Cardio-Oncology 2013

Cardiac complications of chemotherapy

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Acute Cardiac Care, June 16-18 2013
Jerusalem, Israel

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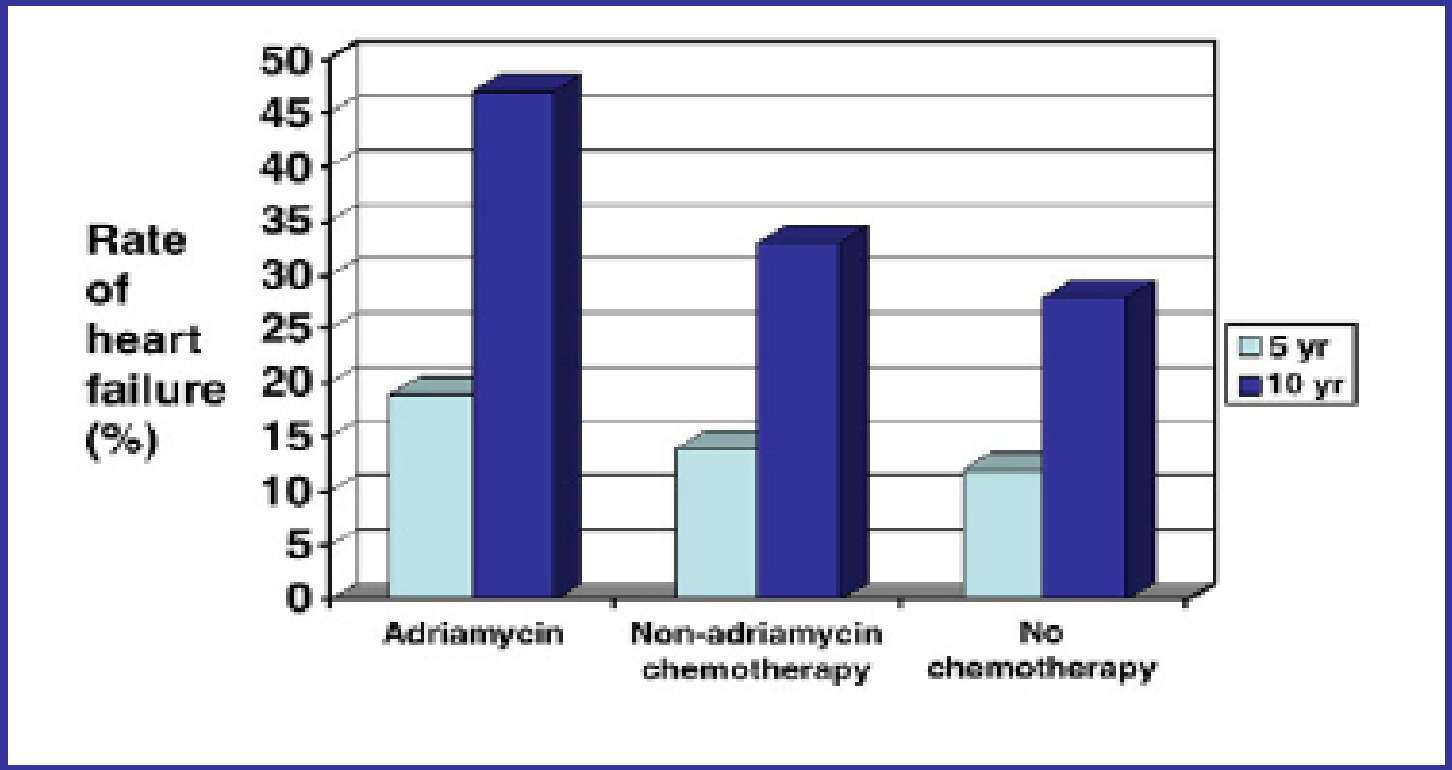
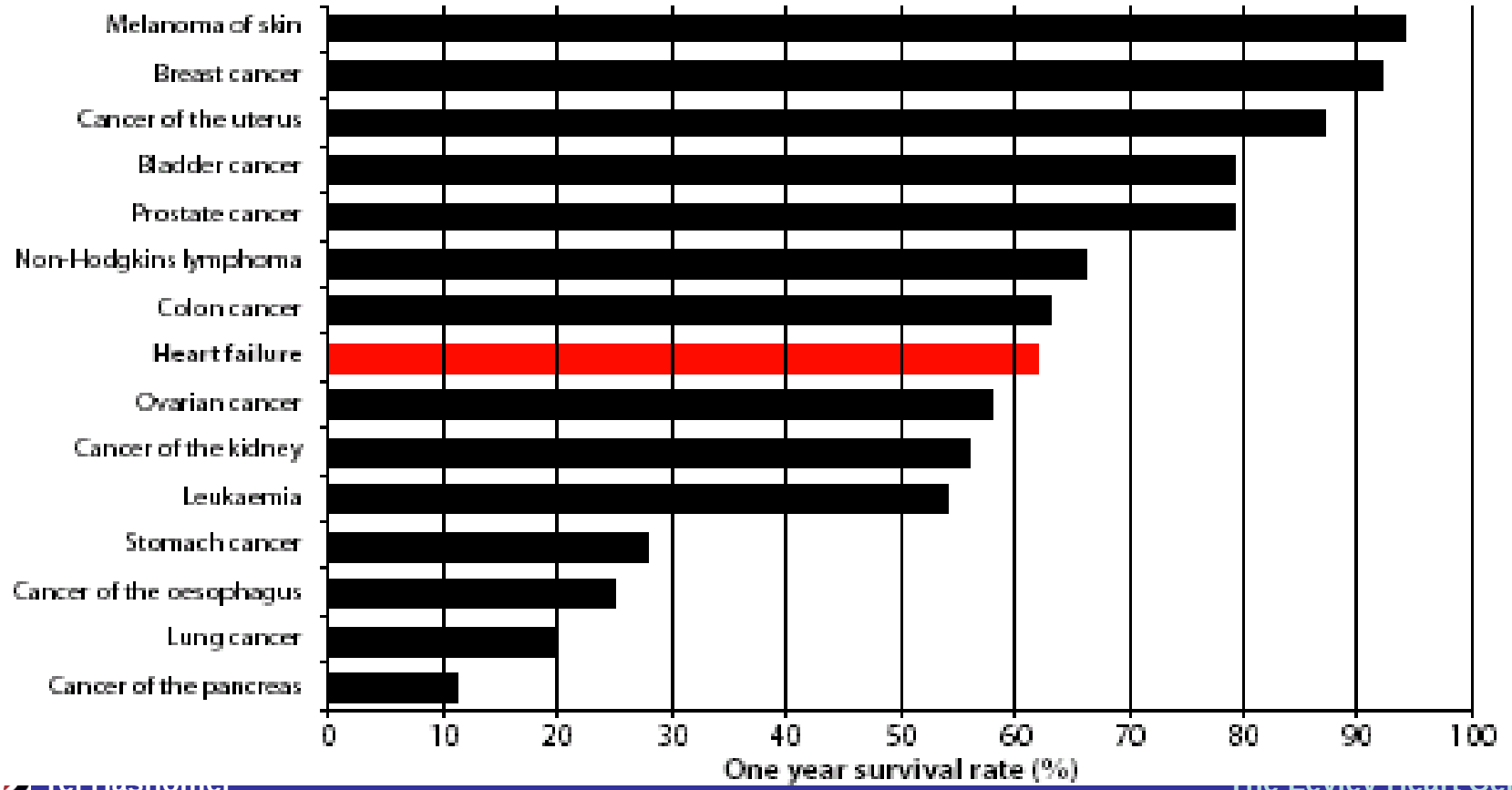
Heart failure prevalence in elderly women with breast cancer



In breast cancer patients who did not receive chemotherapy, the risk of HF at 5 and 10 years was X2 and X5 respectively, compared to the general population.

Comparative Mortality for *advanced* Heart Failure and Common Cancers

Fig 2.3 *One-year survival rates, heart failure and the major cancers compared, mid-1990's, England and Wales*



Cardiotoxicity of anticancer therapeutics

Cardiac response	Drug	Frequency
Contractile dysfunction/heart failure	Anthracyclines	Cumulative dose-related
	Cyclophosphamide	Rare
	Cisplatin	Rare
	Trastuzumab	Variable[a]
Arterial hyperte		dose-dependent
Myocardial ischa		
Thomboembolism	Cisplatin	Moderate
	All angiogenesis inhibitors	Moderate
Arrhythmia/QT prolongation	Arsenic trioxide	Moderate
	Lapatinib	Rare
	Sunitinb	Rare
	Nolitinib	Rare
	Dasatinib	Rare

On Target / Off Target

Reversible / Irreversible

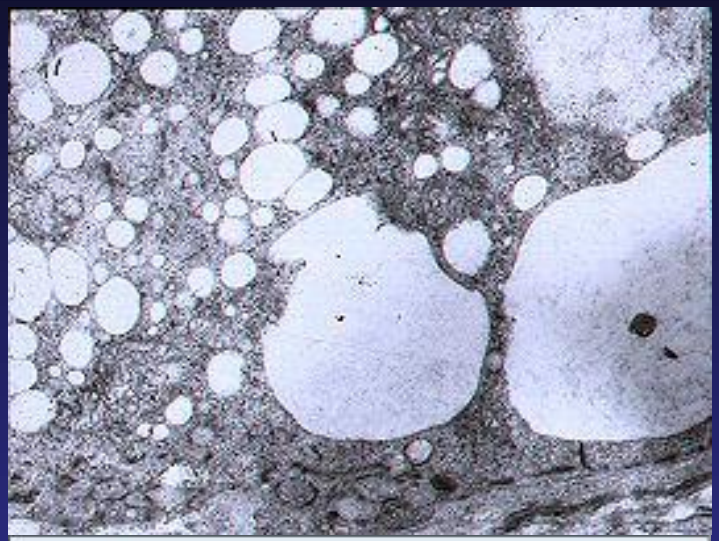
Acute cardiotoxicity of cancer tx.

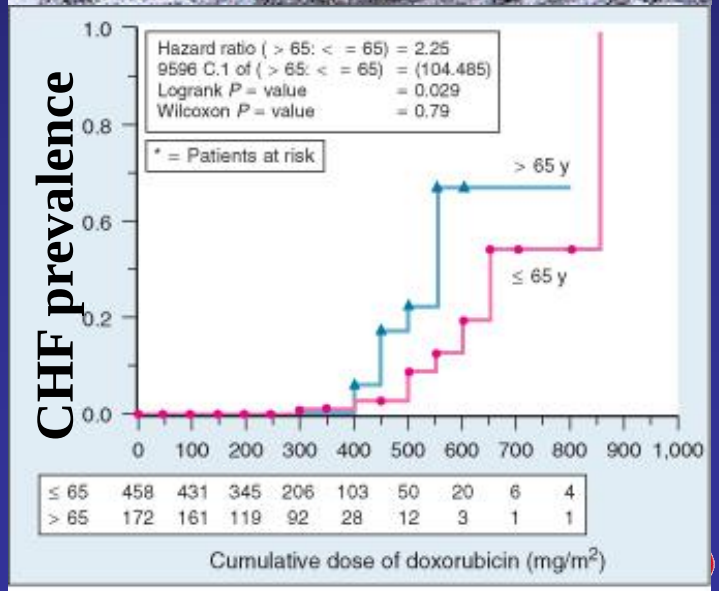
Agent	Mechanism	Manifestations
Antracyclines Ankylating agents (Cytoxan)	Cytotoxicity Cell necrosis	Tachycardia, VPCs Supraventricular arrhythmia, Myo/Pericarditis
5-Fluorouracil	Coronary spasm	Myocardial infarction Myocarditis
Cisplatin	Endothelial dysfunction	Myocardial ischemia Thromboembolism
Bevacizumab Sunitinib	VEGF antagonism	Hypertensive crisis Myocardial ischemia
Arsenic trioxide Lapatinib	HERG blockade	QT prolongation Ventricular arrhythmia

Antracyclines cause an irreversible (Type I) cardiac damage by cellular toxicity

Oxygen radicals → mitochondrial injury
Impaired oxidative phosphorylation
Apoptotic signaling

Topoisomerases are enzymes opening the DNA coil to allow replication and transcription.
Binding of antracyclines to topo IIa in cancer cells is cytotoxic.
Nonselective binding to topo IIb in the heart leads to cardiotoxicity by impairing expression of proteins and growth factors (Zhang, Nat Med 2012)





Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials

S.M. Swain et al. Cancer 2003

A Retrospective Analysis of 630 patients (two studies in patients with breast carcinoma and one study in patients with SCL carcinoma)

- 24% of patients who received doxorubicin developed cardiotoxicity (defined as LVEF 20% drop or 5%<LLN):

16% → 150-250 mg/m² doxorubicin

18% → 350 mg/m² doxorubicin

38% → 450 mg/m² doxorubicin

65% → 550 mg/m² doxorubicin

By Prof Gabizon

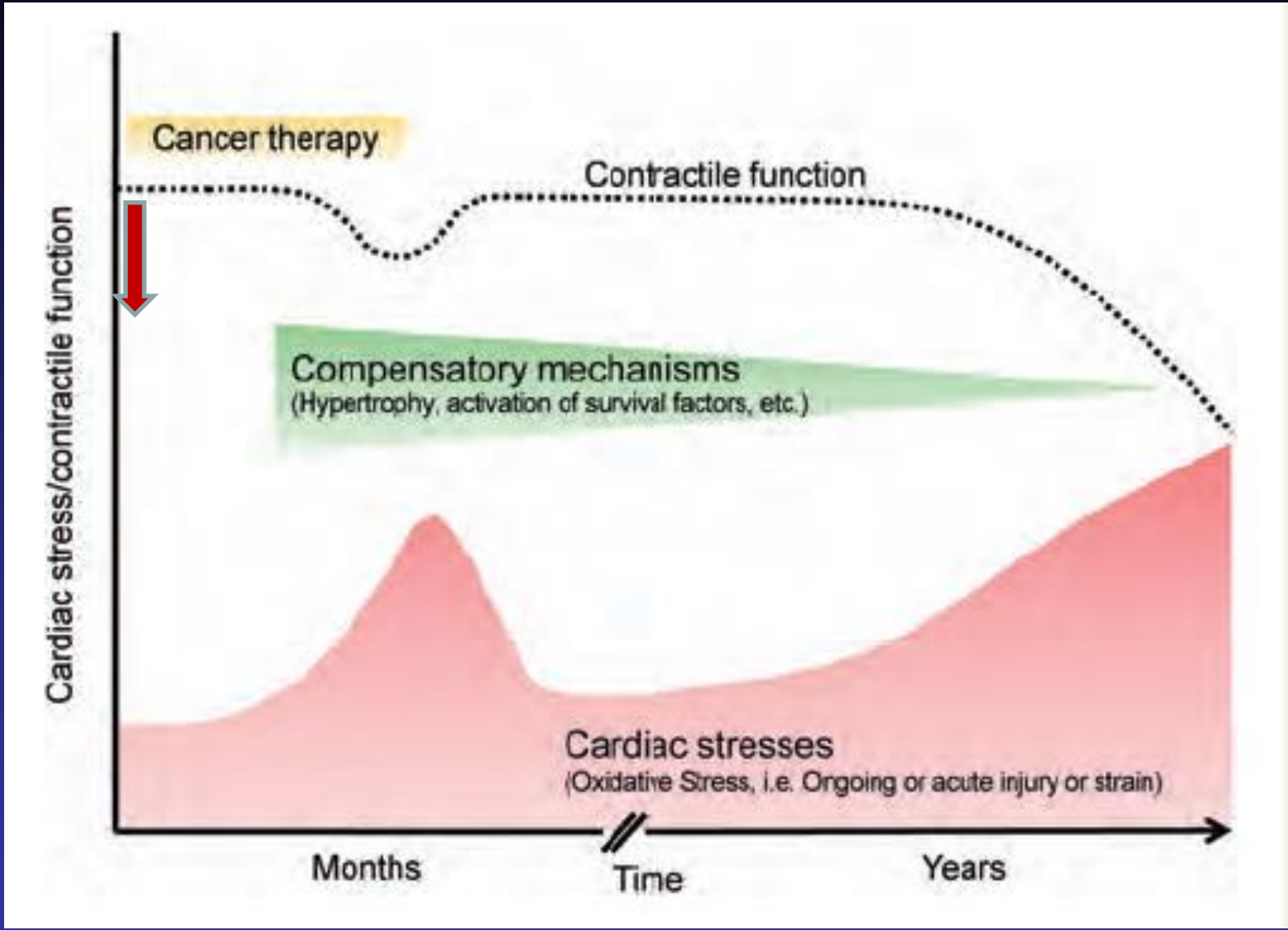
Doxorubicin-related CHF:

5% → 400 mg/m² doxorubicin

16% → 500 mg/m² doxorubicin

26% → 550 mg/m² doxorubicin

Time course of antracycline cardiotoxicity

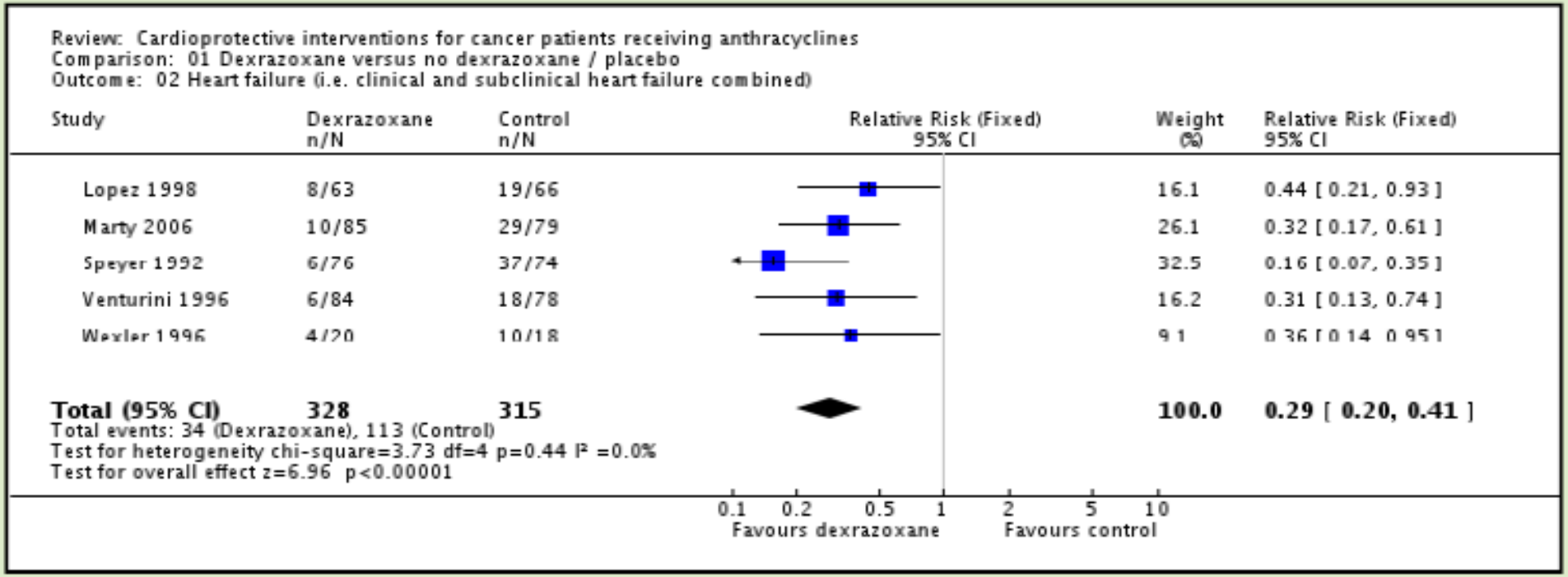


Risk Factors

- Age (young children and the elderly)
- Female
- Chest wall radiation
- Use in combination with other potentially cardiotoxic antineoplastic agents
- Previous heart disease
- HTN
- Diabetes mellitus
- Bolus administration

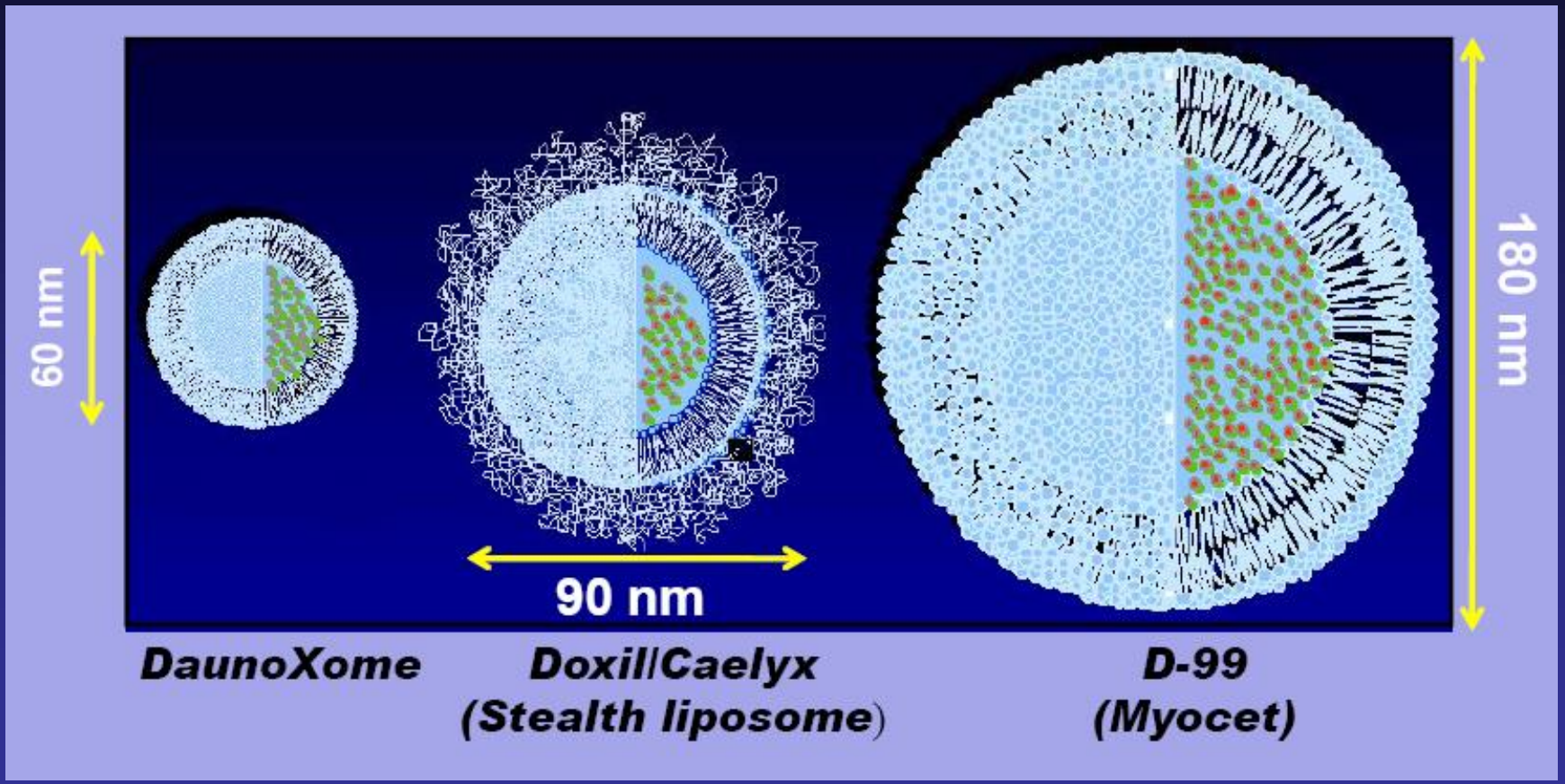
Prevention (1): Dextrazoxane
an iron chelator protecting from ANT cardiotoxicity

- ***Heart failure*** *(i.e. clinical and subclinical heart failure combined)* **- The meta-analysis showed a benefit in favour of dexrazoxane use (RR 0.29, 95% CI 0.20 to 0.41, P < 0.00001).**



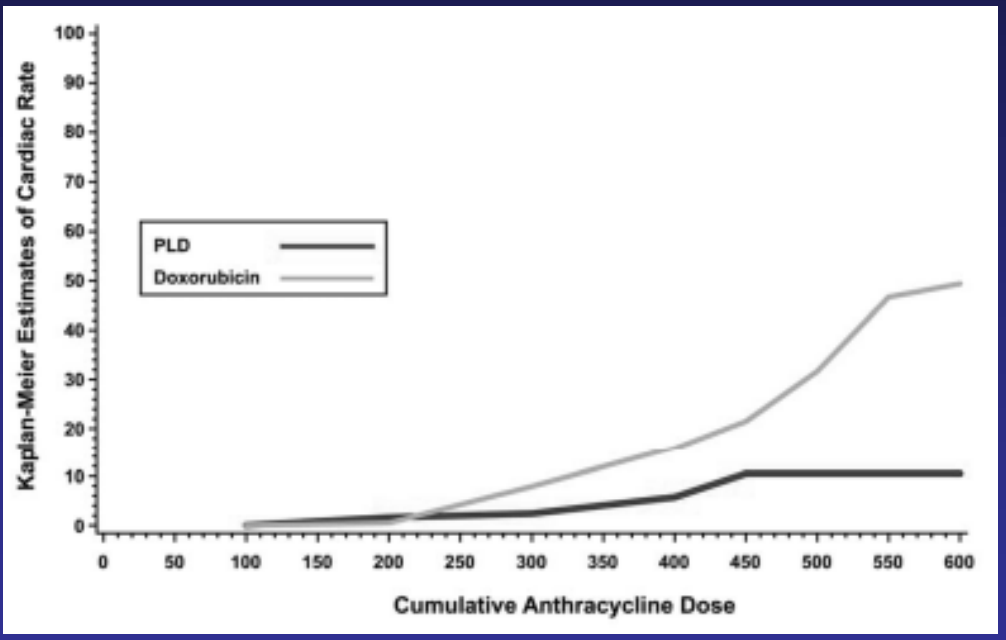
Van Dalen et al, Cochrane Reviews Library 2008

Prevention (2): Liposomal formulations



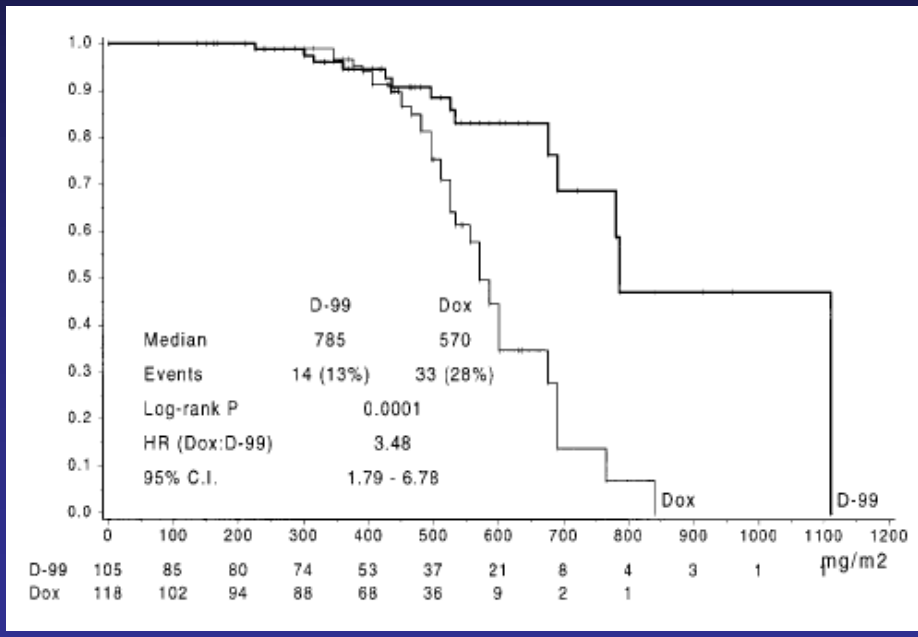
Liposomal doxorubicin in metastatic breast cancer

Doxil – cardiac events rate



O'Brien et al, Ann Oncol 2004

Myocet – max. tolerated dose

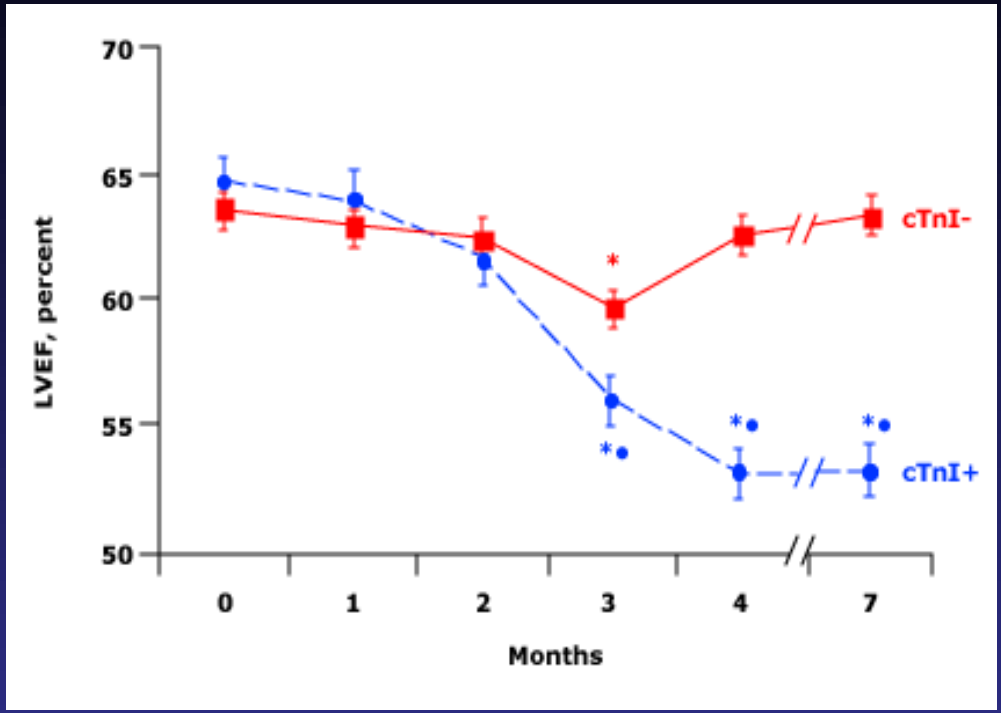


Harris et al, Cancer 2002

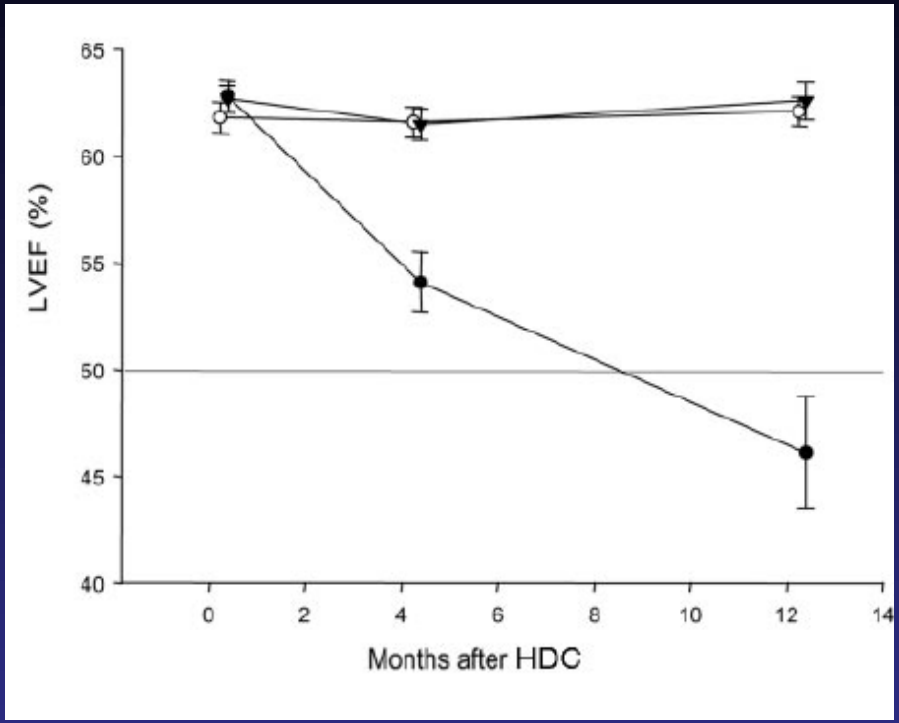
Early detection - How to monitor?

MODALITY	PROS	CONS
MUGA LVEF	Accurate, reproducible	Radiation exposure
Echo LVEF – 2D Simpson's	Easily available, clinically relevant	Low sensitivity
Echo – contractile reserve	More sensitive than resting LVEF	Limited validation in adults
Tissue Doppler & and speckle tracking	May be more sensitive than LVEF	Specificity unknown Clinical correlation?
Tei (Myocardial Performance) Index	More sensitive than LVEF	No correlation with clinical events
Cardiac MRI	Accuracy Tissue imaging	Least available Limited experience

Elevated Cardiac Troponins



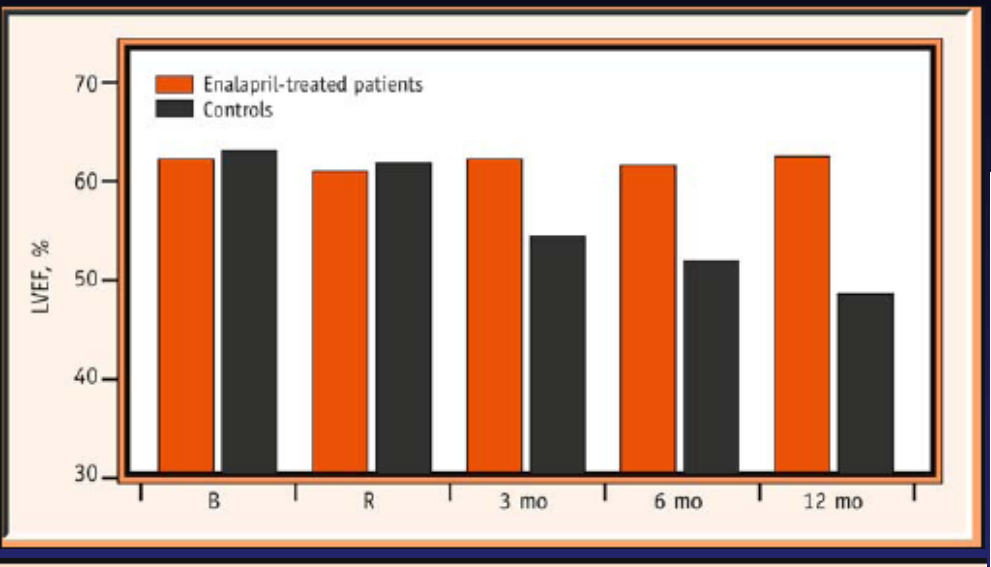
Persistent NTproBNP elevation



Cardinale et al, JACC 2000, Circulation 2004, Clin Chemistry 2005

Persistant elevation of TnI 1 month after completing antracycline chemotherapy is considered to predict a future decline in cardiac function

Early detection may lead to protection



Event	Patients, *n* (%) Enalapril group (n = 56)	Control group (n = 58)	*P*-value
Sudden death	0 (0)	0 (0)	1.0*
Cardiac death	0 (0)	2 (3)	0.49*
Acute pulmonary edema	0 (0)	4 (7)	0.07*
Heart failure	0 (0)	14 (24)	< 0.001
Arrhythmia requiring treatment	1 (2)	10 (17)	0.01
Cumulative events	**1 (2)**	**30 (52)**	**< 0.001**

*By Fisher's exact test.

Enalapril 20 mg/day in TnI positive patients. **Cardinale et al, Circulation 2006**

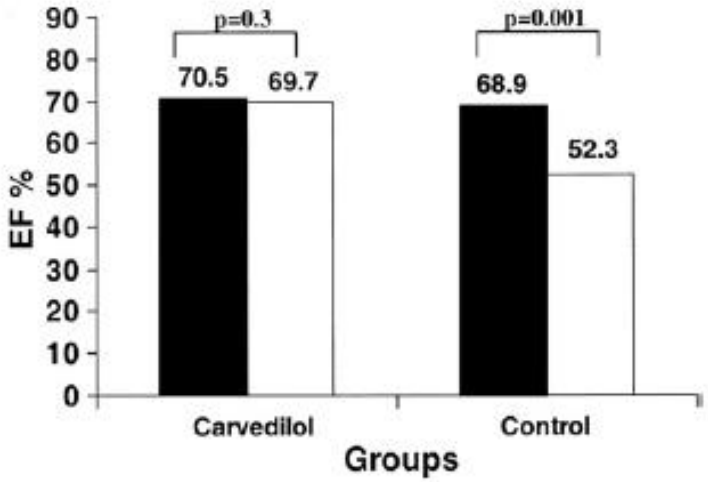


Figure 1. Comparison of left ventricular ejection fraction (EF) at baseline **(black bars)** and after chemotherapy **(white bars)** in the 2 groups. Data expressed as mean values.

Carvedilol 12.5 mg/day
Kalay et al, JACC 2006

Anthracycline-Induced Cardiomyopathy

JACC 2010

Clinical Relevance and Response to Pharmacologic Therapy

Daniela Cardinale, MD, PhD,* ... MD,* Giuseppina Lamantia, MD,*
Nicola Colombo, MD,* Maurizio ... MD,* Mara Rubino, MD,†
Fabrizio Veglia, PhD,† Cesare ... MD*
Milan, Italy

and therapy…

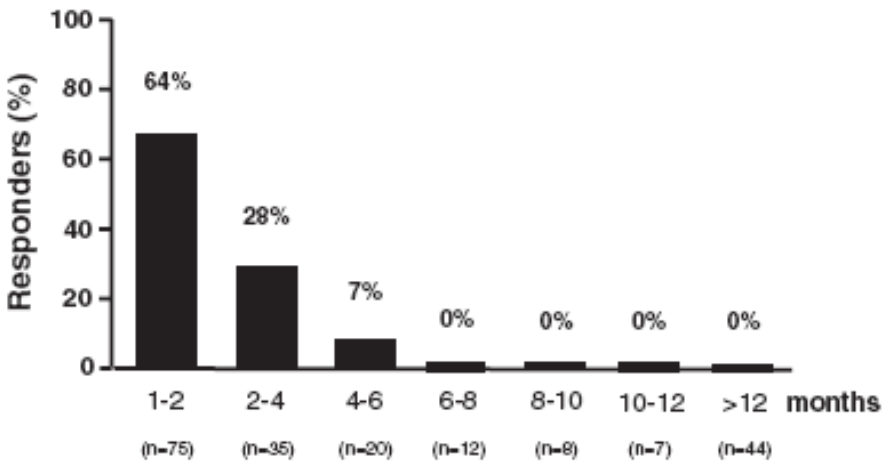


Figure 1 Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy

AC = anthracyclines; HF = heart failure.

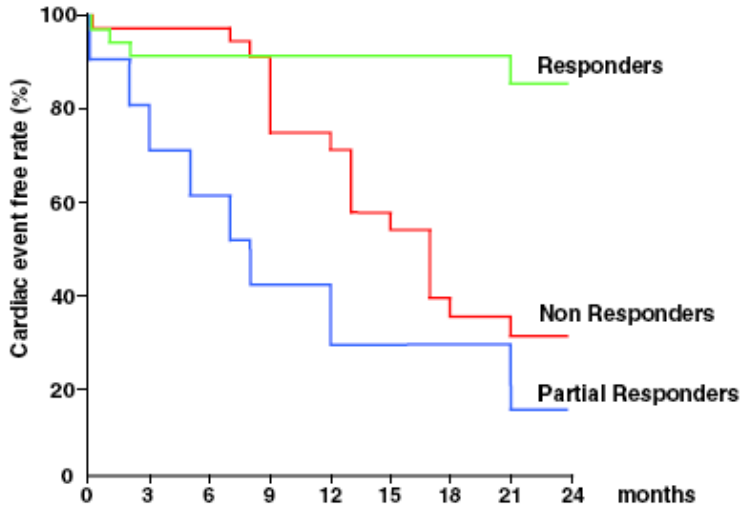
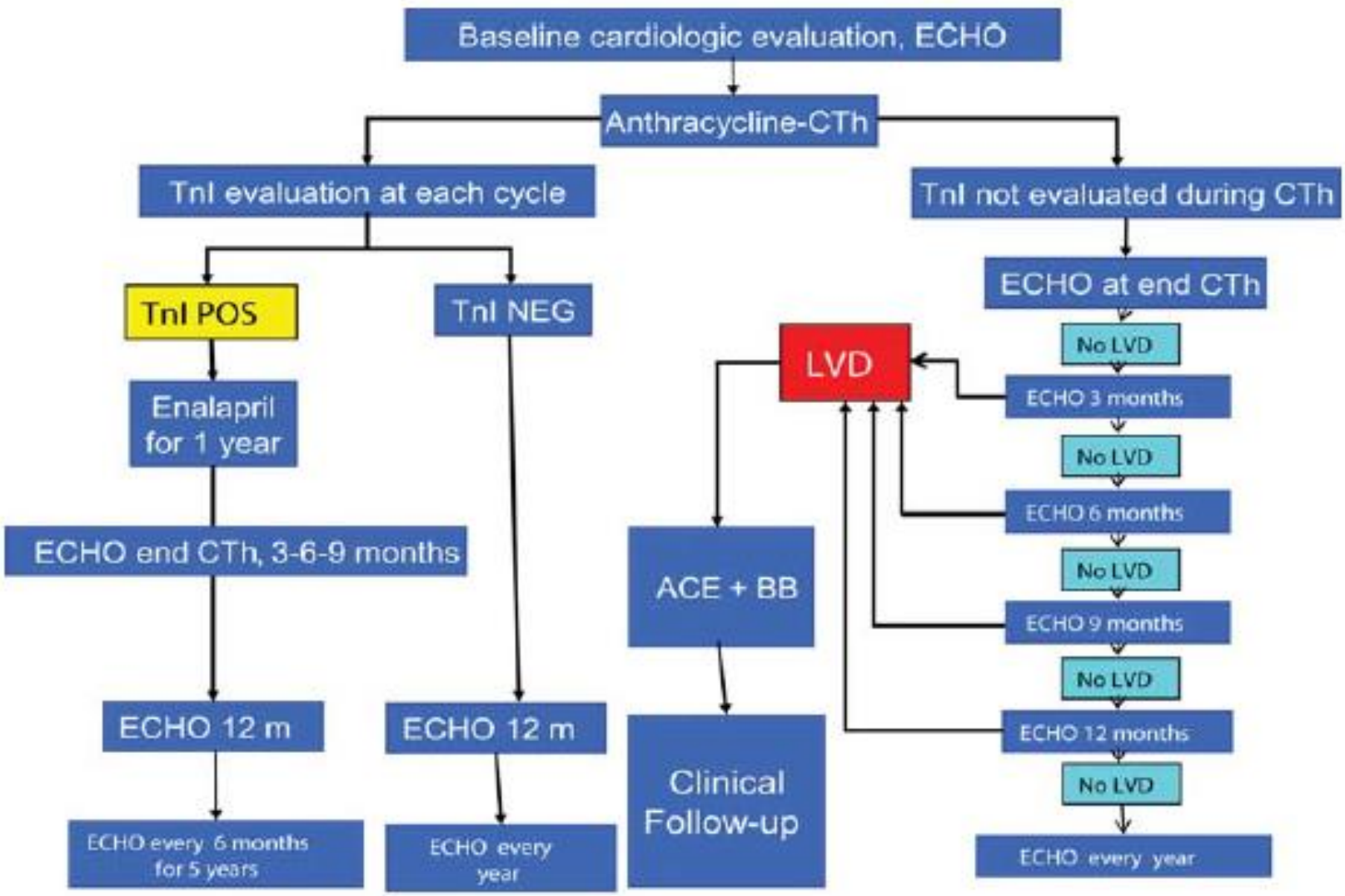


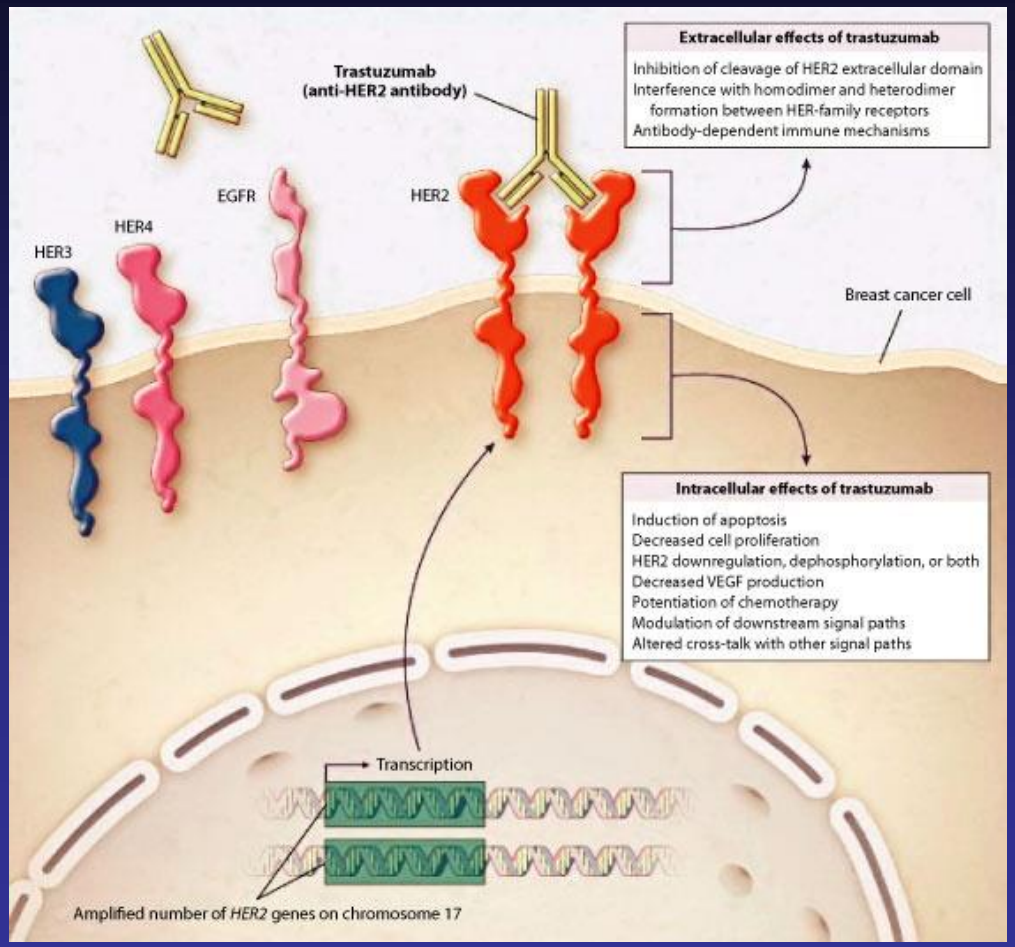
Figure 2 Cumulative Cardiac Event Rate During the Study Follow-Up

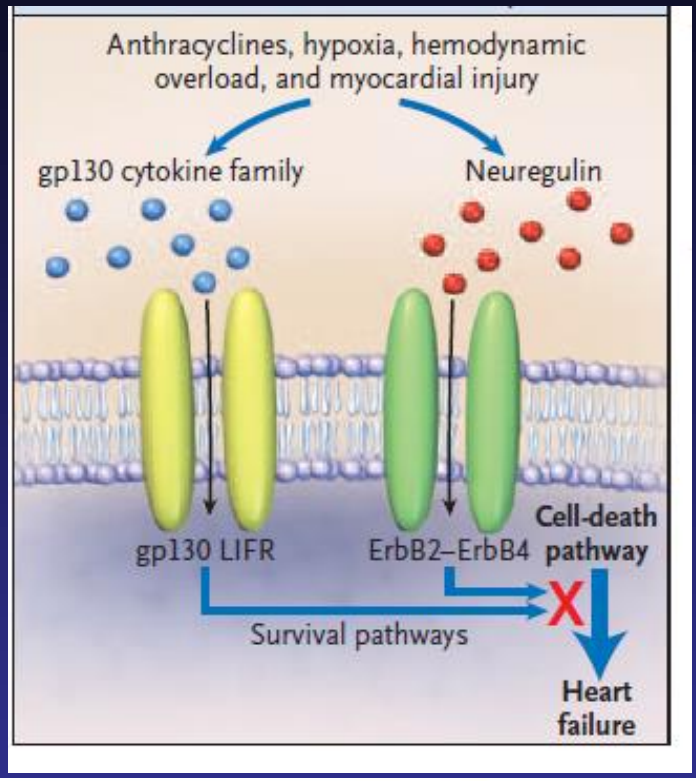
2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. p = 0.0003 (log-rank test).

A Practical Approach

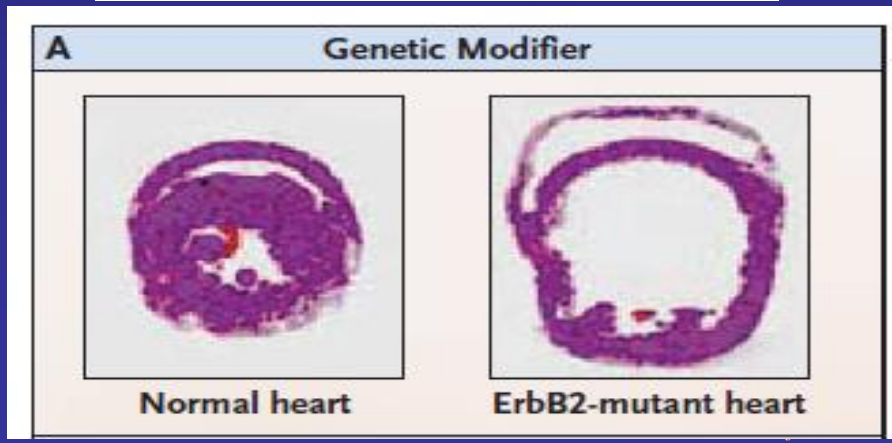


Trastuzumab (*Herceptin*) – a prototype of Type II (potentially reversible) cardiotoxicity





Chien et al . NEJM , 2006



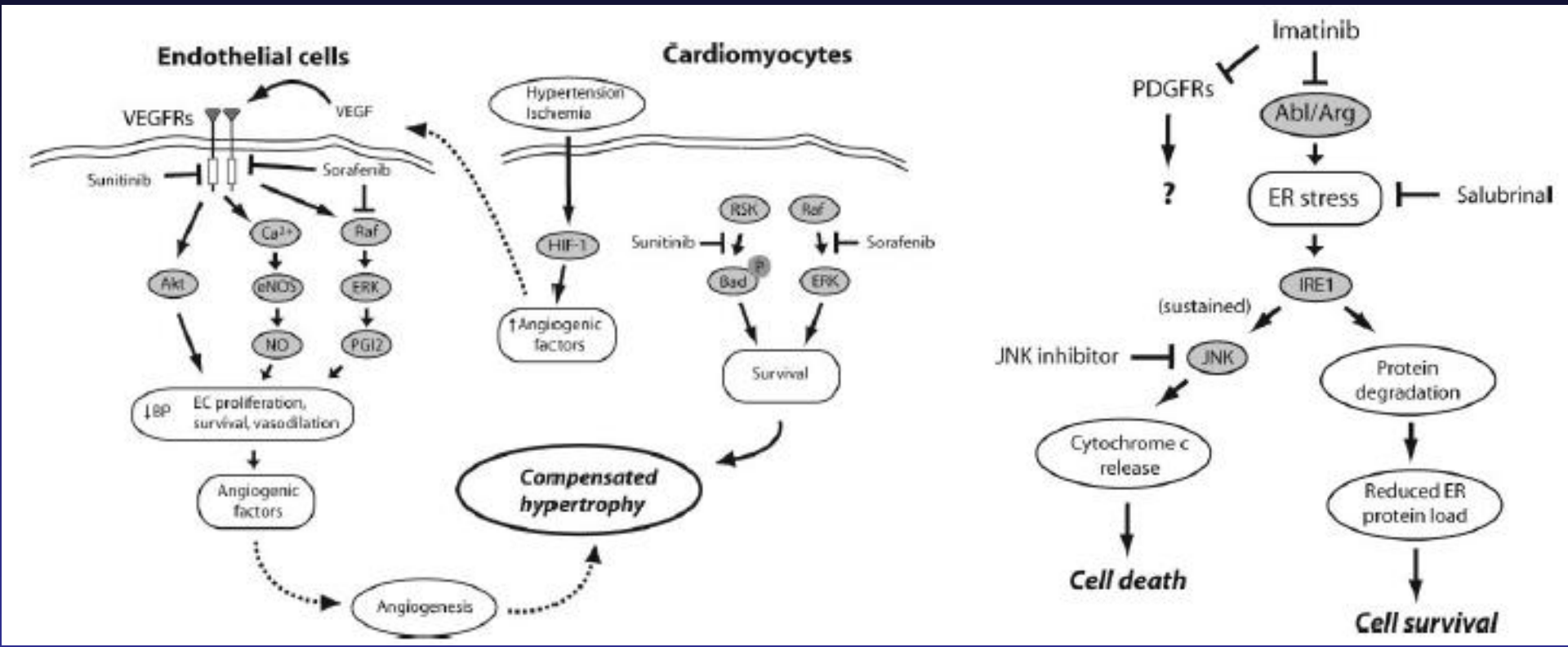
Sheba Medical Center
Tel Hashomer

Risk Factors for Trastuzumab Cardiotoxicity

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

- Do not increase the risk
- Adjuvant radiation therapy
- Diabetes
- Valvular heart disease
- Coronary artery disease

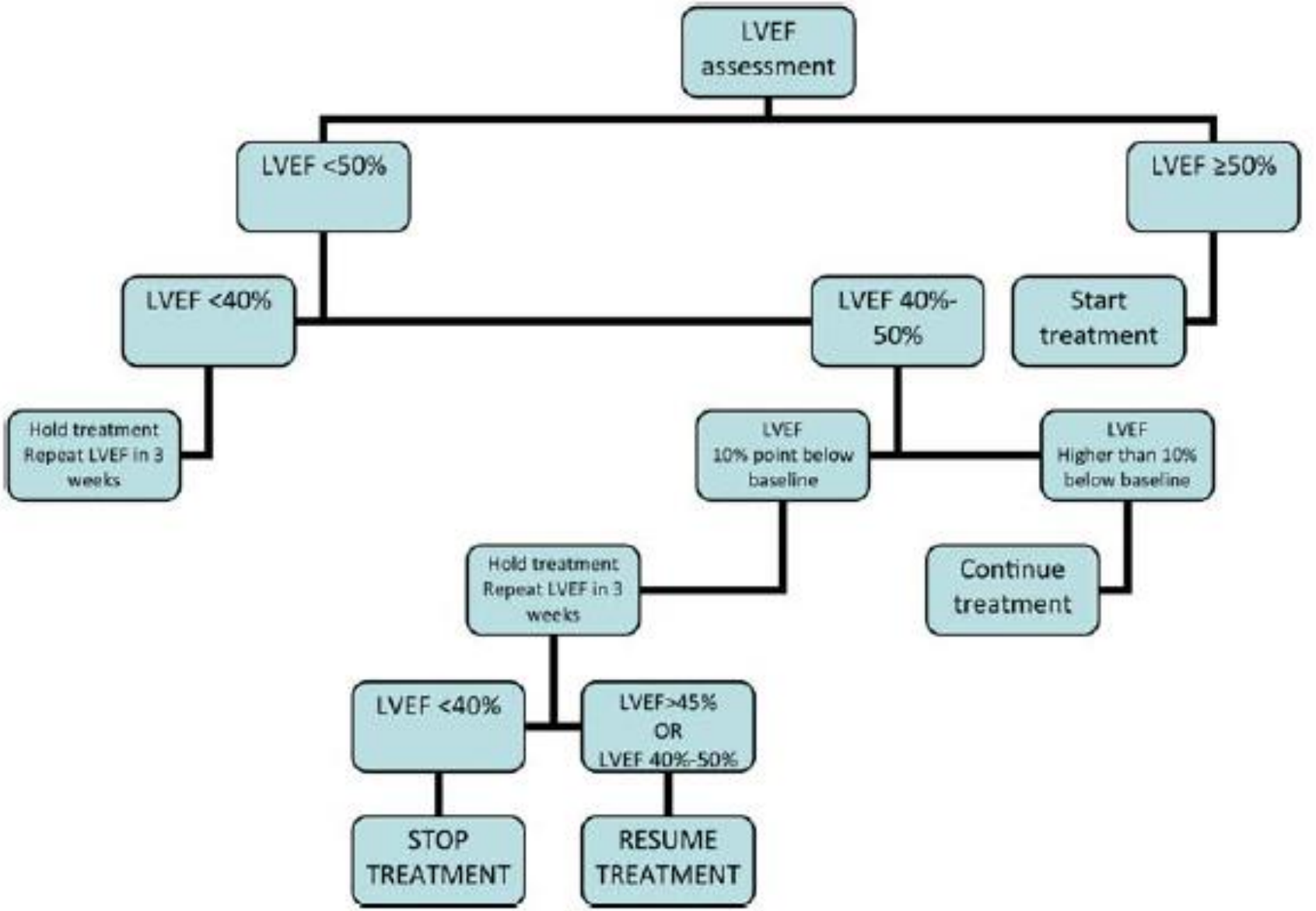
Type II cardiotoxicity by VEGF antagonists and by Imatinib



Mechanisms of Cardiac Dysfunction Associated With Tyrosine Kinase Inhibitor Cancer Therapeutics

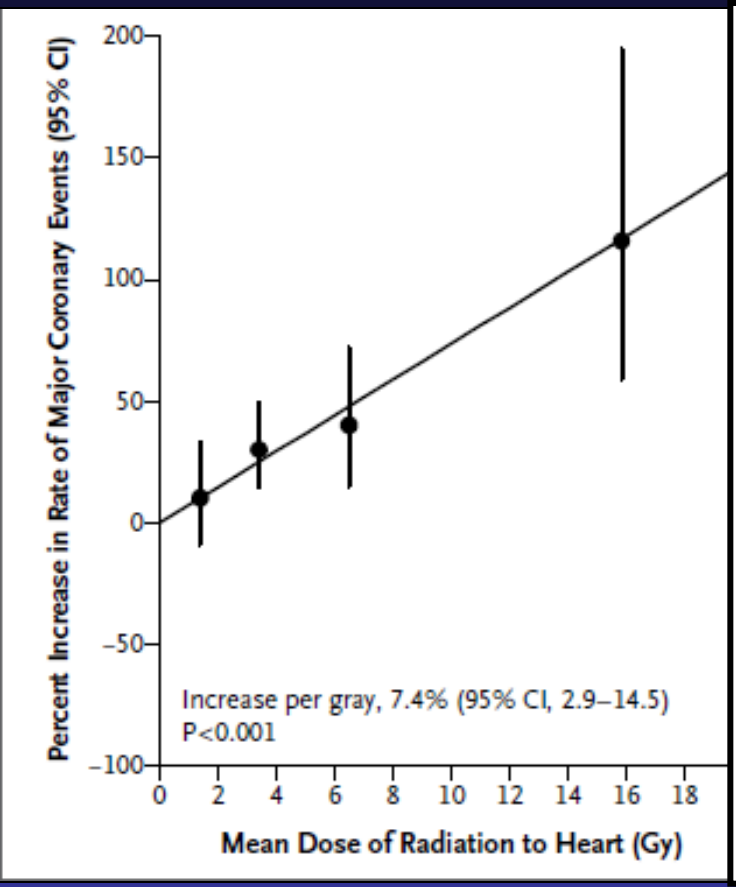
Chen et al, Circulation 2008

A Practical Approach 2



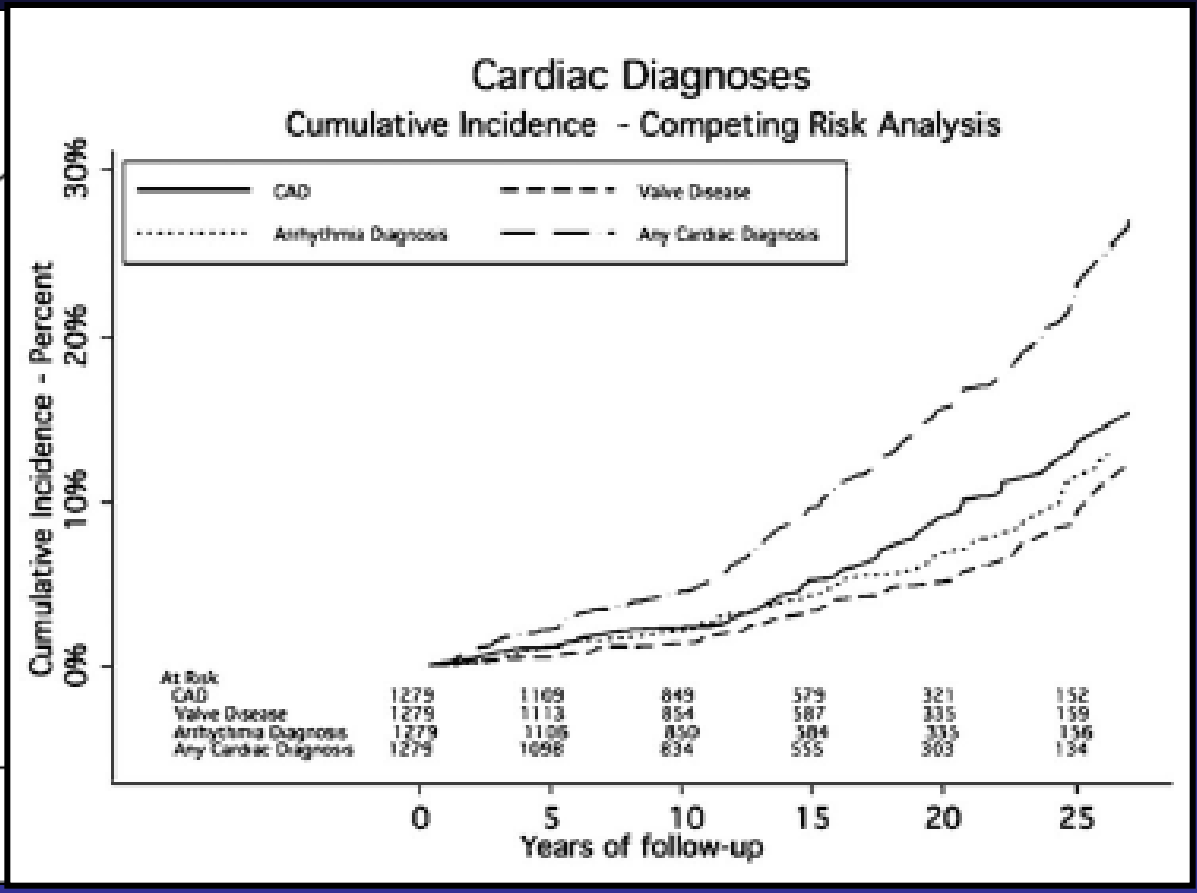
Long-term effects of irradiation

Breast Cancer



Darby et al, NEJM 2013

Hodgkin Disease



Galper et al, Blood 2011

Conclusions

- **Cardiotoxicity and increased CV risk are potentially serious complications of cancer therapy.**

- **Cardiotoxicity is becoming increasingly important in the modern medical practice in parallel with the expanding number, extending age of the cancer patients and the 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.**

Cardio-Oncological Clinic

Heart Failure Service, Sheba MC

Prof. Freimark, Dr. Arad, Dr. Peled

- Pretreatment evaluation & consultation
- Treating oncotherapy-induced cardiotoxicity
- Team approach to difficult cases
- Joint research activities