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

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Ann Partridge, MD, MPH
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
- Discuss tx considerations from oncology and cardiovascular perspectives
- Management pearls at time of diagnosis, during therapy, and after tx

A multi-disciplinary approach is required!
Cardiovascular Risk in Breast Cancer Care Continuum

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

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

Increased cardiotoxicity incidence and mortality for:
- Black patients with diverse cancer diagnoses, particularly breast cancer
- Certain Hispanic/Latinx and API groups
- Women receiving anthracycline and radiation therapy
- AYA survivors of lower SES

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 anthracylines, referral to BJH
Oncologic considerations:
• Stage IIIB (at least)
• Inflammatory Breast Cancer
• Multi-agent therapy indicated

CV considerations:
Patient
• ≥ 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.

<table>
<thead>
<tr>
<th>Events</th>
<th>TC</th>
<th>TaxAC</th>
<th>HR</th>
<th>95% CI</th>
<th>Interaction P</th>
<th>HR</th>
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<tbody>
<tr>
<td>Protocol</td>
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<td>USOR 06-090</td>
<td>98</td>
<td>72</td>
<td>1.31</td>
<td>0.97 to 1.78</td>
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<tr>
<td>B-46/07132</td>
<td>71</td>
<td>54</td>
<td>1.34</td>
<td>0.94 to 1.91</td>
<td>0.57</td>
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<tr>
<td>B-49</td>
<td>51</td>
<td>53</td>
<td>1.00</td>
<td>0.68 to 1.48</td>
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<tr>
<td>Hormone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Negative</td>
<td>96</td>
<td>69</td>
<td>1.42</td>
<td>1.04 to 1.94</td>
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<td></td>
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<tr>
<td>Positive</td>
<td>124</td>
<td>110</td>
<td>1.12</td>
<td>0.86 to 1.45</td>
<td>0.28</td>
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<tr>
<td>No. nodes</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>74</td>
<td>66</td>
<td>1.03</td>
<td>0.74 to 1.44</td>
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<td></td>
</tr>
<tr>
<td>1-3</td>
<td>81</td>
<td>67</td>
<td>1.27</td>
<td>0.92 to 1.76</td>
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<tr>
<td>4-9</td>
<td>40</td>
<td>29</td>
<td>1.38</td>
<td>0.85 to 2.22</td>
<td>0.15</td>
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<tr>
<td>≥ 10</td>
<td>25</td>
<td>17</td>
<td>1.69</td>
<td>0.89 to 3.19</td>
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<td></td>
</tr>
<tr>
<td>Overall</td>
<td>220</td>
<td>179</td>
<td>1.23</td>
<td>1.01 to 1.50</td>
<td></td>
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</tr>
</tbody>
</table>

**Absolute Benefit**

**Personalized Risks**

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

**A Deeper Dive into the Data**

**CENTRAL ILLUSTRATION:** Cardiovascular Events in Pivotal Cancer Trials

<table>
<thead>
<tr>
<th>Grade 5</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 2</th>
<th>Grade 1</th>
<th>Overall toxicity</th>
<th>Blood and lymphatic syndrome</th>
<th>Anemia</th>
<th>Febrile neutropenia</th>
<th>Cardiac disorders</th>
<th>Acute coronary syndrome</th>
<th>Heart failure</th>
<th>Left ventricular systolic dysfunction</th>
<th>Myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

A: Relative Frequency of Cardiovascular Disease (CVD) Events Reported in Cancer Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td>1.0</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.5</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>0.2</td>
</tr>
<tr>
<td>Acute Coronary Syndrome</td>
<td>0.1</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>2.8</td>
</tr>
</tbody>
</table>

B: CVD Incidence Rate per 100,000 Person-Years

- Noncancer Trials: 1,408
- Cancer Trials: 542


**Anthracyclines in Early Breast Cancer: The ABC Trials—USOR 06-090, NSABP B-46/I/USOR 07132, and NSABP B-49 (NRG Oncology)**
# A Deeper Dive into the Data

## Anthracyclines in Early Breast Cancer: The ABC Trials

- USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TaxAC (n = 913)</th>
<th>TC (n = 919)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Overall toxicity</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Status</th>
<th>TaxAC</th>
<th>TC</th>
<th>TaxAC</th>
<th>TC</th>
<th>TaxAC</th>
<th>TC</th>
<th>4-Year IDFS (%)</th>
<th>4-Year IDFS Δ (%)</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>HR negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Node negative</td>
<td>459</td>
<td>488</td>
<td>37</td>
<td>52</td>
<td>89.5</td>
<td>87.0</td>
<td>2.5</td>
<td>1.31 (0.86 to 1.99)</td>
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<tr>
<td>1-3 positive nodes</td>
<td>153</td>
<td>119</td>
<td>21</td>
<td>28</td>
<td>85.5</td>
<td>74.6</td>
<td>10.9</td>
<td>1.58 (0.90 to 2.79)</td>
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<tr>
<td>≥ 4 positive nodes</td>
<td>42</td>
<td>40</td>
<td>11</td>
<td>16</td>
<td>71.8</td>
<td>60.8</td>
<td>11.0</td>
<td>1.34 (0.62 to 2.91)</td>
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<tr>
<td>HR positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>358</td>
<td>378</td>
<td>29</td>
<td>22</td>
<td>91.5</td>
<td>94.2</td>
<td>-2.7</td>
<td>0.69 (0.39 to 1.19)</td>
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<tr>
<td>1-3 positive nodes</td>
<td>771</td>
<td>789</td>
<td>46</td>
<td>53</td>
<td>94.3</td>
<td>92.3</td>
<td>2.0</td>
<td>1.14 (0.77 to 1.69)</td>
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</tr>
<tr>
<td>≥ 4 positive nodes</td>
<td>279</td>
<td>280</td>
<td>35</td>
<td>49</td>
<td>87.2</td>
<td>81.4</td>
<td>5.8</td>
<td>1.46 (0.95 to 2.26)</td>
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</tr>
</tbody>
</table>

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

Annals of Oncology 2009 20816-827 DOI: (10.1093/annonc/mdn728)

DOI: (10.1161/CIRCULATIONAHA.116.023463)
Who is at risk?

- **Doxorubicin ≥ 250 mg/m² (or equivalent)**
Who is at risk?

- Doxorubicin ≥ 250 mg/m² (or equivalent)
- Epirubicin ≥ 600 mg/m²
Who is at risk?

- Doxorubicin $\geq 250$ mg/m² (or equivalent)
- Epirubicin $\geq 600$ mg/m²
- Radiation $\geq 30$ Gy (heart in radiation field)
- Anthracyclines + 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.
Who is at risk?

- Anthracyclines + trastuzumab
- Anthracyclines or trastuzumab + risk factors

Risk Factors:

- Age ≥ 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

Risk Factors:

- Doxorubicin ≥ 250 mg/m² (or equivalent)
- Epirubicin ≥ 600 mg/m²
- Radiation ≥ 30 Gy (heart in radiation field)
- Anthracyclines + radiation
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  - LVEF 50-55%
  - Prior Myocardial Infarction
- 2+ CV Risk Factors (during or after)
  - HTN
  - HLD
  - DM
  - Obesity
  - Smoking

*Not enough data for recommendations on newer treatments such as TKIs
Use alternative therapies if they do not compromise cancer outcomes

Minimize radiation exposure to heart

Risk Factors:
- Age ≥ 60
- Compromised cardiac function

- Doxorubicin ≥ 250 mg/m² (or equivalent)
- Epirubicin ≥ 600 mg/m²
- Radiation ≥ 30 Gy (heart in radiation field)
- Anthracyclines + radiation
- Anthracyclines + trastuzumab
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- LVEF 50-55%
- Prior Myocardial Infarction
- 2+ CV Risk Factors (during or after)
- HTN
- HLD
- DM
- Obesity
- Smoking
General Principles

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

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

• 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


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

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
<th>3-6 Months</th>
<th>12 Months</th>
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<tbody>
<tr>
<td>Example 6 cycles of R-CHOP or ABVD</td>
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</tbody>
</table>

**LOW RISK**
- ECHO
- Biomarkers
- B
- *4C
- 12M

**MEDIUM RISK**
- ECHO
- Biomarkers
- *2C
- 4C
- 12M

**HIGH RISK**
- ECHO
- Biomarkers
- 2C
- 4C
- 3M
- 12M

LOW BASELINE RISK  MEDIUM BASELINE RISK  HIGH BASELINE RISK  * Optional
General Principles

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

Cardioprotection?

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

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


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

<table>
<thead>
<tr>
<th>Class of CV therapy</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
<td>Enalapril</td>
</tr>
<tr>
<td>ARB</td>
<td>Candesartan</td>
</tr>
<tr>
<td>MRA</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Statin</td>
<td>Pravastatin (many statins)</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Iron chelation/topoisomerase II inhibitor</td>
<td>Dexrazoxane</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Enoxaparin</td>
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<tr>
<td></td>
<td>Rivaroxaban/apixaban</td>
</tr>
<tr>
<td>BB</td>
<td>Carvedilol</td>
</tr>
<tr>
<td></td>
<td>Nebivolol</td>
</tr>
<tr>
<td>Combination of ACE-I/BB</td>
<td>Enalapril</td>
</tr>
<tr>
<td></td>
<td>Carvedilol</td>
</tr>
</tbody>
</table>

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 3rd 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%
- AIs improve on tamoxifen
Post-Mastectomy XRT
# CV Effects of RT

## Central Illustration: Therapeutic Radiation: Potential Cardiovascular Effects and Practical Screening Tools

### Head, Neck, and/or Brain Radiation
- **Conditions**
  - Cerebrovascular and carotid disease
  - Autonomic dysfunction
  - Thyroid dysfunction
- **Physical Exam**
  - Carotid bruits
  - Orthostatics
- **Diagnostics**
  - CT/MRI, CTA/MRA
  - Carotid US
  - TSH

### Thoracic Radiation
- **Conditions**
  - Atherosclerosis (any vessel)
  - Valvular disease
  - Pericardial disease
  - Heart failure
- **Physical Exam**
  - Bilateral BP
  - Signs of SVC syndrome
  - Jugular venous pressure
  - Murmurs, rubs, gallops
- **Diagnostics**
  - CT/MRI, CAC, CTA
  - Electrocardiogram
  - Echocardiogram
  - Stress Testing

### Abdominal and Pelvic Radiation
- **Conditions**
  - Aorto-iliac atherosclerosis
  - Renovascular hypertension
- **Physical Exam**
  - Ankle brachial index
  - BP monitoring
- **Diagnostics**
  - Renal US
  - Serum creatinine

---

Minimizing Cardiac Effects

CV Effects of RT

**CENTRAL ILLUSTRATION:** Heart Regions Associated With Radiation-Induced Cardiovascular Disease and/or Survival

- **Key**
  - Non-Small Cell Lung Cancer
  - Esophageal Cancer
  - Breast Cancer
  - Hodgkin Lymphoma/Pediatric Cancer

- **Pulmonary Artery**
  - MI 2017
  - Han 2014

- **Coronary Artery Origin**
  - Castor 2014

- **Left Atrium**
  - Stam 2017
  - Viveloroandjan 2017
  - Wang 2017
  - Cella 2011

- **Left Ventricle**
  - Atkinson 2021
  - Mansour 2019
  - Van Den Bosch 2017
  - Wang 2017
  - Cao 2015
  - de Ville de Goyet 2015
  - Cao 2014

- **Right Atrium**
  - Wang 2017

- **SVC**
  - McWilliam 2017

- **Pericardium**
  - Takahashi 2018
  - Tamari 2014
  - Wei 2008

- **Aortic Valve/Valves**
  - Cutter 2015

- **Ventricles**
  - Abouesanah 2019
  - Wong 2018
  - Yegya-Raman 2018
  - Cella 2011

- **LAD**
  - Atkinson 2021
  - Abouesanah 2019
  - Wennstig 2019
  - Yegya-Raman 2018
  - Moignier 2015

CV Effects of RT

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

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

# Screening Recommendations

<table>
<thead>
<tr>
<th>Head &amp; Neck Region</th>
<th>Thoracic Region</th>
<th>Abdominal &amp; Pelvic Region</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Comprehensive CV history &amp; physical exam</td>
<td>• Review available CT imaging for atherosclerotic calcification</td>
<td></td>
</tr>
<tr>
<td>• Optimize CV risk factors and disease</td>
<td>• Utilize advanced techniques to minimize CV exposure</td>
<td></td>
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<tr>
<td>• ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TTE</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>Annually</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Orthostatic vital signs</td>
<td>• CV exam</td>
<td>• Vascular exam including lower extremity pulses and abdominal bruits</td>
</tr>
<tr>
<td>• Auscultation of carotid arteries</td>
<td>• Blood pressure in both arms</td>
<td>• Symptoms of claudication</td>
</tr>
<tr>
<td></td>
<td>• Signs of superior vena cava obstruction/stenosis</td>
<td>• Renal function</td>
</tr>
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</tr>
<tr>
<td><strong>1 Year</strong></td>
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<tr>
<td>Carotid US in high-risk patients</td>
<td>TTE at 6-12 months in high-risk patients</td>
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<tr>
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<tr>
<td><strong>Every 5 Years</strong></td>
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<tr>
<td>Carotid US</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ischemic evaluation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effects of Estrogens

**Cardiovascular system**
e.g., production of cholesterol, arterial elasticity

**Central nervous system**
e.g., temperature regulation, memory mechanisms

**Breast**
e.g., development of ducts at puberty

**Reproductive system**
e.g., lubrication and thickening of vaginal and urinary tract lining

**Musculo skeletal system**
e.g., bone density

**CANCER**
Increased risk of Breast and Endometrial

Adapted from Clemons, NEJM, 2001
CV Effects of Estrogen

Cardiomyocyte
- ER
- Kinases
- Akt
- Anti-apoptotic proteins
- eNOS
- sGC
- cGMP-PKG
- Apoptosis
- Hypertrophy

Endothelial cell
- ER
- Kinases
- Akt, ERK
- eNOS
- NO
- Vasodilatation
- Growth, migration

Smooth muscle cell
- ER
- Phosphatases
- PP2A, MKP-1, SHP-1, PTEN
- Kinases
- Akt, ERK, JNK, p38
- Growth, migration

Ueda et al. Front Endocrinol 2020
Clinical Effects of Estrogen Deprivation (Anti-Estrogens)

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

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

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

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

**Anti-CANCER**
Overall impact on quality of life (Qol), function, morbidity, late mortality

Adapted from Clemons, NEJM, 2001; EBCTCG, Lancet, 2015; EBCTCG, Lancet, 2011
Clinical Effects of Estrogen Deprivation (Anti-Estrogens)

<table>
<thead>
<tr>
<th>Condition</th>
<th>SERM only</th>
<th>SERM+AI</th>
<th>AI only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular events</td>
<td></td>
<td></td>
<td>BIG, NSABP, TEAM, ATAC, (Intergroup)</td>
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<tr>
<td>MI/Ischemia</td>
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<td></td>
<td>BIG, NSABP, TEAM, (Intergroup)</td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td></td>
<td>BIG, TEAM</td>
</tr>
<tr>
<td>HTN</td>
<td></td>
<td>TEAM, ATAC</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
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<td>TEAM</td>
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</tr>
<tr>
<td>Venous thromboembolism</td>
<td>BIG, TEAM, Intergroup</td>
<td></td>
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<tr>
<td>Cerebrovascular events</td>
<td>BIG, ATAC</td>
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<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>TEAM, ATAC, Intergroup</td>
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<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


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

**Median OS, Mos (95% CI)**
- Pertuzumab + Trastuzumab/Doc: 57.1
- Placebo + Trastuzumab/Doc: 40.8

**HR: 0.69 (95% CI: 0.58-0.82)**

CARDIOVASCULAR RISK CONSIDERATIONS
Trastuzumab and HF

DOI: (10.1161/CIRCULATIONAHA.116.023463)

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

Anne Blaes, MD, MS, Charlotte Manisty, MD, PhD, Ana Barac, MD, PhD

<table>
<thead>
<tr>
<th>First-line treatment options*</th>
<th>Low</th>
<th>Intermediate/High</th>
<th>Low</th>
<th>Intermediate/High</th>
<th>Low/Intermediate</th>
<th>Intermediate/High</th>
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</thead>
<tbody>
<tr>
<td>Treat modifiable risk factors</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Refer to cardio-oncology/cardiology</td>
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<td>x</td>
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<tr>
<td>Baseline echocardiography</td>
<td>x‡</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>3 monthly echocardiograms</td>
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<td>x</td>
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<td>x</td>
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<tr>
<td>Blood biomarkers (troponin, NT-proBNP)</td>
<td>x</td>
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<td>x</td>
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<tr>
<td>Cardioprotection</td>
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<td>x</td>
</tr>
<tr>
<td>Echo 6 to 12 months post-completion</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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


“Permissive Cardiotoxicity”
Non-Trastuzumab HER-2 Antagonists

Pertuzumab†

Cardiotoxicity:
Overall: 4.4%
Symptomatic: 1.0%

Lapatinib†

Cardiotoxicity:
Overall: 1.6%
Symptomatic: 0.2%

T-DMI*

Cardiotoxicity:
Overall: 2.7%
Symptomatic: 0%

* 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

Perez et al. Mayo Clinic Proc 2008;83(6);679-86.
Increased HF with HP?

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>pertuzumab</th>
<th>placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Gianni et al 2016</td>
<td>2</td>
<td>107</td>
<td>215</td>
</tr>
<tr>
<td>Urruticoechea et al 2017</td>
<td>5</td>
<td>218</td>
<td>228</td>
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<tr>
<td>Rimawi et al 2018</td>
<td>3</td>
<td>124</td>
<td>127</td>
</tr>
<tr>
<td>Taberner et al 2018</td>
<td>2</td>
<td>388</td>
<td>385</td>
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<tr>
<td>Von Minckwitz et al 2019</td>
<td>16</td>
<td>2405</td>
<td>2364</td>
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<tr>
<td>Shao et al 2019</td>
<td>0</td>
<td>110</td>
<td>218</td>
</tr>
<tr>
<td>Swain et al 2020</td>
<td>6</td>
<td>396</td>
<td>408</td>
</tr>
</tbody>
</table>

Total (95% CI) 3945 | 3748 | 100.0% | 1.97 [1.05, 3.70] 2020

Total events 34 | 14

Heterogeneity: $\tau^2 = 0.00; \text{Chi}^2 = 4.89, df = 5 (P = 0.43); I^2 = 0$

Test for overall effect: $Z = 2.11$ (P = 0.04)

https://doi.org/10.1016/j.cjco.2021.06.019
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?

**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”