Management of Chemotherapy-Induced Cardiotoxicities

A presentation for HealthTrust Members
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Speaker Disclosures

- The presenter and their preceptor have no financial relationships with any commercial interests pertinent to this presentation.

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Learning Objectives

LIST

the common cardiotoxicities observed with chemotherapy agents

IDENTIFY

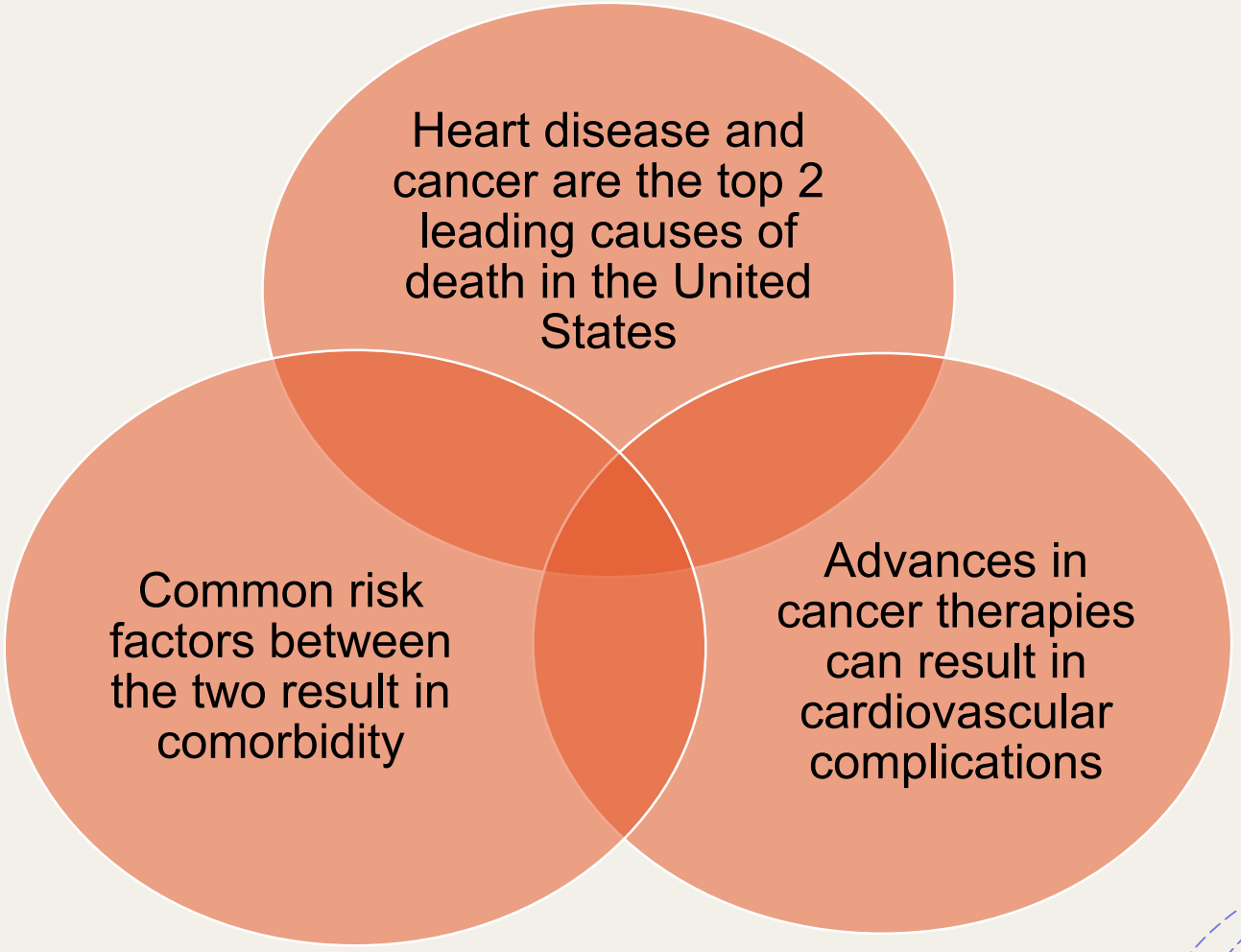
chemotherapy agents that can cause cardiotoxicities

INDICATE

pharmacotherapy options for the management of the cardiotoxicities

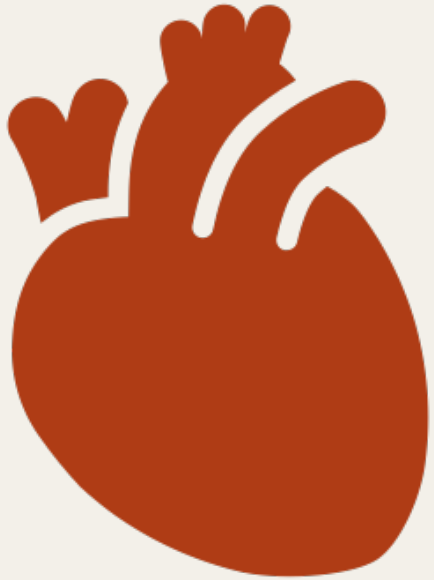
What is Cardio-Oncology?

Correlation is Causation?



Curigliano G, et al. Ann Oncol 2020;31(2):171-190.

Cardio-Oncology



- New discipline within cardiovascular medicine
- Cardiac dysfunction can:
  - Interfere with the efficacy of treatment
  - Decrease quality of life
  - Impact the actual survival of the patient with cancer
- Toxicity can range from asymptomatic and transient to more clinically significant and long-lasting

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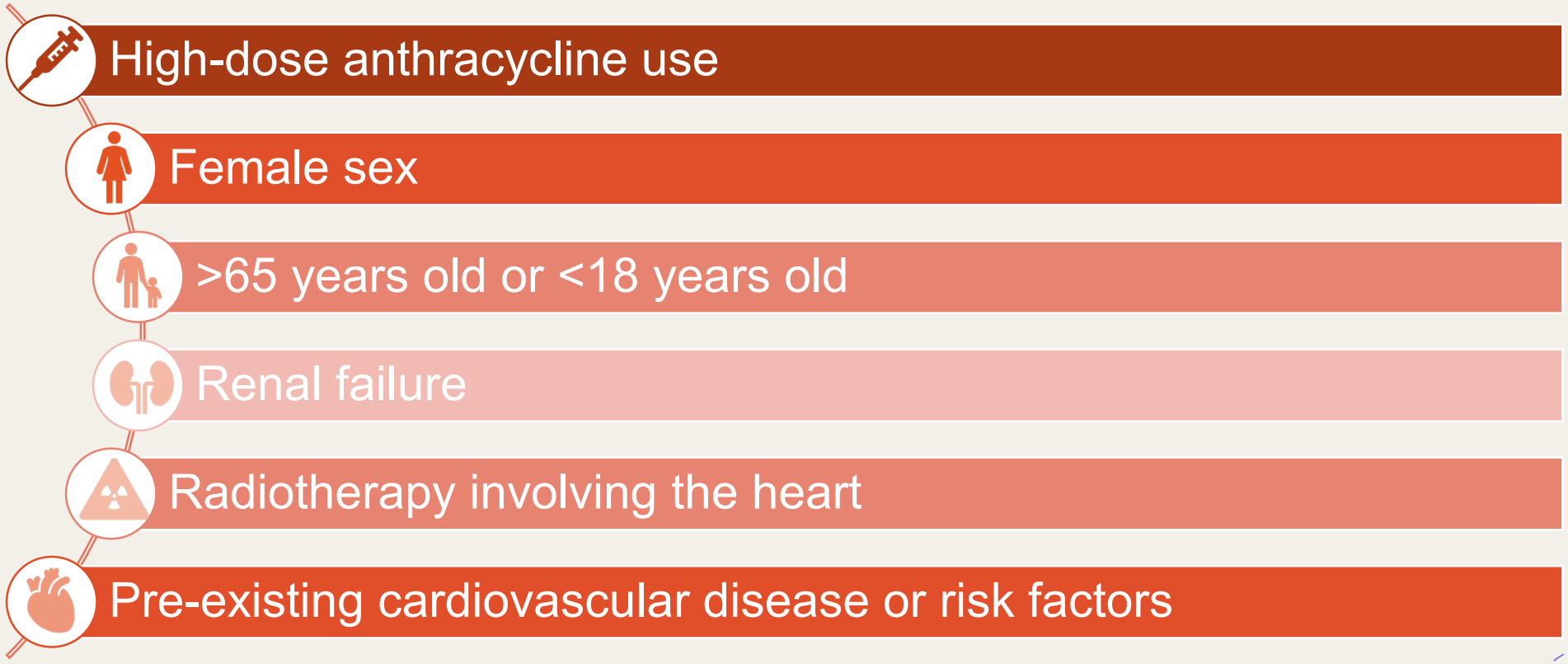
Risk Factors



Alexandre J, et al. J Am Heart Assoc 2020;9:e018403.
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Cardiotoxicities

-Heart Failure

Ischemia

Hypertension

Pericardial Diseases

Thromboembolism

QTc Prolongation

Arrhythmias

Immune Checkpoint Inhibitor-Related Myocarditis

Heart Failure (HF)

Etiology

Chemotherapy-induced cardiomyopathy has been described in 1% to 5% of cancer survivors

- One of the worst survivals among cardiomyopathies
- Early diagnosis and timely intervention

Drug-associated cardiotoxicity is defined as 1 or more of the following:

- Cardiomyopathy characterized by a decrease in ejection fraction (EF) globally or due to regional changes in interventricular septum contraction
- Symptoms associated with HF
- Signs associated with HF, such as S3 gallop, tachycardia, or both
- Decline in initial EF of at least 5% to <55% with signs and symptoms of HF or asymptomatic decrease in EF of at least 10% to <55%

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Chang HM, et al. JACC 2017;70(20):2536-2551.
Curigliano G, et al. Ann Oncol 2020;31(2):171-190.

Contributing Agents

Anthracyclines
doxorubicin

Alkylating Agents
cyclophosphamide
ifosfamide

HER-2 Targeted Therapies
trastuzumab

VEGF Inhibitors
bevacizumab

Small Molecule TKIs
sunitinib
sorafenib

Proteasome Inhibitors
carfilzomib

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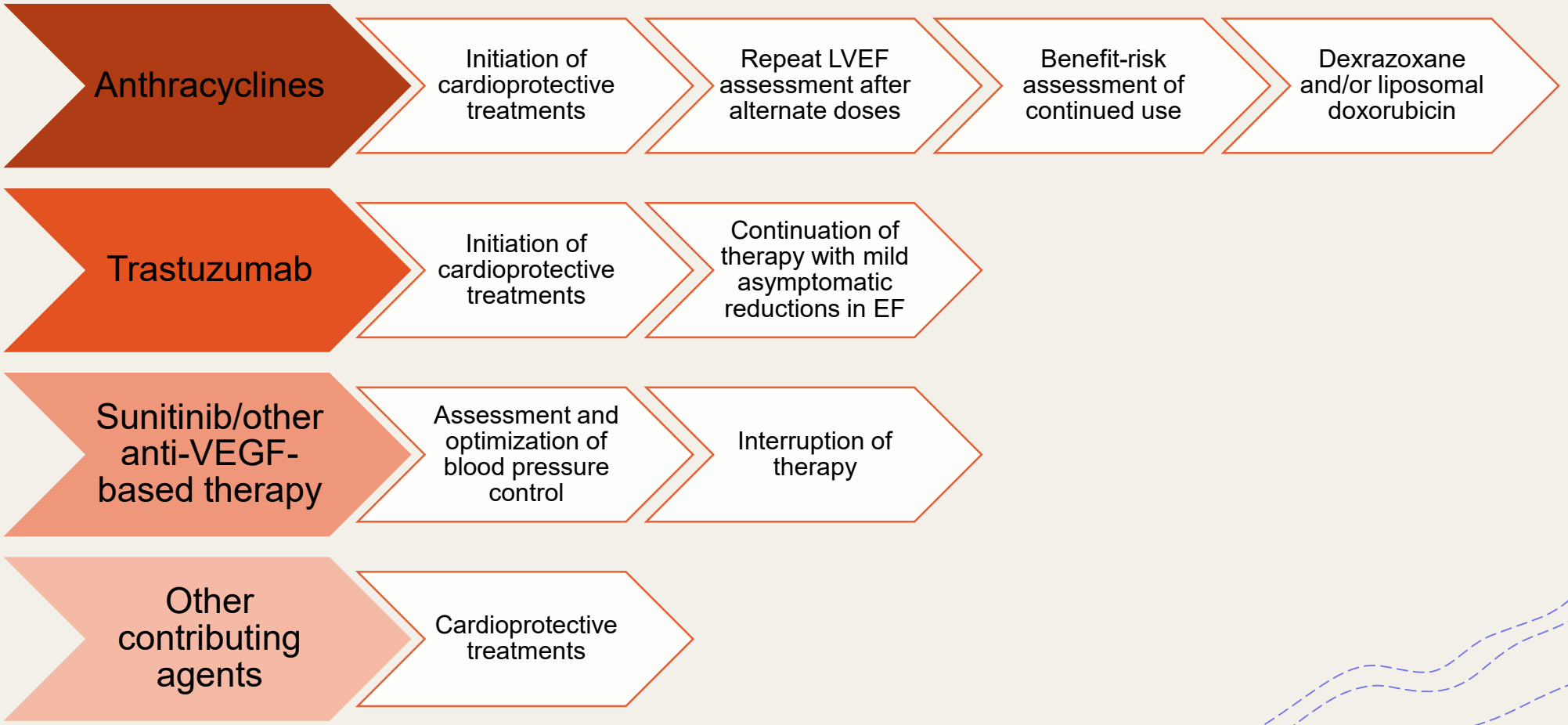
Management



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Dexrazoxane (Zinecard®)

Indication

Reduce the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and who will continue to receive doxorubicin therapy to maintain tumor control

Off-Label Uses

Anthracycline-induced cardiotoxicity

Treatment of other cancers

Dosage/ Administration

Recommended dosage ratio of dexrazoxane to doxorubicin is 10:1

Do not administer doxorubicin before dexrazoxane, use with chemotherapy initiation, use with non-anthracycline chemotherapy regimens

Warnings/ Precautions

Acute myeloid leukemia (AML)

Myelodysplastic syndrome (MDS)

Zinecard (dexrazoxane) package insert. New York, NY: Pfizer; 2016 Oct.

Ischemia

Etiology

Cancer treatment	• Coronary artery disease • Acute coronary syndrome
Cancer	• Pro-thrombotic state • Acute coronary syndrome

Campia U, et al. Circulation 2019;139:e579–e602.
Chang HM, et al. JACC 2017;70(20):2536-2551.

Contributing Agents

Antimetabolites

5-FU

Anti-Microtubule Agents

paclitaxel
docetaxel

Antibody-Based VEGF Inhibitor

bevacizumab

Small Molecular TKIs

sorafenib

Proteasome Inhibitors

carfilzomib

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Management

- Antiplatelet therapy: Aspirin, Clopidogrel
- Anticoagulation therapy: Heparin
- Statins
- Beta-blockers
- Coronary vasodilators: Nitrates, Calcium Channel Blockers
- Treatment discontinuation

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Hypertension

Etiology

- Hypertension: BP >140/90 mmHg
- Most common cardiovascular comorbidity reported in cancer registries
- Early diagnosis and treatment are essential

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Contributing Agents

Systemic Hypertension	Other Contributing Agents
• VEGF inhibitors: *bevacizumab, sorafenib, sunitinib* • Proteasome Inhibitors: *carfilzomib*	• Monoclonal antibody based TKI: *ado-trastuzumab emtansine* • Monoclonal antibodies: *alemtuzumab, ibritumomab, ofatumumab, rituximab* • mTOR inhibitors: *everolimus, temsirolimus* • Small molecule TKIs • Proteasome inhibitors: *bortezomib* • Antimetabolites: *decitabine*
Pulmonary Hypertension	
• *Dasatinib*	

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Angiotensin converting enzyme inhibitors (ACEiS)
Angiotensin II receptor blockers (ARBs)
Dihydropyridine calcium channel blockers (CCBs)
Endothelin receptor antagonists (ERAs)

Management

- Treatment Target: <130/80 mmHg
- Pharmacologic Management:
  - Systemic Hypertension: ACEis, ARBs, CCBs
  - Pulmonary Hypertension: PDE5 Inhibitors, ERAs, CCBs
- Routine blood pressure monitoring
- Manage modifiable cardiovascular risk factors

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Pericardial Diseases

Etiology

Manifestation of late-stage malignancies

- Lung cancer
- Breast cancer
- Leukemia
- Lymphoma

Can also develop due to:

- Chemotherapy
- Radiation therapy
- Opportunistic infections

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Contributing Agents

Anthracyclines	Cyclophosphamide	Cytarabine	Imatinib
Dasatinib	Interferon-alpha	Arsenic Trioxide	Docetaxel/5-FU
All-trans retinoic acid	Busulfan	Radiation Therapy	Immune Checkpoint Inhibitors

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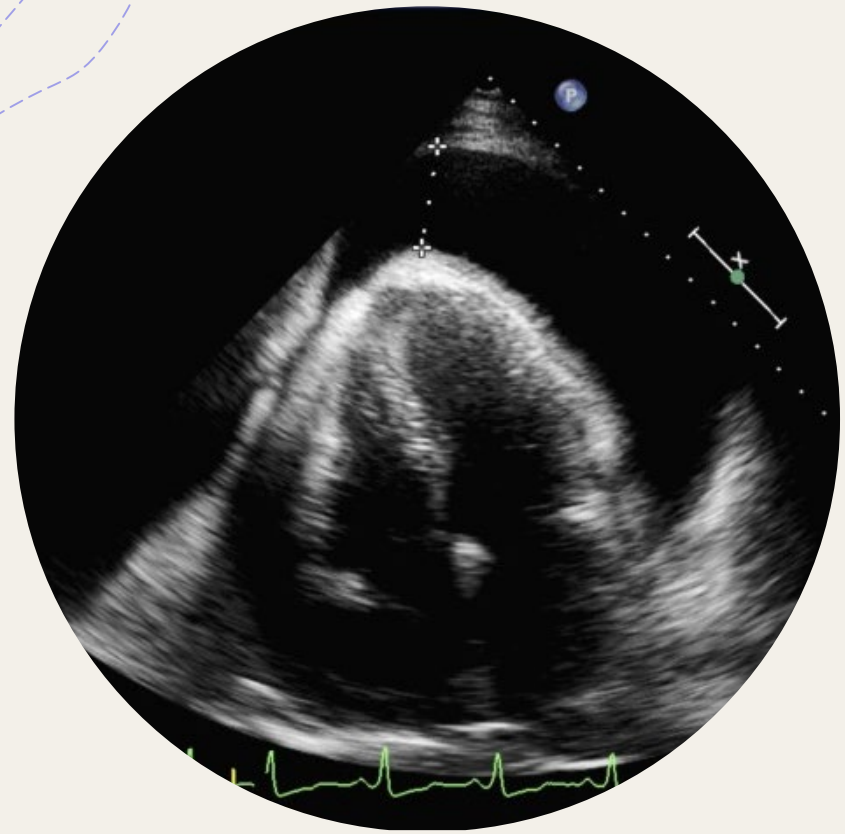
Management



- Diagnosis: Echocardiography, MUGA scan
- Patients are often asymptomatic with small to moderate pericardial effusion but can be symptomatic with impending cardiac tamponade
- Initial management: Find/treat underlying cause, pericardiocentesis
- Recurrent pericardial effusion: Surgery

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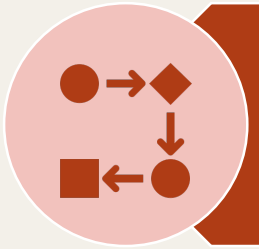
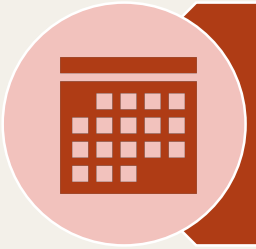
Thromboembolism

Etiology



Release of prothrombotic factors into the circulation that activate the clotting cascade



Risk is higher in the first 6 months after diagnosis and returns to baseline at 1 year

Risk is higher with certain cancers, metastatic diseases, and certain risk factors

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Contributing Agents

Alkylating Agents

cisplatin

Angiogenesis Inhibitors

lenalidomide
thalidomide
pomalidomide

Histone Deacetylase Inhibitors

vorinostat

Small Molecule TKIS

axitinib, dabrafenib, erlotinib, nilotinib, pazopanib, ponatinib, sunitib, trametinib, ziv-aflibercept

VEGF Inhibitors

bevacizumab

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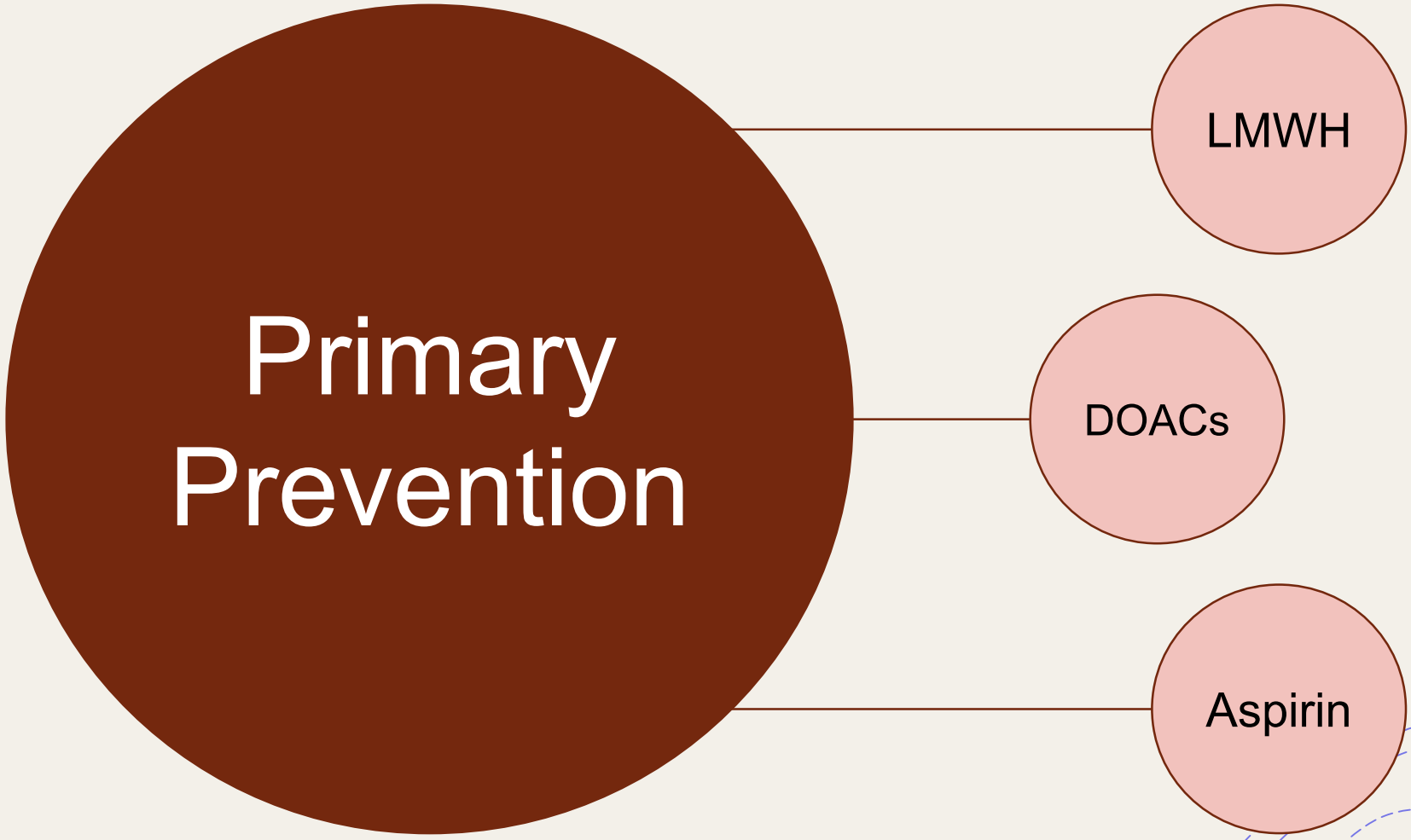
LMWH: Low molecular weight heparin
DOACs: Direct oral anticoagulants

Management



Chang HM, et al. JACC 2017;70(20):2552-2565.
Key NS, et al. J Clin Oncol 2019;38:496-520.

QTc Prolongation

Etiology

- Abnormality in depolarization/repolarization
  - Can lead to torsades de pointes and sudden death
- Normal QTc interval:
  - <430 ms in males
  - <450 ms in females
- QTc interval prolongation is defined as:
  - QTc prolongation >500 ms *AND/OR*
  - ΔQTc of >60 ms *AND/OR*
  - Ventricular arrhythmia occurrence

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Contributing Agents

Histone Deacetylase Inhibitors

belinostat

vorinostat

Small Molecule TKIs

dabrafenib, dasatinib, lapatinib, nilotinib, vandetanib

BRAF Inhibitor

vemurafenib

Arsenic Trioxide

Drug-Drug Interactions

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Management

Baseline ECG

- Repeat 7 days after therapy initiation

Correct electrolyte abnormalities and cardiac risk factors

- Hypokalemia and hypomagnesemia

Identify drug-drug interactions

Temporarily interrupt cancer treatment

Management of torsades de pointes: 2 g IV magnesium

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Arrhythmias

Etiology

Bradycardia/ Heart Block

- Symptoms include fatigue, dizziness, syncope
- Treatment of heart block depends on the type of escape rhythm present (junctional vs. ventricular)

Tachyarrhythmias

- Includes supraventricular arrhythmias, atrial fibrillation and ventricular arrhythmias
- Incidence is higher in patients with stage IV cancer
- Caused by QTc-prolonging agents, inflammation in advanced cancer, direct cardiac involvement by tumor, metabolic abnormalities
- Afib is associated with advanced age, hypoxia, increased sympathetic drive, and/or paraneoplastic conditions

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Contributing Agents

Bradycardia/ Heart Block

- *Arsenic trioxide*
- *Irinotecan*
- *Methotrexate*
- *Mitoxantrone*
- *Octreotide*
- *Thalidomide*

Both

- *5-FU*
- *Cisplatin*
- *Paclitaxel/ Docetaxel*

Tachyarrhythmias/ Atrial Fibrillation

- *Doxorubicin*
- *Gemcitabine*
- *Ibrutinib*
- *Ifosfamide*
- *Mitoxantrone*

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Management

Rhythm vs. Rate Control
Rhythm control: class 1B antiarrhythmic drugs (lidocaine, mexiletine) less likely to cause drug interactions and QTc prolongation
Rate control: beta-blockers, digoxin or the non-dihydropyridine calcium channel blockers

Thromboembolic Prophylaxis
Decision based on CHA2DS2-VASc and HAS-BLED scores
Anticoagulation options include LMWH, warfarin and DOACs

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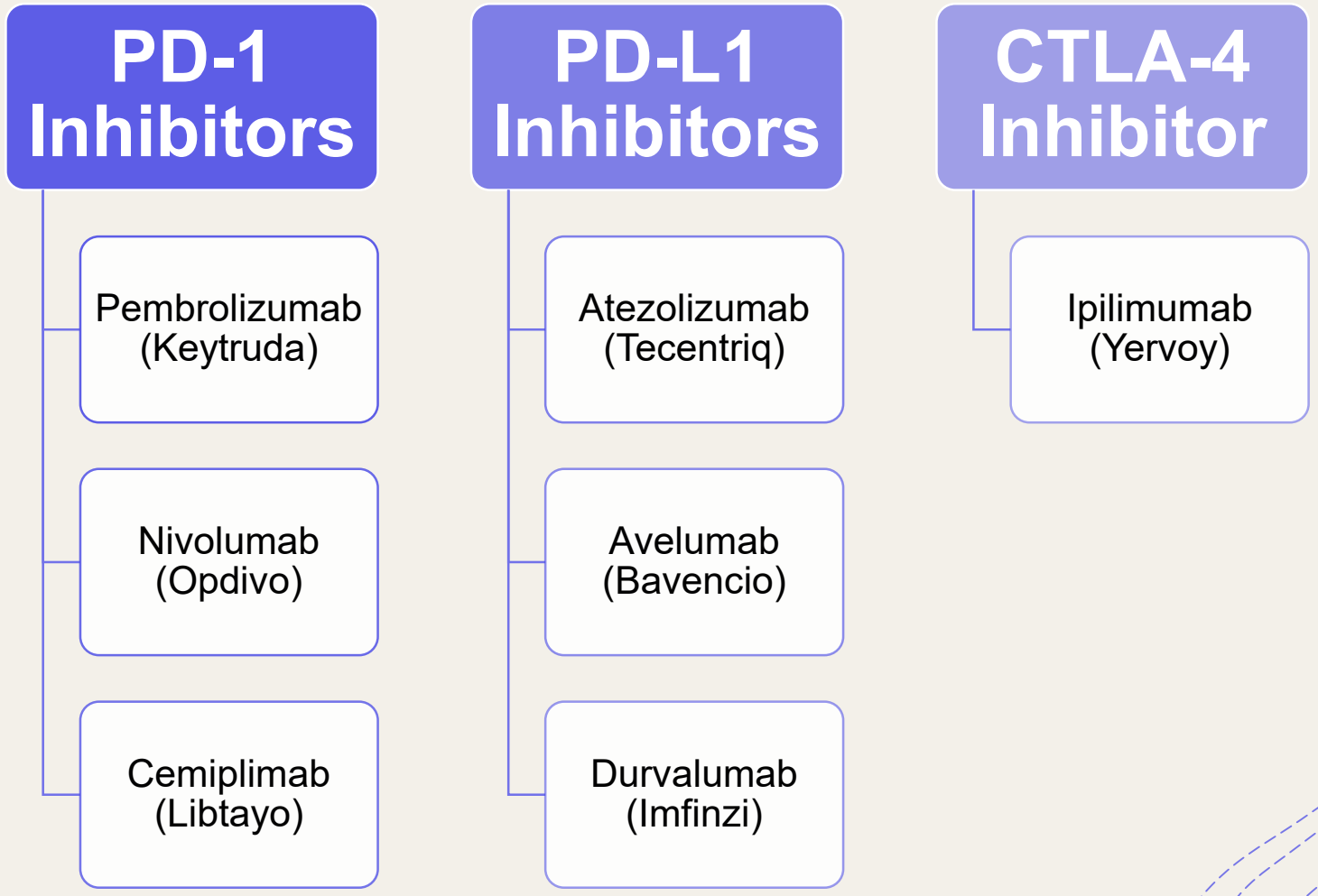
Immune Checkpoint Inhibitor (ICI) – Related Myocarditis

Etiology

- Immune checkpoints are T-cell regulatory pathways that inhibit antitumor T-cell activation
- Leverage the immune system to identify and target cancer cells → target PD-1, PDL-1, and CTLA-4 receptors
- Myocarditis appears to be mediated by T-cells and macrophages
- ICI-related myocarditis has a reported incidence of 0.04% to 1.14%
- Median time to presentation of cardiotoxic effects is within 3 ICI cycles but ranges widely
- Risk Factors: Pre-existing cardiovascular risk factors/disease, combination ICI therapy

Lyon AR, et al. Lancet Oncol 2018;19:e447–58.
Palaskas N, et al. J Am Heart Assoc 2020; 9(2).

Contributing Agents



Immune Checkpoint Inhibitors and Their Side Effects. American Cancer Society. 2019.

Management

Differential Diagnosis: Appropriate work-up for ICI-associated CV toxicity
Gold Standard: Endomyocardial biopsy

Suspicion or confirmation of ICI-associated myocarditis

- Hold ICI therapy
- Initiate high-dose corticosteroids (methylprednisolone 1000 mg/day followed by oral prednisone 1 mg/kg/day)
- For steroid-refractory or high-grade myocarditis with hemodynamic instability:
  - Anti-thymocyte globulin
  - Infliximab (except in patients with HF)
  - Mycophenolate mofetil
  - Abatacept

Permanently discontinue therapy with any clinical myocarditis

- Decision to restart therapy needs to be individualized
- If ICI therapy needs to be restarted, monotherapy with an anti-PD-1 agent might be considered

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Steroid Tapering Example

1000 mg IV methylprednisolone daily x 3 days

2 mg/kg/day PO prednisolone for 14 days

1 mg/kg/day PO prednisolone for 14 days

Taper over at least 4 to 6 weeks

**Monitor troponin levels at dosage change

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Clinical Implications

Scope of cardio-oncology is wide

- Prevention
- Detection
- Monitoring
- Treatment

Future novel cancer treatments

- Safe development to minimize impact on cardiovascular health

Assessment Questions

Assessment Question 1

Which of the following chemotherapeutic agents result in cardiotoxicities? *Select all that apply.*

a) Doxorubicin
b) Trastuzumab
c) Fluorouracil
d) Dasatinib

Assessment Question 1 – Correct Response

Which of the following chemotherapeutic agents result in cardiotoxicities? *Select all that apply.*

a) **Doxorubicin**
b) **Trastuzumab**
c) **Fluorouracil**
d) **Dasatinib**

Assessment Question 2

Which of the following is a common cardiotoxicity associated with anthracycline use?

a) Pulmonary Hypertension
b) Venous Thromboembolism
c) QTc Prolongation
d) Heart Failure

Assessment Question 2 – Correct Response

Which of the following is a common cardiotoxicity associated with anthracycline use?

a) Pulmonary Hypertension
b) Venous Thromboembolism
c) QTc Prolongation
d) **Heart Failure**

Assessment Question 3

Which pharmaceutical agents should not be used for the management of chemotherapy-induced hypertension?

a) ACE Inhibitors
b) Non-DHP Calcium Channel Blockers
c) ARBs
d) DHP Calcium Channel Blockers

Assessment Question 3 – Correct Response

Which pharmaceutical agents should not be used for the management of chemotherapy-induced hypertension?

a) ACE Inhibitors
b) **Non-DHP Calcium Channel Blockers**
c) ARBs
d) DHP Calcium Channel Blockers

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Thank you!

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