The 3rd Indonesia Symposium on Heart Failure and Cardiometabolic Disease 2023

Maximizing CTRCD Management: Strategies for Improved Outcomes

Agnes Lucia Panda, MD, FIHA, FAsCC

Internist – Cardiologist, Echocardiography Consultant
Department of Cardiology and Vascular Medicine,
Faculty of Medicine, Sam Ratulangi University
Prof. Dr. R. D. Kandou Hospital, Manado

Introduction

- With the increased of cancer cases, there has been parallel increase in cancer survivors due to early detection and advanced treatment. Treatment-related side effects have gained more significance.
- Cancer patients have an on average 2–6 times higher CVD mortality risk than the general population.
- The CVD mortality risk is evident throughout the continuum of cancer care, and entails an acute phase (early risk) and a chronic phase (late risk).
- It is important for cancer patients to receive the best possible cancer treatments safely, minimizing cancer therapy-related cardiovascular toxicity (CTR-CVT) across the entire continuum of cancer care

Cardio-oncology Syndrome (COS) Classification

Type I
- Direct
- Progressive development of cancer leads to CV disease

Type II
- Indirect
- Cancer associated treatments causing CV disease

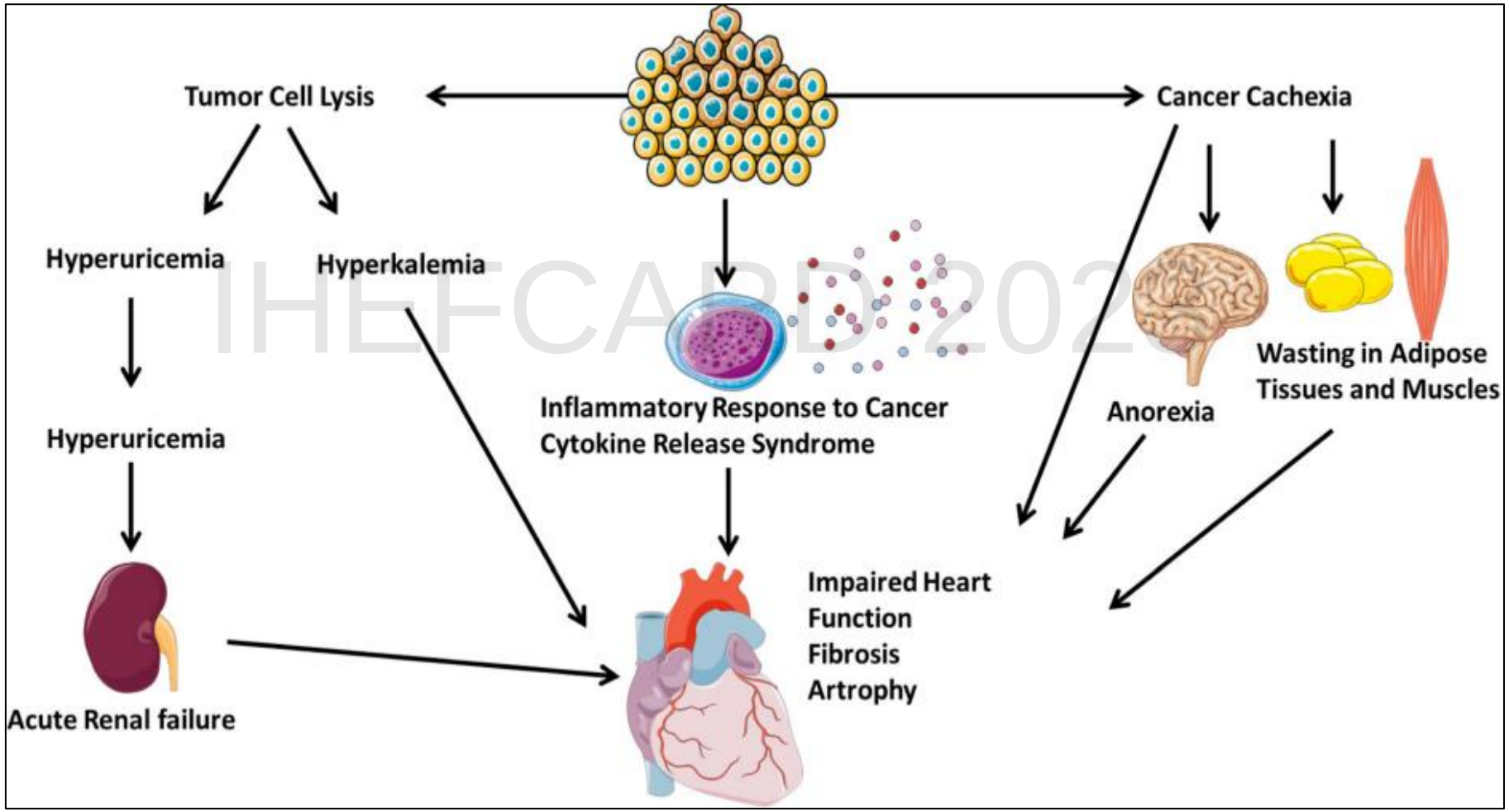
Type III
- Direct
- Progressive scarring and remodelling of heart and kidney causing a pro-oncogenic environment

Type IV
- Indirect
- CV disease associated treatments and diagnostics causing a pro-oncogenic environment

Type V
- Secondary
- Systemic and genetic conditions causing both cancer and CV disease

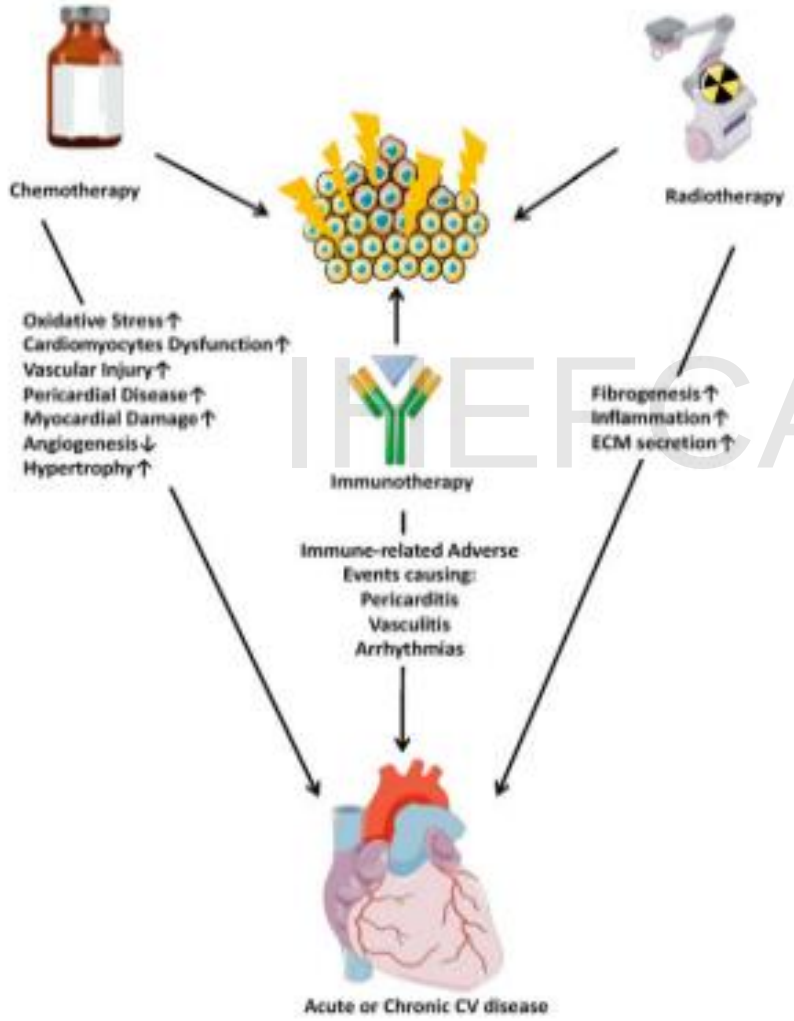
De Boer RA, et al. Cardio-oncology. 2021;7:24

COS Type I



De Boer RA, et al. Cardio-oncology. 2021;7:24

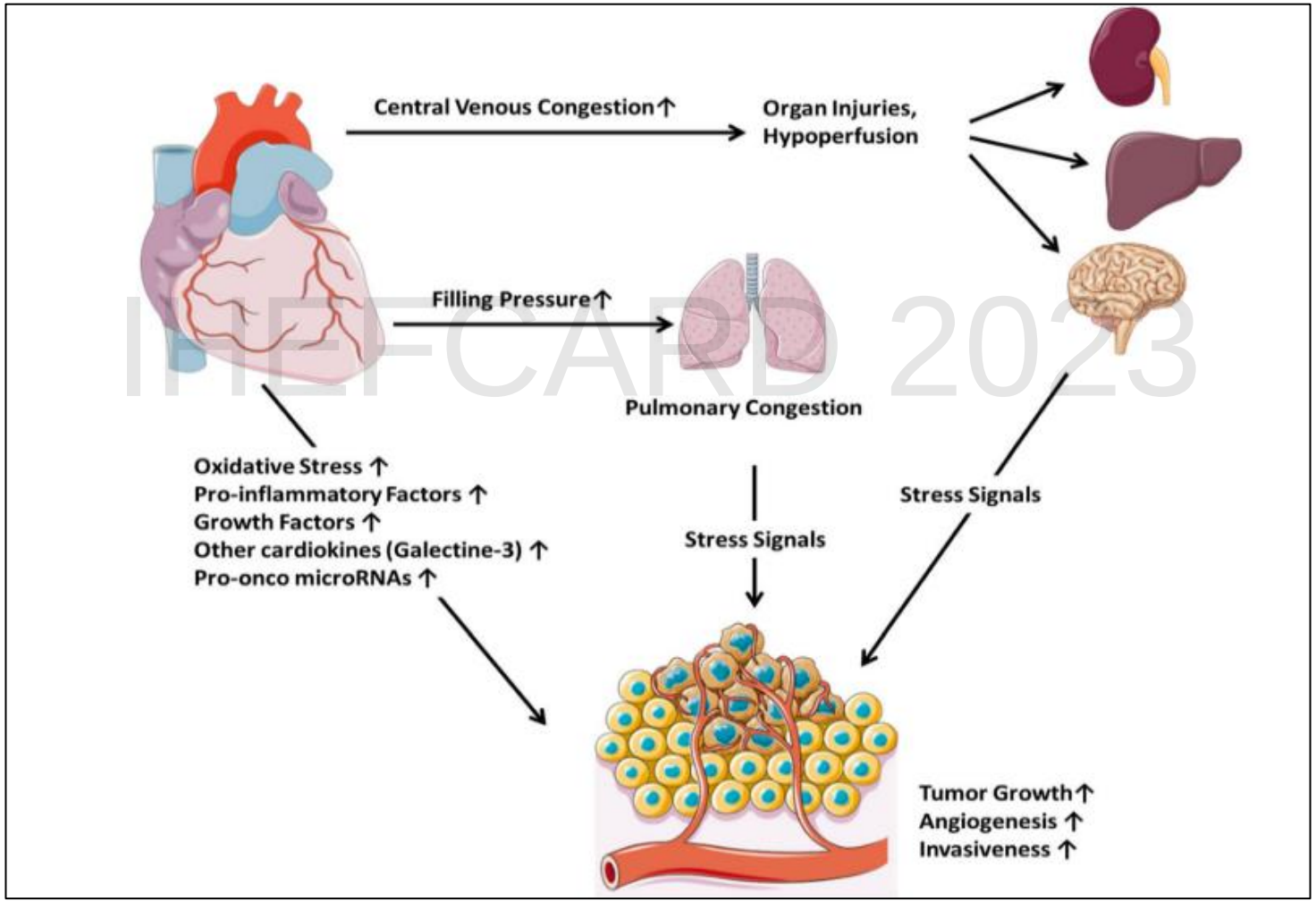
COS Type II



Chemotherapies Associated with Cardiac Dysfunction	Examples of Chemotherapy Agents
Anthracyclines	doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone
Human epidermal growth factor receptor 2 inhibitors	trastuzumab, pertuzumab, and lapatinib
Alkylating agents	cyclophosphamide, ifosfamide, busulfan, mitomycin, and melphalan
Taxanes	paclitaxel and docetaxel
Platinum-based therapies	cisplatin, carboplatin, and oxaliplatin
Fluoropyrimidines	Capecitabine, 5-fluorouracil
Tyrosine kinase inhibitors	dasatinib, imatinib, sorafenib, nilotinib, ponatinib, osimertinib
Bruton's tyrosine kinase	ibrutinib
VEGF signaling pathway inhibitors	bevacizumab, aflibercept, ramucirumab, sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, and lenvatinib
Immune checkpoint inhibitors	pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and ipilimumab
Anaplastic lymphoma kinase inhibitors	crizotinib and ceritinib
Proteasome inhibitors	bortezomib and carfilzomib

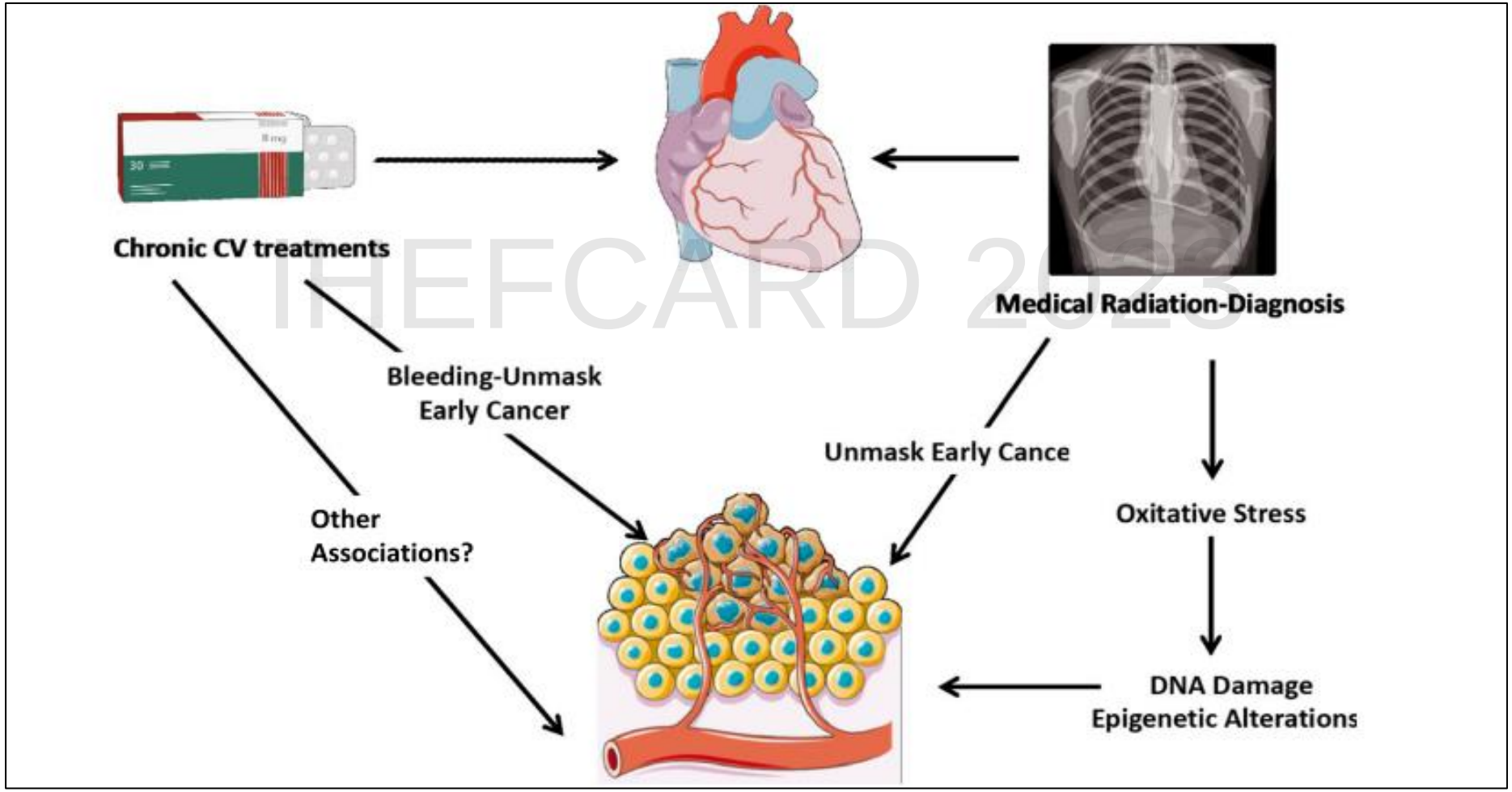
De Boer RA, et al. Cardio-oncology. 2021;7:24

COS Type III



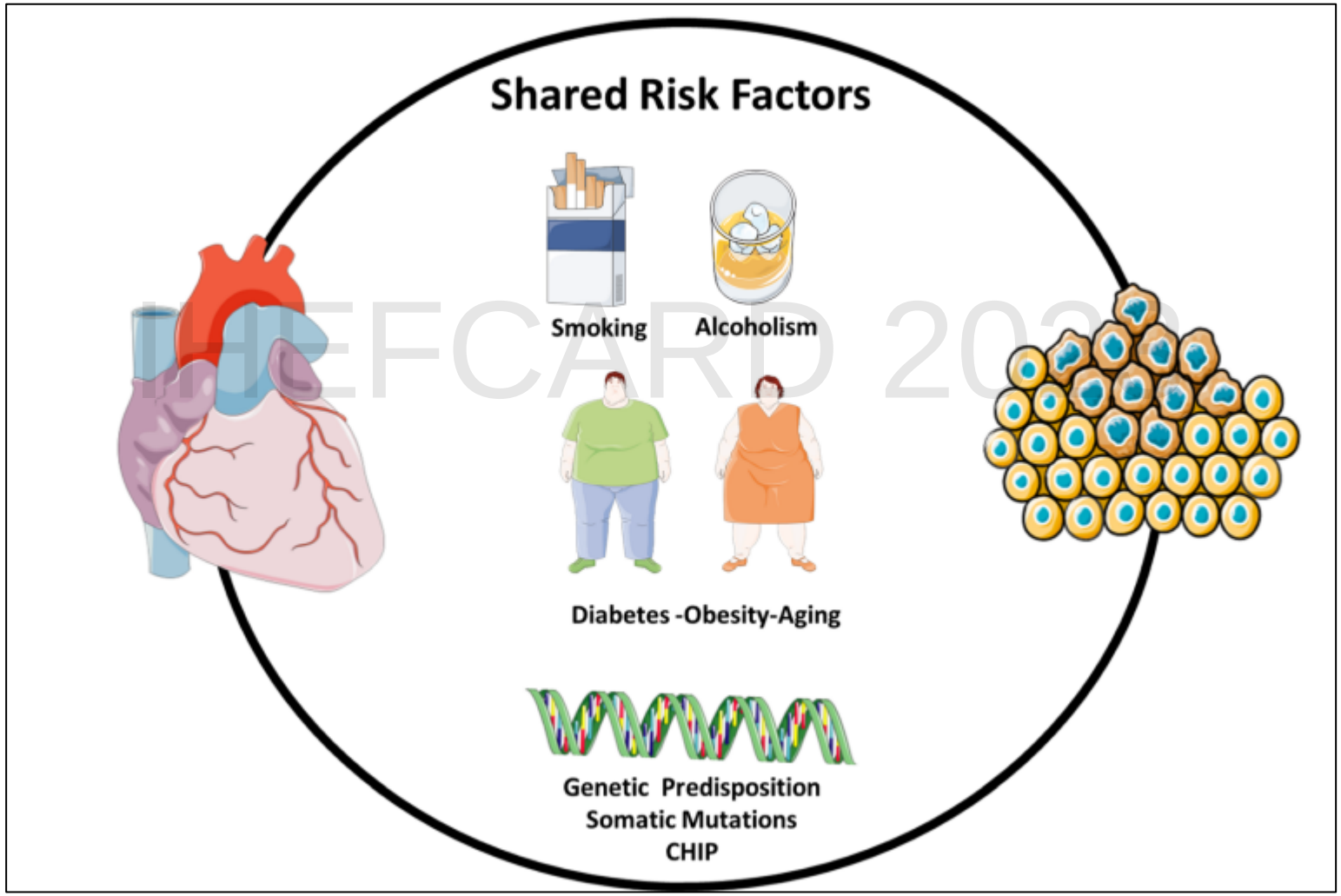
De Boer RA, et al. Cardio-oncology. 2021;7:24

COS Type IV



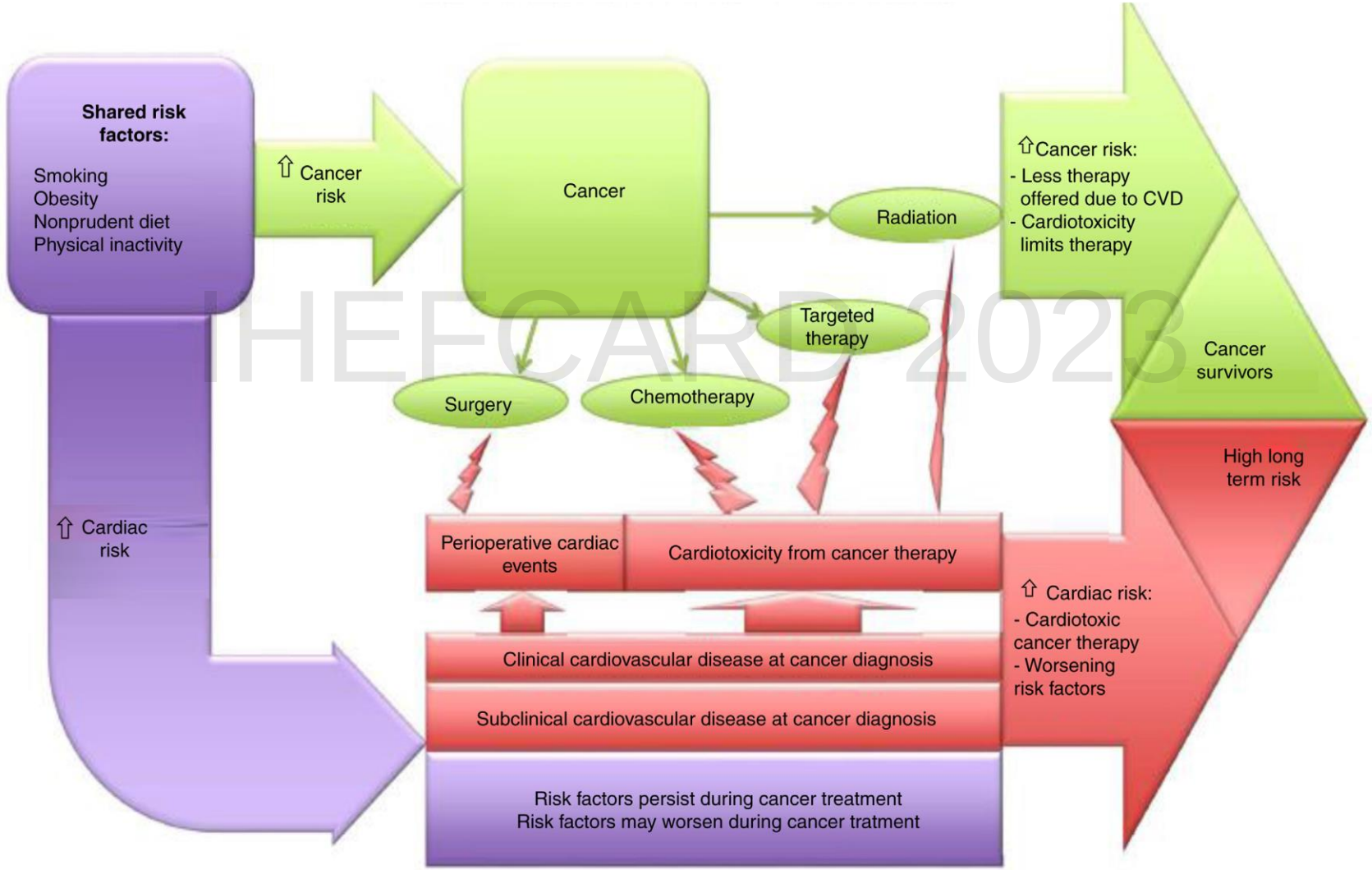
De Boer RA, et al. Cardio-oncology. 2021;7:24

COS Type V



De Boer RA, et al. Cardio-oncology. 2021;7:24

Risk factors contributing to cardiotoxicity associated with cancer treatment



Gottlieb RA, Mehta PK. Cardio-Oncology: Principles, Prevention and Management. Academic Press; 2016

Demographic factors

- Age: <10 years, >65 years
- African ethnicity

Lifestyle factors

- Smoking
- High alcohol intake
- Sedentary lifestyle

Patient history factors

- Positive family history of premature CVD (<50 years of age)
- Family history of sudden death (occult familial dilated cardiomyopathy, rare variants in cardiomyopathy-associated genes, congenital LQTS)
- Reports of syncope
- History of VTE, inherited thrombophilia
- History of transfusions
- Impaired hepatic drug metabolism CVAD
- Elevated cardiac biomarkers
- Comorbidities:
  - Atherothrombotic disease
  - Diabetes mellitus
  - Dyslipidaemia
  - Electrolyte imbalance
  - Hypercholesterolaemia
  - Hypothyroidism
  - Hypertension
  - Impaired renal function, CKD, renal failure
  - Infection
  - Obesity
  - Pulmonary disease

Treatment-related factors

- Prior anthracycline use (including dose, and formulation)
- Prior RT, especially to chest or mediastinum
- Hormone agent use
- Erythropoiesis stimulating agents use
- QT-prolonging agent use

CV-related factors

- HF with preserved or reduced ejection fraction
- Asymptomatic LV dysfunction (LVEF <50%)
- 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
- Cardiomyopathy (hypertrophic, dilated, or restrictive)
- Significant cardiac arrhythmias (e.g. AF, AV block, ventricular tachyarrhythmias), QTc prolongation

Cancer-related factors

- Primary cancer site (mostly pancreatic, brain, stomach, kidney, lung, lymphoma, myeloma)
- Histology (especially adenocarcinoma)
- Advanced stage (metastatic)
- Initial period after cancer diagnosis
- Low performance status

Baseline risk factors for cardiotoxicity

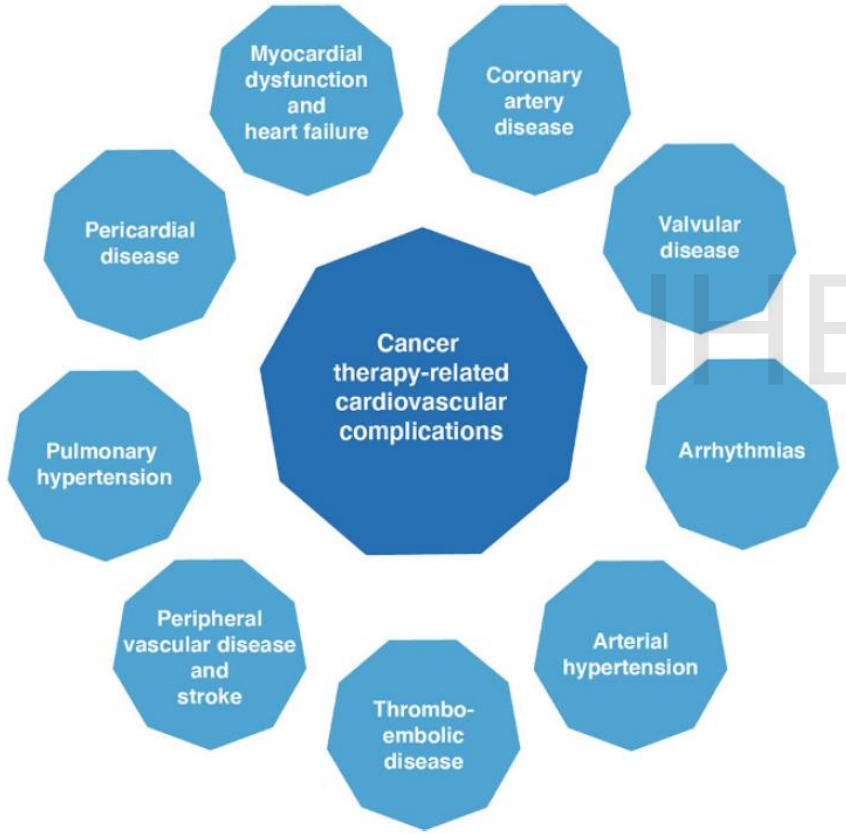
Zamorano JL, et al. Eur J of Heart Failure. 2020;22(12):2290-309

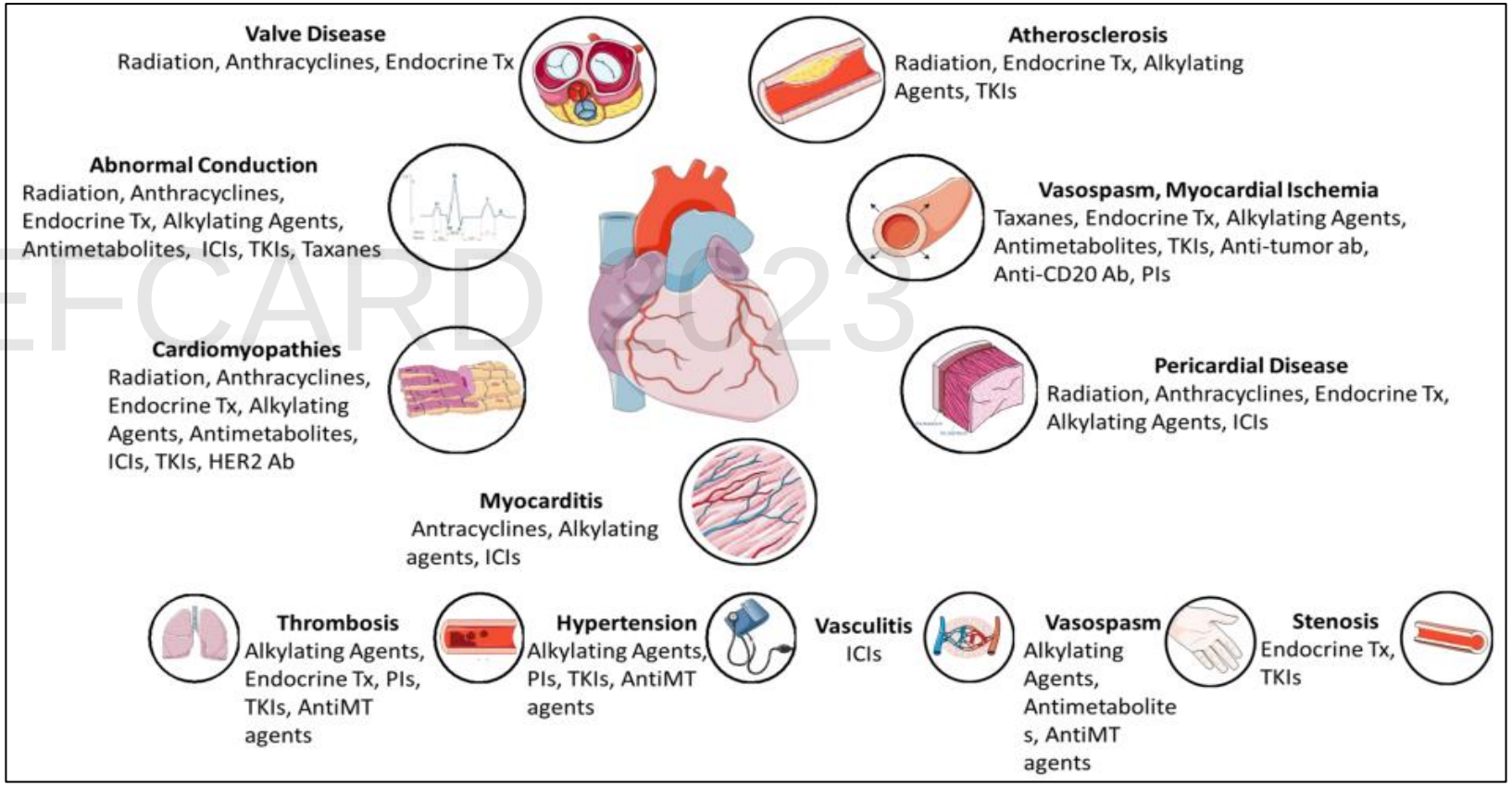
Developing risk factors for cardiotoxicity during cancer-therapy

- High-dose anthracycline (eg, doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2)
- High-dose radiotherapy (≥30 Gy) where the heart is in the treatment field
- Lower-dose anthracycline (eg, doxorubicin <250 mg/m^2, epirubicin <600 mg/m^2) or HER-2$_i$ or VEGF$_i$ or proteasome$_i$ or Bcr-Abl$_i$ and presence of any of the following factors:
  - Age ≥60 y
  - Lower-dose radiotherapy (<30 Gy) where the heart is in the treatment field
  - ≥ 2 Risk factors, including smoking, hypertension, diabetes mellitus, dyslipidemia, chronic renal insufficiency, and obesity
- Previous heart disease
- Elevated cardiac biomarkers before initiation of anticancer therapy

Alexandre J, et al. Journal of the American Heart Association. 2020;9(18):e018403.

Cardiovascular Toxicities of Cancer Therapies





Kamphuis JA, et al. Netherlands Heart Journal. 2021;29(5):288-94
De Boer RA, et al. Cardio-oncology. 2021;7:24

Cancer Therapy-related CV Toxicities

- Symptomatic Cancer Therapy-related Cardiac Dysfunction (CTRCD)
- Asymptomatic CTRCD
- ICI-induced myocarditis
- Vascular toxicity
- Arterial hypertension
- Cardiac arrhythmias

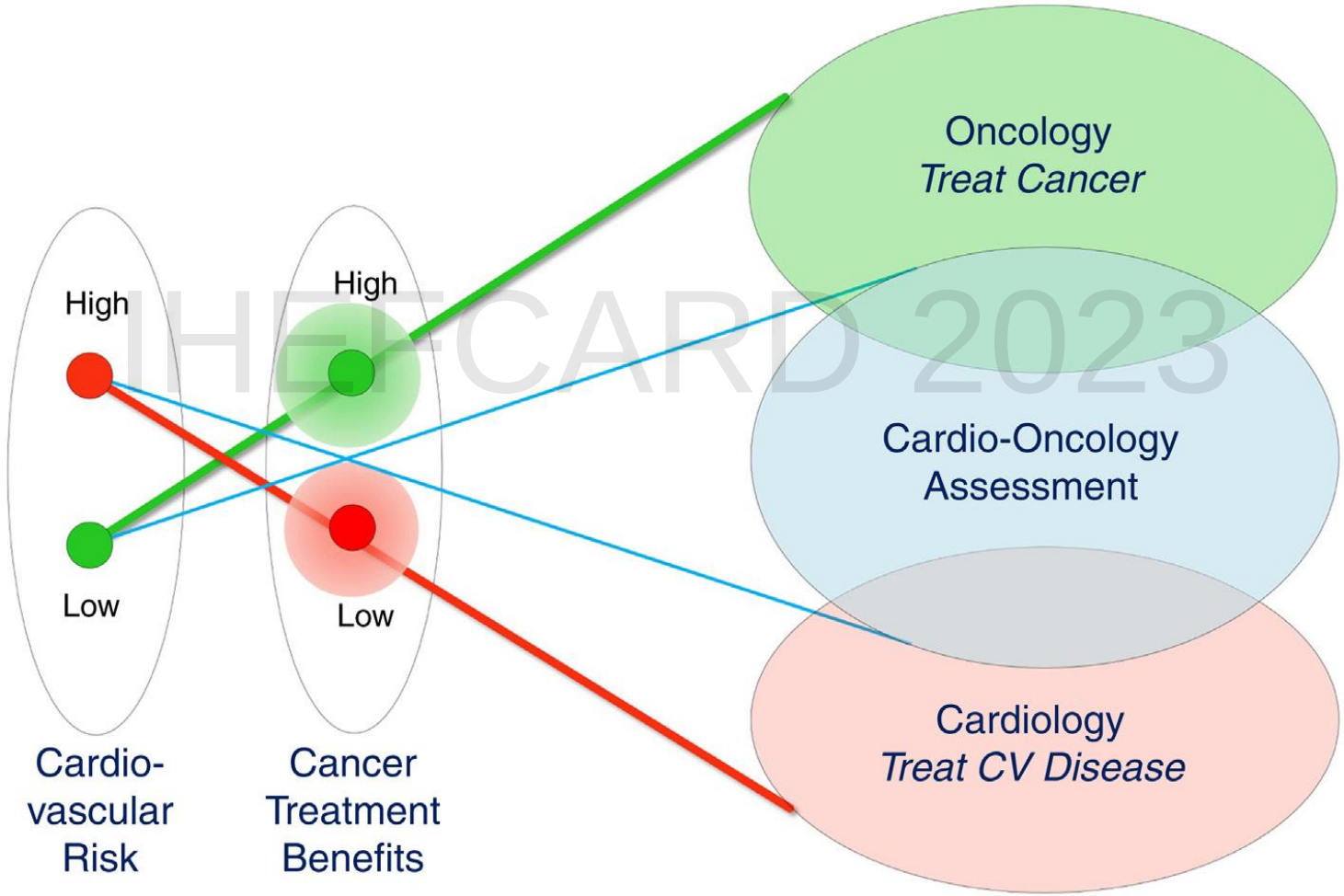
Lyon, A.R., et al. European Heart Journal. 2022; ehac244

Cancer Therapy-related Cardiac Dysfunction (CTRCD)

Symptomatic (HF)	
Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
Severe	HF hospitalization
Moderate	Need for outpatient intensification of diuretic and HF therapy
Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic	
Severe	New LVEF reduction to <40%
Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% *OR* New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers
Mild	LVEF ***≥50%*** AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

General Principle of Management Approach



Gottlieb RA, Mehta PK. Cardio-Oncology: Principles, Prevention and Management. Academic Press; 2016

HFA-ICOS baseline CV toxicity risk stratification

Baseline CV toxicity risk factors	Anthracycline chemotherapy	HER2-targeted therapies	VEGF inhibitors	BCR-ABL inhibitors	Multiple myeloma therapies	RAF and MEK inhibitors
Previous CVD						
HF/cardiomyopathy/ CTRCD	VH	VH	VH	H	VH	VH
Severe VHD	H	H	–	–	–	H
MI or PCI or CABG	H	H	VH	–	–	H
Stable angina	H	H	VH	–	–	H
Arterial vascular disease	–	–	VH	VH	VH	–
Abnormal ankle-brachial pressure index	–	–	–	H	–	–
PH	–	–	–	H	–	–
Arterial thrombosis with TKI	–	–	–	VH	–	–
Venous thrombosis (DVT/PE)	–	–	H	M2	VH	–
Arrhythmia[a]	–	M2	M2	M2	M2	M1
QTc ≥ 480 ms	–	–	H	H	–	–
450 ≤ QTc < 480 ms (men); 460 ≤ QTc < 480 ms (women)	–	–	M2	M2	–	–
Prior PI CV toxicity	–	–	–	–	VH	–
Prior IMiD CV toxicity	–	–	–	–	H	–

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

HFA-ICOS baseline CV toxicity risk stratification

Baseline CV toxicity risk factors	Anthracycline chemotherapy	HER2-targeted therapies	VEGF inhibitors	BCR-ABL inhibitors	Multiple myeloma therapies	RAF and MEK inhibitors
Cardiac imaging						
LVEF < 50%	H	H	H	H	H	H
LVEF 50–54%	M2	M2	M2	–	M2	M2
LV hypertrophy	–	–	–	–	M1	–
Cardiac amyloidosis	–	–	–	–	VH	–
Cardiac biomarkers						
Elevated baseline cTn[b]	M1	M2	M1	–	M2	M2
Elevated baseline NP[b]	M1	M2	M1	–	H	M2
Age and CVRF						
Age ≥ 80 years	H	H	–	–	–	M1
Age 65–79 years	M2	M2	–	–	–	M1
Age ≥ 75 years	–	–	H	H	H	M1
Age 65–74 years	–	–	M1	M2	M1	M1
Age ≥ 60 years	–	–	–	M1	–	–
CVD 10-year risk score > 20%	–	–	–	H	–	–
Hypertension[c]	M1	M1	H	M2	M1	M2
Chronic kidney disease[d]	M1	M1	M1	M1	M1	M1
Proteinuria	–	–	M1	–	–	–
DM[e]	M1	M1	M1	M1	M1	M1
Hyperlipidaemia[f]	–	–	M1	M1	M1	–
Family history of thrombophilia	–	–	–	M1	M1	–

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

HFA-ICOS baseline CV toxicity risk stratification

Baseline CV toxicity risk factors	Anthracycline chemotherapy	HER2-targeted therapies	VEGF inhibitors	BCR-ABL inhibitors	Multiple myeloma therapies	RAF and MEK inhibitors
Current cancer treatment						
Dexamethasone > 160 mg/month	–	–	–	–	M1	–
Includes anthracycline before HER2-targeted therapy	–	M1[g]	–	–	–	–
Previous exposure to						
Anthracycline	H	M2[h]	H	–	H	H
Trastuzumab	–	VH	–	–	–	–
RT to left chest or mediastinum	H	M2	M1	–	M1	M2
Non-anthracycline chemotherapy	M1	–	–	–	–	–
Lifestyle risk factors						
Current smoker or significant smoking history	M1	M1	M1	H	M1	M1
Obesity (BMI > 30 kg/m^2)	M1	M1	M1	M1	M1	M1

Low risk:

No risk factors OR one moderate1 [M1] risk factor

Moderate risk:

Moderate risk factors with a total of 2–4 points (M1=1 point; M2=2 points)

High risk:

Moderate risk factors with a total of ≥5 points OR any high-risk factor

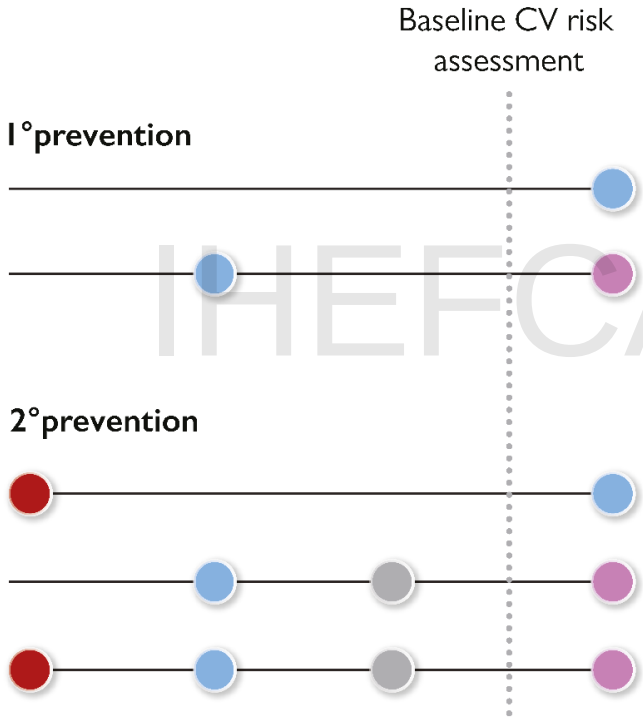
Very-high risk:

Any very-high risk factor

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

Primary and Secondary CTRCD Prevention Strategies

Primary vs secondary prevention



Management of CVD and CVRF according to ESC Guidelines

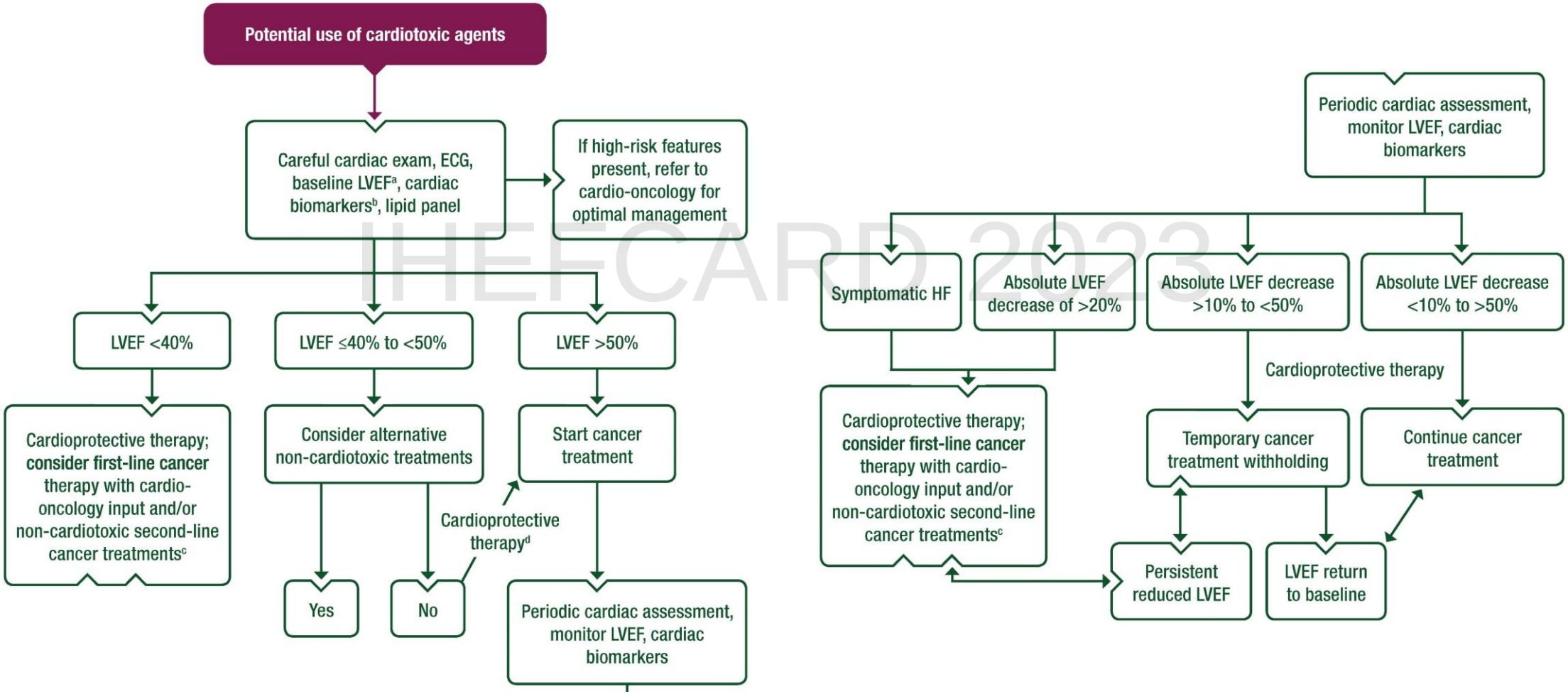
In patients at high and very high risk of CTRCD

- **Minimize the use of cardiotoxic drugs**
- **ACE-I/ARB and beta-blockers**
- **Dexrazoxane/liposomal anthracyclines** (patients treated with anthracyclines)
- **Statins**

Class I Class IIa

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

Proposed monitoring and management approach for patients undergoing potentially cardiotoxic anticancer therapy.



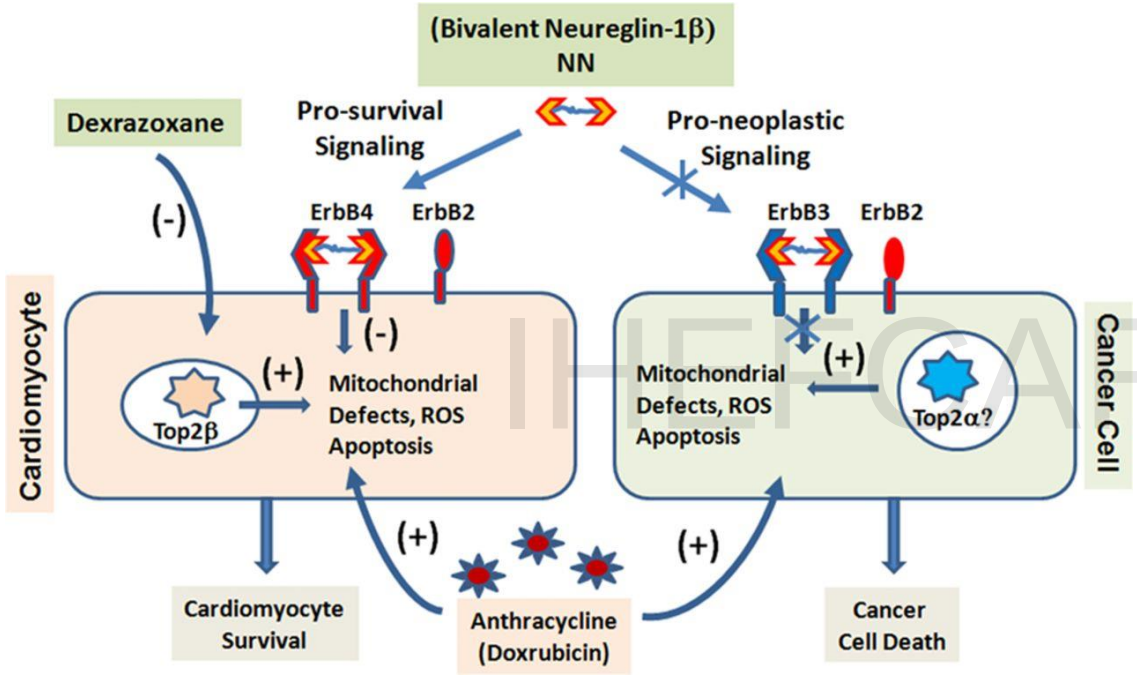
Curigliano G, et al. Annals of Oncology. 2020;31(2):171-90

Cardioprotective Therapies

1. **Dexrazoxane** should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated (≥ 300 mg/m^2 doxorubicin or equivalent). (IIa, B)
2. **Liposomal anthracyclines** should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated. (IIa, B)
3. **ACE-I or ARB and beta-blockers** recommended for HF should be considered for primary prevention in high- and very high-risk patients receiving anthracyclines and/or anti-HER2, VEGFi (evacizumab), RAF inhibitor, MEK inhibitor, Proteasome inhibitors, dasatinib, ponatinib, or osimertinib therapies. (IIa, B-C)
4. **Carvedilol** is preferred beta-blocker for CV protection if there is no contraindication.
5. **Statins** should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk. (IIa, B)

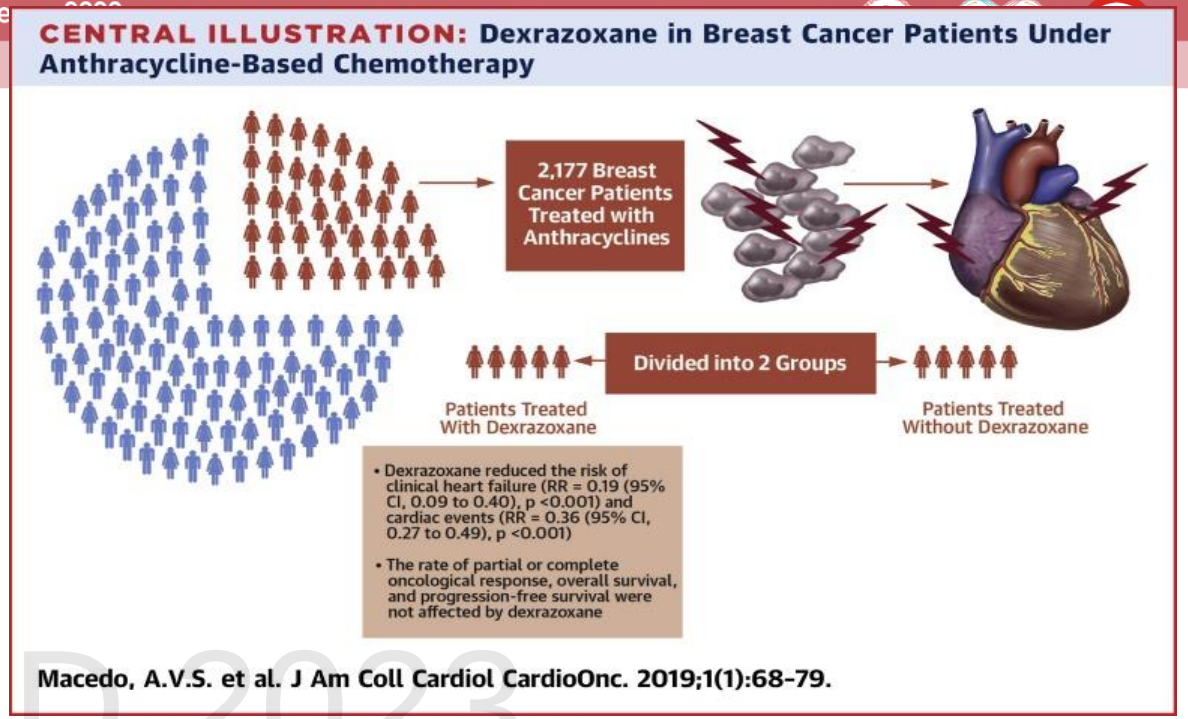
Lyon, A.R., et al. European Heart Journal. 2022; ehac244

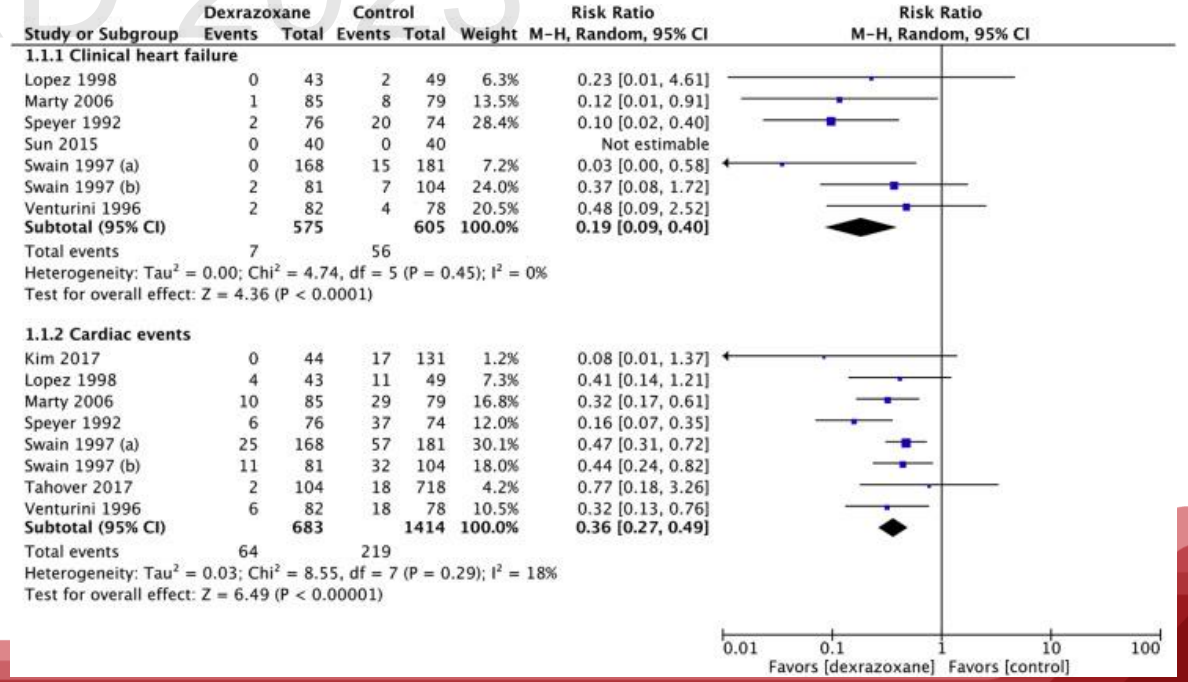
Dexrazoxane



Dexrazoxane should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated.[d,158]	IIa	B

Macedo AV, et al. Cardio Oncology. 2019 Sep 1;1(1):68-79
Lyon, A.R., et al. European Heart Journal. 2022; ehac244



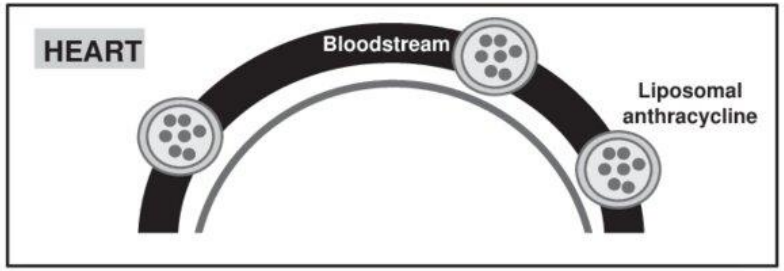


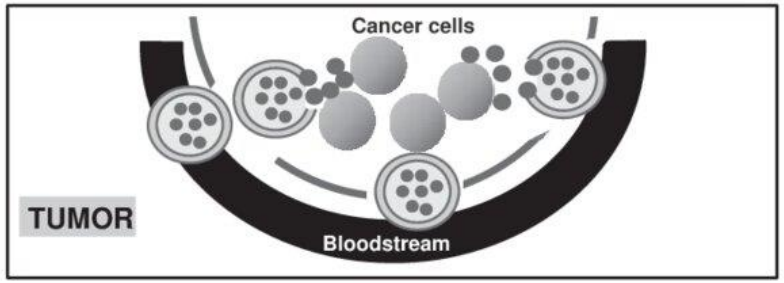
Liposomal Anthracycline

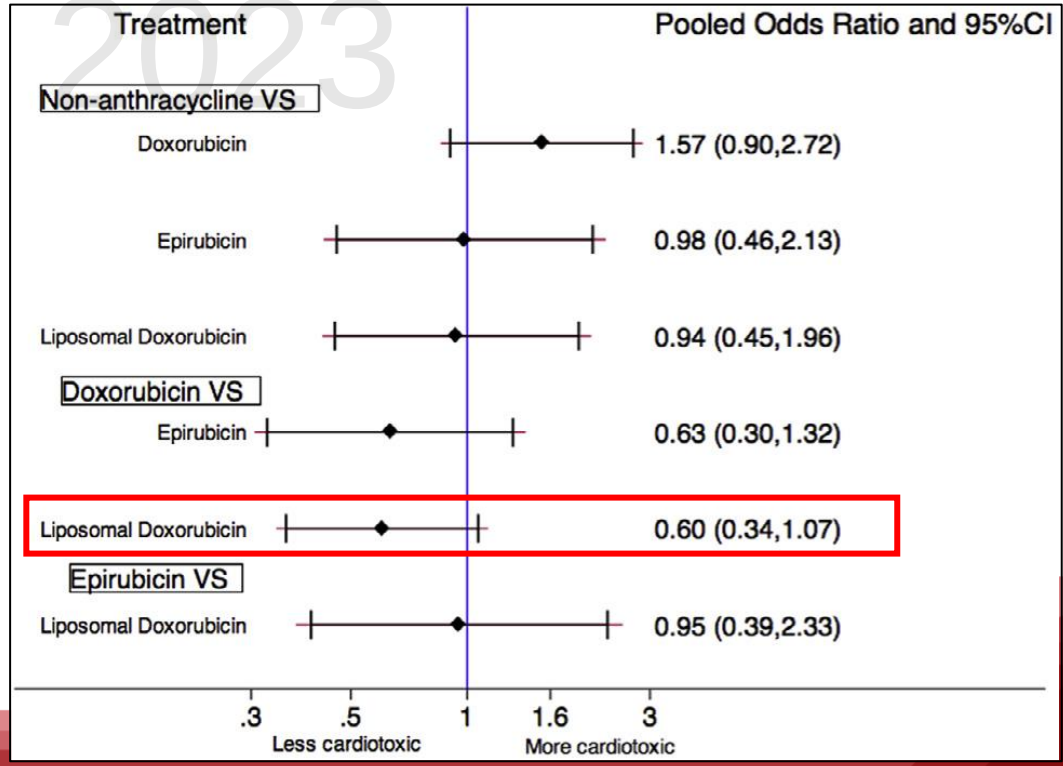
- Pegylated/non-pegylated liposomal doxorubicin modify pharmacokinetics and tissue distribution without compromising antitumour efficacy
- Liposomal doxorubicin was reported to be less cardiotoxic than conventional doxorubicin

Liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated.[e,164,165,168]	IIa	B

Yamaguchi N, et al. European Journal of Cancer. 2015 Nov 1;51(16):2314-20.
Lyon, A.R., et al. European Heart Journal. 2022; ehac244







Neurohormonal Therapy

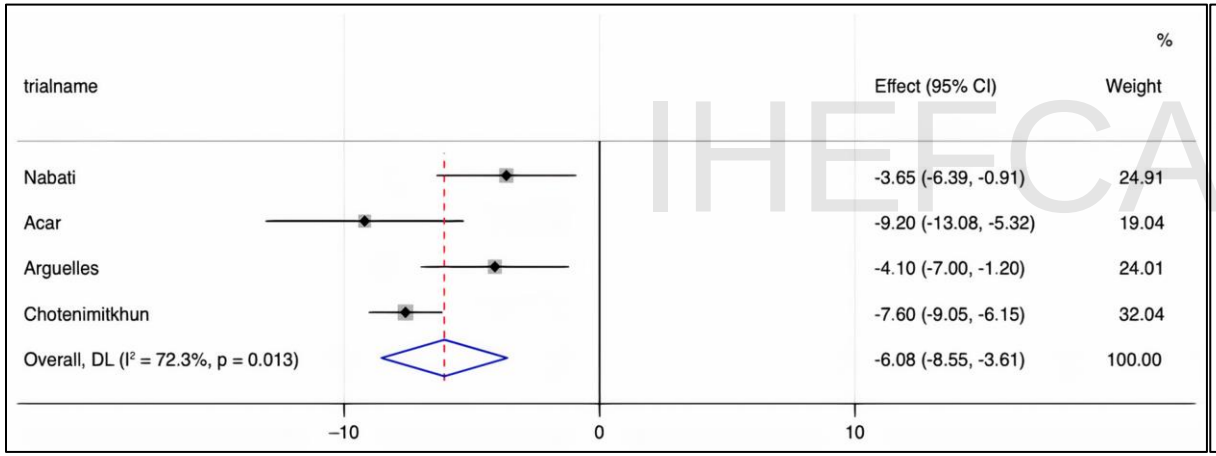
Trial	Trial Design	Trial Intervention	Imaging Method	N	Result of Primary Endpoint and Follow-Up Results	Result of Key Secondary Endpoints and Follow-Up Results
Pharmacologic intervention						
PRADA[22-24]	Randomized Placebo-controlled Double-blind 2 × 2 factorial	Metoprolol Candesartan Metoprolol plus candesartan Placebo	CMR	130	Primary trial: candesartan attenuated the reduction in LVEF Follow-up: no difference in change in LVEF from baseline to extended follow-up in either treatment arm	Primary trial: metoprolol attenuated the rise in troponins Follow-up: no difference in change in troponins from baseline to extended follow-up in either treatment arm
CECCY[25,26]	Randomized Placebo-controlled Double-blind	Carvedilol Placebo	Echocardiography	200	Primary trial: no effect on reduction of LVEF ≥10% from baseline Follow-up: no difference in change of LVEF at 2-y follow-up	Primary trial: carvedilol attenuated the rise in troponin I
SAFE[27]	Randomized Placebo-controlled Double-blind	Bisoprolol/enalapril/bisoprolol plus enalapril/placebo	Echocardiography (3D)	174	Bisoprolol, enalapril, and bisoprolol plus enalapril attenuated the reduction in LVEF Bisoprolol and enalapril prevented worsening in peak GLS	

ACE-I or ARB and beta-blockers recommended for HF[f] should be considered for primary prevention in high- and very high-risk patients receiving anthracyclines and/or anti-HER2 therapies.[145,150,155–157,159,160,175]	IIa	B
ACE-I or ARB and beta-blockers recommended for HF[f] should be considered for primary prevention in high- and very high-risk patients receiving targeted cancer therapies that may cause HF.[g]	IIa	C

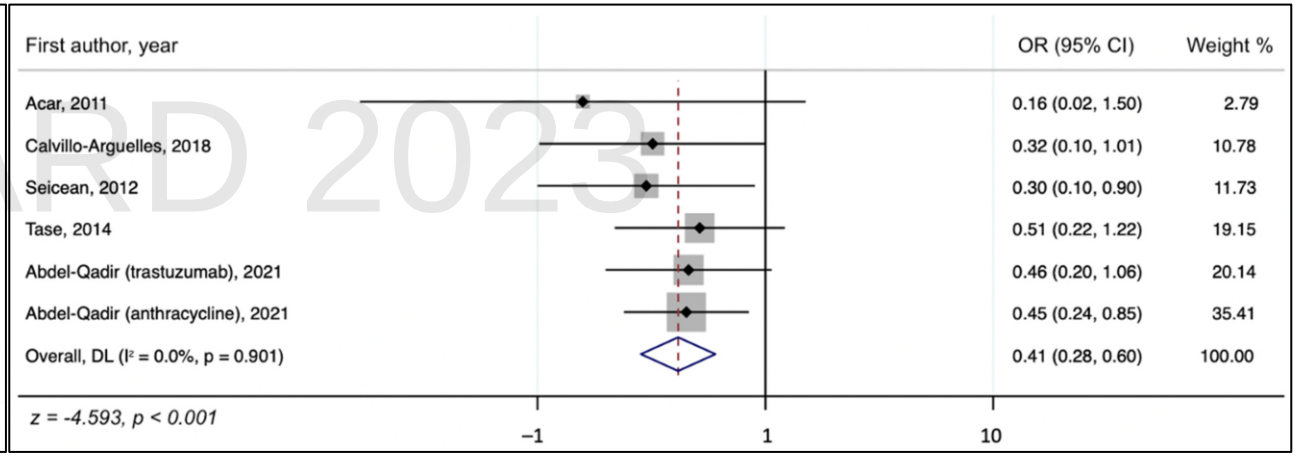
Omland T, Heck SL, Gulati G. JACC: CardioOncology. 2022 Mar 1;4(1):19-37.
Lyon, A.R., et al. European Heart Journal. 2022; ehac244

Statins

No-statin group had 6.1 more mean LVEF change than statin group

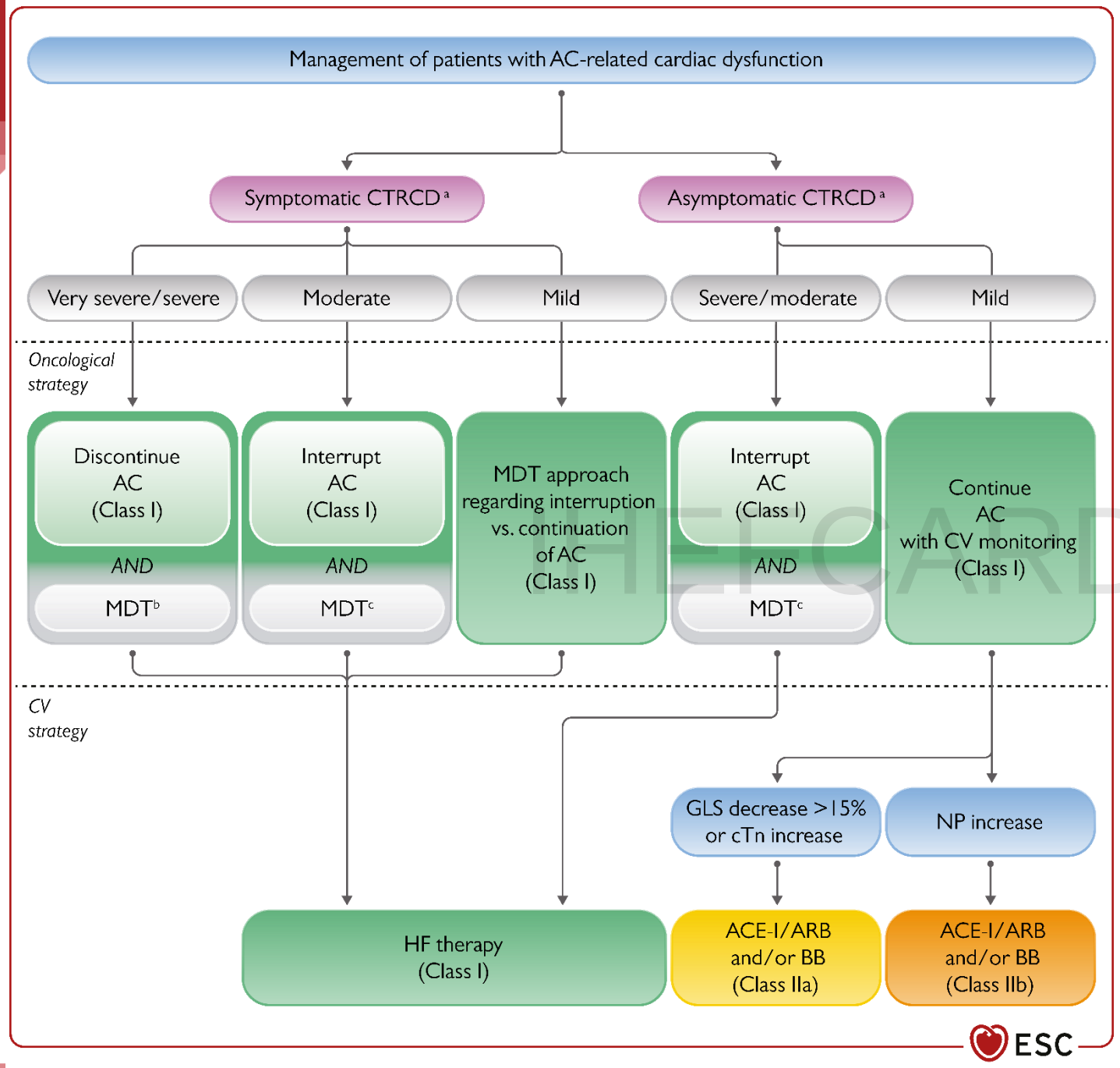


Statin group had 59% lower incidence of chemotherapy-induced cardiomyopathy



Statins should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk.[h,149,176–185]	IIa	B

Kim J, et al. Journal of Clinical Medicine. 2021 Aug 22;10(16):3731
Lyon, A.R., et al. European Heart Journal. 2022; ehac244



Management of Anthracycline chemotherapy (AC)-related cardiac dysfunction

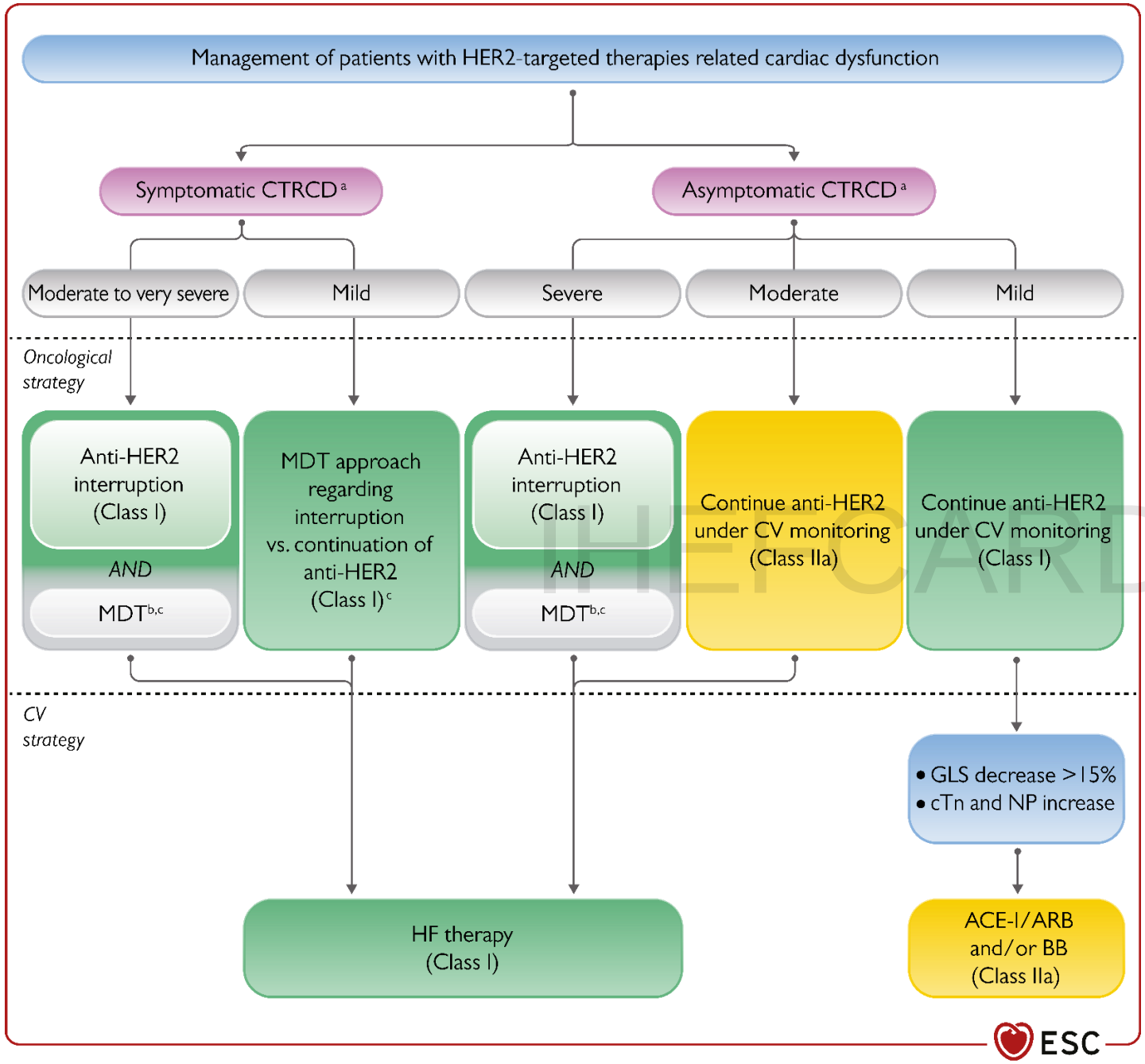
HF therapy (ACEi/ARB/ARNI, BB, SGLT2i, MRA) is recommended in

- All symptomatic CTRCD, or
- Moderate/severe asymptomatic CTRCD

ACEi/ARB and/or BB should be considered in mild asymptomatic CTRCD while chemotherapy continues uninterrupted.

A MDT is recommended before restarting AC in mild/moderate symptomatic CTRCD or moderate/severe asymptomatic CTRCD after recovery of LV function under HF treatment

Lyon, A.R., et al. European Heart Journal. 2022; ehac244



Management of HER2 therapy related cardiac dysfunction

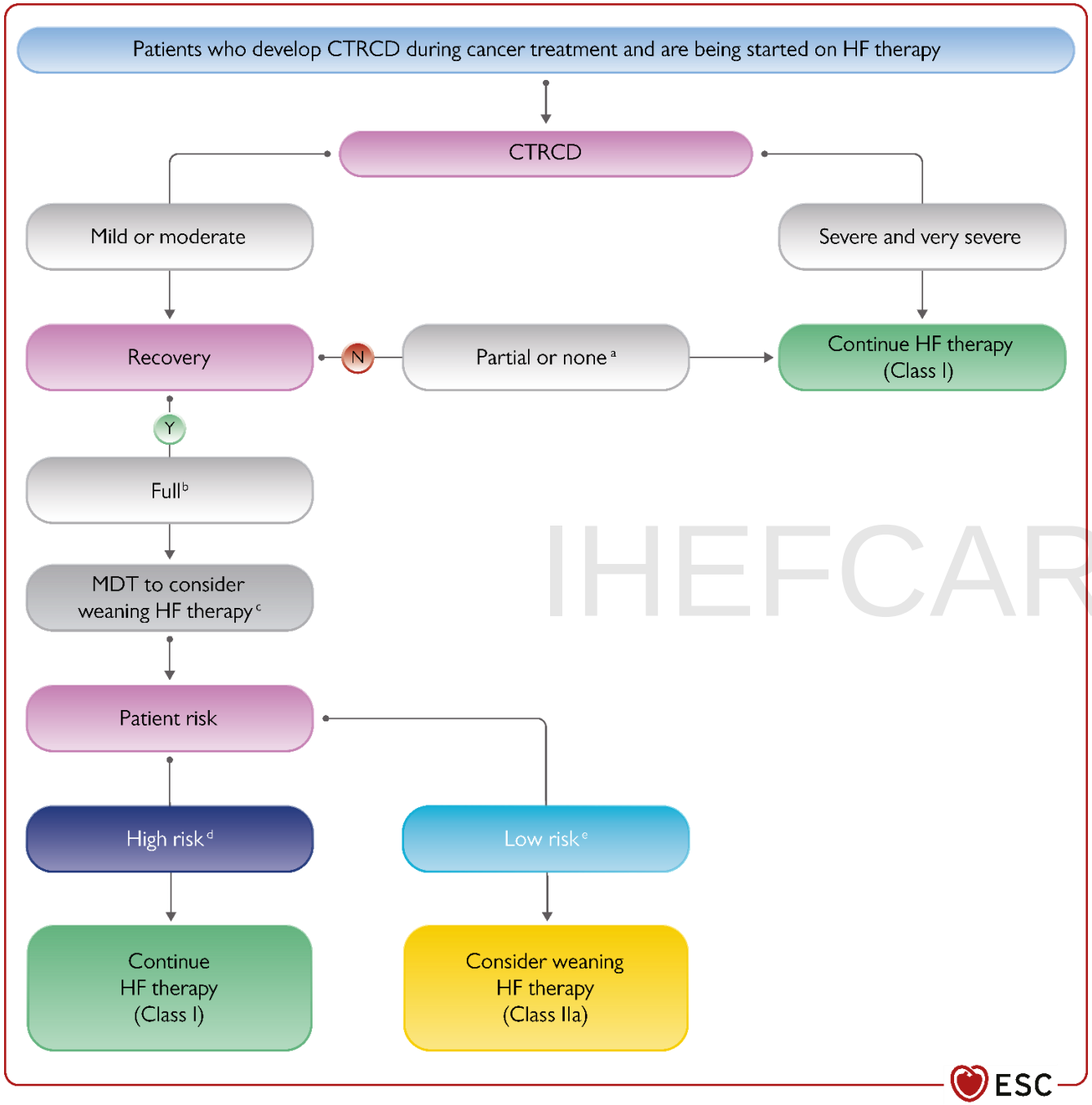
HF therapy (ACEi/ARB/ARNI, BB, SGLT2i, MRA) is recommended in

- All symptomatic CTRCD, or
- Moderate/severe asymptomatic CTRCD

ACEi/ARB and/or BB should be considered in mild asymptomatic CTRCD while chemotherapy continues uninterrupted.

A MDT is recommended before restarting in all symptomatic CTRCD or severe asymptomatic CTRCD after recovery of LV function under HF treatment

Lyon, A.R., et al. European Heart Journal. 2022; ehac244



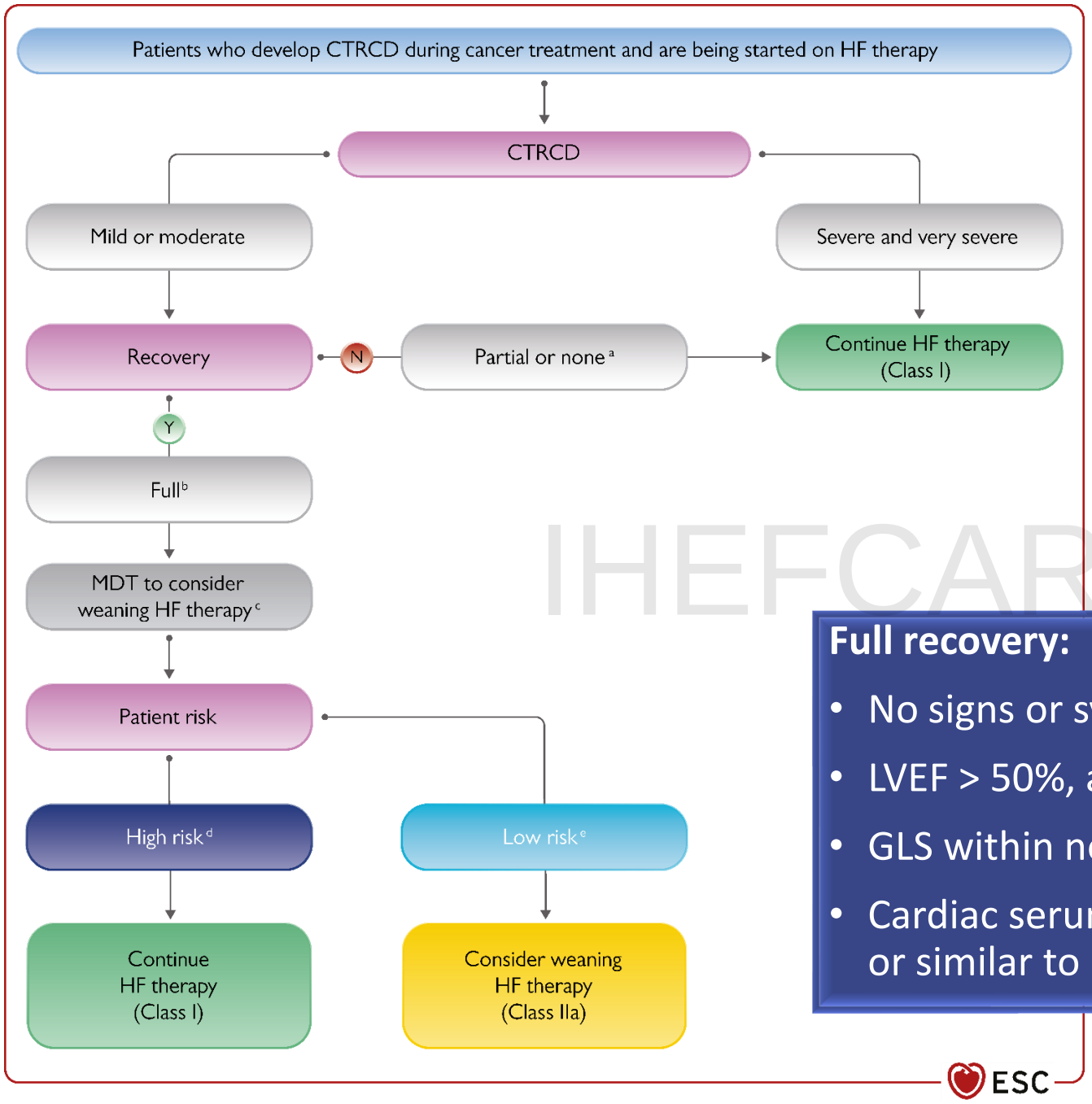
Management of CTRCD after cancer therapy

Continuing HF therapy (ACEi/ARB/ARNI, BB, SGLT2i, MRA) is recommended in

- Severe/very severe CTRCD, or
- Not fully recovered from CTRCD, or
- High-risk patient characteristics

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

Management of CTRCD after cancer therapy



Continuing HF therapy (ACEi/ARB/ARNI, BB, SGLT2i, MRA) is recommended in

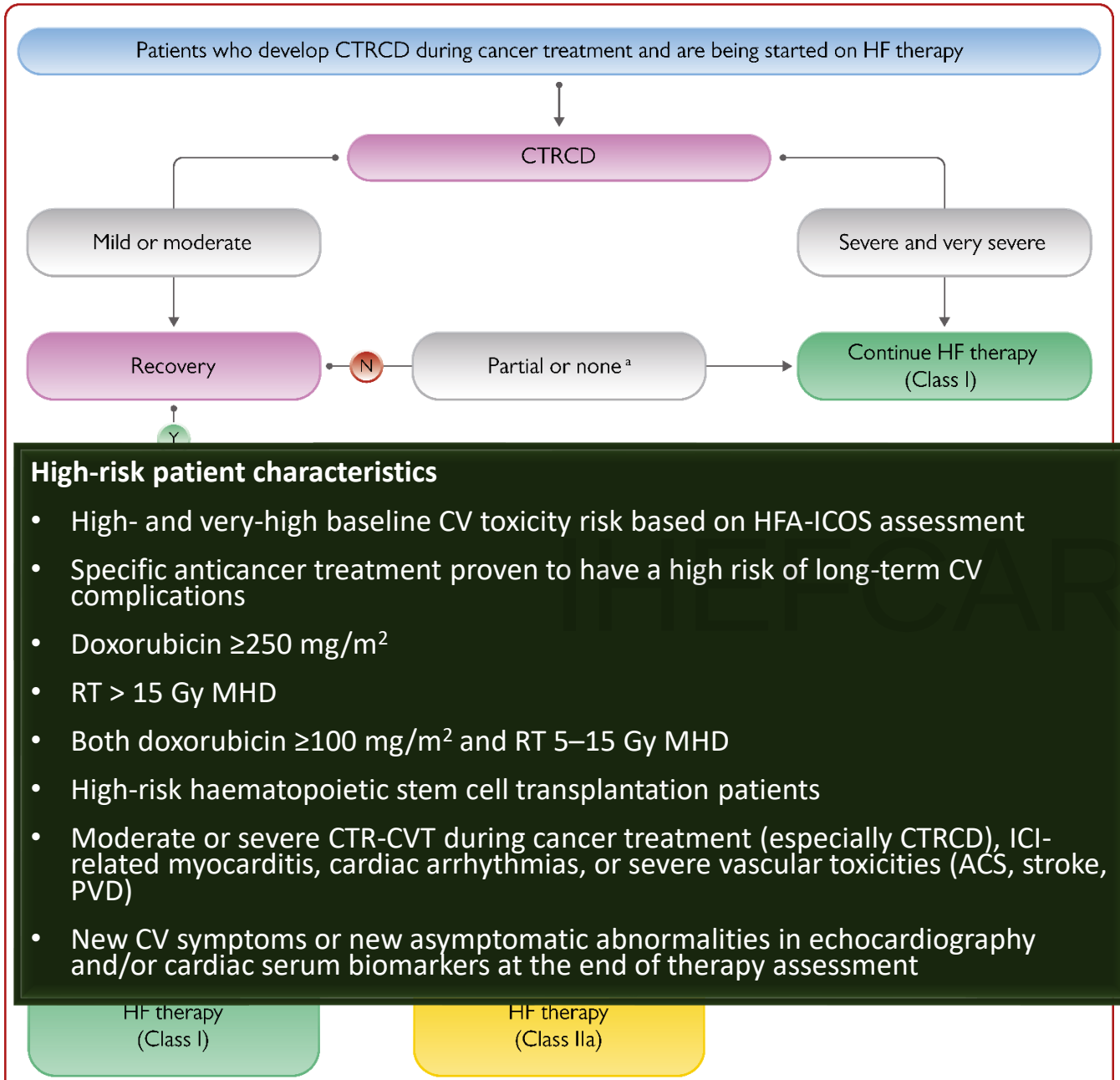
- Severe/very severe CTRCD, or
- Not fully recovered from CTRCD, or
- cs

Full recovery:

- No signs or symptoms of HF, and
- LVEF > 50%, and
- GLS within normal range or similar to baseline, and
- Cardiac serum biomarkers within the normal range or similar to baseline

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

Management of CTRCD after cancer therapy



High-risk patient characteristics

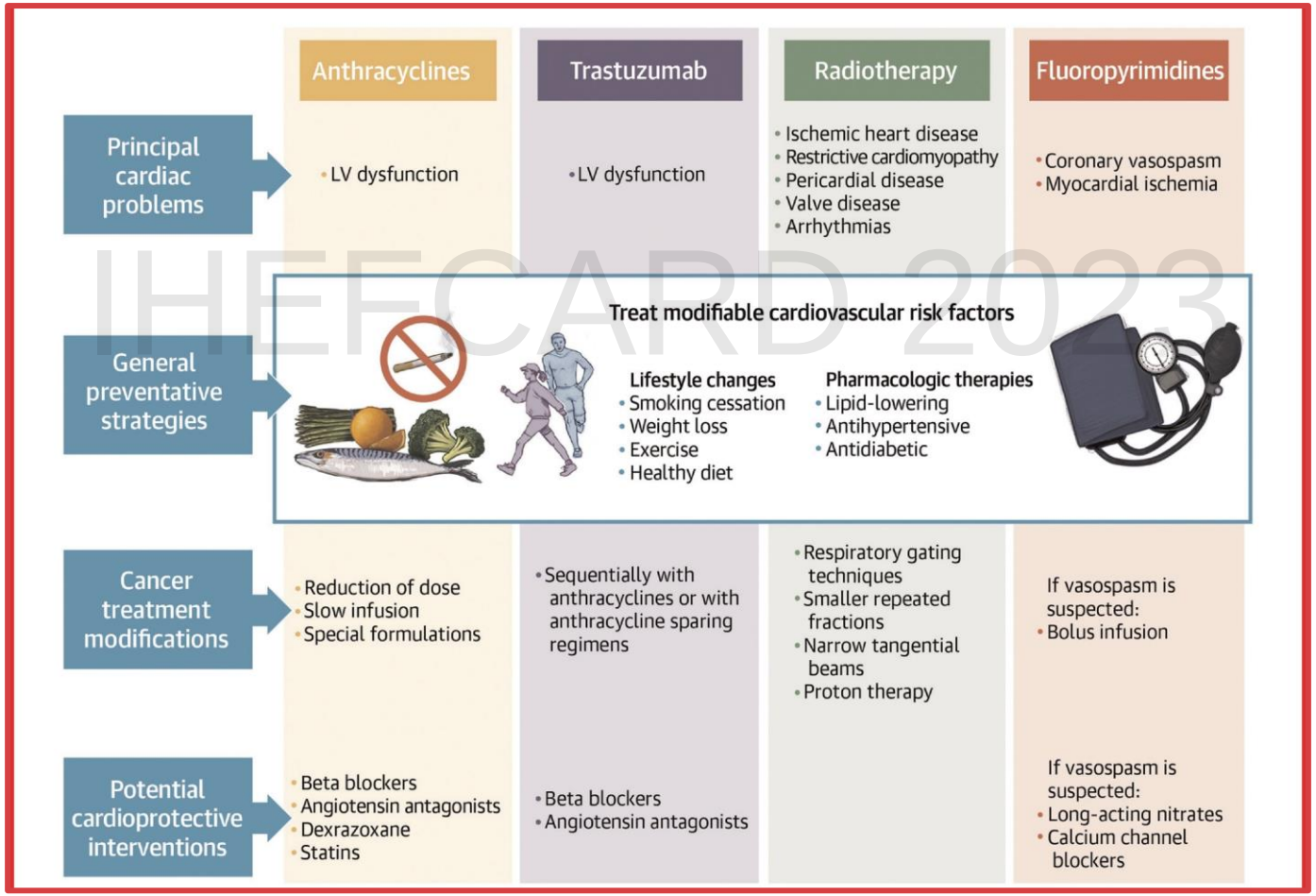
- High- and very-high baseline CV toxicity risk based on HFA-ICOS assessment
- Specific anticancer treatment proven to have a high risk of long-term CV complications
- Doxorubicin ≥250 mg/m^2
- RT > 15 Gy MHD
- Both doxorubicin ≥100 mg/m^2 and RT 5–15 Gy MHD
- High-risk haematopoietic stem cell transplantation patients
- Moderate or severe CTR-CVT during cancer treatment (especially CTRCD), ICI-related myocarditis, cardiac arrhythmias, or severe vascular toxicities (ACS, stroke, PVD)
- New CV symptoms or new asymptomatic abnormalities in echocardiography and/or cardiac serum biomarkers at the end of therapy assessment

Continuing HF therapy (ACEi/ARB/ARNI, BB, SGLT2i, MRA) is recommended in

- Severe/very severe CTRCD, or
- Not fully recovered from CTRCD, or
- High-risk patient characteristics

Lyon, A.R., et al. European Heart Journal. 2022; ehac244

Different cancer treatment has different cardioprotective approach



Omland T, Heck SL, Gulati G. JACC: CardioOncology. 2022 Mar 1;4(1):19-37

Summary

- Advances in cancer diagnosis and treatment have led to an increase in survivorship and the adverse effects of cancer therapy such, as serious cardiovascular toxicities.
- Cancer Therapy-related Cardiac Dysfunction (CTRCD) is the most common cardiotoxicity manifestation with HF presentation or LV function deterioration (LVEF and/or GLS)
- Treating CV risk factors, use of cardioprotective strategies, and cancer treatment modifications are recommended to reduce CTRCD incidence
- Interaction and collaboration among oncologists, cardiologists, and cardio-oncologists play a central role.

Thank You