The Impact of Cancer Treatment on Heart Health and The Role of Cardio-Oncology in Survivorship

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Disclosure

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Journal of Cardio-Oncology

Advisory Board - Pfizer

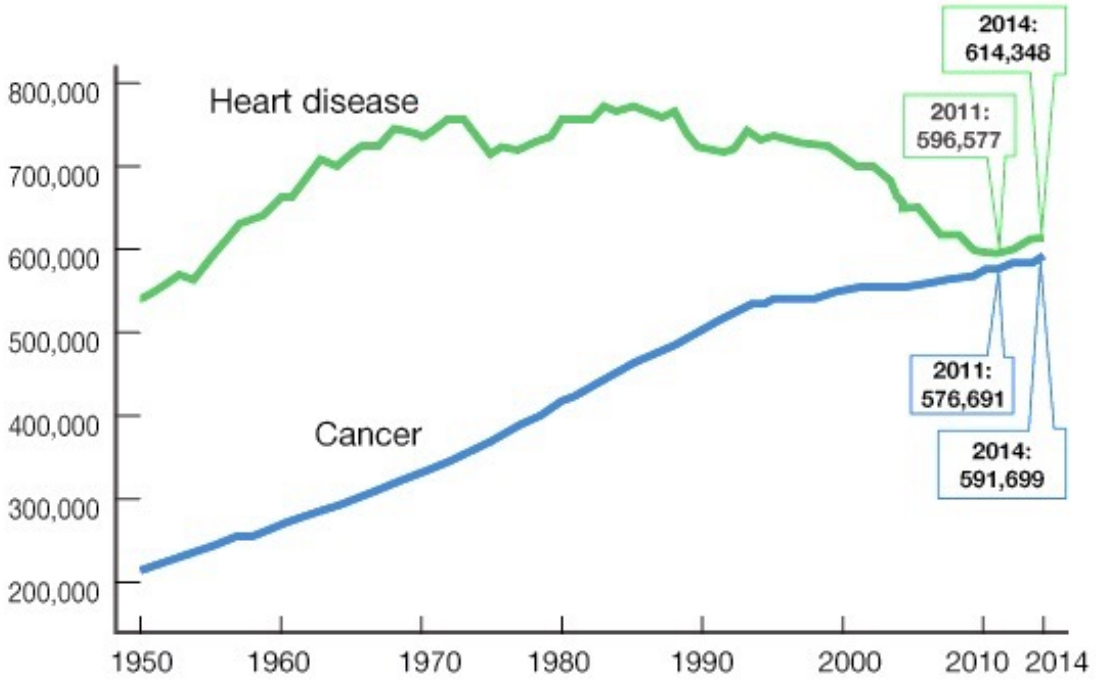
Objectives

- Intersections between Cancer and Heart Diseases
- What is Cardio-Oncology?
- Scientific Foundation and Clinical Mission
- What to know as Providers
- What to know as Patients/Survivors

Intersections between Cancer and Heart Diseases

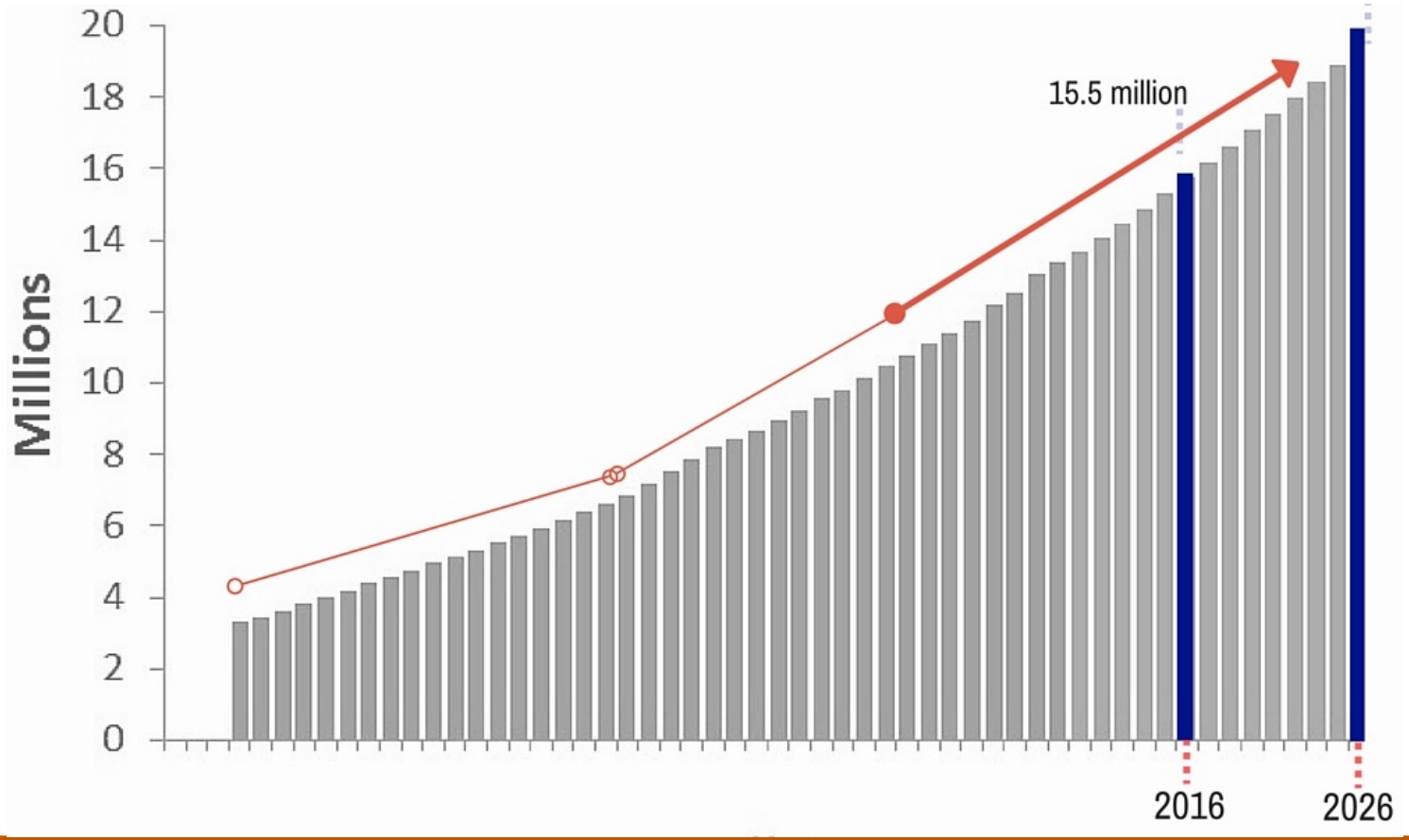
Cancer and Heart Disease

The total number of Americans dying from heart disease rose in recent years following decades in decline. Cancer deaths have nearly tripled since 1950 and continue to climb.



Source: Centers for Disease Control and Prevention *Published Aug. 24, 2016*

Estimated Cancer Survivors in the US



High Prevalence of CVD in Cancer Patients

~ 6 million patients, big data approach-
CVD prevalence: 33% for hematologic, 43% for lung, 17% for breast, 26% for colon, 35% for renal, and 26% for head and neck cancers.

Of those with CVD, only half were seen by cardiologists and received guideline-directed cardiac therapy.

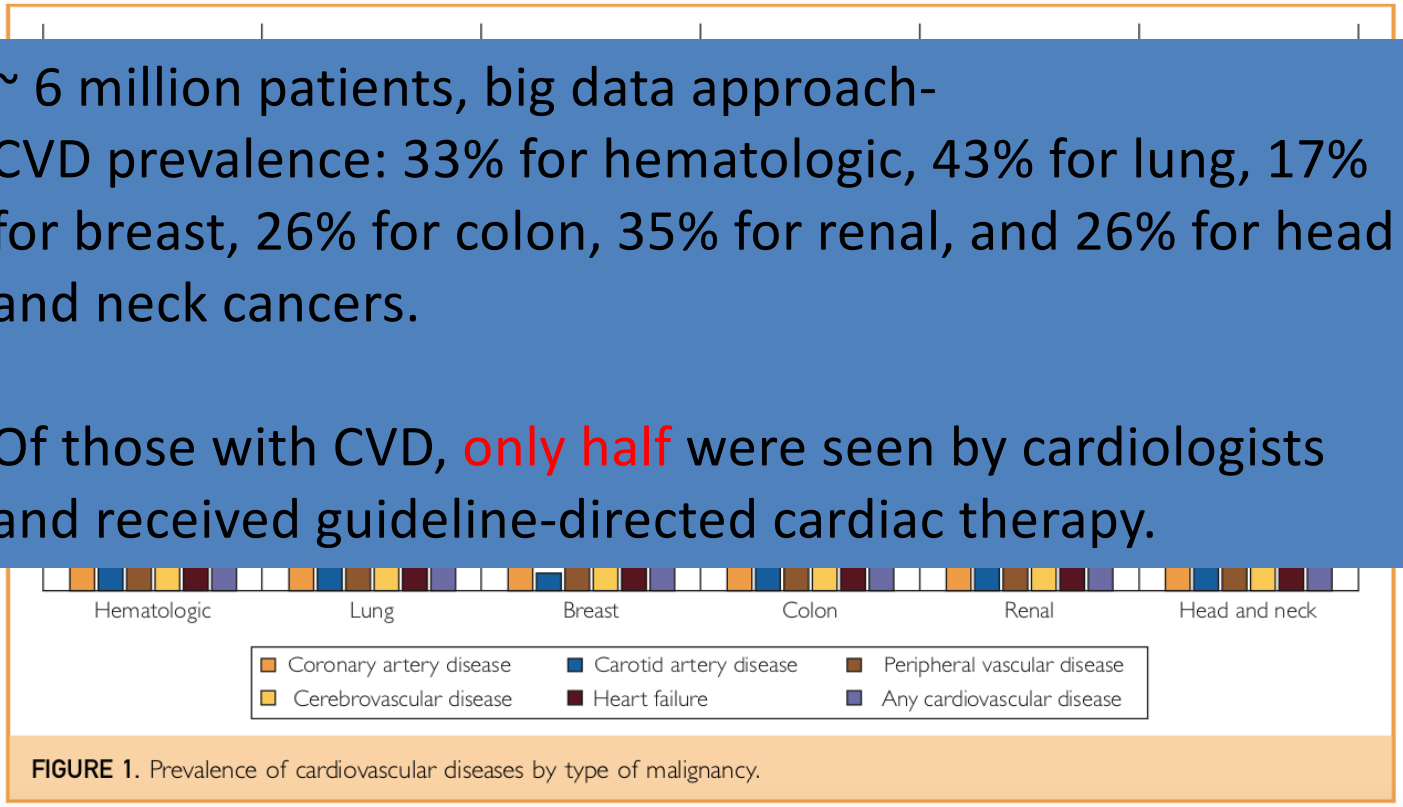
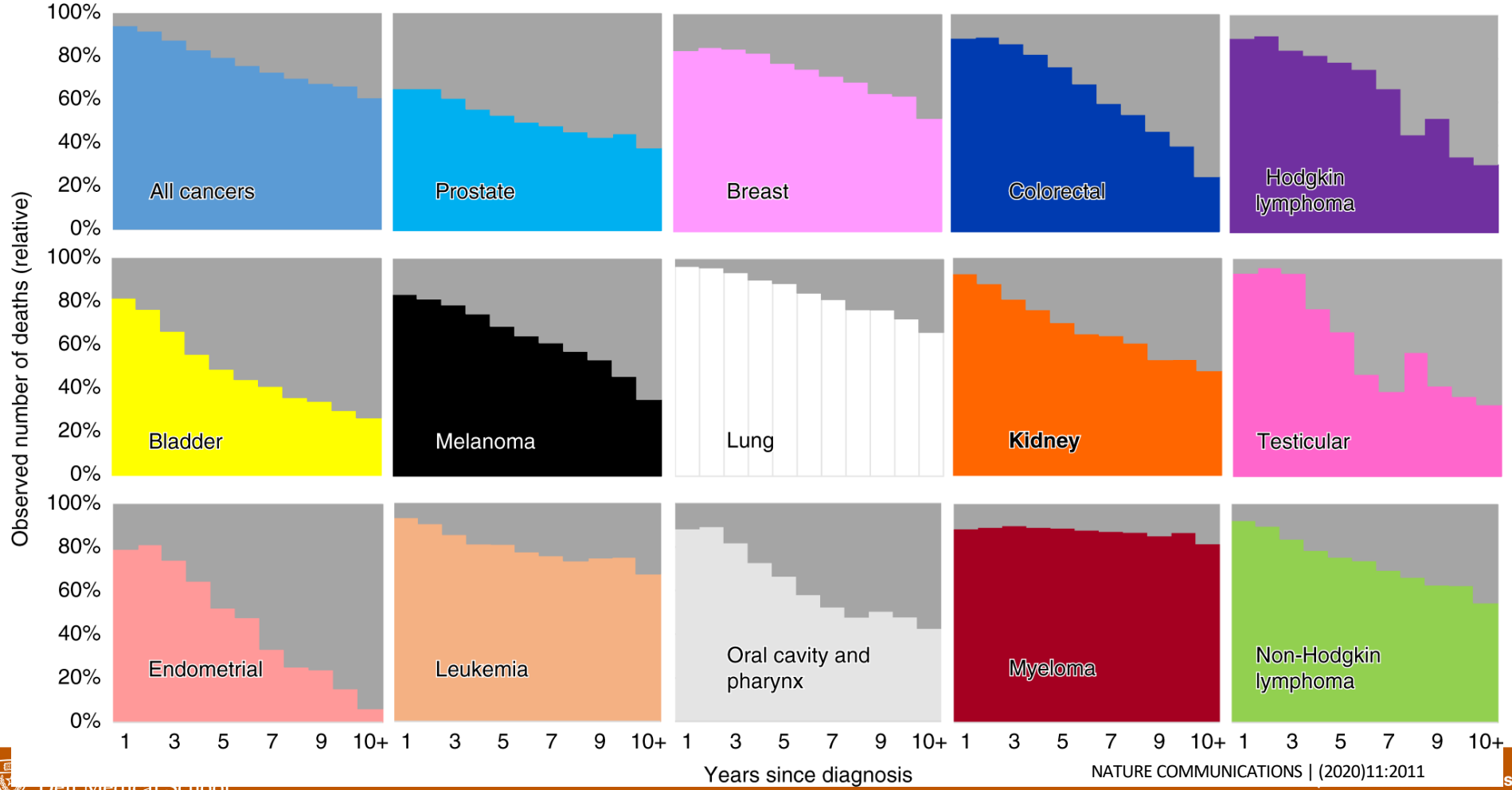


FIGURE 1. Prevalence of cardiovascular diseases by type of malignancy.

CVD – cardiovascular disease

Mortality Due to Primary Cancer vs Heart Disease



NATURE COMMUNICATIONS | (2020)11:2011

Cardio-Oncology Outcome

Mitigating cardiovascular disease in cancer patients not only improves cardiovascular-specific, but also cancer-specific mortality.

Cardiotoxicity

- CTRCD – Cancer Therapy Related Cardiovascular Dysfunction
- ~48% early, ~30% late
- Nearly all cardiovascular structures may be affected
- Nearly all therapies may lead to CTRCD

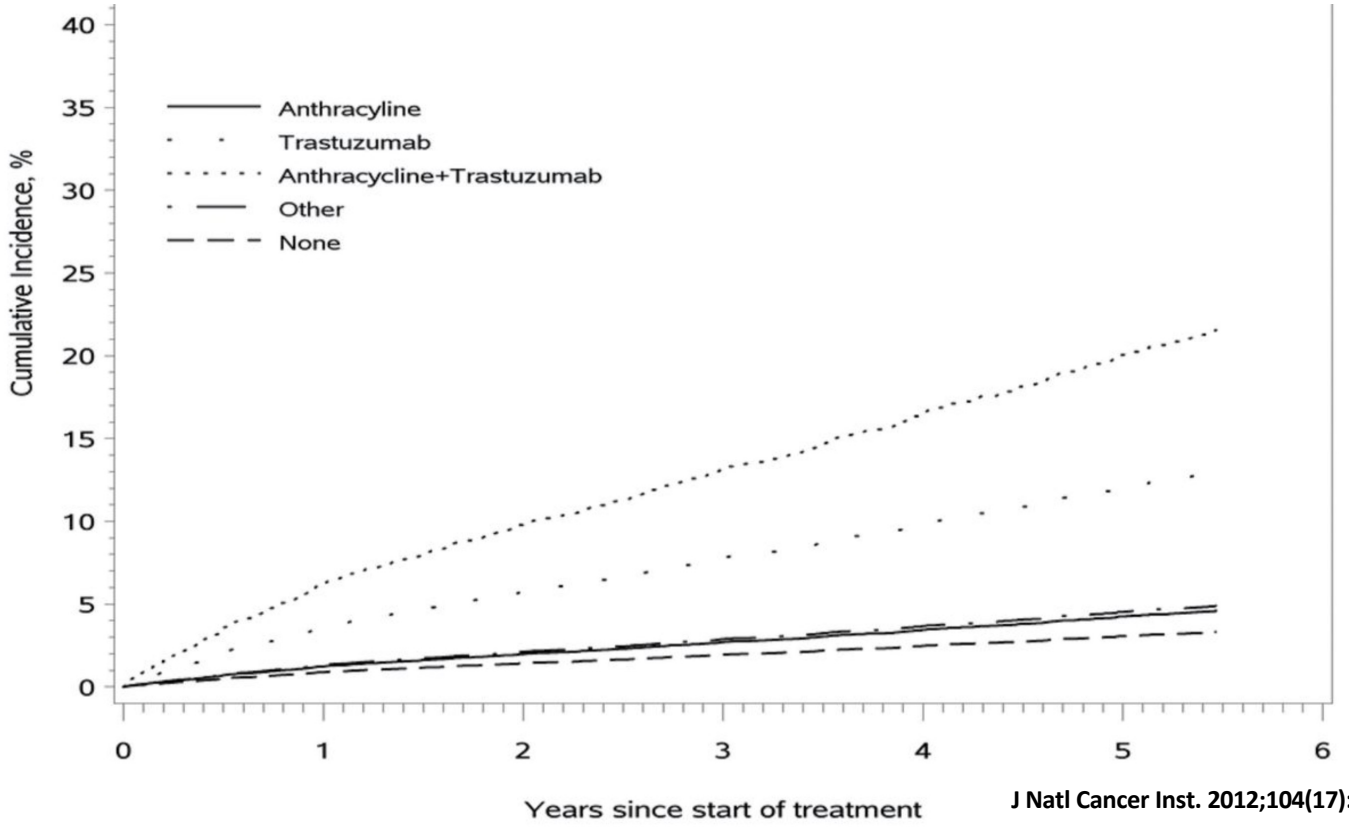
Life-saving therapies  **Life-threatening toxicities**

"Cardio-Oncology → challenges in modern medicine"

Rassaf T. J Thorac Dis. 2018 S4280–S4281

Cumulative Risk of HF in breast cancer patients

12,500 women with breast cancer between 1999-2007



J Natl Cancer Inst. 2012;104(17):1293

Cumulative Risk of HF in breast cancer patients

- Surveillance, Epidemiology and End Results- **Medicare data** from 2000-2007
- 45,537 women age 67-94

Table 2 Cumulative Incidence of Heart Failure or Cardiomyopathy During First 3 Years After Diagnosis by Cancer Therapy

	All Cancer Patients	Anthracycline + Trastuzumab (n = 431)	Anthracycline (n = 5,257)	Trastuzumab (n = 437)	Other Chemotherapy (n = 2,712)	None (n = 36,700)
Observed cumulative incidence						
1 year	7.2	16.4*†	7.7‡	15.7*	7.8	6.8
2 years	12.3	23.8*†	11.9	20.7*	12.4	12.1
3 years	16.9	28.2*†	15.3‡	26.7*	17.0	16.9
Adjusted cumulative incidence						
1 year	7.5	22.0*†	9.8*	16.7*	8.4*	7.0
2 years	13.3	33.2*†	15.3*	23.2*	13.7*	12.8
3 years	18.7	41.9*†	20.2‡	32.1*	19.2	18.1

National Outcomes in Hospitalized Patients With Cancer and Comorbid Heart Failure

Age-Standardized and Unadjusted Clinical and Economic Outcomes

Outcome	No Heart Failure	Heart Failure	*P* Value
Unadjusted			
Median adjusted cost	$13,878	$14,450	
Mean adjusted cost	$20,234	$22,571	<.001
Median (IQR) length of stay	5 (3–9)	7 (4–11)	
Mean length of stay	7.4	9.2	<.001
Inpatient mortality	5.5%	10.1%	<.001
Age-standardized			
Mean adjusted cost	$25,157	$39,053	<.001
Mean length of stay	8.2	12.7	<.001
Inpatient mortality	4.5%	12.2%	<.001
Disposition			<.001
Home/routine	54.7%	33.4%	
Home health care	22.0%	26.1%	
Skilled nursing facility	14.8%	27.5%	

IQR, interquartile range.

55%

37%

2.7-fold

J Card Fail. 2019 July ; 25(7): 516–521

Concept of Cardio-Oncology

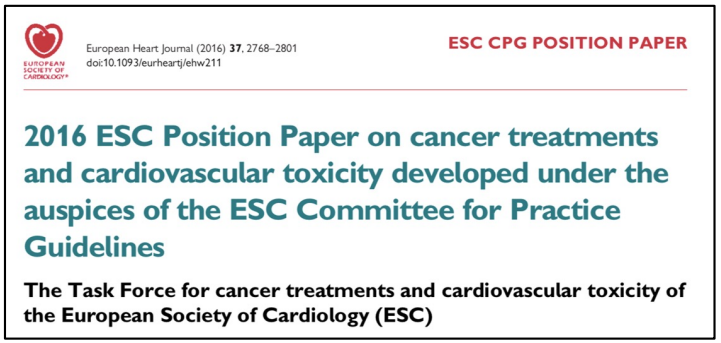
What is Cardio-Oncology

Cardio-Oncology is a new and fast-growing, **cross-disciplinary**, **collaborative** subspecialty focused on the management, mitigation or prevention of cardiovascular disease in cancer patients and cancer survivors, to achieve optimal **overall** patient outcome.

Timeline

1989
First mention of Cardio Oncology in PubMed

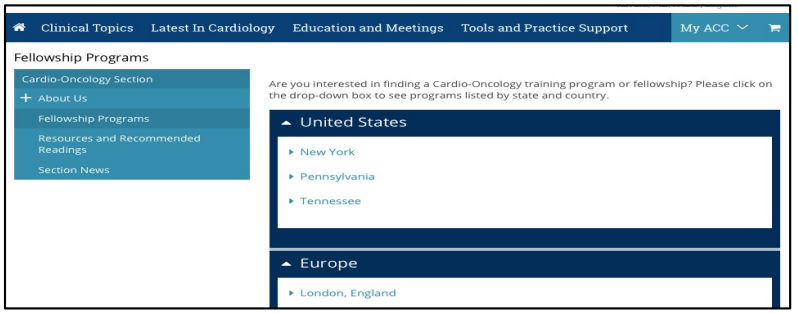
2009
Liu & Sharpless
p16 connects cancer and heart dz



2019
8 Cardio-Oncology fellowships in US- MSK, Upenn, UC, WashU, UAB, USF, Vend, MD Anderson
1 in UK

2015
1st journal launched

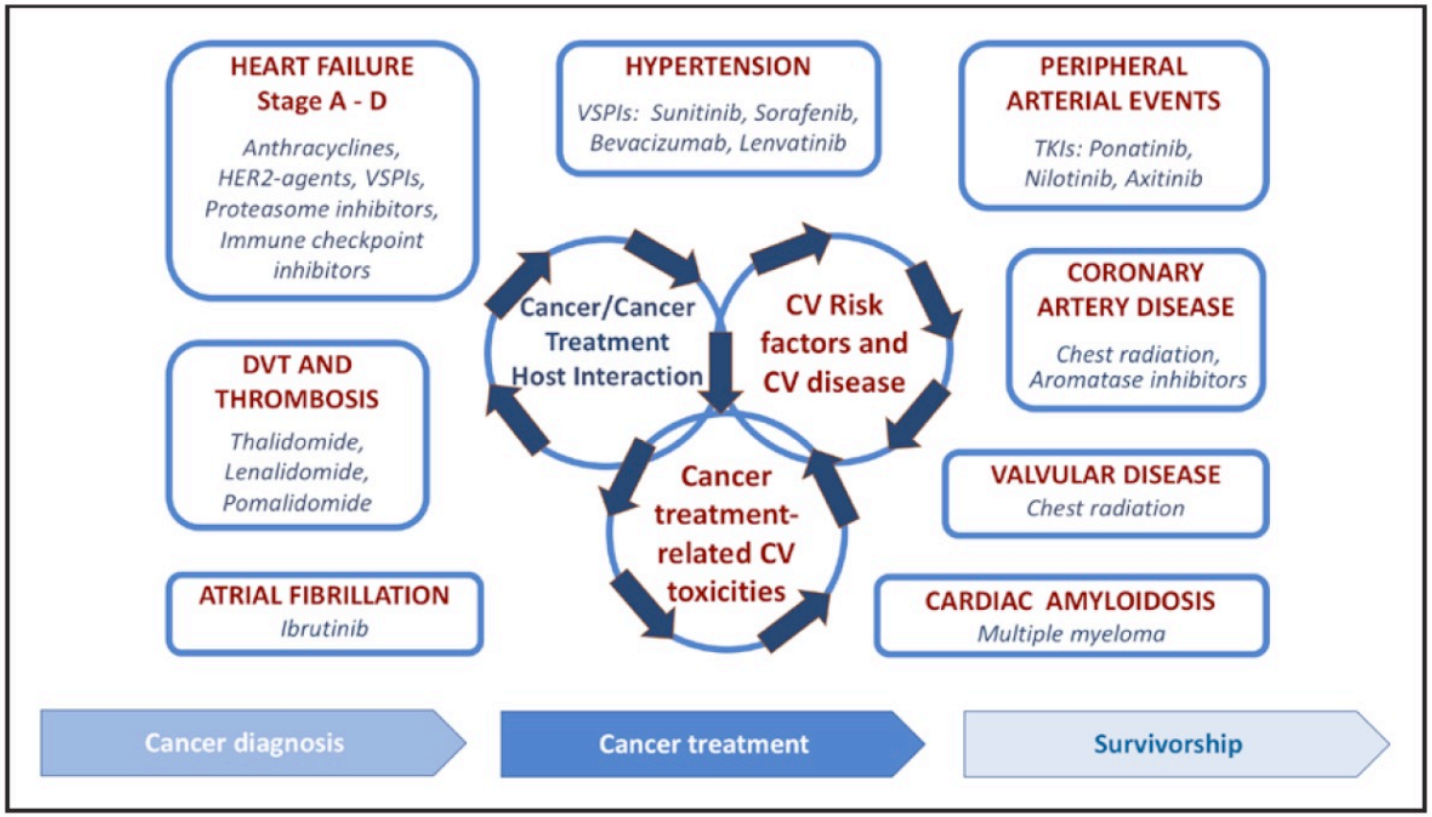
2016
ACC Cardio-Oncology Section Established



2022
First Cardio Oncology Guidelines

Scientific Foundation of Cardio-Oncology

Cardiac and Cancer Care Intersection

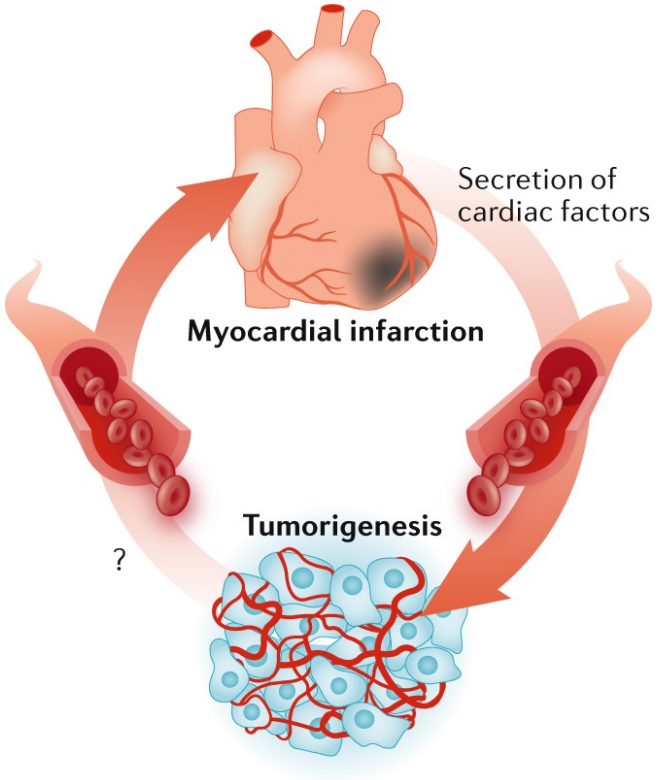


Circulation. 2019; 139:e579-e602.

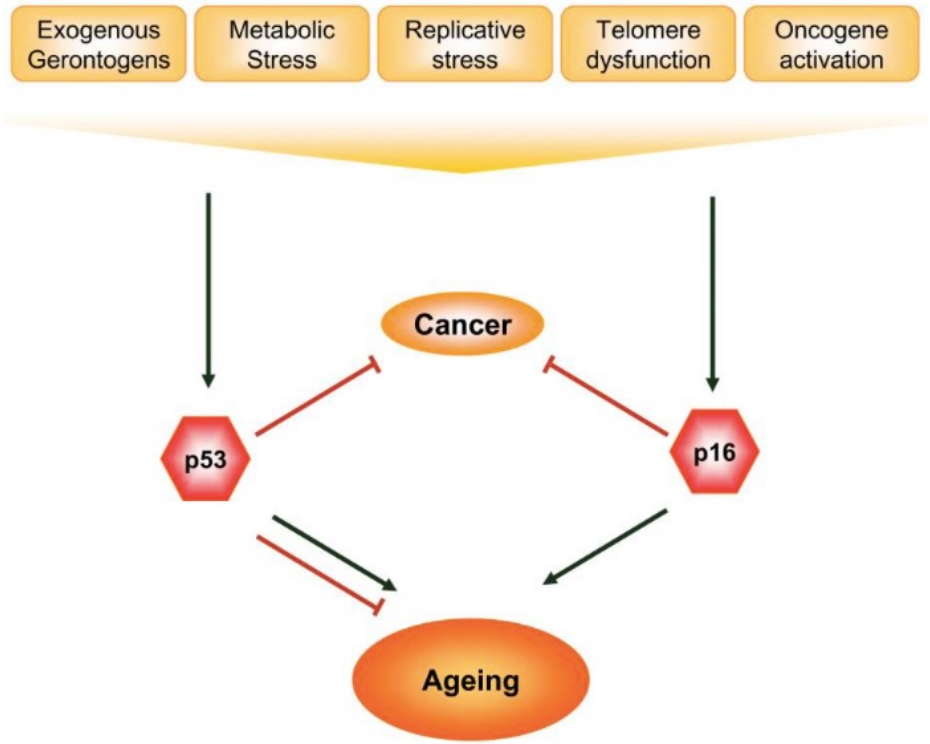
Scientific Foundation of Cardio-Oncology

Multi-level intersections between cancer and cardiovascular disease themselves:

- Shared common risk factors
- Cardiotoxicities of cancer therapeutics
- Unique risk of cardiovascular disease in cancer patients/survivors
- **Shared fundamental molecular biology mechanism**

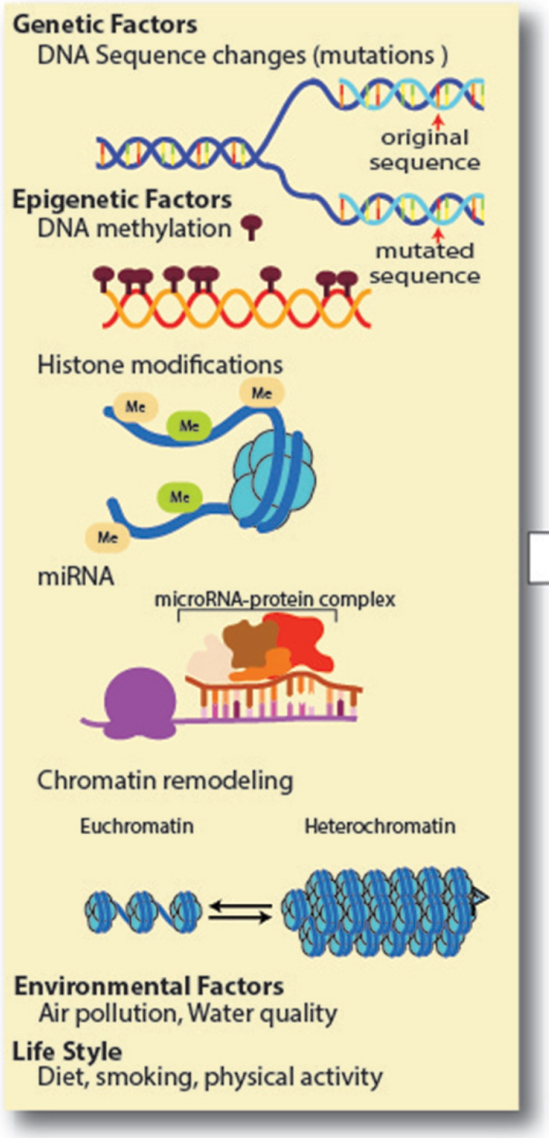


p16 – a shared pathway of cancer & CAD



Liu Y and Sharpless NE. ***Current Opinion in Immunology.*** 2009.21(4): 431-439

Other Common factors involved in CAD/Cancer development



Oxidative Stress

Inflammation

Proliferation

Apoptosis

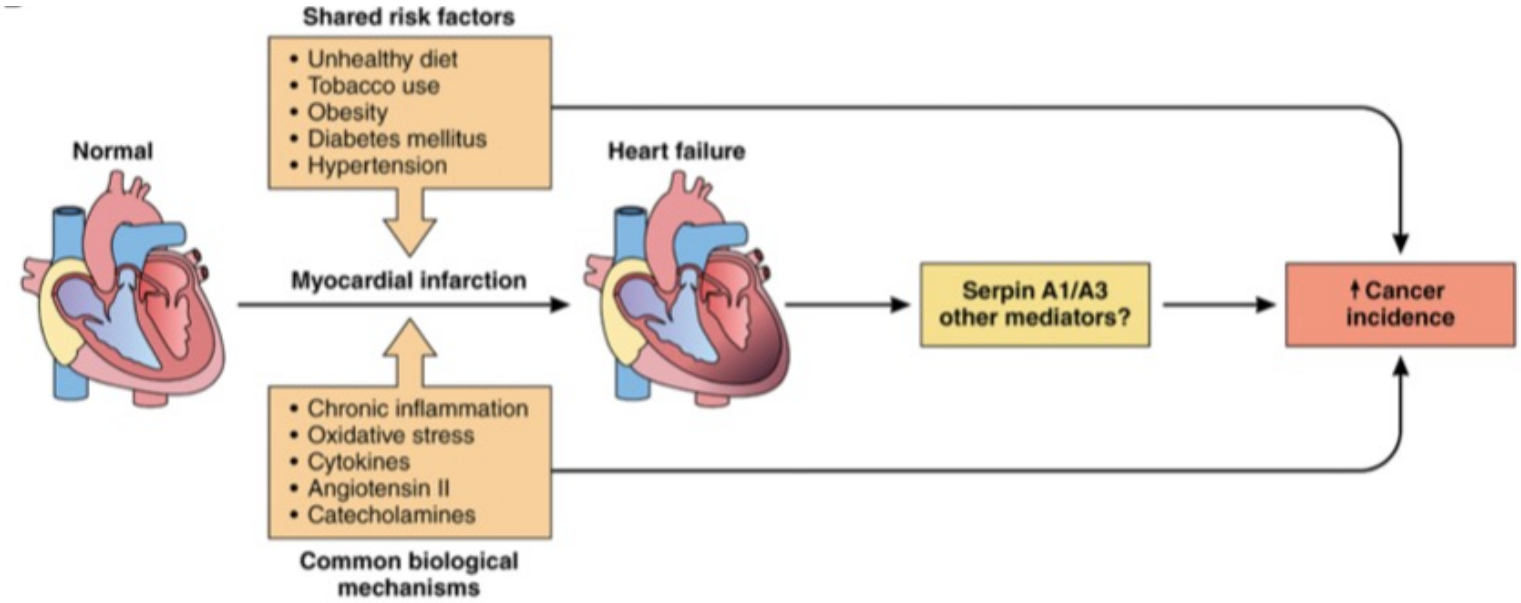
Angiogenesis

ATHEROSCLEROSIS

CANCER

Archives of Medical Research 48 (2017) 12e26

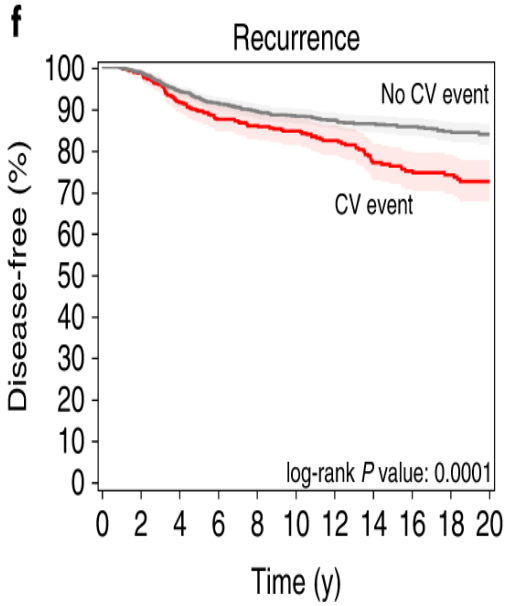
Other shared common molecular pathways by cancer and heart disease

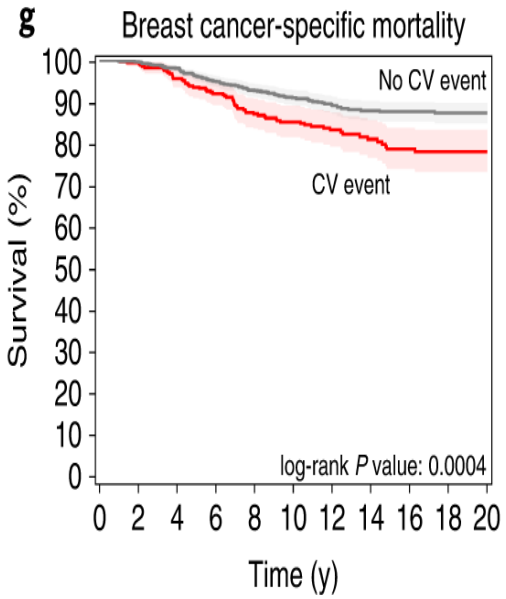


Circulation. 2018;138:692–695

Direct Interaction

MI Accelerates Breast CA





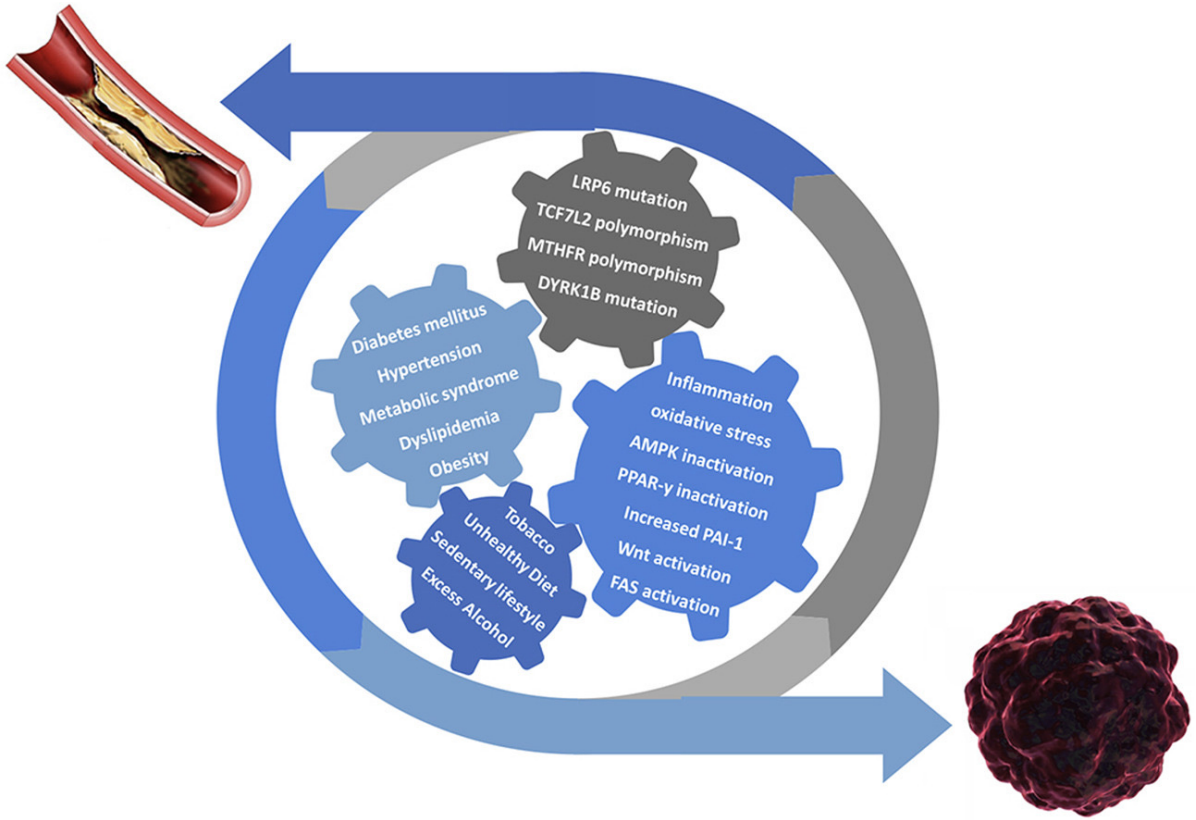
h

	Total	No. events	CV event-multivariable-adjusted HR (95% CI)	P_{trend}
Recurrence	1,724	270	1.59 (1.23–2.05)	0.0004
Breast cancer-specific mortality	1,544	168	1.60 (1.15–2.22)	0.0045

Koelwyn, G. J. et al. *Nat. Med. 7* (2020)

Incident cardiovascular events increase the risk of recurrence and cancer-specific mortality in patients with early-stage breast cancer.

CVD & Cancer: Shared Disease Pathways



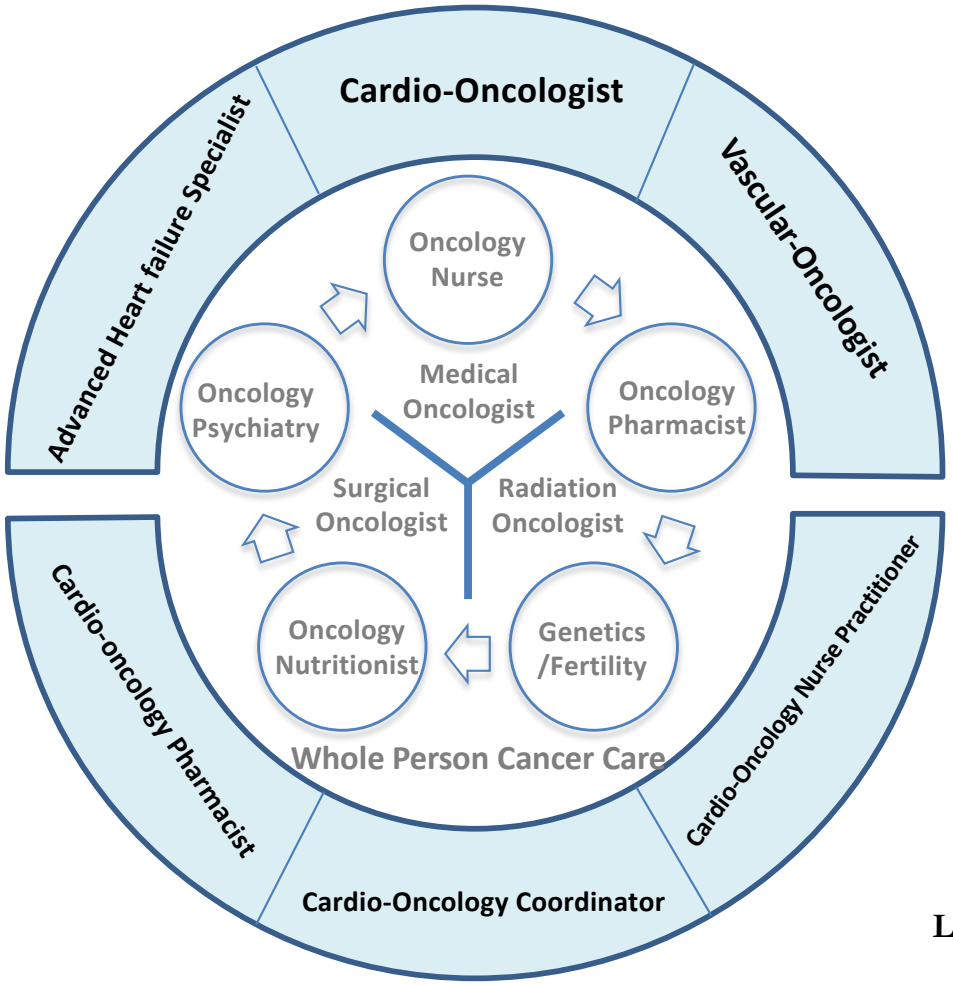
Atherosclerosis. Volume 263, August 2017, Pages 343-351

Clinical Missions of Cardio-oncology

- Early detection of cardiovascular complications
- Prevention, Mitigation & Management of cardiovascular disease and cardiotoxicities in cancer patients & survivors
- Enabling optimal cancer therapy while minimizing cardiovascular risk
- To improve **overall** patient outcome with multidisciplinary care

JACC Council Perspectives
J Am Coll Cardiol. 2020 Nov, 76 (19) 2267
Nature Medicine 2020 **26 (7)**, 1452–1458
Circulation. 2018;138:692–695

Multidisciplinary Approach



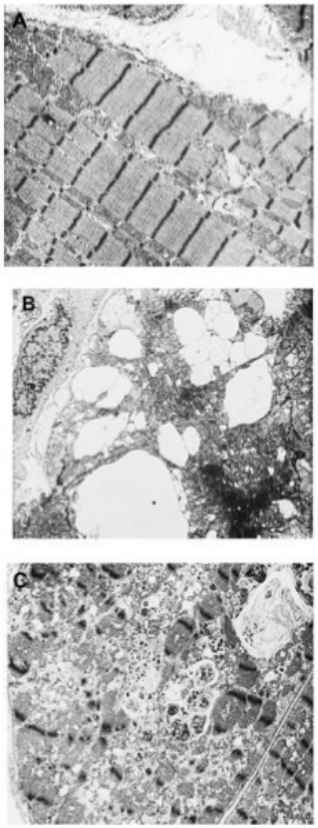
Core Program

Liu Y.. Cardio-Oncology (2023). 9:16

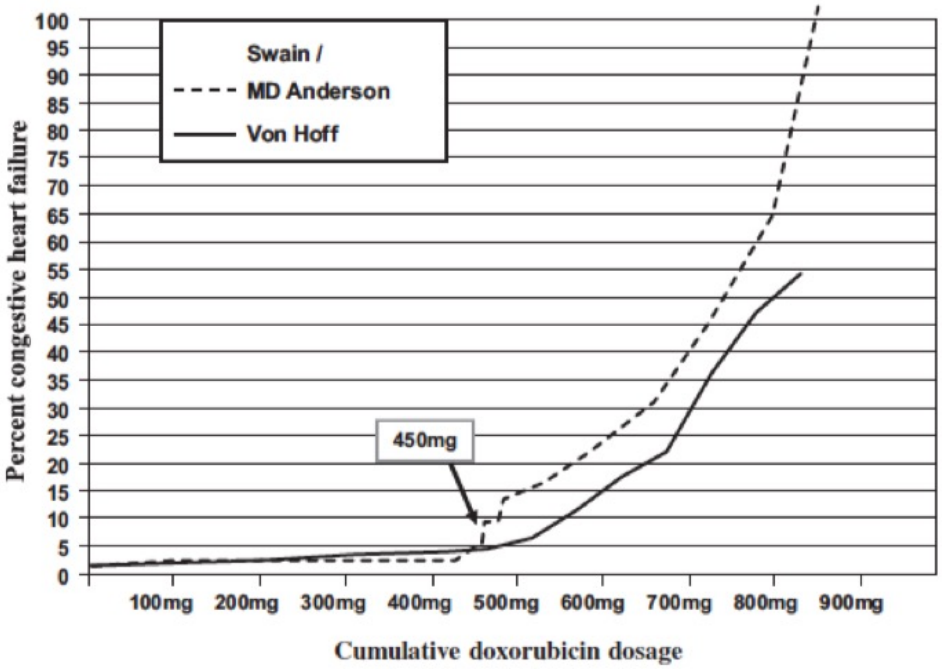
Cardiotoxicity

What to know as providers

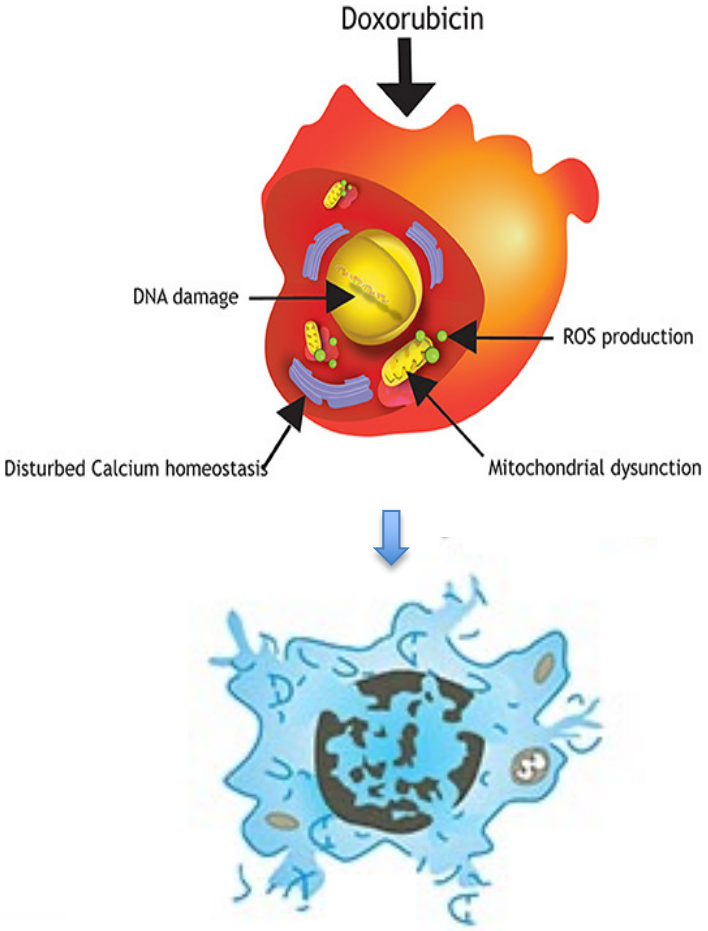
Focus: Cardiomyopathy from Cancer Therapeutics



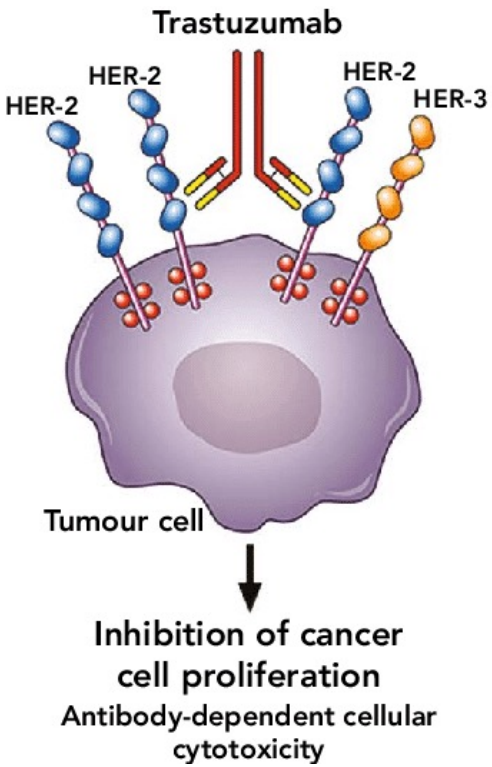
- **Anthracyclines**

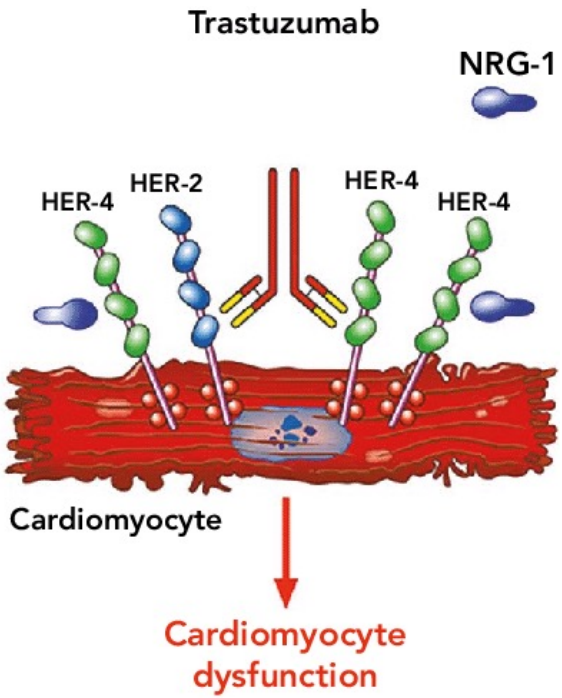


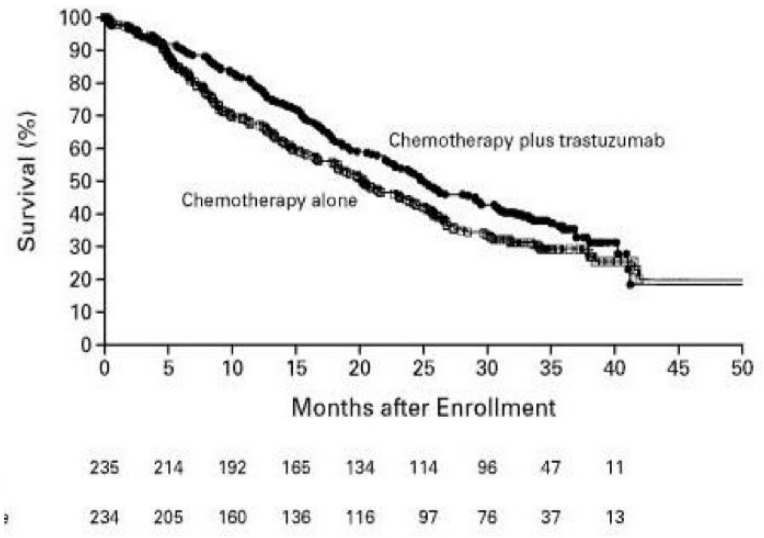
Ewer M et al. Heart Failure Clin 2011:7:363



Focus: Cardiomyopathy from Cancer Therapeutics







Slamon et al. NEJM. 2001;344:783

Spectrum of Cardiotoxicities

- Cardiomyopathy/HF- Doxorubicin/Trastuzumab
- Myocarditis (fulminant)- ICIs
- Coronary ischemia/CAD
  - 5 FU/Pyrimidine analogues -spasm
  - BCR-ABL TKIs(Nilotinib, Ponatinib)- acc CAD
- Arrhythmia
  - QT (arsenic trioxides, TKIs, protease inhibitors)
  - Afib (Ibrutinib)
  - High grade AVB/VT-ICIs

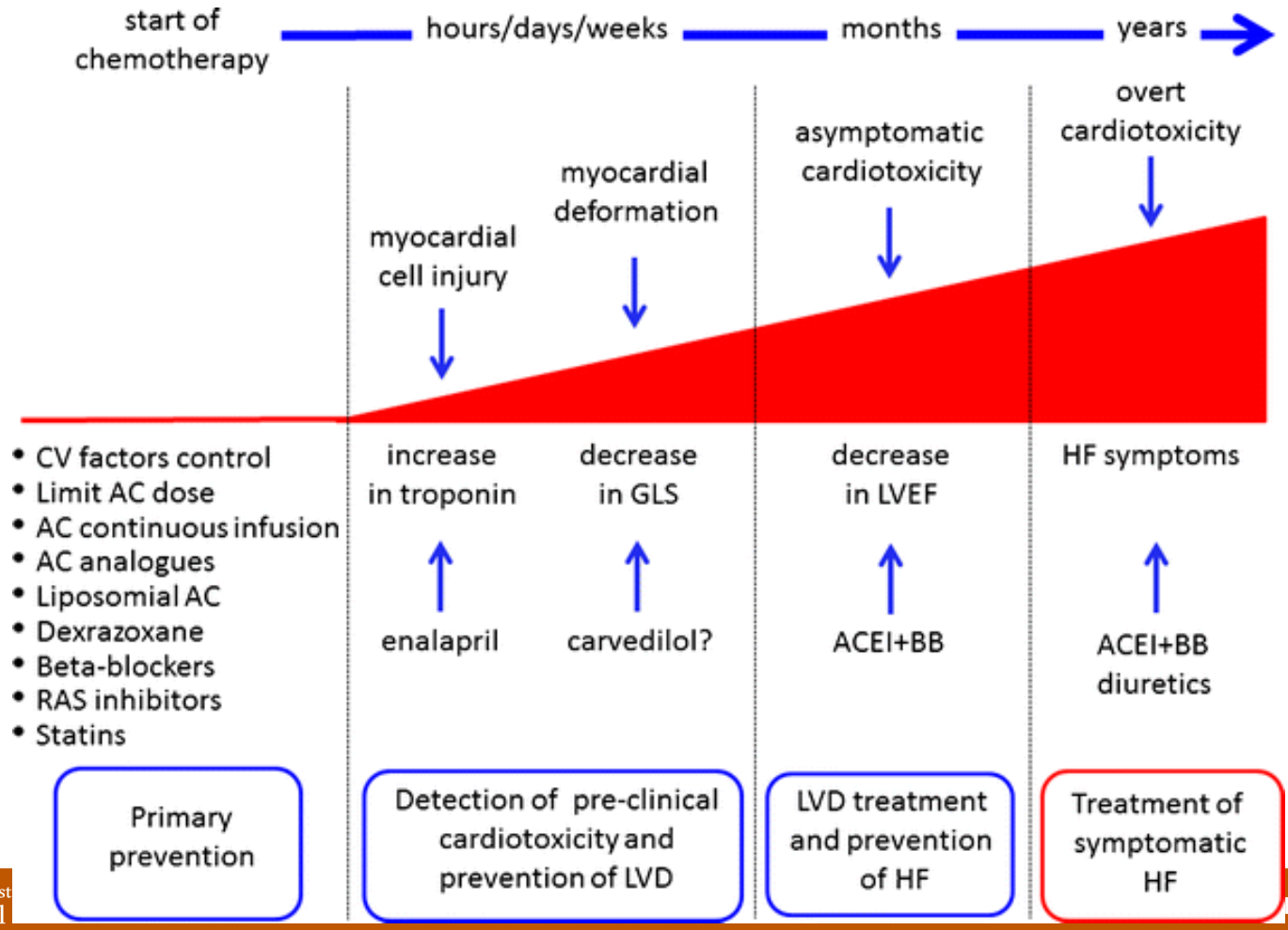
Cardiomyopathy from Cancer Therapeutics

Cardiac response	Drug/intervention	Frequency	Mechanism	Reversibility
Contractile dysfunction/ heart failure	Anthracyclines	Cumulative dose-related	Myocyte death	Minimal
	Cyclophosphamide	Rare	Myocarditis	Partial
	Cisplatin	Rare	Unknown	Unknown
	Trastuzumab	Variable[a]	Contractile protein dysfunction	High
	Lapatinib			Reported
	Bevacizumab	Low	Hypertension?	Reported
	Sunitinib	Low	Mitochondrial dysfunction	Partial
	Sorafenib	Rare		Unknown
	Carfilzomib	Moderate	?	Unknown
	Imatinib	Rare	Mitochondrial dysfunction	High

Spectrum of Cardiotoxicities

- Dyslipidemia (aromatase inhibitors)
- HTN (*angiogenesis inhibitors*/anti-VEGF/TKIs)
- Hypotension (Car-T, mAb, cytokines)
- Pulmonary HTN (Dasatinib)
- Thromboembolic disease(Cisplatin &*angiogenesis inhibitors*)
- Valve disease (radiation)
- Pericardial disease (radiation)

Overview of Treatment Stages



Example- Cardio-Oncology Surveillance for Anthracycline

Baseline	During Treatment	Post Treatment
• Echo (desire LVEF ≥ 50%) • 12 lead ECG • CV risk assessment • Troponin & BNP • Consider pharmacologic therapy in high risk patients (underlying CV, cumulative doxorubicin equivalent > 300 mg/m^2)	• Echo as part of surveillance in at risk patients or if concern for dysfunction during first year (more frequently if concomitant Her2+ therapy) • Troponin and BNP periodically as an ancillary stable • If LVEF < 50% - consider hold anthracycline and recheck LVEF in 3 weeks. If cardiotoxicity confirmed consider pharmacologic therapy • Consider discontinuation of anthracycline therapy if LVEF < 40%	• Assess LVEF 6 months after treatment conclusion and then annually for 2 – 3 years, then every 3 – 5 years for life (COG)

When to refer

- Suspected or confirmed cardiac dysfunction related to cancer therapy
- Abnormal cardiac study/ECG/biomarker without clinical symptoms during therapy
- Primary prevention/pre-chemo optimization in patients with CV toxicity risk factors*
- Secondary prevention for patients with history of cardiotoxicity
- Cancer patients or survivors with concurrent cardiovascular disease or risk factors*
- Pre-clinical trial cardiac optimization for possible cardiotoxic trial agents
- Primary or secondary cardiac tumors
- Cardiac Amyloidosis
- Childhood cancer survivors or cancer survivors received cardiotoxic cancer therapies

Cardiotoxicity

What to know as patients/survivors

Are you at risk?

Cardio-Oncology risk factors

- Age > 60
- HTN, dyslipidemia, DM, FH of cardiomyopathy
- Smoking, alcoholism, obesity
- Low normal LVEF (heart function) at baseline
- pre-existing structural heart disease
- > 250-300mg/m2 doxorubicin
- High dose RT (> 30Gy)
- Sequential anthracyclines + trastuzumab

Adapted from NCCN and ASCO guidelines

What is Cardiotoxicity?

(CTRCD- cancer therapeutics related cardiac dysfunction)

Cardiac Review and Evaluation Committee

- Symptoms or signs associated with heart failure.
- Asymptomatic reduction of LVEF of ≥10% to **<50%.**
- Absolute decrease in LVEF ≥ 16% from pre-treatment level values.

Seidman A, et al. JCO 2002
ASE Consensus Document 2014

Who needs to see cardio-oncologist

- Patients with Cardio-oncology risk factors and/or on High-Risk Cancer Therapy
- **Cancer Survivors, especially Childhood Cancer Servivors**
- Heart Patients Who Are Being Treated for Cancer
- What if I already have a cardiologist?
  - In general, regular cardiologists may not be familiar with new cancer treatments and their heart-related side effects.
  - Many patients see a cardio-oncologist while they are getting cancer treatment and then return to their regular cardiologists once cancer treatment is completed.

What will happen at my visit with the cardio-oncologist?

- During your visit, the cardio-oncologist will review your cancer and heart-related medical history and ask you about symptoms of heart disease. Chest pain, shortness of breath, swelling of your legs, and fatigue are potential signs of a developing heart problem.
- After the visit, additional heart testing may be ordered. These may include electrocardiography (EKG), echocardiography (heart ultrasound), stress testing, heart MRI (magnetic resonance imaging), and/or Holter monitoring. These tests check on the heart's pumping function, blood flow to the heart, and for heart rhythm problems. Blood work may also be ordered to check for signs of heart disease or high cholesterol.
- Finally, the cardio-oncologist will talk to you about strategies to protect your heart health, including lifestyle changes with diet and exercise.
- Follow up visits (some are periodically for life-long) may be needed

Questions to ask your current providers:

- Am I receiving (or have I received) any cancer treatment that could affect my heart either now or in the future?
- What are my risk factors for developing cardiac side effects from treatment?
- Do I need to see a cardio-oncologist during or after cancer treatment?
- If my cancer treatment could damage my heart, how will my heart be monitored during or after cancer treatment?