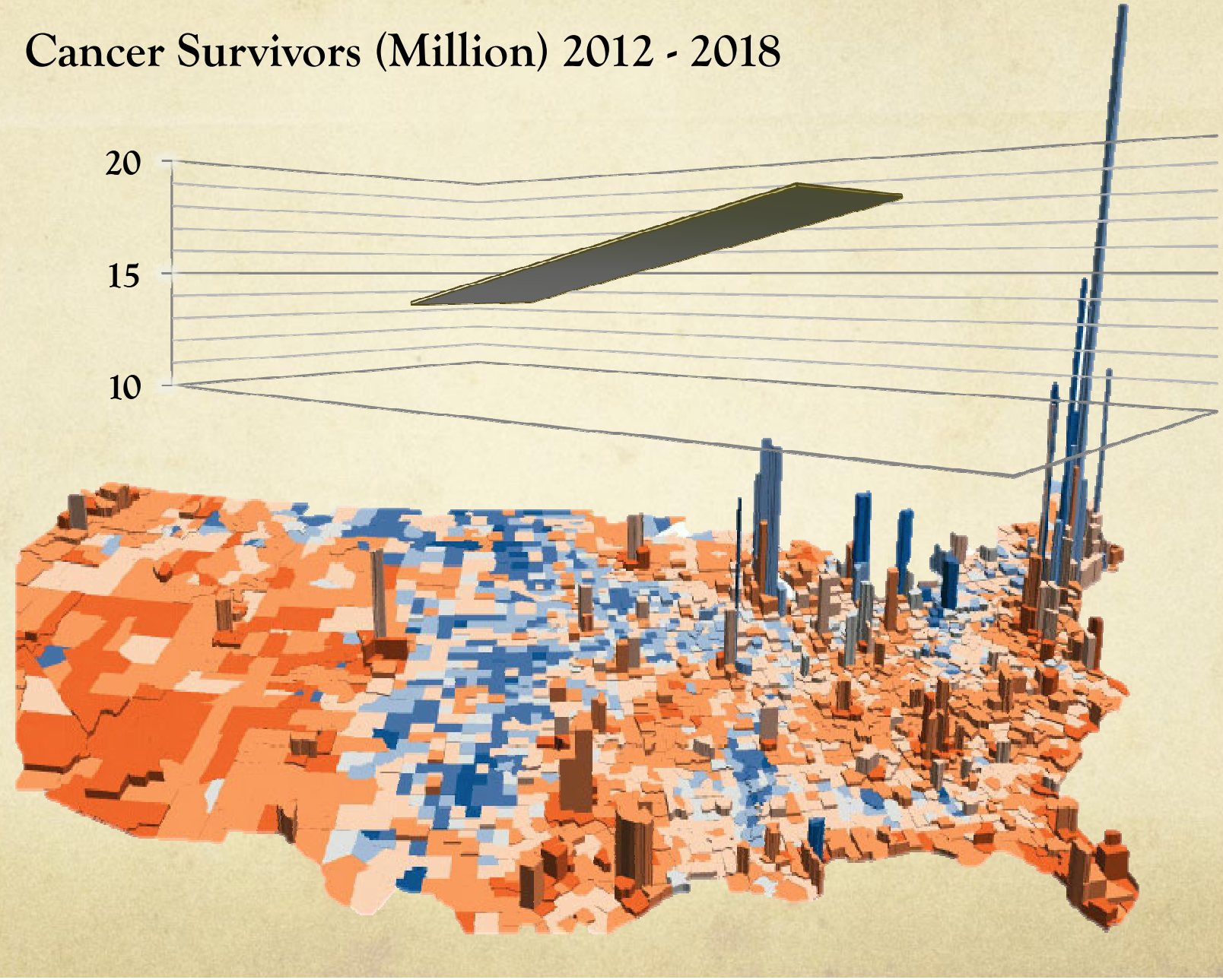
Como estimar o risco de cardiotoxicidade?

Dra Carolina Thé Macêdo, MD
Cardiologista/Ecocardiografista
Pesquisadora/Preceptora de Cardiologia-HSR

Declaro não possuir conflitos de interesse

Cancer Survivors (Million) 2012 - 2018



INCIDÊNCIA DE CÂNCER NO MUNDO E NO BRASIL

Mais de 20 milhões de pessoas no mundo são sobreviventes ao câncer

EUA ~ 15,5 milhões

UK ~ 2 milhões

Brasil ???

OMS 2014

14 milhões de casos novos no Mundo

> 8 milhões de óbitos por Câncer

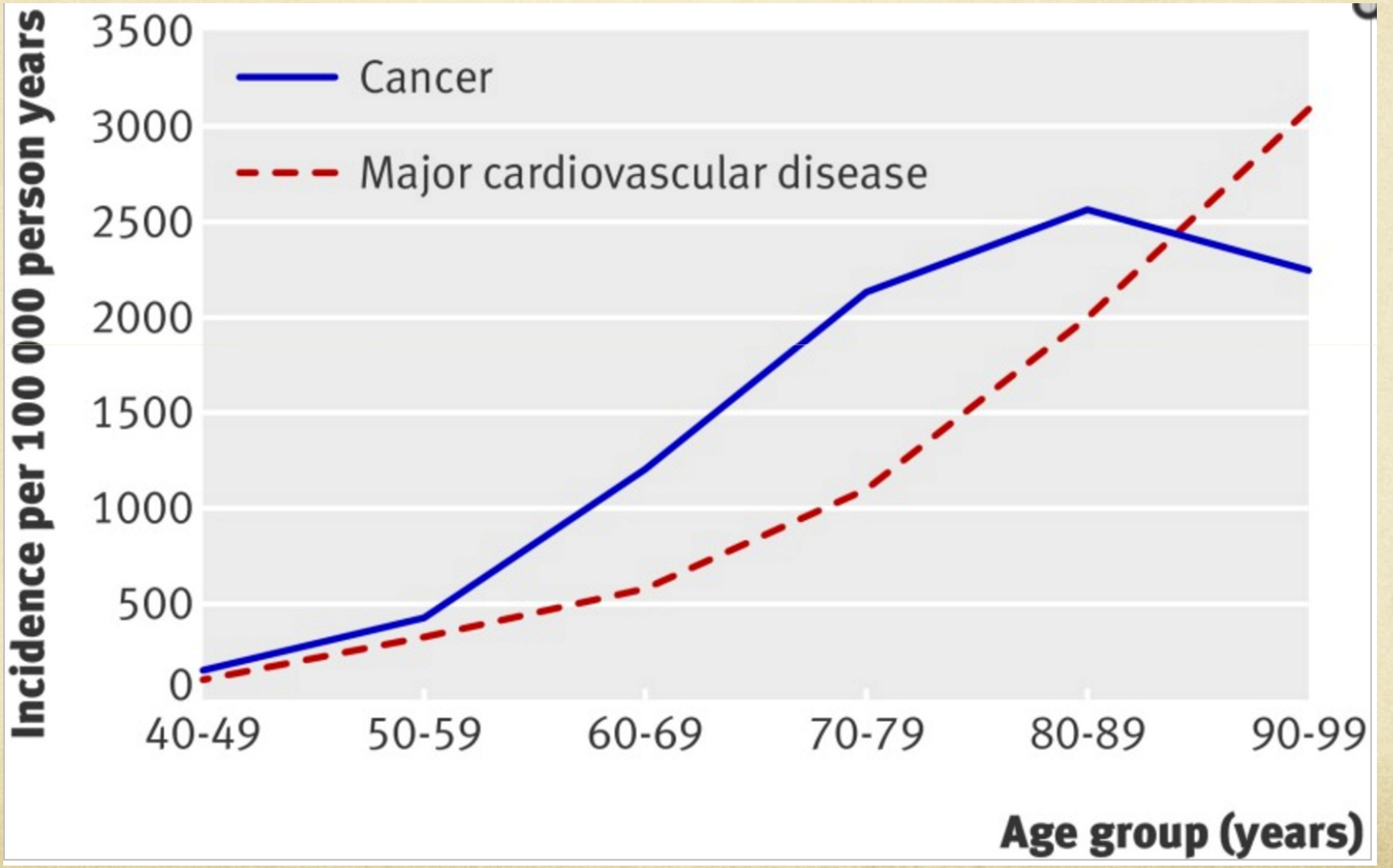
INCA 2016 / 2017

~600 mil casos novos em Adultos (Brasil)

1) Próstata
2) Mama
3) Pulmão
3) Intestino
4) Colo do útero
6) Estômago
7) Cavidade Oral

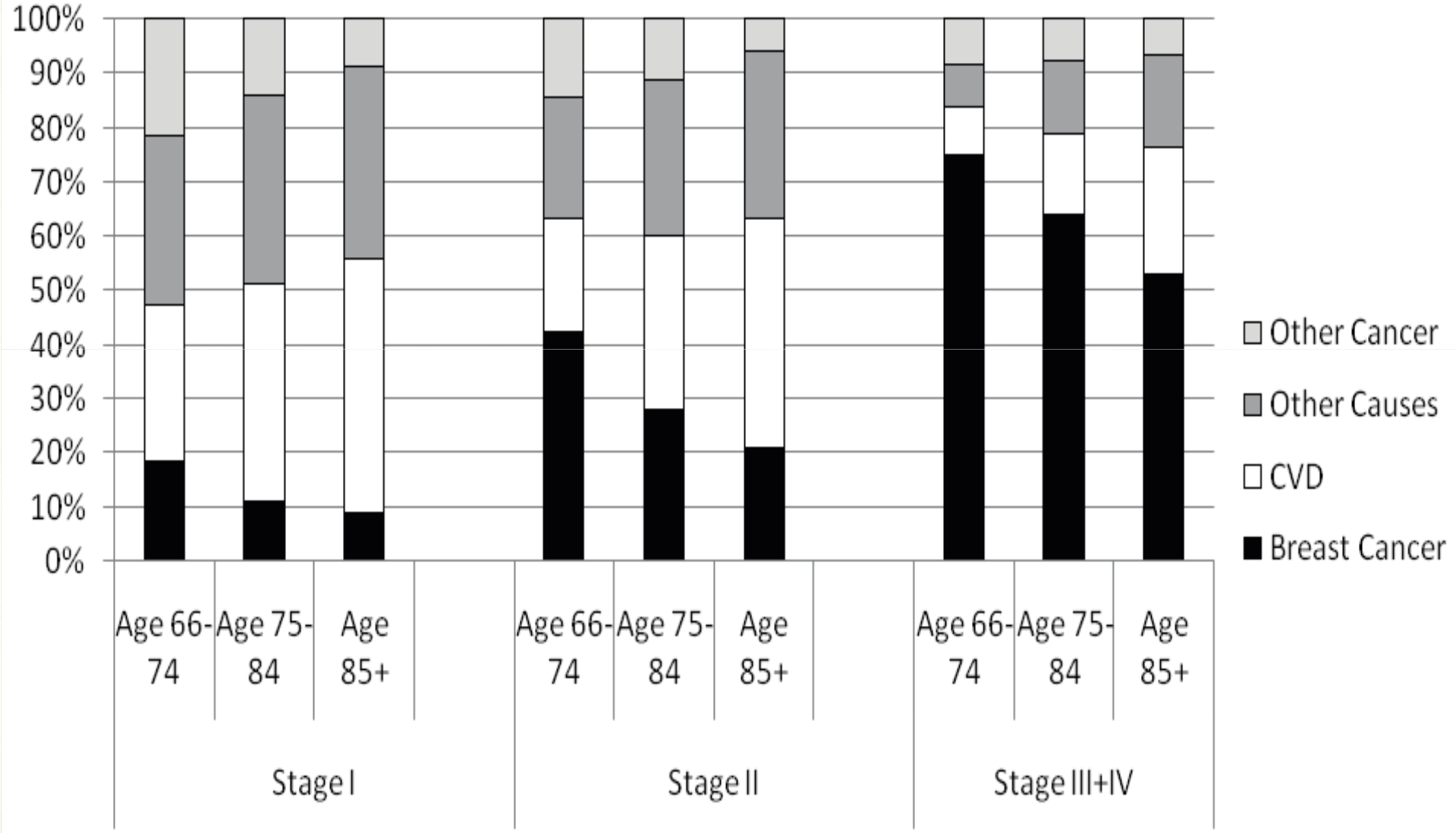
JCO 2010 Mar10
Exp Opin Pharmacother 2013 Aug 14
OMS 2014
INCA 2014/2015

Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study



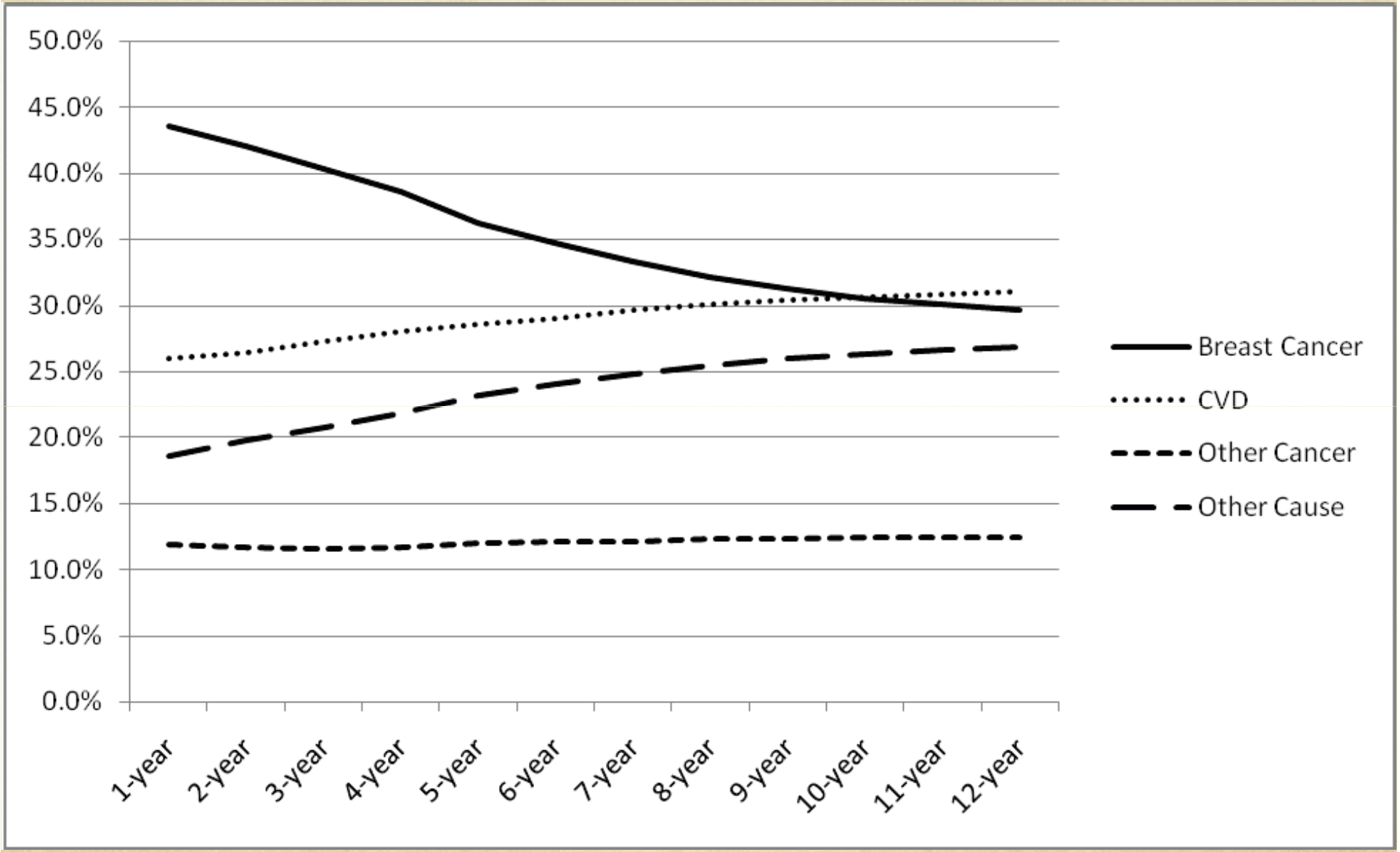
Driver BMJ 2008:337:p. 2467

Proportional distribution of leading causes of death among breast cancer



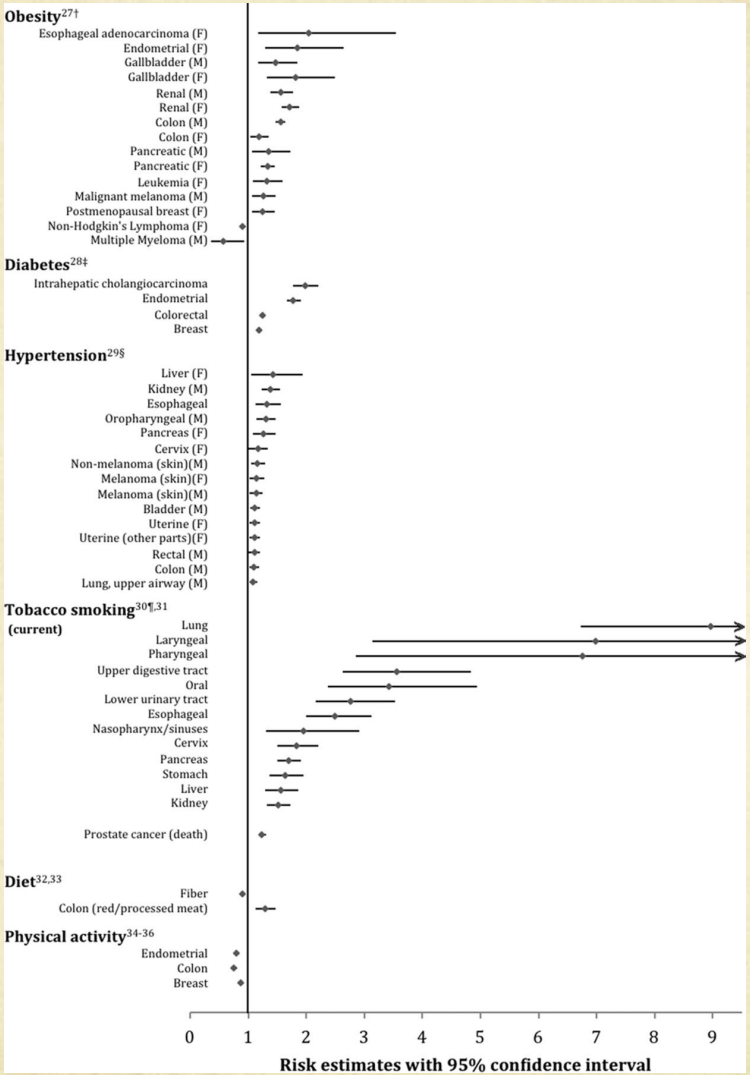
Breast Cancer Research 2011, 13:R64

Cumulative leading causes of death by time



Breast Cancer Research 2011, 13:R64

Shared Risk Factors in Cardiovascular Disease and Cancer

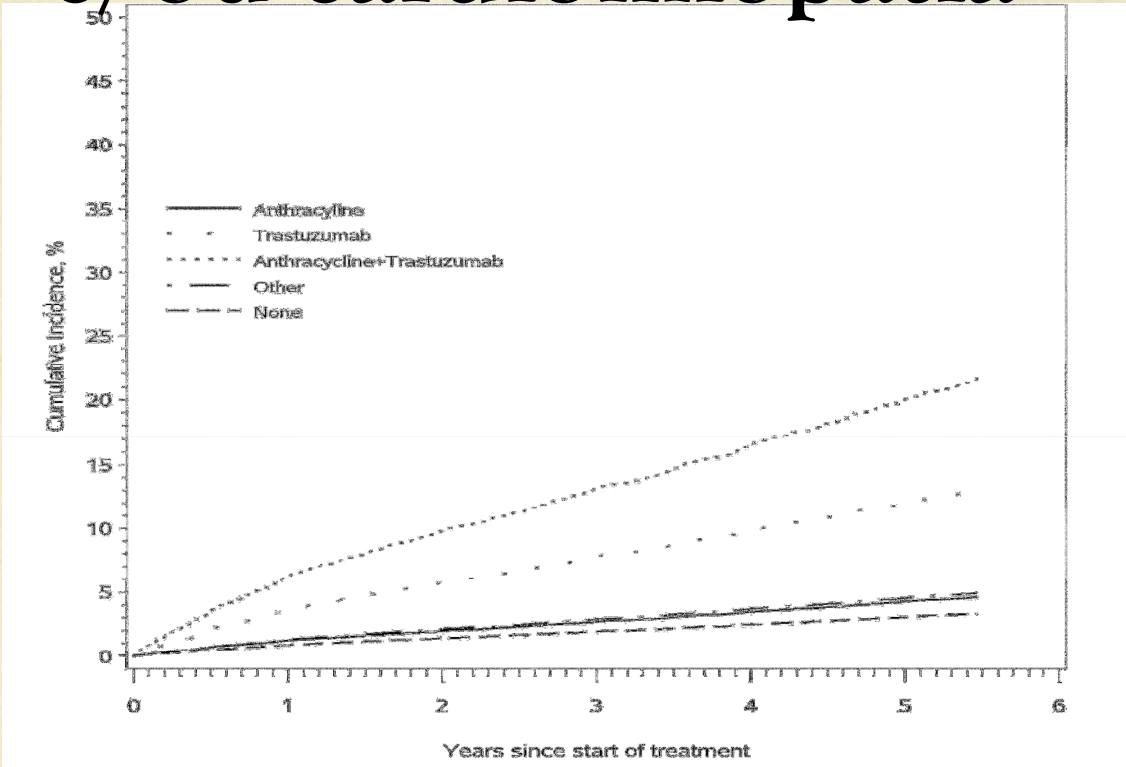


Modifiable cardiac risk factors with their estimated cancer risk.

American Heart Association.

Ryan J. Koene et al. Circulation. 2016;133:1104-1114

Incidência cumulativa de IC e/ou cardiomiopatia



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)

J Natl Cancer Inst 2012;104:1293–1305

Table 5 Anthracycline equivalence dose considering doxorubicin in rapid infusion as a reference[94]

Drug	Relative cardiotoxicity	Incidence of HF rises to >5% when cumulative dose exceeds (mg/m^2)
Doxorubicin rapid infusion	1	400
Epirubicin	0.7	900
Daunorubicin	~0.75	800
Idarubicin	0.53	150

European Heart Journal Advance Access published August 26, 2016
European Heart Journal
doi:10.1093/eurheartj/ehw211
ESC CPG POSITION PAPER

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

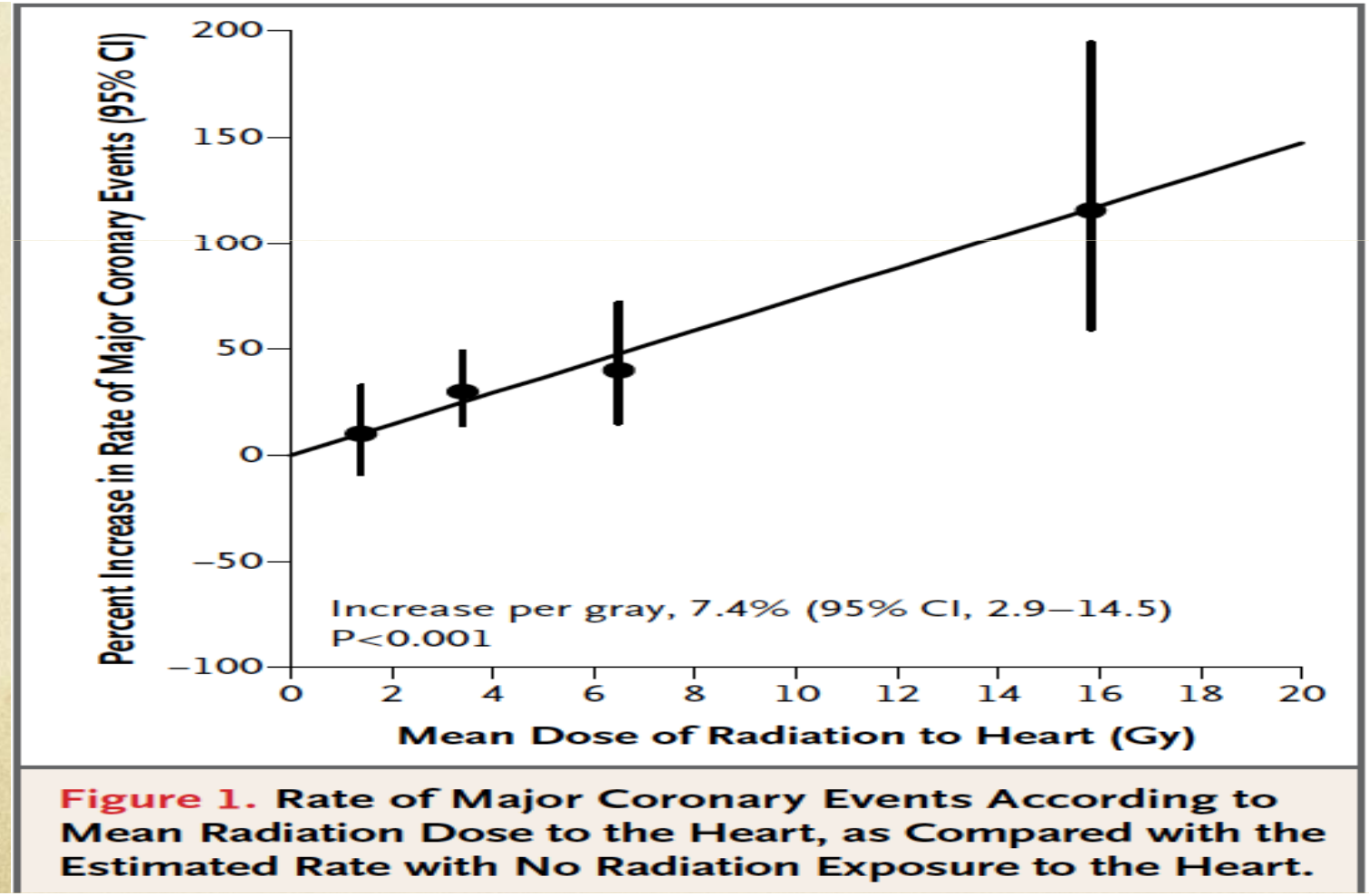
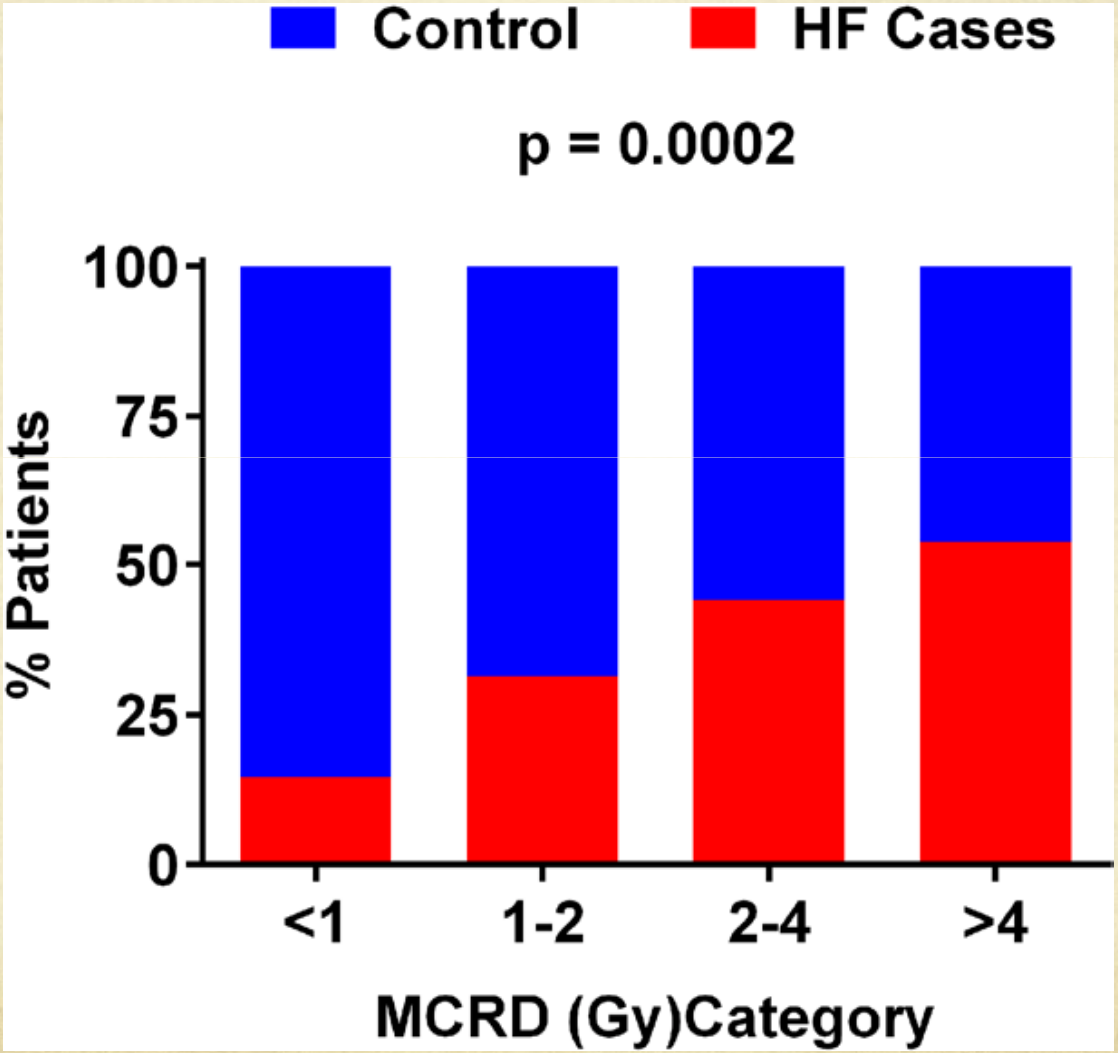


Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.

Risk of Heart Failure With Preserved Ejection Fraction in Older Women After Contemporary Radiotherapy for Breast Cancer



Circulation. 2017;135:1388–1396

Cardiovascular Risk Factors in Adult Survivors of Pediatric Cancer—A Report from the Childhood Cancer Survivor Study

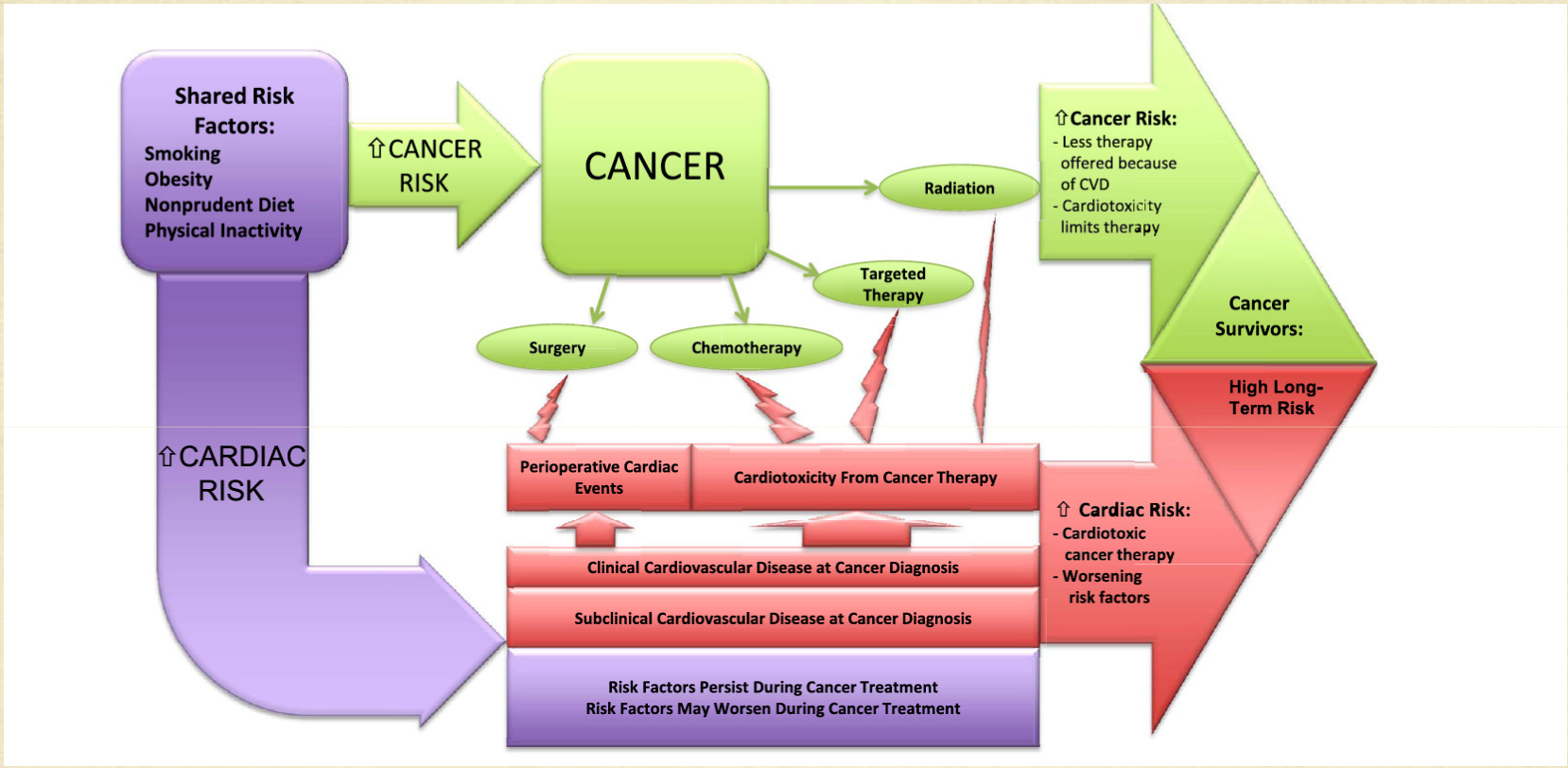
Lillian R. Meacham[1], Eric J. Chow[2], Kirsten K. Ness[3], Kala Y. Kamdar[4], Yan Chen[5], Yutaka Yasui[5], Kevin C. Oeffinger[6], Charles A. Sklar[6], Leslie L. Robison[3], and Ann C. Mertens[1]

Table 1. Risk of cardiac disease and cardiac risk factors in long-term survivors of childhood cancer vs healthy siblings (Childhood Cancer Survivor Study)

	CAD[9]	Heart failure[9]	Hypertension[10]	Diabetes[10]	Dyslipidemia[10]
RR (95% CI)	10.4 (4.1-25.9)	15.1 (4.8-47.9)	1.9 (1.6-2.2)	1.7 (1.2-2.3)	1.6 (1.3-2.0)
n	10,397	10,397	8599	8599	8599

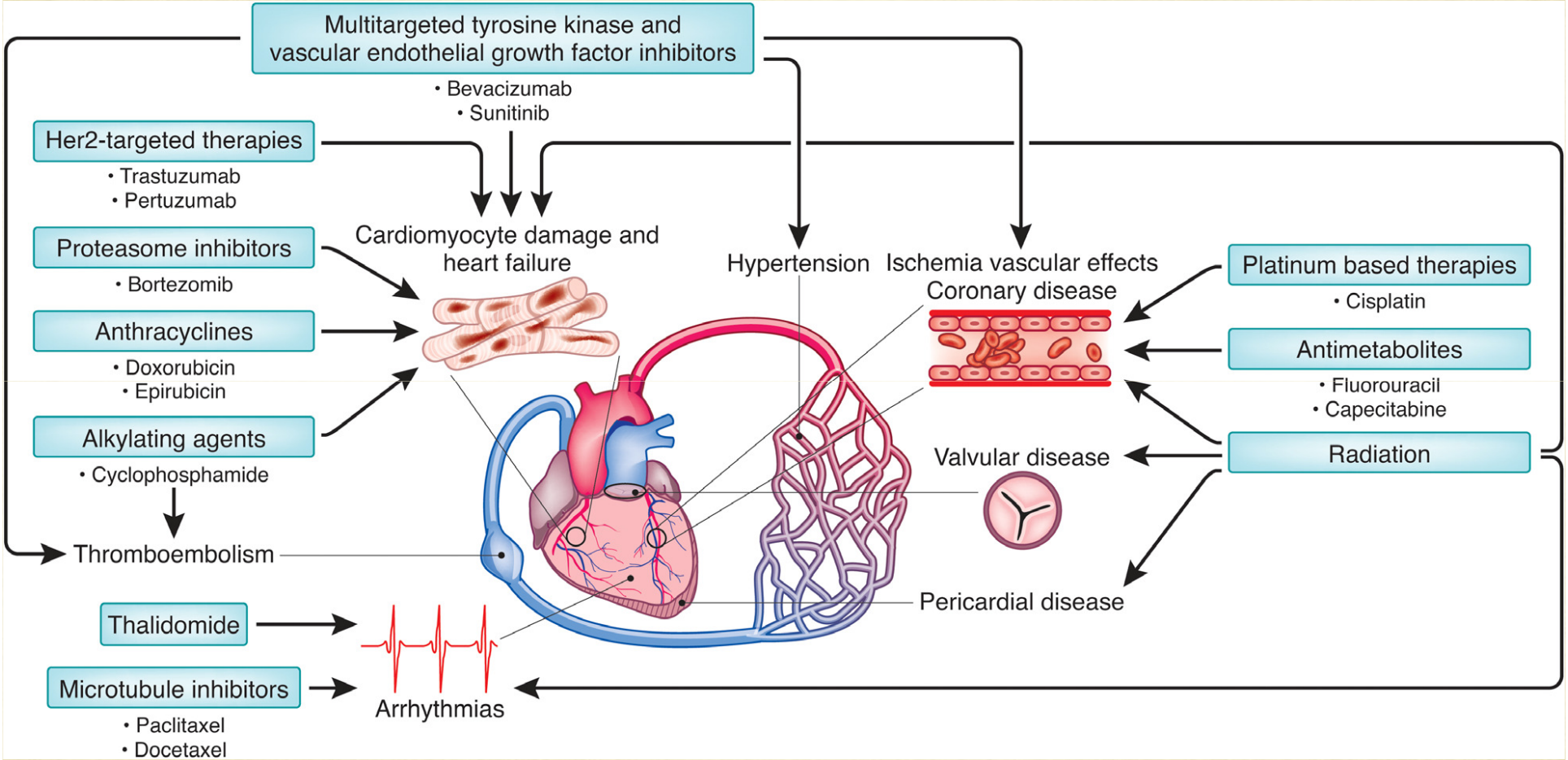
CAD, coronary artery disease; CI, confidence interval; RR, relative risk.

Multi Hit Hypothesis



Canadian Journal of Cardiology 32 (2016) 900e907

Efeitos cardiovasculares



Circ Res. 2016;118:1008-1020

Cardio-oncologia

Skills

The ability to:

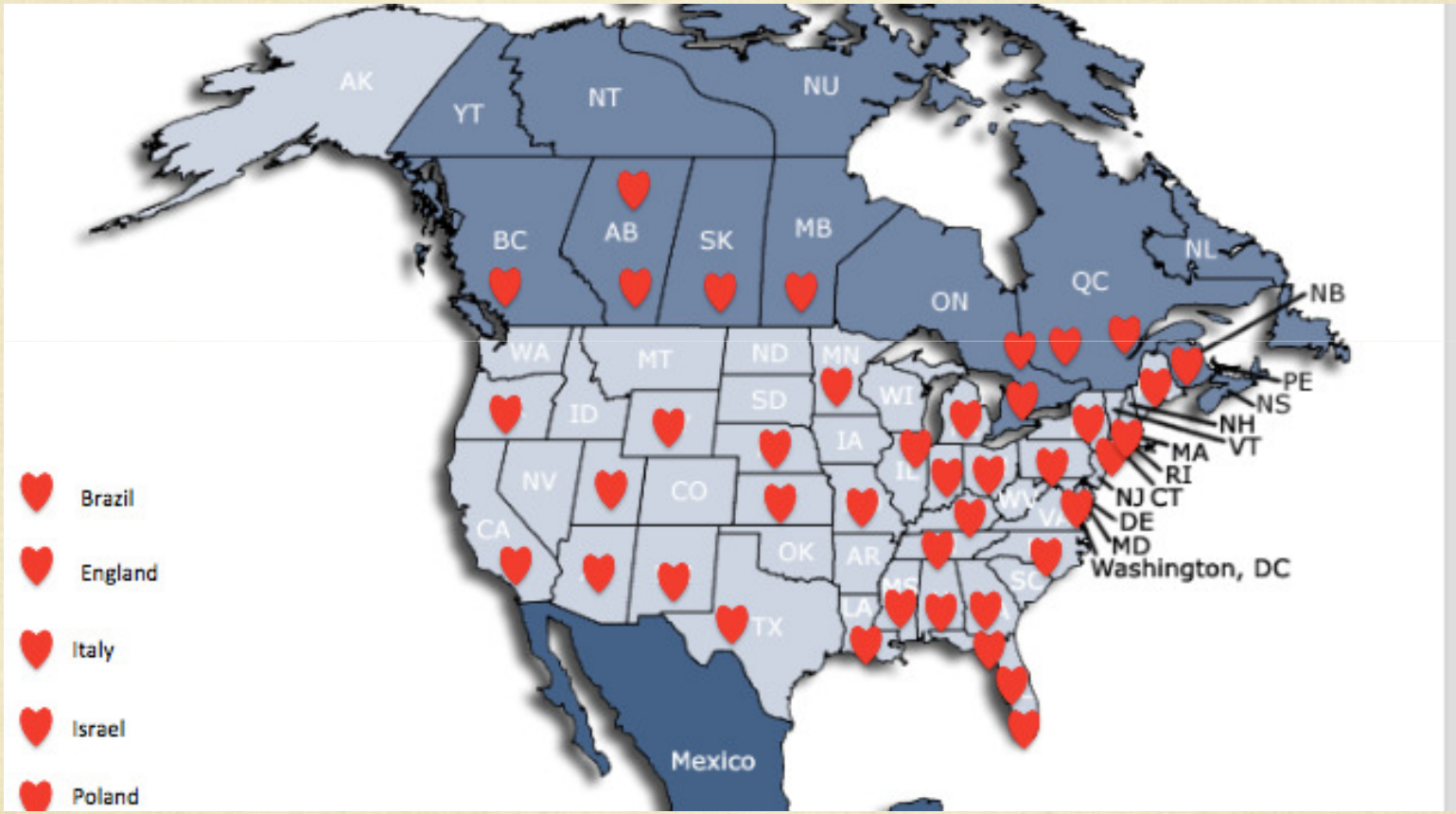
- use appropriate imaging modalities for diagnosing primary and metastatic tumours and for differentiating tumours from non-neoplastic cardiac masses such as thrombi or vegetations, or aberrant variants of normal structures;
- evaluate the cardiovascular system of patients prior to cancer therapy;
- evaluate the cardiovascular system of patients during and after cancer therapy;
- follow-up and treat oncological patients with cardiovascular complications.

Behaviours and attitudes

- Team working with general practitioners, oncologists, oncological nurses, radiologists, and surgeons;
- Willingness to refer the oncological patient for invasive cardiac evaluation and cardiac biopsy when indicated;
- Empathic and supportive approach towards the psychologically vulnerable oncological patient.

European Heart Journal (2013) **34**, 2381–2411

Cardio Oncologia



Como estimar o risco ?

Classificação

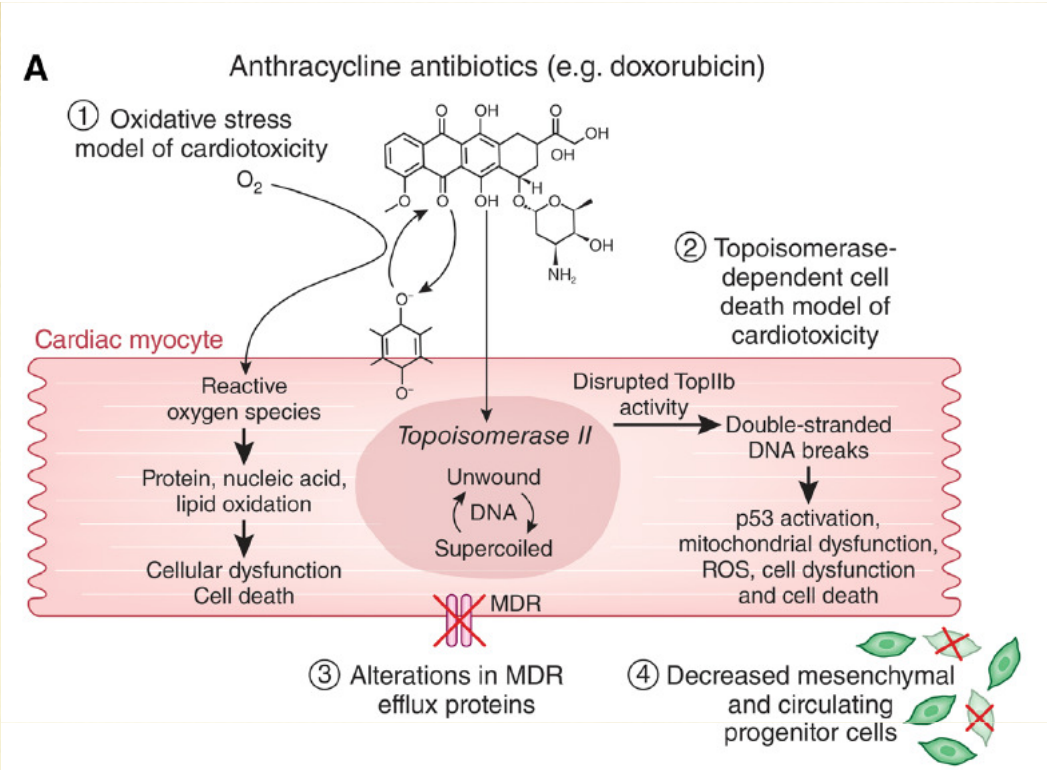
Table 2 | Type I and type II treatment-related cardiac damage

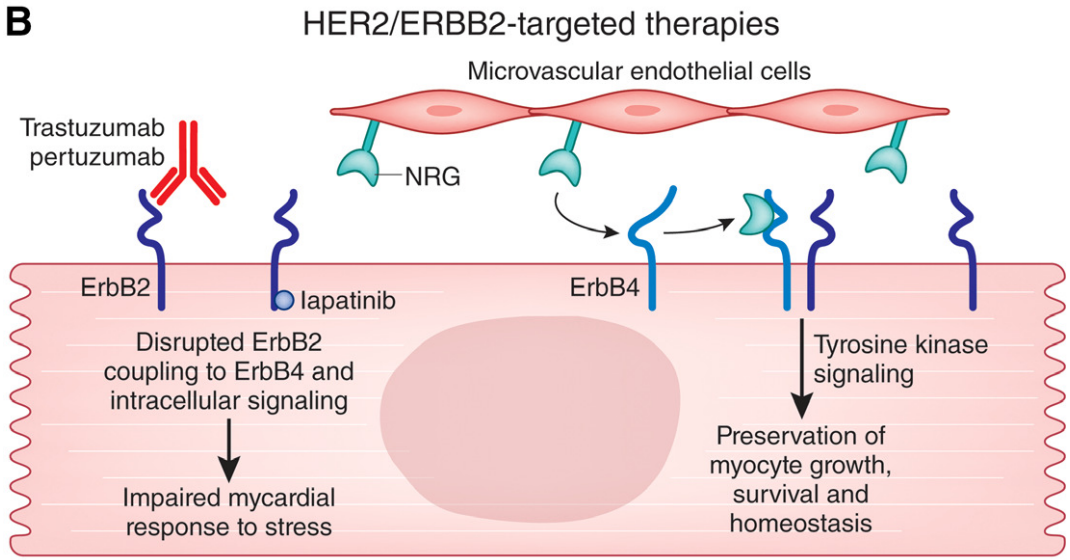
Type of therapy-related cardiac damage	Anticancer agents involved	Cardiac damage induced	Nature of cardiac damage	Biopsy presentation	Relationship of dose and injury	Risk factors
Type I	Doxorubicin Daunorubicin Epirubicin Liposomal doxorubicin Mitoxantrone	Direct myocyte death	Permanent myocyte injury, beginning from first dose	Vacuole formation Myofibril disarray Necrosis	Cumulative dose-related effect	Any condition that has damaged or strained the myocardium Genetic sensitivity to these agents
Type II	Trastuzumab Sunitinib Imatinib Lapatinib	Myocyte dysfunction	Reversible myocyte dysfunction, with favourable prognosis	Minimal changes have been reported; none of the characteristic changes of the type I agents are seen	No cumulative dose-related effect noted	Prior recent exposure to anthracyclines (trastuzumab) Hypertension (sunitinib) Tendency to retain fluid (imatinib) Genetic sensitivity*

*Considerable variation exists between agents.

Nat. Rev. Cardiol. **12**, 547–558 (2015)

Mecanismos de lesão cardiovascular





Circ Res. 2016;118:1008-1020

Table 1. Stages of heart failure as per American College of Cardiology/American Heart Association guidelines with minor modification

Stage	A	B-1*	B-2	C	D
Definition	At high risk for HF	Occult LV dysfunction	Overt LV dysfunction	Symptomatic HF, responsive to conventional therapy	Symptomatic HF, unresponsive to conventional therapy
LVEF	No detectable cardiac dysfunction	LVEF > 53%, abnormal strain and/or biomarkers	LVEF < 53%	LVEF < 53%	LVEF < 53% (usually much lower)
Symptoms	No symptoms	No symptoms	No symptoms	Symptomatic	Persistent NYHA IV
Key management considerations	Aggressive treatment of CV risk factors	Aggressive treatment of CV risk factors	Add ACE-I/ARBs, β-blockers as per established guidelines	Add aldosterone antagonists, with consideration of diuretics, digoxin, device therapy	Establish goals of care. If appropriate, consider inotropes, mechanical support, transplant
Area for further research	Prophylactic therapies such as dexrazoxane, ACE-I/ARBs, statins?	Protective therapies such as dexrazoxane, ACE-I/ARBs, statins?	Threshold for initiation of protective therapy (LVEF < 53% rather than 40%)	Therapy discontinuation in recovered patients?	Criteria for consideration for advanced therapies
Role of further cardiotoxic chemotherapy†	Continue	Continue	Personalized decision making, with preference for continuation or temporary discontinuation	Personalized decision making, with preference for interruption	Discontinue

ACC, American College of Cardiology; ACE-I, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; CV, cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

* Stage B-1 as defined in this table is not part of the ACC/AHA stages of HF.

† These recommendations are predominantly based on experience with patients with breast cancer receiving cancer treatment.

Table 2 Factors associated with risk of cardiotoxicity following treatment with anthracyclines[a]

Risk factors
• Cumulative dose • Female sex • Age - >65 years old - Paediatric population (<18 years) • Renal failure • Concomitant or previous radiation therapy involving the heart • Concomitant chemotherapy - alkylating or antimicrotubule agents - immuno- and targeted therapies • Pre-existing conditions - Cardiac diseases associating increased wall stress - Arterial hypertension - Genetic factors

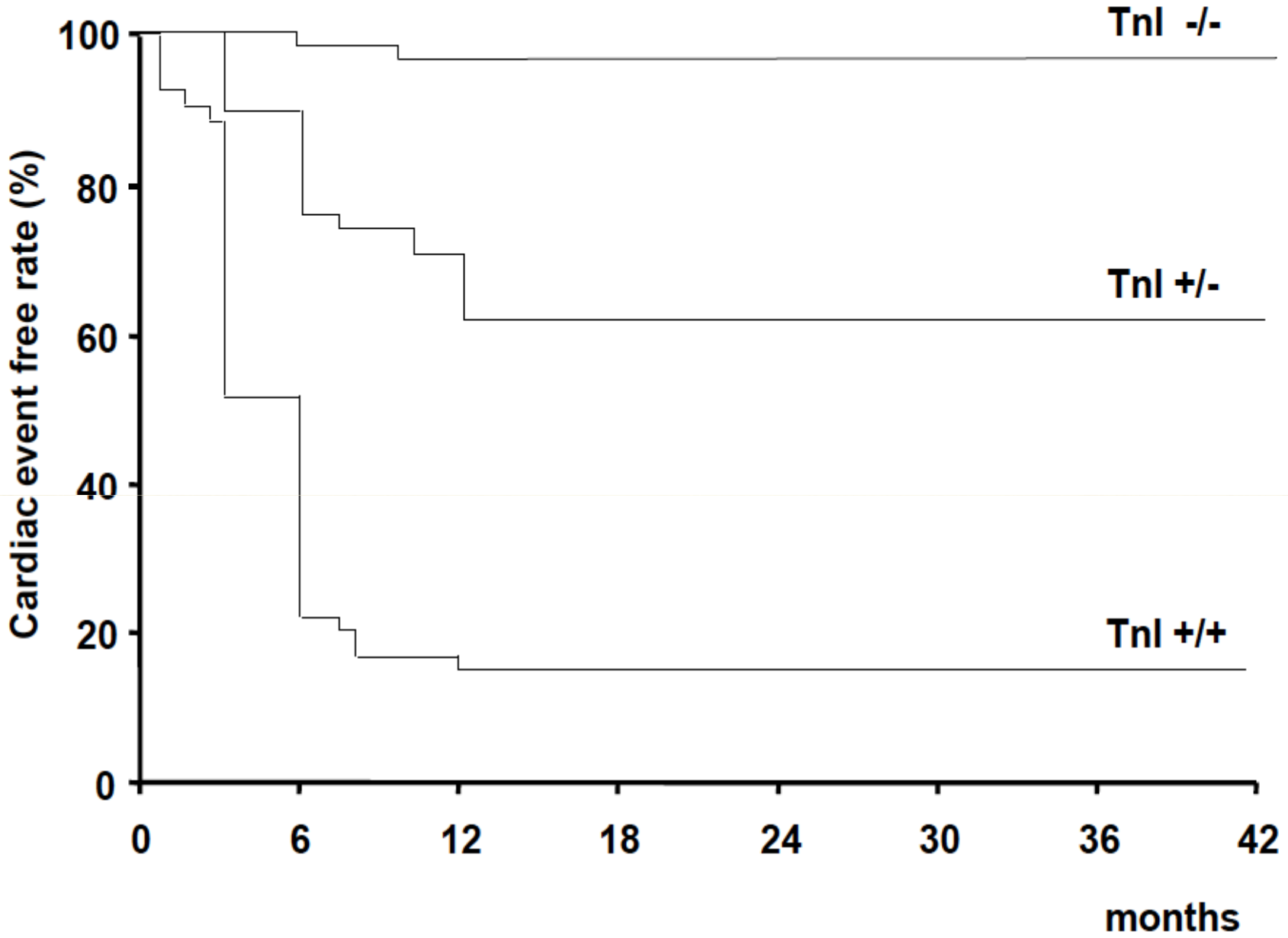
[a]Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).

European Heart Journal Advance Access published August 26, 2016
European Heart Journal
doi:10.1093/eurheartj/ehw211
ESC CPG POSITION PAPER

Tabela 4 – Fatores de risco para cardiotoxicidade associada às antraciclinas

Fatores de risco	Risco aumentado no caso de	
Idade	Menor idade	
Sexo	Feminino	
Modo de administração	Injeção rápida	
Dose cumulativa	Excedendo a dose cumulativa de:	
	Daunorrubicina	550-800 mg/m²
	Doxorrubicina	400-550 mg/m²
	Epirrubicina	900-1.000 mg/m²
	Idarrubicina	150-225 mg/m²
Irradiação mediastinal	Irradiação mediastinal precoce ou concomitante	
Doenças cardiovasculares prévias	Hipertensão arterial, doença coronária	
Distúrbios eletrolíticos	Hipocalcemia, hipomagnesemia	

I Diretriz Brasileira de Cardio-Oncologia da Sociedade Brasileira de Cardiologia



Circulation 2004;109:2749-54

Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy

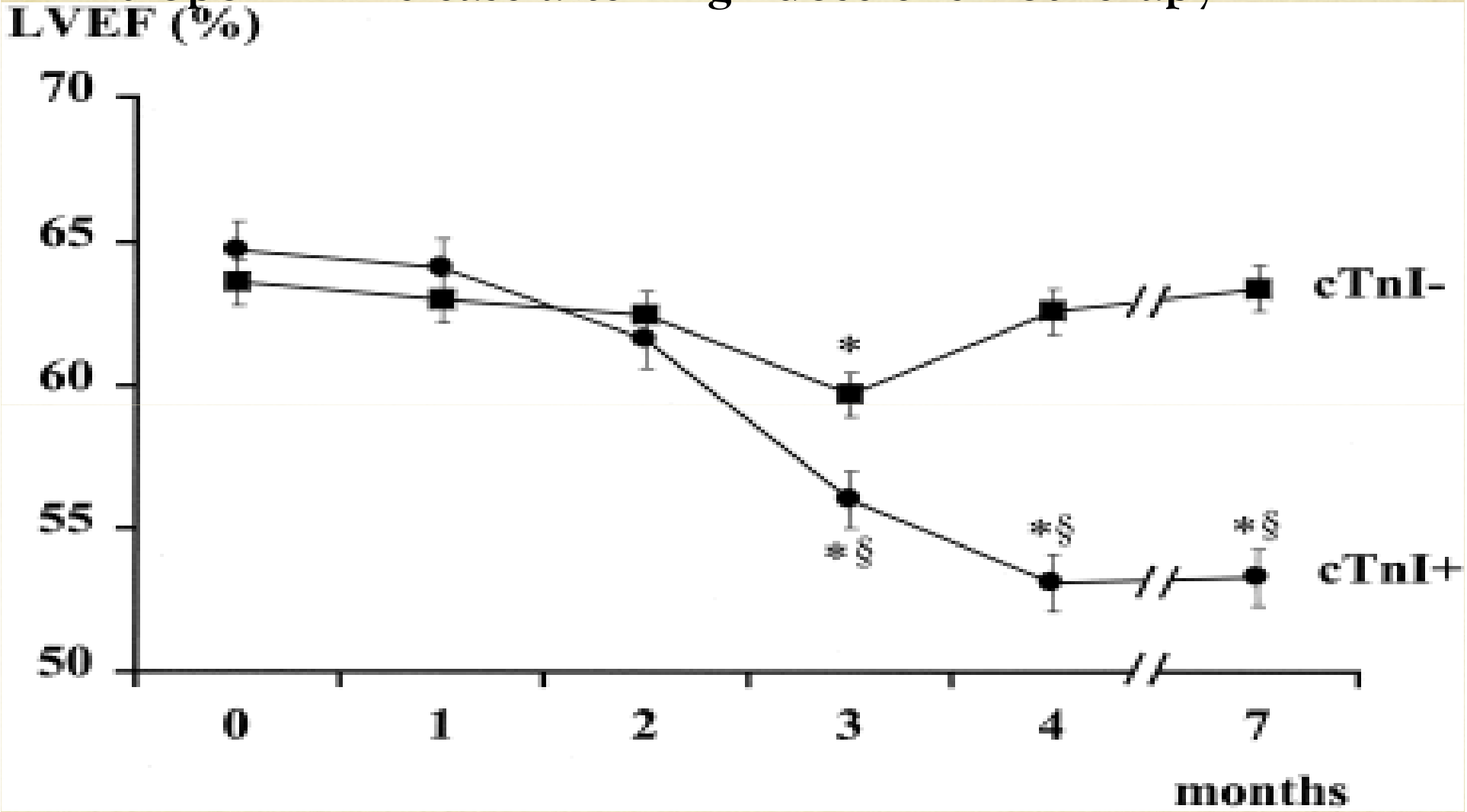


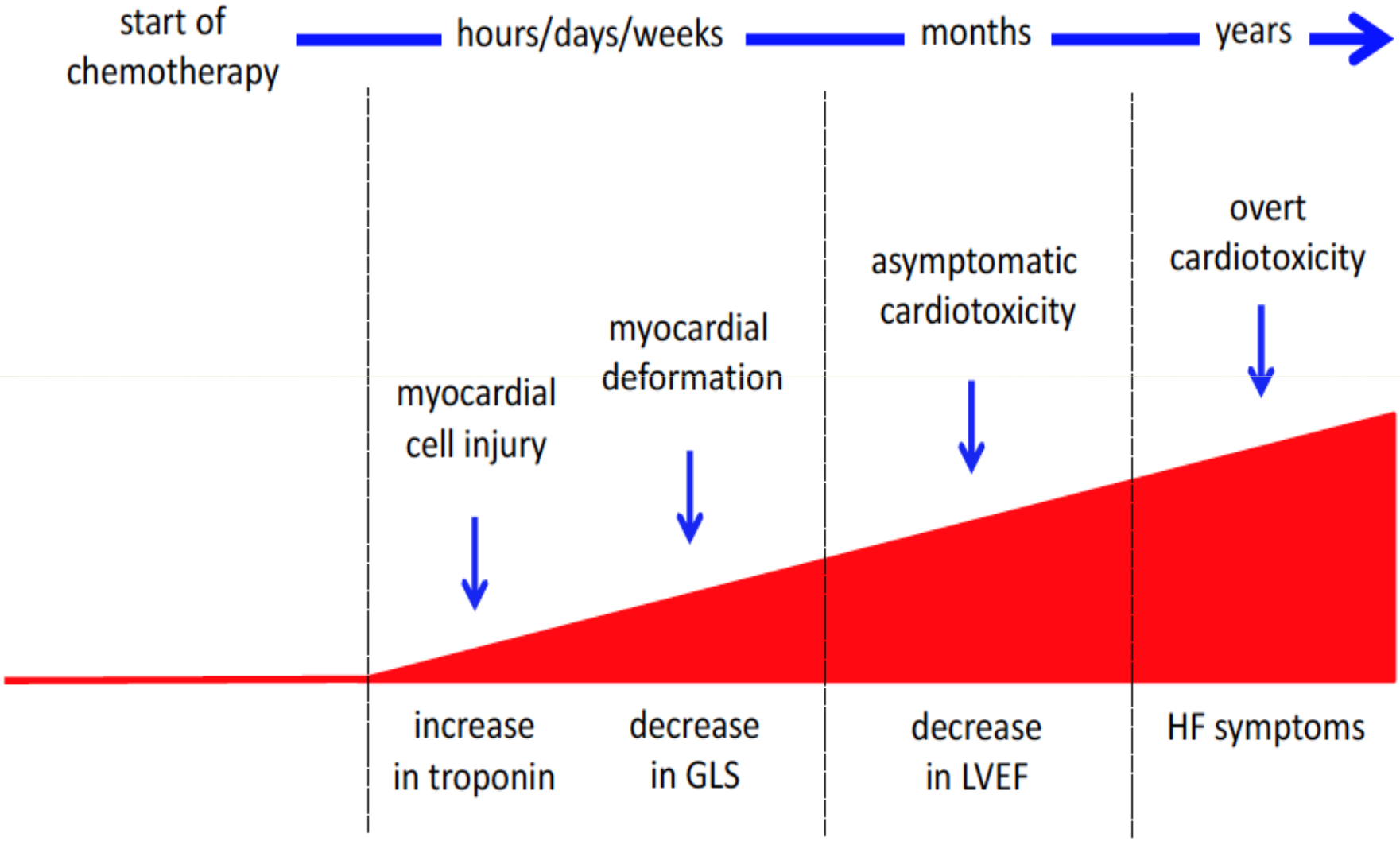
Figure 2. Left ventricular ejection fraction (LVEF) at baseline and during the seven months of follow-up of troponin I positive (cTnI+; solid circle) and negative (cTnI–; solid square) patients. ∗p < 0.001 vs. baseline (month 0); §p < 0.001 vs. cTnI– gro...

Journal of the American College of Cardiology, Volume 36, Issue 2, 2000, 517–522

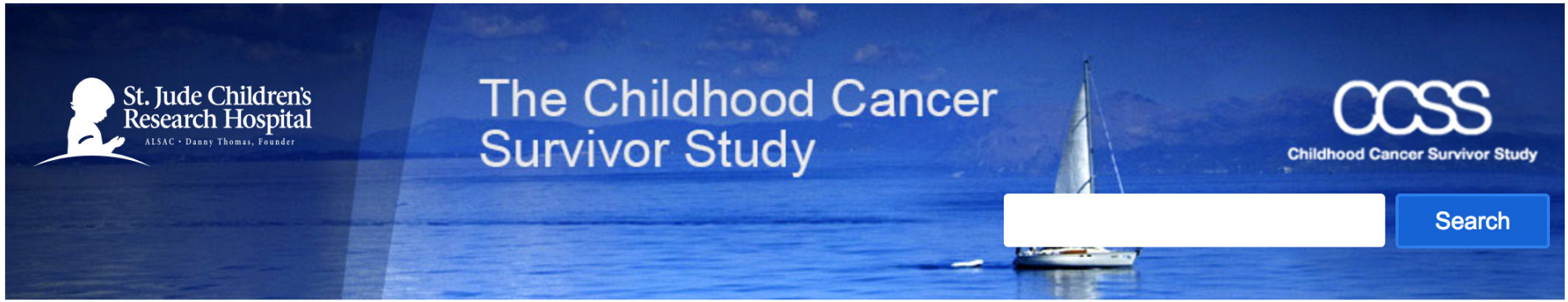
Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: - 3D-based LVEF - 2D Simpson's LVEF - GLS	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: - Troponin I - High-sensitivity Troponin I - BNP - NT-proBNP	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

European Heart Journal Advance Access published August 26, 2016
European Heart Journal
doi:10.1093/eurheartj/ehw211
ESC CPG POSITION PAPER



Curr Cardiol Rep 2016;18:51.



CCSS CHF Risk Calculator

This risk assessment tool predicts risk of congestive heart failure (CHF) by age 40 among survivors of childhood cancer. It uses information from the CCSS paper, "Individual prediction of heart failure among childhood cancer survivors" (Chow et al., ...), which created clinically useful models with readily available demographic and cancer treatment information. These models were designed specifically for patients who have recently completed cancer treatment (5 years from cancer diagnosis). These models have been validated in 3 separate groups of childhood cancer survivors: Emma Children's Hospital and Academic Medical Center (Amsterdam, the Netherlands), the National Wilms Tumor Study, and the St. Jude Lifetime Cohort Study.

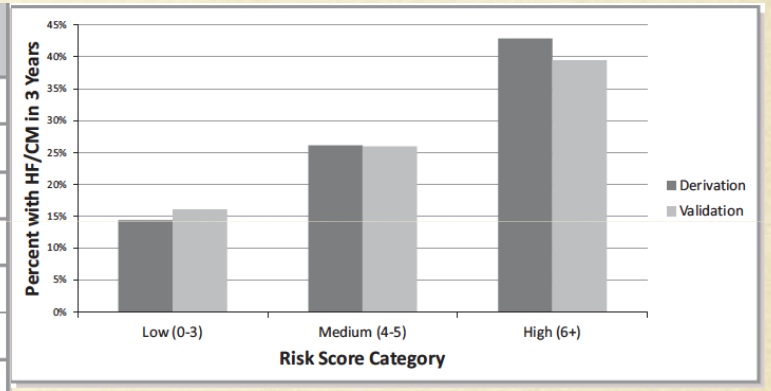
Depending on what level of treatment information is available, we created three different prediction models:

- Simple (if anthracycline and chest radiation exposures are known, but not the doses)
- Standard (if anthracycline and chest radiation doses are known)
- Standard+heart (if anthracycline dose and heart-specific radiation dosimetry are known)

Risk Prediction Model for Heart Failure and Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer

Ghideon Ezaz, MD, MPP; Jessica B. Long, MPH; Cary P. Gross, MD; Jersey Chen, MD, MPH

Risk Factor	Hazard Ratio (95% Confidence Interval)	Regression Coefficient	*P* Value	Points Assigned
Adjuvant therapy				
Anthracycline chemotherapy	1.93 (1.11 to 3.36)	0.66	0.020	2
Non-anthracycline chemotherapy	1.64 (0.99 to 2.73)	0.50	0.055	2
No identified chemotherapy	Reference	Reference		
Age category, y				
67 to 74	Reference	Reference		
75 to 79	1.36 (0.92 to 2.01)	0.31	0.125	1
80 to 94	2.04 (1.29 to 3.24)	0.71	0.003	2
Cardiovascular conditions and risk factors				
Coronary artery disease	2.16 (1.21 to 3.86)	0.77	0.009	2
Atrial fibrillation/flutter	1.69 (0.98 to 2.91)	0.53	0.058	2
Diabetes mellitus	1.50 (1.03 to 2.18)	0.41	0.034	1
Hypertension	1.44 (0.99 to 2.08)	0.36	0.054	1
Renal failure	1.99 (0.96 to 4.14)	0.69	0.065	2



J Am Heart Assoc. 2014;3:e000472

Table 2 Risk assessment and monitoring associated with left ventricular dysfunction

Patient-related risk factors	Medication-related risk factor[a]
1 point for each risk factor present	***High (risk score 4):*** Anthracyclines, Trastuzumab, Ifosfamide, Cyclophosphamide, Clofarabine
Age (bimodal distribution): <15 or > 65 years	***Intermediate (risk score 2):*** Docetaxel, Pertuzumab, Sunitinib, Sorafenib
Female	***Low (risk score 1):*** Bevacizumab, Imatinib, Lapatinib, Dasatinib
Hypertension	***Rare (risk score 0):*** Etoposide, Rituximab, Thalidomide
Diabetes Mellitus	
Atherosclerosis (coronary artery disease, cerebrovascular disease, peripheral artery disease)	
Preexisting heart disease or heart failure	
Prior anthracycline	
Prior radiation therapy to the chest	

Cardiotoxicity Risk Score (CRS)

Medication-related risk score + number of patient-related risk factors = *CRS >6*: very high; *CRS 5-6*: high; *CRS 3-4*: intermediate; *CRS 1-2*: low; *CRS 0*: very low

Mayo Clinic monitoring recommendations

Very high risk: Echocardiogram with GLS before every (other) cycle, end, 3-6 months and 1 year. Optional ECG, cTn with echocardiogram during chemotherapy

High risk: Echocardiogram with GLS every 3 cycles, end, 3-6 months and 1 year after treatment. Optional ECG, cTn with echocardiogram during chemotherapy

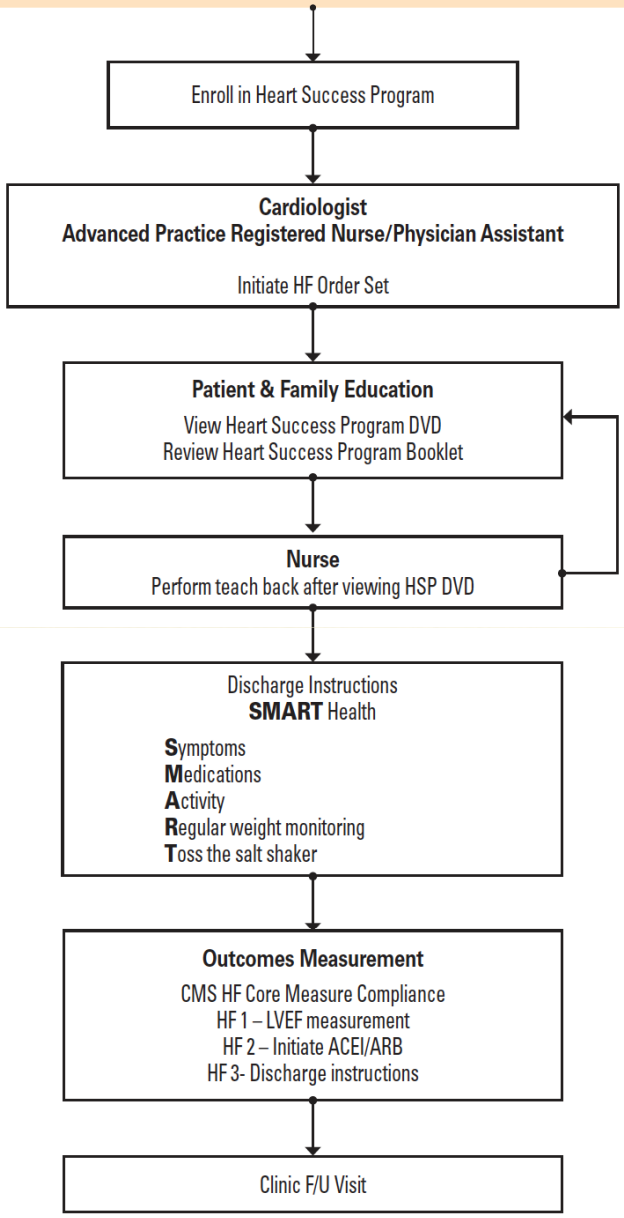
Intermediate risk: Echocardiogram with GLS, mid-term, end and 3-6 after treatment. Optional ECG, cTn mid-term of chemotherapy

Low risk: Optional echocardiogram with GLS and/or ECG. cTn at the end of treatment

Very low risk: None

Risk assessment, cardiotoxicity risk score at the time of baseline assessment, and monitoring for patients undergoing anticancer therapy. ECG indicates electrocardiogram; GLS, global longitudinal strain; cTn, serum cardiac troponin. From Herrmann J et al. [21], with permission. [a]Medication-related risk factor (1-4) was based on the risk for a decline or dysfunction in the ventricular function. Bold to emphasize the most

CHEMOTHERAPY-INDUCED HEART FAILURE



Symptoms

Call your doctor if you have any of the following symptoms:

- Trouble breathing or shortness of breath
- Swelling in your abdomen, legs, or feet
- Racing heartbeat
- Increased weakness or tiredness
- Dizziness, lightheadedness, or restlessness
- Chest pain

Medicines

- Take your medicines at the same time every day as prescribed.
- Do not skip doses, even if you are not feeling well.
- Do not stop taking your medicines without talking to your doctor or nurse.
- Bring your medicines when you come for your clinic visits.

Activity

- Follow your doctor's instructions about physical activity.
- Set up an exercise plan that includes activities that you enjoy.
- Stop and rest if you feel tired or short of breath.
- Be active every day. Try taking the stairs or walking for short periods.

Regular Weight Monitoring

- Weigh yourself every morning at the same time, on the same scale, and with the same amount of clothing.
- Call your doctor or nurse if you gain more than two pounds in one day for two consecutive days or more than five pounds in one week.

Toss the Salt Shaker

- Use salt sparingly, no more than 2 grams per day.
- Read food labels so you will know how much salt is in the food you eat.
- Eat plenty of fresh fruits and vegetables (unless you have restrictions).

References

Bradley EH, Curry L, Horwitz LI, et al. Hospital strategies associated with 30-day readmission rates for patients with heart failure. Circ Cardiovasc Qual Outcomes 2013;6:444-50.

Ewer MS, Swain SM, Cardinale D, et al. Cardiac dysfunction after cancer treatment. Tex Heart Inst J 2011;38:248-52.

Fadol, A. Importance of a heart failure disease management program for chemotherapy-induced toxicity. Am J Manag Care 2015;21:SP261-2.

Fadol AP, Adornetto-Garcia D, Shelton V, Durand JB, Yeh ETH, Summers BL. Heart success program: an interdisciplinary patient-centered approach to cancer patients with concurrent heart failure. Prog Pediatr Cardiol 2015 [E-pub ahead of print]; http://dx.doi.org/10.1016/j.ppedcard.2015.10.007.

Fadol, AP. Heart failure in patients with cancer. In: Fadol AP, editor. Cardiac Complications of Cancer Therapy. Pittsburg, PA: Oncology Nursing Society, 2013:159-88.

Hauptman PJ, Rich MW, Heidenreich PA, et al. The heart failure clinic: a consensus statement of America. J Card Fail 2008;14:801-15.

Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA Diagnosis and Management of Heart Failure in Adults: a report of the American College of C American Heart Association Task Force on Practice Guidelines Developed in Collaboration w for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1-90.

Kociol RD, Peterson ED, Hammill BG, et al. National survey of hospital strategies to reduce findings from the Get With the Guidelines-Heart Failure Registry. Circ Heart Fail 2012;38:248

Schillinger D, Piette J, Grumbach K, et al. Closing the loop: physician communication with di health literacy. Arch Intern Med 2003;163:83-90.

Yeh ETH, Bickford C. Cardiovascular complications of cancer therapy: incidence, pathogenes management. J Am Coll Cardiol 2009;53:2231-47.

MD Anderson Practices In Onco-Cardiology

Edward T. H. Yeh, M.D., F.A.C.C.

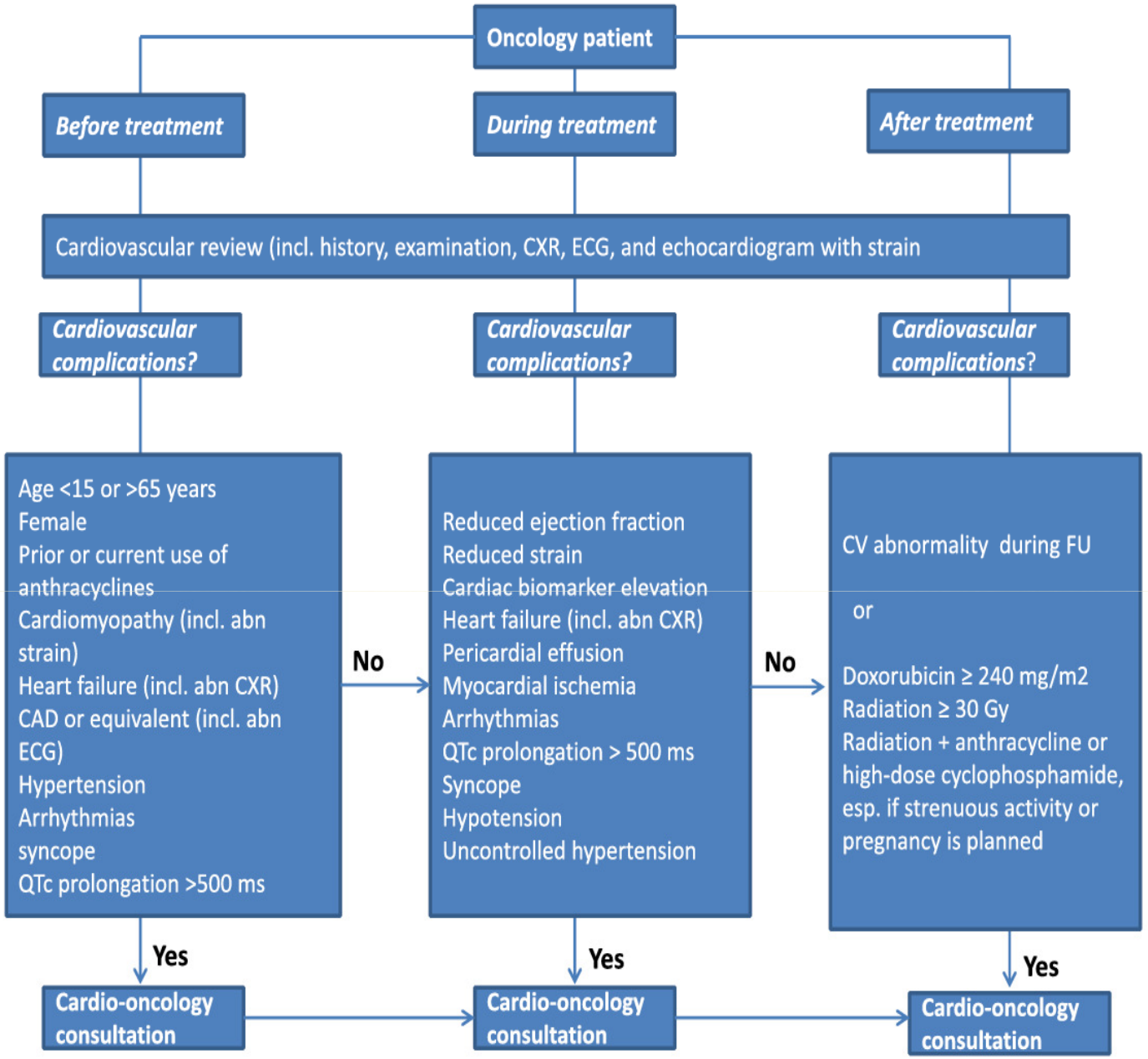
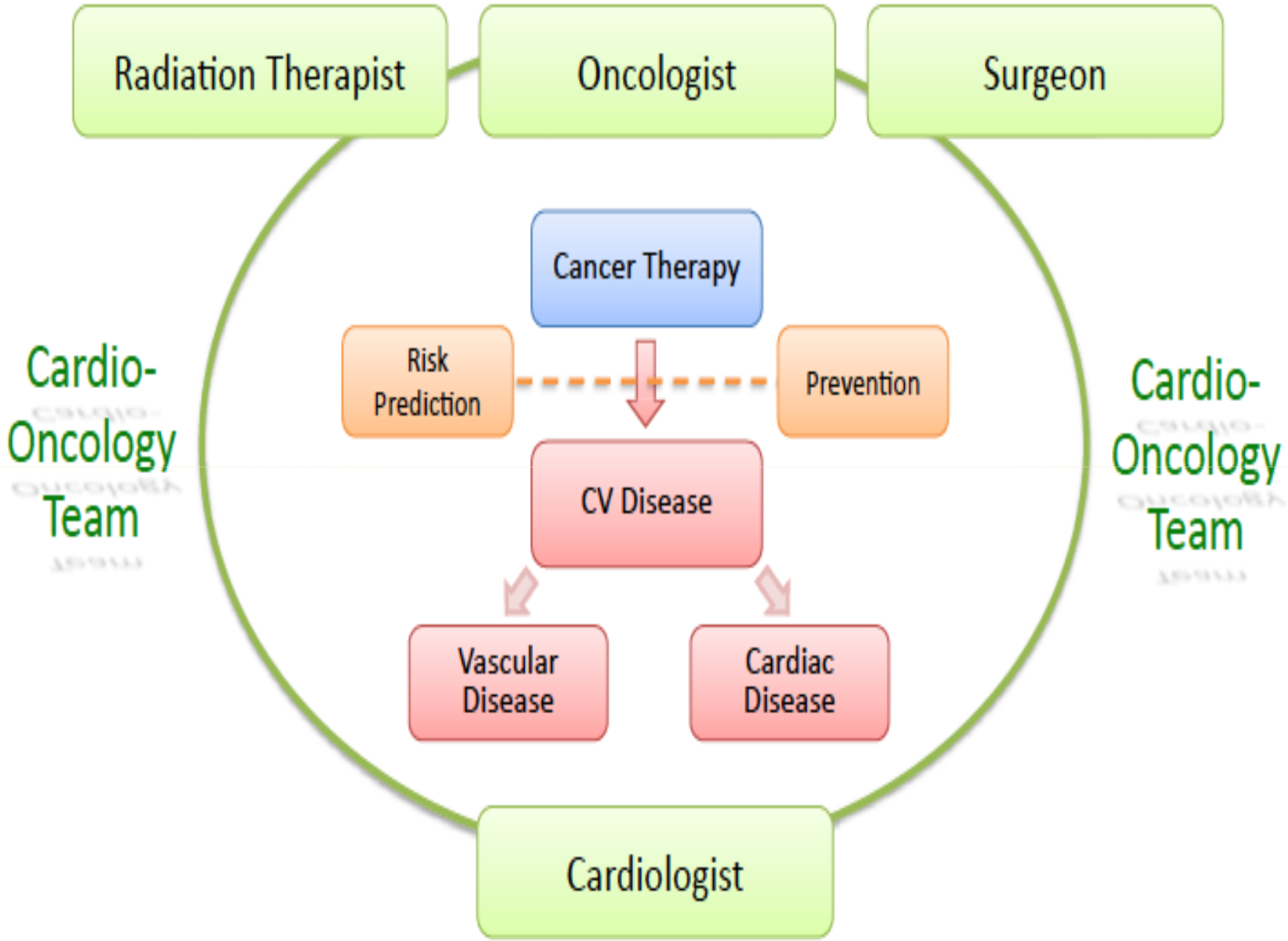


Fig. 4 Cardio-Oncology General Practice. Figure depicts our general cardio-oncology practice before, during and after chemo and/or radiation therapy (from Herrmann J et al. [21], with permission). abn indicates abnormal; CAD coronary artery disease; CXR, chest x-ray; ECG, electrocardiogram; QTc, corrected QT



Heart Failure Clin 13 (2017) 347–359

"The cured cancer patient of today does not want to become the heart failure patient of tomorrow."

Eschenhagen T et al. Eur J of Heart Fail 2011; 3:1-10

GRUPO BRASILEIRO DE CARDIO-ONCOLOGIA

caroltheᵃhotmail.com