New Cardiac Guidelines – Where They Agree, Where They Differ, and How Does It Affect Patient Care

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Faculty Disclosure

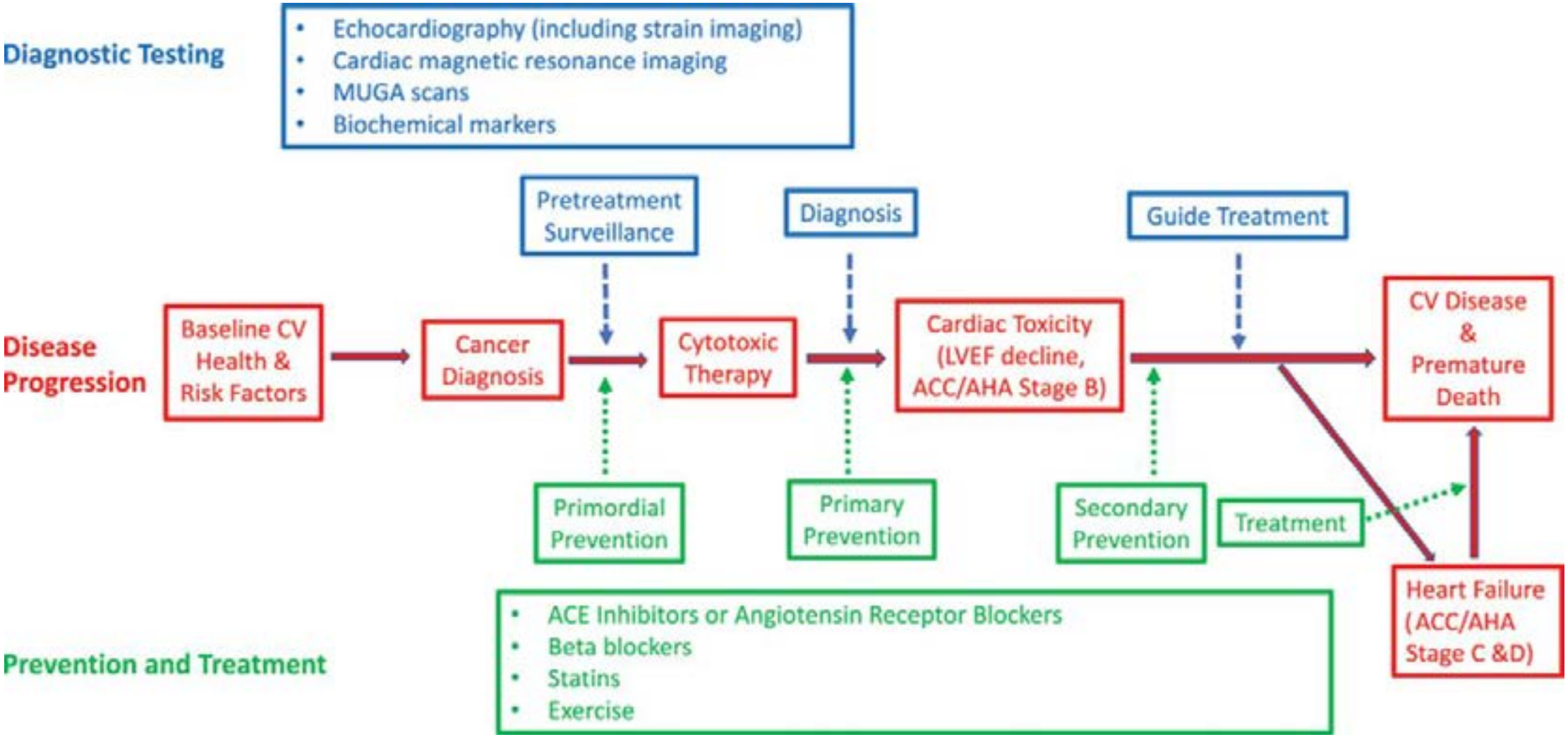
	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
AstraZeneca, PLC.		X						
Eli Lilly and Company		X	X					
Caris Centers of Excellence	X							
Genentech, Inc. /Roche, Ltd.	X	X	X					
Inivata, Ltd.	X	X						
Merrimack Pharmaceuticals			X					
Novartis International AG	X							
Pfizer Inc.								
Pieris Pharmaceuticals Inc.	X	X						
Puma Biotechnology			X					

GUIDELINES in Cardio-Oncology

- American Heart Association
- European Society of Cardiology
- American Society of Clinical Oncology
- American Society of Echocardiography & European Association of Cardiovascular Imaging
- FDA package inserts
  - Trastuzumab
  - Pertuzumab
- NCCN

Detection, prevention, and treatment of left ventricular dysfunction in breast cancer – American Heart Association



Mehta, et al., *Circulation* 2018;137:e30-e66.

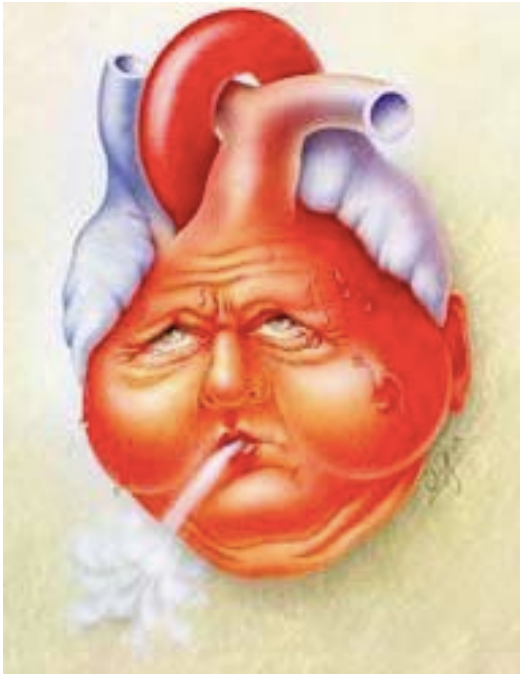
Table 6 **Proposed diagnostic tools for the detection of cardiotoxicity**

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., *Eur Heart J* 2016;37:2768-2801.

European Society of Cardiology
position paper on
cancer treatment and cardiovascular toxicity

Myocardial dysfunction & heart failure

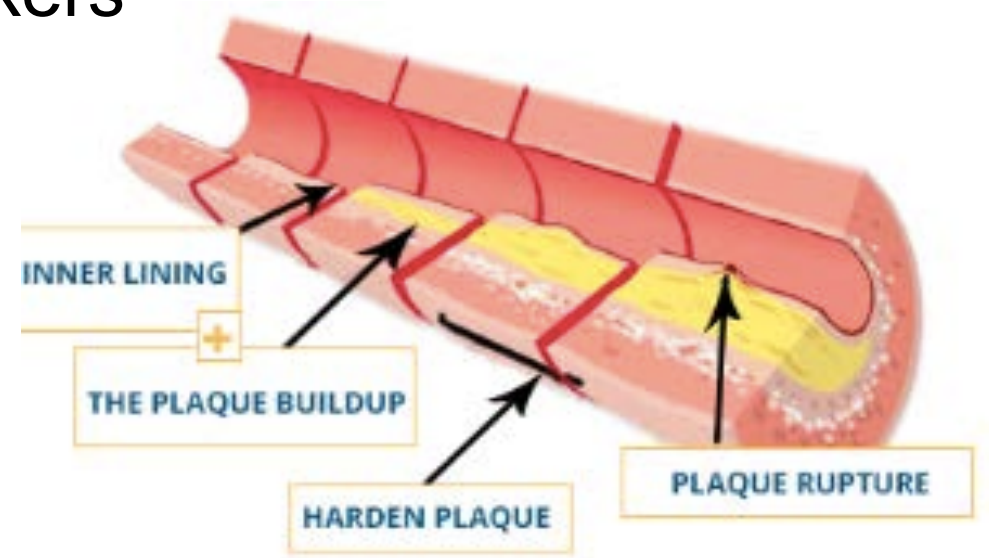


- LVEF should be determined before and during treatment with a method of sufficient image quality
- LLN is 50%
- If LVEF >10% drop and > LLN - repeat assessment
- In asymptomatic pts, If LVEF >10% drop and < LLN
  - ACE inhibitors or ARBs and beta blockers
- In symptomatic pts ACE inhibitors and beta-blockers recommended

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Coronary artery disease

- Assessment based on history, gender, age, and treatment
- Pyrimidine analogs – regular ECGs
- Drug re-challenge after vasospasm only if no alternative and pretreat with nitrates and/or calcium channel blockers
- Long term follow-up and when required, testing for the presence of CAD



Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

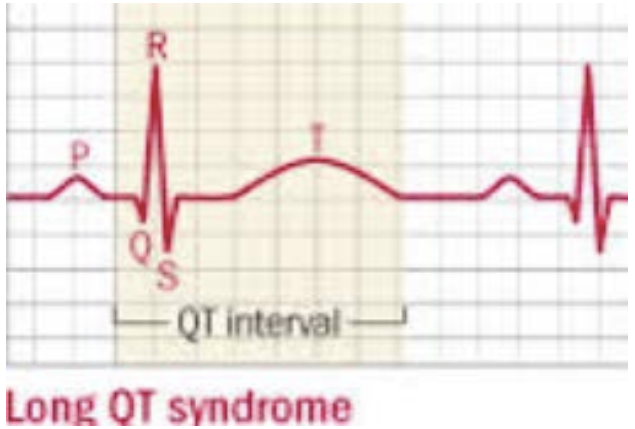
Table 7 Pathophysiological mechanisms of coronary artery disease in cancer treatment[7,60,81,99,117–123]

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	• Endothelial injury • Vasospasm	• Up to 18% manifest myocardial ischaemia • Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	• Procoagulant status • Arterial thrombosis	• 20-year absolute risk of up to 8% after testicular cancer • 2% risk of arterial thrombosis
VEGF inhibitors (bevacizumab, sorafenib, sunitinib)	• Procoagulant status • Arterial thrombosis • Endothelial injury	• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiotherapy	• Endothelial injury • Plaque rupture • Thrombosis	• 2–7-fold increased relative risk of myocardial infarction • Cumulative 30-year coronary events incidence of 10% in Hogdkin lymphoma survivors • Risk proportional to irradiation dose

5-FU = 5-fluorouracil; VEGF = vascular endothelial growth factor.

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Arrhythmias



- ECG and QT interval at baseline
- Pts with history of QT prolongation, cardiac disease, use of QT prolonging drugs, bradycardia, thyroid disease, or electrolyte abnormalities – repeat EKGs
- Discontinue or alternative treatments if QTc >500 ms or prolonged > 60 ms
- Avoid hypokalemia and extreme bradycardia
- Limit exposure to other QT prolonging drugs if QT prolonging chemotherapy

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Table 8 Cancer drug agents associated with cardiac arrhythmias

Type of arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicine, epirubicine, 5-FU, ifosfamide, IL-2, methotrexate, mitoxantrone, paclitaxel, rituximab, thalidomide.
Sinus tachycardia	Anthracyclines, carmustine.
Atrioventricular block	Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5-FU, mitoxantrone, rituximab, taxanes, thalidomide.
Conduction disturbances	Anthracyclines, cisplatin, 5-FU, imatinib, taxanes.
Atrial fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5-FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.
Supraventricular tachycardias	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5-FU, methotrexate), bortezomib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, gemcitabine), arsenic trioxide, doxorubicin, interferons, IL-2, methothrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.
Sudden cardiac death	Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5-FU (probably related to ischaemia and coronary spasm), interferons, nilotinib, romidepsin.

5-FU = 5-fluorouracil; IL-2 = interleukin 2; TKI = tyrosine kinase inhibitor.

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Table 10 **Risk factors for QT prolongation in cancer patients**

Risk factors for QT prolongation	
Correctable	**Non-correctable**
Electrolyte imbalance • Nausea and emesis • Diarrhoea • Treatment with loop diuretics • Hypokalaemia (≤3.5 mEq/L) • Hypomagnesaemia (≤1.6 mg/dL) • Hypocalcaemia (≤8.5 mg/dL) **Hypothyroidism** **Concurrent use of QT-prolonging drugs** • Antiarrhythmic • Anti-infective • Antibiotic • Antifungal • Psychotropic • Antidepressant • Antipsychotic • Antiemetic • Antihistamine	• Family history of sudden death (occult congenital LQTS or genetic polymorphisms) • Personal history of syncope • Baseline QTc interval prolongation • Female gender • Advanced age • Heart disease • Myocardial infarction • Impaired renal function • Impaired hepatic drug metabolism

LQTS = long QT syndrome.

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Arterial Hypertension

- Treat according to clinical guidelines and monitor blood pressure
- Treat early and aggressively to prevent HF
- ACE or ARBs, beta blockers, and dihydropyridine calcium channel blockers are preferred. Avoid non-dihydropyridine (verapamil/diltiazem) due to drug interactions (statins).
- Dose reduction or discontinuation of VEGF inhibitors can be considered if BP not controlled

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Supplementary Table **Most recent reviews and meta-analyses on the incidence of hypertension with major VEGF inhibitor treatment**

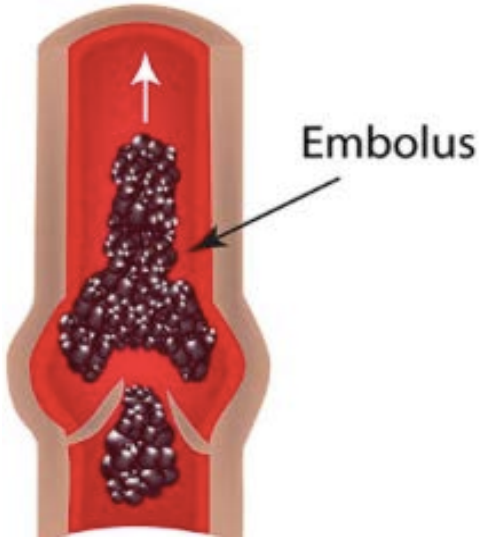
Drug	Number of studies included	Number of patients	Incidence of all grades of HTN, %	Incidence of stage 3-4 HTN, %
Bevacizumab[165]	20	6754	23.6	7.9
Sunitinib[167]	13	4999	21.6	6.8
Sorafenib[168]	13	2492	15.3	4.4
Axitinib[169]	10	1908	40.1	13.1
Vandetanib[170]	11	3154	24.2	6.8
Regorafenib[171]	5	750	44.4	12.5

HTN = hypertension; VEGF = vascular endothelial growth factor.

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Other conditions and patients

- Valvular disease
- Thromboembolic disease
- Pulmonary hypertension
- Pericardial and pleural effusions
- Autonomic dysfunction
- Pediatric
- Elderly
- Pregnant



Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Table 11 Clinical factors associated with increased risk of cancer-associated venous thromboembolism (modified from Khorana et al.[182])

Cancer-related factors
• Primary site of cancer (mostly pancreas, brain, stomach, kidney, lung, lymphoma, myeloma)
• Histology (specially adenocarcinoma)
• Advanced stage (metastatic)
• Initial period after cancer diagnosis
Patient-related factors
• Demographics: older age, female sex, African ethnicity
• Comorbidities (infection, chronic kidney disease, pulmonary disease, atherothrombotic disease, obesity)
• History of venous thromboembolism, inherited thrombophilia
• Low performance status
Treatment-related factors
• Major surgery
• Hospitalization
• Chemotherapy and anti-angiogenic agents
• Hormonal therapy
• Transfusions
• Central venous catheters

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Treatment options to prevent or recover from myocardial dysfunction

- Identify and treat CV risk factors and comorbidities
- For QT prolongation – avoid QT prolonging drugs and manage electrolytes
- For anthracyclines
  - Limit cumulative dose
  - Liposomal delivery
  - Dexrazoxane
  - ACE inhibitors, ARBs, or beta-blockers
  - Statins
  - Aerobic exercise
- For trastuzumab
  - ACE inhibitors or beta-blockers

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Table 14 **Summarizes the potential benefits of exercise during and/or after cancer treatment**

Improvement of:

- Cardiorespiratory and cardiovascular function
- Body composition (preservation or increase in muscle mass, loss of fat mass)
- Immune function
- Chemotherapy completion rates
- Muscle strength and flexibility
- Body image, self-esteem and mood

Reduction in:

- Number and severity of side effects including nausea, fatigue and pain
- Reduction of hospitalization duration
- Reduction of stress, depression and anxiety

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Strategies for the future

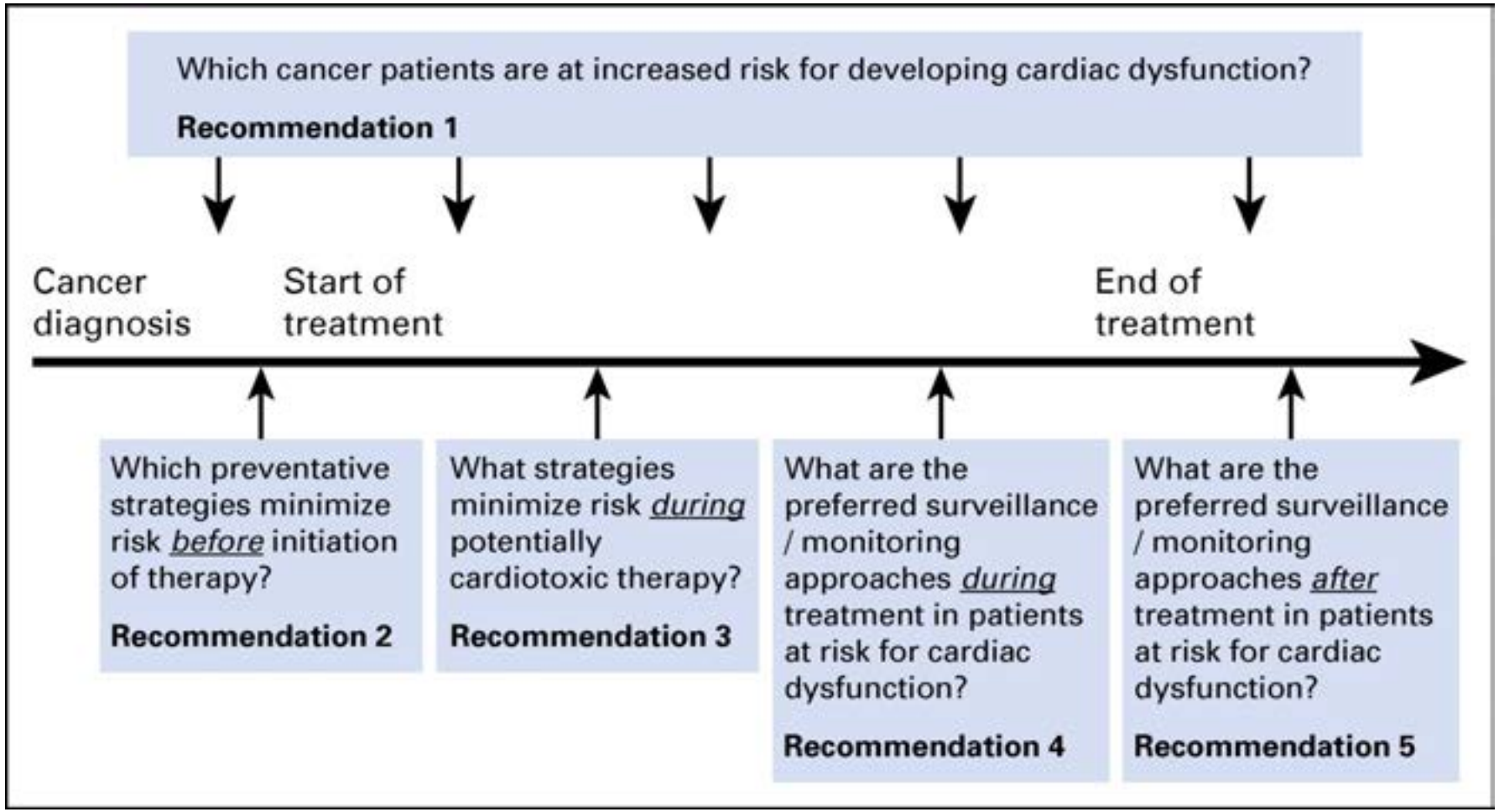
- Refine the predisposing factors for development of CVD related to cancer treatment
- Evaluate the rate of subclinical LV dysfunction and its transition to overt HF
- Define the most reliable cardiac monitoring approach
- Determine the clinical effect and outcome after cancer therapy

Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

ASCO Clinical Practice Guideline:
Prevention and monitoring of cardiac dysfunction in survivors of adult cancers

Armenian, et al., *J Clin Oncol* 2017;35:893-911.

Overarching clinical questions addressed in ASCO clinical practice guideline



Armenian, et al., *J Clin Oncol* 2017;35:893-911.

1. Which pts. at increased risk of cardiac dysfunction?

- High dose anthracyclines (≥ 250 mg/m^2 dox or ≥ 600 mg/m^2)
- High dose RT (≥ 30 Gy) with heart in field
- Lower anthracyclines with RT with heart in field
- Lower dose anthracyclines or trastuzumab alone with:
  - Multiple (≥ 2) risk factors
  - ≥ 60 years
  - LVEF 50-55%, hx of MI, moderate valvular disease
- Lower dose anthracyclines → trastuzumab
- No recommendation for trastuzumab alone, low dose anthracycline or RT, kinase inhibitors

Armenian, et al., *J Clin Oncol* 2017;35:893-911.

2. & 3. Preventive strategies prior to and during Rx

- Avoid cardiotoxic therapies if alternatives exist
- H & P, screen and actively manage cardiac risk factors, ECHO
- Dexrazoxane, Liposomal doxorubicin, continuous infusion
- Mediastinal RT – Deep inspiration breath holding or IMRT

Armenian, et al., *J Clin Oncol* 2017;35:893-911.

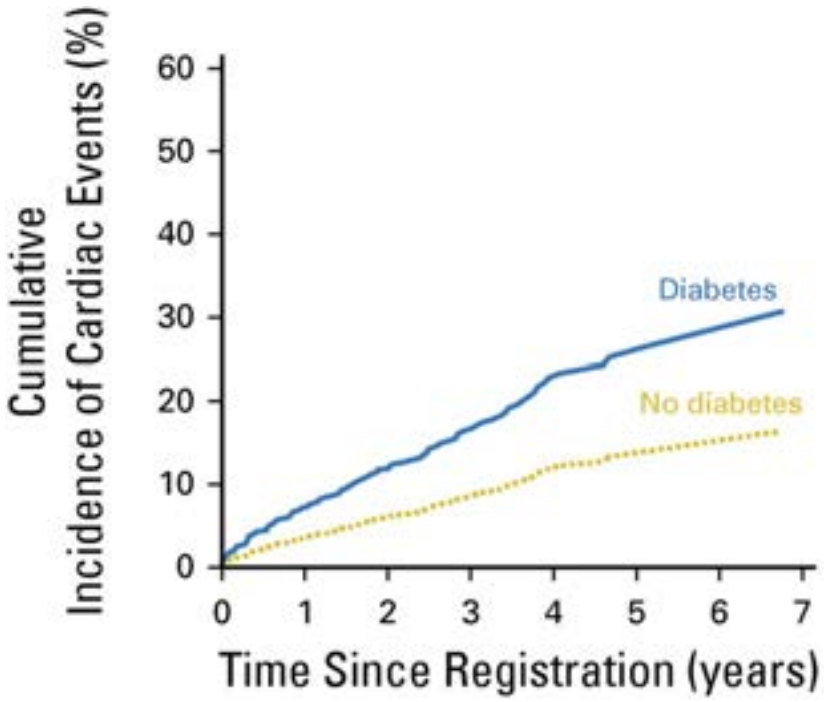
4. & 5. Surveillance prior to and during Rx

- H & P
- Evaluate and manage cardiac risk factors
- If at increased cardiac risk ECHO with frequency to be determined by provider
  - Trastuzumab indefinitely: frequency of monitoring to be determine by provider
  - 6-12 months after completion of treatment
- If signs or symptoms of cardiac dysfunction
  - ECHO
  - If no ECHO, MRI or MUGA
  - Serial biomarkers (troponins, BNP)
  - ECHO derived strain imaging
  - Referral to cardiologist
  - No recommendation for continuing cancer tx

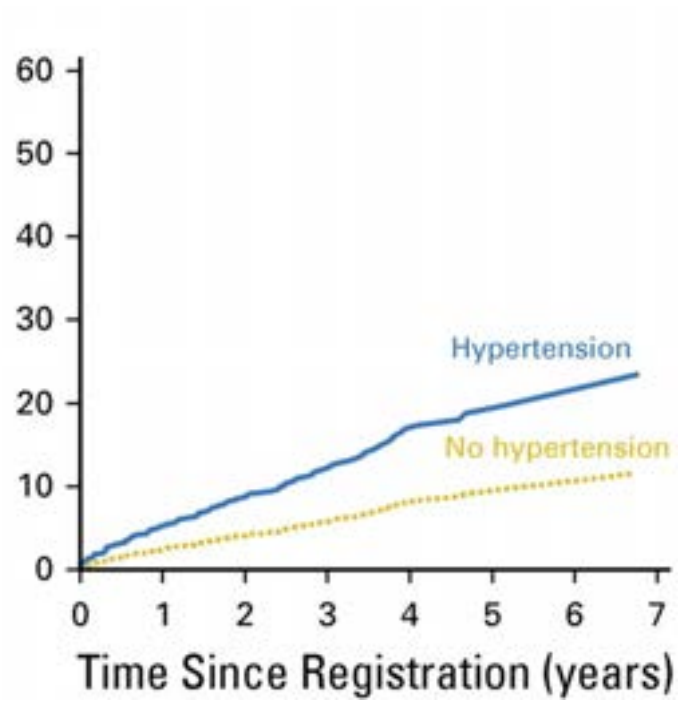
Armenian, et al., *J Clin Oncol* 2017;35:893-911.

Cumulative incidence of cardiac events by baseline CVD risk factors in SWOG adjuvant breast cancer trials

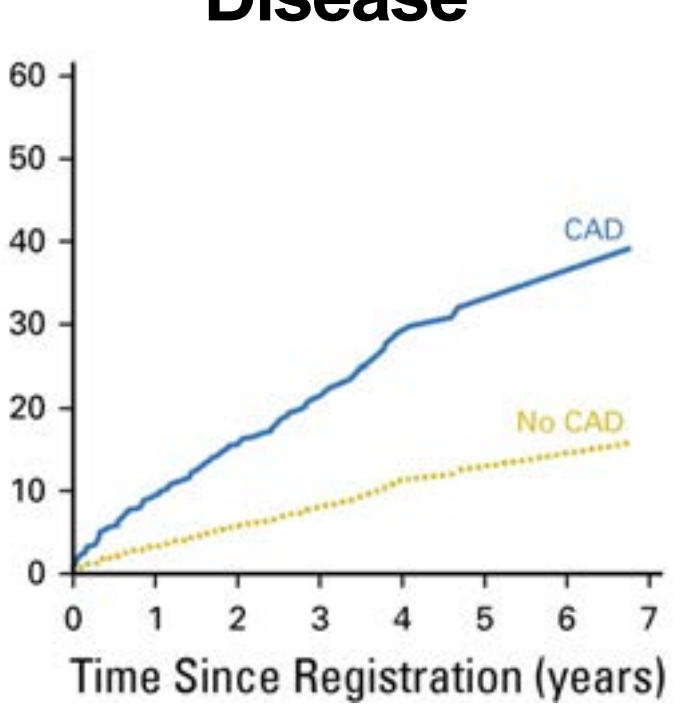
Diabetes



Hypertension

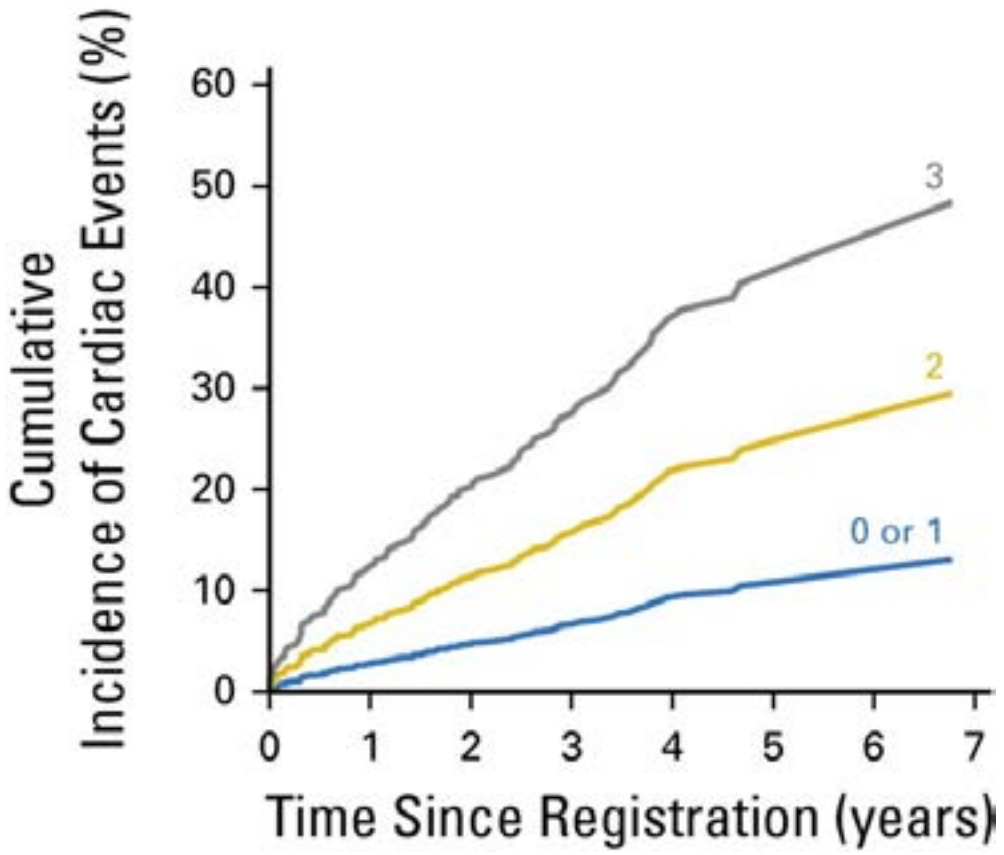


Coronary Artery Disease



Hershman, et al., *J Clin Oncol* 2018. Epub.

Cumulative incidence of cardiac events by baseline CVD risk factors in adjuvant breast cancer



RISK FACTORS:

- **D**iabetes w/ or w/o complications
- **H**ypertension
- **H**ypercholesterolemia
- **C**AD
- **O**besity

Hershman, et al., *J Clin Oncol* 2018. Epub.

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.
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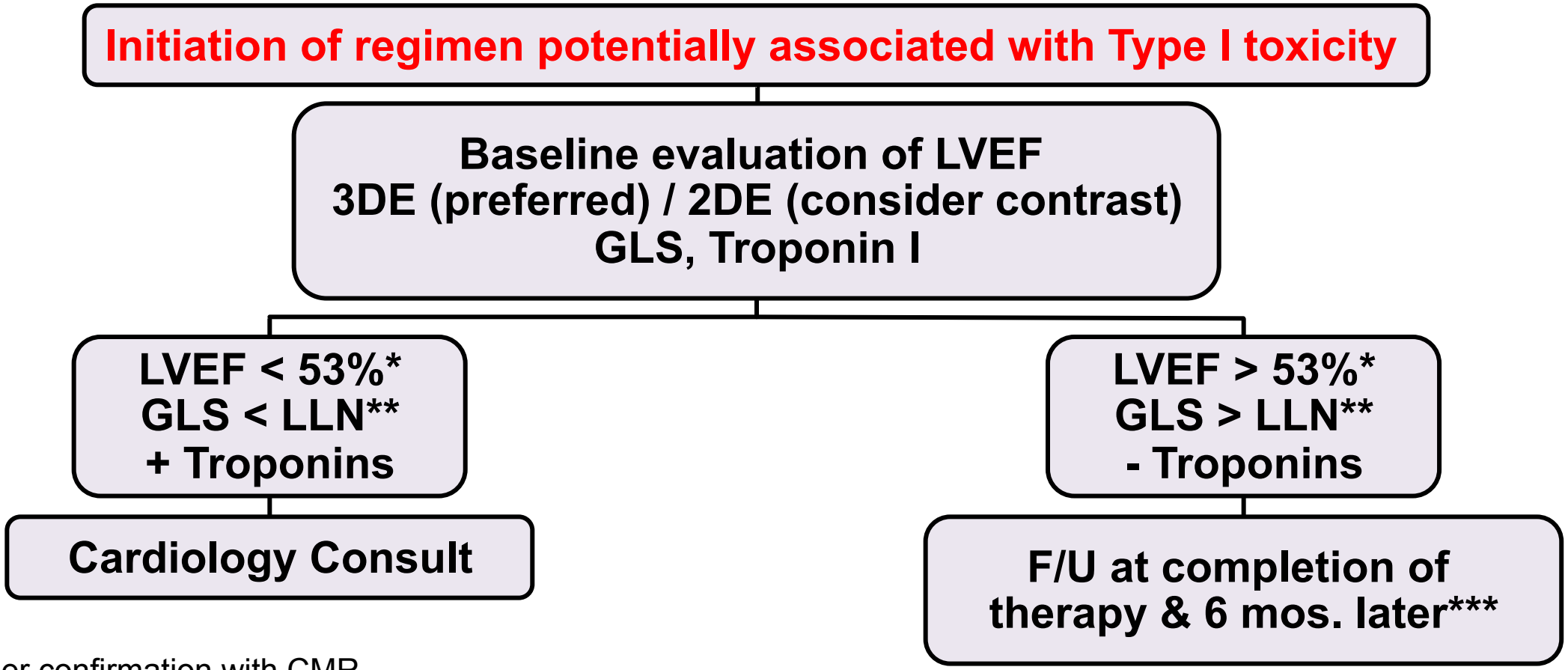
Zamorano, et al., *Eur Heart J* 2016;37:2768-2801.

Consensus from American Society of Echocardiography & European Association of Cardiovascular Imaging: Prefer 3D ECHO

- Type 1 CV toxicity: Anthracyclines
  - Baseline EF and > 53% repeat at completion of therapy and then 6 months
  - If < 53% cardiology consult
- Type 2 CV toxicity: Trastuzumab
  - If > 53% EF every 3 mo during Rx
- Type 1 and 2 agents
  - If > 53% EF every 3 mo during Rx and 6 mo later

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

Expert Consensus on Multimodality Imaging Evaluation in Adults Patients During and After Cancer Therapy



* Consider confirmation with CMR.

** LLN = Lower limit of normal. Please refer to Plana et al., Table 5 for GLS values based on vendor, gender, and age.

*** If the dose if higher than 240 mg/m^2 (or its equivalent), recommend measurement of LVEF, GLS, and troponin prior to each additional 50 mg/m^2

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

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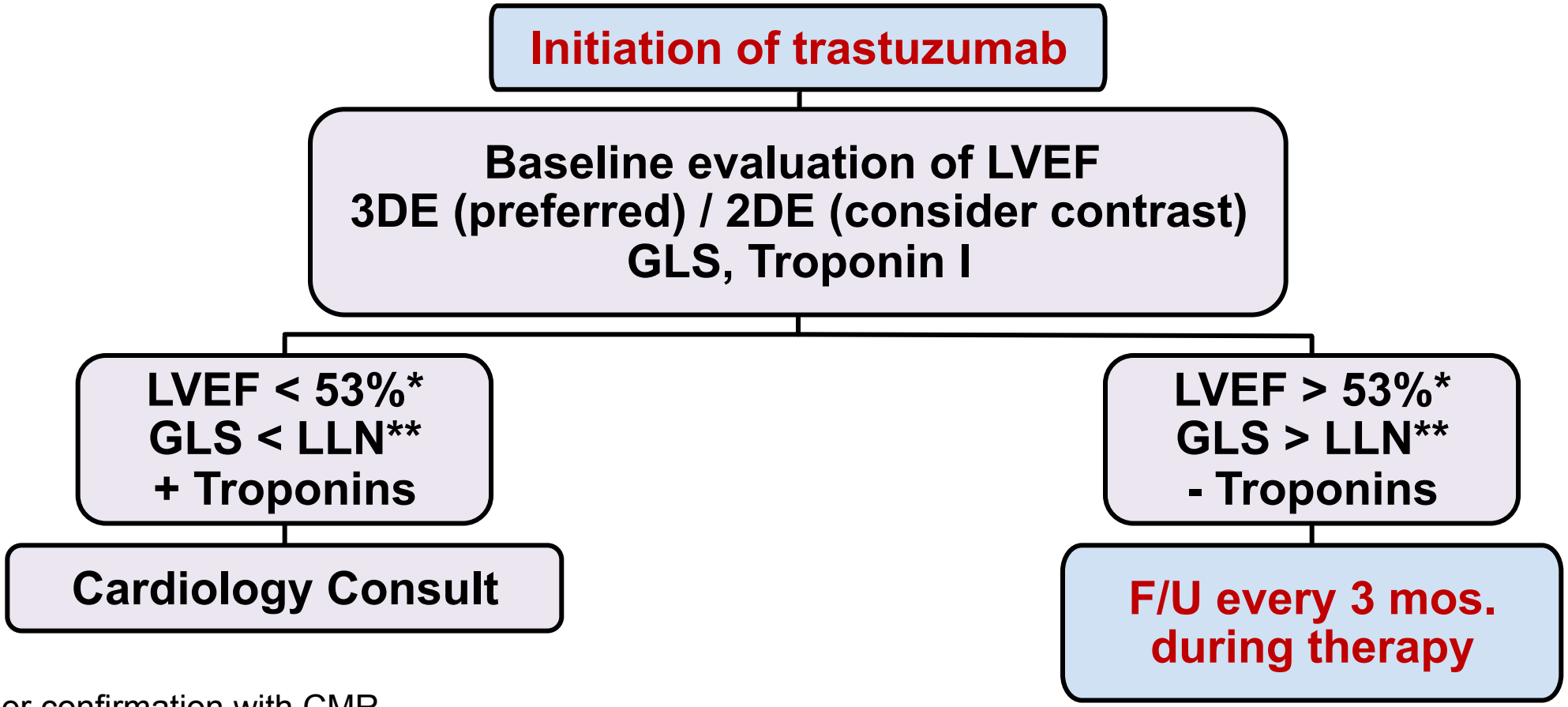

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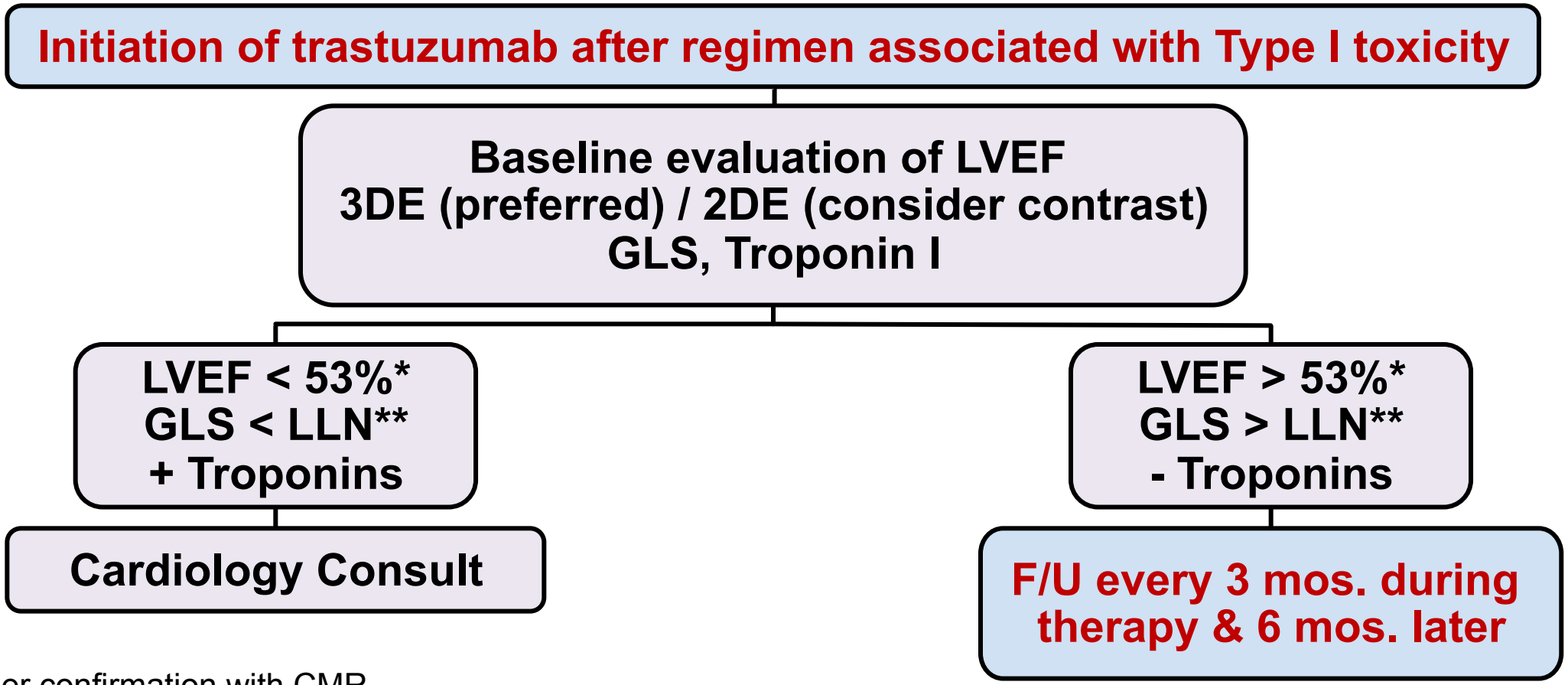

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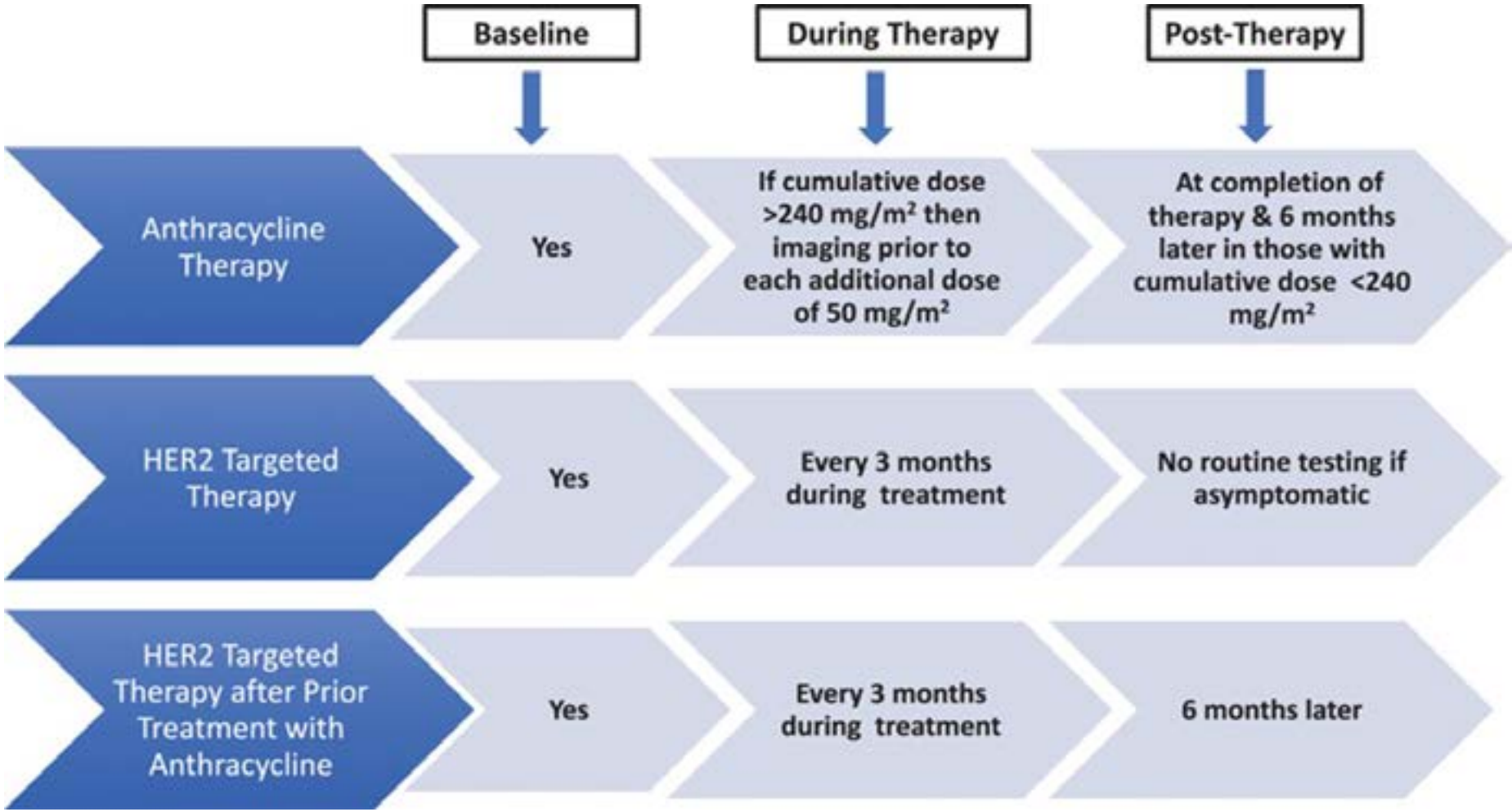
Plana, et al., *J Am Soc Echocardiogr* 2014;27:911-39.

ECHO surveillance: ASE & EACI



Mehta, et al., *Circulation* 2018;137:e30-e66.

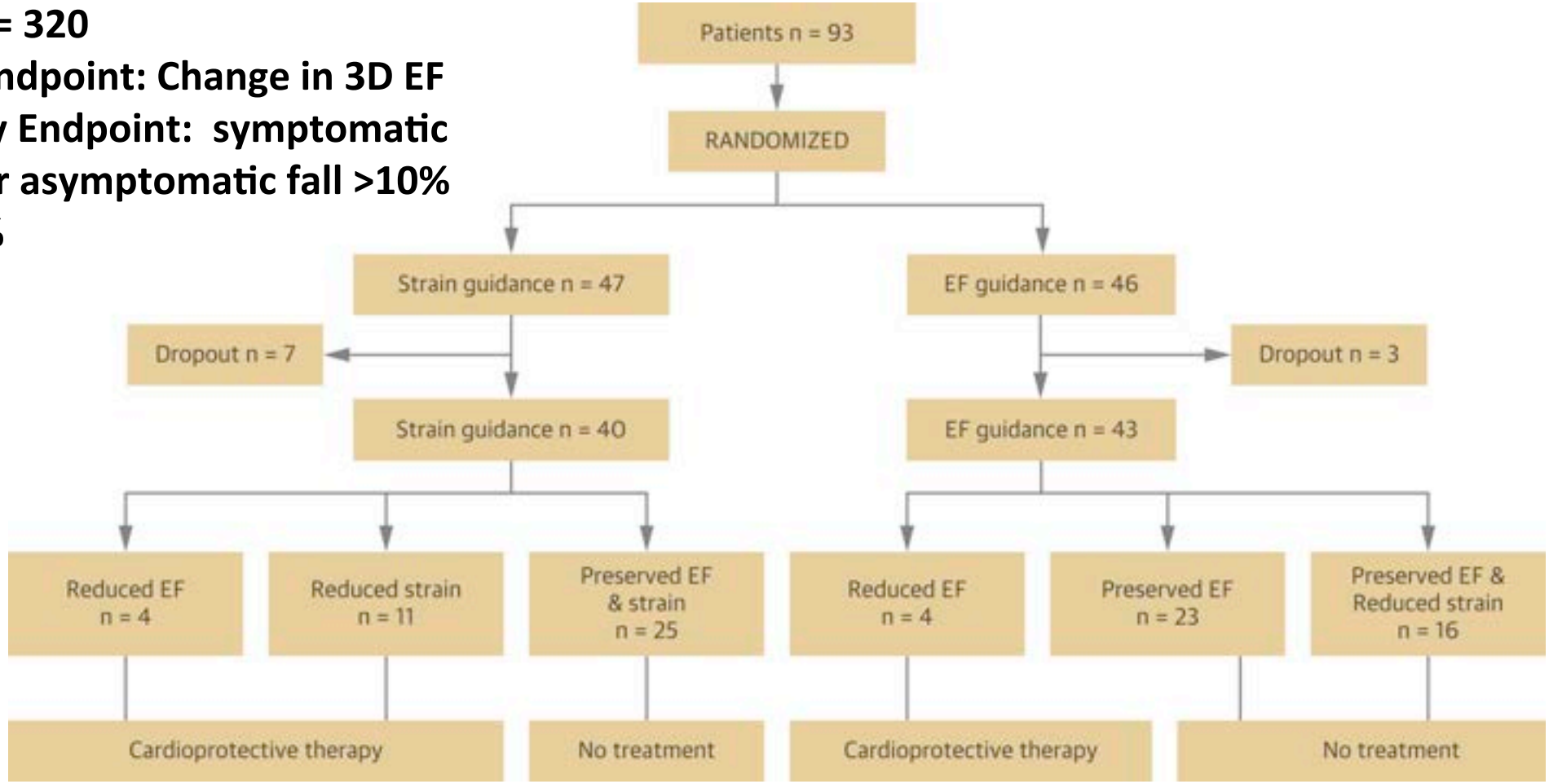
Global Longitudinal Strain

- Strengths
  - Superiority in predicting all cause mortality vs LVEF
  - Improved risk stratification for HF
  - Recognize early LV dysfunction
  - Reproducible by trained operators
- Limitations
  - Heavy dependence on quality of 2D images
  - Influenced by loading
  - Lack of long term randomized trials to predict symptomatic HF or persistent decrease in LVEF
  - Vendor and software specific

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

Strain Surveillance of Chemotherapy for improving Cardiovascular Outcomes (SUCCOUR) Trial:

Accrual N= 320
Primary Endpoint: Change in 3D EF
Secondary Endpoint: symptomatic fall >5% or asymptomatic fall >10% and < 55%



Negishi, et al., *JACC Cardiovasc Imaging* 2018; Jun 8 (Epub ahead of print).

2017 U.S. FDA Package Inserts for Trastuzumab & Pertuzumab

- Trastuzumab: LVEF prior to therapy and every 3 months during Rx and at completion
  - Repeat q 4 weeks if withheld for ↓ LVEF
  - Stop if ≥ 16% ↓ LVEF; below LLN and ≥ 10% ↓ LVEF
  - Resume if LVEF WNL and ↓ ≤ 15%
  - Every 6 months for 2 years after completion
- Pertuzumab and trastuzumab:
  - LVEF q 12 weeks for metastatic and adjuvant (once during neoadjuvant)

Dose Modifications for Left Ventricular Dysfunction

<table>
<tr><th></th><th>Pre- treatment LVEF:</th><th>Monitor LVEF every:</th><th colspan="2">Withhold PERJETA and trastuzumab for at least 3 weeks for an LVEF decrease to:</th><th colspan="2">Resume PERJETA and trastuzumab after 3 weeks if LVEF has recovered to:</th></tr>
<tr><td rowspan="2">Metastatic Breast Cancer</td><td rowspan="2">≥ 50%</td><td rowspan="2">~12 weeks</td><td colspan="2">Either</td><td colspan="2">Either</td></tr>
<tr><td><40%</td><td>40%-45% with a fall of ≥10%-points below pre-treatment value</td><td>>45%</td><td>40%-45% with a fall of <10%-points below pre-treatment value</td></tr>
<tr><td rowspan="2">Early Breast Cancer</td><td rowspan="2">≥ 55%*</td><td rowspan="2">~12 weeks (once during neoadjuvant therapy)</td><td colspan="2" rowspan="2"><50% with a fall of ≥10%-points below pre-treatment value</td><td colspan="2">Either</td></tr>
<tr><td>≥50%</td><td><10% points below pre-treatment value</td></tr>
</table>

*For patients receiving anthracycline-based chemotherapy, a LVEF of ≥ 50% is required after completion of anthracyclines, before starting PERJETA and trastuzumab

Perjeta ® [package insert]. South San Francisco: Genentech, Inc. 2017.

NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)

Breast Cancer (Version 1.2018 – March 20, 2018)

- For treatment w/ trastuzumab or pertuzumab:
  - Evaluate LVEF prior to and during treatment.
  - The optimal frequency is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab & q 3 mos. during tx.

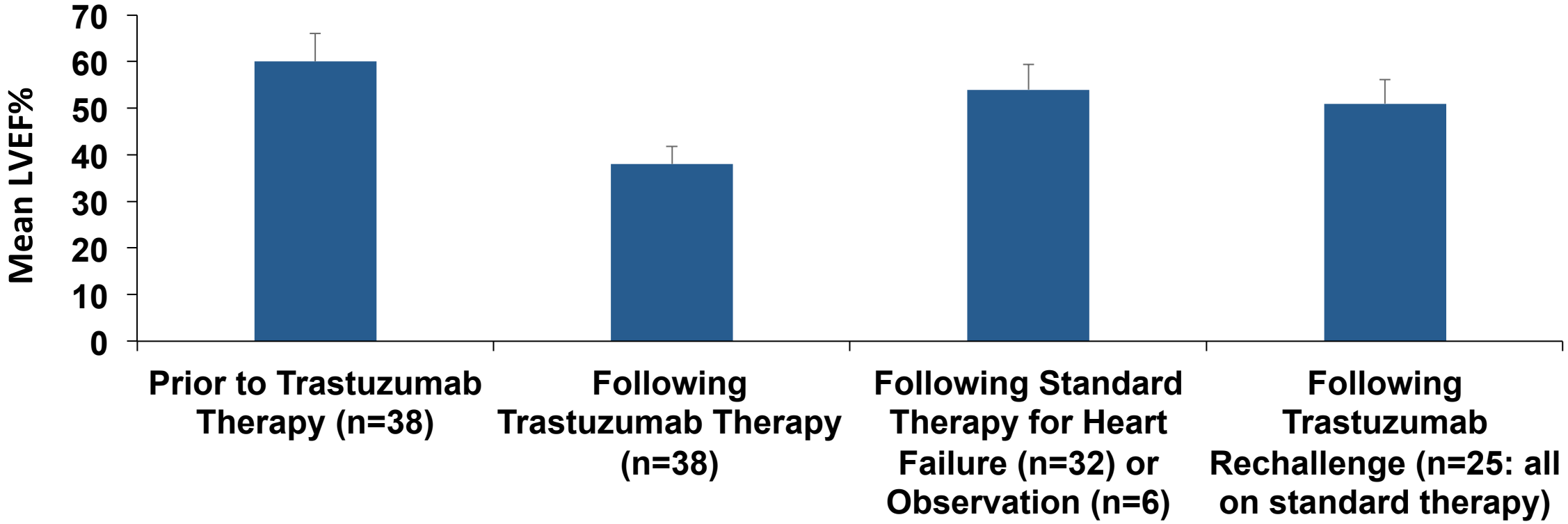
Can we prevent cardiotoxicity and treat during it?

Primary Prevention of Cardiotoxicity

Trial	RX	Study	n	Results	p-value
PRADA[1]	Epirubicin	2x2		CMR ↓ LVEF	
	Tras 12%	Candesartan + placebo	32	1.8% Can *v.* Pla	0.0026
		Candesartan + metoprolol	28		
		Metoprolol + placebo	32	0.2% Met *v.* Pla	0.772
		Placebo + placebo	33		
MANTICORE	Tras	1x1x1		CMR LVEDVi	LVEF
101 Breast[2]		Perindopril	33	+7 p=.36	-3%
		Bisoprolol	31	+8 p=.36	-1% p=0.001
		Placebo	30	+4 p=.36	-5%
CECCY[3]	Dox	1x1		LVEF >10%	
		Carvedilol	96	14.5%	1.00
		Placebo	96	13.5%	

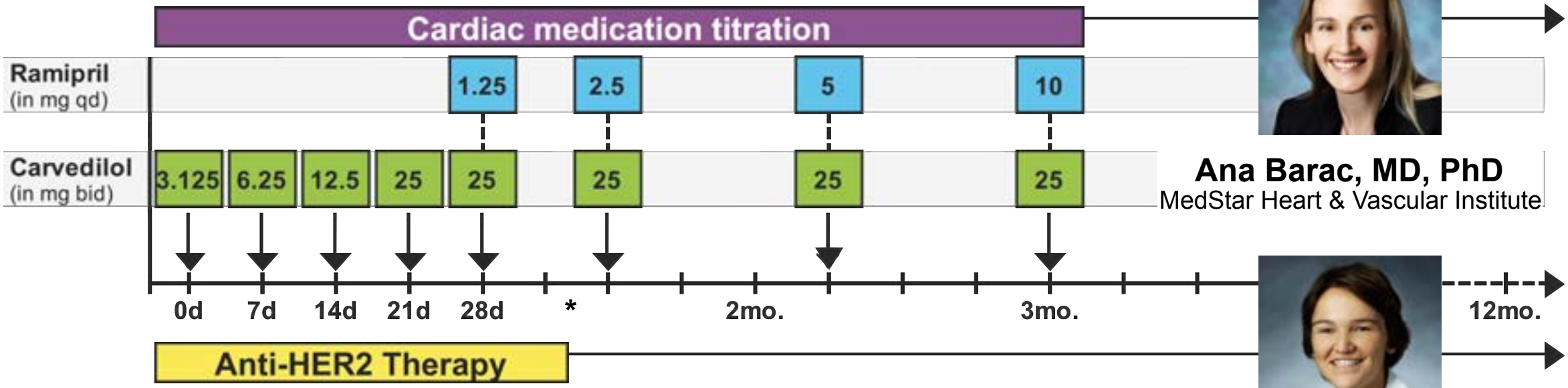
[1] Gulati, et al., *Eur Heart J* 2016;37:1671;
[2] Pituskin, et al., *J Clin Oncol* 2016;35:870; [3] Avila, et al., *JACC* 2018;71:2281-90.

Reversibility of trastuzumab-related Cardiotoxicity and response to medical treatment



Ewer, et al., *J Clin Oncol* 2005;23:7820-7826.

SAFE HEaRt: A Pilot Study Assessing the Cardiac SAFEty of HER2 Targeted Therapy in Patients with HER2 Positive Breast Cancer & Reduced Left Ventricular Function (40-49%)



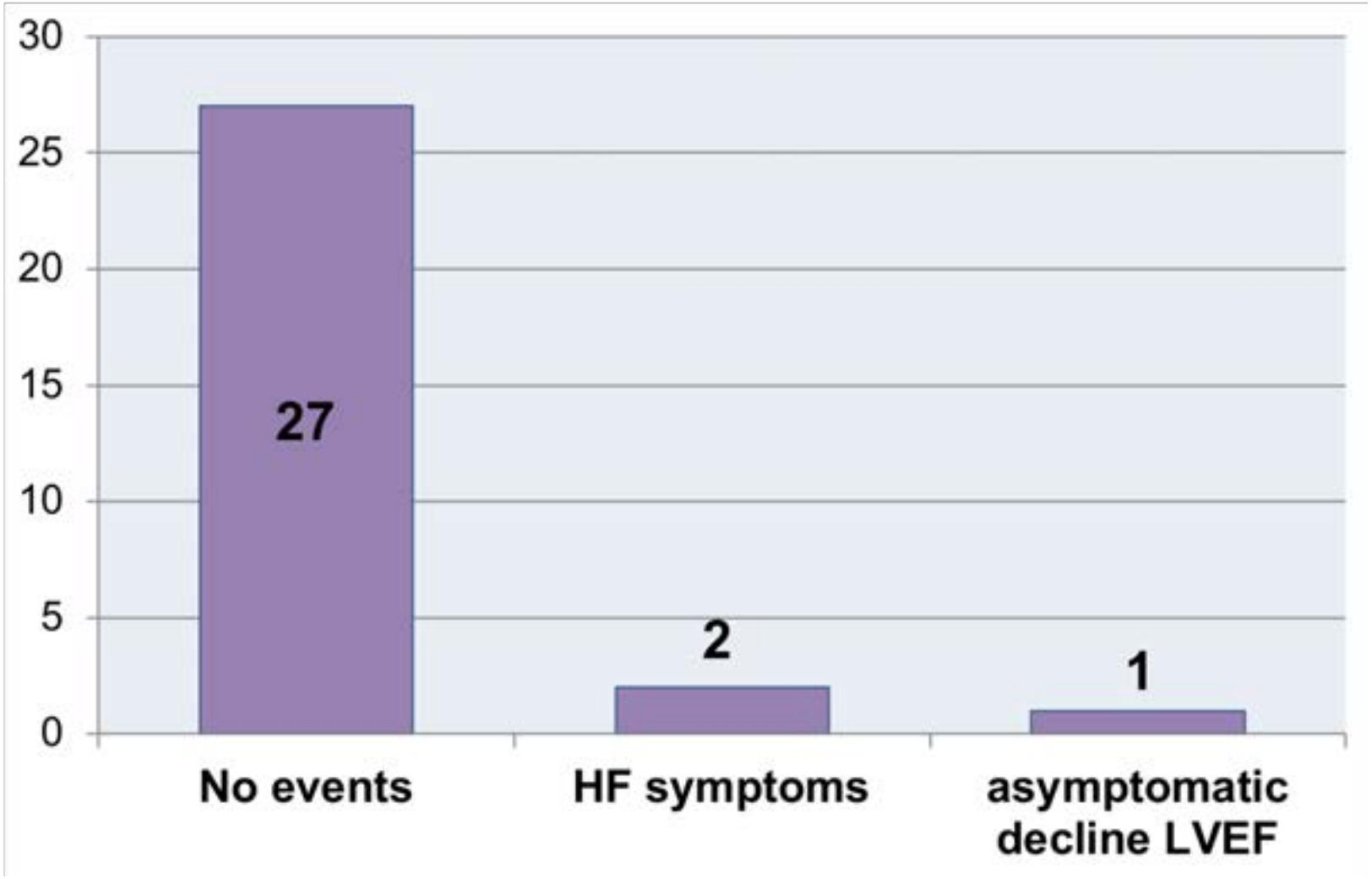
Ana Barac, MD, PhD
MedStar Heart & Vascular Institute

Filipa C. Lynce, MD
Lombardi Comprehensive Cancer Center

***Anti-HER2 Therapy = pertuzumab, trastuzumab, T-DM1**

Lynce, et al., *Oncologist* 2017;22:1-8; ClinicalTrials.gov: NCT01904903.

SAFE-HEaRt: Primary Endpoint



Demographics, previous anthracyclines and baseline LVEF did not predict development of CEs.

Elevation of highly sensitive troponin preceded 2 of 3 CEs which was significant (p=0.003).

Lynce, et al., *J Clin Oncol* 2018;36(15_suppl; abstr 1038).

So what do we do now?

- Screening with 3D Echo and follow up based on treatment
  - Anthracyclines baseline and after treatment (< 240 mg/m^2)
  - Trastuzumab: Baseline and q 3months – practically speaking if on long term trastuzumab and pertuzumab with LVEF wnl, consider stopping surveillance or decreasing to once every 6-12 months
- No evidence of benefit with BB or ARB or ACEi
- No routine measurement of troponins, BNP
- Global strain measurements could predict cardiac dysfunction but currently not in the mainstream for determining cardiac treatment

MedStar Heart & Vascular Institute Cardio-Oncology Program: Goals

- Ensures better outcomes for patients with cancer and cardiac issues
- Provides earlier detection of cardiac toxicity side effects from cancer treatments
- Aims to present or reduce further cardiac damage – and, when possible, reverse it
- Monitors patients with potential cardiac issues who are receiving cancer treatments
- Provides a better understanding of cardiac issues in patients with cancer by participating in research studies
- Eliminates cardiac disease as a barrier to effective cancer therapy

My Friend and Mentor in Cardio-Oncology or is that Onco-Cardiology!