

DIAGNOSTICA E TERAPIA CARDIOLOGICA

Stresa 8 maggio 2015

**BIOMARCATORI CARDIACI NELLE PATOLOGIE
NON CORONARICHE**

Biomarcatori in CardiOncologia

Paolo Spallarossa

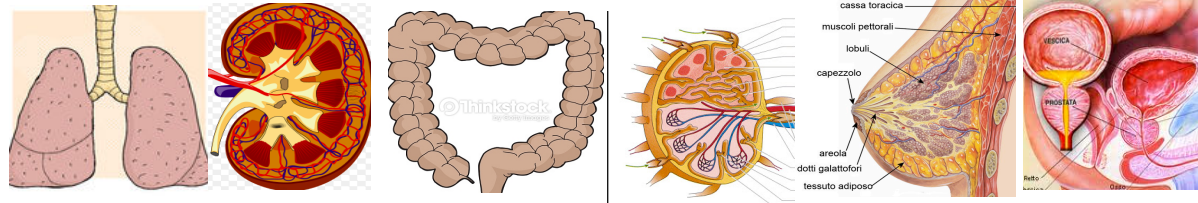
***Clinica di Malattie dell'Apparato Cardiovascolare
IRCCS Azienda Ospedaliera Universitaria San Martino – IST
Genova***

Paolo.Spallarossa@unige.it



Oncologist

CANCER



Anthracyclines

Taxanes

Anti-HER2

5-FU

Bevacizumab

TKI

- Sunitinib
- Sorafenib
- Nilotinib
- ...
-

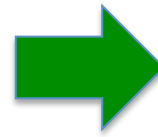
Radiotherapy

Bone Marrow
transplant



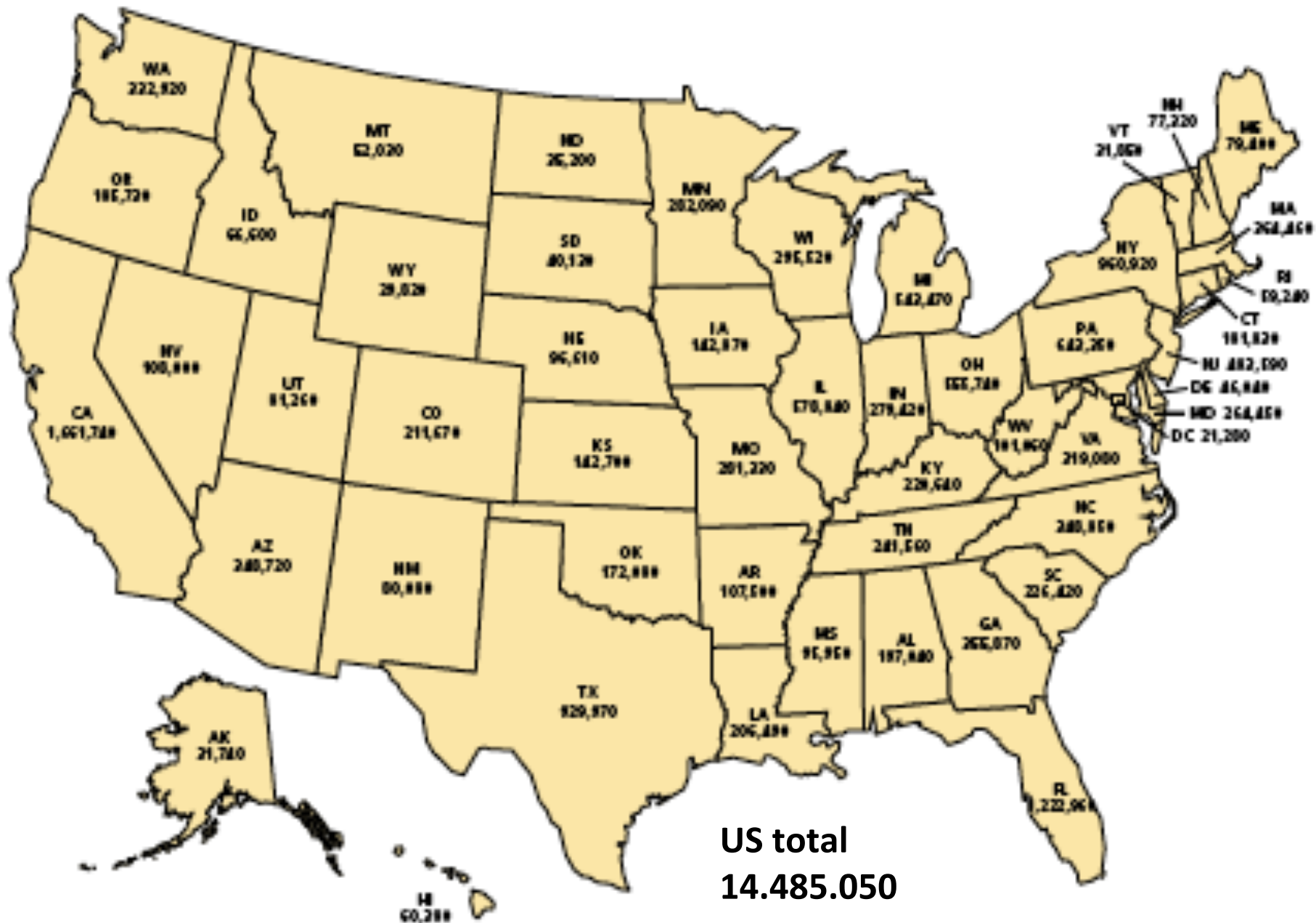
Screening

Early
Diagnosis



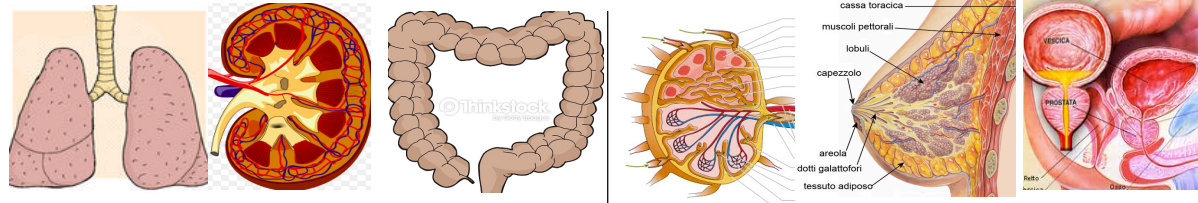
Dramatic
Improvement
In Survival

Estimated Numbers of Cancer Survivors by State as of January 1, 2014



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transplant



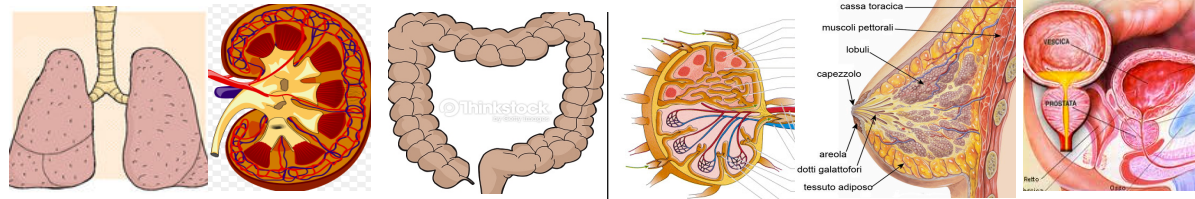
Elderly

Comorbidities

Cardiologist / CardiOncologist

Oncologist

CANCER



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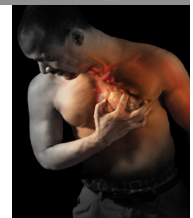
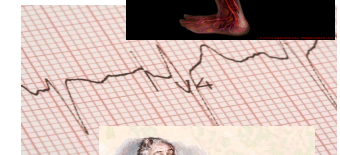
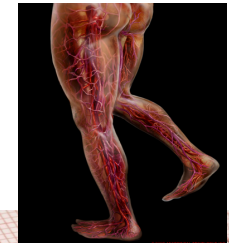
CardiOncology

*A new pharmacological, biological,
and medical Science
aimed to study, prevent,
recognize, and treat
cancer- and cancer treatment-
related cardiovascular diseases.*

Elderly

Comorbidities

Cardiologist / CardiOncologist

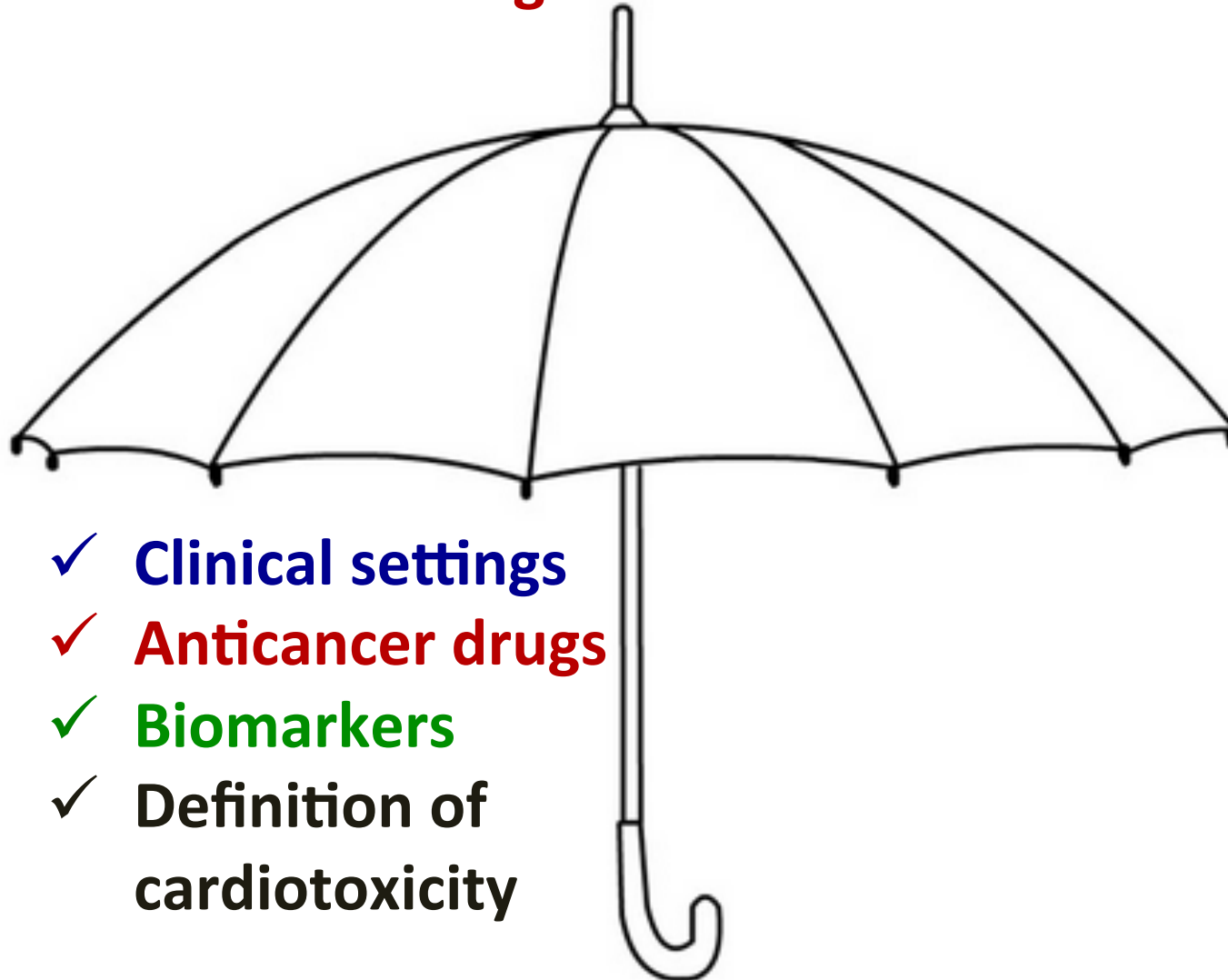


Use of Biomarkers in the Assessment of Chemotherapy-Induced Cardiac Toxicity

	Papers demonstrating correlation between increase in biomarker and Cardiotoxicity.	Papers failing in demonstrate correlation between increase in biomarker and Cardiotoxicity
Troponin I	13	3
Troponin T	5	2
B-Type natriuretic peptide	23	9
Atrial natriuretic peptide	5	1
CRP	1	3
MPO	1	-
Endothelin-1	1	-
ST-2	-	1
Christenson et al , Clinical Biochemistry 2015; 48: 223-235		

Use of Biomarkers in the Assessment of Chemotherapy- Induced Cardiac Toxicity

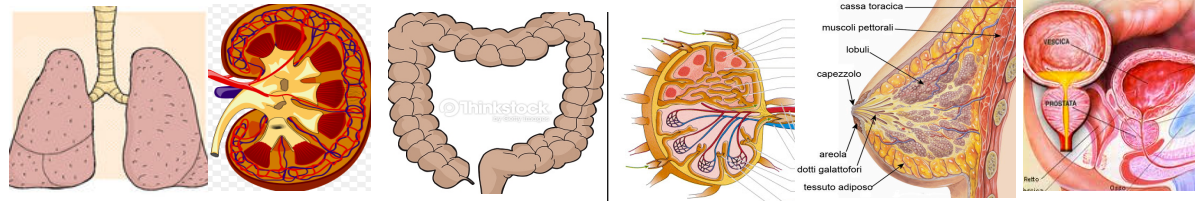
- Heterogeneous studies -



- ✓ Clinical settings
- ✓ Anticancer drugs
- ✓ Biomarkers
- ✓ Definition of cardiotoxicity

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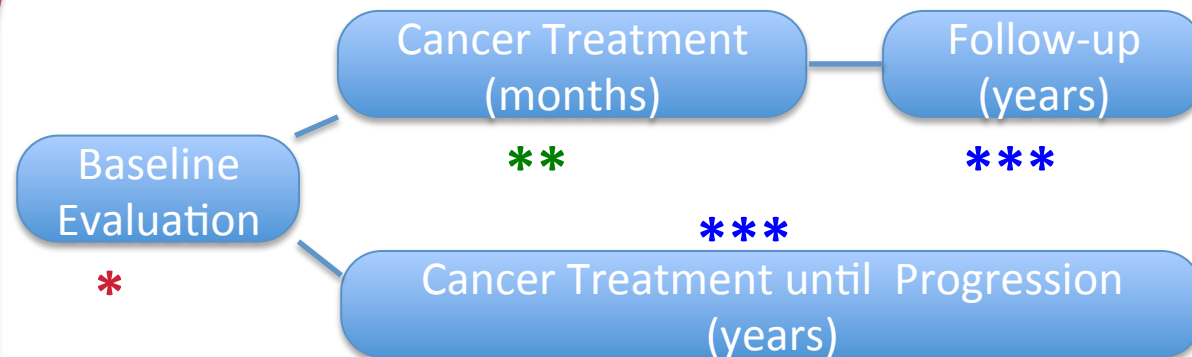
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Radiotherapy

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transplant

Potential Role of Biomarkers

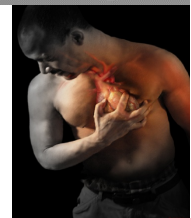
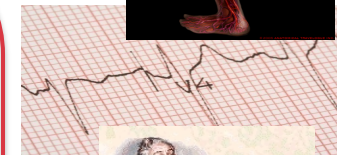
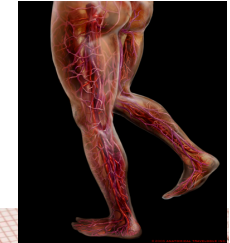


- * General Assessment
- ** Very early detection of cardiotoxicity
- *** Remote control of patients

Elderly

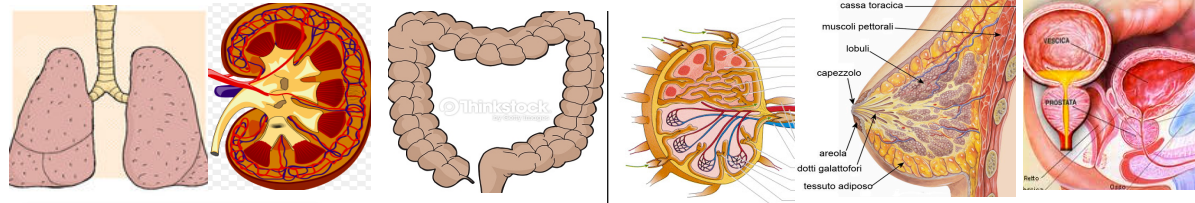
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transplant



Elderly

Comorbidities

Cardiologist / Cardioncologist

Characteristics of Cancer Therapeutics-Related Cardiac Dysfunction

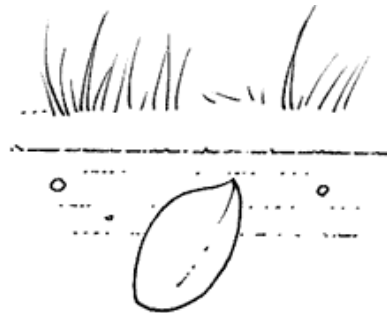
Type I	Type II
Doxorubicin May stabilize, but underlying <u>damage</u> appears to be <u>permanent and irreversible</u> ; recurrence in months or years may be related to sequential cardiac stress	Trastuzumab High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Cumulative, dose related High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Not dose related Increasing evidence for the relative safety of rechallenge (additional data needed)
Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

Anthracycline Cardiotoxicity

Treatment (months)

1

4



*Rich soil
=heart disease*

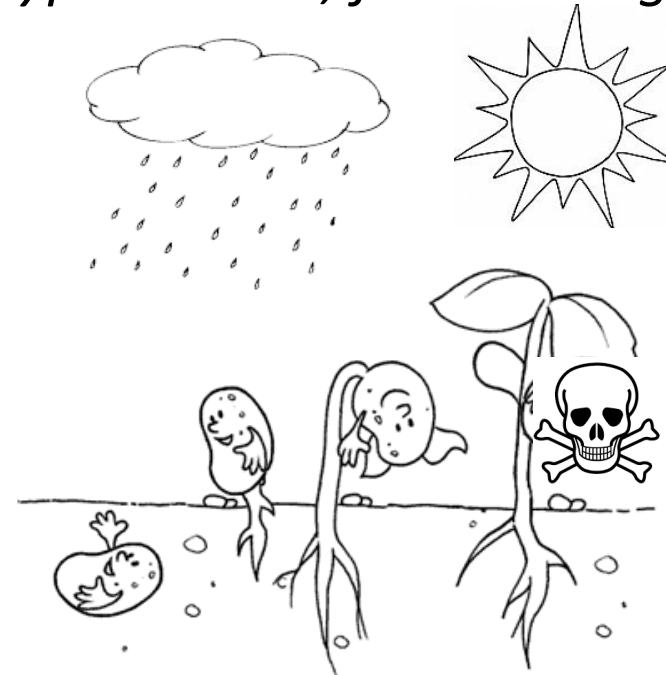
FU (years)

1

15

Stress

(=hypertension, further drugs)



Anthracycline Cardiotoxicity

Anthracycline Cardiotoxicity (at the cellular level) begins with the first administration of the drug

Physical examination, ecg , standard echo do not detect any change during anthracycline treatment

Biomarkers can detect subtle cardiac abnormalities that are predictive of late cardiac events

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

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

Milan, Italy

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

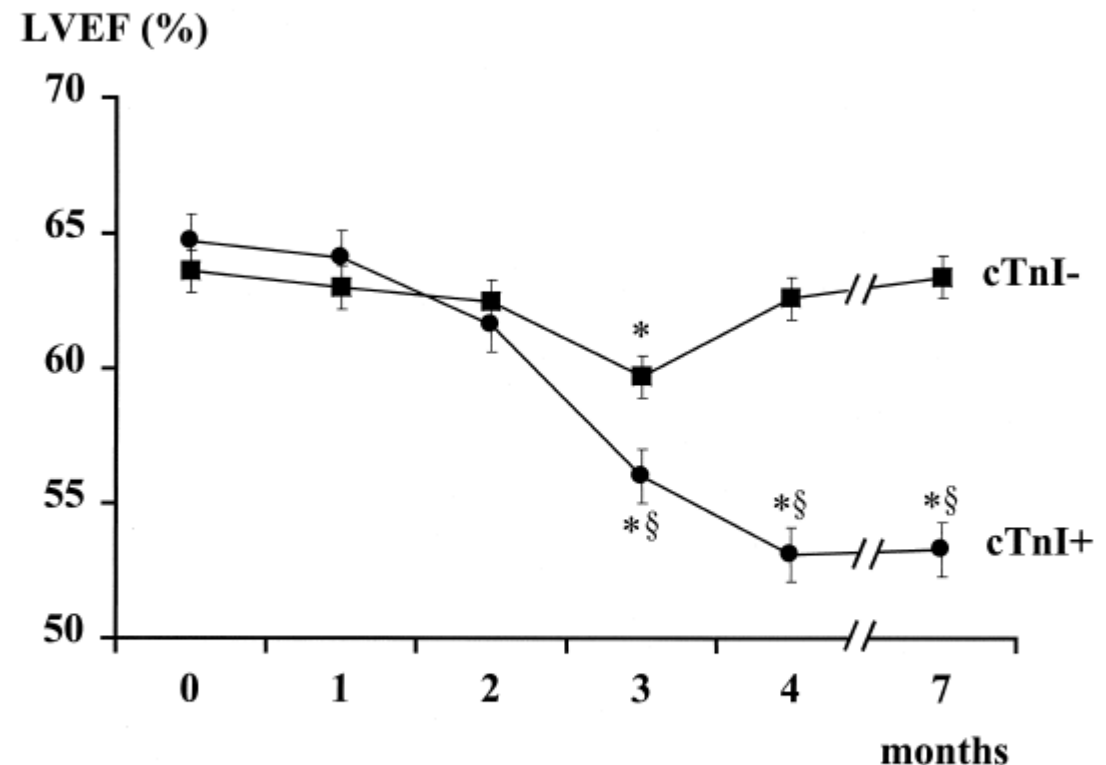
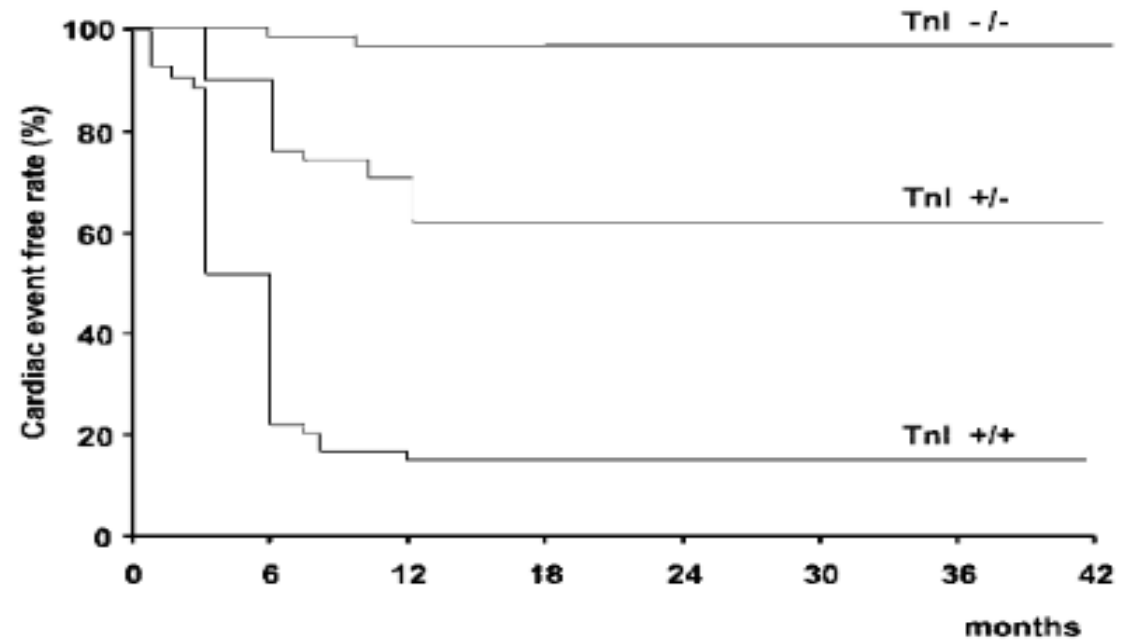
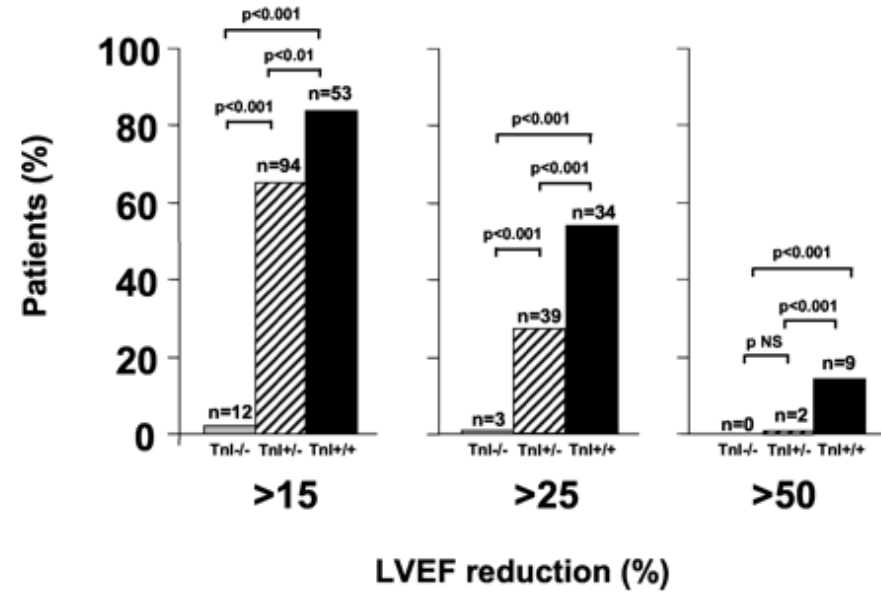
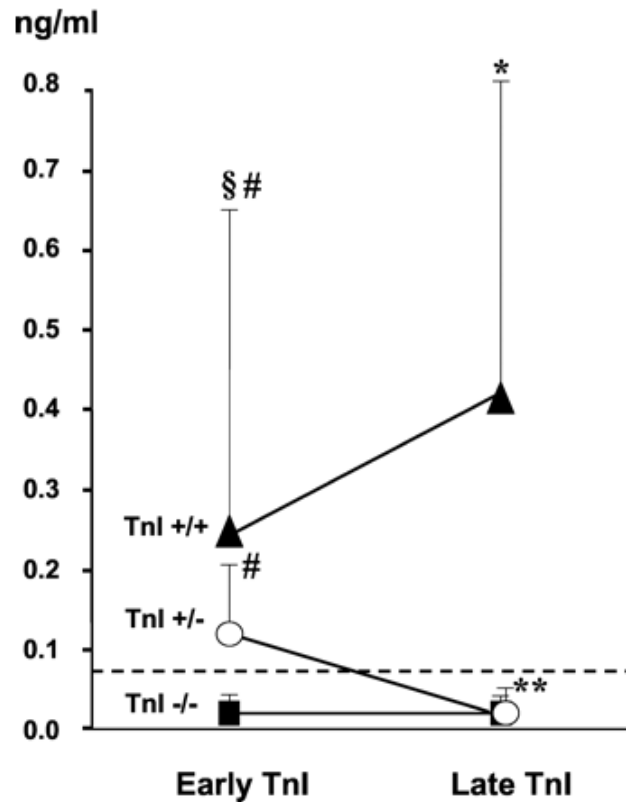


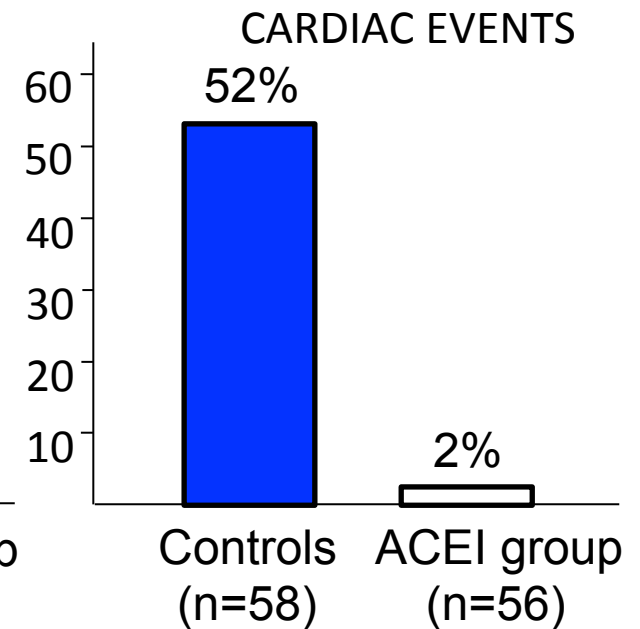
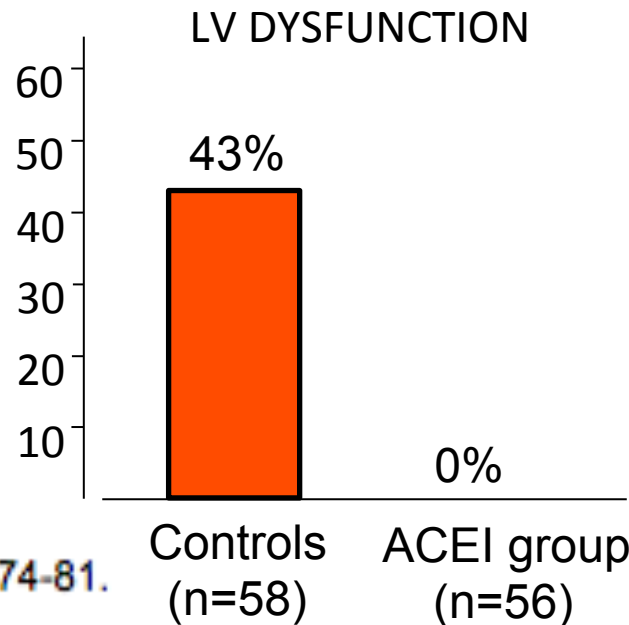
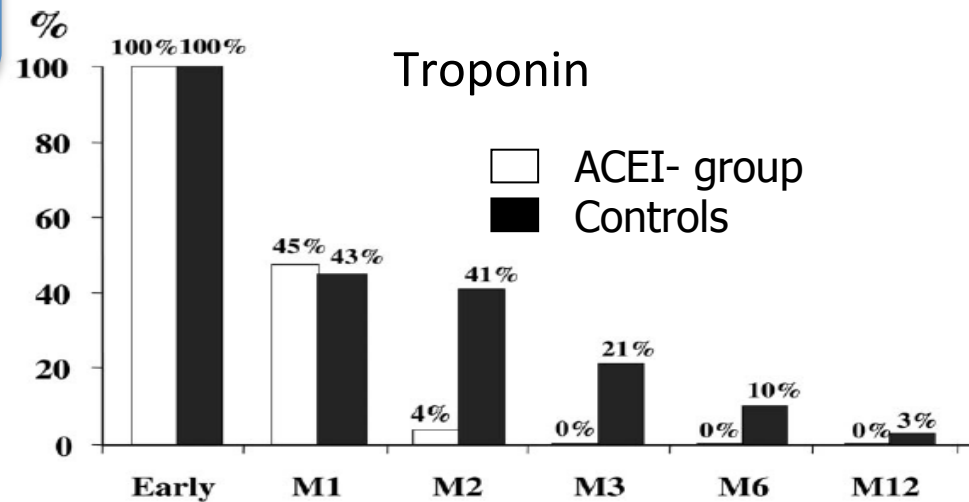
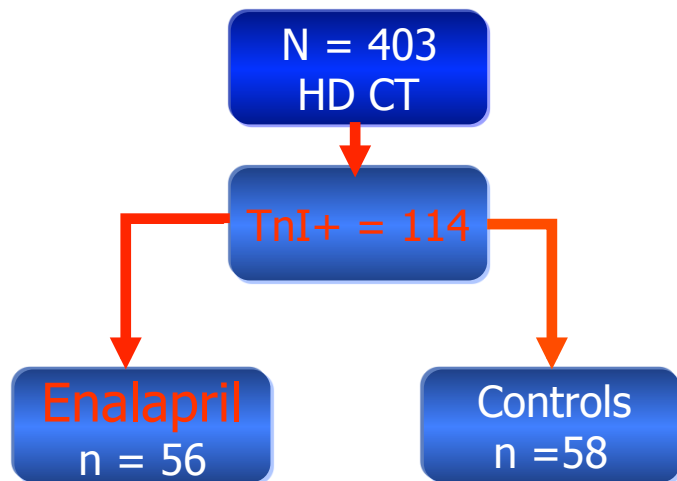
Figure 2. Left ventricular ejection fraction (LVEF) at baseline and during the seven months of follow-up of troponin I positive (cTnI+; solid circle) and negative (cTnI-; solid square) patients. * $p < 0.001$ vs. baseline (month 0); § $p < 0.001$ vs. cTnI- group. Data are shown as mean $\pm$ 95% confidence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

Prognostic Value of Troponin I



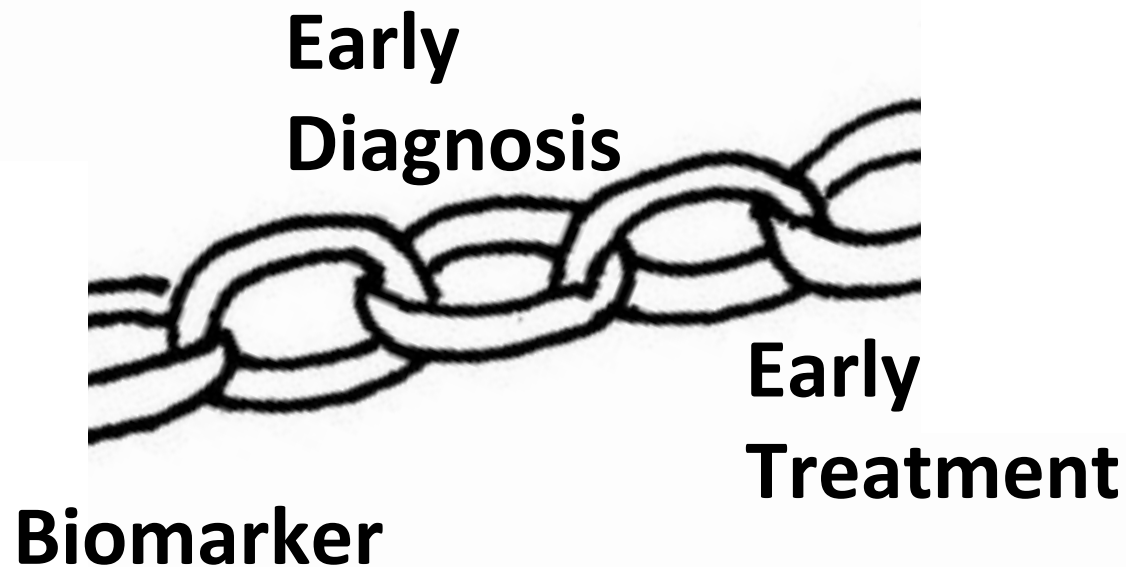
(Circulation. 2004;109:2749-2754.)

Enalapril prevents cardiac dysfunction and cardiac events in TnI+ patients



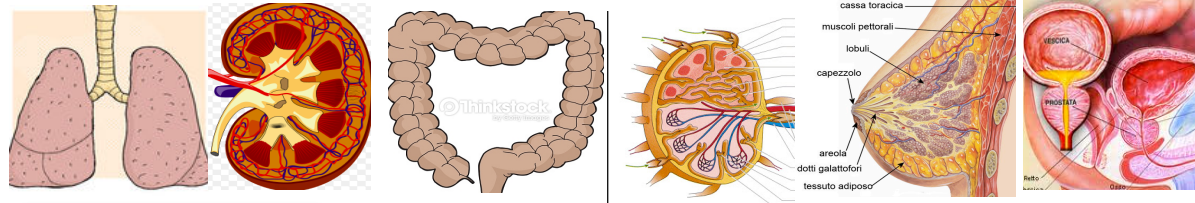
Prevention of Anthracycline Cardiotoxicity

The Chain of Survival



Oncologist

CANCER



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Radiotherapy

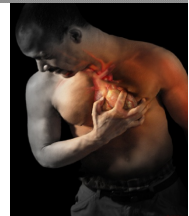
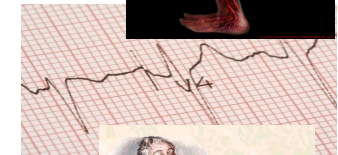
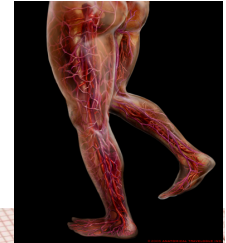
Bone Marrow
transplant

Different Mechanisms

Elderly

Comorbidities

Cardiologist / Cardioncologist

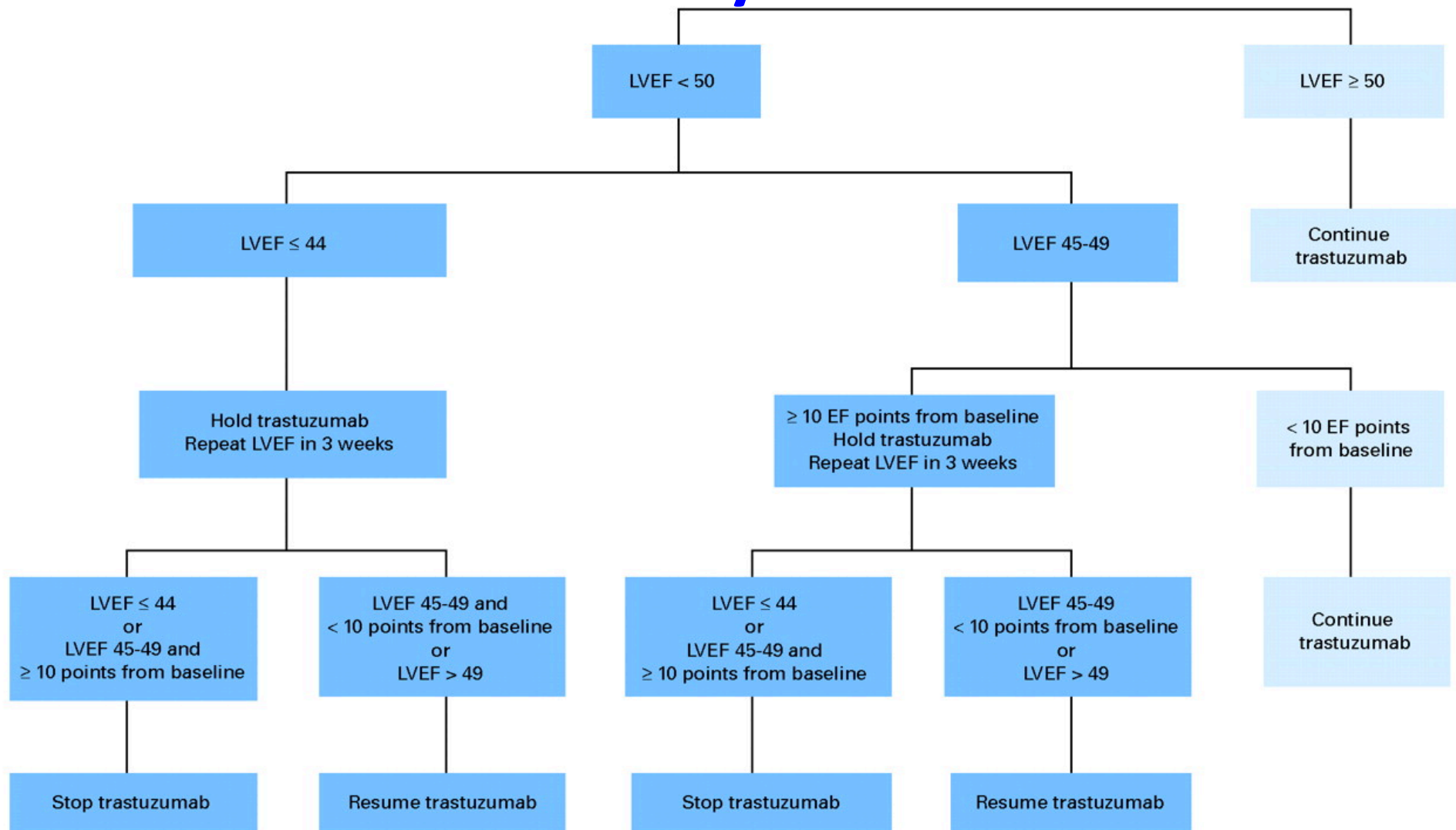


Characteristics of Cancer Therapeutics-Related Cardiac Dysfunction

Type I	Type II
Doxorubicin	Trastuzumab
May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	<u>High likelihood of recovery</u> (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
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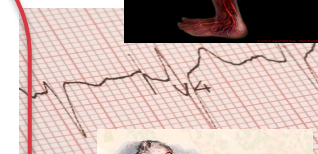
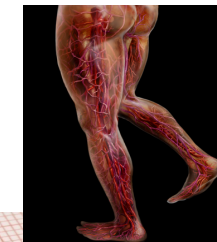
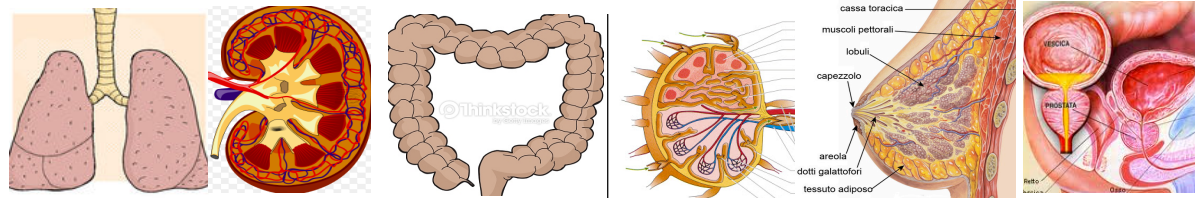
Prevention of Trastuzumab Cardiotoxicity

- ECHO every 3 months -



Oncologist

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Anthracyclines

Taxanes

Anti-HER2

5-FU

Bevacizumab

TKI

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- Sorafenib
- Nilotinib

- ...

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Radiotherapy

Bone Marrow
transplant

Breast Cancer

Anthracyclines

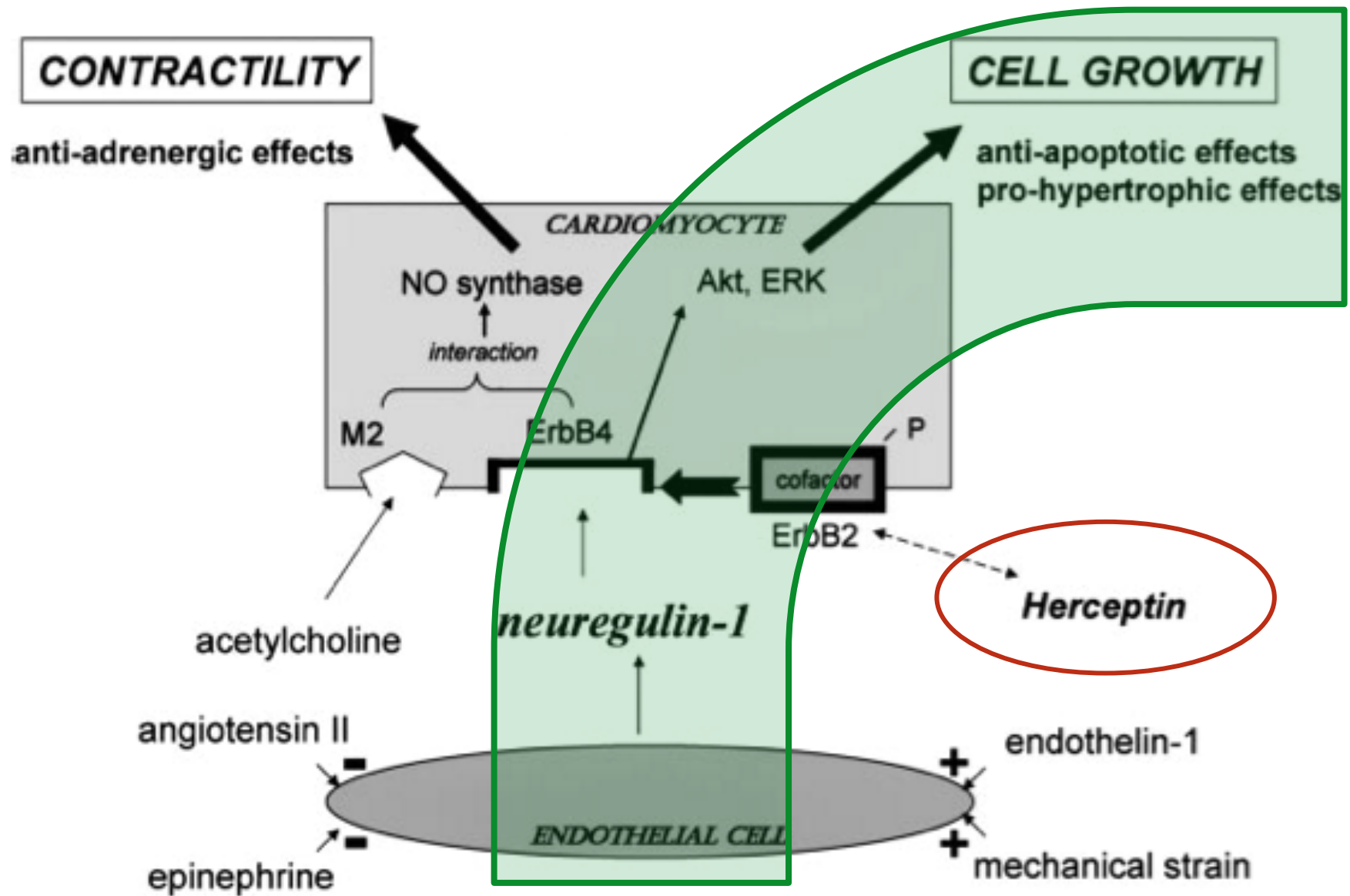


Trastuzumab

Elderly

Comorbidities

Cardiologist / Cardioncologist

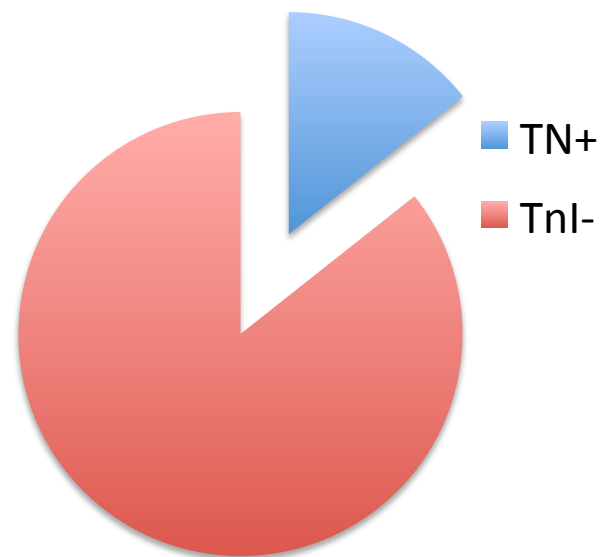


(*Circulation*. 2007;116:954-960.)

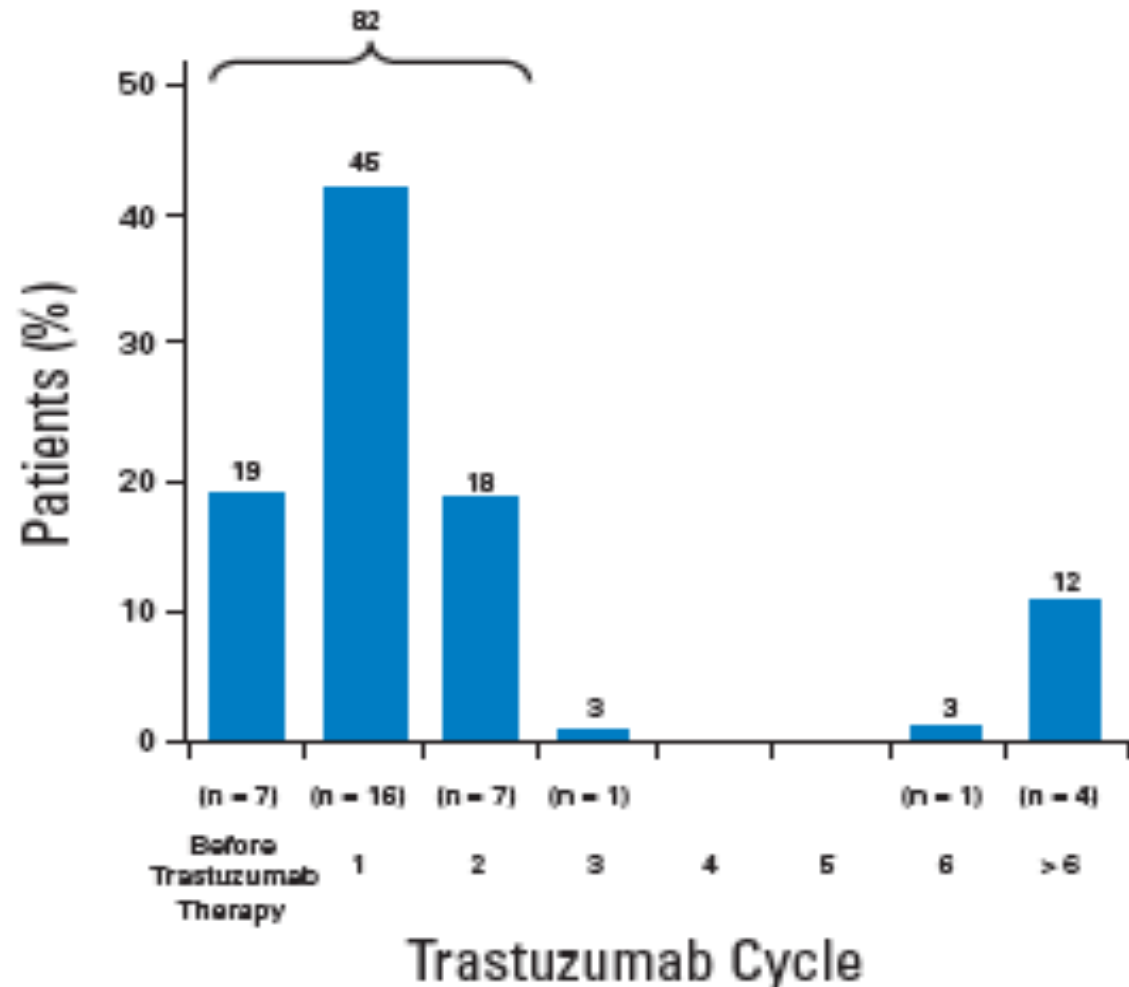
Trastuzumab-Induced Cardiotoxicity: Clinical and Prognostic Implications of Troponin I Evaluation

Daniela Cardinale, Alessandro Colombo, Rosalba Torrisi, Maria T. Sandri, Maurizio Civelli, Michela Salvatici, Giuseppina Lamantia, Nicola Colombo, Sarah Cortinovis, Maria A. Dessanai, Franco Nolè, Fabrizio Veglia, and Carlo M. Cipolla

251 Pazienti



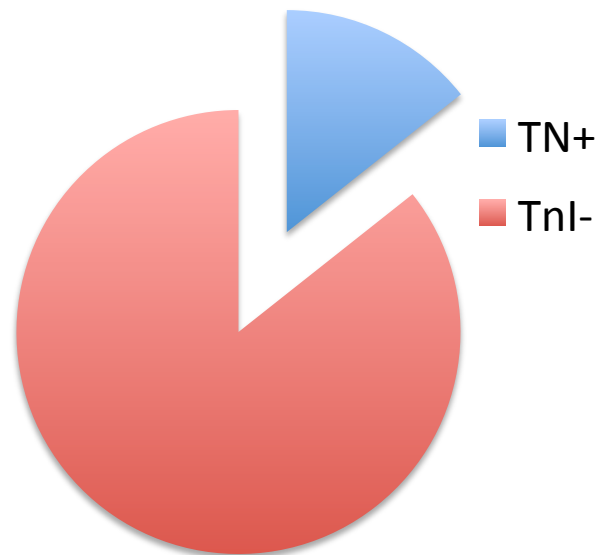
J Clin Oncol 28:3910-3916.



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251 Pazienti



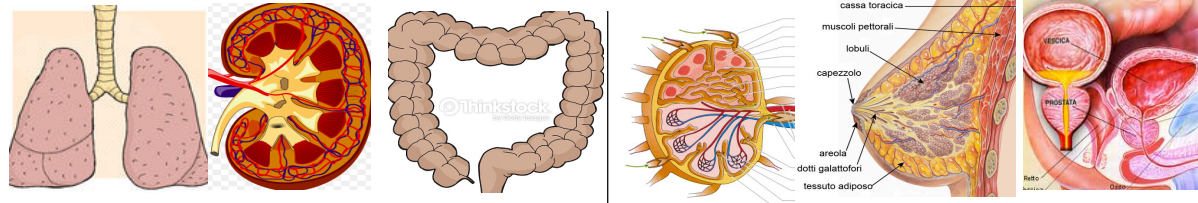
TN+ was predictive of:

LV dysfunction

No LV function recovery

Oncologist

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Bevacizumab

TKI

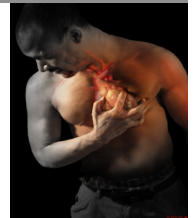
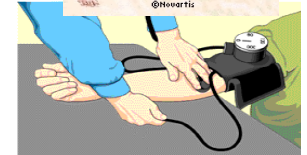
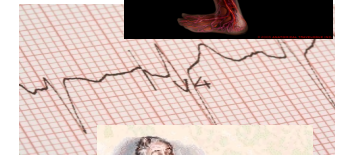
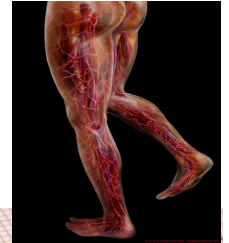
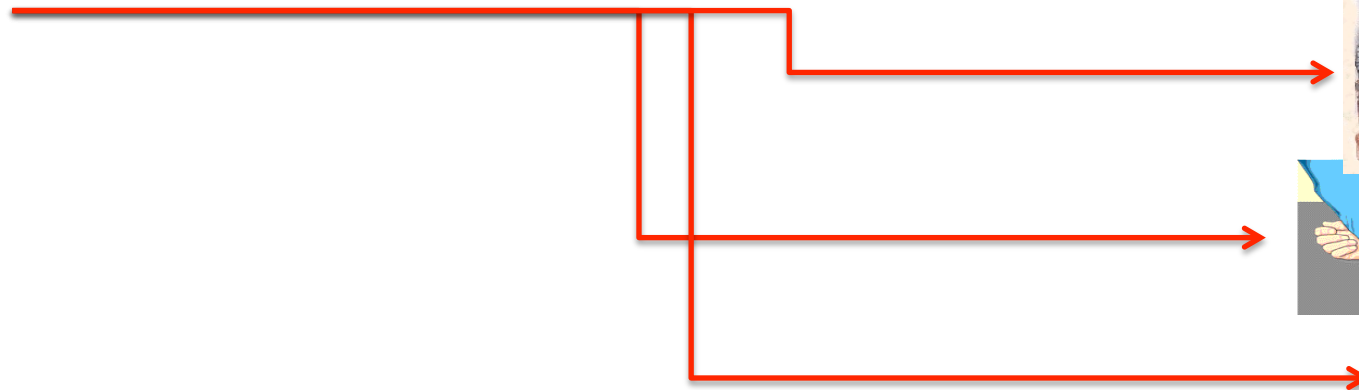
- Sunitinib
- Sorafenib
- Nilotinib

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Radiotherapy

Bone Marrow
transplant



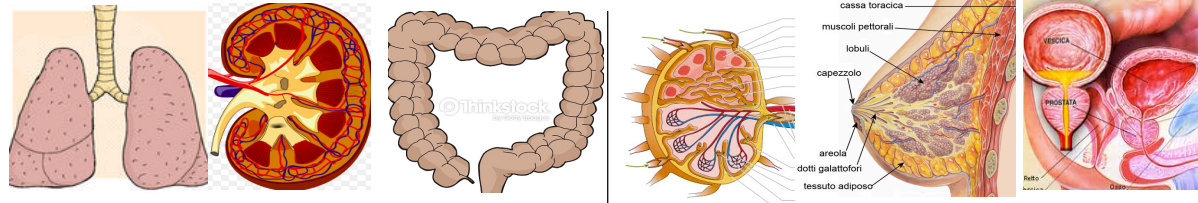
Elderly

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Sunitinib

Baseline
Evaluation

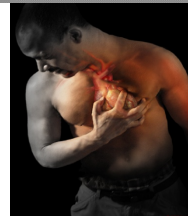
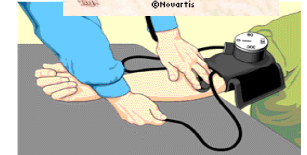
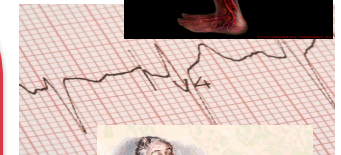
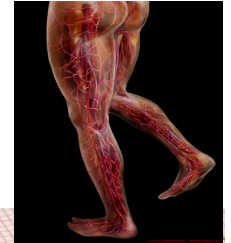
Cancer Treatment
until Progression
(years)

Biomarkers may have a role in the Remote
Control of patients

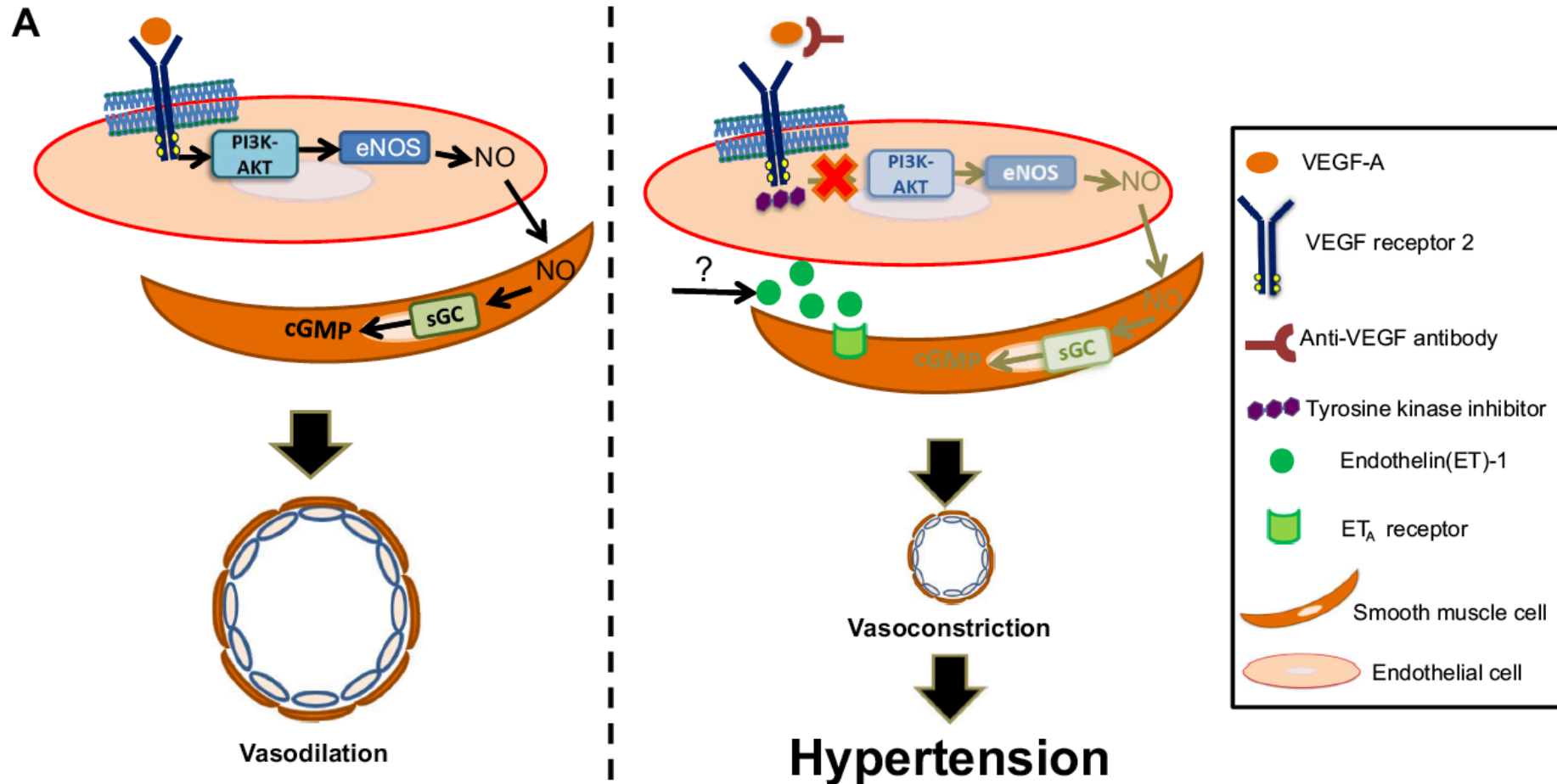
Elderly

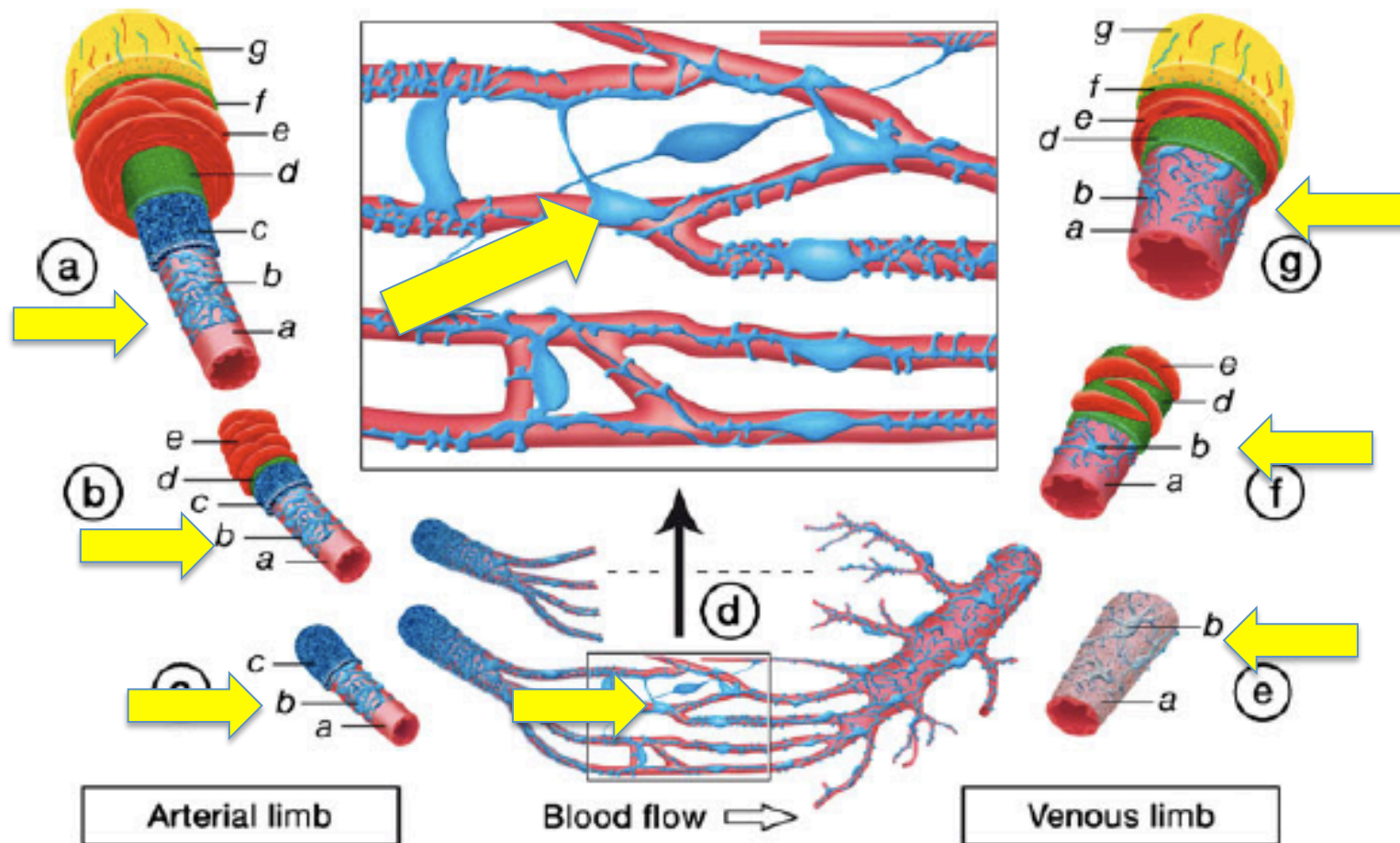
Comorbidities

Cardiologist / Cardioncologist



Proposed mechanisms leading to VEGF and PDGF signaling pathway inhibitor-induced hypertension.



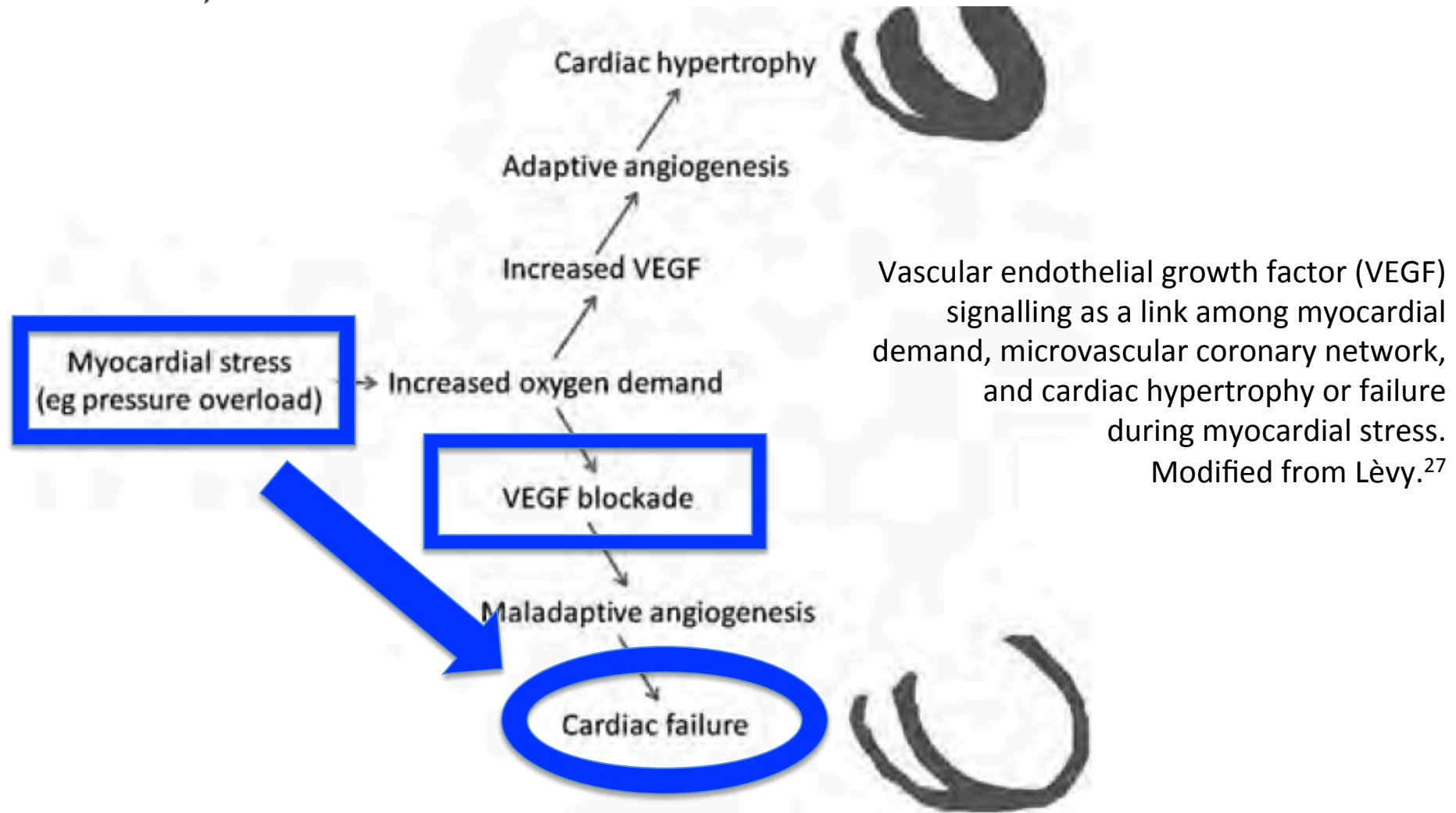


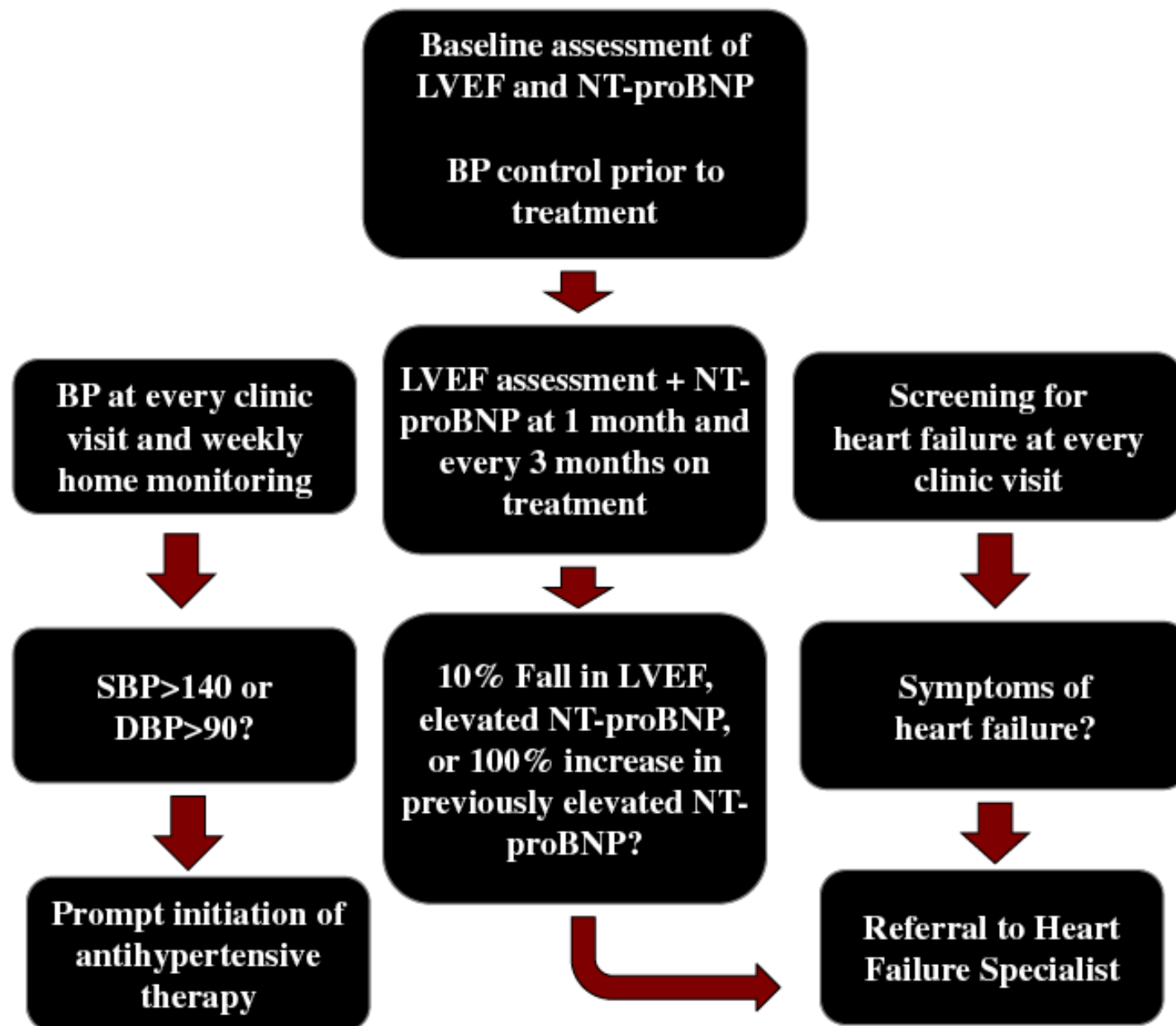
Bizarre-shaped and interconnected pericytes as companion cells in all coronary blood vessels: pericytes as ubiquitous “necessary endothelium embracing satellites” [20]. a Large artery. b Feed arteriole. c Precapillary arterioles. d Capillary bed. e Postcapillary venules, f Collecting venule. g Large vein.

a Endothelial tube, b pericytes, c ECM (the “cocoon” of the pericytes), d internal elastic membrane, e SMC (media), f external elastic membrane, and g adventitia with vasa vasorum or vasa venarum, respectively. Image from Ref. [32] with permission

The emerging issue of cardiac dysfunction induced by antineoplastic angiogenesis inhibitors

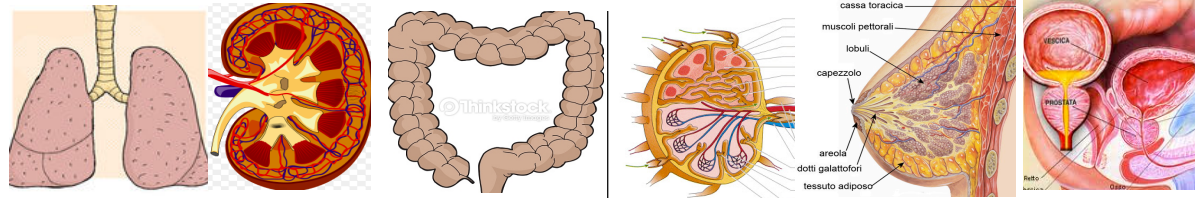
Carlo G. Tocchetti^{1*}, Giuseppina Gallucci², Carmela Coppola¹, Giovanna Piscopo^{1,3}, Clemente Cipresso¹, Carlo Maurea¹, Aldo Giudice⁴, Rosario V. Iaffaioli³, Claudio Arra⁴, and Nicola Maurea¹





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Biomarkers are a tool.....



Elderly

Comorbidities

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