Prevenção, Diagnóstico e Manuseio da Cardiotoxicidade após Terapia Oncológica

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Disclosures

- Consultor:
  - Pfizer
  - Abbott
  - Novartis
  - Amgen
  - Alnylam
  - Abiomed

Outline

- Epidemiology of Cardiotoxicity
- Types of Cardiotoxicity
- Cardiovascular Risk Stratification of Cancer Patients
- Prevention of Cardiotoxicity
- Monitoring Cardiotoxicity
- Treatment of Cardiotoxicity
- Summary

Missão da Cardio-Oncologia

"Ajudar a equipe oncológica a obter os melhores resultados possiveis em pacientes com cancer, atraves de acompanhamento cardiovascular antes, durante e depois da terapia anti-neoplasica."

Impact of Cardiotoxicity

Short term

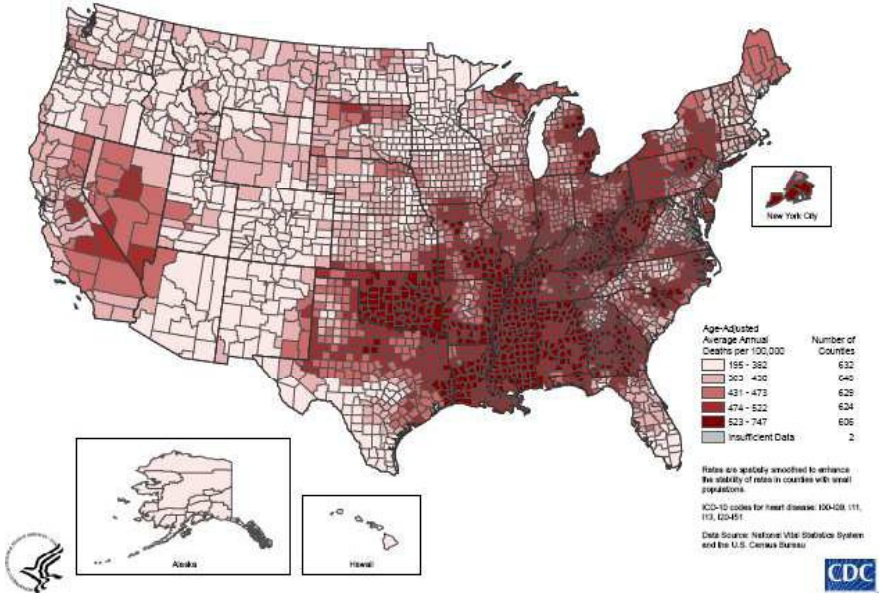
- Treatment interruption
- Treatment discontinuation
- Dose reductions
- Heart dysfunction/failure
- Hypertension
- Acute coronary syndromes
- Pulmonary hypertension
- Thrombosis
- PAD/stroke
- Arrhythmias

Long term

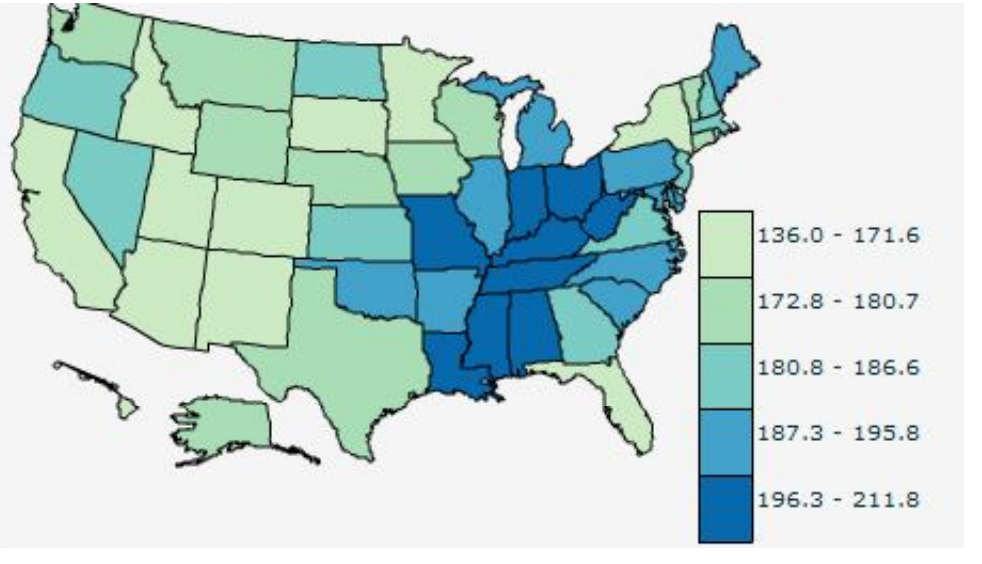
- Cardiomyopathy
- End-stage heart failure
- Valvular heart disease
- Pericardial disease
- Heart transplant
- Heart pumps
- Early death

Epidemiology

Cancer and Heart Disease



Age-adjusted death rates for coronary heart disease



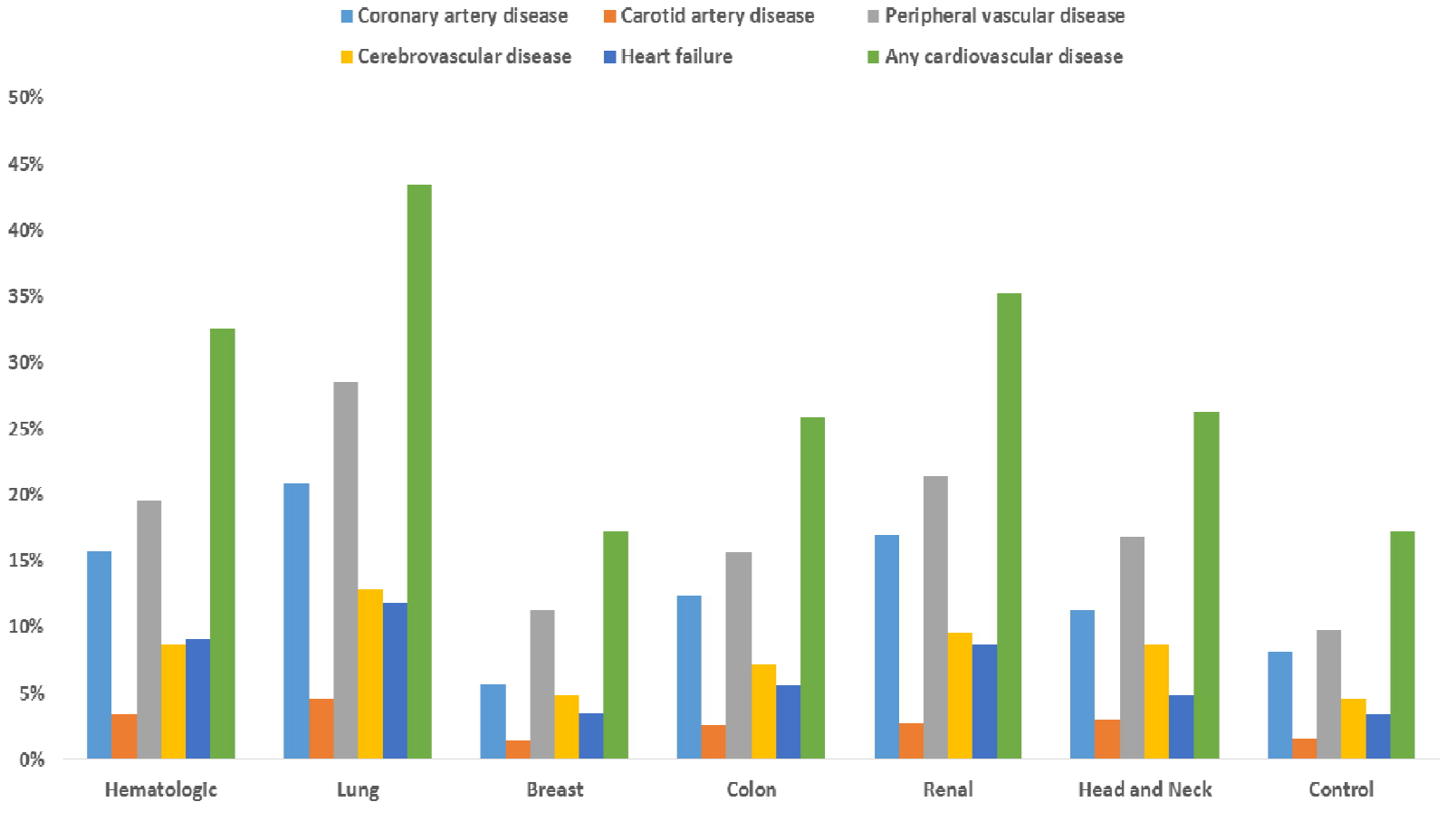
Age-adjusted death rates for all cancers

Herrmann J et al. Mayo Clin Proc 2014

Rising numbers of cancer survivors

Altekruse SE et al., SEER cancer statistics review, 1975--2007. Bethesda, MD: National Cancer Institute; 2010

Prevalence of Heart Disease by Cancer Type



Oliveira GH et al. Mayo Clin Proceedings 2015

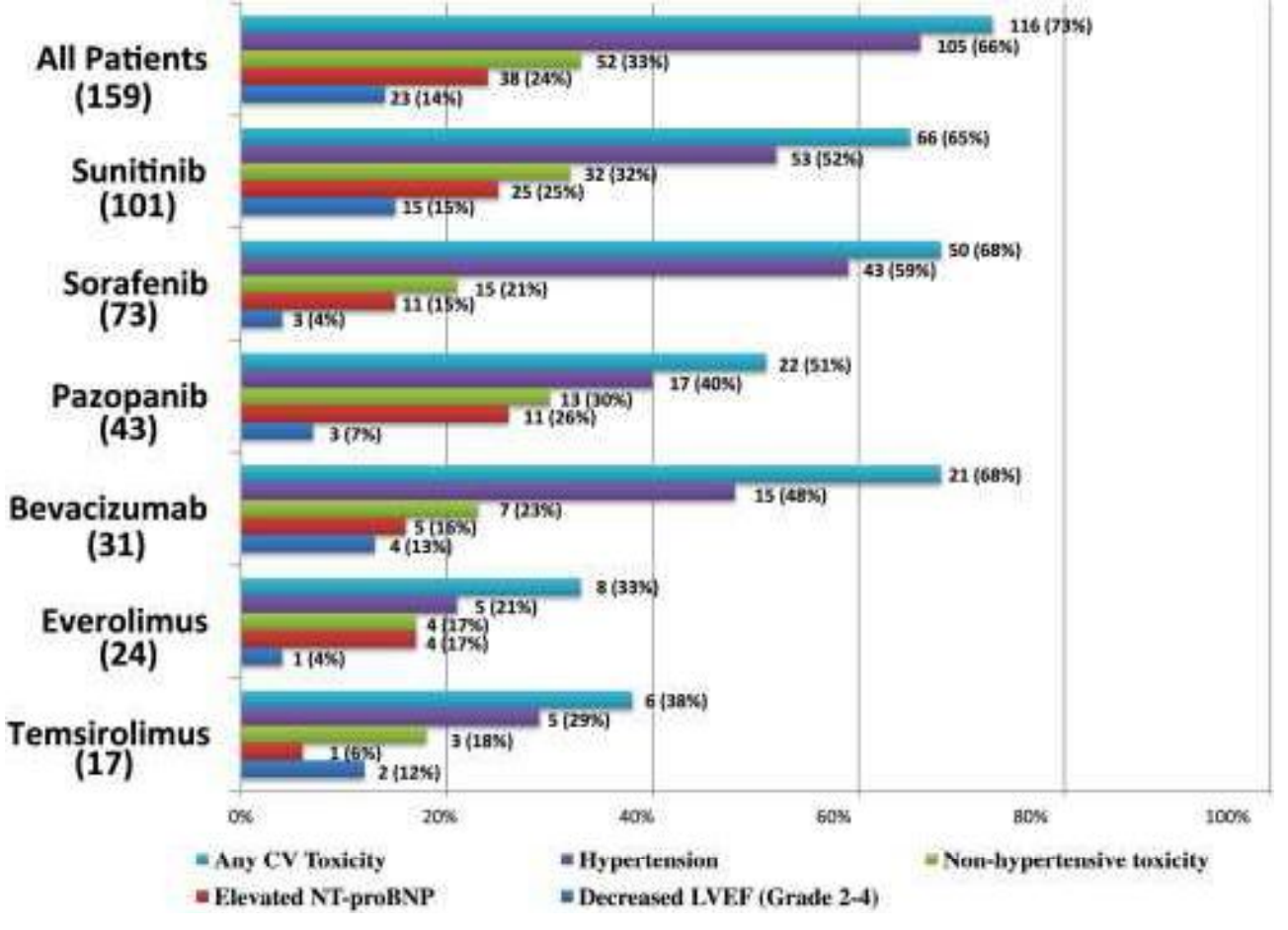
Incidence of HF/LVD after Anthracyclines ± Trastuzumab

Table 2 Cumulative Incidence of Heart Failure or Cardiomyopathy During First 3 Years After Diagnosis by Cancer Ther

	All Cancer Patients	Anthracycline + Trastuzumab (n = 431)	Anthracycline (n = 5,257)	Trastuzumab (n = 437)	Other Chemotherapy (n = 2,712)
Observed cumulative incidence					
1 year	7.2	16.4*†	7.7‡	15.7*	7.8
2 years	12.3	23.8*†	11.9	20.7*	12.4
3 years	16.9	28.2*†	15.3‡	26.7*	17.0
Adjusted cumulative incidence					
1 year	7.5	22.0*†	9.8*	16.7*	8.4*
2 years	13.3	33.2*†	15.3*	23.2*	13.7*
3 years	18.7	41.9*†	20.2‡	32.1*	19.2

Chen et al. JACC Vol. 60, No. 24, 2012

CV Complications of VGEF Inhibitors

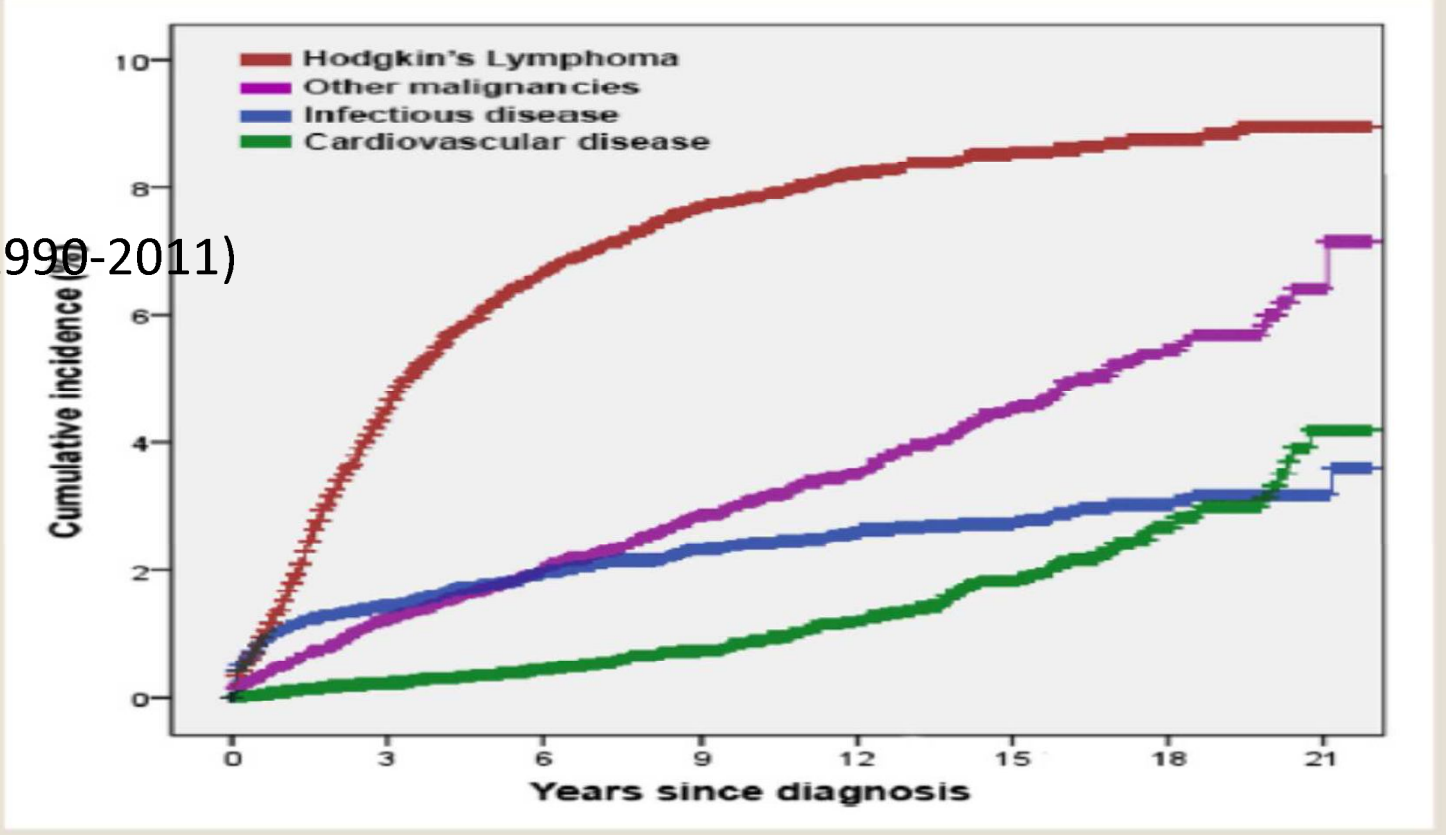


Hall et al. JACCHF Feb 2013

CVD major cause of non-cancer death in survivors

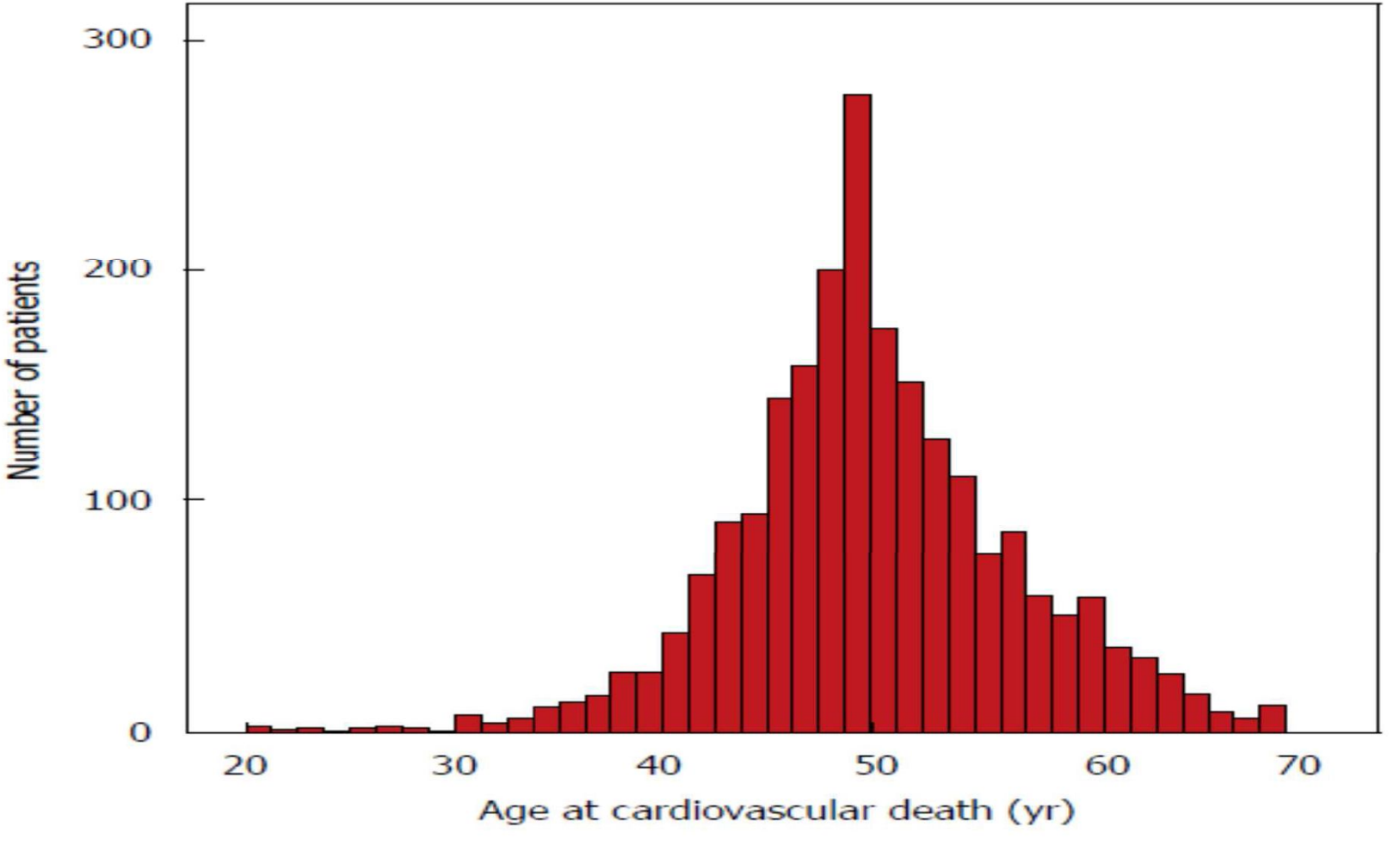
Figure 1 Cumulative Incidence of Major Causes of Death

(1990-2011)



Al-Kindi SG…Oliveira GH. Clin Leuk Myel Lymph 2015

Young age at CV death



Al-Kindi SG, Oliveira GH. World J Cardiology 2015

Types of Cardiotoxicity

Chemotherapy-Induced Cardiotoxicity

Agent	LVD (%)	HTN (%)	ACS (%)	Arrhythmia (5)	Thromboembolism
Anthracyclines	**3-26**				
Cyclophosphamide	7-28				
Docetaxel	2-8		1.7		
Paclitaxel			0.5-5	0.1-31	
Bevacizumab (Avastin)	1.7-3	**4-35**	1.5-3		
Trastuzumab	**2-40**				
Sunitinib	**2.7-11**	**5-30**			
Imatinib	0.5-1.7				
Sorafenib		**17-43**			
Erlotinib			2.3		3.9-11
Fluorouracil (5-FU)	<1		**2-43**		
Capecitabine			3		
Bortezomib (Velcade)	2-5		3-9		
Cisplatin					8.5-13%
Thalidomide				0.2-55%	
Lenalidomide (Revlimid)					**3-75**
Lapatinib	1.5-2.2			16	

Adapted from Yeh ET and Bickford CL. JACC 2009

Classification of Cardiotoxicity

Type I CRCD	Type II CRCD
Cellular death	Cellular dysfunction
Biopsy changes	No Biopsy changes
Cumulative dose-related	Not dose-related
Oxidative stress/DNA damage	Erbb2-signaling
Permanent	Reversible
Model:doxorubicin	**Model:Trastuzumab**

Courtesy of Michael Ewer, MD

Radiation Dose and CAD

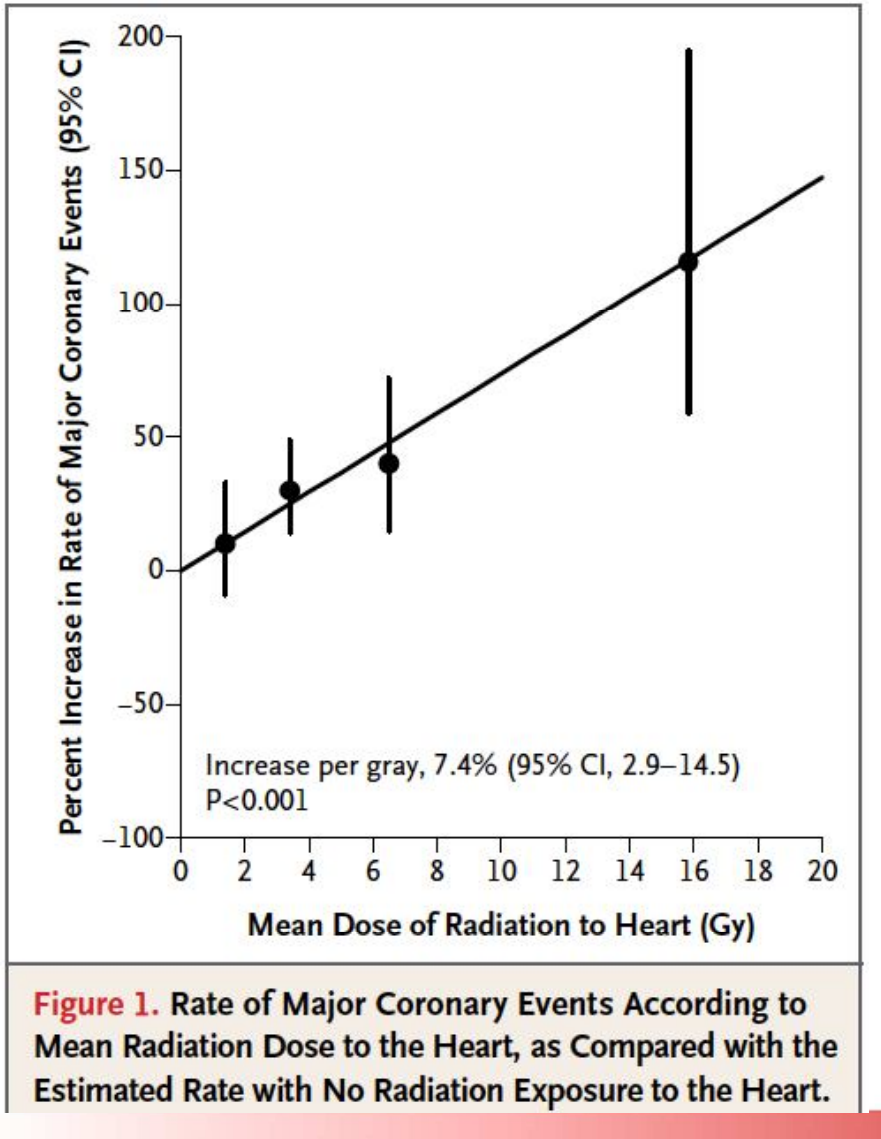
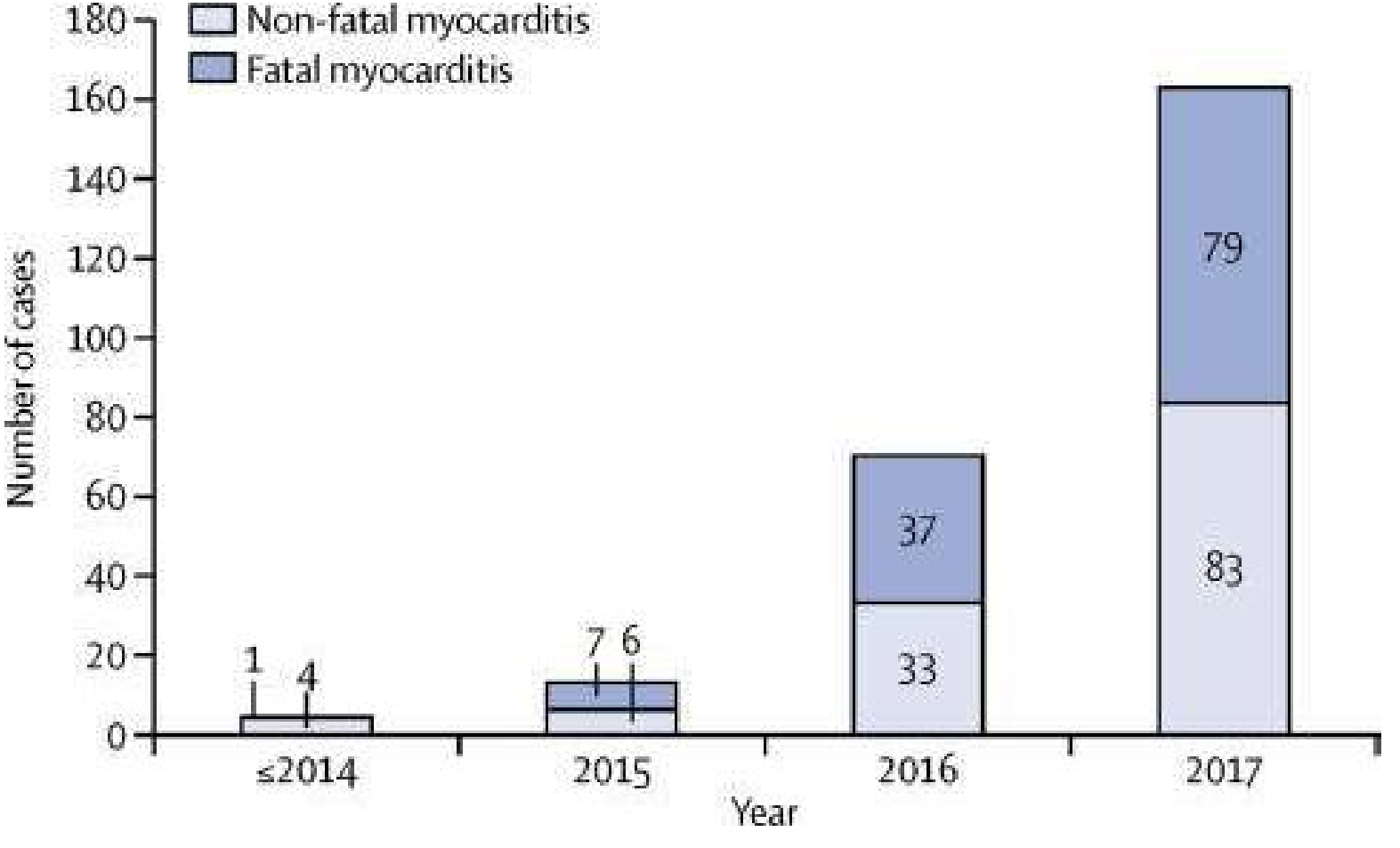


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

N= 2168
963 with MACE

Darby et al. NEJM March 2013

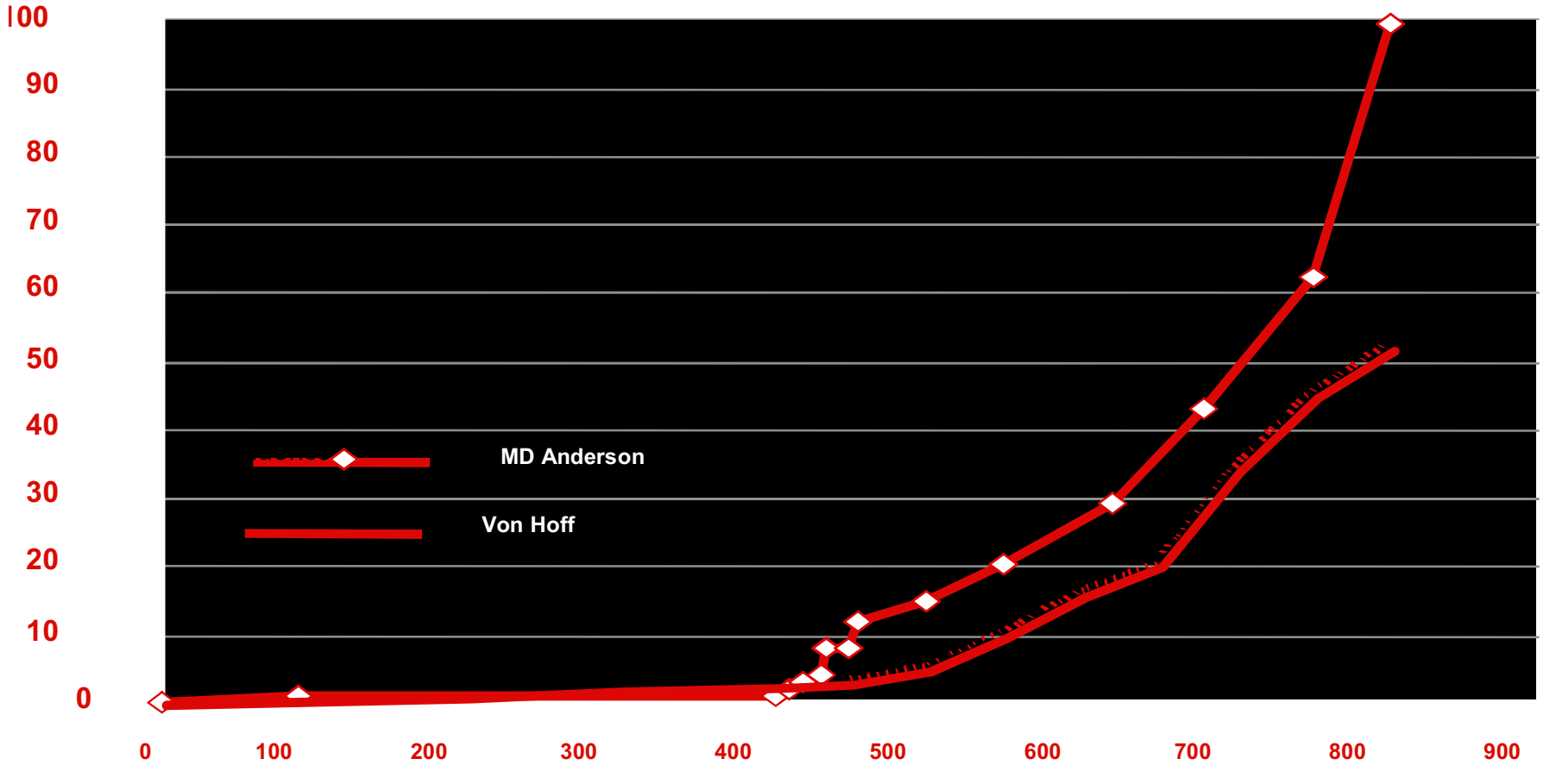
Immune Check Point Inhibitor Myocarditis



Oliveira et al. Lancet 2018

CV Risk Stratification

Doxorubicin Dose and HF



Adapted from Ewer et al. JCO 1984;2:112-117.

Common Anthracycline Regimens and Cancers

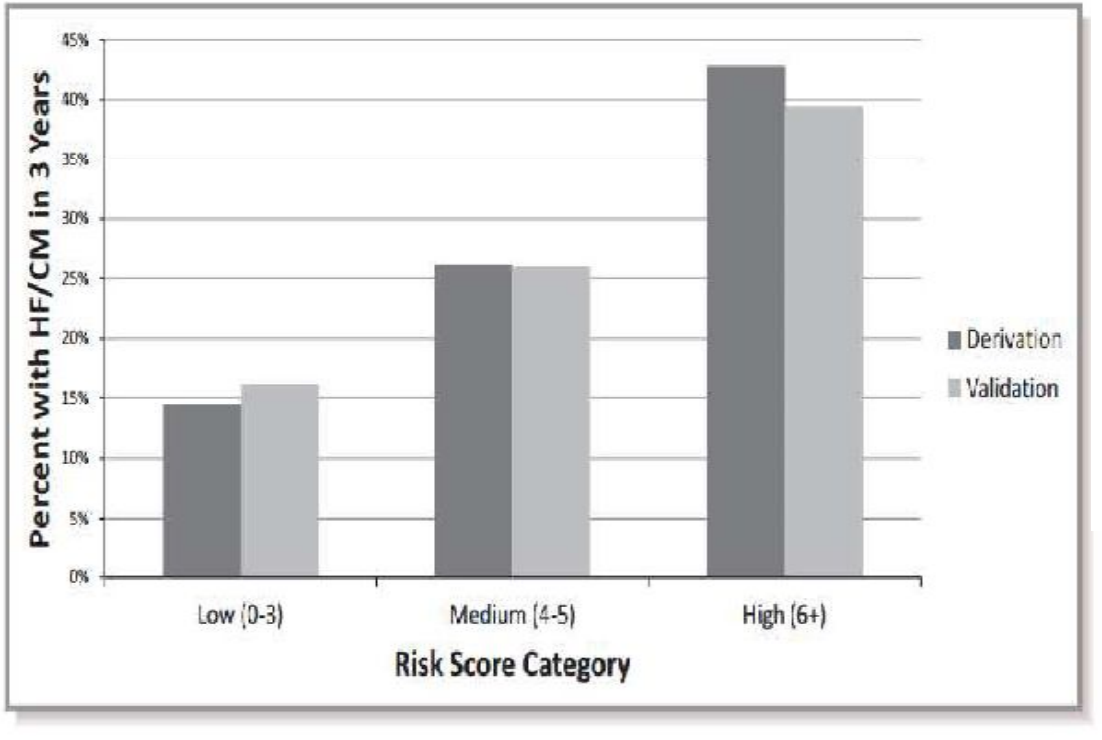
TABLE 1 Anthracycline Regimens in the Most Widely Used Protocols for 4 Types of Cancer

Type of Cancer	Anthracycline Regimens	Other Considerations
Breast cancer	Doxorubicin 50-60 mg/m^2 × 4-6 cycles Epirubicin 75-100 mg/m^2 × 4-8 cycles	Increased cardiotoxicity with trastuzumab (11) Bolus over 15 min
Sarcoma	Doxorubicin 75-90 mg/m^2 × 6-8 cycles	Continuous infusion over 48-72 h or bolus over 15 min + dexrazoxane
Lymphoma	Doxorubicin 40-50 mg/m^2 × 6-8 cycles	Continuous infusion over 48-72 h or bolus over 15 min
Pediatric leukemia	Doxorubicin 30 mg/m^2 × 10 cycles	Bolus over 30 min ± dexrazoxane

Yeh ET et al. JACC 2015

Risk factors for LVD/CHF with Trastuzumab

SEER Analysis of 1664 women

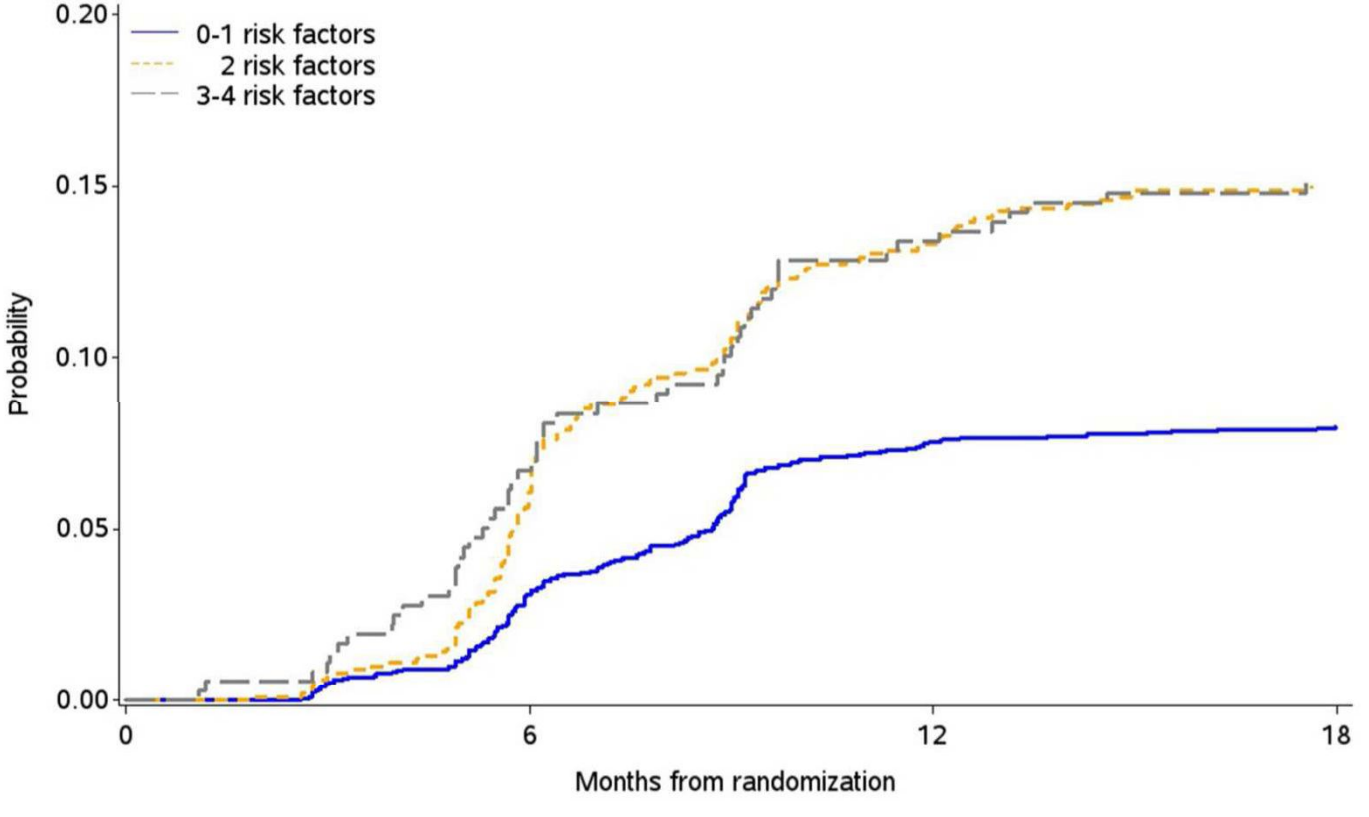


J Am Heart Assoc. 2014; 3: e000472

Risk Factor	Points Assigned
Adjuvant therapy	
Anthracycline chemotherapy	2
Non-anthracycline chemotherapy	2
No identified chemotherapy	
Age category, y	
67 to 74	
75 to 79	1
80 to 94	2
Cardiovascular conditions and risk factors	
Coronary artery disease	2
Atrial fibrillation/flutter	2
Diabetes mellitus	1
Hypertension	1
Renal failure	2

	Total	3 Years	
Risk Score	N	N	%
0, 1, 2, or 3	595	86	14.5
4 or 5	195	51	26.2
6, 7, 8, or 9	42	18	42.9

Risk Prediction for Trastuzumab Cardiotoxicity



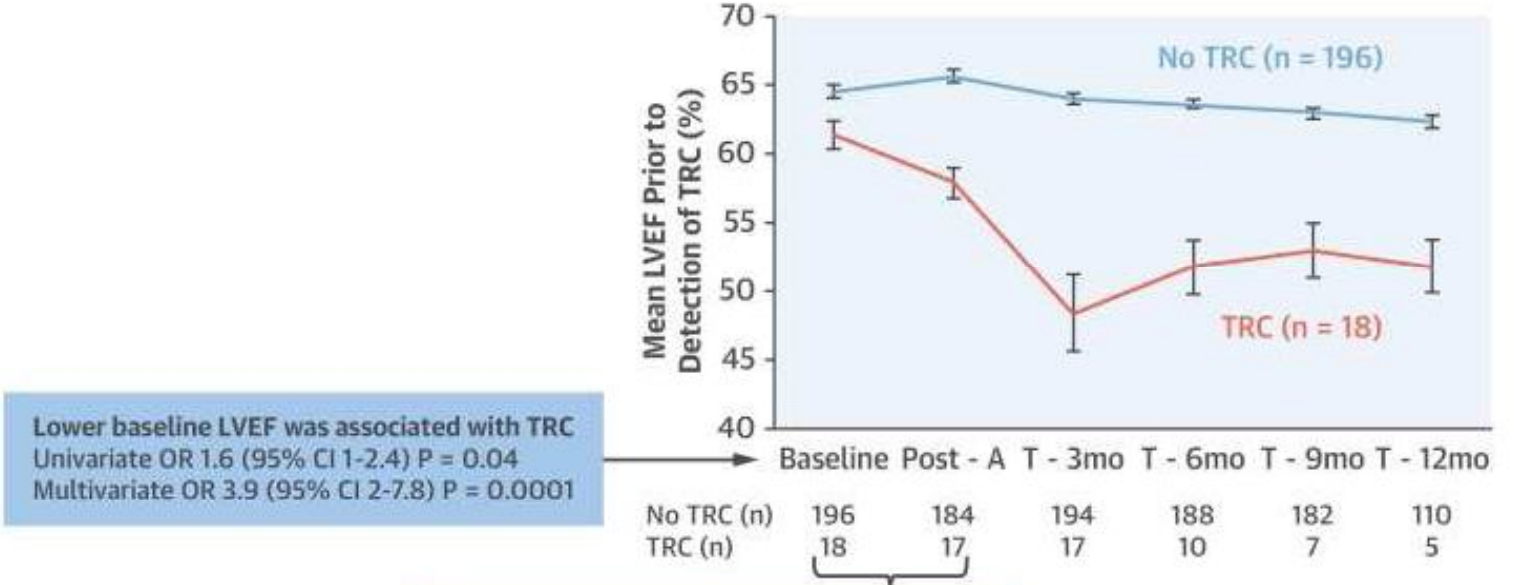
Risk Factors

- LVEF<505
- HTN
- BMI>25
- Age>60

Azambuja et al. Breast Cancer Research and Treatment 2019

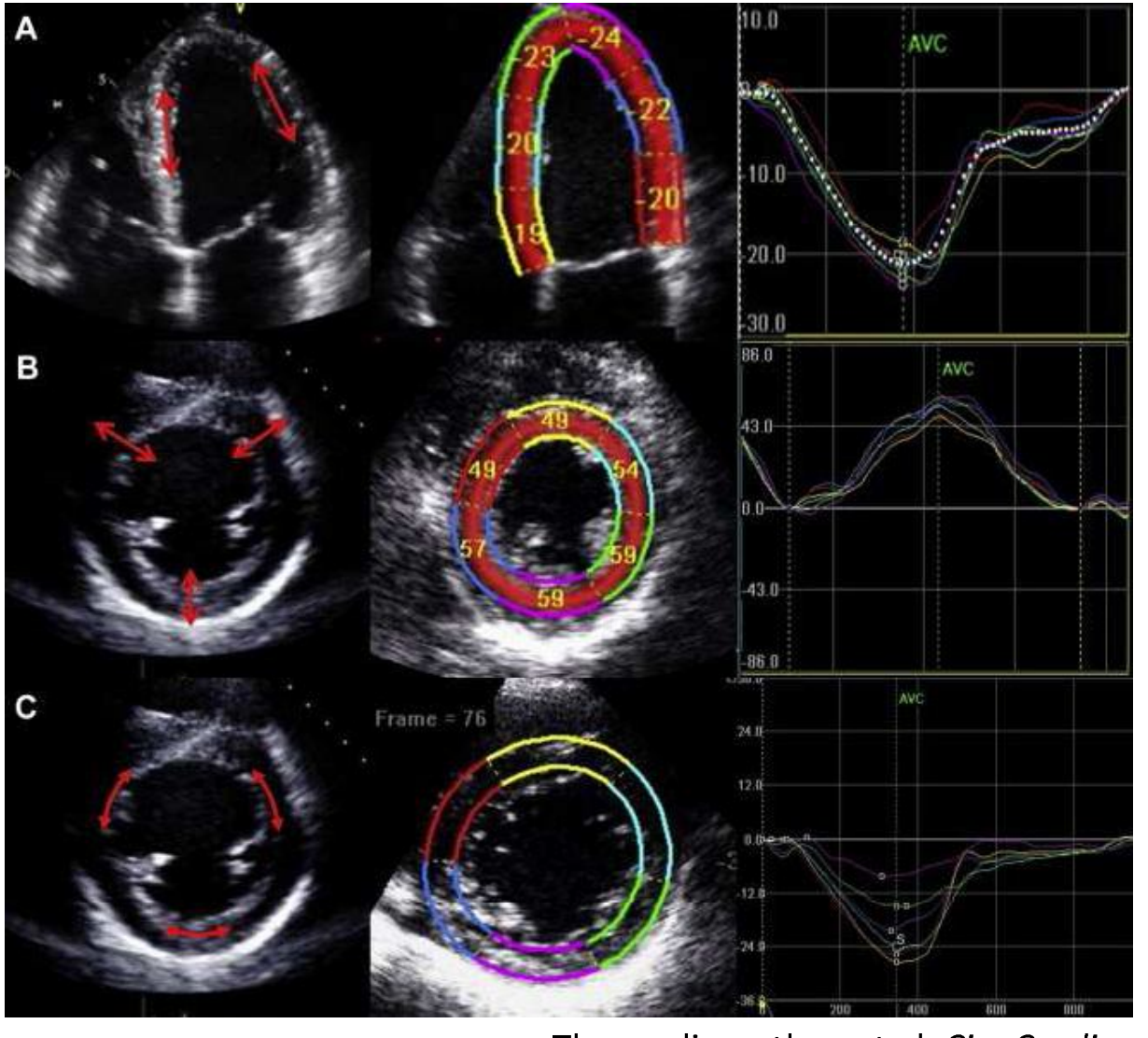
Baseline EF Predicts Cardiotoxicity

CENTRAL ILLUSTRATION: Pre-Trastuzumab Left Ventricular Ejection Fraction Significantly Predicts the Subsequent Development of Trastuzumab-Related Cardiotoxicity

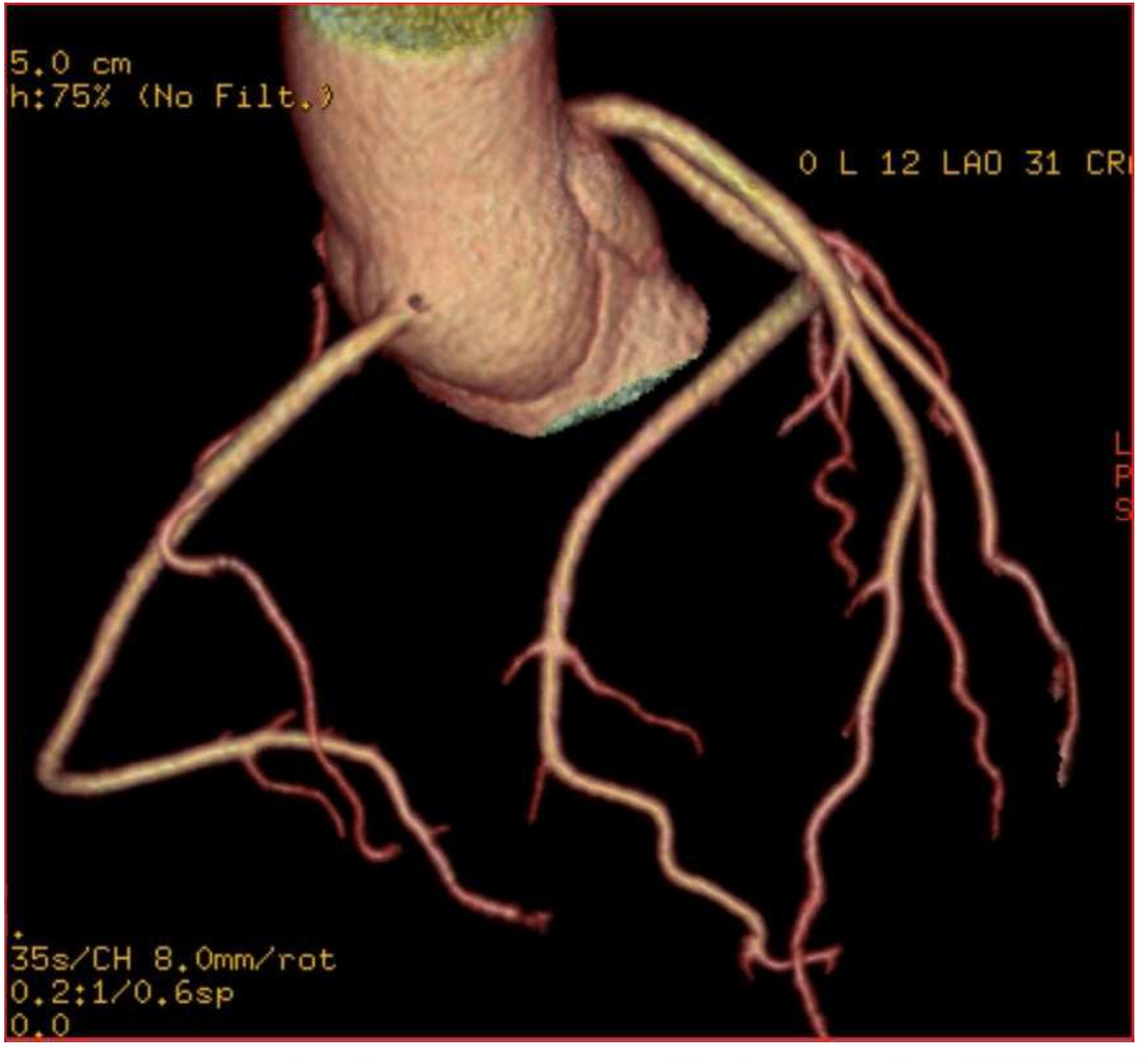


Goel, S. et al. J Am Coll Cardiol HF. 2019;7(9):795-804.

Strain Echocardiography

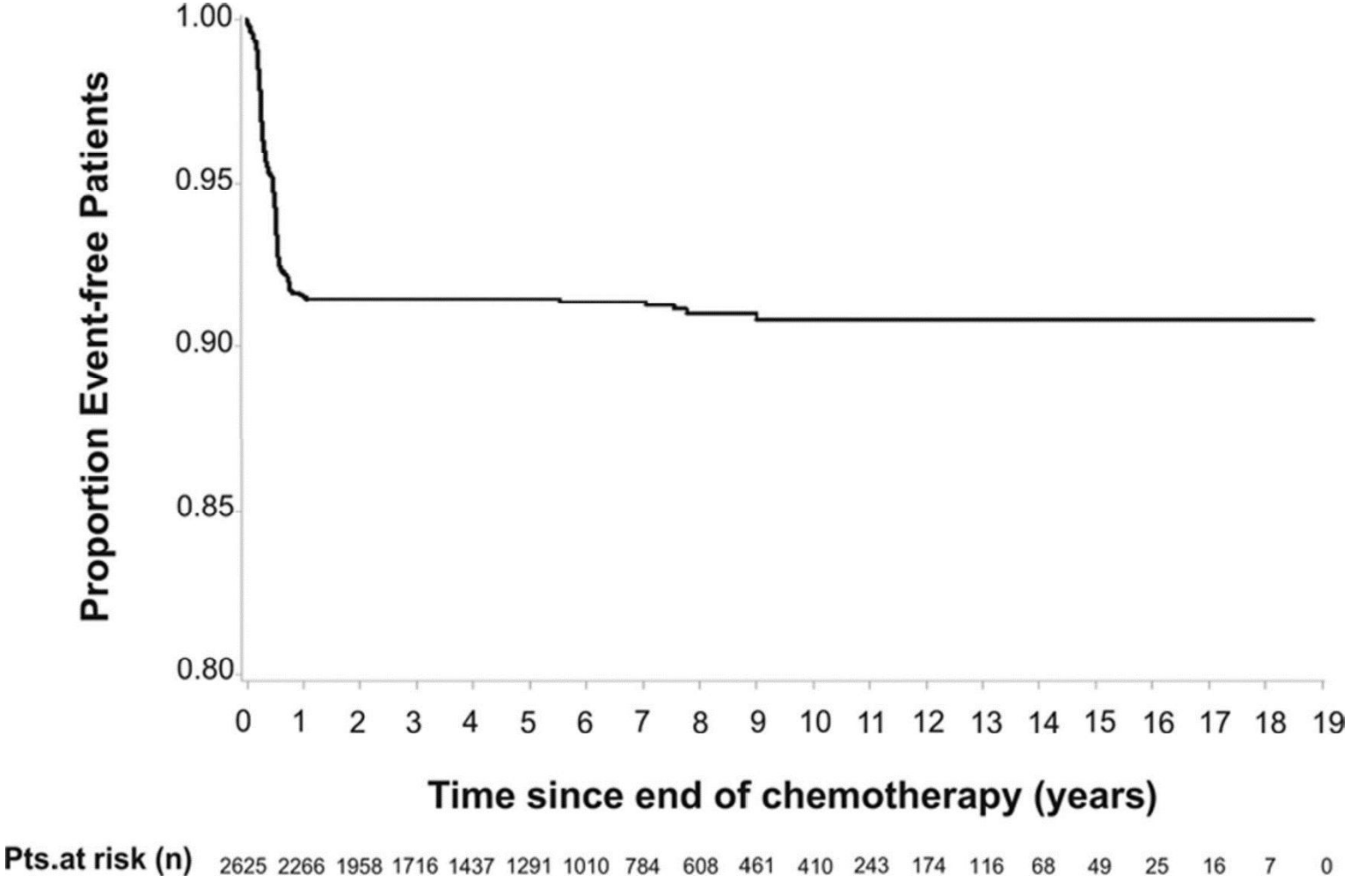


Thavendiranathan et al. *Circ Cardiovasc Imaging 2013*


5.0 cm
h:75% (No Filt.)
0 L 12 LAO 31 CR
35s/CH 8.0mm/rot
0.2:1/0.6sp
0.0

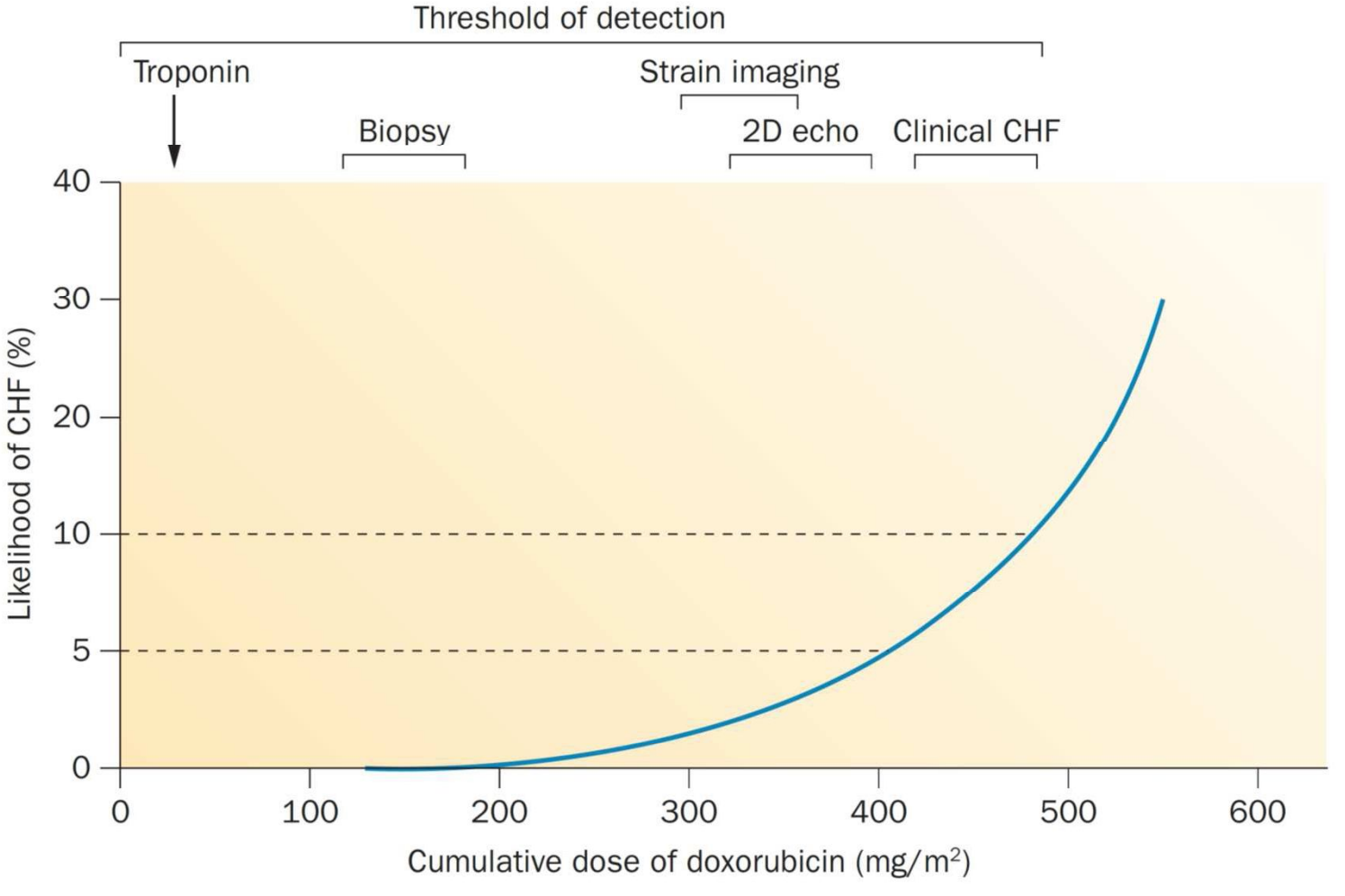
Monitoramento

90% of Anthracycline Cardiotoxicity occurs in first year

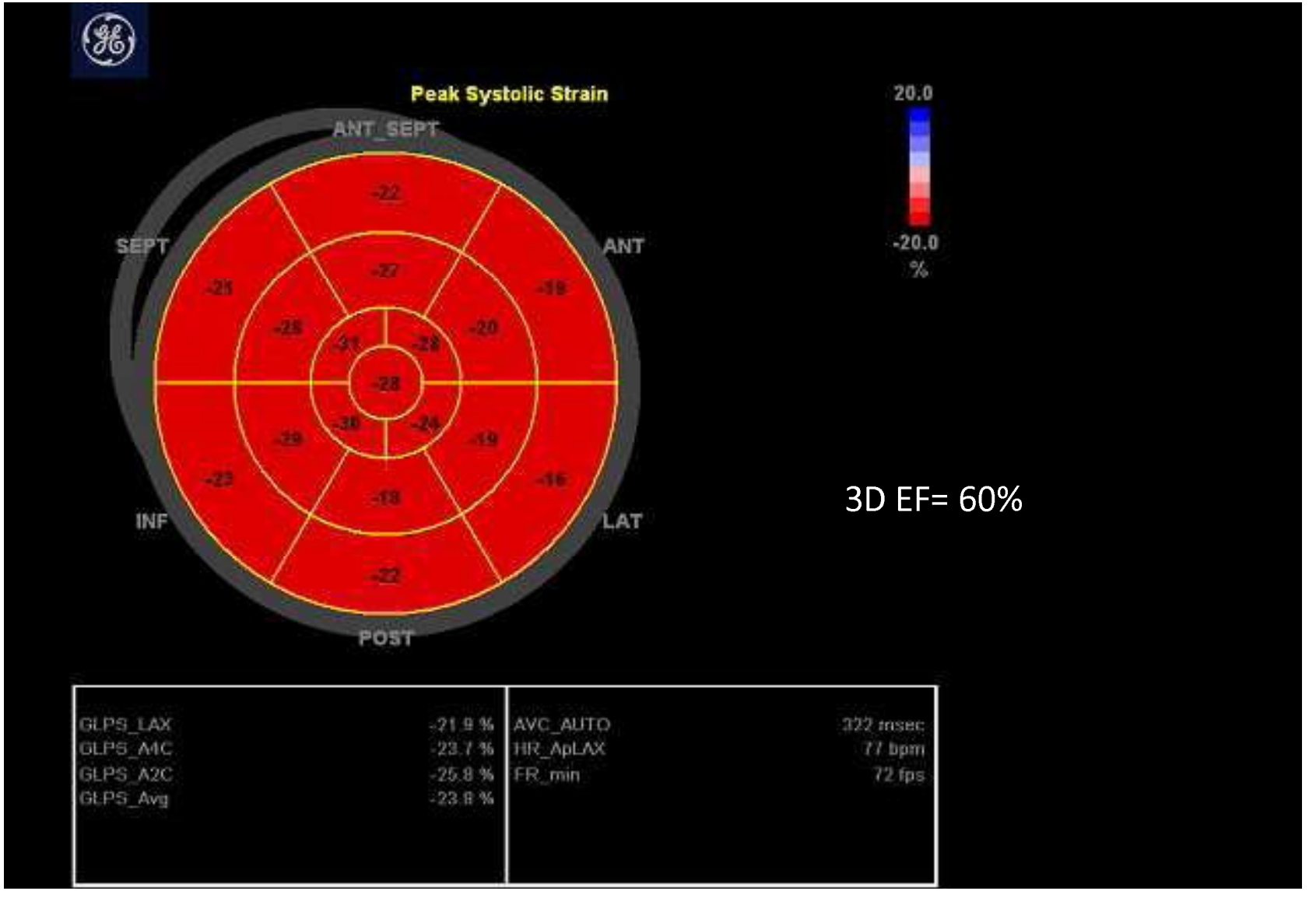


Cardinale et al. Circ 2015

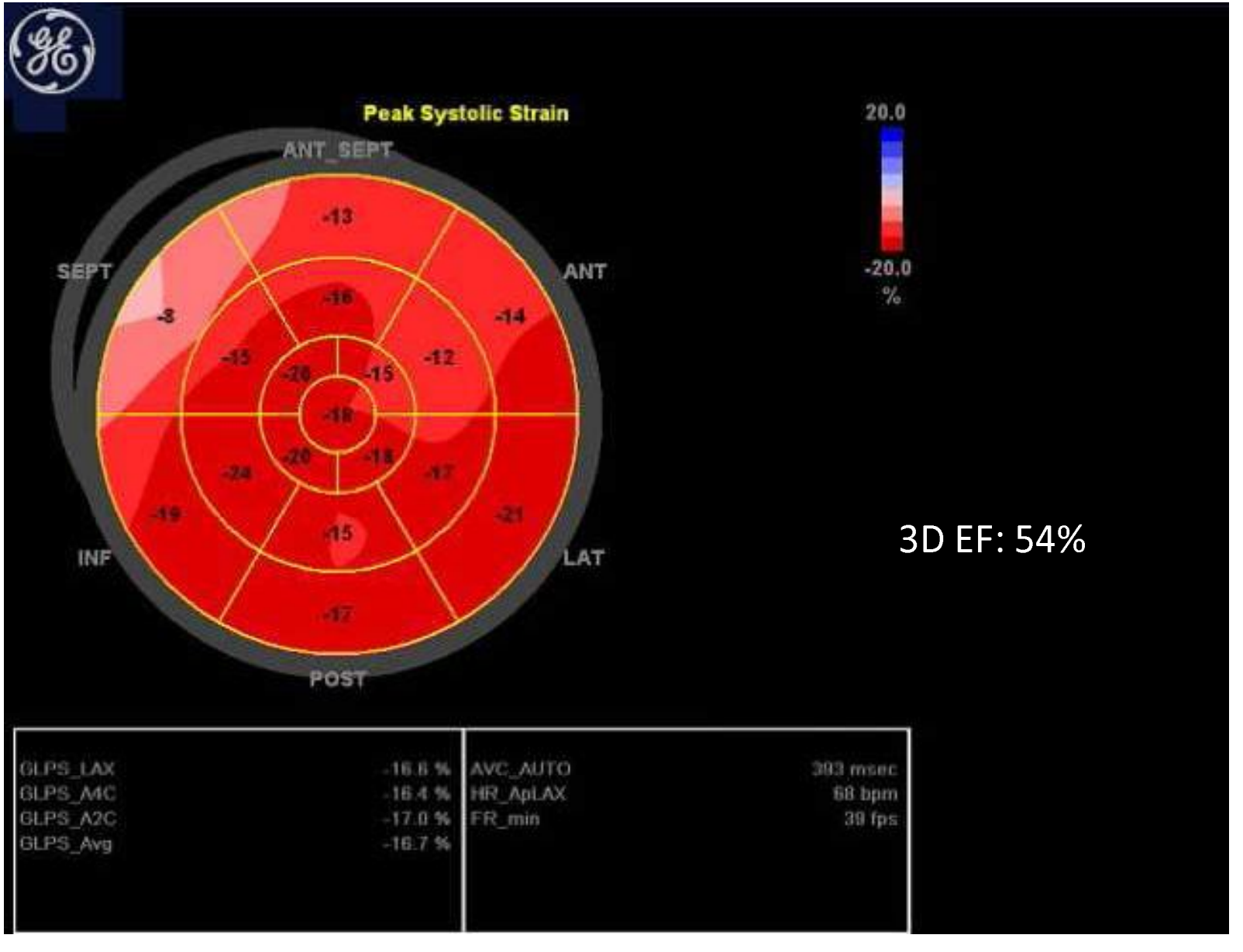
Detection of Cardiotoxicity



Ewer and Ewer. Nat Rev Onc. 2015

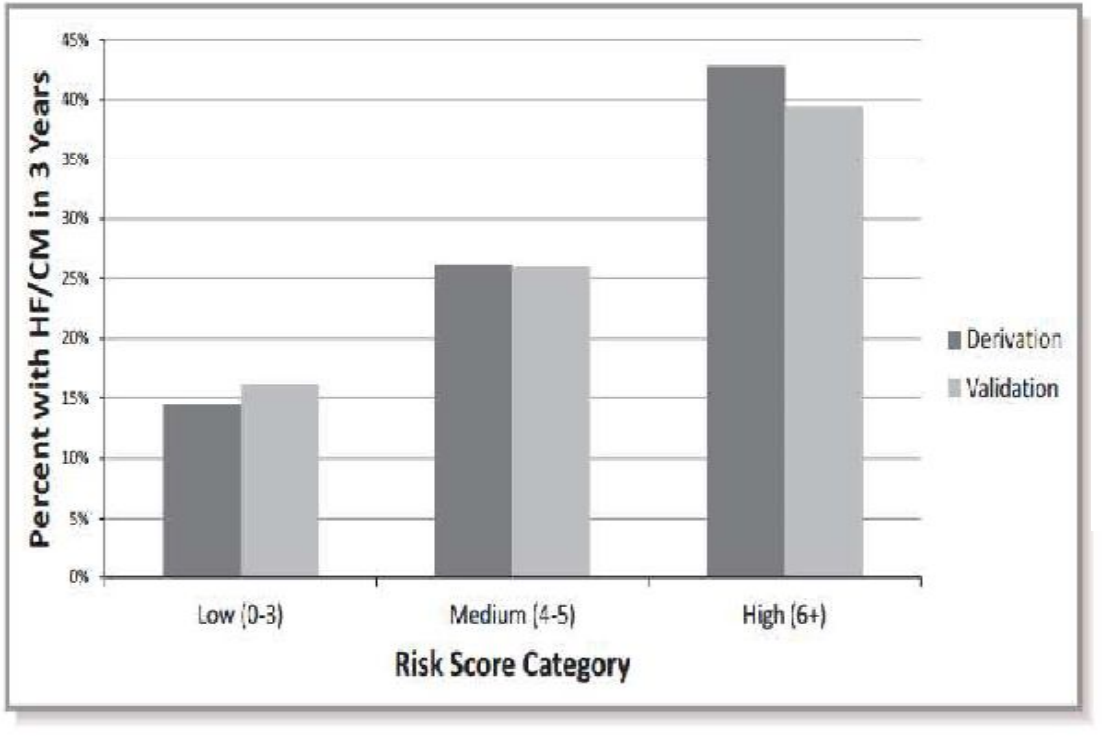

Peak Systolic Strain
ANT_SEPT
ANT
LAT
POST
INF
SEPT
20.0
-20.0
%
-22
-27
-18
-20
-28
-19
-16
-22
-18
-29
-25
-31
-23
-30
-24
GLPS_LAX -21.9 %
GLPS_A4C -23.7 %
GLPS_A2C -25.8 %
GLPS_Avg -23.8 %
AVC_AUTO 322 msec
HR_ApLAX 77 bpm
FR_min 72 fps

3D EF= 60%


Peak Systolic Strain
ANT_SEPT
SEPT
ANT
INF
LAT
POST
-13
-16
-14
-8
-15
-12
-26
-15
-18
-20
-18
-24
-17
-19
-21
-15
-17
20.0
-20.0
%
3D EF: 54%
GLPS_LAX -16.6 %
GLPS_A4C -16.4 %
GLPS_A2C -17.0 %
GLPS_Avg -16.7 %
AVC_AUTO 393 msec
HR_ApLAX 68 bpm
FR_min 39 fps

Risk factors for LVD/CHF with Trastuzumab

SEER Analysis of 1664 women



J Am Heart Assoc. 2014; 3: e000472

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Decreases in strain predict cardiotoxicity

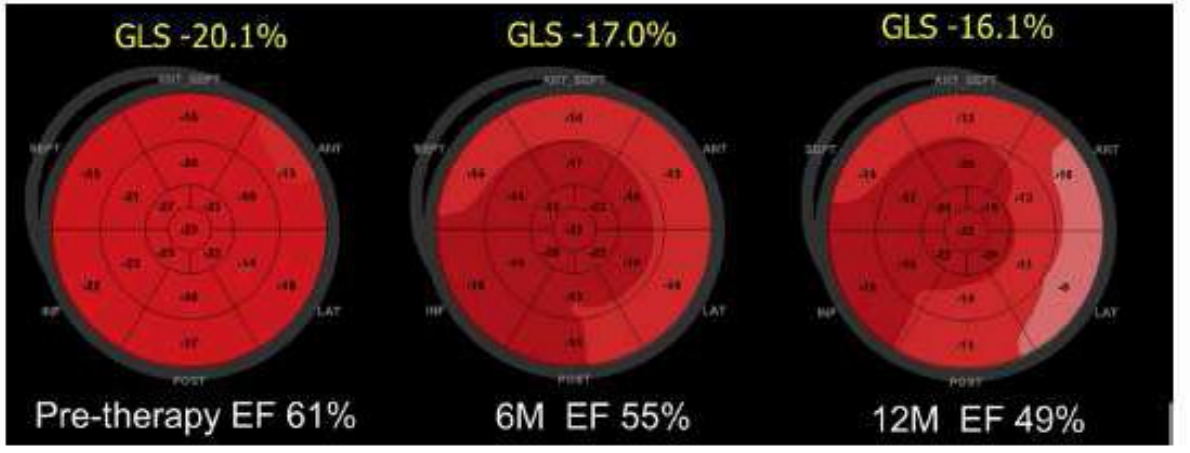


Figure 4 **The Utility of Early Strain Changes to Predict Subsequent Cardiotoxicity**

The images demonstrate a "bull's eye" plot of strain values for each of the 17 myocardial segments. A patient receiving cytotoxic chemotherapy had normal baseline strain and left ventricular (LV) ejection fraction (EF) **(left)**. Six months into therapy, the LVEF dropped by 6% but did not meet criteria for cardiotoxicity. However, the peak systolic global longitudinal strain (GLS) fell by 15.4% (a significant change based on the literature). Then, by 12 months there was a clinically significant fall in LVEF meeting the criteria for cardiotoxicity. See Online Videos 1, 2, and 3 for 4-chamber movie images demonstrating the changes in function. LVEF was calculated using the Biplane Simpson's method. 6M = 6 months; 12M = 12 months.

Thavendiranathan et al. JACC July 2014

Cardiac MRI and Cardiotoxicity Detection

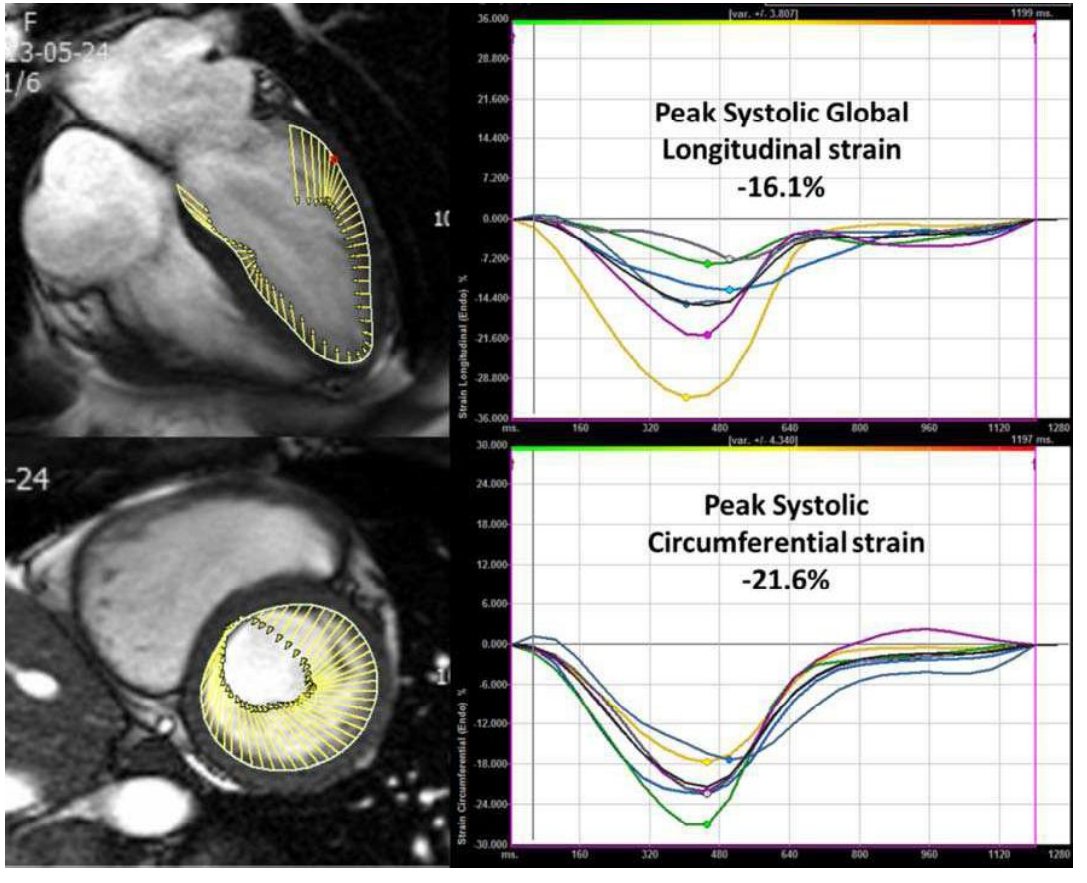
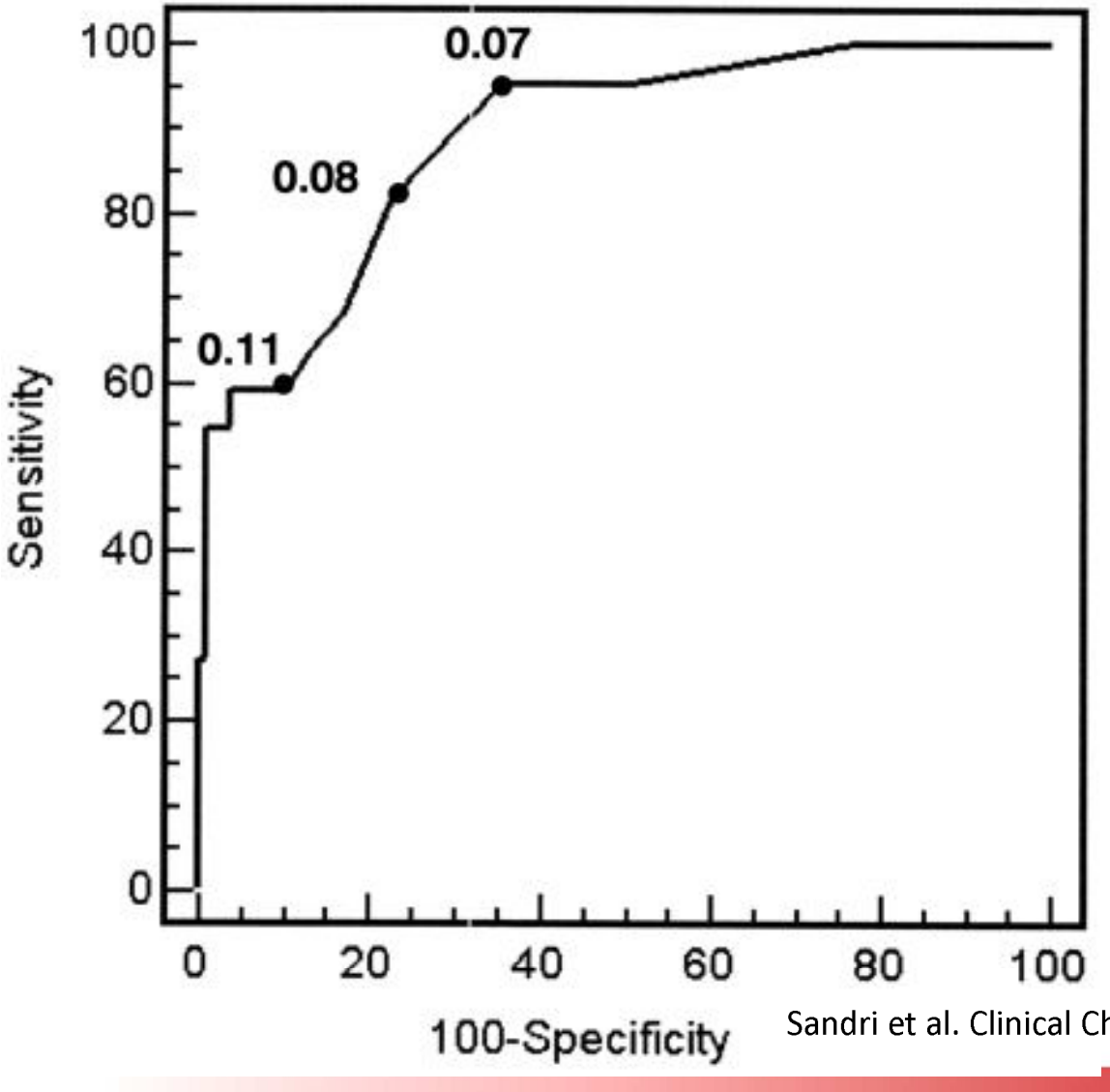


Table 6. Potential Clinical Uses of CMR for Assessment of Cardiac Consequences of Cancer Chemotherapy at Various Stages of Toxicity

	EGE	T2	T1	ECV	Arterial Stiffness	LGE	LV Volume	LVEF
Early injury	√	√	+/–	+/–			√	
Toxicity during or early post-therapy					√	√	√	√
Late cardiotoxicity				√		√	√	√

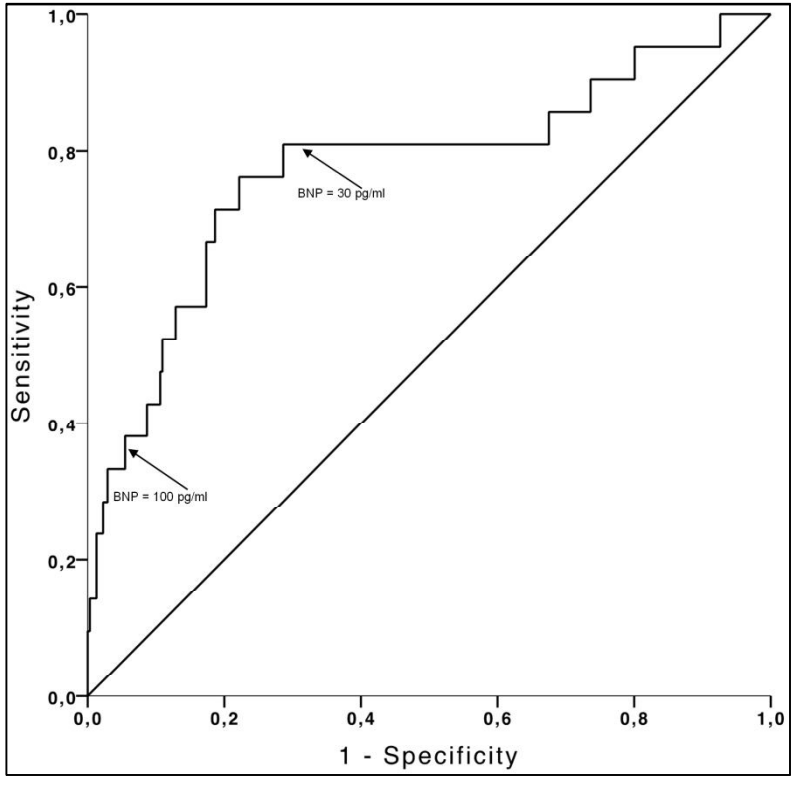
Thavendiranathan et al. *Circ Cardiovasc Imaging 2013*

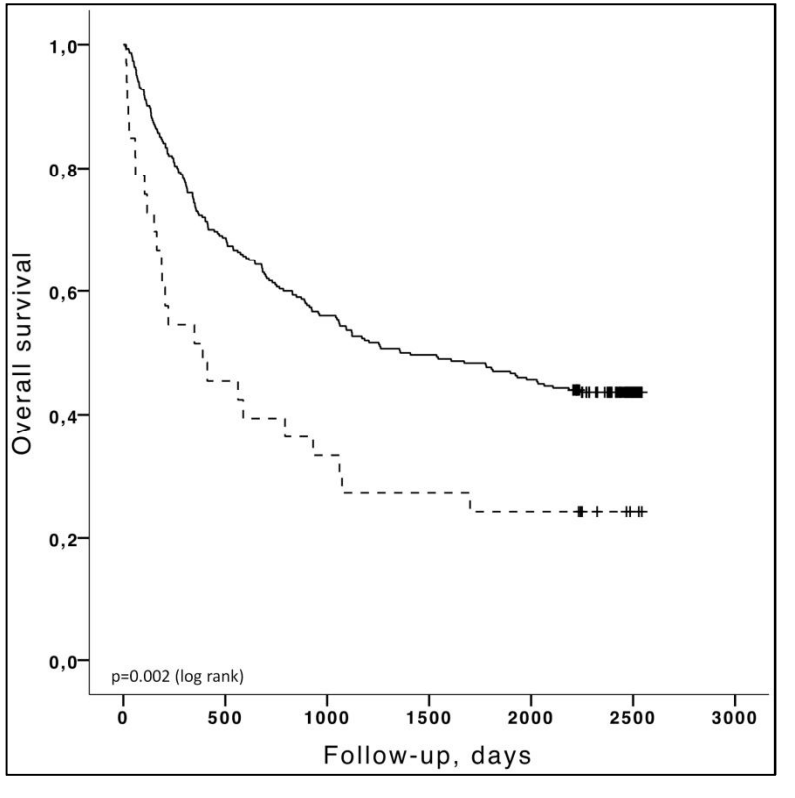
ROC curve for cTnI as marker of cardiotoxicity



Sandri et al. Clinical Chemistry. 2003(49):248-252

BNP predicts cardiotoxicity and death in patients with cancer

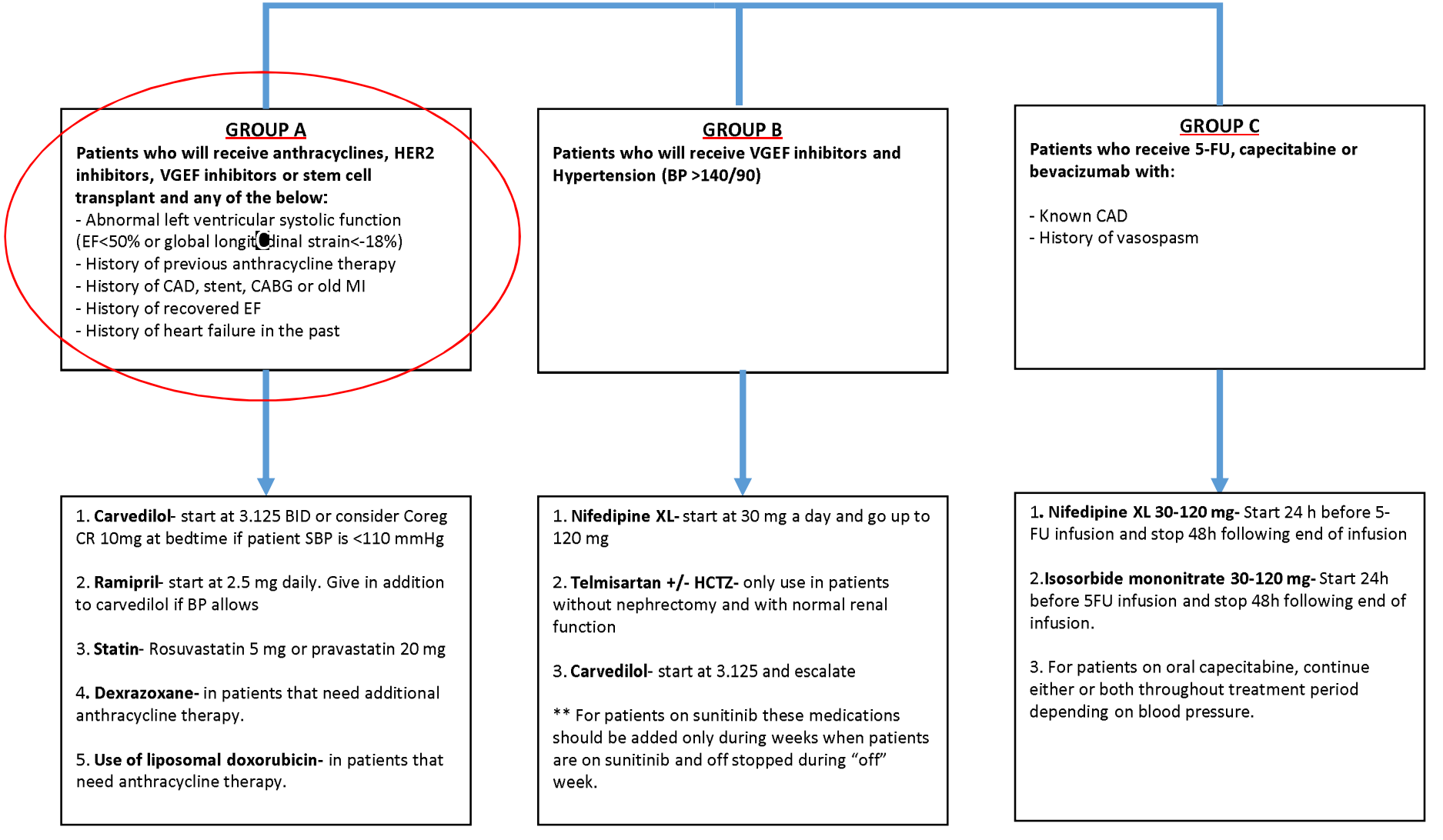




Skovgaard et al. PLOS one 2014

PREVENTION

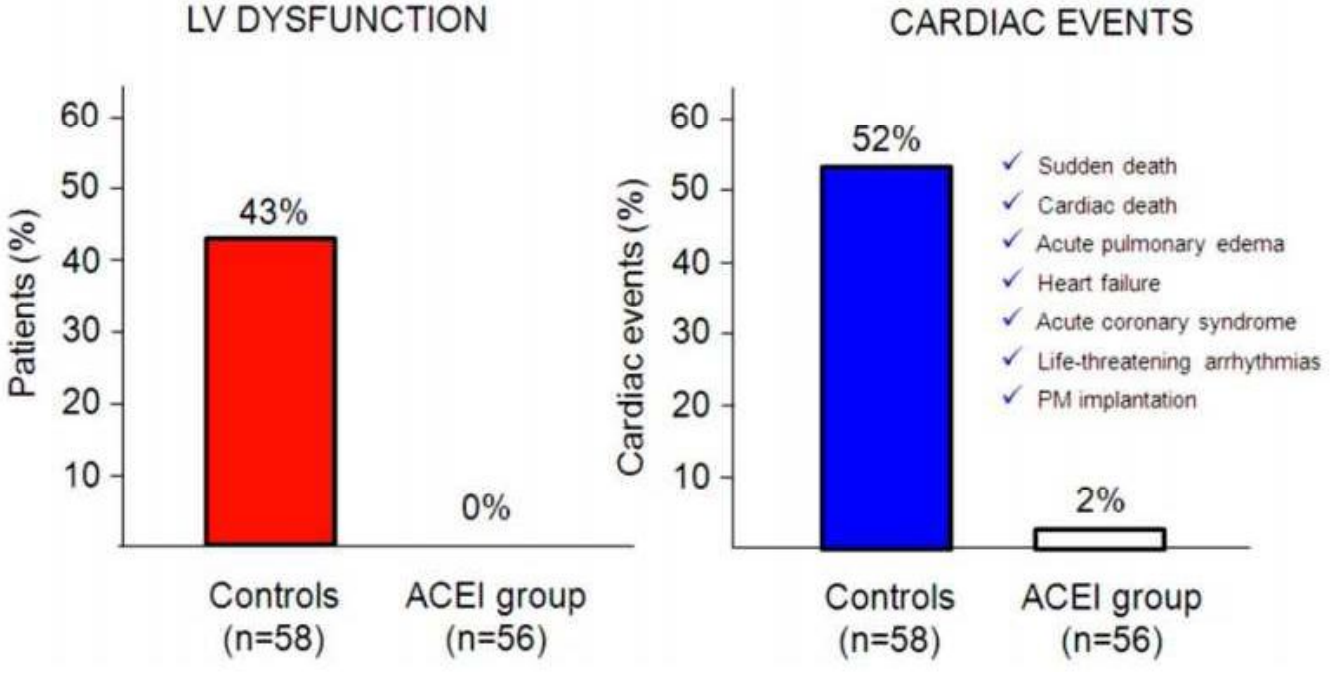
Cardiotoxicity prophylaxis in high-risk patients



UH Cardio-oncology protocols 2016

ACE-I can reduce cardiac events from anthracyclines

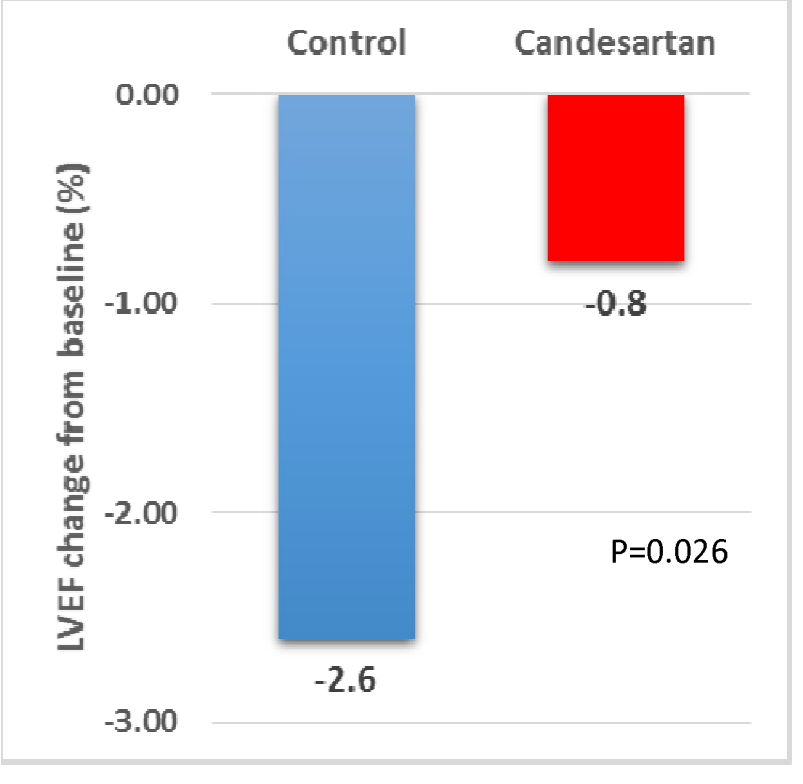
114 women with troponin increase after chemotherapy

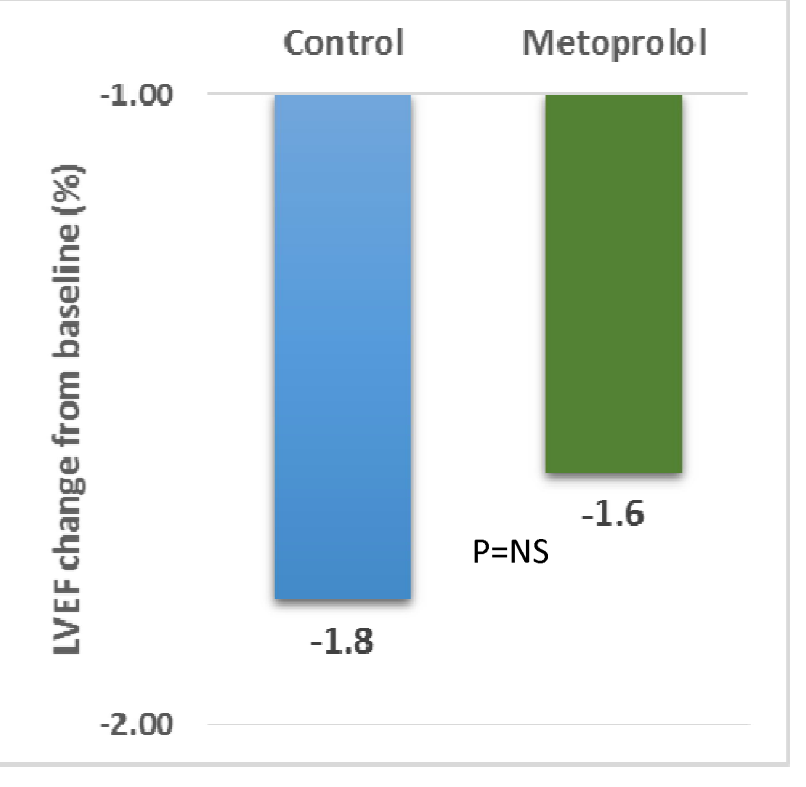


Cardinale et al. Circ 2006

Prevention of cardiotoxicity in Breast Cancer (PRADA Trial)

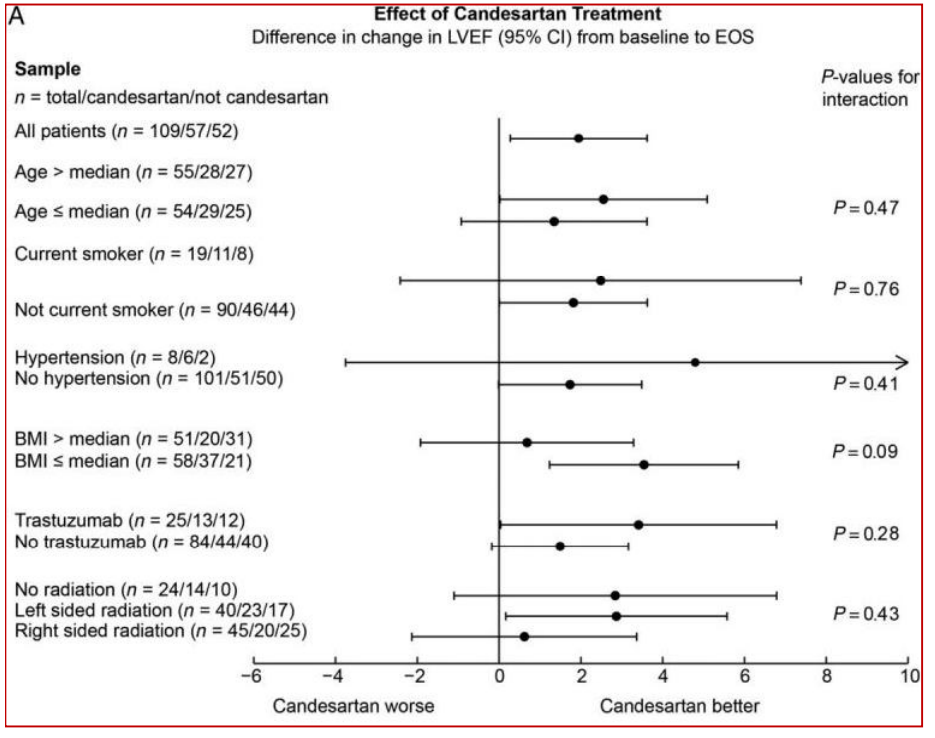
130 women with breast cancer, randomized to metoprolol/candesartan (2x2)

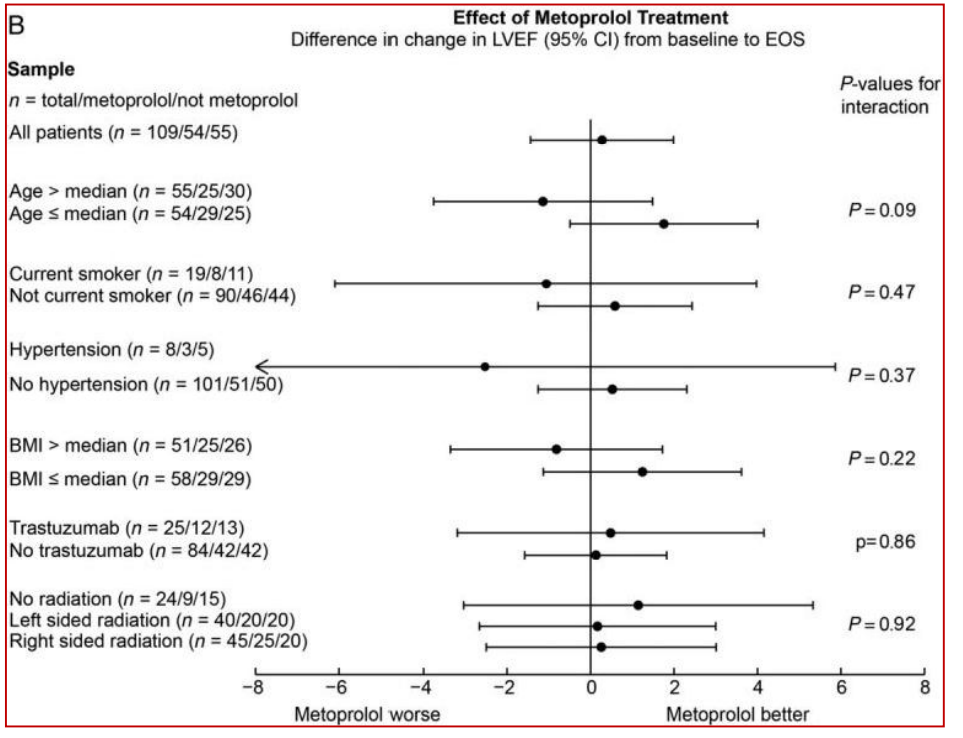




Gulati et al. Eur Heart J 2016

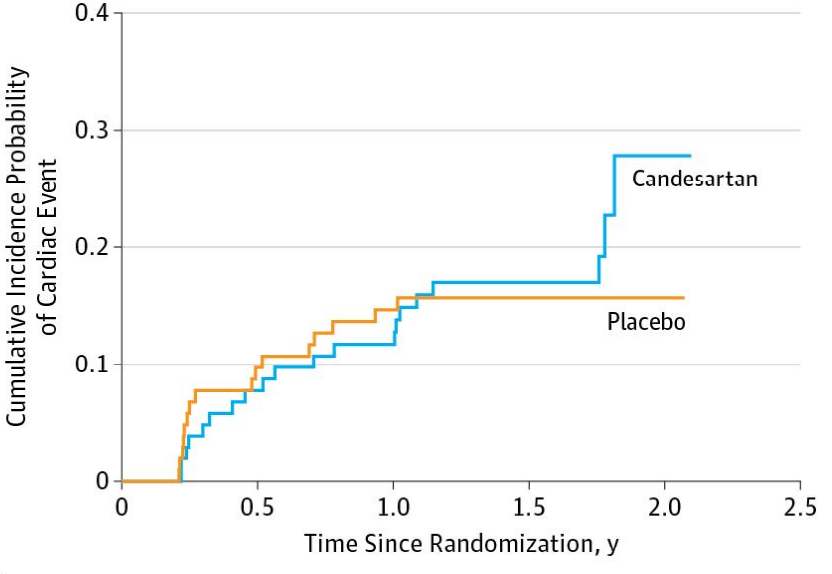
Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA)



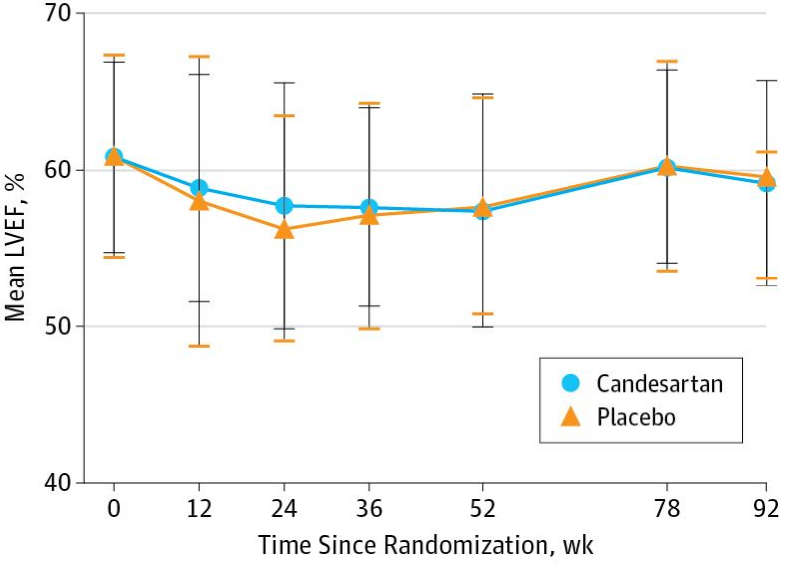


Gulati et al. Eur Heart Jour 2016

Candesartan does not decrease cardiotoxicity in patients undergoing treatment with trastuzumab



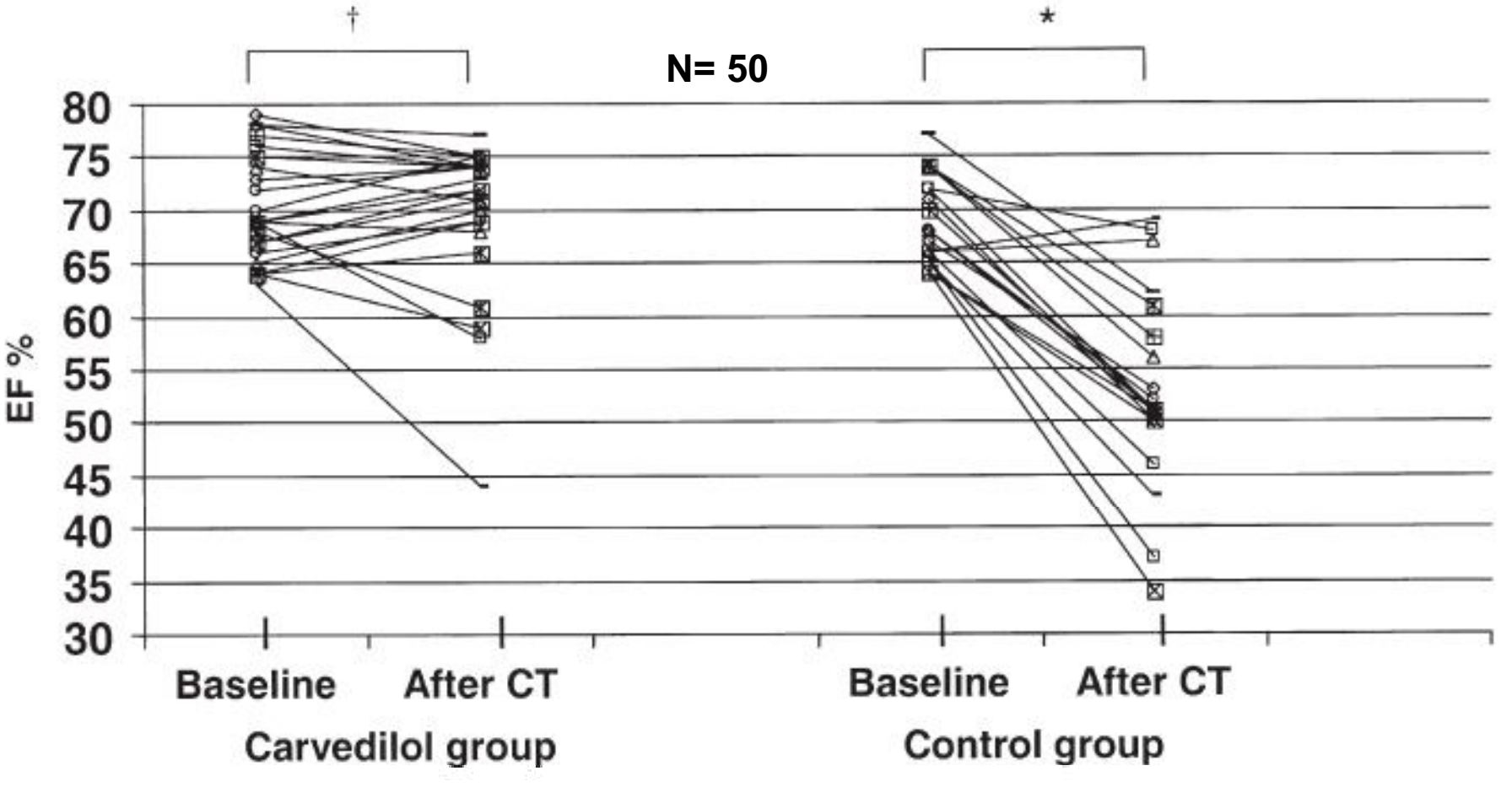
No. at risk						
Candesartan	103	93	84	68	1	0
Placebo	103	92	85	83	4	0



No. at risk							
Candesartan	103	101	100	97	99	85	75
Placebo	103	101	102	96	95	88	84

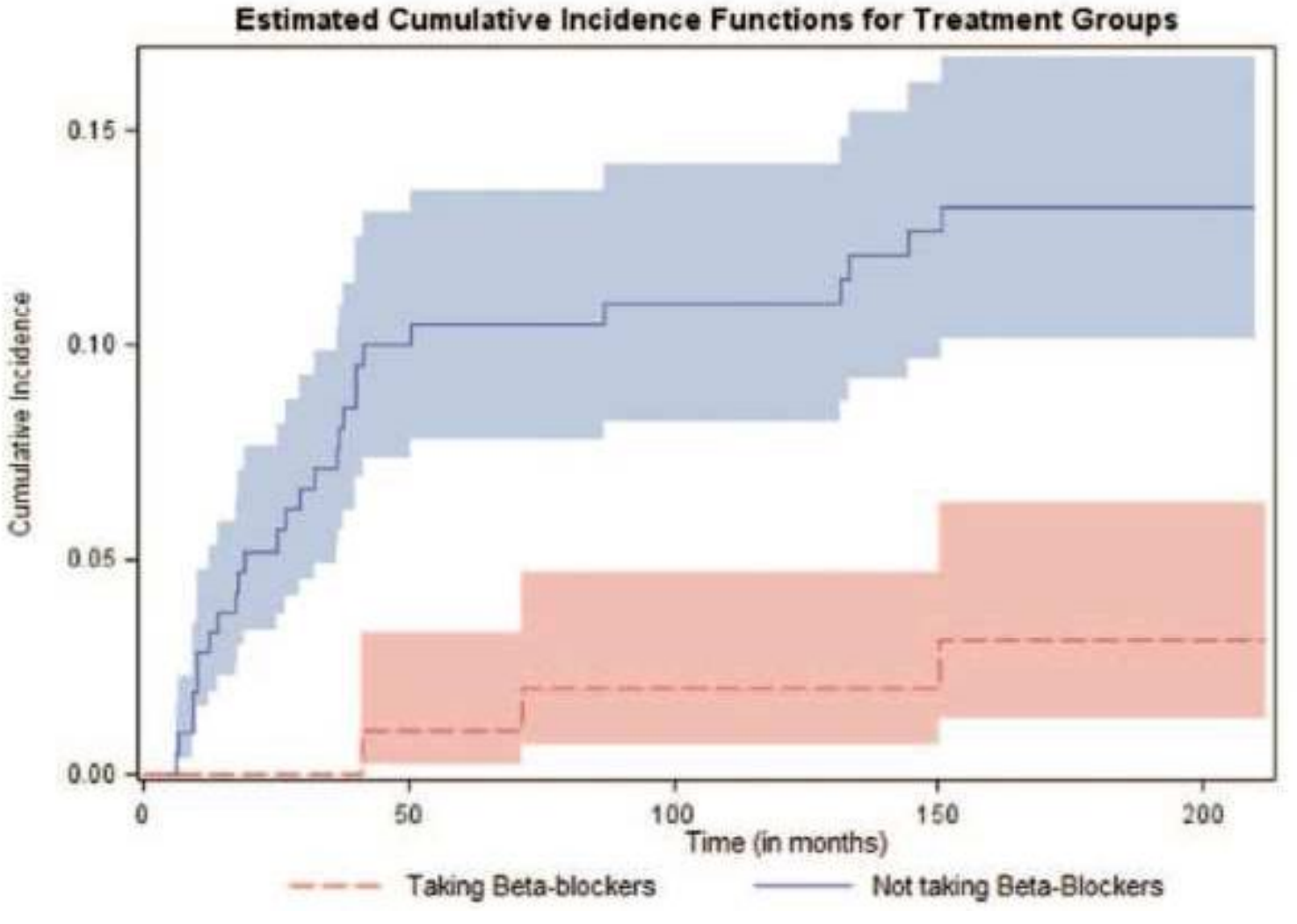
Boekhout et al. JAMA Onc 2016

Carvedilol for cardioprotection



Kalay et al. JACC Dec 2006

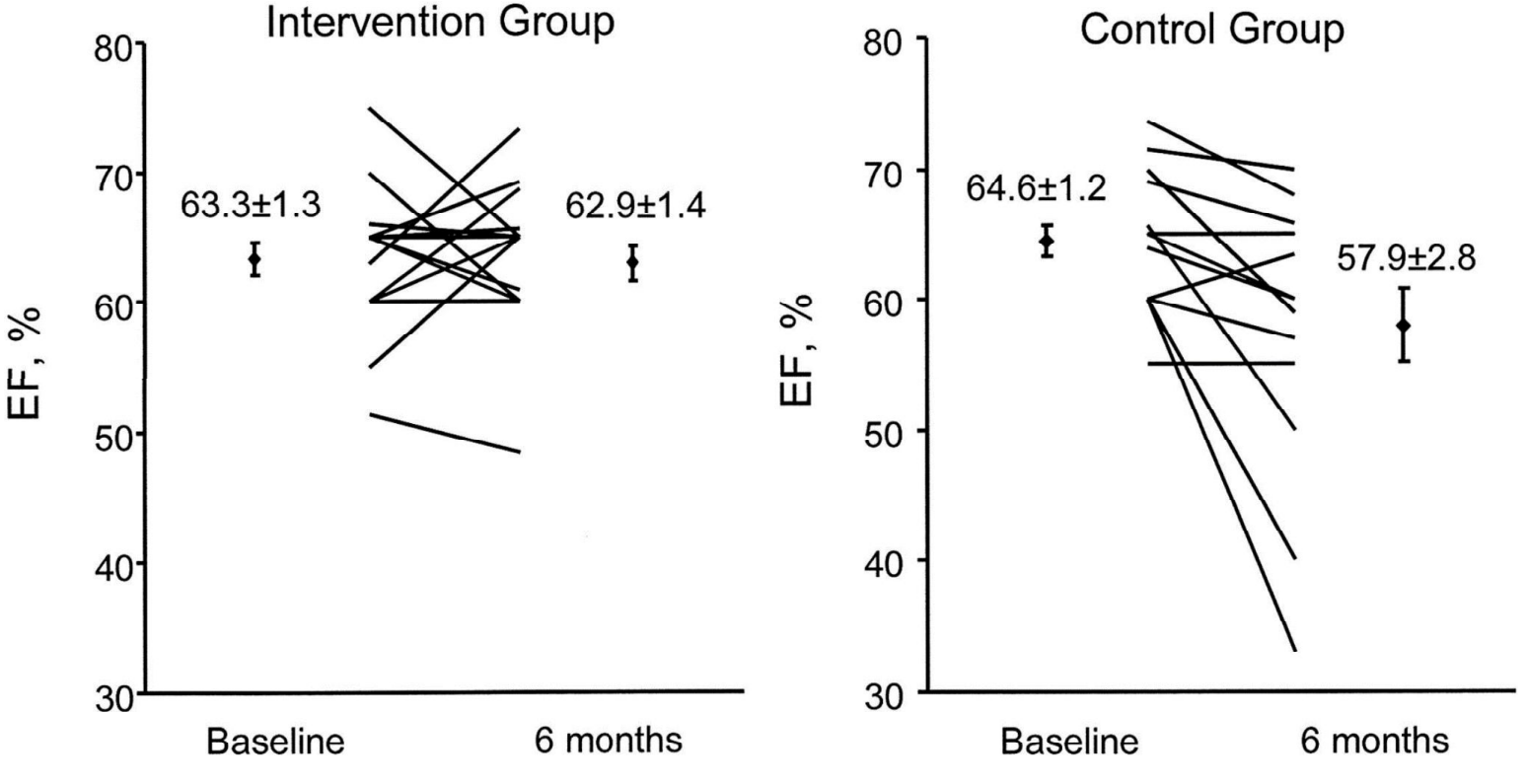
Cardioprotective effects of BB



Seicean et al. Circ Heart Fail. May 2013

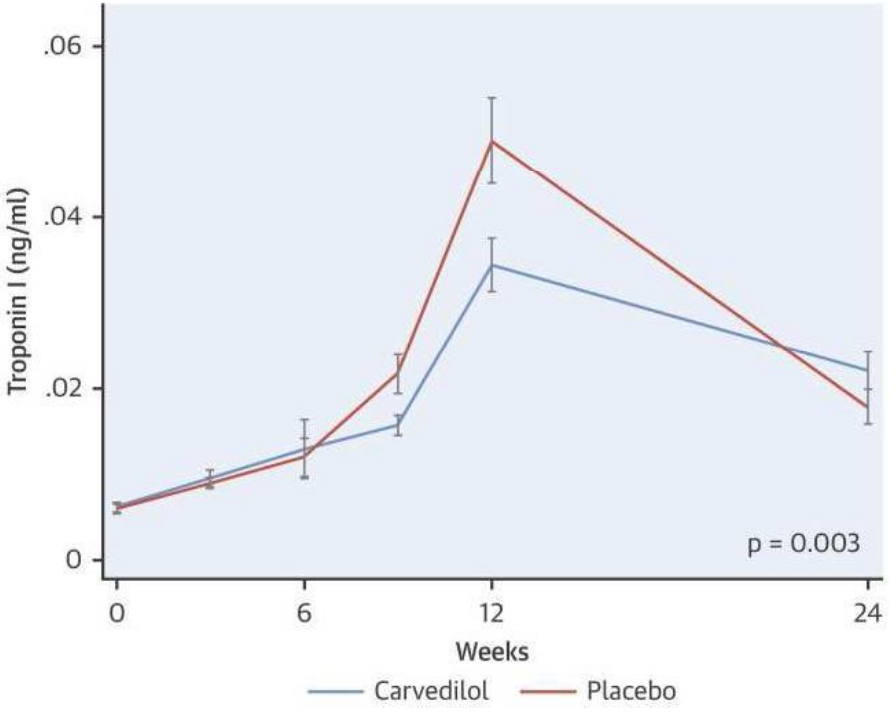
Prevention of cardiotoxicity in hematological malignancy: OVERCOME Trial

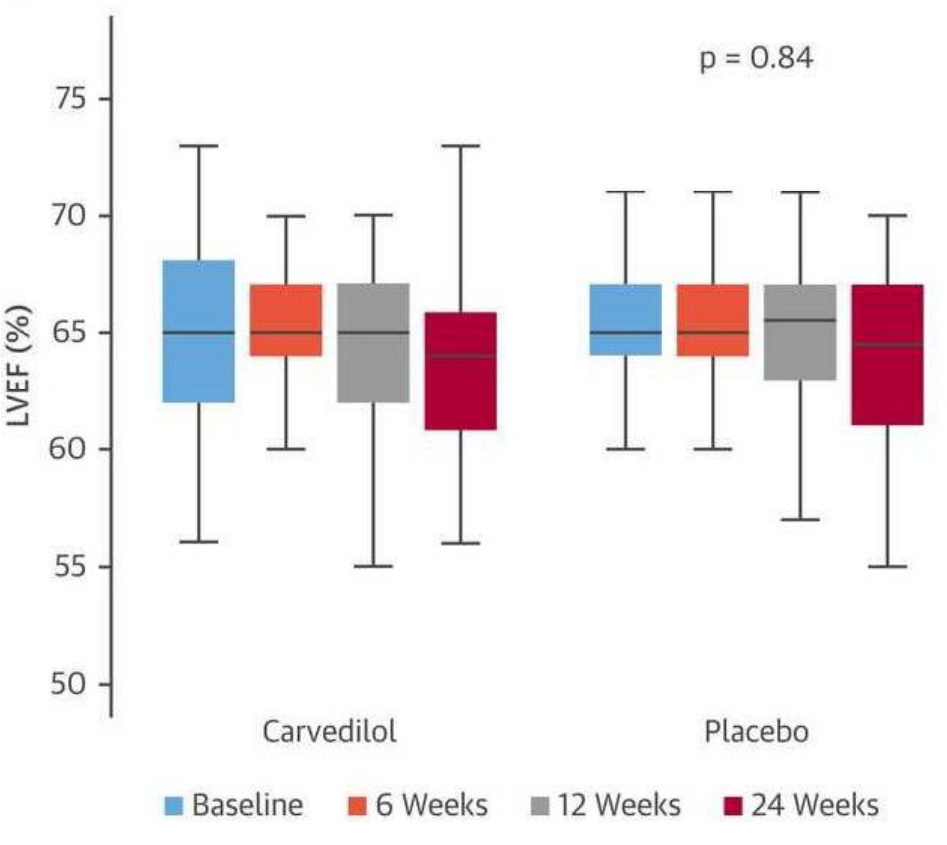
90 patients with hematological malignancies randomized to Enalapril + Carvedilol



Bosch et al. JACC 2013

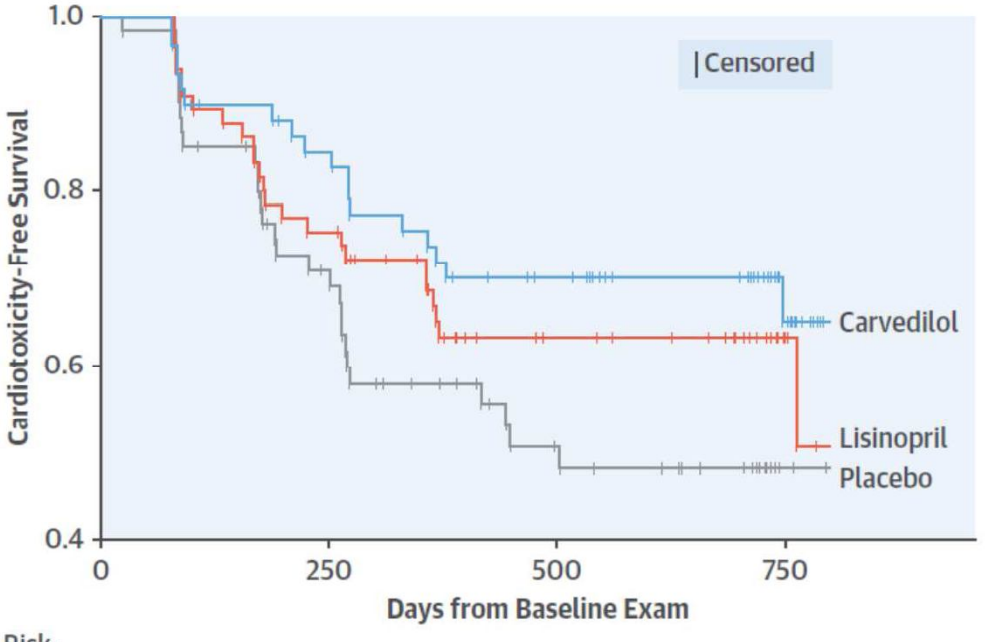
Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial





Avila et al. JACC 2018

CENTRAL ILLUSTRATION **Cardiotoxicity-Free Survival for the Cohort With Trastuzumab and Anthracycline Exposure**



No. at Risk:				
Carvedilol	59	47	34	13
Lisinopril	65	49	27	8
Placebo	60	38	20	4

Guglin, M. et al. J Am Coll Cardiol. 2019;73(22):2859–68.

Kaplan-Meier curves show protective effect of both lisinopril and carvedilol. The hazard ratio for development of cardiotoxicity was 0.49 (95% confidence interval: 0.27 to 0.89) for carvedilol ($p = 0.009$) and 0.53 (95% confidence interval: 0.30 to 0.94) for lisinopril ($p = 0.015$).

Perindopril and Bisoprolol

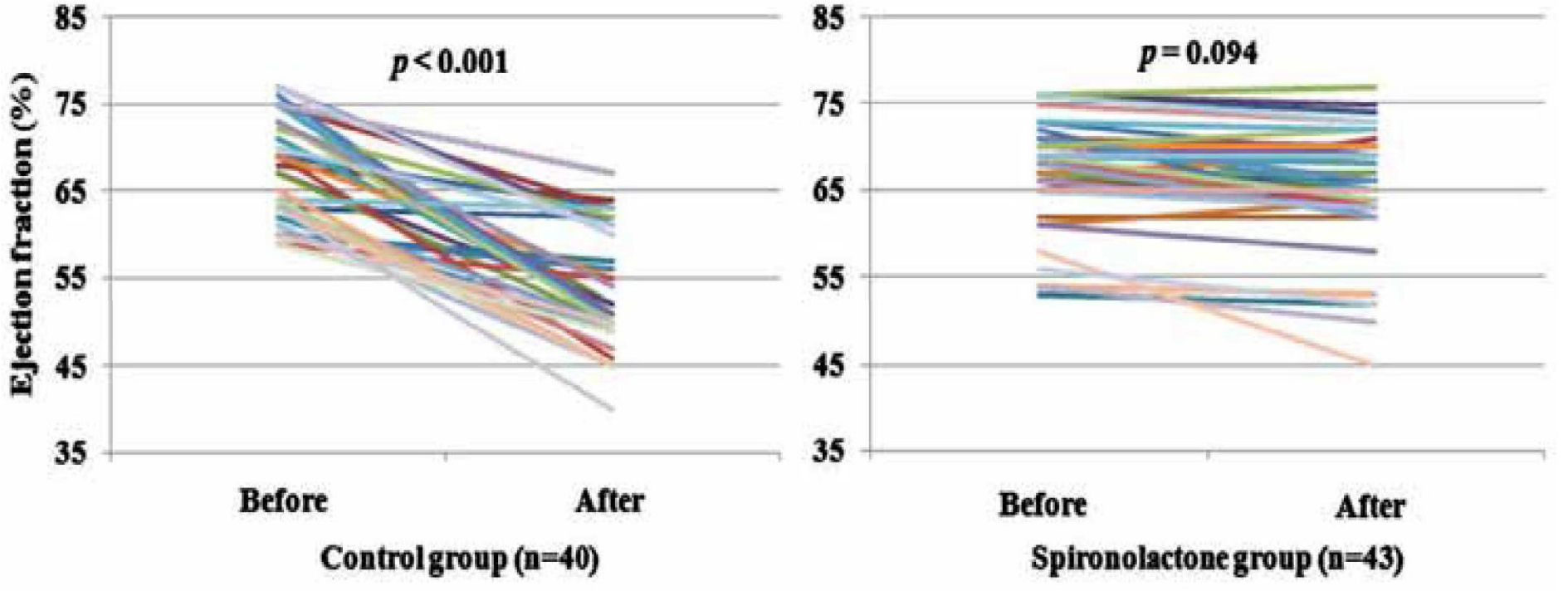
Table 3. Cardiac Magnetic Resonance Imaging Measures Throughout Trastuzumab Therapy

Measure	Placebo (n = 30)	Perindopril (n = 33)	Bisoprolol (n = 31)	ANOVA *P*
LVEDVi, mL/m^2				
Baseline	76 ± 13*	67 ± 14	69 ± 10	.01
Post–cycle 4	77 ± 10	71 ± 16†	76 ± 11†	.09
Change from baseline	+2 ± 9	+4 ± 9	+7 ± 8	.07
Post–cycle 17	79 ± 12	74 ± 16†	76 ± 14†	.27
Change from baseline	+4 ± 11	+7 ± 14	+8 ± 9	.36
LVEF, %				
Baseline	61 ± 5	62 ± 5	62 ± 4	.55
Post–cycle 4	54 ± 5*†	59 ± 6†	59 ± 4†	< .001
Change from baseline	−7 ± 5*	−4 ± 4	−4 ± 5	.01
Post–cycle 17	56 ± 4*†	59 ± 6†	61 ± 4	< .001
Change from baseline	−5 ± 5*	−3 ± 4	−1 ± 5	.001
LVESVi, mL/m^2				
Baseline	30 ± 7*	25 ± 6	26 ± 5	.01
Post–cycle 4	35 ± 7*†	29 ± 8†	31 ± 5†	.002
Change from baseline	6 ± 5	4 ± 5	5 ± 5	.31
Post–cycle 17	35 ± 8*†	30 ± 8†	30 ± 6†	.006
Change from baseline	6 ± 5	5 ± 6	4 ± 4	.37
LV MASSi, g/m^2				
Baseline	53 ± 8	52 ± 7	51 ± 7	.62
Post–cycle 4	55 ± 8†	53 ± 7	53 ± 8	.28
Change from baseline	2 ± 5	1 ± 5	1 ± 5	.58
Post–cycle 17	53 ± 8	52 ± 8	52 ± 6	.61
Change from baseline	0 ± 7	0 ± 5	1 ± 5	.91

NOTE. All values expressed as means ± SD unless indicated.
Abbreviations: LVEDVi, indexed left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, indexed left ventricular end systolic volume; LV MASSi, indexed left ventricular mass.
*$P < 0.05$ compared with other groups.
†$P < 0.05$ from baseline.

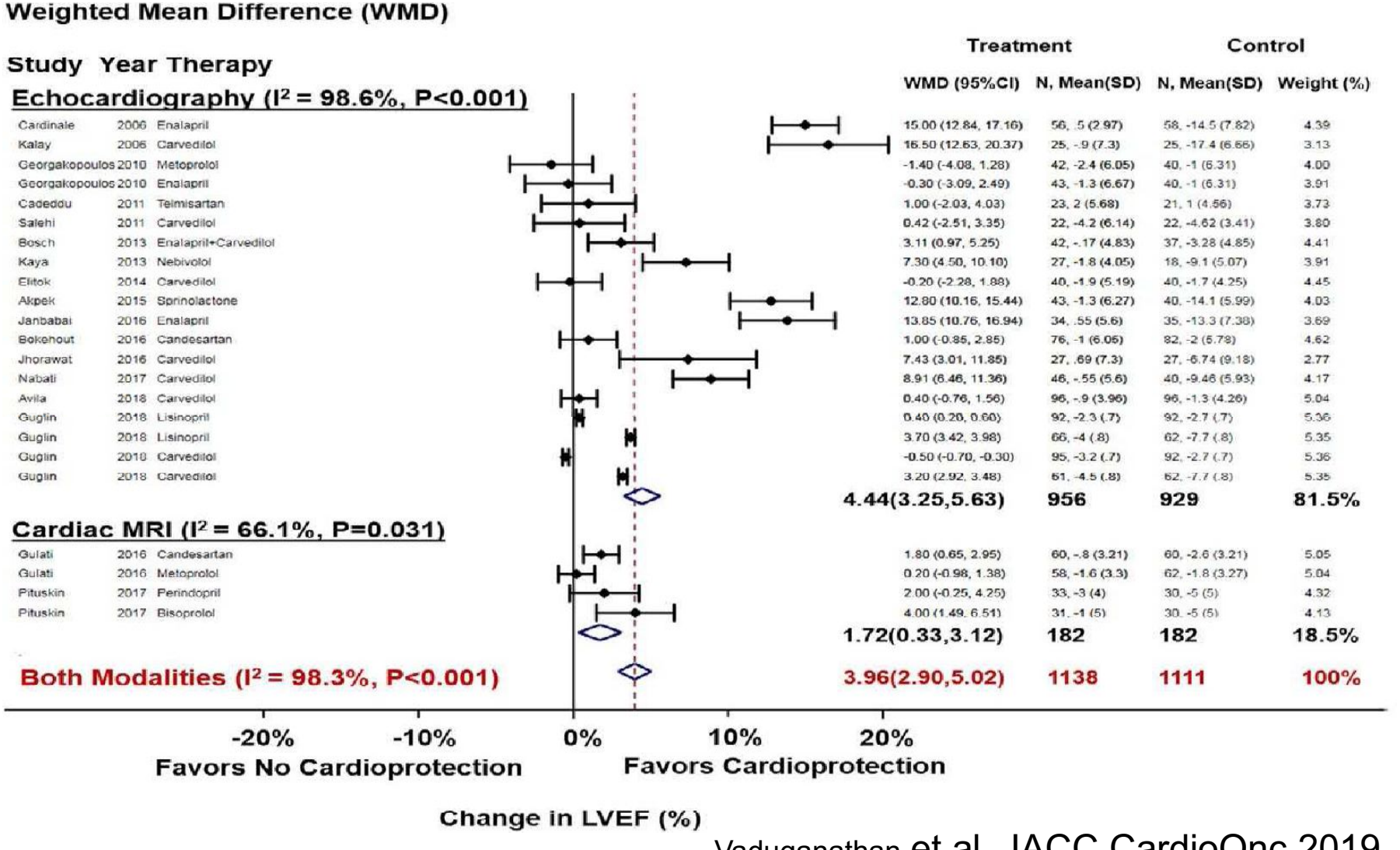
Pituskin et al. JCO 2017

Spironolactone for Cardiotoxicity?



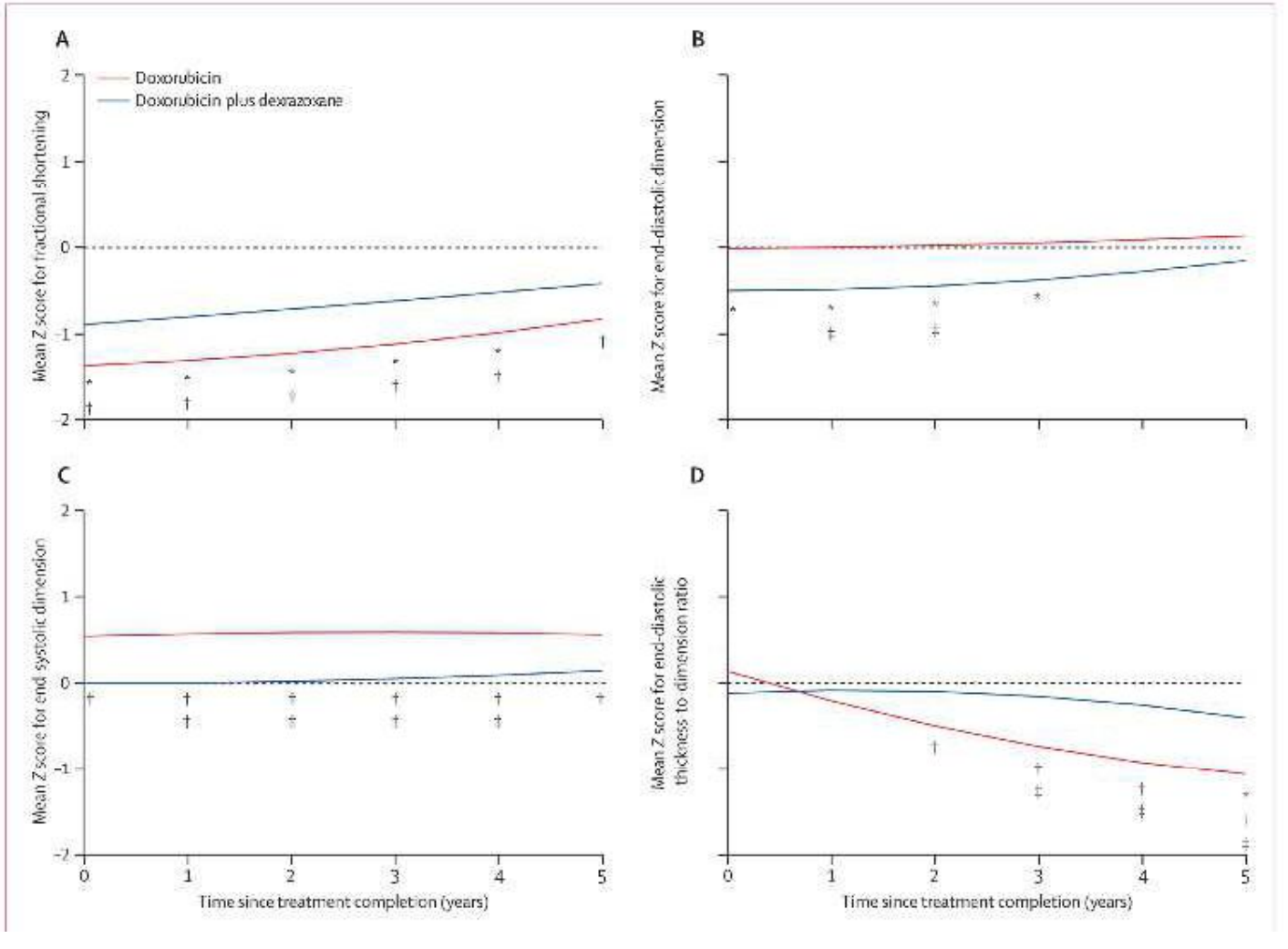
Akpek et al. Eur J Heart Fail. 2015

Meta-Analysis for Prevention with Neurohormonal inhibitors



Vaduganathan et al. JACC CardioOnc 2019

Dexrazoxane for Cardioprotection

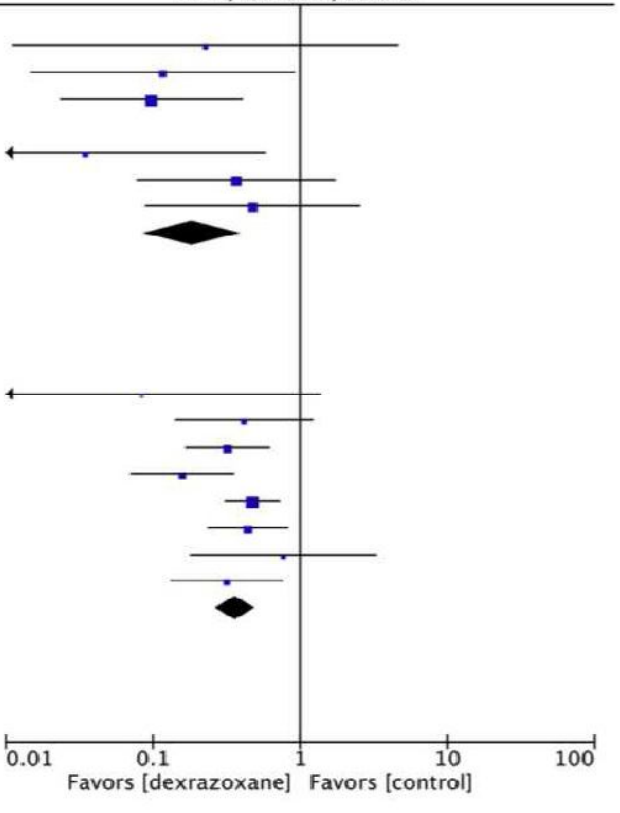


Lipschultz et al. Lancet Oncol. 2010 October

Dexrazoxane Prevents Cardiac Events

FIGURE 3 Forest Plot for the Effect of DEX on the Risk of Clinical Heart Failure and Cardiac Events in BC Patients Treated With ANTs

Study or Subgroup	Dexrazoxane Events	Dexrazoxane Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Clinical heart failure						
Lopez 1998	0	43	2	49	6.3%	0.23 [0.01, 4.61]
Marty 2006	1	85	8	79	13.5%	0.12 [0.01, 0.91]
Speyer 1992	2	76	20	74	28.4%	0.10 [0.02, 0.40]
Sun 2015	0	40	0	40		Not estimable
Swain 1997 (a)	0	168	15	181	7.2%	0.03 [0.00, 0.58]
Swain 1997 (b)	2	81	7	104	24.0%	0.37 [0.08, 1.72]
Venturini 1996	2	82	4	78	20.5%	0.48 [0.09, 2.52]
Subtotal (95% CI)		**575**		**605**	**100.0%**	**0.19 [0.09, 0.40]**
Total events	7		56			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.74$, df = 5 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 4.36 (P < 0.0001)						
1.1.2 Cardiac events						
Kim 2017	0	44	17	131	1.2%	0.08 [0.01, 1.37]
Lopez 1998	4	43	11	49	7.3%	0.41 [0.14, 1.21]
Marty 2006	10	85	29	79	16.8%	0.32 [0.17, 0.61]
Speyer 1992	6	76	37	74	12.0%	0.16 [0.07, 0.35]
Swain 1997 (a)	25	168	57	181	30.1%	0.47 [0.31, 0.72]
Swain 1997 (b)	11	81	32	104	18.0%	0.44 [0.24, 0.82]
Tahover 2017	2	104	18	718	4.2%	0.77 [0.18, 3.26]
Venturini 1996	6	82	18	78	10.5%	0.32 [0.13, 0.76]
Subtotal (95% CI)		**683**		**1414**	**100.0%**	**0.36 [0.27, 0.49]**
Total events	64		219			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.55$, df = 7 (P = 0.29); $I^2 = 18\%$						
Test for overall effect: Z = 6.49 (P < 0.00001)						



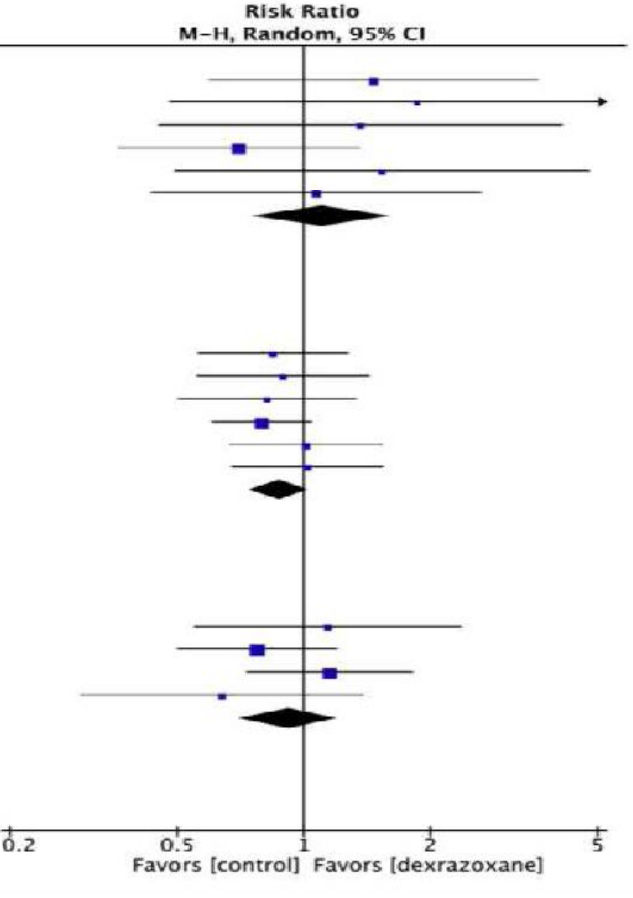
Dexrazoxane (DEX) therapy reduced the risk of cardiac outcomes in patients receiving anthracycline (ANT)-based chemotherapy. CI = confidence interval; df = degree of freedom; M-H = Mantel-Haenszel.

Macedo et al. JACCCO 2019

Dexrazoxane Use and Cancer Response

FIGURE 4 Forest Plot for the Effect of DEX on Oncological Response in BC Patients Treated With ANTs

Study or Subgroup	Dexrazoxane Events	Dexrazoxane Total	Control Events	Control Total	Weight	Risk Ratio M–H, Random, 95% CI
1.2.1 Complete response						
Lopez 1998	9	43	7	49	17.9%	1.47 [0.60, 3.60]
Marty 2006	6	85	3	79	7.9%	1.86 [0.48, 7.18]
Speyer 1992	7	76	5	74	11.9%	1.36 [0.45, 4.10]
Swain 1997 (a)	13	141	20	152	33.2%	0.70 [0.36, 1.36]
Swain 1997 (b)	6	54	5	69	11.3%	1.53 [0.49, 4.76]
Venturini 1996	9	82	8	78	17.8%	1.07 [0.43, 2.63]
Subtotal (95% CI)		**481**		**501**	**100.0%**	**1.10 [0.75, 1.61]**
Total events	50		48			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.24$, df = 5 (P = 0.66); $I^2 = 0\%$						
Test for overall effect: Z = 0.50 (P = 0.62)						
1.2.2 Partial response						
Lopez 1998	20	43	27	49	14.9%	0.84 [0.56, 1.27]
Marty 2006	24	85	25	79	11.3%	0.89 [0.56, 1.43]
Speyer 1992	21	76	25	74	10.6%	0.82 [0.50, 1.33]
Swain 1997 (a)	53	141	72	152	34.0%	0.79 [0.61, 1.04]
Swain 1997 (b)	23	54	29	69	14.4%	1.01 [0.67, 1.54]
Venturini 1996	30	82	28	78	14.7%	1.02 [0.68, 1.54]
Subtotal (95% CI)		**481**		**501**	**100.0%**	**0.88 [0.75, 1.02]**
Total events	171		206			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.62$, df = 5 (P = 0.90); $I^2 = 0\%$						
Test for overall effect: Z = 1.66 (P = 0.10)						
1.2.3 Stable disease						
Lopez 1998	11	43	11	49	13.7%	1.14 [0.55, 2.36]
Marty 2006	25	85	30	79	38.6%	0.77 [0.50, 1.19]
Swain 1997 (a)	31	141	29	152	35.6%	1.15 [0.73, 1.81]
Swain 1997 (b)	8	54	16	69	12.2%	0.64 [0.30, 1.38]
Subtotal (95% CI)		**323**		**349**	**100.0%**	**0.92 [0.70, 1.20]**
Total events	75		86			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.75$, df = 3 (P = 0.43); $I^2 = 0\%$						
Test for overall effect: Z = 0.62 (P = 0.54)						



Oncological outcomes were similar in groups exposed or not exposed to dexrazoxane. Abbreviations as in Figure 3.

Macedo et al. JACCCO 2019

Primary Prevention of Anthracycline Cardiotoxicity

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

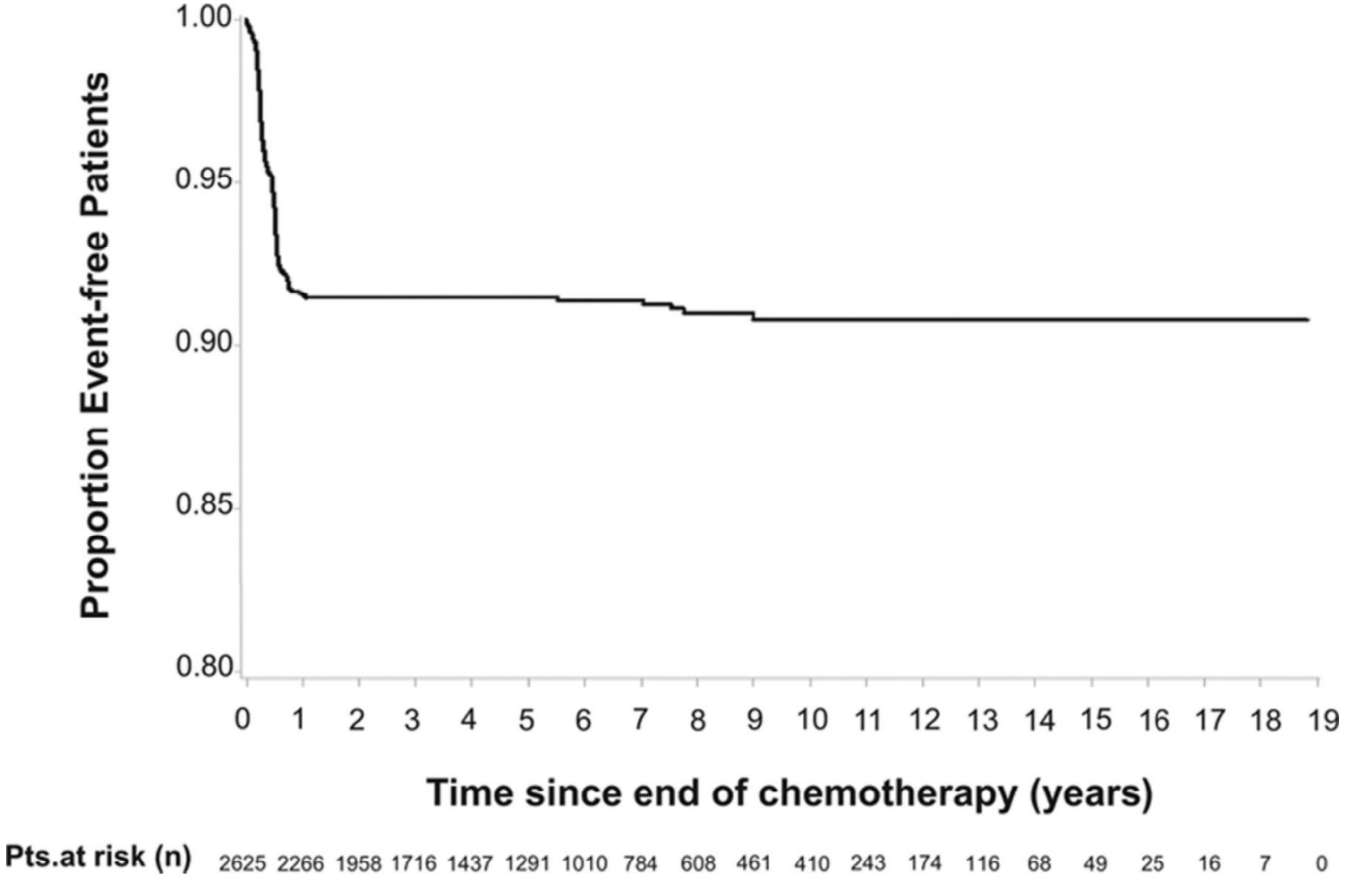
*2014 Walmart pharmacy prices. †May be higher, depending on hospital stay or infusion pump care costs.

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

Yeh ET et al. JACC 2015

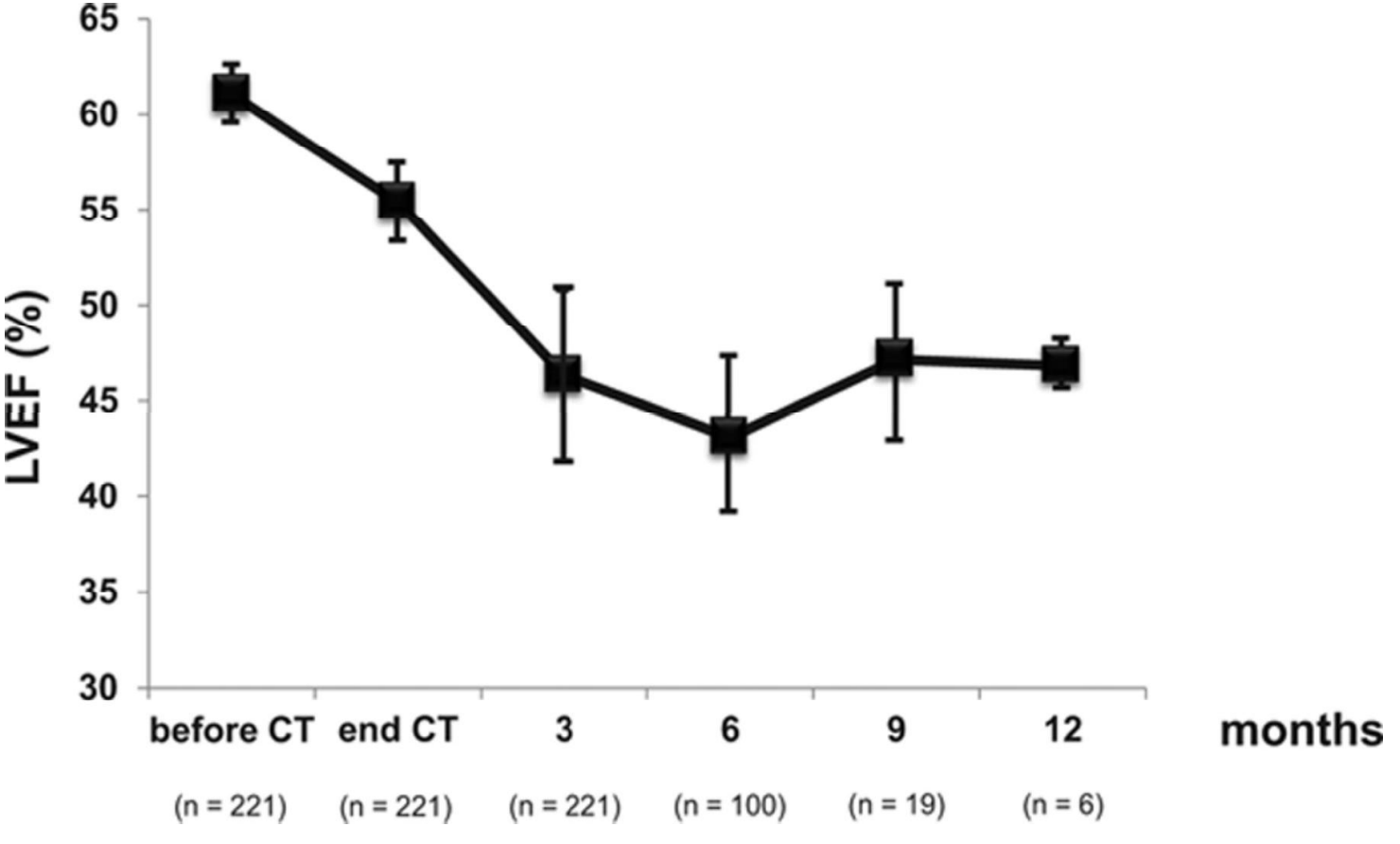
Treatment of Cardiotoxicity

90% of anthracycline cardiotoxicity occurs in the first year



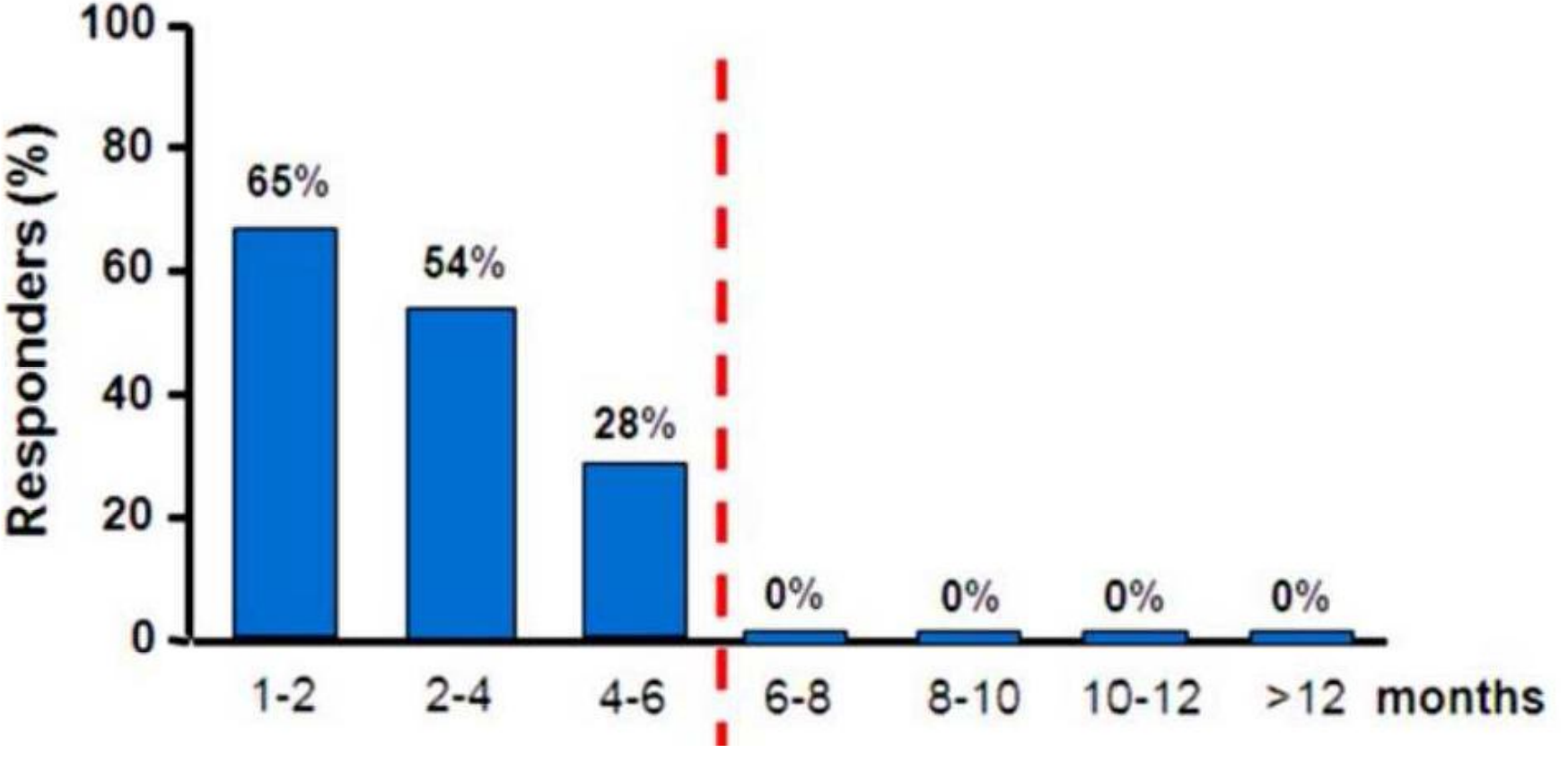
Cardinale et al. Circ 2015

LVEF decline may improve with medical therapy

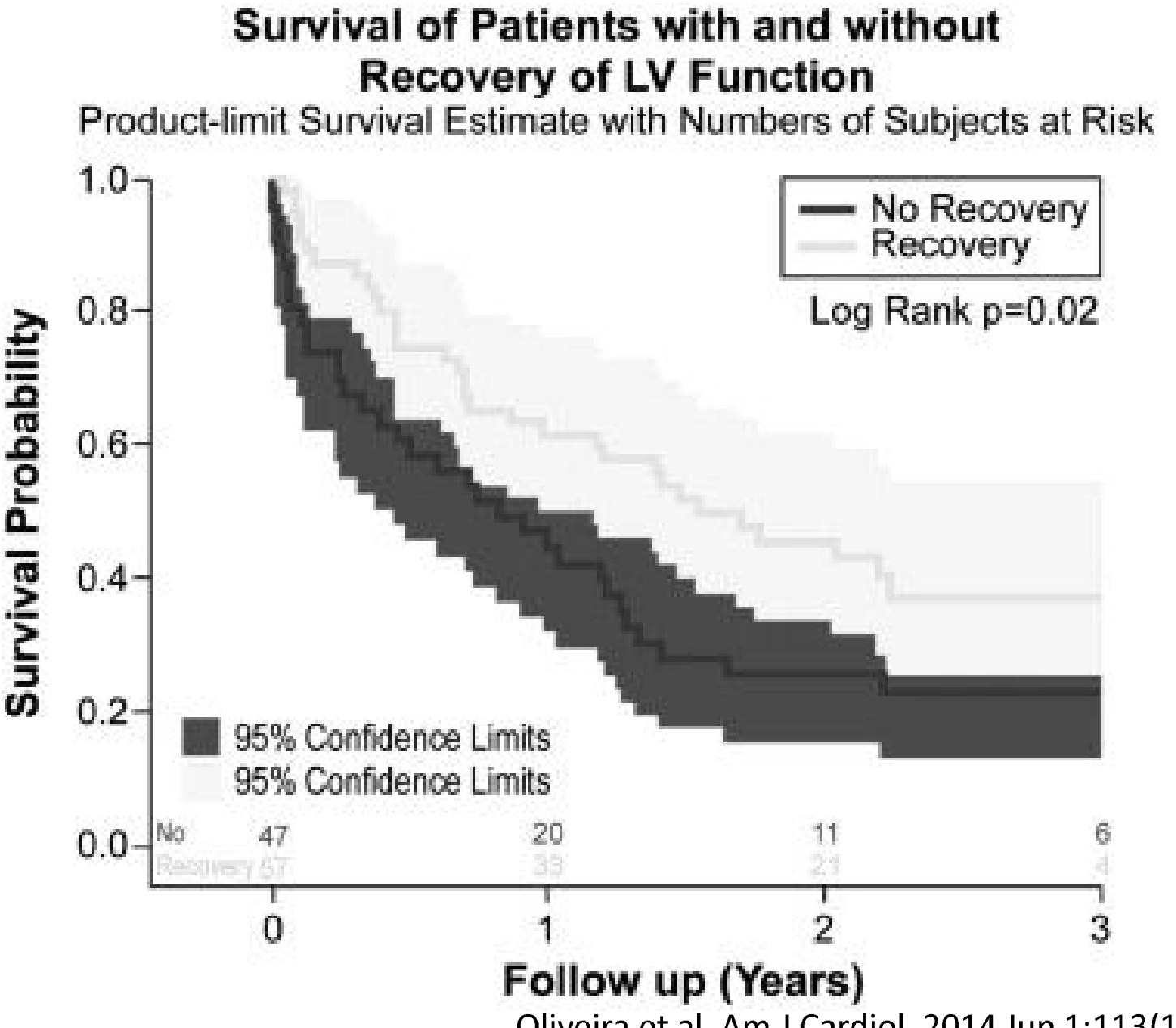


Cardinale et al. Circ 2015

Response to HF therapy decreases with time

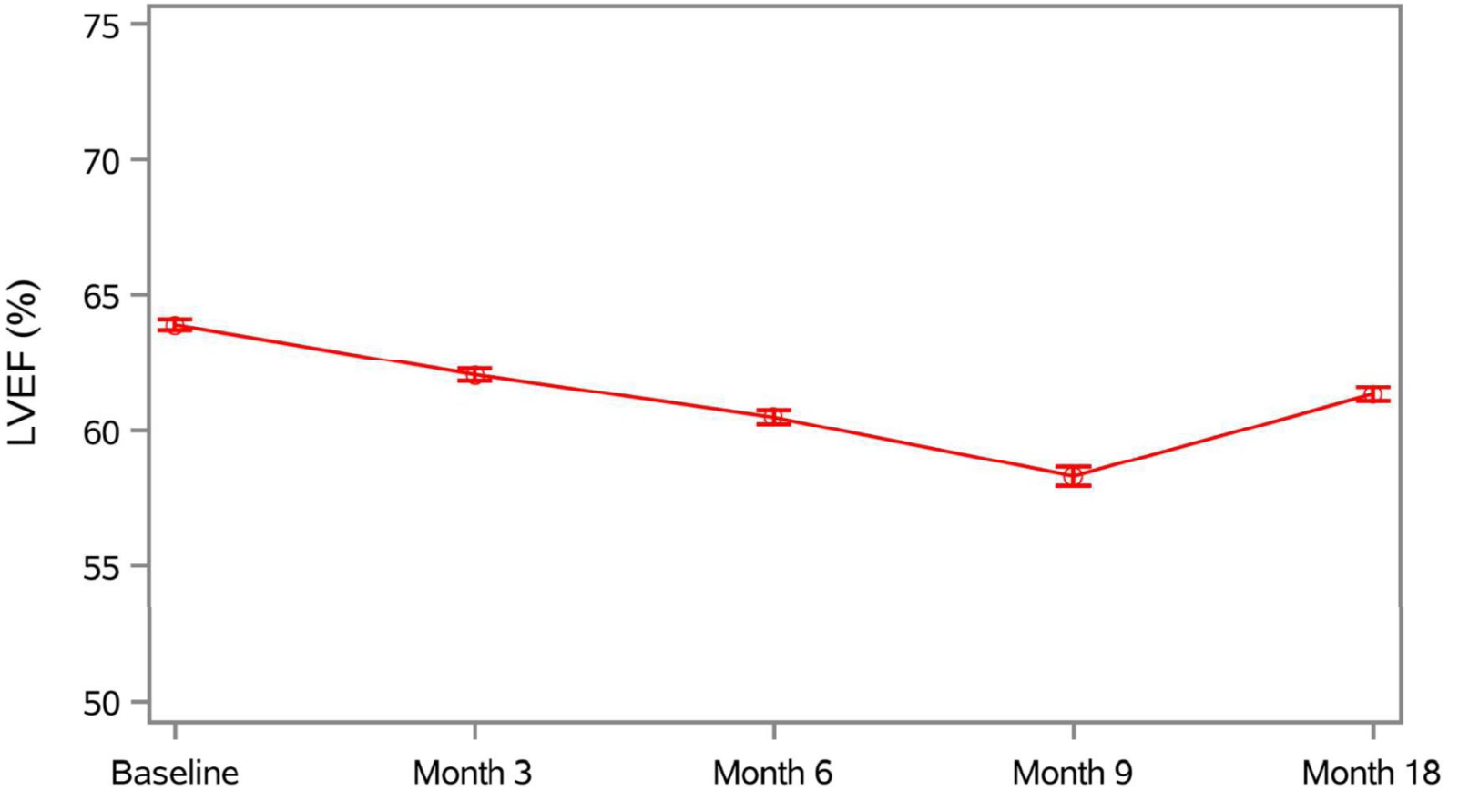


Cardinale et al. J Am Coll Cardiol. 2010



Oliveira et al. Am J Cardiol. 2014 Jun 1;113(11):1893-8.

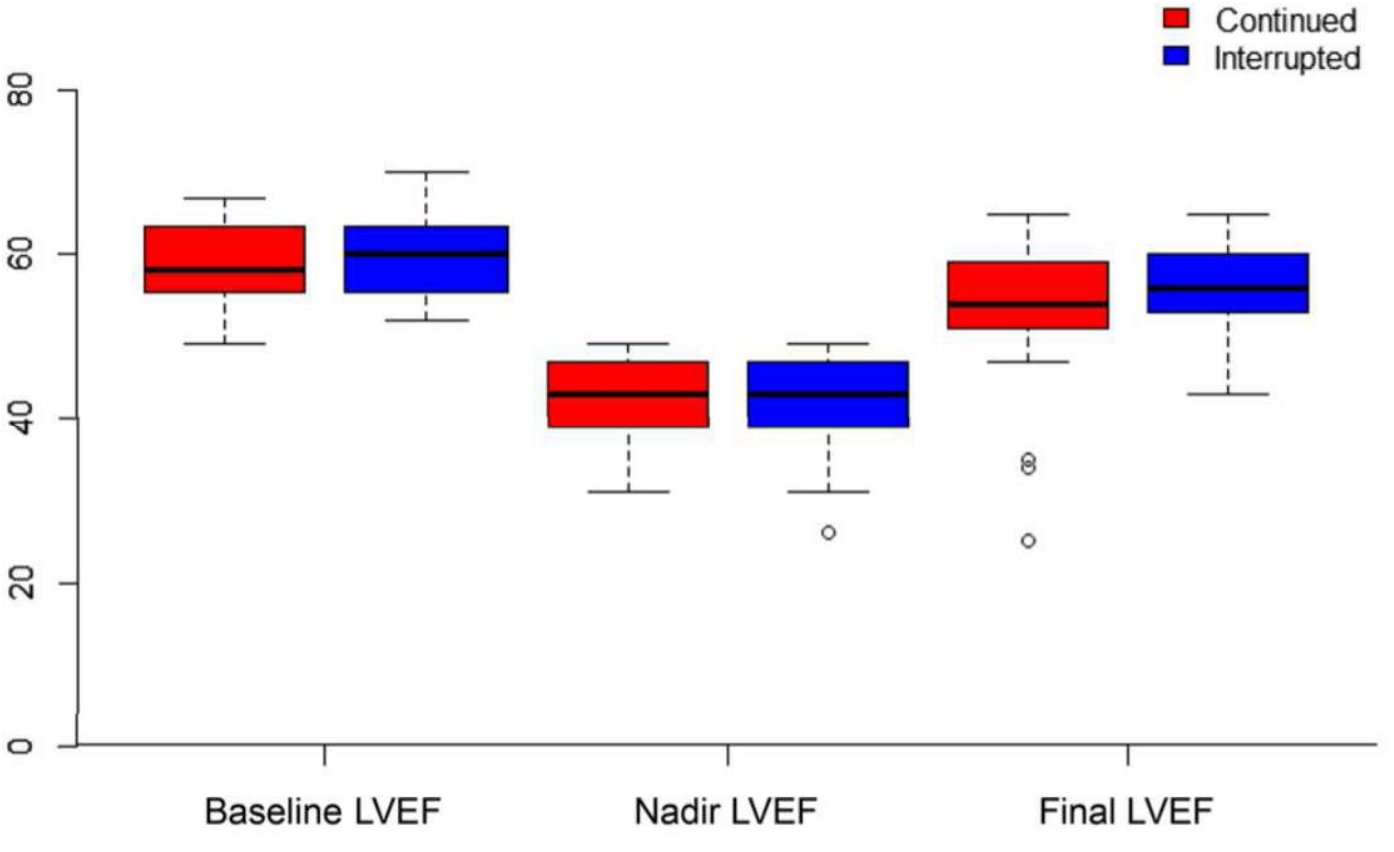
LV Function behavior during trastuzumab therapy



	Baseline	Month 3	Month 6	Month 9	Month 18
Trastruzumab Arms Combined	4015	3914	3811	2146	3197

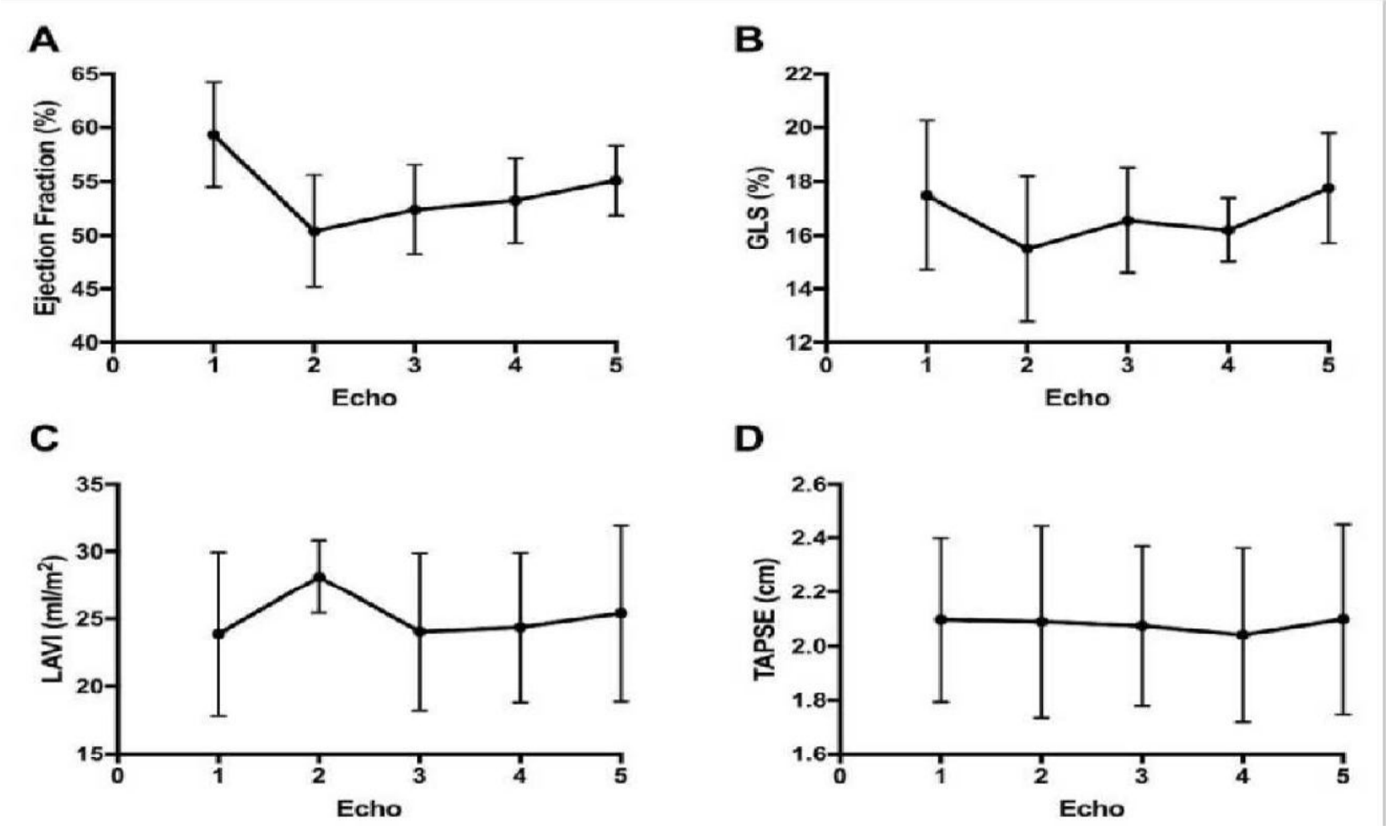
Azambuja et al. Breast Cancer Research and Treatment 2019

Is Discontinuation of Trastuzumab Necessary?



Hussain et al. *Breast Can Res and Treat.* 2019

Continuation of Trastuzumab Despite Cardiotoxicity



Barron et al. Curr Onc. 2019

Conclusões

- Cardiotoxicidade é comum e devastadora
- Pacientes com cancer tem alta prevalência de doença cardiovascular
- Avaliação cardiovascular antes da terapia do cancer é capaz de melhor estratificar o risco de cardiotoxicidade
- Prevenção de cardiotoxicidade é possível
- O monitoramento de pacientes de alto risco pode detectar cardiotoxicidade precocemente
- A prevenção farmacológica da cardiotoxicidade é possível
- O tratamento da cardiotoxicidade é reversíível se o diagnóstico for feito nos primeiros 6 meses
- A interrupção de herceptina raramente é necessária