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جمعية القلب السعودية
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Cardiotoxicity: Recommendations for Prevention and Therapy

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Disclosures

- None



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Cardiotoxicity

- Advances in treatment have led to improved survival of patients with cancer, but have also increased morbidity and mortality due to treatment side effects
- May be **cardiotoxicity** from direct effects of the cancer treatment on heart function and structure or may be due to **accelerated development of CVD**
- Cardiotoxicity is a very relevant issue in clinical practice, with little evidence based on clinical trials

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Cardiotoxicity

- Cardio-oncology is growing field
- Many aspects of radiation-induced and cancer drug–induced CVD are still to be fully elucidated

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Cardiotoxicity

- Complicated by inability to predict the long-term consequences of cancer treatment–associated CV side effects leading to under- or overdiagnosis of CVD
 - Results in the failure to prevent adverse events
 - To inappropriate interruption of a potentially lifesaving cancer treatment

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Cardiotoxicity

- Left ventricular dysfunction (LVD) and HF are relatively common and serious side effects of cancer treatment
 - Survivors of pediatric cancer treated with anthracyclines and/or mediastinal radiotherapy have a 15-fold increased lifetime risk for
 - In older patients with CV risk, the short-term risk for developing HF is increased
 - Growing awareness of the occurrence of LVD/HF caused by tyrosine kinase inhibitors

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Risk Factors for Cardiotoxicity

<i>Current myocardial disease</i>	<i>Demographic and other CV risk factors</i>
- Heart failure (with either preserved or reduced ejection fraction) - Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide²) - Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) - Moderate and severe VHD with LVH or LV impairment - Hypertensive heart disease with LV hypertrophy - Hypertrophic cardiomyopathy - Dilated cardiomyopathy - Restrictive cardiomyopathy - Cardiac sarcoidosis with myocardial involvement - Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	- Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) - Family history of premature CV disease (<50 years) - Arterial hypertension - Diabetes mellitus - Hypercholesterolaemia

<i>Previous cardiotoxic cancer treatment</i>	<i>Lifestyle risk factors</i>
- Prior anthracycline use - Prior radiotherapy to chest or mediastinum	- Smoking - High alcohol intake - Obesity - Sedentary habit

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Cardiotoxicity

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m ² 550 mg/m ² 700 mg/m ² →	3–5 7–26 18–48
Idarubicin (>90 mg/m ²)	5–18
Epirubicin (>900 mg/m ²)	0.9–11.4
Mitoxantrone >120 mg/m ²	2.6
Liposomal anthracyclines (>900 mg/m ²)	2
Alkylating agents	
Cyclophosphamide →	7–28
Ifosfamide <10 g/m ² 12.5–16 g/m ²	0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1

Monoclonal antibodies	
Trastuzumab →	1.7–20.1 ^{28a}
Bevacizumab	1.6–4 ^{14b}
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib →	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellaneous	
Everolimus	<1
Temsirolimus	<1

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Anthracycline Toxicity

- Heart damage after anthracycline therapy can be divided into early and late cardiotoxicity
 - Early cardiotoxicity develops during 1st year of anthracycline therapy
 - Late cardiotoxicity refers to damage that only becomes evident < 1 year after the completion of anthracycline therapy
- The risk of developing heart failure remains a lifelong threat

van Dalen EC. *Cochrane Database of Syst Rev* 2011



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Anthracycline Toxicity: Frequency

- Widely reported values
- In children:
 - Prevalence of subclinical HF at 6 years after treatment reported >57%
 - Incidence of clinical HF is as high as 16% 5 years after treatment

van Dalen EC. *Cochrane Database of Syst Rev* 2011



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Anthracycline Toxicity

- Anthracyclines, doxorubicin, epirubicin and daunorubicin, are among the most effective drugs used in chemotherapy for cancer patients
- Mechanism of cardiac damage is unclear
- Likelihood of toxicity related to the type of anthracycline, the cumulative and the peak dose

van Dalen EC. *Cochrane Database of Syst Rev* 2011



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Anthracycline Toxicity

- Doxorubicin is associated with a 5% incidence of HF when a cumulative lifetime dose of 400 mg/m² is reached
- Higher doses lead to an exponential increase in risk, up to 48% at 700 mg/m²

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Anthracycline Toxicity

Risk factors

- Cumulative dose
- Female sex
- Age
 - >65 years old
 - Paediatric population (<18 years)
- Renal failure
- Concomitant or previous radiation therapy involving 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

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Prevention of Anthracycline Toxicity

- The meta-analysis for dexrazoxane showed a statistically significant benefit in favor of dexrazoxane for the occurrence of HF
- (RR 0.29, 95% CI 0.20 to 0.41)
- No evidence was found for a difference in response rate or survival between the dexrazoxane and control groups

van Dalen EC. *Cochrane Database of Syst Rev* 2011



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Prevention of Anthracycline Toxicity

Study or Subgroup

Lopez 1998
Marty 2006
Speyer 1992
Venturini 1996
Wexler 1996

Total (95% CI)

Total events
Heterogeneity: $\chi^2 = 0.00$
Test for overall $\tau^2 = 0.00$

Reasonable to use dexrazoxane if the risk of cardiac damage is expected to be high in patients with cancer treated with anthracyclines

% CI

2 5 10
ours control

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Immunotherapies and targeted therapies

- Inhibition of HER2 signalling with either antibodies (trastuzumab, pertuzumab) or tyrosine kinase inhibitors (lapatinib) have improved outcomes of patients with HER2-positive breast cancer
- Initially, cardiotoxicity was high when trastuzumab was given concomitantly with anthracyclines in metastatic breast cancer trials (7-34%)

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Immunotherapies and targeted therapies

- Applying trastuzumab after anthracyclines, or using an anthracycline-free chemotherapy regimen, substantially reduced the rate of clinical HF
- Based on several large-scale trials of adjuvant therapy in breast cancer, all of which prospectively assessed cardiac side effects, the RR for cardiac dysfunction and HF were 5.1% and 1.8%

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Immunotherapies and targeted therapies

- Risk factors for anti-HER2 drug-induced cardiotoxicity include:
 - Previous exposure to anthracyclines
 - Short time (3 weeks vs. 3 months) between anthracycline and anti-HER2 treatment
 - Pre-existing arterial hypertension
 - Low LVEF
 - Older age

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Immunotherapies and targeted therapies

- In contrast to anthracyclines, trastuzumab cardiotoxicity **typically manifests during treatment**
 - This has led to the implementation of different cardiotoxicity surveillance protocols
- Trastuzumab-associated cardiotoxicity is not believed to be cumulative-dose related
- Trastuzumab-induced LV dysfunction and **HF are usually reversible** with trastuzumab interruption and/or treatment with HF therapies

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Immunotherapies and targeted therapies

- Treatment interruption of trastuzumab is associated with an increase in cancer recurrence
 - In patients with HER2-positive breast cancer receiving adjuvant trastuzumab, cardiotoxicity was the most common reason for treatment interruption in 13.5% of patients (30% for HF and 70% for asymptomatic LVEF decline)
 - In most trastuzumab breast cancer registration trials, treatment was stopped when patients developed HF or (in asymptomatic patients) when LVEF dropped below 45%

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Immunotherapies and targeted therapies

- There are no randomized trials to prove that HF drugs will improve cardiac function in patients with trastuzumab-associated cardiac dysfunction.
- However, analogous to the experience in patients with anthracycline cardiotoxicity, trastuzumab-associated cardiac dysfunction is likely to improve when these patients are treated with ACE inhibitors.

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Cyclophosphamide Cardiotoxicity

- Cyclophosphamide cardiotoxicity is relatively rare
 - Primarily seen in patients receiving high doses (>140 mg/kg) before bone marrow transplantation
 - HF typically occurs within days of drug administration, and risk factors include total bolus dose, older age, combination therapy with other cancer drugs and mediastinal irradiation

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Platin Cardiotoxicity

- Other alkylating agents such as cisplatin and ifosfamide infrequently cause HF
- Platin-containing chemotherapy requires the administration of a high IVF volume to avoid platin-related toxicity
 - This volume overload in patients with pre-existing myocardial impairment, rather than the direct toxicity of these drugs, is often the cause of first or recurrent episodes of HF

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Prevention of Cardiotoxicity

- Positive health-promoting behavior should be strongly advised:
 - Healthy diet
 - Smoking cessation
 - Regular exercise
 - Weight control

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Prevention of Cardiotoxicity

- Aerobic exercise is considered a promising non-pharmacological strategy to prevent and/or treat chemotherapy-induced cardiotoxicity
 - Walking and cycling activities have been tested, and the benefit was greater when the exercise was more intensive, but not until exhaustion

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Monitoring for Cardiotoxicity

- LVEF should be determined before and periodically during treatment for early detection of cardiac dysfunction in patients receiving potentially cardiotoxic chemotherapy using the same method during follow-up.

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Monitoring for Cardiotoxicity

- The lower limit of normal of LVEF in echocardiography is 50%--the definition of cardiotoxicity commonly used in registries and trials in patients with cancer
- A patient with a significant decrease in LVEF ($>10\%$), to a value that does not drop below the lower limit of normal, should undergo repeated assessment of LVEF shortly after and during the duration of cancer treatment.

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Monitoring for Cardiotoxicity

- If LVEF decreases $>10\%$ to a value below the lower limit of normal (LVEF $>50\%$), ACEi(or ARBs) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated
- ACEi (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.

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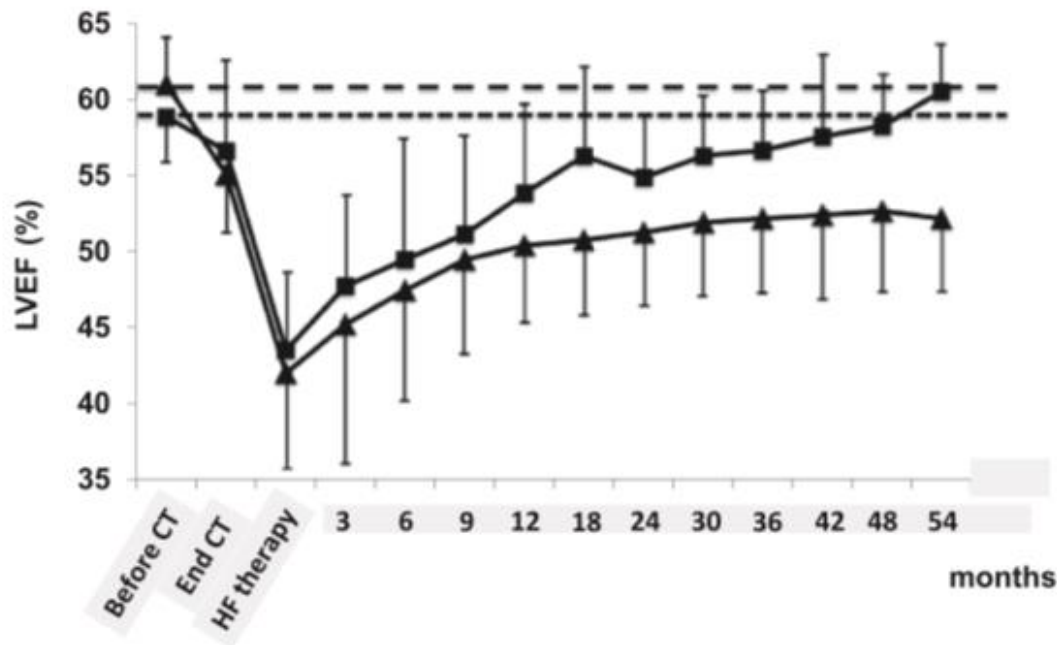


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Treatment for Cardiotoxicity: Anthracycline

- In 98% of cases, cardiotoxicity occurred within the first year.
- 11% of patients had full recovery
- 71% patients had partial recovery
- End-chemotherapy LVEF and cumulative doxorubicin dose were independent correlates of cardiotoxicity



Cardinale D. *Circulation* 2015



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Conclusions

- Monitoring for symptoms and EF is important
- Healthy lifestyle plays a role
- Interruption of drug therapy important if decline in EF
- Standard of care HF drugs are recommended



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