Cardio-Oncology: Preventing and Treating Cardiovascular Complications Associated with Cancer Treatments

Tochi M. Okwuosa, DO, FACC, FAHA
Associate Professor
Rush University Medical Center

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Disclosures

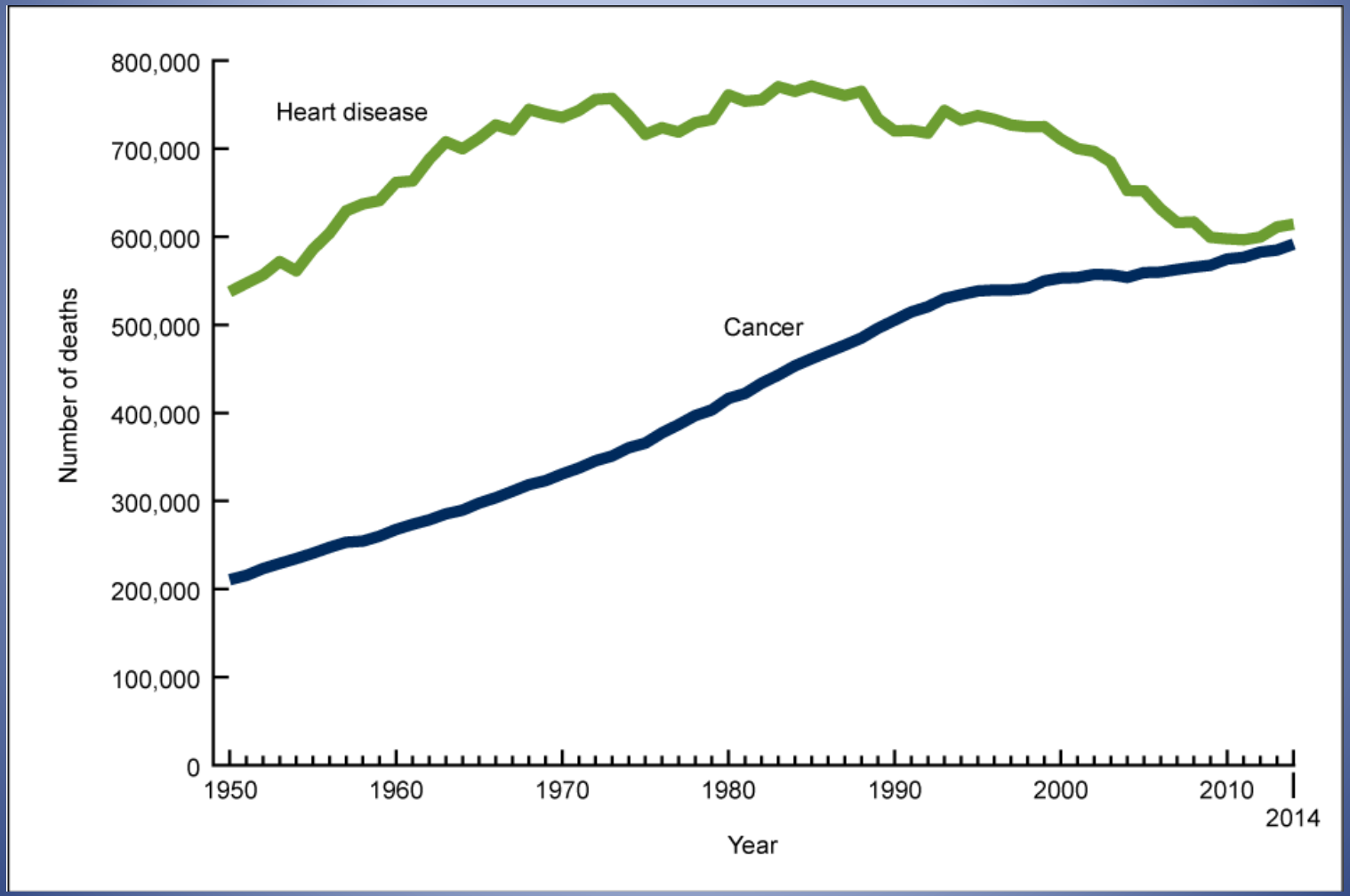
- Cardio-Oncology roundtable advisory for Pfizer

- No conflict of interest

Discussion

- Why Cardio-Oncology?
- Complications of Cancer Therapy
  - Chemotherapy
  - Radiation Therapy
  - Immunotherapy
- Management of these complications
- When and why to refer to Cardio-Oncology

Deaths due to Heart Disease and Cancer



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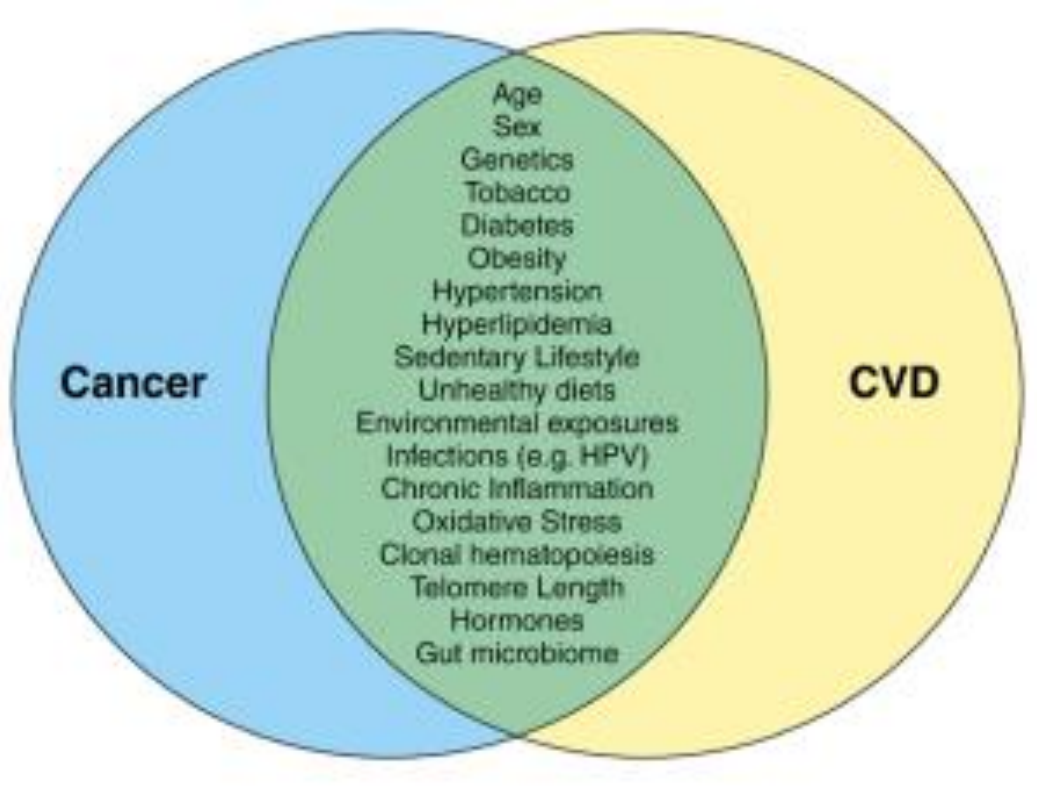
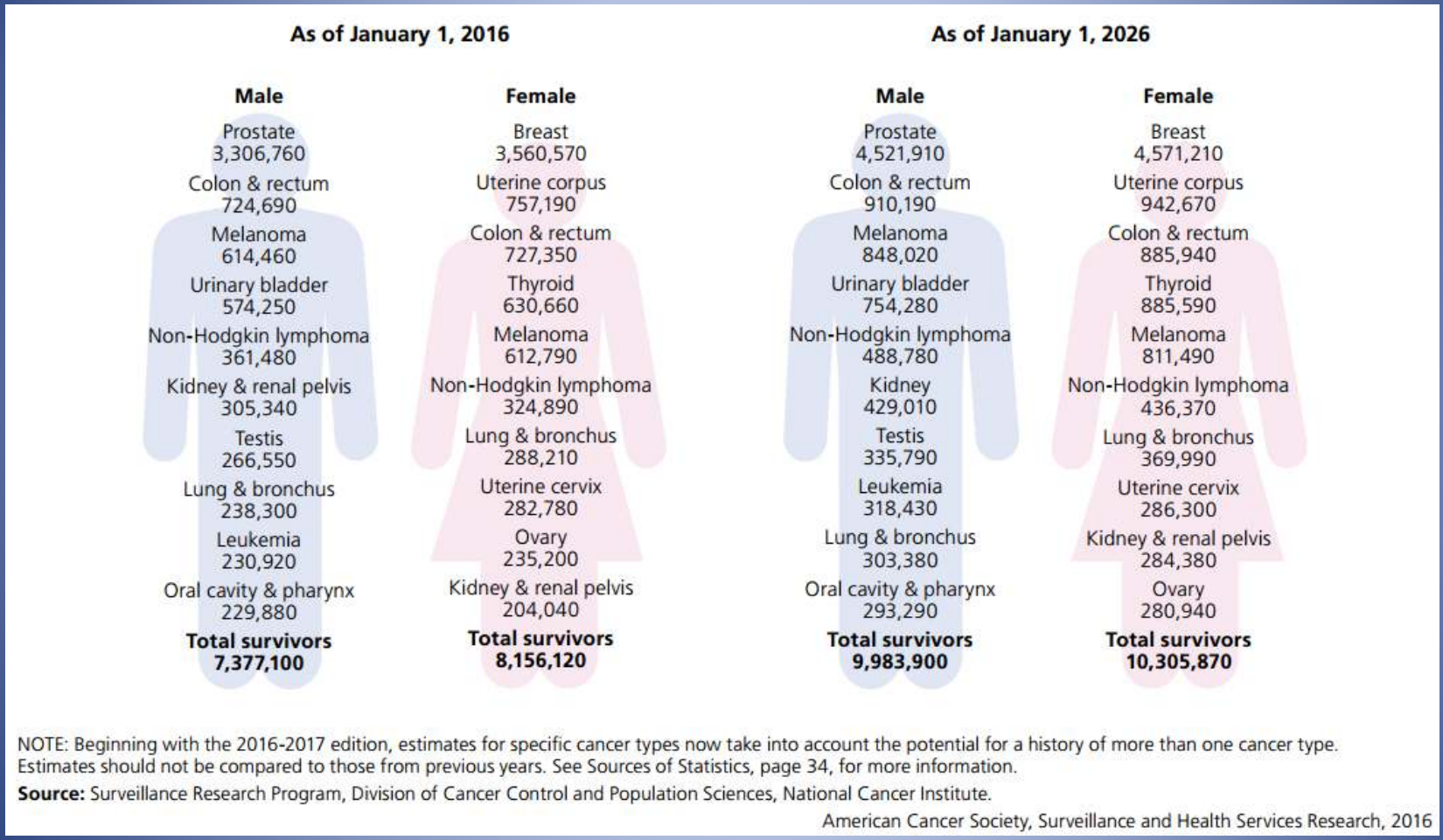
Source: National Vital Statistics System

Links between Cancer and CVD



Handy *et al. Circ*. 2018

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

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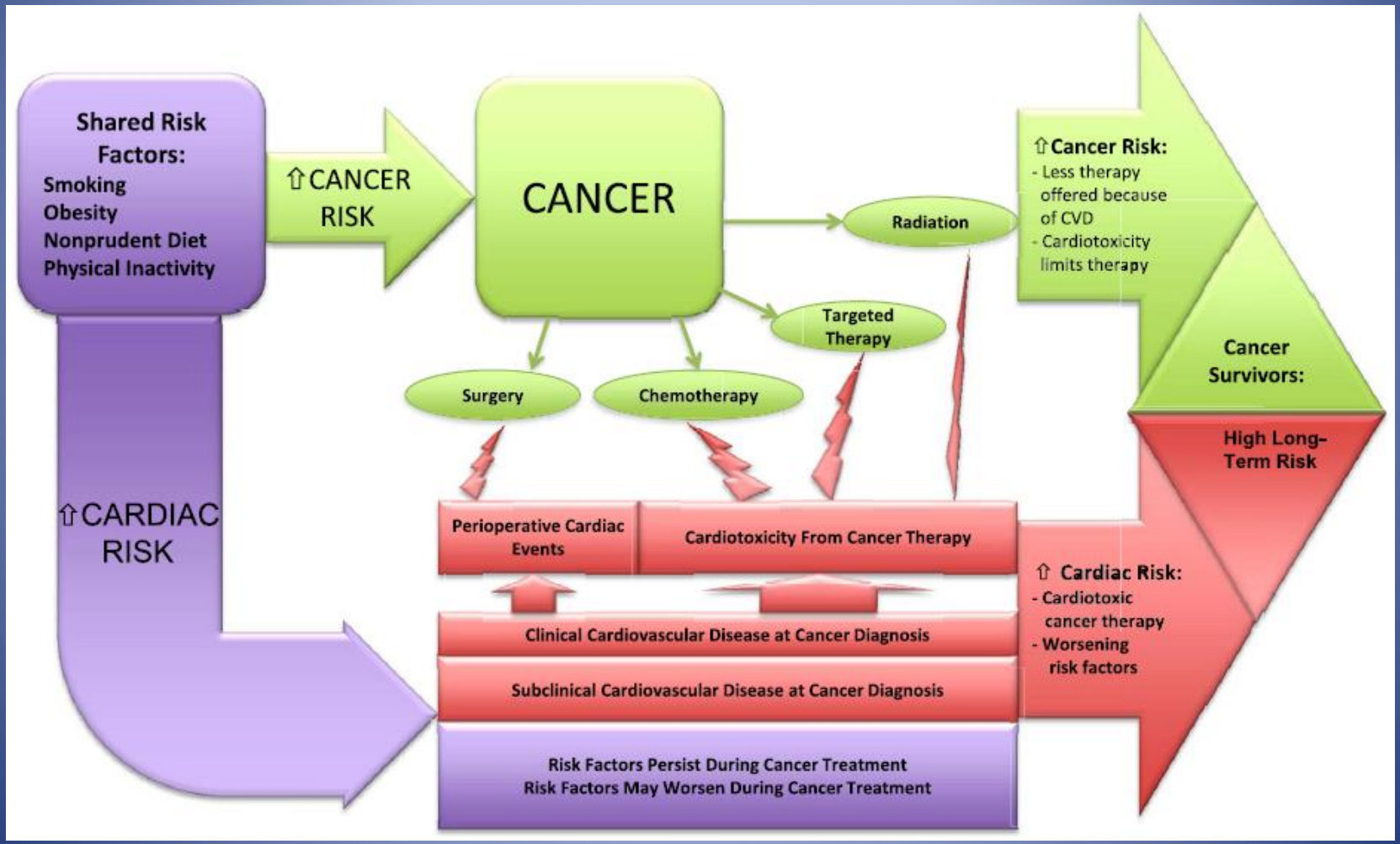
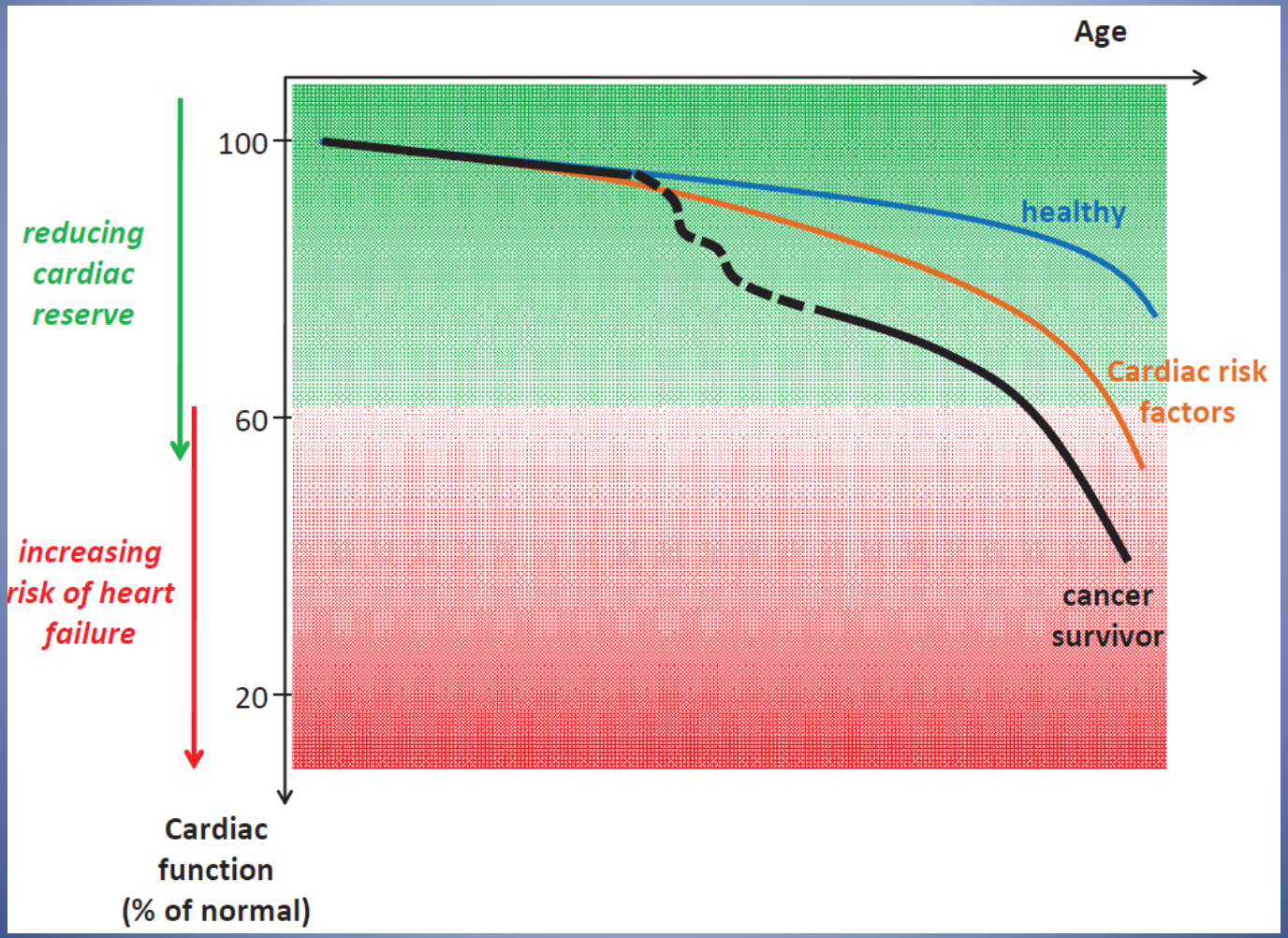
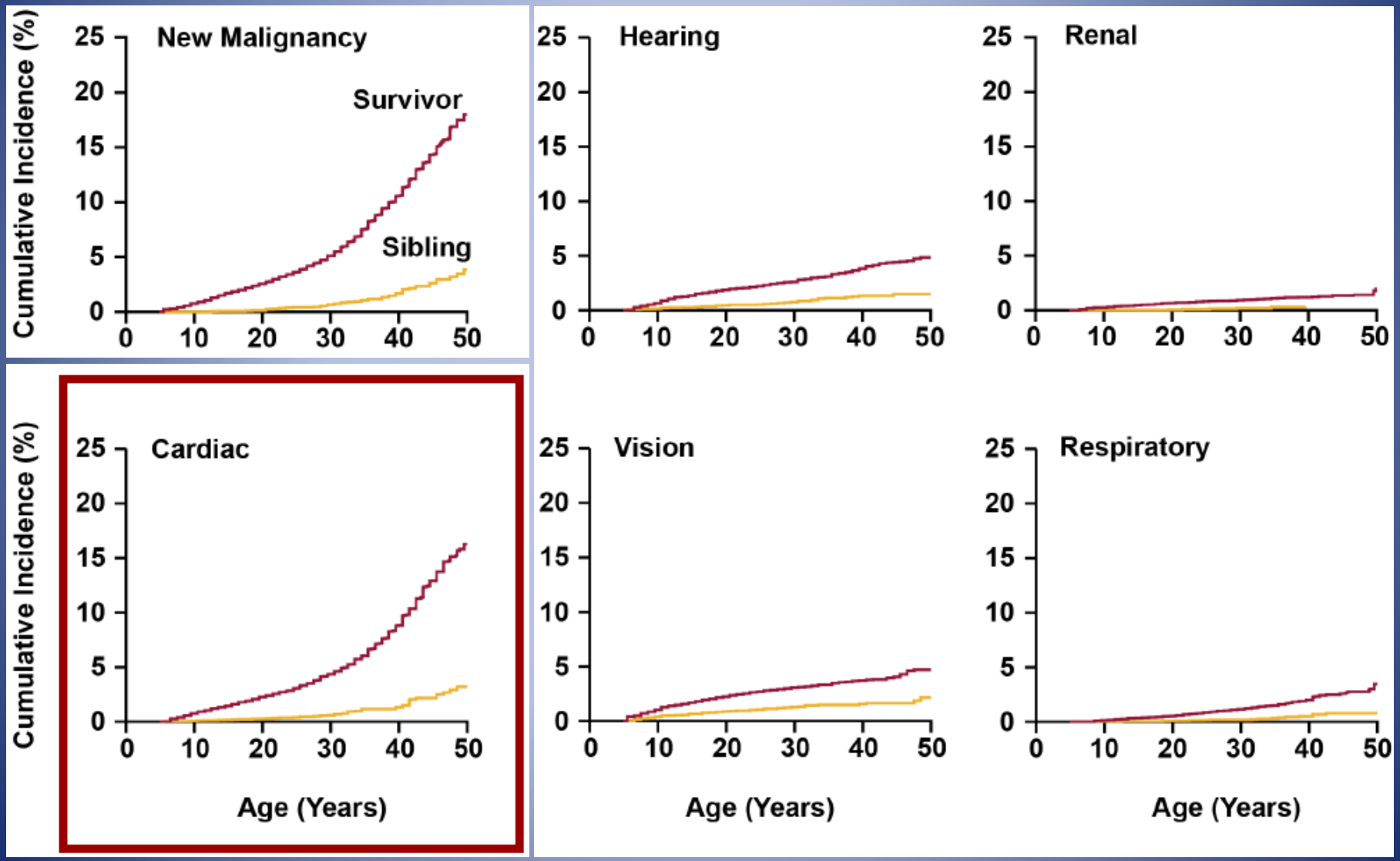
Interactions between Heart Disease, Risk Factors, Cancer, Cancer Therapy



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



Survivors of Childhood Cancer: Cumulative Incidence by Organ Systems



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

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)

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

Anti-Cancer Agents Associated with Heart Failure & Left Ventricular Dysfunction

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/Treatment
Anthracyclines			
Doxorubicin	++++	3-26	Monitor EF, GLS, troponin dexrazoxane, continuous infusion, liposomal preparation, BB/ACEI
Epirubicin	+	0.9-3.3	
Idarubicin	++	5-18	
Alkylating agents			
Cyclophosphamide	++++	7-28	
Ifosfamide	+++	17	
Antimetabolites			
Decitabine	++	5	
Clofarabine	+	27	
Antimicrotubule agents			
Docetaxel	++	2.3-8.0	
Monoclonal antibody-based tyrosine kinase inhibitors			
Trastuzumab	+++	2-28	Avoid concomitant use with anthracyclines
Bevacizumab	++	1.0-10.9	
Adotrastuzumab emtansine	+	1.8	
Pertuzumab	+	0.9-16.0	
Small molecule tyrosine kinase inhibitors			
Pazopanib	++++	0.6-11.0	Treat hypertension aggressively
Ponatinib	+	3-15	Ischemia workup and treatment
Sorafenib	++++	1.9-11.0	
Dabrafenib	++++	8-9	
Sunitinib	++++	1-27	
Dasatinib	++++	8-9	
Lapatinib	++++	0.9-4.9	
Trametinib	++++	7-11	
Proteasome inhibitor			
Carfilzomib	++	7	
Bortezomib	++	2-5	
Miscellaneous			
Tretinoin	++++	6	

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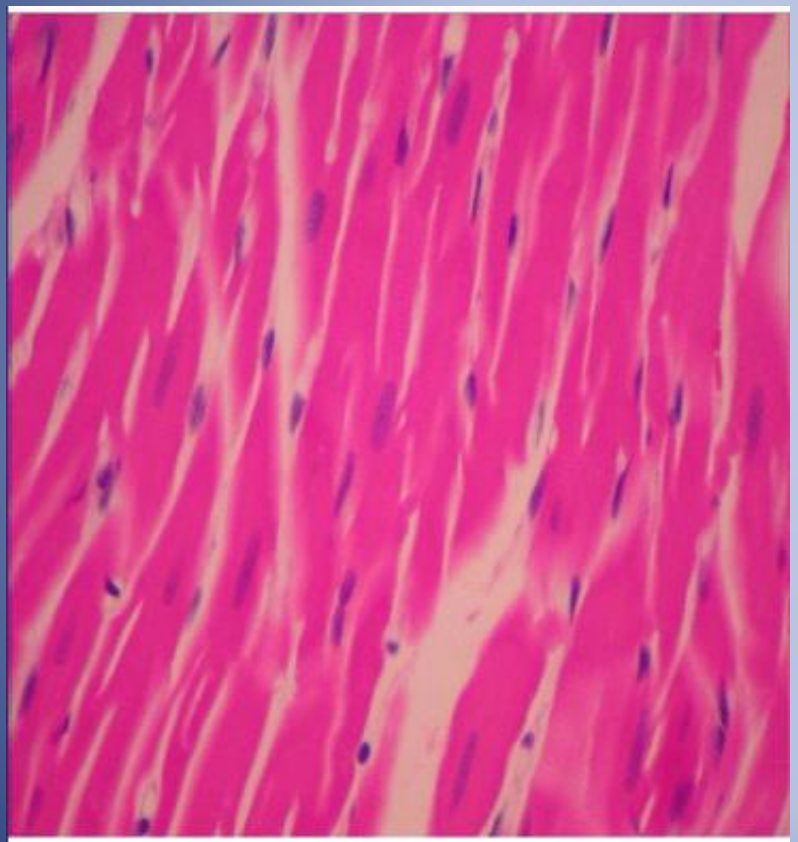
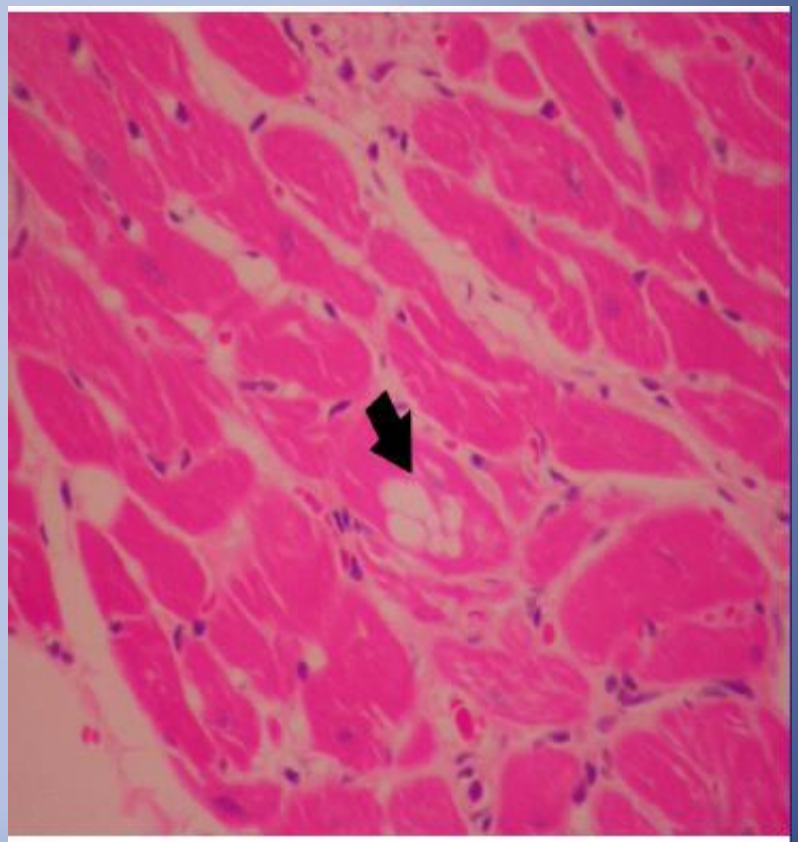
Chang, …. Okwuosa, Yeh, JACC 2017

Vacuolization with Reduced Ejection Fraction due to Anthracycline Cardiotoxicity



Normal Saline Control



Doxorubicin with LVEF Drop

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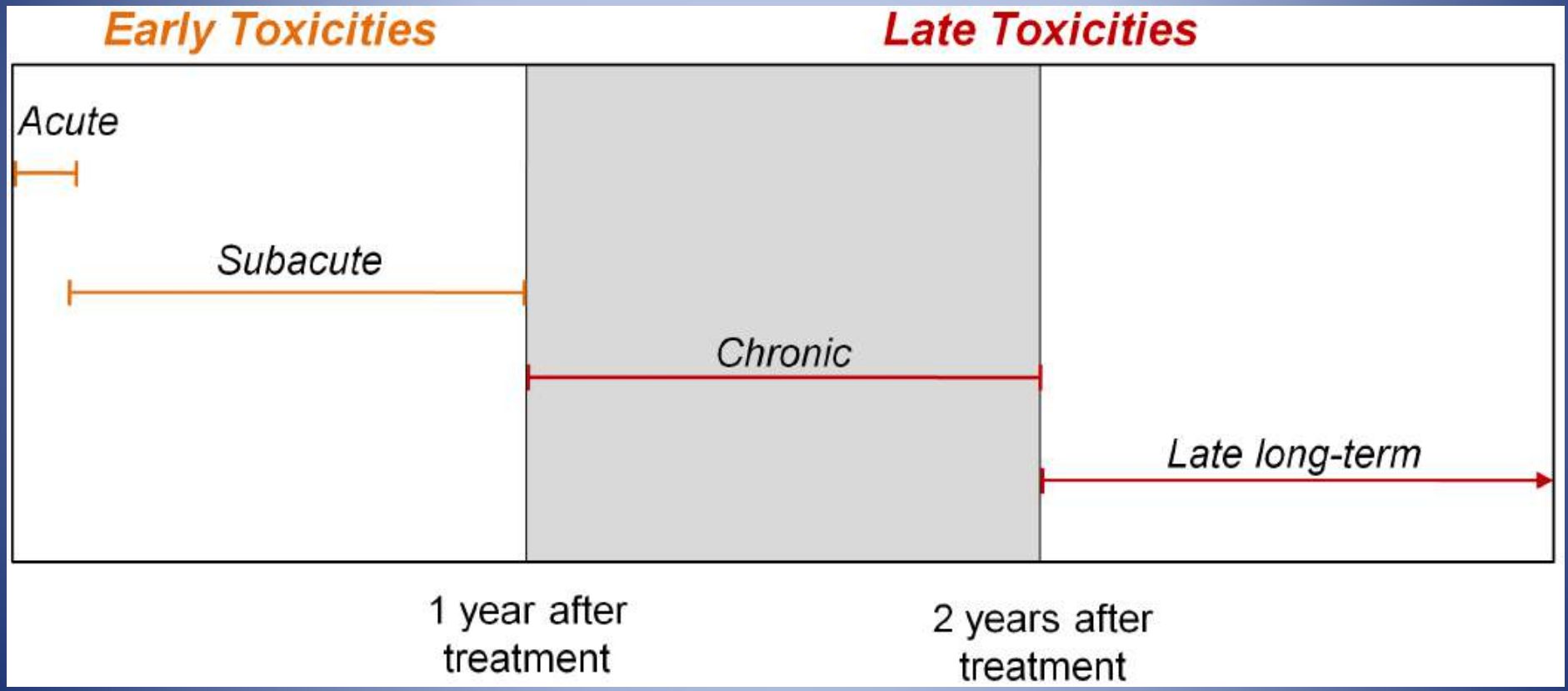
Lightfoot *et al,* Circ. Cardiovasc. Imag. 2010

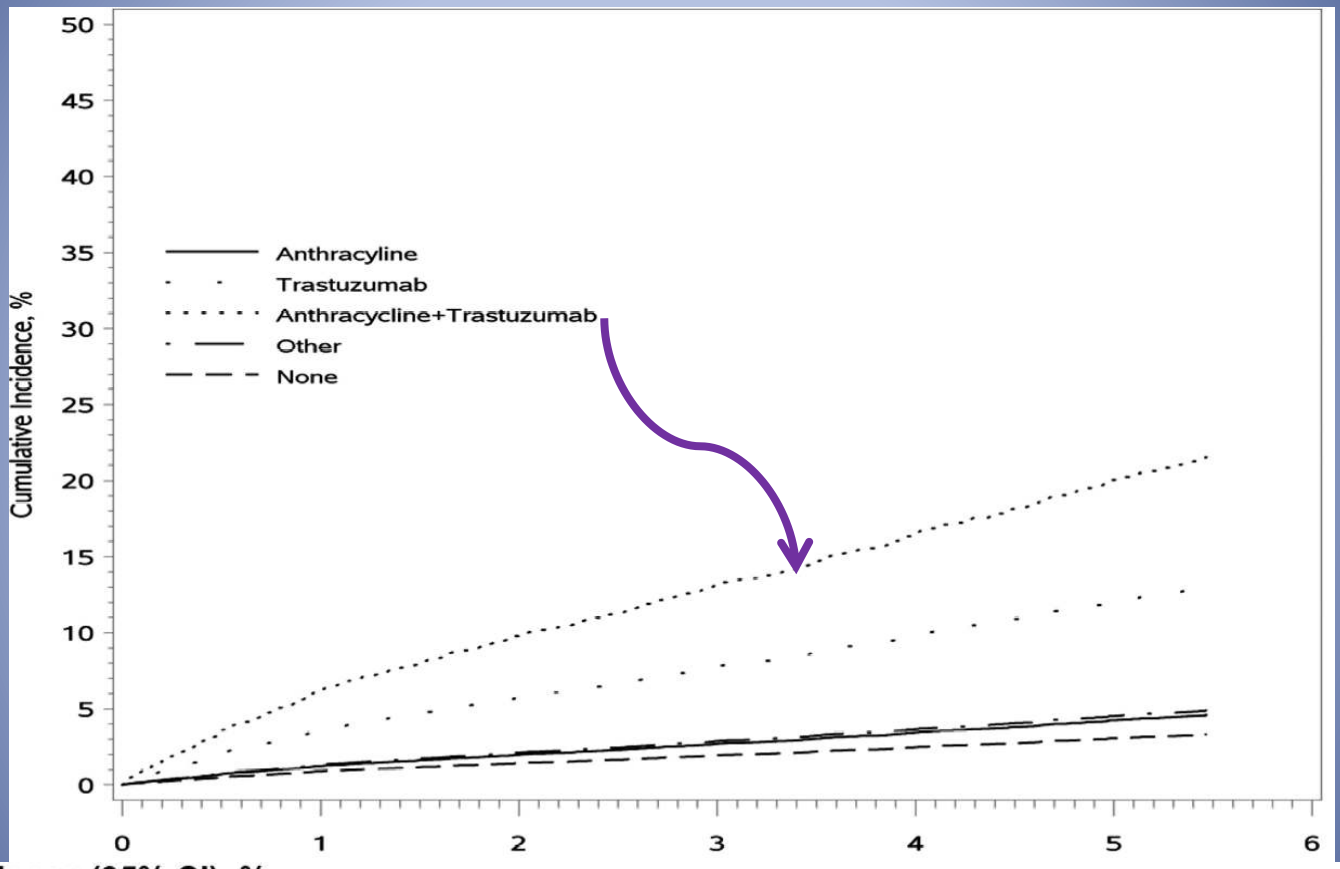
Timing of Injury:

Breast Cancer, Sarcoma, Leukemia, Lymphoma, Prostate Cancer



Hundley 2012

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

Prognostic performances of BNP and LVEF in predicting CHF hospitalizations and Death in Anthracycline Treated Cancer Patients

CHF

	BNP>100 pg/ml	BNP>30 pg/ml	LVEF<50%	LVEF<45%
Sensitivitet	**38** (20–59)	**81** (58–94)	**48** (27–68)	**29** (13–72)
Specificitet	**92** (91–93)	**62** (61–63)	**91** (90–93)	**98** (97–99)
PPV	**24** (13–38)	**13** (09–15)	**27** (16–39)	**46** (21–72)
NPV	**96** (94–97)	**98** (96–99)	**96** (95–98)	**95** (94–96)
p value	*0.000*	*0.000*	*0.000*	*0.000*

Death

	BNP>100 pg/ml	BNP>30 pg/ml	EF<50%	EF<45%
Sensitivitet	**13** (10–15)	**48** (43–52)	**11** (08–14)	**05** (03–06)
Specificitet	**94** (90–97)	**69** (63–75)	**89** (85–93)	**97** (94–99)
PPV	**76** (58–88)	**68** (61–75)	**59** (43–74)	**69** (39–90)
NPV	**44** (42–46)	**49** (44–53)	**42** (40–44)	**42** (41–43)
p value	*0.032*	*0.002*	*0.87*	*0.569*

N = 333, Mean follow up 1360 days

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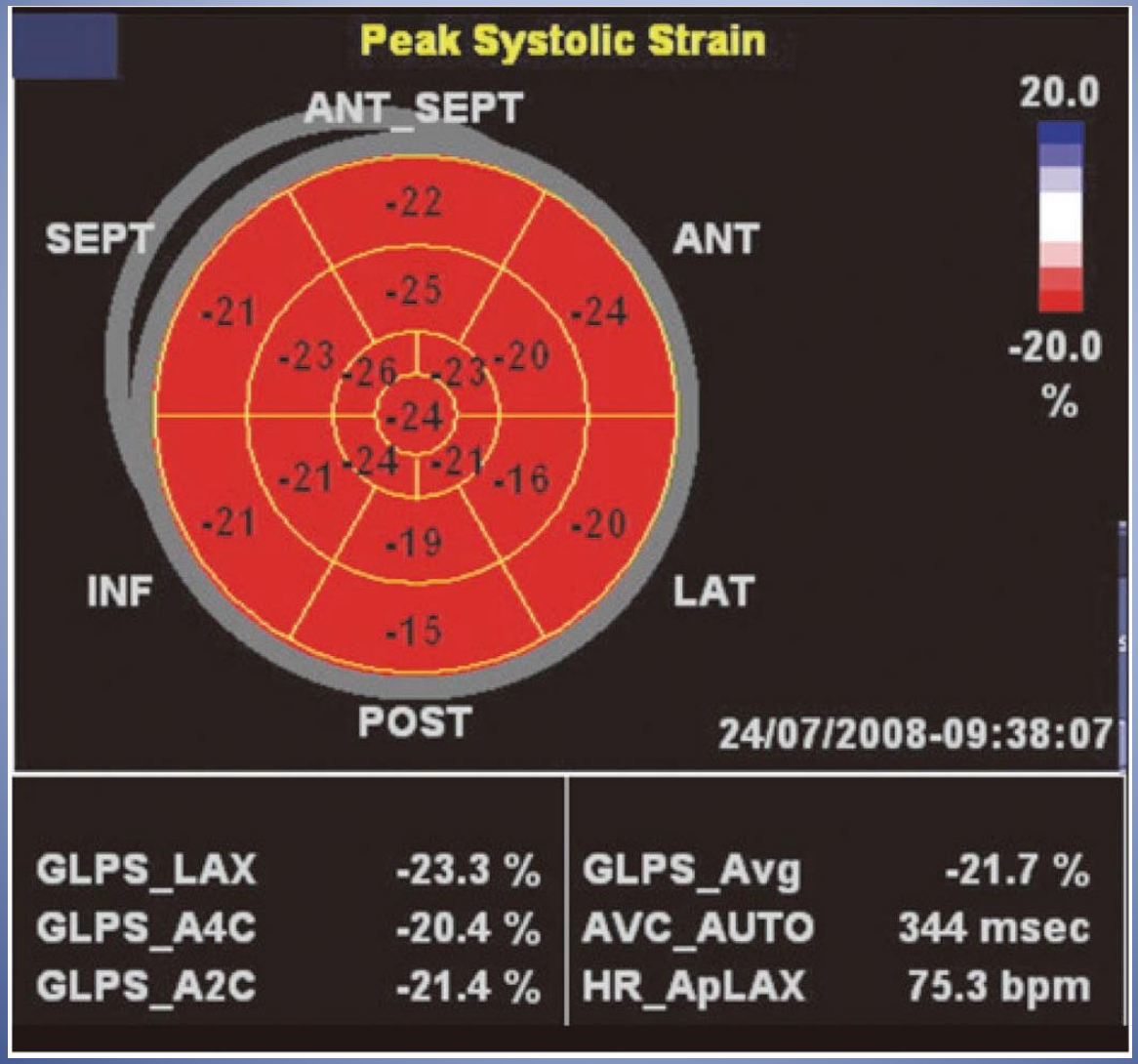
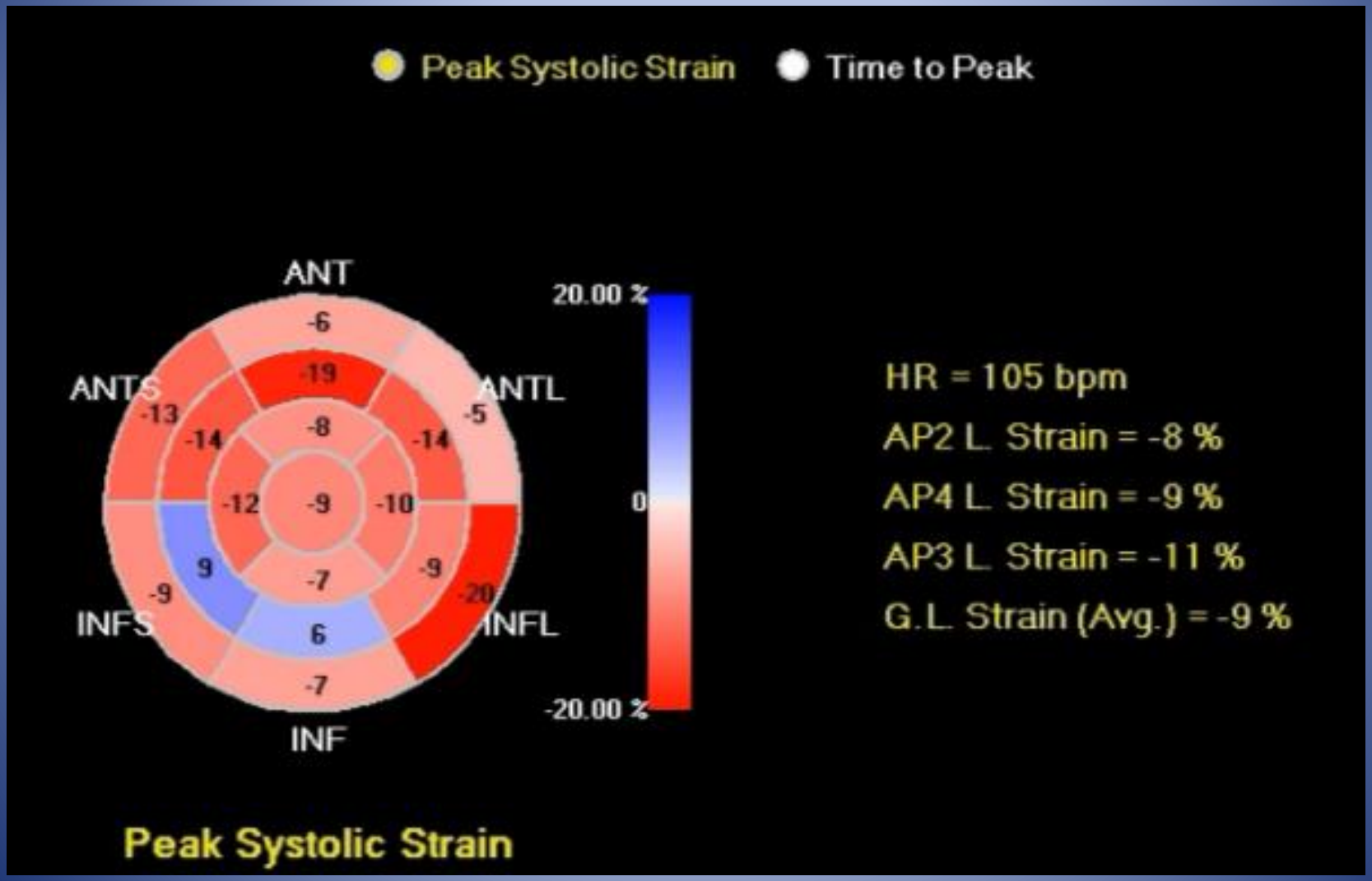
Skovgaard *et al.* Plus One. 2014

Normal LV Myocardial Global and Segmental Longitudinal Strain Data

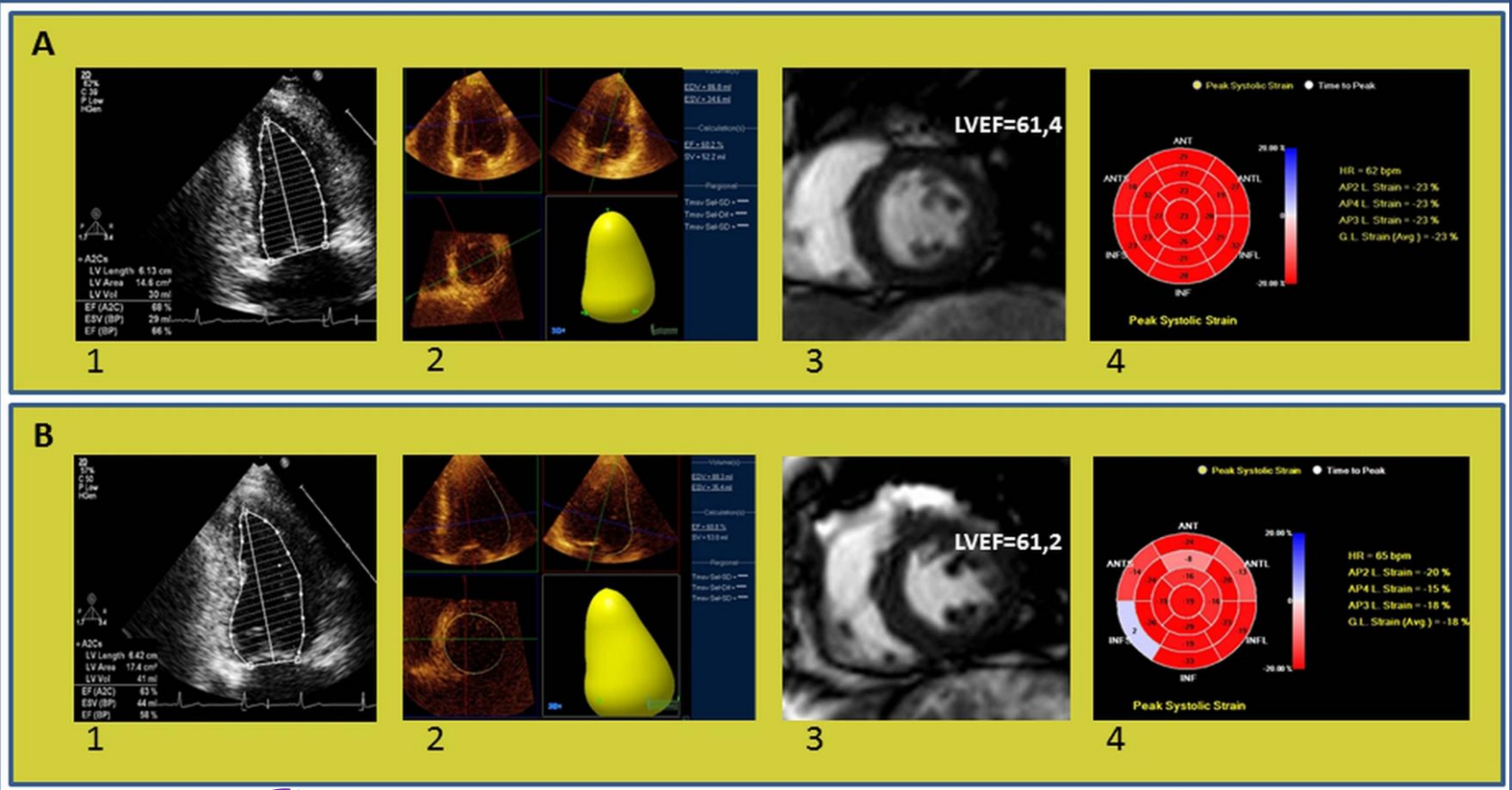


Feigenbaum *et al,* Circulation J. 2012

Chemotherapy Cardiomyopathy



Strain: Prediction of Chemo Cardiotoxicity



C	baseline	3w	6w	9w	3m	6m	9m	12m
NT-proBNP (ng/ml)	**310,4**	191,5	384,9	327,2	**540,6**	377,6	192,2	334,10
BPEF(%)	66	63	59	61	64	59	62	58
GLS (%)	**-23**	-25	-22	-24	**-20**	-17	-18	-19

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Kerkhove *et al,* Heart 2014

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%)

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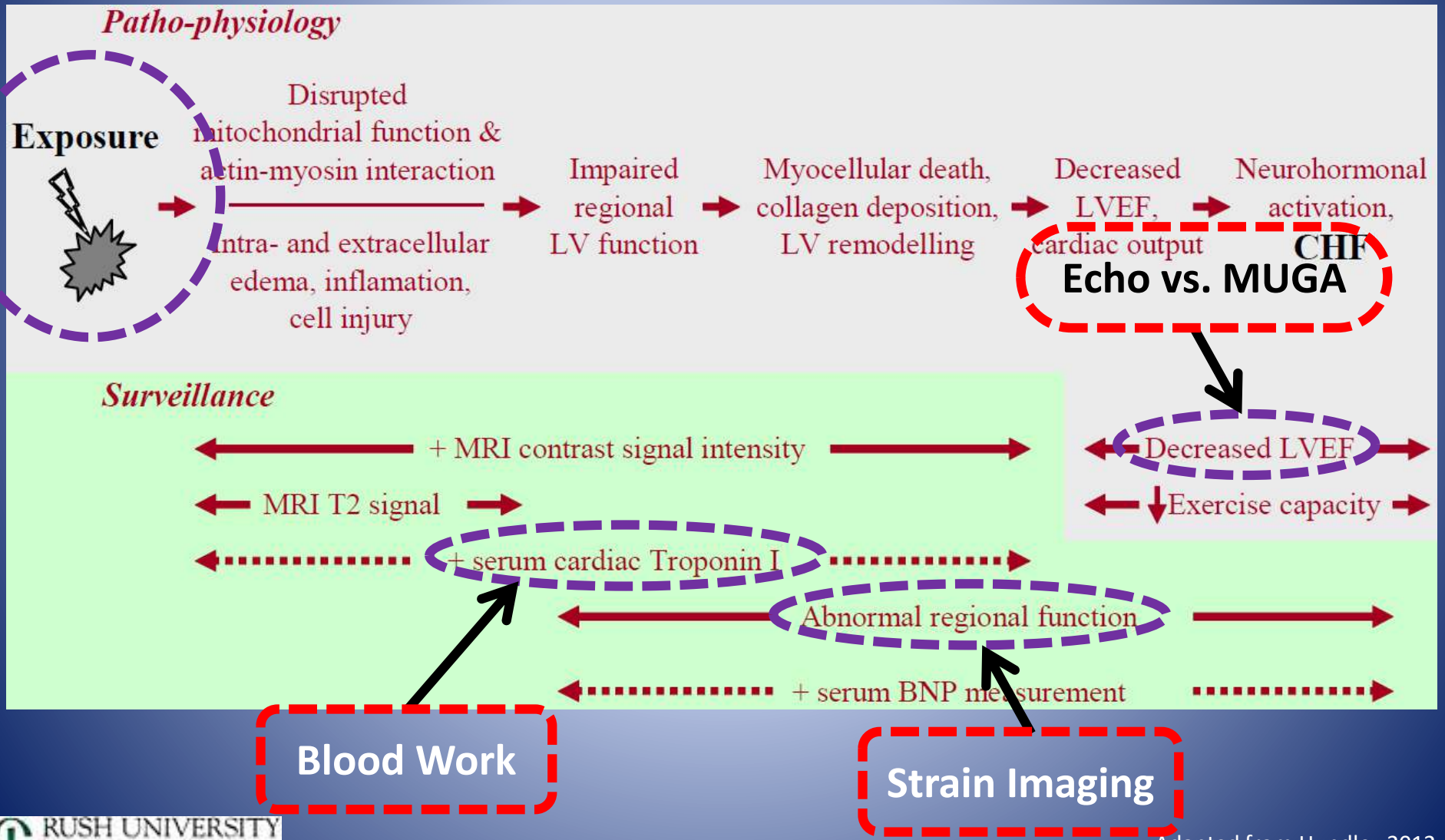
Sawaya *et al, Circulation Cardiovasc. Img.* 2012

Strength of Evidence of Cardiac Markers

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)	++++

Silver, Palomo, Okwuosa 2016

Testing Based on Pathophysiology



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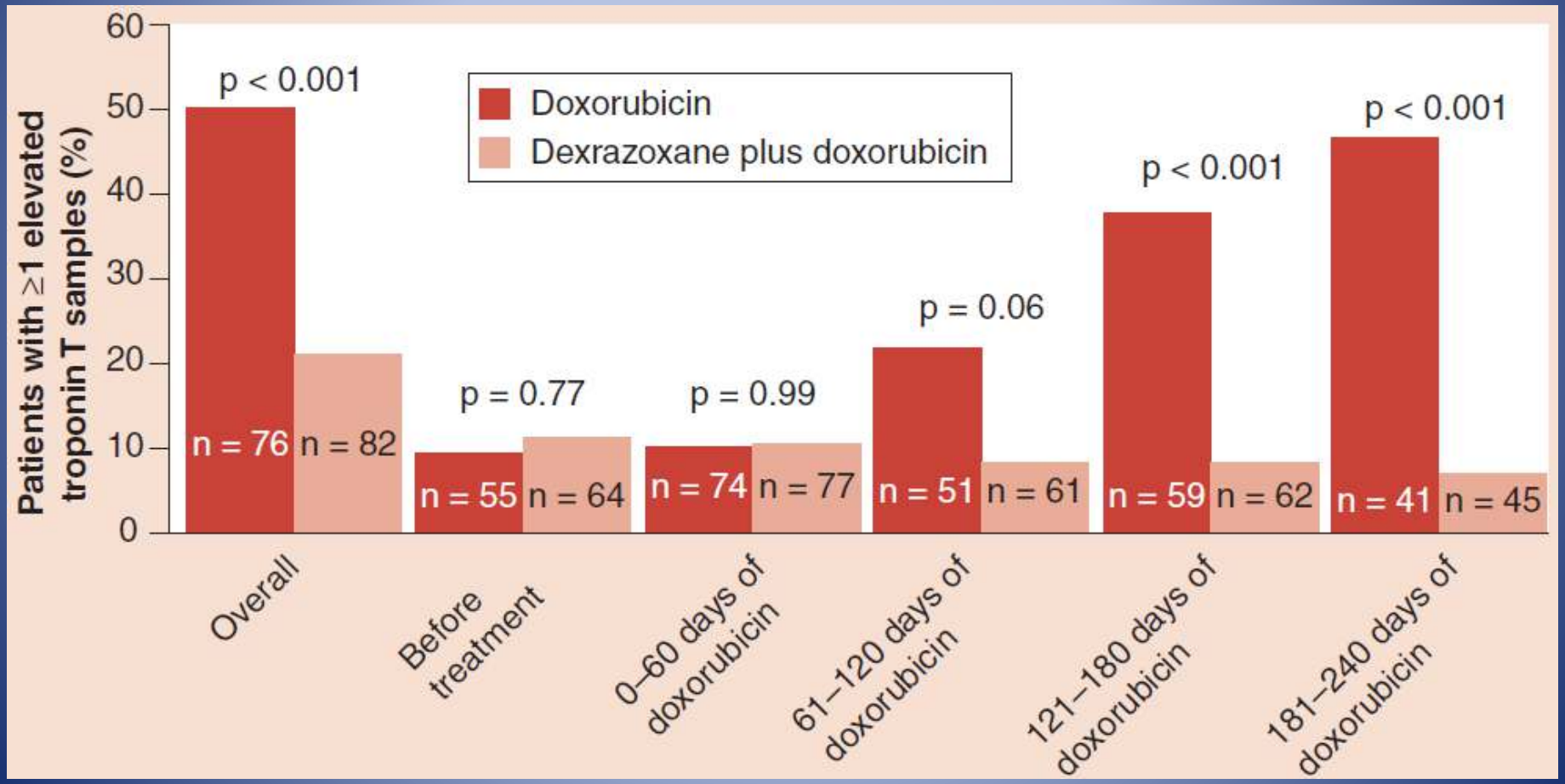
Adapted from Hundley 2012

Dexrazoxane for Preventing Doxorubicin-Induced Cardiotoxicity



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Harake *et al, Future Cardiol.* 2012

ACE-Is/ARBs for Prevention of Chemotherapy-Induced Cardiotoxicity

Study	Year	Cohort	F/u time	Cardiotoxic chemotherapy	Radiation therapy	Preventive therapy	Cardiotoxicity definition	Outcome with vs without previous therapy
Silber et al (AAA study),[131] 2004	2004	Pediatric cancer survivors with ≥1 cardiac abnormalities in f/u (n=135)	35 mo	Anthracyclines 300 mg/m^2	36%	Enalapril 0.05-0.15 mg/kg per d	FS (%) LVESWS (g/cm^2) MCI (L/min per m^2)	Interaction term (change due to treatment) P=.84 Interaction term (change due to treatment) P=.28 Interaction term (change due to treatment) P=.55
Cardinale et al,[132] 2006	2006	HDC (n=114, 60% NHL and breast cancer) + cTnI >ULN within 3 d of any cycle	12 mo	Various, cumulative doxorubicin equivalent dose 335 mg/m^2	11%	Enalapril 2-20 mg/d, administered after cTnI elevation and continued in f/u	LVEF decrease >10% to <50%, rate (%) HF rate (%) Arrhythmia rate (%)	0 vs 43[b] 0 vs 24[b] 2 vs 17[b]
Nakamae et al,[133] 2005	2005	NHL (n=40)	Day 3 after initiation	CHOP	0%	Valsartan 80 mg/d, administered and continued with CT	LVEDD (mm) BNP (pmol/L) QTc interval (ms)	45 vs 49[b] 30 vs 80[b] 420 vs 435[b]
Dessi et al,[134] 2011	2011	Various (n=49, breast cancer 37%)	12 mo	Epirubicin 400 mg/m^2	0%	Telmisartan 40 mg/d, administered 1 wk before and continued 6 mo after CT	Strain rate	1.75 vs 1.5[b]

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

Beta Blockers for Prevention of Chemotherapy-Induced Cardiotoxicity

Study	Year	Cohort	F/u time	Cardiotoxic chemotherapy	Radiation therapy	Preventive therapy	Cardiotoxicity definition	Outcome with vs without previous therapy
Seicean et al,[124] 2013	2013	Breast cancer (n=318)	3±2 y	Anthracyclines and/or Herceptin	59%	Any BB therapy during CT	Rate of new HF admission (%)	4.7 vs 12.7[b] (HR, 0.2; 95% CI, 0.1-0.7)
Randomized controlled trials								
Kalay et al,[125] 2006	2006	Breast cancer (68%), lymphoma (18%)	6 mo	Anthracyclines: doxorubicin 520 mg/m^2 or epirubicin 780 mg/m^2	0%	Carvedilol 12.5 mg/d, administered before CT and continued for 6 mo	LVEF (%)	Carvedilol: no change; Control: significant decrease (68.9-52.3[b])
El-Shitany et al,[126] 2012	2012	Children with ALL (n=50)	1 wk after CT	Doxorubicin 120 mg/m^2	0%	Carvedilol 0.1-1 mg/d, administered 5 d before CT	FS (%) GPSS (%) cTnI (ng/mL)	39.5±6.3 vs 33.5±6.2[b] −19.3±2.0 vs −15.1±1.8[b] 0.02±0.02 vs 0.06±0.05[b]
Elitok et al,[127] 2013	2013	Breast cancer (n=80)	6 mo	Anthracyclines 520 mg/m^2	0%	Carvedilol 12.5 mg/d, administered before CT and continued for 6 mo	Peak systolic strain, septal (%) Peak systolic strain, lateral (%) LVEF (%)	20±5.3 vs 16±4.3[b] 18±5.6 vs 14±6.1[b] 64±5.1 vs 63±4.8
Kaya et al,[128] 2012	2013	Breast cancer (n=45)	6 mo	Anthracyclines: doxorubicin 246 mg/m^2 or epirubicin 354 mg/m^2	27%	Nebivolol 5 mg/d, administered 7 d before CT and continued for 6 mo	LVEF (%) NT-proBNP (pmol/L)	63.8±3.9 vs 57.5±5.6[b] 152±69 vs 204±73[b]
Georgakopoulos et al,[129] 2010	2010	HL and NHL (n=125)	12 mo 30 mo	ABVD R-CHOP	21%	Metoprolol 25-50 mg BID or enalapril 2.5-10 mg BID, administered with CT	New HF rate (%)	2.4 or 4.7 vs 0 (*P*=.56)
Bosch et al (OVER-COME trial),[130] 2013	2013	Acute leukemia (n=36) or HSCT (n=54)	6 mo	Anthracyclines (40% before, 40% during, cumulative 265 mg/m^2)	18%	Carvedilol (6.25-25 mg BID) and enalapril (2.5-10 mg BID), administered 24 h before CT and continued in f/u	LVEF (%), absolute change by TTE LVEF (%), absolute change by CMR imaging	−0.17 vs −3.28[b] 0.36 vs −3.04 (*P*=.09)

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

Statins for Prevention of Chemotherapy-Induced Cardiotoxicity

Study	Year	Cohort	F/u time	Cardiotoxic chemotherapy	Radiation therapy	Preventive therapy	Cardiotoxicity definition	Outcome with vs without previous therapy
Observational studies								
Seicean et al,[123] 2012	2012	Breast cancer (n=628)	2.6±1.7 y	Anthracyclines	66%	Any statin therapy during CT	Rate of new HF admission (%)	6.0 vs 17.2[b] (HR, 0.3; 95% CI, 0.1-0.9)
Acar et al,[124] 2011	2011	Various (n=40)	6 mo	Anthracyclines: doxorubicin 256 mg/m^2; idarubicin 297 mg/m^2	NA	Atorvastatin 40 mg/d, administered before and continued for 6 mo after CT	LVEF (%), absolute change LVEDD (mm), absolute change LVESD (mm), absolute change	1.3 vs −7.9[b] −0.15 vs 2.0[b] −1.35 vs 2.1[b]

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

Anti-Cancer Agents Associated with Hypertension

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Monoclonal antibody-based tyrosine kinase inhibitors			Pre-treatment risk assessment
Bevacizumab	+++	4–35	
Ado-trastuzumab emtansine	+	5.1	BP goal <140/90 mm Hg
Monoclonal antibodies			Weekly BP monitoring in 1st cycle
Alemtuzumab	+	14	
Ibritumomab	NA	7	Every 2–3 weeks BP monitoring for duration of therapy
Ofatumumab	+	5–8	
Rituximab	+++	6–12	
mTor inhibitors			Initiate BP treatment when diastolic BP increases by 20 mm Hg
Everolimus	++++	4–13	
Temsirolimus	++	7	
Small molecule tyrosine kinase inhibitors			More than 1 anti-HTN medication may be needed
Pazopanib	++++	42	
Ponatinib	+	68	
Sorafenib	++++	7–43	Avoid diltiazem and verapamil with sorafenib
Sunitinib	++++	5–24	
Axitinib	++++	40	
Cabozantinib	NA	33–61	Hold chemotherapy as the last resort
Ibrutinib	++++	17	
Nilotinib	++++	10–11	Hold bevacizumab if systolic BP >160 mm Hg or diastolic BP >100 mm Hg
Ramucirumab	+	16	
Regorafenib	++++	30–59	
Trametinib	++++	15	
Vandetanib	NA	33	Early consultation with cardiologist
Ziv-aflibercept	+	41	
Proteasome inhibitors			
Bortezomib	++	6	
Carfilzomib	++	11–17	
Antimetabolites			
Decitabine	++	6	

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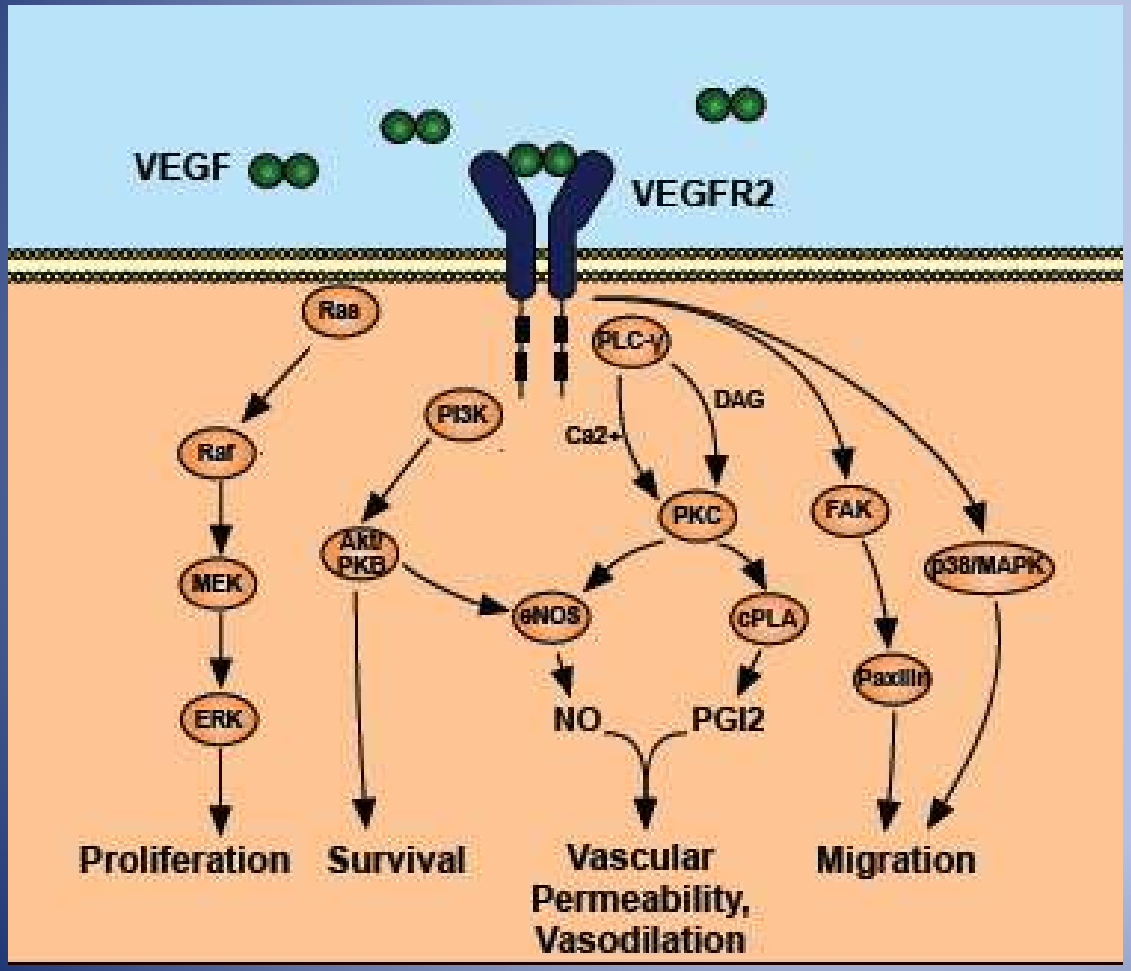
Chang, Okwuosa,… Yeh, JACC 2017

VSP Inhibitors: Mechanism of Action and Effects



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

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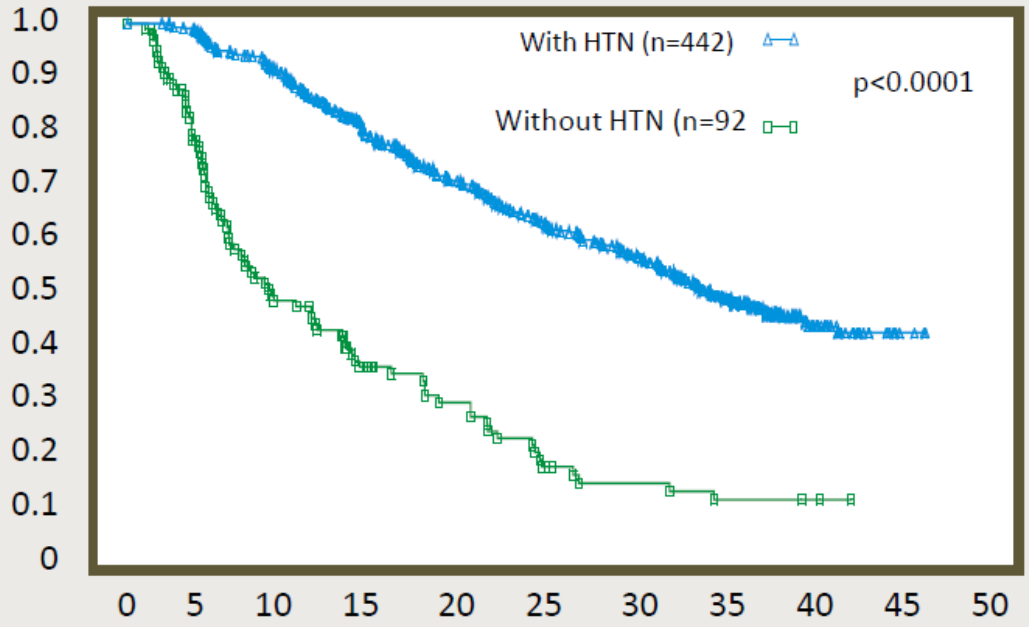
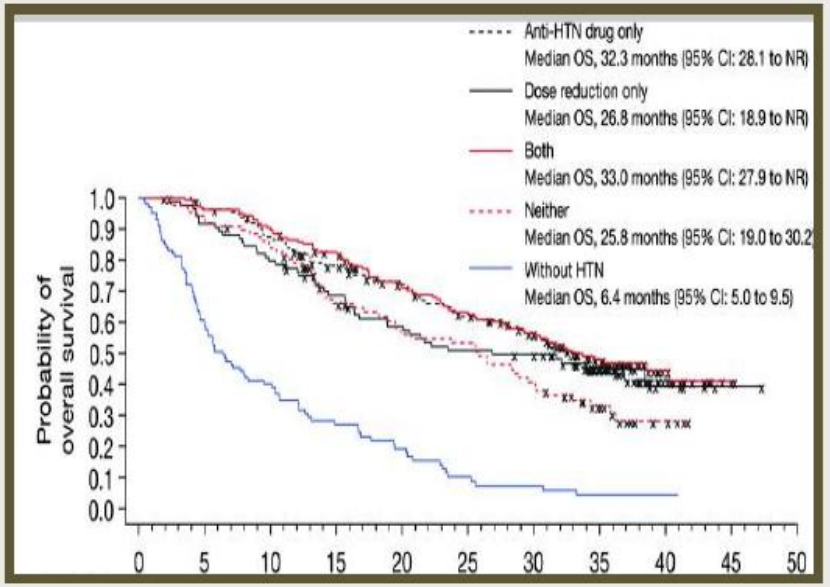
Mouhayar 2012

Hypertension: A Biomarker of TKI Efficacy and/or Cardiotoxicity?

1- Sunitinib-associated HTN was significantly and independently associated with improved clinical outcome.



2- Treatment of HTN did not have a negative impact on cancer management and response



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Rini *et al, JNCI* 2011

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)

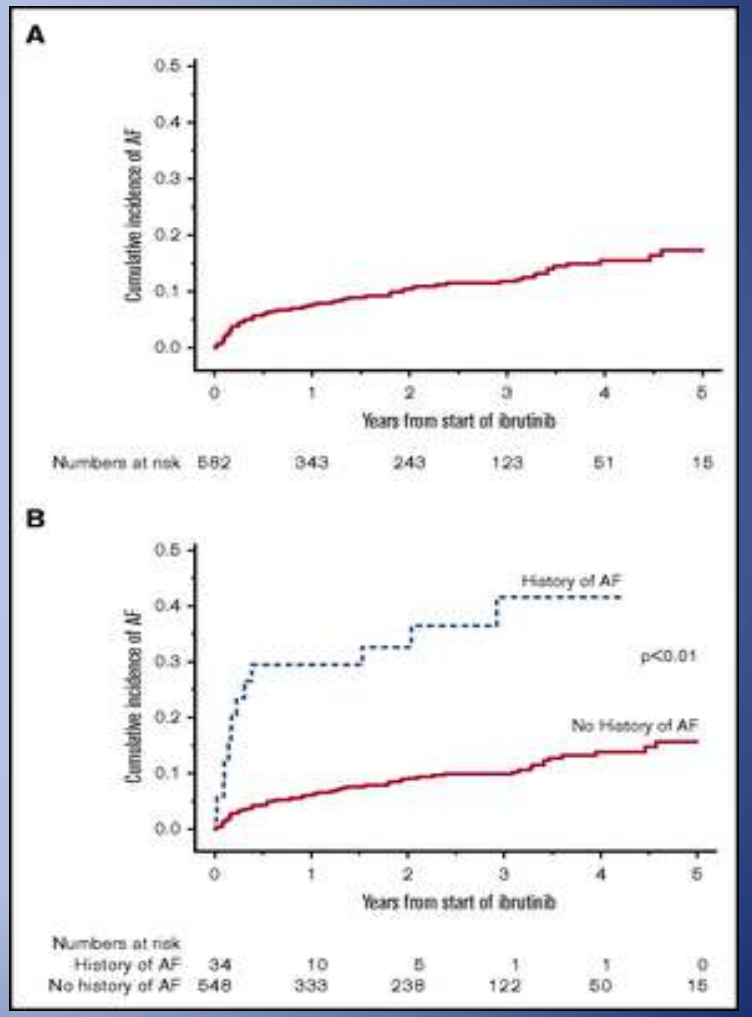
Bair *et al,* Trends in Cardiovascular Medicine 2013

Others

- Arrhythmias: Ibrutinib
- Peripheral arterial disease: nilotinib, ponatinib

Ibrutinib and Atrial Fibrillation

- Retrospective single center study
- 582 patients treated with ibrutinib for hematological malignancies were included
- Median follow-up of 32 months
- 63 patients developed incident AF
- 13 patients developed recurrent AF
- The estimated cumulative incidence of AF at
  - 6 months: was 5.9% (95% CI: 4.2-8.0)
  - 1 year: 7.5% (95% CI: 5.5-9.9
  - 2 years: 10.3% (95% CI: 8.0-13)
- Median time of onset
  - Incident AF: 10.9 months (range 0.2-63.4)
  - Recurrent AF and 2.2 months (range 0.2-35.2)



Wiczer et al 2017

TKIs associated with PAD

	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
PAOD		++		+/−	++
IHD/CVA		+			+
VTE					+
Pulmonary hypertension			+		
Platelet dysfunction			+		+
Hypertension				+	++
Hyperglycemia [a]		+			
Dyslipidemia [a]		+			

- Ponatinib: ALERT: US Boxed Warning
  - Arterial occlusion
  - Heart failure
  - Hepatotoxicity
  - Venous thromboembolism

Pasvolsky et al. Cardio-Oncology (2015)

Management and screening strategies for TKI-associated vascular adverse events

Strategy	Comments
1. Prevention and risk assessment	
Cardiovascular risk scoring for VAE risk stratification	a) For example, the European Society of Cardiology (ESC) 2012 classification b) Reliability of such a stratification in guiding TKI drug choice is uncertain
Atherosclerosis risk factor monitoring and management (hypertension, diabetes mellitus, dyslipidemia, smoking etc.)	a) Use of accepted guidelines b) Especially important for nilotinib and ponatinib
Echocardiogram	Especially relevant for dasatinib as PAH screening
2. Monitoring tools	
Periodic cardiovascular risk score	
Atherosclerosis risk factor surveillance (hypertension, diabetes, dyslipidemia, smoking etc.)	
Subclinical radiological and/or laboratory markers	a) May include ABI, US Doppler of selected blood vessels, IMT measurement b) Clinical implication still investigational. c) ABI is the most commonly used screening measure in clinical practice
3. Treatment	
Specific treatment for vascular toxicity	Interdisciplinary approach (vascular surgeons, cardiologists/neurologists)
CML treatment modification options:	Factors to be considered:
a) Drug continuation with increased vigilance b) Drug discontinuation, choosing different TKI c) Dose reduction	a) Patient-related factors b) VAE-related factors c) Disease-related factors

Pasvolsky et al. Cardio-Oncology (2015)

Anti-Cancer Agents Associated with Myocardial Infarction/Ischemia

Chemotherapy Agents	Frequency of Use	Incidence (%)	Prevention/ Treatment
Antimetabolites			
Capecitabine	++++	3-9	Ischemia workup and treatment
Flourouracil	++++	1-68	
Monoclonal antibody-based tyrosine kinase inhibitors			
Bevacizumab	+++	0.6-8.5	
Small molecule tyrosine kinase inhibitors			
Nilotinib	++++	5.0-9.4	
Ponatinib	+	12	
Angiogenesis inhibitors			
Lenalidomide	+++	0-1.9	
Antimicrotubule agents			
Paclitaxel	++++	<1.5	

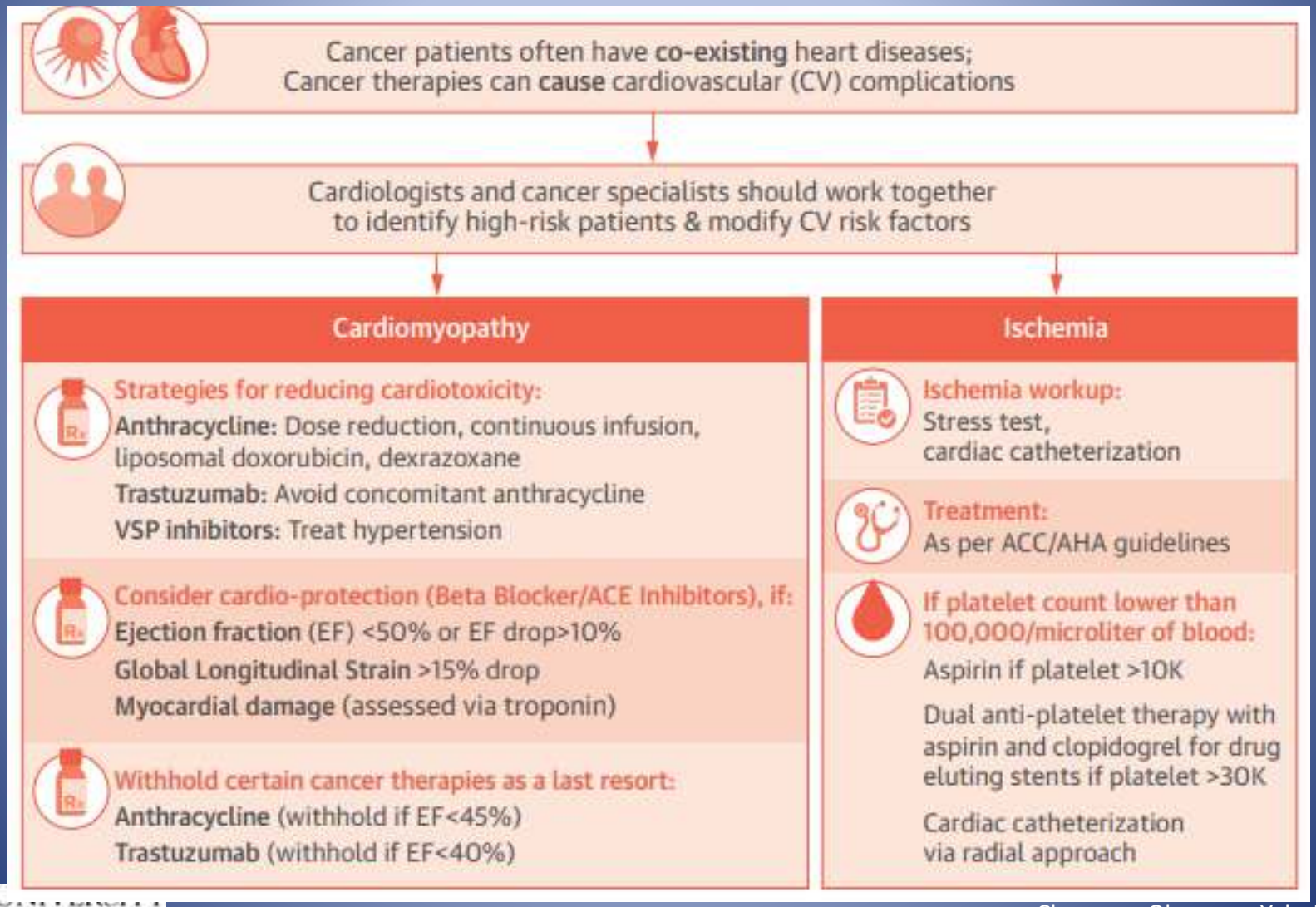
Chang, …. Okwuosa, Yeh, JACC 2017

Anti-Cancer Agents Associated with Thromboembolism

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Alkylating agents			Risk factors: cancer types, metastatic disease, central venous catheter, heart failure, immobility, AF, previous history of thromboembolism, chemotherapy, hormonal therapy, old age, female
Cisplatin	+++	8.5–16.7	
Angiogenesis inhibitors			
Lenalidomide	+++	3–75	
Thalidomide	++	1–58	
Pomalidomide	+	3	
Histone deacetylase inhibitor			
Vorinostat	++++	4.7–8.0	
Monoclonal antibody against VEGF			Diagnosis: compression ultrasonography, spiral CT, MR
Bevacizumab	+++	6.0–15.1	
mTOR inhibitors			
Everolimus	++++	1–4	Treatment options: aspirin, warfarin, LMWH
Small molecule tyrosine kinase inhibitors			
Axitinib	++++	3	Limited data with DOAC
Dabrafenib	++++	7	
Erlotinib	++++	3.9–11.0	
Nilotinib	++++	1–10	
Pazopanib	++++	1–5	
Ponatinib	+	5	
Sunitinib	++++	3	
Trametinib	++++	7	
Ziv-aflibercept	+	9	

Chang, Okwuosa,… Yeh, JACC 2017

Management of Cancer Therapy–Induced Cardiovascular Complications



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Considerations in Patients with Thrombocytopenia

PLATELET TRANSFUSION THRESHOLDS:

- There is no established cutoff point for platelet count below which a coronary angiography is absolutely contraindicated
- Prophylactic platelet transfusion should be used only when oncologic indications are met, such as platelet count < 10,000 µL, < 20,000 µL in the presence of neoplasms with higher bleeding tendencies (eg, bladder, gynecologic, gastrointestinal), or the presence of fever, leukocytosis, coagulopathy, or rapid decrease in platelet count
- Platelet transfusion may not be necessary when performing diagnostic catheterization via radial access
- Platelet transfusion should be considered in patients with thrombocytopenia who develop postprocedural bleeding complications

ANTIPLATELET THERAPY IN PATIENTS WITH TP:

- Aspirin has been used in patients with platelet counts > 10,000 µL, and clopidogrel may be used in patients with platelet counts ≥ 30,000 µL
- Platelet counts < 30,000 µL require input from the hematologist/oncologist in an attempt to provide a more accurate risk/benefit analysis for use of antiplatelet therapy other than aspirin
- Prasugrel, ticagrelor, and glycoprotein IIb/IIIa inhibitors should be avoided if platelet counts are < 50,000/µL

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Iliescu, *et al.* Cath Cardiovasc Int. 2016

Anti-Cancer Agents Associated with QTc Prolongation

Chemotherapy Agents	Frequency of Use	Incidence (%)	Comments
Histone deacetylase inhibitors			Tangent method of QT measurement
Belinostat	+	4–11	
Vorinostat	++++	3.5–6.0	
Chemicals			Fridericia correction formula
Arsenic trioxide	++	26–93	
Small molecule tyrosine kinase inhibitors			Correct low K or Mg
Dabrafenib	++++	2–13	
Dasatinib	++++	<1–3	Remove QTc prolonging medications
Lapatinib	++++	10–16	
Nilotinib	++++	<1–10	QTc >500 ms or >60 ms above baseline associated with TdP
Vandetanib	++++	8–14	
BRAF inhibitor			TdP reported for arsenic trioxide, sunitinib, pazopanib, vandetanib, vemurafenib
Vemurafenib	++++	3	

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Chang, Okwuosa,… Yeh, JACC 2017

Radiation-Induced Heart Disease

Pericardial Disease	
Prevalence	6%-30%
Description	Pericarditis (acute or chronic), pericardial effusion, pericardial constriction Most common manifestation of radiation-induced heart disease, and a diagnosis of exclusion. Due to inflammation and impaired drainages to the pericardial surface, fibrotic changes to the parietal pericardium. Acute pericarditis is often self-limiting. Chronic pericarditis is often effusive-constrictive.
Diagnosis	Diagnosis of exclusion after other causes of pericardial disease have been ruled out Echocardiogram, cardiac magnetic resonance imaging, cardiac CT
Management	Anti-inflammatory drugs for pericarditis Pericardiocentesis for large effusions or tamponade Pericardial window for recurrent pericardial effusions Pericardial stripping for constrictive pericarditis
Coronary Artery Disease	
Prevalence	Up to 85%
Description	Due to epicardial coronary arteries and microcirculatory damage, and sustained inflammation. Usually occurs 10 yrs after radiation therapy. Involves the LM, ostial LAD, and RCA. Lesions are longer, concentric, and tubular.
Diagnosis	Stress echocardiography (could also screen for other causes of RIHD, other than CAD); or stress perfusion imaging; cardiac CTA; possible role for coronary calcium screening
Management	Percutaneous coronary angioplasty or coronary artery bypass graft (challenging surgery due to fibrosis of pericardium and mediastinum). Aggressive cardiovascular risk factor modification
Valvular Heart Disease	
Prevalence	10 yrs: 26% AI, 39% MR, 16% TR, and 7% PR 20 yrs: 60% AI, 16% AS, 52% MR, 26% TR, and 12% PR
Description	Mean time interval of 12 yrs after radiation. Diffuse fibrosis of the valvular cusps or leaflets, with or without calcification; no post-inflammatory changes noted. Left-sided valves > right-sided valves. Initial regurgitation related to valve retraction, later stenosis related to thickening/calcification
Diagnosis	Echocardiogram, cardiac magnetic resonance imaging
Management	Serial monitoring with timing of surgery as in ACC/AHA guidelines Valve replacement is preferred over valve repair Consider TAVR, if mediastinum and cardiac anatomy is not amenable to open heart surgery
Conduction System Abnormalities	
Prevalence	Up to 5%
Description	A-V nodal block (including high-degree block), bundle branch block (right > left), fascicular block Tachycardia can be persistent, usually a result of autonomic dysfunction, similar to denervated hearts. Persistent tachycardia could increase risk of tachycardia-induced cardiomyopathy.
Diagnosis	ECG, telemetry/ambulatory Holter monitor
Management	Permanent pacemaker for high-degree A-V block ICD for life-threatening arrhythmia, sudden death, or secondary prevention Consider subpectoral approach for device implantation, if subcutaneous involvement of thoracic radiation
Cardiomyopathy	
Prevalence	Up to 10%
Description	Diastolic dysfunction > systolic dysfunction; right ventricle > left ventricle Due to increased fibrosis in all 3 layers of the ventricular walls (epicardium, myocardium, and endocardium). May lead to restrictive cardiomyopathy, and rarely to systolic dysfunction.
Diagnosis	Echocardiogram, cardiac magnetic resonance imaging
Management	Slow upward titration of ACEI, beta-blockade, and aldosterone inhibitors in patients with reduced left ventricular systolic function; optimize risk factors for diastolic dysfunction, exercise training Inotropic support, VAD, heart transplantation

Chang, Okwuosa,… Yeh, JACC 2017

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…

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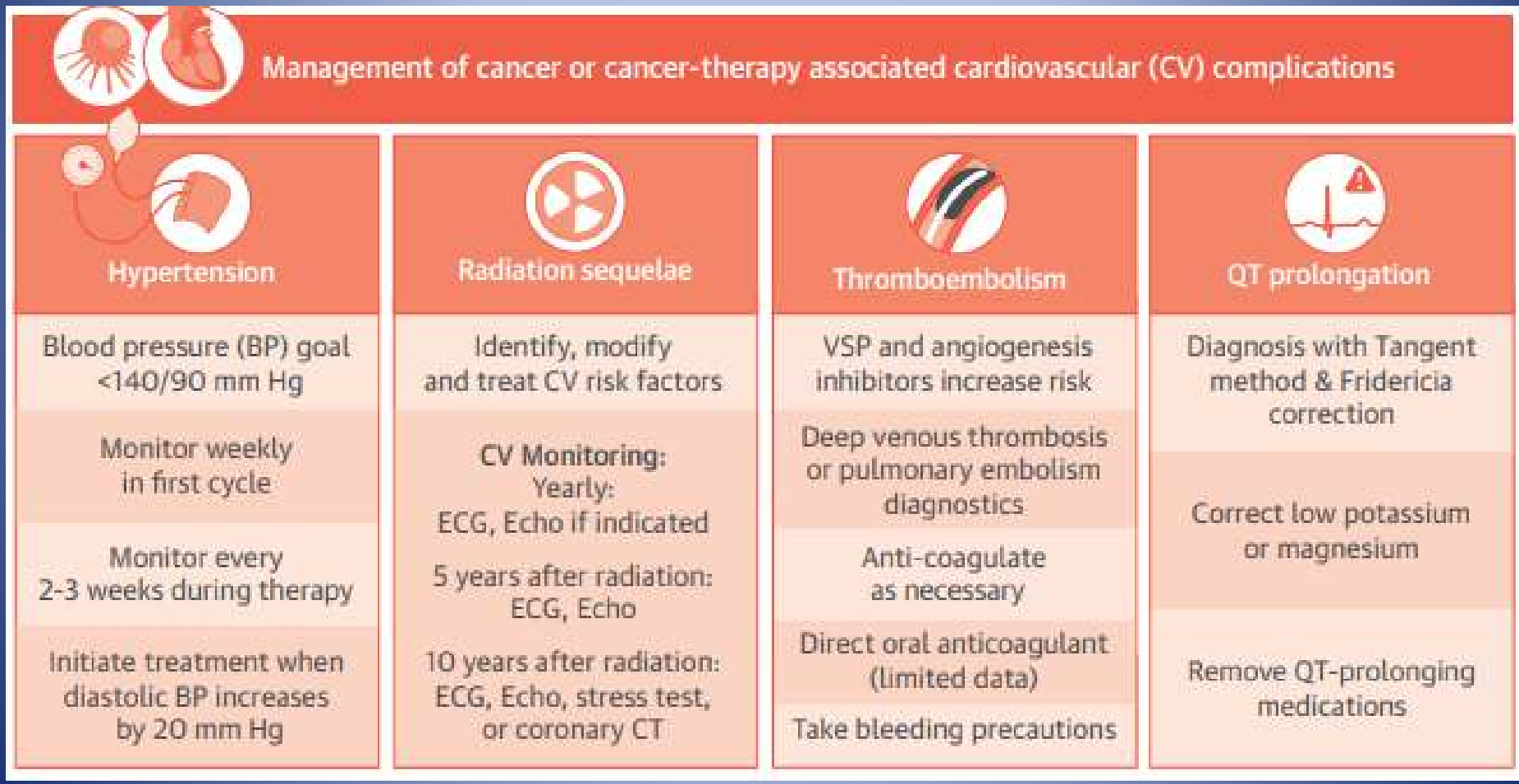
Darby *et al,* NEJM 2013

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)

Management of Cancer Therapy–Induced Cardiovascular Complications



Chang, Okwuosa,… Yeh, JACC 2017

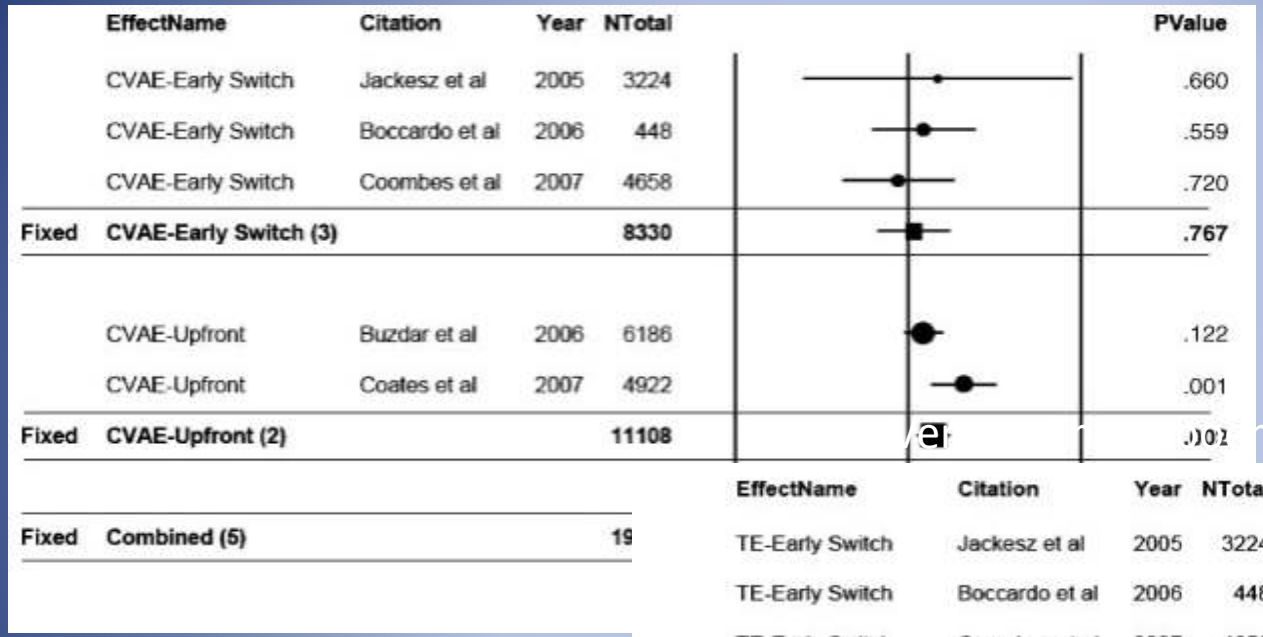
Endocrine Therapy for Breast Cancer

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

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

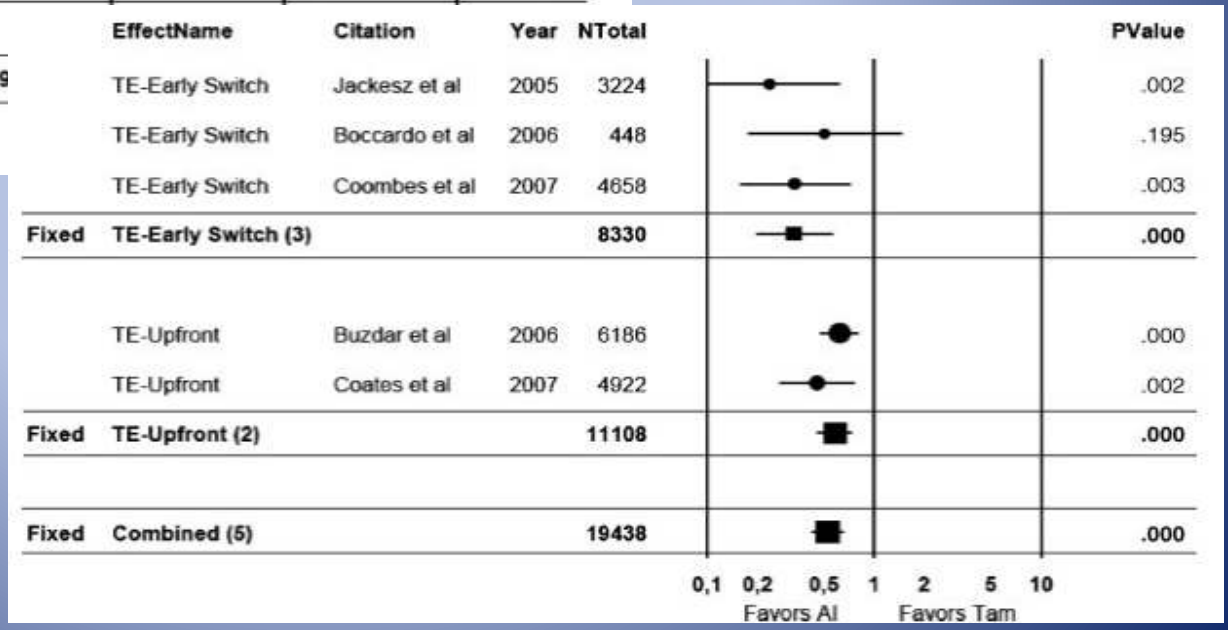
AIs vs. Tamoxifen: Events

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



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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

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Cuppone *et al*, Cancer 2008

Anti-Androgens for Prostate Cancer/ Cardiovascular Effects

GnRH Agonists	GnRH Antagonists	Anti-Androgens	Adrenal Androgen Inhibitors	Estrogens
Leuprolide	Degarelix	Flutamide	Ketoconazole	
Goserelin		Bicalutamide	Corticosteroids	Estradiol
Triptorelin		Nilutamide		
Histrelin		Enzalutamide		Premarin
		Abiraterone Acetate		

Indirect Effects	Direct Effects	Low Testosterone
↑ Fat mass	? ↓ Cardiac contractility	↓ Vasodilation
↓ Lean body mass	↑ T-Cell activation and destabilization of fibrous cap/plaque rupture	↓ HDL
↑ Insulin resistance / Hyperinsulinemia		↑ Visceral Obesity
↑ LDL, ↑ HDL and ↑ Triglycerides		↑ Prothrombotic state
↑ Diabetes mellitus		
↑ Metabolic syndrome		
↑ Endothelial dysfunction		
↑ Arterial wall thickness		

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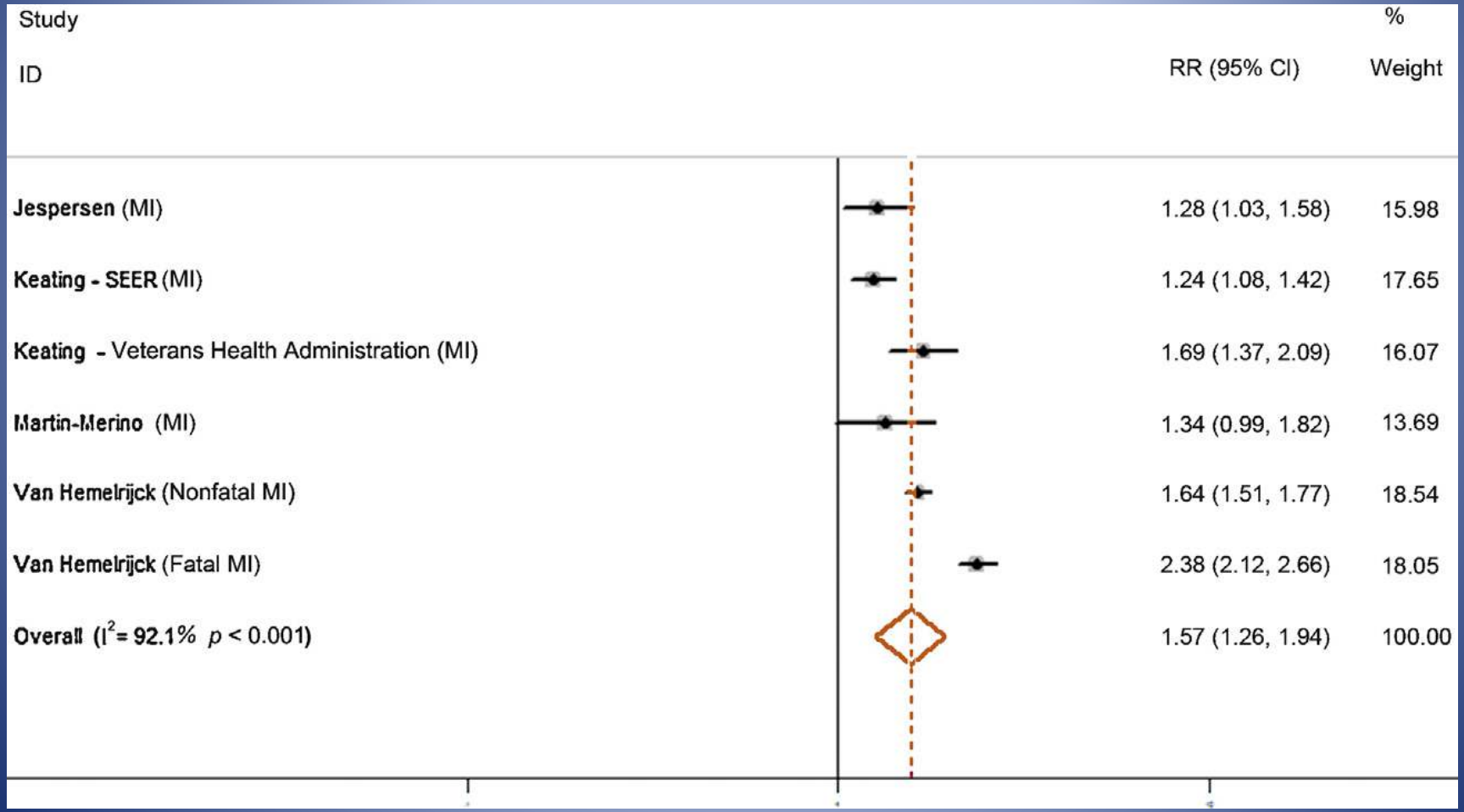
Bhatia *et al.* Circulation, 2016

Association between GRH agonists and Nonfatal or Fatal MI



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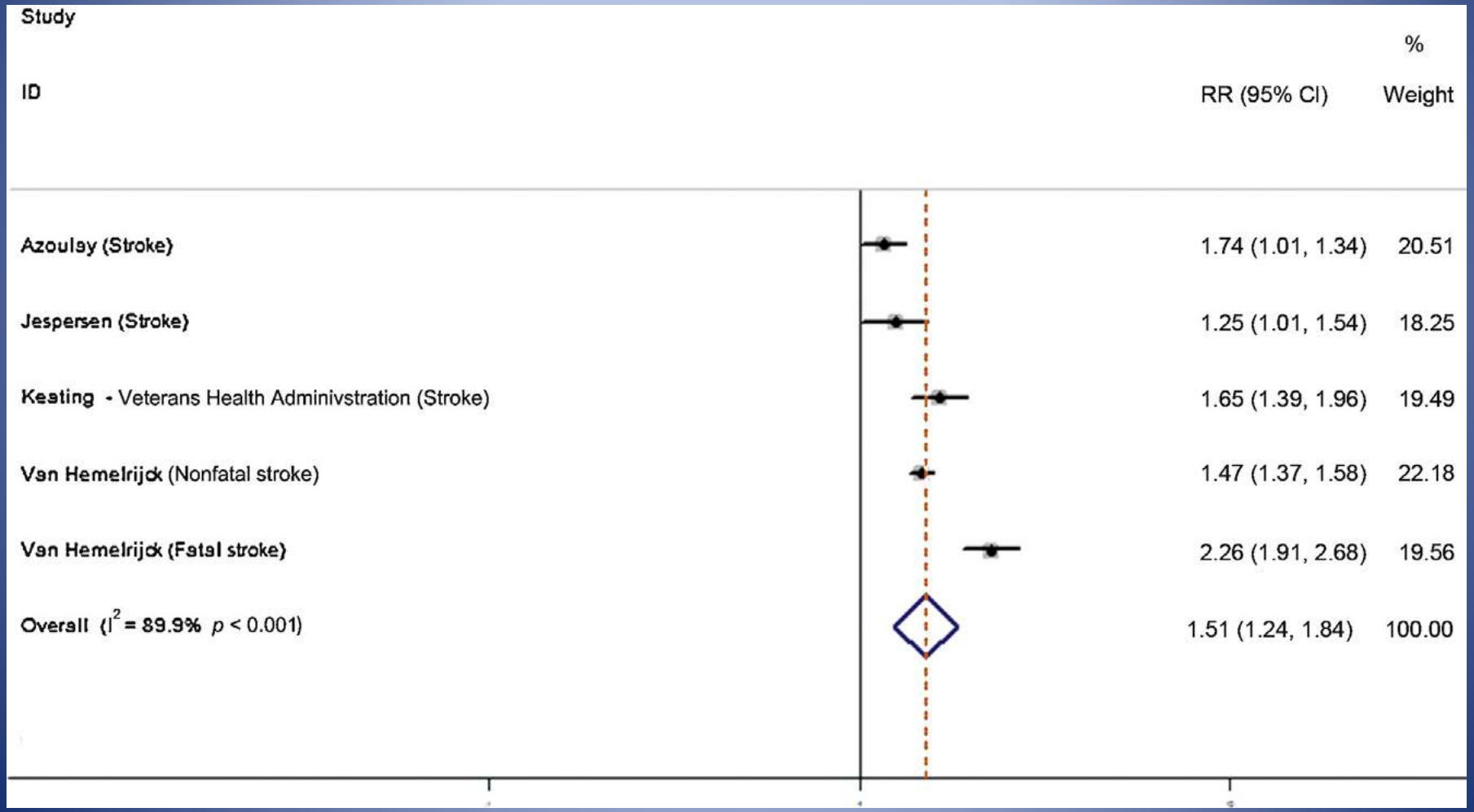
Bosco *et al,* Eur Urol 2014

Association between GRH agonists and Nonfatal or Fatal Stroke



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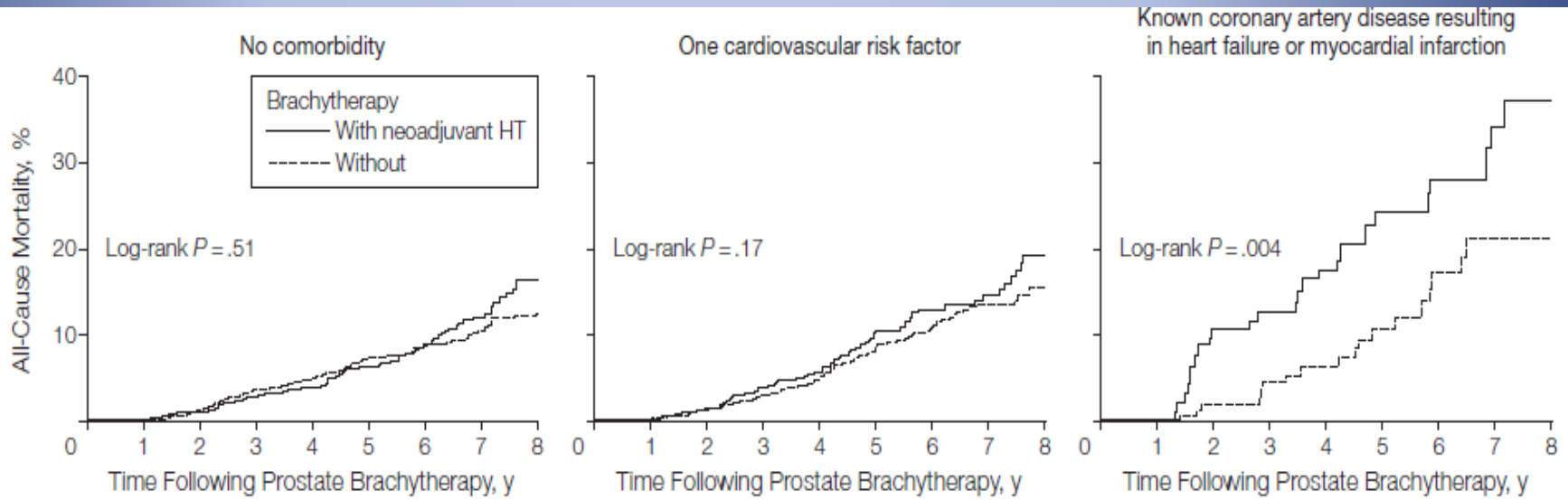
Bosco *et al,* Eur Urol 2014

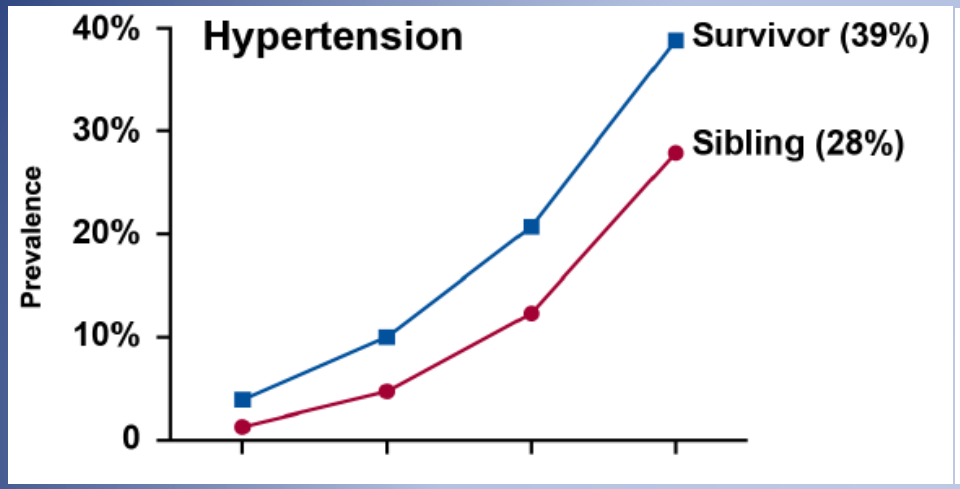
JAMA The Journal of the American Medical Association

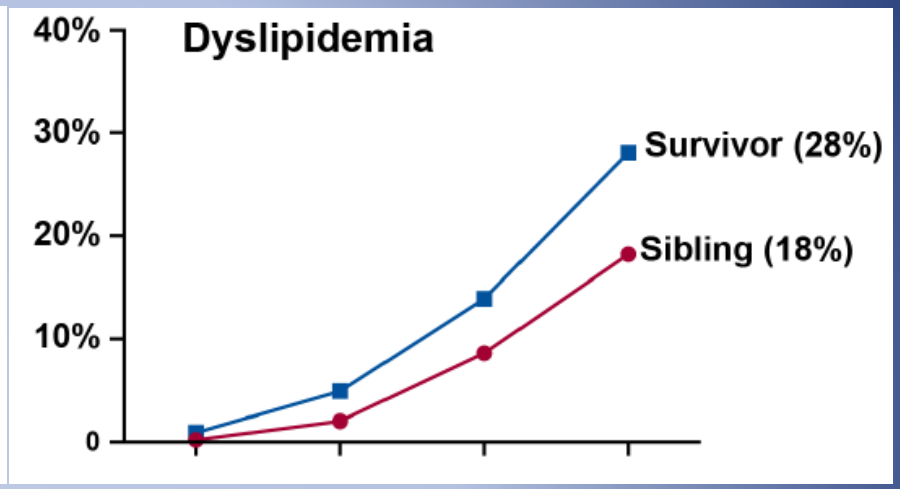
Hormonal Therapy Use for Prostate Cancer and Mortality in Men With Coronary Artery Disease–Induced Congestive Heart Failure or Myocardial Infarction

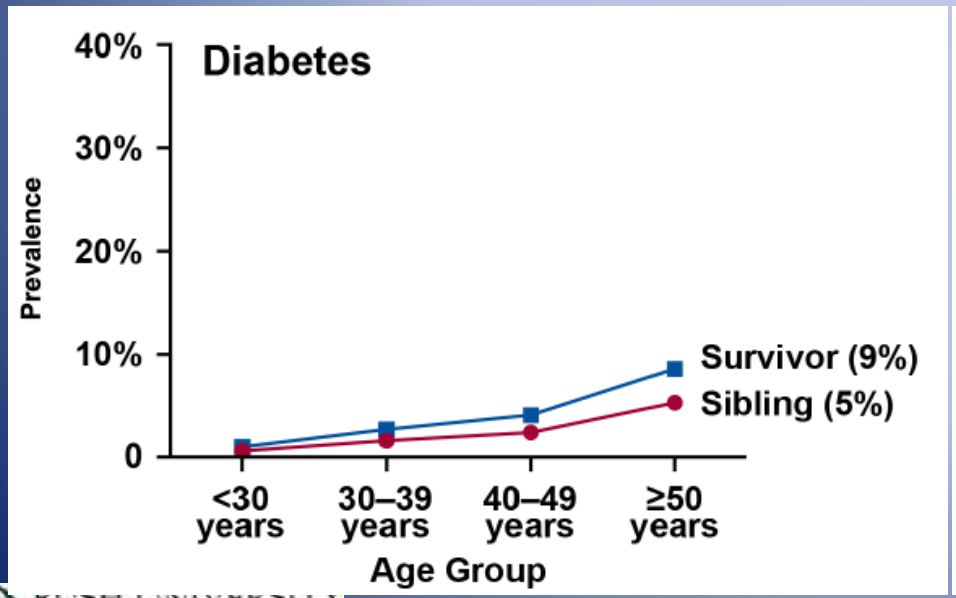
Akash Nanda, MD, PhD

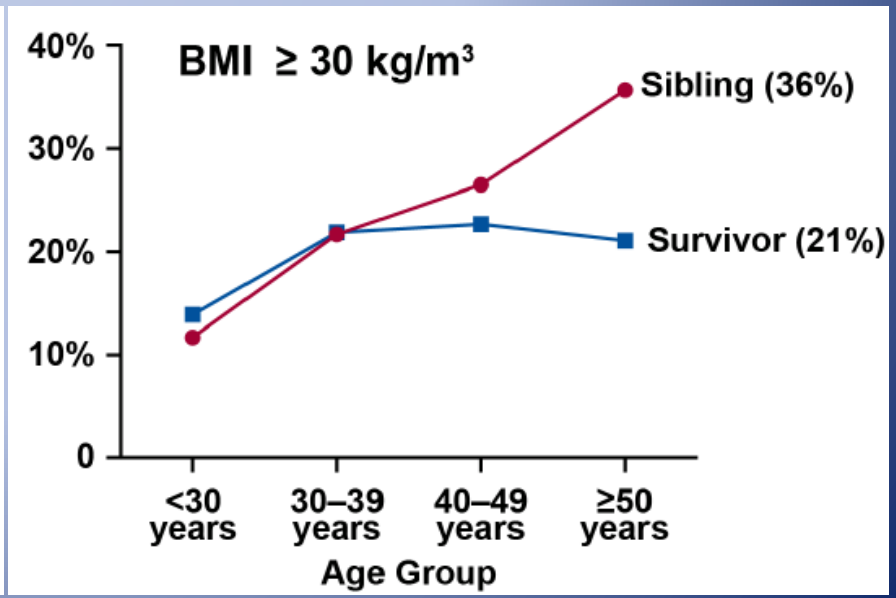


Survivors of Childhood Cancer: Prevalence of Cardiovascular Risk Factors







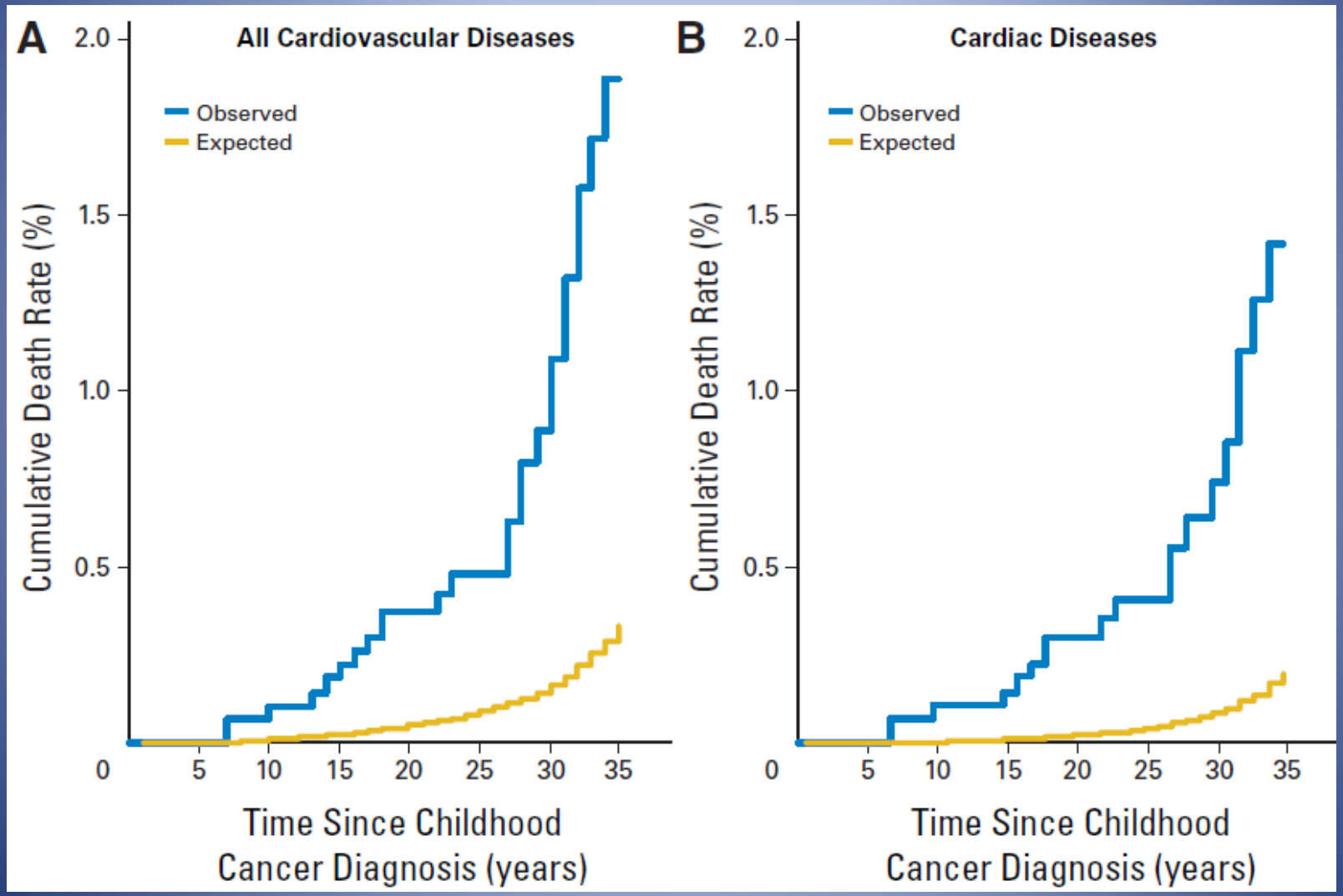


Cardiac Mortality and Risk Factor Cluster in Cancer Patients

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*

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



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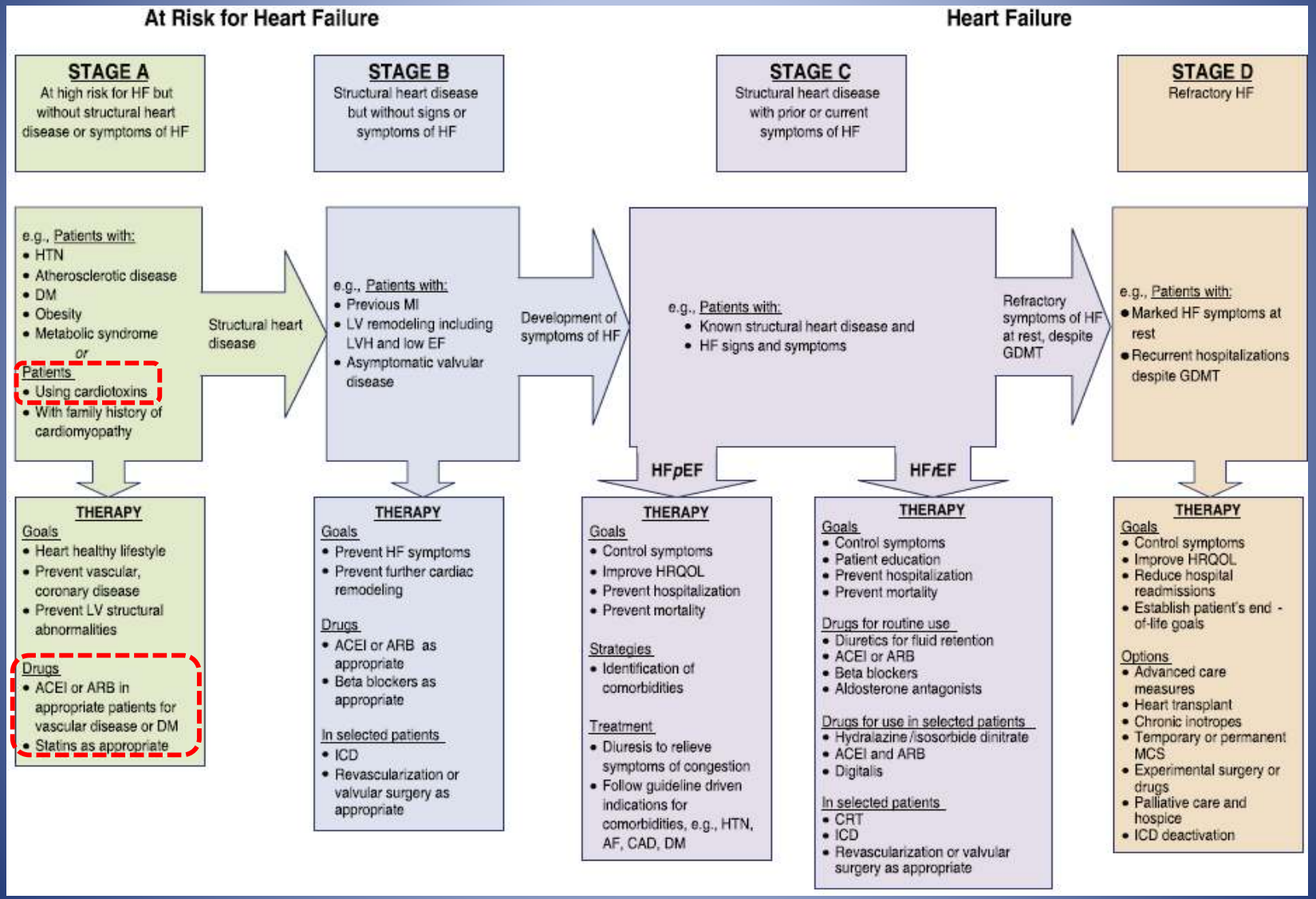
Tukenova *et al,* JCO 2010

Stages in Heart Failure Development/ Recommended Therapy by Stage



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Hunt *et al, Circulation* 2009

Exercise and Cardiovascular Events in Hodgkin Lymphoma Survivors

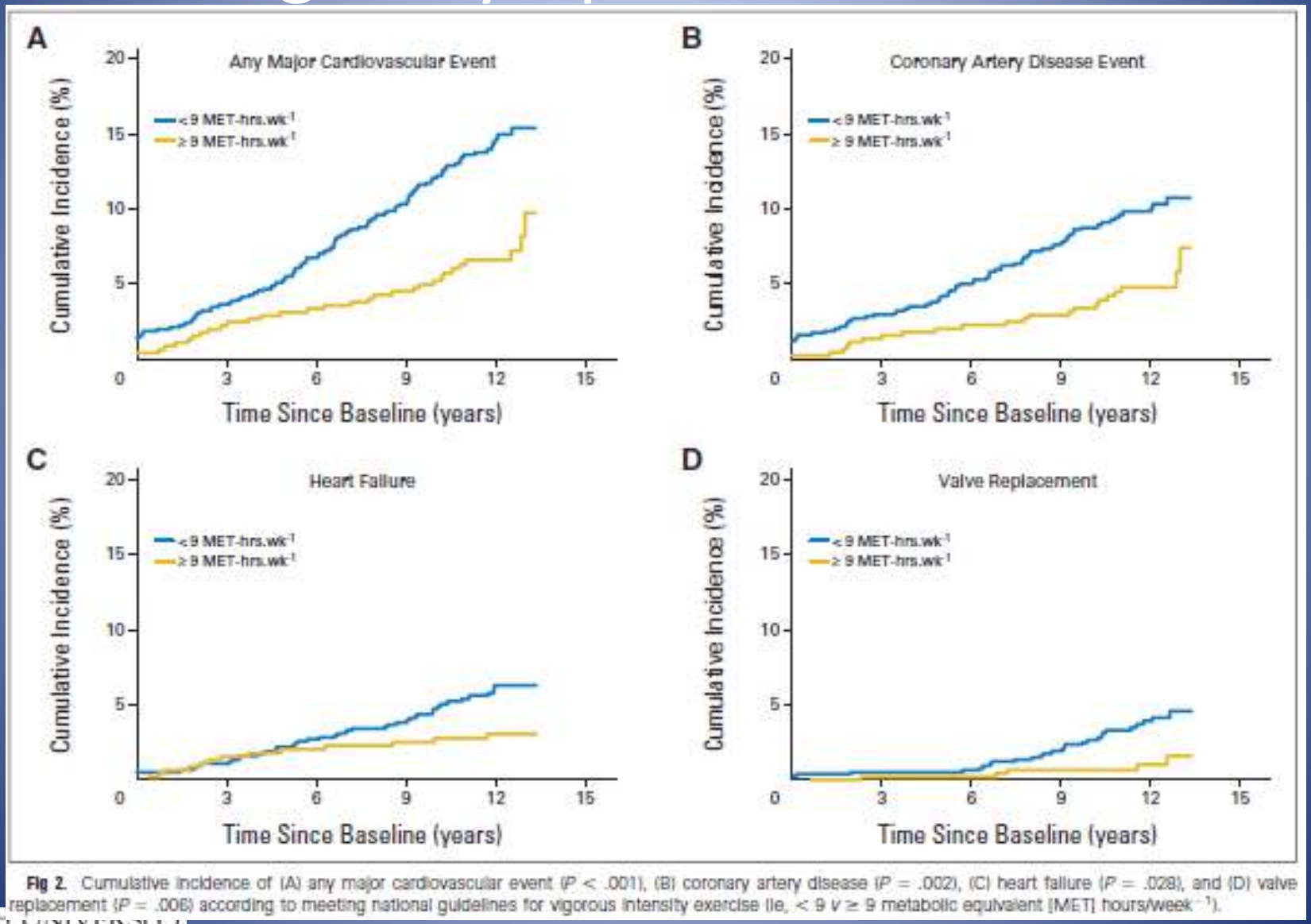

Fig 2. Cumulative incidence of (A) any major cardiovascular event ($P < .001$), (B) coronary artery disease ($P = .002$), (C) heart failure ($P = .028$), and (D) valve replacement ($P = .006$) according to meeting national guidelines for vigorous intensity exercise (ie, < 9 *v* ≥ 9 metabolic equivalent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

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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						
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*

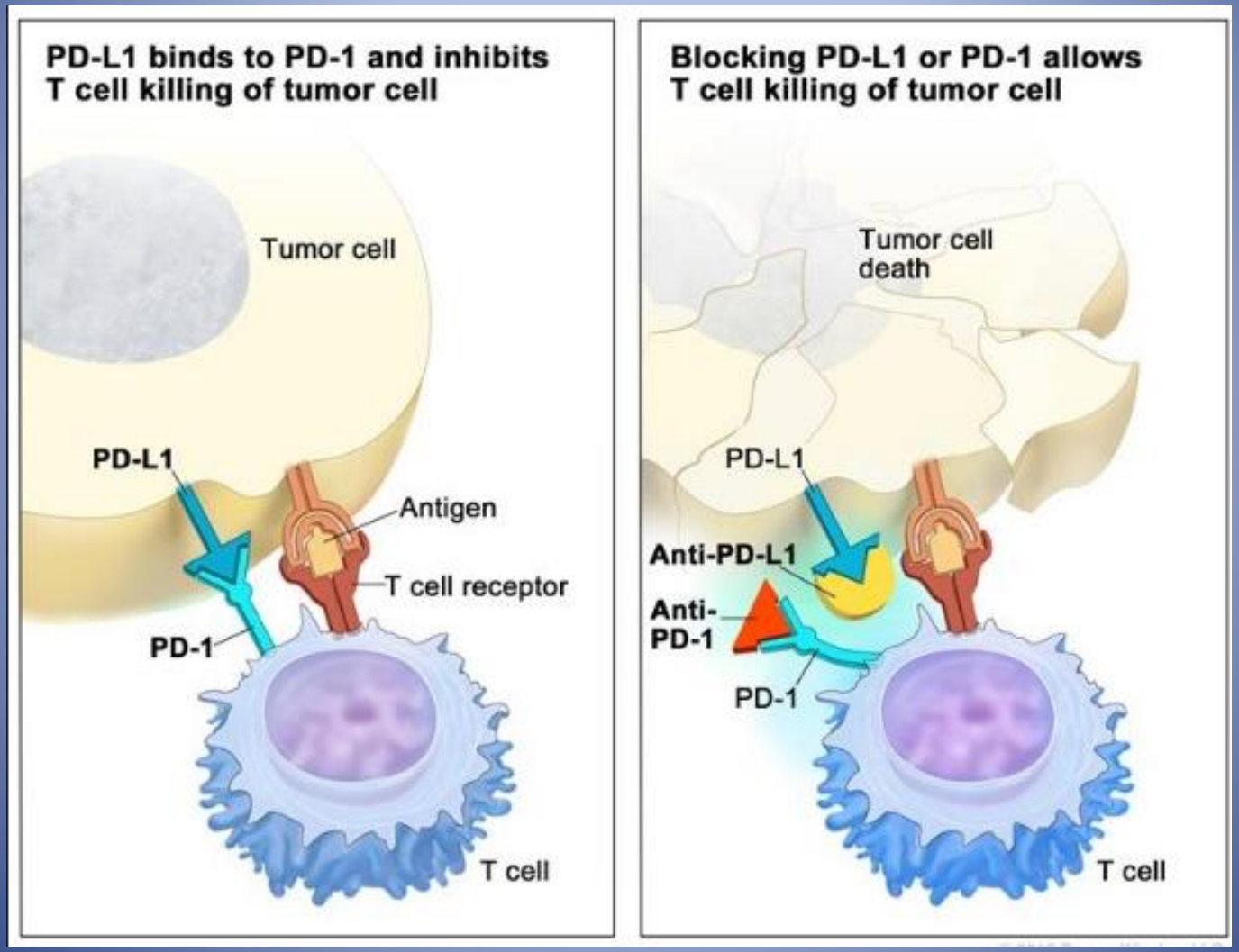
ABCDE Steps to Prevent Heart Disease in Breast Cancer Survivors

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

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:
- Incidence of myocarditis higher in patients receiving a combination of nivolumab and ipilimumab (0·27%)
- Was 0.09% in those receiving nivolumab alone
- Noted 50% fatality
- A 2017 meta-analysis of 22 anti-PD-1 and anti-PD-L1 trials in patients with NSCLC
  - Cardiorespiratory arrest 1·0%; cardiac failure 2·0%; myocardial infarction 1·0%; and stroke 2·0%

Licensed immune checkpoint inhibitors and their reported cardiotoxic effects at the time of FDA approval

	Molecular target	Indication according to FDA label	Cardiotoxic effects included in FDA label
Ipilimumab	CTLA-4	Metastatic melanoma, metastatic renal cell carcinoma (along with nivolumab)	Pericarditis (incidence <1%, including fatal cases), myocarditis (incidence 0·2%, including fatal cases)
Nivolumab	PD-1	Metastatic melanoma, stage IIIB and IIIC melanoma (adjuvant), metastatic non-small-cell lung cancer, metastatic renal cell carcinoma (alone or in combination with ipilimumab), relapsed Hodgkin's lymphoma, recurrent or metastatic head and neck squamous cell carcinoma	Myocarditis (incidence <1%), ventricular arrhythmia
Pembrolizumab	PD-1	Metastatic melanoma, metastatic non-small-cell lung cancer, recurrent or metastatic head and neck squamous cell carcinoma	Cardiac failure (incidence 0·6%)
Atezolizumab	PD-L1	Metastatic urothelial carcinoma, metastatic non-small-cell lung cancer	Myocardial infarction (including fatal cases)
Avelumab	PD-L1	Metastatic Merkel cell carcinoma	Myocarditis (including fatal cases)
Durvalumab	PD-L1	Unresectable stage III non-small-cell lung cancer	Myocarditis (incidence <1%)

FDA=US Food and Drug Administration.

Others: *Tremelimumab, Pidilizumab*

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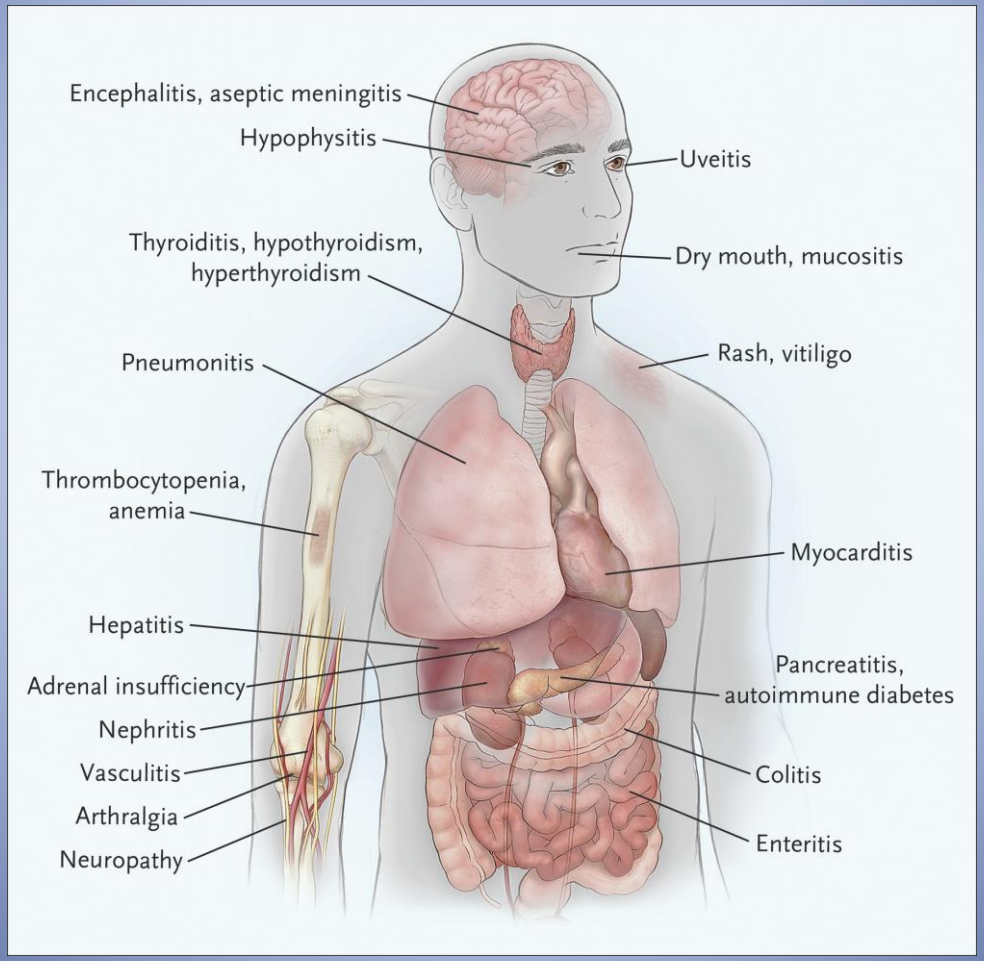
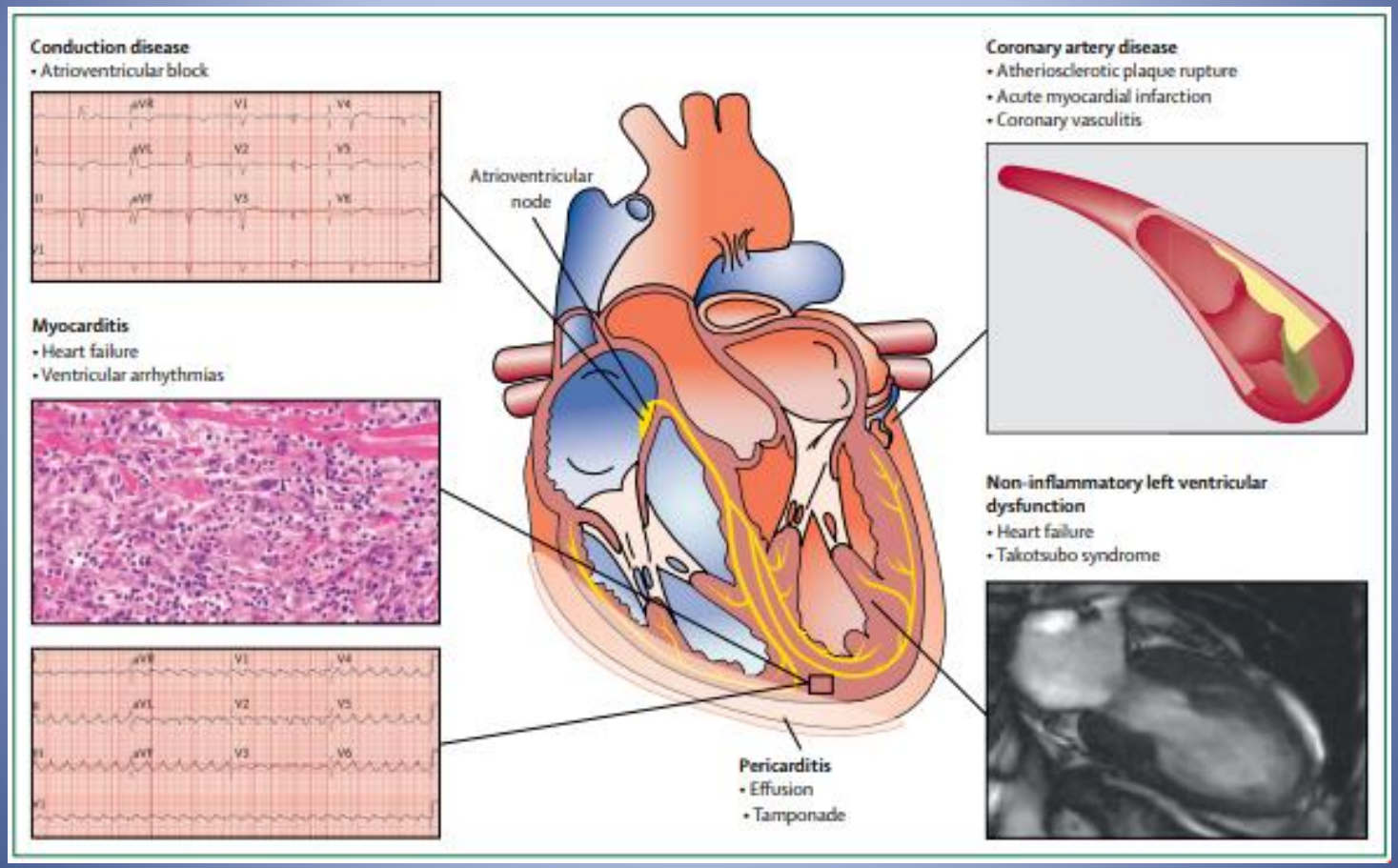
Lyon *et al.* Lancet 2018

Organs affected by ICIs



Postow, et al. NEJM. 2018

ICI-Mediated Cardiotoxicity



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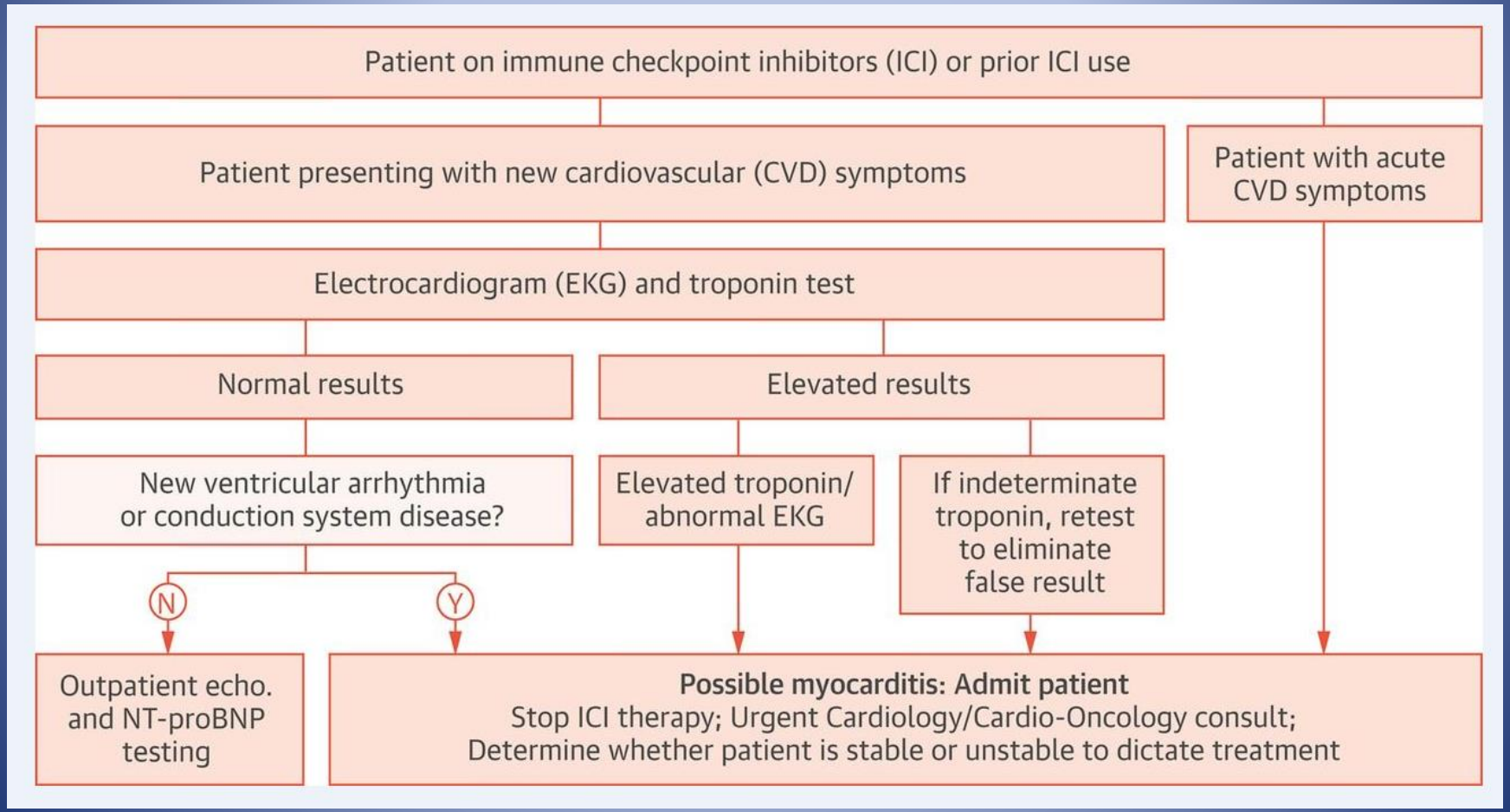
Lyon *et al.* Lancet 2018

Triage for Myocarditis Related to Checkpoint Inhibitors



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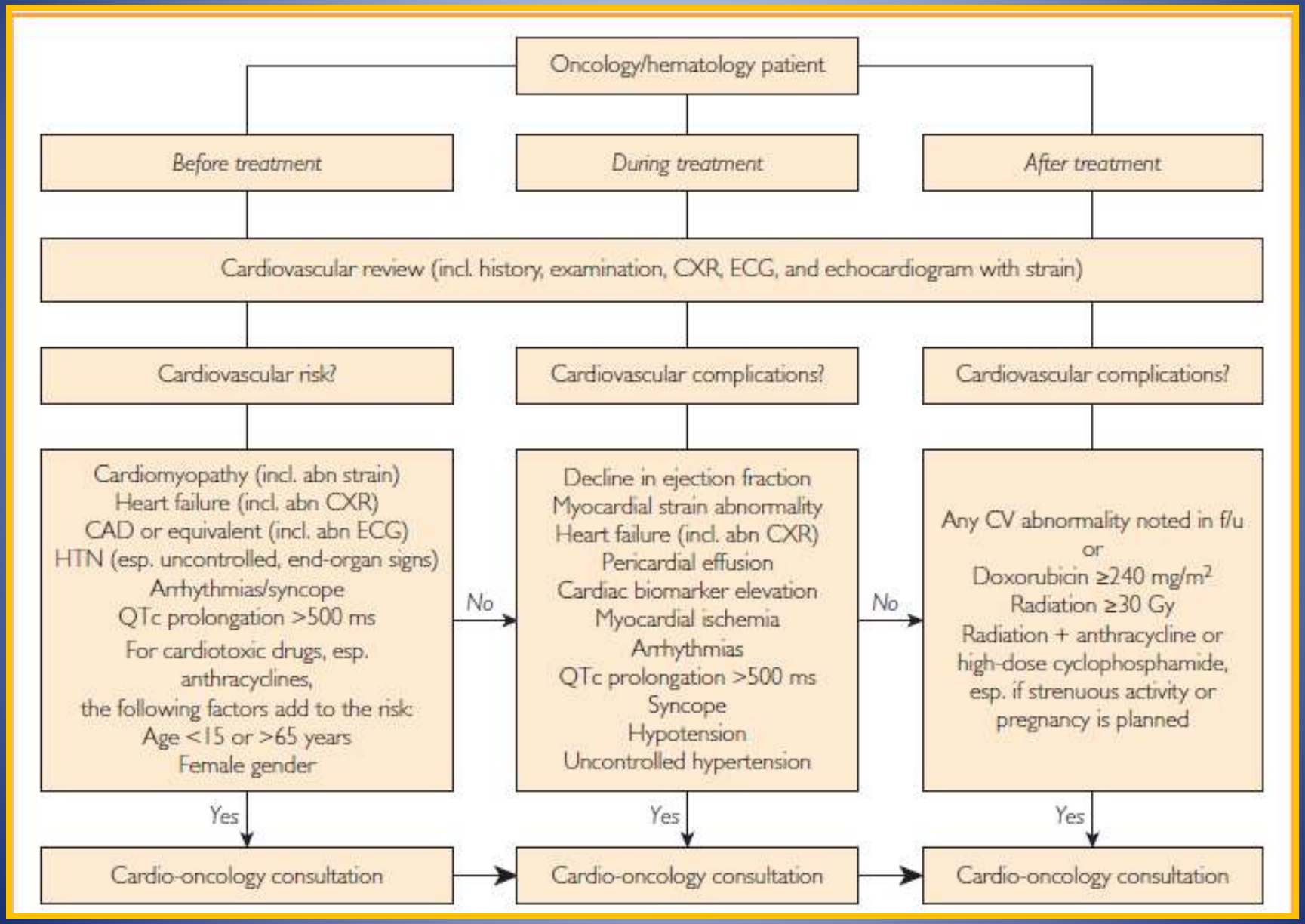
Mahmood *et al*. JACC 2018

WHEN TO REFER TO CARDIO-ONCOLOGY



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

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

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