Acute and Delayed Cardiovascular Complications of Cancer Therapy:

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Objectives of today's discussion

- Describe short-term and delayed cardiotoxic effects of cancer treatments
- Explain strategies for screening and monitoring of cancer patients for cardiovascular toxicity before, during and after cancer treatment
- Outline a multidisciplinary approach to managing cardio-oncology patients using current recommendations to optimize survivorship outcomes

Cardio-Oncology Journals

-JACC Cardio-Oncology

-Cardio-Oncology Journal

Cardiology

NEWS & PERSPECTIVE FOR THE CARDIOVASCULAR SPECIALIST

Cardiology Today. April, 2020

COVER STORY

Cardio-oncology explosion: Increasing awareness, collaboration, research

Bonnie Ky, MD, MSCE, from the University of Pennsylvania Perelman School of Medicine, said CV risk factors must be taken into account in patients with cancer.

The cardio-oncology subspecialty has exploded in recent years, with the launch of dedicated cardio-oncology centers, entire conferences focusing on this area and new research, as awareness of cardiotoxicities associated with cancer treatment has increased.

The number of cancer survivors continues to grow. Today, there are more than 16.9 million cancer survivors in the U.S., and this number is expected to increase to 22.1 million by 2030, according to estimates from the American Cancer Society.

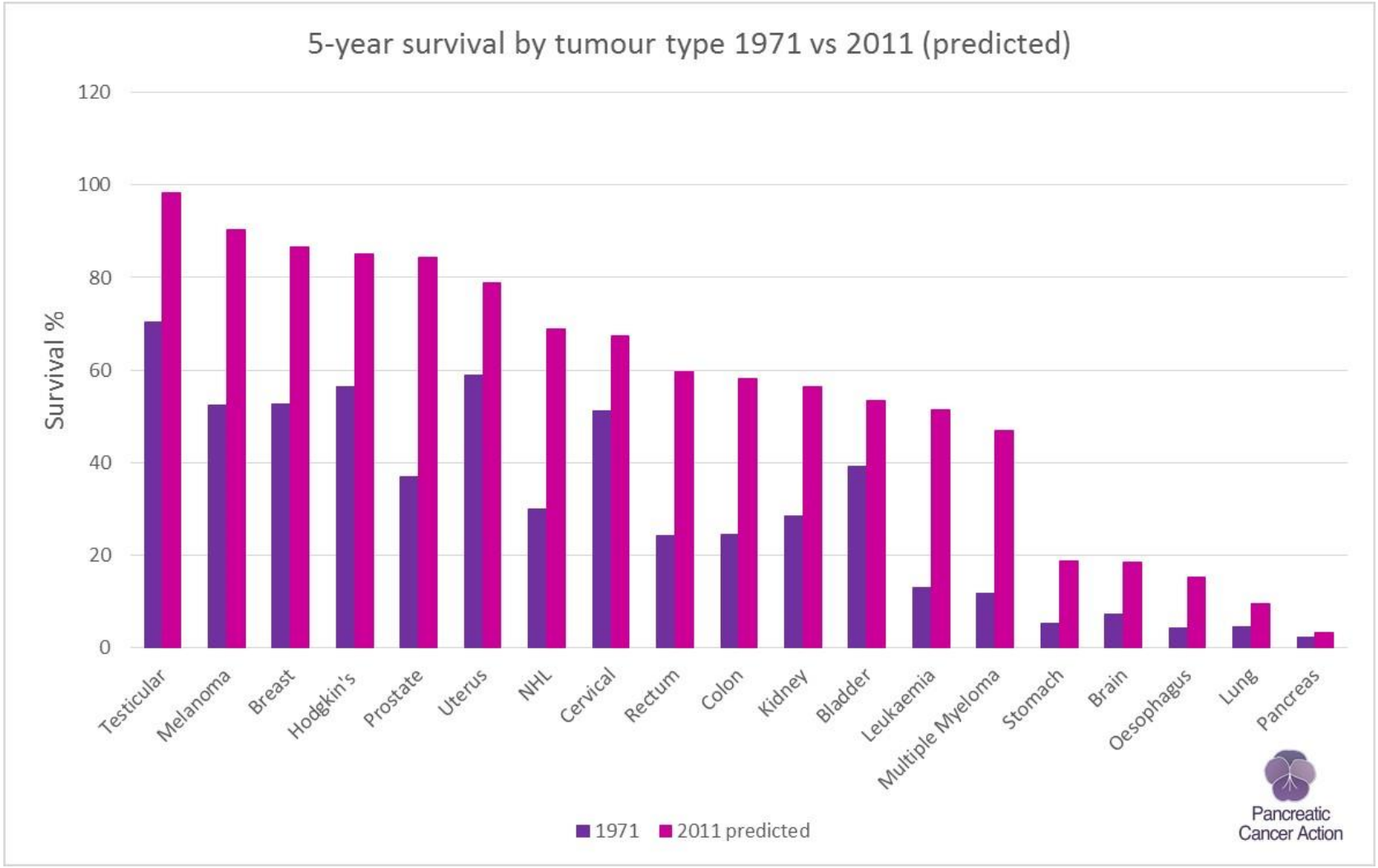
"Patients with cancer are living longer and, in many cases, surviving their disease," **Michael G. Fradley, MD,** director of the cardio-oncology program and associate professor at University of South Florida College of Medicine and Moffitt Cancer Center in Tampa, who at press time was about to become medical director of cardio-oncology and associate professor of clinical medicine at University of Pennsylvania Perelman School of Medicine, told *Cardiology Today.* "We now have a large group of cancer survivors who had exposure to various cancer

Cover story continues on page 10

Scope Of The Problem

- 1 of 3 adults have CV disease (82 million)
- 12 million cancer patients; 14 million cancer survivors
- Approximately 30% of patients receiving cancer therapy will have cardiovascular complications
- Some complications may not become apparent for 10-20 years after completion of treatments

Trends in 5-Year Cancer Survival



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www.pancreaticcanceraction.org

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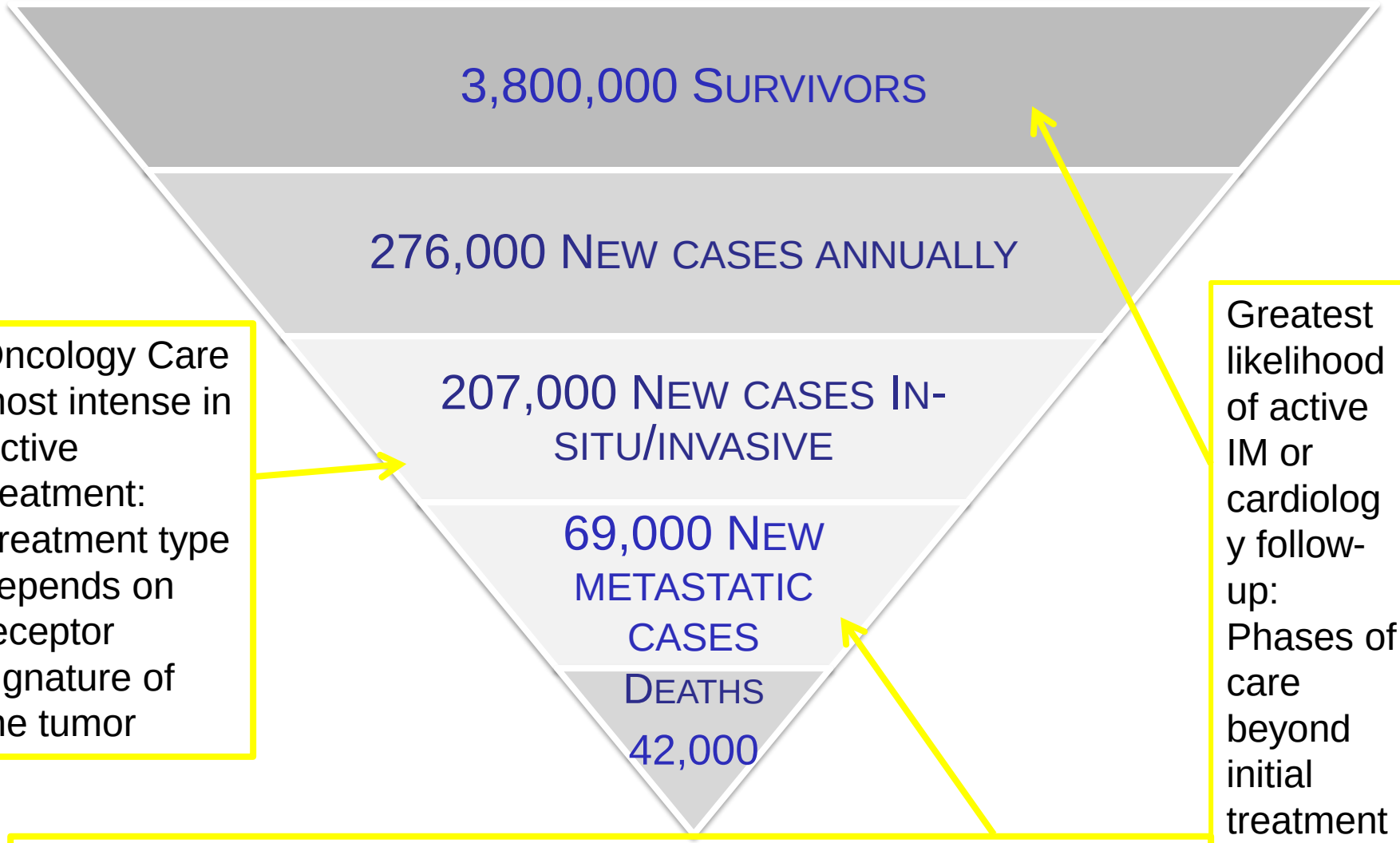
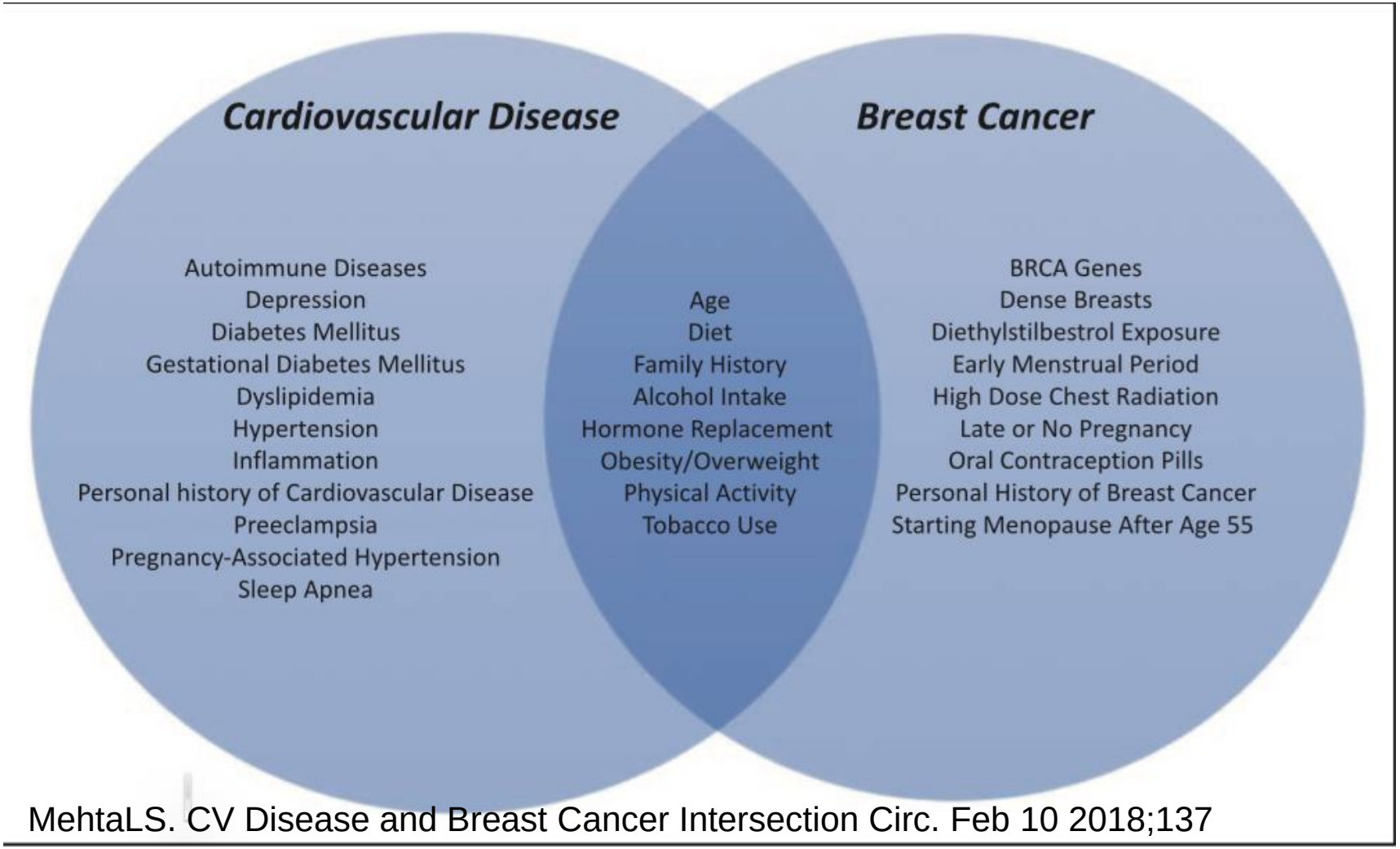
Most breast cancer patients become long term survivors after an intensive initial 12-18 months of therapy

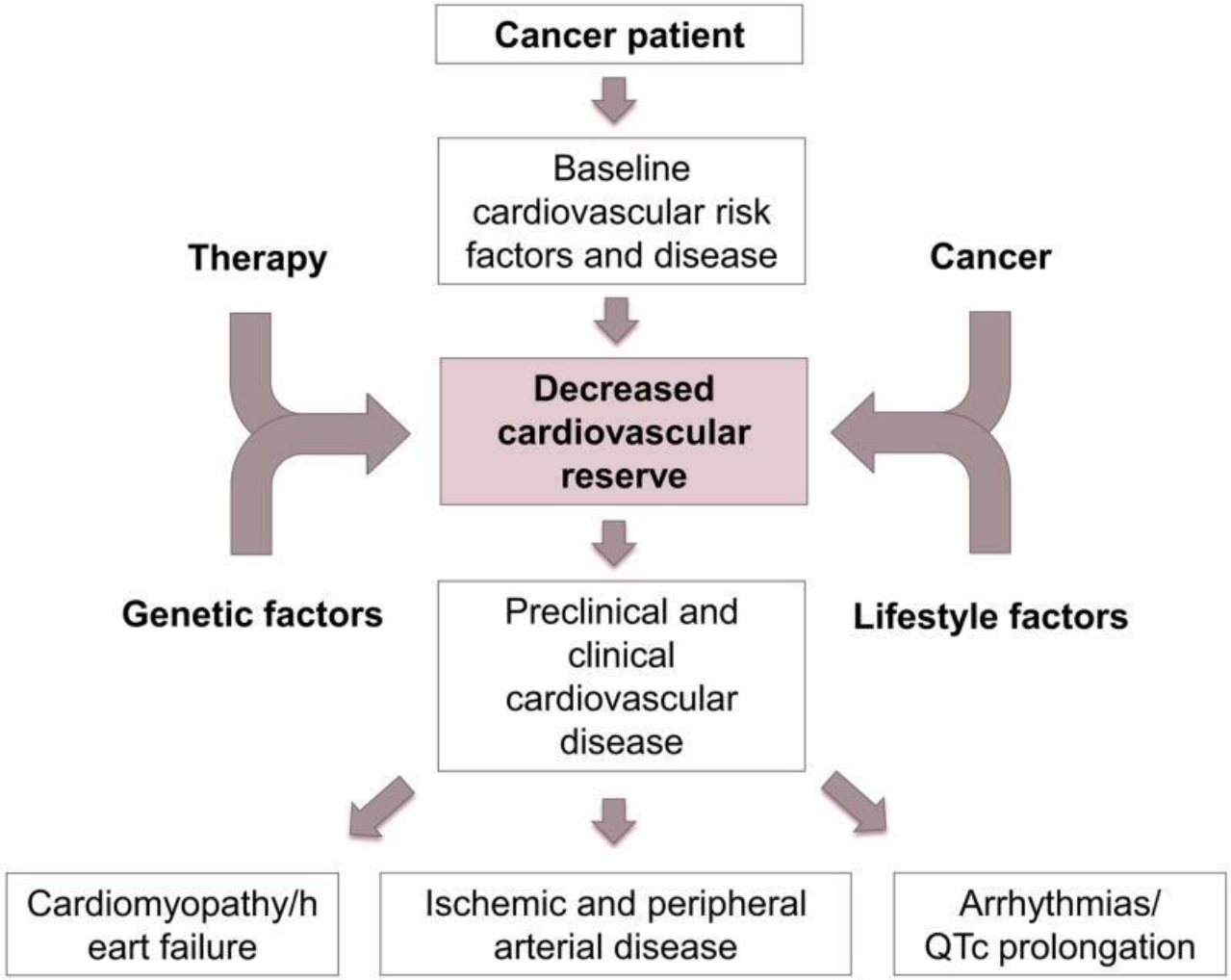


CV Disease and Breast Cancer have multiple risk factors in common



MehtaLS. CV Disease and Breast Cancer Intersection Circ. Feb 10 2018;137

Progression of CV Complications in Cancer Patients



Herman and Lerman. Trends Cardiovasc Med. 2014; 24(7): 285-295.

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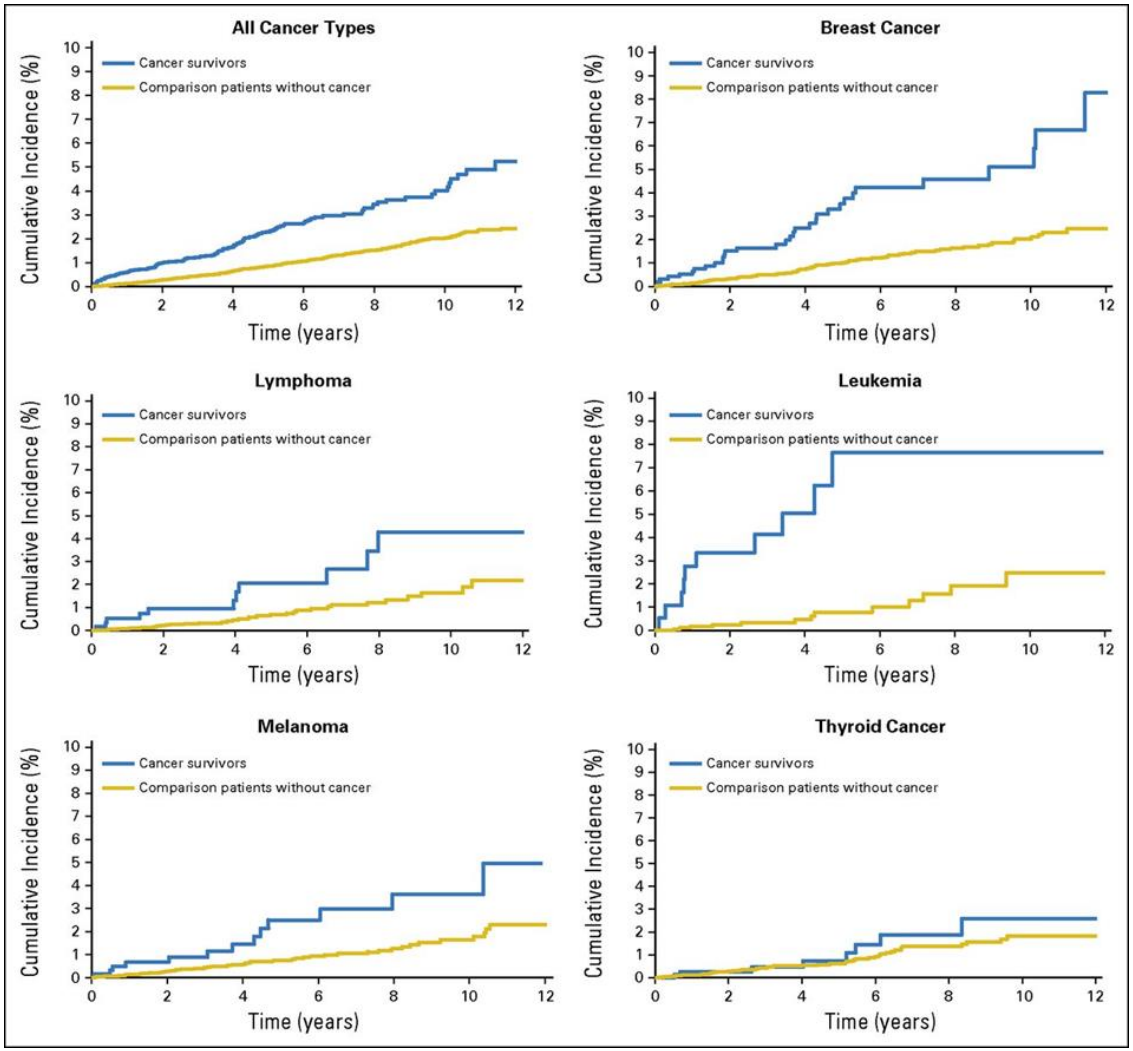
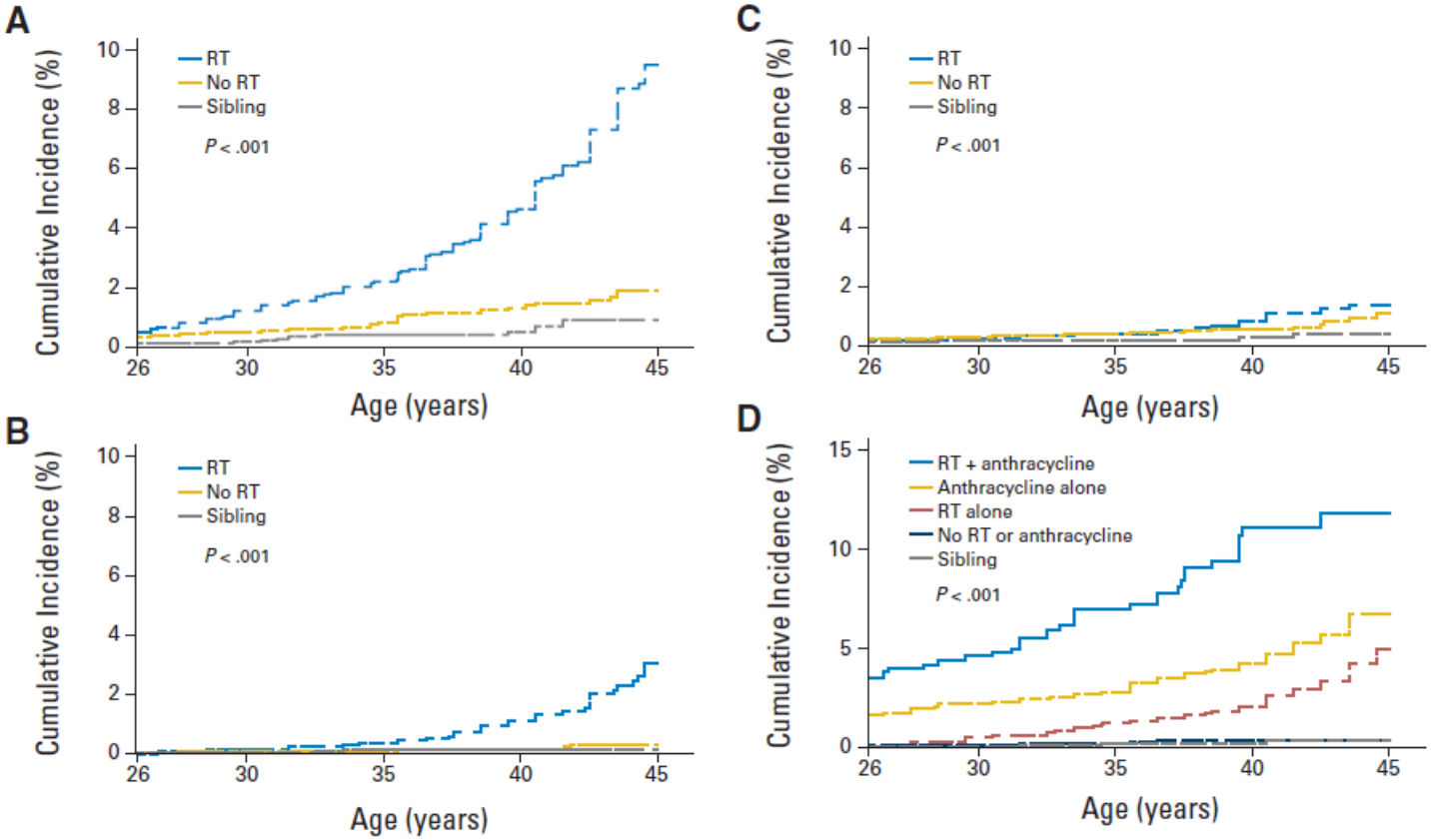
CV Disease: Common after Cancer Treatment



Chun Chao et al. JCO 2016;34:1626-1633

CV Disease: Common after Cancer Treatment



A. Coronary Artery Disease
B. Valve Disease
C. Arrhythmias
D. Heart Failure

Gregory T. Armstrong et al. JCO 2013;31:3673-3680

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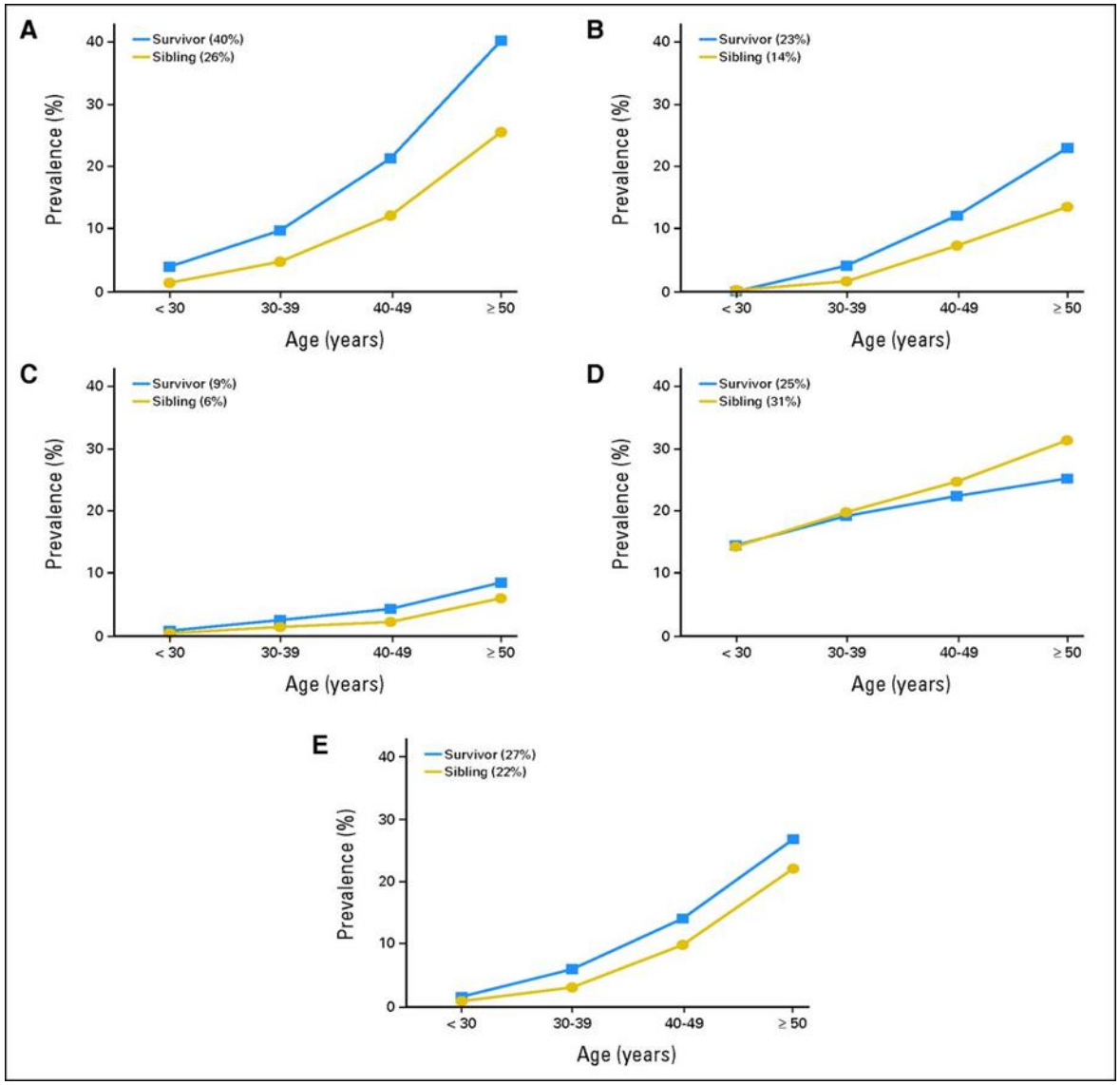
CV Disease: Common after Cancer Treatment



A. Hypertension
B. Dyslipidemia
C. Diabetes
D. Obesity
E. Multiple Cardiac RF

Gregory T. Armstrong et al. JCO 2013;31:3673-3680

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Cardio-Oncology: Definition

- Cardio-oncology is a multidisciplinary field aimed at managing cardiovascular risk and preventing cardiovascular disease in cancer patients and survivors.

- Eliminate cardiac disease as a barrier to effective cancer therapy

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Cardiomyopathy and Heart Failure

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Chemotherapy Induced LV Dysfunction

Chemotherapy Agents	Incidence (%)	Frequency of Use
Anthracycline		
•Doxorubicin	3-26	+++
•Epirubicin	0.9-3.3	++
•Idalrubicin	5-18	+
Alkylating Agents		
•Cyclophosphamide	7-28	+++
•Ifosfamide	17	+++
Antimetabolites		
•Clofarabine	27	+
Antimicrotubule Agents		
•Docetaxel	2.3-8	++
Monoclonal Antibody Inhibitor		
•Bevacizumab	1.7-3	++
•Trastuzumab	2-28	++
Proteasome Inhibitor		
•Bortezomib	2-5	++
•Carfilzomib	11-25	+
Small Molecule Tyrosine Kinase Inhibitor		
•Dasatinib	2-4	++
•Sunitinib	2.7-11	+

Yeh and Bickford. JACC. 2009; 53: 2231-247.
Zamorano et al. Eur Heart J. 2017; 19(1): 9-42.

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Cardiotoxicity – Definitions

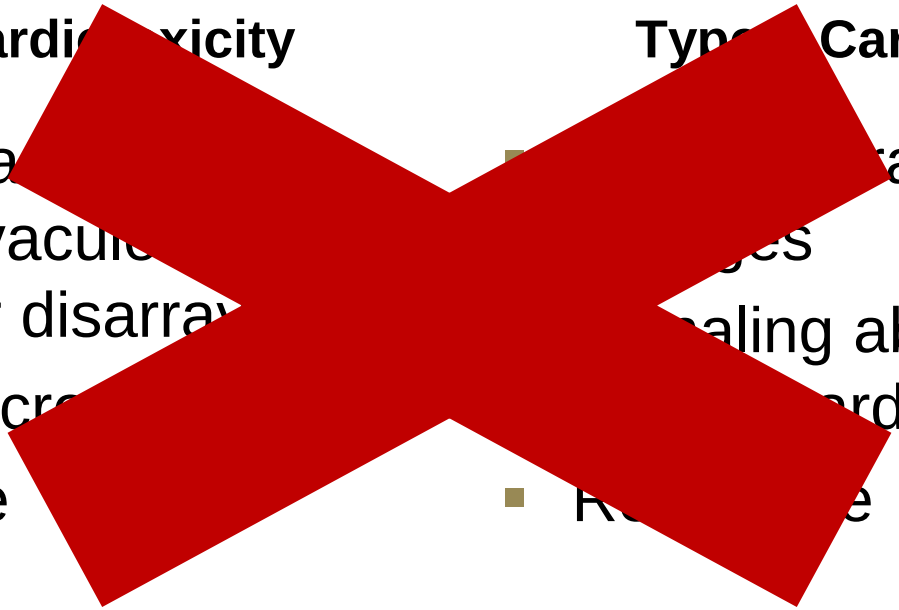
- Decline in initial EF by more than 10% to less 53% regardless of CHF symptoms

Type 1 Cardi xicity

- Structural a
  changes (vacu
  myofibrillar disarra
- Cellular necr
- Irreversible

Typ Cardiotoxicity

- al or cellular
  es
- aling abnormalities
- rdiac stress
- R e



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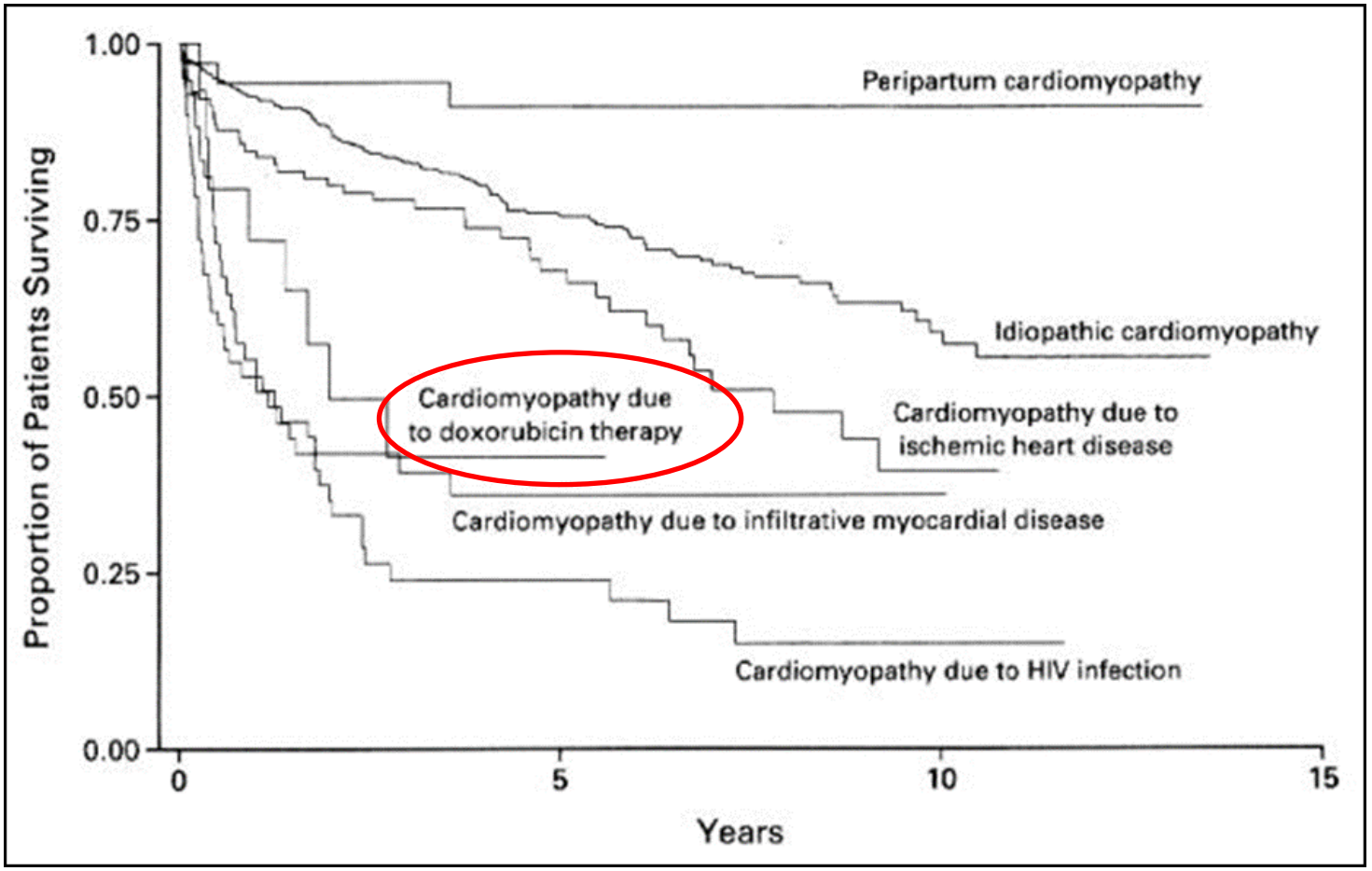
Anthracycline Induced Cardiomyopathy



Felker et al. New Engl J Med. 2000; 342; 1077-1084.

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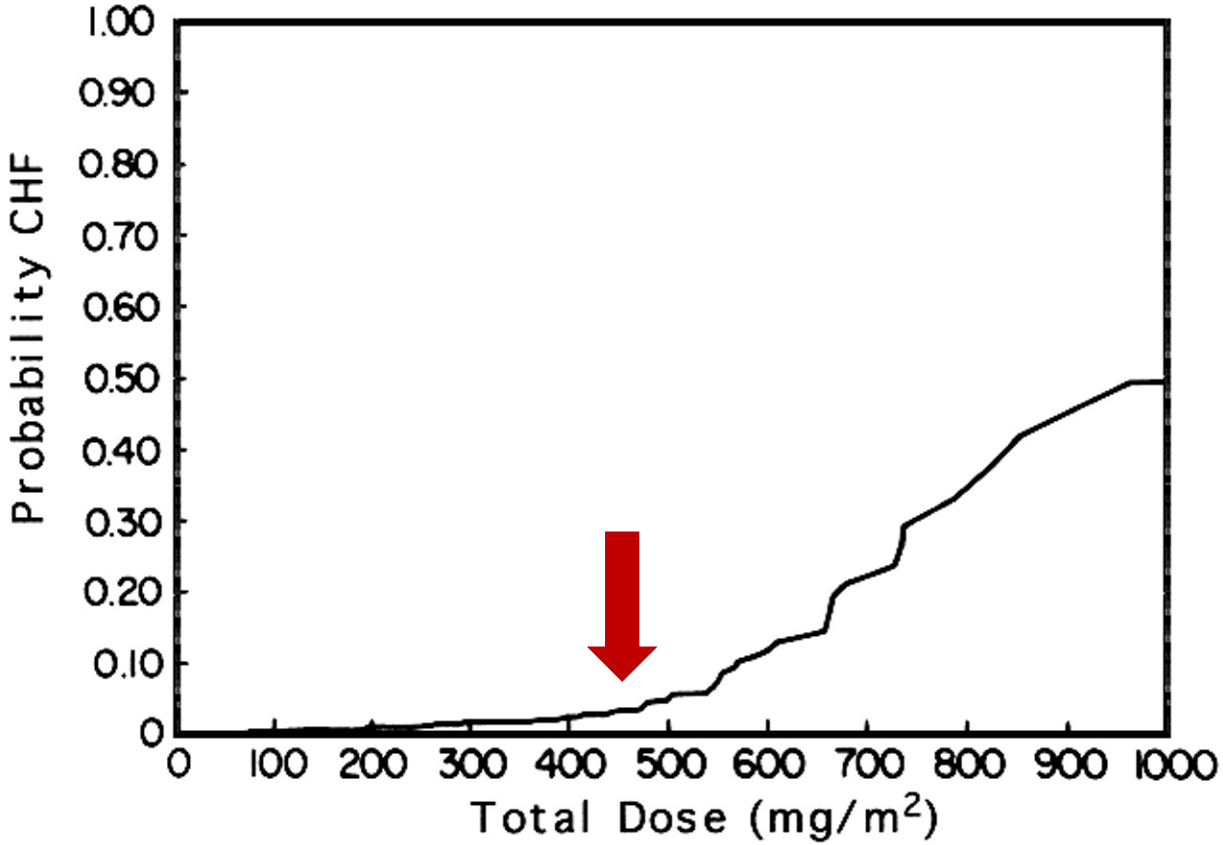
Anthracycline Induced Cardiomyopathy



Von Hoff et al. American Journal of Medicine. 1977; 62: 200-8.

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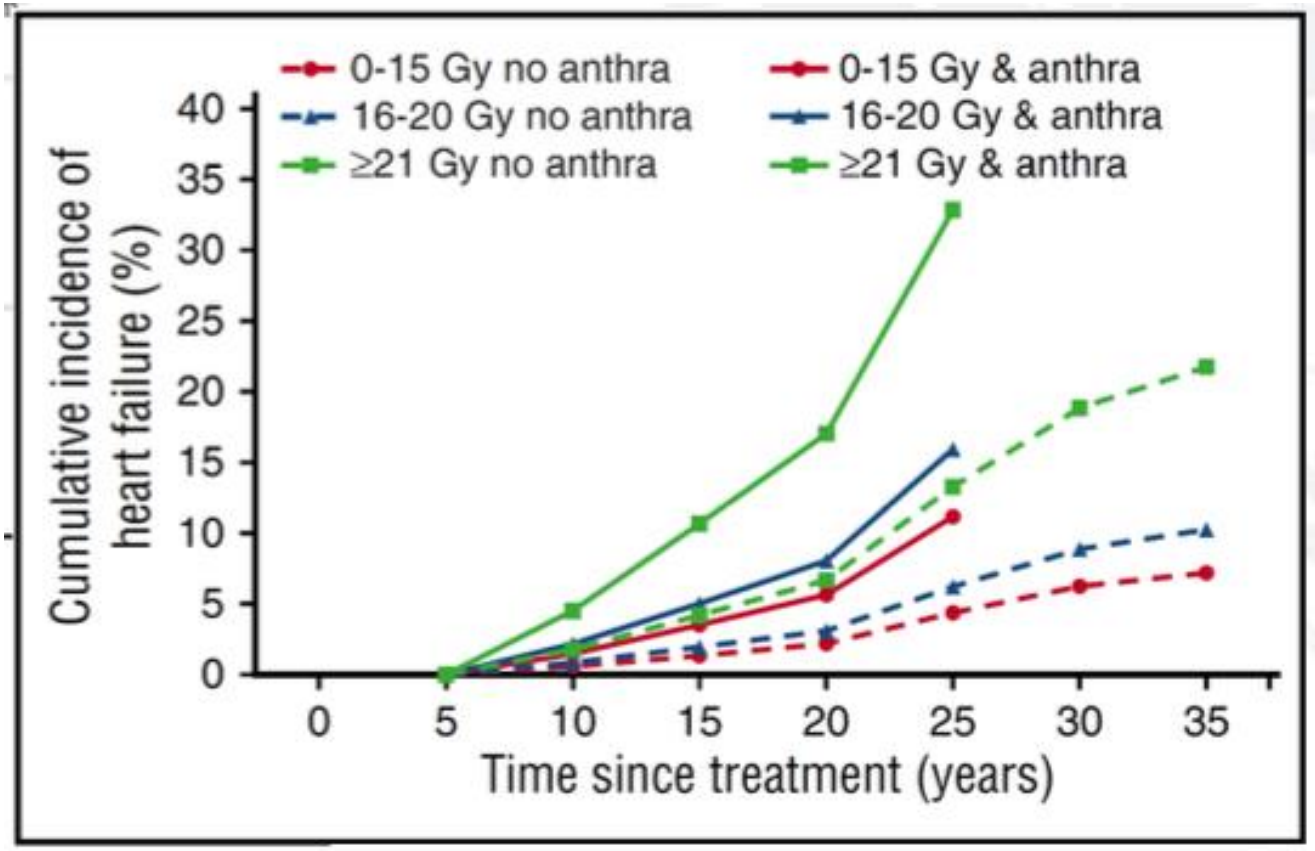
Anthracycline Induced Cardiomyopathy: Risk Factors

- Cumulative Dose
- Age
- Female Gender
- Concomitant use of additional chemotherapy or XRT
- Underlying CV disease

Radiation dose ***amplifies*** anthracycline risk

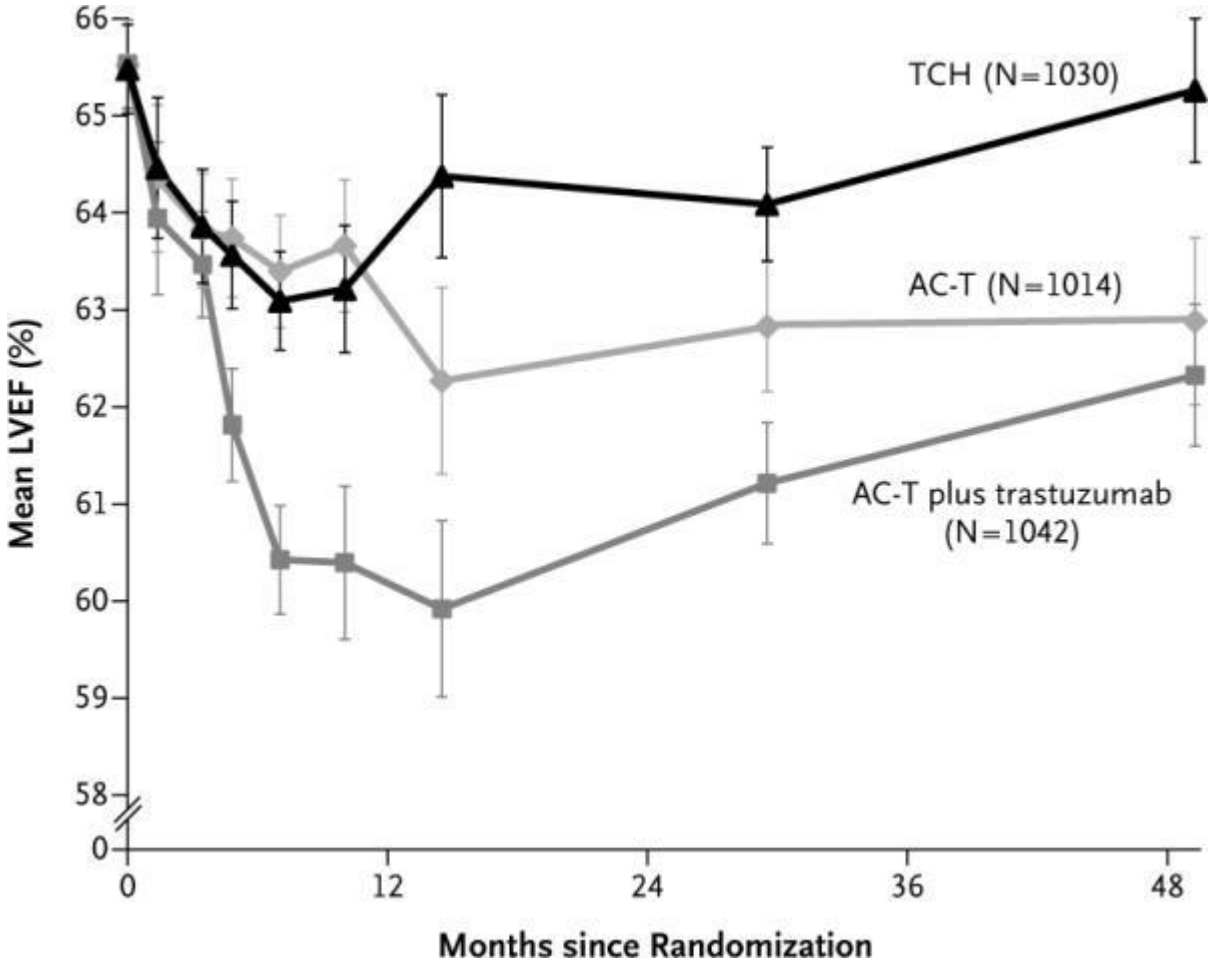


Van Nimwegen FA et al. *Blood*. 2017 Apr 20;129(16):2257-2265

LV Dysfunction and Targeted Therapies

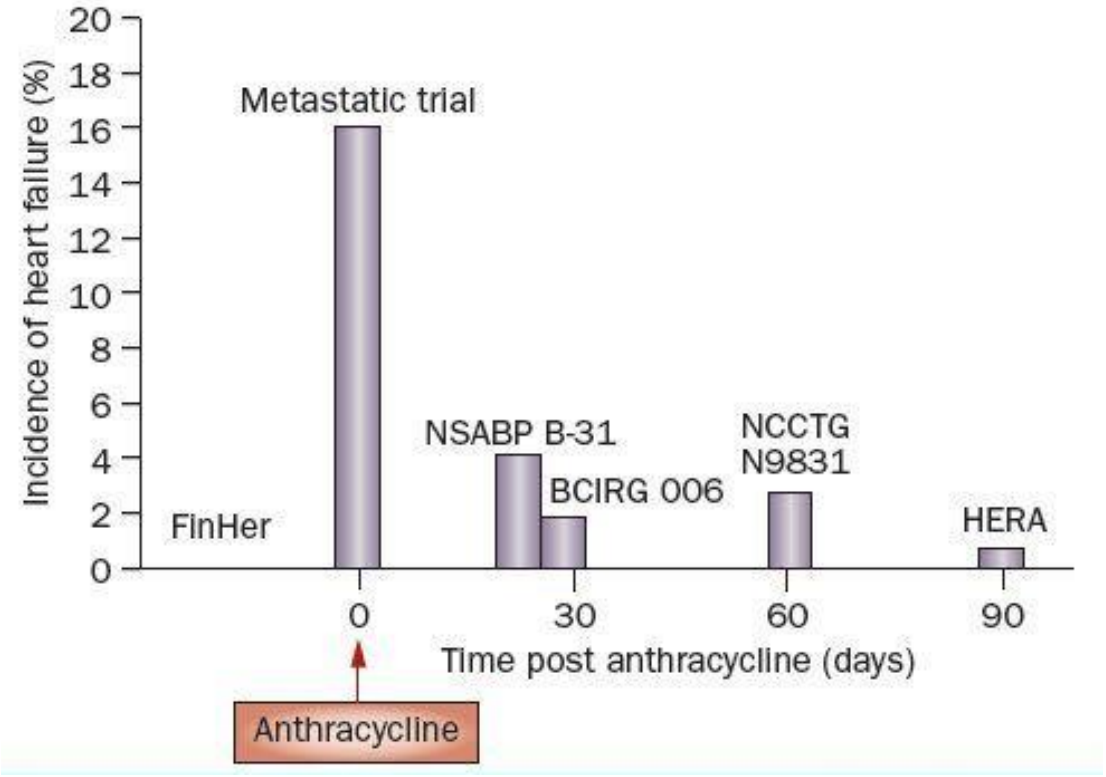
- HER2+ Targeted Therapies
  - Trastuzumab
  - Pertuzumab
  - Ado-Trastuzumab
  - Fam-Trastuzumab deruxtecan-nxki
  - Lapatinib

Trastuzumab and LVEF



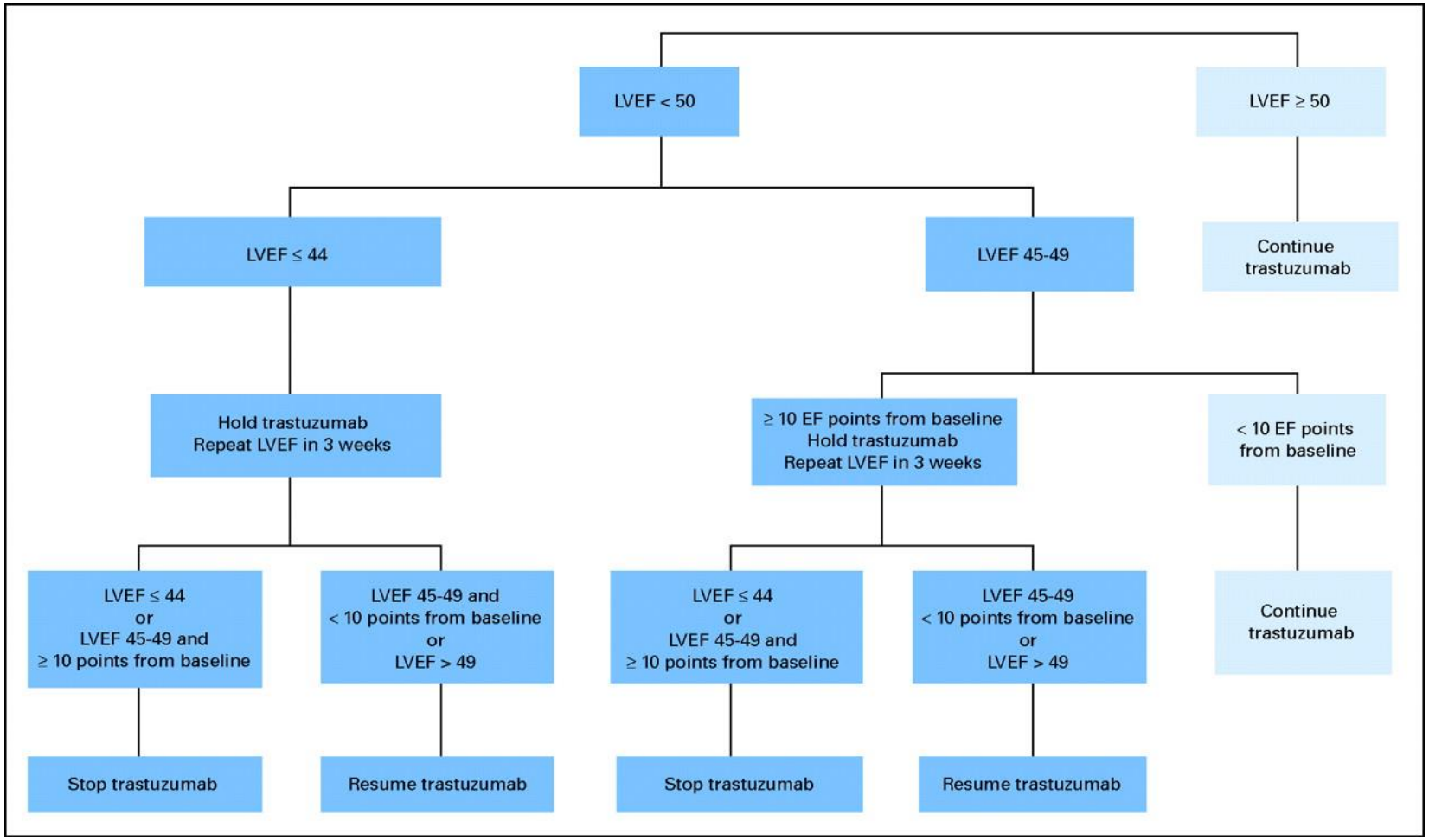
Slamon et al. New Engl J Med. 2011; 365: 1273-83.

Significant Heart Failure Associated with Trastuzumab



Ewer and Ewer. Nat. Rev Cardiovasc Med. 2010; 7: 564-75.

Trastuzumab Cardiac Monitoring Algorithm



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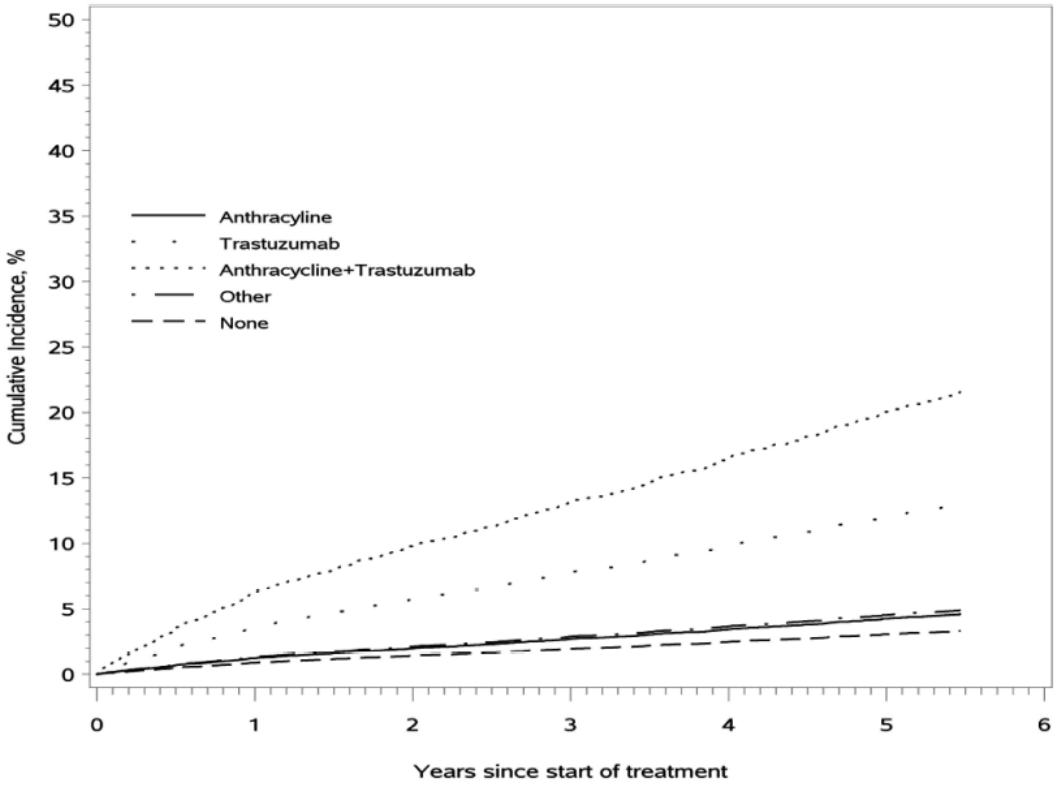
Curigliano et al. Ann Oncol. 2012; 23(Suppl 7): vii155-66.

Trastuzumab Cardiotoxicity Increases Over Time



No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	3443	3125	2699	2146	1659
Trastuzumab only	90	78	49	24	13
Anthracycline+ Trastuzumab	347	339	263	179	94
Other chemotherapy	2159	1905	1548	1192	958
None	5235	4798	4076	3288	2590
Cumulative incidence (95% CI), %					
Anthracycline only	1.2 (1.0 to 1.5)	2.0 (1.6 to 2.4)	2.7 (2.2 to 3.2)	3.5 (2.8 to 4.1)	4.3 (3.5 to 5.0)
Trastuzumab only	3.6 (1.5 to 5.6)	5.8 (2.5 to 8.9)	7.8 (3.4 to 12.0)	9.9 (4.3 to 15.1)	12.1 (5.3 to 18.3)
Anthracycline+ Trastuzumab	6.2 (4.1 to 8.2)	9.8 (6.7 to 12.8)	13.2 (9.1 to 17.1)	16.5 (11.5 to 21.3)	20.1 (14.0 to 25.6)
Other chemotherapy	1.3 (1.0 to 1.6)	2.1 (1.7 to 2.5)	2.9 (2.4 to 3.4)	3.7 (3.0 to 4.3)	4.5 (3.7 to 5.3)
None	0.9 (0.7 to 1.0)	1.4 (1.2 to 1.7)	1.9 (1.6 to 2.3)	2.5 (2.1 to 2.9)	3.1 (2.6 to 3.5)

Bowles et al. J Natl Cancer Inst. 2012; 104: 1293-1305

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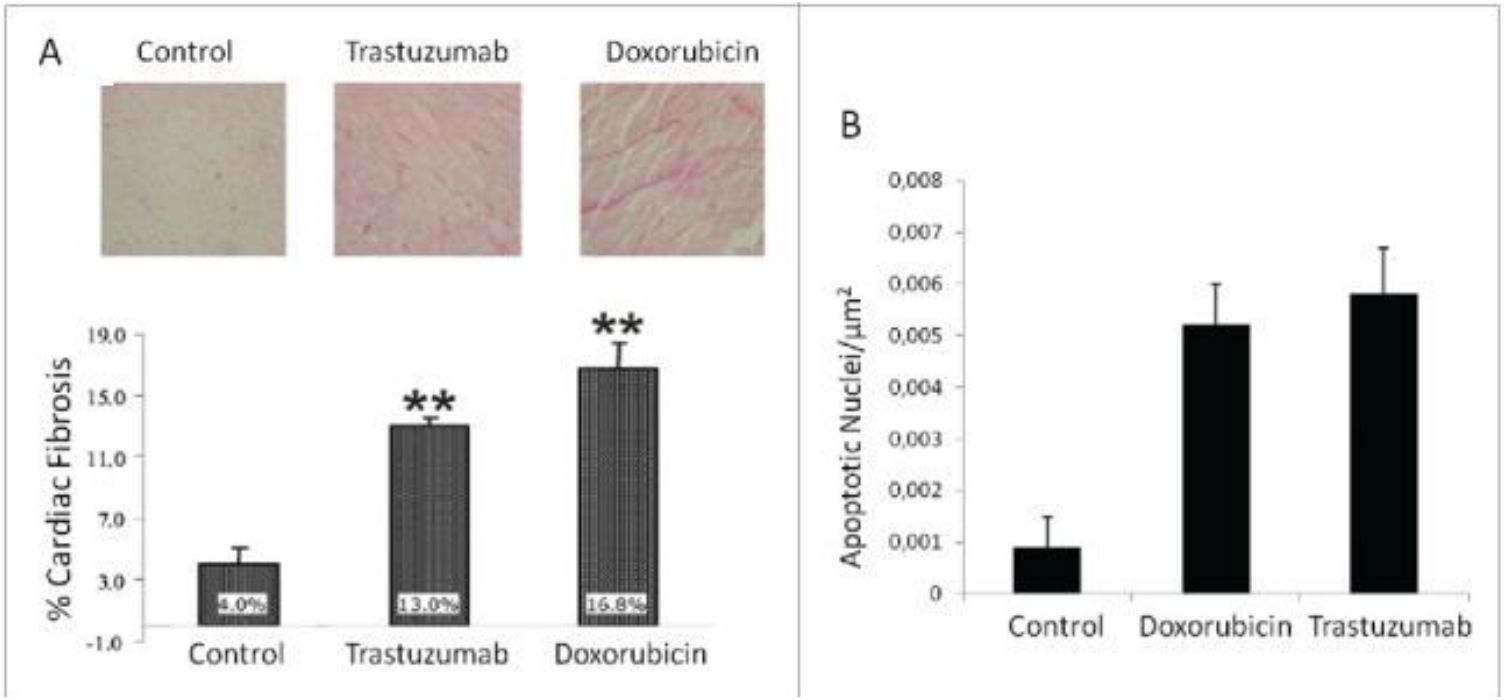
Trastuzumab and Anthracycline Cardiotoxicity: Fibrosis and Apoptosis



Riccio et al. Hum Vaccin Immunother. 2016; 12: 1124-31.

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Techniques to Improve the Identification of Cardiotoxicity: Beyond Ejection Fraction

- Biomarkers
- Strain Imaging

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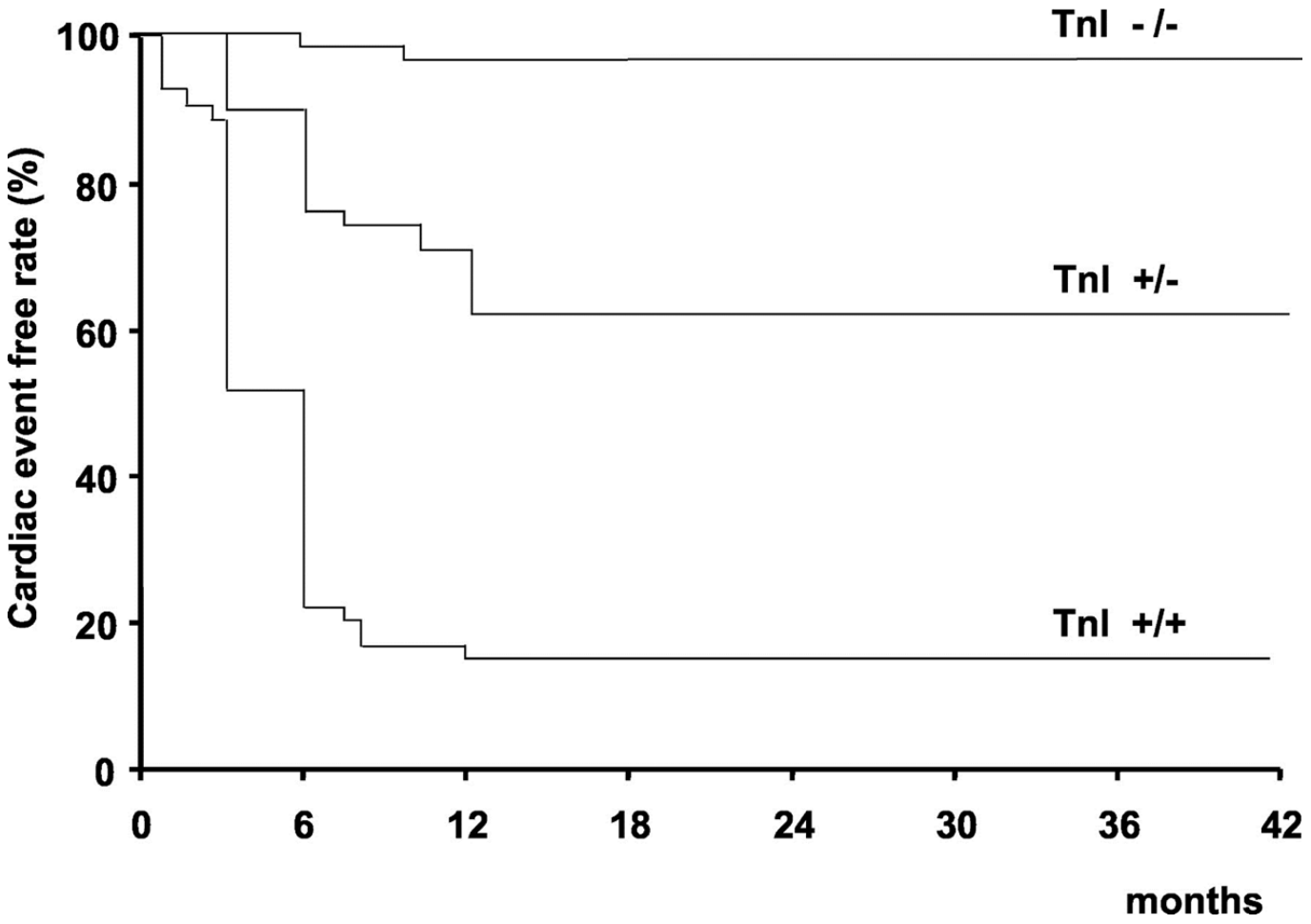
Troponins and Development of Cardiotoxicity



Cardinale et al. Circulation. 2004; 109: 2749-54.

Heart Failure…Just the Tip of The Cardio-Oncology Iceberg

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Coronary Artery Disease, Myocardial Infarction, and Peripheral Arterial Disease

Therapies Associated With Vascular Disease

- Radiation
- Tyrosine Kinase Inhibitors
  - Nilotinib
  - Ponatinib

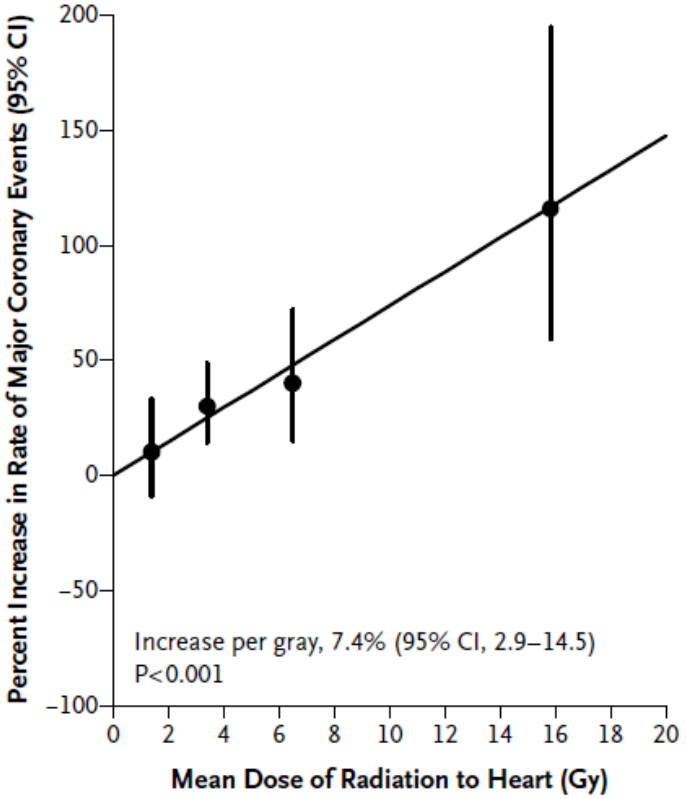
CV Complications of Radiation

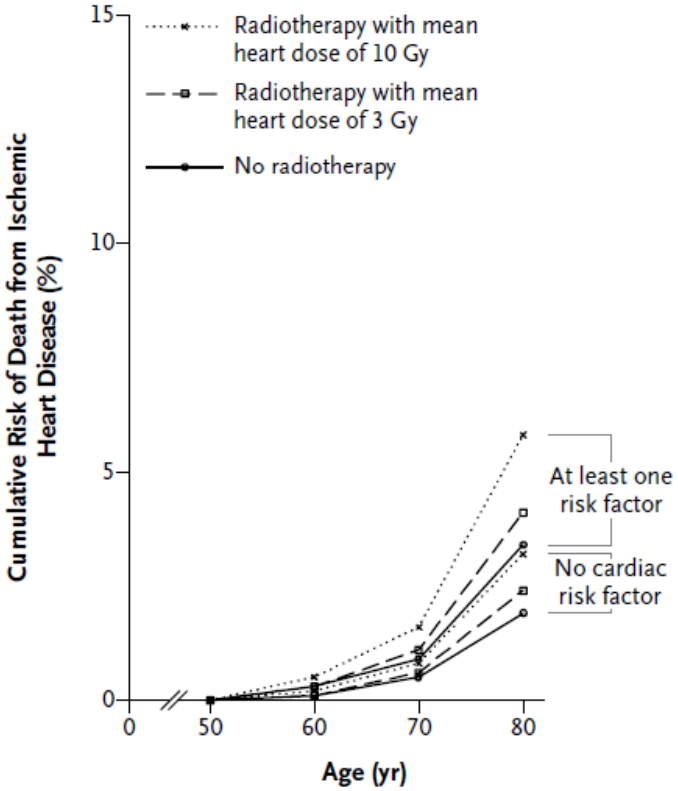
- Important part of treatment for many cancers including breast, lung and lymphoma
- Complications typically seen 5-10 years post exposure
- Complications include:
  - Premature CAD
  - Carotid Disease
  - Valvular disease (especially aortic and mitral disease)
  - Pericardial and myocardial disease
  - Heart failure
  - Conduction abnormalities

Risk Factors for Radiation Induced CV Disease

- Increase risk with increased dose (total dose >30 Gy or fractioned dose >2Gy/day)
- Heart volume exposed
- Time since exposure
- Adjunctive chemo/hormone therapy
- Presence of CV risk factors (diabetes, obesity, smoking, hypertension, dyslipidemia)
- Younger age

Coronary Events Associated with Radiation Therapy For Breast Cancer





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Darby et al. New Engl J Med. 2013; 368: 987-98.

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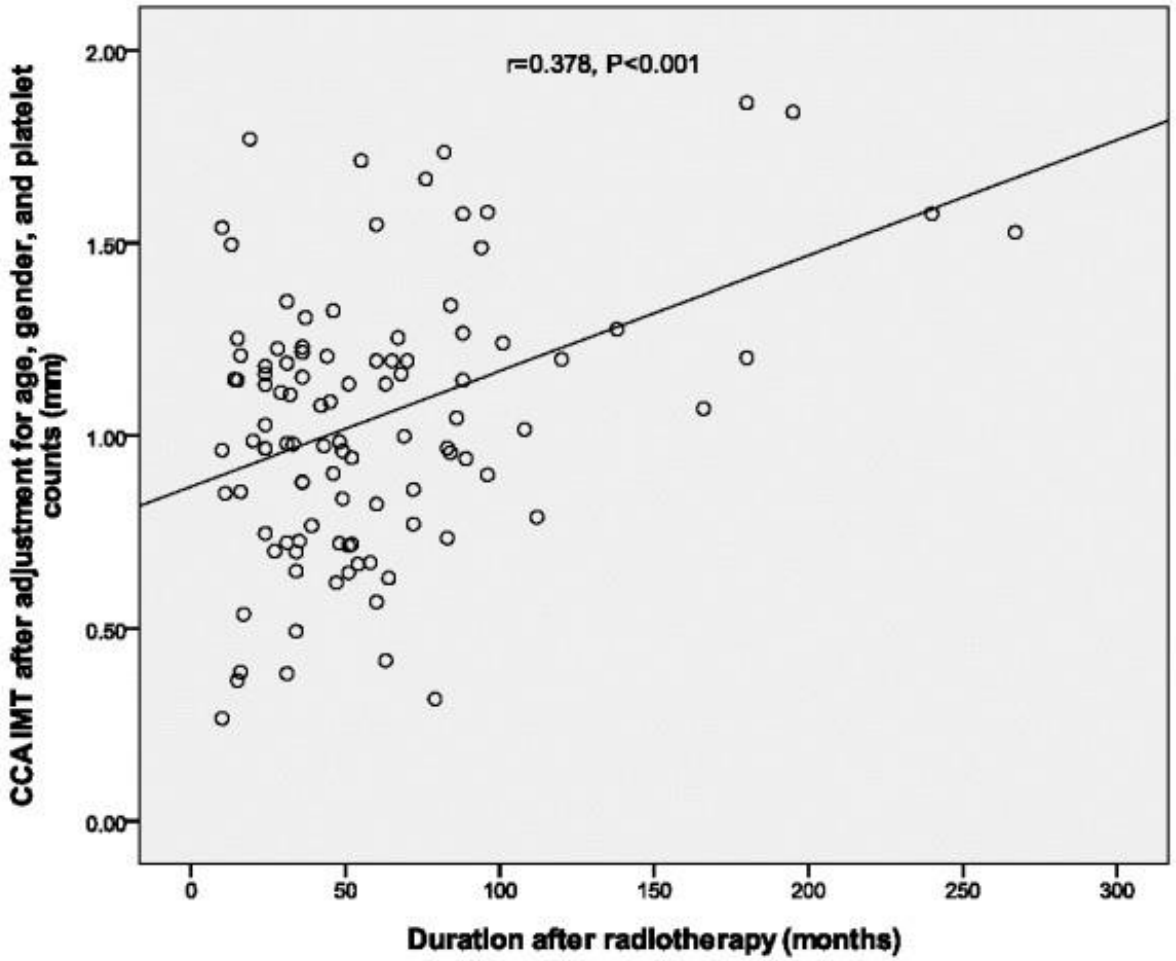
Radiation and Carotid Artery Disease



Huang et al. Radiat Oncol. 2013; 8: 261.

CML and Nilotinib: ENESTnd Trial

ENESTnd 3-Yr Update

Hematologic AEs and Biochemical Abnormalities

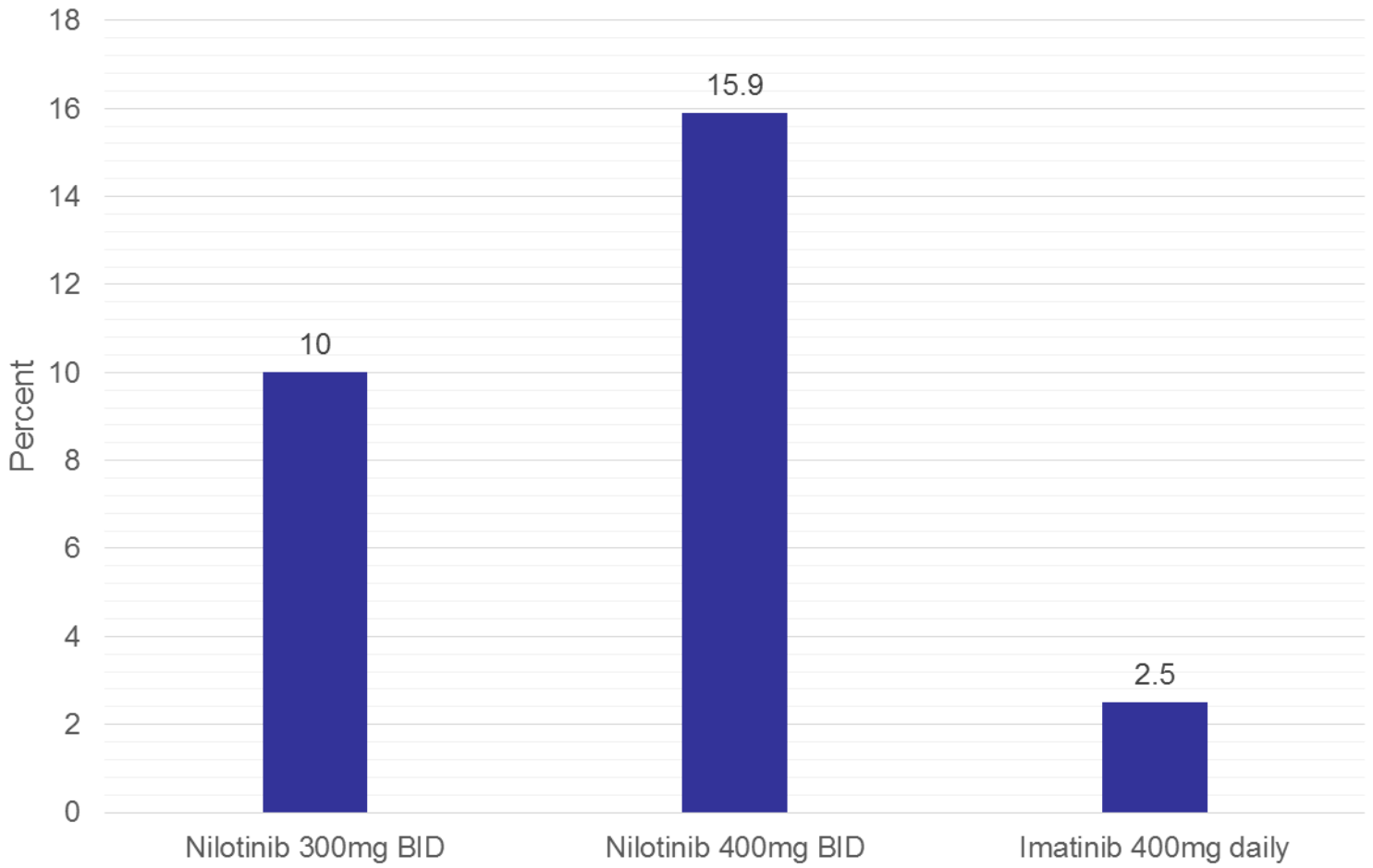
Grade 3/4 AEs, %	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg QD (n = 280)
Neutropenia	11.8	10.8	21.4
Thrombocytopenia	10.4	12.3	8.9
Anemia	3.9	4.7	5.7
Lipase increase	7.5	7.9	3.9
ALT increase	4.3	9.4	2.5
Total bilirubin increase	3.9	7.9	0.4
Hyperglycemia	6.1	5.4	0

Nilotinib Toxicities

- Prolongation of QTc and vascular adverse events
- Coronary events
- Peripheral Arterial Occlusive Disease

Larson RA, et al. Leukemia 2012;26:2197-203. 2. Nilotinib prescribing information, 2013. 3. NCCN Guidelines v.4.2013

Nilotinib and Cardiovascular Events



No of Patients:	28/279	44/277	7/280

Larson RA, et al. Blood. 2014;124:4541.

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CML and Ponatinib: Cardiovascular Events

	US Ponatinib Insert (7/23/12) Median Follow up: 12 Mos (340 pt-years)		PACE Trial (9/3/13) Medial Follow Up: 24 Mos (578 pt-years)	
	Serious AE %	**AE %**	**Serous AE %**	**AE %**
Cardiovascular	5	6	6	10
Cerebrovascular	2	3	4	7
Peripheral Vascular	2	4	4	7
Venous Thromboembolism	2	3	3	5
Total Vascular Occlusion	11	16	17	29

Cortes JE et al. Blood. 2014;124:3135.

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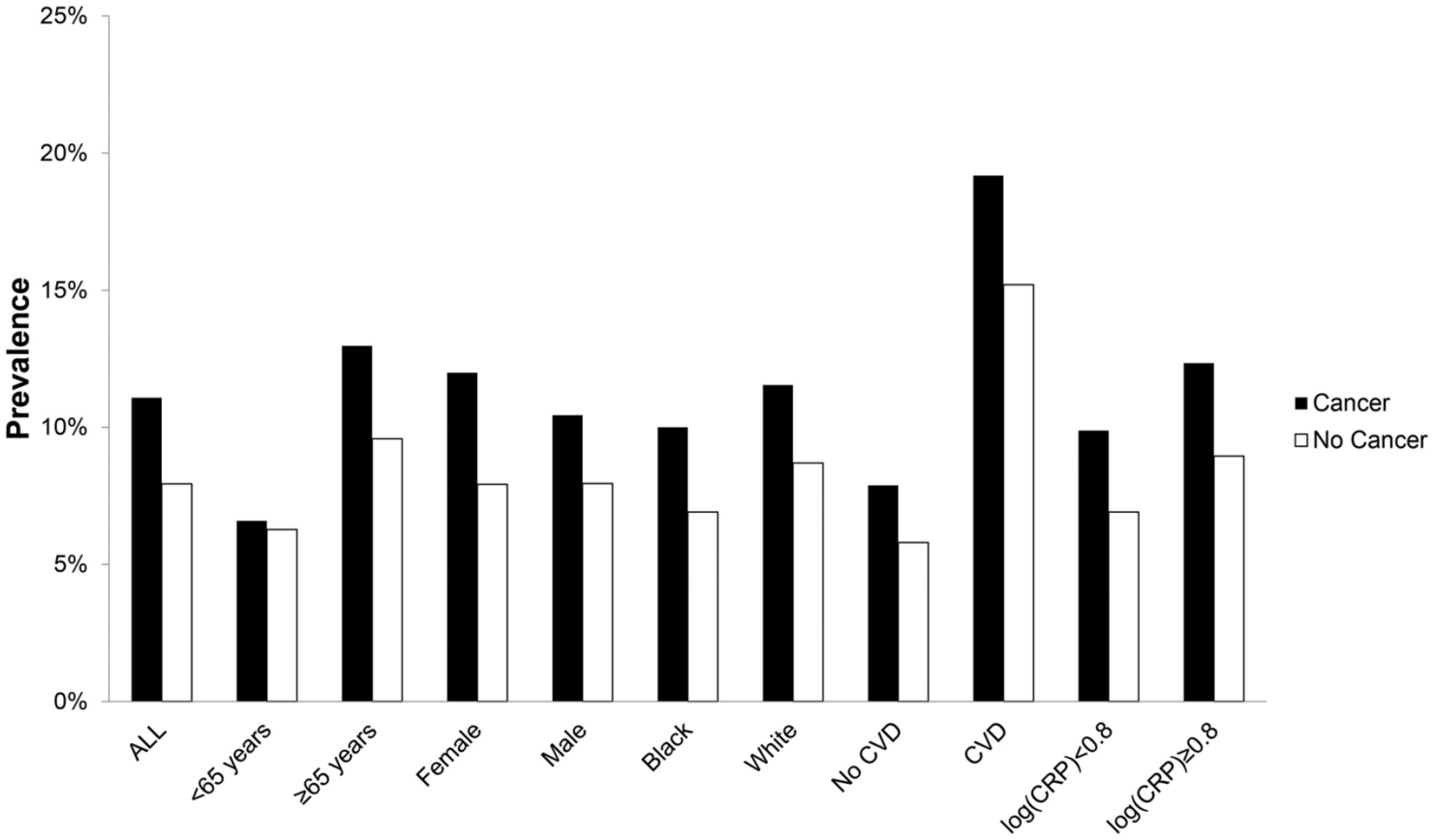
Cancer and Atrial Fibrillation



O'Neal et al. Am J Cardiol. 2015; 116(12): 1858-62.

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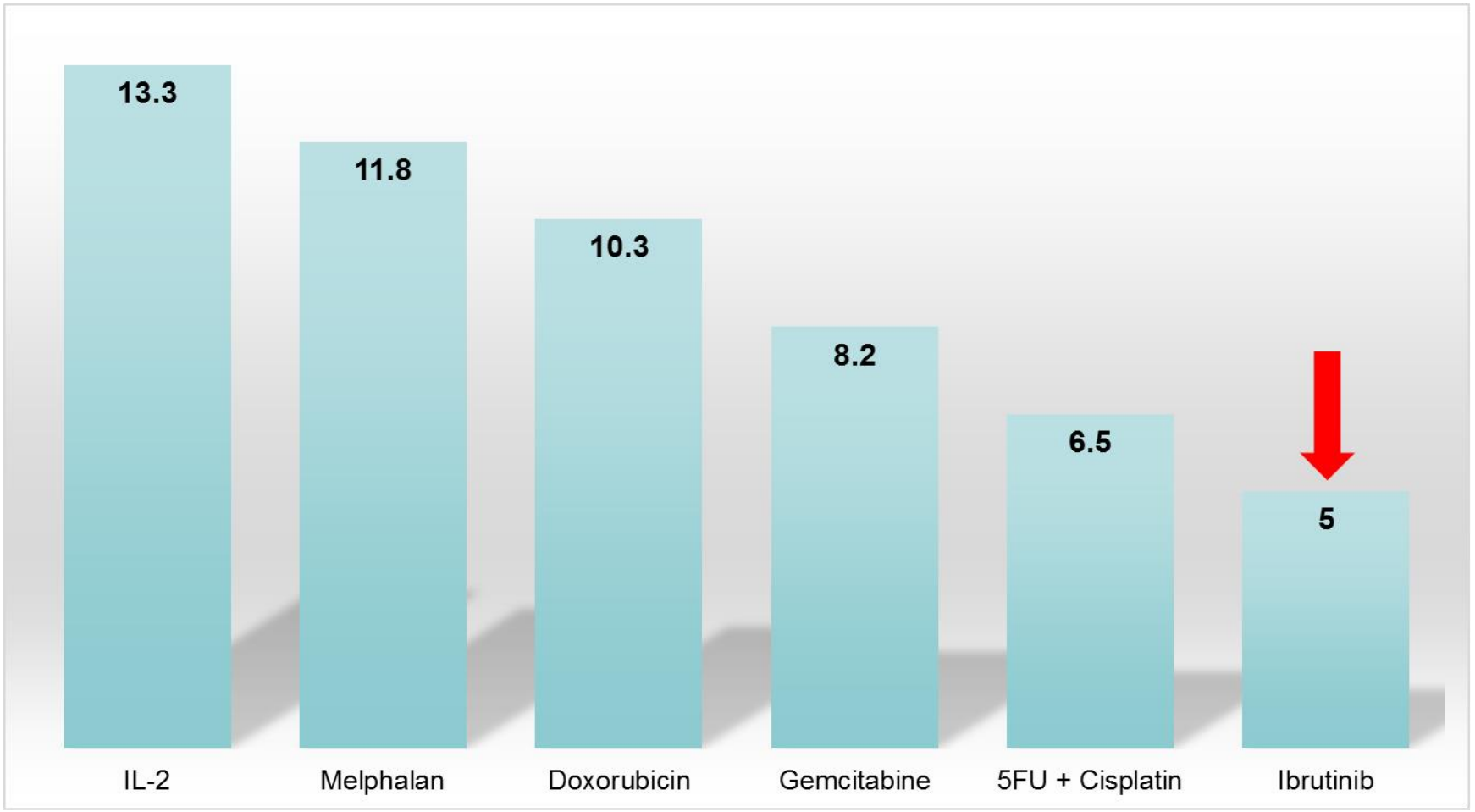
Chemotherapy and the Risk of Atrial Fibrillation



Adapted from Guglin et al. *Europace*. 2009; 11: 1579-1586.
Adapted from McMullen et al. *Blood.* 2014; 124: 3829-3830

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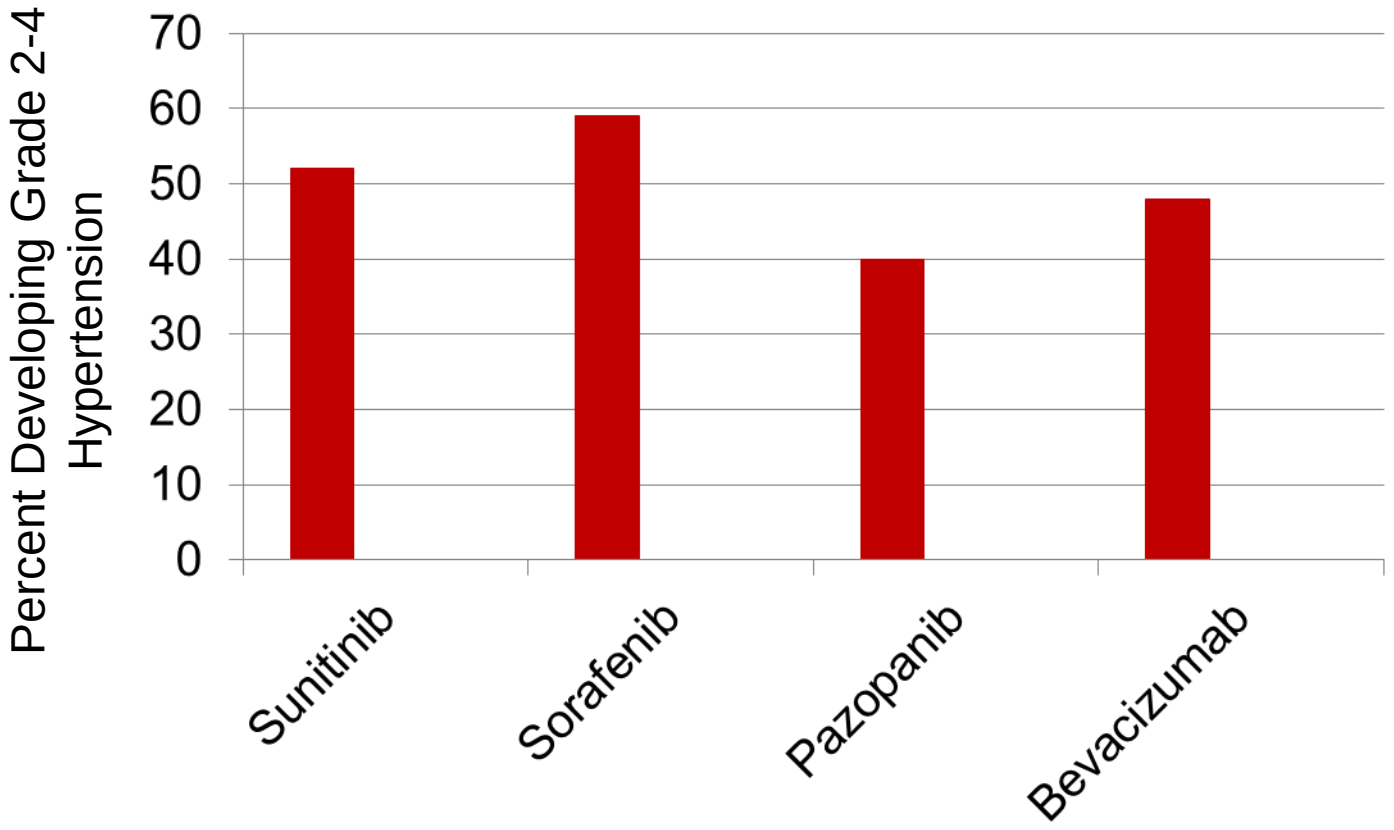
Hypertension

VEGF Inhibitors and Hypertension



Hall PS et al. JACC Heart Fail. 2013; 1(1): 72-8.

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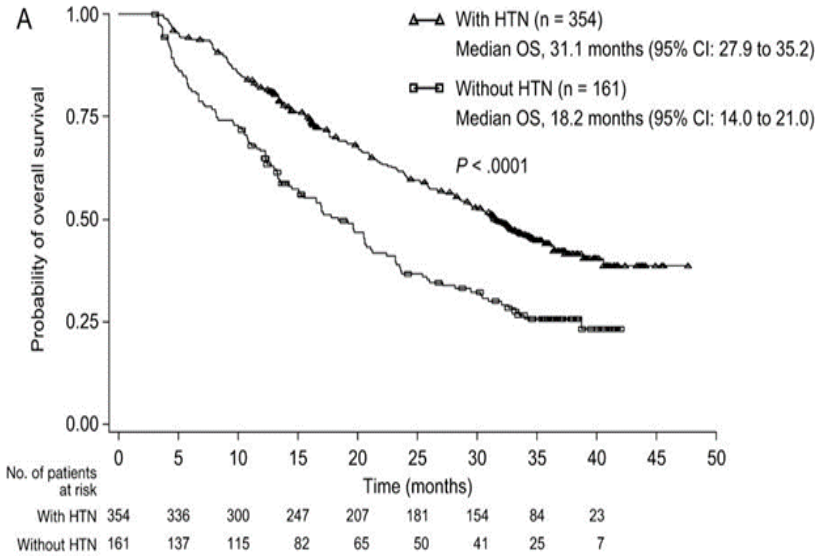
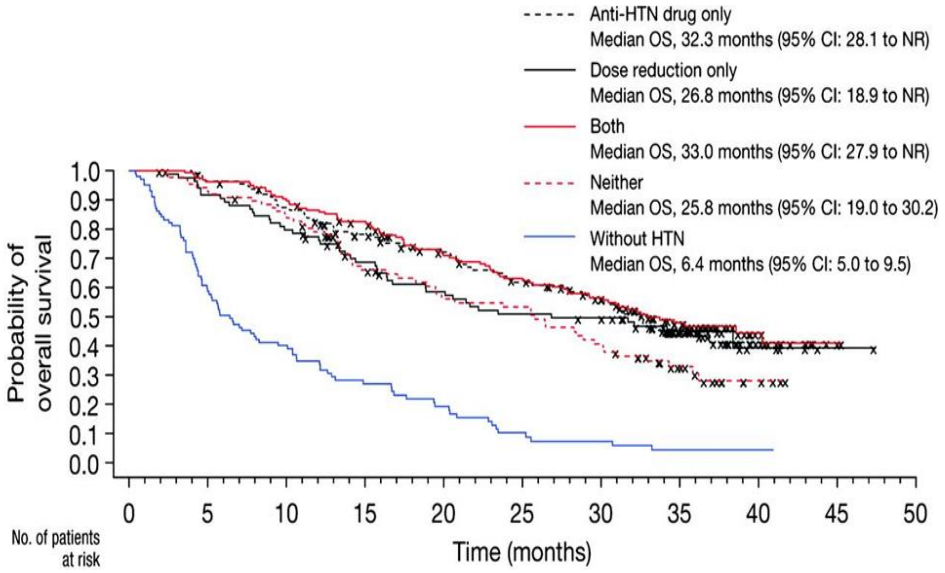
VEGF Inhibitors and Hypertension: Marker of Efficacy?





Rini et al. JNCI J Natl Cancer Inst. 2011;103:763-773

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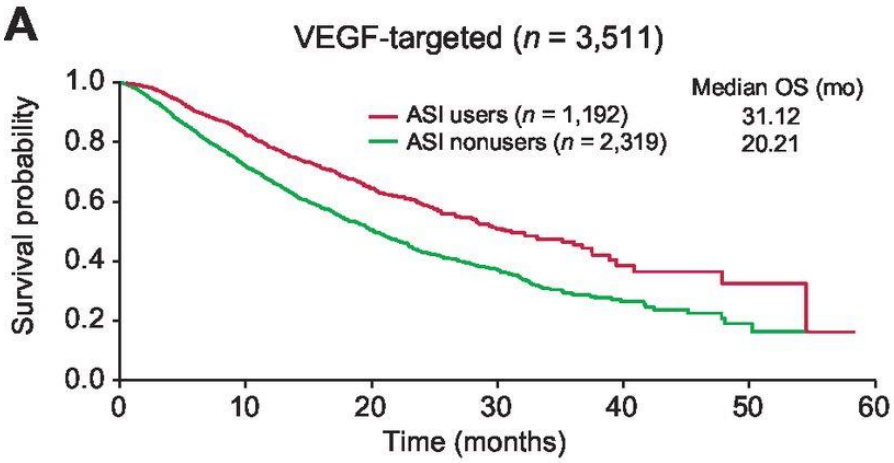
VEGF Inhibitor Induced Hypertension: Treatment Options

- First Line Therapies
  - ACE Inhibitors/Angiotensin Receptor Blockers
  - Dihydropyridine Calcium Channel Blockers (CCBs)
- Second Line Therapies
  - Beta blockers and Diuretics
- Novel/Investigational Therapies
  - Nitric Oxide Donating Medications
  - Endothelin-1 Receptor Antagonists

Kaplan-Meier Estimate of Overall Survival Stratified by Antihypertensive Use



McKay et al. Clin Cancer Res 2015;21:2471-2479

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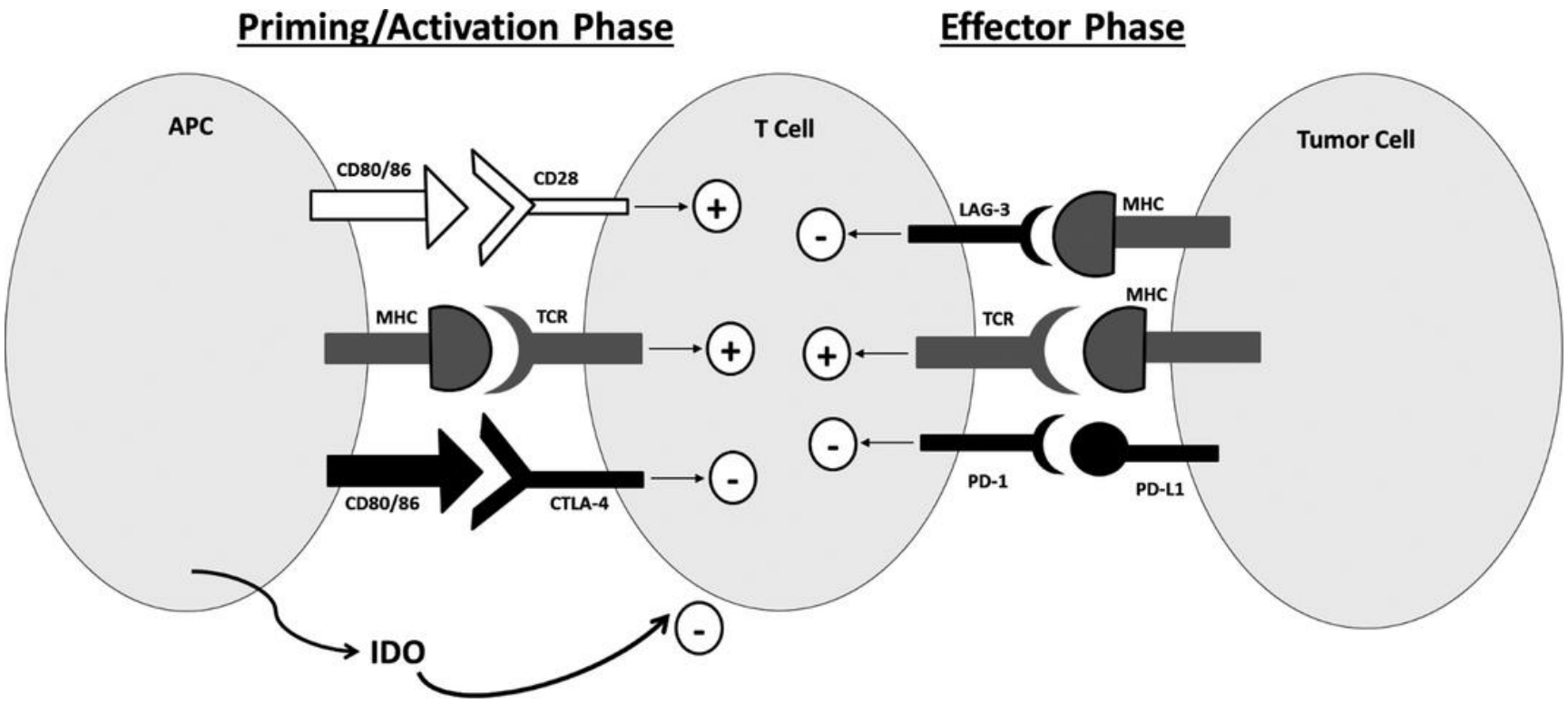
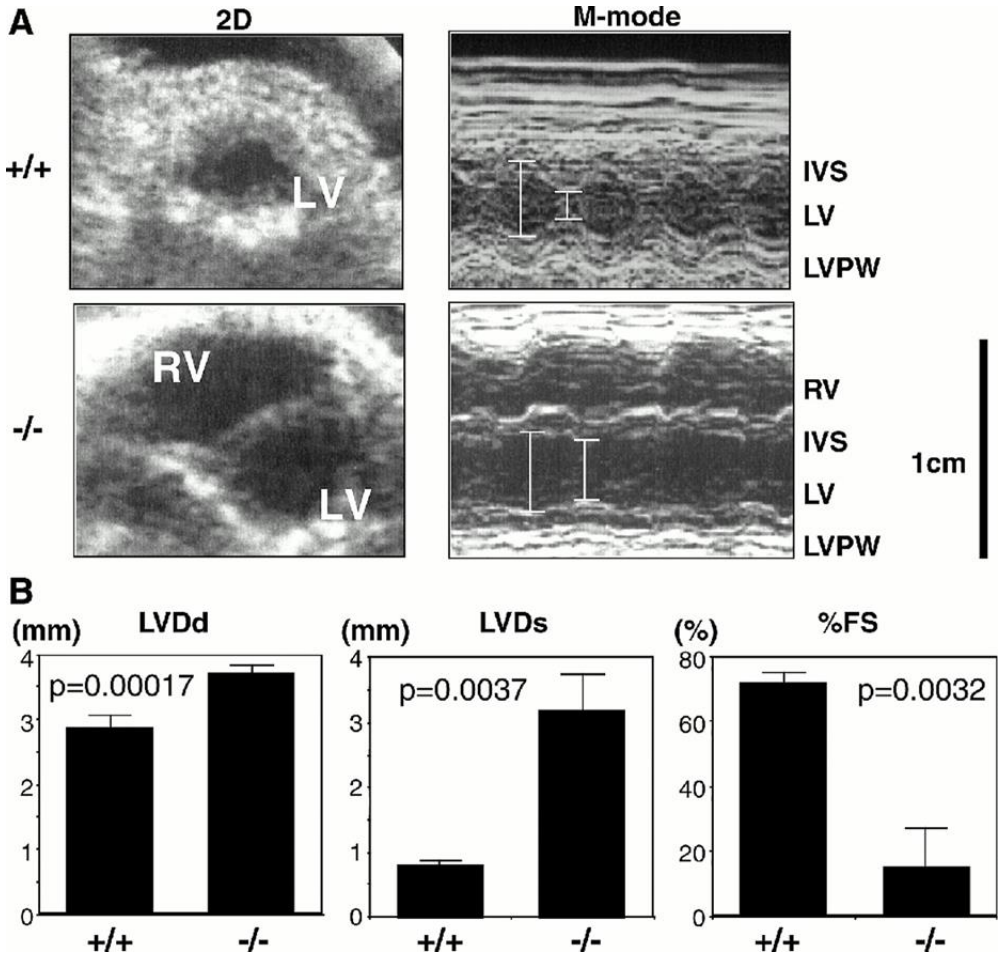
Myocarditis

Mechanism of Check Point Inhibitors

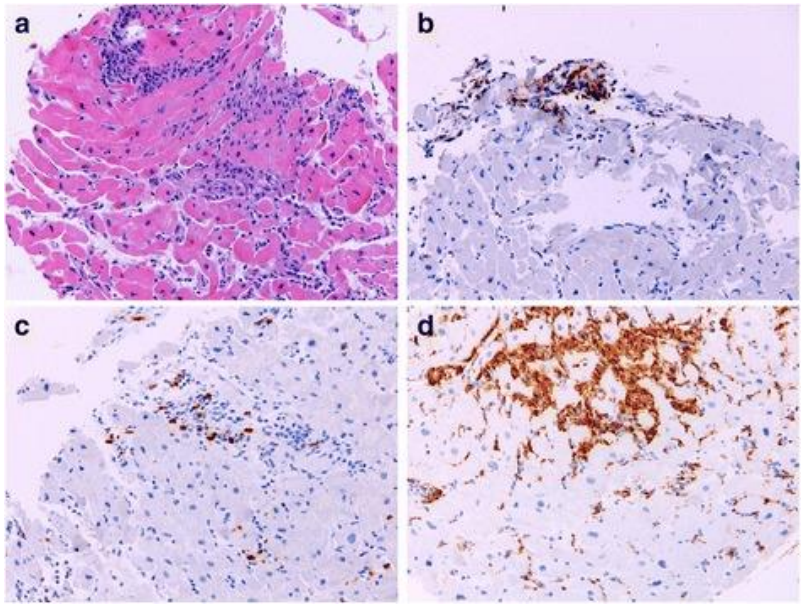


La-Beck et al. *Pharmacotherapy:* 2015; 35: 963-976.

Immune Checkpoint Inhibitor Cardiotoxicity



Nishimura et al. *Science*. 2001;291:319-322



Heinzerling et al. *J Immunother Cancer.* 2016;4: 50.

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Prevention of Cardiovascular Disease in Cancer Patients: Learn your ABCs

- A: Awareness of potential CV dysfunction; aspirin; Ankle-brachial index
- B: Blood pressure control
- C: Cholesterol control; cigarette avoidance
- D: Diabetes control; healthy dieatary choices
- E: Exercise. Echo. EKG.

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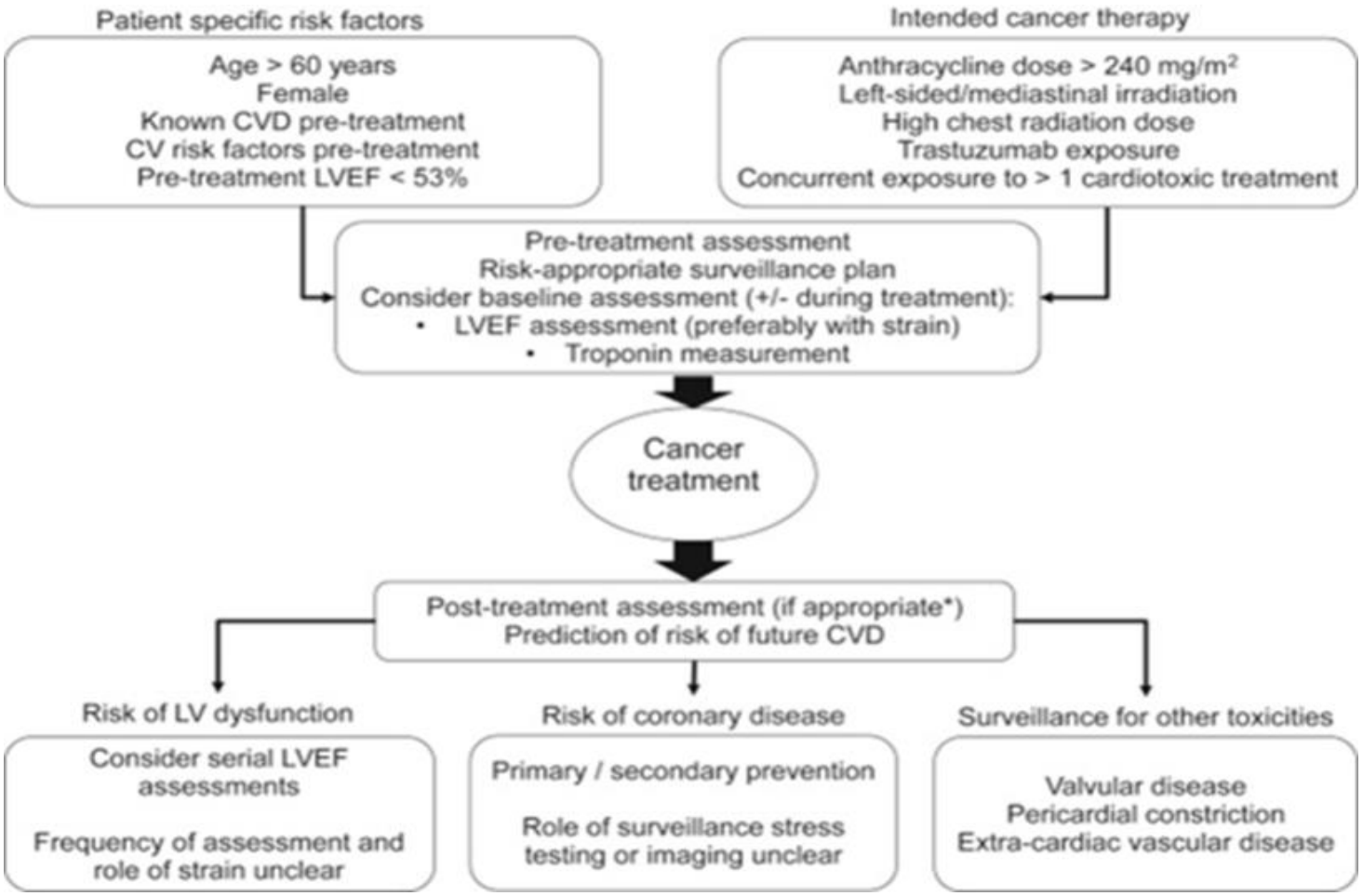
Proposed surveillance and risk stratification for Cancer Patients and Survivors



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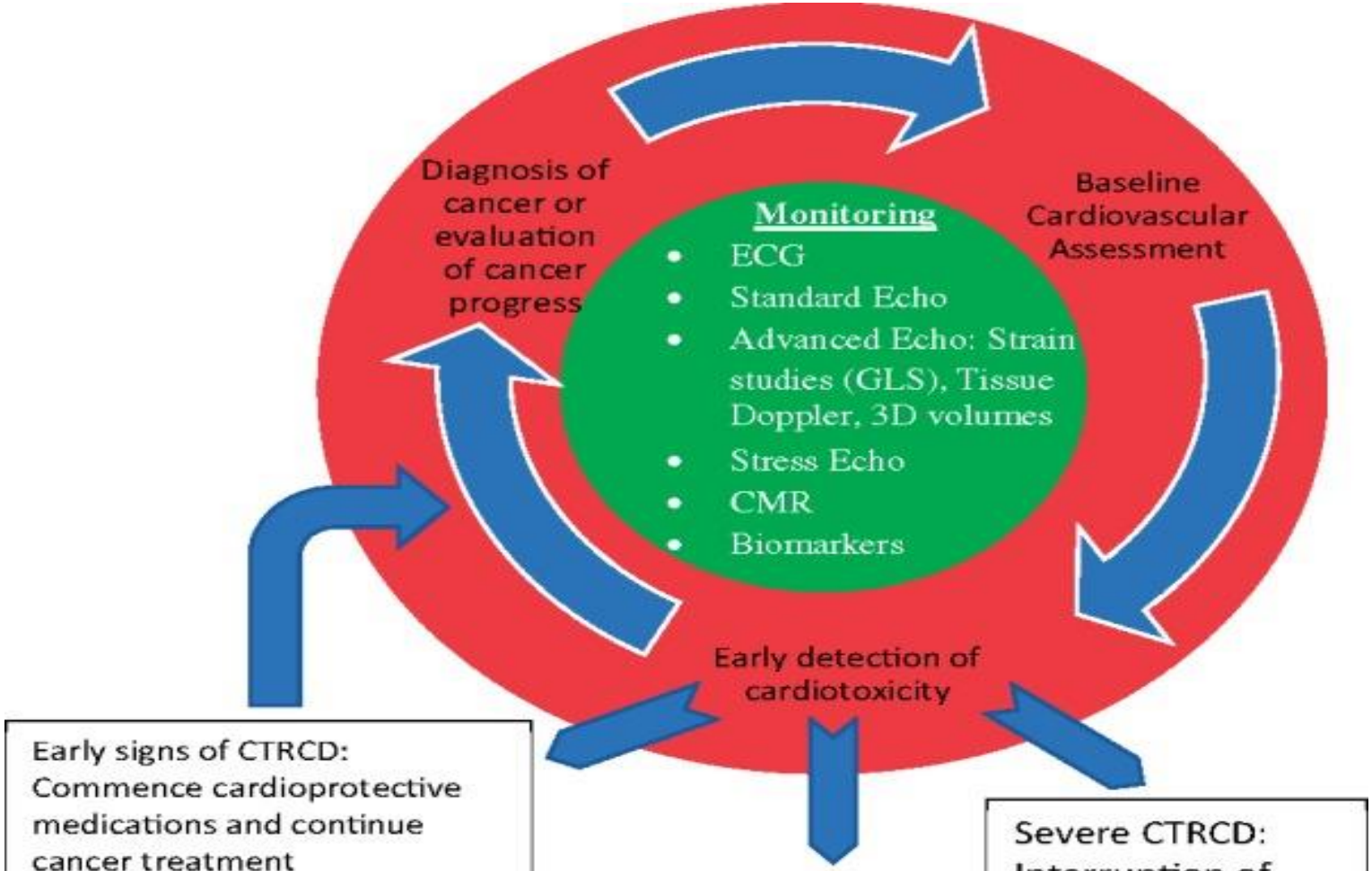
Proposed definitions for cancer therapy-related cardiac dysfunction (CTRCD).

- ⩾10% decline in LVEF to a final value less than 53% confirmed on subsequent imaging performed 2 to 3 weeks after the initial measurement.
- >15% relative decline in global longitudinal strain (GLS) compared with baseline strain.
- Hypertension, arrhythmia, ischemia, thromboembolism, QT prolongation

J Clin Oncol 2002;20:1215-21.



Eur Heart J Suppl. 2019 Dec; 21(Suppl M): M44–M49

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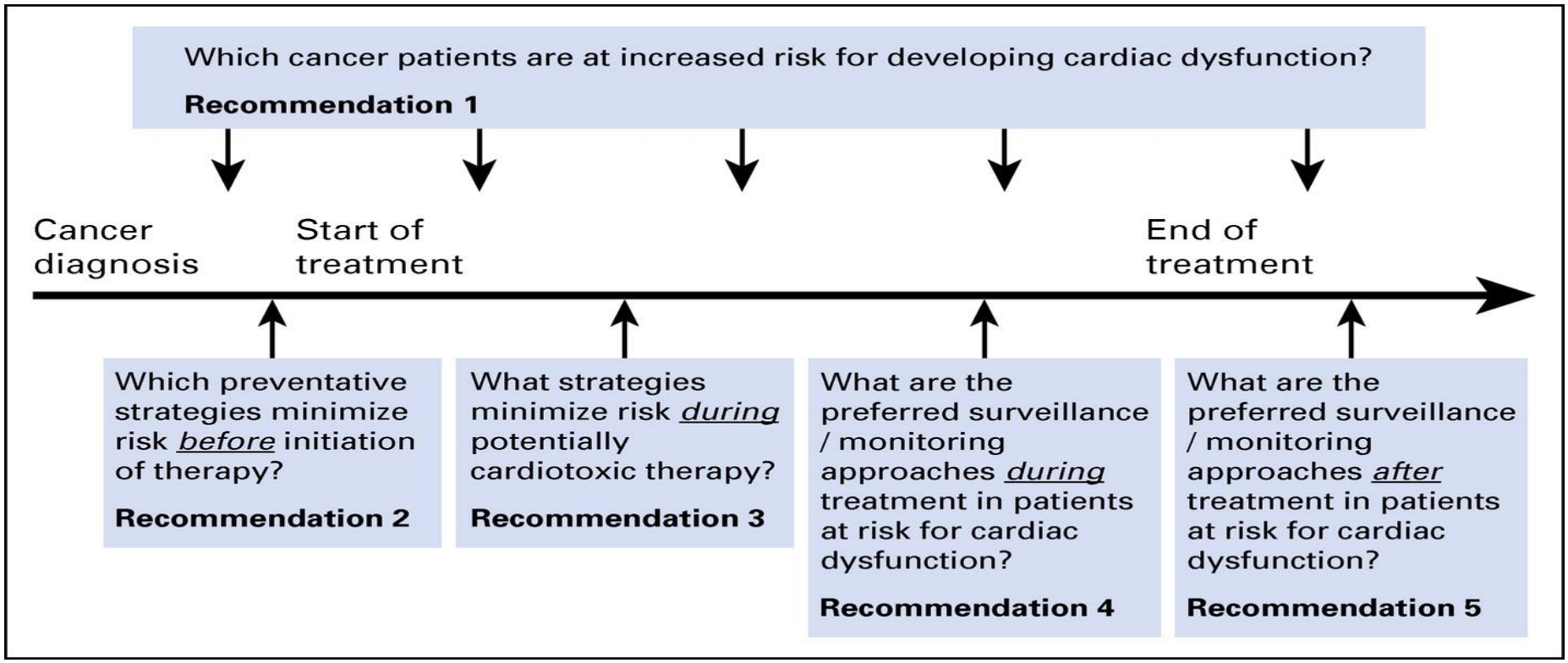

J Clin Oncol 35:893-911.

Strain Imaging to Diagnose Chemotherapy Induced Cardiomyopathy

- Measure of myocardial deformation
- Identification of subclinical LV dysfunction prior to EF changes
- Potential role for early cardiovascular intervention

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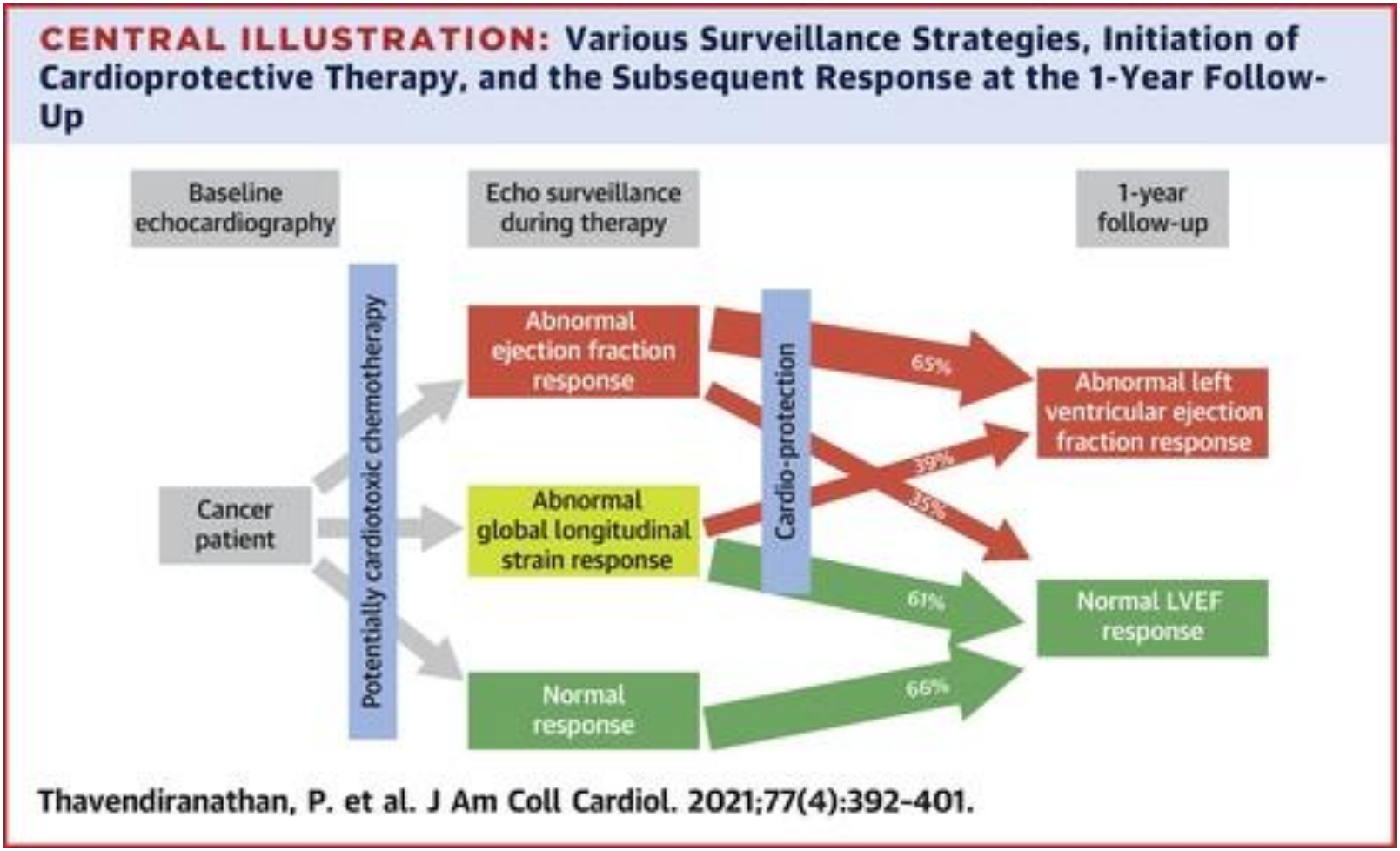
Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy



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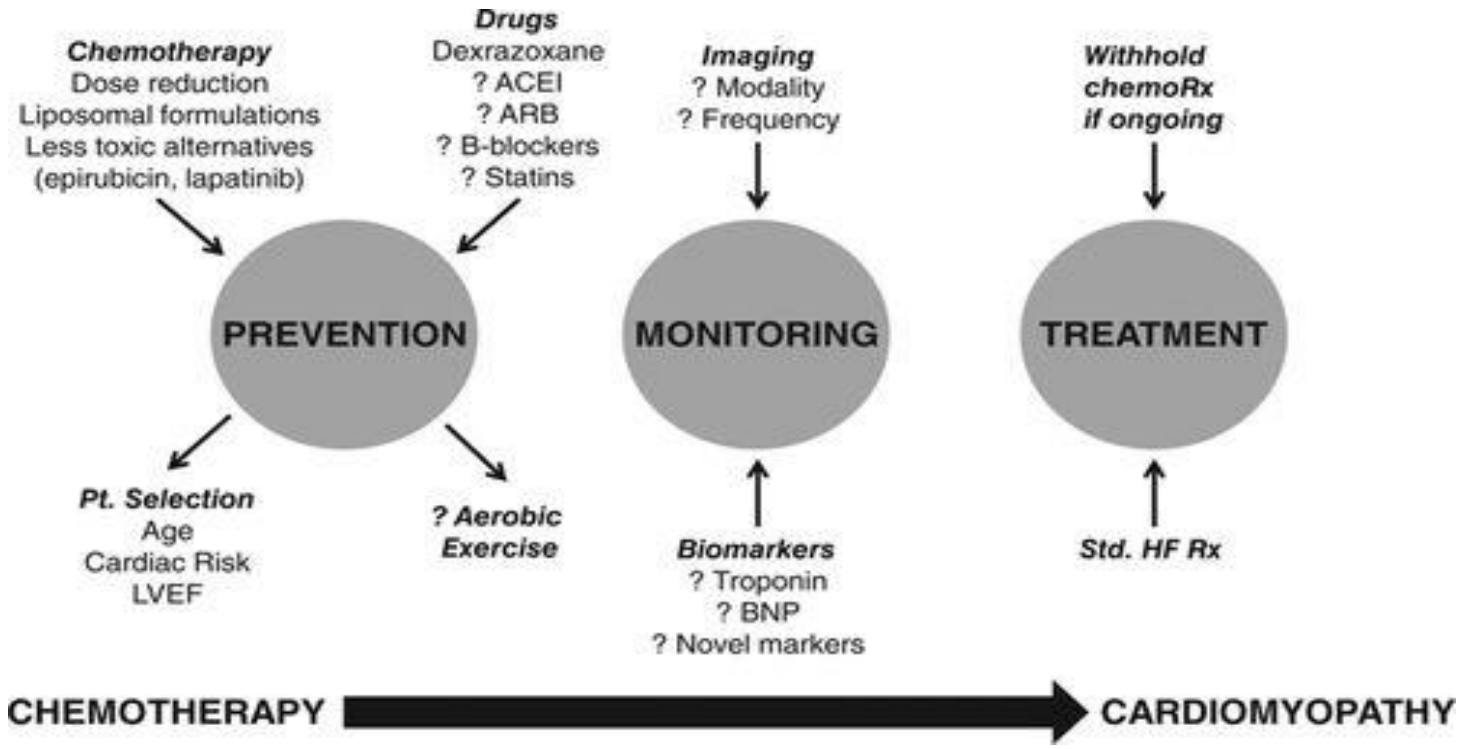
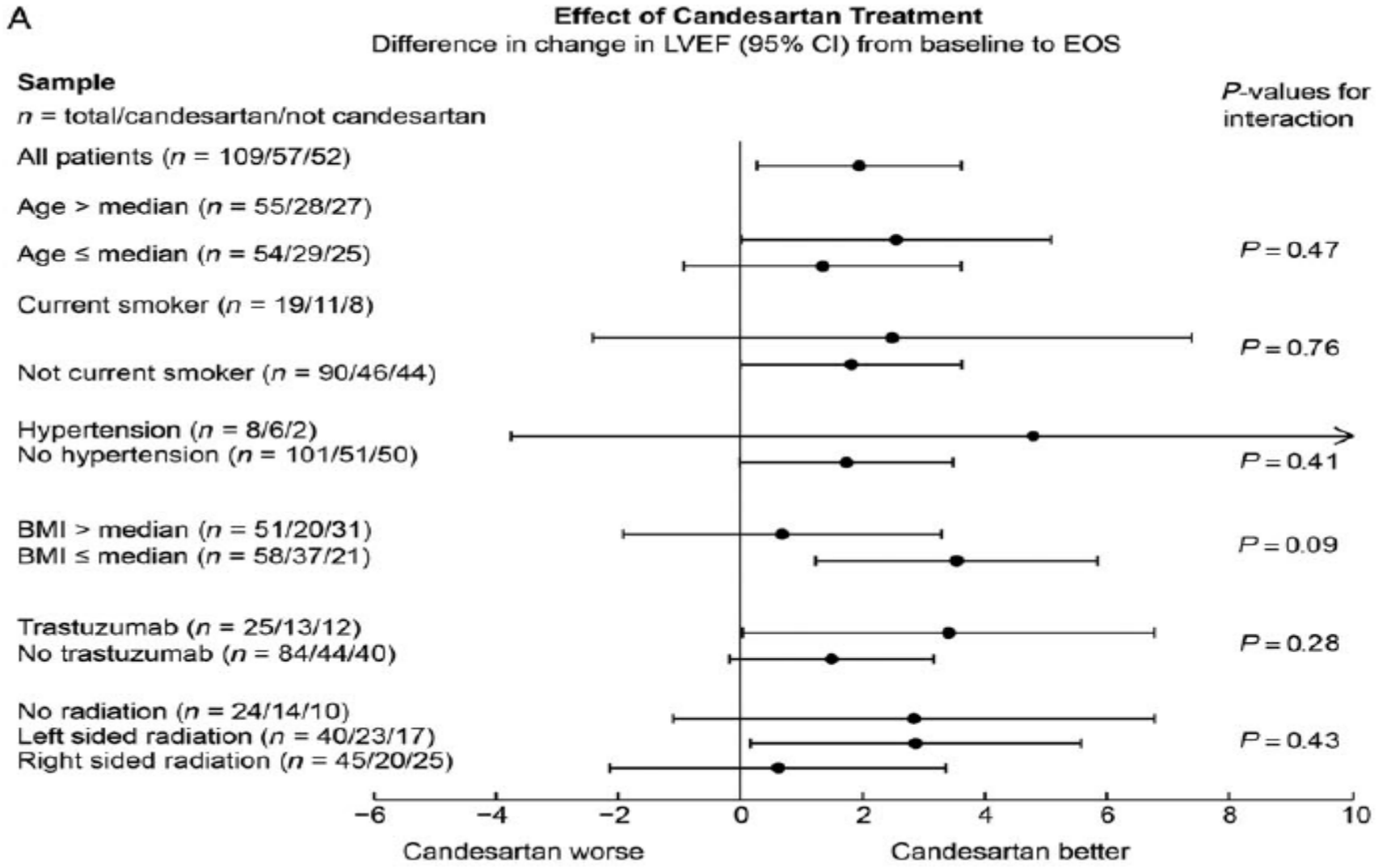
Management of chemotherapy-induced cardiomyopathy.



Circulation: Heart Failure. 2013;6:358–361

Prevention of Chemotherapy Induced



Gulati et al. Eur Heart J. 2016; 37: 1671-80.

Conclusions

- Cardiovascular toxicity has significant impact on both cancer patients and survivors
- Traditional chemotherapy, targeted and immune therapy and radiation therapy are all associated with cardiotoxicity
- LV dysfunction and heart failure, arrhythmias, ischemia and hypertension are commonly observed toxicities
- Biomarkers and strain imaging may help with the early diagnosis of certain forms of cardiotoxicity
- Cardio-oncology collaboration serves as a forum to optimize cardiac health and ensure cancer treatment continuation

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Current and Future Directions in Cardio-Oncology

- Collaboration between oncologists and cardiologists results in completion of cancer therapy in most patients
- Ongoing analysis of referral patterns, management plans, and patient outcomes will help to guide the cardiac care of oncology patients, ultimately optimizing cancer and cardiac outcomes alike
- Cardio-oncology rehabilitation is a concept that aims to reduce the risk of CVD and improve cardiopulmonary fitness in cancer survivors by providing exercise prescriptions and cardiac rehabilitation during and after cancer treatment

Thank You!

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