Role of Cardiovascular Biomarkers in Cancer Therapy Cardiotoxicity

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Outline

- Rationale for Biomarker Use
- Existent CV Biomarkers and Guidelines
- New Biomarker Discovery
  - Discovering and validating newer mechanistic biomarkers
- Multiple Biomarkers
  - Determining the utility of a multi-marker approach
- Conclusions

Question for the Audience

- I routinely use cardiac biomarkers such as troponin or natriuretic peptides in the care of my oncology patients.
  A. True
  B. False

What are the Priorities in the Cardiovascular Care of Oncology Patients?

Prior to Cancer Therapy
Identify high CV risk patients; Mitigate CTX risk; Inform cancer treatment

During Cancer Therapy
Monitoring to identify CTX; Avoid dose interruptions; Prevent CV events

After Cancer Therapy
Survivorship; Decrease risk of late CV events; Improve long-term health

Critical need to improve upon CV screening methods and develop strategies to identify high risk patients; Biomarkers have the potential to meet this need

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Why is Risk Stratification Important?

- Cardiovascular toxicity leads to dose interruptions and discontinuation of necessary cancer therapy
- Combination therapies are associated with increased cardiotoxicity; many newer agents in development
- Early identification of cardiotoxicity and institution of medications may increase likelihood of recovery
- A growing population of survivors are at an increased risk of long-term cardiovascular morbidity and mortality

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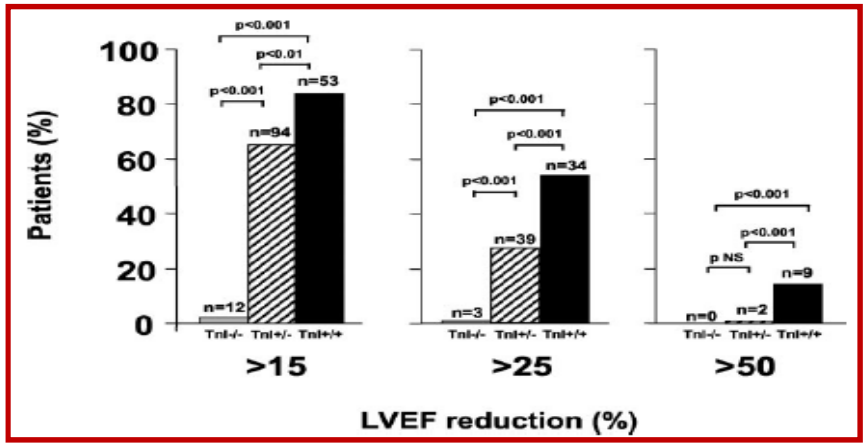
TnI as a Marker of Cardiac Dysfunction with High Dose Chemotherapy

- Frequent measures of TnI with each chemotherapy
  - 703 patients with TnI measured early (0, after, 12, 24, 36, 72 hrs) and late (1 month)
  - TnI assessed via Stratus CS platform with patients divided into 3 groups based upon positivity/timing; only highest TnI considered



	TnI -/- (n=495)	TnI +/- (n=145)	TnI +/+ (n=63)
Events	5 (1%)	53 (37%)	53 (84%)

PPV 84% and NPV 99%

Cardinale, et al. Circulation. 2004.

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TnI as a Marker to Guide Therapy

- TnI measured at 6 timepoints with each chemotherapy cycle
- 114 of 473 (24%) patients showed TnI>0.07 ng/ml
- After completion of chemotherapy, 56 TnI+ patients randomly assigned to ACE-I; 58 TnI+ to no treatment (control)

	Baseline	LVEF at 3 months (%)	LVEF 6 months (%)	LVEF at 12 months (%)	Cardiac events (n)
Control (n=58)	61.8 ± 4.3	54.2 ± 8.1	51.9 ± 7.9	48.3 ± 9.3	31
ACE-I (n=56)	61.1 ± 3.2	61.9 ± 3.3	61.6 ± 3.9	62.4 ± 3.5	1

Cardinale, et al. Circulation. 2006.

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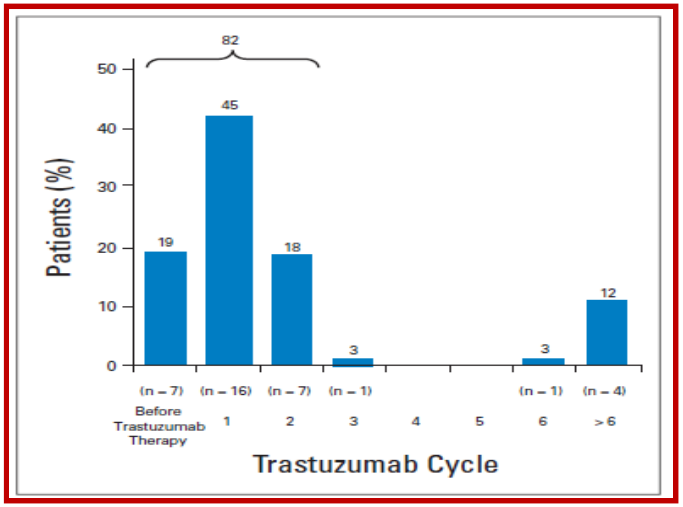
TnI as a Marker to Identify High Risk Trastuzumab Patients

- Frequent measures of TnI with trastuzumab
  - 36 of 251 (14%) women had TnI positivity
  - Positivity occurred early and associated with cardiotoxicity



Variable	Hazard Ratio (95% CI)
TnI +	17.6 (8.85, 3.30)
TnI + duration	16.5 (8.1, 33.6)
Prior anthracyclines	3.25 (0.93, 11.4)

PPV 65% and NPV 100%

Cardinale, et al. JCO. 2010.

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Role of Tn and NT-proBNP with Trastuzumab

- 452 patients from HERA study (doxorubicin + trastuzumab)
- Elevations in cardiac Tn (standard and hs platforms) observed
  - Primarily post anthracyclines (~13%, ~24%); smaller number with first elevations during trastuzumab (~1%, 6%)
- High variability in NT-proBNP observed
- Post-anthracycline Tn and NT-proBNP associated with first significant LVEF decline
  - Effect sizes for Tn (HR 2-4) >> NT-proBNP (HR 1.03)
  - **Poor discriminative ability**

Zardavas, et al. JCO. 2016.

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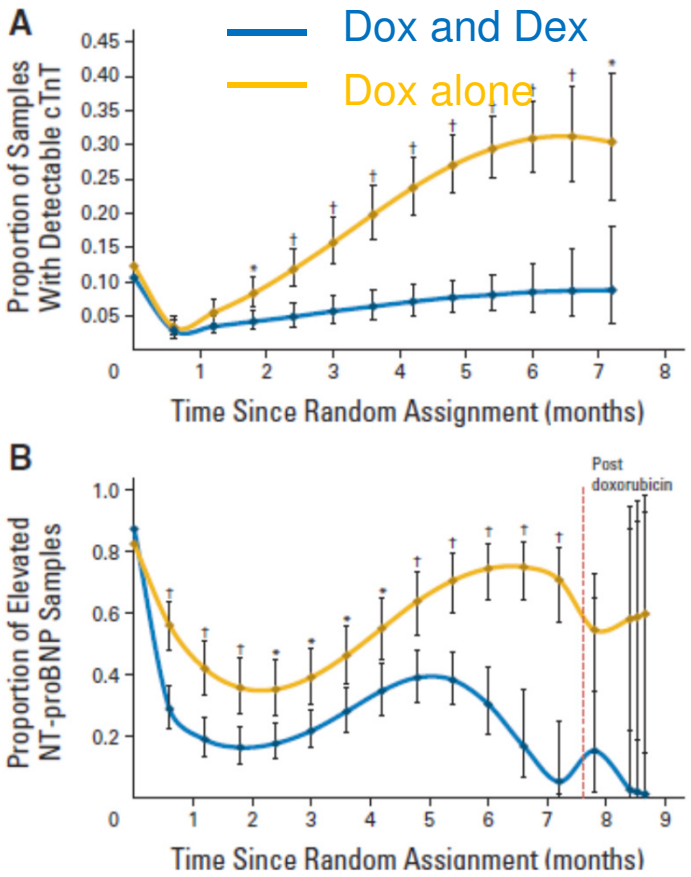
Role of TnT and NT-proBNP in Pediatrics



- Children with high risk ALL treated with doxorubicin alone (n=75) or with dexrazoxane (n=81)
- Greater percentage of elevations in TnT and NT-proBNP in doxorubicin alone
- 3-month changes in TnT associated with 4-year changes in LV mass and posterior wall thickness; NT-proBNP with LV thickness/dimension

Lipshultz, et al. JCO. 2012.

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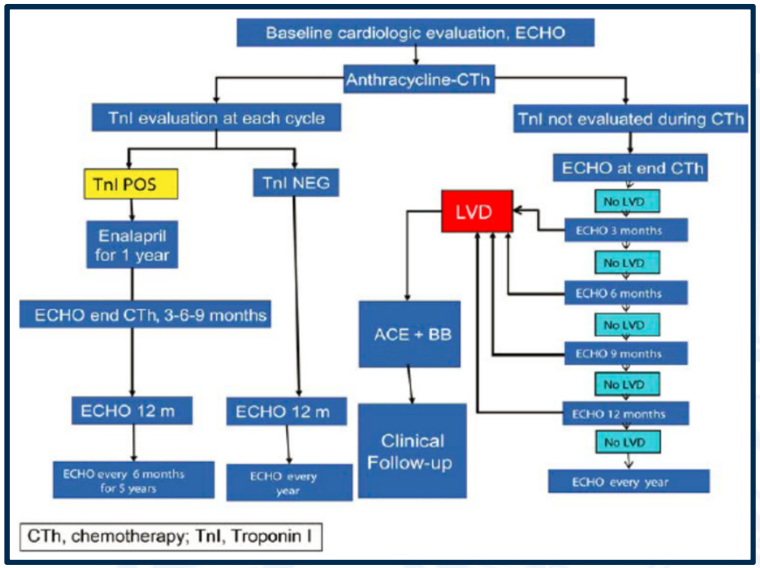
What are the Role of Biomarkers According to the Guidelines?

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

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



Biomarker strategy – level of evidence III, strength of evidence B.

Cardiac biomarkers such as the troponins and brain natriuretic peptides (BNP), and neutrophil glucosaminidase-associated lipocalin as a marker of renal injury, may be expected to be elevated with significant cardiotoxicity. Although it is not yet established whether their routine monitoring is useful in predicting cardiotoxicity, and this needs to be examined in prospective studies, there is a strong case to incorporate their use in the clinical trial setting

Annals of Oncology. 2012.

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2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

Table 6 Proposed diagnostic tools for the detection of cardiotoxicity

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **- 3D-based LVEF** **- 2D Simpson's LVEF** **- GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: **- Troponin I** **- High-sensitivity Troponin I** **- BNP** **- NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

Zamorano, et al. EHJ. 2016.

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ESC Guidelines

- "However, conclusive data are needed to establish whether biomarkers reliably predict clinically relevant late events."
- "Future research needs to establish the optimal timing of measurement for the different cancer treatments, confirm upper limits for each assay and better guide clinicians to target cardioprotective therapy to the appropriate patients."
- "Cardiac biomarkers (natriuretic peptides or troponins) may be considered in addition [to risk scores], preferably using the same assay during follow-up measurements, to increase comparability."

Zamorano, et al. EHJ. 2016.

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Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

- **What surveillance modality should be used?**

Diagnostic value of blood biomarkers of cardiac injury and remodelling	
Poor diagnostic value of cardiac troponins (troponin-T) for detection of asymptomatic cardiomyopathy in survivors of childhood cancer	Level B[48-50]
Poor diagnostic value of cardiac troponins (troponin-I) for detection of asymptomatic cardiomyopathy in survivors of childhood cancer	Level C[51]
Poor diagnostic value of natriuretic peptides (ANP, BNP, NT Pro-BNP) for detection of asymptomatic cardiomyopathy in survivors of childhood cancer	Level B[35,48,52,53]
Cost-benefit of surveillance in survivors of childhood cancer	
Screening for asymptomatic cardiomyopathy using conventional imaging or blood biomarkers is cost-effective	No evidence

Assessment of cardiac blood biomarkers is not recommended as the only strategy for cardiomyopathy surveillance in at-risk survivors

Armenian, et al. Lancet Onc. 2015.

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

4. What are the preferred surveillance and monitoring approaches during treatment in patients at risk for cardiac dysfunction?

Recommendation 4.2. In individuals with clinical signs or symptoms concerning for cardiac dysfunction during routine clinical assessment, the following strategy is recommended:

- Echocardiogram for diagnostic workup

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)

- Cardiac magnetic resonance imaging (MRI) or multigated acquisition (MUGA) scan if echocardiogram is not available or technically feasible (eg, poor image quality), with preference given to cardiac MRI

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

- Serum cardiac biomarkers (troponins, natriuretic peptides) or echocardiography-derived strain imaging in conjunction with routine diagnostic imaging

(Evidence based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)

Recommendation 4.4. No recommendations can be made regarding continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction. This decision, made by the oncologist, should be informed by close collaboration with a cardiologist, fully evaluating the clinical circumstances and considering the risks and benefits of continuation of therapy responsible for the cardiac dysfunction.

(Informal consensus; benefits outweigh harms; Evidence quality: insufficient)

Armenian, et al. JCO. 2016.

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6.3. Biomarkers: Recommendations

A. Ambulatory/Outpatient

CLASS I

1. In ambulatory patients with dyspnea, measurement of BNP to reduce hospitalization or mortality in patients with HF is not well established (230–237). *(Level of Evidence: B)*
2. Measurement of other clinically available tests such as biomarkers of myocardial injury or fibrosis may be considered for additive risk stratification in patients with chronic HF (238–244). *(Level of Evidence: B)*

B. Hospitalized/Acute

CLASS I

1. Measurement of BNP or NT-proBNP is useful to support clinical judgment for the diagnosis of acutely decompensated

Evidence: A)

Yancy, et al. JACC. 2013.

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DCRI announces halt to GUIDE-IT trial

September 23, 2016 – The trial was a comparison of biomarker-guided therapy and usual care for high-risk heart failure patients.

The DCRI announced today that it was terminating the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial due to a lack of difference in the primary outcome between the treatment groups.

GUIDE-IT is a prospective, randomized, multicenter clinical trial that had planned to enroll 1,100 high-risk heart failure patients with left ventricular systolic dysfunction to determine the efficacy of a strategy of biomarker-guided therapy compared with usual care on the composite endpoint of time to cardiovascular death or first hospitalization.

At a recent meeting of the trial's Data Safety Monitoring Board (DSMB), the board members voted to end the trial early (about 18 months earlier than initially planned) based on the available data. Current data showed no evidence of a difference in the primary outcome for biomarker-guided therapy compared to usual care. The National Heart, Lung, and Blood Institute, part of the National Institutes of Health and the DCRI's sponsor for the GUIDE-IT study, accepted the DSMB's decision.

Summary

- Frequent measures of TnI may be associated with an increased risk of subsequent cardiotoxicity
  - Patients with +TnI may benefit from ACE-I therapy
- However, the diagnostic and predictive utility of these measures has been inconsistent
- Existent guidelines suggest a role for biomarkers as ancillary and adjunctive measures

Outline

- Rationale for Biomarker Use
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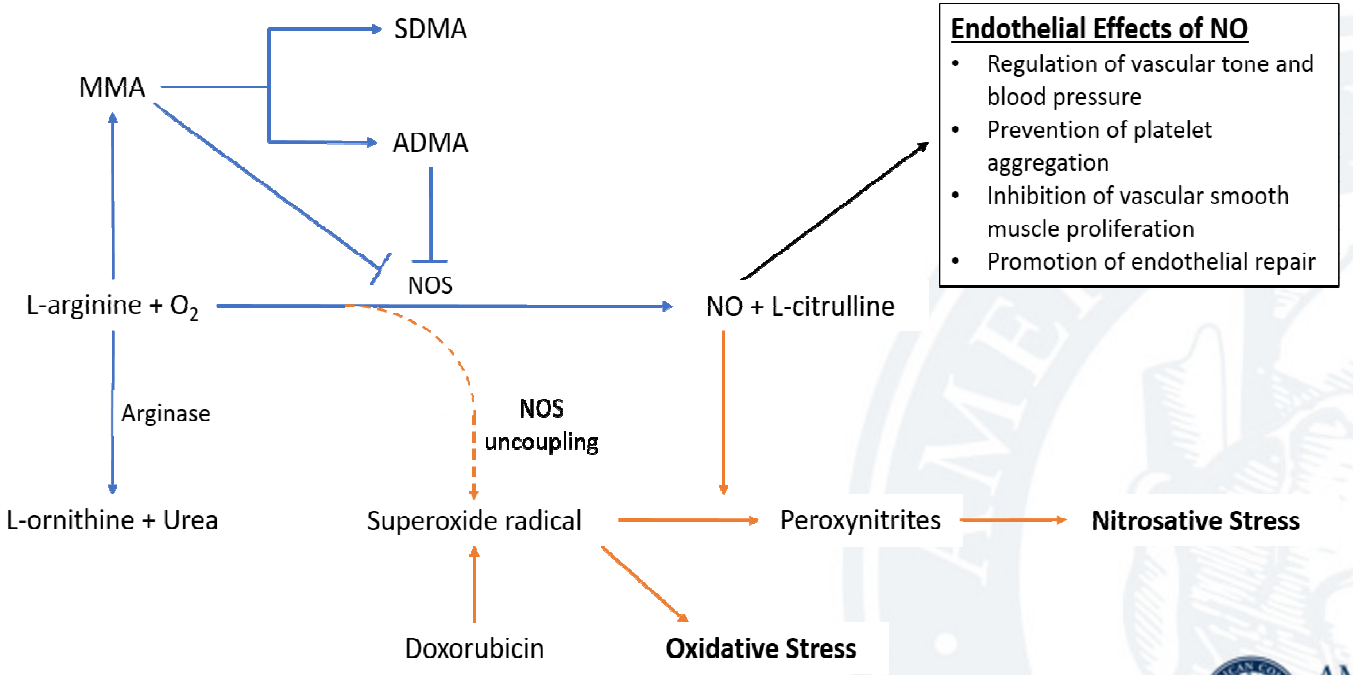
- Conclusions

The Role of Arginine-Nitric Oxide Metabolites in Doxorubicin Cardiotoxicity



Endothelial Effects of NO

- Regulation of vascular tone and blood pressure
- Prevention of platelet aggregation
- Inhibition of vascular smooth muscle proliferation
- Promotion of endothelial repair

Finkelman…Ky, et al. Submitted. 2017.

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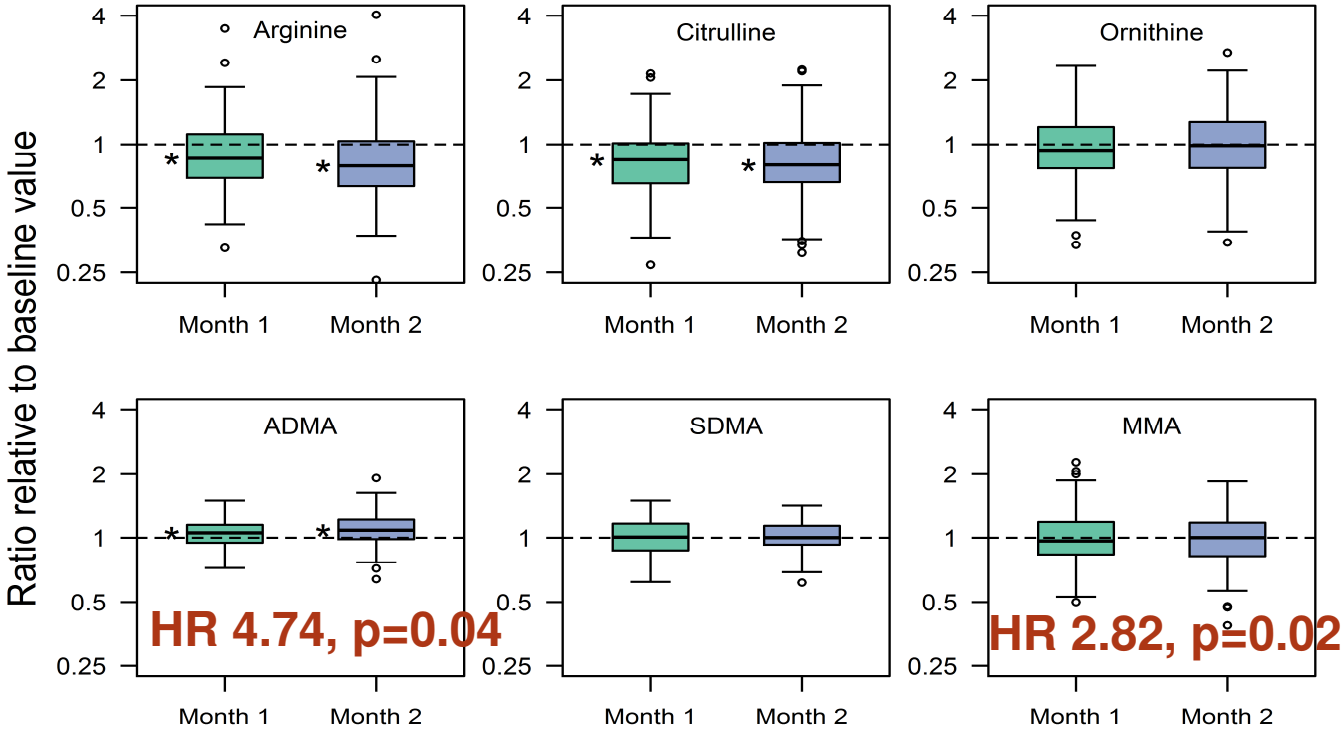

Finkelman…Ky, et al. Submitted. 2017.

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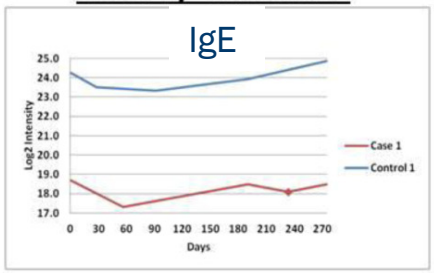
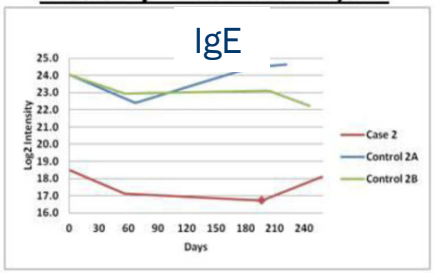
The Role of the Immune System in Doxorubicin and Trastuzumab Cardiotoxicity

Symbol	Description	Case1					Control 1					Case 2				Control 2A				Control 2B				Case 3				Control 3					Probability†			Fold Change‡		
	Plasma*:	p1	p3	p6	p7	p8	p1	p2	p4	p6	p9	p1	p3	p6	p7	p1	p3	p6	p7	p1	p3	p7	p8	p1	p3	p5	p6	p1	p2	p4	p6	p7	1	2	3	1	2	3
	Predictive Biomarkers																																					
IGHE (IgE)	Ig epsilon chain C region																																3E-07	9E-07	2E-04	-54.4	-58.1	-5.4

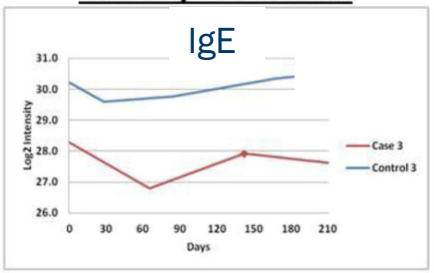
Case 1/ Control 1



Case 2/ Control 2A,2B



Case 3/ Control 3



ImmunoglobulinE (IgE) levels at baseline and throughout therapy consistently higher in controls, 5 to 58-fold, as compared to cases

Beer, Speicher, Ky. Circulation Research. 2016.

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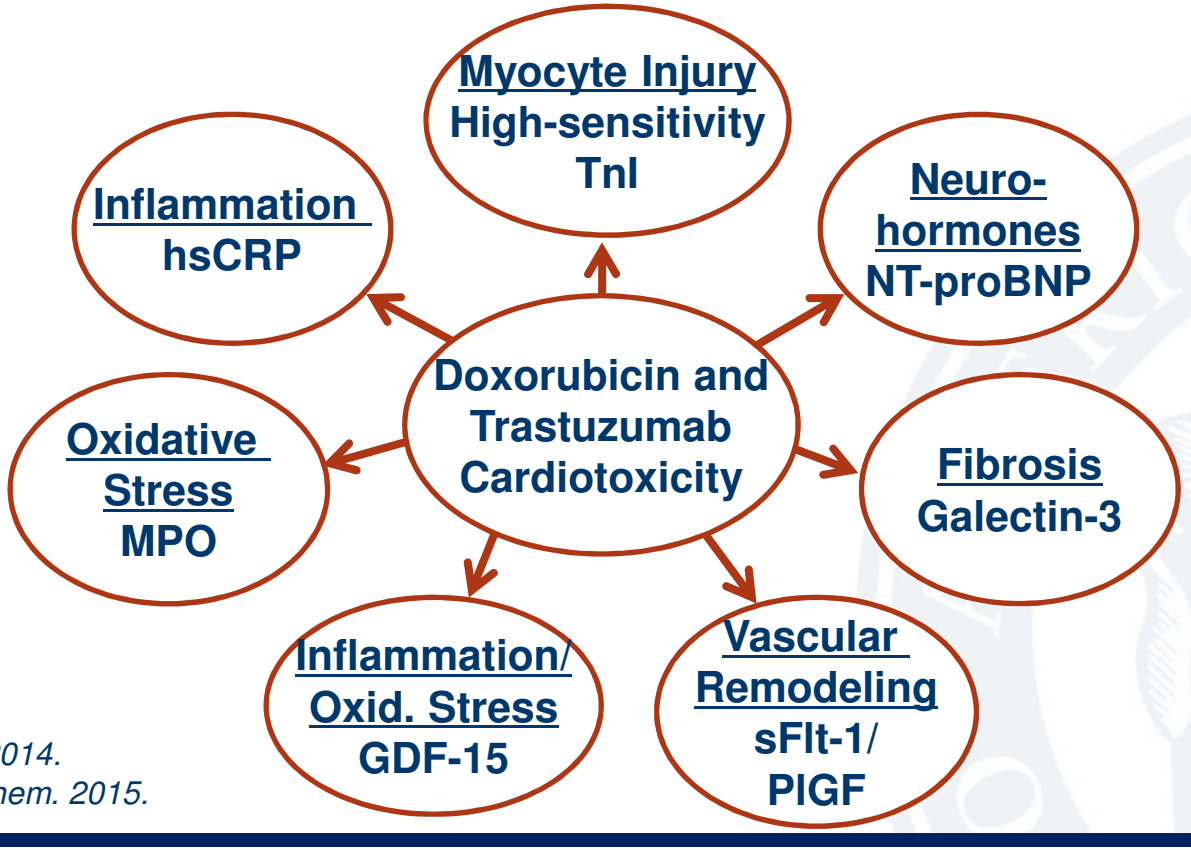
Biomarkers Hypothesized to be Relevant to Doxorubicin & Trastuzumab Cardiotoxicity



Ky, et al. JACC. 2014.
Putt, et al. Clin Chem. 2015.

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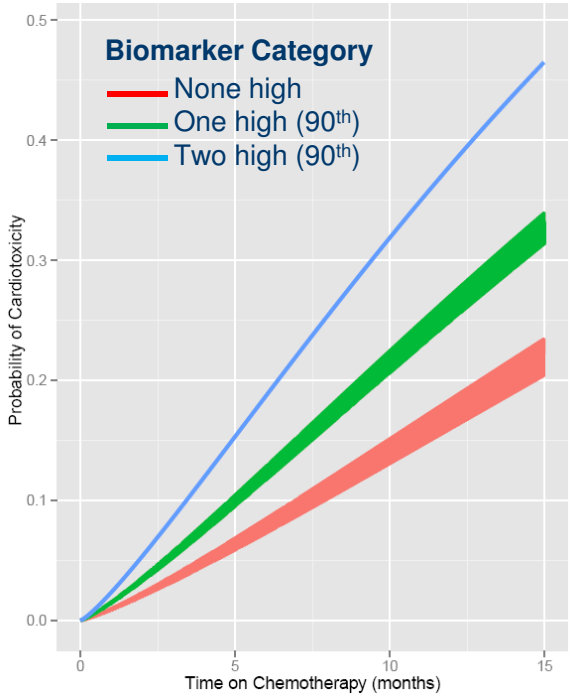
hsTnI and MPO Associated with First Cardiotoxic Event; Additive in Combination

- Biomarkers assessed at baseline and every 3 months during doxorubicin and trastuzumab
  - Patients followed for 15 months
- Baseline values not associated with cardiotoxicity
- **3 month (post-Dox) change** in hsTnI and myeloperoxidase significant (HR 1.34-1.38)



Ky, et al. JACC. 2014.

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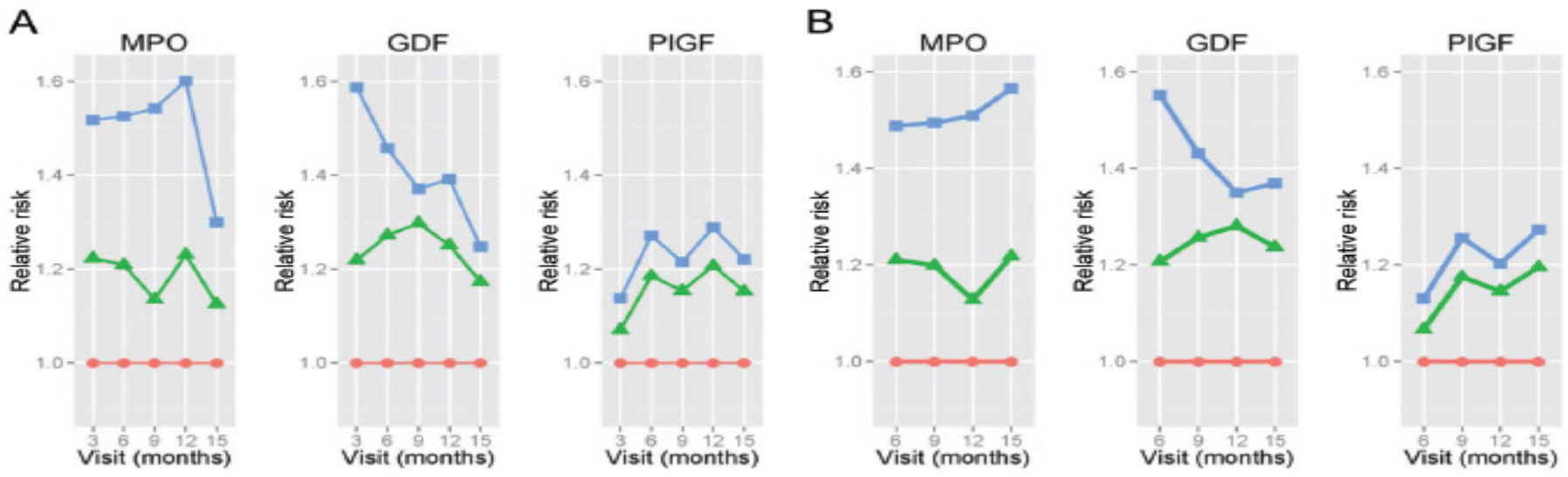
MPO, GDF-15 and PlGF Associated with Cardiotoxicity at Same and Subsequent Visits



A – Cardiotoxicity at Same visit

B – Cardiotoxicity at Subsequent visit

- 90th percentile
- 75th percentile
- 50th percentile

Putt, et al. Clin Chem. 2015.

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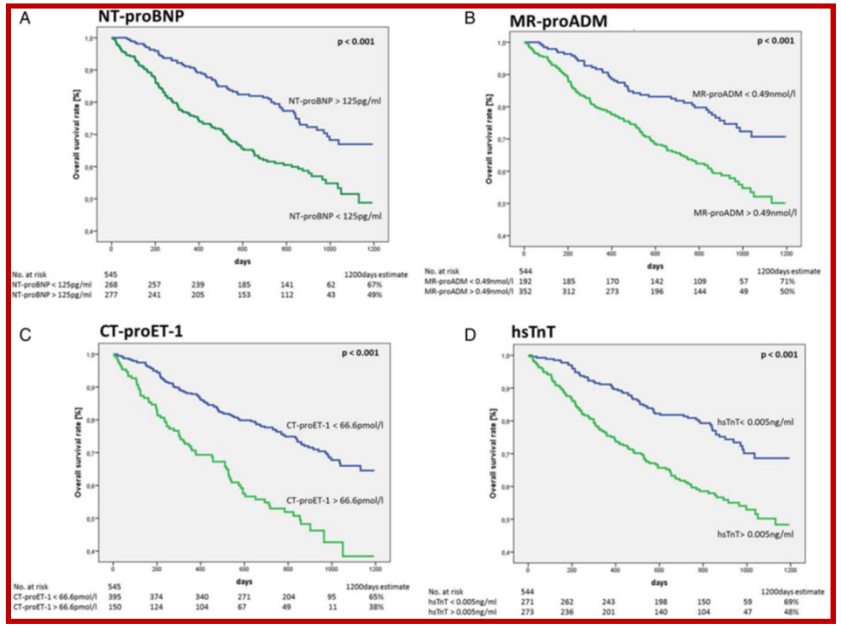
Multiple CV Biomarkers Associated with All-Cause Mortality in Cancer

- 555 cancer patients without prior cardiotoxic cancer therapy
- Median follow-up 25 months; 34% died



Biomarker	Adj. Risk Ratio
NT-proBNP	**1.54**
MR-proADM	**1.31**
CT-proET-1	**1.21**
hsTnT	**1.21**

Pavo, et al. Heart. 2015.

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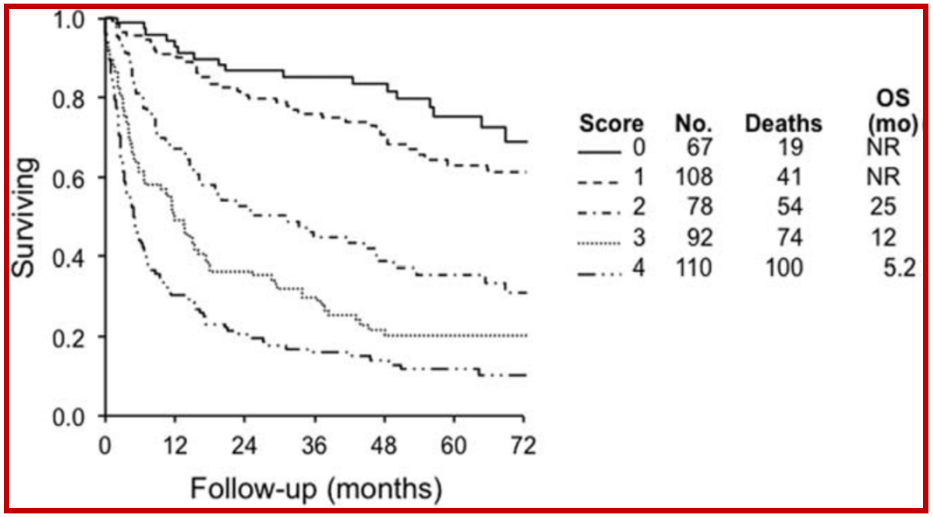
Multi-Marker Strategy Predicts Overall Survival in AL Amyloidosis

- 502 participants with AL amyloidosis, 69% had cardiac involvement
- Median follow-up 63.1 months, 66% died
- Score derived from TroponinT, NT-proBNP, free light chains, and sST2 at diagnosis



Biomarker	Adj. Risk Ratio
TnT	**1.7**
NT-proBNP	**2.3**
Free light chains	**1.3**
sST2	**1.7**
Overall score	**1.8**

Dispenzieri, et al. Am J Hematol. 2015.

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What is the Role of Biomarkers in the Cardiovascular Care of Oncology Patients?

Prior to Cancer Therapy
Identify high CV risk patients; Mitigate CTX risk; Inform cancer treatment

During Cancer Therapy
Monitoring to identify CTX; Avoid dose interruptions; Prevent CV events

After Cancer Therapy
Survivorship; Decrease risk of late CV events; Improve long-term health

Is the goal diagnosis, prognosis, or prediction (guide therapy)?
Is it prior to, during, or after cancer therapy?

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Take Home: What is the Role of Biomarkers?

- Role of biomarkers as primary, solitary measures inconclusive
- Guidelines support role as ancillary measures
- Change in biomarker over time may be more important than baseline level alone
  - In adults undergoing contemporary treatment regimens, post-doxorubicin timepoint critical
  - In children undergoing ALL therapy, greatest changes observed during doxorubicin, possibly associated with late remodeling changes

Take Home: What is the Role of Biomarkers?

- Likely different prognostic cutpoints in metastatic versus non-metastatic disease and possibly in cancer patients versus non-cancer patients
- Abnormalities in CV biomarkers may also be associated with worse oncologic outcomes
- Additional research is needed to establish the role of existent CV biomarkers and new biomarker discovery

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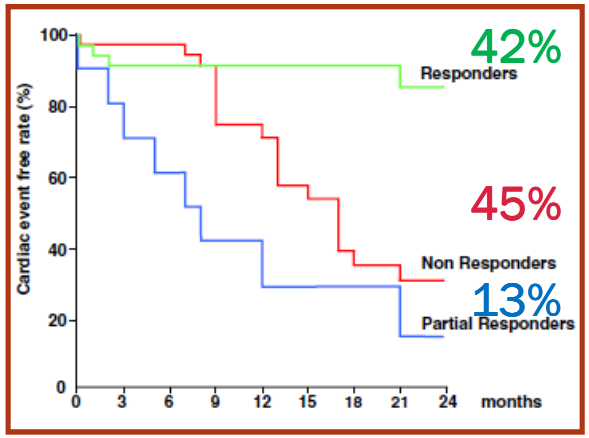
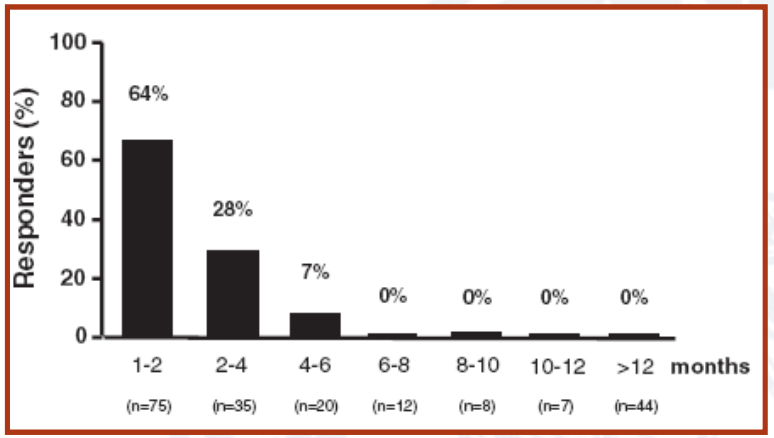
Early Institution of Cardiac Medications Increases Likelihood of LVEF Recovery

- 201 patients with a LVEF≤45% due to anthracyclines followed for 36±27months



Cardiac event-free rate according to "response"



Responders according to time between cardiac diagnosis and HF meds

Partial recovery defined as LVEF increase >10% but <50%; Full recovery LVEF >50%

Cardinale, et al. JACC. 2010.

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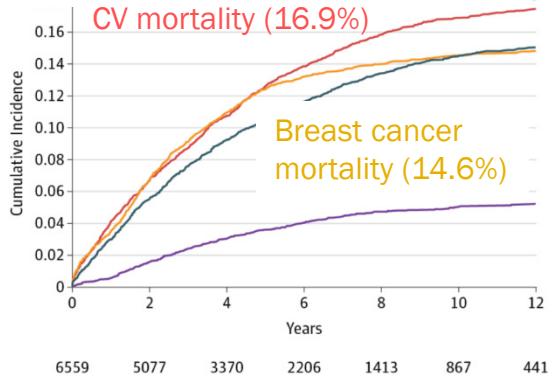
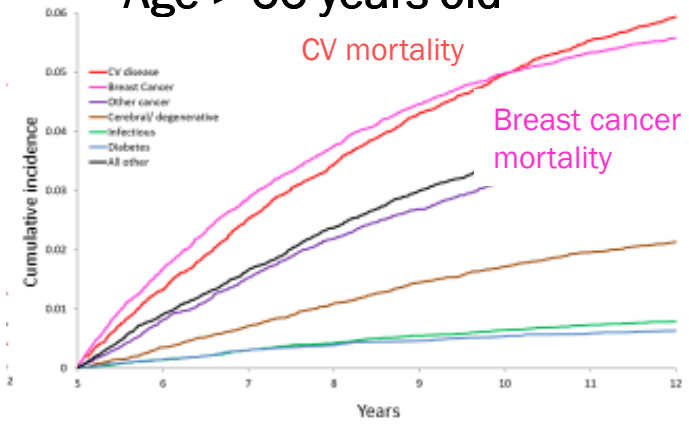
A Growing Population of Breast Cancer Survivors are at Risk for CV Disease

- Ontario Cancer Registry Data: With prior CV disease or older age, risk of CV mortality exceeds cancer at 10 years

Patients with CV disease



Age > 66 years old



Abdel-Qadir, et al. JAMA Cardiol. 2016.

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