New Cardiac Guidelines – Where They Agree, Where They Differ, and How Does It Affect Patient Care

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Associate Dean for Research Development
Georgetown University
Washington DC, USA
## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
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<td>Pfizer Inc.</td>
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</tbody>
</table>
GUIDELINES in Cardio-Oncology

- American Heart Association
- European Society of Cardiology
- American Society of Clinical Oncology
- American Society of Echocardiography & European Association of Cardiovascular Imaging
- FDA package inserts
  - Trastuzumab
  - Pertuzumab
- NCCN
Detection, prevention, and treatment of left ventricular dysfunction in breast cancer – American Heart Association

<table>
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<th>Technique</th>
<th>Currently available diagnostic criteria</th>
<th>Advantages</th>
<th>Major limitations</th>
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<td>Echocardiography:</td>
<td>- LVEF: &gt;10 percentage points decrease to a value below the LLN suggests cardiotoxicity.</td>
<td>- Wide availability.</td>
<td>- Inter-observer variability.</td>
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<td>- 3D-based LVEF</td>
<td>- GLS: &gt;15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.</td>
<td>- Lack of radiation.</td>
<td>- Image quality.</td>
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<td>- 2D Simpson’s LVEF</td>
<td></td>
<td>- Assessment of haemodynamics and other cardiac structures.</td>
<td>- GLS: inter-vendor variability, technical requirements.</td>
</tr>
<tr>
<td>- GLS</td>
<td></td>
<td></td>
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<td>Nuclear cardiac imaging</td>
<td>&gt;10 percentage points decrease in LVEF with a value &lt;50% identifies patients with cardiotoxicity.</td>
<td>Reproducibility.</td>
<td>Cumulative radiation exposure.</td>
</tr>
<tr>
<td>(MUGA)</td>
<td></td>
<td></td>
<td>Limited structural and functional information on other cardiac structures.</td>
</tr>
<tr>
<td>Cardiac magnetic resonance</td>
<td>Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.</td>
<td>Accuracy, reproducibility.</td>
<td>Limited availability.</td>
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<td></td>
<td></td>
<td>Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.</td>
<td>Patient's adaptation (claustrophobia, breath hold, long acquisition times).</td>
</tr>
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<td>Cardiac biomarkers:</td>
<td>A rise identifies patients receiving anthracyclines who may benefit from ACE-Is.</td>
<td>Accuracy, reproducibility.</td>
<td>Insufficient evidence to establish the significance of subtle rises.</td>
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<td>- Troponin I</td>
<td>Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.</td>
<td>Wide availability.</td>
<td>Variations with different assays.</td>
</tr>
<tr>
<td>- High-sensitivity Troponin I</td>
<td></td>
<td>High-sensitivity.</td>
<td>Role for routine surveillance not clearly established.</td>
</tr>
<tr>
<td>- BNP</td>
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<tr>
<td>- NT-proBNP</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
European Society of Cardiology position paper on cancer treatment and cardiovascular toxicity
Myocardial dysfunction & heart failure

- LVEF should be determined before and during treatment with a method of sufficient image quality
- LLN is 50%
- If LVEF >10% drop and > LLN - repeat assessment
- In asymptomatic pts, If LVEF >10% drop and < LLN - ACE inhibitors or ARBs and beta blockers
- In symptomatic pts ACE inhibitors and beta-blockers recommended

Coronary artery disease

- Assessment based on history, gender, age, and treatment
- Pyrimidine analogs – regular ECGs
- Drug re-challenge after vasospasm only if no alternative and pretreat with nitrates and/or calcium channel blockers
- Long term follow-up and when required, testing for the presence of CAD

### Table 7  Pathophysiological mechanisms of coronary artery disease in cancer treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pathophysiological mechanism</th>
<th>Risk of coronary artery disease and acute coronary syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluoropyrimidines</strong></td>
<td>• Endothelial injury</td>
<td>• Up to 18% manifest myocardial ischaemia</td>
</tr>
<tr>
<td>(5-FU, capecitabine, gemcitabine)</td>
<td>• Vasospasm</td>
<td>• Up to 7–10% silent myocardial ischaemia</td>
</tr>
<tr>
<td><strong>Platinum compounds</strong></td>
<td>• Procoagulant status</td>
<td>• 20-year absolute risk of up to 8% after testicular cancer</td>
</tr>
<tr>
<td>(cisplatin)</td>
<td>• Arterial thrombosis</td>
<td>• 2% risk of arterial thrombosis</td>
</tr>
<tr>
<td><strong>VEGF inhibitors</strong></td>
<td>• Procoagulant status</td>
<td>• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%</td>
</tr>
<tr>
<td>(bevacizumab, sorafenib, sunitinib)</td>
<td>• Arterial thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Endothelial injury</td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td>• Endothelial injury</td>
<td>• 2–7-fold increased relative risk of myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>• Plaque rupture</td>
<td>• Cumulative 30-year coronary events incidence of 10% in</td>
</tr>
<tr>
<td></td>
<td>• Thrombosis</td>
<td>Hodgkin lymphoma survivors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk proportional to irradiation dose</td>
</tr>
</tbody>
</table>

5-FU = 5-fluorouracil; VEGF = vascular endothelial growth factor.
Arrhythmias

- ECG and QT interval at baseline
- Pts with history of QT prolongation, cardiac disease, use of QT prolonging drugs, bradycardia, thyroid disease, or electrolyte abnormalities – repeat EKGs
- Discontinue or alternative treatments if QTc > 500 ms or prolonged > 60 ms
- Avoid hypokalemia and extreme bradycardia
- Limit exposure to other QT prolonging drugs if QT prolonging chemotherapy

<table>
<thead>
<tr>
<th>Type of arrhythmia</th>
<th>Causative drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia</td>
<td>Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicine, epirubicine, 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>Anthracyclines, carmustine.</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.</td>
</tr>
<tr>
<td>Conduction disturbances</td>
<td>Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.</td>
</tr>
<tr>
<td>Supraventricular tachycardias</td>
<td>Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5-FU, methotrexate), bortezomib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.</td>
</tr>
<tr>
<td>Ventricular tachycardia/fibrillation</td>
<td>Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine), arsenic trioxide, doxorubicin, interferons, IL-2, methothrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.</td>
</tr>
<tr>
<td>Sudden cardiac death</td>
<td>Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nilotinib, romidepsin.</td>
</tr>
</tbody>
</table>

5-FU = 5-fluorouracil; IL-2 = interleukin 2; TKI = tyrosine kinase inhibitor.
### Table 10  Risk factors for QT prolongation in cancer patients

<table>
<thead>
<tr>
<th>Risk factors for QT prolongation</th>
<th>Correctable</th>
<th>Non-correctable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte imbalance</td>
<td>- Nausea and emesis</td>
<td>- Family history of sudden death (occult congenital LQTS or genetic polymorphisms)</td>
</tr>
<tr>
<td></td>
<td>- Diarrhoea</td>
<td>- Personal history of syncope</td>
</tr>
<tr>
<td></td>
<td>- Treatment with loop diuretics</td>
<td>- Baseline QTc interval prolongation</td>
</tr>
<tr>
<td></td>
<td>- Hypokalaemia (≤3.5 mEq/L)</td>
<td>- Female gender</td>
</tr>
<tr>
<td></td>
<td>- Hypomagnesaemia (≤1.6 mg/dL)</td>
<td>- Advanced age</td>
</tr>
<tr>
<td></td>
<td>- Hypocalcaemia (≤8.5 mg/dL)</td>
<td>- Heart disease</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td>- Myocardial infarction</td>
</tr>
<tr>
<td>Concurrent use of QT-prolonging</td>
<td></td>
<td>- Impaired renal function</td>
</tr>
<tr>
<td>drugs</td>
<td></td>
<td>- Impaired hepatic drug metabolism</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-infective</td>
<td></td>
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<tr>
<td>Antibiotic</td>
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<td>Antifungal</td>
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<td>Psychotropic</td>
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<td>Antidepressant</td>
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<td>Antipsychotic</td>
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<tr>
<td>Antiemetic</td>
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<tr>
<td>Antihistamine</td>
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</tbody>
</table>

LQTS = long QT syndrome.
Arterial Hypertension

• Treat according to clinical guidelines and monitor blood pressure
• Treat early and aggressively to prevent HF
• ACE or ARBs, beta blockers, and dihydropyridine calcium channel blockers are preferred. Avoid non-dihydropyridine (verapamil/diltiazem) due to drug interactions (statins).
• Dose reduction or discontinuation of VEGF inhibitors can be considered if BP not controlled

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of studies included</th>
<th>Number of patients</th>
<th>Incidence of all grades of HTN, %</th>
<th>Incidence of stage 3-4 HTN, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>20</td>
<td>6754</td>
<td>23.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>13</td>
<td>4999</td>
<td>21.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>13</td>
<td>2492</td>
<td>15.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Axitinib</td>
<td>10</td>
<td>1908</td>
<td>40.1</td>
<td>13.1</td>
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<tr>
<td>Vandetanib</td>
<td>11</td>
<td>3154</td>
<td>24.2</td>
<td>6.8</td>
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<tr>
<td>Regorafenib</td>
<td>5</td>
<td>750</td>
<td>44.4</td>
<td>12.5</td>
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</table>

HTN = hypertension; VEGF = vascular endothelial growth factor.

Other conditions and patients

- Valvular disease
- Thromboembolic disease
- Pulmonary hypertension
- Pericardial and pleural effusions
- Autonomic dysfunction
- Pediatric
- Elderly
- Pregnant

Table 11 Clinical factors associated with increased risk of cancer-associated venous thromboembolism (modified from Khorana et al.\textsuperscript{182})

<table>
<thead>
<tr>
<th>Category</th>
<th>Factors</th>
</tr>
</thead>
</table>
| **Cancer-related factors** | • Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma)  
|                     | • Histology (specially adenocarcinoma)                                  |
|                     | • Advanced stage (metastatic)                                           |
|                     | • Initial period after cancer diagnosis                                 |
| **Patient-related factors** | • Demographics: older age, female sex, African ethnicity  
|                     | • Comorbidities (infection, chronic kidney disease, pulmonary disease, atherothrombotic disease, obesity)  
|                     | • History of venous thromboembolism, inherited thrombophilia            |
|                     | • Low performance status                                                |
| **Treatment-related factors** | • Major surgery                                                         |
|                     | • Hospitalization                                                        |
|                     | • Chemotherapy and anti-angiogenic agents                                |
|                     | • Hormonal therapy                                                       |
|                     | • Transfusions                                                           |
|                     | • Central venous catheters                                               |
Treatment options to prevent or recover from myocardial dysfunction

- Identify and treat CV risk factors and comorbidities
- For QT prolongation – avoid QT prolonging drugs and manage electrolytes
- For anthracyclines
  - Limit cumulative dose
  - Liposomal delivery
  - Dexrazoxane
- For trastuzumab
  - ACE inhibitors or beta-blockers

### Table 14  Summarizes the potential benefits of exercise during and/or after cancer treatment

**Improvement of:**
- Cardiorespiratory and cardiovascular function
- Body composition (preservation or increase in muscle mass, loss of fat mass)
- Immune function
- Chemotherapy completion rates
- Muscle strength and flexibility
- Body image, self-esteem and mood

**Reduction in:**
- Number and severity of side effects including nausea, fatigue and pain
- Reduction of hospitalization duration
- Reduction of stress, depression and anxiety

Strategies for the future

• Refine the predisposing factors for development of CVD related to cancer treatment
• Evaluate the rate of subclinical LV dysfunction and its transition to overt HF
• Define the most reliable cardiac monitoring approach
• Determine the clinical effect and outcome after cancer therapy

ASCO Clinical Practice Guideline:
Prevention and monitoring of cardiac dysfunction in survivors of adult cancers

Overarching clinical questions addressed in ASCO clinical practice guideline

[Diagram showing a timeline of cancer diagnosis, start of treatment, and end of treatment with corresponding questions and recommendations.]

- Which cancer patients are at increased risk for developing cardiac dysfunction? **Recommendation 1**
  - Cancer diagnosis
  - Start of treatment
  - End of treatment

- Which preventative strategies minimize risk *before* initiation of therapy? **Recommendation 2**
- What strategies minimize risk *during* potentially cardiotoxic therapy? **Recommendation 3**
- What are the preferred surveillance / monitoring approaches *during* treatment in patients at risk for cardiac dysfunction? **Recommendation 4**
- What are the preferred surveillance / monitoring approaches *after* treatment in patients at risk for cardiac dysfunction? **Recommendation 5**

1. Which pts. at increased risk of cardiac dysfunction?

- High dose anthracyclines ($\geq 250 \text{ mg/m}^2$ dox or $\geq 600 \text{ mg/m}^2$)
- High dose RT ($\geq 30 \text{ Gy}$) with heart in field
- Lower anthracyclines with RT with heart in field
- Lower dose anthracyclines or trastuzumab alone with:
  - Multiple ($\geq 2$) risk factors
  - $\geq 60$ years
  - LVEF 50-55%, hx of MI, moderate valvular disease
- Lower dose anthracyclines $\rightarrow$ trastuzumab
- No recommendation for trastuzumab alone, low dose anthracycline or RT, kinase inhibitors

2. & 3. Preventive strategies prior to and during Rx

- Avoid cardiotoxic therapies if alternatives exist
- H & P, screen and actively manage cardiac risk factors, ECHO
- Dexrazoxane, Liposomal doxorubicin, continuous infusion
- Mediastinal RT – Deep inspiration breath holding or IMRT

4. & 5. Surveillance prior to and during Rx

• H & P
• Evaluate and manage cardiac risk factors
• If at increased cardiac risk ECHO with frequency to be determined by provider
  – Trastuzumab indefinitely: frequency of monitoring to be determine by provider
  – 6-12 months after completion of treatment
• If signs or symptoms of cardiac dysfunction
  – ECHO
  – If no ECHO, MRI or MUGA
  – Serial biomarkers (troponins, BNP)
  – ECHO derived strain imaging
  – Referral to cardiologist
  – No recommendation for continuing cancer tx

Cumulative incidence of cardiac events by baseline CVD risk factors in SWOG adjuvant breast cancer trials

Cumulative incidence of cardiac events by baseline CVD risk factors in adjuvant breast cancer

RISK FACTORS:
- Diabetes w/ or w/o complications
- Hypertension
- Hypercholesterolemia
- CAD
- Obesity

Table 6  Proposed diagnostic tools for the detection of cardiotoxicity

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                                                                       • Lack of radiation.  
                                                                       • Assessment of haemodynamics and other cardiac structures.               | • Inter-observer variability.  
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| Nuclear cardiac imaging (MUGA) | • >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.                                                                                                                                               | • Reproducibility.                                                                 | • Cumulative radiation exposure.  
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| Cardiac magnetic resonance | • Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.                                                                                                                     | • Accuracy, reproducibility.  
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                    - BNP  
                    - NT-proBNP • A rise identifies patients receiving anthracyclines who may benefit from ACE-I.  
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                                                                       • High-sensitivity.                                                                 | • Insufficient evidence to establish the significance of subtle rises.  
                                                                       • Variations with different rises.  
                                                                       • Role for routine surveillance not clearly established.                   |
Consensus from American Society of Echocardiography & European Association of Cardiovascular Imaging: Prefer 3D ECHO

• Type 1 CV toxicity: Anthracyclines
  – Baseline EF and > 53% repeat at completion of therapy and then 6 months
  – If < 53% cardiology consult

• Type 2 CV toxicity: Trastuzumab
  – If > 53% EF every 3 mo during Rx

• Type 1 and 2 agents
  – If > 53% EF every 3 mo during Rx and 6 mo later


* Consider confirmation with CMR.
** LLN = Lower limit of normal. Please refer to Plana et al., Table 5 for GLS values based on vendor, gender, and age.
*** If the dose is higher than 240 mg/m² (or its equivalent), recommend measurement of LVEF, GLS, and troponin prior to each additional 50 mg/m²
Expert Consensus on Multimodality Imaging Evaluation in Adults Patients During and After Cancer Therapy

Initiation of trastuzumab

Baseline evaluation of LVEF
3DE (preferred) / 2DE (consider contrast)
GLS, Troponin I

LVEF < 53%*
GLS < LLN**
+ Troponins

Cardiology Consult

LVEF > 53%*
GLS > LLN**
- Troponins

F/U every 3 mos. during therapy

* Consider confirmation with CMR.
** LLN = Lower limit of normal. Please refer to Plana et al., Table 5 for GLS values based on vendor, gender, and age.
*** If the dose if higher than 240 mg/m² (or its equivalent), recommend measurement of LVEF, GLS, and troponin prior to each additional 50 mg/m²
Initiation of trastuzumab after regimen associated with Type I toxicity

Baseline evaluation of LVEF
3DE (preferred) / 2DE (consider contrast)
GLS, Troponin I

LVEF < 53%*
GLS < LLN**
+ Troponins

Cardiology Consult

LVEF > 53%*
GLS > LLN**
- Troponins

F/U every 3 mos. during therapy & 6 mos. later

* Consider confirmation with CMR.
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ECHO surveillance: ASE & EACI

Mehta, et al., Circulation 2018;137:e30-e66.
Global Longitudinal Strain

• **Strengths**
  – Superiority in predicting all cause mortality vs LVEF
  – Improved risk stratification for HF
  – Recognize early LV dysfunction
  – Reproducible by trained operators

• **Limitations**
  – Heavy dependence on quality of 2D images
  – Influenced by loading
  – Lack of long term randomized trials to predict symptomatic HF or persistent decrease in LVEF
  – Vendor and software specific

Strain Surveillance of Chemotherapy for improving Cardiovascular Outcomes (SUCCOUR) Trial:

Accrual N= 320
Primary Endpoint: Change in 3D EF
Secondary Endpoint: symptomatic fall >5% or asymptomatic fall >10% and < 55%

Negishi, et al., JACC Cardiovasc Imaging 2018; Jun 8 (Epub ahead of print).
2017 U.S. FDA Package Inserts for Trastuzumab & Pertuzumab

• Trastuzumab: LVEF prior to therapy and every 3 months during Rx and at completion
  – Repeat q 4 weeks if withheld for ↓ LVEF
  – Stop if ≥ 16% ↓ LVEF; below LLN and ≥ 10% ↓ LVEF
  – Resume if LVEF WNL and ↓ ≤ 15%
  – Every 6 months for 2 years after completion

• Pertuzumab and trastuzumab:
  – LVEF q 12 weeks for metastatic and adjuvant (once during neoadjuvant)
# Dose Modifications for Left Ventricular Dysfunction

<table>
<thead>
<tr>
<th>Metastatic Breast Cancer</th>
<th>Pre-treatment LVEF: ≥ 50%</th>
<th>Monitor LVEF every: ~12 weeks</th>
<th>Withhold PERJETA and trastuzumab for at least 3 weeks for an LVEF decrease to: Either</th>
<th>Resume PERJETA and trastuzumab after 3 weeks if LVEF has recovered to: Either</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;40% with a fall of ≥10%-points below pre-treatment value</td>
<td>&gt;45% with a fall of &lt;10%-points below pre-treatment value</td>
</tr>
<tr>
<td>Early Breast Cancer</td>
<td>≥ 55%*</td>
<td>~12 weeks (once during neoadjuvant therapy)</td>
<td>&lt;50% with a fall of ≥10%-points below pre-treatment value</td>
<td>Either</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥50%</td>
<td>&lt;10% points below pre-treatment value</td>
</tr>
</tbody>
</table>

*For patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting PERJETA and trastuzumab.


• For treatment w/ trastuzumab or pertuzumab:
  – Evaluate LVEF prior to and during treatment.
  – The optimal frequency is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab & q 3 mos. during tx.
Can we prevent cardiotoxicity and treat during it?
## Primary Prevention of Cardiotoxicity

<table>
<thead>
<tr>
<th>Trial</th>
<th>RX</th>
<th>Study</th>
<th>n</th>
<th>Results</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRADA¹</td>
<td>Epirubicin</td>
<td>2x2</td>
<td></td>
<td>CMR ↓ LVEF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tras 12%</td>
<td>Candesartan + placebo</td>
<td>32</td>
<td>1.8% Can v. Pla</td>
<td>0.0026</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candesartan + metoprolol</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metoprolol + placebo</td>
<td>32</td>
<td>0.2% Met v. Pla</td>
<td>0.772</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo + placebo</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MANTICORE</td>
<td>Tras 1x1x1</td>
<td>CMR LVEDVi LVEF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>101 Breast²</td>
<td>Perindopril</td>
<td>33</td>
<td>+7</td>
<td>p=.36</td>
<td>-3%</td>
</tr>
<tr>
<td></td>
<td>Bisoprolol</td>
<td>31</td>
<td>+8</td>
<td>p=.36</td>
<td>-1% p=0.001</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>30</td>
<td>+4</td>
<td>p=.36</td>
<td>-5%</td>
</tr>
<tr>
<td>CECCY³</td>
<td>Dox 1x1</td>
<td>LVEF &gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carvedilol</td>
<td>96</td>
<td>14.5%</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>96</td>
<td>13.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reversibility of trastuzumab-related Cardiotoxicity and response to medical treatment


Mean LVEF%
SAFE HEaRt: A Pilot Study Assessing the Cardiac SAFETY of HER2 Targeted Therapy in Patients with HER2 Positive Breast Cancer & Reduced Left Ventricular Function (40-49%)

Anti-HER2 Therapy = pertuzumab, trastuzumab, T-DM1

SAFE-HEaRt: Primary Endpoint

Demographics, previous anthracyclines and baseline LVEF did not predict development of CEs.

Elevation of highly sensitive troponin preceded 2 of 3 CEs which was significant ($p=0.003$).

So what do we do now?

- Screening with 3D Echo and follow up based on treatment
  - Anthracyclines baseline and after treatment (< 240 mg/m²)
  - Trastuzumab: Baseline and q 3months – practically speaking if on long term trastuzumab and pertuzumab with LVEF wnl, consider stopping surveillance or decreasing to once every 6-12 months

- No evidence of benefit with BB or ARB or ACEi

- No routine measurement of troponins, BNP

- Global strain measurements could predict cardiac dysfunction but currently not in the mainstream for determining cardiac treatment
MedStar Heart & Vascular Institute
Cardio-Oncology Program: Goals

• Ensures better outcomes for patients with cancer and cardiac issues
• Provides earlier detection of cardiac toxicity side effects from cancer treatments
• Aims to present or reduce further cardiac damage – and, when possible, reverse it
• Monitors patients with potential cardiac issues who are receiving cancer treatments
• Provides a better understanding of cardiac issues in patients with cancer by participating in research studies
• Eliminates cardiac disease as a barrier to effective cancer therapy
My Friend and Mentor in Cardio-Oncology
or is that Onco-Cardiology!