ACC Middle East
Conference 2018

Cardiotoxicity of Cancer Chemotherapy

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Le Meridian Jeddah
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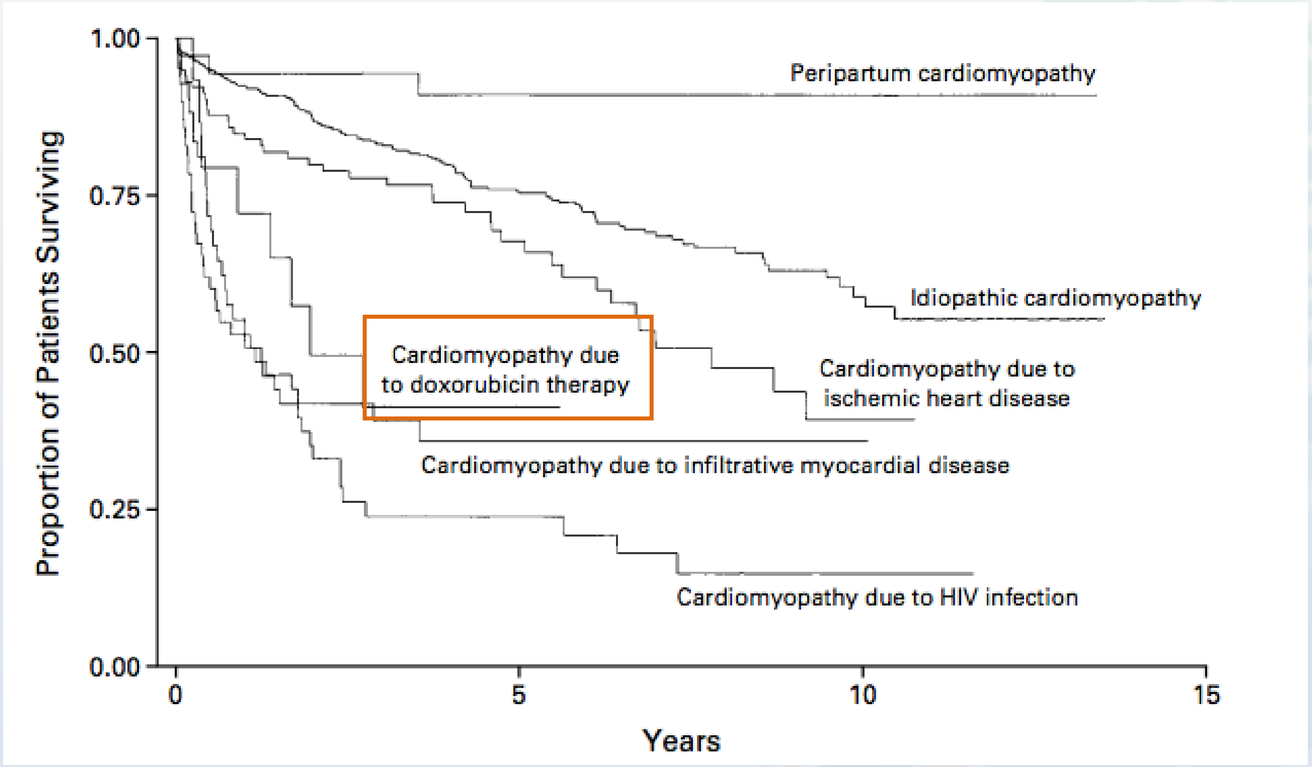
Outline

- Intersection of medical oncology and cardiovascular disease
- Definitions and diagnostic criteria
- Diagnostic modalities
- Review of specific cancer therapeutics

Scope of Cardio-oncology

- **Cancer is poised to become the leading cause of death in the western world**
- **14 million cancer survivors in the US, 18 million by 2022**
- **Among cancer survivors, cardiovascular death is the second leading cause of death (33%) after cancer (51%)**
- **Conventional chemotherapy vs. targeted agents**

Survival in Chemotherapy Induced Cardiotoxicity



1230 patients with unexplained HF undergoing EMB

Felker M et al. N Engl J Med 2000;342:1077-84

Diagnostic Modalities

- **RV biopsy**

  Historic “Gold standard” since widespread use of anthracyclines in 1960s

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- **Non-invasive LV function assessment**

  Echocardiography for EF by volumes (Simpson’s, 3D), strain
  MUGA
  Cardiac MRI

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- **Biomarkers**

  Troponin, BNP/NT-proBNP

Definition of Chemotherapy Induced Cardiotoxicity

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- **PREDICT Trial**
  Effectiveness of Using Biomarkers to Detect and Identify Cardiotoxicity and Describe Treatment

Cardiotoxicity defined as presentation of one or more cardiac events within 12 months of initiation of chemotherapy

Cardiac event defined as any new
- **Symptomatic cardiac arrhythmia, acute coronary syndrome, HF**
- **Development of asymptomatic LV dysfunction, defined as LVEF reduction of 10% to less than 50% or a decrease of greater than 15% from baseline**

PREDICT Trial. ClinicalTrials.gov Identifier: NCT01032278

Spectrum of Chemotherapy Induced Cardiotoxicity

- **Heart failure**

  Anthracyclines, HER2 antagonists, alkylating agents, proteosome inhibitors, tyrosine kinase inhibitors

- **Ischemia**

  Anti-metabolites, VSP inhibitors, proteosome inhibitors, taxanes

- **HTN**

  VSP inhibitors, protesome inhibitors

- **Arrhythmia**

  Taxanes, alkylating agents (bradycardia), TKI (QT prolongation)

- **PH**

  Dasatinib

- **Pericardial diseases**

  Anthracyclines, cyclophosphamide, cytarabine, imatinib, dasatinib, interferon-α, arsenic trioxide

Diagnostic Criteria for Chemotherapy Induced Cardiotoxicity in Clinical Trials

- **Slamon D, et al. N Engl J Med 2001;344:783-92**

  NYHA III/IV HF or LV dysfunction

- **HERA Trial Piccart-Gebhart M, et al. N Engl J Med 2005;353:1659-72**

  LVEF decrease ≥ 10% to < 50%

- **PACS-04 Spielmann M, et al. J Clin Oncol. 2009 Dec 20;27(36):6129-34**

  Decrease in LVEF > 15% to < 50%

Diagnostic Criteria for Chemotherapy Induced Cardiotoxicity Across Guidelines

Cardiac Review and Evaluation Committee (2002)
LVEF decrease > 5% to < 55% with HF symptoms, or > 10% to < 55% without HF symptoms
American Society of Echocardiography/European Association of CV imaging (2014)
LVEF decrease > 10% to < 53%, confirmed on repeat imaging, with or without HF symptoms
European Society of Cardiology (2017)
LVEF decease > 10% to < 50% with or without HF symptoms
Trastuzamab labeling
LVEF decrease > 16% from baseline or >10% to institutionally defined normal
Food and Drug Administration
LVEF decrease > 20% from a normal baseline, or > 10% from abnormal baseline, LVEF <45%

1- Imaging Assessment for Diagnosis of Chemotherapy Induced Cardiotoxicity

- **Echocardiography**

  2DE biplane Simpson's
  Contrast-enhanced imaging
  3DE volumes
  Comparison with previous imaging
  Timing of echo with respect to IV infusion

- Widely available
- No radiation exposure
- Cost effective
- Evaluation of other cardiac structures
- Well-suited for surveillance

Plana J, et al. J Am Soc Echocardiogr 2014;27:911-39

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- Preferred method over linear measurements-derived volumes
- Poor EBD, foreshortening

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- Larger volumes compared to non-contrast imaging
- Susceptible to foreshortening
- Cost

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- More representative volumes
- More reproducible
- Needs specialized training and quality control

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- **MUGA / CMR**

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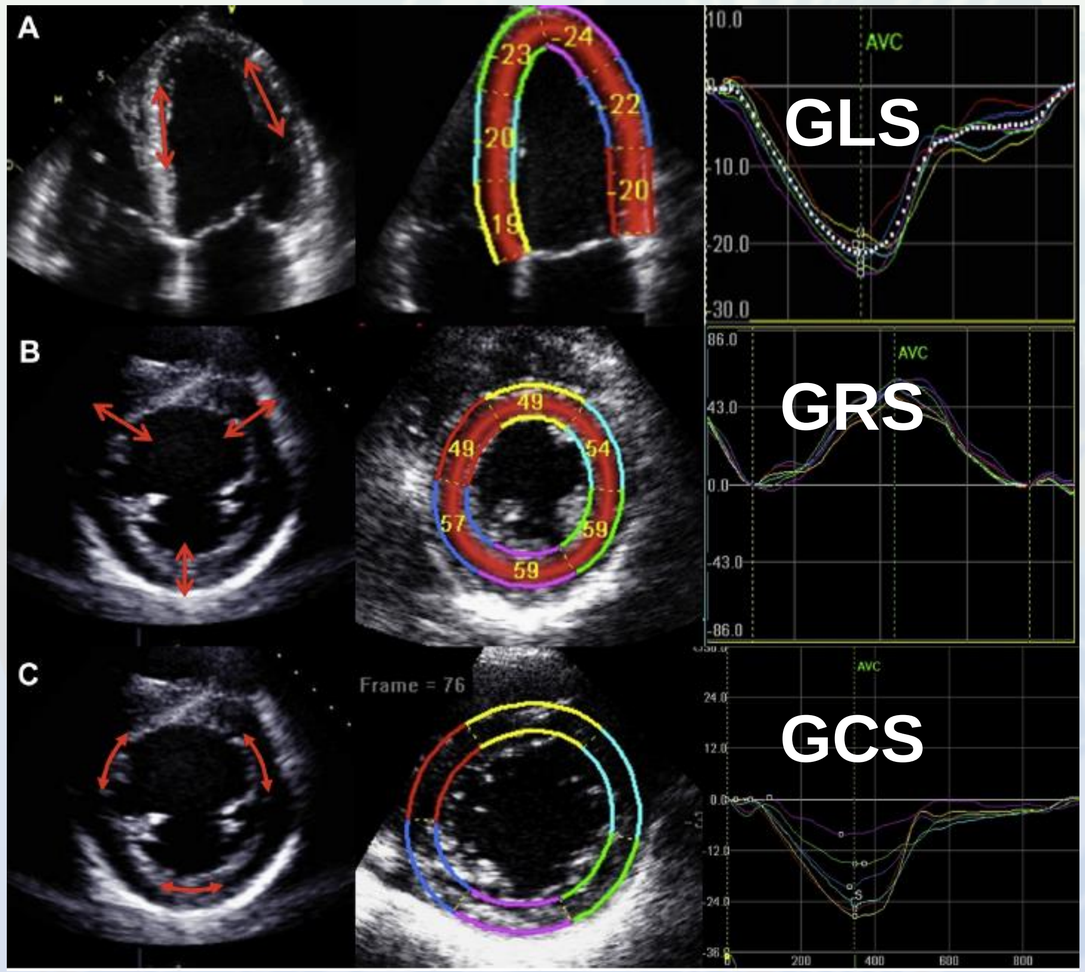
1- Imaging Assessment for Diagnosis of Chemotherapy Induced Cardiotoxicity

- **GLS is more reproducible compared to GRS or GCS**
- **Reduction in GLS by 9-19% is common during or immediately after anthracycline administration, preceding asymptomatic reductions in LVEF**
- **STE measured GLS is the most consistent parameter of future cardiotoxicity (GLS > 15%)**



Thavendrinathan P, et al. J Am Coll Cardiol 2014;63:2751–68

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TnI pre and post HDC at 12, 24, 36, 48, 72 hrs

32% —> +ve TnI <72 hrs post HDC

29% of +ve TnI —> LVEF < 50%
0% in TnI -ve —> LVEF < 50%

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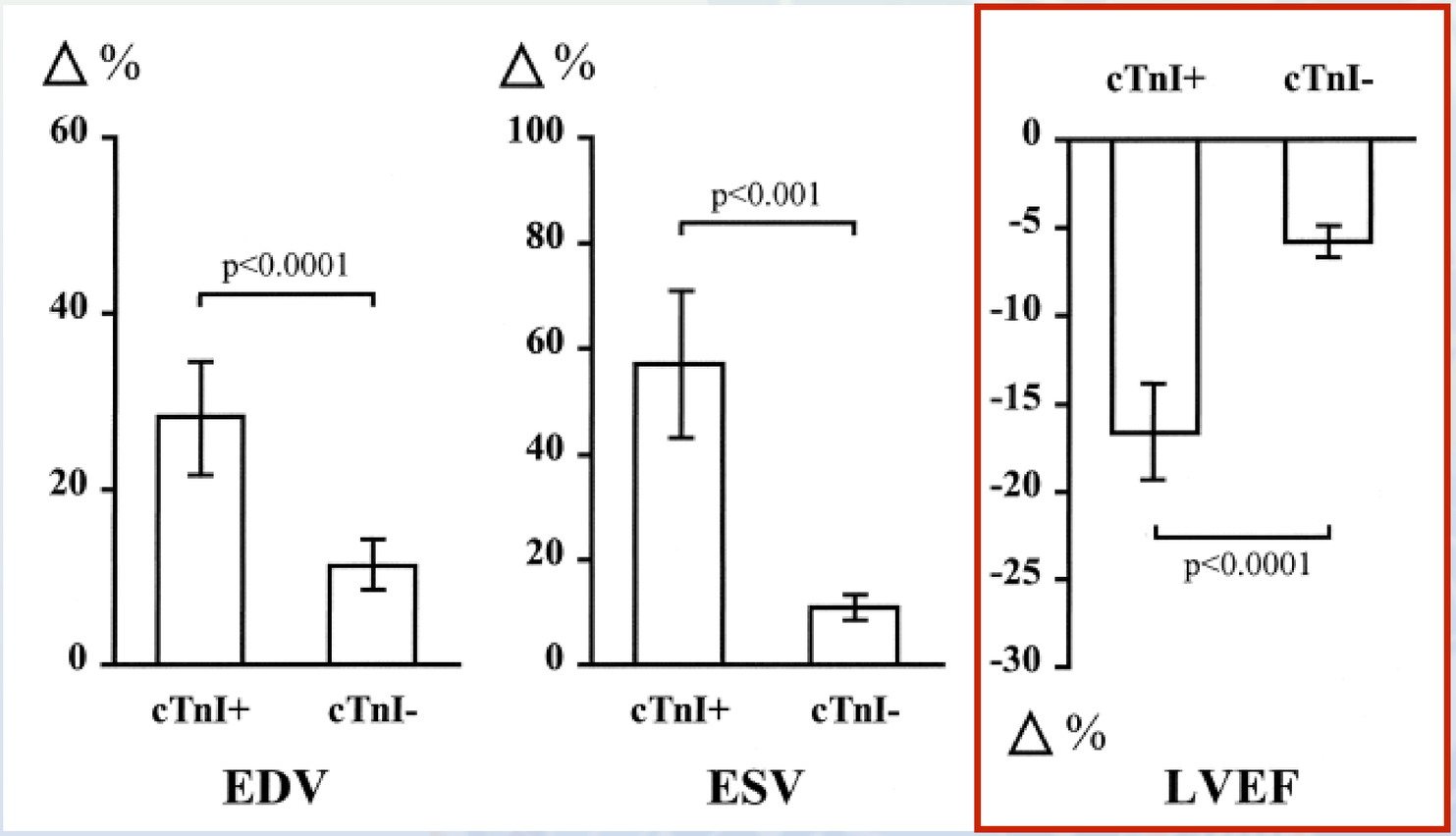

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Late-TnI:
1 month after last HDC dose

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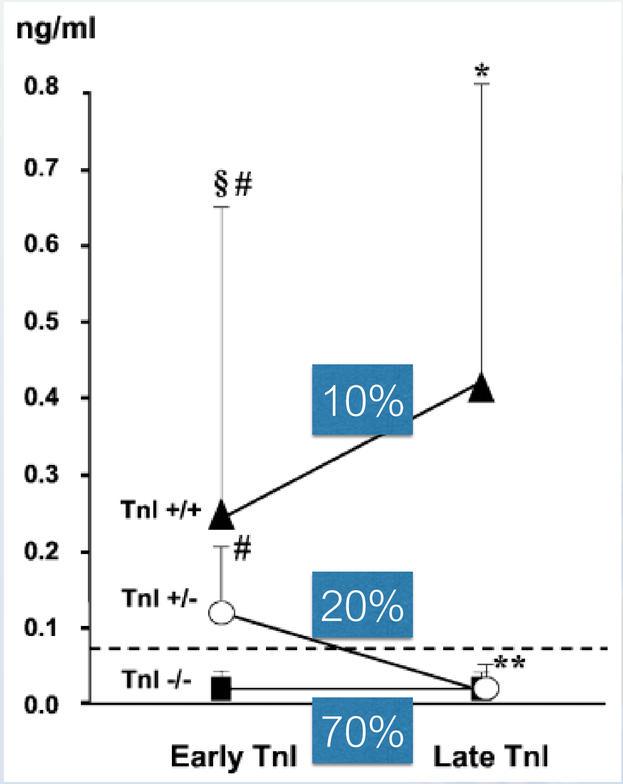

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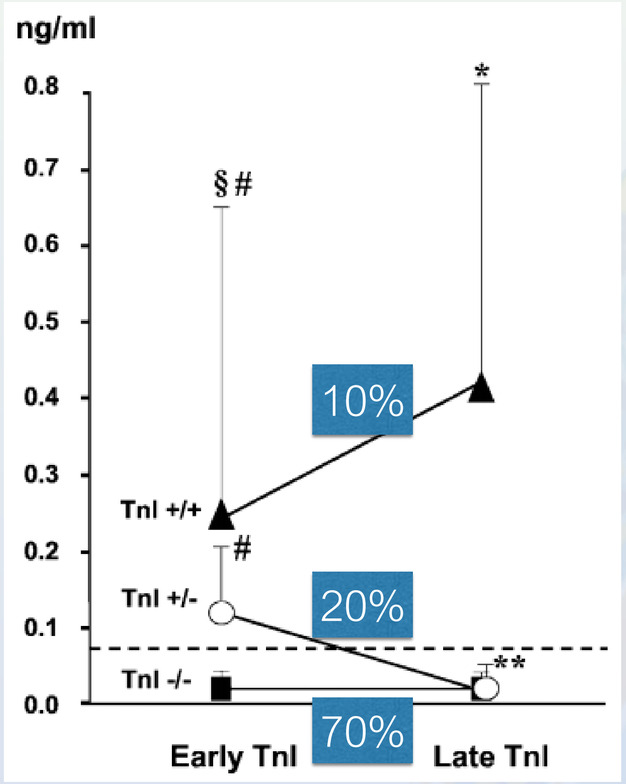

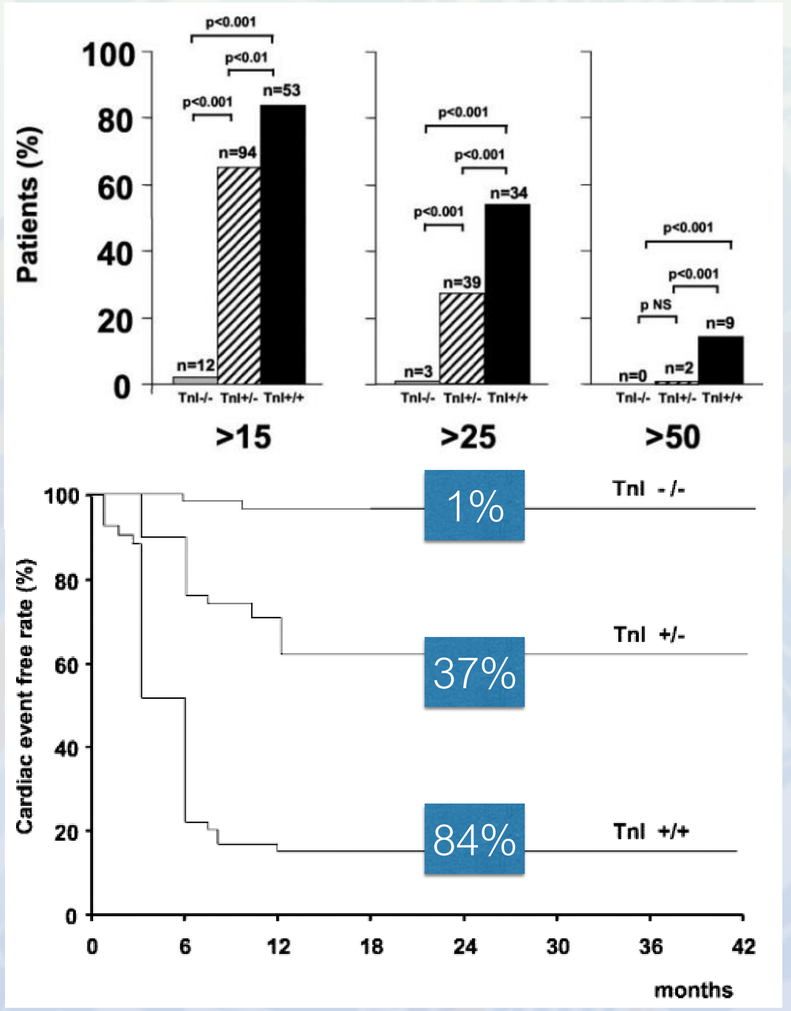

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Late-TnI:
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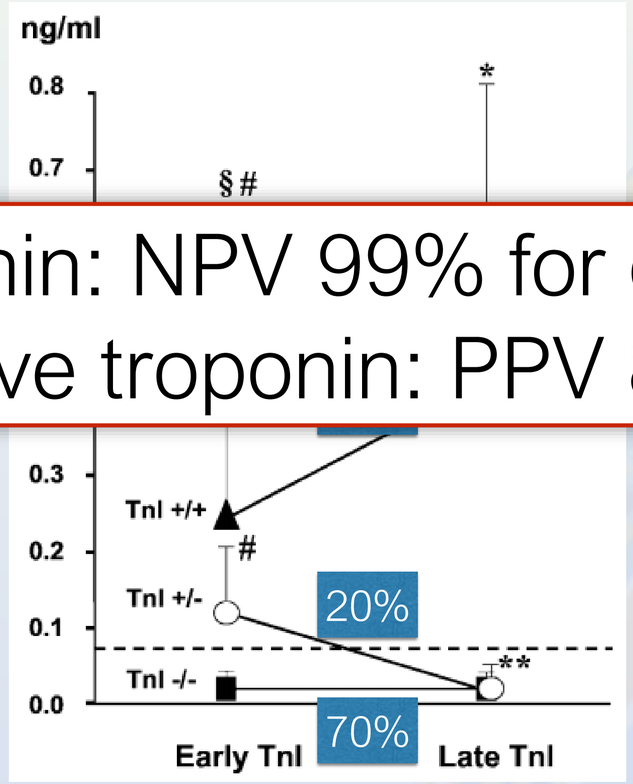
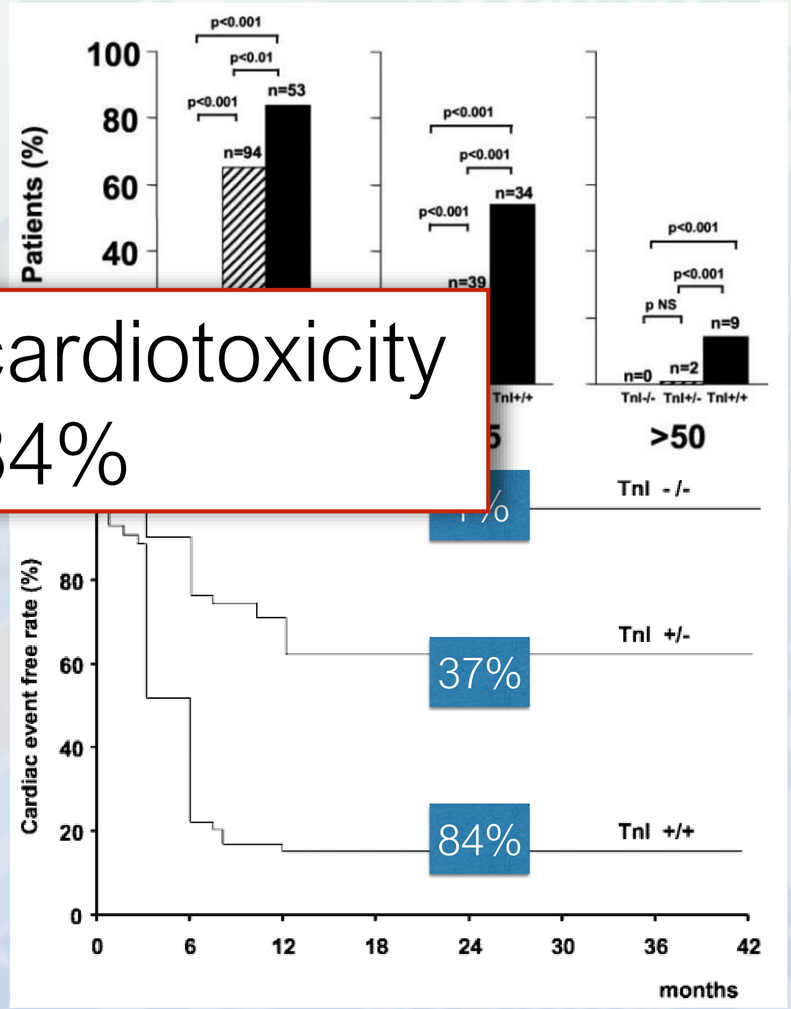
Negative troponin: NPV 99% for cardiotoxicity
Positive troponin: PPV 84%





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Multimodality Approach

- **N = 81 HER2 +ve breast cancer (AC+taxanes/trastuzamab)**

	Sensitivity	Specificity
Ultrasensitive troponin	48%	73%
GLS > -19%	74%	73%
Combined	84%	93%

Sawaya H, et al. Circ Cardiovasc Imaging. 2012 September 1; 5(5): 596–603

Recommendations for Initial Screening of Chemotherapy Induced Cardiotoxicity

American Society of Clinical Oncology
Echo/MRI or MUGA, strain imaging and biomarkers (TnI, BNP) could be considered
American Society of Echocardiography/European Association of CV imaging (2014)
LVEF at baseline with 3DE (preferred) / 2DE (consider contrast), GLS, TnI
European Society for Medical Oncology
Echo or MUGA. May consider MRI as an alternative
European Society of Cardiology
LVEF by 3DE and GLS. MUGA and MRI may be considered as alternative
Canadian Cardiovascular Society
3DE and strain. MUGA and MRI as alternatives. Consider concomitant troponin and BNP

Florido R, et al. J Am Heart Assoc. 2017;6:e006915.

Pharmacotherapy in Prevention of Chemotherapy Induced Cardiotoxicity

	N	Study Arms	Patients	Endpoints	Results
PRADA Trial Gulati G, et al. 2016	130	2x2 Candesartan Metoprolol XL	Breast Ca FEC	Dec LVEF by 5% CMR **GLS** **Troponin**	LVEF dec 2.6% vs. 0,8%, p=0.026 with Candesartan No difference with metoprolol
CECCY Trial Avila M, et al. 2018	192	Carvedilol (3.1 25 mg - 25 mg bid)	Breast cancer pts HER2 negative ANT (<240 mg/m2)	LVEF dec > 10% at 6 months (23% anticipated) **TnI > 0.04, BNP**	1ry: 14% vs. 13.5% **TnI: 26% vs 42% (p = 0.03)** BNP: no difference

Gulati G, et al. European Heart Journal (2016) 37, 1671–1680

Avila M, et al. J Am Coll Cardiol 2018;71:2281–90

Specific Agents

	Anthracycline	Alkylating Agents	HER2/Neu Antagonists	Proteosome Inhibitors	VEGF Inhibitors	Antimetabolites	Immune Checkpoint In
Examples	Doxorubicin Daunorubicin Epirubicin	Cyclophosphamide Ifosfamide melphalan	Trastuzamab Pertuzamab Lapatanib	Bortezomib Carfilzomib	Bevacizumab Sunitinib	5-Flurouracil Cepcitabine	Anti PD-1 Anti CTLA4
Clinical Use	Solid tumors Hematologic Ca.	Solid tumors Hematologic Ca.	Breast Ca (25%) Gastric Ca	Multiple Myeloma	B: Solid tumors S: RCC	Solid tumors	Melonama NSCLC Urologic ca
Mechanism of Toxicity	ROS Top2	Inhibit DNA replication	Inhibit survival pathways Susceptibility to stress	26S proteosome Vasoconstriction	Inhibit endothelial regeneration	Endothelial Injury micro thrombosis	clonal T-cell proliferation
Adverse Effects	LV dysfunction	Arrhythmia LV dysfunction	LV dysfunction	Severe HTN LV dysfunction Ischemia	B: HTN, ACS, HF S: HF	ischemia	Myocarditis
Incidence	HF 5-7% Dose dependent	HF 3-28% Dose dependent	LVD 4.1% - 27%	B: <5% HTN C: 17% HTN, 7% HF, 3% ACS	B: 4% HF S: 13% HF, 3% severe HF	7%	LIkely rare
Natural History	Mostly < 1st year progressive	Peak 1-2 weeks reversible	Mostly reversible < 6 wks	Reversible	Reversible	2-5 days post Rx self limiting (48hr)	Self limiting Potentially fatal
Prevention	< 250 mg/m2 Liposomal prep Daxarzoxane Surveillance	CV monitoring	Avoid concomitant anthracyclnies Surveillance	BP monitoring Multiple anti-HTN PreRx schemia w/u	BP monitoring Cardiac RF management	ECG Pre-emptive use of nitrates/CCB Pre-Rx ischemia	No known strategy

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Risk Factors for Anthracycline Cardiotoxicity

- **Age > 65**
- **Pre-existing LV dysfunction**
- **Female gender**
- **CAD, HTN, obesity, smoking**
- **Concomitant use of other cardiotoxic therapies (e.g. trastuzamab, radiotherapy > 30 Gy)**
- **Cumulative dose***

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Cumulative Dose mg/m2	Incident HF
150	6.5%
250	8.8%
350	17.9%
400	32.4%

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Natural History of Anthracycline Cardiotoxicity

- **Acute (~1%)**
- **Early (1.6-2%)**
- **Late (1.6 - 5%)**

Natural History of Anthracycline Cardiotoxicity

- **N = 2625 (1995 - 2014)**
  Surveillance q 3-6 for 4 yrs
  9% incidence of cardiotoxicity

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- **Clinical characteristics**

NYHA I-II 81%, NYHA III-IV 19%

98% of cases diagnosed with cardiotoxicity in 1 year

Median time to cardiotoxicity since last dose 3.5 months

Partial recovery 71%, full recovery 11%

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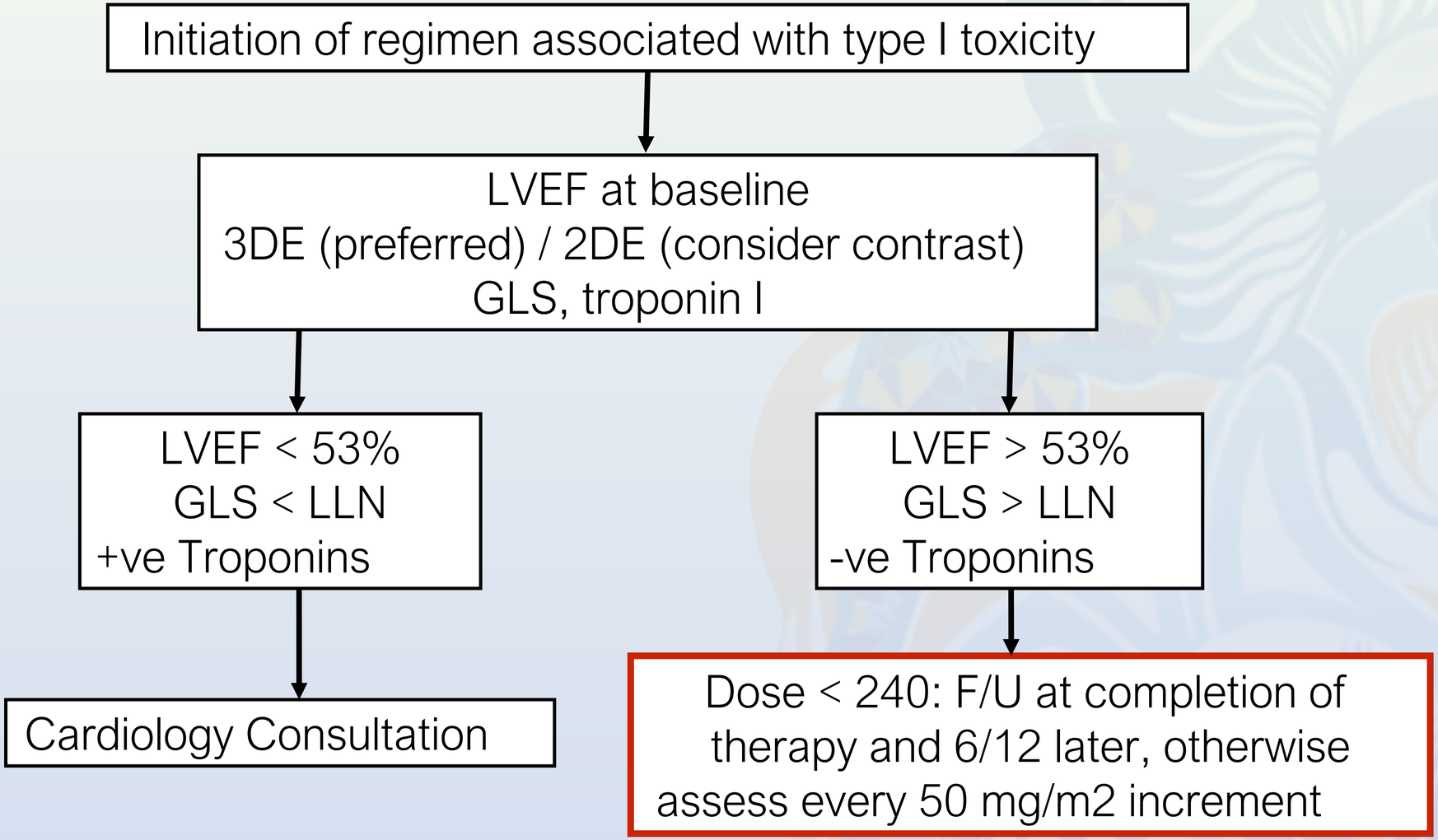
Recommendations for Screening and Diagnosis of Chemotherapy Induced Cardiotoxicity: ASE



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HERA Trial 2005	Anthracyline, taxane Tras 2 yr or 1 yr post adjuvant Rx	MUGA/echo baseline, 3, 6, 12, 18, 24 mo	LVEF dec > 10%, or to < 50% 7.2% (2 yr) vs 4.1% (1 yr) vs 2.2% NYHA III/IV/cardiac death 1%
PACS-04	FEC + Tras 1 yr ET + Tras 1 yr	MUGA/echo 1, 2, 5, 8, 12 mo	Asymptomatic dec LVEF > 15 to < 50% 14.1% (tras) vs. 3.5% 8% (tras) vs. 1.6%

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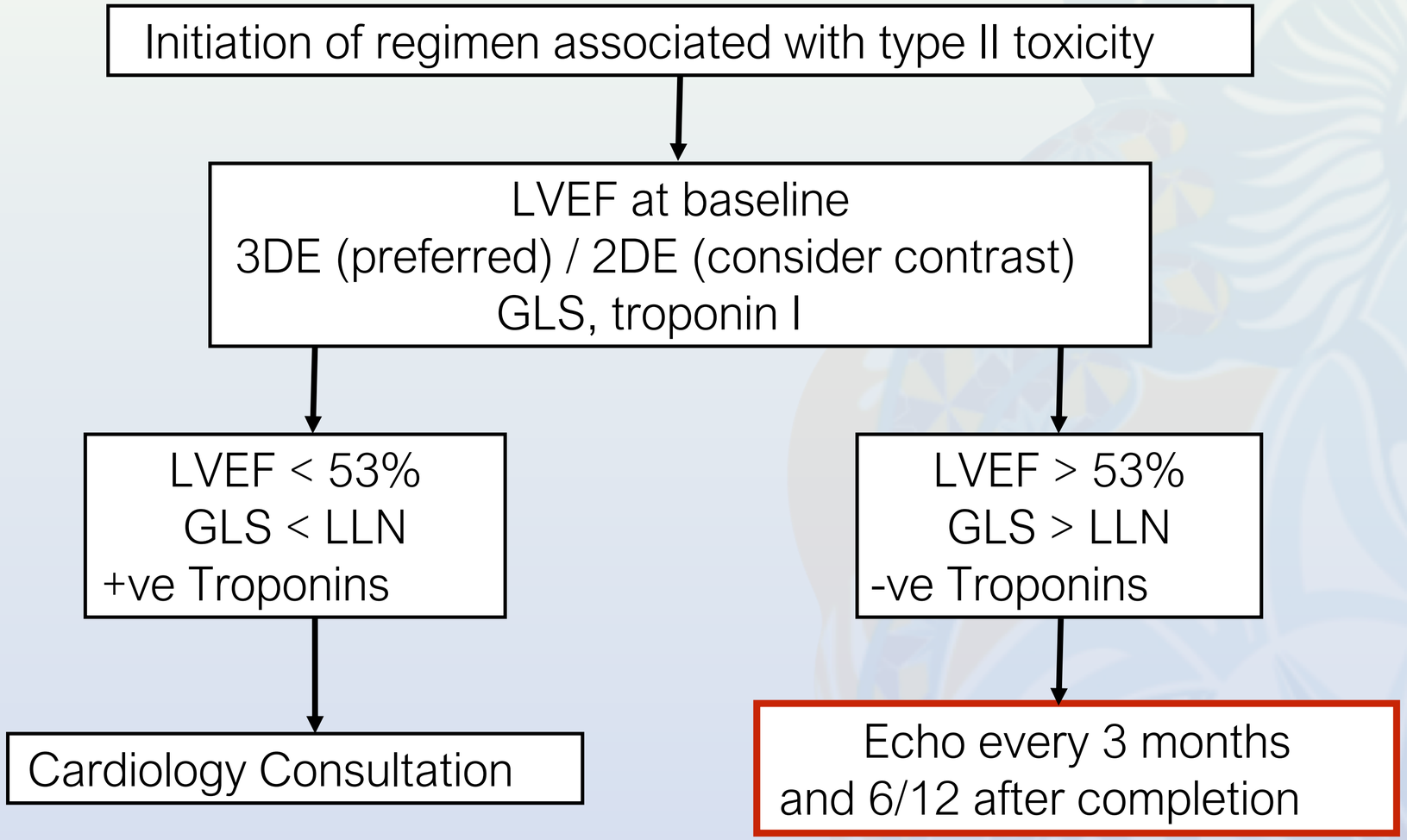

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Natural History	Mostly < 1st year progressive	Peak 1-2 weeks reversible	Mostly reversible < 6 wks	Reversible	Reversible	2-5 days post Rx self limiting (48hr)	Self limiting Potentially fatal
Prevention	< 250 mg/m2 Liposomal prep Daxarzoxane Surveillance	CV monitoring	Avoid concomitant anthracyclnies Surveillance	BP monitoring Multiple anti-HTN PreRx schemia w/u	BP monitoring Cardiac RF management	ECG Pre-emptive use of nitrates/CCB Pre-Rx ischemia	No known strategy

	Anthracycline	Alkylating Agents	HER2/Neu Antagonists	Proteosome Inhibitors	VEGF Inhibitors	Antimetabolites	Immune Checkpoint In
Examples	Doxorubicin Daunorubicin Epirubicin	Cyclophosphamide Ifosfamide melphalan	Trastuzamab Pertuzamab Lapatanib	Bortezomib Carfilzomib	Bevacizumab Sunitinib	5-Flurouracil Cepcitabine	Anti PD-1 Anti CTLA4
Clinical Use	Solid tumors Hematologic Ca.	Solid tumors Hematologic Ca.	Breast Ca (25%) Gastric Ca	Multiple Myeloma	B: Solid tumors S: RCC	Solid tumors	Melonama NSCLC Urologic ca
Mechanism of Toxicity	ROS Top2	Inhibit DNA replication	Inhibit survival pathways Susceptibility to stress	26S proteosome Vasoconstriction	Inhibit endothelial regeneration	Endothelial Injury micro thrombosis	clonal T-cell proliferation
Adverse Effects	LV dysfunction	Arrhythmia LV dysfunction	LV dysfunction	Severe HTN LV dysfunction Ischemia	B: HTN, ACS, HF S: HF	ischemia	Myocarditis
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Conclusions

- **Cancer therapy induced cardiotoxicity is an emerging global problem**
- **Diagnostic criteria for cardiotoxicity and cardiovascular surveillance of cancer patients are inconsistent in clinical trials. Guideline recommendations are consensus driven**
- **While combining strain with biomarkers improves early detection, it remains unknown if such an approach will improve cardiovascular and overall outcomes for cancer patients**
- **A multi-disciplinary approach and patient-centered shared decision-making is necessary to optimize care for this complex population**