ECOCARDIOCHIRURGIA.it

# 6° CONGRESSO NAZIONALE DI ECOCARDIOCHIRURGIA
# MILANO 15-17 OTTOBRE 2012

# Cardioprotezione Farmacologica da Antineoplastici: Realtà o Fantasia.


**Paolo Spallarossa**

**Cattedra di Malattie dell'Apparato Cardiovascolare**
**IRCCS – A.O.U. San Martino IST**
**Genova**

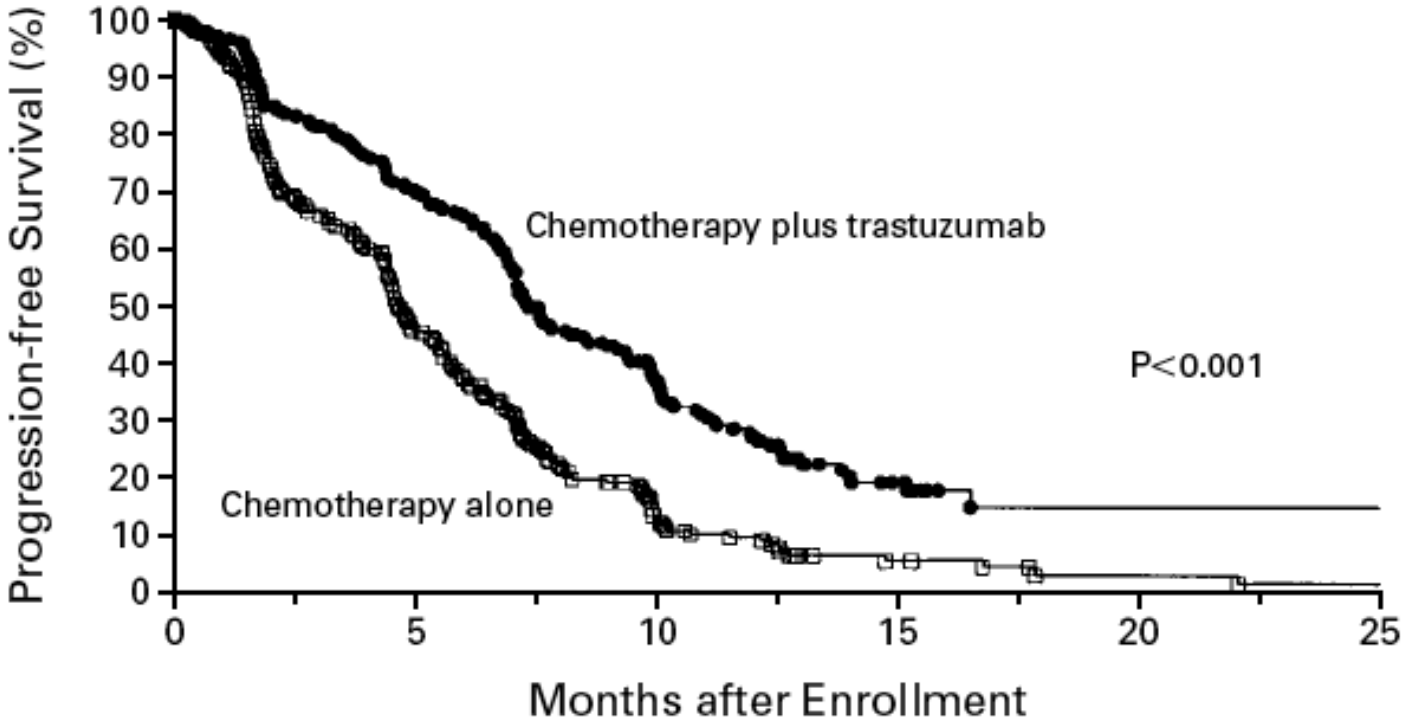
Paolo.Spallarossa@unige.it

# USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

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

A




| No. at Risk | | | | |
|---|---|---|---|---|
| Chemotherapy plus trastuzumab | 235 | 152 | 63 | 15 |
| Chemotherapy alone | 234 | 103 | 25 | 6 |

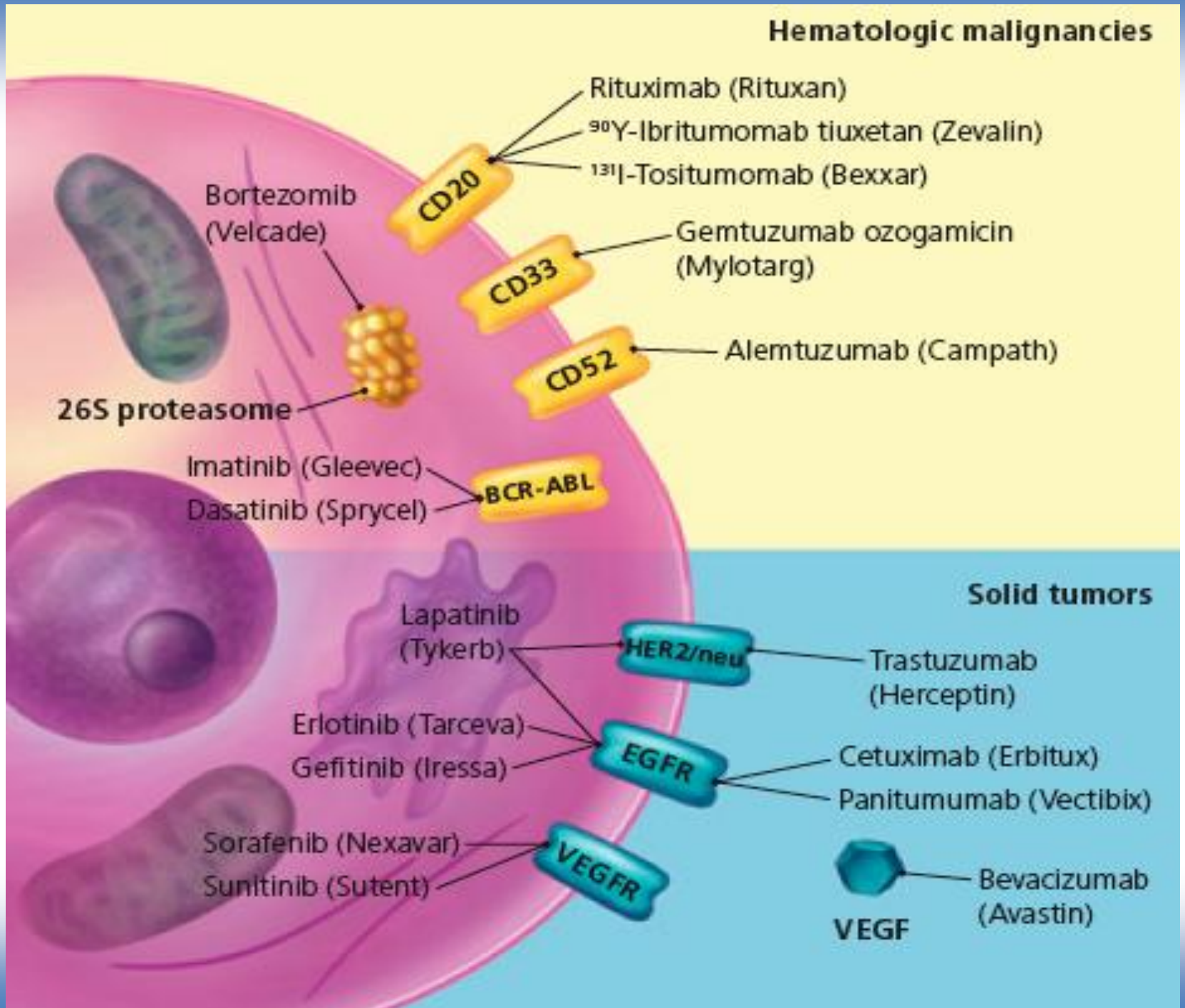
# USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

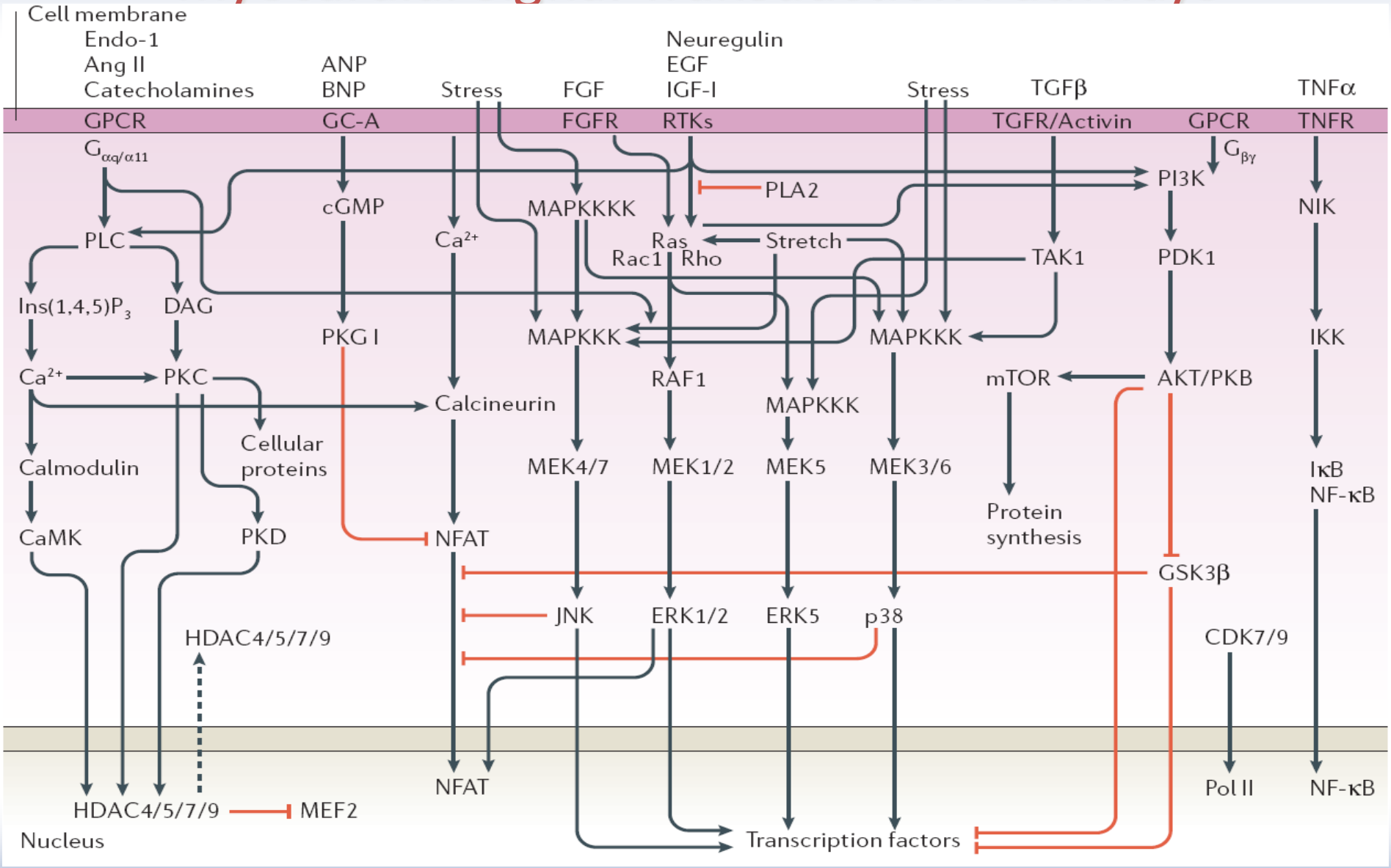
N Engl J Med. Vol. 344. No. 11 · March 15. 2001

**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) |
| Infection | 47 (2) | 29 (2) | 47 (2) | 30 (2) | 46 (1) | 27 (2) |
| Pain | 58 (6) | 50 (7) | 57 (4) | 42 (8) | 60 (10) | 61 (6) |
| **Heart Failure** | **22(10)** | **5(2)** | **27(16)** | **8(3)** | **13(2)** | **1(1)** |

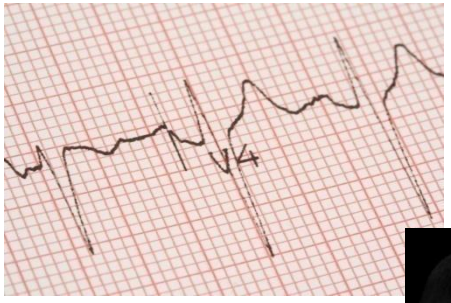

Hematologic malignancies
Rituximab (Rituxan)
90Y-Ibritumomab tiuxetan (Zevalin)
131I-Tositumomab (Bexxar)
CD20
Bortezomib (Velcade)
Gemtuzumab ozogamicin (Mylotarg)
CD33
CD52
Alemtuzumab (Campath)
26S proteasome
Imatinib (Gleevec)
Dasatinib (Sprycel)
BCR-ABL
Solid tumors
Lapatinib (Tykerb)
HER2/neu
Trastuzumab (Herceptin)
Erlotinib (Tarceva)
Gefitinib (Iressa)
EGFR
Cetuximab (Erbitux)
Panitumumab (Vectibix)
Sorafenib (Nexavar)
Sunitinib (Sutent)
VEGFR
Bevacizumab (Avastin)
VEGF

# Myocardial Signal Transduction Pathways




*Heineke J, Molkentin Nat Rev Mol Cell Biol 2006;7:589-600*

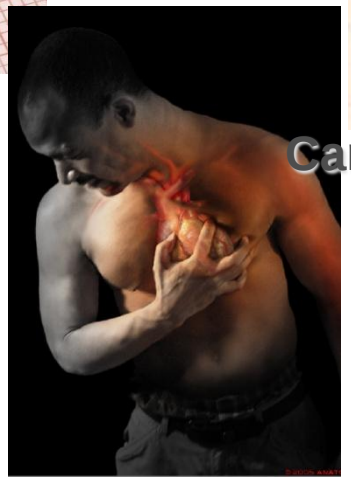
# CV Complications of Cancer Treatment



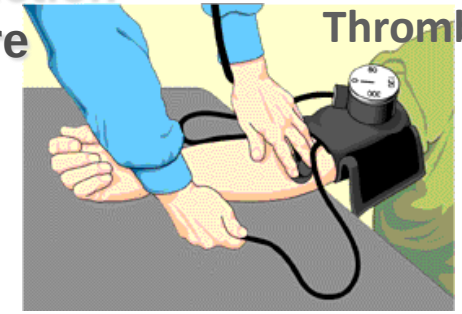

Arrhythmia
QT-Prolongation


Cardiac Dysfunction
Heart Failure

Thromboembolism



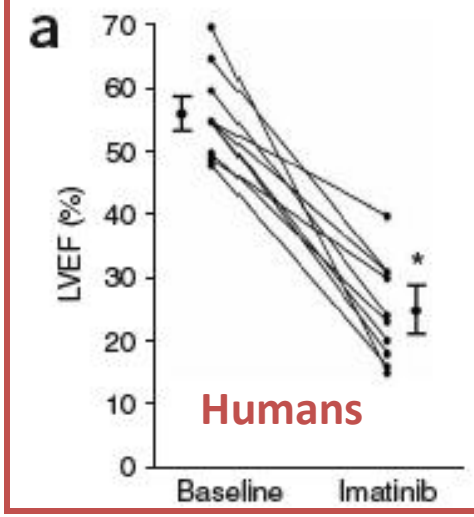
AP / MI

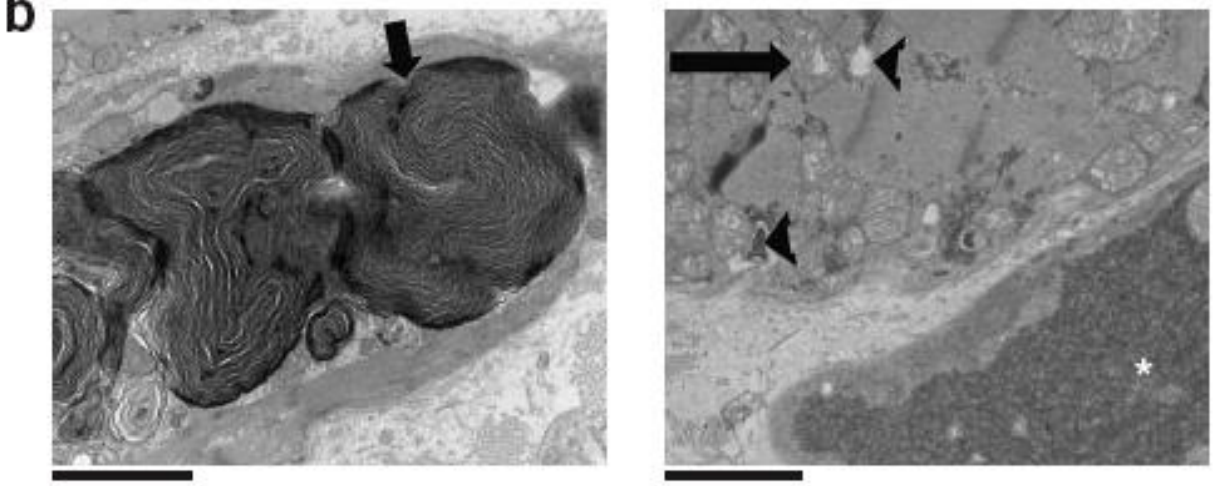


Hypertension

# Cardiotoxicity of the cancer therapeutic agent imatinib mesylate

nature medicine
AUGUST 2006




| Mice | Vehicle | Imatinib 200 mg/kg (5 weeks) |
|---|---|---|
| FS (%) | 28.7 ± 3.63 | 19.9 ± 0.86** |
| EF (%) | 49.0 ± 5.00 | 35.8 ± 1.43** |
| LVEDD (mm) | 3.79 ± 0.19 | 4.17 ± 0.24* |
| LVESD (mm) | 2.76 ± 0.13 | 3.36 ± 0.17*** |
| LVW/BW (mg/g) | 4.68 ± 0.29 | 3.72 ± 0.27** |

# Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition

*Thomas Force*, Daniela S. Krause‡ and Richard A. Van Etten§*

Abstract | Cancer therapy has progressed remarkably in recent years. In no area has this been more apparent than in the development of 'targeted therapies', particularly those using drugs that inhibit the activity of certain tyrosine kinases, activating mutations or amplifications of which are causal, or strongly contributory, to tumorigenesis. However, some of these therapies have been associated with toxicity to the heart. Here we summarize what is known about the cardiotoxicity of cancer drugs that target tyrosine kinases. We focus on basic mechanisms through which interruption of specific signalling pathways leads to cardiomyocyte dysfunction and/or death, and contrast this with therapeutic responses in cancer cells.

NATURE REVIEWS | CANCER VOLUME 7 | MAY 2007

***Cardiotoxicity of imatinib.***

That said, the data are reassuring, because they suggest that CHF of sufficient severity to require hospitalization is uncommon.

# I Mille Volti della Cardiotossicità da Antineoplastici

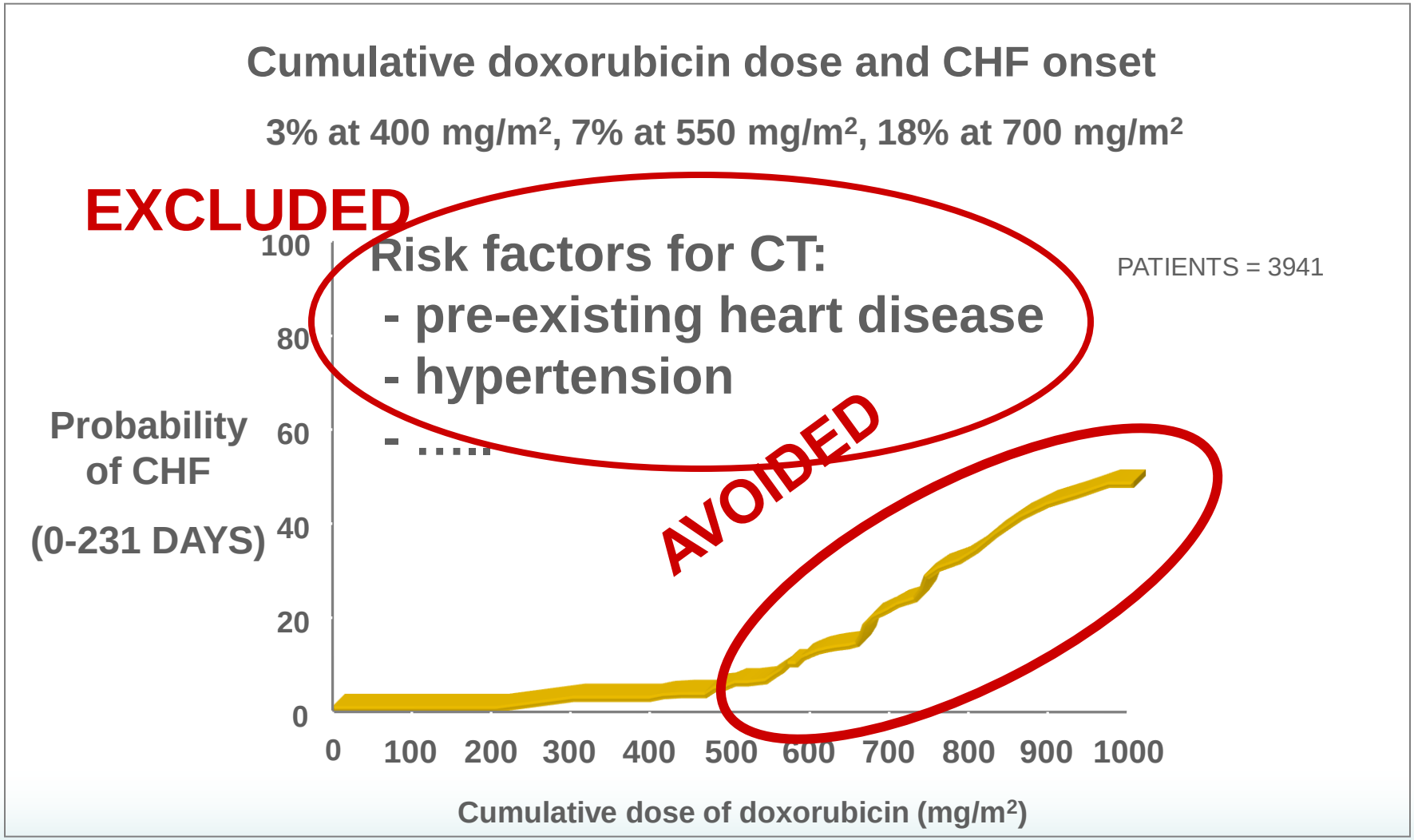
| Farmaci | Meccanismi biochimici | Tipo di Cardiotossicità | Caratteistiche cliniche |
|---|---|---|---|
| Decine | Numerosi | SCA<br>INSUFF CARDIACA<br>IPERTENSIONE<br>TROMBOSI<br>ARITMIE | Rara/Frequente<br>Grave/Lieve<br>Reversibile/Irrev.<br>Acuta/Cronica<br>Precoce/Tardiva<br>Dose dipend/Indip. |

**Cardiotossicità:**
**Non fare**
**di tutt'erba un fascio**

# Tossicità da Antracicline

# ANTHRACYCLINE CARDIOTOXICITY (CT)

## Dose dependent

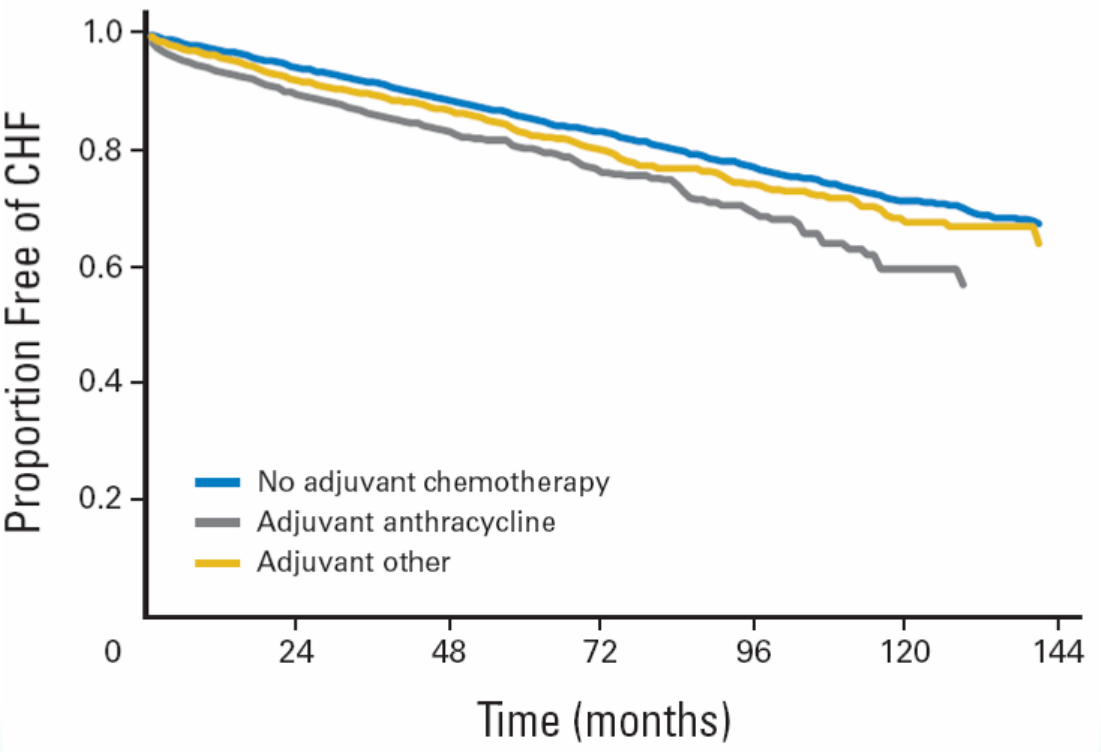



*Von Hoff DD et al. Ann Intern Med 1979*

# ANTHRACYCLINES CARDIOTOXICITY

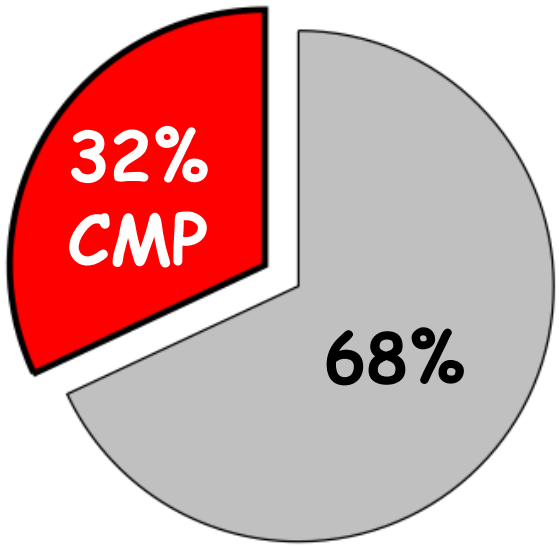
## Time dependent

Surveillance, Epidemiology, and End Results Medicare database: **BREAST CANCER**




*J Clin Oncol.* 2007;91:37-44

Subclinical late cardiomyopatthy (**CMP)** in lymphoma patients treated with low dose anthracyclines. A retrospective study




**9-year FU**

**J Clin Oncol. 2004;22:1864**

# USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D., JANET WOLTER, M.D., MARK PEGRAM, M.D., JOSE BASELGA, M.D., AND LARRY NORTON, M.D.*

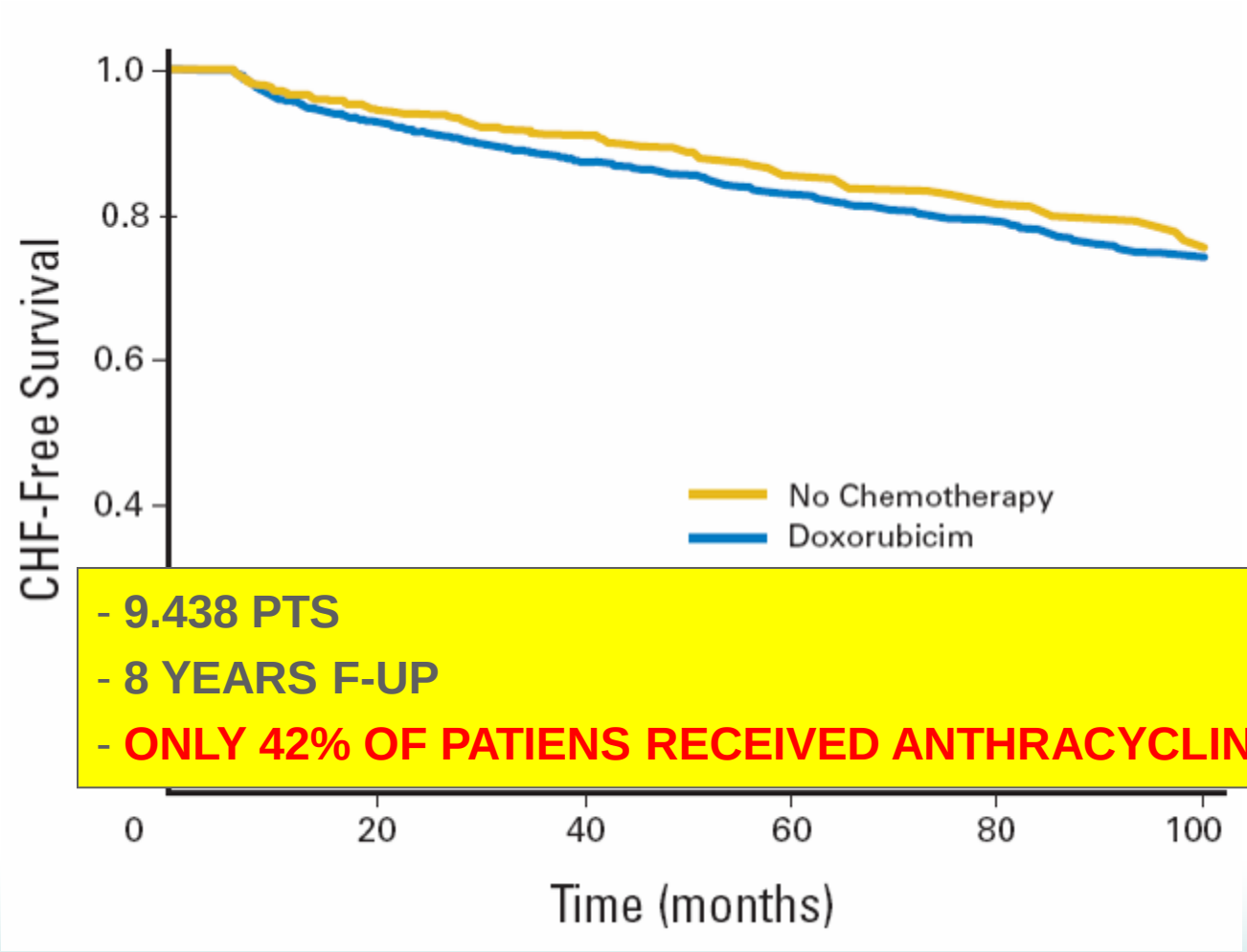
N Engl J Med. Vol. 344. No. 11 · March 15. 2001

**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) |
| Infection | 47 (2) | 29 (2) | 47 (2) | 30 (2) | 46 (1) | 27 (2) |
| Pain | 58 (6) | 50 (7) | 57 (4) | 42 (8) | 60 (10) | 61 (6) |
| **Heart Failure** | **22(10)** | **5(2)** | **27(16)** | **8(3)** | **13(2)** | **1(1)** |

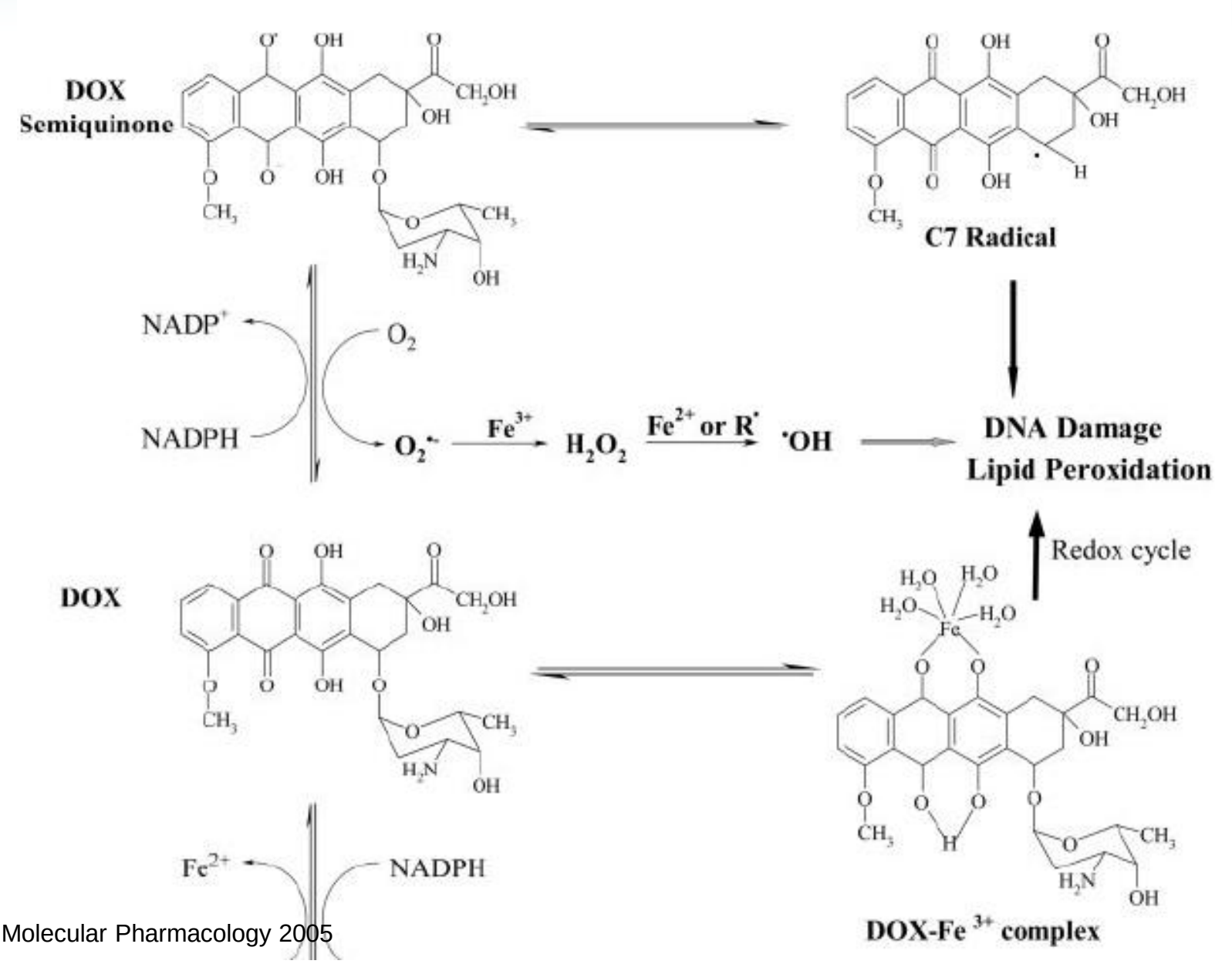
# FEAR OF ANTHRACYCLINE CARDIOTOXICITY LIMITS ANTHRACYCLINE USE

Surveillance, Epidemiology, and End Results Medicare database: **DIFFUSE LARGE B-CELL LYMPHOMA**




Hershman et al. *J Clin Oncol.* 2008

# Iron-dependent ROS Production




Xu et al. Molecular Pharmacology 2005

# Cardiotossicità da Antracicline

## Danni ultrastrutturali

- Perdita di miofibrille
- Dilatazione del reticolo sarcoplasmatico
- Vacuolizzazione citoplasmatica
- Rigonfiamento dei mitocondri
- Aumento del numero dei lisosomi

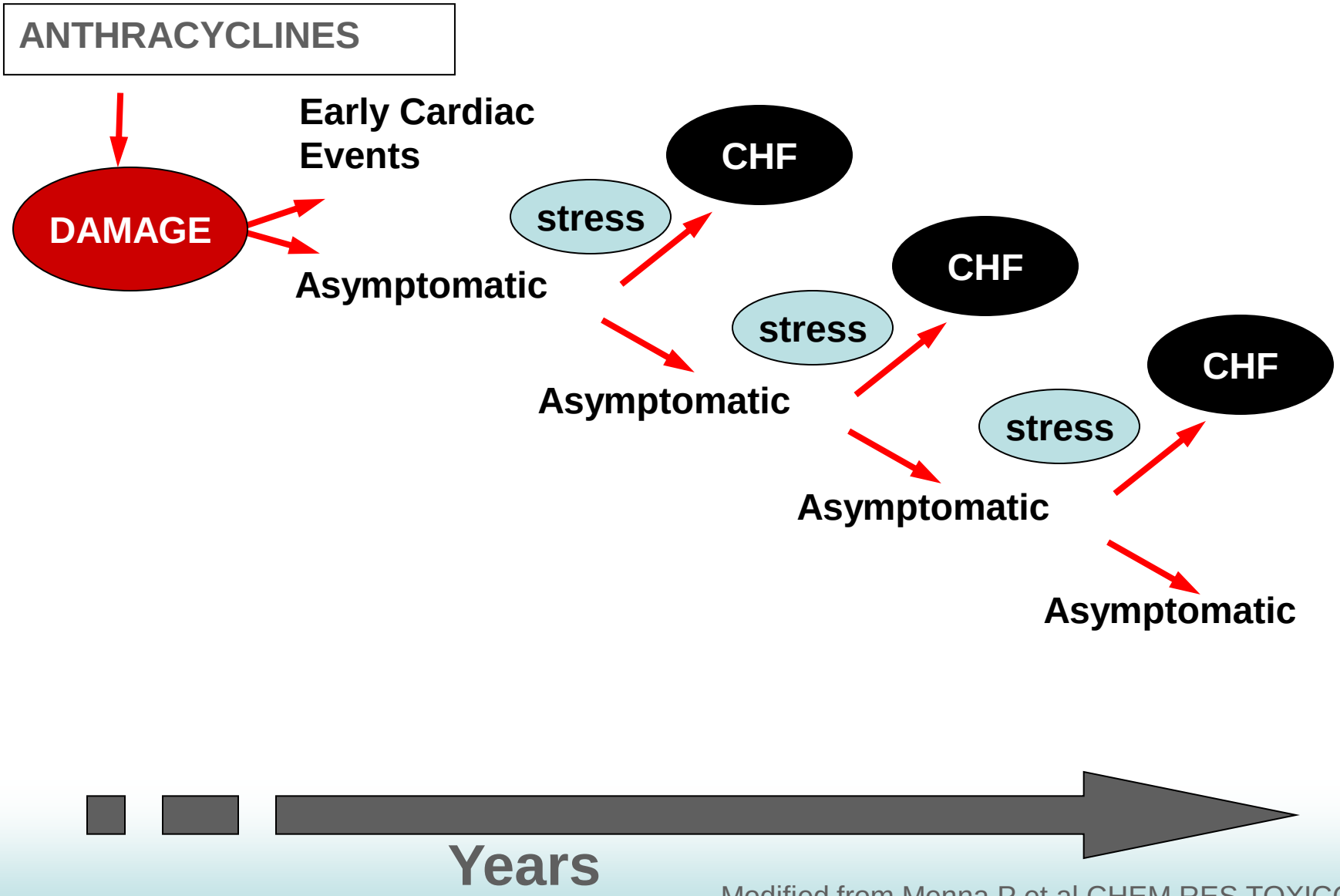
## Risposta cellulare

- Necrosi
- Apoptosi
- Senescenza

## Cellule Bersaglio

- Cardiomiociti
- Fibroblasti
- Cellule vascolari
- Cellule mature/staminali

# LATE ONSET CARDIOTOXICITY




Modified from Menna P et al CHEM RES TOXICOL 2008

# PRIMA DI PARTIRE CON TERAPIE CONTENENTI ANTRACICLINE.

## Proteggere il cuore da tutti gli stress, *Presenti* e *Futuri*

**Verificare che il trattamento dei fattori di rischio eventualmente presenti abbia raggiunto il bersaglio**

**Se c'è ipertensione o disfunzione VS introdurre farmaci bloccanti il Sistema Renina-Angiotensina e/o bloccanti adrenergici di nuova generazione**

**Educare alla prevenzione dei fattori di rischio**

Effetti delle Antracicline sul cuore

Strategie di prevenzione

**Cardioprotezione**

**Cardiotossicità**
con metodiche ultrasensibili
tende al **100%**

**Evidente disfunzione ventricolare sinistra**
in assenza di trattamento dipende dalla selezione dei pazienti, dalla dose di antracicline e dalla durata del follow up (**25-33%** dei pazienti)

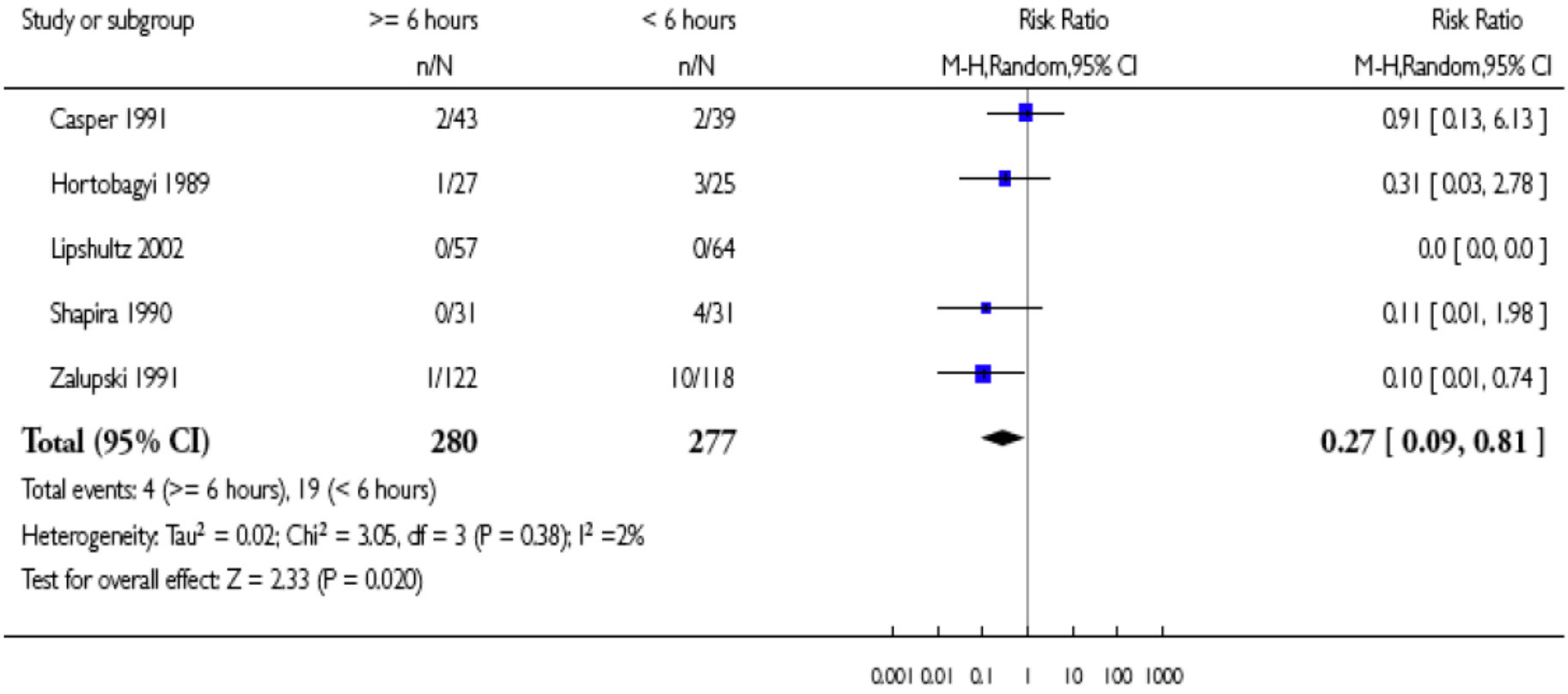
**Insufficienza cardiaca**

# Cardioprotezione

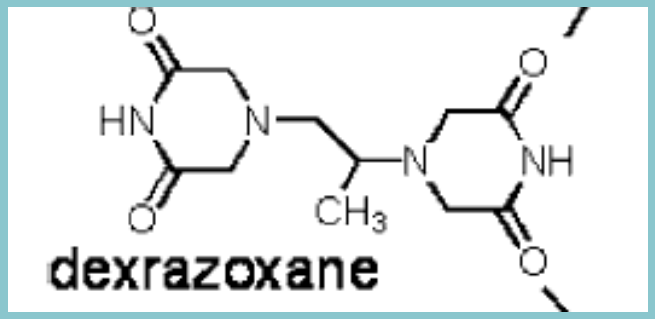
- Antracicline meno cardiotossiche
- Modalità di infusione
- Agenti cardioprotettivi
- Esercizio fisico
- Modificare la farmacodinamica con le antracicline liposomiali.

# ANTRACICLINE E CARDIOPROTEZIONE
# DURATA DELL'INFUSIONE

**Analysis 1.1. Comparison 1 Infusion duration less than 6 hours versus infusion duration 6 hours or more, Outcome 1 Clinical heart failure.**




*Cochrane Database of Systematic Reviews* 2009, Issue 4.



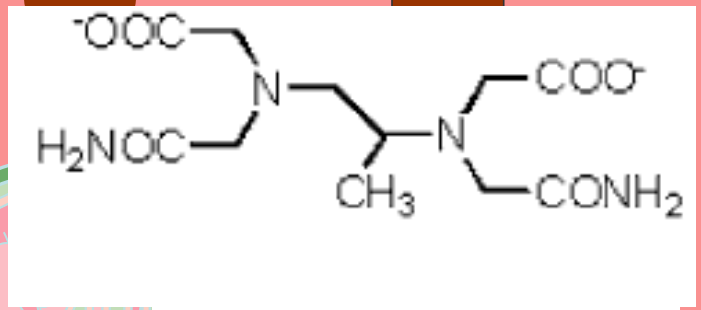

Dexrazoxane
ICRF-187
ADR-529

$Fe^{+++}$

$Fe^{+++}$

DPHasi

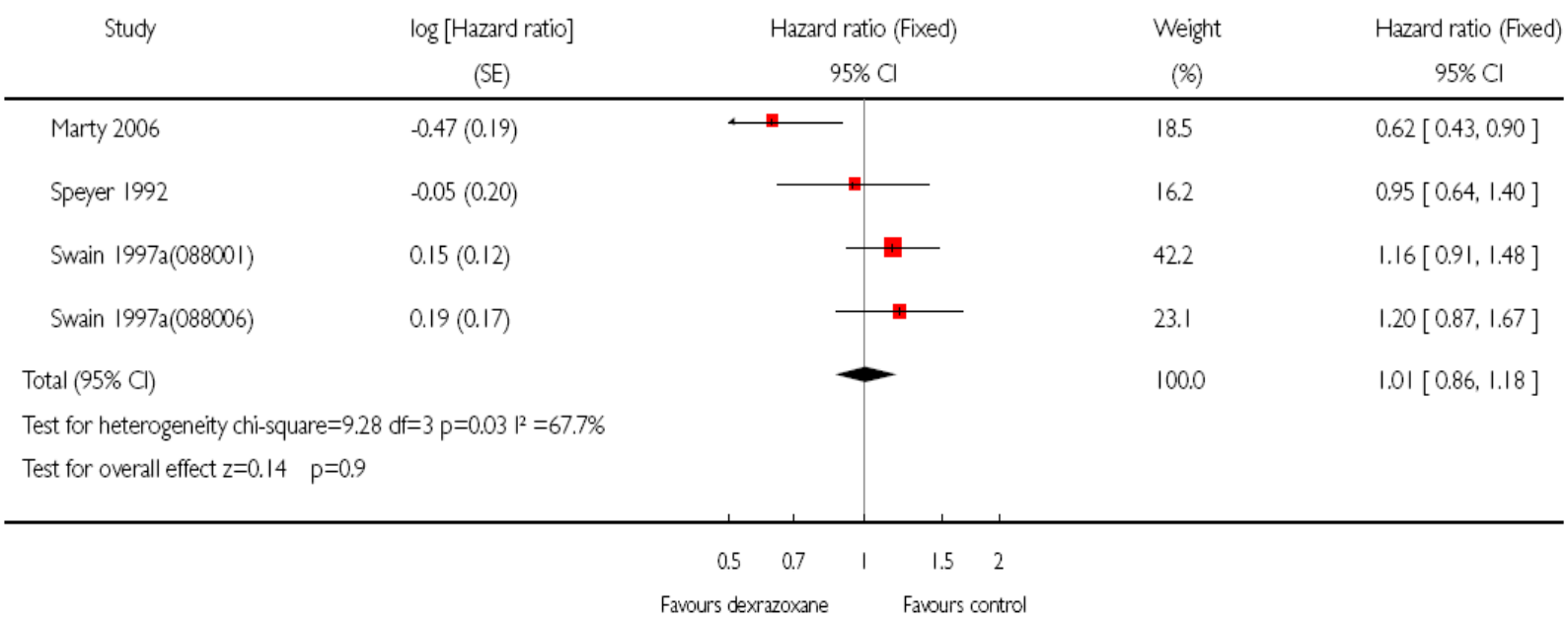
ICRF-198
ADR-925



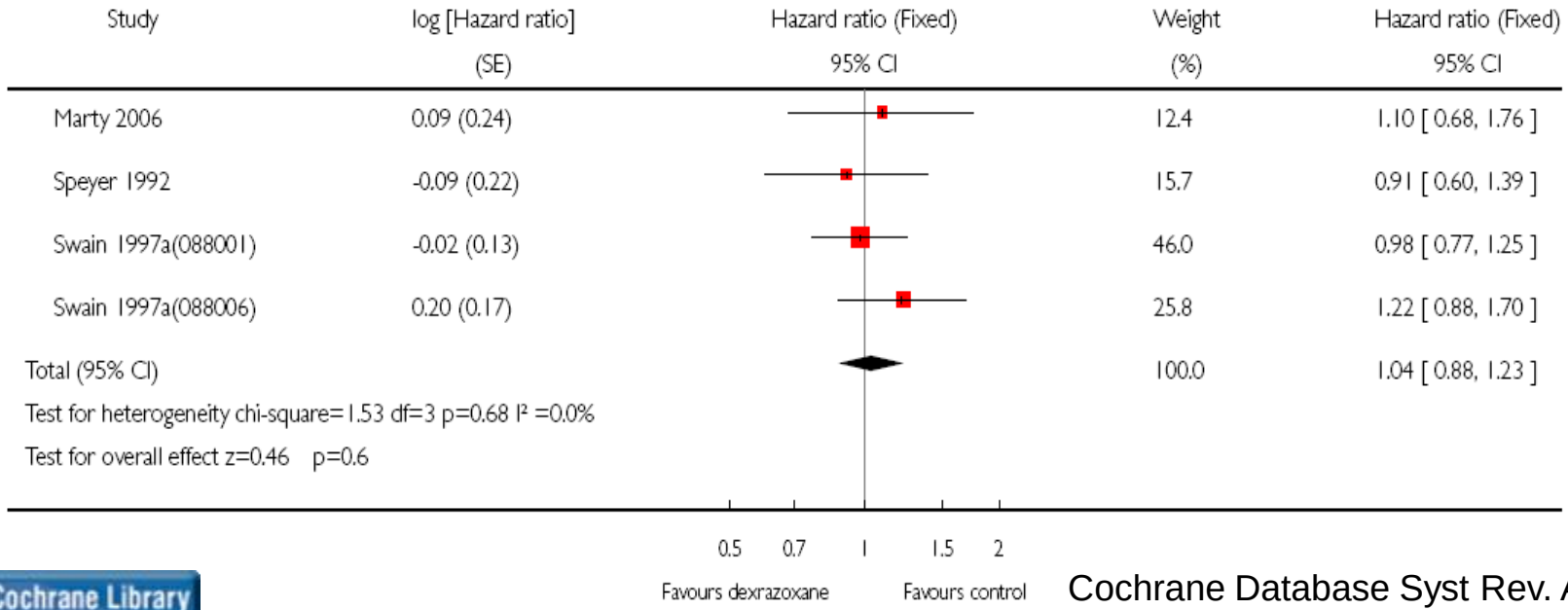
# Dexrazoxane (DX) cardioprotective efficacy in randomized trials in adult cancer patients

| | Pts | Treatment | Dose [cycles] | Cardiac Events (%) | CHF (%) |
|---|---|---|---|---|---|
| Swain 1997 | 168 | CDF50 + **DX** | NR | 15*** | 0*** |
| | 181 | CDF50 + pl | NR | 32 | 8 |
| Swain 1997 | 81 | CDF50 + **DX** | NR | 14** | 3 |
| | 104 | CDF50 + pl | NR | 31 | 7 |
| Marty 2004 | 85 | dox50 or epi90 + **DX** | 669 [2-6] | 13*** | 1* |
| | 79 | dox50 or epi90 | 608 [2-6] | 39 | 11 |
| Speyer 1992 | 76 | CDF50 + DX | 558* [11**] | 8*** | 3*** |
| | 74 | CDF50 | 407 [9] | 50 | 27 |
| Venturini 1996 | 82 | CEF60 or epi120 + **DX** | 702 [6] | 7** | 2 |
| | 78 | CEF60 or epi120 | 713 [6] | 23 | 5 |
| Vici 1998 | 43 | epi160 + **DX** | 960 [6] | 0* | 0 |
| | 49 | epi160 | 980 [6] | 16 | NR |
| Feldmann 1992 | 73 | CDV50 + **DX** | NR | 12* | 4 |
| | 82 | CDV50 | NR | 29 | 10 |
| Lopez 1998 | 18 | Epi160 + **DX** | 960 [6] | 9** | 7* |
| | 16 | Epi160 | 980 [6] | 29 | 24 |

**Analysis 01.04. Comparison 01 Dexrazoxane versus no dexrazoxane / placebo, Outcome 04 Progression-free survival**




**Analysis 01.05. Comparison 01 Dexrazoxane versus no dexrazoxane / placebo, Outcome 05 Overall survival**






Cochrane Database Syst Rev. Apr 2008

Leukemia (2010) 24, 355–370
© 2010 Macmillan Publishers Limited All rights reserved 0887-6924/10 $32.00
www.nature.com/leu

EDUCATIONAL REPORT

# Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984–2001: a report from the children's oncology group

WL Salzer[1], M Devidas[2], WL Carroll[3], N Winick[4], J Pullen[5], SP Hunger[6] and BA Camitta[7]

*[1]National Cancer Institute, Bethesda, MD, USA; [2]Department of Epidemiology and Health Policy Research, College of Medicine, University of Florida and the Children's Oncology Group, Gainesville, FL, USA; [3]Department of Pediatrics, Division of Pediatric Hematology/Oncology, New York University Cancer Institute, New York, NY, USA; [4]Department of Pediatrics, Division of Pediatric Hematology/Oncology, University of Texas Southwestern School of Medicine, Dallas, TX, USA; [5]Department of Pediatrics, Division of Pediatric Hematology/Oncology, University of Mississippi School of Medicine, Jackson, MS, USA; [6]Department of Pediatrics, University of Colorado Denver School of Medicine and the Children's Hospital, Aurora, CO, USA and [7]Department of Pediatrics of the Medical College of Wisconsin and Children's Hospital of Wisconsin, Center for Cancer and Blood Disorders, Milwaukee, WI, USA*

| Regimen | No. of patients | Event-free survival ± s.e. (%) | | | |
|---|---|---|---|---|---|
| | | Year 5 | Year 10 | Year 15 | P-value |
| *9404 (Dexrazoxane)* | | | | | |
| No Dexrazoxane | 176 | 74.4 ± 3.4 | 73.0 ± 6.4 | | 0.85 |
| Dexrazoxane | 187 | 73.6 ± 3.4 | 71.3 ± 7.0 | | |

| Study | Event type | No of patients | Cumulative incidence ± s.e. (%) | | | P-value |
|---|---|---|---|---|---|---|
| | | | Year 5 | Year 10 | Year 15 | |
| *9404 (Dexrazoxane)* | | | | | | |
| No Dexrazoxane | Second malignancy | 159 | 1.3 ± 0.9 | 1.3 ± 0.9 | | 0.15 |
| Dexrazoxane | | 173 | 2.3 ± 1.2 | 4.2 ± 2.2 | | |

# Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial

*Steven E Lipshultz, Rebecca E Scully, Stuart R Lipsitz, Stephen E Sallan, Lewis B Silverman, Tracie L Miller, Elly V Barry, Barbara L Asselin, Uma Athale, Luis A Clavell, Eric Larsen, Albert Moghrabi, Yvan Samson, Bruno Michon, Marshall A Schorin, Harvey J Cohen, Donna S Neuberg, E John Orav, Steven D Colan*

**Lancet Oncol 2010; 11: 950–61**

2%.[71–77] Moreover, we did not find the association between dexrazoxane and second malignant neoplasms[34] that was reported,[78] although questioned,[79,80] in a paediatric Hodgkin's lymphoma trial in which three DNA topoisomerase type II inhibitors, some noted to be associated with second malignancies in childhood cancer survivors,[81,82]

# Agenti cardioprotettivi.

| Agent | Class | Mechanism | Study subject |
|---|---|---|---|
| Carvedilol | B-adrenergic antagonist | Prevention of free radical formation; prevention of depletion of endogenous antioxidants | Humans |
| Nebivolol | B-adrenergic antagonist | Nitric oxid release | Humans |
| Valsartan | Angiotensin II receptor blocker | Inhbition of angiotensin II effects | Humans |
| Dexrazoxane | Chelating agent | Prevention of free radical formation; inhibition of DNA topoisomerase | Humans |
| Coenzyme Q10 | Dietary supplement | Antioxidant | Humans |
| Carnitine | Dietary supplement | Antioxidant; transfer of long chain fatty acids into mitochondria | Humans |
| N-acetylcysteine | Mucolytic agent | Promotion of endogenous antioxidant synthesis | Humans |
| Vitamina A, C and E | Nutrient | Antioxidant | Animal model/Humans |
| Erythropoietin | Hormon | Apoptosis prevention | Animal model |
| Bosentan | endothelin-1 receptor antagonist | Decrease of inflammatory markers (TNF-α) and of apoptotic signaling proteins expression | Animal model |
| Probucol | Lipid-lowering agent | Promotion of endogenous antioxidant synthesis | Animal model |
| Metformine | Insuline sensitizing | -_____ | |
| PPAR-<delta> agonists | ---------- | ---------- | |
| Fluvastatin | Statin | Antioxidant | Animal model |
| Glutathione | Tripeptide thiol | Antioxidant | Animal model |
| Selenium | Trace element | Antioxidant; anticarcinogenic action | Animal model |
| Amifostine | Cytoprotective agent | Antioxidant; scavenging of reactive oxygen species | Animal model |
| Desferoxamine | Iron-chelating agent | Production of reactive oxygen species | Animal model |

# 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*

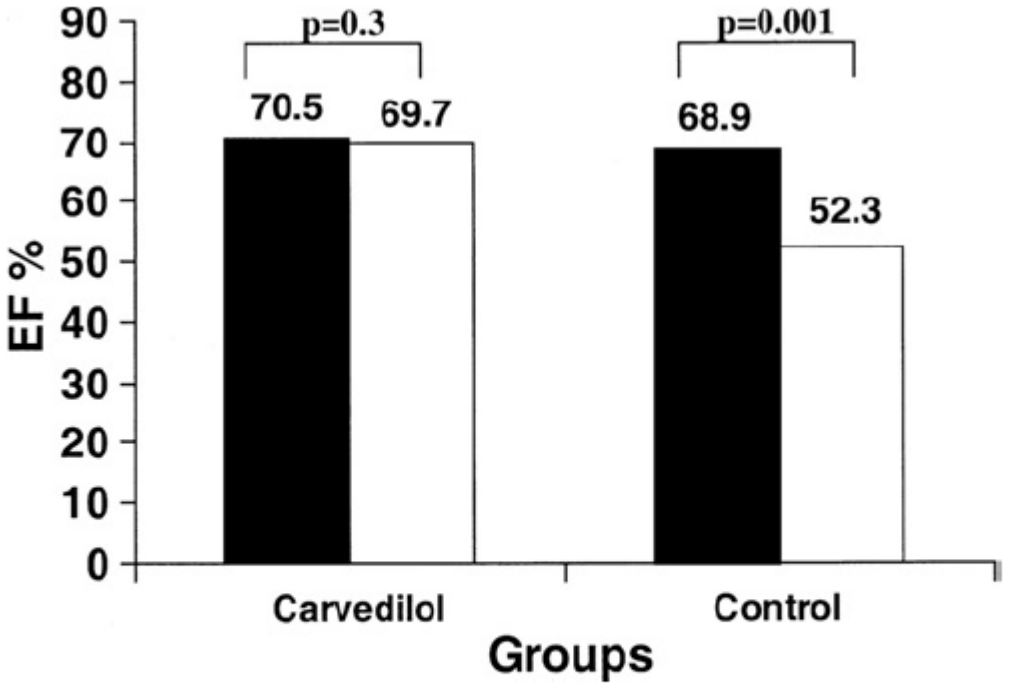



**Figure 1.** Comparison of left ventricular ejection fraction (EF) at baseline **(black bars)** and after chemotherapy **(white bars)** in the 2 groups. Data expressed as mean values.

JACC 2006

International Journal of Cardiology xxx (2012) xxx–xxx

# Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study ☆

Mehmet G. Kaya [a], Metin Ozkan [b], Ozgur Gunebakmaz [a], Hasan Akkaya [a], Esma G. Kaya [c], Mahmut Akpek [a], Nihat Kalay [a], Mustafa Dikilitas [b], Mikail Yarlioglues [a], Halit Karaca [b], Veli Berk [b], Idris Ardic [a], Ali Ergin [a], Yat Yin Lam [d,*]

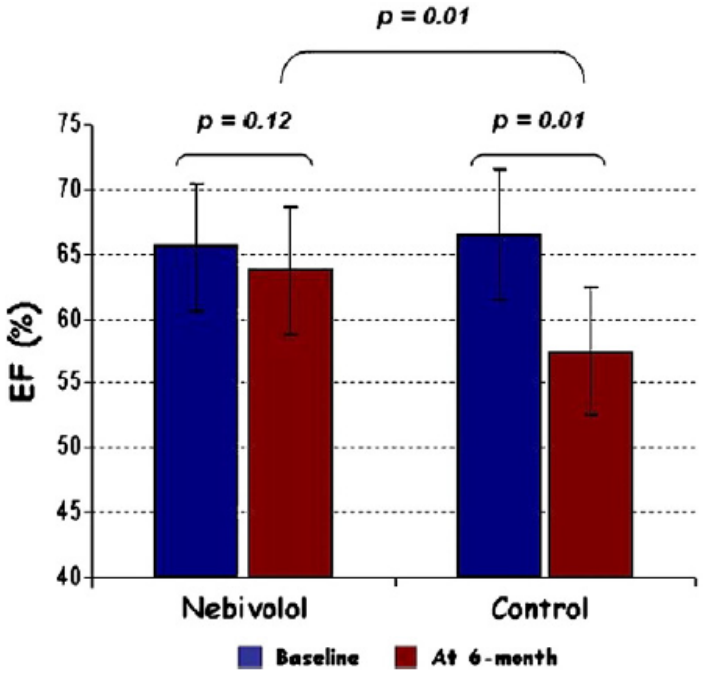



**Fig. 1.** Comparison of LVEF in nebivolol group vs. placebo group at baseline and at six-month.

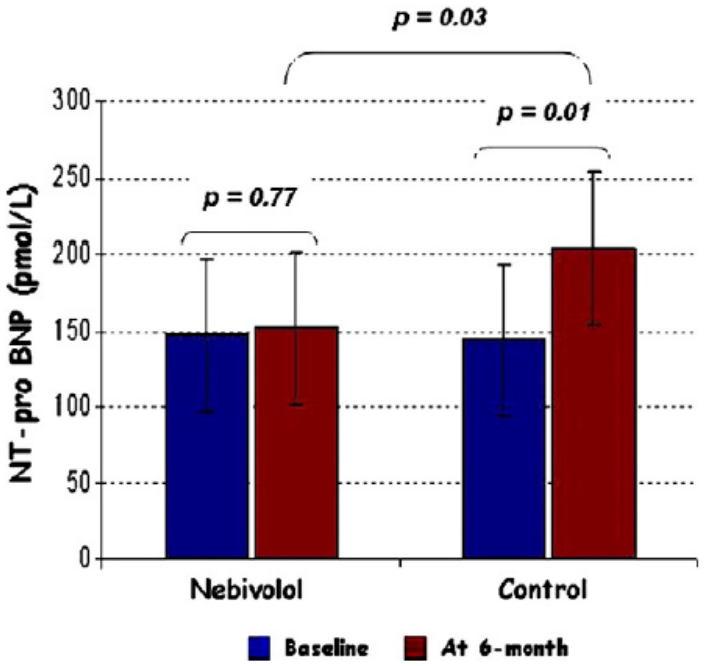


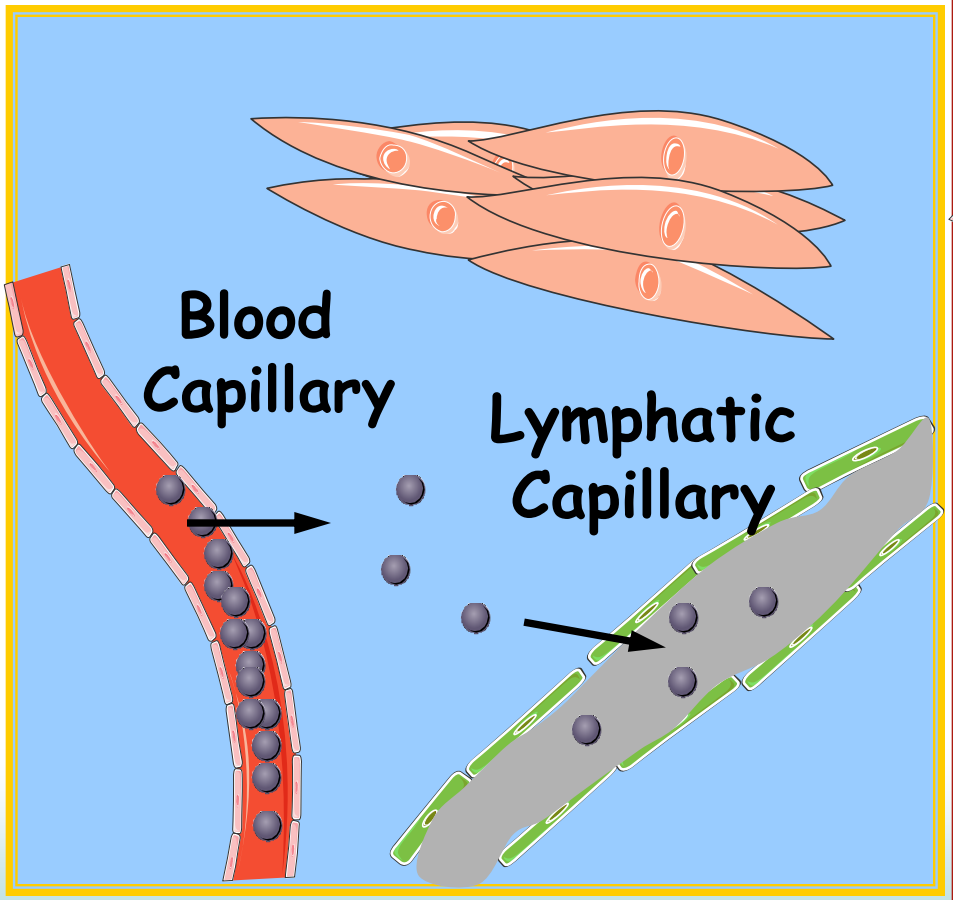

**Fig. 2.** Comparison of NT-pro-BNP levels in nebivolol group vs. placebo group at baseline and at six-month.

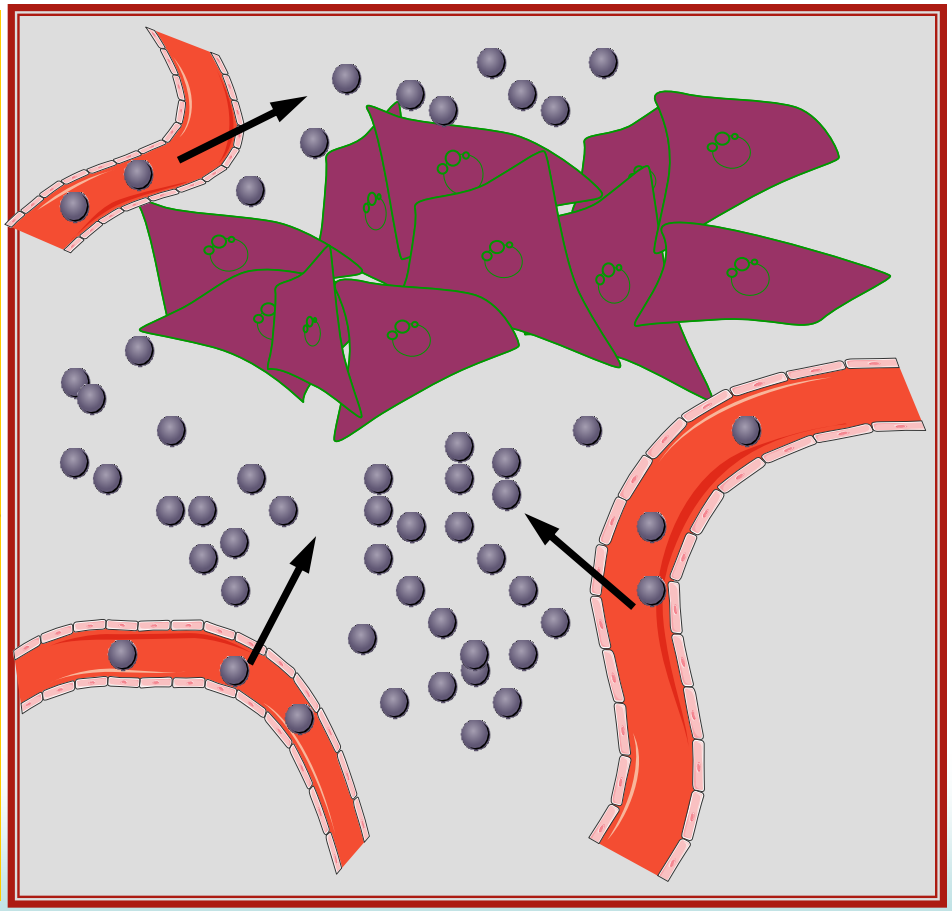
# Antracicline Liposomiali

## Enhanced Permeation Retention Effect

### Heart

### Tumor tissues



# CARDIAC SAFETY
# of Nonpegylated Liposomal Doxorubicin (D-99)

| | Pts | Treatment | Dose at onset | Objective Response Rate (%) | Suvival | Cardiac Events (%) | CHF | Score >2.5 |
|---|---|---|---|---|---|---|---|---|
| Harris | 108 | D-99 75 | 785* | 26 | 16 m | 13*** | 2*** | |
| | 116 | Doxo 75 | 570 | 26 | 20 m | 29 | 8 | |
| | 19 | D-99 75 | | | | | | 5% |
| | 17 | Doxo 75 | | | | | | 70% |
| Batist | 142 | D-99 60 +CP600 | 2000*** | 43 | 19 m | 6*** | 0* | |
| | 155 | Doxo 75 *CP600 | 480 | 43 | 16 m | 21 | 5 | |

# Conventional VS Liposomal Doxorubicin (Myocet®)

| | RR | 95%CI | p |
|---|---|---|---|
| Clinical HF | 0,20 | 0.05-0.75 | 0,02 |
| Clinical /subclinica HF | 0,38 | 0.24-0.79 | <0.0001 |
| | **HR** | **95%CI** | **p** |
| Response Rate | 1.01 | 0.80-1.26 | 0.95 |
| Event-free Survival | 1.01 | 0.83-1.24 | 0.89 |
| Survival | 1.12 | 0.83-1.53 | 0.46 |

*Cochrane 2009*

# Different anthracycline derivates for reducing cardiotoxicity in cancer patients (Review)

van Dalen EC, Michiels EMC, Caron HN, Kremer LCM

**….. We conclude that in adults with a solid tumor liposomal-endocapsulated doxorubicin should be favoured over doxorubicin.**


**2009**

# Effetti delle Antracicline sul cuore

Strategie di prevenzione

**Cardioprotezione**

**Cardiotossicità**
con metodiche ultrasensibili
tende al **100%**

Il marker ideale non è quello che dimostra la presenza di cardiotossicità ma quello che ci predice il rischio di sviluppare disfunzione VS

**Markers predittivi di disfunzione VS**

**Selezione dei pazienti**

**trattamento cardiologico**

**Evidente disfunzione ventricolare sinistra**
in assenza di trattamento dipende dalla selezione dei pazienti, dalla dose di antracicline e dalla durata del follow up (**25-33%** dei pazienti)

**Insufficienza cardiaca**

# Left Ventricular Dysfunction Predicted by Early Troponin I Release After High-Dose Chemotherapy

Daniela Cardinale, MD, Maria Teresa Sandri, MD,† Alessandro Martinoni, MD, Alessio Tricca, LabTech,† Maurizio Civelli, MD, Giuseppina Lamantia, MD, Saverio Cinieri, MD,* Giovanni Martinelli, MD,* Carlo M. Cipolla, MD, Cesare Fiorentini, MD

*Milan, Italy*

- 204 pts
- High-dose chemotherapy
- TnI 0,12,24,48,72 h after CT
- N. 65 (32%) TnI +
- N. 139 (68%) TnI -

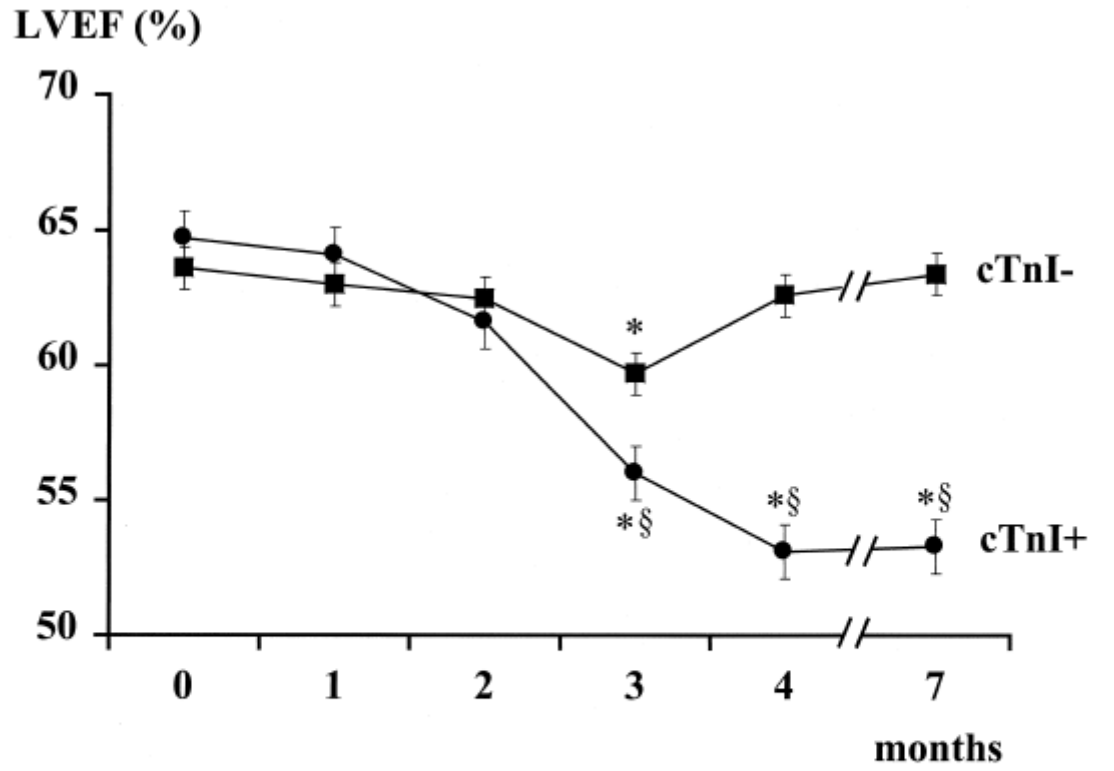



**Figure 2.** Left ventricular ejection fraction (LVEF) at baseline and during the seven months of follow-up of troponin I positive (cTnI+; **solid circle**) and negative (cTnI−; **solid square**) patients. *p < 0.001 vs. baseline (month 0); §p < 0.001 vs. cTnI− group. Data are shown as mean ± 95% confidence interval.

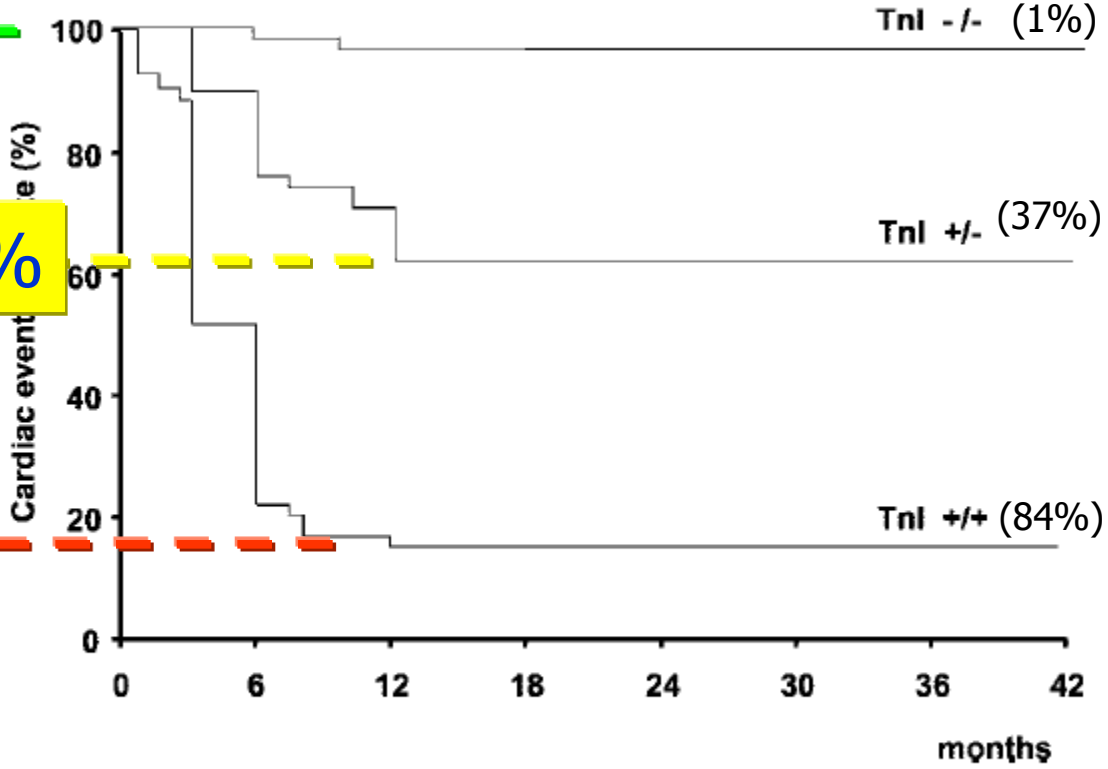
J Am Coll Cardiol 2000

# Pattern of TnI release identifies pts at different risk

Low risk: 70%

Intermediate risk: 21%

High risk: 9%



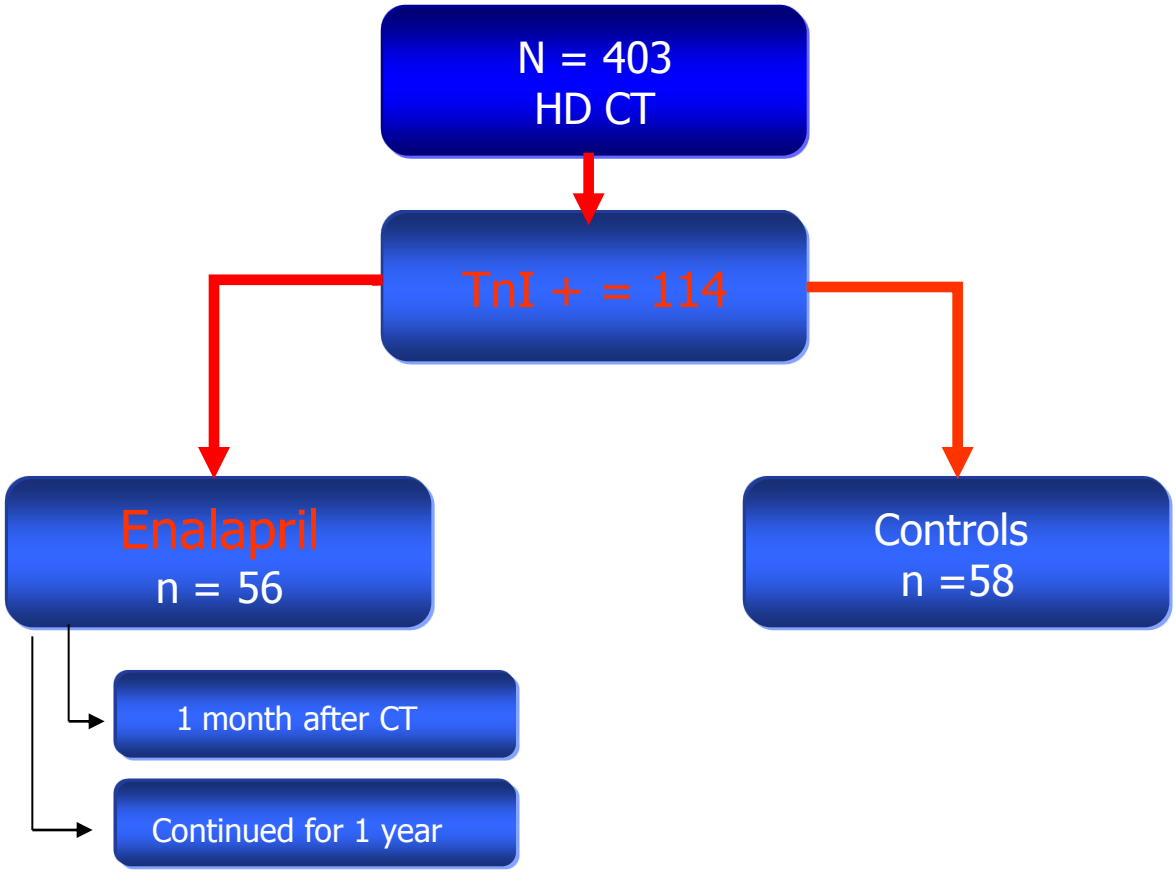

Positive predictive value = 84%

Negative predictive value = 99%

Circulation 2004

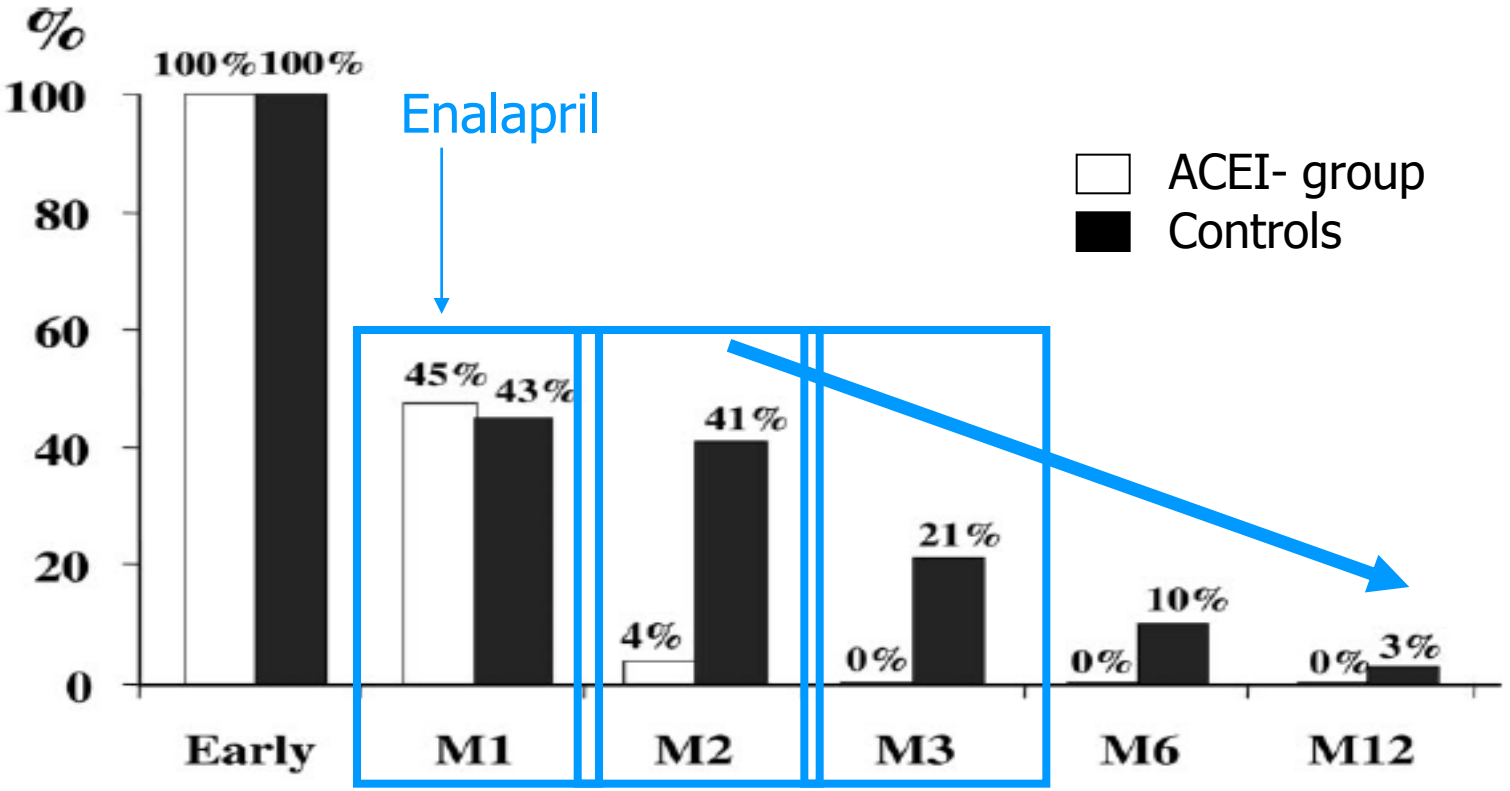
# Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

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



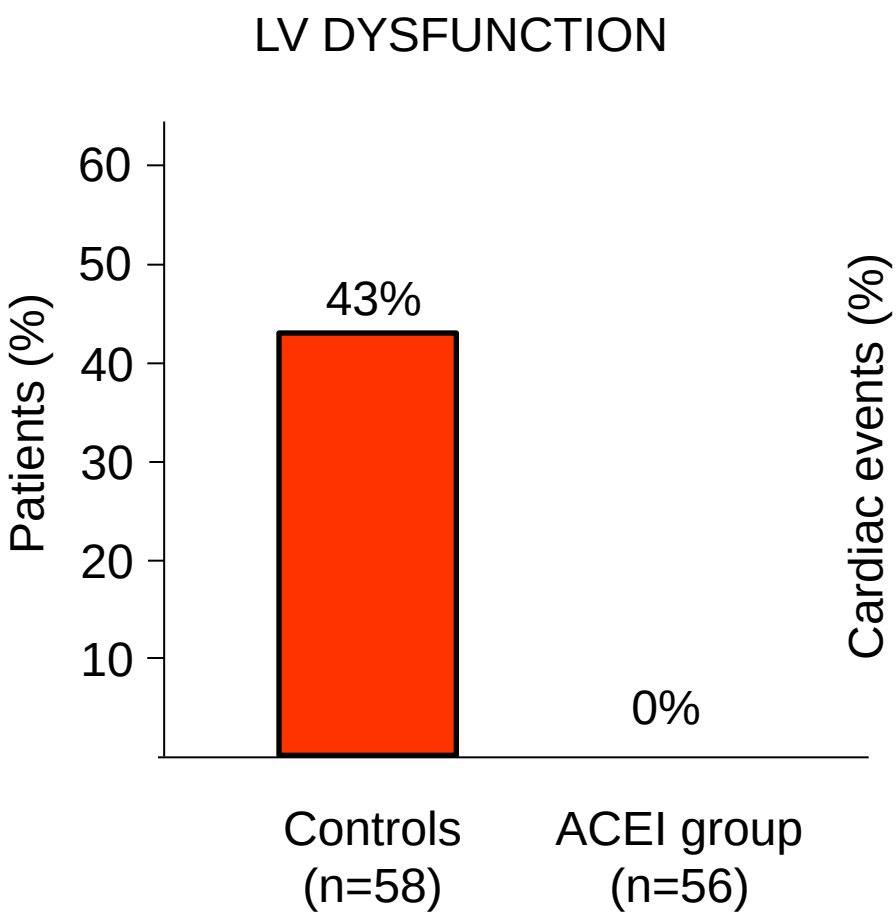

Circulation 2006

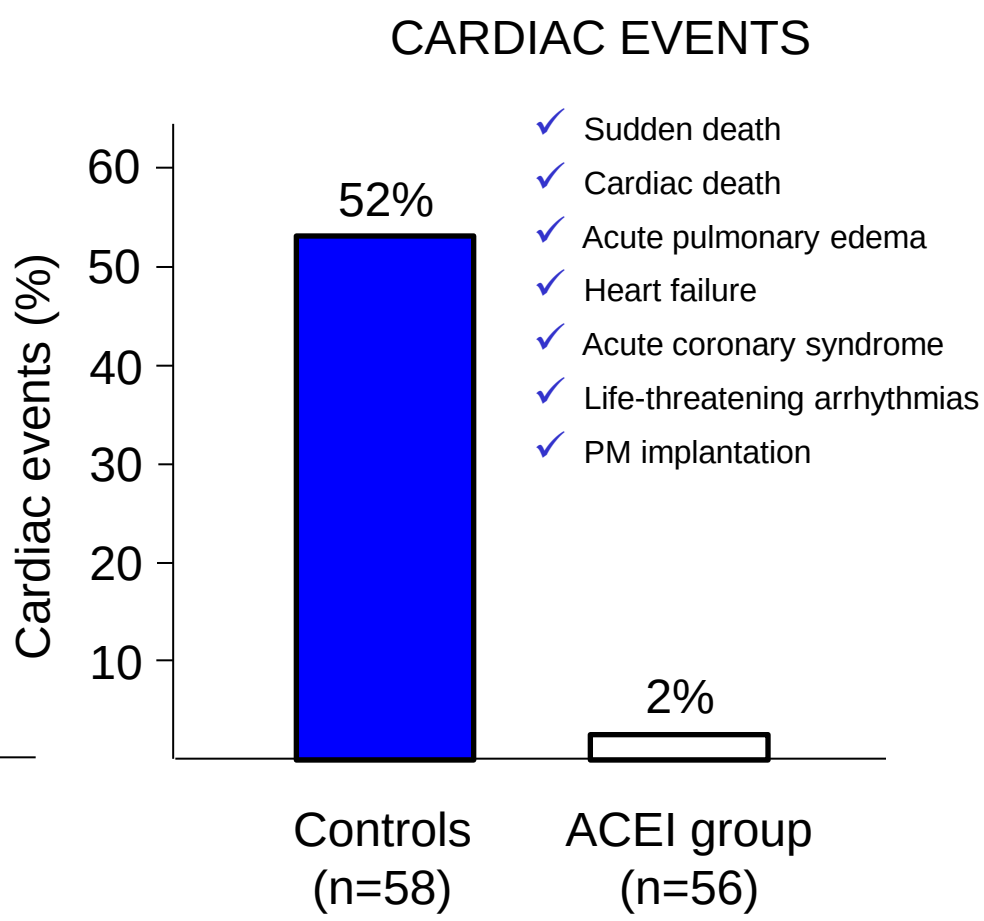
# Enalapril turns off TNI release during the 1 year follow-up




Circulation 2006

# Enalapril prevents cardiac dysfunction and cardiac events in TNI+ patients




Modified from Cardinale et al. Circulation 2006

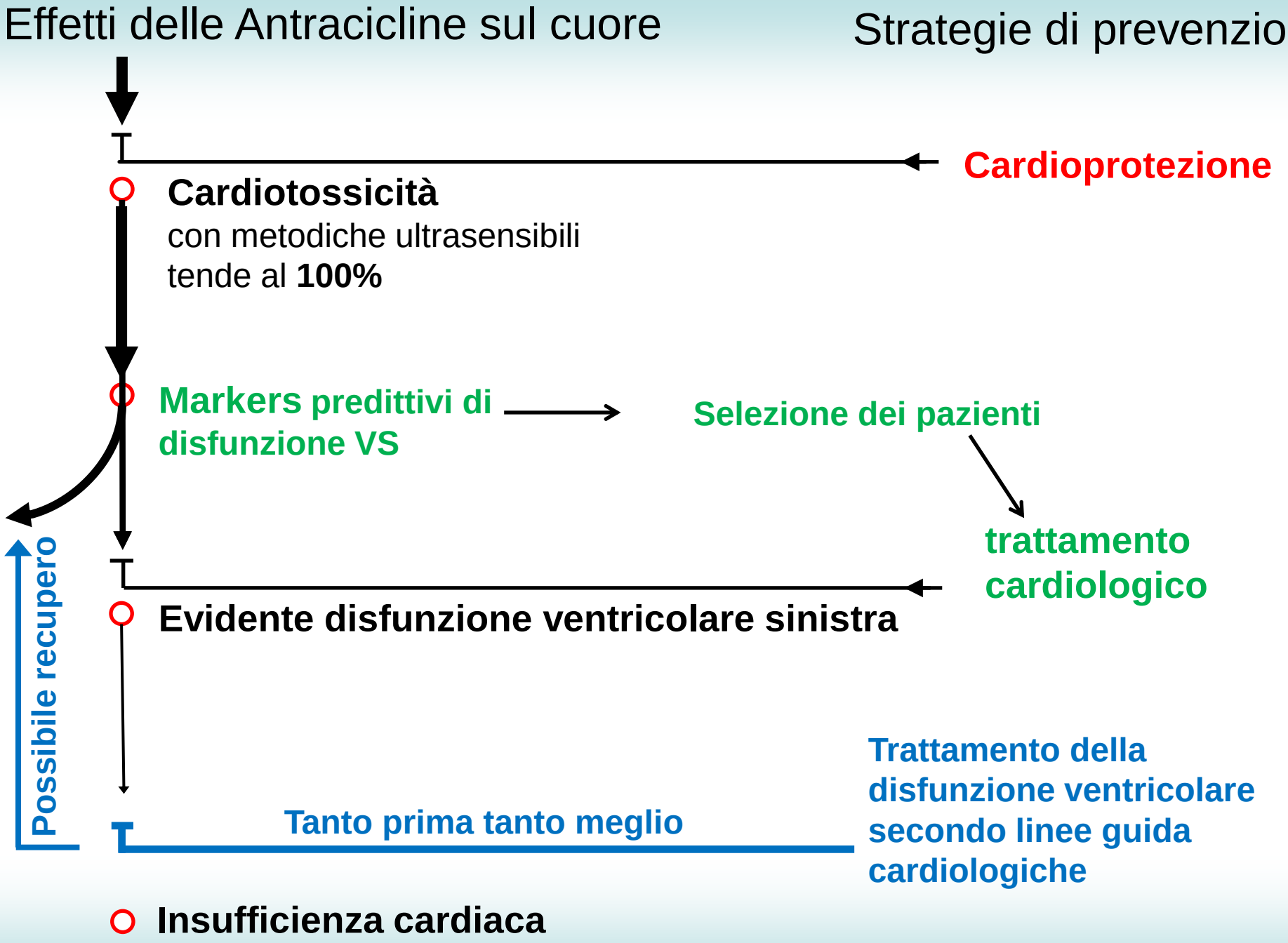
# Altered left ventricular longitudinal diastolic function correlates with reduced systolic function immediately after anthracycline chemotherapy

**Paul W. Stoodley[1,2*], David A.B. Richards[3,4], Anita Boyd[4], Rina Hui[5], Paul R. Harnett[5], Steven R. Meikle[1,2,6], Jillian L. Clarke[1,2], and Liza Thomas[3,4,7]**

tion. 2DSTE measurements included longitudinal diastolic strain, early (E-Sr), and late (A-Sr) myocardial strain rate. 2DSTE and left ventricular ejection fraction (LVEF) were used to measure longitudinal systolic function. Altered LV diastolic function (including E-Sr) was observed in the entire cohort after chemotherapy, with a differential reduction in participants with a post therapy LVEF <55%. Pre-chemotherapy systolic strain was found to predict reduced E-Sr

been described. To our knowledge, our study is the first to report altered diastolic 2DSTE strain measurements and its association with systolic dysfunction immediately after anthracycline therapy: thus, our results provide an important insight to early myocardial changes following anthracyclines. Longer-term follow-up for the development of symptomatic heart failure is required to determine whether the early changes we have demonstrated will help identify patients at risk. For now, identifying altered diastolic function early may assist in the recognition and confirmation of anthracycline-induced systolic dysfunction.

European Heart Journal - Cardiovascular Imaging Advance Access published July 10, 2012


Effetti delle Antracicline sul cuore
Strategie di prevenzione
Cardioprotezione
Cardiotossicità
con metodiche ultrasensibili
tende al 100%
Markers predittivi di disfunzione VS
Selezione dei pazienti
trattamento cardiologico
Evidente disfunzione ventricolare sinistra
Possibile recupero
Tanto prima tanto meglio
Trattamento della disfunzione ventricolare secondo linee guida cardiologiche
Insufficienza cardiaca

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
- treatment: ACEI + BB
- mean follow-up: 36±27 months
- ↑ LVEF 50%: 42% = Responders
- ↑ ≥10 abs.points: 13% = Partial Responders
- ↑ ≤10 abs.points: 45% = No Responders

Cardiac function recovery was associated with a lower incidence of cardiac events during follow up.

JACC 2010

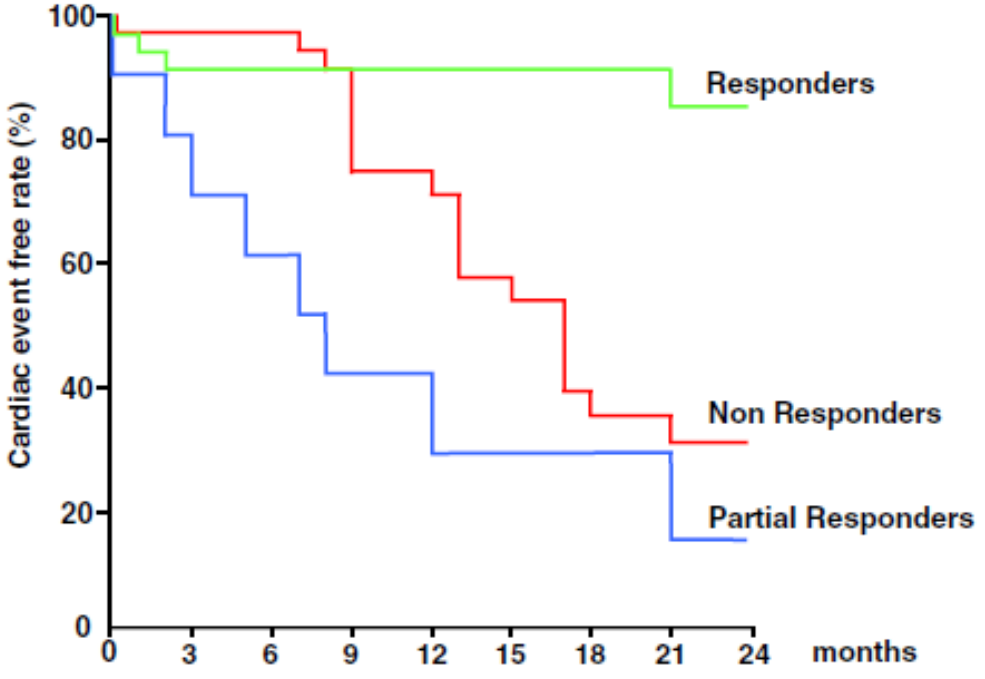



**Figure 2** Cumulative Cardiac Event Rate During the Study Follow-Up

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
- treatment: ACEI + BB
- mean follow-up: 36±27 months
- ↑ LVEF 50%: 42% = Responders
- ↑ ≥10 abs.points: 13% = Partial Responders
- ↑ ≤10 abs.points: 45% = No Responders

Inverse relationship between Time-to-heart-failure therapy and LVEF increase

JACC 2010

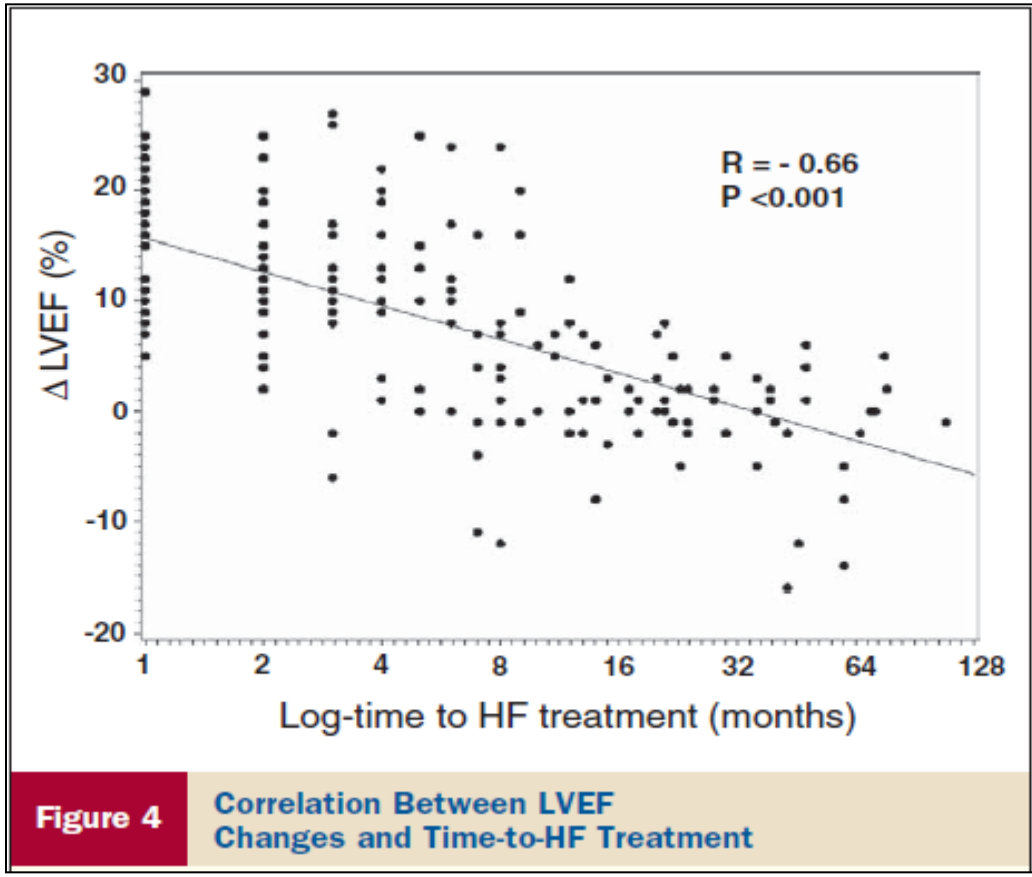



**Figure 4** Correlation Between LVEF Changes and Time-to-HF Treatment

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
- treatment: ACEI + BB
- mean follow-up: 36±27 months

- pts treated within 6 months:
  = ↑ LVEF 50%: 71%

The more time passes,
the less recovery possibility
we have

JACC 2010

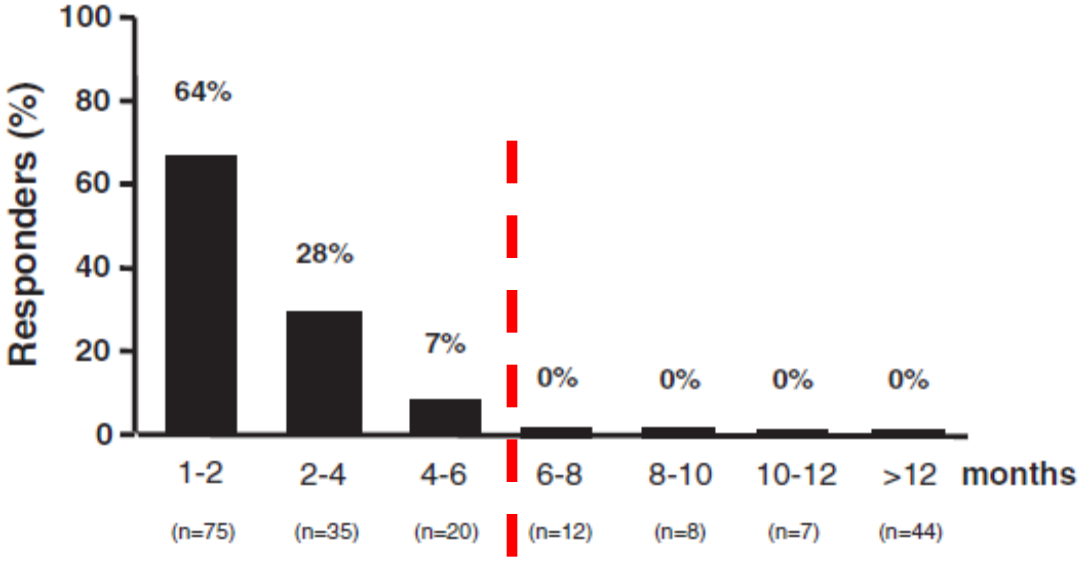
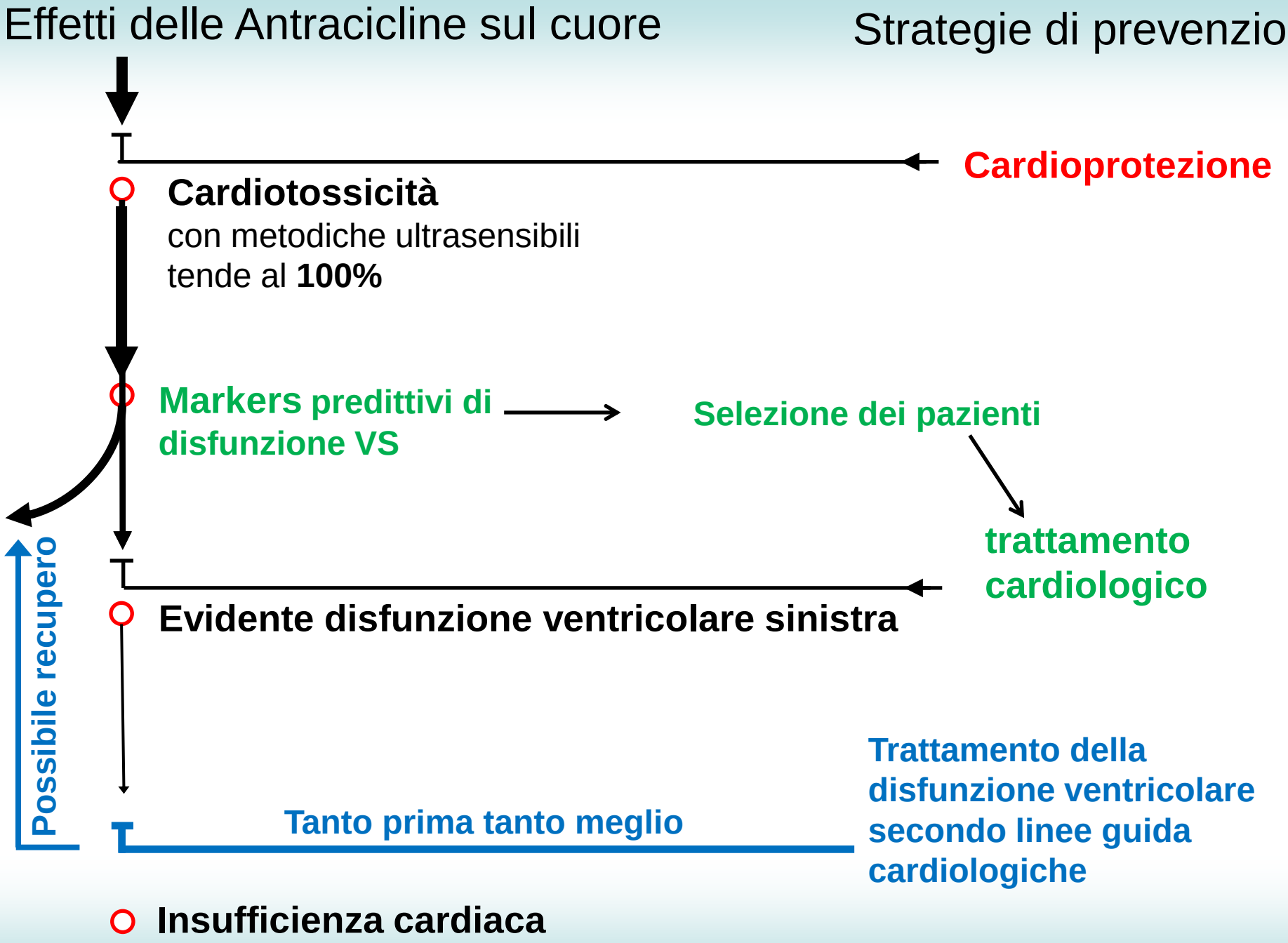



**Figure 1** Percentage of patients with complete cardiac function recovery according to time elapsed from AC administration and start of HF therapy

AC = anthracyclines; HF = heart failure.


Effetti delle Antracicline sul cuore
Strategie di prevenzione
Cardioprotezione
Cardiotossicità
con metodiche ultrasensibili
tende al 100%
Markers predittivi di disfunzione VS
Selezione dei pazienti
trattamento cardiologico
Evidente disfunzione ventricolare sinistra
Possibile recupero
Tanto prima tanto meglio
Trattamento della disfunzione ventricolare secondo linee guida cardiologiche
Insufficienza cardiaca