Chemotherapy-induced cardiotoxicity: Is it reversible?

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Presenter Disclosure Information

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FINANTIAL DISCLOSURE: None

UNLABELED/UNAPPROVED USES DISCLOSURE: None

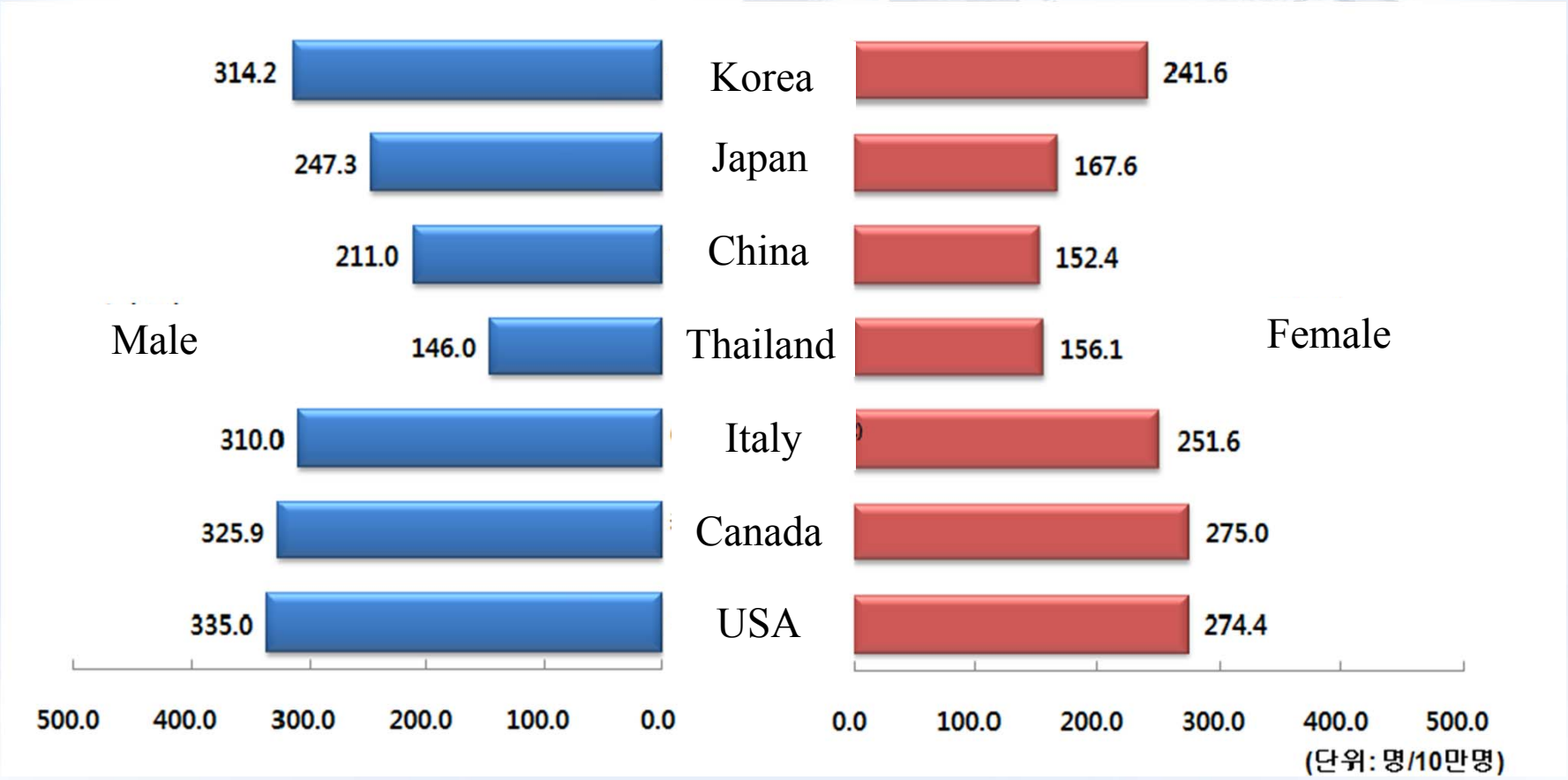
Question

How much interest do you have in the treatment of cardiovascular complications of cancer patients?

1. High interest 2. Low interest 3. None

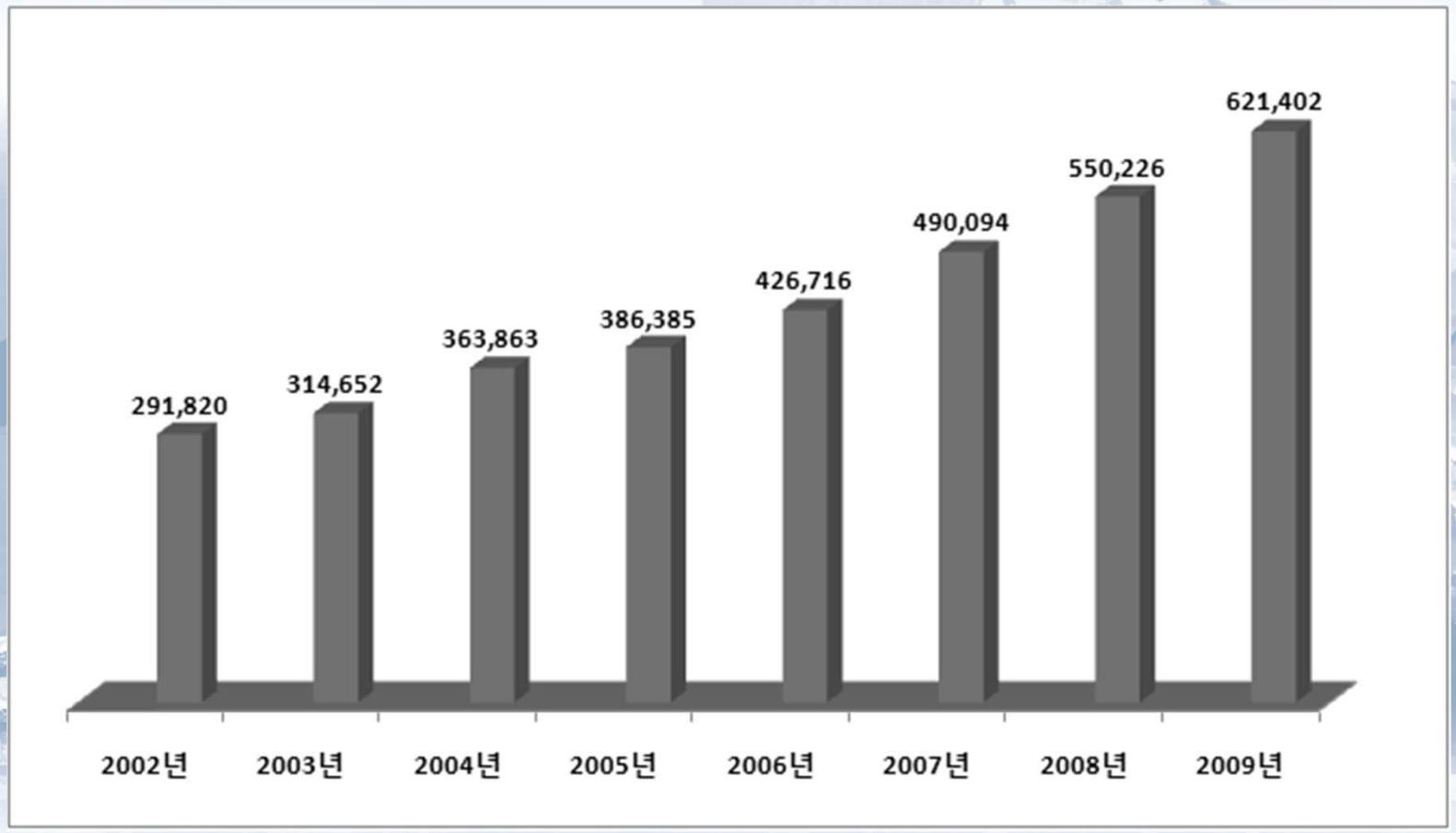
A small number of patients were involved.
Cancer patients have a short life expectancy.
It is an oncologist's business, not the cardiologist's.

Age- and gender-standardized cancer incidence in 2008



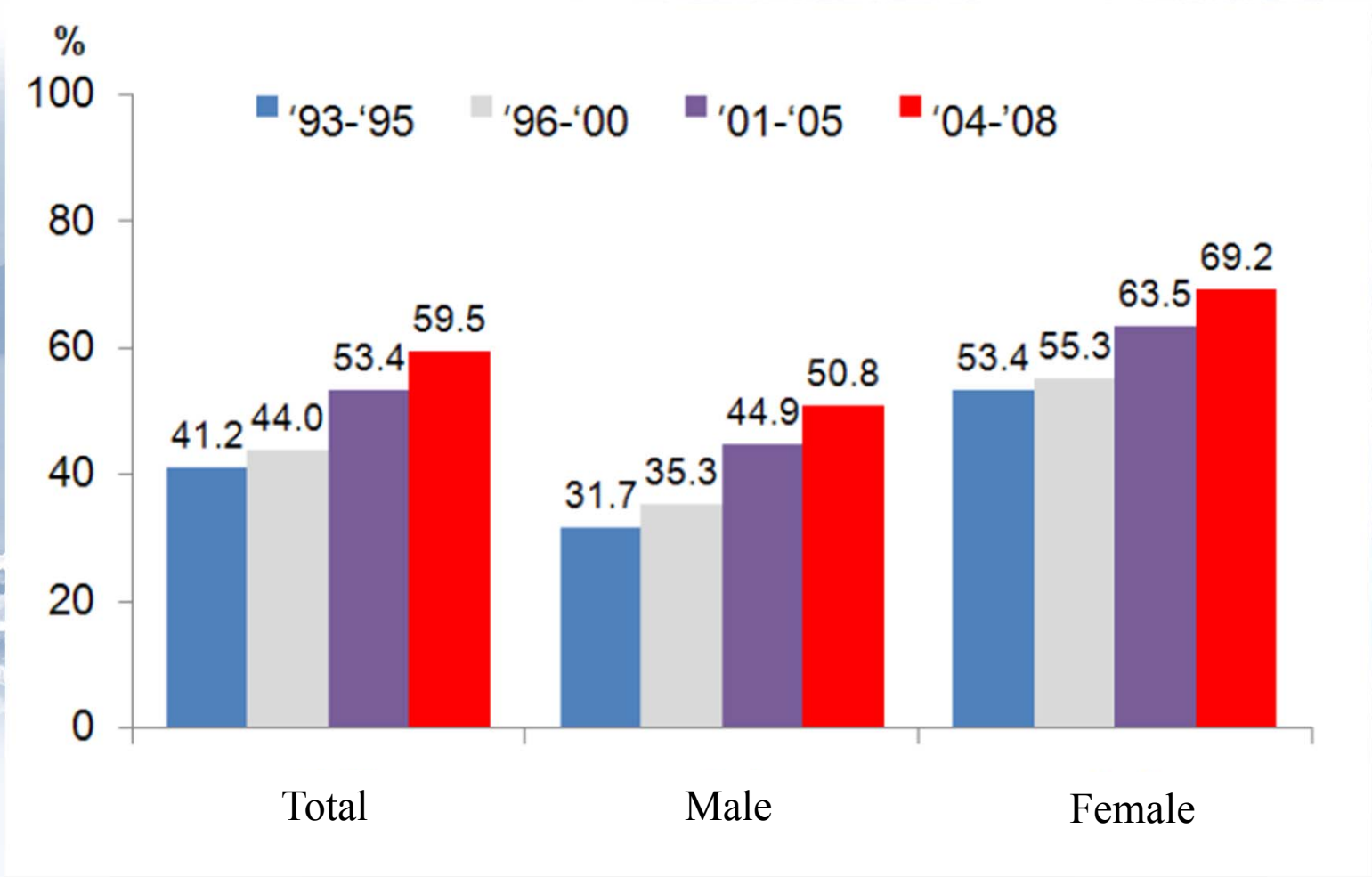
GLOBOCAN 2008, IARC Press, Lyon, 2010

Total number of cancer patients treated in hospital

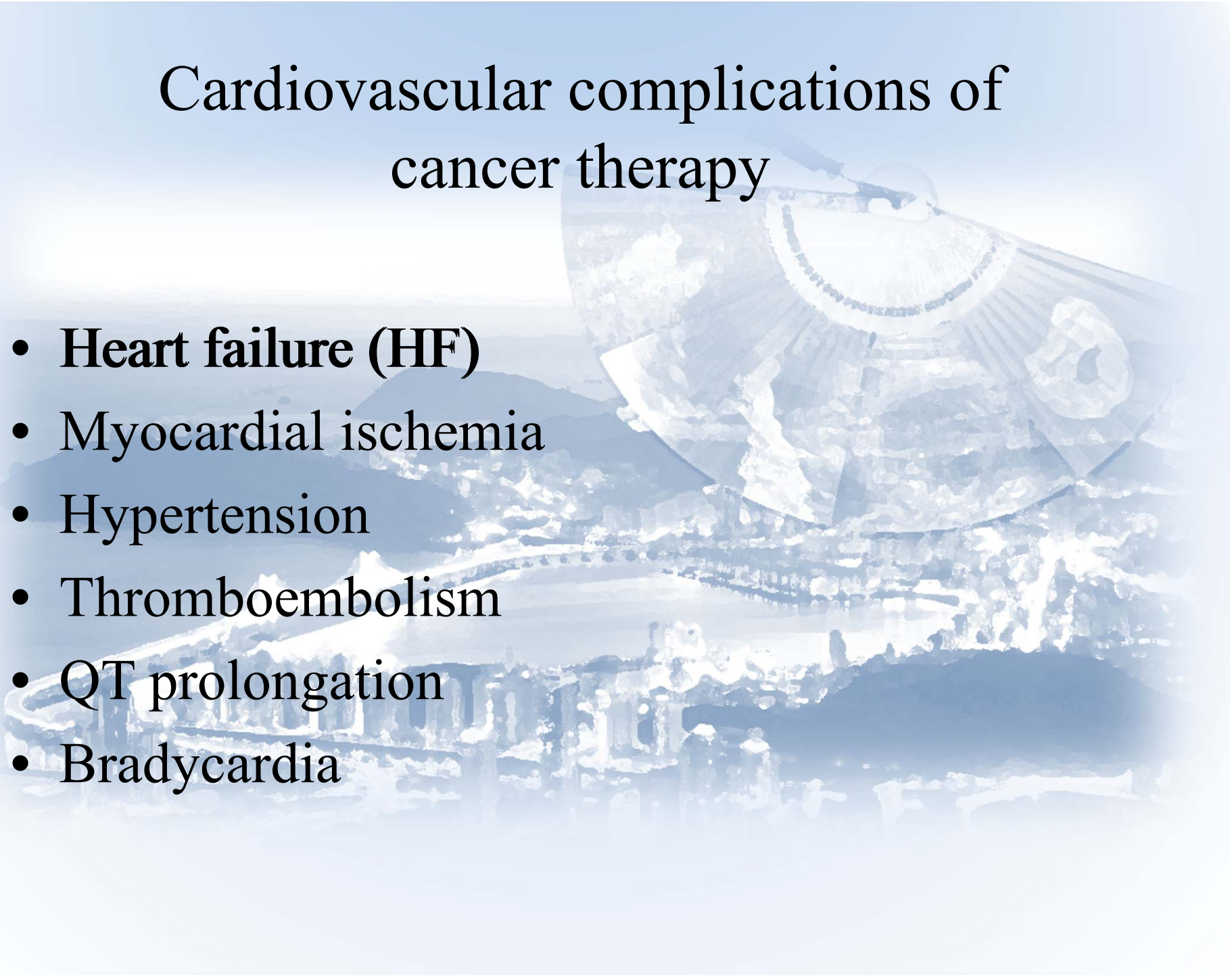


KNHANES, 2010

5-year survival rate: 1993 to 2008



Cardiovascular complications of cancer therapy



- **Heart failure (HF)**
- Myocardial ischemia
- Hypertension
- Thromboembolism
- QT prolongation
- Bradycardia

Chemotherapy-induced HF Definition

"Toxicity that affects the heart" (www.cancer.gov/dictionary/)

What exactly does cardiotoxicity mean?

1) Cardiomyopathy in terms of a reduction in LVEF, either global or more severe in the septum
2) Symptoms associated with HF
3) Signs associated with HF, such as S3 gallop, tachycardia, or both
4) Reduction in LVEF from baseline
   in the range of ≤ 5% to < 55% with signs or symptoms of HF

   or

   in the range of ≥ 10% to < 55% without signs or symptoms of HF

Chemotherapy-induced HF Incidence

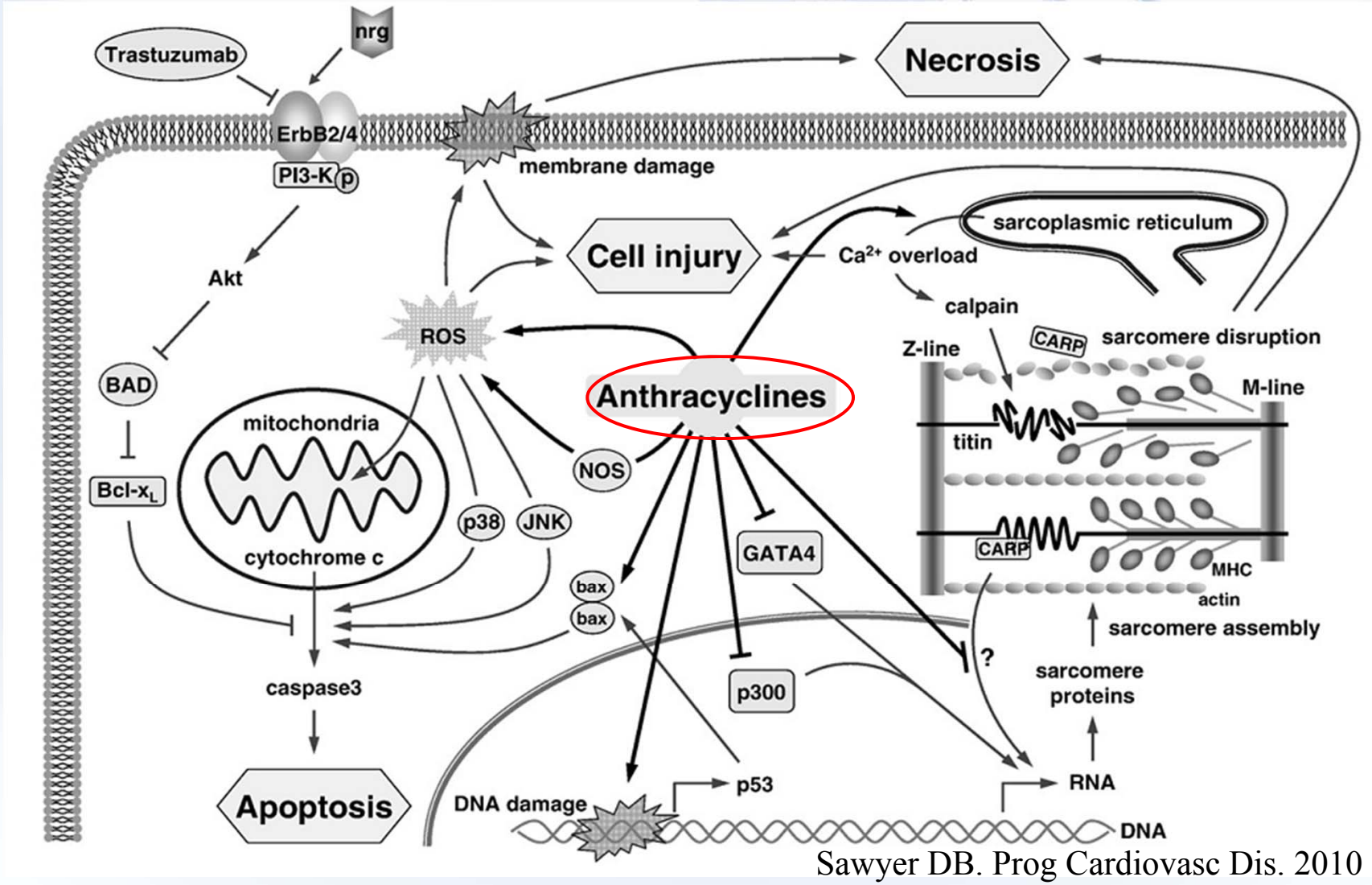
Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracyclines		
Doxorubicin (Adriamycin) (6,7)	3–26*	+++
Epirubicin (Ellence) (10)	0.9–3.3	++
Idarubicin (Idamycin PFS) (8)	5–18	+
Alkylating agents		
Cyclophosphamide (Cytoxan) (8,11–13)	7–28	+++
Ifosfamide (Ifex) (8,14)	17	+++
Antimetabolites		
Clofarabine (Clolar) (10)	27	+
Antimicrotubule agents		
Docetaxel (Taxotere) (10,15,16)	2.3–8	++
Monoclonal 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	+++

Yeh ET. JACC. 2009

Chemotherapy-induced HF Incidence

Acute	Early-onset chronic progressive	Late-onset chronic progressive
< 1%	1.6% - 2.1%	1.6% - 5%
Immediately after infusion	During treatment or within 1st year after treatment	1 year after completion of treatment
Acute, transient decline in myocardial contractility	DCMP	DCMP
Usually reversible	Progressive	Progressive

Chemotherapy-induced HF Pathophysiology



Sawyer DB. Prog Cardiovasc Dis. 2010

Chemotherapy-induced HF Diagnosis

There is no universal consensus or guideline.

Symptoms

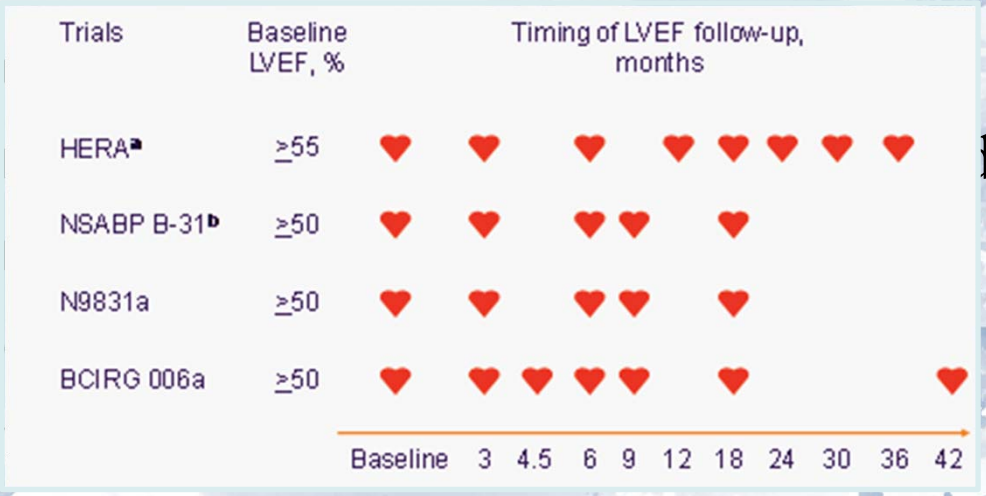
+

- Imaging techniques (echocardiography/multigated acquisition scan)
- Endomyocardial biopsy
- Biochemical markers (troponins/natriuretic peptides)

Chemotherapy-induced HF Diagnosis

Imaging techniques (serial assessment of LV EF)

- Beginning
- After admi lose
- Before eve
- During foll
- After the e



Advantage	Disadvantage
• The most commonly used techniques in clinical practice • Data showing the reduced risk of developing clinically confirmed HF	• Cost-effectiveness • Neither sensitive nor specific to detect early cardiac toxicity after chemotherapy

Chemotherapy-induced HF
Diagnosis
Imaging techniques (tissue Doppler imaging/strain/strain rate)

Abstract

Objective To examine the long-term effects of standard chemotherapy on myocardial function in asymptomatic breast cancer survivors using two-dimensional speckle tracking echocardiography.

Methods Seventy women (chemotherapy group) aged 54±8 years who had received anthracycline treatment with (n=19) or without (n=51) adjuvant trastuzumab up to 6 years

Subclinical systolic and diastolic myocardial abnormalities were present in asymptomatic breast cancer survivors up to 6 years after standard chemotherapy.

Results Despite normal EF% (62±4% vs 60±3%, p=0.051) the chemotherapy group had reduced E/A ratios (0.9±0.3 vs 1.1±0.3, p=0.003), global E' (10.2±2 vs 11.2±2.3, p=0.036), global Sm (9.0±1.3 vs 9.6±1.3, p=0.029) and global longitudinal 2D strain (−18.1±2.2 vs −19.6±1.8, p=0.0001) in comparison with controls. In 18 (26%) of the chemotherapy group, global longitudinal strain was below the lower limit of the control group. Cigarette smoking was a negative predictor of longitudinal strain, but only in the chemotherapy group. Radial strain did not differ significantly between the two groups. There were no significant differences in EF%, global Sm and longitudinal strain between trastuzumab-treated individuals and controls.

Conclusions Subclinical systolic and diastolic myocardial abnormalities were present in asymptomatic breast cancer survivors up to 6 years after standard chemotherapy. Cigarette smoking had a negative effect on longitudinal strain in these individuals. Adjuvant trastuzumab treatment did not appear to have an additive adverse impact on myocardial function in the medium–long term.

Ho E. Heart. 2010

Chemotherapy-induced HF Diagnosis

Biochemical markers (cardiac troponins)

Author/Year	Population Studied	No. (%) Troponin +	Troponin Type	Troponin Method	Cutoff (μg/L)	Comment
Cardinale et al,[42] 2000	Advanced neoplasia treated with HDC	204 (32)	I	Dade Stratus II	>0.50	No longer commercially available
Cardinale et al,[43] 2002	Breast cancer treated with HDC	211 (33)	I	Dade Stratus II	>0.50	No longer commercially available
Sandri et al,[44] 2003	Advanced neoplasia treated with HDC	179 (32)	I	Dade Stratus CS	>0.08	Cutoff established at the concentration measured with an imprecision CV ≤10%
Auner et al,[45] 2003	Blood cancers	78 (15)	T	Roche Elecsys (third generation)	>0.03	Cutoff established at the concentration measured with an imprecision CV ≤10%
Cardinale et al,[46] 2004	Advanced neoplasia treated with HDC	703 (30)	I	Dade Stratus CS	>0.08	Cutoff established at the concentration measured with an imprecision CV ≤10%
Lipshultz et al,[47] 2004	Acute lymphoblastic leukemia in children	76 (32)	T	Roche Elecsys (third generation)	>0.03	Cutoff established at the concentration measured with an imprecision CV ≤10%
Kilickap et al,[48] 2005	Advanced neoplasia treated with HDC	41 (34)	T	Roche Elecsys (third generation)	>0.01	Cutoff corresponding to detection limit of the method*

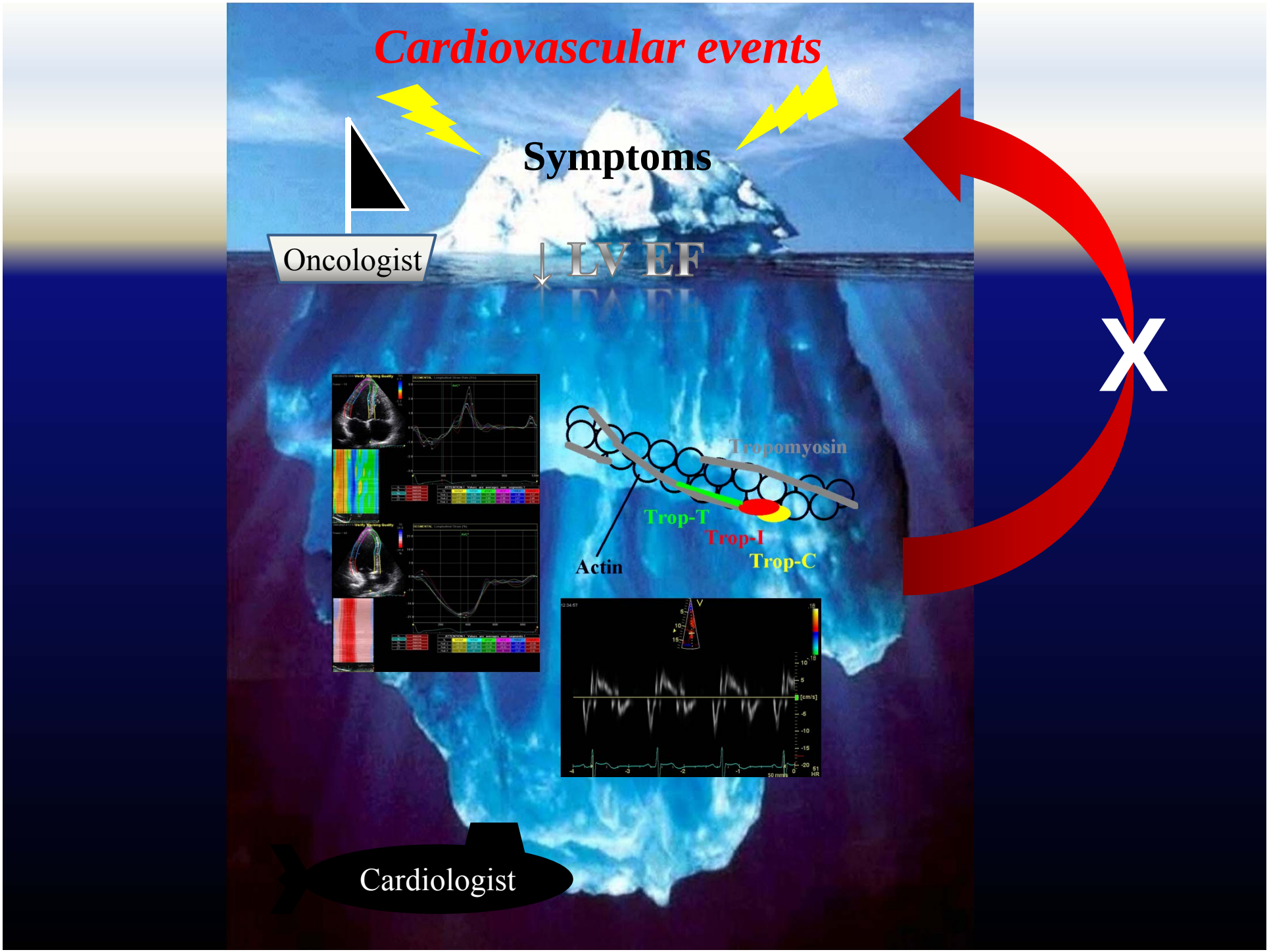
Dolci A. Am J Clin Pathol. 2010

Chemotherapy-induced HF
Diagnosis

Biochemical markers (natriuretic peptides)

Author/Year	Population Studied	No. (%) NP+	NP Evaluated	Method for BNP/NT-proBNP	Cutoff	Conclusions
Suzuki et al,[61] 1998	Blood cancers	27 (?)	BNP	Not defined	Not defined	Concentrations increased after treatment
Nousiainen et al,[62] 1998	Acute myeloid leukemia	10 (?)	BNP	RIA method, homemade	Not defined	BNP associated with diastolic dysfunction
Nousiainen et al,[63] 1999	Non-Hodgkin lymphoma	28 (25)	BNP	RIA method, homemade	8.5 pmol/L	BNP not predictive
Okumura et al,[64] 2000	Acute leukemia	13 (?)	BNP	Shonogi IRMA (manual)	40 ng/L	BNP not correlated with LVEF, but associated with future CHF
Hayakawa et al,[65] 2001	Pediatric cancers	34 (?)	BNP	Shonogi IRMA (manual)	Not defined	Concentrations increased in patients with diastolic dysfunction
Meinardi et al,[66] 2001	Breast cancer	39 (?)	BNP	Shonogi IRMA (manual)	Not defined	Concentrations increased after treatment, but not associated with ventricular dysfunction
Nousiainen et al,[67] 2002	Non-Hodgkin lymphoma	28 (?)	BNP	RIA method, homemade	Not defined	BNP associated with diastolic dysfunction
Poutanen et al,[68] 2003	Pediatric cancers	39 (?)	BNP	Shonogi IRMA (manual)	Not defined	No clinical usefulness
Daugaard et al,[69] 2005	Advanced neoplasia treated with HDC	107 (?)	BNP	RIA method, homemade	Not defined	Not useful to replace estimation of LVEF
Sandri et al,[70] 2005	Advanced neoplasia treated with HDC	52 (69)	NT-proBNP	Roche Elecsys	Male, >88 ng/L (≤50 y); >227 ng/L (>50 y); female, >153 ng/L (≤50 y), >334 ng/L (>50 y)	Persistent increase associated with development of cardiac dysfunction
Horacek et al,[71] 2005	Acute myeloid leukemia	15 (?)	NT-proBNP	Roche Elecsys	Not defined	Concentrations increased after treatment
Pichon et al,[72] 2005	Breast cancer	79 (49)	BNP	Shonogi IRMA (manual)	51.3 ng/L	To predict development of CHF, sensitivity, 83.3% (CI, 52%-97%); specificity, 90.2% (CI, 86%-94%)
Soker and Kervancioglu,[73] 2005	Blood cancers	31 (?)	NT-proBNP	Roche Elecsys	Not defined	Concentrations increased in patients with ventricular dysfunction

Dolci A. Am J Clin Pathol. 2010


Cardiovascular events
Symptoms
Oncologist
↓ LV EF
X
Tropomyosin
Trop-T
Trop-I
Trop-C
Actin
Cardiologist

Chemotherapy-induced HF Prevention

- Reduction of risk factors

Anthracycline	Tyrosine kinase inhibitor
Age	Age
Preexisting cardiac disease	Preexisting cardiac disease
Prior use of anthracycline	Prior use of anthracycline
Cumulative dose related (> 300 mg/m^2)	**Not cumulative dose related**
Hypertension	Obesity
Radiation therapy	

- Addition of cardioprotectant
  : dexrazoxane, erythropoietin, thrombopoietin, iloprost
- Early therapy with AECI in high risk and high dose chemotherapy-treated patients

Chemotherapy-induced HF Prevention

- Addition of cardioprotectant (dexrazoxane)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

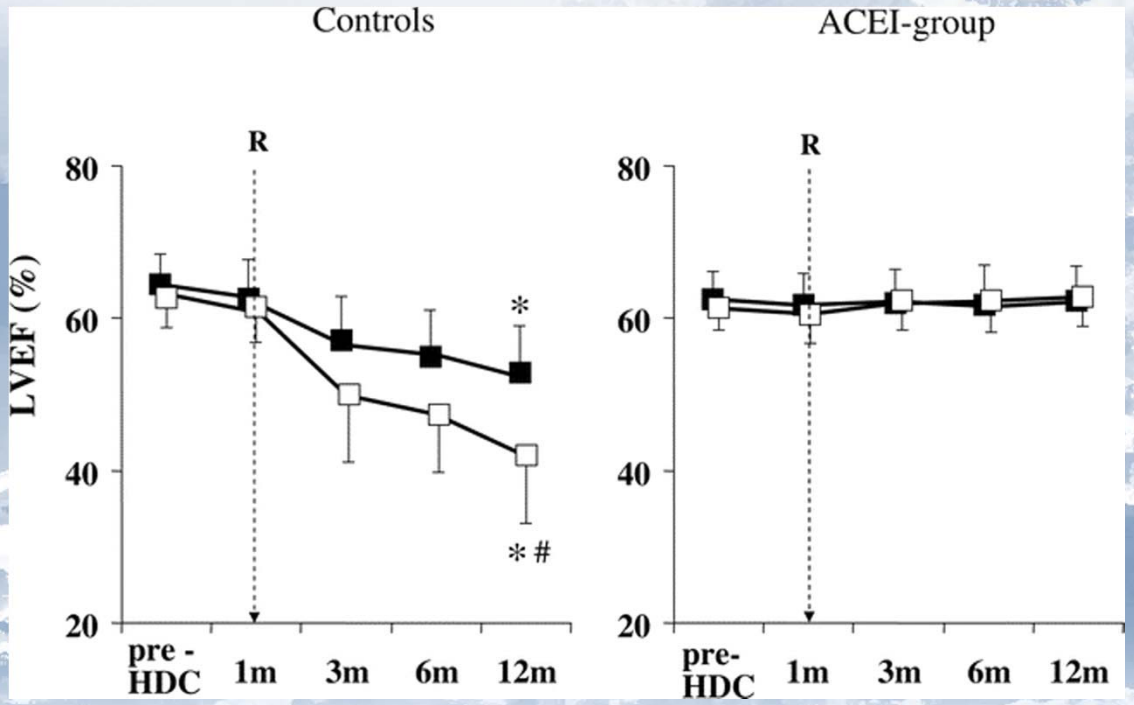
Conclusions

Dexrazoxane prevents or reduces cardiac injury, as reflected by elevations in troponin T, that is associated with the use of doxorubicin for childhood ALL without compromising the antileukemic efficacy of doxorubicin.

Steven D. Colan, M.D., Barbara L. Asselin, M.D., Ronald D. Barr, M.D., Luis A. Clavell, M.D., Craig A. Hurwitz, M.D., Albert Moghrabi, M.D., Yvan Samson, M.D., Marshall A. Schorin, M.D., Richard D. Gelber, Ph.D., and Stephen E. Sallan, M.D.

Chemotherapy-induced HF Prevention

- Early therapy with AECI in high risk and high dose chemotherapy-treated patients



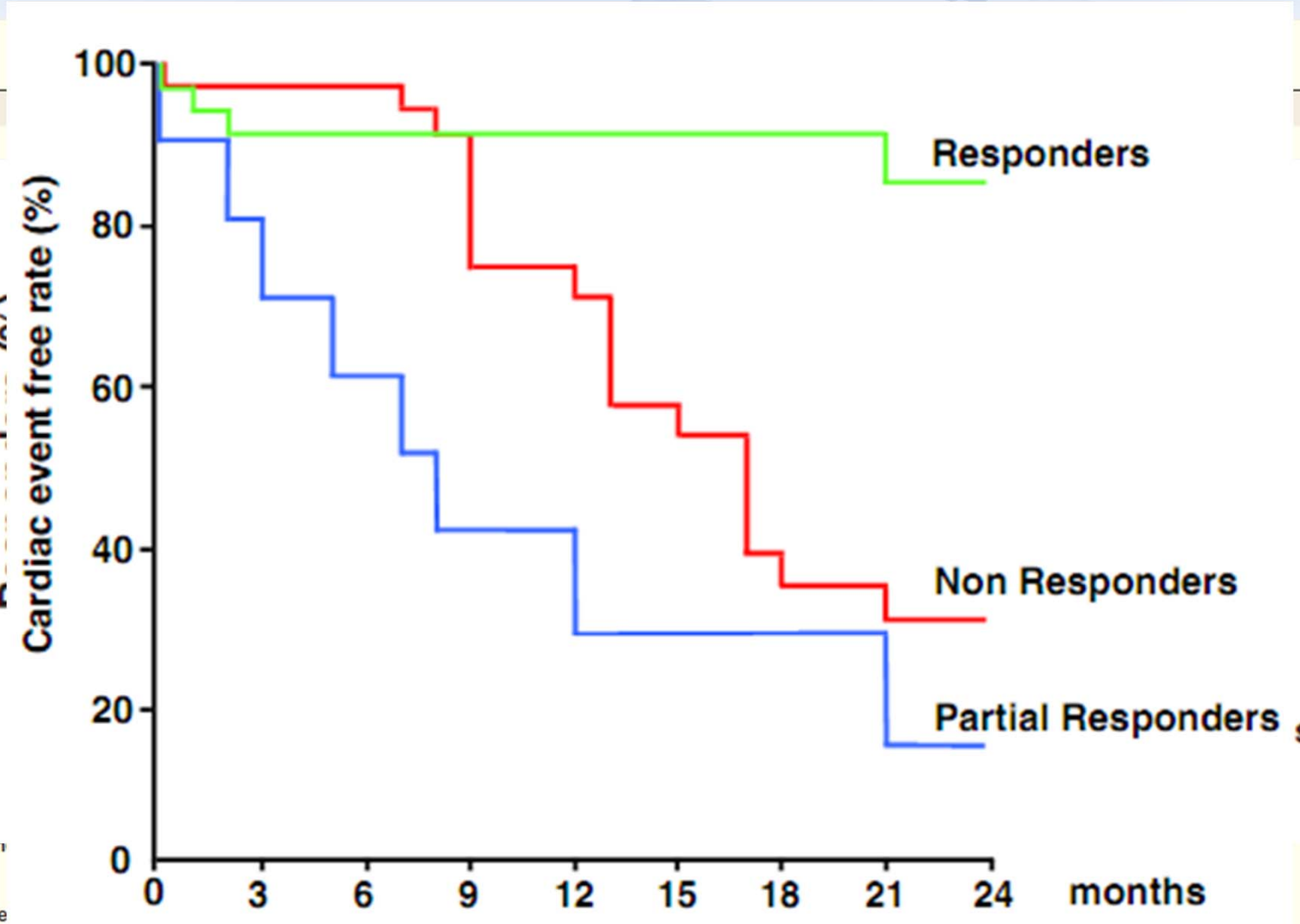
LVEF at baseline and during the 12-month follow-up in control subjects (left) and the ACEI group (right) in patient s with ({square}) or without ({blacksquare}) persistent TnI increase

Cardinale D. Circulation. 2006

Chemotherapy-induced HF Treatment

- There are no HF guidelines developed for cancer patients.
- There is no evidence whether current HF therapy according to current ACC/AHA guidelines shows similar long-term benefits in cancer patients with chemotherapy-induced HF.
- Nevertheless, there are some data supporting the use of ACEI or beta-blocker in patients with anthracycline-induced HF.

Chemotherapy-induced HF Treatment



	p Value
Age, yrs	0.36
Women	0.48*
Hypertensi	0.96
Diabetes	0.49*
Hypercholes	0.59*
Current or	0.98
Family hist	0.53*
NYHA funct	<0.001
LVEF befor	0.16
LVEF befor	<0.001
LVEF at the	<0.001
Mitral regu	0.56*
Creatinine	0.05
Oncologic	0.26‡
Acute ly	
Breast c	
Hodgkin'	
Non-Hod	
Other tu	
Time-to-HF	<0.001
HF therapy	
Enalapril a	0.001
Diuretics	<0.001
Amiodarone	0.001*
Anticoagula	0.15*

Cardinale D. JACC. 2010

Chemotherapy-induced HF Conclusions

- A number of anti-cancer agents used in contemporary oncology are associated with an increased risk of short-and long-term cardiac events.
- Complete resolution of chemotherapy (anthracycline)-induced cardiomyopathy does not usually occur.
- A treatment according to ACC/AHA guidelines should be initiated for a LVEF recovery and a reduction of cardiac events.
- There is a need for stronger collaboration between cardiologists and oncologists to improve the care of oncology patients receiving cardiotoxic therapy.


Thank You!