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14th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice and Post-MASCC

BELGIAN CARDIO-ONCOLOGY GUIDELINES CARDIOTOXICITY : A CARDIOLOGIST'S COOKBOOK

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MÉDECINE SORBONNE UNIVERSITÉ

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OVERVIEW

1. Finally, guidelines !
2. ‘Cardiotoxicity’, what’s in a name?
3. I screen, you screen… but how?
4. ‘Cardioprotection’ : fact or fiction?
5. Trouble on-therapy : the asymptomatic patient
6. Trouble on-therapy : the symptomatic patient
7. Post-therapy follow-up?
8. Take home messages

FINALLY, GUIDELINES !

European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

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

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

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(J Am Soc Echocardiogr 2014;27:911-39.)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

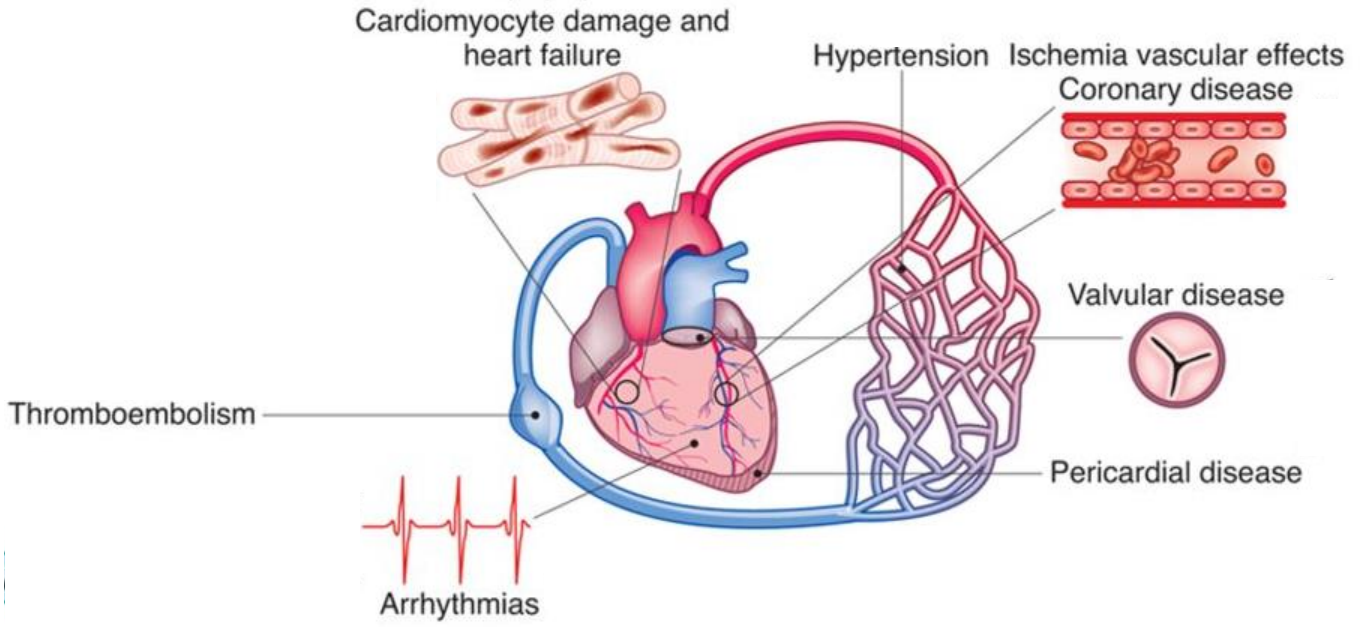
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations

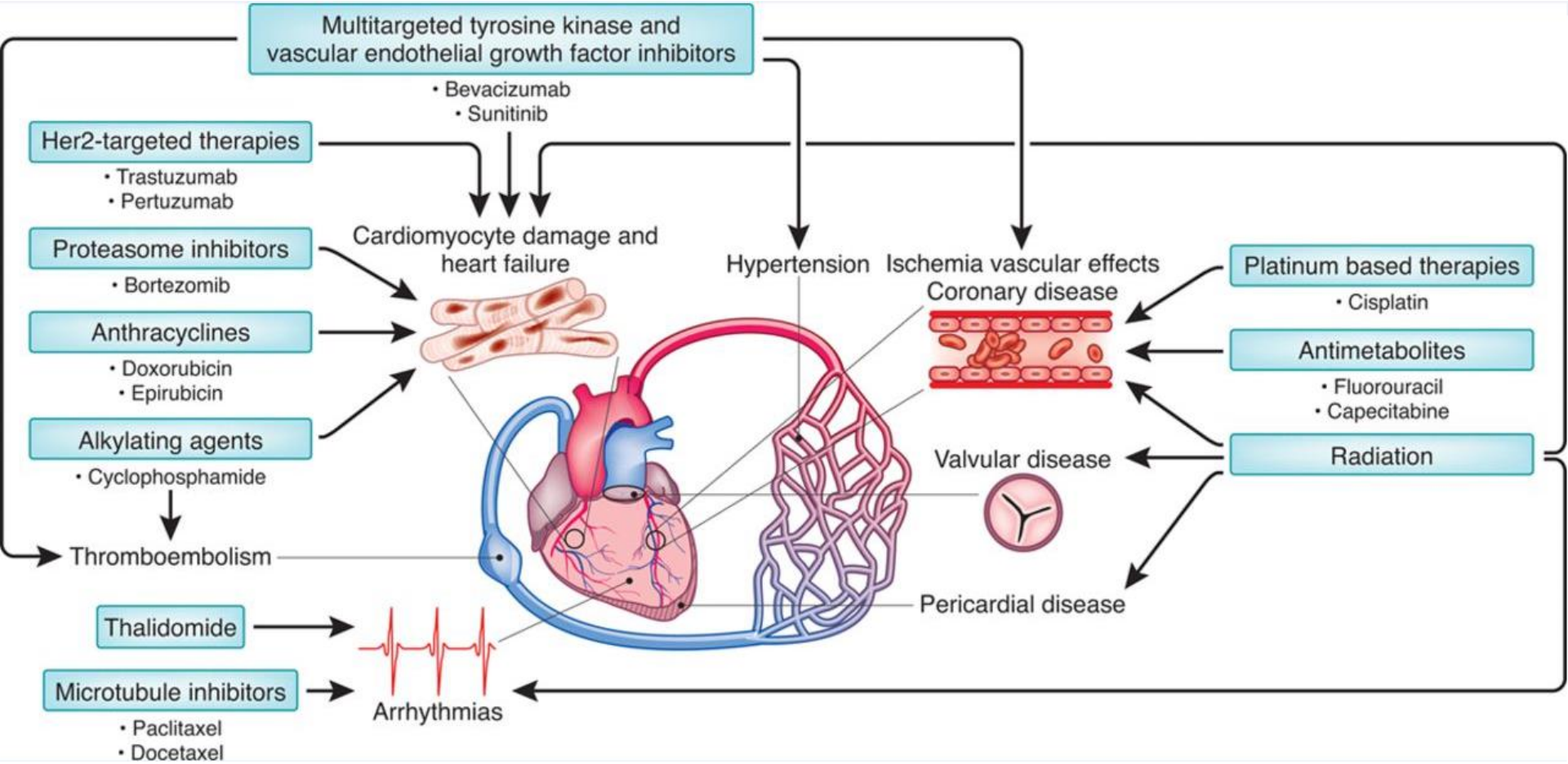
G. Curigliano[1,2†], D. Lenihan[3†], M. Fradley[4], S. Ganatra[5], A. Barac[6], A. Blaes[7], J. Herrmann[8], C. Porter[9], A. R. Lyon[10], P. Lancellotti[11], A. Patel[12], J. DeCara[13], J. Mitchell[14], E. Harrison[15], J. Moslehi[16], R. Witteles[17], M. G. Calabro[18], R. Orecchia[1], E. de Azambuja[19], J. L. Zamorano[20], R. Krone[21], Z. Iakobishvili[22], J. Carver[23], S. Armenian[24], B. Ky[25], D. Cardinale[26], C. M. Cipolla[27], S. Dent[28] & K. Jordan[29], on behalf of the ESMO Guidelines Committee*

CARDIOTOXICITY : WHAT'S IN A NAME?



Lenneman et al, Circ Res 2016

CARDIOTOXICITY : WHAT'S IN A NAME?



Lenneman et al, Circ Res 2016

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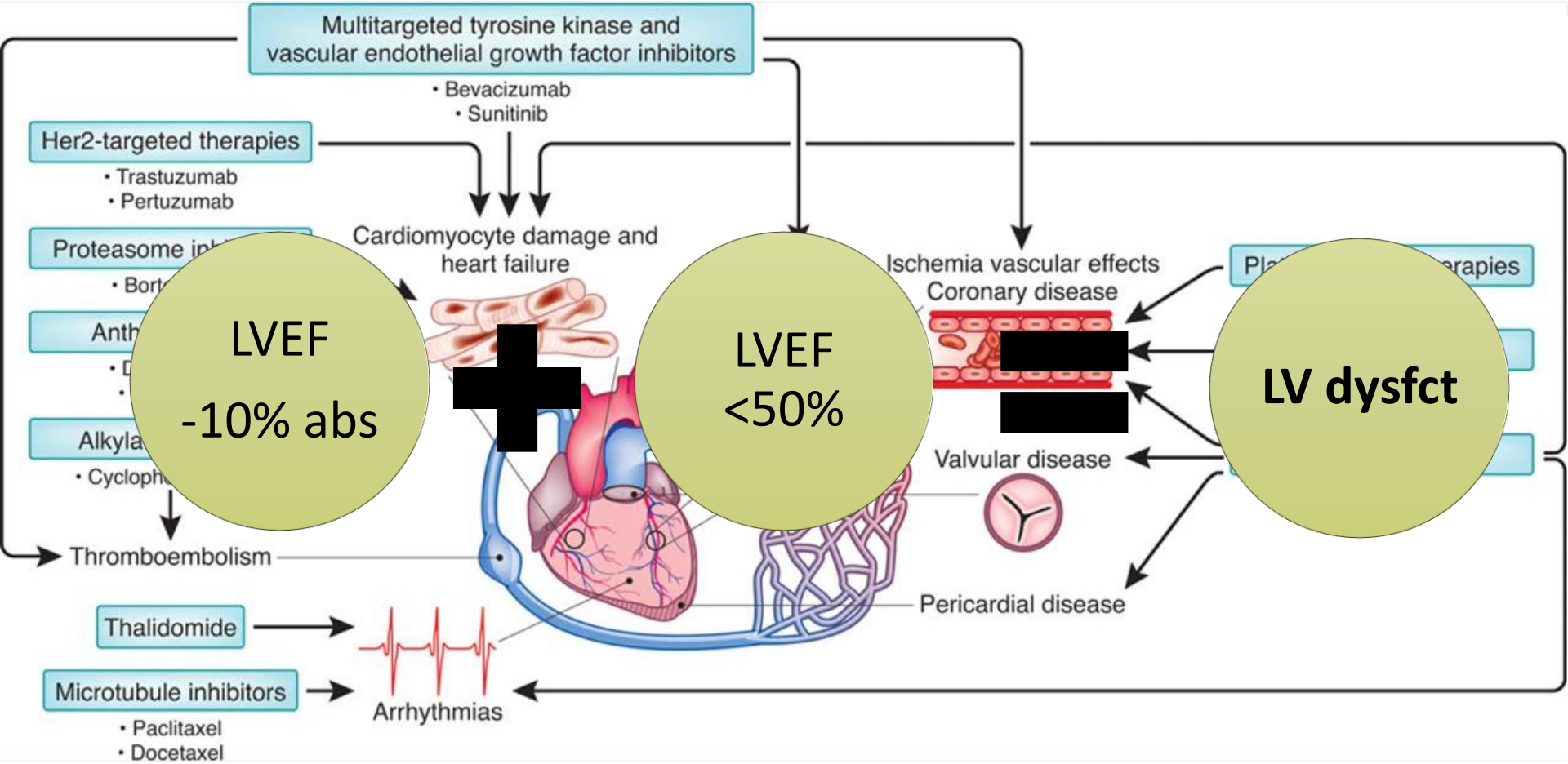

I SCREEN, YOU SCREEN … BUT HOW?

Table 3. Common clinical factors that may indicate a patient at higher risk for cardiovascular dysfunction during contemporary anticancer treatment

Prior anthracycline-based treatment
Elderly (>75 years old)
Prior mediastinal or chest radiotherapy
HTN (before or at the time of treatment)
Smoking exposure (current or previous)
Very young (<10 years of age)
Previous combined treatment with trastuzumab and an anthracycline
Elevated cardiac biomarkers before initiation of anticancer therapy
Baseline abnormal systolic LV function with LVEF <0.50
Pre-existing DM

DM, diabetes mellitus; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction.

Curigliano et al, Ann Oncol 2020

I SCREEN, YOU SCREEN … BUT HOW?

1. Treat cardiovascular **risk factors** … agressively !
   > AHT : target BP <140/90mmHg
   > Dyslipidaemia : LDL cholesterol <115mg/dL
   > Diabetes mellitus type II : HbA1c <7%
   > Smoking cessation
2. **ECG** : QTc ? LV hypertrophy? Repolarisation abnormalities?
3. **Transthoracic echocardiography** :
   > LVEF & GLS (baseline)
   > Diastolic function
   > Valvular status
4. Biomarkers : exact role & timing unclear
   > Troponin ? T ? I? hs-?
   > Natriuretic peptides : BNP? NT-pro BNP?
5. Previous cardiovascular disease

‘CARDIOPROTECTION’ : FACT OR FICTION

A	Awareness and Aspirin	• Increased awareness of patients about CV signs and symptoms. • Aspirin 81 mg daily for primary or secondary prevention of CV events.
B	Blood Pressure	Goal blood pressure < 140/90 mmHg
C	Cholesterol and Cigarettes	• High intensity statin therapy for pre-existing CVD or hyperlipidemia. • Smoking cessation counseling, therapy.
D	Diet and Diabetes	• Frequent blood glucose monitoring • Metformin for diabetes if possible. • Diet rich in fruits, vegetables, whole grain and low in saturated fat with 600 IU of vitamin D daily and adequate calcium (1200 mg/day). • Avoidance of excessive alcohol.
E	Exercise	150 minutes per week of moderate intensity physical activity or 75 minutes per week of vigorous exercise.

‘CARDIOPROTECTION’ : FACT OR FICTION

Brown et al.

J Am Heart Assoc, 2020

Table 1. Summary of 5 Randomized Controlled Trials Evaluating the Effect of β-Blockers and Neurohormonal Medications in Preventing Cardiac Dysfunction During Treatment With Trastuzumab, Anthracyclines, or Their Combination

Year, Citation (Trial Name)	Cancer Therapy; Primary End Point	N	Medication	Follow-Up Period	Results	Conclusion
2006, Cardinale et al[7]	Anthracycline; LVEF decreased by 10%	114	Enalapril	12 mo	0 vs 43%; $P<0.001$	Benefit
2016, Gulati[8] (PRADA)	Anthracycline with or without trastuzumab; change in LVEF by cMRI	130	Candesartan	10–61 wk	Modest decline in LVEF with candesartan vs placebo ($P=0.025$)	Mild benefit with candesartan
			Metoprolol	10–61 wk	No change in LVEF with metoprolol vs placebo (P=NS)	No benefit
2016, Boekhout et al[9]	Trastuzumab; change in LVEF	206	Candesartan	2 mo	Candesartan had higher incidence of cardiac events vs placebo (P=NS)	No benefit, possible harm
2017, Pituskin et al[10] (MANTICORE 101-Breast)	Trastuzumab (25% with anthracyclines); reduce LV remodeling	94	Perindopril	52 wk	Attenuated LVEF decline but did not prevent LV remodeling	Possible benefit
			Bisoprolol	52 wk	Attenuated LVEF decline prevent LV remodeling	Possible benefit
2019, Guglin et al[11]	Trastuzumab only; LVEF decline and treatment interruptions	468	Lisinopril	1+2 y follow-up	No difference from placebo	No benefit
			Carvedilol	1+2 y follow-up	No difference from placebo	No benefit
	Trastuzumab plus anthracyclines; LVEF decline and treatment interruptions		Lisinopril	1+2 y follow-up	HR: 0.53; $P=0.015$	Benefit
			Carvedilol	1+2 y follow-up	HR: 0.49; $P=0.009$	Benefit

cMRI indicates cardiac magnetic resonance imaging; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MANTICORE-101 Breast, Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research; NS, not significant; PRADA, Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy. 1+2 y; 1 year and 2 years of follow up.

‘CARDIOPROTECTION’ : FACT OR FICTION

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Limitations :
- Small sample sizes
- Large heterogeneity in studied patient populations
- Many low-risk patients
- Different anticancer therapies
- Different clinical trial endpoints

cMRI indicates cardiac magnetic resonance imaging; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; MANTICORE-101 Breast, Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research; NS, not significant; PRADA, Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy. 1+2 y; 1 year and 2 years of follow up.

Table 2. Classes of cardiovascular therapeutics that have some clinical trial evidence to suggest cardioprotection during anticancer therapy[a]

Class of CV therapy	Examples
ACE-I	Enalapril
ARB	Candesartan
MRA	Spironolactone
Statin	Pravastatin (many statins) Atorvastatin
Iron chelation/topoisomerase II inhibitor	Dexrazoxane
Antiplatelet	Aspirin
Anticoagulant	Enoxaparin Rivaroxaban/apixaban
BB	Carvedilol Nebivolol
Combination of ACE-I/BB	Enalapril Carvedilol

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CV, cardiovascular; MRA, mineralocorticoid receptor antagonist.
[a] Cardioprotection: any evidence that indicates the medication attenuates any CV dysfunction that may occur with potential cardiotoxic anticancer therapy.

Table 13 Strategies to reduce chemotherapy-induced cardiotoxicity[226–228,245–248]

Chemotherapy drug	Potential cardioprotective measure
All chemotherapy drugs	Identify and treat cardiovascular risk factors
	Treat comorbidities (CAD, HF, PAD, HTN)
	QTc prolongation and torsade de pointes: - Avoid QT prolonging drugs - Manage electrolyte abnormalities
	Minimize cardiac irradiation
Anthracyclines and analogues	Limit cumulative dose (mg/m^2): - Daunorubicin <800 - Doxorubicin <360 - Epirubicin <720 - Mitoxantrone <160 - Idarubicin <150
	Altered delivery systems (liposomal doxorubicin) or continuous infusions
	Dexrazoxane as an alternative
	ACE-Is or ARBs
	β-blockers
	Statins
	Aerobic exercise
Trastuzumab	ACE-Is
	β-blockers

Curigliano et al. Ann Oncol 2020
Zamorano et al. Eur Heart J 2016

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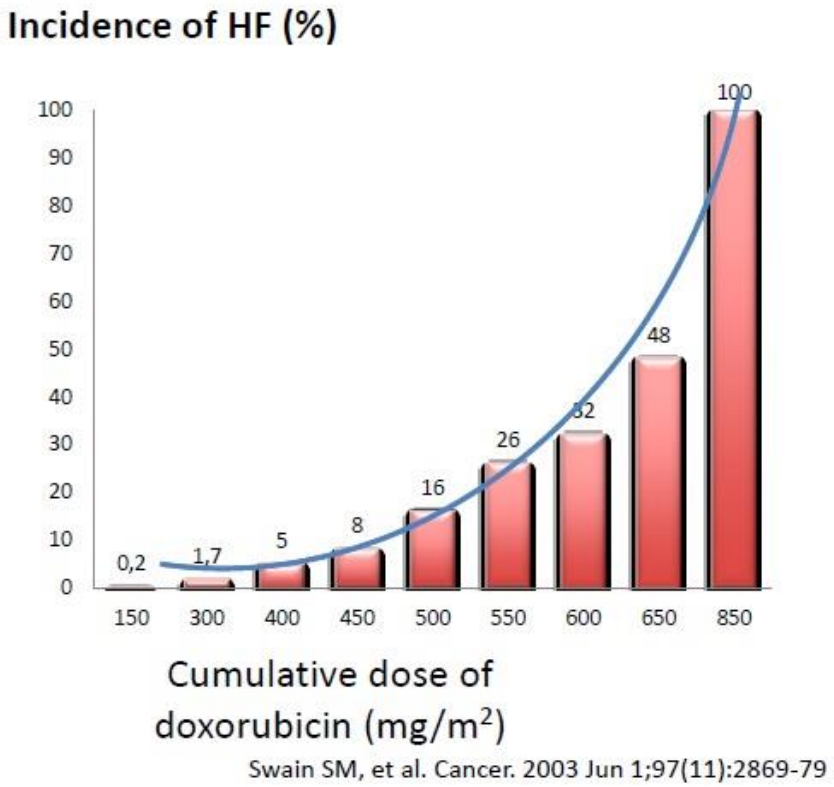
TROUBLE ON-THERAPY : THE **ASYMPTOMATIC** PATIENT



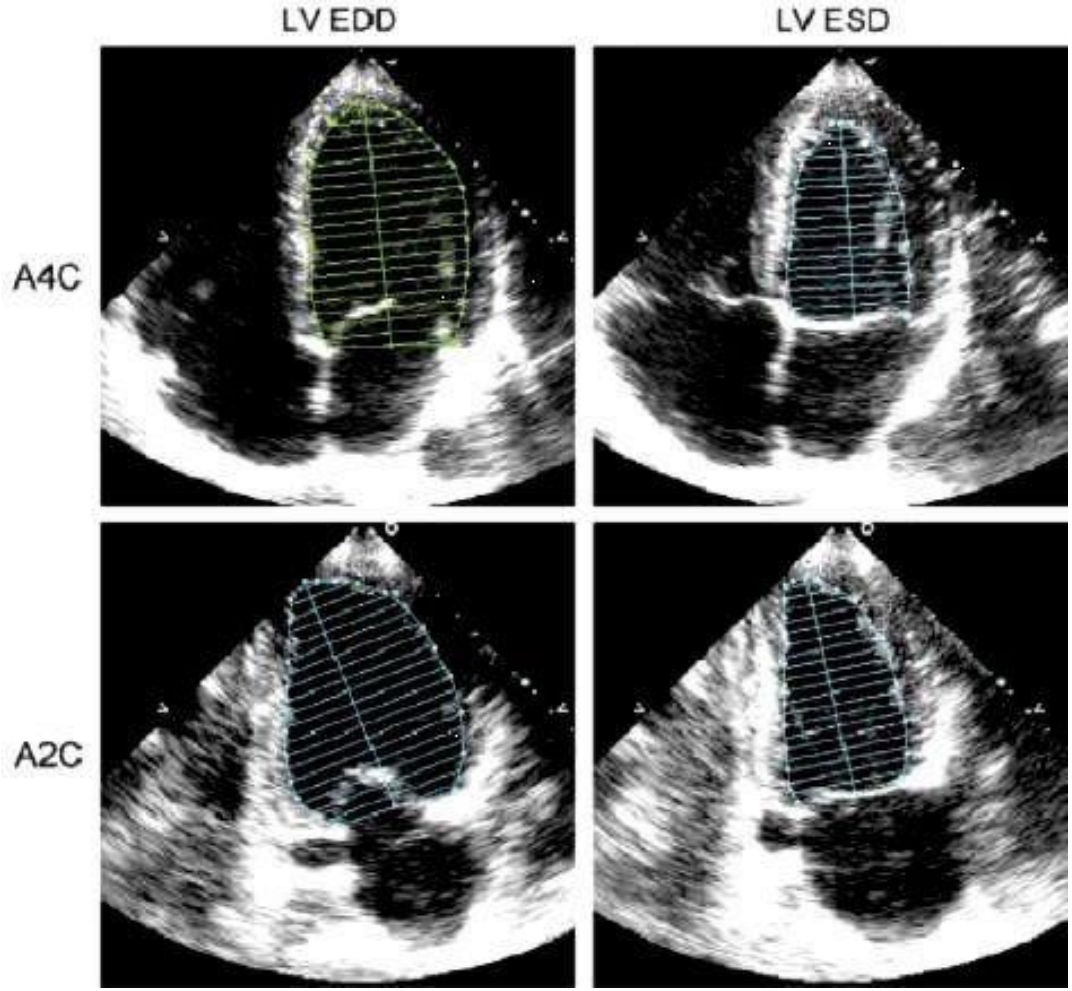
Swain SM, et al. Cancer. 2003 Jun 1;97(11):2869-79

! Early detection & treatment : highest reversibility

AC & trastuzumab : TTE (LVEF + GLS) 1x/3m

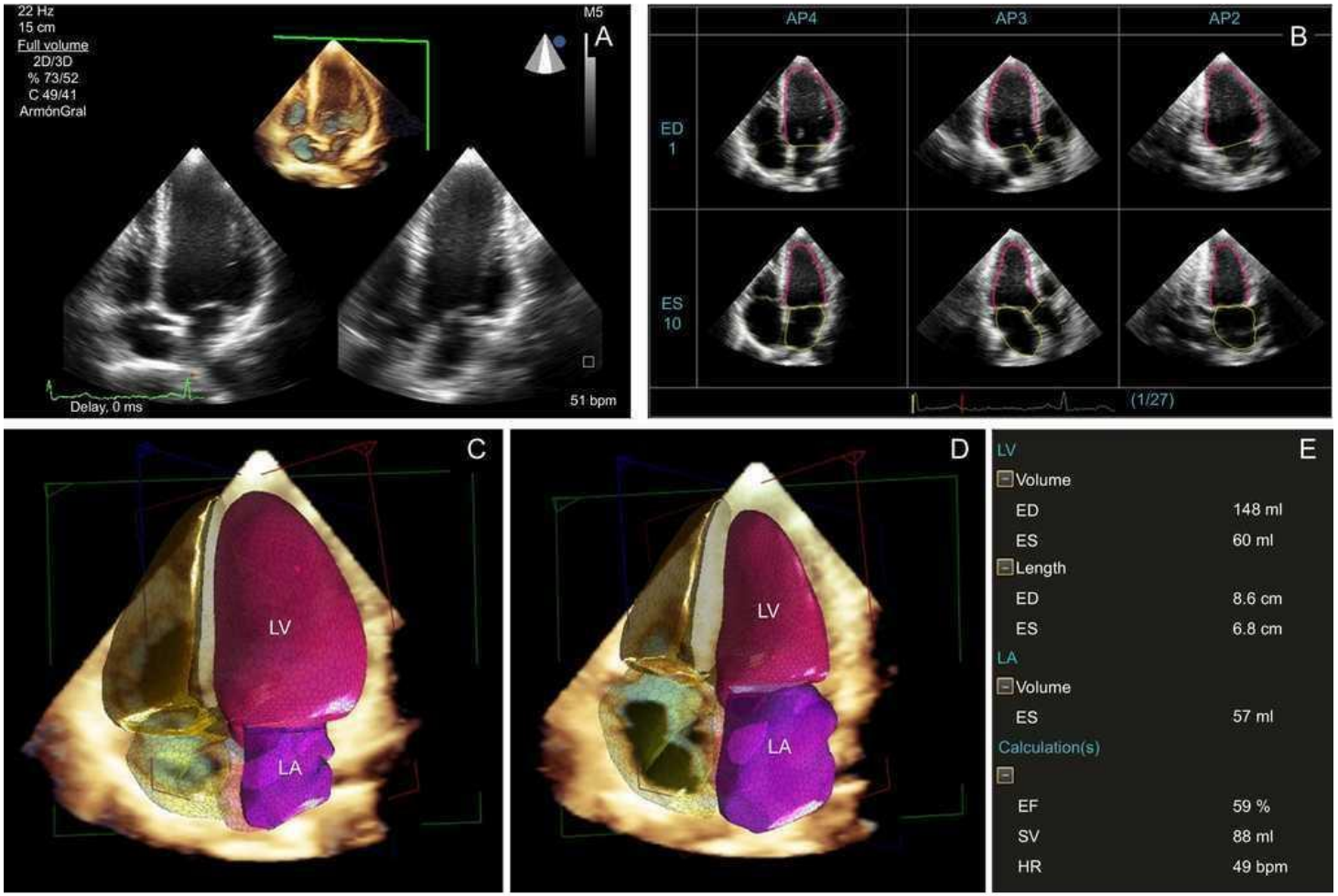
TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

Before everything else : what is LVEF?



TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

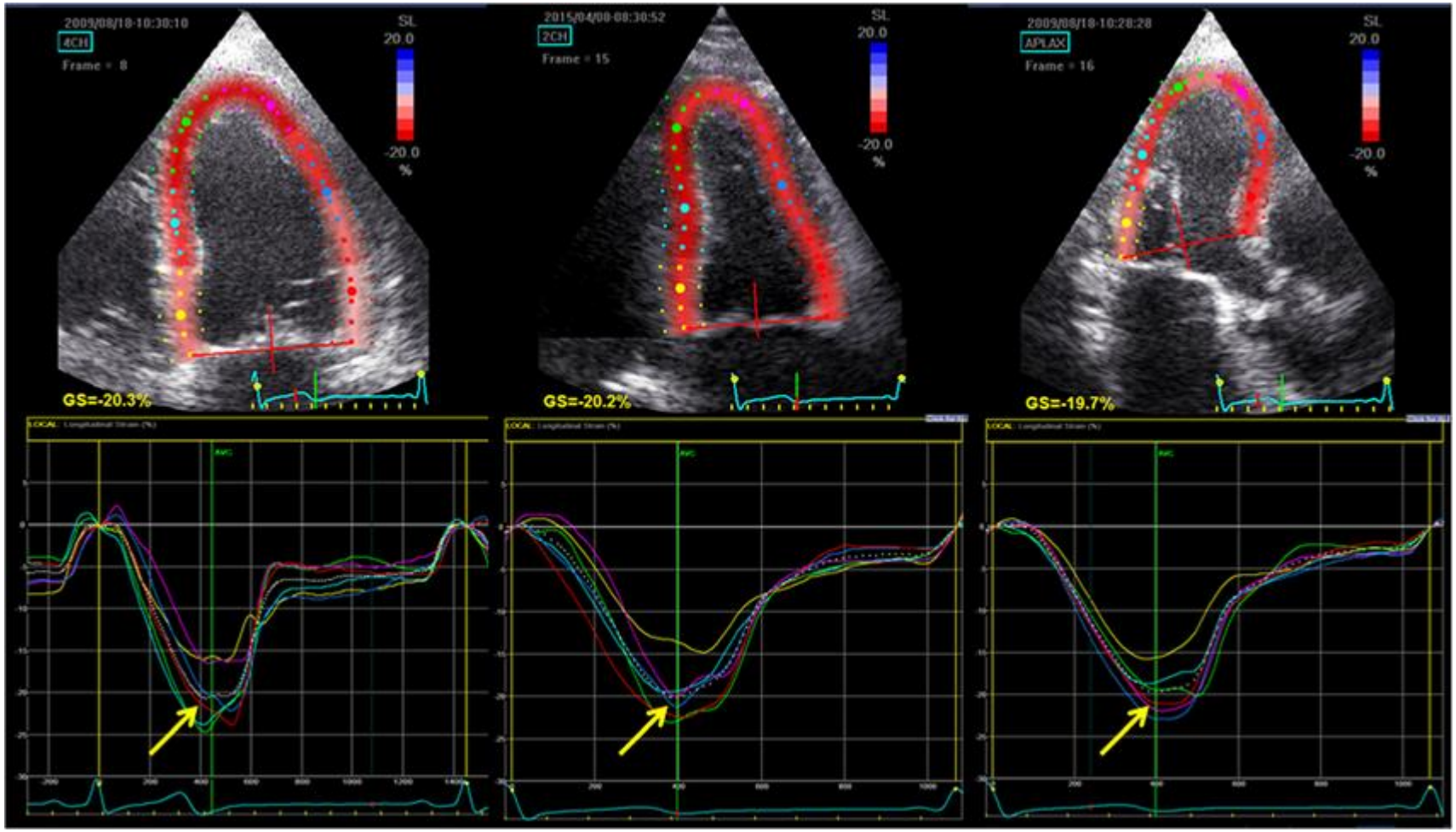
Before everything else : what is LVEF?



Rev Esp Cardiol. 2017;70:487–95

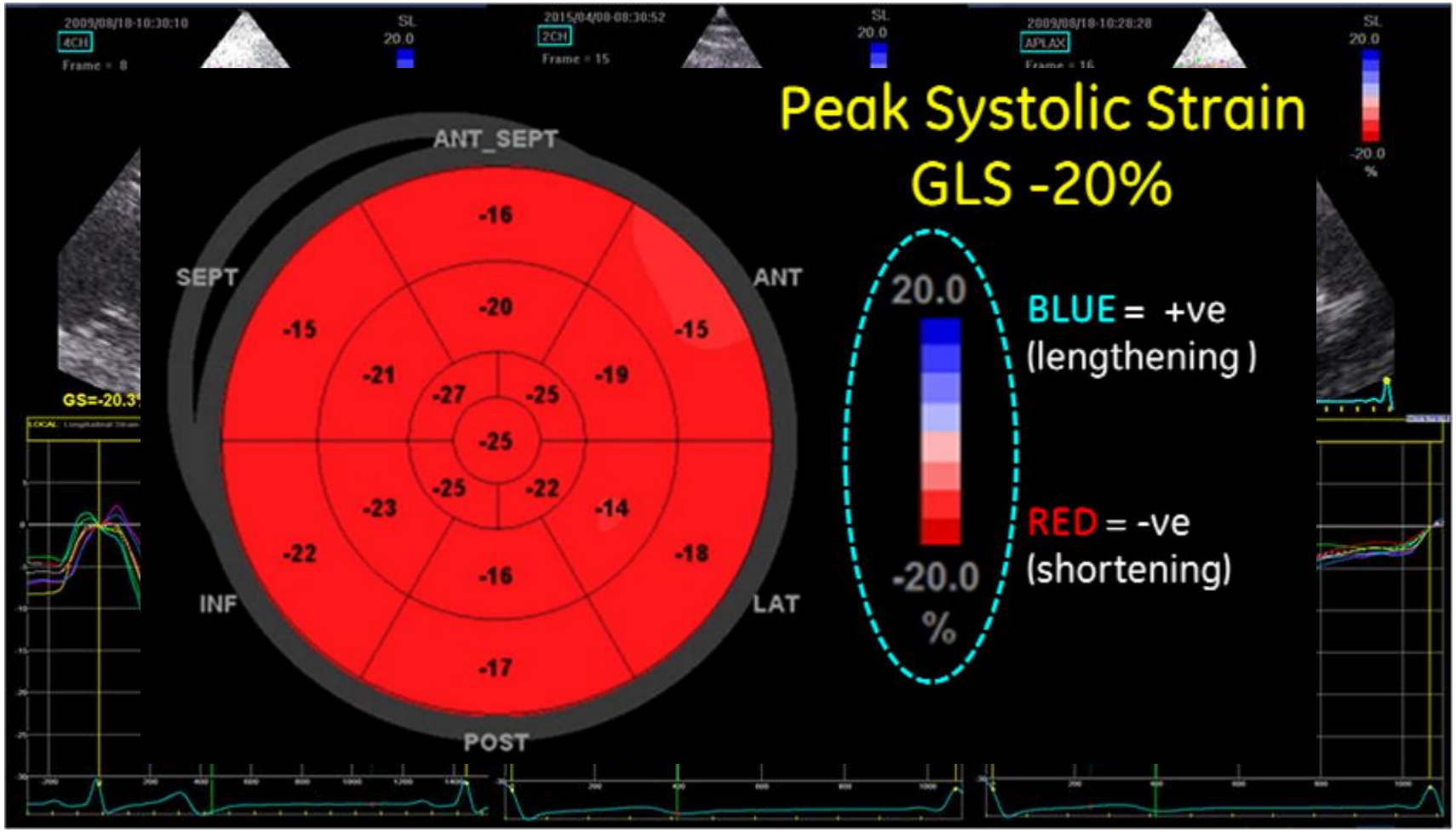
TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

Before everything else : what is GLS?



TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

Before everything else : what is GLS?



TROUBLE ON-THERAPY : THE ASYMPTOMATIC PATIENT

Before everything else : what is GLS?

Table 6 Strengths and limitations of GLS

	GLS
Strengths	• Superiority in the prediction of all-cause mortality in the general population compared with LVEF[237] • Improved risk stratification in patients with HF[238] • Ability to recognize early LV dysfunction in patients undergoing cardiotoxic therapy and prognosticate subsequent CTRCD[155,160] • Reproducible when performed by trained operators
Limitations	• Heavy dependence on the quality of the 2D echocardiographic images • Influenced by loading conditions • Lack of long-term randomized clinical trials evaluating the ability of GLS to predict persistent decreases in LVEF or symptomatic HF • Lack of data as to the reproducibility of GLS in nonacademic centers or community hospitals • Vendor and software specific

Plana et al J Am Soc Echocardiogr 2014

IS THERE A ROLE FOR MRI?

- Excellent LVEF evaluation
- Excellent reproducibility
- Great solution for poor TTE image quality

- Availability…
- Cost…
- Unpleasant exam (>30min, noisy, long breath-hold sequences)

→ Save it for emergencies (e.g. ICI-induced myocarditis)

TROUBLE ON-THERAPY : THE **ASYMPTOMATIC** PATIENT

- Reduced LVEF : **>10%(abs) + LVEF <50% : CARDIO CONSULT**
  - → HF therapy : ACEi (enalapril) + BB (carvedilol)
  - → LVEF 40-50% : Consider withholding therapy until LVEF recovery*
  - → LVEF <40% : Withhold therapy, consider alternative treatment
  - → Short-term re-evaluation (4wks)

- Normal LVEF, **reduced GLS** : -15%(rel)/-5%(abs) → never withhold therapy

- Normal LVEF, **increased biomarkers** → never withhold therapy

TROUBLE ON-THERAPY : THE **SYMPTOMATIC** PATIENT

→ CARDIO CONSULT : ECG, TTE

- LVEF **<40%** : optimize HF treatment (ACEi + BB +/- MRA)

  Avoid AC, consider less cardiotoxic therapy

- LVEF **40-50%** : optimize HF treatment (ACEI + BB +/- MRA)

  Stabilize LV fct prior to potentially cardiotoxic treatment

- Symptoms of HF but LVEF **>50% : HFpEF** ? Other?

+ EARLY RE-EVALUATION : TTE in +/- 4wks

TROUBLE ON-THERAPY : THE SYMPTOMATIC PATIENT

- **Resolution of symptoms** after withholding chemotherapy

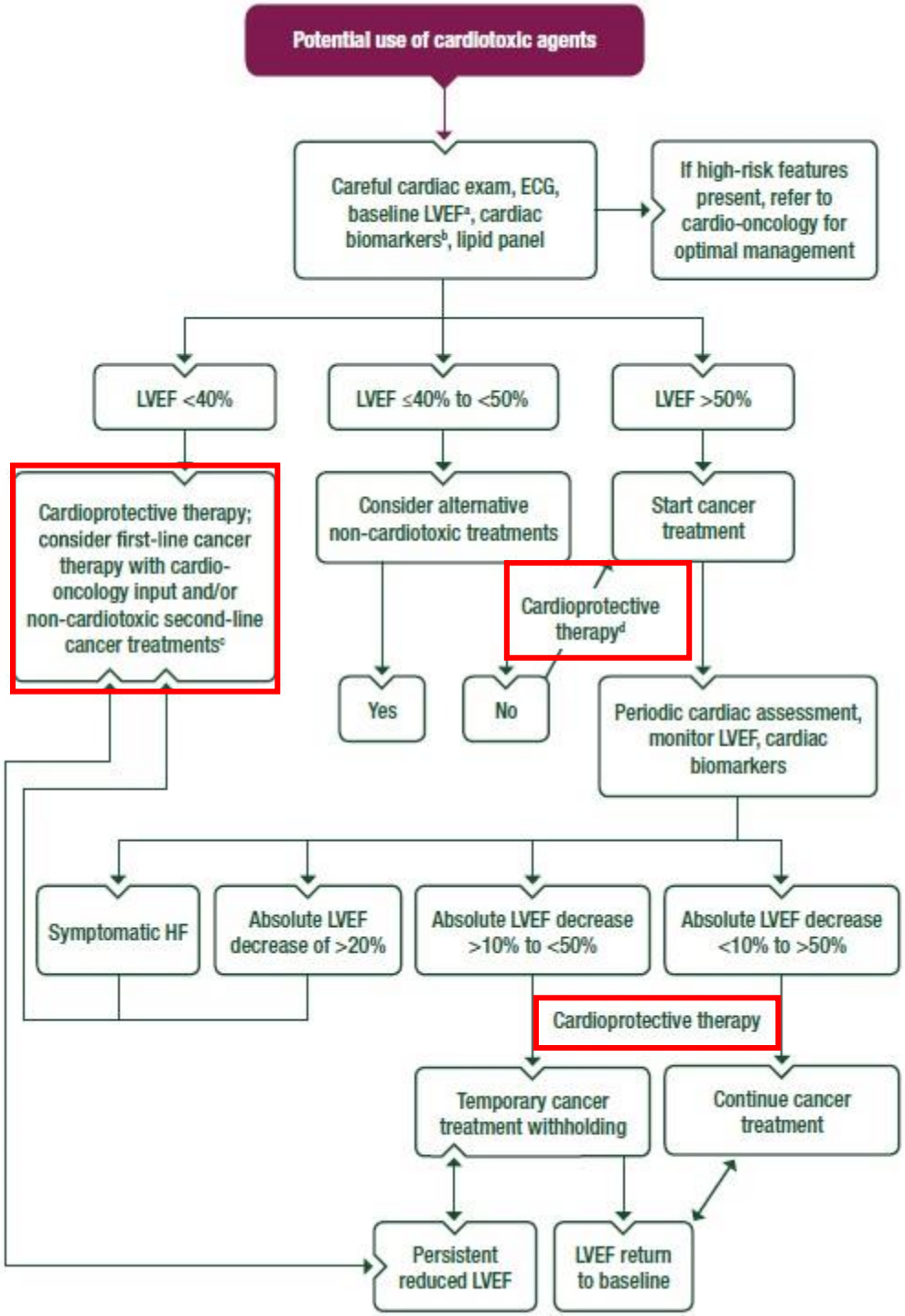
  LVEF recovers >40% : alternative therapy vs. careful rechallenge

  LVEF recovers >50% : consider rechallenge

  Close follow-up

- **Persistence of symptoms** after withholding chemotherapy

  Alternative therapy vs. pursuing current therapy if no other option exists



Curigliano et al

Ann Oncol 2020

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POST-THERAPY FOLLOW-UP

Anthracyclines : Consult + TTE : Y1 = 1x/3m
Y2-5 = 1x/6m
>Y5 = 1x/y

Trastuzumab : Consult + TTE : Y1-2 = 1x/3m
>Y2 = 1x/6m

Targeted therapy (TKI/MAb) + ICI : Consult + TTE : Y1 = 1x/3m
>Y1 = 1x/6m (case-by-case)

Radiotherapy : Consult : 1x/y (CV risk factors, ECG)
TTE : 1x/5y (+/- bike test)

COMPLAINTS = EARLY REFERRAL

TAKE HOME MESSAGES

1. **Identify the high risk patient :**
   AHT, dyslipidaemia, DM II, smoking, known CVD

2. **Low threshold for cardiac consult & TTE**

3. **Low threshold for ‘cardioprotective strategies’**

4. **TTE protocol unclear ? Call for clarification**

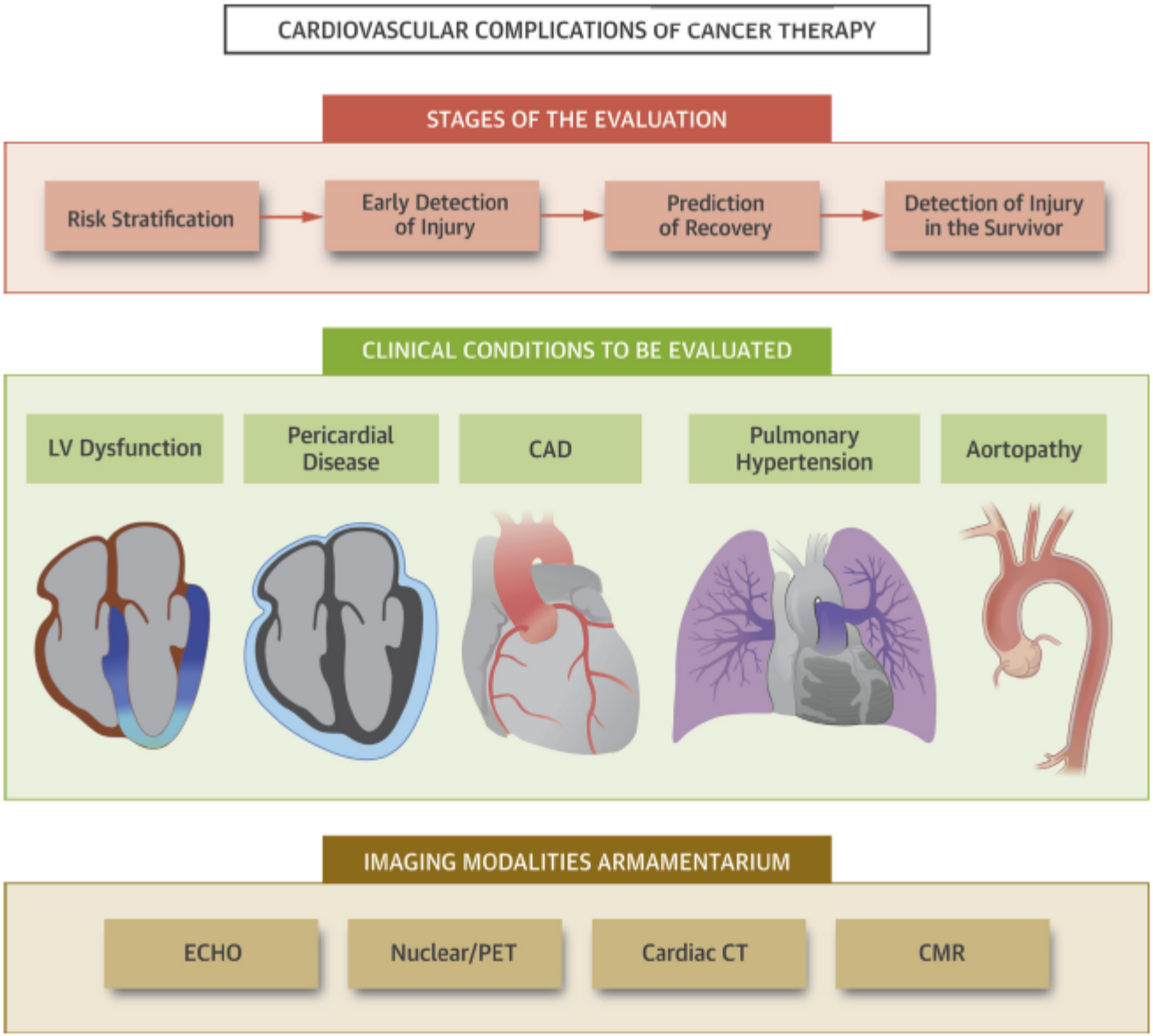
5. **GLS : useful, but not a gamechanger (yet)**

6. **LVEF : <40% = HOLD therapy, rediscuss, re-evaluate**

7. **Image quality is everything : CMR if necessary**

8. **Treat early!**

CENTRAL ILLUSTRATION Cardiovascular Complications of Cancer Therapy



Plana, J.C. et al. J Am Coll Cardiol Img. 2018;11(8):1173-86.

Stages of the evaluation and clinical conditions to be evaluated and imaging modalities available. CAD = coronary artery disease; CMR = cardiovascular magnetic resonance; CT = computed tomography; PET = positron emission tomography.

THANK YOU

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CARDIOTOXICITY : WHAT'S IN A NAME?

Zamorano et al, Eur Heart J 2016

Table 1 Mechanisms and main clinical manifestation of the cardiotoxicity of anti-cancer drugs with known and clinically relevant potential for cardiac adverse effects

Anti-cancer drug class	Main mechanism(s) of cardiotoxicity	Main clinical presentation	Frequency (% of treated patients)
Anthracyclines (doxorubicin, epirubicin)	DNA damage, mitochondrial dysfunction and oxidative stress of cardiomyocytes	LVSD/HFrEF (dose-dependent, irreversible, often delayed-onset)	With current doses 3–5%; with liposomal anthracyclines 2%
Alkylating agents (cyclophosphamide, ifosfamide)	Myocarditis; epicardial coronary artery spasm	LVSD/HFrEF	Up to 28% (cyclophosphamide > ifosfamide)
Fluoropyrimidines (5-fluorouracil, capecitabine)	Epicardial coronary artery spasm and/or coronary microvascular dysfunction	Acute myocardial ischaemia	Up to 18%
Anti-HER2 agents (trastuzumab, lapatinib, pertuzumab)	Inhibition of HER2 pro-homeostatic activities in the heart	LVSD/HFrEF (dose-independent, reversible with discontinuation)	Up to 28% if with anthracyclines (trastuzumab >> lapatinib and pertuzumab)
Multiple TKI (sunitinib, sorafenib)	Inhibition of VEGF and other pro-homeostatic tyrosine kinase receptors	Hypertension Arterial thrombosis LVSD/HFrEF	Up to 47% (sun) – 43% (sora) Up to 1.7% (sun) – 1.4% (sora) Up to 19% (sun) – 8% (sora)
VEGF-directed TKI (bevacizumab)	Systemic endothelial and coronary microvascular dysfunction; ↓ angiogenesis	Hypertension Arterial thrombosis HFrEF	Up to 35% Up to 3.8% Up to 4%
Platinum agents (cisplatin)	Endothelial dysfunction and disruption; platelet activation	Thromboembolism	Up to 2%

The highest frequency reported in the literature are presented in the Table. For more detailed information about the incidence of anti-cancer therapy cardiotoxicity, see Zamorano *et al.*[34]

HER2, human epidermal growth factor receptor 2; HFrEF, heart failure with reduced ejection fraction; LVSD, left ventricular systolic dysfunction; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.