Learning Objectives

1. Recognize the most common cancer therapies associated with cardiac toxicity
2. Differentiate standard approaches to managing major cardiac toxicities including,
   • cardiomyopathy,
   • vascular toxicity (hypertension, ischemia),
   • arrhythmia and
   • thromboembolism
3. Develop evidence-based prevention and treatment interventions for chemotherapy-induced cardiomyopathy
4. Explain the various types of radiation-induced heart disease

Cardiology Alphabet Soup

ASCVD: atherosclerotic cardiovascular disease
CABG: coronary artery bypass graft
CAD: coronary artery disease
CV: cardiovascular
HFrEF: heart failure reduced ejection fraction
MI: myocardial infarction
PCI: percutaneous coronary intervention
TdP: torsades de pointe
### Trends in Cancer Survival Rates (1975-2009)

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<tr>
<td>ALL SITES</td>
<td>49%</td>
<td>55%</td>
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<td>Breast (female)</td>
<td>75%</td>
<td>84%</td>
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<td>Colon</td>
<td>51%</td>
<td>60%</td>
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<td>Leukemia</td>
<td>34%</td>
<td>43%</td>
<td>59%</td>
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<td>Lung and bronchus</td>
<td>12%</td>
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<td>Melanoma (skin)</td>
<td>82%</td>
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<td>Ovary</td>
<td>36%</td>
<td>38%</td>
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Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute 2013.

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### Current myocardial disease
- HFrEF, HFpEF, asymptomatic LV dysfunction
- Evidence of CAD (MI, angina, PCI, CABG)
- Moderate and severe valvular heart disease
- Hypertensive heart disease with LVH
- Hypertrophic, dilated, or restrictive cardiomyopathy
- Cardiac sarcoidosis
- Significant cardiac arrhythmias

### Demographic and other CV risk factors
- Age
  - Pediatric population (< 18 years)
  - > 65 years for anthracyclines
- Family history of premature CVD (< 50 yrs)
- Arterial hypertension
- Diabetes mellitus
- Hypercholesterolemia

### Risk Factors for Cardiotoxicity

**Previous cardiotoxic cancer therapy**
- Prior anthracycline use
- Prior radiotherapy to chest or mediastinum

**Lifestyle risk factors**
- Smoking
- High alcohol intake
- Obesity
- Sedentary habit

### Opportunities to Intervene

Reference pending

Eu Heart J 2016; 37:2768-2801
Cancer Treatment and Cardiovascular Effects

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<th>Cancer Treatment</th>
<th>Cardiovascular Adverse Effect</th>
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<td>Left ventricular dysfunction, heart failure, myocarditis, pericarditis, atrial fibrillation, ventricular tachycardia, ventricular fibrillation</td>
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<tr>
<td>Alkylating agents (e.g. cyclophosphamide)</td>
<td>Left ventricular dysfunction, heart failure, myocarditis, pericarditis, arterial thrombosis, limbicord, atrial fibrillation, supraventricular tachycardia</td>
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<td>Taxanes (e.g. paclitaxel)</td>
<td>Bradycardia, heart block, ventricular ectopy</td>
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<td>Antimetabolites (e.g. 5-FU, capecitabine)</td>
<td>Coronary artery disease, coronary artery spasm, atrial fibrillation, ventricular tachycardia, ventricular fibrillation</td>
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<td>Endocrine therapy (e.g. tamoxifen, anastrozole)</td>
<td>Venous thrombosis, thromboembolism, peripheral atherosclerosis, arrhythmias, cardiac dysfunction, pericarditis, heart failure</td>
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<td>HER-2-directed therapies (e.g. trastuzumab)</td>
<td>Left ventricular dysfunction, heart failure</td>
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<td>Cyclin-dependent kinase 4/6 inhibitors (e.g. palbociclib, ribociclib)</td>
<td>QT prolongation</td>
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<td>Radiation therapy</td>
<td>Coronary artery disease, left ventricular dysfunction, heart failure, valvular heart disease, pericardial disease, arrhythmias</td>
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Circulation 2018; 137:e30-e66
## Cardiotoxicity with Selected Chemotherapeutic Agents

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</table>
Case

58-year old African American woman with a history of triple negative, inflammatory breast cancer

- Stage IV with metastases to bone marrow
- Chemotherapy with doxorubicin and cyclophosphamide
  - Initially at a reduced dose and then at a higher dose
  - Long duration of chemotherapy (chronic) due to her disease

How should you follow this patient?

Should you be concerned about her doxorubicin dose?

Anticancer Agents Associated with Heart Failure/Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Frequency of Use</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Doxorubicin</td>
<td>+++</td>
<td>3-26%</td>
</tr>
<tr>
<td>- Epirubicin</td>
<td>+</td>
<td>1-4%</td>
</tr>
<tr>
<td>- Idarubicin</td>
<td>++</td>
<td>5-18%</td>
</tr>
<tr>
<td>- Mitoxantrone</td>
<td>+++</td>
<td>7-22%</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cyclophosphamide</td>
<td>+++</td>
<td>11%</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Decitabine</td>
<td>++</td>
<td>0%</td>
</tr>
<tr>
<td>- Fluorouracine</td>
<td>++</td>
<td>2-6%</td>
</tr>
<tr>
<td>Antimicrotubule agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Docetaxel</td>
<td>++</td>
<td>2-6%</td>
</tr>
<tr>
<td>Protacron inhibitor</td>
<td>++</td>
<td>7%</td>
</tr>
<tr>
<td>- Cetuximab</td>
<td>++</td>
<td>2-5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Frequency of Use</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibody-based tyrosine kinase inhibitors (TKIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Trastuzumab</td>
<td>+++</td>
<td>2-28%</td>
</tr>
<tr>
<td>- Bevacizumab</td>
<td>++</td>
<td>1-11%</td>
</tr>
<tr>
<td>- Pertuzumab</td>
<td>+</td>
<td>2%</td>
</tr>
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</table>

Magnitude, Mechanism, and Onset

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Magnitude</th>
<th>Evidence</th>
<th>Onset</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Doxorubicin</td>
<td>Major</td>
<td>A</td>
<td>Immediate (rare), intermediate, and delayed</td>
<td>Irreversible; risk increases with increasing cumulative dose; delay can occur &gt;20y after first dose</td>
</tr>
<tr>
<td>- Epirubicin</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
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<tr>
<td>- Idarubicin</td>
<td>A</td>
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<tr>
<td>- Mitoxantrone</td>
<td>A</td>
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<tr>
<td>Antimicrotubule agents</td>
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<tr>
<td>- Docetaxel</td>
<td>Moderate</td>
<td>B</td>
<td>Intermediate</td>
<td>Separate administration of anthracycline from taxane</td>
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<tr>
<td>Protacron inhibitor</td>
<td></td>
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<tr>
<td>- Cetuximab</td>
<td>Major and moderate</td>
<td>C</td>
<td>Intermediate</td>
<td>Can be reversible</td>
</tr>
<tr>
<td>- Bevacizumab</td>
<td>A</td>
<td>A</td>
<td></td>
<td>Can be reversible, also HTN</td>
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</table>

ErbB2 = ErbB2 receptor tyrosine kinase 2, VEGFA = vascular endothelial growth factor A ligand, VEGFR = vascular endothelial growth factor receptor.

Circulation 2016; 134:e32-e69
## Magnitude, Mechanism, and Onset (continued)

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Magnitude</th>
<th>Mechanism(s)</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecule TKIs</td>
<td>- Lapatinib (Major), Sunitinib (Major), Sorafenib (Minor)</td>
<td>A: ErbB2, VEGFR, PDGFR, Flt-3, c-kit, AMP-activated protein kinase</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td>- Cyclophosphamide (Major and moderate), Ifosfamide (Major and moderate), Mitomycin (Moderate)</td>
<td>B: Oxidative stress, Semiquinone radical reduction, oxidative stress</td>
<td>Intermediate</td>
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<tr>
<td>Other</td>
<td>- Thalidomide (Minor), Lenalidomide (Major)</td>
<td>C: Unknown</td>
<td>Unknown</td>
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### Diagnostic Tools for Detection

<table>
<thead>
<tr>
<th>Technique</th>
<th>Diagnostic Criteria</th>
<th>Advantages</th>
<th>Major Limitations</th>
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<tbody>
<tr>
<td>Echocardiography (ECHO)</td>
<td>LVEF &gt; 10% ↓ to a value less than 50% GLS &gt; 15% ↓ (Note: GLS is a negative %)</td>
<td>Wide availability, Lack of radiation, Hemodynamics, other cardiac structures</td>
<td>Inter-observer variability, Image quality, GLS: inter-vendor variability, technical requirements</td>
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<tr>
<td>Nuclear cardiac imaging (MUGA)</td>
<td>&gt; 10% ↓ to a value less than 50%</td>
<td>Reproducibility</td>
<td>Cumulative radiation exposure, Limited structural and functional information</td>
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<tr>
<td>Cardiac magnetic resonance</td>
<td>Typically used if other techniques non-diagnostic or for confirmation if LVEF borderline</td>
<td>Accuracy, reproducibility, Detection of diffuse myocardial fibrosis</td>
<td>Limited availability, Patient adaptation</td>
</tr>
<tr>
<td>Cardiac biomarkers</td>
<td>Rise indicates pts who may benefit from ACEIs</td>
<td>Accuracy, reproducibility, Widely available, High sensitivity</td>
<td>Role for routine surveillance not clearly established</td>
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</table>

GLS = global longitudinal strain

### Common Terminology for Criteria for Adverse Effects

A patient with an asymptomatic left ventricular ejection fraction (LVEF) decline from 60% to 30% may be graded as grade 0 (no event reported), grade 1 or grade 3 toxicity, depending on which adverse event term is used.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Asymptomatic</td>
<td>Hypertrophic cardiomyopathy (HCM), Mitral valve disease</td>
<td>Mitral regurgitation, Systolic dysfunction, LV failure</td>
<td>Systolic dysfunction refractory to intervention</td>
<td>Cardiac death</td>
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</tr>
<tr>
<td>LV systolic dysfunction</td>
<td>Asymptomatic</td>
<td>Hypertrophic cardiomyopathy (HCM), Mitral valve disease</td>
<td>Mitral regurgitation, Systolic dysfunction, LV failure</td>
<td>Systolic dysfunction refractory to intervention</td>
<td>Cardiac death</td>
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<tr>
<td>EF declined</td>
<td>Refractory LV dysfunction</td>
<td>Unremitting LV dysfunction</td>
<td>LV dysfunction due to tumor progression</td>
<td>LV dysfunction due to tumor progression</td>
<td>Cardiac death</td>
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</tbody>
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Circulation 2015; 132:1815-1845.
ECHO Surveillance During and After Therapy

**Anthracycline Therapy**
- Yes
- If cumulative dose > 240 mg/m² prior to each additional dose of 50 mg/m²
- At completion of therapy & 6 months later in those with cumulative dose < 240 mg/m²

**HER2 Targeted Therapy**
- Yes
- Every 3 months during treatment
- No routine testing if asymptomatic

**HER2 Targeted Therapy after Prior Anthracycline**
- Yes
- Every 3 months during treatment
- 6 months later

Reference pending:
Circulation 2018; 137:e30-e66

Primary and Secondary Prevention

Reference pending:

Factors to Consider When Deciding to Intervene

Reference pending:
Indian Heart J; 2017; 69: 556-562
Chemotherapy-induced Cardiomyopathy Best Practices: Prevention, Treatment & Monitoring

**Oncologist**
- Identify high-risk patients:
  - Pre-existing heart disease, DM, HLD, HTN
  - Young or old, female
  - Plan for high dose anthracycline
- Order pre-treatment imaging:
  - If EF < 50% or low normal, refer to cardiologist
- Plan for high dose anthracycline
  - Modify CV risk factors
  - Optimize cardiac medications
  - Optimize glucose control, diet, weight, exercise
- Order pre-treatment imaging:
  - If EF < 50% or low normal, refer to cardiologist
  - Repeat imaging studies
    - Obtain high-quality EF, consider contrast, 3-dimensional, strain
    - Order biomarkers (troponin, BNP)
- Monitor during therapy:
  - Monitor with ECHO at 3-month interval or symptom driven
  - Monitor with ECHO at 1-month interval if given cardioprotective medication
- withheld cardiotoxic therapy only as the last resort (for anthracycline EF < 45%, for anti-HER2 therapy EF < 40%) Monitor after completion of therapy:
  - Obtain post-therapy ECHO in 6 months or 1 year
  - If EF remains abnormal, follow ACC/AHA HF guidelines

**Cardiologist**
- Optimize cardiac medications
- Monitor during therapy:
  - Monitor with ECHO at 3-month interval or symptom driven
  - Monitor with ECHO at 1-month interval if given cardioprotective medication
- withheld cardiotoxic therapy only as the last resort (for anthracycline EF < 45%, for anti-HER2 therapy EF < 40%) Monitor after completion of therapy:
  - Obtain post-therapy ECHO in 6 months or 1 year
  - If EF remains abnormal, follow ACC/AHA HF guidelines

### Summary of Risk Factors

- **At-risk therapies including any of the following:**
  - High-dose anthracycline therapy: doxorubicin > 250 mg/m² or epirubicin > 600 mg/m²
  - High-dose radiation therapy when heart is in the field of treatment: radiotherapy > 30 Gy
  - Sequential therapy: lower-dose anthracycline therapy and then subsequent treatment with trastuzumab
  - Combination therapy: lower-dose anthracycline and trastuzumab combined with lower-dose radiation therapy

- **Presence of any of the following risk factors in addition to treatment with lower-dose anthracycline or trastuzumab alone:**
  - Older age at time of cancer treatment (>60 years)
  - ≥2 CV risk factors during or after cancer treatment: diabetes mellitus, dyslipidemia, hypertension obesity, smoking
  - History of myocardial infarction, moderate valvular disease, or low-normal LV function (50-55%) before or during cancer treatment

**Circulation** 2018; 137:e30-e66

---

Which of the following statements is TRUE regarding chemotherapy induced cardiomyopathy?

1. Cardiomyopathy is generally reversible with doxorubicin but irreversible with trastuzumab
2. ECHO surveillance is warranted if cumulative anthracycline dose is > 240 mg/m² then prior to each additional dose of 50 mg/m²
3. Withhold both doxorubicin and trastuzumab when LVEF falls < 50%
4. Concomitant or prior radiation poses no additional risk
Prevention & Management of Cardiomyopathy

**Strategies for reducing cardiotoxicity:**
- **Anthracyclines:** Dose reduction, continuous infusion, liposomal doxorubicin, dexrazoxane
- **Vascular endothelial growth factor signaling pathway inhibitors:** Treat hypertension

**Consider cardio-protection (e.g. ACE inhibitor, beta blocker), if:**
- Fractionation (EF) < 50% or EF > 10% decline
- Global longitudinal strain > 15% decline (Note: GSL is a negative %)
- Myocardial damage (assessed via troponin)

**Withhold certain cancer therapies as a last resort:**
- Anthracycline (withhold if EF < 45%)
- Trastuzumab (withhold if EF < 40%)

Risk Factors for Anthracycline Mediated Toxicity

- Cumulative dose
- Female sex
- Age - Greater than 65 years old - Pediatric population (less than 18 years)
- Renal failure
- Concomitant or prior radiation to the heart
- Concomitant chemotherapy
  - Alkylating or antimicrotubule agents
  - Immuno- and targeted therapies
- Pre-existing conditions
  - Cardiac diseases associating increased wall stress
  - Arterial hypertension
- Genetic factors

**Doxorubicin Incidence**
- 400 mg/m²: 3-5%
- 550 mg/m²: 7-28%
- 700 mg/m²: 18-48%

**Drug** | **Relative Toxicity** | **HF incidence >5% when cumulative dose exceeds (mg/m²)**
--- | --- | ---
Daunorubicin | 1 | 400
Epirubicin | 0.7 | 900
Daunorubicin | 0.53 | 800
Doxorubicin | 0.75 | 150

**Anthracyclines: Cardioprotective Strategies**

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<thead>
<tr>
<th>Therapies</th>
<th>Hypothesized Mechanism</th>
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<tbody>
<tr>
<td>Dexrazoxane</td>
<td>Decreased ROS formation via prevention of anthracycline-iron complex formation, Reduced anthracycline-induced DNA damage via Top2-DNA cleavage complex inhibition</td>
</tr>
<tr>
<td>Statins</td>
<td>Reduced cell death and Top2-mediated DNA damage via fak1 inhibition</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Increased pro-survival signaling via recruitment of β-arrestin and transactivation of EGFR, Mitigation of oxidative stress, Enhanced contractility</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Attenuated oxidative stress and interstitial fibrosis, Improved intracellular calcium handling, Improved cardiomyocyte metabolism, Improved mitochondrial function</td>
</tr>
<tr>
<td>Exercise training</td>
<td>Decreased ROS formation, Reduced pro-apoptotic signaling, Improved calcium handling, improved myocardial energetics via augmented AMPK activity</td>
</tr>
</tbody>
</table>

AMPK = AMP-activated protein kinase, EGF = epidermal growth factor receptor, NRG = neuregulin, TGF = transforming growth factor.
Which of the following are strategies to minimize cardiac toxicity with anthracyclines?

1. Dose reduction
2. Alternative delivery systems (e.g., liposomal) or continuous infusion
3. Dexrazoxane
4. Separate administration from taxanes
5. All of the above

---

**Primary Prevention of Anthracycline-Induced CM**

<table>
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<tr>
<th>Agent</th>
<th>CT</th>
<th>Intervention</th>
<th>Dose (mg/d)</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>LVEF ↓ &gt;10%</th>
<th>HF</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geogakapoulos et al (2010)</td>
<td>ANT</td>
<td>Enalapril</td>
<td>11</td>
<td>80</td>
<td>12</td>
<td>2.4 / 1.4</td>
<td>6.3 / 3.5</td>
<td>8 / 5</td>
</tr>
<tr>
<td>Cardinale et al (2006)</td>
<td>ANT</td>
<td>Enalapril</td>
<td>14</td>
<td>168</td>
<td>12</td>
<td>2.4 / 0.5</td>
<td>0.4 / 0.4</td>
<td>0 / 0.5</td>
</tr>
<tr>
<td>Cadeddu, Inesi (2010, 2011)</td>
<td>ANT</td>
<td>Telmisartan</td>
<td>60</td>
<td>69</td>
<td>12</td>
<td>0.2 / 0.3</td>
<td>0.7 / 0.6</td>
<td>0 / 0.35</td>
</tr>
</tbody>
</table>

**Beta Blocker**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CT</th>
<th>Intervention</th>
<th>Dose (mg/d)</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>LVEF ↓ &gt;10%</th>
<th>HF</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geogakapoulos et al (2010)</td>
<td>ANT</td>
<td>Metoprolol</td>
<td>89</td>
<td>125</td>
<td>12</td>
<td>2.4 / 2.4</td>
<td>2.4 / 7.5</td>
<td>8 / 5.5</td>
</tr>
<tr>
<td>Kalay et al (2006)</td>
<td>ANT</td>
<td>Carvedilol</td>
<td>12.5</td>
<td>50</td>
<td>6</td>
<td>0.5 / 0.4</td>
<td>0.2 / 0.4</td>
<td>0 / 0.4</td>
</tr>
<tr>
<td>El-Shitany et al (2012)</td>
<td>ANT</td>
<td>Carvedilol</td>
<td>1</td>
<td>50</td>
<td>1</td>
<td>0 / 0</td>
<td>0 / 0</td>
<td>0 / 0</td>
</tr>
<tr>
<td>Kaya et al (2013)</td>
<td>ANT</td>
<td>Nebivolol</td>
<td>5</td>
<td>49</td>
<td>6</td>
<td>0.2 / 0.3</td>
<td>0 / 0</td>
<td>0 / 0.1</td>
</tr>
</tbody>
</table>

**ACE/ARB + Beta Blocker**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CT</th>
<th>Intervention</th>
<th>Dose (mg/d)</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>LVEF ↓ &gt;10%</th>
<th>HF</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosch et al (2013)</td>
<td>ANT</td>
<td>Enalapril + Carvedilol</td>
<td>8.6 + 24</td>
<td>90</td>
<td>6</td>
<td>0.2 / 0.3</td>
<td>9.5 / 19</td>
<td>0 / 4.4</td>
</tr>
</tbody>
</table>

**Aldosterone Receptor Antagonist**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CT</th>
<th>Intervention</th>
<th>Dose (mg/d)</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>LVEF ↓ &gt;10%</th>
<th>HF</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akpek et al (2015)</td>
<td>ANT</td>
<td>Spironolactone</td>
<td>25</td>
<td>83</td>
<td>6</td>
<td>0.2 / 0.4</td>
<td>5.6 / 10</td>
<td>0 / 0</td>
</tr>
</tbody>
</table>

**Statins**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CT</th>
<th>Intervention</th>
<th>Dose (mg/d)</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>LVEF ↓ &gt;10%</th>
<th>HF</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akpek et al (2015)</td>
<td>ANT</td>
<td>Atorvastatin</td>
<td>40</td>
<td>83</td>
<td>6</td>
<td>0.2 / 0.3</td>
<td>5.6 / 10</td>
<td>0 / 0</td>
</tr>
</tbody>
</table>

ANT = Anthracycline, ANT* = Anthracycline + high dose chemotherapy
CECCY Trial

- **Purpose:** To evaluate carvedilol compared with placebo among patients with HER2-negative breast cancer undergoing anthracycline-based chemotherapy.
- **Study Design:** Randomized, parallel, placebo controlled (n=192),
  - Carvedilol (n = 96) vs placebo (n = 96), titrated to 25 mg twice daily if tolerated
  - 24 week follow-up
- **Inclusion criteria:**
  - Women ≥18 years of age
  - Invasive adenocarcinoma undergoing adjuvant or neoadjuvant chemotherapy, including an anthracycline (240 mg/m²)

Results

- Prevention of a >10% reduction LVEF at 6 months: 14.5% vs 13.5%, p=1.0
- Percentage of patients with troponin I >0.04: 26% vs 41.6%, p=0.003

Conclusions

- Among patients with invasive breast cancer undergoing ANT-based chemotherapy, carvedilol was not effective at preventing a reduction in LVEF.
- Carvedilol was associated with a lower frequency of detectable troponin I values.

---

**Anti-HER2 and VEGF Inhibitor Mediated Toxicity**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-HER2 Compounds</strong></td>
<td></td>
</tr>
<tr>
<td>Antibodies</td>
<td></td>
</tr>
<tr>
<td>- Trastuzumab</td>
<td></td>
</tr>
<tr>
<td>- Pertuzumab</td>
<td></td>
</tr>
<tr>
<td>- Lapatinib</td>
<td></td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>Previous or concomitant anthracycline treatment (short time between anthracycline and anti-HER2 treatment)</td>
</tr>
<tr>
<td></td>
<td>Age (&gt; 65 years)</td>
</tr>
<tr>
<td></td>
<td>High BMI &gt; 30 kg/m²</td>
</tr>
<tr>
<td></td>
<td>Previous LV dysfunction</td>
</tr>
<tr>
<td></td>
<td>Arterial hypertension</td>
</tr>
<tr>
<td></td>
<td>Previous radiation therapy</td>
</tr>
</tbody>
</table>

| **VEGF Inhibitors**    |                                                                             |
| Antibodies             |                                                                             |
| - Bevacizumab          |                                                                             |
| - Ramucirumab          | Previous existing HF, significant CAD or left side VHD (e.g., mitral regurgitation), chronic ischemic cardiomyopathy |
| - Sunitinib, sorafenib, etc. | Arterial hypertension                                                        |
|                        | Pre-existing cardiac disease                                                |

---
Targeted Therapies: Cardioprotective Strategies

Monoclonal antibody-based TKIs - Trastuzumab

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Hypothesized Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors</td>
<td>Decreased angiotensin-induced blockade of NRG1/ErbB pathway</td>
</tr>
<tr>
<td>β Blockers</td>
<td>Increased prosurvival signaling via recruitment of β-arrestin and transactivation of EGFR</td>
</tr>
<tr>
<td>Exercise</td>
<td>Enhanced NRG1/ErbB signaling</td>
</tr>
<tr>
<td></td>
<td>Increased myocardial Akt</td>
</tr>
<tr>
<td></td>
<td>Inhibition of TGF-β signaling</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor, NRG1 = neuregulin-1, TGF = transforming growth factor.

Small molecule TKI - Sunitinib

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Hypothesized Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Improved pericyte function via PDGFR signaling</td>
</tr>
<tr>
<td>AMPK activators</td>
<td>Restoration of favorable myocardial energetics</td>
</tr>
</tbody>
</table>

AMPK = AMP-activated protein kinase, PDGFR = platelet-derived growth factor receptor

ACE Inhibitor and Beta Blocker with Trastuzumab

- **Purpose:** To evaluate lisinopril versus carvedilol versus placebo for prevention of cardiomyopathy among patients undergoing trastuzumab chemotherapy for breast cancer.

- **Study Design:** Randomized, parallel, placebo controlled (n=468)
  - Lisinopril 10 mg/d vs carvedilol CR 10 mg/d vs placebo, stratified by treatment with anthracycline
  - Duration of follow-up: 12 months

- **Inclusion Criteria:**
  - Patients > 18 years old
  - HER2-positive breast cancer, planned trastuzumab chemotherapy
  - Baseline LVEF ≥ 50%
  - SBP > 90 mm Hg, HR ≥ 60 bpm, normal renal and hepatic function

Definition of Cardiotoxicity at Time of Trial Design

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>N</th>
<th>Setting</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burstein et al (2001)</td>
<td>40</td>
<td>Metastatic breast cancer</td>
<td>LVEF &lt; 50% or decrease by 15%</td>
</tr>
<tr>
<td>Leyland-Jones et al (2003)</td>
<td>32</td>
<td>Metastatic breast cancer</td>
<td>LVEF &lt; 45% or decrease by &gt; 15%</td>
</tr>
<tr>
<td>Paik et al (2002)</td>
<td>1159</td>
<td>Adjuvant</td>
<td>LVEF &lt; 55% or decrease by &gt; 15%</td>
</tr>
<tr>
<td>Berstein et al (2003)</td>
<td>54</td>
<td>Metastatic breast cancer</td>
<td>EF &lt; 40%</td>
</tr>
<tr>
<td>Bengala et al (2006)</td>
<td>53</td>
<td>Mixed</td>
<td>EF &lt; 50%</td>
</tr>
<tr>
<td>Tan-Chiu et al (2005)</td>
<td>950</td>
<td>Adjuvant</td>
<td>EF decrease by 15% to &lt; 50%</td>
</tr>
<tr>
<td>Piccart-Gebhart et al (2005)</td>
<td>1877</td>
<td>Adjuvant</td>
<td>EF &lt; 50% or decrease by 15%</td>
</tr>
<tr>
<td>Venuturi et al (2006)</td>
<td>45</td>
<td>Metastatic breast cancer</td>
<td>EF &lt; 45% or decrease by 20%</td>
</tr>
<tr>
<td>Guarnieri et al (2006)</td>
<td>175</td>
<td>Metastatic breast cancer</td>
<td>EF &lt; 50% or decrease by 20%</td>
</tr>
</tbody>
</table>
ACE Inhibitor and Beta Blocker with Trastuzumab

**Primary outcome (decrease in LVEF >10%)**: Lisinopril 30% vs carvedilol 29% vs placebo 32% (NSS)

**Secondary outcome**: Trastuzumab interruption was the same between treatment groups

Both ACE inhibitors and beta blockers may prevent chemotherapy induced cardiomyopathy; however, additional studies are warranted. True or False?

1. True
2. False

Anticancer Agents Associated with Hypertension

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Frequency of Use</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibody based TKIs</td>
<td>+</td>
<td>6-10%</td>
</tr>
<tr>
<td>- Bevacizumab</td>
<td>+</td>
<td>5%</td>
</tr>
<tr>
<td>- Adrucilizumab</td>
<td>N/A</td>
<td>0%</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>+</td>
<td>8-12%</td>
</tr>
<tr>
<td>- Brentuximab</td>
<td>+</td>
<td>7%</td>
</tr>
<tr>
<td>- Rituxanumab</td>
<td>+</td>
<td>6-12%</td>
</tr>
<tr>
<td>Proteasome inhibitor</td>
<td>++</td>
<td>0%</td>
</tr>
<tr>
<td>- Carfilizumab</td>
<td>+</td>
<td>0%</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>++</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Frequency of Use</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecule TKIs</td>
<td>+</td>
<td>42%</td>
</tr>
<tr>
<td>- Pazopanib</td>
<td>+</td>
<td>60%</td>
</tr>
<tr>
<td>- Pemetinib</td>
<td>+</td>
<td>7-43%</td>
</tr>
<tr>
<td>- Sunitinib</td>
<td>+</td>
<td>3-24%</td>
</tr>
<tr>
<td>- Dasatinib</td>
<td>+</td>
<td>40%</td>
</tr>
<tr>
<td>- Closoxarib</td>
<td>+</td>
<td>17%</td>
</tr>
<tr>
<td>- Nilotinib</td>
<td>+</td>
<td>10-12%</td>
</tr>
<tr>
<td>- Remestinib</td>
<td>+</td>
<td>10-15%</td>
</tr>
<tr>
<td>- Regorafenib</td>
<td>+</td>
<td>10-50%</td>
</tr>
<tr>
<td>- Trametanib</td>
<td>+</td>
<td>15%</td>
</tr>
<tr>
<td>- Ziv-aflibercept</td>
<td>N/A</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Reference pending**
Prevention and Management of Hypertension

- Pre-treatment risk assessment
- BP goal < 140/90 mmHg
- Weekly BP monitor in 1st cycle, then every 2-3 weeks for duration of therapy
- Initiate BP treatment when diastolic increases by 20 mmHg
- More than 1 anti-HTN medication may be needed
- Avoid diltiazem and verapamil with sorafenib
- Hold chemotherapy as last resort
- Hold bevacizumab if systolic BP > 160 mmHg or diastolic BP > 100 mmHg
- Early consultation with cardiologist

Anticancer Agents Associated with Myocardial Infarction/Ischemia

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Frequency of Use</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cepitabine</td>
<td>+++</td>
<td>3-9%</td>
</tr>
<tr>
<td>- 5-flourouracil</td>
<td>+++</td>
<td>1-68%</td>
</tr>
<tr>
<td>monoclonal antibody-based tyrosine kinase inhibitors (TKIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Nilotinib</td>
<td>++</td>
<td>5-9%</td>
</tr>
<tr>
<td>- Ponatinib</td>
<td>+</td>
<td>9%</td>
</tr>
<tr>
<td>Angiogenesis inhibitors</td>
<td>+++</td>
<td>0-2%</td>
</tr>
<tr>
<td>- Lenalidomide</td>
<td>+++</td>
<td>&lt;1.5%</td>
</tr>
</tbody>
</table>

Prevention & Management of Ischemia

**Ischemia workup:**
Stress test, cardiac catheterization

**Treatment:**
As per ACC/AHA guidelines

**If antiplatelet count lower than 100,000/microliter of blood:**
- Aspirin if > 10K (or > 30K???)
- Dual anti-platelet therapy with aspirin & clopidogrel for drug eluting stents if platelet > 30K
- Cardiac catheterization via radial approach
Anticancer Agents Associated with QT Prolongation

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Frequency of Use</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histone deacetylase inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Belinostat</td>
<td>+</td>
<td>4-11%</td>
</tr>
<tr>
<td>- Vorinostat</td>
<td>+++</td>
<td>6-6%</td>
</tr>
<tr>
<td>Chemicals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Arsenic trioxide</td>
<td>++</td>
<td>26-93%</td>
</tr>
<tr>
<td>Small molecule tyrosine kinase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Dabrafenib</td>
<td>+++</td>
<td>2-13%</td>
</tr>
<tr>
<td>- Dasatinib</td>
<td>+++</td>
<td>-3-9%</td>
</tr>
<tr>
<td>- Lapatinib</td>
<td>+++</td>
<td>10-10%</td>
</tr>
<tr>
<td>- Nilotinib</td>
<td>+++</td>
<td>&lt;1-10%</td>
</tr>
<tr>
<td>- Vandetanib</td>
<td>+++</td>
<td>8-14%</td>
</tr>
<tr>
<td>BRAF inhibitor</td>
<td>+++</td>
<td>3%</td>
</tr>
</tbody>
</table>

Chemotherapy Agents

Cancer drugs: Cyclophosphamide, Taxanes, Tyrosine kinase inhibitor, Thalidomide
Cancer therapy complications: Dehydration, Electrolyte balance, renal and liver disease
Additional Medications: Antiemetics, antidepressants, antifungals, antihistamines, antipsychotics

Multifactorial Causes for QT Prolongation

Prevention and Management of QT Prolongation

- Tangent method of QT measurement
- Fridericia correction formula
- Correct for low potassium and magnesium
- Remove QTc prolonging medications
- QTc > 500 ms or > 60 ms above baseline associated with TdP
- TdP reported for arsenic trioxide, sunitinib, pazopanib, vandetanib, vemurafenib
**Anticancer Agents Associated with Thromboembolism**

<table>
<thead>
<tr>
<th>Chemotherapy Agents</th>
<th>Frequency of Use</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Cisplatin</td>
<td>+++ 9-17%</td>
</tr>
<tr>
<td>Angiogenesis inhibitors</td>
<td>Bevacizumab</td>
<td>+++ 6-15%</td>
</tr>
<tr>
<td>Monoclonal antibody-based tyrosine kinase inhibitors (TKIs)</td>
<td>Bevacizumab</td>
<td>+++ 6-15%</td>
</tr>
<tr>
<td>Histone deacetylase inhibitor</td>
<td>Vorinostat</td>
<td>++++ 5-6%</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>Everolimus</td>
<td>++++ 1-4%</td>
</tr>
</tbody>
</table>

**Prevention and Management of Thromboembolism**

- Risk factors
  - Cancer types, metastatic disease
  - Chemotherapy, hormonal therapy
  - Central venous catheter
  - Heart failure, atrial fibrillation
  - Previous history of VTE, immobility
  - Older age, female
- Diagnosis: compression, ultrasonography, spiral CT, MR
- Treatment options: aspirin, warfarin, LMWH, edoxaban

**2017 ACC/AHA HTN Guidelines**

- Categories & Goals
  - Stage 1 and 2 HTN categories changed from previous versions of the guidelines. 130/80 mmHg is the threshold for the diagnosis of HTN.
  - Goal BP for all populations: <130/80 mmHg

- BP Treatment Threshold
  - Primary prevention of CVD in adults with ASCVD:
    - Primary prevention of CVD in adults with ASCVD: >10% with BP ≥ 130/80 mmHg
    - Secondary prevention of recurrent CVD events in pts with BP ≥ 130/80 mmHg

- Therapeutic options
  - First-line agents include thiazide diuretics, CCBs, and ACEi/ARBs
  - Initiation of a single anti-HTN is reasonable if stage 1 HTN and BP goal <130/80 mmHg
  - Initiation with 2 first-line agents of different classes is recommended if stage 2 HTN and an average BP ≥ 20/10 mmHg over goal

- Follow-up & Monitoring
  - Follow-up evaluation of adherence and response to treatment 4 weeks until control is achieved
2013 ACC/AHA Blood Cholesterol Guidelines

Eliminates LDL-C and non-HDL goals
Focuses on intensity of statin therapy in four key benefit groups (ASCVD, LDL, DM, 10-y risk)

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate to High Risk</th>
<th>Moderate Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ASCVD &lt; 75y</td>
<td>LDL ≥ 190 mg/dL or DM 40-75y with 10-y risk score ≥ 7.5%</td>
<td>Clinical ASCVD &gt; 75y</td>
</tr>
<tr>
<td>High-intensity Statin</td>
<td>Rosuvastatin 40-80 mg</td>
<td>Rosuvastatin 20-40 mg</td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2017 Update of Non-Statin for ASCVD Reduction

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>LDL-C Thresholds</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable ASCVD without comorbidities</td>
<td>LDL-C ≥70 mg/dL</td>
<td>1st ezetimibe, 2nd PCSK9 inhibitor</td>
</tr>
<tr>
<td>ASCVD with comorbidities;</td>
<td>LDL-C ≥100 mg/dL</td>
<td>Either ezetimibe (≥25% LDL-C reduction) or PCSK9 inhibitor (≥25% reduction)</td>
</tr>
<tr>
<td>Baseline LDL &gt;190 mg/dL (w/ or w/o ASCVD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM, primary prevention w/ 10-y risk</td>
<td>LDL-C ≥100 mg/dL</td>
<td>1st increase statin to high-intensity, 2nd ezetimibe, 3rd BAS</td>
</tr>
<tr>
<td>&lt;7.5% or high risk features*</td>
<td>LDL-C ≥100 mg/dL</td>
<td>1st ezetimibe, 2nd BAS</td>
</tr>
<tr>
<td>DM, primary prevention w/ 10-y risk</td>
<td>LDL-C ≥100 mg/dL</td>
<td>1st ezetimibe, 2nd BAS</td>
</tr>
<tr>
<td>≥3.5% OR high risk features*</td>
<td>LDL-C ≥100 mg/dL</td>
<td>1st ezetimibe, 2nd BAS</td>
</tr>
</tbody>
</table>

*Retinopathy, eGFR <60 ml/min, albuminuria, Lp(a) >30 mg/dL, CRP >2 mg/dL or presence of subclinical atherosclerosis

J Am Coll Cardiol. 2017; 70:1785-1822

Example ASCVD Risk Calculator

[Example ASCVD Risk Calculator](http://tools.acc.org/ASCVD-Risk-Estimator/)
Treatment of HFrEF Stage C and D

Step 1
HFrEF NYHA class I-II (Stage C)

Step 2
NYHA class II-II HF
Adrenergic BP on
ACEi or ARB; no C/I
to ARB or sacubitril

Step 3
Discontinue ACEi or
ARB; initiate ARNI
(COR I)

Step 4
NYHA class II-IV, in
black patients
Hydral-Nitrates
(COR I)

Step 5
NYHA class III-IV (Stage D)
Aldosterone
antagonist
(COR I)

Refactory
NYHA class
III-IV
Palliative care
(COR I); Transplant
(COR I); LVAD
(COR IIa); investigational
studies

Step 1
HFrEF NYHA class I-II (Stage C)

ACEi/ARB AND
GDMT = guideline-directed medical therapy

Step 2
NYHA class II-II HF
Adrenergic BP on
ACEi or ARB; no C/I
to ARB or sacubitril

Step 3
Discontinue ACEi or
ARB; initiate ARNI
(COR I)

Step 4
NYHA class II-IV, in
black patients
Hydral-Nitrates
(COR I)

Step 5
NYHA class III-IV (Stage D)
Aldosterone
antagonist
(COR I)

Refactory
NYHA class
III-IV
Palliative care
(COR I); Transplant
(COR I); LVAD
(COR IIa); investigational
studies

DOAC for VTE Treatment*

Dabigatran
150mg BID
8 – 10 days

Rivaroxaban
15mg BID
20mg QD

Apixaban
5mg BID
10mg QD

Edoxaban
60mg QD
8 – 10 days

Radiation-induced Heart Disease

Pericardial Disease
- Prevalence: 6-30%
  - Acute pericarditis often self-limited; chronic pericarditis often effusive-constrictive.
- Diagnosis: Diagnosis of exclusion, ECHO, cardiac CT or MRI
- Management:
  - Anti-inflammatory agents for pericarditis
  - Pericardio-centesis for large effusions or tamponade
  - Pericardial window for recurrent effusions, pericardial stripping for constrictive pericarditis

Coronary Heart Disease
- Prevalence: Up to 85%
  - Usually occurs 10 years after radiation therapy, involves LM, ostial LAD, RCA
- Diagnosis: Stress ECHO, stress perfusion imaging, cardiac CTA
- Management:
  - PCI, CABG (challenging due to fibrosis of pericardium and mediastinum)
  - Aggressive risk factor modification

*Parenteral Anticoagulation
- Pradaxa® [package insert]. Boehringer Ingelhein Pharmaceuticals, Ridgefield, CT
- Savaysa® [package insert]. Daiichi Sankyo, Parsippany, NJ

*DOAC for VTE Treatment
dosing in normal renal and hepatic function

Radiation-induced Heart Disease
Radiation-induced Heart Disease

Valvular Heart Disease

- **Prevalence**:
  - 10 yrs: 25% AI, 39% MR, 16% TR, and 7% PR
  - 20 yrs: 60% AI, 16% AS, 52% MR, 26% TR, and 12% PR
- **Mean 12 yrs after radiation, left > right-sided valves, initial regurgitation, later stenosis.**
- **Diagnosis**: ECHO, cardiac MRI
- **Management**:
  - Serial monitoring with timing of surgery per ACC/AHA guidelines

Conduction System Abnormalities

- **Prevalence**: Up to 5%
- **A-V nodal block, bundle branch block (right > left), tachycardia may be persistent**
- **Diagnosis**: ECG, telemetry, ambulatory Holter monitor
- **Management**:
  - Permanent pacemaker for high-degree A-V block
  - ICD for life-threatening arrhythmia, SCD or secondary prevention; consider subpectoral approach

Cardiomyopathy

- **Prevalence**: Up to 10%
- **Diastolic dysfunction > systolic dysfunction, right ventricle > left ventricle**
- **Due to fibrosis in all 3 layers of the ventricular wall, may lead to restrictive cardiomyopathy, and rarely systolic dysfunction.**
- **Diagnosis**: ECHO, cardiac MRI
- **Management**:
  - Systolic dysfunction: low upward titration of ACEI, beta-blockade, and aldosterone inhibitors
  - Diastolic dysfunction: optimize risk factors, exercise training
  - - Inotropic support, VAD, heart transplantation

Radiation Sequelae Take Home Points

- Identify, modify and treat CV risk factors
- **CV Monitoring**:
  - Yearly: ECG, ECHO if indicated
  - 5 yrs after radiation: ECG, ECHO
  - 10 yrs after radiation: ECG, ECHO, stress test or coronary CT
Which of the following statements is TRUE regarding radiation induced heart disease?

1. Acute pericarditis is rarely self-limiting
2. Coronary heart disease and valvular heart disease usually occur immediately
3. Conduction system abnormalities may include brady- or tachycardia
4. Cardiomyopathy is more commonly systolic dysfunction than diastolic dysfunction

Summary of Strategies to Reduce Cardiotoxicity

- Identify and treat CV risk factors
- Treat comorbidities (HTN, CAD, PAD)
- QTc prolongation and torsades de pointes:
  - Avoid QT prolonging drugs
  - Manage electrolyte abnormalities
- Minimize cardiac irradiation

All Chemotherapy

- Limit cumulative dose (mg/m²):  
  - Daunorubicin <800  
  - Doxorubicin <560
  - Epirubicin <750  
  - Mitoxantrone <160  
  - Idarubicin <150

- Altered delivery systems (liposomal doxorubicin) or continuous infusions
- Dexrazoxane as an alternative
- ACEIs or ARBs, beta blockers, statins, aerobic exercise

Anthracyclines and analogues

Trastuzumab

ACEIs
Beta blockers

Trastuzumab

Questions?
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