# Advances in Cardio-Oncology: Prevention and Management of Cardiovascular Complications Associated with Anticancer Therapies

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# Disclosures

- James E. Tisdale:
  - CredibleMeds - Volunteer (unpaid) member of the Advisory Board for the QT drugs
- Jo Ellen Rodgers:
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# Learning Objectives

- Given a description of a specific patient receiving cancer chemotherapy, develop plans for prevention and treatment of cancer chemotherapy-associated heart failure.
- Given a description of a specific patient receiving cancer chemotherapy, develop plans for prevention and treatment of cancer chemotherapy-associated vascular toxicities such as hypertension, stroke, and coronary artery disease.
- Given a description of a specific patient receiving cancer chemotherapy, develop plans for prevention and treatment of cancer chemotherapy-associated arrhythmias.

# Advances in Cardio-Oncology:

## Prevention and Management of Cancer Chemotherapy-Associated Heart Failure

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# Learning Objectives

1. Identify risk factors for chemotherapy-associated heart failure (HF) and differentiate this risk among the various chemotherapies.
2. Compare and contrast various diagnostic tools for identifying chemotherapy-associated HF.
3. Identify various strategies to minimize the risk of chemotherapy-associated HF.
4. Describe the role of pharmacotherapy in the primary and secondary prevention of chemotherapy-associated HF.

# Question 1:

**Case:** A 44 year-old woman is diagnosed with HER2+ breast cancer.

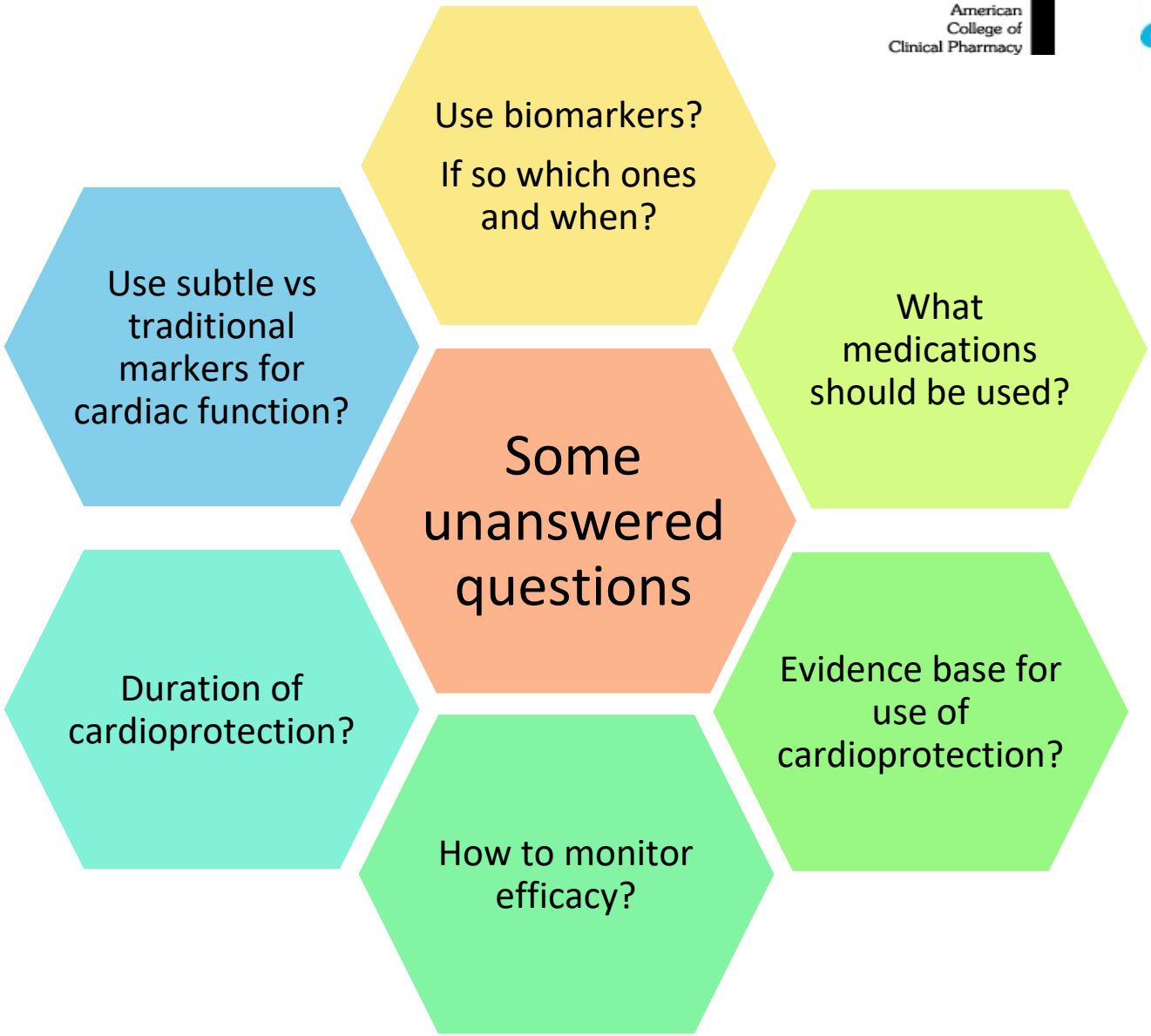
She receives initial chemotherapy, which includes doxorubicin and cyclophosphamide, and is then started on HER2 inhibitor treatment with trastuzumab (Herceptin) and pertuzumab (Perjeta).

Per protocol, she undergoes an ECHO 3 months after initiation of treatment and is now found to have a LVEF 45% (pre-treament EF was 55-60%).

She has no obvious symptoms other than mild edema in her legs. Her PMH includes: HTN, DM and obesity. At this point, you should:

A. Obtain a MUGA to confirm the EF
B. Stop trastuzumab immediately and perform cardiac catheterization
C. Stop trastuzumab, add furosemide, and recheck an ECHO in 1 month
D. Continue trastuzumab and start an ACE inhibitor or beta-blocker

# Factors to Consider




*Indian Heart J*; 2017; 69: 556-562.

# Numbers Check

Proportion of women with breast cancer who had ≥ 1 CVD risk factors

- 73% hypertension, 57% hyperlipidemia
- 62% with ≥ 2 risk factors, 33% with ≥ 3 risk factors
- Strong linear relationship between # of risk factors was associated with cardiac events

87%

Number of hours of moderate exercise/week before a breast cancer diagnosis that was associated with a 40% lower risk of a CV event

Five

Increased risk of death in cancer patients whose radiation shifted slightly towards their heart during therapy versus those who radiation shifted away from their heart

30-50%

*J Clin Oncol* 2018 Mar 27:JCO2017774414, ACC Abstract 1187-05, HealthDay April 23, 2018.

# Risk Factors for Cardiotoxicity

**Current myocardial disease**

- HFrEF, HFpEF, asymptomatic LV dysfunction
- Evidence of CAD (MI, CABG)
- 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
  - Anthracyclines: > 65 years
  - Trastuzumab: > 50 years
- Family history of premature CVD (< 50 years)
- Arterial hypertension
- Diabetes mellitus
- Hypercholesterolemia

**Previous cardiotoxic cancer therapy**

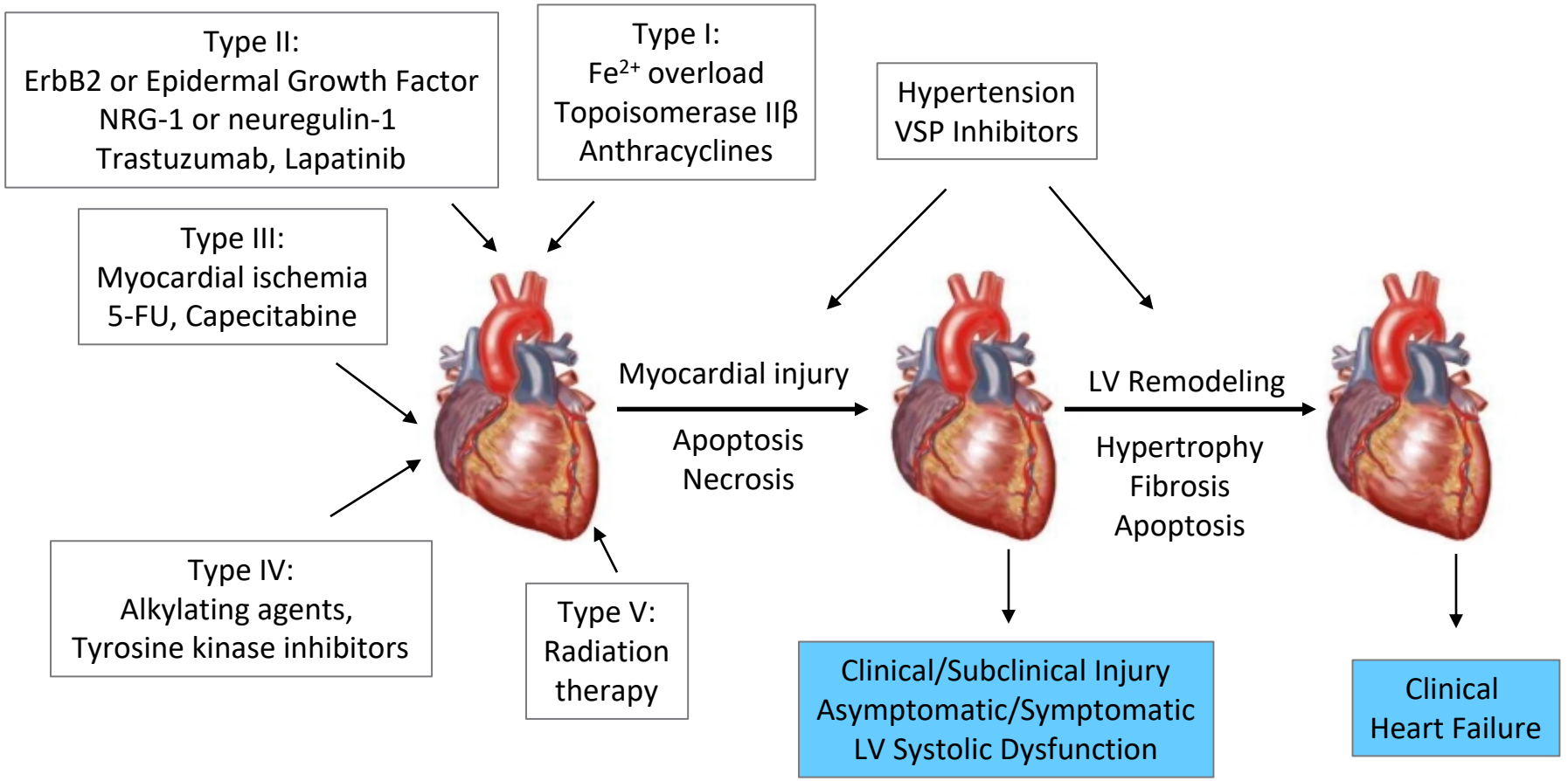
- Prior anthracycline use
- Prior radiotherapy to chest or mediastinum

**Lifestyle risk factors**

- Smoking
- High alcohol intake
- Obesity
- Sedentary habit

*Eu Heart J* 2016; 37:2768-2801.

# Types of Cardiotoxicity




Zheng H et al. In: Abeloff's Clinical Oncology Review E-book, 2015.

# Cancer Treatment and Cardiovascular Effects

| Cancer Treatment | Cardiovascular Adverse Effect |
|---|---|
| Anthracyclines (e.g. doxorubicin, epirubicin) | **Left ventricular dysfunction, heart failure,** myocarditis, pericarditis, atrial fibrillation, ventricular tachycardia, ventricular fibrillation |
| Alkylating agents (e.g., cisplatin, cyclophosphamide) | **Left ventricular dysfunction, heart failure,** myocarditis, pericarditis, arterial thrombosis, bradycardia, atrial fibrillation, supraventricular tachycardia |
| Taxanes (e.g. paclitaxel) | Bradycardia, heart block, ventricular ectopy |
| Antimetabolites (e.g. 5-FU, capecitabine) | Coronary thrombosis, coronary artery spasm, atrial fibrillation, ventricular tachycardia, ventricular fibrillation |
| Endocrine therapy (e.g. tamoxifen, anastrozole) | Venous thrombosis, thromboembolism, peripheral atherosclerosis, arrhythmias, valvular dysfunction, pericarditis, **heart failure** |
| HER-2-directed therapies (e.g. trastuzumab) | **Left ventricular dysfunction, heart failure** |
| Cycline-dependent kinase 4/6 inhibitors (e.g. palbociclib) | QT prolongation |
| Radiation therapy | Coronary artery disease, **left ventricular dysfunction, heart failure,** valvular heart disease, pericardial disease, arrhythmias |

*Circulation* 2018; 137:e30-e66.

# Incidence of Cardiomyopathy

| Class/Drug | Selected Indication | Heart Failure Incidence |
|---|---|---|
| Anthracyclines | | |
| - Doxorubicin | Breast, lymphoma | **Very common** |
| - Daunorubicin | Leukemia | **Very common** |
| - Epirubicin | Breast, gastric | **Very common** |
| - Idarubicin | Leukemia | **Very common** |
| - Mitoxantrone | Leukemia | **Common** |
| Alkylating agents | | |
| - Cyclophosphamide | Hematologic | …. |
| - Cisplatin | Bladder, lung, ovarian | …. |
| - Ifosfamide | Cervical, sarcoma | **Very common** |
| Antimicrotubule agents | | |
| - Paclitaxel | Breast, lung | Very rare |
| - Docetaxel | Breast, lung | Rare |
| Antimetabolites | | |
| - 5-Fluorouracil | Gastrointestinal | Very rare |
| - Capecitabine | Colorectal, breast | …. |

*Circulation.* 2015; 132:1835-1845.

# Incidence of Cardiomyopathy

| Class/Drug | Selected Indication | Heart Failure Incidence |
|---|---|---|
| Monoclonal antibody-based TKIs | | |
| - Trastuzumab | Breast, gastric | **Very common** |
| - Bevacizumab | Colorectal | **Common** |
| Small molecule TKIs | | |
| - Imatinib | Leukemia, GIST | Rare |
| - Dasantinib | Leukemia, GIST | Rare |
| - Sorafenib | RCC, HCC | **Common** |
| - Sunitinib | GIST, RCC | **Very common** |
| - Lapatinib | Breast | Rare |
| - Nilotinib | Leukemia | Rare |
| - Ponatinib | Leukemia | Rare |
| - Bortezomib | Multiple myeloma | Rare |
| Other | | |
| - Everolimus | RCC | **Common** |
| - Temsirolimus | RCC | **Common** |
| - Thalidomide | Multiple myeloma | Rare |
| - Lenalidomide | Multiple myeloma | Rare |

*Circulation* 2015; 132:1835-1845.

# Anticancer Agents and Heart Failure

| Chemotherapy Agents | Frequency of Use | Incidence |
|---|---|---|
| Anthracyclines | | |
| - Doxorubicin | ++++ | 3-26% |
| - Epirubicin | + | 1-3% |
| - Idarubicin | ++ | 5-18% |
| Alkylating agents | | |
| - Cyclophosphamide | ++++ | 7-28% |
| - Ifosfamide | +++ | 17% |
| Antimetabolites | | |
| - Decitabine | ++ | 5% |
| - Clofarabine | + | 27% |
| Antimicrotubule agents | | |
| - Docetaxel | ++ | 2-8% |
| Proteasome inhbitor | | |
| - Carfizomib | ++ | 7% |
| - Bortezomib | ++ | 2-5% |

| Chemotherapy Agents | Frequency of Use | Incidence |
|---|---|---|
| Monoclonal antibody-based TKIs | | |
| - Trastuzumab | +++ | 2-28% |
| - Bevacizumab | ++ | 1-11% |
| - Adotrastuzumab | + | 2% |
| - Pertuzumab | + | 1-16% |
| Small molecule TKIs | | |
| - Pazopanib | ++++ | 0.6-11% |
| - Ponatinib | + | 3-5% |
| - Sorafenib | ++++ | 2-11% |
| - Dabrafenib | ++++ | 8-9% |
| - Sunitinib | ++++ | 1-27% |
| - Dastinib | ++++ | 8-9% |
| - Lapatinib | ++++ | 1-5% |
| - Trametanib | ++++ | 7-11% |

TKIs = tyrosine kinase inhibitors

*J Am Coll Cardiol* 2017; 70:2536-51.

# Molecular Mechanisms of Cardiotoxicity

| Anticancer Therapy | Molecular Mechanisms of Cardiotoxicity | |
|---|---|---|
| Anthracyclines | • Activate Necleus TopIIβ<br>• Generate ROS<br>• Activate TOPImt | • $Fe^{2+}$ overload<br>• Damage transcription<br>• Prevent DNA repair |
| Alkylating agents | • Cause endothelial dysfunction<br>• Cause thrombosis | • Direct DNA damage |
| HER2/ERB2 Antibodies | • Inhibit Pro-survival NRG-1/ErbB Pathway | • Generate ROS |
| TKIs/VEGFR Antibodies | • Inhibit angiogenesis<br>• Cause endothelial dysfunction | • Cause energy depletion |
| Antimetabolites | • Inhibit angiogenesis<br>• Cause endothelial dysfunction | • Generate ROS |
| Antimicrotubules | • Inhibit microtubule formation | • Activate NCS-1 causing $Ca^{2+}$ overload |
| Radiation therapy | • Inhibit angiogenesis<br>• Cause endothelial dysfunction | • Cause energy depletion<br>• Generate ROS |

HER2/ErbB2 = human epidermal growth factor receptor 2, NCS-1 = neuronal calcium sensor 1, NRG-1 = neuregulin-1, ROS = reactive oxygen species, TKIs = tyrosine kinase inhibitors, TopImt = mitochrondrial topoisomerase I, TOPIIβ = topoisomerase IIβ, VEGFR = vascular endothelial growth factor receptor.

*Precision Oncology* 2017; 1:31.

# Magnitude, Mechanism, and Onset

| Therapeutic Class | Magnitude | Evidence | Onset | Comments |
|---|---|---|---|---|
| Anthracyclines<br>- **Doxorubicin**<br>- **Dauorubicin**<br>- Epirubacin<br>- Idarubacin<br>- Mitaxantrone | Major | **A**<br>**A**<br>**A**<br>**A**<br>**A** | Immediate (rare), **intermediate, and delayed** | **Irreversible;** risk increases with increasing cumulative dose; delay can occur >20y after first dose |
| Antimicrotubule agents<br>- Pacilatexal<br>- Docetaxel | Moderate | B<br>B | **Intermediate** | Separate administration of anthracycline from taxane |
| Monoclonal antibody-based TKIs<br>- **Trastuzumab**<br>- Pertuzumab<br>- **Bevacizumab** | Major and moderate | **A**<br>C<br>**A** | **Intermediate** | **Can be reversible**<br>**Can be reversible**<br>**Can be reversible;** also HTN |

*Circulation.* 2016; 134:e32-e69.

# Magnitude, Mechanism, and Onset

| Therapeutic Class | Magnitude | Evidence | Onset | Comments |
|---|---|---|---|---|
| Small molecule TKIs | | | | |
| - **Lapatinib** | Major and moderate | A | **Intermediate** | **Can be reversible** |
| - Sorafenib | Minor | B | | Associated with HTN |
| - Sunitinib | Major | B | | Can be reversible; also HTN |
| Alkylating Agents | | | | |
| - Cyclophosphamide | Major and moderate | B | | **Can be reversible;** usually resolves in 3-4 weeks |
| - Ifosfamide | Major and moderate | B | **Intermediate** | **Can be reversible;** usually resolves in 3-4 weeks |
| - Mitomycin | Moderate | C | | **Can be reversible;** usually occurs after median of 3 cycles at > 30 mg/m$^2$ |
| Other | | | | |
| - Thalidomide | Minor | C | **Unknown** | May worsen edema |
| - Lenalidomide | Major | C | **Intermediate** | Rare |

*Circulation* 2016; 134:e32-e69.

# Diagnostic Tools for Detection

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

GLS = global longitudinal strain

*Eu Heart J* 2016; 37:2768-2801.

# Terminology for Criteria for Adverse Effects

A patient with an asymptomatic left ventricular ejection fraction (EF) decline from 60% to 35% may be graded as grade 0 (no event reported), grade 1 or grade 3 toxicity, depending on which adverse event term is used.

| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|---|
| Heart failure | -- | Asymptomatic with laboratory (e.g. BNP) or cardiac imaging abnormalities | Symptoms with mild to moderate activity or exertion | Severe with symptoms at rest or with activity or exertion; intervention indicated | Life-threatening consequences; urgent intervention necessary | Death |
| LV systolic dysfunction | -- | -- | -- | Symptomatic due to decline in EF responsive to intervention | Refractory or poorly controlled HF due to drop in EF | Death |
| EF declined | -- | -- | Resting EF 40-50%; 10-19% drop from baseline | Resting EF 20-39%; > 20% drop from baseline | Resting EF < 25% | Death |

*Circulation.* 2015; 132:1835-1845.

# ECHO Surveillance During and After Therapy

| | | |
|---|---|---|
| **Anthracycline Therapy** | If cumulative dose > 240 mg/m$^2$ then prior to each additional dose of 50 mg/m$^2$ | At completion of therapy & 6 months later in those with cumulative dose > 240 mg/m$^2$ |
| **HER2 Targeted Therapy** | Every 3 months during treatment | No routine testing if asymptomatic |
| **HER2 Targeted Therapy after Prior Anthracycline** | Every 3 months during treatment | 6 months later |

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

# Cardiac Toxicity and Monitoring Among Chemotherapy-treated Breast Cancer Patients

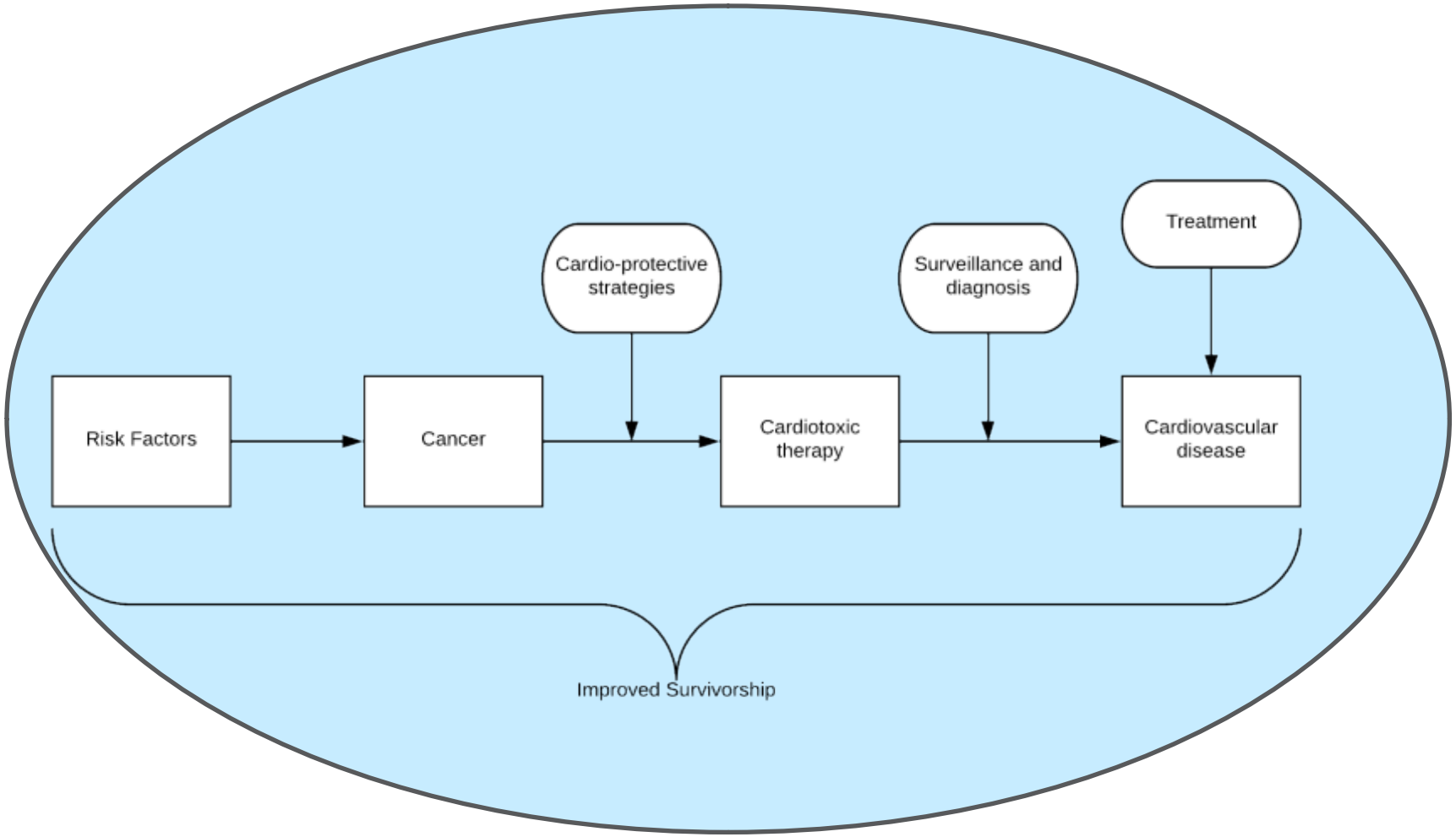
Among 16,456 adults diagnosed with non-metastatic invasive breast cancer (2009-2014), cardiac toxicity was identified in **4.2%** of patients.

| Risk Factor | Incidence of Cardiotoxicity | HR (95% CI) |
|---|---|---|
| Trastuzumab | 8.3% vs 2.7% | 2.01 (1.72-2.36) |
| Anthracyclines | 4.6% vs 4.0% | 1.53 (1.30-1.80) |
| Deyo score = 1 | 5.6% vs 3.4% | 1.38 (1.15-1.66) |
| Deyo score ≥ 2 | 11.7% vs 3.4% | 2.47 (1.94-3.15) |
| Hypertension | 5.8% vs 3.3% | 1.28 (1.09-1.51) |
| Valve disease | 10.1% vs 4.0% | 1.93 (1.48-2.51) |

Among 4,325 patients treated with trastuzumab, guideline-adherent cardiac monitoring was identified in **46.2%** of patients. Therapies using anthracyclines ( OR 1.58; 1.35-1.87), taxanes (OR 1.63; 1.27-2.08), and radiation (OR 1.22; 1.08-1.39) were associated with guideline-adherent monitoring.

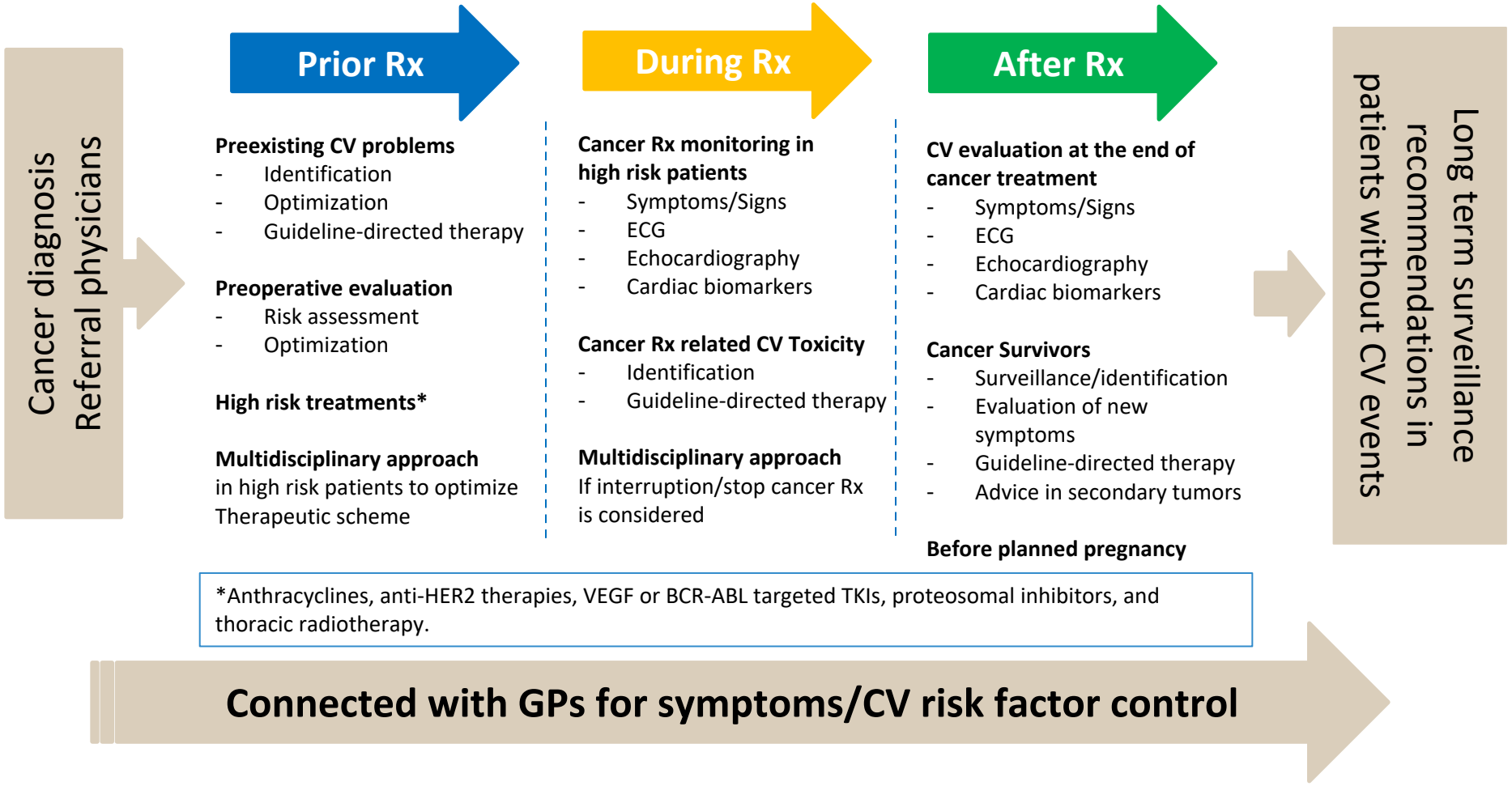
*JACC Cardiovasc Imaging.* 2018; 11:1084-1093.

# Opportunities to Intervene




*Circulation.* 2015; 132:1835-45.

# Team-based Care




*Eur Heart J.* Published online August 06, 2018. doi:10.1093/eurheartj/ehy453.

# Prevention, Treatment & Monitoring

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

*J Am Coll Cardiol* .2017; 70:2536-51.

# Cardiomyopathy Prevention & Management

**Strategies for reducing cardiotoxicity:**
**Anthracycline:** Dose reduction, continuous infusion, liposomal doxorubicin, dexrazoxane
**Trastuzumab:** Avoid concomitant anthracycline
**VSP inhibitors:** Treat hypertension

**Consider cardio-protection (e.g. ACE inhibitor, beta blocker), if:**
Ejection fraction (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:**
Withhold anthracycline if EF < 45%
Withhold trastuzumab if EF < 40%

VSP = vascular endothelial growth factor signaling pathway

*J Am Coll Cardiol.* 2017; 70:2536-51.

# 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/m$^2$ | 3-5% |
| 550 mg/m$^2$ | 7-26% |
| 700 mg/m$^2$ | 18-48% |

| Drug | Relative Toxicity | HF Incidence >5% when cumulative dose exceeds (mg/m$^2$) |
|---|---|---|
| Doxorubicin | 1 | 400 |
| Epirubicin | 0.7 | 900 |
| Daunorubicin | ~0.75 | 800 |
| Idarubicin | 0.53 | 150 |

*Eu Heart J.* 2016; 37:2768-2801.

# Summary of Risk Factors

| At-risk therapies including any of the following: |
|---|
| High-dose anthracycline therapy: doxorubicin ≥ 250 mg/m$^2$ or epirubicin ≥ 600 mg/m$^2$ |
| High-dose radiation therapy when heart is in the field of treatment: radiotherapy ≥ 30 Gy |
| Sequential therapy: lower-dose anthracycline therapy, then subsequent trastuzumab |
| Combination therapy: lower-dose anthracycline with lower-dose radiation therapy |
| **Presence of any of the following risk factors in addition to treatment with lower-dose anthracycline or traztuzumab alone:** |
| Older age at time of cancer treatment (≥ 60 years) |
| ≥ 2 CVD 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.

# Anthracyclines: Cardioprotective Strategies

| Therapies | Hypothesized Mechanism |
|---|---|
| Dexrazoxane | • Decreased ROS formation via prevention of anthracycline-iron complex formation<br>• Reduced anthracycline-induced DNA damage via Top2-DNA cleavage complex inhibition |
| Statins | • Reduced cell death and Top2β-medicated DNA damage via Rac1 inhibition |
| β-blockers | • Increased prosurvival signaling via recruitment of β-arrestin and transactivation of EGFR<br>• Mitigation of oxidative stress<br>• Enhanced lusitropy |
| ACE inhibitors | • Attenuated oxidative stress and interstitial fibrosis<br>• Improved intracellular calcium handling<br>• Improved cardiomyocyte metabolism<br>• Improved mitochrondrial function |
| Exercise training | • Decreased ROS formation<br>• Reduced pro-apoptotic signaling<br>• Improved calcium handling, improved myocardial energetics via augmented AMPK activity |

*J Am Heart Assoc.* 2014; 3:e00065.

# Anthracycline Derivatives and Infusion Protocols

- Dexrazoxane
  - Inhibits formation of drug-induced Top2α- and Top2β-DNA cleavage complexes, reducing ANT-induced DNA damage
    - interference with antitumor effects
    - potential to increase secondary leukemias
- Continuous infusion vs bolus administration
  - Lower cardiac concentrations in mice
  - Less cardiotoxicity in patients with adult sarcoma and lymphoma, but not children with ALL
- Liposomal encapsulation of anthracyclines
  - Lower rates of clinical HF and subclinical changes in LV function
  - Expensive, use restricted to ovarian cancer, AIDS-related Kaposi's sarcoma and multiple myeloma after failure of at least one initial treatment

*J Am Heart Assoc.* 2014; 3:e000665.

*Heart.* 2018; 104:971-7.

# Prevention of Anthracycline-Induced CM

| ACEI/ARB | CT | Intervention | Dose mg/d | n | Follow-up, mo | Selected Endpoints, % | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ☐LVEF | ↓ ≥10% LVEF | HF | Mortality |
| Geogakapoulos et al (2010) | ANT | Enalapril | 11 | 125 | 12 | -2.4 / -1 | … | 4.7 / 7.5 | 0 / 0 |
| Cardinale et al (2006) | ANT* | Enalapril | 16 | 114 | 12 | +0.5 / -14.5 | 0 / 43 | 0 / 24 | 0 / 3 |
| Cadeddu, Dessi (2010, 2011) | ANT | Telmisartan | 40 | 49 | 12 | +2 / +1 | 0 / 0 | 0 / 0 | 8 / 12.5 |

| Beta Blocker | CT | Intervention | Dose mg/d | n | Follow-up, mo | Selected Endpoints | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ☐LVEF | ↓ ≥ 10% LVEF | HF | Mortality |
| Geogakapoulos et al (2010) | ANT | Metoprolol | 89 | 125 | 12 | -2.4 /-1 | … | 2.4/7.5 | 0 / 0 |
| Kalay et al (2006) | ANT | Carvedilol | 12.5 | 50 | 6 | -0.8 / -16.6 | 4 / 20 | 0 / 4 | 4 / 16 |
| El-Shitany et al (2012) | ANT | Carvedilol | 1 mg/kg | 50 | 1 | … | … | … | … |
| Kaya et al (2013) | ANT | Nevibolol | 5 | 45 | 6 | -1.8 / -9.1 | … | 0 / 0 | 0 /0 |

| ACEI/ARB + Beta Blocker | CT | Intervention | Dose mg/d | n | Follow-up, mo | Selected Endpoints | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ☐LVEF | ↓ ≥ 10% LVEF | HF | Mortality |
| Bosch et al (2013) | ANT* | Enalapril + Carvedilol | 8.6 + 24 | 90 | 6 | -0.2 / - 3.3 | 9.5 / 19 | 0 / 4.4 | 7/ 18 |

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

*Circulation* 2015; 132:1835-1845.

# Prevention of Anthracycline-Induced CM

| Aldosterone Receptor Antagonist | CT | Intervention | Dose mg/d | n | Follow-up, mo | Selected Endpoints, % | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ☐LVEF | ↓ ≥10% LVEF | HF | Mortality |
| Akpek et al (2015) | ANT | Spironolactone | 25 | 83 | 6 | -1.3 / -14.1 | 5 / 45 | 0 / 0 | 0 / 0 |

| Statins | CT | Intervention | Dose mg/d | n | Follow-up, mo | Selected Endpoints | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ☐LVEF | ↓ ≥ 10% LVEF | HF | Mortality |
| Acar et al (2011) | ANT | Atorvastatin | 40 | 40 | 6 | +1.3 / -7.9 | 5 / 25 | … | … |

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

*Circulation.* 2015; 132:1835-1845.

# CECCY Trial

- **Purpose:** To evaluate carvedilol compared with placebo among patients with HER2-negative breast cancer undergoing anthracycline-based chemotherapy

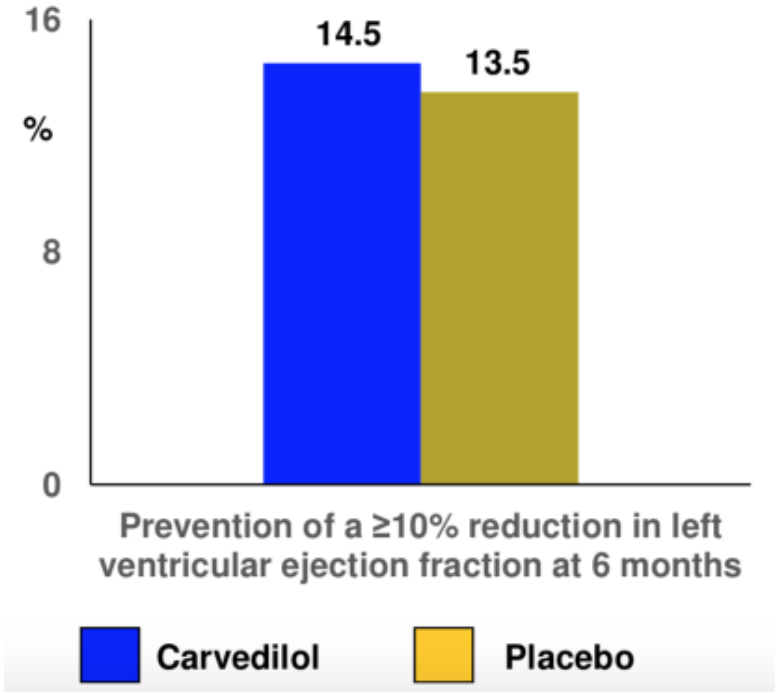
- **Study Design:** Randomized, parallel, placebo controlled (n=192)
  - Carvedilol (n = 96) vs placebo (n = 96), titrated to 50 mg/d if tolerated
  - 24 week follow-up

- **Inclusion criteria:**
  - Women ≥18 years of age
  - Invasive adenocarcinoma undergoing adjuvant or neoadjuvant chemotherapy, including an anthracycline (240 mg/m$^2$)

*J Am Coll Cardiol* 2018; 71:2281-90.

# CECCY Trial

**Trial design:** HER2-negative breast cancer, ANT-based chemotherapy
Carvedilol (n = 96) vs placebo (n = 96), Follow-up: 24 weeks




**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.

*J Am Coll Cardiol.* 2018; 71:2281-90.

# Anti-HER2 / VEGF Inhibitor Mediated Toxicity

| Agent | Risk Factors |
|---|---|
| **Anti-HER2 Compounds** | |
| **Antibodies**<br>- Trastuzumab<br>- Pertuzumab<br>**Tyrosine kinase inhibitors**<br>- Laptinib | • Previous or concomitant anthracycline treatment (short time between anthracycline and anti-HER2 treatment)<br>• Age (> 65 years)<br>• High BMI > 30 kg/m$^2$<br>• Previous LV dysfunction<br>• Arterial hypertension<br>• Previous radiation therapy |
| **VEGF Inhibitors** | |
| **Antibodies**<br>- Bevacizumab<br>- Ramucirumab | • Pre-existing HF, significant CAD or left side VHD (e.g., mitral regurgitation), chronic ischemic cardiomyopathy<br>• Previous anthracycline |
| **Tyrosine kinase inhibitors**<br>- Sunitinib, sorafenib, etc. | • Arterial hypertension<br>• Pre-existing cardiac disease |

*Eu Heart J.* 2016; 37:2768-2801.

# Targeted Therapy: Cardioprotective Strategies

**Monoclonal antibody-based TKIs - Trastuzumab**

| Therapies | Hypothesized Mechanism |
|---|---|
| ACE inhibitors | • Decreased angiotensin-induced blockade of NRG-1/ErbB pathway |
| β blockers | • Increased prosurvival signaling via recruitment of β-arrestin and transactivation of EGFR |
| Exercise | • Enhanced NRG-1/ErbB signaling<br>• Increased myocardial Akt<br>• Inhibition of TGF-β signaling |

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

*J Am Heart Assoc*. 2014; 3:e00065.

# ACE Inhibitor & 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

*Am Heart J.* 2017;188:87-9.

# Cardiotoxicity Definition at Time of Trial Design

| Author (Year) | N | Setting | Definition |
|---|---|---|---|
| Burstein et al (2001) | 40 | Metastatic breast cancer | LVEF < 50% or decrease by 15% |
| Leyland-Jones et al (2003) | 32 | Metastatic breast cancer | LVEF < 40% or decrease by > 15% |
| Romond et al (2005) | 1159 | Adjuvant | LVEF < 55% or decrease by > 16% |
| Berstein et al (2003) | 54 | Metastatic breast cancer | EF < 40% |
| Bengala et al (2006) | 53 | Mixed | EF < 50% |
| Tan-Chiu et al (2005) | 850 | Adjuvant | EF decrease by 10% to < 55% |
| Piccart-Gebhart et al (2005) | 1677 | Adjuvant | EF < 50% or decrease by 10% |
| Venturini et al (2006) | 45 | Metastatic breast cancer | EF < 45% or decrease by 20% |
| Guarneri et al (2006) | 173 | Metastatic breast cancer | EF < 50% or decrease by 20% |

*Am Heart J.* 2017;188:87-9.

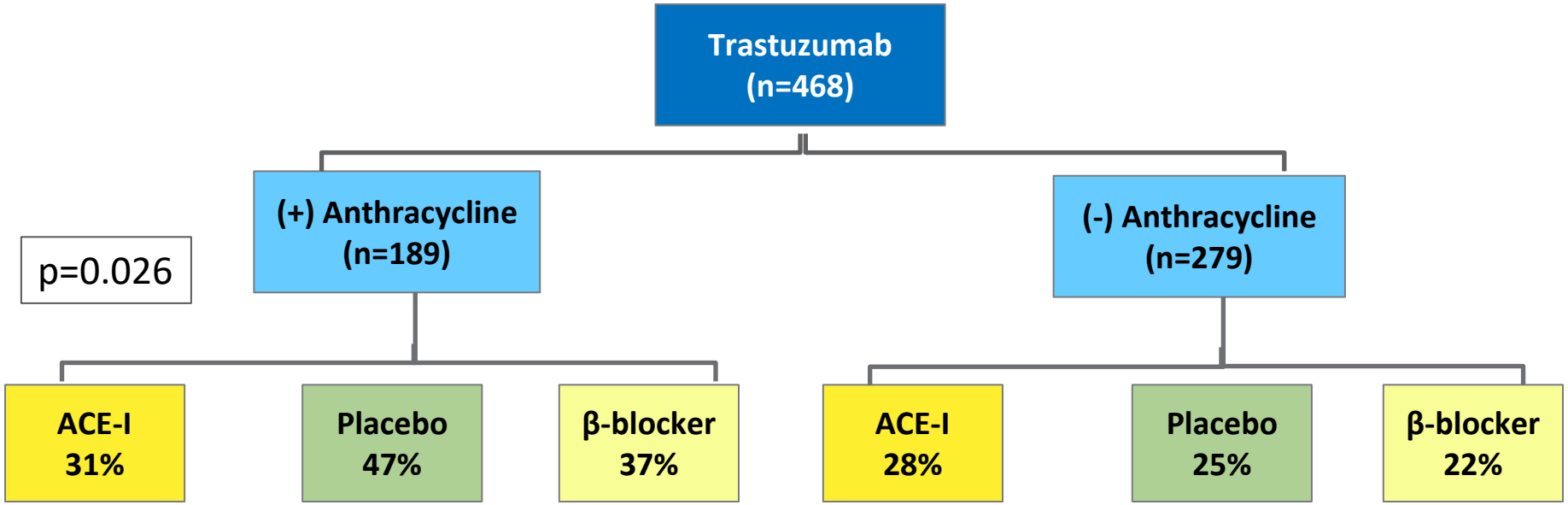
# ACE Inhibitor & Beta Blocker with Trastuzumab

**Primary outcome (decrease in LVEF >10%):**

Lisinopril 30% vs carvedilol 29% vs placebo 32% (NSS)

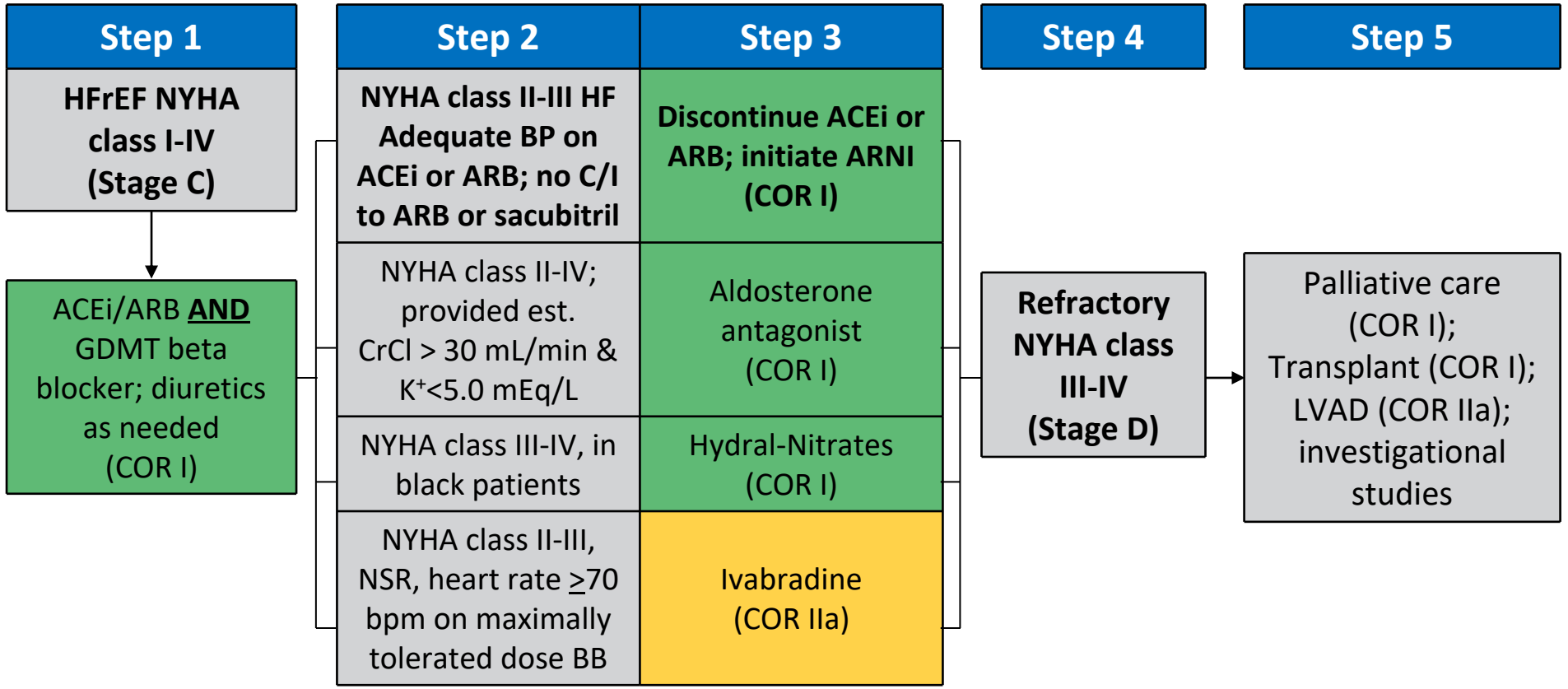
**Secondary outcome:**

Trastuzumab interruption was the same between treatment groups




https://www.dicardiology.com/content/acc-2018-late-breaking-trials

# Treatment of HFrEF Stage C and D




GDMT = guideline-directed medical therapy

*Circulation* 2017; 135:1-45.

# Radiation-induced 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:**

- Yearly: ECG, ECHO if indicated
- 5 years after radiation: ECG, ECHO
- 10 years after radiation: ECG, ECHO, stress test or coronary CT

**Management:**

- Identify, modify and treat CV risk factors
- Systolic dysfunction: ACEI, beta-blockade, and ARAs
- Diastolic dysfunction: optimize risk factors, exercise training

*J Am Coll Cardiol.* 2017; 70:2552-65.

# Comparison of Guidelines

| Recommendations | SIOG | ESMO | ASE/EACVI | NCCN | ASCO |
|---|---|---|---|---|---|
| Identifying risk factors pre-treatment | Yes | Yes | Yes | Yes | Yes |
| Preventative strategies to minimize risk during therapy | Yes | Yes | No | No | Yes |
| Monitor for cardiactoxcity using LVEF | Yes | Yes | Yes | Yes | Yes |
| Use of cardiac biomarkers (troponin I, BNP) | No | Yes | Yes (troponin) | No | No |
| Use of ACEIs or BBs | Yes | Yes | No | No | No |
| Evaluation and management of CV risk factor | Yes | Yes | No | Yes | Yes |
| Referral to cardiologist or cardio-oncologist | Yes | Yes | Yes | Yes | Yes |

SIOG: International Society of Geriatric Oncology, ESMO: European Society for Medical Oncology, ASE/EACVI: American Society of Echocardiography/ European Association of Cardiovascular Imaging, NCCN: National Comprehensive Cancer Network, ASCO: American Society of Clinical Oncology

https://www.acc.org/latest-in-cardiology/articles/2018/06/29/12/57/cv-toxicity-in-cancer-survivors

# Comparison of Guidelines

| Recommendation | SIOG | ESMO | ASE/EACVI | NCCN | ASCO |
|---|---|---|---|---|---|
| Cardiac imaging of choice for cardiac monitoring | ECHO or MUGA | ECHO | ECHO | ECHO | ECHO |
| Timing of cardiac monitoring in asymptomatic patients | Every 2-3 cycles of ANT exposure | Adjuvant ANT and/or Traztuzumab: q3 mos during therapy, then 12 and 18 mos after initiation of therapy | Agents associated with Type 1 toxicity: completion of therapy, then 6 mos after for doses <240 mg/m$^2$ or equivalent. Trastuzumab: every 3 months | Consider in high-risk patients within 1 yr of the last ANT dose | Consider in high-risk patients 6-12 mos after completion of therapy |

SIOG: International Society of Geriatric Oncology, ESMO: European Society for Medical Oncology, ASE/EACVI: American Society of Echocardiography/ European Association of Cardiovascular Imaging, NCCN: National Comprehensive Cancer Network, ASCO: American Society of Clinical Oncology

https://www.acc.org/latest-in-cardiology/articles/2018/06/29/12/57/cv-toxicity-in-cancer-survivors

# Question 2:

**Case:** A 44 year-old woman is diagnosed with HER2+ breast cancer.

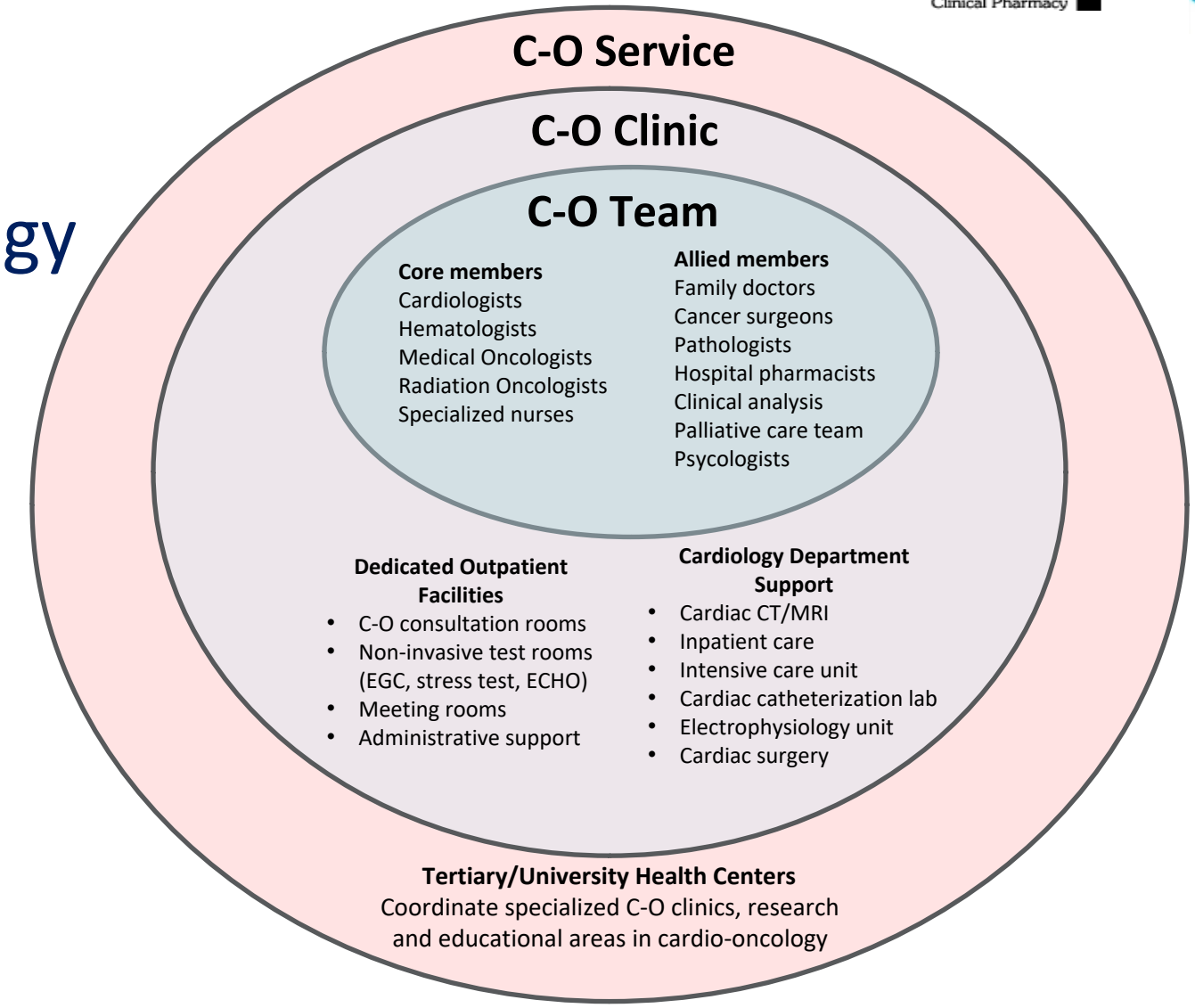
She receives initial chemotherapy, which includes doxorubicin and cyclophosphamide, and is then started on HER2 inhibitor treatment with trastuzumab (Herceptin) and pertuzumab (Perjeta).

Per protocol, she undergoes an ECHO 3 months after initiation of treatment and is now found to have a LVEF 45% (pre-treament EF was 55-60%).

She has no obvious symptoms other than mild edema in her legs. Her PMH includes: HTN, DM and obesity. At this point, you should:

A. Obtain a MUGA to confirm the EF
B. Stop trastuzumab immediately and perform cardiac catheterization
C. Stop trastuzumab, add furosemide, and recheck an ECHO in 1 month
D. Continue trastuzumab and start an ACE inhibitor or beta-blocker

# Cardio-oncology Services, Clinics and Teams




*Eur Heart J.* Published online August 06, 2018. doi:10.1093/eurheartj/ehy453.

# Conclusions

- Multiple barriers to developing evidence-based guidelines for cardiotoxicity management
  - No consistent definition of *cardiotoxicity* and adverse event classification systems
  - Many studies exclude patients with underlying CVD or risk factors
  - Trials with long-term follow-up is sparse
  - Small, typically single-institution studies have inconsistent findings
- Strict management of risk factors and routine surveillance monitoring is imperative
- Large randomized studies are currently underway
  - Role of strain and biomarkers in identifying subclinical disease
  - Role of standard GDMT in primary prevention

# Advances in Cardio-Oncology:

## Prevention and Management of Vascular Toxicities with Anticancer Therapies

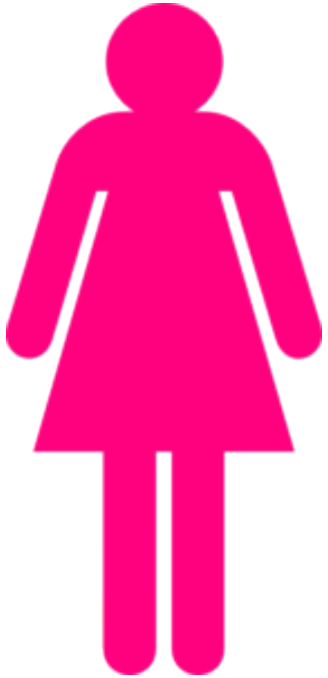
**Sandra Cuellar, Pharm.D., BCOP**
Clinical Assistant Professor
University of Illinois College of Pharmacy
Clinical Oncology Pharmacist
Director, PGY2 Oncology Residency
University of Illinois Hospital & Health Sciences System
Chicago, Illinois

accp American College of Clinical Pharmacy
ashp Certification Resources

# Learning Objectives

- Review anticancer therapies that cause vascular toxicities
- Describe pathophysiology of anticancer therapies induced vascular toxicities
- Describe monitoring and management of vascular toxicities cause by anticancer therapy
- Describe cardiotoxicity associated with immune checkpoint inhibitors

# Meet JP



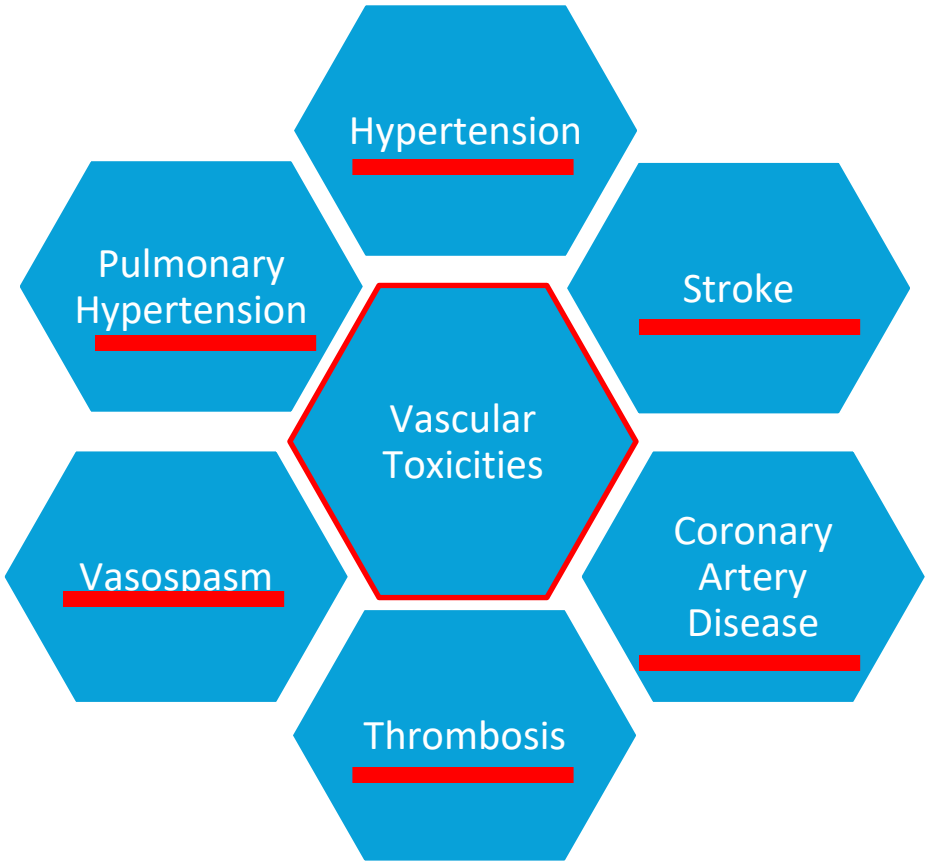
- 55 yo female diagnosed with metastatic renal cell carcinoma
- PMH significant for HTN, hypothyroidism, and depression
- Meds: amlodipine 5mg daily, levothyroxine 0.75 mcg daily, and escitalopram 20 mg daily
- Baseline BP: 145/92  Labs: WNL

# Question 3:

**Case:** Oncologist would like to start pazopanib 800mg once daily today. Which of the following is the best recommendation?

A. Hold until BP is <140/80
B. Reduce dose to 600mg once daily
C. Start at full dose and monitor q week
D. Add enalapril 5mg daily and start pazopanib 800mg daily concomitantly
E. Start enalapril 5mg daily and RTC in 1 week for assessment

# Spectrum of Vascular Toxicity




- Novel anti-cancer therapies target specific molecular pathways that inhibit kinases
- Kinase inhibition
  - Critical Role in cardiovascular homeostasis

*Circulation* 2016;133:1272-89. *NEJM* 375;15:1457-1467.

# Anticancer Agents and Hypertension

| Anticancer Agent | Frequency of Use | All Grades Incidence (%) |
|---|---|---|
| <u>Monoclonal Antibodies (VEGF*)</u> | | |
| Bevacizumab | +++ | 4-35 |
| Ramurcirumab | + | 16 |
| Ziv-Aflibercept | + | 41 |
| <u>Monoclonal Antibodies (Non VEGF)</u> | | |
| Ado-trastuzumab | + | 5.1 |
| Alemtuzumab | + | 14 |
| Ofatumumab | + | 5-8 |
| Rituximab | +++ | 6-12 |
| <u>mTOR inhibitors</u> | | |
| Everolimus | ++++ | 4-13 |
| Temsolimus | ++ | 7 |
| <u>Proteasome Inhibitors</u> | | |
| Bortezomib | ++ | 6 |
| Carfilizomib | ++ | 11-17 |

*VEGF = vascular endothelial growth factor

*J Am Coll Cardiol.* 2017;70:2552-65.

# Anticancer Agents and Hypertension

| Anticancer Agent | Frequency of Use | All Grades Incidence (%) |
|---|---|---|
| Small molecule (NON VEGF TKI**) | | |
| Ponatinib | + | 68 |
| Nilotinib | ++++ | 10-11 |
| Ibrutinib | ++++ | 17 |
| Trametinib | ++++ | 15 |
| Niraparib | NA | 20 |
| Copanlisib | NA | 35 |
| Small molecule (VEGF TKI) | | |
| Pazopanib | ++++ | 42 |
| Sorafenib | ++++ | 7-43 |
| Sunitinib | ++++ | 5-24 |
| Axitinib | ++++ | 40 |
| Cabozantinib | NA | 33-61 |
| Regorafenib | ++++ | 30-59 |
| Vandetanib | NA | 33 |
| Lenvatinib | NA | 42-73 |

VEGF TKI = vascular endothelial growth factor tyrosine kinase inhibitor

*J Am Coll Cardiol* 2017;70:2552-65.
Lenvima (Lenvatinib)[package insert].
Eisai Inc; 2018 Zejula (niraparib [package insert].
Tesaro;2017. Aliqopa (copanlisib)[package insert]. Bayer 2017.

# Phosphatidylinositol 3-kinase (PI3k)

- PI3K family
  - 3 classes exist
    - Class I implicated in carcinogenesis via signal transduction pathways
  - 4 isoforms exist (α,β,δ,γ)
    - Tissue distribution of isoforms implicate toxicity with inhibition
      - Isoform γ implicated in blood pressure homeostasis
      - Angiotensin II requires PI3K γ to stimulate calcium channels in smooth muscle
        - » Results in vascular contraction

*Onco Targets Ther.* 2016;9:203-210.

*Cardiovasc res*. 2012;95:403-8.

# PI3K Inhibitors

| Drug | Inhibits α | Inhibits β | Inhibits δ | Inhibits γ | % all Grade HTN |
|---|---|---|---|---|---|
| Idelalisib (PO) | | | x | | None |
| Copanlisib (IV) | xxx | X | XXX | X | 35% |
| Duvelisib (PO) | | | X | X | None |

Copanlisib

- Hypertension off target adverse event
- Grade 3 hypertension occurred in 27%
- Mean change of systolic and diastolic BP from baseline to 2 hrs
  - 16.8 mmHg and 7.8 mmHg
- Mean BP started decreasing ~ 2 hrs post infusion
- BP remained elevated for 6 to 8 hours after start of infusion

*Current Opin in Pharm* 2015:23;98-107.

Aliqopa (copanlisib)[package insert]. Bayer 2017.

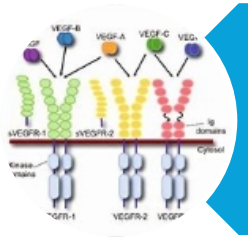
# Management

- Monitor baseline BP prior to administration
- Administer if BP <150/90 mmHg
  - Hold if ≥150/90 mmHg
    - 2 consecutive BP measurements 15 min apart
- Check BP 30 min into infusion and again post infusion
  - If post treatment BP ≥150/90 and requires antihypertensive tx
    - Dose reduce copansilib

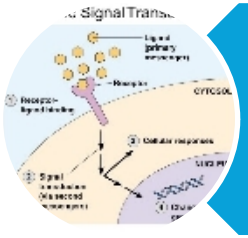
Aliqopa (copanlisib)[package insert]. Bayer 2017.

# Role of Angiogenesis in Cancer


"Angiogenic Switch" : transition from pre-vascular hyperplasia tumor to highly vascularized tumor



Increased production of angiogenic stimulators: VEGF* Family

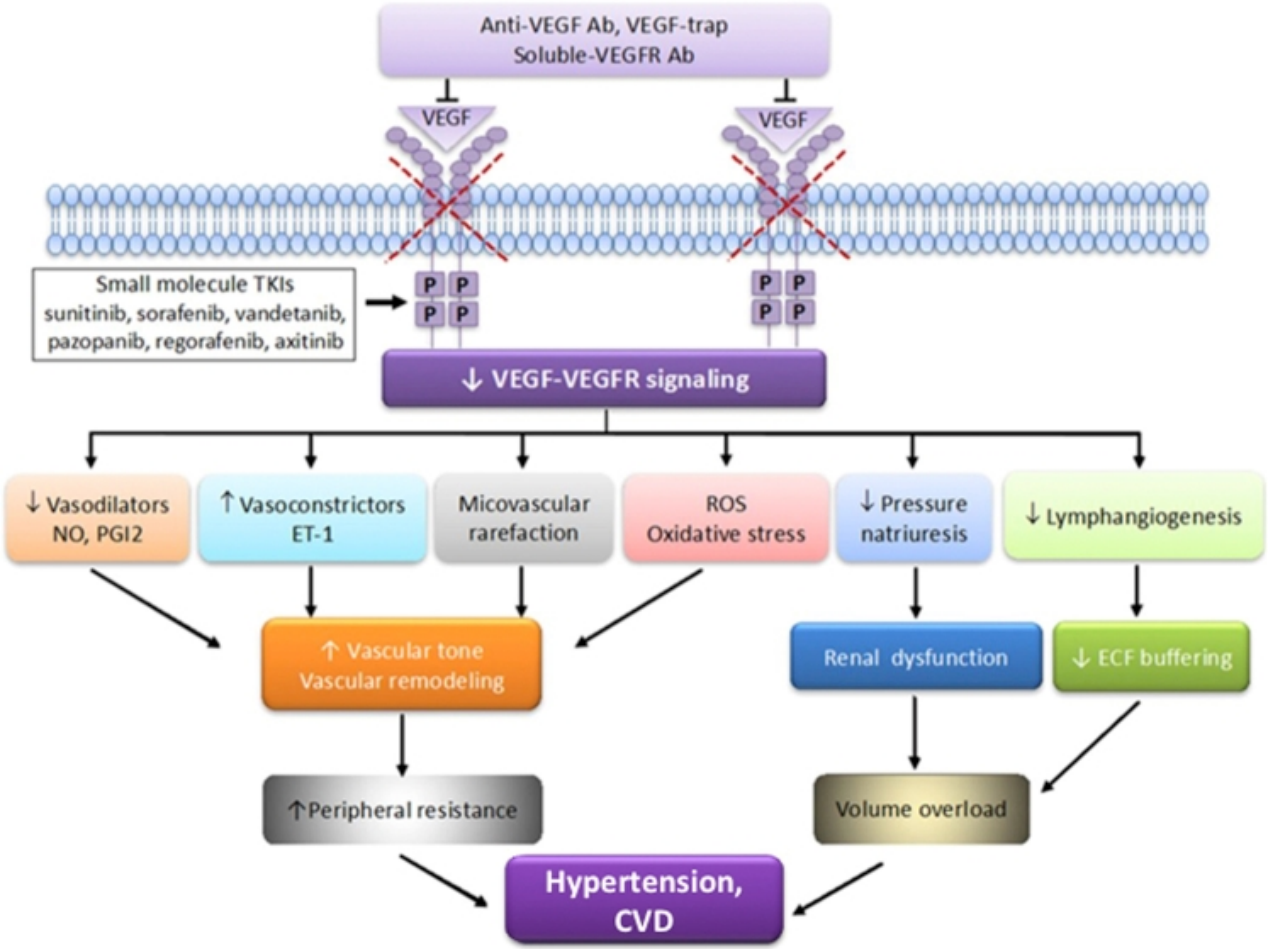


Leads to increased angiogenesis which promotes tumor survival

*VEGF: vascular endotheial growth factor

Sem in Can Bio 2009: 329-37.

# Mechanism of VEGF induced HTN




*JASH* 2018;409-25.

# VEGF Inhibition and Hypertension

- High risk (11-45%) of inducing new hypertension or destabilizing previously controlled hypertension
  - BP increase on average 10-20 mmHg systolic & 5-15 diastolic
  - Severe hypertension in 2-20% of cases
  - Uncommon to discontinue anticancer therapy due to uncontrolled HTN

- Incidence and severity depend on patient factors
  - Age, hx of HTN, CVD hx, type of cancer (renal vs non renal), drug type, dose, schedule, and other associated cancer therapies
  - Limited evidence genetic predisposition
    - No reliable markers to predict risk

*Cardio-Oncology*: 2015;1:6. Br J Cancer 2014;111:1241.

# VEGF Inhibition and Hypertension

- Onset is variable
  - Common w/in the first month of therapy
    - May occur within 24hrs of first dose
- Reversible
  - BP falls quickly w/in 1 week of d/c therapy
    - May not return to pre-therapy BP

- Surrogate marker for efficacy
  - Several reports note an association b/w improved antitumor efficacy & development of systolic or diastolic HTN during therapy
    - Rini BI et al HTN as biomarker for efficacy
    - Houk et al Relationship b/w sunitinb exposure & efficacy
    - Hurwitz et al Analysis of early HTN & clinical outcome
  - More studies warranted to validate HTN as predictive marker of efficacy

*Oncologist.* 2013:18:273.
*JASH,* 2018:409-25.
*J Am Coll Cardiol.* 2017;70:2552-65.
Wasserstrum et al *Cardio-Oncology:* 2015.
*Cancer Chemother Pharmoacol.* 2010;66:357.

# Recommendations for Monitoring:

## National Cancer Institute Investigational Drug Steering Committee

- Pretreatment assessment of CVD risk factors
- Identify and treat preexisting HTN before using agents
  - Goal to maintain <140/90 during therapy
    - Lower goal in those w/ preexisting CV risk factors
- Monitor BP during therapy
  - Weekly during 1st cycle , then q2-3 weeks
- Other
  - Control Pain & review other medications that can increase BP

*Eu Heart* J (2016)37:2768-2801.

# Management

- Initiate BP treatment if BP >140/90 or diastolic increases by 20 mmHg
- Hold therapy if systolic BP >160 mmHg or diastolic BP > 100 mm Hg
- Consider discontinue therapy if systolic > 200 mm Hg or diastolic > 100 mm Hg or hypertensive crisis

*J Am Coll Cardiol.* 2017;70:2536-51.

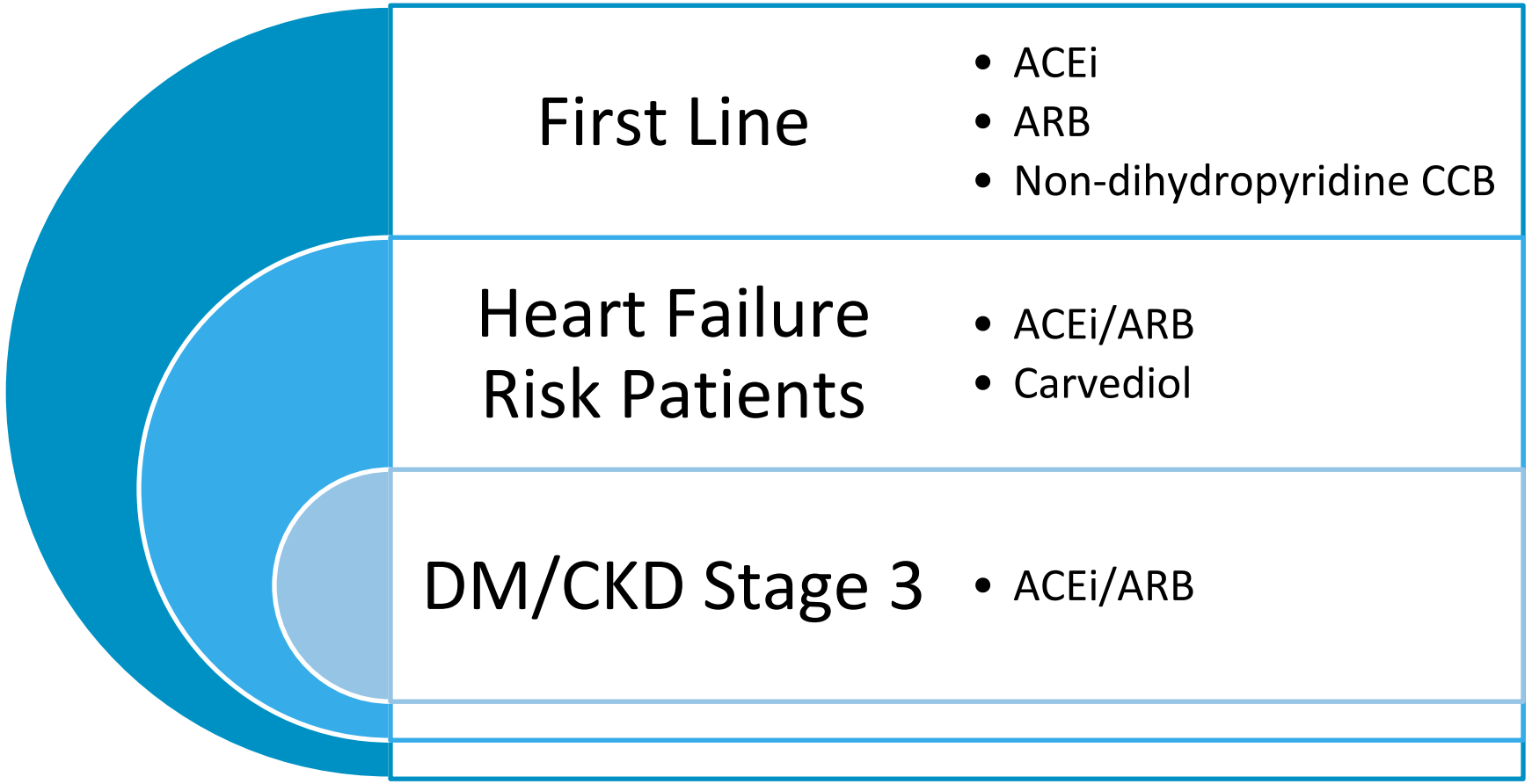
# Pharmacology Management

## Optimal Anti-Hypertensive

- Not well defined
- Other considerations
  - Drug interactions
  - Comorbidities
  - Side effects

*J Am Coll Cardiol.* 2017;70:2536-51.

# Pharmacologic Management




**Resistant Cases = Add long acting nitrate**

*JASH* 2018;409-25.

*J Am Coll Cardiol.* 2017;70:2536-51.

# Pulmonary Arterial Hypertension (PAH)

Precapillary form of pulmonary hypertension defined by ↑ in mean pulmonary arterial pressure at least 25 mmHg at rest with pulmonary arterial wedge pressure ≤ 15 mmHg during right heart catheterization

Endothelial dysfunction w/ obliteration, proliferation, inflammation and remodeling of the small pulmonary arteries, resulting in progressive ↑ in pulmonary vascular resistance (PVR) and progressive right ventricular failure

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic (NT-proBNP) clinical markers used in clinical practice

Clinical presentation: exertional dysapnea, fatigue, atypical chest pain, right upper quadrant pain

*Br J Clin Pharmacol* 2018:84;835-45.

*Circulation* 2016:133(13);1272-89.

# PAH

| Anticancer Agent | Mechanism | Frequency | Onset |
|---|---|---|---|
| Dasatinib | • Remodeling of pulmonary vessel<br>• Exudative pleural effusions, pericardial effusions<br>• Thrombosis | 11% | • May not be fully reversible (switch to another agent)<br>• Delayed onset (~8 to 40 months)<br>• No risk factors identified |

| Kinase/TKI | Bosutinib | Dasatinib | Imatinib | Nilotinib | Ponatinib |
|---|---|---|---|---|---|
| ABL1 | 100 | 105 | 83 | 98 | 101 |
| ABL1(T315I) | 93 | 68 | 9 | 15 | 100 |
| FGFR1 | 79 | 47 | 0 | 0 | 101 |
| FGFR2 | 95 | 73 | 3 | 0 | 100 |
| FGFR3 | 83 | 34 | 1 | 0 | 101 |
| FGFR4 | 3 | 9 | 8 | 0 | 98 |
| FLT1 (VEGFR1) | 97 | 39 | 5 | 0 | 101 |
| FLT3 | 77 | 17 | 68 | 60 | 99 |
| FLT4 (VEGFR3) | 92 | 31 | 3 | 17 | 101 |
| KDR (VEGFR2) | 101 | 22 | 7 | 22 | 94 |
| KIT | 23 | 100 | 97 | 96 | 101 |
| PDGFRα | 77 | 100 | 98 | 103 | 103 |
| PDGFRβ | 95 | 99 | 91 | 93 | 102 |
| SRC | 96 | 101 | 5 | 23 | 102 |
| TIE2 | 22 | 16 | 0 | 41 | 101 |

*Br J Clin Pharmacol.* 2018:84;835-45.

# Strategies for Surveillance and Management

| | |
|---|---|
| Baseline Assessment | • Assess Risk Factors of PAH<br>• Assess NYHA/WHO functional class<br>• Consider 6 min walk test<br>• Assess echocardiographic level of probability of PH<br>• Consider NT-proBNP |
| Surveillance Strategy | **Asymptomatic**<br>• Assess NYHA/WHO functional class q 3 months<br>• Assess echocardiographic level q 3 months<br>• Assess indication for right heart catheterization<br><br>**Symptomatic**<br>• Assess NHHA/WHO functional class<br>• Perform 6 min walk test<br>• Test NT-proBNP<br>• Cardiac work up<br>• Consider interruption of cancer therapy |

*Eu Heart J.* (2016)37:2768-2801.

# Take Home Points

- Hypertension is the most common vascular toxicity
- Anti-VEGF mechanism leads to risk of HTN
- Onset is variable and is reversible usually w/in 7 days with anti-VEGF agents
- Assess patients for CVD risk factors
- Monitor BP weekly upon initiation
- Selection of antihypertensive depends on individual patient characteristics

# Anticancer Agents and Myocardial Infarction/Ischemia

| Anticancer Agent | Frequency of Use | All Grades Incidence (%) |
|---|---|---|
| <u>Antimetabolites</u><br>Capecitabine<br>Flourouracil | ++++<br>++++ | 3-9<br>1-68 |
| <u>Monoclonal Antibodies (VEGF)</u><br>Bevacizumab | +++ | 0.6-9 |
| <u>Small Molecule TKI</u><br>Nilotinib<br>Ponatinib | ++++<br>++ | 4-13<br>7 |
| <u>Immunomodulators/Angiogenesis Inhibitors</u><br>Lenalidomide | ++ | 11-17 |

*J Am Coll Cardiol.* 2017;70:2552-65.

# Mechanisms of Coronary Artery Disease (CAD) in Cancer Treatment

| Agent | Pathophysiological Mechanism | Risk of Coronary Artery Disease and Acute Coronary Syndrome |
|---|---|---|
| Fluoropyrimidines (5FU, capecitabine) | • Endothelial injury<br>• Vasospasm | • Up to 18% manifest myocardial ischemia<br>• Up to 7-10% silent myocardial ischemia |
| BCR-ABL Ponatinib | • Vasospasm<br>• Arterial Thrombosis<br>• Atherosclerotic event | • Maybe dose related<br>• Severe PAD* reported up to 30%<br>• Onset of PAD vary from months to years |
| VEGF Inhibitors | • Procoagulant status<br>• Plaque rupture<br>• Thrombosis | • Risk of arterial thrombosis 1.4 – 3.8% |

*PAD – Peripheral arterial disease

*Eu Heart J.* (2016)37:2768-2801.

# Antimetabolites

**5FU**

- 5FU >800mg/m2 & continuous infusion
- Short lasting (up to 48hrs and last 2-5 days after initiation)
- ECG ischemic alterations have been reported in 68% & associated with biomarker elevations in 43% of cases
- Mortality ranges from 2.2 to 13%

**Capecitabine**

- Selective activation of capecitabine in cancer cells leads to less cardiotoxicity compared to 5FU
- 3 - 9% incidence
- ECG ischemic changes in 5.2%
- Seldom associated with elevation of cardiac markers

*J Am Coll Cardiol* .2017;70:2536-51.

# Ischemia and Anticancer Therapy

**Ponatinib & Nilotinib**

- Peripheral arterial occlusive disease (PAOD)
- Rapid progressive atherosclerosis, vessel occlusions
- May consider antiplatelet, statins, ACEi, and amlodipine

**VEGF Inhibitors**

- 10% ischemic events are peripheral
- Acute myocardial infarction rare
- Modified risk if concomitant 5FU therapy

*Circulation.* 2016:133(13);1272-89.

# Monitoring & Assessment

- Assessment of CAD
- Patients treated with 5FU/capecitabine
  - Consider regular ECG & hold chemo if ischemia occurs
- Drug rechallenge after coronary spasm
  - No other alternative exist
  - Consider hospital admission for close monitoring
  - Pretreatment with nitrates and/or CCB

*Eu Heart J.* (2016)37:2768-2801.

# Prevention & Management of Ischemia

## Ischemia work up

- Stress test, cardiac catheterization

## Treatment

- As per ACC/AHA guidelines
- Antiplatelet drugs in symptomatic PAD
  - Oncology population
    - Anemia, thrombocytopenia, other coagulation abnormalities

*J Am Coll Cardiol* 2017;70:2552-65.

# Cerebrovascular Events & Anticancer Therapy

| Agent | Mechanism |
|---|---|
| Cisplatin | • Endothelial cell death may generate systemic pro-coagulant mediators |
| Methotrexate | • Unknown |
| Bevacizumab | • Related to HTN, arterial thrombosis, and bleeding<br>• Intracranial hemorrhage 1.9% occur often with tumor progression<br>• Ischemic stroke associated with prolonged therapy(median 16 mo) |
| Nilotinib | • Diffuse intracranial atherosclerosis<br>• Carotid artery disease |

Herrmann et al. *Circulation.* 2017.

# Management

## Signs/symptoms of Stroke

- Per Published guidelines
- Head CT (r/o CNS metastases)
- Cancer pts often excluded from fibrinolysis trials
  - PLT <100 contraindication for lytic therapy

## Other work up

- Thrombotic etiology
- 12 lead ECG

*J Am Coll Cardiol* . 2017;70:2552-65.

# Take Home Points

- Ischemia, cerebrovascular events, and myocardial infarction have been reported with anticancer agents
- Frequency is relatively low
- Management depends on type and severity of event
  - May require discontinuation of anticancer therapy

# Anticancer Agents and Thromboembolism

| Anticancer Agent | Frequency of Use | All Grades Incidence (%) |
|---|---|---|
| **Angiogenesis Inhibitors** | | |
| Lenalidomide | +++ | 3-75 |
| Pomalidomide | + | 3 |
| Histone deacetylase Inhibitor | ++++ | 5-8 |
| Vorinostat | | |
| mTOR inhibitors | | |
| Everolimus | ++++ | 1-4 |
| Small Molecule TKI | | |
| Axitinib | ++++ | 3 |
| Erlotinib | ++++ | 7 |
| Nilotinib | ++++ | 4-11 |
| Pazopanib | ++++ | 1-5 |
| Ponatinib | + | 5 |
| Sunitinib | ++++ | 3 |
| Trametinib | ++++ | 7 |
| Ziv-aflibercept | + | 9 |

*J Am Coll Cardiol.* 2017;70:2552-65.

# Risk Factors

**Cancer Related Risk Factors**

- Pancreas, brain, stomach, kidney, lung, lymphoma, myeloma
- Histology (adenocarcinoma)
- Metastatic disease
- Initial period after cancer diagnosis

**Patient Related Risk Factors**

- Age, gender, ethnicity
- Comorbidities
- Hx of venothromboembolism
- Low performance status

**Treatment Related Risk Factors**

- Major surgery
- Hospitalization
- Anticancer Therapy
- Hormonal Therapy
- Transfusions
- Central venous catheter

*J Am Coll Cardiol.* 2017;70:2552-65.

# Management

- No systematic screening recommended
- Prophylaxis indicated in high risk myeloma patients based on IMWG guidelines & NCCN guidelines
- Treatment of VTE
  - Preferred LMWH
  - Assess bleeding risk
  - NOAC data limited in cancer patients
- Duration of therapy may be indefinite
- Continuation of anticancer therapy
  - Depends on grade of event
    - Grade 3 or 4 discontinue therapy
  - Depends on risk versus benefit

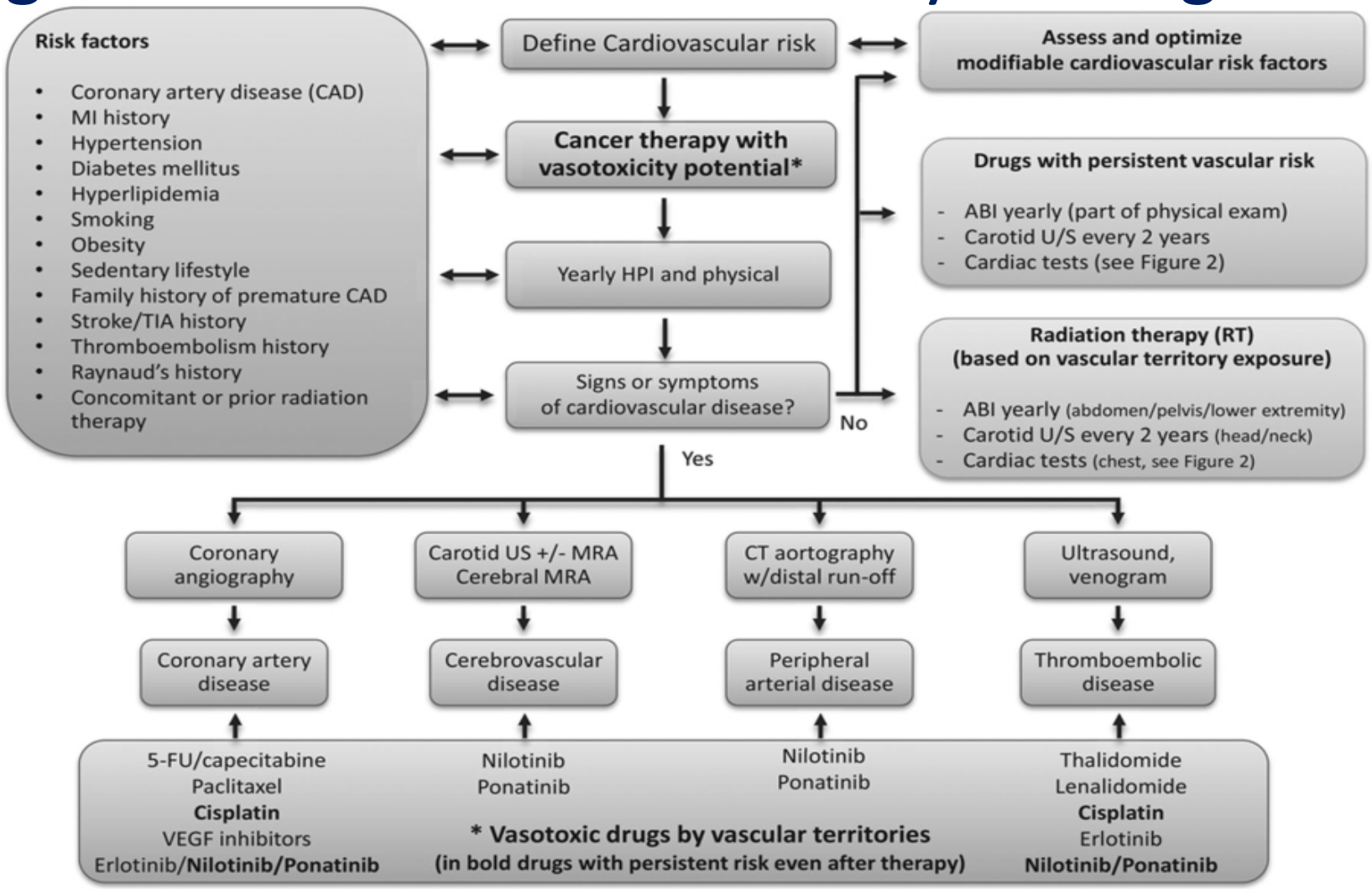
*J Am Coll Cardiol.* 2017;70:2552-65.

# Take Home Points

- VTE is a common occurrence in cancer patients
  - Etiology is multifactorial
- Treatment considerations
  - Pt baseline platelets, weight, renal function, hx of HIT
- Duration of therapy
  - 3 to 6 months to indefinite
- Discontinuation of anticancer therapy
  - Risk versus benefit
  - Severity of event

*J Am Coll Cardiol.* 2017;70:2552-65.
NCCN Cancer Associated Thromboembolic Disease v2.2018.

# Algorithm For Vascular Toxicity Management




Vascular Toxicities of Cancer Therapies, Volume: 133, Issue: 13, Pages: 1272-1289, DOI: (10.1161/CIRCULATIONAHA.115.018347)

# Immune Checkpoint Inhibitors (ICI) & Cardiotoxicity

| Drug | Target | Cardiotoxic Effects |
|---|---|---|
| Ipilumumab | CTLA-4 | Pericarditis: <1%<br>Myocarditis: 0.2% |
| Nivolumab | PD-1 | Myocarditis: <1% |
| Pembrolizumab | PD-1 | Cardiac Failure: 0.4% |
| Atezolizumab | PD-L1 | Myocardial infarction |
| Avelumab | PD-L1 | Myocarditis |
| Durvalumab | PDL-1 | Myocarditis: <1% |

**Other cardiac clinical sub-types toxic effects:**

- Pericarditis
- Atrioventricular block
- Heart failure
- Ventricular arrhythmias
- Acute myocardial infarction
- Takotsubo syndrome

*Lancet Oncology* 2018:19:e447-58.

# Immune Checkpoint Inhibitors (ICI) & Cardiotoxicity

- Rare events reported in clinical trials
  - 50% of ICI myocarditis reported were fatal
- Incidence is > with CTLA-4 plus PD-1 (0.26%)
- Moslehi et al
  - Review of 101 cases of ICI mediated cardiotoxicity
    - 64% occurred after first or second dose
    - 76% w/in first 6 weeks of treatment
- Escudier et al
  - Review of 30 cases of ICI mediated cardiotoxicity
    - Median time to onset ~ 65 days, ranged from 2 days to 454 days
- Mahmood et al
  - Review of 35 cases of ICI mediated cardiotoxicity
    - Median time to onset ~34 days

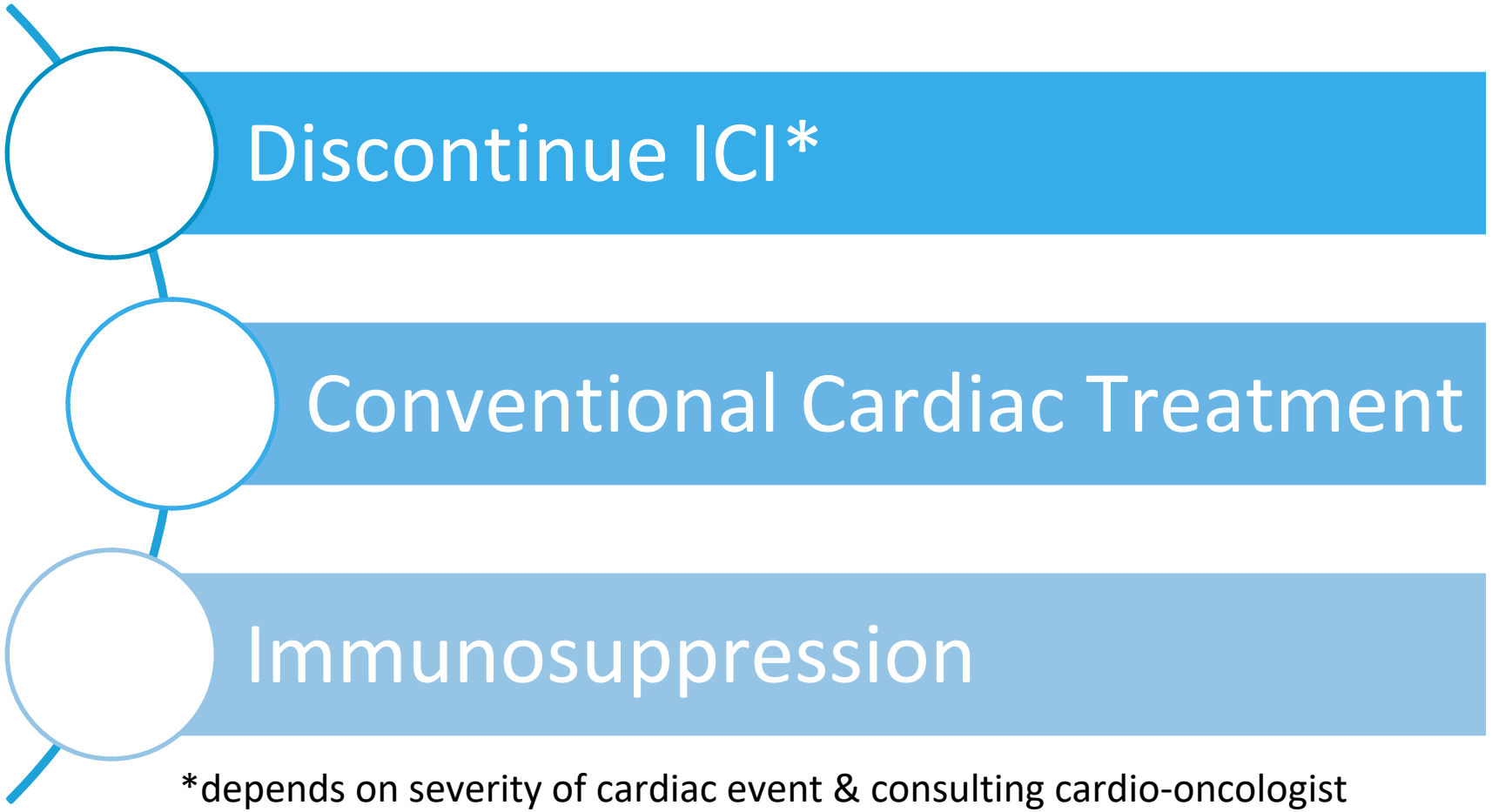
*Lancet Oncology* 2018:19:e447-58.

# ICI Mechanisms of Cardiotoxicity

- Cardiomyocytes express PD-L1
  - Cardioprotective mechanism against immune response
- T-cells could be targeting antigens shared by tumor, skeletal muscle, and heart
  - Autoimmune T-cell mediated cardiotoxic effects
- Emerging pre-clinical data suggest role of T cells in the progression of pressure overloaded hypertrophy to heart failure
  - Direct inhibitor of PD-L1 may accelerate pre-existing heart disease & potentially cause non-flammatory cardiomyocyte dysfunction in diseased hearts even in absence of immune response

*NEJM* 375;18:1749-1755.
*Lancet Oncology* 2018:19:e447-58.

# Management




*depends on severity of cardiac event & consulting cardio-oncologist

*Lancet Oncology* 2018:19:e447-58.

# ICI Cardiotoxicity Summary

- Rare adverse event
  - consequences are serious and sometimes fatal
- Mechanisms are not fully elucidated
- Monitoring strategies
  - No evidence based algorithm exists
    - Proposed surveillances strategies
      - Monitor ECG, cardiac troponin, BNP, and Echocardiogram
        - » More aggressive monitoring if high risk patients
- Management
  - Conventional cardiac measures and immunosuppression

*Lancet Oncology* 2018:19:e447-58.

# Summary

Vascular toxicities from anticancer therapy occur more commonly with novel targeted agents compared to classic chemotherapy

Vascular toxicities include:  hypertension, coronary artery disease, cerebrovascular events, and thromboembolic disease

Knowledge of etiology, onset, and management of vascular toxicity is vital for pharmacists to optimize safety and efficacy of anticancer therapy

# Advances in Cardio-Oncology:

## Prevention and Management of Cancer Chemotherapy-Associated Arrhythmias

**James E. Tisdale, Pharm.D., BCPS, FACC, FAHA, FAPhA, FCCP, FNAP**
Professor
College of Pharmacy, Purdue University
Adjunct Professor
School of Medicine Indiana University
Indianapolis, Indiana

accp American College of Clinical Pharmacy

ashp Certification Resources

# Cancer Chemotherapy-Associated Arrhythmias

## Learning Objectives

1. Describes the types of arrhythmias that may be caused by cancer chemotherapy drugs.
2. Describe the pathophysiology and adverse outcomes associated with cancer chemotherapy-associated arrhythmias.
3. Describe strategies for prevention and management of cancer chemotherapy-associated arrhythmias.

# Cancer Chemotherapy-Associated Arrhythmias

- Types of arrhythmias induced by cancer chemotherapy drugs:
  - Sinus bradycardia/AV block
  - Premature atrial complexes (PACs)
  - Sinus tachycardia
  - Atrial fibrillation
  - Supraventricular tachycardia (SVT)
  - Premature ventricular complexes (PVCs)
  - Ventricular tachycardia
  - QT interval prolongation/Torsades de pointes (TdP)

# Cancer Chemotherapy-Associated Arrhythmias

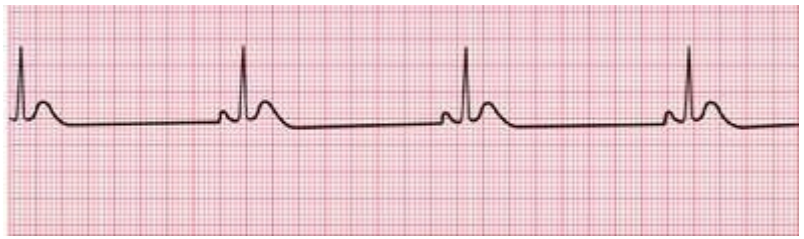
- Types of arrhythmias induced by cancer chemotherapy drugs:
  - **Sinus bradycardia/AV block**
  - Premature atrial complexes (PACs)
  - Sinus tachycardia
  - **Atrial fibrillation**
  - Supraventricular tachycardia (SVT)
  - Premature ventricular complexes (PVCs)
  - **Ventricular tachycardia**
  - **QT interval prolongation/Torsades de pointes (TdP)**

# Cancer Chemotherapy-Associated Arrhythmias

- **Sinus bradycardia/AV block**
- Atrial fibrillation
- Ventricular tachycardia
- QT interval prolongation/Torsades de pointes (TdP)

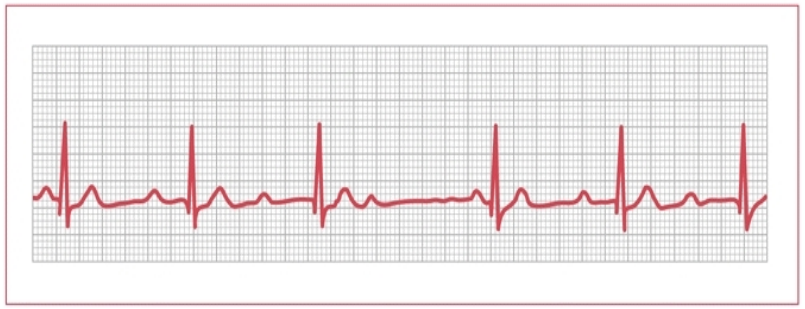
# ECG Characteristics of Sinus Bradycardia

- Sinus bradycardia
  - Regular rhythm
  - Heart rate < 60 bpm
  - PR intervals constant

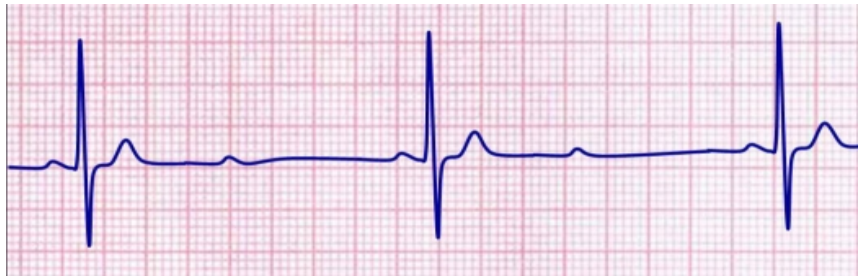


# ECG Characteristics of AV Blocks

- 2nd degree AV block (Mobitz Type 1)
  - Regularly irregular
  - Heart rate < 60 bpm
  - Progressively prolonging PR intervals until QRS complex is lost

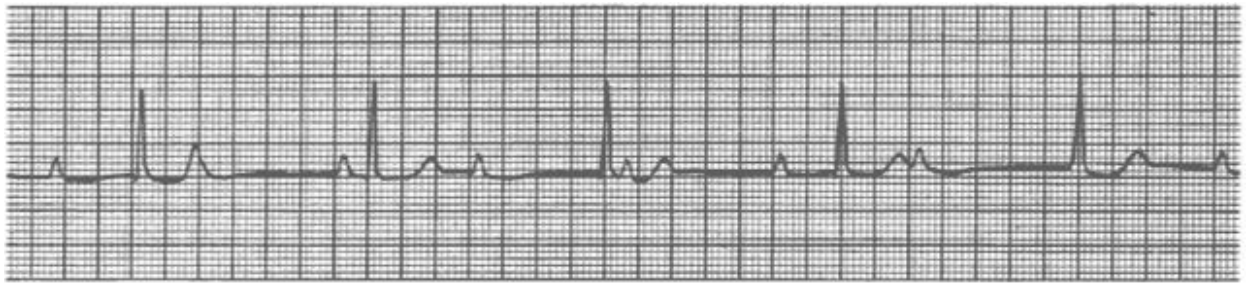


- 2nd degree AV block (Mobitz Type 2)
  - Often regular
  - Heart rate < 60 bpm
  - PR intervals constant
  - QRS complex lost every 2nd, 3rd, 4th beat



# ECG Characteristics of AV Blocks

- 3rd degree AV block (complete heart block, AV dissociation)
  - Regular rhythm
  - Heart rate < 60 bpm
  - P-P intervals constant
  - R-R intervals constant
  - No relationship between P waves and QRS complexes



# Signs/Symptoms of Sinus Bradycardia/AV Block

- Dizziness
- Lightheadedness
- Hypotension
- Syncope
- Not associated with mortality
  - Unless occurs while driving, operating machinery

# Cancer Chemotherapy-Associated Sinus Bradycardia/AV Block

| Drug class | Drugs within class | Incidence | Proposed Mechanism(s) |
|---|---|---|---|
| Anthracyclines | Daunorubicin<br>Doxorubicin<br>Epirubicin<br>Idarubicin<br>Mitoxantrone | 1-10% (for the class) | Direct sinus/AV node fibrosis<br>Conduction system damage 2º to microangiopathy<br>Immune reaction/hypersensitivity |
| Antimetabolites | Capecitabine<br>5-FU<br>Cytarabine<br>Fludarabine | 1-10%<br>12% (SB)<br>NK<br>NK | Direct injury to sinus/AV node<br>Myocardial ischemia<br>Release of vasoactive compounds |
| HER2 inhibitors | Pertuzumab | < 1% | NK |
| MET inhibitors | Tivantinib | 21% | NK |
| Immunomodulatory drugs | Thalidomide | 26-53% | NK |
| Platinum compounds | Cisplatin | NK | NK – direct sinus node damage? |

NK = Not known; SB = Sinus bradycardia

*Drug Saf* 2015;38:129-52.
*Circ Arrhythm Electrophysiol* 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443.
Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.

# Cancer Chemotherapy-Associated Sinus Bradycardia/AV Block

| Drug class | Drugs within class | Incidence | Proposed Mechanism(s) |
|---|---|---|---|
| Taxanes | Paclitaxel | 3-29% (SB)<br>Up to 4.4% (AVB) | Stimulation of $H_1$ and $H_2$ receptors<br>Direct damage to sinus/AV node |
| Topoisomerase inhibitors | Irinotecan | NK | NK |
| Tyrosine kinase inhibitors | Alectinib<br>Ceritinib<br>Crizotinib<br>Ponatinib | 5.1% (SB); 2.8% (AVB)<br>1-10%<br>31%<br><1% | NK |
| VEGF inhibitors | Dovitinib<br>Vemurafenib | 5%<br><1% | NK |

AVB = AV block; NK = Not known; SB = Sinus bradycardia

Drug Saf 2015;38:129-52.
Circ Arrhythm Electrophysiol 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443
Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.

# Management of Cancer Chemotherapy-Associated Sinus Bradycardia/AV Block

- Majority of patients are asymptomatic
- For symptomatic patients:
  - Consider alternative therapy
  - If no suitable alternative therapy, monitor patient closely
  - Consider isoproterenol
  - Consider temporary pacemaker
  - For thalidomide-induced bradycardia with no suitable alternative therapy, permanent pacemaker implantation may be required to allow continuation of therapy

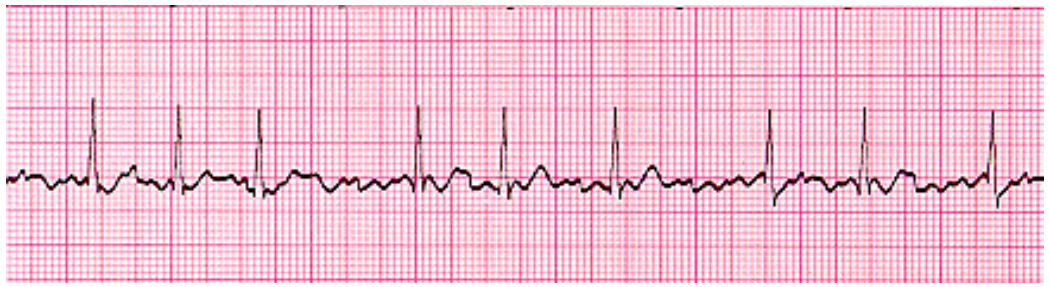
*J Am Coll Cardiol.* 2017;70:2552-2565.

# Cancer Chemotherapy-Associated Arrhythmias

- Sinus bradycardia/AV block
- **Atrial fibrillation**
- Ventricular tachycardia
- QT interval prolongation/Torsades de pointes (TdP)

# Cancer Chemotherapy-Associated Atrial Fibrillation

- ECG characteristics:
  - Irregularly irregular
  - No visible p waves
  - Undulating baseline
  - QRS complexes normal or narrow
  - Heart rate 100-200 bpm



- Signs/Symptoms:
  - May be asymptomatic
  - Palpitations
  - Fatigue
  - Dizziness
  - Dyspnea
  - Hypotension
  - Syncope
  - Heart failure

*J Am Coll Cardiol.* 2014;64:e1-e76.

# Cancer Chemotherapy-Associated Atrial Fibrillation

- Morbidity/Mortality:
  - Stroke/systemic embolism – risk increased 3-7x
  - Heart failure – risk increased 3x
  - Dementia – risk increased 2x
  - Mortality – risk increased 2x

*J Am Coll Cardiol.* 2014;64:e1-e76.

# Cancer Chemotherapy-Associated Atrial Fibrillation

| Drug class | Drugs within class | Incidence | Proposed Mechanism(s) |
|---|---|---|---|
| Alkylating agents | Cyclophosphamide<br>Melphalan<br>Busulfan*<br>Anthracyclines | 1-10%<br>6.6-22.5%<br>≤ 6.4%<br>1.4-13.8% | Conduction system damage 2º to microangiopathy<br>Atrial hypertrophy & fibrosis<br>Accumulation of reactive oxygen species<br>Activation of pro-inflammatory pathways |
| Antimetabolites | Capecitabine<br>Clofarabine<br>5-FU<br>Gemcitabine | NK<br>7.4-19%<br>NK<br>8.2% | Myocardial ischemia<br>Release of vasoactive compounds<br>Immune-mediated atrial damage<br>Atrial fibrosis |
| Histone deacetylase inhibitors | Interleukin-2 | 4.3-8.0% | NK |
| Immunomodulatory drugs | Lenalidomide<br>Thalidomide | 4.6-7%<br>1.3% | NK |
| Platinum compounds | Cisplatin | 12-18%¶ | Coronary vasospasm<br>Direct pericardial irritation<br>Hypomagnesemia<br>LV dysfunction<br>Mitochondrial dysfunction<br>Promotion of inflammation |

LV = Left ventricular
NK = Not known
*In combination with 5-FU
¶Intrapericardial

*Circ Arrhythm Electrophysiol* 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443.
*Pharmacol Ther* 2018; Apr 24. pii: S0163-7258(18)30072-X.
Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.

# Cancer Chemotherapy-Associated Atrial Fibrillation

| Drug class | Drugs within class | Incidence | Proposed Mechanism(s) |
|---|---|---|---|
| Taxanes | Docetaxel<br>Paclitaxel | NK<br>1-1.7% | Stimulation of $H_1$ and $H_2$ receptors<br>Myocardial ischemia |
| Tyrosine kinase inhibitors | Irutinib<br>Ponatinib | 5-7%<br>5% | PI3K-AKT signaling inhibition, leading to increases in late sodium current and decreases in L-type calcium current |
| Other monoclonal antibodies | Alemtuzumab<br>Rituximab | NK<br>NK | NK |
| VEGF inhibitors | Sorafenib*<br>Vemurafenib | Up to 5.1%<br>1.5% | NK |
| Other drugs | Amsacrine | NK | NK |

NK = Not known
PI3K = Phosphoinositide 3 kinase
*In combination with 5-FU

*Drug Saf* 2015;38:129-52.
*Circ Arrhythm Electrophysiol.* 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443.
*Pharmacol Ther.* 2018; Apr 24. pii: S0163-7258(18)30072-X.
Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.

# Prognostic Significance of Cancer Chemotherapy -Associated Atrial Fibrillation

- 15/249 (6%) of patients with Non-Hodgkin's lymphoma treated with anthracyclines developed AF
- Mean followup of 34 months after development of AF

| Outcome | AF (n=15) | No AF (n=234) | p |
|---|---|---|---|
| Incidence of acute HF | 40% | 3.8% | <0.001 |
| Incidence of all-cause mortality | 60% | 14.1% | <0.001 |

| Influence of AF on Outcome | Hazard ratio (95% CI) |
|---|---|
| Acute HF | 12.78 (3.36-52.96) |
| All-cause mortality | 4.77 (2.03-10.28) |

HF = Heart failure

*Am J Cardiol.* 2016;118:1386-9.

# Management of Cancer Chemotherapy-Associated Atrial Fibrillation

- Implement alternate chemotherapy if possible
- Ventricular rate control:
  - β-blocker or nondihydropyridine CCB
  - β-blocker and/or digoxin in patients with HFrEF
- Rhythm control:
  - Direct current cardioversion if hemodynamically unstable
  - Individualized antiarrhythmic treatment if rate control not sufficient to control symptoms

ESC Position Paper on cancer treatments and cardiotoxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J* 2016;37:2768-2801.

# Management of Cancer Chemotherapy-Associated Atrial Fibrillation

- Anticoagulation:
  - $CHA_2DS_2$-VASc and HAS-BLED scores have not been validated in patients with cancer
  - In patients with $CHA_2DS_2$-VASc score $\geq 2$, anticoagulation can be considered if platelet count is > 50,000/$mm^3$
  - Vitamin K antagonist can be used if INR stable, otherwise NOAC
  - LMWH recommended over warfarin in patients with metastatic disease and high bleeding risk
  - Role and safety of NOACs in patients with cancer requires clarification

ESC Position Paper on cancer treatments and cardiotoxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J.* 2016;37:2768-2801.

# Meta-Analysis of Safety and Efficacy of NOACs Compared to VKA in Patients with VTE and Cancer

- n=4 RCTs included
- n=759 patients with active cancer

| Endpoint | OR | 95% |
|---|---|---|
| Efficacy<br>(Recurrent VTE) | 0.56 | 0.29-1.08 |
| Safety<br>(Minor and major bleeding) | 0.88 | 0.57-1.35 |

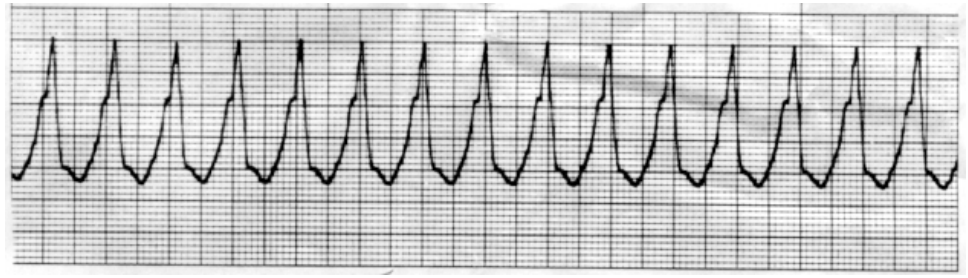
PLOS One 2014;Dec 5;9(12):e114445. doi: 10.1371/journal.pone.0114445.

# Cancer Chemotherapy-Associated Arrhythmias

- Sinus bradycardia/AV block
- Atrial fibrillation
- **Ventricular tachycardia**
- QT interval prolongation/Torsades de pointes (TdP)

# Cancer Chemotherapy-Associated Ventricular Tachycardia

- ECG Characteristics
  - Regular
  - P waves not visible
  - Wide QRS complexes
  - Heart rate 100-250 bpm



- Signs/Symptoms
  - May be asymptomatic (nonsustained VT)
  - Palpitations
  - Hypotension
  - Dizziness
  - Lightheadedness
  - Syncope
  - Angina
- Mortality
  - May degenerate into ventricular fibrillation, causing sudden cardiac death

*J Am Coll Cardiol* 2018;72:e91-220.

# Cancer Chemotherapy-Associated Ventricular Tachycardia

| Drug class | Drugs within class | Incidence | Proposed Mechanism(s) |
|---|---|---|---|
| Alkylating agents | Anthracyclines | NK | Conduction system damage 2º microangiopathy<br>Direct myocyte damage<br>Myocardial ischemia<br>Increases amplitude of L-type calcium current, prolonging ventricular APD |
| Antimetabolites | 5-FU | 3.7-7.4% | Myocardial ischemia/coronary vasospasm<br>Release of vasoactive compounds<br>Direct myocardial damage |
| Antimicrotubule agents | Arsenic trioxide | NK | Increases cardiac calcium current, prolongs ventricular APD |
| Histone deacetylase inhibitors | Interleukin-2 | NK | NK |
| HER2 inhibitors | Pertuzumab | NK | NK |

APD = Action potential duration; NK = Not known

*Drug Saf* 2015;38:129-52
*Circ Arrhythm Electrophysiol* 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443.
*J Am Coll Cardiol* 2018;72:697-8.
Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.

# Cancer Chemotherapy-Associated Ventricular Tachycardia

| Drug class | Drugs within class | Incidence | Proposed Mechanism(s) |
|---|---|---|---|
| HER2 inhibitors | Pertuzumab | NK | NK |
| Immune checkpoint inhibitors | Nivolumab | NK | NK |
| Platinum compounds | Cisplatin | NK | NK |
| Tyrosine kinase inhibitors | Dasatinib<br>Ibrutinib | NK<br>596/100,00 person-years* | NK |

*Includes PVCs and VF

NK = Not known

*Drug Saf* 2015;38:129-52.
*Circ Arrhythm Electrophysiol* 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443
*J Am Coll Cardiol* 2018;72:697-8.
Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.

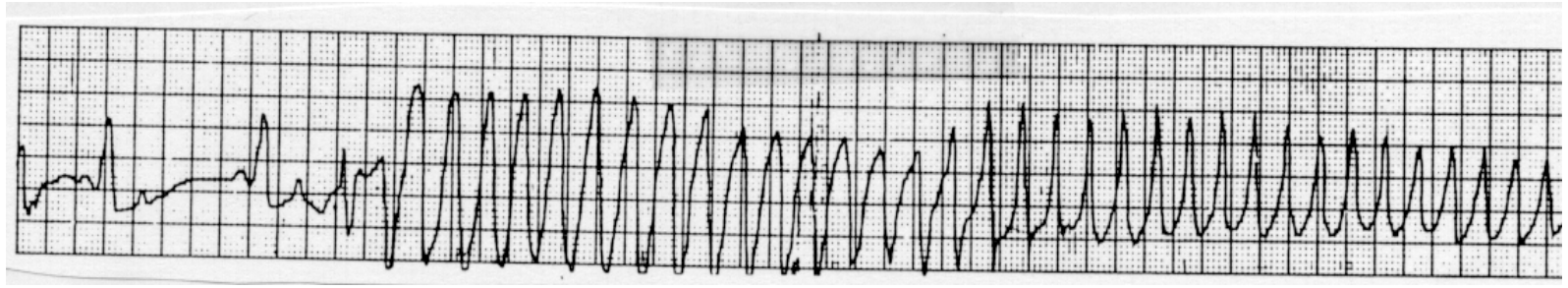
# Treatment of Ventricular Tachycardia

- Per guidelines

*J Am Coll Cardiol* 2018;72:e91-220.

# Cancer Chemotherapy-Associated Arrhythmias

- Sinus bradycardia/AV block
- Atrial fibrillation
- Supraventricular tachycardia (SVT)
- Ventricular tachycardia
- **QT interval prolongation/Torsades de pointes (TdP)**




NEW
Limited time only
Chocolate & Crème and
Golden Raisin & Crème Torsades
Flaky croissant with French pastry crème

# Cancer Chemotherapy-Associated Arrhythmias

## Patient Case

- Chief complaint:
  - A 70-year old man was admitted to the ED after recurrent syncope
- History of Present Illness:
  - Two recent episodes of syncope were diagnosed as seizures, and he was initiated on levitiracetam 500 mg tid
- Past Medical History:
  - Coronary artery disease
  - Metastatic cholangiocarcinoma

*J Cardiovasc Electrophysiol* 2015;26:811-813.

# Cancer Chemotherapy-Associated Arrhythmias

## Patient Case

- Medications PTA:
  - Acetylsalicyclic acid 100 mg once daily
  - Metoprolol 25 mg twice daily
  - Vandetanib 300 mg once daily
- Physical exam and laboratory values:
  - Unremarkable
- Past Medical History:
  - Coronary artery disease
  - Metastatic cholangiocarcinoma

*J Cardiovasc Electrophysiol* 2015;26:811-813.

# Cancer Chemotherapy-Associated Arrhythmias

## Patient Case

- Transthoracic echocardiogram:
  - Normal left ventricular function
- ECG:
  - Sinus bradycardia (46 bpm)
  - QTc = 523 ms
- Telemetry not available; 3-channel Holter monitor recording was initiated:
  - During Holter recording, patient experienced recurrent episodes of syncope

*J Cardiovasc Electrophysiol* 2015;26:811-813.

# Cancer Chemotherapy-Associated Arrhythmias

## Patient Case

- Telemetry not available; 3-channel Holter monitor recording was initiated:
  - Holter recording revealed 28 episodes of TdP
  - One TdP episode degenerated into VF, but terminated spontaneously after briefly re-organizing back into TdP

*J Cardiovasc Electrophysiol* 2015;26:811-813.

# Cancer Chemotherapy-Associated QT Interval Prolongation/Torsades de Pointes

- QT drugs list at www.crediblemeds.org
- Categories of QT-prolonging drugs that may cause TdP:

| Category | Definition |
|---|---|
| Known risk | Prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended |
| Possible risk | Can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended |
| Conditional risk | Are associated with TdP BUT only under certain conditions (eg excessive dose, hypokalemia, interacting drugs) OR by creating conditions that facilitate or induced TdP (inhibit metabolism of a QT-prolonging drug or cause electrolyte disturbances) |
| Drugs to avoid in CLQTS | Pose a high risk of TdP for patients with CLQTS and include all those drugs in the above 3 categories plus additional drugs that do not prolong the QT interval per se but which have a special risk because of their other actions |

CLQTS = Congenital long QT syndrome

www.CredibleMeds.org, QTdrugs list.

# Cancer Chemotherapy-Associated QT Interval Prolongation/Torsades de Pointes

| Drug class | Drugs within class | Incidence | Crediblemeds category | Proposed Mechanism(s) |
|---|---|---|---|---|
| Alkylating agents | Bendamustine | NK | Possible | NK |
| Anthracyclines | Daunorubicin<br>Doxorubicin<br>Epirubicin<br>Idarubicin<br>Mitoxantrone | 11.5% for the class | NC<br>NC<br>Possible<br>NC<br>NC | Intracellular calcium dysregulation<br>$I_{Ks}$ inhibition |
| Antimetabolites | Capecitabine<br>5-FU | NK<br>NK | Possible<br>Possible | Myocardial ischemia due to coronary vasospasm |
| Antimicrotubule agents | Arsenic trioxide<br>Eribulin | 2.5% (TdP) | Known<br>Possible | $I_{Kr}$ and $I_{Ks}$ inhibition |
| Cyclin-dependent kinase inhibitors | Ribociclib | NK | Possible | $I_{kr}$ inhibition |

NC = Not classified; NK = Not known
Bold type signifies black box warning for QTc/TdP

Circ Arrhythm Electrophysiol 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443
Pharmacol Ther 2018; Apr 24. pii: S0163-7258(18)30072-X
Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.
www.crediblemeds.org

# Cancer Chemotherapy-Associated QT Interval Prolongation/Torsades de Pointes

| Drug class | Drugs within class | Incidence | Crediblemeds category | Proposed Mechanism(s) |
|---|---|---|---|---|
| GnRH receptor antagonists | Degarelix<br>Leuprolide | NK<br>NK | Possible<br>Possible | Testosterone deprivation |
| Histone deacetylase inhibitors | Panobinostat<br>Romidepsin<br>Vorinostat | 8.6-28%<br>NK<br>NK | Possible<br>Possible<br>Possible | $I_{kr}$ inhibition |
| Monoclonal antibodies | Inotuzumab<br>Necitumumab* | NK<br>NK | Possible<br>Possible | NK |
| Platinum compounds | Oxaliplatin | NK | Known | Impairment of potassium and magnesium homeostasis |
| Proteasome inhibitors | Bortezomib | NK | Possible | NK |
| HER2 inhibitors | Lapatinib | 6.2% | Possible | $I_{kr}$ inhibition |

*Black box warning for hypomagnesemia

NC = Not classified; NK = Not known

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# Cancer Chemotherapy-Associated QT Interval Prolongation/Torsades de Pointes

| Drug class | Drugs within class | Incidence | Crediblemeds category | Proposed Mechanism(s) |
|---|---|---|---|---|
| Tyrosine kinase inhibitors | Bosutinib | 0.2% | Possible | PI3K-AKT signaling inhibition, leading to increases in late sodium current and decreases in L-type calcium current |
| | Cabozantinib | NK | Possible | |
| | Ceritinib | 4% | Possible | |
| | Crizotinib | 3.5% | Possible | |
| | Dabrafenib | NK | Possible | |
| | Dasatinib | 1% | Possible | |
| | Lenvatinib | 1.5% | Possible | |
| | Midostaurin | 4.7-6.3% | Possible | |
| | Nilotinib | 2.1% | Possible | |
| | Osimertinib | 0.2% | Possible | |
| | Pazopanib | 1-2% | Possible | |

NK = Not known
PI3K = Phosphoinositide 3 kinase
Bold type signifies black box warning for QTc/TdP

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Pharmacol Ther 2018;Apr 24. pii: S0163-7258(18)30072-X.
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# Cancer Chemotherapy-Associated QT Interval Prolongation/Torsades de Pointes

| Drug class | Drugs within class | Incidence | Crediblemeds category | Proposed Mechanism(s) |
|---|---|---|---|---|
| VEGF inhibitors | Sorafenib<br>Sunitinib<br>Vandetanib<br>Vemurafenib | NK<br>0.5%<br>7-14%<br>1.5-3.0% | Possible<br>Possible<br>Known<br>Possible | $I_{kr}$ inhibition |
| Other | Trifluridine and tipiracil<br>Toremifene | NK<br>NK | Possible<br>Possible | NK |

NC = Not classified; NK = Not known
Bold type signifies black box warning for QTc/TdP

Circ Arrhythm Electrophysiol 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443.
Pharmacol Ther 2018; Apr 24. pii: S0163-7258(18)30072-X.
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# Cancer Chemotherapy-Associated Arrhythmias

## Patient Case

- Which of this patient's medications likely caused QTc interval prolongation and TdP?

*J Cardiovasc Electrophysiol* 2015;26:811-813.

# Risk Factors for Torsades de Pointes

- QTc interval > 500 ms
- Increases in QTc interval > 60 ms from baseline
- Age > 65 years
- Female sex
- Acute MI
- HF with reduced EF
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Bradycardia
- Treatment with diuretics
- Concurrent administration of > 1 QT-prolonging drug
- Elevated plasma concentrations of QT-prolonging drugs
  - Inadequate dose adjustment for kidney or liver disease
  - Rapid IV infusion
  - PK drug interactions

Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed. ASHP, 2018.

# Cancer Chemotherapy-Associated Arrhythmias

## Patient Case

- What risk factors did this patient have for TdP?

*J Cardiovasc Electrophysiol.* 2015;26:811-813.

# Monitoring and Prevention of QT Interval Prolongation/TdP Associated with Cancer Chemotherapy

- 12-lead ECG should be obtained and QTc interval measured in all patients at baseline
- Repeated 12-lead ECGs should be performed in patients with:
  - A history of QT prolongation
  - Relevant cardiac disease
  - Bradycardia
  - Thyroid dysfunction
  - Electrolyte abnormalities
  - Treated with QT-prolonging drugs

ESC Position Paper on cancer treatments and cardiotoxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J* 2016;37:2768-2801.

# Monitoring and Prevention of QT Interval Prolongation/TdP in Patients Receiving Arsenic Trioxide

- At baseline, obtain:
  - 12-lead ECG
  - Serum $K^+$, $Mg^{2+}$, $Ca^{2+}$, creatinine
- At baseline:
  - Discontinue other concomitant QT-prolonging drugs
- During therapy:
  - Maintain serum $K^+ > 4.0$ mEq/L
  - Maintain serum $Mg^{2+} > 1.8$ mg/dL
  - If QTc > 500 ms:
    - Correct risk factors where possible
    - Reconsider risk/benefit of arsenic therapy

Arsenic trioxide (Trisenox) package insert, Cell therapeutics, Inc, 2000.

# Cancer Chemotherapy-Associated Arrhythmias

## Patient Case

- Patient management:
  - Patient was admitted to coronary care unit
  - Received MgSO4, lidocaine, and transvenous ventricular overdrive pacing
  - Metoprolol, levetiracetam and vandetanib were discontinued
- No further recurrences of TdP
- ECG on hospital day 11 showed normal QTc

*J Cardiovasc Electrophysiol.* 2015;26:811-813.

# Monitoring and Prevention of QT Interval Prolongation/TdP Associated with Cancer Chemotherapy

- Consider treatment discontinuation or alternative regimens if the QTc is > 500 ms, QT prolongation is > 60 ms or arrhythmias occur
- Conditions known to provoke TdP, especially hypokalemia and extreme bradycardia should be avoided in patients with drug-induced QT prolongation
- Exposure to other QT-prolonging drugs should be minimized in patients treated with potentially QT-prolonging chemotherapy

ESC Position Paper on cancer treatments and cardiotoxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J* 2016;37:2768-2801.

# Sudden Cardiac Death Associated with Cancer Chemotherapy

| Drug class | Drugs within class | Incidence | Reported Cause of Death |
|---|---|---|---|
| Anthracyclines | Daunorubicin<br>Doxorubicin<br>Epirubicin<br>Idarubicin<br>Mitoxantrone | NK | Unspecified ventricular arrhythmias |
| Antimetabolites | Capecitabine<br>5-FU | NK<br>NK | Unspecified ventricular arrhythmias |
| Antimicrotubule agents | Arsenic trioxide | | Torsades de pointes |
| Histone deacetylase inhibitors | Romidepsin<br>Interleukin-2 | 1.5-4% | Unspecified ventricular arrhythmias |
| Tyrosine kinase inhibitors | **Nilotinib** | 0.6% | Unspecified ventricular arrhythmias |
| Other monoclonal antibodies | **Cetuximab**<br>**Necitumumab** | 2%<br>2.5-3.0% | Unspecified ventricular arrhythmias<br>Hypomagnesemia? |
| VEGF inhibitors | **Vandetanib** | NK | Torsades de pointes |

NK = Not known

Bold type indicates sudden cardiac death included in black box warning

*Circ Arrhythm Electrophysiol* 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443.

# Cancer Chemotherapy-Associated Arrhythmias

## Summary and Conclusions

- Cancer chemotherapy can cause a wide variety of arrhythmias, including sinus bradycardia, AV block, atrial fibrillation supraventricular tachycardia, ventricular tachycardia, and QT interval prolongation/torsades de pointes
- ECG monitoring is recommended for patients at rick for cancer chemotherapy-associated arrhythmias
- Attention to risk factors for QT interval prolongation/TdP may aid in reducing the risk

# Questions?