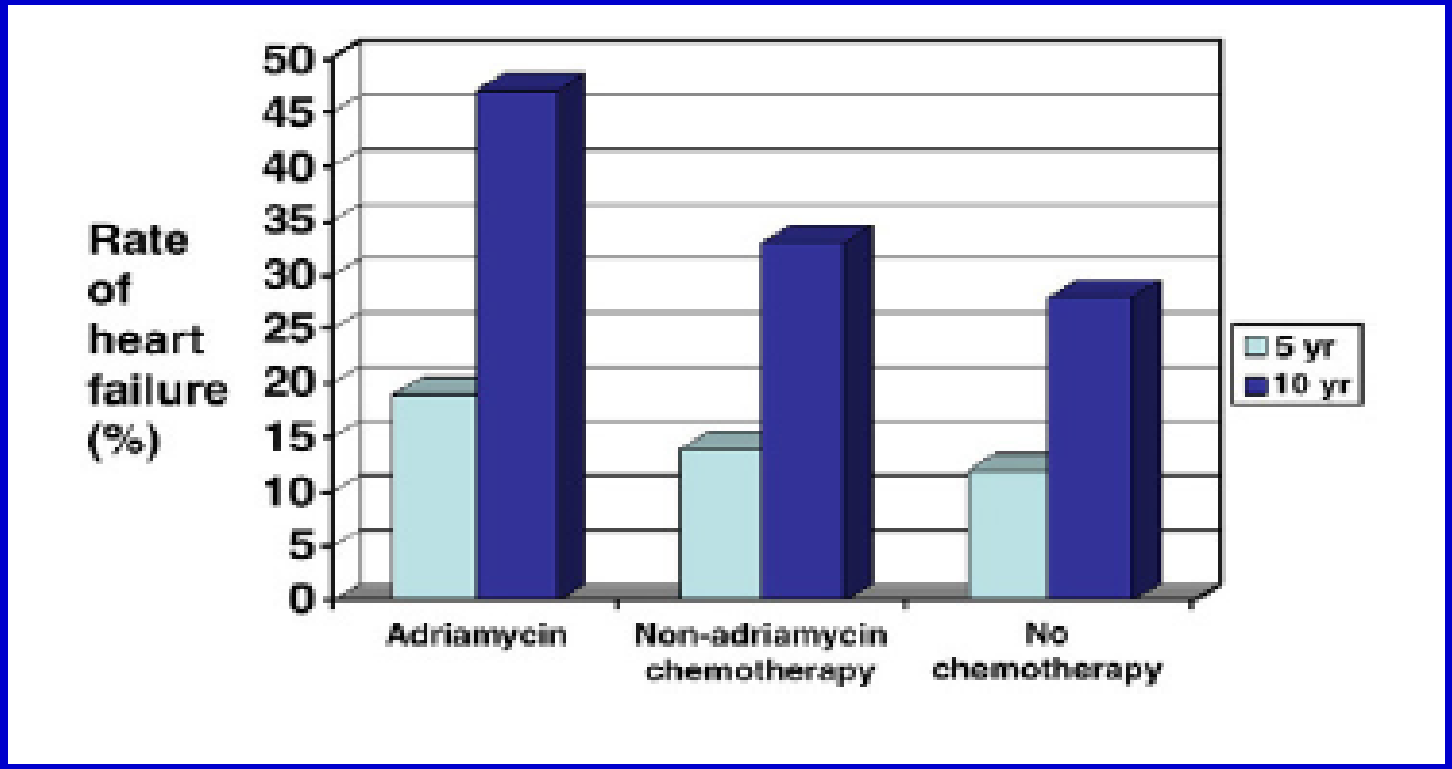
Cardio-Oncology Interactions:

1. Cardiotoxicity following chemotherapy
2. Co existence of cancer and CVD
   Aging & common risk factors

cardiac disease and cancer together make up more than 70% of disease-related mortality in the developed world

Sanz et al. JACC 2007

in elderly breast cancer prevalence of HF is increased substantially compared with the general population



Lindenfeld , Prog Cardiovasc Dis 2010

in breast cancer patients who did not receive chemotherapy, the risk of HF at 5 and 10 years was still twofold and fivefold greater than in the general population.

LONG-TERM TRENDS IN THE INCIDENCE OF AND SURVIVAL WITH HEART FAILURE

TABLE 2. TEMPORAL TRENDS IN AGE-ADJUSTED MORTALITY AFTER THE ONSET OF HEART FAILURE AMONG MEN AND WOMEN 65 TO 74 YEARS OF AGE.*

PERIOD	30-DAY MORTALITY		1-YEAR MORTALITY		5-YEAR MORTALITY	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
	percent (95 percent confidence interval)					
1950–1969	12 (4–19)	18 (7–27)	30 (18–40)	28 (16–39)	70 (57–79)	57 (43–67)
1970–1979	15 (7–23)	16 (6–24)	41 (29–51)	28 (17–38)	75 (65–83)	59 (45–69)
1980–1989	12 (5–18)	10 (4–16)	33 (23–42)	27 (17–35)	65 (54–73)	51 (39–60)
1990–1999	11 (4–17)	10 (3–15)	28 (18–36)	24 (14–33)	59 (47–68)	45 (33–55)

*All values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and ≥85 years).

J Med 2002;347:1397-402

CVD affects survival and QOL independent of a coexisting cancer. Indeed, the prognosis of HF may be more limiting than some cancers. Accordingly, the onset of HF may change the therapeutic priorities of caregivers and patients

Cardiotoxicity of Anticancer Treatments

- Cardiomyopathy
- Vascular injury
  - Ischemia (5-FU, capecitabine, ,bevacizumab)
  - Hypertension (sunitinib, sorafenib, bevacizumab)
- Pericardium- imbalance in fluid equilibrium,pericardial thickening
- Arrhythmias (Arsenic trioxide , paclitaxel ,thalidomide)
- Venous Thromboembolic Disease (cisplatin, thalidomide,erlotinib)
- Cardiovascular toxicity induced by radiotherapy

Type of drug	Prototype	Findings on endomyocardial biopsy (electron microscopy)	Cumulative dose relationship	Reversibility	Associated with increased cardiovascular mortality
Type I	Doxorubicin (anthracycline)	Vacuoles, sarcomere disruption, necrosis	Yes	No (might respond to very early treatment)	Yes
Type II	Trastuzumab (monoclonal antibody)	Benign ultrastructural appearance	No	Yes, in most cases	No

Type I (permanent damage) anticancer agents

- Doxorubicin (anthracycline)
- Daunorubicin (anthracycline)
- Epirubicin (anthracycline)
- Idarubicin (anthracycline)
- Mitoxantrone (anthracenedione)
- Cyclophosphamide (oxazophorine alkylating agent)

Type II (reversible damage) anticancer agents

- Trastuzumab (monoclonal antibody)
- Sunitinib (tyrosine kinase inhibitor)
- Lapatinib (tyrosine kinase inhibitor)

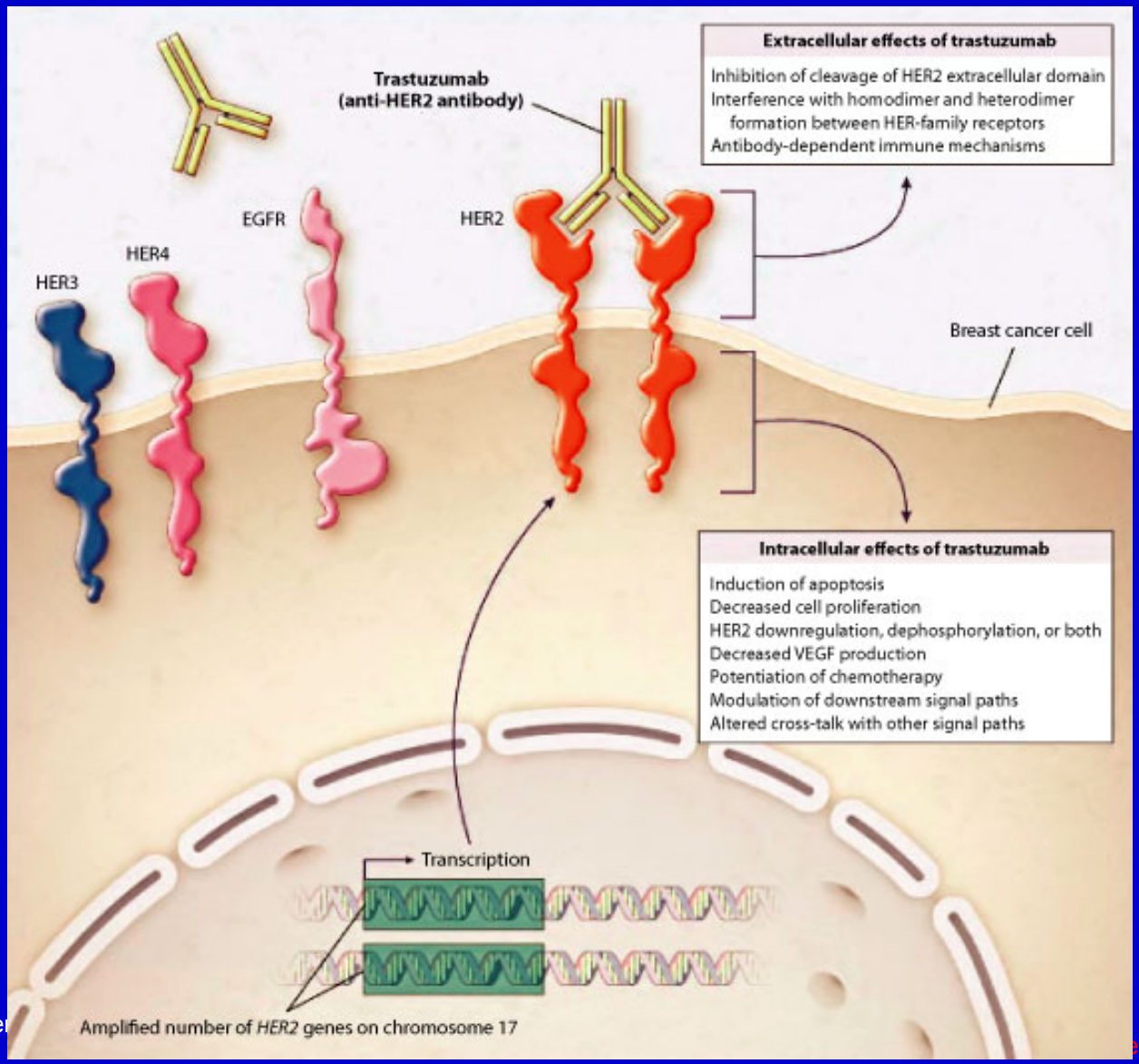
nature REVIEWS CARDIOLOGY

Topics to be discussed

- Trastuzumab-Related Cardiac Dysfunction
- Anthracyclines-Related Cardiac Dysfuntcion
- General Approcach : Cardio-Oncology Collaboration

Trastuzumab (Herceptin) - Related Cardiac Dysfunction

Trastuzumab- Mechanism of Action



Efficacy in Metastatic Breast Cancer (MBC)

TABLE 2. RESULTS OF AN INTENTION-TO-TREAT ANALYSIS OF THE END POINTS.*

END POINT	CHEMOTHERAPY PLUS TRASTUZUMAB (N=235)	EITHER TYPE OF CHEMOTHERAPY ALONE (N=234)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)	PACLITAXEL AND TRASTUZUMAB (N=92)	PACLITAXEL ALONE (N=96)
Median time to disease progression — mo	7.4	4.6	7.8	6.1	6.9	3.0
P value	<0.001		<0.001		<0.001	
Relative risk of progression (95% CI)	0.51 (0.41–0.63)		0.62 (0.47–0.81)		0.38 (0.27–0.53)	
Median time to treatment failure — mo	6.9	4.5	7.2	5.6	5.8	2.9
P value	<0.001		<0.001		<0.001	
Relative risk of treatment failure (95% CI)	0.58 (0.47–0.70)		0.67 (0.52–0.86)		0.46 (0.33–0.63)	
Median survival — mo	25.1	20.3	26.8	21.4	22.1	18.4
P value	0.046		0.16		0.17	
Relative risk of death (95% CI	0.80 (0.64–1.00)		0.82 (0.61–1.09)		0.80 (0.56–1.11)	

N Engl J Med, Vol. 344, No. 11 · March 15, 2001

Adverse Events –MBC

TABLE 4. ADVERSE EVENTS THAT OCCURRED IN MORE THAN 10 PERCENT OF PATIENTS AS A GROUP.*

TYPE OR LOCATION OF ADVERSE EVENT	CHEMOTHERAPY PLUS TRASTUZUMAB (N=234)	CHEMOTHERAPY ALONE (N=230)	AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)	AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=135)	PACLITAXEL AND TRASTUZUMAB (N=91)	PACLITAXEL ALONE (N=95)
	percentage with event (percentage with severe event)					
Any type						
Abdominal pain	27 (3)	20 (3)	23 (2)	18 (2)	34 (3)	22 (4)
Asthenia	57 (7)	56 (7)	54 (7)	55 (7)	62 (8)	57 (8)
Back pain	31 (4)	22 (4)	27 (2)	16 (2)	36 (8)	30 (5)
Chest pain	24 (3)	24 (4)	20 (3)	21 (2)	30 (3)	27 (5)
Chills	38 (<1)	8 (<1)	35 (<1)	11 (2)	42 (1)	4 (0)
Fever	53 (8)	29 (4)	56 (11)	33 (7)	47 (2)	23 (1)
Headache	41 (4)	30 (4)	44 (3)	31 (5)	36 (7)	28 (2)
Heart failure	22 (10)	5 (2)	27 (16)	8 (3)	13 (2)	1 (1)
Digestive tract						
Anorexia	28 (<1)	22 (2)	31 (0)	26 (2)	24 (1)	16 (2)
Constipation	32 (1)	28 (3)	36 (2)	28 (3)	25 (0)	27 (2)
Diarrhea	45 (1)	27 (3)	45 (1)	25 (3)	45 (1)	30 (3)
Nausea	66 (5)	66 (7)	76 (6)	79 (10)	50 (3)	48 (3)
Stomatitis	22 (<1)	21 (0)	30 (1)	31 (3)	10 (0)	7 (0)
Vomiting	47 (5)	40 (7)	53 (3)	49 (8)	37 (9)	28 (5)
Hematologic and lymphatic systems						
Anemia	27 (2)	19 (2)	35 (3)	25 (2)	14 (1)	10 (1)
Leukopenia	41 (11)	26 (9)	52 (15)	33 (11)	24 (6)	17 (5)
Musculoskeletal system						
Arthralgia	20 (4)	14 (2)	8 (<1)	10 (<1)	37 (9)	21 (4)
Myalgia	23 (3)	22 (3)	13 (<1)	13 (<1)	38 (7)	36 (6)
Nervous system						
Paresthesia	29 (<1)	23 (<1)	17 (0)	11 (0)	47 (2)	39 (1)
Respiratory tract						
Increased coughing	43 (<1)	26 (<1)	43 (<1)	28 (0)	42 (0)	22 (1)
Dyspnea not related to heart failure	36 (3)	25 (3)	42 (4)	24 (4)	28 (1)	26 (1)
Pharyngitis	27 (0)	16 (<1)	30 (0)	18 (0)	22 (0)	14 (2)
Skin						
Alopecia	57 (26)	58 (35)	58 (25)	59 (42)	56 (26)	56 (26)
Rash	31 (<1)	17 (<1)	27 (0)	17 (<1)	38 (1)	18 (1)

*The analysis of adverse events excluded five patients who were never treated.

Cardiac Events –MBC

Table 3. Cardiac Events

Event	No. of Patients	%
Total assessable patients	173	
Patients with cardiac event	49	28.3
Asymptomatic decrease of 20 points, > 50%	3	1.7
Grade 2 cardiac toxicity (asymptomatic; LVEF range, 40% to 50%)	27	15.6
Grade 3 cardiac toxicity (symptomatic CHF responsiveto intervention; LVEF range, 20% to 40%)	18*	10.4
Cardiac-related death	1†	0.5

Abbreviations: LVEF, left ventricular ejection fraction; CHF, congestive heart failure.
*13 patients with asymptomatic decrease of LVEF (range, 20% to 40%); 1 patient with CHF with normal LVEF; and 4 patients with symptoms and LVEF > 40%.
†Diagnosed with CHF despite normal LVEF.

Valentina Guarneri, et al . J Clin Onclol 2006

A multivariate analysis showed that in this cohort of patients, a low baseline LVEF was significantly associated with cardiac events (HR, 0.9444; P = .001).

Efficacy and Safety of Trastuzumab in the Adjuvant Setting

Design of adjuvant trials using trastuzumab

Trial (number of patients)	Treatment arms	Definition of severe cardiotoxicity	Monitoring frequency
NSABP B-31[1] (n = 2030)	AC x4, Pacli x4, then observation AC x4, followed by Pacli x4 with concurrent tras x1y	Grade III/IV HF or cardiac death; or LVEF decrease >15 points*	MUGA 3 weeks, 6 months, and 9 months after end of initial AC, and 3 months after last trastuzumab
NCCTG N9831 [1] (n = 3505)	AC x4, Pacli x12w, then observation AC x4, Pacli x12w with concurrent tras x1y AC x4, Pacli x12w, followed by tras x1y	Grade III/IV HF or cardiac death; or LVEF decrease >15 points*	MUGA or Echo at entry, after AC, and 6, 9, 18, and 21 months after entry
HERA[2] (n = 5090)	Any CT regimen, then observation Any CT regimen, then tras x1y Any CT regimen, then tras x2y	Severe HF; symptomatic HF; or LVEF decrease >10 points*	LVEF (Echo or MUGA) at baseline, 3, 6, 12, 18, 24, 30, 36, 60 months
BCIRG-006[3] (n = 3222)	AC x4, Doce x4, then observation AC x4, followed by Doce x4 with concurrent tras x1y DoceCarbo x6 with concurrent tras x1y	Grade III/IV HF; cardiac death; grade 3-4 arrhythmias; grade 3-4 ischemia/infarction; or LVEF decrease >10 points*	After AC, after second dose of docetaxel, at end of CT, and 3, 12, and 36 months after randomization
FinHer[4] (n = 232)•	DoceVnb x3, then CEF x3 DoceVnb x3 + Tras x9w, then CEF x3	Myocardial infarction; HF; or LVEF decrease >15 points	Echo or MUGA before CT, after CEF, and 12 and 36 months after CT

Overall in The Adjuvant Treatment:

- **Severe HF (NYHA III/IV) :**
- Trastuzumab-treated pts up to 3.9 %
- Not trastuzumab tx pts up to 1.3 %

- **Decline in EF of 10-15% or greater* ‡**
- Trastuzumab-treated pts 3-34%
- Not trastuzumab tx pts 2-17%

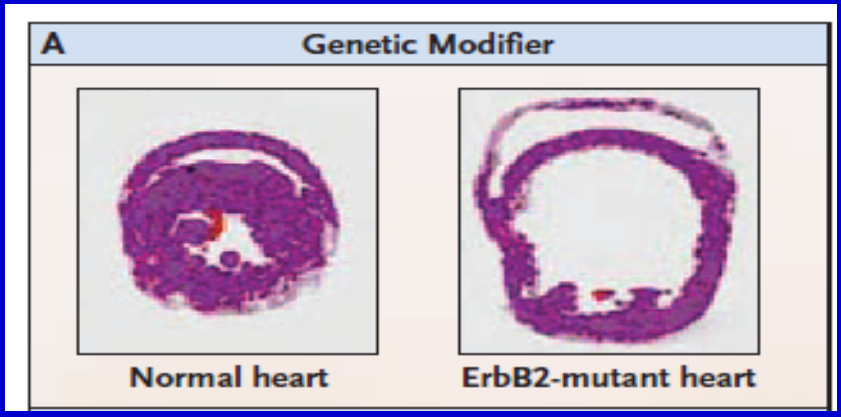
- *This excludes the FinHER trial, in which a decline in ejection fraction occurred more frequently in patients not receiving trastuzumab
- ‡ was mostly reversible

Risk Factors for Cardiotoxicity

- Previous or concurrent anthracycline use
- Age greater than 50 years
- Preexisting cardiac dysfunction
- High body mass index

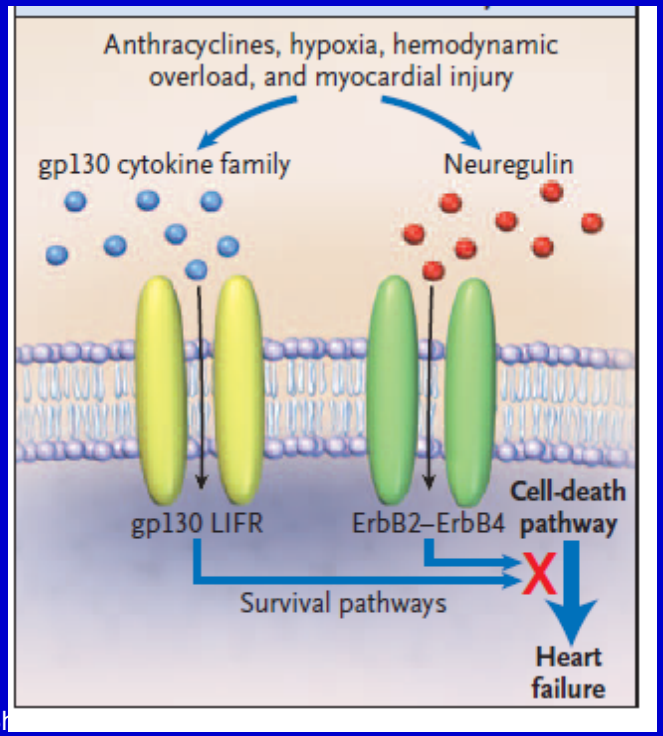
- **<u>Does not increase the risk :</u>**
- Adjuvant radiation therapy
- Diabetes
- Valvular heart disease
- Coronary artery disease

Proposed Mechanism of Cardiac Dysfunction



Murine experiments have shown that the ERB2 receptor plays a crucial role in cardiogenesis and when not present in the heart, the resulting lack of signaling leads to either in-utero death or early severe dilated cardiomyopathy.

O¨zcelik et al. PNAS, 2002



Trastuzumab, by inhibiting the ErbB2 receptor, leads to a loss of the neuregulin-dependent pathways that result in the survival of cardiac myocytes.

Chien et al . NEJM , 2006

The evaluation of left ventricular function for patients being considered for, or receiving Trastuzumab (Herceptin) therapy

KF Fox*,1

British Journal of Cancer 2006

1. The NICE have recently extended their guidance on indications for Trastuzumab. As part of the care of patients considered for Trastuzumab pre-treatment measurement of LV function is required and 3 monthly during treatment according to most protocols. This is because of the known potential for cardiac damage occurring in patients receiving Trastuzumab.
2. Although local guidelines may vary, current guidelines typically state that patients should not normally be commenced on Trastuzumab if their baseline Ejection Fraction (EF) is $\leqslant 55\%$. If the EF falls by more than 10% or to $<50\%$ cessation of treatment should be considered.

Heart Failure Treatment

- Trastuzumab-related cardiotoxicity usually responds to standard medical treatment for heart failure and discontinuation of trastuzumab in most, although not all, patients .

Reversibility & Rechallenge

- Trastuzumab-related cardiotoxicity is largely reversible in the majority of cases, and treatment continuation and/or resumption of trastuzumab after resolution of cardiac abnormalities may be safe in some women

Practical Approach

Table 3
Practical approach used at the Abramson Cancer Center for the management of cardiac dysfunction in patients receiving adjuvant Trastuzumab

Treatment phase	Patient profile	Management strategy
Before trastuzumab-based therapy	A. No cardiac history or risk factors with normal LVEF	Treat and monitor LVEF every 3 months
♠	B. Cardiac history and/or risk factors with normal LVEF	Treat. Ask about symptoms and perform thorough PE before each cycle Measure troponin level after therapy and BNP level before next cycle
	C. Decreased LVEF	Teat low EF (ACE-I or ARB, BB) and remeasure Individual decisions about initiating trastuzumab
During trastuzumab-based therapy	First decrease in LVEF	Trastuzumab holiday for 1 mo A. Treat HF and remeasure 1. Return to baseline. Restart trastuzumab 2. Remains low: intensify HF treatment and remeasure. 3. If LVEF remains low: individual decisions
♣	Second decrease in LVEF	A Stop trastuzumab B If trastuzumab only option: "Holiday" and maximize HF Rx
Completion of trastuzumab-based therapy	No change in LVEF and no symptoms during treatment	No monitoring post treatment completion
	LVEF decreased or symptoms	Continue HF treatment Monitor according to clinical practice for HF
♠		

J.R. Carver / Progress in Cardiovascular Diseases 53 (2010) 130–139

Before Trastuzumab-Based Therapy ♠

Treatment phase	Patient profile	Management strategy
Before trastuzumab-based therapy	A. No cardiac history or risk factors with normal LVEF	Treat and monitor LVEF every 3 months
	B. Cardiac history and/or risk factors with normal LVEF	Treat. Ask about symptoms and perform thorough PE before each cycle Measure troponin level after therapy and BNP level before next cycle
	C. Decreased LVEF	Teat low EF (ACE-I or ARB, BB) and remeasure Individual decisions about initiating trastuzumab

During Trastuzumab-Based Therapy ♣

During trastuzumab-based therapy	First decrease in LVEF	Trastuzumab holiday for 1 mo A. Treat HF and remeasure 1. Return to baseline. Restart trastuzumab 2. Remains low: intensify HF treatment and remeasure. 3. If LVEF remains low: individual decisions
	Second decrease in LVEF	A Stop trastuzumab B If trastuzumab only option: "Holiday" and maximize HF Rx

Completion of Trastuzumab-Based Therapy

Completion of trastuzumab-based therapy	No change in LVEF and no symptoms during treatment	No monitoring post treatment completion
	LVEF decreased or symptoms	Continue HF treatment Monitor according to clinical practice for HF

Anthracyclines Cardiotoxicity

DAUNOMYCIN, AN ANTITUMOR ANTIBIOTIC, IN THE TREATMENT OF NEOPLASTIC DISEASE

Clinical Evaluation with Special Reference to Childhood Leukemia

CHARLOTTE TAN, MD, HIDEKO TASAKA, MD, KOU-PING YU, MD, M. LOIS MURPHY, MD, AND DAVID A. KARNOFSKY, MD

Daunomycin is a new antibiotic in the anthracycline group obtained from Streptomyces peucetius. It consists of a pigmented aglycone (daunomycinone) in glycoside linkage with an amino sugar (daunosamine). Differences in the biological effects of daunomycin, which reacts with DNA, and actinomycin D which complexes with DNA in a different manner to inhibit RNA production, are discussed. The toxic effects of daunomycin are a severe local reaction if the drug extravasates, bone marrow depression resulting in leucopenia, anemia, thrombocytopenia and bleeding, fever, oral ulcers and alopecia. In patients receiving maintenance doses of daunomycin the development of tachypnea, tachycardia pulmonary insufficiency, heart failure and hypotension possibly is associated with daunomycin but the evidence is unclear. Sixty per cent of children with leukemia obtained brief complete or partial hematological remissions from a single course of daunomycin. The remission could be prolonged by maintenance therapy. Daunomycin is temporarily effective in some cases of neuroblastoma, reticulum cell sarcoma and rhabdomyosarcoma.

Cancer *March* 1967

Acute and sub-acute cardiotoxicity are rare
ECG changes

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Cancer *March* 1967

Irreversible CMP

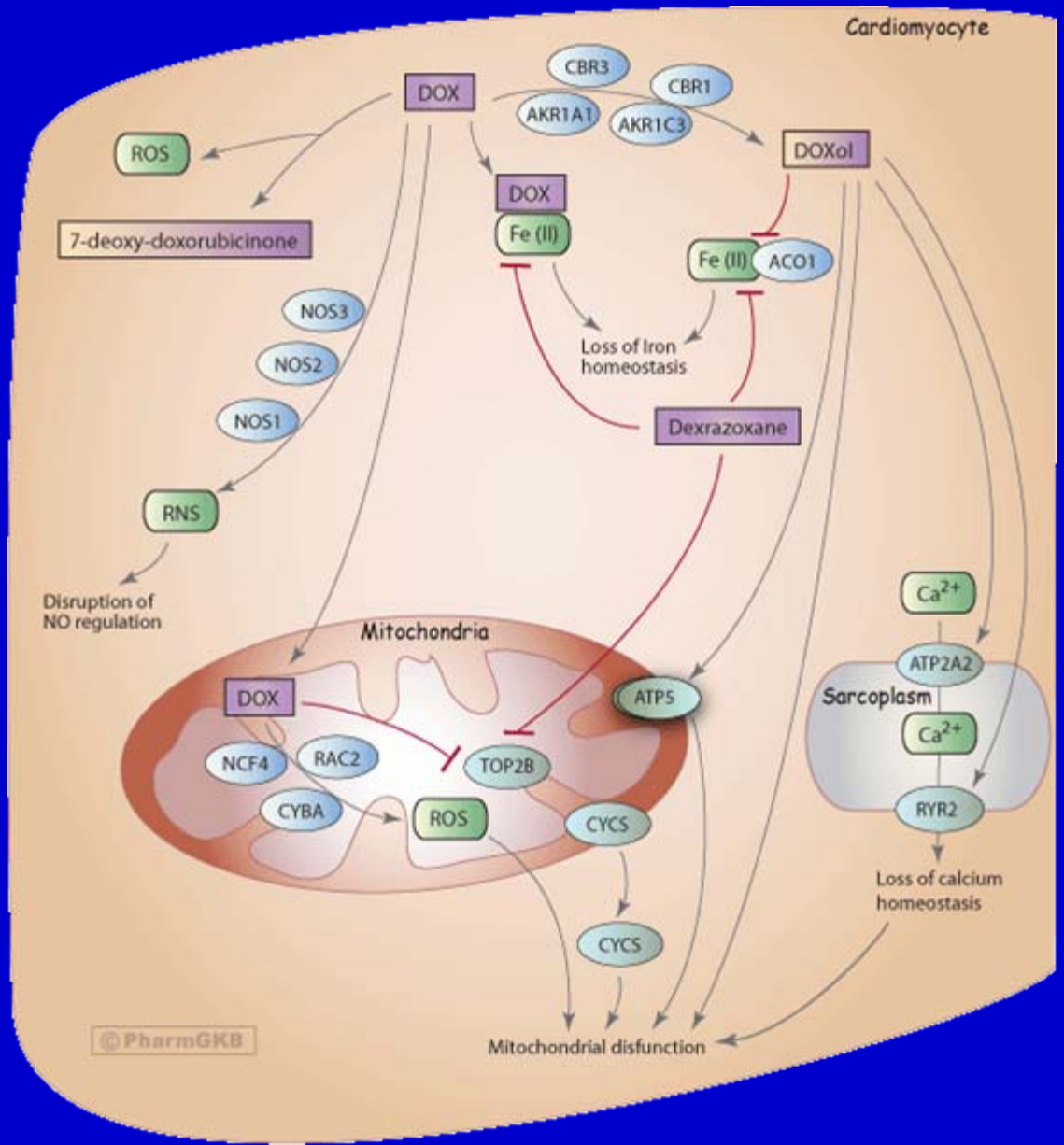
Acute and sub-acute cardiotoxicity are rare

ECG changes

Frequency of Cardiotoxicity

- Doxorubicin- 3% at 400 mg/m^2, 7% at 500 mg/m2 and 18% at 700 mg/m^2.
- Epirubicin - less cardiotoxic -up to 900 mg/m^2 before cardiotoxicity limits further therapy.
- However, it tends to be given at 25-50% higher to achieve similar anticancer benefit.
- There is considerable variation between patients in their susceptibility to anthracycline-induced cardiotoxicity

Cardiotoxicity- Mechanism



Risk Factors

- Age (young children and the elderly)
- Chest wall radiation
- Female
- Use in combination with other potentially cardiotoxic antineoplastic agents
- Previous CVD
- HTN

Prevention

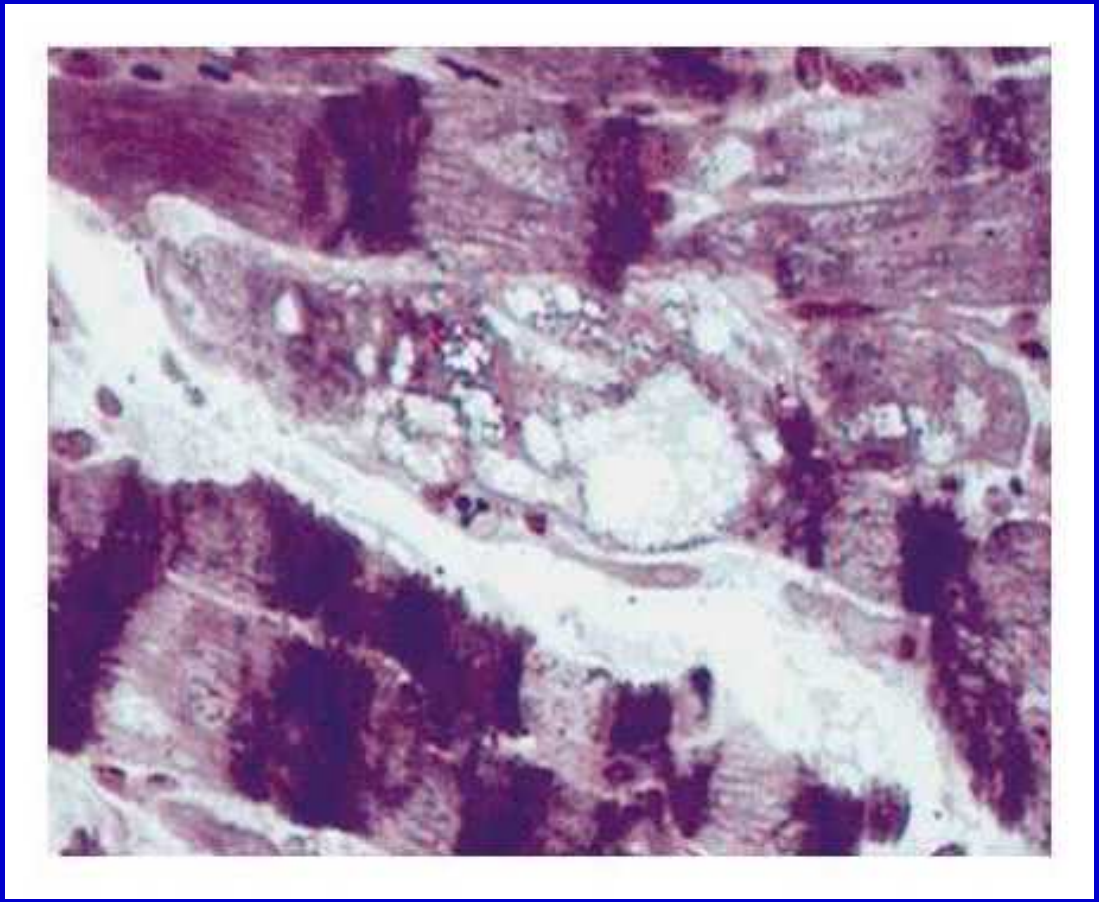
- ***Monitoring !***
- Total cumulative anthracycline dose
- New anthracycline analogues
- Protracted infusions
- Drug formulations (liposome encapsulation)
- Concomitant protective drugs
- Adequate selection of patients

Monitoring & Follow Up

- No clear guidelines from any expert group on the frequency or optimal method of LVEF assessment, or the best parameter to follow .
- Echo
- Radionuclide angiogrpahy (first pass or MUGA)
- C-MRI ? !

Cardiac Biopsy

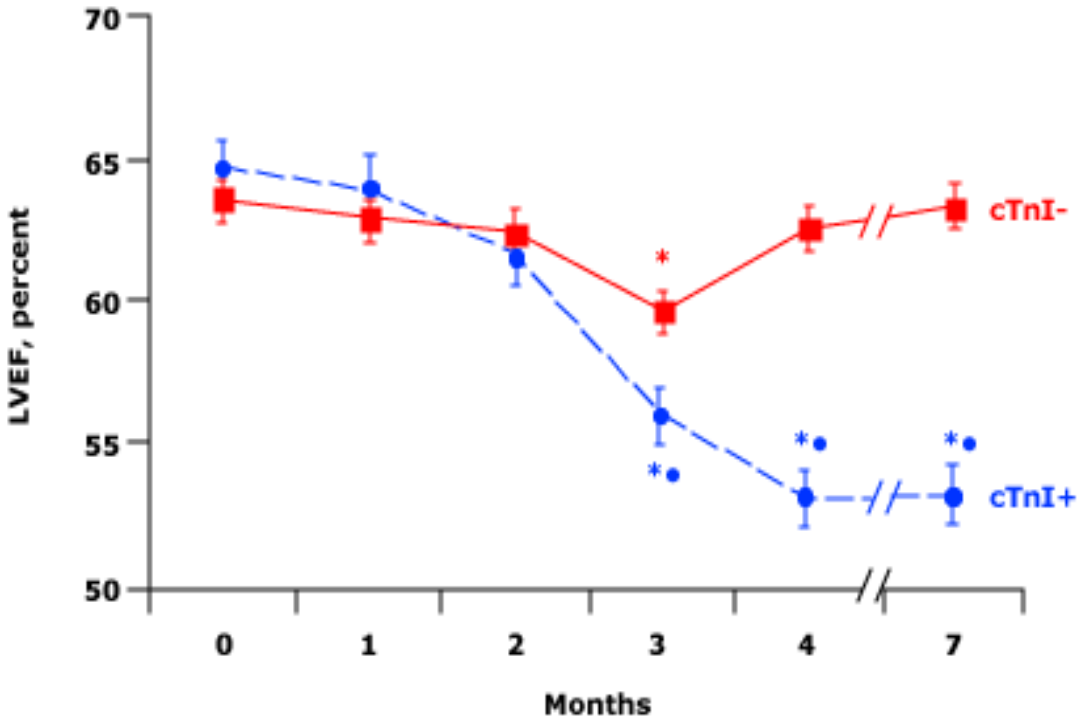
- *loss of myofibrils and the vacuolization of cytoplasm characteristic of doxorubicin induced myopathy*



Cardiac Biomarkers

- A decrease in LVEF - a marker of advanced damage
- Early indication of cardiac damage and increased risk for a cardiac event:
- **Serum troponins** :
- elevations in troponin I may be an early marker of acute myocardial injury .
- **BNP**

Cardiac troponins predict left ventricular dysfunction from chemotherapy



204 pts

TnI after every single cycle of HDC

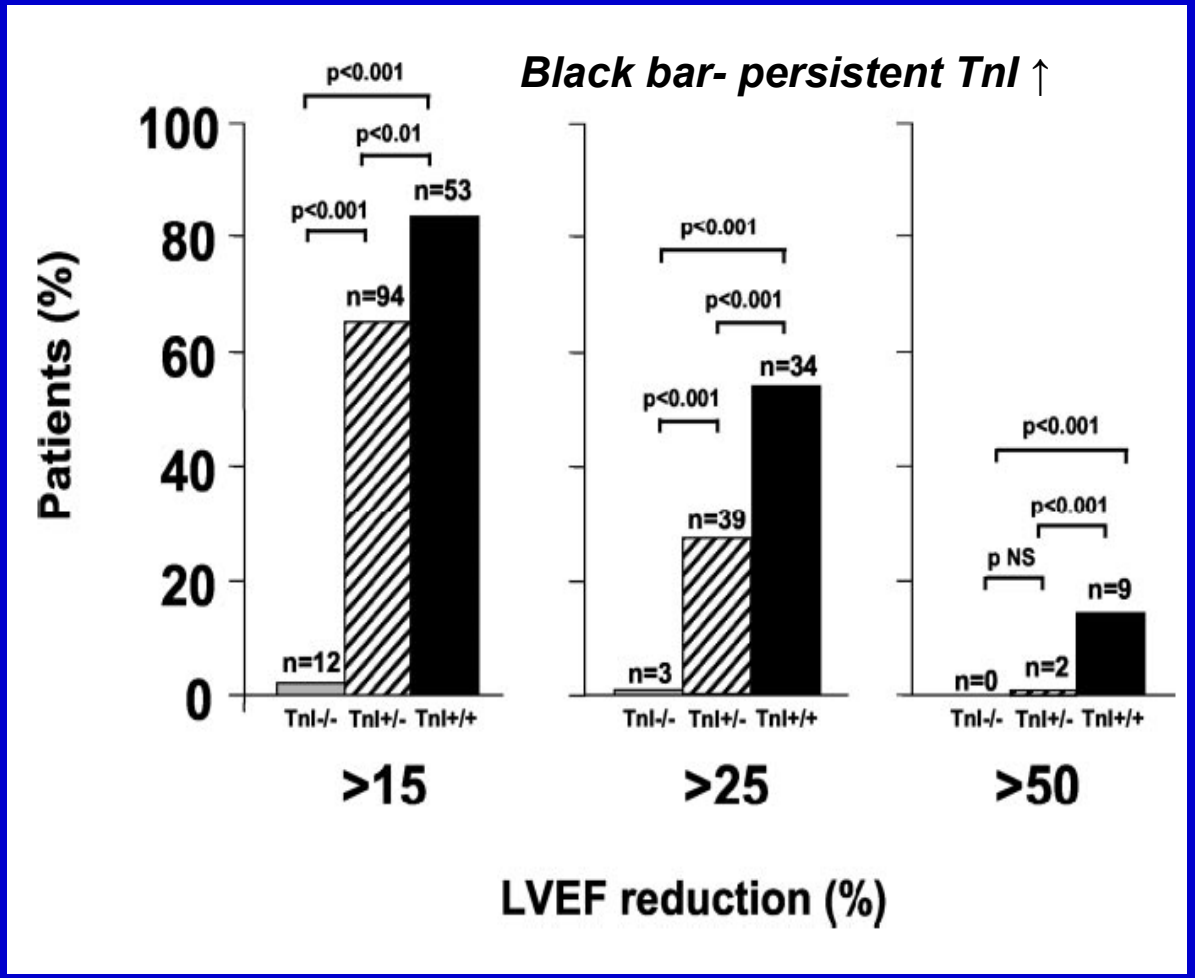
echo -7 m

in the cTnI+ group LVEF reduction was more marked and still evident at the end of the follow-up

Cardinale et al. J Am Coll Cardiol 2000

Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

Daniela Cardinale, MD; Maria T. Sandri, MD; Alessandro Colombo, MD; Nicola Colombo, MD; Marina Boeri, MD; Giuseppina Lamantia, MD; Maurizio Civelli, MD; Fedro Peccatori, MD; Giovanni Martinelli, MD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD



703 cancer pts
TnI soon after CT (early TnI)
1 month later (late TnI)

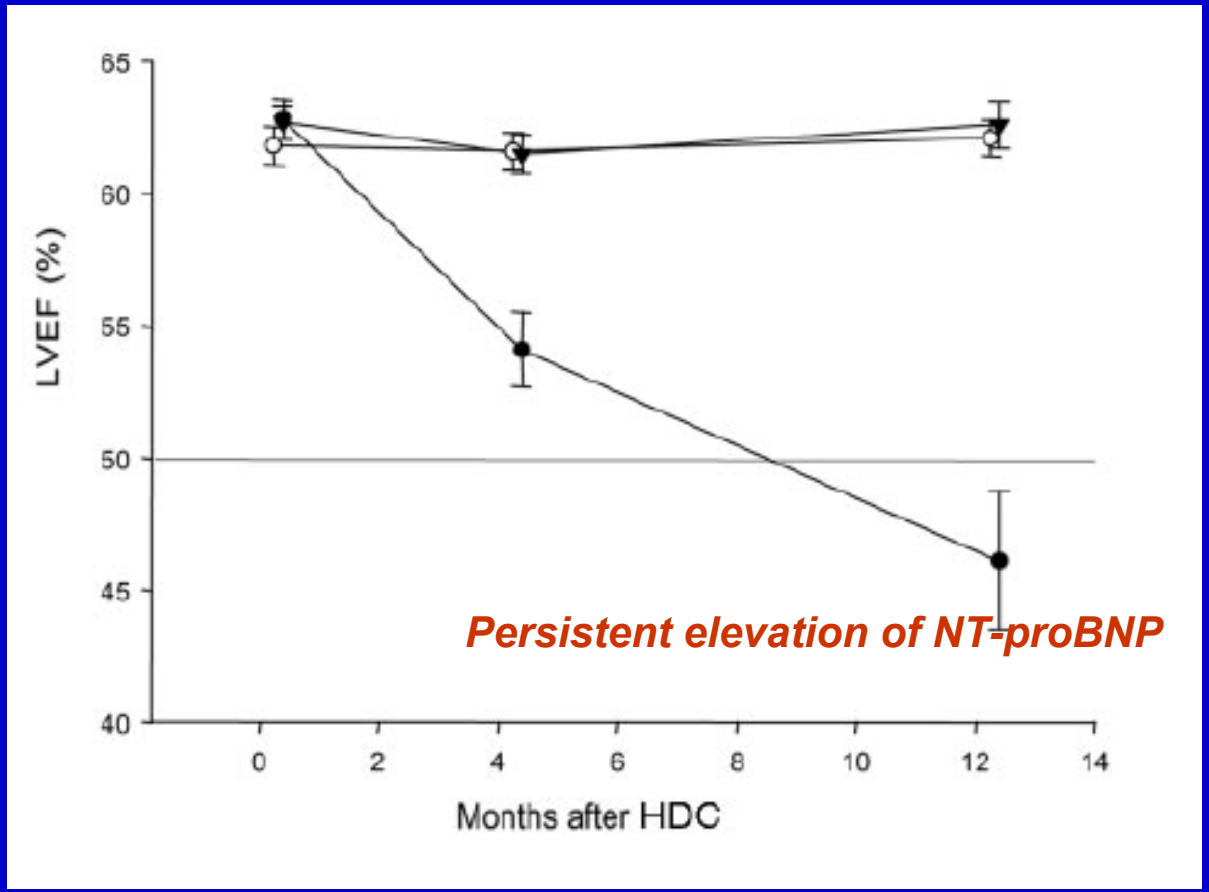
Echo
0,1m,2m,6m,12m,18m,24m

f/u 20 m

Circulation. 2004;109:2749-2754

N-Terminal Pro-B-Type Natriuretic Peptide after High-Dose Chemotherapy: A Marker Predictive of Cardiac Dysfunction?

Maria T. Sandri,[1*] Michela Salvatici,[1] Daniela Cardinale,[2] Laura Zorzino,[1] Rita Passerini,[1] Paola Lentati,[1] Maria Leon,[3] Maurizio Civelli,[2] Giovanni Martinelli,[4] and Carlo M. Cipolla[2]



52 pts
NT-proBNP measurements:
0, 12h,36h,72h,
echo 1 y

Conclusions: **Persistently ↑NT-proBNP early after administration of HDC is strongly associated with development of cardiac dysfunction.**

Clinical Chemistry 51, No. 8, 2005

Cardiac Monitoring

Anthracycline cumulative dose (mg/m^2*)	Pre-treatment	During treatment	At end of treatment	First year following treatment	Years 2–5 following treatment	>Year 5 following treatment
<200	Yes	As clinically indicated	Yes	Follow-up at 1 year	Follow-up at 2 years and at 5 years	As clinically indicated
200–300	Yes	After 200 mg/m^2	Yes	Follow-up at 6 months and at 1 year	Follow-up at 2 years, 3 years and at 5 years	As clinically indicated
300–400	Yes	After 200, 300 and 350 mg/m^2	Yes	Follow-up at 6 months and at 1 year	Follow-up annually	Follow-up every 2 years
>400	Yes	After 200, 300, 350 and 400 mg/m^2	Yes	Follow up at 3 months, 6 months and at 1 year	Follow-up annually	Follow-up annually

*Cumulative doses are given for doxorubicin; for mitoxantrone multiply dose by 0.2, for epirubicin and liposomal preparations multiply dose by 1.5.

For patients at increased cardiac risk, a more aggressive monitoring schedule is appropriate

nature REVIEWS CARDIOLOGY

FDA-approved Labeling Guidelines for Adriamycin

- In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function.
- The benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage.

Prevention

- Monitoring !
- Total cumulative anthracycline dose
- New anthracycline analogues
- Protracted infusions
- Drug formulations (liposome encapsulation)
- Concomitant protective drugs
- Adequate selection of patients

Reduced Cardiotoxicity of Doxorubicin by a 6-Hour Infusion Regimen

A Prospective Randomized Evaluation

J. SHAPIRA, MD, M. GOTFRIED, MD, M. LISHNER, MD, AND M. RAVID, MD

TABLE 1. Doxorubicin Cardiotoxicity: Comparison Between Standard Short Infusion and 6-Hour Infusion*

Doxorubicin infusion	No. of patients	Age (yr)	Doxorubicin total dose (mg/m^2)	LVEF			QRS in standard leads percent of change (range)	CHF
				Initial	After 300 mg/m^2 doxorubicin	Percent of change (range)		
15–20 mins 8 am	28	55 ± 14	410 ± 42	0.6 ± 0.03	0.48 ± 0.05	−17 ± 5 (−7 to −35)	−29 ± 7 (−22 to −68)	4
360 mins 8 am–2 pm	30	53 ± 12	428 ± 48	0.61 ± 0.03	0.58 ± 0.05	−4 ± 6 (+5 to −15)	−5 ± 8 (+28 to −47)	0

LVEF: left ventricular ejection fraction; CHF: congestive heart failure. * All values are given as mean ± standard deviation.

Cancer 65:870–873, 1990.

DEXRAZOXANE

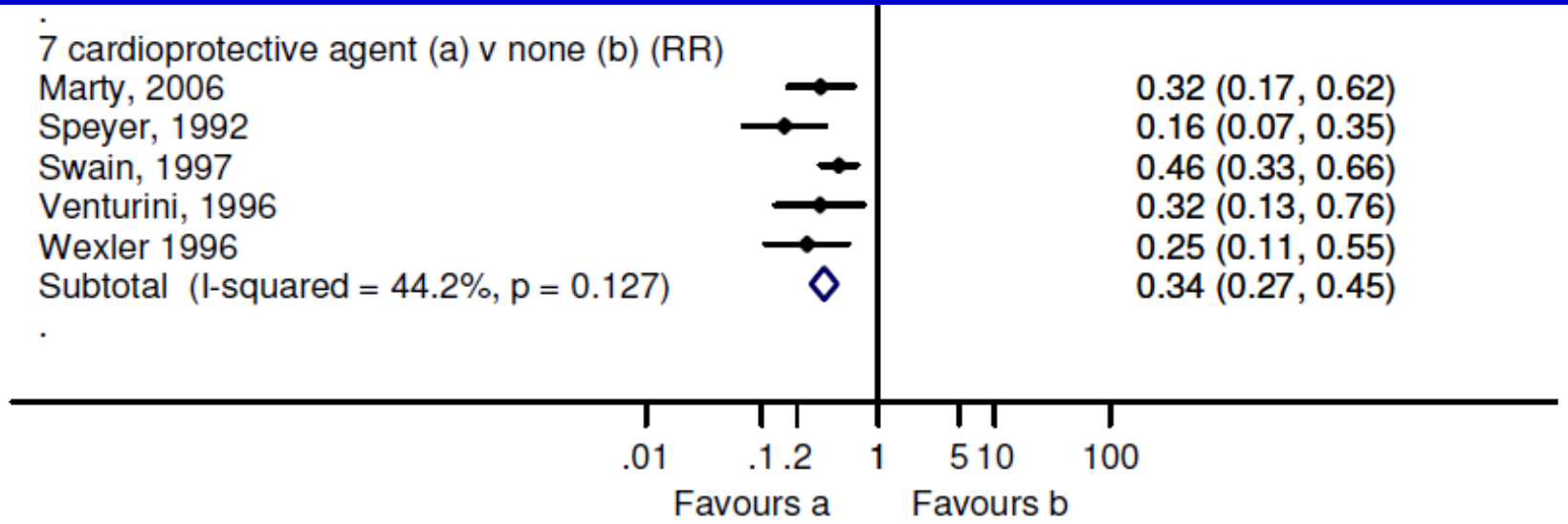


Figure 4 Clinical and subclinical cardiotoxicity in RCTs where cardiotoxicity outcomes could not be categorised as one or the other. The open diamond represents the pooled Peto Odds Ratio and 95% CI for treatment comparisons 1, 2 and 4, and relative risk (RR) with 95% CI for comparisons 5-7. I-squared represents the proportion of variability between studies in excess of that expected due to chance, and p = probability that differences between study estimates are due to chance.

Smith *et al. BMC Cancer* 2010, **10**:337

Liposomal Doxorubicin

- non-pegylated liposomal doxorubicin (Myocet)
- pegylated liposomal doxorubicin (Caelyx, Doxil)

Treatment

- Prevention
  - Beta blockers
  - ACEI
- Cardiomyopathy
  - Beta blockers
  - ACEI
  - Withdrawl
  - Reversibility ? (!)

Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy

Nihat Kalay, MD,* Emrullah Basar, MD,* Ibrahim Ozdogru, MD,* Ozlem Er, MD,†
Yakup Cetinkaya, MD,* Ali Dogan, MD,* Tugrul Inanc, MD, Abdurrahman Oguzhan, MD,*
Namik Kemal Eryol, MD,* Ramazan Topsakal, MD,* Ali Ergin, MD*

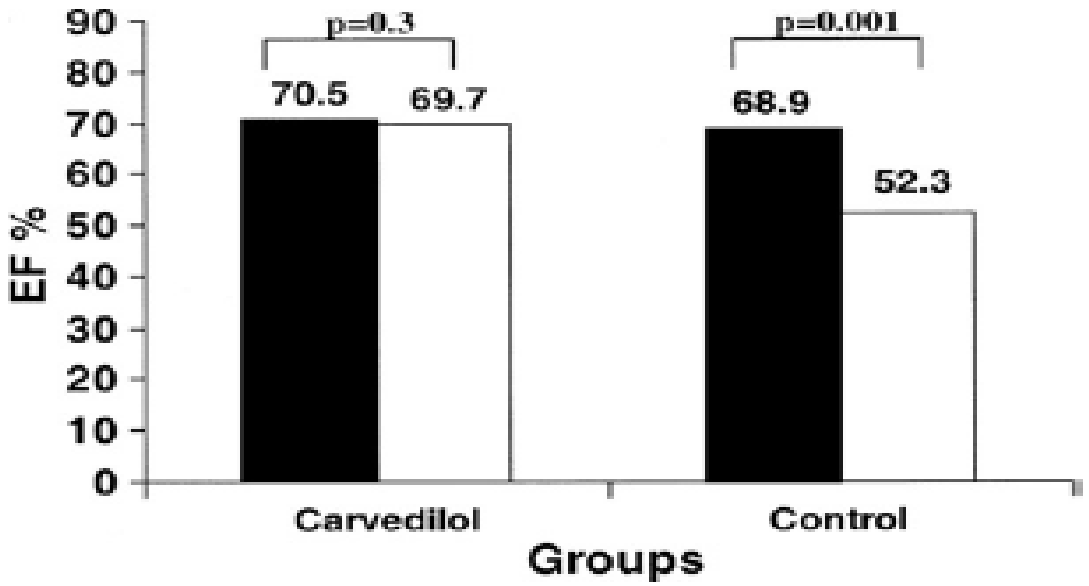


Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline **(black bars)** and after chemotherapy **(white bars)** in the 2 groups. Data expressed as mean values.

ANT therapy , carvedilol vs placebo

25 pts, 12.5 mg

f/u 6 m

Echo baseline , 6m

J Am Coll Cardiol 2006;48:2258–62

Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

Daniela Cardinale, MD; Alessandro Colombo, MD; Maria T. Sandri, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Maurizio Civelli, MD; Giovanni Martinelli, MD; Fabrizio Veglia, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

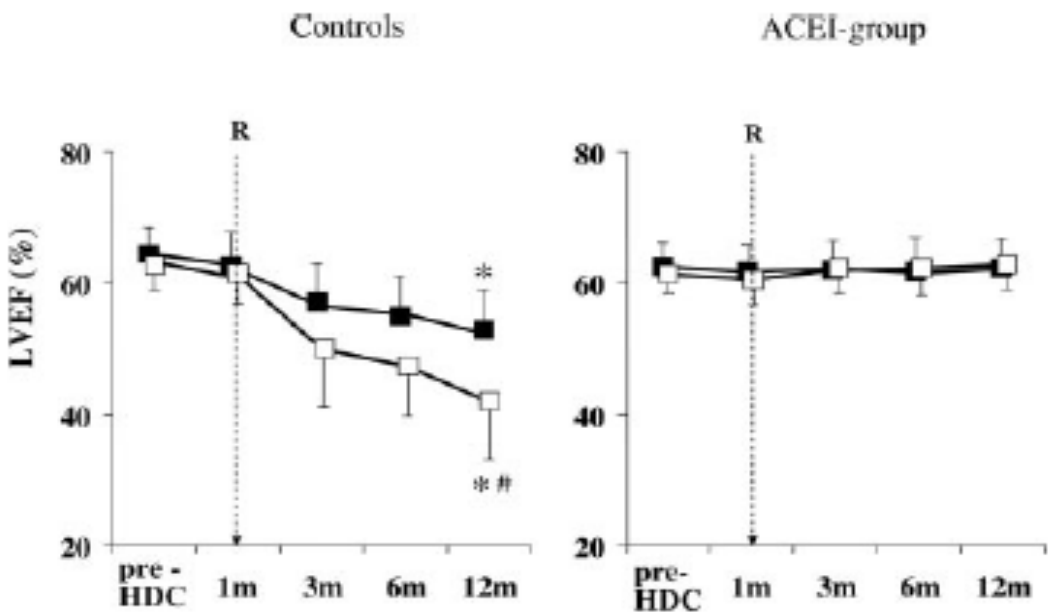


Figure 1. LVEF at baseline and during the 12-month follow-up in control subjects (left) and the ACEI group (right) in patients with (□) or without (■) persistent TnI increase. For treatment effect, $P<0.001$; for effect of persistent TnI increase, $P<0.001$; for interaction between treatment and persistent TnI increase, $P<0.001$. R indicates randomization. *$P<0.001$ vs baseline and randomization for all time points; #$P<0.001$ vs patients without persistent TnI increase.

114 pts HDC
Early TnI ↑
ACEI (enalapril 20 mg); placebo
f/u 12 m

Circulation. 2006;114:2474-2481

Treatment

- Prevention
  - Beta blockers
  - ACEI
- Cardiomyopathy
  - Beta blockers
  - ACEI
  - Withdrawl
  - Reversibility ? (!)

Treatment of CT-induced CMP

Author	Journal	Year	N. pts	Therapy
Lefrak	Cancer	1973	2	Digitalis + Diuretics
Cohen	Arch Intern Med	1982	1	Digitalis + Diuretics
Haq	Cancer	1985	43	Digitalis + Diuretics
Saini	Ann Intern Med	1987	3	ACEI
Jensen	Lancet	1996	8	ACEI
Fazio	Clin Cardiol	1998	1	Beta-Blockers
Noori	J Card Fail	2000	10	ACEI + Beta-Blockers
Jensen	Ann Oncol	2002	10	ACEI
Mucai	Intern Med	2004	5	Beta-blockers
Tallaj	Heart Lung Transplant	2005	25	ACEI + Beta-blockers
Ajijola	Am J Cardiol	2008	4	ACEI + Beta-blockers
		Total	**112**	

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Heart Failure

CME

Anthracycline-Induced Cardiomyopathy

Clinical Relevance and Response to Pharmacologic Therapy

Daniela Cardinale, MD, PHD,* Alessandro Colombo, MD,* Giuseppina Lamantia, MD,* Nicola Colombo, MD,* Maurizio Civelli, MD,* Gaia De Giacomi, MD,* Mara Rubino, MD,† Fabrizio Veglia, PHD,† Cesare Fiorentini, MD,† Carlo M. Cipolla, MD*

Milan, Italy

- 201 pts with AC-induced CMP (baseline LVEF 37±28 %)
- 148 women (74%)
- mean follow-up: 36±27 months (range 12-96)
- enalapril (36%); enalapril +carvedilol(71%)
- Responders:LVEF ≥50% from baseline
- Partial Responders:LVEF <50% +10 abs. points
- Non Responders:LVEF <50% <10 abs. points

Clinical characteristics of the three study groups.

	Responders (n=85; 42%)	Partial Responders (n=26; 13%)	NON Responders (n=90; 45%)	P
Age (yrs)	52±12	53±12	54 13	0.36
Women	65 (776)	21 (81%)	63 (70%)	0.48
Hypertension	27 (32%)	6 (23%)	24 (27%)	0.96
Diabetes	5 (6%)	2 (8%)	10 (11%)	0.49
Hypercolesterolemia	6 (7%)	3 (11%)	10 (11%)	0.59
Current or past smokers	32 (38%)	10 (38%)	33 (37%)	0.98
Family history of CAD	11 (13%)	5 (19%)	10 (11%)	0.53
NYHA class III-IV	11 (13%)	18 (69%)	24 (27%)	<0.001
LVEF before AC therapy	62 4	60 4	60 4	0.16
LVEF before HF therapy	41 5	28 4	38 7	<0.001
Time-To-HF-Treatment (months)	2 (1-3)	4 (2-6)	17 (8-36)	<0.001
HF therapy				
Enalapril e Carvedilol	67 (78%)	13 (50%)	49 (54%)	0.001
Diuretics	21 (25%)	18 (69%)	49 (50%)	<0.001
Amiodarone	0 (0%)	4 (9%)	8 (9%)	0.001
Anticoagulants	1 (1%)	2 (8%)	5 (6%)	0.15
Cumulative AC dose (mg/mq)	301 124	341 130	222 150	0.24
Creatinine clearance (ml/min)	106 42	107 42	95 27	0.18
Mean follow-up duration (months)	34 26	46 30	36 27	0.10
Cancer death during follow-up	23 (27%)	9 (35%)	30 (33%)	0.60

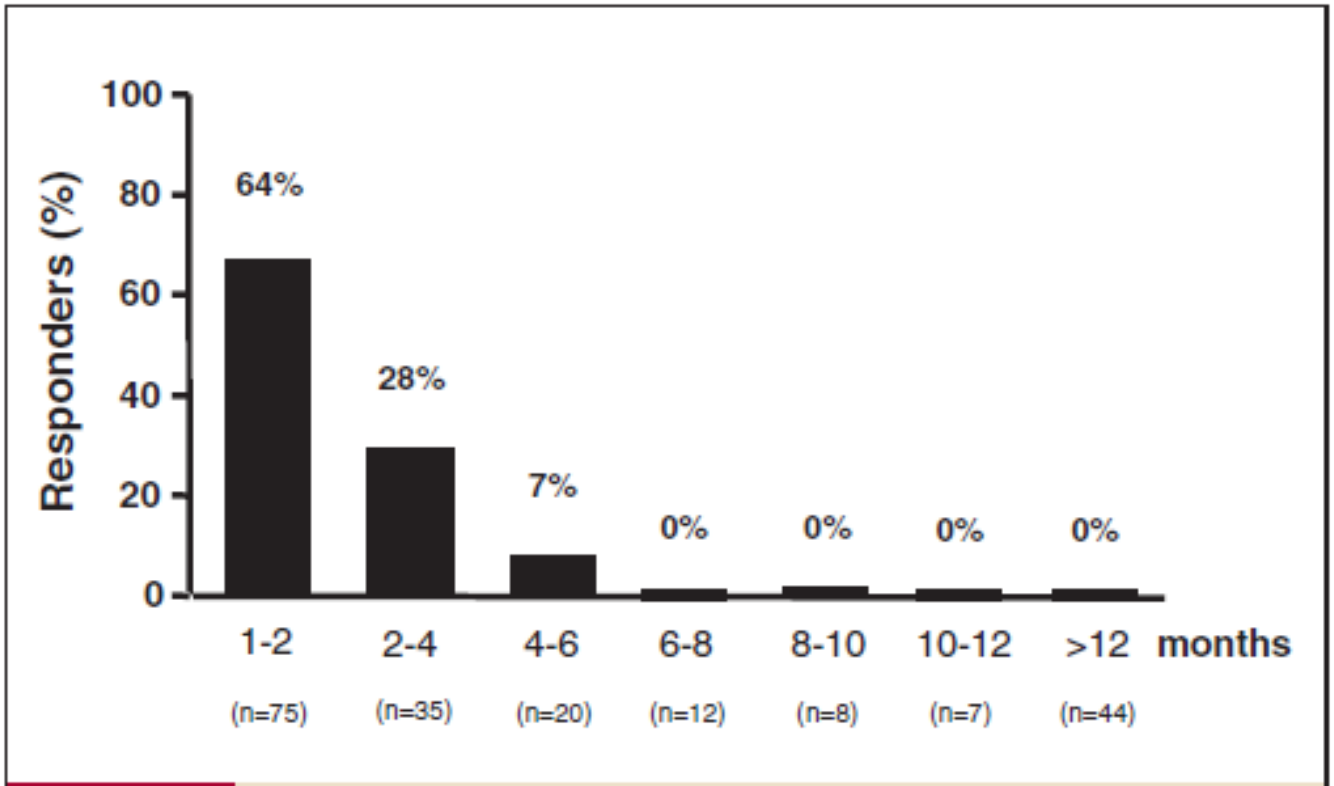
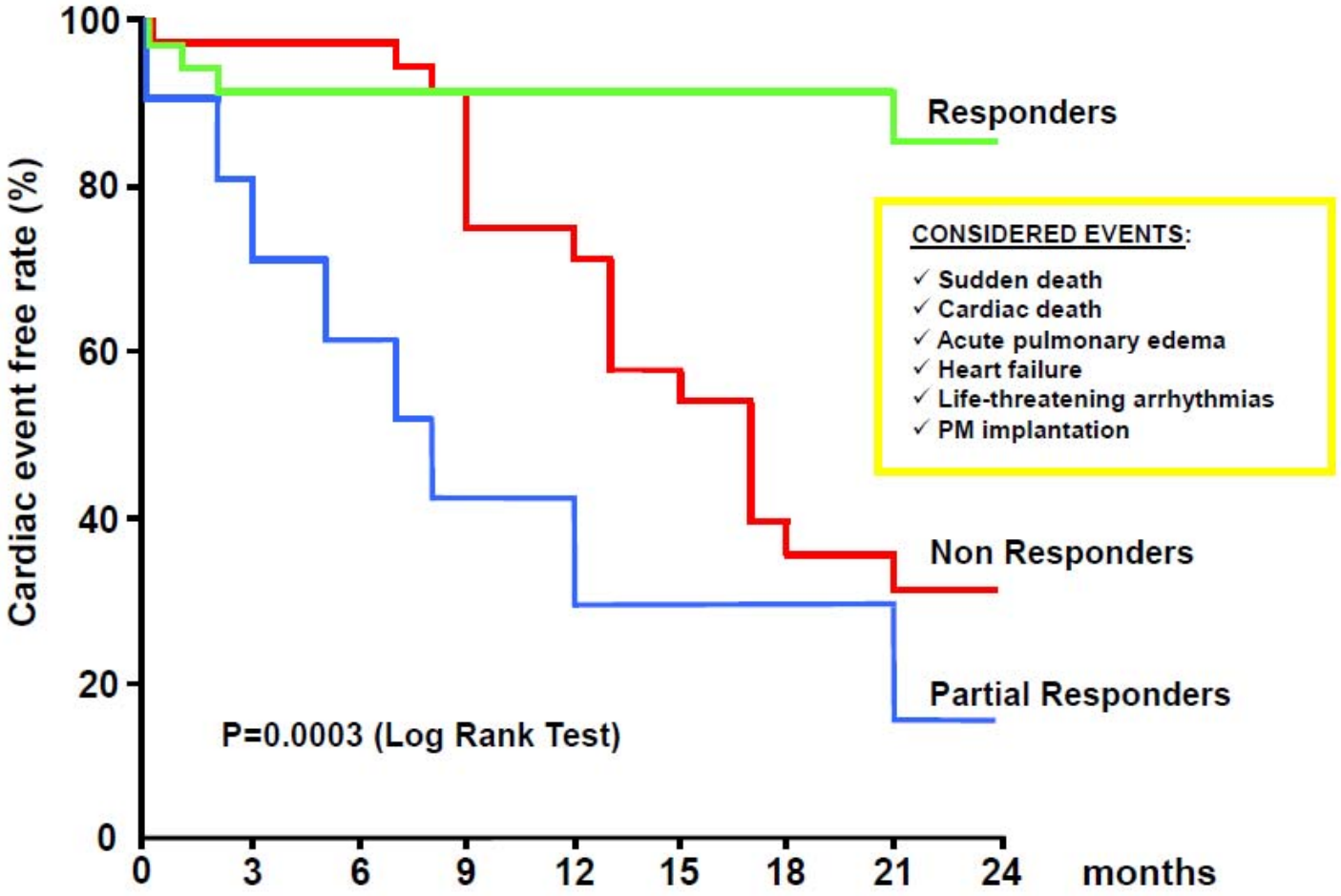


Figure 1 **Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy**

AC = anthracyclines; HF = heart failure.

The more time passes, the less is the possibility of recovery

Cumulative cardiac events during study follow-up.



Under Investigation:

Erythropoietin improves myocardial performance in doxorubicin-induced cardiomyopathy

European Heart Journal (2006)

Saher Hamed[1], Iris Barshack[1], Galia Luboshits[1], Dov Wexler[1], Varda Deutsch[2], Gad Keren[1], and Jacob George[1*]

The protective roles of nitric oxide and superoxide dismutase in adriamycin-induced cardiotoxicity

Cardiovascular Research 69 (2006)

Marsha P. Cole [a], Luksana Chaiswing [b,c], Terry D. Oberley [b], Stephanie E. Edelmann [d], Michael T. Piascik [d], Shu-Mei Lin [a], Kinsley K. Kiningham [e], Daret K. St. Clair [a,*]

Adenosine A_3 receptor-mediated cardioprotection against doxorubicin-induced mitochondrial damage

Biochemical Pharmacology 79 (2010) 180–187

Avishag K. Emanuelov [a], Asher Shainberg [a], Yelena Chepurko [b], Doron Kaplan [c], Alex Sagie [d], Eyal Porat [d], Michael Arad [e], Edith Hochhauser [b,*]

Phospholipase C-δ1 Is a Critical Target for Tumor Necrosis Factor Receptor–Mediated Protection against Adriamycin-Induced Cardiac Injury

Yu-Chin Lien,[1] Teresa Noel,[1] Hua Liu,[2,4] Arnold J. Stromberg,[2,4] Kuey-Chu Chen,[3,4] and Daret K. St. Clair[1]

Cancer Res 2006

Phosphodiesterase-5 Inhibition With Sildenafil Attenuates Cardiomyocyte Apoptosis and Left Ventricular Dysfunction in a Chronic Model of Doxorubicin Cardiotoxicity

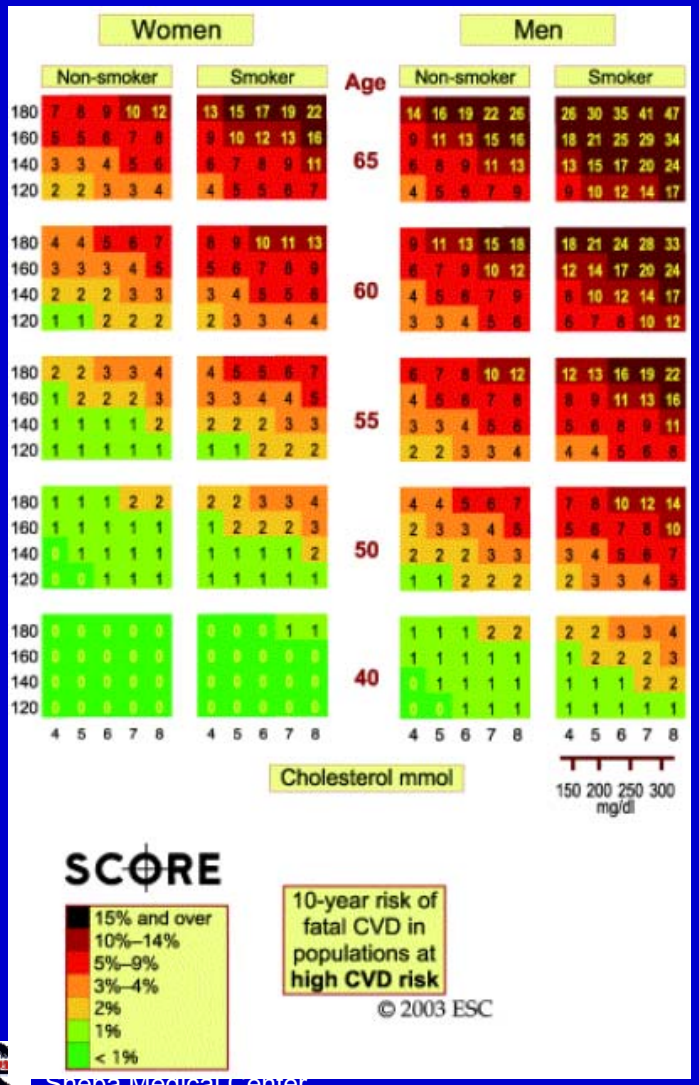
Patrick W. Fisher, DO; Fadi Salloum, BS; Anindita Das, PhD; Haroon Hyder, MD; Rakesh C. Kukreja, PhD

Circulation April 5, 2005

General Approach

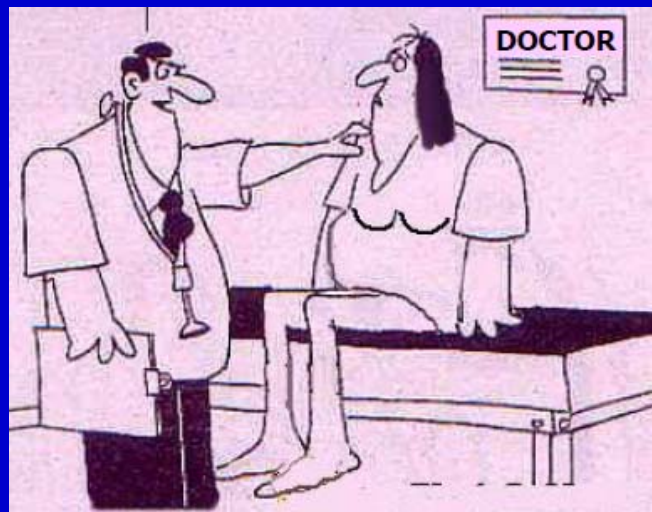
Cardio-Oncology Collaboration

New cardiologic approach ?



-sex
-age
-family history for CAD
-smoking
-hypertension
-diabetes
-dyslipidemia
-obesity
-sedentariness

-chemotherapy !



Chemotherapy as CV risk factor !!

Treatment-Specific Risks of Second Malignancies and Cardiovascular Disease in 5-Year Survivors of Testicular Cancer

Purpose
To compare radiotherapy and chemotherapy effects on long-term risks of second malignant neoplasms (SMNs) and cardiovascular diseases (CVDs) in testicular cancer (TC) survivors.

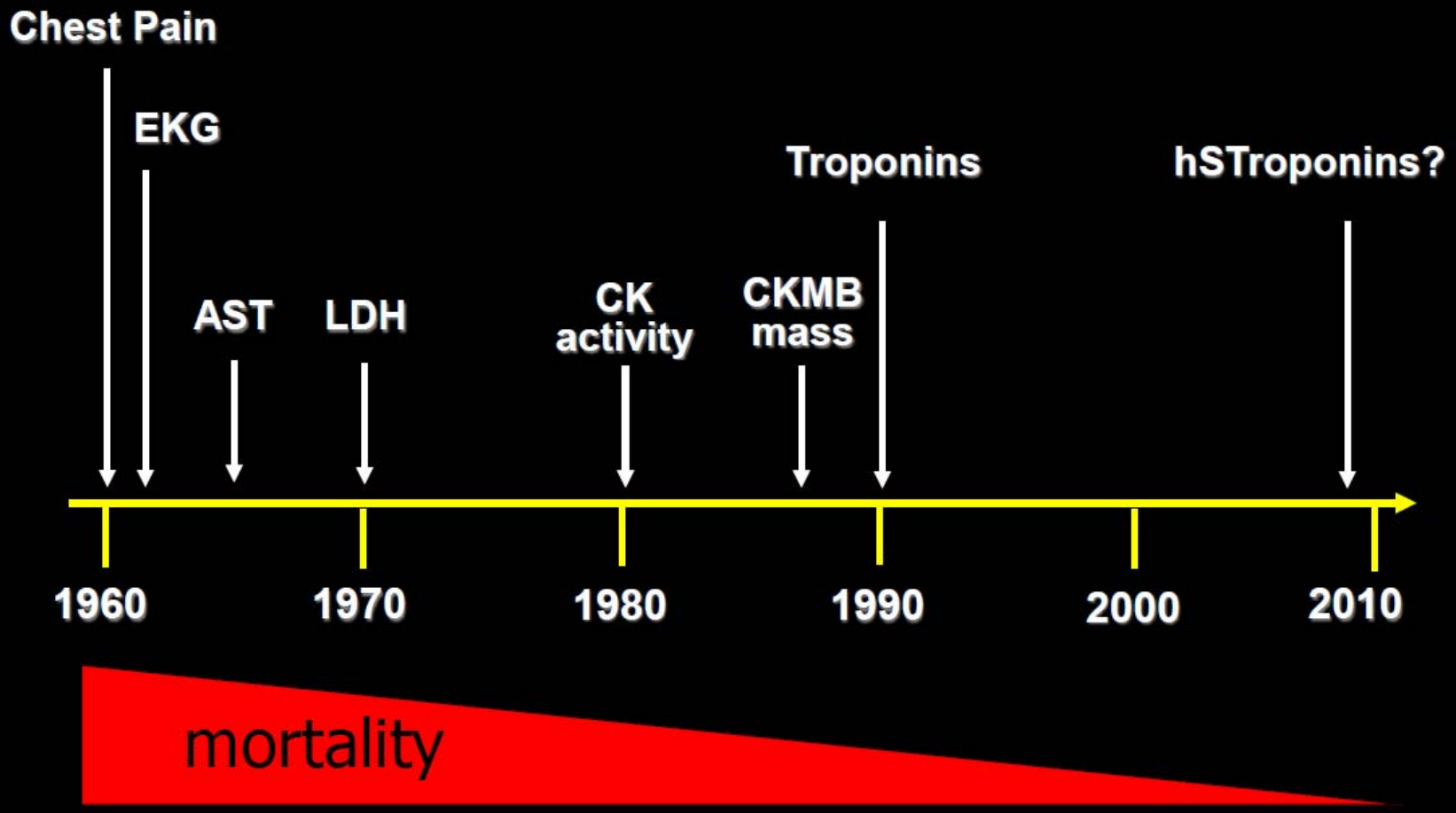
Patients and Methods
In our nationwide cohort comprising 2,707 5-year TC survivors, incidences of SMNs and CVDs were compared with general-population rates by calculating standardized incidence ratios (SIRs) and absolute excess risks (AERs). Treatment effects on risks of SMN and CVD were quantified in multivariable Cox regression and competing risks analyses.

Results
After a median follow-up time of 17.6 years, 270 TC survivors developed SMNs. The SIR of SMN overall was 1.7 (95% CI, 1.5 to 1.9), with an AER of 32.3 excess occurrences per 10,000 person-years. SMN risk was 2.6-fold (95% CI, 1.7- to 4.0-fold) increased after subdiaphragmatic radiotherapy and 2.1-fold (95% CI, 1.4- to 3.1-fold) increased after chemotherapy, compared with surgery only. Subdiaphragmatic radiotherapy increased the risk of a major late complication (SMN or CVD) 1.8-fold (95% CI, 1.3- to 2.4-fold), chemotherapy increased the risk of a major late complication 1.9-fold (95% CI, 1.4- to 2.5-fold), and smoking increased the risk of a major late complication 1.7-fold (95% CI, 1.4- to 2.1-fold), compared with surgery only. The median survival time was 1.4 years after SMN and 4.7 years after CVD.

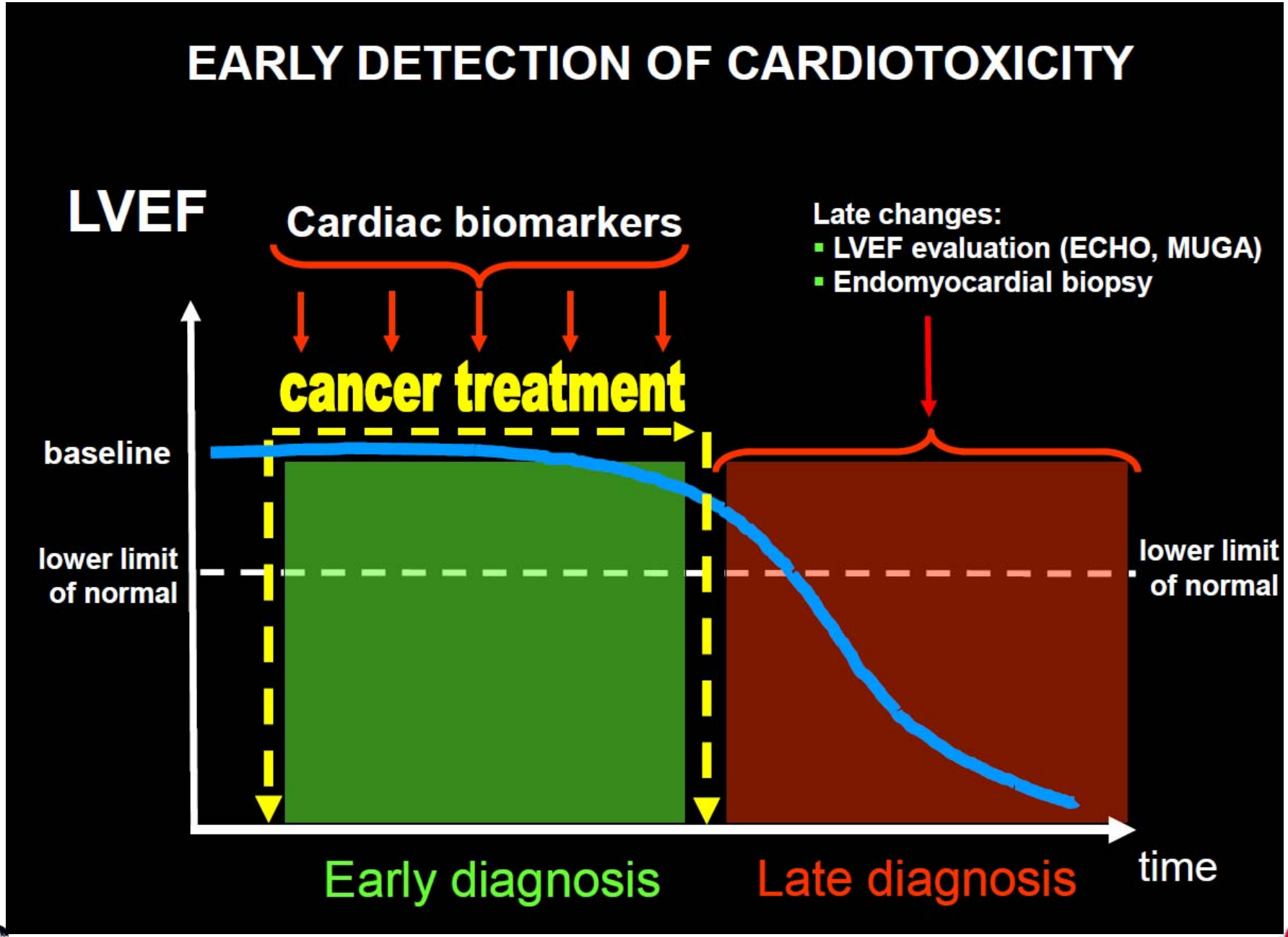
Conclusion
Radiotherapy and chemotherapy increased the risk of developing SMN or CVD to a similar extent as smoking. Subdiaphragmatic radiotherapy strongly increases the risk of SMNs but not of CVD, whereas chemotherapy increases the risks of both SMNs and CVDs. Prolonged follow-up after chemotherapy is needed to reliably compare the late complications of radiotherapy and chemotherapy after 20 years.

Van den Belt-Dusebout et al. J Clin Oncol 2007

Diagnosis of Acute Myocardial Infarction



EARLY DETECTION OF CARDIOTOXICITY



Conclusions

- Cardiotoxicity and increased CV risk are potentially serious complications of chemotherapy.

- Cardiotoxicity is becoming increasingly important in the modern medical practice in parallel with the ever-expanding number of treated cancer patients and growing complexity and toxicity of oncologic treatments

Conclusions

- Cardiologists should be involved early in the management of cancer patients eligible for antitumoral treatment in joint collaboration with oncologists.

- Guidelines regarding cardiotoxicity should be updated by oncologists and cardiologists together, in order to optimize the management of cancer patients, and improve both oncologic and cardiologic outcome.

INTERNATIONAL

CardiOncology

SOCIETY

January 2009: The International CardiOncology Society is born.

Thank you four your attention !!!