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Reunión Riesgo Vascular

II Reunión de Ecografía Clínica

**Seguridad cardiovascular de los  
tratamientos oncológicos**

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REVIEW

## Cardiotoxicity of Anticancer Drugs: The Need for Cardio-Oncology and Cardio-Oncological Prevention

Adriana Albini, Giuseppina Pennesi, Francesco Donatelli, Rosaria Cammarota, Silvio De Flora, Douglas M. Noonan

clinical practice guidelines

**Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†**

G. Curigliano<sup>1</sup>, D. Cardinale<sup>2</sup>, T. Suter<sup>3</sup>, G. Plataniotis<sup>4</sup>, E. de Azambuja<sup>5</sup>, M. T. Sandri<sup>6</sup>, C. Criscitiello<sup>1</sup>, A. Goldhirsch<sup>1</sup>, C. Cipolla<sup>2</sup> & F. Poilla<sup>7</sup>, on behalf of the ESMO Guidelines Working Group\*

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Pharmacological Foundations of Cardio-Oncology

Journal of the American Heart Association



Antonio Menna  
Alberto Sordi-Research Institute on Aging, University Campus

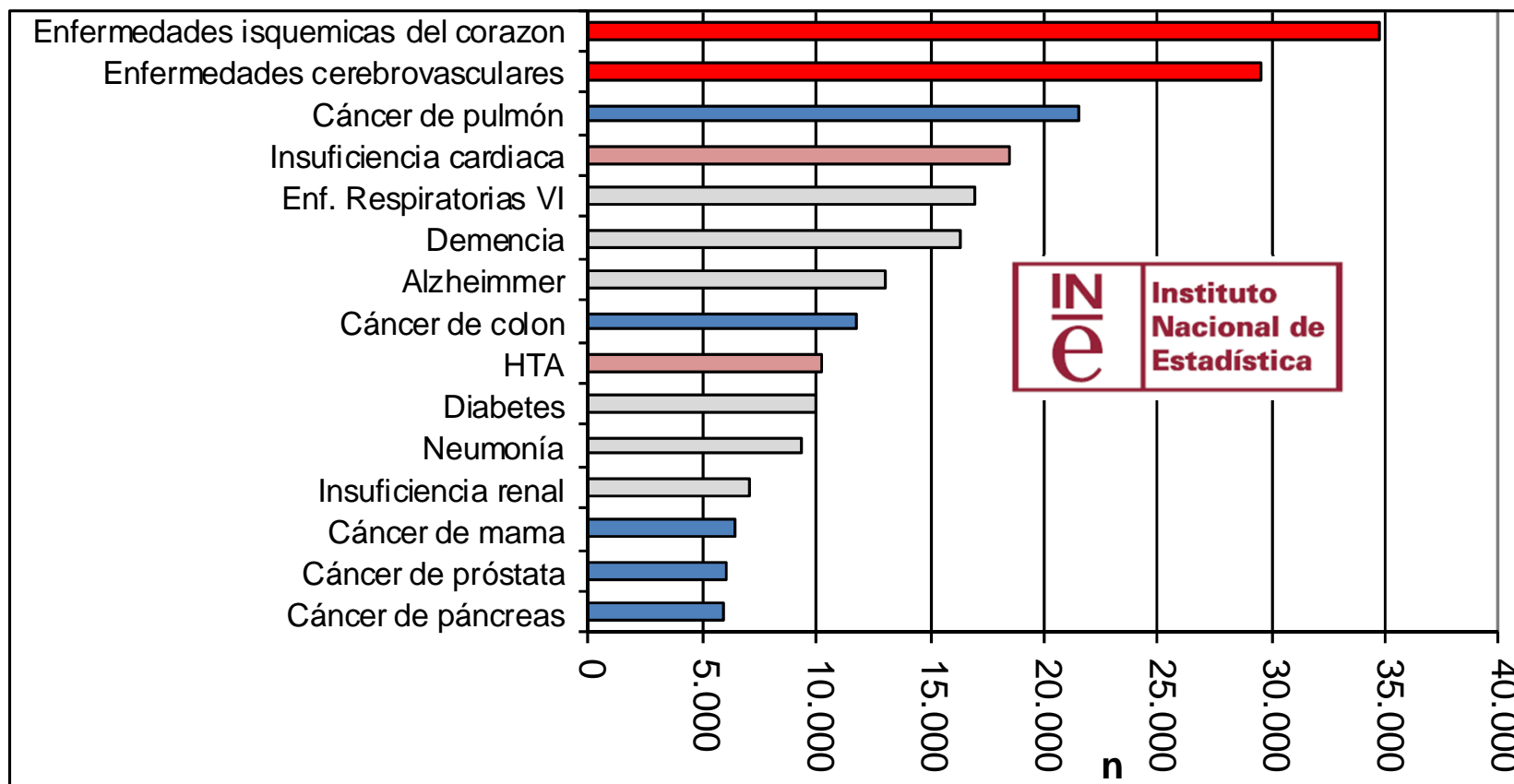
### Cancer Therapy-Induced Cardiotoxicity: Basic Mechanisms and Potential Cardioprotective Therapies

Virginia Shalkey Hahn, Daniel J. Lenihan and Bonnie Ky

# Cáncer y Riesgo Cardiovascular

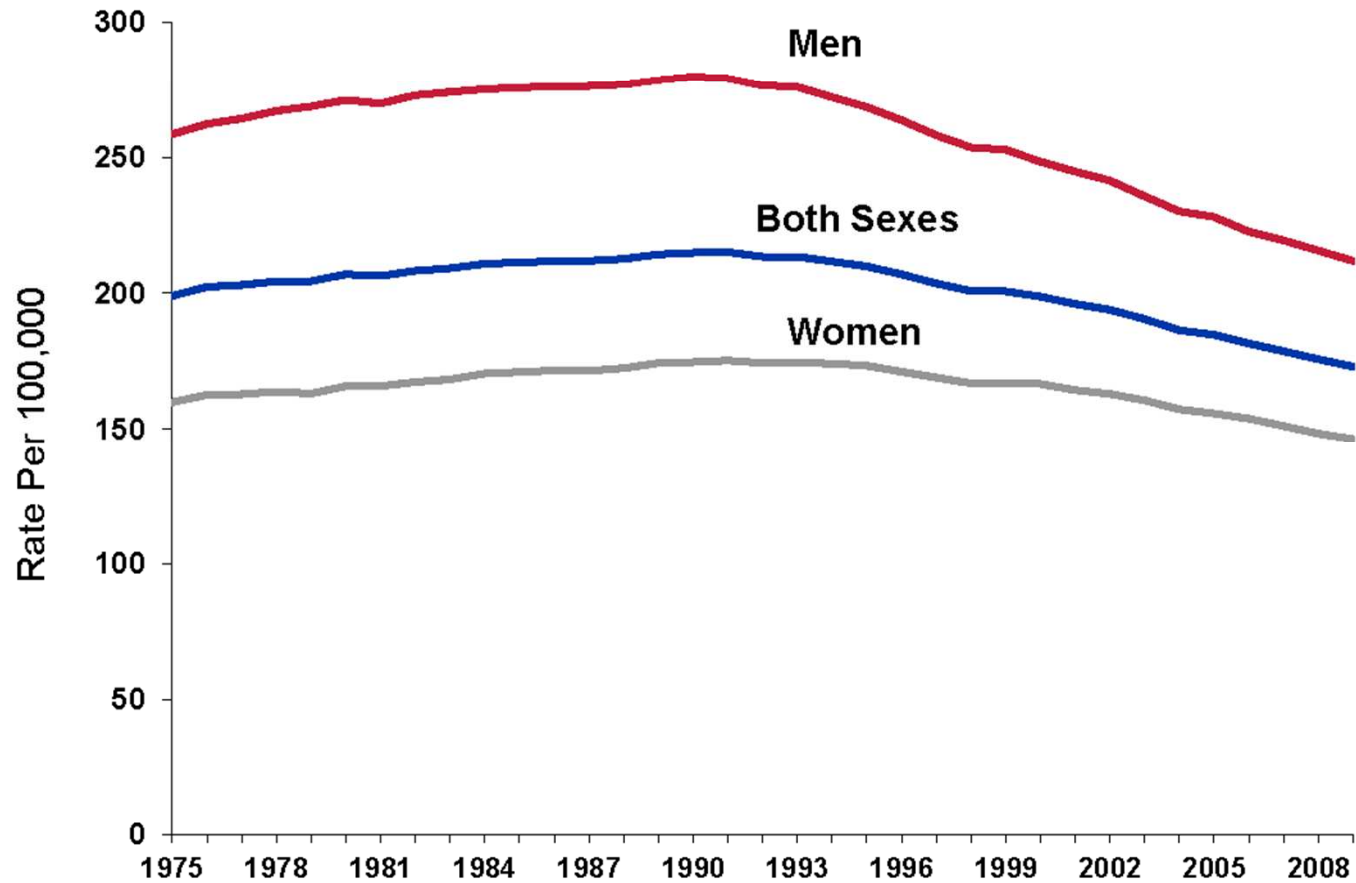
- Asociación de factores de riesgo
  - Tabaco, obesidad, dieta
- Riesgos competitivos
  - Pac. R vascular que desarrollan cáncer
    - Ajuste del tratamiento FR vascular
- Supervivientes de cáncer
  - Toxicidad de fármacos antineoplásicos
    - Antraciclinas; anti-erb-2, antiangiogénicos
  - Mecanismos protectores

# MORTALIDAD EN ESPAÑA 2012



<http://www.ine.es/jaxi/menu.do?type=pcaxis&path=%2Ft15%2Fp417&file=inebase&L=0>

## Cancer Death Rates\* by Sex, US, 1975-2009

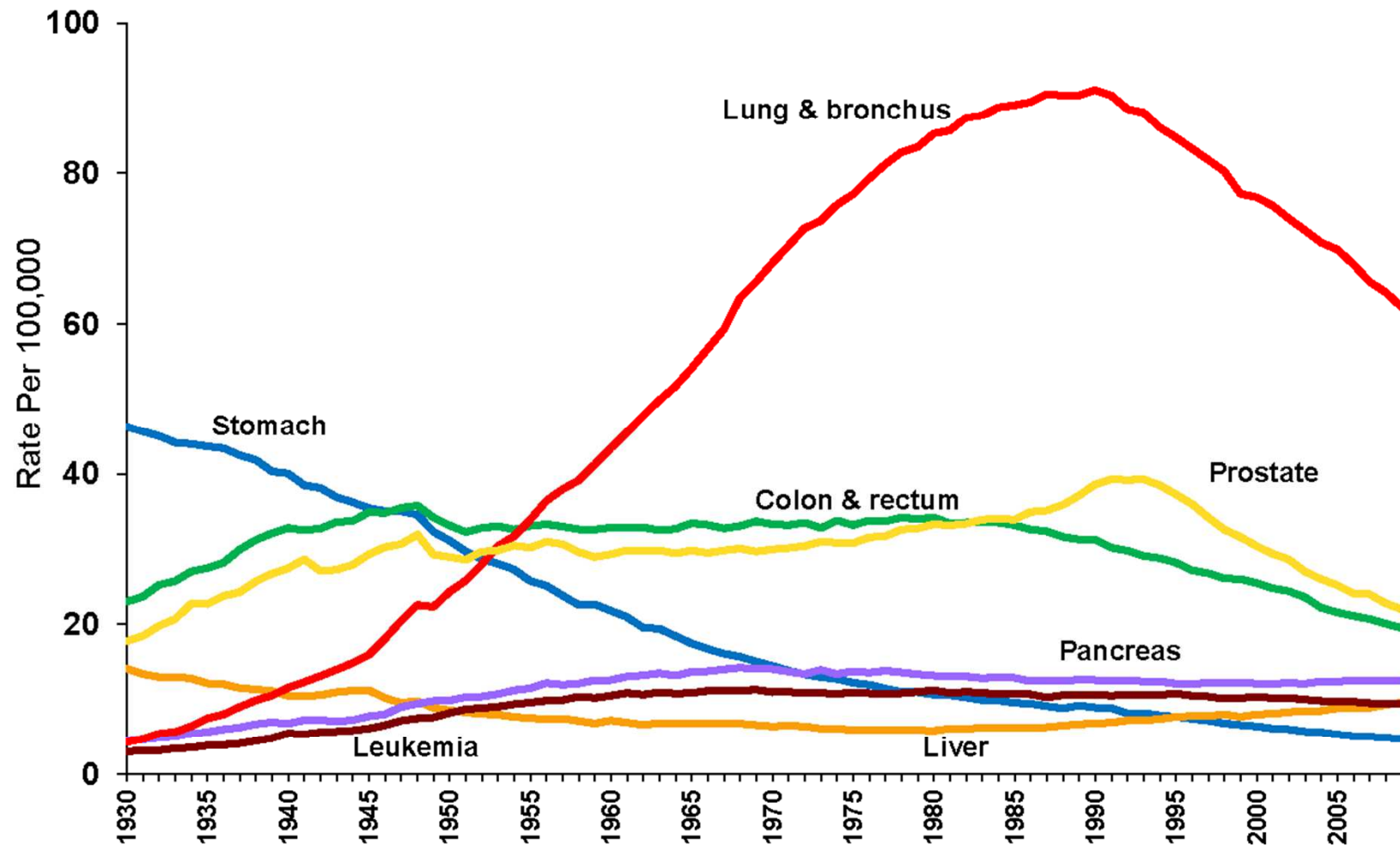


\*Age-adjusted to the 2000 US standard population.

Source: US Mortality Data 1975-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.



## Cancer Death Rates\* Among Men, US, 1930-2009

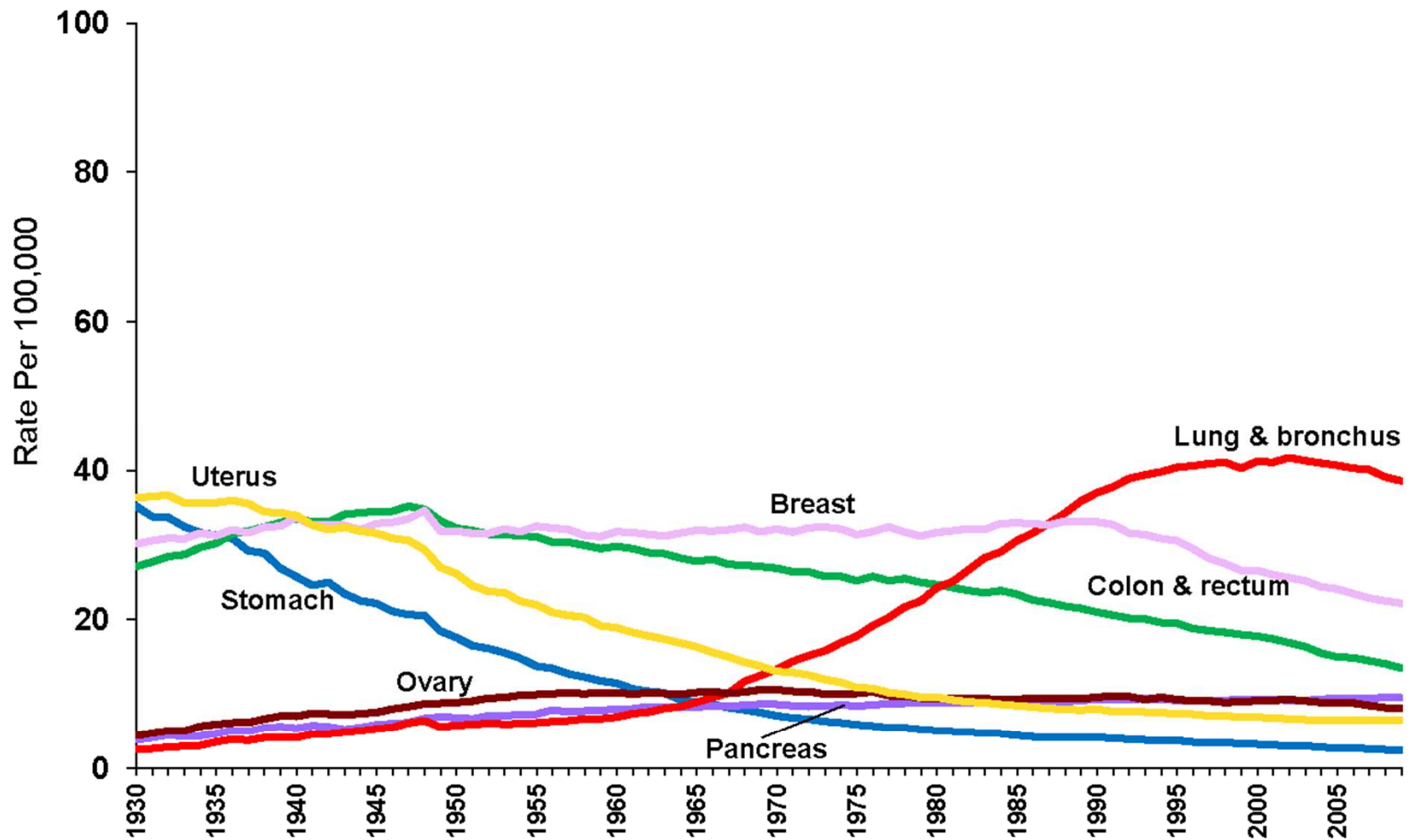


\*Age-adjusted to the 2000 US standard population.

Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959,

National Center for Health Statistics, Centers for Disease Control and Prevention.

## Cancer Death Rates\* Among Women, US, 1930-2009

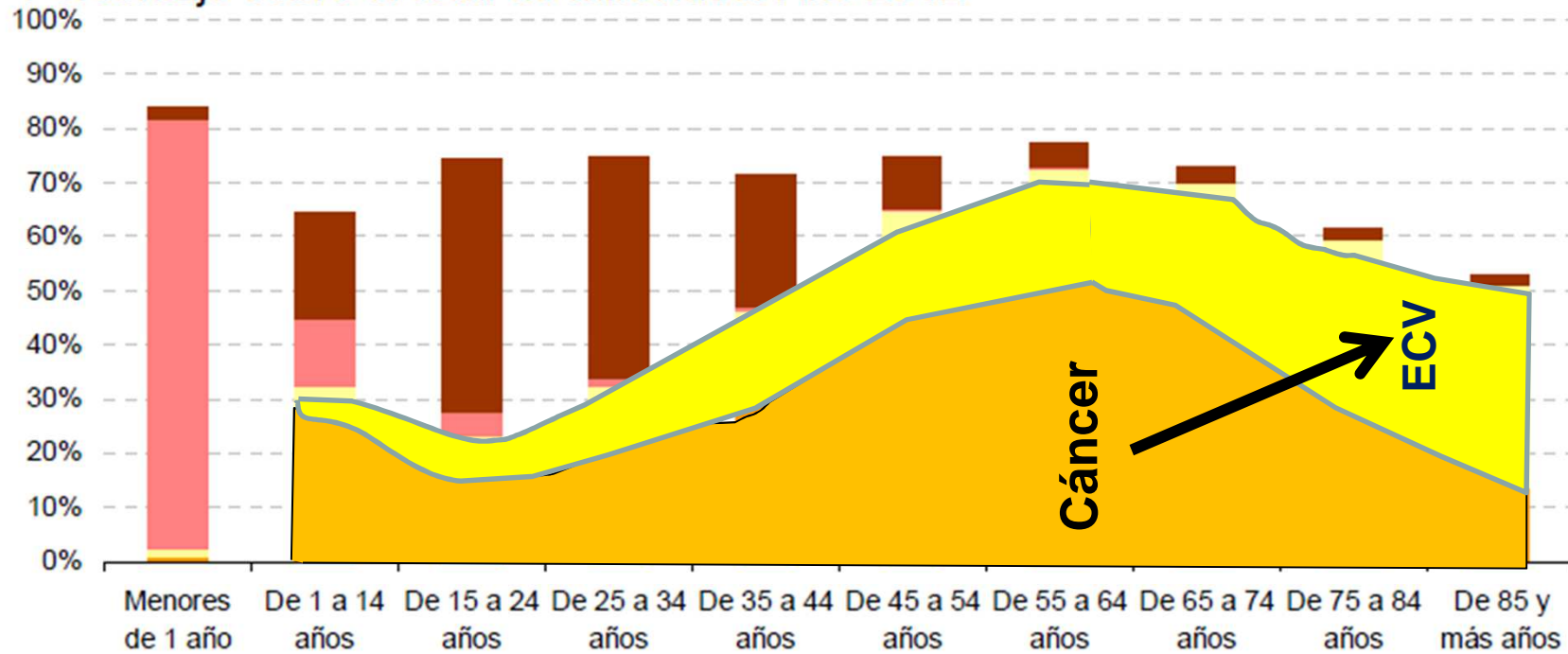


\*Age-adjusted to the 2000 US standard population.

Source: US Mortality Data 1960-2009, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

# Principales causas de muerte según la edad

Porcentaje sobre el total de fallecidos. Año 2012



- Tumores
- Sistema circulatorio
- Perinatales y malformaciones congénitas
- Causas externas





# ***In breast cancer patients, heart disease has a great impact....***

**Table 3.** Cause of Death According to Age Group\*

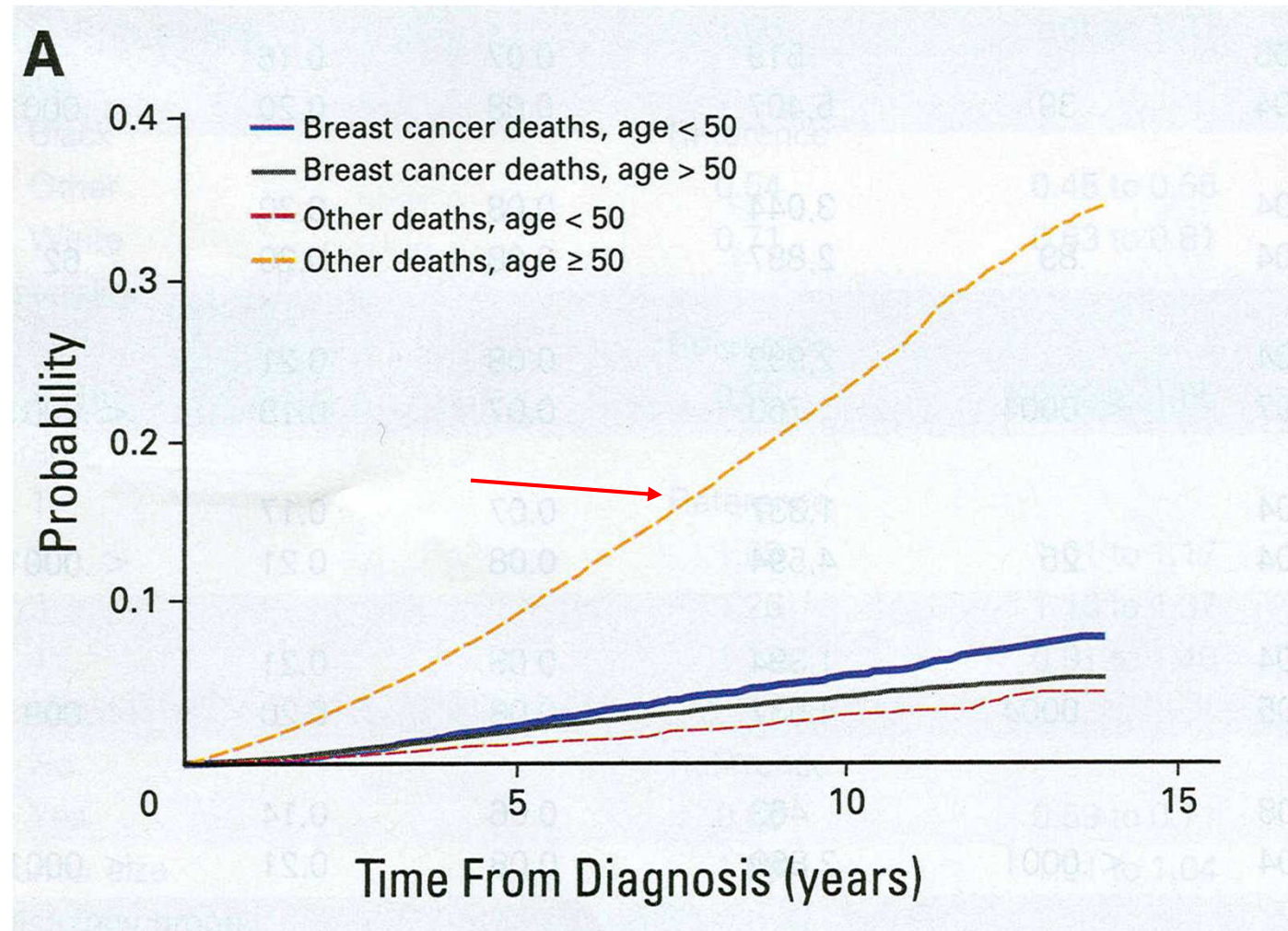
	Age, y				Total
	55-64	65-74	75-84	≥85	
Breast cancer	48 (75.0)	33 (58.9)	38 (44.7)	16 (27.6)	135 (51.3)
Other cancer	4 (6.2)	6 (10.7)	9 (10.6)	3 (5.2)	22 (8.4)
Heart disease	4 (6.2)	4 (7.1)	18 (21.2)	19 (32.8)	45 (17.1)
Cerebrovascular disease	0	1 (1.8)	4 (4.7)	8 (13.8)	13 (4.9)
Digestive system	1 (1.6)	1 (1.8)	3 (3.5)	4 (6.9)	9 (3.4)
Alzheimer disease/dementia					7 (2.7)
Pneumonia					5 (1.9)
COPD/other respiratory					5 (1.9)
Other					13 (4.9)
Unknown					9 (3.4)
<b>Total No. of Deaths</b>	<b>64</b>	<b>56</b>	<b>65</b>	<b>58</b>	<b>263</b>
<b>Total No. of Patients</b>	<b>622</b>	<b>624</b>	<b>427</b>	<b>127</b>	<b>1800</b>

\*COPD indicates chronic obstructive pulmonary disease. Data are presented as No. (%) unless otherwise indicated.

JAMA. 2001;285:885-892

# ***Even in early stage breast cancer, cardiac disease does matter...***

- ***Patients with early stage breast cancer are 4x more likely to die of non-cancer conditions (up to 45 % are cardiac in nature)***



JAMA. 2001;285:885-892



# Are you a Cancer Survivor?

Know your heart disease risk



# Cáncer y Riesgo Cardiovascular

- Asociación de factores de riesgo
  - Tabaco, obesidad, dieta
- Riesgos competitivos
  - Pac. R vascular que desarrollan cáncer
    - Ajuste del tratamiento FR vascular
- Supervivientes de cáncer
  - Toxicidad de fármacos antineoplásicos
    - Antraciclinas; anti-erb-2, antiangiogénicos
  - Mecanismos protectores

# FR. VASCULAR Y CÁNCER

Tratamientos habituales:

- Reevaluar riesgo / beneficio
- Hipotensores
- Hipolipemiantes / estatinas
- Antitrombóticos
  - Antiplaquetarios
  - Anticoagulantes

## INTERACCIONES FARMACOLÓGICAS

# Interacciones: CYP3A4

Oncología	Cardiovascular	Alternativa
<b>Inhibidores tirosin-cinasa</b> <ul style="list-style-type: none"> <li>• Crizotinib, Dasatinib, Imatinib, Lapatinib, Sunitinib,...</li> </ul>	<b>Estatinas <sup>1</sup>:</b> <ul style="list-style-type: none"> <li>• Atorvastatina / Simva</li> </ul>	Prava / Rosu / Pitavastatina
Doxorubicina	Hipotensores <ul style="list-style-type: none"> <li>• Amlodipino, Diltiazem, Verapamil; Nifedipino</li> </ul>	Captopril, carvedilol
Etopósido	<b>Antiarrítmicos <sup>2</sup></b> <ul style="list-style-type: none"> <li>• Amiodarona / Quinidina</li> </ul>	
Irinotecan	<b>Antitrombóticos</b> <ul style="list-style-type: none"> <li>• Rivaroxaban</li> </ul>	Acenocumarol, heparina
Ifosfamida		
Tamoxifen	Ranolazina	

1. **Inhibidores transportador drogas Pgp**

2. **Prolongación intervalo QT: antraciclinas, Inhibidores tirosin cinasa, antibióticos, antiéméticos.**



# Toxicidad cardiovascular de fármacos antineoplásicos

- Antraciclinas
- Inhibidores erb-2-HER
  - Trastuzumab
  - Lapatinib
- Inhibidores VEGF
  - Bevacizumab
  - Sorafenib

# ¿qué es toxicidad cardiaca?

- Ausencia de definición unánime

## Definición operativa

- 1) Reducción de FEVI
- 2) Síntomas de ICC
- 3) Signos de ICC (r. galope, taquicardia)
- 4) Reducción de FEVI  $< 10\%$  ( $< 5\%$  con ICC)

## ¿afectación precoz subclínica?

## Cronología

## Reversibilidad

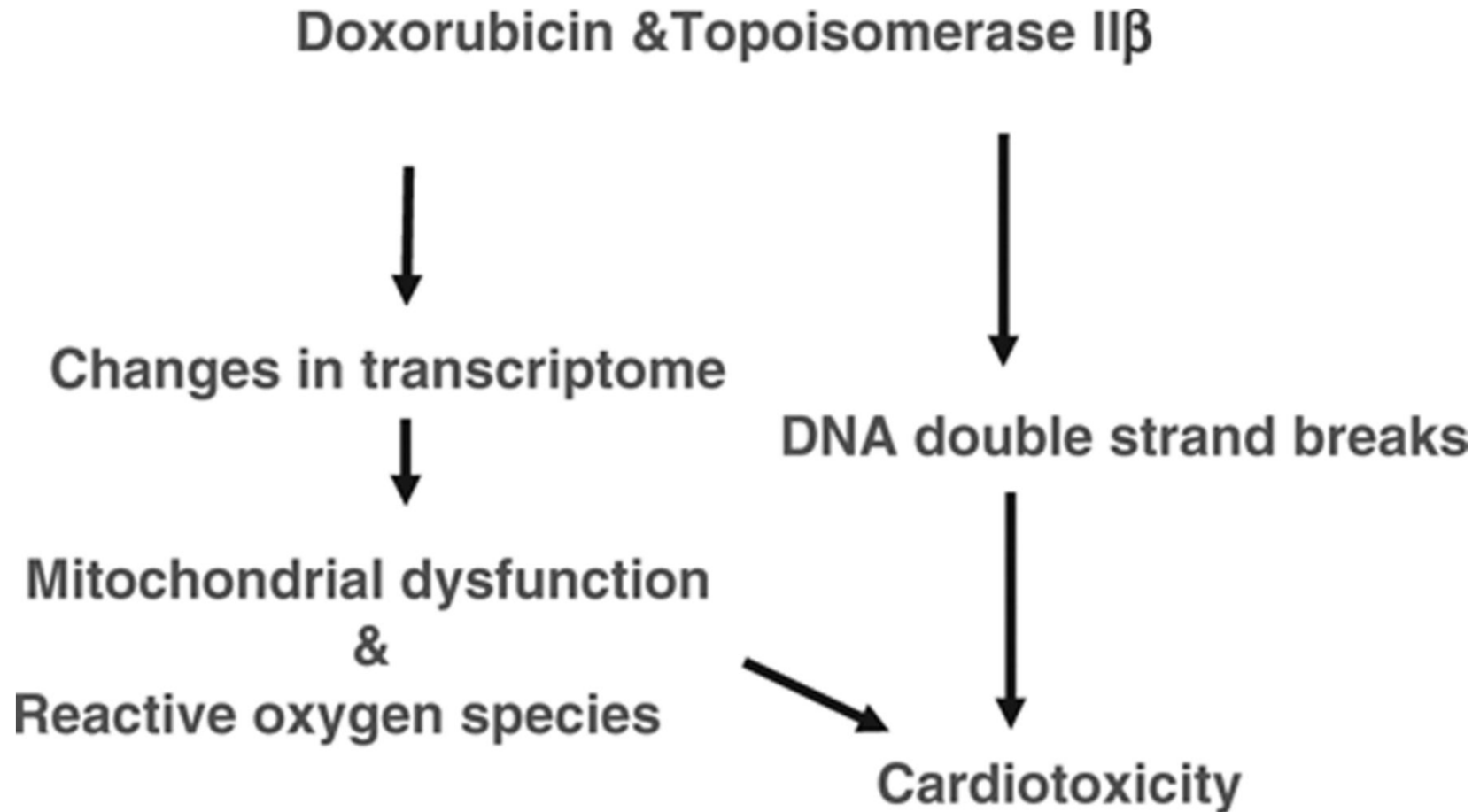
# Chemotherapy Induced Cardiomyopathy

Table 1 Chemotherapy Associated With Left Ventricular Dysfunction		
Chemotherapy Agents	Incidence (%)	Frequency of Use
<b>Anthracyclines</b>		
Doxorubicin (Adriamycin) (6,7)	3-26*	+++
Epirubicin (Ellence) (10)	0.9-3.3	++
Idarubicin (Idamycin PFS) (8)	5-18	+
<b>Alkylating agents</b>		
Cyclophosphamide (Cytosan) (8,11-13)	7-28	+++
Ifosfamide (Ifex) (8,14)	17	+++
<b>Antimetabolites</b>		
Clofarabine (Clolar) (10)	27	+
<b>Antimicrotubule agents</b>		
Docetaxel (Taxotere) (10,15,16)	2.3-8	++
<b>Monoclonal antibody-based tyrosine kinase inhibitors</b>		
Bevacizumab (Avastin) (10,18,19)	1.7-3	++
Trastuzumab (Herceptin) (20-28)	2-28	++
<b>Proteasome inhibitor</b>		
Bortezomib (Velcade) (10,17)	2-5	++
<b>Small molecule tyrosine kinase inhibitors</b>		
Dasatinib (Sprycel) (10)	2-4	++
Imatinib mesylate (Gleevec) (34,35)	0.5-1.7	+
Lapatinib (Tykerb) (32)	1.5-2.2	+
Sunitinib (Sutent) (36,37)	2.7-11	+++

If 5,000 doses per year were dispensed, then the agent was assigned +++; If 1,000 to 5,000 doses per year were dispensed, the agent was assigned ++; lastly, if 1,000 doses were dispensed per year, then + was assigned to correspond to its frequency of use. \*At a cumulative dose of 550 mg/m<sup>2</sup>. Medication manufacturers (and locations): Adriamycin, Pharmacia & Upjohn SpA, Milano.

- LVEF <50% or a 10% drop in LVEF is widely accepted as LV dysfunction in the oncology community.
- LV dysfunction could be symptomatic or asymptomatic.
- LV dysfunction could manifest acutely or have a late onset and can also be chronic and progressive.

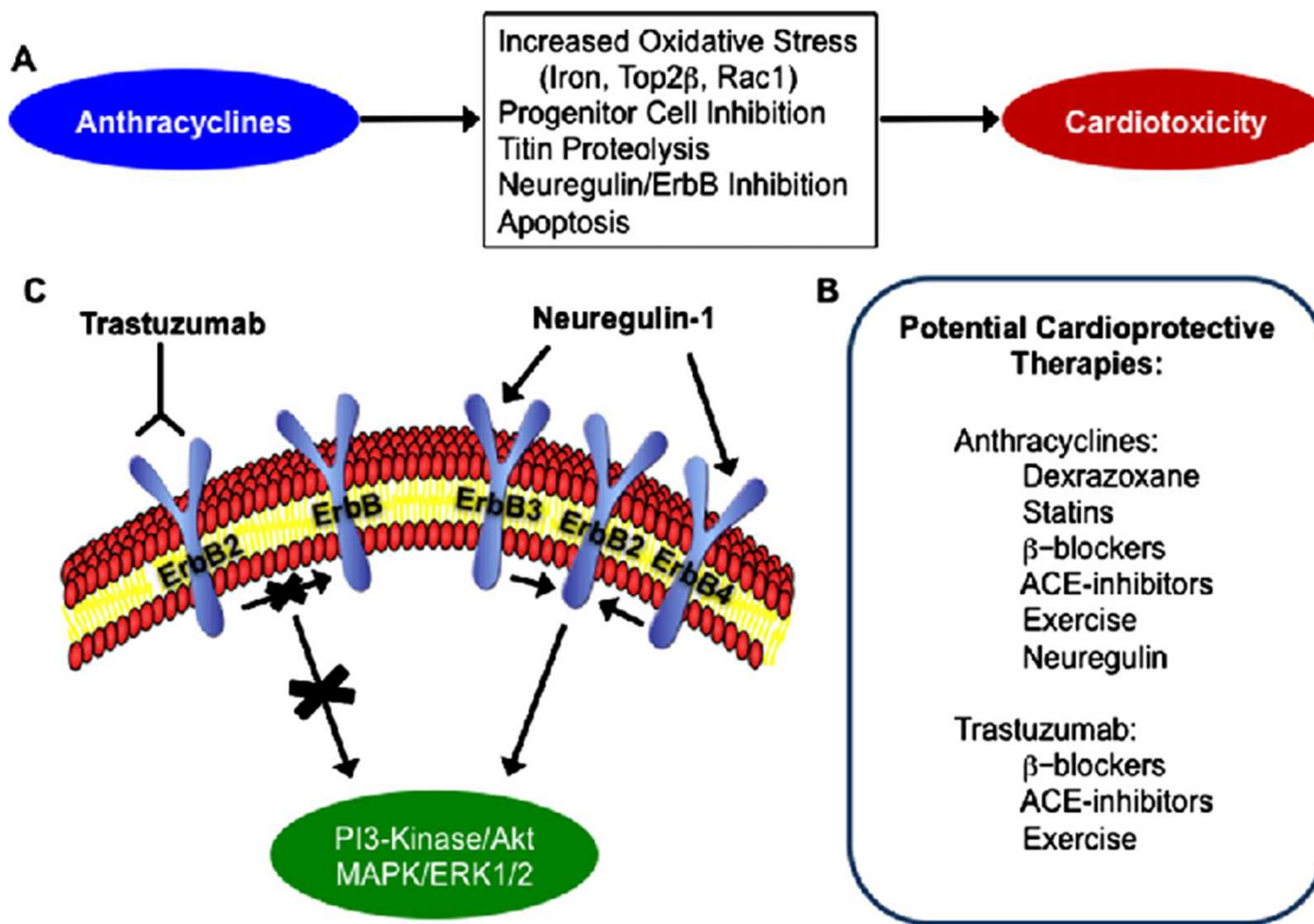
## Schematic of the mechanisms of doxorubicin-mediated cardiomyopathy.



Ky B et al. Circulation Research 2013;113:754-764

# Anthracyclines and ErbB inhibitors

## Cardiotoxicity: Mechanisms and protections



, *J Am Heart Assoc.* 2014;3:e000665;  
 doi: 10.1161/JAHA.113.000665

# ANTRACICLINAS

## Toxicidad

- Inhibidores de topoisomerasa
- Apoptosis
- Especies reactivas del oxígeno
- Activación beta adrenergica
- Daño mitocondrial
- Daño membranas

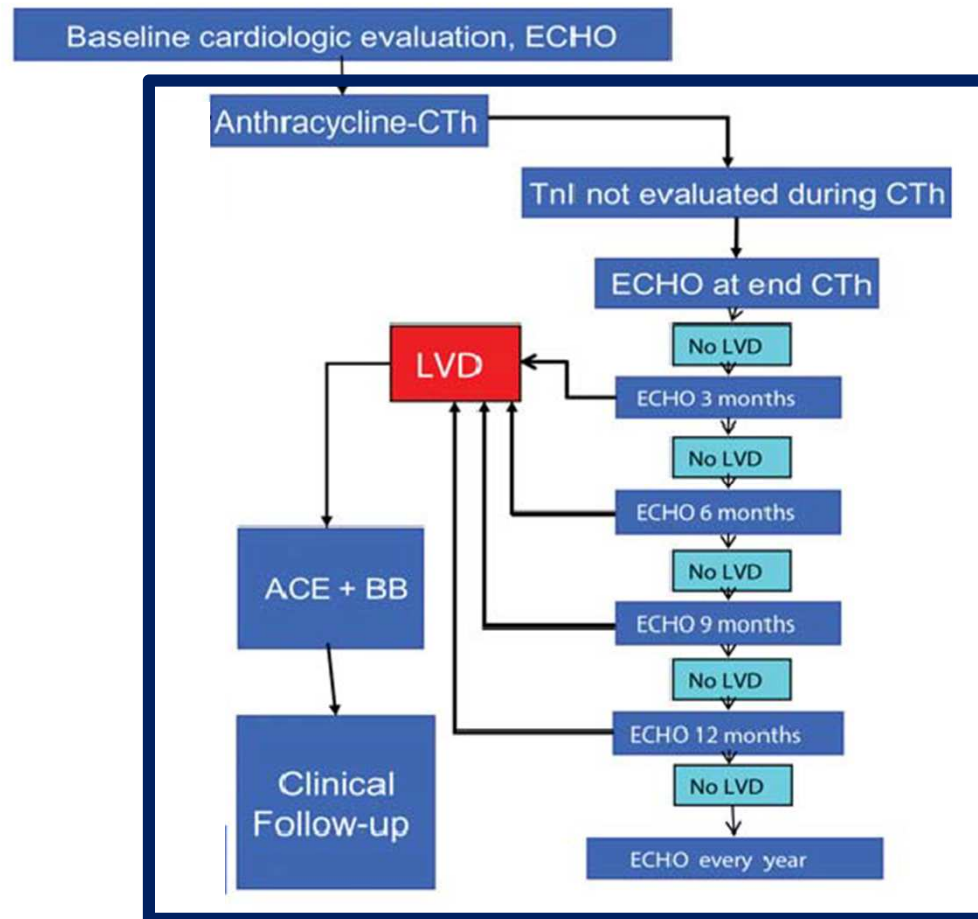
## Factores de riesgo

- Dosis acumulada
- Dosis elevada
- Radioterapia
- Trastuzumab (otros)
- Sexo femenino
- Enf. Cardiovascular
- Elevacion de biomarcadores



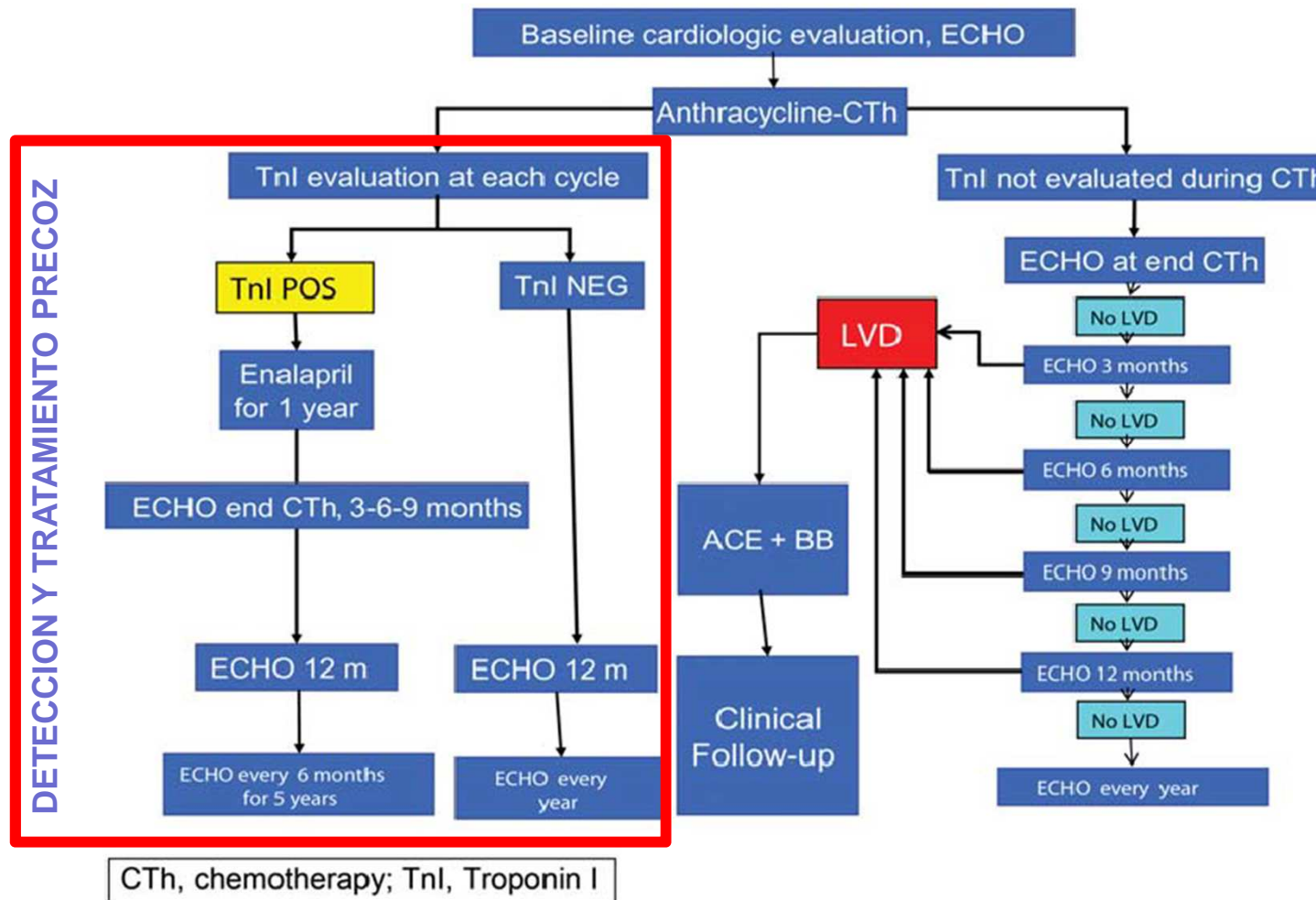
# Management of cardiotoxicity in patients receiving anthracyclines.

DETECCION  
Y  
TRATAMIENTO  
TARDIO



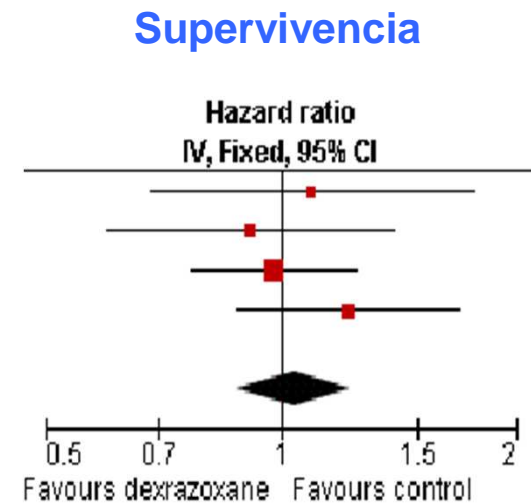
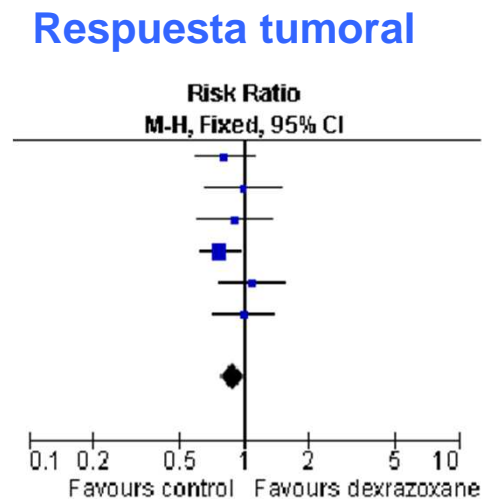
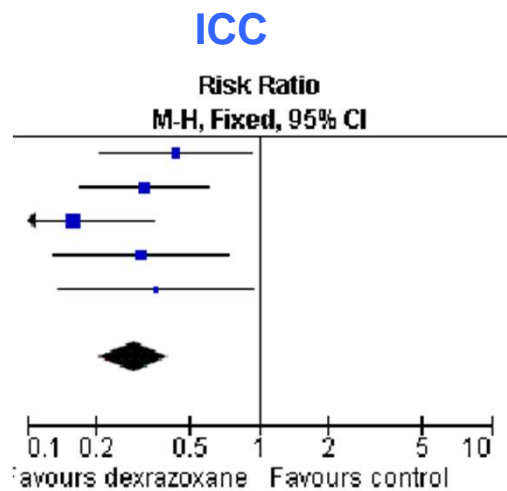
CTh, chemotherapy; TnI, Troponin I

# Management of cardiotoxicity in patients receiving anthracyclines.

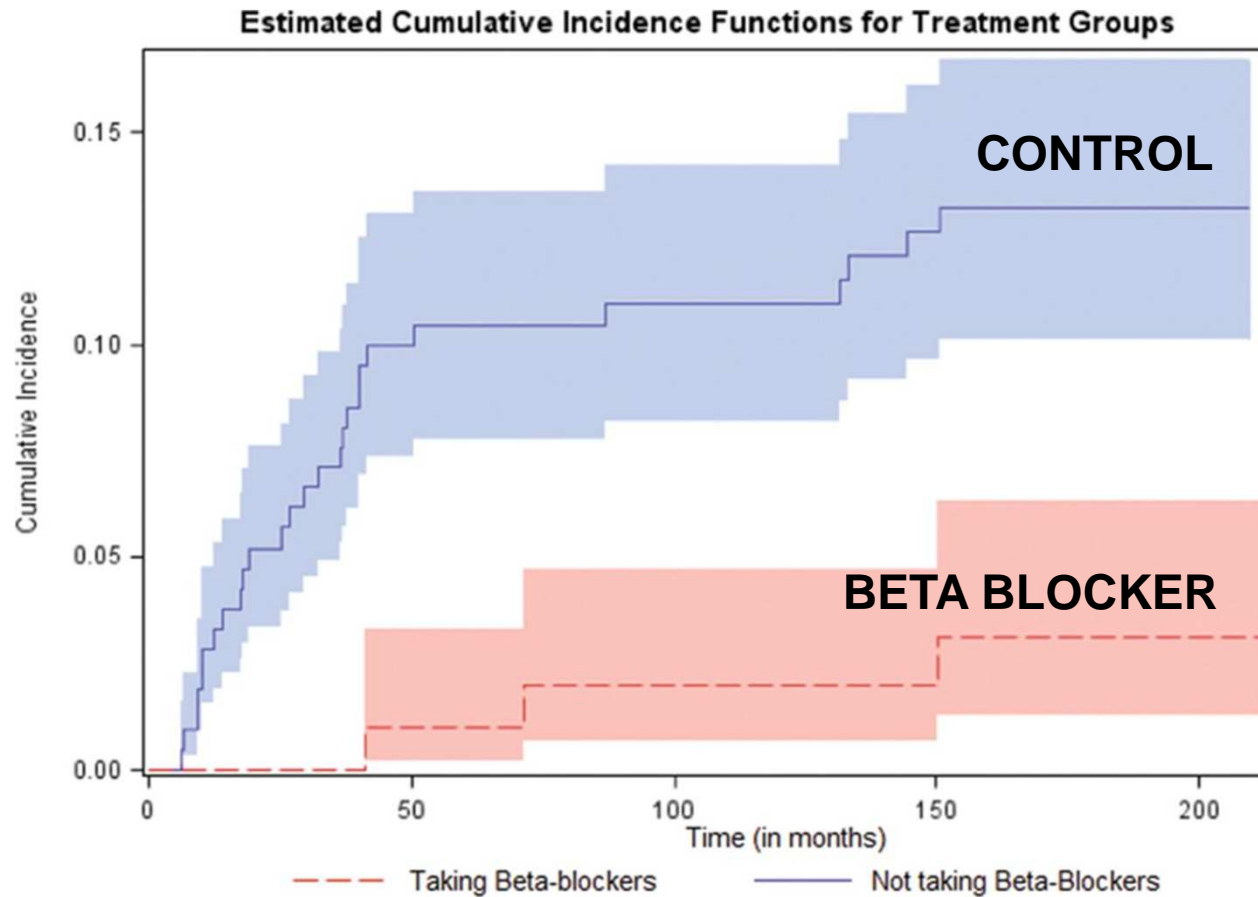


# Cardioprotective interventions for cancer patients receiving anthracyclines.

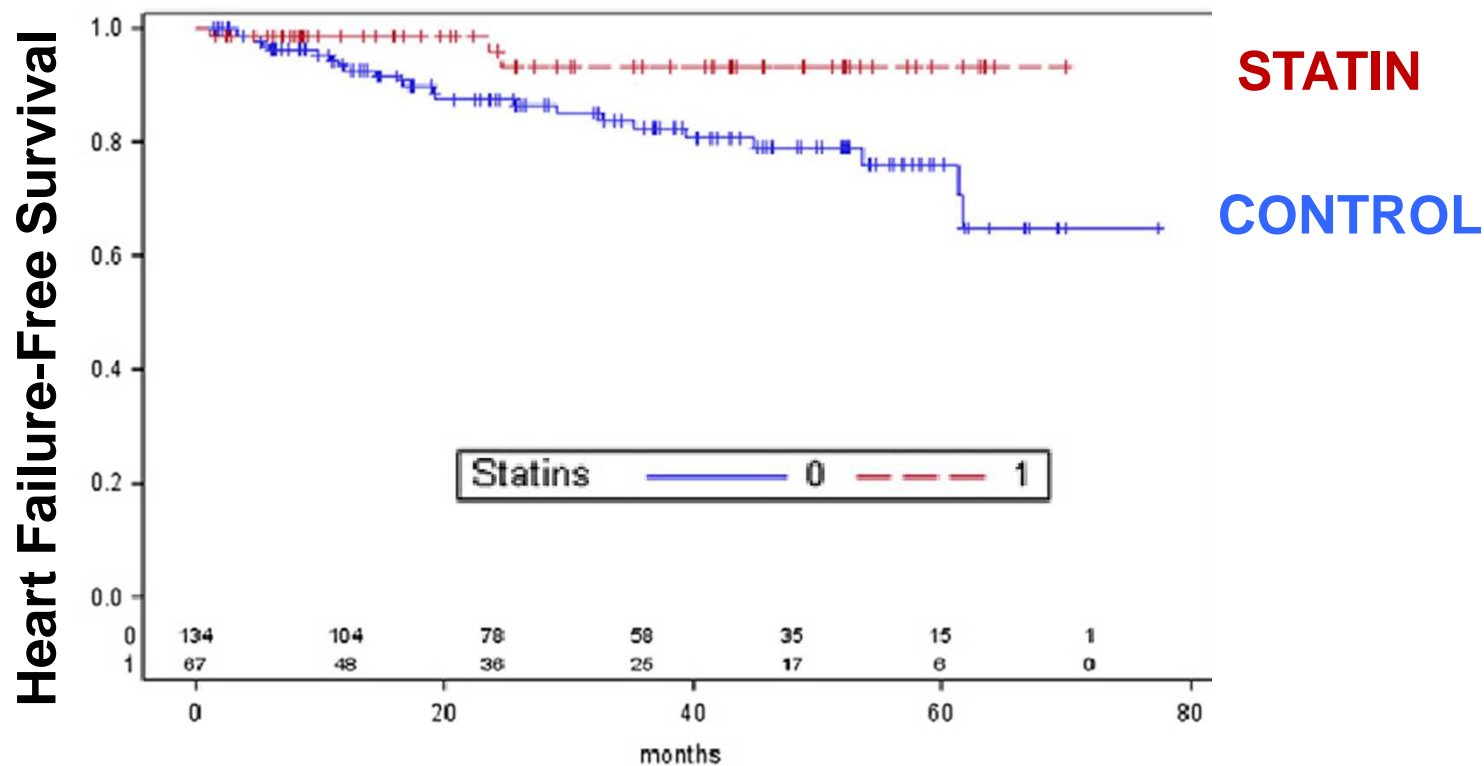
- Important methodological limitations
- Few studies
  - [N-acetylcysteine](#), phenethylamines, [coenzyme](#) Q10, a combination of vitamins E and C and [N-acetylcysteine](#), L-[carnitine](#), [carvedilol](#), [amifostine](#)
- [dexrazoxane](#) 10 studies 1619 patients



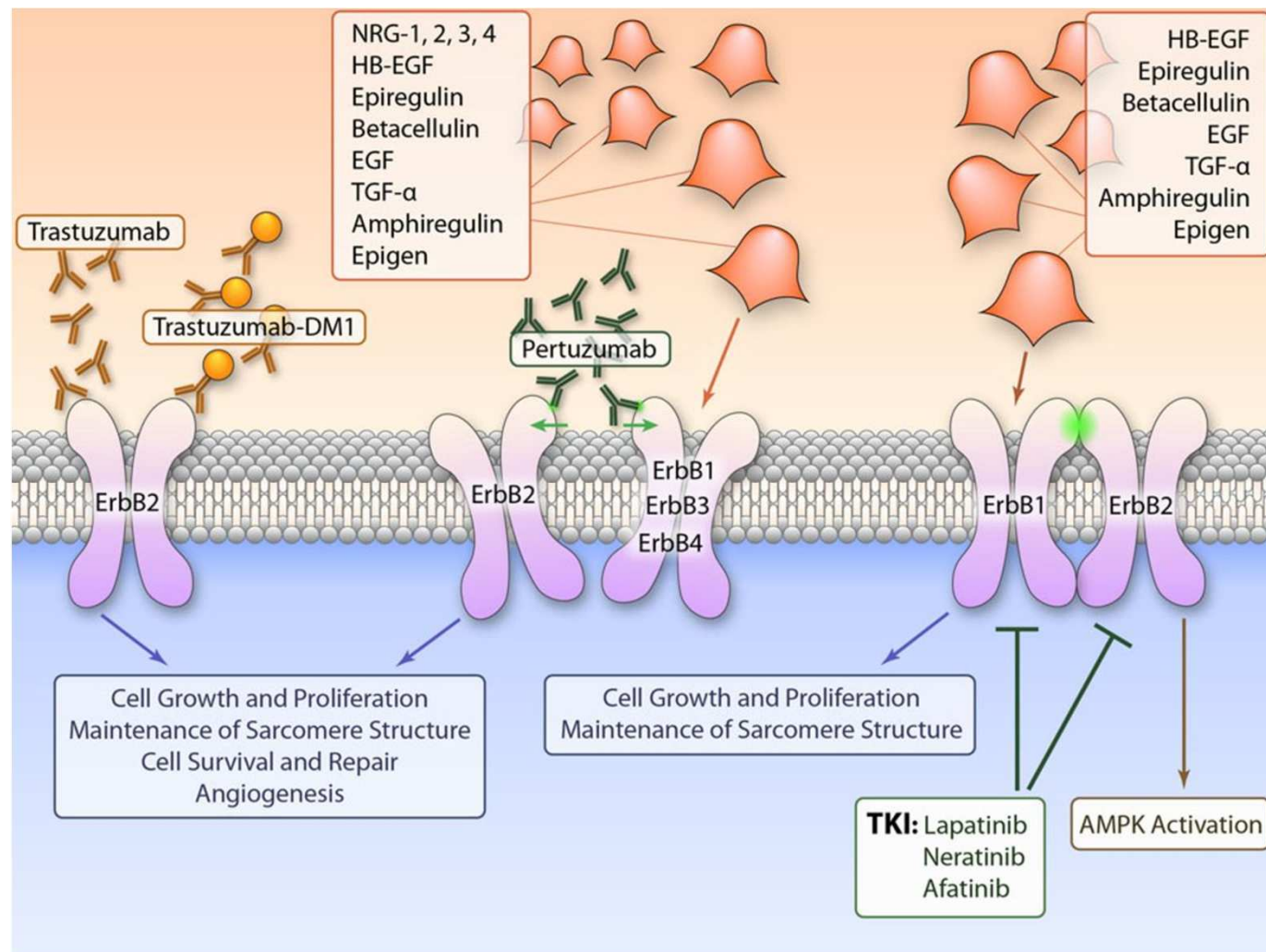
# EFFECTS OF **BETABLOCKERS** ON THE INCIDENCE OF HEART FAILURE IN WOMEN WITH BREAST CANCER



# Effect of **Statin Therapy** on the Risk for Incident **Heart Failure** in Patients With Breast Cancer Receiving **Anthracycline** Chemotherapy: An Observational Clinical Cohort Study

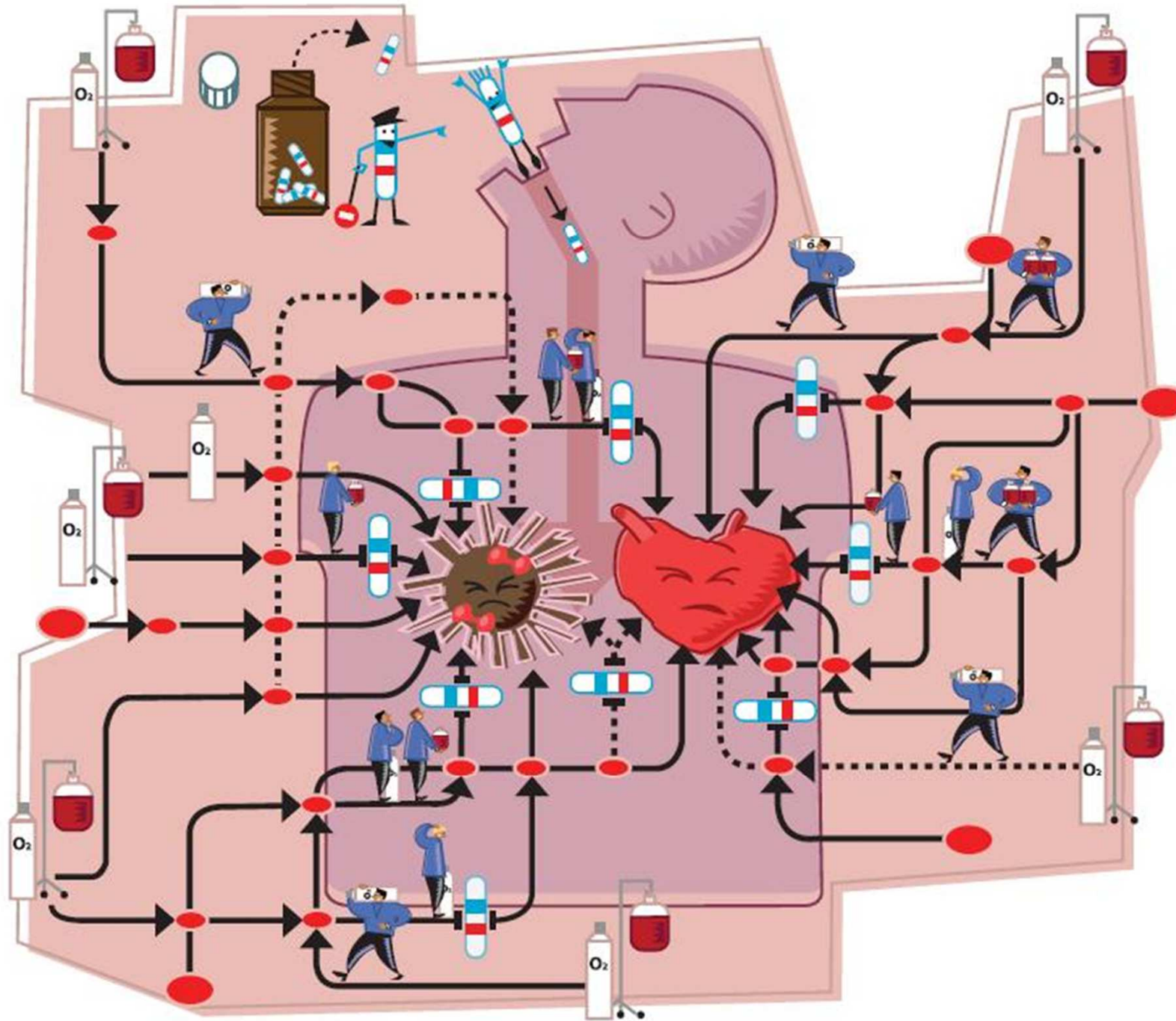


# Novel Food and Drug Administration (FDA)–approved and investigational human epidermal growth factor receptor-2 (HER2)–targeted agents being used for the treatment of breast cancer.



Ky B et al. Circulation Research 2013;113:754-764





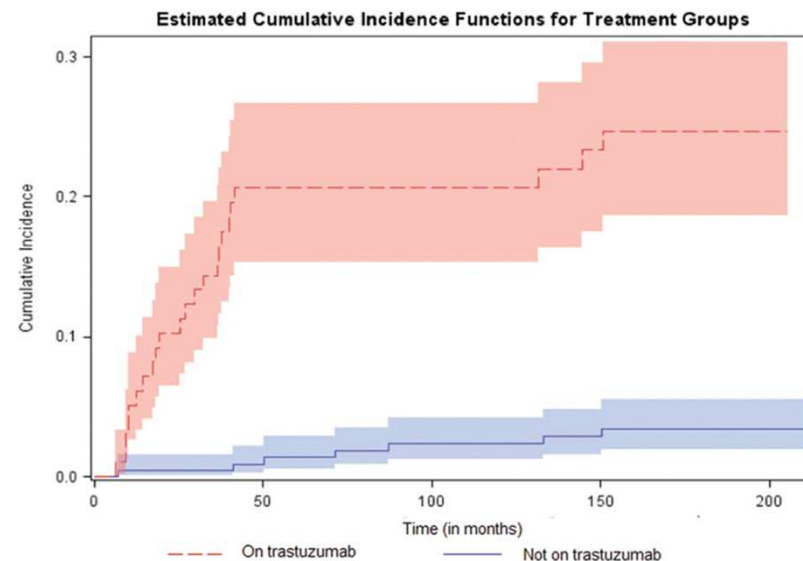
# TRASTUZUMAB

## Toxicidad

- Monoclonal anti erb-2
- ErbB2 se expresa en el miocardio
- Regulación de crecimiento celular en respuesta al estrés
- Erb-2 KO miocardiopatía dilatada

## Factores de riesgo

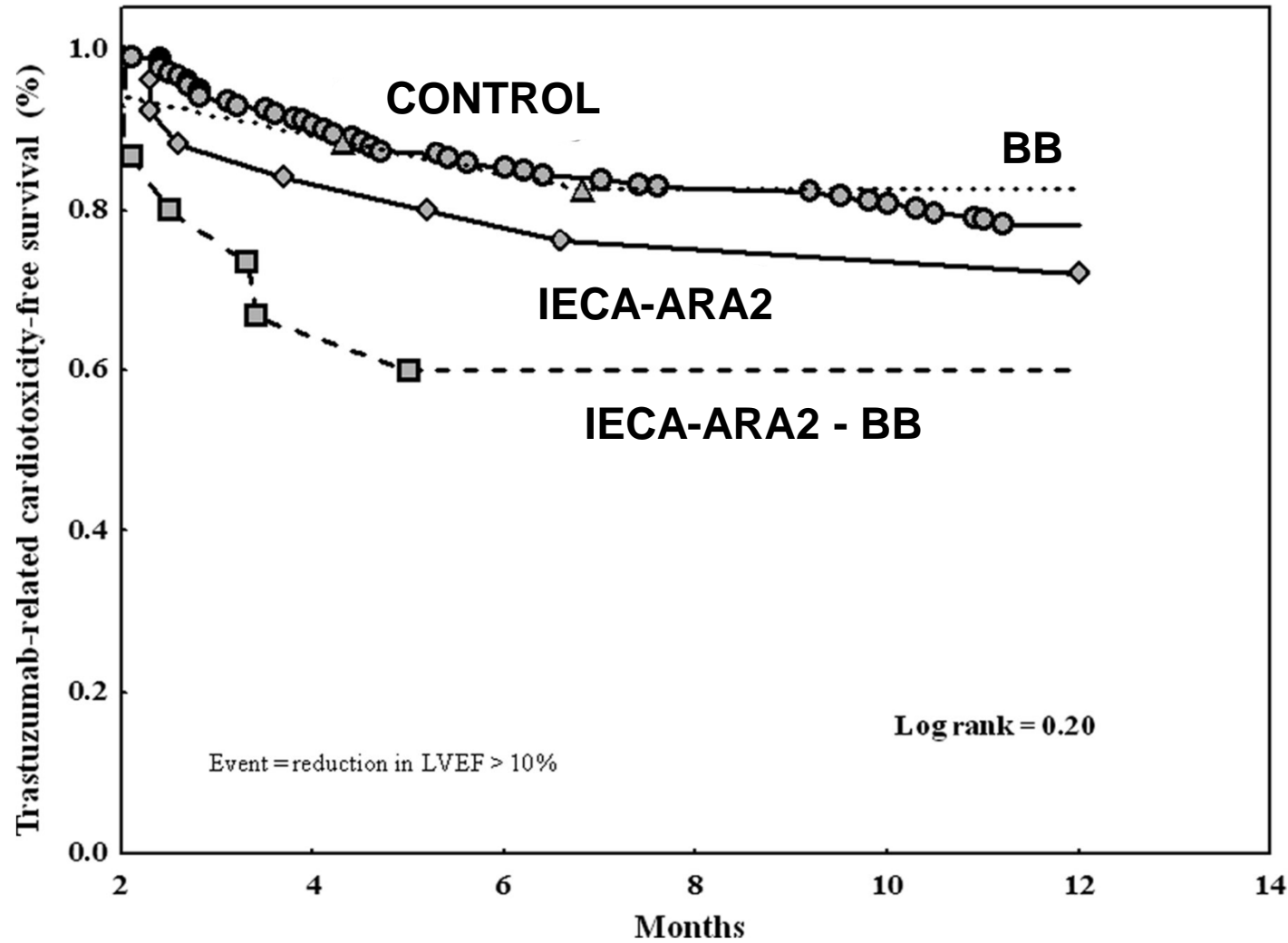
- Enf o FR vascular
- Antraciclinas !!!



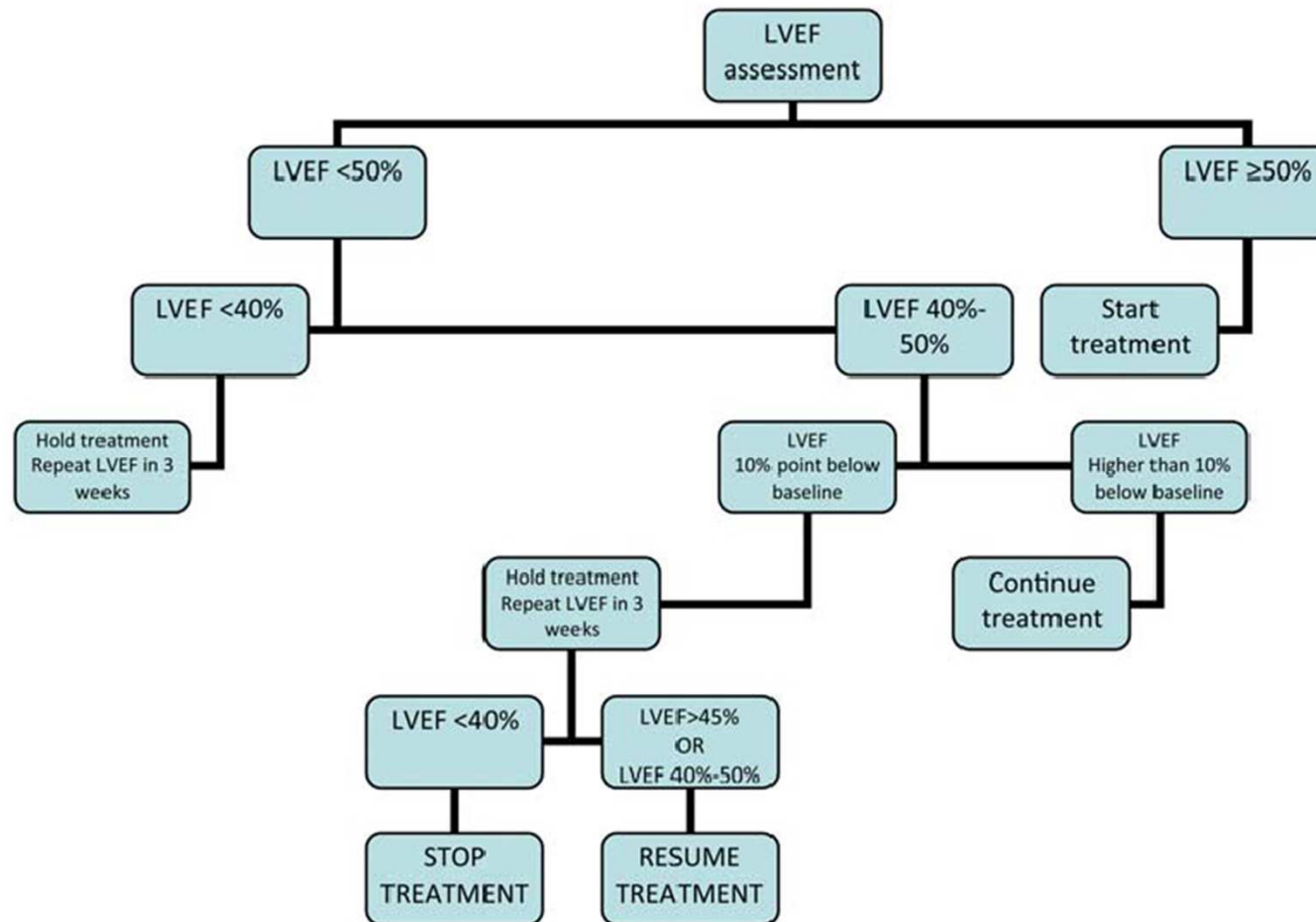
Seicean S et al. Circ Heart Fail. 2013;6:420-426

,J Am Heart Assoc. 2014;3:e000665;  
doi: 10.1161/JAHA.113.000665

# TRASTUZUMAB RELATED CARDIOTOXICITY AND MEDICAL THERAPY

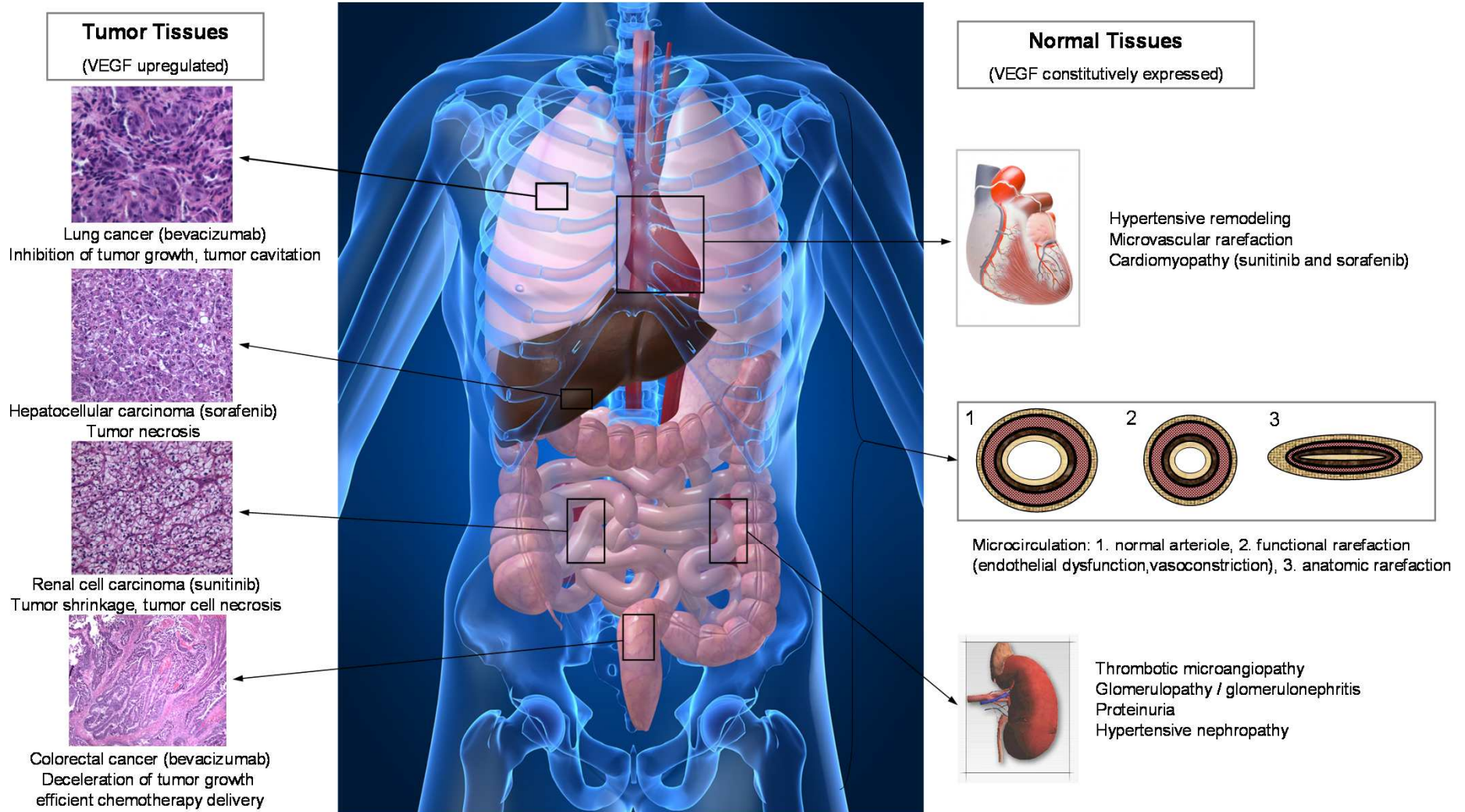


# Continuation and discontinuation of trastuzumab based on LVEF

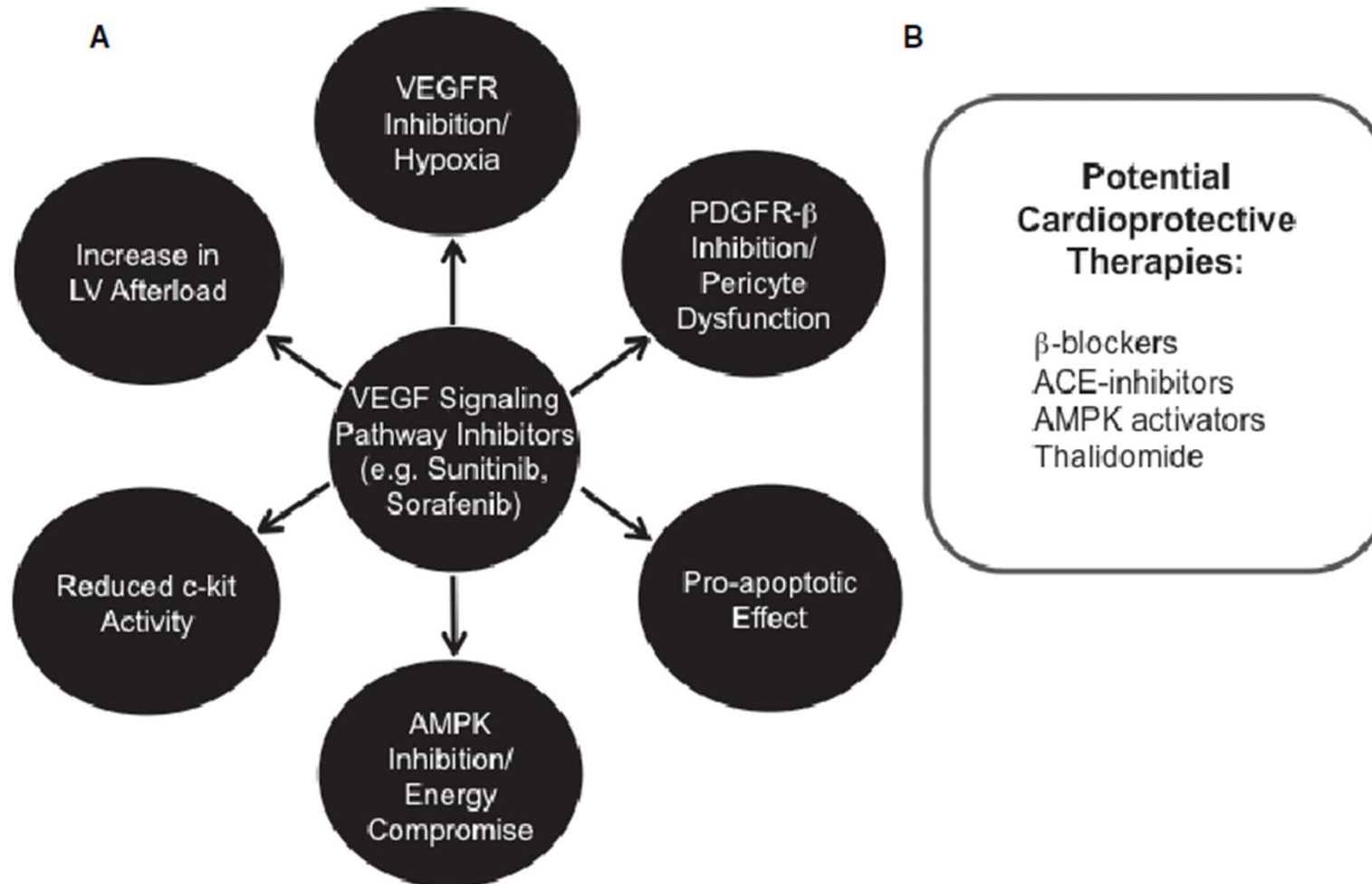




# Systemic Effects of Anti-VEGF Therapy



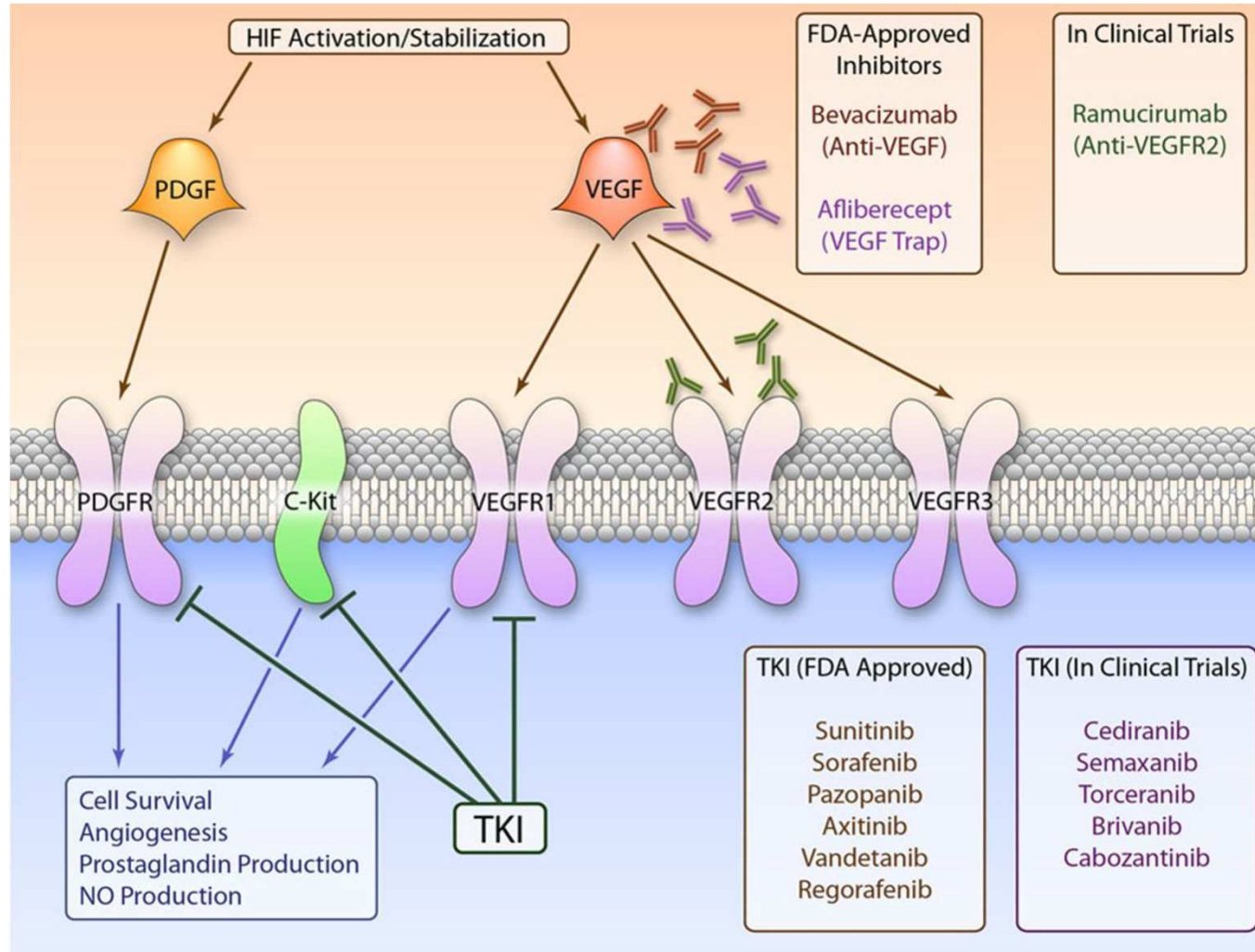
# Cardiotoxicity due to VEGF signaling pathway inhibitors



, *J Am Heart Assoc.* 2014;3:e000665;  
doi: 10.1161/JAHA.113.000665



# Angiogenesis inhibitors (vascular endothelial growth factor [VEGF] signaling pathway [VSP] inhibitors) being tested in human cancer trials.



Ky B et al. Circulation Research 2013;113:754-764

# Toxicidad vascular de los antiangiogénicos: sorafenib

## Mecanismos

- Efecto vasodilatador (NO)
- Nuevos vasos: disminución de resistencias periféricas
- Hipertensión 20-40%
  - RR x 5
- Disfunción ventricular
  - 5-10% (subclínica >25%)

## Tratamiento

- Hipotensores
- IECAs
  - Betabloqueantes
  - Metformina (?)
    - Act. AMPK
  - Talidomida

# Conclusiones

- Coexistencia de neoplasias y enfermedad vascular
- Aumento de supervivencia
  - Necesidad de mejor control de FR en pacientes (supervivientes) de cáncer
- Vigilancia toxicidad CV tratamientos oncológicos
- Valoración íntegra de los pacientes
- Control 'óptimo' de FR vascular

# El herido (II)

*Para la libertad sangro, lucho, pervivo,  
para la libertad, mis ojos y mis manos,  
como un árbol carnal, generoso y cautivo,  
doy a los cirujanos.*

*Retoñarán aladas de savia sin otoño  
reliquias de mi cuerpo que pierdo en cada herida.  
porque soy como el árbol talado, que retoño  
porque aún tengo la vida.*

*Miguel Hernández*

