Pharmacologic Review of Cardiotoxic Chemotherapies

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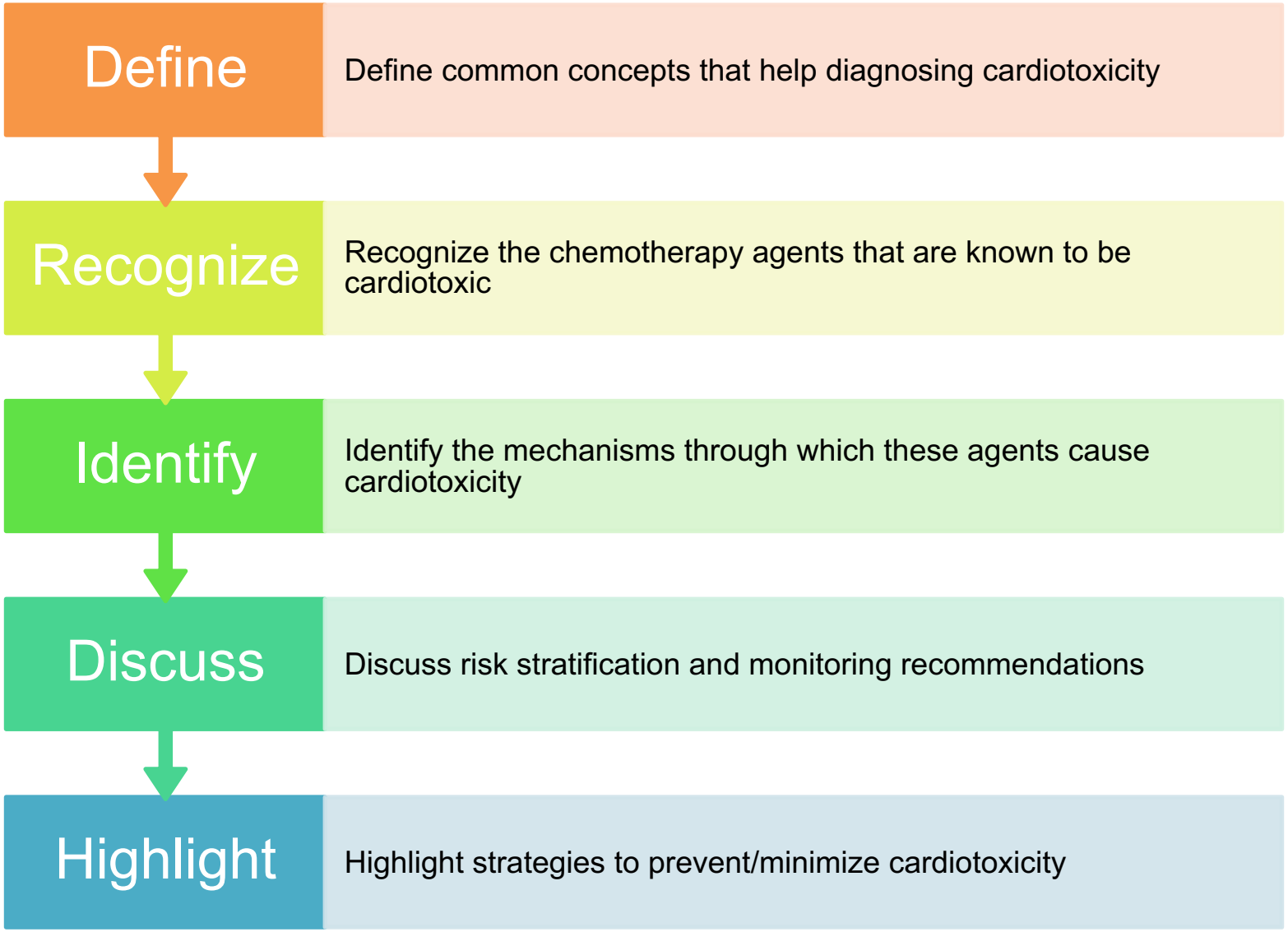
Objectives


Define
Define common concepts that help diagnosing cardiotoxicity
Recognize
Recognize the chemotherapy agents that are known to be cardiotoxic
Identify
Identify the mechanisms through which these agents cause cardiotoxicity
Discuss
Discuss risk stratification and monitoring recommendations
Highlight
Highlight strategies to prevent/minimize cardiotoxicity

Abbreviations

- ACEi: Angiotensin-converting-enzyme inhibitors
- ACS: Acute coronary syndrome
- ARB: Angiotensin II receptor blocker
- BB: Beta blockers
- BCR-ABL: Breakpoint cluster region (chromosome 22)-Abelson protooncogene (chromosome 9)
- BTK: Bruton's tyrosine kinase
- CCB: Calcium channel blocker
- CKD: Chronic kidney disease
- CMR: Cardiac magnetic resonance
- CV: Cardiovascular
- DM: Diabetes mellitus
- DNA: Deoxyribonucleic acid
- DOAC: direct oral anticoagulant
- ECG: Electrocardiogram
- ECHO: Echocardiography
- EBC: Early Breast Cancer
- HER2: Human epidermal growth factor receptor 2
- HF: Heart failure
- HFrEF: Heart failure with reduced ejection fraction
- HSCT: Hematopoietic stem-cell transplantation
- HTN: Hypertension
- LMWH: Low molecular weight heparin
- LVEF: Left ventricular ejection fraction
- LV: Left ventricular
- LVSD: Left ventricular systolic dysfunction
- MBC: Metastatic Breast Cancer
- NT-proBNP: N-terminal pro-b-type natriuretic peptide
- RNA: Ribonucleic acid
- NYHA: New York Heart Association
- TKI: Tyrosine kinase inhibitor
- TTE: Transthoracic echocardiogram
- VEGFR: Vascular endothelial growth factors
- VSP: Vascular endothelial growth factor signaling pathway
- 5-FU: 5-fluorouracil

Cardio-Oncology

Cardio-oncology is an emerging discipline focused predominantly on the detection and management of cancer treatment-induced cardiac dysfunction

Its goal is to allow patients with cancer to receive the best possible therapy minimizing cancer treatment related CV toxicity

Identify and treat CV risk factors and preexisting CVD complications

Herrmann J, Lenihan D et al Eur Heart J. 2021 Dec 14; 43

Why Cardio-Oncology?

Improvement survival of patients with cancer

Increase of short and long-term complications of cancer therapies that affect morbidity and mortality, including CV toxicities

Herrmann J, Lenihan D et al Eur Heart J. 2021 Dec 14; 43

Epidemiology

Mortality in the United States, 2020		
Heart Disease	Cancer	COVID-19
696,962	602,350	350,831

Incidence of Cardiotoxicities				
Anthracyclines	Trastuzumab	TKI	Fluorouracil	Bortezomib
1-16%	27%	VEGF: 8% Ibrutinib 11.2%	1.6-68%	2-5%

Piper S, McDonagh T.ECR Volume 10 Issue 1 Summer 2015.
Touyz RM, Herrmann J. NPJ Precis Oncol. 2018;2:13. Published 2018 May 8.
Cho, H., Lee, S., Sim, S.H. et al. Breast Cancer Res Treat 182, 333–343 (2020).
Pai VB, Nahata MC. Drug Saf. 2000 Apr;22(4):263-302.
Murphy SL, Kochanek KD, Xu JQ, et al. NCHS Data Brief, no 427. Hyattsville, MD: National Center for Health Statistics. 2021.

Morbidity/Mortality in Breast Cancer women

Cardiovascular disease competes with breast cancers as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study

Study population: 63, 566 women of age >66 diagnosed with breast cancer between 1992-2000

Results:

Comorbidity	ALIVE	Breast Cancer deaths	Other causes deaths
None	21,017 (56.7%)	5,500 (14.8%)	10,544 (28.4%)
Previous cancer	4,280 (41.4%)	1, 533 (14.8%)	4,534 (43.8%)
Cardiovascular disease	1,955 (24.1%)	1,353 (16.7%)	4,794 (59.2%)
COPD	1,886 (33.6%)	798 (14.2%)	2,927 (52.2%)
Diabetes	3,000 (36.4%)	1,308 (15.9%)	3,939 (47.8%)

Conclusion: Cardiovascular disease was the leading cause of death among older female breast cancer survivors without an initial diagnosis of cardiovascular condition

Patnaik JL, Byers TD et al. Breast Cancer Res. 2011; 13

Types of Chemotherapy-induced Cardiotoxicity

Acute or subacute cardiotoxicity

- Any time from the initiation of treatment up to 2 weeks after the completion of therapy
  - Characteristics: arrhythmias, abnormalities in ventricular repolarization and QT intervals, ACS or pericardial reaction and alteration in myocardial function

Chronic cardiotoxicity

- Early cardiotoxicity: within 1 year after the completion the treatment
- Late cardiotoxicity: more than 1 year after the chemotherapy
- Characteristics: subclinical, asymptomatic systolic or diastolic cardiac dysfunction

Florescu M, Cinteza M, Vinereanu D. Maedica (Bucur). 2013;8(1):59-67.

Cardiac Dysfunction/HF

Any of the following:

- Reduction of LVEF, either global or more severe in the interventricular septum
- Symptoms of congestive heart failure
- Signs associated with heart failure (HF), such as S3 gallop, tachycardia, or both
- Reduction in LVEF from baseline by ≥5% to <55% in the presence of sings or symptoms of HF, or a reduction in LVEF by ≥10% to <55% without signs or symptoms of HF

Herrmann J et al. 2022 43, 280-299.

Myocarditis

Pathohistological diagnosis:

- Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples

Clinical Diagnosis:

- Troponin elevation (new or significant change from baseline) with 1 major criterion or a troponin elevation with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion

Herrmann J et al. 2022 43, 280-299.

Myocarditis

Major Criterion:

- Cardiac Magnetic Resonance diagnosis for acute myocarditis

Minor Criteria:

- Clinical syndrome (fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)
- Ventricular arrhythmia and or new conduction system disease
- Decline in cardiac (systolic) function, with or without regional wall motion abnormalities in a non-Takotsubo pattern
- Other immune-related adverse event, particularly myositis, myopathy, myasthenia gravis
- Suggestive cardiac magnetic resonance

Herrmann J et al. 2022 43, 280-299.

Asymptomatic Vascular Toxicity

Event		Definition
Atherosclerosis	Coronary Artery Disease	New Coronary artery stenosis >50% on coronary computed tomography (CT) angiogram or >70% on coronary angiogram, or newly abnormal electrocardiogram (ECG), nuclear or echo stress test
	Peripheral Artery Disease	New ankle-brachial index (ABI) value <0.9 is considered abnormal, with 0.7-0.9 being mildly reduced, 0.4-0.69 moderately reduced, and <0.4 severely reduced; ABI value >1.3 is suggestive of non-compressible vessels, or Change in ABI from baseline by -0.15
	Carotid artery disease	New intima media thickness (IMT) >0.9mm or new plaque on carotid ultrasound, or Change in IMT >0.04/year from baseline
Thrombosis	Venous Thrombosis	New characteristics features on Duplex ultrasound, contrast CT, or venogram
	Arterial Thrombosis	New characteristic features on ultrasound or angiogram, or optical coherence tomography (OCT)
Abnormal vasoreactivity	Peripheral	New flow-mediated dilation of the brachial artery (FMD) <7.1% or reactive hyperemia index (RHI) <2 on Endo-PAT, or Change in FMD or RHI by > 50% from baseline
	Coronary Epicardial	New coronary vasoconstriction (reduction in coronary artery diameter) in response to acetylcholine infusion
	Coronary microvascular	New <50% increase in coronary blood flow in response to acetylcholine infusion, or a coronary flow velocity reserve <2 in response to adenosine

Herrmann J et al. 2022 43, 280-299.

Symptomatic Vascular Toxicity

Defined by guidelines:

- Stroke
- Transient Ischemic Attack
- Myocardial infarction
- Acute Coronary Syndrome
- Chronic Coronary Syndrome
- Peripheral Arterial Disease
- Vasospastic Angina
- Microvascular Angina
- Raynaud’s Syndrome

Herrmann J et al. 2022 43, 280-299.

Hypertension

Event	Definition
Normal	SBP ≤130 mmHg and DBP ≤80 mmHg
Treatment Threshold for HTN before, during, and off therapy/Cancer Survivors	CVD or ASCVD risk ≥10%: ≥130mmHg systolic and/or ≥80mmHg diastolic Otherwise: ≥140mmHg systolic and/or ≥90mmHg diastolic
Cancer Therapy holding threshold	≥180mmHg systolic and/or ≥110mmHg diastolic
Exaggerate hypertensive response	Systolic BP increase >20mmHg or mean arterial BP increase >15mmHg
Hypertensive emergency response	Very high BP elevations associated with acute hypertension-mediated organ damage (heart, retina, brain, kidneys, and large arteries), therefore requiring immediate BP reduction to limit extension or promote regression of target organ damage

Herrmann J et al. 2022 43, 280-299.

Arrhythmias/QT Prolongation

Event	Definition	
QTc prolongation	QTcF <480ms	Acceptable: continue current treatment
	QTcF 480-500ms	Prolonging: proceed with caution; minimize other QT prolonging medications, replete electrolytes
	QTcF >500ms	Prolonged: stop treatment and evaluate. May require dose reduction or alternative therapy

Definition of arrhythmia according to guidelines

Herrmann J et al. 2022 43, 280-299.

Cardiotoxic Chemotherapies

- Anthracyclines
- Human epidermal growth factor-2 inhibitor ($HER2_i$)
- Proteasome Inhibitors
- Tyrosine Kinase Inhibitors
- Antimetabolites

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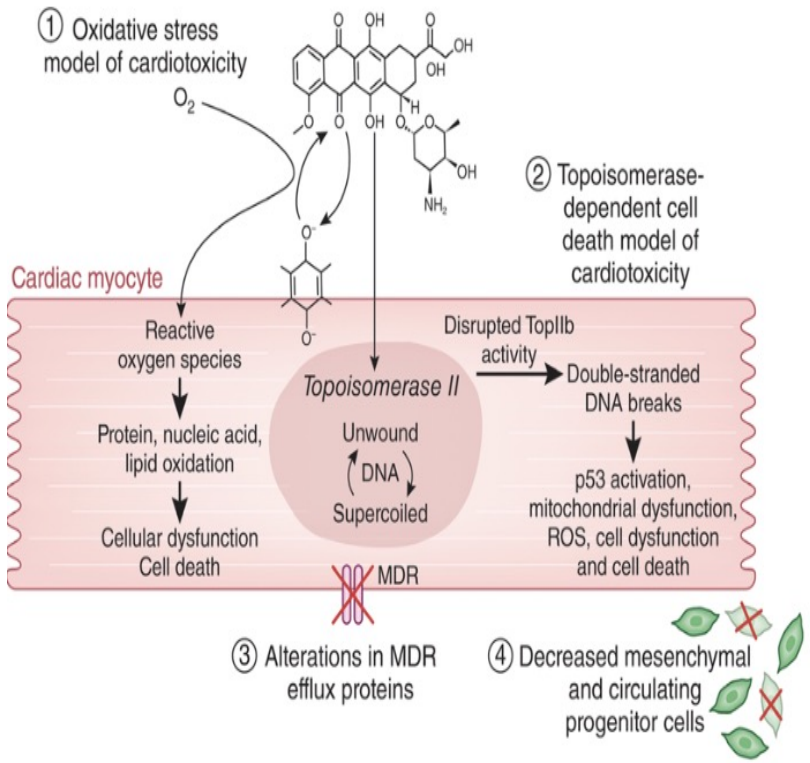
Anthracyclines



Agents: Daunorubicin, Doxorubicin, Doxorubicin liposomal, Epirubicin, Idarubicin, Mitoxantrone

Pharmacologic Category: Topoisomerase II Inhibitor

Mechanism of Action:

- Through the Topoisomerase Inhibition the DNA breaks and the ligase repair mechanism is prevented
- Disrupt DNA and RNA synthesis by intercalating in base pairs

CV Toxicities:

- Left Ventricular Systolic Dysfunction
- Heart Failure

Doxorubicin [prescribing information]. March 2020.

Anthracyclines

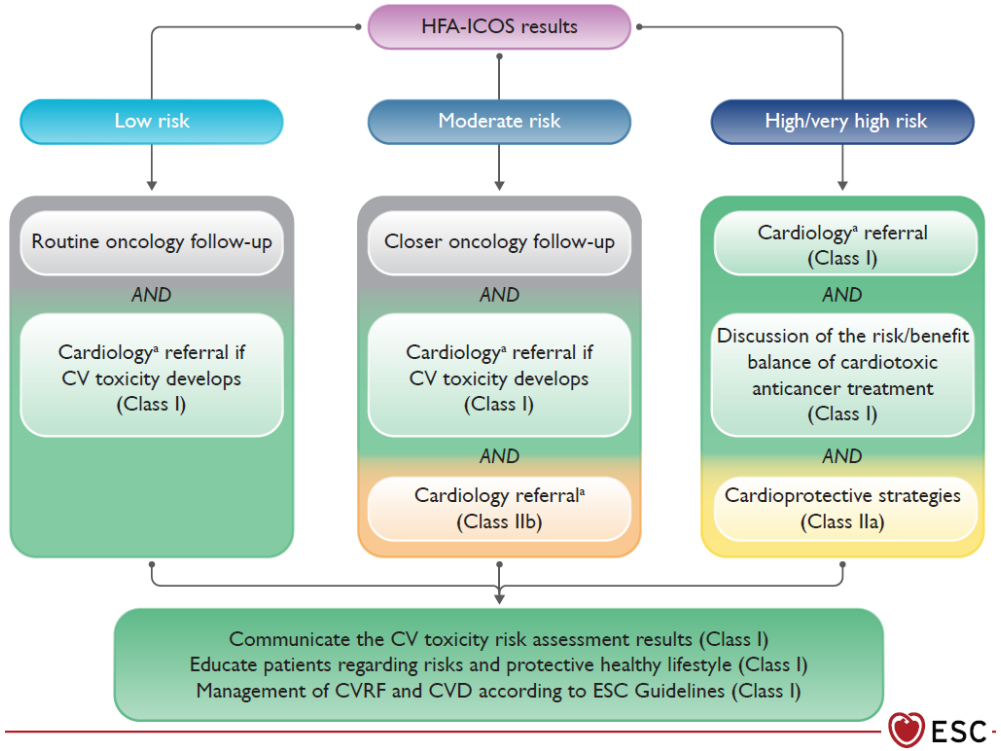
Anthracycline	Maximum cumulative dose	Incidence of cardiotoxicity	Suggested monitoring threshold
Doxorubicin	500mg/m2-21 day 700mg/m2-weekly	400mg/m2-3% 500mg/m2-7% 700mg/m2-18%	>250mg/m2
Daunorubicin (non liposomal)	400-550mg/m2-adults 300mg/m2->2YO 10mg/kg-<2YO	450-550mg/m2-11%*	>200mg/m2
Epirubicin	900,g/m2	550mg/m2-0.9% 700mg/m2-1.6% 900mg/m2-3.3%	600mg/m2
Idarubicin	150mg/m2	150-290mg/m2-5%	150mg/m2
Mitoxantrone	140mg/m2	140mg/m2-2.6%	N/A
Pegylated Liposomal Doxorubicin	No lifetime maximum dose has been established >900mg/m2	>500-550mg/m2-11% 500-1450mg/m2-1% (n=34)	N/A

	Doxorubicin	Daunorubicin	Epirubicin	Idarubicin	Mitoxantrone
CV toxicity dose ratio	1	0.6	0.8	5	10.5
Isoequivalent dose	100 mg/m2	167 mg/m2	125 mg/m2	20 mg/m2	9.5 mg/m2

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Anthracycline Risk Stratification

- Very High Risk
  - Heart Failure, Cardiomyopathy, Cancer Therapy-Related Cardiac Dysfunction (before treatment initiation)
- High Risk
  - Severe Valvular Heart Disease
  - MI or PCI or CABG history
  - Stable Angina
  - LVEF <50%
  - Age >80YO
  - Previous anthracycline exposure
  - Previous RT to left chest or mediastinum
- Moderate Risk
  - LVEF 50-54%**
  - Elevated baseline cardiac troponins*
  - Elevated baseline Natriuretic peptides*
  - Age 65-79YO**
  - Hypertension*
  - CKD*
  - Diabetes Mellitus*
  - Smoke or significant smoking history*
  - Obesity (BMI >30 Kg/m2)*
  - Previously non-anthracycline based treatment*



Low Risk = no risk factors or one moderate risk factor→*
Moderate risk = 2-4 points
High Risk = moderate risk factors total of ≥5 points or any high-risk factor
Very High Risk = any very-high risk factor

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Anthracycline Monitoring Protocol

	Low Risk	Moderate Risk	High and Very High Risk
ECG	**Baseline**	**Baseline**	**Baseline**
TTE	**Baseline** **Cycle 4** **12 months post treatment**	**Baseline** **Cycle 4** **12 months post treatment**	**Baseline** **Every 2 cycles** **3- & 12-months post treatment**
cTn/NP	**Baseline** **Every 2 cycles** **3 months post treatment**	**Baseline** **Every 2 cycles** **3 months post treatment**	**Baseline** **Every cycles** **3- & 12-months post treatment**

In moderate and low risk patients, additional echocardiography should be considered after cumulative dose of ≥250 mg/m2 of doxorubicin or equivalent (Class IIa)

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Primary Prophylaxis
Dexrazoxane

FDA Indication: Approved to reduced cardiomyopathy in patients with cumulative doses of 300mg/m2 and who will continue to receive doxorubicin therapy

Dosing: Ratio of 10:1 Dexrazoxane:Doxorubicin

Administration: 15 minutes before the administration of doxorubicin. Start doxorubicin within 30 minutes of completion of Dexrazoxane infusion

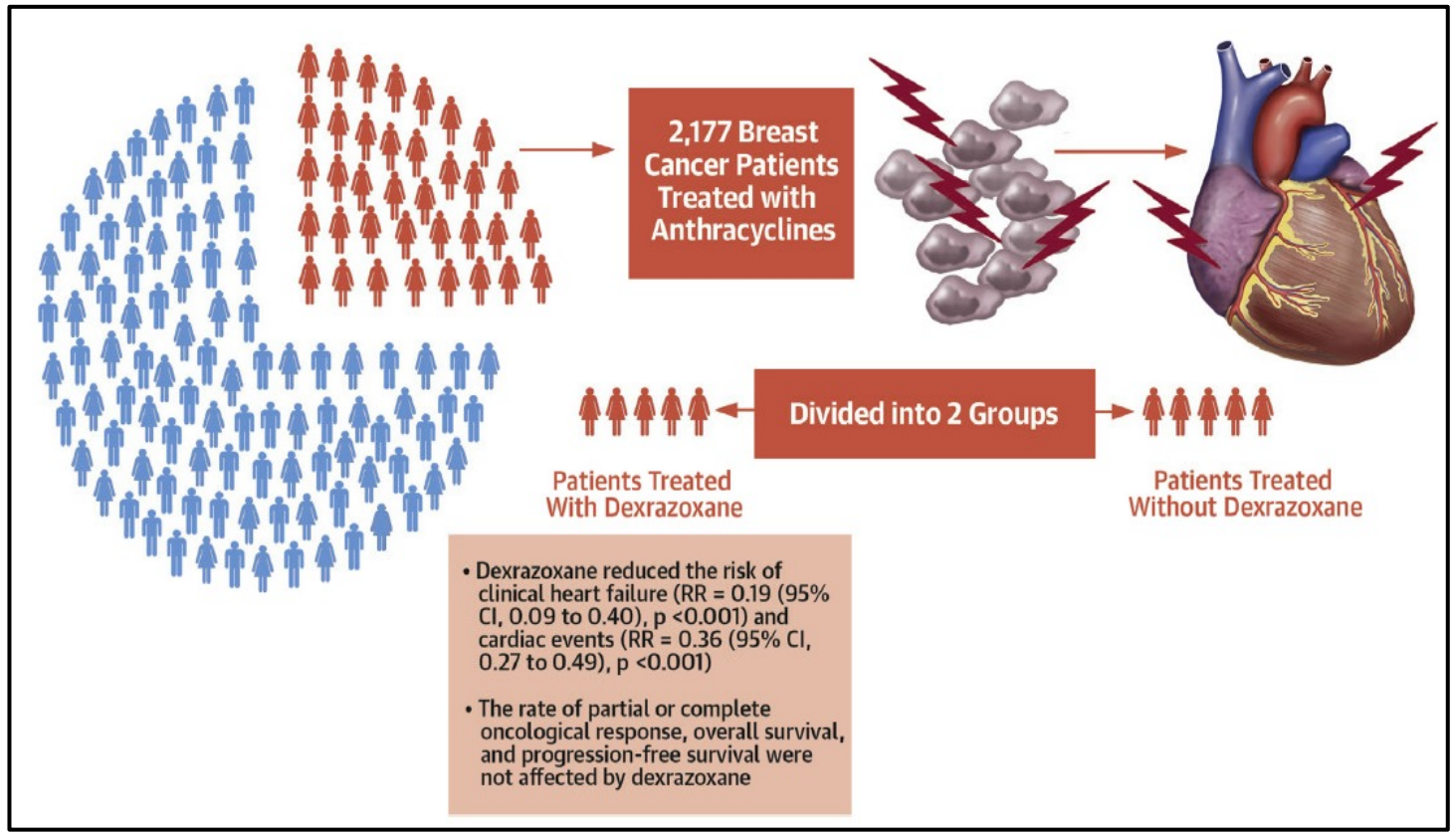
Adjustments: Reduce dose by 50% in patients with CrCl<40ml/min

MOA: Iron chelation, catalytic inhibition and depletion of topoisomerase II

Dexrazoxane (package insert). 2016

Dexrazoxane in Breast Cancer Patients

Trial design	Study population
Systematic review and meta-analysis was conducted for clinical trials on the use of dexrazoxane for the prevention of cardiotoxicity; N=2,177	Patients with breast cancer receiving anthracyclines with or without trastuzumab



Macedo, A.V.S. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):68–79.

Cardioprotective Strategies

Category	Agent	MOA	Study	Population	Intervention	Results
Beta Blocker	Carvedilol	Antioxidant activity preventing mitochondrial damage	Huang S. Heart Fail Rev. 2019	10 studies, 775 patients who received anthracyclines, LVEF >50%, no history of HF or coronary condition.	Carvedilol (different doses-meta-analysis)	Exerts no impact on early asymptomatic LVEF decrease, but seemingly attenuates the frequency of cardiotoxicity and prevents ventricular remodeling
	Carvedilol	As above	Nabati M. J Cardiovascular Pharmacol 2017	91 patients recently diagnosed with breast CA	Carvedilol 25mg BID	No increase in left ventricular end systolic volume, left atrial diameter, pulmonary vein peak atrial reversal velocity, no change in troponins
	Nebivolol	Antioxidant activity preventing mitochondrial damage	Kaya MG. Int J Cardiology. 2013	45 breast CA patients receiving AC or CEF	Bisoprolol 5mg starting 1 wk prior to treatment until 6 months later	Prophylactic nebivolol treatment may protect the myocardium against anthracycline-induced cardiotoxicity in BC patients
ACEi/ARBi	Enalapril	Free radical scavenger, and RAS inhibition	Cardinale D. Circulation. 2006	114 patients with elevated troponin I increased after HDC	Enalapril 20mg 1 month after HDC and continued for 1 yr	In high-risk patients, defined by an increased troponin I value, early treatment with enalapril seems to prevent the development of late cardiotoxicity
	Valsartan	RAS inhibitor	Nakamae. Cancer. 2005	40 patients with NHL, tx with CHOP	Valsartan 80mg daily	Prevented the acute CHOP induced cardiotoxicity (increased left ventricular end diastolic diameter, QTc interval)

Cardioprotective Strategies

Category	Agent	MOA	Study	Population	Intervention	Results
K sparing diuretics	Spironolactone	RAS inhibition	Akpek. Eurioean J of HF. 2015	84 BC patients	Spironolactone 25mg daily started 1 wk before and continued 3 wks after	Spironolactone used concomitantly with anthracycline protects both myocardial systolic and diastolic functions through its antioxidant effect
	Eplerenone	RAS inhibition	Davis MK. J American College of Cardiology. 2019	41 anthracycline naïve women ≥ 19YO, normal LV function, K <5, and SI-III BC, to initiate doxorubicin-based treatment with curative intent	Eplerenone 50mg daily started 2 days before treatment	Eplerenone did not show a significant impact on systolic or diastolic function.
Combinations	Candesartan vs Metoprolol	As described for each category	Gulati G. European Heart J. 2019	120 patients with early BC, tx with Epirubicin (FEC)	Candesartan 32mg + metoprolol succinate 100mg (n=32); candesartan 32mg (n=33) or metoprolol succinate 100mg (n=32)	Metoprolol succinate: No short-term beneficial effect was observed. Candesartan: Significantly alleviated the decline in LVEF (prevention of remodeling), no benefit in right ventricular EF, left ventricular GLS, cardiac troponin (no benefit on prevention direct cardiotoxicity)
	Carvedilol + Enalapril	As described for each category	Bosch B. J Am Coll Cardiol. 2013	90 patients recently diagnosed with ALL, or pt undergoing HSCT	Carvedilol 25mg BID + Enalapril 10mg BID starting >24 hours before chemo and continued for 6M	Prevent a decline in left ventricular systolic dysfunction in patients treated with intensive chemotherapy
	Carvedilol vs Lisinopril	As described for each category	Guglin M. J Am Coll Cardiol. 2019	468 patients who previously received anthracyclines followed by trastuzumab x1yr	Carvedilol E, Lisinopril , both 10mg QD	Comparable cardiotoxicity between intervention vs placebo groups; however, cardiotoxicity free survival was greater in treatment groups, as well as less treatment interruptions

The OVERCOME trial

Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies

- Randomized, controlled trial
- Study population: 90 patients with hematological malignancies undergoing chemotherapy and/or autologous hematopoietic stem cell transplantation (HSCT)
- Interventions: Carvedilol 25mg BID and Enalapril 10mg BID starting ≥24 hours before chemo and continued for 6 months

Clinical Endpoints

	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45% (%)	3 (6.7)	11 (24.4)	0.020
≥10% decrease in LVEF with a final LVEF<50% (%)	2 (4.8)	2 (5.4)	0.90
Heart failure or ≥10% decrease in LVEF (%)	4 (9.5)	7 (19)	0.22
Severe adverse events* (%)	9 (20)	15 (33)	0.15

Values are n (%).

LVEF = left ventricular ejection fraction.

* Defined as a serious adverse event that resulted in death or was life-threatening.

Conclusion: The combination of enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with high-dose chemotherapy regimens. In addition, clinical events were less frequent in patients treated with the cardioprotective drugs.

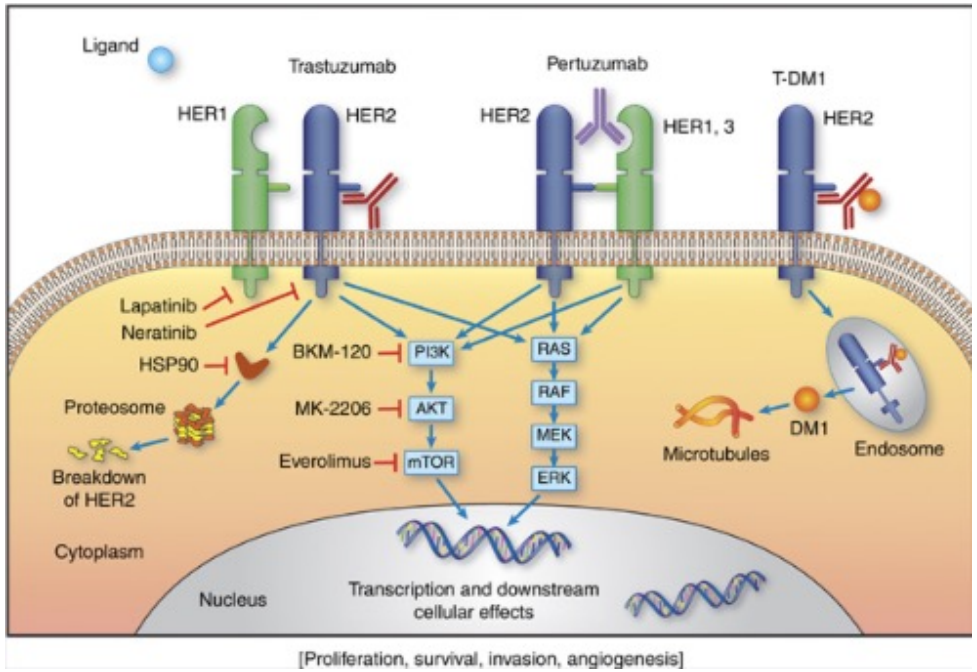
Bosch X, . et al. J Am Coll Cardiol. 2013;61(23):2355–62.

Cardiotoxic Chemotherapies

- Anthracyclines
- **Human epidermal growth factor-2 inhibitor ($HER2_i$)**
- Proteasome Inhibitors
- Tyrosine Kinase Inhibitors
- Antimetabolites

HER-2 Targeted Therapy

HER-2 TT Mechanism of Action:



Agents: Ado-Trastuzumab Emtansine*, Fam-Trastuzumab Deruxtecan*, Lapatinib**, Neratinib**, Pertuzumab, Trastuzumab, Margentuximab

Pharmacologic Category: anti HER-2 agents

*Antibody-drug conjugate

**EGFR Tyrosine Kinase Inhibitor

Mechanism of Action:

- Humanized monoclonal antibodies that block the activation of specific growth factors with the HER2/neu receptor
- Disrupt the phosphorylation of intracellular tyrosine kinases that are critical regulators of cell growth and survival

CV Toxicities:

LVSD and HF

Ado-Trastuzumab Emtansine (package insert). 2013
Fam-Trastuzumab Deruxtecan (package insert). 2019
Pertuzumab (package insert). 2012
Trastuzumab (package insert). 1998
Neratinib (package insert). 2017
Lapatinib (package insert). 2007

HER2i

Agents	Continue	Hold	Stop
Ado-Trastuzumab Emtansine	LVEF ≥50% (EBC) LVEF ≥45% (MBC)	EBC: LVEF 45% to <50% and decrease is ≥10% points from baseline→ withhold treatment and repeat ECHO within 3 weeks LVEF<45%→withhold treatment and repeat ECHO within 3 weeks MBC: LVEF 40% to ≤45% and decrease is ≥10% points from baseline→ withhold treatment and repeat ECHO within 3 weeks LVEF<40%→withhold treatment and repeat ECHO within 3 weeks	Symptomatic HF grade 3 to 4 LVEF dysfunction, grade 3 to 4 heart failure, or grade 2 heart failure with LVEF <45% (EBC) After holding treatment repeated ECHO shows LVEF not recovered (EBC & MBC) Symptomatic HF (MBC)
Fam-Trastuzumab Deruxtecan	LVEF >45% and absolute decrease from baseline 10-20%	LVEF 40-45% and absolute decrease from baseline 10-20%→withhold treatment and repeat ECHO within 3 weeks LVEF <40% or absolute decrease >20%→ withhold treatment and repeat ECHO within 3 weeks	After holding treatment repeated ECHO shows LVEF not recovered Symptomatic Heart Failure
Pertuzumab	LVEF >55% or >50% after anthracycline therapy (EBC) LVEF ≥50% (MBC)	LVEF <50% with >10% points from baseline→ withhold treatment and repeat ECHO in 3 weeks LVEF <40% or LVEF 40-45% with ≥10% points from baseline→ withhold treatment and repeat ECHO in 3 weeks	After holding treatment repeated ECHO shows LVEF not recovered (EBC)

Ado-Trastuzumab Emtansine (package insert). 2013
Fam-Trastuzumab Deruxtecan (package insert). 2019
Pertuzumab (package insert). 2012

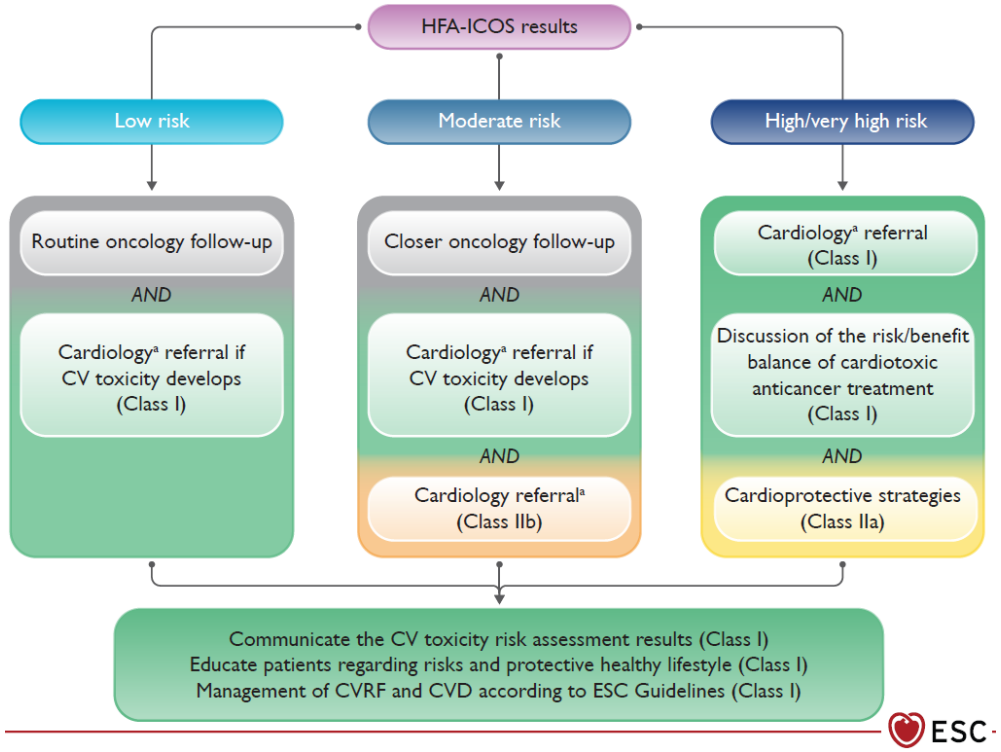
HER2i

Agents	Continue	Hold	Stop
Trastuzumab	Referred to PI	LVEF ≥16% decrease from baseline or LVEF below normal limits and ≥10% decrease from baseline→ withhold treatment, repeat ECHO at 4 weeks	Persistent (>8 weeks) LVEF decline or for >3 incidents of treatment interruptions for cardiomyopathies
Neratirib	N/A	N/A	N/A
Lapatinib	Referred to PI	LVEF < lower limit of normal or ≥ grade 2→ withhold for at least 2 weeks and repeat ECHO	After holding treatment repeated ECHO shows LVEF not recovered
Margentuximab-cmkb	ECHO at normal limit or absolute decrease from baseline ≤15% within 8 weeks	LVEF ≥16% decrease from baseline, or below <50% or institutional value AND ≥10% absolute decrease→ hold treatment, repeat ECHO at 4 weeks	LVEF decline persists for >8 weeks, or if dosing is interrupted for LVEF decline on more than 3 occasions

Trastuzumab (package insert). 1998
Neratinib (package insert). 2017
Lapatinib (package insert). 2007
Margentuximab (package insert). 2020

HER2i Risk Stratification

- Very High Risk
  - Heart Failure, Cardiomyopathy, Cancer Therapy-Related Cardiac Dysfunction (before treatment initiation)
  - Previous treatment with trastuzumab
- High Risk
  - Severe Valvular Heart Disease
  - MI or PCI or CABG history
  - Stable Angina
  - LVEF <50%
  - Age >80YO
- Moderate Risk
  - Arrhythmia**
  - LVEF 50-54%**
  - Elevated baseline troponins**
  - Elevated baseline natriuretic peptides**
  - Age 65-79 YO**
  - Hypertension*
  - CKD*
  - Diabetes Mellitus*
  - Anthracycline prior HER2i*
  - Prior RT to chest of mediastinum**
  - Current smoker or significant history of smoking*
  - Obesity (BMI > 30kg/m2)*



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Moderate risk = 2-4 points
High Risk = moderate risk factors total of ≥5 points or any high-risk factor
Very High Risk = any very-high risk factor

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

HER2i Monitoring Protocol

	Low and Moderate Risk	High and Very High Risk
ECG	**Baseline**	**Baseline**
TTE	**Baseline** **Every 3 months** **12 months post treatment**	**Baseline** **Every 3 months** **3- & 12-months post treatment**
cTn/NP	**Baseline** **Every 3 months** **12 months post treatment**	**Baseline** **Every 3 months** **3- & 12-months post treatment**

In low-risk HER2 and early breast cancer patients who are asymptomatic and with a normal assessment after 3 months, reducing monitoring to every 4 months may be considered (Class IIb)

In metastatic HER2, echocardiography is recommended every 3 months during the first year; if the patient remains asymptomatic without CV toxicity, surveillance can be reduced to every 6 months during future treatment (Class I)

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Cardioprotective Strategies

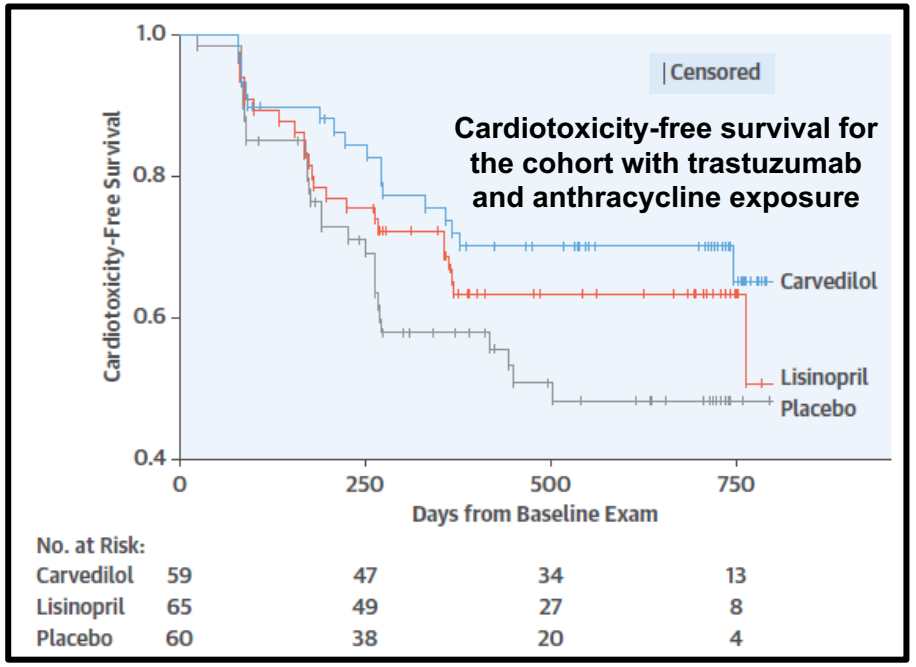
Category	Agent	MOA	Study	Population	Intervention	Results
Combination	Carvedilol vs Lisinopril vs placebo	Beta Blocker ACEi	Guglin M.J Am Coll Cardiol. 2019	HER2-positive breast cancer patients treated with trastuzumab for 1 year and with previous anthracycline use (n=468)	Carvedilol XR or Lisinoprol 10 mg QD vs placebo	Comparable cardiotoxicity among arms placebo vs carvedilol vs lisinopril Cardiotoxicity free survival was longer on carvedilol and lisinopril than on placebo leading to less treatment interruptions
	Perindopril vs Bisoprolol vs placebo	ACEi Beta Blocker	Manticore 101 (Pituskin. J Clin Oncol)	Newly diagnosed HER2 early breast cancer	Perindopril 8mg daily Bisoprolol 10mg daily Placebo	No difference in LVDF, but lower mean change in LVEF in the bisoprolol arm vs placebo vs perindopril
	Candesartan vs placebo	ARB	Beokhout et al (JAMA Oncol 2016)	HER2 positive early breast cancer	Candesartan 32mg daily	No effect

Benefits of anti-hypertensives

Lisinopril vs Carvedilol to Prevent Trastuzumab Cardiotoxicity in Patients with Breast Cancer

- Double-blind, multicenter, placebo-controlled trial
- Study population: HER2(+) breast cancer patients treated with trastuzumab for 12 months
  - Stratified by anthracycline use
- Interventions: Lisinopril 10 mg daily, carvedilol XR 10 mg daily, or placebo

Conclusion: In patients with HER2(+) breast cancer treated with trastuzumab, both lisinopril and carvedilol prevented cardiotoxicity in patients receiving anthracyclines.



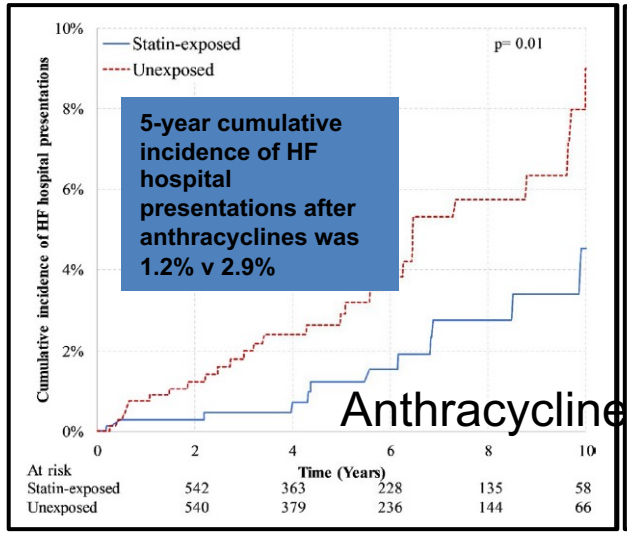
Hazard ratio for development of cardiotoxicity was **0.49** (0.27 to 0.89) for **carvedilol (p= 0.009)** and **0.53** (0.30 to 0.94) **for lisinopril (p= 0.015)**

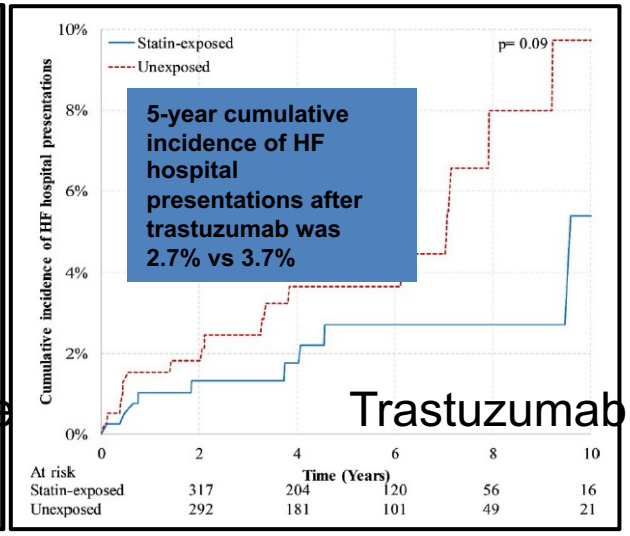
Guglin, M. et al. J Am Coll Cardiol. 2019;73(22):2859–68.

Benefits of statins

Statin Exposure and Risk of Heart Failure after Anthracycline- or Trastuzumab-Based Chemotherapy

- Propensity Score–Matched Cohort Study
- Study population: women aged ≥66 years without prior HF
  - Received anthracyclines or trastuzumab for newly diagnosed early breast cancer
  - Stratified by statin-exposed v unexposed





Conclusion: Statin-exposed women had a lower risk of HF hospital presentations after early breast cancer chemotherapy involving anthracyclines, with non-significant trends towards lower risk following trastuzumab

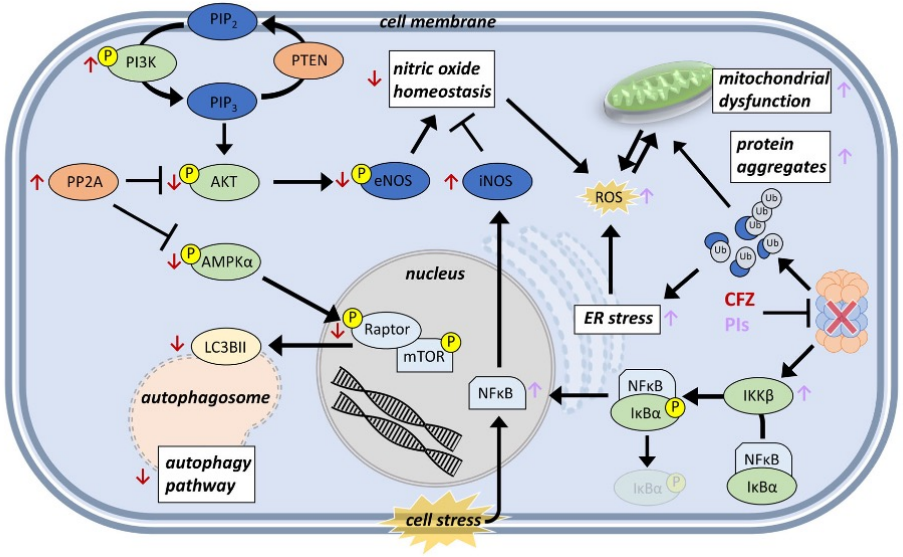
Abdel-Qadir H, Bobrowski D, Zhou L, et al. J Am Heart Assoc. 2021;10:e018393.

Cardiotoxic Chemotherapies

- Anthracyclines
- Human epidermal growth factor-2 inhibitor ($HER2_i$)
- **Proteasome Inhibitors**
- Tyrosine Kinase Inhibitors
- Antimetabolites

Proteasome Inhibitors

PI Mechanism of Action:



Agents: Bortezomib, Carfilzomib, Ixazomib

Pharmacologic Category: Proteasome Inhibitors

Mechanism of Action:
The barrel shape 20S catalytic core particle of the proteasome degradation complex comprise 4 heptameric rings, with 2 internal beta rings containing proteasome active sites comprised proteolytic subunits. These subunits have capase-like activity, trypsin-like activity, and chymotrypsin-like activity, and mediate proteolytic cleavage

CV Toxicities:
LVSD, HF, arterial hypertension, and myocardial ischemia

Bortezomib (package insert). 2003
Carfilzomib (package insert). 2012
Ixazomib (package insert). 2015

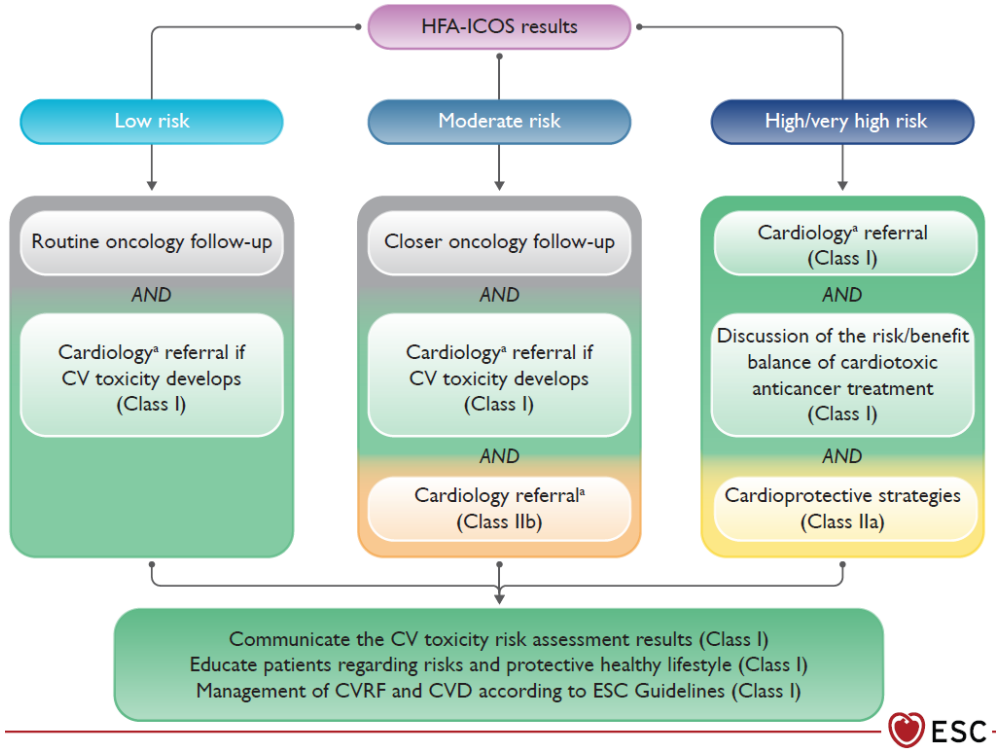
Proteasome Inhibitors

Agents	Approval	Cardiac monitoring per PI	Cardiac monitoring per ESMO 2020
Bortezomib	Cardiac transplantation, T-cell lymphoma, Follicular and Mantle cell lymphoma, Multiple Myeloma, amyloidosis, Waldenstrom's macroglobulinemia	None	Baseline evaluation: Clinical, EKG, TTE with GLS, BP, cTn or NP in high-risk patients, manage modifiable risk factors, LVEF <50% but ≥40%--ACE, ARB and or BB In normal EF and CV risk factors—prophylactically use ACE, ARB or BB Monitoring: Serial BP, cardiac biomarkers, cardiac imaging. If clinical s/s of HF—cardio consult with reassessment of LVEF and cardiac biomarkers, manage modifiable risk factors. Posts Treatment: In asymptomatic with normal cardiac function—periodic consultation, EKG, TTE with GLS at 6-12 months, and 2 years post treatment, manage modifiable risk factors
Carfilzomib	Multiple Myeloma, Waldenstrom's macroglobulinemia	-BP throughout treatment -S/S of HF: Grade 3 or 4, new onset or worsening of HF, decrease LVEF, or myocardial ischemia: withhold dose	
Ixazomib	Multiple Myeloma	None	

Alexandre J, Cautela J, Ederhy S, et al. J Am Heart Assoc. 2020 Sep 15;9(18):e018403.

Multiple Myeloma Risk Stratification

- Very High Risk
  - Heart Failure, Cardiomyopathy, Prior PI cardiotoxicity, Venous Thrombosis (VTE or PE), Cardiac Amyloidosis, Arterial Vascular Disease (IHD, PCI, CBG, Stable angina, TIA, Stroke, PVD)
- High Risk
  - Prior Immunomodulatory drug use
  - Baseline LVEF <50%
  - Elevated baseline BNP or NT-proBNP
  - Age ≥75
  - Prior anthracycline exposure
- Moderate Risk
  - Arrhythmia**
  - LVEF 50-54%**
  - LV hypertrophy*
  - Elevated baseline troponins**
  - Age 65-74 YO*
  - Hypertension*
  - Diabetes Mellitus*
  - Hyperlipidemia*
  - CKD*
  - Family history of thrombophilia*
  - Prior thoracic spine RT*
  - High dose dexamethasone >160mg/month*
  - Current smoker or significant smoking history*
  - Obesity (BMT >30kg/m2)*



Low Risk = no risk factors or one moderate risk factor→*
Moderate risk = 2-4 points
High Risk = moderate risk factors total of ≥5 points or any high-risk factor
Very High Risk = any very-high risk factor

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Proteasome Inhibitors monitoring Protocol

	Low-Moderate Risk	High and Very High Risk	Cardiac Amyloidosis
BP and ECG	**Baseline** **BP at every clinical visit and home**	**Baseline** **BP at every clinical visit and home**	**Baseline** **BP at every clinical visit and home**
TTE	**Baseline** **Every 3 cycles under Carfilzomib**	**Baseline** **Every 3 cycles under Carfilzomib**	**Baseline TTE and CMR** **Every 3 cycles**
cTn/NP	**Baseline NP** **NP every cycle during the first 6 cycles under IV PI**	**Baseline NP** **NP every cycle during the first 6 cycles under IV PI**	**Baseline NP & cTn** **NP and cTn every 3-6 months**
Clinical Assessment	**Baseline and During Therapy**	**Baseline and During Therapy**	**Baseline and During Therapy**

Therapeutic doses of LMWH are recommended in patients with MM with previous VTE (Class I)

Prophylactic doses of LMWH are recommended in patients with MM with VTE-related risk factors (excluding previous VTE) at least during the firs 6 months of therapy (Class I)

Acetylsalicylic acid should be considered an alternative to LMWH in patients with MM wit no risk factors or one VTE-related factor (excluding previous VTE) at least during the first 6 months of therapy (Class IIa)

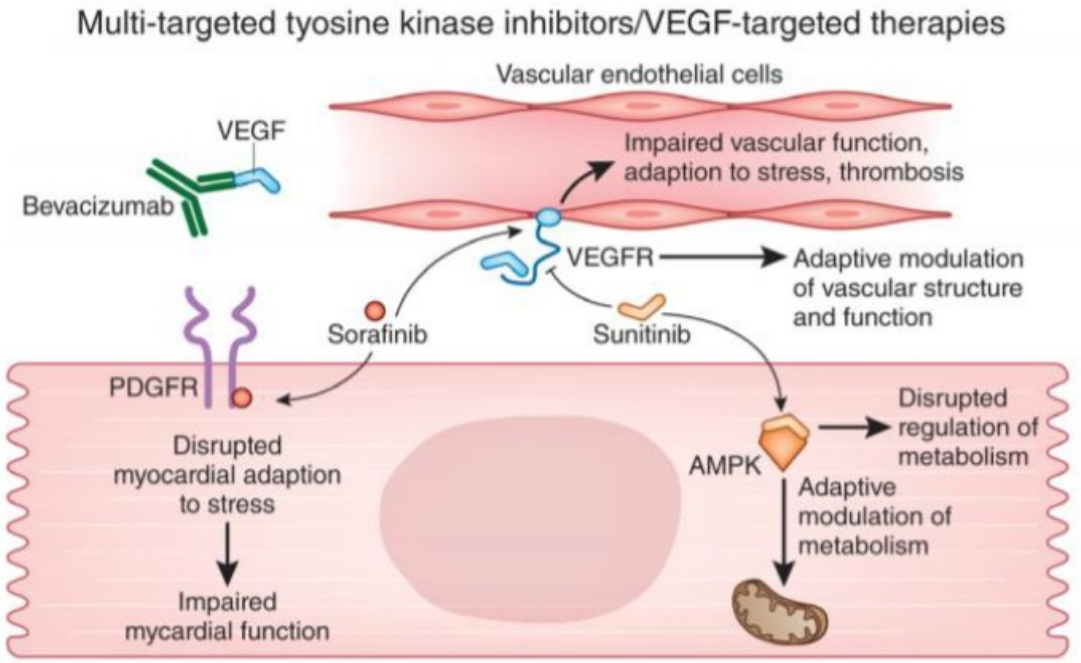
Low doses of apixaban or rivaroxaban may be considered as an alternative to LMWH or acetylsalicylic acid in patients with MM with VTE-related risk factors (excluding previous VTE) at least during the first 6 months of therapy (Class IIb)

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Cardiotoxic Chemotherapies

- Anthracyclines
- Human epidermal growth factor-2 inhibitor ($HER2_i$)
- Proteasome Inhibitors
- **Tyrosine Kinase Inhibitors**
- Antimetabolites

Vascular Endothelial Growth Factor Inhibitor (VEGFi-TKI)



Agents: Sunitinib, sorafenib, pazopanib, cabozatinib, lenvatinib, vandetanib, axitinib, regorafenib, tivozanib

Pharmacologic Category: VEGFi TKI

Mechanism of Action:

Exhibit antitumor and antiangiogenic properties

CV Toxicities:

MI, HTN, LVSD, QTc prolongation, arterial thromboembolic events- within days from treatment initiation

LennemanCG. CircRes. 2016

Alexandre J, Cautela J, Ederhy S, et al. J Am Heart Assoc. 2020 Sep 15;9(18):e018403.

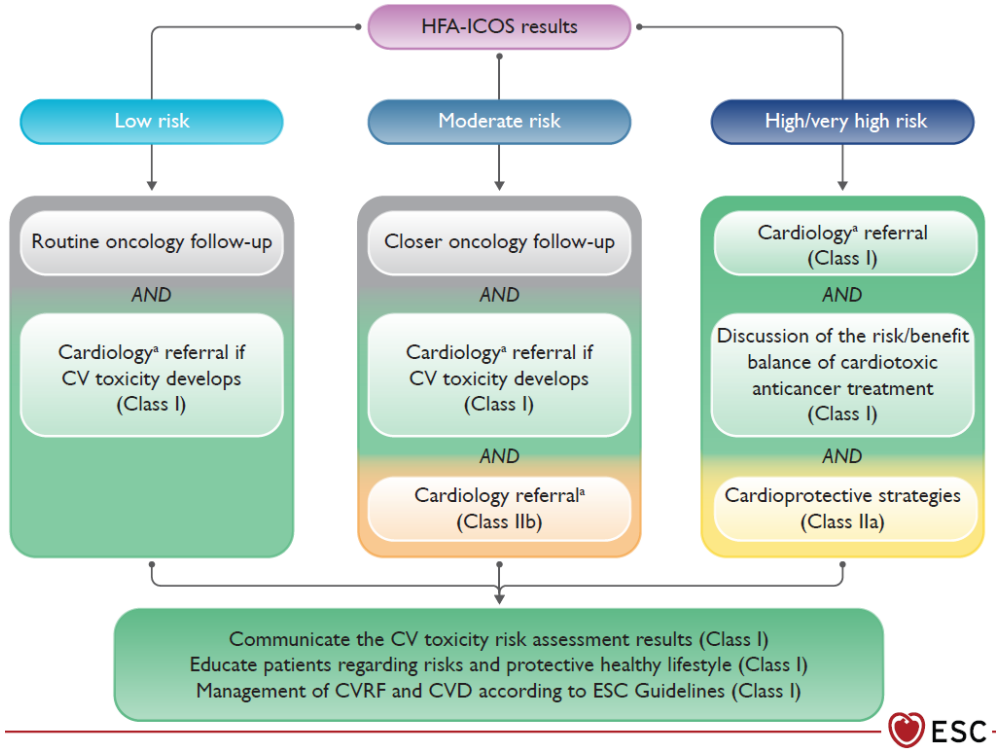
Sunitinib[prescribing information]. August 2020.

VEGFi-TKI
Risk Stratification

- Very High Risk
  - Heart Failure, Cardiomyopathy, Arterial Vascular Disease (IHD, PCI, CBG, Stable angina, TIA, Stroke, PVD)

- High Risk
  - Venous Thrombosis (DVT or PE)
  - QTc ≥480 ms
  - LVEF <50%
  - Age >75
  - Hypertension
  - Prior anthracycline exposure

- Moderate Risk
  - 450ms ≤QTc<480ms (men)**
    460ms ≤QTc<480ms (women)**
  - Arrhythmia**
  - LVEF 50-54%**
  - Elevated cTn or proBNP*
  - Age 65-74*
  - DM*
  - Hyperlipidemia*
  - CKD*
  - Proteinuria*
  - Prior RT to left chest or mediastinum*
  - Current smoker or significant smoking history*
  - Obesity (BMT >30 kg/m2*



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Very High Risk = any very-high risk factor

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

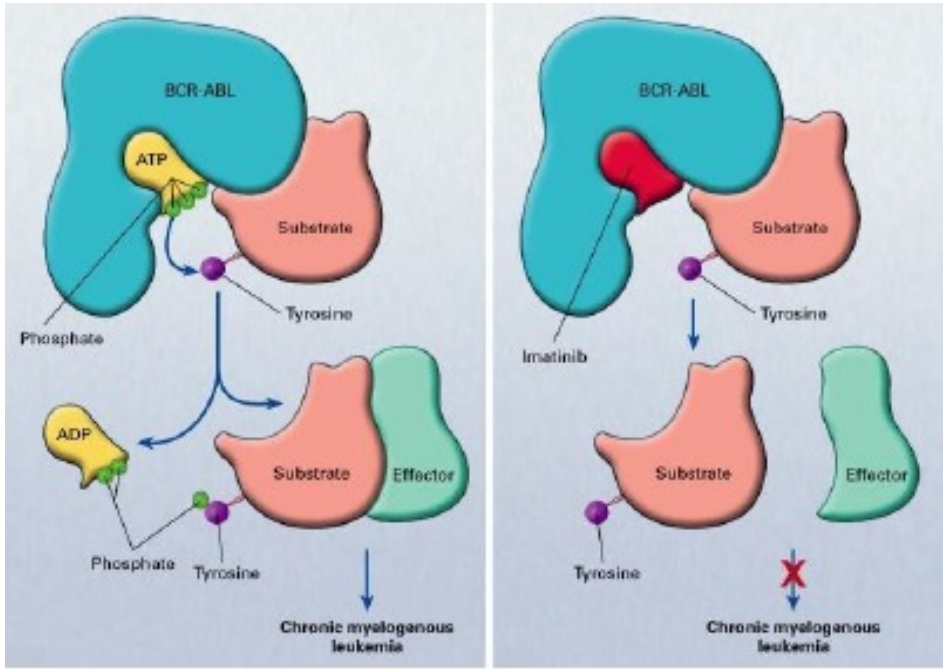
VEGFi TKI monitoring Protocol

	Low Risk	Moderate Risk	High and Very High Risk
ECG	**Baseline**	**Baseline**	**Baseline**
TTE	**Baseline**	**Baseline** **Every 4 months** **6-12 months post treatment**	**Baseline** **Every 3 months** **6-12 months post treatment**
NP		**Baseline** **Every 4 months**	**Baseline** **4 weeks after starting treatment, and every 3 months**
BP	BP is recommended at every clinical visit Daily home monitoring of BP during the first cycle, after each increase of VEGFi TKI dose, and every 2-3 weeks thereafter		

If moderate or high risk of QTc prolongation, monitoring is recommended monthly during the firsts 3 months and every 3-6 months thereafter (Class I)

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Breakpoint Cluster Region-Abelson Oncogene locus TKI (BCR-ABL TKI)



Agents: Imatinib, Nilotinib, Dasatinib, Bosutinib, Ponatinib

Pharmacologic Category: BCR-ABL TKI

Mechanism of Action:

Inhibit BCR-ABL tyrosine kinase by blocking the proliferation and inducing the apoptosis in BCR-ABL positive cell lines

CV Toxicities:

Atherosclerosis, PAD development, ACS, stroke, HTN, hyperglycemia, hypercholesterolemia, pericardial effusion, PAH, QTc prolongation, and occasionally LVSD

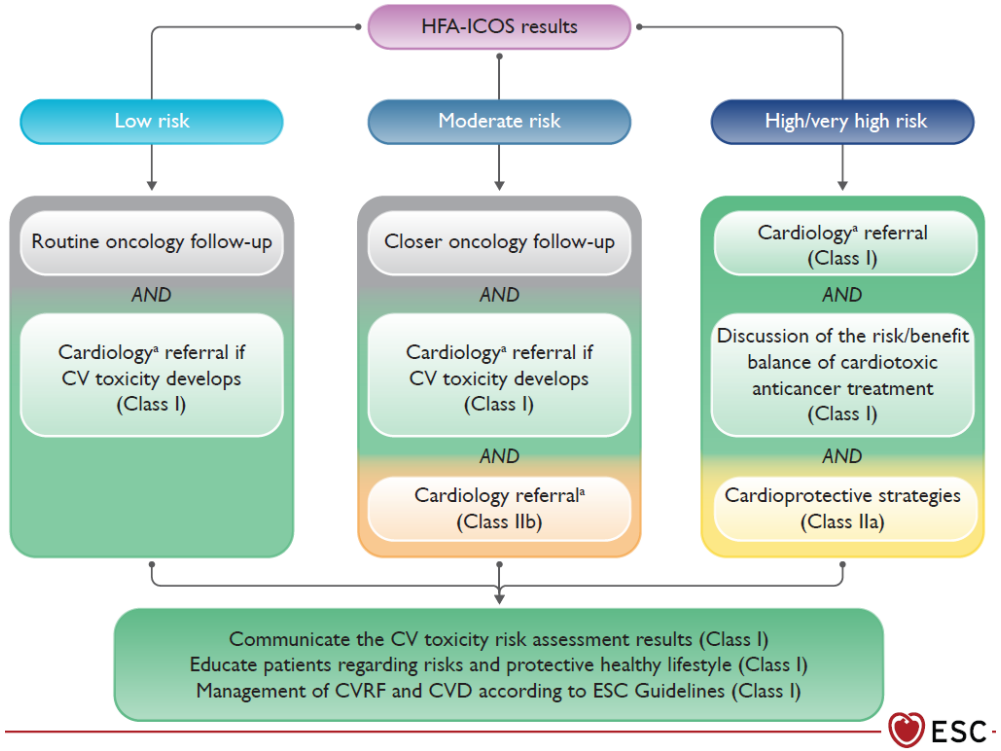
Severe peripheral atherosclerosis with nilotinib

Serious arterial thrombotic events with ponatinib*

Steegmann, J., Baccarani, M., Breccia, M. et al. Leukemia 30, 1648–1671 (2016).
Singh AP, Umbarkar P, Tousif S, et al. Int J Cardiol. 2020 Oct 1;316:214-221.
Imatinib [prescribing information]. August 2020.
Bosutinib [prescribing information]. June 2020.

BCR-ABL TKI Risk Stratification

- Very High Risk
  - Arterial Vascular Disease (IHD, PCI, CBG, Stable angina, TIA, Stroke, PVD), arterial thrombosis with TKI
- High Risk
  - HF or LVSD
  - BCR-ABL TKI-mediated LVSD
  - Abnormal ankle-brachial pressure index
  - PH
  - QTc ≥480ms
  - Baseline LVEF <50%
  - CVD 10-year score >20%
  - Age >75
  - Current smoker or significant smoking history
- Moderate Risk
  - VTE (DVT/PE)**
  - 450ms ≤QTc<480ms (men)**
    460ms ≤QTc<480ms (women)**
  - Arrhythmia**
  - Hypertension**
  - DM*
  - Hyperlipidemia*
  - Age 65-74**
  - Age >60*
  - CKD*
  - Family history of thrombophilia*
  - Obesity (BMT >30 kg/m2*



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Moderate risk = 2-4 points
High Risk = moderate risk factors total of ≥5 points or any high-risk factor
Very High Risk = any very-high risk factor

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

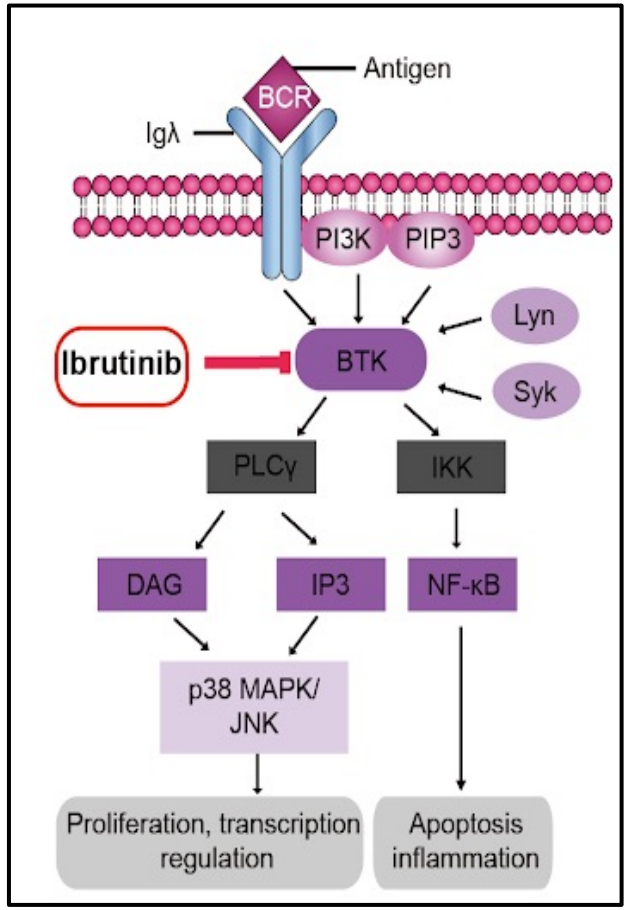
BCR-ABL TKI Monitoring Protocol

	Bosutinib	Dasatinib	Nilotinib	Ponatinib
Physical Examination	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**
BP	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**
ECG	**Baseline**	**Baseline**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**
Lipid profile/HbA1c			**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**	**Baseline** **Every 3M during the 1st year** **Every 6-12M thereafter**
Ankle-brachial Index			**Baseline** **6 and 12M during the 1st year** **Every 6-12M thereafter**	**Baseline** **6 and 12M during the 1st year** **Every 6-12M thereafter**
TTE	**Baseline**	**Baseline** **Every 3M during the 1st year in high and very high-risk patients** **Every 6-12M thereafter**	**Baseline**	**Baseline** **Every 3M during the 1st year in high and very high-risk patients** **Every 6-12M thereafter**

QTc measures should be considered at baseline, 2 and 4 weeks after starting nilotinib and 2 weeks after any dose increase (Class IIa)

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Bruton TKI



Agents: Ibrutinib, Acalabrutinib, Zanubrutinib

Pharmacologic Category: Bruton TKI

Mechanism of Action:
Irreversible inhibitor of Bruton's tyrosine kinase (BTK) → decreased malignant B-cell proliferation and survival

CV Toxicities:
Atrial fibrillation, hypertension, HF, ventricular arrhythmias, sudden cardiac death, and conduction disorders

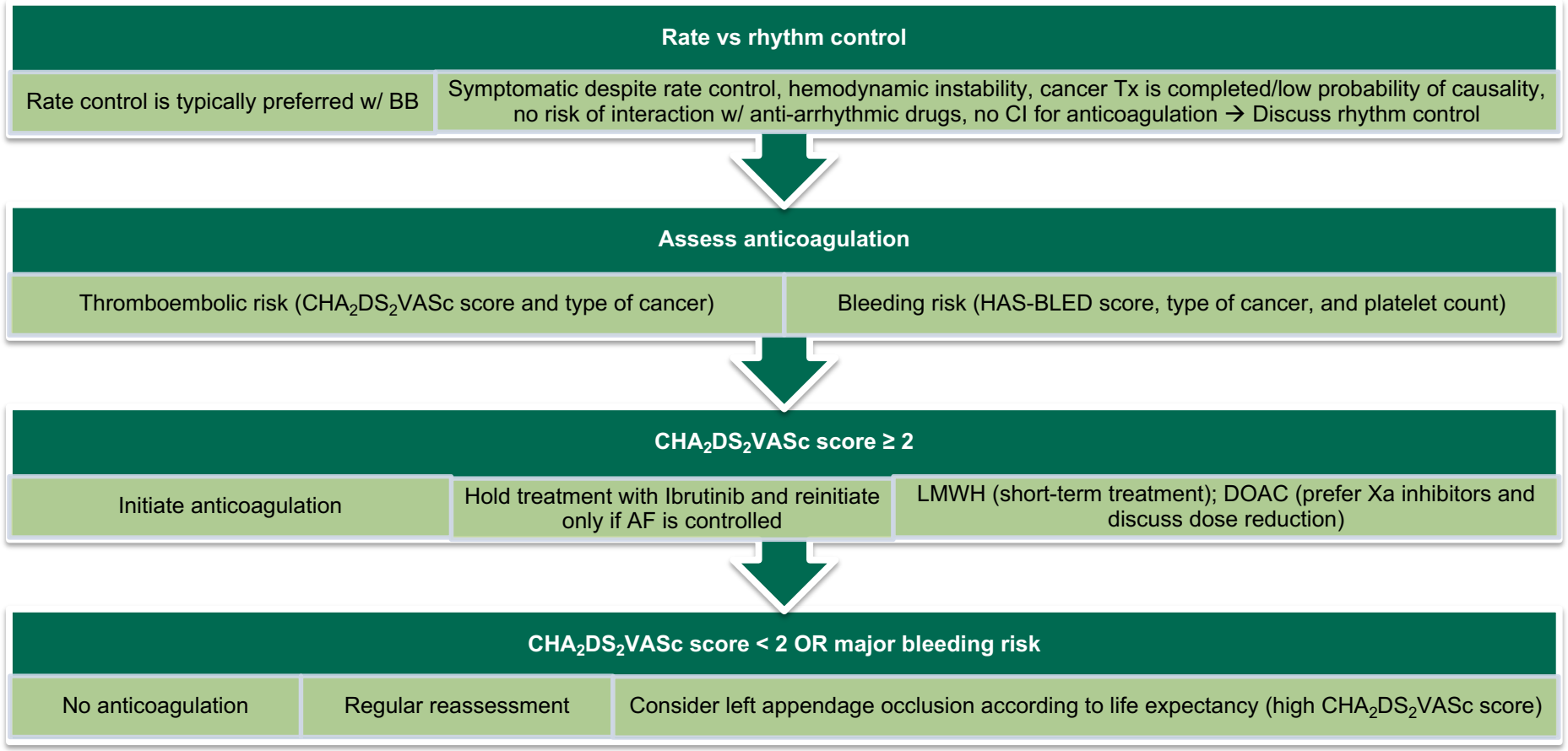
Alexandre J, Cautela J, Ederhy S, et al. J Am Heart Assoc. 2020 Sep 15;9(18):e018403.
Ibrutinib [prescribing information]. December 2020.

BTKI monitoring Protocol

	Low Risk	Moderate Risk	High and Very High Risk
BP	**Baseline** **BP at every clinical visit** **Weekly BP during the first 3 months and monthly thereafter**	**Baseline** **BP at every clinical visit** **Weekly BP during the first 3 months and monthly thereafter**	**Baseline** **BP at every clinical visit** **Weekly BP during the first 3 months and monthly thereafter**
TTE	**Monitoring recommended if AF develops during treatment**	**Monitoring recommended if AF develops during treatment**	**Baseline** **Monitoring recommended if AF develops during treatment**
ECG	**Baseline** **At every clinical visit**	**Baseline** **At every clinical visit**	**Baseline** **At every clinical visit**

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

Managing Ibrutinib AF



β-Blockers: metoprolol, sotalol atenolol and nebivolol; Avoid digoxin and CCB (verapamil, diltiazem), flecainide, propafenone, dofetilide, dronedarone, and amiodarone due to DDI

CHA2DS2-VASc & HAS-BLED scores have not been validated in patients with cancer

No anticoagulation if major bleeding risk or estimated life expectancy <3 months or thrombocytopenia < 50,000/mm^3

Alexandre J, Cautela J, Ederhy S, et al. J Am Heart Assoc. 2020 Sep 15;9(18):e018403.

Ibrutinib and Warfarin

- Increase risk of subdural hematoma in patients receiving Warfarin and Ibrutinib
  - Four patients had subdural hematomas (grade 1 in one patient, grade 2 in one, and grade 3 in two); the incidents were associated with falls and head trauma.

Table S2: Bleeding and Infectious Adverse Events (≥Grade 3)

	Grade 3	Grade 4	Grade 5	Overall
	n (%)			
Bleeding Event	**5 (5)**	**0 (0)**	**0 (0)**	**5 (5)**
Subdural hematoma	2 (2)	0 (0)	0 (0)	2 (2)
Hematuria	2 (2)	0 (0)	0 (0)	2 (2)
Lower gastrointestinal hemorrhage	1 (1)	0 (0)	0 (0)	1 (1)

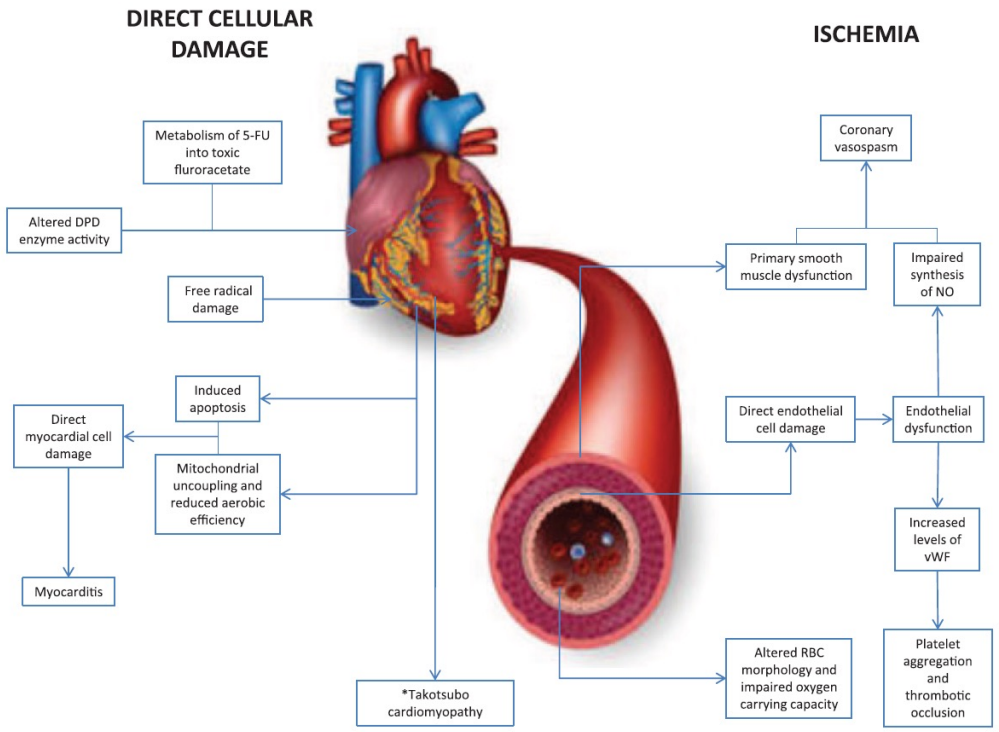
Conclusion: Subsequent studies have excluded the use of warfarin in clinical trials of Ibrutinib; however, other anticoagulant agents are permitted

Wang ML, Rule S, Martin P, et al. N Engl J Med. 2013; 369 (6): 507-516

Cardiotoxic Chemotherapies

- Anthracyclines
- Human epidermal growth factor-2 inhibitor ($HER2_i$)
- Proteasome Inhibitors
- Tyrosine Kinase Inhibitors
- **Antimetabolites**

Antimetabolite



Agents: Fluorouracil, Capecitabine

Pharmacologic Category: Antimetabolite (pyrimidine analog)

Mechanism of Action:

Its active metabolite (5-UMP) is incorporated into RNA to replace uracil and inhibits cell growth

Inhibits thymidylate synthetase, depleting thymidine triphosphate (a necessary component of DNA synthesis)

CV Toxicities:

Typical or atypical chest pain

Chest pain consistent with acute coronary syndrome

Asymptomatic EKG changes

Fluorouracil [prescribing information]. 1962
Capecitabine [prescribing information]. 1998

Antimetabolite and cardiotoxicity Studies

Reference	Sample Size	Study Design	Drug	Risk estimate
Pottage et al.	140	Prospective Study	5-FU	2.9% developed cardiotoxicity: 2.1% developed chest pain and EKG changes and 0.8% developed MI
Labianca et al.	1083	Retrospective Study	5FU	1.6% of all patients developed angina or MI versus 4.5% in patients with previous cardiac disease
Eskilsson et al.	76	Prospective study	Continuous infusions of 5-FU	17.1% developed cardiac events: 13.2% experienced angina or ECG changes, 1.3% experienced AF, 1.3% had VF and 1.3% experienced sudden death
Jeremic et al.	80	Prospective study	5-FU	15% developed angina or ECG changes
de Forni et al.	367	Prospective study	Continuous infusions of 5-FU	7.6% developed cardiotoxicity: 5.4% had chest pain or shortness of breath, 2.2% had unstable angina and 1.1% experienced sudden death
Ng et al.	153	Two prospective studies	Capecitabine	6.5% developed cardiotoxicity: 2.6% experienced angina, 2.0% had an MI, 0.7% had heart failure, 0.7% had ventricular tachycardia and 0.7% experienced sudden death
Jensen et al.	668	Retrospective review	Capecitabine or 5-FU	4.3% developed cardiotoxicity: 0.4% had angina on exertion, 3.6% had angina at rest and 0.3% had an MI
Kosmas et al.	644	Prospective study	Capecitabine or 5-FU	4.0% of all patients developed angina or ECG changes versus 6.7% of those receiving a continuous infusion
Koca et al.	52	Retrospective review	Capecitabine	34.6% developed cardiac symptoms, 11.5% developed new cardiac signs on exam and 32.6% had new ECG changes

Sara JD, Kaur J, Khodadadi R, et al. Ther Adv Med Oncol. 2018; 10: 1-18

Antimetabolites Monitoring Protocol

- Baseline:
  - Risk assessment
  - Blood pressure
  - EKG
  - Lipid profile
  - HbA1c
  - SCORE2/SCORE2-OP
  - ECHO—patients with history of symptomatic CVD prior to treatment initiation
  - Screening for CAD in patients at high and very high risk of CAD before treatment initiation

Lyon AR, Lopez-Fernandez T, et al. Eur Heart J. 2022; 00

SCORE2/SCORE2-OP

1. Select European region
2. Gender
3. Age **(40-69YO)**
4. Smoking status
5. Systolic BP (100-200mmHg)
6. Total Cholesterol level (3-9mmol/L)
7. HDL cholesterol level (0.7-2.5mmol/L)
8. LDL cholesterol level-optional (0.1-9mmol/L)

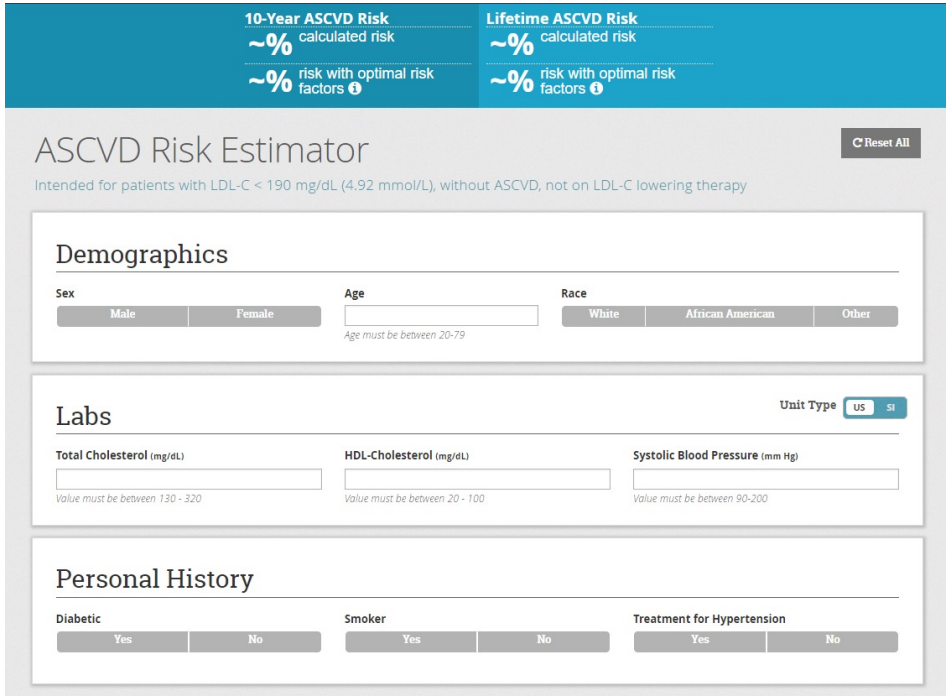
1. Select European region
2. Gender
3. Age **(70-89YO)**
4. Smoking status
5. Systolic BP (100-200mmHg)
6. Total Cholesterol level (3-9mmol/L)
7. HDL cholesterol level (0.7-2.5mmol/L)
8. LDL cholesterol level-optional (0.1-9mmol/L)

	<50YO	50-69YO	≥70YO
🟢	<2.5%	<5%	<7.5%
🟠	2.5 to <7.5%	5 to <10%	7.5 to <15%
🔴	≥7.5%	≥10%	≥15%

Eur Heart J (2021). 42, 2455-2467
Eur Heart J (2021). 42, 2439-2454

ASCVD

1. Gender
2. Age **(20-79YO)**
    1. for ASCVD risk ≥10% age is 40-79
3. Ethnicity (White/African American/Other
4. Diabetes Mellitus
5. Smoking status
6. On hypertension treatment
7. Systolic BP (90-200mmHg)
8. Total Cholesterol level (130-320mg/dL)
9. HDL cholesterol level (20-100mg/dL)



*Intended for patients with LDL-C <190 mg/dL (4.92 mmol/L), without ASCVD, not on LDL-C lowering therapy

ASCVD Risk Estimator. American Heart Association. American College of Cardiology

Re-challenge Risks & Recommendations

Risk

- 80% recurrent cardiotoxicity and death rates as high as 18% when no change in original drug dosing

Recommendations

- Switch to 2nd line of therapy
- Dose reduce by 20-50%
- Switch from infusional (FOLFOX) to bolus (FLOX)
- Add nitrates and calcium channel blockers to any rechallenge protocol

Clasen SC J Gastrointest Oncol 2017

Challenging Strategies

Prophylaxis

- Nifedipine XR 30mg PO QD
- Isosorbide dinitrate 10 mg every 8 hours. Start prior to infusion and continue it for 24 hours after completion

Fluorouracil Infusion

- Restart at 50% of dose (1200 mg/m2 cycle IV infusion administered over 46 hours) for 1st rechallenge
- For second rechallenge administer 5FU at 75% of the original dose (1800 mg/m2/cycle IV infusion over 46 hours)
- Administer full dose thereafter

Supportive Tests

- Admit patient for telemetry during 1st rechallenge
- Perform ECHO after vasospasm to identify serious cardiac damage. It is unclear if prophylactic medications can be safely administered in this population.

Clasen SC J Gastrointest Oncol 2017

Summary

- **Cardio-oncology is an emerging discipline**
  - Focused predominantly on the detection and management of cancer treatment-induced cardiac dysfunction
- **Cardio-oncological services**
  - Evaluate ECG, BG, lipid, GFR, TTE, CMR, manage modifiable CV risk factors/diseases, exercise and dietary habits
- **Early monitoring of cardiovascular toxicities is critical for cardiotoxic chemotherapies**
  - Anthracyclines, $HER2_i$, TKI, Antimetabolites, Proteasome
- **Appropriate monitoring strategies depend on the specific drug class**
  - Cardio-oncological evaluation, ECG, troponin, BP, BNP/NT-proBNP, and doppler (supra-aortic/lower extremity arteries)
- **Important to evaluate the benefits/risks of continuing the involved cancer treatment**
  - Depends on the offending agent and type of cardiovascular toxicity

References

1. Babiker HM, McBride A., Newton, M. et al., Cardiotoxic effect of chemotherapy: A review of borth cytotoxic and molercular targeted oncology therapies and their effect on the cardiovascular system. Critical Reviews in Oncology/Hematology Volume 126, June 2018, Pages 186-200
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