Terapia della disfunzione ventricolare sx da antineoplastici: come e quando iniziare?

Daniela Cardinale

Unità di Cardioncologia
Istituto Oncologico Europeo – Milano

Milano, 16 Ottobre 2012

Cardiotoxicity

- One of the major factors limiting the use of anticancer therapy
- Hypokinetic CMP
- Dose-dependent (anthracyclines)
- Poor prognosis (anthracyclines)
- Refractory to HF therapy (anthacyclines)

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**	

Treatment of AC-induced CMP

- AC-induced CMP **is believed to be refractory** to conventional therapy (but much of these data are anecdotal and based on reports of small number of patients).
- Typically, these patients **have been excluded** from large randomized trials evaluating the efficacy of recommended HF therapy.
- There isn't any evidence whether **the use** of modern HF therapy **can be directly transferred** to this particular setting, with similar long-term benefits.
- As a consequence, **evidence-based recommendations** for the management of AC-induced CMP **are still lacking**, and **no definitive guidelines** have been adopted yet .

Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies

Are Clinicians Responding Optimally?

Geoffrey J. Yoon, MD,* Melinda L. Telli, MD,† David P. Kao, MD,‡ Kelly Y. Matsuda, PharmD,* Robert W. Carlson, MD,† Ronald M. Witteles, MD*

Stanford, California; and Denver, Colorado

Population: n. 88

Treatment: AC (n.66)
AC + TRZ (n. 15)
TRZ (n. 7)

LVEF <50%: n.35 (40%)

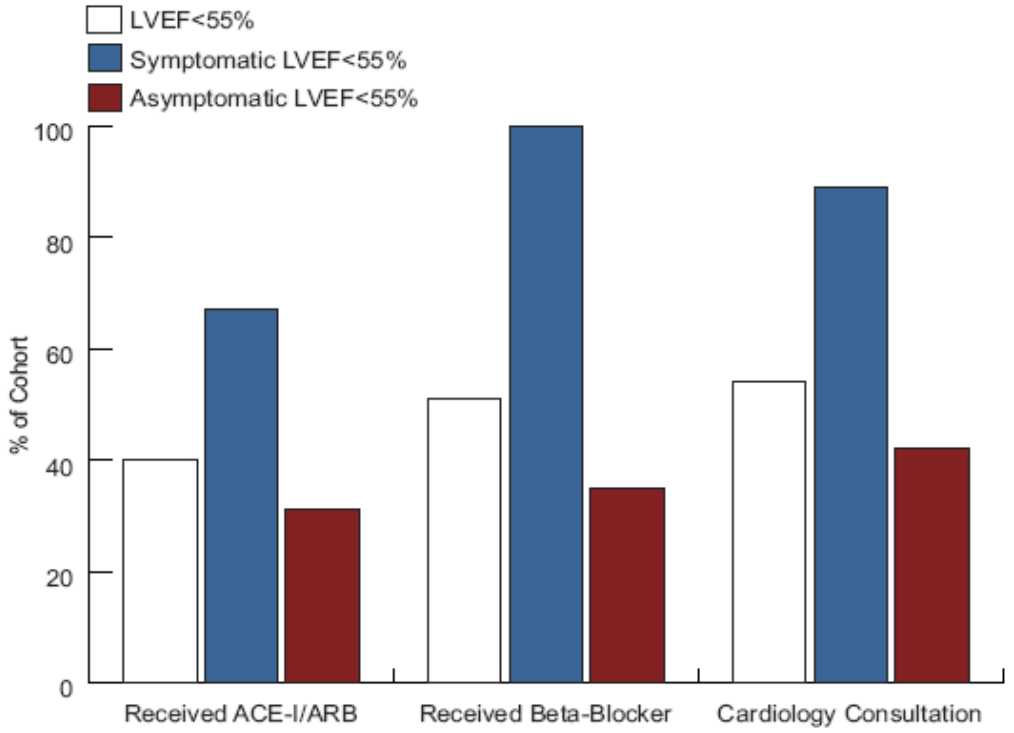


Figure 1 Percentage of Patients Who Received ACEIs/ARBs, Beta-Blockers, and/or Cardiology Consultation After the Start of Chemotherapy

JACC 2011

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

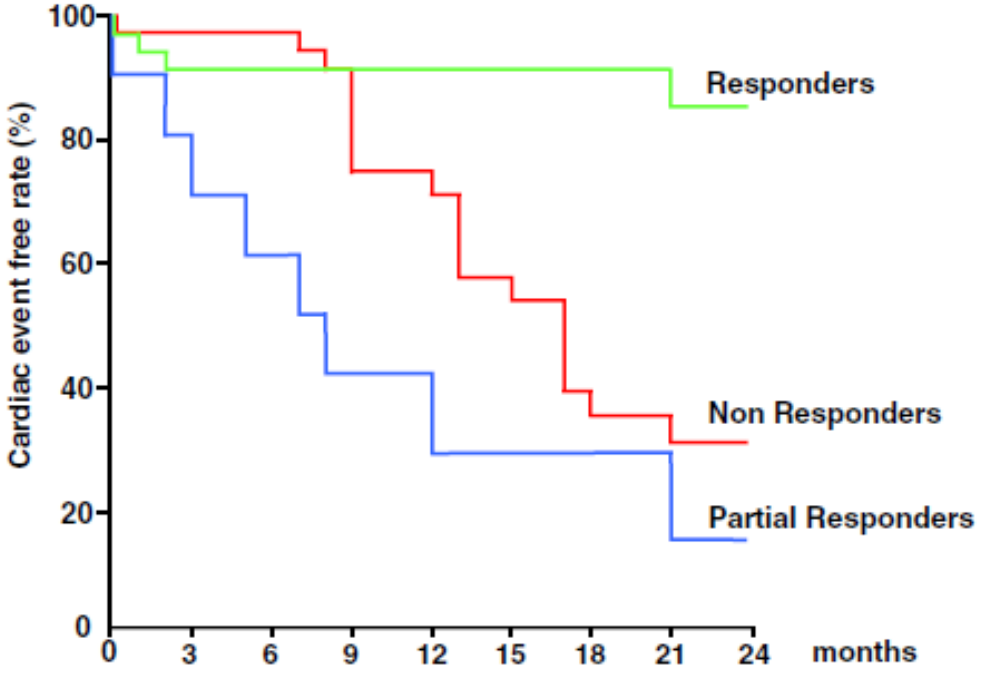


Figure 2 Cumulative Cardiac Event Rate During the Study Follow-Up

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

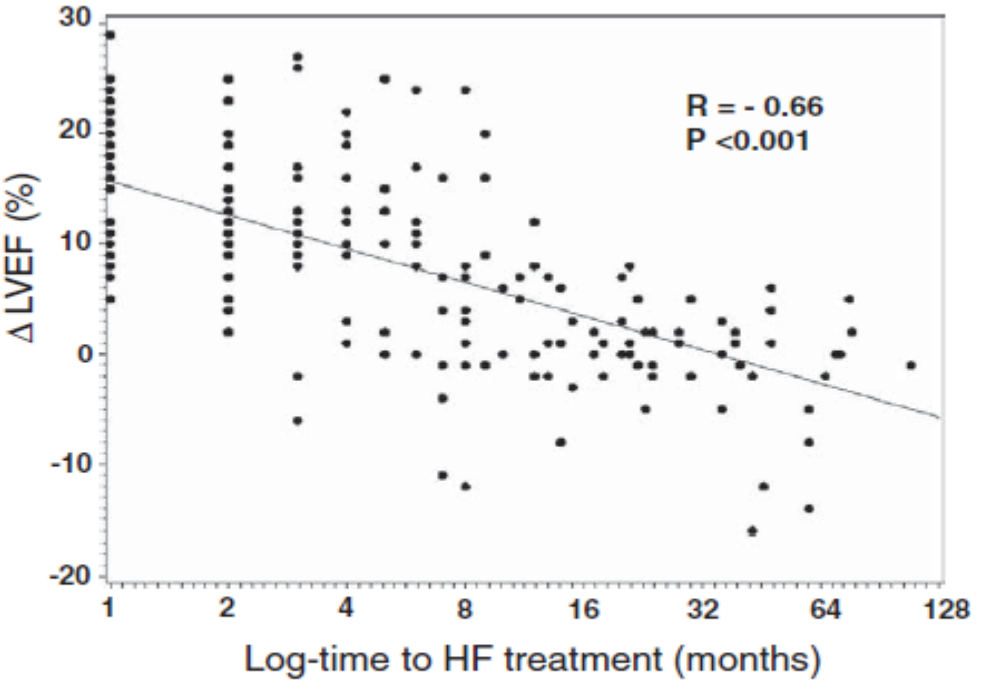


Figure 4 Correlation Between LVEF Changes and Time-to-HF Treatment

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

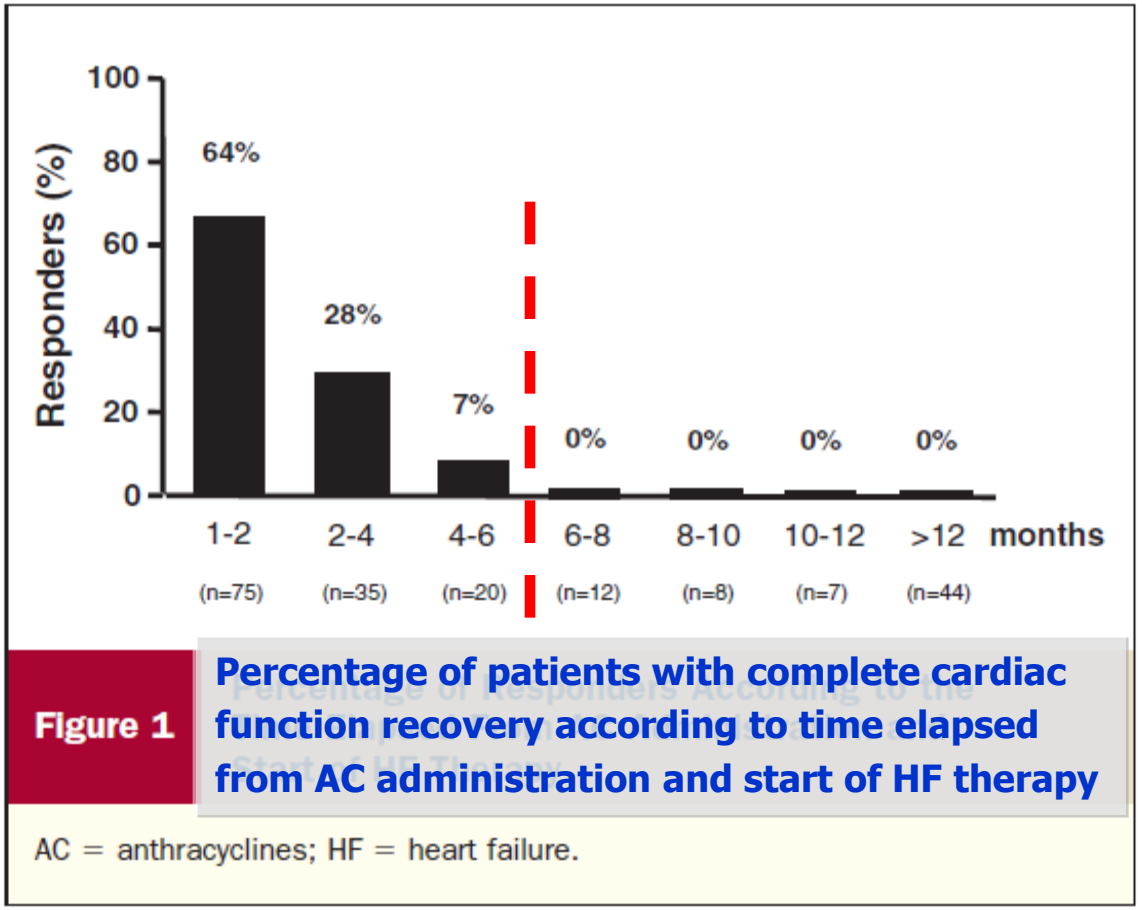
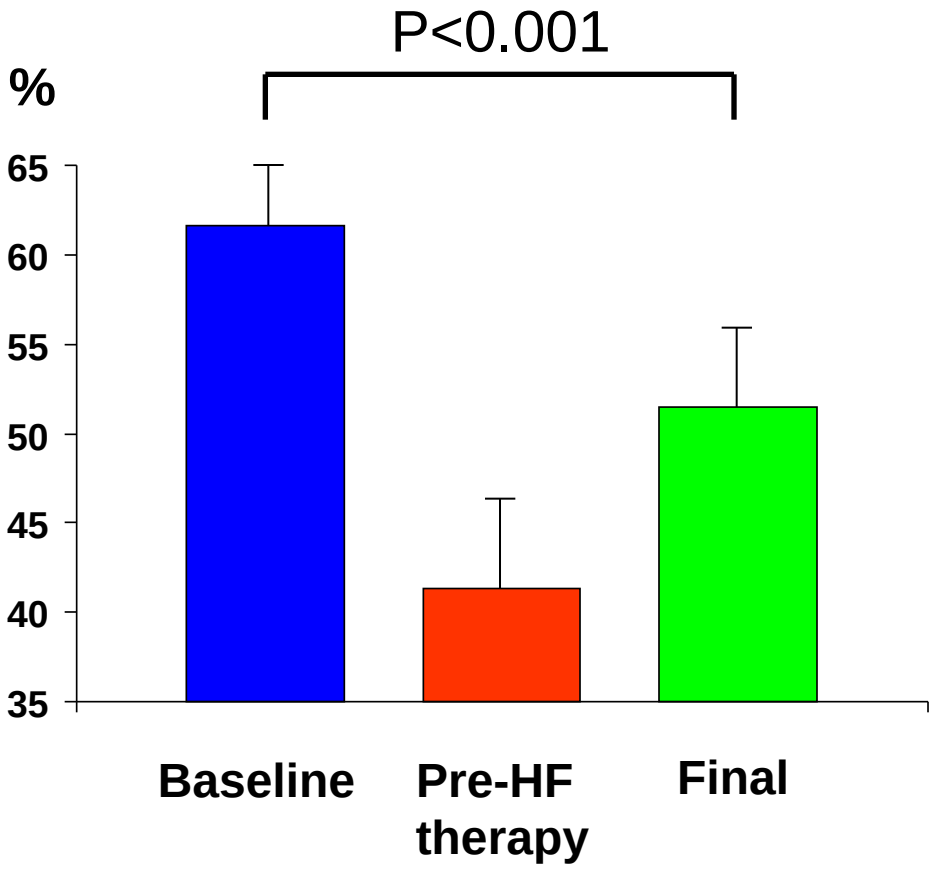


Figure 1 **Percentage of patients with complete cardiac function recovery according to time elapsed from AC administration and start of HF therapy**

AC = anthracyclines; HF = heart failure.

BUT….

LVEF changes after anti-HF therapy



- 226/2625 pts
- Regular LVEF monitoring
- Early HF therapy initiation
- ACEI and BB in 90% pts
- Final LVEF ≥50% in 185 (82%) pts
- Mean time to LVEF normalization
  = 8±5 months

Cardinale et al. Submitted

Pharmacologic prevention of cardiotoxicity

Cardiotoxicity Prevention Possible Strategies

Table VI. Strategies for prevention or reduction of anthracycline (ATC)-induced cardiac toxicity[2,6,7,56,69-75]

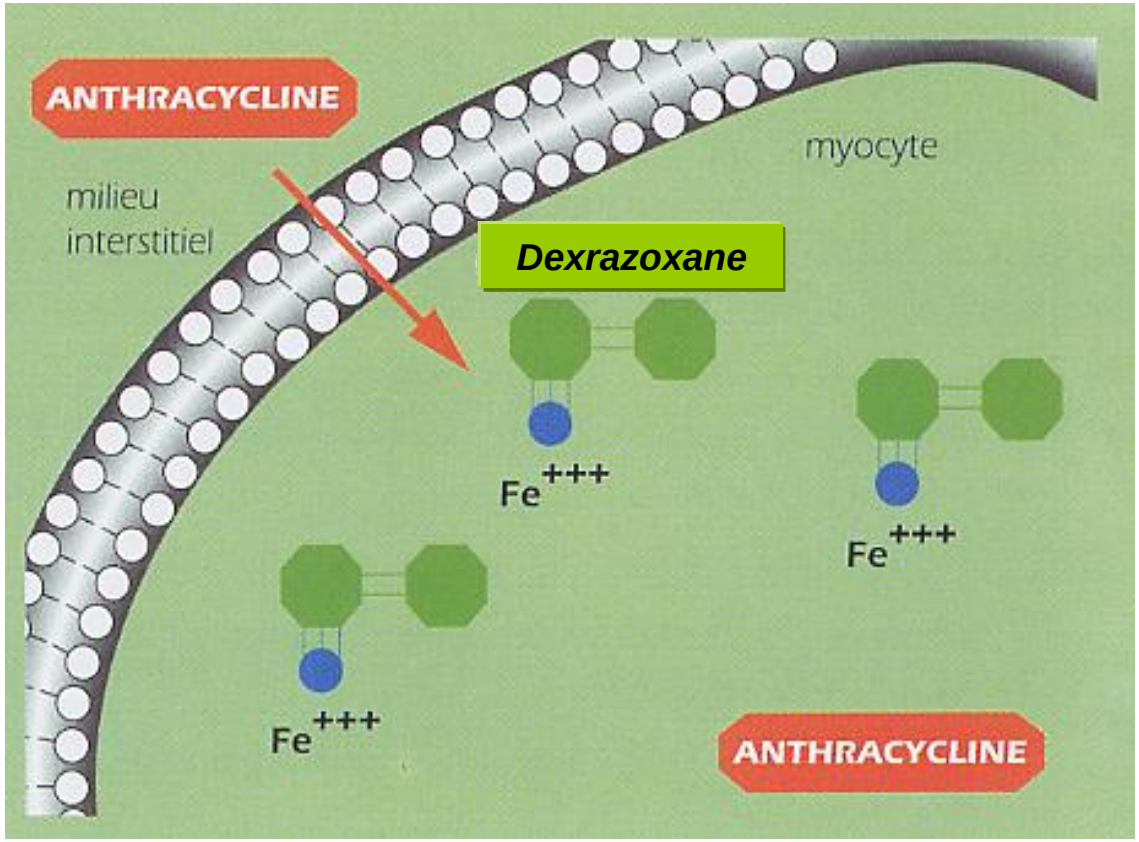
Strategy	Benefit	Potential limitations
No ATC in chemotherapy	No toxicity	↓ chemotherapy efficacy
Limit cumulative ATC dose[a]	↓ toxicity in some patients[b]	Compromised chemotherapy efficacy
Modify ATC administration schedule[c]	↓ toxicity	↓ chemotherapy efficacy; ↑ AE; ↑ costs
Monitoring-guided ATC chemotherapy	↓ impact of toxicity	↑ costs; low sensitivity ± specificity;[d] invasiveness
Newer ATC analogues[f]	↓ toxicity; ↑ or ≡ efficacy;	↑ costs; some ↑ AE
Cardioprotectants[g]	↓ toxicity	↑ costs; some ↑ AE

Cvetkovic et al. Drugs 2005

Concurrent therapies for reducing anthracycline toxicity

Agent	Class	Mechanism	Study subject
Carvedilol	B-adrenergic antagonist	Prevention of free radical formation; prevention of depletion of endogenous antioxidants	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
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

dexrazoxane



Dexrazoxane enters myocytes, binds free iron, removes iron from the iron-doxorubicin complex, preventing oxygen radical formation.

Hasinoff BB Drug Metab Dispos 1990; 18: 344–9

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

Summary

Background Doxorubicin chemotherapy is associated with cardiomyopathy. Dexrazoxane reduces cardiac damage during treatment with doxorubicin in children with acute lymphoblastic leukaemia (ALL). We aimed to establish the long-term effect of dexrazoxane on the subclinical state of cardiac health in survivors of childhood high-risk ALL 5 years after completion of doxorubicin treatment.

Methods Between January, 1996, and September, 2000, children with high-risk ALL were enrolled from nine centres in the USA, Canada, and Puerto Rico. Patients were assigned by block randomisation to receive ten doses of 30 mg/m² doxorubicin alone or the same dose of doxorubicin preceded by 300 mg/m² dexrazoxane. Treatment assignment was obtained through a telephone call to a centralised registrar to conceal allocation. Investigators were masked to treatment assignment but treating physicians and patients were not; however, investigators, physicians, and patients were masked to study serum cardiac troponin-T concentrations and echocardiographic measurements. The primary endpoints were late left ventricular structure and function abnormalities as assessed by echocardiography; analyses were done including all patients with data available after treatment completion. This trial has been completed and is registered with ClinicalTrials.gov, number NCT00165087.

Findings 100 children were assigned to doxorubicin (66 analysed) and 105 to doxorubicin plus dexrazoxane (68 analysed). 5 years after the completion of doxorubicin chemotherapy, mean left ventricular fractional shortening and end-systolic dimension Z scores were significantly worse than normal for children who received doxorubicin alone (left ventricular fractional shortening: –0·82, 95% CI –1·31 to –0·33; end-systolic dimension: 0·57, 0·21–0·93) but not for those who also received dexrazoxane (–0·41, –0·88 to 0·06; 0·15, –0·20 to 0·51). The protective effect of dexrazoxane, relative to doxorubicin alone, on left ventricular wall thickness (difference between groups: 0·47, 0·46–0·48) and thickness-to-dimension ratio (0·66, 0·64–0·68) were the only statistically significant characteristics at 5 years. Subgroup analysis showed dexrazoxane protection (p=0·04) for left ventricular fractional shortening at 5 years in girls (1·17, 0·24–2·11), but not in boys (–0·10, –0·87 to 0·68). Similarly, subgroup analysis showed dexrazoxane protection (p=0·046) for the left ventricular thickness-to-dimension ratio at 5 years in girls (1·15, 0·44–1·85), but not in boys (0·19, –0·42 to 0·81). With a median follow-up for recurrence and death of 8·7 years (range 1·3–12·1), event-free survival was 77% (95% CI 67–84) for children in the doxorubicin-alone group, and 76% (67–84) for children in the doxorubicin plus dexrazoxane group (p=0·99).

Interpretation Dexrazoxane provides long-term cardioprotection without compromising oncological efficacy in doxorubicin-treated children with high-risk ALL. Dexrazoxane exerts greater long-term cardioprotective effects in girls than in boys.

Lipshultz et al.
Lancet Oncology 2010

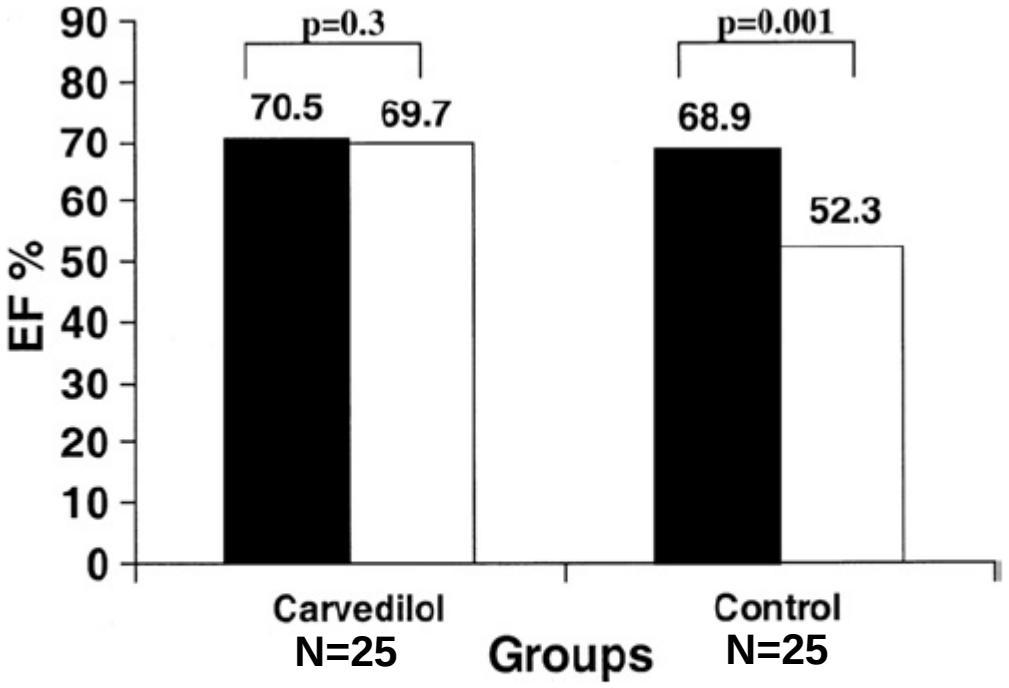
Dexrazoxane (DX) cardioprotective efficacy in randomized trials in adult cancer patients

	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

**p<0.05; **p<0.01; ***p<0.001*

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*

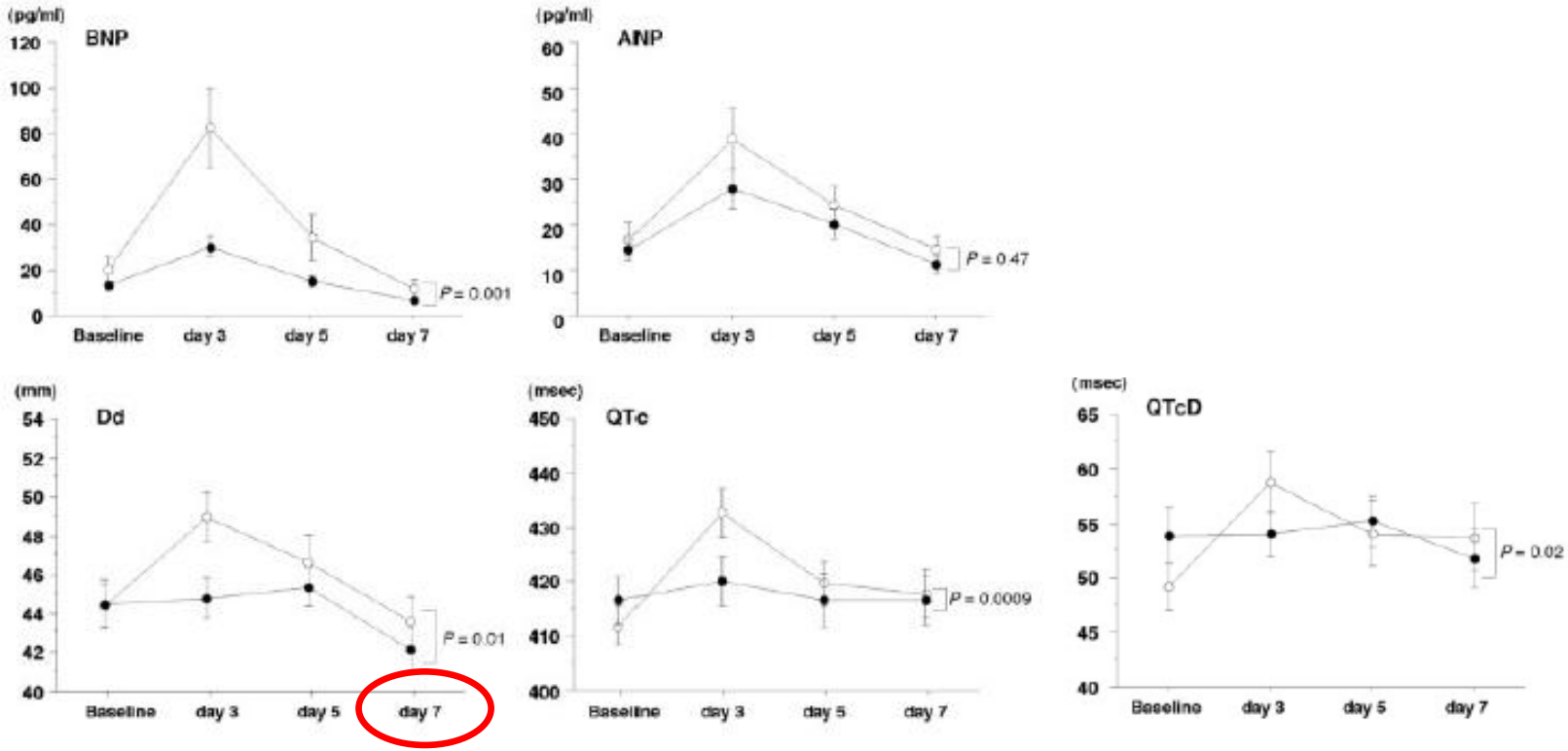


Follow-up = 6 months

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

Notable Effects of Angiotensin II Receptor Blocker, Valsartan, on Acute Cardiotoxic Changes after Standard Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone



Nakamae et al. Cancer 2005;104:2492-8

Long-term protective effects of the angiotensin receptor blocker telmisartan on epirubicin-induced inflammation, oxidative stress and myocardial dysfunction

MARIELE DESSÌ[1*], ALESSANDRA PIRAS[2*], CLELIA MADEDDU[1], CHRISTIAN CADEDDU[2], MARTINO DEIDDA[2], ELENA MASSA[1], GIORGIA ANTONI[1], GIOVANNI MANTOVANI[1] and GIUSEPPE MERCURO[2]

EXPERIMENTAL AND THERAPEUTIC MEDICINE 2: 1003-1009, 2011

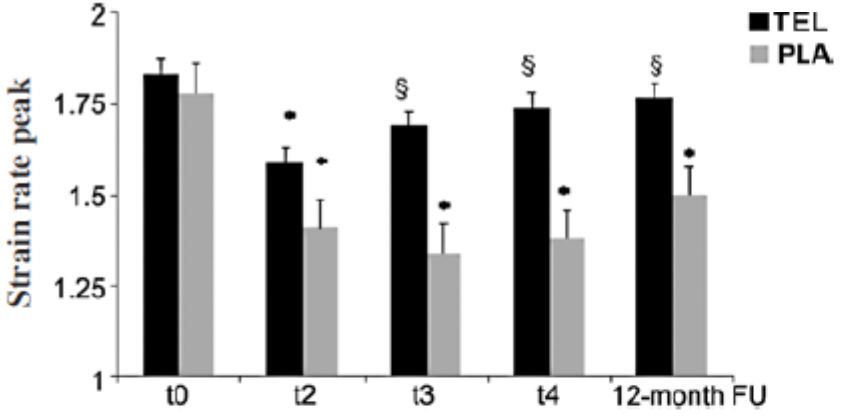


Figure 2. SR analysis with TDI in the two arms. *p<0,05 vs. baseline; §p<0.05 between arms.

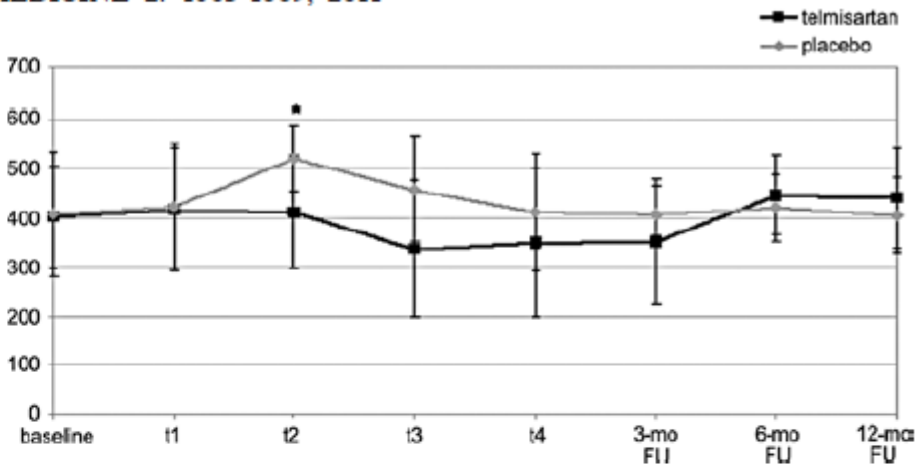


Figure 4. Blood levels of ROS (FORT U) during the EPI treatment and FU in the TEL and PLA arms. *p<0.05 between arms.

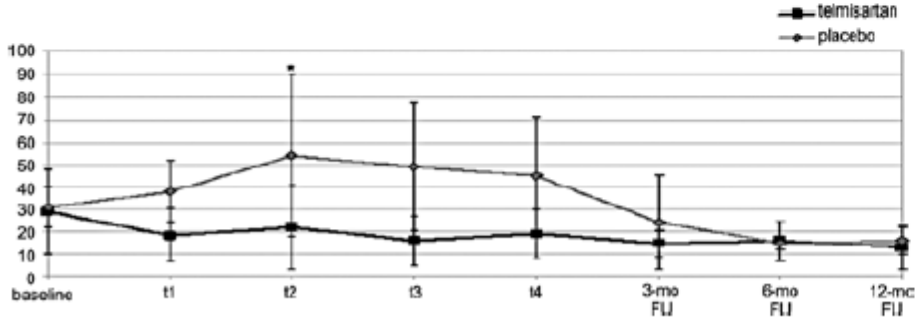


Figure 3. Serum levels of IL-6 (pg/ml) during the EPI treatment and FU in the TEL and PLA arms. *p<0.05 between arms.

Table II. Conventional echocardiographic parameters of systolic and diastolic function in both arms.

Conventional echo	t_0 (n=49)	t_2 (n=49)	t_3 (n=49)	t_4 (n=49)	12-month FU (n=44)
LVEF					
PLA	66±5%	68±6%	66±5%	66±5%	67±5%
TEL	66±7%	67±6%	68±4%	70±6%	68±4%
DecT					
PLA	0.22±0.04	0.24±0.05	0.22±0.02	0.23±0.04	0.22±0.03
TEL	0.19±0.04	0.21±0.04	0.20±0.02	0.21±0.03	0.21±0.04
E/A					
PLA	1.13±0.14	1.08±0.12	0.92±0.05[a]	0.90±0.06[a]	1.06±0.42
TEL	0.96±0.12	0.86±0.08	0.83±0.07	0.95±0.14	0.87±0.31

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,*]

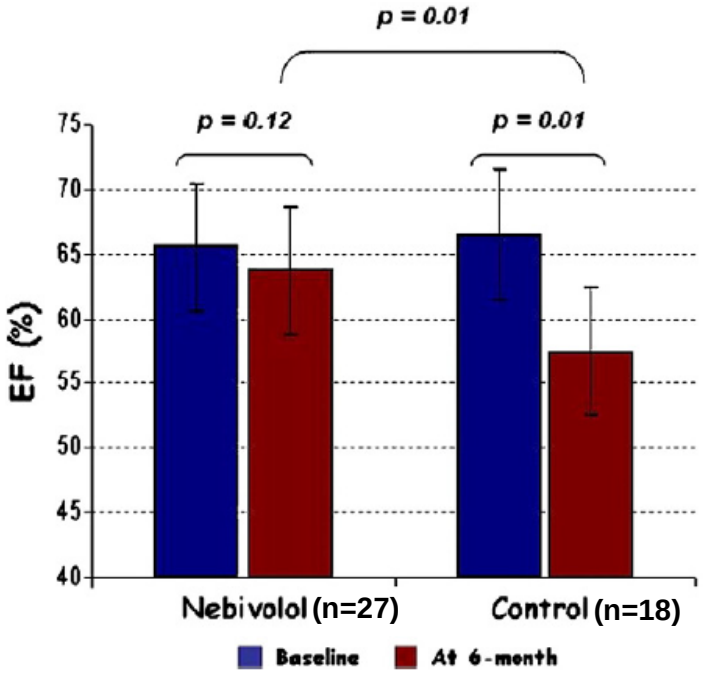


Fig. 1. Comparison of LVEF in nebivolol group vs. placebo group at baseline and at six-month.

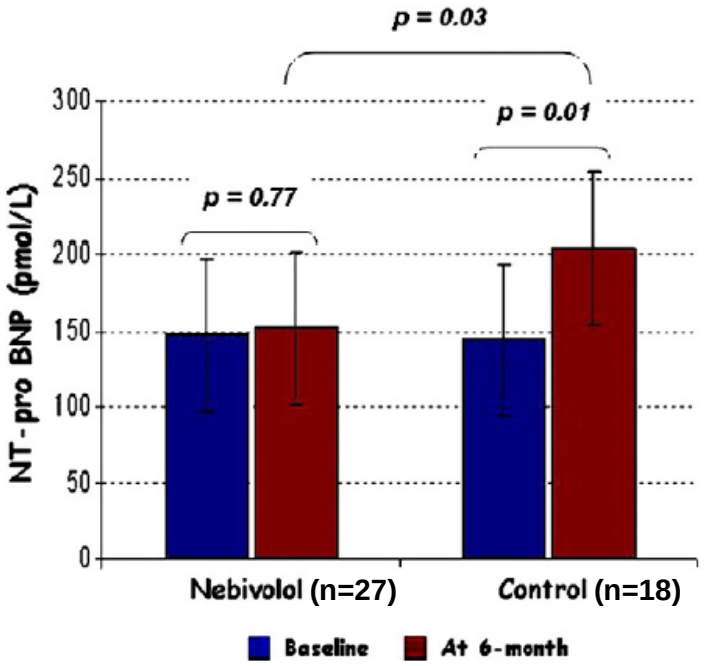


Fig. 2. Comparison of NT-pro-BNP levels in nebivolol group vs. placebo group at baseline and at six-month.

Clinical Trials: Methods & Design

Prevention of Chemotherapy-Induced Left Ventricular Dysfunction With Enalapril and Carvedilol: Rationale and Design of the OVERCOME Trial

XAVIER BOSCH, MD, PhD,[1,6] JORDI ESTEVE, MD, PhD,[2,6] MARTA SITGES, MD, PhD,[1,6] TERESA M. DE CARALT, MD, PhD,[3] ARIADNA DOMÈNECH, RN,[2] JOSÉ T. ORTIZ, MD, PhD,[1,6] MARIANO MONZÓ, MD, PhD,[5,6] MANUEL MORALES-RUIZ, PhD,[4,6] ROSARIO J. PEREA, MD, PhD,[3] AND MONTSERRAT ROVIRA, MD, PhD[2,6]

Barcelona, Spain

Enalapril + Carvedilol

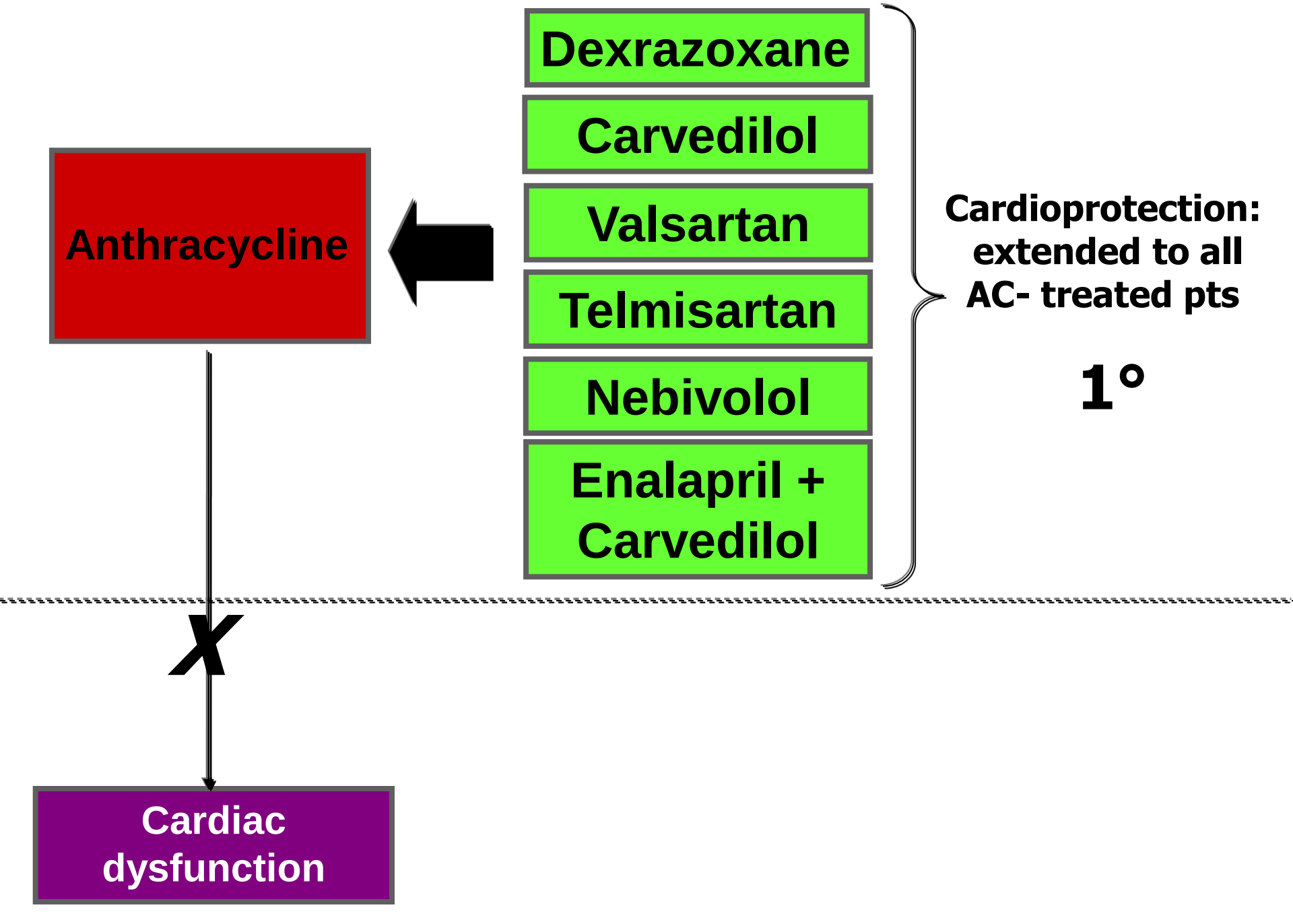
ABSTRACT

Background: The current treatment of hematologic malignancies includes diverse potentially cardiotoxic chemotherapy agents, including high-dose myeloablative regimens used in autologous hematopoietic stem cell transplantation (HSCT). Many of these treatments could induce left ventricular dysfunction (LVD), and limit their efficacy. Angiotensin-converting enzime inhibitors and beta-blockers prevent LVD and prolong survival after infarction, and recent animal and pilot clinical studies suggest that they can prevent the development of chemotherapy-induced cardiac toxicity.

Methods: This is a prevention, parallel-assignment, randomized, controlled, clinical efficacy study. Ninety patients recently diagnosed of acute leukemia or undergoing autologous HSCT and with normal LV ejection fraction will be randomized to enalapril and carvedilol or to the control group. Echocardiogram and a cardiac magnetic resonance imaging studies will be performed at baseline and 6–9 months after randomization. The primary efficacy endpoint is the change from baseline in LV ejection fraction. Secondary endpoints include the assessment of LV volumes and diastolic function, and the incidence of death, heart failure, or LVD.

Conclusions: The OVERCOME study will be the first clinical trial to test the preventive efficacy on LVD of combined treatment with enalapril and carvedilol administered to patients with hematologic malignancies submitted to current treatment with intensive chemotherapy. (*J Cardiac Fail 2011;17:643–648*)

Key Words: Cardiotoxicity, carvedilol, chemotherapy, enalapril, prevention, ventricular dysfunction.


Dexrazoxane
Carvedilol
Valsartan
Telmisartan
Nebivolol
Enalapril + Carvedilol
Cardioprotection: extended to all AC- treated pts
1°
Anthracycline
X
Cardiac dysfunction

Pharmacologic prevention in selected high-risk patients

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

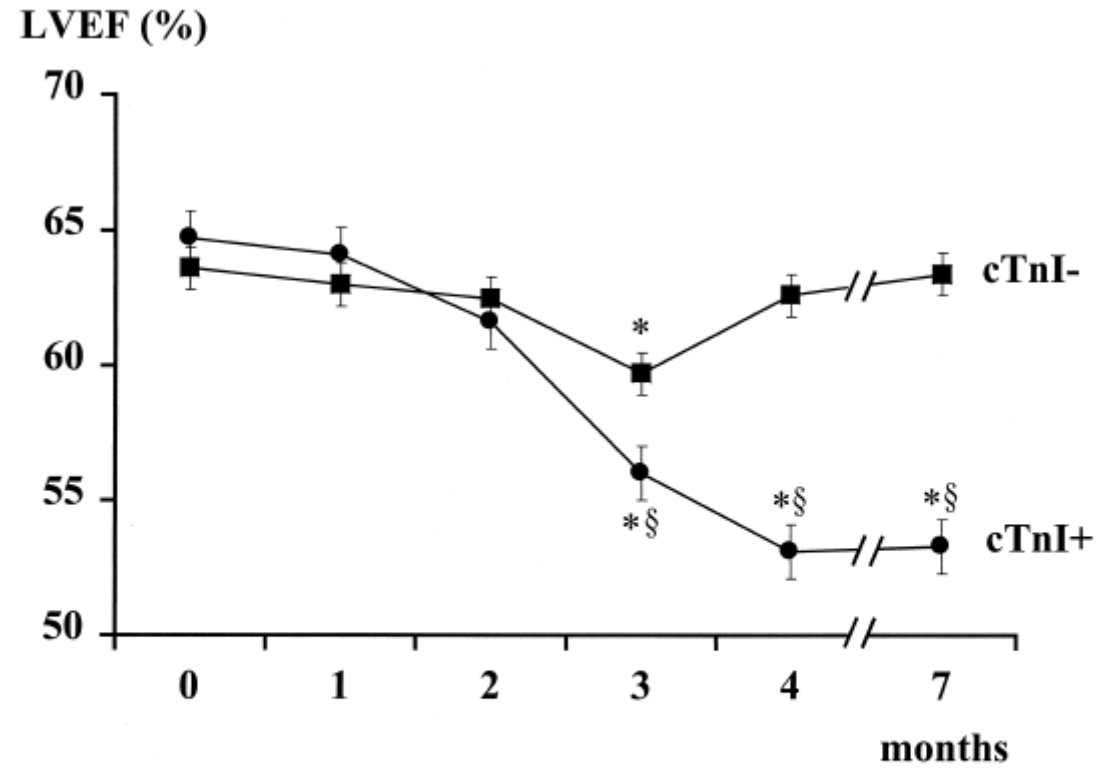


Figure 2. Left ventricular ejection fraction (LVEF) at baseline and during the seven months of follow-up of troponin I positive (cTnI+; **solid circle**) and negative (cTnI−; **solid square**) patients. *p < 0.001 vs. baseline (month 0); §p < 0.001 vs. cTnI− group. Data are shown as mean ± 95% confidence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

J Am Coll Cardiol 2000

TnI maximal value predicts the degree of cardiac dysfunction

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

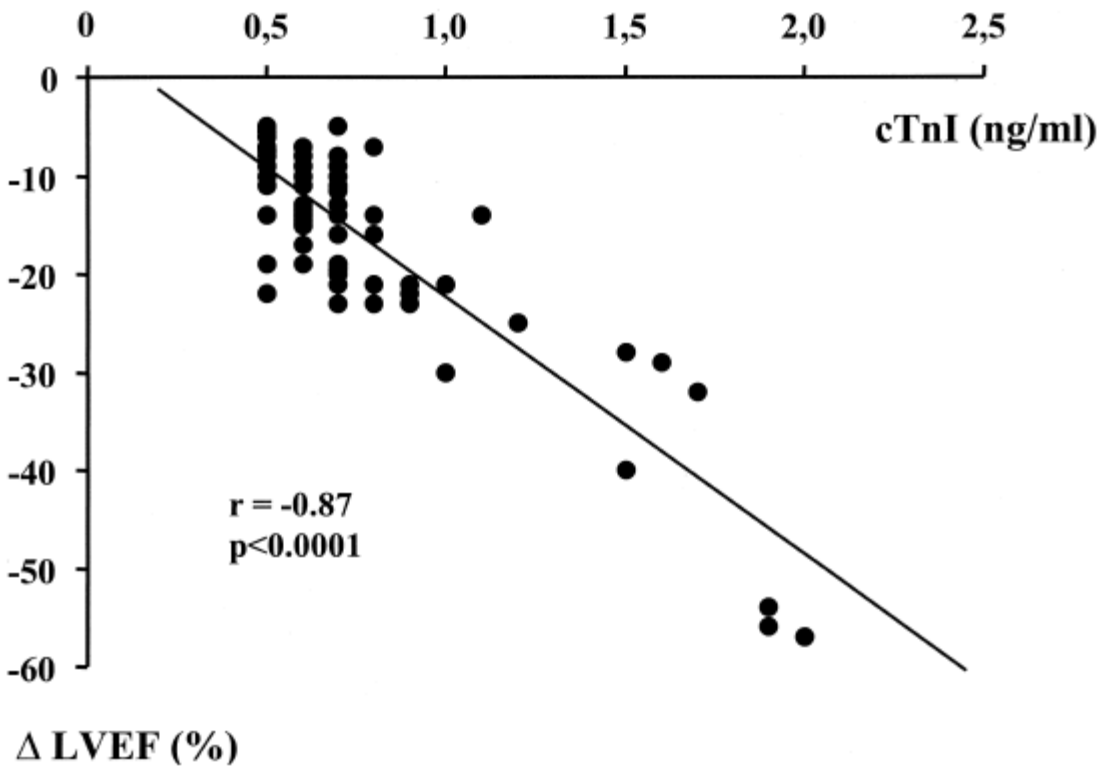
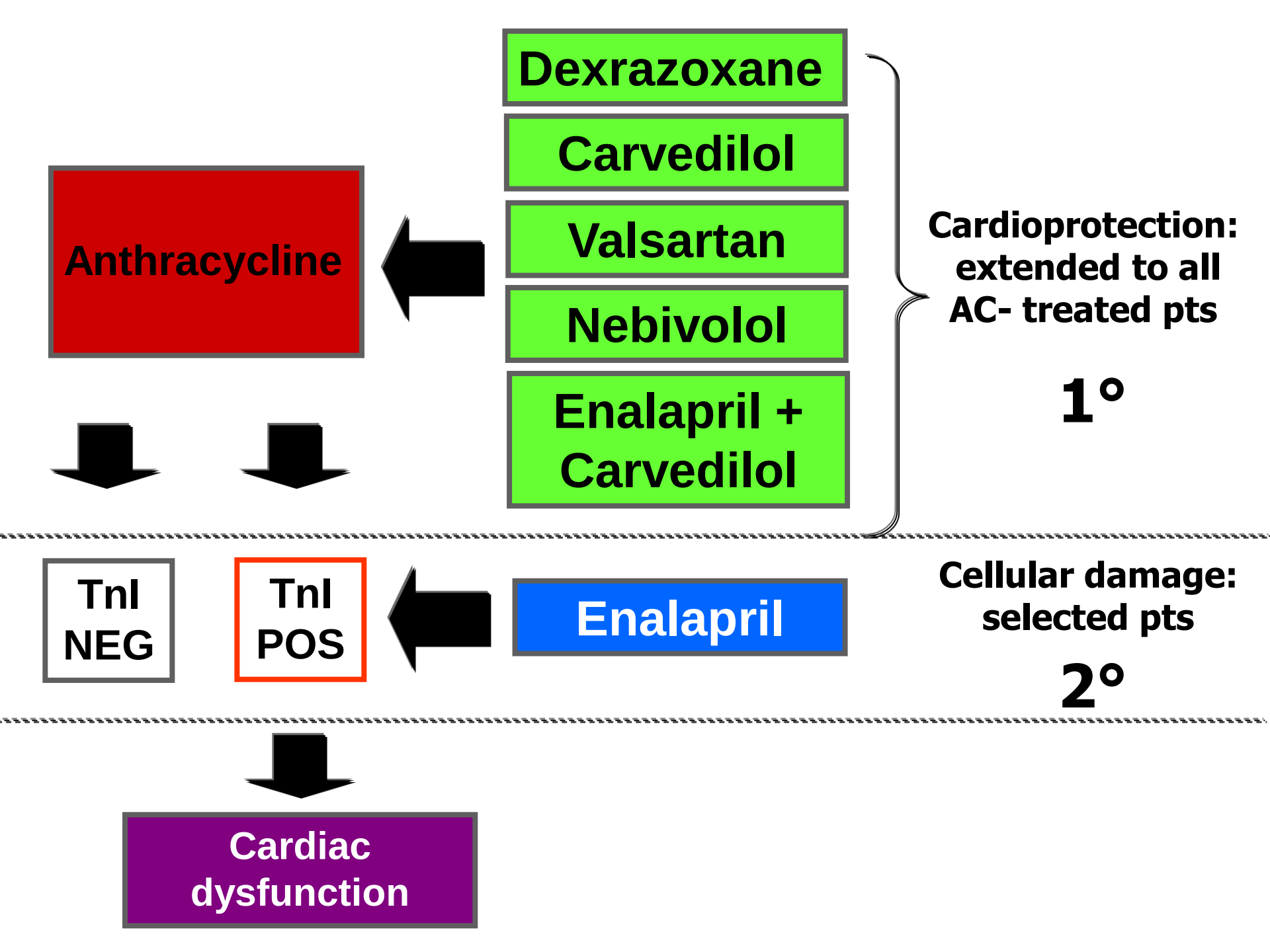


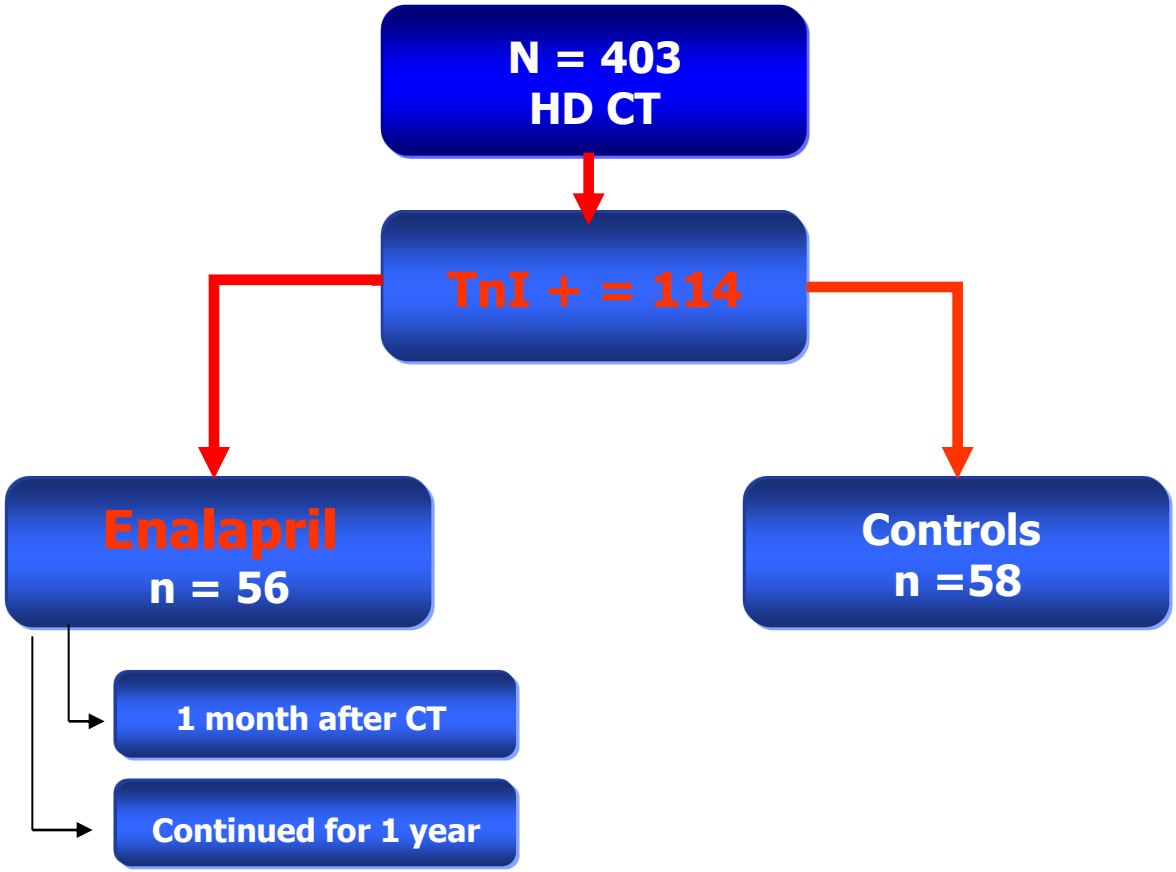
Figure 4. Scatterplot of left ventricular ejection fraction (LVEF) changes against troponin I value in cTnI+ patients. cTnI = cardiac troponin I.

J Am Coll Cardiol 2000


Dexrazoxane
Carvedilol
Valsartan
Nebivolol
Enalapril + Carvedilol
Anthracycline
Cardioprotection: extended to all AC- treated pts
1°
TnI NEG
TnI POS
Enalapril
Cellular damage: selected pts
2°
Cardiac dysfunction

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

Beneficial Effects of Angiotensin-Converting Enzyme Inhibition in Adriamycin-Induced Cardiomyopathy in Hamsters

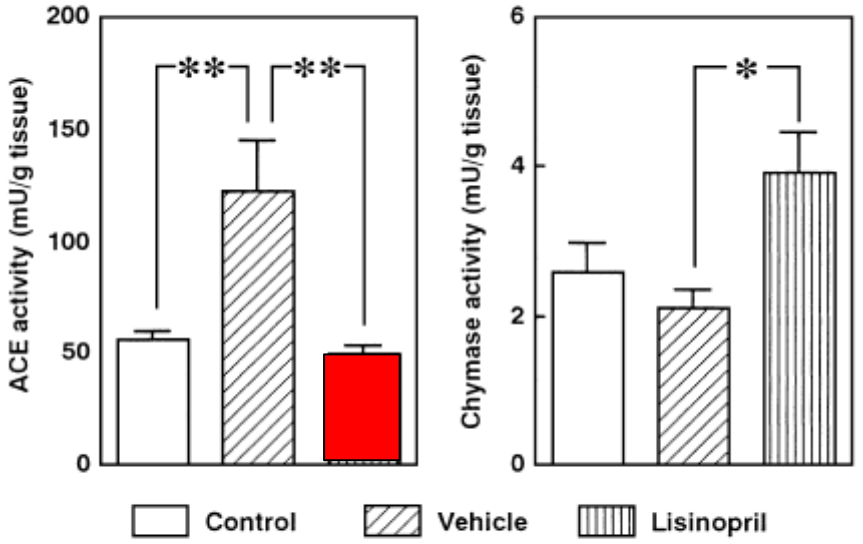


Fig. 3. Bar graphs show the ACE and chymase activities of cardiac tissues in the control, the vehicle and the ACE inhibitor-treated groups 28 days after the first injection of adriamycin. *P<0.05 and **P<0.01 vs vehicle group.

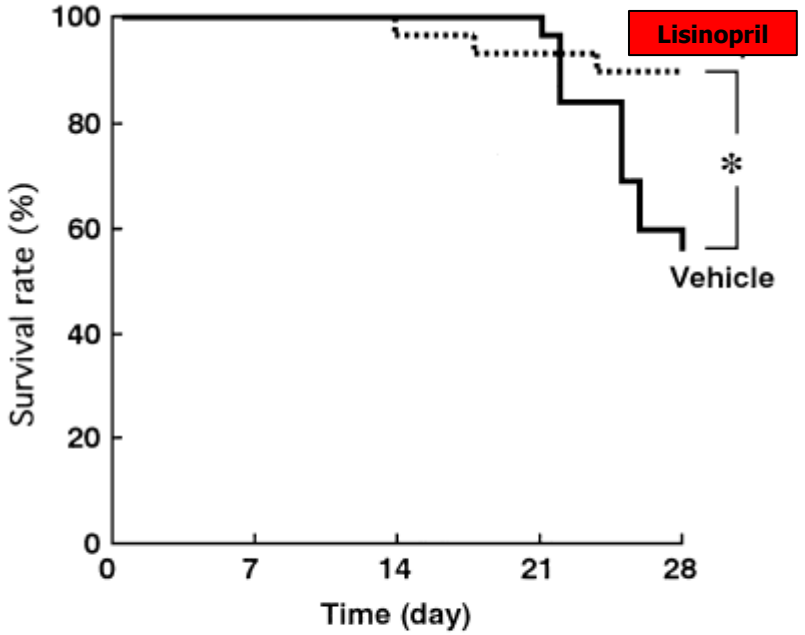


Fig. 1. Kaplan-Meier survival curves of the vehicle and the ACE inhibitor-treated hamsters. Lisinopril treatment (20 mg/kg per day, p.o.) was initiated starting from the last injection of adriamycin. *P<0.05 vs vehicle group.

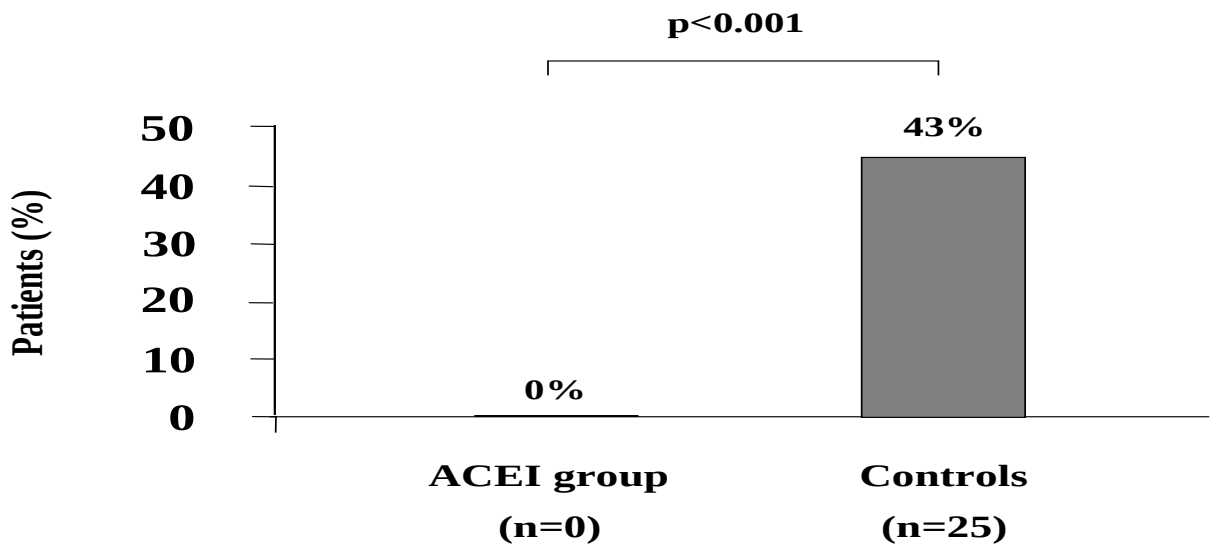
Okumura et al. Jpn J Pharmacol 2002

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

Primary end-point:

LVEF decrease >10 percent units + <50%



Circulation 2006

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

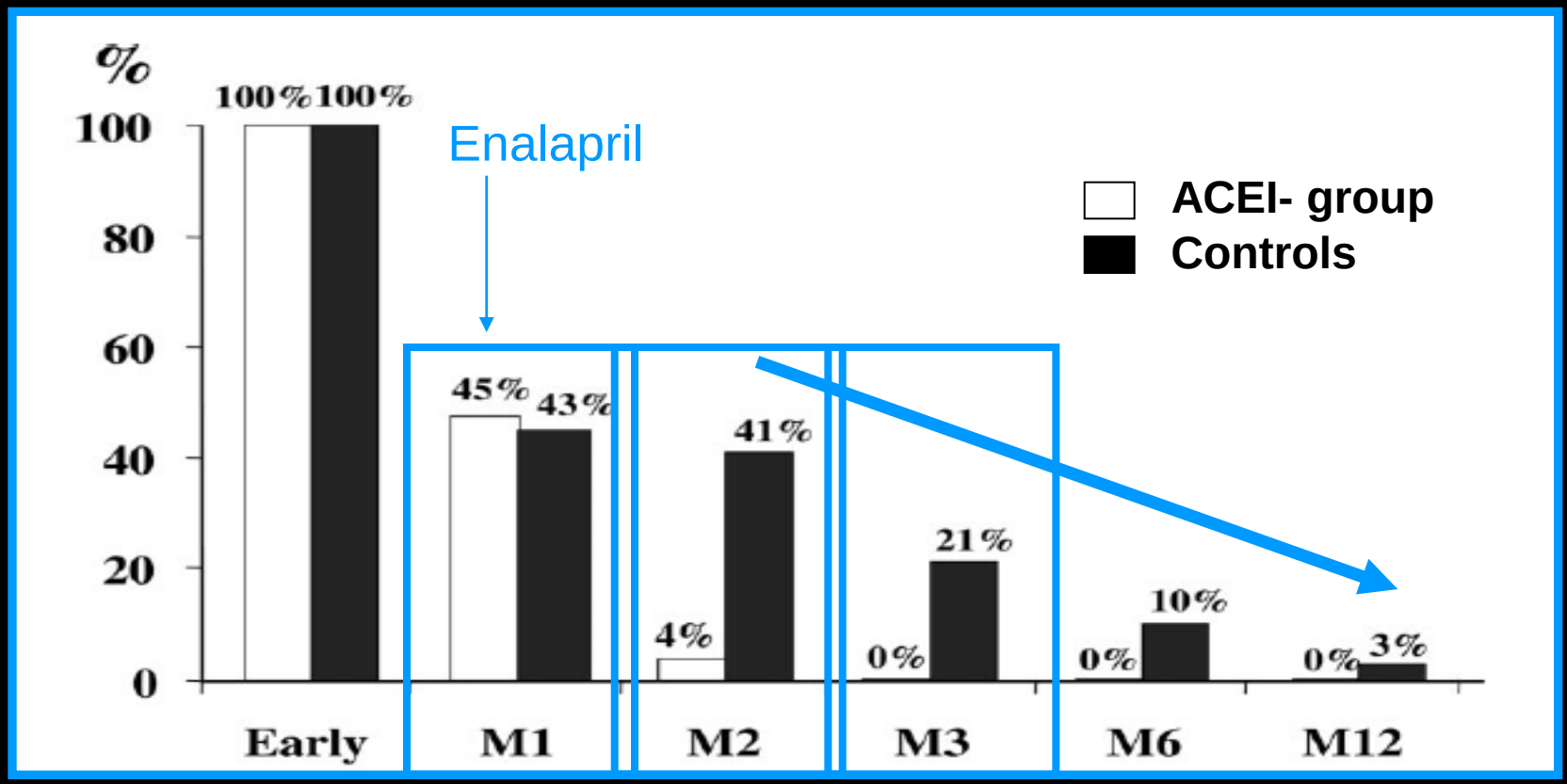
TABLE 4. Cardiac Events in the Study Groups

	Total (n=114), n (%)	ACEI Group (n=56), n (%)	Control Subjects (n=58), n (%)	*P*
Sudden death	0 (0)	0 (0)	0 (0)	1.0*
Cardiac death	2 (2)	0 (0)	2 (3)	0.49*
Acute pulmonary edema	4 (3)	0 (0)	4 (7)	0.07*
Heart failure	14 (12)	0 (0)	14 (24)	<0.001
Arrhythmias requiring treatment	11 (10)	1 (2)	10 (17)	0.01
CUMULATIVE EVENTS	**31 (28%)**	**1 (2%)**	**30 (52%)**	**<0.001**

Circulation 2006

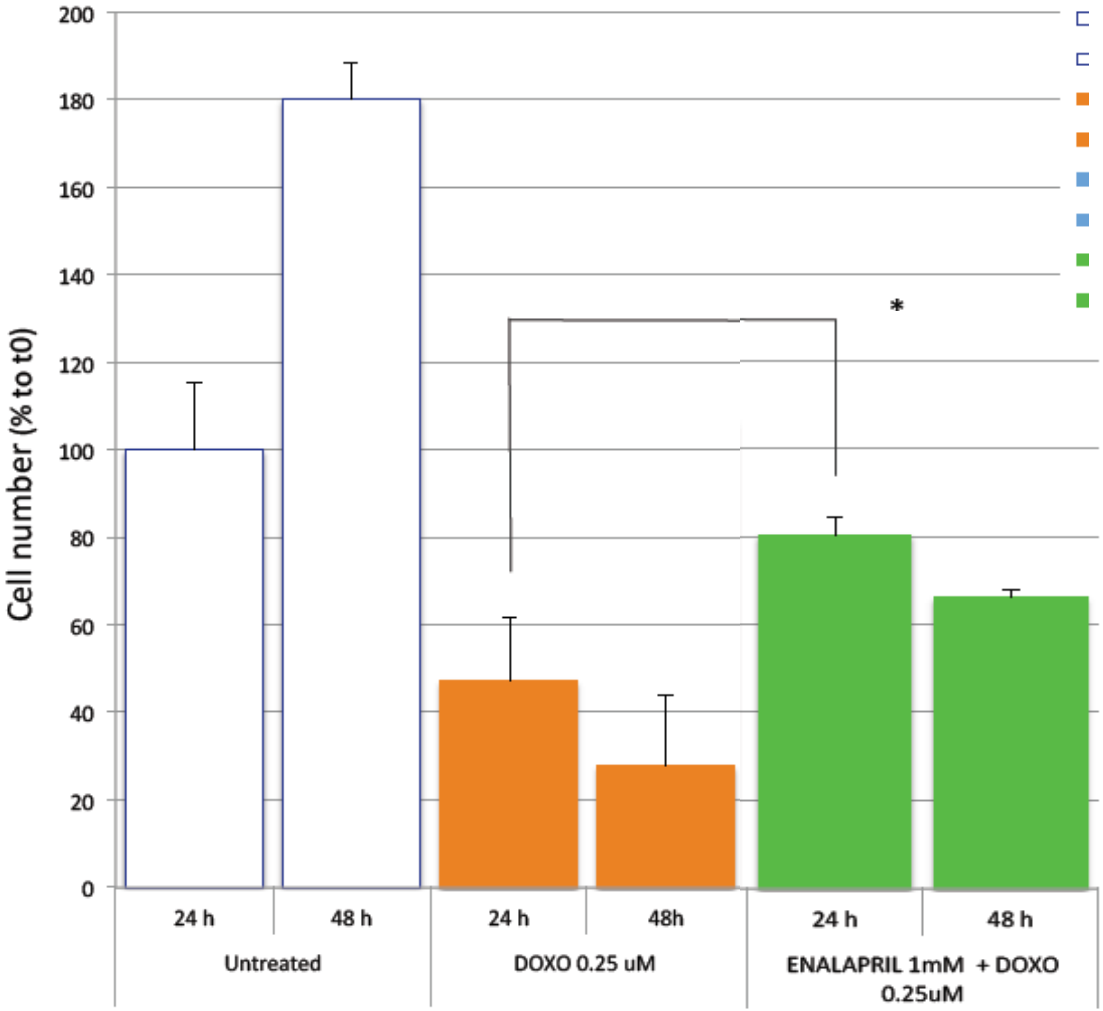
Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

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 improves resistance of HL-1 cells to doxorubicin



Giorgio M. Experimental Cardioncology Unit - IEO. Unpublished data

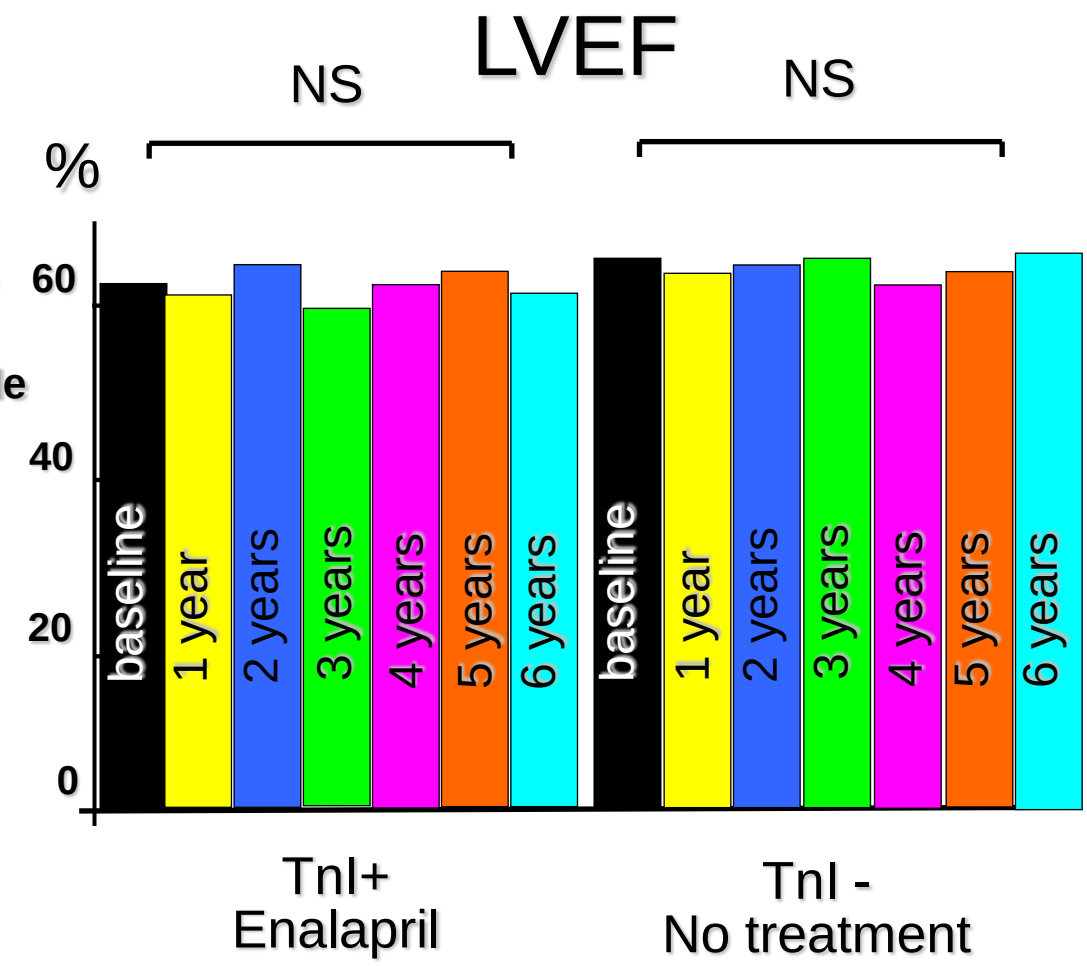
Our real-world experience

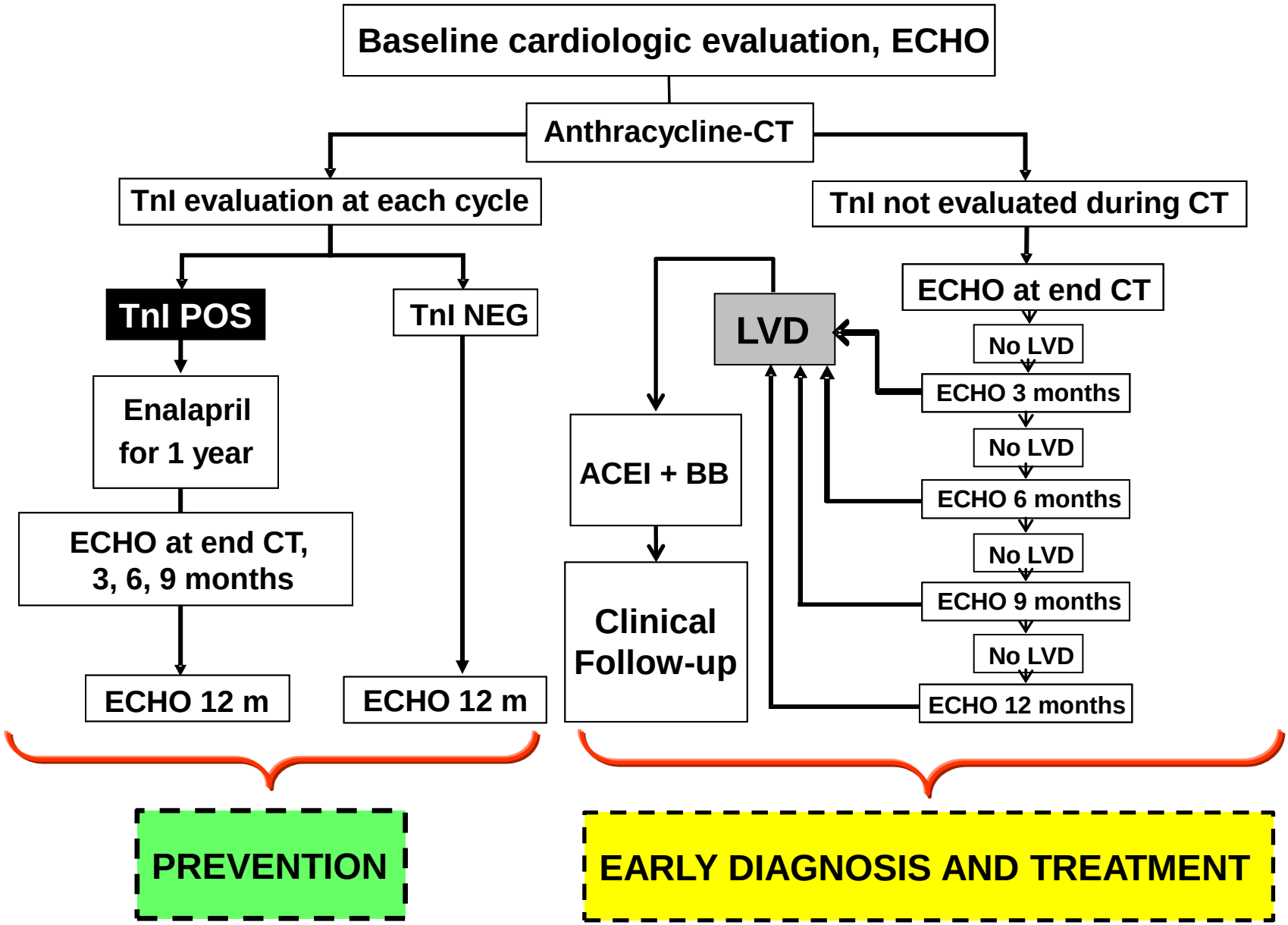
Troponin + Enalapril approach

- **1682 post-study pts**
- **Negative cardiovascular history**
- **Different kinds of tumor**
- **Cardiotoxic oncologic treatments**

- **TnI before and after every CT cycle**
- **TnI + = n. 252 (15%)**
- **Enalapril in TNI+ pts**
- **Serial LVEF measurements**

- **6-year FU**
- **NO significant LVEF reduction from baseline**

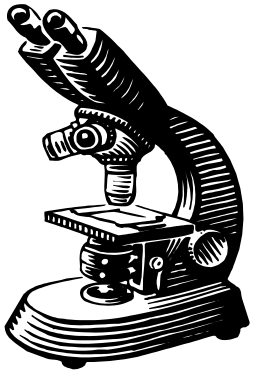




Modified from Cardinale D. Braunwald Heart Disease E-dition 2012

Cardiotoxicity

Prevention	Complete or partial recovery	No recovery



Myocardial cell injury

LV dysfunction

Overt HF

Cardinale D.