

# Breast Cancer and Risk of Cardiovascular Disease: The Landscape of Neoadjuvant, Adjuvant, and Metastatic Treatment

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# Disclosures

- JM:
  - Pfizer (unrelated) – research support, modest consulting fees
  - BridgeBio (unrelated) – modest consulting fees
  - Myocardial Solutions – research support
  - Abbott Laboratories – research support
- AP:
  - UpToDate – royalties for authorship of breast cancer survivorship section

# Agenda

- Review potential CV effects of breast cancer tx

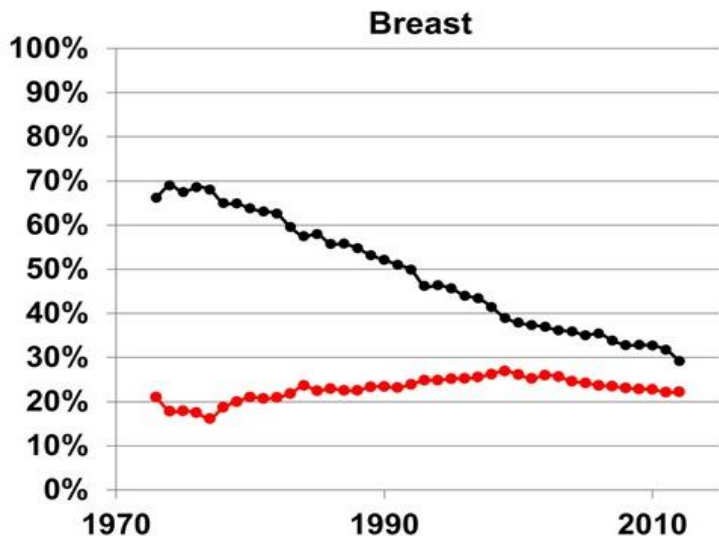
- Disc  
carc

**A multi-disciplinary approach  
is required!**

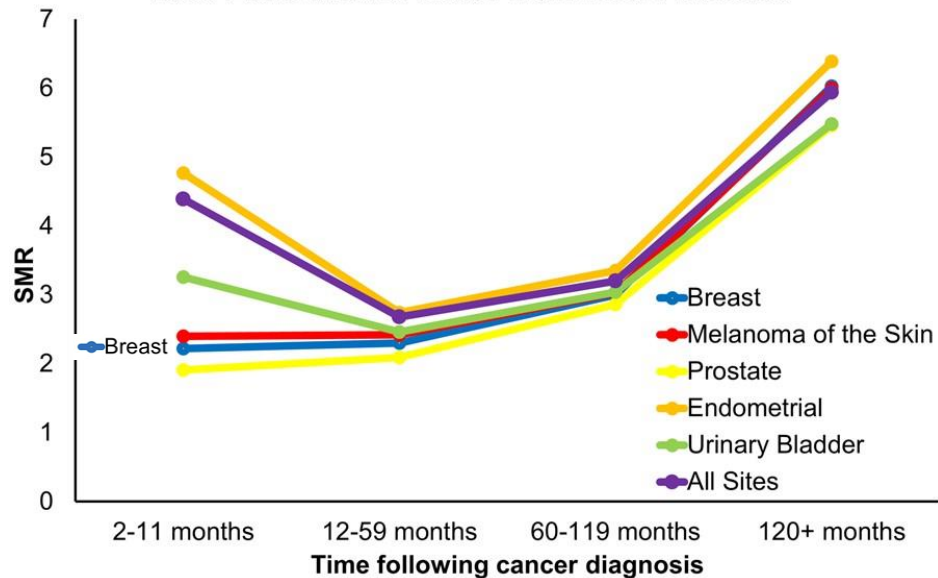
- Mar  
therapy, and arter tx

ng

## Cancer Death (Black) vs CV Death (Red)



## 2000-2015 Risk of Death from Heart Disease



# Cardiovascular Risk in Breast Cancer Care Continuum

## Pre-Diagnosis



## Diagnosis and Treatment

- Surgery
- Chemotherapy and Biologics
- Radiation
- Ovarian suppression (OS) with chemotherapy (CRA)

## Survivorship

- 5-10 years of hormonal tx
- chronic OS tx and premature menopause

## Recurrence / Advanced Dz

- Re-irradiation
- Chronic tx:
  - Hormonal, chemotherapy, biologic and targeted tx

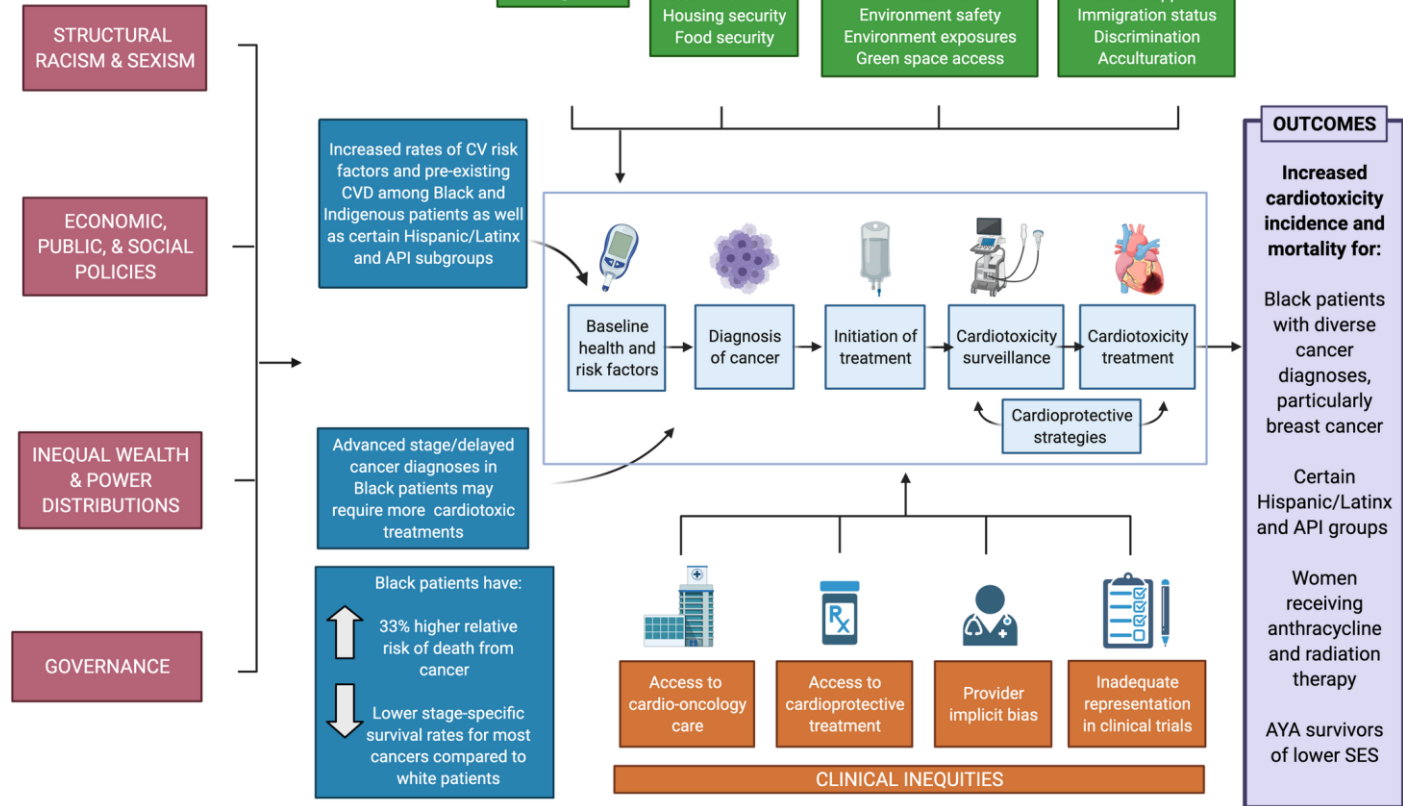
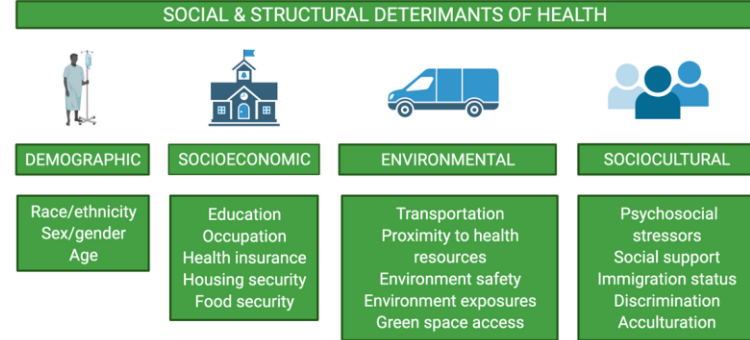


# Evaluation of Cardiac Morbidity After Breast Cancer is Complicated

- Most data from post-menopausal women
- Select populations in clinical trials
- Multiple potential exposures including aging
- Difficult to assess causality
- CV disease common and misattribution may be frequent
- Long latency period for some, lack of long-term data
- Several endocrine strategies utilized over the years



# Disparities in Cardio-Oncology



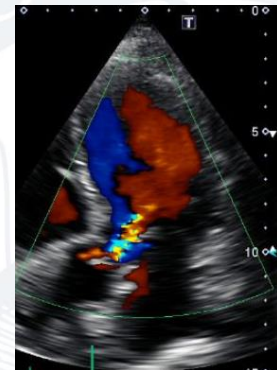
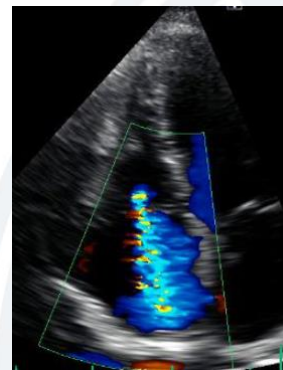
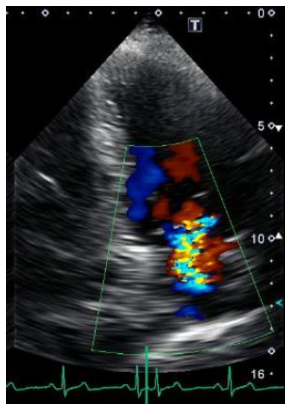
Melissa L. Abel. Journal of the American Heart Association. Inequity in Cardio-Oncology: Identifying Disparities in Cardiotoxicity and Links to Cardiac and Cancer Outcomes, Volume: 10, Issue: 24, DOI: (10.1161/JAHA.121.023852)

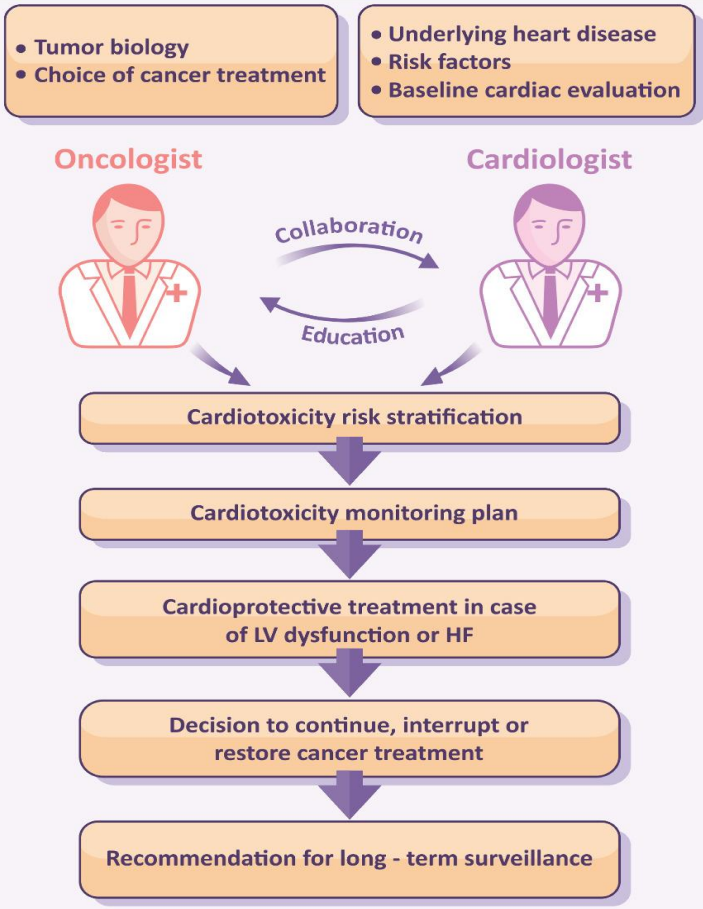
# A REPRESENTATIVE CASE



# Triple Negative Breast Cancer

- 63-year-old woman
- PMH: Valvular disease for 6 years, HTN, pulm HTN, hypothyroid
- Clinically T4dN2, stage IIIB at least, inflammatory breast cancer, ER-, PR-, HER2-
- Baseline TTE, LVEF 55%, severe MR/TR, mod AR
- Oncologist recommends neoadjuvant ddAC-T
- Local cardiologist recommends no anthracyclines, referral to BJH





European J of Heart Fail, Volume: 22, Issue: 9, Pages: 1504-1524, First published: 04 July 2020, DOI: (10.1002/ejhf.1957)

## CV considerations:

### Patient

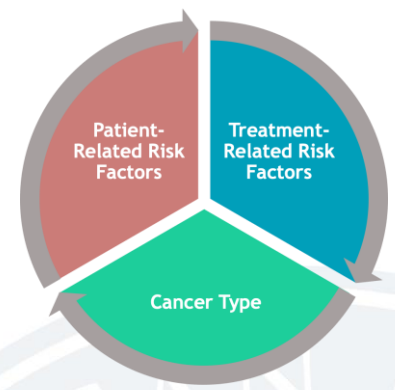
- $\geq$  moderate valvulopathy
- Hypertensive (153/88)
- Normal cholesterol (LDL 70, HDL 85)
- Age > 60

### Treatment

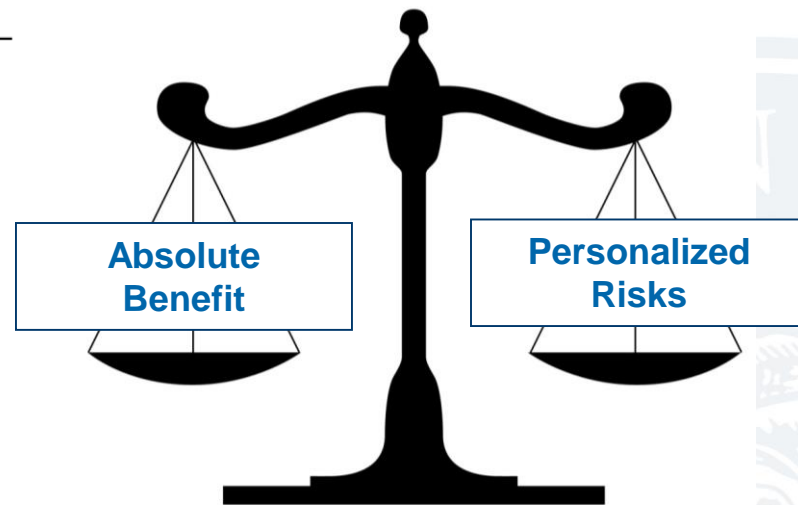
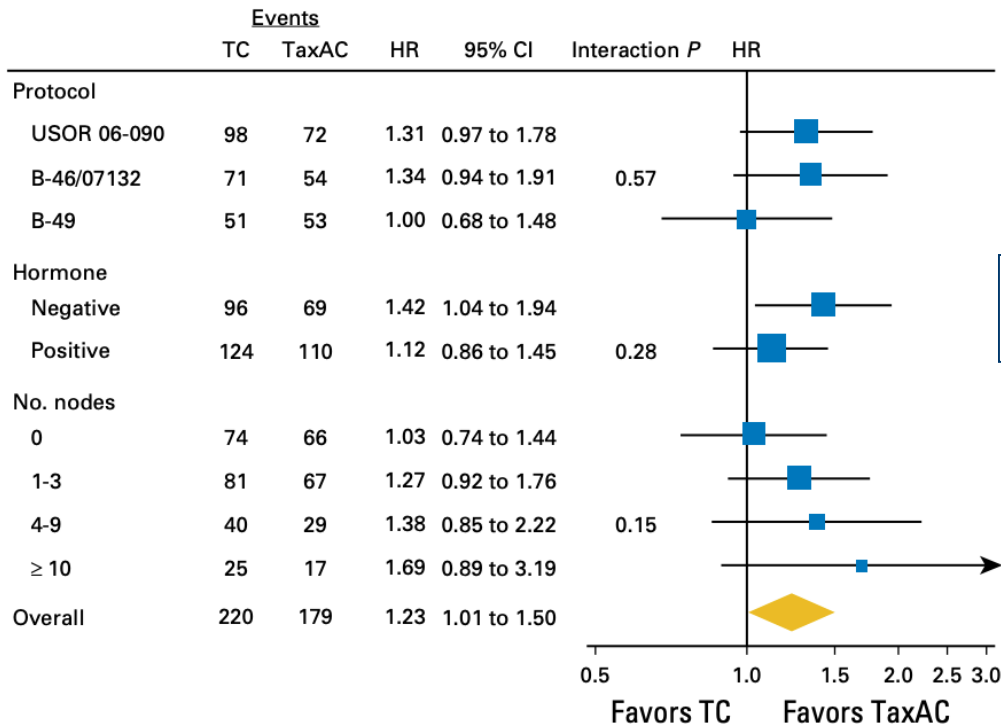
- Increased risk of HF with anthracyclines

### Oncologic considerations:

- Stage IIIB (at least)
- Inflammatory Breast Cancer
- Multi-agent therapy indicated



# Chemotherapy can save lives but can also cause morbidity and mortality



[Anthracyclines in Early Breast Cancer: The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 \(NRG Oncology\)](#)

Blum Jet al, Journal of Clinical Oncology 2017 35:23, 2647-2655

# A Deeper Dive into the Data

## CENTRAL ILLUSTRATION: Cardiovascular Events in Pivotal Cancer Trials

Adverse E

Overall toxicity

Blood and lymphatic sy

Anemia

Febrile neutropenia

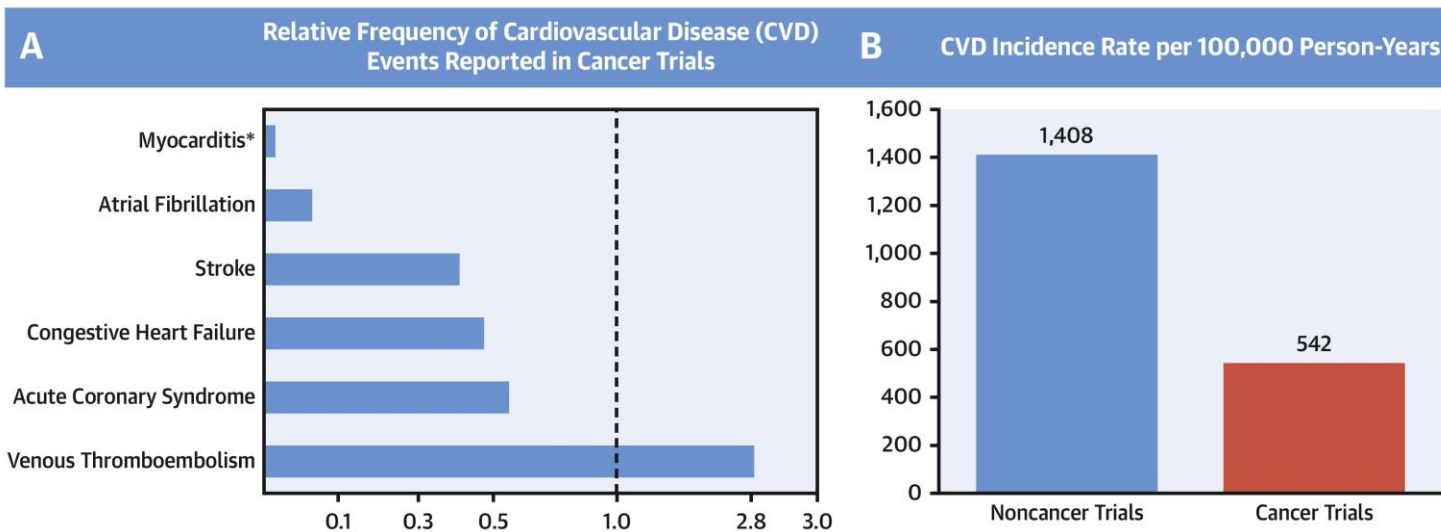
Cardiac disorders

Acute coronary synd

Heart failure

Left ventricular systo

Myocardial infarction



Bonsu, J.M. et al. J Am Coll Cardiol. 2020;75(6):620-8.

Grade 5

0

0

0

0

0

0

0

[Anthracyclines in Early Breast Cancer: The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 \(NRG Oncology\)](#)

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# A Deeper Dive into the Data

Adverse Event	TaxAC (n = 913)			TC (n = 919)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Overall toxicity	38	4	0	37	3	0
Blood and lymphatic system disorders						
Anemia	2	0	0	< 1	0	0
Febrile neutropenia	3	< 1	0	7	1	0
Cardiac disorders						
Acute coronary syndrome	0	0	0	0	0	0
Heart failure	0	0	0	0	0	0
Left ventricular systolic dysfunction	< 1	0	0	< 1	0	0
Myocardial infarction	0	0	0	0	0	0

Status	No. of Patients		No. of Events		4-Year IDFS (%)		4-Year IDFS Δ (%)	HR (95% CI)
	TaxAC	TC	TaxAC	TC	TaxAC	TC		
HR negative								
Node negative	459	488	37	52	89.5	87.0	2.5	1.31 (0.86 to 1.99)
1-3 positive nodes	153	119	21	28	85.5	74.6	10.9	1.58 (0.90 to 2.79)
≥ 4 positive nodes	42	40	11	16	71.8	60.8	11.0	1.34 (0.62 to 2.91)
HR positive								
Node negative	358	378	29	22	91.5	94.2	-2.7	0.69 (0.39 to 1.19)
1-3 positive nodes	771	789	46	53	94.3	92.3	2.0	1.14 (0.77 to 1.69)
≥ 4 positive nodes	279	280	35	49	87.2	81.4	5.8	1.46 (0.95 to 2.26)

Abbreviations: HR, hormone receptor; IDFS, invasive disease-free-survival; TaxAC, doxorubicin and cyclophosphamide regimens with a taxane; TC, docetaxel and cyclophosphamide.

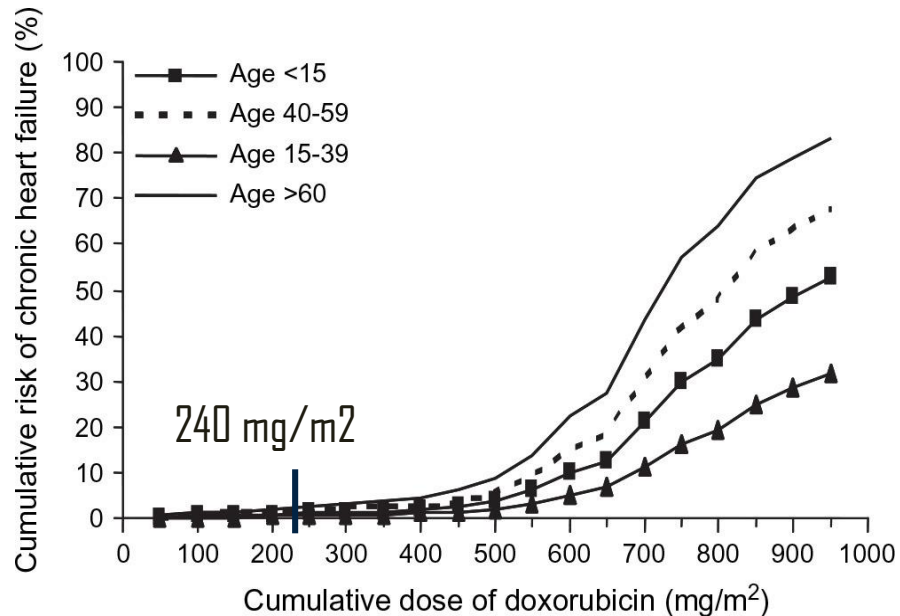
# CARDIOVASCULAR RISK CONSIDERATIONS

ACC Education   
Always Learning.



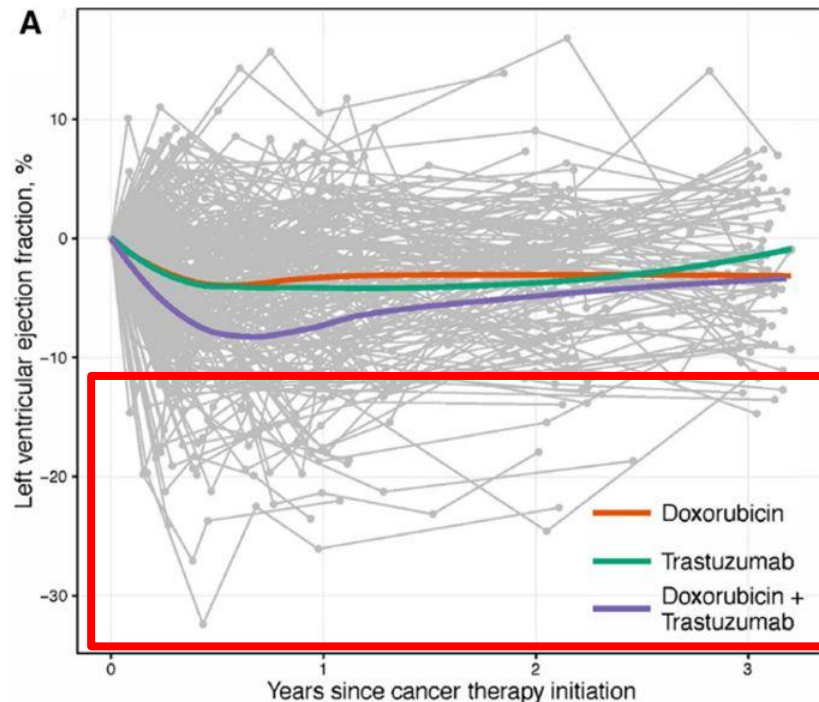
AMERICAN  
COLLEGE of  
CARDIOLOGY<sup>®</sup>

# Anthracycline Toxicity



*Annals of Oncology* 2009 20816-827 DOI: (10.1093/annonc/mdh728)  
Adapted from: von Hoff. *Annals of Internal Medicine*. 1979;91:710-717.

Narayan, Ky et al. *Circulation*. Detailed Echocardiographic Phenotyping in Breast Cancer Patients, 2017.  
DOI: (10.1161/CIRCULATIONAHA.116.023463)



## Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

*Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan*

### Who is at risk?

- Doxorubicin  $\geq 250$  mg/m<sup>2</sup> (or equivalent)



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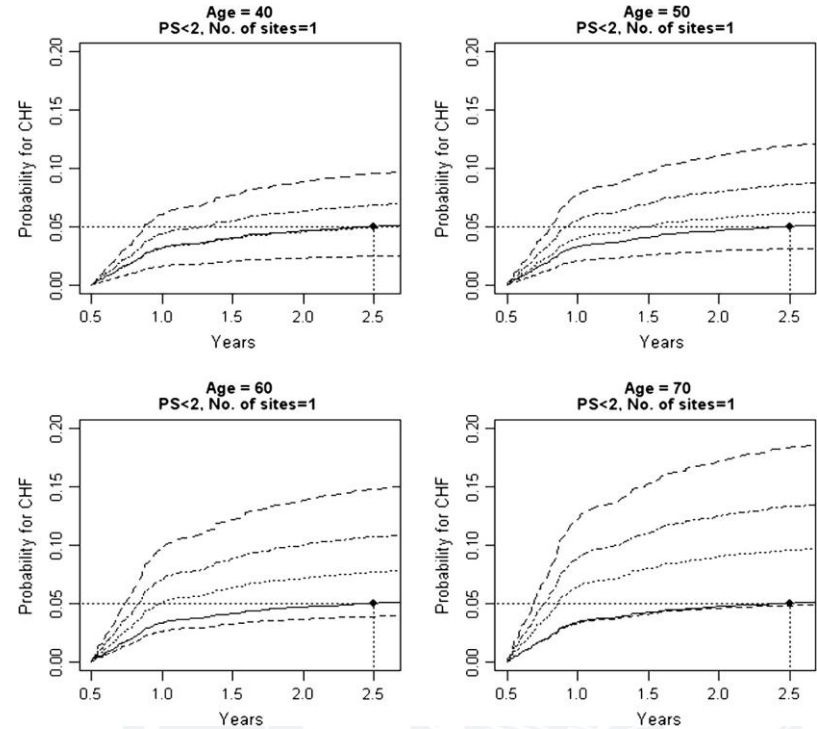
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- Epirubicin  $\geq 600$  mg/m<sup>2</sup>

1000 mg/m<sup>2</sup>  
 900 mg/m<sup>2</sup>  
 800 mg/m<sup>2</sup>  
 600 mg/m<sup>2</sup>

## Epirubicin and HF



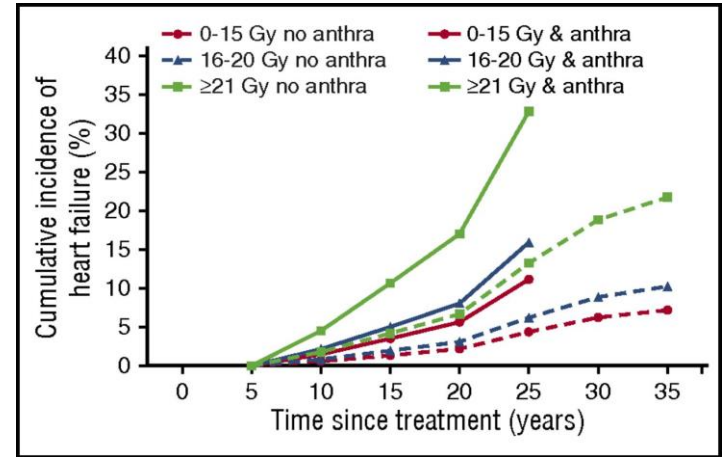
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- Radiation  $\geq 30$  Gy (heart in radiation field)
- Anthracyclines + radiation

### Anthracyclines $\pm$ Radiation



van Nimwegen, et al, Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines, *Blood*, 2017, Figure 2.

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- Anthracyclines + radiation
- **Anthracyclines + trastuzumab**
- **Anthracyclines or trastuzumab + risk factors**

### Risk Factors:

- Age  $\geq 60$
- Compromised cardiac function
  - Mod valve disease
  - LVEF 50-55%
  - Prior Myocardial Infarction
- 2+ CV Risk Factors (during or after)
  - HTN
  - HLD
  - DM
  - Obesity
  - Smoking

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- Anthracyclines + radiation
- Anthracyclines + trastuzumab
- Anthracyclines or trastuzumab + risk factors

\*Not enough data for recommendations on newer treatments such as TKIs

### Risk Factors:

- Age  $\geq 60$
- Compromised cardiac function
  - Mod valve disease
  - LVEF 50-55%
  - Prior Myocardial Infarction
- 2+ CV Risk Factors (during or after)
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  - HLD
  - DM
  - Obesity
  - Smoking

Prevention and Monitoring of Cardiac Dysfunction in

Survivors of Solid Tumor Cancer: A Review of Clinical

Onc

Saro H  
Susan L  
Mariell  
Kathryn

Risk Factors:

- Age  $\geq$  60
- Compromised cardiac function

Use alternative therapies if they do not compromise cancer outcomes

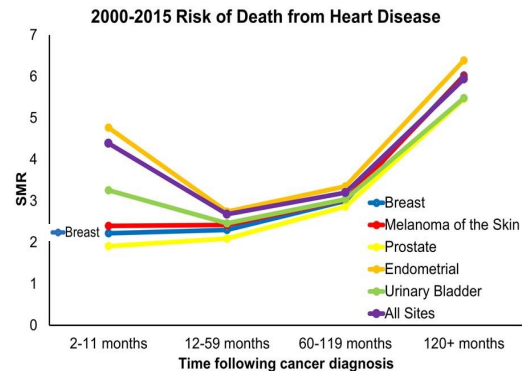
Minimize radiation exposure to heart

## Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

G. Curigliano<sup>1,2†</sup>, D. Lenihan<sup>3†</sup>, M. Fradley<sup>4</sup>, S. Ganatra<sup>5</sup>, A. Barac<sup>6</sup>, A. Blaes<sup>7</sup>, J. Herrmann<sup>8</sup>, C. Porter<sup>9</sup>, A. R. Lyon<sup>10</sup>, P. Lancellotti<sup>11</sup>, A. Patel<sup>12</sup>, J. DeCara<sup>13</sup>, J. Mitchell<sup>14</sup>, E. Harrison<sup>15</sup>, J. Moslehi<sup>16</sup>, R. Witteles<sup>17</sup>, M. G. Calabro<sup>18</sup>, R. Orecchia<sup>1</sup>, E. de Azambuja<sup>19</sup>, J. L. Zamorano<sup>20</sup>, R. Krone<sup>21</sup>, Z. Iakobishvili<sup>22</sup>, J. Carver<sup>23</sup>, S. Armenian<sup>24</sup>, B. Ky<sup>25</sup>, D. Cardinale<sup>26</sup>, C. M. Cipolla<sup>27</sup>, S. Dent<sup>28</sup> & K. Jordan<sup>29</sup>, on behalf of the ESMO Guidelines Committee\*

# General Principles

- Screen for CV Risk factors
  - HTN
  - HLD
  - DM
  - Obesity
  - Smoking

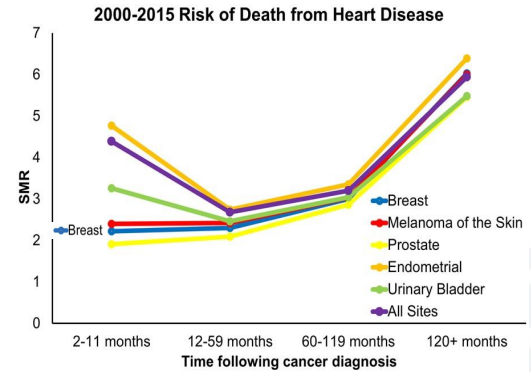


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## General Principles

- Screen for CV Risk factors
- Monitor for CV Safety
  - CV History and Exam
  - TTE/MRI
  - Biomarkers

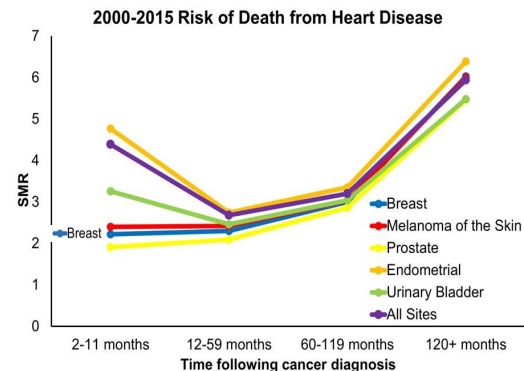


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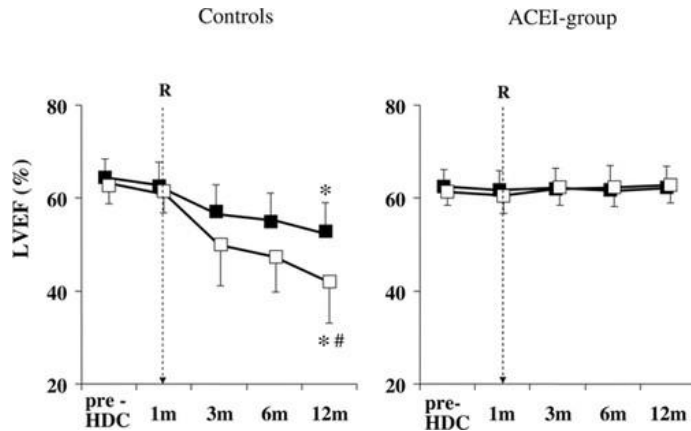
- Screen for CV Risk factors
- Monitor for CV Safety
- Multi-disciplinary approach
  - Ensure lifelong CV health
  - Avoid unnecessary discontinuation of cancer therapy



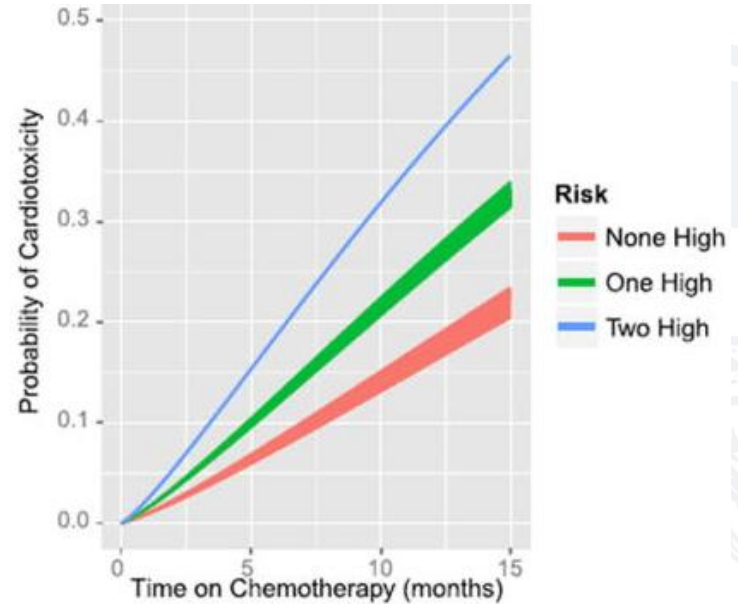


# Screening

## Troponin Guided Enalapril Prevents LVEF Decline



Daniela Cardinale. Circulation. Prevention of High-Dose Chemotherapy-Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition, Volume: 114, Issue: 23, Pages: 2474-2481, DOI: (10.1161/CIRCULATIONAHA.106.635144)



Bonnie Ky et al. *J Am Coll Cardiol.* 2014; 63(8):809-816.

- Tumor biology
- Choice of cancer treatment

- Underlying heart disease
- Risk factors
- Baseline cardiac evaluation

Oncologist



Cardiologist



Collaboration  
Education

Cardiotoxicity risk stratification

Cardiotoxicity monitoring plan

Cardioprotective treatment in case  
of LV dysfunction or HF

Decision to continue, interrupt or  
restore cancer treatment

Recommendation for long - term surveillance

# Screening

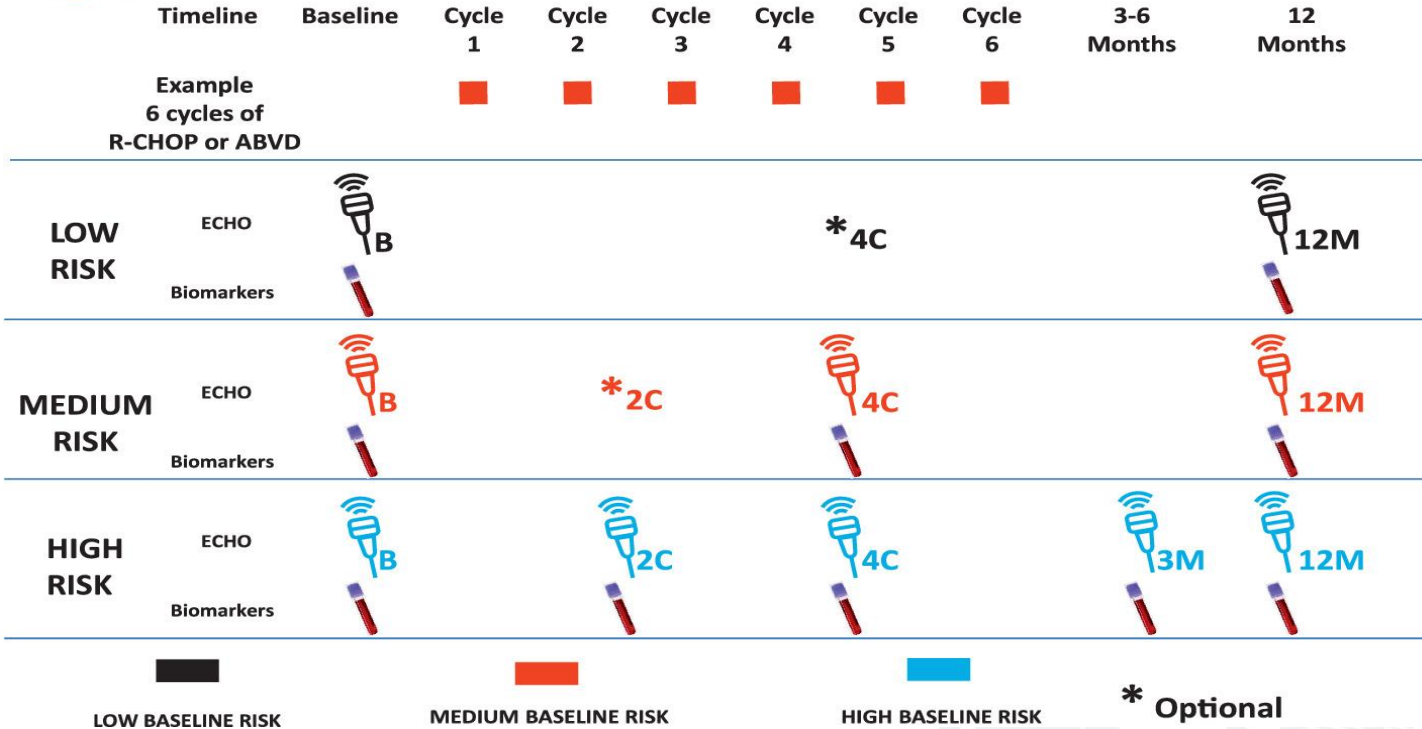
## ASCO Guidelines:

- Routine imaging surveillance may be offered during treatment to patients at risk
- TTE 6-12 months after cancer therapy completion may be offered in patients at risk

Side Note: Be aware of possible breast spacers if considering MRI



# Anthracycline Surveillance Protocol



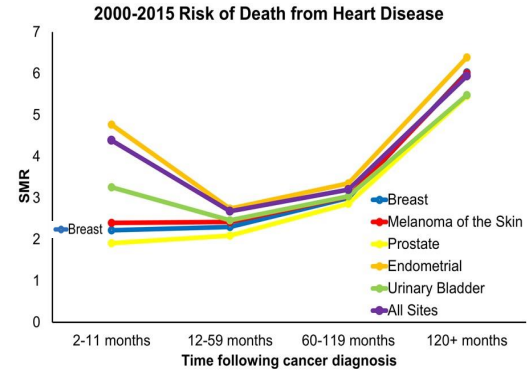
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  - Ensure lifelong CV health
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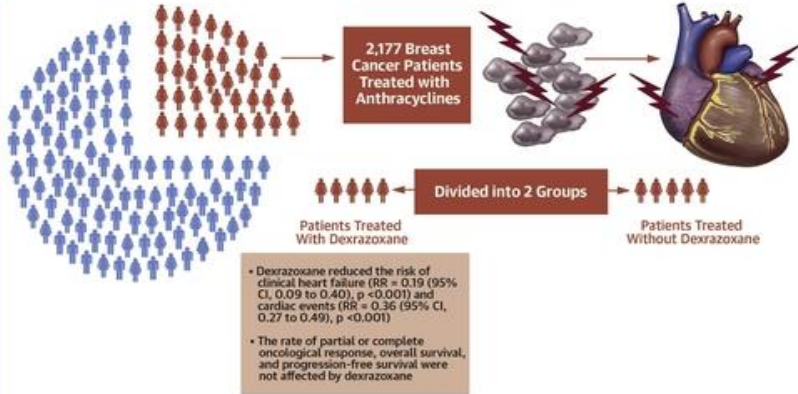


## Cardioprotection?

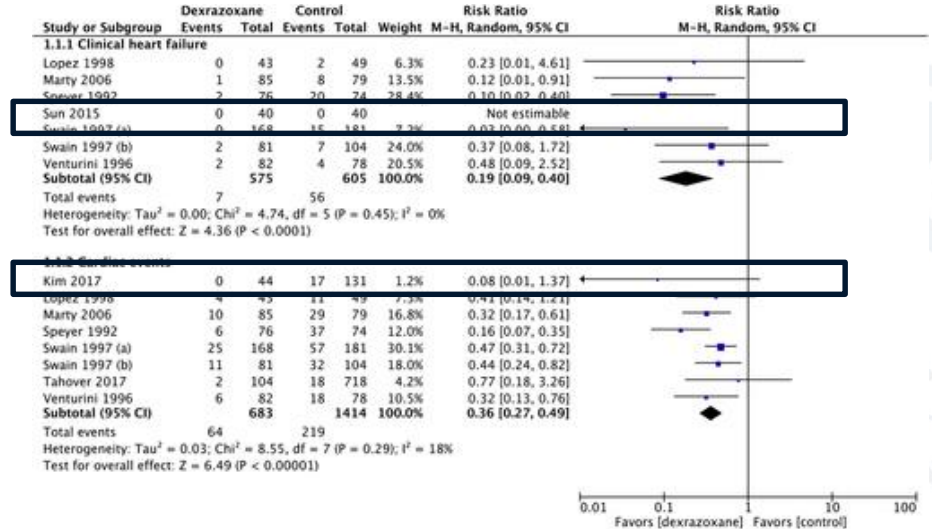
- ACEs or ARBs
- Selected BBs
- Dexrazoxane
- Treat Hyperlipidemia

# Dexrazoxane

## CENTRAL ILLUSTRATION: Dexrazoxane in Breast Cancer Patients Under Anthracycline-Based Chemotherapy



Macedo, A.V.S. et al. *J Am Coll Cardiol CardioOnc*. 2019;1(1):68-79.



Ariane V.S. Macedo et al. *J Am Coll Cardiol CardioOnc* 2019; 1:68-79.



# Other Cardioprotection

- Mixed results
- Different study populations
- Modest clinical benefit
- Targeted use in higher risk patients most likely to show benefit

**Table 2.** Classes of cardiovascular therapeutics that have some clinical trial evidence to suggest cardioprotection during anticancer therapy<sup>a</sup>

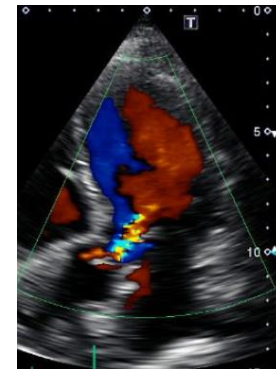
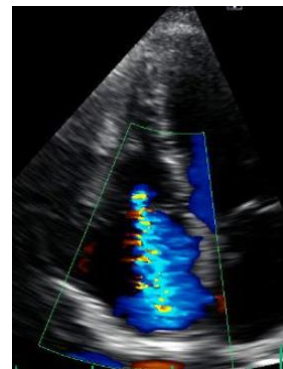
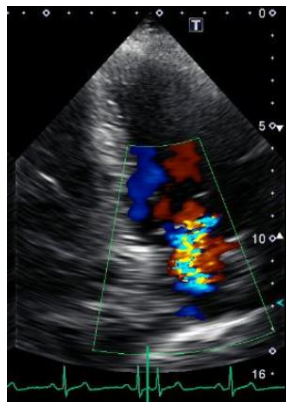
Class of CV therapy	Examples
ACE-I	Enalapril
ARB	Candesartan
MRA	Spirolactone
Statin	Pravastatin (many statins) Atorvastatin
Iron chelation/topoisomerase II inhibitor	Dexrazoxane
Antiplatelet	Aspirin
Anticoagulant	Enoxaparin Rivaroxaban/apixaban
BB	Carvedilol Nebivolol
Combination of ACE-I/BB	Enalapril Carvedilol

<https://doi.org/10.1016/j.annonc.2019.10.023>

# BACK TO THE CASE

# Patient Follow-up

- 63 yo with T4dN2, stage IIIB at least, inflammatory breast cancer, ER-, PR-, HER2-
- Independent review of TTE – valve disease no more than moderate (LVEF 55%)
- Recommend proceeding forward with ddAC-T
- Increase lisinopril to 20 mg PO BID
- Add carvedilol 6.25 mg PO BID
- Obtained NT-Pro BNP after 1 week
- Repeat TTE after 3<sup>rd</sup> cycle



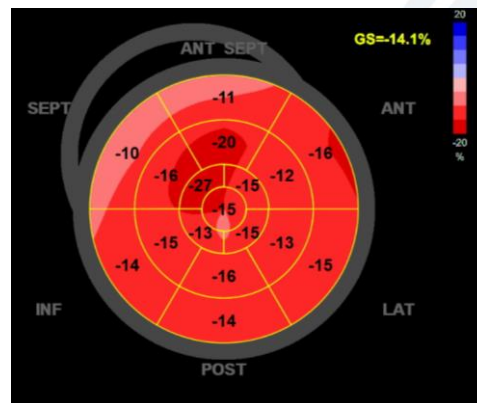
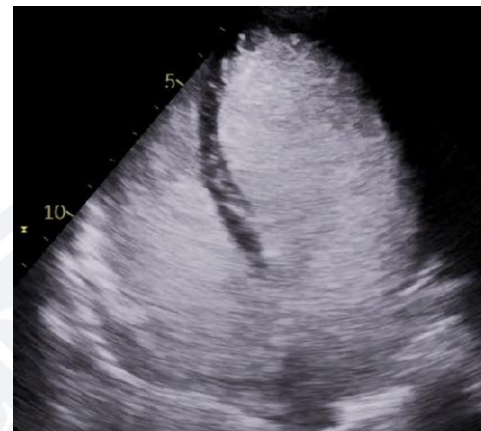


# Patient Follow-up

## Surveillance

- NT-Pro BNP after 1 week: 144
- TTE in 4 weeks after cycle 3:
  - LVEF 53%, GLS -14%
- TTE additional 2 months later:
  - LVEF 50%, GLS -14%
- TTE remained stable at 1 year
- Patient clinically stable at 2 years

Normal LV cavity size  
LVEF 50%  
GLS -14%  
Mild MR/AR, Mod TR



# ANOTHER REPRESENTATIVE CASE

# ER+/PR+/HER2-

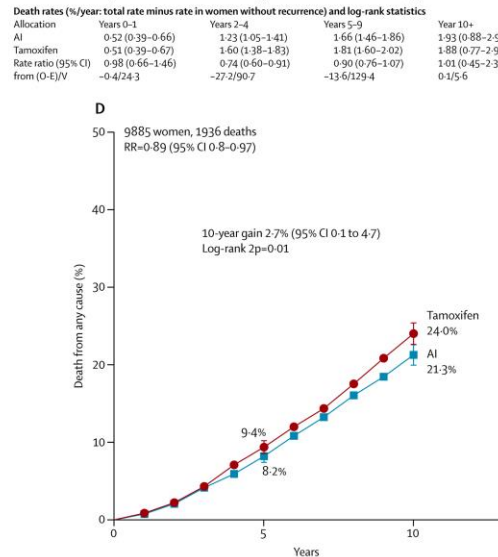
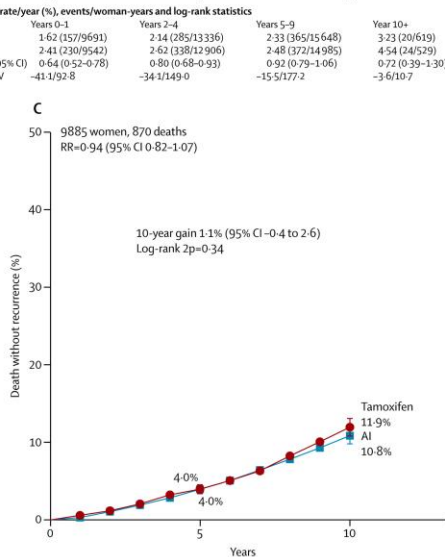
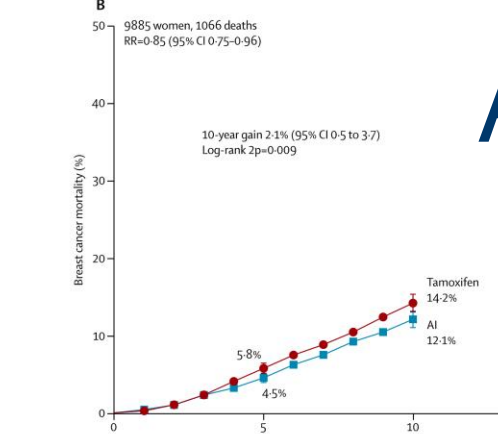
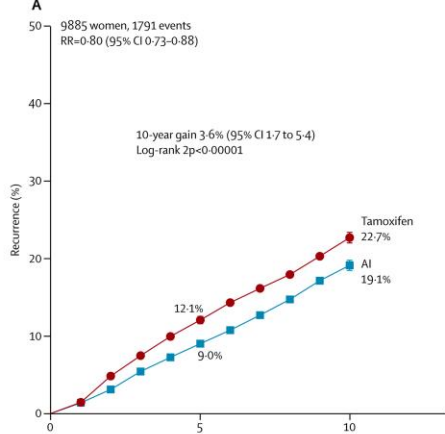
- 44-year-old woman
- Clinical Stage IIIA, T3N1M0 left breast
- ILC, ER+, PR+, HER-2/neu -. Ki 67 20-25%, grade 2
- 1 out of 2 sentinel lymph nodes +
- Neoadjuvant letrozole and OS with Ki67 2% at 1 month
- Left modified radical mastectomy, multifocal ILC, 5 cm, grade 1, 7 negative lymph nodes
- Prophylactic right mastectomy – no pathology
- -> adjuvant radiation therapy with IMRT to left chest wall

# Treatment considerations

- (Neo)adjuvant Endocrine +/- Chemo
- Surgery
- Radiation

# Adjuvant Hormonal Therapy

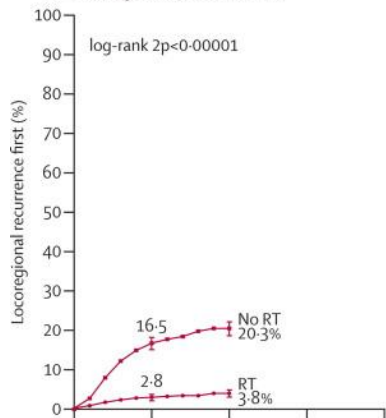
- Tamoxifen reduces recurrence by ~50%, survival by ~30%
- Als improve on tamoxifen



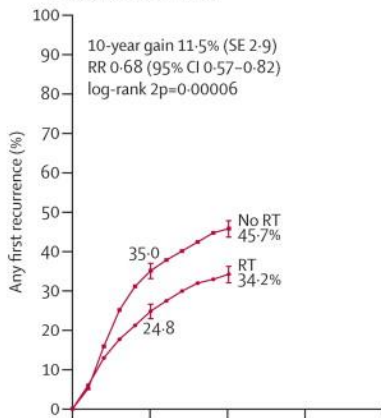
EBCTG Lancet 2015

### 1314 pN1-3 women with Mast+AD

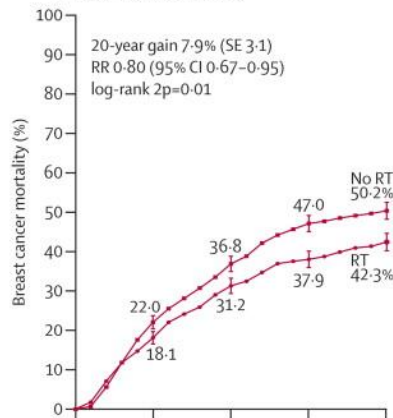
**A** Locoregional recurrence first



**B** Any first recurrence

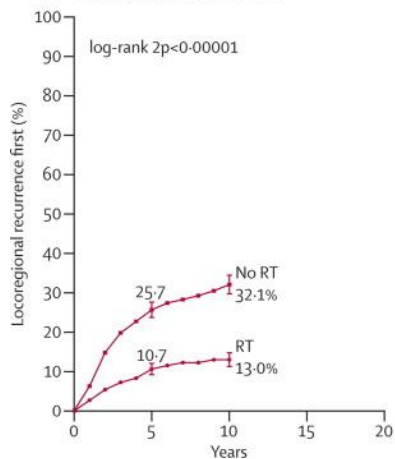


**C** Breast cancer mortality

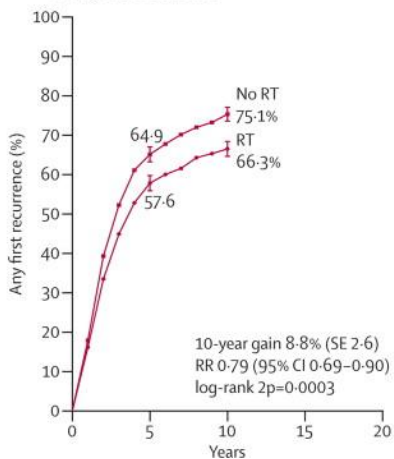


### 1772 pN4+ women with Mast+AD

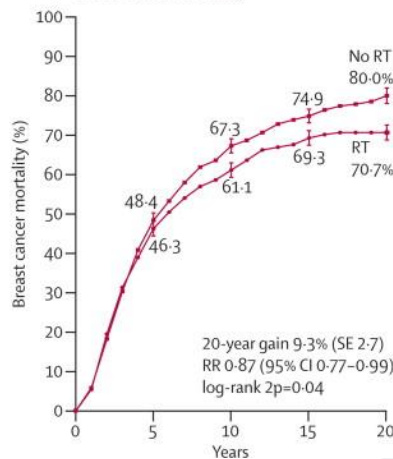
**D** Locoregional recurrence first



**E** Any first recurrence



**F** Breast cancer mortality



# Post-Mastectomy XRT

EBCTCG Lancet 2014

# CARDIOVASCULAR RISK CONSIDERATIONS

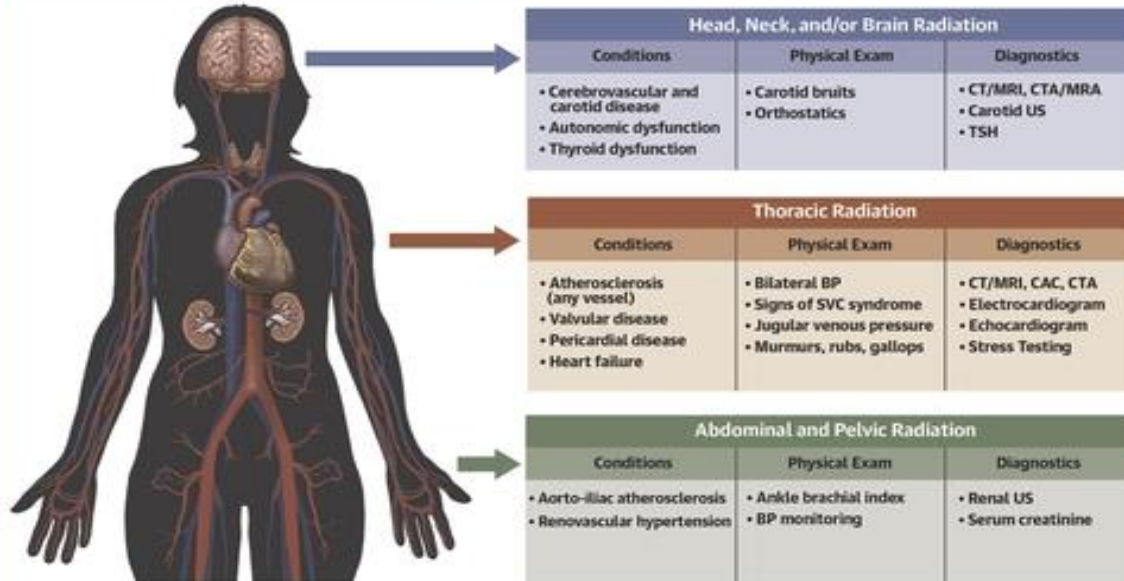
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# CV Effects of RT

## CENTRAL ILLUSTRATION: Therapeutic Radiation: Potential Cardiovascular Effects and Practical Screening Tools

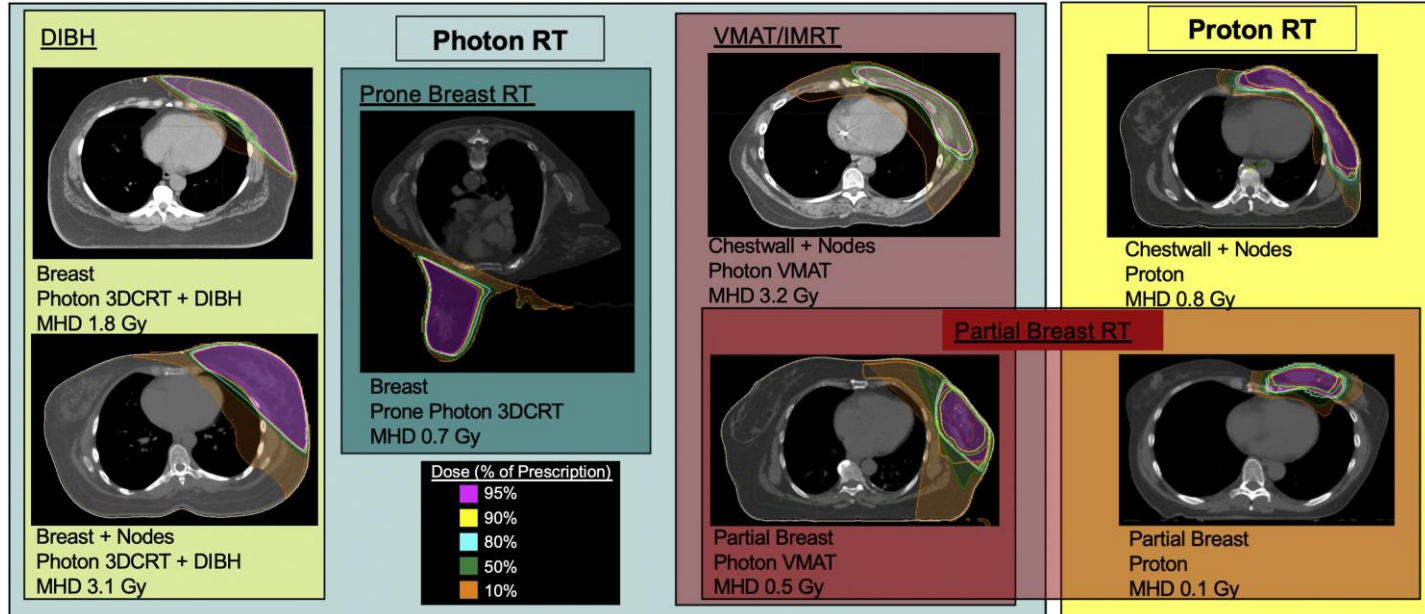


Mitchell, J.D. et al. J Am Coll Cardiol CardioOnc. 2021;3(3):360-380.





# Minimizing Cardiac Effects



Bergom C, Mitchell JD, et al. *J Am Coll Cardiol CardioOnc* 2021; 3:343-359.



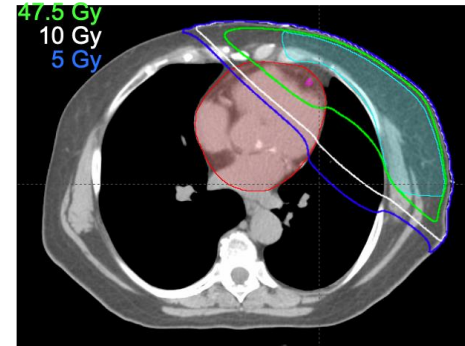
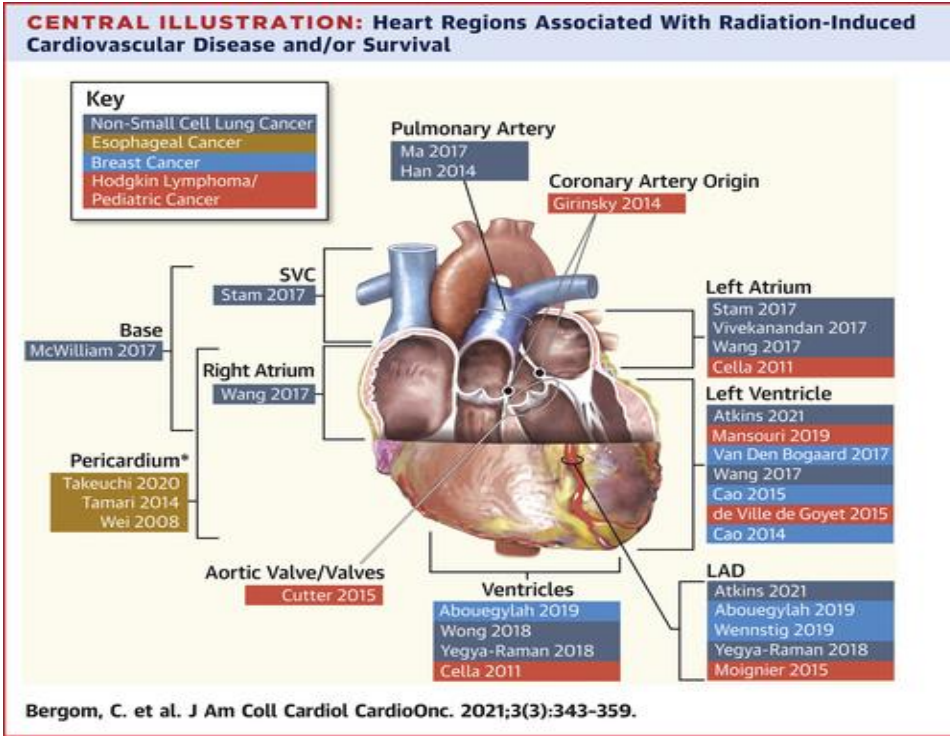
**JACC**  
CardioOncology  
An Open Access Journal

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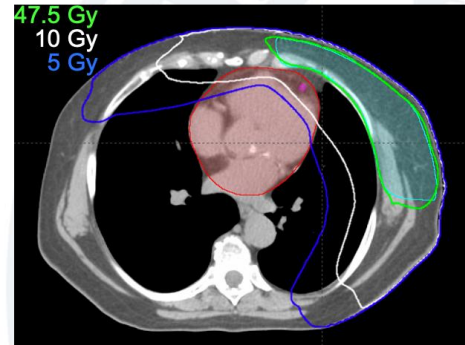


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# CV Effects of RT



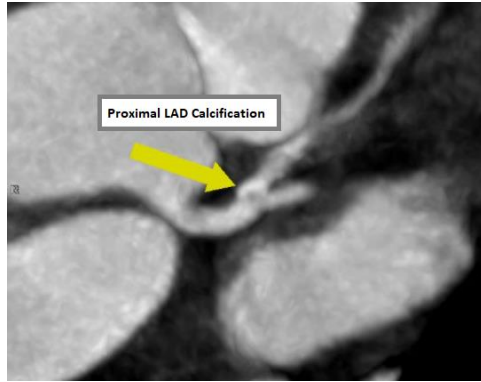
3D CRT  
DIBH



VMAT  
DIBH

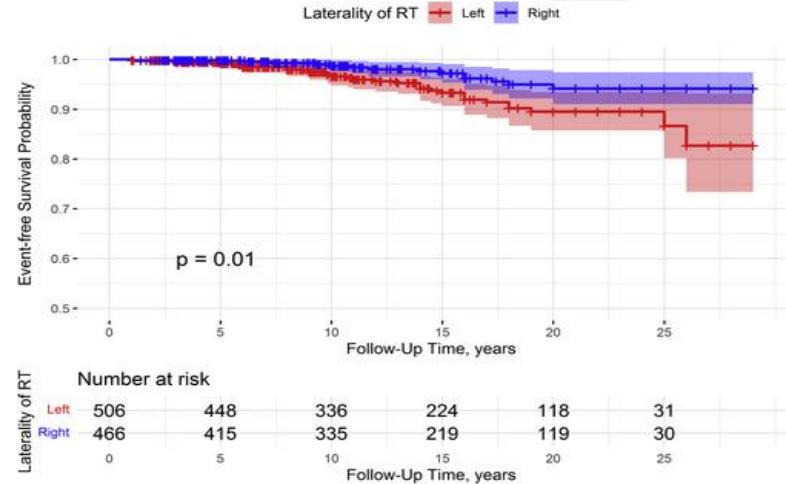


# CV Effects of RT



57 yo; 70% prox LAD  
13 years after RT in 2007  
(Negative cath 2013)

## CAD Incidence in Left vs Right RT for Breast Cancer in Women < 55 years



Lauren E. Carlson et al. *J Am Coll Cardiol CardioOnc* 2021; 3:381-392.



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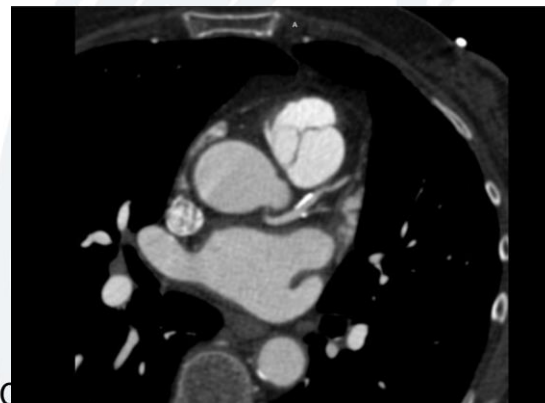
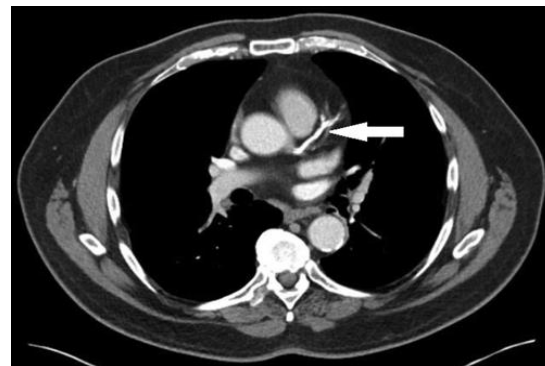


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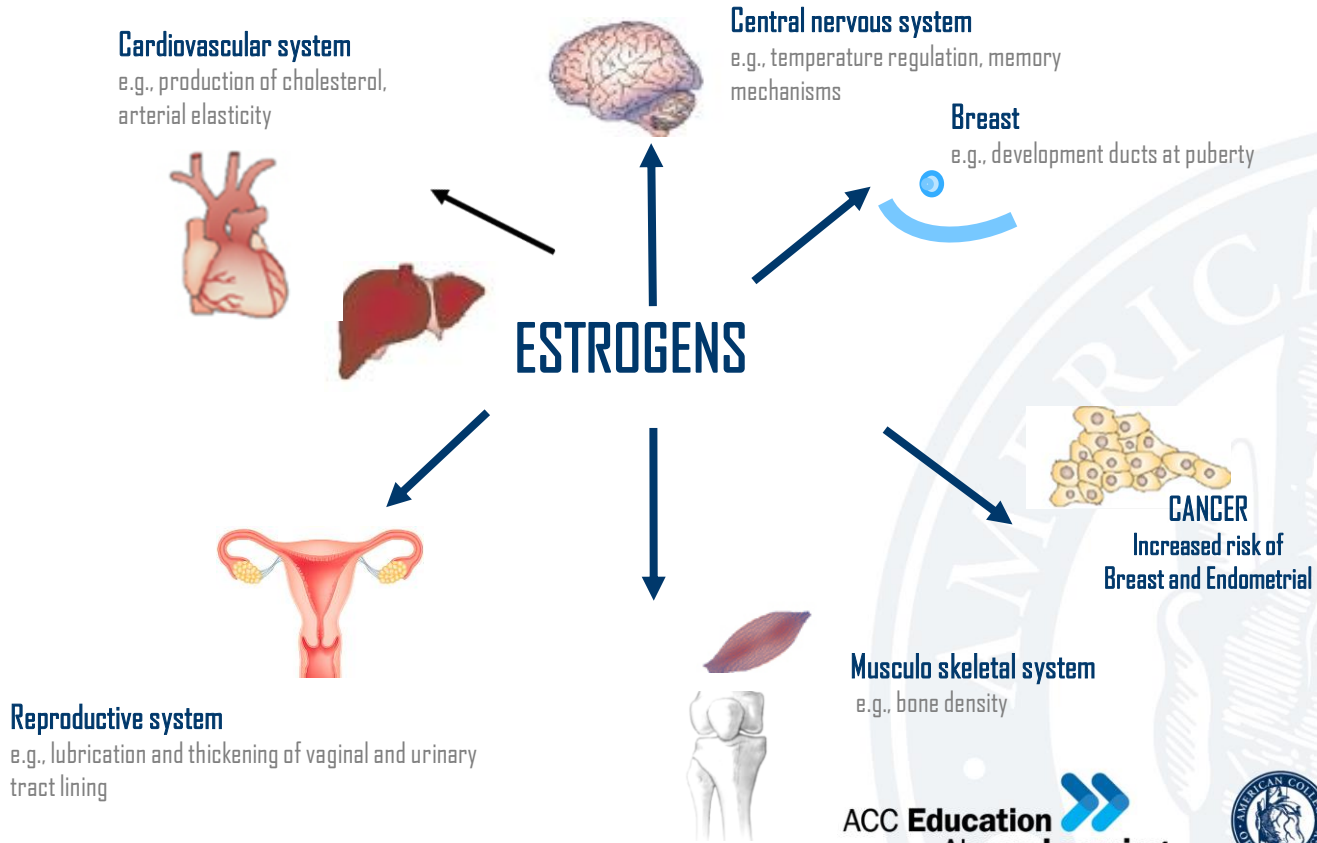
# Screening Recommendations

	HEAD & NECK REGION	THORACIC REGION	ABDOMINAL & PELVIC REGION
Baseline	<ul style="list-style-type: none"> <li>Comprehensive CV history &amp; physical exam</li> <li>Review available CT imaging for atherosclerotic calcification</li> <li>Optimize CV risk factors and disease</li> <li>Utilize available advanced techniques to minimize CV exposure</li> </ul>		
Annually	<ul style="list-style-type: none"> <li>Comprehensive CV history &amp; physical exam</li> <li>Review available CT imaging for atherosclerotic calcification</li> <li>Optimize CV risk factors and disease</li> </ul>		
	<ul style="list-style-type: none"> <li>Orthostatic vital signs</li> <li>Auscultation of carotid arteries</li> </ul>	<ul style="list-style-type: none"> <li>CV exam</li> <li>Blood pressure in both arms</li> <li>Signs of superior vena cava obstruction/stenosis</li> </ul>	<ul style="list-style-type: none"> <li>Vascular exam including lower extremity pulses and abdominal bruits</li> <li>Symptoms of claudication</li> <li>Renal function</li> </ul>
1 Year	Carotid US in high-risk patients	TTE at 6-12 months in high-risk patients	
Every 5 Years	Carotid US	<ul style="list-style-type: none"> <li>TTE</li> <li>Ischemic evaluation</li> </ul>	

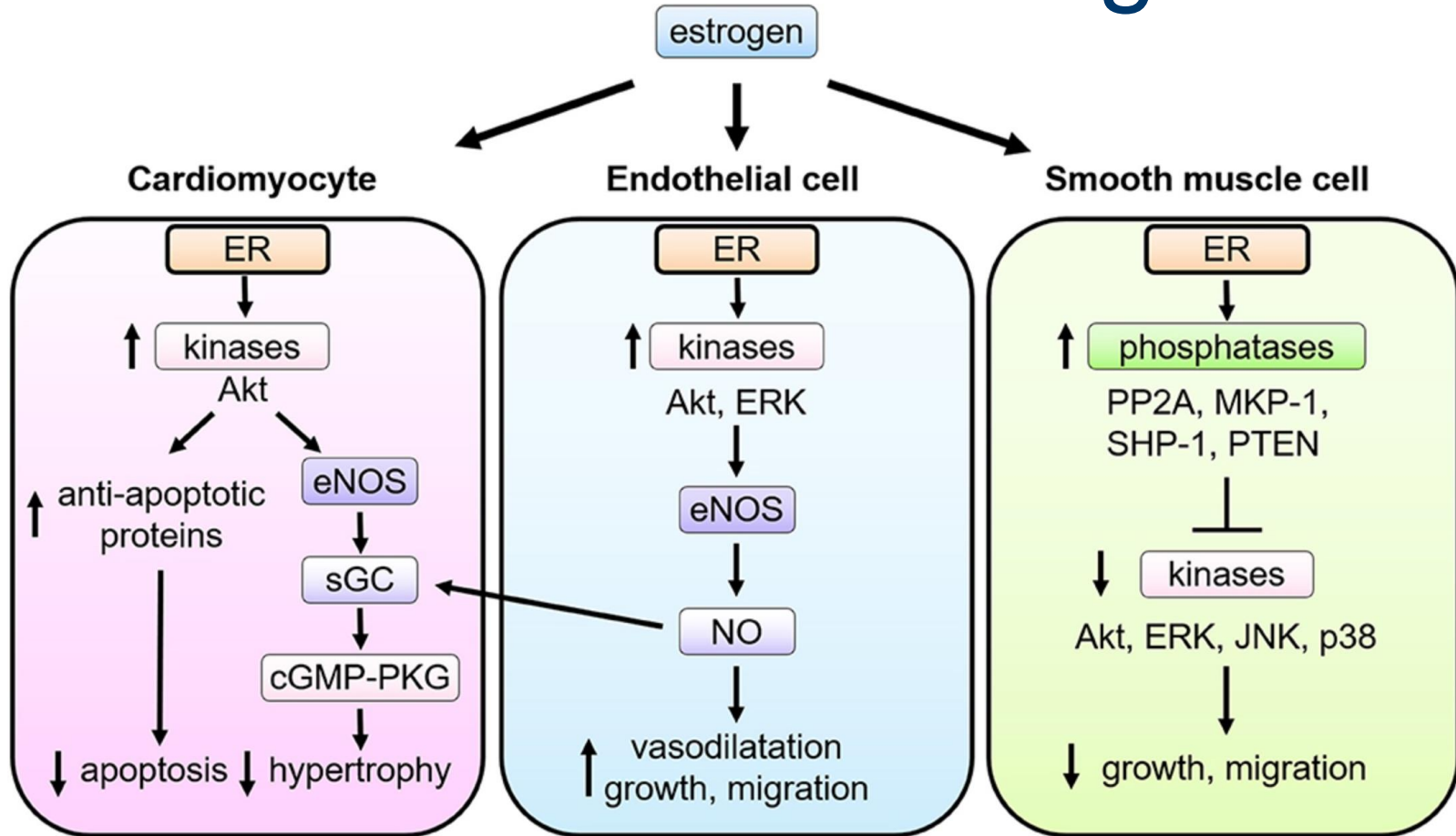
Joshua D. Mitchell et al. *J Am Coll Cardiol CardioOnc* 2021; 3:360-380.



# Effects of Estrogens

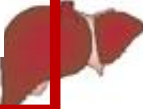



# CV Effects of Estrogen



# Clinical Effects of Estrogen Deprivation (Anti-Estrogens)

**Cardiovascular system**  
Hypercholesterolemia  
Myocardial infarction and ischemia  
Angina  
Cerebrovascular accident



**Central nervous system**  
Hot flashes and night sweats  
Depression  
Headache  
Cognitive dysfunction  
Fatigue

**ANTI-ESTROGENS**

**Anti-CANCER**

Overall impact on quality of life (QoL),  
function, morbidity, late mortality



**Reproductive system**  
Vaginal and urothelial irritation, dryness  
Atrophic vaginitis, urinary issues and  
incontinence



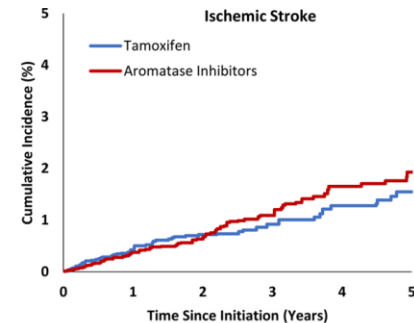
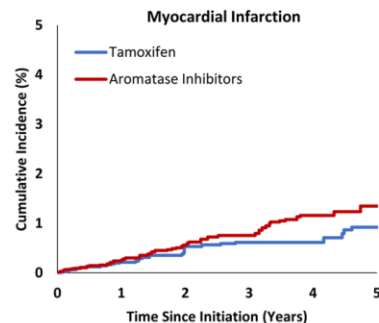
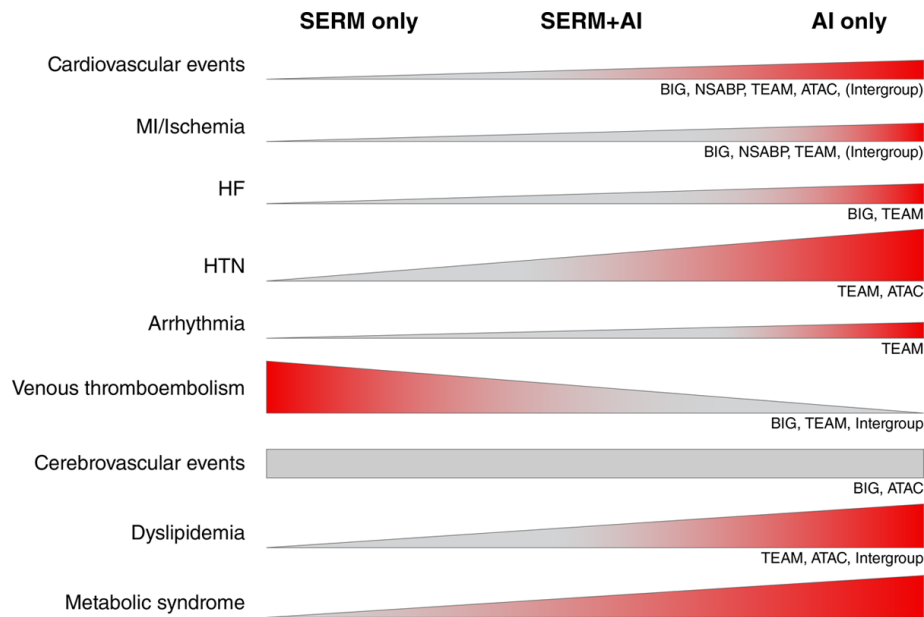
**Musculo skeletal system**  
Osteopenia  
Osteoporosis, Bone fracture  
Arthralgias

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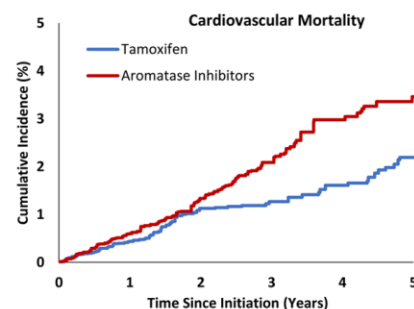
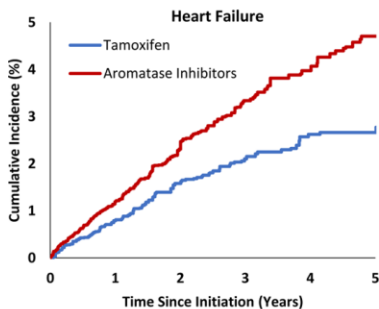
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# Clinical Effects of Estrogen Deprivation (Anti-Estrogens)



10330 6034 3744 2283 1555 834  
9083 5374 3416 2252 1478 804

10340 6052 3762 2293 1563 840  
9161 5402 3436 2266 1493 812



10340 6052 3762 2293 1563 840  
9161 5402 3436 2266 1493 812

10356 6066 3777 2306 1573 844  
9110 5405 3447 2278 1500 817

Okwuosa, et al. Circulation: Genomic and Precision Medicine. 2021  
DOI: (10.1161/HCG.0000000000000082)

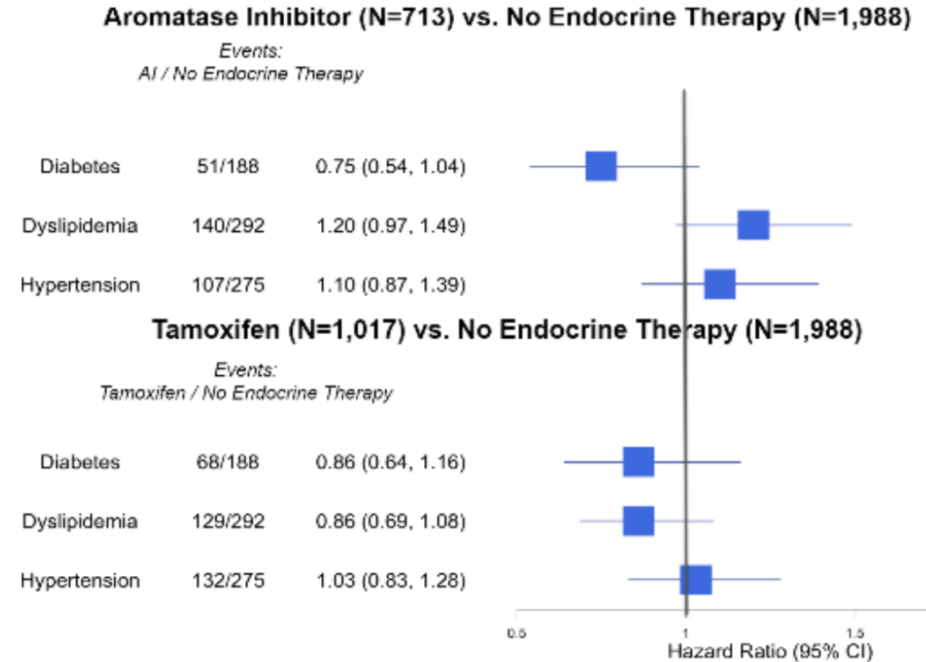
Khosrow-Khavar, et al. Circulation. Aromatase Inhibitors and the Risk of Cardiovascular Outcomes in Women With Breast Cancer, 2020. DOI: (10.1161/CIRCULATIONAHA.119.044750)



# Endocrine Tx Effects- Premenopausal Women in the Pathways Heart Study

## Results

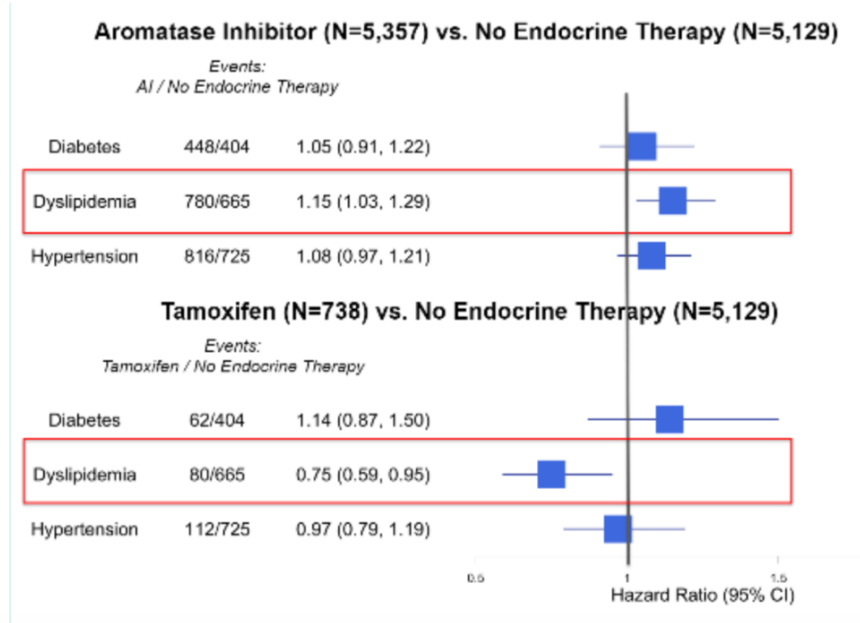
- 14,942 breast cancer survivors
- 24.9% premenopausal at baseline
  - 27.3% used tamoxifen
  - 19.2% used AI
  - 53.5% did not use endocrine therapy
  - Neither tamoxifen nor AI associated with increased risk of diabetes, dyslipidemia or hypertension compared to those who did not



# Endocrine Tx Effects- Postmenopausal Women in the Pathways Heart Study

## Results

- 11,224 postmenopausal patients
  - 6.6% took tamoxifen
  - 47.7% took AI
  - 45.7% did not take ET
- Tamoxifen and AI not associated with DM or HTN
- AI users had higher risk of dyslipidemia
- Tamoxifen users had lower risk of dyslipidemia



# PATIENT FOLLOW-UP

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# Metastatic Disease

- L2 Bone met diagnosed 7 years later
- ER+, PR+, HER2+ (3+ on IHC). FISH HER2:CEP17 9.95, HER2 copy number 20.4
- Palliative spine radiation
- Palliative Herceptin, Perjeta + weekly Taxol (x 6 months then Exemestane)



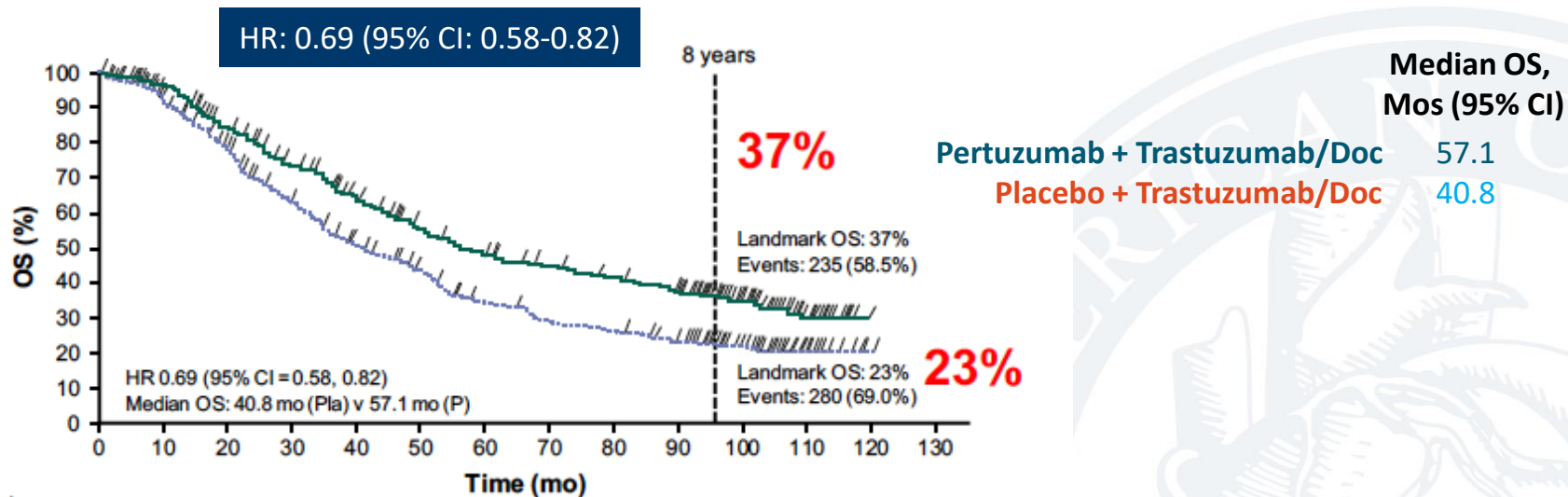
# TREATMENT CONSIDERATIONS

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# CLEOPATRA: Standard First-Line Treatment for HER2+ MBC with Pertuzumab, Trastuzumab, and Docetaxel



Number at risk

	0	10	20	30	40	50	60	70	80	90	100	110	120	130
— P + H + D	402	371	318	269	228	188	165	150	137	120	71	20	0	0
- - - Pla + H + D	406	350	289	230	181	149	115	96	88	75	44	11	1	0

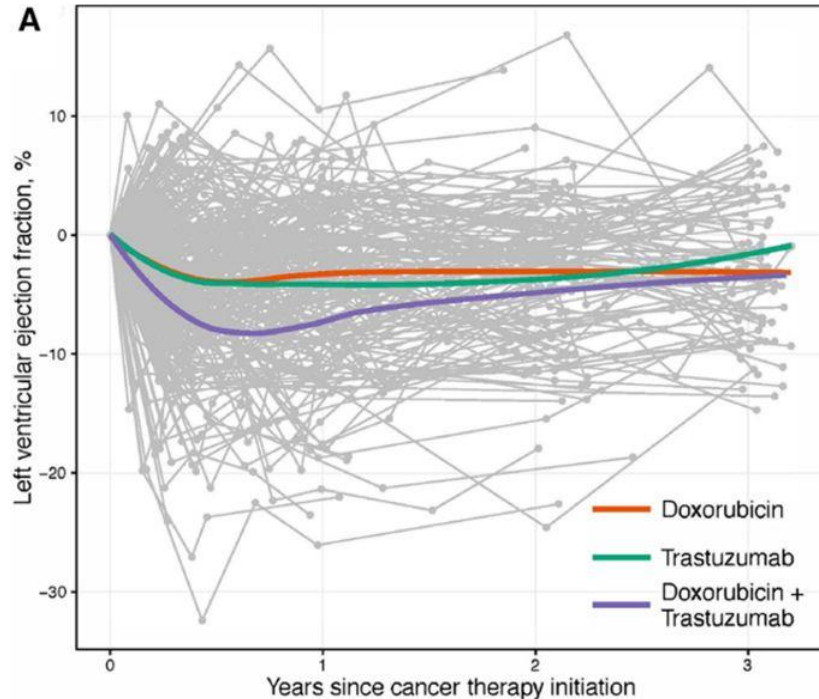
# CARDIOVASCULAR RISK CONSIDERATIONS

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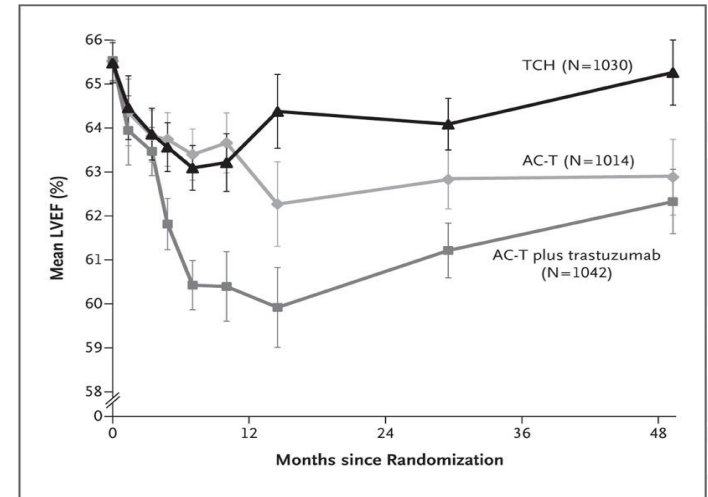


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# Trastuzumab and HF



Narayan, Ky et al. *Circulation*. Detailed Echocardiographic Phenotyping in Breast Cancer Patients, 2017.  
DOI: (10.1161/CIRCULATIONAHA.116.023463)



Slamon D et al. *N Engl J Med* 2011;365:1273-1283.



# How to Follow, Manage and Treat Cardiac Dysfunction in Patients With Her2+ Breast Cancer

Anne Blaes, MD, MS,<sup>a</sup> Charlotte Manisty, MD, PhD,<sup>b</sup> Ana Barac, MD, PhD<sup>c</sup>

**TABLE 1 Proposed Framework for Cardiology and Oncologic Risk Stratification for Cardiac Monitoring With Trastuzumab-Based Therapies in HER2-Positive Breast Cancer**

Oncology Risk Group CV Risk Group	Early Disease				Metastatic Disease	
	Low		Intermediate/High		Low/Intermediate	Intermediate/High
	Low	Intermediate/High	Low	Intermediate/High		
First-line treatment options*	TH	TH	ACTHP, TCHP, TCH	ACTHP,† TCHP, TCH	THP	THP, TH
Treat modifiable risk factors	x	x	x	x	x	x
Refer to cardio-oncology/cardiology		x		x		x
Baseline echocardiography	x	x	x	x	x	x
3 monthly echocardiograms	x‡	x	x	x	x§	x§
Blood biomarkers (troponin, NT-proBNP)		x		x		x
Cardioprotection		x		x		x
Echo 6 to 12 months post-completion	x	x	x	x	NA	NA

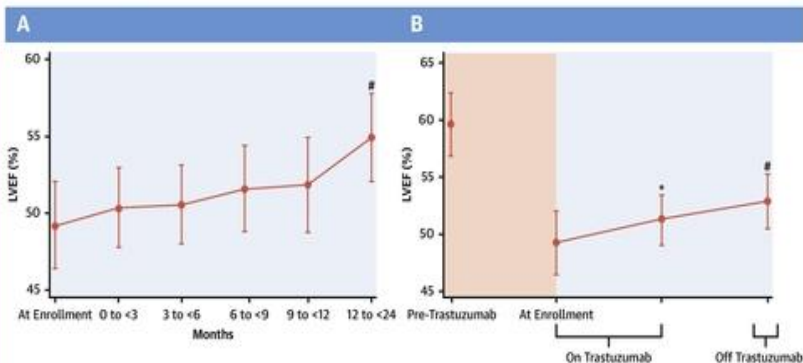
Low CV risk: 0 or 1 CV risk factors. Intermediate/high CV risk: presence of >2 CV risk factors, presence of cardiac dysfunction, significant valvular disease, or other. \*First-line oncology treatment options will continue to evolve based on new trial results and should be discussed with oncologist. †ACTHP in this situation could be considered with cardiology input. ‡Reasonable to reduce frequency of echocardiograms. §Consider reduced frequency if stable for 12 months.

ACTHP = doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, pertuzumab; CV = cardiovascular; NA = not applicable; NT-proBNP = N-terminal pro-brain natriuretic peptide; TCHP = docetaxel, carboplatin, trastuzumab, pertuzumab; TH = paclitaxel (Taxol) and trastuzumab (Herceptin); THP = docetaxel or paclitaxel, trastuzumab, pertuzumab.

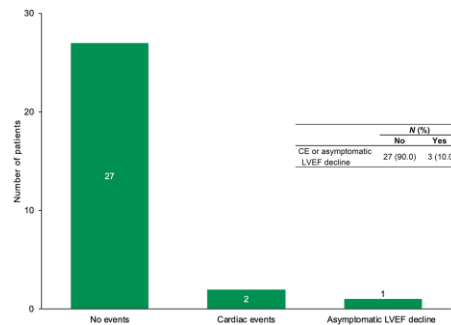


# SCHOLAR and SAFE-HEART

## CENTRAL ILLUSTRATION: Continuing Trastuzumab Despite Mild Cardiotoxicity: LVEF Over Time

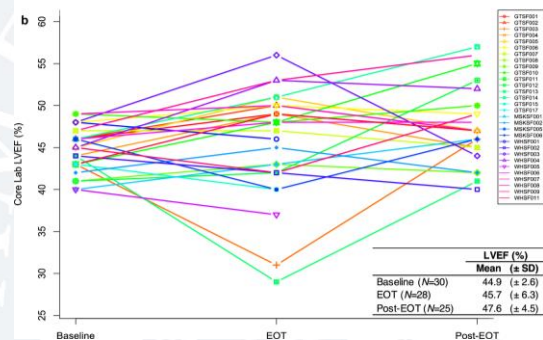


Leong, D.P. et al. J Am Coll Cardiol. 2019;1(1):1-10.

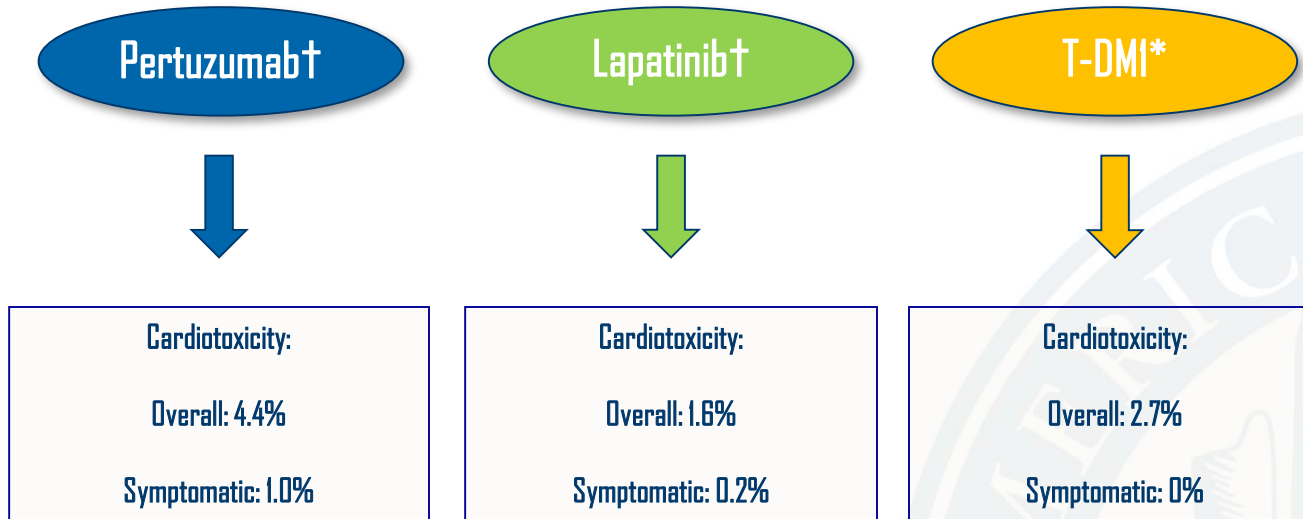


*Breast Cancer Research and Treatment* volume 175, pages 595–603 (2019)

“Permissive Cardiotoxicity”



# Non-Trastuzumab HER-2 Antagonists



\*Toxicity over 12 mos with monotherapy  
†Frequently administered as part of combination HER2 therapy

\* Dual Her-2 antagonist therapy generally w/ no ↑ cardiotoxicity compared to monotherapy

Swain et al. *Oncologist* 2013;18:257-264.  
Perez et al. *Mayo Clinic Proc* 2008;83(6):679-86.  
Krop et al. *JCO* 2015;33:1136.

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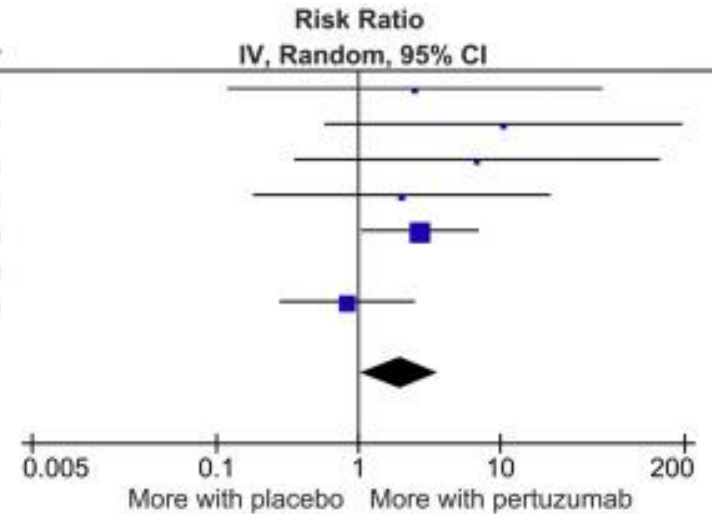


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# Increased HF with HP?

Study or Subgroup	pertuzumab		placebo		Weight	Risk Ratio	
	Events	Total	Events	Total		IV, Random, 95% CI	Year
Gianni et al 2016	2	215	0	107	4.3%	2.50 [0.12, 51.62]	2016
Urruticochea et al 2017	5	228	0	218	4.8%	10.52 [0.59, 189.12]	2017
Rimawi et al 2018	3	127	0	124	4.6%	6.84 [0.36, 130.99]	2018
Tabernero et al 2018	2	385	1	388	6.9%	2.02 [0.18, 22.14]	2018
Von Minckwitz et al 2019	16	2364	6	2405	45.4%	2.71 [1.06, 6.92]	2019
Shao et al 2019	0	218	0	110		Not estimable	2019
Swain et al 2020	6	408	7	396	34.0%	0.83 [0.28, 2.45]	2020
<b>Total (95% CI)</b>		<b>3945</b>		<b>3748</b>	<b>100.0%</b>	<b>1.97 [1.05, 3.70]</b>	

Total events 34 14  
 Heterogeneity: Tau<sup>2</sup> = 0.00; Chi<sup>2</sup> = 4.89, df = 5 (P = 0.43); I<sup>2</sup> = 0%  
 Test for overall effect: Z = 2.11 (P = 0.04)



# BACK TO THE CASE

# Surveillance TTEs

- Baseline: LVEF 57%
- 3 mo: LVEF 54%, GLS -19.6%
- 6 mo: LVEF 70%
- 10 mo: LVEF 57%, GLS -14.8%
- 14 mo: LVEF 50-54%, mod LV dilation, GLS -12.5%
- 20 mo: LVEF 45%, GLS -13% -> referred to Cardio-Onc

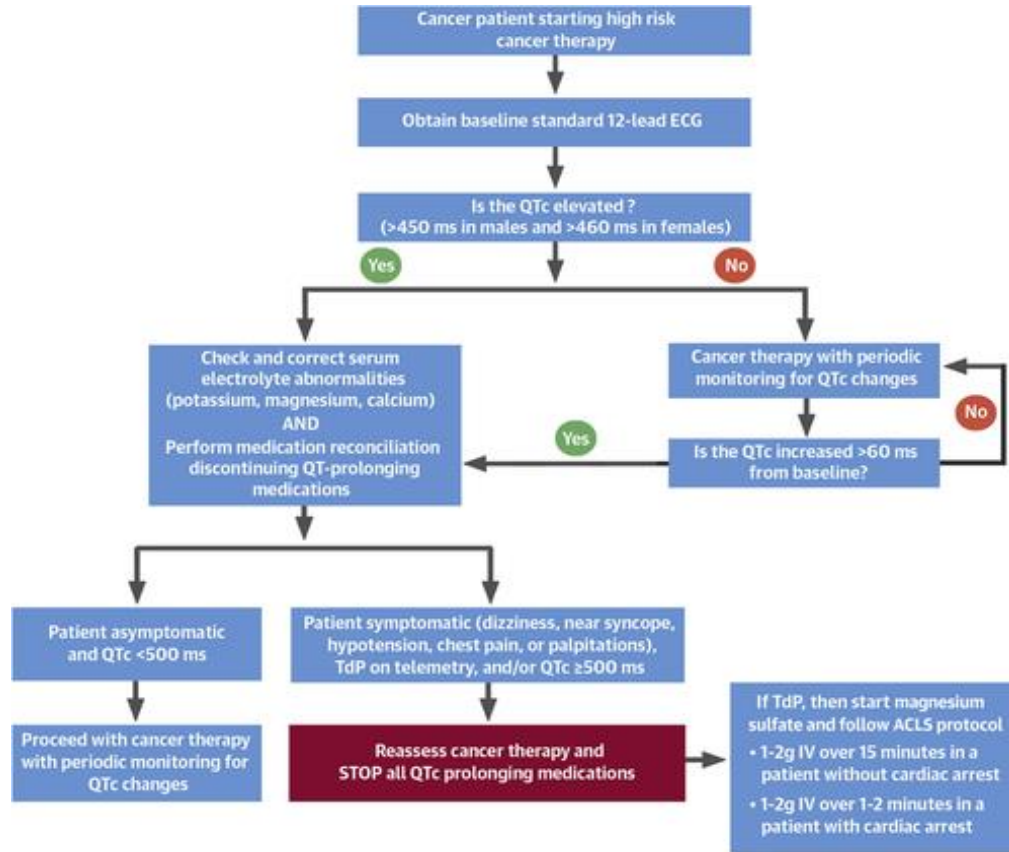
# Cardio-Oncology Consult

- Lipid panel (LDL 110 -> rosuvastatin 10 mg)
- Continue lisinopril, add carvedilol
- Continue trastuzumab
- Hold pertuzumab
- Enrolled in cardiac MRI surveillance -> confirmed reduced LVEF
- LVEF recovers to 56%, GLS -16.1% on most recent TTE 3 years after starting therapy

# OTHER NOTABLE DRUG SIDE EFFECTS AND FUTURE DIRECTIONS



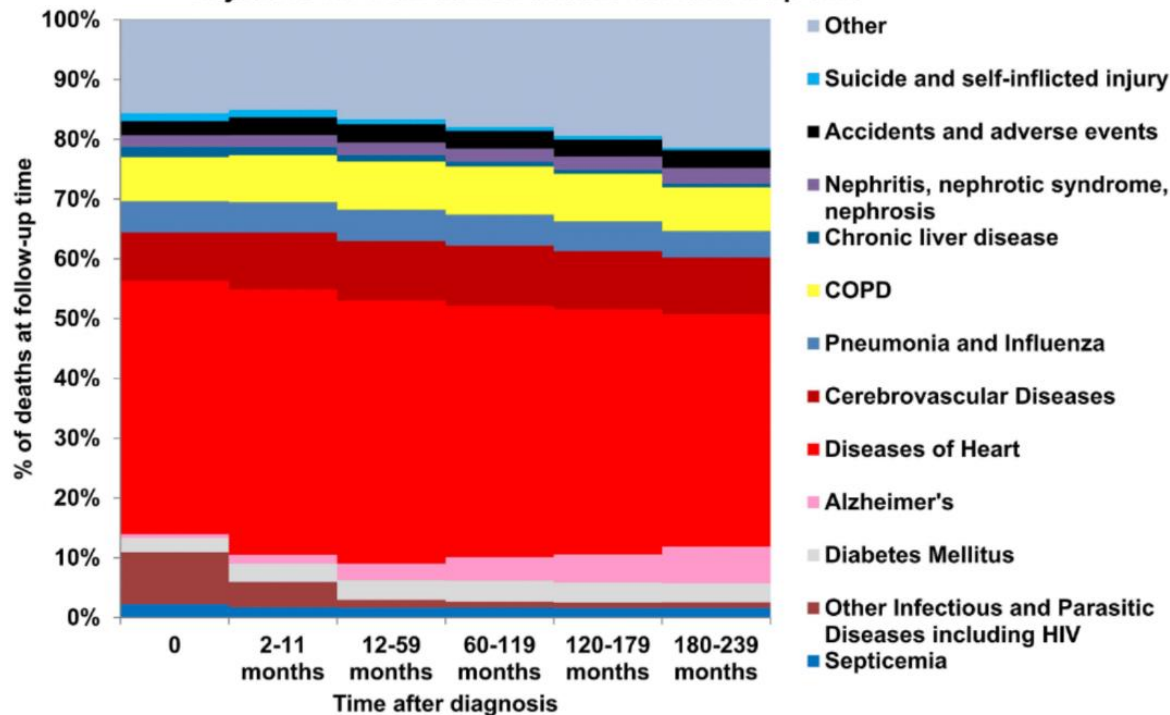
# Other Notable Side Effects



- Capecitabine
  - Vasospasm, Long QTc
- Ribociclib
  - Long QTc

# What do cancer survivors die of?

Objective III: Non-cancer deaths vs. follow-up time



## GOAL:

- Maximize cancer therapy
- Optimize CV health

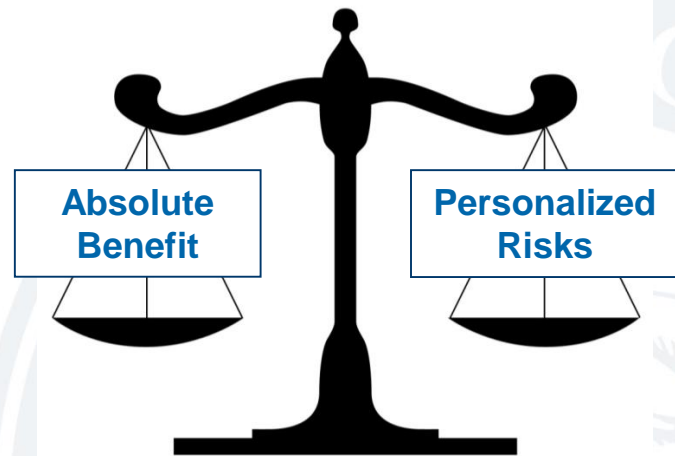
## Future Directions:

- CHIP
- Other novel screening and prevention strategies



# Summary

- Breast CA patients are at increased risk for CV mortality
- Multidisciplinary approach is necessary
- Baseline CV Risk Assessment
- Appropriate CV Monitoring
- “Permissive Cardiotoxicity”



# QUESTIONS?

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