TURIN,
October
25th-27th
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Starhotels
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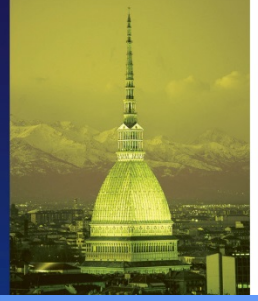


UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

# CARDIOPROTECTION STRATEGIES

## When and how to intervene: traditional therapies and new strategies. The role of ranolazine and ivabradine

PAOLA LUSARDI

S.C.Cardiologia

HUMANITAS
GRADENIGO

rete oncologica
PIEMONTE | VALLE D'AOSTA
si prende cura di te

VOLUME 25 · NUMBER 31 · NOVEMBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Overall Survival and Cause-Specific Mortality of Patients With Stage T1a,bN0M0 Breast Carcinoma

*Emer O. Hanrahan, Ana M. Gonzalez-Angulo, Sharon H. Giordano, Roman Rouzier, Kristine R. Broglio, Gabriel N. Hortobagyi, and Vicente Valero*

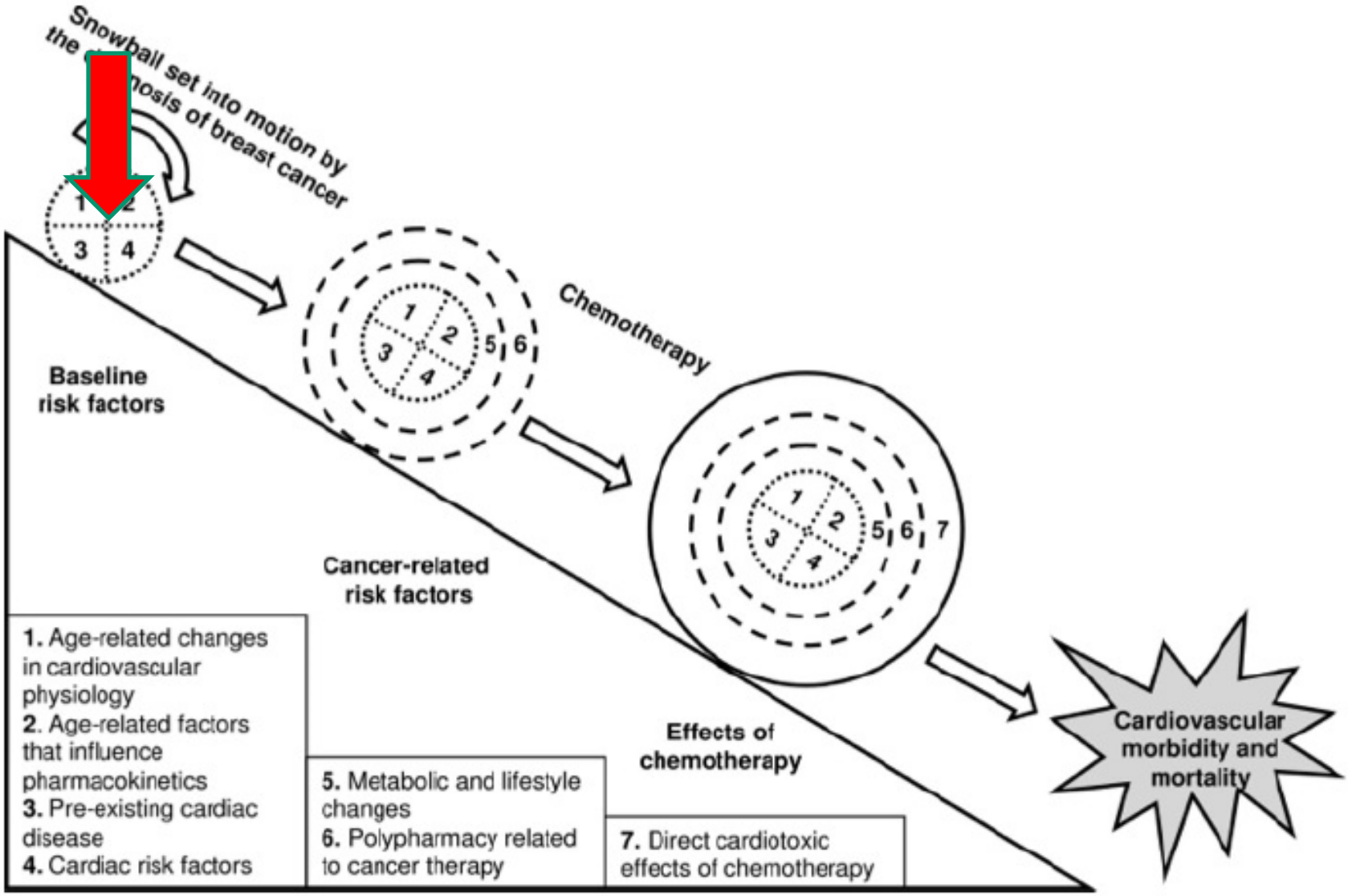
Patients suffering from T1a-b N0 M0 breast cancer

***are at higher risk to die from heart disease***

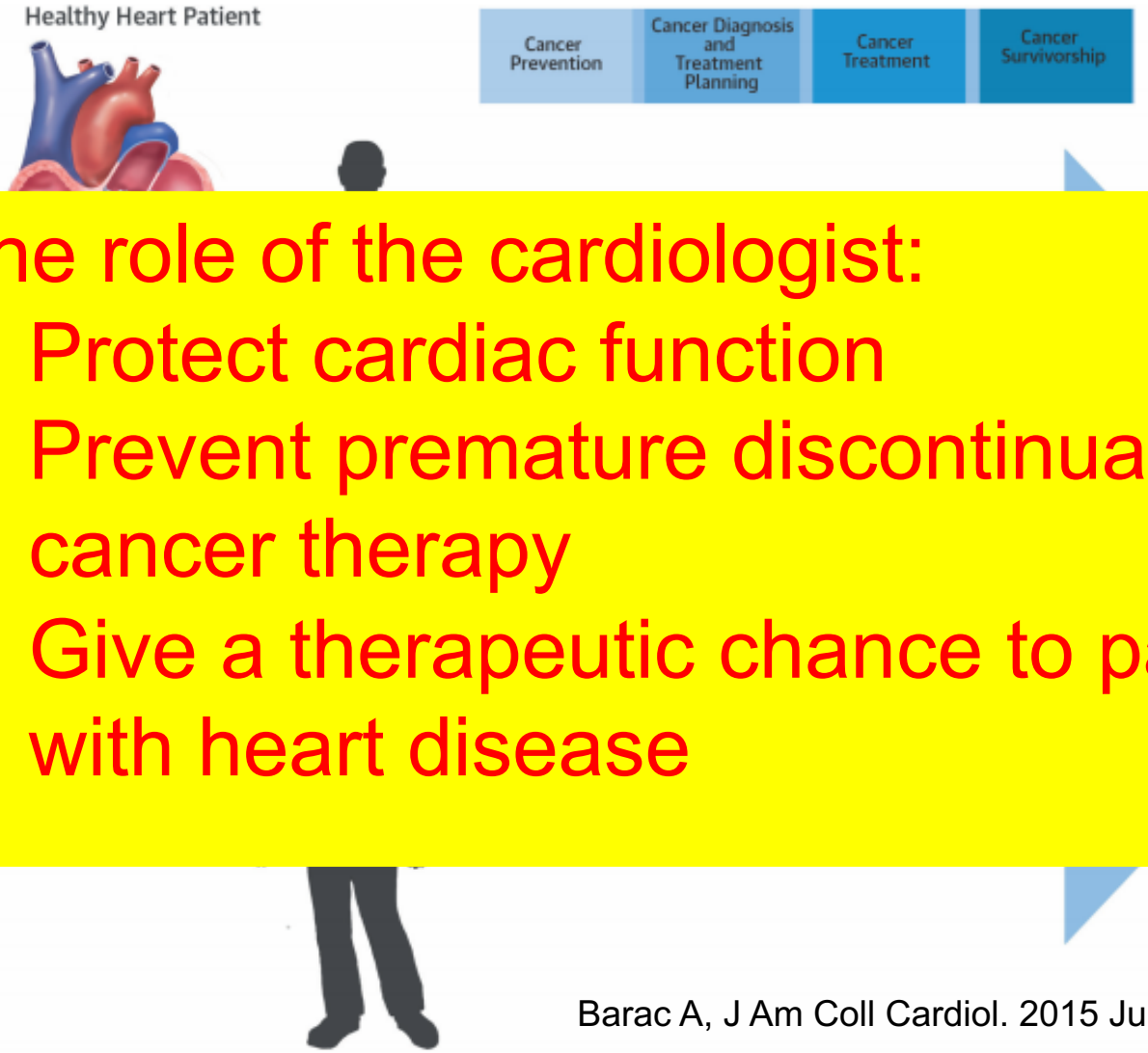
***than from the cancer itself***

# The «snowball effect»

Shenoy C, The Oncologist 2011



# Teamwork

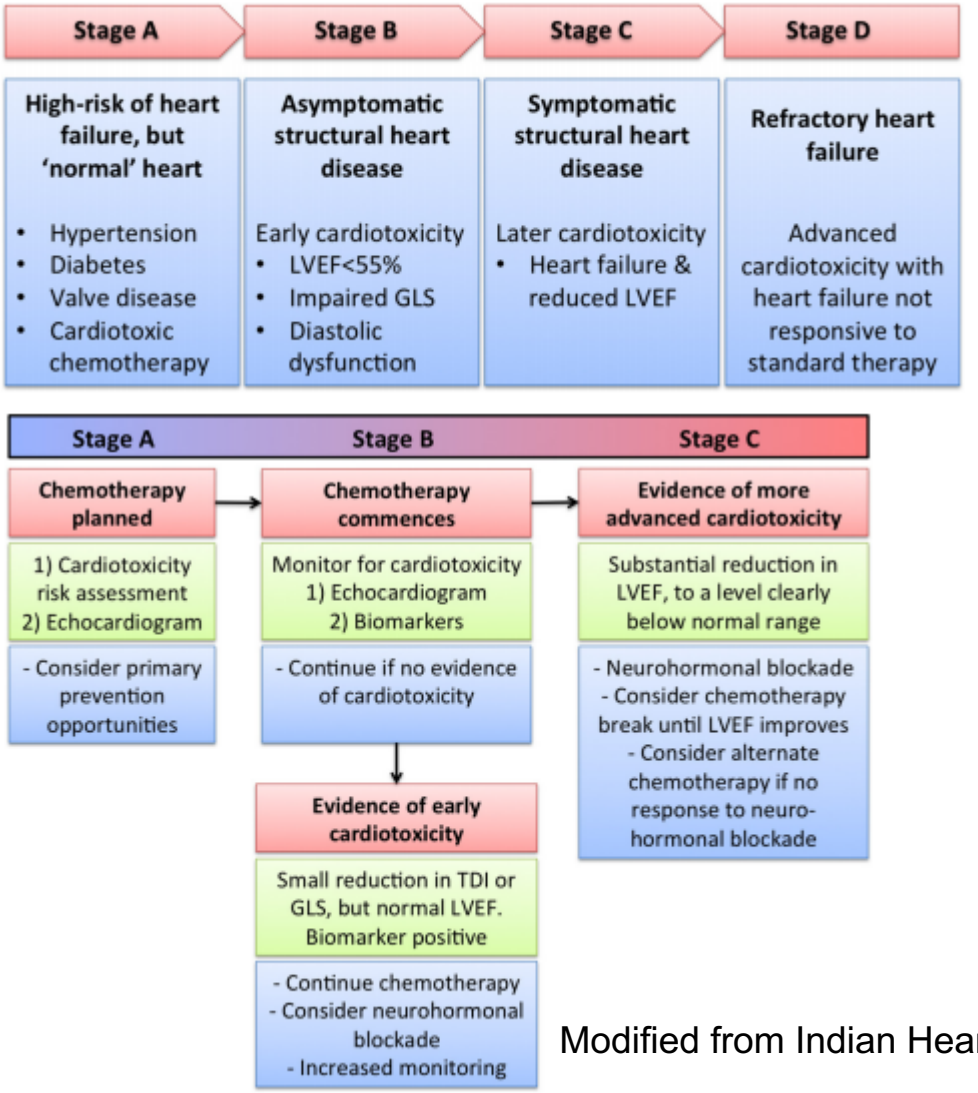



The role of the cardiologist:

- Protect cardiac function
- Prevent premature discontinuation of cancer therapy
- Give a therapeutic chance to patients with heart disease

Barac A, J Am Coll Cardiol. 2015 Jun 30;65(25):2739-46.

# Heart failure staging in the contest of cardio-oncology




Modified from Indian Heart Journal 68 (2016)s7 7-s85

European Heart Journal Advance Access published August 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

# 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

## The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

**Authors/Task Force Members: Jose Luis Zamorano* (Chairperson) (Spain), Patrizio Lancellotti* (Co-Chairperson) (Belgium), Daniel Rodriguez Muñoz (Spain), Victor Aboyans (France), Riccardo Asteggiano (Italy), Maurizio Galderisi (Italy), Gilbert Habib (France), Daniel J. Lenihan[1] (USA), Gregory Y. H. Lip (UK), Alexander R. Lyon (UK), Teresa Lopez Fernandez (Spain), Dania Mohty (France), Massimo F. Piepoli (Italy), Juan Tamargo (Spain), Adam Torbicki (Poland), and Thomas M. Suter (Switzerland)**

# Baseline risk factors for cardiotoxicity

| ***Current myocardial disease*** | ***Demographic and other CV risk factors*** |
|---|---|
| • Heart failure (with either preserved or reduced ejection fraction)<br>• Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide)<br>• Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia)<br>• Moderate and severe VHD with LVH or LV impairment<br>• Hypertensive heart disease with LV hypertrophy<br>• Hypertrophic cardiomyopathy<br>• Dilated cardiomyopathy<br>• Restrictive cardiomyopathy<br>• Cardiac sarcoidosis with myocardial Involvement<br>• Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias) | • Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines)<br>• Family history of premature CV disease (<50 years)<br>• Arterial hypertension<br>• Diabetes mellitus<br>• Hypercholesterolaemia |
| ***Previous cardiotoxic cancer treatment*** | ***Lifestyle risk factors*** |
| • Prior anthracycline use<br>• Prior radiotherapy to chest or mediastinum | • Smoking<br>• High alcohol intake<br>• Obesity<br>• Sedentary habit |



European Heart Journal doi:10.1093/eurheartj/ehw211 - EHJ 2016;37:2768-2801

# Educazione del paziente

- Diario dei valori pressori e FC
- Controllo del peso corporeo
- Dieta con adeguato apporto nutrizionale ma iposodica
- Astensione dal fumo
- Riconoscimento dei sintomi di disfunzione cardiaca, ischemia e aritmie
- Profilassi della TVP
- NON SOSPENDERE I FARMACI PRECEDENTEMENTE ASSUNTI!

Journal of the American College of Cardiology
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Vol. 61, No. 23, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.072



# 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)

Xavier Bosch, MD, PhD,*† Montserrat Rovira, MD, PhD,†‡ Marta Sitges, MD, PhD,*†

**Il trattamento combinato con enalapril e carvedilolo 24 ore prima dell'avvio della chemioterapia in pz con emopatie maligne può prevenire la disfunzione ventricolare sinistra (eco +RMN).**

La rilevanza clinica di tale strategia deve essere confermata in studi clinici più vasti (90pz)

European Heart Journal (2016) **37**, 1671–1680
doi:10.1093/eurheartj/ehw022

AHA FASTTRACK
CLINICAL RESEARCH

***Heart failure/cardiomyopathy***

# Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol

Geeta Gulati[1,2†], Siri Lagethon Heck[1,2†], Anne Hansen Ree[3,4], Pavel Hoffmann[5],
Je
F
T
T

- 130 donne con k mammario senza comorbidità
- Trattate con candesartan/metoprololo/candesartan+ metoprololo o placebo durante terapia adiuvante con antracicline ± trastuzubab e Rx terapia

**Candesartan ha attenuato la riduzione della FE (RMN)**
**Nessun effetto su GLS o su incremento di troponina**

# Strategies to reduce chemotherapy-induced cardiotoxicity

| Chemotherapy drug | Potential cardioprotective measure |
|---|---|
| **All chemotherapy drugs** | Identify and treat cardiovascular risk factors |
| | Treat comorbidities (CAD, HF, PAD, HTN) |
| | QTc prolongation and torsade de pointes:<br>- Avoid QT prolonging drugs<br>- Manage electrolyte abnormalities |
| | Minimize cardiac irradiation |
| **Anthracyclines and analogues** | Limit cumulative dose (mg/m$^2$):<br>- Daunorubicin <800<br>- Doxorubicin <360<br>- Epirubicin <720<br>- Mitoxantrone <160<br>- Idarubicin <150 |
| | Altered delivery systems (liposomal doxorubicin) or continuous infusions |
| | Dexrazoxane as an alternative |
| | ACE-Is or ARBs |
| | β-blockers |
| | Statins |
| | Aerobic exercise |
| **Trastuzumab** | ACE-Is |
| | β-blockers |

European Heart Journal doi:10.1093/eurheartj/ehw211 - EHJ 2016;37:2768-2801

# Quanto costa la cardioprotezione?

**TABLE 2** Primary Prevention for Anthracycline-Induced Cardiotoxicity

| Prevention Strategy | Cost* | Comments |
|---|---|---|
| Continuous doxorubicin infusion (48-72 h) | $67/50 mg† | Effective in cardioprotection in sarcoma and lymphoma, but not in the pediatric population |
| Liposomal doxorubicin | $2,851/50 mg | FDA-approved for ovarian cancer, AIDS-related Kaposi sarcoma, and multiple myeloma, after failure of at least 1 prior therapy |
| Dexrazoxane | $362/500 mg | FDA-approved only for women with metastatic breast cancer who received at least 300 mg/m$^2$ doxorubicin and need additional doxorubicin to maintain tumor control |
| ACEI/ARB/β-blockers | $4/month | Unknown whether they were cardioprotective or simply changed hemodynamics |

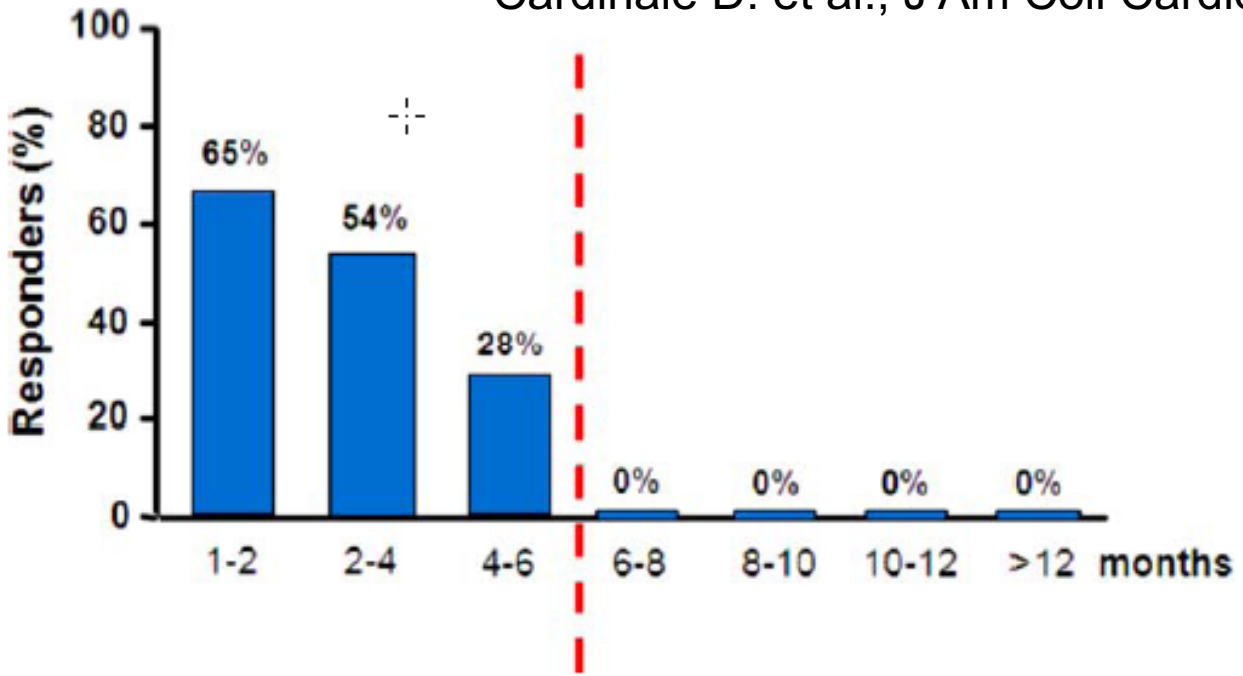
*2014 Walmart pharmacy prices. †May be higher, depending on hospital stay or infusion pump care costs.

ACEI = angiotensin-converting enzyme inhibitor; AIDS = acquired immune deficiency syndrome; ARB = angiotensin receptor blocker; FDA = U.S. Food and Drug Administration.

Pimprapa Vejpongsa, JACC 2014, Vol 64 N°9

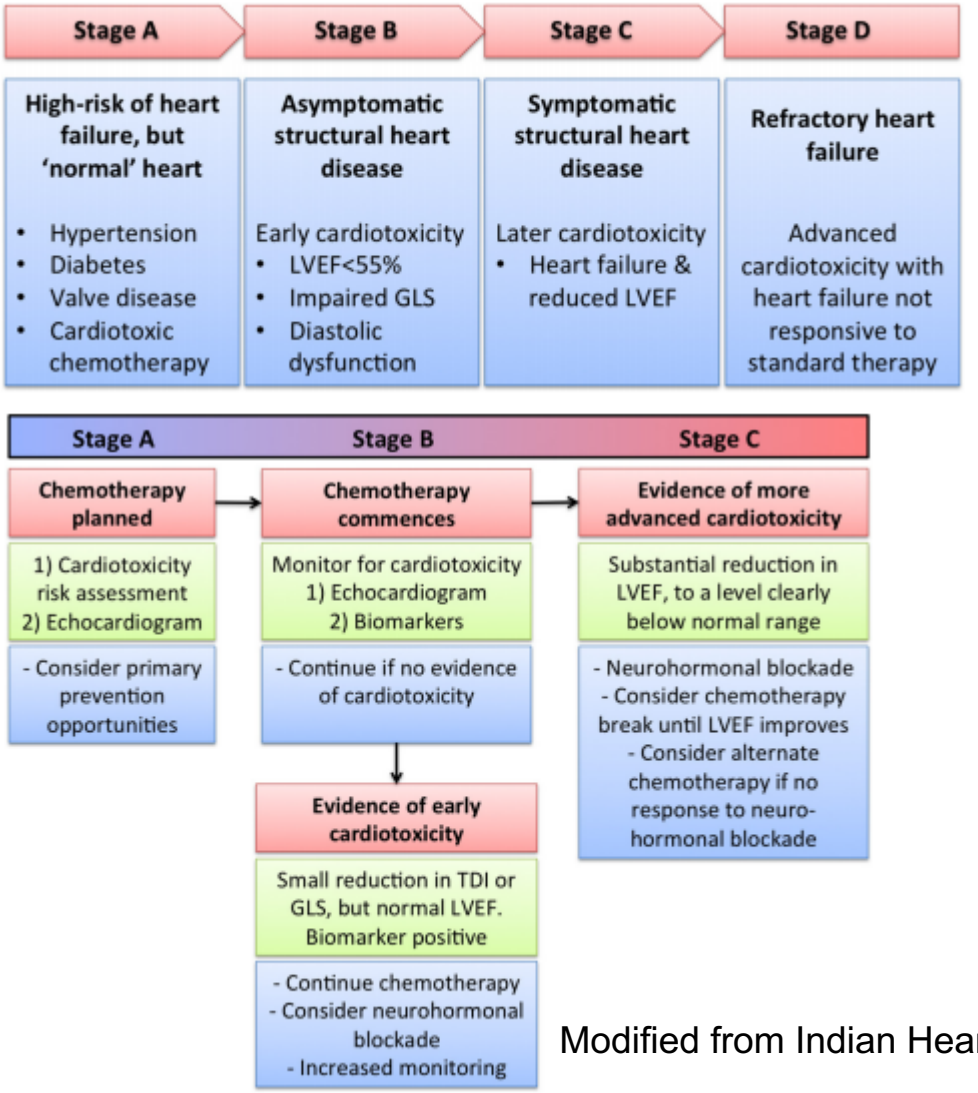
# Cardioprotezione quando?

Cardinale D. et al., J Am Coll Cardiol 2010;55(3):213–20.




- Nessun paziente risponde al trattamento dello scompenso dopo un ritardo di 6 mesi dalla diagnosi
- Esiste una relazione diretta tra il ritardo della diagnosi e l'outcome clinico.

# Heart failure staging in the contest of cardio-oncology

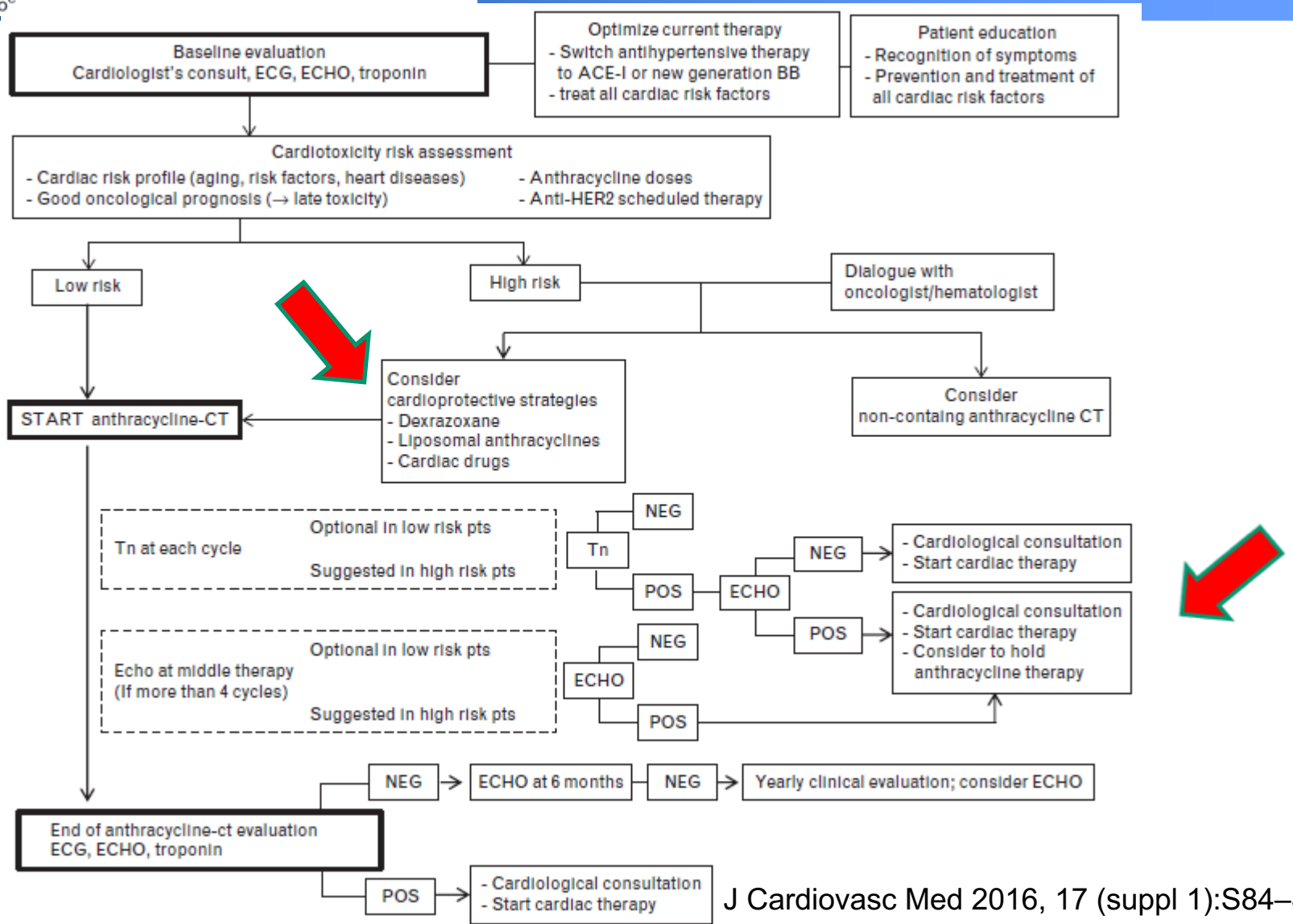



Modified from Indian Heart Journal 68 (2016)s7 7-s85

Supplement submission
OPEN

# Algorithm for the management of cardiotoxicity in patients receiving anthracyclines

**A recommended practical approach to the management of anthracycline-based chemotherapy cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology**
Paolo Spallarossa[a], Nicola Maurea[b], Christian Cadeddu[c], Rosalinda Madonna[d], Donato Mele[e], Ines Monte[f], Giuseppina Novo[g], Pasquale Pagliaro[h], Alessia Pepe[i], Carlo G. Tocchetti[j], Concetta Zito[k] and Giuseppe Mercuro[c]




J Cardiovasc Med 2016, 17 (suppl 1):S84–S92

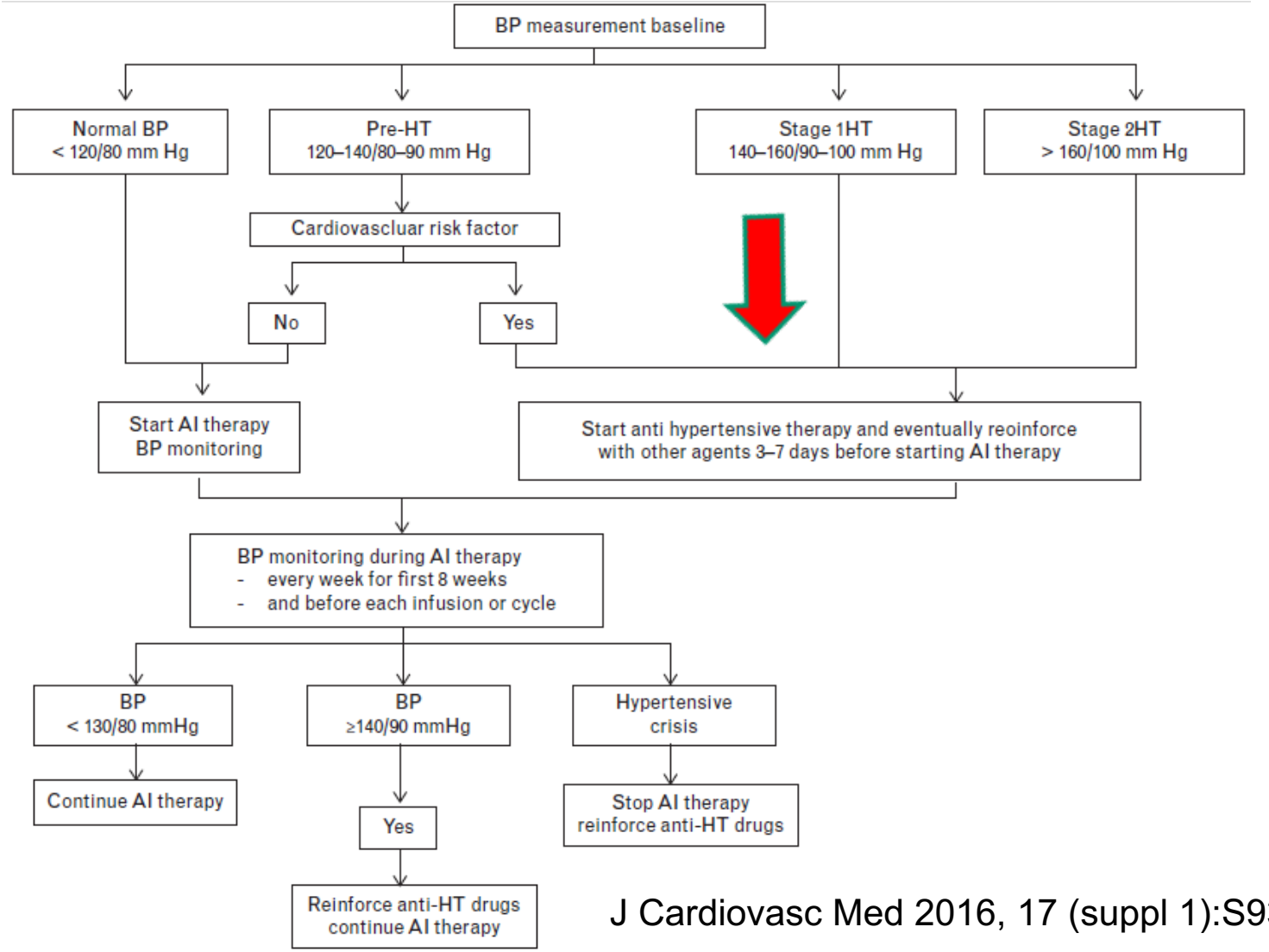
Supplement Submission

OPEN

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

# A recommended practical approach to the management of target therapy and angiogenesis inhibitors cardiotoxicity: an opinion paper of the working group on drug cardiotoxicity and cardioprotection, Italian Society of Cardiology

# The management of hypertension induced by angiogenic inhibitors




J Cardiovasc Med 2016, 17 (suppl 1):S93–S104

# The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 4.03) grading severity of cardiac events associated with tyrosine kinase inhibitors

| Cardiac event | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Hypertension | Prehypertension | Stage 1 hypertension – SBP 140–159 mmHg or DBP 90–99 mmHg); medical intervention indicated; recurrent or persistent (>24 h); symptomatic increase by >20 mmHg (DBP) or to >140/90 mmHg if previously within normal limits; monotherapy indicated | Stage 2 hypertension – SBP >160 mmHg or DBP >100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated | Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated | Death |
| Heart failure | Asymptomatic with laboratory (e.g. brain natriuretic peptide) or cardiac imaging abnormalities | Symptoms with mild-to-moderate activity or exertion | Severe with symptoms at rest or with minimal activity or exertion; intervention indicated | Life-threatening consequences; urgent intervention indicated (e.g. continuous intravenous therapy or mechanical hemodynamic support | Death |
| QT prolongation | QTc 450–480 ms | QTc 481–500 ms | QTc >501 ms on at least two separate electrocardiograms | QTc >501 ms or >60 ms change from baseline and torsades de pointes, or polymorphic ventricular tachycardia, or signs or symptoms of serious arrhythmia | - |

J Cardiovasc Med 2016, 17 (suppl 1):S93–S104

# CARDIOTOSSICITA’

- **MANIFESTAZIONE DI SINTOMI**

(dd: dolore neoplastico, neuropatico, dispnea non cardiogena)

- **RIDUZIONE ASINTOMATICA DELLA FE**

(nei malati di cancro la riduzione della FE può essere indotta da fattori diversi dalla terapia oncologica: sovraccarico volemico, valori pressori, tachicardia, anemia, sepsi, modificazioni neuroormonali transitorie, terapia corticosteroidea)

- **INCREMENTO DELLA TROPONINA**

Modified from ESMO Clinical Practice Guidelines, Ann. Oncol. 23 (Suppl. 7) (2012) 155–166.

# Farmaci convenzionali ed effetti additivi

- **ACE-INIBITORI E SARTANI:**

le angiotensine II-IV sono risultate essere proangiogeniche nel tumore → possibile azione sinergica anti-VEGF

- **BETA-BLOCCANTI:**

lo stress neuro-ormonale e la stimolazione beta-adrenergica favoriscono la crescita tumorale e la metastatizzazione.

# Quale beta-bloccante?

**CARVEDILOLO:**

- Riduce la formazione di ROS nei miocardiociti isolati esposti alla doxorubicina

  Spallarossa P, Mol. Cell. Cardiol. 37 (2004) 837–846.

- Previene la perossidazione lipidica ed aumenta le concentrazioni di vit. E

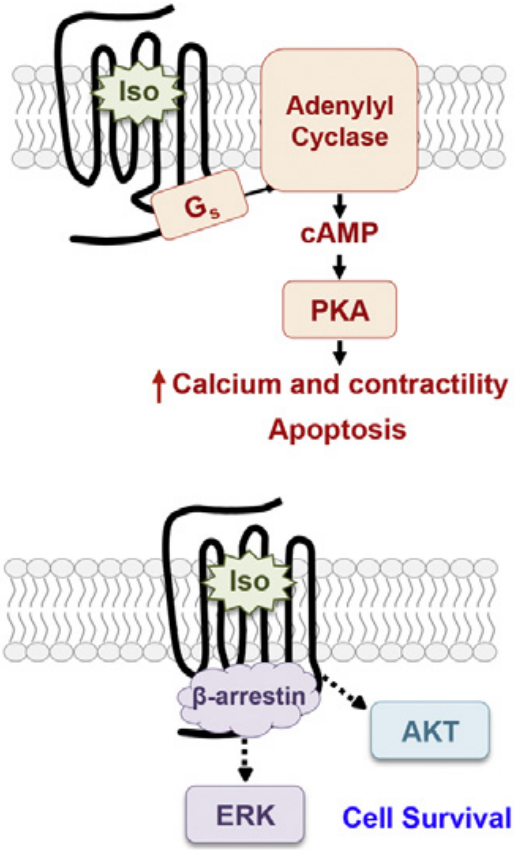
**NEBIVOLOLO:**

- Induce l'espressione di NO-sintasi endoteliale, con effetto vasodilalatore
- Previene la formazione di radicali liberi

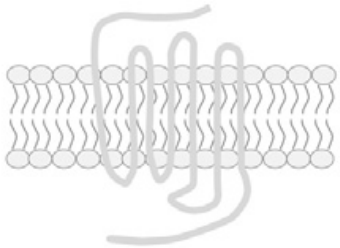
Moen MB, Drugs 66 (2006) 1389–1409 R.P. Mason, *Circulation 112 (2005)3795-3801.*

# Carvedilol Prevents Redox Inactivation of Cardiomyocyte b1-Adrenergic Receptors

**The classical paradigm for Iso-dependent $\beta_1$AR responses**



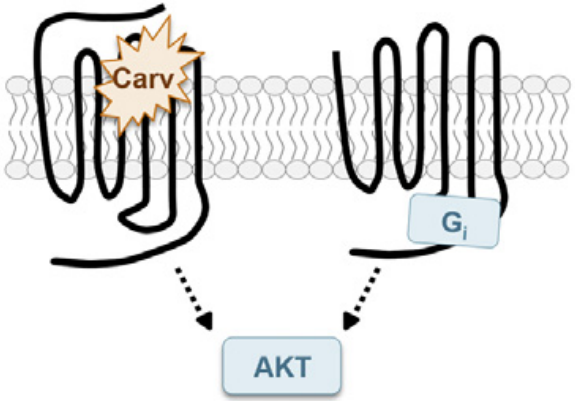

**Effect of $H_2O_2$ or Doxorubicin treatment**



**Decreased $\beta_1$AR levels and a defect in Iso-dependent signaling responses**

*The decrease in $\beta_1$ARs in HF may be due to enhanced oxidative stress, rather than catecholamine-induced desensitization*

**Effect of doxorubicin + carvedilol on $\beta_1$AR signaling**




***Carvedilol protects FL-$\beta_1$ARs from $H_2O_2$- or doxorubicin-induced inactivation***

***Carvedilol treatment leads to the accumulation of N-terminally truncated $\beta_1$ARs that constitutively activate AKT and protect against doxorubicin-dependent apoptosis***

Park, M. et al. J Am Coll Cardiol Basic Trans Science. 2018;3(4):521–32.

# Statine

Uno studio osservazionale di coorte che ha arruolato pazienti con tumore mammario trattato con antracicline ha mostrato che le statine possono ridurre il rischio di scompenso cardiaco

S. Seicean, J. Am. Coll. Cardiol. 60 (2012) 2384–2390.

Quale meccanismo?
La simvastatina in studi sull'animale è in grado di proteggere i cardiomiociti attraverso l'attivazione della NO-sintasi ed i canali ATP-sensibili del potassio (riduzione del danno del DNA e della fibrosi)

S.P. Jones, Circ. Res. 93 (2003) 697–699.

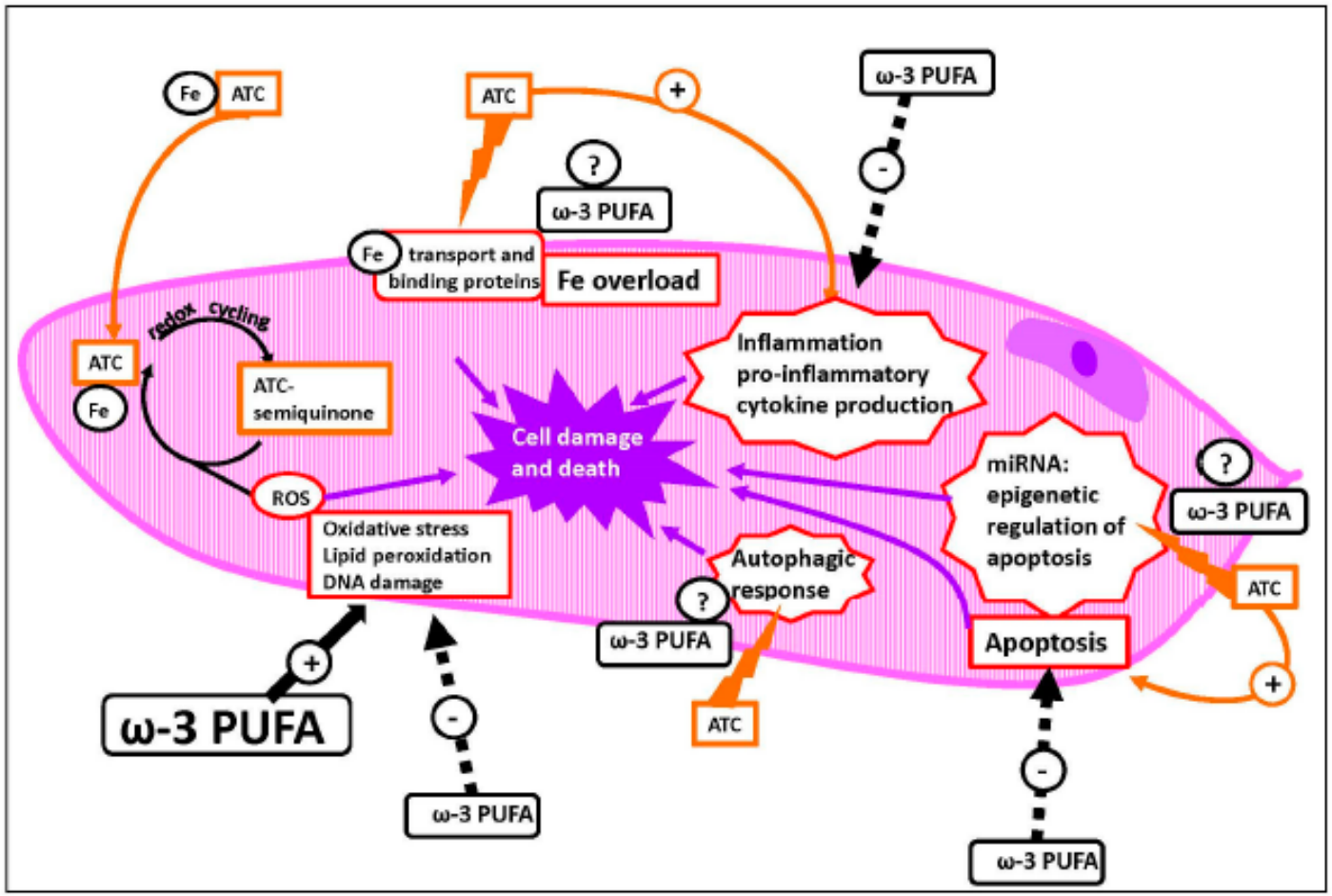
International Journal of
*Molecular Sciences*

MDPI

*Review*

# Protective Effects of ω-3 PUFA in Anthracycline-Induced Cardiotoxicity: A Critical Review

Int. J. Mol. Sci. 2017, 18, 2689



# Esercizioterapia

**Table 14 Summarizes the potential benefits of exercise during and/or after cancer treatment**

**Improvement of:**

- Cardiorespiratory and cardiovascular function
- Body composition (preservation or increase in muscle mass, loss of fat mass)
- Immune function
- Chemotherapy completion rates
- Muscle strength and flexibility
- Body image, self-esteem and mood

**Reduction in:**

- Number and severity of side effects including nausea, fatigue and pain
- Reduction of hospitalization duration
- Reduction of stress, depression and anxiety

# Esercizio aerobico

Ha dimostrato di ridurre la mortalità per tutte le cause in pazienti trattati con antracicline.

Ipotesi: riduzione formazione ROS.

Jones LW, Lancet Oncol 2009; 10:598-605.

Scott JM, Circulation 2011; 124:642-650

# Riduzione della FC come strategia di cardioprotezione?

European Journal of Heart Failure (2016) **18**, 1524–1534
doi:10.1002/ejhf.670

## Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study

**Markus S. Anker[1], Nicole Ebner[2], Bert Hildebrandt[3], Jochen Springer[2], Marianne Sinn[3], Hanno Riess[3], Stefan D. Anker[2], Ulf Landmesser[1], Wilhelm Haverkamp[4], and Stephan von Haehling[2]***

Whether or not patients received any chemotherapy, or whether or not such chemotherapy (if provided) was a known cardiotoxic medication, made no difference to the main result that a resting heart rate ≥75 b.p.m. predicts poorer survival in patients with cancer.

# Riduzione della FC come strategia di cardioprotezione



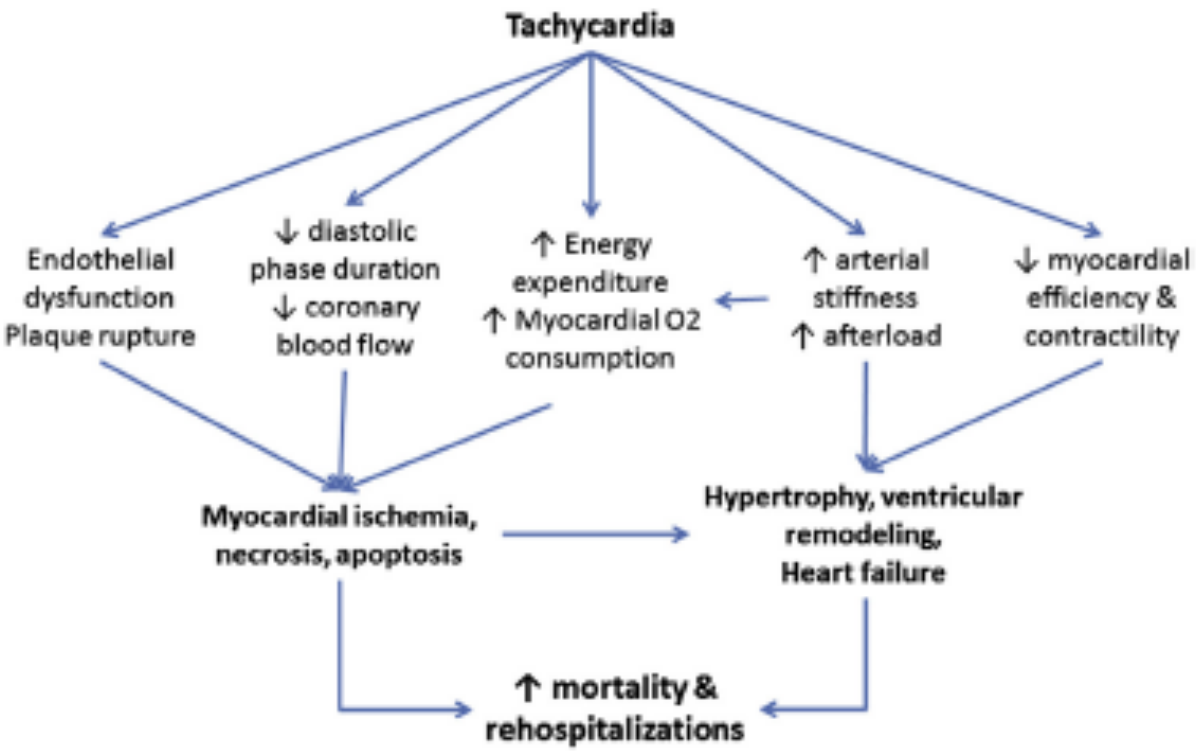



**Figure 1** Tachycardia as a Cause of Heart Failure and Increased Mortality

Mechanisms potentially involved in the untoward effects of tachycardia on the development of heart failure and increased mortality.

M. Metra M.JACC: Heart Failure Vol.1, No.6, Dec 2013: 497-9

# Riduzione della FC come strategia di cardioprotezione?

- Tachycardia might be the first sign of cardiac damage.

Senkus E. Cardiovascular effects of systemic cancer treatment. Cancer Treat Rev 2011;37:300–311.

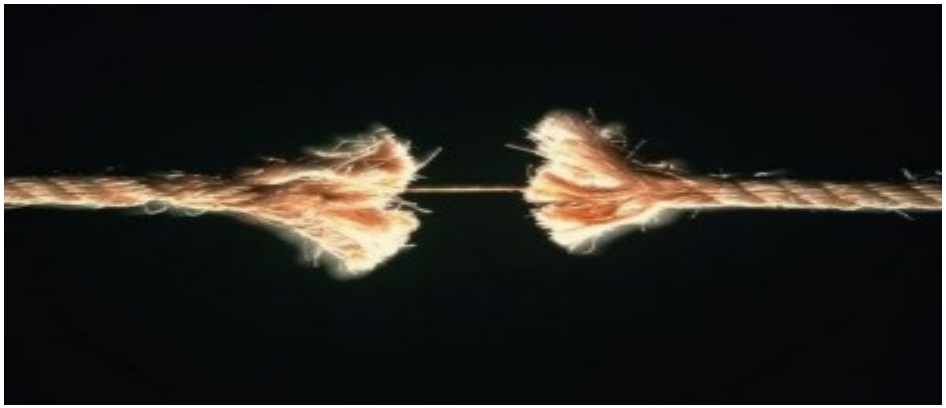
- Beta-adrenergic regulation is not only an important factor for the commencement, but is even considered to promote metastasis and growth of tumors through extensive interaction between epinephrine, norepinephrine, and adrenergic receptors.

Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. Clin Cancer Res 2012;1:1201 –1206

# MA…..

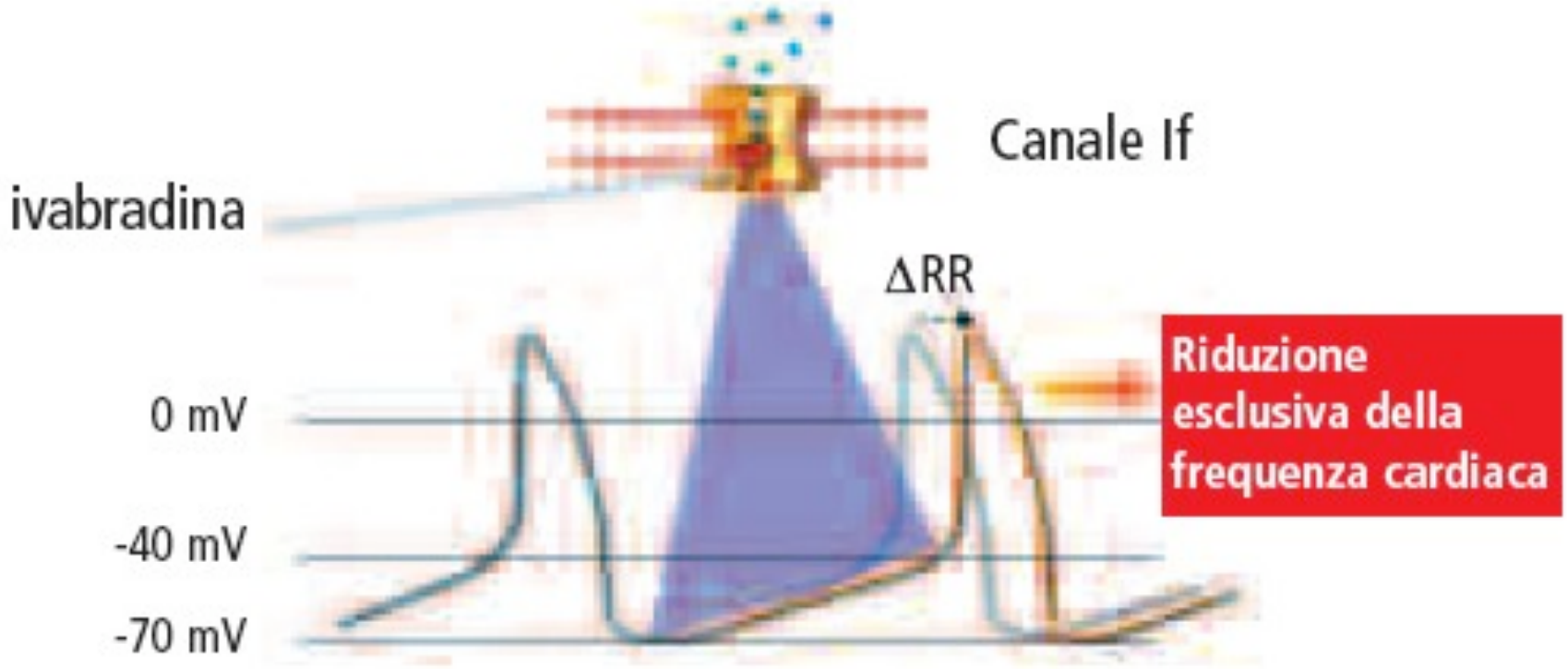
Paziente oncologico:

- ipoteso
- astenico
- stato catabolico
- BPCO



# Ivabradina
# Meccanismo d'azione

Inibitore selettivo e specifico della corrente If




*Di Francesco D, Camm AJ. Drugs. 2004;64:1757-1765.*

# Ivabradina: indicazioni

**ANGINA PECTORIS** cronica stabile negli adulti con coronaropatia e normale ritmo sinusale e frequenza cardiaca ≥ 70 bpm.

- negli adulti che non sono in grado di tollerare o che hanno una controindicazione all'uso dei beta- bloccanti
- o in associazione ai beta-bloccanti nei pazienti non adeguatamente controllati con una dose ottimale di beta-bloccante

**INSUFFICIENZA CARDIACA CRONICA** in classe NYHA da II a IV con disfunzione sistolica, in pazienti con ritmo sinusale e la cui frequenza cardiaca sia ≥ 75 bpm, in associazione con la terapia convenzionale che include il trattamento con un beta-bloccante o nel caso in cui la terapia con un beta-bloccante sia controindicata o non tollerata.

**TACHICARDIA SINUSALE INAPPROPRIATA SINTOMATICA**

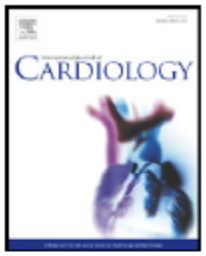
# Case report

International Journal of Cardiology 176 (2014) 1374–1376

Contents lists available at ScienceDirect

International Journal of Cardiology

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




Letter to the Editor

## Effectiveness of the combination therapy with lisinopril, ivabradine and multivitamin supplementation in anthracycline-induced severe cardiotoxicity

**Ca mammario**

**Completo recupero (RMN) della funzione ventricolare dopo lisinopril 20 mg ed ivabradina 10 mg**

# Oltre l'effetto sulla FC: ipotesi

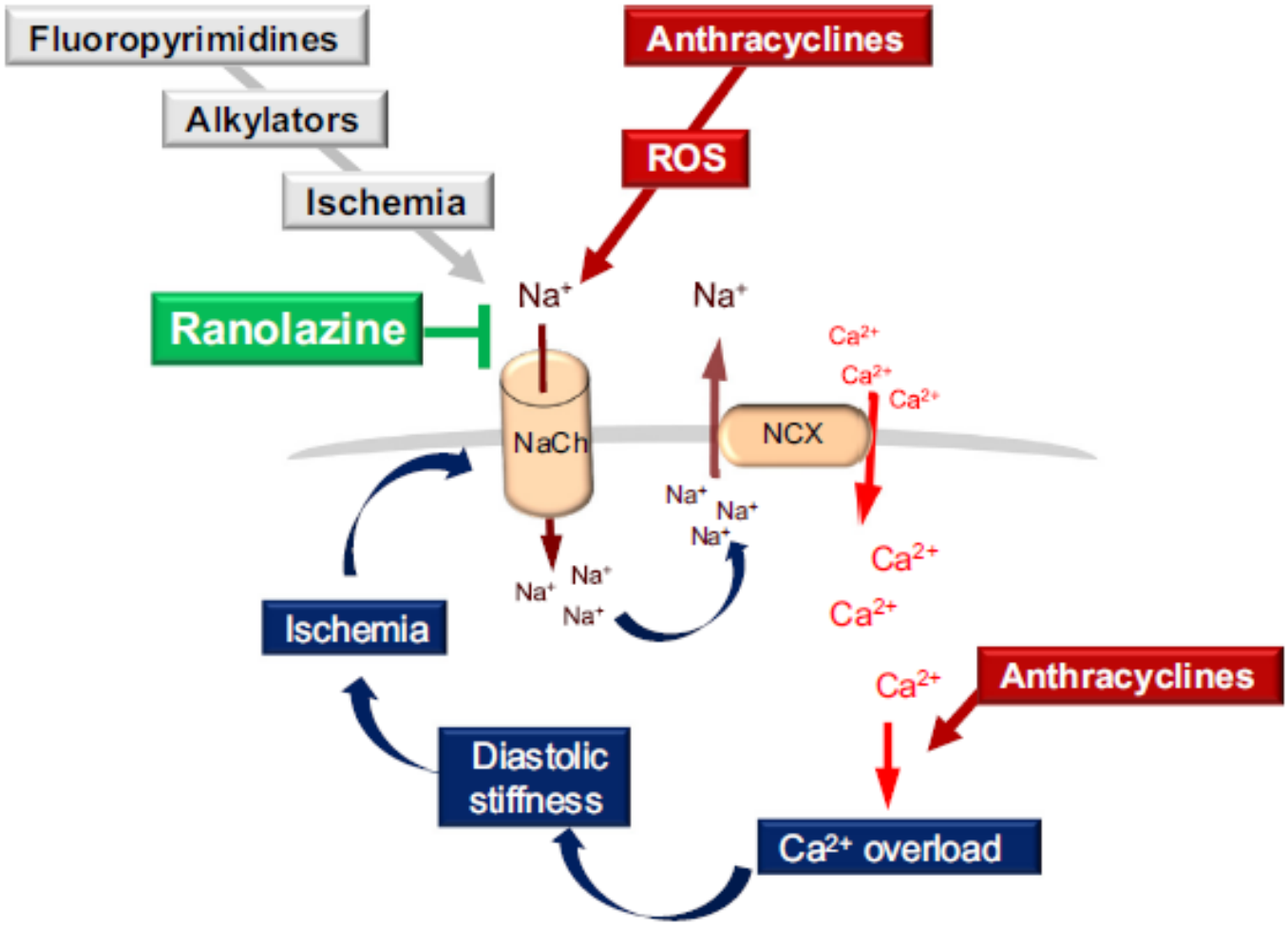
Nel modello animale ivabradina:

- riduce lo stress ossidativo (riduzione dell'attività della NADPH ossidasi, della produzione di superossidi, della perossidazione lipidica)

- Migliora la funzione endoteliale

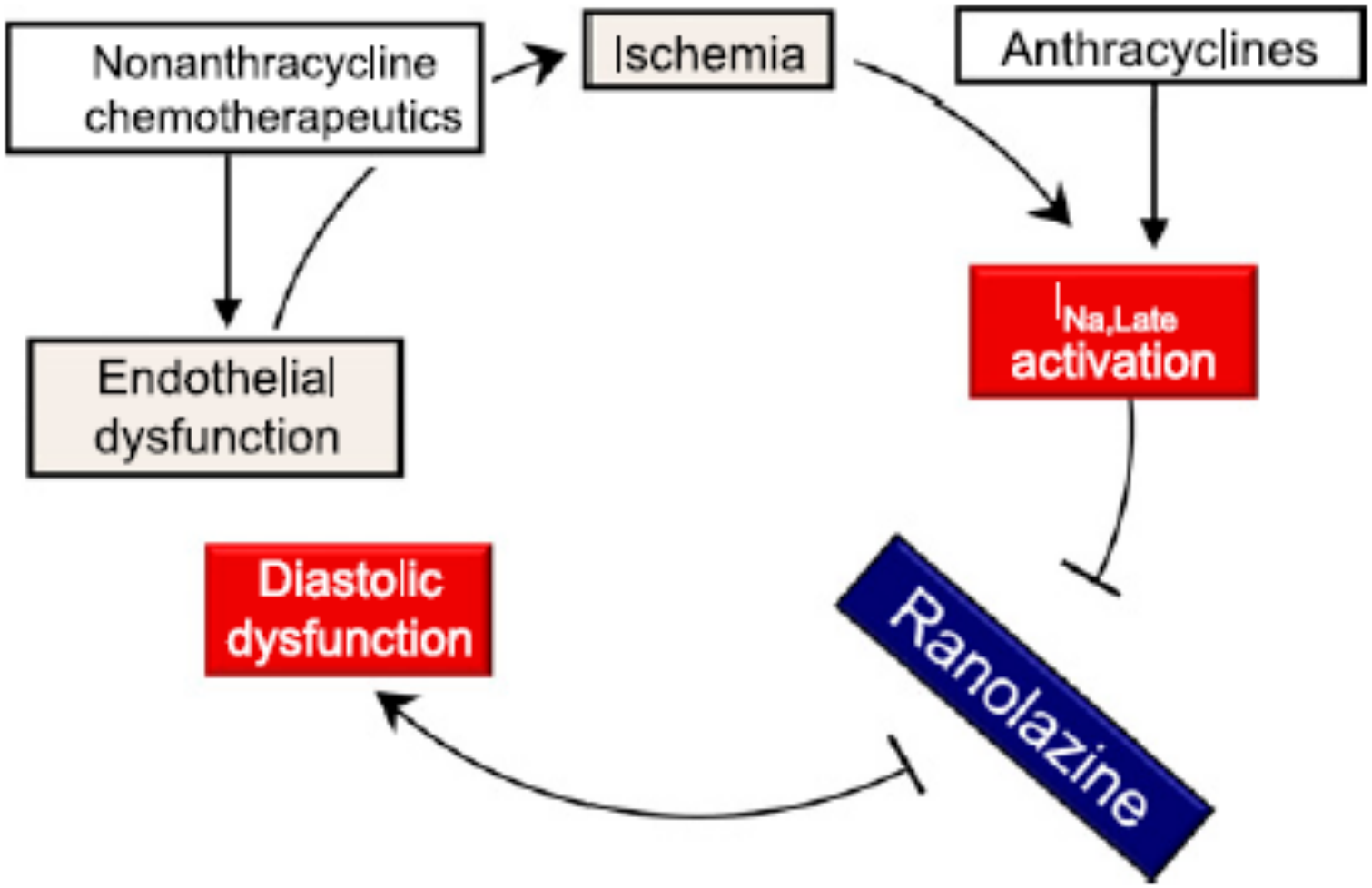
Custodis F et al. Circulation 2008; 117(18): 2377-2387

# Sovraccarico di calcio citosolico



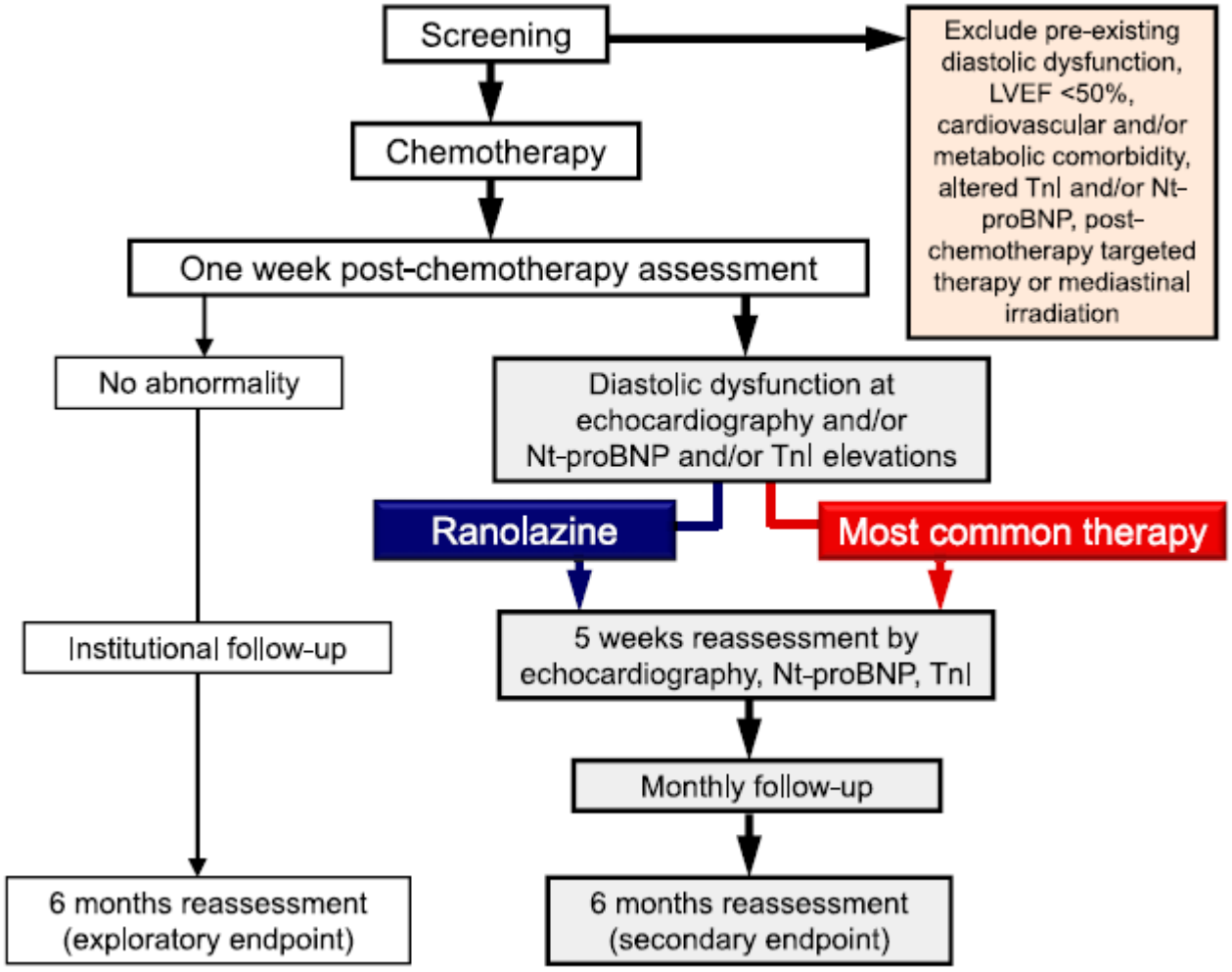

Salvatorelli E. et al., Biochim. Biophys. Acta 2015

# Polichemioterapie




Salvatorelli E. et al., Biochim. Biophys. Acta 2015

# The INTERACT Study
## The Ranolazine to Treat Early Cardiotoxicity Induced by Antitumor Drugs




Minotti G et al. J Pharmacol Exp Ther 2013

# Ranolazina e cardioprotezione: le evidenze sperimentali

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2014) **16**, 358–366
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[7], Giovanna Piscopo[3], Clemente Cipresso[3], Maria Gaia Monti[6], Claudia De Lorenzo[4], Claudio Arra[5], Gerolama Condorelli[4], Fabio Di Lisa[2], and Nicola Maurea[3]**

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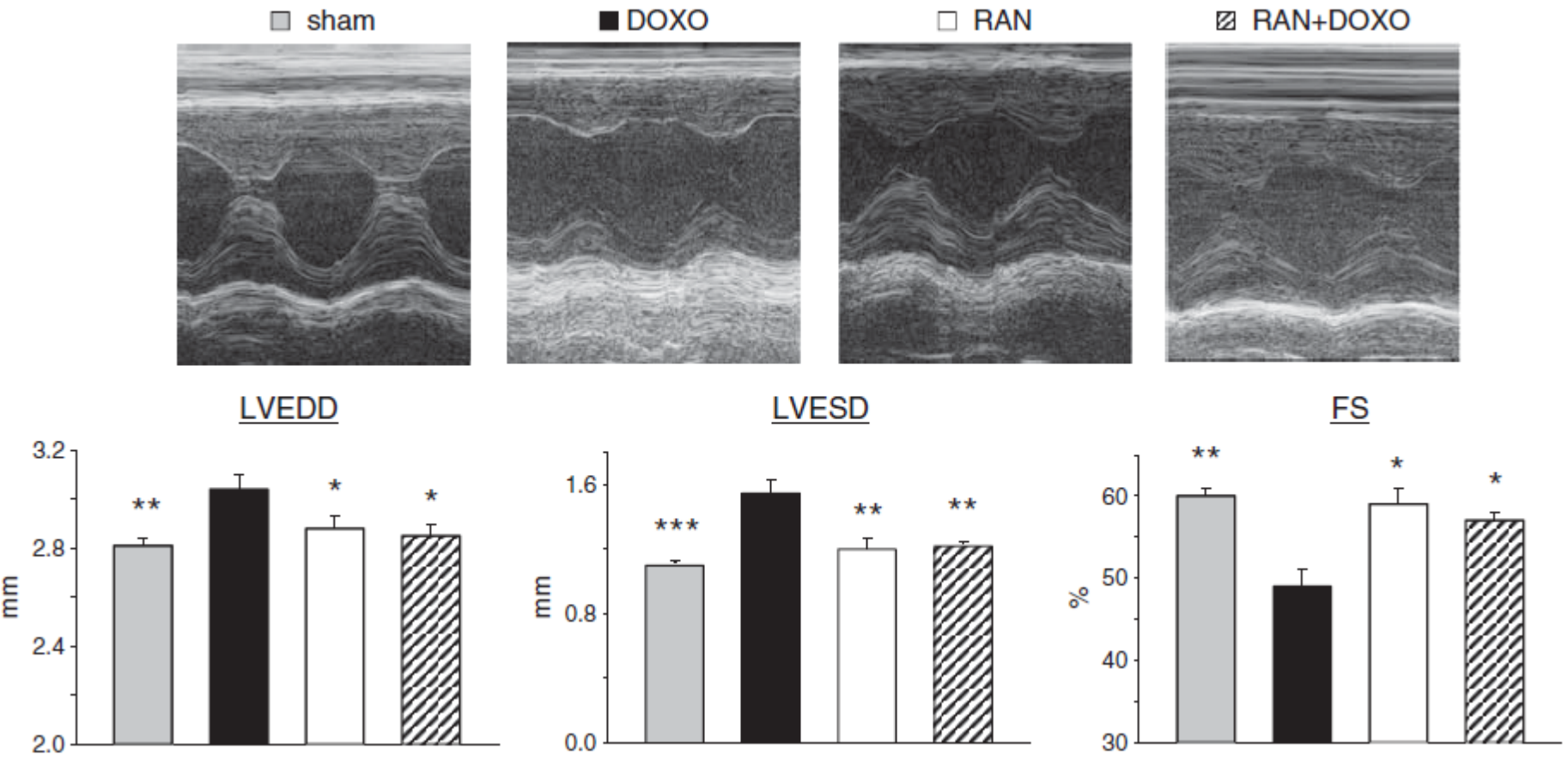
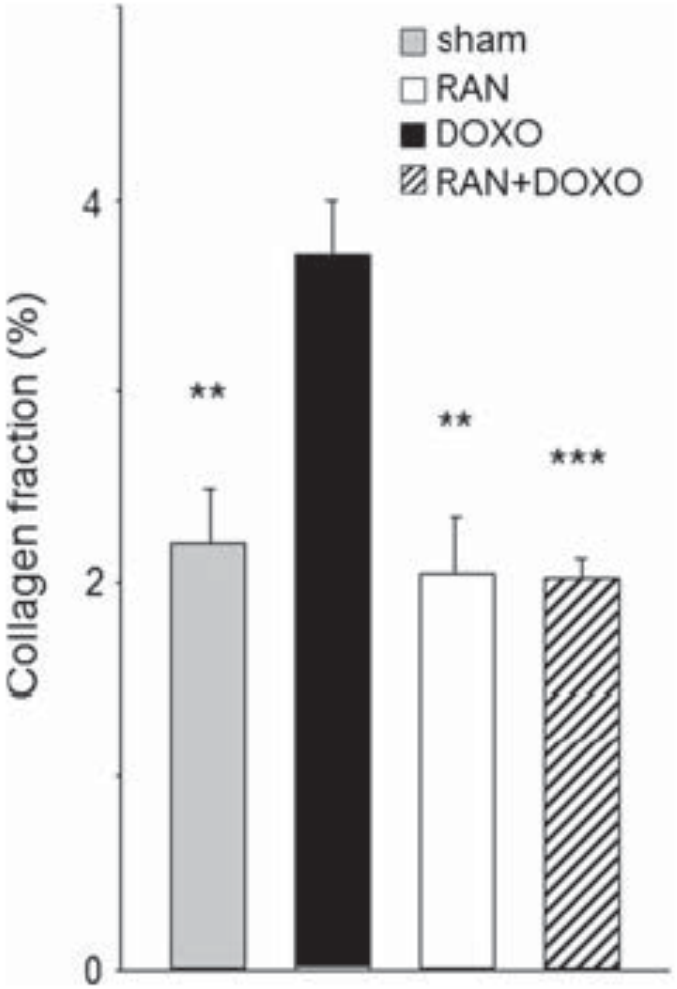
# Ranolazina previene la disfunzione ventricolare indotta dalla doxorubicina nei topi



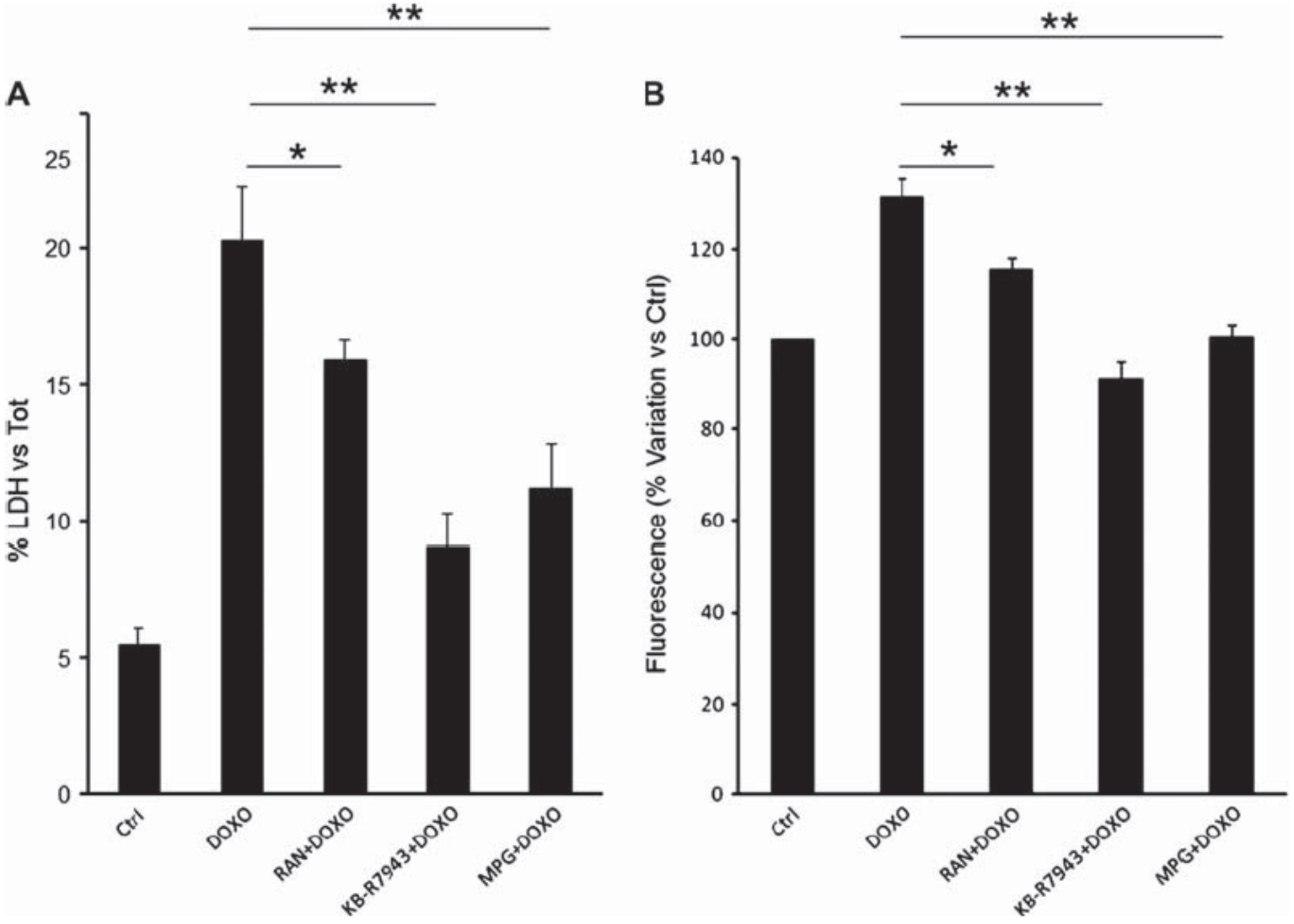

Tocchetti C.G et al, European Journal of Heart Failure (2014) 16, 358–366

# Ranolazina attenua l'incremento del collagene interstiziale e la morte cellulare cardiaca indotta dalla doxorubicina



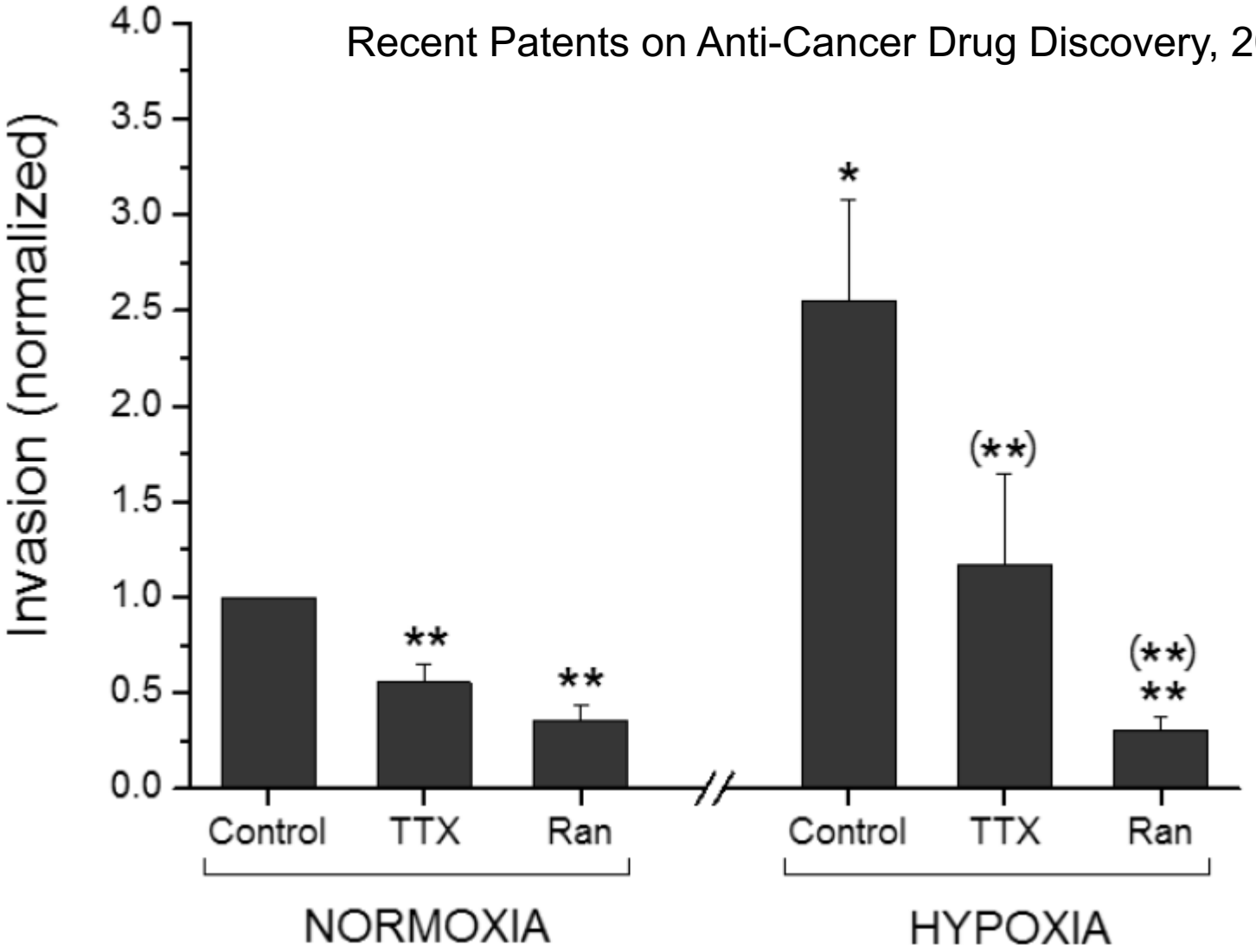

Tocchetti C.G et al, European Journal of Heart Failure (2014) 16, 358–366

# Ranolazina riduce la formazione di ROS indotta dalla doxorubicina nei cardiomiociti



# Invasione tumorale
# Ipossia e blocco del canale del Na+

Recent Patents on Anti-Cancer Drug Discovery, 2013, 8, 66-8



Driffort *et al. Molecular Cancer* 2014, **13**:264
http://www.molecular-cancer.com/content/13/1/264

MOLECULAR CANCER

SHORT COMMUNICATION Open Access

# Ranolazine inhibits $Na_V1.5$-mediated breast cancer cell invasiveness and lung colonization

Virginie Driffort[1], Ludovic Gillet[1], Emeline Bon[1], Séverine Marionneau-Lambot[2], Thibauld Oullier[2], Virginie Joulin[3], Christine Collin[4], Jean-Christophe Pagès[4,5], Marie-Lise Jourdan[1,4], Stéphan Chevalier[1,6], Philippe Bougnoux[1,4], Jean-Yves Le Guennec[7], Pierre Besson[1,6*†] and Sébastien Roger[1,8*†]

Medical Hypotheses 84 (2015) 11–13

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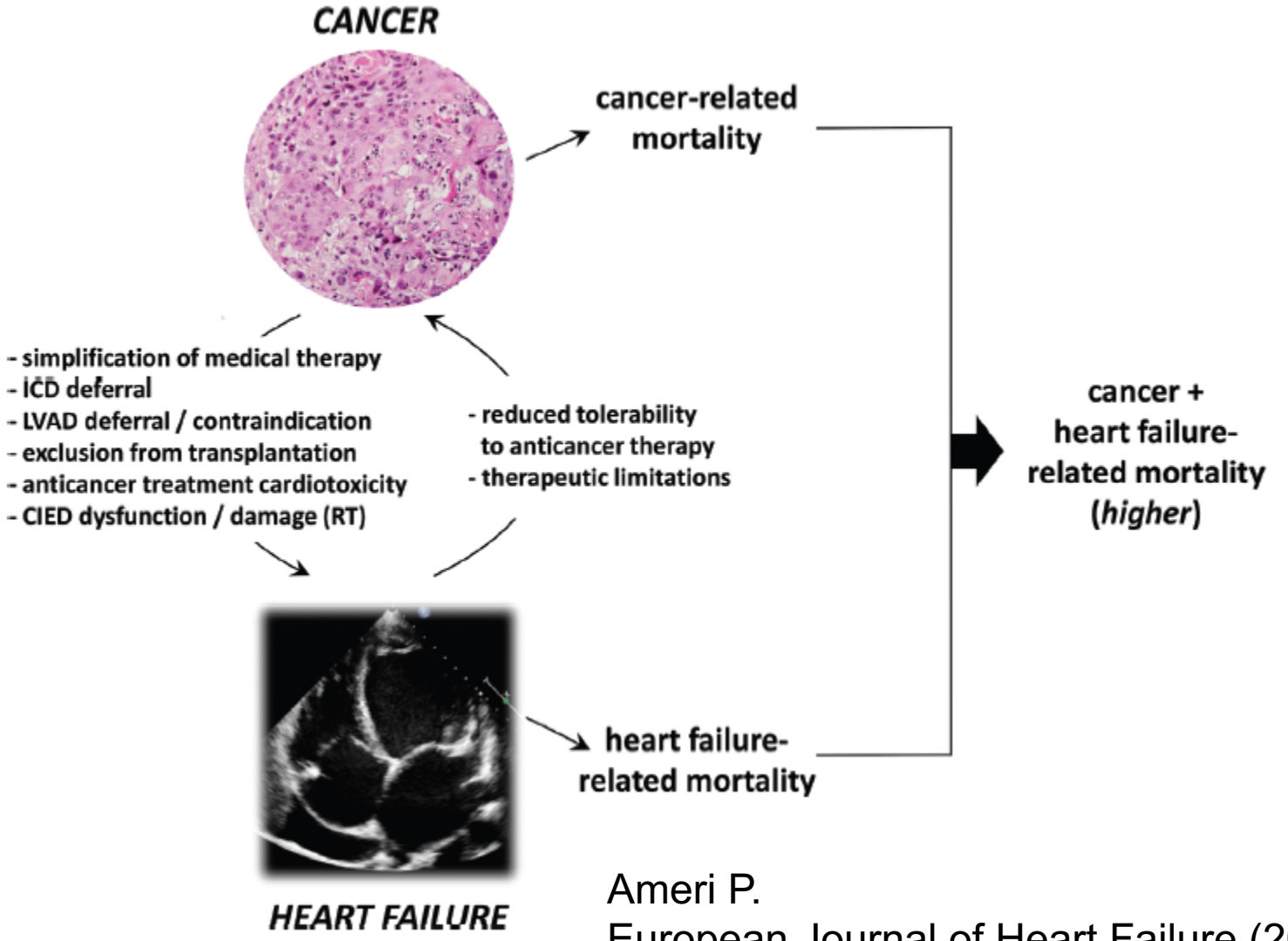
**IL BLOCCO DEI CANALI DEL SODIO VOLTAGGIO-DIPENDENTI ASSOCIATO ALLE TERAPIE ANTITUMORALI PUO' ESSERE EFFICACE SIA IN UN CONTESTO ADIUVANTE CHE PALLIATIVO**

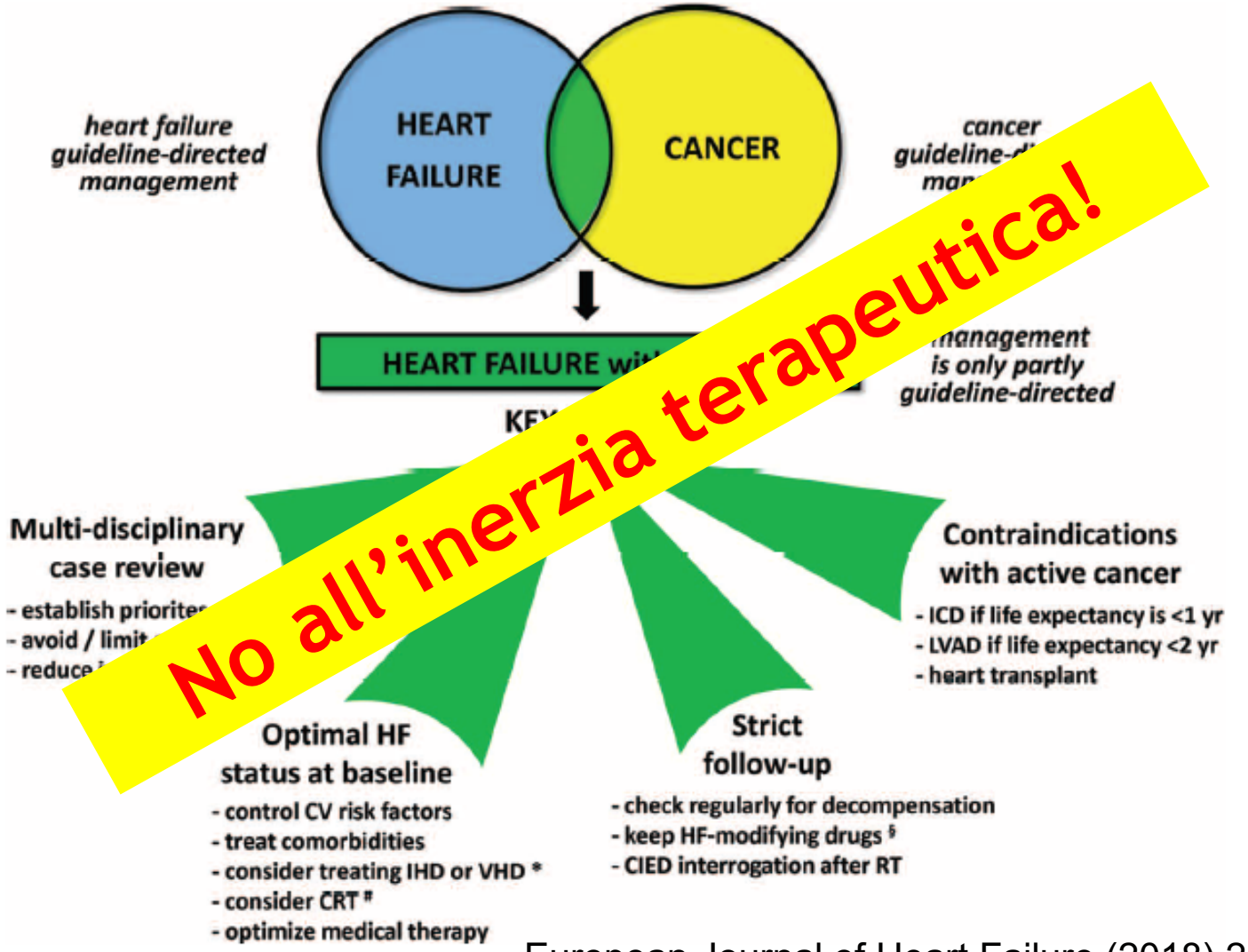
[a] *Department of Internal Medicine, Medical Oncology Section, Yeditepe University Hospital, Istanbul, Turkey*
[b] *Department of Internal Medicine, Yeditepe University Hospital, Istanbul, Turkey*

# Cancer in pre-existing HF




Ameri P.
European Journal of Heart Failure (2018) 20, 879–887

# Preparing patients with heart failure for anti-tumour therapies




European Journal of Heart Failure (2018) 20, 879–887

# Following patients with heart failure during cancer therapy

- "Cardiotossicità" del carico idrico (prolungare le in[illegible]ni, rimodulare la terapia diuretica, controllo st[illegible] elettroliti e della funz. renale)
- Correggere l'anemia e la car[illegible]one al rischio trombotico)
- Interrogare ICD [illegible]apia (>10 MV or neutr[illegible]uld be avoided, and the [illegible]dose to CIED should be limited)
- [illegible] indicazioni a scoagulazione ([illegible]embolismo venoso)

**SFIDA**

**Down-titration/interruzione terapia cardiologica**

# Warning!

«The safety of spironolactone in hormone-sensitive malignancies has not been clearly established, and it is best avoided in women with oestrogen receptor- and/or progesterone receptor-positive breastcancers; we believe that in these patients eplerenone is a suitable alternative»

*Cardiovasc Res* 2018;**114**:282–290.

# Grazie dell'attenzione!