Cardio-Oncology: Past Present and Future

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Outline

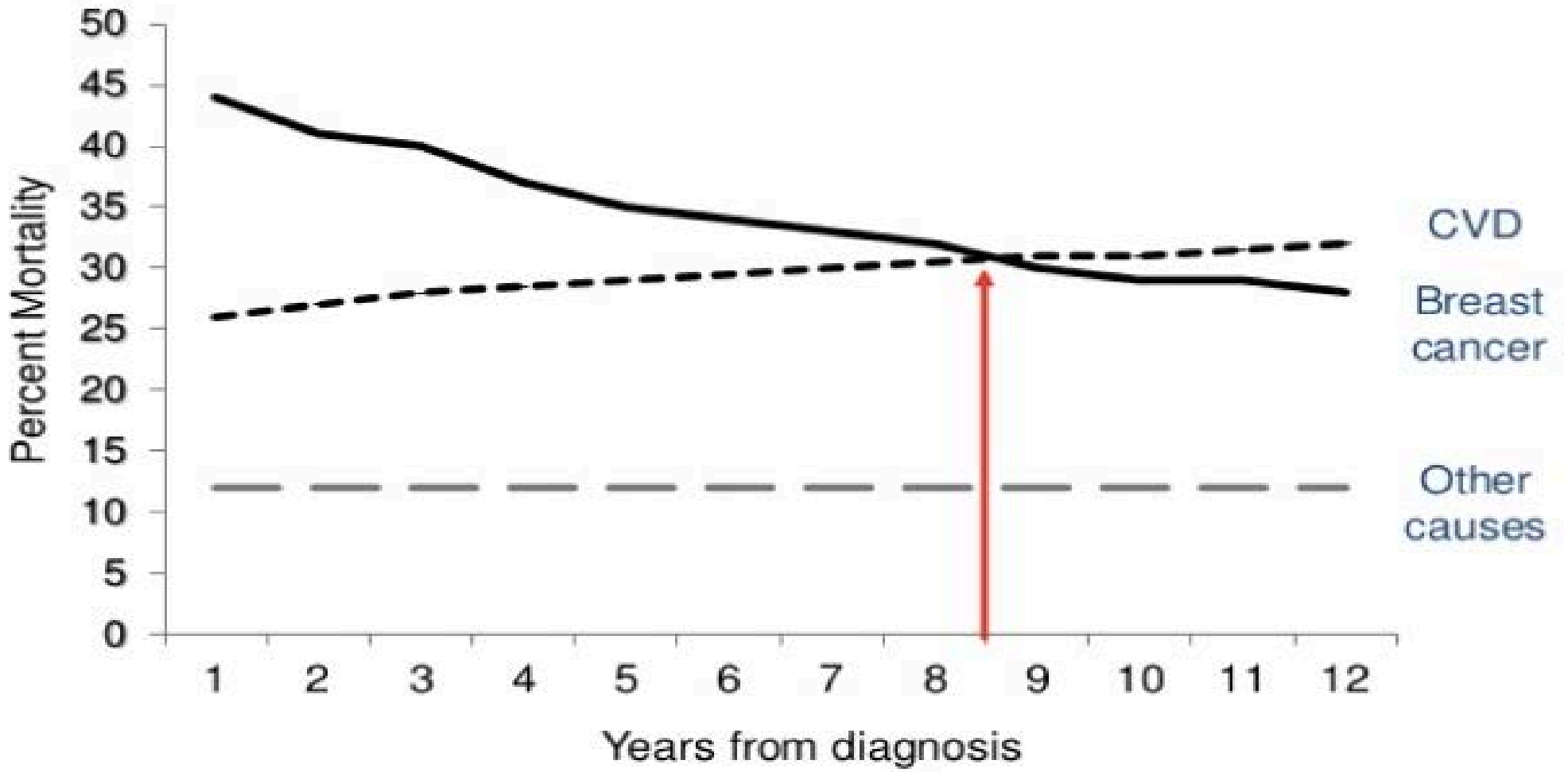
I. Cardiovascular disease & cancer therapy
   a. The basic
   b. Treatment related cardiovascular diseases
   c. Integrated concept of CVD and cancer

II. The future of Cardio- Oncology

The longevity of cancer survivors

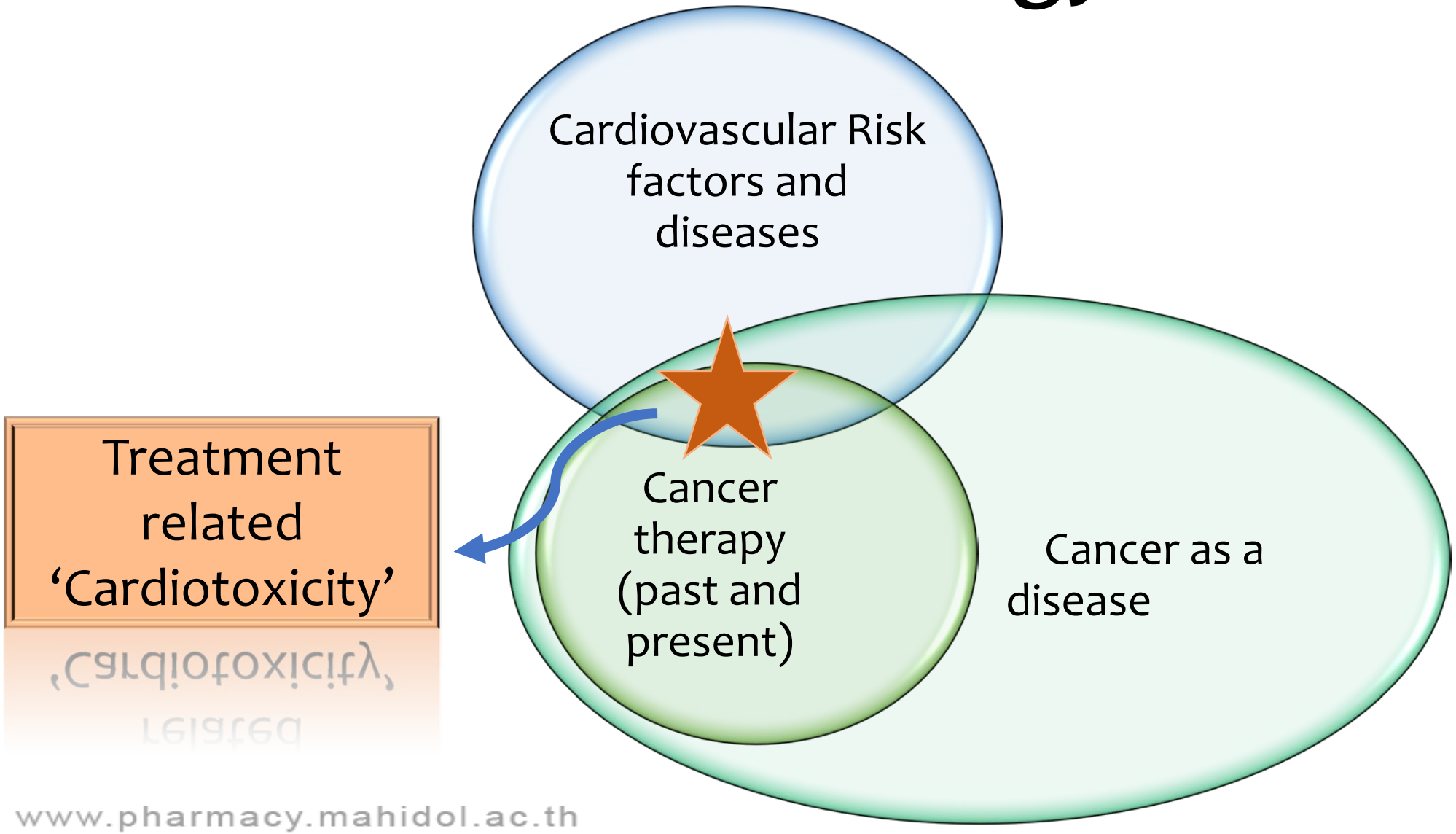
Site	5 years survival		% increase
	1975 (%)	2007 (%)	
Overall	50	67	17
Childhood	30	79	49
Prostate	67	99	32
Breast	75	90	15
Colon	51	65	14
Lung	12	16	4

CVD-related Mortality in Early Breast Cancer

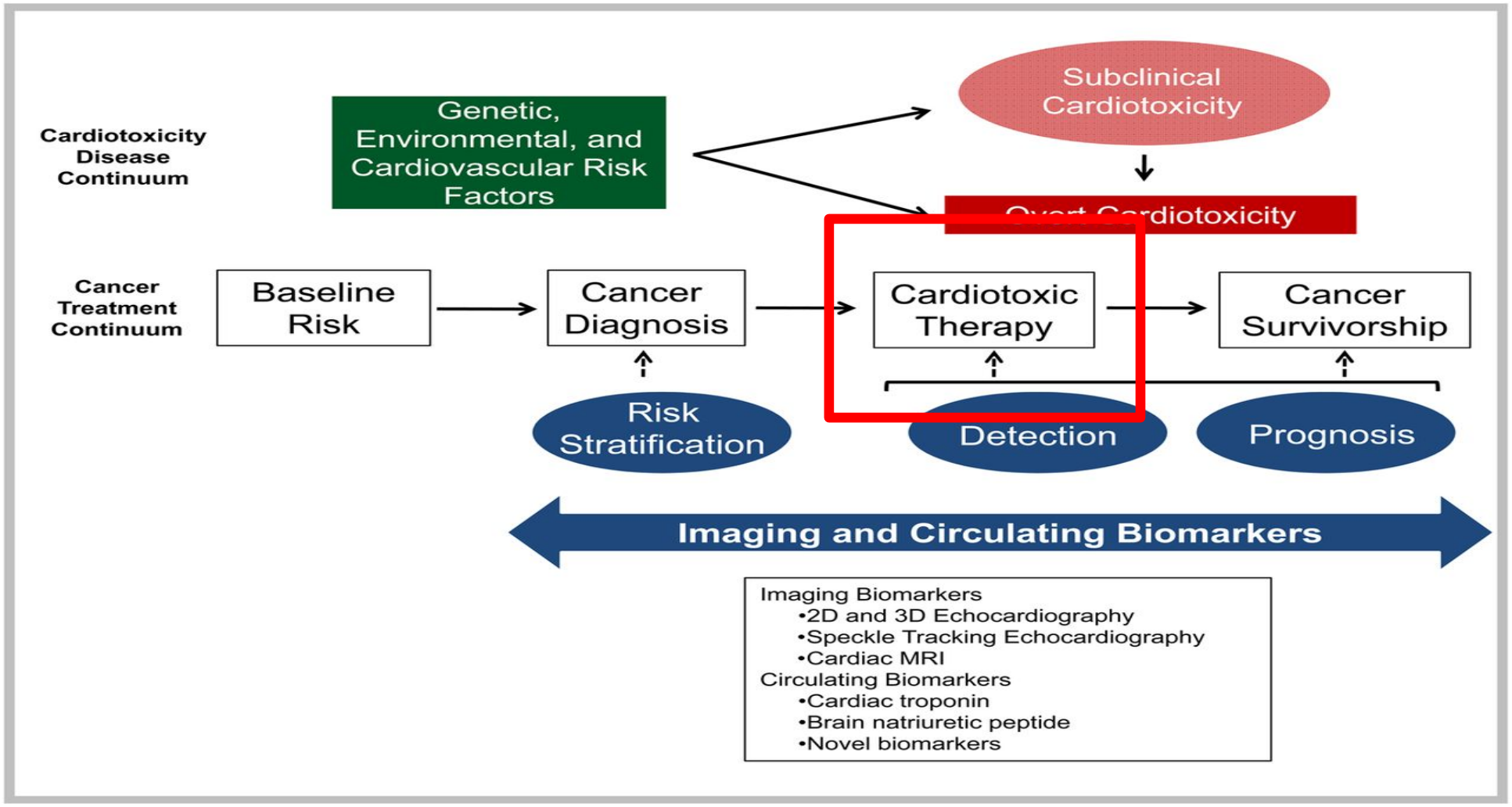


Patnaik et al. *Breast Ca Res*, 2011

What is Cardio-Oncology



Continuum of Cardio-Oncology care



Cancer therapies associated Cardiovascular Toxicities

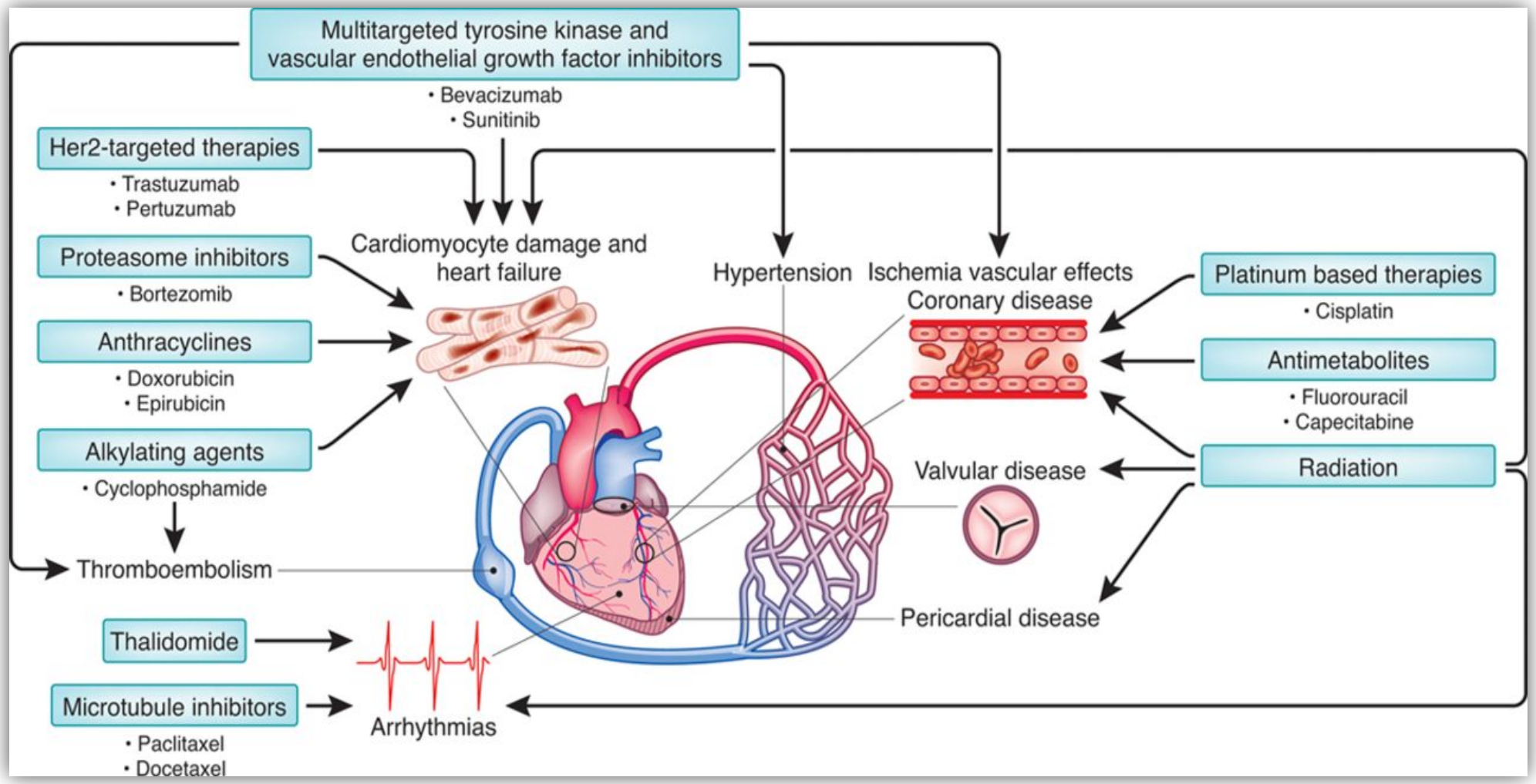
Conventional Therapies

Cytotoxic	Hormonal
Anthracyclines Doxorubicin, daunorubicin, epirubicin, Idarubicin	Androgen deprivation therapy Bicalutamide, enzalutamide, abiterone
Fluoropyrimidines 5-fluorouracil, capecitabine, gemcitabine	Antiestrogen Tamoxifen
Microtubules inhibitors Docetaxel, paclitaxel	
Alkylating agents Cisplatin, cyclophosphamide	

Novel (Targeted Therapies)

Signaling Pathways	Other targets
Anti-HER-2 Trastuzumab Pertuzumab Lapatinib	Proteosome Inhibitors Bortezumib
VEGF signaling Bevacizumab, Ramucirumab Sunitinib, Sorafenib, Axitinib, Regorafenib, Vandetanib	Immunomodulators Thalidomide, lenalidomide
Anti-BCR-ABL TKIs Imatinib, crizotinib, dasatinib vemorafenib etc…	HDAC inhibitors Vorinostat Depsipeptide
mTOR inhibitors Hypertension Myocardial ischemia	Others Asenic

Spectrum of Cardiotoxicity



Lennamen CG. Circ Res 2016 Mar 18;118(6):1008-20.

Spectrum of Cardiotoxicities

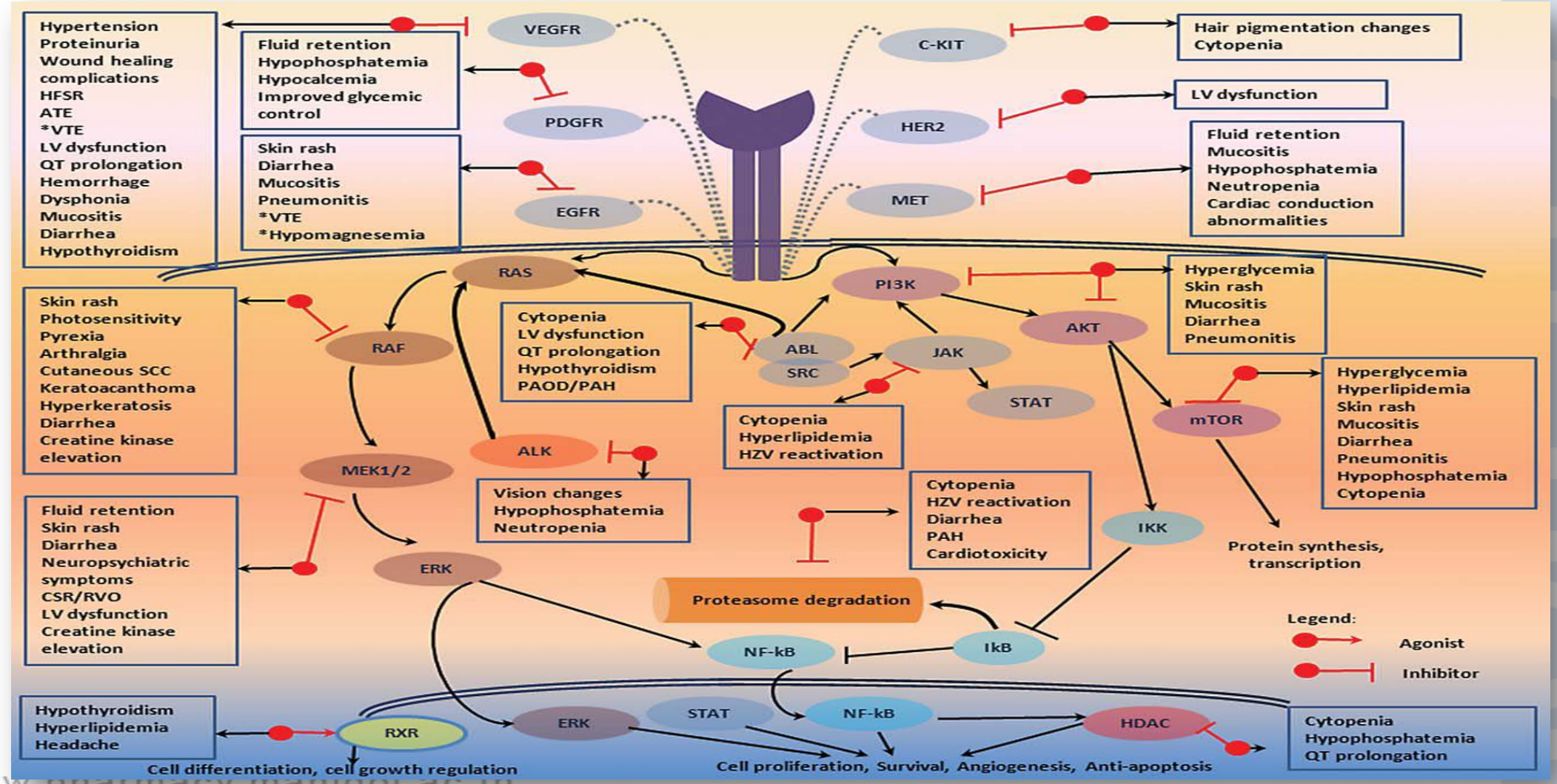
Conventional Therapies

Cytotoxic	Hormonal
Anthracyclines Cardiomyopathy, Heart failure	Androgen deprivation therapy Metabolic syndrome, VTE
Fluoropyrimidines Myocardial ischemia (reversible), Tachycardia	Anti-estrogen VTE
Microtubules inhibitors Arrythmias	
Alkylating agents Myocardial ischemia	

Novel (Targeted Therapies)

Signaling Pathways	Other targets
Anti-HER-2 Cardiomyopathy Heart failure	Proteosome Inhibitors Arrythmia Hypertension
VEGF signaling Hypertension VTE Hemorrhage	Immunomodulators VTE
Anti-BCR-ABL TKIs Pulmonary hypertension Pericardial effusion	HDAC inhibitors Hypertension Dyslipidemia Cardiomyopathy
mTOR inhibitors Hypertension Myocardial ischemia	Other Asenic – QTc prolongation

Molecular mechanism of toxicity for targeted therapy



Left Ventricular Dysfunction

- Mechanism of toxicity
- LV dysfunction
  - Type I: anthracycline associated with radical species resulting in structural abnormality, apoptosis.
  - **Type II**: related to targeted therapy targeting Erb2 (HER2) causing mitochondria apoptosis resulting in failure of myofibril contractile element. Likely to be reversible if offending agents discontinued

Hasinoff et al.Cardiovasc Toxicol. 2010;10:1-8

Hypertension

- Mechanism of toxicity
  - Usually occurs within the first few weeks after therapy initiated
  - Associated with anti-VEGF
  - VEGF is known to increase the synthesis of nitric oxide (NO)
  - Therefore, decreased level of endogenous NO causing vasoconstriction
  - Also, up-regulation of baroreceptor function and increased vascular tone
  - May be an indicator of efficacy

Hasinoff et al.Cardiovasc Toxicol. 2010;10:1-8

Hemorrhagic Events/VTE

- Mechanism of toxicity
  - Associated with VEGF pathway
  - Nitric oxide (NO) maintains the integrity of endothelial cells
  - Activate platelets aggregation and degranulation to trigger thrombosis when drugs bind to Fc RII receptor
  - Risk factors included
    - Elderly
    - Past medical history of diabetes
    - Dose intensity

Hasinoff et al.Cardiovasc Toxicol. 2010;10:1-8

Risk factors to cardiovascular toxicities

- Baseline CV diseases
- Age (> 50 years old for trastuzumab, > 65 years old for anthracyclines)
- Family history of premature CV disease
- Diabetes, dyslipidemia, hypertension
- Smoking
- Obesity
- Prior cancer therapy history (e.g. radiation or pre-exposure to anthracyclines)
- Advanced cancer
- Site of cancer (for thromboembolism)
- Impaired organ function
- Concomitant drugs
- Alcohol consumption

Strategies to reduce toxicities

All cancer treatment

- Identify and treat risk factors/comorbidities
- Avoid drugs to potentiate CV toxicities e.g. QT prolonging agents
- Minimize irradiation
- Monitoring protocol

Anthra cyclines

- Limit life time accumulating dose
- Alter delivery system/formulation
- Antidote (dexrazoxane)
- CHF management

Strategies to reduce toxicities

Trastuzumab

- Reversible cardiomyopathy
- CHF management

Immuno modulators

- Risk VS benefit of bleeding VS embolism
- Antiplateletes or anticoagulation

VEGF inhibitors/TKIs

- Baseline blood pressure
- Hypertension management

Challenges in Cardio-Oncology

- Most data are from cancer clinical trials that excluded patients with history of CVD and metabolic disorders
- Toxicities assessments stop after drug discontinuation
- Toxicities can appear late and/or intermittently
- Essential to distinguish between treatment-related CVD and treatment – independent metabolic adverse effects

To sum up

- Increased number of cancer survivors worldwide
- Conventional and novel cancer treatments are associated with cardiovascular toxicities
- Baseline risk factors must be evaluated prior to initiate treatment
- Monitoring and better standardized assessment will help minimize CVD-associated cancer care