Heart Disease in Cancer Patients & Survivors

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Professor of Internal Medicine

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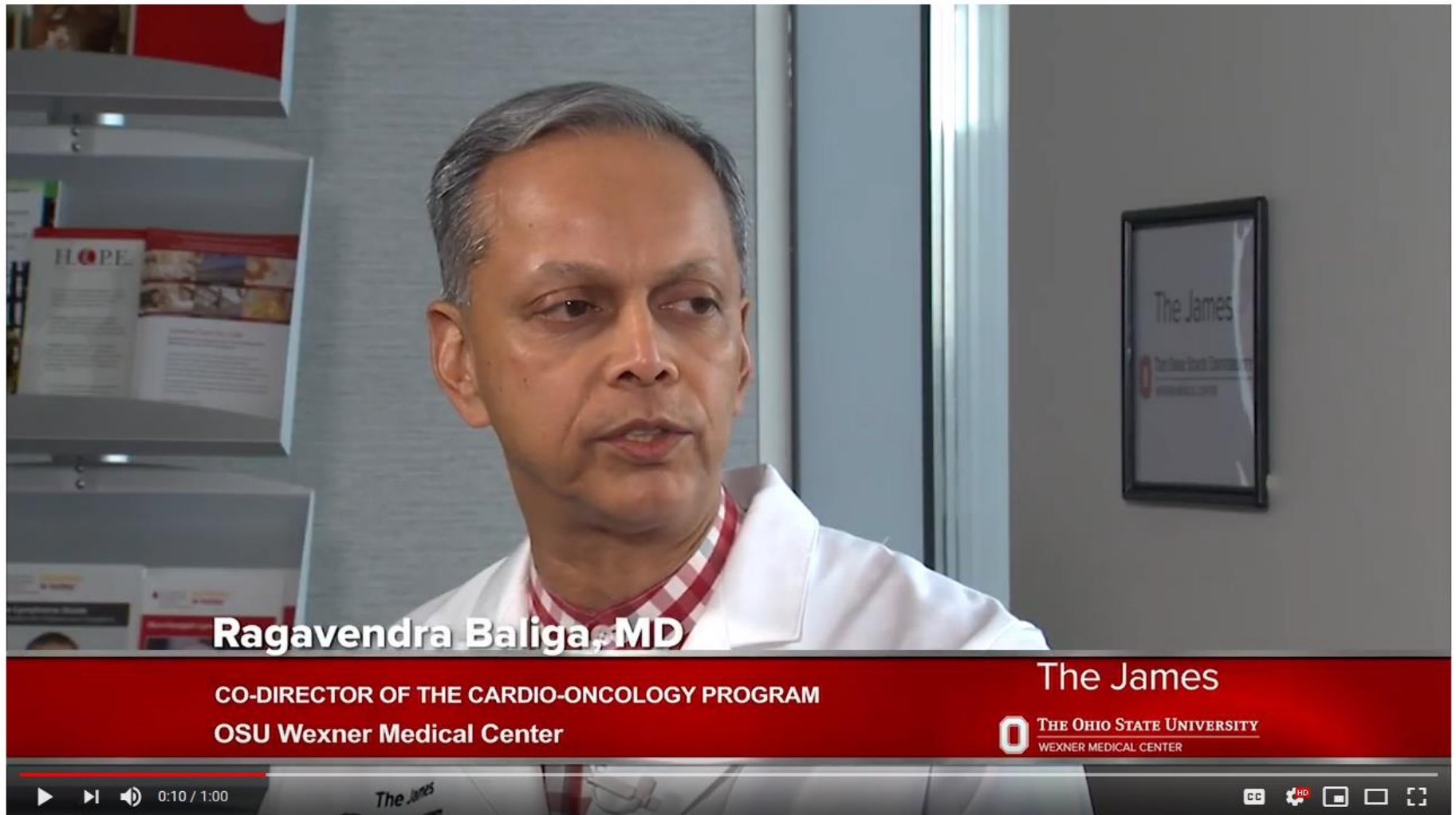**The** Ohio State University Wexner Medical Center

Editor-in-Chief, *Textbook of Cardiology, McGraw Hill*
Associate Editor, Education, American College of Cardiology.org

CME Editor, Journal of American College of Cardiology-flagship journal
CME Editor, Journal of American College of Cardiology-Imaging

Deputy Editor, Global Heart Journal 2008-2018

Editor-in Chief/Consulting Editor Heart Failure Clinics of North America 2007-2012

THE AMERICAN COLLEGE OF CARDIOLOGY

Presents

The Gifted Educator Award

To

RAGAVENDRA R. BALIGA, MBBS, FACC

*In Recognition of His Significant Contributions to
Cardiovascular Education and the Training
of Professionals in Cardiovascular Disease*

WASHINGTON, DC   MARCH 19, 2017

Cardio-Oncology Experts Providing Heart Help to Ohio State Cancer Patients

https://youtu.be/xbD6fXN-KJ0

Why discuss cardiac disease and cancer?

Cardiac Disease & Cancer by far the two most common disease conditions

1. Cardiac disease may pre-exist cancer therapy or may be caused/exacerbated by it

2. Cancer therapy is more effective than ever before at treating cancer, but has a price..

Oncology Trials Stress *Symptomatic* Heart Failure

"Most oncology trials that look at cardiotoxicity place far more importance than most cardiologists and certainly most heart-failure specialists would on 'symptomatic heart failure' and pay very little attention to asymptomatic left ventricular dysfunction,

These are by far the two most common disease conditions in the developed world....
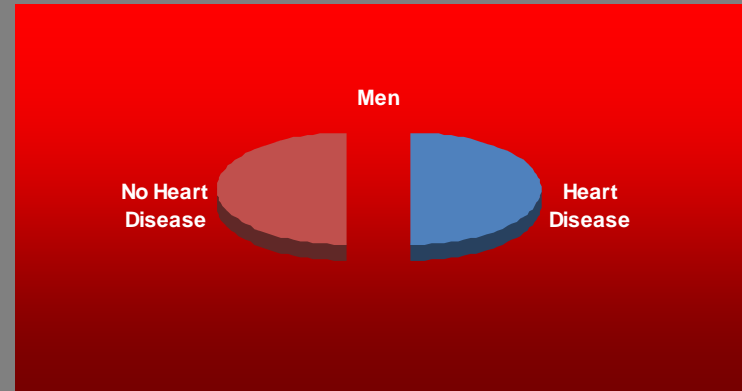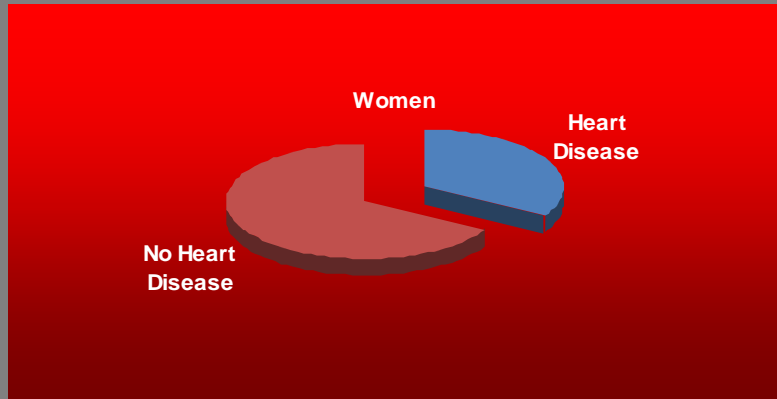
• Lifetime risk of developing coronary heart disease at age 40 years (U.S.)
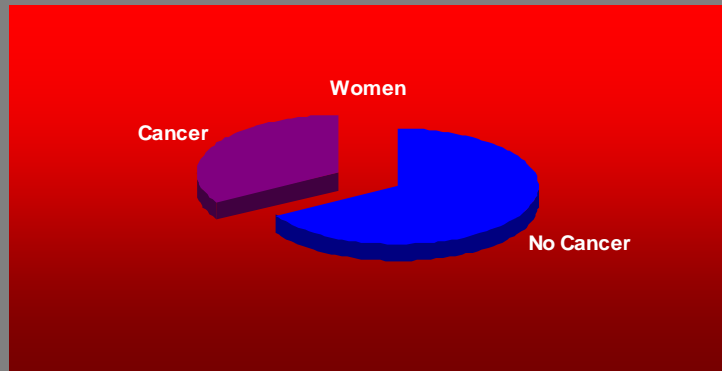
• Lifetime risk of developing cancer (U.S.)

American Cancer Society. Cancer facts & figures 2007,
Lancet 1999;353:89-92.
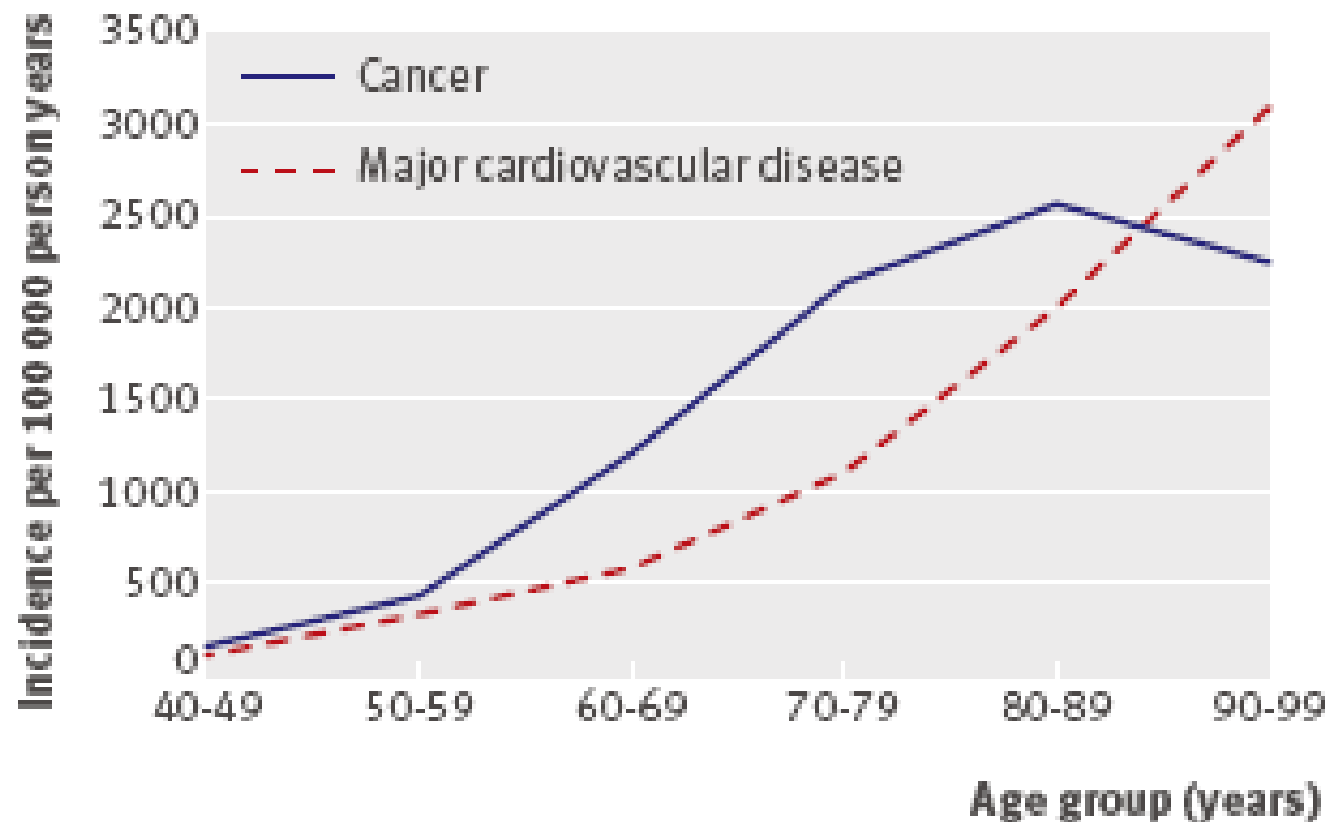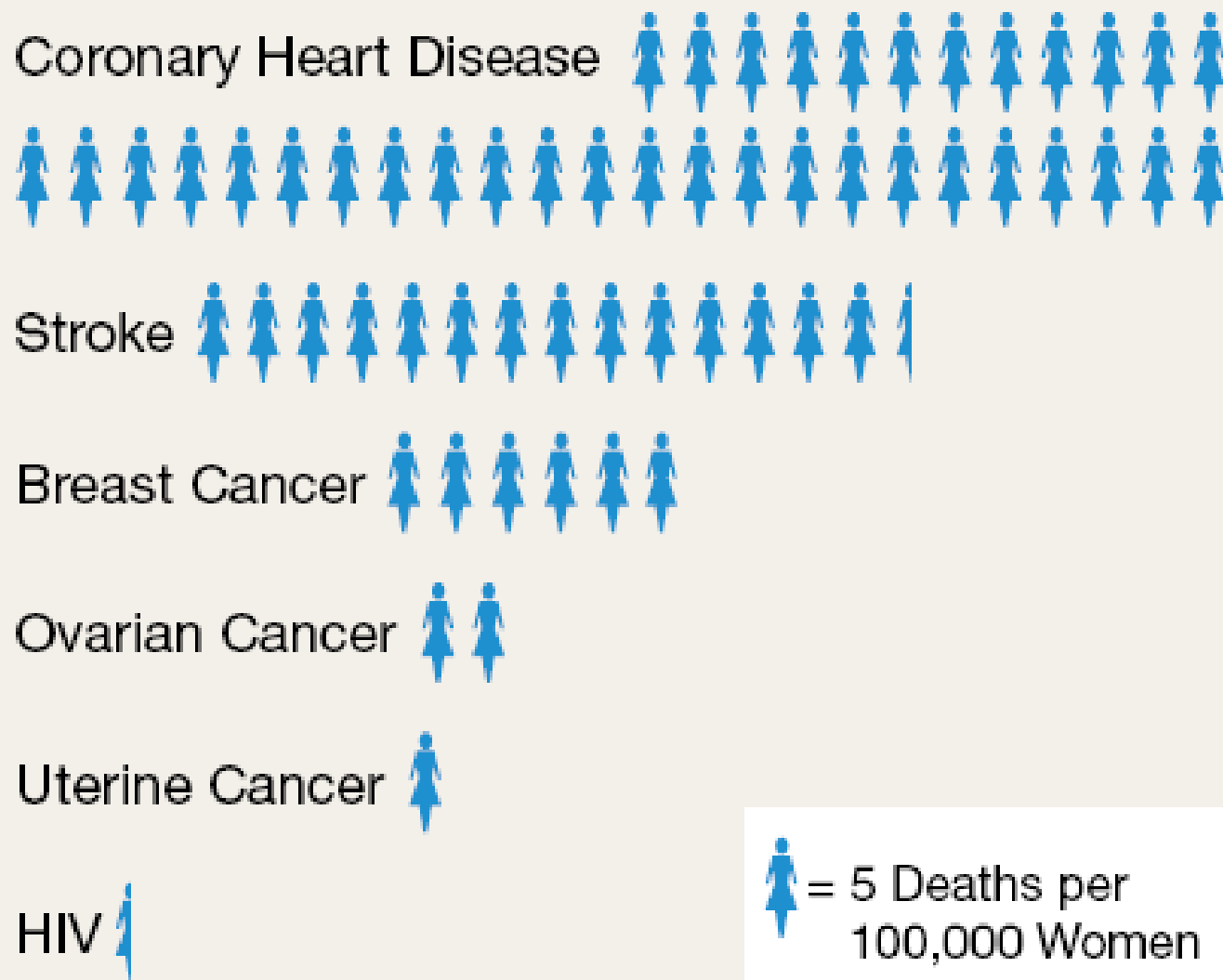
Heart Disease and cancer are likely to overlap

Fig 1 | Crude incidence of overall cancer and major cardiovascular disease by age
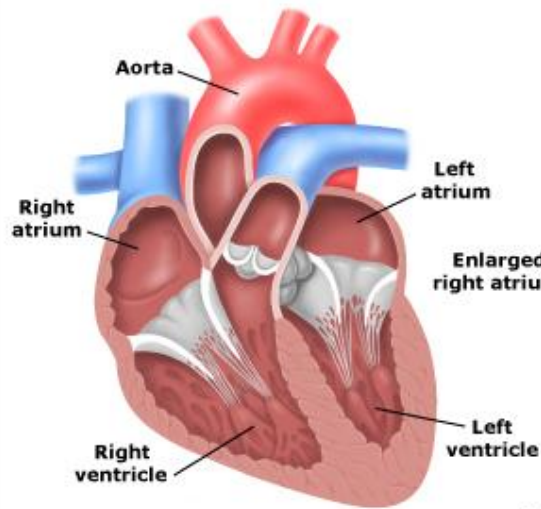
Driver BMJ 2008:337:a2467

Disease-Specific Mortality in US Women, 2000

Specifically, cancer survivors living at least 5 years beyond diagnosis have a 1.3- to 3.6-fold increased risk of cardiovascular-specific mortality and a 1.7- to 18.5-fold increased incidence of CVD risk factors such as hypertension, diabetes mellitus, and dyslipidemia compared with age-matched counterparts with no cancer history.[5,6] The elevated risk of CVD in cancer survivors is likely the result of normal age-related pathologies coupled with the direct (eg, radiation, chemotherapy, targeted therapy) and indirect (eg, deconditioning, weight gain)[7] effects of cancer therapy that extend across multiple systems (ie, whole-organism cardiovascular toxicity).[8] CVD is likely to become even more pervasive in the oncology setting as a result of continued improvements in cancer-specific mortality in conjunction with the rapidly aging population.[9]
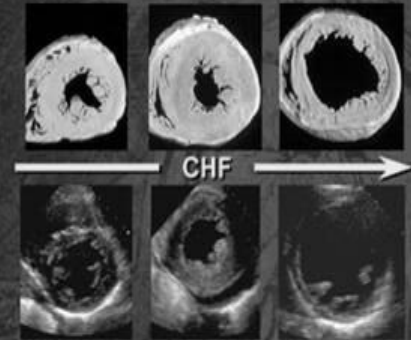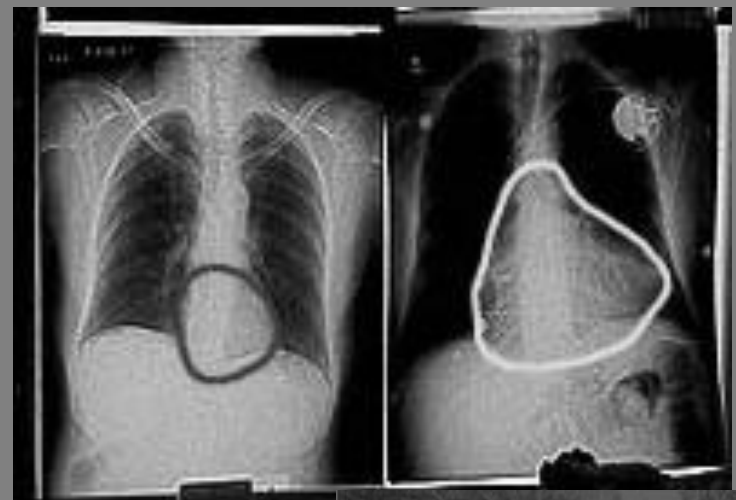
Circulation. 2019

Weak Heart/HF

Normal

Dilated cardiomyopathy

Heart Attack?

Normal Artery

Diseased Artery

Atherosclerosis

Narrowing of Artery

Aorta

Coronary Arteries

Heart

C. Lynm

PCI

Blocked Coronary Artery

Insertion of Stent After Balloon Angioplasty

Stent in Place and Blood Flow Restored

Heart

Aorta

Femoral Artery

Catheter

Blood Clot

Atherosclerotic Plaque

Balloon Catheter

Stent

NO BLOOD FLOW

BLOOD FLOW

C. Lynm
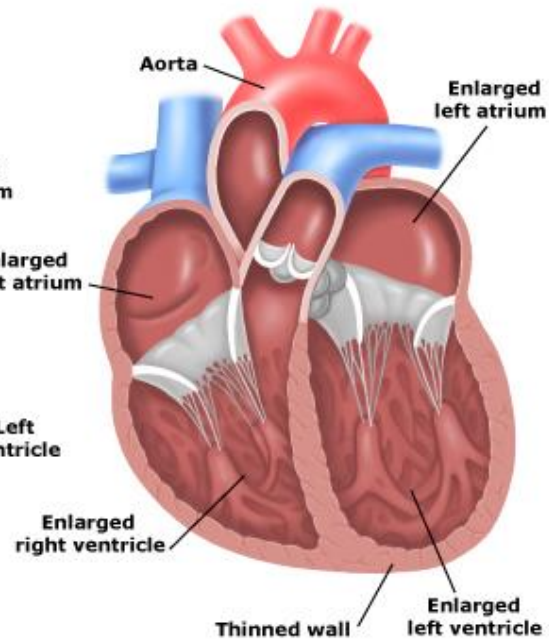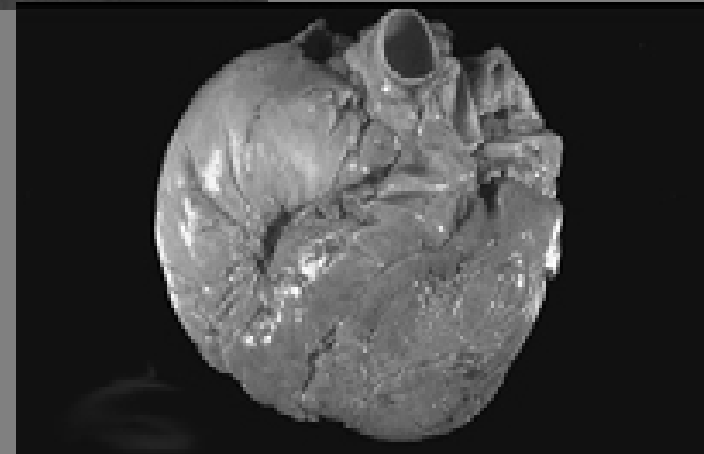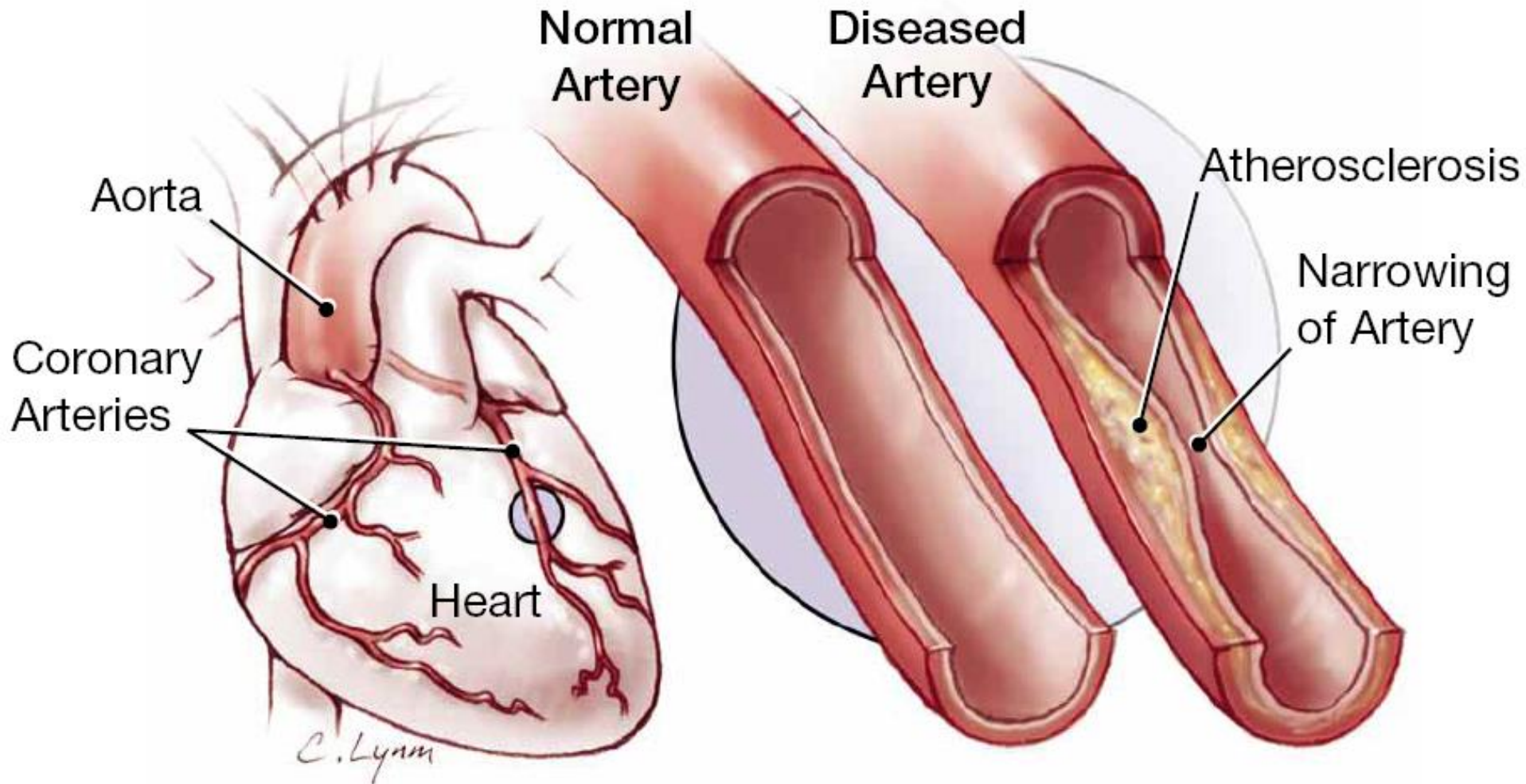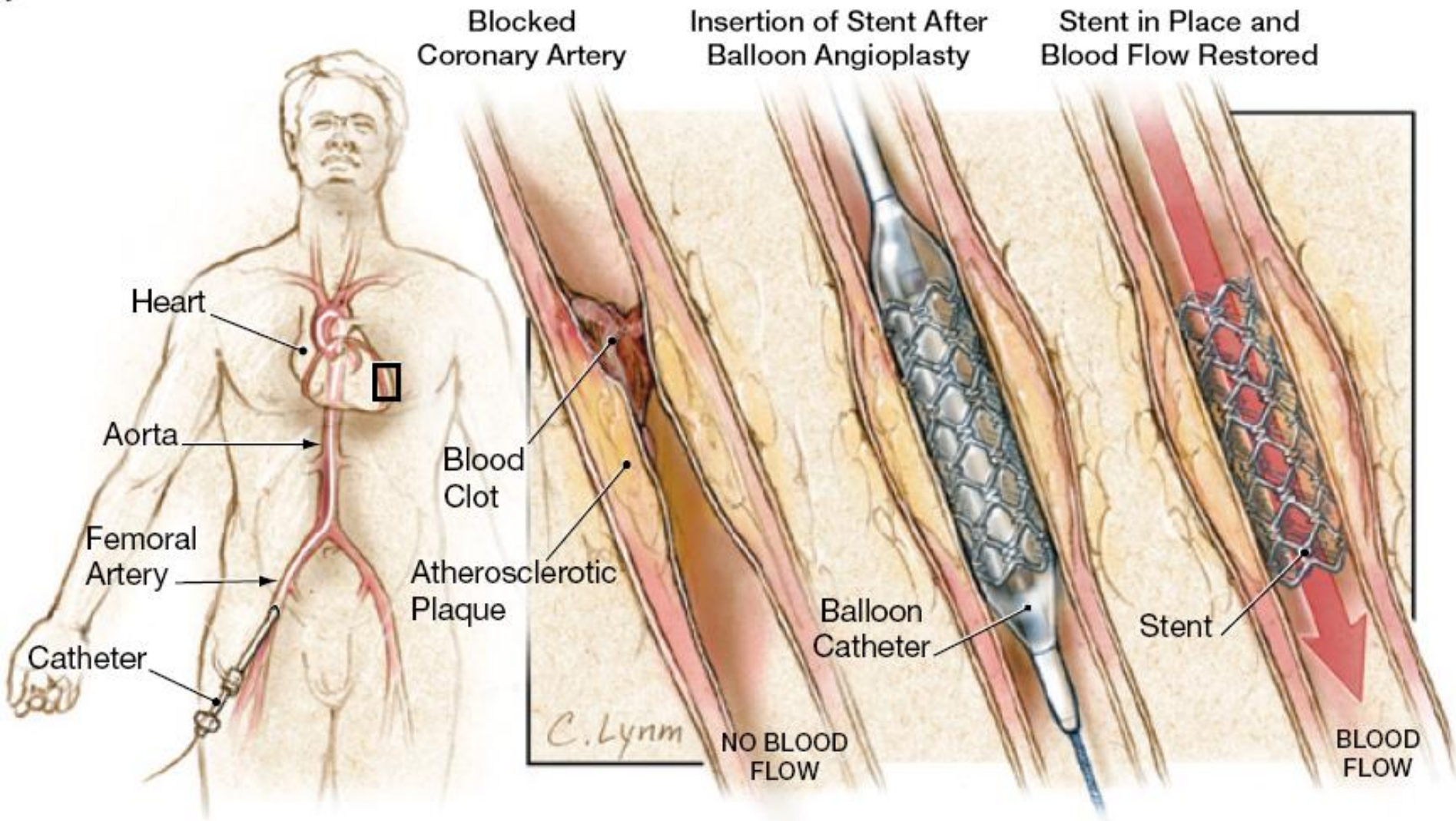
BYPASS/CABG

Off-pump coronary artery bypass graft surgery
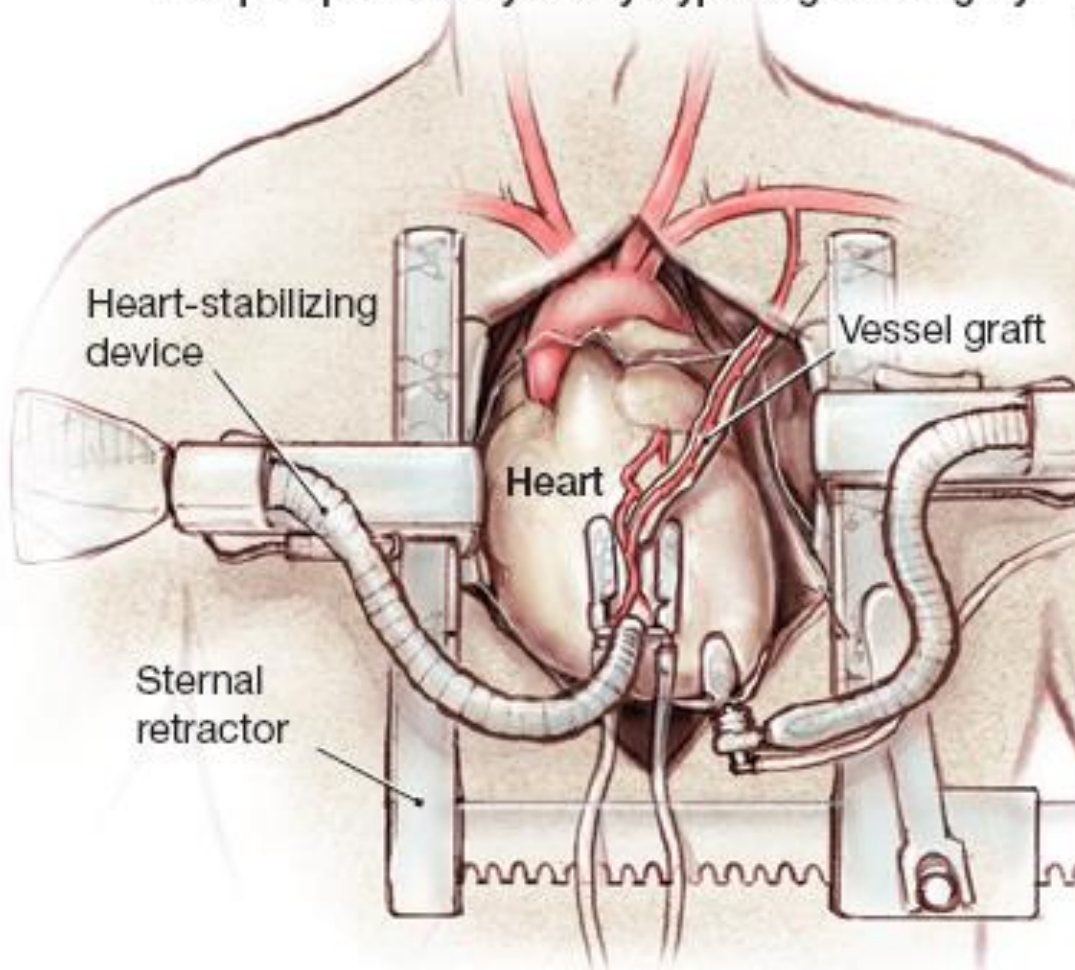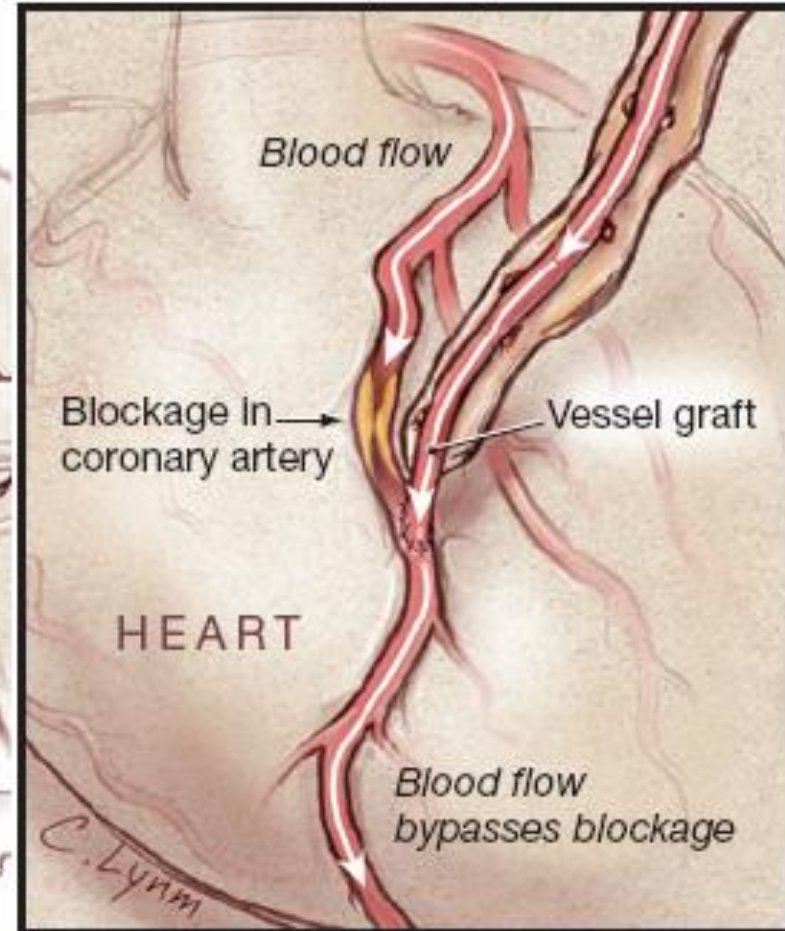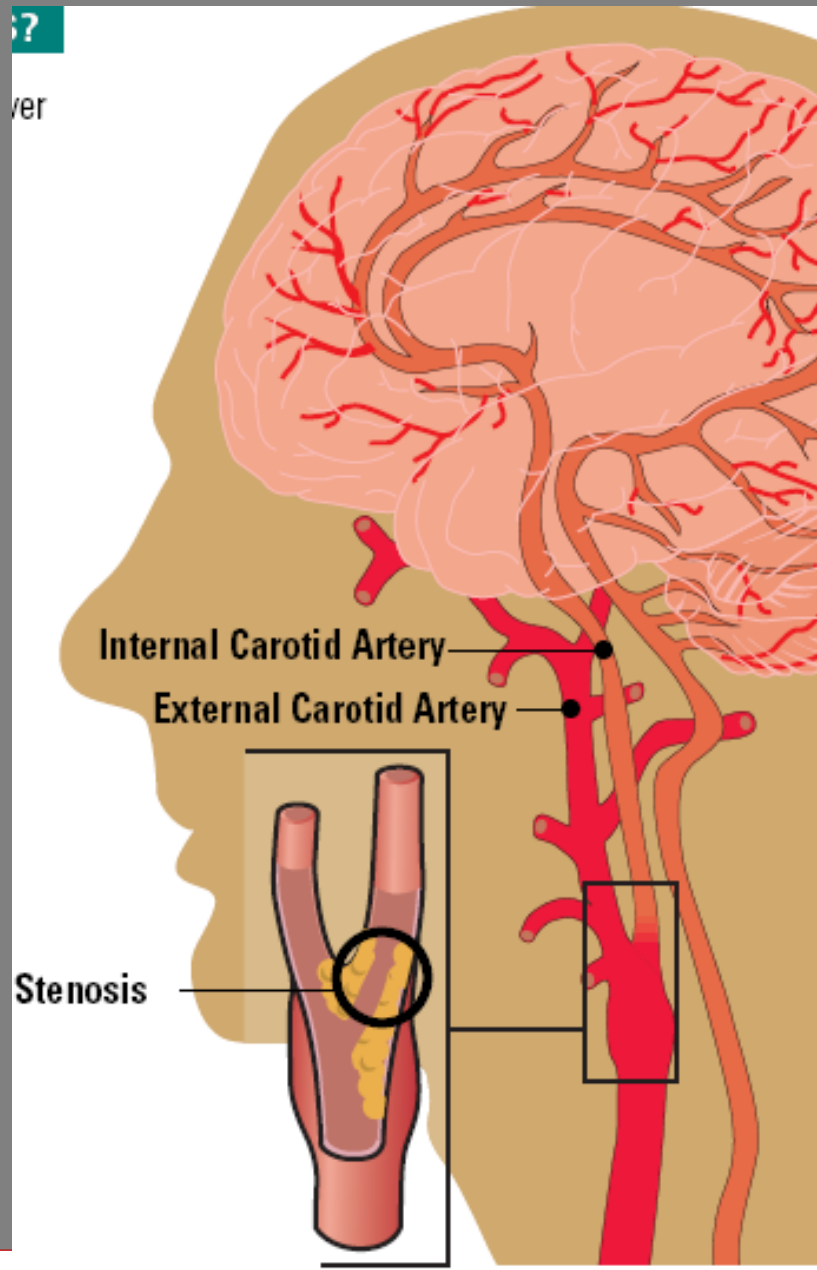
Heart-stabilizing device

Vessel graft

Heart

Sternal retractor

Close-up of bypass

Blood flow

Blockage in coronary artery

Vessel graft

HEART

Blood flow bypasses blockage

C. Lynn

Stroke

Internal Carotid Artery

External Carotid Artery

Stenosis

ver

Definitions of cardiotoxicity-related terms

Angina: acute pain in the chest

Arrhythmias: variation from the normal heart rhythm

Cardiogenic shock: acute peripheral circulatory failure secondary to primary cardiac problem

Cardiomyopathy: primary myocardial disease

Edema: accumulation of excess fluid

Effusion, pericardial: accumulation of fluid in the pericardium

Fibrosis: formation of fibrous tissue

Heart block: impairment of conduction in heart excitation

Hypertension: high blood pressure, typically > 140/80

Hypotension: low blood pressure, typically < 100 systolic

Infarction: interruption of blood supply causing necrosis

Ischemia: deficiency of blood supply to the heart

Infarction: interruption of blood supply causing necrosis

Myocarditis: inflammation of the muscular wall of the heart

Pericarditis: inflammation of the pericardium

Thromboembolism: obstruction of blood vessel with thrombic material

Vasospasm: spasm of blood vessel decreasing caliber

PARTIAL LIST OF ADVERSE EFFECTS

Adverse Effect	Therapy
Heart failure	Anthracycline, mitomycin, cyclophosphamide, cisplatin, trastuzumab, alemtuzumab
Pericardial effusion	Cyclophosphamide, cytarabine, imatinib, busulfan, radiation therapy
Myocardial ischemia	Cisplatin, vinca alkaloids, capecitabine, IL-2, bevacizumab, 5-fluorouracil, radiation therapy
Arterial hypertension	Cisplatin, bevacizumab, interferon-α
Arterial hypotension	Etoposide, paclitaxel, alemtuzumab, cetuximab, rituximab, interleukin-2, interferon-α
Myocarditis	Busulfan, cyclophosphamide, radiation therapy
Bradycardia	Paclitaxel
Thromboembolus	Bevacizumab, paclitaxel

Cardiotoxicity of chemotherapeutic agents used to treat breast cancer - synthesis of the literature [18,19,20,21]

Generic Name	Brand Name	Cardiotoxicity
Albumin-bound paclitaxel	Abraxane	None significant
Aromatase inhibitors	Arimidex, Aromasin, Faslodex, Femara	Angina, hypertension, infarction, thromboembolism
Bevacizumab	Avastin	Hypertension Ischemia Congestive heart failure
Capecitabine	Xeloda	Angina Congestive heart failure Ischemia
Carboplatin	Paraplatin	Ischemia
Cyclophosphamide	Cytoxan	Cardiomyopathy Myocarditis
Docetaxel	Taxotere	Edema
Doxorubicin	Adriamycin	See text
Epirubicin	Ellence	Arrhythmias Cardiomyopathy Congestive heart failure Ischemia
Fluorouracil	5-FU	Arrhythmias Congestive heart failure Ischemia
Gemcitabine	Gemzar	None significant
Lapatinib	Tykerb	Prolonged QT Decreased left ventricular ejection fraction
Methotrexate	Trexall	Arrhythmias Ischemia
Tamoxifen	Nolvadex	Thromboembolism
Trastuzumab	Herceptin	See text
Paclitaxel	Taxol	Arrhythmias Congestive heart failure Hypotension Ischemia
Pegylated liposomal doxorubicin	Doxil	CHF (must be included in measuring accumulated dose of athracycline)
Vinorelbine	Navelbine	Ischemia

Trends in Five-year Relative Cancer Survival Rates (%), 1975-2009

Site	1975-1977	1987-1989	2003-2009
All sites	49	55	68
Breast (female)	75	84	90
Colon	51	60	65
Leukemia	34	43	59
Lung & bronchus	12	13	18
Melanoma of the skin	82	88	93
Non-Hodgkin lymphoma	47	51	71
Ovary	36	38	44
Pancreas			6
Prostate			100*
Rectum			68
Urinary bladder			80

5-year relative survival rates based on patients diagnos[...]3-2009, all followed
through 2010.
*99.5%
Source: Surveillance, Epidemiology, and End Results (S[...]

The percentage of patients at diagnosis and the associated 5-year survival rates for the stages of breast cancer

Stage	Diagnosis (%)	5-year Survival (%)
0 and 1 (localized)	61	98
2 (local spread)	31 (combined with stage 3)	81–92
3 (locally advanced)	31	54–67
4 (distant spread)	6	20–26

Classic Triad of Heart Failure

- Shortness of breath or Dyspnea

- Lower extremity edema

- Fatigue

Survival According to Cause
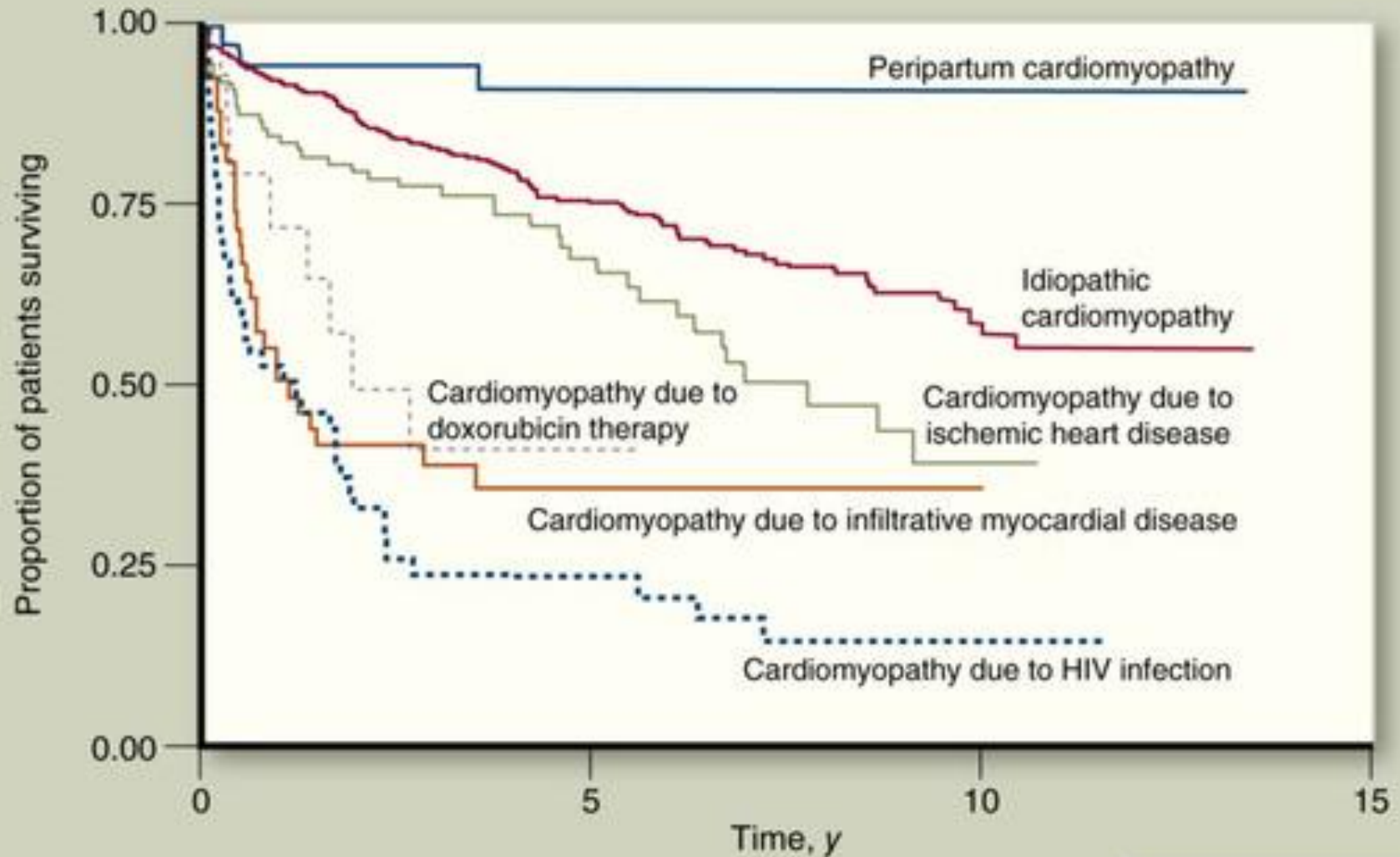
Doxorubicin induced HF & cumulative dose
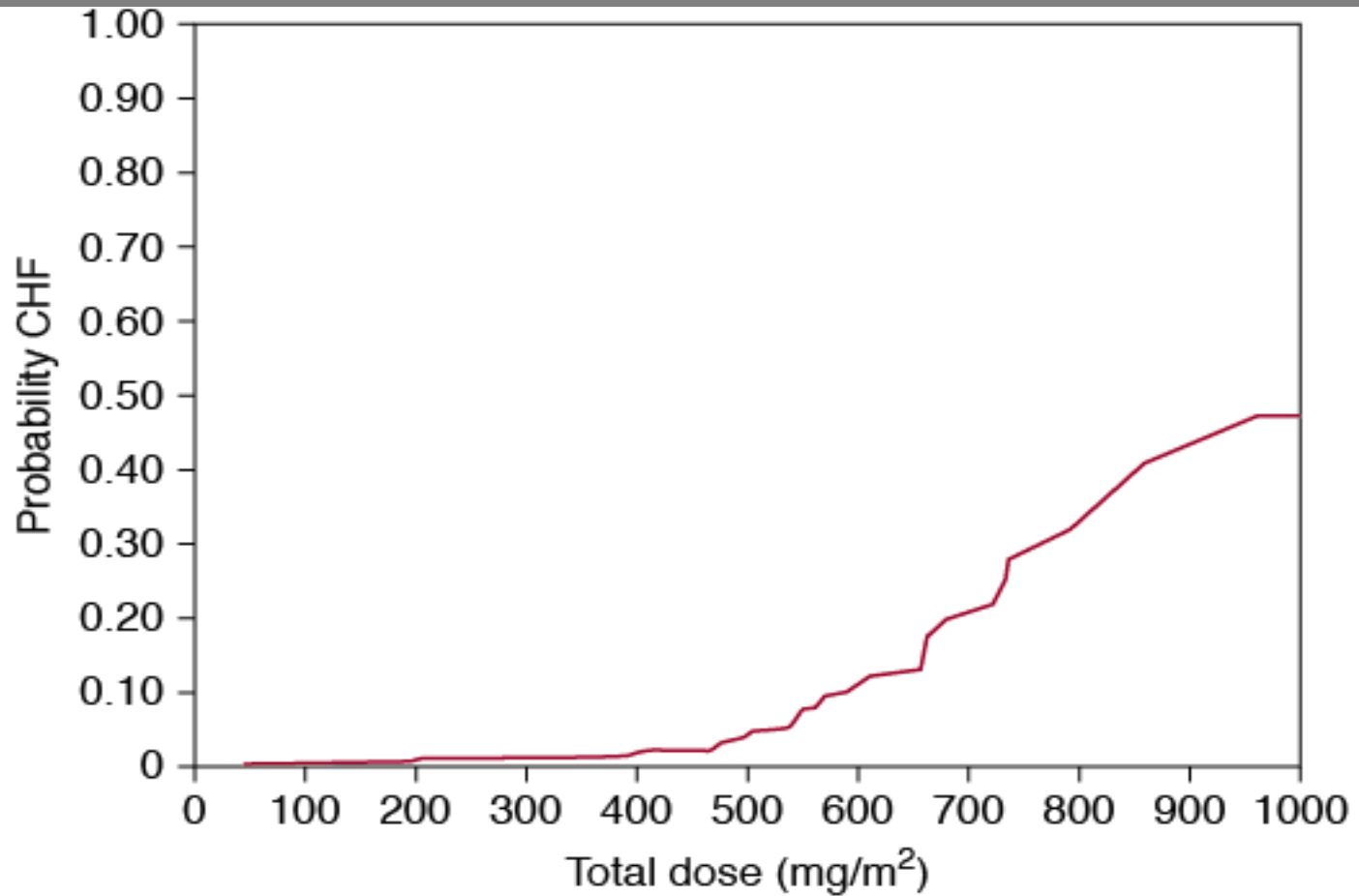
Heart-Failure Treatment Inadequate

Many patients, whether symptomatic or not, did not get appropriate heart-failure therapy, nor were they referred to a cardiologist.

Percent of Patients Who Received Drug Therapy and Referral After Chemotherapy

Patients	Received ACE-I/ARB	Received beta blocker	Referred to cardiologist
Asymptomatic, %	33	41	37
Symptomatic, %	47	56	50

ACE-I, ACE inhibitor; ARB, angiotensin-receptor blocker

American College of Cardiology (ACC) 2009
Scientific Sessions.
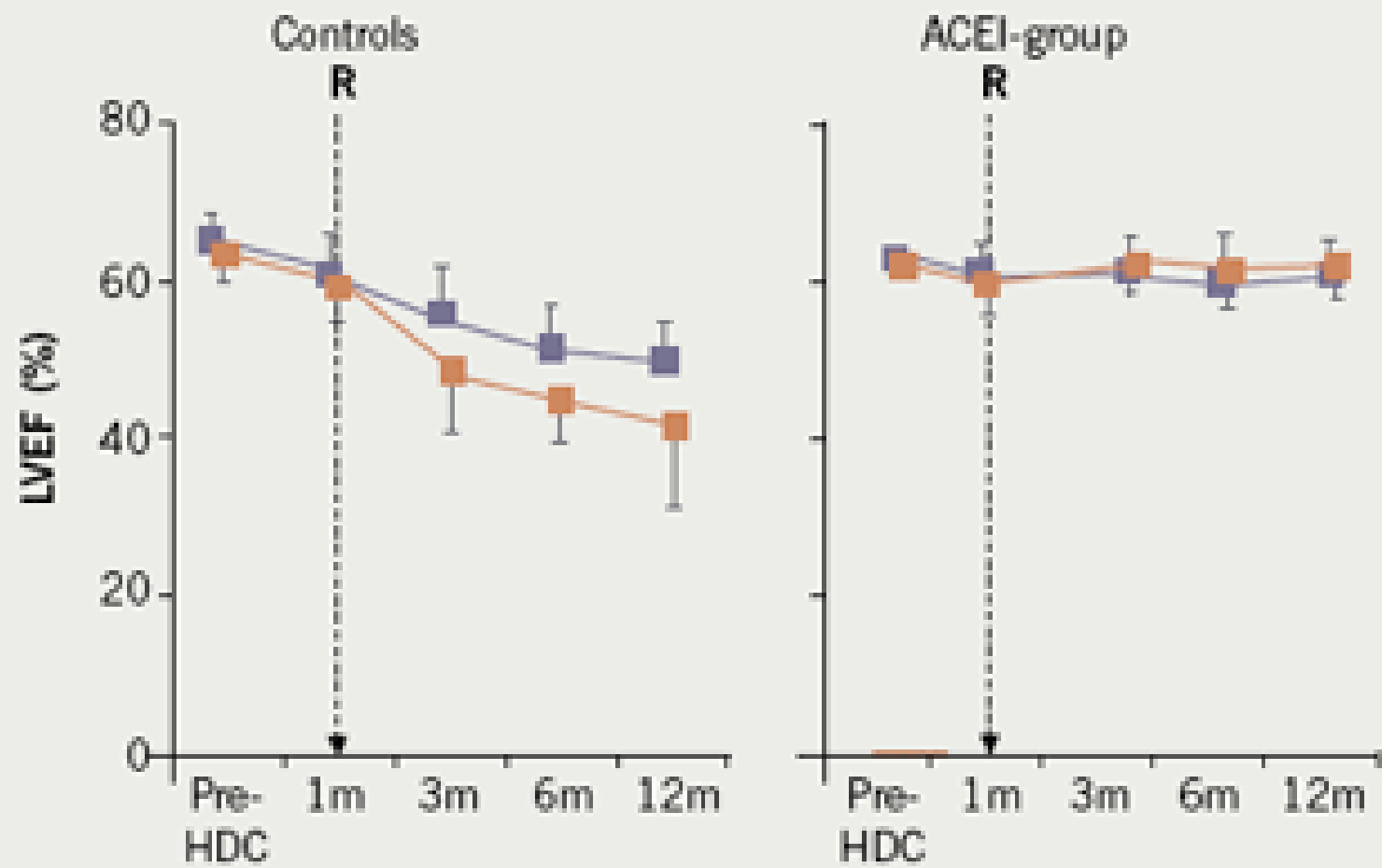
Key: ACEI = angiotensin-converting enzyme inhibitor; HDC = high-dose chemotherapy

Carvedilol Against Anthracycline-Induced Cardiomyopathy

Kalay N, et al. *J Am Coll Cardiol.* 2006;48:2258-62.
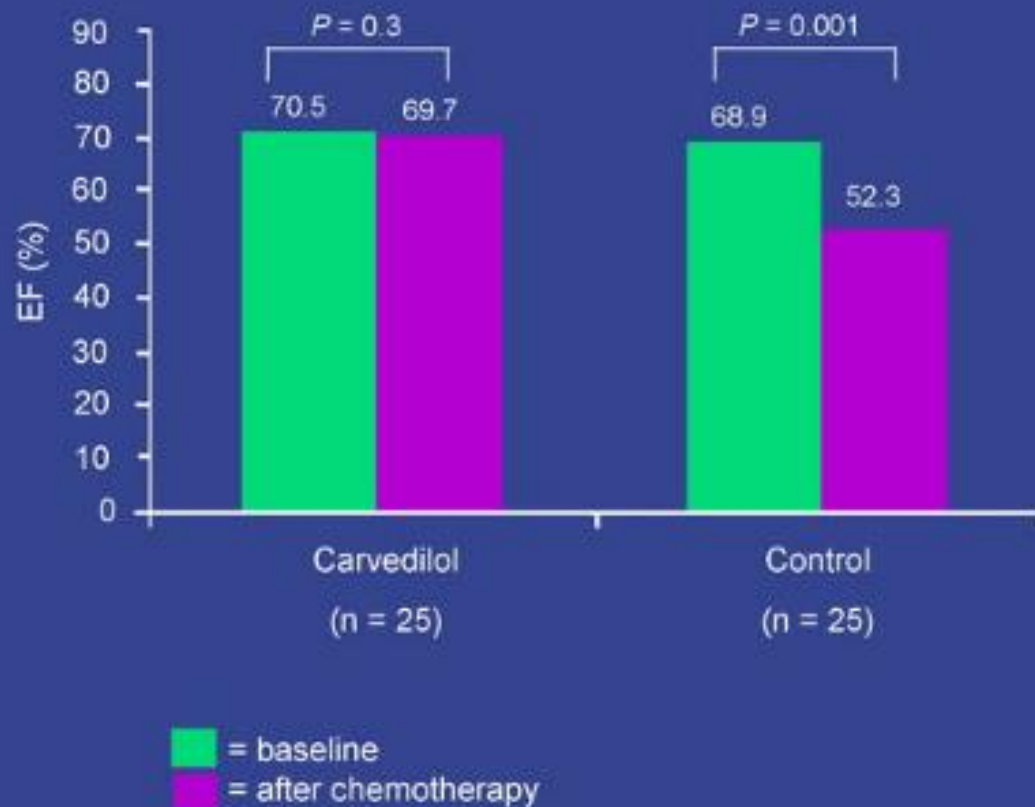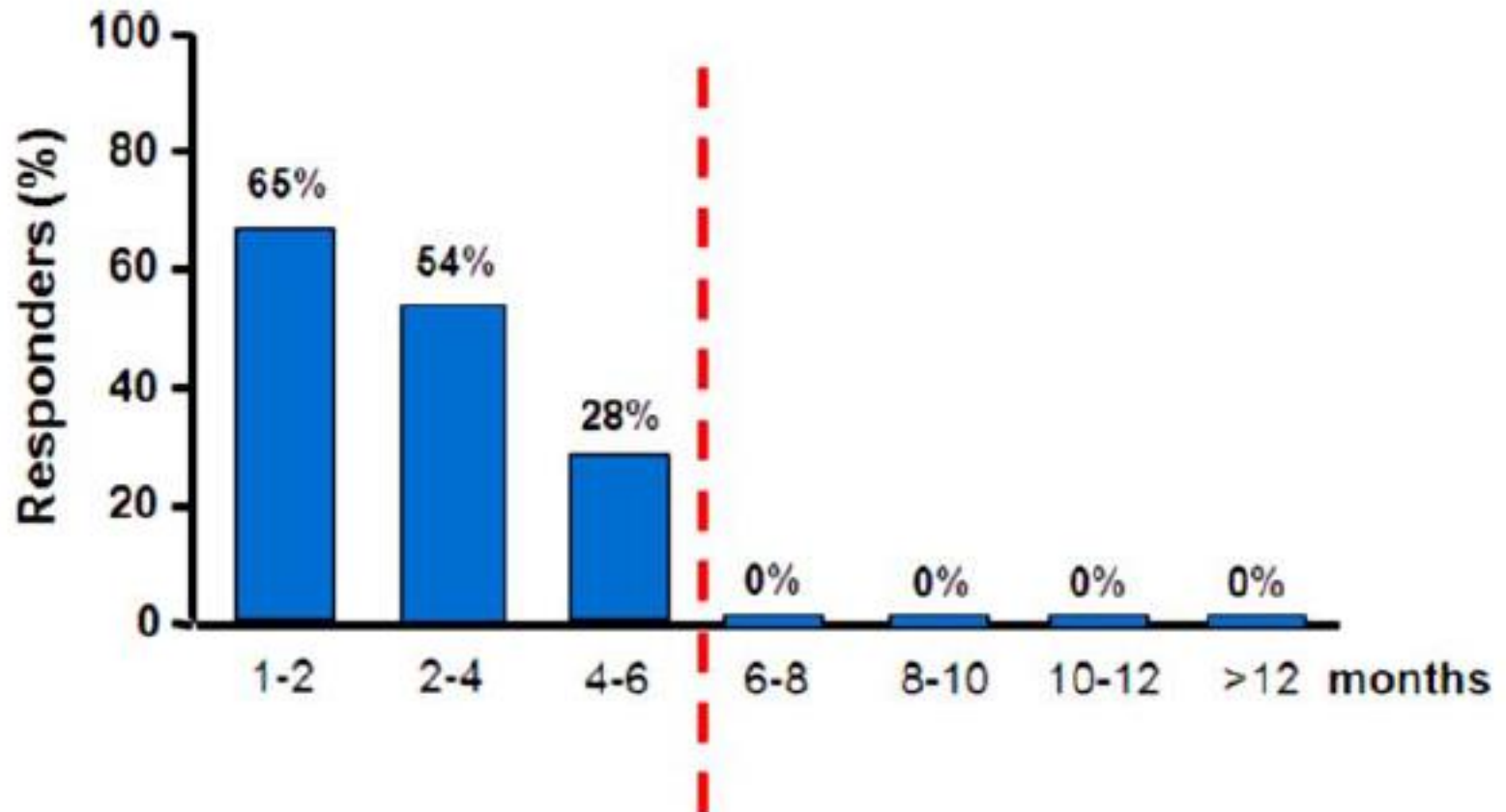
The reversibility of left ventricular dysfunction (both symptomatic and asymptomatic) in patients undergoing treatment with anthracyclines depends critically on the timing of the initiation of cardioprotection therapy with beta blockers and angiotensin-converting enzyme inhibitors. If initiation of therapy is delayed longer than 6 months since the time of anthracycline exposure, then the likelihood that patients will respond to therapy is greatly reduced J Am Coll Cardiol. 2010;55:213-220

Trastuzumab

1. HeR2 (erB-2) is expressed in the heart, and imp for cardiomyocyte survival

2. Adaptation to stress can result in trastuzumab cardio toxicity

3. NRG-1-induced cardiomyocyte hypertrophy. Role of PI-3-kinase, p70(S6K), and MEK-MAPK-RSK. Baliga RR, Pimental DR, Zhao YY, Simmons WW, Marchionni MA, Sawyer DB, Kelly RA. Am J Physiol. 1999 Nov;277(5 Pt 2):H2026-37.

4. Neuregulins promote survival and growth of cardiac myocytes. Persistence of ErbB2 and ErbB4 expression in neonatal and adult ventricular myocytes. Zhao YY, Sawyer DR, Baliga RR, Opel DJ, Han X, Marchionni MA, Kelly RA. J Biol Chem. 1998 Apr 24;273(17):10261-9.

In the case of HER2+ breast cancer, treatment clearly benefitted the disease but came at a cost

**Table 2. Therapeutic Index for Critical Clinical Events.***

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
		number of events	
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†

Table 4. Cardiac Risk Factors and Events.*

Variable	AC-T (N=1073)	AC-T plus Trastuzumab (N=1074)	TCH (N=1075)
		number of patients (percent)	
Risk factors			
Diabetes	38 (3.5)	36 (3.4)	28 (2.6)
Hypertension	178 (16.6)	178 (16.6)	190 (17.7)
Obesity†	214 (19.9)	242 (22.5)	234 (21.8)
Hypercholesterolemia	54 (5.0)	47 (4.4)	43 (4.0)
Left-side radiotherapy	378 (35.2)	349 (32.5)	364 (33.9)
Events			
Cardiac-related death	0	0	0
Congestive heart failure‡	7 (0.7)	21 (2.0)	4 (0.4)§
>10% relative reduction in left ventricular ejection fraction¶	114 (11.2)‖	194 (18.6)	97 (9.4)**

Slamon D et al; NEJM 2011:365:1273-83

Incidence of Heart Failure Following Doxorubicin and Trastuzumab Therapy
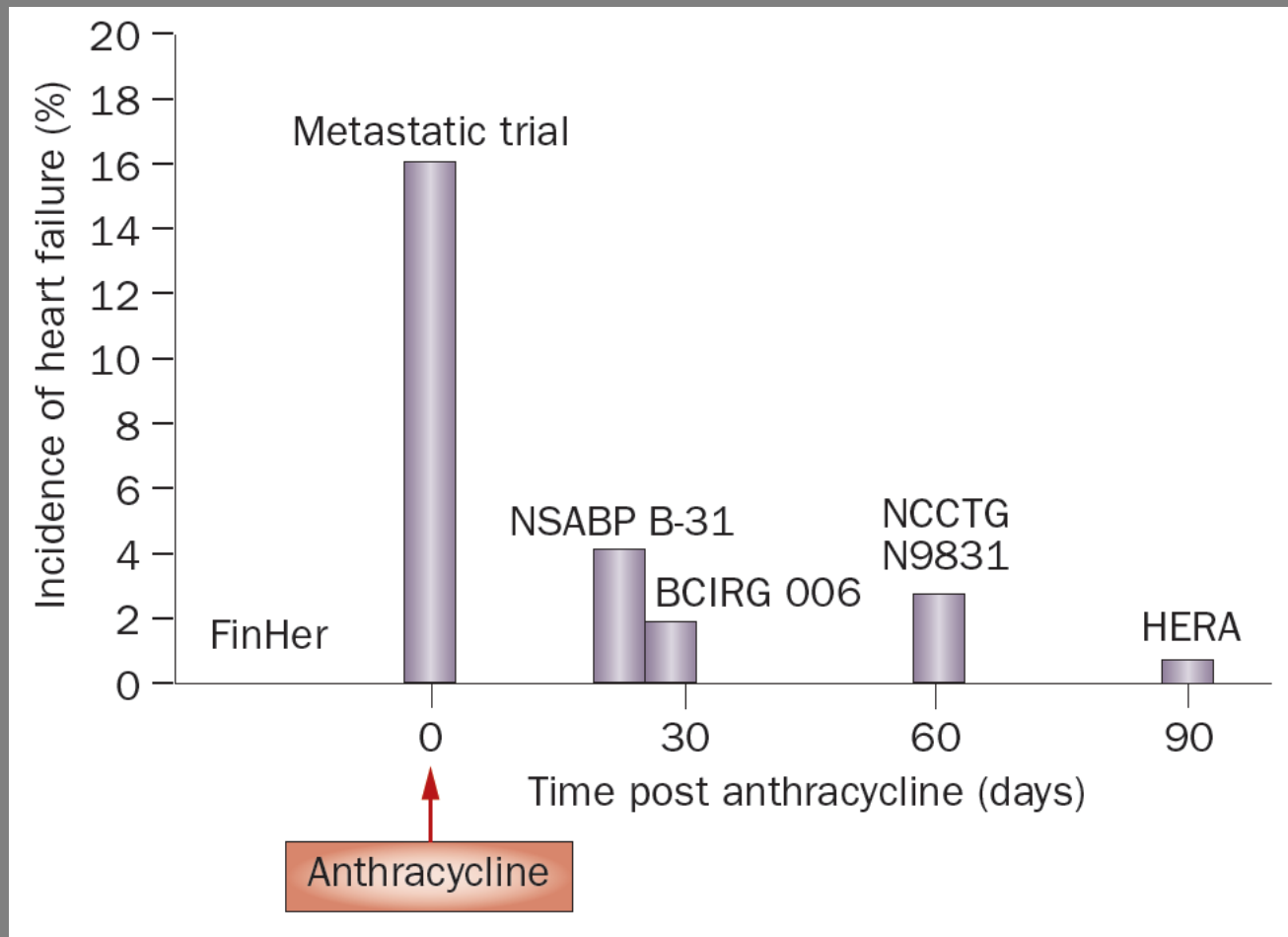
Incidence of NYHA class III or class IV heart failure as a factor of the interval of time between the completion of doxorubicin and administration of trastuzumab, as reported in the major adjuvant trials. In a pivotal metastatic trial, the drugs were given concomitantly, and in the FinHer trial, trastuzumab administration preceded anthracycline. A higher incidence of heart failure was observed in the trials that administered trastuzumab with or shortly after anthracycline. Ewer, M. S. & Ewer, S. M. *Nat. Rev. Cardiol. 7, 564–575 (2010)*

RISK FACTORS

Anthracyclines	Trastuzumab
• Cumulative dose	• Prior or concomitant anthracyclines
• Combination chemotherapy	• Time on anthracyclines > anti-HER2
• Prior or concomitant mediastinal radiotherapy	• Concomitant paclitaxel?
• Age (pediatric and elderly)	• Age > 50 years
• Previous cardiac disease (associated with increased LVEDP)	• Previous cardiac disease (associated with systolic dysfunction; LVEF < 55%)
• Hypertension	• Hypertension (medication)
	• Higher BMI

Prior Damage or Factors that Make it Susceptible to Damage

Table 2 | Risk factors for the development of anthracycline cardiomyopathy

Risk factor	Hazard ratio	Reference
Prior anthracycline use (cumulative dose)	NA	Von Hoff et al. (1979)[27]
Cardiac irradiation	NA	Steinherz et al. (1991)[112]
Other heart disease	1.53	Hershman et al. (2008)[113]
Hypertension	1.58	Hershman et al. (2008)[113]
Coronary artery disease	2.21	Hershman et al. (2008)[113]
Age >65 years	2.25	Swain et al. (2003)[33]
Abbreviation: NA, not available.		

TABLE 2
Risk Factors for Trastuzumab Cardiotoxicity

Documented[a]	• Treatment with trastuzumab plus chemotherapy (highest risk combination is trastuzumab plus concurrent anthracyclines)
	• Age > 60 yrs
Suspected	• Previous cumulative anthracycline dose ≥ 400 mg/m²
	• Prior chest wall irradiation
	• Preexisting cardiac dysfunction

[a] Data adapted from Sparano JA. Cardiac toxicity of trastuzumab (Herceptin): implications for the design of adjuvant trials. *Semin Oncol.* 2001;28:20–27.

Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.
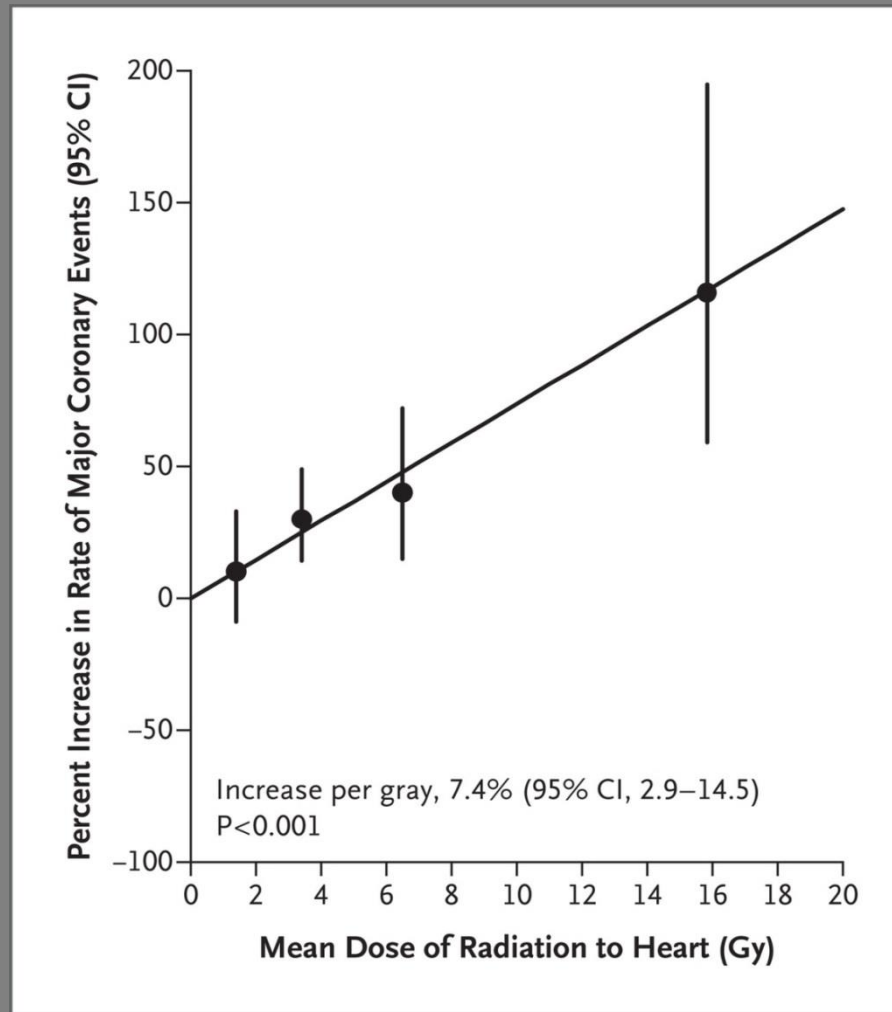
The NEW ENGLAND
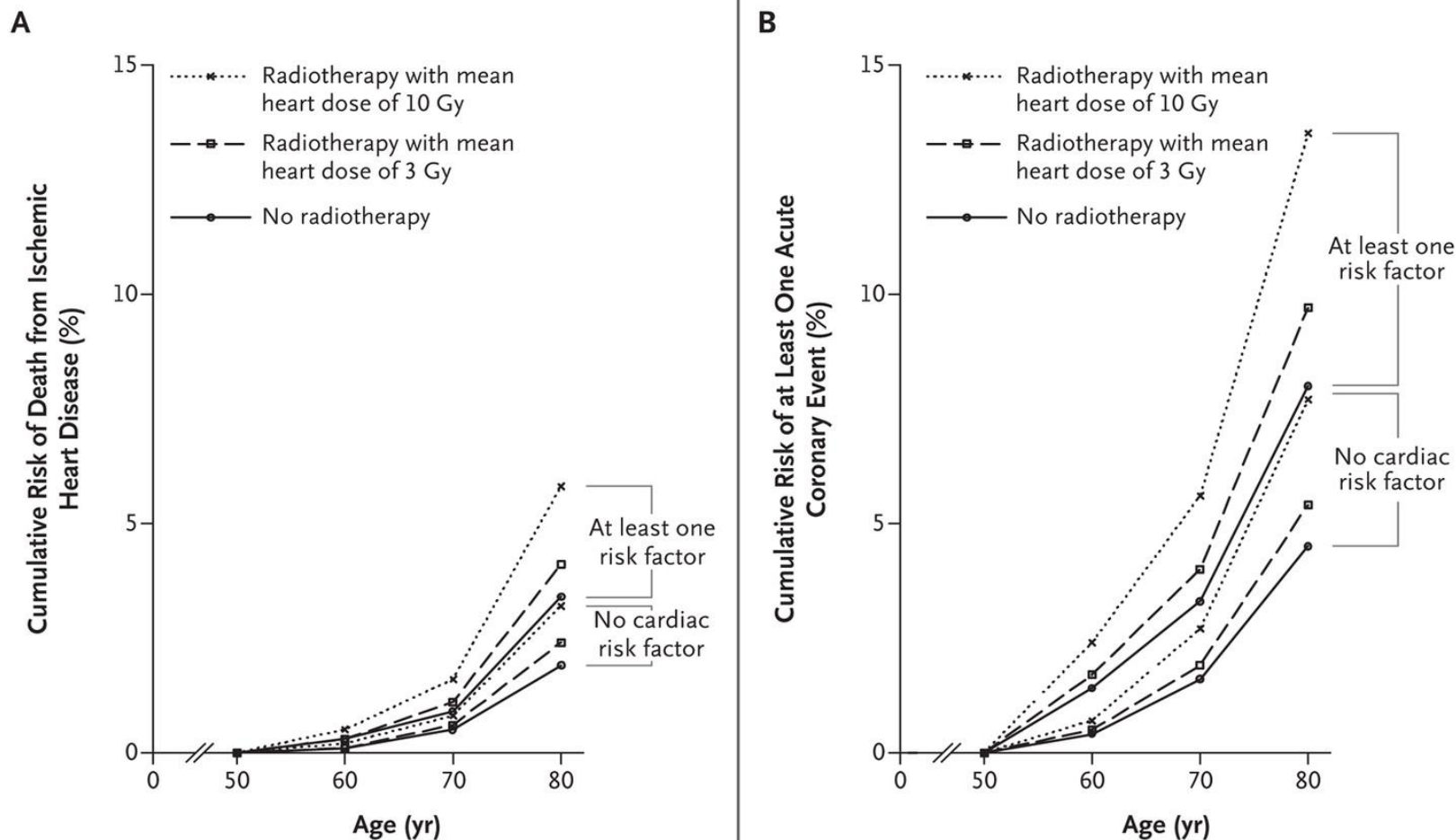JOURNAL of MEDICINE

Cumulative Risks of Death from Ischemic Heart Disease and of at Least One Acute Coronary Event.

Prone position proves effective in breast cancer radiation therapy. (The Ohio State University)

Eat like a horse at breakfast, a puppy at lunch and a bird at dinner.

As a cardiologist, this is advice I've been telling my patients for years. You basically reverse the typical American way of eating and front load the day with the most calories. Eat hearty with breakfast foods that are high in protein, fiber and have some carbohydrates. A few suggestions include: veggie and egg muffin cups, yogurt with fresh fruit and granola, hard-boiled eggs with sugar-free trail mix, overnight oats, whole wheat bread with nut butter or a low-fat breakfast burrito.

I also tell my patients to avoid carbs after 5 p.m. because they're 'fuel food.' We sleep at night, so we don't need as many carbs. This is lifelong advice that is supported by a recent study. I now follow it myself. Simply by eating a bigger breakfast and reducing carbs in the evening, I've lost 10 pounds in the last 18 months. I encourage you to make the change, and see how it benefits you.

Dr. Baliga is a cardiologist and a professor of internal medicine at The Ohio State University Wexner Medical Center.

https://myfox28columbus.com/good-day-columbus/new-study-eat-breakfast-every-day?jwsource=cl

If You Not Sweating You Are Not Exercising

Exercise, exercise, exercise till you are sweating
Sweat means every cell in your body with oxygenated blood perfusing
Physical activity every day resulting in warm perspiring
Is energizing, exhilarating and uplifting

Remember if you are not sweating you are not adequately exerting
The aim is to get the blood flow rolling and flowing
The goal is for every pore perspiring
The sweat drenching skin is invigorating

Always do a warm up
Until you are mildly sweating do not do not give-up
Slow the pace and reduce intensity to cool down for wrap-up
Exercise every day to a sweat for your health to go up and up

Start every day with exercise and energy
Sweaty exertion improves your health, mood and memory
Exercising every morning until you are sweating and perspiring
Makes your day snappy, preppy energizing, exhilarating and uplifting

R.R. Baliga
April 6, 2019

The Columbus Dispatch

Take care of your heart, doctors warn, or it can turn on you

By JoAnne Viviano
The Columbus Dispatch
Posted Feb 5, 2017 at 12:34 PM
Updated Feb 5, 2017 at 12:34 PM

When Dr. Ragavendra Baliga tries to stress the importance of heart care to his patients, he often refers to their cars.

Exercising the heart for 30 to 40 minutes a day, he said, is like regularly taking a car out of the garage for a spin.

Anything less than that is like letting that car idle in the garage. Overdoing it, he said, is akin to drag racing.

"They need to take better care of their bodies than they take care of their cars," said Baliga, associate director of cardiovascular medicine at Ohio State University's Wexner Medical Center. "When it comes to servicing their cars, they go by the book."

According to the Centers for Disease Control and Prevention, heart disease is the No. 1 killer in America, claiming about 610,000 men and women each year.

Association Between Push-up Exercise Capacity and Future Cardiovascular Events Among Active Adult Men

Justin Yang, MD, MPH[1,2]; Costas A. Christophi, PhD[1,3]; Andrea Farioli, MD, PhD[4]; et al

» Author Affiliations | Article Information

Key Points | Español | 中文 (Chinese)

Question Is there an office-based objective measurement that clinicians can use to assess the association between fitness and cardiovascular disease risk?

Findings This longitudinal cohort study of 1104 occupationally active adult men found a significant negative association between baseline push-up capacity and incident cardiovascular disease risk across 10 years of follow-up. Participants able to complete more than 40 push-ups were associated with a significant reduction in incident cardiovascular disease event risk compared with those completing fewer than 10 push-ups.

Meaning Push-up capacity is a no-cost, fast, and simple measure that may be a useful and objective clinical assessment tool for evaluating functional capacity and cardiovascular disease risk.
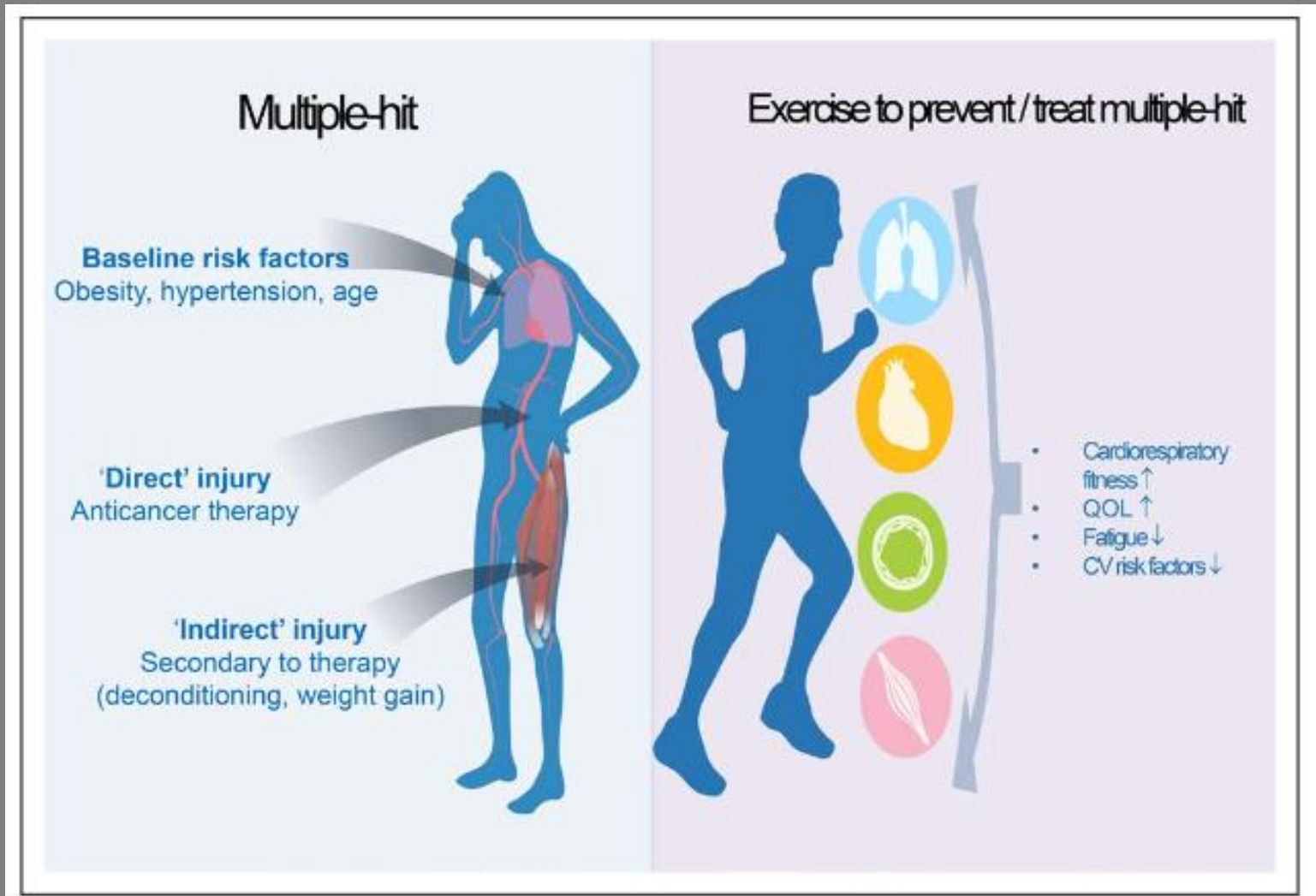
Our website uses cookies to enhance your ex

606 views   0:12 / 0:41

Potential benefits that exercise training may confer to patients with cancer at heightened risk for cardiovascular (CV) disease

American Society of Clinical Oncology (ACO) criteria for those considered at increased CVD risk and to be considered for CR include: (1) Therapy with high-dose anthracycline (e.g., doxorubicin ≥250 mg/m^2, epirubicin ≥600 mg/m^2) or high-dose radiotherapy ≥30 Gy when the heart is in the treatment field or lower-dose anthracycline in combination with lower dose radiotherapy; and (2) Therapy with lower-dose anthracycline or trastuzumab alone plus the presence of ≥2 risk factors (smoking, hypertension, diabetes mellitus, obesity, dyslipidemia), older age (≥60 years) at cancer treatment, or compromised cardiac function (history of myocardial infarction, borderline or low left ventricular ejection fraction, moderate valvular disease); or therapy with lower-dose anthracycline followed by trastuzumab.

Patient assessment

Nutrition counseling

Weight management

BP management

Lipid/lipoprotein management

Diabetes mellitus management

Tobacco cessation

Psychosocial management

PA counseling

Exercise training

American Heart Association | American Stroke Association.
life is why®

My Life Check®
Live Better With Life's Simple 7®

TAKE ACTION WITH LIFE'S SIMPLE 7

1. MANAGE BLOOD PRESSURE

High Blood Pressure is a major risk factor for Heart Disease and Stroke. When your Blood Pressure stays within healthy ranges, you reduce the strain on your heart, arteries, and kidneys, which keeps you healthier longer.

2. CONTROL CHOLESTEROL

High Cholesterol contributes to plaque, which can clog Arteries and lead to Heart Disease and Stroke. When you control your Cholesterol, you are giving your arteries their best chance to remain clear of blockages.

3. REDUCE BLOOD SUGAR

Most of the food we eat is turned into glucose (or blood sugar) that our bodies use for energy. Over time, high levels of Blood Sugar can damage your heart, kidneys, eyes, and nerves.

4. GET ACTIVE

Living an active life is one of the most rewarding gifts you can give yourself and those you love. Simply put, daily physical activity increases your length and quality of life.

5. EAT BETTER

A healthy diet is one of your best weapons for fighting Cardiovascular Disease. When you eat a heart-healthy diet, you improve your chances for feeling good and staying healthy - for life!

6. LOSE WEIGHT

When you shed extra fat and unnecessary pounds, you reduce the burden on your heart, lungs, blood vessels and skeleton. You give yourself the gift of active living, you lower your Blood Pressure and you help yourself feel better, too.

7. STOP SMOKING

Cigarette smokers have a higher risk of developing Cardiovascular Disease. If you smoke, quitting is the best thing you can do for your health.

https://youtu.be/-1UW8NvCw7I

Salt >3.7 g/day Had Adverse Effects on Heart Structure and Function

CENTRAL ILLUSTRATION: Urinary Sodium and Cardiac Mechanics: ESI and Adverse Cardiac Structure and Function as Well as Heart Failure
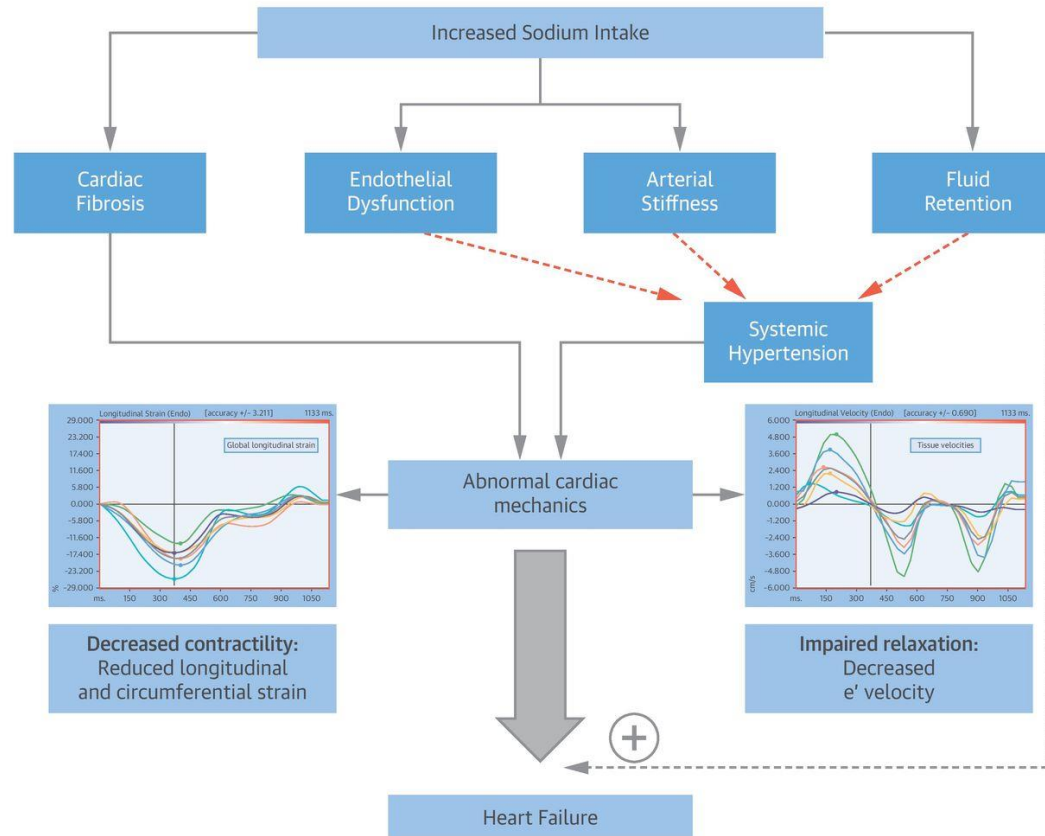
Selvaraj, S. et al. J Am Coll Cardiol. 2017;70(6):715-24.

Conclusions ESI >3.7 g/day is associated with adverse cardiac remodeling and worse systolic strain and diastolic e' velocity

THE MAKING *of* HERCEPTIN,

a REVOLUTIONARY TREATMENT

for BREAST CANCER

Her
2

ROBERT BAZELL