MAYO CLINIC

Hot Topics in Cardiology 2015:

Cardio-oncology and Cardio-toxicity

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Associate Director, Preventive Cardiology
Mayo Clinic
Rochester MN, USA

Disclosures: None

Learning Objectives:

- Review the need for and practice of the emerging field of cardio-oncology
- Know the factors that increase the risk of cardiovascular complications in cancer patients
- Understand the difference between type I and type II cardiotoxicity
- Know how to monitor for and manage chemotherapy-induced cardiomyopathy

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Case 1: Ms. M - 25 yo female

- Age 13 months: Acute myelomonocytic
- Chemotherapy X 2 yrs: etoposide, cytosine, adriamycin
- Age 3: Radiation therapy to cranium
- Complete remission since then
- Grade school: Decreasing exercise tolerance and DOE
- Age 20: “asthma”
- Age 25: CHF

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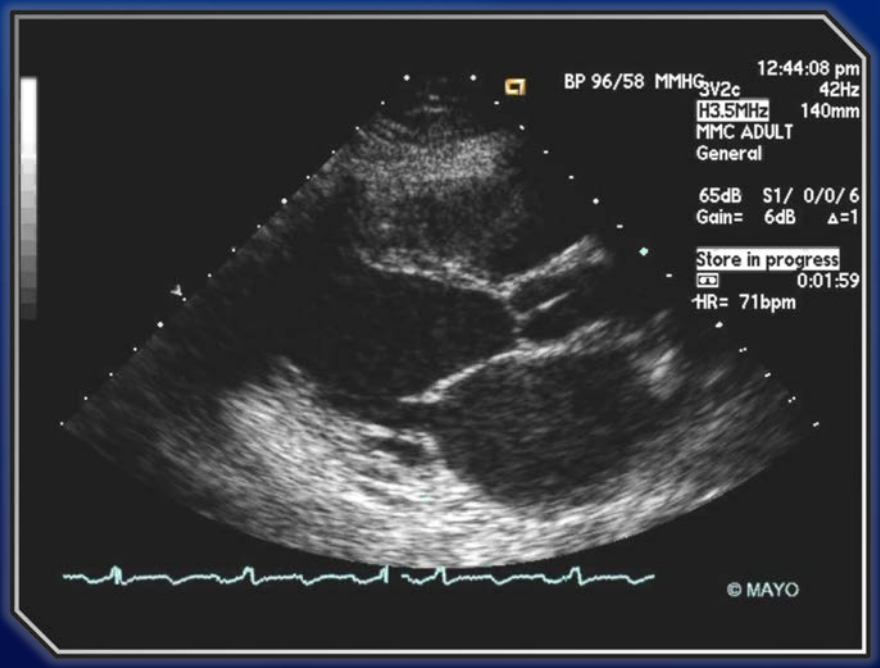
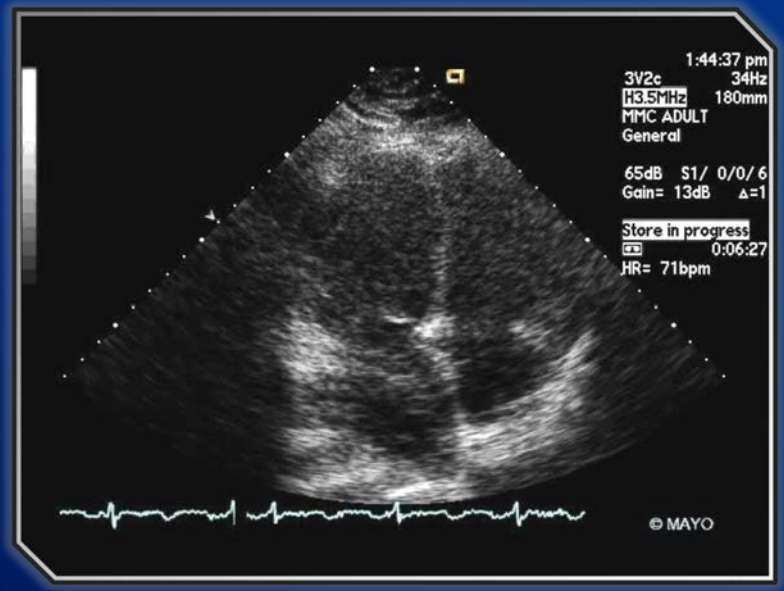
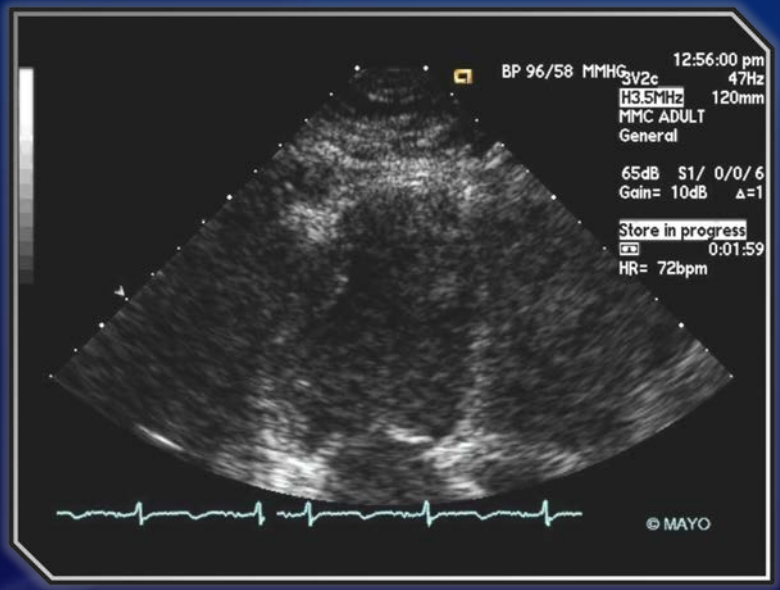
Ms M. - 25 yo female







Biventricular heart failure

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Ms M. – childhood cancer “survivor”

- Age 27: ICD implantation
- Inappropriate shocks due to recurrent atrial fibrillation
- Age 34: A fib ablation
- Recurrent heart failure hospitalizations
- Age 35: Upgrade to CRT-D
- Cardiogenic shock and LVAD implantation
- Heart transplantation w/early graft failure
- ECMO, Lower extremity compartment syndrome
- Comfort care; death at age 36

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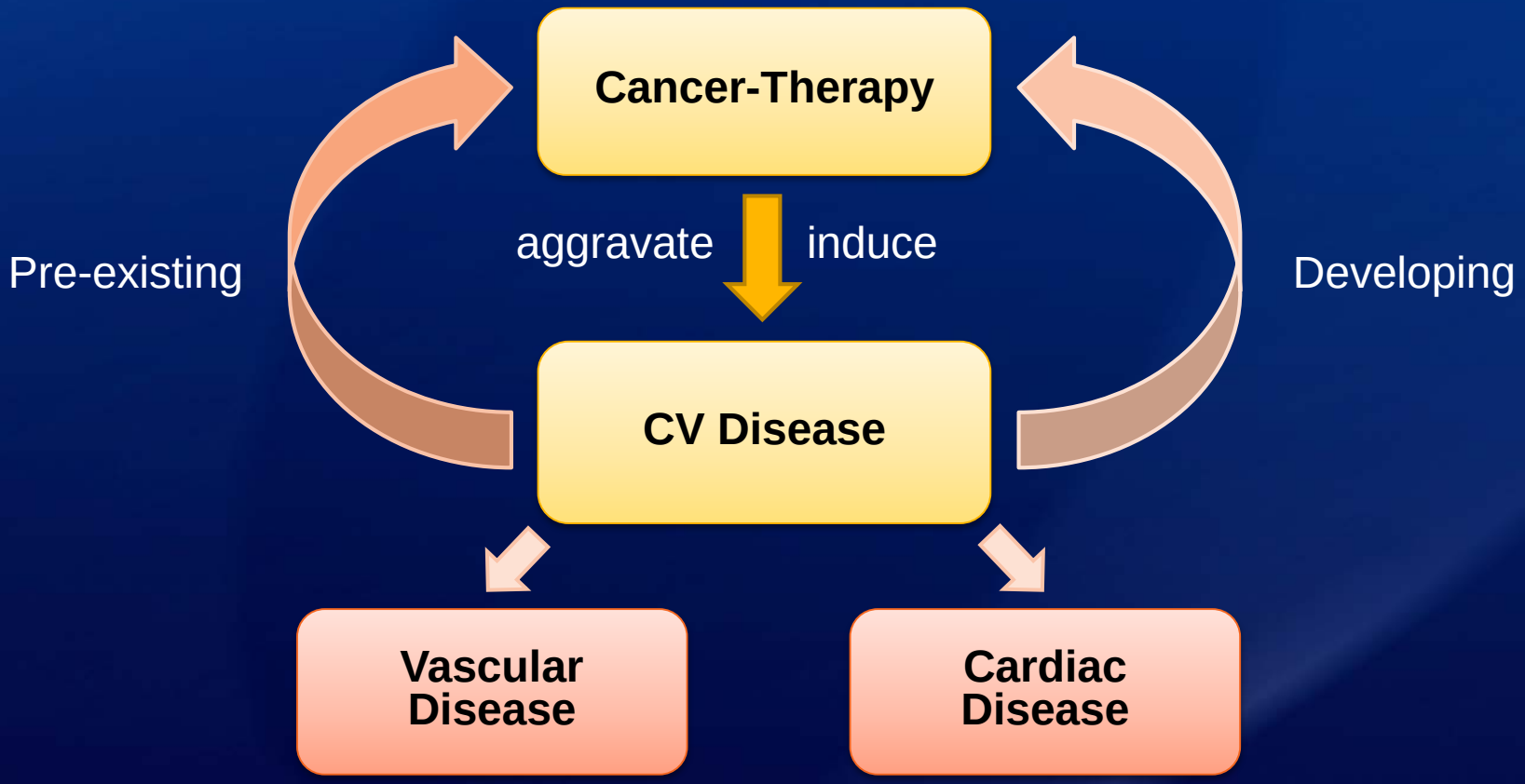
Chemotherapy and Cardiotoxicity



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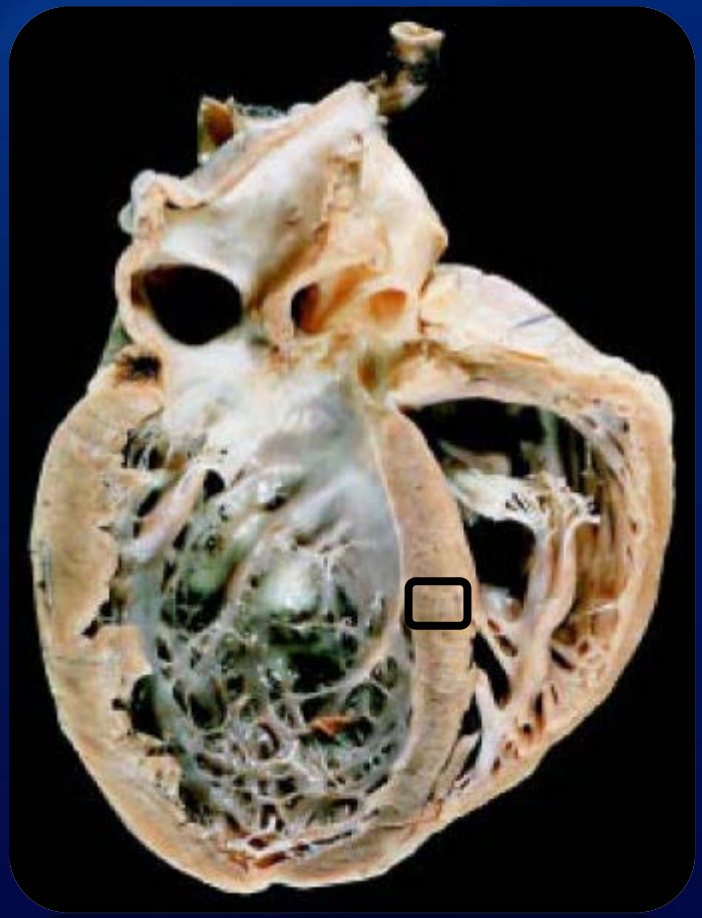
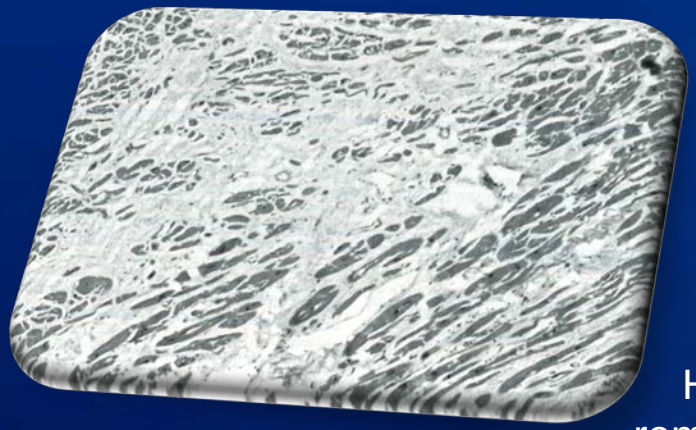
Anthracycline-Induced Cardiotoxicity
Pathology



Dilated Cardiomyopathy



Myocyte loss with replacement fibrosis

Hypertrophy of remaining myocytes

Steinherz et al: Med Ped Oncol 24:352, 1995
Dr. Glacy Sabra Vieria in Arq. Bras. Cardiol. 75, 2000

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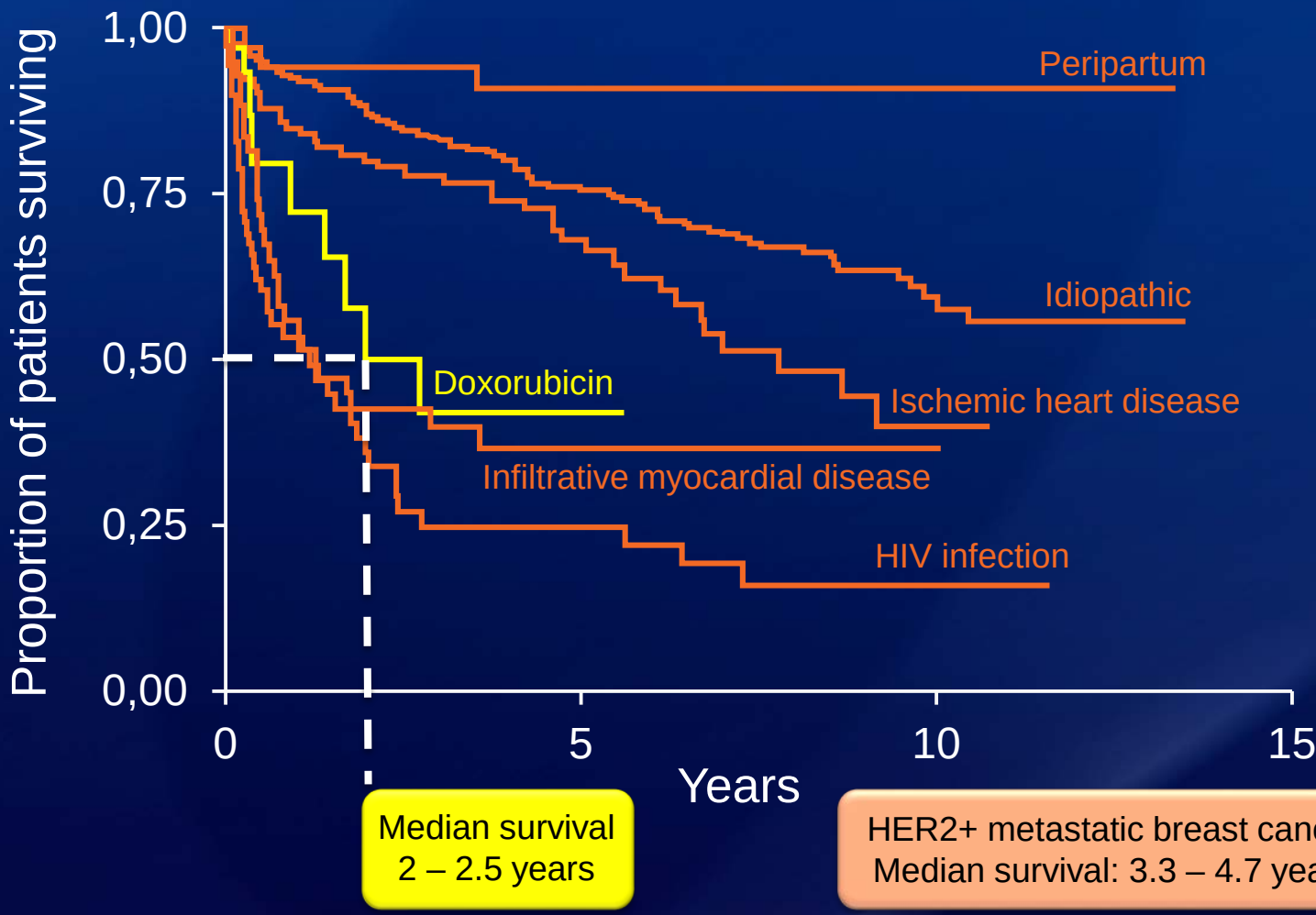
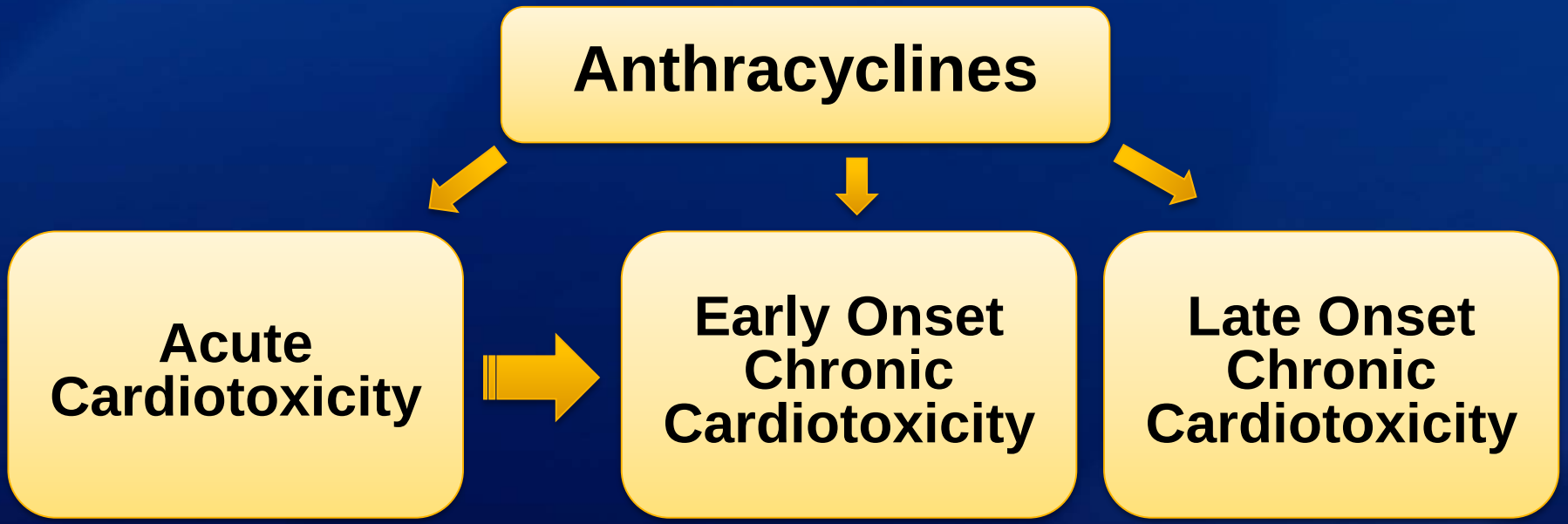
Prognosis
Anthracycline-Induced HF



Felker et al: NEJM 342:1077, 2000

Swain et al: CLEOPATRA NEJM 2015

Anthracycline-Induced Cardiotoxicity (CHF)



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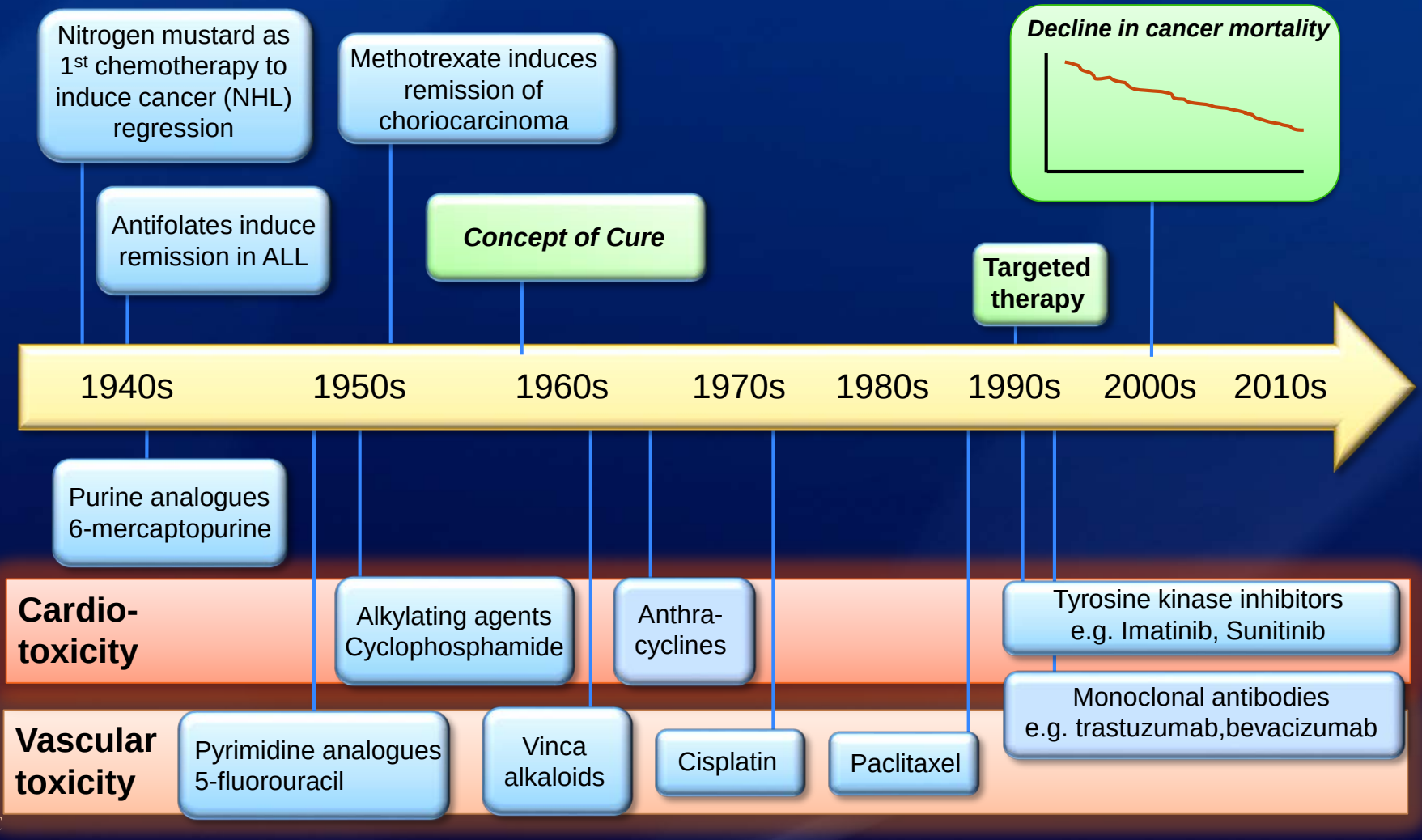
Chemotherapy and Cardiotoxicity



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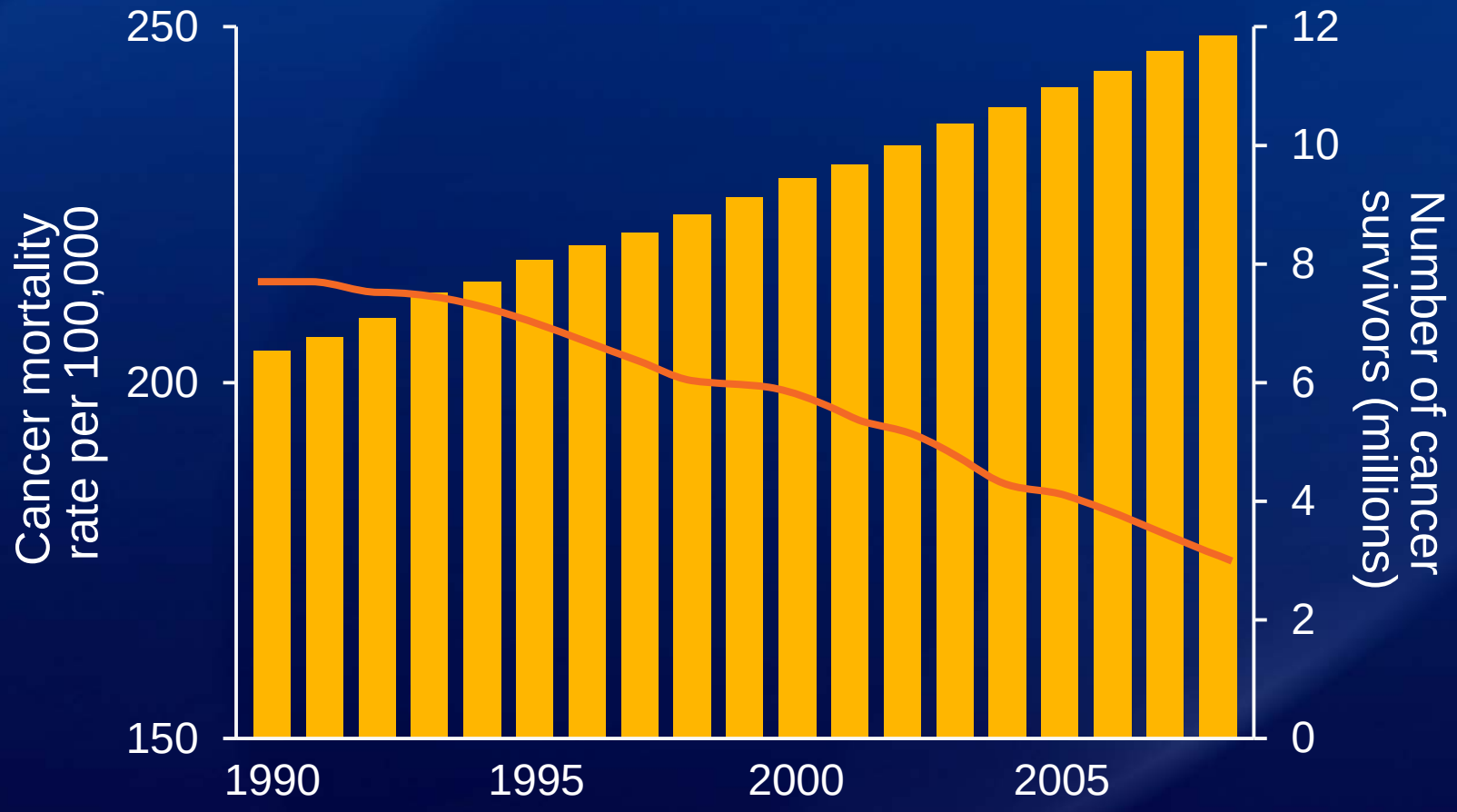
Cancer Statistics USA – 1990-2008

Survivors Increasing, Mortality Decreasing



Data from National Cancer Institute on estimated number of cancer survivors and age-adjusted cancer deaths/100,000 people

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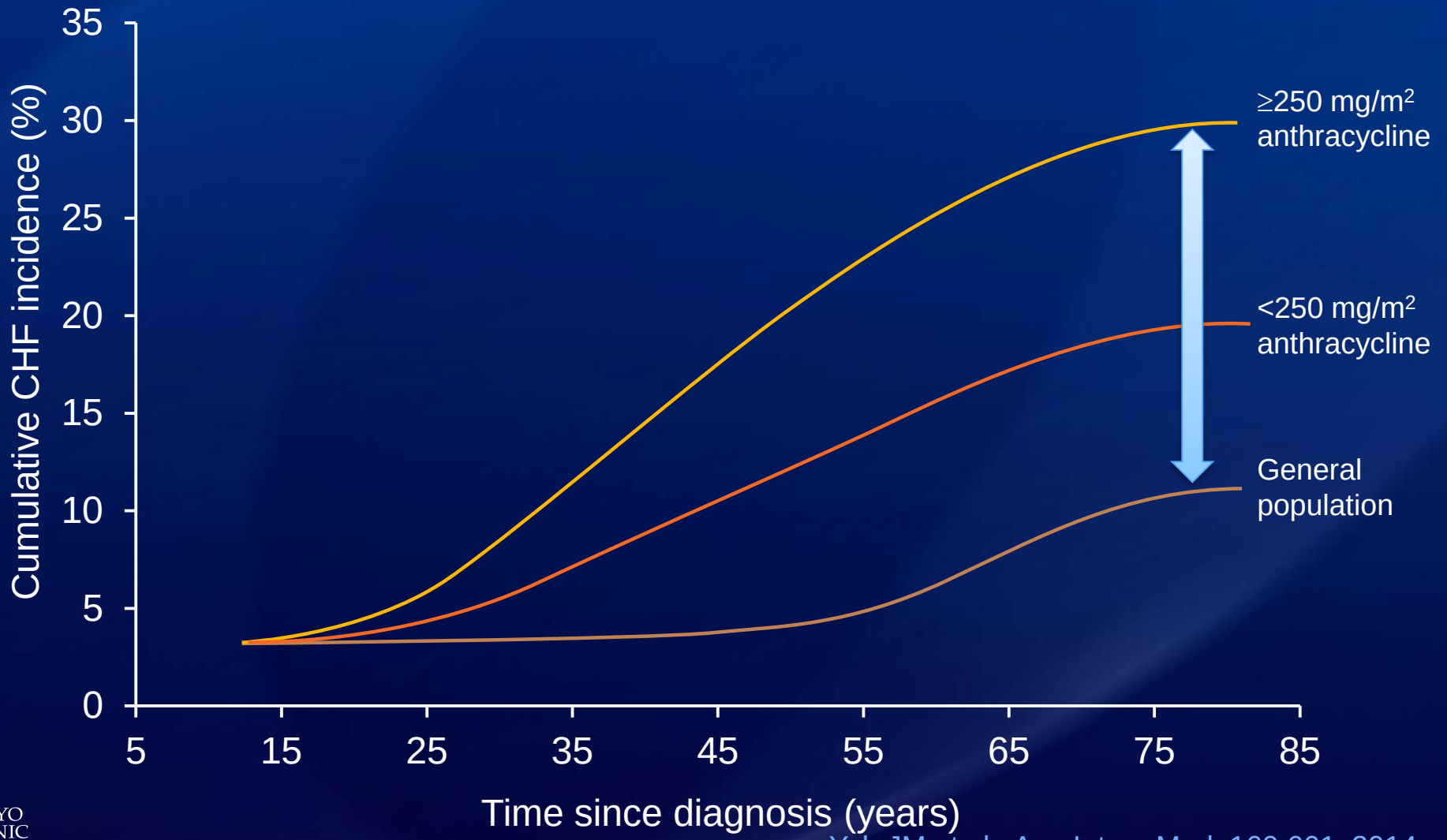
Childhood Cancer Survivors

Congestive Heart Failure – Stage C HF



Yeh JM et al: Ann Intern Med; 160:661, 2014

LIFE, INTERRUPTED

Lost in Transition After Cancer

The New York Times

By SULEIKA JAOUAD MARCH 16, 2015 5:01 PM 191 Comments

Suleika Jaouad, who was 22 when she learned she had leukemia, has been told she is in remission, but said she felt far from healthy at age 26. Ashley Woo

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doi:10.1016/j.jacc.2010.07.023

Heart Failure

Left Ventricular Dysfunction in Patients Receiving Cardiotoxic Cancer Therapies

Are Clinicians Responding Optimally?

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

Stanford, California; and Denver, Colorado

Objectives The purpose of this study was to examine treatment practices for cancer therapy-associated decreased left ventricular ejection fraction (LVEF) detected on echocardiography and whether management was consistent with

trastuzumab treatment. Of these patients, 40% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 51% beta-blocker therapy, and 54% cardiology consultation. Of patients with asymptomatic decreased LVEF, 31% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 35% beta-blocker therapy, and 42% cardiology consultation. Of those with symptomatic decreased LVEF, 67% received angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, 100% beta-blocker therapy, and 89% cardiology consultation.

Conclusions Many cancer survivors are not receiving treatment consistent with heart failure guidelines. There is substantial opportunity for collaboration between oncologists and cardiologists to improve the care of oncology patients receiving cardiotoxic therapy. (J Am Coll Cardiol 2010;56:1644–50) © 2010 by the American College of Cardiology Foundation

Conclusions: Many cancer survivors are not receiving treatment consistent with heart failure guidelines. There is substantial opportunity for collaboration between oncologists and cardiologists to improve the care of oncology patients receiving cardiotoxic therapy.

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The call for “Cardio-Oncology”

DOI: 10.1093/jnci/djp440
Advance Access publication on December 10, 2009.

REVIEW

Cardiotoxicity of Anticancer Drugs: The Need for Cardio-Oncology and Cardio-Oncological Prevention

Adriana Albini, Giuseppina Pennesi, Francesco Donatelli, Rosaria Cammarota, Silvio De Flora, Douglas M. Noonan

Manuscript received April 12, 2009; revised October 9, 2009; accepted November 4, 2009.

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Due to the aging of the populations of developed countries and a common occurrence of risk factors, it is increasingly probable that a patient may have both cancer and cardiovascular disease. In addition, cytotoxic agents and targeted therapies used to treat cancer, including classic chemotherapeutic agents, monoclonal antibodies that target tyrosine kinase receptors, small molecule tyrosine kinase inhibitors, and even antiangiogenic drugs and chemoprevention agents such as cyclooxygenase-2 inhibitors, all affect the cardiovascular system. One of the reasons is that many agents reach targets in the microenvironment and do not affect only the tumor. Combination therapy often amplifies cardiotoxicity, and radiotherapy can also cause heart problems, particularly when combined with chemotherapy. In the past, cardiotoxic risk was less evident, but it is increasingly an issue, particularly with combination therapy and adjuvant therapy. Today’s oncologists must be fully aware of cardiovascular risks to avoid or prevent adverse cardiovascular effects, and cardiologists must now be ready to assist oncologists by performing evaluations relevant to the choice of therapy. There is a need for cooperation between these two areas and for the development of a novel discipline, which could be termed cardio-oncology or onco-cardiology. Here, we summarize the potential cardiovascular toxicities for a range of cancer chemotherapeutic and chemopreventive agents and emphasize the importance of evaluating cardiovascular risk when patients enter into trials and the need to develop guidelines that include collateral effects on the cardiovascular system. We also discuss mechanistic pathways and describe several potential protective agents that could be administered to patients with occult or overt risk for cardiovascular complications.

J Natl Cancer Inst 2010;102:14–25

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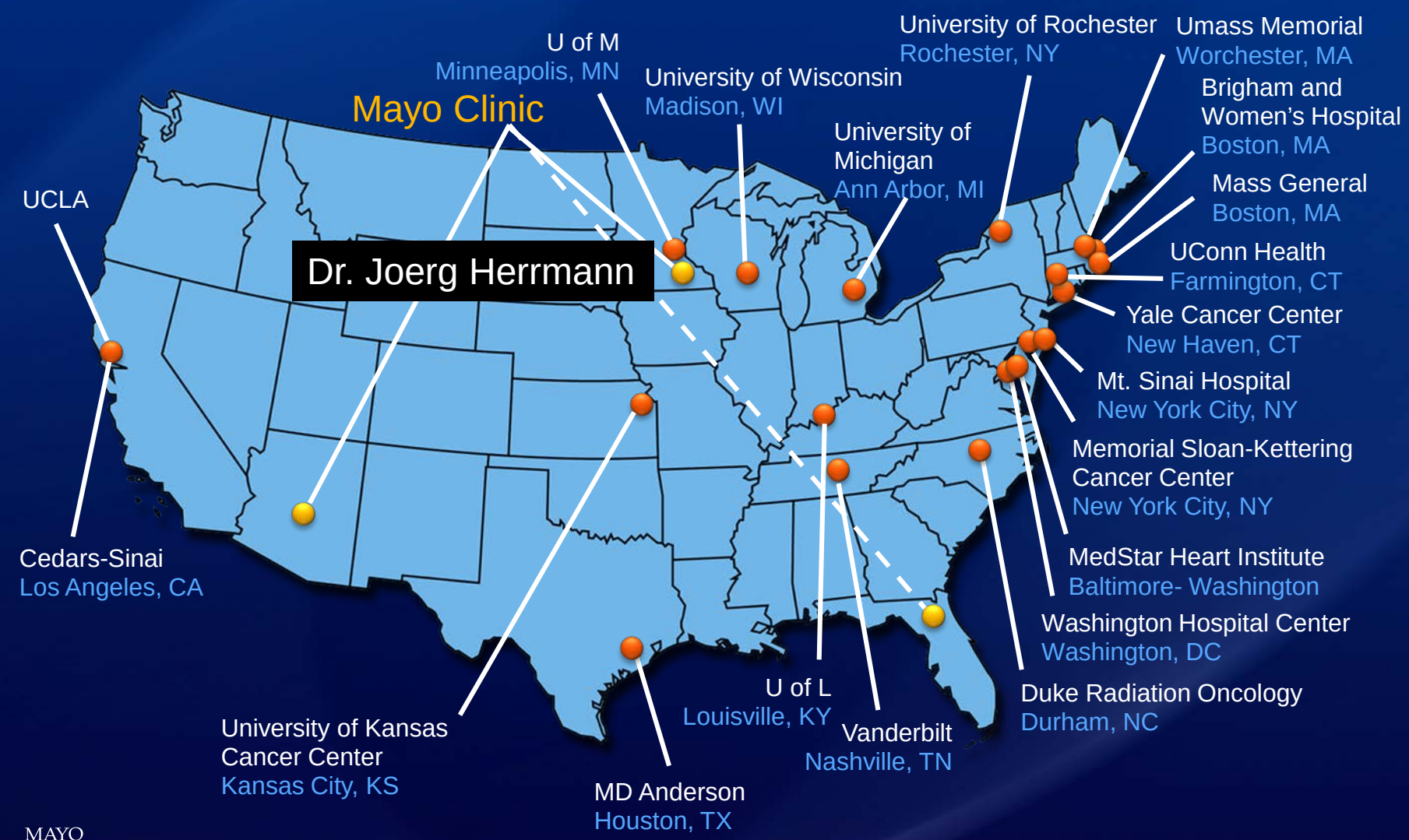
U.S. Cardio-Oncology Centers – 2015



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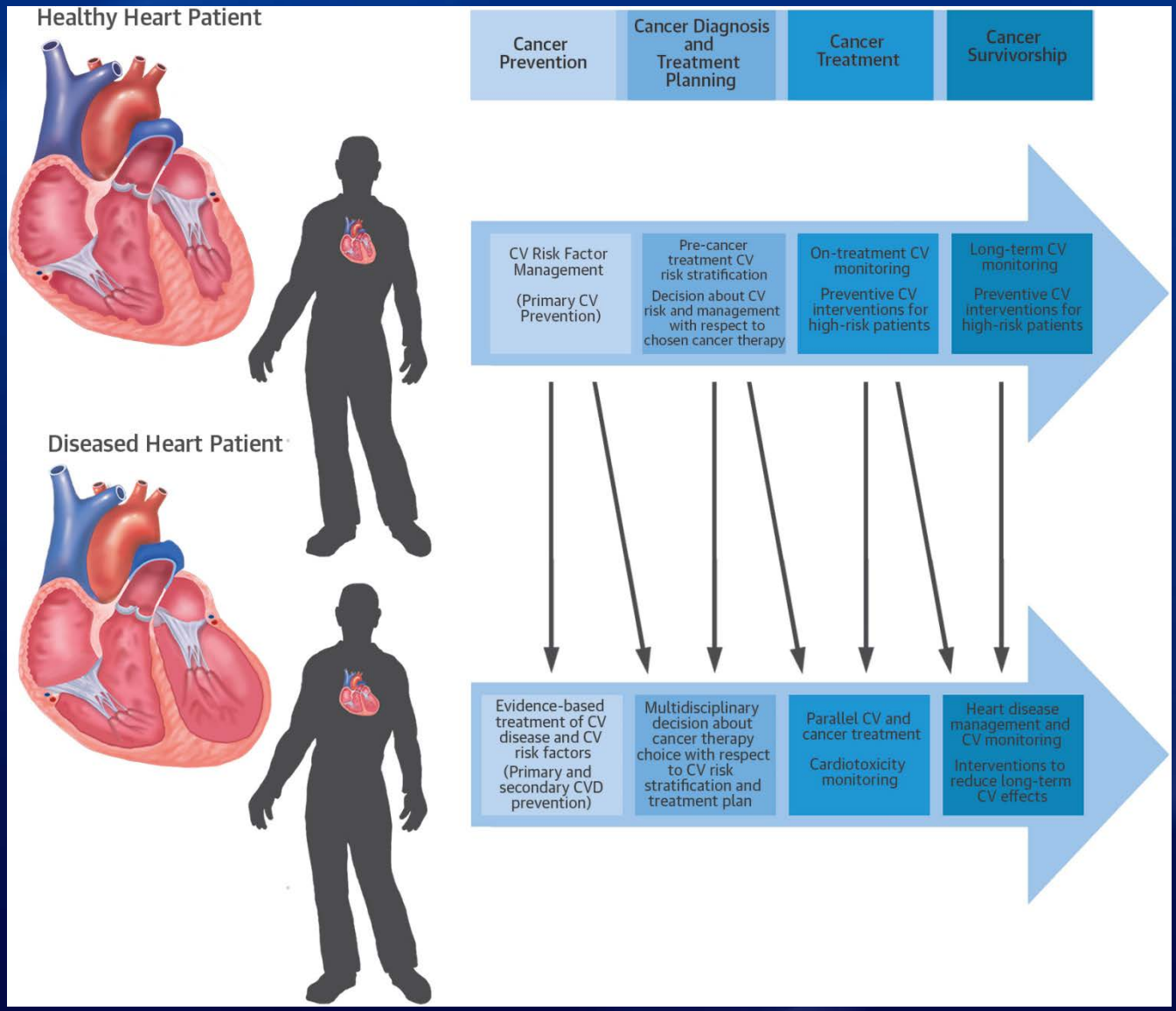
Continuum of CV Care in Cardio-Oncology



Barac A et al JACC 2015;65(25):2739–2746

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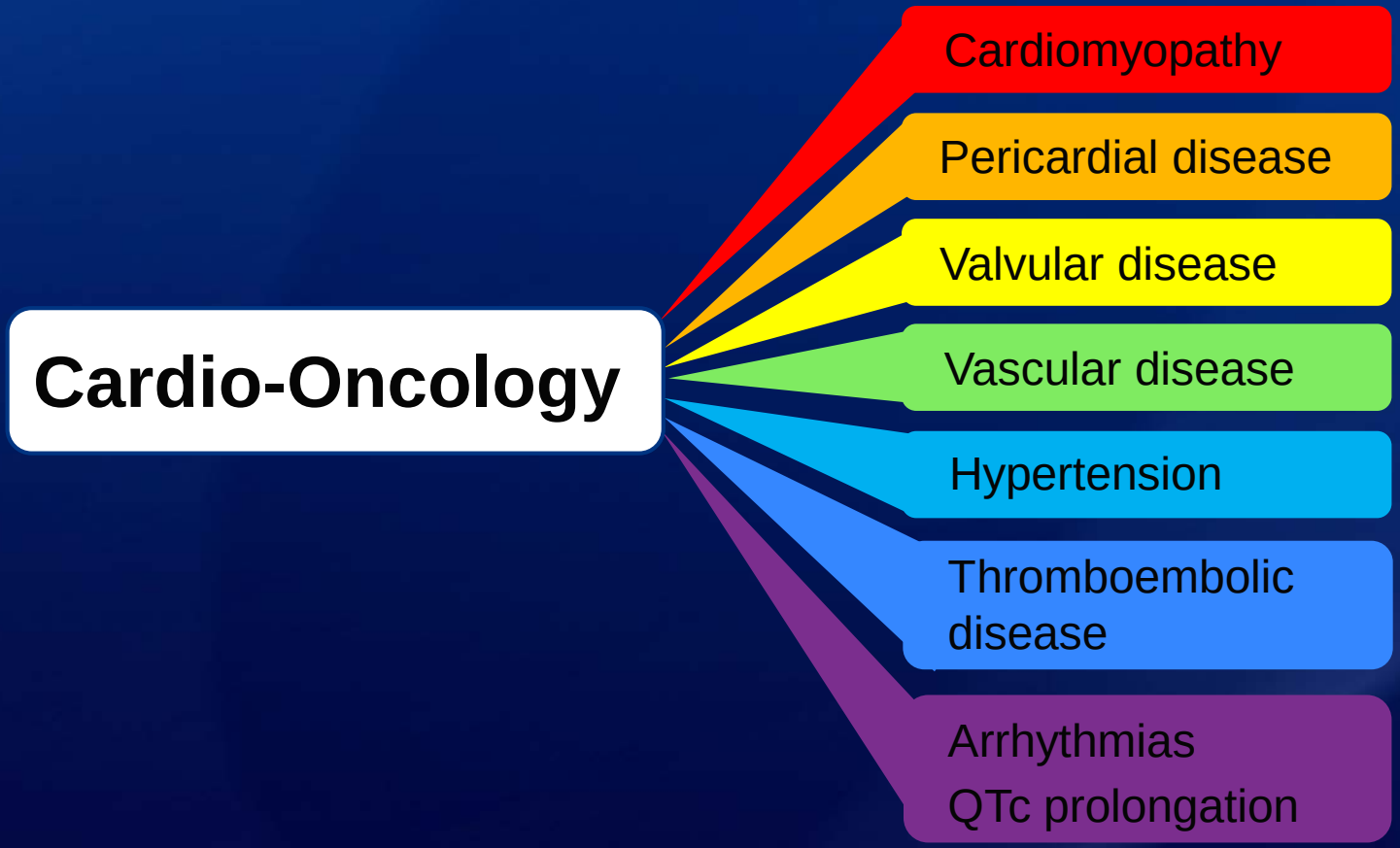
The Spectrum of Cardio-Oncology



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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]

In many cases, early-stage breast cancer is now curable, and metastatic disease can be chronic consequent to the advent of new therapeutic tools. Unfortunately, some treatments have been associated with adverse cardiovascular effects. Indeed, in many breast cancer survivors, the risk of cardiovascular disease is higher than the risk of cancer recurrence. The clinical challenge of preventing cardiovascular complications in patients undergoing antineoplastic treatment has two aims, more effective life-saving treatment of patients, and prevention of morbidity and cardiovascular mortality in the short term and long term. The aim of the present study is to review the rapidly evolving therapeutic strategies designed to treat early-stage breast cancer. The review highlights the need for more data on the impact of new biological drugs (targeted therapy) on the cardiovascular apparatus. Finally, given the complexity of targeted and other novel treatments, cancer patients are best managed through a multidisciplinary approach. *J Cardiovasc Med* **11:861–868**

Journal of Cardiovascular Medicine 2010, 11:861–868

Keywords: breast cancer, cardiac insufficiency, cardiotoxicity, target therapy

[a]Cardiology Division Institute, INT 'Fondazione G. Pascale', [b]Department of Colorectal Oncology and [c]Department of Senology, National Cancer Institute G. Pascale Foundation, Naples, Italy

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Received 25 August 2009 **Revised** 25 November 2009
Accepted 15 December 2009

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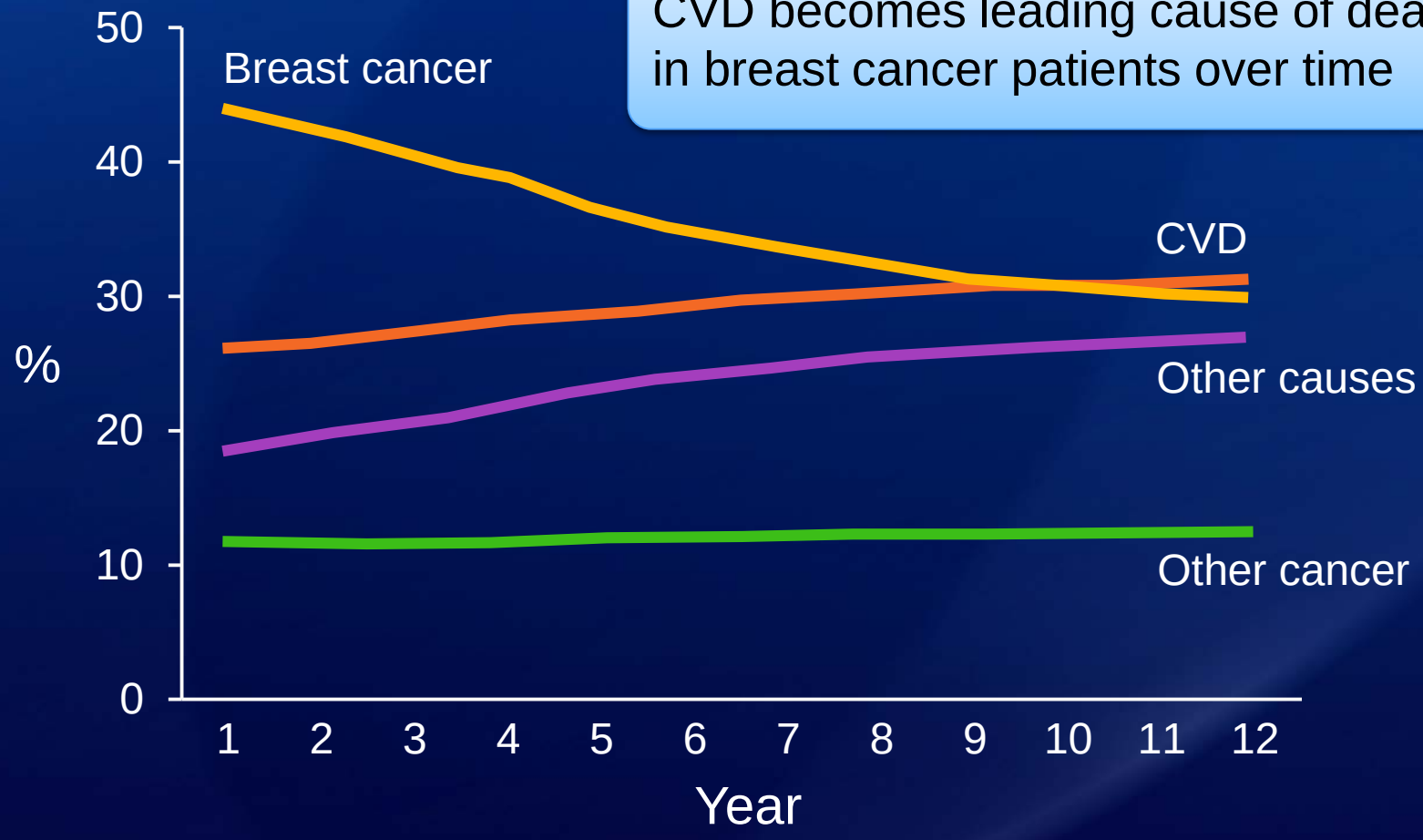
Breast Cancer Patients
Cause of Death

CVD becomes leading cause of death in breast cancer patients over time



Patnaik JL et al: Breast Cancer Res 13:R64, 2011

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The New England
Journal of Medicine

VOLUME 344 MARCH 15, 2001 NUMBER 11

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

DENNIS J. SLAMON, M.D., PH.D., BRIAN LEYLAND-JONES, M.D., STEVEN SHAK, M.D., HANK FUCHS, M.D., VIRGINIA PATON, PHARM.D., ALEX BAJAMONDE, PH.D., THOMAS FLEMING, PH.D., WOLFGANG EIERMANN, M.D.,

ABSTRACT

Background growth fact is overexpre increasing t

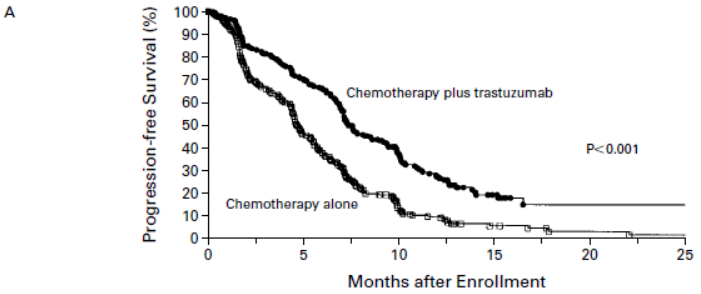
Methods trastuzumab against HER cer that over 234 patients and 235 pat plus trastuzu ceived adju thracycline v cin in the ca with (143 wo en). Patients anthracyclin women) or (

Results T apy was ass gression (me er rate of obj P<0.001), a vs. 6.1 month (22 percent (median sur a 20 percent important a which occur anthracycline, cyclophosphamide, and trastuzumab), 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management.

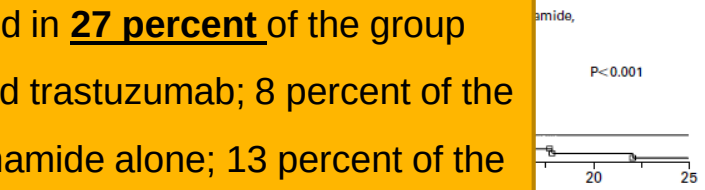
Conclusions Trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2. (N Engl J Med 2001; 344:783-92.)

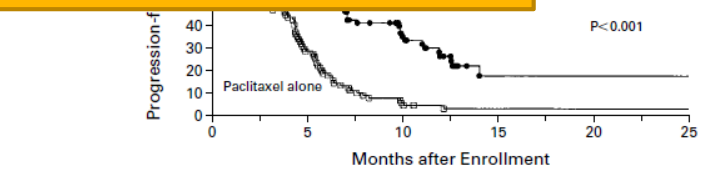
From the Division of Hematology and Oncology, UCLA School of Medicine, Los Angeles (D.J.S., M.P.); the Department of Oncology, McGill University, Montreal (B.L.-J.); Medical Affairs, Genentech, South San Francisco, Calif. (S.S., V.P., A.B.); IntraBiotics, Mountain View, Calif. (H.F.); the Department of Biostatistics, University of Washington, Seattle (T.F.); the Department of Obstetrics and Gynecology, Frauenklinik vom Roten Kreuz, Munich, Germany (W.E.); the Department of Oncology, Rush–Presbyterian–St. Luke's Medical Center, Chicago (J.W.); the Department of Oncology, Hospital General Universitari Vall d'Hebron, Barcelona, Spain (J.B.); and the Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York (L.N.). Address reprint requests to Dr. Slamon at UCLA School of Medicine, Division of Hematology/Oncology, 11-244 Factor Bldg., 10833 Le Conte, Los Angeles, CA 90095-1678, or at dslamon@mednet.ucla.edu.

*Additional study investigators are listed in the Appendix.



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





No. at Risk			
Paclitaxel and trastuzumab	92	54	23
Paclitaxel alone	96	26	5

The **most important adverse event** was **cardiac dysfunction** of New York Heart Association class III or IV, which occurred in **27 percent** of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was **potentially severe and, in some cases, life-threatening**, the symptoms generally improved with standard medical management.

Chemotherapy-Induced Cardiotoxicity
Type I vs. Type II

	Type I (damage)	Type II (dysfunction)
Prototype	Doxorubicin	Trastuzumab
Ultrastructure	vacuoles, necrosis microfibrillar disarray	no abnormalities
Mechanism	Oxidative injury mitochondrial function ↓ altered calcium homeostasis altered cardiac gene expression apoptosis of cardiomyocytes	ErbB2 signaling inhibition

Ewer, Lippman J Clin Oncol 2005;23:2900-2

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Radiation Rx and Cardiac Disease:
Hodgkin's Lymphoma Rx'd w/ mediastinal irradiation

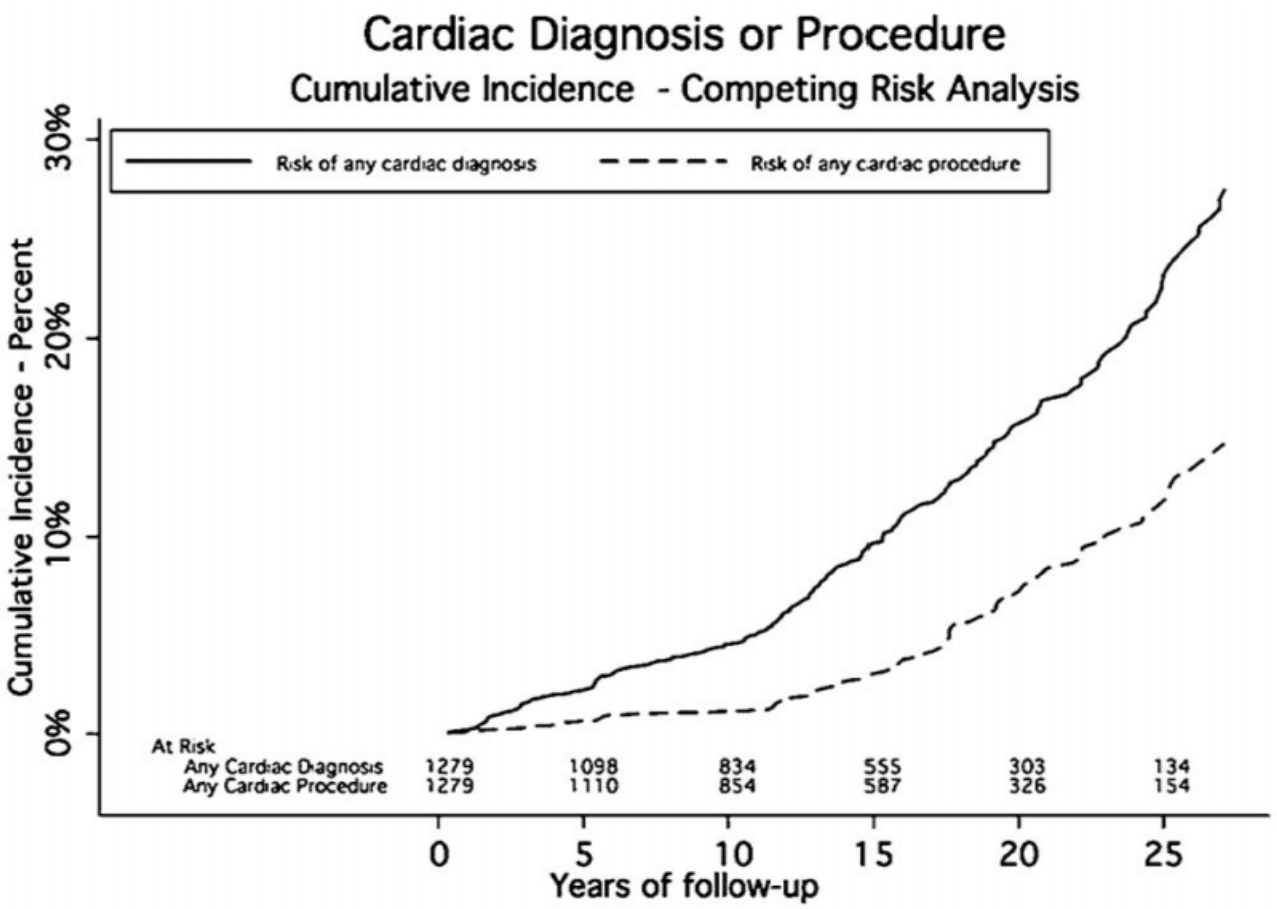


Figure 1. Cumulative incidence rates of any cardiac diagnosis or procedure.

Galper SL et al., Blood 117 (2): 415 2011

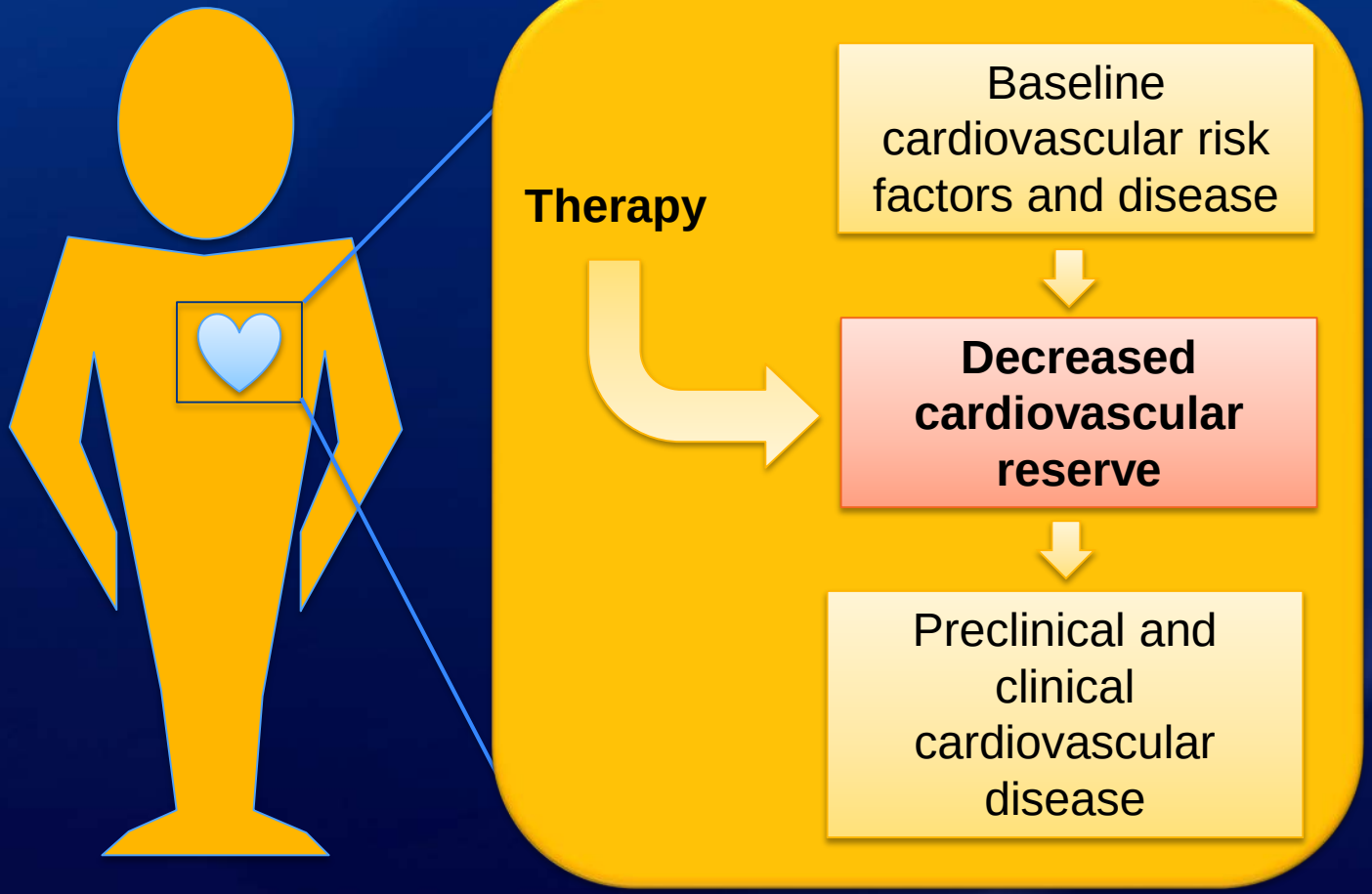
Radiation Effects on the Heart

Tissue Involved	Clinical Presentation	Histology
Pericardium	Acute Pericarditis, Chronic effusion Constrictive Pericarditis	Fibrous thickening of the pericardium , collagen & fibrin deposition on the mesothelial surfaces
Conduction system	Heart block	Fibrosis of the conduction system
Vessels	Premature CAD, Myocardial infarction Asymptomatic CAD, vessel occlusion	Intimal proliferation of fibrous tissue, Media destroyed with adventitia markedly thickened and fibrotic
Valves	Valvular Disease (Stenosis / Regurgitation)	Leaflets /Cusps fibrosis, calcification, thickening
Myocardium	Myocarditis, CMP, CHF. Diastolic dysfunction	Increased collagen, ***Type 1, Interstitial fibrosis, Myocardial perfusion defects

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

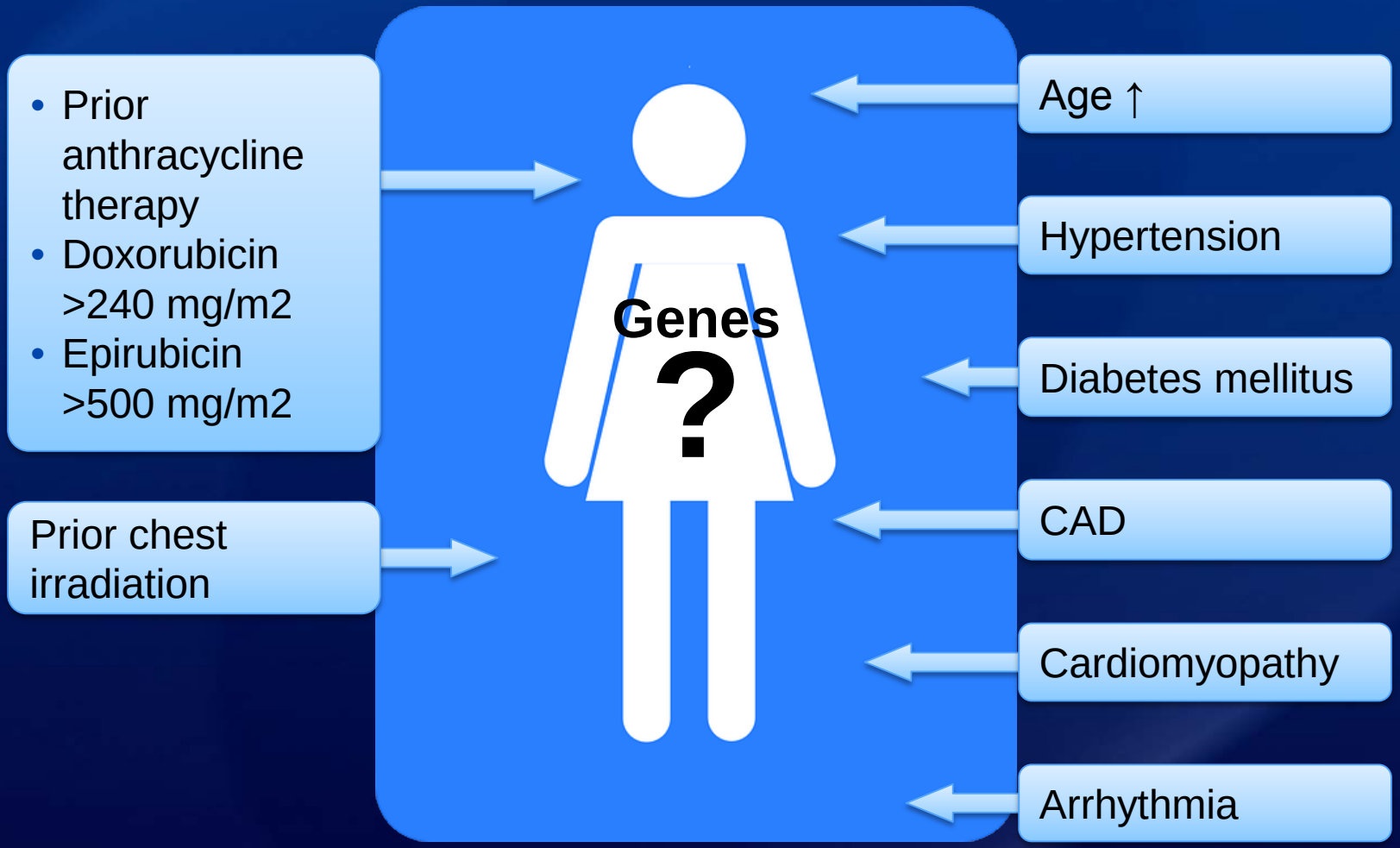
Courtesy of Dr. J Banchs, MD Anderson

Cancer Therapy and CVD
Significance of the Cardiovascular Reserve



Herrmann J, Lerman A. Trends Cardiovasc Med 2014

Trastuzumab Cardiotoxicity
Clinical Predictors



Martin et al: The Oncologist 14:1, 2009
Ewer and Ewer: Na. Rev Cardiol 7,564, 2010

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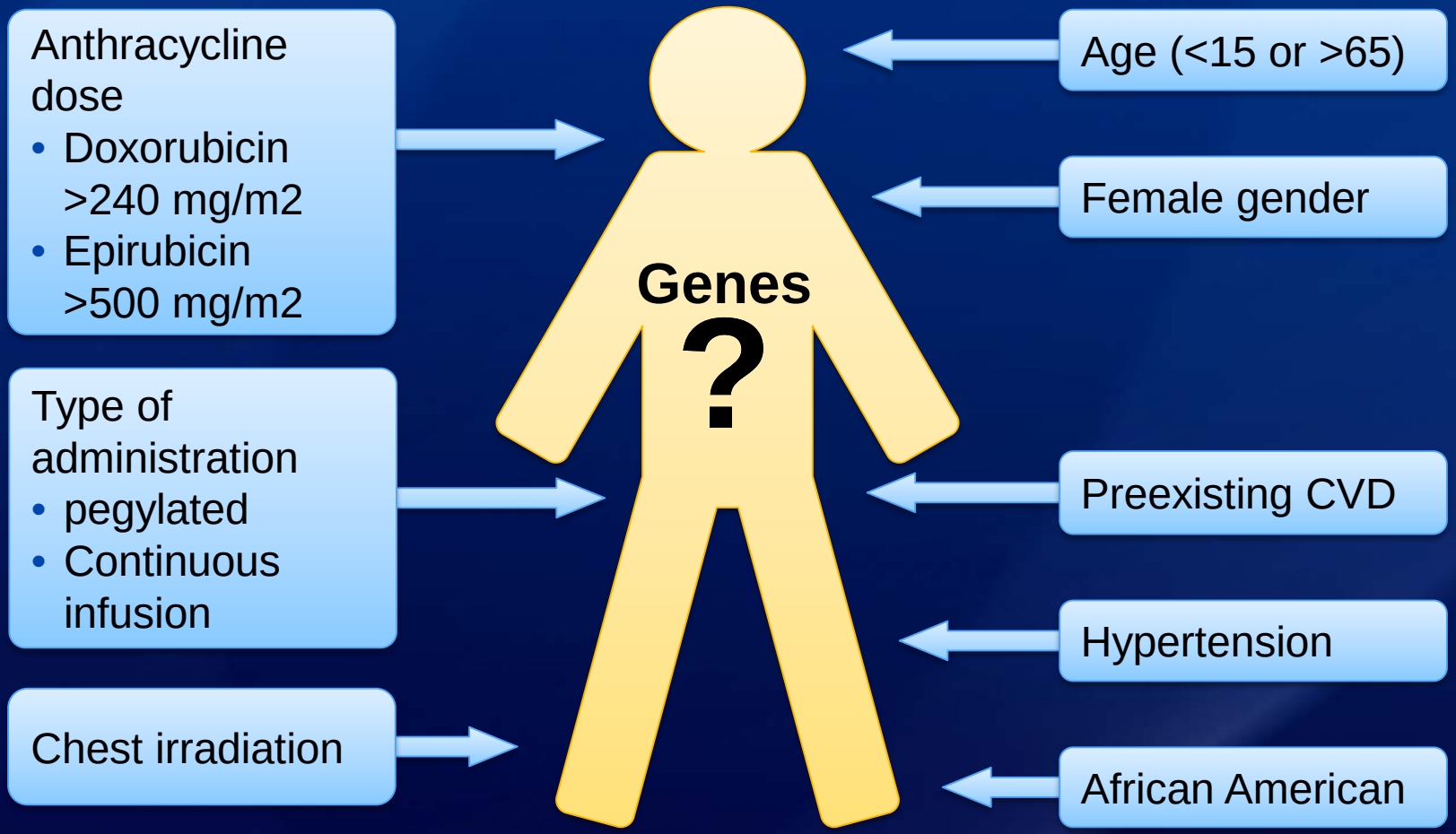
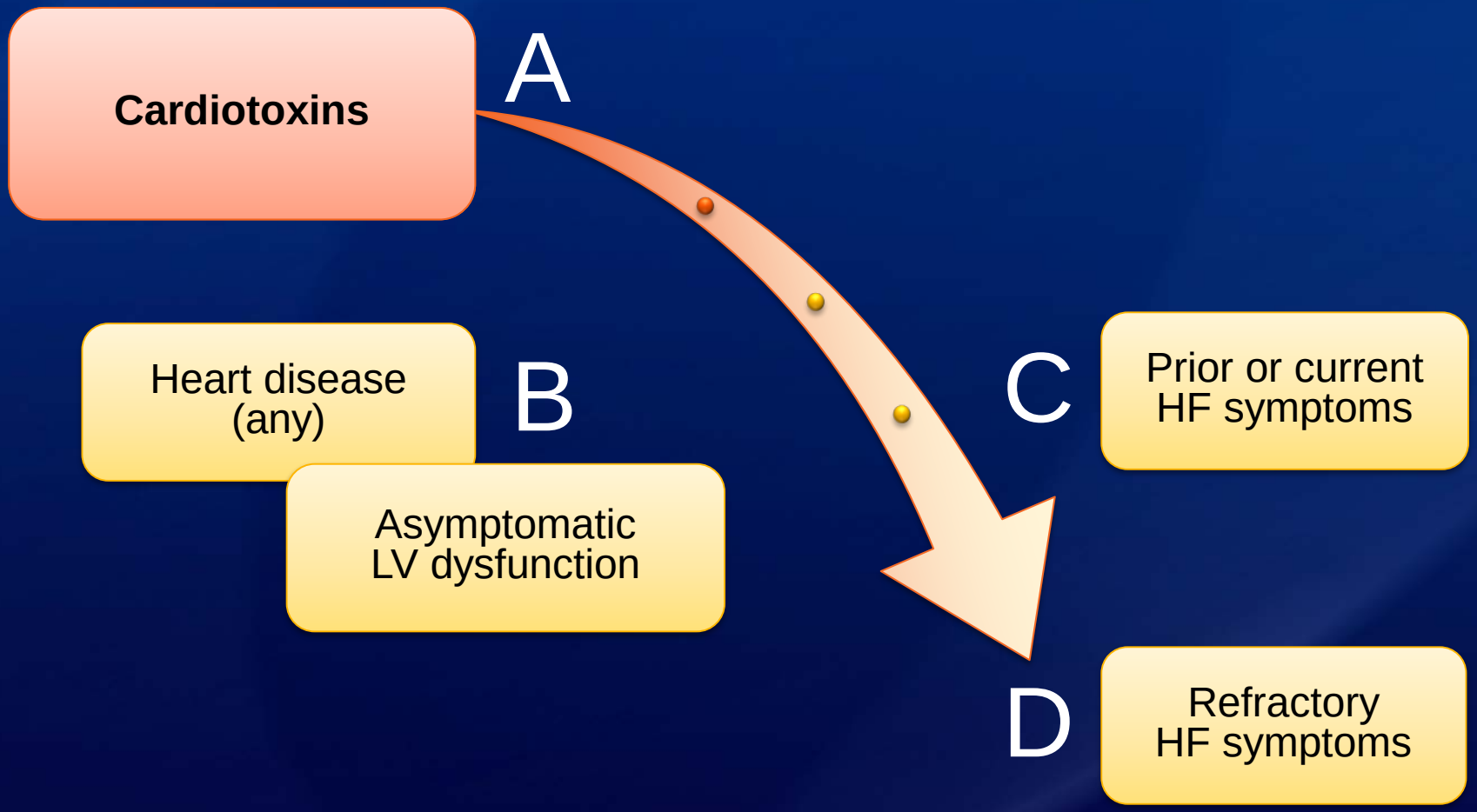
Anthracycline Cardiotoxicity
Clinical Predictors



Ewer MS and Ewer SM. Nat. Rev. Cardiol. 2010; 7,564–75

Chemotherapy-induced Cardiotoxicity
Progression Through the Heart Failure Stages



2013 ACCF/AHA Guideline for Management of Heart Failure

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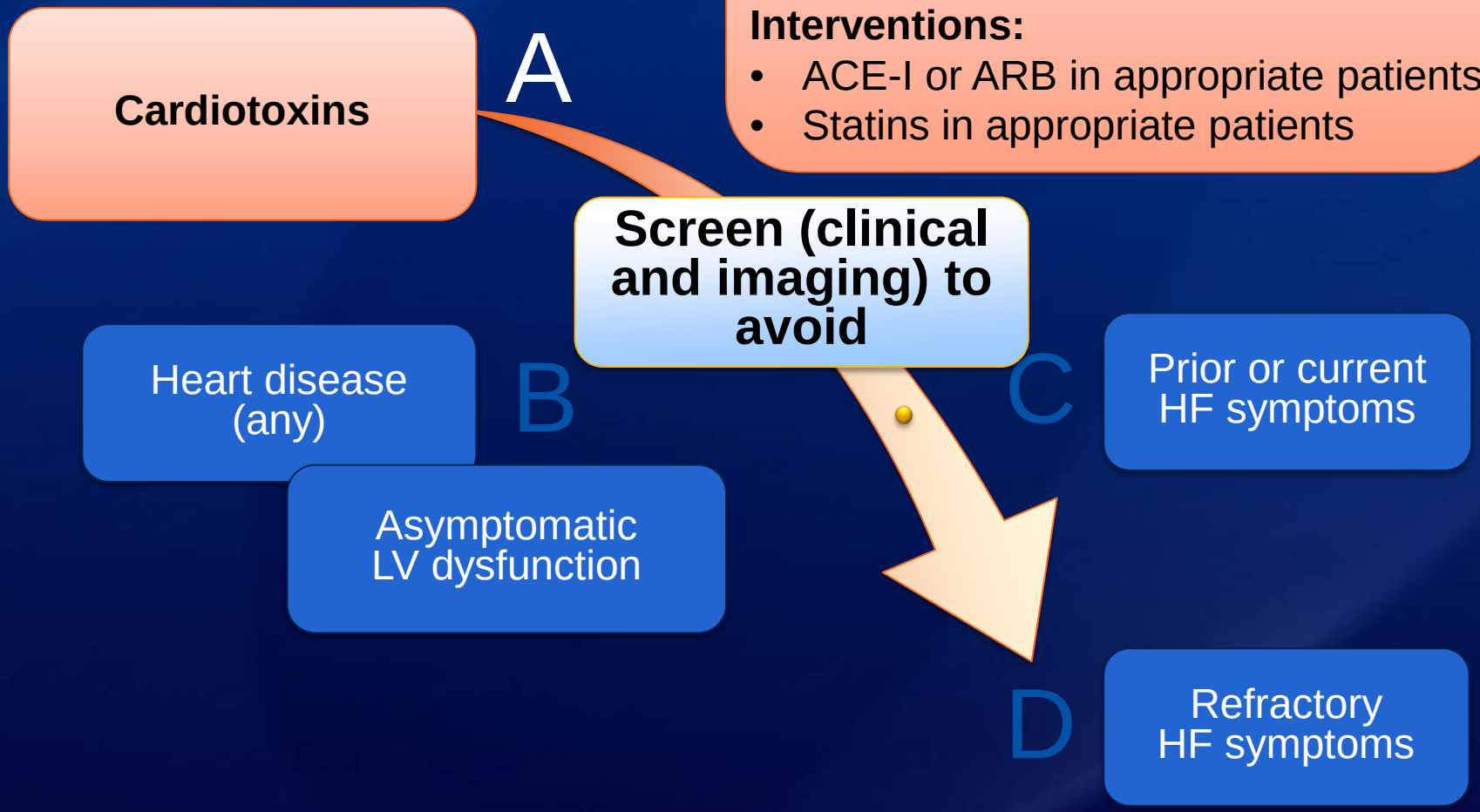
How to Respond?
Predict and Prevent

Goals:
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Interventions:
- ACE-I or ARB in appropriate patients
- Statins in appropriate patients



2013 ACCF/AHA Guideline for Management of Heart Failure

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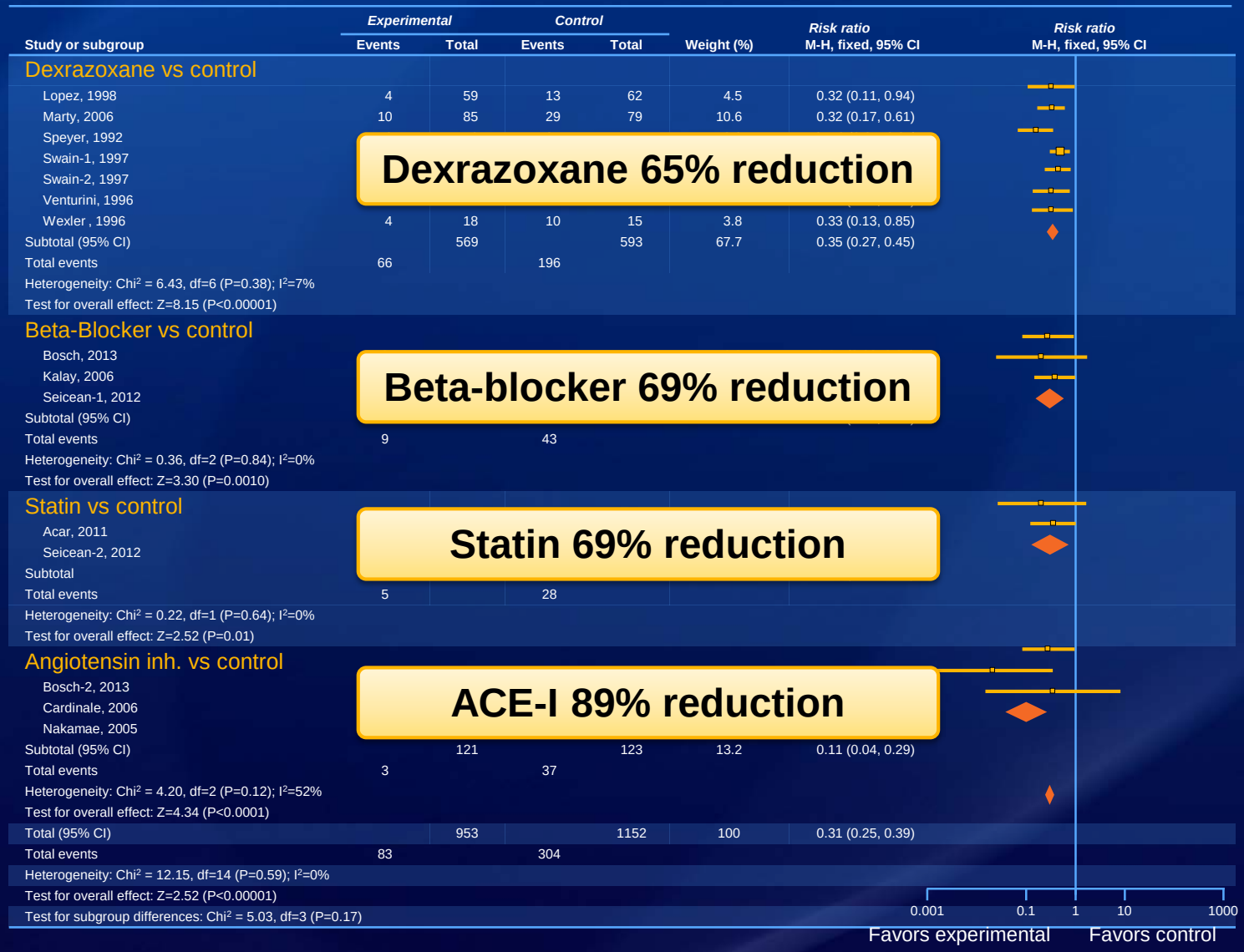
Cardiotoxicity Prevention

Stratified by Prophylactic Drug Group



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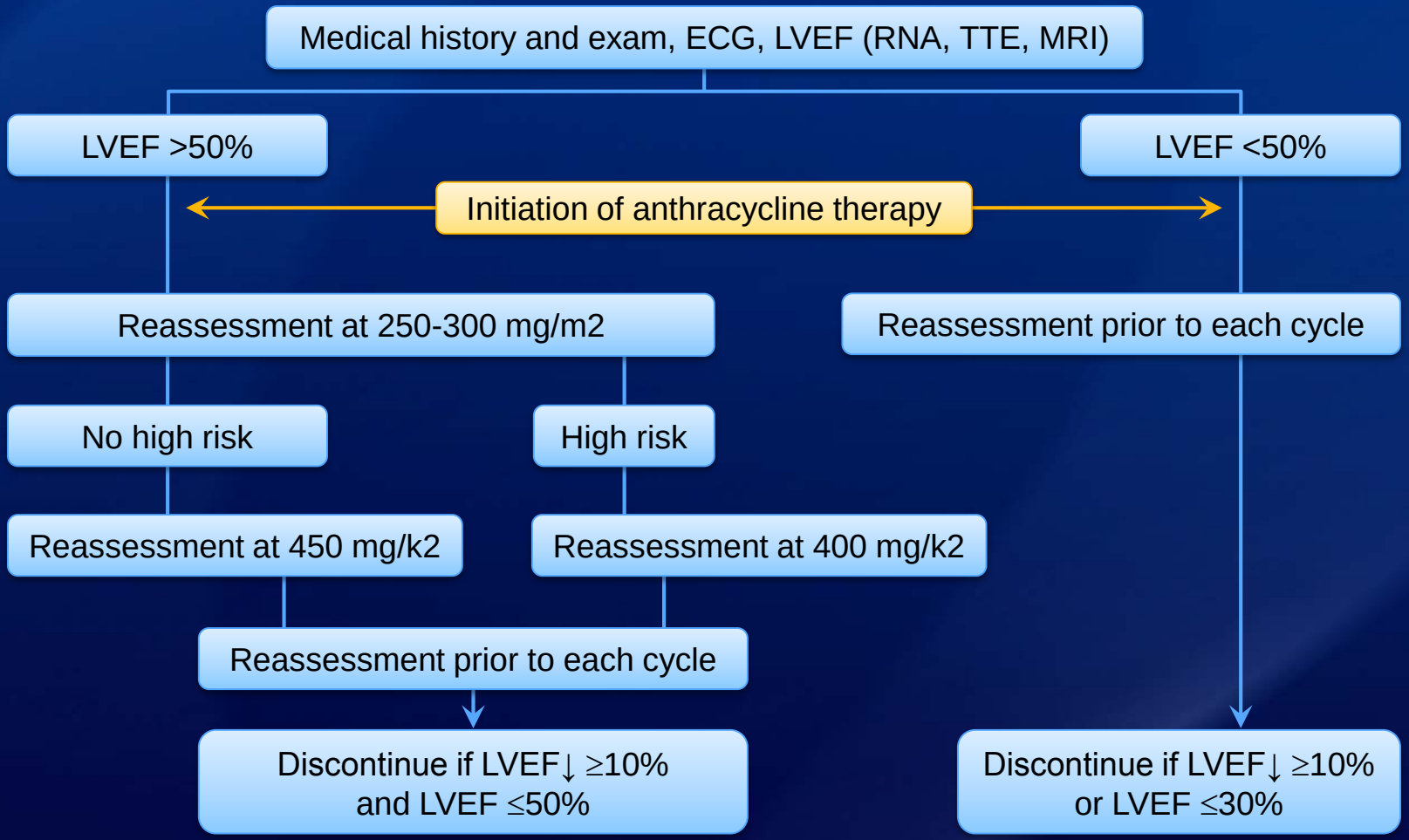
Management Algorithm
Anthracyclines



Herrmann J et al. Mayo Clin Proc. 2014;89:1287-306

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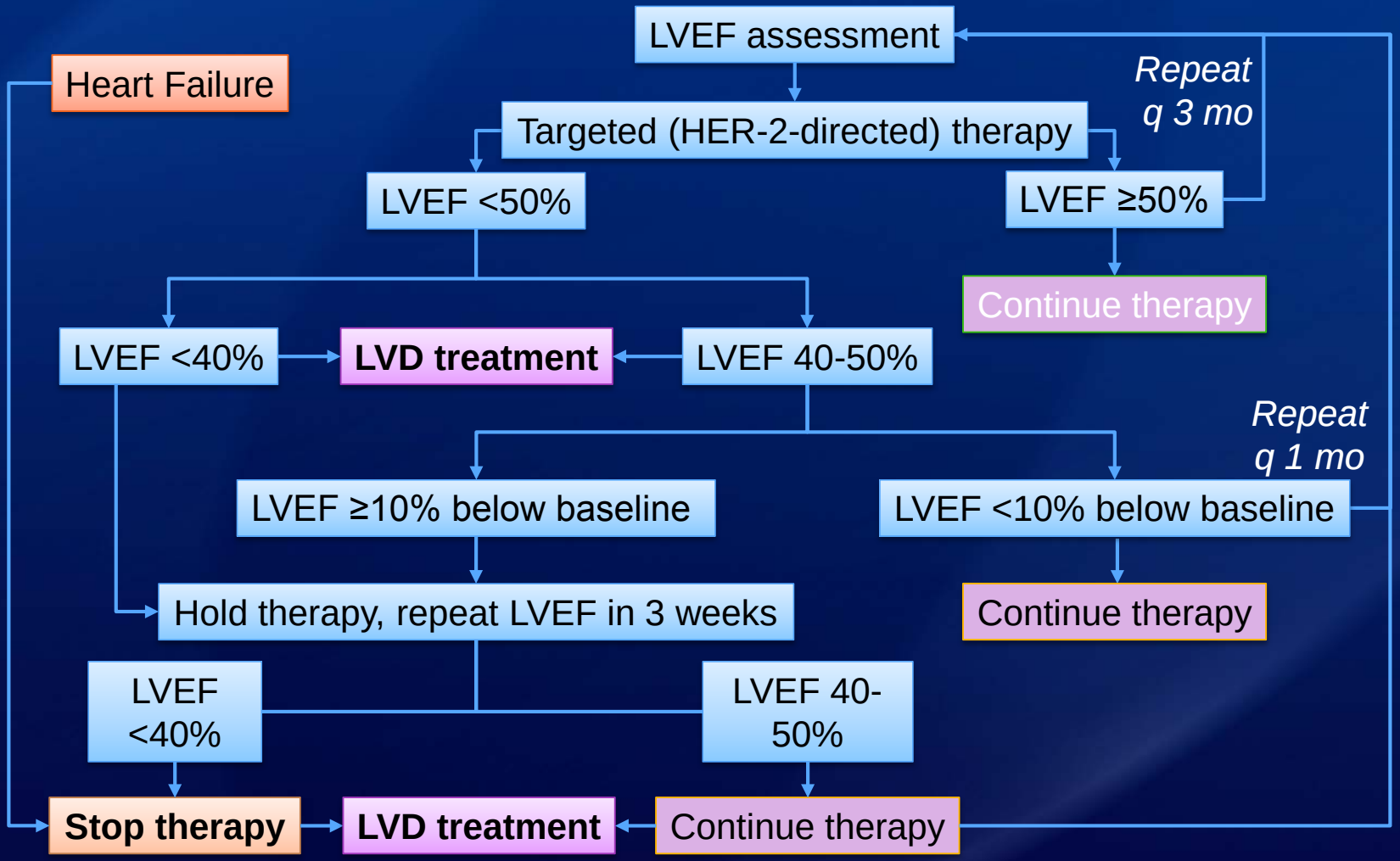
Management Algorithm
Trastuzumab



Modified from Curigliano G. et al: Ann Oncol 2012:23 (Suppl. 7): vii155-vii166
ESMO Guidelines

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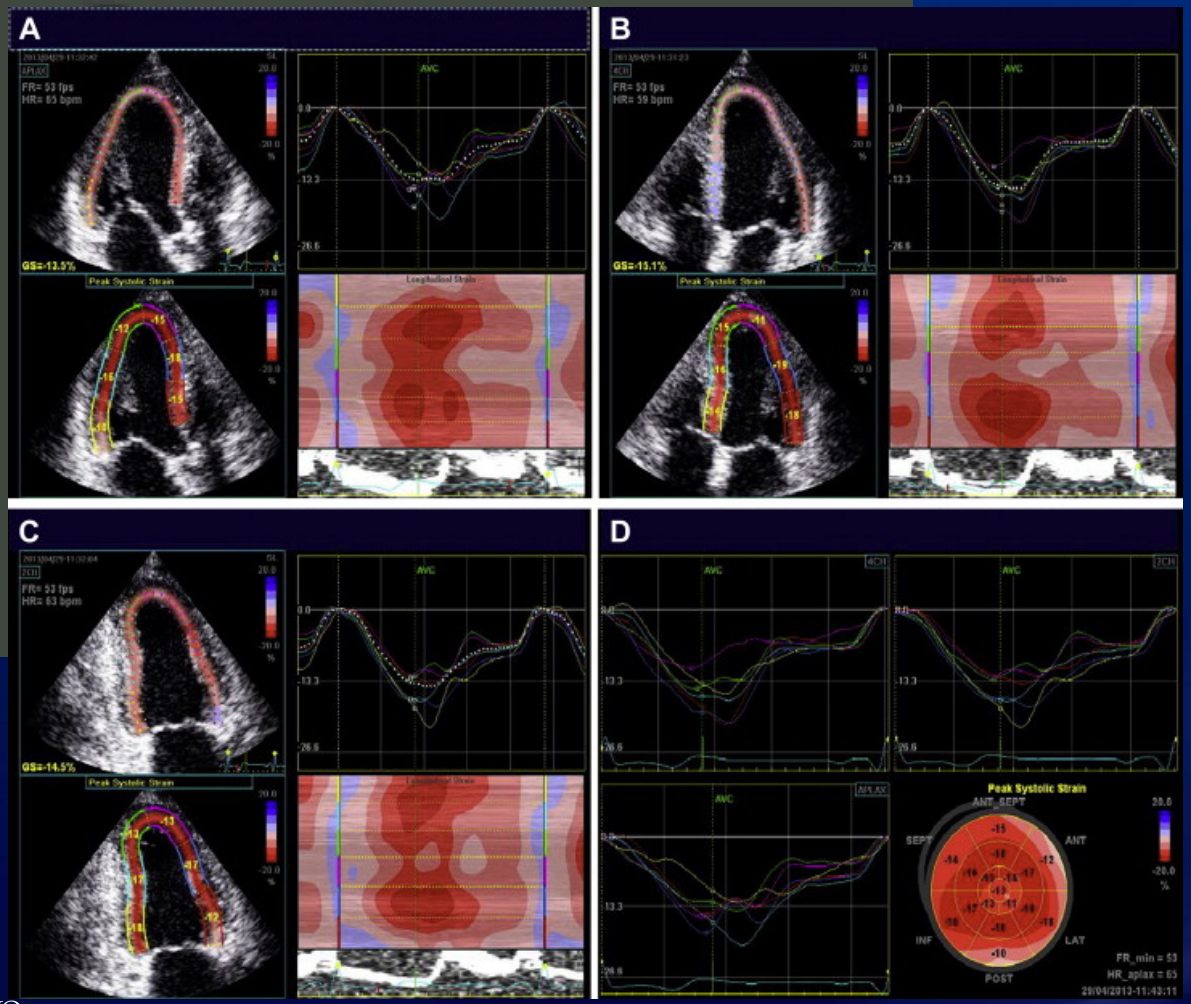
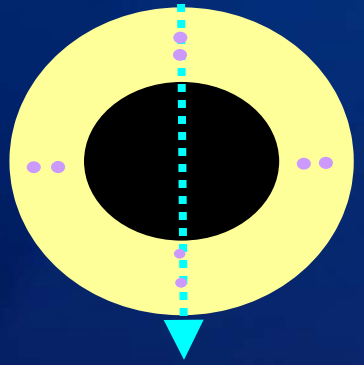
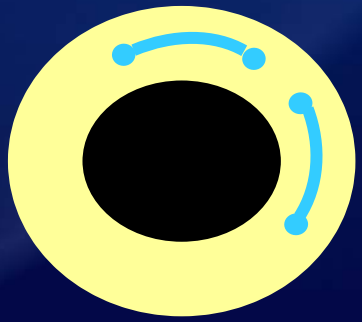
Echo Strain Imaging:
a more sensitive detector of LV dysfunction





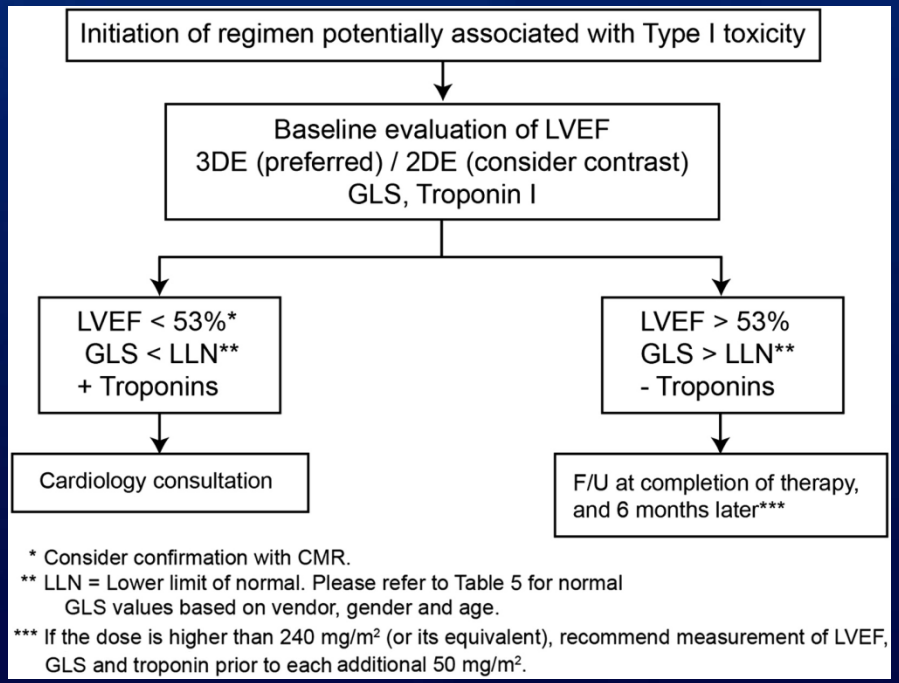


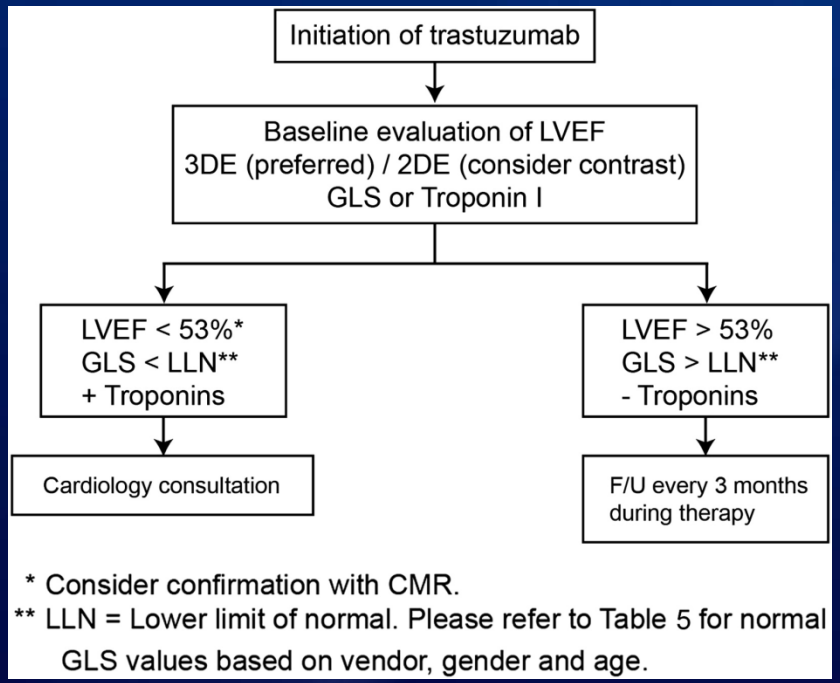
Courtesy of Drs. Chinami Miyazaki , Fletcher Miller, and Jae Oh

Plana JC et al: Am Soc Echocardiogr. 2014 Sep;27(9):911-39

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging





Plana JC et al: Am Soc Echocardiogr. 2014 Sep;27(9):911-39
Eur Heart J Cardiovasc Imaging. 2014 Oct;15(10):1063-93

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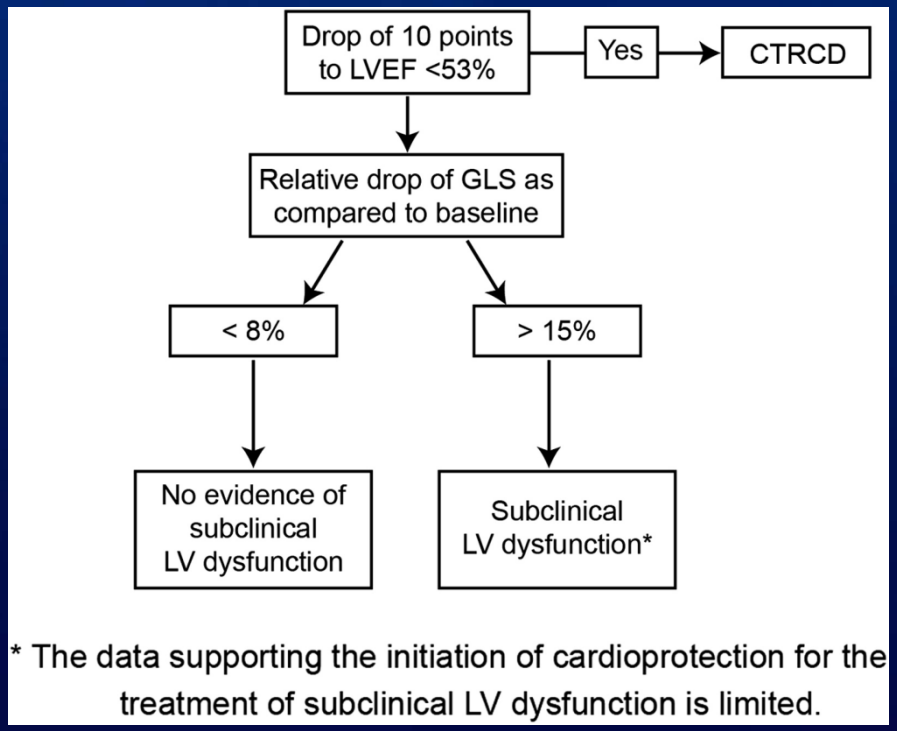

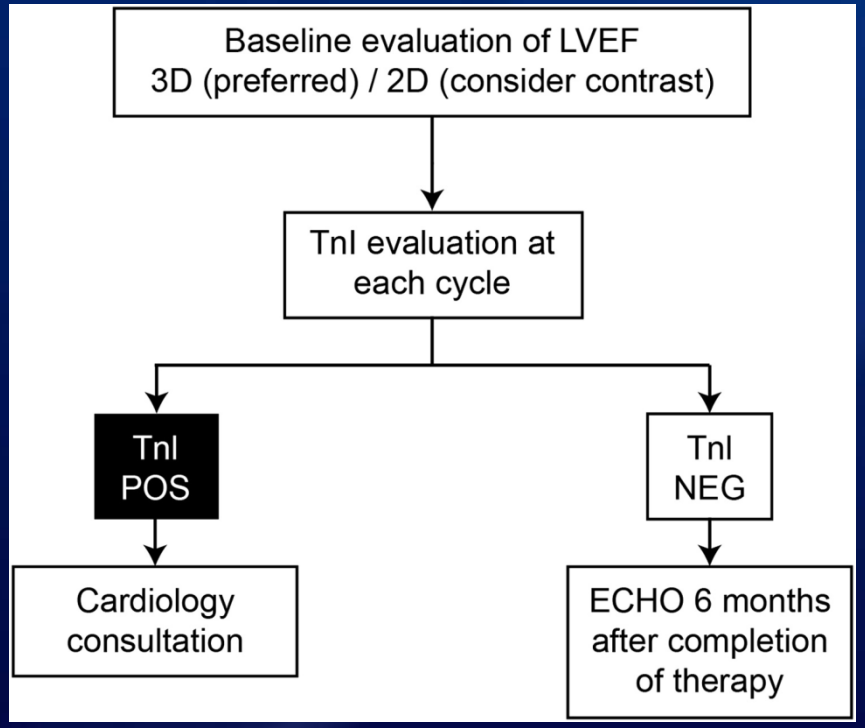

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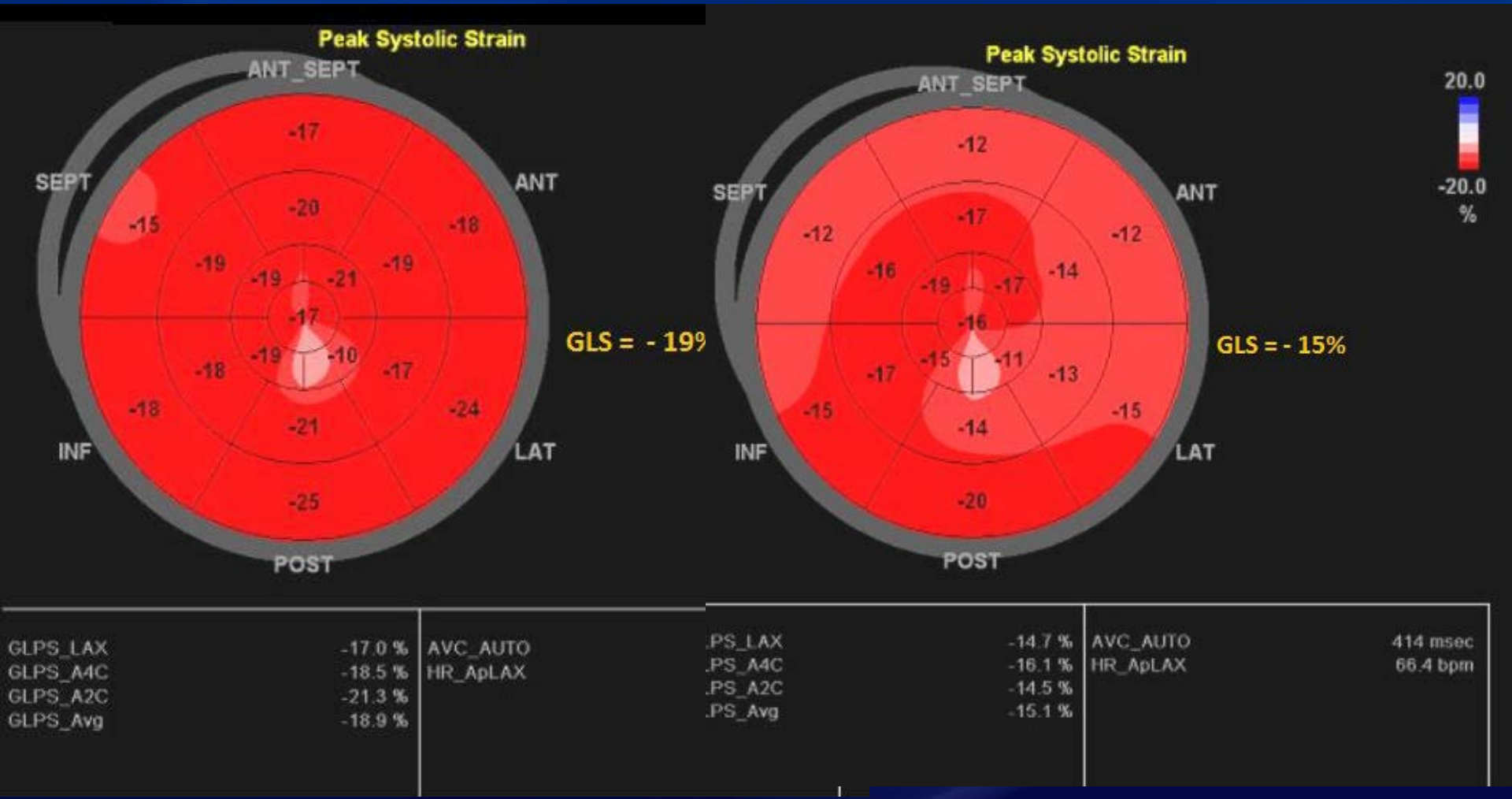
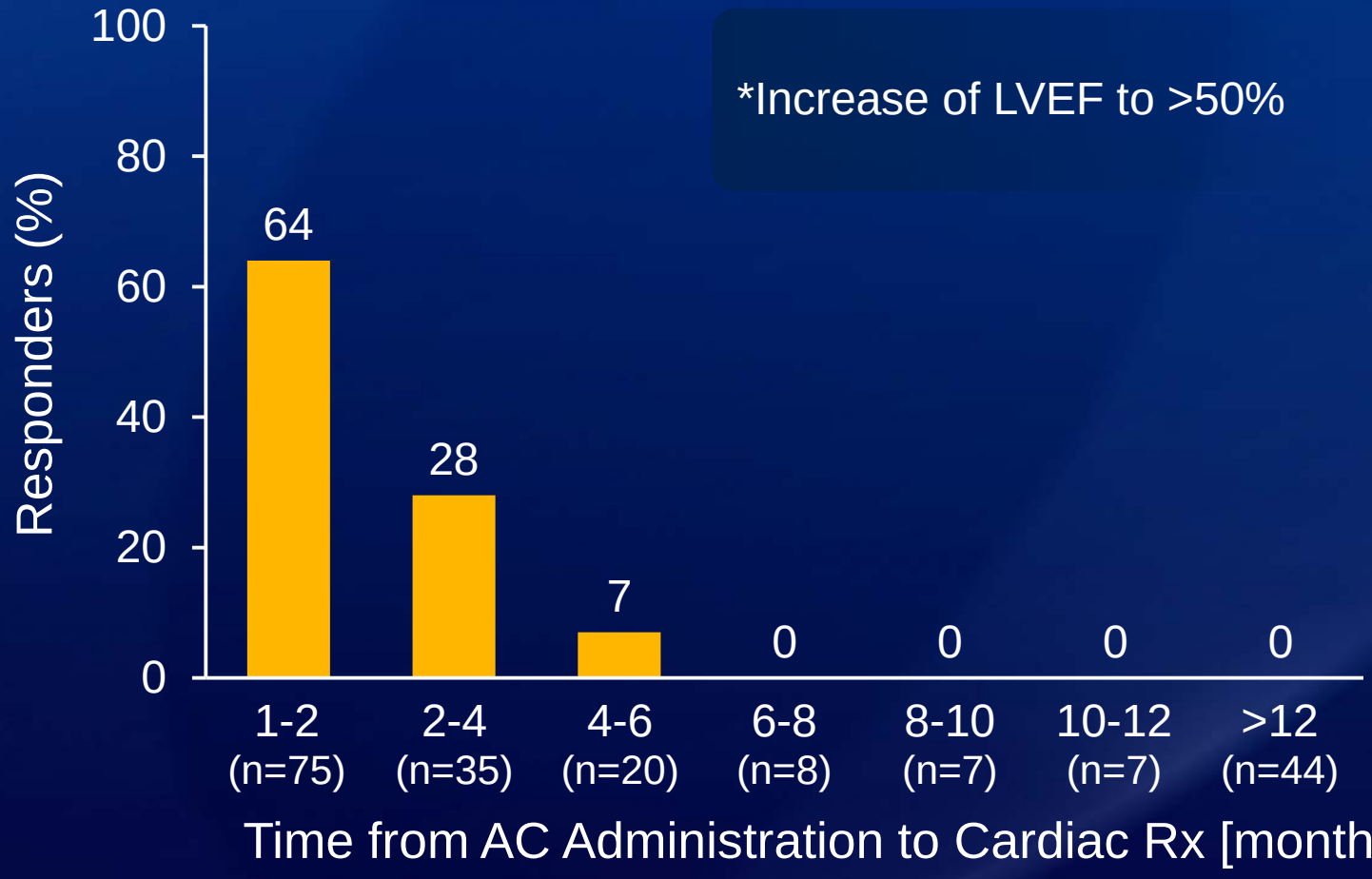
45 yo female breast CA; adriamycin/cytoxan Rx



Baseline: normal EF, normal strain (-19%)

3 mos: normal EF, abnormal strain (-15%)

Timing of Initiation of Treatment (ACE-I/BB) Predicts LVEF Recovery Potential*



Cardinale et al: JACC 55:213, 2010

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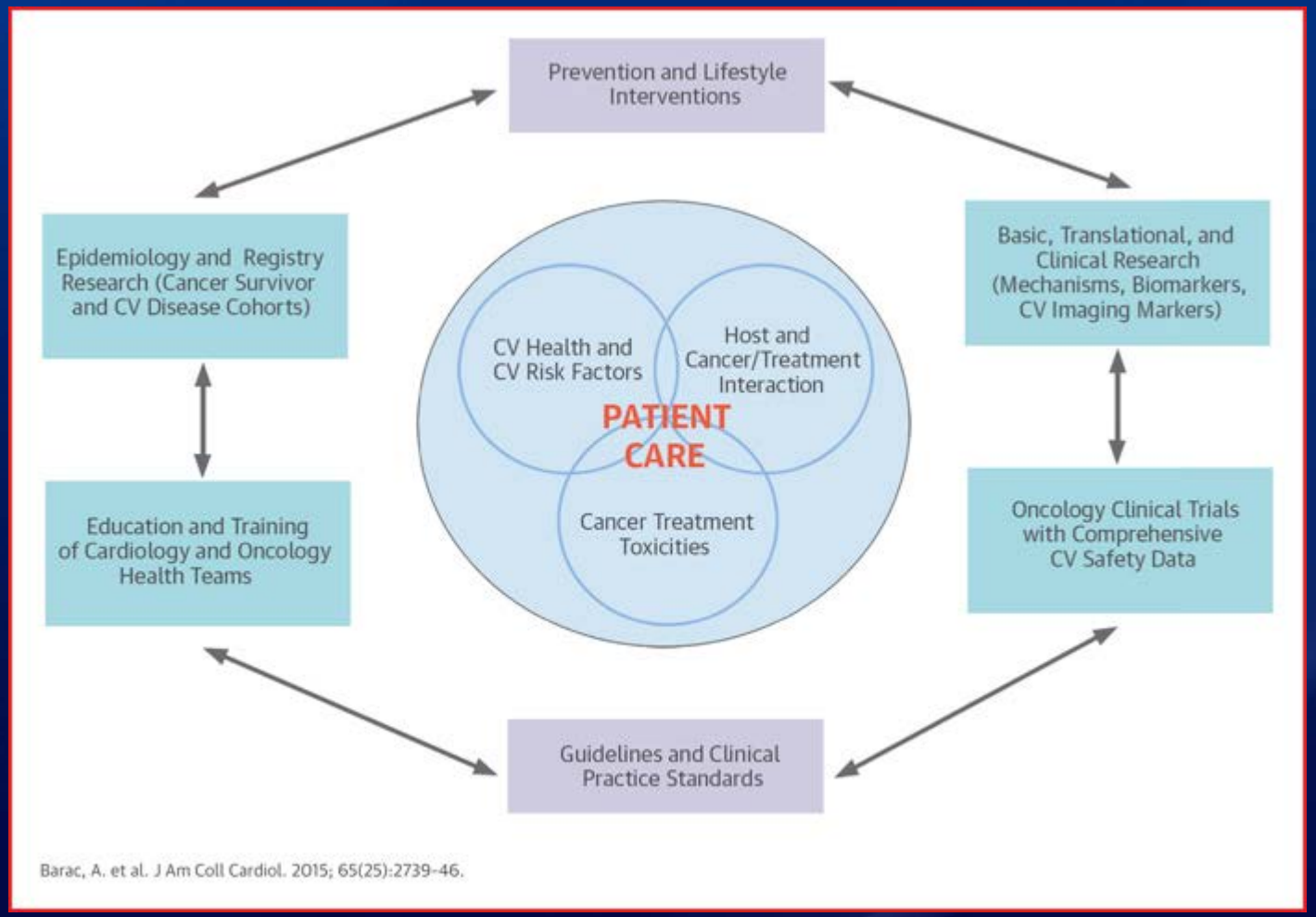
Overview of the Spectrum of Cardio-Oncology: Bench to Bedside to Community Partnerships



Barac A et al JACC 2015;65(25):2739–2746

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Cardiotoxicity and Cardio-Oncology
Summary

- Cancer is a chronic disease, cardio-oncology addresses CV care in cancer patients
- Cardiovascular disease impacts cancer survivorship
- Early detection and early treatment to prevent CHF
- Strategies include risk prediction, preventive Rx and individualization of care

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Gracia!

Questions & Discussion

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