Drug Induced Cardiomyopathy

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Cardiomyopathy

- A group of diseases that affect the heart muscle itself
- *Cardiomyopathy* should be restricted to a condition *primarily* involving the myocardium.
- Classified on an etiologic basis,

  (1) a primary type, consisting of heart muscle disease of unknown cause

  (2) a secondary type, consisting of myocardial disease of known cause or associated with a disease involving other organ systems

Harrison's 16th edition

Etiologic Classification of Cardiomyopathies

PRIMARY MYOCARDIAL INVOLVEMENT

Idiopathic (D,R,H)
Familial (D,R,H)
Eosinophilic endomyocardial disease (R)
Endomyocardial fibrosis (R)

SECONDARY MYOCARDIAL INVOLVEMENT

Infective (D)
- Viral myocarditis
- Bacterial myocarditis
- Fungal myocarditis
- Protozoal myocarditis
- Metazoal myocarditis
- Spirochetal
- Rickettsial

Metabolic (D)
Familial storage disease (D,R)
- Glycogen storage disease
- Mucopolysaccharidoses
- Hemochromatosis
- Fabry's disease

Deficiency (D)
- Electrolytes
- Nutritional

Connective tissue disorders (D)
- Systemic lupus erythematosus
- Polyarteritis nodosa
- Rheumatoid arthritis
- Progressive systemic sclerosis
- Dermatomyositis

Infiltrations and granulomas (R,D)
- Amyloidosis
- Sarcoidosis
- Malignancy

Neuromuscular (D)
- Muscular dystrophy
- Myotonic dystrophy
- Friedreich's ataxia (H,D)

Sensitivity and toxic reactions (D)
- Alcohol
- Radiation
- Drugs

Peripartum heart disease (D)

WHO/ISFC task force report 1980

Drug Induced Cardiomyopathy

- Acute myocardial damage (myocarditis)
  or chronic damage (idiopathic DCMP)
- ECG abnormalities, fulminant CHF and death
- Some pts with CHF, recovery of cardiac function with aggressive management with ACEI and diuretics
- Late asymptomatic contractile dysfunction may occur, even in those without initial cardiotoxicity.

Chemotherapeutic Agents

Chemotherapeutic Agents

Agent	Short-term Toxicity	Long-term Toxicity
Doxorubicin	Arrhythmias Pericarditis-myocarditis MI, SCD	Cardiomyopathy CHF
Trastuzumab	Ventricular dysfunction CHF	Cardiomyopathy
Amsacrine	Ventricular arrhythmia ECG change	Cardiomyopathy
Interferon-α-2a	Hypotension Arrhythmia	Cardiomyopathy
Interleukin-2	Myocardial injury Myopericarditis Ventricular arrhythmia Hypotension, SCD	Dilated cardiomyopathy

LV dysfunction - HF

Anthracyclines

Doxorubicin

Highly dose-dependent

Risk factors; age, prior mediastinal XRT, history of heart disease, decreased EF, drop in EF on drug therapy, female gender (for children), and other agents (especially trastuzumab)

Risk decreased by liposomal encapsulation or dexrazoxane

Mitoxantrone

Derivative with somewhat lower risk; efficacy questionable; used in patients with multiple sclerosis at lower doses

Alkylating agents

Cyclophosphamide, ifosfamide

Primarily seen with high dose “conditioning” regimens;

Risk factors: prior mediastinal XRT or anthracycline drug therapy, and imatinib or pentostatin (?);

Can have myocarditis, pericarditis, myocardial necrosis

LV dysfunction - HF

Alkylating agents

Mitomycin

Risk increased with high doses, anthracyclines, or XRT

Taxanes

Paclitaxel

Seen with concurrent anthracycline therapy; caused by retarded metabolism of anthracycline; largely preventable with dosing regimen; not seen with docetaxel; trastuzumab increases risk of heart failure

Targeted therapeutics

Trastuzumab

Relatively uncommon as single agent;
Increased risk with anthracyclines, paclitaxel, cyclophosphamide

Anthracyclines

- Doxorubicin (Adriamycin), daunorubicin (Cerubidine), epirubicin (Ellence), and idarubicin (Idamycin PFS),
  - efficacy in lymphomas and many solid tumors, including breast and small cell lung cancer

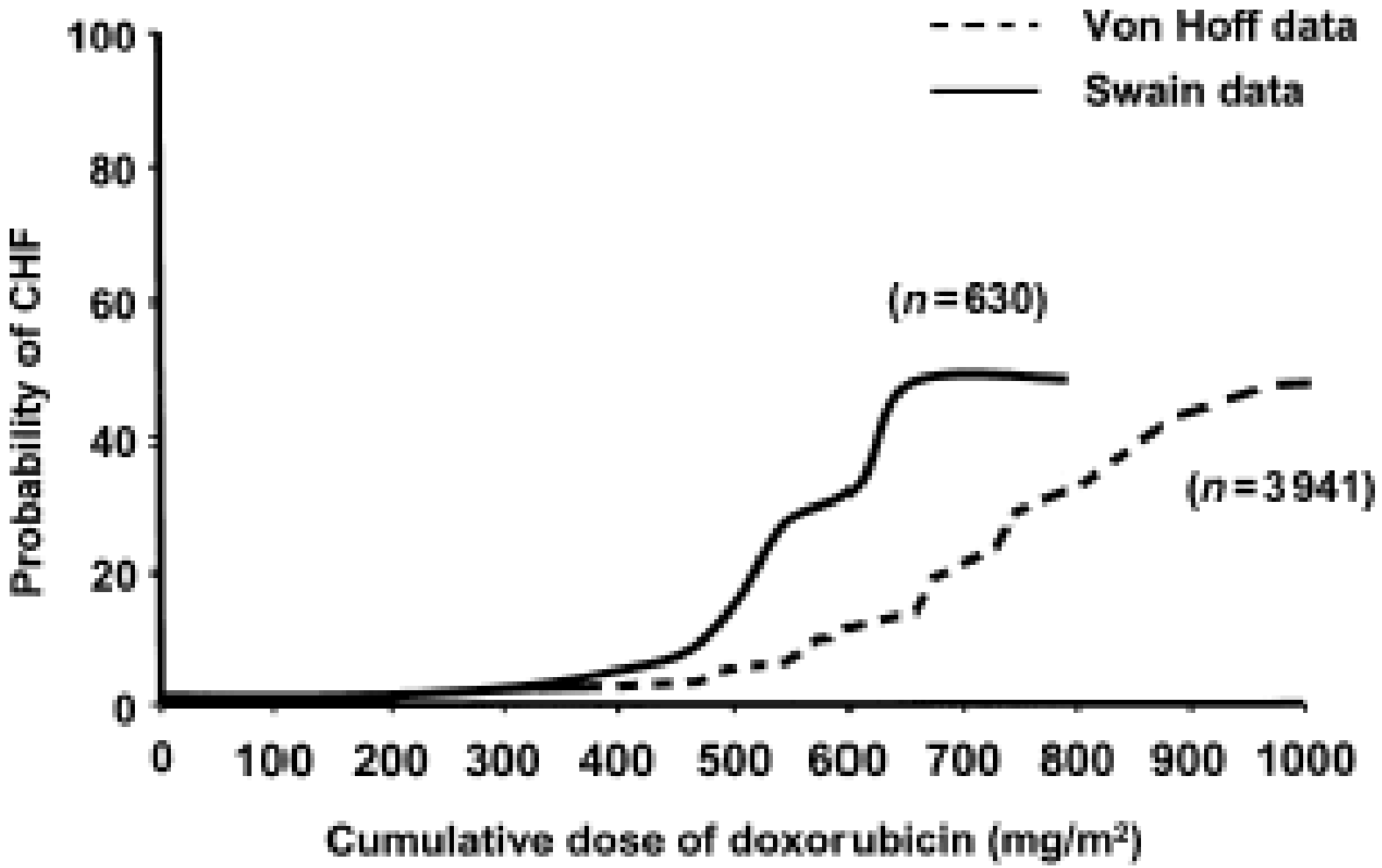
- Cardiotoxic: arrhythmias, LV dysfunction, and pericarditis, and heart failure (HF)
- Cardiac toxicity: cumulative dose-dependent
- Predictors of cardiotoxicity

  Baseline LV EF < 50 % or a decline in LVEF of more than 10 % on treatment to a level less than 50 %

Anthracyclines

- Incidence of HF: 2.2 % overall &
  7.5 % in pts with cumulative dose of 550 mg/m^2
- Incidence rises significantly for cumulative doses above 400-450 mg/m^2 for doxorubicin
- Oncologists limit the dose to 450-500 mg/m^2

- Anthracycline cardiomyopathy:
  within the first year of completing therapy,
  with a median of 5 to 9 months
- The cardiomyopathy may be progressive over years.



	Estimation of doxorubicin-induced CHF		
	400 mg/m²	550 mg/m²	700 mg/m²
Von Hoff	3%	7%	18%
Swain	5%	26%	48%

Wouters KA, Br J Haematol 2005;131:561

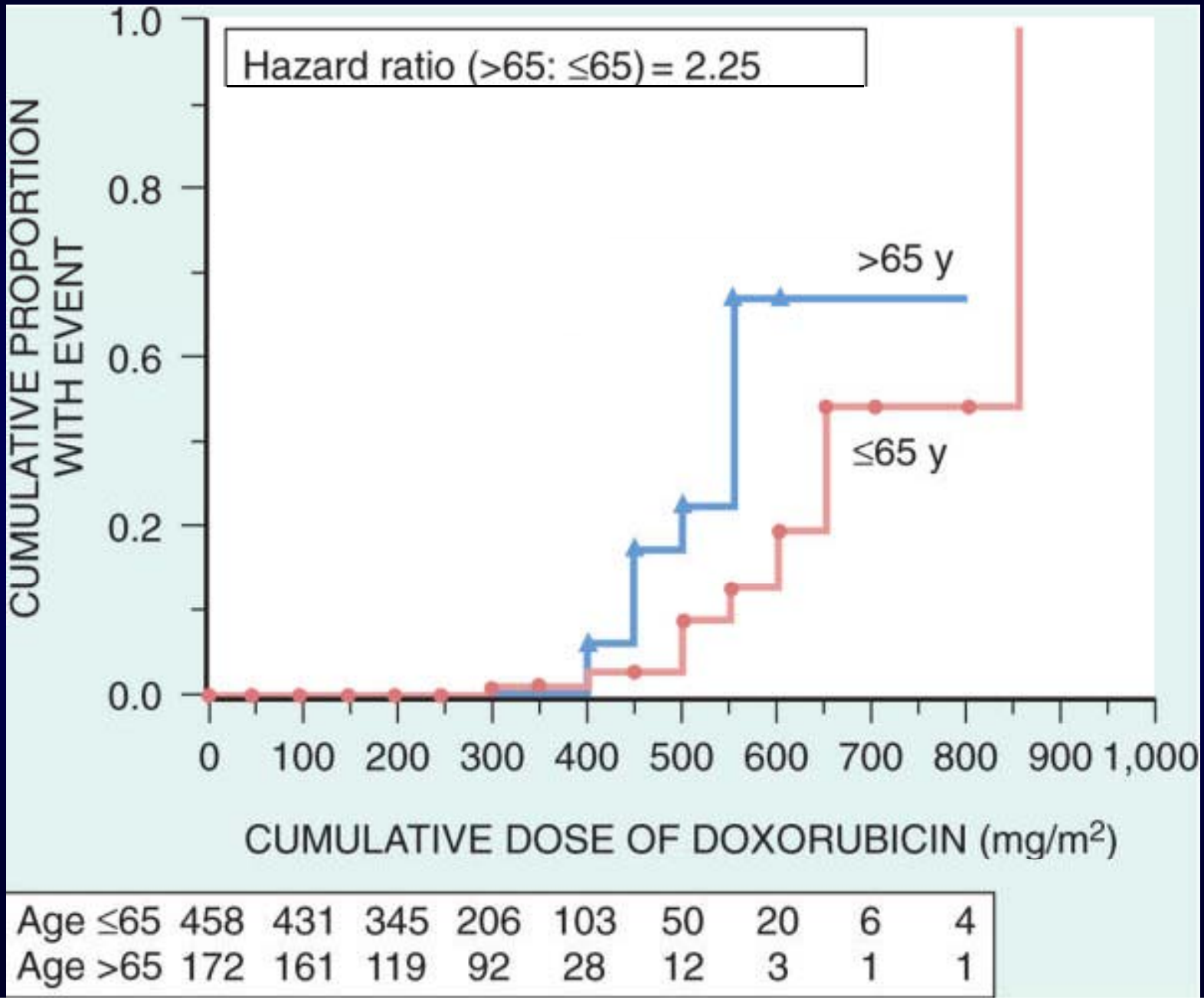
Anthracyclines

Risk factors for cardiomyopathy

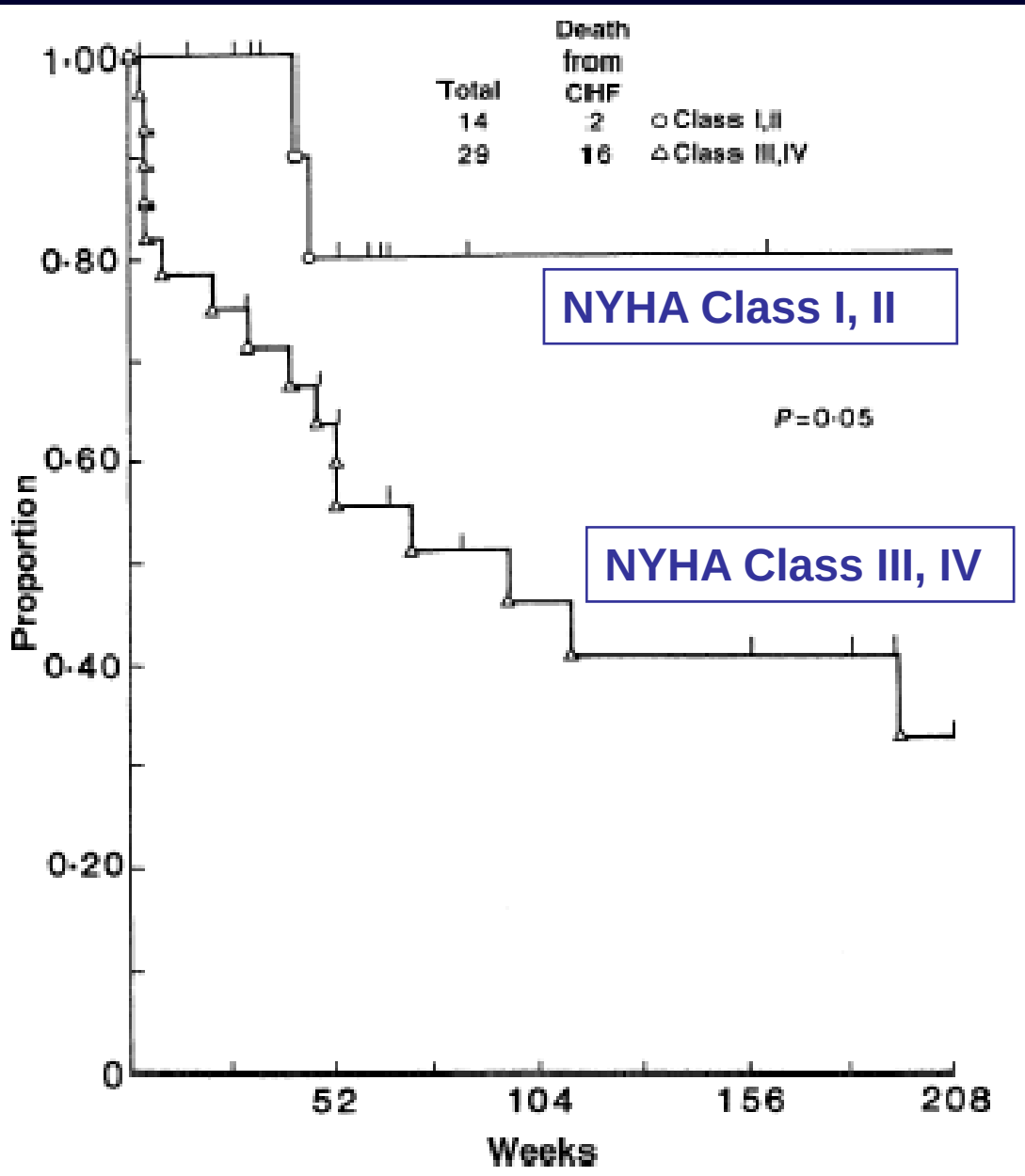
- Degree of anthracycline exposure
  (high-dose anthracycline infusion or
  higher cumulative doses above 450 mg/m^2)
- Age (the elderly and very young patients)
- History of cardiac disease
- Previous cancer therapies (e.g. mediastinal radiation)
- Concurrent use of chemotherapy regimens
  (cyclophosphamide, paclitaxel or trastuzumab)
- Hypertension
- Liver disease

Outomuro D, et al. Int J Cardiol 2007;117:6
Takemura G, et al. Prog Cardiovasc Dis 2007;49:330

Risk of doxorubicin-associated CHF by patient age



Survival of patients with doxorubicin-induced HF



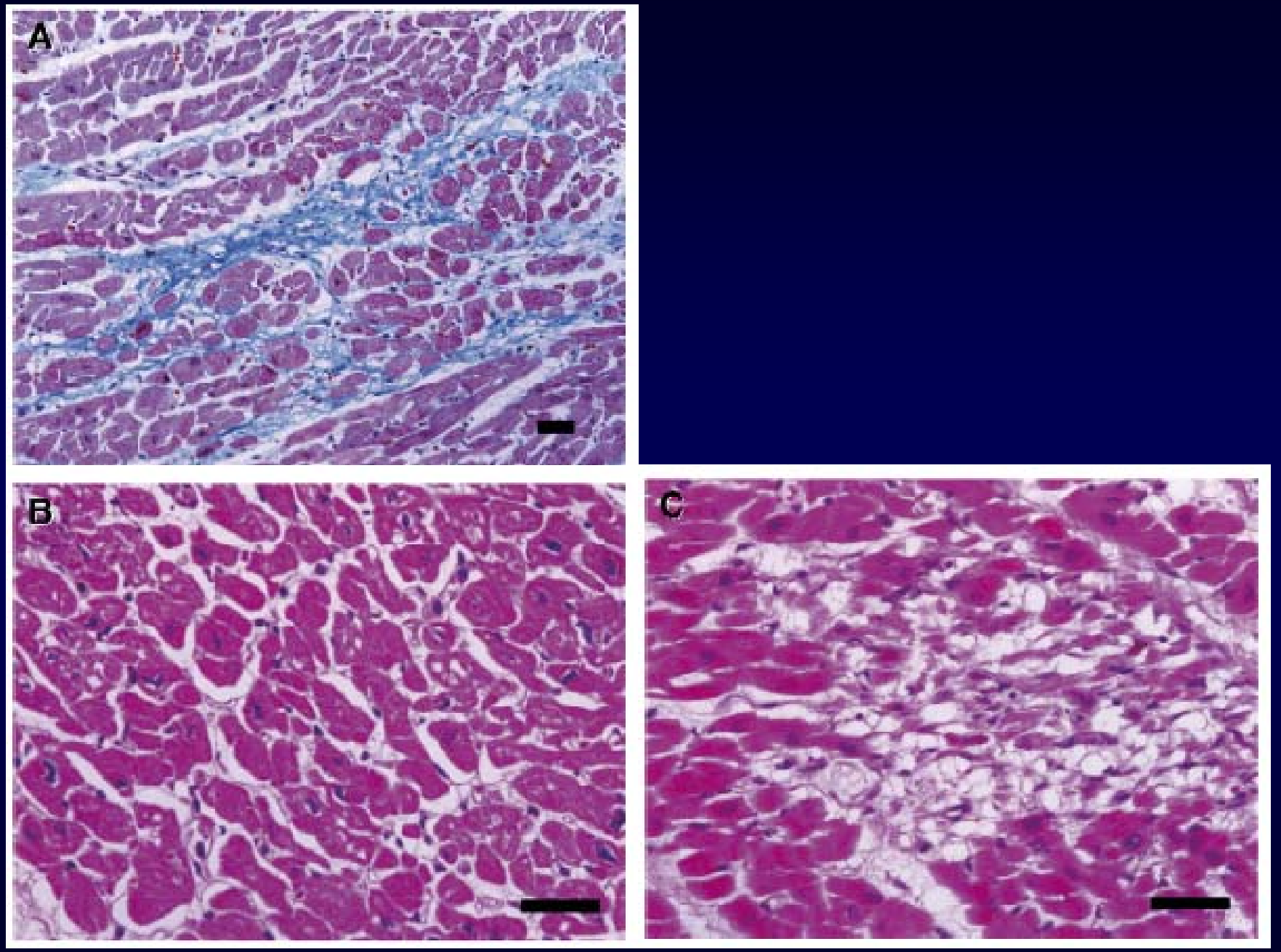
1-year mortality rate for ambulatory pts with doxorubicin-induced NYHA class III–IV HF is 40%,
and the 2-year mortality rate 60%

Wouters KA, Br J Haematol 2005;131:561

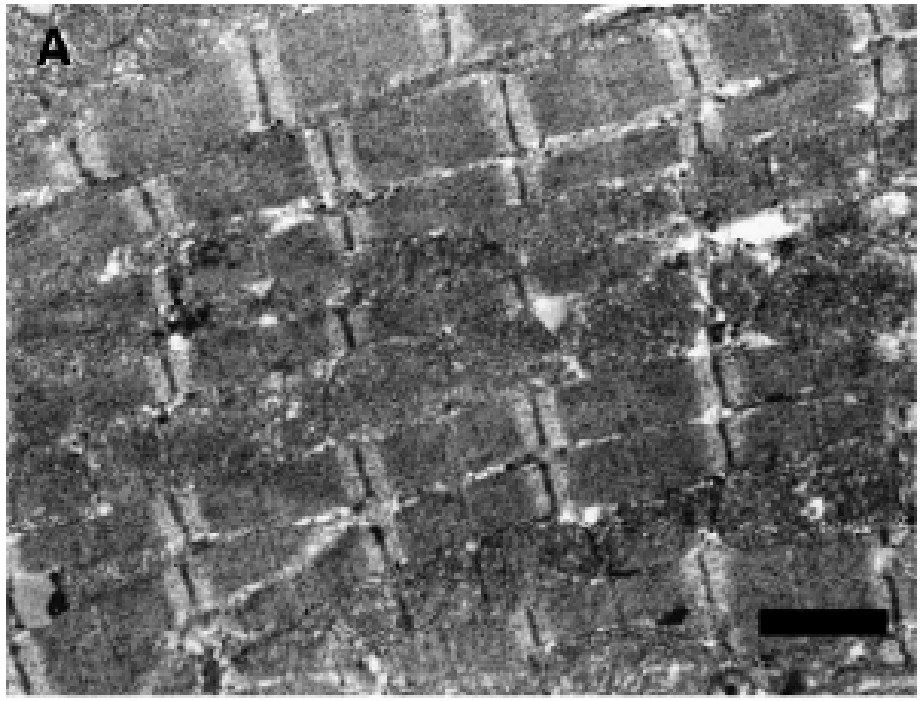
Anthracyclines

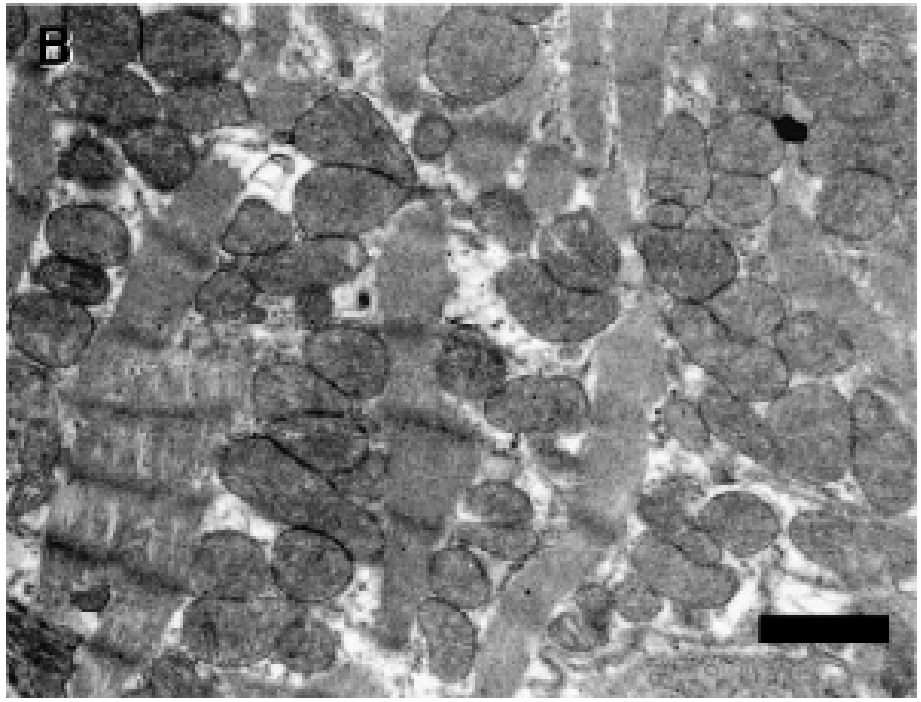
- Endomyocardial biopsy:
  - The most sensitive method to detect cardiotoxicity
  - Cytosolic vacuolization, lysis of myofibrils, cellular swelling, necrotic form of cell death
  - Not a practical way to detect or follow pts with anthracycline cardiotoxicity

- Serial determination of LV function, although insensitive, is the currently accepted method.



Takemura G, et al. Prog Cardiovasc Dis 2007;49:330

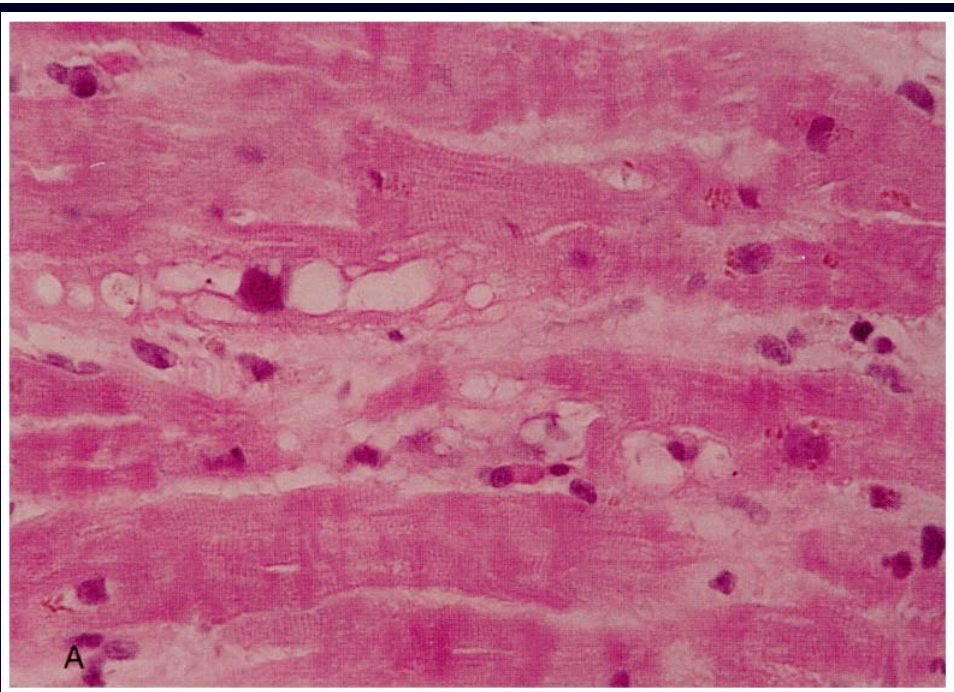


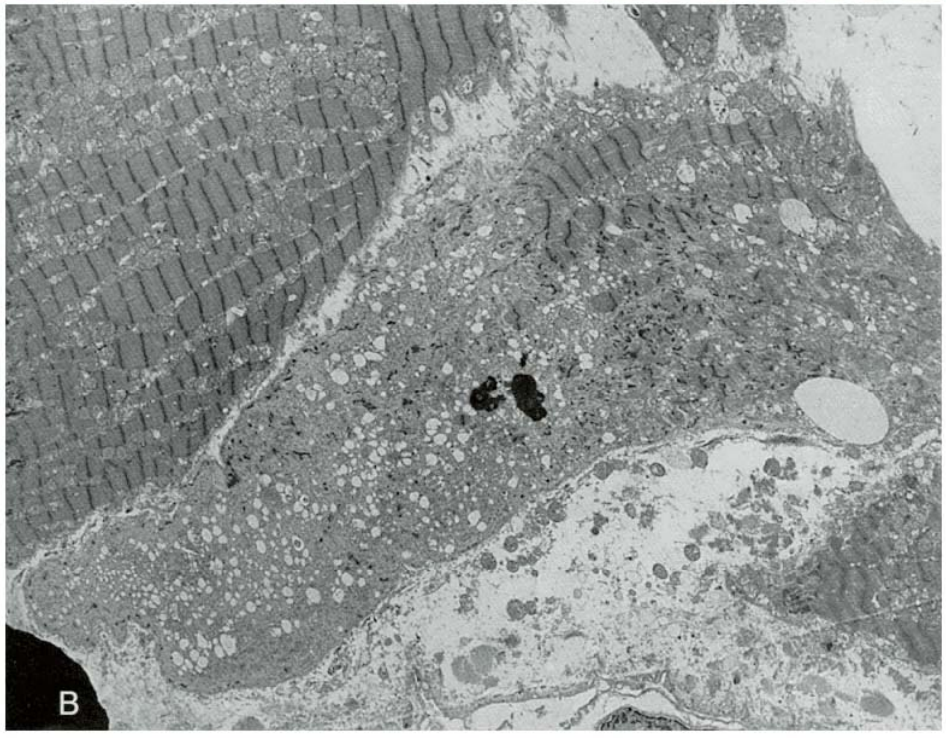


Healthy mouse heart

Heart affected by DOX-induced cardiomyopathy

Takemura G, et al. Prog Cardiovasc Dis 2007;49:330





Doxorubicin-associated cardiomyopathy

Grade 2 doxorubicin toxicity

Pt with breast ca

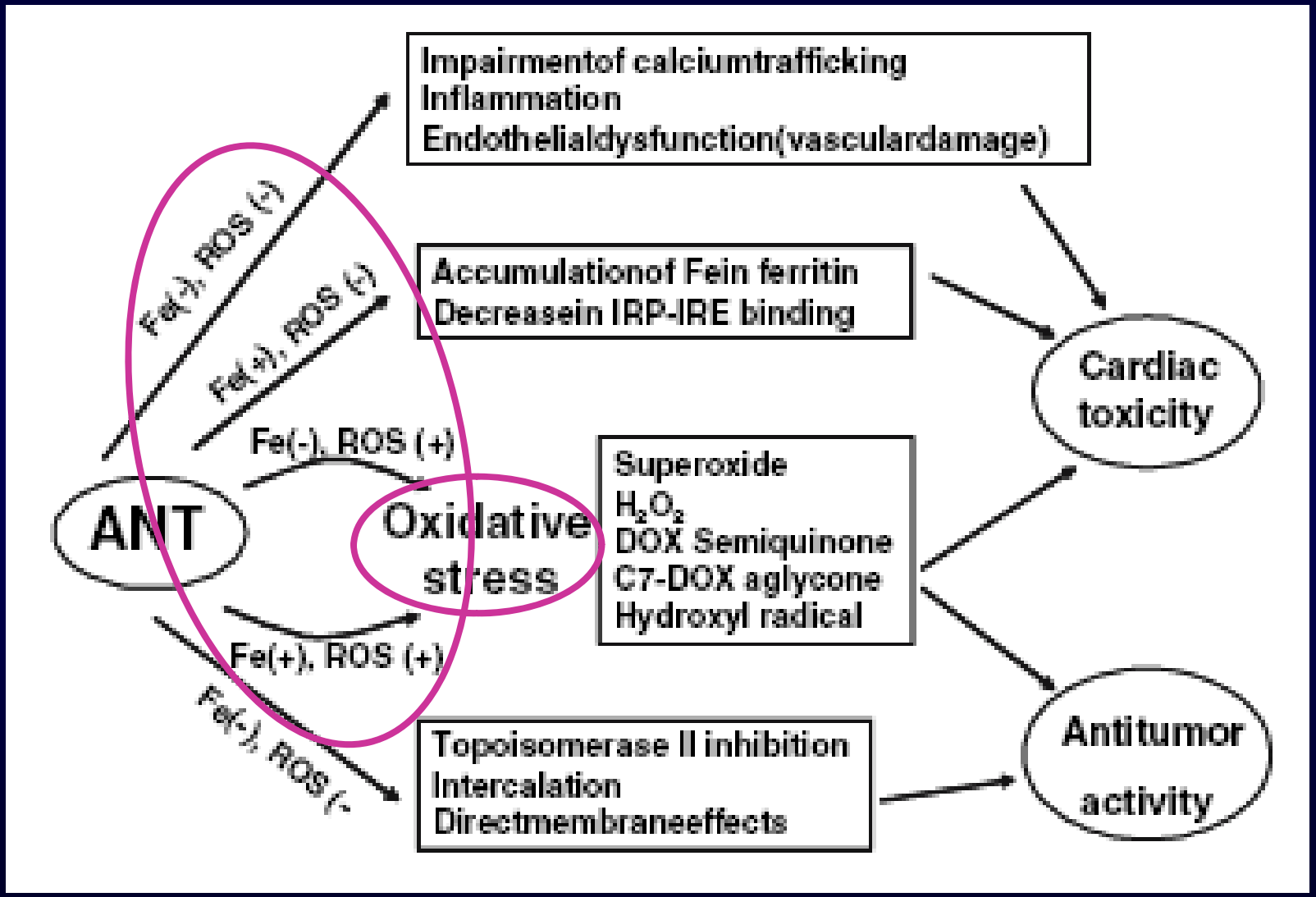
Felker GM, et al. Medicine 1999;78:270

Anthracyclines

- The cellular mechanisms
  - Oxidant stress leading to iron oxidation and generation of free radicals that damage cell and organelle membranes via peroxidation of lipids
  - Activation of calpains, proteases that degrade structural proteins in the cardiomyocyte

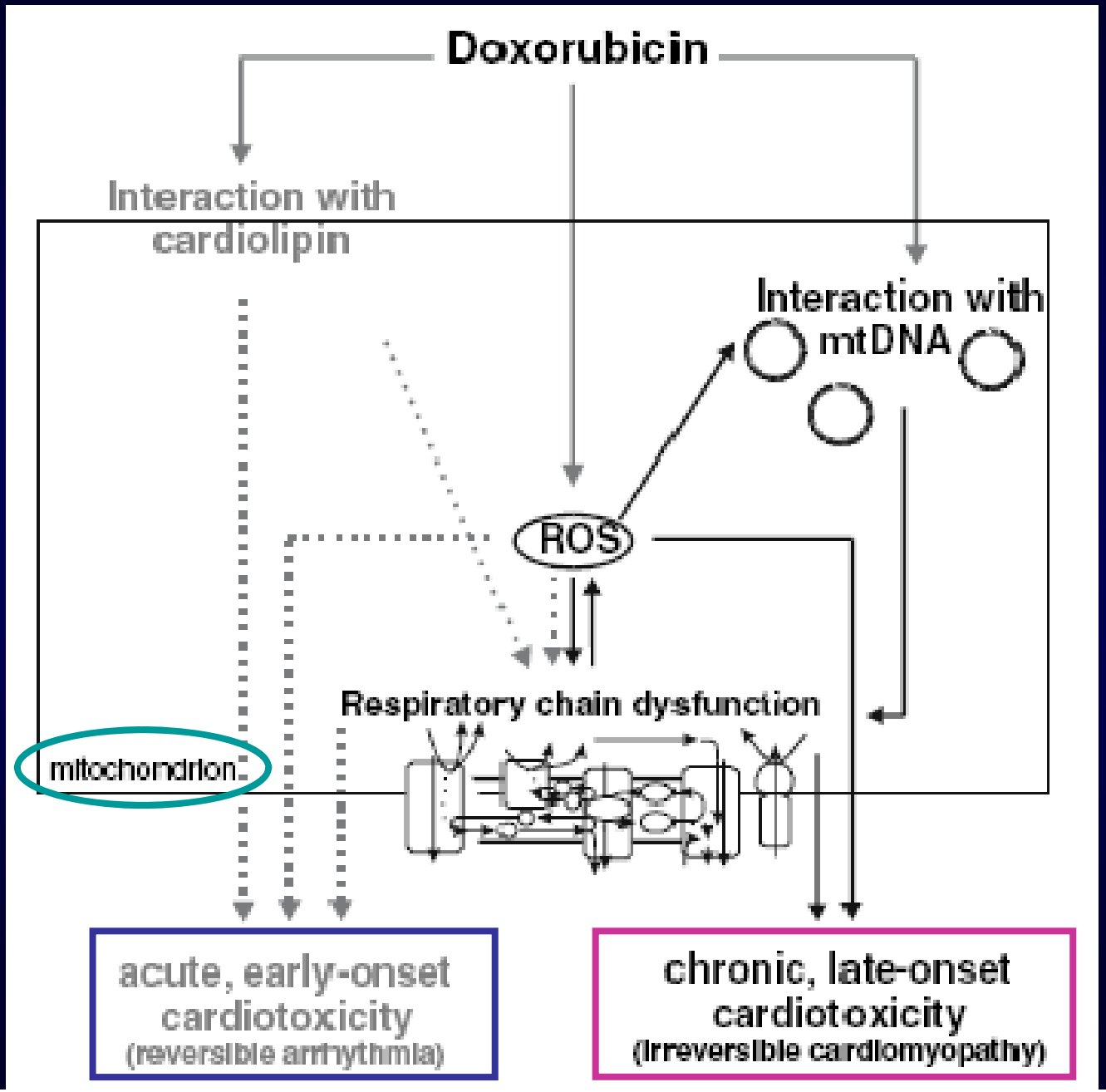
- Anthracyclines form complexes with iron ions
  → production of reactive oxygen species responsible for the lipid peroxidation of mitochondrial and endoplasmatic reticulum membranes
  - The major cause of anthracycline-induced cardiotoxicity

Proposed interactions of Anthracyclines with tumor and cardiac cells



Kaiserova H, et al. Cardiovasc Toxicol 2007;7:145

Mechanism of late-onset doxorubicin cardiomyopathy



Lebrecht D, et al. Cardiovasc Toxicol 2007;7:108

Adriamycin-induced interference with cardiac mitochondrial calcium homeostasis

- Mitochondria: principal target for cardiomyopathy
- Adriamycin redox cycles on complex I of the mitochondrial electron transport chain to liberate highly reactive free radical species of oxygen
- Interference with oxidative phosphorylation and inhibition of ATP synthesis
- Free radicals liberated from adriamycin redox cycling lipid peroxidation, the oxidation of both proteins and DNA, and the depletion of glutathione and pyridine nucleotide reducing equivalents in the cell

Wallace KB. Cardiovasc Toxicol 2007;7:101

Adriamycin-induced interference with cardiac mitochondrial calcium homeostasis

- Altered redox status → assorted changes in intracellular regulation: induction of the mitochondrial permeability transition and complete loss of mitochondrial integrity and function
- Interference with mitochondrial-mediated cell calcium signaling, essential in bioenergetic regulation

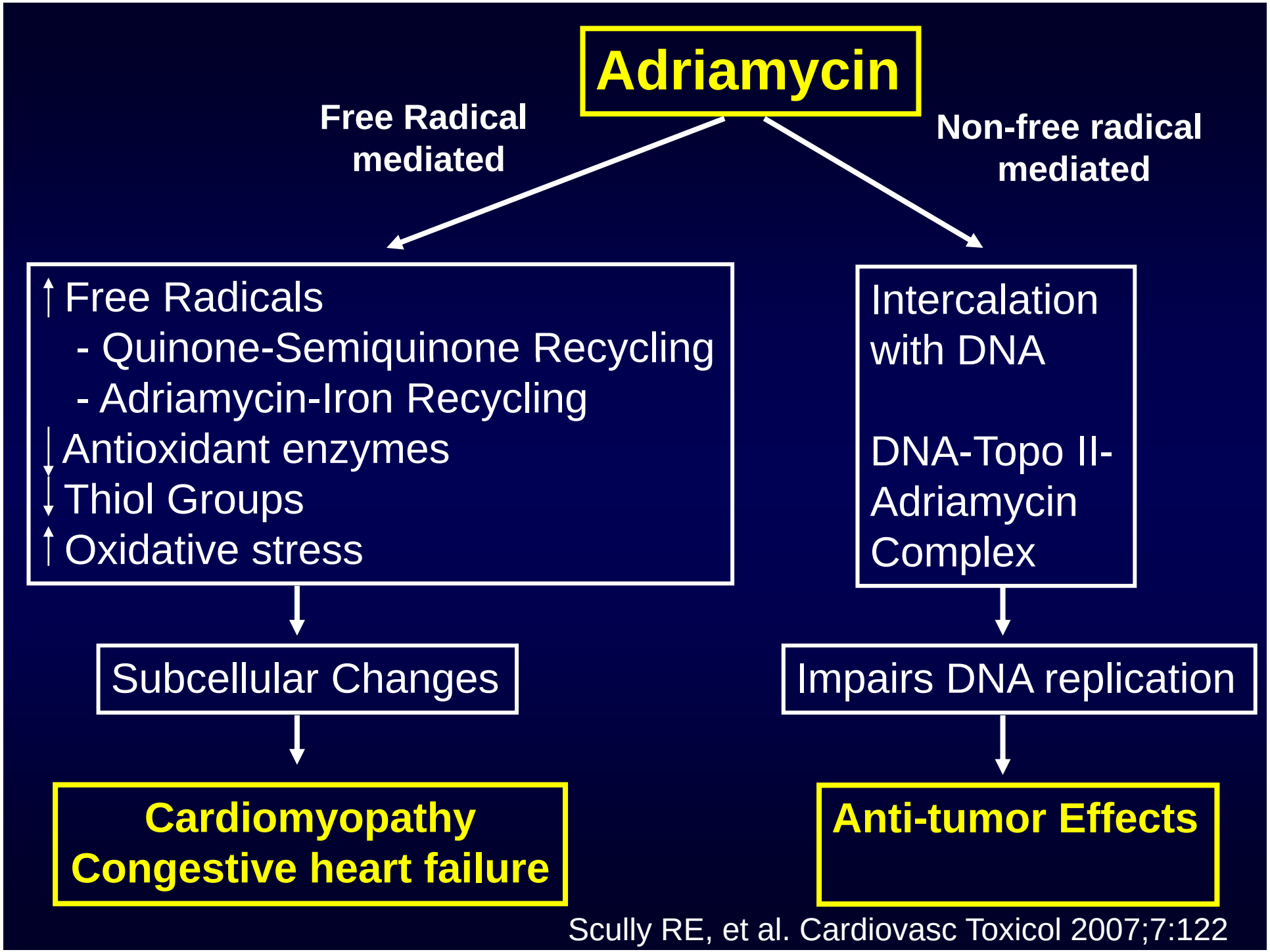
  → signals mediating either oncotic or necrotic cell death, further perpetuating the cardiac failure associated with adriamycin-induced mitochondrial cardiomyopathy

Wallace KB. Cardiovasc Toxicol 2007;7:101

Pathophysiology of anthracycline-induced cardiotoxicity

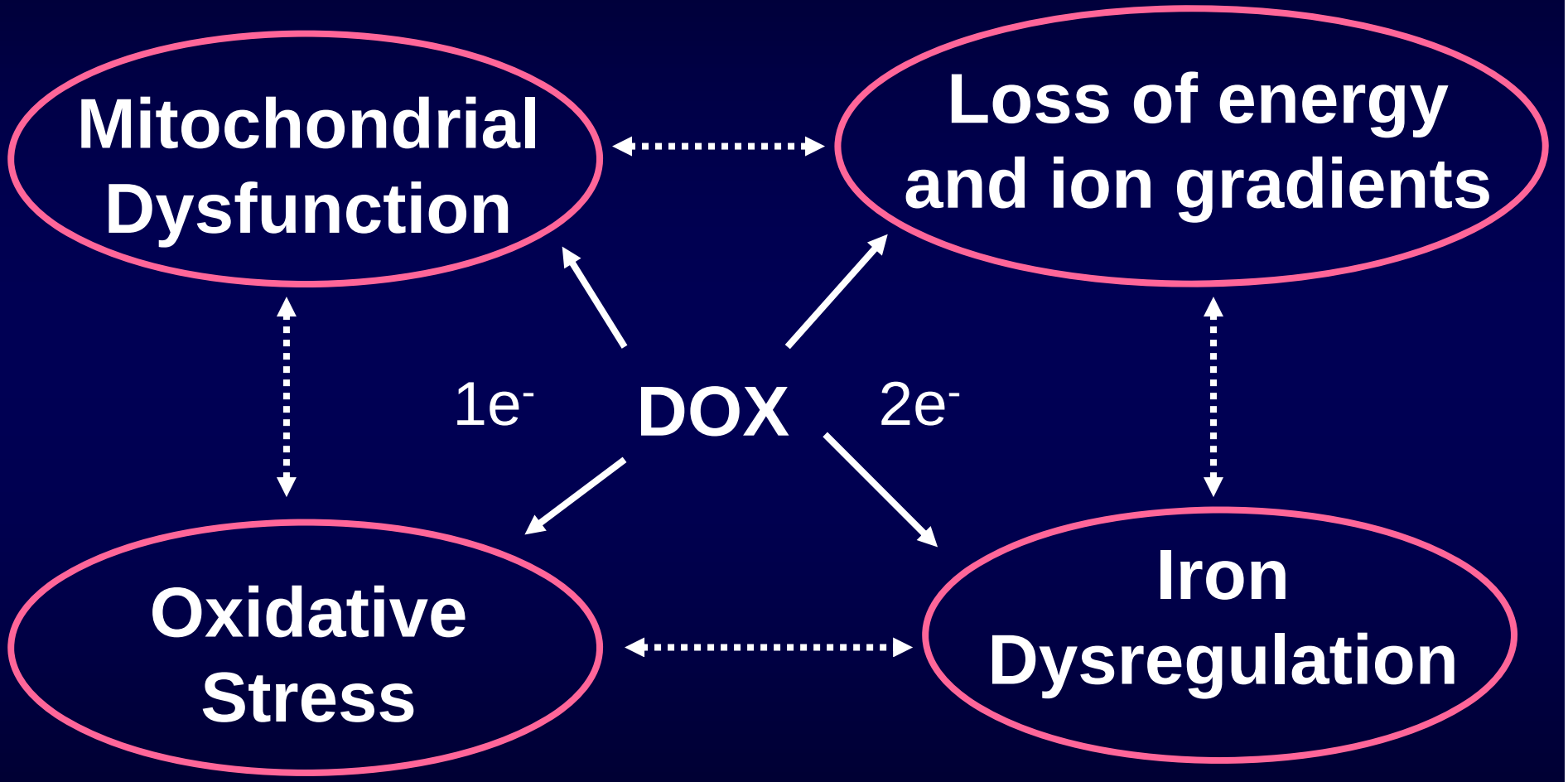
- Myocyte damage: concentration-dependent increase of intracellular oxidative stress → increase in cytosolic calcium, mitochondrial dysfunction, and induction of myocyte apoptosis or necrosis
- Role of reactive oxygen species (ROS) as a mediator of anthracycline-induced damage to the heart
- ROS not only lead to cell death, but also directly affect excitation-contraction coupling and calcium signaling in cardiomyocytes.

Zuppinger C, et al. Cardiovasc Toxicol 2007;7:61



Scully RE, et al. Cardiovasc Toxicol 2007;7:122

Anthracycline metabolism and toxicity



Menna P, et al. Cardiovasc Toxicol 2007;7:80

Mechanisms of Anthracyclines-Cardiotoxicity

- Oxidative stress hypothesis
- Metabolite theory
- Influence on calcium homeostasis
- Role of immune system
- Apoptosis

Schimmel KJ, et al. Cancer Treat Rev 2004;30:181
Outomuro D, et al. Int J Cardiol 2007;117:6

Monitoring and markers of cardiotoxicity

- Routine cardiac imaging studies (echocardiogram or multiple gated acquisition scans):
  identify (sub)clinical myocardial dysfunction
- Endomyocardial biopsy: limited by its invasiveness
- Ttroponin T: myocardiocyte damage & dysfunction
- BNP: detection of subclinical LV dysfunction

Schimmel KJ, et al. Cancer Treat Rev 2004;30:181
Takemura G, et al. Prog Cardiovasc Dis 2007;49:330

Protection of Anthracyclines-Cardiotoxicity

- Oxidized iron hypothesis → use of dexrazoxane (ICRF-187, Zinecard), a chelator of intracellular iron

- Dexrazoxane: rapid and complete binding of ferric and ferrous ions, even by displacing the metal ions from complexes with anthracyclines

- American Society of Clinical Oncology recommendations: the use of dexrazoxane be limited to pts who have received more than 300 mg/m^2 of doxorubicin or the equivalent

Protection of Anthracyclines-Cardiotoxicity

- Epirubicin, a stereoisomer of doxorubicin
  - Less cardiotoxicity than doxorubicin
  - 900-1000 mg/m^2 of epirubicin produces cardiotoxicity comparable to 450-500 mg/m^2 of doxorubicin

- Encapsulating doxorubicin within liposomes (Myocet, approved in Europe)
  - Reduce delivery of the drug to the heart
  - Reduce cardiotoxicity, as assessed by clinical criteria or assessment of LV function

Protection of Anthracyclines-Cardiotoxicity

- Lipid lowering agents: Probucol
  Rats treated with doxorubicin and probucol
  (lipid lowering and antioxidant agent)
  → increase in the antioxidant enzymes superoxide dismutase and glutathione peroxidase activities and a decrease in lipid peroxidation

Schimmel KJ, et al. Cancer Treat Rev 2004;30:181

Prevention of DOX-induced cardiomyopathy

- Dose limitation: cumulative dose < 450 mg/m2
- Close cardiac monitoring
- Alternative methods for drug delivery
  - Continuous slow infusion
  - Liposomal encapsulation
- Development of new anthracycline analogs: EPI, IDA
- Administration of protective agents
  - Probucol
  - Dexrazoxane (ICRF-187)
- Hematopoetic cytokines:
  Erythropoietin, thrombopoietin, GCSF

Outomuro D, et al. Int J Cardiol 2007;117:6
Takemura G, et al. Prog Cardiovasc Dis 2007;49:330

Trastuzumab

- Trastuzumab for metastatic breast cancer
  - Decrease in LV EF, especially in conjunction with paclitaxel or anthracyclines
  - Not cumulative or dose dependent
  - Cardiac function often returns to normal after it is discontinued

Trastuzumab

- Cardiotoxicity in three key trials in breast cancer pts
- Pts who underwent surgery plus adjuvant or neoadjuvant chemotherapy and/or radiotherapy, were randomized to received herceptin or simply observation.
- Excluded (1) more than 360 mg/m^2 of doxorubicin or 720 mg/m^2 of epirubicin, (2) prior mediastinal radiation (3) EF < 55%
- At 1 year of f/u,

  significant declines in LVEF: 7.1% in the trastuzumab vs 2.2% in the observation arm

  symptomatic HF: 1.7% in the trastuzumab vs 0% in the observation arm

Trastuzumab

- The other two studies with more aggressive regimens—doxorubicin+cyclophosphamide followed by (1) placebo versus paclitaxel versus paclitaxel plus trastuzumab, followed by (2) placebo versus trastuzumab.
- Follow-up was for a mean of 27 months. In this trial, 8.7% of pts in the trastuzumab arms vs 1.6% in the no-trastuzumab arm developed symptomatic HF.
- 2.2-4.1% developed severe HF on trastuzumab vs 0.2-0.8% on placebo.
- Significant declines in EF were roughly twice, 18-34% of pts on trastuzumab vs 8-17% on placebo

Mechanisms of Toxicity of Trastuzumab

- Trastuzumab is an antibody therapy against the human epidermal growth factor receptor-2 (HER2)
- Her2 gene knockout mice(designated ErbB2 in mice) developed a spontaneous dilated cardiomyopathy.
- Inhibition of Her2 in pts may have amplified the severity of doxorubicin toxicity by preventing repair neuregulin, the endogenous ligand for Her2, can decrease anthracycline cardiotoxicity
- Cellular mechanisms of the toxicity of ErbB2 inhibition may include activation of the intrinsic-mitochondrial proapoptotic pathway by downregulating antiapoptotic BclxL and upregulating BclxS, leading to mitochondrial dysfunction and cell death.

Management of HF induced by cancer therapeutic agents

- As any pt with newly diagnosed HF
- Trastuzumab: some degree of reversibility of LV dysfunction with aggressive Tx with ACEI & beta blockers.
- Pts whose LV dysfunction largely resolves after withdrawal of the agent and institution of a HF regimen may be safely rechallenged with the agent, although continuing the HF regimen.

Cocaine

Cocaine-Induced Myocardial Dysfunction

- Long-term cocaine abuse: LVH, LV diastolic and/or systolic dysfunction, dilated cardiomyopathy
- Approximately 7% of asymptomatic long-term abusers have radionuclide ventriculographic evidence of LV systolic dysfunction.

Cocaine-Induced Myocardial Dysfunction

- Cocaine cause an acute or chronic deterioration of LV performance.

- Acute cocaine toxicity:
  - Focal myocyte necrosis
  - Focal myocarditis
  - Sarcoplasmic vacuolization
  - Myofibrillar loss

Cocaine-Induced Myocardial Dysfunction

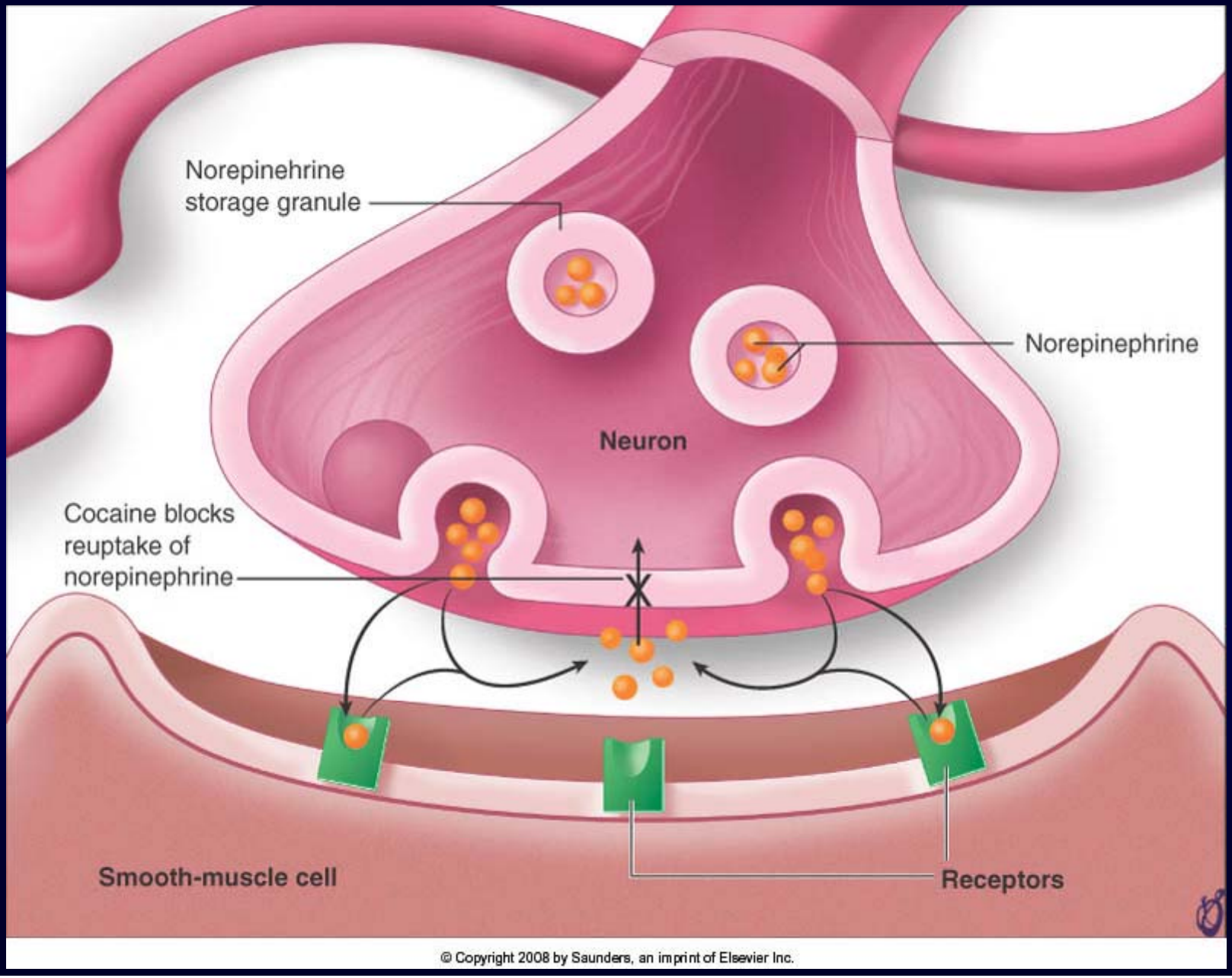
1. Myocardial ischemia or infarction
2. Repetitive sympathetic stimulation → cardiomyopathy and subendocardial contraction band necrosis
3. Concomitant administration of adulterants or infectious agents → myocarditis
4. Animal studies: cocaine alters cytokine production in the endothelium and in circulating leukocytes, induces the transcription of genes; changes in the composition of myocardial collagen and myosin, and induces myocyte apoptosis

Cocaine-Induced toxic effects on the myocardium

- Scattered foci of myocyte necrosis, myocarditis, and foci of myocyte fibrosis → cardiomyopathy
- Block sodium channels → local anesthetic or membrane-stabilizing effect
- Block reuptake of catecholamines in the presynaptic neurons in the central and peripheral nervous system, resulting in increased sympathetic output and increased catecholamines.
- Direct calcium effect leading to contraction of vessels and contraction bands in myocytes, hypersensitivity, and increased platelet aggregation

Kloner RA, et al. Circulation 1992;85:407

Cocaine alters sympathetic tone



Amphetamines

- Sympathomimetic agents:
  associated with systemic arterial HTN, MI, myocardial damage consistent with catecholamine excess, and lethal arrhythmias
- Amphetamines may induce intense coronary arterial vasoconstriction with or without thrombus formation.
- Dilated cardiomyopathy following repetitive amphetamine use

Cathecholamines

- Catecholamines,
  administered exogenously or secreted by a neuroendocrine tumor (e.g., pheochromocytoma or neuroblastoma), may produce
  acute myocarditis, cardiomyopathy, tachycardia, and arrhythmias.

- *Takotsubo* or *stress cardiomyopathy*,
  The secretion of large amounts of endogenous catecholamines: SAH or intense stress,
  →Transient LV apical dyskinesis
  & anterior T wave inversions

Cathecholamines

- Acute and chronic myocardial damage associated with catecholamines
  - Direct toxic effect on the myocardium through changes in autonomic tone, enhanced lipid mobility, calcium overload, free radical production, increased sarcolemmal permeability

- Myocardial damage secondary to a sustained increase in myocardial oxygen demands and/or decrease in myocardial oxygen supply

Antiretroviral Agents (Protease inhibitors)

- Increased risk of atherosclerosis
- Dilated cardiomyopathy in association with HIV antiretroviral therapy
- In mice, zidovudine produces a cardiomyopathy, with pathologic changes in the mitochondria
  - similar ultrastructural mitochondrial changes in myocardial biopsy specimens from HIV-infected patients treated with this agent

Environmental Exposures: Cobalt

- In the mid-1960s, an acute and fulminant form of dilated cardiomyopathy was described in heavy beer drinkers.
- Cobalt chloride, as a foam stabilizer: causative agent
- More recently, several reports of dilated cardiomyopathy after occupational exposure to cobalt
  - high concentrations of cobalt in endomyocardial biopsy specimens

Alcohol

Alcoholic Cardiomyopathy

- Clinical picture identical to idiopathic DCMP
- The risk of developing cardiomyopathy is partially genetically determined.
- Reducing or ceasing alcohol consumption: reverse the course

- Alcoholic pts with advanced HF have a poor prognosis, particularly if they continue to drink; fewer than 1/4 survive 3 years

- *Holiday heart syndrome*
  typically appears after a drinking binge; Afib, atrial flutter & ventricular premature depolarizations

Mechanisms of Ethanol-Induced Myocardial Injury

Direct Toxic Effects

- Uncoupling of the excitation/contraction system
- Reduced calcium sequestration in sarcoplasmic reticulum
- Inhibition of sarcolemmal ATP-dependent Na^{+}/K^{+} pump
- Reduction in mitochondrial respiratory ratio
- Altered substrate utilization
- Increased interstitial / extracellular protein synthesis

Mechanisms of Ethanol-Induced Myocardial Injury

Toxic Effect of Metabolites

- Acetaldehyde
- Ethyl esters

Nutritional or Trace Metal Deficiencies

- Thiamine
- Selenium

Electrolyte Disturbances

- Hypomagnesemia
- Hypokalemia
- Hypophosphatemia

Toxic Additives

- Cobalt, Lead

Antimalarials-induced Cardiomyopathy

- Rare but severe cardiotoxicity
  following prolonged use of antimalarials
  conduction disturbances (45 pts) & CHF (25 pts)
- Cardiac toxic effects: with chloroquine
  less frequently with hydroxychloroquine use alone

- Restrictive pattern and biventricular hypertrophy
- Histologic findings are essential

  light microscopy: enlarged and vacuolated cardiocytes

  electron microscopy: presence of curvilinear bodies in cardiac myocytes

Costedoat-Chalumeau N, et al. Cardiology 2007;107:73

Fatal cardiomyopathy associated with pegylated interferon/ribavirin

- Reversible cardiomyopathy is a rare complication of high dose of standard interferon

- A 45-yr-old man with HCV treated with pegylated interferon-alpha/ribavirin; fatal cardiomyopathy

Condat B, et al. Eur J Gastroenterol Hepatol 2006;18:287

Clozapine

- Use of clozapine is restricted to patients with treatment-refractory schizophrenia.
- Clozapine is associated with a low (0.015% to 0.188%) risk of potentially fatal myocarditis or cardiomyopathy.

Merrill DB, et al. J Clin Psychopharmacol 2005;25:32
La Grenade L, et al. N Engl J Med 2001;345:224

Cyclophosphamide-induced cardiomyopathy

- Fatal cardiomyopathy developed in 2 pts receiving cyclophosphamide in preparation for bone marrow transplantation.

- One patient died of CHF and hypotension while the other patient developed tamponade

- Acute onset
- Not a cumulative result of drug dosing
- Thickened LV with intramyocardial hemorrhage

Mills BA, et al. Cancer 1979;43:2223

감사합니다.