JADPRO Cardio-Oncology Updates: Basics 101

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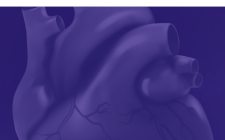
Objectives

- Examine the relationship between CV risk and cancer
- Define cardiotoxicity
- Identify CV risk in general and cancer populations
- Describe screening and surveillance recommendations
- Discuss effective preventative and management strategies

CV = cardiovascular.

What Is Cardio-Oncology?



Cancer Facts

- There are 16.9 million cancer survivors in the United States and close to 30 million worldwide
- Rates of survival have improved even for metastatic disease
- Competing causes of death have increased all cause mortality

National Cancer Institute. Division of Cancer Control and Population Sciences. https://cancercontrol.cancer.gov; American Cancer Society. Cancer Facts & Figures 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf.

Cancer Facts: The Past

- 5-year survival rate for all cancers between 1975 and 1977: **49%**
- Entire treatment focus was survival
- No interest in treatment-related effects or QOL
- CV risk not considered

QOL = quality of life; National Cancer Institute. Division of Cancer Control and Population Sciences. https://cancercontrol.cancer.gov; American Cancer Society. Cancer Facts & Figures 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf.

Cancer Facts: Today

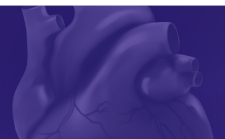
- 5-year relative survival rate for all cancers diagnosed between 2008-2012: **83.8%**

Cancer Type	Current 5-Year Relative Survival Rate
Breast	91%
Melanoma	92%
Colorectal	64%
Early lung	56%
Leukemia	65%
Childhood leukemia	98.3%

National Cancer Institute. Division of Cancer Control and Population Sciences. https://cancercontrol.cancer.gov; American Cancer Society. Cancer Facts & Figures 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf.

What Is Cardio-Oncology?

- Subspecialty of cardiology
- Increased need for specialized care
- Purpose
  - To design surveillance strategies and interventions to reduce CV risk
  - To prevent cardiotoxicities
  - To explore the interplay of cancer, cancer treatment, and CV risk



What Is Cardio-Oncology? (cont)

…or is it onco-cardiology?

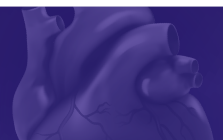
Cardio-Oncology Goals

- Goals for management
  - Keep patients safe during cancer chemotherapy and/or radiation
  - Assess CV risk that contributes to chemotherapy- and/or radiation-induced toxicity
  - Institute interventions to reduce overall risk
- Surveillance is based on CV risk and risk of drug cardiotoxicity
- CV risk is treated aggressively with medications found to be cardio-protective
- Following completion of cancer treatment, yearly visits are instituted for 5 years

Section Summary

- Cancer survival rates are increasing, which means the number of cancer survivors is growing. Yet, long-term cancer treatment toxicity data remain scarce.
- Cardio-oncology is a subspecialty of cardiology developed as a result of the oncology data indicating that newly developed drugs for cancer treatment were having unanticipated cardiac side effects.
- Cardio-oncology designs surveillance strategies and interventions to reduce CV risk and prevent cardiotoxicities.

Link Between Cancer, Treatment, and Heart Disease



Link 1: CV Risk and Cancer

- CVD is the most common cause of death in breast cancer survivors
- CVD may be due to pre-existing disease
- CVD may be due to cancer treatment
  - Weight gain, HTN, diabetes, dyslipidemias

CVD = cardiovascular disease; HTN = hypertension

Mehta L, et al. *Circulation.* 2018;137:e30-e66; Pituskin E, et al. *BMJ Cancer.* 2016;16(1):733.

Link 1: CV Risk and Cancer (cont)

- Barriers
  - Lack of routine CV risk screening
  - Failure to recognize and treat risk in light of cancer therapies known to exacerbate risk factors
- No US standards exist for CV assessment before or after cancer therapy
- This new knowledge gave justification for new subspecialty

Link 2: CV Risk and CVD in the United States

- An estimated 121.5 million American adults have one or more types of CVD[1]
  - Stroke
  - Heart attack
  - Peripheral vascular disease
- CVD is the leading cause of death in women[2]
  - 1 in 2 women will die of heart disease or stroke
  - 1 in 25 women will die of breast cancer
  - Since 1984 CV-related death in women has exceeded that among CVD in men[3]
  - Estimated lifetime risk: 39% at age 50

1. Benjamn EJ, et al. *Circulation*. 2019;139:e56-e528; 2. Centers for Disease Control and Prevention. Women and Heart Disease. https://www.cdc.gov/heartdisease/women.htm; Moran B, et al. *Nurs Womens Health.* 2013;17:63-68; BreastCancer.org. U.S. Breast Cancer Statistics. https://www.breastcancer.org/symptoms/understand_bc/statistics; 3. American Heart Association. Women & Cardiovascular Disease. 2013. https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_319576.pdf.

Link 2: CV Risk and CVD in the United States (cont.)

- CVD related to metabolic syndrome is common in mid-life women
  - Metabolic syndrome: a set of risk factors that includes abdominal obesity, a decreased ability to process glucose (increased blood glucose and/or insulin resistance), dyslipidemia, and HTN
- NHANES III,[1] WISE, WISEWOMAN,[2] and metabolic risk
- Perception of CV risk in women low[3]
- 53.8 million women with total cholesterol > 200 mg/dL[4]
- 71.3 million women overweight or obese[4]

1. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. https://www.cdc.gov/nchs/nhanes/index.htm; 2. Centers for Disease Control and Prevention. WISEWOMAN. https://www.cdc.gov/wisewoman/index.htm; 3. Mosca L, et al. *Circulation.* 2007;115:1481-1501; 4. American Heart Association. Women & Cardiovascular Disease. 2013. https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_319576.pdf.

Link 2: CV Risk and CVD in the United States (cont)

- Newly diagnosed women with cancer may be at risk for CVD unrelated to their cancer treatment
- Guidelines support CV risk assessment for all at age 20
  - But provider compliance is low

Arnett DK, et al. *Circulation*. 2019;140:e596-e646.

Burden of CV Risk in the Cancer Population

- 7-fold higher mortality rate
- 15-fold increase in HF
- 10-fold higher rates of CVD
- 9-fold higher rate of stroke
- Survivors have higher rates of HTN, stroke, dyslipidemia, and MI

HF = heart failure; MI = myocardial infarction

Hermann J, et al. *Mayo Clin Proc.* 2014;89-1287-1306.

Burden of CV Risk in the Cancer Population (cont)

- CVD risk associated with chemotherapy has been reported to be similar to smoking
- Risk higher with anthracyclines
- Risk of HF and MI increased in survivors subsequent 20 years

Hermann J, et al. *Mayo Clin Proc.* 2014;89-1287-1306.

CV Risk Pre-Chemotherapy

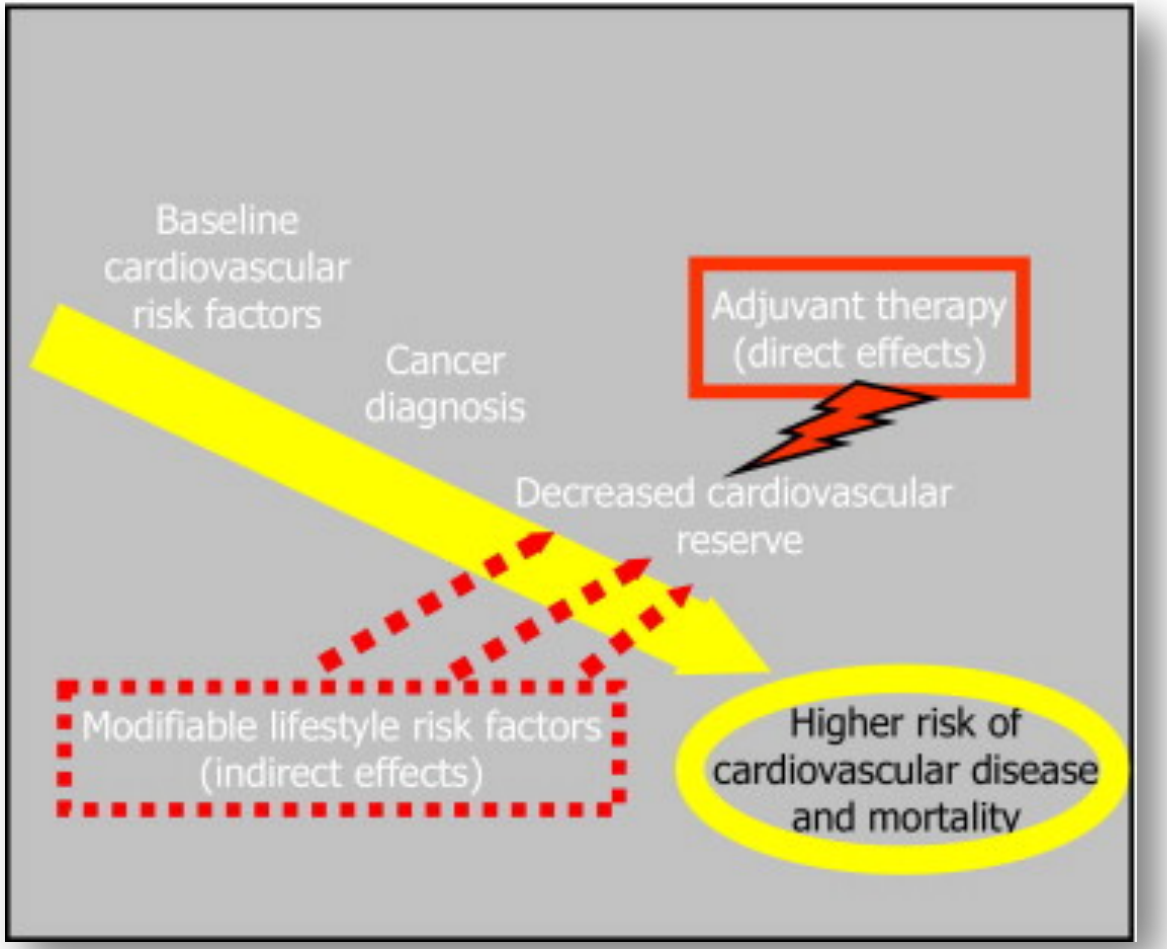
- Breast cancer most common cancer in women
- Substantial amount of CV research has emerged in those diagnosed and treated
- Few studies included CV risk prior to treatment

American Heart Association. Women & Cardiovascular Disease. 2013. https://www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_319576.pdf; Coviello JS. *JADPRO.* 2018;9(2):160-176.

Burden of CV Risk Among Women Prior to Receiving Chemotherapy

- How does this burden of CV risk impact cardiac sequelae in cancer treatment?

Link 3: Multiple Hit Theory of CV Risk

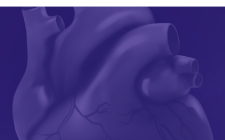


Cardinale D, et al. *Semin Oncol.* 2013;40:186-198.

Section Summary

- CVD has been reported to be the most common cause of death among breast cancer survivors, even more common than cancer reoccurrence.
- There is a lack of routine CV risk screening among patients undergoing cancer treatments, and no US standards exist for CV assessment before or after cancer therapy in adult cancer survivors.
- A large proportion of Americans have CVD, and CVD is the leading cause of death in women although they perceive their risk to be lower than that of men.
- The multiple hit theory hypothesizes that patients who may have baseline CV risk factors receive cancer treatment, which has direct and indirect impacts on their CV risk, combining to increase the risk of CVD and mortality.

Cardio-Oncology Standards of Care



Cardio-Oncology Standards of Care

- No specific standard in the United States
- 2017 update of the 2013 ACCF/AHA Guidelines for the Management of Heart Failure
- 2020 ESMO Clinical Practice Guidelines
- Pharmaceutical company recommendations
- Institution-based (Mayo Clinic) guidelines including comprehensive review of literature

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ESMO = European Society for Medical Oncology

2017 Update ACCF/AHA Guidelines for the Management of Heart Failure

- Stage A
  - At high risk for HF
  - No structural heart disease
  - No symptoms
  - “Patients using cardiotoxins”
  - Goals for therapy
    - Heart-healthy lifestyle
    - Prevent structural abnormalities
    - Prevent CVD
  - Drug therapy
    - ACE inhibitors
    - ARBs
    - HMG-CoA reductase inhibitors (statins)

- Stage B
  - Structural heart disease (echo)
    - LVH
    - Diastolic dysfunction
    - Left atrial enlargement
  - Goals
    - Prevent further cardiac remodeling
    - Prevent heart failure symptoms
  - Drugs
    - ACE inhibitors
    - ARBs
    - Beta or alpha-beta blockers
    - HMG-CoA reductase inhibitors (statins)

ACE = angiotensin converting enzyme; ARBs = angiotensin receptor blockers; echo = echocardiogram; LVH = left ventricular hyperatrophy.

Yancy CW, et al. *Circulation.* 2017;136:e137-e161.

ESMO Clinical Practice Guidelines

- Literature support and expert panel
  - No randomized control trials
- Purpose: To summarize state of the science regarding CV complications in the context of cancer therapy
  - LVD
  - Myocardial ischemia
  - HTN
  - QTc prolongation
- Recommendations for cancer patients
  - CV assessment and prevention
  - Optimal screening and monitoring of cardiac function during cancer treatment

LVD = left ventricular dysfunction

Curigliano G, et al. *Ann Oncol.* 2020;31:171-190.

Mayo Clinic Practical Aspects of Care

- Based on the review of the literature (1960-2014)
- Meta-analysis–based risk tool for assessment, monitoring, and management
  - Risk categories are determined by the number of CV risk factors and drug used
  - Monitoring and management based on risk level
- Medication-risk related factors
  - High (risk score of 4)
    - Anthracyclines, cyclophosphamide, ifosfamide, clofarabine, trastuzumab
  - Intermediate (risk score of 2)
    - Docetaxel, pertuzumab, sunitinib, sorafenib
  - Low (risk score of 1)
    - Bevacizumab, dasatinib, imatinib, lapatinib
  - Rare (risk score of 0)
    - Etoposide, rituximab, thalidomide

Herrmann J, et al. *Mayo Clin Proc. 2014;*89(9):1287-1306.

Mayo Clinic Practical Aspects of Care (cont.)

- Patient-related risk factors
  - Cardiomyopathy, HF, CAD or PAD, HTN, diabetes
  - Prior anthracycline use, prior radiation, age < 15
  - Age > 70, female gender
- Risk by cardiotoxicity risk score
  - Risk categories by drug-related risk score plus number of patient risks
- Monitoring recommendations based on risk score
- Developed management algorithms for anthracyclines, trastuzumab, radiation

CAD = coronary artery disease; PAD = peripheral artery disease

Herrmann J, et al. *Mayo Clin Proc. 2014;*89(9):1287-1306.

Industry Guidelines

- Recommendations
  - Based on clinical trials associated with use of trastuzumab in treatment protocols
  - Include a thorough CV assessment prior to and every 3 months during and at end of treatment
  - Include CV follow-up every 6 months for 2 years

AHA and American Institute for Cancer Research Recommendations

- Be as lean as possible without becoming underweight.
- Be physically active for at least 30 minutes every day.
- Avoid sugary drinks and limit consumption of energy-dense foods (particularly processed foods high in added sugar, low in fiber or high in fat).
- Eat a variety of vegetables, fruits, whole grains and legumes (such as beans).
- Limit consumption of red meats (such as beef, pork and lamb) and avoid processed meats.
- If consumed at all, limit alcoholic drinks to two a day for men and one a day for women.
- Limit consumption of salty foods and foods processed with salt (sodium).
- Do not rely on supplements to protect against cancer.

Arnett DK, et al. *Circulation*. 2019;140:e596-e646; Kushi LH, et al. *CA Cancer J Clin.* 2012;62(1):30-67.

Issues

- The ESMO Guidelines use hs-troponin I for ongoing monitoring during each treatment
  - Hs-troponin I is just being introduced in the United States
- Any recommendations that use echo with strain as an early indicator of LVD need to be interpreted with caution
  - No industrial standard for various strain programs

hs = high sensitivity

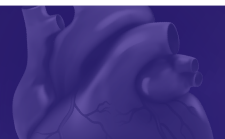
Section Summary

- Evidence-based guidelines for monitoring of cardiotoxicity during and after cancer therapies in adults do not currently exist in the United States.
- The 2017 Update of the 2013 ACCF/AHA Guidelines for HF are the only guidelines based on randomized controlled trials that address the cancer population.
- The ESMO Guidelines—based on literature review and expert panel discussion—are very first guidelines specifically regarding CV risk in cancer patients.
- The Mayo Clinic's practical aspects of care model includes a risk tool for assessment, monitoring, and management based on an analysis of the literature specific to drug categories.
- The AHA and American Institute for Cancer Research have provided recommendations for the prevention of heat disease among cancer patients, including maintaining an appropriate weight, eating a healthy and balanced diet low in salt and red meats, and being physically active for at least 30 minutes per day.
- However, none of these guidelines is one size fits all.

CV Evaluation of Patients Before and During Cancer Therapy

CV Evaluation of Patients Before and During Cancer Therapy

- Standardize assessment
  - To aid in communication across disciplines
  - To aid in treatment decisions
  - To aid in follow-up planning
- Pre-chemo CV risk assessment and physical
- Stratify patients according to cardiotoxicity risk profile



CV Evaluation of Patients Before and During Cancer Therapy (cont)

- Determine baseline CV risk
- 3-D echo with strain/cardiac MRI
- EKG
- Lipids, glucose, baseline insulin, AST, ALT, lipoprotein(a)
- Cardiac toxicity potential of planned regimen

- Follow-up determined by:
  - Baseline CVR profile
  - Specific cancer treatment regimen
  - Development of any cardiac symptoms or events
    - Decline in LVEF
    - HF, effusion
    - Myocardial ischemia
    - Arrythmias
    - QTc > 500 ms
    - Syncope
    - Hypotension
    - Uncontrolled HTN

AST = aspartate aminotransferase; ALT = alanine aminotransferase; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.

Coviello JS, et al. In: A. Fadol, ed. Pittsburg: 2013. Oncology Nursing Society, 267-296.

CV Evaluation of Patients Before and During Cancer Therapy (cont)

- Conversation with oncology to determine any change in chemotherapy
- The addition of cardio-protective agents
- A change in monitoring or surveillance
  - Example: a drop in EF > 10% bringing LVEF < 50% in a patient on trastuzumab
  - Plan would now include:
    - Dose held until EF returns to 50%
    - An echo between each dose instead of every 3 months

EF = ejection fraction

Genentech Herceptin (trastuzumab) prescribing information. Genentech, Inc. 2014 http://www.gene.com/download/pdf/Herceptin_prescribing.

CV Evaluation of Patients After Cancer Therapy

- Individualized recommendations dependent upon the following:
  - Survival prognosis
  - Specific anti-cancer therapy
  - Patient's CV risk and comorbidities
  - Side effects experienced during treatment
- At Yale:
  - Echo, EKG, and CV risk assessment every 3 months for 1 year, then 6 months
  - Yearly for 5 years if they have received anthracyclines, radiation, trastuzumab alone or in combination
  - Yearly Echo
  - Yearly lipids

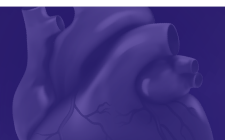
EKG = electrocardiogram

Coviello JS. *JADPRO.* 2018;9(2):160-176.

Section Summary

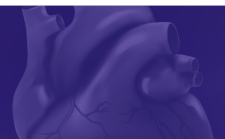
- We have a need to standardize CV risk assessment to aid in communication across disciplines, treatment decisions, and follow-up planning.
- Despite the lack of standards, most cardio-oncology programs evaluate the patient for baseline CV risk and perform a 3-D echo with strain.
- In the case of untoward cardiac events, a conversation with oncology is in order to determine need for change in therapy, including dose reduction, a medication held, or addition of a cardio-protective medication.
- Individualized recommendations depend on various patient factors.

Cancer Treatment–Related Cardiotoxicity



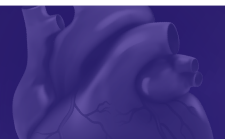
What Is Cardiotoxicity?

- Targeted cancer therapy inhibits growth of cancer cells
- Biologically active in non-cancer cells
- Can disrupt normal physiology of organ systems
- In the CV system, this may lead to cardiac toxicity
- Cardiotoxicity encompasses a number of side effects
  - Arrythmias
  - HTN
  - Myocardial ischemia
  - Thromboembolism
  - LVD (Type II)



Cardiac Sequelae of Cancer and Chemotherapy

- Pericardial effusions, cardiac tamponade
- Extrinsic compression by tumors
- Secreting tumors (ie, pheochromocytomas)
- Coronary spasm, pericarditis from chemotherapy or from access devices in the immunosuppressed
- Myocarditis, myopericarditis

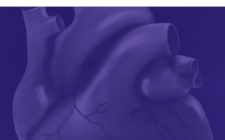


Treatment-Related Risk Factors

- Anthracyclines, trastuzumab
- Immune checkpoint inhibitors
- Combination therapy
- Dose/cumulative dose/rate of administration
- Interval of administration
- Other cardiac risk factors
- Mediastinal radiation
- Presence of underlying heart disease
- Use of other cardiotoxic agents
- Age > 70
- Liver disease

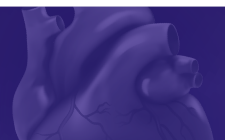
Not Every Symptom Is Toxicity

- Consider nature of acute illness
  - Infection --> sepsis --> HF
  - Bradycardia from antiemetic
  - Causal relationships may be difficult to identify because of the multiplicity of factors



Cardiac Toxicities of Chemotherapeutic Agents

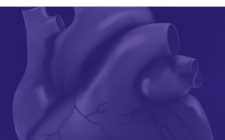
- Myocardial depression
  - Anthracyclines
  - Mitoxantrone
  - Cyclophosphamide
  - Trastuzumab
  - Ifosfamide
  - All-trans retinoic acid
- Ischemia
  - 5-fluorouracil
  - Cisplatin
  - Capecitabine
  - IL-2
- HTN
  - Bevacizumab
  - Cisplatin
- Hypotension
  - Etoposide
  - Paclitaxel
  - Alemtuzumab
  - Cetuximab
  - Rituximab
  - IL-2
  - Denileukin
  - Interferon-γ
  - All-trans retinoic acid
- Bradyarrhythmias
  - Paclitaxel
  - Thalidomide
- Myocarditis/effusions
  - Busulfan
  - Cyclophosphamide



Section Summary

- Targeted cancer therapy is biologically active in non-cancer cells and may lead to short-lived cardiotoxicity during active treatment or long-term toxicity.
- Literature does inform us of the most common risk factors for the development of cardiotoxicities, including certain cancer therapies, interval of administration, patient age, and existence of comorbidities.
- However, not every side effect is directly caused by cancer treatment. Causal relationships may be difficult to recognize due to the multiplicity of factors.

Breast Cancer Drugs and Cardiotoxicity



Cardiac Toxicities of Chemotherapeutic Agents

- Myocardial depression
  - **Anthracyclines**
  - Mitoxantrone
  - Cyclophosphamide
  - **Trastuzumab**
  - Ifosfamide
  - All-trans retinoic acid
- Ischemia
  - 5-fluorouracil
  - Cisplatin
  - Capecitabine
  - IL-2
- HTN
  - Bevacizumab
  - Cisplatin
- Hypotension
  - Etoposide
  - Paclitaxel
  - Alemtuzumab
  - Cetuximab
  - Rituximab
  - IL-2
  - Denileukin
  - Interferon-γ
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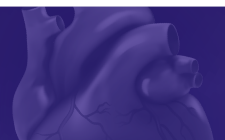
- Bradyarrhythmias
  - Paclitaxel
  - Thalidomide
- Myocarditis/effusions
  - Busulfan
  - Cyclophosphamide



Myocardial Toxicity

- With anthracycline:
  - Toxicity is dose related: 5% to 20% of patients develop DCM depending on risk factors and total dose
  - As a toxin, anthracycline appears to affect individual cardiac cells while leaving others unaffected
- Different from other forms of DCM where insult affects cells more uniformly
- Threshold effect: Gross cardiac function remains normal until threshold % of cells are affected
  - Research now focuses on earlier detection

DCM = dilated cardiomyopathy

Yancy CW, et al. *Circulation.* 2017;136:e137-e161.

Hypotheses for Cardiac Effects

- O_2 free radicals (cell toxic)
- Lipid peroxidation (creates toxic atmosphere for cells)
- Direct toxic effect on the sarcoplasmic reticulum
- Mechanism for cardiotoxicity lack a unifying explanation

Singal PK, et al. Cardiovascular Research. 1998;40(3):426-432.

Stages of Anthracycline Cardiotoxicity

	Acute	Early Chronic	Late Chronic
Onset	Within the first week of treatment	< 1 year after the completion of treatment	> 1 year after the completion of treatment
Risk factor dependence	Unknown	Yes	Yes
Clinical features	Transient LVD; myocardial necrosis; arrhythmia	DCM; arrhythmia	DCM; arrhythmia
Course	Usually reversible on discontinuation of anthracycline	Can be progressive/irreversible	Can be progressive/irreversible

Herrmann J, et al. *Mayo Clin Proc.* 2014;89(9):1287-1306.

Deciding on Anthracycline Use

- Risk factors: > 300 mg/m^2, age > 65, HTN, CAD, other cardiac disease, cardiac irradiation

Potential Cardiac Risk	Potential Oncologic Benefit		
	High	**Intermediate**	**Uncertain or low**
Low (no risk factors)	Standard monitoring	Use with caution; consider non-AC regimen	Consider non-AC regimen
Moderate (1-2 risk factors)	Consider increased monitoring; consider cardio-protective regimen	Use with caution; consider increased monitoring; consider cardio-protective regimen	Avoid AC
High (>2 risk factors)	Use with extreme caution; consider cardio-protective regimen	Avoid AC	Avoid AC

AC = anthracycline

Herrmann J, et al. *Mayo Clin Proc.* 2014;89(9):1287-1306.

Monitoring of LV Function

- Baseline echo with strain for assessment of LVEF
- If baseline LVEF ≥ 50%
  - Repeat after cumulative dose of 250-300 mg/m^2
  - Repeat after cumulative dose of 450 mg/m^2
  - In high risk patients, repeat after cumulative dose of 400 mg/m^2
  - Discontinue if LVEF ↓ > 10% or LVEF < 30%
- If baseline LVEF < 50%
  - Assess LVEF before each dose if LVEF < 50%
  - Discontinue doxorubicin if LVEF decreases ≥ 10% or LVEF < 30%
  - Do not initiate doxorubicin if baseline LVEF < 30%

Tan TC, et al. *Curr Cardiovasc Imaging Rep.* 2012;5(6):403-409.

Anthracyclines and Other Agents

- Anthracyclines + cyclophosphamide + trastuzumab increases the incidence of LVD 3-fold (8% vs. 27%) compared with trastuzumab alone
- Toxicity of doxorubicin increases with addition of 5-fluorouracil
- Taxanes also increase the LVD associated with doxorubicin treatment

Curigliano G, et al. *CA Cancer J Clin.* 2016;66(4):304-325.

Cardiotoxicity

	Type I	Type II (Type III?)
Prototypic agent	Doxorubicin	Trastuzumab
Mechanism	Myocyte death	Myocyte dysfunction
Cumulative dose relationship	Yes	No
Reversible	No	Yes
Increased cardiac mortality	Yes	No

Palaskas N, et al. *J Am Heart Assoc.* 2020;9:e013757.

Myocardial Toxicity

- ErbB2 antagonists (trastuzumab) improve cancer survival but interfere with homeostatic processes in the heart
- Homeostatic processes governed by NRG1
  - Activate intracellular signaling cascades --> various cellular responses
- Feature of NRG-1/ErbB2 performance is its role in cardiac cell growth and survival, AND systolic and diastolic function
- Type II cardiotoxicity may be related to dynamic changes in in NRG1/ErbB2 expression vs actual myocyte loss as in Type I

NRG1 = neuregulin 1.

Lemmens K, et al. *Circulation.* 2007;116(8):954-960; Rupert CE, et al. *Biomarker Insights*. 2015;10(s1):1-7.

Nature of HF

- Incidence of HF in the general population, across the board for all causes:
  - Age 50 to 75: 1%
  - Age 75 to 80: 5%
  - Older than age 80: 10%

Roger VL. *Circ Res.* 2013;113:646-659.

A Brief Look at Pathophysiology

- Whether Type I or Type II, process of LVD occurs independently from symptom development
  - Symptoms do not accurately reflect the extent of LVD
  - Symptom expression depends on compensatory mechanisms and their length of play
- LV remodeling is dependent upon changes in the myocyte structure and function
- LV changes occur during compensated and decompensated failure
  - Change in structure is dependent upon several factors

Herrmann J, et al. 2020. [Epub ahead of print]. DOI:10.1038/s4 1569-020-0348-1.

A Brief Look at Pathophysiology (cont)

- Overexpression of neurohormones, peptides (norepinephrine, angiotensin II, cytokines, vasopressin, aldosterone)
- These factors:
  - Increase hemodynamic stress on LV
  - Cause sodium retention
  - Cause peripheral vasoconstriction
  - Exert toxic effect on myocyte leading to fibrosis (Type I)
  - Are cyclical unless treated → further disruption of LV architecture and performance

Herrmann J, et al. 2020. [Epub ahead of print]. DOI:10.1038/s4 1569-020-0348-1.

Medications to Treat CV Risk and Cardiotoxicity

- ACE inhibitors (lisinopril)
- Beta blockers (carvedilol, metoprolol)
- Do not delay treatment
  - Timing is everything
  - Delay > 6 months may mean reduced response

Cardinale D, et al. *J Am Coll Cardiol.* 2010;55:213-250.

ACCF/AHA Guideline “Truths”

- HF has risk factors just as CAD has risk factors
- HF has asymptomatic and symptomatic phases
- Appropriate treatment at each stage can reduce morbidity and mortality of HF
- Providers need to appreciate progressive nature of HF
- Need to place HF in the global risk category superimposed on cancer treatment
- Recognize the need for early recognition and intervention

Section Summary

- Patients receiving anthracycline or trastuzumab for treatment of breast cancer have increased risk for cardiotoxicity. The risk is even greater for those receiving combination anthracycline and trastuzumab.
- The reversibility of LVD (both symptomatic and asymptomatic) in patients undergoing treatment with anthracyclines depends critically on the timing of the initiation of cardio-protection therapy with beta-blockers and ACE inhibitors.
- Follow established monitoring parameters for overall CV risk in patients receiving these treatments.

Cardio-Oncology Basics: Conclusions

Major Considerations in Managing Potential Cardiotoxicity

- With active treatment
  - Continue to support CV prevention
  - Treat HTN, dyslipidemia, diabetes
  - Continue medication that supports vascular health such as clopidogrel for the patient with a stent
- Monitor physical activity
  - What is baseline, pre-treatment activity tolerance?
    - Typical daily activity tolerance (stair climbing, lifting)
    - Exercise
- Provide adequate monitoring and surveillance during and after treatment
  - Reduces risk of long-term sequelae such as HF
  - Supports early initiation of treatment if symptoms occur

The Future of Cardio-Oncology

- Biomarkers that will tell us if any cardiac cells, no matter how few, have been destroyed by the cancer therapy
- Ways to reduce the emergence of CV risk during cancer treatment

Presentation Summary

- There are no standards for CV risk assessment prior to or following adjuvant therapy
- Compliance among providers to screen the general public for CV risk is inconsistent
- CVD in cancer survivors is multifactorial requiring the scientific and clinical knowledge of cardiology and oncology professionals to create guidelines to improve long-term outcomes