Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy and its management, considering also cachexia

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And Honorary President of AFSOS

(French-speaking Association for Supportive Care)

clinical practice guidelines

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doi:10.1093/annonc/mds293

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

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review

Annals of Oncology 22: 257–267, 2011
doi:10.1093/annonc/mdq609
Published online 18 October 2010

Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper

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SIOG APAC 2014
12th to 13th July

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Breast Cancer in Older Adults
Cardiac Toxicity in Breast Cancer

Dr Vivianne Shih, Pharm.D., BCPS, BCOP
Specialist Pharmacist (Oncology)

Learning Objectives

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- At the end of this short presentation, one should be able to
  - List the common chemotherapy &/or targeted therapies that can cause cardiotoxicity
  - Distinguish cardiotoxicity arising from conventional chemotherapy & targeted agents
  - Discuss the appropriate preventive, monitoring & treatment of cardiotoxicity caused by drugs used in cancer therapy

Overview

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- Introduction – drugs involved & definition
- Mechanism of cardiotoxicity
- Risk Factors
- Monitoring of cardiotoxicity
- Review of trastuzumab-induced cardiotoxicity in elderly
- Treatment of chemotherapy-induced cardiotoxicity

Cardiovascular Side Effects of Modern Cancer Therapy

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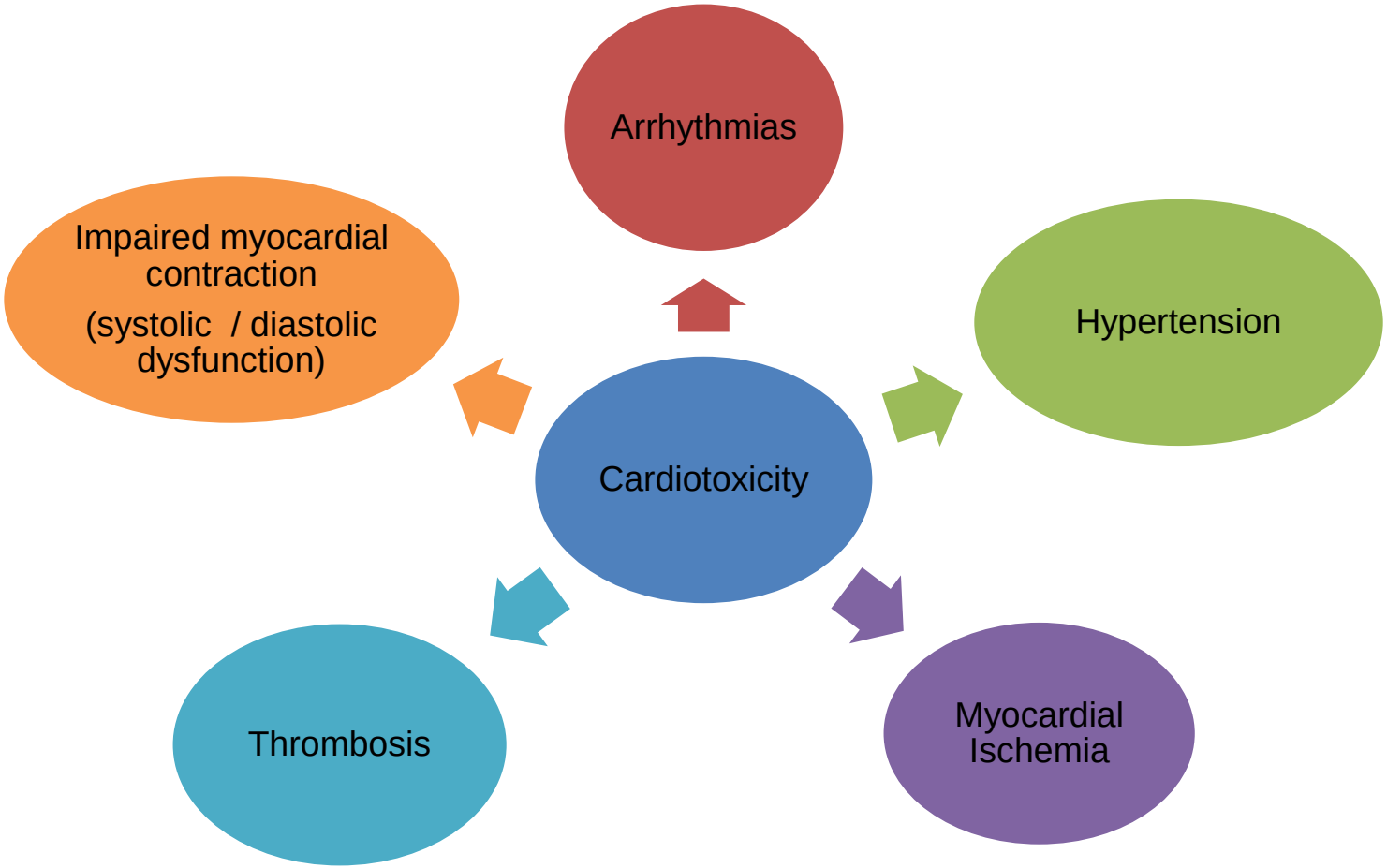

Cardiotoxicity of Antineoplastics

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Antitumour antibiotics Eg Anthracycline	• Cardiomyopathy, arrhythmias, CHF • Cumulative dose
Microtubule targeting agents Eg Taxanes	• Bradycardia, arrhythmias, CHF, MI • Typically reversible, may potentiate anthracycline toxicity
Alkylating agents Eg Cisplatin, Cyclophosphamide	• Arrhythmias, heart block, CHF • Mechanism: Electrolyte abnormalities ; endothelial capillary damage
Antimetabolites Eg Fluorouracil	• Cardiac failure, MI • Likely Mechanism: Coronary vasospasm

Floyd JD et al. JCO 2005;23:7685-7696

Cardiotoxicity Associated with Targeted Therapies

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Drugs	Incidence (%)	Clinical Characteristics	Comments
Monoclonal Antibodies			
Trastuzumab	2 – 28	Potentially reversible, significant decline in LVEF	**Clinical:** Age, preexisting cardiac disease, borderline LVEF before ttherapy **Treatment related:** prior anthracycline exposure , sequence of chemotherapy exposure
Bevacizumab	1.7 – 3	Not completely defined, systolic dysfunction	Previous anthracycline use
Tyrosine Kinase Inhibitors			
Lapatinib	1.5 – 2.2	Not completely defined, systolic dysfunction	Not completely defined, perhaps prior anthracycline use
Sunitinib	2.7 -11	Possibly reversible, significant decline in LVEF, HF	History of coronary disease
Imatinib	0.5 – 1.7	Not completely defined, systolic dysfunction	Not completely defined

Wells QS, Lenihan DJ. Prog Cardiovasc Dis 2010;53:140-8

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Definition of Cardiotoxicity

Definition of Cardiotoxicity

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National Cancer Institute

- Toxicity that affects the heart

Cardiac Review & Evaluation Committee

- Cardiomyopathy in terms of ↓ LVEF, either global or more severe in the septum
- Symptomatic HF
- Signs associated with HF, such as S3 gallop, tachycardia or both
- Reduction in LVEF
  - **≤ 5%** to < 55% **WITH** OR
  - **≥ 10%** to < 55% **WITHOUT** S/Sx of HF

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Anthracycline vs Trastuzumab

(1) How does Cardiotoxicity arise?

Anthracycline-induced Cardiotoxicity (AIC)

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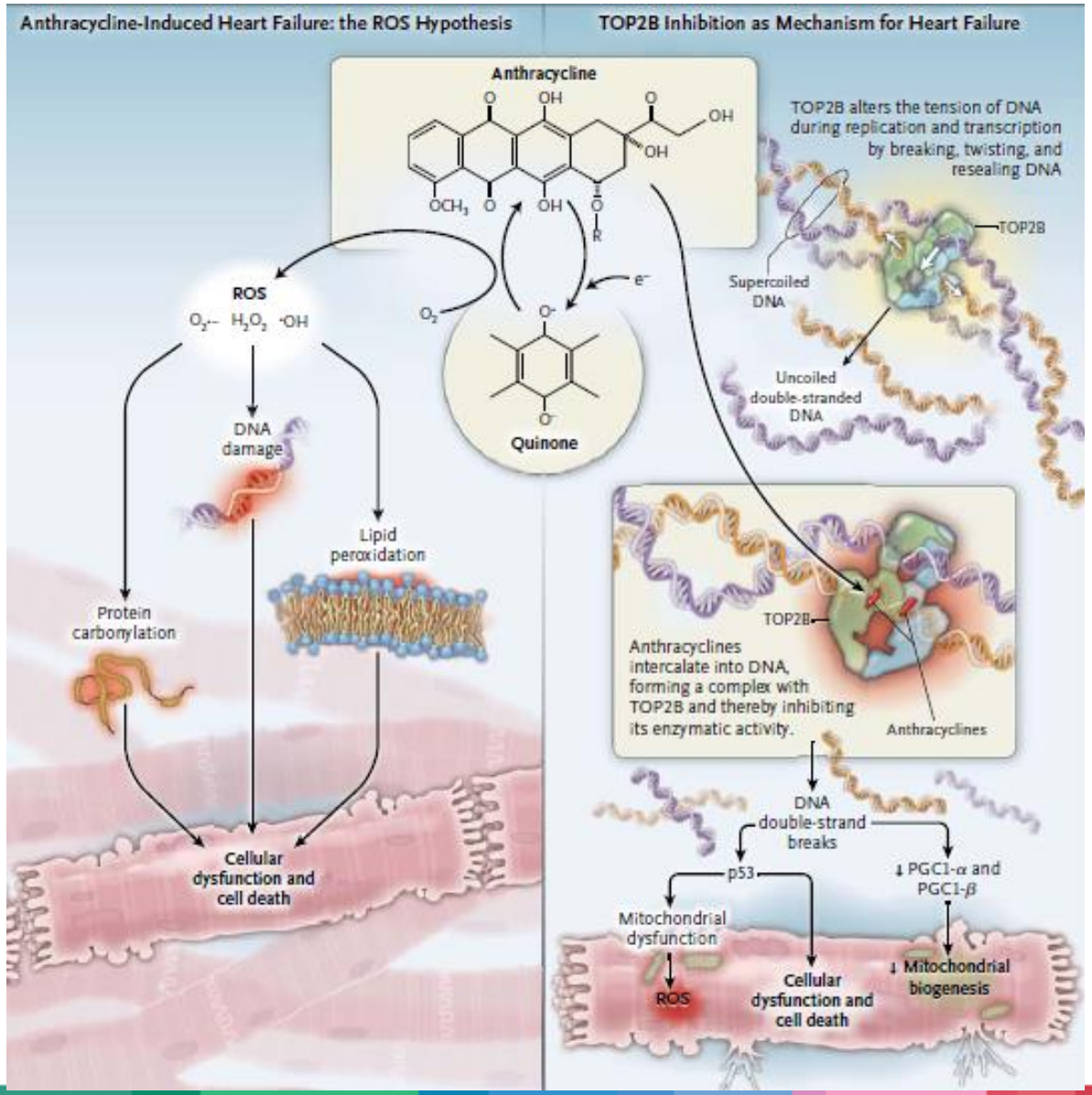

- Top 2B alters the tension of DNA during replication & transcription by breaking, twisting & resealing DNA

- Anthracyclines intercalate into DNA
→ forms complex with Top2B
→ inhibits Top2B enzymatic activity

- DNA double strand breaks

Swyer DB. N Engl J Med 2013;368(12):1154-6.

Anthracycline-induced Cardiotoxicity (AIC)

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Stage 1

Injury
(days to wk after therapy)

- Troponin I released at time of exposure
- Cell death

Heart compensates & remodelling occurs

- Either short phase or indefinitely
- EF may remain substantially normal

Heart <u>NO</u> longer compensates

- Symptomatic HF ensues

Stage 4

Trastuzumab induced Cardiotoxicity (TIC)

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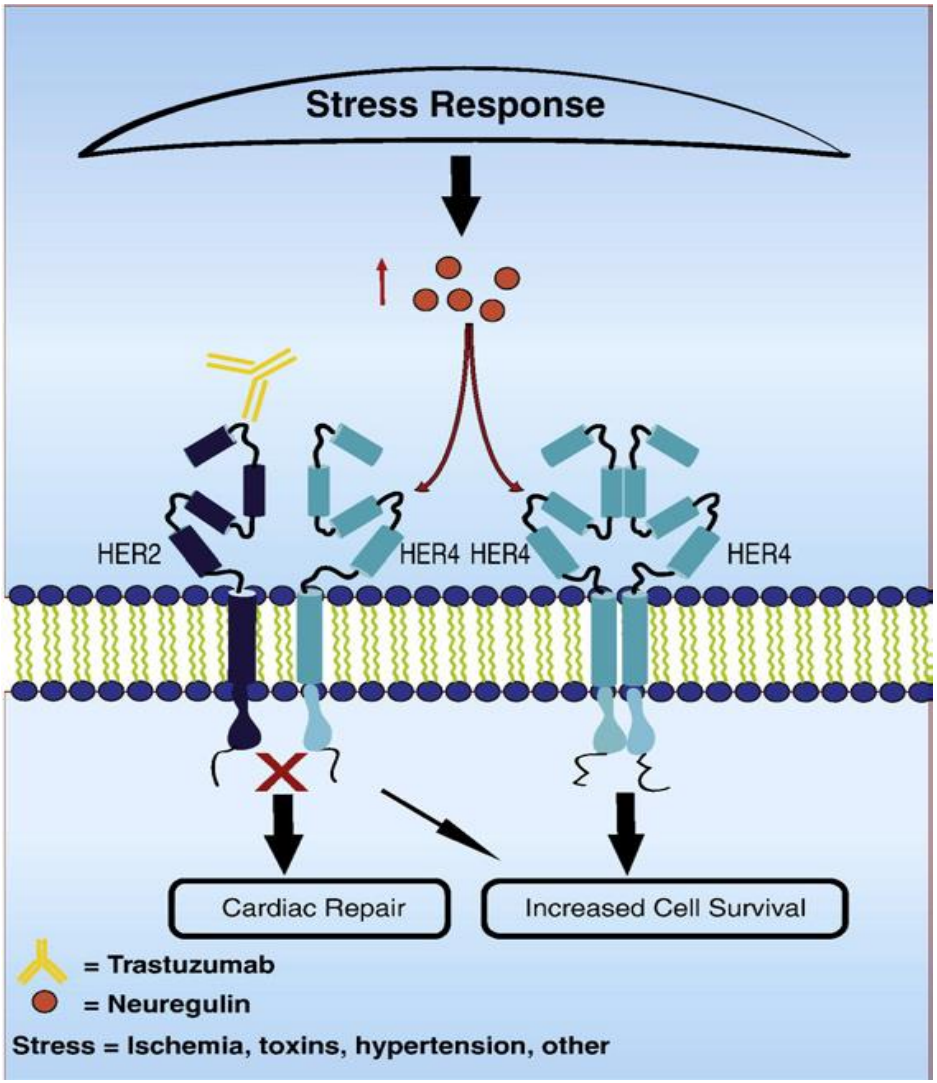

♥ Cardiac endothelial cells
→ Neuregulin 1 (NRG1)

♥ Binds to human epidermal growth factor receptor 4
→ Promotes heterodimerization with HER2

♥ Activation of downstream intracellular signalling pathways

Wells QS, Lenihan DJ. Prog Cardiovasc Dis 2010;53:140-8.

Type I vs Type II Cardiotoxicity

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	Type I Cardiotoxicity (eg anthracycline)	Type II Cardiotoxicity (eg Trastuzumab)
Clinical course, response to medication	May stabilise, but subclinical **damage** seems to **persist**; recurrence in mths or yrs may be related to sequential cardiac stress	**High likelihood** of **complete or near-to-complete recovery** upon withdrawal &/or medication
Dose dependence	**Cumulative**; "lifetime" dose-related	Dose-**independent**
Mechanism	Free radical formation (?), alcohol metabolite formation (?)	Elimination of HER2-related survival factors
Ultrastructure	Vacuoles, myofibrillar disarray & dropout, apoptosis & necrosis	With limited exceptions, no apparent ultrastructural abnormalities
Non-invasive testing	↓ LVEF , global ↓ in wall motion	
Effect of rechallenge	**High probability of recurrent** dysfunction that progresses toward treatment-resistant CHF	↑ evidence for **safety of rechallenge**
Effect of late sequential stress	High likelihood of sequential stress-related cardiac dysfunction	Low likelihood of sequential stress-related cardiac dysfunction

Menna P et al. Expert Opin Drug Saf 2012;11 (Suppl 1): S21-36.

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Anthracycline vs Trastuzumab

(2) Risk factors

Risk Factors (AIC)

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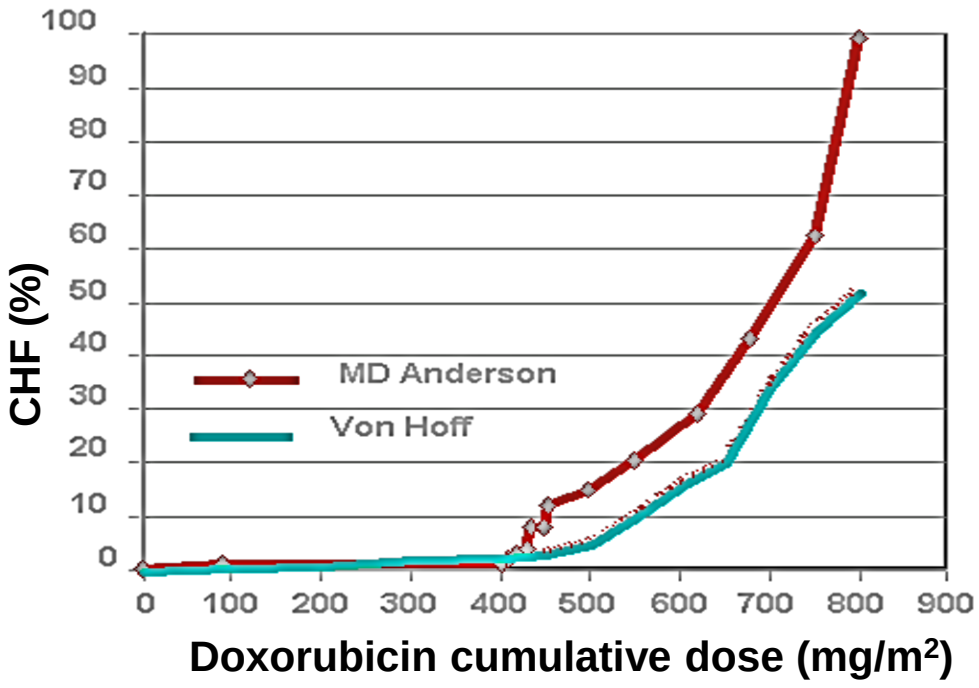
- Therapy-related
  - Type & formulation of anthracyclines
  - Cumulative dose
  - Infusion time (eg IVP or CI)
  - Combination &/or sequence of chemotherapy
  - Prior or concomitant mediastinal RT



Bovelli D et al. Ann Oncol 2010;21 (Suppl 5):277-82.
Von Hoff DD et al. Ann Intern Med 1979;91:710-7.
Swain SM et al. Cancer 2003; 97:2869-79.

Risk Factors (AIC)

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- Patient-related
  - Age
  - Gender (eg females)
  - Cardiovascular disease (CVD)
  - Presence of cardiovascular (CV) risk factors

Bovelli D et al. Ann Oncol 2010;21 (Suppl 5):277-82.

Risk Factors (TIC)

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- Age > 60 yr
- Low baseline LVEF
- Prior anthracycline exposure
- Current or previous treatment with anti-hypertensive medication
- Higher body mass index (> 25kg/m^2)
- Alcohol intake
- HER2 polymorphisms

Slamon DJ et al. N Engl J Med 2011;344:783-92.
Guarneri V et al. J Clin Oncol 2006;24:4107-15.
Seidman A et al. J Clin Oncol 2002;20:1215-21.
Tan-Chiu E et al. J Clin Oncol 2005;23:7811-9.
Suter TM et al. J Clin Oncol 2007;25:3859-65.
Perez EA et al. J Clin Oncol 2008;26:1231-38.
Lemieux J et al. Anticancer Res 2013;33(6):2569-76.

FROM ESMO GUIDELINES

Risk factors for radiation-associated heart damage include:

- dose >30–35 Gy
- dose per fraction >2 Gy
- large volume of irradiated heart
- younger age at exposure
- longer time since exposure
- use of cytotoxic chemotherapy
- endocrine therapy or trastuzumab
- presence of other risk factors such as diabetes, hypertension, dyslipidaemias, obesity, smoking etc.

ESMO Clinical Practice Guidelines: Recommendations for Cardiotoxicity Monitoring

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- Periodic monitoring of cardiac function with Decho is suggested especially for anthracyclines & their derivates or monoclonal Ab

- Periodic monitoring (every 12 wks) of cardiac function is also suggested for patients receiving monoclonal Ab, esp if prev treated with anthracycline

- LVEF reduction of > / = 20% from baseline despite normal function OR LVEF decline < 50% necessitate reassessment or discontinuation of therapy & further frequent clinical & echographic checks

Bovelli D et al. Ann Oncol 2010;21 Suppl 5:277-82.

Limitations / Imperfections of LVEF

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- Subjectivity
- ↓ LVEF often deemed as being related to offending agent
  - Unchanged LVEF = Lack of cardiotoxicity?
  - ↓ LVEF after treatment may be a marker for advanced myocyte damage

E Raschi et al. Pharmacol Thera 2010;125:196-218.

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Treatment of Chemotherapy-induced Cardiotoxicity

Treatment of anthracyline-induced cardiotoxicity

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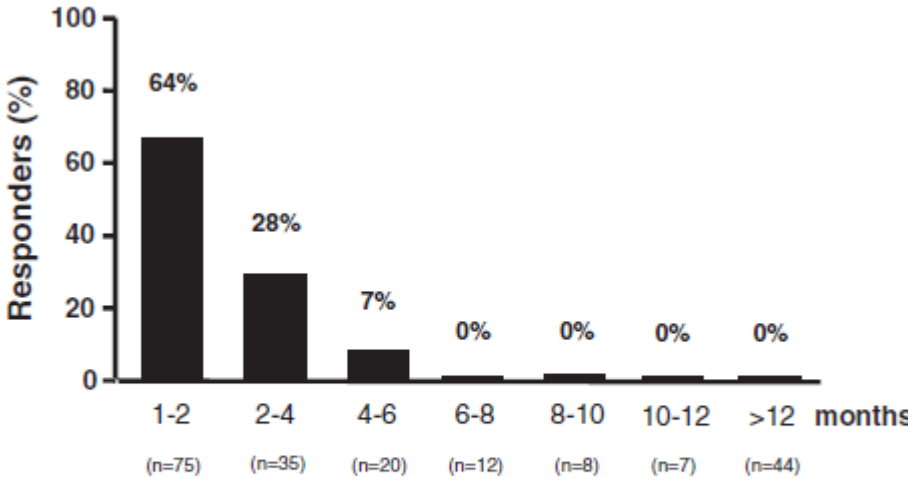

Figure 1 Percentage of Responders According to the Time Elapsed From AC Administration and Start of HF Therapy

Responders: LVEF ↑ up to 50%
Partial responders: LVEF ↑ at least 10% but < 50%
Non-responders: LVEF ↑ < 10% & not reach 50%

- Prospective, single centre study (N = 201)
- Patients with LVEF ≤ 45% & absence of any identifiable cause of CMP
- Primary end point: LVEF response to HF therapy
- Treatment: Enalapril &/or carvedilol

Cardinale D et al. JACC 2010;55:213-20

Change in LVEF from baseline to rechallenge with trastuzumab

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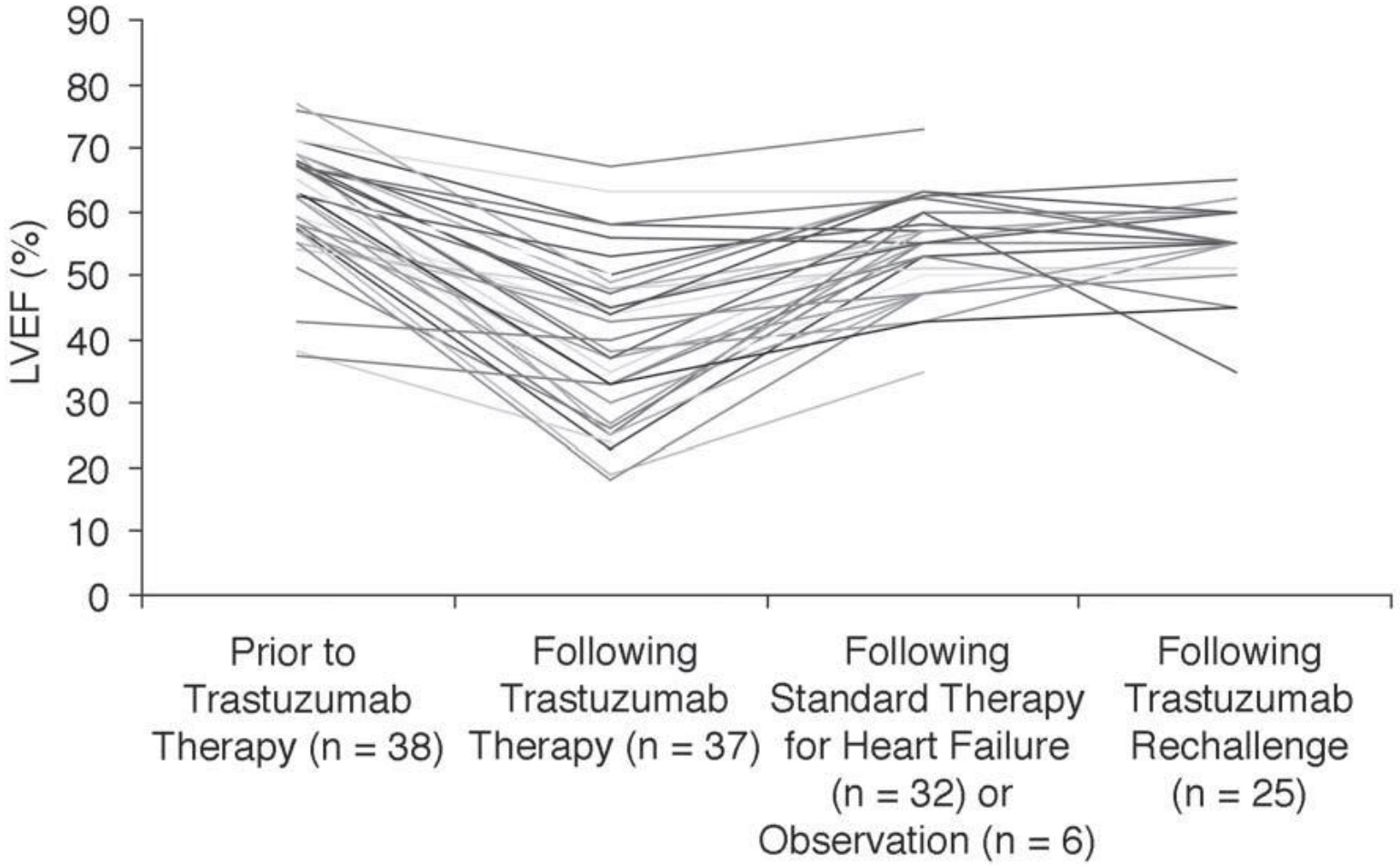
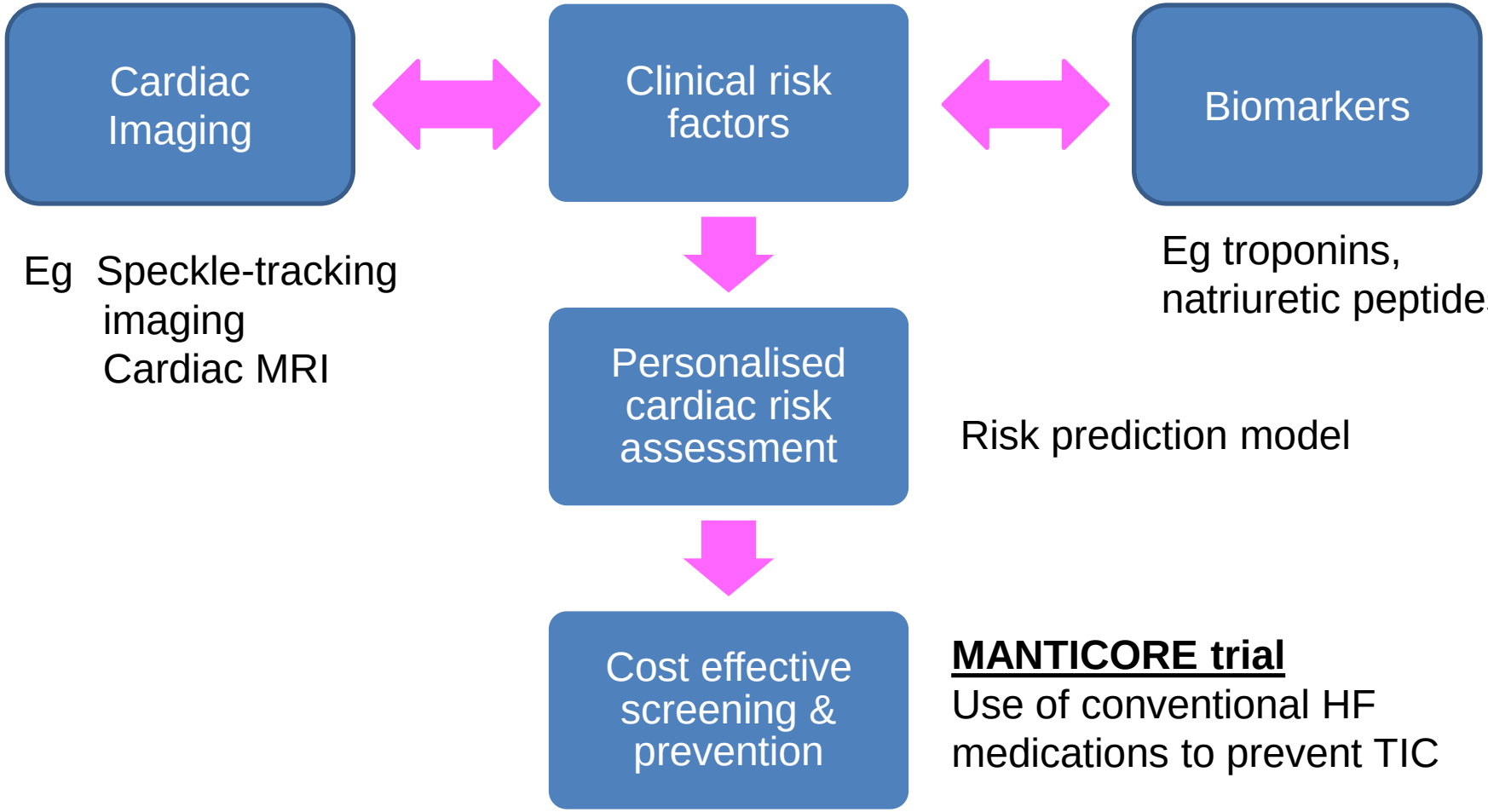


Ewer MS et al. J Clin Oncol 2005;23 (31): 7820-6.

Cardiac Risk Assessment



Eg Speckle-tracking imaging
Cardiac MRI

Eg troponins, natriuretic peptides

Risk prediction model

MANTICORE trial
Use of conventional HF medications to prevent TIC

Francis SA et al. J Am Heart Assoc 2014;3(1):e000780. doi: 10.1161/JAHA.113.000780.

Effect of Various Modifying Factors on Risk of Cardiotoxicity

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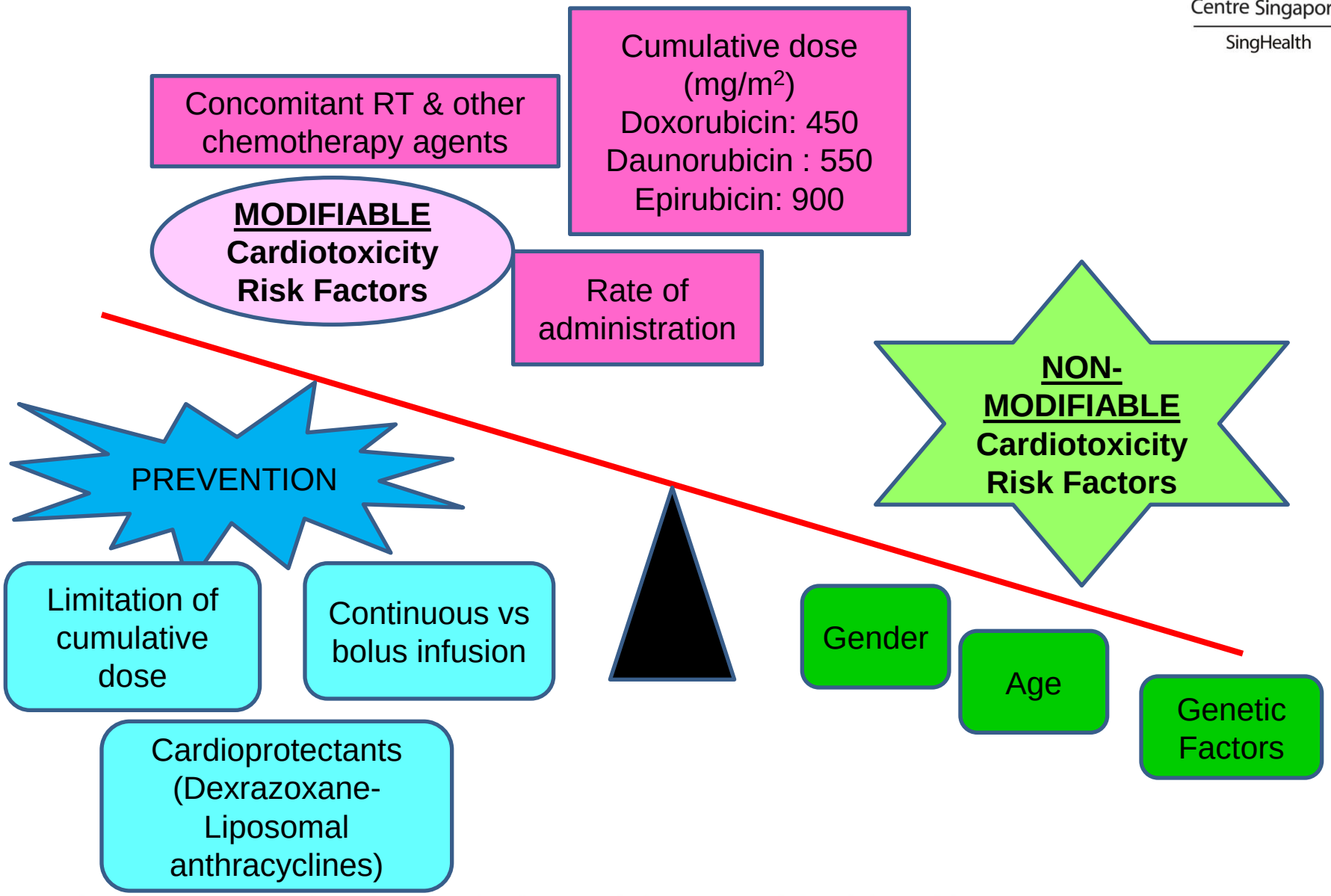

E Raschi et al. Pharmacol Ther 2010;125:196-218.

Take home message…

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- Cardiotoxicity is one of the most important complications arising from cancer treatment
- Crucial to have reliable biomarkers to identify high risk patients & initiate prompt treatment when necessary
- Clinical endpoints of cardiotoxicity & cardiac monitoring need to be standardised
- Multidisciplinary team approach is required


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