Cardiac Toxicities Associated with Cancer Treatment

Hot Topics in Oncology Care 2017
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Overview of Presentation

- Epidemiology of cardiac toxicities
- Radiation-induced cardiac toxicities
- Androgen deprivation and cardiac toxicities
- Chemotherapy-induced cardiac toxicities
- Targeted therapy related cardiac toxicities
- ASCO Guidelines for the Prevention and Monitoring of Cardiac Dysfunction in Cancer Survivors

Epidemiology of Cardiac Toxicities

- Cancer and cardiovascular disease are the two leading causes of cancer deaths
  - Responsible for 50% of overall mortality
- Advances in cancer treatments have dramatically improved survival rates
- Newer treatments are associated with deleterious effects on the cardiovascular system
  - Development of cardiovascular events
  - Exacerbation of underlying cardiovascular disease

Epidemiology of Cardiac Toxicities

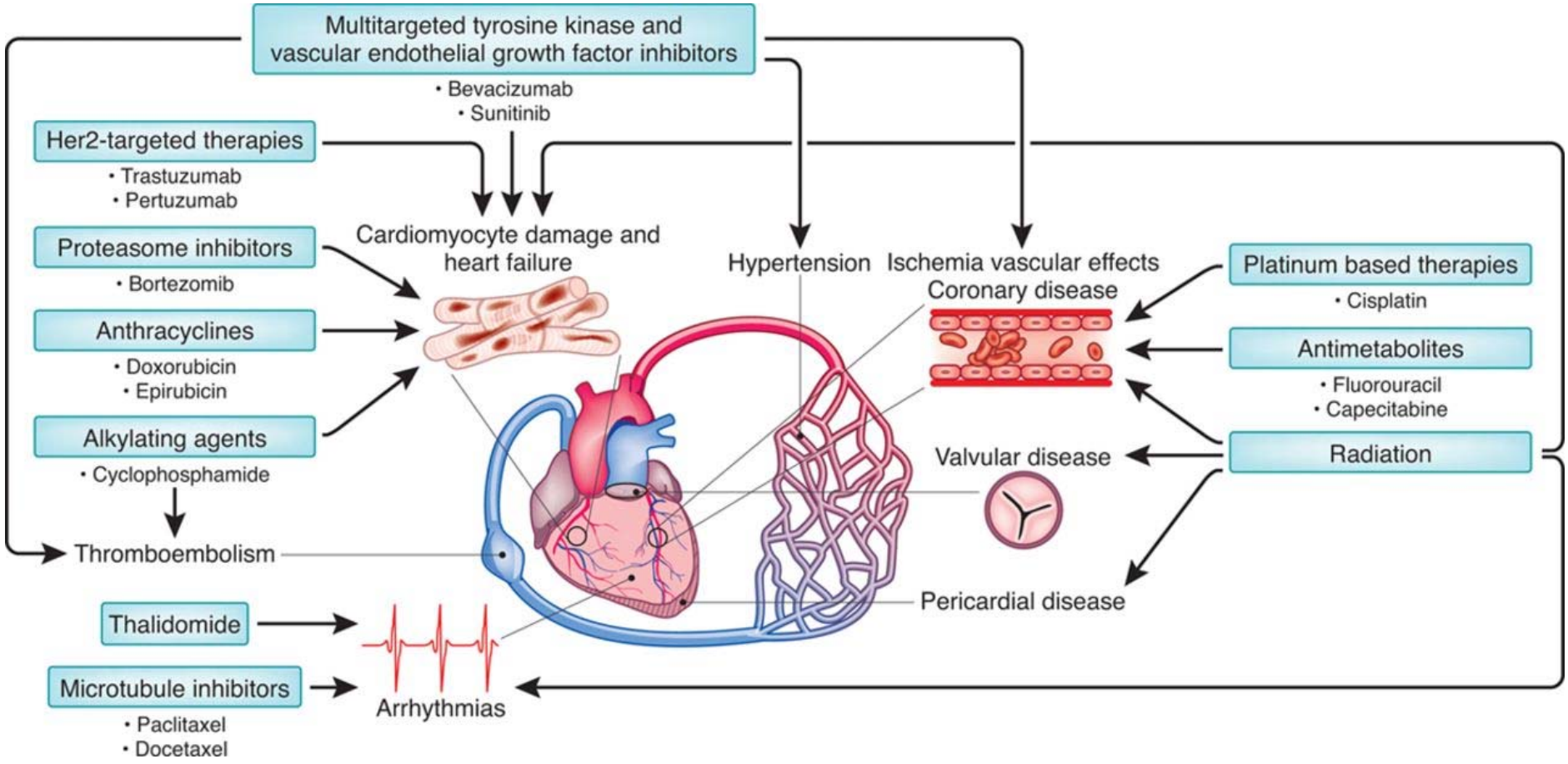
- Median age of cancer patients has increased
  - Associated with an increase in comorbidities
  - Patient population with an increased number of risk factors
- Risk of CV disease in cancer survivors is greater than that of recurrent malignancy
  - Childhood cancer survivors have a 15-fold increased risk of developing heart failure
  - Childhood cancer survivors have a 7-fold increased risk of premature death due to cardiac events
  - In women with breast cancer, cardiovascular disease is the leading cause of death

Current Challenges

- True estimates of CV toxicities are difficult to determine
  - Patients with CV disease were excluded from clinical trials of newer therapies
- Rapid development and approval of new therapies does not allow for sufficient time for long term follow-up
- “Real life” data has revealed higher incidence rates for CV disease in oncology patients
- Development of cardio-oncologists
- Lack of evidence for monitoring patients and survivors
- Lack of evidence to guide treatment of patients and survivors with CV toxicities

Scope of CV Toxicities

- Virtually all cancer treatments
  - Chemotherapy
  - Radiation therapy
  - Targeted therapies
- Appear to induce CV toxicity through a variety of mechanisms
  - Myocytes
  - Endothelial cells
  - Cardiac conduction system


Multitargeted tyrosine kinase and vascular endothelial growth factor inhibitors
• Bevacizumab
• Sunitinib
Her2-targeted therapies
• Trastuzumab
• Pertuzumab
Proteasome inhibitors
• Bortezomib
Anthracyclines
• Doxorubicin
• Epirubicin
Alkylating agents
• Cyclophosphamide
Thromboembolism
Thalidomide
Microtubule inhibitors
• Paclitaxel
• Docetaxel
Cardiomyocyte damage and heart failure
Arrhythmias
Hypertension
Ischemia vascular effects
Coronary disease
Valvular disease
Pericardial disease
Platinum based therapies
• Cisplatin
Antimetabolites
• Fluorouracil
• Capecitabine
Radiation

Types of CV Toxicities

- Direct myocardial injury with or without heart failure
- Systemic hypertension
- QTc prolongation
- Arrhythmias
- Myocardial ischemia
- Hypertension
- Arterial/venous thromboembolic events
- Accelerated atherosclerosis
- Pericardial diseases
- Valvular heart diseases
- CTX drugs can have metabolic effects that increase the risk of CV disease

RT-Induced CV Toxicities

- RT induces vascular endothelial damage
  - Promotes inflammation
  - Accelerates atherosclerosis
- Mediastinal radiation
  - Hodgkin's lymphoma
  - Breast cancer
  - Esophageal and lung cancer
- Delayed onset of CV disease
  - 10 to 30 years after exposure
- RT affects
  - Coronary arteries, valves
  - Pericardium, conduction system, myocardium

RT-Induced Coronary Artery Disease

- Endothelial inflammation damages the intima and promotes the development of plaques in the coronary arteries
- CAD can develop 5 to 20 years after RT
- Clinical presentation
  - Sudden cardiac death
  - Syncope
  - Acute coronary syndrome
- Indications for CABG are same as for patients without RT
- Need to prevent or reduce traditional cardiac risk factors
  - Diabetes
  - Hyperlipidemia
  - Hypertension

RT-Induced Valvular Disease

- Incidence of valvular disease is difficult to determine
- 81% in patients who received mediastinal radiation
- Valvular disease may be worse in patients who received >30 Gy
- Aortic regurgitation is the most common problem
  - Can occur 20 years after RT
- Valve replacement improves survival

RT-Induced Pericardial Disease

- Common problems
  - Acute pericarditis
  - Pericardial effusion
  - Constriction pericarditis
- Chronic problems occur 3 to 5 years after RT
- Acute pericarditis
  - Rare complication
  - Usually seen with doses of >40 Gy to mediastinum
  - Symptoms – chest pain, fever, ECG changes
  - Treatment – NSAIDs, steroids

RT-Induced Pericardial Disease

- Pericardial Effusion
  - May present months to years after RT
  - Fibrotic changes can occur in the pericardium
  - Effusions can be rapid or slow
  - Result in cardiac tamponade
- Constrictive pericarditis
  - Most severe form of pericarditis
  - Occurs 10 years after RT
  - Presents as CHF
  - Initial treatment – diuretics
  - Definitive treatment - pericardectomy

RT-Induced Cardiomyopathy

- Types of cardiomyopathy
  - Restrictive (via myocardial dysfunction)
  - Constrictive (due to pericarditis)
- Occurs 20 years after RT
- Defined as LVEF of less than 50%
- Medical management of HF
  - Beta blockers
  - Angiotensin-converting enzyme inhibitors

RT-Induced Conduction Diseases

- Exact incidence is not known
- Causes of conduction system abnormalities
  - Myocardial fibrosis
  - Ischemia
- Most common condition is right bundle branch block
- AV block is the most serious complication

Androgen Deprivation Therapy

- Cornerstone of treatment for advanced prostate cancer
- Mechanisms for CV disease
  - Obesity
  - Hyperlipedemia
  - Insulin resistance
  - Metabolic syndrome
  - Acute kidney injury
  - Hypecoagulability
  - Atherosclerosis

Androgen Deprivation Therapy

- At physiological levels, testosterone is cardioprotective
  - Decreased in atherosclerosis
  - Increased arterial compliance
- Findings from studies on the relationship between androgen deprivation therapy and increased CV risk are inconsistent
  - High risk elderly were excluded from most trials

Anthracycline-Induced CV Toxicities

- Anthracycline regimens (doxorubicin)
  - Causes breaks in DNA – cardiac cell death
- Associated with LV dysfunction
  - Cardiomyopathy
- Acute toxicity
  - Primarily arrhythmias – atrial fibrillation
- Chronic toxicity
  - CHF
  - Not reversible
- Two thirds of asymptomatic childhood cancer survivors had evidence of cardiomyopathy
  - Warrants ongoing monitoring

Risk Factors for Anthracycline-Induced Cardiomyopathy

- Cumulative dose >500 mg/m^2
- Age $\geq$60 years
- Hypertension
- Previous heart disease
- Previous radiation therapy
- Concurrent CTX
- Hematopoietic cell transplant
- Obesity (BMI $\geq$30)
- Diabetes

Alkylating Agents – CV Toxicity

- Cyclophosphamide
  - Dose dependent reduction in LV function
  - Acute cardiomyopathy (days to weeks)
  - High dose – 180 mg/kg over 4 days
    - 28% incidence rate
- Ifosfamide
  - Supraventricular arrhythmias can occur
  - Acute and dose dependent reduction in LV function (16 to 18 g/m^2 – 33% to 67% of patients)

Trastuzumab-Induced CV Toxicities

- Herceptin is a monoclonal antibody that targets HER2
- Standard treatment for patients with HER2 positive breast cancer
- Mechanism for LV dysfunction is not clear
- Exact incidence is not clear
  - 3% when given alone
  - 5% when given after anthracyclines
  - 27% when give concurrently with anthracycline
- Considered to be reversible cardiotoxicity

Risk Factors for Trastuzumab-Induced Cardiomyopathy

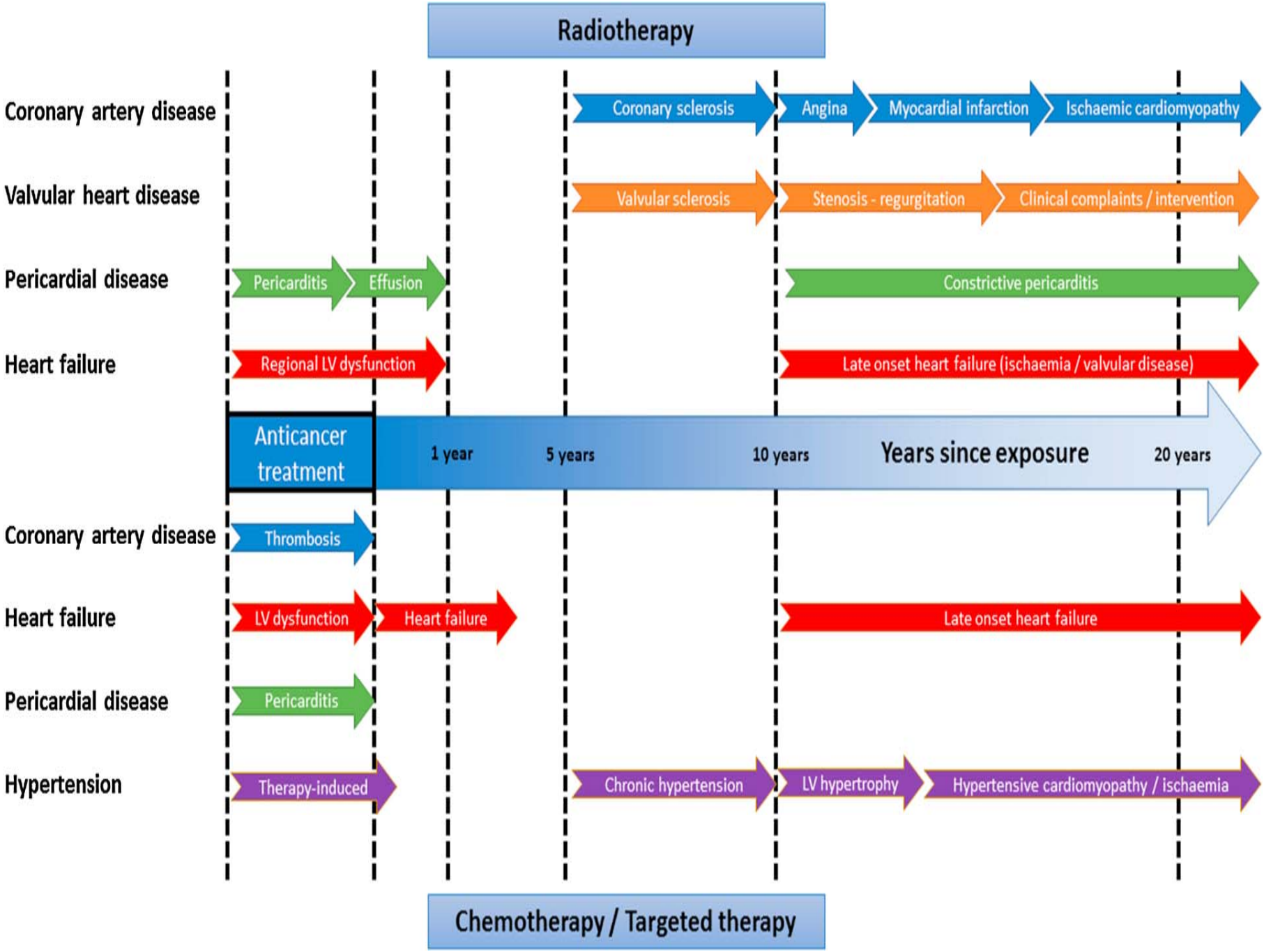
- Age ≥50 years
- Hypertension
- Concurrent CTX
- Obesity (BMI ≥30)
- Lower baseline ejection fraction (≤55%)
- Diabetes
- Smoking

Protein Kinase Inhibitors - CV Toxicities

- PKIs target tyrosine kinases
- PKIs that target the VEGF receptor can cause cardiomyopathy
- Sunitinib
  - 28% risk of asymptomatic HF
  - 15% risk of symptomatic HF
  - Not entirely clear if the HF is reversible

Protein Kinase Inhibitors - CV Toxicities

- **Lapatinib**
  - **Targets EGFR and HER-2 kinases**
  - **1.6% of patients had ≥20% decline in LV function**
  - **0.2% experienced symptomatic HF**
  - **Appears reversible**
- **Imatinib**
  - **HF is rare but associated with increased age and pre-existing CV risk factors**


Radiotherapy
Coronary artery disease
Coronary sclerosis
Angina
Myocardial infarction
Ischaemic cardiomyopathy
Valvular heart disease
Valvular sclerosis
Stenosis - regurgitation
Clinical complaints / intervention
Pericardial disease
Pericarditis
Effusion
Constrictive pericarditis
Heart failure
Regional LV dysfunction
Late onset heart failure (ischaemia / valvular disease)
Anticancer treatment
1 year
5 years
10 years
Years since exposure
20 years
Coronary artery disease
Thrombosis
Heart failure
LV dysfunction
Heart failure
Late onset heart failure
Pericardial disease
Pericarditis
Hypertension
Therapy-induced
Chronic hypertension
LV hypertrophy
Hypertensive cardiomyopathy / ischaemia
Chemotherapy / Targeted therapy

ASCO Guidelines for Prevention and Monitoring

JCO 35(8):893-911, 2017

- Focus on cardiac dysfunction
  - Primarily HF
- Evidenced-based guidelines
- Multidisciplinary expert panel
- Weighed the consistency of the evidence
- Recommendations based on an analysis of benefits versus harms

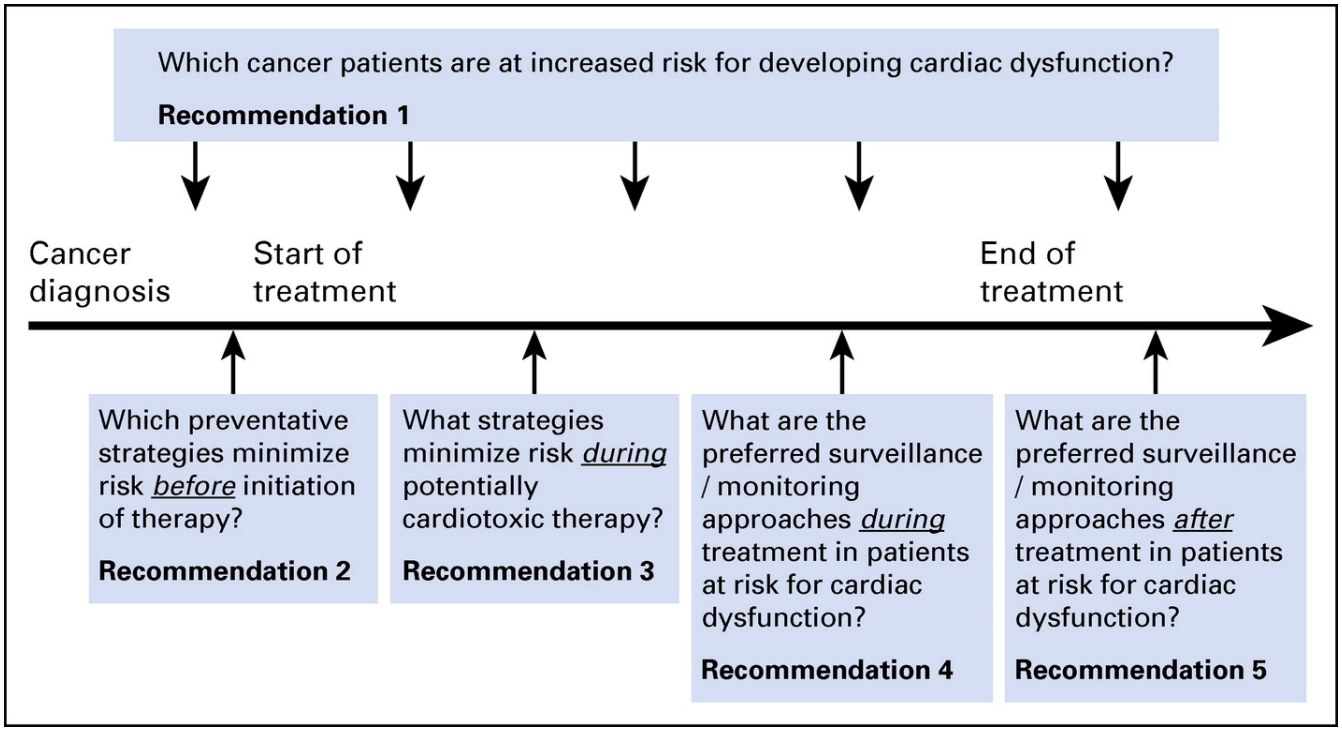


Fig 1. Overarching clinical questions addressed in the clinical practice guideline.

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Patients at Increased Risk for Cardiac Dysfunction - 1

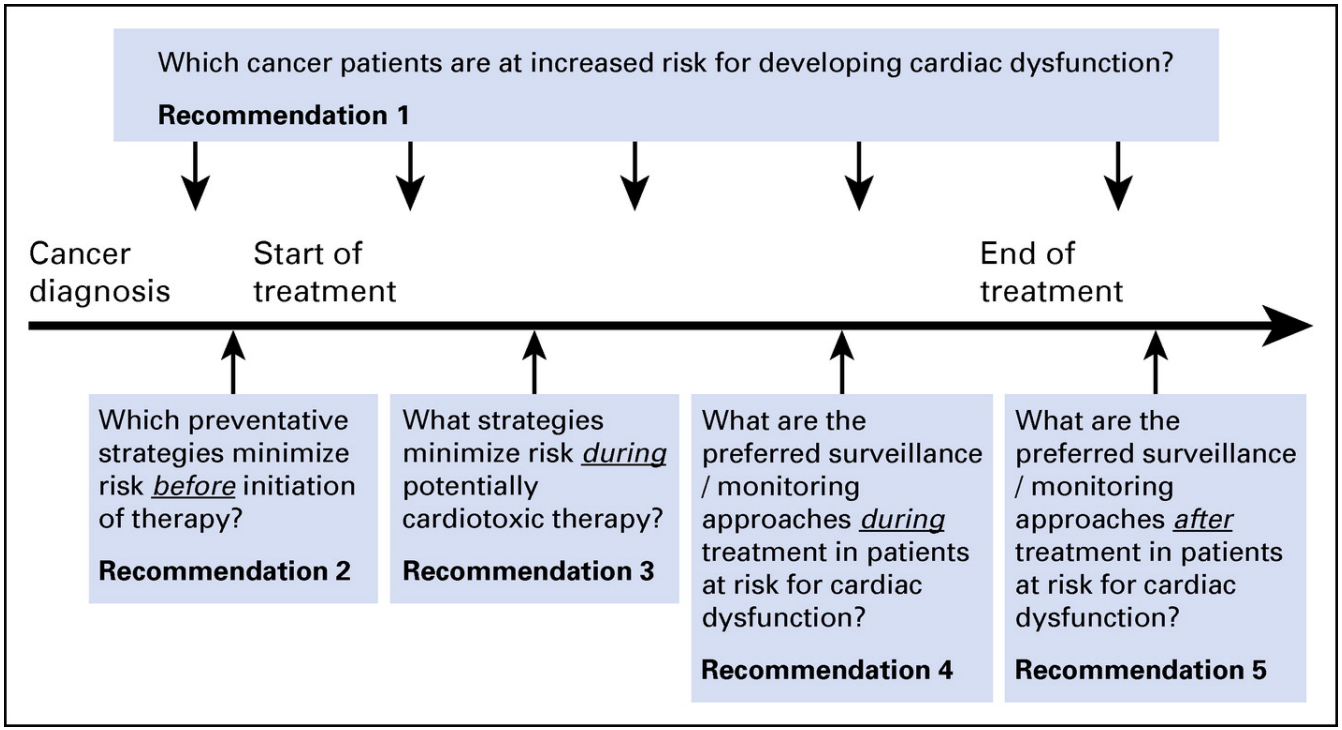
- High dose anthracycline treatment
  - Doxorubicin $\geq$250 mg/m^2
  - Epirubicin $\geq$600 mg/m^2
- High dose RT ($\geq$30 Gy) where the heart is in the treatment field
- Lower dose anthracycline in combination with lower RT dose where the heart is in the treatment field

Patients at Increased Risk for Cardiac Dysfunction -2

- Treatment with lower dose anthracycline or trastuzumab alone, and the presence of any of the following risk factors
  - Multiple cardiac risk factors (≥2) including: smoking, hypertension, diabetes, dyslipidemia, during or after completion of treatment
  - Age ≥60 years
  - Compromised cardiac function at any time during treatment
    - Borderline low LVEF – 50% to 55%
    - History of MI
    - Moderate valvular heart disease

Patients at Increased Risk for Cardiac Dysfunction - 3

- Treatment with lower dose anthracycline followed by trastuzumab
  - Sequential therapy
- No recommendation was made regarding the administration of kinase inhibitors



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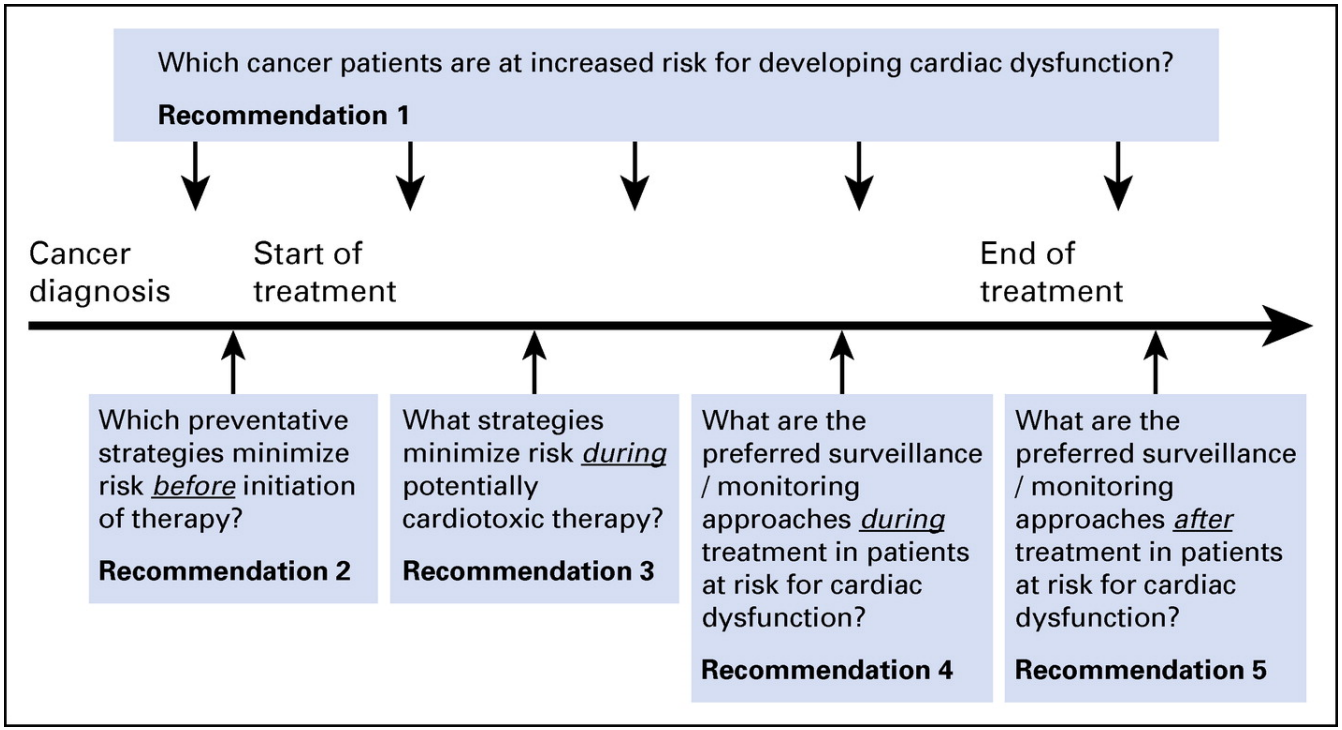
Minimize Risk BEFORE Treatment

- Avoid or minimize use of potential cardiotoxic therapy if alternatives exist
- Perform a comprehensive assessment of patients and screen for CV disease risk factors
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Obesity
  - Smoking
- Obtain an echocardiogram before treatment



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Minimize Risk DURING Treatment - 1

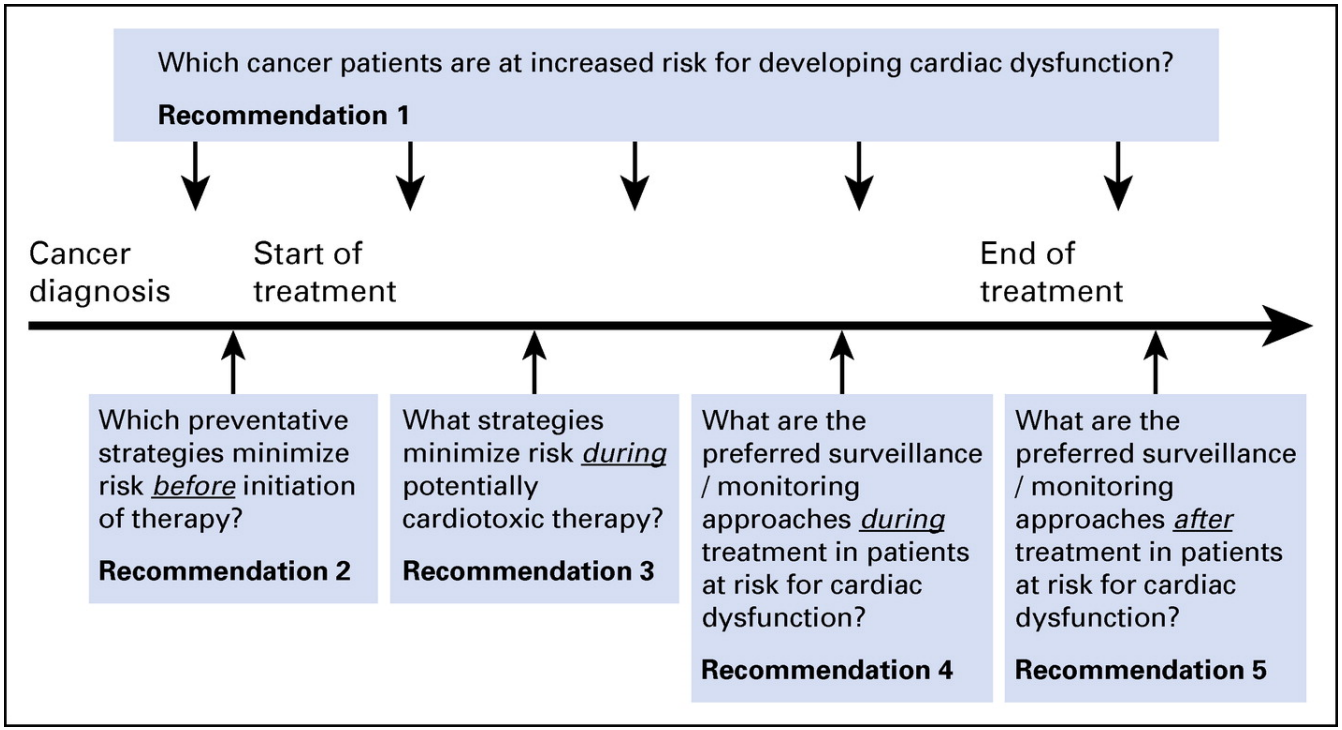
- Screen and manage CV disease risk factors
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Obesity
  - Smoking
- In patients who will may receive high dose anthracyclines (i.e., doxorubicin $\geq$250 mg/m^2, epirubicin $\geq$600 mg/m^2)
  - Use liposomal formulation of doxorubicin
  - Use a continuous infusion of anthracycline
  - Administer dexrazoxane (cardioprotectant)

Dexrazoxane

- Cardioprotectant
- July 2011 – FDA restricted its use
- Increased rate of secondary cancers and acute myelogenous leukemia in pediatric patients
- Mechanism of action
  - Chelates iron
  - Reduces the number of metal ions complexed with anthracycline
  - Decreases the formation of superoxide radicals

Minimize Risk During Treatment - 2

- For patients who require mediastinal RT
  - Lowest dose possible
  - Use more tailored and precise RT fields that exclude the heart as much as possible
  - Use deep inspiration breath holding



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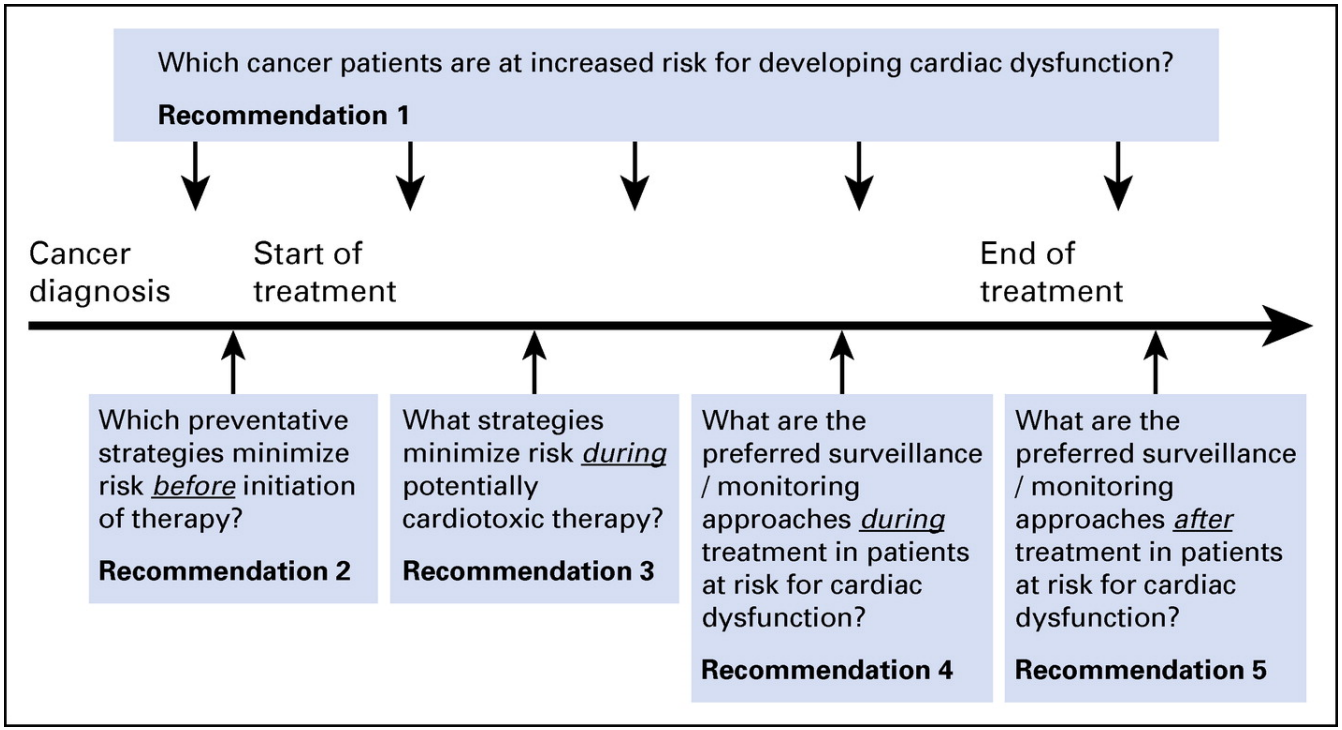
Monitoring DURING Treatment - 1

- Careful history and physical exam
- If patient has clinical signs/symptoms of cardiac dysfunction
  - Echocardiogram
  - Cardiac MRI or MUGA scan if echocardiogram is not available
  - Serum cardiac biomarkers (troponins, natriuretic peptides)
  - Referral to a cardiologist

Monitoring DURING Treatment - 2

- For asymptomatic patients considered to be at increased risk
  - Echocardiogram for monitoring
  - Frequency of monitoring is based on clinical judgement
- No recommendation could be made on discontinuation of treatment
  - Collaboration with cardiologist, oncologist, and patient
- Use echocardiogram surveillance in patients with breast cancer receiving trastuzumab
  - Frequency at clinicians discretion



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Monitoring AFTER Treatment - 1

- Careful history and physical exam
- If patient has clinical signs/symptoms of cardiac dysfunction
  - Echocardiogram
  - Cardiac MRI or MUGA scan if echocardiogram is not available
  - Serum cardiac biomarkers (troponins, natriuretic peptides)
  - Referral to a cardiologist

Monitoring AFTER Treatment - 1

- In asymptomatic patients who are at increased risk for cardiac dysfunction
  - Perform an echocardiogram between 6 and 12 months after completion of treatment
- Patients identified with asymptomatic cardiac dysfunction
  - Refer to cardiologist or cardio-oncologist

LIFESTYLE MODIFICATIONS

- Management of cardiovascular risk factors
  - Smoking
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Obesity
- Healthy lifestyles
  - Diet
  - Exercise
  - Stress reduction
- Maintenance of a high index of suspicion