BELGIAN CARDIO-ONCOLOGY GUIDELINES
CARDIOTOXICITY: A CARDIOLOGIST’S COOKBOOK

Dr. B. von Kemp
Universitair Ziekenhuis Brussel
OVERVIEW

1. Finally, guidelines!
2. ‘Cardiotoxicity’, what’s in a name?
3. I screen, you screen… but how?
4. ‘Cardioprotection’ : fact or fiction?
5. Trouble on-therapy : the asymptomatic patient
6. Trouble on-therapy : the symptomatic patient
7. Post-therapy follow-up?
8. Take home messages
FINALLY, GUIDELINES!

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Go-Chair, Ana Barac, MD, PhD, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marielle Scherrer-Crosbie, MD, PhD, FASE, Javier Ganaume, MD, PhD, FASE, Igal A. Schug, MD, FASE, Deborah A. Agler, RCT, RDOS, FASE, Luigi P. Radano, MD, PhD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, PhD, FESC, Joseph Carver, MD, Manuel Cerqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott D. Fiamm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andreia Magalhães, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector R. Villarraga, MD, FASE, and Patrizio Lancellotti, MD, PhD, FESC, Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, District of Columbia; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Quebec, Canada; Chicago, Illinois; Oslo, Norway; Liège, Belgium; New York, New York; Lisbon, Portugal; Hobart, Australia; Rochester, Minnesota

(Special Article ESMO 2014;27:911-39.)

Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

CARDIOTOXICITY : WHAT’S IN A NAME?

CARDIOTOXICITY: WHAT’S IN A NAME?

CARDIOTOXICITY: WHAT’S IN A NAME?
### I SCREEN, YOU SCREEN … BUT HOW?

**Table 3. Common clinical factors that may indicate a patient at higher risk for cardiovascular dysfunction during contemporary anticancer treatment**

- Prior anthracycline-based treatment
- Elderly (>75 years old)
- Prior mediastinal or chest radiotherapy
- HTN (before or at the time of treatment)
- Smoking exposure (current or previous)
- Very young (<10 years of age)
- Previous combined treatment with trastuzumab and an anthracycline
- Elevated cardiac biomarkers before initiation of anticancer therapy
- Baseline abnormal systolic LV function with LVEF <0.50
- Pre-existing DM

DM, diabetes mellitus; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction.

Curigliano et al, Ann Oncol 2020
I SCREEN, YOU SCREEN … BUT HOW?

1. Treat cardiovascular **risk factors** … agressively!
   - AHT: target BP <140/90mmHg
   - Dyslipidaemia: LDL cholesterol <115mg/dL
   - Diabetes mellitus type II: HbA1c <7%
   - Smoking cessation

2. **ECG**: QTc? LV hypertrophy? Repolarisation abnormalities?

3. **Transthoracic echocardiography**:
   - LVEF & GLS (baseline)
   - Diastolic function
   - Valvular status

4. Biomarkers: exact role & timing unclear
   - Troponin? T? I? hs-?
   - Natriuretic peptides: BNP? NT-pro BNP?

5. Previous cardiovascular disease
‘CARDIOPROTECTION’ : FACT OR FICTION

<table>
<thead>
<tr>
<th></th>
<th>Awareness and Aspirin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>• Increased awareness of patients about CV signs and symptoms.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Aspirin 81 mg daily for primary or secondary prevention of CV events.</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Blood Pressure</td>
<td>Goal blood pressure &lt; 140/90 mmHg</td>
</tr>
<tr>
<td>C</td>
<td>Cholesterol and Cigarettes</td>
<td>• High intensity statin therapy for pre-existing CVD or hyperlipidemia.</td>
</tr>
<tr>
<td></td>
<td>• Smoking cessation counseling, therapy.</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Diet and Diabetes</td>
<td>• Frequent blood glucose monitoring</td>
</tr>
<tr>
<td></td>
<td>• Metformin for diabetes if possible.</td>
<td>• Diet rich in fruits, vegetables, whole grain and low in saturated fat with 600 IU of vitamin D daily and adequate calcium (1200 mg/day).</td>
</tr>
<tr>
<td></td>
<td>• Avoidance of excessive alcohol.</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Exercise</td>
<td>150 minutes per week of moderate intensity physical activity or 75 minutes per week of vigorous exercise.</td>
</tr>
</tbody>
</table>
‘CARDIOPROTECTION’ : FACT OR FICTION

Brown et al.
J Am Heart Assoc, 2020

Table 1. Summary of 5 Randomized Controlled Trials Evaluating the Effect of β-Blockers and Neurohormonal Medications in Preventing Cardiac Dysfunction During Treatment With Trastuzumab, Anthracyclines, or Their Combination

<table>
<thead>
<tr>
<th>Year; Citation (Trial Name)</th>
<th>Cancer Therapy; Primary End Point</th>
<th>N</th>
<th>Medication</th>
<th>Follow-Up Period</th>
<th>Results</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>2006, Cardinale et al⁷</td>
<td>Anthracycline; LVEF decreased by 10%</td>
<td>114</td>
<td>Enalapril</td>
<td>12 mo</td>
<td>0 vs 43%; $P&lt;0.001$</td>
<td>Benefit</td>
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<td>2016, Gulati⁸ (PRADA)</td>
<td>Anthracycline with or without trastuzumab; change in LVEF by cMRI</td>
<td>130</td>
<td>Candesartan</td>
<td>10–61 wk</td>
<td>Modest decline in LVEF with candesartan vs placebo ($P=0.025$)</td>
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<td></td>
<td></td>
<td></td>
<td>Metoprolol</td>
<td>10–61 wk</td>
<td>No change in LVEF with metoprolol vs placebo ($P=NS$)</td>
<td>No benefit</td>
</tr>
<tr>
<td>2016, Boekhout et al⁹</td>
<td>Trastuzumab; change in LVEF</td>
<td>206</td>
<td>Candesartan</td>
<td>2 mo</td>
<td>Candesartan had higher incidence of cardiac events vs placebo ($P=NS$)</td>
<td>No benefit, possible harm</td>
</tr>
<tr>
<td>2017, Ptuskin et al¹⁰ (MANTICORE 101-Breast)</td>
<td>Trastuzumab (25% with anthracyclines); reduce LV remodeling</td>
<td>94</td>
<td>Perindopril</td>
<td>52 wk</td>
<td>Attenuated LVEF decline but did not prevent LV remodeling</td>
<td>Possible benefit</td>
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<td>Lisinopril</td>
<td>1+2 y follow-up</td>
<td>No difference from placebo</td>
<td>No benefit</td>
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cMRI indicates cardiac magnetic resonance imaging; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MANTICORE-101 Breast, Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research; NS, not significant; PRADA, Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy. 1+2 y; 1 year and 2 years of follow up.
‘CARDIOPROTECTION’ : FACT OR FICTION

Table 1. Summary of 5 Randomized Controlled Trials Evaluating the Effect of β-Blockers and Neurohormonal Medications in Preventing Cardiac Dysfunction During Treatment With Trastuzumab, Anthracyclines, or Their Combination

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Limitations:
- Small sample sizes
- Large heterogeneity in studied patient populations
- Many low-risk patients
- Different anticancer therapies
- Different clinical trial endpoints
Table 2. Classes of cardiovascular therapeutics that have some clinical trial evidence to suggest cardioprotection during anticancer therapy

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

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.

*Cardioprotection: any evidence that indicates the medication attenuates any CV dysfunction that may occur with potential cardiotoxic anticancer therapy.

Curigliano et al. Ann Oncol 2020
Zamorano et al. Eur Heart J 2016
TROUBLE ON-THERAPY: THE ASYMPTOMATIC PATIENT

Incidence of HF (%)

Cumulative dose of doxorubicin (mg/m²)


! Early detection & treatment: highest reversibility

AC & trastuzumab: TTE (LVEF + GLS) 1x/3m
TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

Before everything else : what is LVEF?
TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

Before everything else : what is LVEF?

Rev Esp Cardiol. 2017;70:487–95
TROUBLE ON-THERAPY: THE ASYMPTOMATIC PATIENT

Before everything else: what is GLS?
TROUBLE ON-THERAPY: THE ASYMPTOMATIC PATIENT

Before everything else: what is GLS?
Before everything else: what is GLS?

**Table 6** Strengths and limitations of GLS

**Strengths**
- Superiority in the prediction of all-cause mortality in the general population compared with LVEF
- Improved risk stratification in patients with HF
- Ability to recognize early LV dysfunction in patients undergoing cardiotoxic therapy and prognosticate subsequent CTRCD
- Reproducible when performed by trained operators

**Limitations**
- Heavy dependence on the quality of the 2D echocardiographic images
- Influenced by loading conditions
- Lack of long-term randomized clinical trials evaluating the ability of GLS to predict persistent decreases in LVEF or symptomatic HF
- Lack of data as to the reproducibility of GLS in nonacademic centers or community hospitals
- Vendor and software specific

Plana et al J Am Soc Echocardiogr 2014
IS THERE A ROLE FOR MRI?

- Excellent LVEF evaluation
- Excellent reproducibility
- Great solution for poor TTE image quality

- Availability…
- Cost…
- Unpleasant exam (>30min, noisy, long breath-hold sequences)

→ Save it for emergencies (e.g. ICI-induced myocarditis)
TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

- Reduced LVEF: $>10\% (\text{abs}) + \text{LVEF} <50\%$ : CARDIO CONSULT
  - HF therapy: ACEi (enalapril) + BB (carvedilol)
  - LVEF 40-50%: Consider withholding therapy until LVEF recovery*
  - LVEF <40%: Withhold therapy, consider alternative treatment
  - Short-term re-evaluation (4wks)

- Normal LVEF, reduced GLS: $-15\% (\text{rel})/ -5\% (\text{abs})$ → never withhold therapy

- Normal LVEF, increased biomarkers → never withhold therapy
TROUBLE ON-THERAPY: THE SYMPTOMATIC PATIENT

→ CARDIO CONSULT: ECG, TTE

- LVEF <40%: optimize HF treatment (ACEi + BB +/- MRA)
  Avoid AC, consider less cardiotoxic therapy

- LVEF 40-50%: optimize HF treatment (ACEI + BB +/- MRA)
  Stabilize LV fct prior to potentially cardiotoxic treatment

- Symptoms of HF but LVEF >50%: HFpEF? Other?

+ EARLY RE-EVALUATION: TTE in +/- 4wks
TROUBLE ON-THERAPY : THE SYMPTOMATIC PATIENT

- **Resolution of symptoms** after withholding chemotherapy
  - LVEF recovers >40% : alternative therapy vs. careful rechallenge
  - LVEF recovers >50% : consider rechallenge
  - Close follow-up

- **Persistence of symptoms** after withholding chemotherapy
  - Alternative therapy vs. pursuing current therapy if no other option exists
Curigliano et al
Ann Oncol 2020
POST-THERAPY FOLLOW-UP

Anthracyclines: Consult + TTE:
Y1 = 1x/3m
Y2-5 = 1x/6m
>Y5 = 1x/y

Trastuzumab: Consult + TTE:
Y1-2 = 1x/3m
>Y2 = 1x/6m

Targeted therapy (TKI/MAb): Consult + TTE:
Y1 = 1x/3m
+ ICI
>Y1 = 1x/6m (case-by-case)

Radiotherapy: Consult:
1x/y (CV risk factors, ECG)
TTE:
1x/5y (+/- bike test)

COMPLAINTS = EARLY REFERRAL
TAKE HOME MESSAGES

1. Identify the high risk patient:
   AHT, dyslipidaemia, DM II, smoking, known CVD

2. Low threshold for cardiac consult & TTE

3. Low threshold for ‘cardioprotective strategies’

4. TTE protocol unclear? Call for clarification

5. GLS: useful, but not a gamechanger (yet)

6. LVEF: <40% = HOLD therapy, rediscuss, re-evaluate

7. Image quality is everything: CMR if necessary

8. Treat early!
CENTRAL ILLUSTRATION  
Cardiovascular Complications of Cancer Therapy

CARDIOVASCULAR COMPLICATIONS OF CANCER THERAPY

STAGES OF THE EVALUATION

- Risk Stratification
- Early Detection of Injury
- Prediction of Recovery
- Detection of Injury in the Survivor

CLINICAL CONDITIONS TO BE EVALUATED

- LV Dysfunction
- Pericardial Disease
- CAD
- Pulmonary Hypertension
- Aortopathy

IMAGING MODALITIES ARMAMENTARIUM

- ECHO
- Nuclear/PET
- Cardiac CT
- CMR


Stages of the evaluation and clinical conditions to be evaluated and imaging modalities available. CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; CT = computed tomography; PET = positron emission tomography.
THANK YOU
# CARDIOTOXICITY: WHAT’S IN A NAME?

Zamorano et al, Eur Heart J 2016

**Table 1** Mechanisms and main clinical manifestation of the cardiotoxicity of anti-cancer drugs with known and clinically relevant potential for cardiac adverse effects

<table>
<thead>
<tr>
<th>Anti-cancer drug class</th>
<th>Main mechanism(s) of cardiotoxicity</th>
<th>Main clinical presentation</th>
<th>Frequency (% of treated patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines (doxorubicin, epirubicin)</td>
<td>DNA damage, mitochondrial dysfunction and oxidative stress of cardiomyocytes</td>
<td>LVSD/HFrEF (dose-dependent, irreversible, often delayed-onset)</td>
<td>With current doses 3–5%; with liposomal anthracyclines 2%</td>
</tr>
<tr>
<td>Alkylating agents (cyclophosphamide, ifosfamide)</td>
<td>Myocarditis; epicardial coronary artery spasm</td>
<td>LVSD/HFrEF</td>
<td>Up to 28% (cyclophosphamide &gt; ifosfamide)</td>
</tr>
<tr>
<td>Fluoropyrimidines (5-fluorouracil, capecitabine)</td>
<td>Epicardial coronary artery spasm and/or coronary microvascular dysfunction</td>
<td>Acute myocardial ischaemia</td>
<td>Up to 18%</td>
</tr>
<tr>
<td>Anti-HER2 agents (trastuzumab, lapatinib, pertuzumab)</td>
<td>Inhibition of HER2 pro-homeostatic activities in the heart</td>
<td>LVSD/HFrEF (dose-independent, reversible with discontinuation)</td>
<td>Up to 28% if with anthracyclines (trastuzumab &gt; lapatinib and pertuzumab)</td>
</tr>
<tr>
<td>Multiple TKI (sunitinib, sorafenib)</td>
<td>Inhibition of VEGF and other pro-homeostatic tyrosine kinase receptors</td>
<td>Hypertension, Arterial thrombosis, LVSD/HFrEF</td>
<td>Up to 47% (sunitinib) – 43% (sorafenib)</td>
</tr>
<tr>
<td>VEGF-directed TKI (bevacizumab)</td>
<td>Systemic endothelial and coronary microvascular dysfunction; ↓ angiogenesis</td>
<td>Hypertension, Arterial thrombosis, HFrEF</td>
<td>Up to 35%</td>
</tr>
<tr>
<td>Platinum agents (cisplatin)</td>
<td>Endothelial dysfunction and disruption; platelet activation</td>
<td>Thromboembolism</td>
<td>Up to 2%</td>
</tr>
</tbody>
</table>

The highest frequency reported in the literature are presented in the Table. For more detailed information about the incidence of anti-cancer therapy cardiotoxicity, see Zamorano et al.³⁴

**HER2**, human epidermal growth factor receptor 2; HFrEF, heart failure with reduced ejection fraction; LVSD, left ventricular systolic dysfunction; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.