Mitigating Adverse Effects: Cardiotoxicities

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Overview

Anthracyclines

HER-2 blockers

Fluoropyrimidines

VGEF Inhibitors

Tyrosine Kinase Inhibitors

Multitargeted Kinase Inhibitors (BCR-ABL

Ibrutinib/Acalabrutinib

Multiple Myeloma Therapies

Immune Checkpoint Inhibitors

RAF/MEK Inhibitors

Radiation Therapy

CAR-T, BiTE, TIL

Anthracyclines

Doxorubicin, daunorubicin, and epirubicin used to treat many solid tumor and hematologic malignancies

Cardiotoxicity related to anthracyclines:

- Dose related, Cumulative
- At sufficiently high doses, can lead to left ventricular dysfunction

Asymptomatic or symptomatic

Risk factors for CV toxicity:

- Cumulative dose, IV bolus administration, higher single doses, prior cardiotoxic cancer treatments, concomitant agents
- History of underlying CV disease, female, age (young, geriatric), delayed diagnosis, increased cardiac biomarkers at baseline

Baseline monitoring: Echocardiogram, ECG, cardiac biomarkers

Anthracyclines

Cardiotoxicities:

- LV dysfunction, heart failure, myocardial ischemia or infarct, arrhythmias, valvular disease

Cardioprotectant strategies:

Dexrazoxane, continuous infusion, or liposomal formulation of doxorubicin

For prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines

Echocardiogram for diagnostic workup: Before therapy, 6 months after completion, and annually-biannually thereafter.

Cardiac magnetic resonance imaging or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI

Serum cardiac biomarkers (troponins, natriuretic peptides)

Data on prevention is conflicting. Generally, BB and ACEi/ARB are used

HER-2 Blockers

Agents: Trastuzumab, Pertuzumab, Ado-trastuzumab, Trastuzumab emtansine, Neratinib

Treats HER2 positive breast cancer in early and metastatic diseases, as well as some HER2 over-expressive metastatic gastric adenocarcinoma

HER-2 is expressed in cardiomyocytes and required for survival of cardiomyocytes. HER2 deficiency in mice lead to dilated cardiomyopathy and increased sensitivity to doxorubicin.

HER2 blockers lead to LVD in up to 15-20% of patients

Improvement is usually seen in 4-6 weeks after trastuzumab withdrawal. After symptomatic improvement, re-institution of trastuzumab treatment is usually possible

Risk factors: concomitant cardiotoxic treatment like anthracyclines/pertuzumab/Taxotere/taxol, preexisting CV diseases, smoking history, alcohol use, lower functional capacity, obesity

HER-2 Blockers

Baseline monitoring: ECG, echocardiogram, cardiac biomarkers in moderate to high risk patients or with existing history of CV diseases.

Routine LVEF assessment has been recommended including a transthoracic echocardiogram every 3 months during first year of Trastuzumab therapy.

In metastatic disease, after the first year, consider frequency depending on LV function and/or present symptoms.

Consider GLS if available.

Cardiac biomarkers as indicated if LVD present or patient becomes symptomatic.

Most patients who experience reduced systolic function related to trastuzumab therapy have subsequent improvement in cardiac function

Management for LV Dysfunction or Heart Failure: ACC/AHA guidelines for heart failure therapy.

- ACE-I/ARB/ARNI, BB, Spironolactone/eplerenone
- Statin if CAD indicated

Fluoropyrimidines

Agents: 5-FU (5-Fluorouracil), capecitabine

Used to treat solid tumors such as GI and breast malignancies.

CV Effects: ischemic syndrome (angina pectoris, ischemia related ECG changes, MI), coronary vasospasm, HTN

- Rare: myocarditis, arrhythmias, peripheral arterial toxicity

Exposure to 5-FU reproduces clinical cardiotoxicity.

Ischemia reversible with 5-FU cessation and initiation of anti-ischemic medical therapy

Capecitabine believed to be less toxic.

Baseline monitoring: ECG, consider echo if h/o of CAD/MI

Standards for treatment of CV toxicities: ACC/AHA guidelines

Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors

VGEF is a growth factor promoting angiogenesis, including cancer angiogenesis.

Used for many hematological and solid tumor malignancies

Monoclonal antibodies: aflibercept, bevacizumab, ramucirumab

TKI: axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib

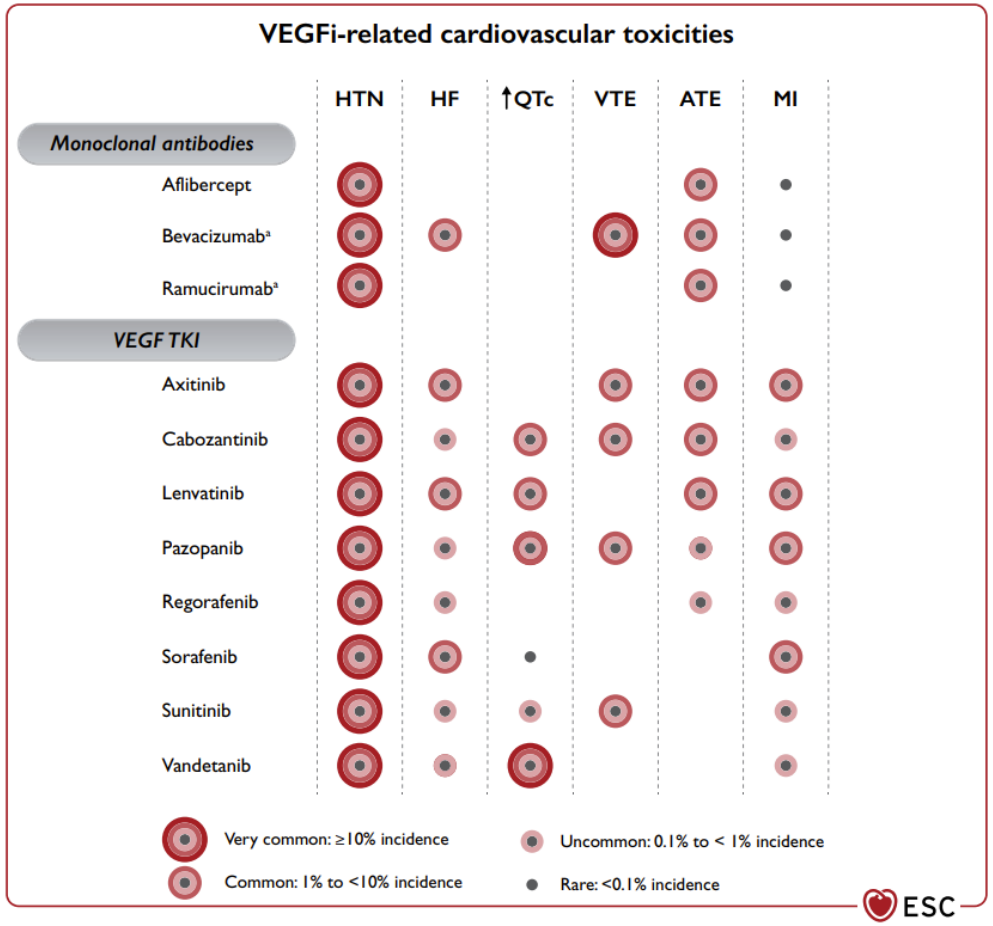
Cardiac adverse effects:

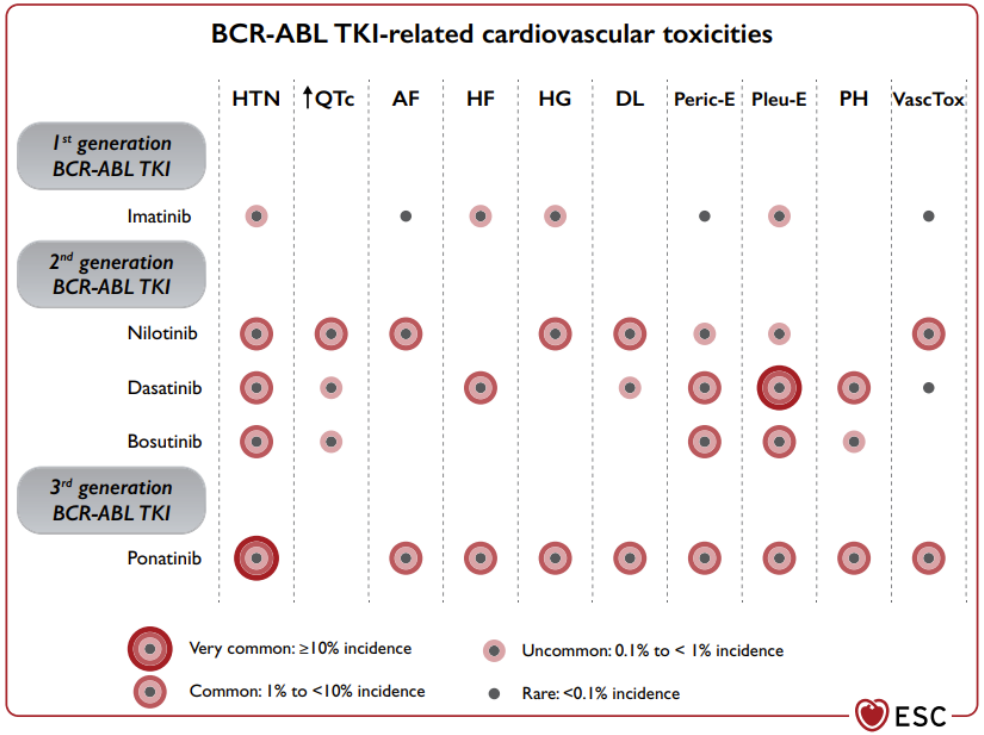
- Hypertension
- LV dysfunction, MI, CVA, PAD, VTE

Strict risk factor modification

Recommendations:

- Ideal: Continue VGEF and TKI while optimizing CV care.
- ACEi/ARB, CCB, BB, statin, aspirin
- Monitoring dependent upon underlying CV disease and symptoms


VEGFi-related cardiovascular toxicities
HTN
HF
↑QTc
VTE
ATE
MI
Monoclonal antibodies
Aflibercept
Bevacizumab[a]
Ramucirumab[a]
VEGF TKI
Axitinib
Cabozantinib
Lenvatinib
Pazopanib
Regorafenib
Sorafenib
Sunitinib
Vandetanib
Very common: ≥10% incidence
Common: 1% to <10% incidence
Uncommon: 0.1% to < 1% incidence
Rare: <0.1% incidence
ESC


BCR-ABL TKI-related cardiovascular toxicities
HTN
↑QTc
AF
HF
HG
DL
Peric-E
Pleu-E
PH
VascTox
1st generation BCR-ABL TKI
Imatinib
2nd generation BCR-ABL TKI
Nilotinib
Dasatinib
Bosutinib
3rd generation BCR-ABL TKI
Ponatinib
Very common: ≥10% incidence
Common: 1% to <10% incidence
Uncommon: 0.1% to < 1% incidence
Rare: <0.1% incidence
ESC

Multitargeted Kinase Inhibitors (BCR-ABL)

Used in hematological cancers such as CML

TKI such as imatinib, bosutinib, dasatinib, nilotinib, ponatinib

Cardiac Adverse Effects:

- Dasatinib: grade 1 pulmonary htn, HF, pleural and pericardial effusion
- Nilotinib and ponatinib: HTN, vascular events
  - ABI
- Second generation TKI BCR-ABL: QTc prolongation
  - Measure QTc on EKG using Fridericia method

Increased risk if pre-existing cardiac history, 65 years or older, DM

Prior to use: ECG, blood pressure monitoring, check glucose, lipids

TTE at baseline for higher risk individuals

Ibrutinib

Ibrutinib- Bruton kinase inhibitor, used to treat chronic lymphocytic leukemia

- Significantly associated with atrial fibrillation (Af)
- RESONATE trial: 3% of patients receiving ibrutinib developed AF, whereas the ofatumumab arm had no AF
- Majority of AF occurrences develop within first year of taking ibrutinib
- Other impacts from ibrutinib: increased bleeding risk
  - Inhibits glycoprotein VI collagen activation pathway and glycoprotein 1b-mediated platelet function leading to decreased platelet aggregation and adhesion to Von Willebrand factor
- Management of AF in setting of ibrutinib:
  - Betablockers for rate control
    - Calcium channel lockers can increase ibrutinib levels
    - Digoxin levels may be increased by ibrutinib
  - Consider direct acting oral anticoagulation (apixaban, rivaroxaban).
    - Closely monitor platelets. Stop if < 50,000.

Acalabrutinib

Second generation Bruton TKI

Also treats hematological malignancies

CV adverse effects including arrhythmias especially atrial fib.

ECG monitoring

Afib? Transthoracic echo.

Multiple Myeloma Therapies

Combination therapy leads to increased cardiovascular risk.

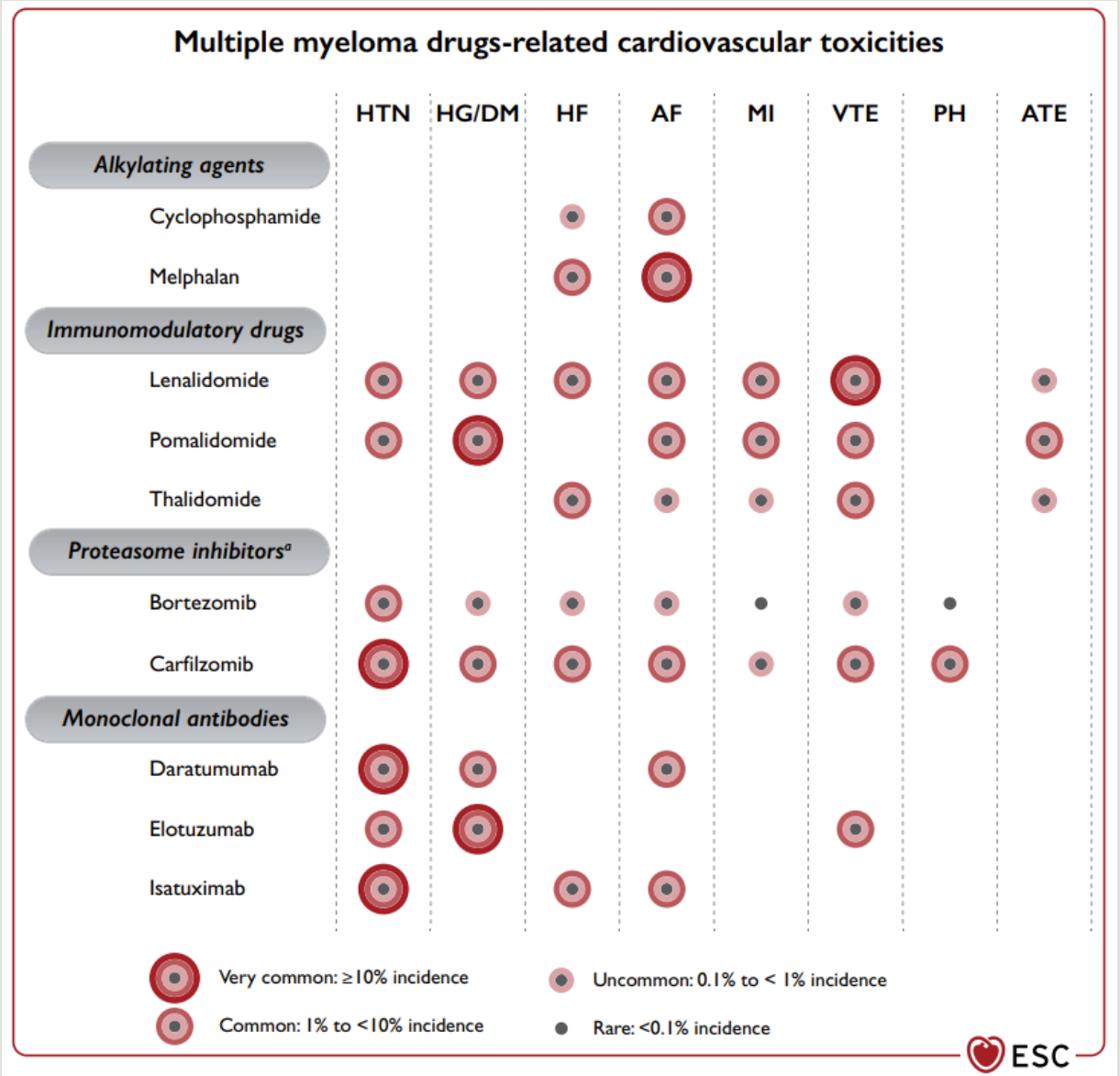
Consider for monitoring:

- ECG
- Cardiac biomarkers
- TTE surveillance

Optimize cardiac care while continuing therapies if possible

Patients on thalidomide or lenalidomide:

- Consider aspirin 81mg due to increased clotting risk



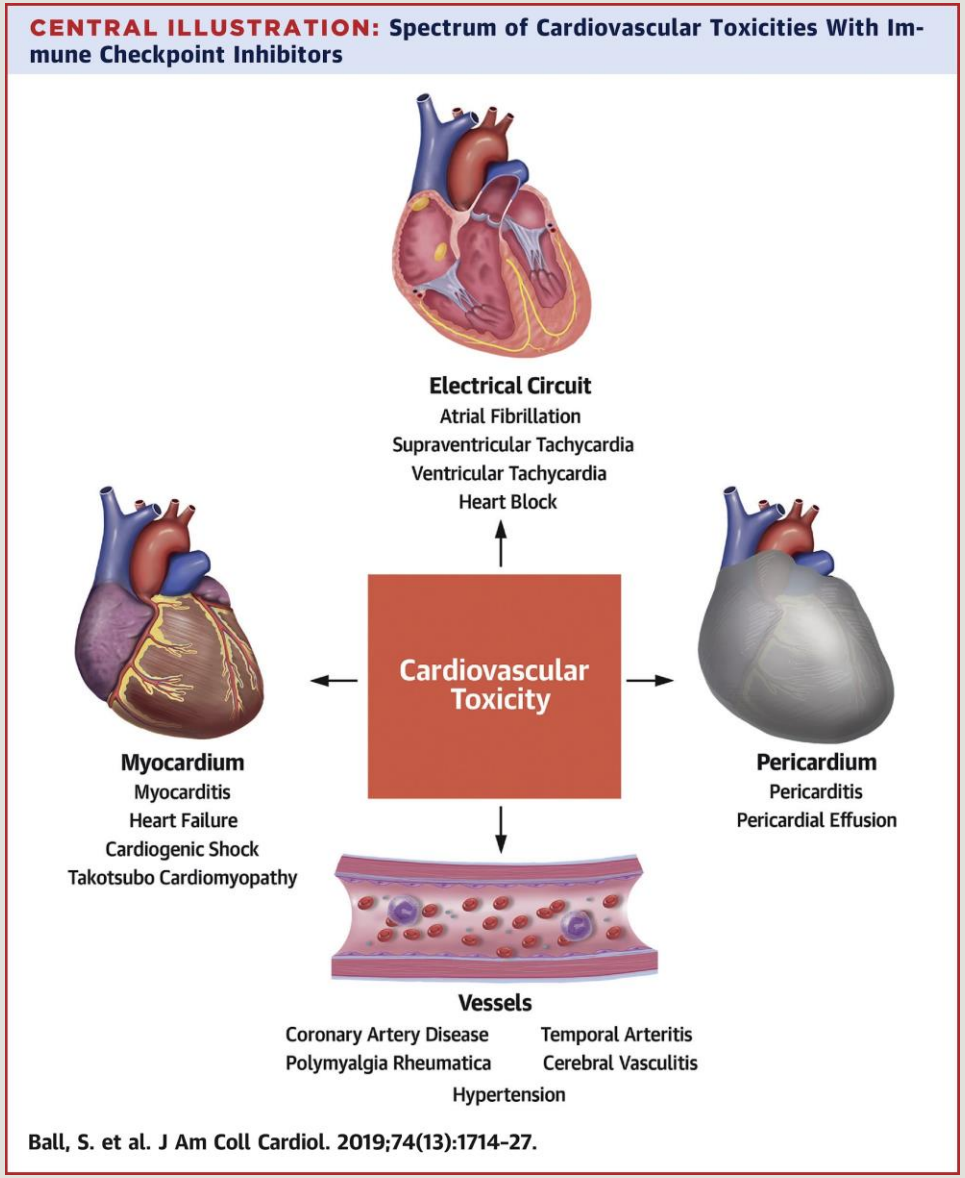
Immune Checkpoint Inhibitors

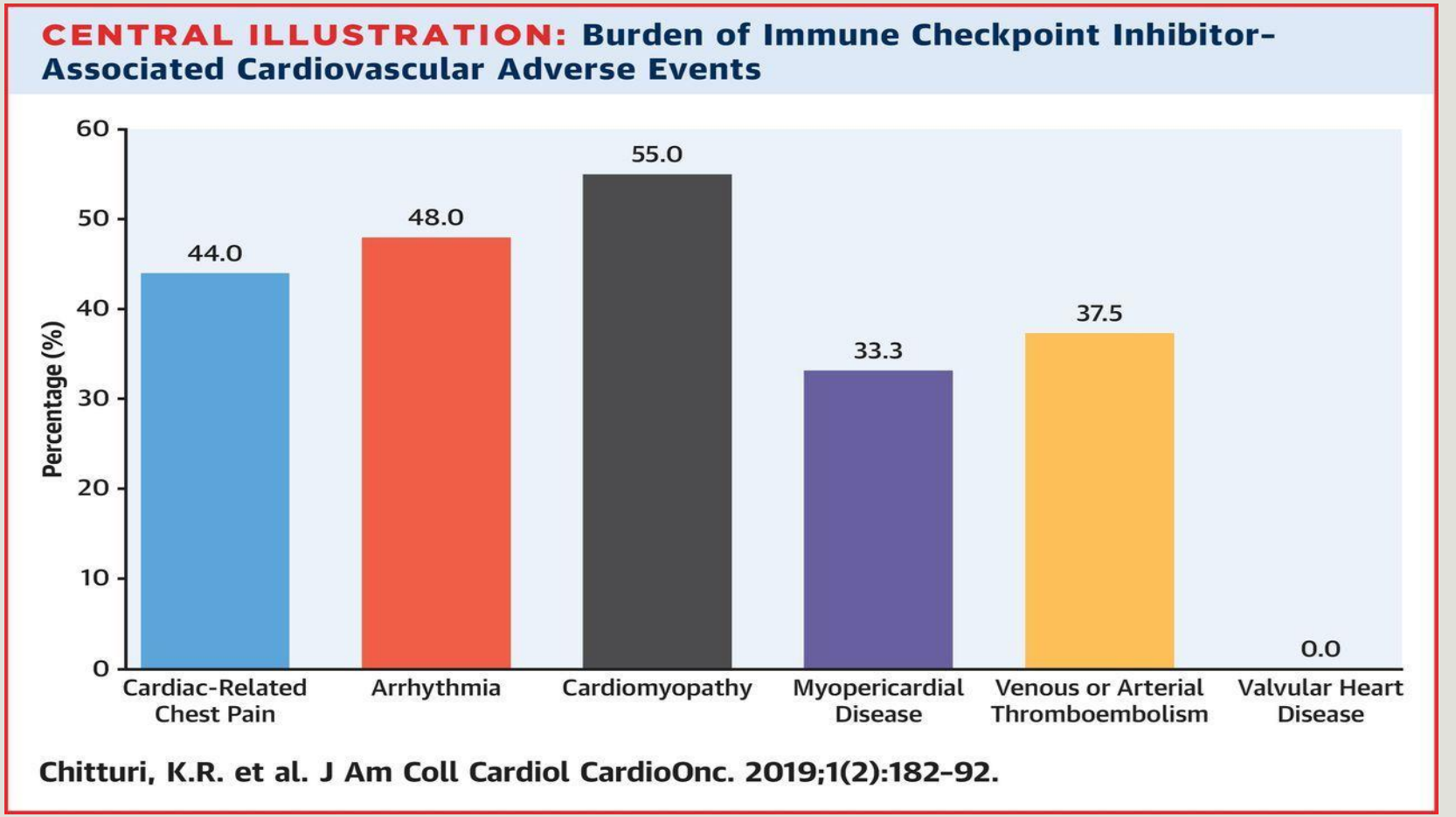
Developed to enhance activity of body's own immune cells against cancer cells.

Contributory in prolongation of clinical remission, stabilization, and overall survival in patients with various advance solid tumor and hematological cancers.

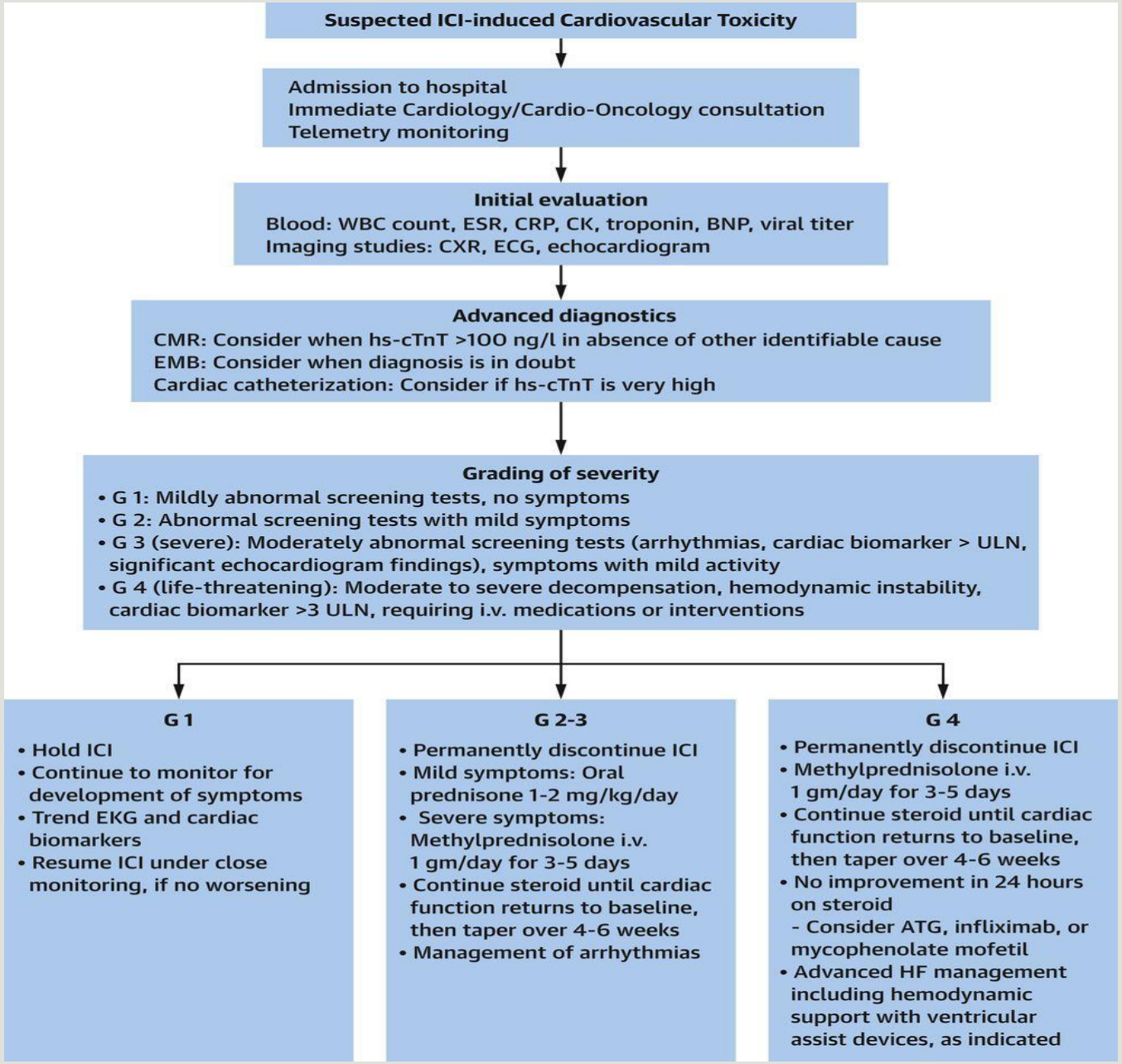
Cardiotoxicity profiles vary.

ICI related cardiac events are rare but potentially life-threatening, mostly represented by acute myocarditis, risk of death up to 50%.





According to the Common Terminology Criteria of Adverse Events (CTCAE) version 5.0, 37.8% of patients receiving immune checkpoint inhibitors (ICIs) developed cardiovascular adverse events. This bar graph depicts the distribution of cardiovascular adverse events, identified by CTCAE, that were adjudicated as major adverse cardiac events. For example, 25 patients on ICI had chest pain by CTCAE, and in 11 patients (44%), these were adjudicated as a major adverse cardiac event. Some patients developed multiple major adverse cardiac events, and each event is counted in this figure. Of note, myopericardial disease includes both pericardial disease and myocarditis.



Management of ICI Cardiotoxicity

RAF and MEK Inhibitors

Rapidly Accelerating Fibrosarcoma Inhibitors
- Vemurafenib
- Dabrafenib
- Encorafenib

Mitogen-activated Extracellular Signal-Regulated Kinase Inhibitors
- Trametinib
- Cobetinib
- Binimetinib
- Selumetinib

Treats malignancies such as melanoma

Main CV Adverse Effects:
- HTN, PE, CTRCD, QTc prolongation
- MI and Afib (RAF monotherapy or with MEKi)

Increased risk if preexisting CVD

Baseline CV risk stratification and optimization
- Vitals, ECG, baseline TTE for moderate or high risk patients

CV protective medications: ACEi, ARB, BB
- BB might prevent CTRCD induced by MEKi

Chemotherapy-Related LV Dysfunction

Definition:

- ≥10% decline in LVEF to final LVEF < 53%
- GLS drop of 15% or more (no evidence to support holding therapy based on GLS worsening alone)

The American College of Cardiology/American Heart Association HF guidelines recognize anthracycline-associated injury as a risk for development of HF (stage A).

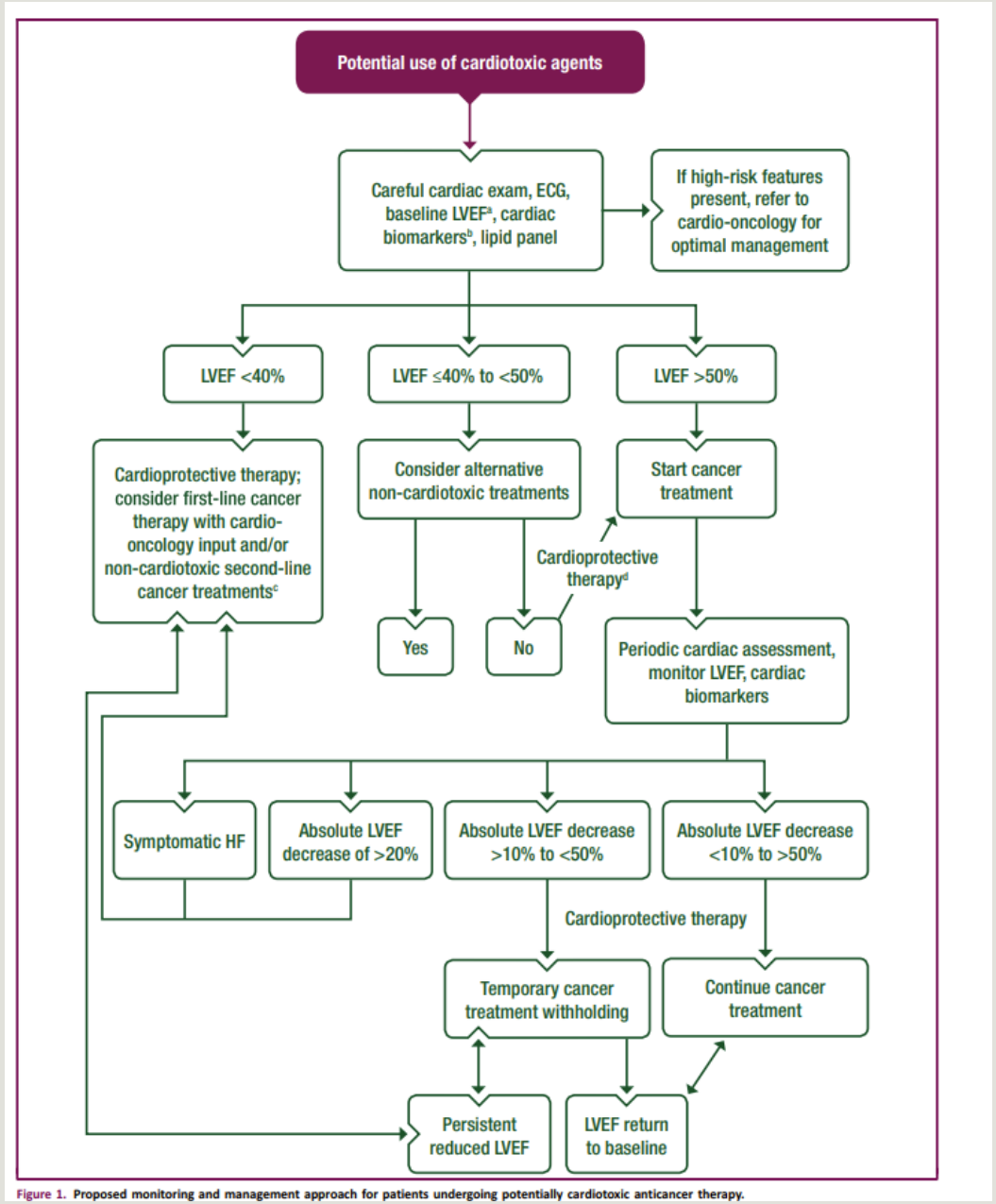


Figure 1. Proposed monitoring and management approach for patients undergoing potentially cardiotoxic anticancer therapy.

Curiglano et al., 2020.

Radiation Therapy

Radiation therapy is used to treat various malignancies.

Potential cardiotoxicity adverse risk occurs in patients receiving RT for left sided breast cancer, esophageal cancer, lung cancer, mantle RT, or TBI for hematological cancers.

Increased risk for coronary artery disease, valvular diseases, arrhythmias, pericardial diseases.

- CAD occurs at increased rate 2 to 4 years after irradiation.
- Radiation related valvular disease occurs at median 22 months post exposure.

Screening 3 to 5 years post radiation exposure.

Consider screenings every 5 years.

Screenings: echocardiogram, stress testing, coronary CTA, cardiac PET if indicated.

Management of CV diseases per ACC/AHA guidelines.

Chimeric Antigen Receptor T-cell (CAR-T)

Bispecific T-cell Engager (BiTE)

Tumor-Infiltrating Lymphocytes (TIL)

Immunotherapies act by provoking a de novo antitumor immune response or by reactivating an existing immune response that had become ineffective

Each treats different types of cancers

- CAR-T: multiple myeloma, diffuse large B-cell lymphoma
- BiTE: B-cell acute lymphocytic leukemia
- TIL: melanoma

Mechanisms of Cardiotoxicity:

- On-target, on-tumor effects that lead to cytokine release syndrome
- On-target, off tumor effects: direct T-cell mediated injury of recipient organs that share target antigens with tumor
- Off-target, off-tumor effects: T-cells unexpectedly attack an antigen other than intended tumor antigen

CAR-T

CRS

Lymphodepletion with potentially cardiotoxic agents

Cross-reactivity against titin, a striated muscle protein in the heart, to cause fatal, fulminant myocarditis

Arrhythmias (mostly atrial), heart failure, myocardial infarction and vascular leak syndrome with associated circulatory collapse and multiorgan failure (10-15%)

Blood Adv. 2023. PMID: 37307173

BiTE

CRS

Capillary leak

Common cardiovascular adverse events include hypertension, hypotension, and sinus tachycardia (5-14%), which are usually mild

Serious cardiovascular adverse events are rare (<0.5%)

Heart Failure Clinics, 2022-07-01

TIL

CRS

Lymphodepletion with potentially cardiotoxic agents

Systemic IL-2 administration leads to increased nitric oxide production, excessive vascular wall relaxation, vascular leakage and disrupted myocardial signaling

Arrhythmia, hypotension, heart failure, similar to sepsis-induced cardiomyopathy, and multi-organ failure (10-15%)

J Immunother. 2021 Feb-Mar;44(2):86-89
Int J Cardiol. 2021 Jan 15;323:179-187

Management for CAR-T, BiTE, TIL

PRE-TREATMENT

TTE and Biomarkers for RF optimization
- BNP and Troponin (CAR-T)

Functional Capacity
- Able to complete > 4 METS?

HF and CAD goal directed therapy

Severe valve disease

Cytopenia, timing of cardiac intervention

DURING TREATMENT

Arrhythmia monitoring
- Atrial fibrillation, atrial flutter

Volume status monitoring

Limit cardiac intervention if possible
- STEMI, temporary venous pacemaker

Drug-drug interaction

Monitor for CRS

Tocilizumab improves cardiac outcomes

POST-TREATMENT

Cardiac Optimization

Cardiac procedures when cytopenia improves

Oncology drugs-cardiology drug interactions

QT monitoring on prophylactic antibiotics

Aggressive risk factor control
- 3 month follow-up with echocardiogram

Conclusion

Cardiovascular adverse effects of cancer therapy (chemotherapy, immunotherapy, radiation therapy) are common.

Most cardiotoxicities are easily treated.

As cancer treatments continues and treatment indications expand, prevalence of cardiotoxicities is likely to increase.

Assess CV risk before, during, after treatments, especially for moderate to high risk patients.

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