Dilluns 1 de desembre 2014. Societat Catalana de Cardiologia

Prevenció de la cardiotoxicitat del tractament del càncer

programa d'onco-cardiologia

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complicacions cardiovasculars dels tts oncològics:

- *disfunció ventricular i insuficiència cardiaca*

  IECA
  ~~antag Ca~~

- *vasculars*
  - hipertensió arterial — *bevacizumab, sorafenib, sunitinib, interferon*
  - trombosi arterial — *cisplatí, erlotinib, bleomicina,*
  - trombosi venosa — *vimblastina, paclitaxel*
  - isquèmia miocàrdica — *5-fluorouracil, capecitabina*

  nitrats-antag Ca ?
  re-ttm ?
  alternatives ttm
  vigilància

- *arrítmiques*

  trióxide d'arsènic, dasatinib, lapatinib
  paclitaxel, talidomida

  observació ECG

- *estructurals*
  - malaltia coronària
  - pericarditis / vessament pericàrdic
  - constricció pericàrdica
  - valvulopaties

  radioteràpia

radioteràpia

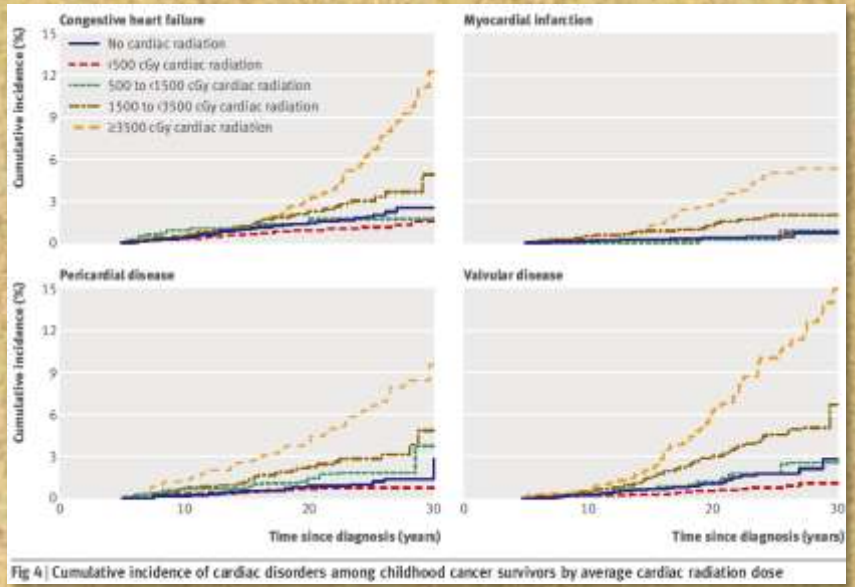
-complicacions cròniques
amb incidència progressiva

-↓ en el futur per avenços en RDT

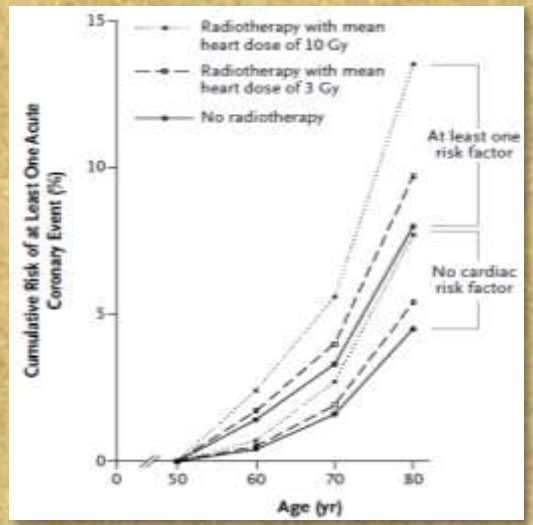
- malaltia coronària prematura
afectant artèries proximals

- sinèrgic amb altres factors de risc

- control de factors de risc,
seguiment clínic a llarg plaç
(tests de detecció d'isquèmia ?)



DA Mulrooney, BMJ 2009 (RDT entre 1970-1986)



SC Darby, NEJM 2013

disfunció ventricular i insuficiència cardiaca

fàrmacs de tipus I:

- antraciclines lesionen en el moment del tractament
- la reserva normal del cor compensa inicialment
- *multiple hit hypothesis* *(LW Jones, JACC 2007)*
- la forma més freqüent de cardiotoxicitat és la tardana

fàrmacs de tipus II:

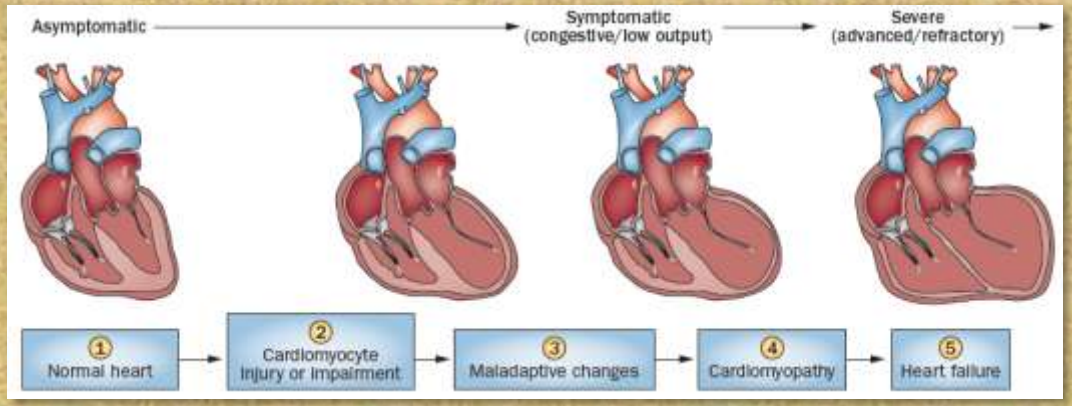
- atordiment
- disfunció reversible ( )
- sense cardiotoxicitat a llarg plaç

estratègies per prevenir la cardiotoxicitat

→ minimització de la lesió / prevenció primària

→ detecció precoç de dany miocàrdic

→ seguiment clínic-FE



SE Lipshultz,
Nat Rev Clin Oncol 2013

estratègies per prevenir la cardiotoxicitat

→ minimització de la lesió / prevenció primària

→ detecció

limfomes
leucèmies
sarcomes
n mama

→ seguiment

· alternatives terapèutiques

· mínima dosis possible

· infusió contínua vs bolus

· anàlegs d'antraciclines

· antraciclines liposomals

· dexrazoxane

· carvedilol

· IECA - ARAII

· estatines

New Insight Into Epirubicin Cardiac Toxicity: Competing Risks Analysis of 1097 Breast Cancer Patients

Variable	β	HR	95% CI	*P* value
Predictors for risk of developing cardiotoxicity				
Cumulative dose of epirubicin (per 100 mg/m² increase)	0.334	1.40	1.21 to 1.61	<.001
Predisposition to heart disease†	1.102	3.01	2.00 to 4.53	<.001
Previous antihormonal‡ treatment for relapse	0.628	1.87	1.23 to 2.85	.003
Mediastinal irradiation	0.734	2.08	1.27 to 3.41	.004
Every additional year of age at epirubicin start§	0.025	1.03	1.01 to 1.05	.012
CMF at cumulative dose of epirubicin 500 mg/m²	−1.350	0.26	0.07 to 1.02	.053
CMF at cumulative dose of epirubicin (per 100 mg/m²)‖	0.316	1.37	1.08 to 1.74	.0092
Predictors for risk of overall mortality				
Cumulative dose of epirubicin during the first 3 mo of follow-up (per 100 mg/m²)	−1.047	0.35	0.25 to 0.48	<.001
Cumulative dose of epirubicin during mo 4–6 (per 100 mg/m²)	−0.504	0.60	0.54 to 0.68	<.001
Cumulative dose of epirubicin during and after mo 7 (per 100 mg/m²)	−0.106	0.90	0.87 to 0.93	<.001
Every additional year of age at epirubicin start§	0.012	1.01	1.00 to 1.02	.003
Adjuvant CMF	0.254	1.29	1.11 to 1.50	.001
Two or more metastatic sites at start of epirubicin treatment	0.721	2.06	1.77 to 2.39	<.001

M Ryberg, J Natl Cancer Inst 2008

estratègies per prevenir la cardiotoxicitat

→ minimització de la lesió / prevenció primària

→

→

daunorubicina

doxorubicina (=adriamicina)

epirubicina

idarubicina

· alternatives terapèutiques

· mínima dosis possible

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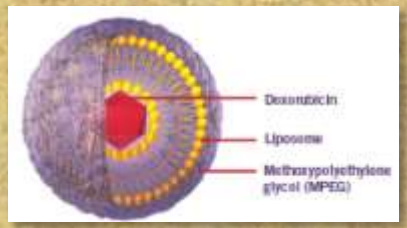
estratègies per prevenir la cardiotoxicitat

→ minimització de la lesió / prevenció primària

- 

antraciclines liposomals

- *521 n de mama:*
  IC / disf VE: 24,7% vs 9,2%
  (EC Van Dalen, Cochrane Database Syst Rev 2010)

Continuous doxorubicin infusion (48–72 h)	$67/50 mg†
Liposomal doxorubicin	$2,851/50 mg

  P Vejpongsa, JACC 2014

- *aprobat per a:* (EMA)
  -n mama metastàtica
  -n ovari avançada
  -mieloma múltiple 2ª línia
  -sarcoma Kaposi

· alternatives terapèutiques

· mínima dosis possible

· infusió contínua vs bolus

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· estatines

estratègies per prevenir la cardiotoxicitat

Table 3 Strategies evaluated for cardioprotective potential in the presence of anthracyclines

Class	Example
Antihistamines	Chlorpheniramine
	Ketotifen
	Disodium cromoglycate
Antioxidants	N acetyl cysteine
	α tocopherol
	Carvedilol
	Coenzyme Q10
	Resveratrol
Chelating agents	Dexrazoxane
Cytokines	Erythropoietin
	Granulocyte stimulating factor
	Thrombopoietin
Energy regulators	Adenosine
	Carnitine
Enzyme inhibitors	COX 2 inhibitors
	Digoxin
	Amrinone
Exercise	
Hormones	Oestrogen
Inhibitors of mediator release	Cromolyn
Ion regulators	Calcium channel blockers
	α and β adrenergic antagonists
Membrane stabilisers	Steroids
	Taurine
Metabolic agents	Probucol
	Lovastatin
Miscellaneous agents	Bismuth
	Zinc
	Cadmium
Uptake inhibitors	Tetracyclines

SE Lipshultz, Heart 2008

- alternatives terapèutiques
- mínima dosis possible
- infusió contínua vs bolus
- anàlegs d'antraciclines
- antraciclines liposomals
- dexrazoxane
- carvedilol
- IECA - ARAII
- estatines

estratègies per prevenir la cardiotoxicitat

→minimització de la lesió / prevenció primària

dexrazoxane

8 estudis:
IC : 8,7% vs 1,4%
(EC Van Dalen, Cochrane Database Syst Rev 2011)

-eficàcia antitumoral?
-↑ risc de leucèmia/sd mielodisplàsic

→aprobat per neo de mama metastásica

· alternatives terapèutiques

· mínima dosis possible

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· carvedilol

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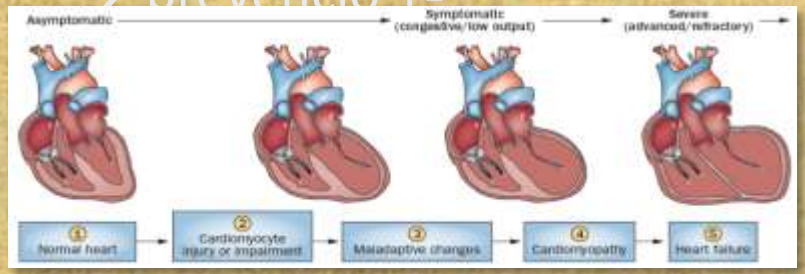
· estatines

estratègies per prevenir la cardiotoxicitat

→ detecció precoç de...

→ prevenció 1ª



· alternatives terapèutiques

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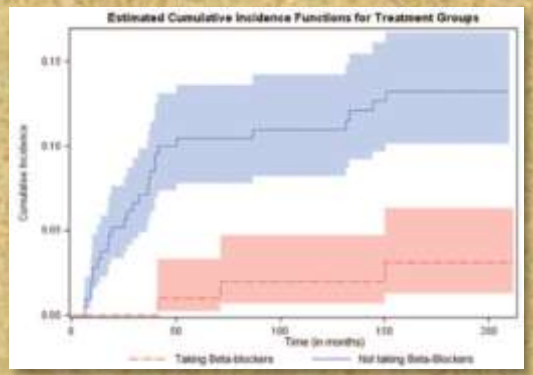
prevenció primària

- *betabloquejants*



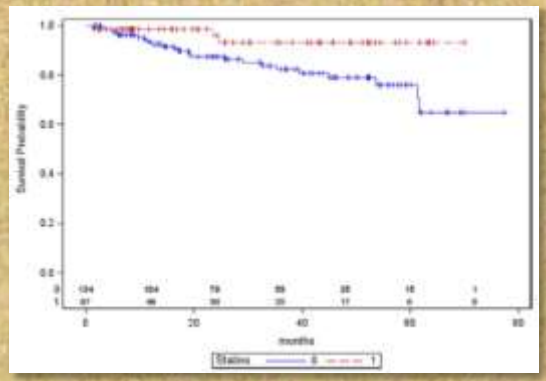
S Seicean, Circ Heart Fail 2013

- *inhibidors SRAA*

Risk factor	Odds ratio	90% CI	*P*
Age	1.038	1.005–1.072	.03
Use of ace-inhibitor	0.267	0.057–1.253	.09

AH Blaes, Breast Cancer Res Treat 2010

- *estatines*



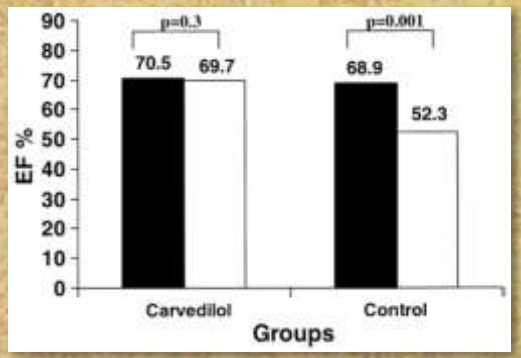
S Seicean, JACC 2012

prevenció primària

- *betabloquejants*

-n=50
-carvedilol 12,5 mg/d
-seguiment 6 mesos

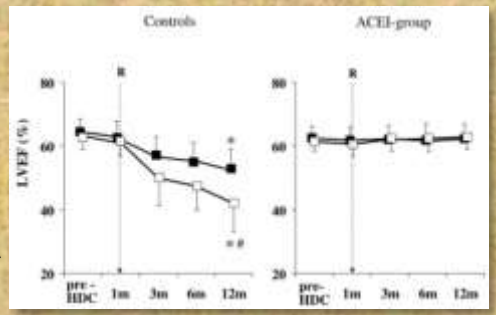
N Kalay, JACC 2006



- *inhibidors SRAA*

-n=114
-enalapril 20 mg/d
-seguiment 12 mesos

D Cardinale, Circulation 2006



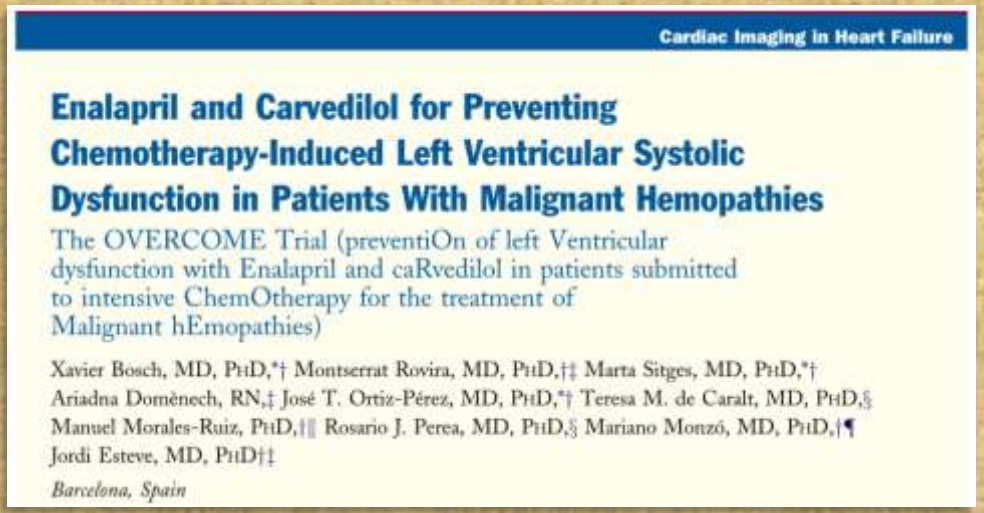
- *estatines*

-n=40, -atorvastatina 40 mg/d; -seguim 6 mesos

	Statin Group (n = 20)	Control Group (n = 20)	p Value
LVEF (%)			
Baseline	61.3 ± 7.9	62.9 ± 7.0	
After 6 months	62.6 ± 9.3	55.0 ± 9.5	
Mean change	1.3 ± 3.8	−7.9 ± 8.0	<0.001

Z Acar, JACC 2011

prevenció primària



Cardiac Imaging in Heart Failure

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)

Xavier Bosch, MD, PhD,*† Montserrat Rovira, MD, PhD,†‡ Marta Sitges, MD, PhD,*† Ariadna Domènech, RN,‡ José T. Ortiz-Pérez, MD, PhD,*† Teresa M. de Caralt, MD, PhD,§ Manuel Morales-Ruiz, PhD,†‖ Rosario J. Perea, MD, PhD,§ Mariano Monzó, MD, PhD,‖¶ Jordi Esteve, MD, PhD†‡

Barcelona, Spain

X Bosch, JACC 2014

Randomització 1:1 a rebre enalapril i carvedilol / no rebre

-enalapril dosis inicial de 2.5 mg/12 h (1.25 mg si TAs entre 90 y 100 mmHg) i augment progressiu / 3-6 dies fins a 5 mg - 10 mg /12 h si TAs >90 mm Hg i creat <2.5 mg/dl

-carvedilol dosis inicial de 6.25 mg/12 hs augmentant progressivament / 3 -6 días fins 12.5 mg - 25 mg /12 h en absència d'insuficiència cardiaca, bradicàrdia significativa o bloqueig AV

prevenció primària

Table 1 Baseline Clinical Differences Between Groups

	Intervention (n = 45)	Control (n = 45)	p Value
Age (yrs)	49.7 ± 13.9	50.9 ± 13.2	0.67
Women (%)	18 (40)	21 (47)	0.52
BSA (m^2)	1.86 ± 0.26	1.83 ± 0.21	0.62
Hypertension (%)	6 (13)	8 (18)	0.77
Hypercholesterolemia (%)	7 (16)	3 (7)	0.32
Statin treatment (%)	4 (9)	2 (4)	0.68
Diabetes (%)	3 (7)	1 (2)	0.62
Smokers (%)	13 (29)	4 (9)	0.03
Patient cohort (%)			1.00
Acute leukemia	18 (40)	18 (40)	
Autologous PBSCT	27 (60)	27 (60)	
SBP (mm Hg)	118 ± 17	118 ± 16	1.00
DBP (mm Hg)	73 ± 12	74 ± 10	0.66
HR (beats/min)	75 ± 12	78 ± 13	0.24
eC_{Cr} (ml/min)	105 ± 30	100 ± 30	0.30
Hemoglobin, g/l	107.8 ± 17	108 ± 20	0.97
TnI (ng/ml)	0.013 ± 0.008	0.013 ± 0.010	0.80
BNP (ng/l)	19 (9, 38)	21 (12, 35)	0.88
LVEF (%)	62 ± 5.9	63 ± 5.9	0.50

Table 2 Anticancer Treatment Received by Patients Prior to and During the Study Period

	Intervention (n = 45)	Control (n = 45)	p Value
Radiotherapy			
Prior (%)	6 (13)	2 (4)	0.27
During study (%)	6 (13)	2 (4)	0.27
Total (%)	12 (27)	4 (9)	0.05
Chemotherapy			
Prior (%)	27 (60)	27 (60)	1.00
No. of lines of therapy	1.4 ± 1.6	1.6 ± 1.9	0.47
During study	45 (100)	45 (100)	1.00
No. of cycles	1.73 ± 1.5	1.44 ± 0.8	0.27
Anthracyclines			
Prior (%)	19 (42)	17 (38)	0.67
Dose (mg/m^2)	151 ± 208	108 ± 150	0.26
During study (%)	18 (40)	18 (40)	1.00
Dose (mg/m^2)	139 ± 188	133 ± 182	0.87
Total (%)	37 (82)	35 (78)	
Dose (mg/m^2)	290 ± 189	241 ± 162	0.15
HSCT during study (%)	37 (82)	34 (78)	0.76

enalapril 8.2 ± 5.9 mg /dia

carvedilol 26.1 ± 18.2 mg /dia

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)

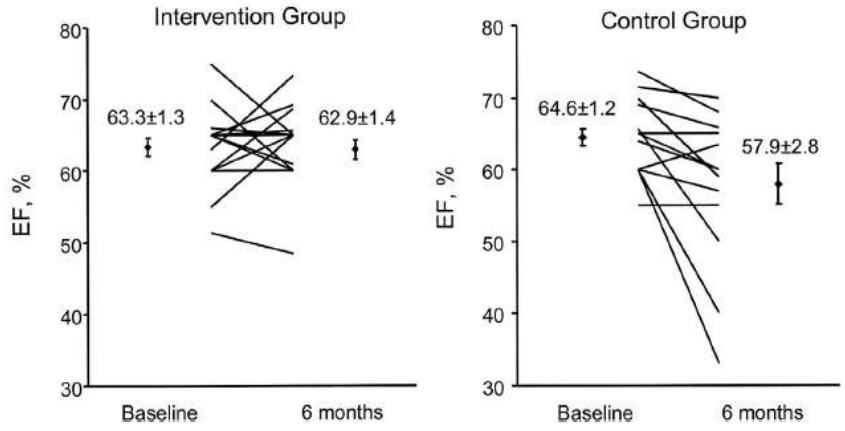
prevenció primària

Table 3 Differences in Change in LVEF Between the Intervention and Control Groups

	Enalapril + Carvedilol	Control	Intergroup Difference	p Value
Echocardiography				
LVEF (%)	n = 42	n = 37		
Baseline	61.67 ± 5.11	62.59 ± 5.38		
6 months	−0.17 (−2.24 to 1.90)	−3.28 (−5.49 to −1.07)	−3.11 (−6.10 to −0.11)	0.04

→ *malignancies undergoing PBSCT*: - 1.01 (95% CI: 4.46 to 2.45, p=0.56)

→ *acute leukemia*: - 6.38 (95% CI: 11.88 to 0.87, p=0.025)



Change From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)

TABLE 3 Summary of β-Blocker and/or ACE Inhibitor Studies for Primary Prevention of Anthracycline-Induced Cardiotoxicity

First Author (Ref. #)	Medication	Patients*	Follow-Up, Months	Results
Kalay et al. (54)	Carvedilol 12.5 mg daily vs. placebo	50 (25/25)	6	Placebo: LVEF 68.9% → 52.3%† Carvedilol: LVEF 70.5% → 69.7%
Georgakopoulos et al. (55)	Metoprolol‡ vs. enalapril‡ vs. placebo§	125 (42/43/40)	31	Cardiotoxicity incidence not statistically different among 3 groups No difference in echocardiographic parameters among 3 groups at 12 months
Kaya et al. (53)	Nebivolol 5 mg daily vs. placebo‖	45 (27/18)	6	Placebo: LVEF 66.6% → 57.5%† Nebivolol: LVEF 65.6% → 63.8%
Bosch et al. (52)	Enalapril‡ + carvedilol‡ vs. no treatment‖	90 (45/45)	6	Control: LVEF 64.6% → 57.9%† Enalapril + carvedilol: LVEF 63.3% → 62.9% TnI levels not significantly different between 2 groups (p = 0.59)

P Vejpongsa, JACC 2014

edat m: 49 a, tractament de limfomes (388 mg/m² doxorubicina)

metoprolol (88 mg/d) vs enalapril (11 mg/d) vs placebo

sense diferències en FE:

	Metoprolol group	Enalapril group	Control group
Baseline	65.7 (5.0)	65.2 (7.1)	67.6 (7.1)
12 months	63.3 (7.4)	63.9 (7.5)	66.6 (6.7)

prevenció primària

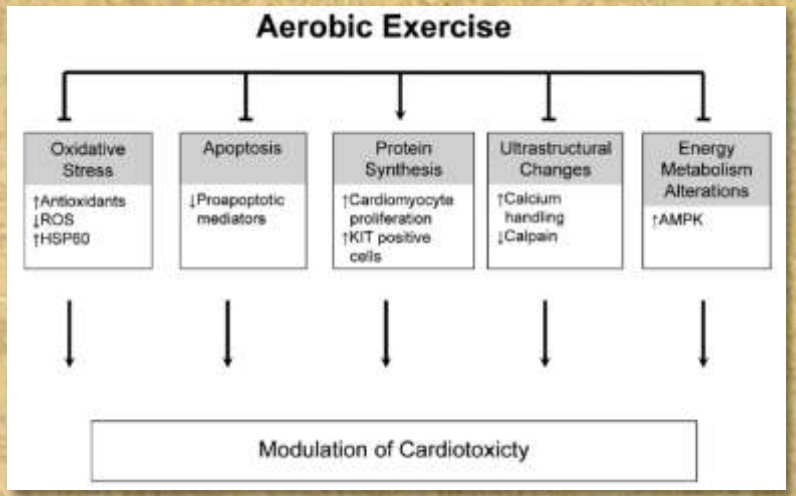
Modulation of Anthracycline-Induced Cardiotoxicity by Aerobic Exercise in Breast Cancer

Current Evidence and Underlying Mechanisms

Jessica M. Scott, PhD; Aarif Khakoo, MD; John R. Mackey, MD; Mark J. Haykowsky, PhD; Pamela S. Douglas, MD; Lee W. Jones, PhD

JM Scott, Circulation 2011

Author	Animal Species	Doxorubicin Schedule	Exercise	Outcome
Ascensao et al (2011)[36]	Rats	Bolus (20 mg/kg)	Acute exercise (60 min) before doxorubicin	Maintained mitochondrial function in exercise group
Ascensao et al (2005)[37]	Mice	Bolus (20 mg/kg)	60–90 min/d; 5 d/wk; 14 wk before doxorubicin	↓ ROS production, oxidative damage, and apoptosis in ET group
Ascensao et al (2005)[38]	Mice	Bolus (20 mg/kg)	60–90 min/d; 5 d/wk; 14 wk before doxorubicin	↑ Glutathione, HSP60 in ET group
Combs et al (1979)[39]	Mice	Bolus (23 mg/kg)	Acute exercise (30 min) after doxorubicin	Improved survival in exercise group
Chicco et al (2006)[40]	Rats	Bolus (15 mg/kg)	20 min/d; 5 d/wk; 2 wk during doxorubicin	Maintained dP/dt_{max}, dP/dt_{min}, and coronary flow in ET group
Chicco et al (2005)[41]	Rats	10 μmol/L for 60 min (perfused hearts)	Voluntary exercise; 8 wk before doxorubicin	↑ HSP72, maintained dP/dt_{max}, dP/dt_{min} in ET group
Chicco et al (2006)[42]	Rats	2.5 mg/kg; 3 d/wk for 2 wk	20–60 min/d; 5 d/wk; 12 wk before doxorubicin	↑ HSP72, maintained dP/dt_{max}, dP/dt_{min} in ET group
Heon et al (2003)[43]	Rats	Bolus (3 mg/kg)	10–45 min/d; 7 d/wk; 2 wk after doxorubicin	↓ Expression of proapoptotic markers
Hydock et al (2009)[44]	Rats	2.5 mg/kg; 1 d/wk for 6 wk	Voluntary exercise; 6 wk during doxorubicin	Maintained α-MHC isoform in ET group
Hydock et al (2007)[45]	Rats	Bolus (10 mg/kg)	Voluntary exercise; 10 wk before doxorubicin	Attenuated ↑ β-MHC isoform, maintained dP/dt_{max}, dP/dt_{min} in ET group
Ji and Mitchell (1994)[46]	Rats	Bolus (4 mg/kg; twice)	Acute exercise (60 min) before doxorubicin	Maintained mitochondrial respiration
Jones et al (2011)[47]	Mice	8 mg/kg; 1 d/wk for 4 wk	45 min/d; 5 d/wk; 8 wk during doxorubicin	↓ LV dysfunction, attenuated ↑ in SERCA2a and ANP in ET group
Jones et al (2011)[47]	Humans	60 mg/m^2	60 min/d; 3 d/wk; 12 wk during doxorubicin	↑ Aerobic capacity and attenuated ↑ in ANP in ET group
Kavazis et al (2010)[48]	Rats	Bolus (20 mg/kg)	60 min/d; 5 consecutive days (estimated work rate of 70% Vo_2max) before doxorubicin	↓ ROS production, oxidative damage, attenuated ↑ in calpain in ET group
Kanter et al (1985)[49]	Rats	4 mg/kg; 2 d/wk for 7 wk	60 min/d; 5 d/wk; 21 wk during doxorubicin	↓ Histological damage in ET group
Werner et al (2008)[70]	Rats	Bolus (22.5 mg/kg)	Voluntary exercise; 21 d before doxorubicin	↓ p53 expression in ET group
Wonders et al (2008)[71]	Rats	Bolus (15 mg/kg)	Acute exercise (60 min) before doxorubicin	↑ LVESP, dP/dt_{max}, dP/dt_{min} in exercise group



-múltiples beneficis

-prevenir / tractar cardiotoxicitat ?

-utilitat de programes de rehabilitació ?

estratègies per prevenir la cardiotoxicitat

→ minimització de la lesió / prevenció primària

als de ↑ risc

- *-re-tractament amb antraciclines*
- *-FE 50-55%*
- *-RDT mediastínica*
- *-HTA*
- *-cardiopatia de base*
- *-estratificació genètica / metabòlica*

IECA ?

betabloq

IECA + betabloq

Peripheral blood leukocyte Topoisoemrase 2b:

21 pts FE<50% dox≤ 250 mg/m² → 0.4 ± 0.28 ng/mg

15 pts FE≥50% dox≥ 450 mg/m² → 0.23 ± 0.1 ng/mg p=0.026

P Vejpongsa, Circulation 2013

estratègies per prevenir la cardiotoxicitat

→ minimització

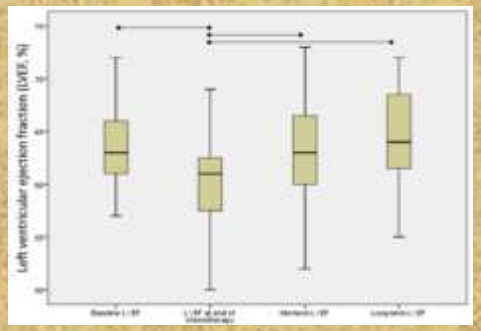
→ detecció precoç de dany miocàrdic → ttm cardiològic vigilància

→ ttm oncològic

→ seguiment

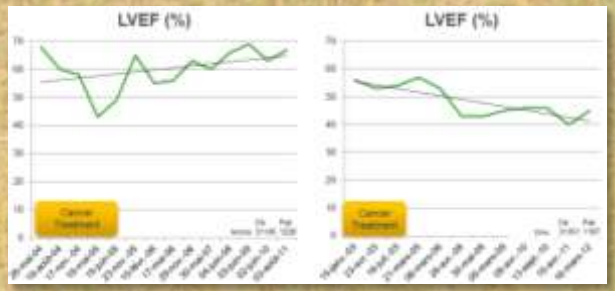
detecció precoç de dany miocàrdic

- (fracció d'ejecció del VE)
  - - FEVE deprimida = dany molt extens (?)
  - - ↓ FEVE inicial = ↓ FEVE tardana (??)



M Lotriente, Am J Cardiol 2013

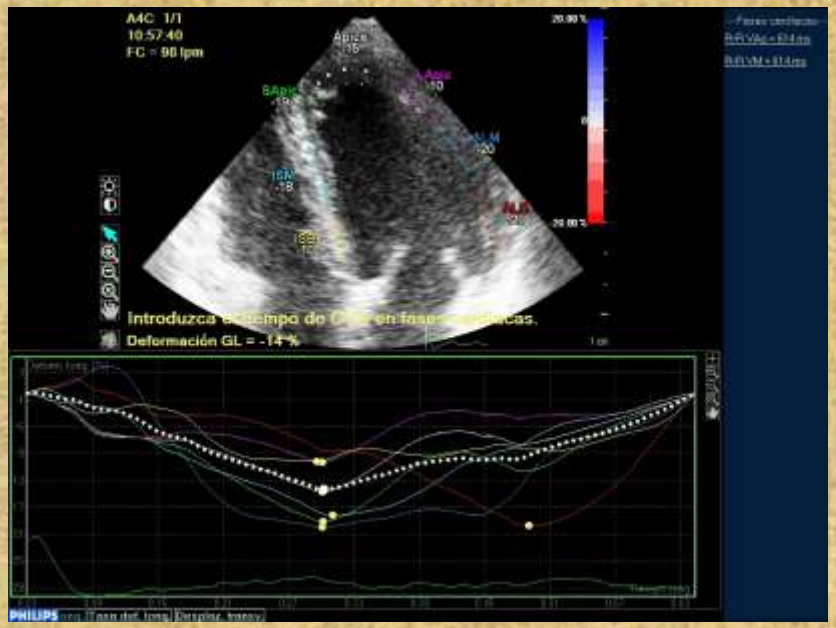
- strain ecocardiogràfic
  - ***G**lobal **L**ongitudinal **S**train*

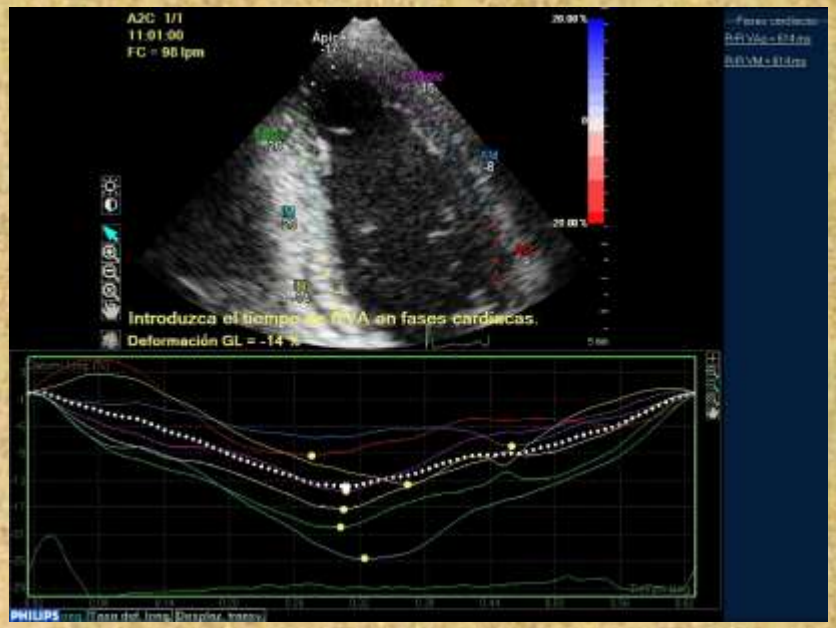


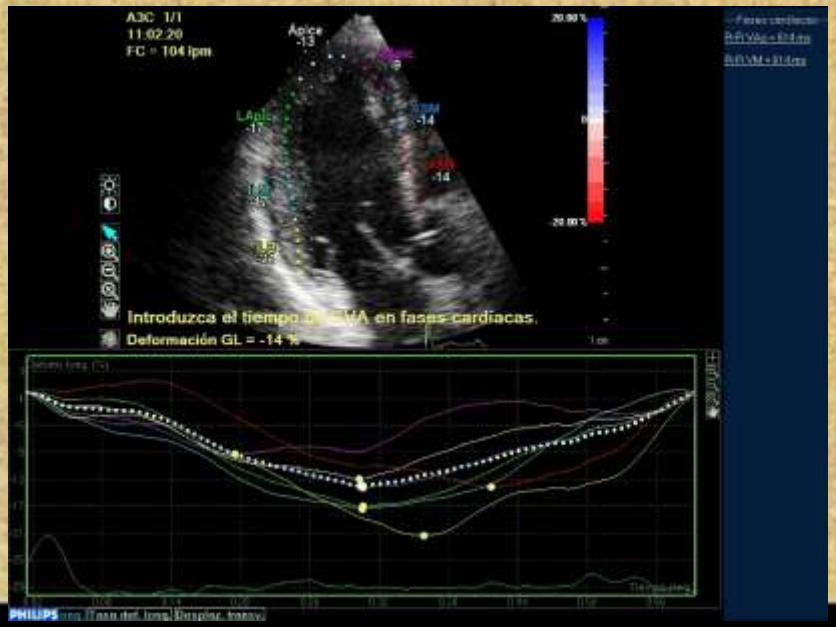
TM Suter

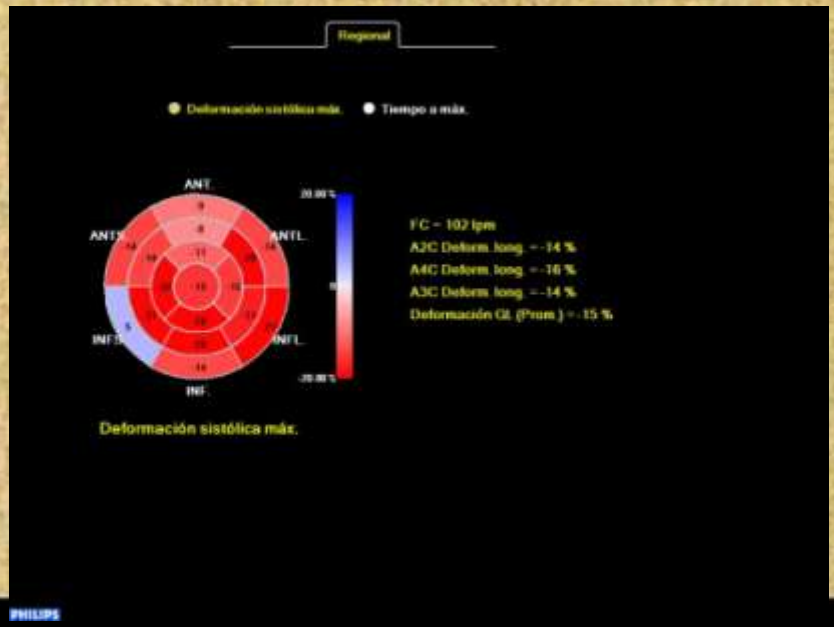
- biomarcadors
  - *troponina*
  - *pèptids natriurètics*
  - *. . .*

strain ecocardiogràfic









strain ecocardiogràfic

Assessment of Echocardiography and Biomarkers for the Extended Prediction of Cardiotoxicity in Patients Treated With Anthracyclines, Taxanes, and Trastuzumab

Heloisa Sawaya, MD, PhD; Igal A. Sebag, MD; Juan Carlos Plana, MD; James L. Januzzi, MD; Bonnie Ky, MD, MSCE; Timothy C. Tan, MBBS, PhD; Victor Cohen, MD; Jose Banchs, MD; Joseph R. Carver, MD; Susan E. Wiegers, MD; Randolph P. Martin, MD; Michael H. Picard, MD; Robert E. Gerszten, MD; Elkan F. Halpern, PhD; Jonathan Passeri, MD; Irene Kuter, MD; Marielle Scherrer-Crosbie, MD, PhD

H Sawaya, Circ Cardiovasc Imaging 2012

	Before Treatment	Postanthracyclines (3 Mo)	6 Mo	9 Mo	12 Mo	End of Treatment
LVEF, %	64±5	62±5*	59±5†	58±5†	58±6†	59±6†
Longitudinal strain, %	21±2	19±2†	18±3†	18±3†	19±2†	19±2†
Radial strain, %	53±15	50±17*	43±16‡	37±16‡	34±16†	41±17‡
Circumferential strain, %	18±4	16±4‡	15±3‡	15±3‡	15±3‡	16±3§
UsTnI, pg/mL	1.3 (0.7–6)	23 (10–42)*	14 (8–28)*	9 (6–16)*	6 (3–15)*	6 (3–11)*
NT-proBNP, pg/mL	71 (37–139)	75 (34–117)	59 (32–100)	62 (39–109)	61 (32–113)	75 (38–148)
ST2, pg/mL	26 (23–35)	27 (23–42)	26 (21–32)	27 (21–33)	25 (22–32)	25 (22–31)

Predictors (Measured At the Completion of Anthracyclines)	Sensitivity	Specificity	PPV	NPV
Long strain <19%	17/23 (74%) (0.51–0.90)	40/55 (73%) (0.59–0.84)	17/32 (53%)	40/46 (87%)
usTnI >30 pg/mL	11/23 (48%) (0.27–0.69)	40/55 (73%) (0.59–0.84)	11/26 (44%)	40/52 (77%)
Long strain <19% and usTnI>30 pg/mL	8/23 (35%) (0.16–0.57)	51/55 (93%) (0.82–0.98)	8/12 (67%)	51/66 (77%)
Long strain <19% or usTnI>30 pg/mL	20/23 (87%) (0.66–0.97)	29/55 (53%) (0.39–0.66)	20/46 (43%)	29/32 (91%)

strain ecocardiogràfic

Valor afegit:

- ✓ *superior a FEVE en pronòstic*
- ✓ *capacitat de detectar disfunció precoç*
- ✓ *reproduïble als estudis*

Limitacions:

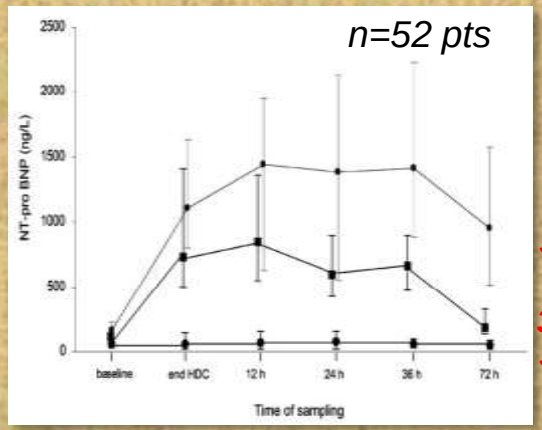
- ✓ *reproduïble a la vida real ?*
- ✓ *depén de qualitat d'imatge*
- ✓ *canvis evolutius més que valors absoluts*
- ✓ *mateix aparell i operador*

biomarcadors: pèptids natriurètics

N-Terminal Pro-B-Type Natriuretic Peptide after High-Dose Chemotherapy: A Marker Predictive of Cardiac Dysfunction?

Maria T. Sandri,[1*] Michela Salvatici,[1] Daniela Cardinale,[2] Laura Zorzino,[1] Rita Passerini,[1] Paola Lentati,[1] Maria Leon,[3] Maurizio Civelli,[2] Giovanni Martinelli,[4] and Carlo M. Cipolla[2]

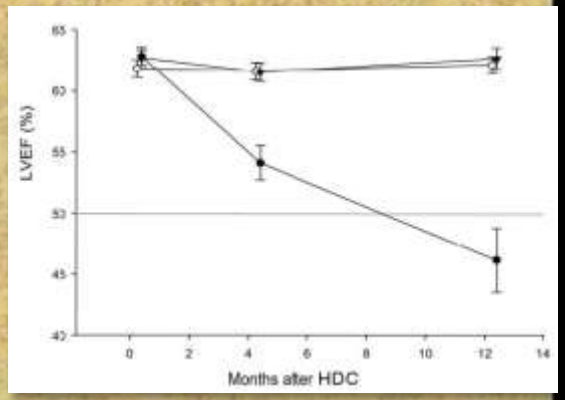
MT Sandri, Clin Chem 2005



33%

36%

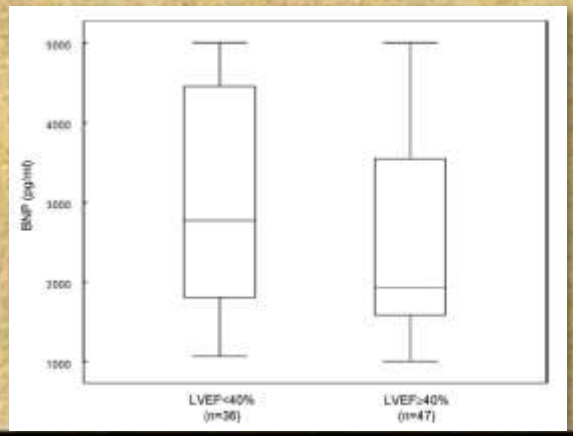
31%



Cancer Patients With Markedly Elevated B-Type Natriuretic Peptide May Not Have Volume Overload

Sukesh C. Burjonroppa, MD, Ann T. Tong, MD,† Lian-Chun Xiao, MS,‡ Marcella M. Johnson, MS,‡ S. Wamique Yusuf, MBBS,† and Daniel J. Lenihan, MD†*

SC Burjonroppa, Am J Clin Oncol 2007



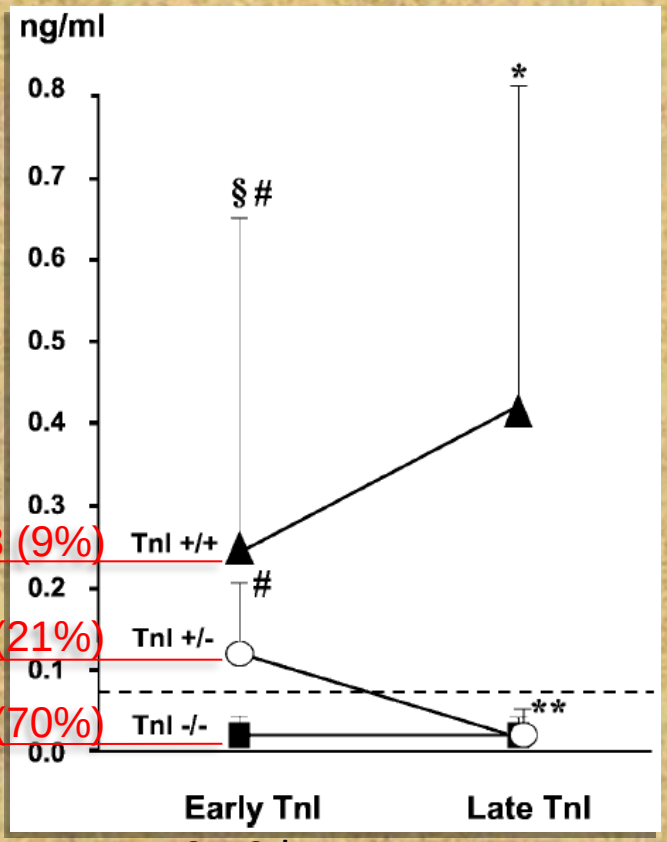
biomarcadors: troponina

Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

Daniela Cardinale, MD; Maria T. Sandri, MD; Alessandro Colombo, MD; Nicola Colombo, MD; Marina Boeri, MD; Giuseppina Lamantia, MD; Maurizio Civelli, MD; Fedro Peccatori, MD; Giovanni Martinelli, MD; Cesare Fiorentini, MD; Carlo M. Cipolla, MD

D Cardinale, Circulation 2004

703 pacients (46% neo de mama, 37% limfoma)



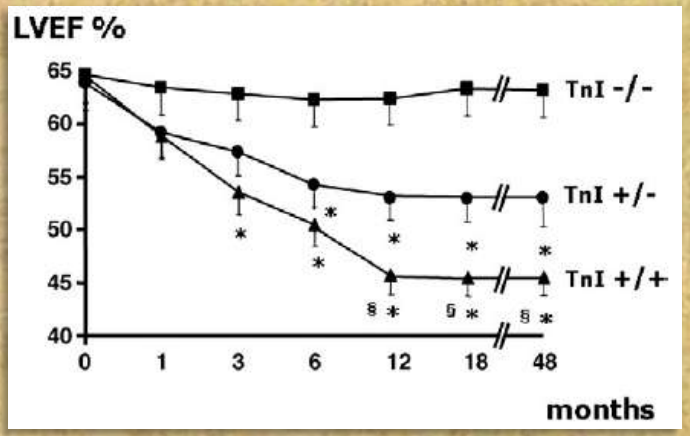
63 (9%)

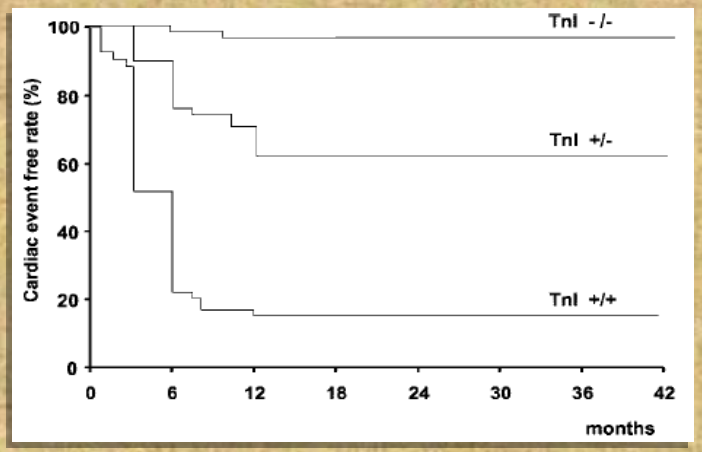
145 (21%)

495 (70%)

0-72 hs

1 mes





biomarcadors

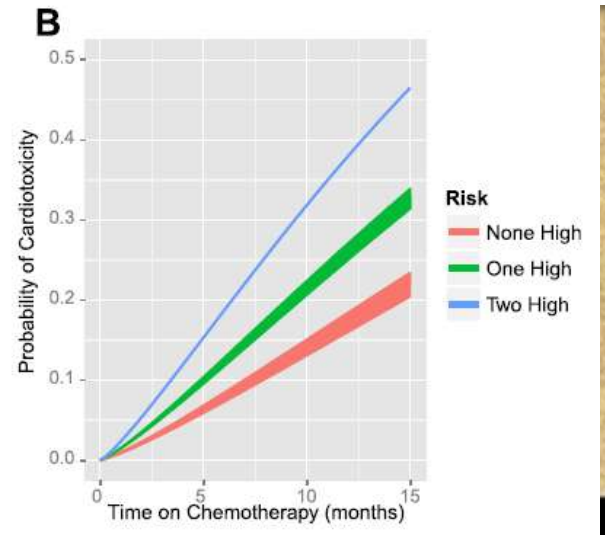
Early Increases in Multiple Biomarkers Predict Subsequent Cardiotoxicity in Patients With Breast Cancer Treated With Doxorubicin, Taxanes, and Trastuzumab

Bonnie Ky, MD, MSCE,*† Mary Putt, ScD,*† Heloisa Sawaya, MD, PhD,‡ Benjamin French, PhD,*† James L. Januzzi, Jr, MD,‡ Igal A. Sebag, MD,§ Juan Carlos Plana, MD,‖ Victor Cohen, MD,¶ Jose Banchs, MD,# Joseph R. Carver, MD,* Susan E. Wiegers, MD,** Randolph P. Martin, MD,†† Michael H. Picard, MD,‡ Robert E. Gerszten, MD,‡ Elkan F. Halpern, PhD,‡‡ Jonathan Passeri, MD,‡ Irene Kuter, MD,§§ Marielle Scherrer-Crosbie, MD, PhD‖

Philadelphia, Pennsylvania; Boston, Massachusetts; Montreal, Canada; Cleveland, Ohio; Houston, Texas; and Atlanta, Georgia

B Ky, JACC 2014

Biomarker	Baseline HR (95% CI)*	Baseline p Value†	Visit 2 HR (95% CI)*	Visit 2 p Value†	Interval Change HR (95% CI)*	Interval Change 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



biomarcadors: troponina

Trastuzumab-Induced Cardiotoxicity: Clinical and Prognostic Implications of Troponin I Evaluation

Daniela Cardinale, Alessandro Colombo, Rosalba Torrisi, Maria T. Sandri, Maurizio Civelli, Michela Salvatici, Giuseppina Lamantia, Nicola Colombo, Sarah Cortinovis, Maria A. Dessanai, Franco Nolè, Fabrizio Veglia, and Carlo M. Cipolla

D Cardinale, J Clin Oncol 2010

Table 4. Major Adverse Cardiac Events in the Overall Study Population and in Patients With Normal or Elevated TNI Value

Event	Total (n = 251)		TNI+ (n = 36)		Normal TNI (n = 215)	
	No.	%	No.	%	No.	%
Severe LVEF reduction (≤ 30%)	7	3	6	17	1	0.5
Cardiac death	0	0	0	0	0	0
Acute coronary syndrome	2	1	2	5	0	0
Acute pulmonary edema	1	0.5	1	3	0	0
Heart failure	7	3	7	19	0	0
Arrhythmias requiring treatment	5	2	2	8	3	1.4
Cumulative events	22	9	18	50	4	2*

Abbreviations: TNI, troponin I; TNI+, elevated TNI; LVEF, left ventricular ejection fraction.
*$P < .001$ *v* elevated troponin I (by Fisher's exact test).

Analisi multivariat:

- *TNI+ únic predictor de FE< 50%*

  (HR 22,9 (11,6-45,5), p<0,001)

- *TNI+ únic predictor de no-recuperació*

  (HR 2,88 (1,78-4,65), p<0,001)

Clinical update

Cancer drugs and the heart: importance and management

Thomas M. Suter[1*] and Michael S. Ewer[2]

TM Suter, Eur H J 2012

and colleagues successfully used troponin to identify anthracycline-treated patients who would benefit from treatment with an ACE inhibitor.[70] Despite these promising results, the assessment of cardiac biomarkers is not being done routinely in patients undergoing potentially cardiotoxic cancer treatment and there is a need for large, multicentre trials to evaluate the role of biomarkers in this population.

European Journal of Heart Failure (2011) 13, 1–10
doi:10.1093/eurjhf/hfq213

POSITION STATEMENT

Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology

T Eschenhagen, Eur J Heart Fail 2011

beyond the completion of chemotherapy should be considered especially in those receiving high doses of anthracyclines.

(vii) The identification and validation of reliable biomarkers for the prediction and detection of cardiotoxicity to non-anthracycline agents is urgently required. The use of simple biomarkers such as troponins and brain natriuretic peptide (BNP) should be strongly considered but is not a substitute for objective evaluation by echocardiography or similar modalities.

Review

Role of biomarkers in cardioncology

D Cardinale, Clin Chem Lab Med 2011

troponins and NP, permits better stratification of the cardiac risk for cancer patients treated with CT. Standardization of routine biomarkers use in this clinical setting is a current need, and future, larger prospective multicenter studies should provide clear indications for the appropriate use of these biomarkers in clinical practice.

EDITORIAL COMMENT

Cardiac Biomarkers, Cardiotoxicity, and Active Collaboration

Is This the Final Frontier or the Wave We Should Catch?*

Daniel J. Lenihan, MD
Nashville, Tennessee

DJ Lenihan, JACC 2014

- *moment de determinació*
- *límit de normalitat*
- *protocol senzill i aplicable universalment*

estratègies per prevenir la cardiotoxicitat

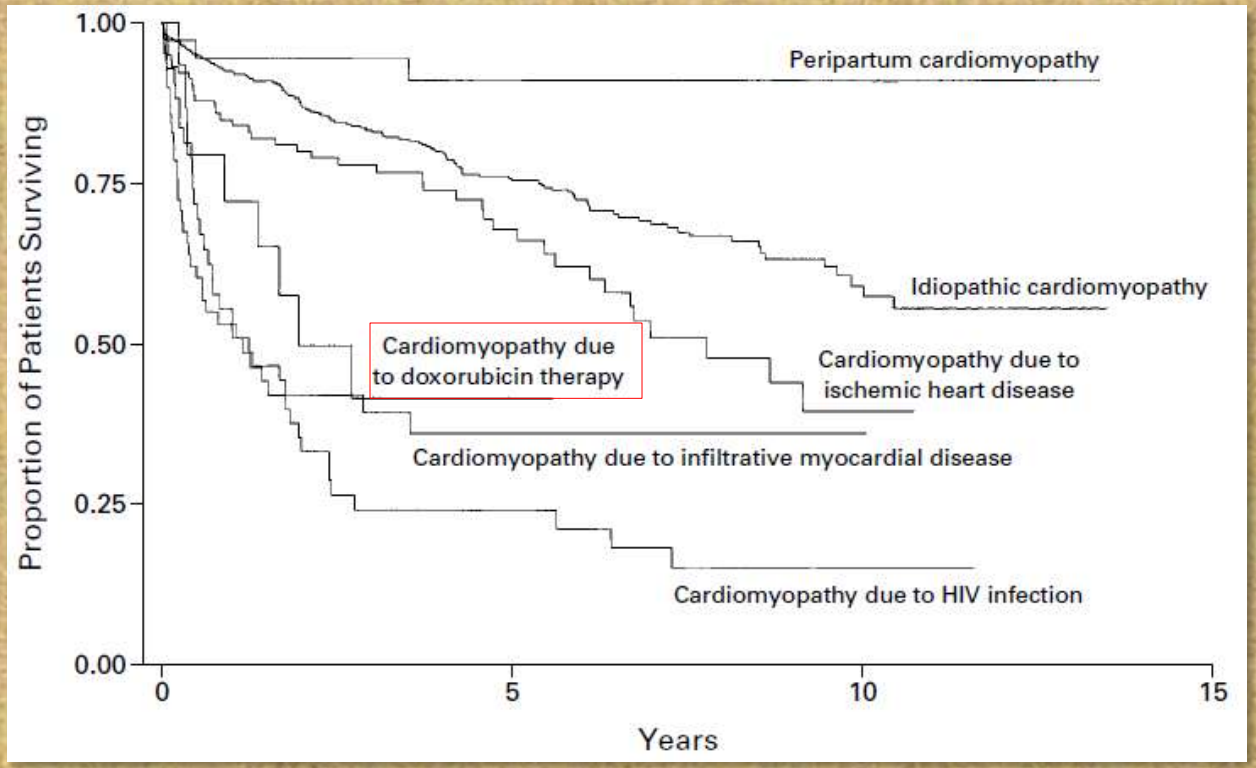
→ minimització de la lesió / prevenció primària

→ detecció precoç de dany miocàrdic

→ seguiment clínic-FE

- *història natural*
- *reversibilitat*

història natural i reversibilitat

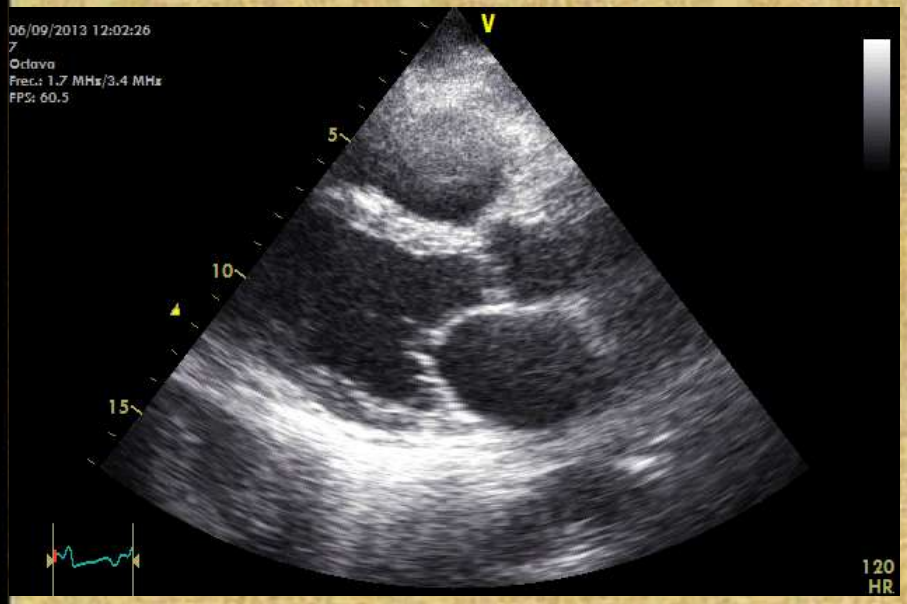


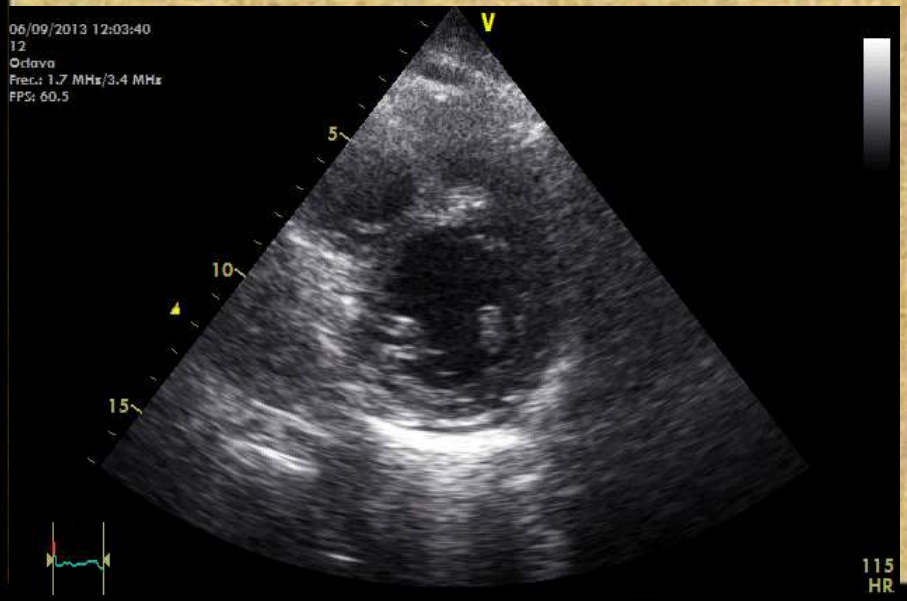
GM Felker, N Eng J Med 2000

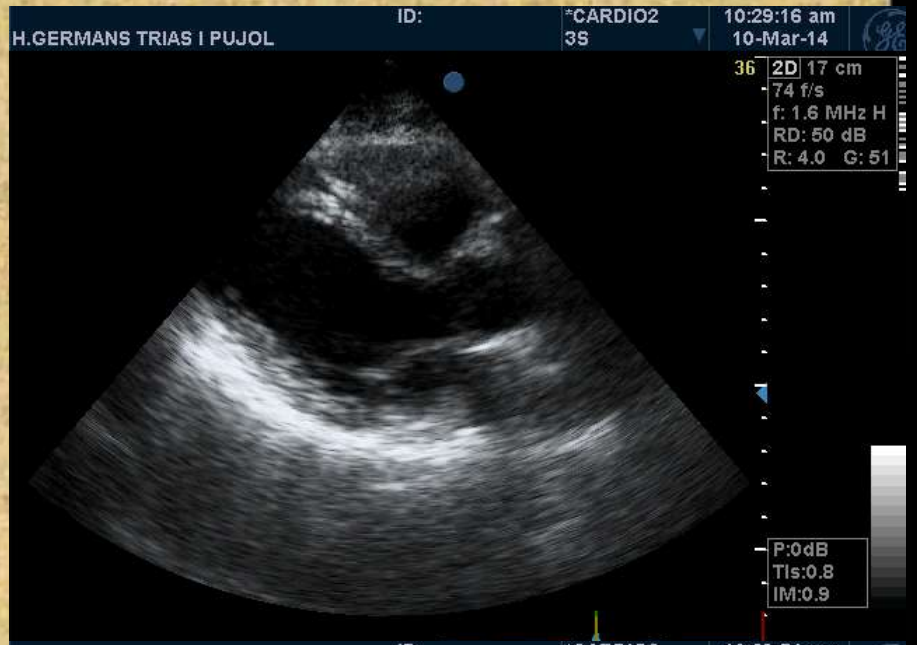
♀ *62 a; limfoma noH (‘96), recidiva 2012→ R-CHOP (abril ’13):*

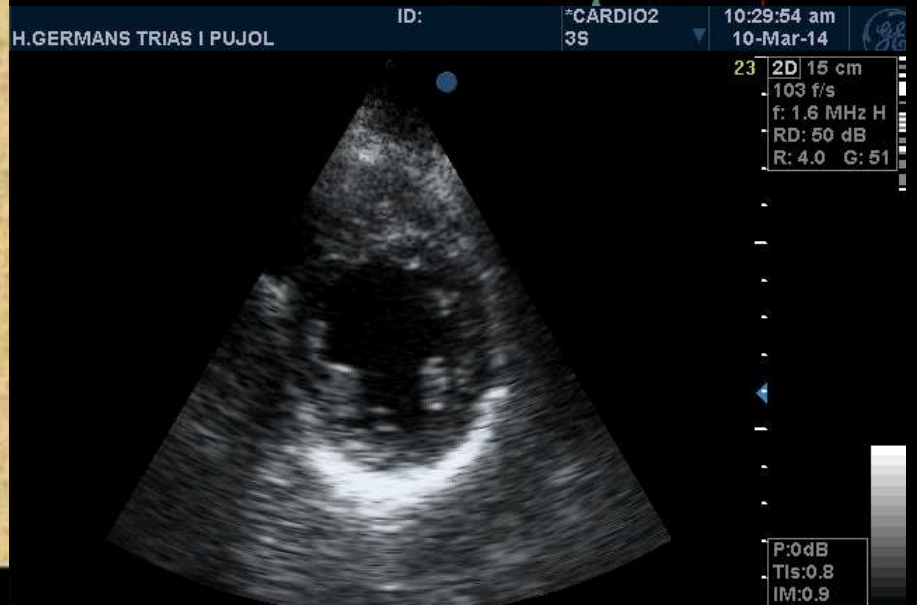
sept ’13: FE 22%

març ’14: FE 53%









història natural i reversibilitat

Anthracycline-Induced Cardiomyopathy

Clinical Relevance and Response to Pharmacologic Therapy

Daniela Cardinale, MD, PhD,* Alessandro Colombo, MD,* Giuseppina Lamantia, MD,* Nicola Colombo, MD,* Maurizio Civelli, MD,* Gaia De Giacomi, MD,* Mara Rubino, MD,† Fabrizio Veglia, PhD,† Cesare Fiorentini, MD,† Carlo M. Cipolla, MD*

Milan, Italy

D Cardinale, JACC 2010

Incidence, Predictors, and Impact on Survival of Left Ventricular Systolic Dysfunction and Recovery in Advanced Cancer Patients

Guilherme H. Oliveira, MD[a,e], Siddarth Mukerji, MD[b], Adrian V. Hernandez, MD[c,d], Marwan Y. Qattan, MD[a], Jose Banchs, MD[e], Jean-Bernard Durand, MD[e], Cezar Iliescu, MD[e], Juan Carlos Plana, MD[f], and W.H. Wilson Tang, MD[f]

GH Oliveira, Am J Cardiol 2014

Clinical Investigations

Cancer Therapy-Induced Left Ventricular Dysfunction: Interventions and Prognosis

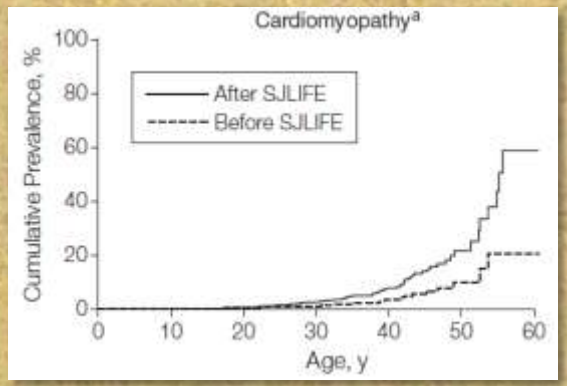
AKANKSHA THAKUR, MD,[1] AND RONALD M. WITTELES, MD[2]

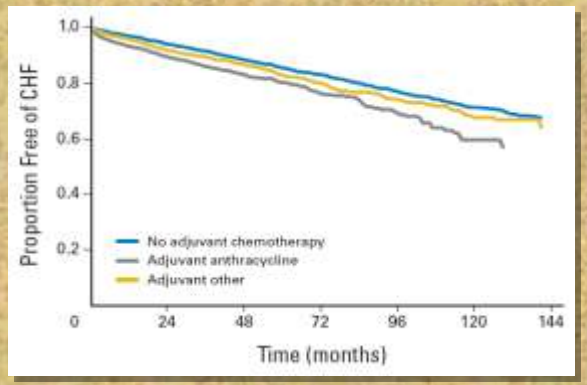
Stanford, California

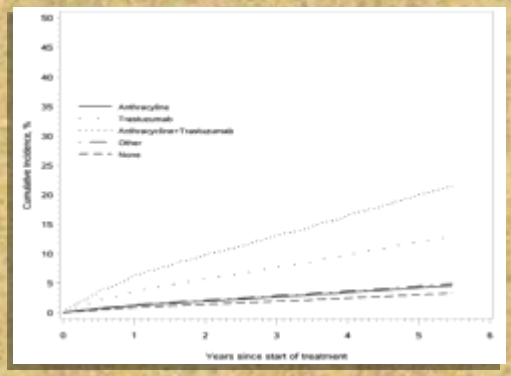
A Thakur, J Card Fail 2014

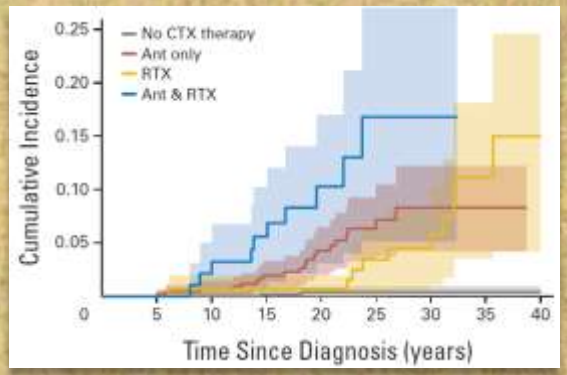
- *normalització de la FE en 42-32-77%*
- *predictors de recuperació:* *-CF NYHA poc avançada*
  -AE petita i BNP no elevat
  -beta-bloq i IECA/ARAII
  -poc temps des de fi de QMT

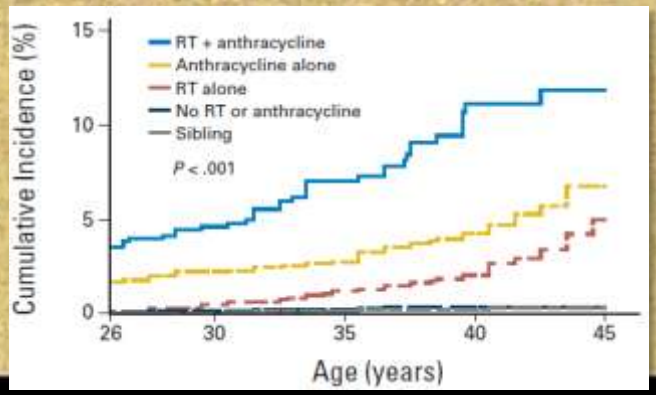
història natural i reversibilitat

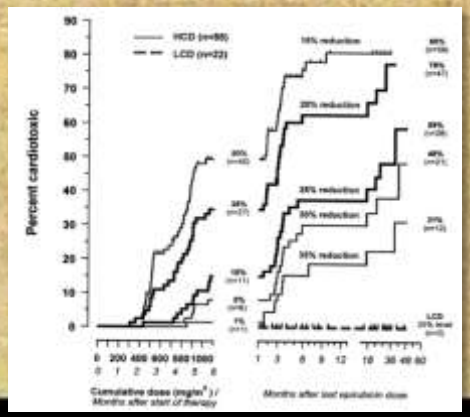












seguiment

- quins pacients ?

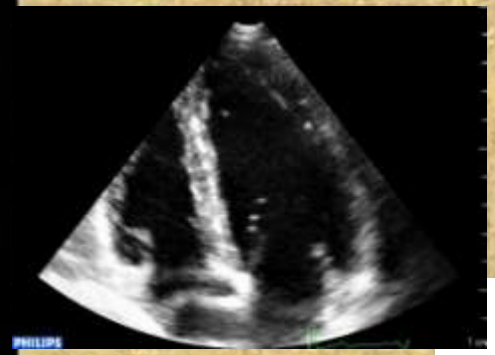
- en quin moment – amb quina freqüència ?

- per quan temps ?

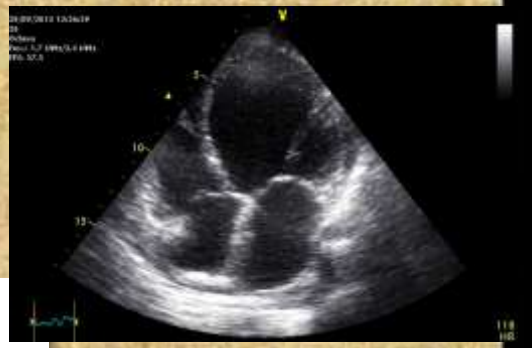
- cóm fem el seguiment ?

punt/s òptims de screening **?**

FE 56%

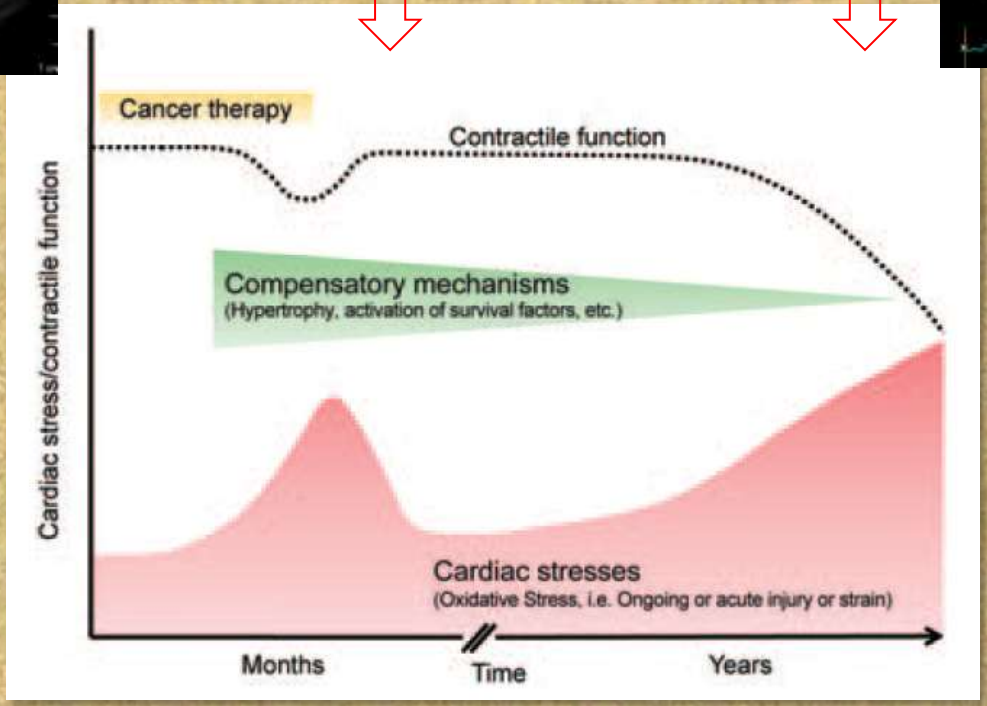


FE 26%



massa prest

massa tard



TM Suter, Eur H J 2012

seguiment

The Dutch Childhood Oncology Group guideline for follow-up of asymptomatic cardiac dysfunction in childhood cancer survivors

E Sieswerda, Ann Oncol 2012

What is the time interval for screening?	
Echocardiography	
Anthracyclines <300 mg/m^2	*Once every 5 years*
Anthracyclines ≥300 mg/m^2	*Once every 2/3 years*
Anthracyclines and cardiac radiotherapy (regardless of received doses)	*Once every 2/3 years*
Cardiac radiotherapy <30 Gy	*Once every 5 years*
Cardiac radiotherapy ≥30 Gy	*Once every 2/3 years*
Mitoxantrone ≥40 mg/m^2	*Once every 5 years*
Pregnant survivors treated with any cardiotoxic treatment	*Once in the third trimester of pregnancy*

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

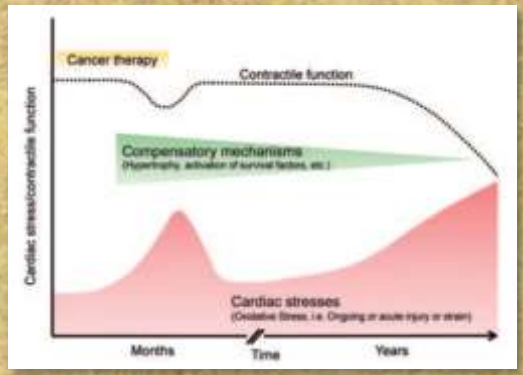
G Curigliano, Ann Oncol 2012

Patients receiving anthracyclines and/or trastuzumab in the adjuvant setting should perform serial monitoring of cardiac function at baseline, 3, 6 and 9 months during treatment, and then at 12 and 18 months after the initiation of treatment. Monitoring should be repeated during or following treatment as clinically indicated. Limited data are available for elderly patients: increased vigilance is recommended for patients ≥60 years old

Assessment of cardiac function is recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age, or even at age >15 years but with cumulative dose of doxorubicin of >240 mg/m^2 or epirubicin >360 mg/m^2

seguiment

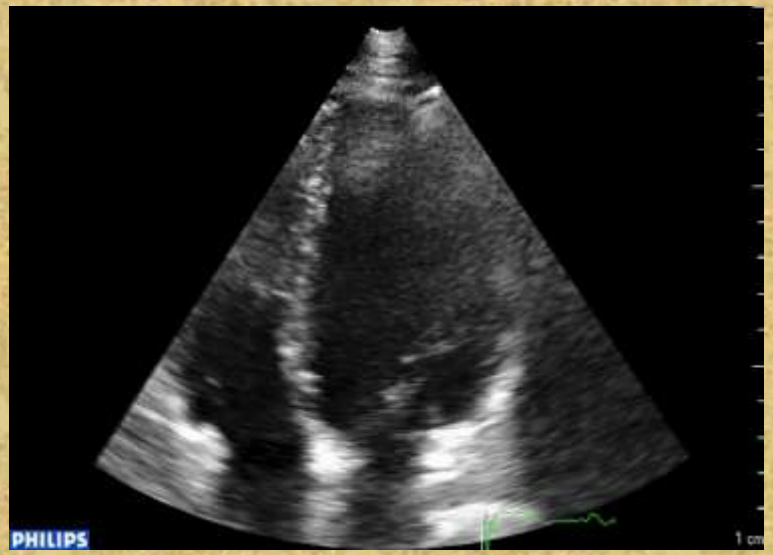
punt/s òptims de screening **?**



- ✓ *1 i 5 anys després de fi de tractament*
- ✓ *1ª aparició de símptomes*

34 anys, leucèmia 9 anys enrera

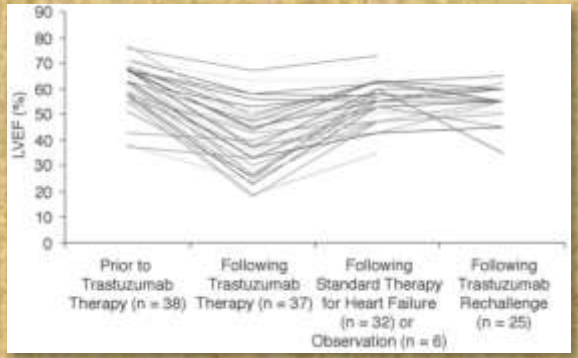
Als últims mesos dispnea de molt grans esforços



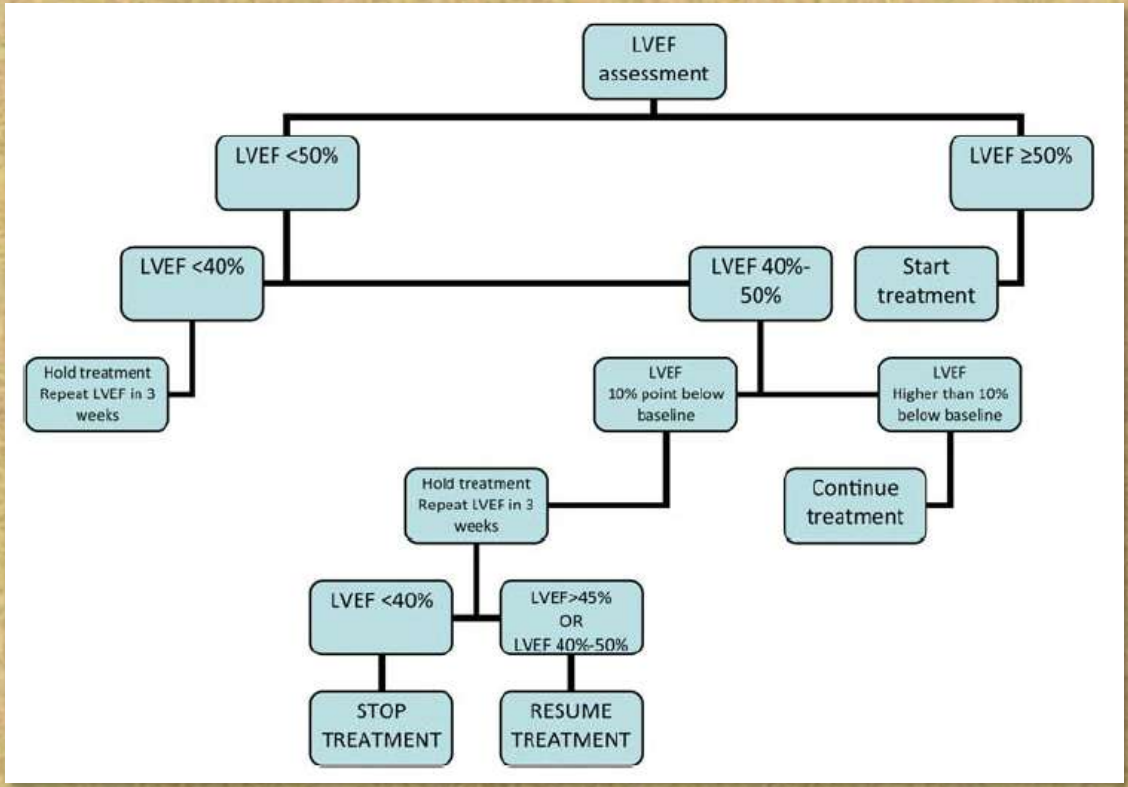
FE 47%

seguiment

Type I (e.g. doxorubicin)	Type II (e.g. trastuzumab)
Predominant cell death	Cell dysfunction
Typical anthracycline biopsy	No anthracycline-like changes on biopsy
Cumulative and dose related	Not cumulative or dose related
Permanent damage	Generally reversible



MS Ewer, J Clin Oncol 2005




clinical practice 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. Rolla[7], on behalf of the ESMO Guidelines Working Group*

G Curigliano, Ann Oncol 2012

sense controls de FE després de fi de ttm

?

seguiment

Trastuzumab-Related Cardiotoxicity: Calling Into Question the Concept of Reversibility

Melinda L. Telli, Sharon A. Hunt, Robert W. Carlson, and Alice E. Guardino

ML Telli, J Clin Oncol 2007

Table 7. NSABP B-31: Assessment of LVEF ≥ 6 Months After Diagnosis of Cardiotoxicity

Assessment	Cardiac Event (n = 31)	Symptomatic Cardiac Dysfunction (n = 43)	Asymptomatic Decline in LVEF (n = 102)
No follow-up LVEF	7	13	29
Decrease in LVEF compared to baseline	17 of 24	22 of 30	NA
Recovery of LVEF to baseline	7 of 24	8 of 30	NA
Developed symptoms subsequently			21 of 102
Follow-up LVEF < 50%			13 of 52
Follow-up LVEF > 50%			39 of 52

25%

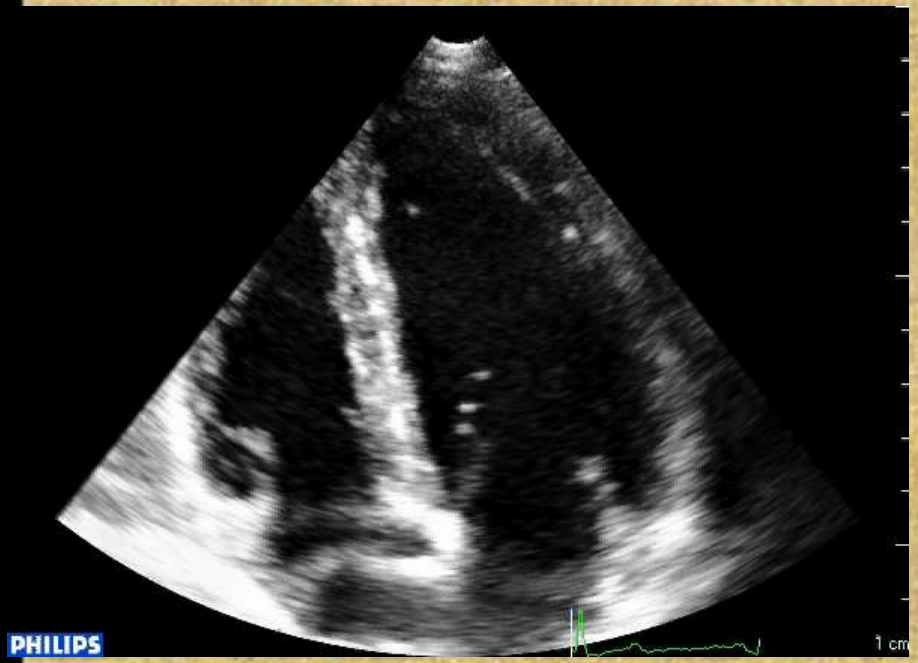
seguiment

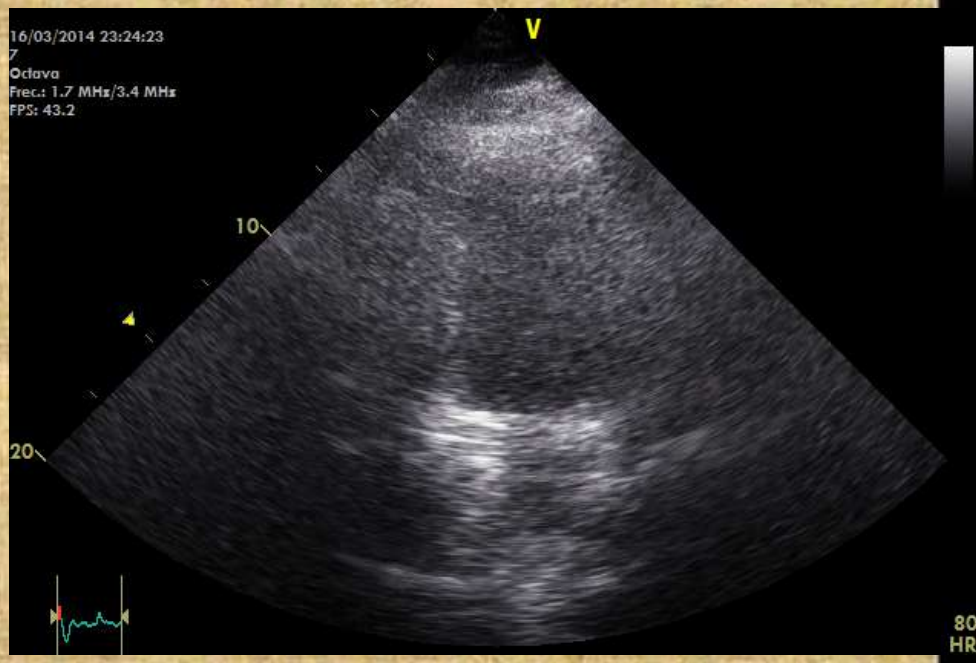
** GT Armstrong, JCO 2012*

- *ecocardiograma*

alta disponibilitat/baix cost	reproduïbilitat baixa ( )
informació funcional/valv/pericardi	depén de finestra acústica
FE normal ≥ 60% *	sobrestima respecte RM

- *MUGA*
  (multiple gated radionuclide angiography)
- *resonància magnètica*
- *biomarcadors*


PHILIPS
1 cm


16/03/2014 23:24:23
7
Octava
Frec.: 1.7 MHz/3.4 MHz
FPS: 43.2
V
10
20
80
HR

seguiment

** GT Armstrong, JCO 2012*

- *ecocardiograma*

alta disponibilitat/baix cost	reproduïbilitat baixa ( )
informació funcional/valv/pericardi	depén de finestra acústica
FE normal ≥ 60% *	sobrestima respecte RM

f diastòlica →	afectació inicial	inespecífic
strain →	valor pronòstic afegit / subclínic	subclínic
3D →	més precís i reproduïble	laboriós i depén de qualitat
exercici/DBT →	avalua reserva contràctil	laboriós i pocs estudis

- *MUGA*
  (multiple gated radionuclide angiography)

alta disponibilitat i rapidesa	irradiació
reproduïbilitat més alta que eco	sense informació adicional tall planar

- *resonància magnètica*

gold standard de FE	alt cost/poca disponibilitat
fibrosi / *T1 mapping*	

- *biomarcadors*

diferència IC d'altres	↓ especificitat

Conclusions i futures direccions

- ✓  *millor tractament del càncer minimitzant complicacions cardiològiques*
- ✓ *coneixer potencial cardiotòxic – status cardiològic del malalt*
- ✓ *benefici del tractament > risc cardiològic*
- ✓ *factors de risc controlats i tractament cardiològic optimitzat*
- ✓ *seguiment a llarg plaç*
- ✓ *actuacions "apropiades"*
- ✓ *protocols "sostenibles"*

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estratègies per a prevenir la cardiotoxicitat

→ minimització de la lesió / prevenció primària → als de ↑ risc

→ detecció precoç de dany miocàrdic
- *troponina*
- *strain*

→ seguiment clínic-FE

Conclusions i futures direccions

- *aprofundir:*
  - *-curs de la disfunció ventricular*
  - *-paper de biomarcadors i strain*
  - *-paper de prevenció primària i a qui*
  - *-factors genètics de cardiotoxicitat*
- *conscienciació de onco-hematologia / at primària / malalt*
  - *-control de factors de risc*
  - *-cardiotox tardana*
  - *-reconeixement de 1º símptomes*
- *beneficiar als pacients oncològics de la comunicació i actuacions coordinades entre oncologia/hematologia i cardiologia*
- *fomentar els programes/unitats d'oncocardiologia*

programa de onco-cardiologia

disfunció ventricular	*tromboemb. pulmonar*	*anasarca*	*amiloïdosi cardiaca*
insuficiència cardiaca	*fibril·lació auricular*	*anticoagulació*	*masses cardiaques*
optimització de ttm	*dolor toràcic isquèmic*	*sd QT llarg*	*vessament pericàrdic*
seguiment a llarg plaç	*f de risc CV*	*sospita endocarditis*	. . . . .

gràcies per la vostra atenció

prevenció primària

Table 4 Clinical Endpoints

	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45% (%)	3 (6.7)	11 (24.4)	0.020
≥10% decrease in LVEF with a final LVEF<50% (%)	2 (4.8)	2 (5.4)	0.90
Heart failure or ≥10% decrease in LVEF (%)	4 (9.5)	7 (19)	0.22
Severe adverse events* (%)	9 (20)	15 (33)	0.15

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)

Primordial prevention *consists of actions to minimize future hazards to health and hence inhibit the establishment factors (environmental, economic, social, behavioural, cultural) known to increase the risk of disease. It addresses broad health determinants rather than preventing personal exposure to risk factors, which is the goal of primary prevention.*

Examples: outlawing alcohol, improving sanitation, establishing healthy communities, promoting a healthy lifestyle in childhood or developing green energy approaches.

Primary prevention *seeks to prevent the onset of specific diseases via risk reduction: by altering behaviours or exposures that can lead to disease, or by enhancing resistance to the effects of exposure to a disease agent.*

Examples include smoking cessation and vaccination.

estratègies per prevenir la cardiotoxicitat

→ minimització de la lesió / prevenció primària

→ detecció

→ seguiment

n=49.017, seguiment mig de 9 anys

- *disfunción sistólica: 17,9%*
- *insuficiencia cardiaca: 6,3%*

M Lotrionte, Am J Cardiol 2013

Administration of Angiotensin-Converting Enzyme Inhibitors and β-Blockers During Adjuvant Trastuzumab Chemotherapy for Nonmetastatic Breast Cancer: Marker of Risk or Cardioprotection in the Real World?

S Oliva, Oncologist 2012