Cardio-Oncology: Core Concepts

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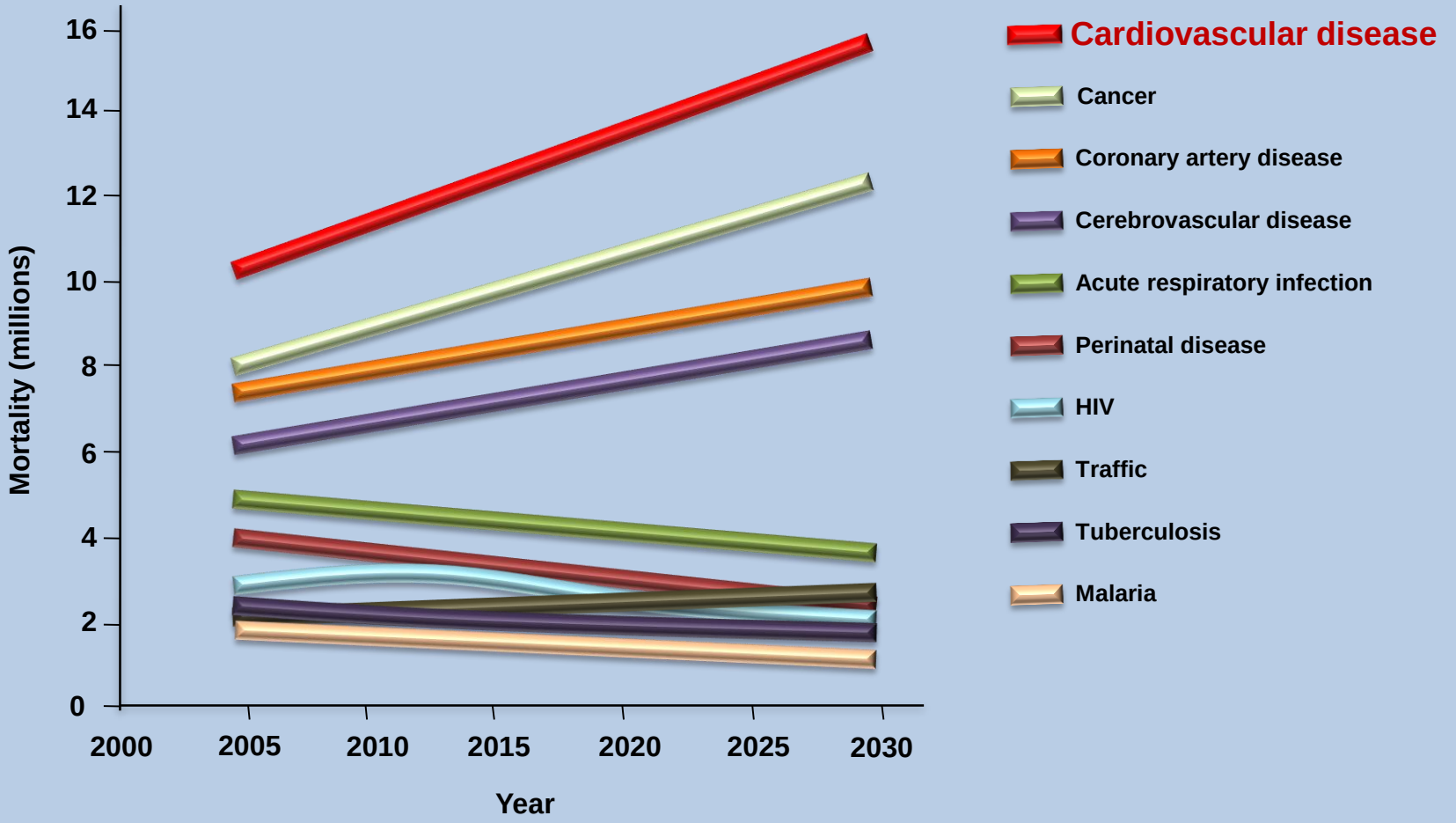
Cancer and cardiovascular diseases as the main causes of mortality

Global mortality, 2004-2030



Adaptado de World Health Statistics 2007
www.who.int/entity/whosis/whostat2007_10highlights.pdf

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Overlapping between cardiovascular disease and cancer

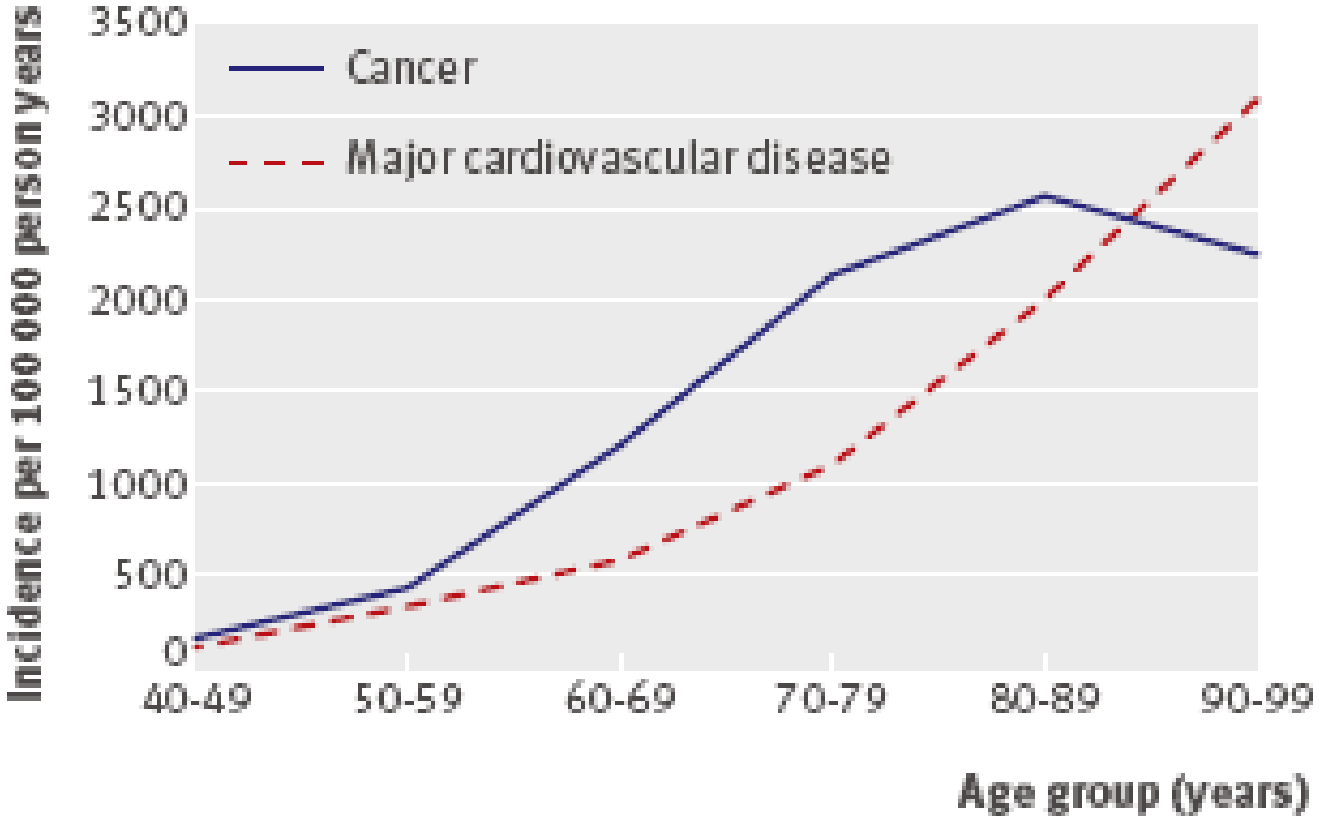

Fig 1 | Crude incidence of overall cancer and major cardiovascular disease by age

Driver BMJ 2008:337:p. 2467

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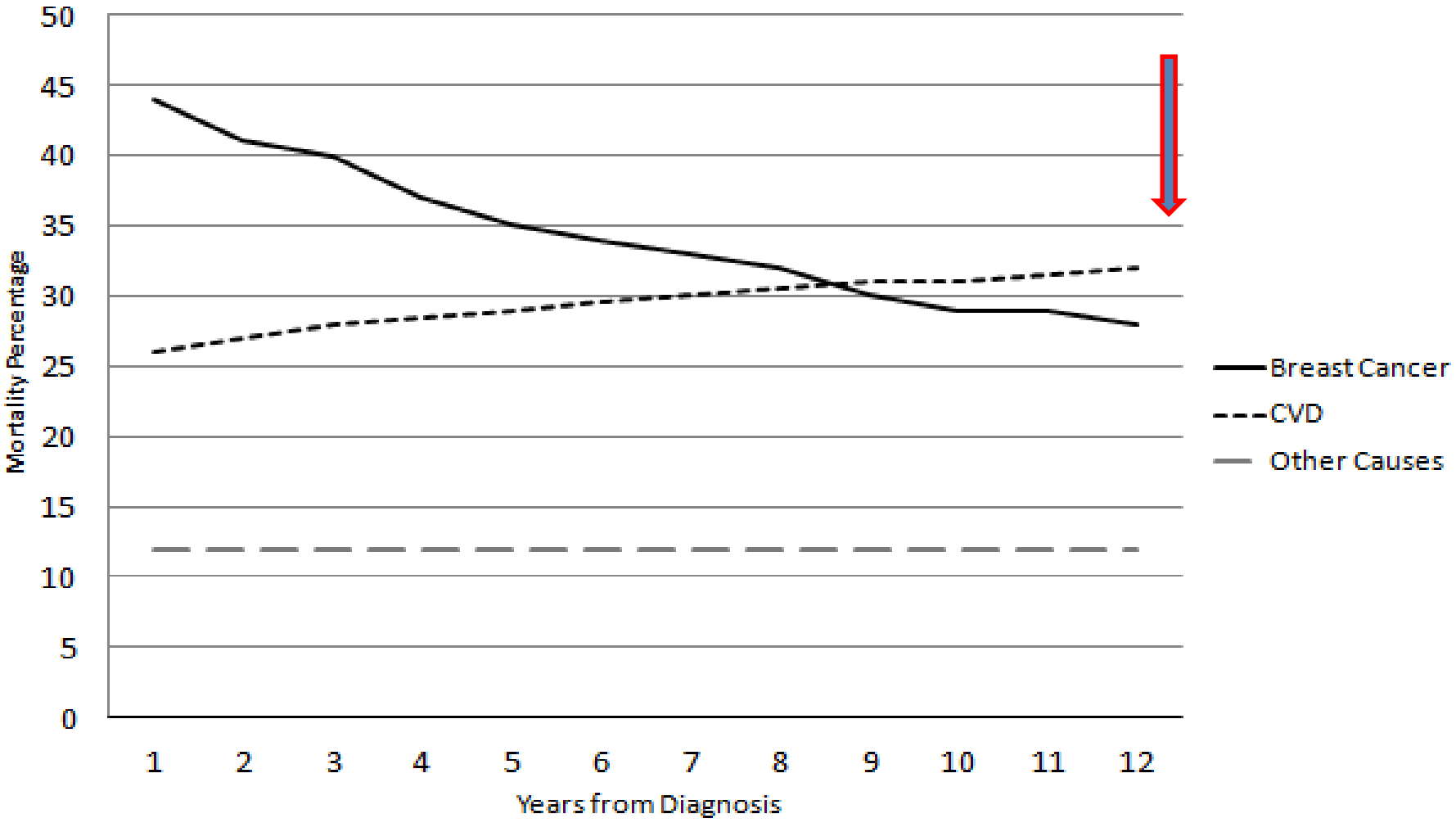
Cardiovascular Disease:

Important cause of mortality in early breast cancer



Patnaik et al. *Breast Ca Res*, 2011

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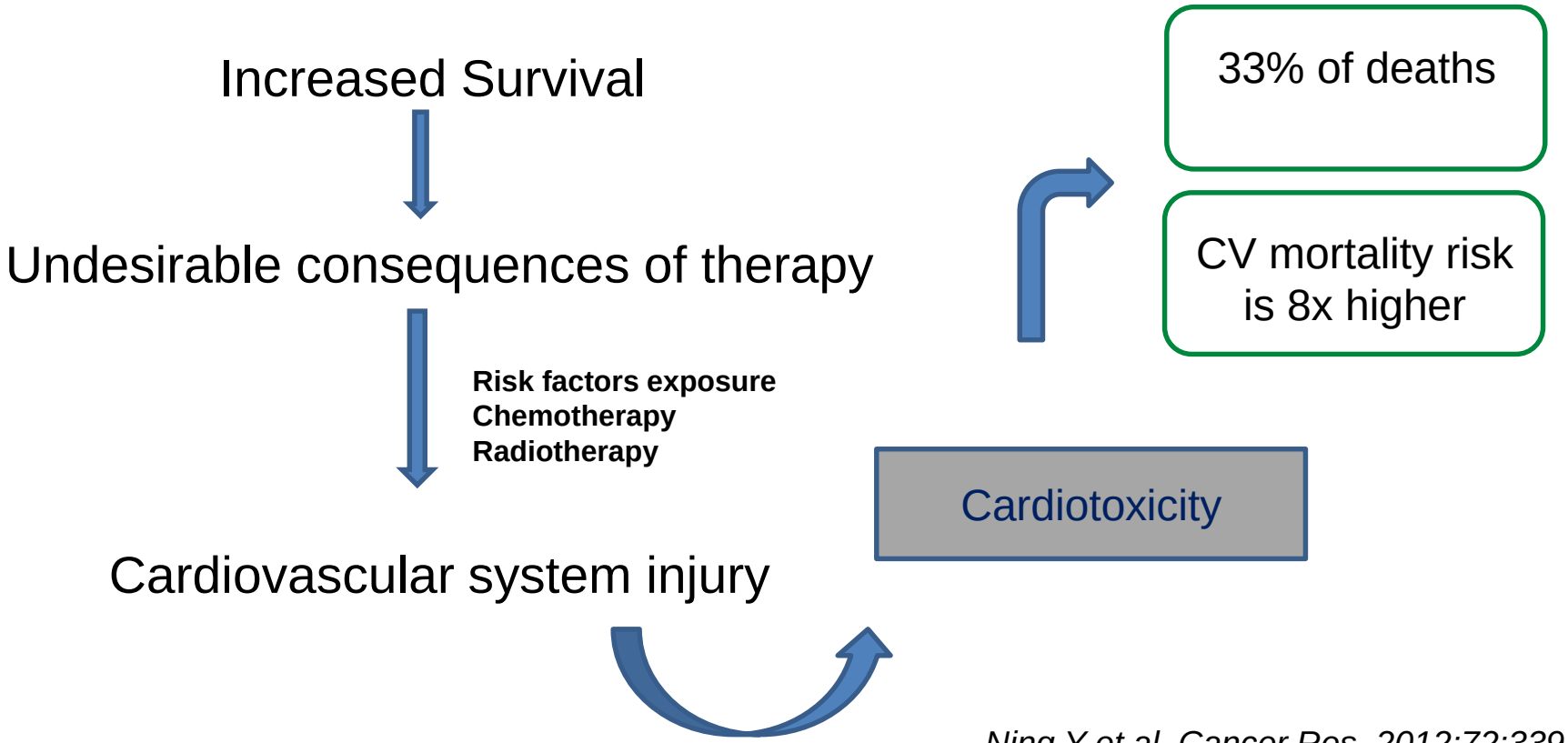
Goals of cancer therapy:

a. Promote cure and avoid recurrence
b. Promote improvement in quality of life



Ning Y et al. Cancer Res. 2012;72:339.

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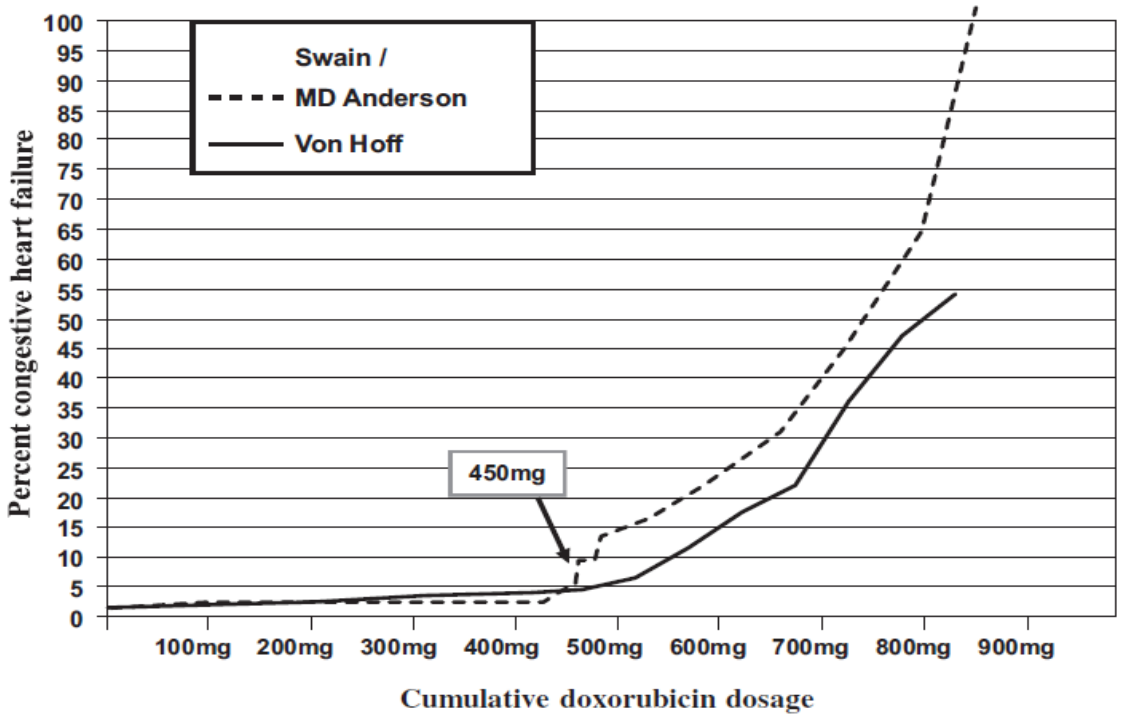
Daniel D. Von Hoff

Risk Factors for Doxorubicin-Induced Congestive Heart Failure

DANIEL D. VON HOFF, M.D.; MAXWELL W. LAYARD, Ph.D.; PETER BASA, B.S.; HUGH L. DAVIS, Jr., M.D.; ANN L. VON HOFF, M.A.;



Ann Intern Med. 1979;91:710-7.

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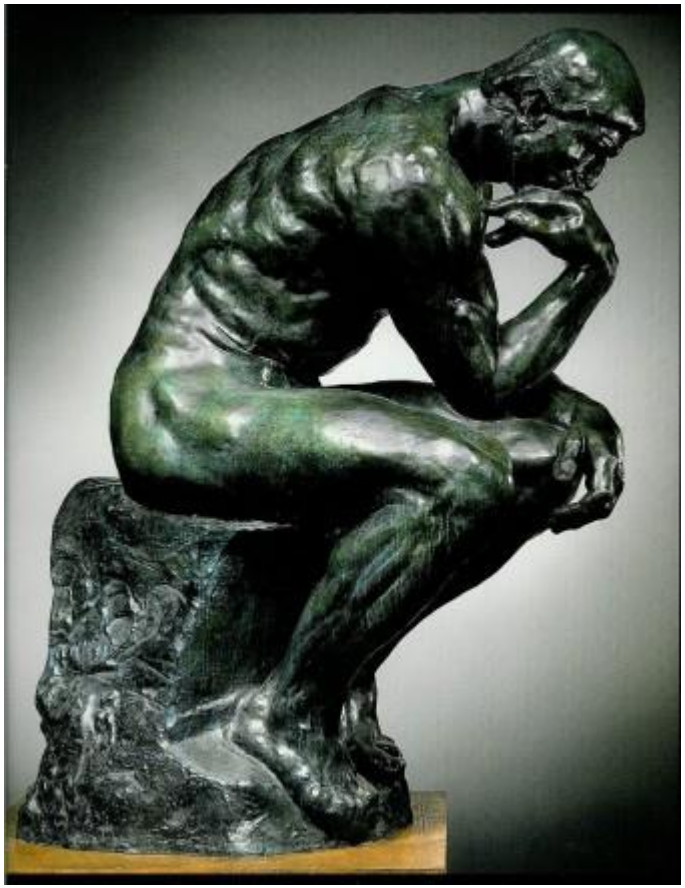


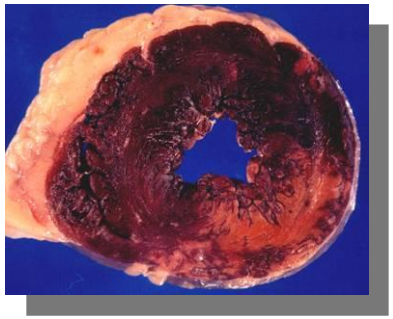
Le penseur, 1904
Auguste Rodin

Cardio-oncology

- Time of injury is known
- We understand the injury
- We can apply strategies to avoid

Improve outcomes

Definition of Cardiotoxicity



1. Any cardiovascular alterations induced by chemotherapy

- **Clinical abnormality**
- **Positive biomarkers**
- **Altered imaging (ECHO, STRAIN, MR, CT, PET)**

2. Reduction of at least 10% of EF to less than 50%.

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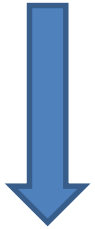
Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m^2 550 mg/m^2 700 mg/m^2	 3–5 7–26 18–48
Idarubicin (>90 mg/m^2)	5–18
Epirubicin (>900 mg/m^2)	0.9–11.4
Mitoxanthone >120 mg/m^2	2.6
Liposomal anthracyclines (>900 mg/m^2)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m^2 12.5–16 g/m^2	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[28a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8

CARDIOTOXICITY



HEART FAILURE

Zamorano JL et al. European Heart Journal 2016.
Kalil Filho R et al. Arq Bras Cardiol 2016, In Press.

The real world incidence of HF with chemotherapy is higher than expected

Table 2: Cumulative Incidence of HF/CM during first three years after diagnosis, by cancer therapy

	All Cancer patients	A + T (N=431)	Anthracycline (N=5257)	Trastuzumab (N=437)	Other chemo (N=2712)	None (N=36700)
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

Per 100 patients if surviving for the full time, Poisson model used to measure significance.

* $p<0.001$ versus no adjuvant therapy group

† $p<0.001$ versus anthracycline group, only in model containing A+T and Anthracycline adjuvant therapy

‡ $p<0.05$ versus no adjuvant therapy group

Chen J, et al
JACC 2012

23% increased rate of developing HF compared to age matched controls

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CARDIOTOXICITY

Table 7 Pathophysiological mechanisms of coronary artery disease in cancer treatment[7,60,81,99,117–123]

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	• Endothelial injury • Vasospasm	• Up to 18% manifest myocardial ischaemia • Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	• Procoagulant status • Arterial thrombosis	• 20-year absolute risk of up to 8% after testicular cancer • 2% risk of arterial thrombosis
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	• Procoagulant status • Arterial thrombosis • Endothelial injury	• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiotherapy	• Endothelial injury • Plaque rupture • Thrombosis	• 2–7-fold increased relative risk of myocardial infarction • Cumulative 30-year coronary events incidence of 10% in Hogdkin lymphoma survivors • Risk proportional to irradiation dose

Zamorano JL et al. European Heart Journal 2016.
Kalil Filho R et al. Arq Bras Cardiol 2016, In Press.

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CARDIOTOXICITY

Table 8 Cancer drug agents associated with cardiac arrhythmias

Type of arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicine, epirubicine, 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.
Sinus tachycardia	Anthracyclines, carmustine.
Atrioventricular block	Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.
Conduction disturbances	Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.
Atrial fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.
Supraventricular tachycardias	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5-FU, methotrexate), bortezomib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine), arsenic trioxide, doxorubicin, interferons, IL-2, methothrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.
Sudden cardiac death	Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nilotinib, romidepsin.

Zamorano JL et al. European Heart Journal 2016.
Kalil Filho R et al. Arq Bras Cardiol 2016, In Press.

Classification of Cardiotoxicity

	Type I (anthracycline-like)	Type II (trastuzumab-like)
Cellular mechanism	Cells death	Cells dysfunction
Dose related	Cumulative	Not-cumulative
Reversibility	Permanent	Reversible

Kalil Filho R, Hajjar L, Bacal F, Hoff PM et al. Arq Bras Cardiol.2011;96:1-52.

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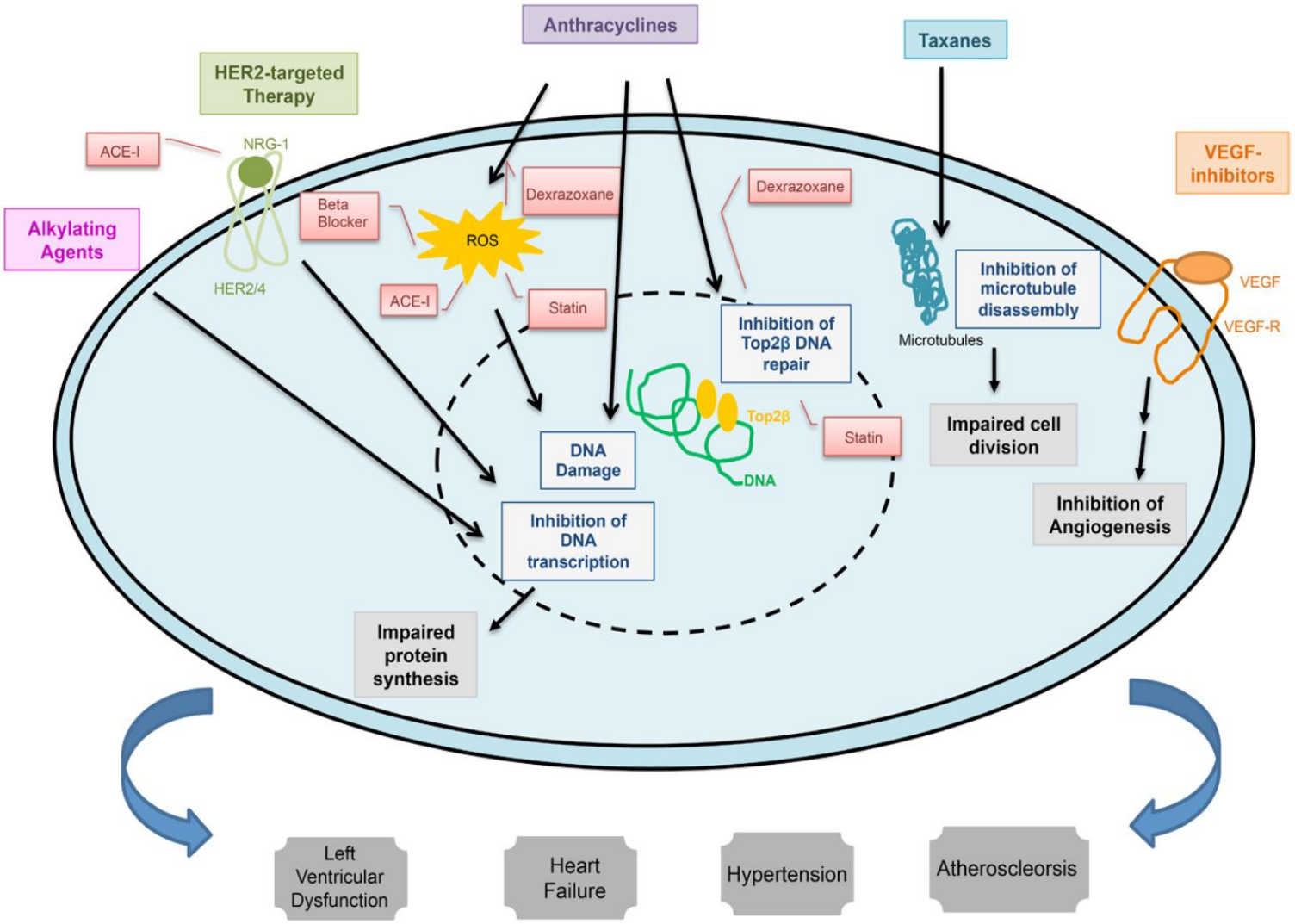

Circ Heart Fail. 2016;e002843.

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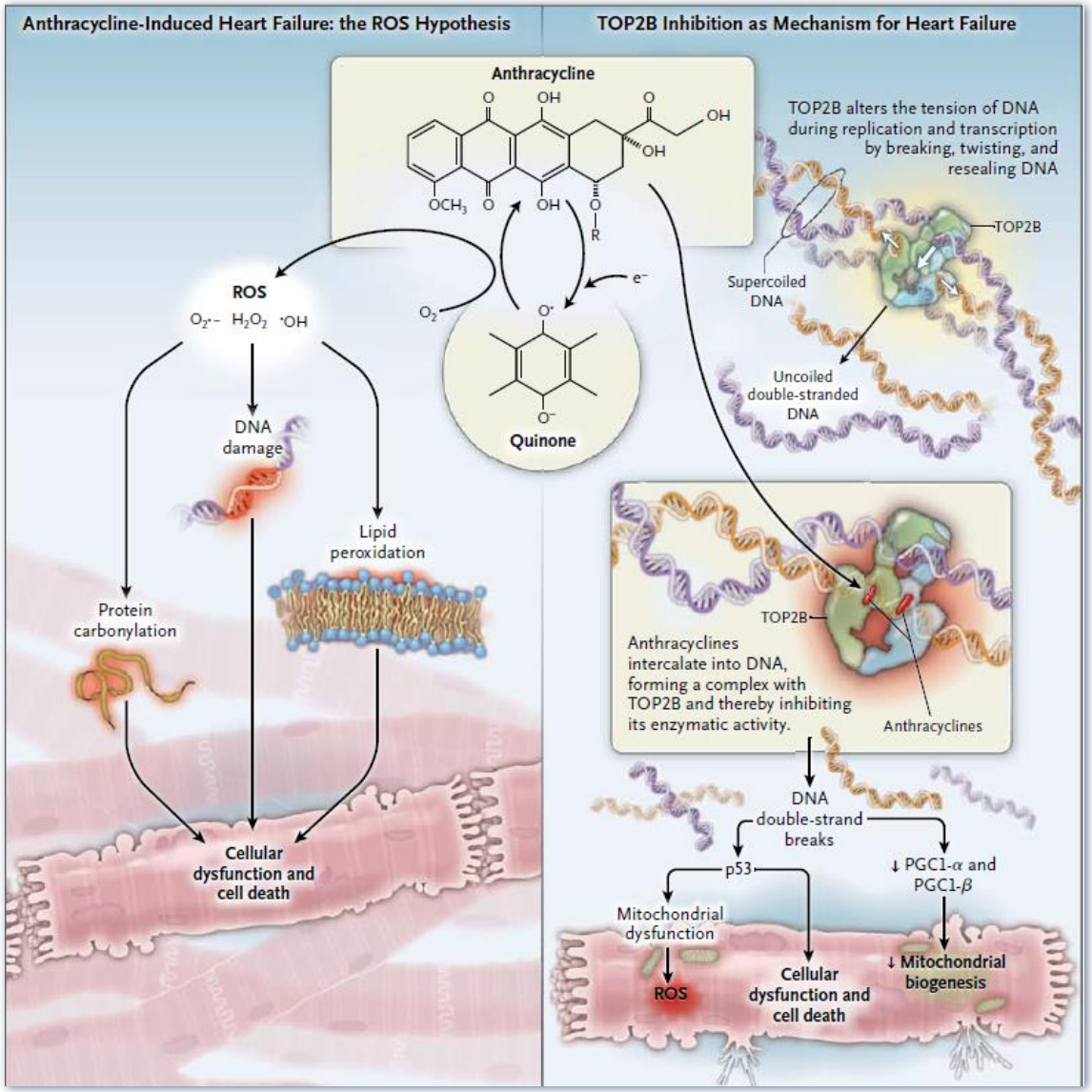
Anthracyclines



Sawyer D. N Engl J Med. 2013;368:12.

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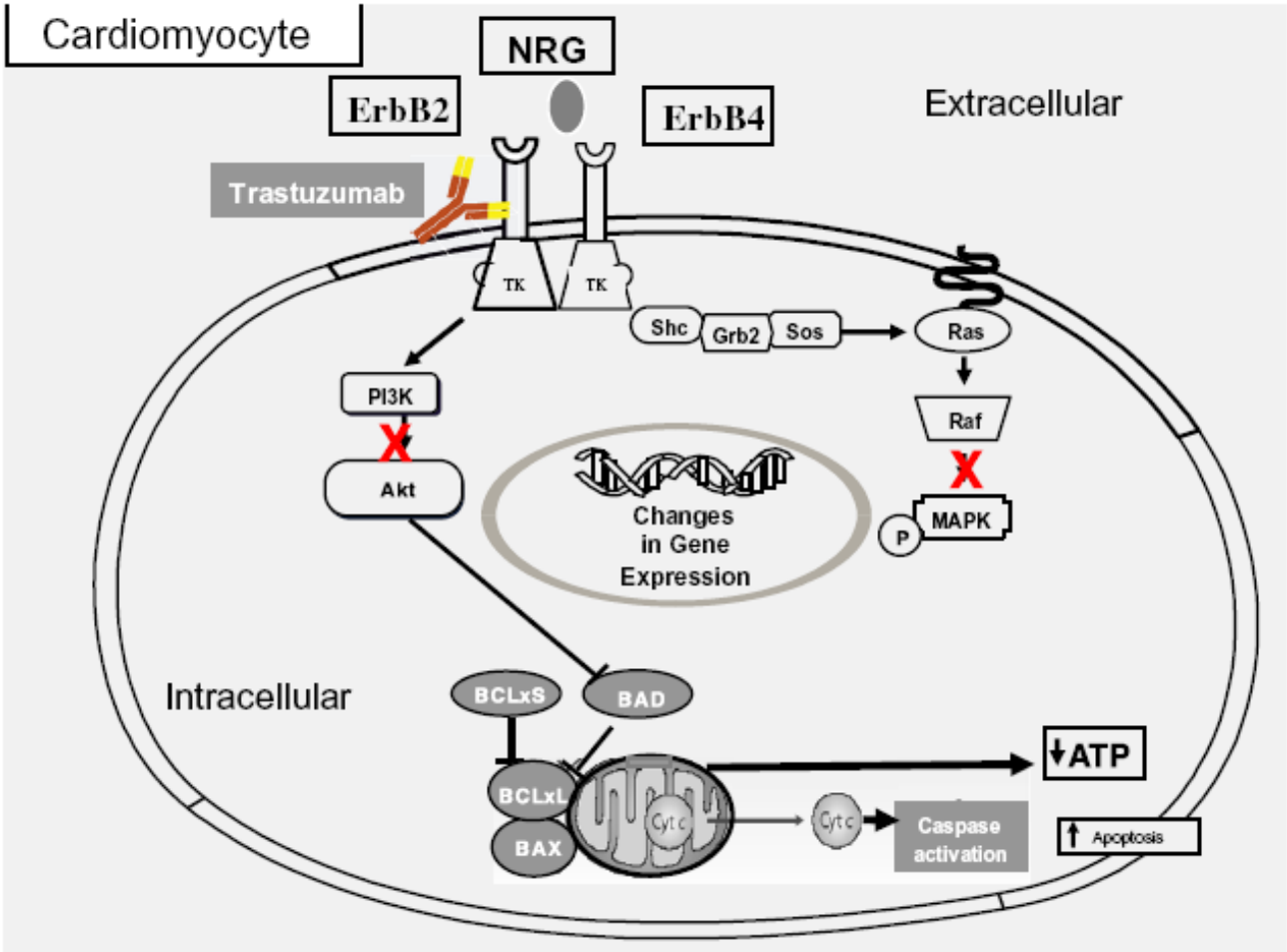
TRASTUZUMAB CARDIOTOXICITY



Inhibition of HER2 signalling by trastuzumab impairs all downstream events and affects mitochondrial integrity, in particular reversing BAD inhibition, leading to BAX oligomerization at the mitochondrial membrane. This results in ATP depletion and contractile dysfunction with minimal or no overt apoptosis (release of cytochrome-c and caspase activation). These molecular events occur without profound changes in cardiomyocyte ultrastructure.

Azim H et al. Cancer Treatment Reviews. 2009; 35:633-8.

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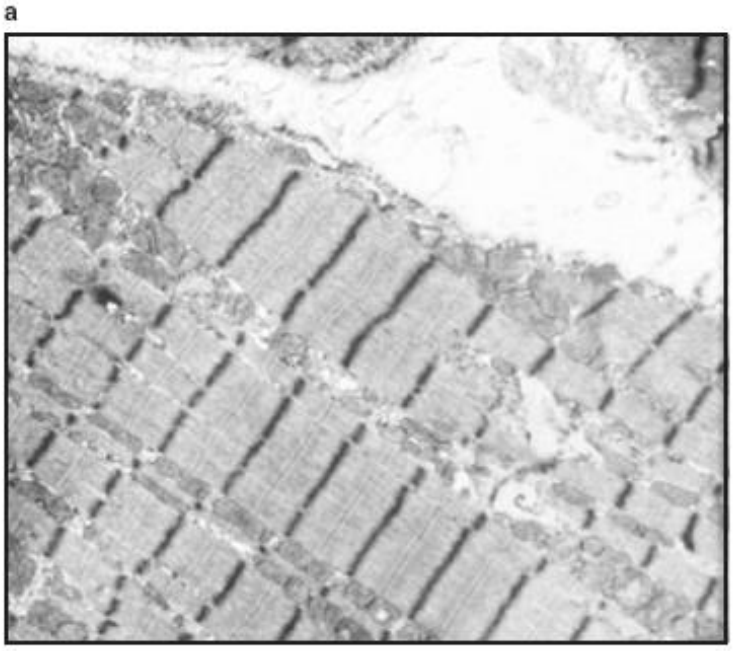
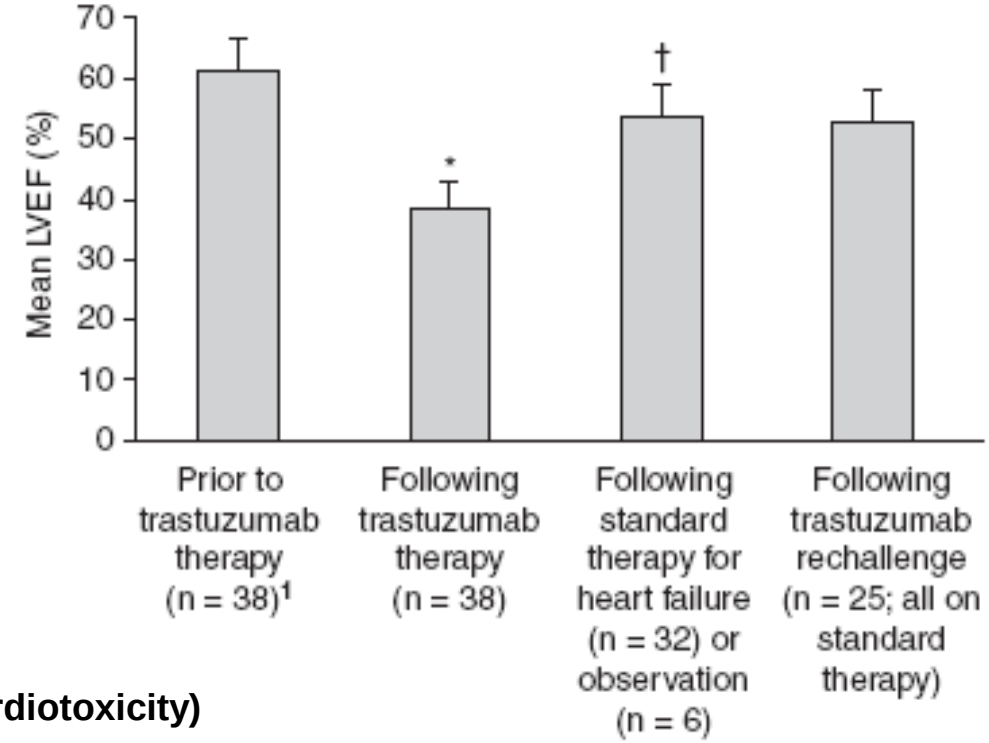
TRASTUZUMAB

1. No structural damage
2. Good outcomes
3. Exception: previous use of anthracycline

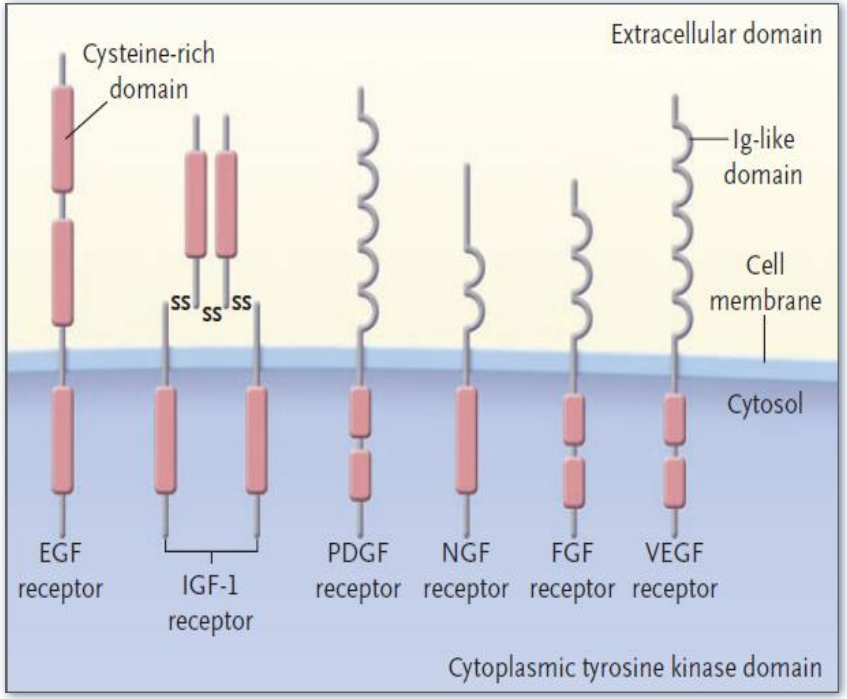


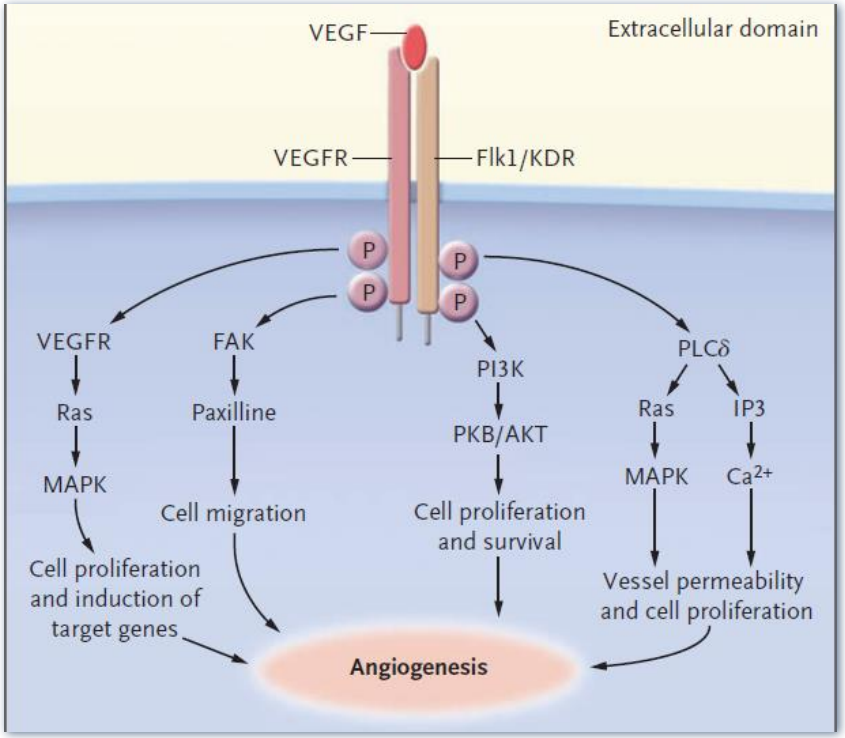
Eletronic microscopy: no lesions (Type II cardiotoxicity)



Ewer MS et al. J Clin Oncol. 2005; 23 (31):7820-6. Guarneri V et al. J Clin Oncol. 2006; 24 (25):4107-15.

Targeted chemotherapy = physiologic cardiac function





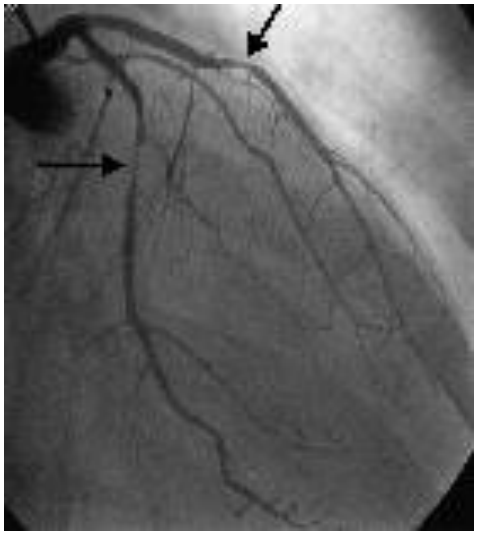
N ENGL J MED 358;5 WWW.NEJM.ORG JANUARY 31, 2008

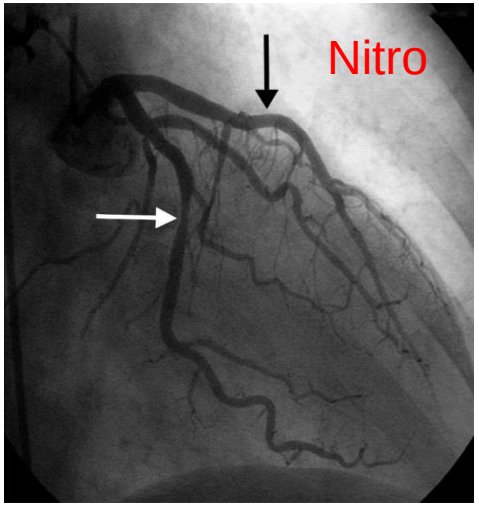
Antimetabolites (5-fluorouracil and capecitabine)

CARDIOTOXICITY

1. Vasospasm
2. Endothelial dysfunction
3. Procoagulant mechanisms
4. Myocarditis

Chest pain
EKG abnormalities
2-18%





Radiotherapy and cardiotoxicity (ESMO)

1. **Coronary arteritis – accelerated atherosclerosis – 10 to 15 years**
2. **Pericarditis – 6 to 12 months**
3. **Myocarditis and HF (fibrosis)**
4. **Valvular disease (mitral and aortic valves)**
5. **Conduction system fibrosis (AV Blocks)**

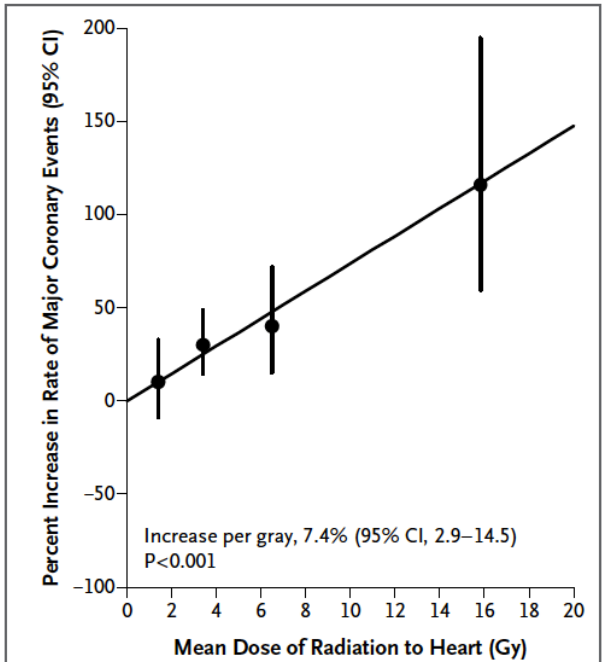
Prevention: new radiation techniques
Dose < 40 cGy

Annals of Oncology 21 (Supplement 5): v277–v282, 2010
doi:10.1093/annonc/mdq200

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



Factors associated with subsequent coronary event			<0.001
No known cardiac risk factors	353	600	1.00
History of ischemic heart disease‖	109	38	6.67**
Risk factors other than ischemic heart disease††	458	527	1.96**
Unknown	43	40	1.23

Darby et al. *NEJM*, 2013.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

The Cardiovascular Perils of Cancer Survivorship

Javid Moslehi, M.D.

- Important to put in context: radiation and cancer treatment have allowed breast cancer patients to become survivors in the first place
- Not enough focus in cardiovascular disease prevention
- Cardiovascular cancer survivorship issues begin at the time of diagnosis…not years after completion of treatment

Moslehi. *New England Journal of Medicine*, 2013.

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Diagnostic of cardiotoxicity

Table 4 Baseline risk factors for cardiotoxicity

Current myocardial disease	*Demographic and other CV risk factors*
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide[a]) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia
Previous cardiotoxic cancer treatment	***Lifestyle risk factors***
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

1. Clinical history
2. Physical examination
3. Individual risk analysis
4. Risk prediction

Prevention strategies
Follow-up
Therapeutic management

Zamorano JL et al. European Heart Journal 2016.
Kalil Filho R et al. Arq Bras Cardiol 2016, In Press.

Diagnostic of cardiotoxicity

IMAGE AND BIOMARKERS

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.

Zamorano JL et al. European Heart Journal 2016.
Kalil Filho R et al. Arq Bras Cardiol 2016, In Press.

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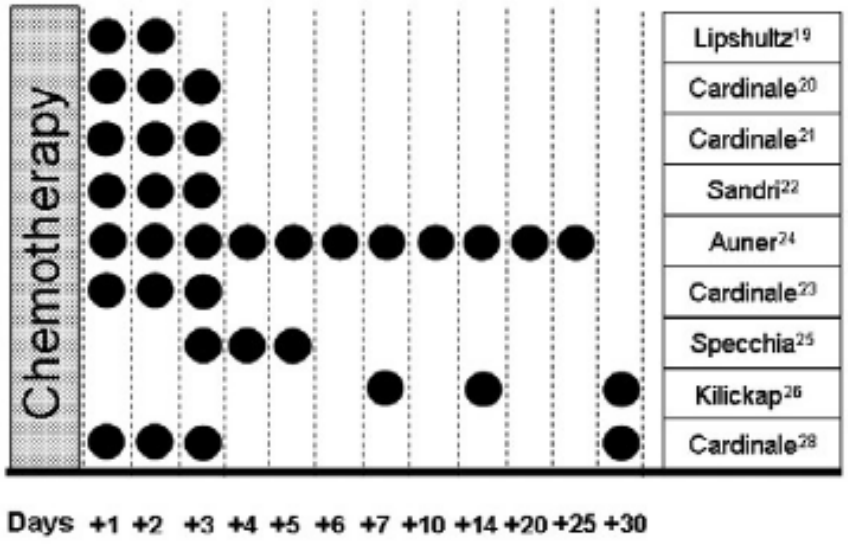
TROPONIN I positive after chemotherapy = ventricular dysfunction prediction
Troponin negative = 5% events Tropo positive = 62% events



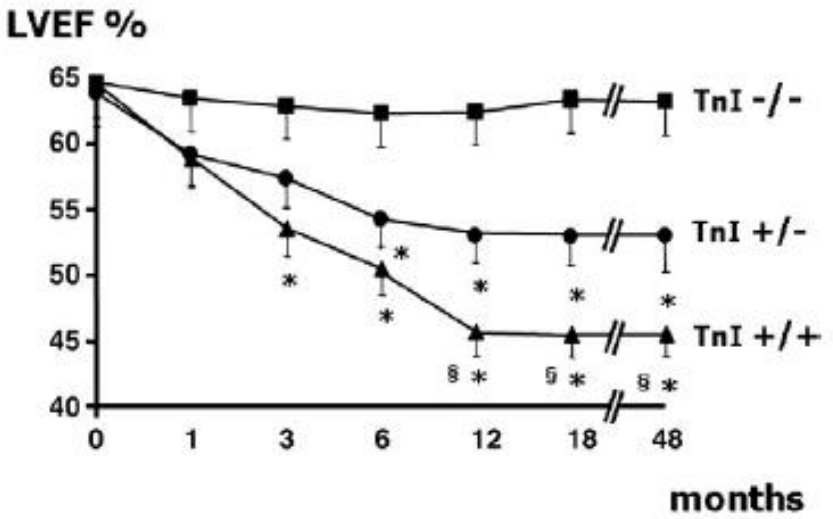


Fig 2. Timing for sampling troponins in different studies.

Progress in Cardiovascular Diseases 53 (2010) 121 – 129

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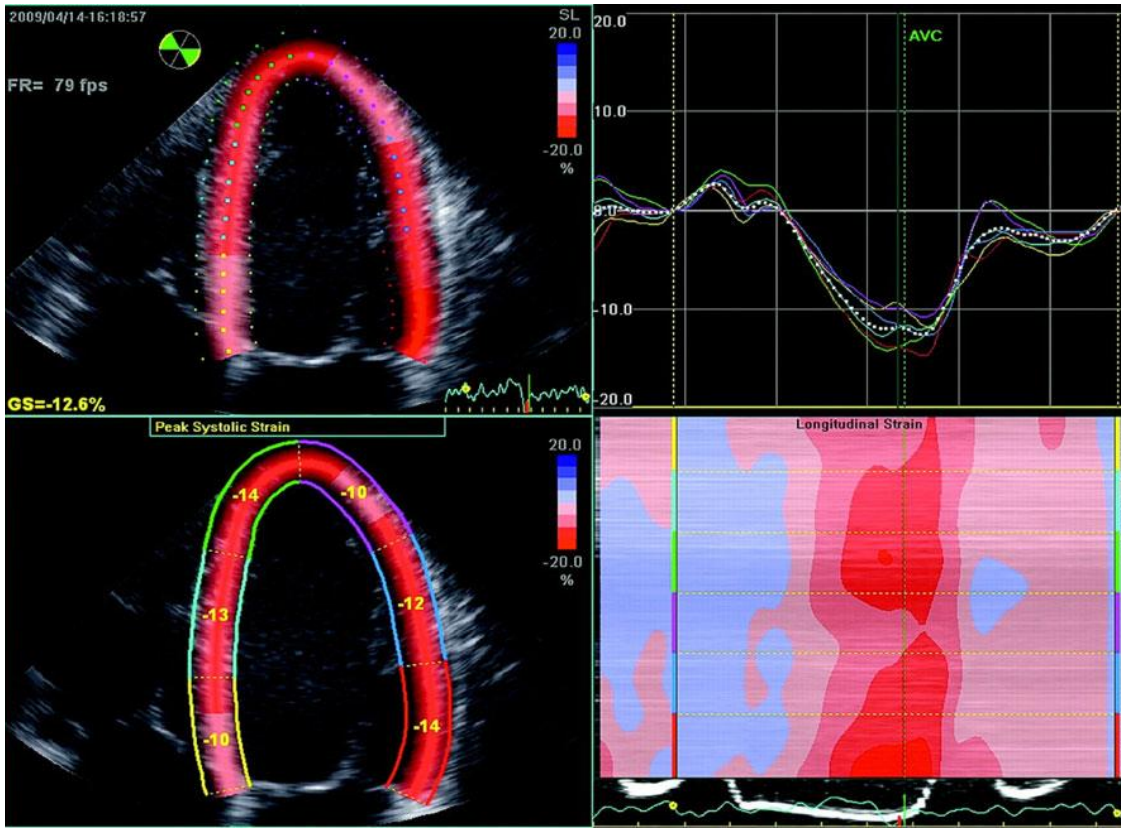
Curr Cardiol Rep
DOI 10.1007/s11886-012-0256-z

ECHOCARDIOGRAPHY (RM LANG, SECTION EDITOR)

Early Detection of Chemotherapy-Related Left Ventricular Dysfunction

Jeanne M. DeCara



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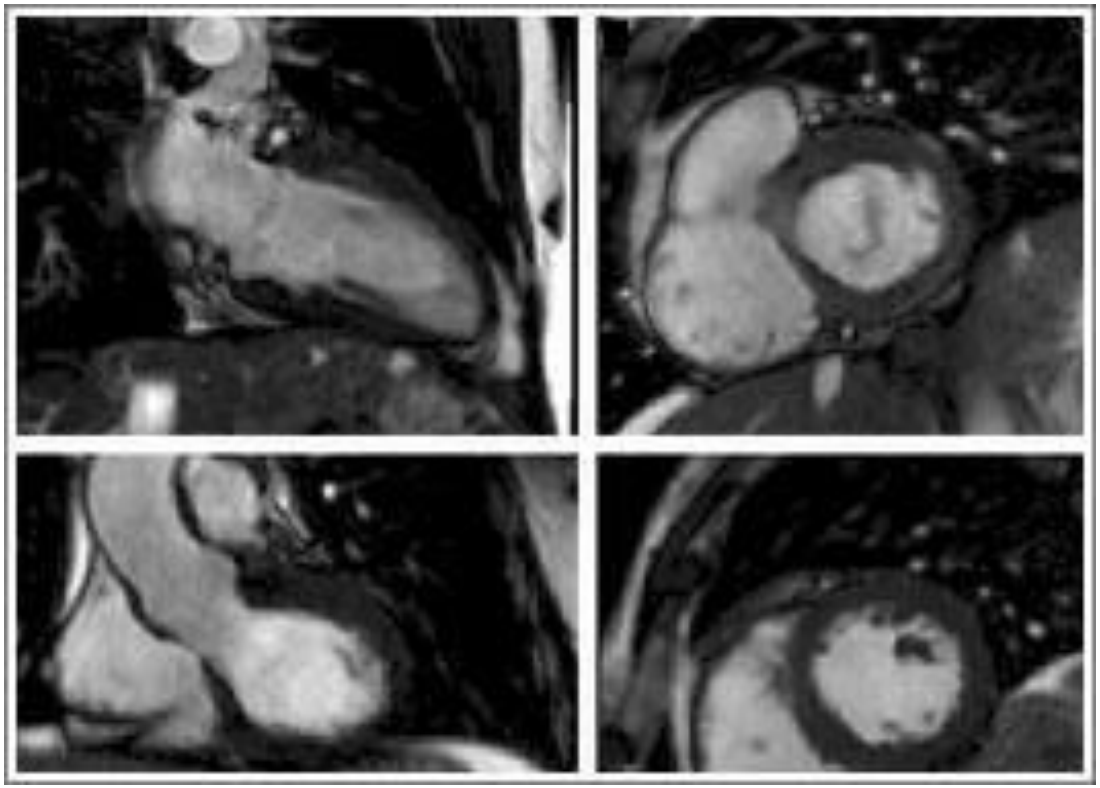
A Novel Approach to Early Detection of Doxorubicin Cardiotoxicity using Gadolinium Enhanced Cardiovascular Magnetic Resonance Imaging in an Experimental Model



Circ Cardiovasc Imaging. 2010 September 1; 3(5): 550–558.

Enhanced myocardial fluorodeoxyglucose uptake following Adriamycin-based therapy: Evidence of early chemotherapeutic cardiotoxicity?

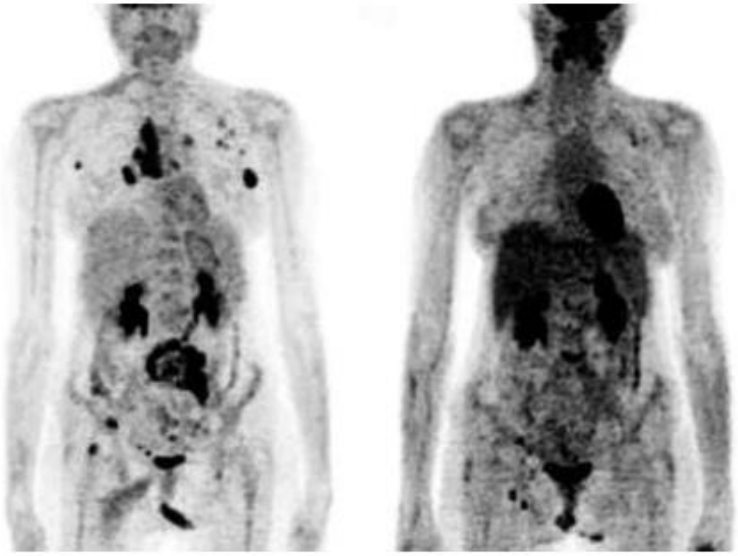


Figure 1 **Significant increase in cardiac fluorodeoxyglucose uptake in** post-adriamycin treatment (on right) fluorodeoxyglucose positron emission tomography scan compared to pre-treatment fluorodeoxyglucose positron emission tomography scan (on left).

World J Radiol 2012 May 28; 4(5): 220-223

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Coronary CT: risk prediction, stratification

Figure 1

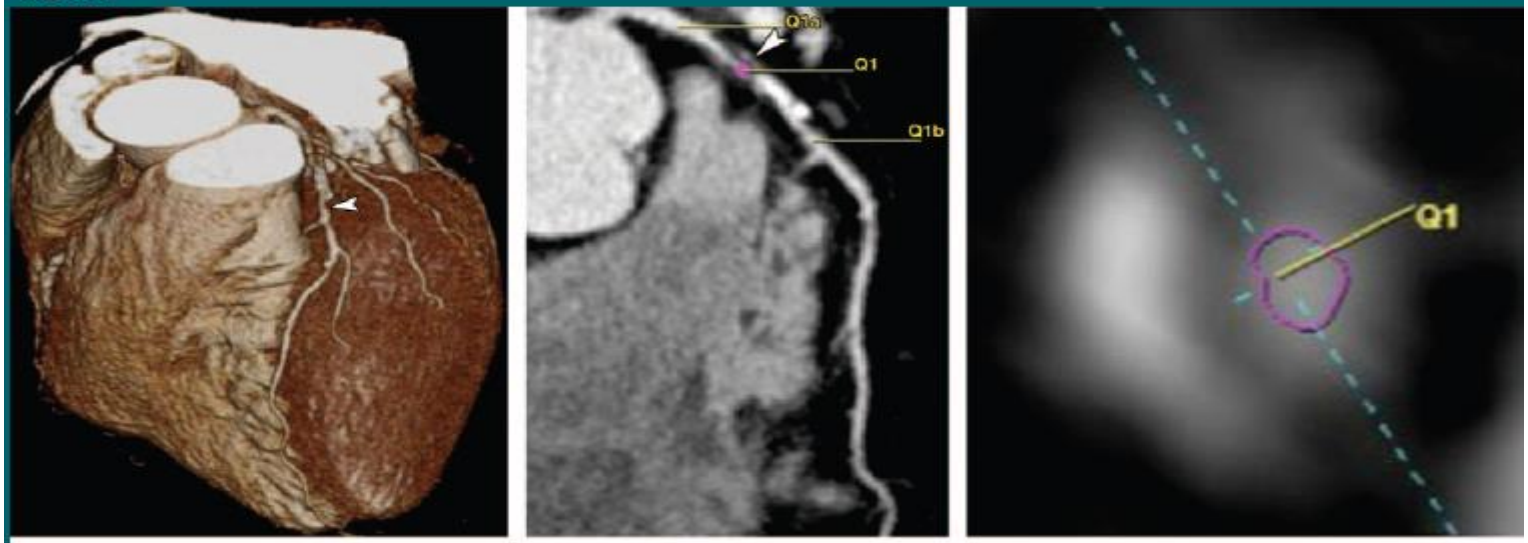

Figure 1: Contrast-enhanced retrospectively ECG-gated dual-source coronary CT angiography in 79-year-old man with atypical chest pain. Average heart rate during scan acquisition was 129 beats per minute (minimum, 103 beats per minute; maximum, 150 beats per minute). (a) Three-dimensional (3D) volume rendering from left anterior oblique perspective, (b) curved multiplanar reformation, and (c) transverse section orthogonal to the vessel lumen demonstrate significant coronary artery stenosis (arrowhead) in the proximal left anterior descending coronary artery (LAD) caused by predominantly noncalcified plaque.

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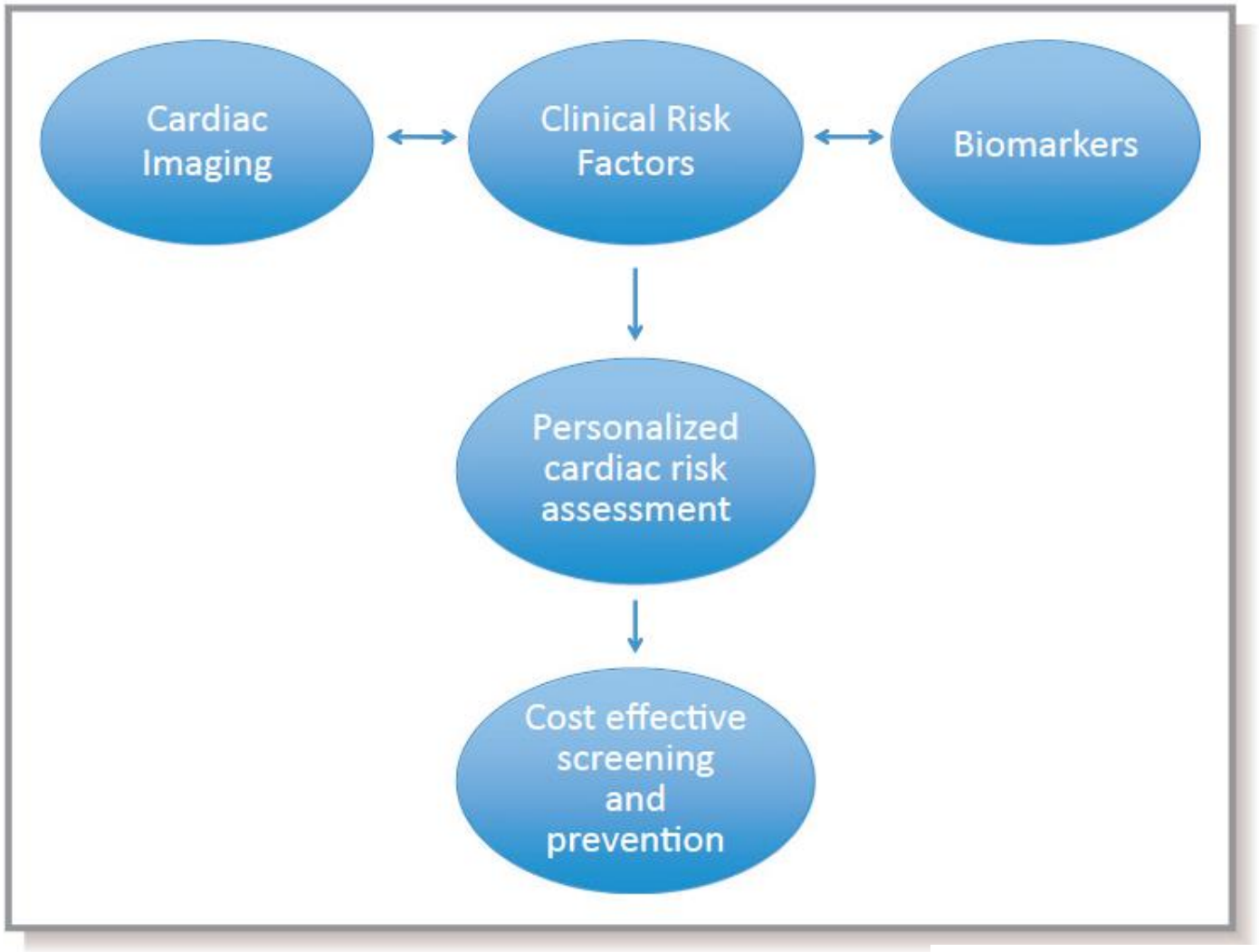
Personalized medicine: purpose for evaluation of cardiotoxicity



J Am Heart Assoc. 2014;3:e000780;

CHALLENGES

Early diagnoses of cardiotoxicity

- Stop chemotherapy ?

- Maintain chemotherapy, start specific cardiovascular medication and clinical follow-up ?

- Discussion with oncologist about alternative chemotherapy

- Cancer risk vs. Cardiovascular risk

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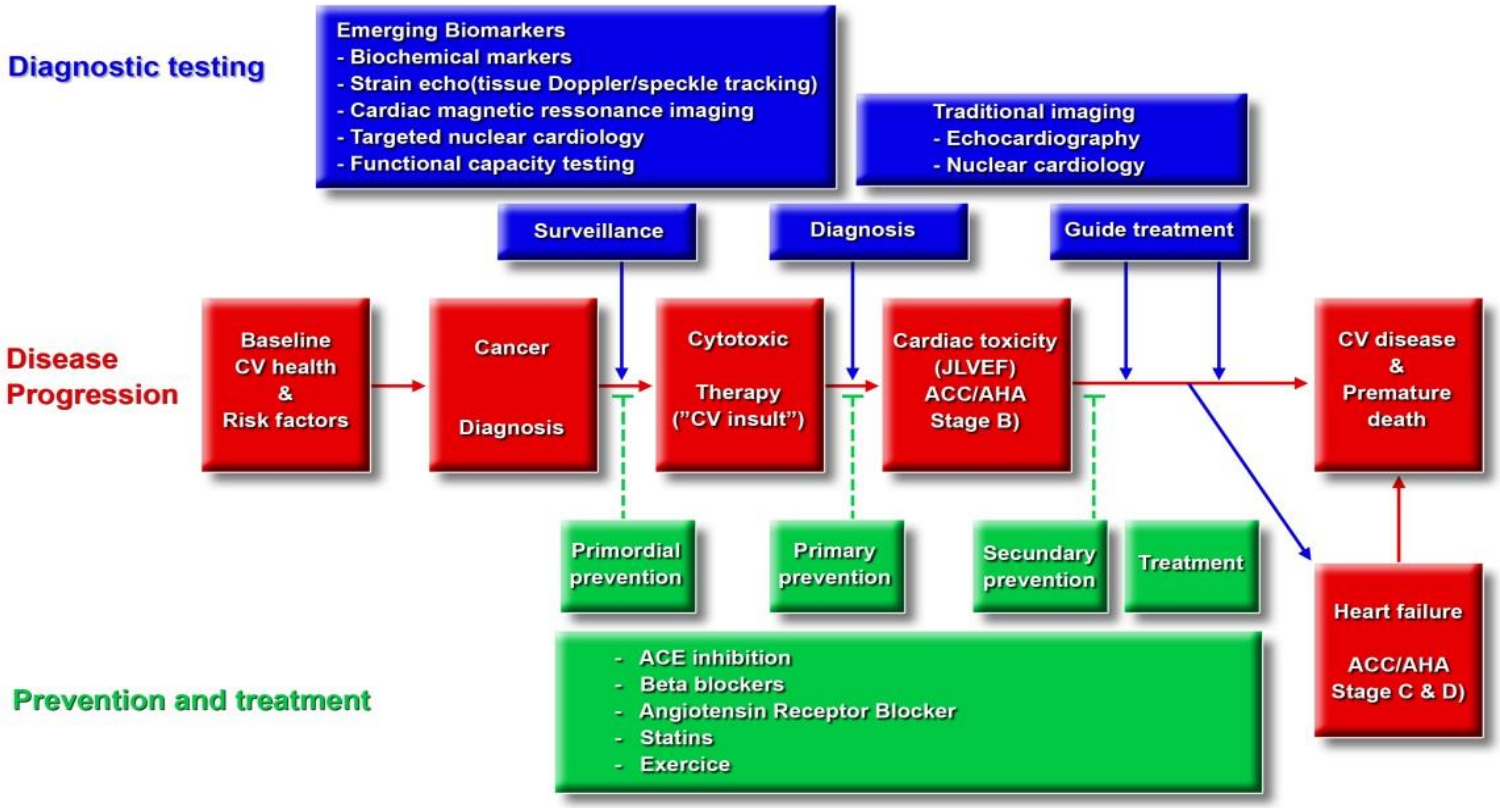
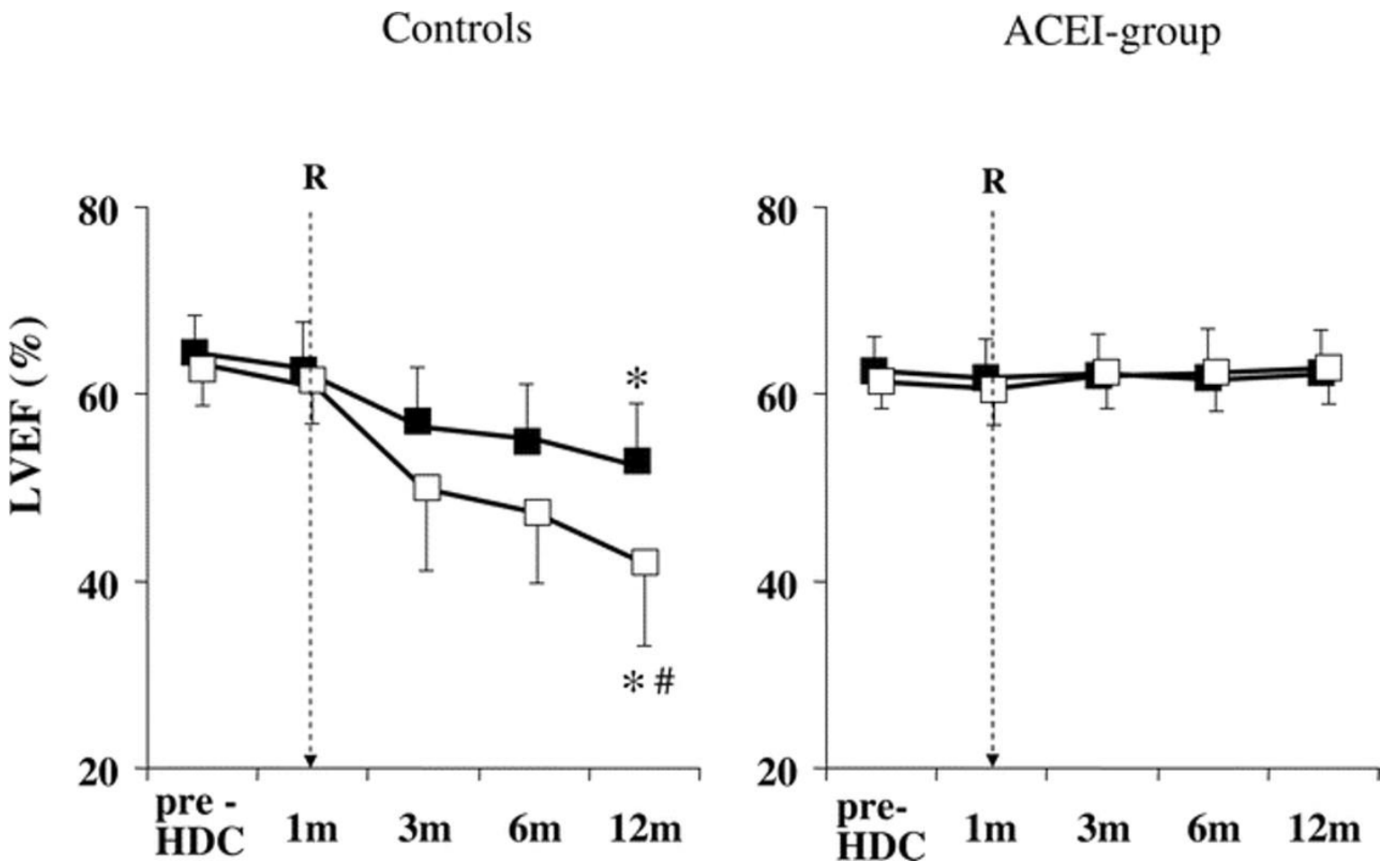
Cardiovascular disease detection, prevention and treatment in early breast cancer



Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition

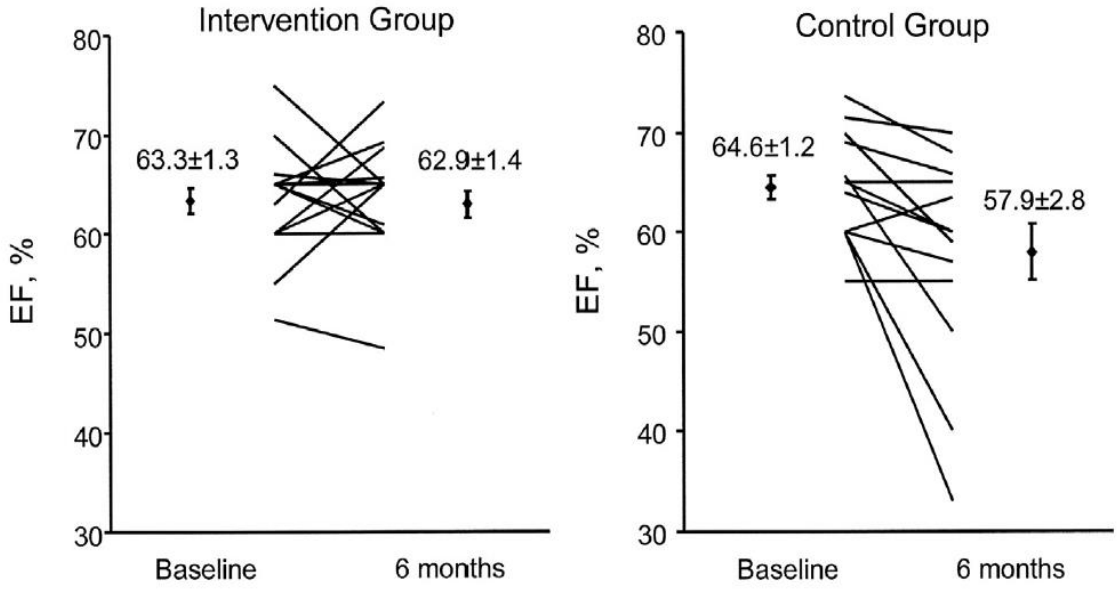
Figure 1. LVEF at baseline and during the 12-month follow-up in control subjects (left) and the ACEI group (right) in patients with (☐) or without (·) persistent TnI increase.



Daniela Cardinale et al. Circulation. 2006;114:2474-2481.

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)



Bosch X et al. J Am Coll Cardiol. 2013;61:2355-62.

Statins decrease mortality in cancer patients

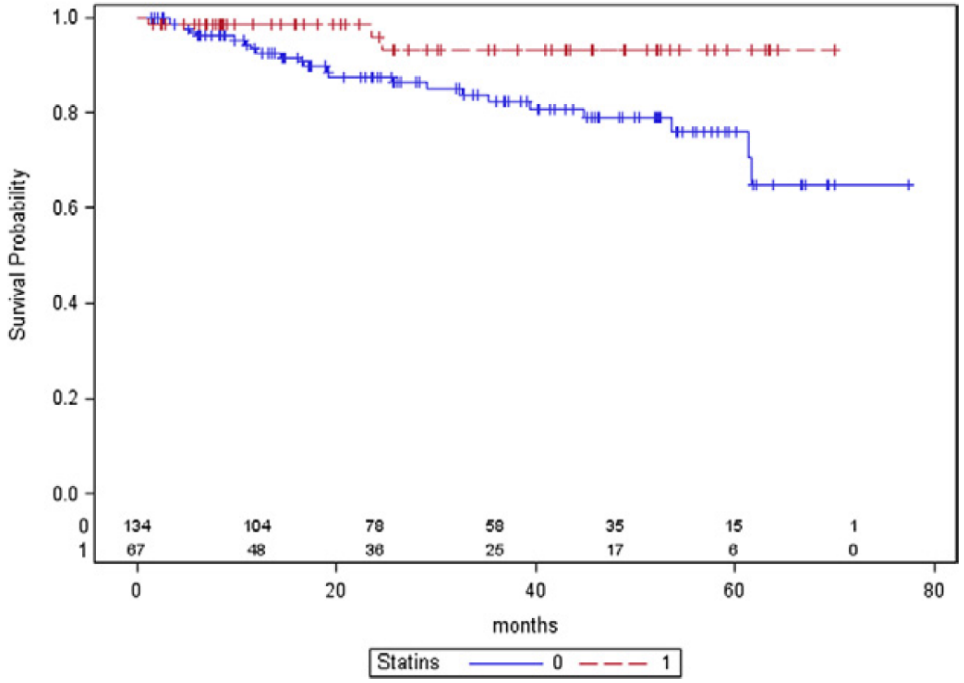
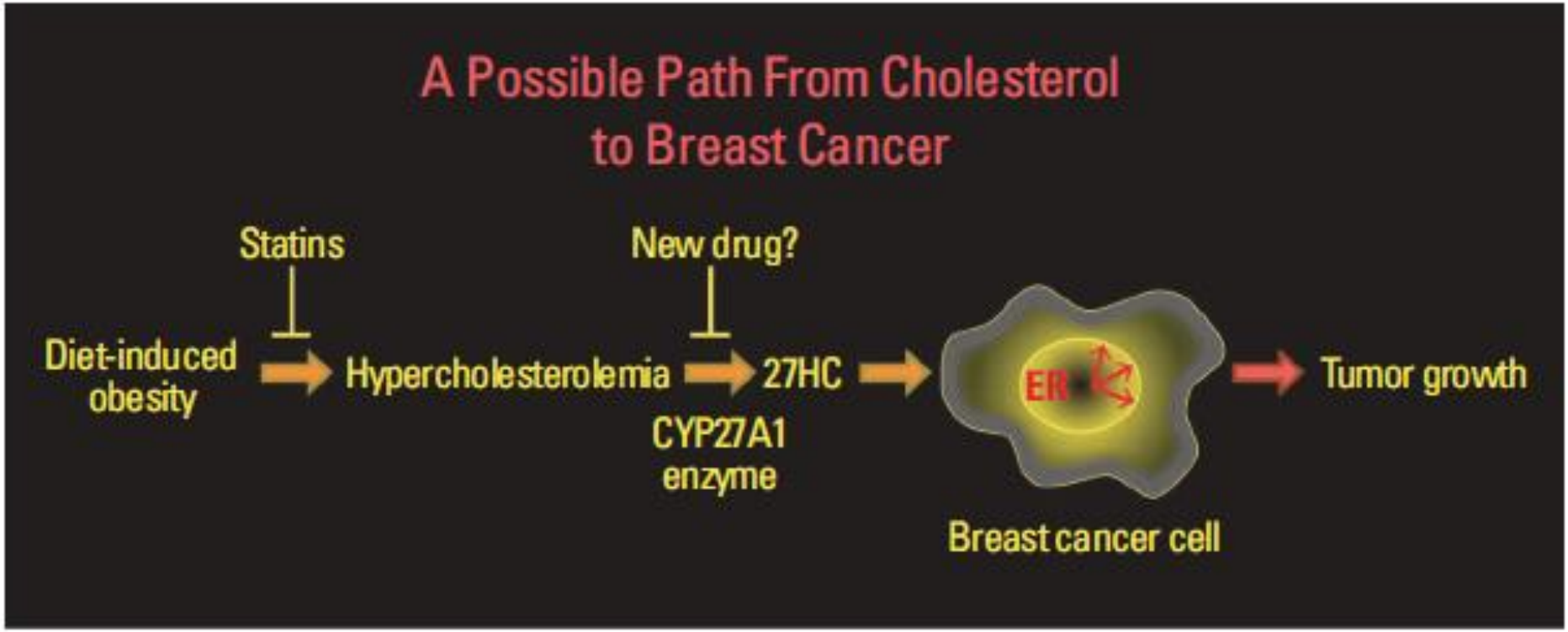


Figure 1 Heart Failure-Free Survival

(J Am Coll Cardiol 2012;60:2384–90)

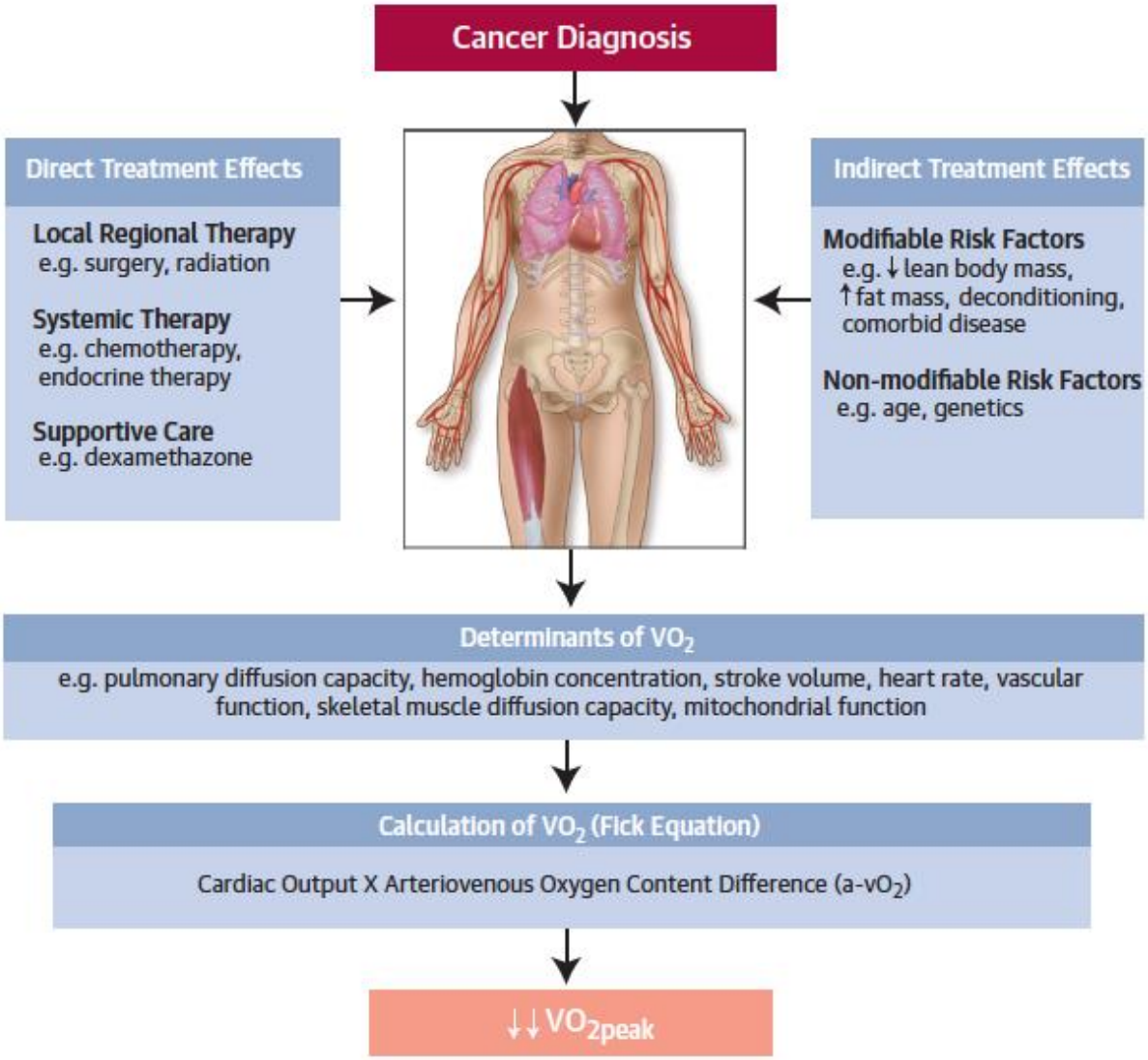
27-Hydroxycholesterol Links Hypercholesterolemia and Breast Cancer Pathophysiology

Erik R. Nelson,[1] Suzanne E. Wardell,[1] Jeff S. Jasper,[1] Sunghee Park,[1] Sunil Suchindran,[2] Matthew K. Howe,[1] Nicole J. Carver,[1] Ruchita V. Pillai,[1] Patrick M. Sullivan,[3] Varun Sondhi,[4] Michihisa Umetani,[4] Joseph Geradts,[5] Donald P. McDonnell[1]*



Nelson et al. *Science*, 2013.

Understanding fatigue in the cancer patient: Decreased Cardiorespiratory Fitness and Role for Exercise



Koelwyn, Jones, Moslehi. *JACC*.

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Cardiotoxicity prevention

TABLE 4 Primary and Secondary Prevention Strategies

Clinical Setting	Primary Prevention	Level of Evidence*	Class of Recommendation*
High-risk profile from genetic testing	Dexrazoxane Liposomal doxorubicin Continuous infusion	C	IIb
Breast cancer (metastatic >300 mg/m^2)†	Dexrazoxane	A	I
Sarcoma‡	Dexrazoxane Continuous infusion	A	IIa
High-risk pediatric ALL§	Dexrazoxane	A	IIa
All patients receiving anthracycline	β-blockers, ACEI, ARB	C	IIb
	Secondary Prevention		
Abnormal strain/LV function ± elevated cardiac biomarkers	β-blockers, ACEI, ARB	B	IIa

Vejpongsa and Yeh. JACC. 2014;64:9.

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

Objectives:

1.Protocols of monitoring and diagnosis of cardiotoxicity.

2.Early diagnosis.

3.Patterns of therapy.

II Diretriz, 2016 – november

Kalil Filho R et al. Arq Bras Cardiol 2011; 96(2 supl 1): 1-52.

Cardio-Oncology

European Heart Journal Advance Access published August 26, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

(J Am Soc Echocardiogr 2014;27:911-39.)

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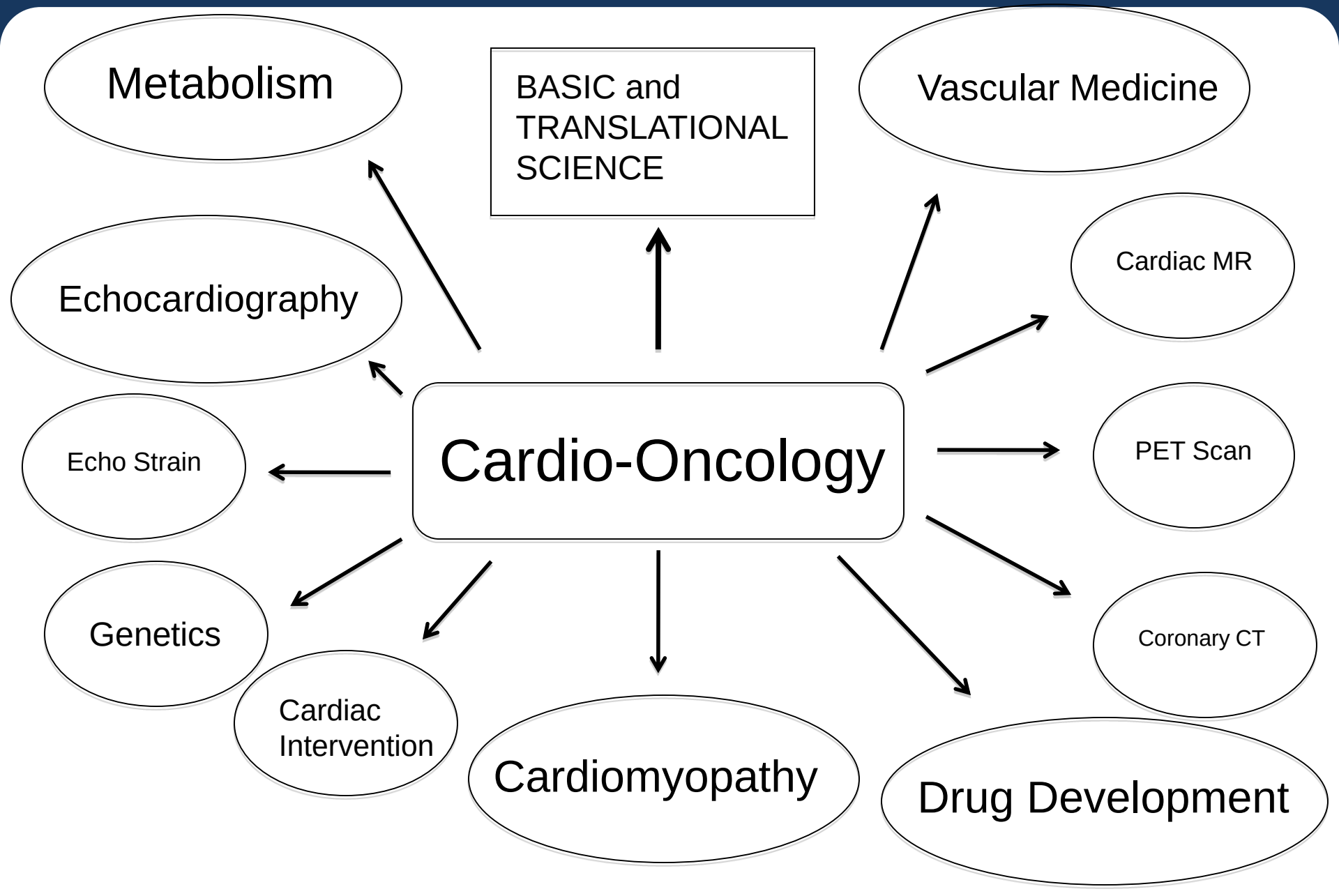


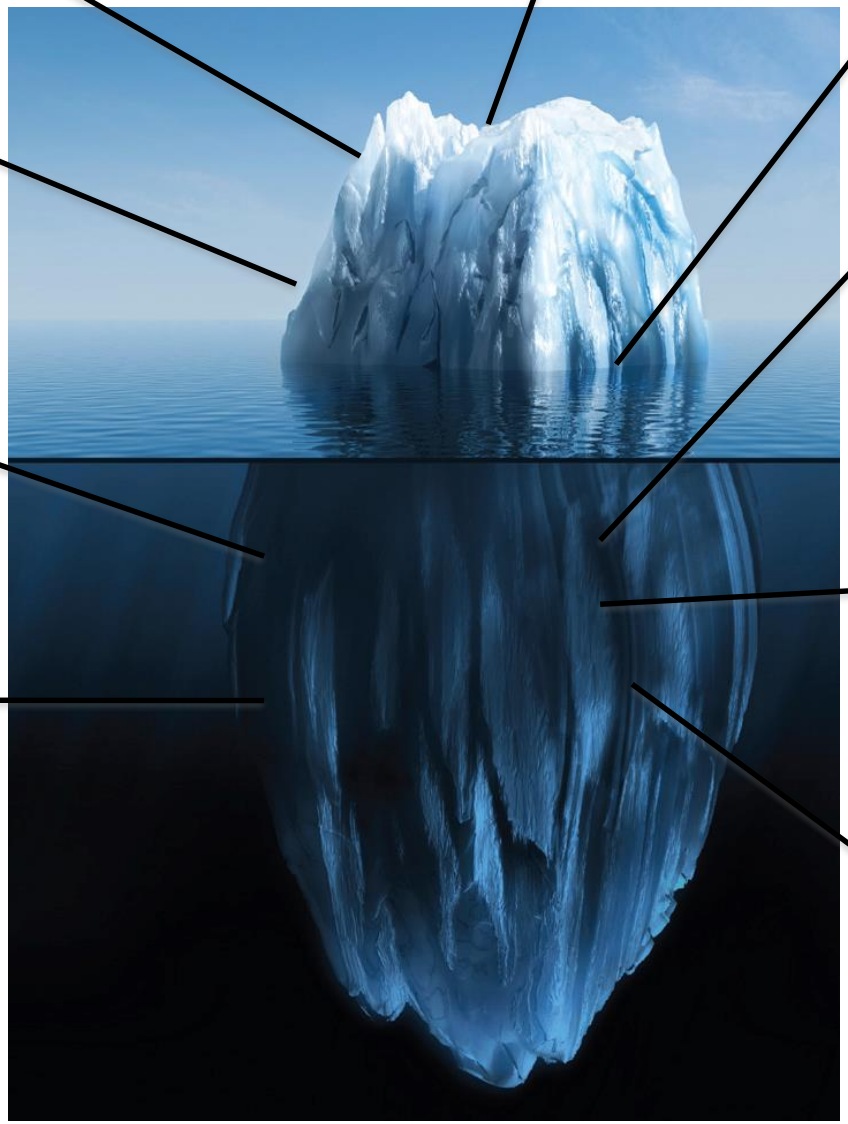
Anthracyclines
Radiation
Heart Failure
CAD

Anti-metabolites (5FU)
Ischemia
Vasospasm

VSP Inhibitors
Hypertension
Heart Failure
Thrombosis

Her2 Targeted Therapies
Cardiomyopathy

HDAC Inhibitors
Arrhythmia



CML TKIs
Imatinib: protective
Nilotinib/Ponatinib:
Vascular/Athero

PI3K Inhibitors
Hyperglycemia
Metabolic
?Myocardial

Drugs Affecting UPS
Immunomodulators (IMiDs): thrombosis
Proteasome inhibitors (e.g. bortezomib, carfilzomib): vascular

BTK Inhibitors
Ibrtutinib:
Arrhythmia/AF

Adapted from Moslehi, Cheng. *Science Translational Medicine*, 2013.

Research in Cardio-Oncology

Brazil Cardio-Oncology Center 2016

InCor

National database

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Sírio-Libanês

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