CardioTox 2019

Clinical Heart Failure Guidelines: are they different for cancer patients?

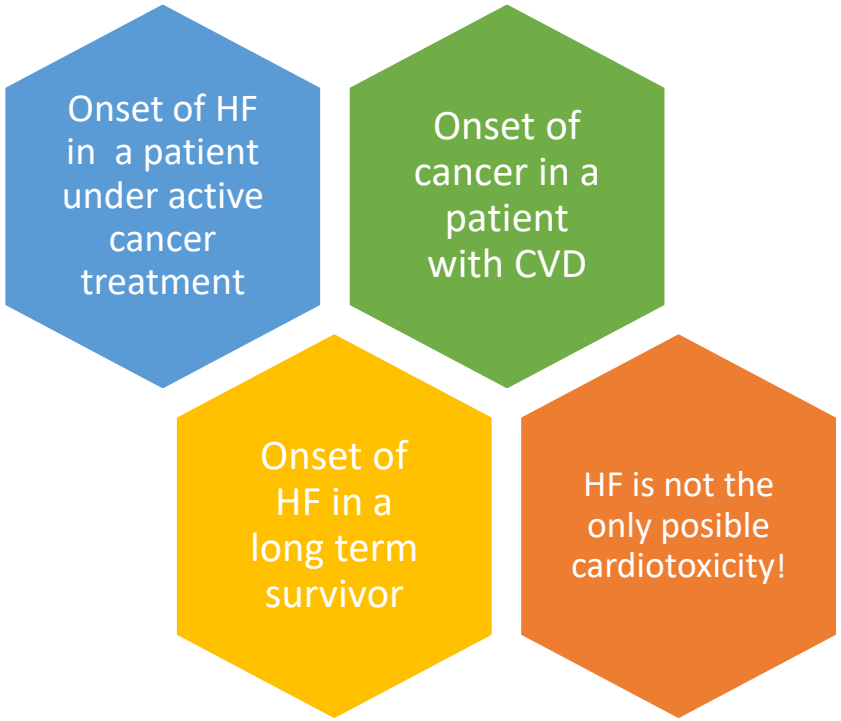
Guidelines for cardiac monitoring

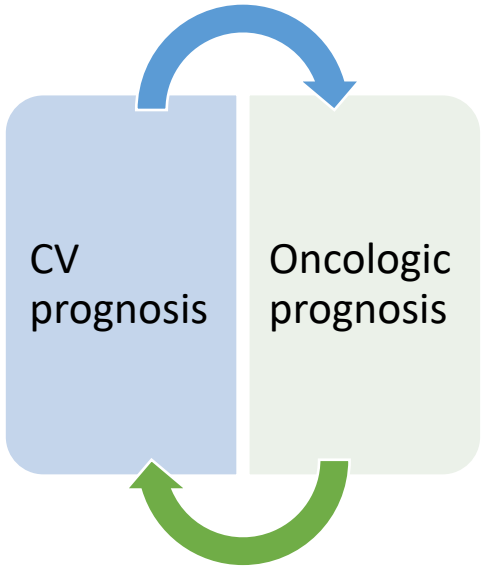
Regina Dalmau González-Gallarza

Servicio de Cardiología

Hospital Universitario la Paz

Do we need a guideline for cardiac monitoring in oncologic patients?

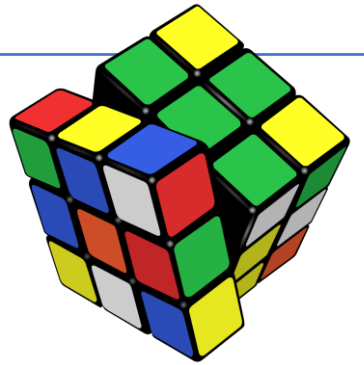

Onset of HF in a patient under active cancer treatment
Onset of cancer in a patient with CVD
Onset of HF in a long term survivor
HF is not the only posible cardiotoxicity!


CV prognosis
Oncologic prognosis


Predisposing factors before treatment
Early signs of cardiotoxicity
Acute CVD during treatment
CVD after treatment
CVD in long-term survivors

Do we need a guideline for cardiac monitoring in oncologic patients?

- A guideline to prevent.
- A guideline to determine which patients should be monitored and how.
- A guideline to early diagnose.
- A guideline to avoid unnecessary disruptions of oncologic treatment.
- A guideline to follow up.



2009

British Journal of Cancer (2009) 100, 684 – 692

www.bjcancer.com

BJC OPEN

Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring

AL Jones*[,1], M Barlow[2], PJ Barrett-Lee[3], PA Canney[4], IM Gilmour[5], SD Robb[2], CJ Plummer[6], AM Wardley[7] and MW Verrill[8]

[1]Department of Oncology, Royal Free and University College London Hospitals, London, UK; [2]Department of Cardiology, Western Infirmary, Glasgow, UK; [3]Breast Unit, Velindre Hospital Cardiff, Wales, UK; [4]Beatson West of Scotland Cancer Centre, Gartnavel General Hospital, Glasgow, UK; [5]Deemess Park Medical Centre, Sunderland Teaching Primary Care Trust, Sunderland, UK; [6]Department of Cardiology, Freeman Hospital, Newcastle upon Tyne, UK; [7]Department of Medical Oncology, Christie Hospital, Manchester, UK; [8]Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, UK

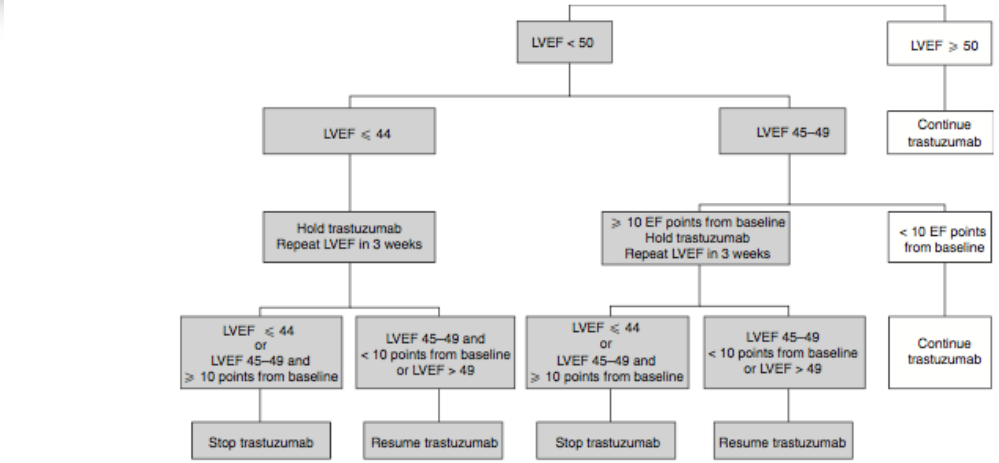


Figure 1 Current recommendations for cardiac monitoring in trastuzumab-treated patients (reproduced from Suter *et al*, 2007; online Appendix only). Reproduced with permission of the American Society of Clinical Oncology, from Suter *et al*, 2007.

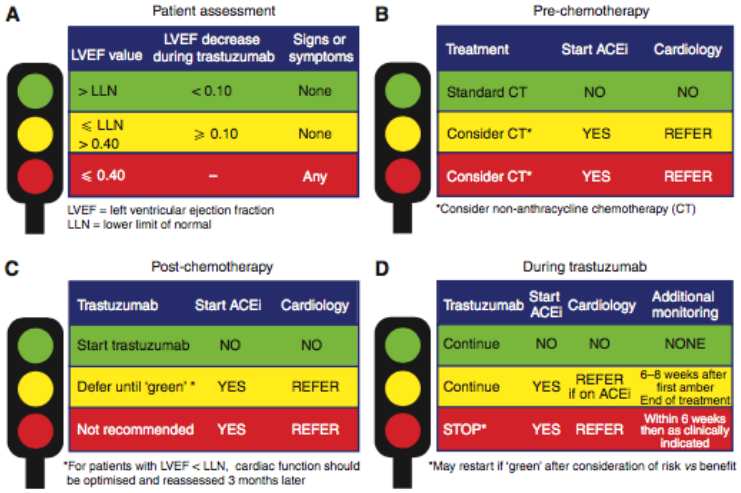


Figure 2 Traffic light system to prevent, monitor, and manage cardiac events in patients undergoing cytotoxic chemotherapy. (**A**) Patient assessment during trastuzumab therapy; (**B**–**D**) indications for ACEi therapy and referral to a cardiologist before (**B**) and after (**C**) chemotherapy, and (**D**) during trastuzumab therapy, when additional cardiac assessments may also be required. ACEi = angiotensin-converting enzyme inhibitor.

Key recommendations:

- A monitoring schedule that assesses baseline and on-treatment cardiac function (every 4 months)
- Simplified recommendations for trastuzumab treatment interruption and restarting
- Clear advice on initiating an ACE inhibitor and when to consult a cardiologist.

2012

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii155–vii166, 2012
doi:10.1093/annonc/mds293

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. Roila[7], on behalf of the ESMO Guidelines Working Group*

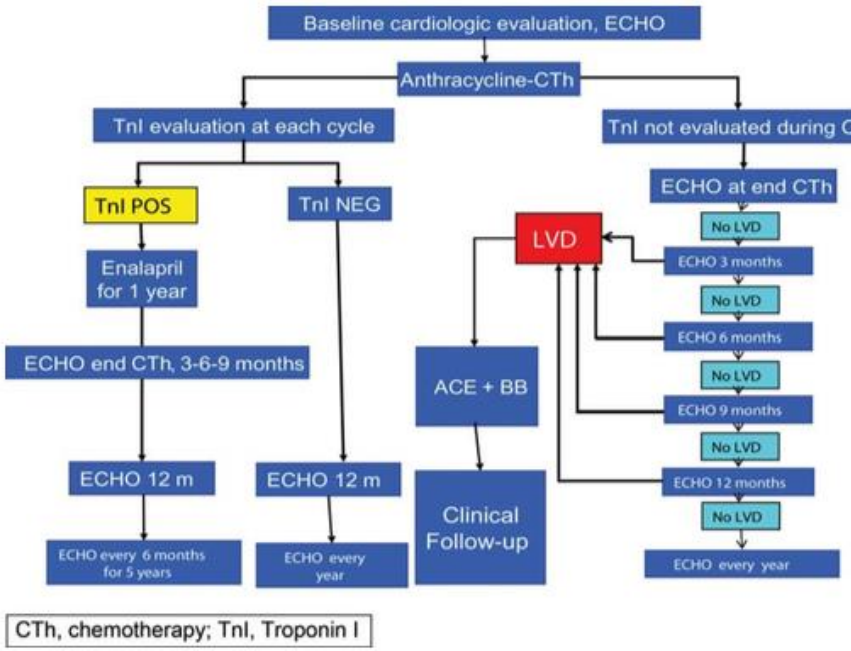


Figure 1. Algorithm for the management of cardiotoxicity in patients receiving anthracyclines.

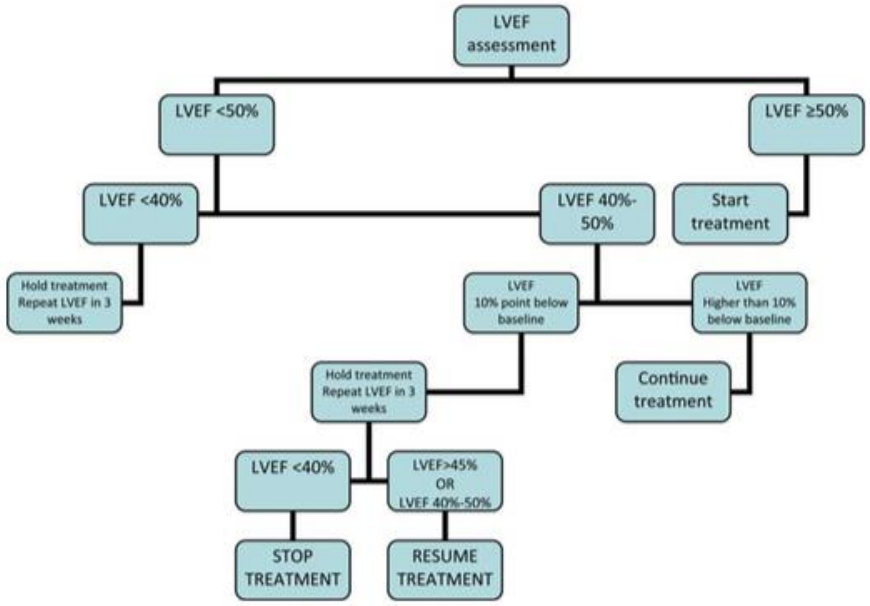


Figure 2. Algorithm for continuation and discontinuation of trastuzumab based on LVEF assessments.

Feb 2016

Canadian Journal of Cardiology 32 (2016) 831–841

Society Guidelines

Canadian Cardiovascular Society Guidelines for Evaluation and Management of Cardiovascular Complications of Cancer Therapy

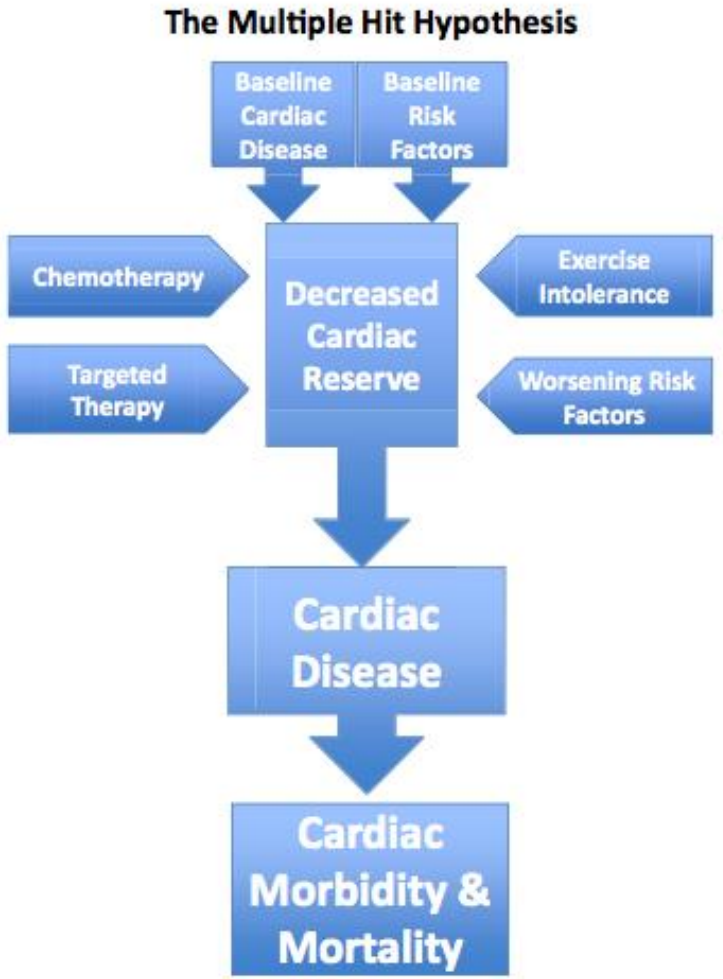
Primary Panel: Sean A. Virani, MD, MSc, MPH, FRCPC, Co-Chair,[a,*]

Table 1. Risk of cardiac disease and cardiac risk factors in long-term survivors of childhood cancer vs healthy siblings (Childhood Cancer Survivor Study)

	CAD[9]	Heart failure[9]	Hypertension[10]	Diabetes[10]	Dyslipidemia[10]
RR (95% CI)	10.4 (4.1-25.9)	15.1 (4.8-47.9)	1.9 (1.6-2.2)	1.7 (1.2-2.3)	1.6 (1.3-2.0)
n	10,397	10,397	8599	8599	8599

CAD, coronary artery disease; CI, confidence interval; RR, relative risk.

Increasing responsibility to identify patients with adverse health outcomes related to past cancer treatments



Canadian Journal of Cardiology 32 (2016) 831–841

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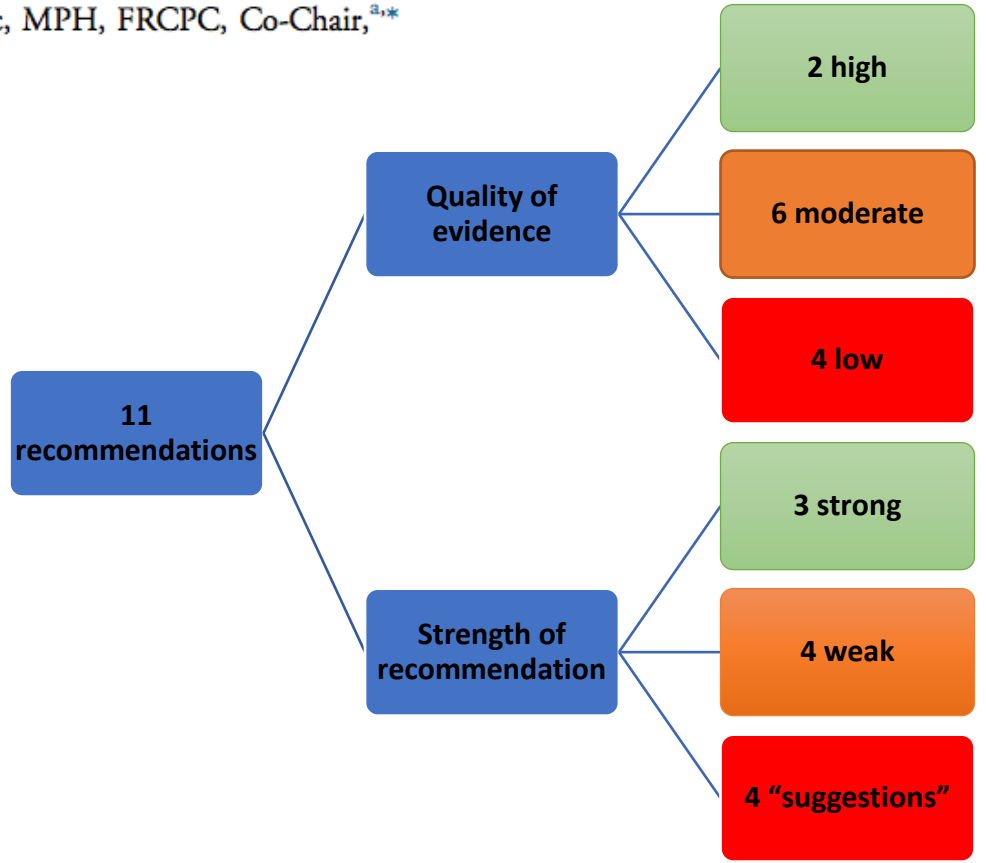

Sept 2016

European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

Sept 2016

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

ESC CPG POSITION PAPER

2016 ESC Positi
and cardiovascu
auspices of the E
Guidelines

The Task Force for ca
the European Society

Authors/Task Force Membe
Patrizio Lancellotti* (Co-Cl
Victor Aboyans (France), R
Gilbert Habib (France), Da
Alexander R. Lyon (UK), T
Massimo F. Piepoli (Italy), Juan Tamargo (Spain), Adam Torbicki (Poland), and
Thomas M. Suter (Switzerland)

Table 3 Factors associated with risk of cardiotoxicity following anti-HER2 compounds and VEGF inhibitors[70–72]

Agent	Risk factors
Anti-HER2 compounds	
- Antibodies - Trastuzumab - Pertuzumab - T-DM1 - Tyrosine kinase inhibitor - Lapatinib	• Previous or concomitant anthracycline treatment *(short time between anthracycline and anti-HER2 treatment)* • Age (>65 years) • High BMI >30 kg/m^2 • Previous LV dysfunction • Arterial hypertension • Previous radiation therapy
VEGF inhibitors	
- Antibodies - Bevacizumab - Ramucirumab	Pre-existing HF, significant CAD or left side VHD (e.g. mitral regurgitation), chronic ischaemic cardiomyopathy • Previous anthracycline
- Tyrosine kinase inhibitors - Sunitinib - Pazopanib - Axitinib - Neratinib - Afatinib - Sorafenib - Dasatinib	• Arterial hypertension • Pre-existing cardiac disease

BMI = body mass index; CAD = coronary artery disease; HER2 = human epidermal growth factor receptor 2; HF = heart failure; MI = myocardial infarction; VEGF = vascular endothelial growth factor; VHD = valvular heart disease.

Table 4 Baseline risk factors for cardiotoxicity

Current myocardial disease	*Demographic and other CV risk factors*
• Heart failure (with either preserved or reduced ejection fraction) • Asymptomatic LV dysfunction (LVEF <50% or high natriuretic peptide[a]) • Evidence of CAD (previous myocardial infarction, angina, PCI or CABG, myocardial ischaemia) • Moderate and severe VHD with LVH or LV impairment • Hypertensive heart disease with LV hypertrophy • Hypertrophic cardiomyopathy • Dilated cardiomyopathy • Restrictive cardiomyopathy • Cardiac sarcoidosis with myocardial involvement • Significant cardiac arrhythmias (e.g. AF, ventricular tachyarrhythmias)	• Age (paediatric population <18 years; >50 years for trastuzumab; >65 years for anthracyclines) • Family history of premature CV disease (<50 years) • Arterial hypertension • Diabetes mellitus • Hypercholesterolaemia
Previous cardiotoxic cancer treatment	***Lifestyle risk factors***
• Prior anthracycline use • Prior radiotherapy to chest or mediastinum	• Smoking • High alcohol intake • Obesity • Sedentary habit

AF = atrial fibrillation; CABG = coronary artery bypass graft; CAD = coronary artery disease; CV = cardiovascular; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; VHD = valvular heart disease.
[a]B-type natriuretic peptide >100pg/ml or N-terminal pro-B-type natriuretic peptide >400pg/ml with no alternative cause.

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 to… auspices of the ESC … Guidelines

- Myocardial dysfunction and heart failure
- Coronary artery disease
- Valvular heart disease
- Arrythmias and QT
- Arterial hypertension
- Throembolic disease
- Peripheral vascular disease and stroke
- Pulmonary hypertension
- Pericardial complications

March 2017

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Saro H. Armenian, Christina Lacchetti, Ana Barac, Joseph Carver, Louis S. Constine, Neelima Denduluri, Susan Dent, Pamela S. Douglas, Jean-Bernard Durand, Michael Ewer, Carol Fabian, Melissa Hudson, Mariell Jessup, Lee W. Jones, Bonnie Ky, Erica L. Mayer, Javid Moslehi, Kevin Oeffinger, Katharine Ray, Kathryn Ruddy, and Daniel Lenihan

- Focused on HF and LVEF monitoring

1. Which patients with cancer are at increased risk for developing cardiac dysfunction?
2. Which preventive strategies minimize risk before initiation of therapy?
3. Which preventive strategies are effective in minimizing risk during the administration of potentially cardiotoxic cancer therapy?
4. What are the preferred surveillance and monitoring approaches during treatment in patients at risk for cardiac dysfunction?
5. What are the preferred surveillance and monitoring approaches after treatment in patients at risk for cardiac dysfunction?
6. No recommendations can be made regarding continuation or discontinuation of cancer therapy in individuals with evidence of cardiac dysfunction.

J Clin Oncol 35:893-911

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

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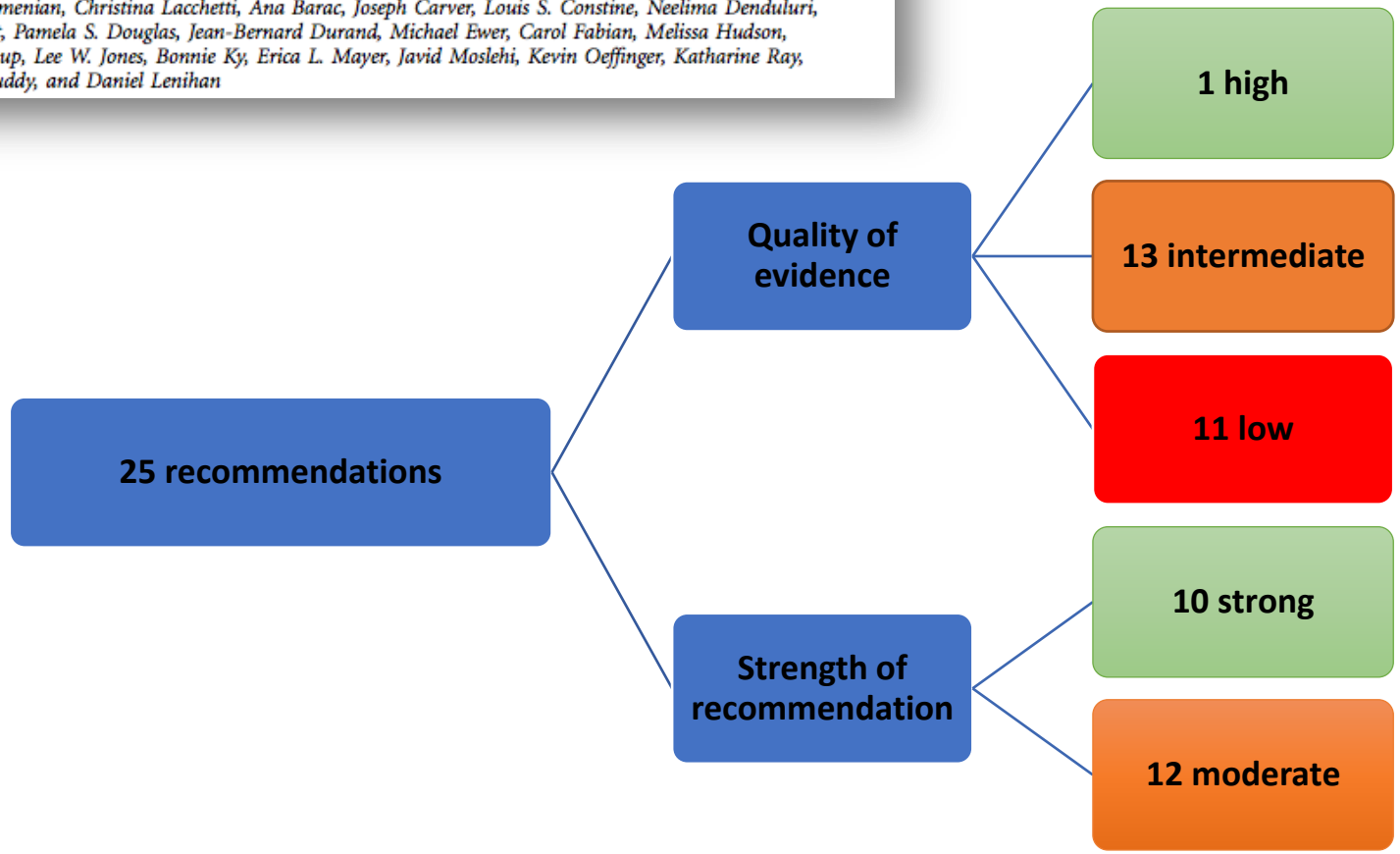


J Clin Oncol 35:893-911

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 4.2018 — February 8, 2019

- Evaluate left ventricular ejection fraction (LVEF) prior to and during treatment.
- The optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is **not known.**
- The FDA label recommends LVEF measurements prior to initiation of trastuzumab and every 3m during therapy.

https://www.nccn.org/professionals/physician_gls/ pdf/breast.pdf.

Trastuzumab FDA label

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline.

Withhold Herceptin for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values *[see Dosage and Administration (2.3)]*. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Cardiac Monitoring

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement immediately prior to initiation of Herceptin
- LVEF measurements every 3 months during and upon completion of Herceptin
- Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (2.3)]*
- LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy.


LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED

The meeting points between the guidelines

- Identifying the **high-risk** population
  - ✓ Patient related factors
  - ✓ Therapy related factors
- CV risk factors control and **life-style** intervention
- Detection and Prevention of Cardiotoxicity
  - ✓ Evaluation of **LVEF before initiation** of cancer treatments known to cause impairment in LV function.
  - ✓ Whenever needed, monitoring with the **same imaging** technique.
  - ✓ Subclinical LV dysfunction evaluation using novel echocardiographic techniques
  - ✓ Utility of **cardiac biomarkers** for the early detection of chemotherapy-mediated cardiotoxicity
- Baseline ECG and periodic monitoring of the QTc interval in patients receiving QT-prolonging drugs
- Recommendations for a **Multidisciplinary Approach** to Cardio-oncology

The gaps

- Feasibility
- Cost effectiveness
- It is unclear if early detection strategies decrease the burden of CVD and ultimately improve the outcome of cancer survivors
- Lack of high-quality evidence for effective primary and secondary prevention strategies.
- When to stop a cancer therapy in individuals with evidence of cardiac dysfunction.
- Urgent need for collaborative studies to help guide patient management.
  - ✓ Large prospective registries that enable the development of risk models.
  - ✓ Multicentre randomized controlled trials for primary and secondary interventions.
  - ✓ Genetic and epigenetic characterization to define susceptibility to cardiotoxicity

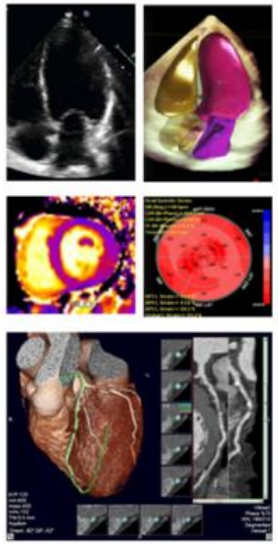
ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 1083–1091
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12386

REVIEW

Modern-day cardio-oncology: a report from the 'Heart Failure and World Congress on Acute Heart Failure 2018'

Markus S. Anker[1,2,3,4]*, Alessia Lena[1,2,3,4], Sara Hadzibegovic[1,2,3,4], Yury Belenkov[5], Jutta Bergler-Klein[6], Rudolf A. de Boer[7], Alain Cohen-Solal[8,9,10], Dimitrios Farmakis[11,12], Stephan von Haehling[13,14], Teresa López-Fernández[15], Radek Pudil[16], Thomas Suter[17], Carlo G. Tocchetti[18], Alexander R. Lyon[19] for the Heart Failure Association Cardio-Oncology Study Group of the European Society of Cardiology

Figure 2 Role of cardiac imaging in cardio-oncology.



Before therapy

- **Stratify Cardio-Toxicity risk**
- **Optimize CV conditions**

During therapy

- **Reproducible EF: 3DE-MRI**
- **Early diagnosis: GLS**
- **Preventive strategies**
- **↓ Treatment interruptions**

After therapy

- **Minimize CV events**

Unidad multidisciplinar de Cardio-Oncología. Visita inicial

Edad……Sexo……....Peso…….Talla……IMC……TA……..

Diagnóstico……

Esquema terapéutico……

Riesgos cardiovasculares potenciales del tratamiento

☐ I. Cardiaca ☐ Cardiopatía isquémica ☐ Arritmias ☐ Enf. Vascular periférica ☐ Trombosis ☐ HTA/DM/Dislipemia

Factores de riesgo cardiovascular

- Fumador/exfumador---------- No Sí
- Hipercolesterolemia (Objetivo LDL < 100) --------- No Sí
- Hipertensión arterial (Objetivo < 130/80 mm Hg) - No Sí
- Diabetes (Objetivo HbA1C <7,5-8) ---------- No Sí
- Insuficiencia renal moderada-severa ---------- No Sí

Optimizar tratamiento (solicitar interconsulta electrónica rápida en caso necesario)

Antecedentes de

- Quimioterapia cardiotóxica ---------- No Sí
  - Esquema……..
- Radioterapia torácica ---------- No Sí
  - Fecha fin tratamiento……
- Cardiotoxicidad ---------- No Sí
- Cardiopatía conocida ---------- No Sí
- Sospecha cardiopatía ---------- No Sí
  - ❑ Disnea de esfuerzo ☐ Síncope o presíncope
  - ❑ Edemas ☐ Dolor precordial

Cualquier respuesta Sí

Enviar a **consulta de Cardio-Oncología** (3CAR07)

Seguir protocolos específicos según patología

Pruebas complementarias basales

- ❑ **Todos**
  - ❑ **Analítica basal +**
    - ❑ Troponina
    - ❑ Perfil lipídico
    - ❑ Hb A1c
  - ❑ **ECG basal**
- ❑ **Ecocardiograma si:**
  - ❑ >65 años
  - ❑ > 2 FRCV

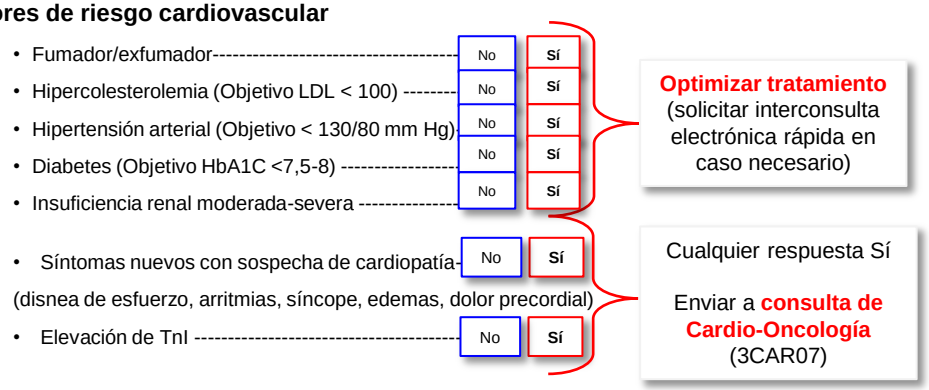
- **Si ECG o ECO anormal**
- **Si Troponina elevada**

Seguimiento durante el tratamiento

Pruebas complementarias

TnI antes de cada ciclo iv / trimestral en tratamientos orales si ANT, anti HER2, MEKi, TKi

Factores de riesgo cardiovascular



Otras pruebas complementarias durante el tratamiento

ECG

- En tratamientos que prolonguen el QT seguimiento individualizado
- Fin de tratamiento

Ecocardiograma:

- Cada 6 m en pacientes con >2FRCV y tratamiento prolongado con ANT, HER2, MEKi, TKi
- Previo a trasplante de progenitores hematopoyéticos (TPH) y a los 100 días
- Fin de tratamiento a todos (en los siguientes 6-8 meses)

Pacientes tratados sólo con radioterapia torácica

- **Visita inicio**: Check List de FRCV, cardiopatía y tratamientos previos
  - ❑ **Analítica** (Perfil lipídico y Hb A1c) ☐ **ECG**
  - ❑ **ECO** (alteraciones ECG, cardiopatía o tratamientos antitumorales previos)
- **Seguimiento clínico**. Control de FRCV. Si sospecha de cardiopatía remitir al cardiólogo
- **Fin de tratamiento**: ECG y ECO al año

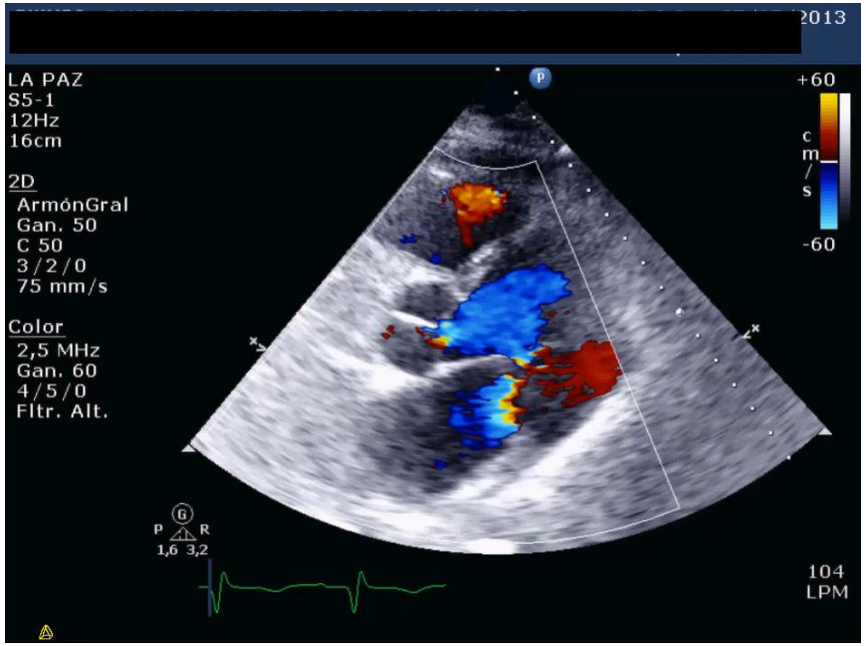
Largos supervivientes

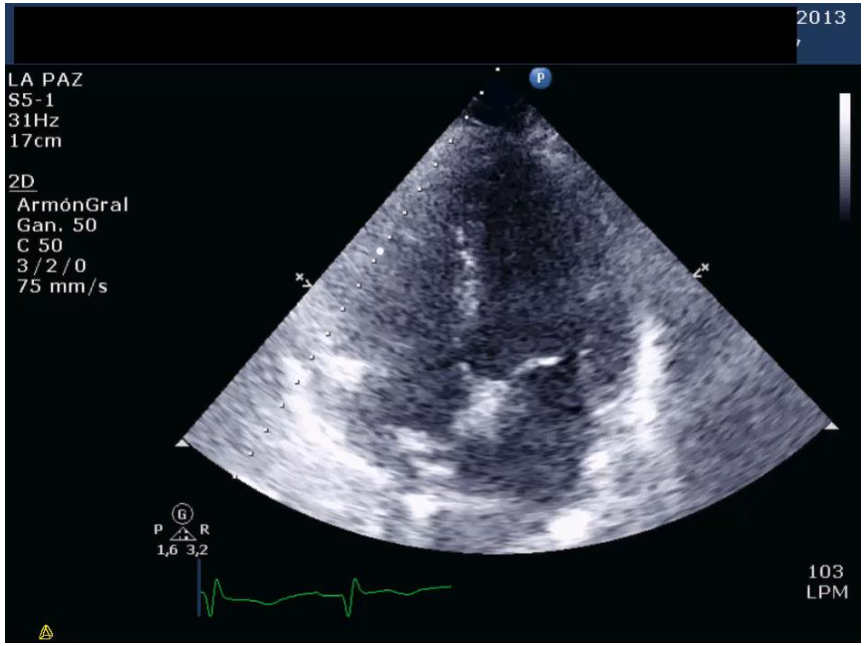
- Control estricto de FRCV
- **ECG** 1, 2 y 5 años post tratamiento
- **ECO** a los 5 años si FRCV, antraciclinas, radioterapia torácica o tratamiento con <15 años.
- **Interconsulta a la unidad de cardio-oncología**
  1. Cáncer + síntomas nuevos o mal control de FRCV a pesar de ajuste de medicación
  2. Alteraciones nuevas en el ECG
  3. Tratamiento con cardiotóxicos sin monitorización específica durante el tratamiento
  4. Antes de una gestación

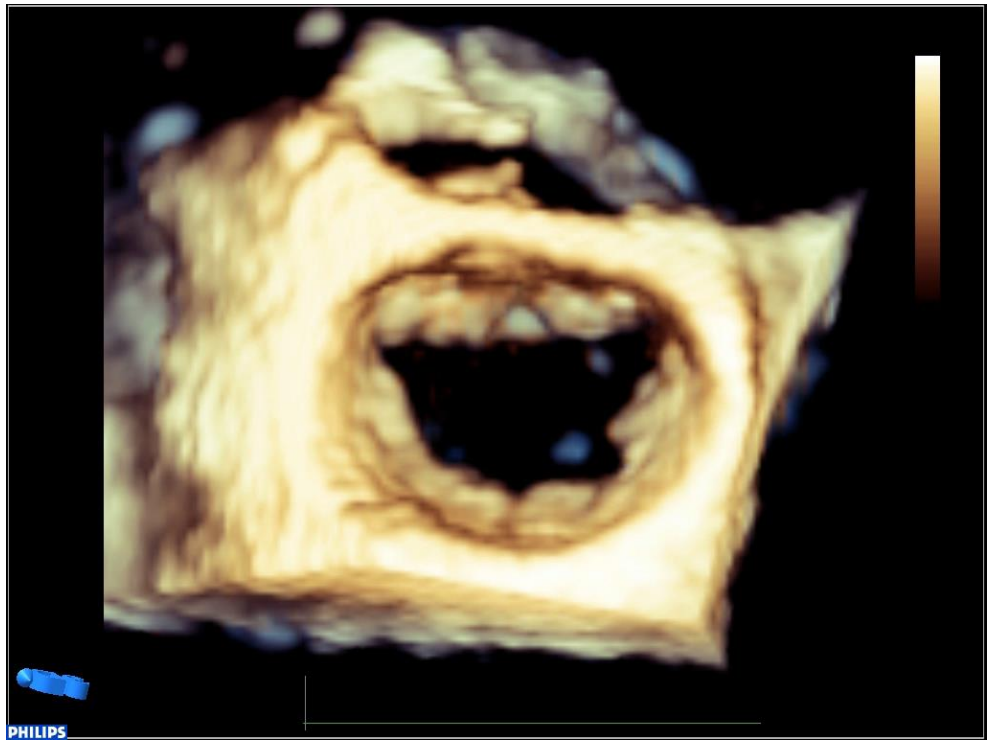
Key messages

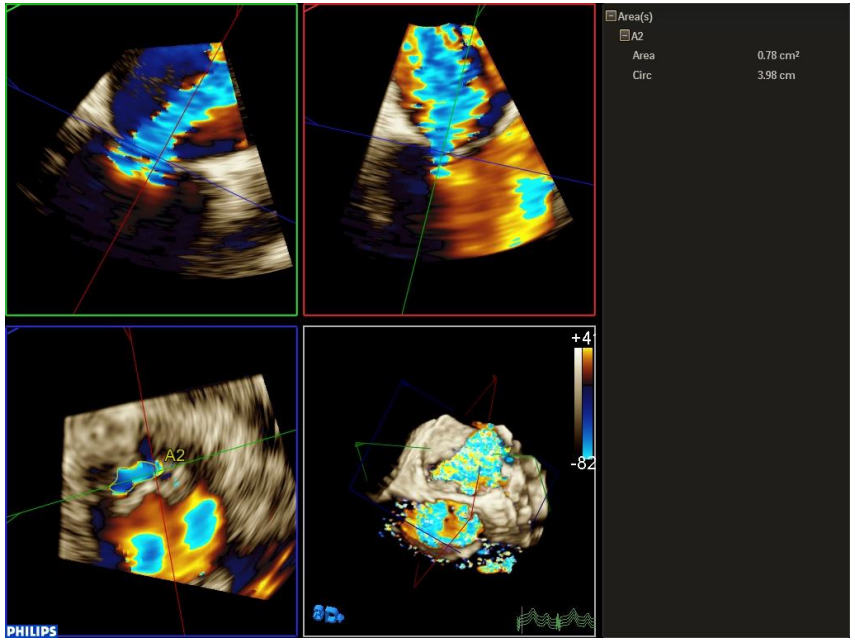
- We should continue to look for a more cost-effective way of detecting cardiotoxicity, with the primary objective to improve outcomes.
- Additional research is needed to better define monitoring guidelines.
- An effective cardio-oncology team work is crucial in order to improve CV health in cancer patients.

- 31 y.o pregnant woman (week 36)
- Admitted for acute pulmonary edema
- Hodgkin lymphoma 13 years before (QT and RT)
- Obese, BMI 36
- Sedentary
- Arterial HT






PHILIPS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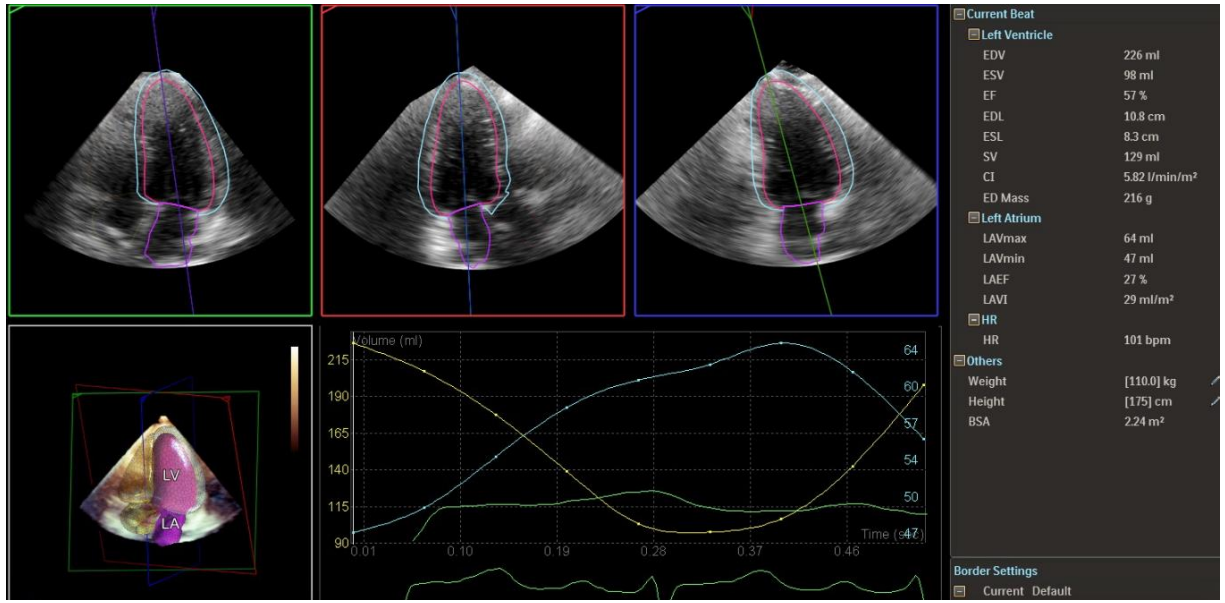
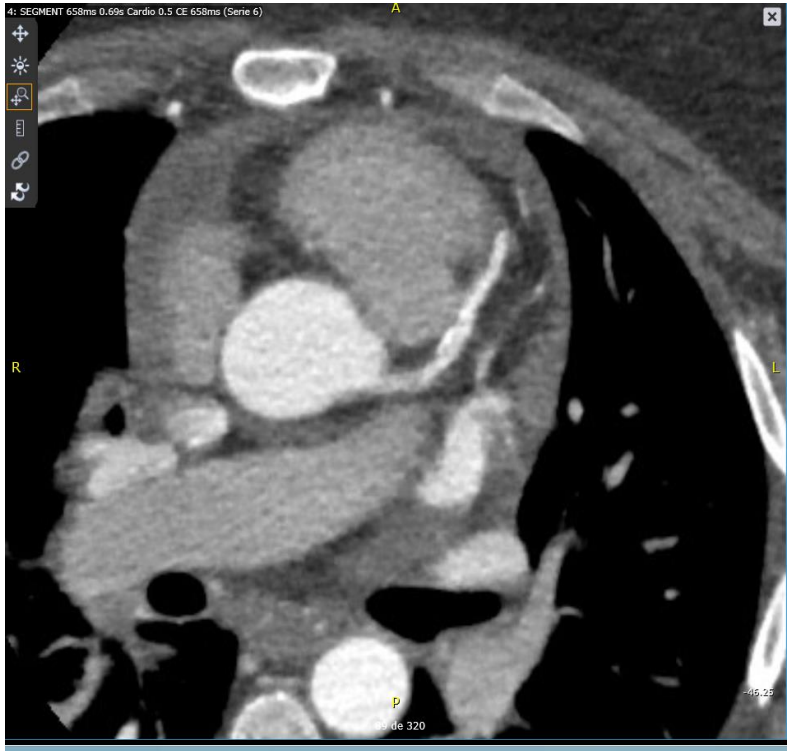
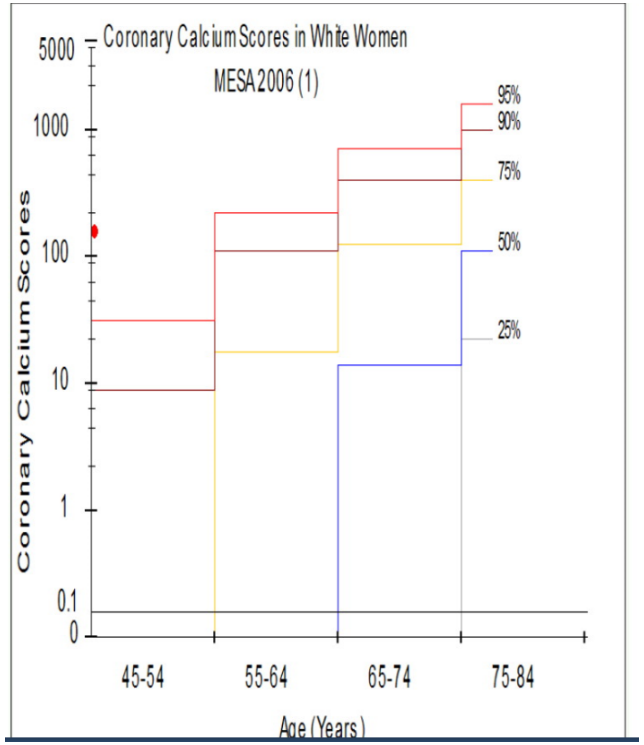
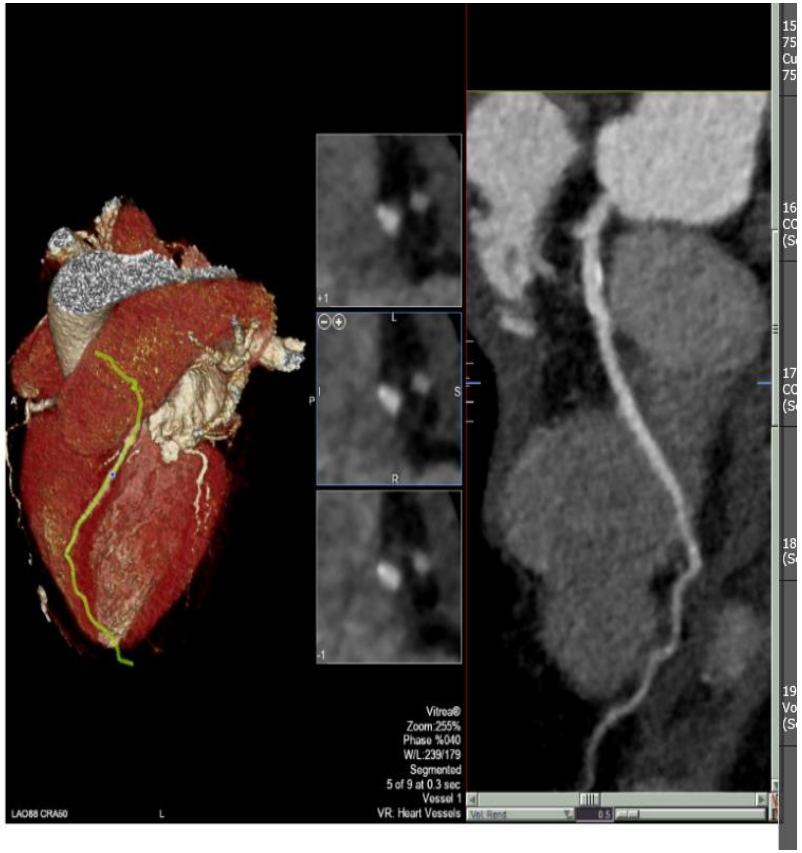
Area 0.78 cm²
Circ 3.98 cm
+4
-82
A2
PHILIPS


Current Beat
Left Ventricle
EDV 226 ml
ESV 98 ml
EF 57 %
EDL 10.8 cm
ESL 8.3 cm
SV 129 ml
CI 5.82 l/min/m²
ED Mass 216 g
Left Atrium
LAVmax 64 ml
LAVmin 47 ml
LAEF 27 %
LAVI 29 ml/m²
HR
HR 101 bpm
Others
Weight [110.0] kg
Height [175] cm
BSA 2.24 m²
Border Settings
Current Default
LV
LA
Volume (ml)
215
190
165
140
115
90
64
60
57
54
50
47
0.01
0.10
0.19
0.28
0.37
0.46
Time (s)


4: SEGMENT 658ms 0.69s Cardio 0.5 CE 658ms (Serie 6)
A
R
L
P


Coronary Calcium Scores in White Women
MESA 2006 (1)
Coronary Calcium Scores
5000
1000
100
10
1
0.1
0
95%
90%
75%
50%
25%
45-54
55-64
65-74
75-84
Age (Years)


Vitrea®
Zoom:255%
Phase %040
W/L:239/179
Segmented
5 of 9 at 0.3 sec
Vessel 1
VR: Heart Vessels
LAO88 CRA60

Teorema de Pitágoras

En un triángulo rectángulo,
el cuadrado de la hipotenusa es $a^2 + b^2 = c^2$
igual a la suma de los cuadrados de los catetos.