Cancer & heart failure:

Avoiding LV injury in Stage A/B patients?

Mariell Jessup MD, FAHA, FACC, FESC
Professor of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

I have no disclosures to report.

CARDIOLOGY PATIENT PAGE

Breast Cancer Chemotherapy and Your Heart

Christine Unitt, BS; Kamaneh Montazeri, MD; Sara Tolaney, MD; Javid Moslehi, MD

Circulation June 24, 2014

Epidemiology of cancer chemotherapy related cardiomyopathy.

**150 000 to 250 000 patients with advanced heart failure in the U.S.

**UNOS and INTERMACS:
0.8% to 2.5% of all OHT recipients.
0.5% of those implanted with MCS

**prevalence of end-stage HF from CCMP between 0.5% and 2.5%.

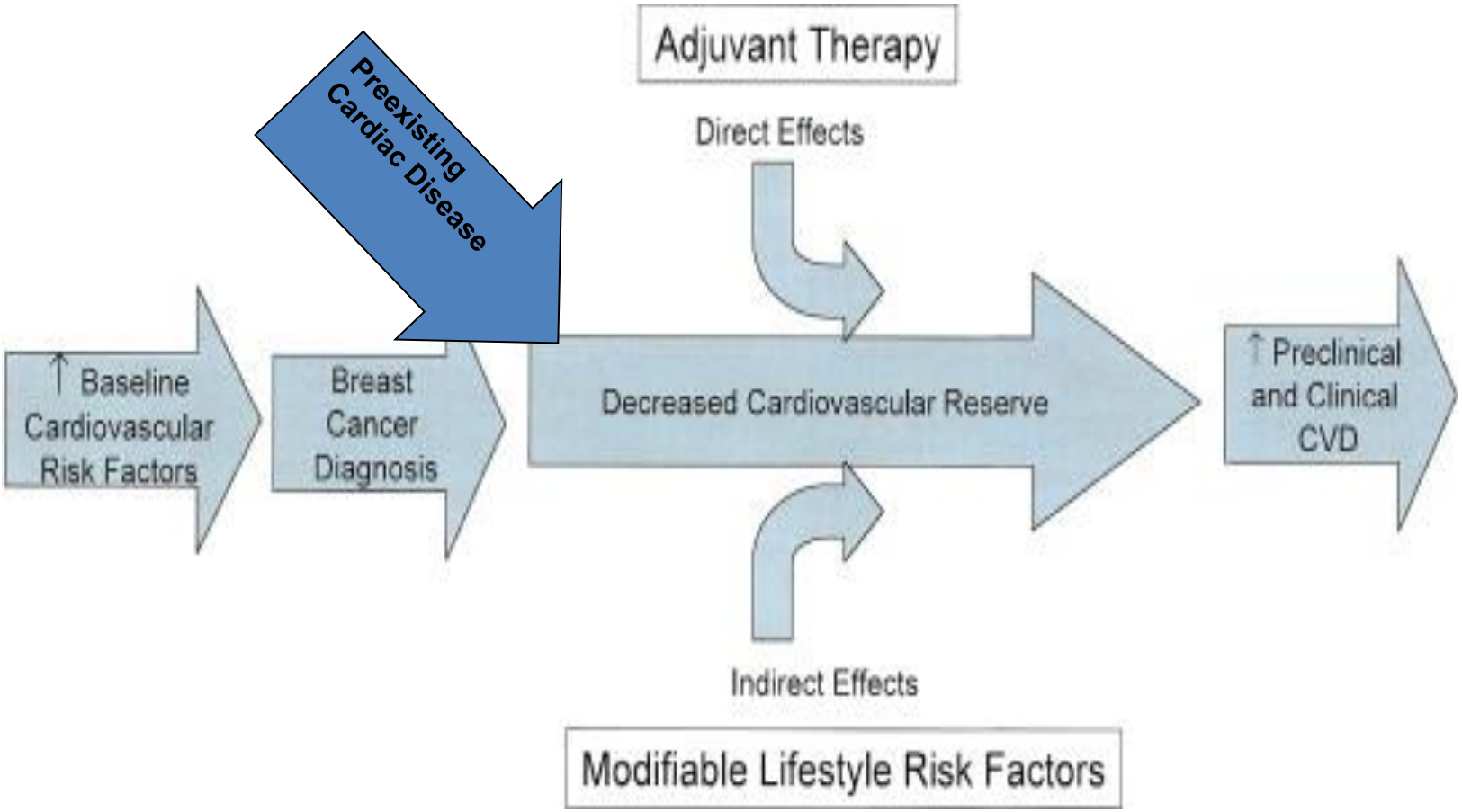
Oliveira et al. Circulation Heart Failure 2014; 7: 1050

Risk Factors Common to Cancer and Heart Disease

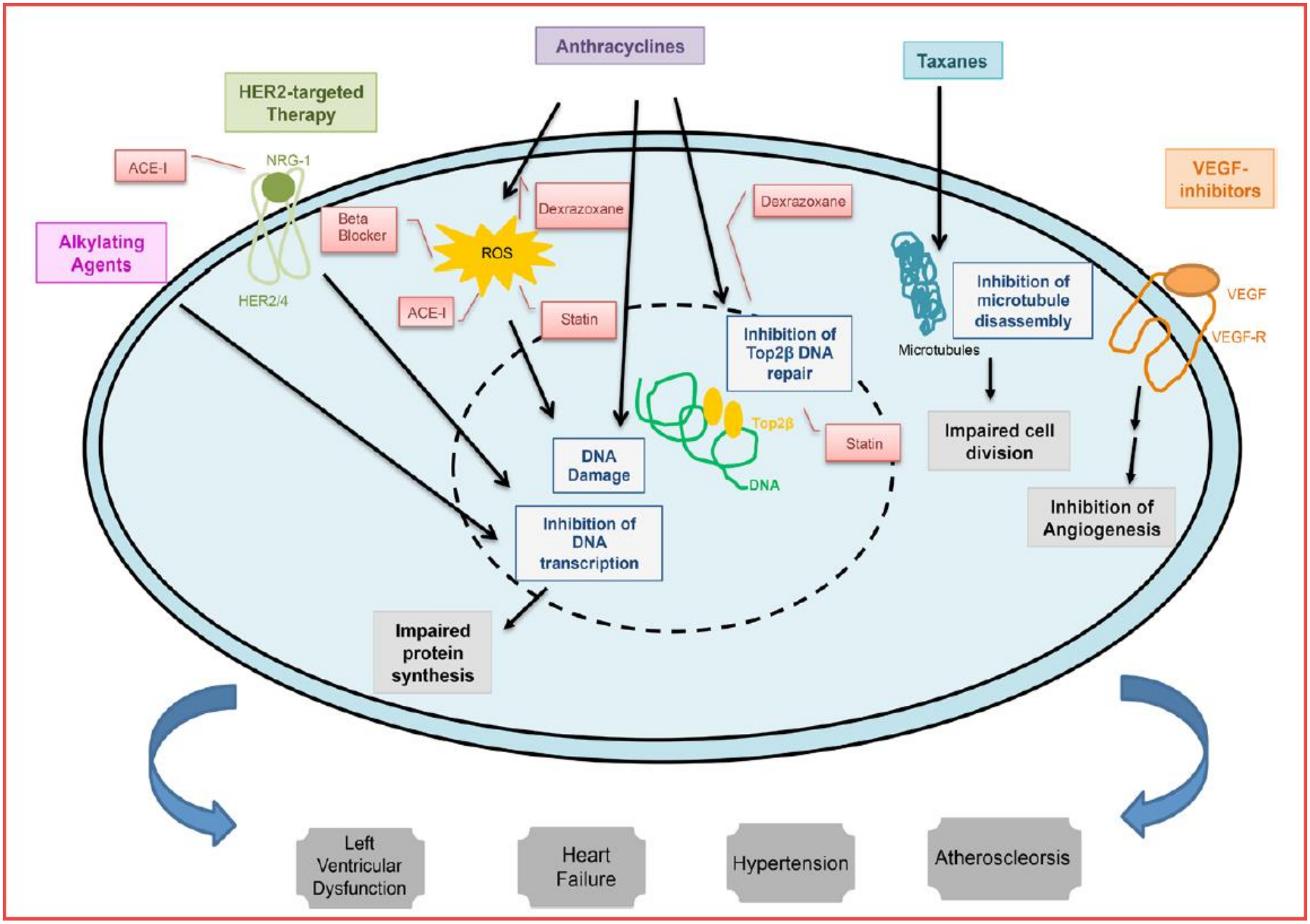
	Heart Disease	Cancer
Diabetes	√ √ √	√
Obesity	√	√
Hypertension	√ √	
Hyperlipidemia	√	√
Physical Inactivity	√	√
Smoking	√	√
Dietary factors	√	√

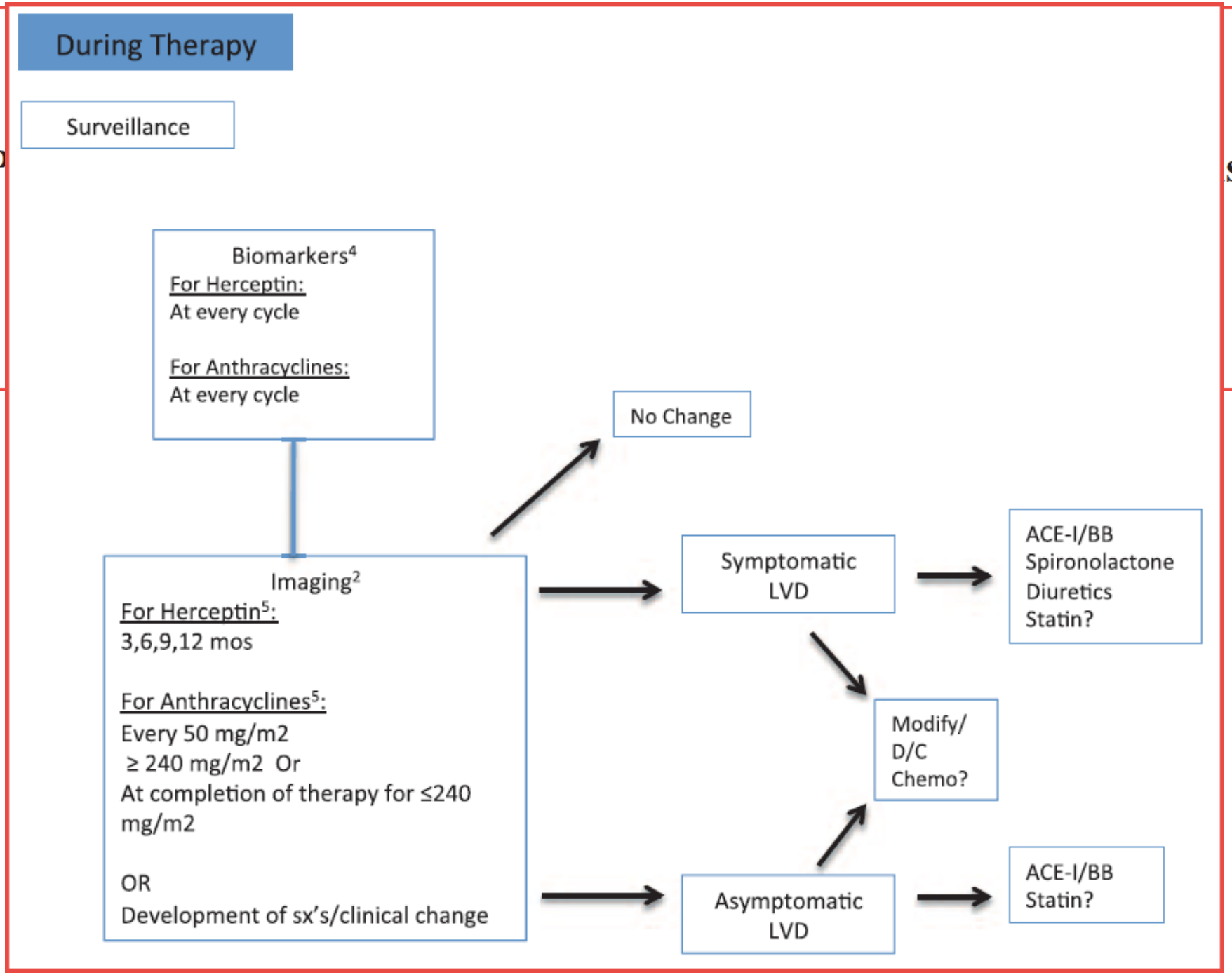
Lindenfeld J. *J Geriatric Card* 2007

Multi-Hit Hypothesis



Jones LW et al. JACC 2007;50:1435-41

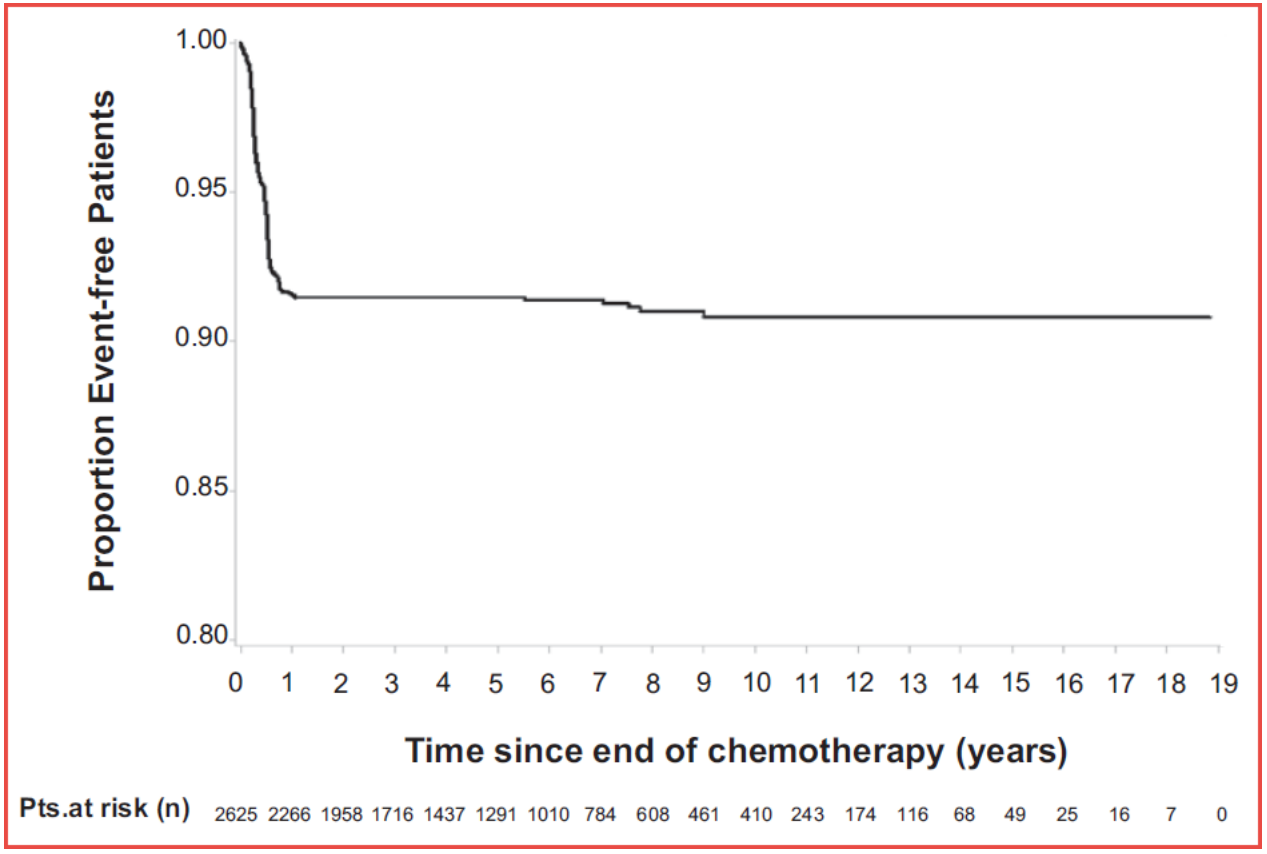

Anthracyclines
Taxanes
HER2-targeted Therapy
ACE-I
NRG-1
HER2/4
Alkylating Agents
Beta Blocker
ROS
Dexrazoxane
Dexrazoxane
ACE-I
Statin
VEGF-inhibitors
Inhibition of microtubule disassembly
Microtubules
VEGF
VEGF-R
Inhibition of Top2β DNA repair
Top2β
Statin
DNA
DNA Damage
Impaired cell division
Inhibition of Angiogenesis
Inhibition of DNA transcription
Impaired protein synthesis
Left Ventricular Dysfunction
Heart Failure
Hypertension
Atherosclerosis


During Therapy
Surveillance
Biomarkers[4]
For Herceptin:
At every cycle
For Anthracyclines:
At every cycle
No Change
Imaging[2]
For Herceptin[5]:
3,6,9,12 mos
For Anthracyclines[5]:
Every 50 mg/m2
≥ 240 mg/m2 Or
At completion of therapy for ≤240 mg/m2
OR
Development of sx's/clinical change
Symptomatic LVD
ACE-I/BB
Spironolactone
Diuretics
Statin?
Modify/ D/C Chemo?
Asymptomatic LVD
ACE-I/BB
Statin?

Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy

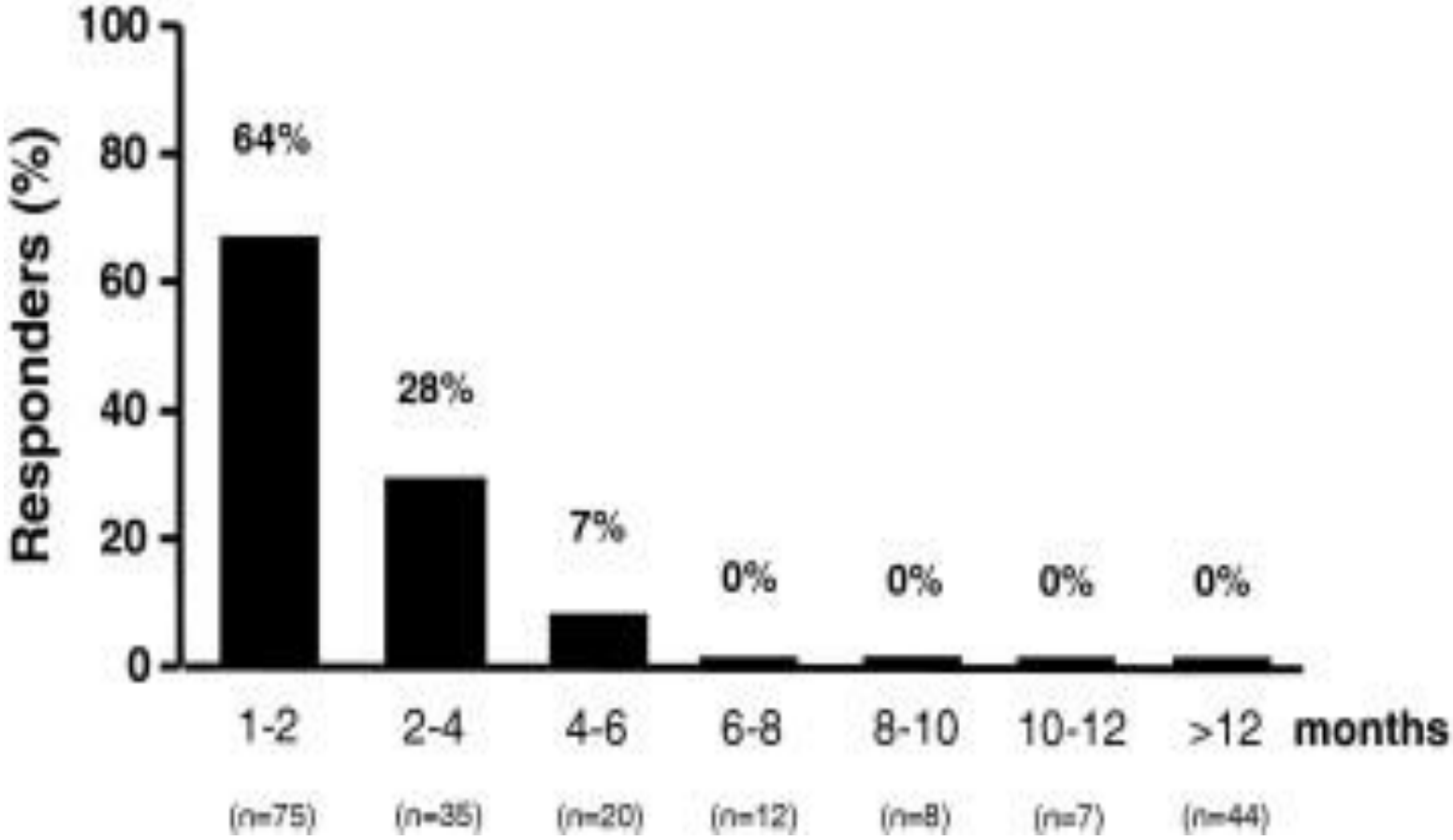
Circulation. 2015;131:1981-1988

Daniela Cardinale, MD, PhD, FESC; Alessandro Colombo, MD; Giulia Bacchiani, MD; Ines Tedeschi, MSc; Carlo A. Meroni, MD; Fabrizio Veglia, PhD; Maurizio Civelli, MD; Giuseppina Lamantia, MD; Nicola Colombo, MD; Giuseppe Curigliano, MD, PhD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD



Most cardiotoxicity after anthracycline-therapy occurs within the 1st year and is associated with anthracycline dose and LVEF at the end of Tx.

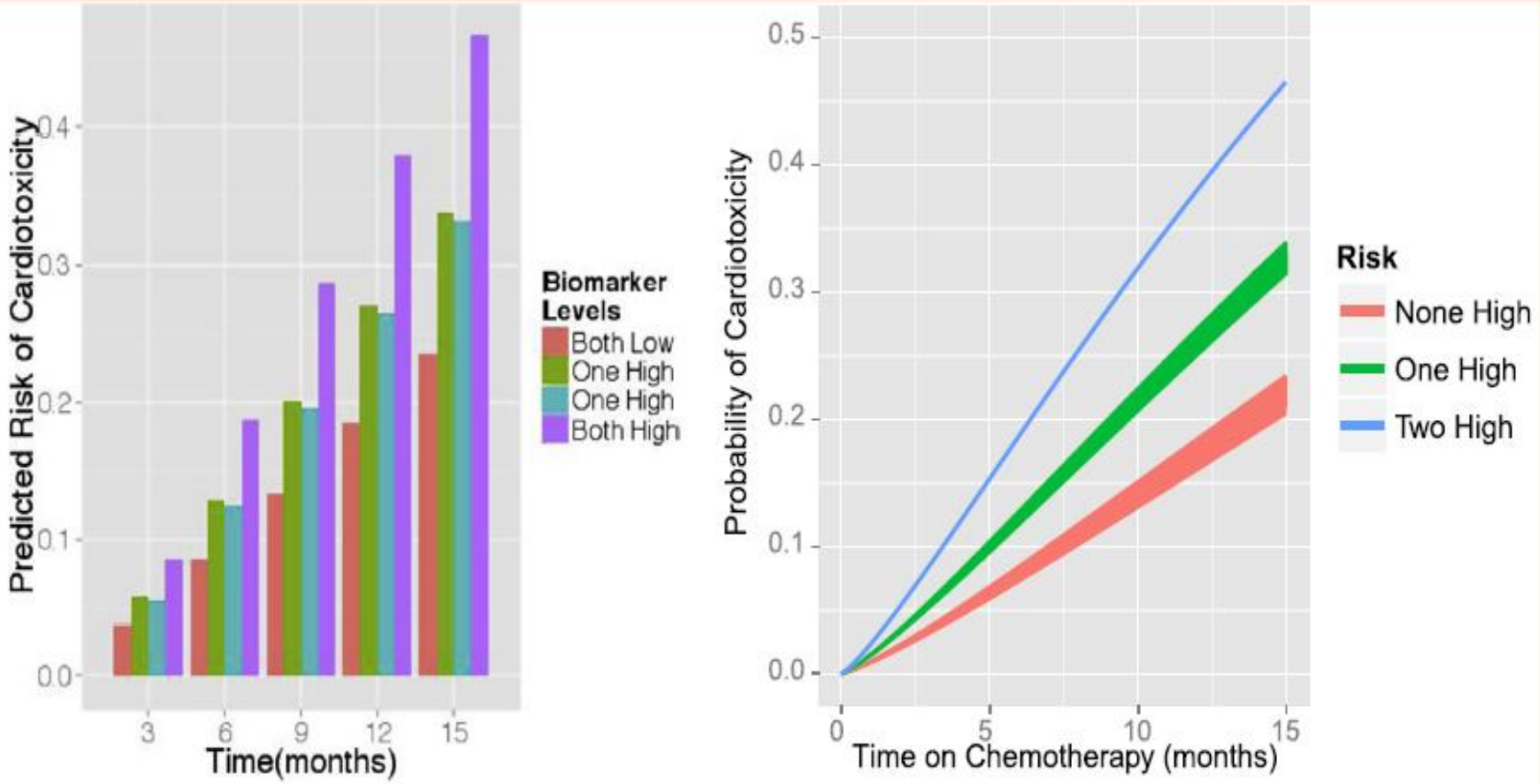
Therapuetic Response was best in those treated early after detection



Cardinale D et al. *Circulation* 2010;55:213-20

Early Increases in Multiple Biomarkers Predict Subsequent Cardiotoxicity in Patients With Breast Cancer Treated With Doxorubicin, Taxanes, and Trastuzumab

J Am Coll Cardiol 2014;63:809-16



Model-Based Probability of Cardiotoxicity According to Changes in MPO and TnI Levels

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)

JACC Vol. 61, No. 23, 2013

Differences in Change in LVEF

	Enalapril + Carvedilol	Control	p Value
Echocardiography			
LVEF (%)	n = 42	n = 37	
Baseline	61.67 ± 5.11	62.59 ± 5.38	
6 months	−0.17 (−2.24 to 1.90)	−3.28 (−5.49 to −1.07)	0.04
CMR			
LVEF (%)	n = 31	n = 27	
Baseline	56.00 ± 6.00	60.18 ± 7.16	
6 months	0.36 (−2.41 to 3.13)	−3.04 (−6.01 to −0.07)	0.09

Prevention of Anthracycline-Induced Cardiotoxicity

J Am Coll Cardiol 2014;64:938-45

Challenges and Opportunities

Pimprapa Vejpongsa, MD,* Edward T.H. Yeh, MD*†

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)

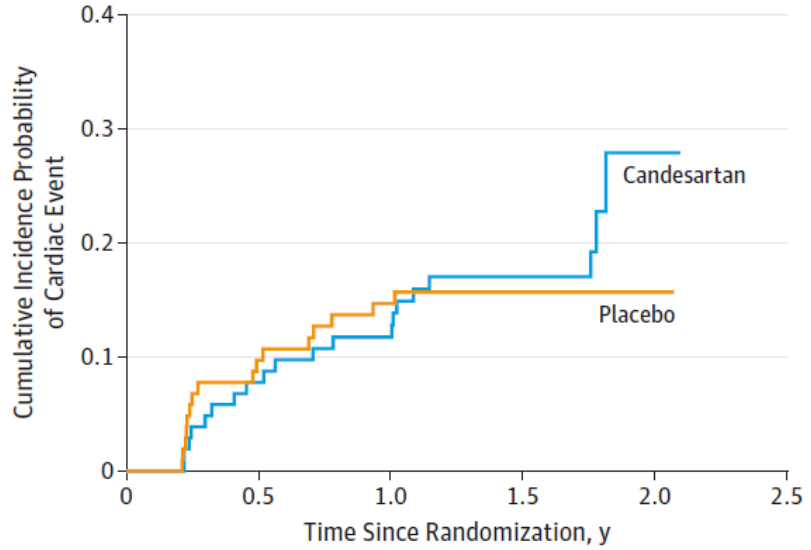
Angiotensin II–Receptor Inhibition With Candesartan to Prevent Trastuzumab-Related Cardiotoxic Effects in Patients With Early Breast Cancer

A Randomized Clinical Trial

JAMA Oncology 2016

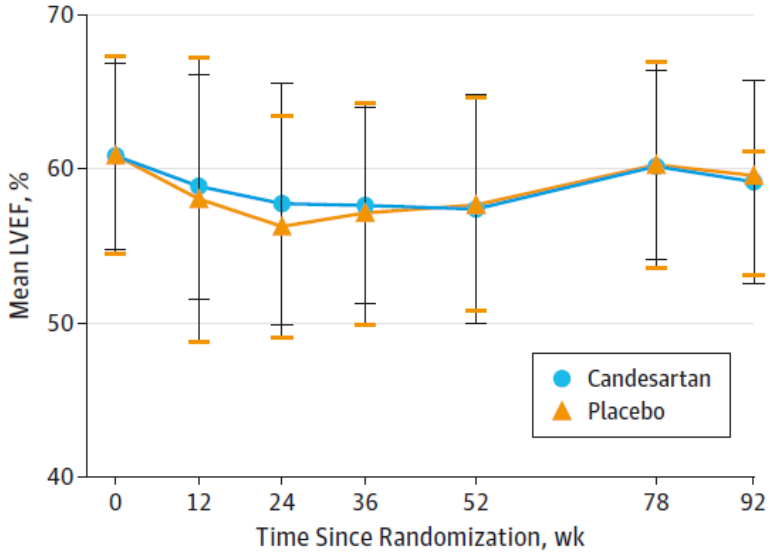
Annelies H. Boekhout, PhD; Jourik A. Gietema, MD, PhD; Bojana Milojkovic Kerklaan, PhD; Erik D. van Werkhoven, MSc; Renske Altena, MD, PhD; Aafke Honkoop, MD, PhD; Maartje Los, MD, PhD; Willem M. Smit, MD, PhD; Peter Nieboer, MD, PhD; Carolien H. Smorenburg, MD, PhD; Caroline M. P. W. Mandigers, MD, PhD; Agnes J. van der Wouw, MD, PhD; Lonneke Kessels, MD; Annette W. G. van der Velden, MD; Petronella B. Ottevanger, MD, PhD; Tineke Smilde, MD, PhD; Jaap de Boer, MD; Dirk J. van Veldhuisen, MD, PhD; Ido P. Kema, PhD; Elisabeth G. E. de Vries, MD, PhD; Jan H. M. Schellens, MD, PhD

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

Cancer & heart failure:
Avoiding LV injury in Stage A/B patients?

1. The problem of heart failure following cancer therapy is now well recognized.

2. The problem of heart failure following cancer therapy is responsible for a growing group of patients who are symptomatic.

3. The problem involves multiple drugs and multiple pathophysiologic mechanisms.

4. Definitions have not been agreed upon by the oncology and cardiology community.

5. Endpoints have not been agreed upon by the oncology and cardiology community.

6. Imaging modalities are in evolution.