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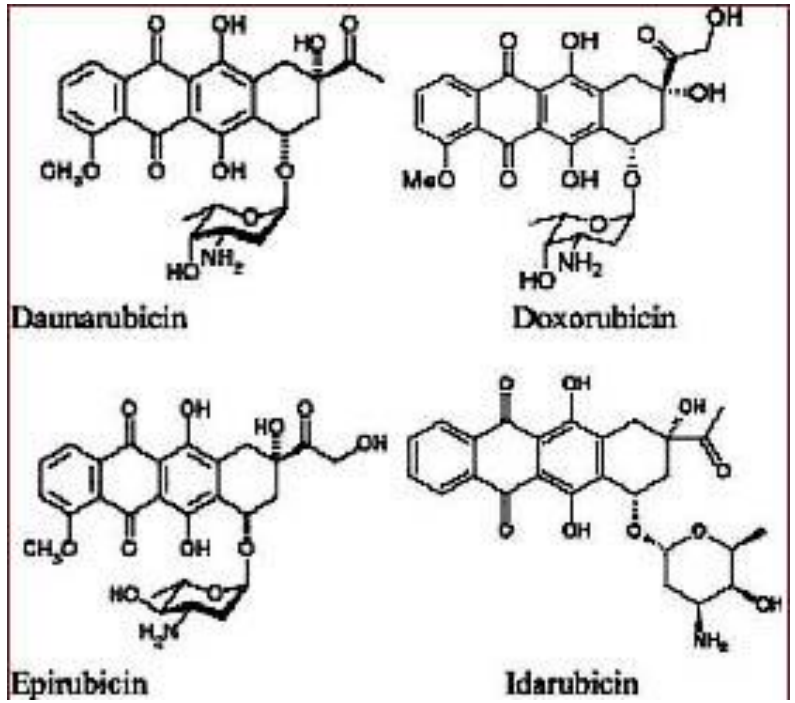

SESSION CARDIO-ONCOLOGIE 24 SEPTEMBRE 2020

Dépistage et prise en charge des complications cardio-vasculaires sous anthracyclines

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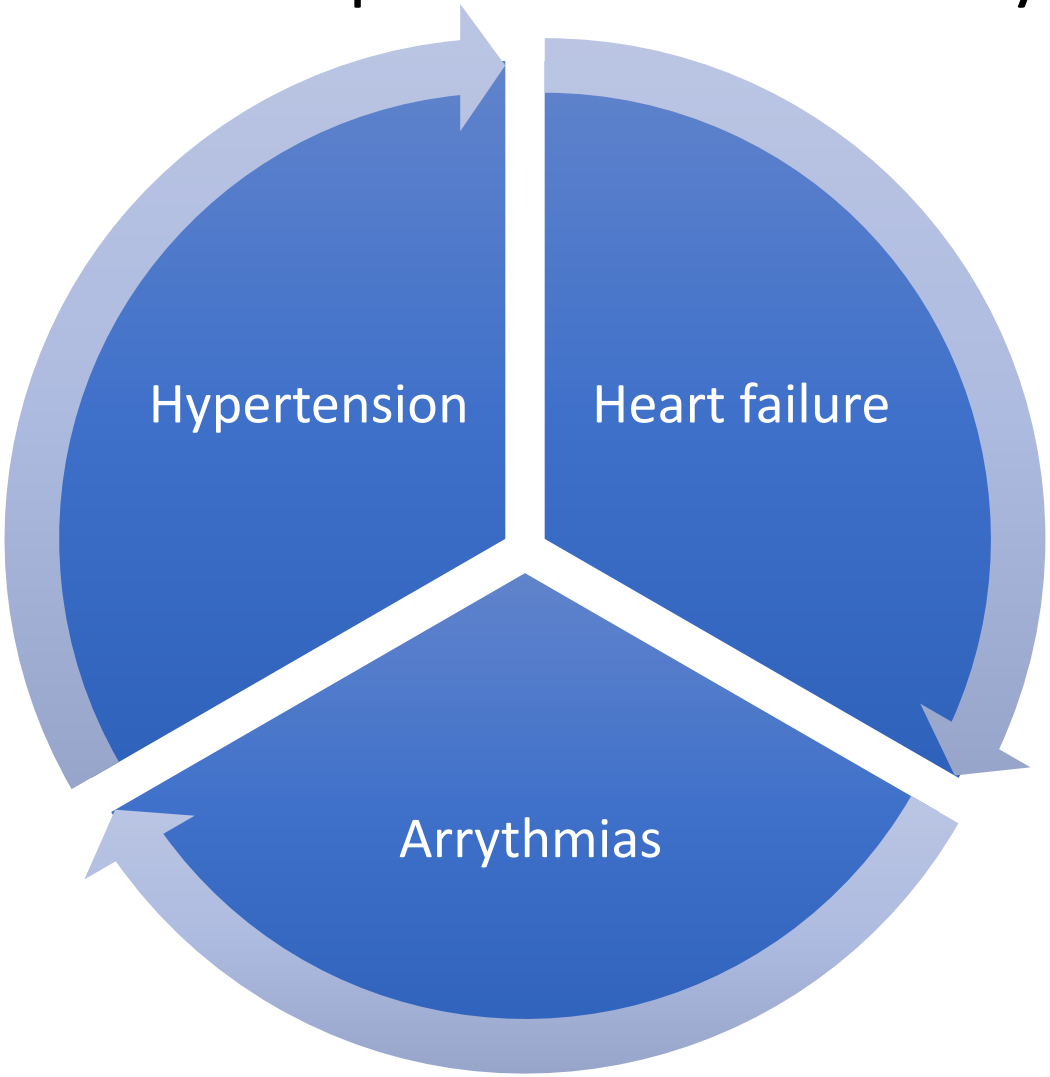
Disclosure Statement of Financial Interest

I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company :

Speaker's name : Clément, Charbonnel, Le Chesnay

☑ Je n'ai pas de lien d'intérêt potentiel à déclarer

Main cardiovascular complications of anthracycline therapy



Arrythmias

Table 8 Cancer drug agents associated with cardiac arrhythmias

Type of arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomi… …oxorubicine, epirubici… IL-2, methotrexate…
Sinus tachycardia	Anthr…
Atrioventricular block	…omib, cyclophospham… …idomide.
Conduction disturban…	…FU, imatinib, taxanes
Atrial fibril…	…nts (cisplatin, cyclop… …, gemcitabine), IL-2, in… …e TKIs (ponatinib, sorafenib, sunitinib, ibrutinib), topois… …anes, vinca alkaloids.
Sup… …dias	Alky… …mide, melphalan), amsacrine, anthracyclines, antimetabolites …omib, doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventri…ular tachycardia/fi…	…ophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5-FU, …rioxide, doxorubicin, interferons, IL-2, methothrexate, paclitaxel, proteasome inhibitors …, carfilzomib), rituximab, romidepsin.
S…	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-flu… …, IL-2 = interleukin 2; TKI = tyrosine kinase inhibitor.

AF = RR X 12 of Heart failure

β blockers = best safety profile

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CHARBONNEL Clément

Dépistage et prise en charge des complications cardio-vasculaires sous anthracyclines

Zamorano J et al. European Heart Journal (2016) 37, 2768–2801

Hypertension

-Rare, much more prevalent with other treatments
-Home-measurement of blood pressure ++++
-Target <135/85
-Beware of drug-drug interaction +++
-Prefer:
    -ACEi or ARB
    -dihydropiridin calcium inhibitors
    -β blockers (BB)

-Avoid:
    -Verapamil and diltiazem
    -Diuretics

Anthracycline

=

Risk of heart failure

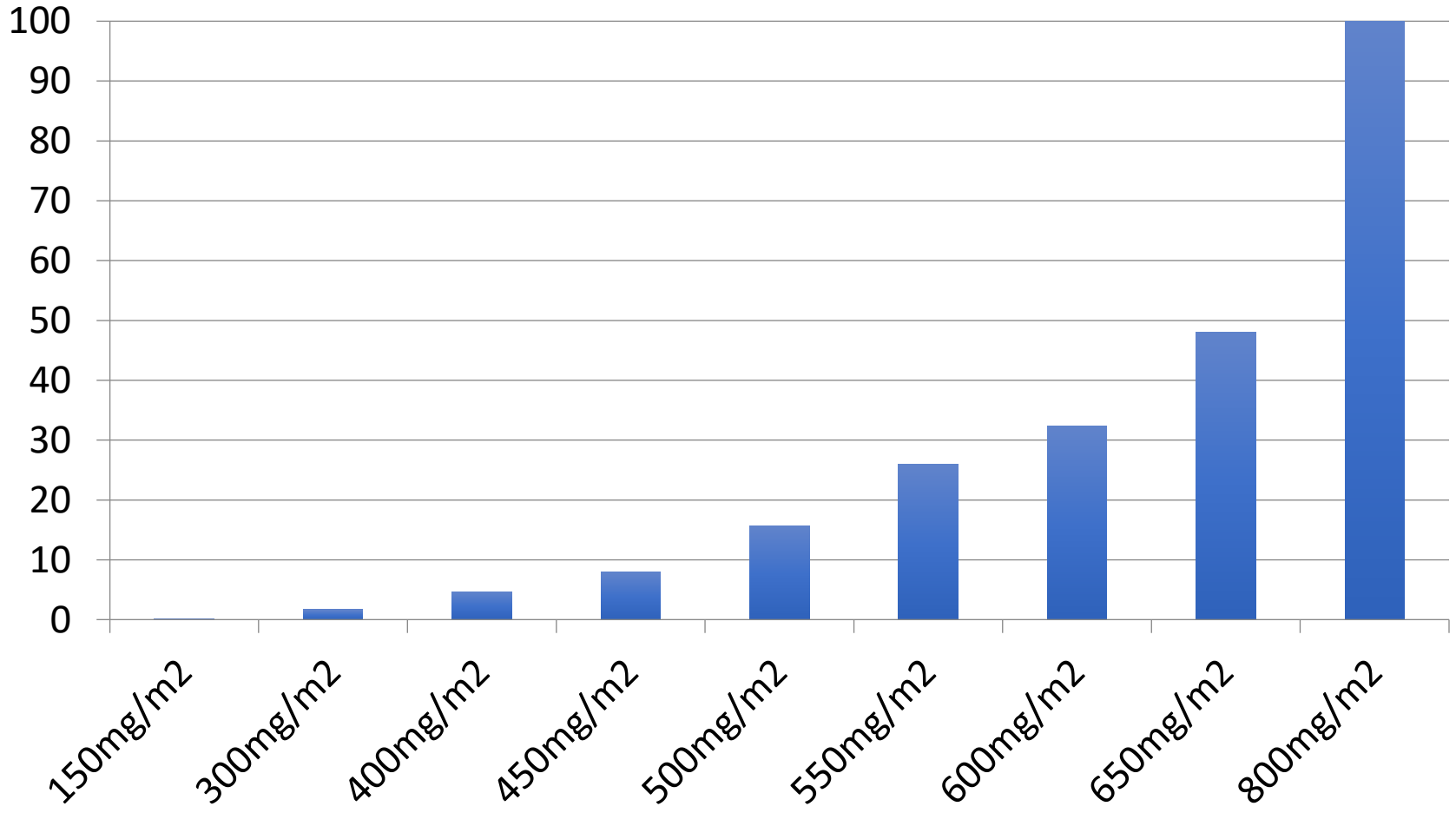
Acute heart failure

- Rare <1%
- Predominantly:
  - Supraventricular arrhythmia
  - Transient LV dysfunction
  - Electrocardiographic changes
- Immediately after infusion
- Usually reversible

Anthracycline therapy

- Mainly induce « chronic » cardiac dysfunction and heart failure
- Type 1 cardiotoxicity
- Cumulative toxicity
- Risk factors for cardiac toxicity:
  - History of cardiomyopathy
  - Radiation
  - Dose administrated
- Poor prognosis of Anthracycline induced cardiotoxicity (AIC)

Incidence of anthracycline induced cardiotoxicity (congestive heart failure)



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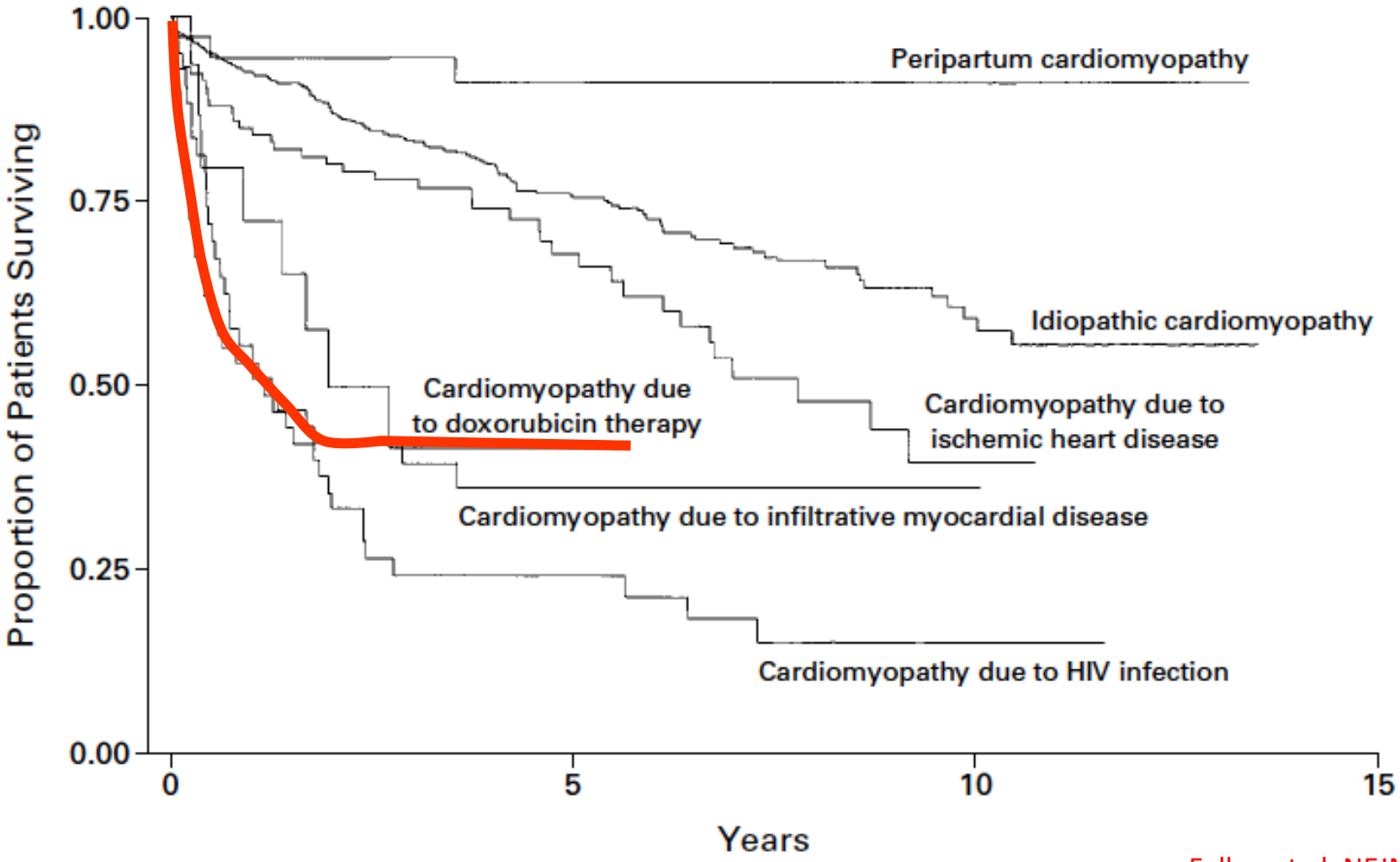
Adapted from Swain et al. Cancer 2003;97:2869–79

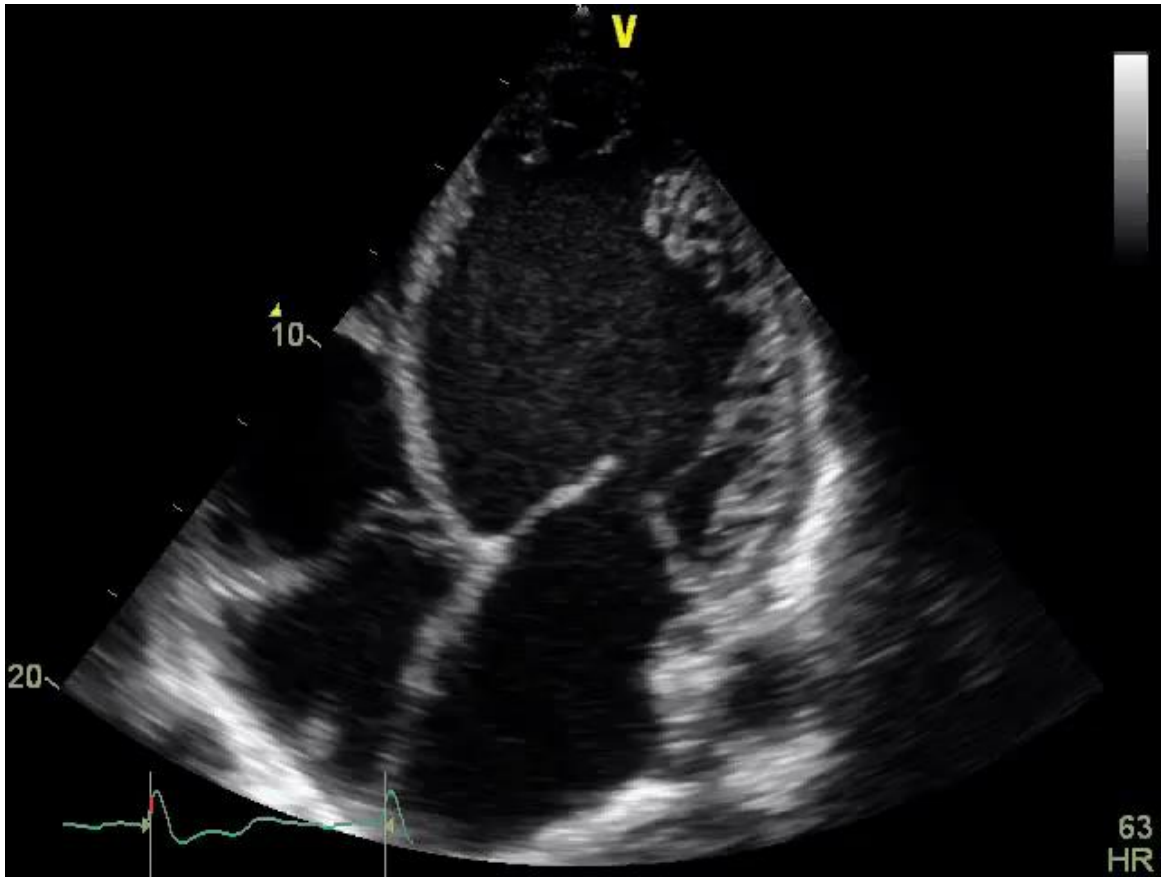
Prognosis of AIC



Felker et al. NEJM 2000; 342: 1077-1084

Definition of anthracycline induced cardiotoxicity (AIC)

Most of the time asymptomatic decrease in LVEF of >10 % to a value <50%.



Measurement of LVEF

3D EF:

-preferred method

-more acurrate and reproducible (interobserver variability 5-8%)

-lower limit of normal < 50%

2D EF: simpson rule

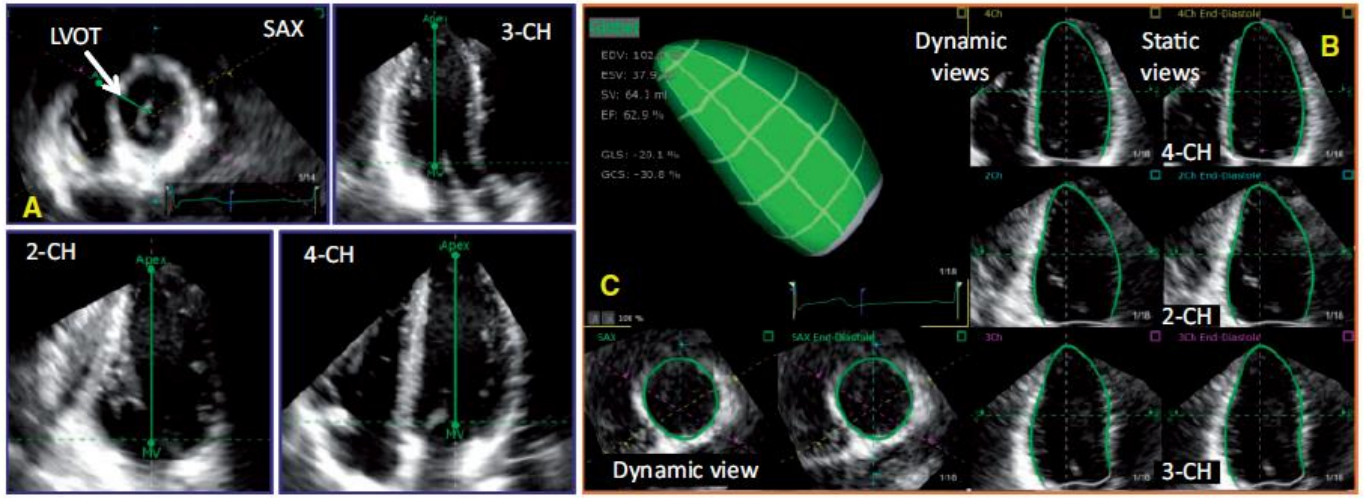
-less reproducible (interobserver variability 10-15%)

-lower limit of normal < 53%

-consider contrast in case of poor echogenicity

Table 2 Normal values for 2D echocardiographic parameters of LV size and function according to gender

Parameter	Male		Female	
	Mean ± SD	2-SD range	Mean ± SD	2-SD range
LV internal dimension				
Diastolic dimension (mm)	50.2 ± 4.1	42.0–58.4	45.0 ± 3.6	37.8–52.2
Systolic dimension (mm)	32.4 ± 3.7	25.0–39.8	28.2 ± 3.3	21.6–34.8
LV volumes (biplane)				
LV EDV (mL)	106 ± 22	62–150	76 ± 15	46–106
LV ESV (mL)	41 ± 10	21–61	28 ± 7	14–42
LV volumes normalized by BSA				
LV EDV (mL/m^2)	54 ± 10	34–74	45 ± 8	29–61
LV ESV (mL/m^2)	21 ± 5	11–31	16 ± 4	8–24
LV EF (biplane)	62 ± 5	52–72	64 ± 5	54–74



Plana et al. JASE 2014; 27: 811-39

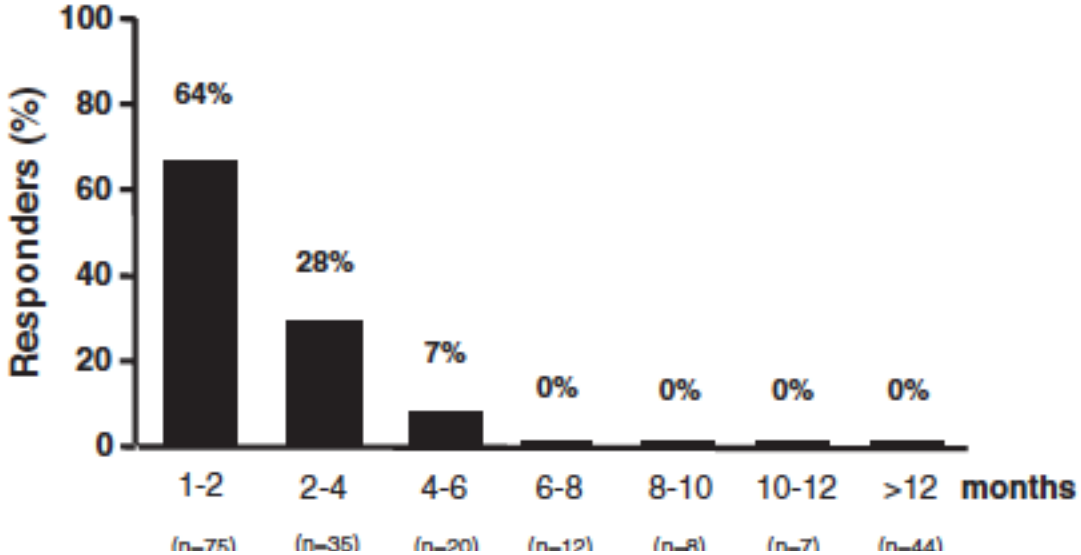
Bernard A et al. European Heart Journal CVI 2017;18, 475–483

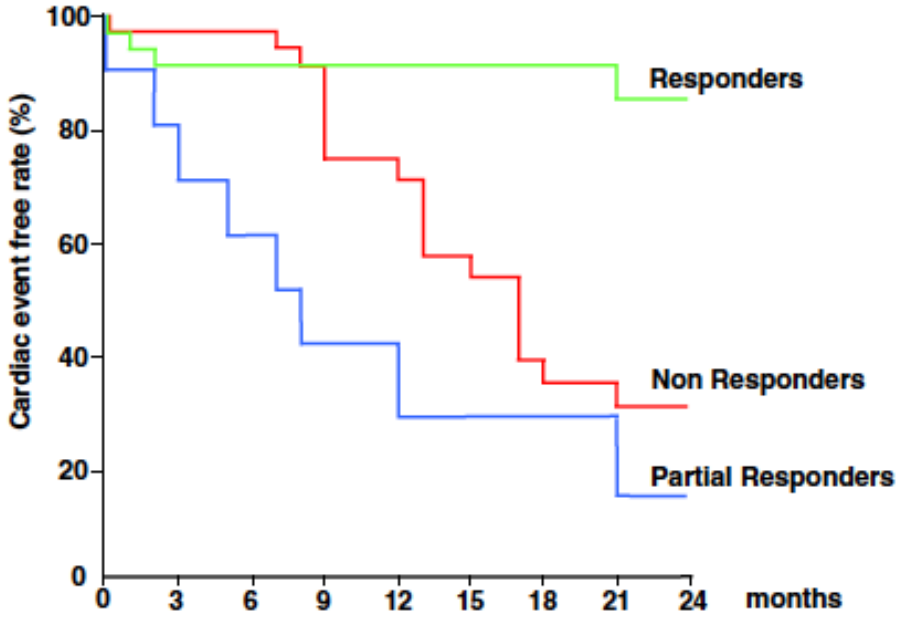
Lang R et al. Eur Heart J Cardiovasc Imaging. 2015 Mar;16(3):233-70

Tools to predict AIC

- Medical history and clinical status
- Biomarkers
  - NT-ProBNP, BNP (myocardial wall stress)
  - Troponine I (myocardial damage)
  - CRP (inflammation), STS 2, GDF 15 (oxydative stress)…
- Echocardiography (global longitudinal strain and ejection fraction)
- Cardiac MRI
- PET scan

- 201 patients with AIC defined by LVEF ≤ 45%
- Enalapril +/- carvédilol as soon as possible
- Clinical and echo Follow up:
  - M0,M1,M2,M3,M6,M9,M12, M15, M18, M24, M30...
- Primary endpoint: LVEF
  - Responder: LVEF >50%
  - Partial responder: Δ>10% and LVEF<50%
  - Non responder
- Secundary endpoint: MACEs





Cardinale D et al. J Am Coll Cardiol 2010; 55:213–20

Synthesis of NT ProBNP or BNP as a predictor of AIC

-More than 30 studies (NT ProBNP>BNP)
-Various population and timing of assessment
-Conflicting results regarding the ability of natriuretic peptides to predict AIC
-Insufficient evidence to establish the significance of subtle rises
-Role for routine surveillance not clearly established

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

EXPERT CONSENSUS STATEMENT

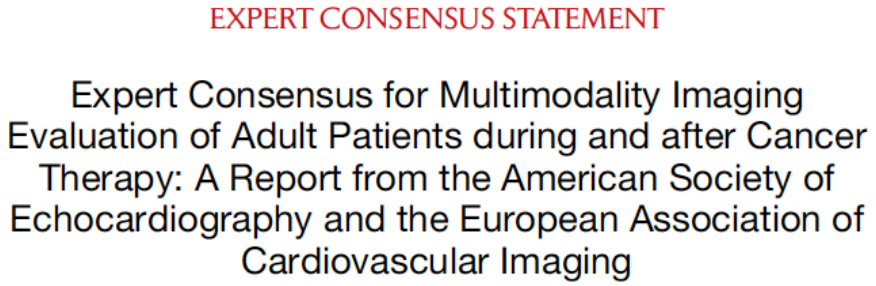
Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Plana et al. JASE 2014; 27: 811-39

Tian et al. Front Oncol. 2014; 4: 277

Synthesis of Troponin as a predictor of AIC

-More than 30 studies (Troponin I>Troponin T>Hs troponin)
-Various population and timing of assessment
-Ability to predict AIC
-Cut off value ?
-Single vs multiple assessment ?
-Integrated approach with GLS +++

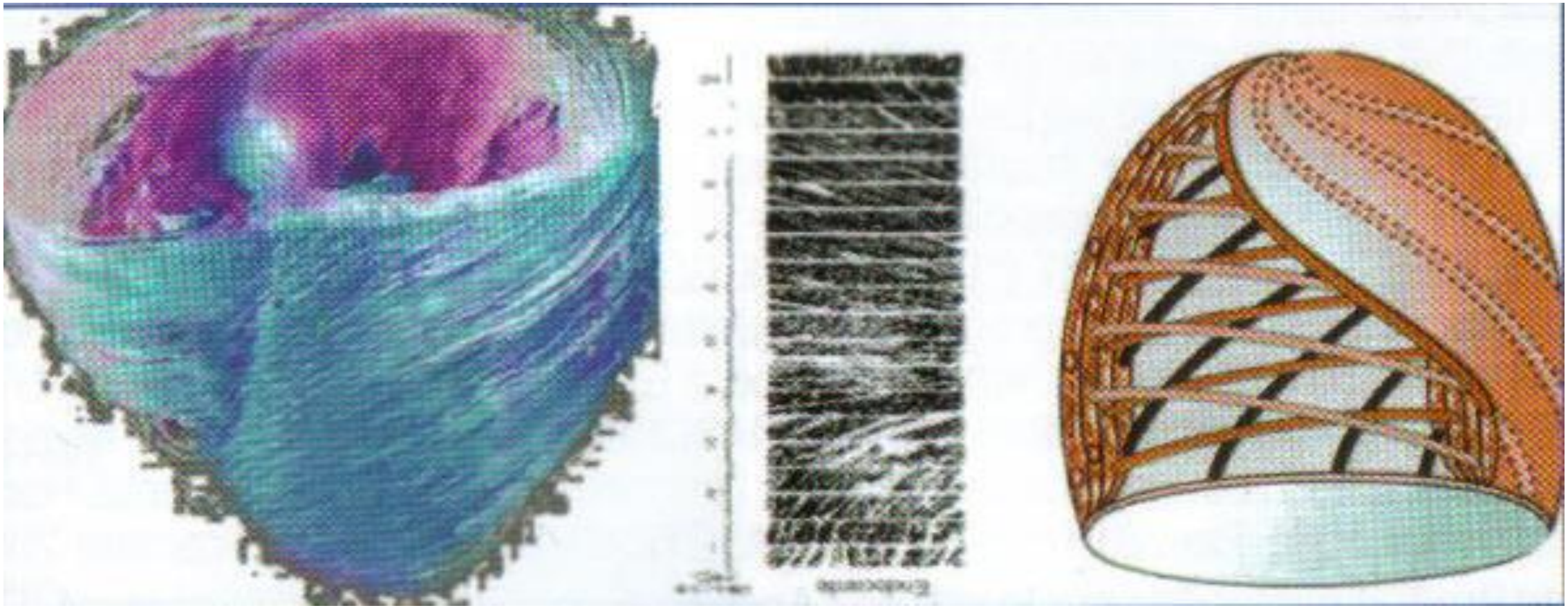


Plana et al. JASE 2014; 27: 811-39

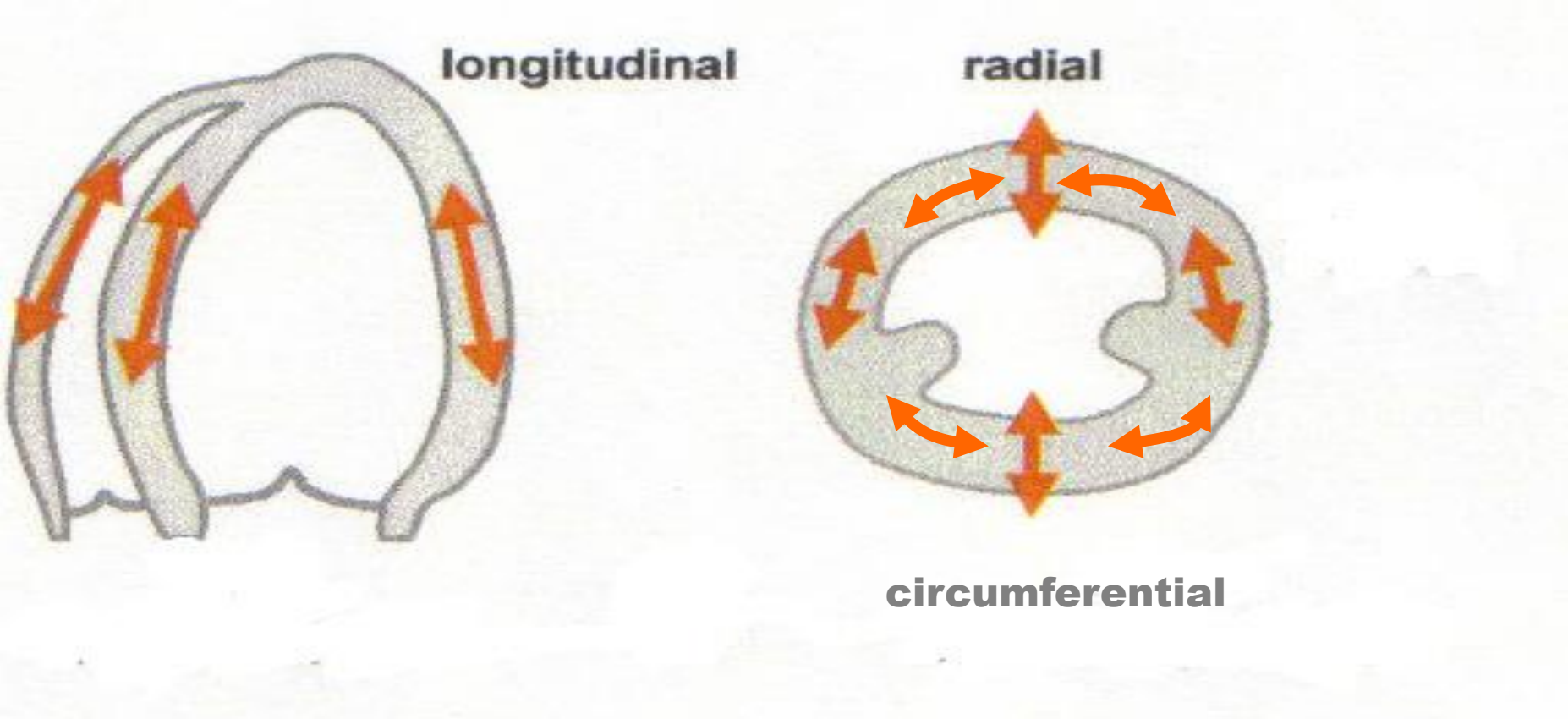
Tian et al. Front Oncol. 2014; 4: 277

Echocardiographic parameters

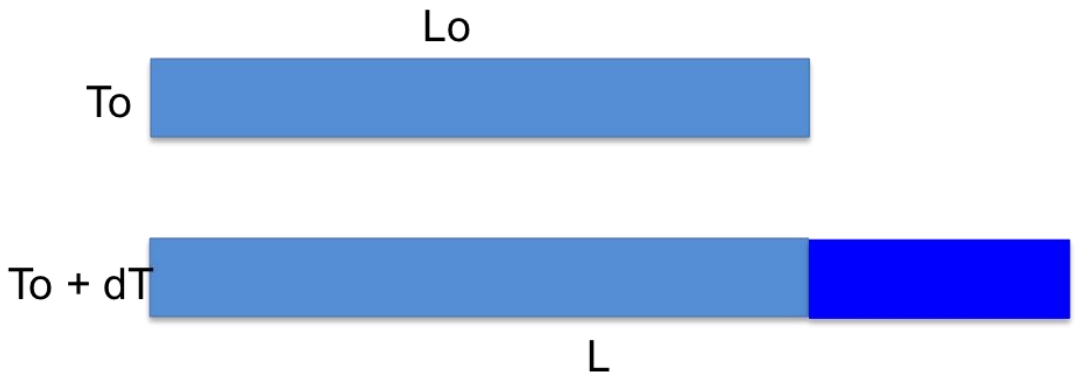
Global longitudinal strain (GLS)



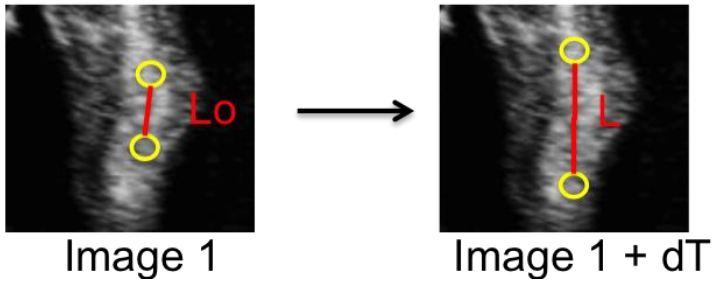
3 components of strain



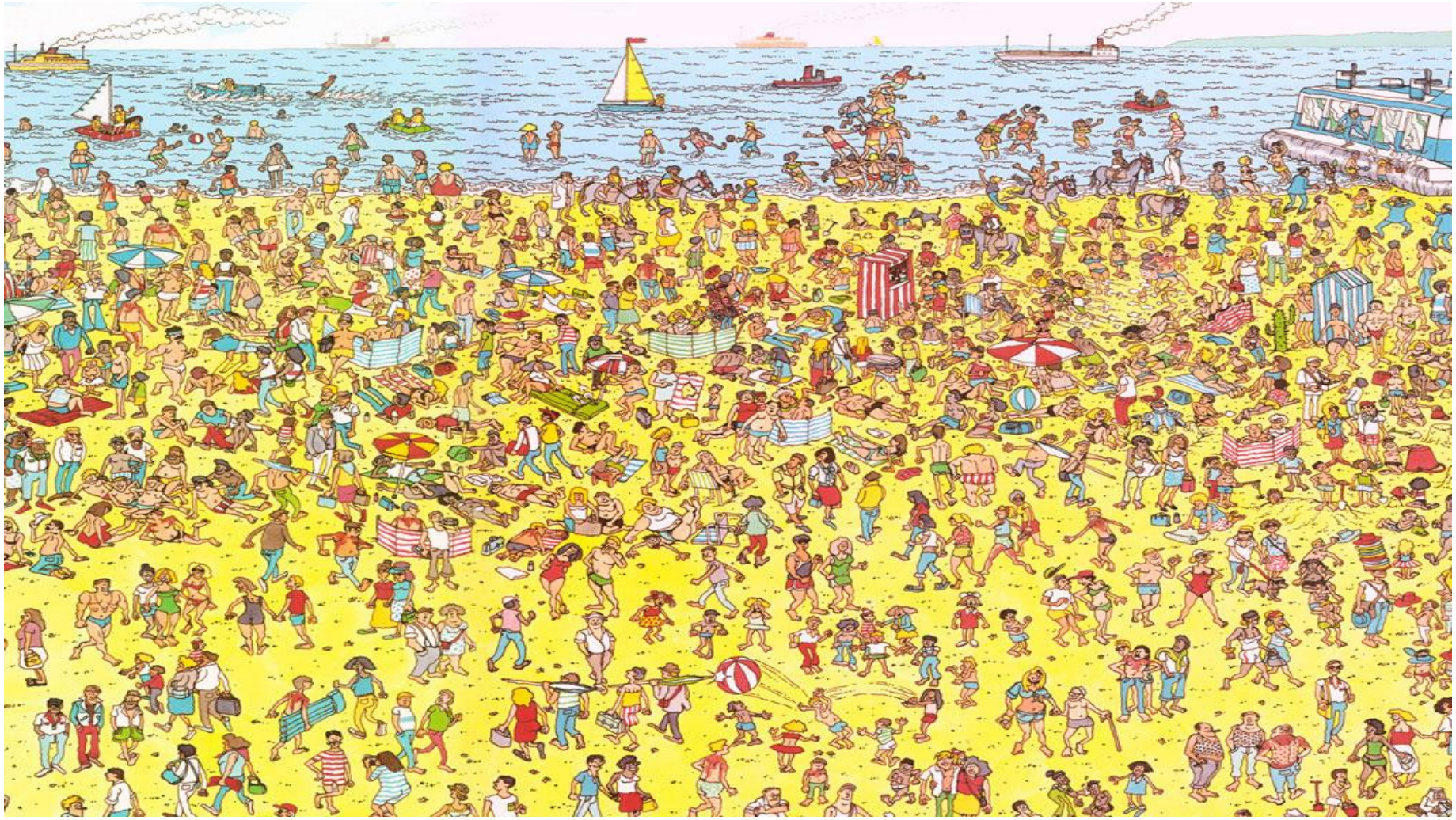
« SPECKLE TRACKING»



$$\text{Déformation} = \frac{L - Lo}{Lo}$$



Where is Charly???



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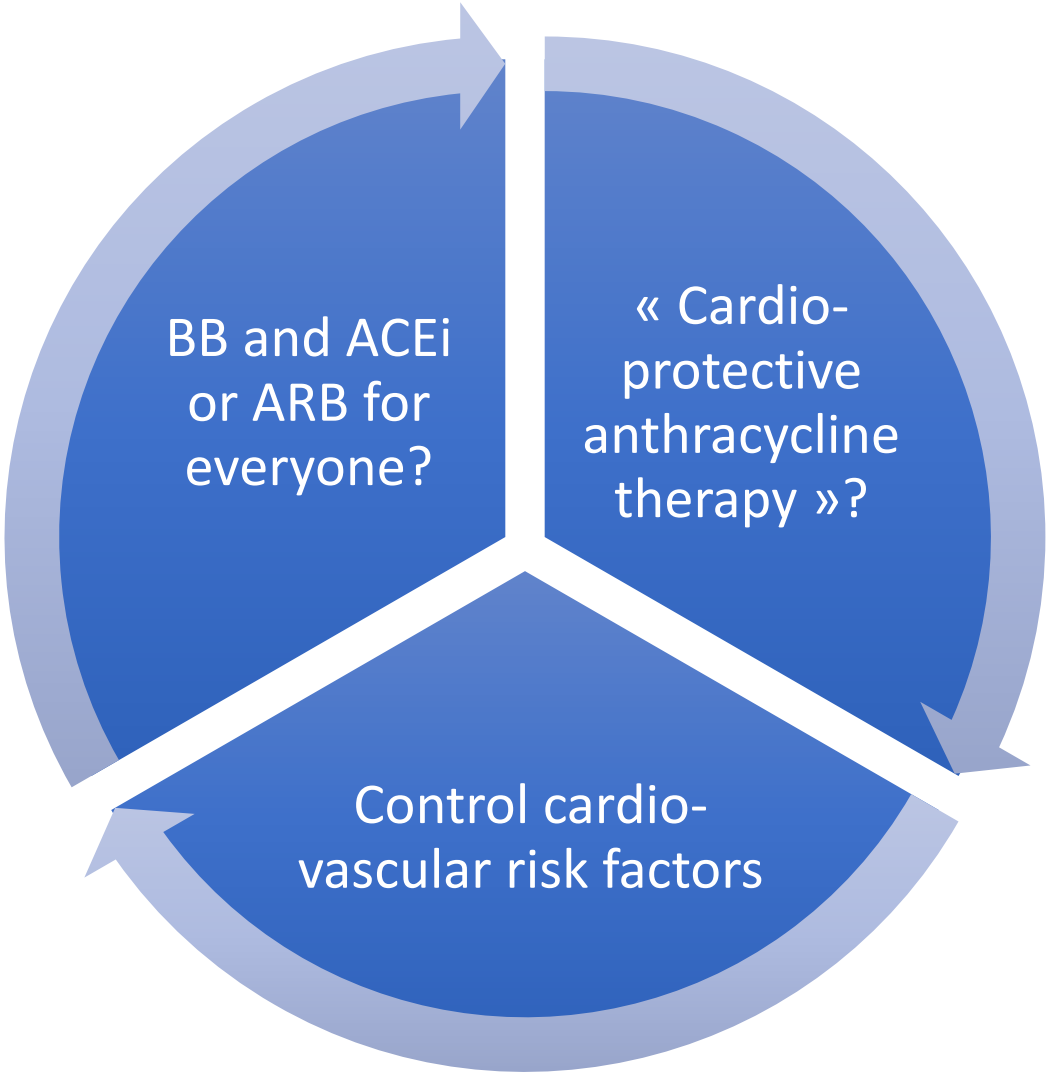
Global longitudinal strain

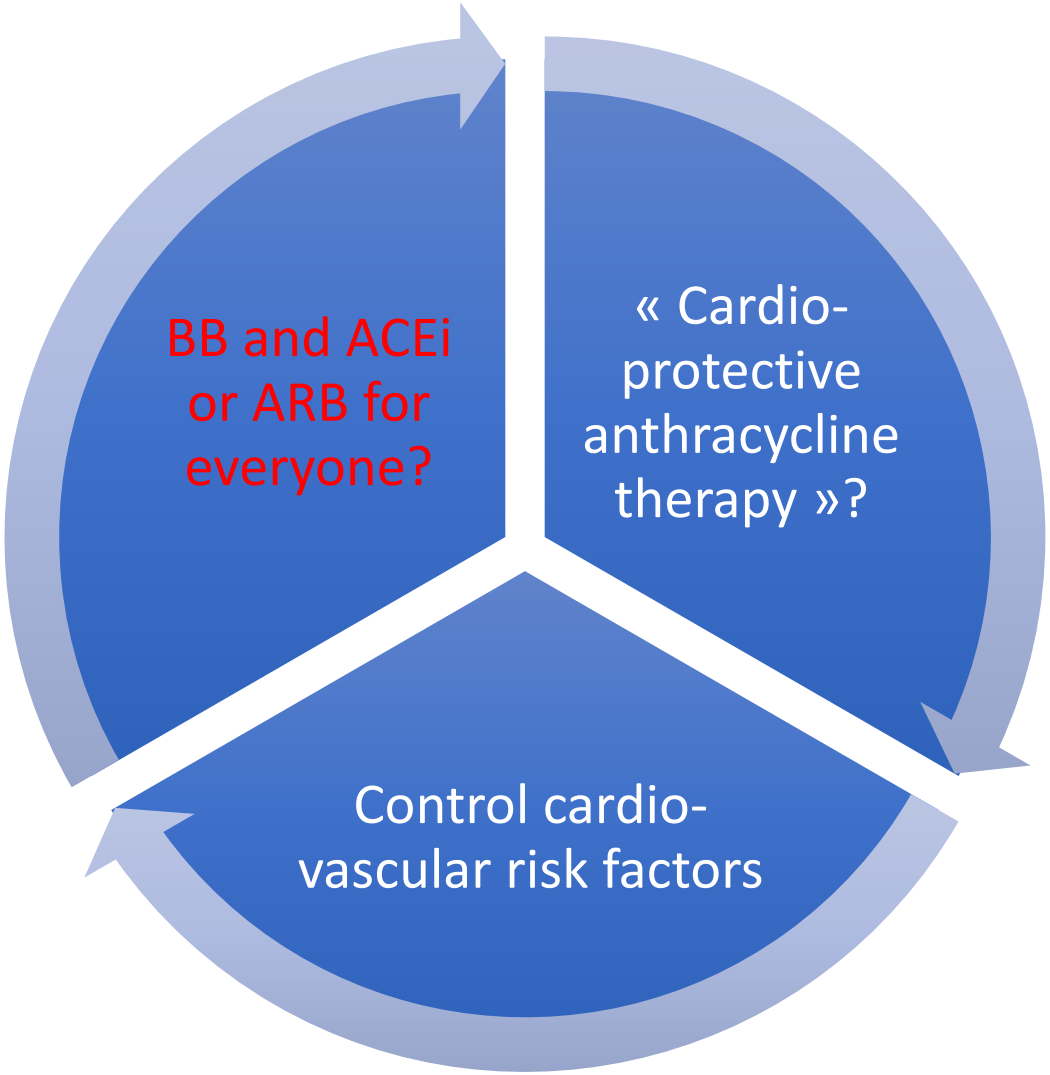
- Fair and reproducible technique
- Normal value: -20% +/- 2%
- Role of GLS to detect slight alterations in systolic function, especially in the setting of potentially cardiotoxic drugs and even after only low to moderate doses of anthracyclines.
- GLS assessment for the detection of subclinical left ventricular dysfunction due to anthracycline therapy
  - Baseline GLS
  - Drop of GLS during chemotherapy

Studies	N	Type of cancer	Treatment	Radiotherapy	Cardiotoxicity rate	Timing of assessment of GLS	Thresholds	Sensitivity	Specificity
Absolute value of GLS									
Sawaya et al.	81	Breast	Anthracyclines, Trastuzumab	60%	32%	End of treatment (3 months)	>-19%	74%	73%
Negishi et al.	81	Breast	Anthracyclines, Trastuzumab	62%	30%	6 months	>-20.5%	96%	66%
De Almeida Gripp et al.	49	Breast	Anthracyclines, Trastuzumab	53%	10%	3 months	>-16.6%	80%	95%
El Sherbeny et al.	61	Breast	Anthracyclines, Trastuzumab	90%	29.5%	3 months	>-18%	92.5%	83%
Charbonnel et al.	86	Lymphoma and leukaemia	Anthracyclines	15%	7%	after 150mg/m2 of anthracycline	>-17.45%	67%	97%
Arciniegas Calle et al.	66	Breast	Anthracyclines, Trastuzumab	76%	20%		>-14.06%	91%	83%
Relative reduction in GLS									
Fallah et al.	42	Breast	Anthracyclines, Trastuzumab	97%	24%	3 months	≥10.1%	79%	82%
Negishi et al.	81	Breast	Anthracyclines, Trastuzumab	62%	30%	6 months	≥11%	65%	94%
Sawaya et al.	43	Breast	Anthracyclines, Trastuzumab	12%	21%	End of treatment (3 months)	>10%	78%	79%
Baratta et al.	36	Breast, lymphoma,	Anthracyclines, Trastuzumab	0%	19.4%	3 months	≥15%	86%	86%
Mornos et al.	74	Breast, osteosarcoma lymphoma and leukaemia	Anthracyclines	0%	13%	6 weeks	≥13.1%	79%	73%
Kang et al.	75	Lymphoma	Anthracyclines	0%	18.7%	After the third cycle of chemotherapy	>15.9%	86%	75%
Florescu et al.	40	Breast	Anthracyclines	0%	35%	After the third cycle of chemotherapy	>9%	84%	80%
De Almeida Gripp et al.	49	Breast	Anthracyclines, Trastuzumab	53%	10%	3 months	>14%	100%	93%

PREVENTION


BB and ACEi or ARB for everyone?
« Cardio-protective anthracycline therapy »?
Control cardio-vascular risk factors

PREVENTION


BB and ACEi or ARB for everyone?
« Cardio-protective anthracycline therapy »?
Control cardio-vascular risk factors

Primary prevention: BB and ACEi/ARB

- Small number of patients
- Open label vs blinded trials
- Heterogeneous populations
- Different Definition of cardiac toxicity
- Conflicting results
- Lack of strong evidence

→ BB and ACEi or ARB not recommended in primary prevention

Gulati et al, Eur Heart J. 2016 Jun 1; 37(21): 1671–1680.
Bosch et al, J Am Coll Cardiol 2013 ; 61 : 2355-62
Pituskinet al, J Clin Oncol. 2017 Mar 10;35(8):870-877.

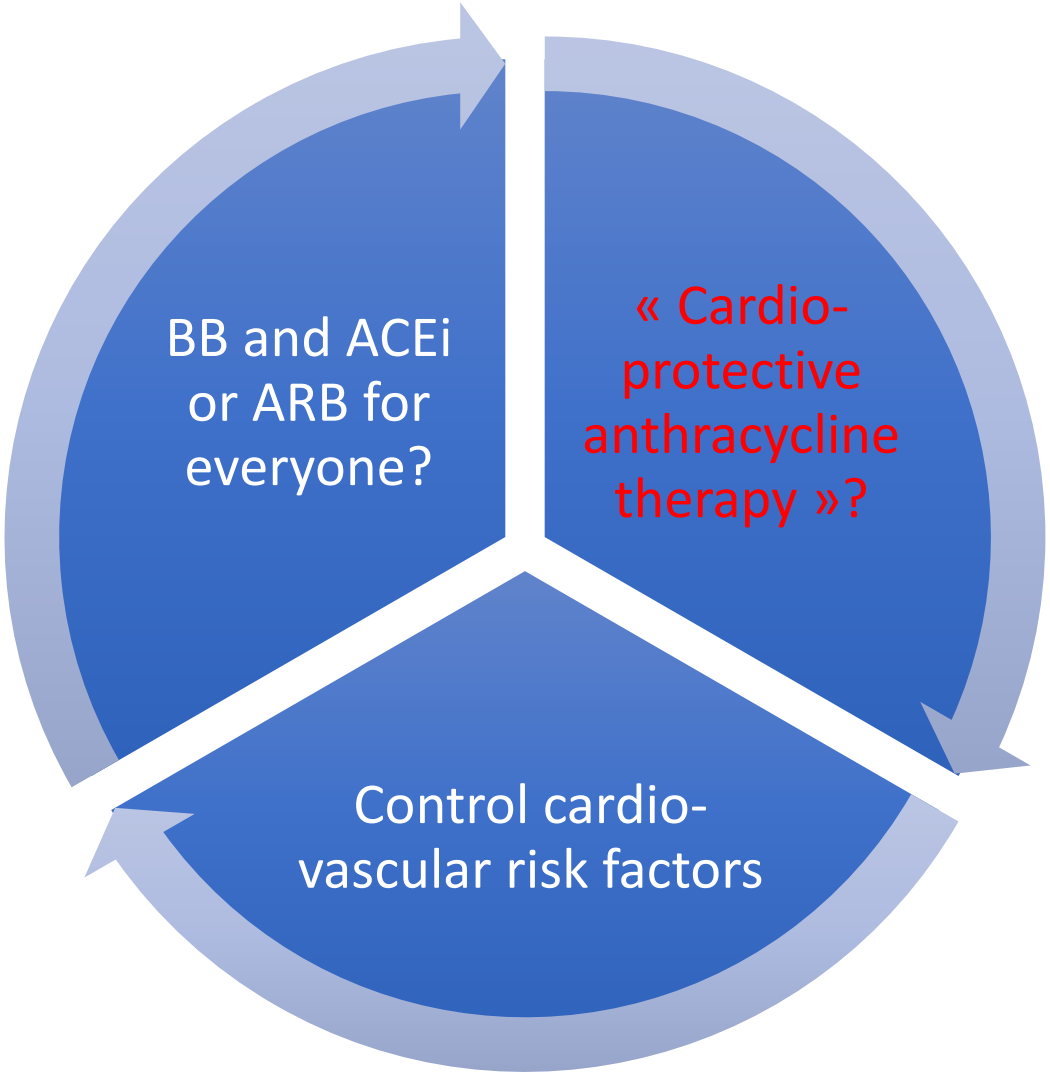
Primary prevention: ongoing studies

Table 3 Ongoing clinical trials on the treatment of cardiotoxicity

Location	NCT number	Title	Intervention	Start date	
USA	NCT02943590	STOP-CA (Statins TO Prevent the Cardiotoxicity from Anthracyclines)	Atorvastatin or placebo	January 2017	Recruiting
USA	NCT02674204	STOP Heart Disease in Breast Cancer Survivors Trial	Atorvastatin or placebo	May 2016	Recruiting
USA	NCT02096588	Detection and Prevention of Anthracycline-Related Cardiac Toxicity with Concurrent Simvastatin	Simvastatin or placebo	May 2014	Active, not recruiting
Canada	NCT03186404	Statins for the Primary Prevention of Heart Failure in Patients Receiving Anthracycline: Pilot Study	Atorvastatin or placebo	July 2017	Not yet recruiting
UK	NCT03265574	PROACT: Can We Prevent Chemotherapy-Related Heart Damage in Patients with Breast Cancer?	Enalapril or placebo	September 2017	Not yet recruiting
Italy	NCT01968200	Prevention of Anthracycline-Induced Cardiotoxicity	Enalapril	December 2012	Active, not recruiting
USA	NCT02177175	Carvedilol for the Prevention of Anthracycline/Anti-HER2 Therapy Associated Cardiotoxicity among Women with HER2-Positive Breast Cancer Using Myocardial Strain Imaging for Early Risk Stratification	Carvedilol or placebo	June 2014	Active, not recruiting
Brazil	NCT01724450	Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity	Carvedilol or placebo	June 2012	Recruiting
USA	NCT02717507	Carvedilol in Preventing Heart Failure in Childhood Cancer Survivors	Carvedilol or placebo	April 2016	Recruiting
USA	NCT01347970	Pharmacologic Reversal of Ventricular Remodeling in Childhood Cancer Survivors at Risk for Congestive Heart Failure (PREVENT-CHF): A Phase III Randomized Placebo-Controlled Trial	Carvedilol or placebo	May 2012	Active, not recruiting
Italy	NCT02236806	Cardiotoxicity Prevention in Breast Cancer Patients Treated with Anthracyclines and/or Trastuzumab	Bisoprolol or ramipril or placebo	July 2015	Recruiting
Canada	NCT01016886	Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research	Perindopril or bisoprolol or placebo	September 2010	Active, not recruiting
USA	NCT01009918	Lisinopril or Coreg CR® in Reducing Side Effects in Women with Breast Cancer Receiving Trastuzumab	Carvedilol or lisinopril or placebo	March 2010	Active, not recruiting

Teske et al. Neth Heart J 2018; 26:521–532

PREVENTION


BB and ACEi or ARB for everyone?
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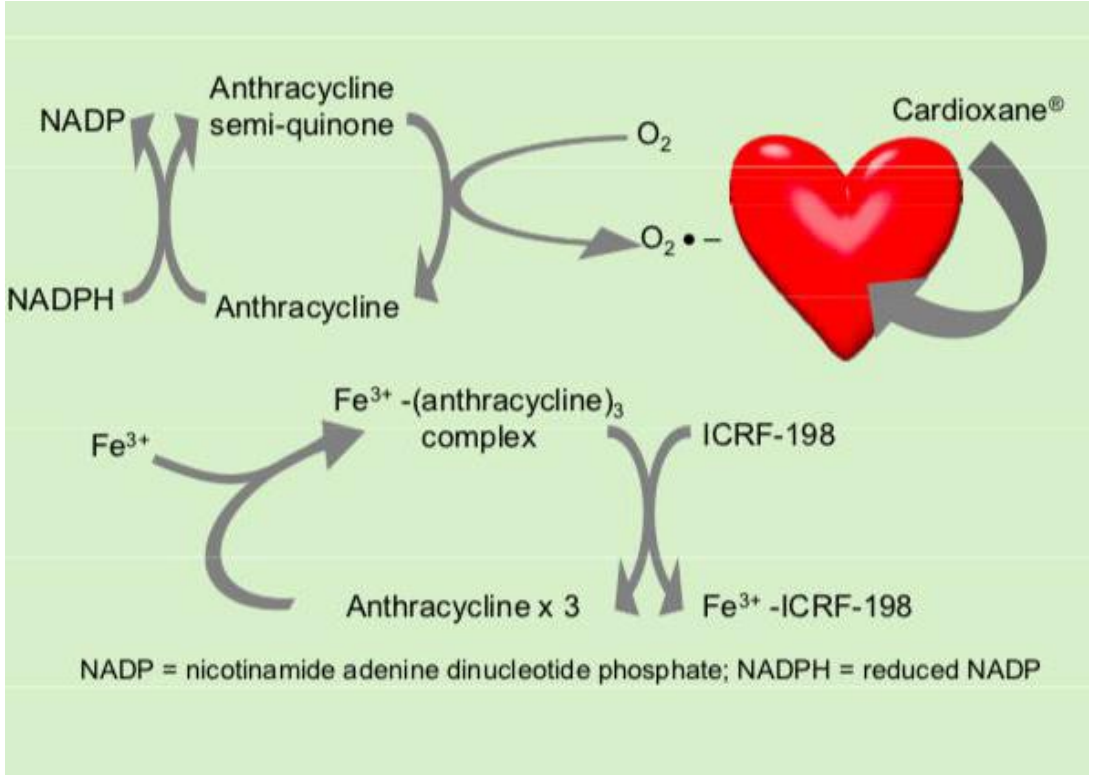
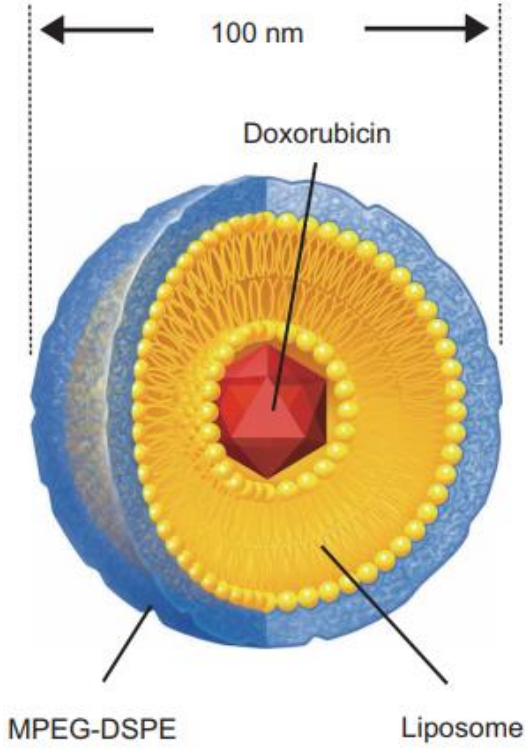
Cardio-protective agents ?

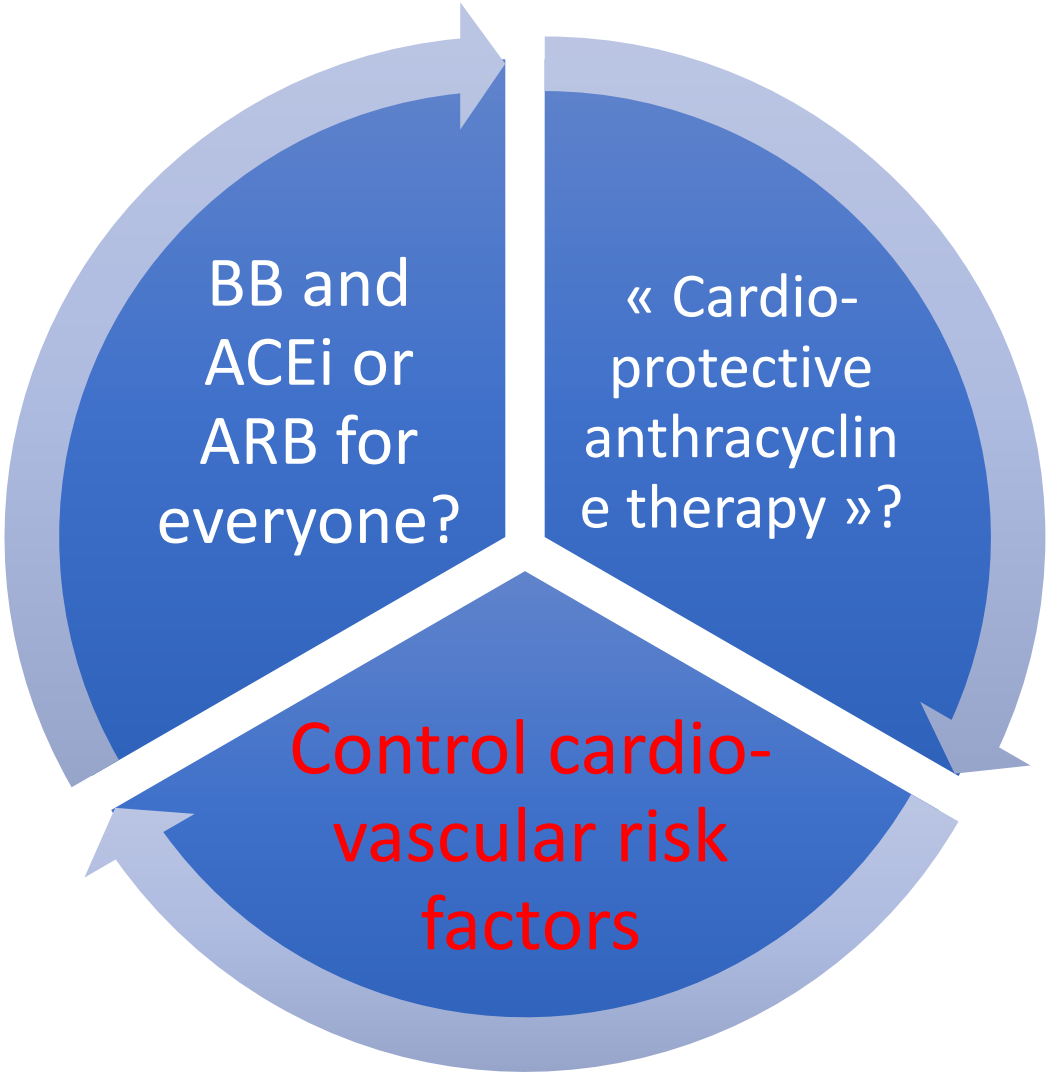
Dexrazoxane - CARDIOXANE



Pelygated doxorubicin - CAELYX



PREVENTION


BB and ACEi or ARB for everyone?
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Control cardio-vascular risk factors

Overlap between CV risk factors and risk factors for developing AIC

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.

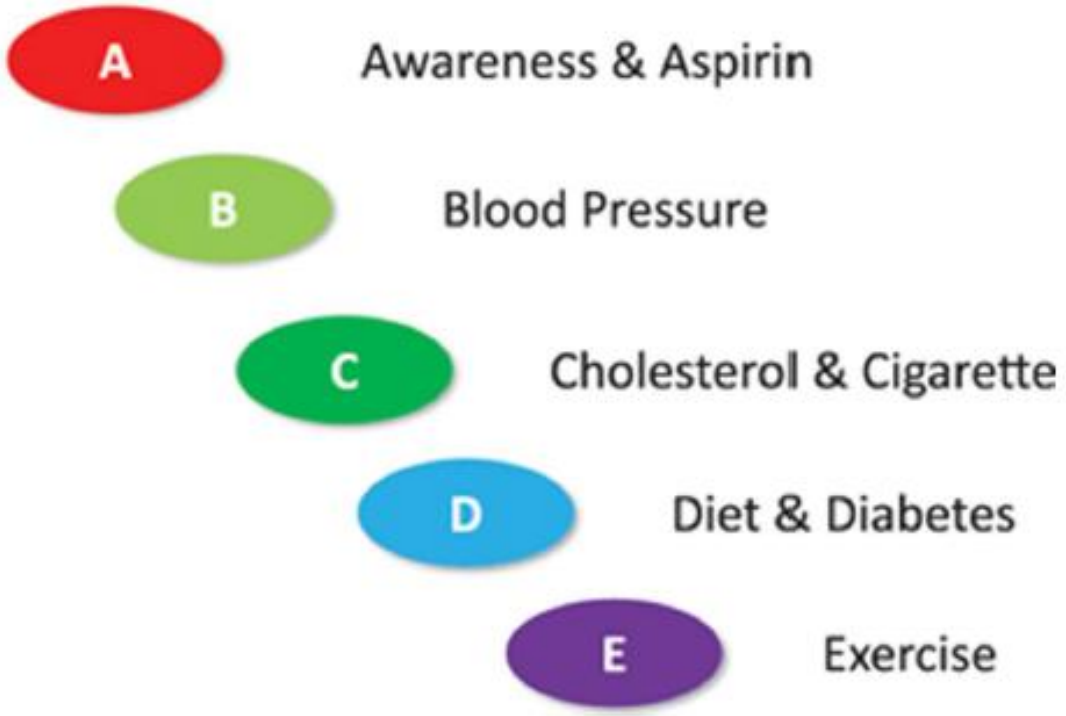
Table 2 Factors associated with risk of cardiotoxicity following treatment with anthracyclines[a]

Risk factors
• Cumulative dose
• Female sex
• Age
- >65 years old
- Paediatric population (<18 years)
• Renal failure
• Concomitant or previous radiation therapy involving the heart
• Concomitant chemotherapy
- alkylating or antimicrotubule agents
- immuno- and targeted therapies
• Pre-existing conditions
- Cardiac diseases associating increased wall stress
- Arterial hypertension
- Genetic factors

[a]Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).

Zamorano J et al. European Heart Journal (2016) 37, 2768–2801
Curigliano G et al. Ann Oncol. 2020 Feb;31(2):171-190

Corner stone of prevention



Anthracyclines
(e.g., doxorubicin, epirubicin, idarubicin, daunorubicin, mitoxantrone)

↓

Cardio-oncological evaluation*, BNP or NT-proBNP and Troponin**
before cancer treatment begins

- In patients with LVEF <40%, anthracyclines are not recommended unless there are no effective alternative cancer treatment options.
- In patients with LVEF <50% but ≥40%, ACEi (or ARB) and/or BB are recommended before treatment.
- In patients exposed to multiple cardiotoxic agents with a normal LVEF and cardiovascular risk factors, ACEi (or ARB) and/or BB may be considered.
- In patients with advanced or metastatic breast cancer who have received a cumulative dose of >300 mg/m2 doxorubicin or >540 mg/m2 epirubicin and would benefit from continued anthracycline-based therapy, dexrazoxane can be considered.

Cumulative dose doxorubicin ≥250 mg/m2 or epirubicin ≥600 mg/m2)	Cumulative dose doxorubicin <250 mg/m2 or epirubicin <600 mg/m2)
↓	↓
Cardio-oncological evaluation* *before each cycle* ***AND*** **Troponin**** *after each cycle (end of infusion)*	Presence of any of the following factors: age ≥ 60, mediastinal radiotherapy, previous heart disease, ≥two risk factors (including smoking, hypertension, diabetes, dyslipidemia, chronic renal insufficiency, and obesity), baseline elevation of cardiac biomarkers
	↓ yes / ↓ no
	Troponin** *after each cycle (end of infusion)*

↓

CV symptoms/signs *OR* Troponin +

↓ yes / ↓ no

Cardio-oncological evaluation* *before the next cycle and tailored monitoring on case-by-case basis*	**Cardio-oncological evaluation*** *at the end of cancer treatment and at 6 months, 1 year, 2 years, and periodically thereafter*

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Discontinuation of anthracycline is warranted if:

Symptoms/signs of heart failure

Asymptomatic Drop of LVEF under an absolute value <40%

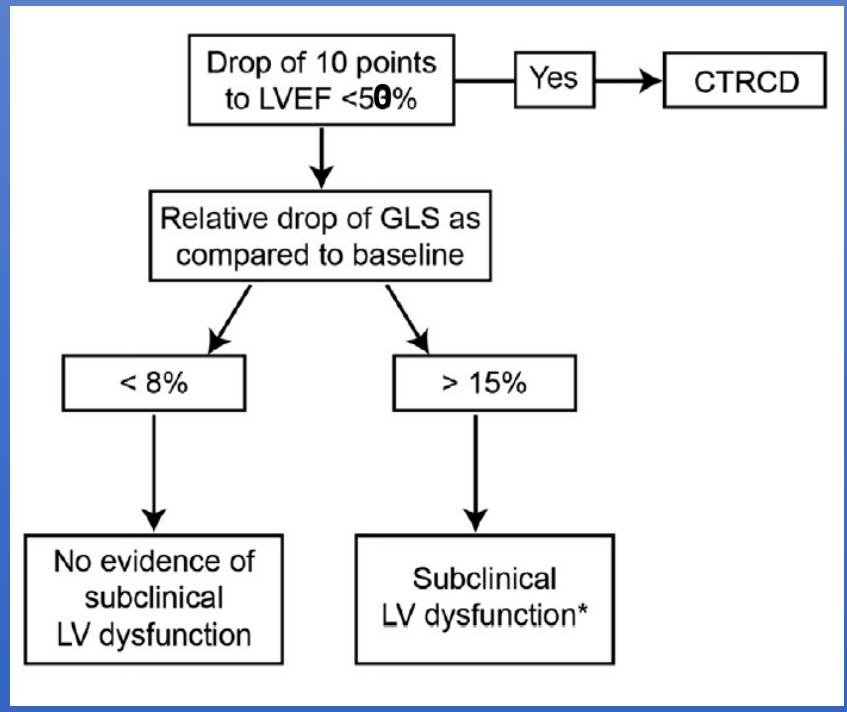
Asymptomatic Drop of 10% of LVEF with an absolute value Between 40% and 50%

In case of increased troponin or GLS drop

Increased Troponin

=

Consider cardioprotective treatment



Take home messages

-Prevention is the corner stone of cardio-oncology

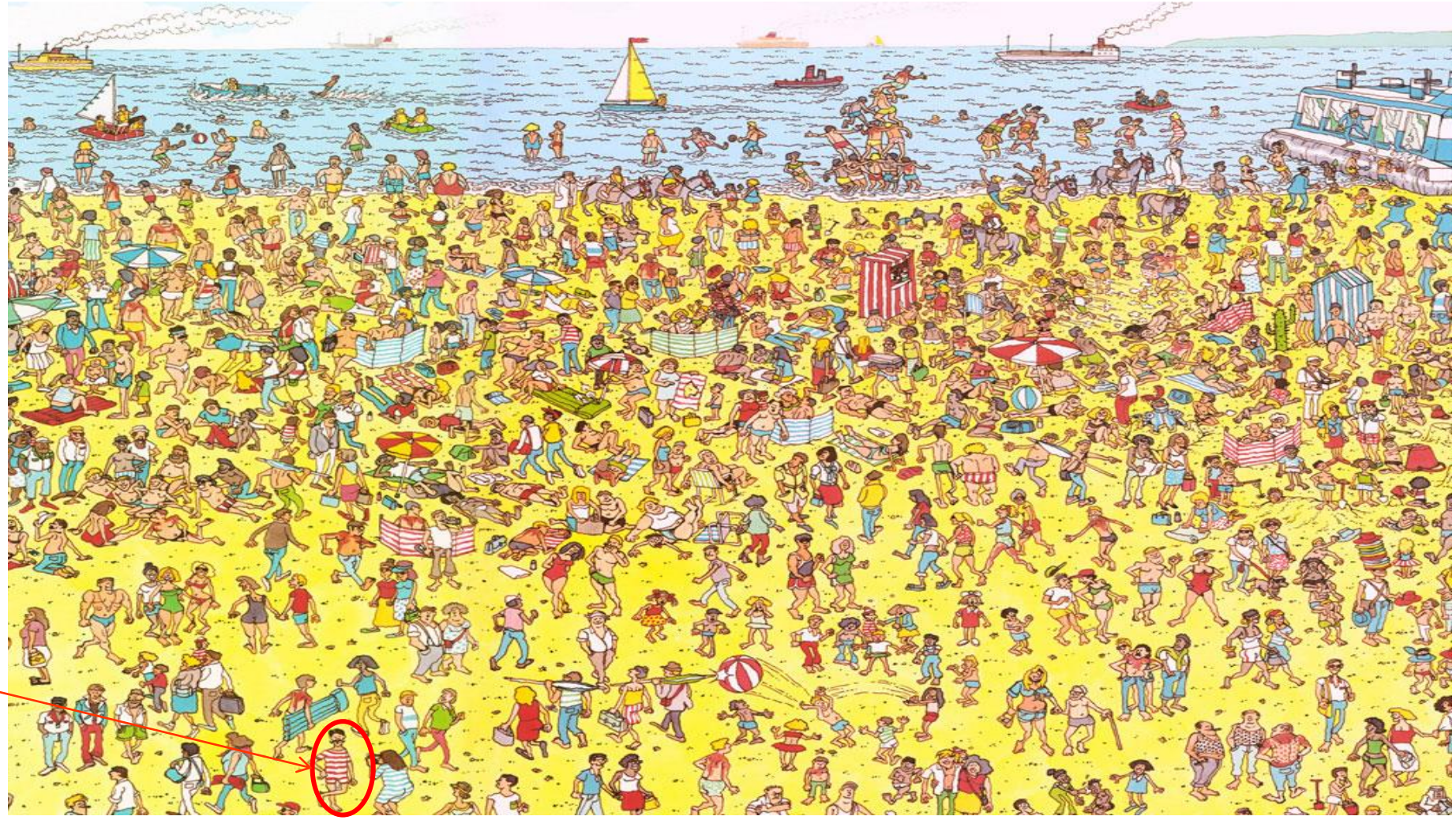
-Combined troponin and GLS is probably the best approach to rule out AIC

-In case of AIC, BB and ACEi/ ARB should be introduced as quickly as possible

-Everything must be done to facilitate hematologic treatment

Thank you for your attention

ccharbonnel@ch-versailles.fr



Charly was here

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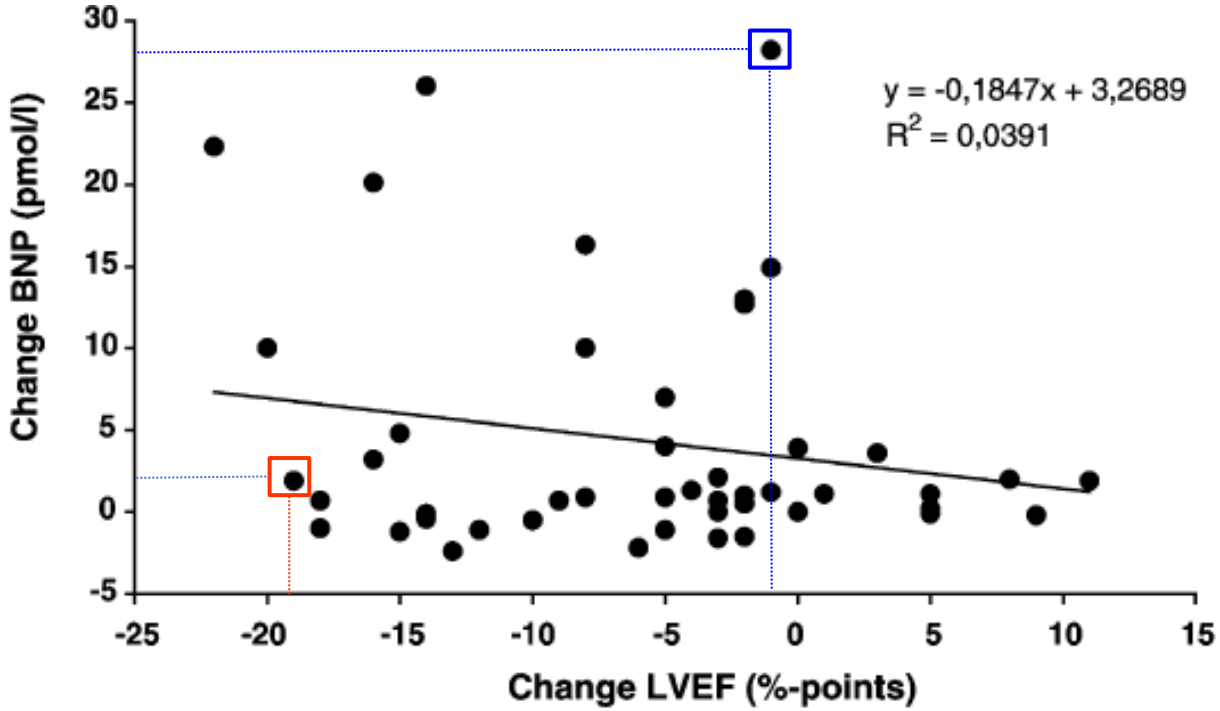
BNP

-107 patients
-Various cancer:
- breast (65%)
- sarcoma
- lymphoma

-Epirubicin or doxorubicin
-BNP before and various point
During treatment



Daugaard et al. eur journal heart failure 2005;7:87

NT Pro-BNP

Table 3 Risk of Cardiotoxicity According to Biomarker Levels at Baseline, Visit 2, and Early Interval Changes (Baseline to Visit 2)

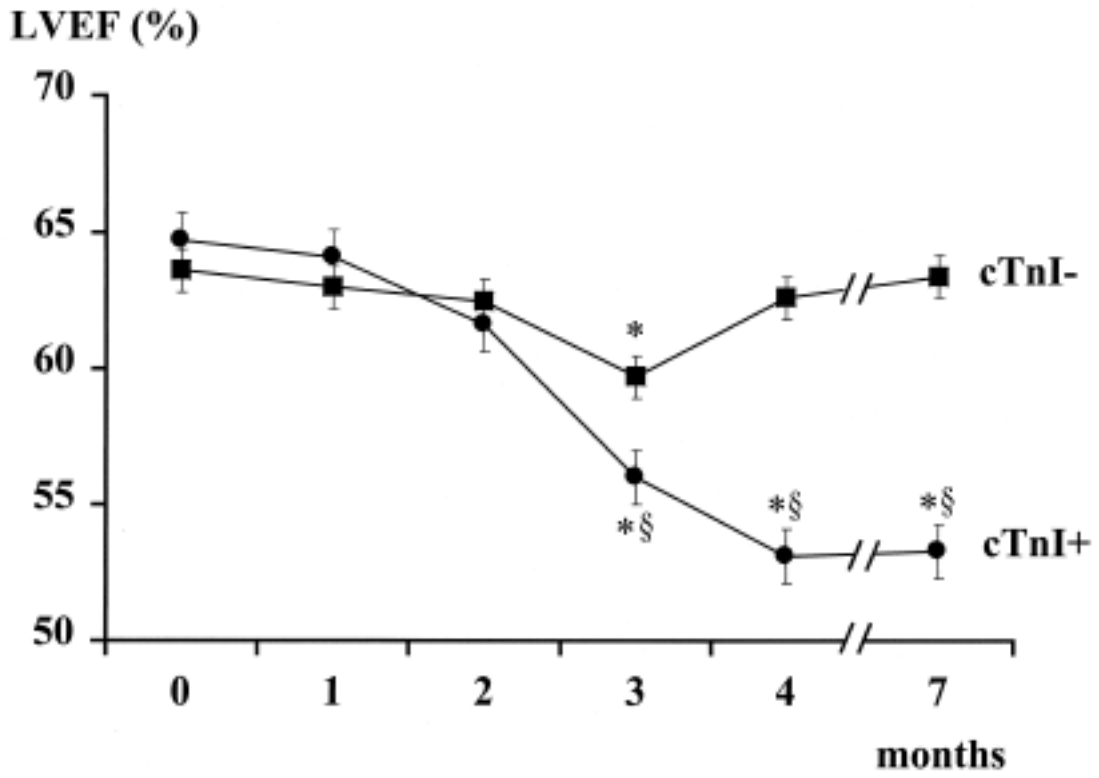
	Baseline		Visit 2		Interval Change	
Biomarker	HR (95% CI) *	p Value†	HR (95% CI) *	p Value†	HR (95% CI) *	p Value†
TnI	1.21 (0.92–1.61)	0.177	1.36 (1.07–1.73)	0.012	1.38 (1.05–1.81)	0.020
NT-proBNP	0.78 (0.48–1.25)	NS	0.89 (0.59–1.35)	NS	1.11 (0.80–1.54)	NS
CRP	1.18 (0.85–1.63)	NS	1.07 (0.72–1.60)	NS	0.95 (0.52–1.73)	NS
GDF-15	0.90 (0.59–1.37)	NS	1.26 (0.89–1.78)	0.189	1.33 (0.93–1.92)	0.118
MPO	0.66 (0.44–1.00)	0.052	1.23 (0.93–1.62)	0.149	1.34 (1.00–1.80)	0.048
PlGF	0.88 (0.55–1.40)	NS	1.17 (0.82–1.65)	NS	1.16 (0.77–1.73)	NS
sFlt-1	1.05 (0.70–1.56)	NS	0.76 (0.54–1.06)	0.109	0.75 (0.51–1.10)	0.139
Gal-3	0.70 (0.44–1.11)	0.128	0.94 (0.62–1.41)	NS	1.33 (0.86–2.05)	0.195

-78 patients
-Breast cancer
-Anthracycline and trastuzumab
-NT ProBNP assessment before chemotherapy and at 3 and 6 months
-No relationship between NT Pro-BNP values and cardiotoxicity

Ky et al. JACC 2014;63:809-16

Troponin

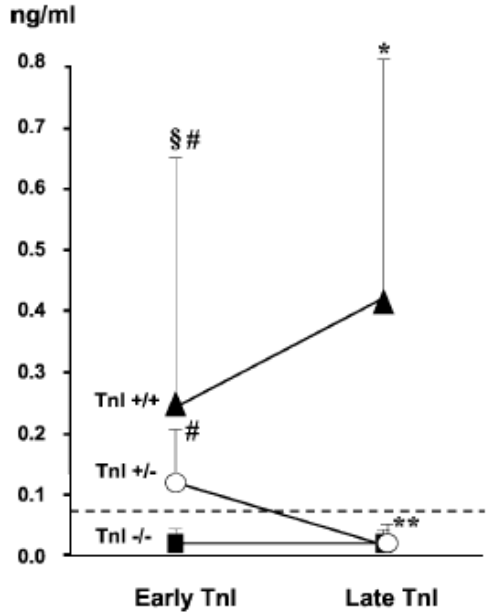
-204 patients
-Troponin I
-Various cancer:
- breast (65%)
- lymphoma (25%)
-TnI before and 12-24-36-72 hours after each cycle
-Cut off value: TnI+≥0.5ng/ml at least at
One of the points of measurement

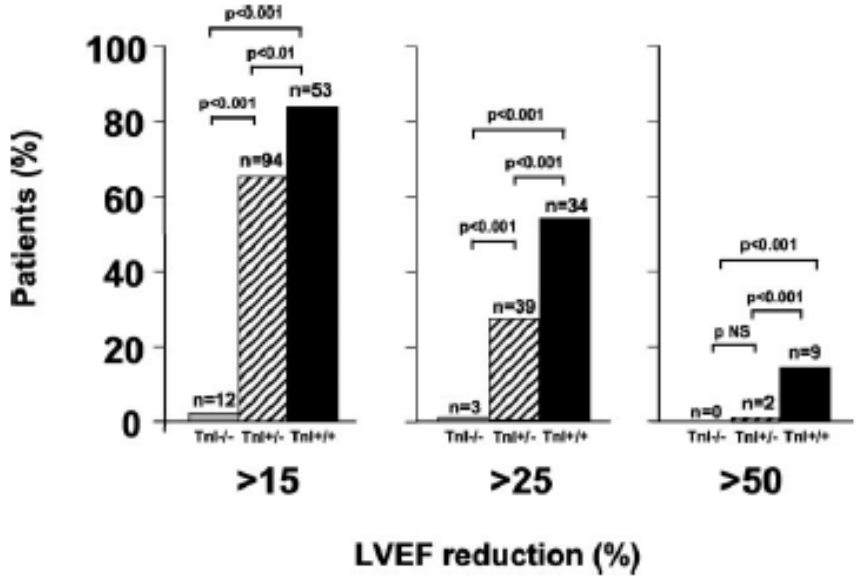


Cardinale et al. JACC 2000; 36:517-22

Troponin

-703 patients
-Troponin I
-Various cancer:
- breast (46%)
- lymphoma (42%)
-Early TnI before and 12-24
36-72 hours after each cycle
-Late TnI at 1 month

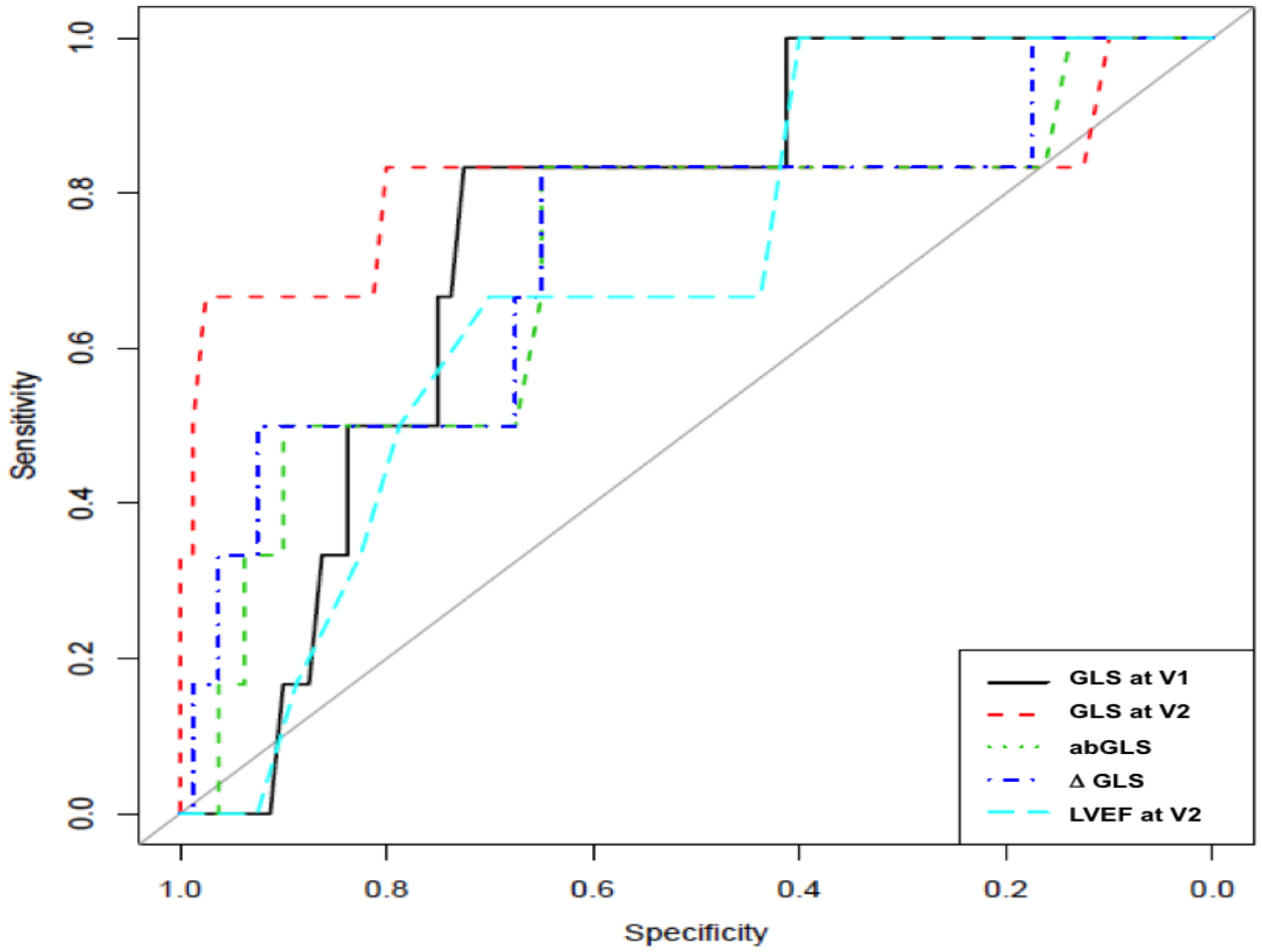




Cardinale et al. Circulation 2004;109:2749-54

What is the best timing for GLS assessment ?

Best threshold to predict cardiotoxicity			
	Threshold	Sensitivity	Specificity
GLS at V1	-19.95	0.833 [0.5 - 1]	0.725 [0.625 - 0.813]
GLS at V2	-17.45	0.667 [0.333 - 1]	0.975 [0.938- 1]
abGLS	-0.45	0.833 [0.5 - 1]	0.65 [0.55 - 0.75]
ΔGLS	-2.256	0.833 [0.5 - 1]	0.65 [0.55 - 0.75]
LVEF at V2	66.5	1 [1- 1]	0.4 [0.288 - 0.5]



Charbonnel C et al. Eur Heart J Cardiovasc Imaging. 2017 Apr 1;18(4):392-401

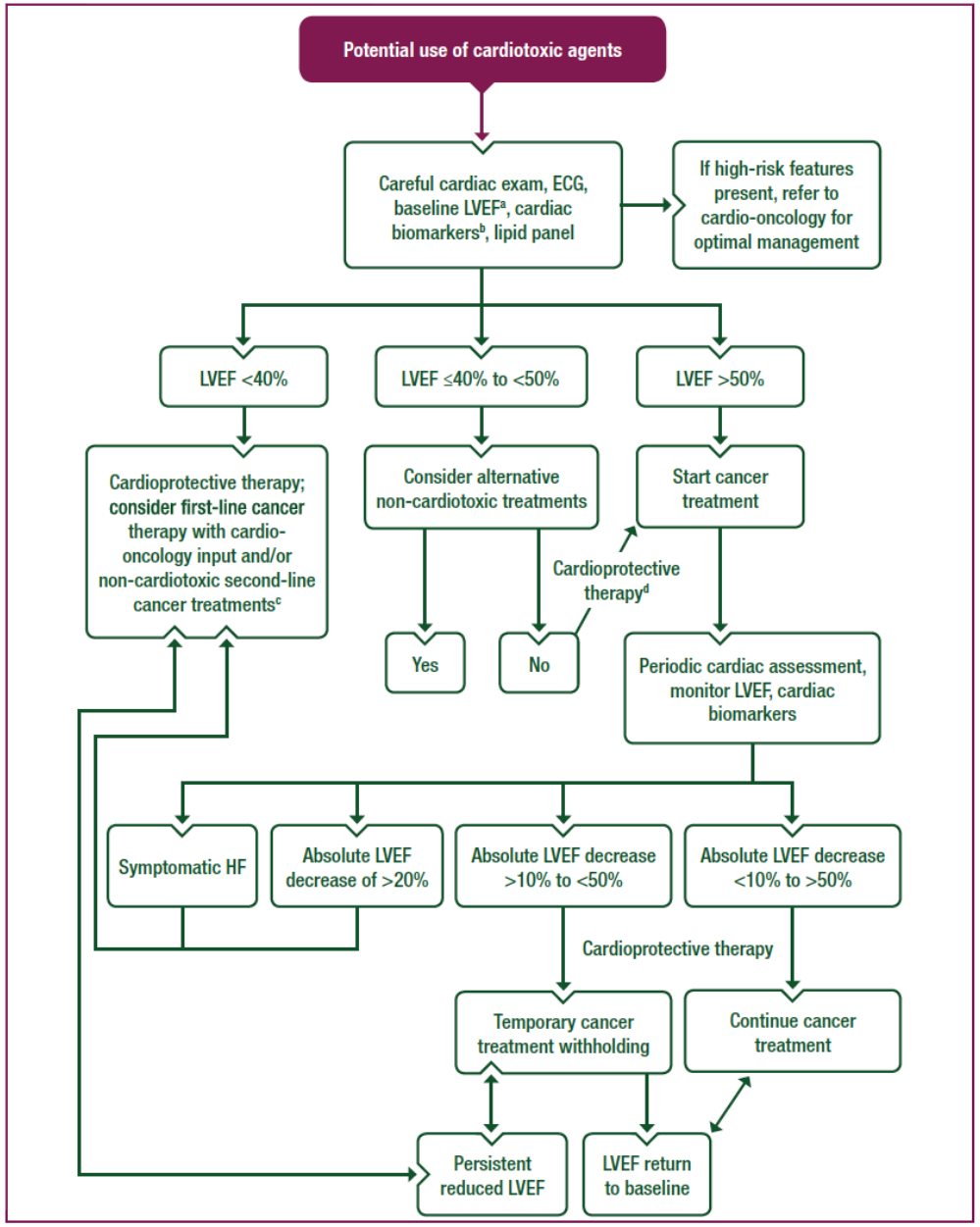


Figure 1. Proposed monitoring and management approach for patients undergoing potentially cardiotoxic anticancer therapy.
ECG, electrocardiogram; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction.
[a] LVEF assessment may include GLS as well if available.
[b] Cardiac biomarkers include: troponin and natriuretic peptides.
[c] Under certain circumstances, if cardiotoxic therapy is the only viable option for anticancer treatment, it can be considered after close collaboration with cardio-oncology.
[d] Cardioprotective therapy includes: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, carvedilol, spironolactone ± statin.

Curigliano G et al. Ann Oncol. 2020 Feb;31(2):171-190