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ONCO-CARDIOLOGY: Optimizing Outcomes

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Ohio ACC Summit 2016

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Onco-Cardiology Mission

- To achieve better outcomes of cancer patients by providing cardiovascular care before, during and after cancer treatment.

Content

- **The Impact of CVD and Cardiotoxicity**
- Mechanisms of Selected Cardiotoxicities
- Risk Stratification and Prevention
- Newer Modalities for Surveillance
- Interventions
- UH Protocols

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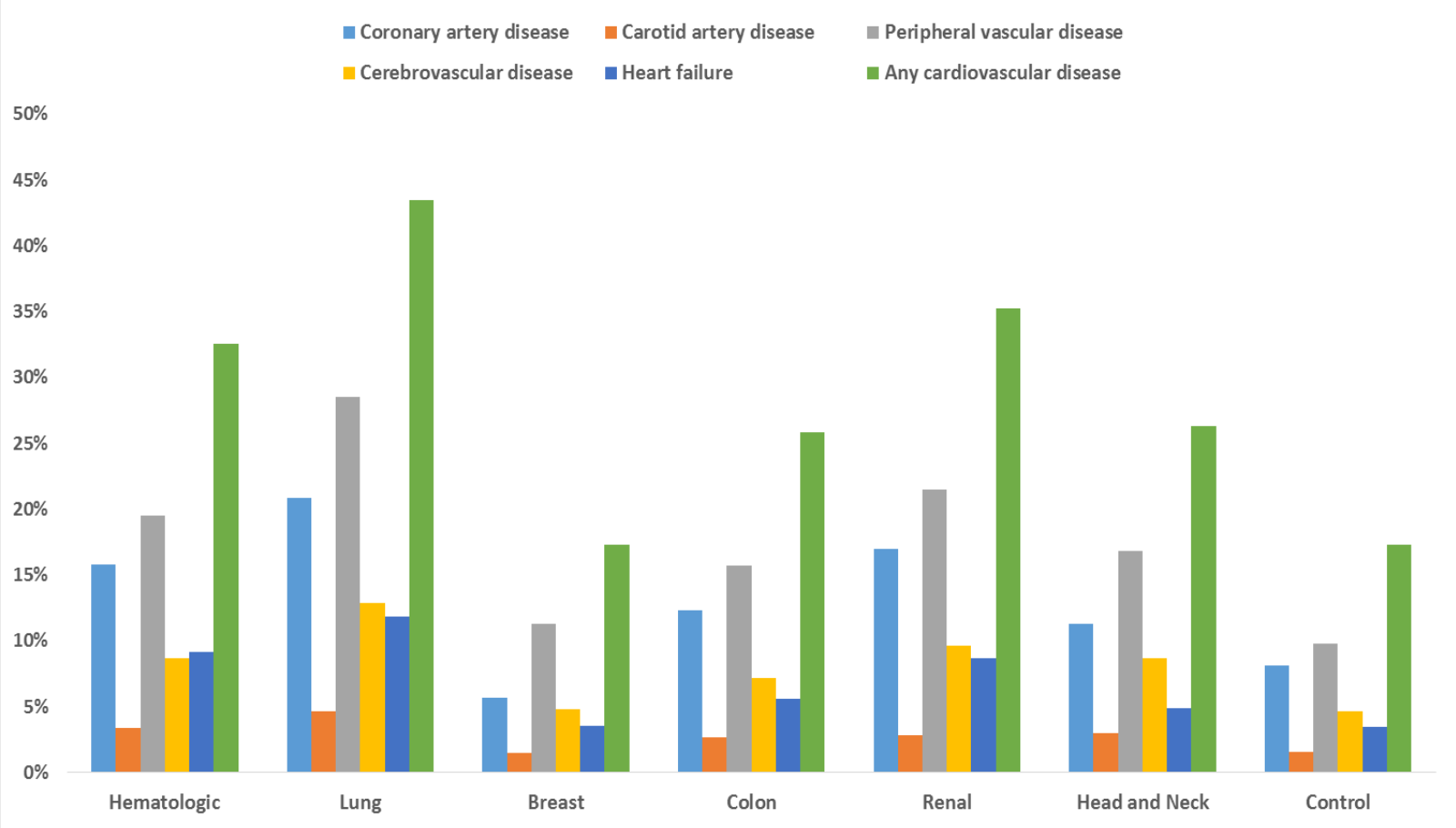
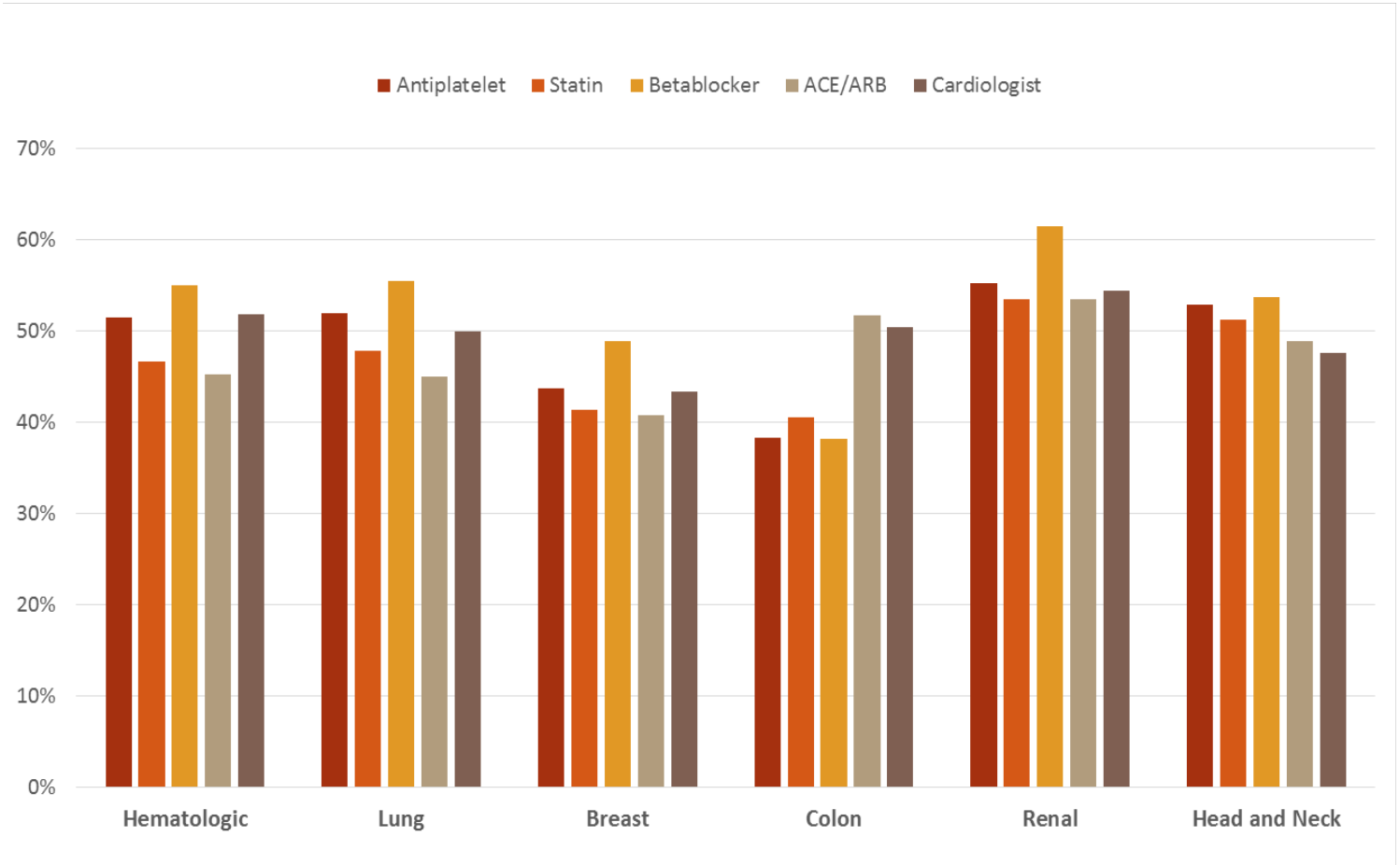
Burden of CVD by Cancer Type



Oliveira GH et al. Mayo Clin Proceedi 2015

CVD Management in Cancer Patients



Oliveira GH et al. Mayo Clin Proceedi 2015

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Impact of Cardiotoxicity

Short term

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

Long term

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

Breast Cancer Res Treat (2014) 146:411–419
DOI 10.1007/s10549-014-3029-0

EPIDEMIOLOGY

Cardiovascular events, early discontinuation of trastuzumab, and their impact on survival

Shi-Yi Wang · Jessica B. Long · Arti Hurria · Cynthia Owusu · Richard M. Steingart · Cary P. Gross · Jersey Chen

- 5-41% of patients on trastuzumab undergo interruptions at some time for cardiotoxicity.

J Card Fail. Epub June 5 2014; J Card Fail. 2012 Feb;18(2):113-9.

Relationship between cardiac events and discontinuation

Table 4 Cardiovascular events occurring 45 days before or after last trastuzumab treatment

	Early discontinuation no. = 239 (41 %)		Completion group no. = 346 (59 %)		*p* value
	N	%	N	%	
Any cardiovascular[a]	60	25.1	25	7.2	<0.001
Heart failure/ cardiomyopathy	45	18.8	14	4.0	<0.001
Atrial fibrillation[b]	13	5.4	<11	<3.2	0.006
Other cardiovascular events[c]	19	7.9	12	3.5	0.017

[a] Individuals may be in multiple sub-categories of cardiovascular events, therefore, numbers of specific events will not sum to the number presented as Any cardiovascular

[b] Cell values less than 11 were not reported per SEER-Medicare DUA to protect the privacy of human subjects

[c] Including acute myocardial infarction, acute coronary syndrome, angina, ventricular fibrillation, cardiac arrest, stroke, transient ischemia accident, pulmonary embolism, deep vein thrombosis, or acute embolism

Breast Cancer Res Treat (2014) 146:411–419

Effect of Discontinuation on Survival

Group	*N*
Complete-No CV	321
Incomplete-No CV	174
Complete-CV	25
Incomplete-CV	52

[a]Survival was evaluated starting from the date 1 year after initiating trastuzumab treatment
CV cardiovascular events

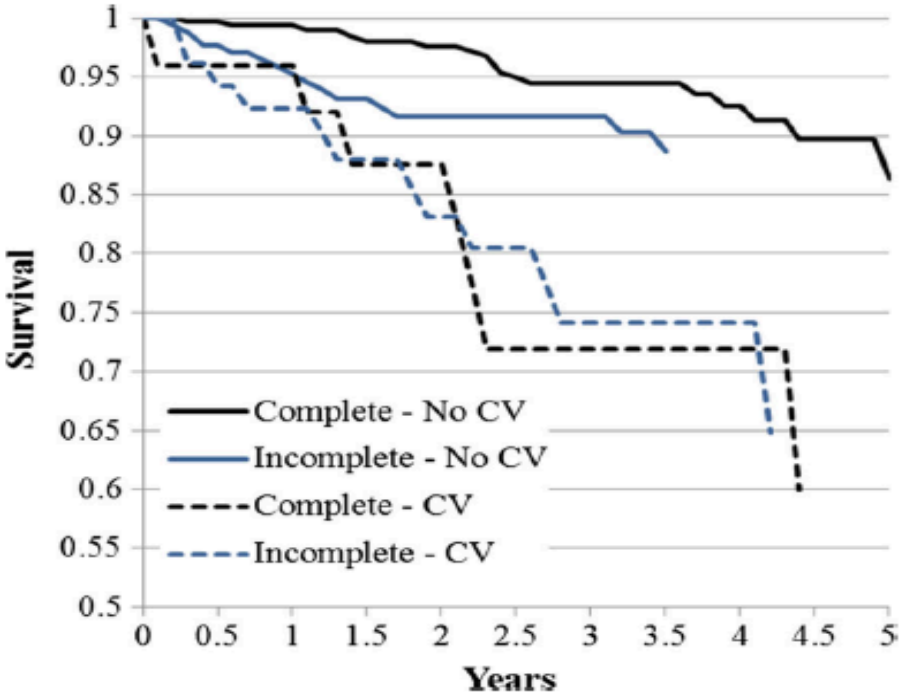


Fig. 1 Survival among patients receiving trastuzumab treatment according to completion of trastuzumab treatment and cardiovascular events[a]

Breast Cancer Res Treat (2014) 146:411–419

Association of discontinuation CV events and death

Table 5 Factors associated with all-cause mortality

Characteristic	Hazard ratio (95 % CI)
Complete trastuzumab	
Yes	Reference
No (Early discontinuation)	1.74 (0.94–3.23)
Any CV event in 45 days before or after last trastuzumab	
Yes	3.54 (1.87–6.68)
No	Reference
Age groups (years)	
67–69	Reference
70–74	0.88 (0.46–1.68)
75–94	0.38 (0.15–0.95)

Breast Cancer Res Treat (2014) 146:411–419

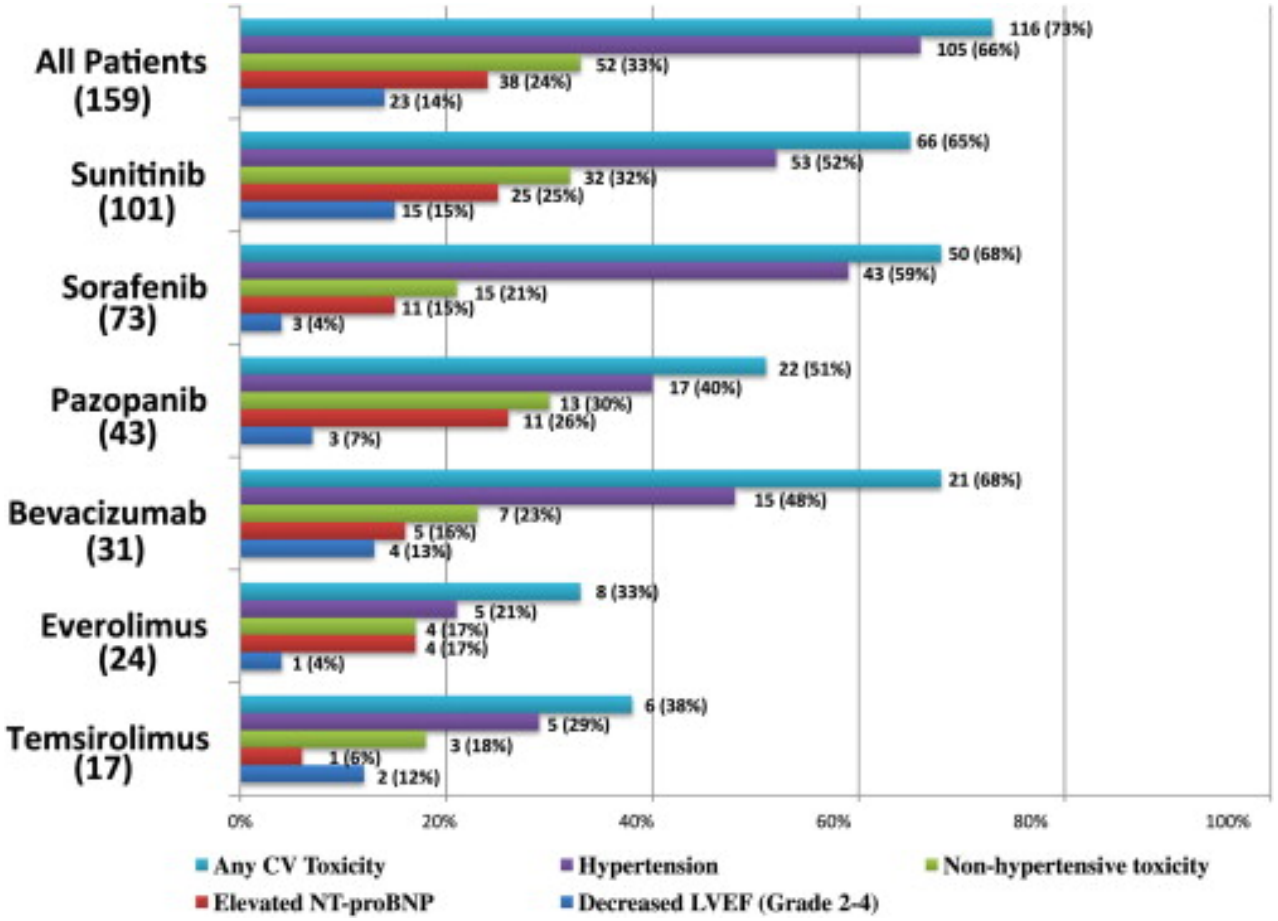
Incidence of HF/LVD after Anthracyclines ± Trastuzumab

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

	All Cancer Patients	Anthracycline + Trastuzumab (n = 431)	Anthracycline (n = 5,257)	Trastuzumab (n = 437)	Other Chemotherapy (n = 2,712)	(n =
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	

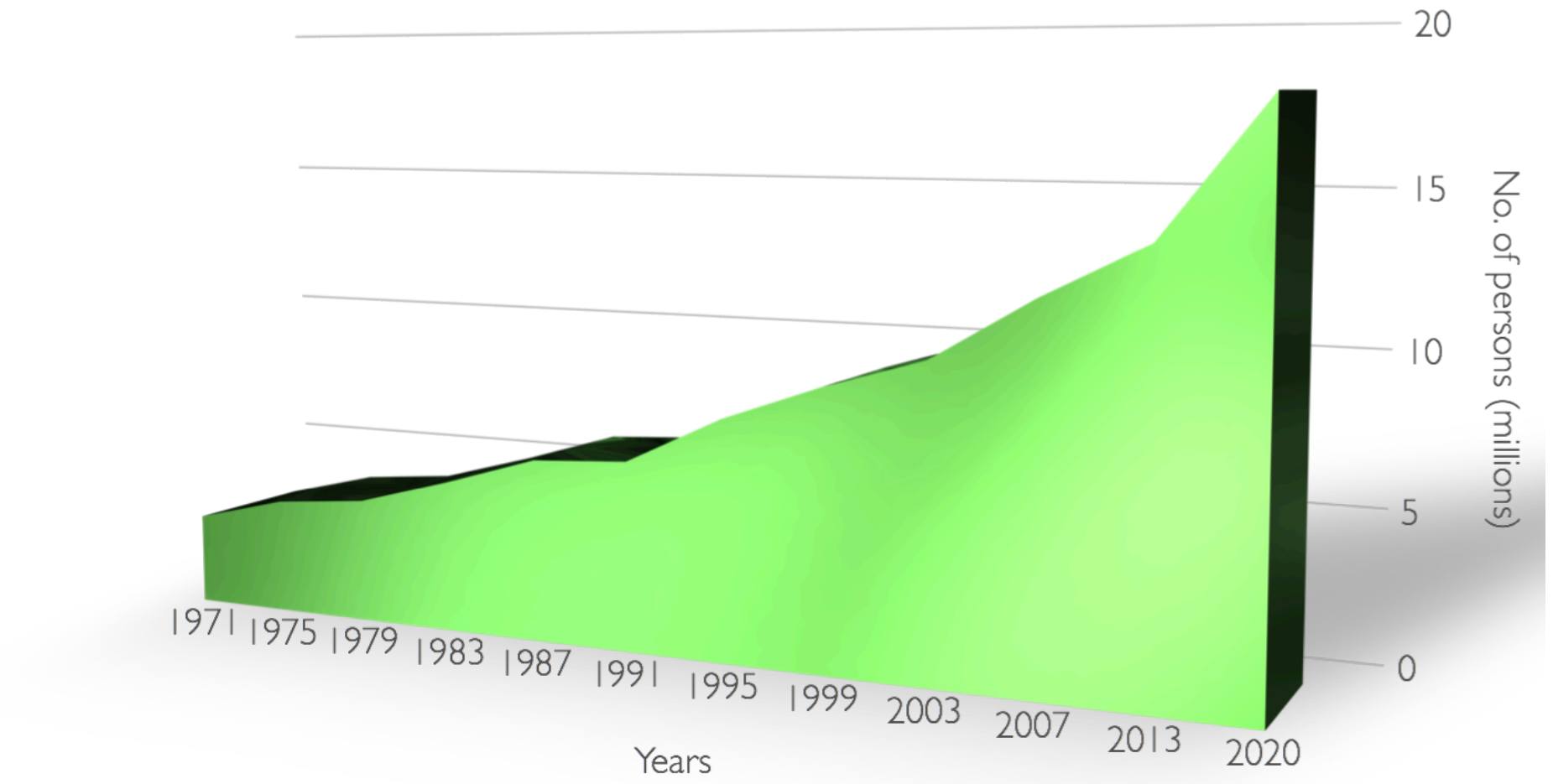
Chen et al. JACC Vol. 60, No. 24, 2012

CV Complications of VGEF Inhibitors



Hall et al. JACCHF Feb 2013

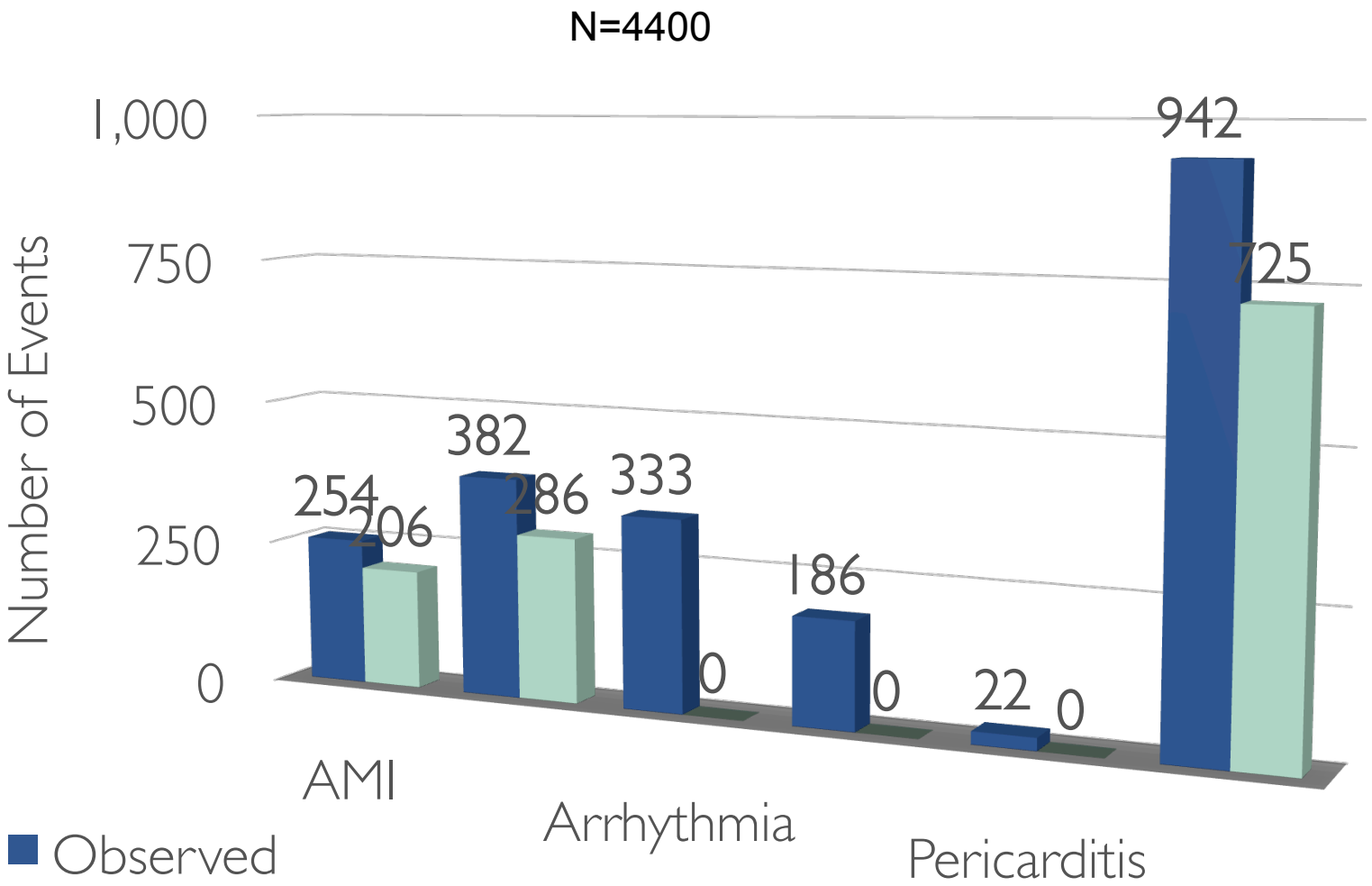
Cancer Survivors in the US



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

AACR Cancer Progress Report 2013

Incidence of CVD in 10-year Breast Cancer Survivors



J Natl Cancer Inst. 2007 Mar 7;99(5):365-75.

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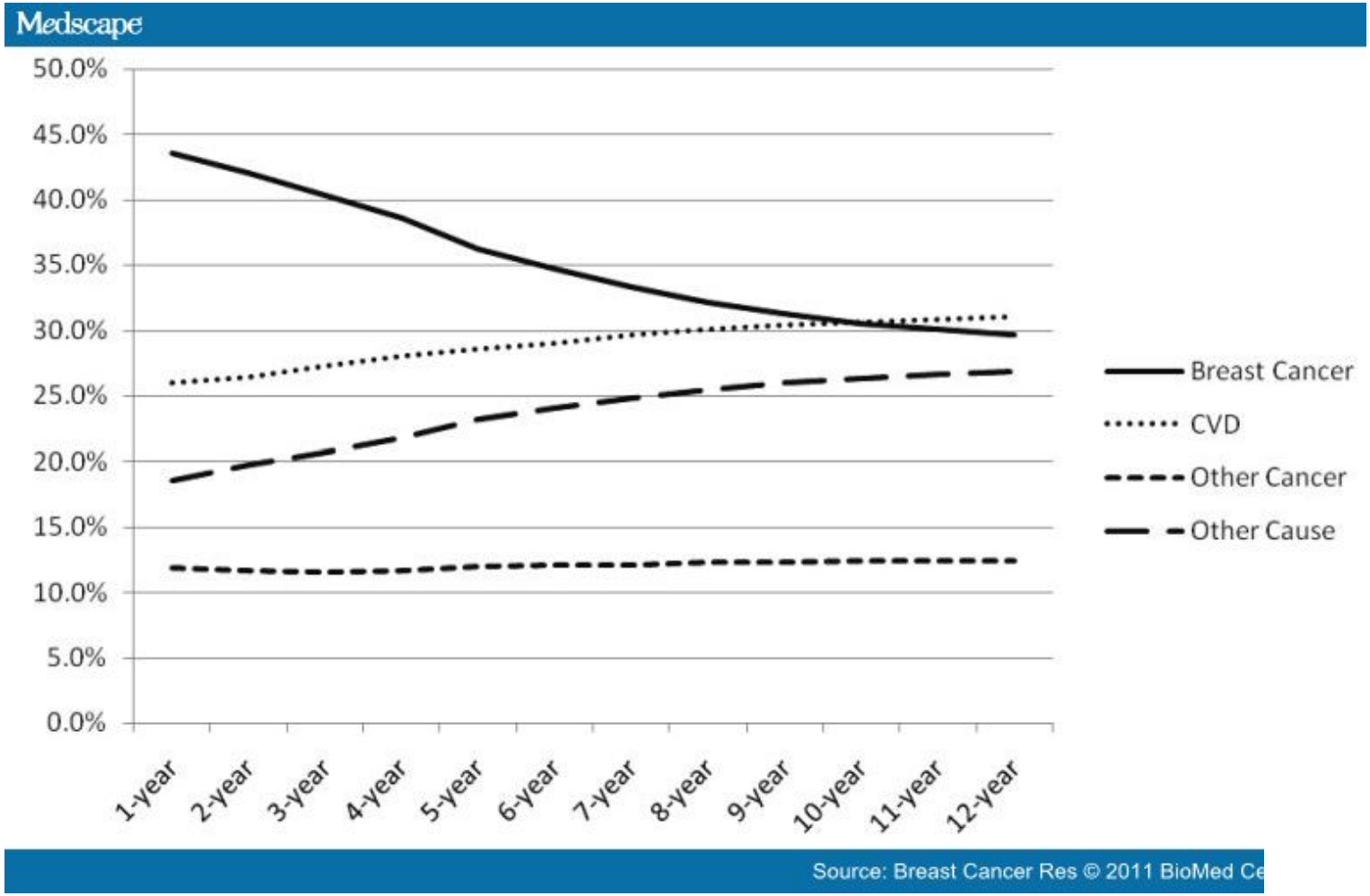
Breast Cancer Survivors CV Mortality



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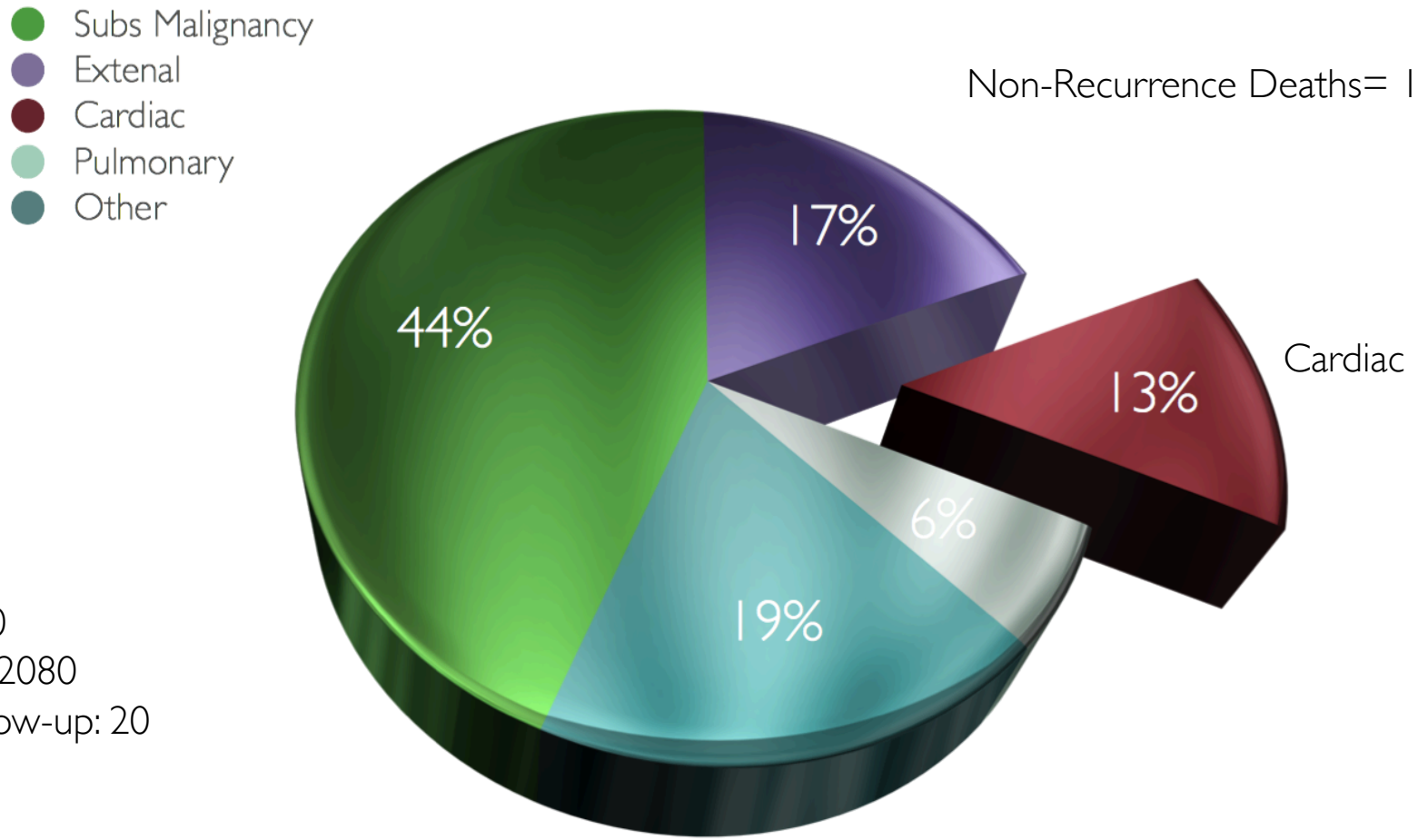
Mortality Among Childhood Cancer Survivors



N=20,400
Deaths: 2,2080
Years Follow-up: 20

J Clin Oncol. 2009 May 10; 27(14): 2328–2338.

Types 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

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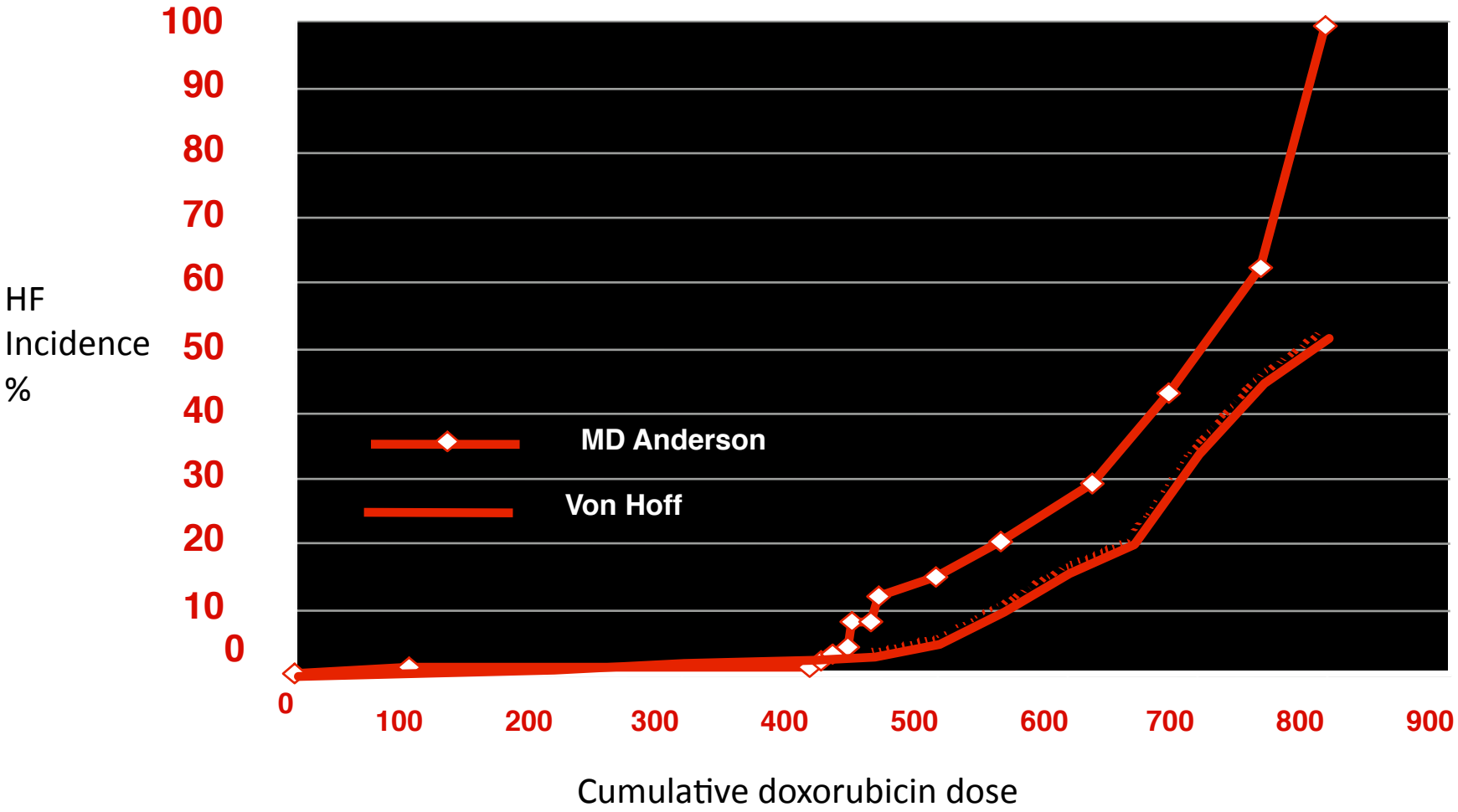
Chemotherapy-Induced Cardiotoxicity

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

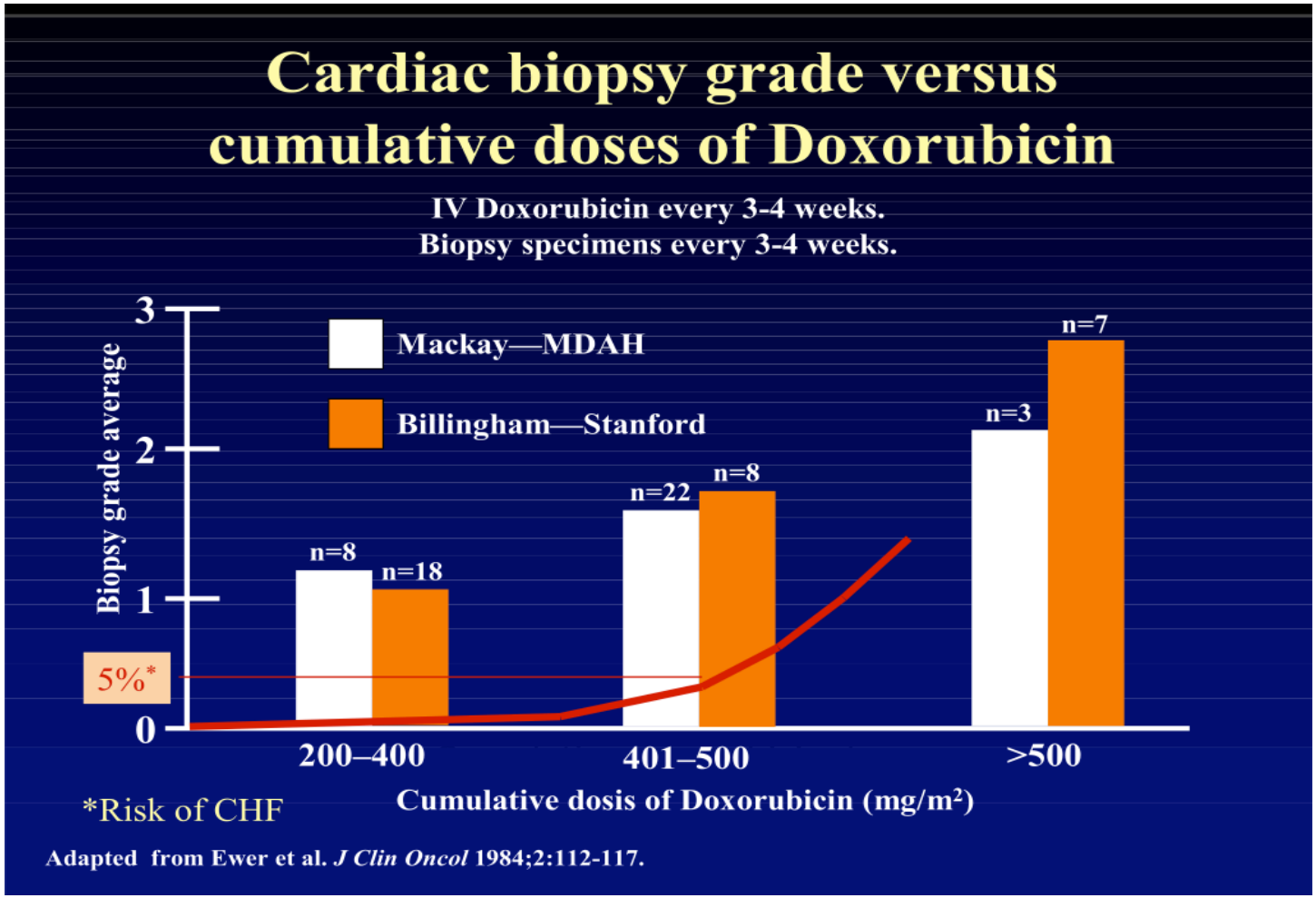
Doxorubicin Dose and HF



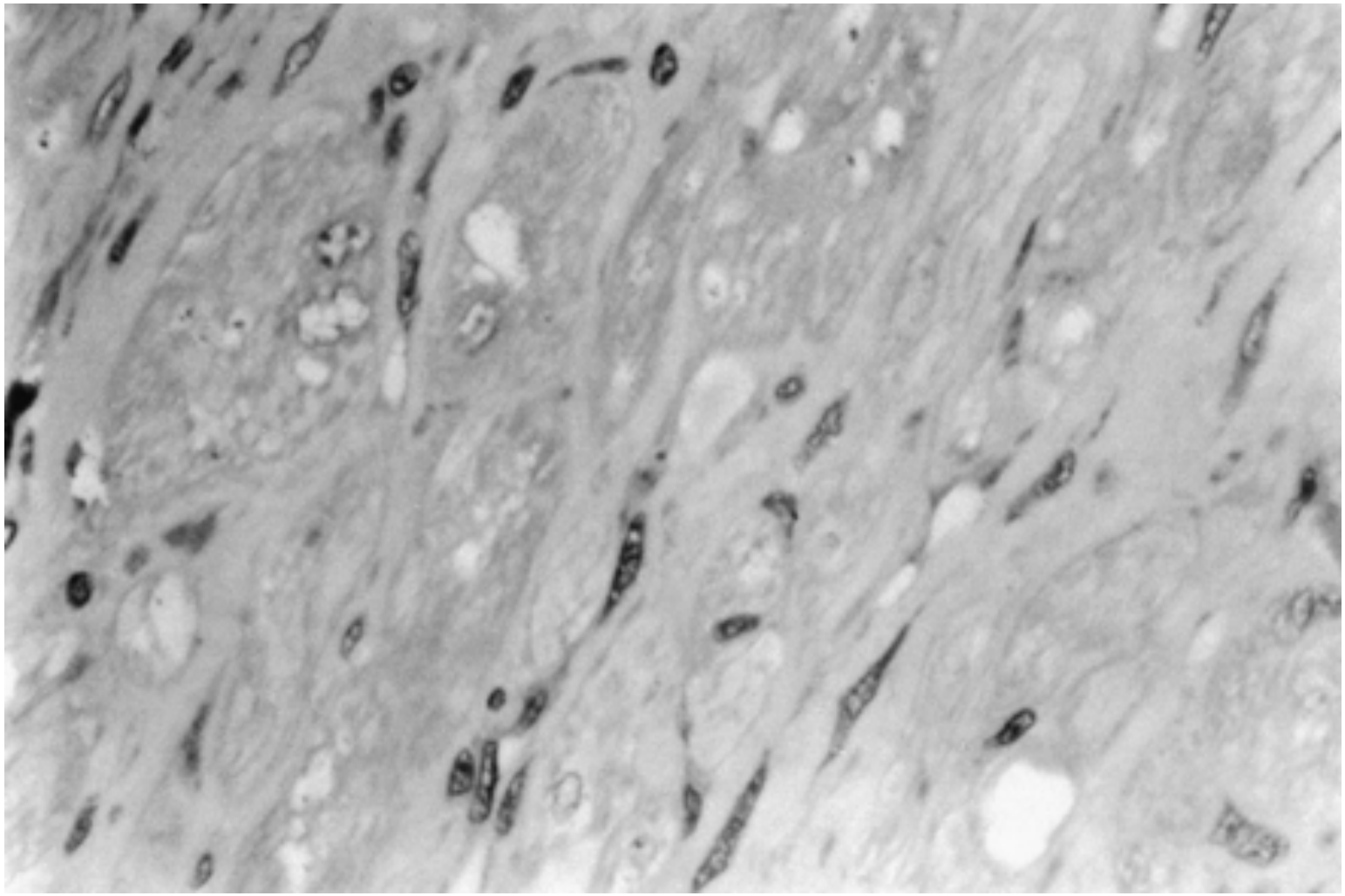
Adapted from Ewer et al. JCO 1984;2:112-117.

Dose Biopsy Grade and HF Incidence

HF Incidence %



Pathology of Adriamycin Cardiotoxicity



Risk of IHD with Radiation Dose

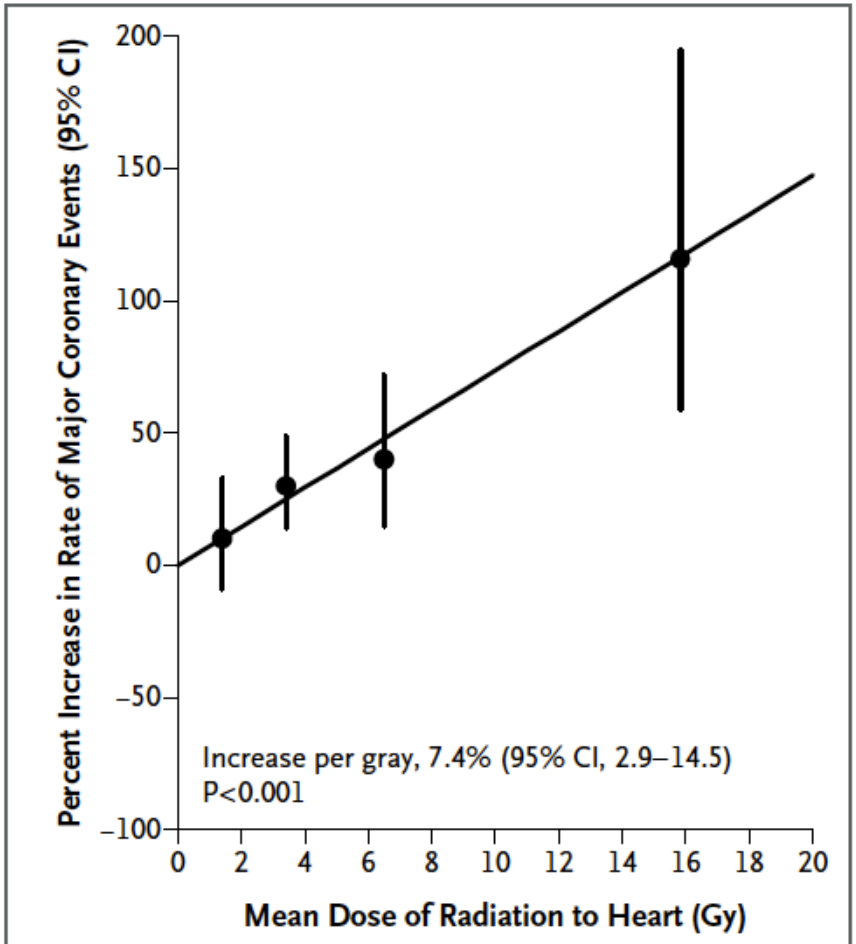


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

N= 2168
963 with MACE

Darby et al. NEJM March 2013

Incidence of CVD after Radiation Therapy

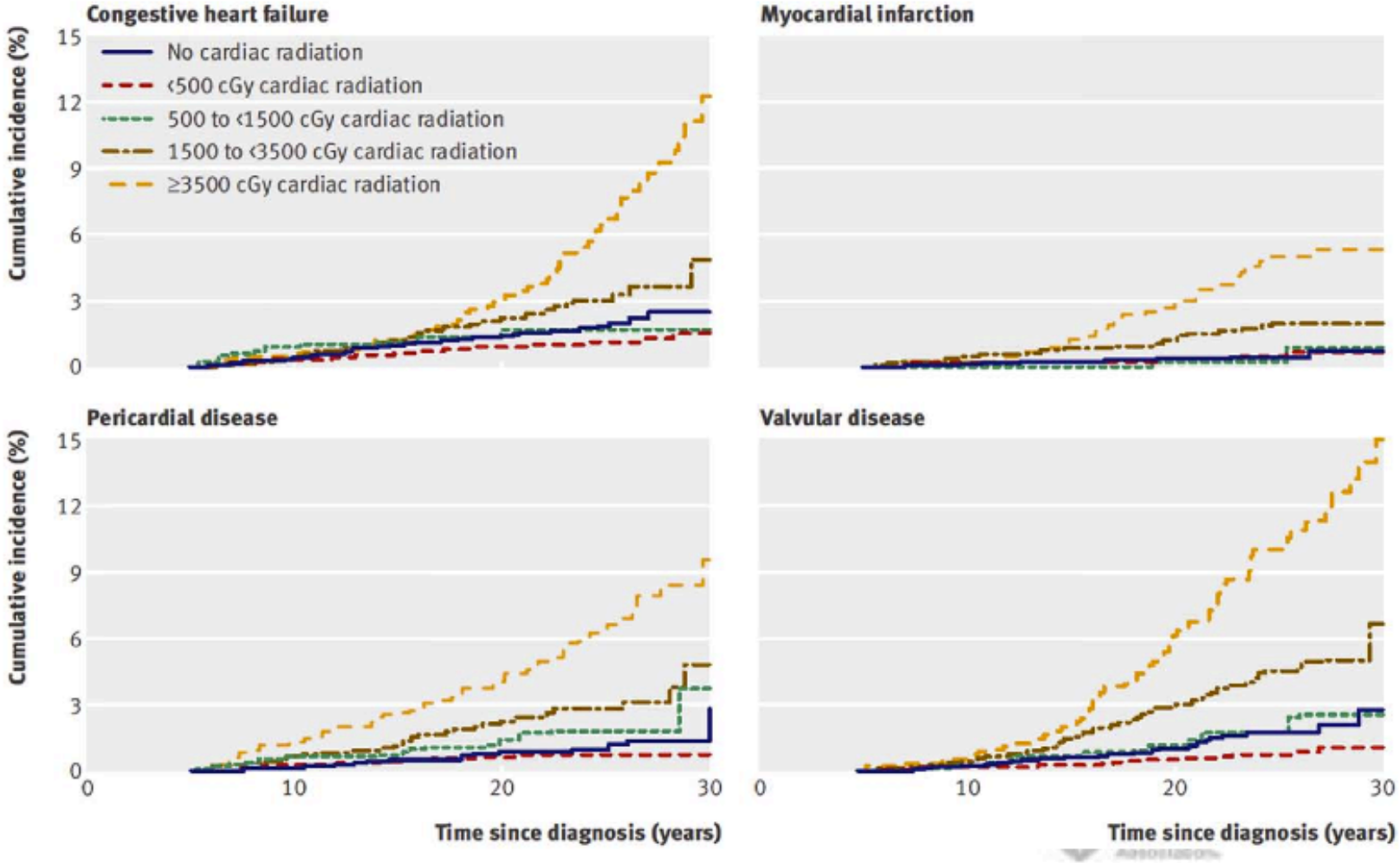
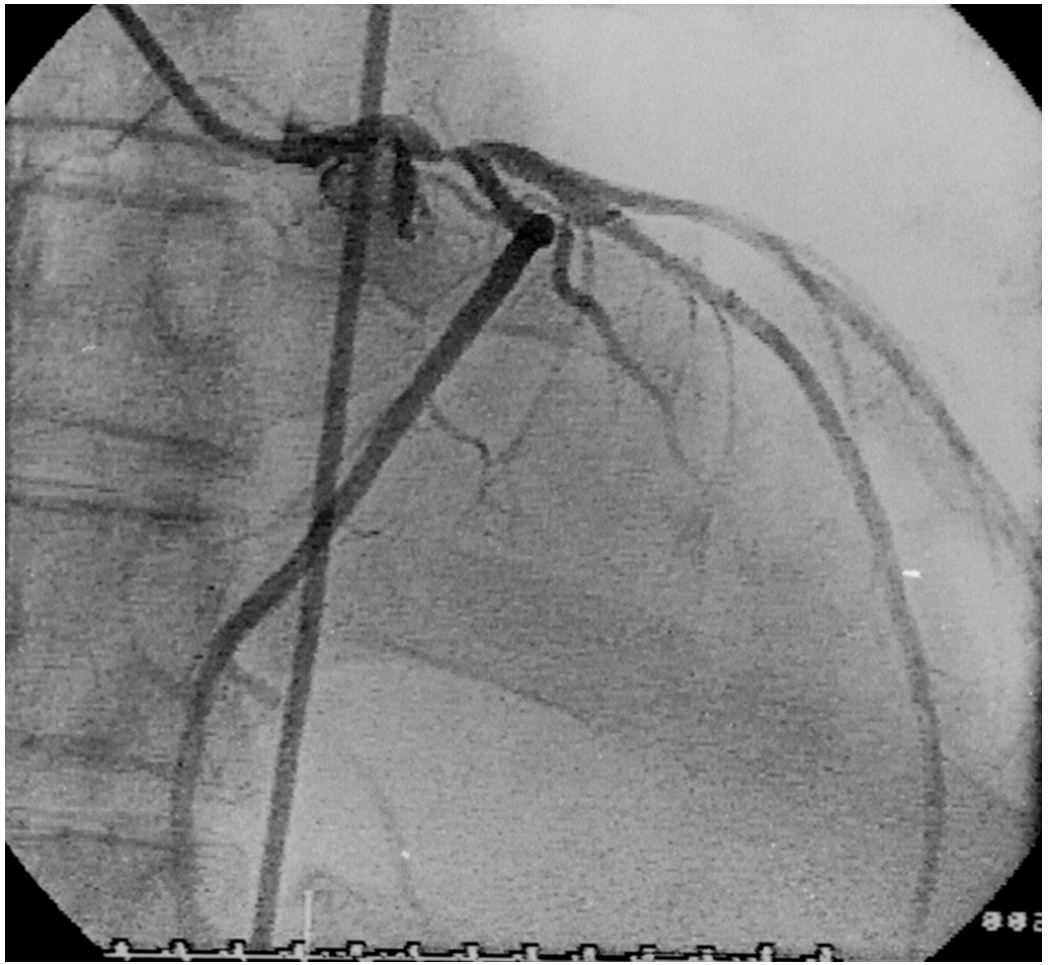


Figure 2. Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose. Reproduced from Mulrooney et al[170] with permission from BMJ Publishing Group Ltd. Copyright © 2009, BMJ Publishing Group Ltd.

Lipshultz et al. Circulation. Oct 22 2013

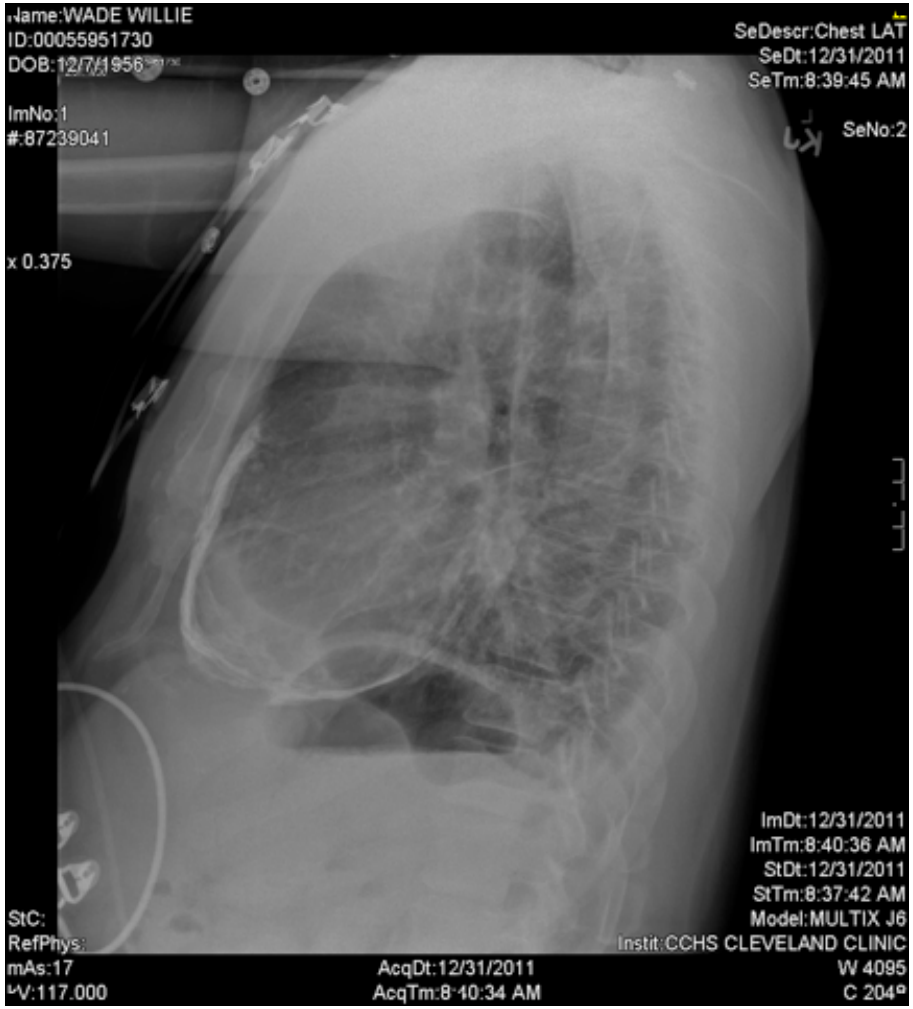
Radiation Coronary Disease



- LMT 1.8:1
- Ostial LAD
- Ostial RCA
- >30 Gy
- Younger age
- Longer time since exposure

Adams MJ, et al. Critical Reviews in Oncology/Hematology 2003 (45):55-75

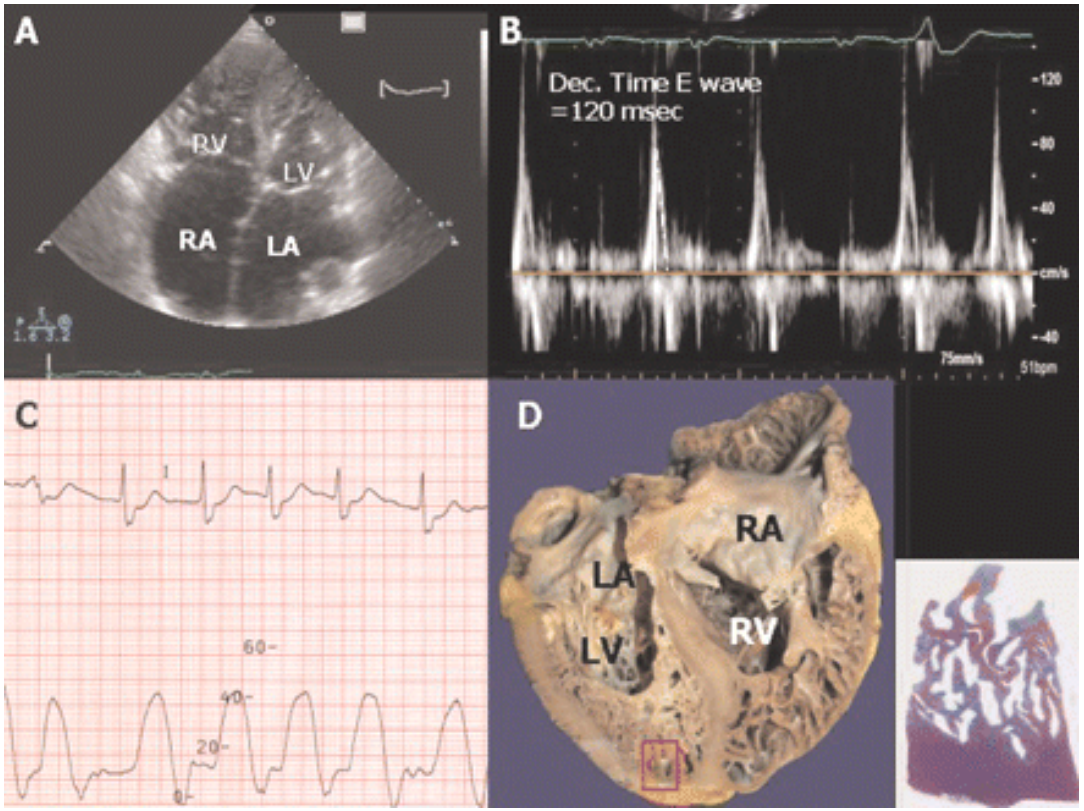
Radiation Pericarditis



- ≥35Gy- 20-40%
  <30 Gy- 2.5%
- 4 months-years
- Acute (effusion)
- Delayed Acute (effusive-constrictive)
- Delayed Chronic
- Pancarditis >60 Gy

Adams MJ, et al. Critical Reviews in Oncology/Hematology 2003 (45):55-75

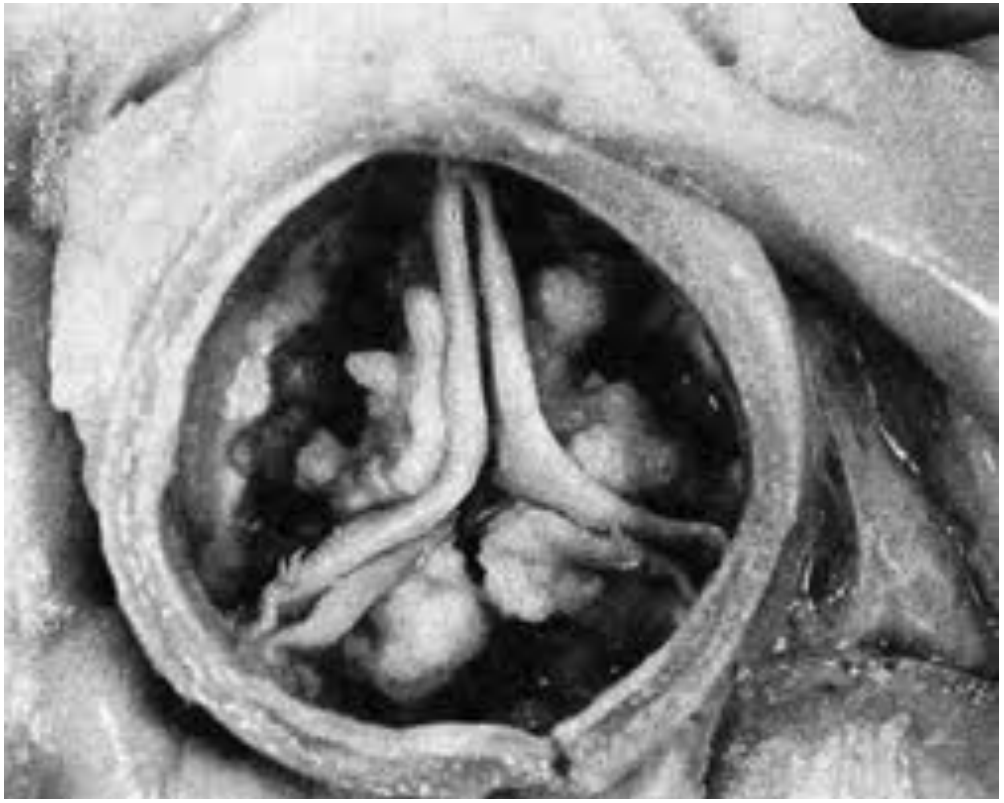
Radiation Cardiomyopathy



- 16% at >20 Gy
- Systolic dx with Chemo
- Perfusion defects common
- Longer time since exposure
- Younger age

Adams MJ, et al. Critical Reviews in Oncology/Hematology 2003 (45):55-75

Radiation Valvular Heart Disease



- ≥35Gy
- 11-16 years
- Mitral and Aortic
- RVOT stenosis

Adams MJ, et al. Critical Reviews in Oncology/Hematology 2003 (45):55-75

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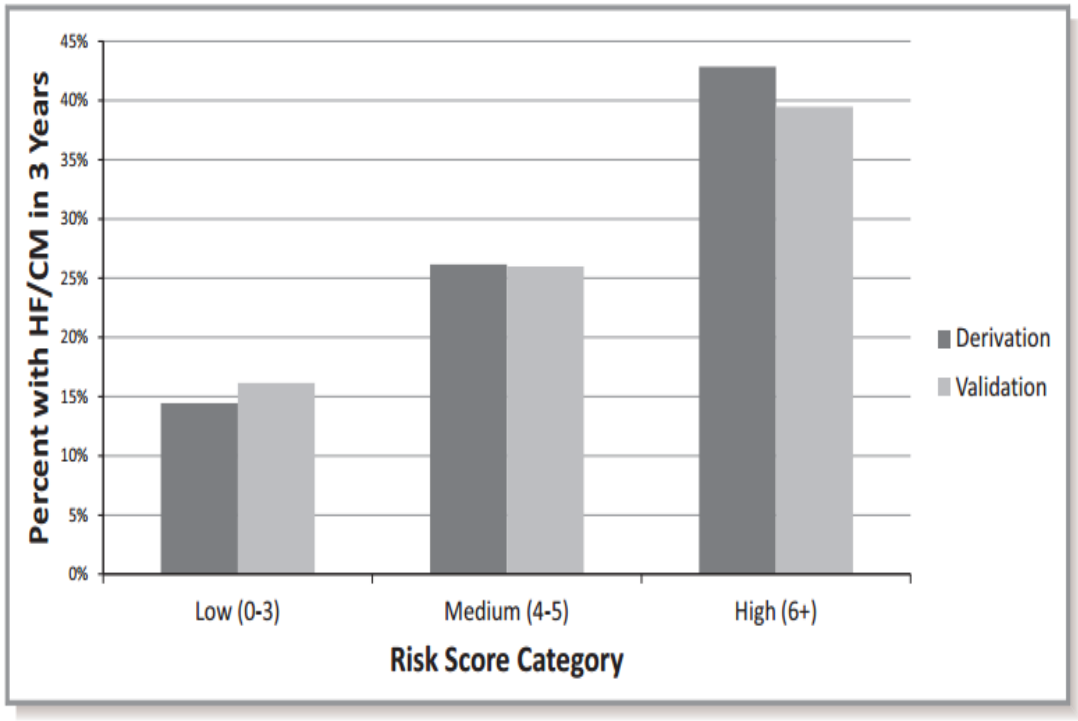
Risk factors for LVD/CHF with Trastuzumab

SEER Analysis of 1664 women



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	HF/CM 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

J Am Heart Assoc. 2014; 3: e000472

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

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

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The **OVERCOME** Trial

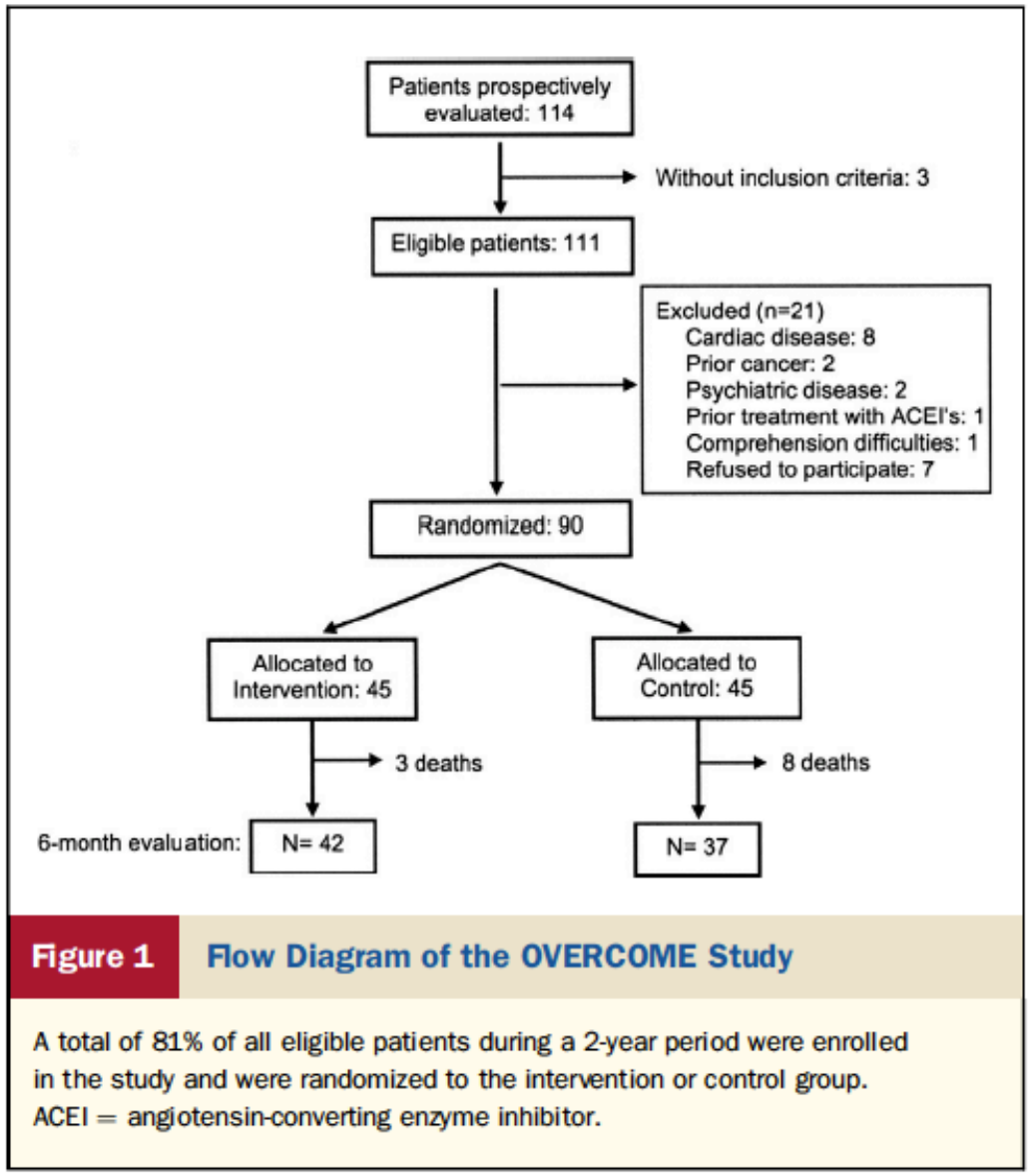

Figure 1 **Flow Diagram of the OVERCOME Study**

A total of 81% of all eligible patients during a 2-year period were enrolled in the study and were randomized to the intervention or control group.
ACEI = angiotensin-converting enzyme inhibitor.

Bosch et al. JACC June 2013

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The **OVERCOME** Trial

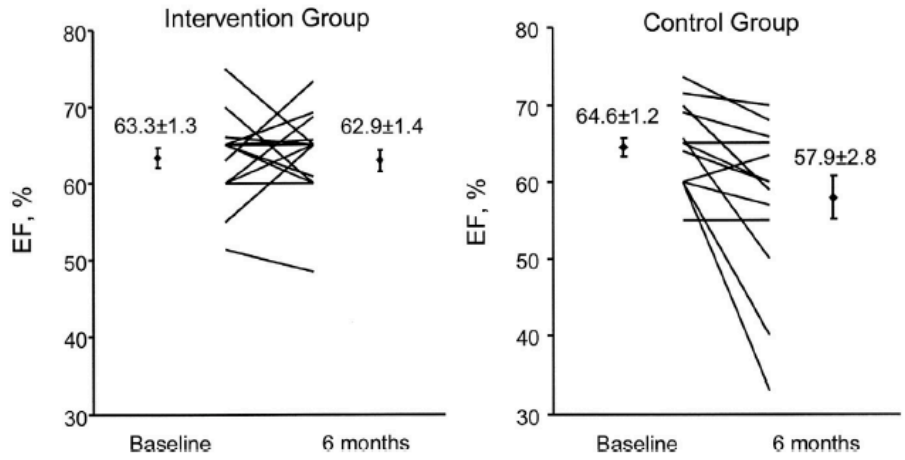


Figure 2 Change From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

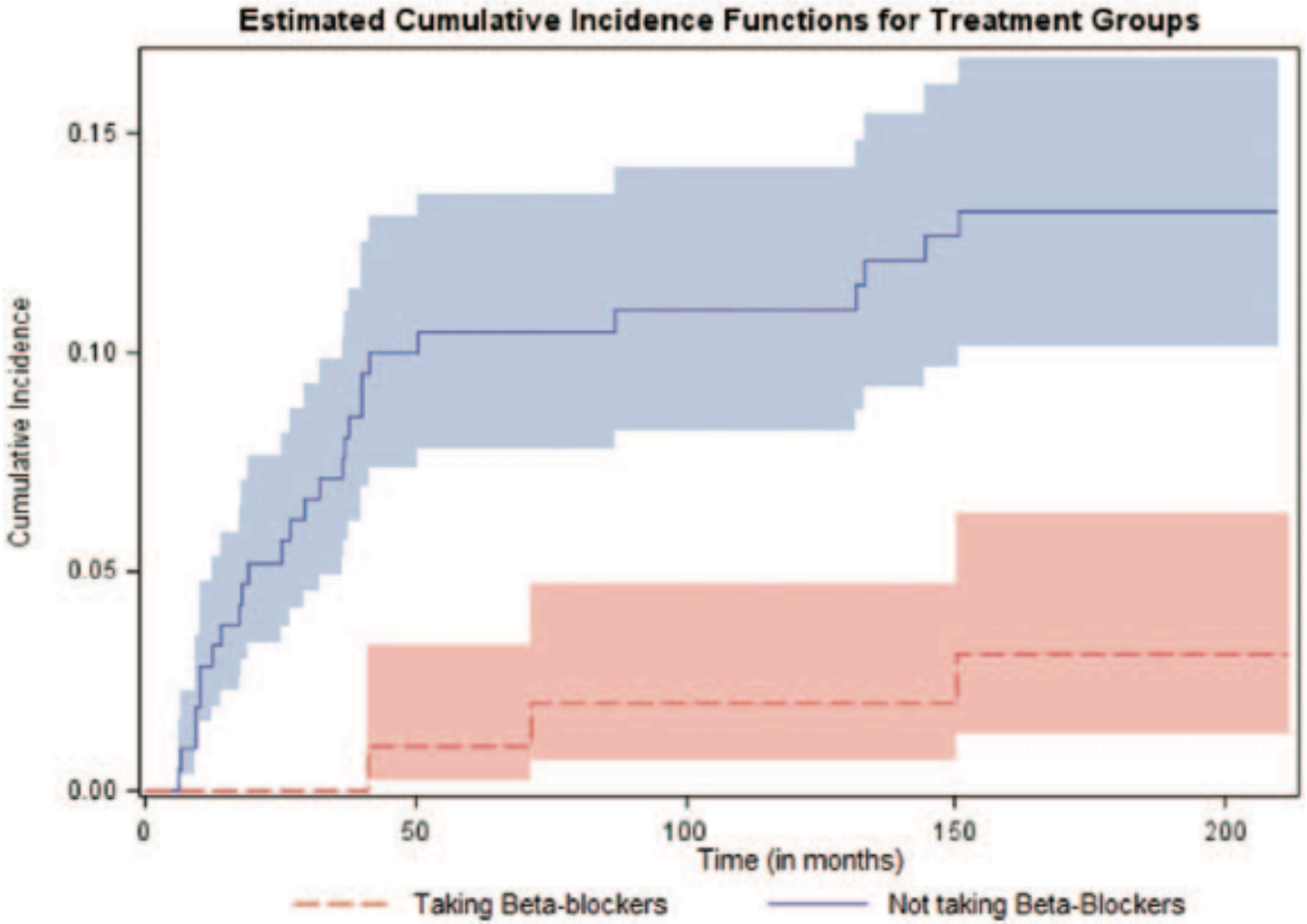
While no differences were observed in the intervention group, patients in the control group had a 6.7% absolute decrease in their mean left ventricular ejection fraction (LVEF) ($p = 0.025$), with all but 3 patients having some degree of LVEF reduction. Values are mean ± SEM.

Table 4 Clinical Endpoints

	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45% (%)	3 (6.7)	11 (24.4)	0.020
≥10% decrease in LVEF with a final LVEF<50% (%)	2 (4.8)	2 (5.4)	0.90
Heart failure or ≥10% decrease in LVEF (%)	4 (9.5)	7 (19)	0.22
Severe adverse events* (%)	9 (20)	15 (33)	0.15

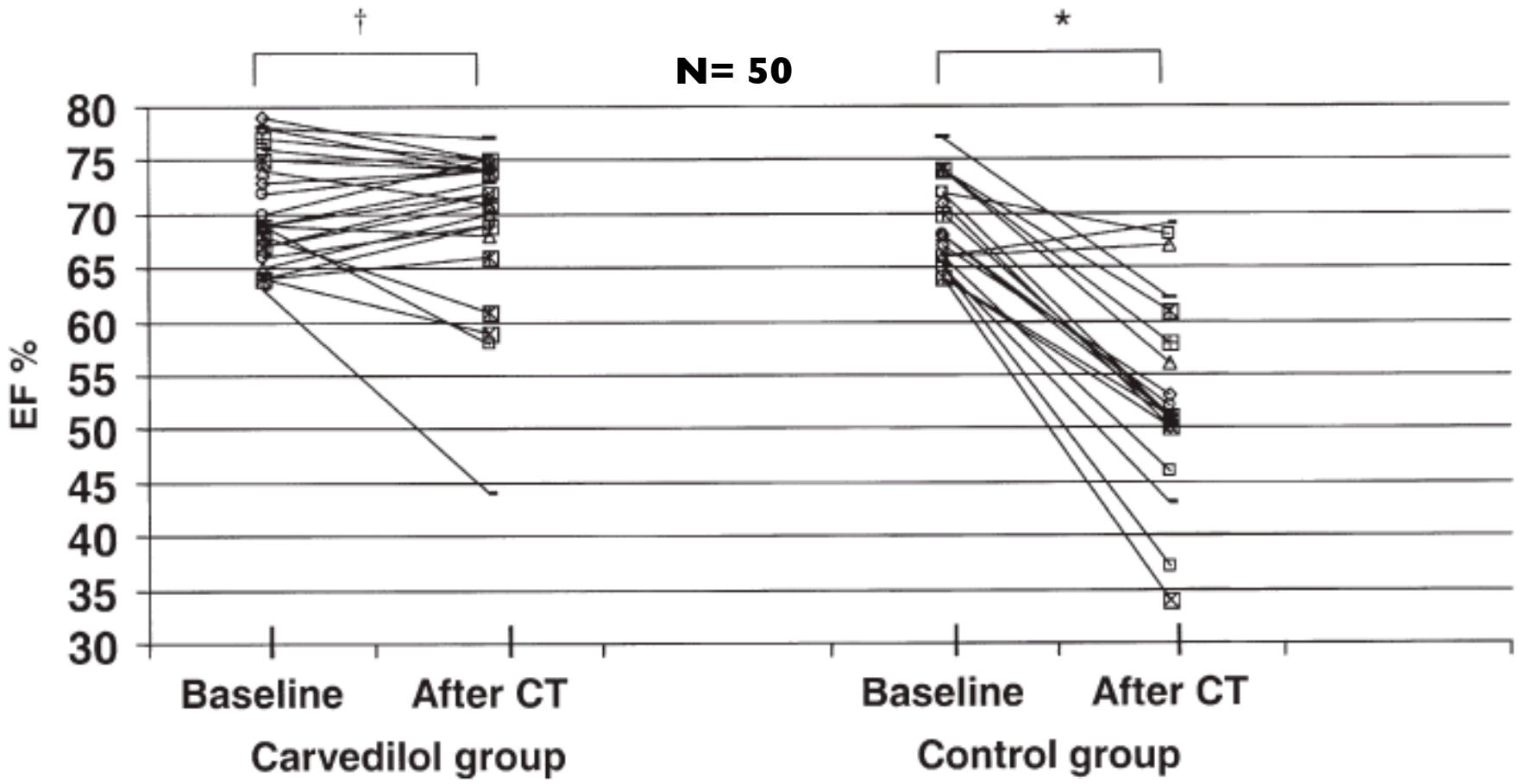
Bosch et al. JACC June 2013

Cardioprotective effects of BB



Seicean et al. Circ Heart Fail. May 2013

Carvedilol for cardioprotection



Kalay et al. JACC Dec 2006

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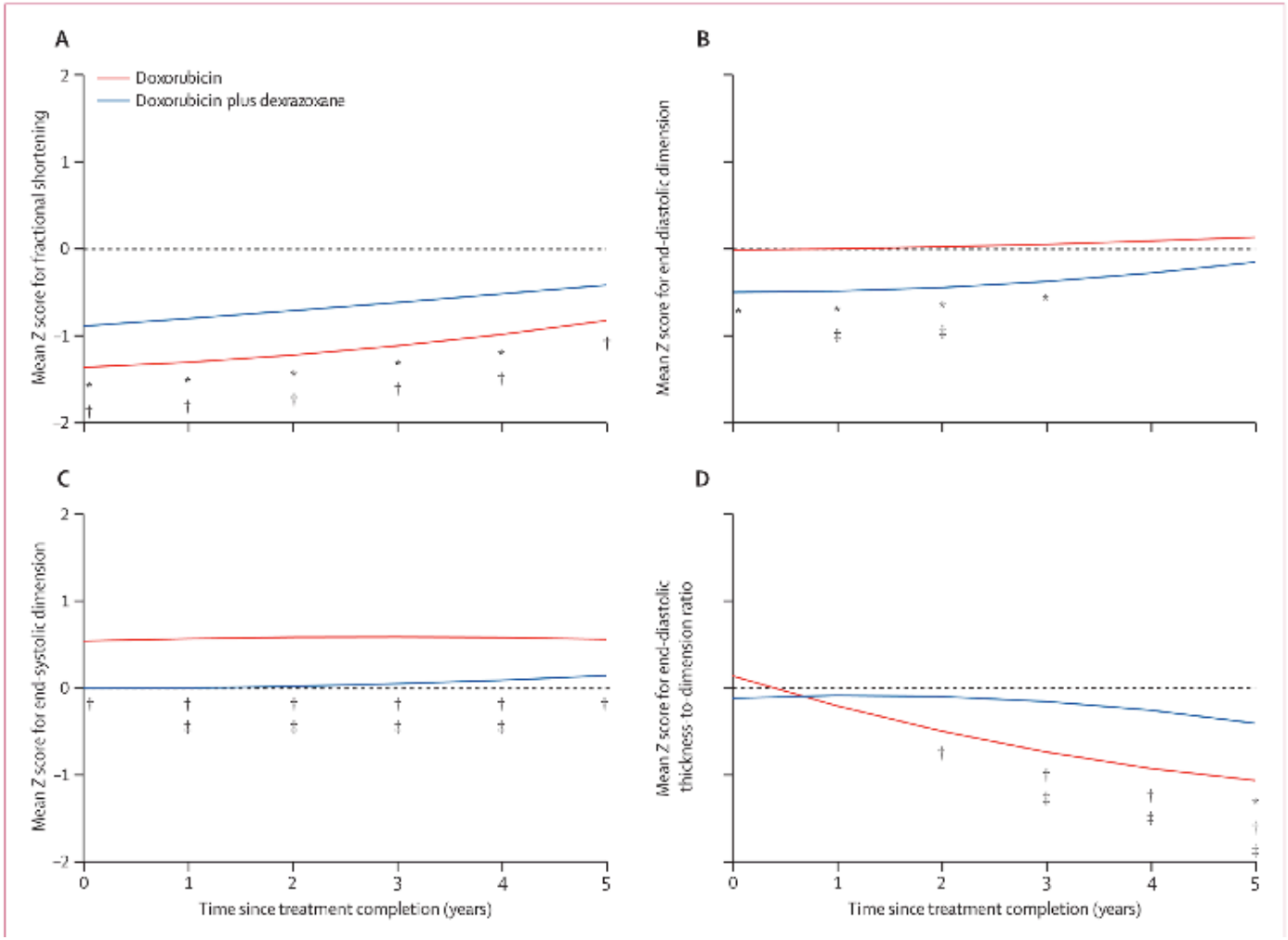
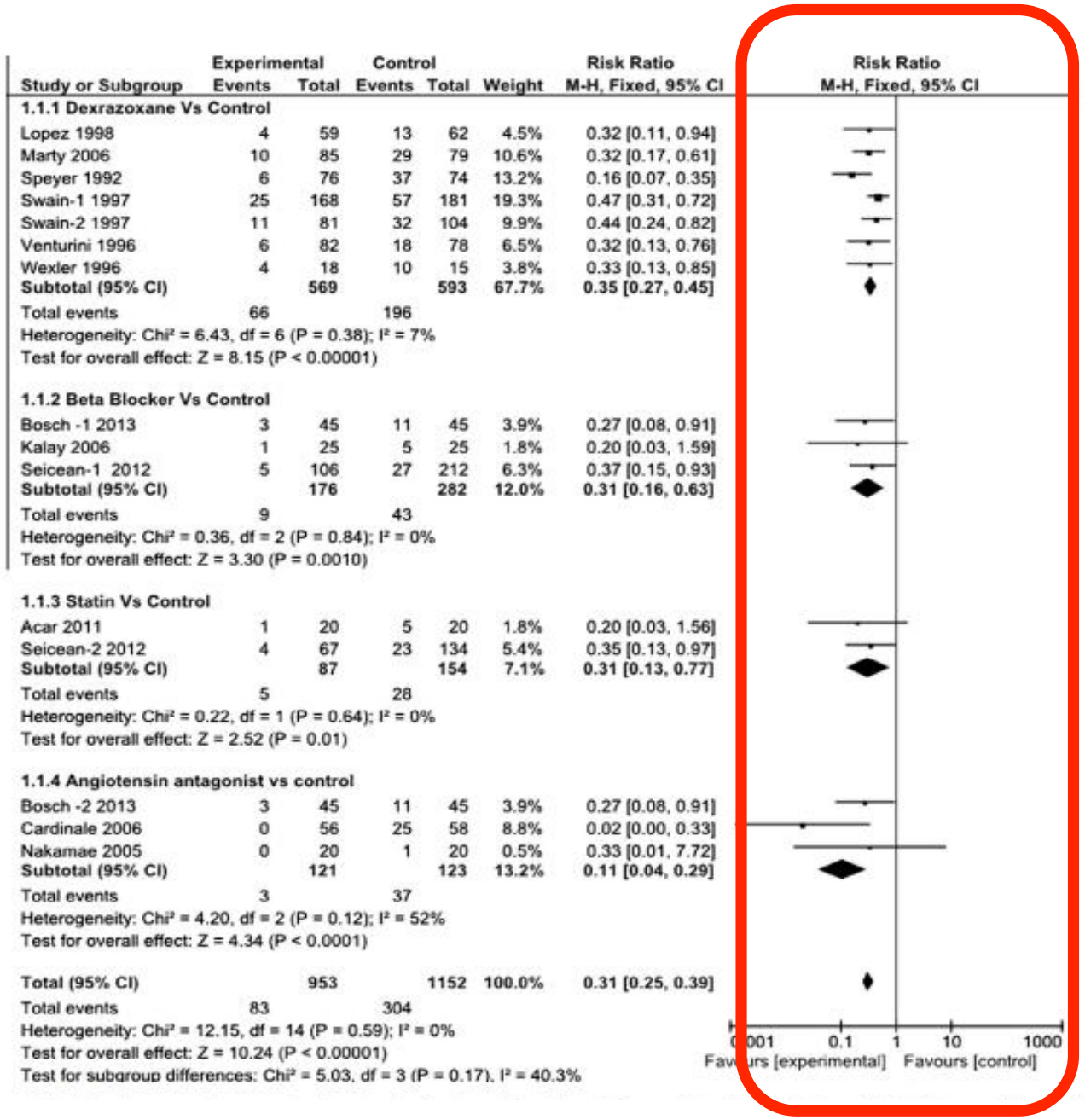
Dexrazoxane for Cardioprotection



Lipschultz et al. Lancet Oncol. 2010 October



Kalam et al. Eur J Cancer. 2013 Sep;49(13):2900-9.

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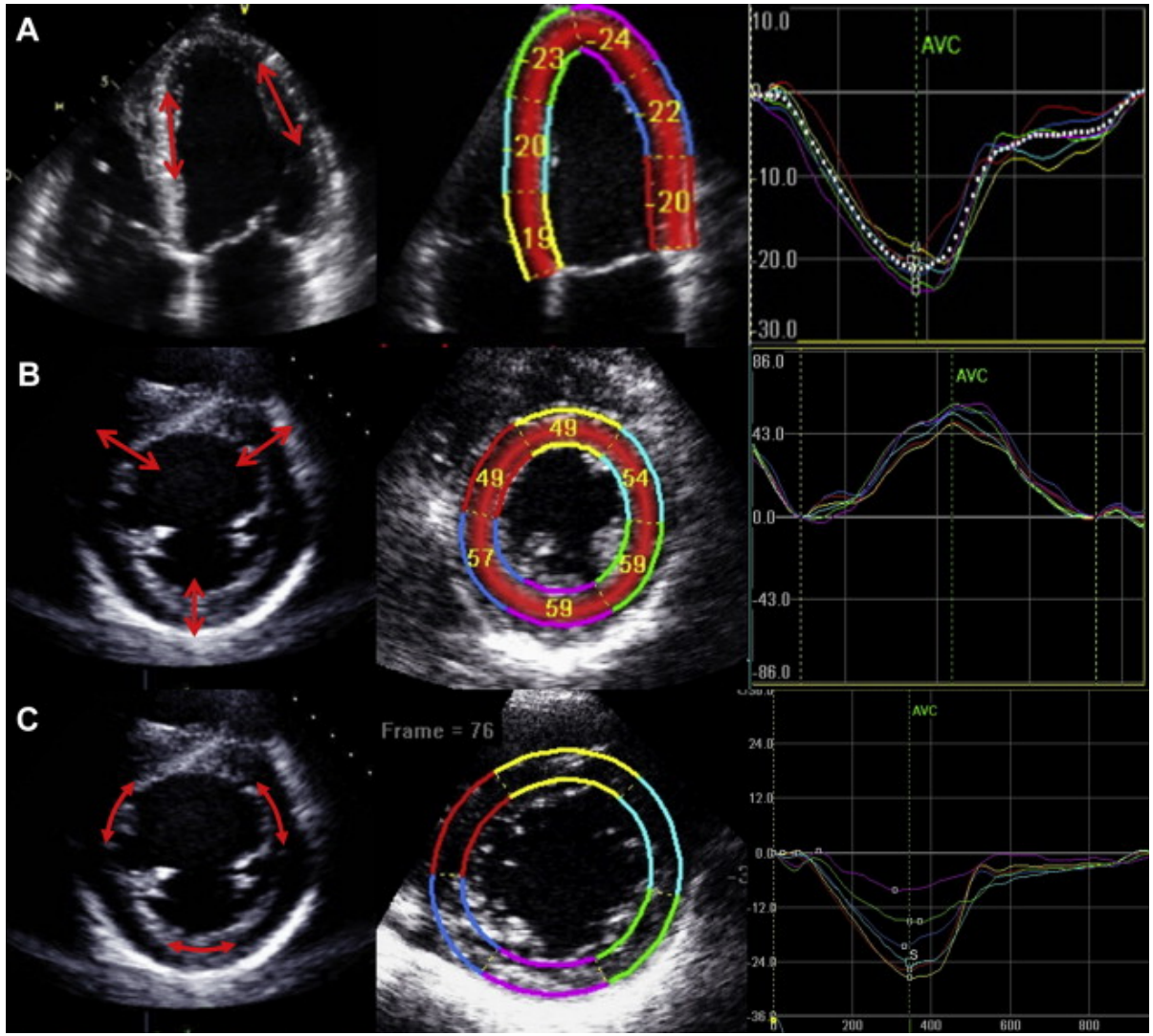
Strain Echocardiography



Thavendiranathan et al. *Circ Cardiovasc Imaging 2013*

Decreases in strain predict cardiotoxicity

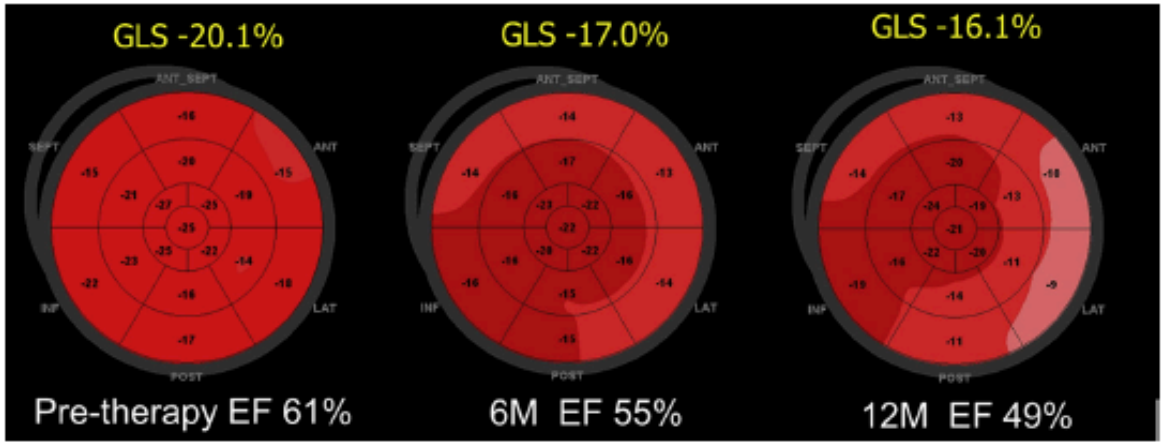


Figure 4 **The Utility of Early Strain Changes to Predict Subsequent Cardiotoxicity**

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

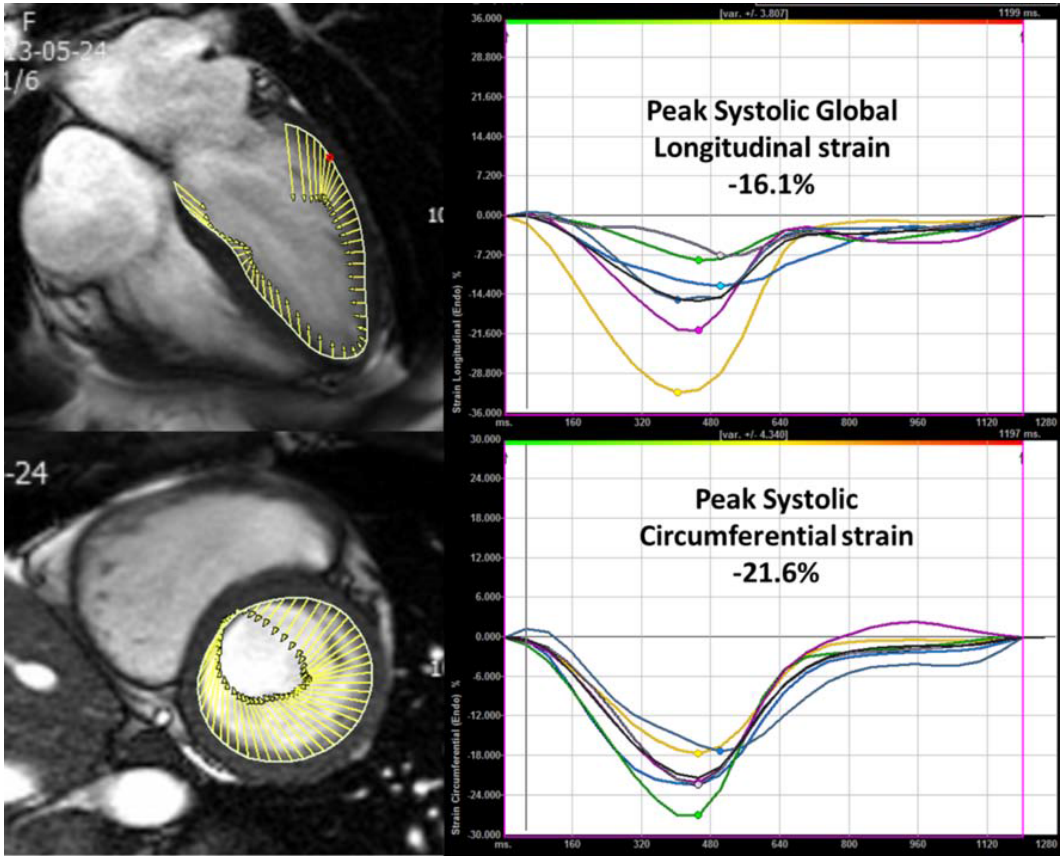
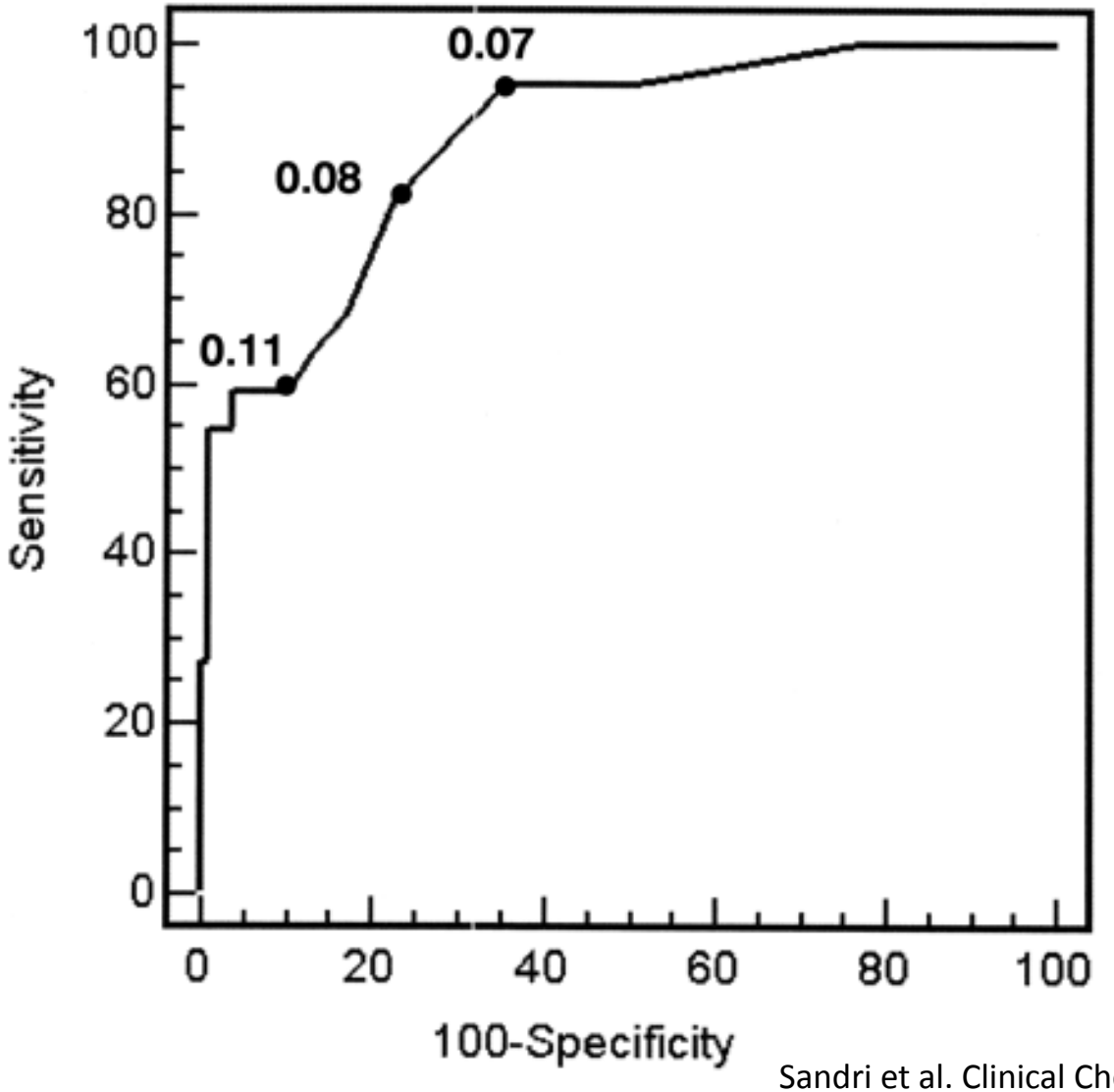


Table 6. Potential Clinical Uses of CMR for Assessment of Cardiac Consequences of Cancer Chemotherapy at Various Stages of Toxicity

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

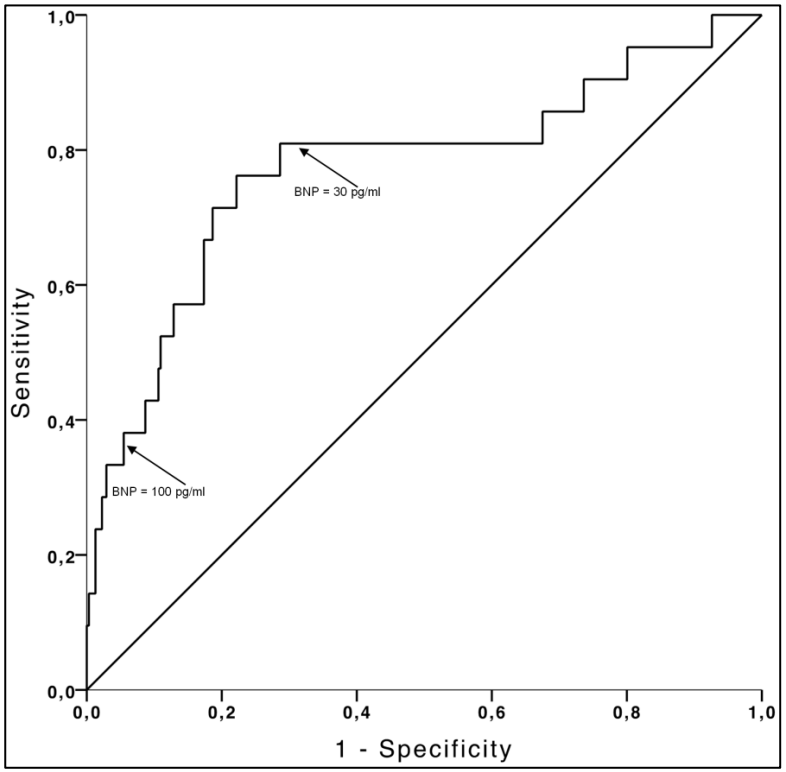
Thavendiranathan et al. *Circ Cardiovasc Imaging 2013*

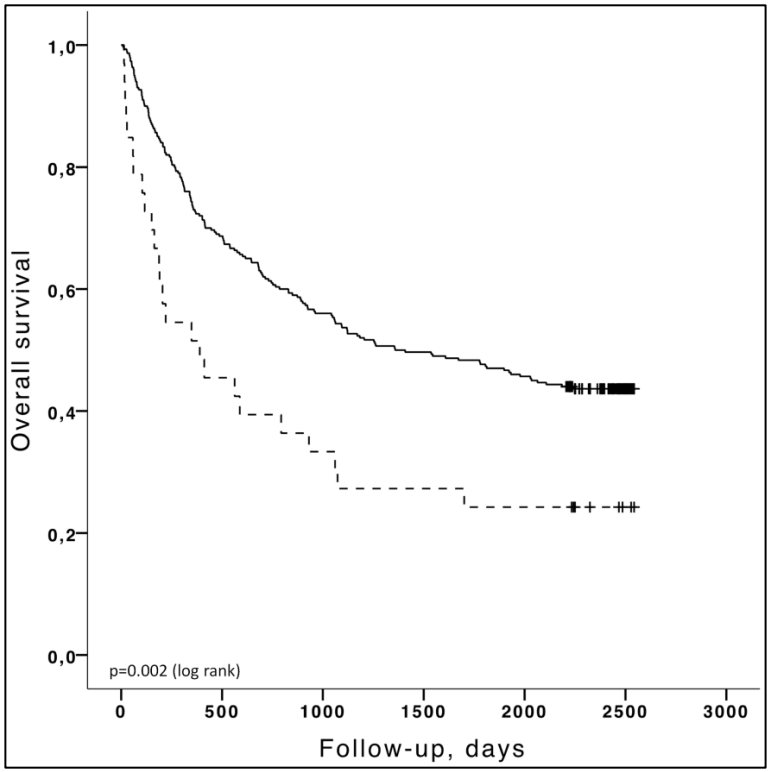
ROC curve for cTnI as marker of cardiotoxicity.



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

BNP predicts cardiotoxicity and death in patients with cancer





Skovgaard et al. PLOS one 2014

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- The Impact of Cardiovascular Morbidity
- Mechanisms of Selected Cardiotoxicities
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- **Interventions**
- UH Protocols

Response of Anthracycline-Induced Cardiomyopathy to HF therapy

45% of patients did not respond

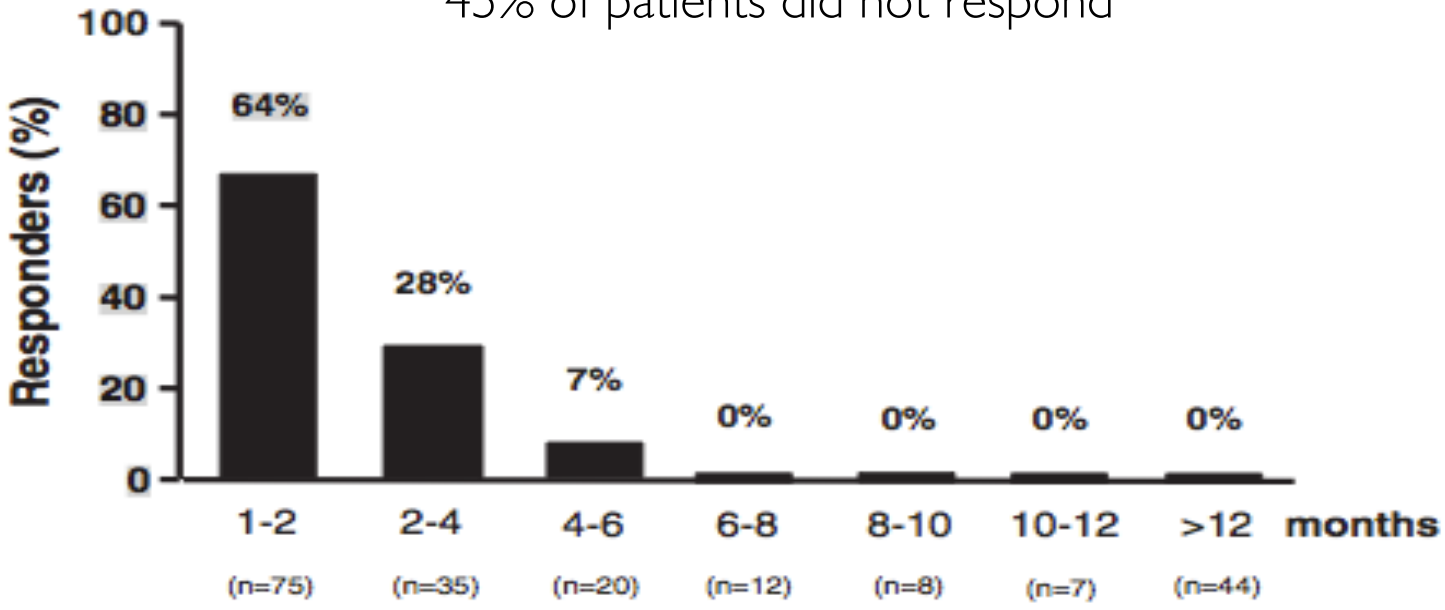


Figure 1 **Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy**

AC = anthracyclines; HF = heart failure.

Cardinale et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. JACC 2010; 55(3):213-20

Survival of Responders vs. Non-responders

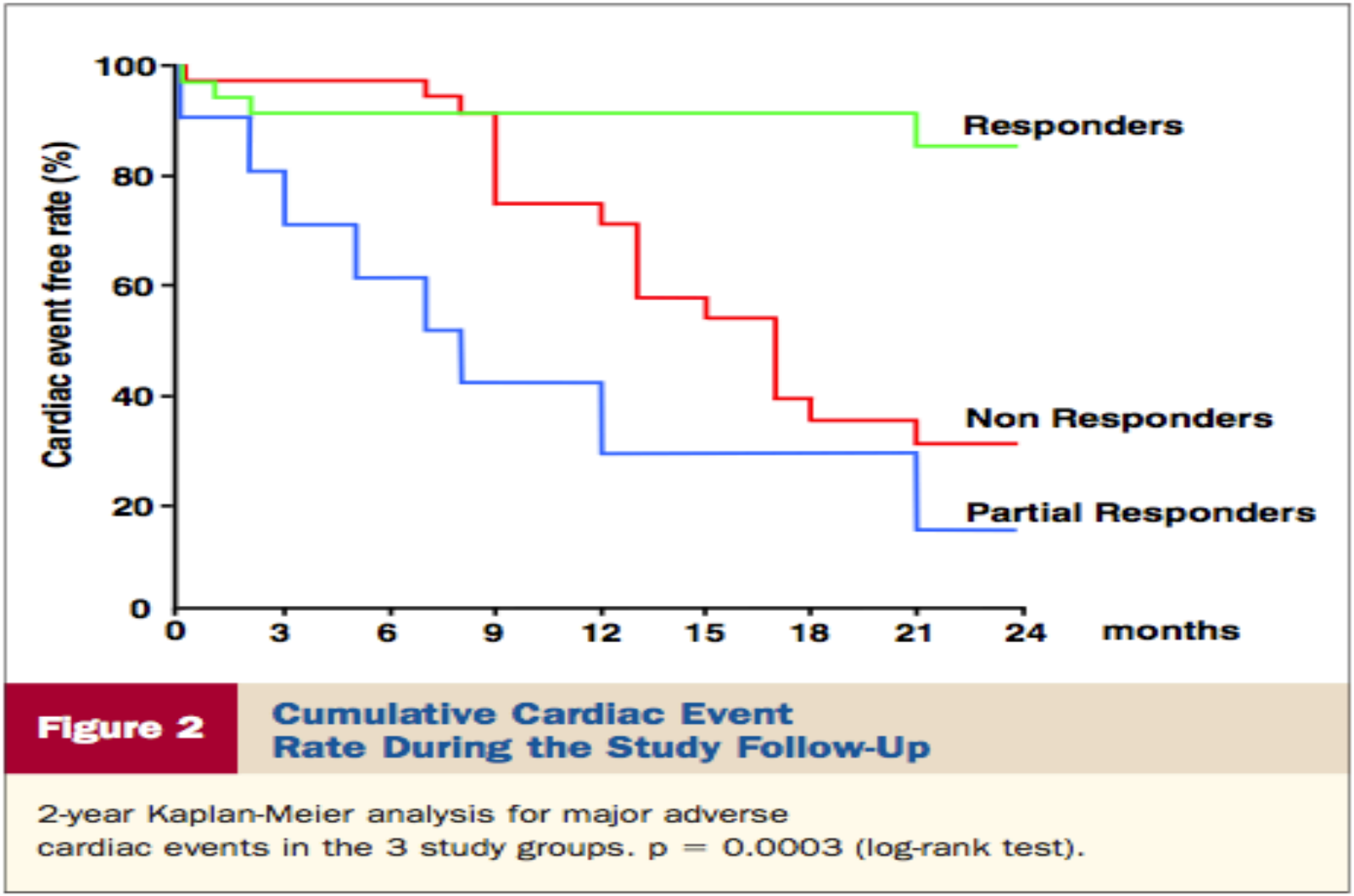


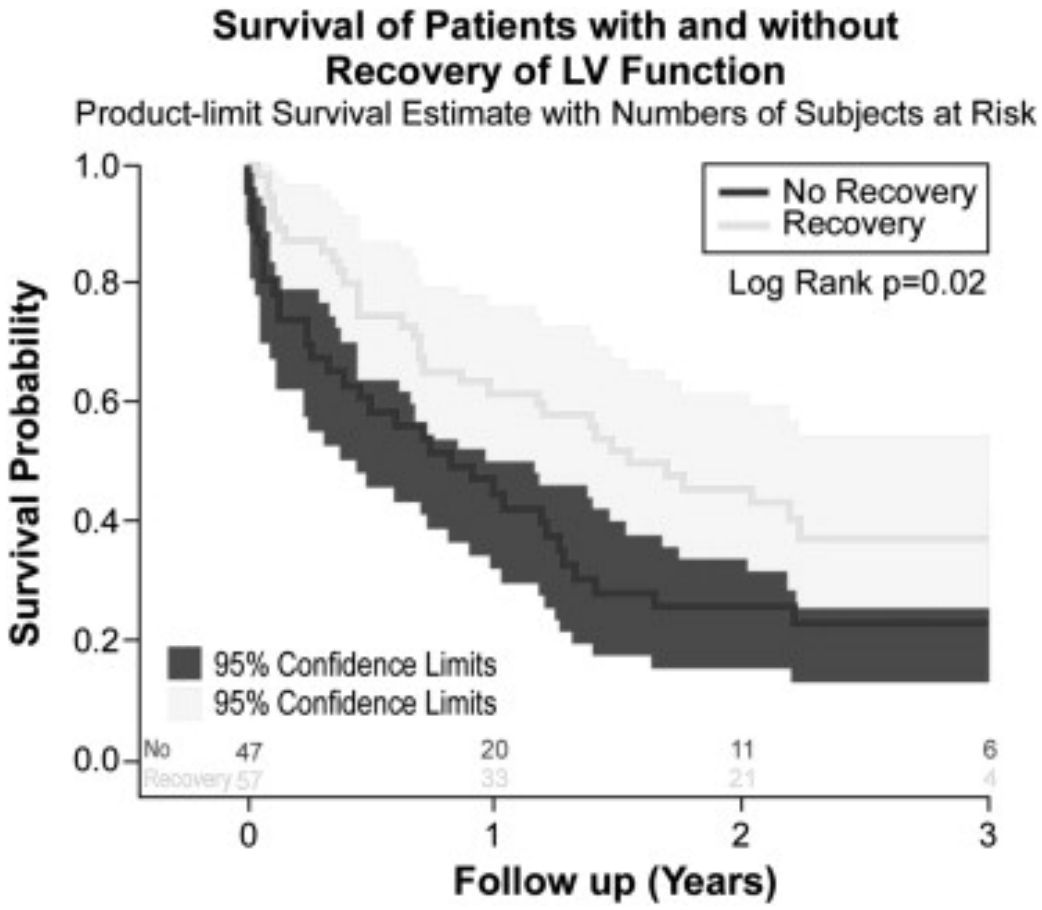
Figure 2 **Cumulative Cardiac Event Rate During the Study Follow-Up**

2-year Kaplan-Meier analysis for major adverse cardiac events in the 3 study groups. p = 0.0003 (log-rank test).

Cardinale et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. JACC 2010; 55(3):213-20

Incidence, Predictors, and Impact on Survival of Left Ventricular Systolic Dysfunction and Recovery in Advanced Cancer Patients

Guilherme H. Oliveira, MD[a,*], Siddarth Mukerji, MD[b], Adrian V. Hernandez, MD[c,d], Marwan Y. Qattan, MD[a], Jose Banchs, MD[e], Jean-Bernard Durand, MD[e], Cezar Iliescu, MD[e], Juan Carlos Plana, MD[f], and W.H. Wilson Tang, MD[f]



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

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Patients Appropriate for Onco-Cardiology Referral

PREEXISTING HEART DISEASE

1. CAD (stents, CABG, previous myocardial infarction)
2. History of heart failure
3. Abnormal LV function
4. Valvular heart disease (> mild)
5. Congenital heart disease
6. Previous stroke
7. Peripheral vascular disease
8. Uncontrolled hypertension
9. Cardiac tumors
9. Arrhythmias

ABNORMAL CARDIAC TESTS

1. Abnormal EKG
2. Abnormal Echo/MUGA
3. Abnormal stress test
4. CT of chest showing coronary calcification
5. Previous heart catheterization with non-obstructive coronary disease
6. Abnormal carotid ultrasound

ACTIVE CARDIAC SYMPTOMS

1. Shortness of breath
2. Chest pressure or pain
3. Lower extremity edema
4. Palpitations
5. Syncope

HIGH CARDIOVASCULAR RISK

1. Men > 50 years; Women > 60 years
2. History of anthracycline use (independent of cumulative dose)
3. History of chest radiation
4. DM type 1 or 2
5. Smoking
6. Family history of early CAD
7. Familial hypercholesterolemia
8. Morbid obesity

CARDIOTOXIC TREATMENTS

1. Any anthracycline
2. HER2, tyrosine kinase inhibitors (trastuzumab, pertuzumab, lapatinib)
3. VGEF inhibitors (sorafenib, sunitinib, axitinib, pazopanib, bavacizumab)
4. Antimetabolites (capecitabine, fluorouracil)
5. Cytokines (iL-2)
6. Radiotherapy to the chest or neck

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CARDIOVASCULAR EVALUATION AND TESTING

ALL PATENTS

- History
- Physical examination
- EKG
- Complete 2D and 3D echocardiogram with strain
- NT pro-BNP
- Lipid profile

SUSPICION OF CAD

1. High suspicion (abnormal stress test, CT arteriogram, CT calcium scoring >1000, classic angina, anginal equivalent): heart catheterization

2. Intermediate suspicion: CT arteriogram with heart flow

3. Low suspicion (rule out CAD for history of previous chest radiation without other risk factors or symptoms): CT calcium scoring

LOW EF

1. Repeat echocardiogram if outside study

2. Heart catheterization

3. Cardiac MRI with DGE

Multiple myeloma undergoing stem cell transplant

1. Cardiac MRI with DGE to rule out cardiac amyloidosis

2. Consider endomyocardial biopsy if MRI equivocal

HISTORY OF CHEST RADIATION

1. Calcium CT scoring (if asymptomatic)

2. CTA with heartflow or heart catheterization depending on degree of CAD suspicion

ARRYTHMIA/PALPITATONS

1. Ziopatch

2. Holter monitor

3. Thyroid function tests

Known CAD, stent, CABG or old MI

1. CTA with heartflow if no stent or CABG

2. Heart catheterization if previous stent or CABG or symptomatic

VASOSPASM WITH 5-FU

- Heart catheterization before next dose

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Cardiotoxicity prophylaxis in high-risk patients

GROUP A

Patients who will receive anthracyclines, HER2 inhibitors, VGEF inhibitors or stem cell transplant and any of the below:

- Abnormal left ventricular systolic function (EF<50% or global longitudinal strain<-18%)
- History of previous anthracycline therapy
- History of CAD, stent, CABG or old MI
- History of recovered EF
- History of heart failure in the past

1. **Carvedilol**- start at 3.125 BID or consider Coreg CR 10mg at bedtime if patient SBP is <110 mmHg

2. **Ramipril**- start at 2.5 mg daily. Give in addition to carvedilol if BP allows

3. **Statin**- Rosuvastatin 5 mg or pravastatin 20 mg

4. **Dexrazoxane-** in patients that need additional anthracycline therapy.

5. **Use of liposomal doxorubicin-** in patients that need anthracycline therapy.

GROUP B

Patients who will receive VGEF inhibitors and Hypertension (BP >140/90)

1. **Nifedipine XL-** start at 30 mg a day and go up to 120 mg

2. **Telmisartan +/- HCTZ-** only use in patients without nephrectomy and with normal renal function

3. **Carvedilol**- start at 3.125 and escalate

** For patients on sunitinib these medications should be added only during weeks when patients are on sunitinib and off stopped during "off" week.

GROUP C

Patients who receive 5-FU, capecitabine or bevacizumab with:

- Known CAD
- History of vasospasm

1. **Nifedipine XL 30-120 mg-** Start 24 h before 5-FU infusion and stop 48h following end of infusion

2.**Isosorbide mononitrate 30-120 mg-** Start 24h before 5FU infusion and stop 48h following end of infusion.

3. For patients on oral capecitabine, continue either or both throughout treatment period depending on blood pressure.

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Cardiotoxicity surveillance during HER-2 antagonist therapy

Normal baseline echo (EF >50% or GLS >-18%) and non-high risk CV risk assessment

If normal, Repeat echo, BNP and clinical assessment every 3 months

Repeat last echo 3 months following end of treatment

Normal baseline echo and high risk CV profile

1. **Repeat echo, BNP and clinical assessment in 1 month**
2. **If echo, BNP are normal and patient is asymptomatic, repeat echo, BNP and clinical assessment in 3 months**
3. **if echo or BNP are abnormal or patient has HF symptoms, repeat echo, BNP and clinical assessment before each cycle at 1 month intervals**

Abnormal baseline echo (EF <50% or GLS <-18%)

Repeat echo, BNP and clinical assessment before each cycle at 1 month intervals

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Cardiotoxicity surveillance during anthracycline therapy

Normal baseline echo (EF >50% or GLS >-18%) and non-high risk CV risk assessment

1. Repeat echo, BNP, and clinical assessment at 1 month and then every 3 months
2. Perform troponin I measurement immediately after first cycle and at 3 months (doesn't make sense since this is under low risk – no coverage if asymptomatic)
3. Repeat echos at 3 months, 6 months, 1 year, 3 years, 5 years and 10 years after end of treatment if asymptomatic and normal EF maintained throughout treatment

Normal baseline echo and high risk CV profile

1. Repeat echo, BNP, and clinical assessment in 1 month
2. If echo, BNP are normal and patient is asymptomatic, repeat echo, (BNP, troponin – won't be covered if asymptomatic) I and clinical assessment in 3 months
3. If echo or BNP are abnormal or patient has HF symptoms, repeat echo, BNP, and clinical assessment before each cycle and troponin I immediately after each cycle
4. Repeat echos at 3 months, 6 months, 1 year, 3 years, 5 years and 10 years after end of treatment if asymptomatic and normal EF maintained throughout treatment.

Abnormal baseline echo (EF <50% or GLS <-18%)

1. Repeat echo, BNP, and clinical assessment before each cycle at 1 month intervals
2. Perform troponin I measurement immediately after each cycle
3. Repeat echos at 3 months, 6 months, and then annually

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Management of cardiotoxicity from HER-2 antagonists

≥15% drop in GLS and or >10 points in EF, but EF > 50% and no HF symptoms and normal BNP

1. ***Continue HER2 inhibitor***
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg a day)
4. Repeat echo, BNP and clinical assessment prior to each cycle

Drop in EF to <50% but >40% without HF symptoms or elevated BNP

1. ***Continue HER2 inhibitor***
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5- 50 mg/day)
5. Consider ivabradine for HR in patients who cannot tolerate high dose carvedilol
6. Repeat echo, BNP and clinical assessment prior to each cycle

Drop in EF to <40% and/or HF symptoms and abnormal BNP

1. ***Stop HER 2 inhibitor***
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5- 50 mg/day)
5. Start furosemide for volume control
6. Consider digoxin, hydralazine and nitrates
7. Consider ivabradine for HR control in patients who cannot tolerate high dose carvedilol
8. Repeat echo, BNP and clinical assessment monthly until HF resolves and EF returns to >40%
9. Resume HER2 inhibitor when HF resolves and EF returns to >40%

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Cardiotoxicity surveillance during VEGF therapy and stem cell transplant

VEGF INHIBITORS

<u>Normal baseline echo and non-high CV risk profile and BP, < 140/90 mmHg</u>

1. Repeat echo in 3 months.
2. If 3 month echo is normal, no more echos
3. Repeat echo if patient becomes symptomatic or develops S/S of HF at any point throughout treatment

High risk and/or abnormal baseline echo

Repeat echo at the end of therapy

HSCT

1. Obtain pre-transplant echo (post any cardiotoxic treatment and within 1 month prior to transplant)
2. Repeat echo 1 month following discharge from transplant
3. If previous anthracycline therapy, follow monitoring schedule above

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Management of cardiotoxicity from Anthracyclines

≥15% drop in GLS and or >10 EF points, but EF > 50% and no HF symptoms and normal BNP

1. ***Continue anthracyclines***
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg a day)
4. Repeat echo, BNP and clinical assessment prior to each cycle

Drop in EF to <50% but >40% without HF symptoms or elevated BNP

1. ***Hold anthracyclines***
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. if BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5- 50 mg/day)
5. Consider ivabradine for HR in patients who cannot tolerate high dose carvedilol
6. Repeat echo, BNP and clinical assessment in 1 month to evaluate LV recovery
7. Consider rechallenging with liposomal anthracycline or concomitant dexrazoxane

Drop in EF to <40% and/or HF symptoms and abnormal BNP

1. ***Stop anthracyclines***
2. Start carvedilol or Coreg CR (in patients with low BP), at lowest dose as 1st line of therapy
3. If BP allows, start Ramipril (2.5-10 mg/day) or valsartan/sacubitril
4. Start spironolactone (12.5- 50 mg/day)
5. Start furosemide for volume control
6. Consider digoxin, hydralazine and nitrates
7. Consider ivabradine for HR control in patients who cannot tolerate high dose carvedilol
8. Repeat echo, BNP and clinical assessment in 1 month to evaluate LV recovery
9. No more anthracyclines unless endomyocardial biopsy shows <1.5 anthracycline cardiotoxicity

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Management of cardiotoxicity from VEGF Inhibitors and 5-FU

VEGF INHIBITORS

Hypertension Grade 1-2

1. Continue therapy
2. Initiate nifedpine XL 30-120 mg/ day
3. Initiate telmisartan/HCTZ 40/12.5- 80/25 mg/day (in absence of prior nephrectomy or abnormal creatinine)

Hypertension Grade 3

1. Hold therapy
2. Initiate nifedpine XL 30-120 mg/ day
3. Initiate telmisartan/HCTZ 40/12.5- 80/25 mg/day (in absence of prior nephrectomy or abnormal creatinine)
4. Consider labetolol 200-800 mg 3x/day
5. R-echallenge again on antihypertensive therapy

5-FU

Coronary vasospasm without left ventricular dysfunction or troponinemia

1. Stop therapy
2. Perform heart catheterization +/- revascularization
3. Initiate nifedipine XL 30-120 mg/day 2 days before and continue 2 days after infusion
4. Initiate Imdur 30-120 mg/day 2 days before and continue 2 days after infusion
5. Resume 5-FU infusions as outpatient

Coronary vasospasm with left ventricular dysfunction or increased troponins

1. Stop therapy
2. Perform heart catheterization +/- revascularization
3. Admit patient for 5-FU re-challenge
4. Initiate nifedipine XL 30-120 mg a day 2 days before and continue 2 days after infusion
5. Initiate intravenous nitroglycerin 12h before and continue 12h following infusion.

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Evaluation of Cancer Survivors

History of anthracycline exposure

ASYMPTOMATIC

1. History and physical exam
2. EKG
3. Complete 2D and 3D
4. echocardiogram with strain
5. BNP, lipid profile

SYMPTOMATIC

(chest pain, dyspnea, palpitations, syncope, fatigue or decreased exercise capacity)

1. History and physical exam
2. EKG
3. Complete 2D and 3D
4. echocardiogram with strain
5. Metabolic stress test
6. BNP, lipid profile
7. Consider cardiac MRI,
8. Consider RHC at rest and with exercise
9. Ziopatch/ Holter
10. CT angiography of coronaries with heartflow (intermediate suspicion for CAD)
11.. Left heart catheterization (high CAD suspicion)

History of chest radiation

ASYMPTOMATIC

1. History and physical exam
2. EKG
3. Complete 2D and 3D
4. echocardiogram with strain
5. CT of chest for calcium scoring

SYMPTOMATIC

(chest pain, palpitations, syncope, dyspnea, fatigue or decreased exercise capacity)

1. History and physical exam
2. EKG
3. Complete 2D and 3D echocardiogram with strain
4. BNP, lipid profile, TSH
5. CT angiography of coronaries with heartflow (intermediate suspicion for CAD)
6. Left heart catheterization (high suspicion)
7. Consider metabolic stress test
8. Consider rest and exercise right heart catheterization
9. Ziopatch/Holter

Conclusions

- Cardiovascular morbidity can impair outcomes of both cancer patients and survivors
- Field of intense research- clinical, translational and basic
- Targeted cancer therapies potentially shed light on mechanisms of cardiac injury
- Prevention, surveillance and treatment are important for patient outcomes.
- Advanced heart failure therapies may play a major role in cancer survivors with irreversible cardiovascular injuries

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Thank You!

Questions?