CARDIO-ONCOLOGY

FACTS

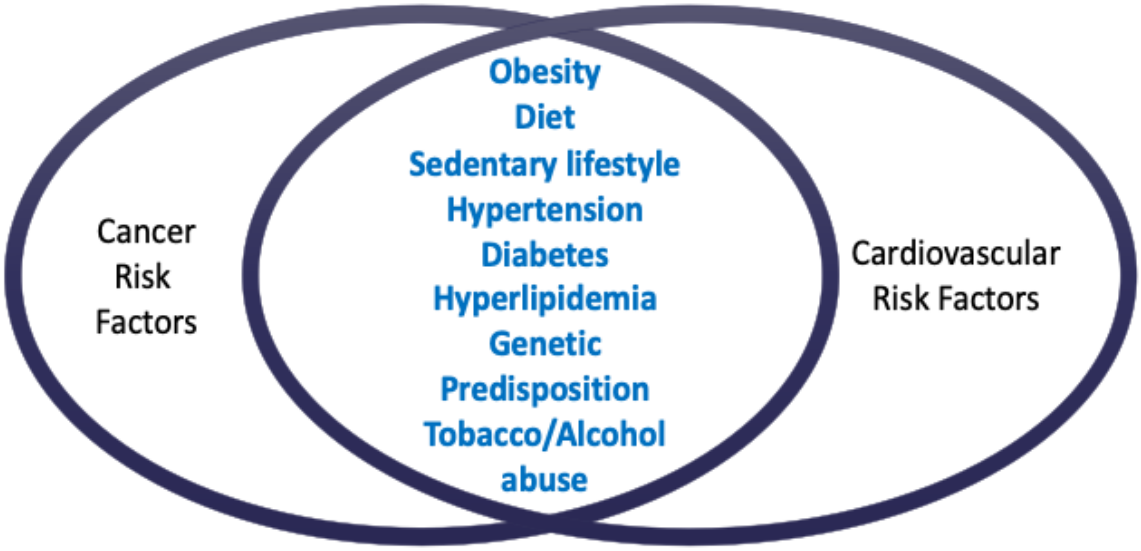
IC-OS

Cancers Facts relate to Cardiovascular Disease (CVD)

- 1 out of 6 cancer patients have **CVD**
- 2020, **~19.3 million people were diagnosed with cancer globally**, resulting in approximately 10 million deaths
- **Cancer and heart disease are the leading causes of morbidity and mortality** in the world – approx. 70%
- **CVD second most common cause of death** second to cancer
- Cancer patient have a **2-fold increase risk of CV mortality**
- A Childhood Cancer Survivor Study showed: 15 to 25 years after diagnosis, **survivors of childhood cancer have an 8.2-fold higher rate of cardiac death** compared with the age-matched and sex-matched national average
- **Cancer is now becoming a chronic illness**, with a prolonged life as well as adverse effects from anti-tumor therapy both short and long-term cardiotoxic effects of cancer therapy lending to a greater incidence of CVD
- **The incidence of cardiovascular events** - cardiac injury or cardiovascular toxicity i**s higher than malignant tumors' recurrence rate**
- **First year of cancer is the period with the highest mortality** from cardiovascular complications

- Cancer patients can present with **a variety of cardiovascular problems** not all of which are directly related to cancer therapy (medications or radiotherapy)
- **Types of CVD vary** among different types cancer treatment
- Similar **pathophysiological processes and co-morbidities** > burden of CVD due to shared risk factors

Cardiovascular and Cancer Shared Risk Factors



Source: Coviello JS. *J Adv Pract Oncol.* 2018;9(2):160-176. 2. Versmissen J, et al. *Vasc Med*. 2020;25(3):205-207.

Cardio-Oncology (CO) is the care of cancer patients with cardiovascular(CV) disease, already established or acquired during treatment, and in survivorship.

- CO is the **integration of knowledge** in oncology, as well as cardiology
- The guiding principle of the CO approach is to enable patients to complete **the best possible cancer therapy with the lowest possible CV impact**
- **CO addresses the CV needs of patients** throughout the entire cancer journey: before (risk assessment), during (detection of CV toxicity), and after (survivorship) cancer treatment. It thus covers a broad spectrum of disease processes.
- A **variety of cardiovascular problems** seen by oncology patients: ischemia, arrhythmias, valvular and heart failure
- **Identifying patients who are at a higher risk for developing cardiotoxicity** so that appropriate surveillance, treatment and follow-up strategies may be instituted early to help mitigate adverse effects
- Leading reasons for referral to the CO clinic are **pretherapy evaluation for patients with high baseline risk and complications of cancer therapy**, especially cardiomyopathy or heart failure, vascular disease, and arrhythmia.

Goals of Cardio-Oncology

- The primary goal is to **allow patients with cancer to receive the best possible cancer treatment safely**, while minimizing both unnecessary cancer therapy interruptions and CTR-CVT (cancer treatment related cardiovascular toxicity) risk .
- I**mprove clinical outcomes and survivorship** by minimizing any cardiovascular effects of cancer treatment.
- **Decrease burden of cardiovascular morbidity and mortality** in patients treated with cardio-toxic agents and/or patients who have pre-existing cardiovascular conditions.

The objective is management of cardio-toxicity across the cancer treatment continuum:

Prior to initiating cancer therapy

Identification of CV risk factors and unique patient specific factors increasing the risk of cardiotoxicity and optimally managing any risks identified to assure administration of the most efficacious cancer treatment.

During cancer treatment

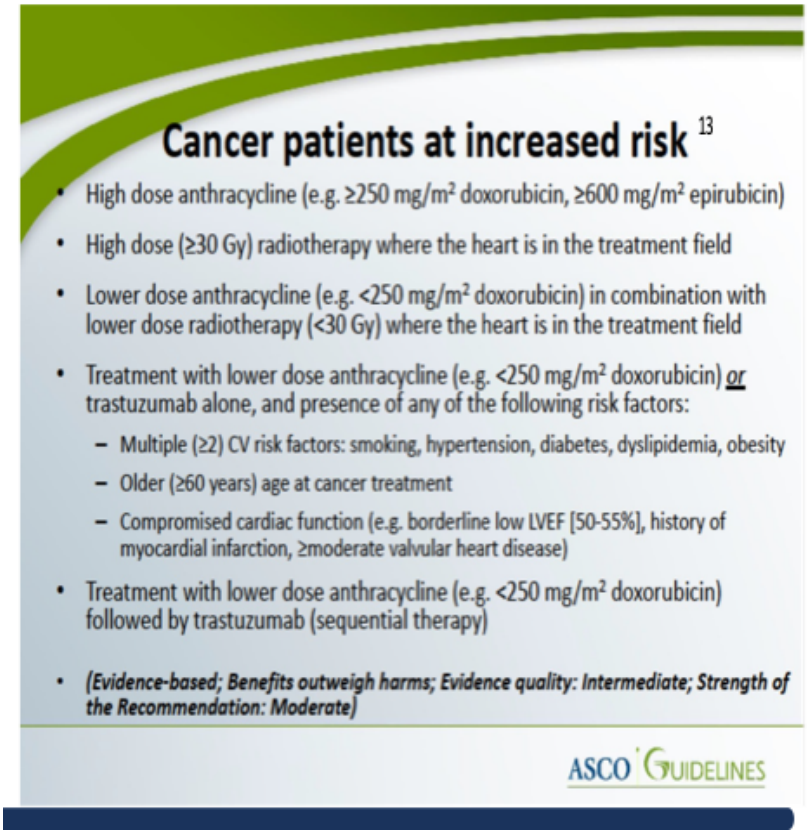
Early detection utilizing biomarkers and advanced imaging where appropriate, and prompt management of cardiotoxicity and related symptoms to minimize interruption, if any, of the cancer treatment.

After cancer treatment

Optimization of preventive strategies, screening for late-onset CV effects of cancer therapies and continuous reassessment of emerging CV risk in patients that may occur as a result of complex cancer therapies.

Early recognition and treatment of cardio - toxicities through cardiovascular risk stratification and prevention

Proactive Cardio-Oncology



Initial guidelines 2016, Additions to guidelines 2021(Bolded)

Lower-dose anthracycline (eg, doxorubicin <250 mg/m2, epirubicin <600 mg/m2) or **HERis or VEGFis or proteasomes or Bcr-Abl kinase inhibitors**

- ◯ ≥2 Risk factors, including smoking, hypertension, diabetes mellitus, dyslipidemia, chronic renal insufficiency, and obesity
- **Previous heart disease**
- **Elevated cardiac biomarkers* before initiation of anticancer therapy (*N-terminal pro-B-type natriuretic peptide B-type natriuretic peptide) and/or troponin)**

NCCN Guidelines Version 2.2017
Anthracycline-Induced Cardiac Toxicity

INITIAL CLINICAL ASSESSMENT FOR PATIENTS WHO HAVE RECEIVED PREVIOUS ANTHRACYCLINE THERAPY

- History and physical
  - Assess for signs and symptoms of heart failure[a,d]
  - Assess patient's ability to perform routine and desired activities of daily living
  - Look for signs of volume overload
- Evaluate for presence of heart failure risk factors
  - Hypertension
  - Dyslipidemia
  - Diabetes mellitus
  - Family history of cardiomyopathy
  - Age >65 years
  - High cumulative anthracycline dose (ie, cumulative doxorubicin dose at or higher than 250 mg/m^2 or equivalent)
  - Low-normal LVEF (50%–54%) at baseline
  - History of other cardiovascular comorbidities (ie, atrial fibrillation, known coronary artery disease [CAD], baseline evidence of structural heart disease)
  - Smoking
  - Obesity
- Review medications, alcohol use, and other substance use
- Review oncologic history
  - Review total cumulative dose of anthracycline
  - Other systemic therapy[b] and/or chest radiation therapy

→

- Cardiovascular risk factor management[c]
- Consider two-dimensional echocardiogram (ECHO) with doppler flow study for survivors with one or more risk factors within 1 year after completion of anthracycline therapy[d,e]

→ No evidence of structural heart disease, but symptomatic[a]

→
- Workup for other causes of symptoms
- Referral to other specialties (eg, pulmonology or cardiology)

→ No evidence of structural heart disease and asymptomatic
or
No ECHO performed and asymptomatic

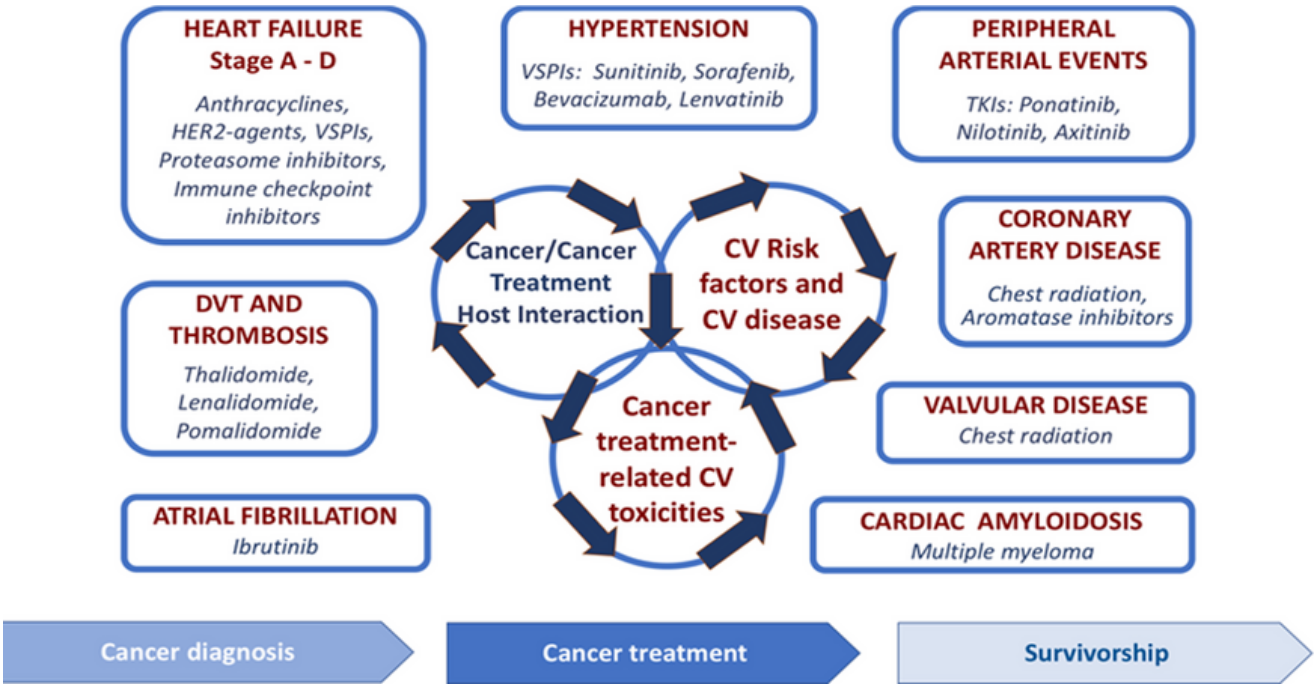
→ See Stage A (SCARDIO-3)

→ Evidence of structural heart disease (asymptomatic or symptomatic[a]):
- Evidence of left ventricular (LV) dysfunction
- Evidence of LV hypertrophy
- Valvular disease

→ Determine stage of cardiomyopathy (heart failure) See SCARDIO-3

[a]Signs and symptoms of heart failure include: Shortness of breath or chest pain after physical activity or exercise, shortness of breath when sleeping, waking up at night due to shortness of breath, and swelling in the legs.
[b]Trastuzumab, pertuzumab (other HER2-targeted therapy), VEGF signaling pathway (VSP) inhibitors, taxanes in combination with anthracyclines.
[c]Encourage primary care provider involvement in treatment of cardiovascular risk factors and encourage routine follow-up in coordination with primary care provider.
[d]Patients with symptoms of heart failure should undergo an echocardiogram.
[e]Referral to cardiologist/cardio-oncologist if there are echocardiographic abnormalities.

Cardiovascular Disease related to Cancer Therapies



- **Anthracycline chemotherapy**: LVD and HF, and atrial and ventricular arrhythmias
- **HER2 targeted therapies**: LVD and HF, and systemic hypertension
- **Vascular endothelial growth factor (VEGF) inhibitors [also known as angiogenesis inhibitors or VEGF tyrosine kinase inhibitors (TKIs):** systemic hypertension, LVD and HF, QTc prolongation and arterial thrombosis including MI

- **Multi-targeted kinase inhibitors** for chronic myeloid leukemia (CML) targeting BCR-ABL (often called **BCR-ABL TKIs**): arterial thrombosis leading to MI, stroke and peripheral arterial occlusive disease (ponatinib), venous thromboembolism, systemic hypertension, LVD and HF, accelerated atherosclerosis (ponatinib and nilotinib), QTc prolongation (nilotinib) and pulmonary hypertension (dasatinib)

- **Proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs):** LVD, HF, ischemia and MI, atrial and ventricular arrhythmias, venous thromboembolism and arterial thrombosis

- **Combination RAF and MEK inhibitor treatment:** LVD, HF and systemic hypertension for all combinations and QTc prolongation (vemurafenib and cobimetinib)

- **Androgen deprivation therapies (ADT)** for prostate cancer treatment including **gonadotropin release hormone (GnRH) agonists:** ADT are associated with an increased risk of diabetes mellitus, htn and atherosclerosis

- **Immune checkpoint inhibitors:** myocarditis including fulminant myocarditis, non-inflammatory HF, ventricular arrhythmias, atrio-ventricular block, sudden cardiac death, acute coronary syndromes including atherosclerotic plaque rupture and vasculitis

Cardiac Adverse Effects from Radiotherapy

The **pro-inflammatory effect** of radiation on the coronary vasculature mimics atherosclerosis in that endothelial damage promotes fibrin deposition and intimal proliferation, hastening the progression of coronary artery disease.

Atherosclerotic heart disease exacerbated by radiation as low as 6 Gy

A 7.4% increase of coronary events with each additional Gray of mean cardiac dose resulting in RICT (Radiation induced Cardio-toxicity).

The heart is affected by radiation in a dose-dependent manner with higher radiation doses, particularly >30-40 Gy, associated with significantly increased post-radiation-induced mortality.

Damages can occur with doses as low as 2 Gy, and there is no apparent "safe" dose of radiation that the heart may receive.

Valvular disease is a late complication. Fibrosis, calcification, and thickening of the valves can occur asymptomatically for over 15 years before becoming clinically apparent.

- Head and Neck – baroreceptors – autonomic disorders
- Atherosclerotic disease
- Valvular disease
- Conduction disorders
- Radiation nephropathy is a renal injury
- Abdominal leading to renal artery stenosis

Hypertension

The threshold for initiating the hypertension treatment increases as the patient has a worse prognosis. **Starting the hypertension treatment at the proper time is crucial** in managing hypertension in cancer patients, especially in patients under treatment of VEGFi, efficacy is related to blood pressure increase in these pts.

Hypertension in Cancer Patient

Cancer Survivor	135-139
Curable cancer under cancer treatment	135-139
Metastatic cancer with prognosis > 3 years	140-159
Metastatic cancer w/prognosis between 1-3 yrs.	140-159
Metastatic cancer prognosis < 1 year	160

Lifestyle modifications to assist in BP management

- Healthy weight maintained
- Exercise routinely
- Health Diet suggested as the following:
  - Low in salt, abundant in fruits and vegetables as well as whole grains Or DASH diet (dietary approach to stop hypertension)
  - Limited Alcohol consumption
- Cessation of smoking

There is no consistent evidence that the use of anti-hypertensive medicines impacts cancer pt. treatment.

Cardiac Surveillance

- **Cardiac Risk Assessment** with admission to oncology service – comorbidities, medical history, and possible cardio-toxic cancer therapies

- If risk assessment indicates cardio-oncology consult needed: **ensure done timely, cardiac surveillance testing** (result to oncologist prior to medical therapy regiment)

- **Monitor vital signs and medications during every visit** and any home vitals may be indicated

- **EKG's and Echoes may be done prior** to initiation of therapy to establish baseline and may be done at different times during various treatment regimens to ensure cardiac safety

- **Baseline biomarkers as troponin and BNP or NT-ProBNP**

- **Ensure CV testing** identified as needed is done prior to treatment regimen initiation and resulted

- **Educate patient on cardiac symptomology** and importance of sharing concerns has or experiences in timely manner with healthcare professionals (including ED visits)

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC)

131 page document – App

References

Mamas A. Mamas et al. *J Am Coll Cardiol CardioOnc* 2022; 4:254-257 Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines; Joachim Alexandre et al; **Originally published** 5 Sep 2020 https://doi.org/10.1161/JAHA.120.018403 Journal of the American Heart Association. 2020;9:e018403

Alexander R Lyon, Teresa López-Fernández et al.ESC Scientific Document Group , 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC), European Heart Journal, Volume 43, Issue 41, 1 November 2022, Pages 4229–4361, https://doi.org/10.1093/eurheartj/ehac244

- **Roth, Fuster**, et al. GBD. JACC. 2019 & 2022. *Global Burden of Disease*. JAMA Onc. 2022. www.aacr.org
- **Herrmann J, Lerman A, Sandhu NP, Villarraga HR**, et al. *Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc.* 2014;89(9):1287–1306.
- **Ewer MS, Ewer SM.** *Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Natl Rev Cardiol.* 2010;7(10):564-575. doi: 10.1038/nrcardio.2010.121.
- **Centers for Disease Control and Prevention.** Available online at https://www.cdc.gov/nchs/products/databriefs/db293.htm. Last accessedAug. 5, 2020.

References

- **Shan K, Lincoff AM, Young JB**. *Anthracycline-induced cardiotoxicity*. Ann Int Med. 1996;125(1):47-58.
- **ASCO Guidelines**. asco.org/research-guidelines/quality-guidelines/guidelines.
- **Van Dalen EC, Michiels EMC, Caron HN, Kremer LCM**. *Different anthracycline derivates for reducing cardiotoxicity in cancer patients*. Cochrane Systematic Review – Intervention; 2010. doi.org/10.1002/14651858.CD005006.pub3.
- **Ewer MS, Ewer SM**. *Cardiotoxicity of anticancer treatments: what the cardiologist needs to know*. Natl Rev Cardiol. 2010;7(10):564-575. doi: 10.1038/nrcardio.2010.121. Howlader N, et al. SEER Cancer Statistics Review, 1975-2008. Available online at seer.cancer.gov/archive/csr/1975_2008. Last accessed Aug. 5, 2020.
- **Alvarez-Cardona J, Ray J, Carver J**, et al. *Cardio-Oncology Education and Training. J Am Coll Cardiol*. 2020 Nov, 76 (19) 2267–2281.https://doi.org/10.1016/j.jacc.2020.08.079with important contribution.
- **Hufnagle JJ, Andersen SN, Maani EV**. *Radiation-Induced Cardiac Toxicity*. [Updated 2023 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554453/
- **Siaravas KC, Katsouras CS, Sioka C**. *Radiation Treatment Mechanisms of Cardiotoxicity: A Systematic Review.* Int J Mol Sci. 2023 Mar 27;24(7):6272. doi: 10.3390/ijms24076272. PMID: 37047245; PMCID: PMC10094086.