



Approach to cardiovascular disease in women with breast cancer: a position statement of the National Association of Cardiologists of Mexico (ANCAM)

Abordaje de la enfermedad cardiovascular en mujeres con cáncer de mama: posicionamiento de la Asociación Nacional de Cardiólogos de México (ANCAM)

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ABSTRACT

Cardiovascular disease is the leading cause of death in breast cancer survivor women. The magnitude of cardiotoxic effects depends not only on antineoplastic treatment, but also on individual susceptibility, which is determined by pre-existing cardiovascular disease and concurrent risk factors, as well as on prevention interventions, early identification and treatment of cardiotoxicity. The National Association of Cardiologists of Mexico, immersed in this reality, shares in this document an approach that explains the interaction of the two entities from the perspective of high-risk women and summarizes current detection and cardio-protection strategies.

RESUMEN

La enfermedad cardiovascular es la primera causa de muerte en la mujer que sobrevive al cáncer de mama. La magnitud de los efectos cardiotoxícos depende no sólo del tratamiento antineoplásico, sino de la susceptibilidad individual, que está determinada por la enfermedad cardiovascular preexistente y los factores de riesgo concurrentes, así como de las intervenciones en la prevención, identificación y tratamiento oportuno de la cardiotoxicidad. La Asociación Nacional de Cardiólogos de México, inmersa en esta realidad, comparte en el presente documento un abordaje que explica la interacción de las dos entidades desde la perspectiva de la mujer de alto riesgo y resume las estrategias de detección y cardioprotección actuales.

INTRODUCTION

The main causes of death worldwide are cardiovascular disease (CVD) and cancer. In Mexico ischemic heart disease (IHD) and cerebrovascular events are responsible for 20.8% of total mortality in women.¹ Parallel, breast cancer (BC) is the main oncological disease of Mexican women and responsible of 15.2% of the overall cancer mortality. As in other regions of the world, both entities show a growing trend of 14.5% and 21% respectively in the last quinquenio.^{1,2}

More than half of survivors of BC are > 65 years,³ people at increased risk of cardiovascular (CV) outcomes, considering high prevalence

of risk factors (RF) and aging.⁴ As a result of anti-cancer therapies, the cancer population has five times more CV risk than its peers, including increased susceptibility to the development of heart failure (HF), myocardial infarction (IM), valvulopathies and pericardial disease.^{5,6} CVD is the leading cause of death in BC survivors regardless of cancer subtype.⁷⁻⁹

The BC and CVD are linked during evolution in different ways: a) 27% of cases of BC are attributable to overweight/obesity, physical inactivity and alcohol,¹⁰ among other RF shared with CVD such as a family history and smoking.¹¹ b) selection of oncological therapy will depend on the cardiovascular status of women and the early and late potential cardiotoxic

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effects.¹² c) an early pathophysiology in both entities^{3,12,13} would explain the increased risk for incident CVD in women with BC and a high incidence of cardiovascular mortality in survivors.⁷⁻⁹

The problem with BC in Mexico lies not only in its impact on health, but also in the lack of interdisciplinary guidelines as well as the limited number of specialists and reference centers in cardio-oncology for the comprehensive management of these patients. The National Association of Cardiologists of Mexico (ANCAM) in this document attempts from a cardiological perspective to issue practical recommendations for the identification of women at risk, monitoring measures and early detection and prevention strategies to limit the damage. We hope that this review will be complementary to the current Mexican consensus¹⁴ as a strategy for the multidisciplinary management of women with BC.

I. CARDIOVASCULAR DISEASE AND BREAST CANCER. WHY IS IT IMPORTANT TO CONSIDER THEM AS A CONTINUUM?

1. Shared multiple risk factors

Radiation and chemotherapy for breast cancer are currently recognized as nontraditional atherosclerosis cardiovascular disease risk factor (CVRF) in women.¹⁵ In the same way factors such as age, eating patterns, obesity, sedentary lifestyle and smoking have demonstrated causality in both entities.^{14,16}

Age. The incidence of any cancer is proportional to age. BC sees its highest mortality rates in ages 64 and onward. This is true for myocardial infarction (MI) or CVD as well.¹ According to the Framingham study ages older than 55 years is considered as a CVRF for women.¹⁶

Dietary pattern. Epidemiological studies have demonstrated the association of an atherogenic diet (excessive intake of processed products, high sodium, refined carbohydrates and saturated fats with a low-fiber, polyunsaturated fatty acids and mono-, antioxidants and vegetable protein) with the development of hypertension (HTN), diabetes mellitus (DM), dyslipidemia and eventually CVD.¹⁷⁻²¹ Red

meat intake increases the risk of total death, cardiovascular death and overall cancer mortality.²² Saturated fats in meat are related to the positive subtype to estrogen receptors and to the human epidermal growth factor receptor 2 (HER2-positive);²² this was evidenced by the EPIC study in 337,327 patients.²³ A high intake of carbohydrates, is associated with a negative BC subtype to estrogen receptor (RR 1.28 CI 95% 1.08-1.52).²¹

Sedentary lifestyle. A person with a daily energy expenditure equivalent to 1.5 of the basal metabolic rate (Mets) is considered sedentary.^{16,17} It is characterized by long periods of sitting, lying, or facing a screen or driving.^{16,24} In Mexico 16.7% of women do not comply with the physical activity recommendations of the World Health Organization (WHO) and 49.9% spend more than two hours/day in front of a screen.²⁵ Inactivity is responsible for 12.2% of the MI burden²⁶ in the world, and is associated with overweight and obesity, favouring other RF such as HTN, DM and dyslipidemia.^{26,27} Sedentary behavior is associated with both BC and CVD.^{24,26,28} In an observational study with 71,018 women, those sitting 10 hours/day had an increase (HR 1.18) in CVD compared to five hours.²⁷ On the other hand, moderate physical activity reduces the risk of coronary heart disease (CHD), venous thromboembolism and CVD ($p = 0.001$ for each), as demonstrated in the nine-year follow-up of one million women in the United Kingdom.²⁹ In Latin women, physical activity decreases the risk of BC, regardless of subtype.³⁰

Obesity. Overweight and obesity (O&O) are the main risk factors for CVD. Obesity is an independent risk factor (RF), not only for HTA and DM, but for MI, heart failure (HF) and cerebrovascular disease.^{31,32} In our country the prevalence of O&O in women is 75.6%,²⁵ with abdominal obesity in 87.7%, with high prevalence of metabolic syndrome (52%); an entity that doubles the risk of CVD³³ and quadruples that of MI in Latino women (HR 4.10; RR IC 95% 2.59 to 6.48).^{26,31} O&O are associated with increased BC, especially in postmenopause (12 and 25% respectively) and condition worse prognosis at any age.^{20,32,34} In the premenopause increase the risk of triple negative BC; in the post menopause the positive subtype

to hormone receptors (39% increase) and the inflammatory in both.³⁰

Smoking. The prevalence of smoking in Mexican women is 9.9%.³⁵ Smoking is the main modifiable RF in women for the development of heart disease. Suspension reduces the risk of death in women with BC.³⁶ Among the main causes of mortality attributable to this habit are MI and cerebrovascular disease. Mortality is proportional to its intensity, being 1.3 (95% CI 1.2-1.4) with 10 cigars/day and 1.8 (95% CI 1.7-1.9) with more than 10.³⁷ It is attributed 50% of heart attacks in middle-aged women with an exponential increase when combined with the use of oral contraceptives or hormonal therapy.^{38,39} Smoking is associated with the modest but significant increase in BC in women with family history, mainly if it begins at ages close to the menarche. This association is still 10, 20 or 30 years after quitting the habit (RR of 28%, 21% and 10% respectively).⁴⁰ If the woman smokes at diagnosis increases the risk of death from any cause 69%; if she continues to smoke, the risk increases by 130%.³⁶

Alcoholism. Alcohol consumption in women cannot be suggested as a CV⁴¹ prevention measure, as epidemiological and meta-analysis (MA) have shown beneficial effects as harmful in relation to consumption level and age.⁴² A moderate consumption has shown a protective effect by reducing mortality from all causes and decreased risk of CVD compared to abstemics.⁴³ For ischemic disease, in some MA a cardioprotective effect is demonstrated. The systematic review of 44 observational studies found a J-curve effect for ischemic heart disease morbidity and mortality in which the lower risk threshold was 11 g alcohol/day losing effect with 14 g.⁴⁴ However, oncological societies classify it as carcinogenic, by increasing the risk of BC by 7-10% for every 10 g of alcohol/day in the adult woman. Prolonged use before the first pregnancy confers a significant risk for BC and breast proliferative disease, especially if initiated in the adolescent and younger adult.⁴⁵

Hormone replacement therapy (HRT). Despite the obvious benefit of estrogen in women in the cardiovascular system,⁴⁶ prescription of post-menopausal hormone replacement therapies for CVD prevention is not yet recommended.⁴¹ An increase in the risk of

BC prevails as demonstrated by the WHI study (26% increase in the group that received progestogens). In a sub analysis, potential benefit was found by prescribing minimal doses for a period of 5-7 years, in peri-menopausal women of ages 50-60, with hysterectomy and moderate to severe vasomotor symptoms, and in control of CVRF.⁴⁷⁻⁴⁹ In a recent MA with 55,757 women, its association with BC (except vaginal estrogens) is reaffirmed, mainly with the positive subtype to estrogen receptors. Use of combination therapy for 1-4 years in 50-year-old women, increased the risk by 60% (95% CI 1.52-1.69); with estrogens alone 17% (95% CI 1.10-1.26); the risk doubled in those who continued to use them for > 5-14 years.⁵⁰

2. Shared pathophysiological mechanisms

Current evidence suggests that the CVD and cancer share mechanisms in their pathogenesis (*Figure 1*).

Chronic inflammation. Atherosclerosis is considered an inflammatory disease. The persistent immunological response derived from inflammation promotes the development of atherosclerosis plaque. The plaque contains foaming cells that activate pro-inflammatory cytokines: interleukin-1, interleukin-6, tumor necrosis factor- α and interferon- γ ; reactive oxygen species (ROS), nuclear factor-K β ,⁵¹ hypoxia inducible factor-1 α .⁵² Secondary activation of fibroblasts and endothelial cells causes synthesis of adhesion proteins (VCAM-1, ICAM-1, p-selectins), growth factors (PDGF and FGF), activated plasminogen inhibitor (PAI-1) and fatty acid synthetase rate (FAS) which perpetuates cell recruitment, foaming cells and angiogenesis.⁵³ This inflammatory microenvironment is similar to what happens in cancer. Epidemiological studies consider that up to 25% of cancers are triggered by a chronic inflammatory response.⁵⁴ Chronic inflammation promotes cell proliferation, ROS production, vascular endothelium-derived growth factor (VEGF), PAI-1 and FAS, causing angiogenesis, damage and decrease in DNA repair with apoptosis limited⁵⁵⁻⁵⁷ which stimulates cancer.⁵⁸ In a succession of events, genetic changes favour the activation of oncogenes (RAS, Myc, RET)

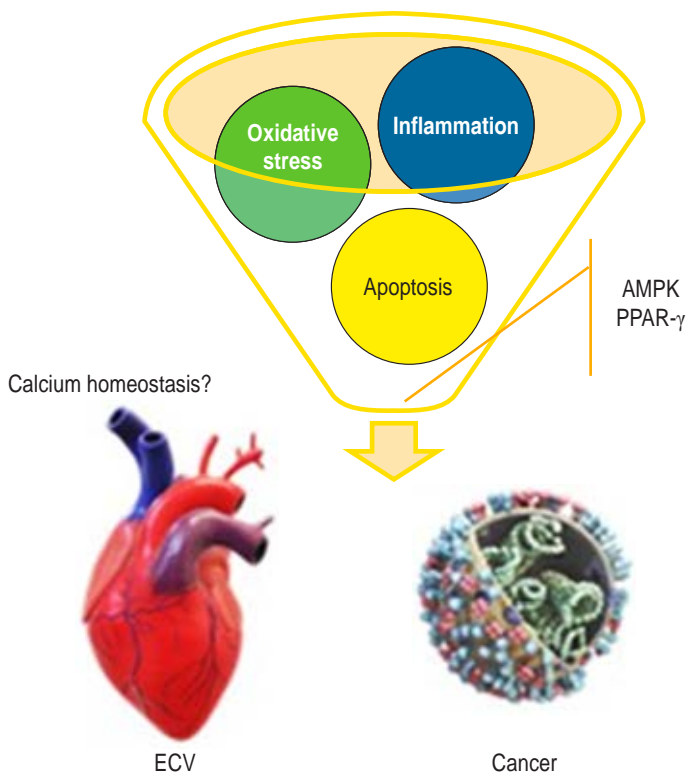


Figure 1: Pathophysiological mechanisms underlying between breast cancer and cardiovascular disease.

Inflammation, oxidative stress and apoptosis are phenomena and conditions AMPK and PPAR- γ inhibiting factors are considered.

Inflammation, oxidative stress and apoptosis are conditioning factors.

AMPK and PPAR- γ are considering inhibitors factors.

CVD = cardiovascular disease; AMPK = adenosine 5'-monophosphate-activated protein kinase; PPAR- γ = activated receptor peroxisome proliferator-gamma.

and the inhibition of suppressor genes. Several oncoproteins activate the production of inflammatory cytokines and chemokines (IL-6, IL-8, IL-1 β , CCL2, CL20).⁵⁹ Other intracellular pathways such as activated Janus kinase (JAK), activated protein kinase B (Akt) and activated mitogen protein kinase (MAPK), present in atherosclerosis and tumor angiogenesis are activated in adipose tissue.⁶⁰⁻⁶² Leptin promotes the migration of endothelial cells, secretion of VEGF and cytokines facilitate metastases.⁶³

Oxidative stress. It is the result of the imbalance between the production of ROS and reactive nitrogen species (RNS) associated with a failure in the antioxidant system responsible for its neutralization.⁶⁴ In cancer the modulator pyruvate dehydrogenase (PDH) is altered and

PDH kinase (PDK) producing cell damage by oxidation⁶⁵ and DNA instability, reducing the repair of its mutations.⁶⁴

Apoptosis. It is a self-regulating mechanism of cell growth and survival. In atherosclerosis, oxidized LDL can cause macrophage apoptosis. In cancer this mechanism seems to be altered as the cells promote the growth factor.^{64,65}

Calcium homeostasis. In hypercalcemic cancers (breast, prostate) the calcium-sensitive receptor (Casr) promotes the action of the parathyroid hormone-related peptide (PTHrP) generating osteolysis and release of bone growth factors promote the progression of cancer. In atherosclerosis, loss of Casr is associated with vascular calcification.⁶⁶

Substances inhibitory or regulatory atherosclerosis and cancer. The activated peroxisome-proliferator gamma receptor (PPAR- γ) enhances endothelial function and inhibits the production of pro-inflammatory cytokines and vascular smooth muscle cell proliferation (VSMC). In cancer it acts as a tumor growth suppressor reducing angiogenesis and proliferation.⁶⁷ Adenosine 5 monophosphate-protein kinase activated (AMPK), has anti-inflammatory effects (reduces ROS, foaming cells and VSMC and inhibits cell adhesion). In cancer it has been shown to prevent the growth of tumors such as breast,⁶⁷ lung and prostate^{68,69} by inhibiting oncogenesis by regulating specific signaling pathways.^{70,71} These protective mechanisms are targeted in the investigation of current therapies.

II. WHAT CONDITIONS FAVOR THE DEVELOPMENT OF HEART DISEASE IN PATIENTS WITH BC?

1. Pre-existing cardiovascular disease

According to the National Cancer Institute in the United States,² the average survival rate for breast cancer is 90% at 5 years and 83% at 10 years. In Mexico, five-year disease-free survival is only similar for early stages at diagnosis (96.8 and 93.4% for stages I/II, 74.6% for locally advanced and 36.4% for metastatic).⁷² In patients > 66 years, it is 48.7% to nine years, according to what was reported in a retrospective cohort of 63,566 women.⁷ Due to progress

in oncological therapies and early identification, mortality due to non-oncological cause has been increased.⁷³ In the study of Patnaik and collaborators,⁷ CVD was the leading cause of global death (15.9%). The relative risk (RR) for cardiovascular mortality was 1.24 (95% confidence interval [CI] 1.13-1.26), higher than for resolved cancer (RR 1.13, 95% CI 1.05-1.22). In a population study in Sweden in 3.68 million women with cancer only 46% died from this cause; the rest were due to CVD and myocardial infarction (hazard ratio [HR] 1.08 IC 95%, 1.03-1.13), heart failure (HR 1.29) and dementia.⁷³ Half of women in Mexico have 3 CVRF at 60 years^{4,74} conditions that potentiate the risk of developing CVD or BC. 63.2% of women aged 20-69 have abdominal obesity, 80% are obese at ages 45-69. Overall, 10-14% have DM and impaired fasting glucose that increase to 40% at age 60.⁴ Hypercholesterolemia and hypertension have an average of 13%. The prevalence of metabolic syndrome is 52.7%⁷⁵ (according to criteria of the International Diabetes Federation). The association of CVRF and breast cancer is shown in a case-control study of 96 women > 45 years with without CVD. The cases were more likely to develop metabolic

syndrome (OR = 4.21, 95% CI, 2.28-7.76), diabetes (OR = 4.42; 95% CI, 1.86-10.49), carotid atheromatous plaques (OR = 2.61, 95% CI, 1.19-5.72), hypertriglyceridemia (OR = 2.32, 95% CI, 1.33-4.0) and abdominal obesity (OR = 11.22, 95% CI, 4.0-31.65).⁹ In a retrospective study of 1,460 patients aged 66 years on average followed for five years, the linear association between the number of CVRF and the incidence of IHD, heart failure or lower survival was demonstrated (HR 1.41 for each RF; 95% CI, 1.17-1.69; p = 0.001).¹³

In various current revisions^{76,77} and clinical practice guidelines, both the traditional CVRF patient and history of receiving oncological treatment are considered at risk for HF (Stage A)⁷⁸ (Table 1).

2. The cardiotoxic effect of antineoplastic agents

There is a wide variety of clinical syndromes as an expression of antineoplastic CV toxicity (Table 2). In general cancer therapy-related cardiac dysfunction and HF are known as cardiotoxicity (CT).^{76,77,79} CT was previously classified as type I when it causes structural cardiac disturbance (injury) and type II when it causes transient

Table 1: Baseline risk factors for cardiotoxicity.

Cardiac disease current	Demographic factors and other CVRF
<ul style="list-style-type: none"> Heart failure (LVEF reduced o preserved) Asymptomatic left ventricular dysfunction (LVEF < 50% or elevated natriuretic peptide) Evidence of CHD (previous MI, angina, or coronary revascularization) Moderate to severe valvular disease with hypertrophy or impairment LV Hypertensive heart disease Cardiomyopathies (hypertrophic, dilated, restrictive) Sarcoidosis of the heart with myocardial involvement Severe cardiac arrhythmia (AF, ventricular tachyarrhythmias) Previous cardiotoxic antineoplastic treatment (use of anthracyclines or thoracic or mediastinal radiation therapy) 	<ul style="list-style-type: none"> Age (18 years; for trastuzumab > 50 years; for anthracyclines > 65 years) Family history of premature CVD (> 50 years) Hypertension Diabetes Mellitus Hypercholesterolemia Risk factors for lifestyle (smoking, high alcohol intake, obesity, sedentary lifestyle)
<p>LVEF = left ventricular ejection fraction, LV = left ventricle, CHD = coronary heart disease, MI = myocardial infarction, AF = atrial fibrillation, CVD = cardiovascular disease, CRFR = cardiovascular risk factors. Modified from: Zamorano JL et al.⁷⁶</p>	

Table 2: Toxicity of chemotherapy agents.

Agent	Most frequent toxicity	Dose associated with CD
5-Fluorouracil	Ischaemia and myocardial infarction	
Doxorubicin, epirubicin	Cardiomyopathy, myopericarditis, arrhythmias	> 250 mg/m ² > 600 mg/m ²
Cisplatin	Myopericarditis, arrhythmias	
Cyclophosphamide	Heart failure, myopericarditis, arrhythmias	Not specified
Paclitaxel, docetaxel	Heart failure, ischaemia, arrhythmias	Not specified
Methotrexate	Ischaemia, arrhythmias	
Trastuzumab	Heart failure	Therapy > 1 year
Sunitinib	Hypertension, heart failure	Not specified
Radiotherapy	Restrictive cardiomyopathy, atherosclerosis accelerated, pericardial effusion	> 30 Gy

Gy = Gray; CD = cardiac dysfunction.
Modified from: Plana JC et al.⁸⁰

cardiac dysfunction,⁷⁹ according to the harmful effect of different chemotherapeutics. Latest accumulating data on the specific incidence and reversibility⁸¹ of cardiotoxicity have forced to abandon this classification.⁷⁹ Although there is a variation in its definition across guidelines and position statements, currently definition adopted in 2016 ESC Cardio-oncology position statement, is defined as any reduction of LVEF to below 50% or a > 10% reduction from baseline falling below the lower limit of normal (a reduction of LVEF below 53% was classified as abnormal).^{76,77} The surveillance of myocardial function prior and during cancer treatment in patients without overt CVD can be the most important preventive strategy to identify asymptomatic cardiotoxicity and potentially to reduce morbidity and mortality from CVD.⁸²

The development of CT not only depends on the type(s) and dose of the agents, but also on the individual and RF susceptibility that have been identified⁷⁶⁻⁷⁹ (Table 1). The agents with recognized toxicity that are used in BC therapy are described below.

Anthracyclines. They are the cornerstone in the treatment of BC and other neoplasms. Anthracycline damage to cardiomyocyte is the prototype of type 1 chemotherapy-induced cardiotoxicity. (CCM)^{77,83} Anthracycline CT is a known ill-prognostic entity for ischemic

or dilated cardiomyopathy. However, early identification and therapy can reverse the injury. Acute form (week 1) may cause myocarditis with electrocardiographic changes and arrhythmias (20-30% and 3% respectively) and occasionally ventricular dysfunction. The chronic form occurs from the year of initiation of chemotherapy.⁸³ Occurs in 23% of cases late (mean of seven years) with ventricular dysfunction.⁸⁴ Its harmful effect is due to chelation and accumulation of intracellular iron, which produces reactive oxygen species (ROS) with the complex Topoisomerase 2 α (Top2 α) doxorubicin-DNA. Cancer cells have elevated Top2 α expression.^{12,80} Generation of ROS, xanthine oxidase, NAD(P)H oxidase (NOX) and mitochondrial complexes I and III cause damage to DNA and mitochondrial membrane, causing cell death. Inhibition of Topoisomerase 1- β has recently been proposed as a mechanism of direct cardiotoxicity, as is the case with doxorubicin.^{76,80}

Monoclonal antibodies. Inhibitors of human epidermal growth factor receptor 2 (HER2) with antibodies like trastuzumab or pertuzumab, improve tumor cure and recurrence rates in patients with HER-2 positive BC. Trastuzumab has been shown to reduce mortality by 33%.⁸⁵ But its use after anthracyclines increases the incidence of

CT.⁸⁶ Although cardiac dysfunction is usually transient in the first year, its administration for more than one year (> 1-2 years) increases the risk of mild long-term HF (7.3 and 4.45% vs with 0.9% in controls).⁸⁵ These drugs interfere with the signaling pathways of cardiomyocytes (HER2/ErbB2) reducing adaptation to stress and its survival. Its maximum cardiotoxic effect occurs when combined with other agents (anthracyclines) or in subjects with pre-existing CVD and/or 50% LVEF.^{83,86,87}

Taxanes (antimicrotubule agents). Paclitaxel and docetaxel are used in early and late phases of BC, sometimes associated with anthracyclines. They act at the level of microtubules blocking mitosis and inducing apoptosis and cell death.⁸⁰ In acute form, they cause electrical disturbances such as left bundle branch block, sustained ventricular tachycardia (in combination with cisplatin) and severe bradycardia most frequently.^{12,77,80}

Antimetabolites. 5 fluorouracil and capecitabine have rates of cardiotoxicity ranging from 1 to 68%. Most toxicity occurs in the first five days. It may occur with atrial fibrillation, no sustained ventricular tachycardia, or coronary vasospasm and MI (during infusion). Late toxicity is rare.^{76,80}

Alkylating agents. Cyclophosphamide and Cisplatin cause cardiomyocyte damage at DNA-level and its death.^{76,80} In the acute form they cause arrhythmias such as tachycardia and atrial fibrillation. Cases of fibrinous myopericarditis, a rare entity with high mortality, have been reported.^{76,80,83}

Tyrosine kinase inhibitors (TKI) and vascular endothelial growth factor inhibitors (VEGF). This group of drugs indicated for advanced and metastatic BC may produce reversible or irreversible CT, especially if combined with other therapies.^{76,77,88} Sunitinib a non-specific TKI [inhibition of VEGF, platelet-derived growth factor (PDGF) and tyrosine kinase-3] produces cardiac dysfunction in 3-15% and HF in 1-10% of patients.⁸⁹ In a meta-analysis of 21 randomized controlled clinical trials (RTC) with 1,090 patients, the risk of HF, was 2.69 times for all HF stages.⁹⁰ Inhibition of VEGF signaling also causes HTN by reduction of nitric oxide an increase of endothelin-1.^{76,88} In an RTC of 11,801 patients treated with sunitinib as mo-

notherapy or combination therapy in BC, renal and lung cancer, RR for hypertension at any stage was 3.13 (95% CI; 1.97-5.00; $p = 0.001$) and 2.44 (95% CI 1.44-4.14; $p = 0.001$) for severe HTN.⁹¹

Cyclin-dependent kinase inhibitors (CDK 4/6). Ribociclib is used in the treatment of locally advanced or metastatic BC with hormone-positive receptors and HER2-negative in combination with an aromatase inhibitor.^{12,77,88} It has cardiovascular effects, due to the prolongation of the QT interval because of its action on the conduction system.^{76,77} It is indicated only if the corrected QT interval is 450 ms or less and monitored 24 hours, 14 and 28 days after administration, and the concomitant use of other drugs that prolong QT should be avoided.^{80,88}

3. Cardiac damage secondary to radiotherapy

Radiotherapy (RT) is indicated in 50% of BC cases; it has been shown to reduce the risk of mortality from BC, however, it increases cardiovascular mortality. Acute heart exposure induces coronary endothelial damage and dysfunction, cholesterol plaque formation, and thrombosis within days of radiation. Fibrosis can evolve over time, and the manifestations can vary from accelerated atherosclerosis, thickening of the intima and atherothrombosis, with the consequent development of IHD. This usually occurs within the next 10-15 years of irradiation.^{92,93} Acute pericarditis and chronic pericardial effusion may occur six to 12 months after RT.⁹³ In the chronic form it can cause valvular disease with stenosis or regurgitation of mitral and aortic valves, disturbed heart rate and heart block due to fibrosis of the conduction system and diastolic dysfunction due to myocardial damage.^{93,94} The cardiovascular mortality RR is 1.27 times compared to women who do not receive radiation therapy.⁹⁴ The risk of CT increases with time and exposure to radiation,^{12,95} having a linear and proportional relationship between the dose received at heart level and the risk of CVD, in particular IHD. In the high-risk category, 30 Gy doses are considered when the heart is included in the radiation field.⁹⁶ The average dose received at heart is 4-5.4 Gy (range, 0.1 to 28.6 Gy) for left BC and

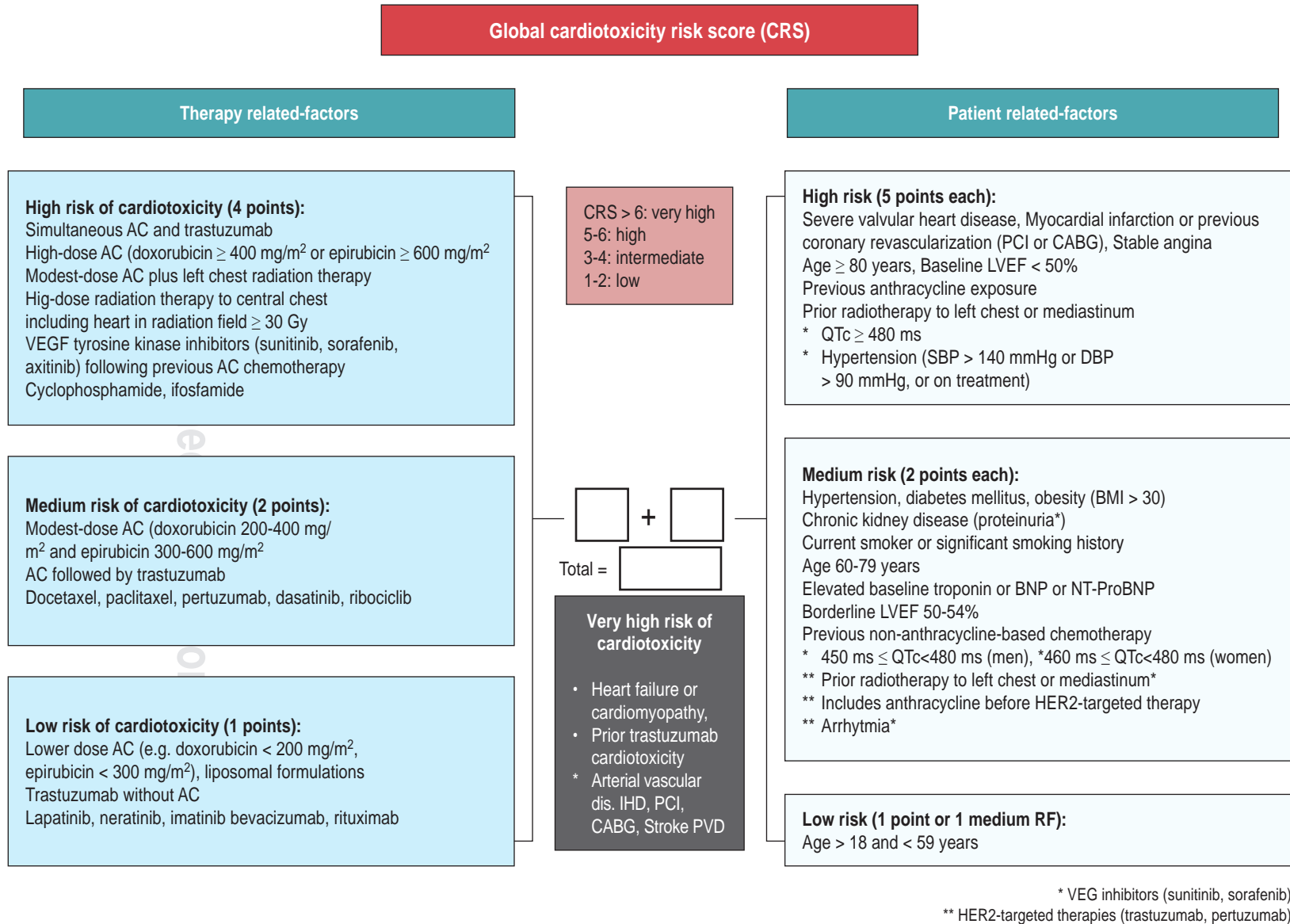


Figure 2: Global cardiotoxicity risk score (CRS).

AC = anthracyclines, VEGF = vascular endothelial growth factor, IHD = Ischaemic heart disease, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, PAD = peripheral artery disease, LVEF = left ventricular ejection fraction, QTc = corrected QT Interval, SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, BNP = brain natriuretic peptide, NT-proBNP = N-terminal pro-brain natriuretic peptide, HER = human epidermal growth factor receptor.

Modified from: Čelutkienė J et al.;⁷⁹ Herrmann J et al.⁸³

3.3 Gy (range, 0.4 to 21.6 Gy) for right side.⁹⁷ The usual dose of 4Gy at heart level increases heart mortality by 1.16 times. Coronary events are independent of coexistent CVRF.^{12,95} For each Gy in the average radiation dose, the RR of major coronary events is increased 7.4% without any safe threshold dose (95% CI 2.9-14.5; $p = 0.001$). CT occurs on average five years after radiation and remains latent for the next 20-30 years.⁹⁶ In order to reduce cardiac dose, deep inspiration, frequent apneas and prone position are practiced.^{98,99} An average heart dose of 4 Gy including regional lymph nodes is an international protocol for an allowable dose limit.¹⁰⁰ The mean cardiac doses of 1.0-2.0 Gy (left side) and 1.0 Gy (right side) are generally harmless and are achieved when regional lymph nodes are excluded. Advanced modalities such as proton therapy significantly reduce dose, especially in advanced stages of BC, however, their impact on cardiovascular events has not been defined.¹⁰¹

III. HOW SHOULD WE IDENTIFY THE HIGH-RISK PATIENT FOR CARDIOTOXICITY AND WHAT STRATEGIES SUPPORT US IN DIAGNOSIS AND SURVEILLANCE?

Patients and survivors of BC have a higher risk of developing HF, MI, pericardial disease or valvular heart disease;⁵ risk that increases with age, anthracyclines, and concurrent CVRF.^{12,13,16,77} Therefore, identification of the patient at risk begins with stratification of cardiovascular risk and relies on specific biomarkers and/or imaging techniques, which together will define the course of therapy for patients with BC.^{102,103}

In a multidisciplinary cardio-oncological approach to the evaluation of women with BC, an algorithm has been proposed to determine the general risk of suffering cardiotoxicity (*Figure 2*). This proposal includes individual risk factors and the medication related risk.^{79,83} Although there is no evidence to define the absolute risk for each of the risk groups, based on discussion and expert opinion, those can be considered as follows: low risk < 2%, medium risk 2-9%, high risk 10-19%, very high risk $\geq 20\%$. Therefore, patients with medium, high, or very high risk should be referred to

cardio or cardio-oncological assessment to optimize their management.⁸²

1. Determining the cardiovascular risk

Global Cardiovascular Risk (GCR) is the probability of developing a coronary or cardiovascular event within a given period of time and its calculation is considered the best way to address atherosclerotic disease.¹⁶ Women have special conditions to increase their GCR: (a) 52.7% of women has metabolic syndrome.^{4,74,75} Obesity, hypertriglyceridemia and diabetes have a greater impact on the development of CVD than in men.¹⁰⁴ Depression and stress are significantly associated with myocardial infarction.²⁶ b) There are women-only RF (hypertensive pregnancy disorders, fetal loss or low-weight products, polycystic ovaries, menopause and hormone therapy) and predominant factors such as systemic lupus erythematosus (SLE), rheumatoid arthritis (AR), scleroderma and BC itself.^{16,17,41} c) At least 1 of 4 women who survive BC will develop HF or premature IHD.^{6,9} d) The risk of cardiac events and/or CT is higher in patients with CVD and multiple RF.^{13,76,105} e) Framingham's risk score underestimates CVD in women with BC.¹⁰⁶ Although there is no prospective scale that integrates both risks (GCR + cardiotoxicity), it is recommended to calculate initial GCR in every woman who will receive antineoplastic therapy even in the absence of known CVD, since both patients with established CVD and those at high risk for cardiovascular outcomes and exposure to combination cancer therapy are at increased risk for CT.^{12-14,16}

The most suitable scales for the calculation of GCR in women are:

- Framingham risk scale modified (General Framingham CVD risk).¹⁰⁷ Framingham risk score estimates more accurately the GCR in Mexicans compared to the SCORE.¹⁰⁸ It allows stratification of 10-year hard events (death from coronary disease, fatal and non-fatal MI, and fatal and non-fatal CVD) and 30-year GCR. This score allows predicting HF and coronary insufficiency, common pathologies in women with BC. In 2011, a global

Table 3: Classification of CVD risk in women.

Risk level	Criteria
High risk (≥ 1 criteria)	CHD clinically manifest Cerebrovascular disease clinically Peripheral arterial disease manifests clinically Abdominal Aortic Aneurysm Chronic kidney disease or end stage Mellitus diabetes CVD risk ≥ 10% (Framingham) to 10 years
At risk (Criterion ≥ 1)	Active smoking SBP ≥ 120 mmHg, DBP ≥ 80 mmHg or hypertension treatment Total cholesterol ≥ 200 mg/dL, HDL-C < 50 mg/dL or treatment for dyslipidemia Obesity, particularly central adiposity Inadequate diet Physical inactivity Family history of premature CVD in first-degree relatives (men < 55; women < 65 years) Metabolic syndrome Evidence of advanced subclinical atherosclerosis (p. Ex., coronary calcification, carotid IMT plate or high) Systemic autoimmune collagen vascular disease (p. eg., lupus or rheumatoid arthritis) History of preeclampsia, gestational diabetes or hypertension induced by pregnancy
Ideal cardiovascular health (all the criteria)	Total cholesterol < 200 mg/dL (untreated) BP < 120/< 80 mmHg (untreated) Fasting blood glucose < 100 mg/dL (untreated) BMI < 25 kg/m ² Physical activity in goal for adults > 20 years old (≥ 150 min/week moderate intensity or vigorous intensity ≥ 75 min) Healthy diet (like DASH)

CVD = cardiovascular disease, CHD = coronary artery disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL-C = high density cholesterol, IMT = carotid media thickness, DASH = dietary approaches to stop hypertension.
 Taken from: Mosca L et al.⁴¹

risk classification was developed based on clinical data, emerging factors and women’s own RF, which facilitates the evaluation of the female risk (Table 3);⁴¹ in this classification a score of ≥ 10% on the Framingham risk score is considered high risk.

- Reynolds risk score.¹⁰⁹ Derived from the study of 25,000 women (Women’s Cardiovascular Health Study), it predicts cardiovascular outcomes to 10 years (MI, stroke, coronary revascularization, and cardiovascular death). Its objective is to reclassify the female gender with the inclusion of biomarkers (ultrasensitive reactive protein C, hemoglobin 1Ac) to traditional epidemiological RF.²²

- QRISK3-2018 risk calculator.¹¹⁰ The risk score QRISK 3 estimates risk of MI or stroke at 10 years and is applicable for ages 25-84 years. This method includes emerging CVRF with a high impact on women (body mass index, RA, SLE, atrial fibrillation, chronic kidney disease, migraine, severe mental illness).

2. Use of biomarkers to identifying myocardial damage

Chemotherapy-associated cardiomyopathy (CCM) can be detected early by myocardial biopsy or by the release of troponins into the

blood. Later stages of CCM are expressed as ventricular dysfunction and by cardiac natriuretic peptides.¹¹¹ The importance of biomarkers is in predicting the problem or subclinical detection.^{16,79,82} Cardiac biomarkers, such as troponins, BNP and NT-proBNP are used in combination with other imaging techniques during BC treatment surveillance, because their isolated use has not been shown to change clinical results^{12,79,111} (Table 4).

Troponin I. Current evidence points to troponin I (TnI) as the preferred safety indicator for predicting myocardial injury.^{111,112} It rises in 50% of patients at the end of the chemotherapy infusion.¹¹² TnI has an excellent negative predictive value for immediate CCM and during treatment.¹¹¹ The elevation of its values in the first three days of high-dose chemotherapy, predicts reduction in LVEF. In patients with TnI negative (0.08 ng/mL) immediate and at the time of chemotherapy and one month after, LVEF is not altered and they have lower rates of cardiac events (HF and asymptomatic LV dysfunction).¹¹² Other studies showed a 90% NPV to rule out doxorubicin systolic dysfunction or reversible trastuzumab-associated LV dysfunction and cardiovascular outcomes in patients with high-dose or combination chemotherapy.¹¹³ Elevation of ultrasensitive TnI is also a predictor of adverse outcomes.¹¹¹

Natriuretic peptides. Its use involves some difficulties (biological variation, variability with age, weight, renal function, and body mass index).¹¹⁴ However, its greater effectiveness in detecting asymptomatic LV dysfunction compared to troponins¹¹¹ and its ability to predict 1-year mortality are in favor of its use.¹¹² Clinical studies have used BNP and NT-proBNP as biomarkers of early damage in CCM.¹¹⁵ Elevation of BNP during anthracycline treatment is transient; if persistent symptomatic HF will develop, supporting its usefulness in long-term surveillance.^{114,116} In an early anthracycline study, elevation of BNP correlated with increased E/A ratio, suggesting its value in predicting diastolic dysfunction. Other studies demonstrate correlation with altered echocardiographic parameters when doxorubicin doses of 500 mg/m² are reached.¹¹⁷ The inverse relationship between elevation of BNP in plasma and

decrease in LVEF has been described, even in asymptomatic patients.¹¹⁸

New biomarkers in risk identification. A study of 78 patients with 15-month follow-up, in chemotherapy with doxorubicin and trastuzumab, found that early changes in ultrasensitive TnI and myeloperoxidase have a better prediction of risk for the first cardiotoxic event; elevations of placental growth factor and growth differentiation factor were also associated with risk.¹¹⁹ Determination of the N-terminal fragment of BNP (NT-proBNP) in the diagnosis and prognosis of patients with BC has heterogeneous results despite that one study points to this as the only predictor of subclinical CT after treatment with anthracyclines.¹¹⁵

3. Using imaging techniques to diagnose cardiac damage

Baseline LVEF should be reviewed as a general recommendation in all patients receiving cardiotoxic chemotherapy (Figure 3) and during treatment.^{103,120} In some cases, due to the potential risk of CVD reported in long term studies, LVEF should be examined until seven years later,^{5,8} and even monitor the patient throughout her whole life, because of the increases of HF with ageing.^{79,82,105} Due to variety of the techniques available for the measurement of LVEF, it is recommended that the same modality is used throughout the follow-up and preferably performed by the same operator to optimize the accuracy of diagnosis.^{77,79,120} Although the calculation of LVEF is the most used method for detecting CT,^{77,79,120} the best modality for early detection of myocardial damage is not yet identified.^{104,120,121} In practical terms, the selection should be based on accessibility, operator experience and specific indication of the test. Consider techniques that have less radiation dose, which provide additional information and have lower cost (Table 5).^{76,79,120,122} In general, all imaging methods have the following objectives: 1) To identify stage B of HF for the planning of therapeutic strategies. 2) To calculate with precision the volumes in the evaluation of the ventricular remodeling. 3) To identify changes in load conditions that may affect LVEF and ventricular mechanics.

Table 4: General imaging surveillance protocol during and after breast cancer therapies.

Baseline*	During therapies (qumiotherapy, radiotherapy, surgery)*:‡			Follow up*	
	Very high risk and high risk	Medium risk	Low risk	Very high risk and high risk	Medium and low risk
	Anthracycline chemotherapy surveillance				
2 DE/3DE (ideal) + GLS + cTn	3DE/2DE/+GLS • Every 2 cycles • Consider after every cycle above 240 mg/m ² doxorubicin or equivalent [§]	3DE/2DE/+GLS • Following 50% of planned total treatment or every 2 cycles (optional) • Following cycle completing cumulative lifetime cycle of 240 mg/m ² Doxorubicin or equivalent [¶]	3DE/2DE/+GLS • After 4 cycle (optional) • Following cycle completing cumulative lifetime dose of 240 mg/ m ² doxorubicin or equivalent [¶] • Every additional 100 mg/m ² doxorubicin above 240 mg/m ² or every 2 cycles	3DE/2DE/+GLS • 6 and 12 months after final cycle • Annually for 2 or 3 years thereafter and the in 3- to 5-year intervals for life	3DE/2DE/+GLS • 12 months after final cycle • 5yearly review
ECG ⁻	Biomarkers every 2 cycles	Biomarkers after 4 cycles		Biomarkers 3 and 12 months after final cycle	Biomarkers 12 months after final cycle
	Neoadjuvant HER2.targeted therapies (trasluzumab, pertuzumab) surveillance				
or CMR*	3DE/2DE/+GLS • After final AC cycles • Every 2 cycles then reduce to every 3 if stable at 3 months [‡]	3DE/2DE/+GLS • After final AC cycles • Every 3 cycles then reduce to every 4 if stable at 4 months [‡]	3DE/2DE/+GLS • After final AC cycles • Every 4 cycles	3DE/2DE/+GLS • 3 and 12 months after final cycle • Optional 6 months after final cycle	3DE/2DE/+GLS • Low risk 12 months after final cycle (6 months optional) • Medium risk: 6 months after final cycle (12 months optional)

Continue the Table 4: General imaging surveillance protocol during and after breast cancer therapies.

Baseline*	During therapies (qumiotherapy, radiotherapy, surgery)*,†			Follow up*	
All patients	Very high risk and high risk	Medium risk	Low risk	Very high risk and high risk	Medium and low risk
	Biomarkers after AC and every 2 cycles or every 3 months‡	Biomarkers after AC and every 3 cycles every 4 months‡	Biomarkers after AC every 4 cycles		
	Radiotherapy and 12 months adjuvant trastuzumab surveillance				
	3DE/2DE/GLS • Every 3 cycles + biomarkers • Optional 2 nd or 3 rd cycle	3DE/2DE/GLS • After 3 rd cycle and every 4 cycles + biomarkers	3DE/2DE/GLS • Every 4 cycles + biomarkers	3DE/2DE/GLS • 3 and 12 months after final cycle • Optional 6 months after final cycle	3DE/2DE/GLS • Low risk: 12 months after final cycle (6 months optional) • Medium risk: 6 months after final cycle (12 months optional)
	Or CMR (if pericardial effusion/constriction of vascular toxicity are suspected)	or CMR (if pericardial effusion/constriction or vascular toxicity are suspected)	or CMR (if pericardial effusion/constriction of vascular toxicity are suspected)		

* CMR or VRIE may be offered for if an echocardiogram is not available or technically feasible. Neoadjuvant or adjuvant trastuzumab, pertuzumab; VEGF inhibitors (sunitinib, sorafenib)

† In evidence of new LV dysfunction (symptomatic or asymptomatic) during treatment all low and medium CV risk cancer patients have to be reclassified as high CV risk.

‡ 300 mg/m² doxorubicin is equivalent to 420 mg/m² epirubicin, 400 mg/m² daunorubicin and 60 mg/m² idarubicin.

¶ 240 mg/m² doxorubicin is equivalent to 360 mg/m² epirubicin, 320 mg/m² daunorubicin and 50 mg/m² idarubicin

DE = dimensional echocardiography, GLS = global longitudinal strain, cTn = cardiac troponin, ECG = electrocardiogram, CMR = cardiac magnetic resonance, biomarkers = cTn/BNP, proBNP, BNP = brain natriuretic peptide, AC = anthracycline, HER = human epidermal growth factor receptor.

Adapted from: Čelutkienė J et al.;⁷⁹ Plana JC et al.;¹²⁰ Armenian SH et al.;¹²³

ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF CARDIOTOXICITY

- Left ventricular ejection fraction (LVEF). LVEF it is the most widely accepted parameter for evaluating ventricular function and for modifying systemic chemotherapy if necessary (Figure 3).^{77,79,120} CCM is defined as the absolute reduction of LVEF > 10% from baseline (in an asymptomatic patient), with LVEF below the normal limit for two-dimensional echocardiogram (2DE) considered to be 53% (American Echocardiography Society and European Cardiovascular Imaging Association).^{79,82,123} The 2DE although it is the most used method, has low sensitivity for subtle alterations since its variability is close to the diagnostic range of myocardial damage by chemotherapy (8~11%).^{76,79} Contrast use decreases inter- and intraobserver variability by defining endocardium.⁷⁶ The method of choice for calculating LVEF is real-time three-dimensional echocardiography

(3DE).^{76,79,103,120} It directly quantifies ventricular volumes and has low inter-operator variability (5.8%). Cardiac magnetic resonance imaging (CMR) is recommended in patients with suboptimal window or in case of inconclusive echocardiographic results.^{76,103,120}

- Ventricular deformation (strain) in the detection of subclinical damage. One disadvantage of LVEF is that when CT damage is detected, it may be irreversible.^{82,88} Changes in myocardial deformation are detected in patients during and immediately after treatment. Those occur before the fall in LVEF,¹²⁷ even with low doses of anthracyclines (200 mg/m²)^{124,125} and are independent of age, type of cancer and follow-up time (a 9-19% reduction of the peak of longitudinal systolic deformation, an 6-17% reduction of global radial deformation or global circumferential systolic deformation in 11-16.7%).^{124,126} 2D speckle tracking echocardiography, is most commonly used technique to global

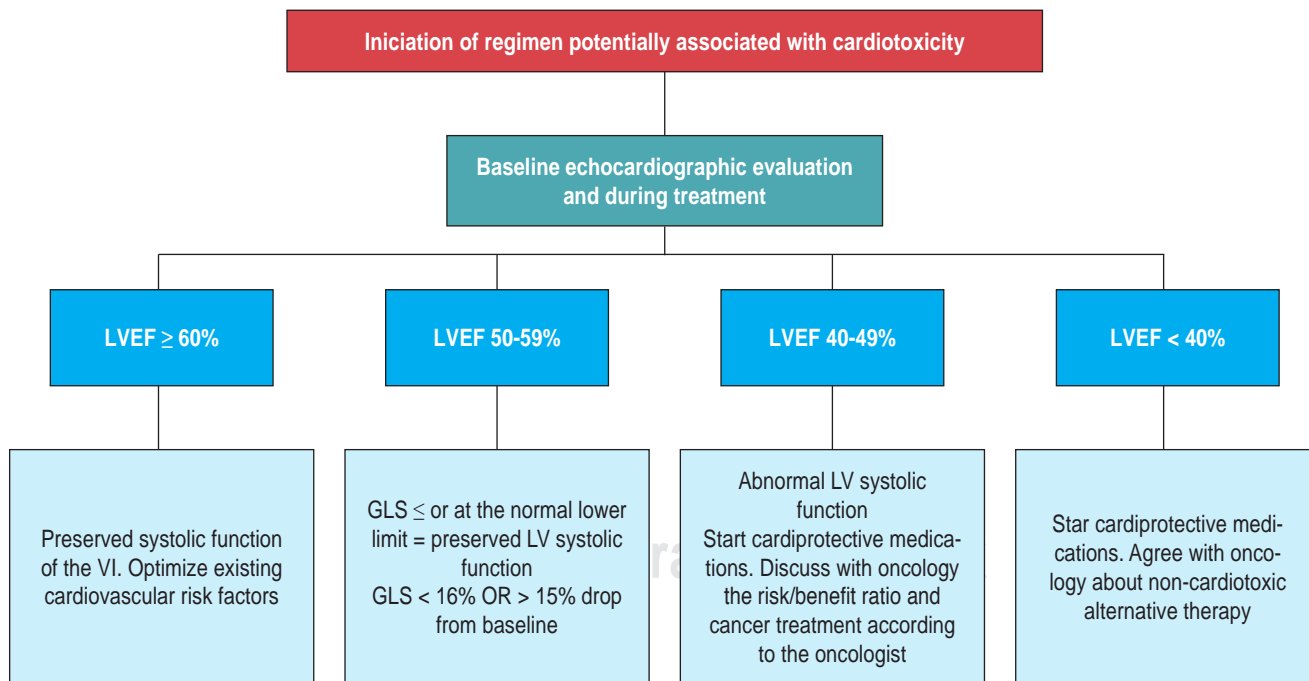


Figure 3: Follow-up algorithm in patients who will receive potentially cardiotoxic therapy. LVEF = left ventricular ejection fraction, LV = left ventricle, GLS = global longitudinal strain. Modified from: Plana JC et al.¹⁰³

longitudinal strain (GLS) assessment due to superior reproducibility (5.5 e 9.5% variability) compared with 2DE LVEF (12 e 15% variability).^{79,120} Based on GLS has being created the term subclinical CT, which is defined as a > 15% reduction in GLS compared to baseline.^{76,79,103} An 8% reduction defines patients with low risk of subclinical damage, but between 8-15% does not rule out patients at risk.¹²⁶⁻¹²⁹ In addition, changes in circumferential deformation have been associated with a higher probability of toxicity in women who received treatment for BC (RR of 31% for every 1% reduction compared to baseline).¹³⁰

- Echocardiogram in the follow-up. Although anthracycline CT may be detected several years after the end of therapy,^{125,126} there are limited recommendations for appropriate follow-up in these patients.¹³¹ Nevertheless, screening with an LVEF assessment should be considered at 6-12 months, and possibly two years post-treatment, and consideration for reassessment periodically thereafter.⁷⁷ In a two years prospective-cohort of 63 breast cancer patients treated with anthracyclines, a significant longitudinal peak systolic strain (LPSS) reduction occurred in 32.4% of 1,071 segments examined following chemotherapy.¹³² Since the endocardium is the most vulnerable structure to the toxic effects of chemotherapy, assessment of myocardial deformation with GLS surveillance may become the most sensitive strategy for early detection of CT.^{79,126,127} It has been reported that the reduction of GLS > 15% from baseline at three months, predicts LVEF drop with 79% sensitivity and 82% specificity.¹²⁹

CARDIAC MAGNETIC RESONANCE (CMR) IN THE DIAGNOSIS OF CARDIOTOXICITY

In cardio-hemato-oncology patients, magnetic resonance imaging (CMR) due to its cost, limited availability, and dependence on patient adaptation (claustrophobia, need for repeated apneas)^{79,120,133} is not usually the first-line tool to identify heart damage. However, it complements other image modes (Table 5). Due to their high accuracy and reproducibility^{76,120,133}

late reinforcement and T1 mapping techniques identify myocardial fibrosis and T1 weighted sequences including T2 mapping, detect inflammation and intracellular and interstitial oedema, even in small territories.^{103,134} So far it is not defined if the parameters obtained with CMR after treatment identify patients at risk of CT.^{76,120,135} CMR is considered as a choice between echocardiography and nuclear imaging in the following clinical scenarios:

(a) Baseline pretreatment assessment. In the confirmation of a LVEF > 50% in the patient who will start with potentially cardiotoxic chemotherapy (Figure 3), especially when a borderline LVEF has been calculated by transthoracic echocardiography (TTE). When you have a poor acoustic window for other imaging modes.^{102,103,123,133} (b) As part of the diagnostic algorithm of a coexisting cardiomyopathy.^{78,83,133} (c) Identification of early myocardial damage markers that precede clinical symptomatology and the evident decrease in LVEF, such as diffuse fibrosis and extracellular volume increase; as well as subclinical left ventricular dysfunction by myocardial deformation study.^{120,133,136} (d) Detection of acute myocarditis by the compromised immune system.^{102,120,123} (e) In the diagnosis of vascular toxicity, microvascular and endothelial dysfunction.^{76,83,133} (f) Valvular heart disease in patients with a history of radiation therapy.^{76,83,120} (g) Pericardial disease in patients receiving chest radiotherapy.^{76,103,120} (h) In the evaluation of patients with intermediate probability of CHD and/or who have received oncological regimens that cause ischemia. Especially in patients with mastectomy or implants that make echocardiographic evaluation difficult.¹⁰⁴ CMR has high diagnostic accuracy for induced ischemia and its extension.^{104,133}

In BC there are no standardized protocols, but it is recommended to review the following elements and measurements regardless of the type(s) of therapy received:^{76,102,123,136}

1. For the use of chemotherapy (with or without anthracyclines). To evaluate the structure, size, volumes and areas of the left ventricle and atrium; the quantification of LVEF and subclinical dysfunction of the left ventricle; as well as to perform analysis of tissue characterization in search of focal

- and/or diffuse fibrosis in left cavities; and to determine by myocardial stress perfusion study the presence of microvascular coronary artery disease.^{88,78,134,135}
- For the use of radiation therapy. To evaluate LVEF and rule out subclinical left ventricular dysfunction and constrictive physiology; as well as to carry out analysis of tissue characterization in search of focal and/or diffuse fibrosis in both ventricle and left atrium and of pericardial inflammation/thickening and to determine by myocardial perfusion study the diagnosis of epicardial

and microvascular CHD.^{79,133,135} For all its advantages and despite its disadvantages, the use of CMR in cardio-oncology is in many cases the first option after echocardiography (Table 4).

NUCLEAR CARDIOLOGY IN THE DIAGNOSIS OF CARDIOTOXICITY

- Radio isotopic ventriculography in equilibrium (VRIE). It evaluates the function of the left ventricle by quantifying LVEF. It has a low interobserver variability (5%), high

Table 5: Imaging techniques advantages according with cardiotoxicity type.

Type of toxicity	Anti-cancer agents	Proposed technique
CCM, myocarditis	Anthracyclines, alkylating agents, antimetabolites, monoclonal antibodies, tyrosine kinase inhibitors and anti-VEGF, proteasome inhibitors, antimicrotubule agents, immunotherapy	2D-3D Echo + GLS (ideal) CMR
Valvular disease	Radiation-induced cardiotoxicity	2D-3D echo, CT, CMR
Pericardial disease	Metrotexate, arsenic trioxide, antimetabolites, antimicrotubule agents, radiotherapy	Echo 2D, TC, CMR
Coronary heart disease	Antimetabolites, monoclonal antibodies, anti-microtubule agents, tyrosine kinase inhibitors and anti VEGF	Stress Echo, TC/SPECT or PET, stress CMR
Pulmonary hypertension	Tyrosine kinase inhibitors small molecule (anti VEGF)	2D Echo
Vascular toxicity	Anthracyclines, tyrosine kinase inhibitors, monoclonal antibodies, proteasome inhibitors, antimetabolites	Vascular ultrasound, CMR, TC
IMAGE	ADVANTAGE	DISADVANTAGES
2D Echocardiography	Availability and low cost, experience	Low reproducibility, image quality, established LV dysfunction diagnostic
3D Echocardiography	Reproducibility	Low reproducibility, image quality, established LV dysfunction diagnostic
GLS	Reproducibility, LV subclinical dysfunction detection, highly predictive negative	Availability, image quality, there are no absolute values of normality
CMR	Reproducibility, image quality, structure characterization, detection of myocardial ischemia	Availability and costs, technical limitations (obesity, pacemakers, etc.)
VRIE	Reproducibility, expertise	Radiation (5mSv), availability, information limited to DV
CT ± SPECT	Reproducibility, myocardial ischemia detection, characterization of structures	Radiation (12-14mSv), availability and cost, technical limitations (arrhythmias)
CT/PET	Reproducibility, detection of myocardial ischemia	Radiation (2-4mSV), availability and cost

CCM = chemotherapy-induced cardiotoxicity, LV = left ventricle, GLS = global longitudinal strain, CMR = cardiac magnetic resonance imaging, VRIE = radionuclide ventriculography, CT = computed tomography, SPECT = emission computed tomography single photon, PET = positron emission tomography.
Modified from: Zamorano JL et al.;⁷⁶ Čelutkienė J et al.⁷⁹

diagnostic efficacy and reproducibility. Its use at the beginning and during treatment, significantly detects CT compared to patients who are not evaluated (2.86 vs 20.8%).^{88,120} Serial monitoring of LVEF has been shown to decrease the incidence of cardiotoxicity (7:1) and development of HF.¹³⁷ Its implementation involves exposure to 5mSv of radiation per study and has limited information on the rest of cardiac functions and structures.¹³⁸

- Myocardial perfusion with gated-SPECT (single photon emission computed tomography synchronized with electrocardiogram). Highly reproducible technique, independent operator (Table 5). It determines ventricular function by LVEF and calculation of tele diastolic and tele systolic volumes.^{77,139} It is indicated in the detection of myocardial ischemia in patients with a history of chemotherapy and radiotherapy.^{79,135,138} Myocardial ischemia with impaired mobility and systolic thickening has been reported by gated-SPECT in asymptomatic women following radiation therapy (in half of the patients), with an increase of 27% to six months and 42% to 24 months.^{135,140} Its disadvantage is the patient's exposure to radiation (12-14 mSv per study) availability and cost.^{121,122}
- Positron emission tomography (PET/CT). Its main utility is the evaluation of microvascular dysfunction in patients with a history of chemotherapy and radiotherapy.¹³⁵ It allows real-time evaluation of ventricular function (LVEF and ventricular volumes at rest and effort), quantification of the myocardial flows (at rest-effort) and coronary flow reserve. Useful in the detection of myocardial ischemia (Table 5), with a diagnostic efficacy of 100% for the detection of CHD.¹⁴¹ The disadvantage of the technique is exposure to ionizing radiation (2-4 mSv), cost and low accessibility.^{134,135}

IV. WHICH ALTERNATIVES ARE USEFUL IN PREVENTING CARDIOTOXICITY AND WHEN ARE THEY INDICATED?

CT prevention begins the identification of high-risk groups (Figures 2, 3 y 4, Table 4),^{78,82,83,134}

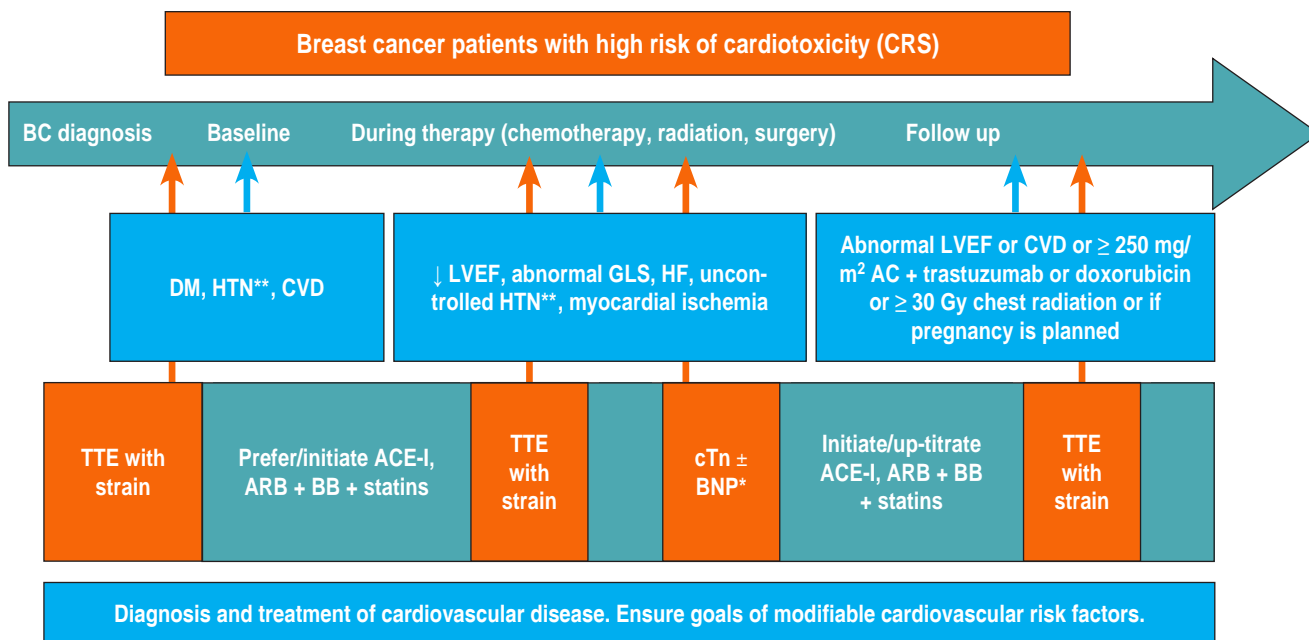
and includes diagnosis, RF control and timely prescription of cardioprotective drugs at the right time,^{12,77,82,88} as well as the careful selection of the chemotherapy scheme.^{12,16,77}

1. Oncological strategies to prevent cardiotoxicity

The magnitude of effects by CT is very variable so the patient with a history of cancer treatment is considered with Stage A HF.⁷⁸ Unfortunately the most cardiotoxic agents such as anthracyclines (doxorubicin and epirubicin) are widely used in BC and other neoplasms.^{6,12,88} The documented incidence of HF by anthracyclines is 5% for cumulative doses of 400 mg/m², for cumulative doses of 500 is 16% and 26% for doses of 550 mg/m².¹⁴² Even if an attempt is made to decrease the cumulative dose limits, the CT effect of oncological treatment may remain undercover by compensatory cardiac mechanisms, becoming apparent later, when the patient gains age and comorbidities (Table 1).^{6,16,78,143}

Oncological strategies that may be helpful in minimizing anthracycline CT are the following: a) To reduce the cardiotoxicity of the drug by selecting the least cardiotoxic, adjusted dose and/or divided infusion patterns. b) Prior administration of cardioprotective agents (dexrazoxane).

- Adjusted dose. Maintain cumulative dose of doxorubicin between 240-360 mg/m² and epirubicin 450-600 mg/m². For other anthracyclines, the equivalent doses should be used.^{77,143,144} For all patients, the dose calculation should be performed with the updated weight in each cycle of chemotherapy. The calculation of dose per-kg of weight does not carry an increased risk of toxic effects in obese women.¹⁴⁵
- Patterns of continuous infusion. Current evidence points to greater myocardial damage from bolus administration compared to divided doses.⁶ Continuous infusion during 48 to 72 hours decreases the plasma peaks of the drug with a cardioprotective effect in adults, without modifying the efficacy of the drug.¹³⁵
- Selection of the least cardiotoxic drug. A recent comparative MA of the cardiotoxic



* At every anthracycline ± trastuzumab cycle. ** HTN goal 140/90 mmHg or lower, before VEGF inhibitor initiation (sunitib, sorafenib) if ≥ 200/100 mmHg despite treatment reinforcement, withdrawal drug.⁷⁷

Figure 4: Cardioprotective strategies in breast cancer women before, during and after treatment. CRS = cardiotoxicity risk score, BC = breast cancer, DM = diabetes mellitus, HTN = hypertension, CVD = cardiovascular disease, LVEF = left ventricular ejection fraction, GLS = global longitudinal strain, HF = heart failure, AC = anthracycline, Gy = Gray, TTE = transthoracic echocardiogram, ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BB = beta-blocker, cTn = cardiac troponin, BNP = brain natriuretic peptide, VEGF = vascular endothelial growth factor.

effects of doxorubicin, epirubicin, liposomal doxorubicin, doxorubicin + dexrazoxane and epirubicin + dexrazoxane in 3,484 patients with BC, found that liposomal doxorubicin and the combination of epirubicin + dexrazoxane are the least toxic treatments. Doxorubicin was found to be the most effective cardiotoxic therapy and liposomal doxorubicin.¹³⁷ In a previous MA, a trend in ischemic heart disease (IHD) reduction with epirubicin was observed compared with doxorubicin (RR = 0.36, 95% CI 0.12 to 1.11). Finally, therapies other than anthracyclines should be considered when they are superior or equally effective (e.g., docetaxel/cyclophosphamide) for cases of BC.¹⁴⁶⁻¹⁴⁸ Use of doxorubicin liposomal. There is an alternative formulation of either encapsulated doxorubicin or liposomal (instead of doxorubicin or in patients who have already exceeded doses). This agent is distributed preferably in malignant tis-

sues by increased vascular permeability, demonstrating to be highly effective and less cardiotoxic.¹⁴⁹ In a recent MA, a lower clinical and subclinical HF rate was concluded in adult patients treated with this type of doxorubicin (RR = 0.20, 95% CI 0.05 vs 0.75 and RR = 0.38, 95% CI 0.24 to 0.59).¹⁵⁰ In an RCT of 224 women with average age of 54 years and metastatic BC, the liposomal doxorubicin group had a lower frequency of cardiotoxicity (13 vs 29%; p = NS), with similar anti-tumor activity and survival compared to doxorubicin.¹⁵¹

- Avoid concurrent use of anthracyclines and trastuzumab. The addition of trastuzumab to chemotherapy in women with HER2-positive improves survival and reduces mortality by up to 33%,⁸⁵ but increases CT by 28% compared to 10% with anthracycline alone.⁸⁶ Although severe cardiac dysfunction has been documented to be

transient in the first year, its use at 1 and 2 years increases the frequency of mild heart failure (NYHA class I-II) long-term (7.3 and 4.45% vs with 0.9% in controls).⁸⁵ The incidence is significantly reduced (0.6 vs 3.6%) if administered 90 days after the last anthracycline dose, and discontinuation rates due to severe LV dysfunction are also reduced (4.3 vs 15.6%).¹⁵²

- Concomitant therapy with dexrazoxane. Dexrazoxane attenuates the cardiac toxicity of anthracycline through iron chelation and decreases the production of free radicals. Its cardioprotective effect has been demonstrated in both MA of adults with cancer treated with anthracyclines, with 65% significant reduction in HF and left ventricular dysfunction (RR = 0.35; 95% CI 0.27-0.45 p = 0.00001),¹⁵³ with the same antitumor efficacy.¹⁵⁴ In women with BC, dexrazoxane has shown a reduction in HF. In an RCT of 164 women randomized to receive dexrazoxane or

placebo 30 minutes before their treatment with doxorubicin, cardiac events were significantly reduced (LV dysfunction in 39 vs 13%; p = 0.001 and HF 11 vs 1%, p = 0.05).¹⁵⁵ In a retrospective analysis of 318 cases of early- or late-stage BC (metastases), a cardioprotective effect on the incidence of HF of 1.57% at 10 years was demonstrated, mortality free.¹⁵⁶ However, it is currently only recommended in patients with advanced metastatic BC who achieve cumulative doses of 300 mg/m² of doxorubicin or 540 mg/m² of epirubicin and benefit from additional doses of anthracyclines.^{157,158}

2. Addition of cardioprotective drugs

Drugs with an effect on neurohumoral blockade as beta-blockers (BB) angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin-II receptor blockers (ARBs)¹⁵⁹ and mineralocorticoid receptor antagonists (MRA),

Table 6: Drugs cardiovascular prophylactic effect in anthracycline/trastuzumab cardiotoxicity.

Study	Design/follow-up	Patients	Cancer	Agent	Intervention	Results
ACEI inhibitors						
Cardinale 2006	RCT/12m	114	Various	QT dose↑	Enalapril	Not ↓LVEF; MACE↓
ACEI + BB Bosch 2013	RCT/6m	90	Hematol	AC	Enalapril + carvedilol	Not↓LVEF; ↓ death and HF
ARBs						
Cadeddu 2010	RCT/18m	49	Various	AC	Telmisartan	No GLS ↓; Not↑ IL6
BB						
Kalay 2006	RCT/6m	50	Various	AC	Carvedilol	Not ↓LVEF
Kaya 2013	RCT/6m	45	Breast	AC	Nebivolol	Not ↓LVEF
Seicean 2013	Retrospective/5y	318	Breast	AC + TZ	BB	No ↑pro-BNP ↓HF
Statins						
Acar 2011	RCT/6m	40	Hematol	AC	Atorvastatin	Do not ↓LVEF
Seicean 2012	Retrospective/5y	67	Breast	AC	Statins	↓ HF

ACEI = angiotensin converting enzyme inhibitors, ARBs = angiotensin-II receptor blockers, BB = beta blockers, RCT = randomized controlled clinical trials, m = month, y = year, QT = chemotherapy, AC= anthracycline, TZ = trastuzumab, LVEF = left ventricular ejection fraction, MACE= cardiovascular outcomes, GLS = overall longitudinal strain, HF = heart failure, BNP = brain natriuretic peptide.
Modified from: Curigliano G et al.⁸⁸

are those with the most studies⁸⁸ and report reduction in rates of left ventricular dysfunction compared with placebo (3.96%; 95% CI, 2.90-5.20)¹² (Table 6). Early initiation of cardioprotective therapy has been shown to be decisive in recovery from ventricular dysfunction. In an RCT of patients LVEF of 45% due to chemotherapy, 64% of patients who started the intervention with enalapril-carvedilol in the first 2 months after treatment, recovered ventricular function and had fewer cardiovascular events¹⁶⁰ (Figure 4).

- Renin angiotensin-aldosterone system inhibitors (ACEI and ARBs). Enalapril compared to placebo demonstrated reduced LVEF impairment and decreased troponin elevation. Benefit is also attributed in the reduction of serum markers and left ventricular diastolic function.¹⁶¹ In a study with candesartan, a smaller reduction of LVEF was achieved [(2.66% (95% CI 1.5-3.8) vs 0.8% (95% CI 0.4-1.9)] compared with metoprolol and for both against placebo.¹⁶² In treatment with anthracyclines, lisinopril has been shown to be effective in reducing CT.¹³⁴ In patients with HER2-positive BC treated with trastuzumab the reduction of LVEF impairment was not demonstrated.¹⁶³
- Beta blockers. Carvedilol has more evidence in this group of drugs. It is attributed a cardioprotective mechanism against doxorubicin.¹⁶⁴ In different studies it has shown improvement in GLS more than in LVEF; in others, lower release of Tnl and better diastolic function.^{165,166} Nebivolol¹⁶⁷ and bisoprolol have some benefit;¹⁶⁵ metoprolol has a neutral effect¹⁶² on results and propranolol has a cardiotoxic role.^{165,166}
- Statins. There is evidence of its favorable effect on the prognosis with reduction in the BC recurrence at 5 years (0.67 for users vs non-users 95% CI, 0.39 to 1.13);¹⁶⁸ as well as in the preservation of ventricular function. Prescribing atorvastatin in 40 patients prior to initiation of chemotherapy maintained unchanged LVEF compared to controls (8% absolute reduction) at six months follow-up.¹⁶⁹ 67 women previously treated with statins showed a lower risk for incident HF at 2.5 years.¹⁷⁰ Its cardiopro-

TECTIVE action is attributed to its antioxidant and pleiotropic effects, independent of the baseline lipid level.¹⁷¹

- Mineralocorticoid receptor antagonists (MRA). The cardioprotective effect of aldosterone antagonism compared to placebo is weak. Although the only alethorized study that exists shows a modest benefit on left ventricular function (LVEF), lower elevation of biomarkers and diastolic function, the findings are a reflection of a small group (83 patients), most with low cardiovascular risk and different chemotherapy regimens.^{77,88}

3. Diet and exercise in secondary prevention

Approximately 80% of CVD can be prevented with RF control, such as promoting healthy diet and weight, physical activity, tobacco withdrawal, blood pressure control, diabetes mellitus and a normal lipid profile.^{16,172-176} According to the main cardiovascular prevention guidelines, the recommended therapeutic goals for adults are described in the Table 7.

- Heart-healthy diet. It is recommended that BC survivors adopt a diet rich in vegetables, fruits, whole grains and legumes; low in saturated fat and limited in alcohol consumption.^{3,177} According to the results of 2 RCT, a diet that controls body weight, will have an impact on cancer recurrence and a best prognosis.¹⁷⁸⁻¹⁸⁰ A healthy diet has been associated with a 15-43% reduction in the risk of death from all causes, compared to the Western diet (high consumption of saturated fats).¹⁸¹⁻¹⁸⁴ Consumption of polyunsaturated fatty acids, especially marine, is associated with a 14% reduction (RR 0.86; 95% CI, 0.78 on 0.94) at the risk of BC according to a recent MA.¹⁸⁵ As a general rule and due to the carcinogenic effect of alcohol when consumed in excess,¹⁸⁶⁻¹⁸⁸ its consumption should be limited in women, to no more than 1 drink/day.^{45,192}
- Physical activity. It is recommended that the primary care physician prescribes regular physical activity at least 150 minute per week of moderate-intensity exercise or 75 minutes per week of vigorous intensity. Exercises with

Table 7: Cardiovascular risk factors goals in cancer patients.

Risk factor	Initial goal	Optimal goal
Arterial blood pressure ¹⁸⁹	< 140/90 mmHg	< 130/80 mmHg
LDL cholesterol ¹⁸	< 100 mg/dL at moderate risk < 115 mg/dL at low risk	< 70 mg/dL at high risk < 55 mg/dL at very high risk
Glycosylated haemoglobin ¹⁹⁰	7-8% patient with comorbidities, advanced age	7% patients with more life expectancy
Physical activity ¹⁹¹	Moderate intensity exercise 150 minutes per week (30 minutes/day for five days)	In obese patient moderate exercise 45 minutes/7 weekdays
Diet ¹⁷⁷⁻¹⁷⁹	Healthy diet type DASH or mediterranean diet	
Ideal weight ^{180,181}	< BMI < 25 kg/m ²	BMI < 25 kg/m ²
Smoking ¹⁸⁰⁻¹⁸¹	Quit	Quit

LDL = low density lipoprotein, BMI = body mass index, DASH = dietary approaches to stop hypertension.

strength and endurance should be included in the routine at least two days/week. Avoid inactivity and return to physical activities as soon as possible.^{13,177,180} Prospective, observational studies have shown a decrease in the recurrence of colorectal, ovarian and breast cancer, in survivors who perform physical activity and also achieved an improvement in overall mortality.¹⁷⁷ A recent MA showed that post-diagnosis exercise reduces 34% risk of BC death, 24% recurrence and 41% overall mortality.¹⁹³ Numerous MA have confirmed other benefits of physical activity in BC survivors ranging from mitigating fatigue (adverse effect to treatment) to improving quality of life.^{83,180,194}

CONCLUSIONS

CVD is the leading cause of death in female BC survivors, due to the potential cardiac dysfunction because of oncological therapies, the concurrence of other CVRF, comorbidities and aging itself. Therefore, our fundamental objectives are to determine the patient's baseline cardiovascular risk (considering the patient-related risk factors and the oncological treatment-related risk); to establish preventative strategies to reduce the risk and to monitor the patient during and after cancer treatment

with imaging techniques (LVEF and GLS) and biochemical markers for the early implementation of cardioprotective strategies.

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