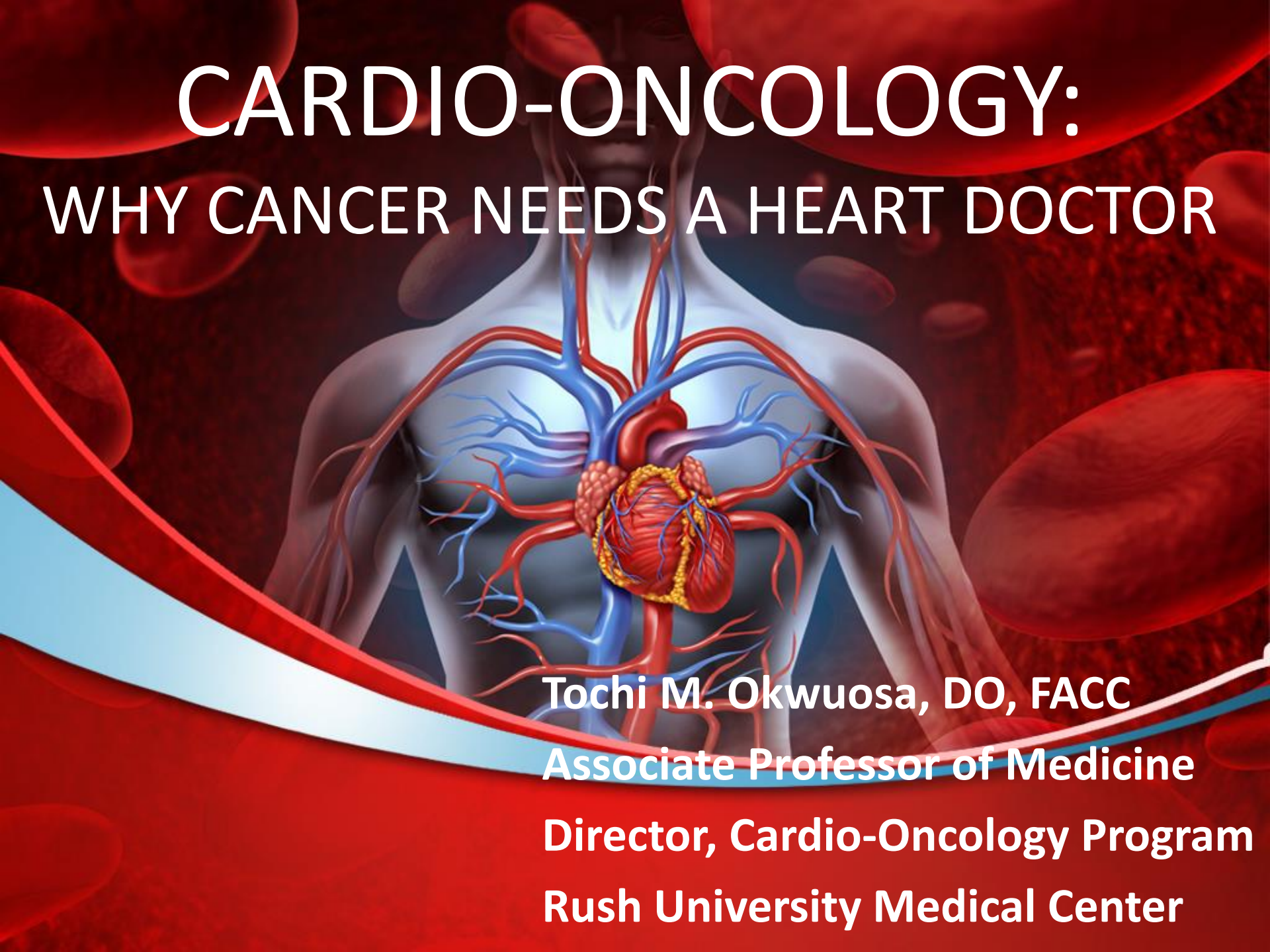
CARDIO-ONCOLOGY:
WHY CANCER NEEDS A HEART DOCTOR



Tochi M. Okwuosa, DO, FACC
Associate Professor of Medicine
Director, Cardio-Oncology Program
Rush University Medical Center

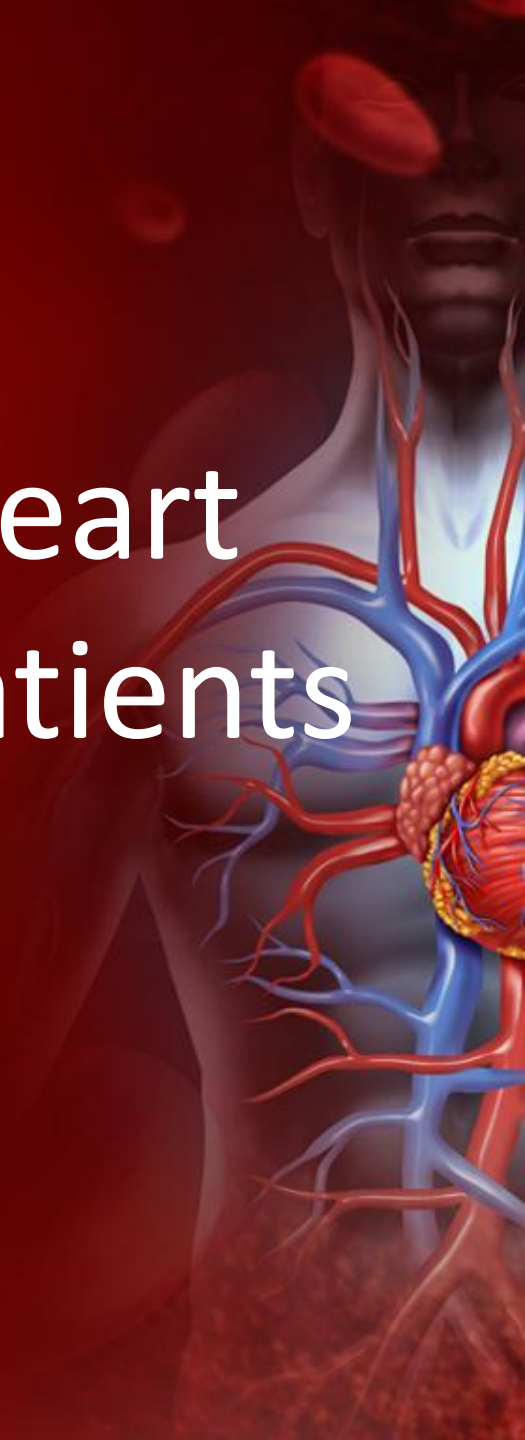
Disclosure Statement

- I have no conflict of interest to disclose

Learning Objectives

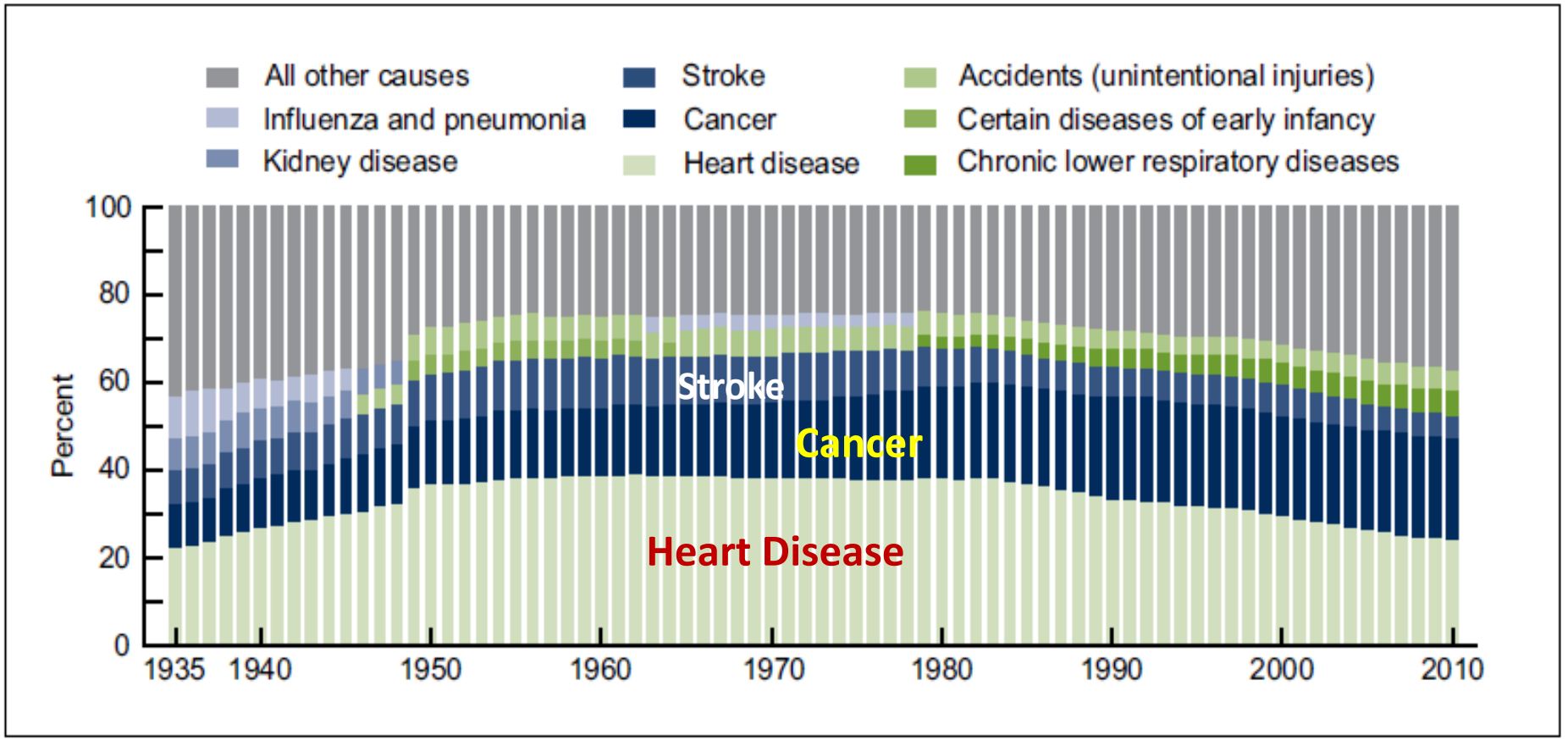
- Epidemiology of heart disease in cancer patients
- Cardiotoxicity of various Chemotherapeutic agents
- Cardiotoxicity of Radiation Therapy
- Cardiotoxicity of Hormonal Therapy
- Risk Factors for chemo/radiation-induced cardiotoxicity
- Markers of, and Diagnostic modalities for cardiotoxicity related to cancer therapy
- Cardiac therapy in cancer patients
- When to refer to Cardio-Oncology

Epidemiology of Heart Disease in Cancer Patients



Heart disease and cancer remained the 1st and 2nd leading causes of death, respectively, over the 75-year period.

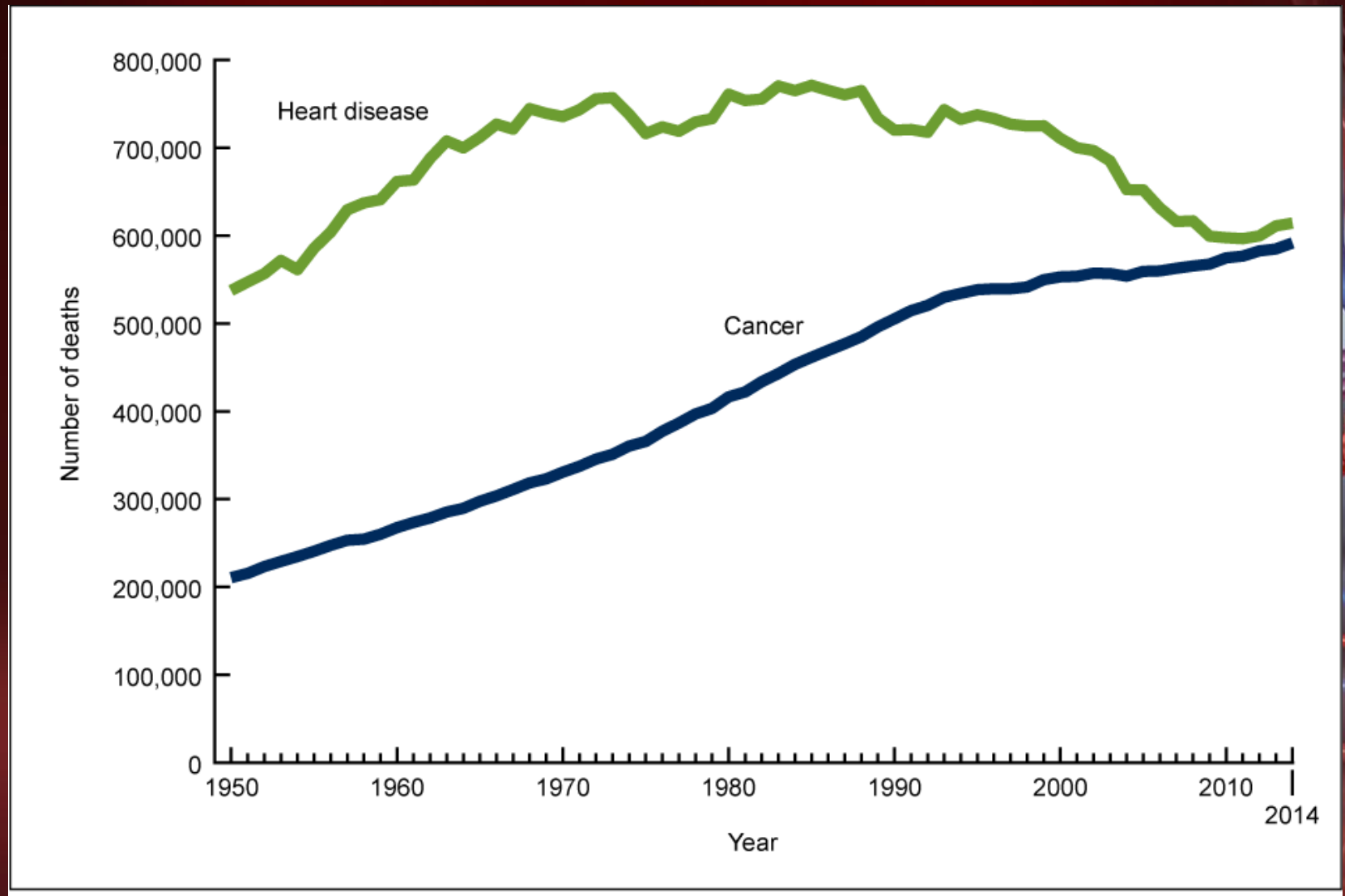
Figure 2. Percentage of all deaths due to five leading causes of death by year: United States, 1935–2010



NOTE: 2010 data are preliminary.

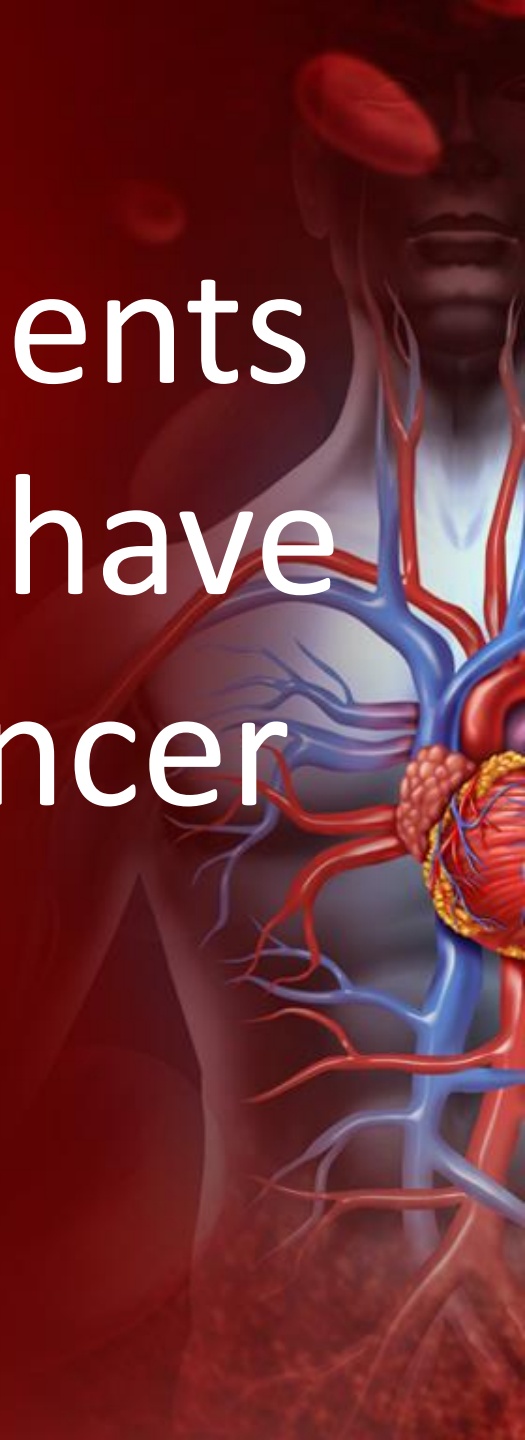
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

Deaths due to Heart Disease and Cancer

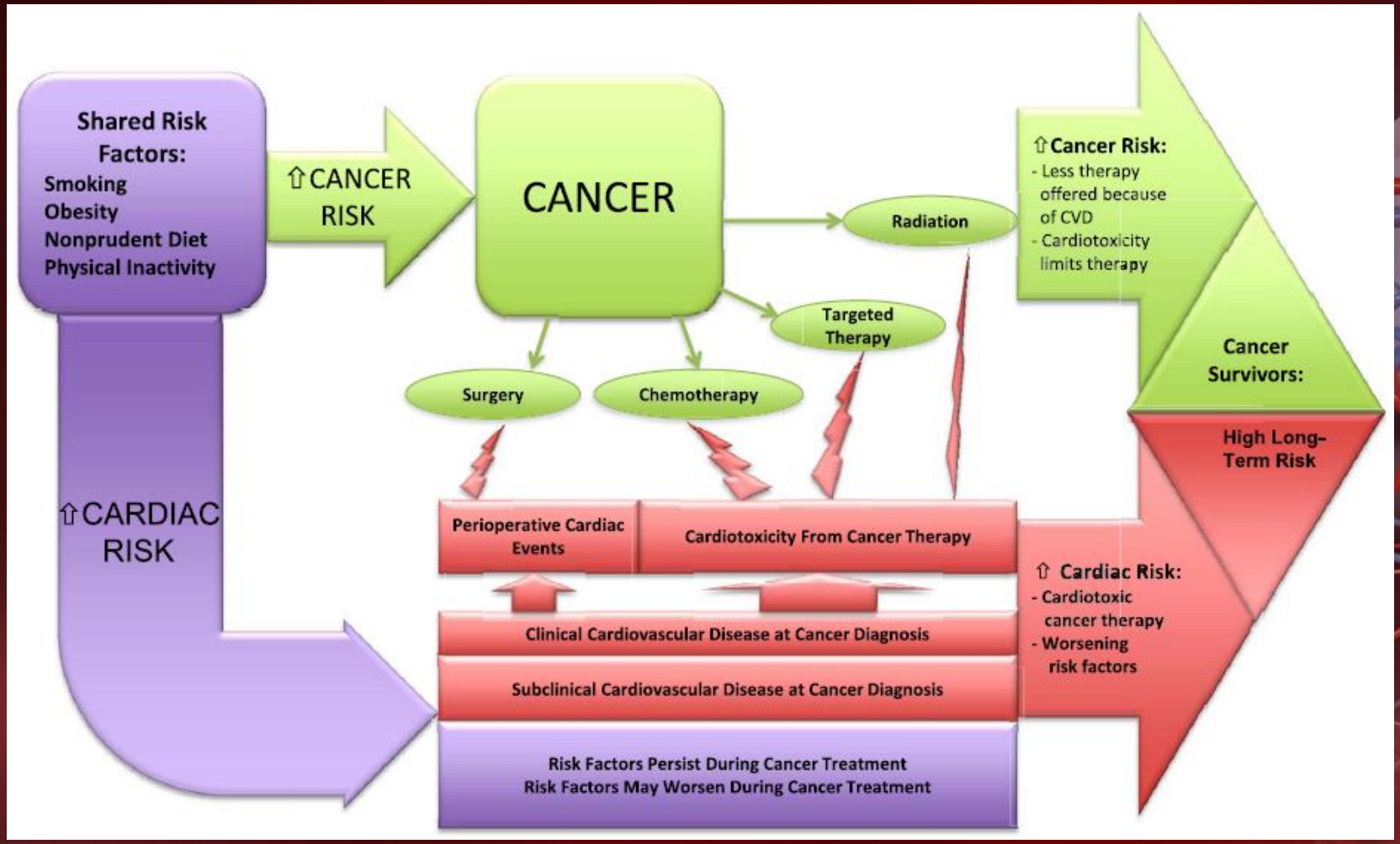


NOTES: Leading cause is based on number of deaths. Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db254_table.pdf#1.
SOURCE: NCHS, National Vital Statistics System, Mortality.

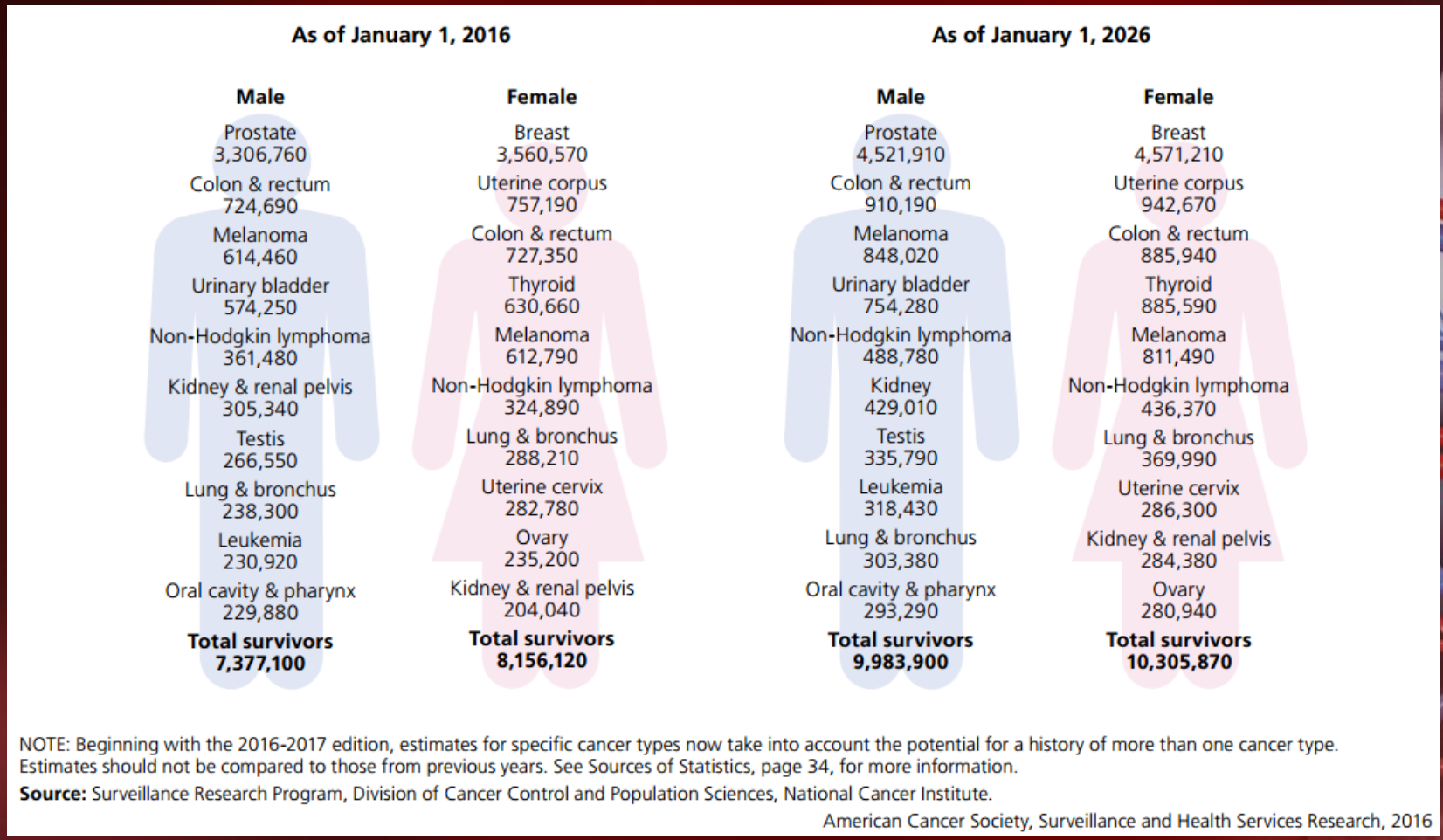
Heart disease patients are more likely to have a higher risk of cancer than the general population



Interactions between Heart Disease, Risk Factors, Cancer, Cancer Therapy



Estimated Numbers of US Cancer Survivors by Site



NOTE: Beginning with the 2016-2017 edition, estimates for specific cancer types now take into account the potential for a history of more than one cancer type. Estimates should not be compared to those from previous years. See Sources of Statistics, page 34, for more information.

Source: Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance and Health Services Research, 2016

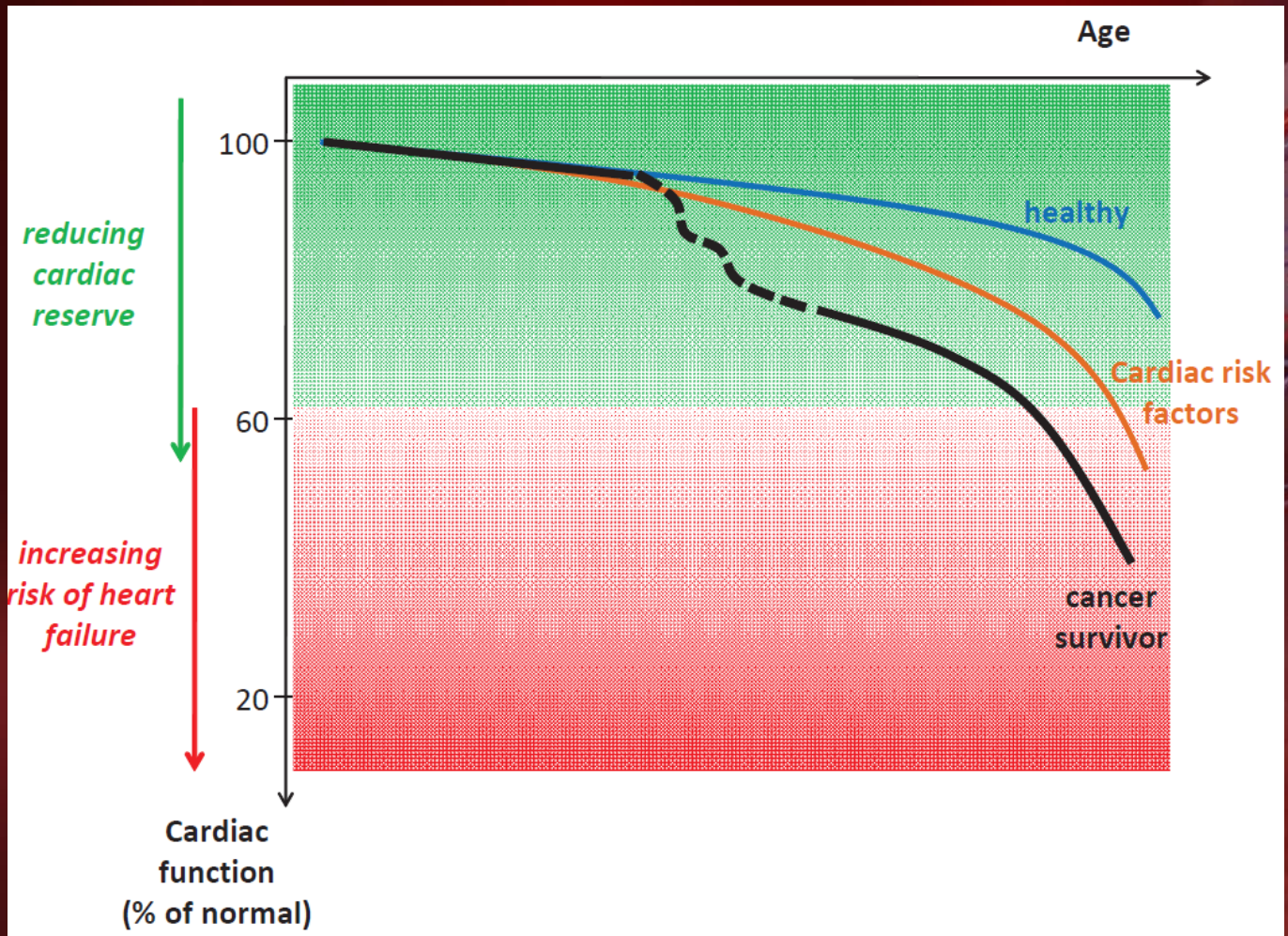
Many of these survivors have had radiation or chemotherapy, with potential long-term cardiovascular toxicities; attenuate clinical success of oncologic treatments

Estimated Numbers of Cancer Survivors by State as of January 1, 2016

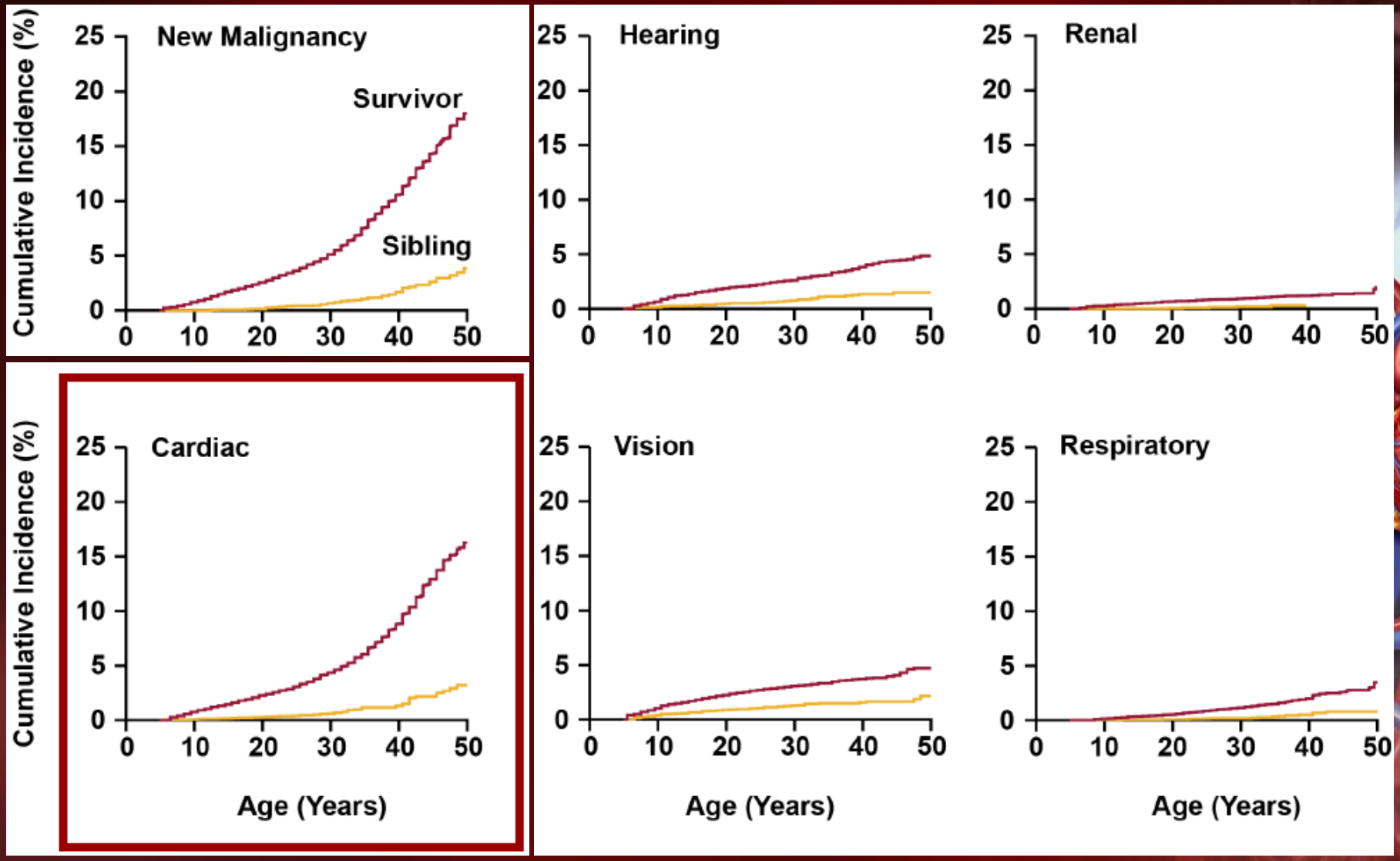
Heart Disease in Cancer: Risks

- > 50% of all patients exposed to chemotherapy will show some degree of cardiac dysfunction 10 to 20 years after chemotherapy
  - 5% will develop overt heart failure
  - 40% will experience arrhythmias
  - Eight-fold higher cardiovascular mortality when compared with the general population

Oncologic Treatments: Long-term Risk of HF, Despite Short-term Reassurance



Survivors of Childhood Cancer: Cumulative Incidence by Organ Systems



Armstrong *et al*, ASCO 2012
Tukenova *et al*, JCO 2010

Chemotherapy

Chemotherapy and the Heart: **Why?**

- Cardiac Cells do not divide
  - High protein synthesis
  - High metabolism
- Do not regenerate?
- Rely heavily on ordered cell-cell communication
- Responsive to biologic stress
- Consist of terminally differentiated cells unprotected by a vascular barrier
- Susceptible to permanent and adverse effects of chemo and radiation therapy

Chemotherapy-Induced Cardiovascular Toxicity

Cardiomyopathy/ Heart Failure

Anthracyclines (doxorubicin, epirubicin, idarubicin)
Alkylating agents (cyclophosphamide, ifosfamide)
Antimicrotubule agents (docetaxel)
Monoclonal antibody (bevacizumab, trastuzumab)
TKIs (dasatinib, imatinib, lapatinib, sunitinib)
Antimetabolites (clofarabine)
Proteasome inhibitors (bortezomib)

Hypertension

- **Monoclonal antibody-based TKI** (bevacizumab)
- **Small molecule TKIs** (sorafenib, sunitinib, pazopanib, axitinib, cediranib)
- **VEGF trap:** Afibercept

Ischemia

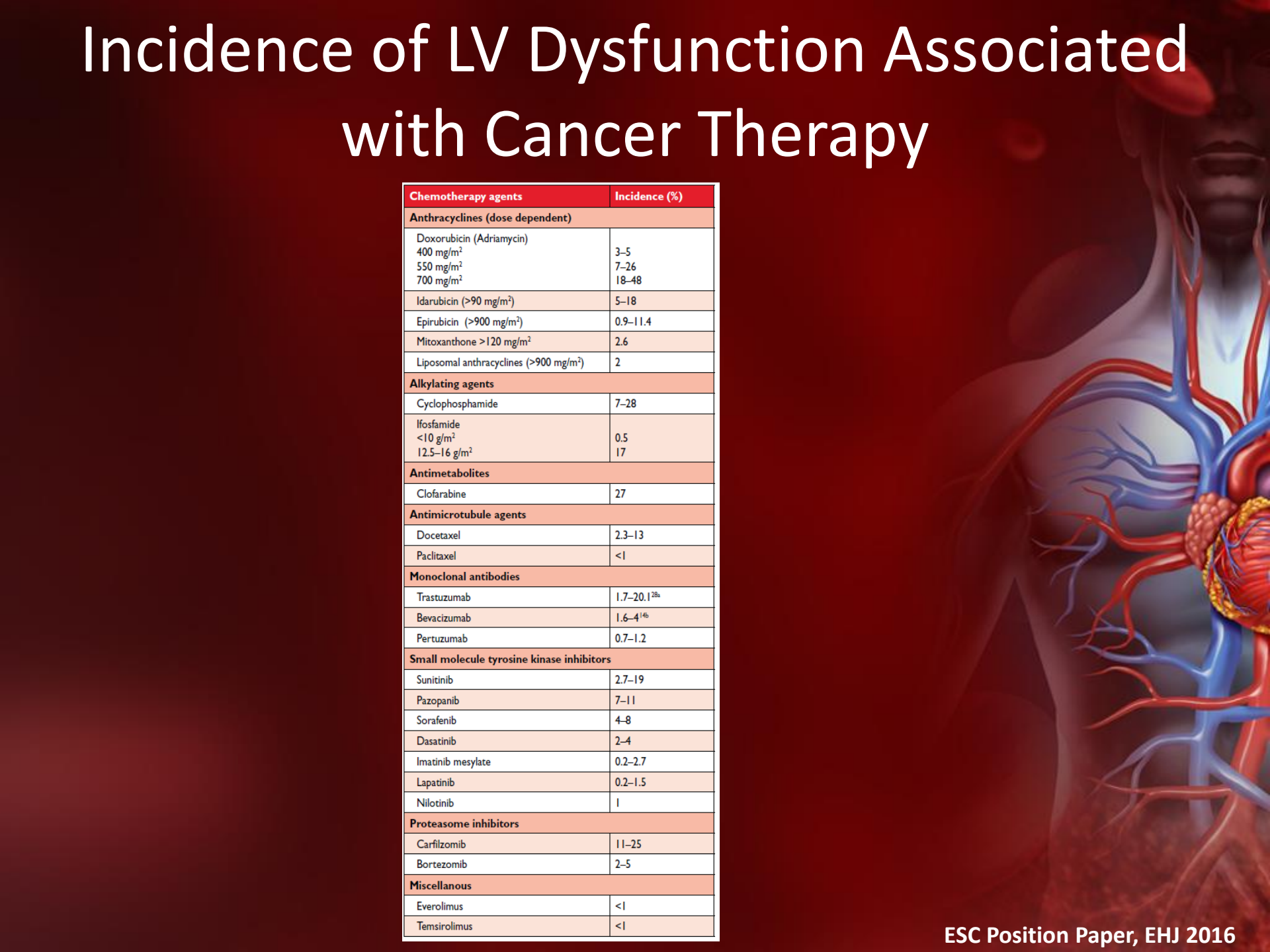
- **Antimetabolites** (5-FU, capecitabine)
- **Antimicrotubule agents** (docetaxel, paclitaxel)
- **Monoclonal antibody-based TKI** (bevacizumab)
- **Small molecule TKIs** (erlotinib, sorafenib)

Arrhythmias (bradycardia, QT prolongation)

Angiogenesis inhibitor (thalidomide)
Antimicrotubule agent (paclitaxel)
Histone deacetylase inhibitor (vorinostat)
Small molecule TKIs (dasatinib, lapatinib, nilotinib)
Miscellaneous (arsenic trioxide)

Incidence of LV Dysfunction Associated with Cancer Therapy

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m^2 550 mg/m^2 700 mg/m^2	 3–5 7–26 18–48
Idarubicin (>90 mg/m^2)	5–18
Epirubicin (>900 mg/m^2)	0.9–11.4
Mitoxanthone >120 mg/m^2	2.6
Liposomal anthracyclines (>900 mg/m^2)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m^2 12.5–16 g/m^2	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[28a]
Bevacizumab	1.6–4[146]
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellanous	
Everolimus	<1
Temsirolimus	<1

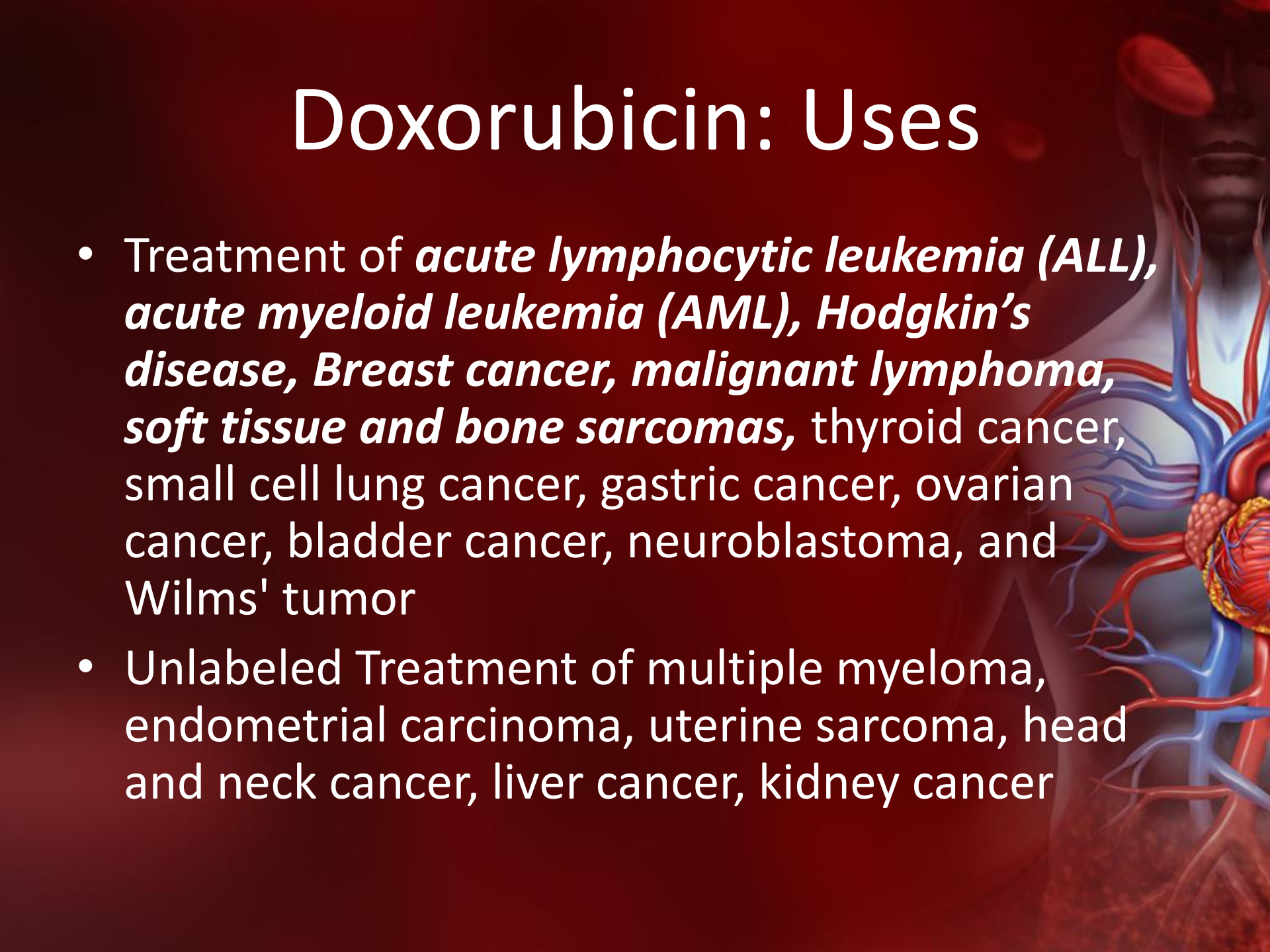


ESC Position Paper, EHJ 2016

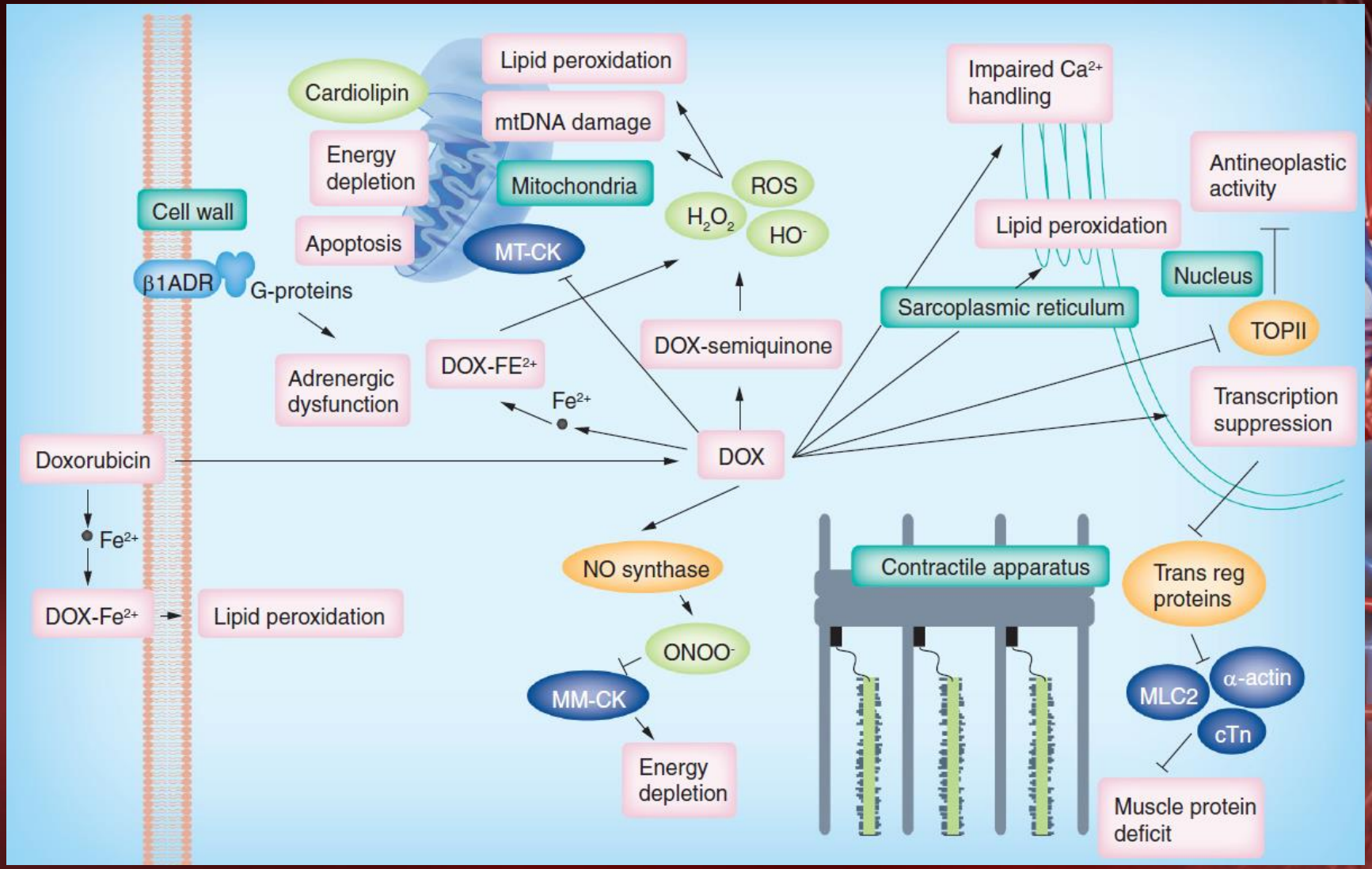
ANTHRACYCLINES

Doxorubicin: Uses

- Treatment of ***acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin's disease, Breast cancer, malignant lymphoma, soft tissue and bone sarcomas,*** thyroid cancer, small cell lung cancer, gastric cancer, ovarian cancer, bladder cancer, neuroblastoma, and Wilms' tumor
- Unlabeled Treatment of multiple myeloma, endometrial carcinoma, uterine sarcoma, head and neck cancer, liver cancer, kidney cancer

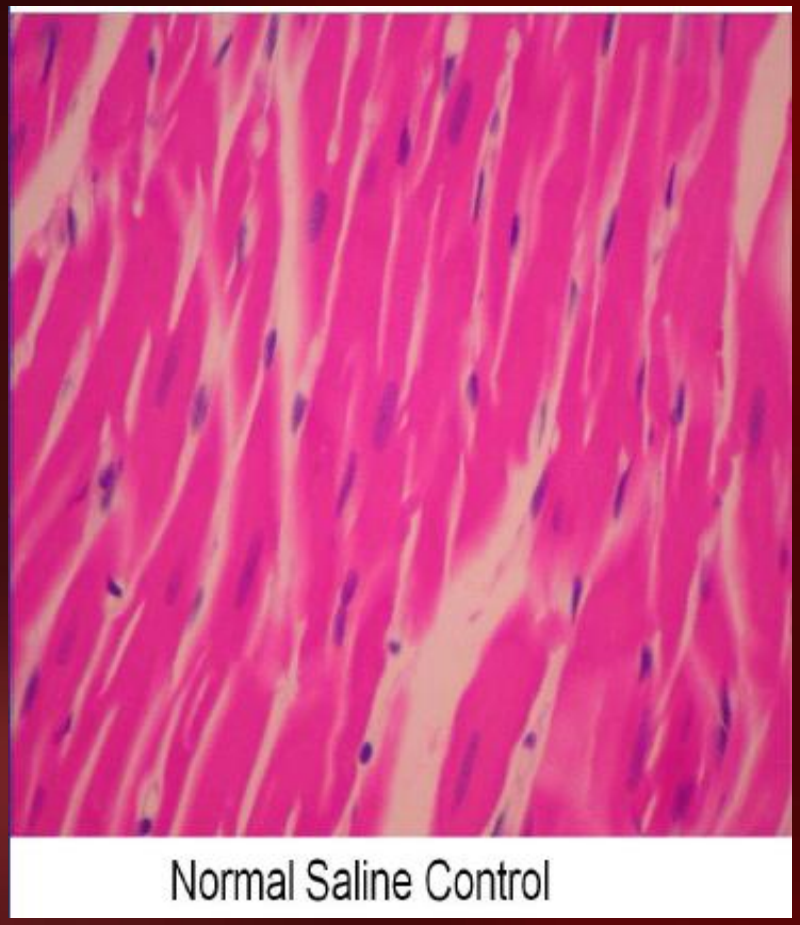


Mechanism of Anthracycline-Induced Cardiotoxicity

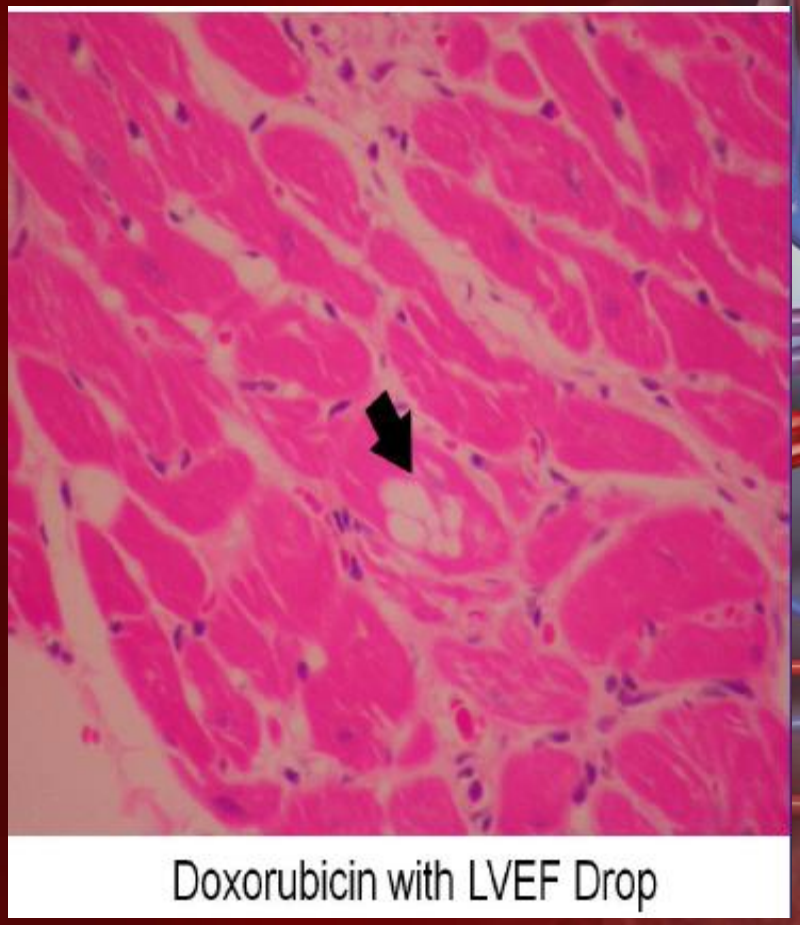


Harake *et al, Future Cardiol.* 2012

Vacuolization with Reduced Ejection Fraction due to Anthracycline Cardiotoxicity



Normal Saline Control

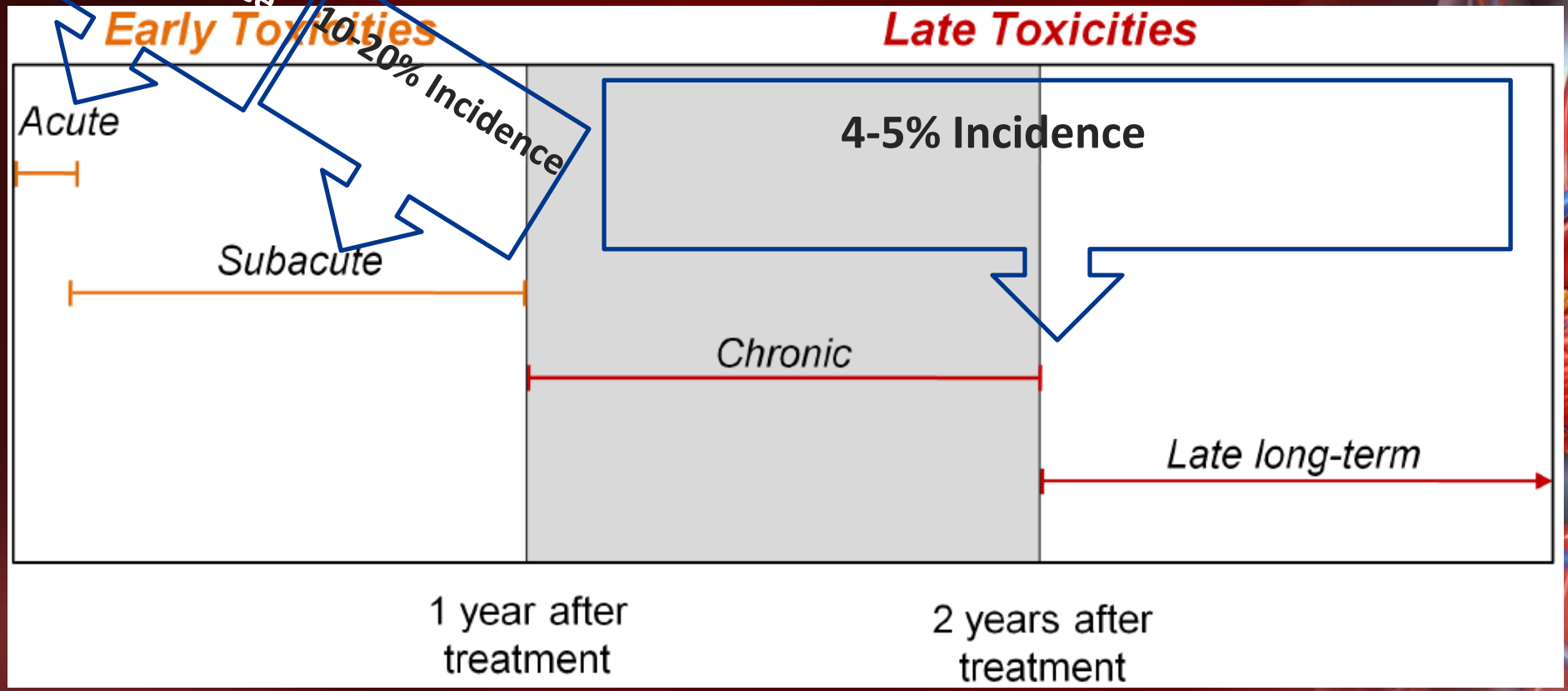


Doxorubicin with LVEF Drop

Lightfoot *et al,* Circ. Cardiovasc. Imag. 2010

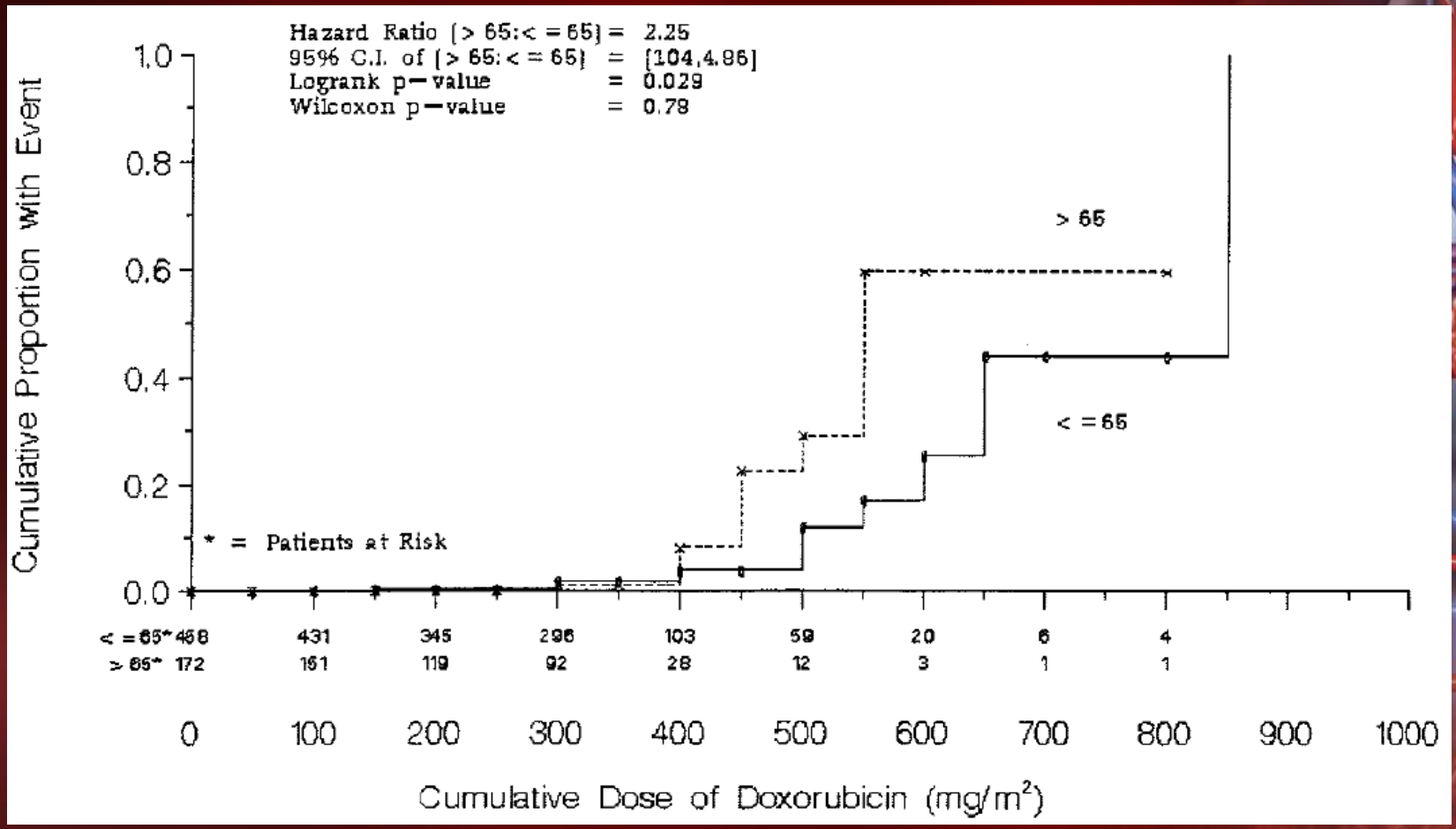
Timing of Injury:

Breast Cancer, Sarcoma, Leukemia, Lymphoma, Prostate Cancer



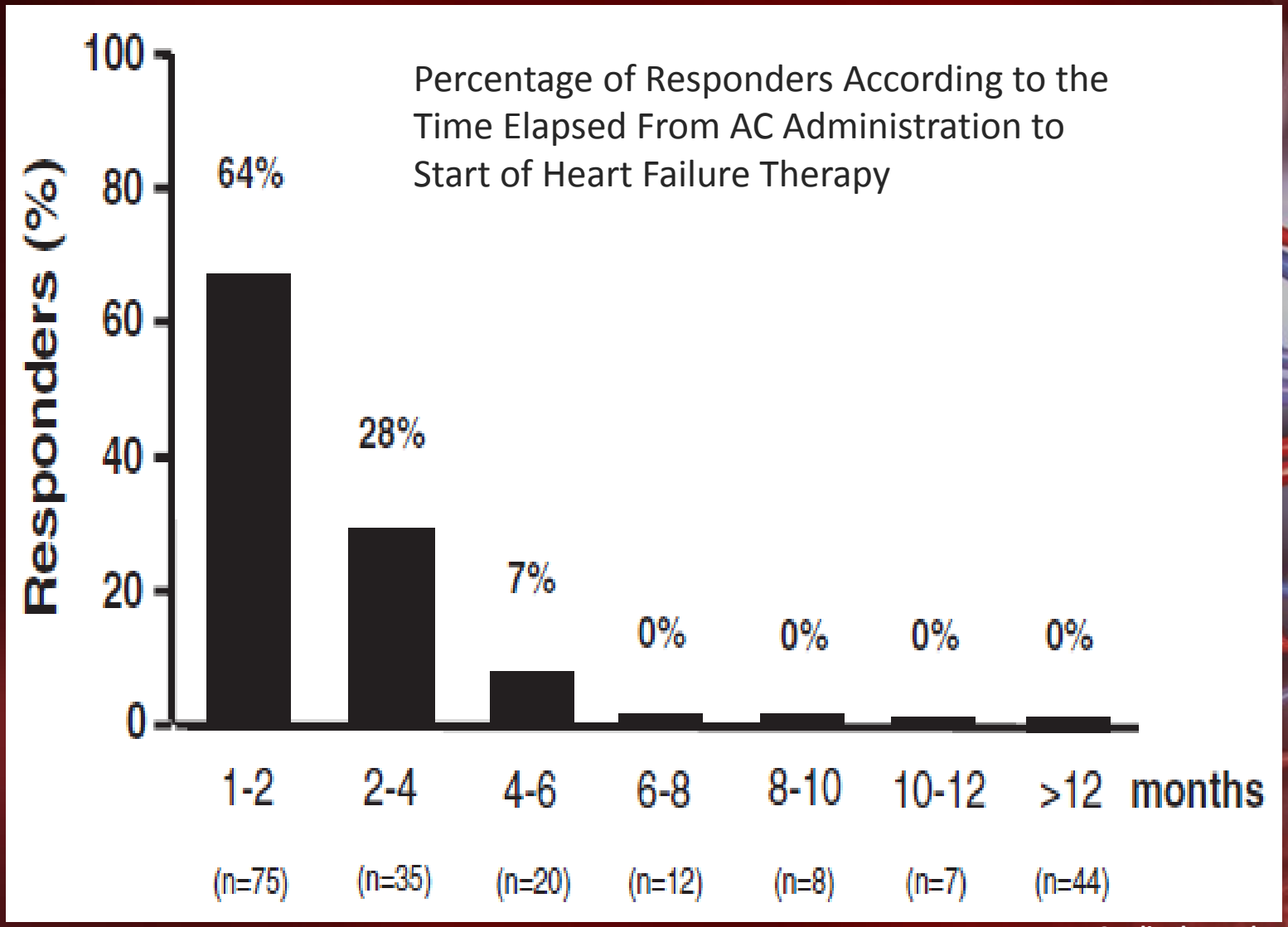
Hundley 2012

Dose-Dependent Doxorubicin-Related Heart Failure



Cancer 2003

Recovery of LV Systolic Function is Dependent on Time to Heart Failure Treatment

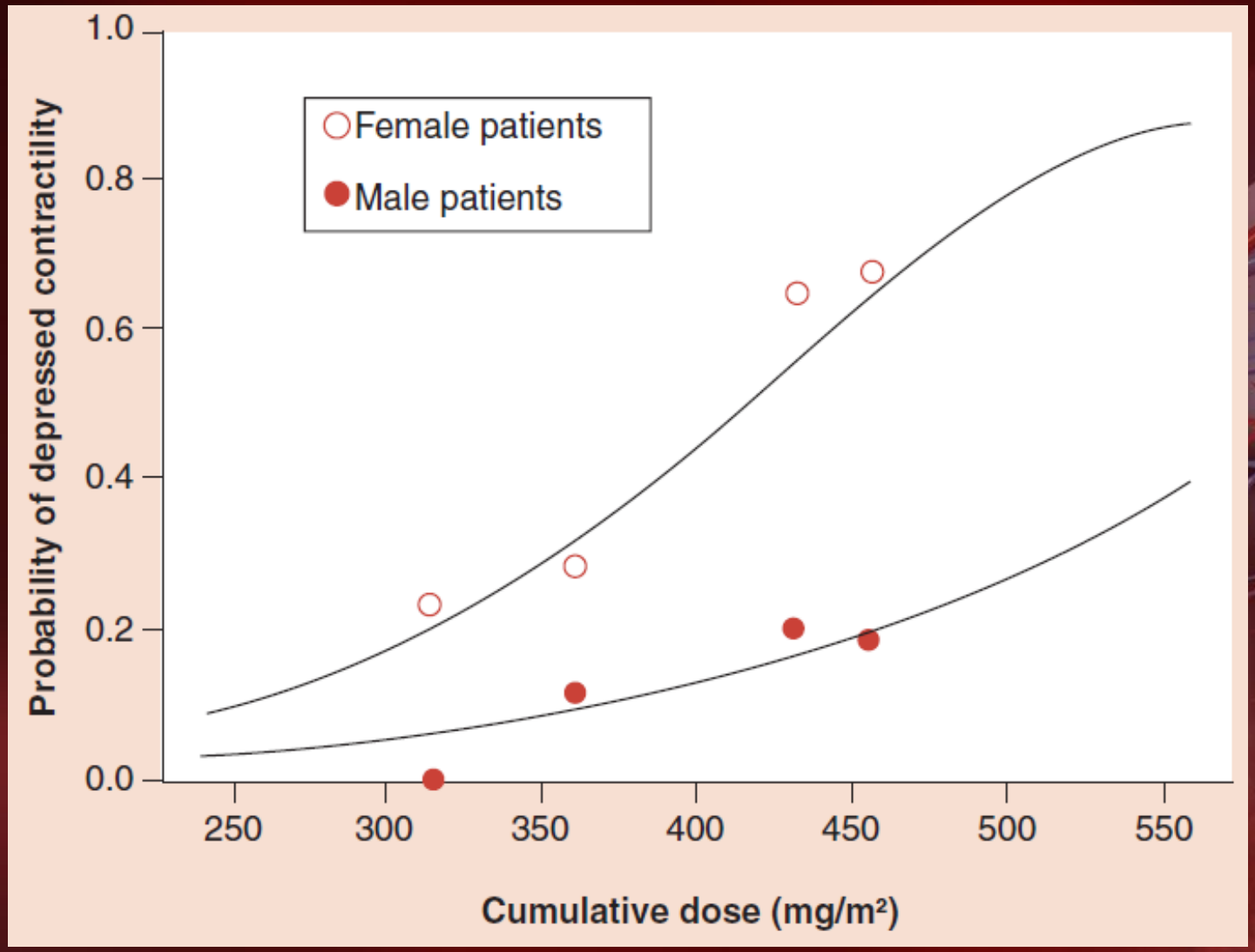


Cardinale *et al*, *JACC* 2010

Risk Factors for Anthracycline-Induced CT

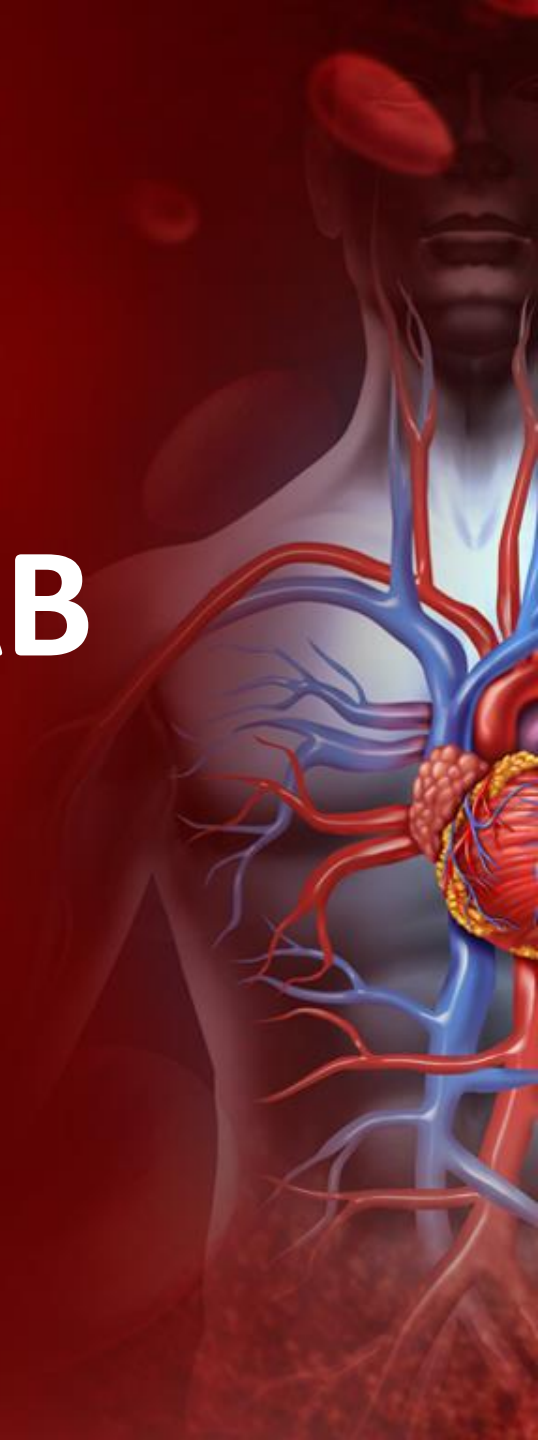
Risk factor	Aspects
Cumulative anthracycline dose	Cumulative doses >500 mg/m^2 associated with marked long-term risk
Length of post-therapy interval	Incidence of clinically important cardiotoxicity increases progressively after therapy
Rate of anthracycline administration	Prolonged administration to minimize circulating dose volume may decrease toxicity; results are mixed
Individual anthracycline dose	Higher individual anthracycline doses are associated with increased late cardiotoxicity, even when cumulative doses are limited
Type of anthracycline	Liposomal encapsulated preparations may reduce cardiotoxicity. Data detailing anthracycline analogs and cardiotoxicity differences are conflicting
Radiation therapy	Cumulative radiation dose >30 Gy; prior or concomitant anthracycline treatment
Concomitant therapy	Trastuzamab, cyclophosphamide, bleomycin, vincristine, amsacrine and mitoxantrone, among others, may increase susceptibility or toxicity
Pre-existing cardiac risk factors	Hypertension; ischemic, myocardial and valvular heart diseae; prior cardiotoxic treatment
Comorbidities	Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy
Age	Both young and advanced age at treatment are associated with increased risk
Sex	Females are at greater risk than males
Additional factors	Trisomy 21; African–American ancestry

Greater Risk of Anthracycline Cardiotoxicity in Females vs. Males



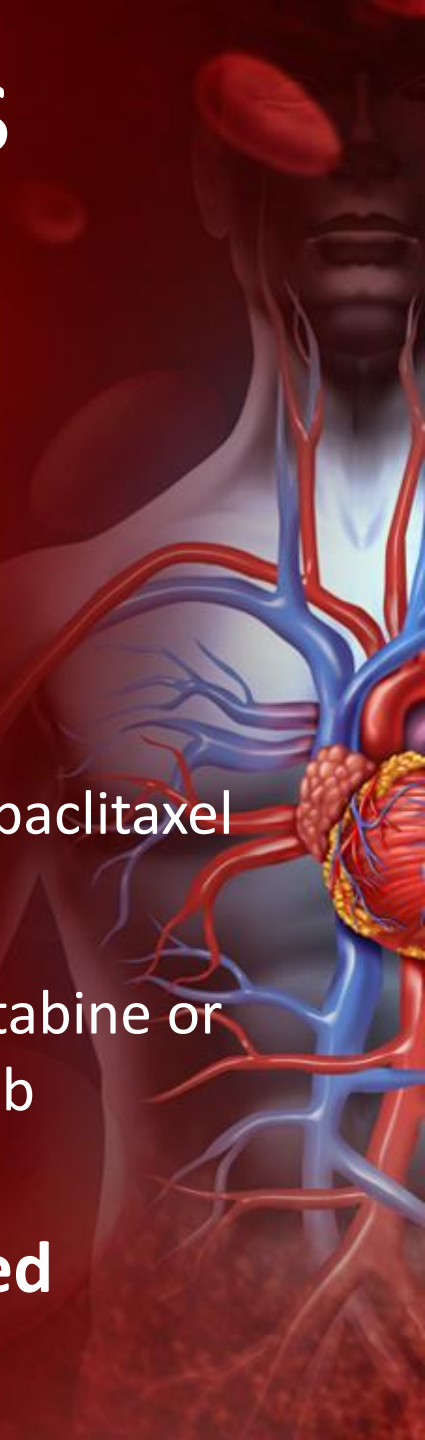
Harake *et al, Future Cardiol.* 2012

TRASTUZUMAB

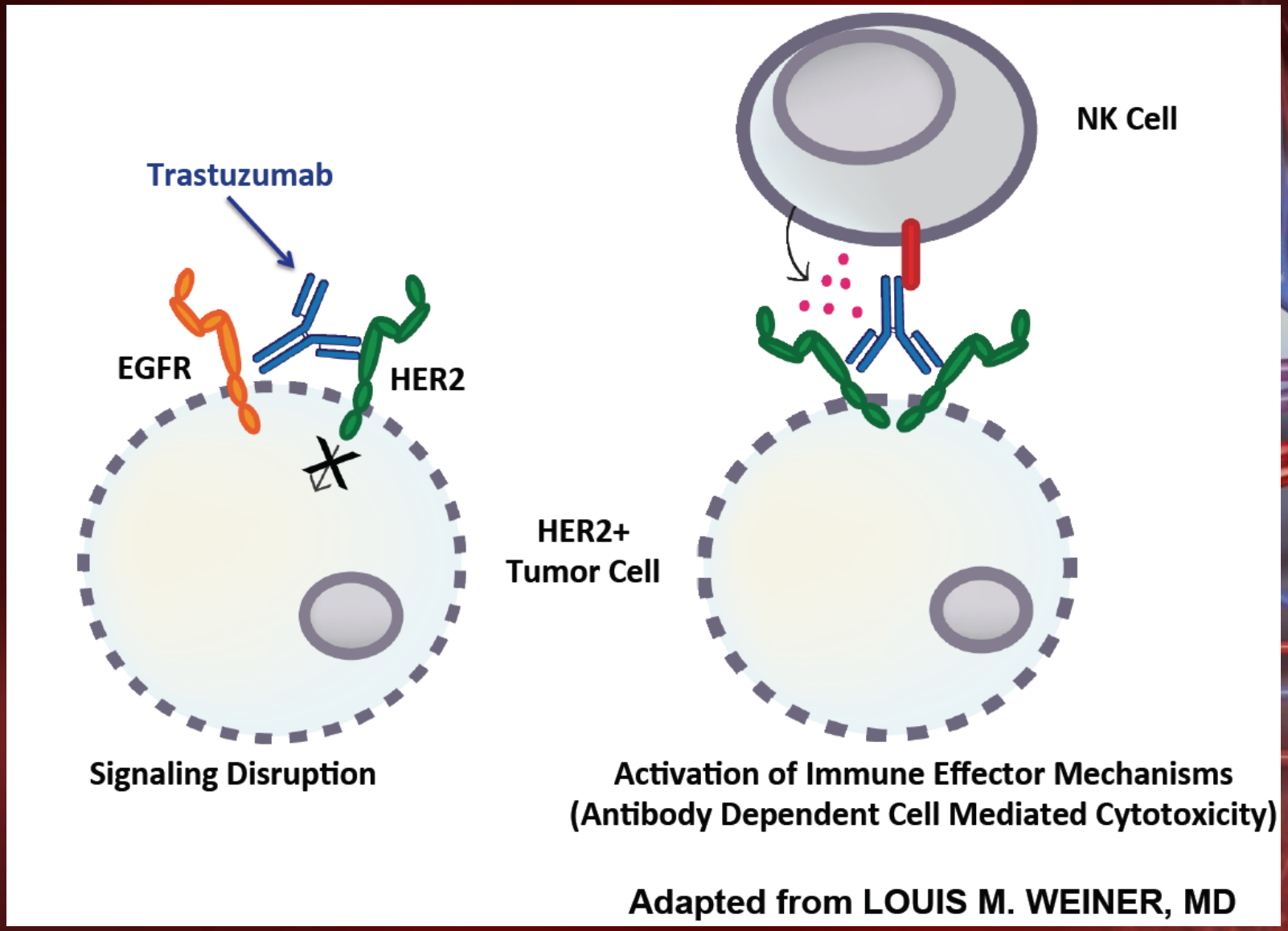


Trastuzumab: Uses

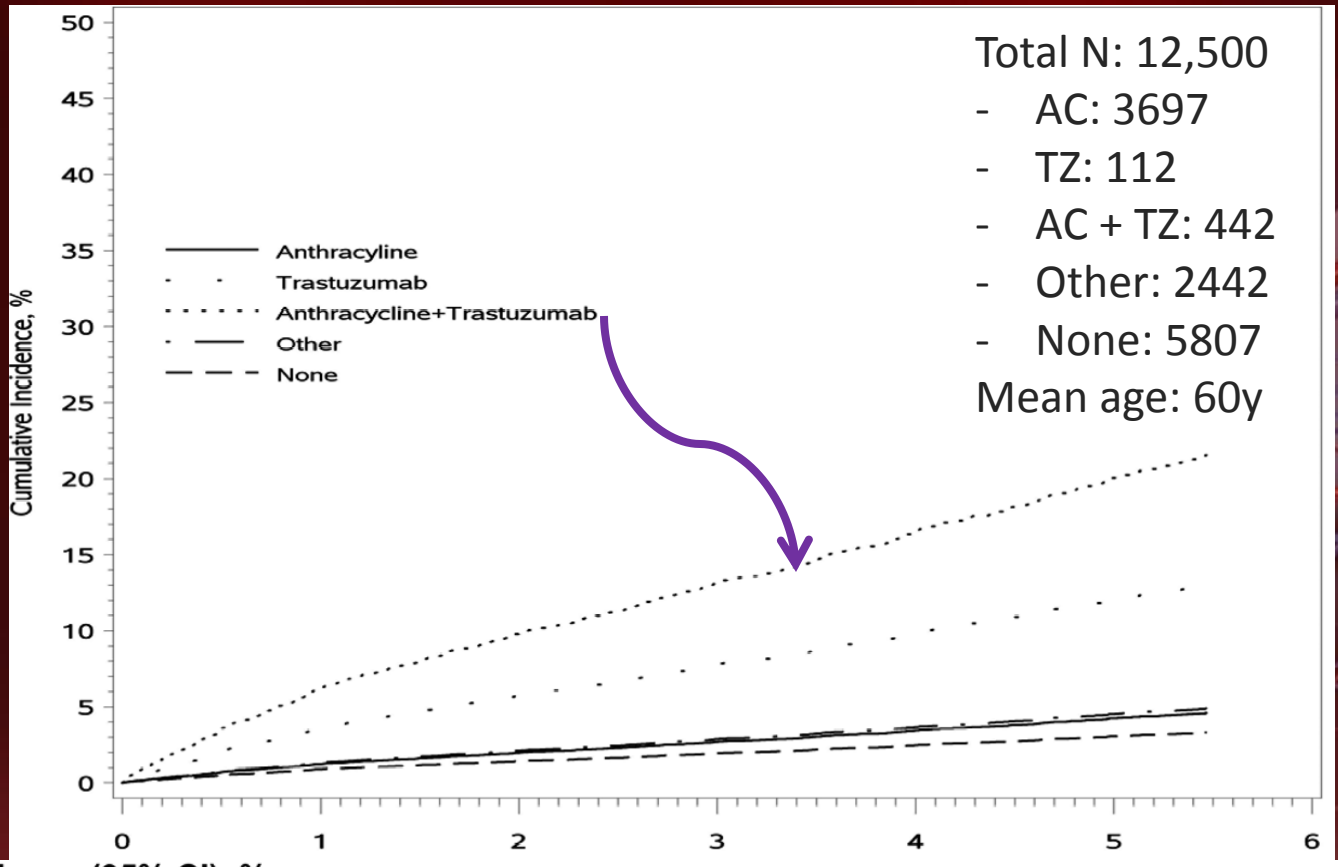
- **Breast cancer, adjuvant treatment, HER2+**
  - Following completion of anthracycline-based chemotherapy
  - With concurrent paclitaxel or docetaxel
  - With concurrent docetaxel/carboplatin
- **Breast cancer, metastatic, HER2+**
  - Either as a single agent or in combination with paclitaxel
- **Gastric cancer, metastatic, HER2+**
  - In combination with cisplatin and either capecitabine or fluorouracil for 6 cycles followed by trastuzumab monotherapy
- **Breast cancer, metastatic, HER2+ (unlabeled combinations)**



Trastuzumab: Mechanism of Action



Cumulative Incidence of Heart Failure: Anthracycline vs. Trastuzumab



Cumulative incidence (95% CI), %					
Anthracycline only	1.2 (1.0 to 1.5)	2.0 (1.6 to 2.4)	2.7 (2.2 to 3.2)	3.5 (2.8 to 4.1)	4.3 (3.5 to 5.0)
Trastuzumab only	3.6 (1.5 to 5.6)	5.8 (2.5 to 8.9)	7.8 (3.4 to 12.0)	9.9 (4.3 to 15.1)	12.1 (5.3 to 18.3)
Anthracycline+ Trastuzumab	6.2 (4.1 to 8.2)	9.8 (6.7 to 12.8)	13.2 (9.1 to 17.1)	16.5 (11.5 to 21.3)	20.1 (14.0 to 25.6)
Other chemotherapy	1.3 (1.0 to 1.6)	2.1 (1.7 to 2.5)	2.9 (2.4 to 3.4)	3.7 (3.0 to 4.3)	4.5 (3.7 to 5.3)
None	0.9 (0.7 to 1.0)	1.4 (1.2 to 1.7)	1.9 (1.6 to 2.3)	2.5 (2.1 to 2.9)	3.1 (2.6 to 3.5)

Bowles *et al, J Natl Cancer Inst* 2012

Potential risk factors for the development of trastuzumab-associated cardiac dysfunction]

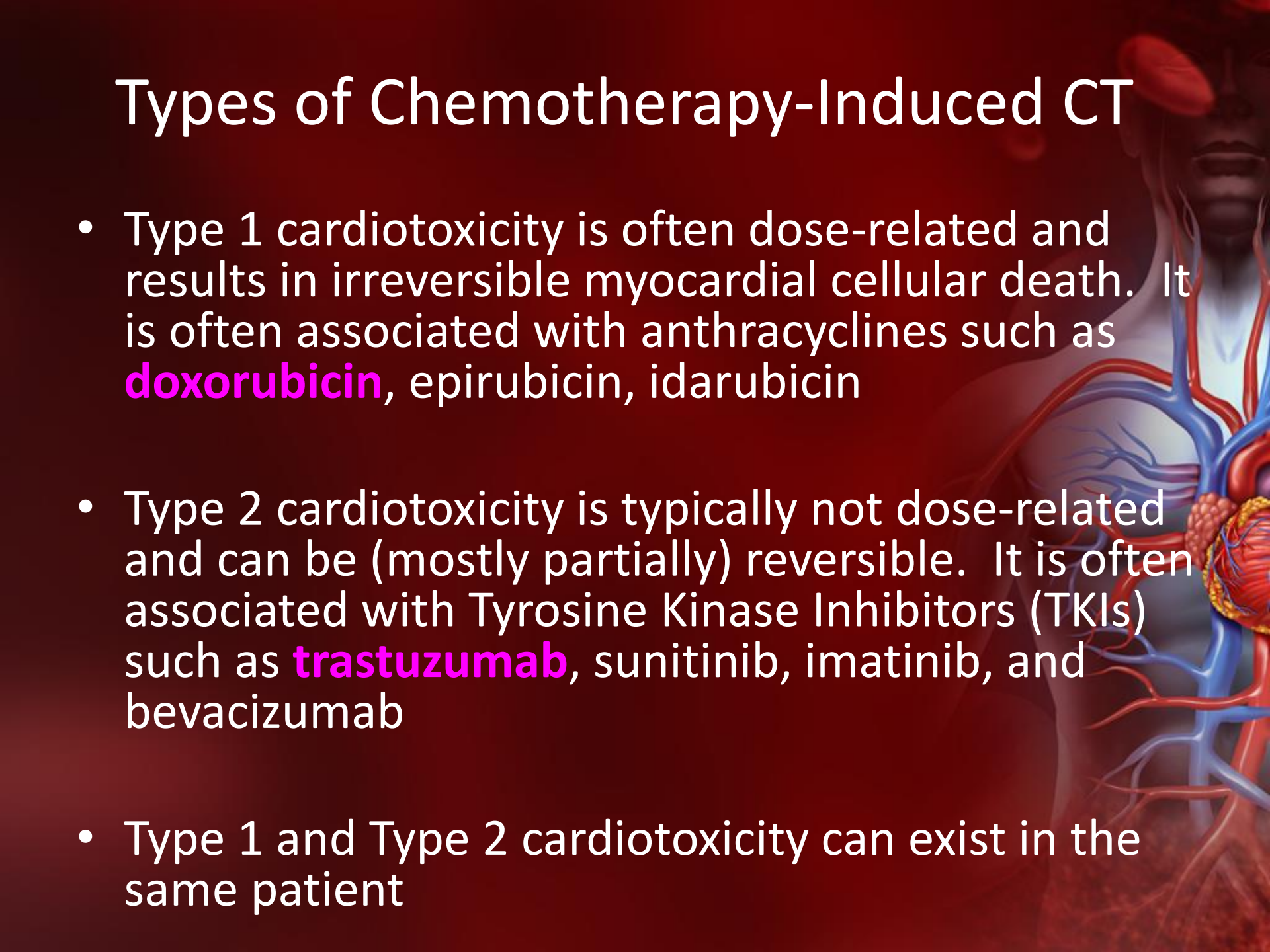
Cardiovascular factors	**Noncardiovascular factors**
Left ventricular dysfunction	Doxorubicin exposure
Coronary artery disease	Older age
Uncontrolled hypertension	Chest wall irradiation (especially to the left side)
Valvular heart disease	Diabetes
Cardiac arrhythmia	Obesity

Types of Chemotherapy-Induced CT

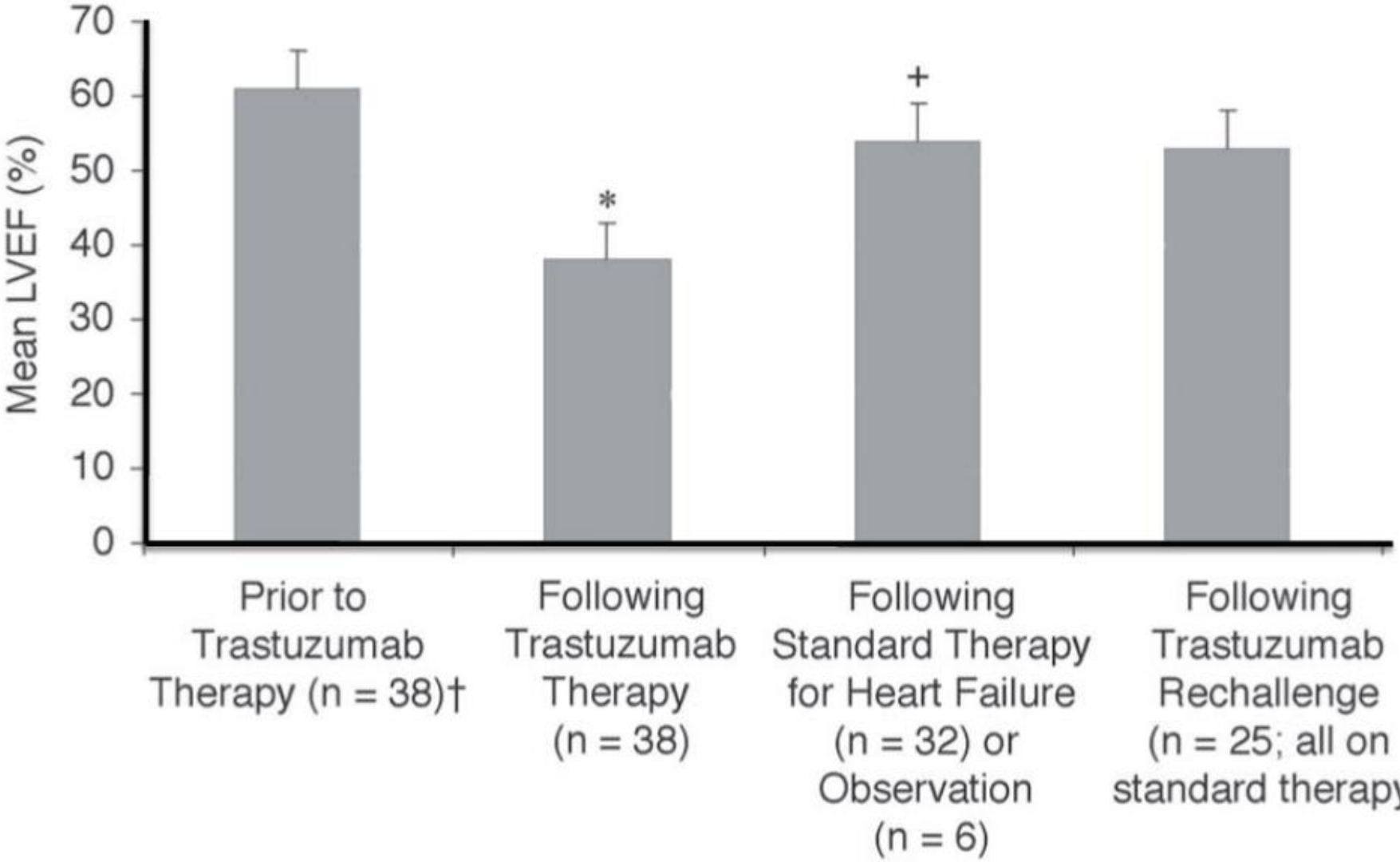
- Type 1 cardiotoxicity is often dose-related and results in irreversible myocardial cellular death. It is often associated with anthracyclines such as **doxorubicin**, epirubicin, idarubicin

- Type 2 cardiotoxicity is typically not dose-related and can be (mostly partially) reversible. It is often associated with Tyrosine Kinase Inhibitors (TKIs) such as **trastuzumab**, sunitinib, imatinib, and bevacizumab

- Type 1 and Type 2 cardiotoxicity can exist in the same patient

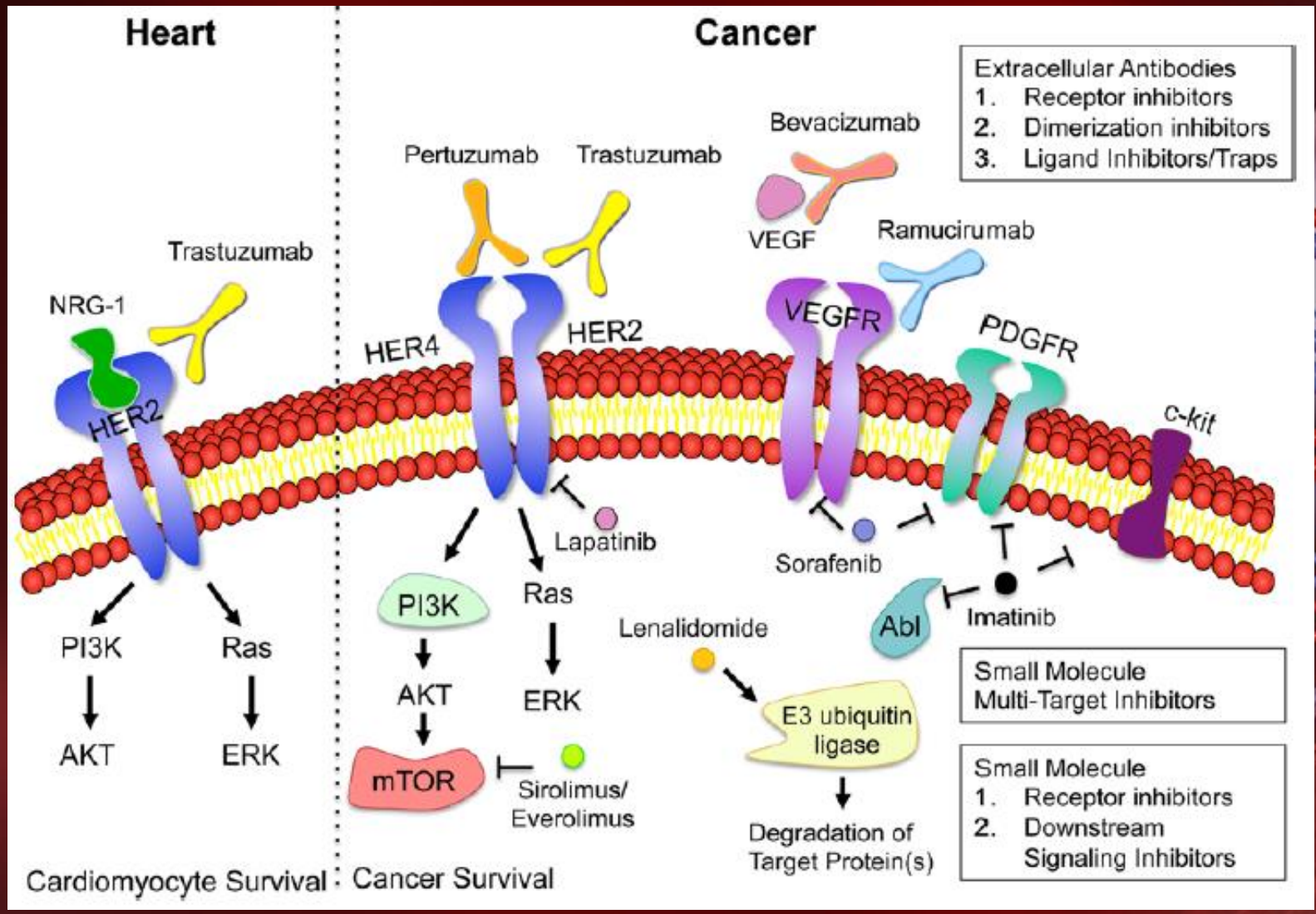


Trastuzumab Cardiotoxicity: Reversibility



Ewer *et al, JCO* 2005

Targeted Therapies and the Heart



Moslehi, Circ. 2015

TYROSINE KINASE INHIBITORS (TKIS)

TKIs → VEGF Signaling Pathway (VSP) Inhibitors

Drug Name	*Drug Type*	*Year approved*	*Current Indications*
Bevacizumab	mAb	2004	Metastatic colorectal cancer, advanced NSCLC (in combination with cytotoxic chemotherapy), and renal cell carcinoma (in combination with interferon-alpha immunotherapy); Monotherapy in progressive glioblastoma following previous therapy
Sorafenib	TKI	2005	Hepatocellular carcinoma, renal cell carcinoma
Sunitinib	TKI	2006	Gastrointestinal stromal tumor following progression or resistance to imatinib, advanced renal cell carcinoma, progressive pancreatic neuroendocrine tumors
Pazopanib	TKI	2009	Advanced renal cell carcinoma, advanced soft tissue sarcoma
Vandetanib	TKI	2011	Advanced and metastatic medullary thyroid cancer
Axitinib	TKI	2012	Advanced renal cell carcinoma (second line)

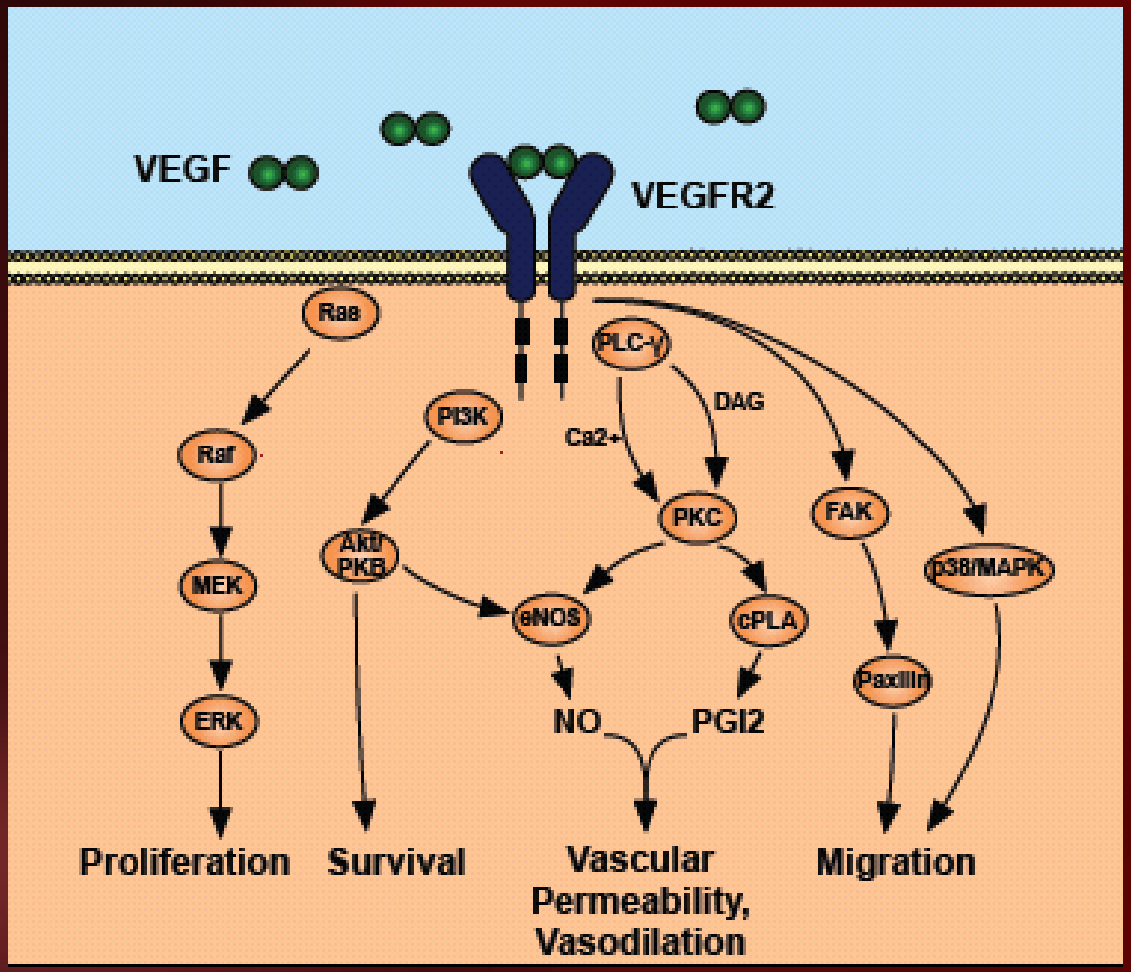
Other VSP Inhibitors in Clinical Development

Ramucirumab – VEGFR2 mAb
Aflibercept – VEGF Trap
Cediranib – TKI
Semaxanib –TKI
Brivanib – TKI
Torceranib – TKI
Regorafenib – TKI
Tivozanib-TKI
Cabozantinib-TKI

***mAb, Monoclonal Antibody; TKI, tyrosine kinase inhibitor**

Bair *et al*

VSP Inhibitors: Mechanism of Action and Effects



- Hypertension
- Cardiomyopathy
- Arterial thrombosis
- QT Prolongation
-- Edema

Management of Adverse Effects of VSPs

Adverse event	*Prior to treatment*	*After initiation of treatment*
Hypertension (HTN)	1. Aggressive management of blood pressure consistent with JNC7 guidelines 2. Urine analysis for proteinuria	1. Frequent (weekly) monitoring of blood pressure in the first 6 weeks 2. Use of automated home blood pressure cuff for high-risk patients 3. Urine analysis for proteinuria 4. Aggressive blood pressure management with the use of angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers (1st and 2nd line therapy) 5. Titration of blood pressure medications during chemotherapy "holiday" (if necessary)
Arterial thromboembolism (ATE)	1. Ensure no active angina or symptomatic CAD 2. Initiation of anti-platelet therapy in high-risk individuals (patients with previous coronary artery disease or peripheral arterial disease)	
Cardiomyopathy	1. Baseline echocardiogram to assess for structural heart disease in all patients 2. Aggressive management of cardiac risk factors (especially hypertension)	1. Low threshold for repeat echocardiogram if signs or symptoms consistent with cardiomyopathy 2. If cardiomyopathy detected, then prompt stopping of VSP inhibitor and initiation of cardioprotective médications (ACE inhibitors and beta-blockers)

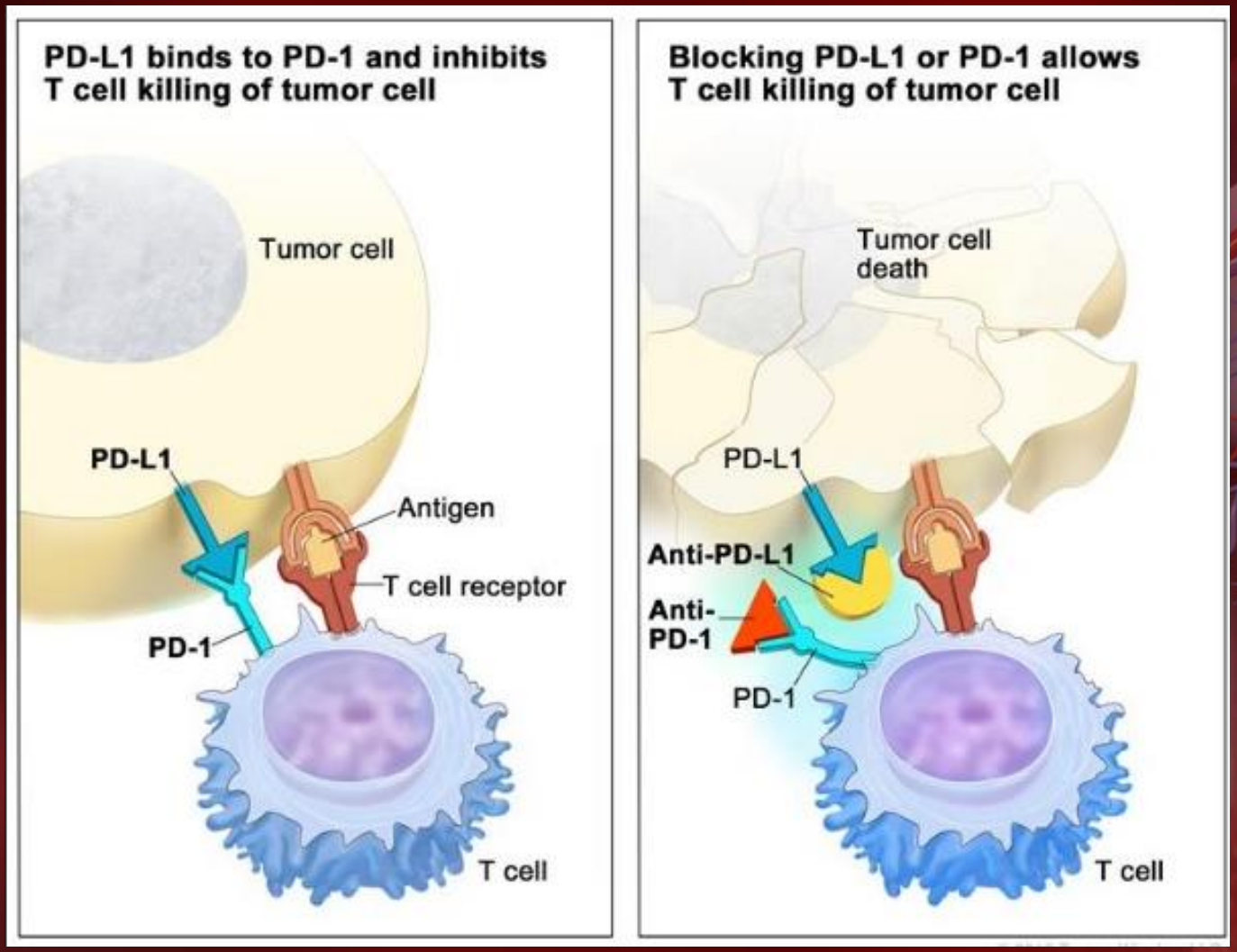
Bair *et al*, Trends in Cardiovascular Medicine 2013

Systemic Effects of Various Chemotherapeutic Agents

Chemotherapy Cardiotoxicity	Major Culprit Chemotherapeutic Classes (Incidence)	Diagnostic Methodologies	Management/Prevention
Cardiomyopathy (with systolic and/or diastolic dysfunction)	• Anthracyclines* • Monoclonal antibodies* • VSP inhibitors* • Alkylating agents • Antimicrotubule agents • Antimetabolites • Proteasome inhibitors*	• Echocardiography • Myocardial strain imaging by echo • Cardiac MRI • MUGA/RNA • Biomarkers: troponin, BNP, newer biomarkers • Possible role for genetics	• ACE-I/ARB • Beta blockers • Desferoxamine • Possible role for statins • Possible role for ranolazine • Serial LVEF/biomarker monitoring • Discontinue chemotherapy, then reinstitute with LVEF recovery • Long-term consideration for ICD and possible heart transplantation
Ischemia	• Antimetabolites (vasospasm) • VSP – inhibitor TKIs (Mab and Smol) – arterial thrombosis • Antimicrotubule agents (arterial thrombosis) • Alkylating agents* • Angiogenesis inhibitor – arterial thrombosis	• ECG • Troponin • Stress test • Coronary angiography • Cardiac MRI	• Nitrates for coronary spasms • Aspirin for thrombosis risk • Limited data for other anti-anginal agents
Thrombosis	• Alkylating agents – venous • Angiogenesis inhibitor - arterial • VSP inhibitors – venous and arterial • Histone deacetylase inhibitors – venous • Immunomodulators – arterial • Hormonal therapy (tamoxifen) – arterial/venous**	• Doppler ultrasound • CT angiography • Other concern as for ischemia above	• Unfractionated heparin • Low molecular weight heparin • Fondaparinux
Hypertension	• VSP inhibitors/targeted therapies* • VEGF trap • Alkylating agents*	• On-site blood pressure checks • Ambulatory blood pressure monitoring	• Amlodipine • ACE-I/ARB • Other anti-hypertensive regimens as third-line agents
Hypotension	• Interferons • Interleukins • Monoclonal antibodies • All-trans retinoic acid (differentiation syndrome)	• On-site blood pressure checks • Ambulatory blood pressure monitoring	• IV fluids • Midodrine (if normal LVEF) • Discontinue chemotherapy if in shock, then reinstitute when stable
Dysrrhythmias	• Interleukins • Interferons • Angiogenesis inhibitors (bradycardia) • Antimicrotubule agents (bradycardia) • Histone deacetylase inhibitors • Non-VSP inhibitor small molecule TKIs • Arsenic trioxide	• ECG • Telemetry	• Beta blockers • Propafenone • Anticoagulation with low molecular weight heparin
QTc Prolongation	• Arsenic trioxide • Histone deacetylase inhibitors • Small molecule TKIs	• ECG	• Replete electrolytes (K/Mg) • Serial ECG monitoring • Discontinue other QTc prolonging drugs, where possible • Discontinue chemotherapy agent, if significant risk of torsades
Pericardial Disease	• Busulfan* • Non-VSP inhibitor small molecule TKIs	• Echocardiography • Cardiac MRI • Cardiac CT	• Pericardiocentesis • Pericardial window • Pericardial stripping (with constriction) • Colchicine (if no interaction with chemotherapy) • NSAIDs (if normal blood pressure and LVEF)

Okwuosa *et al.,* Post Grad. Med. 2016

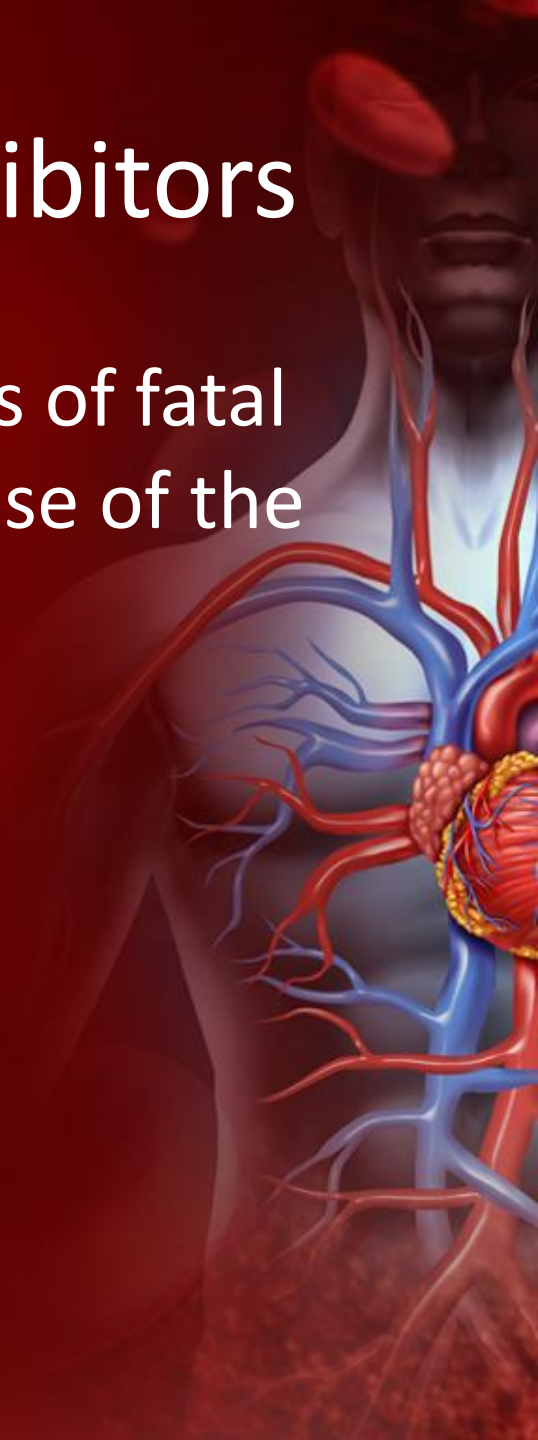
Immune Checkpoint Inhibitors



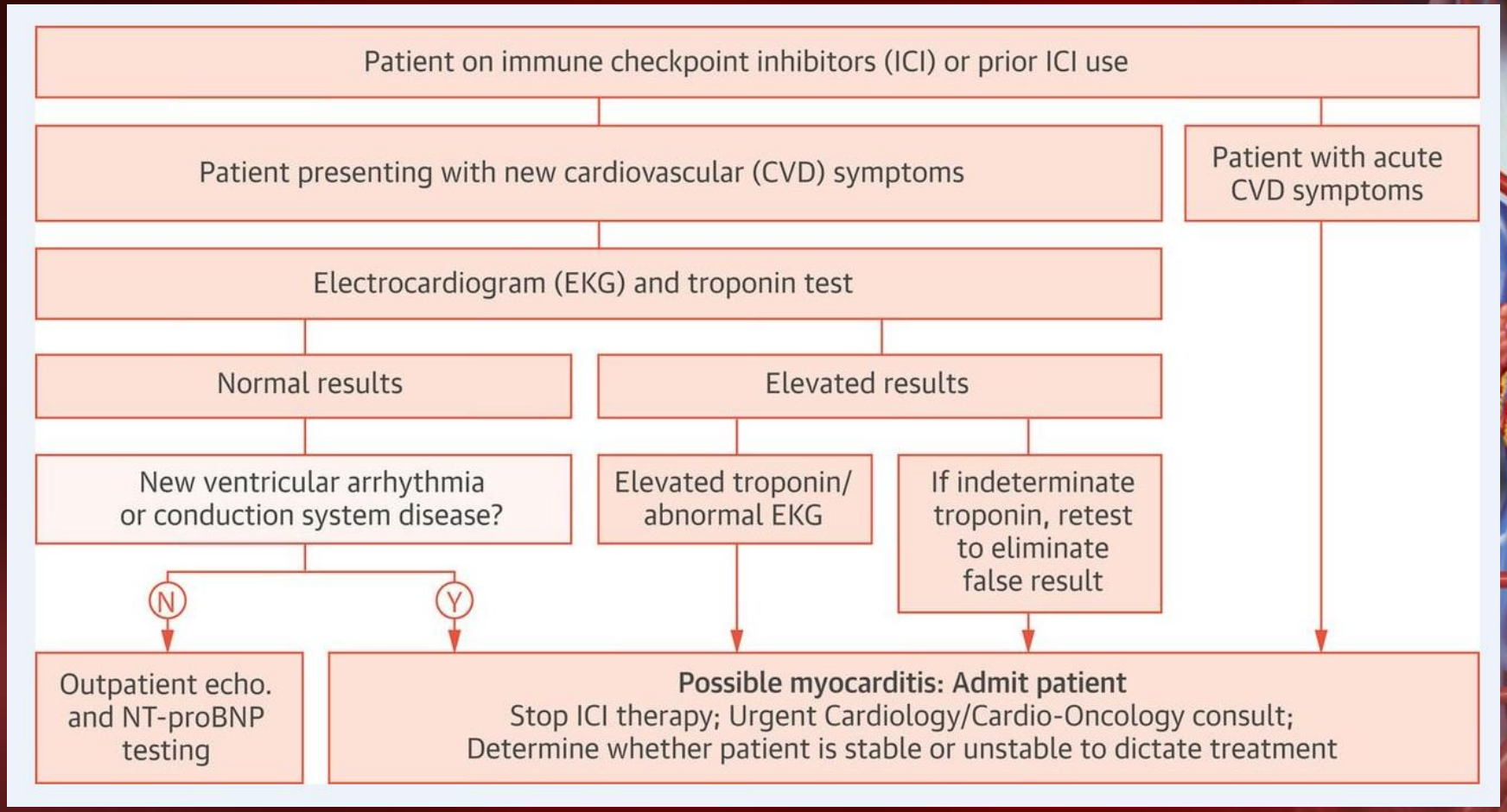
National Cancer Institute

Immune Checkpoint Inhibitors

- There have been increasing reports of fatal myocarditis in the literature with use of the PD-1, PD-L1 and CTLA-4 inhibitors:
  - Pembrolizumab (Keytruda)
  - Nivolumab (Opdivo)
  - Atezolizumab (Tecentriq)
  - Avelumab (Bavencio)
  - Durvalumab (Imfinzi)
  - Ipilimumab (Yervoy)

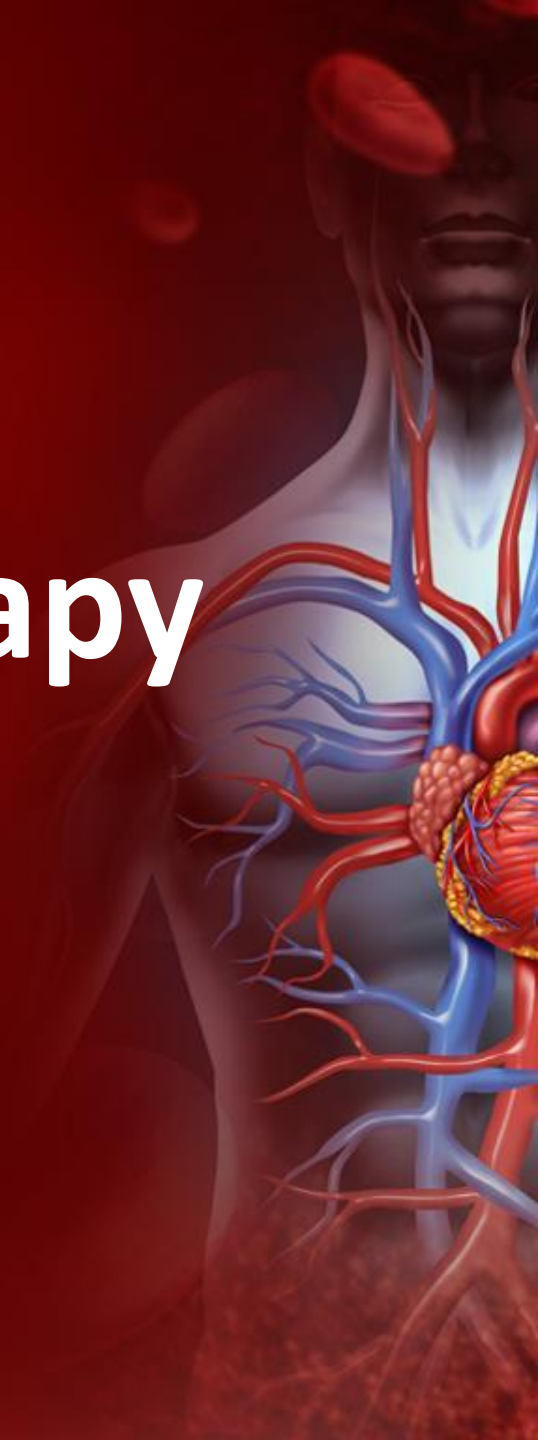


Triage for Myocarditis Related to Checkpoint Inhibitors



Mahmood *et al.* JACC 2018

Radiation Therapy



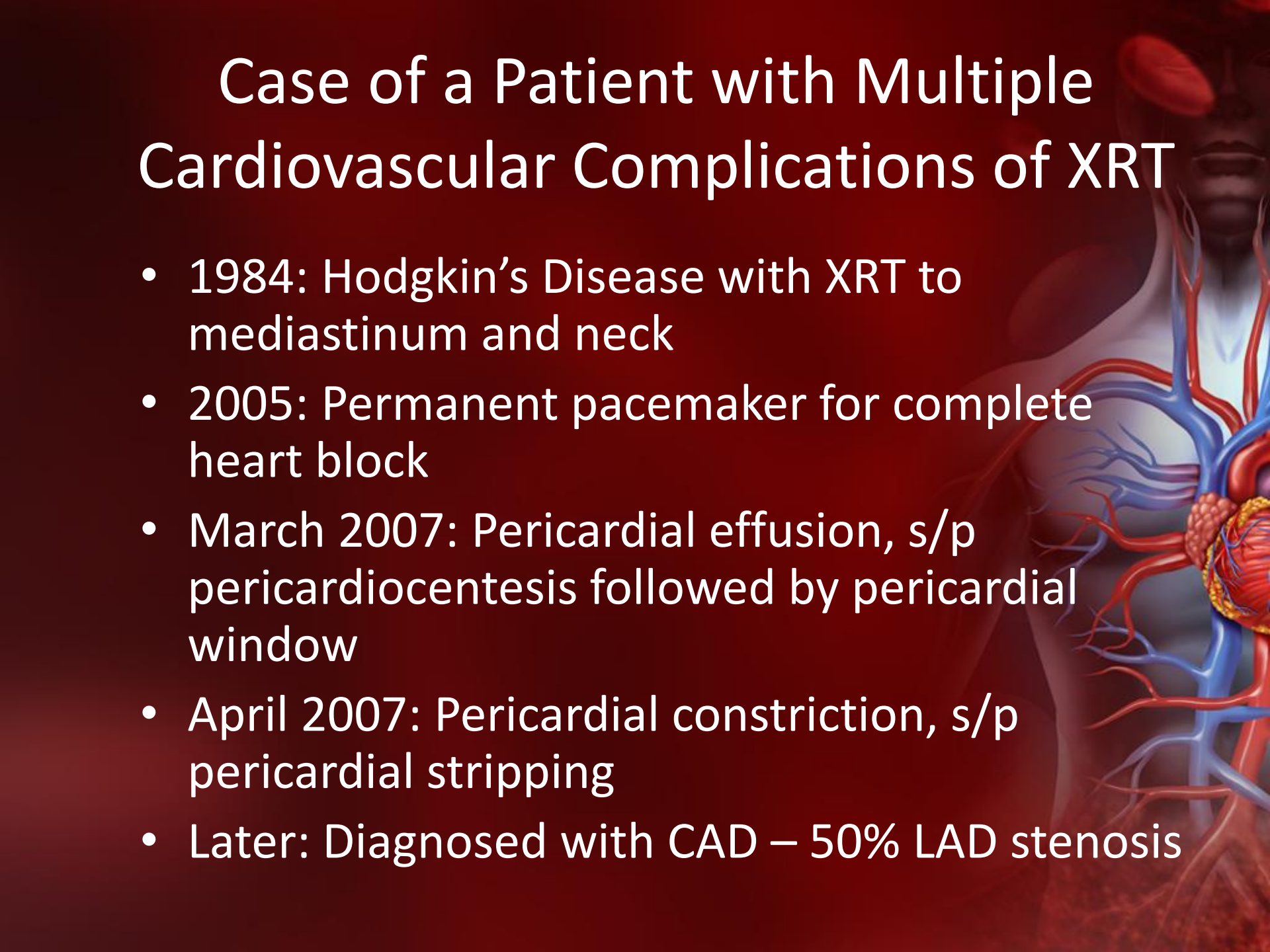
Radiation-Induced Heart Disease

(1) Radiation-induced atherosclerosis
  (a) *Symptomatic*
  (b) *Asymptomatic*
(2) Pericardial disease
  (a) *Acute pericarditis*
  (b) *Delayed pericarditis*
  (c) *Pericardial effusion*
  (d) *Constrictive pericarditis*
(3) Myocardial and Endocardial disease
  (a) *Pancarditis*
  (b) *Cardiomyopathy*
(4) Valvular disease
(5) Conduction disturbances
  (a) *RBBB*
  (b) *Atrioventricular nodal block*

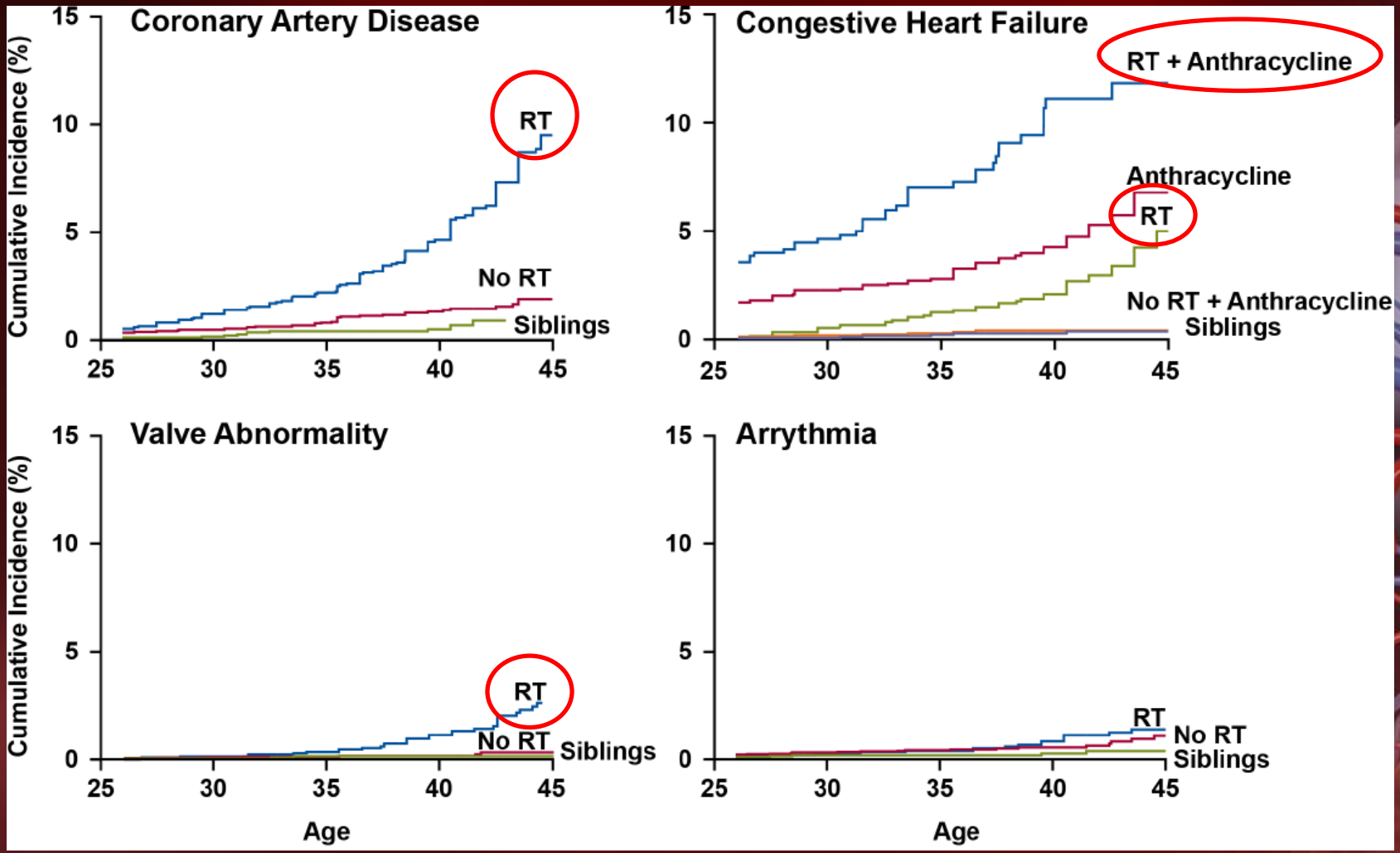
Yusuf *et al, Cardiol. Research and Practice* 2011

Case of a Patient with Multiple Cardiovascular Complications of XRT

- 1984: Hodgkin's Disease with XRT to mediastinum and neck
- 2005: Permanent pacemaker for complete heart block
- March 2007: Pericardial effusion, s/p pericardiocentesis followed by pericardial window
- April 2007: Pericardial constriction, s/p pericardial stripping
- Later: Diagnosed with CAD – 50% LAD stenosis



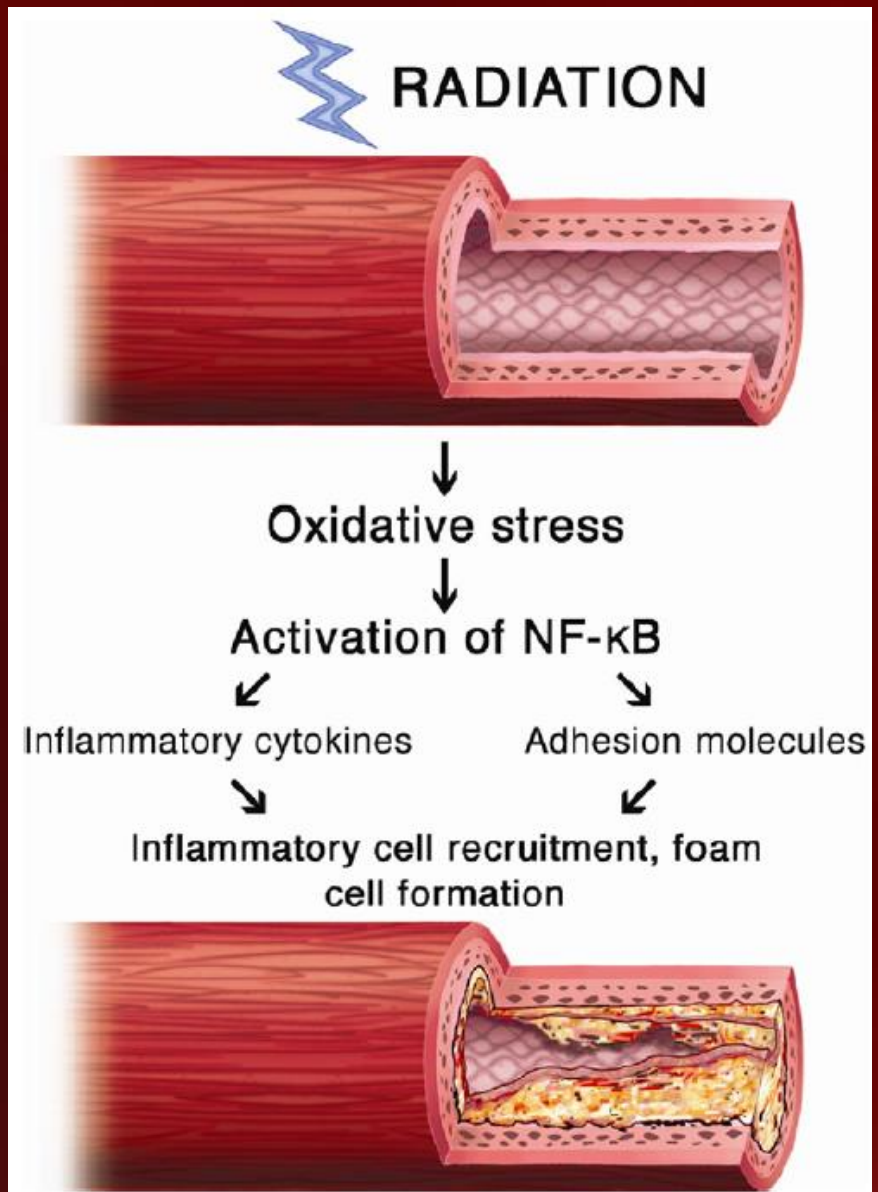
Survivors of Childhood Cancer: Cumulative Incidence of CV Events at Age 45 Years



N = 10,724; 5101 Female, 5623 Male

Childhood Cancer Survivor Study

Radiation-Induced Vascular Disease: Activation of NF-ƙB and Proinflammatory Cytokines



Weintraub *et al, JACC 2010*

Rate of Major Coronary Events According to Time Since Radiation Therapy

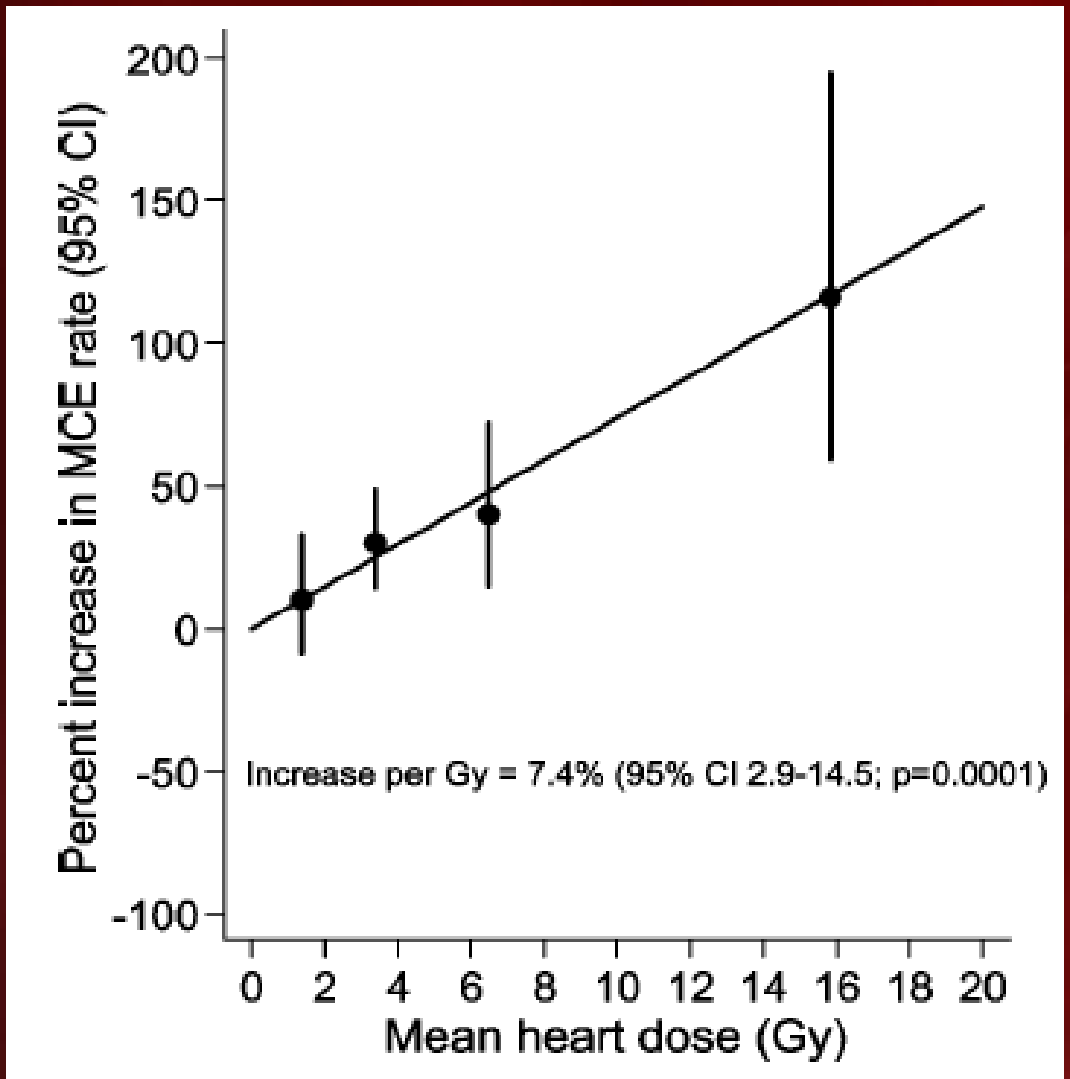
MACE: myocardial infarction, coronary revascularization, or death from ischemic heart

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% *increase/Gy*
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (–2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

…Study was conducted prior to the much more selective 3-D radiotherapy with far fewer complications expected…

Darby *et al,* NEJM 2013

Dose-Dependent Effect of XRT on Major Coronary Event

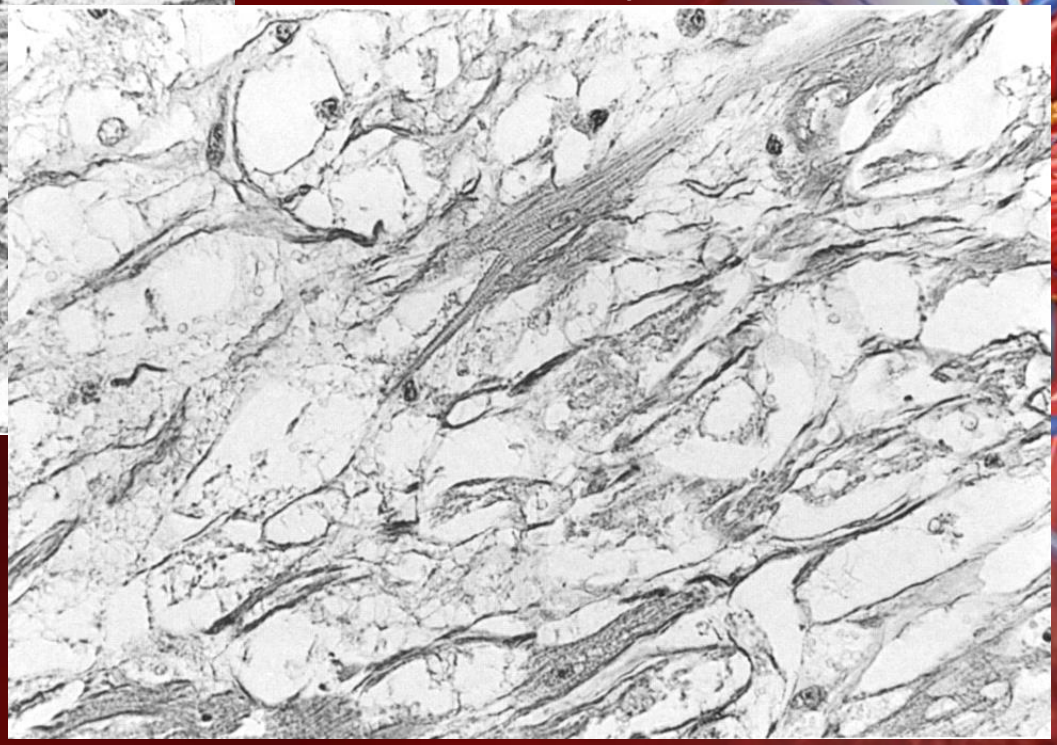


Darby *et al, Circulation* 2012

Dose-Dependent Radiation-Induced Damage to Myocardium

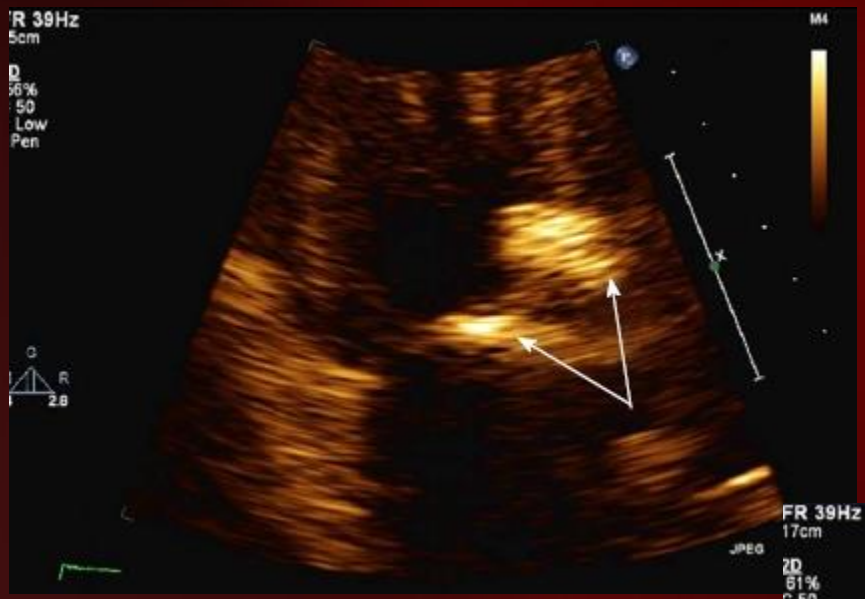
15 cGy

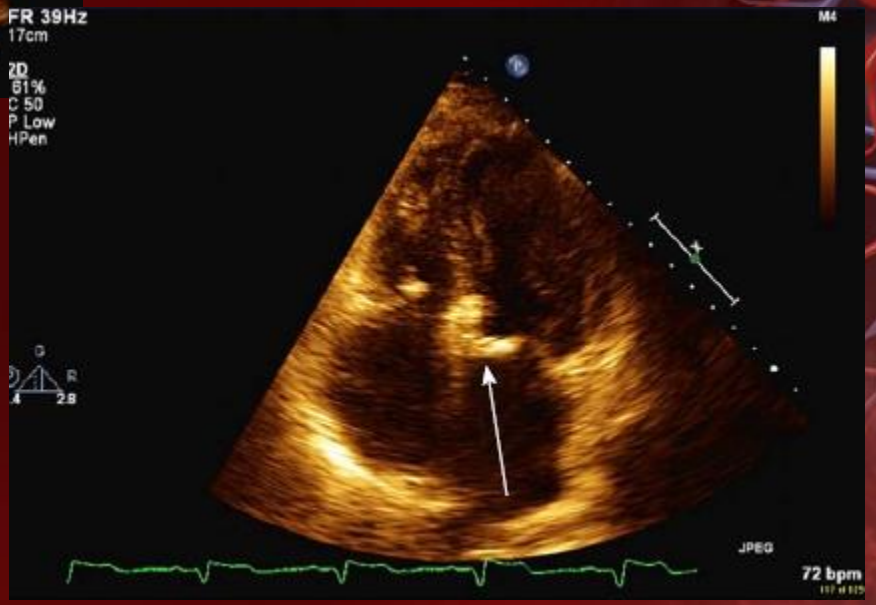
20 cGy



Lauk *et al, Int. J. Radiation Oncology Biol. Phys*. 1985

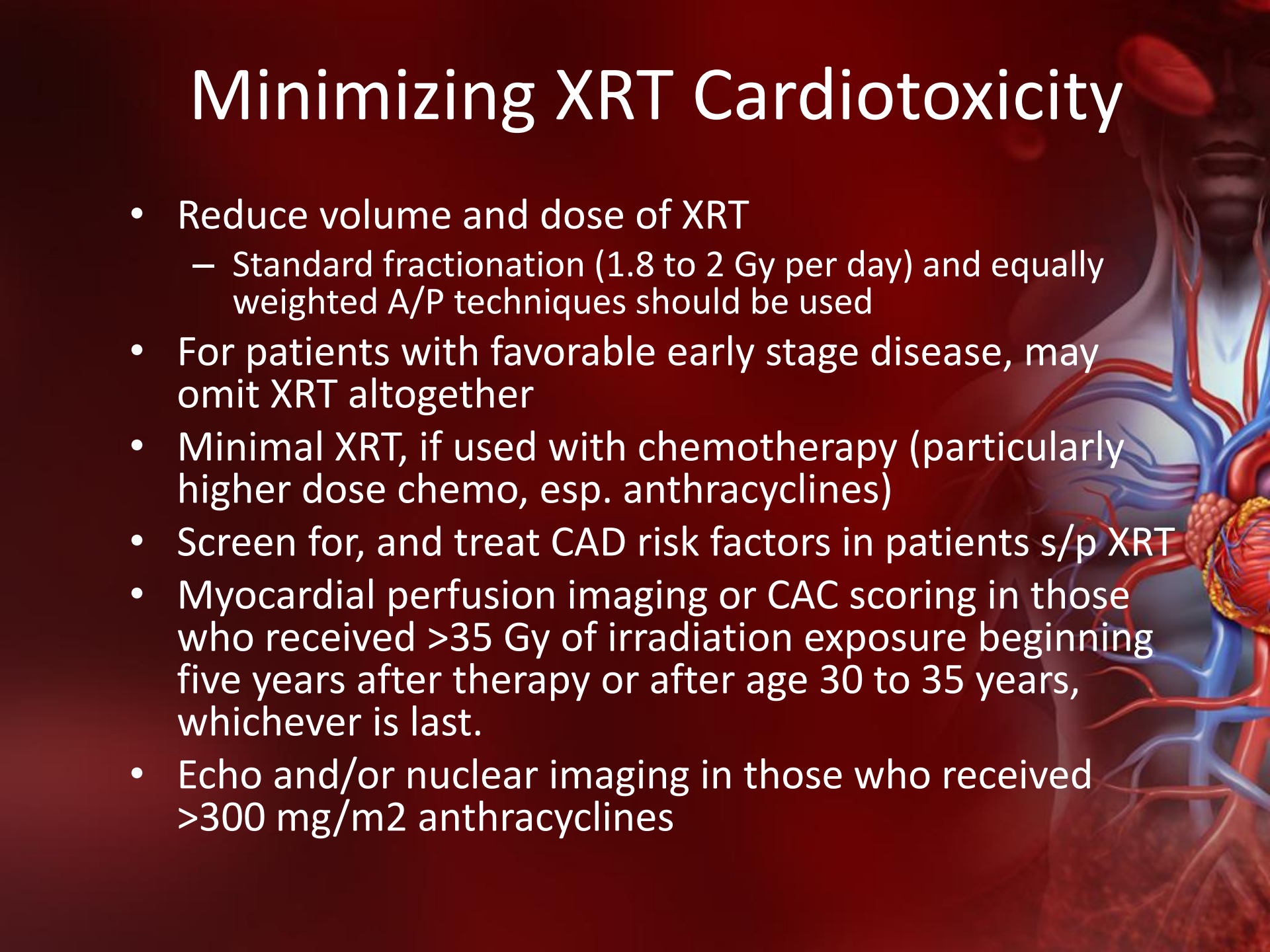
Valvular Heart Disease Associated with Radiation Therapy





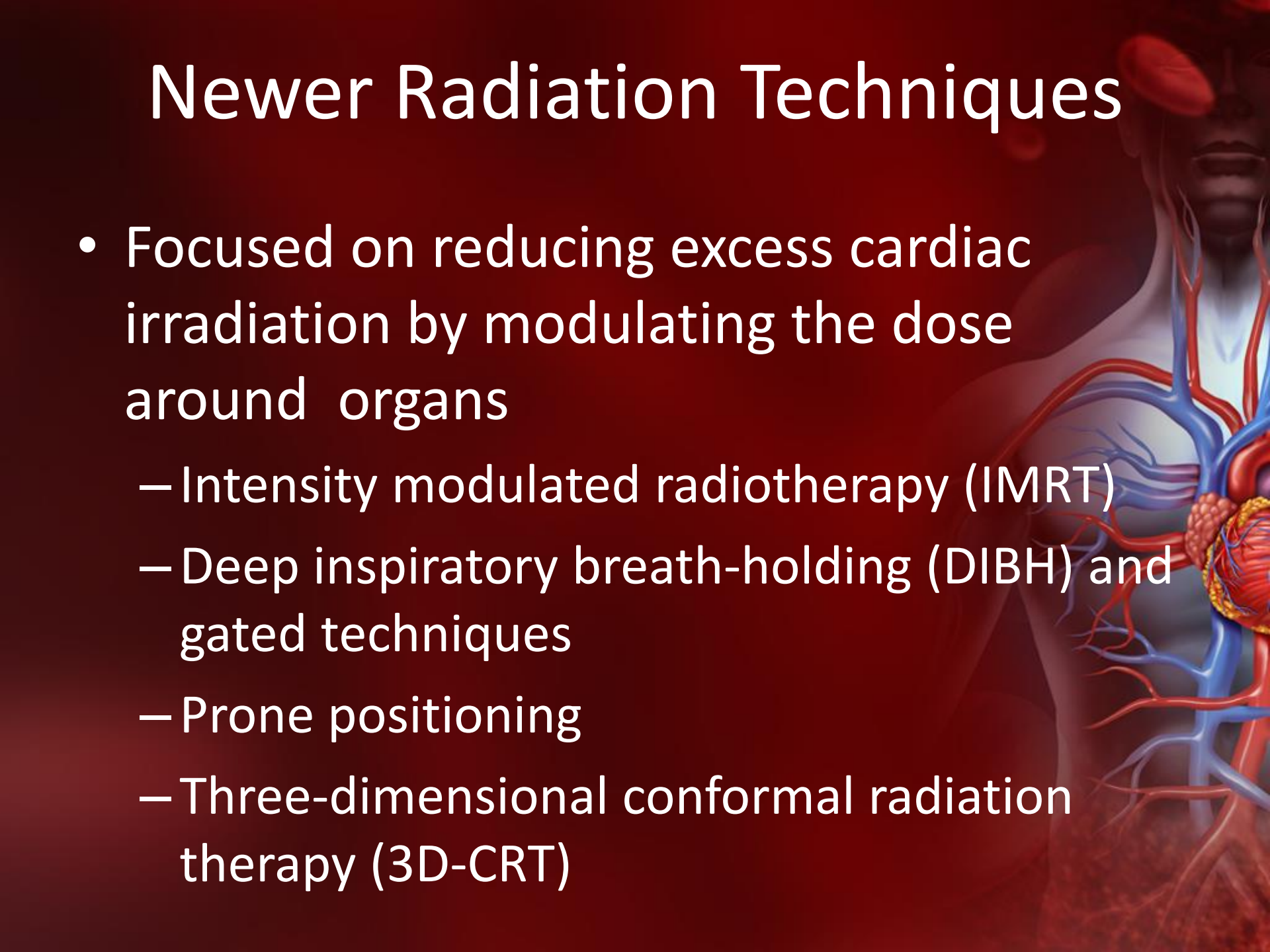
Minimizing XRT Cardiotoxicity

- Reduce volume and dose of XRT
  - Standard fractionation (1.8 to 2 Gy per day) and equally weighted A/P techniques should be used
- For patients with favorable early stage disease, may omit XRT altogether
- Minimal XRT, if used with chemotherapy (particularly higher dose chemo, esp. anthracyclines)
- Screen for, and treat CAD risk factors in patients s/p XRT
- Myocardial perfusion imaging or CAC scoring in those who received >35 Gy of irradiation exposure beginning five years after therapy or after age 30 to 35 years, whichever is last.
- Echo and/or nuclear imaging in those who received >300 mg/m2 anthracyclines

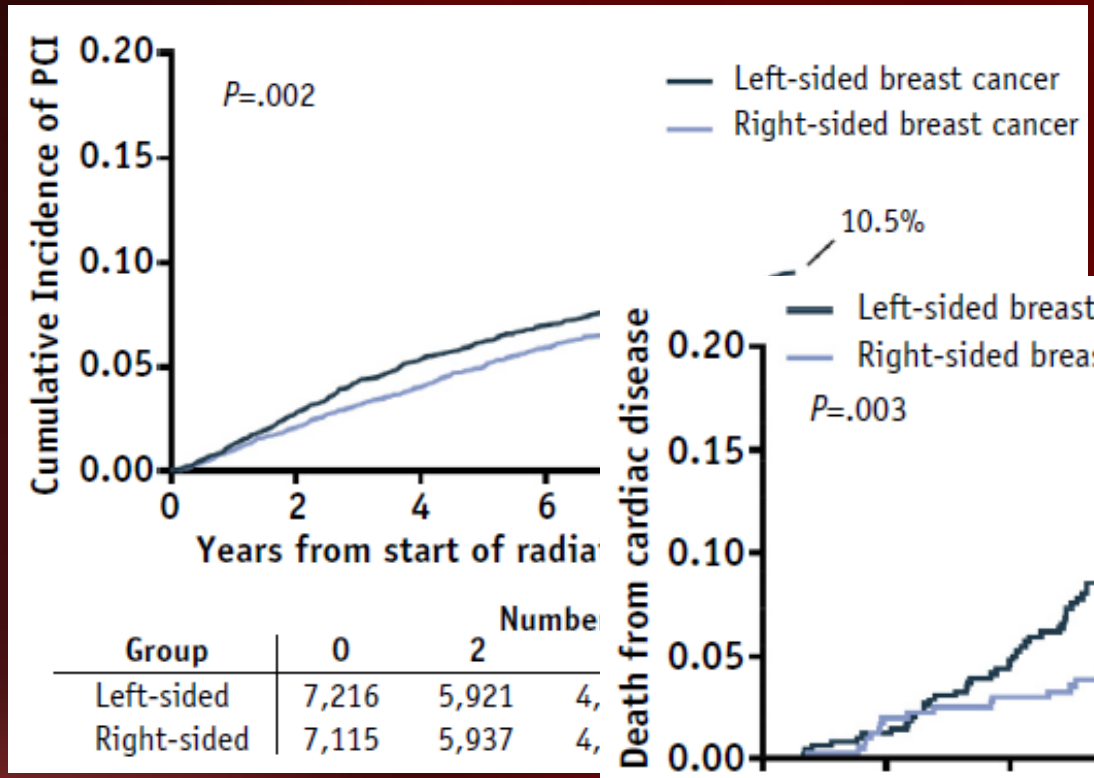


Newer Radiation Techniques

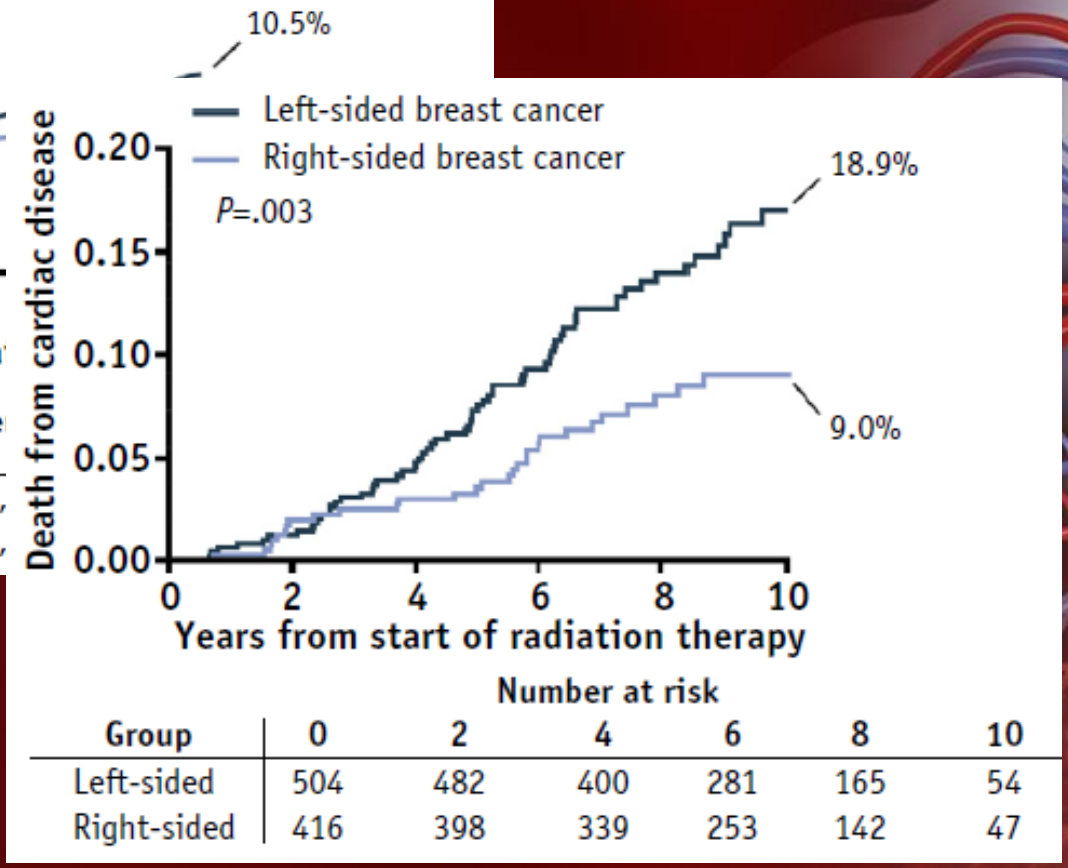
- Focused on reducing excess cardiac irradiation by modulating the dose around organs
  - Intensity modulated radiotherapy (IMRT)
  - Deep inspiratory breath-holding (DIBH) and gated techniques
  - Prone positioning
  - Three-dimensional conformal radiation therapy (3D-CRT)



Incidence of PCI and Cardiac Disease with Modern Radiotherapy Techniques



Group	0	2	
Left-sided	7,216	5,921	4,
Right-sided	7,115	5,937	4,



Number at risk

Group	0	2	4	6	8	10
Left-sided	504	482	400	281	165	54
Right-sided	416	398	339	253	142	47

Boero *et al, Int. J. Radiat. Oncol. Biol. Phys.* 2016

Associations of Heart Rate Parameters with Radiation Therapy

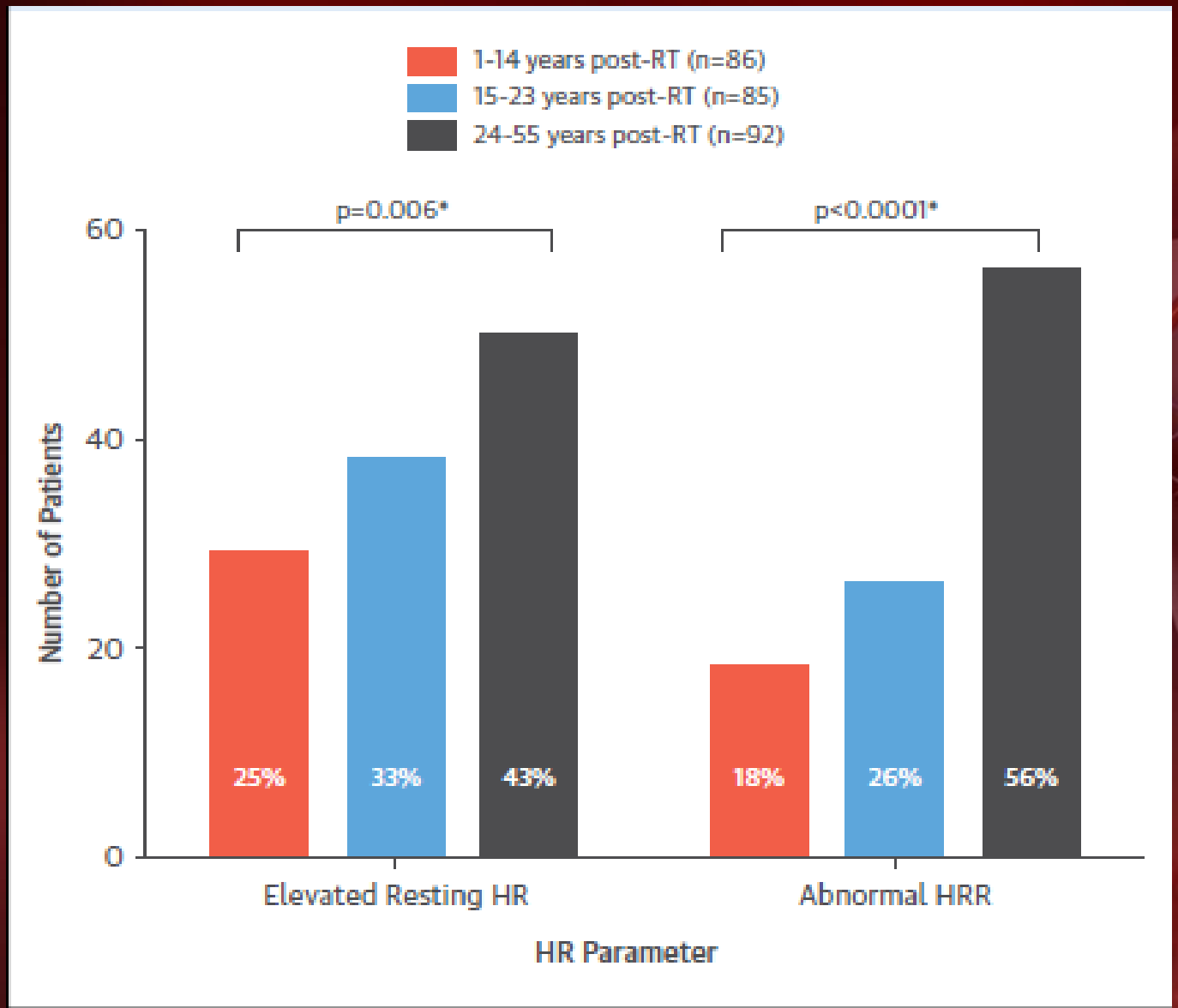
	Unadjusted		Adjusted	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Primary endpoints				
Elevated resting heart rate	3.68 (2.65-5.12)	<0.0001	3.96 (2.52-6.22)*	<0.0001
Abnormal heart rate recovery at 1 min	4.57 (3.09-6.76)	<0.0001	5.32 (2.94-9.66)†	<0.0001
Secondary endpoints				
Heart rate reserve (lowest tertile)	2.15 (1.57-2.93)	<0.0001	3.20 (1.64-6.27)†	0.0007
Chronotropic incompetence	0.95 (0.65-1.39)	0.85	1.57 (0.87-2.84)†	0.14
Abnormal systolic BP response	1.88 (1.25-2.81)	0.003	1.44 (0.76-2.71)‡	0.26
Abnormal reserve pulse pressure	1.45 (1.08-1.96)	0.02	1.41 (0.90-2.23)‡	0.14

*Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, AVN-blocking medications, congestive heart failure/IHD, and anthracycline exposure. †Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, AVN-blocking medications, congestive heart failure/IHD, resting HR, exercise time, result of ETT, and anthracycline exposure. ‡Adjusted for age, sex, Morise risk score, diabetes, indication for ETT, antihypertensive medications, congestive heart failure/IHD, resting HR, exercise time, result of ETT, and anthracycline exposure.

AVN = atrioventricular nodal; BP = blood pressure; ETT = exercise treadmill test; IHD = ischemic heart disease.

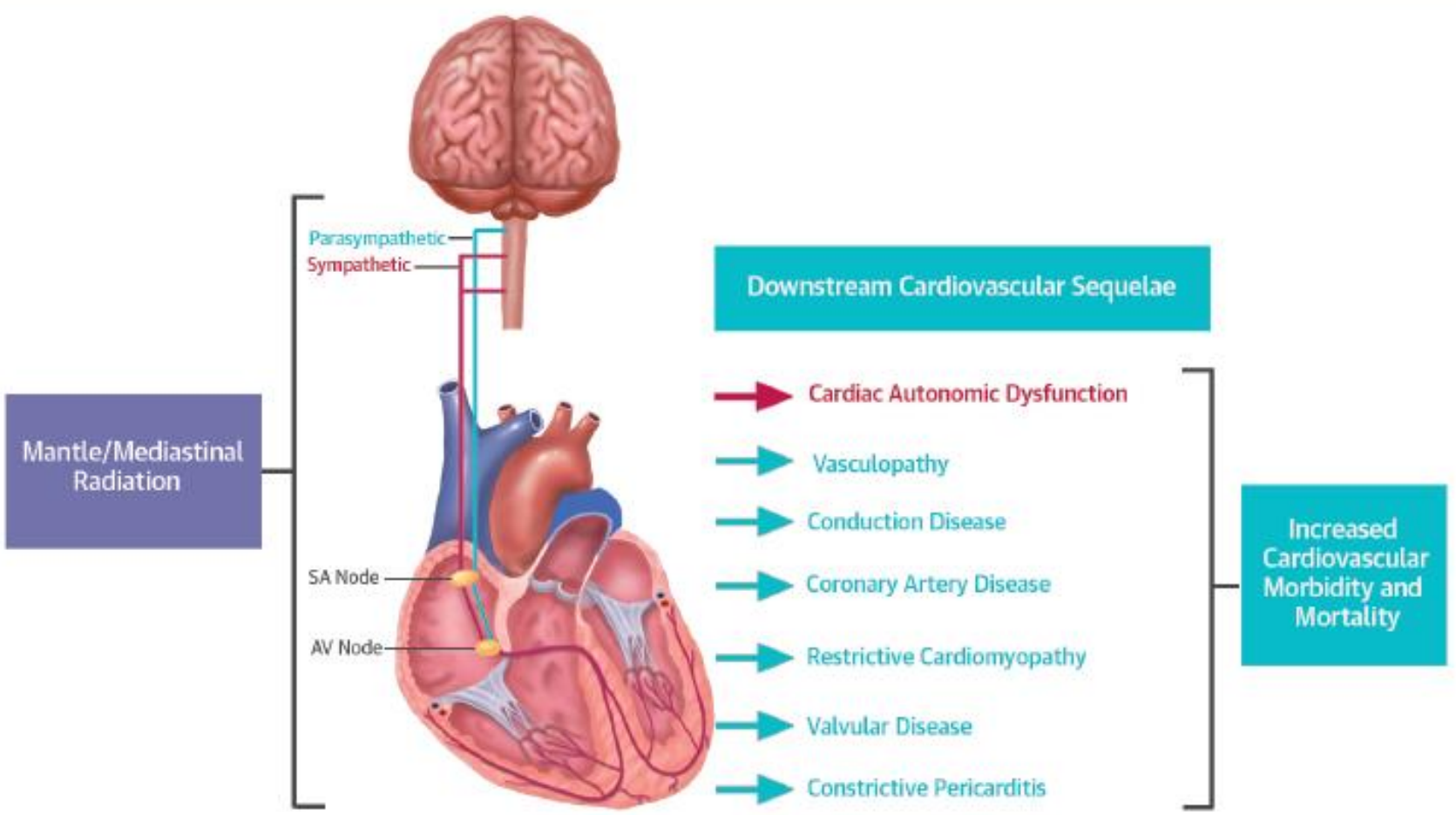
Groarke *et al*, *JACC* 2015

Heart Rate Abnormalities Worsen with Time from Radiation Therapy



Groarke *et al*, *JACC* 2015

CENTRAL ILLUSTRATION Autonomic Dysfunction in Radiation Survivors

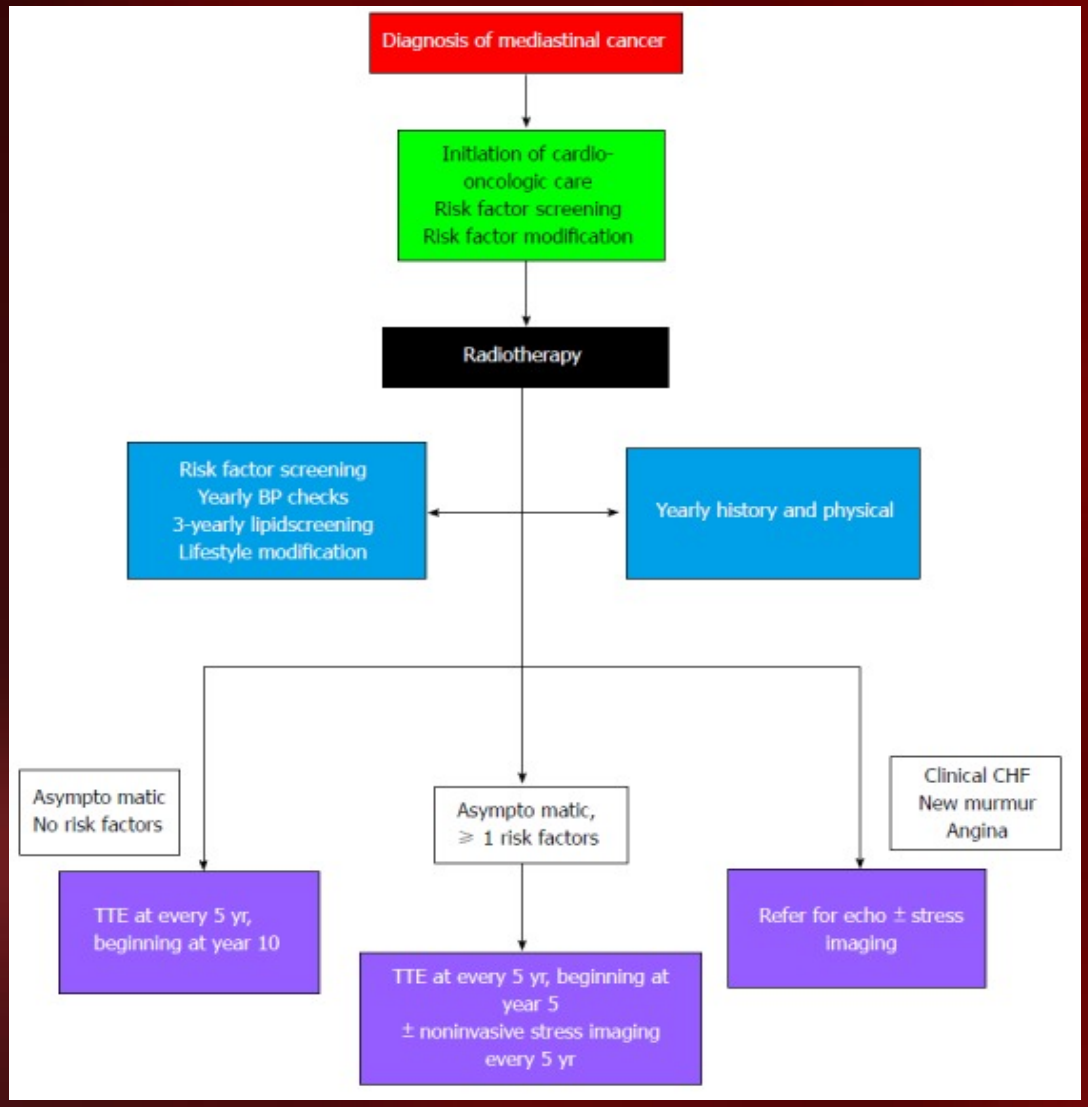


OUTCOME	ELEVATED RESTING HEART RATE*	ABNORMAL HEART RATE RECOVERY†
Exercise Duration	- 1.1 ± 0.3, p = 0.001	- 1.0 ± 0.4, p = 0.006
Mortality, HR (95% CI)	0.99 (0.40-2.45)	5.50 (1.97-15.36)

Relative to radiation patients without elevated resting heart rate*/with normal heart rate recovery†

Groarke *et al*, *JACC* 2015

Proposed Algorithm for Screening for Radiation-Induced Cardiotoxicity



Cuomo *et al,* World J. Cardiol. 2016

Endocrine/Hormonal Therapy

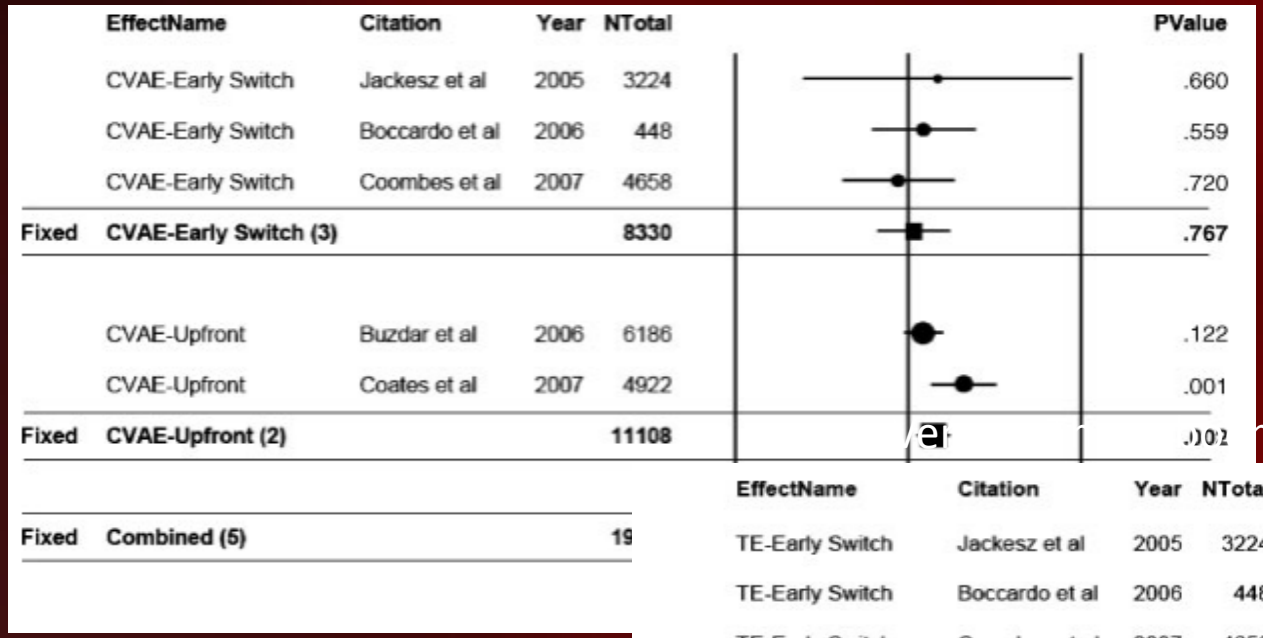
Endocrine Therapy for Breast Cancer

- Selective Estrogen Receptor Modulators (SERMs)
  - Tamoxifen
  - Raloxifene
  - Newer generation SERMs
    - Lasofoxifene
    - Bazedoxifene

- Aromatase Inhibitors (AIs)
  - Letrozole
  - Anastrozole
  - Exemestane

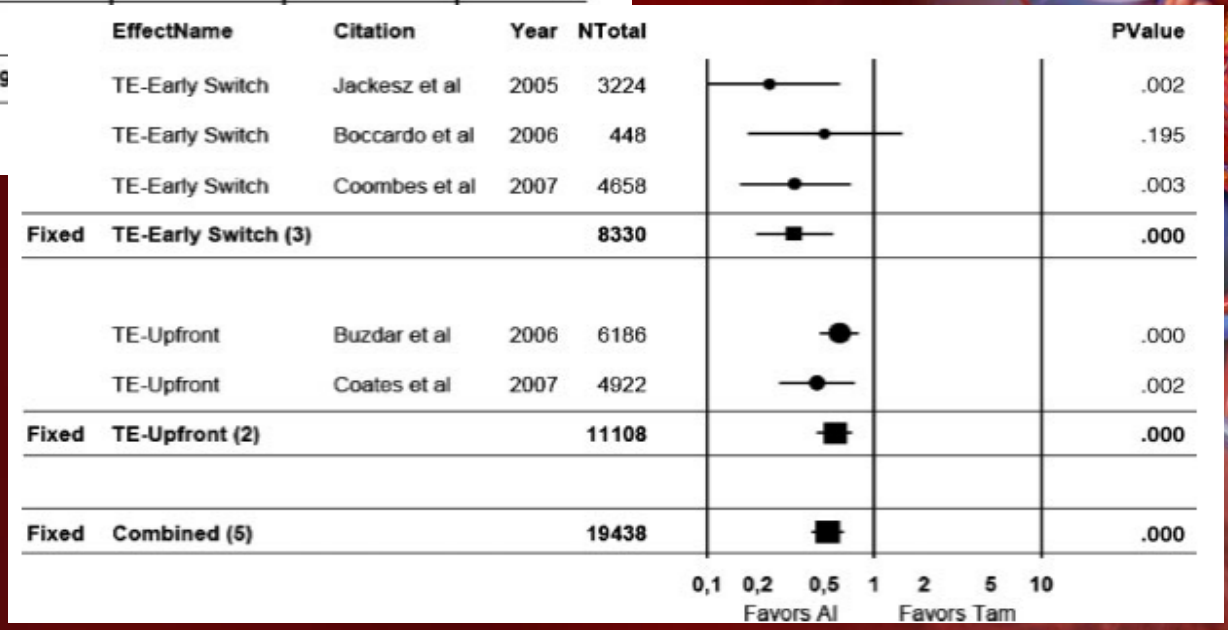
AIs vs. Tamoxifen: Events

Cardiovascular Adverse Events



	EffectName	Citation	Year	NTotal	PValue
	CVAE-Early Switch	Jackesz et al	2005	3224	.660
	CVAE-Early Switch	Boccardo et al	2006	448	.559
	CVAE-Early Switch	Coombes et al	2007	4658	.720
Fixed	**CVAE-Early Switch (3)**			**8330**	**.767**
	CVAE-Upfront	Buzdar et al	2006	6186	.122
	CVAE-Upfront	Coates et al	2007	4922	.001
Fixed	**CVAE-Upfront (2)**			**11108**	**.002**
Fixed	**Combined (5)**			**19**	

ve[illegible]mbolic Disease



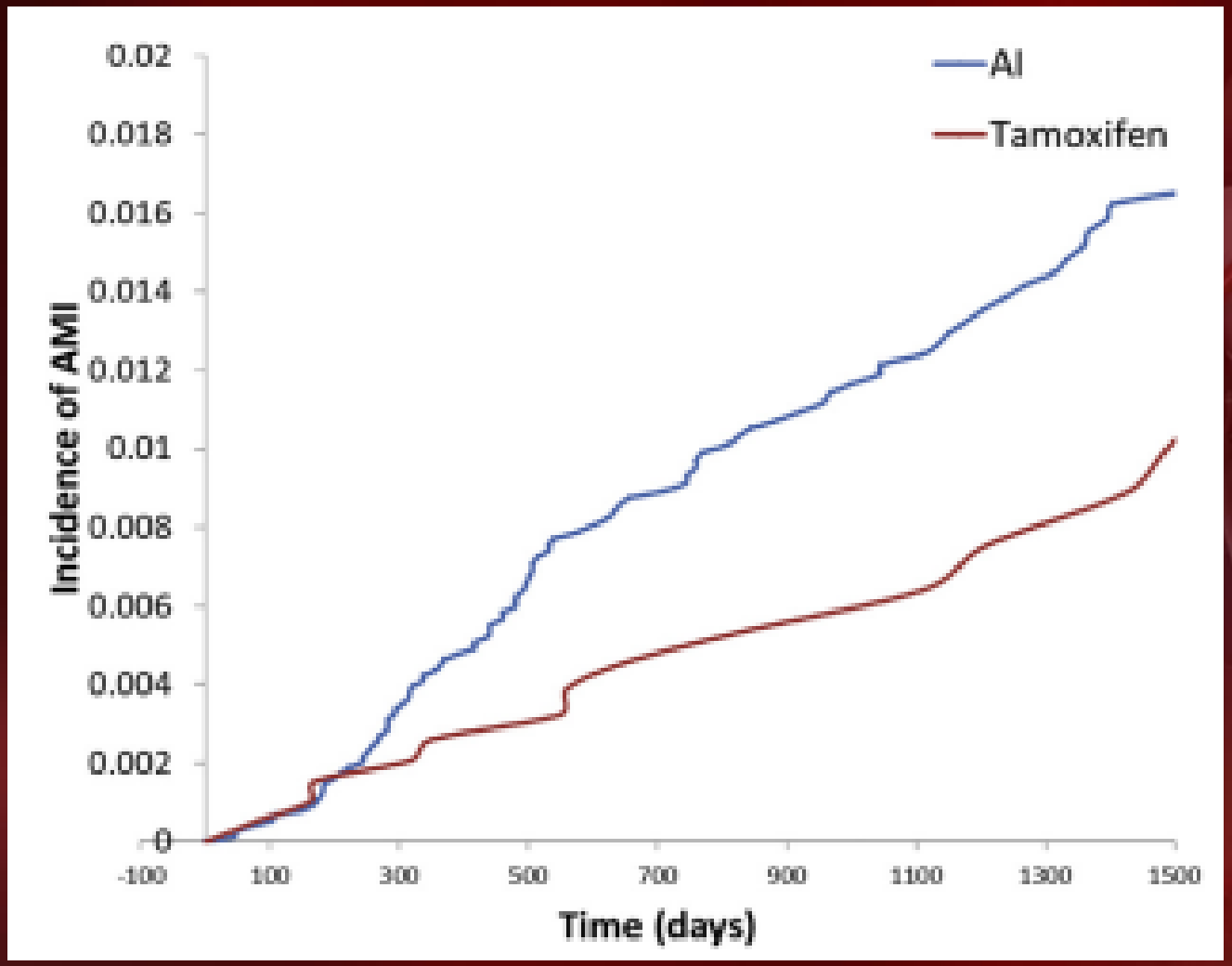
	EffectName	Citation	Year	NTotal	PValue
	TE-Early Switch	Jackesz et al	2005	3224	.002
	TE-Early Switch	Boccardo et al	2006	448	.195
	TE-Early Switch	Coombes et al	2007	4658	.003
Fixed	**TE-Early Switch (3)**			**8330**	**.000**
	TE-Upfront	Buzdar et al	2006	6186	.000
	TE-Upfront	Coates et al	2007	4922	.002
Fixed	**TE-Upfront (2)**			**11108**	**.000**
Fixed	**Combined (5)**			**19438**	**.000**

0,1 0,2 0,5 1 2 5 10

Favors AI Favors Tam

Cuppone *et al*, Cancer 2008

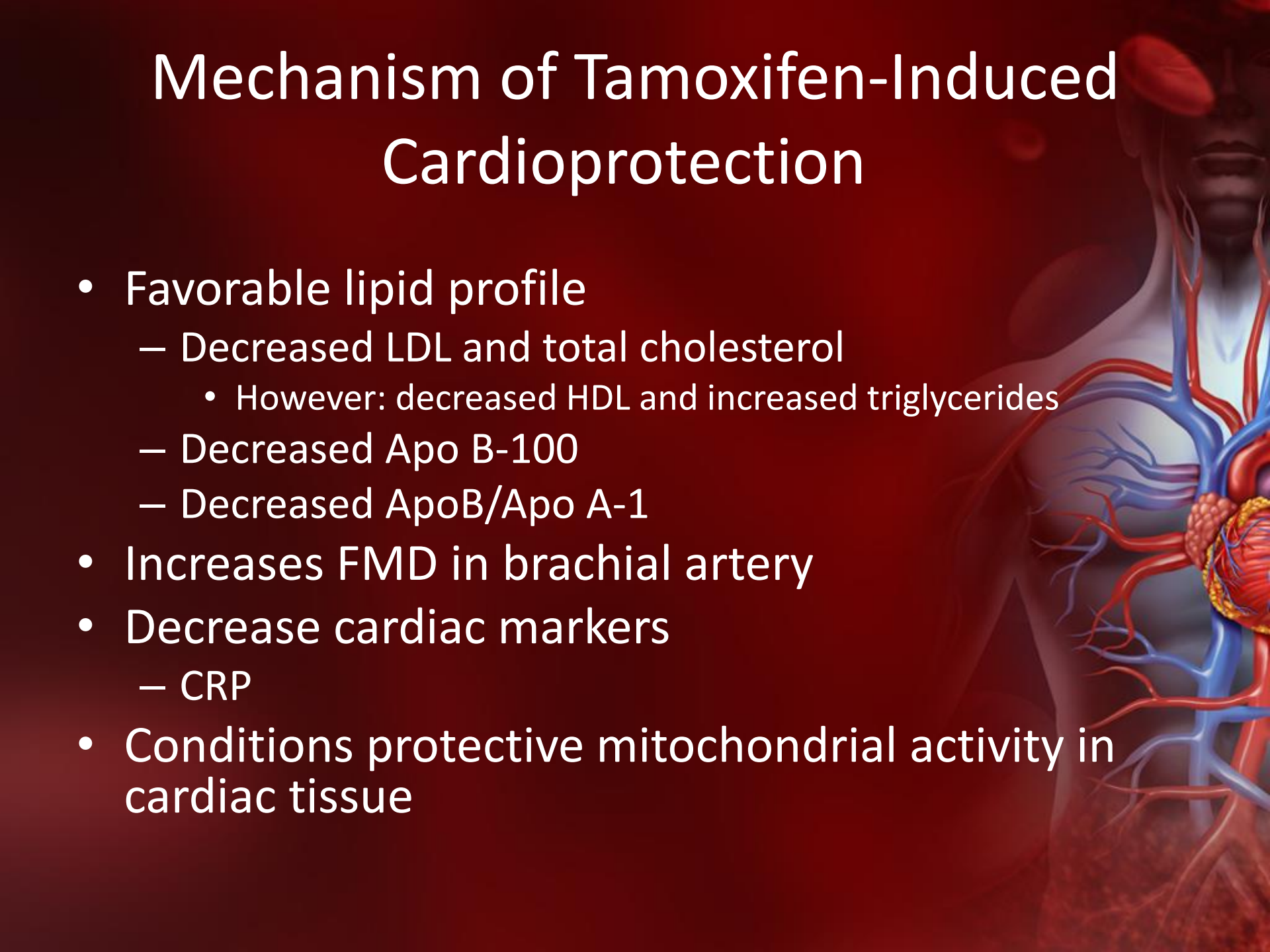
Cumulative Incidence of Myocardial Infarction: Aromatase Inh vs. Tamoxifen



Abdel-Qadir *et al.*, Eur J Cancer 2016

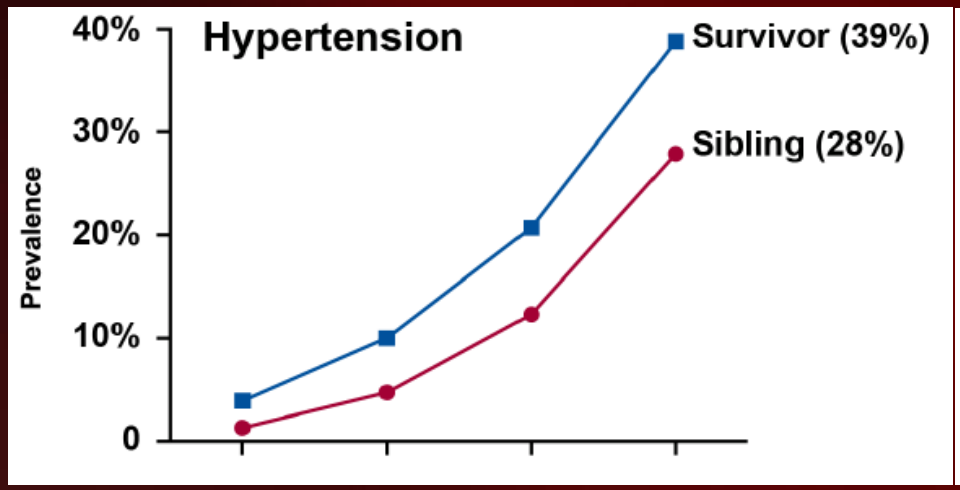
Mechanism of Tamoxifen-Induced Cardioprotection

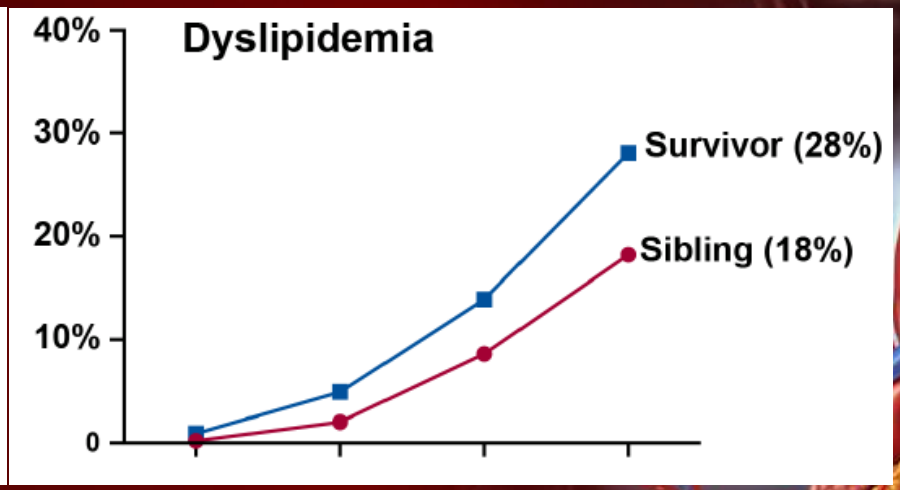
- Favorable lipid profile
  - Decreased LDL and total cholesterol
    - However: decreased HDL and increased triglycerides
  - Decreased Apo B-100
  - Decreased ApoB/Apo A-1
- Increases FMD in brachial artery
- Decrease cardiac markers
  - CRP
- Conditions protective mitochondrial activity in cardiac tissue

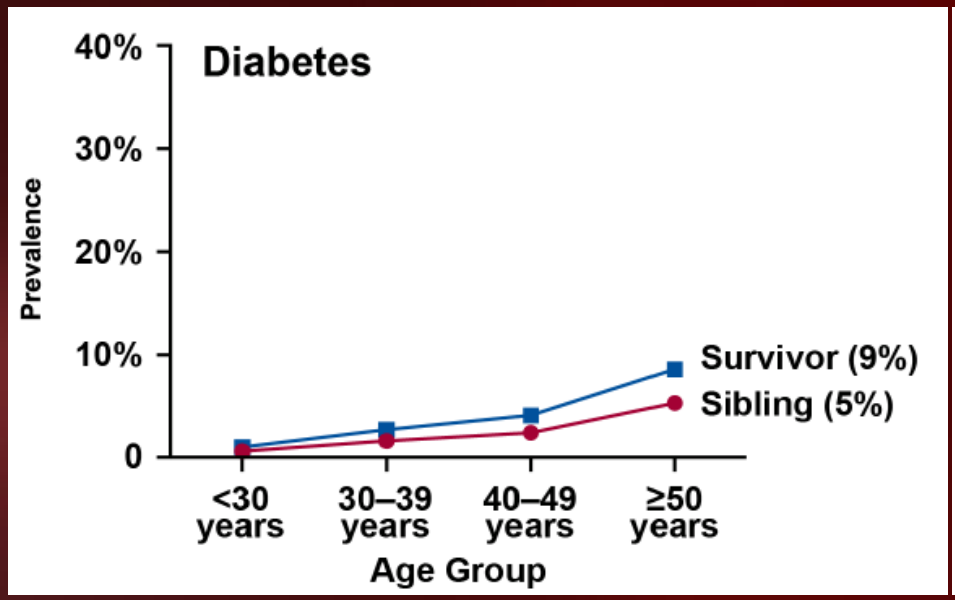


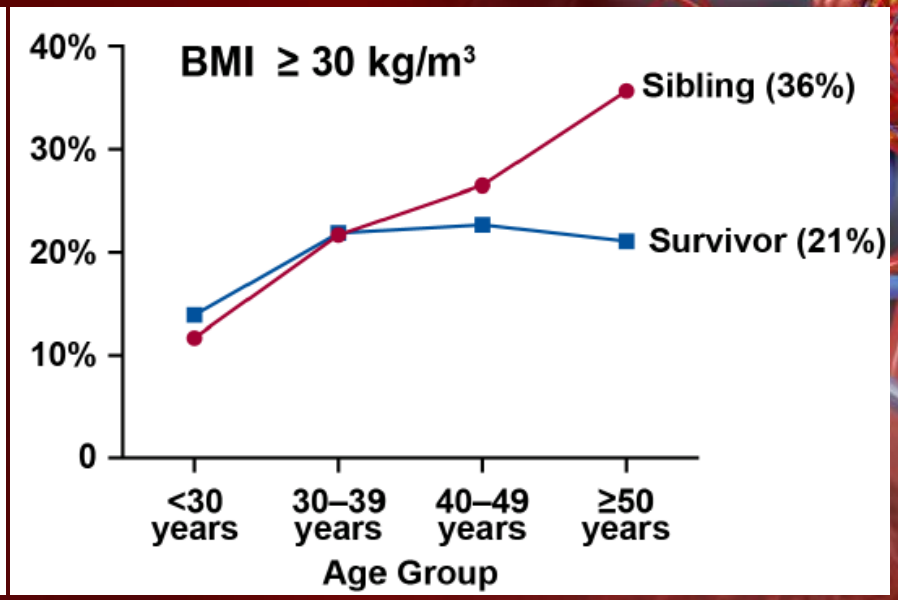
Traditional Risk Factors and Risk for Cardiotoxicity Post Chemo-Radiation

Survivors of Childhood Cancer: Prevalence of Cardiovascular Risk Factors









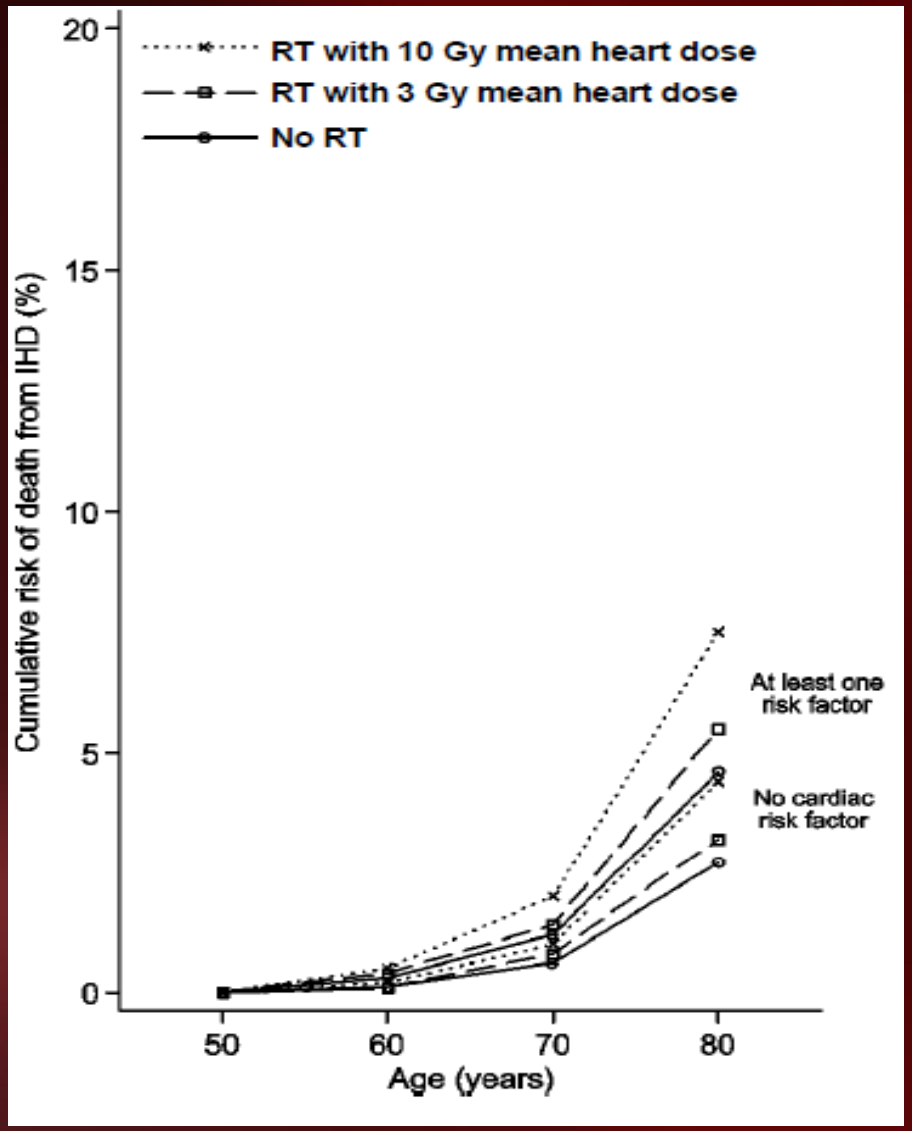
Childhood Cancer Survivor Study

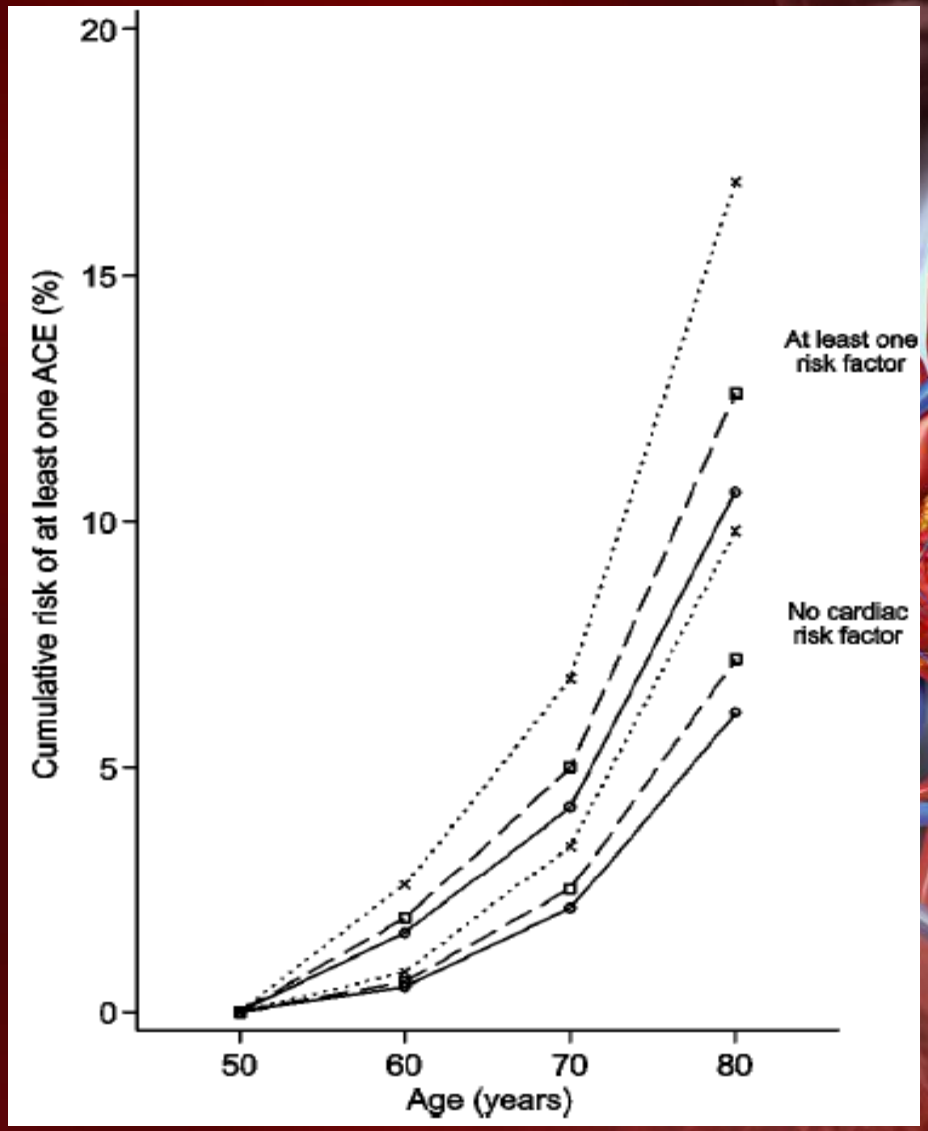
Cardiac Mortality and Risk Factor Cluster in Cancer Patients

Characteristic	Hazard Ratio	95% CI
Diabetes	2.2	0.8-6.1
Hypertension	5.5	3.2-9.7
Dyslipidemia	1.7	0.7-3.8
Obesity	1.2	0.6-2.3
Multiple Risk Factors	2.4	1.2-4.9

Armstrong *et al*

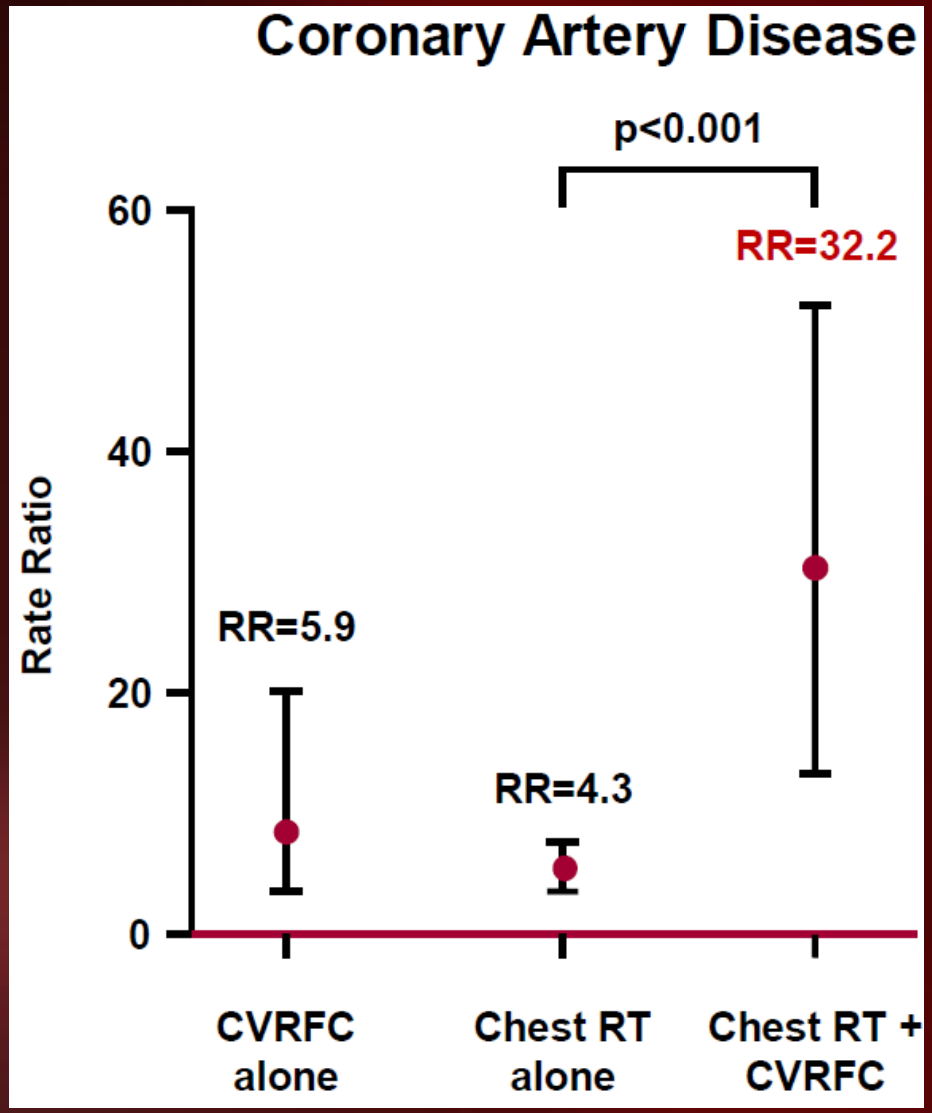
Influence of Age on XRT Plus Cardiovascular Risk Factors

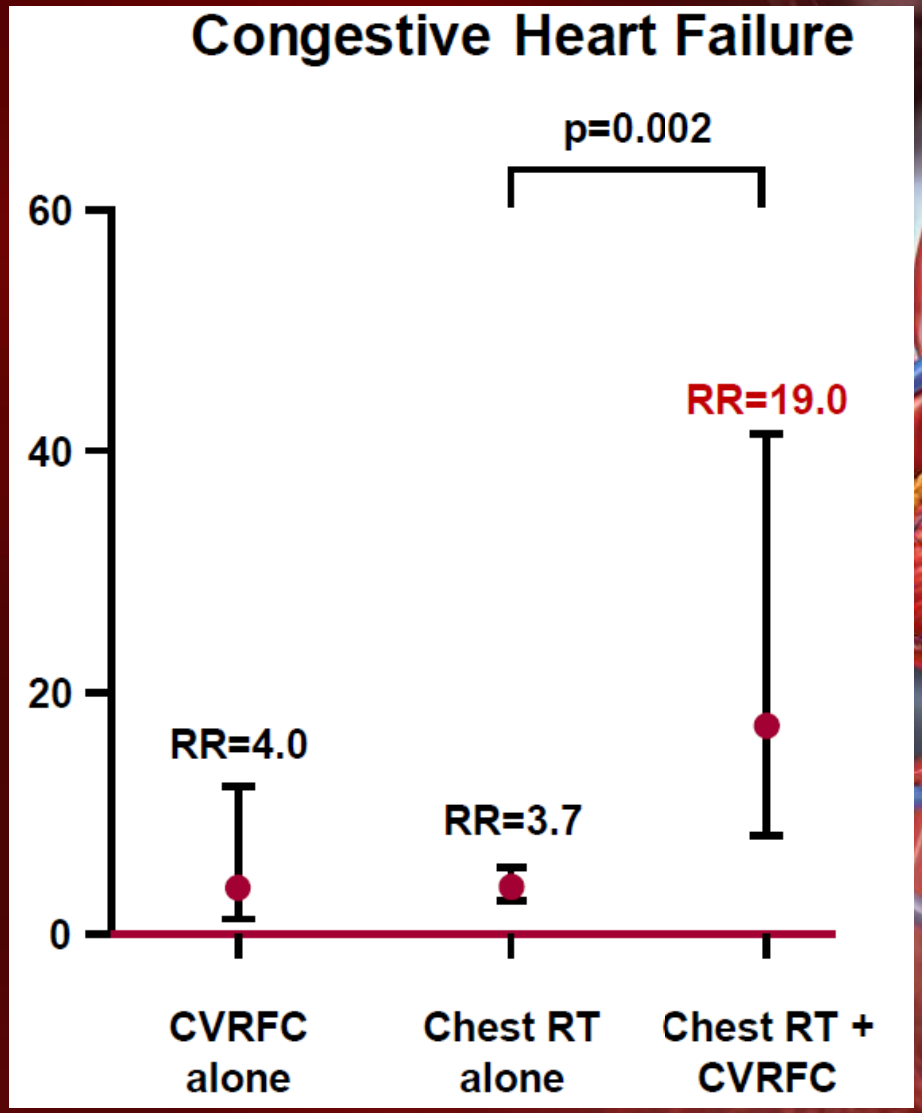




Darby *et al, NEJM* 2013

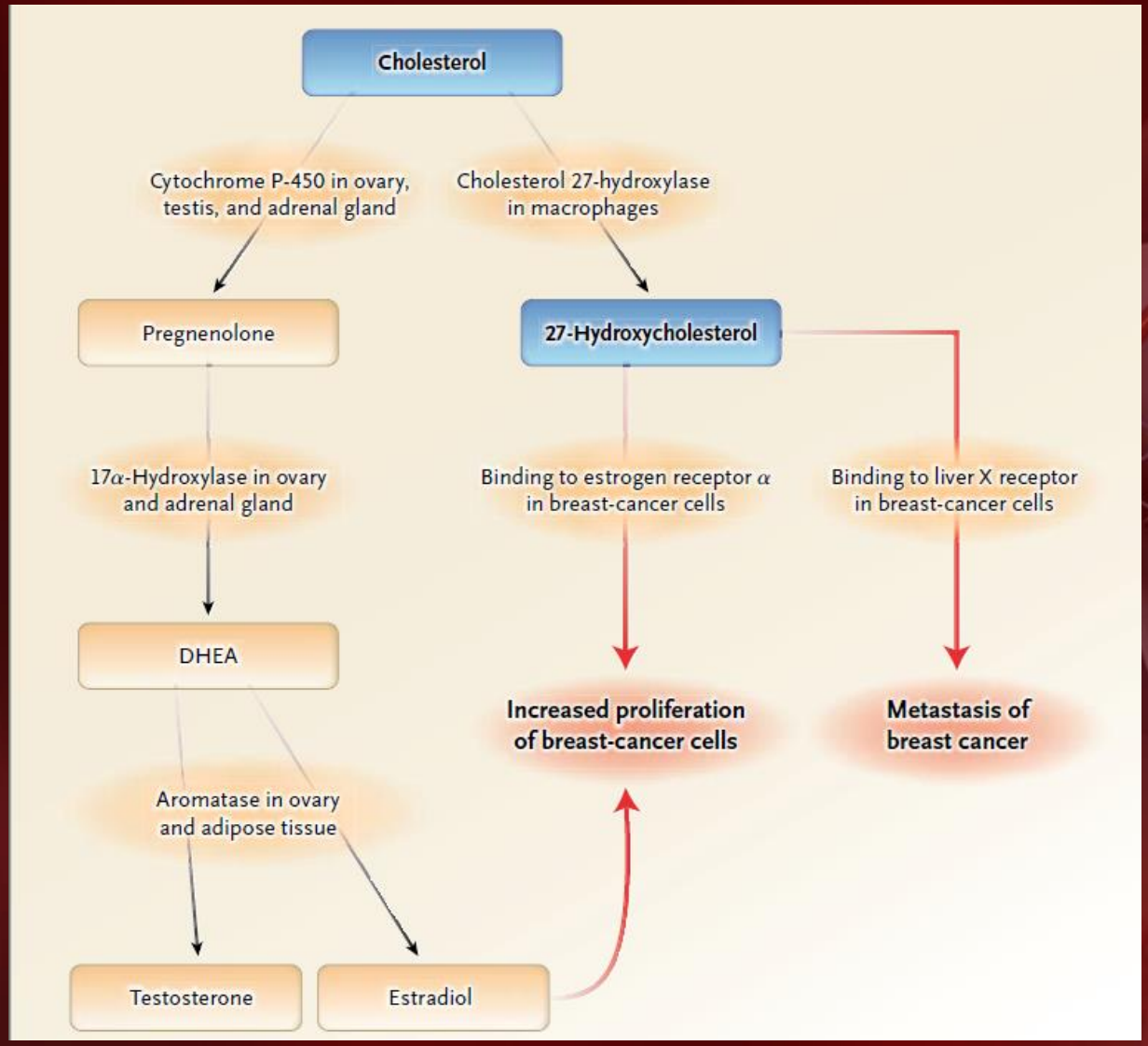
Chest Radiation and Cardiovascular Risk Factor Cluster





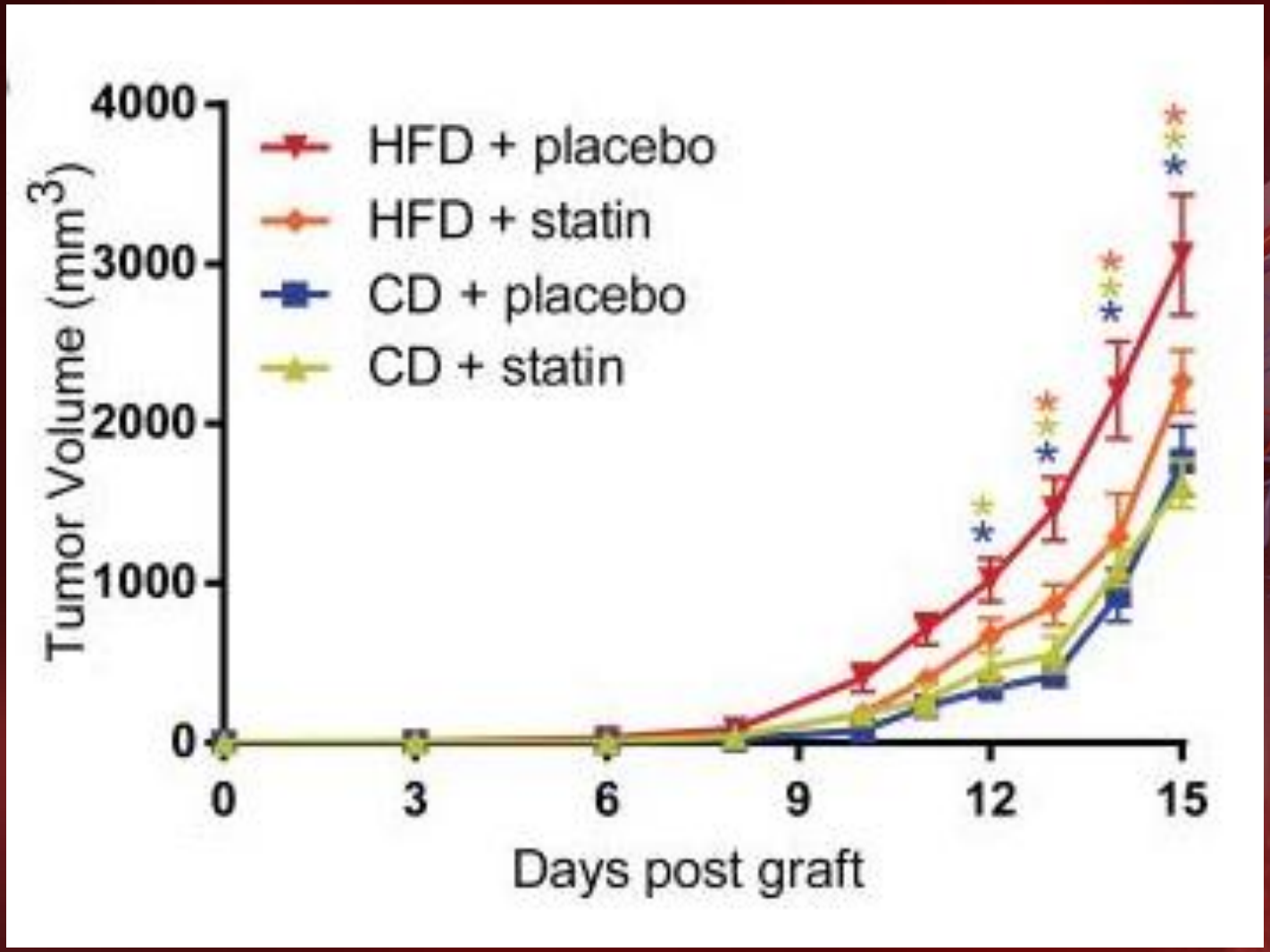
Armstrong *et al*

Cholesterol Metabolism and Breast Cancer



Warner and Gustafsson, NEJM 2014

Hypercholesterolemia and Breast Cancer Pathophysiology



Nelson *et al*, Science 2013

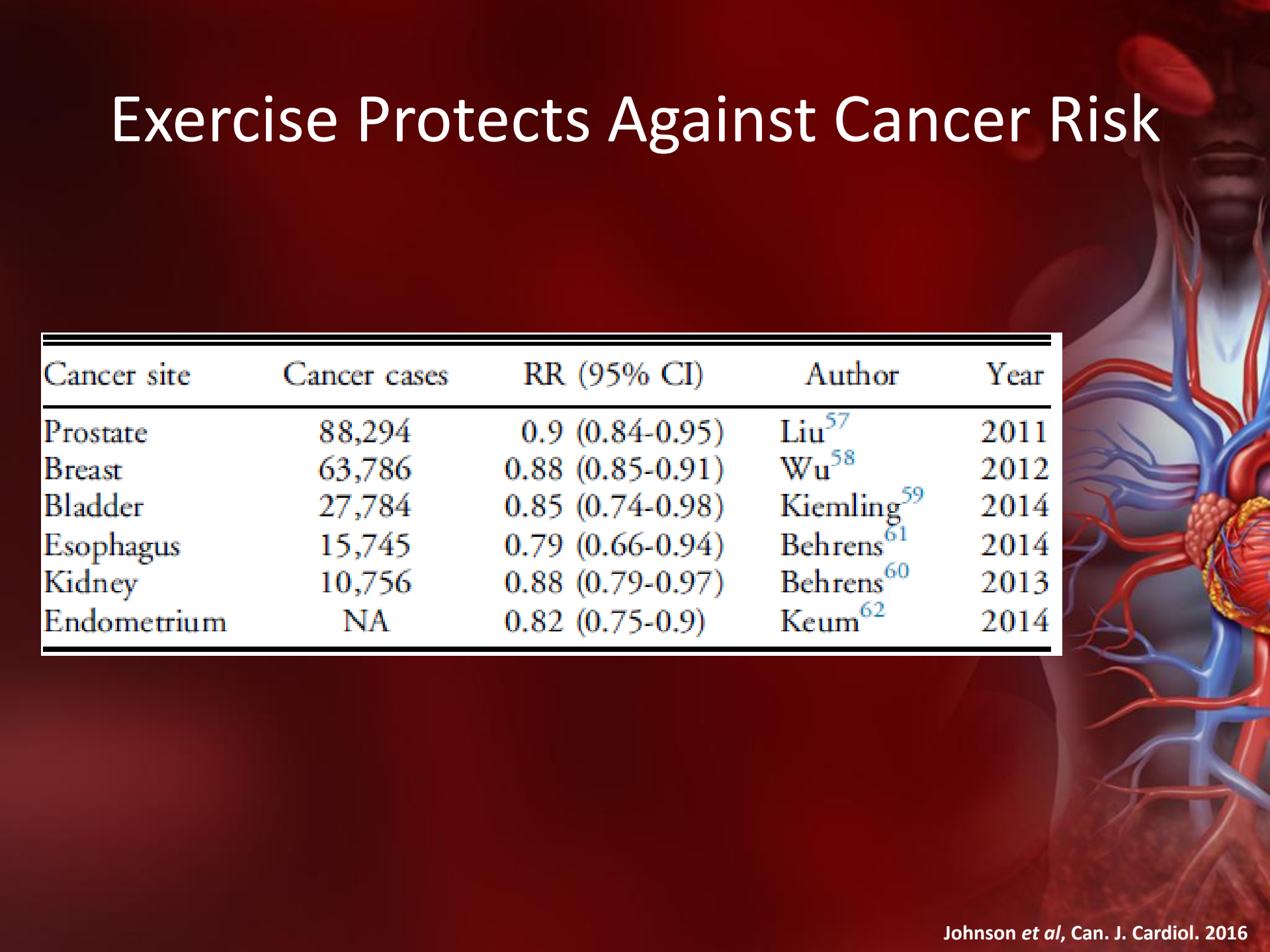
Statin Use and Risk of Cancer in Patients with COPD

Variable	No. of patients	No. of person-years	No. of patients with any cancer	Incidence Rate (per 10^5 person-years) (95% CI)			aHR (95%CI)	*P* for Trend
Total statin use								
Nonuser (<28 cDDDs)	33716	194933.6	5279	2708.1	(2635.0,	2781.2)	1.00	<0.001
User (≥28 cDDDs)	10086	80239.4	964	1201.4	(1125.6,	1277.2)	0.46(0.43, 0.50)***	
28–90 cDDDs	2346	17095.6	294	1719.7	(1523.2,	1916.3)	0.65(0.58, 0.73)***	
91–365 cDDDs	3215	24193.1	343	1417.8	(1267.7,	1567.8)	0.54(0.48, 0.60)***	
>365 cDDDs	4525	38950.7	327	839.5	(748.5,	930.5)	0.32(0.29, 0.36)***	
Lipophilia statin use†								
Nonuser (<28 cDDDs)	35008	204288.0	5379	2633.0	(2562.7,	2703.4)	1.00	<0.001
User (≥28 cDDDs)	8794	70885.0	864	1218.9	(1137.6,	1300.2)	0.57(0.53, 0.61)***	
28–90 cDDDs	2296	17069.8	270	1581.7	(1393.1,	1770.4)	0.67(0.59, 0.75)***	
91–365 cDDDs	3012	23258.7	332	1427.4	(1273.9,	1581.0)	0.65(0.58, 0.73)***	
>365 cDDDs	3486	30556.4	262	857.4	(753.6,	961.3)	0.42(0.37, 0.48)***	
Hydrophilia statin use†								
Nonuser (<28 cDDDs)	39878	242812.7	5974	2460.3	(2397.9,	2522.7)	1.00	<0.001
User (≥28 cDDDs)	3924	32360.4	269	831.3	(731.9,	930.6)	0.48(0.42, 0.55)***	
28–90 cDDDs	1122	8876.1	102	1149.2	(926.1,	1372.2)	0.62(0.51, 0.75)***	
91–365 cDDDs	1531	12432.2	94	756.1	(603.2,	909.0)	0.45(0.36, 0.55)***	
>365 cDDDs	1271	11052.0	73	660.5	(509.0,	812.0)	0.40(0.31, 0.50)***	
Individual statin use (≥28 cDDDs)‡								
Simvastatin	3418	28625.0	257	897.8	(788.0,	1007.6)	0.55(0.49, 0.63)***	
Lovastatin	2109	18281.5	262	1433.1	(1259.6,	1606.7)	0.92(0.81, 1.04)	
Atorvastatin	5484	44678.1	484	1083.3	(986.8,	1179.8)	0.59(0.54, 0.65)***	
Fluvastatin	1510	12855.7	151	1174.6	(987.2,	1361.9)	0.78(0.66, 0.92)**	
Pravastatin	1501	12654.5	122	964.1	(793.0,	1135.2)	0.66(0.55, 0.79)***	
Rosuvastatin	2741	22641.7	158	697.8	(589.0,	806.6)	0.42(0.36, 0.49)***	

Chen *et al*, J. Cancer 2016

Exercise Protects Against Cancer Risk

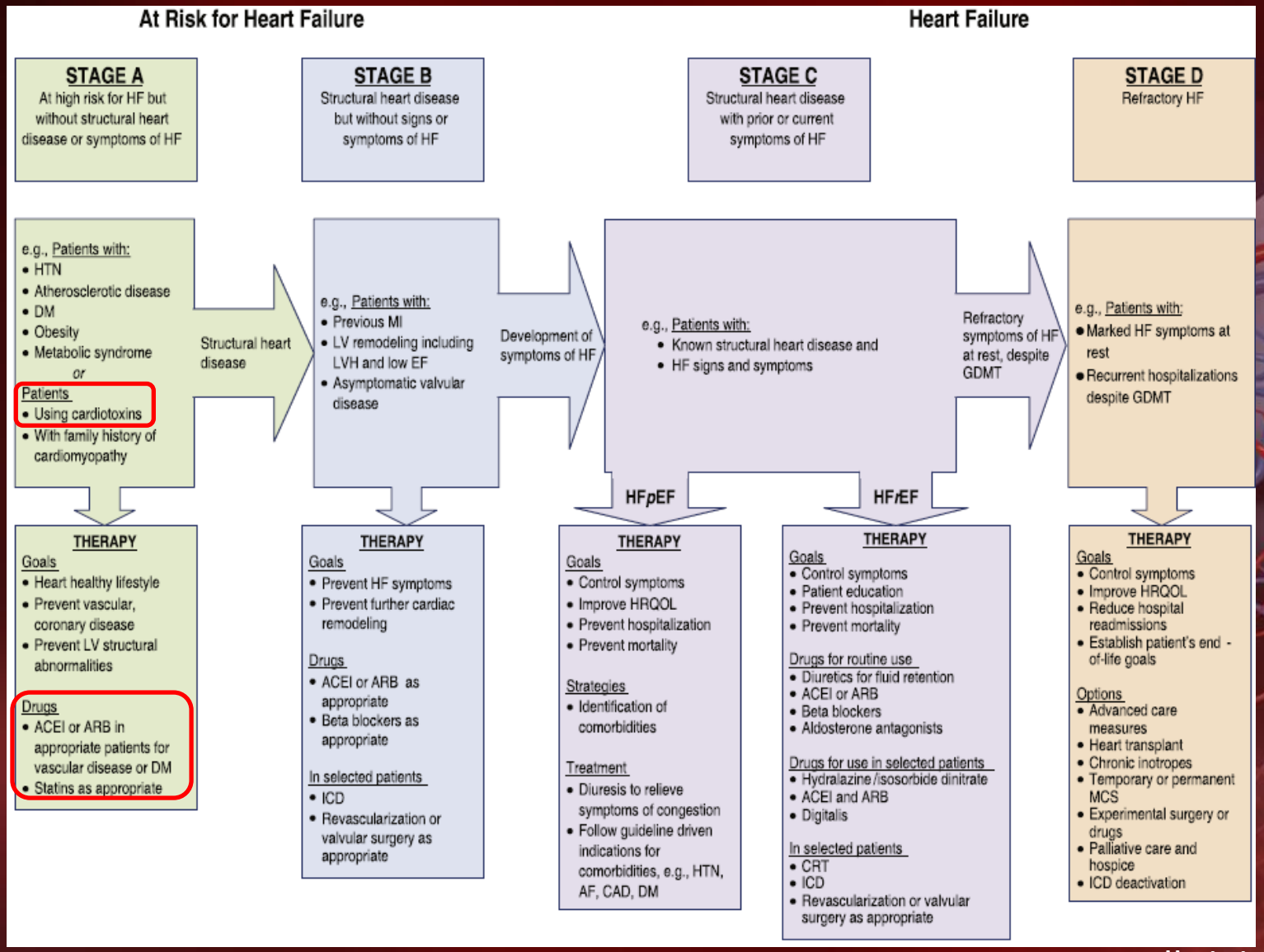
Cancer site	Cancer cases	RR (95% CI)	Author	Year
Prostate	88,294	0.9 (0.84-0.95)	Liu[57]	2011
Breast	63,786	0.88 (0.85-0.91)	Wu[58]	2012
Bladder	27,784	0.85 (0.74-0.98)	Kiemling[59]	2014
Esophagus	15,745	0.79 (0.66-0.94)	Behrens[61]	2014
Kidney	10,756	0.88 (0.79-0.97)	Behrens[60]	2013
Endometrium	NA	0.82 (0.75-0.9)	Keum[62]	2014



Johnson *et al*, Can. J. Cardiol. 2016

Biomarker/Imaging for Detection of Cardiotoxicity

Stages in Heart Failure Development/ Recommended Therapy by Stage



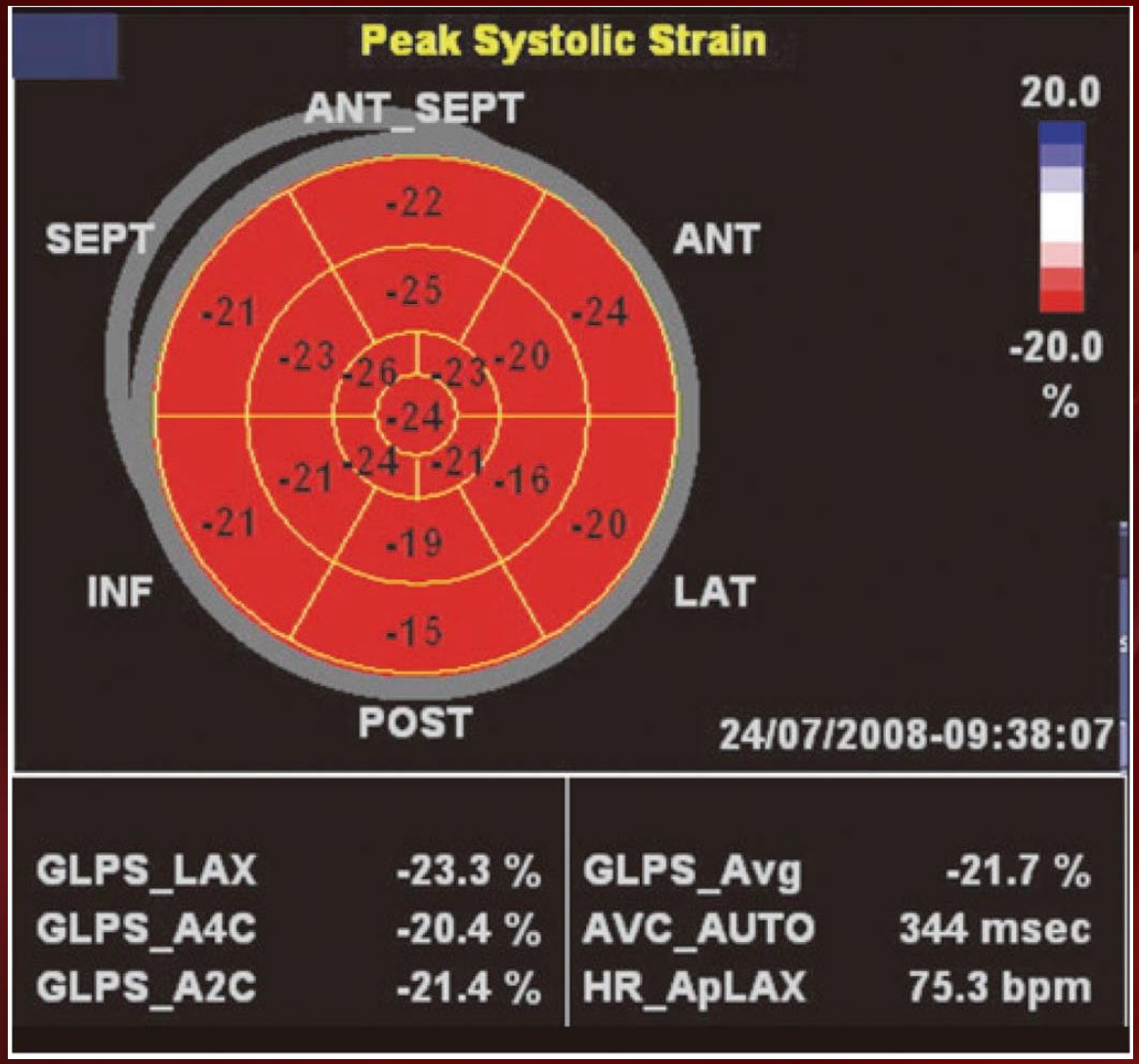
Hunt *et al*, *Circulation* 2009

Strain and Troponin-I for Prediction of Cardiotoxicity

	Sensitivity	Specificity	PPV	NPV
10% decrease long strain	7/9 (78%)	27/34 (79%)	7/14 (50%)	27/29 (93%)
Increased cTnI at 3 months	6/9 (67%)	28/34 (82%)	6/12 (50%)	28/31 (90%)
10% decrease long strain and increased cTnI at 3 months	5/9 (55%)	33/34 (97%)	5/6 (83%)	33/37 (89%)
10% decrease long strain or increased cTnI at 3 months	8/9 (89%)	22/34 (65%)	8/20 (40%)	22/23 (97%)

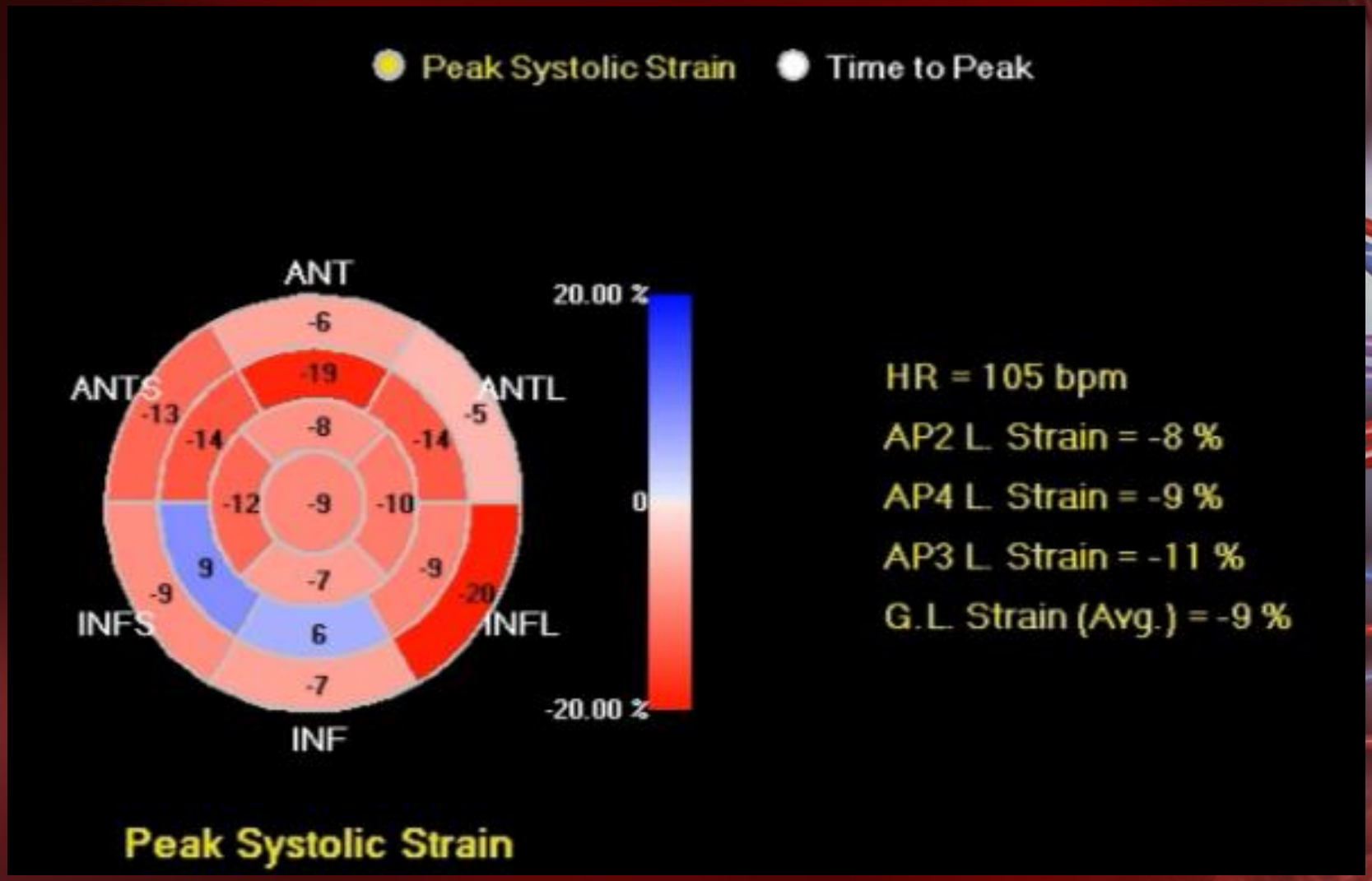
Sawaya *et al, Circulation Cardiovasc. Img.* 2012

Normal LV Myocardial Global and Segmental Longitudinal Strain Data



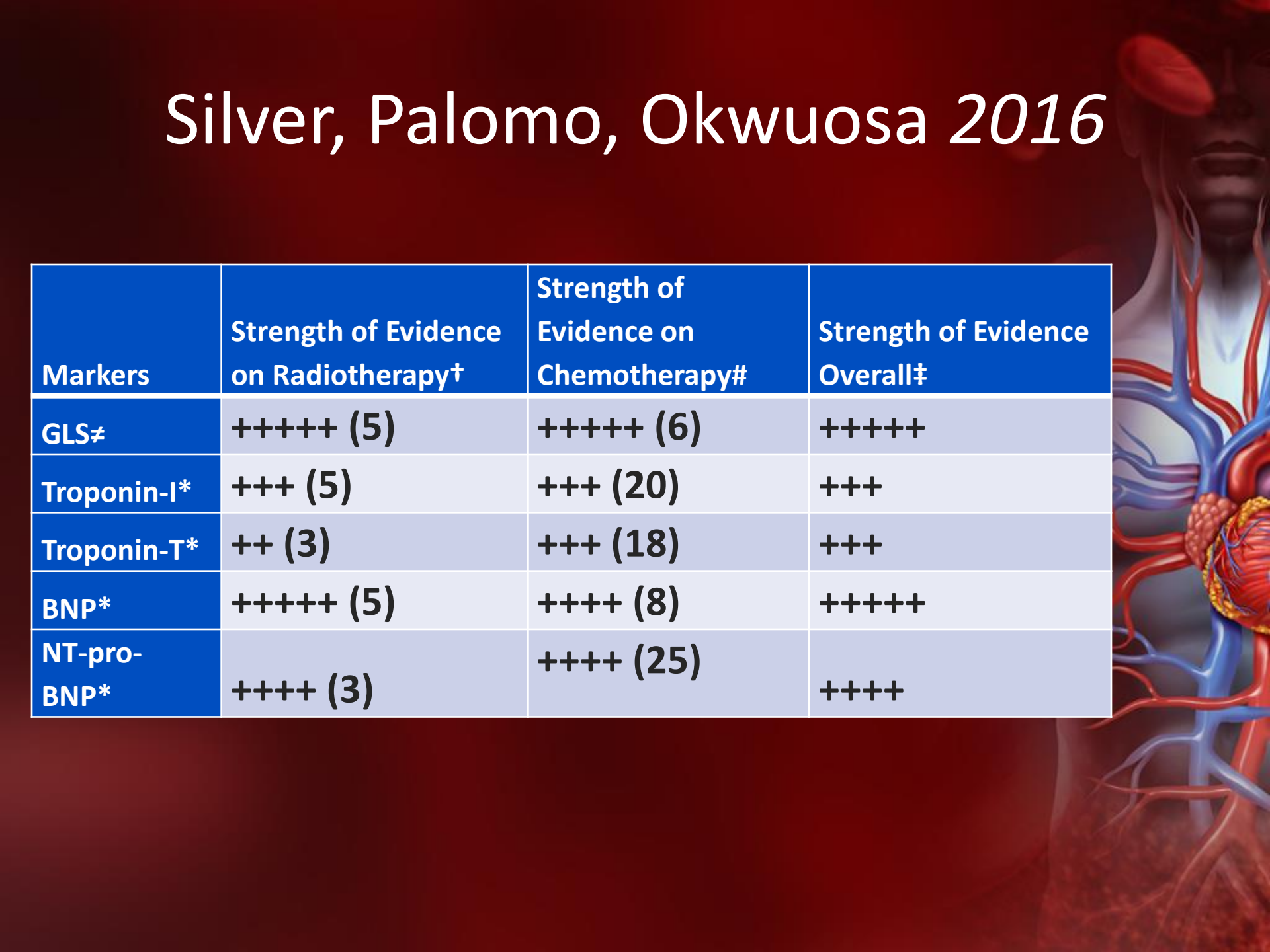
Feigenbaum *et al,* Circulation J. 2012

Chemotherapy Cardiomyopathy

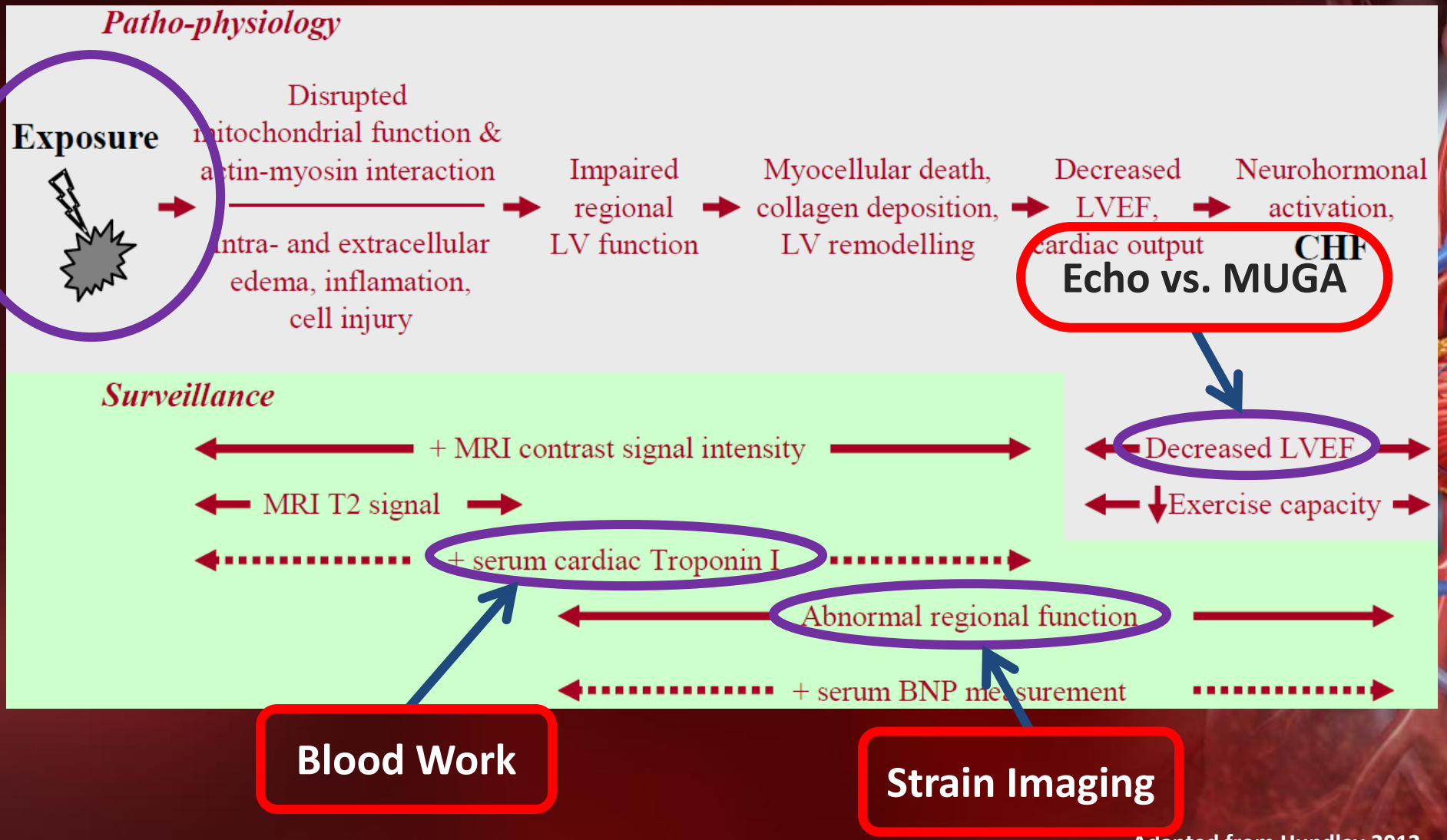


Silver, Palomo, Okwuosa *2016*

Markers	Strength of Evidence on Radiotherapy†	Strength of Evidence on Chemotherapy#	Strength of Evidence Overall‡
GLS≠	+++++ (5)	+++++ (6)	+++++
Troponin-I*	+++ (5)	+++ (20)	+++
Troponin-T*	++ (3)	+++ (18)	+++
BNP*	+++++ (5)	++++ (8)	+++++
NT-pro-BNP*	++++ (3)	++++ (25)	++++



Testing Based on Pathophysiology



Adapted from Hundley 2012

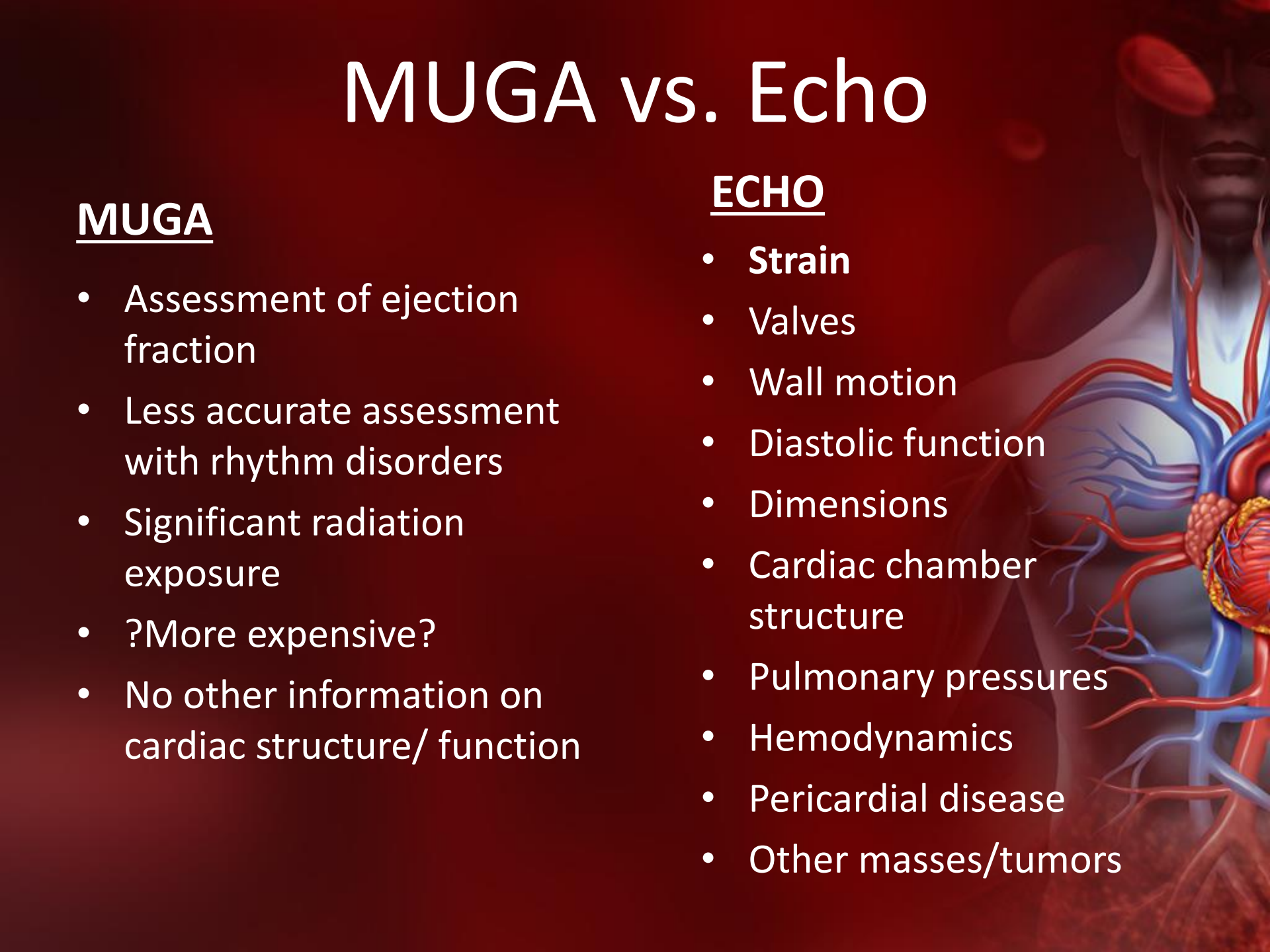
MUGA vs. Echo

MUGA

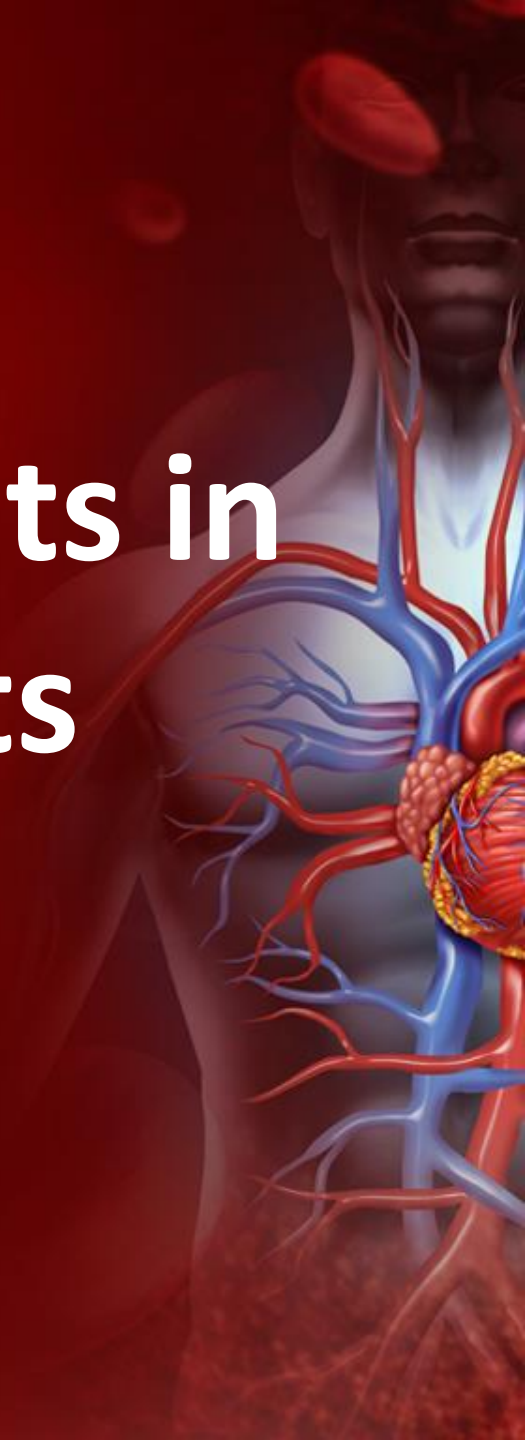
- Assessment of ejection fraction
- Less accurate assessment with rhythm disorders
- Significant radiation exposure
- ?More expensive?
- No other information on cardiac structure/ function

ECHO

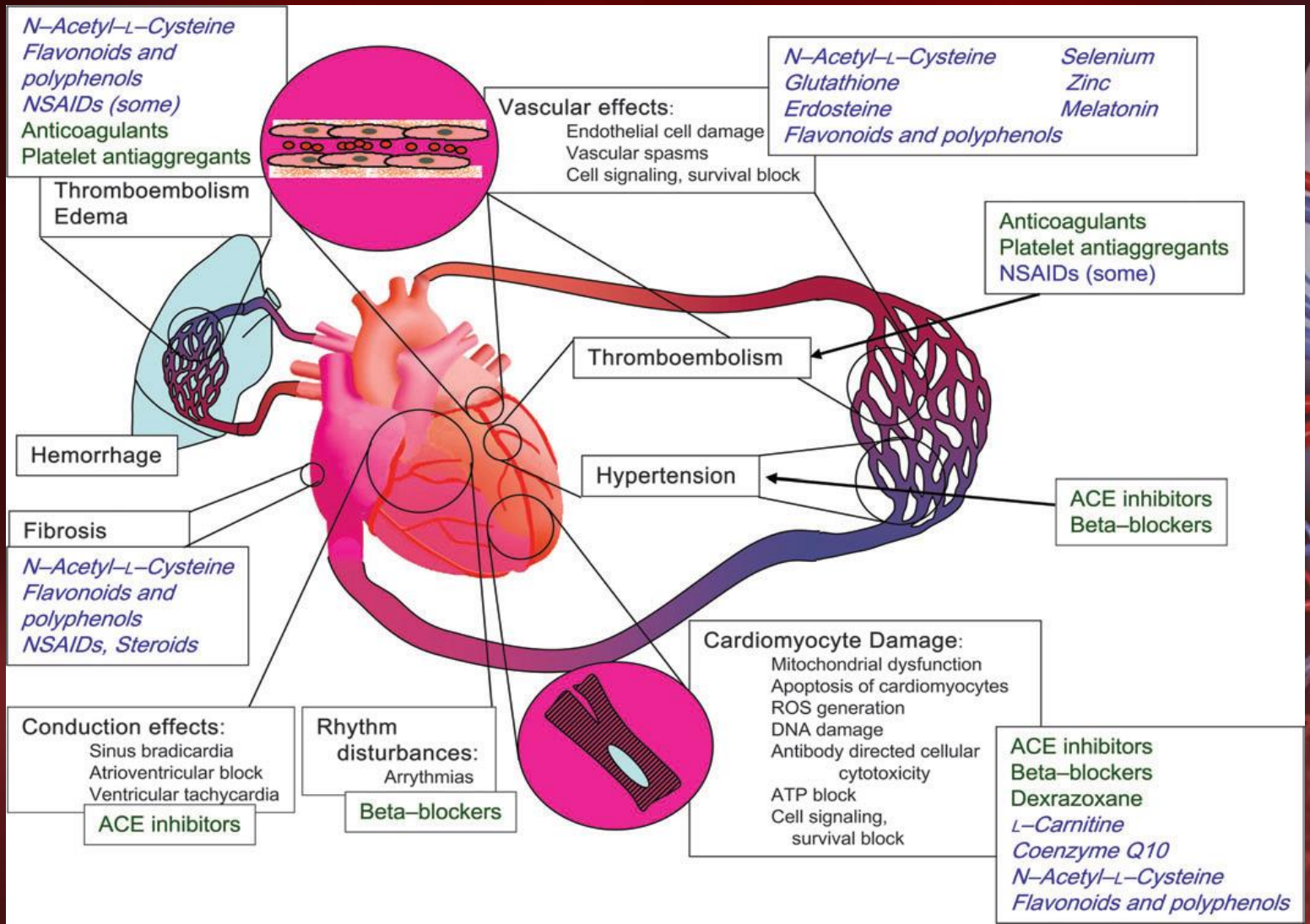
- **Strain**
- Valves
- Wall motion
- Diastolic function
- Dimensions
- Cardiac chamber structure
- Pulmonary pressures
- Hemodynamics
- Pericardial disease
- Other masses/tumors



Cardiac Treatments in Cancer Patients



Examples of major mechanisms causing cardiotoxicity of anticancer treatments, clinically used therapeutic agents, *and potential protective agents*

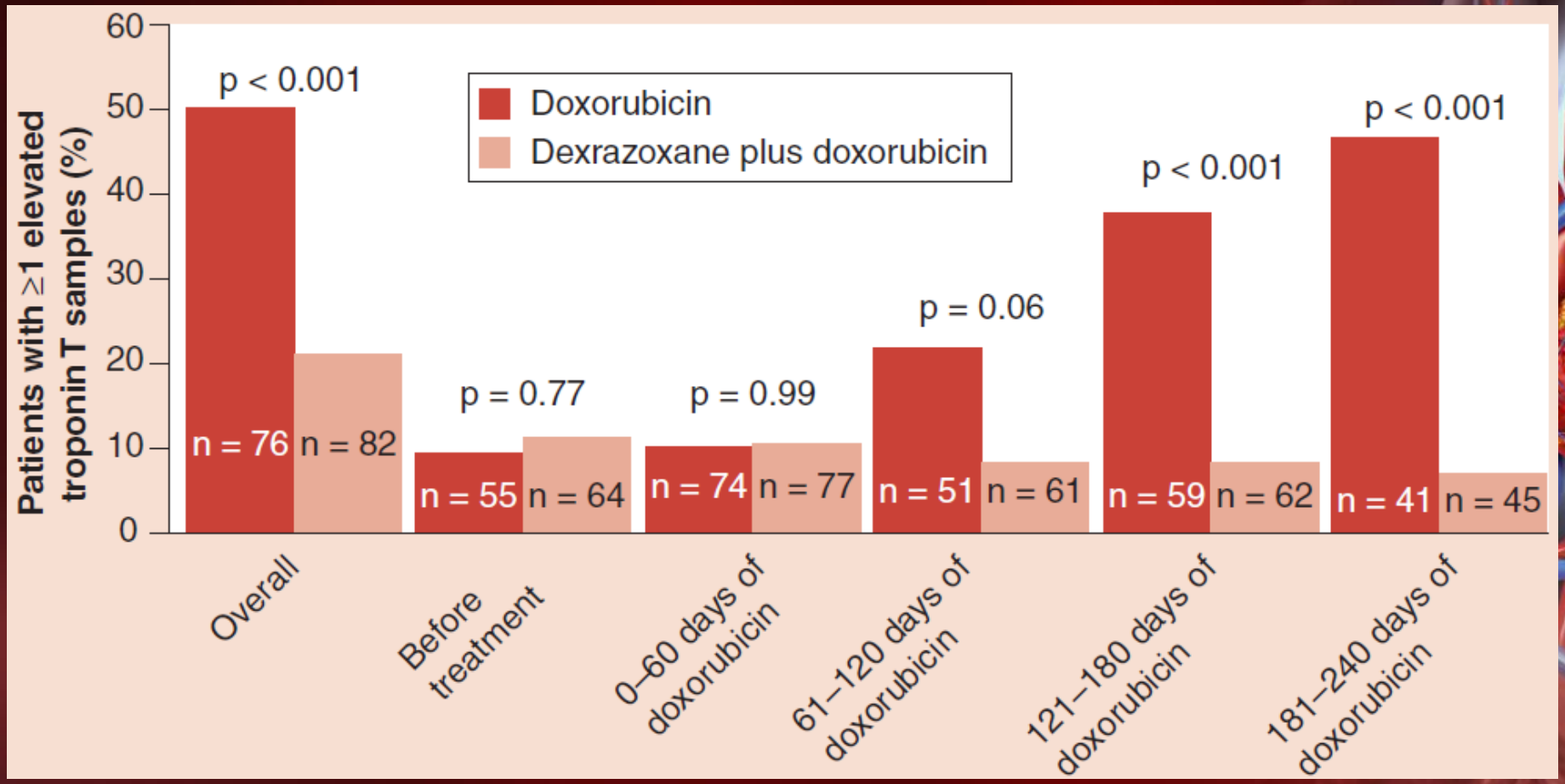


Prevention of Chemotherapy-Induced Cardiotoxicity

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy drugs	Identify and treat cardiovascular risk factors
	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities
	Minimize cardiac irradiation
Anthracyclines and analogues	Limit cumulative dose (mg/m^2): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	β-blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	β-blockers

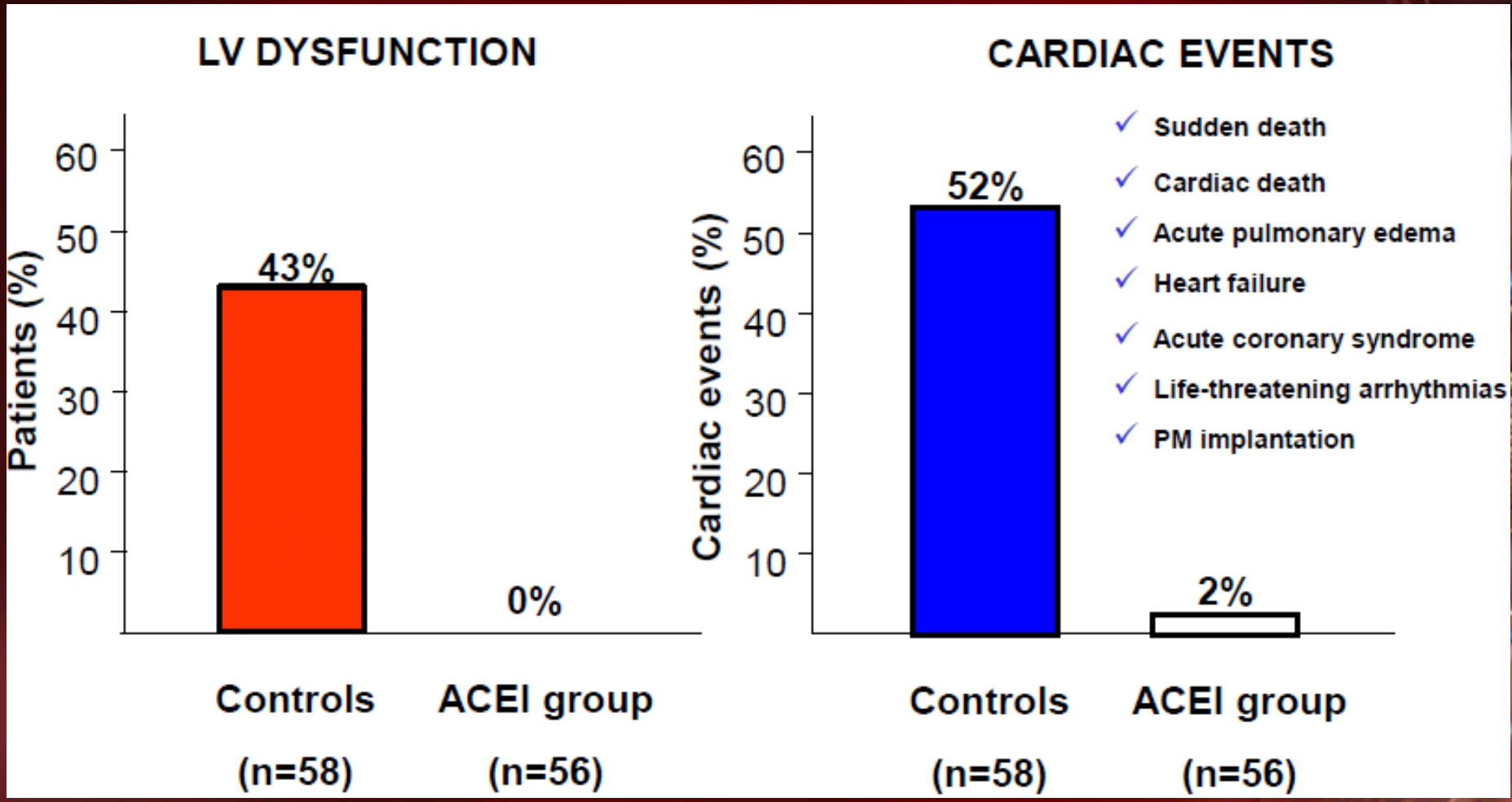
ESC Position Paper, EHJ 2016

Dexrazoxane for Preventing Doxorubicin-Induced Cardiotoxicity



Harake *et al, Future Cardiol.* 2012

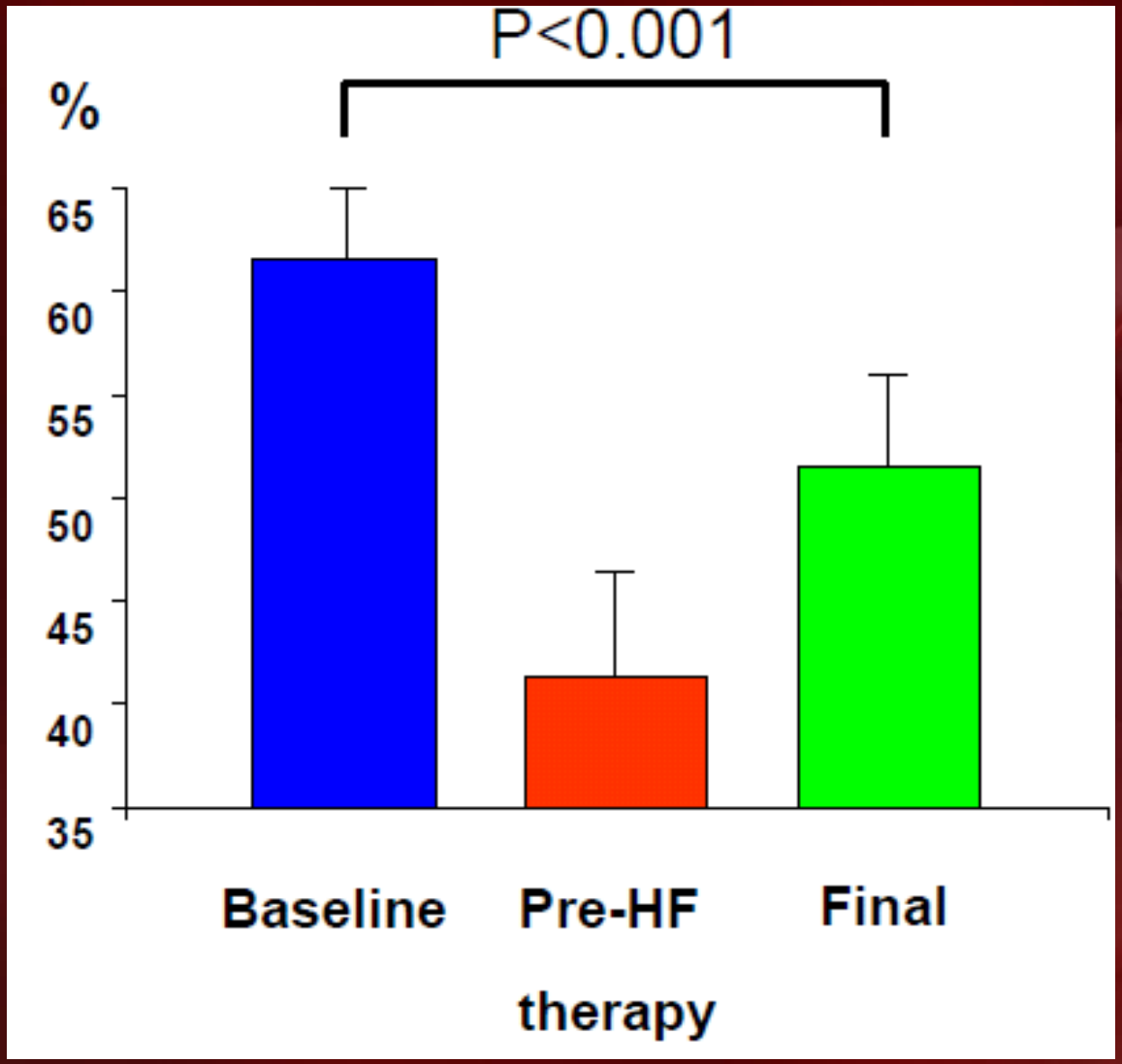
Prevention with ACE Inhibitors



- Therapy given based on increase in troponin I

Modified from Cardinale et al. *Circulation* 2006

Changes in LV Ejection Fraction after Heart Failure Therapy (ACE-I/BB)



Cardinale *et al, JACC* 2010

Cancer and the Heart

Cardiovascular Interventions in Thrombocytopenic Cancer Patients

Patients and Methods. Thrombocytopenia has been a contraindication for interventional cardiology procedures due to the increased risk of bleeding. Starting in September 2008, we treated cancer patients who presented with abnormal cardiovascular stress tests or acute coronary syndromes in a systematic fashion according to current cardiovascular guidelines, independent of their platelet counts (excluding patients with sepsis or active bleeding). We identified a total of 30 patients with chronic thrombocytopenia, defined as absolute platelet count <100,000/mm^3 (mean platelet count, 49,000/mm^3; lowest platelet count, 9,000/mm^3). These patients underwent cardiac catheterization and appropriate coronary artery disease treatment.

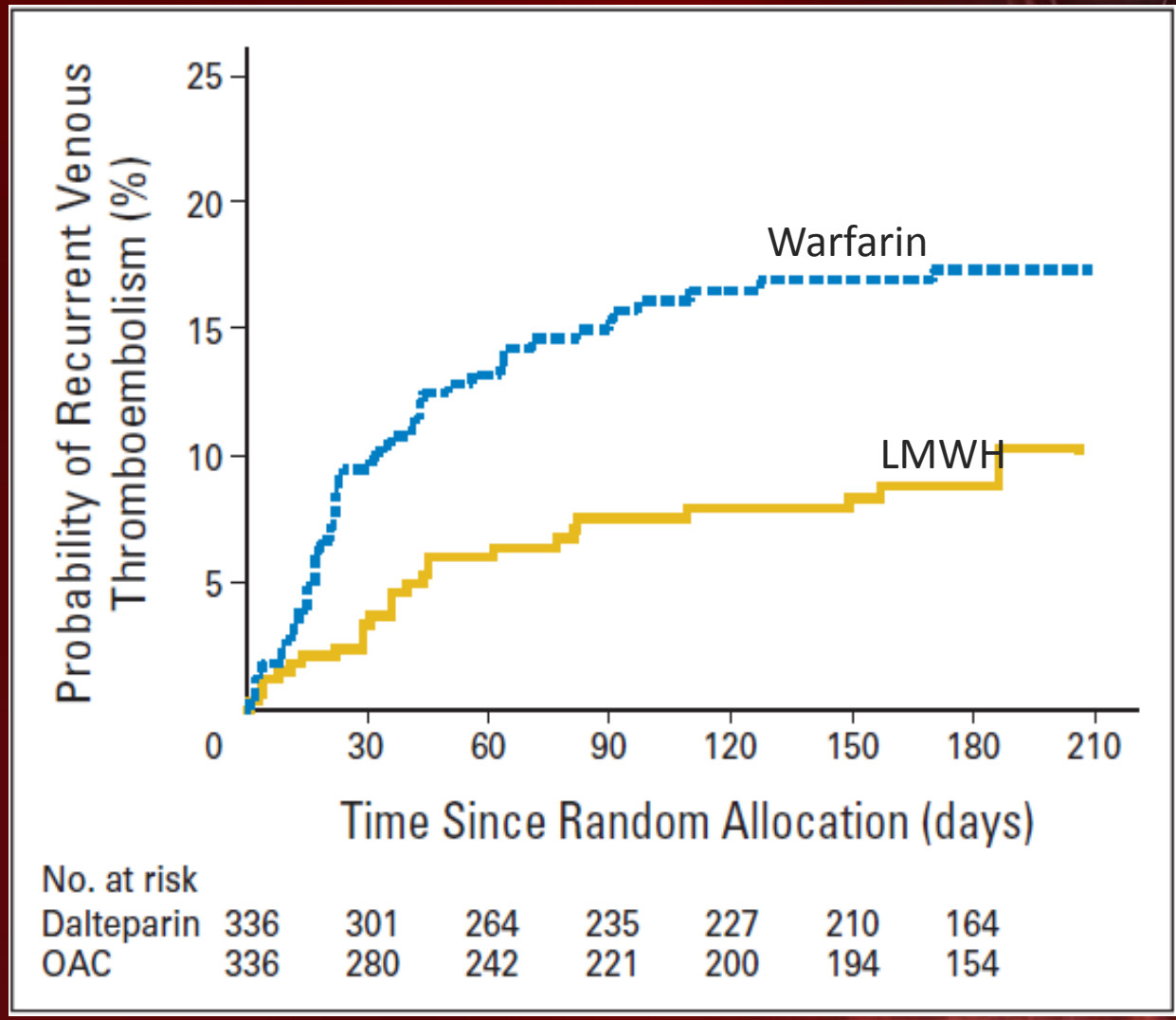
Results. In all patients who had thrombocytopenia, the procedures were completed without major bleeding complications. No platelet transfusions were administered before or during the procedures.

Anticoagulation in Cancer Patients

- **Cardiac Indications**
  - Atrial Fibrillation
  - Artificial Heart Valves
  - Thromboembolic Disease

- **Severe thrombocytopenia:**
  - platelet infusion, keep counts > 50
- **Platelets 20 – 50:**
  - Cut LMWH in half
- **Platelets < 20**
  - consider discontinuation of anticoagulation
  - use prophylactic LMWH

- ***Individualized management***



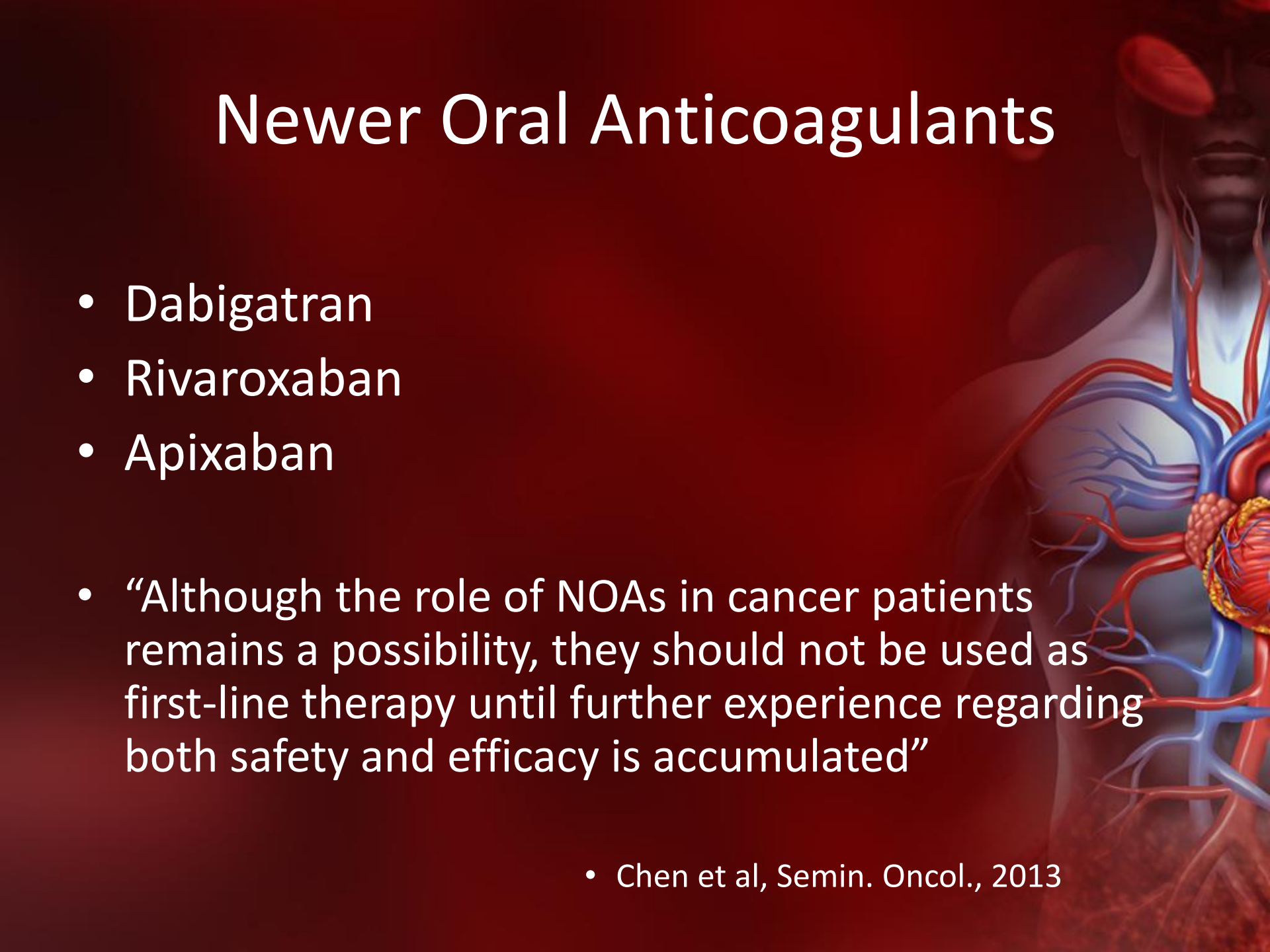
Lee, *JCO* 2009

Newer Oral Anticoagulants

- Dabigatran
- Rivaroxaban
- Apixaban

- "Although the role of NOAs in cancer patients remains a possibility, they should not be used as first-line therapy until further experience regarding both safety and efficacy is accumulated"

  - Chen et al, Semin. Oncol., 2013



Anticoagulation for Afib in Cancer, 2016

A subanalysis of the ARISTOTLE study (N = 18201) evaluated the effects of active cancer on the efficacy and safety outcomes of apixaban versus warfarin in patients with nonvalvular atrial fibrillation (NVAF).[1]

At baseline, history of cancer was reported in 1236 (6.8%) of the 18201 randomized patients. There were 157 (12.7%) patients with active cancer or treated within 1 year and 1079 (87.3%) patients with a remote history of cancer.[1]

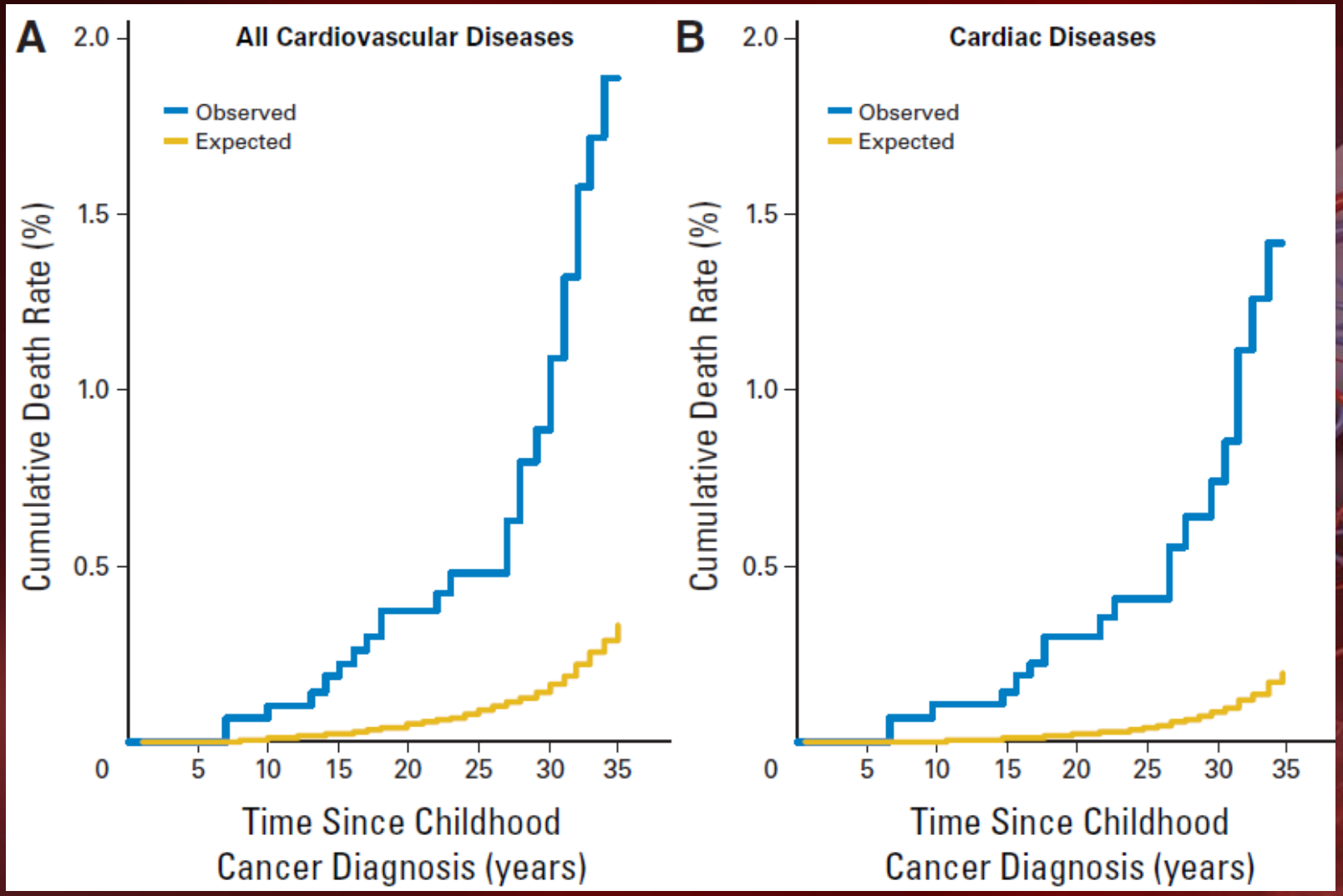
Results from the subanalysis showed[1]:

- In patients with active cancer, stroke or systemic embolism occurred at an event rate/100 person-years of 0 in the apixaban arm and 3.8 in the warfarin arm (HR not available). In patients with no active cancer, stroke or systemic embolism occurred at an event rate/100 person-years of 1.3 in the apixaban arm and 1.6 in the warfarin arm (HR 0.77, 95% CI 0.64-0.93) (*P* interaction = 0.95).
- Irrespective of cancer history, the treatment effect of apixaban versus warfarin for the primary efficacy outcome of stroke or systemic embolism was consistent among patients with cancer and without cancer (*P* interaction 0.37).
- In patients with active cancer, ISTH major bleeding occurred at an event rate/100 person-years of 0.8 in the apixaban arm and 4.5 in the warfarin arm (HR 0.19, 95% CI 0.02-1.59). In patients with no active cancer, ISTH major bleeding occurred at an event rate/100 person-years of 2.1 in the apixaban arm and 3.1 in the warfarin arm (HR 0.69, 95% CI 0.59-0.80) (*P* interaction = 0.23)

- Study sponsored by Bristol-Myers Squibb and Pfizer

PREVENTION IN SURVIVORS

Risk of Cardiac and Cardiovascular Diseases Worsen with Time in Cancer Survivors



Tukenova *et al,* JCO 2010

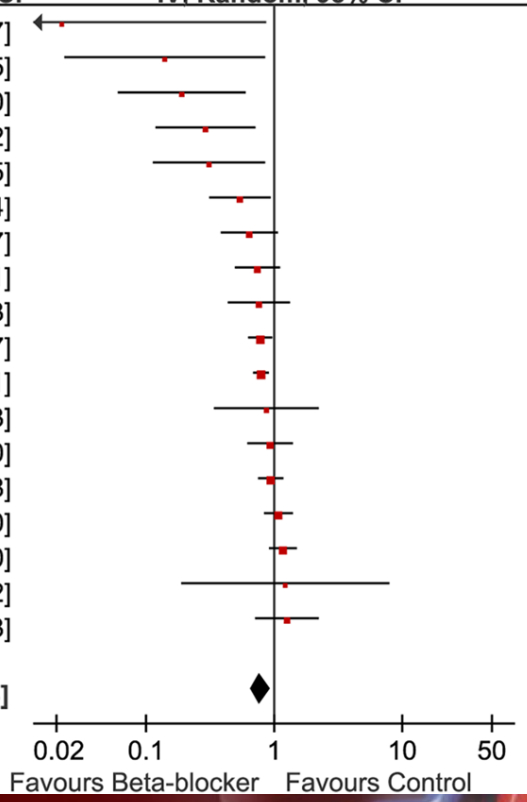
Meta-analysis of the effects of beta blocker on survival time in cancer patients

Findings independent of cancer stage

Study or Subgroup	log[Hazard Ratio]	SE	Beta blocker Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
De Giorgi 2011	-3.8167	1.87448802	30	91	0.2%	0.02 [0.00, 0.87]
Grytli 2013-1	-1.9661	0.92020098	35	228	0.8%	0.14 [0.02, 0.85]
Barron 2011-1	-1.6607	0.58668652	70	140	1.7%	0.19 [0.06, 0.60]
Powe 2010	-1.2344	0.45865269	43	374	2.6%	0.29 [0.12, 0.72]
Lemeshow 2011-3	-1.1712	0.51462452	247	2638	2.2%	0.31 [0.11, 0.85]
Diaz 2012	-0.6162	0.28210636	23	225	5.3%	0.54 [0.31, 0.94]
Melhem-Bertrandt 2011	-0.4463	0.26221722	102	1311	5.7%	0.64 [0.38, 1.07]
Heitz 2013	-0.3011	0.20686995	38	343	7.3%	0.74 [0.49, 1.11]
Ganz 2011	-0.2744	0.28551826	204	1372	5.2%	0.76 [0.43, 1.33]
Wang 2013	-0.2485	0.11122559	155	567	10.8%	0.78 [0.63, 0.97]
Grytli 2014	-0.2357	0.0721488	1115	2446	12.1%	0.79 [0.69, 0.91]
Lemeshow 2011-4	-0.1393	0.48023656	28	278	2.4%	0.87 [0.34, 2.23]
Lemeshow 2011-1	-0.0726	0.20869537	216	2638	7.2%	0.93 [0.62, 1.40]
Hole 1993-1	-0.0619	0.11601523	2676	0	10.6%	0.94 [0.75, 1.18]
Barron 2011-2	0.077	0.13240367	525	1050	10.0%	1.08 [0.83, 1.40]
Hole 1993-2	0.157	0.126766	1164	0	10.2%	1.17 [0.91, 1.50]
Grytli 2013-2	0.1989	0.95435732	25	202	0.7%	1.22 [0.19, 7.92]
Lemeshow 2011-2	0.2311	0.29127034	21	278	5.0%	1.26 [0.71, 2.23]
Total (95% CI)			**6717**	**14181**	**100.0%**	**0.79 [0.67, 0.93]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 41.97$, df = 17 (P = 0.0007); $I^2 = 59\%$

Test for overall effect: Z = 2.86 (P = 0.004)



	No. of comparisons	HR (95 % CI)	*p*
Overall survival			
All trials (fixed)	18	0.84 (0.78–0.92)	<0.0001
All trials (random)	18	0.79 (0.67–0.93)	0.004
Exclusion of trials before 2000	16	0.73 (0.61–0.88)	0.0009
Exclusion of small trials (<300 patients)	12	0.84 (0.73–0.97)	0.02

Choi *et al,* J Cancer Res Clin Oncol. 2014

Exercise and Cardiovascular Events in Hodgkin Lymphoma Survivors

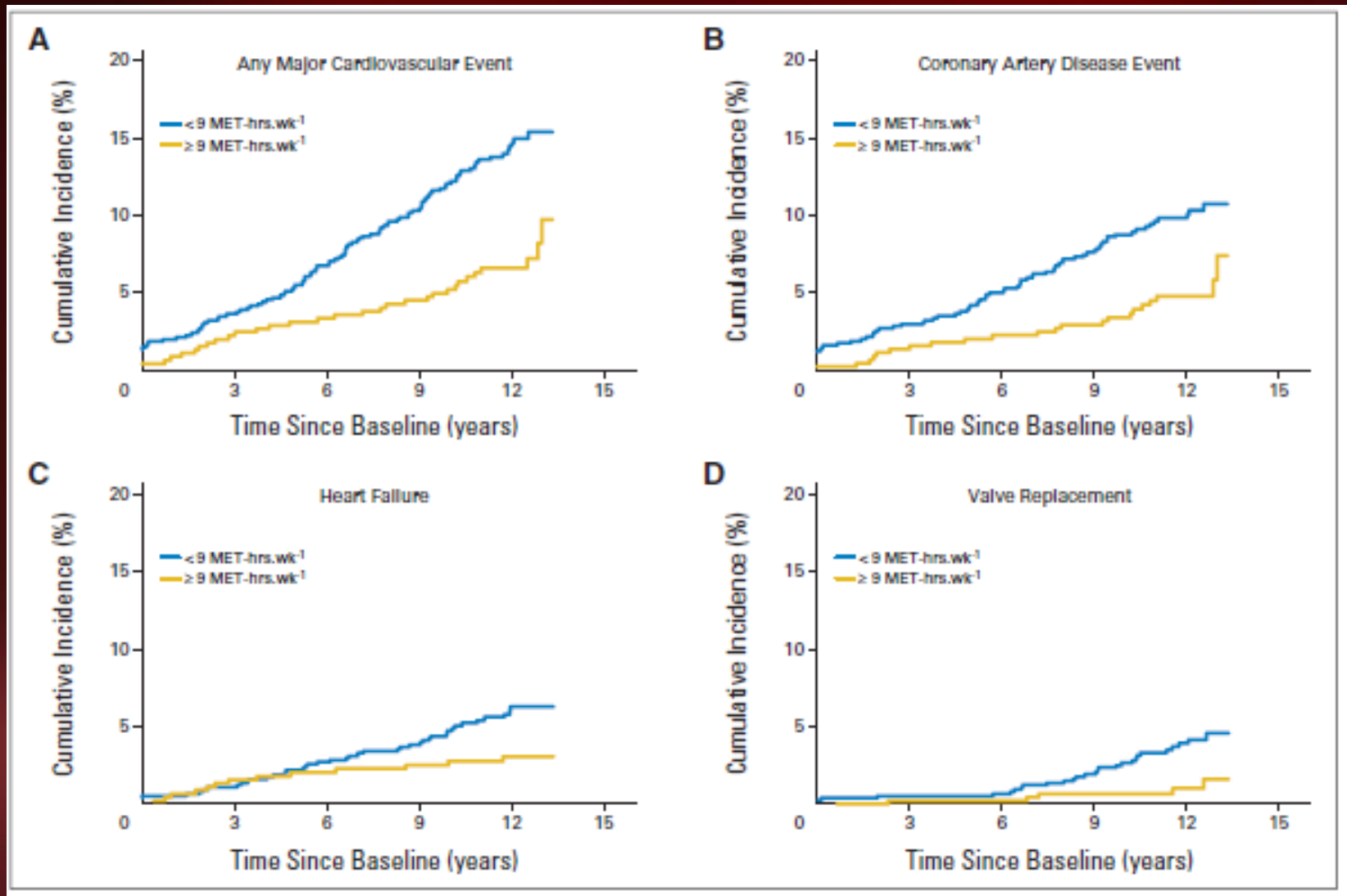


Fig 2. Cumulative incidence of (A) any major cardiovascular event ($P < .001$), (B) coronary artery disease ($P = .002$), (C) heart failure ($P = .028$), and (D) valve replacement ($P = .006$) according to meeting national guidelines for vigorous intensity exercise (ie, < 9 *v* ≥ 9 metabolic equivalent [MET] hours/week^{-1}).

Jones *et al*, *JCO* 2014

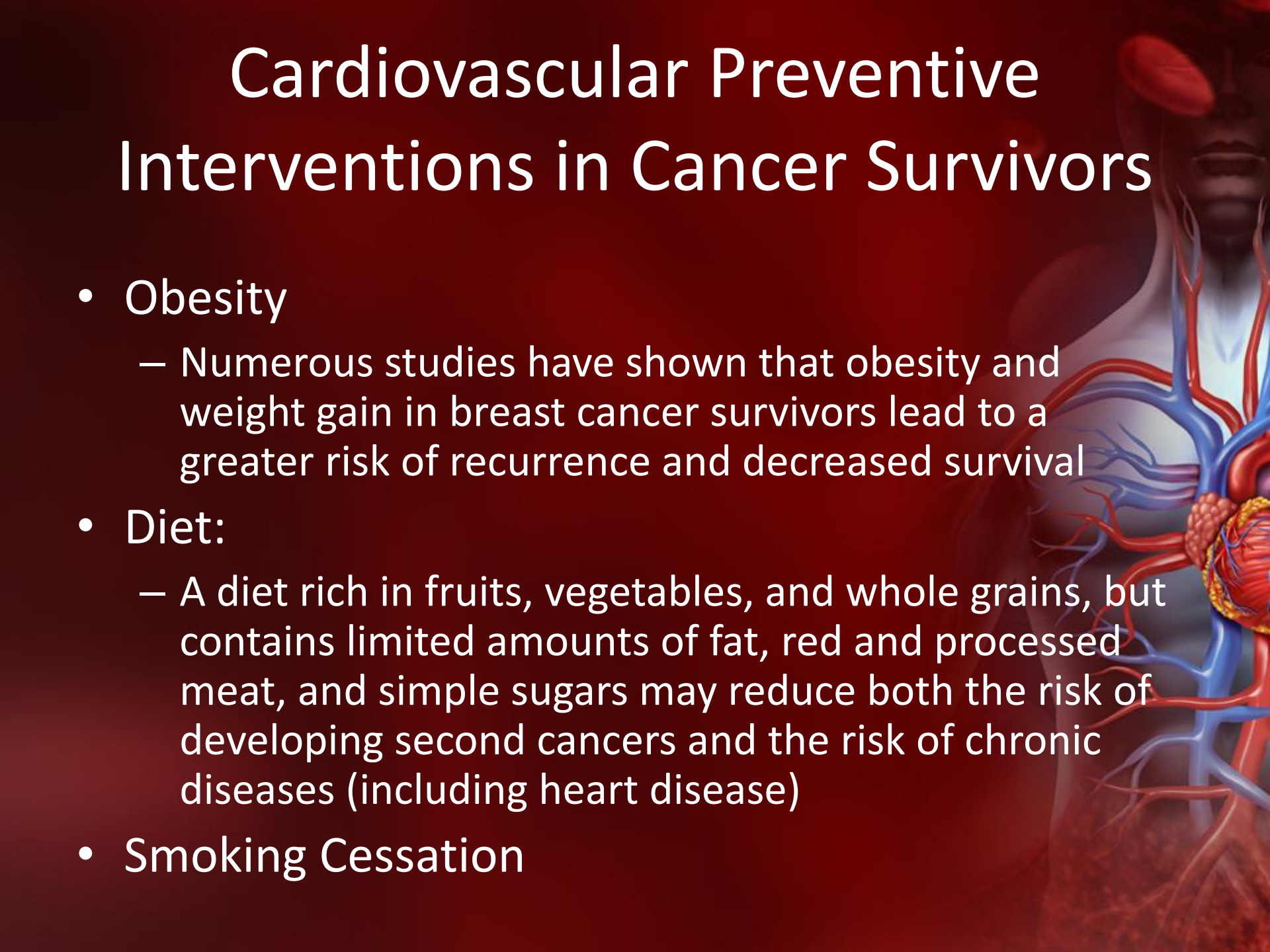
Exercise Pre Cancer Diagnosis and Cardiovascular Events After Breast Cancer Treatment: WHI

Based on quartiles in breast cases		MET·hrs·wk^{-1}				
	Total (N = 4015)	<2.50 (n = 994)	2.50 to < 8.625 (n = 1008)	8.625 to <18.00 (n = 1011)	≥18.00 (n = 1002)	P_{trend}
Median MET-hrs·wk^{-1}	8.67	0.0	5.25	13.00	26.33	
Cardiovascular events^{T}						
No. of events	342	103	88	86	65	
Age-adjusted HR (95% CI)		Ref	0.77 (0.58 to 1.03)	0.75 (0.56 to 0.99)	0.59 (0.43 to 0.80)	0.001
Multivariable-adjusted HR (95% CI)*		Ref	0.80 (0.59 to 1.09)	0.86 (0.64 to 1.17)	0.63 (0.45 to 0.88)	0.02
MI						
No. of events	89	25	22	24	18	
Age-adjusted HR (95% CI)		Ref	0.79 (0.45 to 1.40)	0.84 (0.48 to 1.48)	0.67 (0.37 to 1.24)	0.26
Multivariable-adjusted HR (95% CI)*		Ref	0.83 (0.44 to 1.53)	1.05 (0.57 to 1.92)	0.68 (0.34 to 1.36)	0.37
Heart failure						
No. of events	49	18	11	12	8	
Age-adjusted HR (95% CI)		Ref	0.58 (0.27 to 1.22)	0.63 (0.30 to 1.31)	0.43 (0.19 to 1.00)	0.08
Multivariable-adjusted HR (95% CI)*		Ref	0.64 (0.29 to 1.43)	0.94 (0.43 to 2.04)	0.57 (0.23 to 1.44)	0.37
Cardiovascular death						
No. of events	215	69	54	45	47	
Age-adjusted HR (95% CI)		Ref	0.68 (0.47 to 0.98)	0.56 (0.38 to 0.82)	0.62 (0.43 to 0.90)	0.02
Multivariable-adjusted HR (95% CI)*		Ref	0.73 (0.50 to 1.06)	0.60 (0.40 to 0.90)	0.69 (0.46 to 1.04)	0.11
CHD death						
No. of events	96	36	25	19	16	
Age-adjusted HR (95% CI)		Ref	0.59 (0.36 to 0.99)	0.45 (0.26 to 0.79)	0.40 (0.22 to 0.72)	0.003
Multivariable-adjusted HR (95% CI)*		Ref	0.65 (0.38 to 1.10)	0.46 (0.25 to 0.83)	0.41 (0.21 to 0.78)	0.006

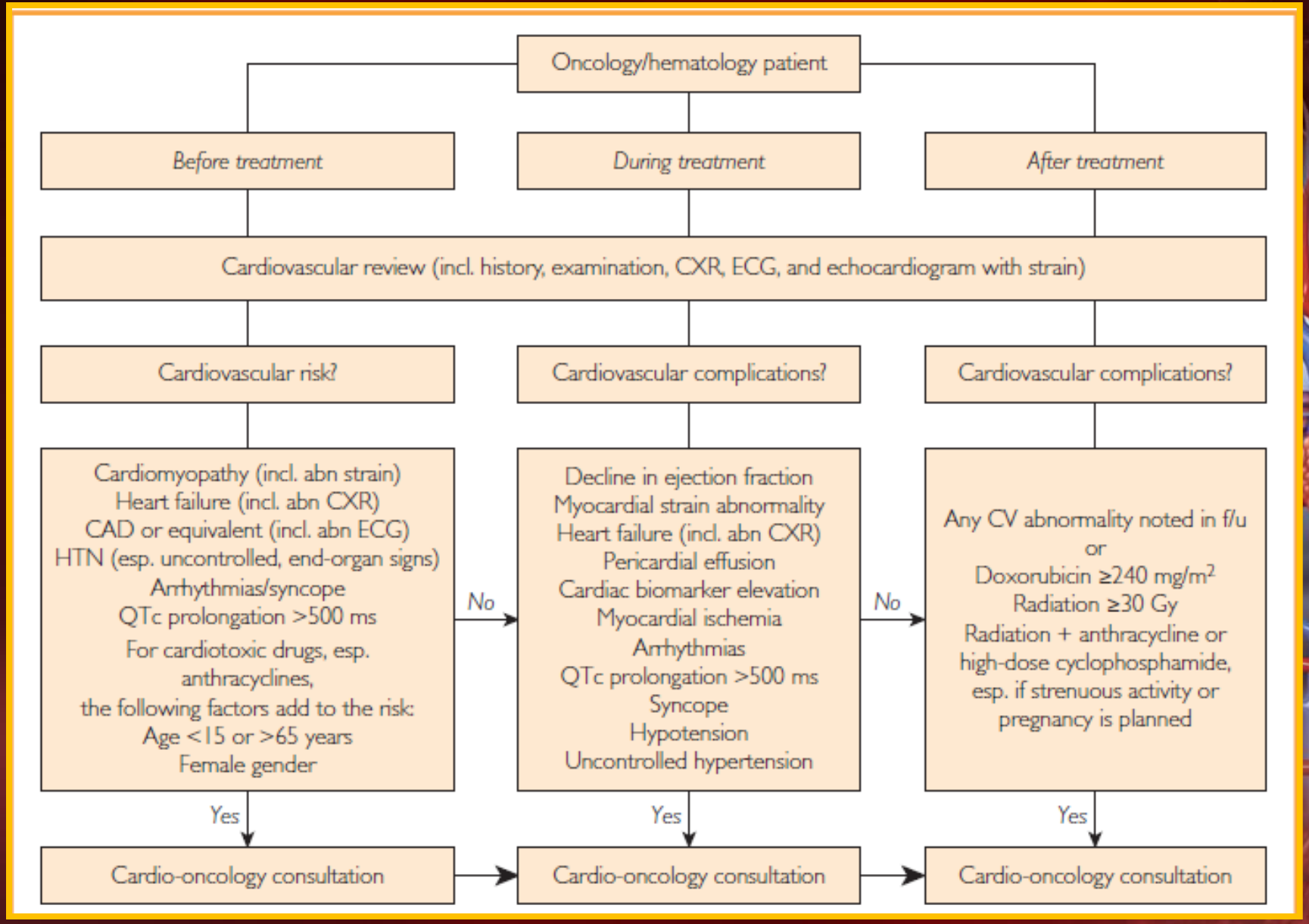
Okwuosa, Palomo *et al, Unpublished data*

Cardiovascular Preventive Interventions in Cancer Survivors

- Obesity
  - Numerous studies have shown that obesity and weight gain in breast cancer survivors lead to a greater risk of recurrence and decreased survival
- Diet:
  - A diet rich in fruits, vegetables, and whole grains, but contains limited amounts of fat, red and processed meat, and simple sugars may reduce both the risk of developing second cancers and the risk of chronic diseases (including heart disease)
- Smoking Cessation



WHEN TO REFER TO CARDIO-ONCOLOGY



Herrmann *et al,* Mayo Clin. Proc., 2014

ABCDE Steps to Prevent Heart Disease in Breast Cancer Survivors

Kamaneh Montazeri, MD; Christine Unitt, BS; JoAnne M. Foody, MD; Jay R. Harris, MD; Ann H. Partridge, MD; Javid Moslehi, MD

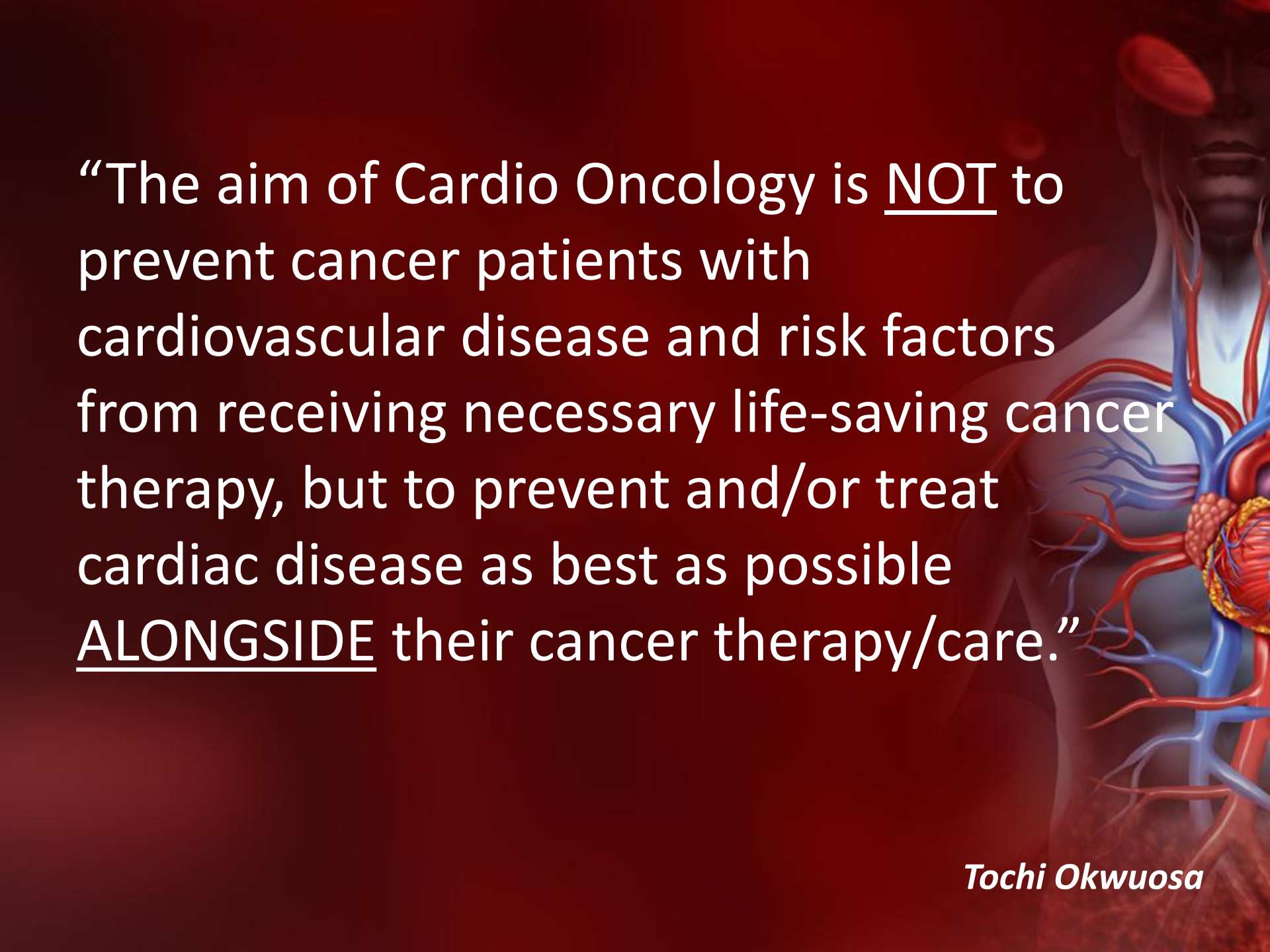
Table. ABCDEs to Prevent Heart Disease in Breast Cancer Survivors

ABCDE	ABCDEs
A	Awareness of risks of heart disease
	Aspirin
B	Blood Pressure
C	Cholesterol
	Cigarette/Tobacco cessation
D	Diet and weight management
	Dose of chemotherapy or radiation
	Diabetes mellitus prevention/ treatment
E	Exercise
	Echocardiogram

Cardio-Oncology Program: Cardiovascular Disease in Cancer Patients

"The aim of Cardio Oncology is NOT to prevent cancer patients with cardiovascular disease and risk factors from receiving necessary life-saving cancer therapy, but to prevent and/or treat cardiac disease as best as possible ALONGSIDE their cancer therapy/care."

Tochi Okwuosa



Future Directions

- Identification of persons at risk for cardiotoxicity
  - Age, sex, prior use of cardiotoxic agents, CV risk factors
  - ?Role of genetics
- Identification of markers of chemotherapy-induced cardiotoxicity
  - Strain imaging, Troponin-I, maybe BNP
  - ?Galectin-3, myeloperoxidase, other markers
- Medications for cardiotoxicity
  - Based on markers
  - ?Prophylactic

Future Directions

- Screening for cardiotoxicity in survivors:
  - ?modality, frequency
    - Echo, strain,
    - ?Based on symptoms, risk score
    - ?Stress testing, CAC in radiation therapy
- Studies on other cardiotoxic agents?
  - TKIs, VEGF inhibitors, monoclonal antibodies, antimetabolites, etc…
- Hormonal Therapy:
  - Meta-analysis of patient studies evaluating differences in cardiovascular risk