ESC Position Paper on cancer treatments and cardiovascular toxicity

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ESC CPG POSITION PAPER

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

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

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CARDIO-ONCO-EMATOLOGIA

Una nuova branca della Cardiologia che studia:

- la **cardiotossicità** provocata da terapie antitumorali (CHTh e RXTh) ed ematologiche
- la possibilità di **diagnosticarla precocemente** e a livello subclinico
- strategie di **cardioprotezione**

AICO

InternationalCardiOncologySociety

- **Cardiovascular diseases (CVDs) are one of the most frequent of side effects**, and there is a **growing concern** that they may lead to **premature morbidity and death** among cancer survivors.
- **Many aspects of both radiation-induced and cancer drug-induced CVD are still to be fully elucidated**.
- The **inability** to predict the long-term consequences of cancer treatment associated cardiovascular side effects leads to **under- or overdiagnosis of CVD**, sometimes resulting in the ***A)*** **failure to prevent adverse events** and ***B)*** sometimes to **inappropriate interruption of a potentially lifesaving cancer treatment**.
- The complex issue of CVD as a consequence of previous cancer treatment requires the creation of **multidisciplinary teams** involving specialists in cardiology, oncology and other related fields (**cardio-oncology teams**).
- The complexity of the clinical questions will require the definition of a **curriculum** describing the necessary **knowledge and skills** to deliver optimal care and the hospital setting in which these experts will be active.
- …also be involved in the **longterm surveillance** of cancer survivors with a potential for late-onset cardiovascular complications and in the development of **potential new treatments that may have cardiotoxic effects**

In general, the cardiovascular complications of cancer therapy can be divided into nine main categories, which are discussed in this document:

- myocardial dysfunction and heart failure (HF);
- coronary artery disease (CAD);
- valvular disease;
- arrhythmias, especially those induced by QT-prolonging drugs;
- arterial hypertension;
- thromboembolic disease;
- peripheral vascular disease and stroke;
- pulmonary hypertension and
- pericardial complications.

CAD

SCOMPENSO

rete oncologica
PIEMONTE | VALLE D'AOSTA

ARITMIE

IPERTENSIONE

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MYOCARDIAL DYSFUNCTION AND HEART FAILURE

Table 1 **Incidence of left ventricular dysfunction associated with chemotherapy drugs**[10–21]

Chemotherapy agents	Incidence (%)
Anthracyclines (dose dependent)	
Doxorubicin (Adriamycin) 400 mg/m² 550 mg/m² 700 mg/m²	 3–5 7–26 18–48
Idarubicin (>90 mg/m²)	5–18
Epirubicin (>900 mg/m²)	0.9–11.4
Mitoxanthone >120 mg/m²	2.6
Liposomal anthracyclines (>900 mg/m²)	2
Alkylating agents	
Cyclophosphamide	7–28
Ifosfamide <10 g/m² 12.5–16 g/m²	 0.5 17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3–13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7–20.1[28a]
Bevacizumab	1.6–4[14b]
Pertuzumab	0.7–1.2
Small molecule tyrosine kinase inhibitors	
Sunitinib	2.7–19
Pazopanib	7–11
Sorafenib	4–8
Dasatinib	2–4
Imatinib mesylate	0.2–2.7
Lapatinib	0.2–1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11–25
Bortezomib	2–5
Miscellanous	
Everolimus	<1
Temsirolimus	<1

[a]When used in combination with anthracyclines and cyclophosphamide.
[b]In patients receiving concurrent anthracyclines.

The cardiotoxicity of **ANTHRACYCLINES** may be **acute, early or late**.

Acute toxicity, predominantly supraventricular arrhythmia, transient LV dysfunction and electrocardiographic (ECG) changes, develops in *<1% of patients* immediately after infusion and is *usually reversible*

Early effects occur within the *first year* of treatment,
while **late** effects manifest themselves after *several years* (median of *7 years* after treatment).

If anthracycline-associated cardiac dysfunction is **detected early and treated** with HF medications, patients frequently have a *good functional recovery*.

Conversely, if patients are identified **late after** the onset of cardiac dysfunction, HF is *typically difficult to treat*.

Classification of AC-induced cardiotoxicity

	ACUTE	EARLY-CHRONIC	LATE
Characteristics	**Acute cardiotoxicity**	**Early-onset, chronic cardiotoxicity**	**Late-onset, chronic cardiotoxicity**
Onset	During or within 2 weeks after AC treatment	Within 1 year after the completion of AC treatment	>1 year after the completion of AC treatment
Dose dependent	Unknown	Yes	Yes
Clinical features	Depression of myocardial contractility	Dilated/Hypokinetic cardiomyopathy	Dilated/Hypokinetic cardiomyopathy
Course	Usually reversible	Usually irreversible. Refractory to traditional HF therapy Poor prognosis	Usually irreversible. Refractory to traditional HF therapy Poor prognosis

Modified from Grantis et al. Crit Rev Oncol Hematol 1998, and Grenier and Lipshultz Semin Oncol1998

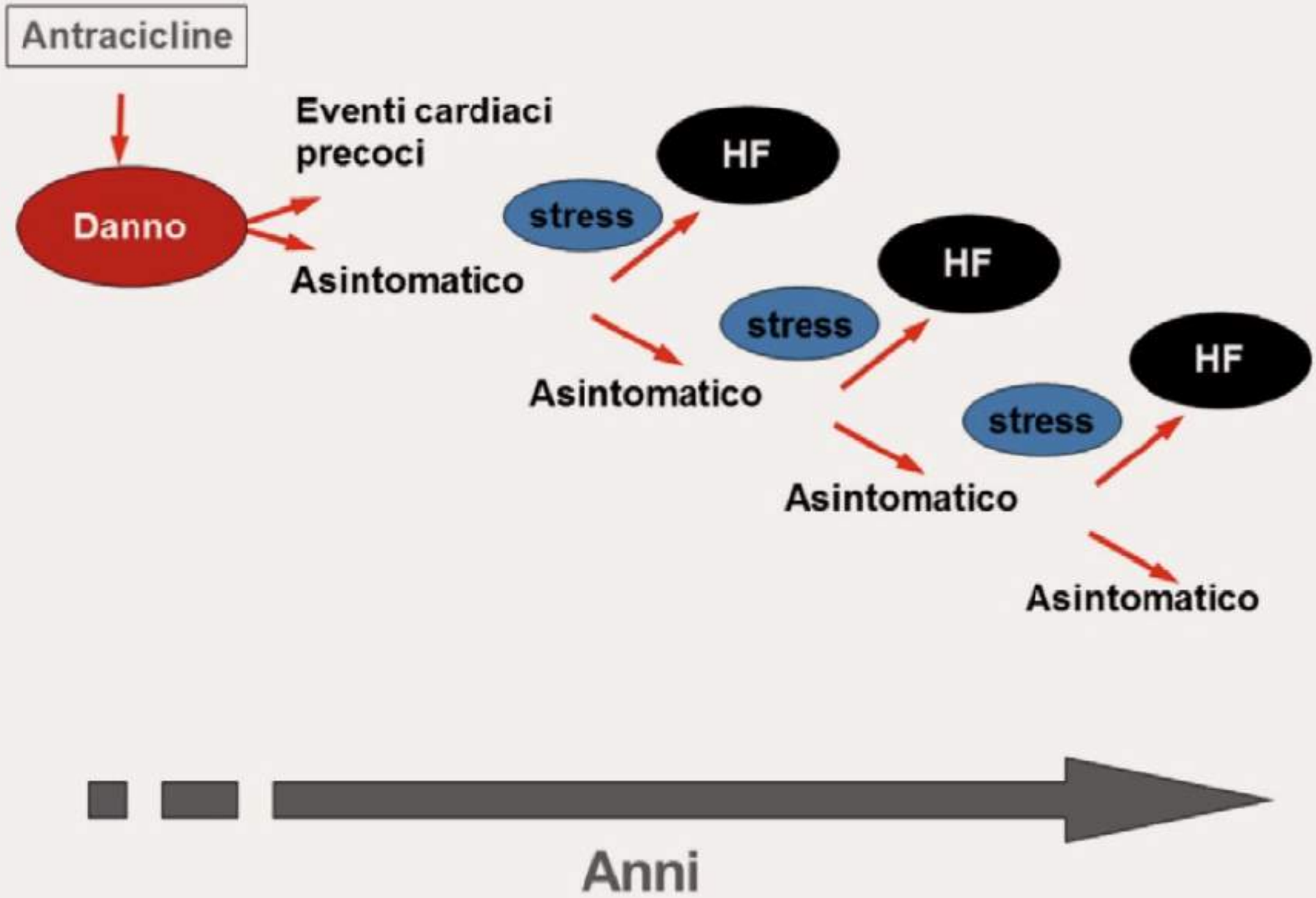

Figura 2.1 **Teoria degli stress multipli.** Secondo tale teoria, il danno da antracicline può rimanere asintomatico fino a che non si verificano, anche a distanza di anni, eventi stressogeni che possono determinare scompenso (Hearth Failure, HF)

CLASSIFICAZIONE della CTX

Table 1 Characteristics of type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

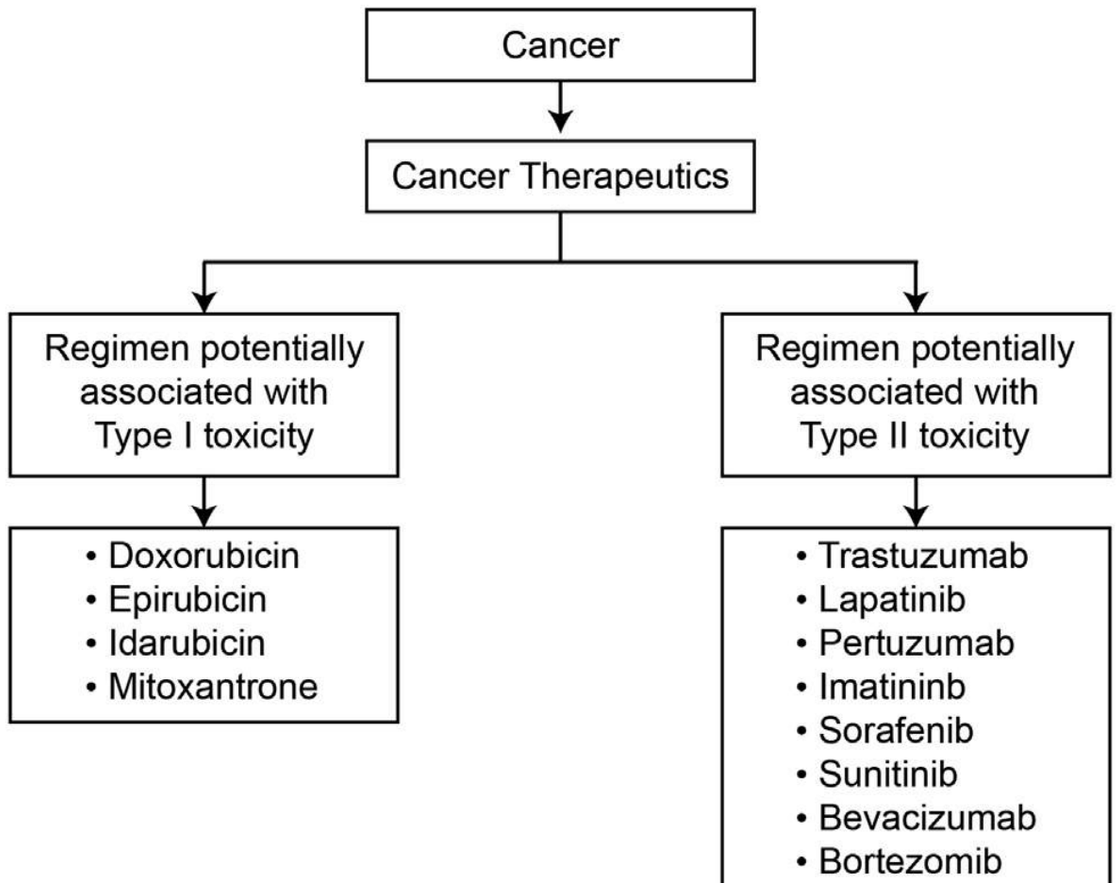

Table 2 **Factors associated with risk of cardiotoxicity following treatment with anthracyclines**[a]

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).

Table 5 Anthracycline equivalence dose considering doxorubicin in rapid infusion as a reference[94]

Drug	Relative cardiotoxicity	Incidence of HF rises to >5% when cumulative dose exceeds (mg/m^2)
Doxorubicin rapid infusion	1	400
Epirubicin	0.7	900
Daunorubicin	~0.75	800
Idarubicin	0.53	150

OTHER CONVENTIONAL CHEMOTHERAPIES

Other conventional chemotherapies that can induce myocardial dysfunction and HF are **cyclophosphamide, cisplatin, ifosfamide and taxanes (paclitaxel and docetaxel)**.

Cyclophosphamide cardiotoxicity is relatively rare and is primarily seen in patients receiving high doses (**>140 mg/kg**) before bone marrow transplantation.

Risk factors include **total bolus dose**, **older age**, **combination therapy** with other cancer drugs and mediastinal irradiation

IMMUNOTHERAPIES AND TARGETED THERAPIES

Inhibition of human epidermal growth factor receptor 2 (**HER2**) signalling with either antibodies [**trastuzumab, pertuzumab, trastuzumab-emtansine** (T-DM1)] or **TKIs** (**lapatinib**) have **improved outcomes** of patients with HER2-positive breast cancer when used in conjunction with chemotherapies

Concomitant or previous use of anthracyclines substantially increases the cardiotoxicity of trastuzumab

Applying **trastuzumab after anthracyclines**, or using an anthracycline-free chemotherapy regimen, substantially reduced the rate of clinical HF

2.1.1.4 INHIBITION OF THE VASCULAR ENDOTHELIAL GROWTH FACTOR SIGNALLING PATHWAY

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

CTX II

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 - TKIs-inhibitors - Proteosome-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 - Bortezomib - Dasatinib - Carfilzomib	• 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.

RADIOTHERAPY

Marked **interstitial myocardial fibrosis** is common in RxT-induced cardiotox

- The actual **incidence** of radiation-induced cardiotoxicity is **difficult** to evaluate for several reasons:
  - long delay between exposure and clinical manifestation of heart disease
  - use of concomitant cardiotoxic chemotherapy
  - continuous improvements in radiation techniques

- Some studies found a relative risk of **fatal cardiovascular events** between 2.2 and 12.7 in survivors of Hodgkin lymphoma and 1 - 2.2 in breast cancer.
- Absolute excess risk of mortality = 9.3-28/10 000 person-years of follow-up.
- Among survivors, the **risk of HF** was increased **4.9-fold**.

- 1820 adult survivors of childhood cancer:
  - **22%** exposed to **radiotherapy alone** had evidence of **diastolic dysfunction**
  - **27.4%** showed **reduced exercise capacity** (<490 m 6-min walk).
  - **Systolic dysfunction** observed when **RxT combined with anthracyclines**.

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.

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DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

The **first step** to identify patients at increased risk for cardiotoxicity consists of a **careful baseline assessment of cardiovascular risk factors**

It is **critical to detect subclinical** cardiac abnormalities, which may **influence clinical decisions** regarding the **choice** of chemotherapy, indication for **cardioprotection** or increased **surveillance frequency** (e.g. asymptomatic LV dysfunction

CARDIOVASCULAR MANAGEMENT OF PTS TREATED WITH ANTHRACYCLINES

For Pt treated with adjuvant anthracyclines, **baseline cardiac function should be assessed**.

If **systolic dysfunction or significant VHD** is found, the patient should be discussed with the **oncology team** and options for **non-anthracycline–containing chemotherapy** and/or **cardioprotection** should be considered. If used, a **second assessment** of cardiac function should be performed at the **end of the treatment**, particularly when the patient has an increased risk for cardiotoxicity or consecutive treatment

For **higher-dose** anthracycline-containing regimens **and** in patients with **high baseline risk**, **earlier** **assessment of cardiac function** after a cumulative total doxorubicin (or equivalent) **dose of 240 mg/m^2** should be considered.

Measurement of at least one cardiac **biomarker**— high-sensitivity **troponin** (I or T) or a **natriuretic peptide**—may be considered at *baseline* and with *each cycle* of anthracycline-containing chemotherapy.

To date, this suggested strategy has **not been validated** to prevent or improve longer-term toxicity events, but identifies **patients at greater risk for cardiotoxicity**, who may benefit from measures to prevent cardiotoxicity

DEFINIZIONI E LIMITI EF

- Differenze di “**cut-off**” di normalità tra le diverse Guidelines:
  - ESC: **50%**
  - ESMO: **55%**
  - Expert consensus imaging ESC: **53%**

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*

La cardiotossicità è caratterizzata da almeno uno tra:

-sintomi di scompenso cardiaco

-segni clinici di scompenso cardiaco (es. T3 o tachicardia)

-Riduzione di EF di almeno 5% sotto i 55% con sintomi o segni di scompenso

-Riduzione del 10% sotto i 55% senza segni o sintomi associati

European Heart Journal – Cardiovascular Imaging (2014) **15**, 1063–1093
doi:10.1093/ehjci/jeu192

POSITION PAPER

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

Juan Carlos Plana[1], Maurizio Galderisi[2], Ana Barac[3], Michael S. Ewer[4], Bonnie Ky[5], Marielle Scherrer-Crosbie[6], Javier Ganame[7], Igal A. Sebag[8], Deborah A. Agler[1], Luigi P. Badano[9], Jose Banchs[4], Daniela Cardinale[10], Joseph Carver[11], Manuel Cerqueira[1], Jeanne M. DeCara[12], Thor Edvardsen[13], Scott D. Flamm[1], Thomas Force[14], Brian P. Griffin[1], Guy Jerusalem[15], Jennifer E. Liu[16], Andreia Magalhães[17], Thomas Marwick[18], Liza Y. Sanchez[4], Rosa Sicari[19], Hector R. Villarraga[20], and Patrizio Lancellotti[15]

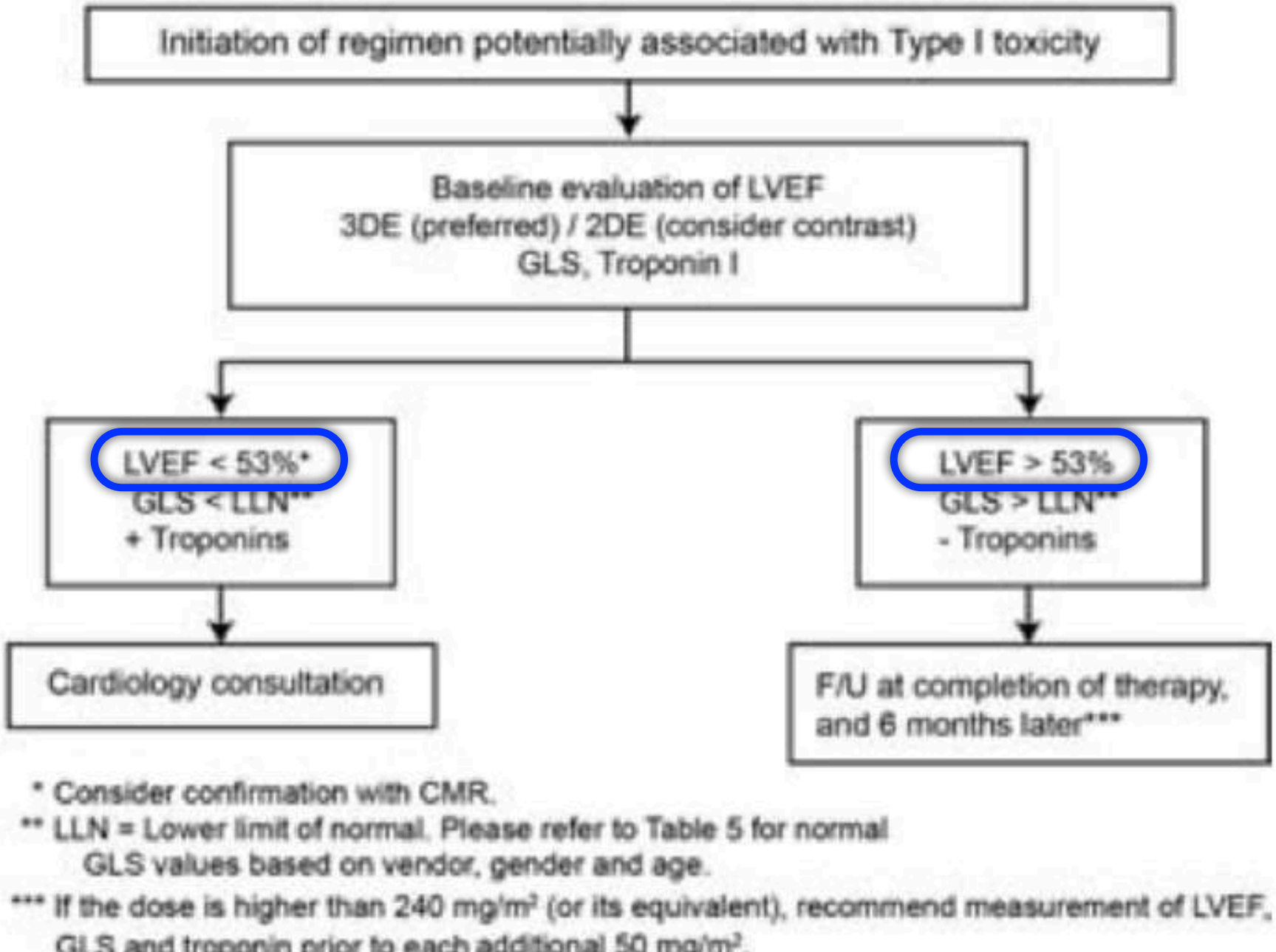

Figure 13 Initiation of a regimen potentially associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Follow-up is recommended at the completion of therapy and 6 months later for doses < 240 mg/m^2 or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m^2.

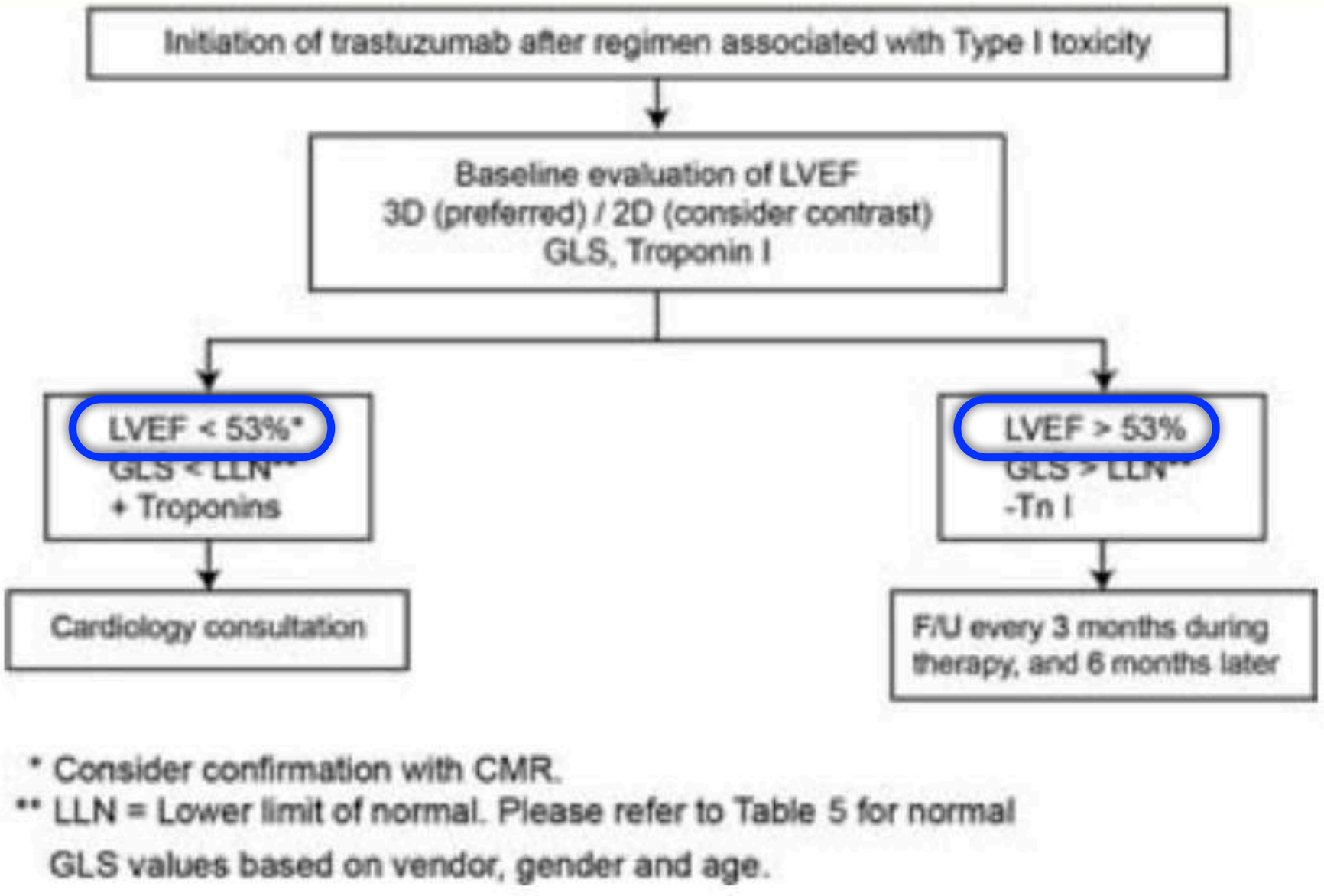

Figure 15 Initiation of trastuzumab after regimen associated with type I toxicity. A baseline evaluation including measurements of LVEF, GLS, and troponin is recommended. If any are abnormal, a cardiology consultation is recommended. Measurements of LVEF, GLS, and troponin are recommended every 3 months during therapy and 6 months later.

LINEE GUIDA ONCOLOGICHE

INTERROMPERE C.T. se:

- ↓ EF > 10p% con EF 45-49%
- EF < 45%

LIMITAZIONE delle OPPORTUNITÀ della CHEMIOTERAPIA

CARDIOTOSSICITÀ: CONSEGUENZE

- Condizionamento dell'oncologo nella scelta della terapia
- Riduzione della dose per evitare danni permanenti (**riduzione dose = limitazione efficacia**)
- Limitazione della potenziale efficacia della cura

TERAPIE ONCO EFFICACI, MA MENO DANNOSE

DIAGNOSI PRECOCE di CARDIOTOX

CARDIOPROTEZIONE

OBBIETTIVO

NON DISMETTERE LA TERAPIA ONCO-EMATOLOGICA

VALUTAZIONE dell'EF: LIMITI

- ↓ *EF = perdita di cardiomiociti (danno irreversibile)*
- *EF normale anche con alterazioni cinesi segmentaria*
- *EF = indice tardivo, poco sensibile e poco specifico, con bassa accuratezza diagnostica e scarso potere predittivo*

OBIETTIVO DEL CARDIONCOLOGO:

identificazione precoce dei Pts a rischio di sviluppare una disfunzione VS → personalizzazione del programma terapeutico cht e cardioprotezione

(= identificazione del danno in fase pre-clinica)

Classificazione AHA/ACC dello scompenso

STADIO A

Alto rischio per scompenso ma senza malattia cardiaca strutturale o sintomi di scompenso

STADIO B

Pazienti con malattia cardiaca strutturale ma senza sintomi di scompenso

STADIO C

Pazienti con malattia cardiaca strutturale e sintomi presenti o passati di scompenso

STADIO D

Scompenso refrattario che necessiti di interventi specializzati

…ppo di …logia …ca strut…

Comparsa di sintomi scompenso cardiaco

Sintomi di scompenso cardiaco refrattari, a riposo

Es.
pazienti con
- **ipertensione**
- **cardiopatia ischemica**
- **diabete mellito**

pazienti con
- **uso di farmaci cardiotossici**
- **storia familiare di cardiomiopatie**

Es.
pazien…on
- **pregresso IMA**
- **disfunzione sistolica ventricolo sinistro**
- **valvulopatie asintomatiche**

Es.
pazienti con
- **malattia cardiaca strutturale nota**
- **dispnea, fatigabilità, ridotta tolleranza allo sforzo**

Es.
pazienti con sintomi severi nonostante terapia massimale (pazienti con frequenti ospedalizzazioni che richiedono supporto terapeutico speciale)

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

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **- 3D-based LVEF** **- 2D Simpson's LVEF** **- GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA)	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures.
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: **- Troponin I** **- High-sensitivity Troponin I** **- BNP** **- NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

ACE-
LLN
pepti
ular;
retic

The same imaging modality and/or biomarker assay should be used for continued screening throughout the treatment pathway

- **Echocardiography** is the **method of choice** for the evaluation of patients before, during, and after cancer therapy.
- **Accurate calculation of LVEF** should be done with the **best method available** in the echo laboratory (ideally **3DE**).
- When using 2DE, the **modified biplane Simpson's technique** is the method of choice.
- LVEF should be combined with the calculation of **wall motion score index**.
- In the absence of **global longitudinal strain (GLS) by STE**, quantification of LV longitudinal function using mitral annular displacement by M-mode echocardiography (**MAPSE**) and/or peak systolic velocity (**S wave**) of the mitral annulus by pulsed-wave **DTI** is recommended.
- LVEF assessed by 2DE often fails to detect small changes in LV contractility.

- A quantitative assessment of **RV chamber** and function should be performed because of possible RV involvement.
- **Cardiac valves** should be **carefully evaluated** in patients undergoing chemotherapy.
- Patients with baseline or **changing valvular findings** during chemotherapy should undergo **careful reevaluation** of valve structure and function on serial echocardiography during and after the course of their treatment.
- **Pericardial disease** in oncologic patients can be associated with cardiac **metastasis** or be a **consequence** of chemotherapy and/or radiotherapy.
- **Pericardial effusion should be quantified and graded** according to standard methods.
- Echocardiographic and Doppler signs of **cardiac tamponade** should be investigated,

DIASTOLIC FUNCTION

- Use of the **E/E' ratio** remains questionable in the oncologic setting, as E and E' velocities fluctuation in these patients could be the consequence of changes in loading conditions as a result of side effects associated with the chemotherapy (nausea, vomiting, and diarrhea)
- a **conventional assessment of LV diastolic function**, including grading of diastolic function and noninvasive estimation of LV filling pressures, should be added to the assessment of LV systolic function, per ASE and EAE recommendations

STRAIN

- Myocardial deformation (strain) can be measured using DTI or 2D STE. The latter is favored because of a lack of angle dependency.
- GLS is the optimal parameter of deformation for the early detection of subclinical LV dysfunction.
- Ideally, the measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements, a relative percentage reduction of GLS of <8% from baseline appears not to be meaningful, and those >15% from baseline are very likely to be abnormal.
- When applying STE for the longitudinal follow-up of patients with cancer, the same vendor-specific ultrasound machine should be used.

The precise **timing** and **frequency** of imaging and/or biomarker sampling will depend upon:

- the specific cancer treatment
- total cumulative dose of cardiotoxic chemotherapy
- delivery protocol and duration
- the patient's baseline cardiovascular risk

SURVEILLANCE AND TREATMENT STRATEGIES

The **timing of cardiotoxicity** surveillance using **echocardiography** and **biomarkers needs to be personalized** to the patient in the context of their baseline cardiovascular risk and the specific cancer treatment protocol prescribed.

The **most important element** is **risk stratification** to guide the frequency of assessment and ensure that **higher-risk patients** have an **earlier review** to avoid missing early toxicity.

CARDIOVASCULAR MANAGEMENT OF PTS TREATED WITH ANTI-HER2

Typically cardiac monitoring is performed **every 3 months during and once after** completion of anti-HER2 treatment

CARDIOVASCULAR MANAGEMENT OF PTS TREATED WITH VEGF INHIBITORS

- The **optimal timing** of surveillance strategies for the various VEGF inhibitors known to cause myocardial dysfunction **still needs to be clarified**.
- After baseline assessment, some patients appear to develop LV dysfunction **early** after treatment onset, whereas in others this is **delayed for several months**.
- If **baseline risk is high**, it may be appropriate to consider early clinical follow-up **in the first 2 – 4 weeks**.
- Thereafter, the drug labels for all of these drugs suggest a **periodic reassessment** of cardiac function, but **do not state specifically when and how**.
- Currently, it is reasonable to consider periodic echocardiography, for example, **every 6 months** until stability in LVEF values is achieved.

2.1.3 KEY POINTS

- Cancer Pts treated with potentially cardiotoxic therapy are at high risk of developing HF and should therefore receive medical care aimed at obtaining **strict control of cardiovascular risk factors**.

- **LVEF** should be **determined before and periodically during treatment** for early detection of cardiac dysfunction in Pt receiving potentially cardiotoxic chemotherapy, with a method that provides **sufficient image quality** and, preferably, **using the same method during follow-up**.

- **The lower limit of normal of LVEF in echocardiography as 50%**, in line with the definition of cardiotoxicity commonly used in registries and trials in patients with cancer.

- A patient with a **significant decrease in LVEF** (e.g. a decrease >10%), to a value that does not drop below the lower limit of normal, should **undergo repeated assessment of LVEF shortly after and during** the duration of cancer treatment.

- If **LVEF decreases >10%** to a value **below the lower limit of normal** (considered as an LVEF **<50%**), **ACE inhibitors (or ARBs)** in combination with **beta-blockers** are recommended to prevent further LV dysfunction or the development of symptomatic HF.

- **ACEinhibitors (orARBs)** and **beta-blockers** are recommended in patients with **symptomatic HF** or **asymptomatic cardiac dysfunction** unless contraindicated.

Non solo scompenso !

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CORONARY ARTERY DISEASE

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

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

*… typically manifests **10 – 15 years after** the initial treatment, and **younger** patients are more susceptible*

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

Ann Hematol
DOI 10.1007/s00277-016-2820-x

REVIEW ARTICLE

Identification, prevention and management of cardiovascular risk in chronic myeloid leukaemia patients candidate to ponatinib: an expert opinion

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- Assessment of CAD should be based on the **history**, **age** and **gender** of the patient, considering the **use of chemotherapy drugs as a risk factor for CAD**.

- **Clinical evaluation** and, when necessary, **testing** for detection of myocardial ischemia is key to identify pts with **latent pre-existing CAD**. This may have **implications in the selection of cancer treatment**.

- Patients treated with **pyrimidine analogues** should be **closely monitored** for myocardial ischaemia using **regular ECGs**, and chemotherapy should be withheld if myocardial ischaemia occurs.

- Drug **rechallenge** after coronary vasospasm should be reserved for **when no other alternatives exist**, and only under prophylaxis and close monitoring of the patient. **Pretreatment with nitrates and/or calcium channel blockers** may be considered in this setting.

- **Long-term clinical follow-up** and, when required, testing for the presence of CAD may be useful to identify patients with cardiac disease who develop long-term complications of chemotherapy and radiotherapy.

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ARRHYTHMIAS

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Table 8 Cancer drug agents associated with cardiac arrhythmias

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

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

Arrhythmias can be present at baseline in **16–36%** of treated patients with cancer.

Table 9 Cancer drug agents associated with QT prolongation and Torsade de Pointes[151,153,154]

Cancer drug agents	Average QT prolongation (ms)	Increase in QTc >60 ms (%)	QTc >500 ms (%)	Torsade de pointes (%)
Anthracyclines				
Doxorubicin	14	11–14	NA	NA
Histone deacetylase inhibitors				
Depsipeptide	14	20–23.8	NA	NA
Vorinostat	<10	2.7–6	<1	NA
Tyrosine kinase inhibitors				
Axitinib	<10	NA	NA	NA
Bosutinib	NA	0.34	0.2	NA
Cabozantinib	10–15	NA	NA	NA
Crizotinib	9–13	3.5	1.3	NA
Dasatinib	3–13	0.6–3	<1.4	NA
Lapatinib	6–13	11	6.1	NA
Nilotinib	5–15	1.9–4.7	<1.2	NA
Pazopanib	NA	NA	2	<0.3
Ponatinib	<10	NA	NA	NA
Sorafenib	8–13	NA	NA	NA
Sunitinib	9.6–15.4	1–4	0.5	<0.1
Vandetanib	36	12–15	4.3–8	Described, % NA
Vemurafenib	13–15	1.6	1.6	Described, % NA
Others				
Arsenic trioxide	35.4	35	25–60	2.5

NA = not available.

Table 10 Risk factors for QT prolongation in cancer patients

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

LQTS = long QT syndrome.

QTc normale: < 450 ms ♂, < 460 ms ♀

Gradi di tossicità (National Cancer Institute):

I : QTc > 450-470 msec

II : QTc 470-500 msec o > 60 ms rispetto al basale

III : QTc > 500 msec

IV : QTc > di 500 con segni e sintomi (TV, torsioni di punta, ipotensione, scompenso)

Tabella . Farmaci potenzialmente a rischio di prolungare il tratto QT.

Farmaci Cardiovascolari	Farmaci SNC	Farmaci GI	Farmaci Antibatterici	Farmaci Antiparassitari	Farmaci Decongestionanti nasali e antistaminici
Amiodarone	Aloperidolo	Dolasetron	Azitromicina	Clorochina	Fenilefrina
Chinidina	Amitriptilina	Domperidone	Ciprofloxacina	Meflochina	Fenilpropanolamina
Disopiramide	Citalopram	Granisetron	Claritromicina	Pentamidina	Pseudoefedrina
Dobutamina	Cloralio idrato	Ondansetron	Eritromicina		Terfenadina
Dopamina	Clorpromazina		Levofloxacina		
Efedrina	Clomipramina		Moxifloxacina	**Farmaci Antimicotici**	**Altri Farmaci**
Epinefrina	Droperidolo	**Farmaci Respiratorio**	Ofloxacina		
Flecainide	Felbamato		Cotrimossazolo		
Ibutilide	Fluoxetina			Fluconazolo	Alfuzosina
Indapamide	Galantamina	Salbutamolo		Itraconazolo	Octreotide
Isradipina	Imipramina	Salmeterolo	**Farmaci Antivirali**	Ketoconazolo	Sibutramina
Midodrina	Levomepromazina	Terbutalina		Voriconazolo	Tacrolimus
Norepinefrina	Litio				Tamoxifene
Sotalolo	Metadone		Amantidina		Vardenafil
	Metilfenidato		Foscarnet		
	Nortriptilina				
	Olanzapina				
	Paroxetina				
	Quetiapina				
	Risperidone				
	Sertindolo				
	Sertralina				
	Tioridazina				
	Tizanidina				
	Trimipramina				
	Venlafaxina				

- A **12-lead ECG** should be recorded and the **QT interval**, corrected for heart rate with Bazett's or Fridericia's formula, should be obtained in **all** patients at baseline.

- Patients with a history of QT prolongation, relevant cardiac disease, treated with QT-prolonging drugs, bradycardia, thyroid dysfunction or electrolyte abnormalities should be **monitored** by repeated 12-lead ECG.

- Consider treatment **discontinuation or alternative** regimens if the QTc is **>500 ms**, QTc **prolongation is >60 ms** or **dysrhythmias** are encountered.

- Conditions known to provoke torsades de pointes, especially **hypokalaemia** and extreme bradycardia, should be avoided in patients with drug-induced QT prolongation.

- Exposure to **other QT-prolonging drugs** should be **minimized** in patients treated with potentially QT-prolonging chemotherapy.

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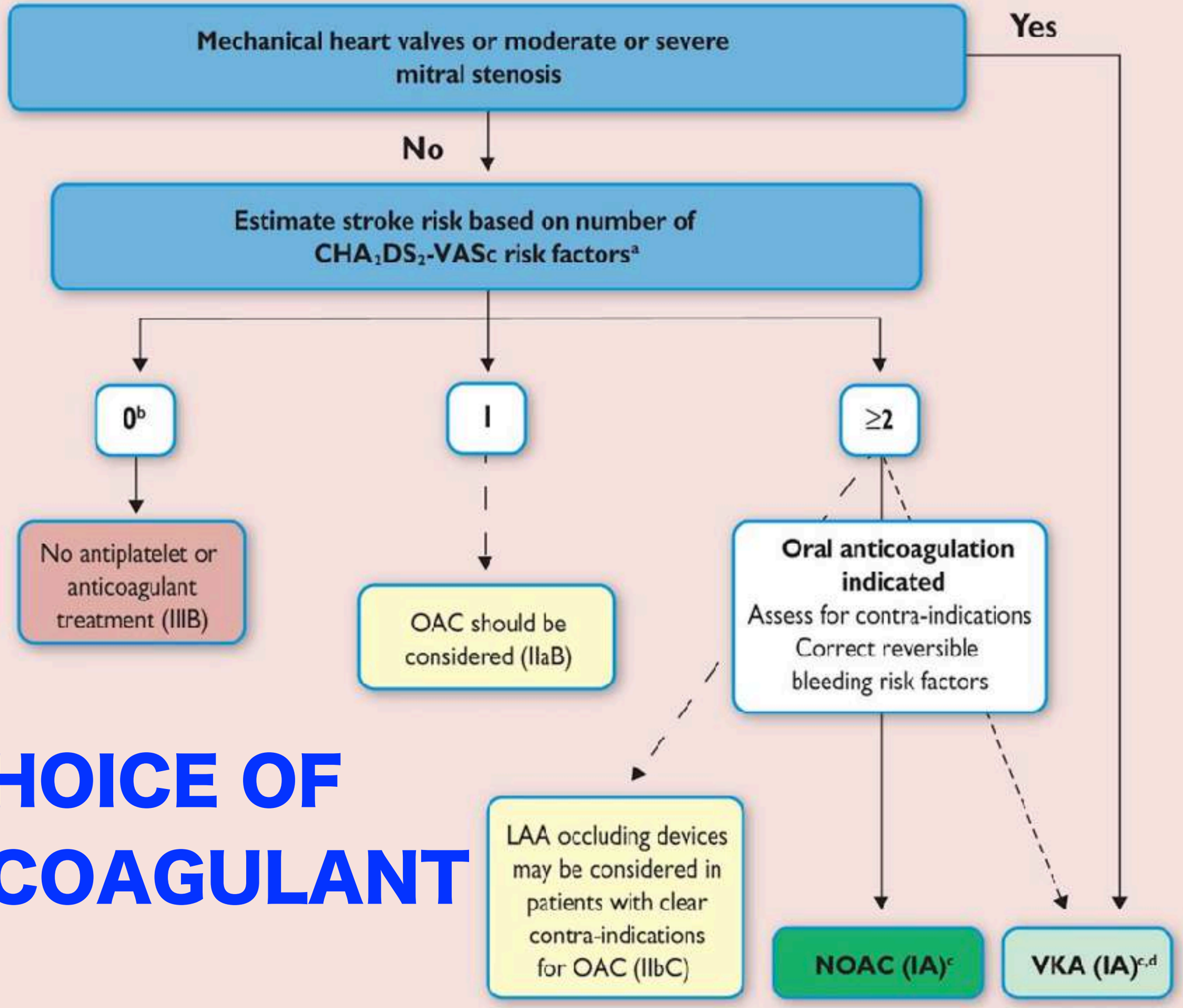
ATRIAL FIBRILLATION

- The initial approach to the **management of atrial fibrillation and atrial flutter** requires the **usual decisions** regarding rhythm management, thromboembolic prophylaxis and effective stroke prevention with oral anticoagulation

- The **balance** between **thromboembolic and bleeding risks** of atrial fibrillationis particularly **challenging** in patients with cancer. While cancer may cause a prothrombotic state, it may also predispose to bleeding. On the other hand, the CHA2DS2-VASc and HAS-BLED risk scores have **not been validated** in patients with cancer

- In patients with a **CHA_2DS_2-VASc score ≥ 2**, anticoagulation can generally be considered if the **platelet count is >50 000/mm^3**

CHOICE OF ANTICOAGULANT



Role of NOAC in Cancer Patients

Overall similar efficay, better safety for NOAC.

<u>However:</u>

- All major **NOAC trials** included **few cancer patients** (1.1% to 6%)
- Many chemotherapy drugs induce or **inhibits CYP3A4** *(rivaroxaban, apixaban)* and **p-gp** *(dabigatran, edoxaban)*
- Cancer patients **predisposition to bleeding** (thrombocytopenia, mucositis/enteritis, anti-angiogenic therapy)
- Renal dysfunction *(spt dabigatran)*
- Difficulty in swallowing, nausea, vomiting, diarrhea may limit intake and absorption
- GI bleedings may be increased *(dabigatran)*
- Availability of antidotes *(rivaroxaban, apixaban, edoxaban)*

Carrier M et al., Journal of Thrombosis and Haemostasis, 2013 11: 1760–1765

Digoxin

- Particular attention should be given to patients treated with digoxin, which can be used in atrial fibrillation to achieve heart rate control.
- In **vitro** studies characterized **ponatinib-digoxin interactions that** might increase digoxin plasma levels.
- **Periodic assessment of digoxin serum levels** should therefore be planned, similar to what is done for any patient treated with digoxin.

Breccia M et al, Ann Hematol 2016, DOI 10.1007/s00277-016-2820-x

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HYPERTENSION

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

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

HTN = hypertension; VEGF = vascular endothelial growth factor.

- Hypertension should be adequately treated **according to the current standing clinical practice guidelines**, and blood pressure should be monitored **before** initiating cancer treatment and **periodically during** treatment, depending on the patient's characteristics and adequate blood pressure control (<140/90 mmHg or lower in case of proteinuria).

- Hypertension in Pts with cancer is manageable with conventional antihypertensive treatment, but **early and aggressive treatment is encouraged** to prevent the development of cardiovascular complications.

- **ACEi** or **ARBs**, **beta-blockers** and **dihydropyridine calcium channel blockers** are the preferred antihypertensive drugs.

- **Non-dihydropyridine** (Verapamil, Diltiazem) calcium channel blockers should preferably be **avoided** due to drug interactions (*CYP3A4*)

- **Dose reduction** and reinforcement of antihypertensive treatment or **discontinuation** of **VEGF inhibitors** can be considered if blood pressure is not controlled. Once blood pressure control is achieved, VEGF inhibitors can be restarted to achieve maximum cancer efficacy.

Trattamento dell'ipertensione in pazienti in terapia con anti VEGF

Target pressorio

<140/90 → si → **Stop**

no ↓ no

FdR Cardiov → es. DM, CAD, CHF, fumo, dislipidemia → Ecocardio

C **Calcioantagonisti**

Es.
- Amlodipina (5-10 mg)
- Felodipina (5-10 mg)
- Manidipina (10-20 mg)

Potenza
Eff.collat.

Buona maneggevolezza

Eff.collat.: tachicardia, edemi declivi

e/o

A **RAAS inibitori**

ACE-I

Ramipril (2.5-10 mg)

Antagonisti recettoriali dell'ang II

Telmisartan 20-80 mg, Valsartan 80-320 mg, Candesartan 4-32 mg, Irbesartan 150-300 mg, Losartan 12.5-100 mg

Eff.collat.: tosse Controind.: GFR<30 cc/m
Controllo periodico di Creatinina Na+ K+

Eventualmente associati a

B **Beta bloccanti**

Es. Nebivololo a dosaggi crescenti 2.5 mg aumentabile a 5 mg dopo 15 gg

Eff.collat.: bradicardia
Controind.: bradicardia, asma (relativa)

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THROMBOEMBOLIC DISEASE

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

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

- Tumour cells **can trigger coagulation through different pathways**, including procoagulant, antifibrinolytic and pro-aggregating activities, release of pro-inflammatory and pro-angiogenic cytokines and interaction with vascular and blood cells through adhesion molecules

- Venous thrombosis and VTE occur frequently in patients with cancer, may affect **up to 20% of hospitalized** patients

- **Antithrombotic prophylaxis** should be given for a **minimum of 4 weeks after surgery**

- The detection of thrombotic events in patients undergoing chemotherapy is based **mainly on clinical symptoms**. **No systematic screening strategy has shown any benefit**

- The decision to administer **anticoagulation** for VTE prevention in patients with cancer should always take into consideration the patient's **bleeding risk and life expectancy**

- **Treatment** of a confirmed episode of acute VTE in haemodynamically stable patients consists of **LMWH** given over a period of **3–6 months**. This strategy is **superior to VKA** therapy in patients with cancer in terms of reduced VTE events, with no difference regarding mortality or bleeding in clinical trials.

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PERIPHERAL VASCULAR DISEASE AND STROKE

- Can occur (in **up to 30%**) in patients treated with **nilotinib, ponatinib or BCR-ABL TKIs** used for chronic **myeloid leukaemia**, even in the absence of CVD risk factors

- PAD can occur as **early** as in the first months of therapy or as a **late effect** several years after treatment. Other cancer therapy–related peripheral arterial toxicity includes **Raynaud's** phenomenon and ischaemic stroke (i.e. with L-asparaginase, cisplatin, methotrexate, 5-FU and paclitaxel)

- The risk of **stroke** is increased—**at least doubled**—after mediastinal, cervical or cranial **radiotherapy**.

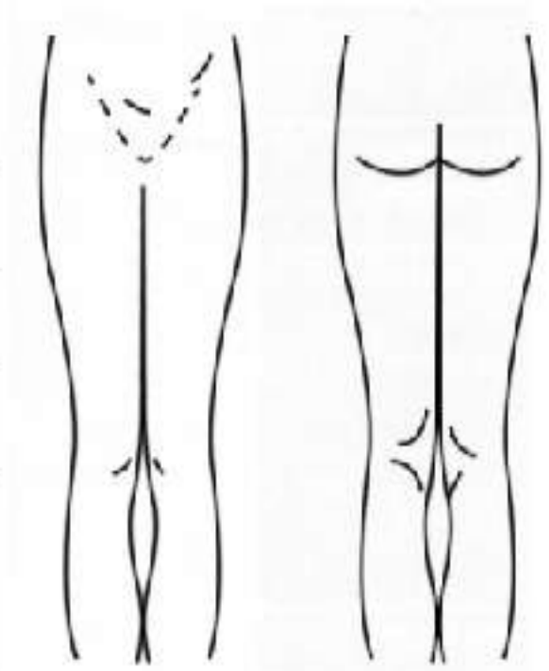
- The **assessment of PAD risk at baseline** (risk factor assessment, clinical examination, ankle–brachial index measurement) is recommended.

- **Antiplatelet drugs** should be considered mostly in **symptomatic** PAD.

Edinburgh Claudication Questionnaire

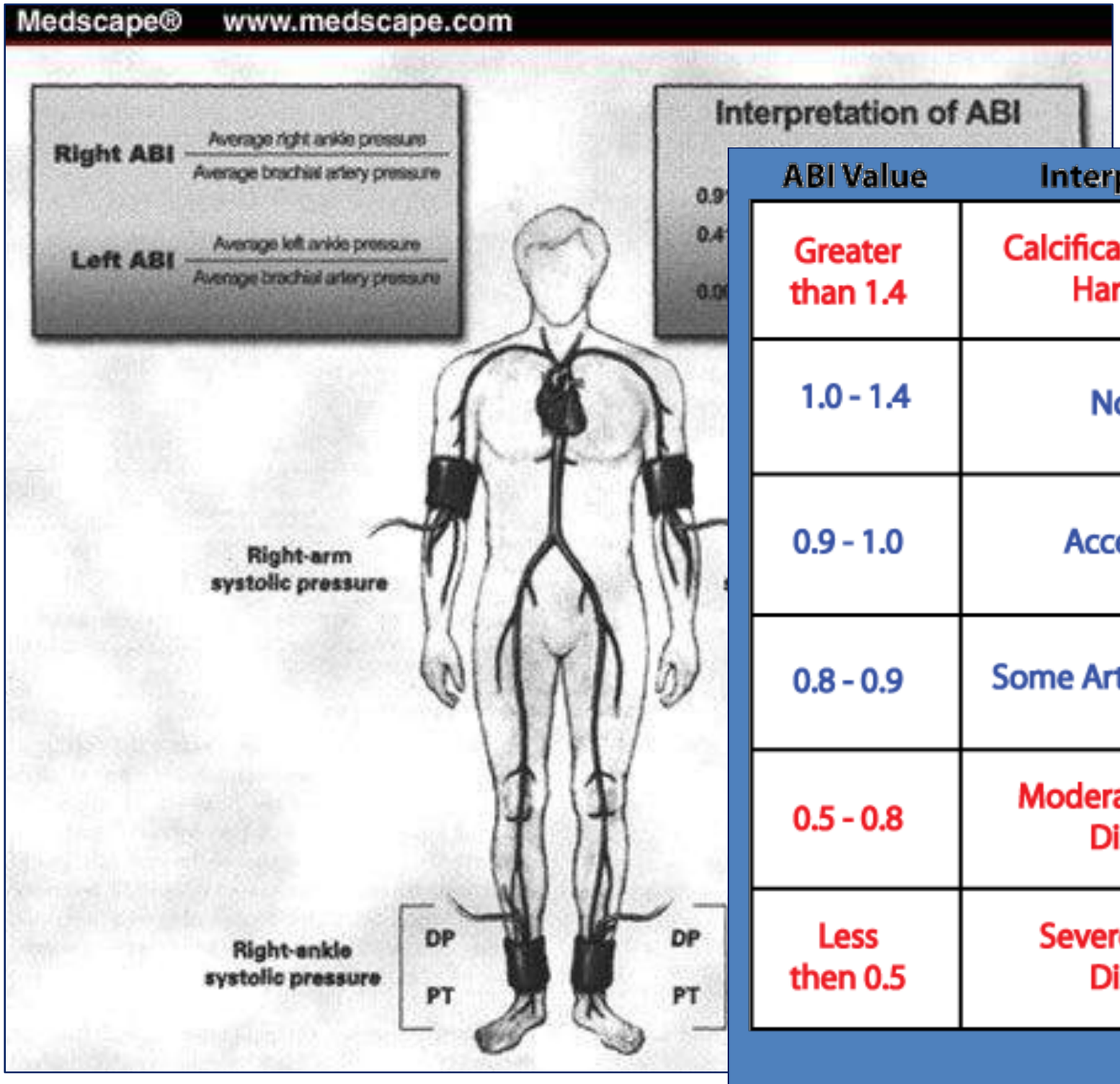
The Edinburgh Claudication Questionnaire:
CAD/PVD

* A positive questionnaire diagnosis of claudication is made only if the ***"correct"*** answer is given to ***all questions***

Questions	Correct Answer	
1. Do you get pain or discomfort in your legs(s) when you walk? ○ Yes ○ No ○ Unable to walk • If you answered "yes" to question 1, please answer the following questions	Yes	
2. Does the pain ever begin when you are standing or sitting still?	No	
3. Do you get it when you walk uphill or in a hurry?	Yes	
4. Do you get it when you walk at an ordinary pace on the level?	Yes	
5. What happens if you stand still? • Usually continues for more than 10 minutes? • Usually disappears in 10 minutes or less?	 No Yes	
6. Where do you get this pain or discomfort? • Mark the places with an "X" on the diagram		

Leng G et al., J Clin Epidemiol 1992; 45: 1101-1109.

Ankle-Brachial Index



ABI Value	Interpretation	Recommendation
Greater than 1.4	Calcification / Vessel Hardening	Refer to vascular specialist
1.0 - 1.4	Normal	None
0.9 - 1.0	Acceptable	
0.8 - 0.9	Some Arterial Disease	Treat risk factors
0.5 - 0.8	Moderate Arterial Disease	Refer to vascular specialist
Less then 0.5	Severe Arterial Disease	Refer to vascular specialist

Primary Prophylaxis

- Given that arterial thrombotic risk from ponatinib is high, and that ponatinib per se introduces thrombotic risk, **primary prophylaxis** with aspirin (75-100 mg/day) or clopidogrel (75 mg/day) might be considered even for low risk patients.
- There is **no level of evidence** to support such therapeutic decision, which therefore rests with haematologists and cardiologists jointly assessing patients risk scores and the added risk introduced by ponatinib.
- In cases when antiplatelet drugs were prescribed, **platelet count** should be checked periodically and prophylaxis should be discontinued when platelet counts decreases to below 50.000/µL, a safety cut-off reported in the summary of product characteristics.

Breccia M et al, Ann Hematol 2016, DOI 10.1007/s00277-016-2820-x

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PULMONARY HYPERTENSION

- Pulmonary hypertension is a rare but serious complication of some cancer agents and stem cell bone marrow transplantation (**TKIs family**: imatinib, dasatinib)

- **Dasatinib**, used as second-line treatment for chronic myelogenous leukaemia, can induce severe precapillary pulmonary hypertension.

- This condition appears **8–40 months after exposure** to dasatinib, with clinical and haemodynamic presentation suggestive of PAH.

- Unlike other forms of PAH, this is **often reversible** after drug discontinuation or replacement with another TKI, such as nilotinib.

- Recently, **cyclophosphamide** and other alkylating agents were suggested as contributing to the development of pulmonary veno-occlusive disease

Table 12 Strategies for surveillance and management of drug-induced pulmonary hypertension

Baseline assessment	• Consider risk factors and associated conditions for PAH[a] • Assess NYHA/WHO functional class • Consider 6-minute walk test • Consider NT-proBNP • Assess echocardiographic level of probability of PH
Surveillance strategy	**Asymptomatic** • Assess NYHA/WHO functional class every 3 months • Assess echocardiographic level of PAP every 3 months • Consider presence of other indications for right heart catheterization • Consider further evaluation for suspected PH[a] **Symptomatic** • Assess NYHA/WHO functional class • Perform 6-minute walk test • Sample blood for NT-proBNP • Assess echocardiographic level of probability of PH • Consider indications for right heart catheterization in PH referral centre[a] • Consider interruption of cancer therapy[b]

NT-proBNP = N-terminal fragment B-type natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; WHO = World Health Organization.

[a]See diagnostic algorithms for suspected PH in European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines on Pulmonary Hypertension (2015)[208].

[b]Dasatinib-incuced PH usually reversible with drug cessation.

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STRATEGIES FOR PREVENTION AND ATTENUATION OF CARDIOVASCULAR COMPLICATIONS OF CANCER THERAPY

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

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

Improvement of:

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

Reduction in:

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

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oncologica
PIEMONTE | VALLE D'AOSTA

TERMINE CHT e F.U. 6 MESI:
VISITA, ECG, ECHO

F.U. 1 ANNO:
VISITA + ECG; *ECHO se indicato*

F.U. 5 ANNI:
VISITA, ECG, ECHO

F.U. 10 ANNI:
VISITA, ECG, ECHO

RIDUZIONE EF e CARDIOPROTEZIONE

- EF > 50% e ⬇ EF ≥ 10 p.% rispetto al basale: proseguire CHT (antracicline) o transtuzumab
- EF 45-49% e ⬇ EF ≥ 10 p.%: rivalutazione dopo 3 settimane --> se confermata, sospensione trattamento
- EF < 45%: stop CHT e considerare regimi CHT alternativi

In tutti iniziare CARDIOPROTEZIONE con:
- ACEinibitori (*ramipril*) **e/o sartani** (*val-,telmisartan*)
- Beta-bloccanti (*bisoprololo, carvedilolo*)
- Ivabradina? - Cardioxane? - Ranolazina?

VALUTAZIONE BASALE
anamnesi, EO, TnT, ECG, ECHO

RIVALUTAZIONE PERIODICA

Troponina
prima di ogni ciclo CHT

Alterazioni Troponina

CENTRO RIFERIMENTO
Molinette, Mauriziano, Candiolo, S.Giovanni Bosco

ECHO AVANZATO

ECHO
dopo 3 - 6- 12 mesi, quindi a 5 anni

SE VARIAZIONI

ALTERATO

RIVALUTAZIONE + CARDIOPROTEZIONE

NORMALE

RMN ?