Cardioprotezione farmacologica
PRO

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1° Congresso Nazionale di Cardioncologia
Negrar, 25 Gennaio 2019

DISCLOSURE INFORMATION

Nicola Maurea

negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Bayer
Boehringer Ingelheim
Bristol-Myers Squibb
Clinigen
Daiichi-Sankyo

Journal of Cardiovascular Medicine 2010, 11:861–868

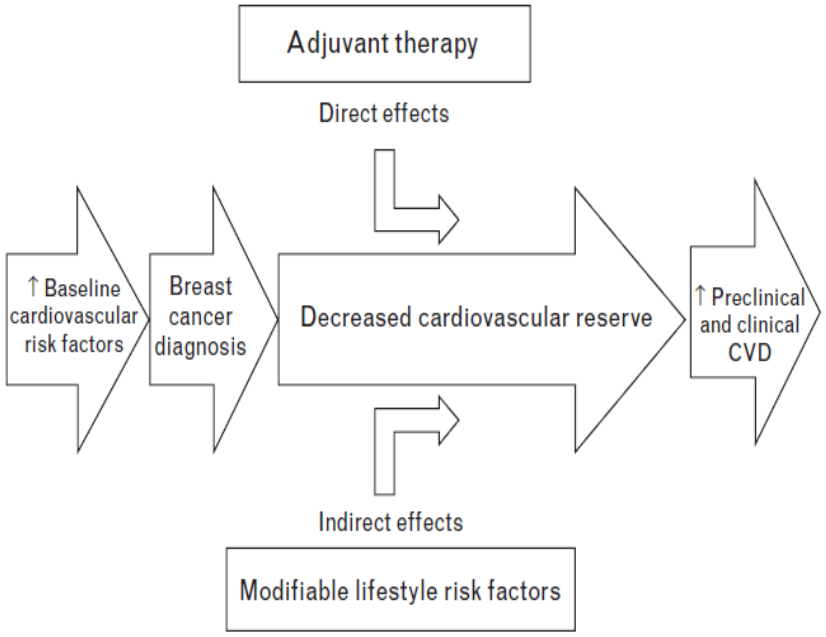
Review article

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Women survive breast cancer but fall victim to heart failure: the shadows and lights of targeted therapy

Nicola Maurea[a], Carmela Coppola[a], Gianluca Ragone[b], Giuseppe Frasci[c], Annamaria Bonelli[a], Carmela Romano[b] and Rosario Vincenzo Iaffaioli[b]

Fig. 3



'Multiple-hit' hypothesis. CVD, cardiovascular disease. Adapted from [3].

Women diagnosed with breast cancer should be evaluated for cardiovascular risk before undergoing treatment with antineoplastic drugs [3]. Depending on the type of risk factor, patients should be advised as regards lifestyle changes, and, in some cases, their drug regimen may have to be changed. Physical exercise is known to have positive effects on cardiovascular reserve, risk factors and total mortality [6]. β-blockers and ACE inhibitors are recommended for initial hypertension therapy. Statins are recommended to maintain LDL-C less than 100 mg/ml. Sulphonylureas and biguanids are recommended to maintain glycosylated hemoglobin less than 7% [31].

VOLUME 35 · NUMBER 8 · MARCH 10, 2017
JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

Survivorship Guidelines

Which cancer patients are at increased risk for developing cardiac dysfunction?

Recommendation

It is recommended that cancer patients who meet any of the following criteria be categorized by healthcare providers as **high risk for developing cardiac dysfunction**.

Treatment that includes any of the following:

- **High dose anthracycline** (e.g. ≥250 mg/m^2 doxorubicin, ≥600 mg/m^2 epirubicin)
- **High dose radiotherapy** (≥30 Gy) where a substantial portion of the heart is in the treatment field
- **Lower dose anthracycline** (e.g. <250 mg/m^2 doxorubicin, <600 mg/m^2 epirubicin) in combination with **lower dose radiotherapy** (<30 Gy) where a substantial portion of the heart is in the treatment field

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Survivorship Guidelines

Treatment with lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:

- **Multiple cardiovascular risk factors** (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia and obesity, during or after completion of therapy
- **Older age** (> 60 years) at cancer treatment
- **Compromised cardiac function** (eg, borderline low LVEF [50% to 55%], **history of myocardial infarction, ≥ moderate valvular heart disease**) at any time before or during treatment

Treatment with lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) followed by trastuzumab (sequential therapy)

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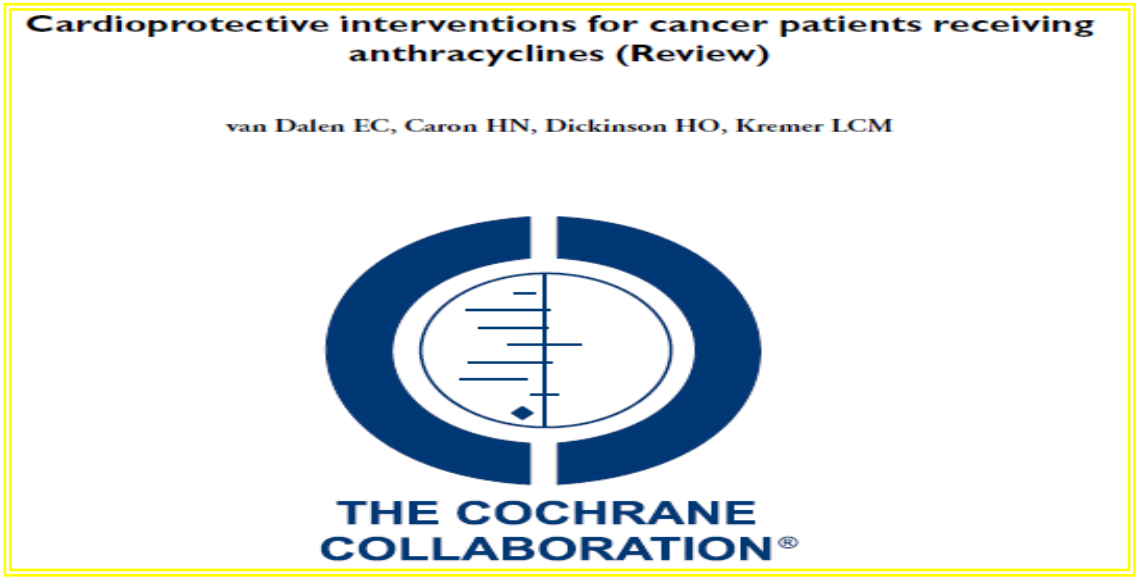
Survivorship Guidelines

Which preventive strategies are effective in minimizing risk during the administration of potentially cardiotoxic cancer therapy?

Recommendation

Clinicians may incorporate a number of strategies, including use of the **cardioprotectant dexrazoxane, continuous infusion, or liposomal formulation of doxorubicin**, for prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines (eg, doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2).

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)



Identified RCTs for the eight cardioprotective agents N-acetylcysteine, phenethylamines, coenzymeQ10, a ***combination of vitamins E and C and N-acetylcysteine, L-carnitine, carvedilol, amifostine*** **and** ***dexrazoxane*** (mostly for adults with advanced breast cancer).

All studies had methodological limitations and ***for the first seven agents there were too few studies to allow pooling of results.***

None of the individual studies showed a cardioprotective effect.

van Dalen et al, Cochrane Database Syst Rev. 2011

Figure 1. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane / placebo, outcome: 1.1 Clinical heart failure.

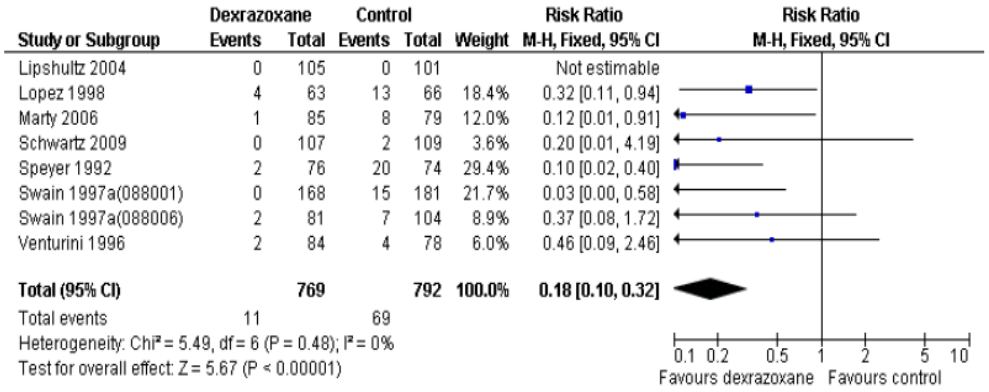
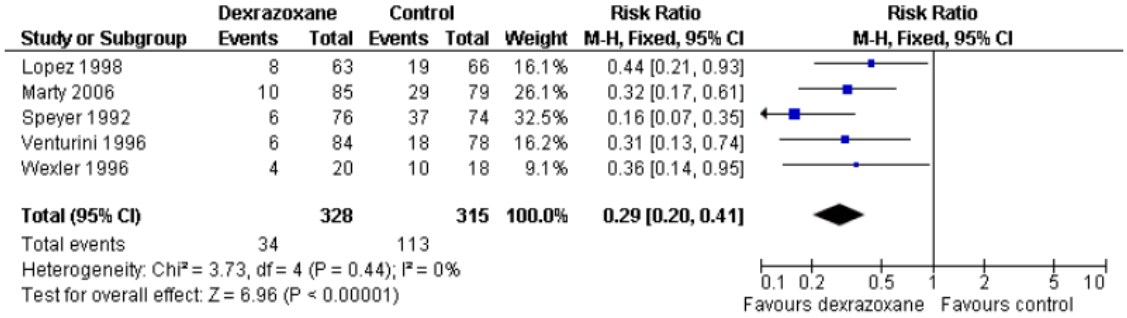


Figure 2. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane / placebo, outcome: 1.2 Heart failure (i.e. clinical and subclinical heart failure combined).



The 8 included studies on dexrazoxane enrolled **1561 patients**. The meta- analysis for dexrazoxane showed a ***statistically significant benefit in favour of dexrazoxane for occurrence of clinical and subclinical HF (↓> 70%).***

van Dalen et al, Cochrane Database Syst Rev. 2011

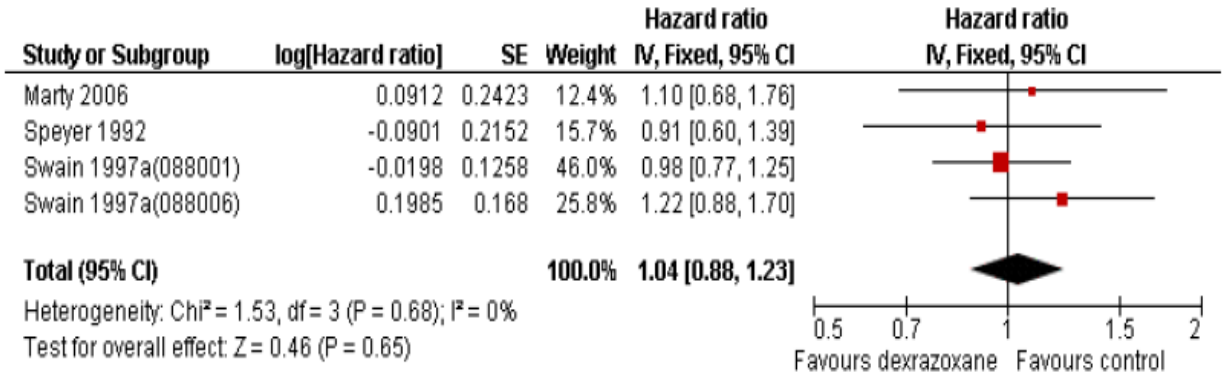
Cardioprotective interventions for cancer patients receiving anthracyclines (Review)

van Dalen EC, Caron HN, Dickinson HO, Kremer LCM

THE COCHRANE COLLABORATION®

Dexrazoxane

Figure 5. Forest plot of comparison: 1 Dexrazoxane versus no dexrazoxane / placebo, outcome: 1.5 Overall survival.



No evidence was found for a difference in response rate or survival between the dexrazoxane and control groups. *The results for adverse effects were ambiguous.* ***No significant difference in the occurrence of secondary malignancies was identified.***

van Dalen et al, Cochrane Database Syst Rev. 2011

Leukemia Research Reports 7 (2017) 36–39

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Dexrazoxane for cardioprotection in older adults with acute myeloid leukemia

Pankit Vachhani[a,*,1], Sarah Shin[b,1], Jeffrey Baron[c], James E. Thompson[a], Meir Wetzler[a], Elizabeth A. Griffiths[a], Evelena P. Ontiveros[a], Edward J. Spangenthal[a], Eunice S. Wang[a]

A B S T R A C T

Anthracyclines constitute the backbone of intensive adult acute myeloid leukemia (AML) therapy. Cardiotoxicity is one of its most serious adverse effects, and its incidence increases with cumulative dose. Dexrazoxane is a cardioprotective agent used in conjunction with anthracycline therapy. There is limited data of its usage in adult AML patients. We report the outcomes of six older adults at high risk of anthracycline-induced cardiotoxicity who received dexrazoxane during induction/re-induction therapy. Five had preserved left-ventricular function while two proceeded onto stem-cell transplantation. Additional investigation of dexrazoxane in adult leukemia therapy is warranted, particularly in older patients at highest risk for cardiovascular mortality.

VOLUME 34 · NUMBER 8 · MARCH 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404

Barbara L. Asselin, Meenakshi Devidas, Lu Chen, Vivian I. Franco, Jeanette Pullen, Michael J. Borowitz, Robert E. Hutchison, Yaddanapudi Ravindranath, Saro H. Armenian, Bruce M. Camitta, and Steven E. Lipshultz

Conclusion

Dexrazoxane was cardioprotective and did not compromise antitumor efficacy, did not increase the frequencies of toxicities, and was not associated with a significant increase in second malignancies with this doxorubicin-containing chemotherapy regimen. We recommend dexrazoxane as a cardioprotectant for children and adolescents who have malignancies treated with anthracyclines.

The use of dexrazoxane is recommended in ASCO guidelines

- ASCO guidelines:
  - The use of **dexrazoxane** should be considered in patients with metastatic breast cancer and other malignancies, for patients who have received more than 300 mg/m^2 doxorubicin who may benefit from continued doxorubicin containing therapy

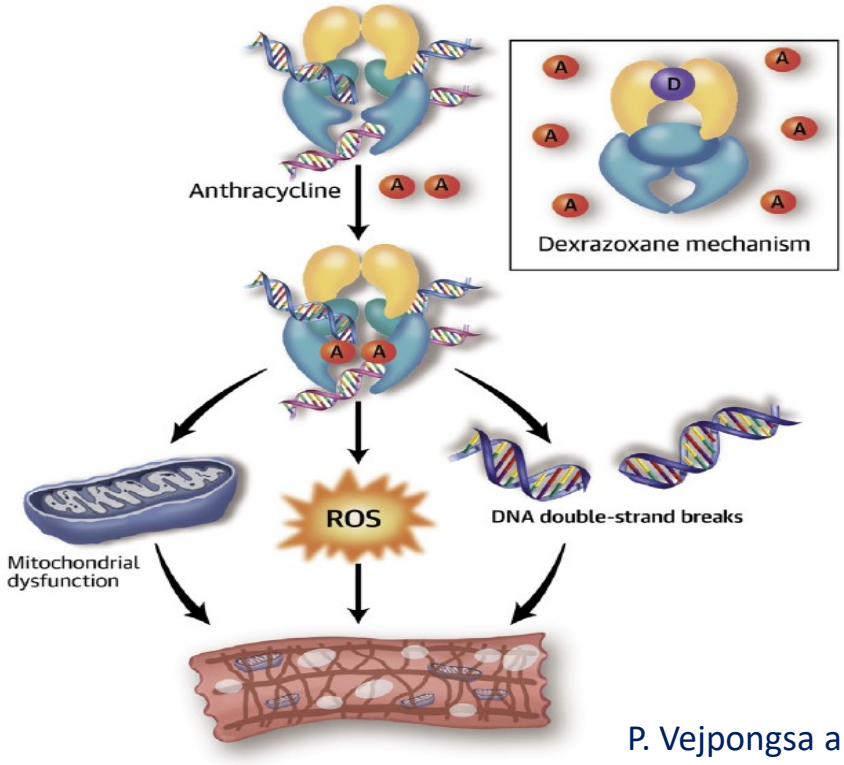
EMA recommended alterations to the marketing authorisation for dexrazoxane

Main breast cancer indication remains unchanged

- Indication was not widened to include «cancer patients»
- **Dexrazoxane is indicated for adult patients with advanced or metastatic breast cancer who have already received a minimum cumulative dose of 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin**

Dexrazoxane - Question to resolve

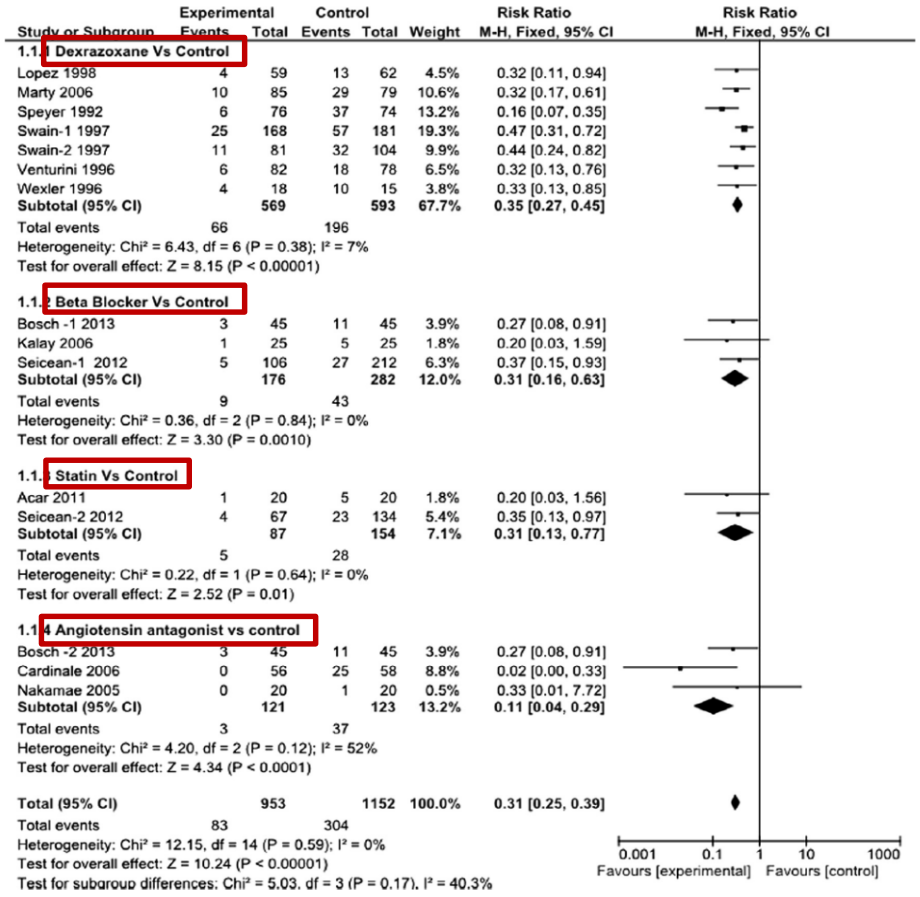
- There are clear indications to revisiting the use of Dexrazoxane. No doubt that there are sufficient and convincing data to expand the use of dexrazoxane in the adjuvant setting and to other patients (women with breast cancer with bad prognosis, young patients with lymphoma and leukaemia…etc...)



P. Vejpongsa and E. Yeh, J Am Coll Cardiol. 2014

Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: A systematic review and meta-analysis

Kashif Kalam, Thomas H. Marwick *



Interpretation: Prophylactic treatment with dexrazoxane, beta-blocker, statin or angiotensin antagonists appear to have similar efficacy for reducing cardiotoxicity.

Eur J Cancer 2013

European Journal of Cancer (2013) 49, 2900–2909

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.com

Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: A systematic review and meta-analysis

Kashif Kalam, Thomas H. Marwick *

Study limitations

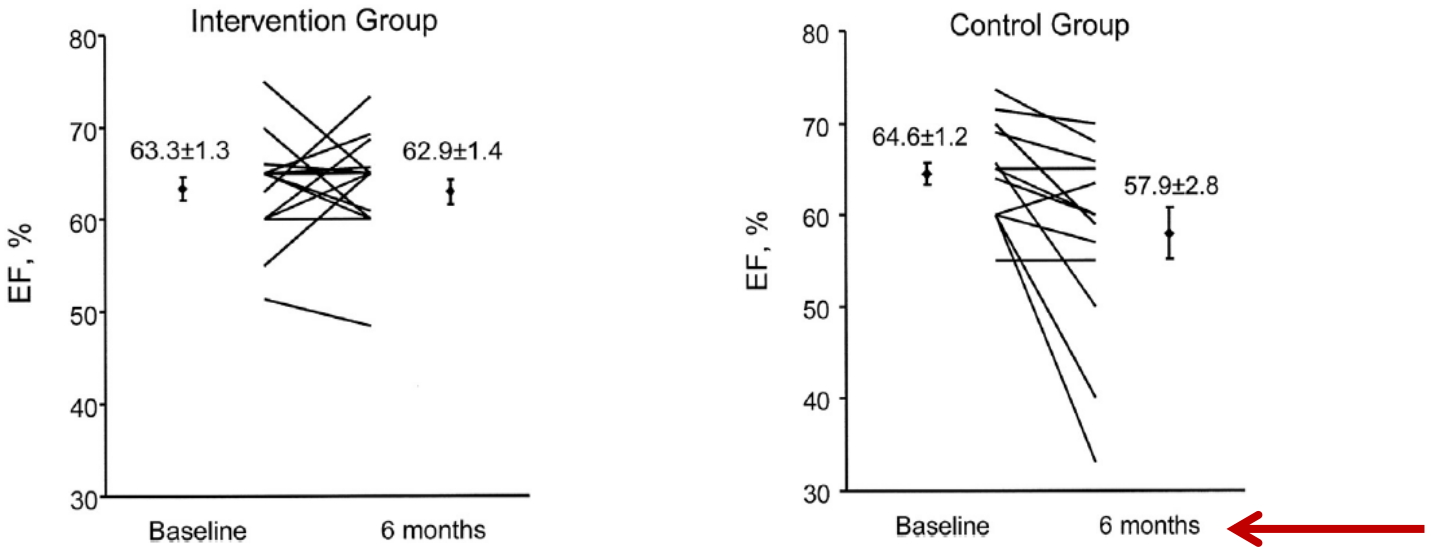
- Significant heterogeneity of study design (RCT's and observational trials) and outcomes.
- Some trials had a very small number of patients with short follow up periods.
- It is difficult to know whether use of concomitant treatments with other cardioprotective agents is fully adjusted for the primary drug in investigation.
- The studies involved a variety of oncological conditions with different chemotherapeutic agents and combinations, different dose schedules and age groups.

Journal of the American College of Cardiology Vol. 61, No. 23, 2013

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)

N= 79



Conclusions

Combined treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with intensive chemotherapy. The clinical relevance of this strategy should be confirmed in larger studies.

Beta-blockers and ACE inhibitors: truly cardioprotective? We don't really know… Only hemodynamic changes?

TABLE 3 Summary of β-Blocker and/or ACE Inhibitor Studies for Primary Prevention of Anthracycline-Induced Cardiotoxicity

First Author (Ref. #)	Medication	Patients*	Follow-Up, Months	Results
Kalay et al. (54)	Carvedilol 12.5 mg daily vs. placebo	50 (25/25)	6	Placebo: LVEF 68.9% → 52.3%† Carvedilol: LVEF 70.5% → 69.7%
Georgakopoulos et al. (55)	Metoprolol‡ vs. enalapril‡ vs. placebo§	125 (42/43/40)	31	Cardiotoxicity incidence not statistically different among 3 groups No difference in echocardiographic parameters among 3 groups at 12 months
Kaya et al. (53)	Nebivolol 5 mg daily vs. placebo‖	45 (27/18)	6	Placebo: LVEF 66.6% → 57.5%† Nebivolol: LVEF 65.6% → 63.8%
Bosch et al. (52)	Enalapril‡ + carvedilol‡ vs. no treatment‖	90 (45/45)	6	Control: LVEF 64.6% → 57.9%† Enalapril + carvedilol: LVEF 63.3% → 62.9% TnI levels not significantly different between 2 groups ($p = 0.59$)

*Numbers in parentheses represent the numbers of patients in intervention and control/placebo groups, respectively. †Statistically significant between baseline and 6 months ($p < 0.05$). ‡Medications titrated as tolerated. §Medications started on the first day of chemotherapy and continued throughout the study. ‖Medications started within 1 week before the first chemotherapy cycle and continued for 6 months.

ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; TnI = troponin I.

P. Vejpongsa and E. Yeh, J Am Coll Cardiol. 2014

J Am Coll Cardiol 2018;71:2281-90

Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity

The CECCY Trial

METHODS The authors randomized 200 patients with HER2-negative breast cancer tumor status and normal left ventricular ejection fraction (LVEF) referred for ANT (240 mg/m^2) to receive carvedilol or placebo until chemotherapy completion. The primary endpoint was prevention of a ≥10% reduction in LVEF at 6 months. Secondary outcomes were effects of carvedilol on troponin I, B-type natriuretic peptide, and diastolic dysfunction.

CONCLUSIONS In this largest clinical trial of β-blockers for prevention of cardiotoxicity under contemporary ANT dosage, the authors noted a 13.5% to 14.5% incidence of cardiotoxicity. In this scenario, carvedilol had no impact on the incidence of early onset of LVEF reduction. However, the use of carvedilol resulted in a significant reduction in troponin levels and diastolic dysfunction.

EDITORIAL COMMENT

Beta-Blockers for Primary Prevention of Anthracycline Cardiotoxicity

Not Quite Ready for Prime Time*

Aarti Asnani, MD

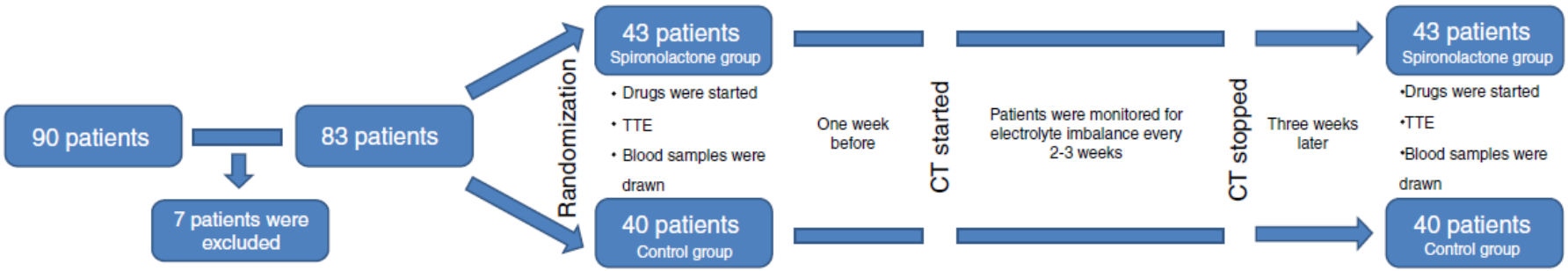
Given the negative primary endpoint, should findings from this study change clinical practice? In the absence of long-term outcomes data, the low incidence of abnormal left ventricular systolic function after contemporary chemotherapy argues against a primary prevention strategy for all-comers treated with anthracyclines. Although the observed improvements in secondary endpoints associated with the use of carvedilol are promising, they warrant cautious interpretation. It remains unclear whether troponin-based management improves cardiovascular outcomes in this patient population, and larger studies with longer follow-up will be necessary to assess the degree to which amelioration of secondary endpoints affects hard outcomes, such as clinical congestive heart failure and mortality.

The study by Avila et al. (4) highlights the need for additional randomized, controlled trials of prophylactic beta-blockade in larger cohorts as well as in patient populations with more marked left ventricular dysfunction and congestive heart failure, such as those with aggressive hematologic malignancies or refractory cancer requiring high-dose chemotherapy.

Protective effects of spironolactone against anthracycline-induced cardiomyopathy

Mahmut Akpek[1]*, Ibrahim Ozdogru[1], Omer Sahin[1], Mevlude Inanc[2], Ali Dogan[1], Cevat Yazici[3], Veli Berk[2], Halit Karaca[2], Nihat Kalay[1], Abdurrahman Oguzhan[1], and Ali Ergin[1]

n=83
Follow-up: 6 months



Echocardiographic properties of study population

	Spironolactone group ($n = 43$)			Control group ($n = 40$)			
	Before	After	*P*-value	Before	After	*P*-value	*P*-value*
LVEF (%)	67.0 ± 6.1	65.7 ± 7.4	0.094	67.7 ± 6.3	53.6 ± 6.8	<0.001	<0.001
LVESD (cm)	2.9 ± 0.3	3.1 ± 0.3	0.007	2.9 ± 0.4	3.6 ± 0.5	<0.001	<0.001
LVEDD (cm)	4.6 ± 0.4	4.9 ± 0.4	0.001	4.6 ± 0.5	5.2 ± 0.4	<0.001	0.002

*P-value for interaction between groups in the general linear model.

European Journal of Heart Failure (2015) **17**, 81–89

Journal of the American College of Cardiology Vol. 58, No. 9, 2011

CORRESPONDENCE

Research Correspondence

Efficiency of Atorvastatin in the Protection of Anthracycline-Induced Cardiomyopathy

Zeydin Acar, MD

Table 1 Comparison of Echocardiographic Parameters in the Study Group Between Baseline and Follow-Up Values

	Statin Group (n = 20)	Control Group (n = 20)	p Value
LVEF (%)			
Baseline	61.3 ± 7.9	62.9 ± 7.0	
After 6 months	62.6 ± 9.3	55.0 ± 9.5	
Mean change	1.3 ± 3.8	−7.9 ± 8.0	<0.001
LVEDD (mm)			
Baseline	46.5 ± 7.2	47.2 ± 5.2	
After 6 months	46.3 ± 6.8	49.2 ± 6.2	
Mean change	−0.15 ± 4.0	2.0 ± 3.3	0.021
LVESD (mm)			
Baseline	30.9 ± 7.2	30.3 ± 5.4	
After 6 months	29.6 ± 6.1	32.3 ± 5.4	
Mean change	−1.35 ± 4.0	2.1 ± 1.8	<0.001

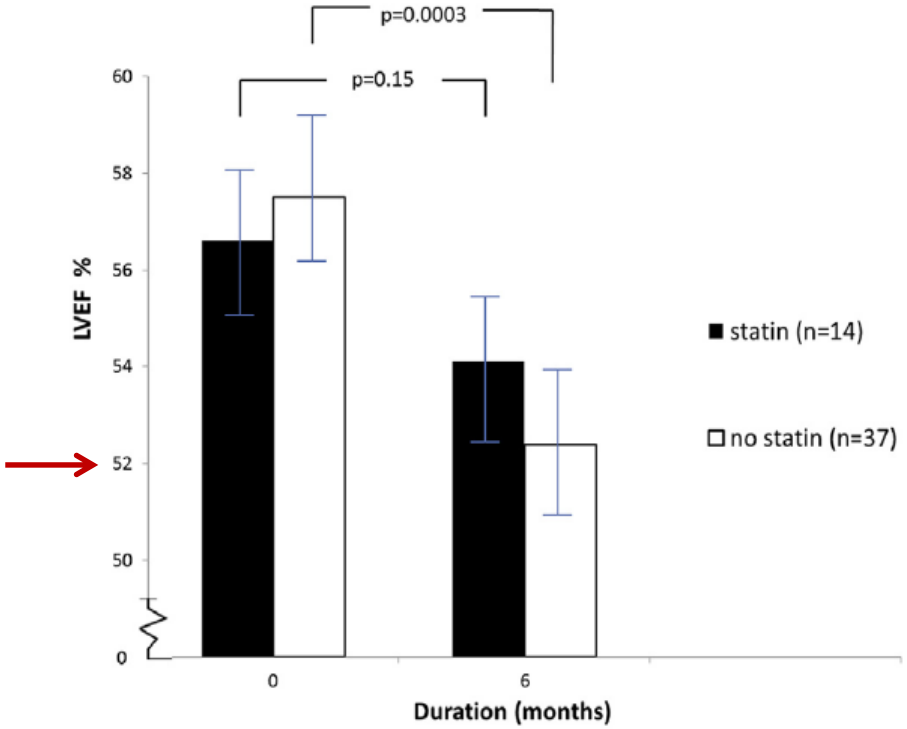
LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter.

- **Prospective randomized study**
- **Follow-up: 6 months**

  n= 40
- **n 20= atorvastatin**
- **n 20= Controls**
- **End-points=LVEF<50%**

Clinical Research

Chronic Statin Administration May Attenuate Early Anthracycline-Associated Declines in Left Ventricular Ejection Function



n=51 patients
Analysis by CMRI
Follow-up: 6 months

Conclusions: These data highlight the finding that individuals receiving statin therapy for prevention of cardiovascular disease may experience less deterioration in LVEF with early receipt of Anth-bC than individuals not receiving statins. Further studies with large numbers of participants are warranted to determine if statins protect against LVEF decline in patients receiving Anth-bC.

Chotenimitkhun et al. Can J Cardiol 2015

Primary prevention – Anthracycline cardiotoxicity

TABLE 4 Primary and Secondary Prevention Strategies

Clinical Setting	Primary Prevention	Level of Evidence*	Class of Recommendation*
High-risk profile from genetic testing	Dexrazoxane Liposomal doxorubicin Continuous infusion	C	IIb
Breast cancer (metastatic >300 mg/m^2)†	Dexrazoxane	A	I
Sarcoma‡	Dexrazoxane Continuous infusion	A	IIa
High-risk pediatric ALL§	Dexrazoxane	A	IIa
All patients receiving anthracycline	β-blockers, ACEI, ARB	C	IIb
	Secondary Prevention		
Abnormal strain/LV function ± elevated cardiac biomarkers	β-blockers, ACEI, ARB	B	IIa

*According to American College of Cardiology Foundation/American Heart Association guideline criteria (65). †Metastatic breast cancer patients requiring doxorubicin >300 mg/m^2. ‡To receive doxorubicin >450 mg/m^2. §Patients age <12 months or 10 to 18 years; white blood cell count ≥50,000 cells/μl; or have T-cell phenotype, presence of anterior mediastinal mass, or any lymphoblasts in a cerebrospinal fluid sample.

ALL = acute lymphoblastic leukemia; LV = left ventricular; other abbreviations as in Table 2.

Vejpongsa et al, JACC 2014

Trastuzumab - induced cardiotoxicity

MRI imaging - Results

PRADA

LVEF % (primary endpoint)		Δ from baseline
No candesartan	63.2(±1.2)→60.6(±1.2)	**-2.6 (±1.2)***
Candesartan	62.1(±1.1)→61.4(±1.2)	**-0.7 (±1.2)**
No metoprolol	62.8(±1.2)→61.0(±1.2)	-1.8 (±1.1)
Metoprolol	62.5(±1.2)→61.0(±1.2)	-1.5 (±1.2)

MANTICORE

LVEDVi (primary endpoint) ml/m^2		Δ from baseline
Placebo	76(±13)→79(±12)	+4(±11)
Perindopril	67(±14)→74(±16)	+7(±14)
Bisoprolol	69(±10)→76(±14)	+8(±9)
LVEF % (secondary endpoint)		
Placebo	61(±5)→56(±6)	-5(±5)
Perindopril	62(±5)→59(±6)	-3(±4)
Bisoprolol	62(±4)→61(±5)	**-1(±5)***

*p<0,05

PRADA: the overall decline in LVEF was 2.6% in the placebo group and 0.6% in the candesartan group, a significant but very modest difference. Metoprolol didn't put a dent in the LVEF decline.

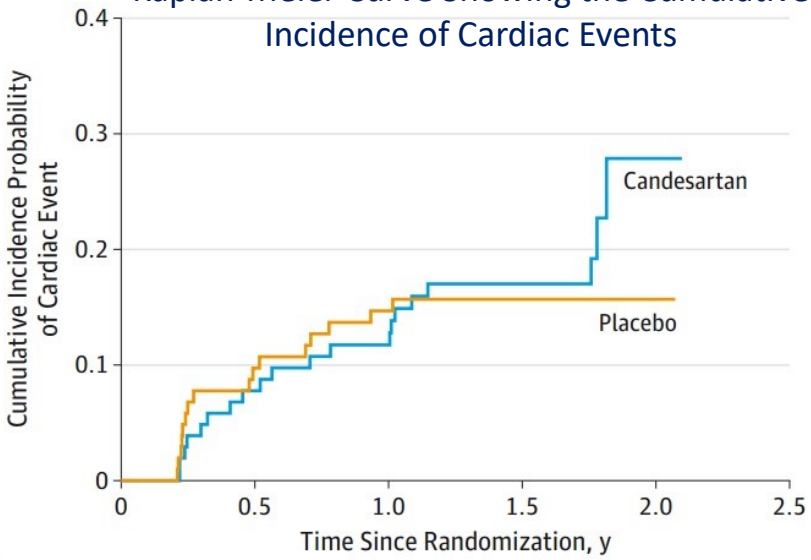
MANTICORE: ACE inhibitors and beta blockers did not prevent trastuzumab associated LV remodeling. Although Bisoprolol protected against trastuzumab-associated declines in LVEF, the overall decline was 5% in placebo group and 1% in Bisoprolol group, also in this case a significant but very modest difference. Perindopril didn't put a dent in the LVEF decline.

Angiotensin II–Receptor Inhibition With Candesartan to Prevent Trastuzumab-Related Cardiotoxic Effects in Patients With Early Breast Cancer

A Randomized Clinical Trial

N=206 pts
78 weeks Candesartan 32 mg

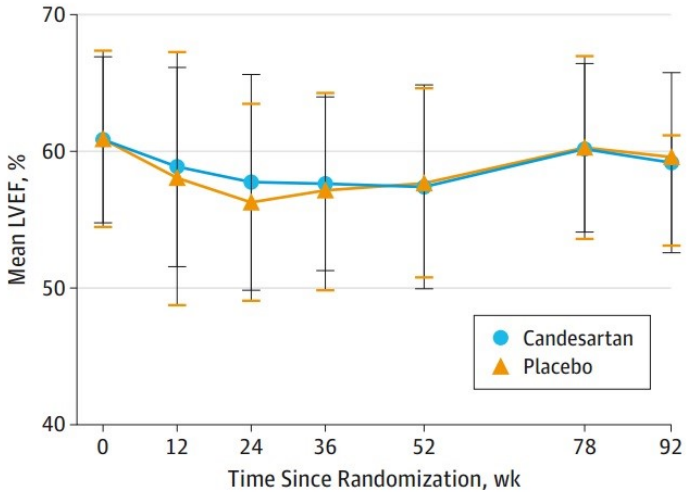
Kaplan-Meier Curve Showing the Cumulative Incidence of Cardiac Events



No. at risk

Candesartan	103	93	84	68	1	0
Placebo	103	92	85	83	4	0

Mean (SD) Left Ventricular Ejection Fraction (LVEF) Over Study Follow-up Time



No. at risk

Candesartan	103	101	100	97	99	85	75
Placebo	103	101	102	96	95	88	84

CONCLUSIONS AND RELEVANCE

The findings do not support the hypothesis that concomitant use of candesartan protects against a decrease in left ventricular ejection fraction during or shortly after trastuzumab treatment in early breast cancer.

Annelies H. Boekhout, et al. JAMA Oncology 2016

AMERICAN COLLEGE of CARDIOLOGY

Lisinopril or Carvedilol for Prevention of Trastuzumab Induced Cardiotoxicity - Lisinopril or Carvedilol for Cardiotoxicity

Mar 11, 2018

Presented by Dr. Maya E. Guglin at the American College of Cardiology Annual Scientific Session (ACC 2018), Orlando, FL, March 11, 2018.

- **The Lisinopril or Carvedilol for Cardiotoxicity trial failed** to show that lisinopril or carvedilol was superior to placebo at preventing left ventricular systolic dysfunction.

- The primary outcome, **decrease in LVEF >10%, occurred in 30% of the lisinopril group vs. 29% of the carvedilol group vs. 32% of the placebo group (p = not significant).** Among those **who received an anthracycline, decrease in LVEF >10% occurred in 37% of the lisinopril group vs. 31% of the carvedilol group vs. 47% of the placebo group (p = 0.009).**

- Among patients with breast cancer undergoing chemotherapy with trastuzumab, neither lisinopril nor carvedilol was effective at preventing cardiomyopathy compared with placebo. **Among those who were treated with an anthracycline, lisinopril and carvedilol appeared to be effective at preventing cardiomyopathy versus placebo.**

ClinicalTrials.gov

Carvedilol for the Prevention of Anthracycline/Anti-HER2 Therapy Associated Cardiotoxicity Among Women With HER2-Positive Breast Cancer Using Myocardial Strain Imaging for Early Risk Stratification

ClinicalTrials.gov Identifier: NCT02177175

Recruitment Status : Active, not recruiting
First Posted : June 27, 2014
Last Update Posted : May 30, 2018

Sponsor:

Memorial Sloan Kettering Cancer Center

Study Description

Brief Summary:

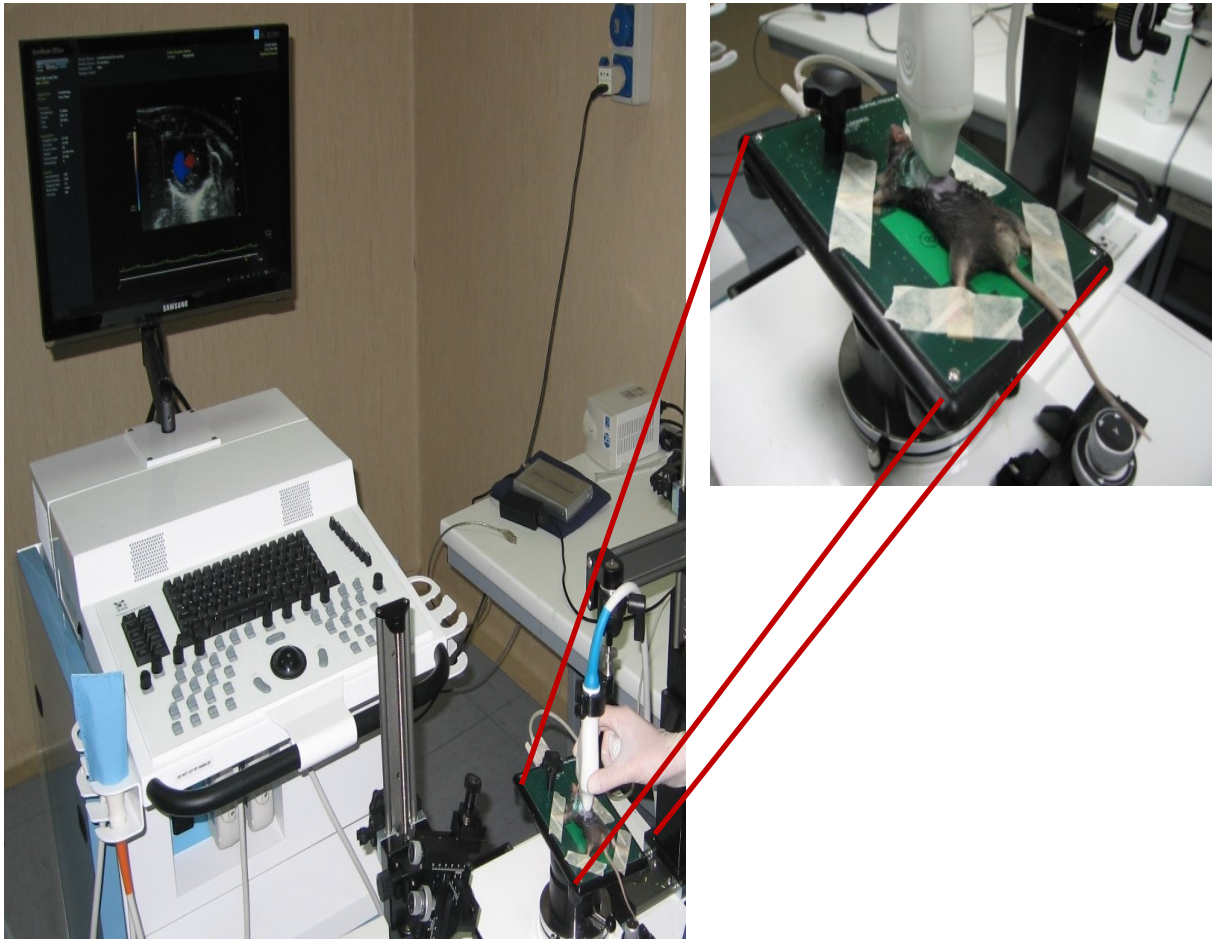
The purpose of this study is to find out the effects, good and/or bad, of a beta blocker (carvedilol) on heart function during treatment with anti-HER2 medication(s) including trastuzumab (Herceptin).

Condition or disease	Intervention/treatment	Phase
Breast Cancer	Drug: Carvedilol Other: placebo	Phase 2

in vivo 30: 279-290 (2016)

Strain Analysis in the Assessment of a Mouse Model of Cardiotoxicity due to Chemotherapy: Sample for Preclinical Research

DOMENICA REA[1], CARMELA COPPOLA[2], ANTONIO BARBIERI[1], MARIA GAIA MONTI[3], GABRIELLA MISSO[4], GIUSEPPE PALMA[1], SABRINA BIMONTE[5], MAYRA RACHELE ZARONE[4], ANTONIO LUCIANO[1], DAVIDE LICCARDO[4], PIERA MAIOLINO[6], ANTONIO CITTADINI[3], GENNARO CILIBERTO[7], CLAUDIO ARRA[1*] and NICOLA MAUREA[2*]



European Journal of Heart Failure (2014)
doi:10.1002/ejhf.50

Ranolazine protects from doxorubicin-induced oxidative stress and cardiac dysfunction

Carlo G. Tocchetti[1]*, Andrea Carpi[2], Carmela Coppola[3], Cristina Quintavalle[4], Domenica Rea[5], Marika Campesan[2], Antonella Arcari[8], Giovanna Piscopo[3], Clemente Cipresso[3], Maria Gaia Monti[7], Claudia De Lorenzo[6], Claudio Arra[5], Gerolama Condorelli[4], Fabio Di Lisa[2], and Nicola Maurea[3]

[1]Clinica Montevergine, Mercogliano (AV), Italy; [2]Department of Biomedical Sciences and CNR Institute of Neuroscience, University of Padova, Padova, Italy; [3]Division of Cardiology, National Cancer Institute, Pascale Foundation, Naples, Italy; [4]Department of Molecular Medicine and Medical Biotechnology, Federico II University, Naples, Italy; [5]Division of Animal Experimental Research, National Cancer Institute, Pascale Foundation, Naples, Italy; [6]Department of Structural and Functional Biology, Federico II University, Naples, Italy; [7]Department of Translational Medical Sciences, Federico II University, Naples, Italy; and [8]IRCCS Neuromed, Pozzilli, Italy

Conclusions Ranolazine protects against experimental doxorubicin cardiotoxicity. Such protection is accompanied by a reduction in oxidative stress, suggesting that I_{Na} modulates cardiac redox balance, resulting in functional and morphological derangements.

Ranolazine Attenuates Trastuzumab-Induced Heart Dysfunction by Modulating ROS Production

Gennaro Riccio[1], Salvatore Antonucci[2], Carmela Coppola[3], Chiara D'Avino[4,5], Giovanna Piscopo[3], Danilo Fiore[4], Carlo Maurea[3], Michele Russo[6], Domenica Rea[7], Claudio Arra[7], Gerolama Condorelli[4], Fabio Di Lisa[2], Carlo G. Tocchetti[6], Claudia De Lorenzo[4,5]* and Nicola Maurea[3]**

Our data support previous findings on the efficacy of ranolazine in experimental heart dysfunction (Sabbah et al., 2002; Rastogi et al., 2008; Coppini et al., 2013, 2017; Tocchetti et al., 2014; Cappetta et al., 2017). We acknowledge that further experiments may be necessary to conclude that the mechanism of action involves the levels of ROS, also considering that ranolazine has been recently shown to be able to antagonize β-adrenergic stimulation and decrease myofilaments Ca2+ sensitivity (Flenner et al., 2016), with little therapeutic efficacy in a HCM murine model *in vivo*. Nevertheless, we show that in the cardio-oncologic setting, beside doxorubicin cardiotoxicity (Tocchetti et al., 2014; Cappetta et al., 2017), RAN could also be a promising cardioprotective drug in the setting of trastuzumab toxicity. More efforts involving both experimental and clinical studies will be needed in order to establish whether ranolazine might be introduced clinically in the therapeutic strategies that aim at addressing cardiotoxicity induced by trastuzumab or anthracyclines.

Cardiotoxic effects of the novel approved anti-ErbB2 agents and reverse cardioprotective effects of ranolazine

This article was published in the following Dove Press journal:
OncoTargets and Therapy

Claudia De Lorenzo[1,2,*]
Rolando Paciello[1,2,*]
Gennaro Riccio[3]
Domenica Rea[4]
Antonio Barbieri[4]
Carmela Coppola[4]
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*These authors contributed equally to this work

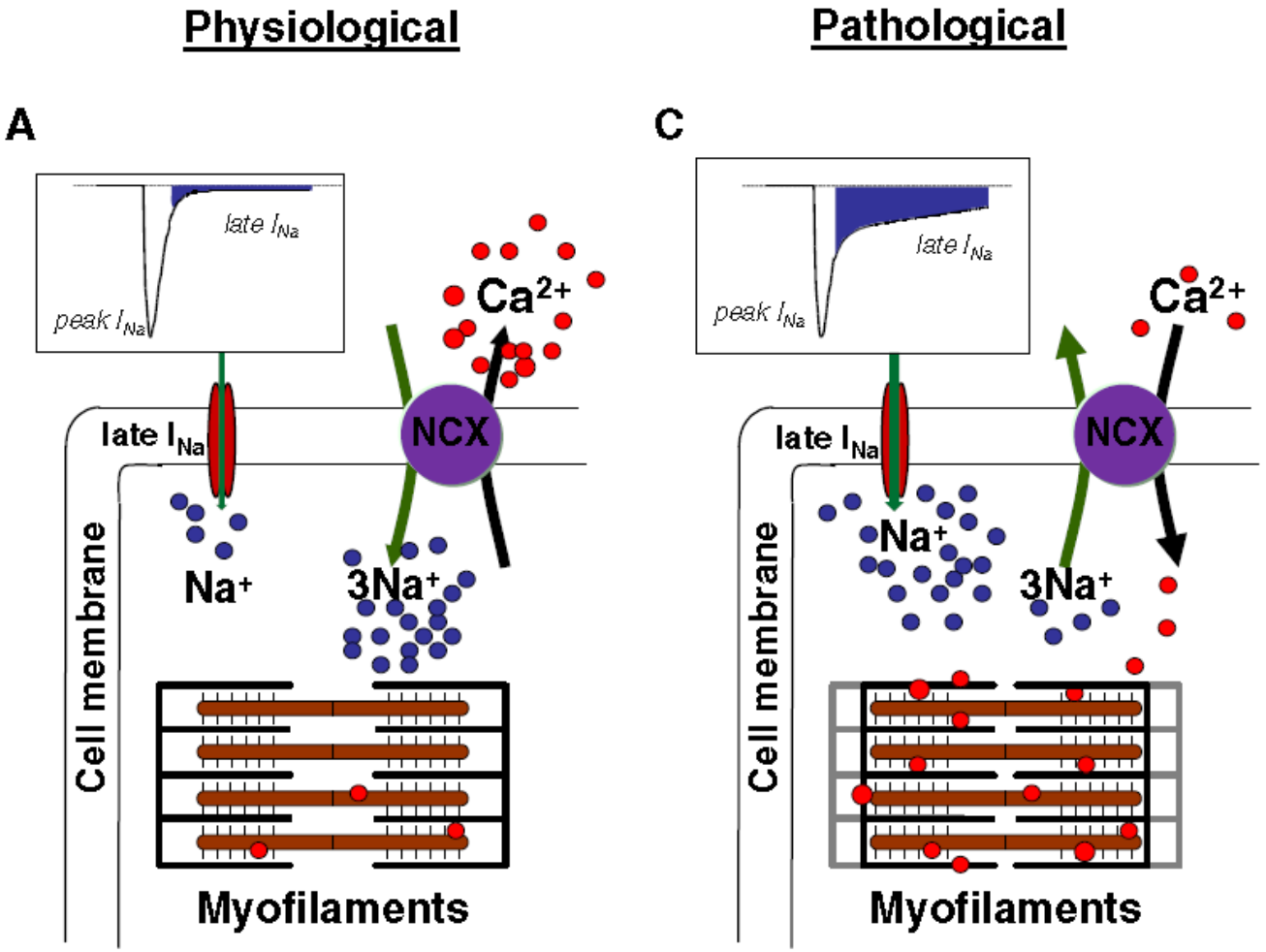
Purpose: Pertuzumab, a novel anti-epidermal growth factor receptor 2 humanized monoclonal antibody, and trastuzumab-emtansine (TDM1), a novel antibody–drug conjugate made up of trastuzumab covalently linked to the highly potent microtubule inhibitory agent DM1, have been recently approved by the US Food and Drug Administration for increasing the efficiency and safety of breast cancer therapy with trastuzumab. We investigated for the first time the potential cardiotoxic effects of pertuzumab and TDM1, which are not yet fully elucidated, and we tested whether ranolazine could blunt their cardiotoxicity.

Methods: The cardiotoxic effects were tested in vitro on rat cardiomyoblasts, human fetal cardiomyocytes, adult-like cardiomyocytes, and in vivo on a mouse model.

Results: All the treated cardiac cell lines were significantly affected by treatment with the tested drugs. Surprisingly, TDM1 showed stronger inhibitory effects on cardiac cells with respect to trastuzumab and pertuzumab by more significantly reducing the cell viability and by changing the morphology of these cells. TDM1 also affected the beating phenotype of adult-like cardiomyocytes in vitro and reduced fractional shortening and ejection fraction in vivo in a mouse model. We also found that ranolazine attenuated not only the cardiotoxic side effects of trastuzumab but also those of pertuzumab and TDM1, when used in combinatorial treatments both in vitro and in vivo, as demonstrated by the recovery of fractional shortening and ejection fraction values in mice pretreated with TDM1.

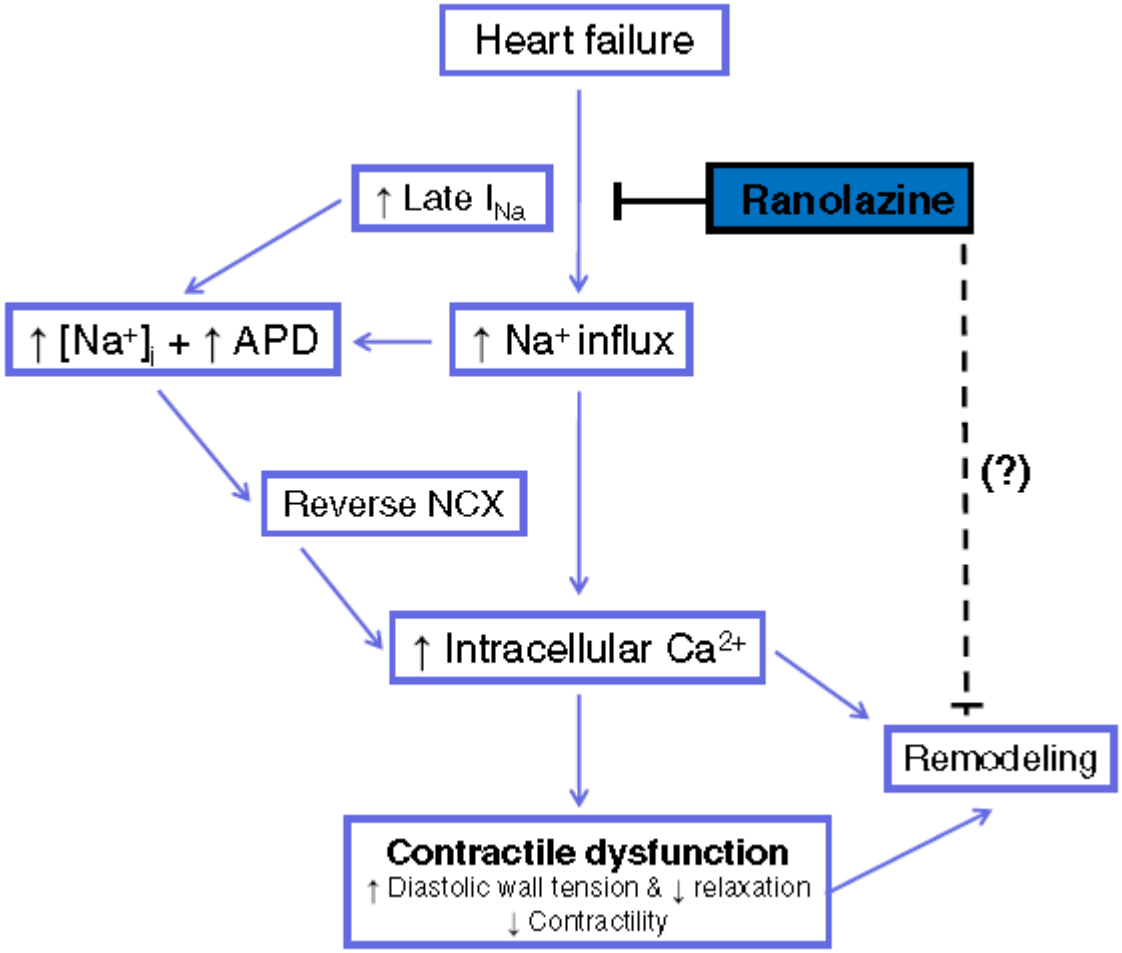
Conclusion: We demonstrated that it is possible to predict the eventual cardiotoxic effects of novel approved anticancer drugs early by using in vitro and in vivo approaches, which can also be useful to screen in advance the cardioprotective agents, so as to avoid the onset of unwanted cardiotoxic side effects.

Physiological condition and pathologically (HF) elevated late I_{Na}



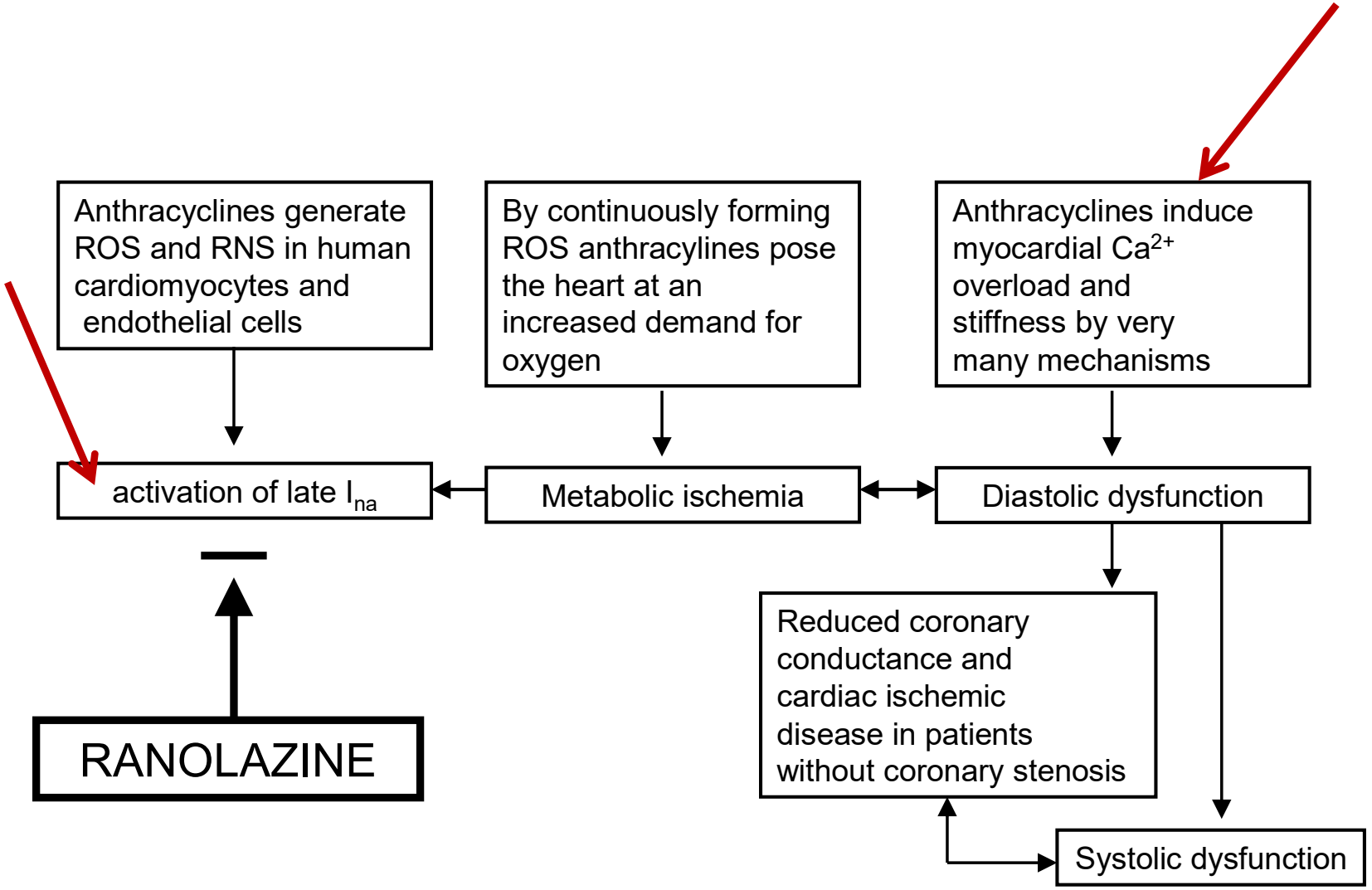
Sossalla and Maier. Pharmacology and Therapeutics 2012

Ranolazine acts against contractile dysfunction



Sossalla and Maier. Pharmacology and Therapeutics 2012

HYPOTHESIS


Anthracyclines generate ROS and RNS in human cardiomyocytes and endothelial cells
By continuously forming ROS anthracylines pose the heart at an increased demand for oxygen
Anthracyclines induce myocardial Ca^{2+} overload and stiffness by very many mechanisms
activation of late I_{na}
Metabolic ischemia
Diastolic dysfunction
RANOLAZINE
Reduced coronary conductance and cardiac ischemic disease in patients without coronary stenosis
Systolic dysfunction

Presentation Title: Cardioprotective and Anti Inflammatory Effects of a Selective Inhibitor of the Sodium Glucose Cotransporter 2 (Empaglifozin) in Doxorubicin Induced Cardiotoxicity

Name: Nicola Maurea

Session Type: Oral Contributions

Session Number: 908

Session Title: Highlighted Original Research: Heart Failure and Cardiomyopathies and the Year in Review

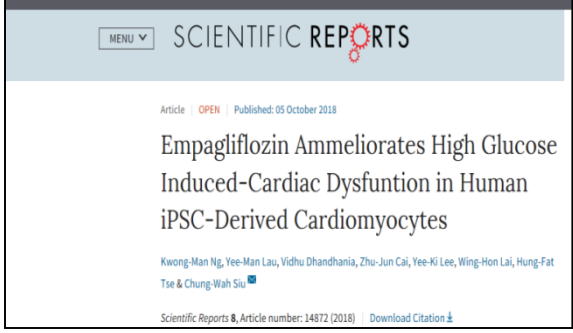
Session Time and Date: Monday Mar 18, 2019 8:00 AM - 9:30 AM

Session Location: Room 257

Presentation Time: 8:12am - 8:22am

Presentation Number: 908-04

Ipotesi scientifica


MENU SCIENTIFIC REPORTS

Article | OPEN | Published: 05 October 2018

Empagliflozin Ammeliorates High Glucose Induced-Cardiac Dysfuntion in Human iPSC-Derived Cardiomyocytes

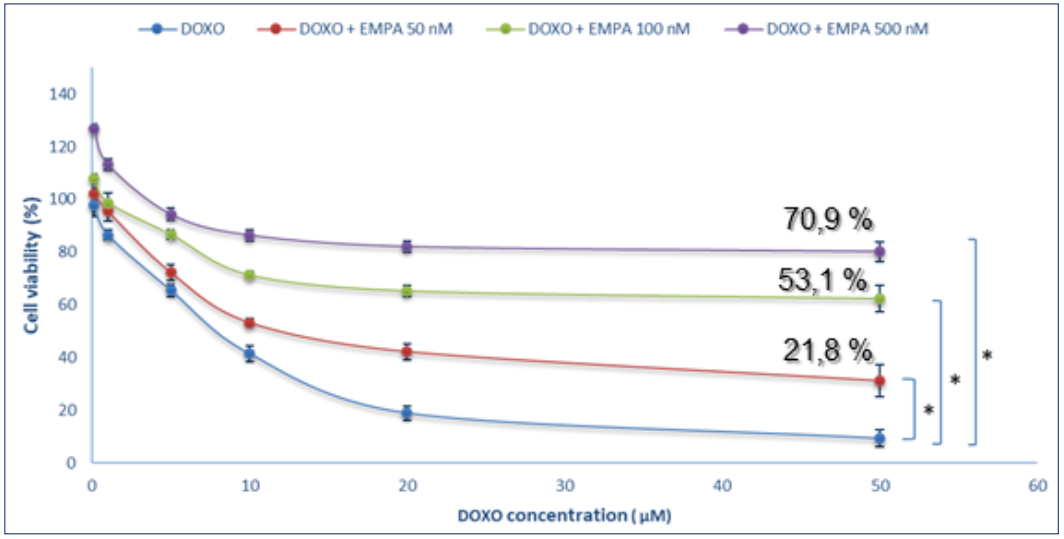
Kwong-Man Ng, Yee-Man Lau, Vidhu Dhandhania, Zhu-Jun Cai, Yee-Ki Lee, Wing-Hon Lai, Hung-Fat Tse & Chung-Wah Siu

Scientific Reports 8, Article number: 14872 (2018) | Download Citation

- Empaglifozin, essendo un inibitore del sodium-glucose co-transporter (SGLT), con possibili azioni antiossidanti, potrebbe essere un **agente cardioprotettore** dal danno cardiaco derivante dalla Doxorubicina. Recentemente è stato dimostrato che SGLT di tipo 1-2 è iperespresso in tessuti cardiaci di pazienti affetti da patologie cardiovascolari.

- Empaglifozin può migliorare il microambiente cardiaco, avere effetti anti-infiammatori e conseguentemente proteggere i cardiomiociti dal danno ossidativo (perossidi) e metabolico (overload di calcio, pathways legati all'NFkB e Leucotrieni) della Doxorubicina.

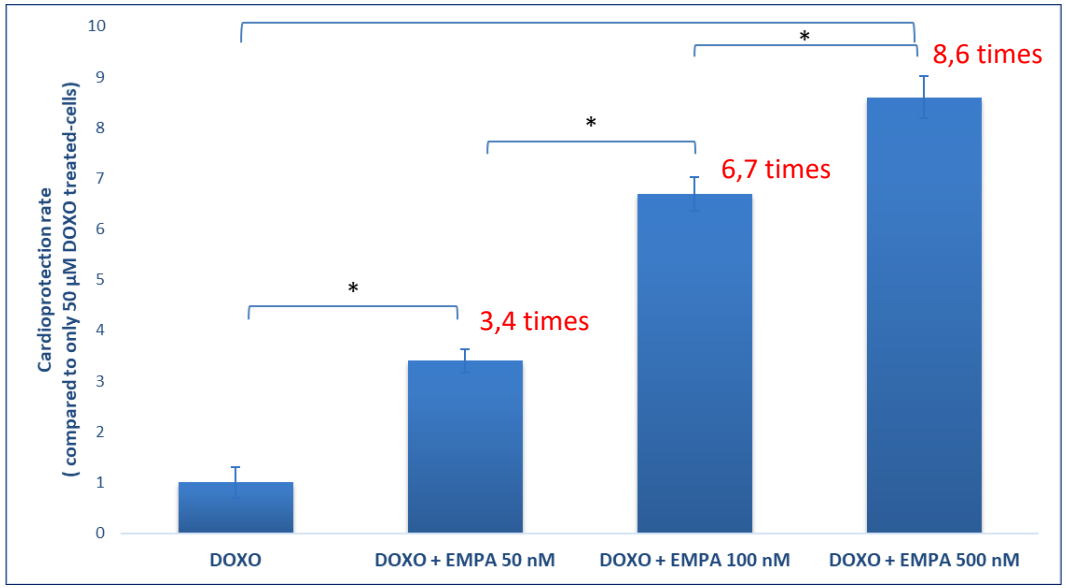
Cardioprotection of Empaglifozin during Doxorubicin exposure in cardiomyocytes



* $p < 0.001$

Il trattamento con doxorubicina riduce la vitalità cellulare del 90% circa, rispetto al controllo. La co-incubazione con empaglifozin 50, 100 o 500 nM, aumenta del 21,8%, 53,1% e 70,9% la vitalità dei cardiomiociti adulti, rispetto al solo trattamento con doxorubicina.

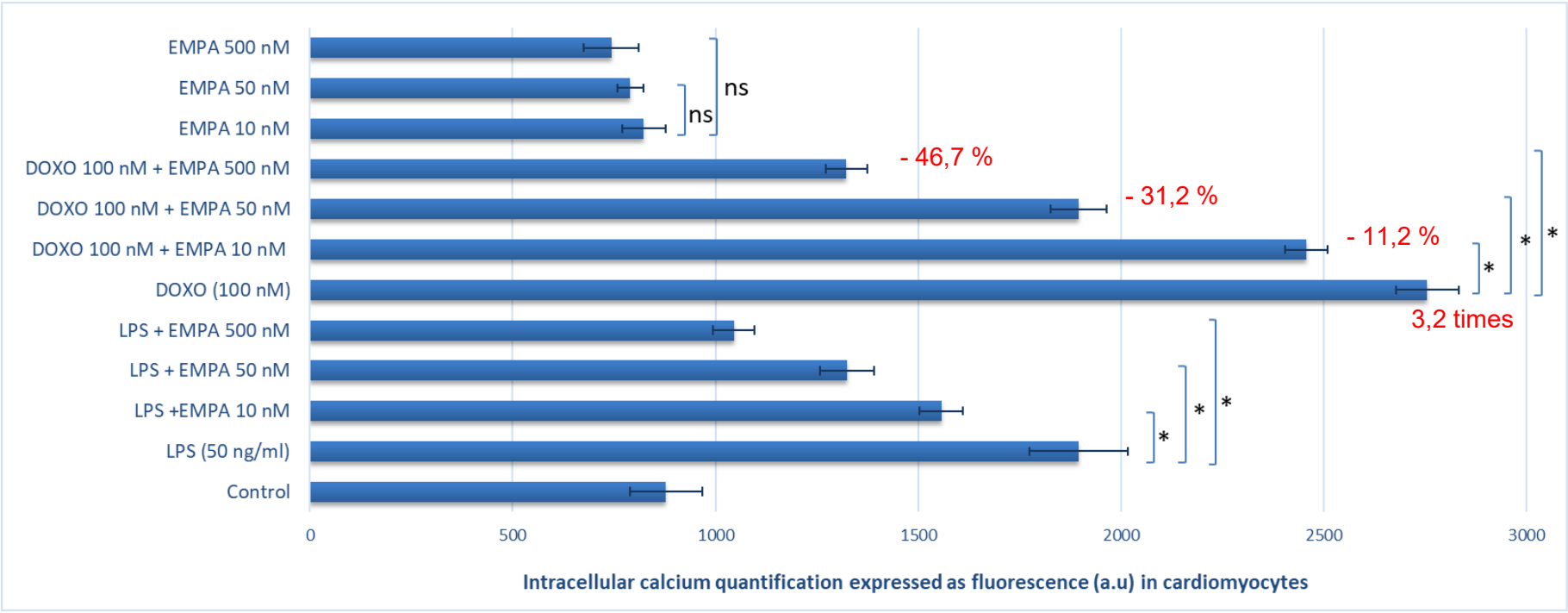
In altre parole, il tasso di cardioprotezione dell'empaglifozin, ponendo il trattamento con sola doxorubicina a 50 µM uguale ad 1, corrisponde a:
3,4: doxorubicina + empaglifozin 50 nM
6,7: doxorubicina + empaglifozin 100 nM
8,6: doxorubicina + empaglifozin 500 nM



HL-1 cells: adult mouse cardiomyocytes

Intracellular calcium overload (Fura2 assay)

* p < 0.001; ns: not significant



Il trattamento con doxorubicina incrementa l'accumulo di calcio intracellulare. La co-incubazione con empaglifozin determina una riduzione dell'accumulo di calcio con effetti concentrazione-dipendenti. L'empaglifozin alla massima dose testata, corrispondente a 500 nM, riduce del 46,7 % l'accumulo di calcio.

Questi dati spiegano gli effetti cardioprotettivi dell'empaglifozin durante il trattamento con doxorubicina.

HL-1 cells: adult mouse cardiomyocytes

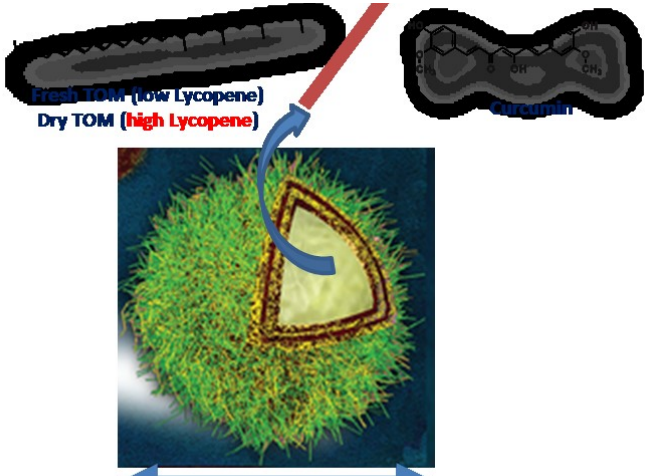
H9c2 cells: cardiomyoblasts of rabbit

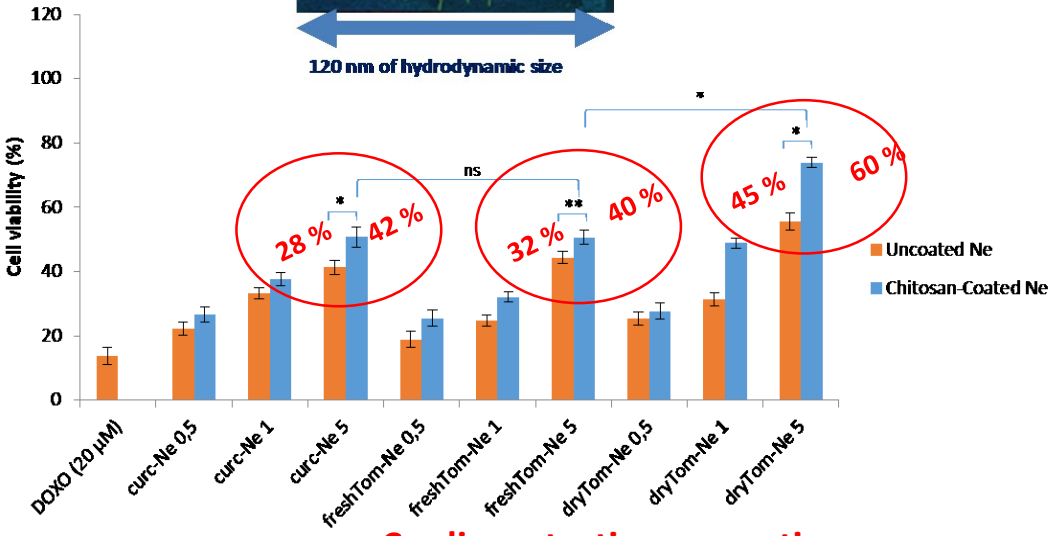
Nanoemulsions (coated with chitosan) loaded with dry tomato extract (having high quantity of lycopene) showed the best anti-inflammatory properties.

Nutrients **2018**, *10*, 1304;

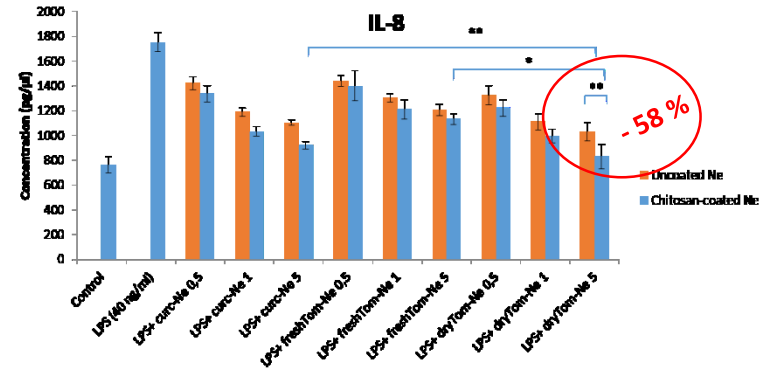
Cardioprotective Effects of Nanoemulsions Loaded with Anti-Inflammatory Nutraceuticals against Doxorubicin-Induced Cardiotoxicity

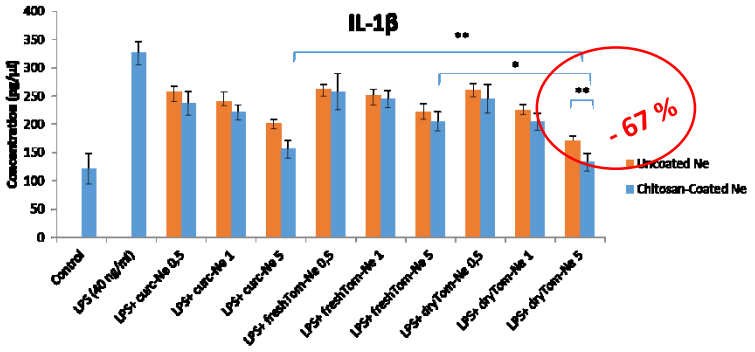
Vincenzo Quagliariello [1,*], Raffaele Vecchione [2,*], Carmela Coppola [1], Chiara Di Cicco [2], Alberta De Capua [2], Giovanna Piscopo [1], Rolando Paciello [1], Viviana Narciso [3], Carmen Formisano [3], Orazio Taglialatela-Scafati [3], Rosario Vincenzo Iaffaioli [4], Gerardo Botti [5], Paolo Antonio Netti [2] and Nicola Maurea [1]

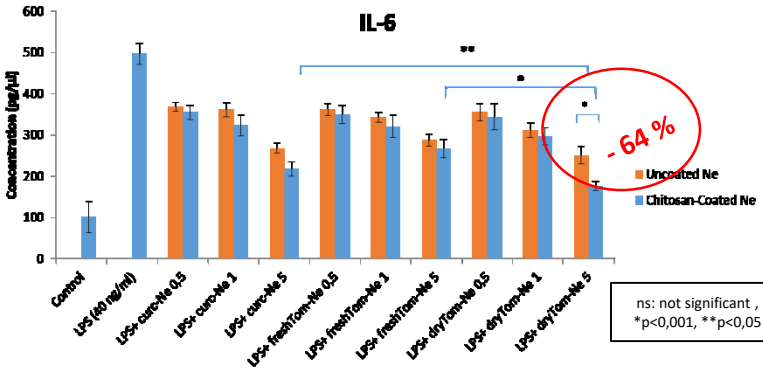




Cardioprotective properties







ns: not significant ,
*p<0,001, **p<0,05

Anti-inflammatory properties

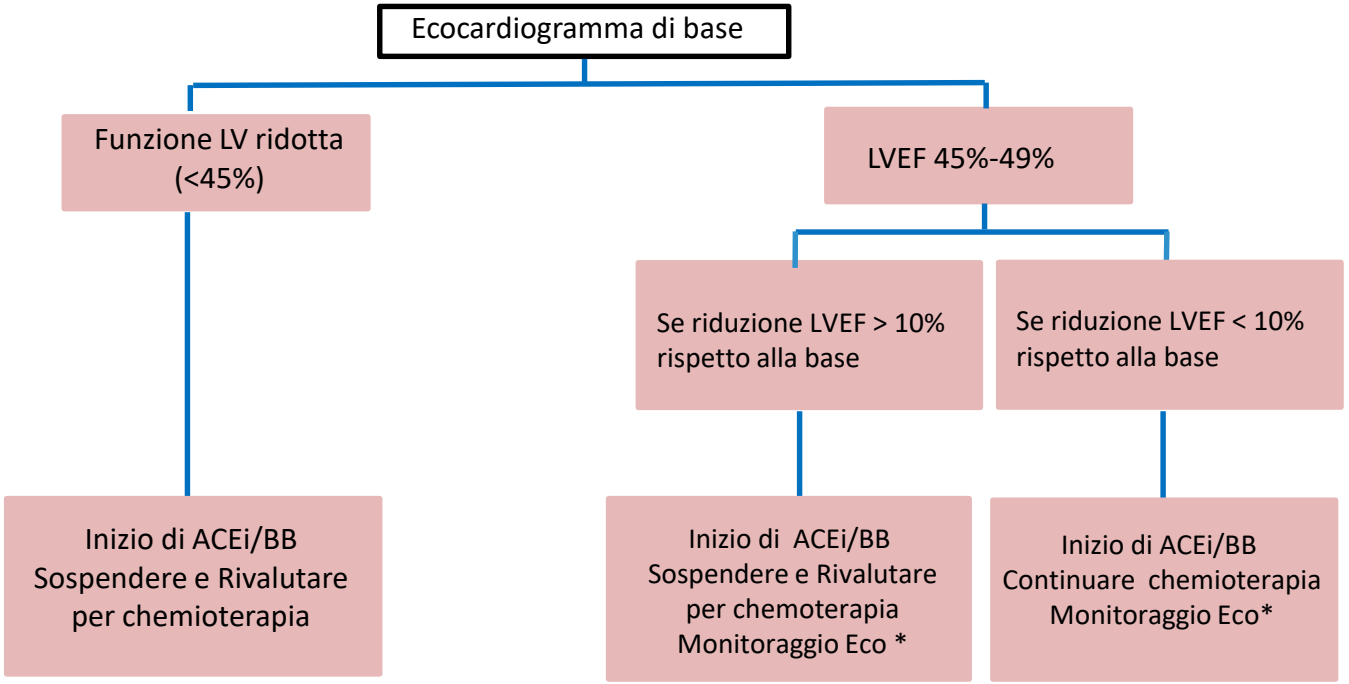
E la prevenzione secondaria?

Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **- 3D-based LVEF** **- 2D Simpson's LVEF** **- GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: **- Troponin I** **- High-sensitivity Troponin I** **- BNP** **- NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

Zamorano et al, European Journal of Heart Failure 2016

Quando iniziare i farmaci cardiologici nella Cardiomiopatia da Antracicline



Inizio con beta bloccanti e/o ACEinhibitori

- La dose di inizio teorica per il carvedilolo dovrebbe essere di 3.125 mg due volte al giorno con una lenta titolazione, fino un massimo di 25 mg due volte al giorno.
- La dose di inizio teorica per il lisinopril dovrebbe essere di 2.5 mg al giorno con una lenta titolazione, fino un massimo di 20 mg.

G ITAL CARDIOL | VOL 18 | GENNAIO 2017

Documento di consenso ANMCO/AICO/AIOM: Snodi clinico-gestionali in ambito cardioncologico

European Journal of Heart Failure (2012) **14**, 130–137

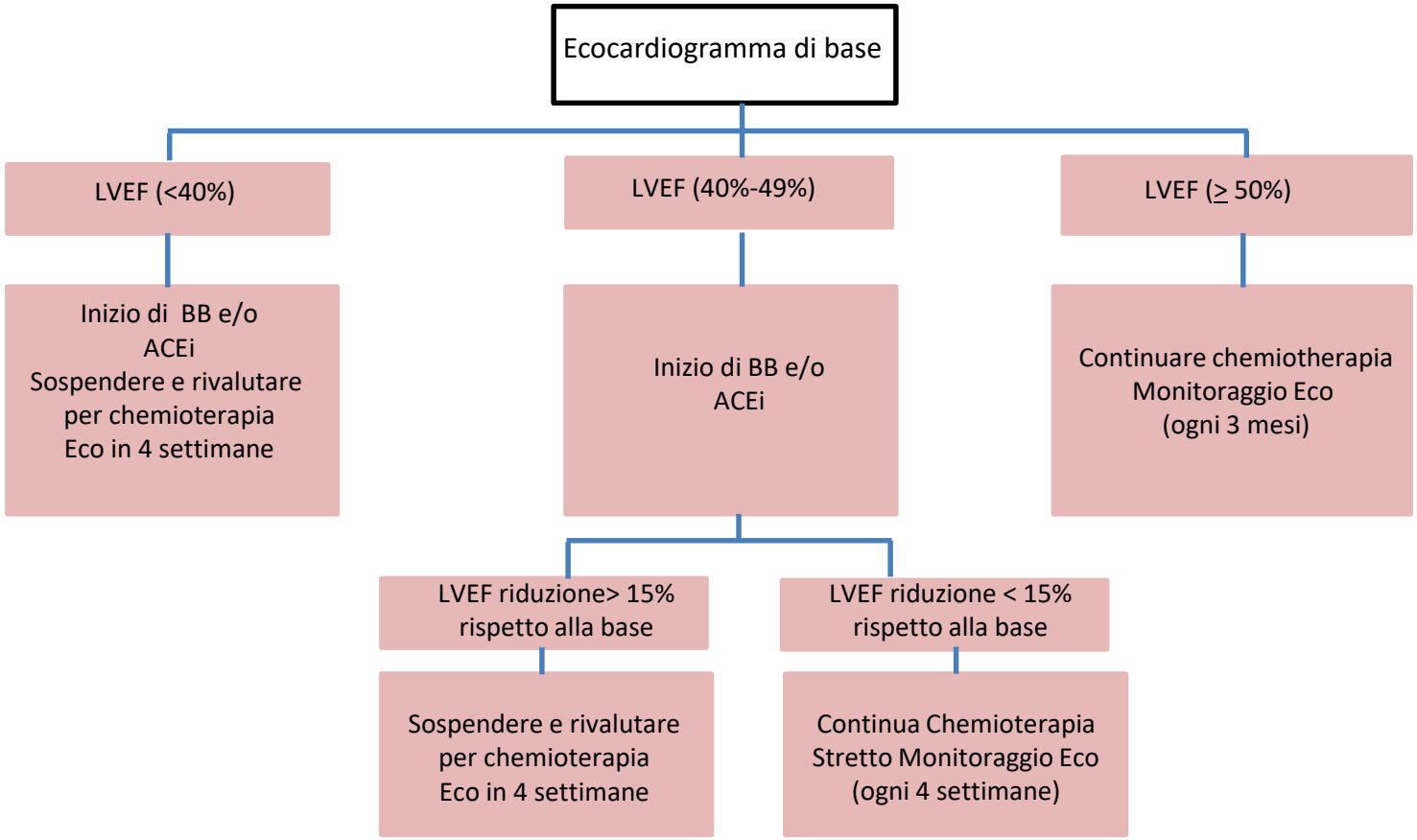
Detection, monitoring, and management of trastuzumab-induced left ventricular dysfunction: an actual challenge

Carlo G. Tocchetti[1]*, Gianluca Ragone[2], Carmela Coppola[1], Domenica Rea[3], Giovanna Piscopo[1], Stefania Scala[4], Claudia De Lorenzo[5], Rosario V. Iaffaioli[2], Claudio Arra[3], and Nicola Maurea[1]

Table 2 The prevention, monitoring, and management of cardiac events in patients undergoing cytotoxic chemotherapy[22,25]

Treatment phase	Patient profile	Management strategy
Before trastuzumab-based therapy	A. No cardiac history of risk factors with normal EF	Treat and monitor EF every 3 months
	B. Cardiac history and/or risk factors with normal EF	Treat. Ask of symptoms and perform PE before each cycle
	C. Decreased EF	Treat low EF (ACE-I or ARB, BB) and remeasure Individual decisions about initiating trastuzumab
During trastuzumab-based therapy	First decrease in EF	Trastuzumab holiday for 1 month A. Treat HF and remeasure 1. Return to baseline. Restart trastuzumab 2. If EF remains low: intensify HF treatment and remeasure 3. If EF remains low: individual decisions
	Second decrease in EF	A. Stop trastuzumab B. If trastuzumab only option: 'holiday' and maximize HF therapy
Completion of trastuzumab-based therapy	No change in EF and no symptoms during treatment	If you have already used anthracyclines is necessary to monitor LVEF at the end of treatment and after 1.2 and 5 years if doxorubicin $<200\ mg/m^2$. More strict monitoring if dosage $>200 mg/m^2$. In the case of only trastuzumab, we advice, anyway, follow-up, considering the last results of real-world retrospective studies
	EF decreased or symptoms of heart failure during therapy with trastuzumab	Continue HF treatment. Monitor according to clinical practice for HF. The duration of therapy for HF is variable, if previous anthracyclines may be required for life

Quando iniziare i farmaci cardiologici nella Cardiomiopatia da Trastuzumab



G ITAL CARDIOL | VOL 18 | GENNAIO 2017

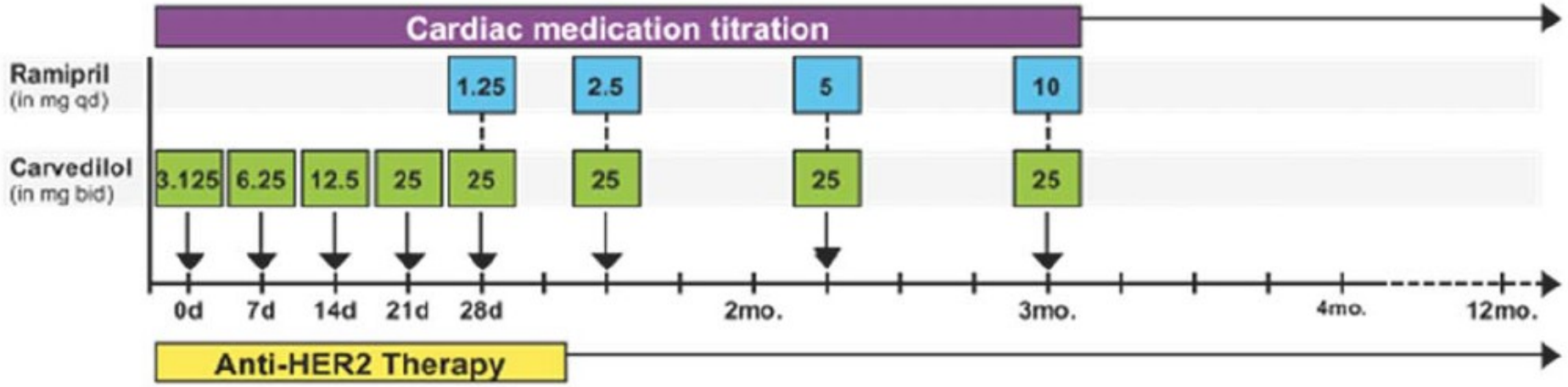
Documento di consenso ANMCO/AICO/AIOM: Snodi clinico-gestionali in ambito cardioncologico

Treatment of Trastuzumab Related Cardiotoxicity

Medication	Starting dose (mg)	Target dose (mg)	Suggested titration plan
ACE Inhibitors			▪ Increase the dose at 1-2-w intervals ▪ Monitor renal function and electrolytes w or every 2w ▪ Maintain blood pressure normal ▪ Try to reach target dose in 3-4 w
Captopril	6.25-12.5 x 3/day	25-50 x 3/day	
Enalapril	1.25-2.5 x 2/day	10 x 2/day	
Ramipril	1.25-2.5 x 2/day	5x2/day	
Lisinopril	2.5-5 x 1/day	20-35 x 1/day	
Beta-blockers			
Carvedilol	3.125 x 2/day	25 x 2/day	
Bisoprolol	1.25 x 1/day	10 x 1/day	

Canadian Trastuzumab Working Group, 2008

SAFE-HEaRt: Rationale and Design of a Pilot Study Investigating Cardiac Safety of HER2 Targeted Therapy in Patients with HER2-Positive Breast Cancer and Reduced Left Ventricular Function



Implications for Practice: Human epidermal growth receptor 2 (HER2) targeted therapies have survival benefit in adjuvant and metastatic HER2 positive breast cancer but are associated with cardiac dysfunction. To our knowledge, SAFE-HEaRt is the first clinical trial that prospectively tests the hypothesis that HER2 targeted therapies may be safely administered in patients with mildly reduced cardiac function in the setting of ongoing cardiac treatment and monitoring. The results of this study will provide cardiac safety data and inform consideration of clinical practice changes in patients with HER2 positive breast cancer and reduced cardiac function, as well as provide information regarding cardiovascular monitoring and treatment in this population.

Lynce F, The Oncologist 2017

SAFE-HEaRt: A pilot study assessing the cardiac safety of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function.

Journal of Clinical Oncology 36, no. 15_suppl (May 2018) 1038-1038.

2018 ASCO ANNUAL MEETING

June 1-5, 2018
McCormick Place | Chicago, IL | #ASCO18

Conclusions: Patients with BC and mildly reduced LVEF can safely receive HER2 therapies in the setting of regular cardiac monitoring and treatment with BB and ACEi. Our results provide new safety data in this unique population and have potential to contribute to clinical practice changes.

Lynce F. et al.

Abstract: **P1578**

European Heart Journal (2018) 39 (Supplement), 304-305

ESC Congress Munich 2018

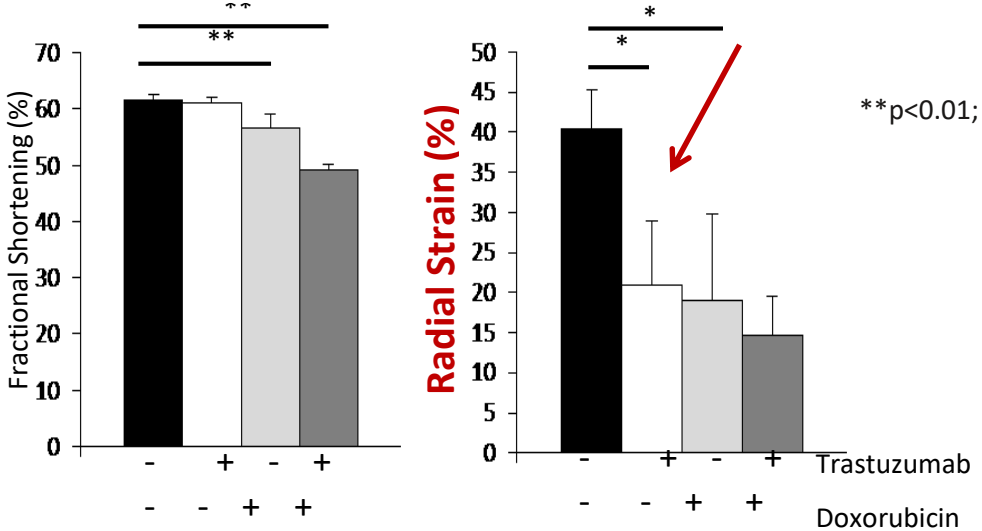
Global longitudinal strain in the SAFE-HEaRT study (Cardiac SAFEty of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function)

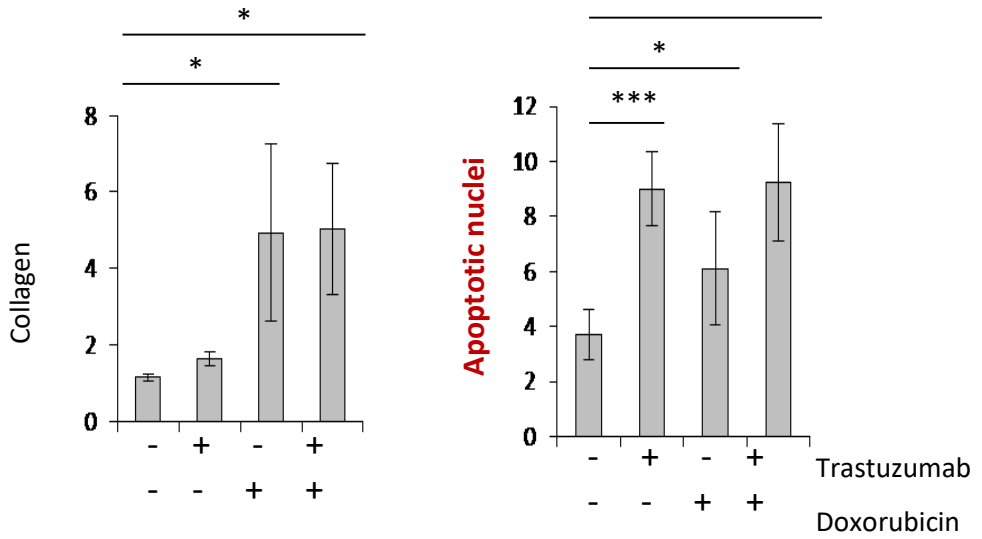
Conclusions: In this prospective study of patients with BC and baseline reduced LV function, H2TT therapy proved to be safe with cardiac treatment and close monitoring. GLS at baseline was lower in those who subsequently developed CE. While the change in LVEF from baseline to EOT was not statistically significant, GLS mildly worsened. The implications of this change in GLS should be further investigated in a larger population.

Barac A. et al.

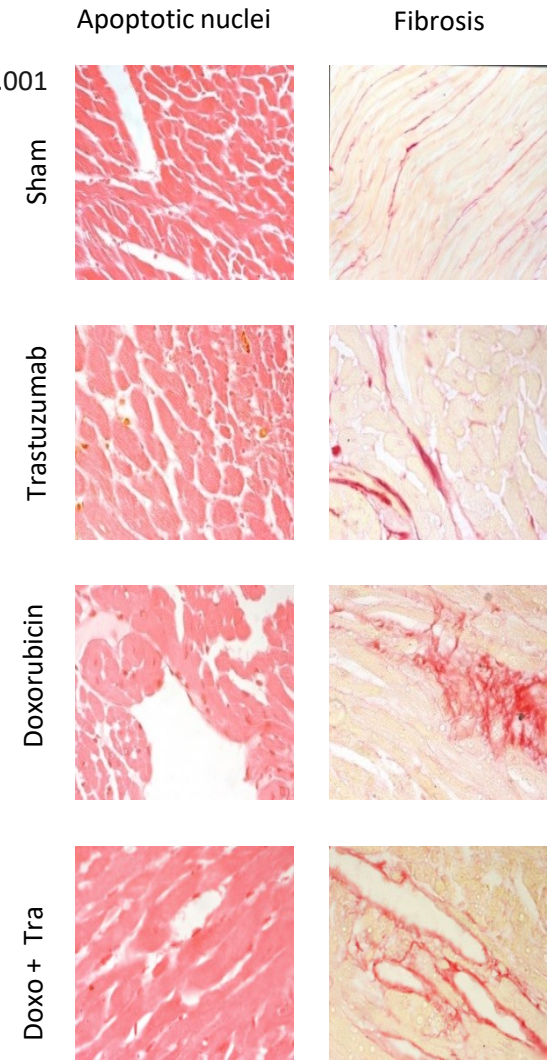
Antineoplastic-related cardiotoxicity, morphofunctional aspects in a murine model: contribution of the new tool 2D-speckle tracking

2 days of Trastuzumab





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



Coppola C et al. Onco Targets and Therapy 2016

Global Longitudinal Strain: diagnosi precoce

Riduzione di LVEF < 50% → Cardiotossicità → **Cardioprotezione**

No

Strain basale disponibile

Riduzione > 15% rispetto alla base

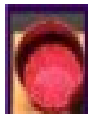
No

continua la terapia oncologica

Si

Strain basale Non disponibile

Peggiore di – 16%



-16 to -19%

-19% o migliore

continua la terapia oncologica

Disfunzione subclinica LV

Considerare Cardioprotezione

Negishi K et al. JASE 2013

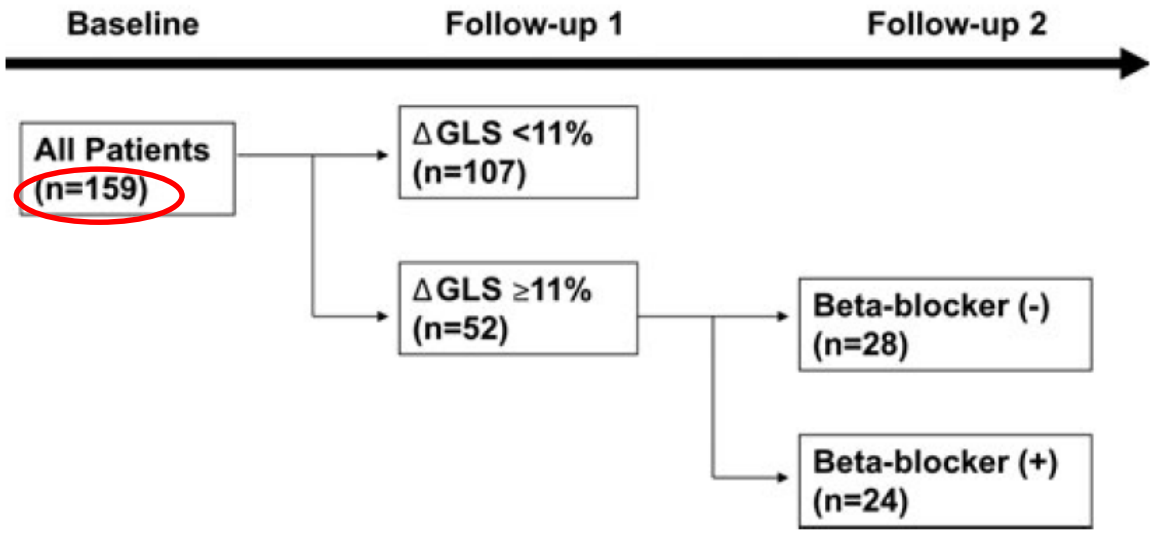
Negishi et al JACC 2012

European Heart Journal – Cardiovascular Imaging (2014) **15**, 324–331
doi:10.1093/ehjci/jet159

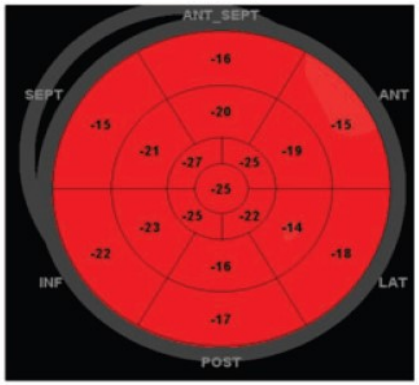
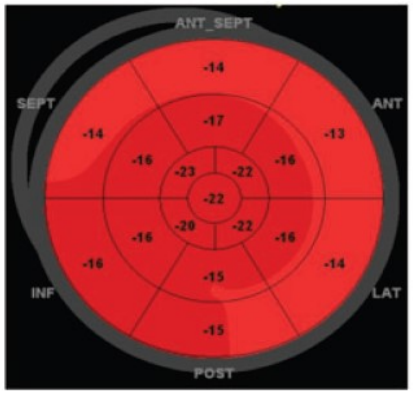
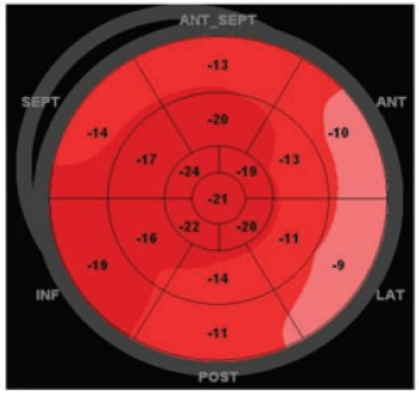
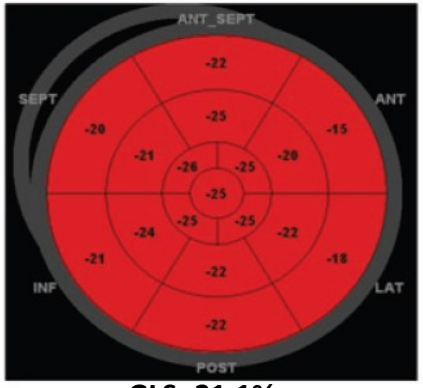
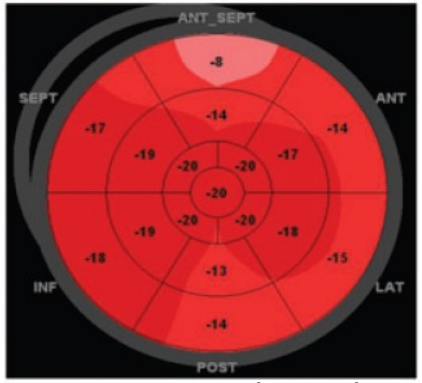
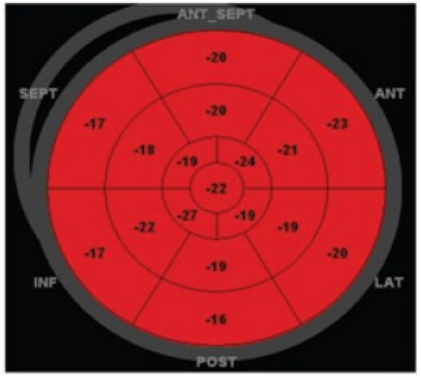
Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection

Kazuaki Negishi[1†], Tomoko Negishi[1†], Brian A. Haluska[2], James L. Hare[2], Juan Carlos Plana[1], and Thomas H. Marwick[1,3*]

GLS is an effective parameter for identifying systolic dysfunction (which appears worst with combined anthracycline and trastuzumab therapy) and responds to cardioprotection in patients administered beta-blockers.



Il GLS identifica precocemente la disfunzione e la risposta alla cardioprotezione

Baseline	F/U1	F/U2	
			No beta-blocker therapy
GLS -20.1% EF 61%	GLS -17.0% (Δ -15.4%) EF 55%	GLS -16.1% EF 49%	
			Beta-blocker therapy
GLS -21.1% EF 62%	GLS -16.6% (Δ -24%) EF 54% 6 months	GLS -20.2% EF 58% 12 months	

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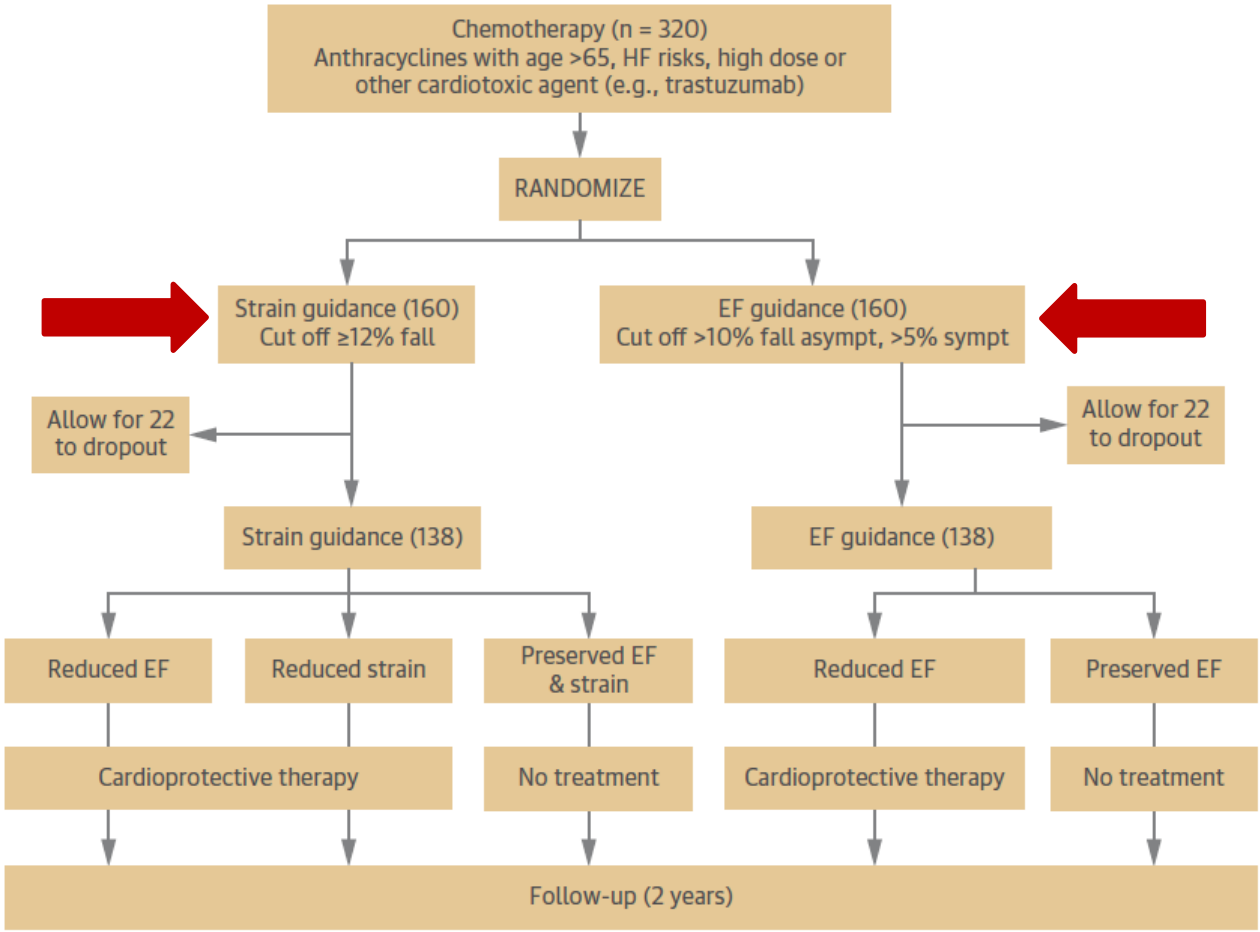
Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes

The SUCCOUR Trial

Tomoko Negishi, MD,[a] Paaladinesh Thavendiranathan, MD, SM,[b] Kazuaki Negishi, MD, PhD,[a] Thomas H. Marwick, MBBS, PhD, MPH,[a,c] on behalf of the SUCCOUR investigators



Conclusioni

- Il dexrazoxano è l' unico farmaco approvato **in prevenzione primaria**. Beta bloccanti, ACE inibitori e sartani etc., non hanno ancora dimostrato di poter prevenire la disfunzione ventricolare sinistra .

- In **prevenzione secondaria** è invece necessario identificare quanto più precocemente possibile la disfunzione ventricolare sinistra e istituire una terapia cardioprotettiva.

- A tal fine, il **Global Longitudinal Strain** sembrerebbe particolarmente utile, anche come indicatore di risposta alla cardioprotezione.

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