# Current Landscape of LV Dysfunction Monitoring: What are the Challenges and Opportunities?

Ana Barac, MD, PhD, FACC

MedStar Heart and Vascular Institute

Chair, ACC Cardio-oncology Council

AMERICAN COLLEGE of CARDIOLOGY

# Disclosures

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# Objectives

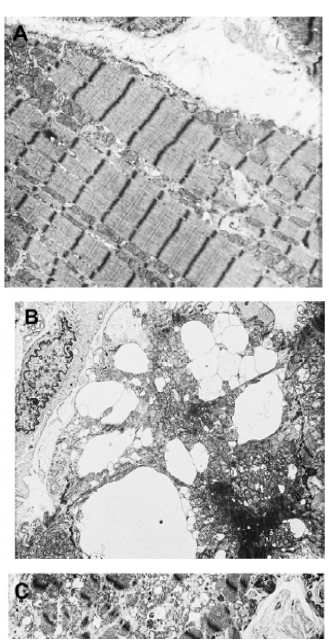
- Left Ventricular (LV) dysfunction - Definitions
- Cardiac imaging techniques
- Cancer therapeutics ~ LV dysfunction
- Current regulatory and clinical practices of LV function monitoring
- How to utilize Cardiac function Monitoring to Advance CV Safety and Improve Patient Outcomes?

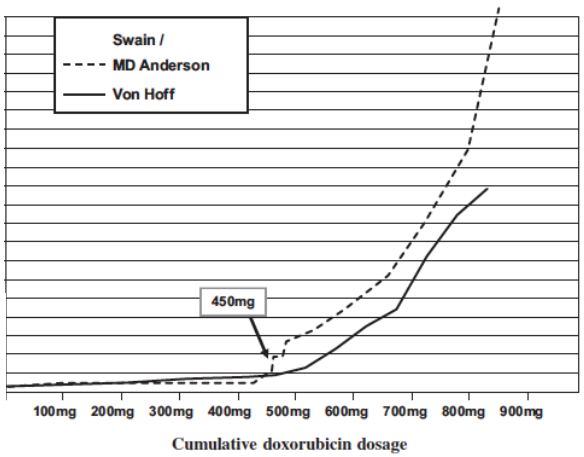
# LV function, LVEF and LV dysfunction

- **Left ventricular (LV) systolic function ≠ LV Ejection Fraction (LVEF)**
  - LVEF = One (heart beat) measure of the contractile function of the left ventricle
    - Physiologic and technique-related variability (MUGA, Echo, CMR)
  - **LVEF is a key predictor** of Outcomes
    - In cardiovascular cohorts
    - In patients receiving cancer therapies (anthracyclines)
  - **LV dysfunction** has many definitions
    - Decrease in **LVEF** of >10% to a value of <53% (50%)
    - Or presence of HF symptoms with LVEF decrease

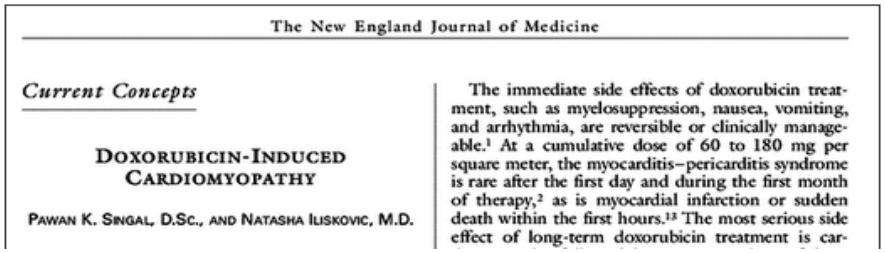
# Cardiac Function in Oncology Practice

1970 -1990-ies: LV dysfunction in patients receiving anthracycline-based cancer treatment




*Ewer M et al. Heart Failure Clin 2011: 7(3):363*



The New England Journal of Medicine

*Current Concepts*

**DOXORUBICIN-INDUCED CARDIOMYOPATHY**

PAWAN K. SINGAL, D.SC., AND NATASHA ILISKOVIC, M.D.

The immediate side effects of doxorubicin treatment, such as myelosuppression, nausea, vomiting, and arrhythmia, are reversible or clinically manageable.[1] At a cumulative dose of 60 to 180 mg per square meter, the myocarditis–pericarditis syndrome is rare after the first day and during the first month of therapy,[2] as is myocardial infarction or sudden death within the first hours.[13] The most serious side effect of long-term doxorubicin treatment is car-

*Singal & Iliskovic. NEJM 1998; 339:900*

## CHANGES IN CLINICAL PRACTICE

- ✓ Reduce the anthracycline dose
- ✓ Check <u>baseline</u> LV systolic function
- ✓ Monitor LVEF (only <u>during treatment</u> at high doses)
- ✓ ERNA (MUGA)

# LVEF Monitoring in Trastuzumab Trials

2001: Trastuzumab improves survival in metastatic HER2-positive breast cancer *Slamon et al. NEJM. 2001;344:783*

| Cardiotoxicity | trastuzumab + AC | AC |
|---|---|---|
| Cardiac dysfunction % | **28** | **10** |
| NYHA III/IV CHF, % | **19** | **3** |

*Seidman A et al. 2002. J Clin Oncol : 20:1215*

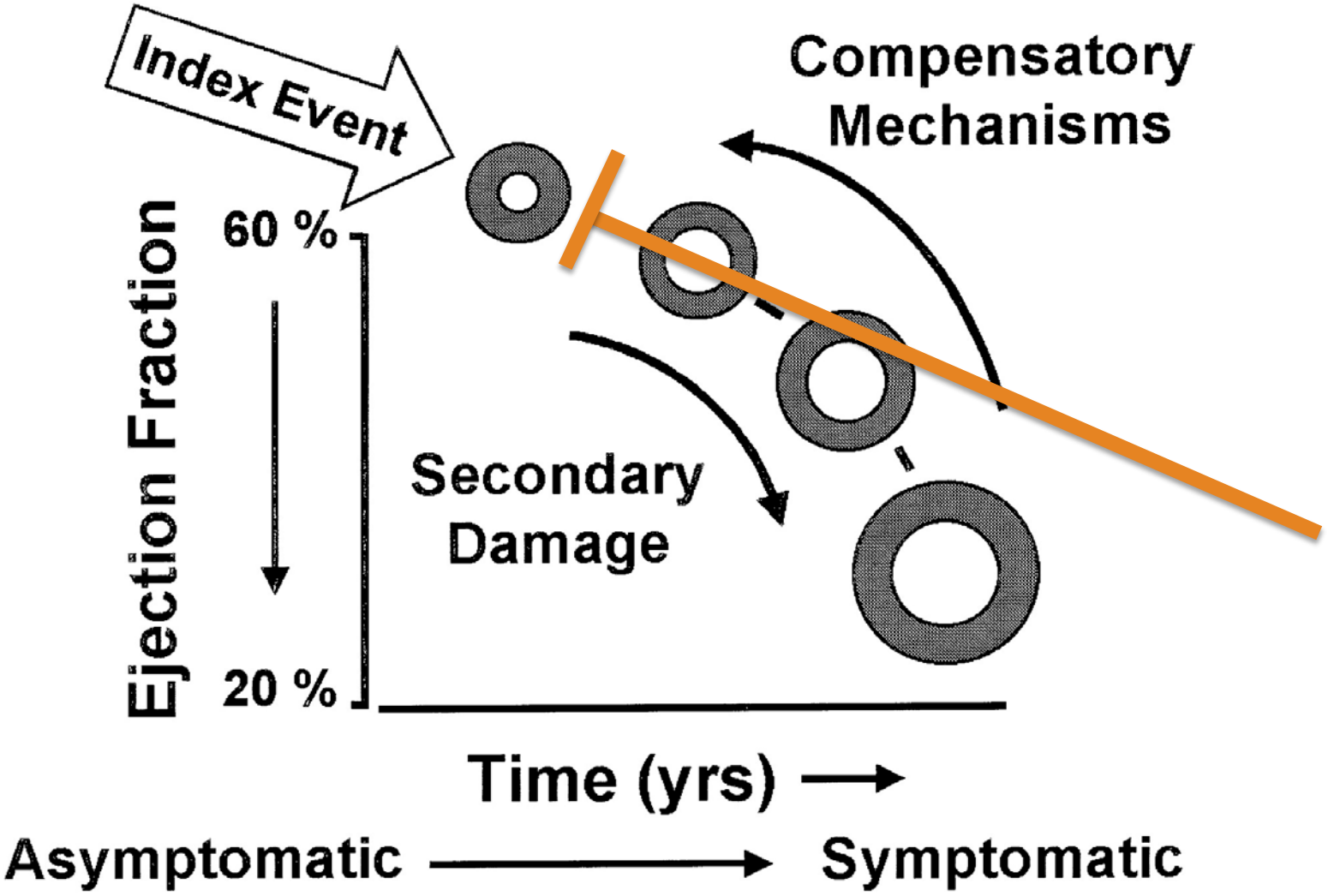
**CHANGES IN THE DESIGN OF CLINICAL TRIALS OF TRASTUZUMAB IN EARLY BREAST CANCER**

- Changes in administration
- **Stringent CV eligibility criteria**
- **Cardiac monitoring schema with early stopping rules**
- NEW ERA OF CARDIAC MONITORING IN ONCOLOGY TRIALS

# Current Monitoring LV Dysfunction in Oncology Clinical Practice

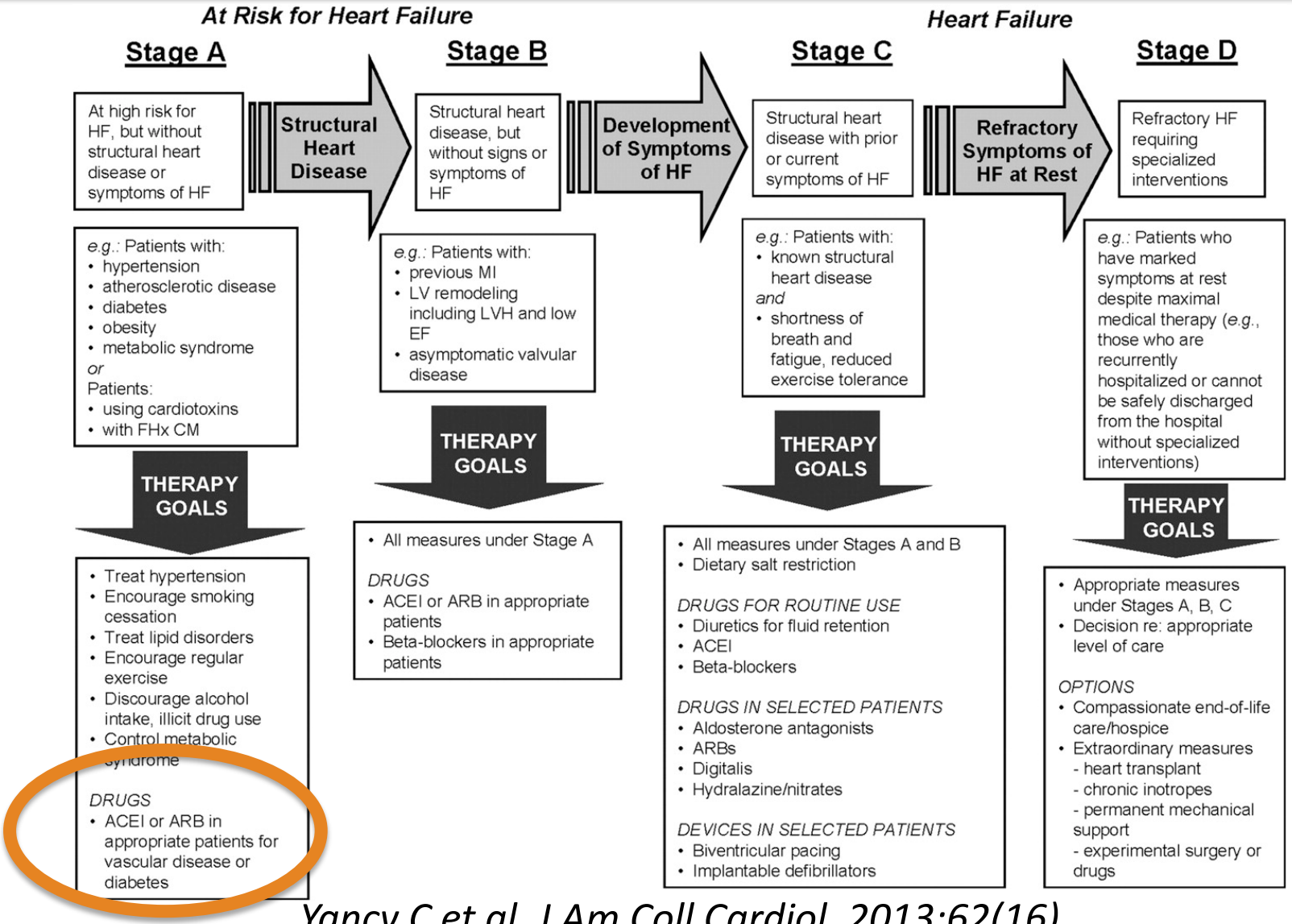
- **Anthracyclines**
  - Pre-treatment LVEF assessment
  - Repeat LVEF assessment with higher cumulative doses
  - Avoid anthracycline in patients with LV dysfunction
- **HER2 targeted agents** (trastuzumab, pertuzumab and TDM-1)
  - Pre-treatment LVEF assessment
  - On-treatment "frequent LVEF assessment" (q 3 months)
  - Therapy held for LVEF decreases, stopped if not improved
- **Other Cancer Therapeutics including Novel Agents: No routine LV assessment**

# Pathogenesis of heart failure




*Mann D L Circulation 1999;100:999-1008*

# Stages of heart failure, ACC/AHA 2013

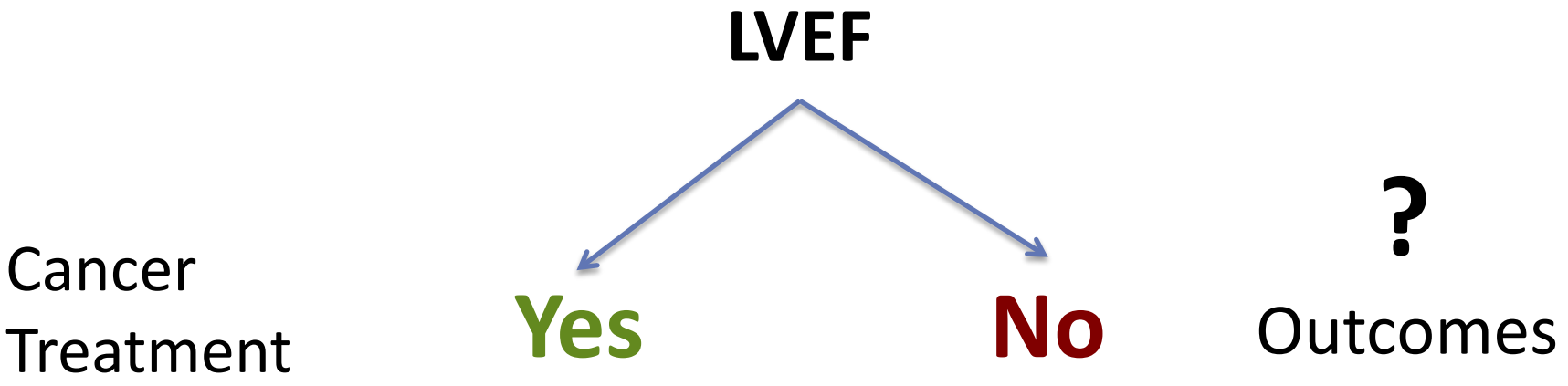



*Yancy C et al. J Am Coll Cardiol. 2013;62(16)*

# Current LV Landscape of LV Dysfunction Monitoring

- **CV Risk Prediction and Outcomes**
  - **Predictors:** LV function parameters (strain), biomarkers
  - **Outcomes:** CV and Oncology outcomes, surrogate outcomes (LVEF)
- **Evidence-based Prevention and Treatment**
  - Which agent? - beta-blockers, ACE-inhibitor, statin
  - For which patient? - strategies for high risk patients
- **Long term CV safety and Outcomes**
- **Design of New Trials**
  - What are the CV parameters needed for drug approval?

# Current LV Landscape of LV Dysfunction Monitoring




**CV Risk Stratification**

- CV risk factors
- Cardiac imaging parameters (LVEF, strain, diastole)
- Biomarkers

**Individualized CV Intervention**

- Based on cardiac risk stratification
- Based on cancer treatment plan

**Improved Outcomes**

- CV and Oncology outcomes
- Relevant surrogate outcomes

# PRESENTATIONS

# PANEL DISCUSSION

# PANEL DISCUSSION: Question 1

- **How do we include CV safety in a contemporary cancer-therapeutics trial?**

Comprehensive CV assessment and follow-up

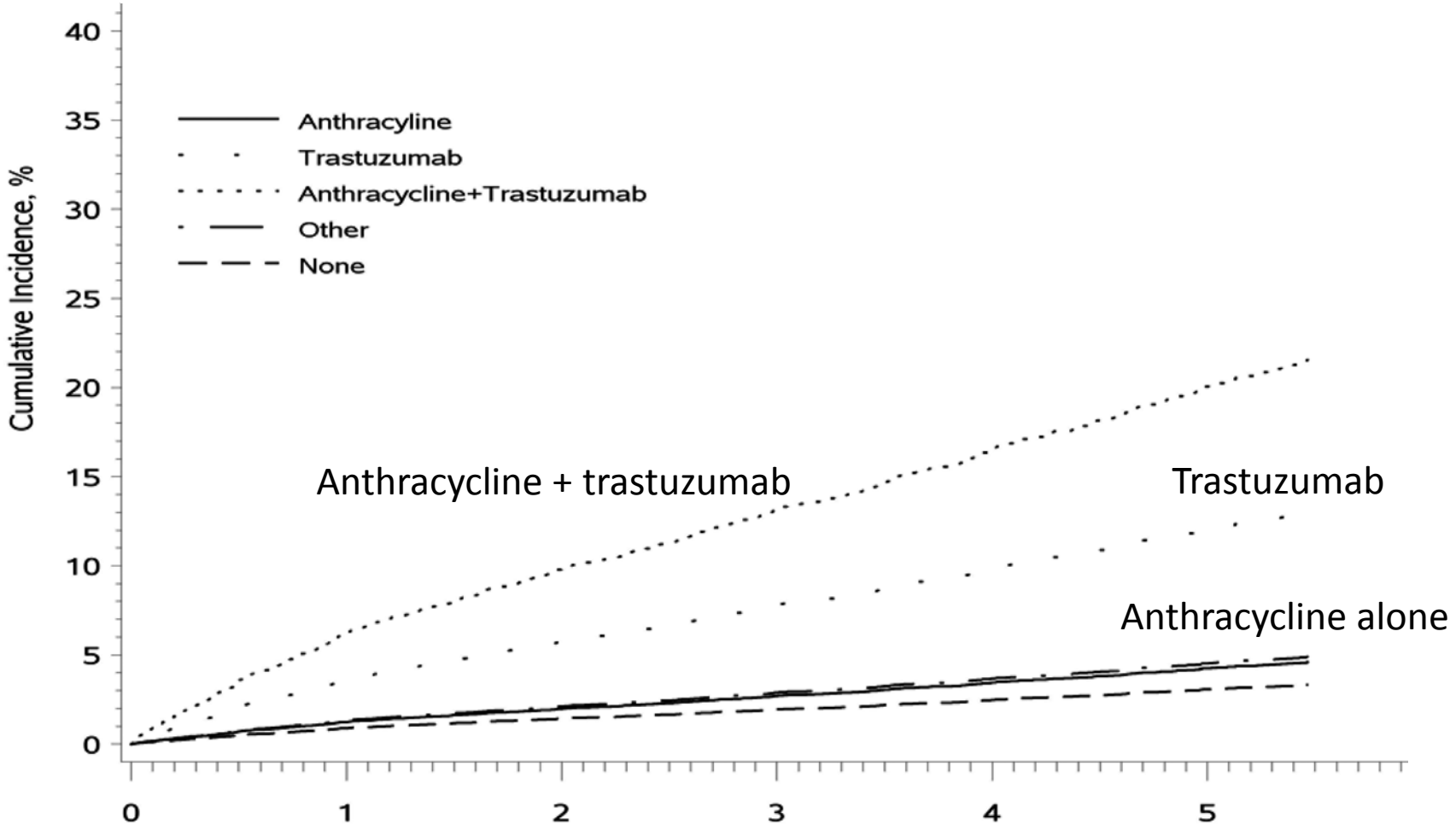
- Baseline CV risk data
- Informed choice of CV imaging modalities (Core labs)
- Biomarkers
- **Outcomes –** Strategies for prevention?
- Long term follow-up

# PANEL DISCUSSION: Question 2

- **What are the elements need to be collected to assure CV safety of a cancer-therapeutics <u>prior</u> to drug approval?**
  - Can CV imaging data in clinical trials inform drug development, approval and labeling?
  - Can CV imaging impact treatment - oncology and CV treatment?

# Population-based Cohort and Risk Prediction

- 12,500 women with breast cancer dg between 1999-2007




Bowles et al. J Natl Cancer Inst 2012; 104:109

# PANEL DISCUSSION: Question 3

- **How do we assure CV safety after the drug approval?**
- **Can we design post-marketing Registries to measure and improve outcomes?**
  - Designed based on trial data
  - Invaluable resource for **Safety Monitoring**, **Improved CV Risk stratification** and **Intervention**
  - Must have **Validation and Quality** control systems: examples from CV world

Thank you.