GUIDELINE-DRIVEN CARE ACROSS THE LIFESPAN: WHERE IS THE EVIDENCE? WHERE ARE THE GAPS?

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Overview

- Childhood cancer survivors (Lancet Oncol. 2015 Mar;16(3):e123-36)
  - Cardiac dysfunction, patients treated as children
  - Cardiac dysfunction, patients treated as adults
  - Evidence-based; strength of the recommendation
- ESC position paper (Eur Heart J. 2016 Sep 21;37:2768-2801)
  - Comprehensive recs across several cardiovascular outcomes
- ESA and EACI consensus statement (J Am Soc Echocardiogr. 2014 Sep;27(9):911-39)
  - Recommendations for imaging
- Opportunities to identify gaps in knowledge
ASC0 Guidelines

Clinical Questions

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 prior to 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
Robust Risk Estimation Depends on the Following

- Large population-based cohort studies
  - Recognized healthy bias with clinical trial data
- Validated CV outcomes
  - Registry or claims-based outcomes vs. standardized/validated outcomes
- Long-term and complete follow-up
- Treatment dose-specific information
  - Dose-thresholds for risk – potential variation by dz/ treatment regimen
- Comparison to no exposure
  - CVD as an aging disease
- Multivariable regression analysis (adjusting for confounders)
  - Age, sex, CV risk factors, other treatment risk factors
Population-Based Research to Characterize Risk

Cardiovascular Disease After Hodgkin Lymphoma Treatment
40-Year Disease Risk

Frederik A. van Nimwegen, MSc, Michael Schapmels, PhD, Cécile P. M. Janus, MD,
Augustinas D. G. Iroš, MD, PhD, Effie J. Petersen, MD, PhD, John M. M. Raemaekers, MD, PhD,
Wouter E. M. Kolk, MD, PhD, Berthe M. F. Aleman, MD, PhD, Flora E. van Leeuwen, PhD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any Cardiovascular Event</th>
<th>First Events, HR (95% CI)</th>
<th>CHDP</th>
<th>VHD</th>
<th>HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No./Total No.</td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No. mediastinal radiotherapy or anthracyclines</td>
<td>47/302</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
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<tr>
<td>Anthracycline dose, mg/m²</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;250 (No mediastinal radiotherapy)</td>
<td>15/83</td>
<td>3.1 (1.8-5.5) ( ^2 )</td>
<td>3.1 (1.6-6.0) ( ^a )</td>
<td>4.0 (1.3-12.6) ( ^a )</td>
<td>1.6 (0.3-7.5)</td>
</tr>
<tr>
<td>≥250 (No mediastinal radiotherapy)</td>
<td>8/77</td>
<td>2.1 (0.9-4.9)</td>
<td>0.6 (0.1-2.4)</td>
<td>3.9 (0.9-17.5)</td>
<td>4.5 (1.2-16.8) ( ^d )</td>
</tr>
<tr>
<td>Mediastinal radiotherapy</td>
<td>566/1448</td>
<td>3.5 (2.6-4.8) ( ^a )</td>
<td>2.4 (1.6-3.4) ( ^a )</td>
<td>7.1 (4.0-12.7) ( ^a )</td>
<td>2.6 (1.3-5.2) ( ^a )</td>
</tr>
<tr>
<td>No anthracyclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;250</td>
<td>77/338</td>
<td>4.9 (3.4-7.1) ( ^a )</td>
<td>2.2 (1.4-3.6) ( ^a )</td>
<td>12.3 (6.4-23.9) ( ^a )</td>
<td>5.4 (2.5-11.9) ( ^a )</td>
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<tr>
<td>≥250</td>
<td>77/241</td>
<td>6.5 (4.4-9.5) ( ^a )</td>
<td>2.9 (1.8-4.8) ( ^a )</td>
<td>17.3 (8.8-33.0) ( ^a )</td>
<td>6.5 (2.8-15.1) ( ^a )</td>
</tr>
</tbody>
</table>

Odds Ratio*
Population-based Research to Characterize Risk

**Blood, 2011, 118: 6023-9**

- Thyroid
- Dyslipidemia
- Diabetes
- Hypertension

\[ \text{† p<0.05} \]

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**Cardiac Outcomes of Patients Receiving Adjuvant Weekly Paclitaxel and Trastuzumab for Node-Negative, ERBB2-Positive Breast Cancer**  

**RESULTS** Overall, 2 patients (0.5%) (95% CI, 0.1%-1.8%) developed grade 3 LVSD and came off study, and 13 (3.2%) (95% CI, 1.9%-5.4%) had significant asymptomatic LVEF decline, 11 of whom completed study treatment. Median LVEF at baseline was 65%; 12 weeks, 64%; 6 months, 64%; and 1 year, 64%.

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* Adjusted for: Sex, Diagnosis, Pre-Tx CV Risk Factor
Cancer patients at increased HF risk

- High dose anthracycline (e.g. ≥250 mg/m² doxorubicin, ≥600 mg/m² epirubicin)
- High dose (≥30 Gy) radiotherapy where the heart is in the treatment field
- Lower dose anthracycline (e.g. <250 mg/m² doxorubicin) + lower dose radiotherapy (<30 Gy)
- Lower dose anthracycline (e.g. <250 mg/m² doxorubicin) or trastuzumab alone, and:
  - Multiple (≥2) CV risk factors: smoking, hypertension, diabetes, dyslipidemia, obesity
  - Older (≥60 years) age at cancer treatment
  - Compromised CV function (e.g. borderline low LVEF [50-55%], history of MI, ≥moderate valvular heart disease)
- Treatment with lower dose anthracycline (e.g. <250 mg/m² doxorubicin) followed by trastuzumab (sequential therapy)

No determination of HF risk

- Lower dose anthracycline (e.g. <250 mg/m² doxorubicin) or trastuzumab alone, and no CV risk factors
- Lower dose radiotherapy (<30 Gy), and no additional cardiotoxic therapeutic exposures or CV risk factors
- Targeted therapies (e.g. Kinase inhibitors)
ASCO Guidelines for Prevention and monitoring of cardiac dysfunction in survivors of adult cancers

J Clin Oncol. 2017 Mar 10;35(8):893-911

Clinical Questions

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 prior to 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
Recommendation 2.1
Avoid or minimize the use of potentially cardiotoxic therapies if established alternatives exist that would not compromise cancer-specific outcomes.
(Consensus-based; Benefits outweigh harms; Strength of Recommendation: Strong).

Recommendation 2.2
Comprehensive assessment in cancer patients that includes an H&P, screening for cardiovascular disease risk factors (hypertension, diabetes, dyslipidemia, obesity, smoking), and an echocardiogram prior to initiation of potentially cardiotoxic therapies.
(Evidence and consensus-based; Benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)
Primary prevention

- Considerations:
  - Screening/management of modifiable risk factors *during* treatment
  - More established cardioprotection (e.g. dexrazoxane, liposomal, continuous)
  - Newer strategies (ACE-inhibitors, B-Blockers, ARB-blockers, statins)
    - Single arm vs. randomized
    - +/- Clinical (e.g. heart failure prevention) endpoints
  - Biomarker-based screening and intervention (+/- secondary prevention)
CV Risk Factor Management

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015
Effective Primary Prevention

- Longer (>6 hours) infusion
  - Cochrane Rev 2009
- Liposomal formulation
  - Cochrane Rev 2010
Primary Prevention

Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA)

European Heart Journal
doi:10.1093/eurheartj/ehw022

<table>
<thead>
<tr>
<th></th>
<th>Candesartan</th>
<th>No metoprolol</th>
<th>Metoprolol</th>
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<tbody>
<tr>
<td>LVEF</td>
<td>60</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>63.2 (62.0, 64.4)</td>
<td>61.0 (59.8, 62.2)</td>
<td>62.5 (61.3, 63.7)</td>
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<tr>
<td></td>
<td>60.6 (59.4, 61.8)</td>
<td>61.0 (59.8, 62.2)</td>
<td>61.0 (59.8, 62.2)</td>
</tr>
<tr>
<td></td>
<td>−2.6 (−3.8, −1.5)</td>
<td>−1.8 (−3.0, −0.7)</td>
<td>−1.6 (−2.8, −0.4)</td>
</tr>
<tr>
<td></td>
<td>1.9 (0.2, 3.5)*</td>
<td>0.2 (−1.4, 1.9)</td>
<td>0.772</td>
</tr>
<tr>
<td></td>
<td>0.026</td>
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Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101–Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity
## Primary Prevention Clinical Trials

<table>
<thead>
<tr>
<th>Trial Name (PI) and Sample Size</th>
<th>Trial Intervention</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVENT (Hundley, Wake Forest) N=250</td>
<td>Statins vs Placebo</td>
<td>Breast cancer, lymphoma, anthracyclines</td>
<td>MRI, biomarkers, symptoms @ 2y</td>
</tr>
<tr>
<td>USF (Guglin, USF) N=468</td>
<td>Carvedilol vs Lisinopril vs Placebo</td>
<td>Breast cancer, trastuzumab</td>
<td>Echo, BNP, Tn, symptoms 2 years</td>
</tr>
<tr>
<td>CECCY (Bocchi, Univ of Sao Paulo) N=200</td>
<td>Carvedilol (50 mg/day, 24 wks) vs Placebo</td>
<td>Breast cancer, anthracyclines</td>
<td>During therapy and 24 months</td>
</tr>
<tr>
<td>STOP-CA (Neilan, Scherrer Crosbie) N= 300</td>
<td>Statins vs Placebo</td>
<td>Non Hodgkin’s lymphoma, anthracyclines</td>
<td>MRI, echo at 12 months</td>
</tr>
<tr>
<td>ICOS-ONE (Latini, Cipolla, Milan) N=268</td>
<td>Biomarker strategy (hsTnT) and ACE-I</td>
<td>Any cancers with anthracyclines</td>
<td>Tn, CV hosp. or death</td>
</tr>
<tr>
<td>SUCCOUR (Marwick, Australia) N=320</td>
<td>Strain imaging strategy and Ramipril, Carvedilol</td>
<td>Any cancers with anthracyclines, trastuzumab, TKIs</td>
<td>3D LVEF at 3 years</td>
</tr>
<tr>
<td>SWOG S1501 (Floyd) N=533</td>
<td>Carvedilol versus no intervention</td>
<td>Metastatic HER2+ breast cancer</td>
<td>Echo and many secondary endpoints</td>
</tr>
<tr>
<td>PCORI RADCOMP</td>
<td>Proton versus photon therapy</td>
<td>Breast cancer</td>
<td>Clinical endpoints only (CTCAE)</td>
</tr>
</tbody>
</table>
Guideline Development

Clinical Questions

Which cancer patients are at increased risk for developing cardiac dysfunction?

Recommendation 1

Cancer diagnosis

Which preventative strategies minimize risk prior to initiation of therapy?

Recommendation 2

Start of treatment

What strategies minimize risk during potentially cardiotoxic therapy?

Recommendation 3

End of treatment

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

J Clin Oncol. 2017 Mar 10;35(8):893-911
Considerations in the Selection of Population Screening Tests

• Detects injury before irreversible impairment
• Non-invasive
• Inexpensive
• Widely available
• Reproducible (esp. for asymptomatic disease)
• Actionable in guiding therapy
• Highly predictive of clinically significant disease

*Courtesy of M. Khoury*
### Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

<table>
<thead>
<tr>
<th>Technique</th>
<th>Currently available diagnostic criteria</th>
<th>Advantages</th>
<th>Major limitations</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
<tr>
<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>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Nuclear cardiac imaging (MUGA)</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>Cardiac magnetic resonance</td>
<td>• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderline.</td>
<td>• Accuracy, reproducibility.</td>
<td>• Limited structural and functional information on other cardiac structures.</td>
</tr>
<tr>
<td>Cardiac biomarkers:</td>
<td>• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is.</td>
<td>• Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.</td>
<td>• Limited availability.</td>
</tr>
<tr>
<td>- Troponin I</td>
<td>• Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.</td>
<td>• Accuracy, reproducibility.</td>
<td>• Patient’s adaptation (claustrophobia, breath hold, long acquisition times).</td>
</tr>
<tr>
<td>- High-sensitivity Troponin I</td>
<td></td>
<td>• Wide availability.</td>
<td></td>
</tr>
<tr>
<td>- BNP</td>
<td></td>
<td>• High-sensitivity.</td>
<td></td>
</tr>
<tr>
<td>- NT-proBNP</td>
<td></td>
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</tbody>
</table>
The Screening Cascade and Patient Considerations

Persons who are screened

- Negative screening result
- Positive screening result
- Incidental finding

Work-up

- True-positive result
- False-negative result
- Indeterminate finding

Surveillance

Treatment

- Earlier treatment is better
- Rapidly progressive and irreversible injury
- Mild, easily treatable disease, irrespective of pick-up timing
- Person would never have developed symptoms, even if untreated

Death from CVD

Remaining life expectancy

Death from cancer/Other Causes

- Symptomatic
- Detectable but Not Symptomatic
- Not Detectable

Patients:
- Patient 1: True-positive result; Benefit
- Patient 2: False-negative result; No Benefit
- Patient 3: Indeterminate finding; Surveillance
- Patient 4: Negative screening result; Work-up

Surveillance *during* therapy

- Routine surveillance imaging may be offered during treatment in *asymptomatic* patients considered to be at increased risk (Recommendation 1.1) of developing cardiac dysfunction. In these individuals, echocardiography is the surveillance imaging modality of choice that should be offered. Frequency of surveillance should be determined by healthcare providers based upon clinical judgment and patient circumstances.

  *(Evidence-based; Benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Moderate)*

- No recommendations can be made regarding continuation/discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction. This decision, made by the oncologist, should be informed by close collaboration with a cardiologist, fully evaluating the clinical circumstances, and considering the risks/benefits of continuation of therapy responsible for the cardiac dysfunction.

  *(Informal consensus; Benefits outweigh harms; Evidence quality: Insufficient)*
Surveillance after therapy

- An echocardiogram may be performed between 6 to 12 months after completion of cancer-directed therapy in asymptomatic patients considered to be at increased risk (Recommendation 1.1) of cardiac dysfunction. *(Evidence-based; Benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Moderate)*

- Cardiac MRI or MUGA may be offered for surveillance in asymptomatic individuals if an echocardiogram is not available or technically feasible (e.g. poor image quality), with preference given to cardiac MRI. *(Evidence-based; Benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Strong)*

- **Knowledge Gaps**
  - Risk of new-onset Stage B disease in patients with normal baseline/6-12 month echo (above and beyond gen. pop)
  - Optimal pharmacologic/other interventions & their duration
  - Cost-effectiveness of different screening frequencies/strategies
  - PPV, NPV of echocardiography by risk category

- No recommendations can be made re: frequency and duration of surveillance in patients at increased risk (Rec 1.1) who are asymptomatic and have no evidence of cardiac dysfunction during their 6-12 month post-treatment echo.
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