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- Pharmacological terms based on receptor ligand interactions
- Severe pericardial effusion etiologies
- Position statement on cardiovascular disease in women with breast cancer
- The history of myocardial infarction

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Basic Science Corner

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Defining pharmacological terms based on receptor ligand interactions

Definiendo términos farmacológicos basados en las interacciones ligando receptor

Andrés Portilla-Martínez,* Miguel Ortiz-Flores,* Isabel Hidalgo,* Cristian González-Ruiz,* Guillermo Ceballos,* Nayelli Nájera*

Keywords:
Ligands, agonist, antagonism, receptor theory, biased agonist, GPCR.

Palabras clave:
Ligandos, agonista, antagonismo, teoría del receptor, agonista selectivo, GPCR.

ABSTRACT

There are several theories of how a drug interacts with a receptor. This review discuss the theories considered the most relevant to elucidate the mechanisms that govern drug-receptor interactions such as the occupational theory proposed by A. J. Clark, who stablished that drug-receptor interactions can be interpreted as processes that obey the laws of physics and chemistry, proposing for the first time a mathematical approach describing the behavior of a ligand-receptor interaction. This theory has been modified with the development of new technics, such as recombinant technology, protein crystallization and in silico methodologies, which all contribute with important experimental data for a better understanding of ligand-receptor interaction. Over time the drug-receptor interactions theories became more complex and accurate, and gain a few fundamental parameters such as potency, efficacy, dose, types of agonism (partial, total, inverse), antagonism (competitive and non-competitive) or modulation. The deep understanding of these new concepts in drug-receptor pharmacology, can make the difference between success or failure in pharmacological treatment in the clinical area.

RESUMEN

Existen varias teorías sobre cómo un fármaco interactúa con un receptor. Esta revisión muestra las teorías que se consideran más relevantes para dilucidar los mecanismos que rigen las interacciones fármaco-receptor, como la propuesta por A.J. Clark, quien establece que las interacciones fármaco-receptor pueden interpretarse como procesos que obedecen las leyes de la física y la química, y establece por primera vez un enfoque matemático que describe el comportamiento de una interacción ligando-receptor, este modelo se conoce como teoría ocupacional. Sin embargo, esta teoría se ha modificado con el desarrollo de nuevas tecnologías, como la tecnología recombinante, la cristalización de proteínas y las metodologías in silico, que contribuyen con importantes datos experimentales para comprender la interacción ligando-receptor. De esta manera, las teorías de interacciones fármaco-receptor se volvieron más complejas, precisas y obtuvieron algunos parámetros fundamentales como potencia, eficacia, dosis, tipos de agonismo (parcial, total, inverso), antagonismo (competitivo y no competitivo) o modulación. Es por esto que la implementación de estos nuevos conceptos en la farmacología de las teorías fármaco-receptor en el área clínica puede marcar la diferencia entre el éxito o el fracaso en el tratamiento farmacológico.

INTRODUCTION

In medicine it is common to assume that the majority of medications induce their pharmacological effect(s) through interaction with protein structures called receptors «a beta blocker is administered to decrease the function of beta receptors» however, what is behind these interactions or how they develop? Or how a molecule is able to block the activity of a receptor? Is not always clear for everyone. On this regard, to understand the mechanisms involved in the drug-receptor interactions, we must first know the models that described these phenomena, although in this review we will not describe the mathematical base of the models, it is necessary to point out that they are essential to fully understand them.

There are several theories describing how a drug interacts with a receptor however, in this short review we will discuss only those considered the most relevant to elucidate. In an introductory manner, the mechanisms

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behind drug-receptor interactions were described first by the occupational theory and the two-state theory. There are other models that further describe parameters to consider before choosing one medication over another to induce a specific response, examples of these models are; the Operational model that describes the necessary intrinsic properties of a molecule allowing its actions on receptors in a tissue-specific manner and at the same time contemplates the molecule velocities of association and dissociation from a receptor[1] and the ternary complex model, useful when describing the interactions of drugs with G coupled protein receptors, where in addition of the inactive and active state of the receptor (this model will be described later), whether or not G protein is bound to the receptor influences the interaction, thus adding more complex states.[2-4]

THEORIES OF DRUG RECEPTOR INTERACTION

Paul Ehrlich with his salvarsan and the Magic Bullet, was the first to discuss possible structures capable of interacting with drugs naming them receptors. In 1933 AJ Clark[5] established that drug-receptor interactions could be interpreted as processes that follow the known laws of physics and chemistry and with this, for the first time, a mathematical approach describing the behavior of a receptor's occupation by a drug was made, this model is known as the Occupational Theory and he postulated that the pharmacological effect of a substance is directly proportional to the number of cellular receptors occupied by the substance.[6] A representation of this model is shown in *Figure 1*.

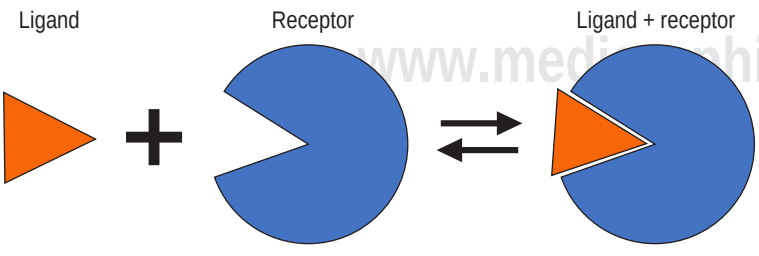

Figure 1: Graphical representation of the occupational theory.

Afterwards Clark clarified some limitations that this model had, in his words. «The application of these formulae to biological data involves certain assumptions which are unproven. In the first place the formulae assume that the receptors in a cell resemble the surface of a polished metal, in that they are all equally accessible to the drug. In the second place the interpretation assumes that the amount of biological effect produced is directly proportional to the number of specific receptors occupied by the drug».[5]

This idea was modified when molecular techniques including recombinant technologies, protein crystallization and computational methodologies (such as molecular modeling and docking) were available. Consequently, the understanding of how a drug is capable of interacting with a receptor is getting more and much closer to what actually really happens.

Other proposed theory suggest that receptors can exist in several states, experiencing different conformational changes and therefore inducing different responses, this theory is called Two-state Receptor Theory. This model emerged from the studies conducted on ion channels, they are observed in two state possibilities or variants, open or closed channel.[7] Therefore, it was assumed that any other type of receptor could have also two states, active and inactive *(Figure 2)*.

In this theory, the receptor adopts two possible conformational states that coexist dynamically changing from an active to an inactive state (and viceversa). Therefore, the drug capable to bind to a receptor showing two possible activation states, must have affinity for one of these states. There are known drugs that can bind to the inactive state of the receptor, these drugs are called inverse agonists (this idea will be discussed later), examples are: carvedilol and propanolol, when they interact with specific receptors, they do not only block the inotropic effect induced by natural agonists, but they also lower the inotropism baseline *(Figure 3)*.[8]

Taking as example drugs used to control arterial hypertension, there are many parameters that influence the binding of a drug to a receptor that are associated with the ligand's properties and structure. Although there are several pathways implicated in the develop-

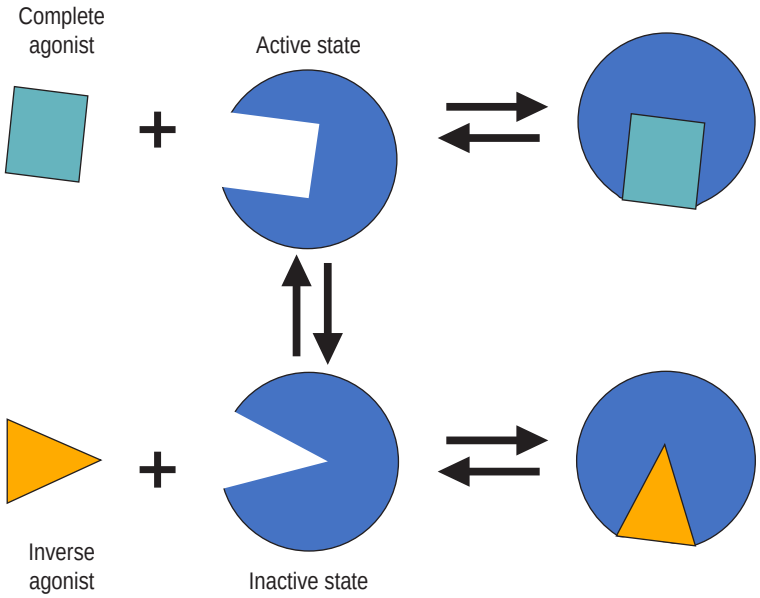

Figure 2: Graphical representation of the **two-state receptor theory**; here is shown the concept of partial and complete agonist that will be discussed later.

ment of arterial hypertension, its treatment involves the use of antihypertensive drugs. The modulation of the activity of alpha and beta adrenergic receptors has been the main target of antihypertensive therapy; due to its direct effect over the peripheral resistance (acting on vascular smooth muscle or interfering with the activity of the systems that inhibits vasoconstriction) or over the cardiac output (with a negative inotropic effect or lowering the ventricular filling pressure) and the renin release.

On this regard, drugs acting on the beta-adrenergic receptor (βAR), i.e. at the β1 isoform, are the recommended first-line therapy for the management of hypertension in younger patients and in patients with coronary artery disease comorbidities. βAR is activated endogenously, by epinephrine, this molecule is a full agonist of this receptor, because it is able to bind to the receptor, inducing conformational modifications and triggering an effect, in this case, an increase in the cardiac output. Based on these effects and taking in consideration the Occupational Theory, those designed drugs having effects similar to the induced by the endogenous agonist are also called agonist.

In general, agonists may act interacting in the same site reached by the endogenous ligand at the receptor (orthosteric site). A common example of a molecule that binds to β2 receptor is isoproterenol (full agonist), this drug can increase cardiac rate and myocardial contractility (positive chronotropic and inotropic effects) *(Figure 3)*. Interestingly, some drugs are capable to bind at the same site as the agonist, but the action that they trigger is a «submaximal» action, in other words, they do not induce the maximum effect compared with the normal or natural agonist, this type of drugs are called partial agonist, examples are formoterol or albuterol *(Figure 3)*.

From a molecular point of view, three categories of agonist are known: 1) full agonist, triggers the maximum possible effect, occupying the minimum number of available receptors; 2) agonist, triggers the same effect but occupying more receptors compared to the full agonist and 3) partial agonist, triggers an effect, but do not reach the maximum effect despite occupying the same number of receptors as an agonist.

On the other hand, in order to ameliorate the effects produced by agonists of the β2AR antagonist drugs are used. Antagonists are drugs that bind to the same receptor as an agonist, but they do not activate the receptor and have no efficacy. An example of this type of drugs is alprenolol *(Figure 3)*, this molecule after binding β2AR inhibits the production of renin, thereby inhibiting angiotensin II and aldosterone production and therefore inhibiting their vasoconstriction and water retention effects.[9]

Antagonists are classified depending on their binding site in the receptor, i.e. same site for agonist binding or not. When the antagonist shares the orthosteric site with the agonist, it is called competitive antagonist (bounds easy to break). Since bound antagonists can be removed from the orthosteric site by increasing the concentration of the agonist, i.e. agonist and antagonist compete for the same site (reversible antagonism).

Some antagonists bind covalently (bounds not easy to break) in the binding (orthosteric) site or modify structurally the orthosteric site leading to an impossibility to be displaced by the agonist, when this interaction occurs, the antagonist is called irreversible.

Conversely, when the antagonist binds to an allosteric site (a different site on the receptor

that is able to modulate receptor activity), the interaction is called non-competitive antagonist. In this case, there are two possibilities, 1) the agonist cannot bind into the receptor orthosteric site (because this site changes) or 2) it does bind in it, but the effect is partially or totally annulated even when the agonist concentration is increased.

The drugs classifications described above were the base of therapeutics, however, when the G protein coupled receptors (GPCRs) were discovered the scenario turned more complicated. GPCRs have basal or intrinsic activity; the activation of heterotrimeric G-proteins by receptors involves an equilibrium between conformational states (active and inactive). These states do not need agonist binding (two-state receptor theory). This is even more complicated to understand. Some drugs that were originally classified as antagonists now are classified as inverse agonists, because they favour the possibility of the receptor to adopting an inactive conformation and by this reducing the intrinsic or basal activity of the receptor.

It is clear that the study of the drug-receptor interactions is a process that is continuously evolving, as example, the effects of inverse agonists on β2 receptor (a family of GPCRs) - is mediated by «non canonical» or «classic» molecular pathways, that involve the participation of β-arrestin proteins leading to cardioprotective effects. Nadolol and propranolol are examples of these kind of drugs.

New approaches exploring the ligand/receptor interactions have been developed recently. On this regard and based on the fact that there are two possible pathways that can be activated after an agonist binds to its receptor, the concept and creation of the term «biased agonist» is a trending topic in actual pharmacological research. Biased agonists activate selectively one of the two possible pathways, leading to a selective effect depending on the microsite reached by this type of agonist inside the pockect or active site in the receptor. Several studies have suggested that β-arrestin-biased signaling at the β-adrenoceptor induce cardioprotection, leading to the hypothesis suggesting that β-arrestin-biased agonism at the βAR may be a novel therapeutic target for heart failure and/or other cardiovascular diseases. The most representative drug of this group and also the most used drug, is carvedilol. This proposal suggests that the unique efficacy of carvedilol in the treatment of heart failure may be related to the activation of β-arrestin signaling. In addition, carvedilol has other independent of the activation of βAR effects, like relaxation of smooth muscle in vasculature, leading to reduced peripheral vascular resistance and an overall reduction in blood pressure. At higher doses it has also calcium channel blocking and antioxidant capacities. Following the carvedilol example, science is making an effort to find new molecules that can act as biased compounds, leading to better and specific therapeutic results.[10,11]

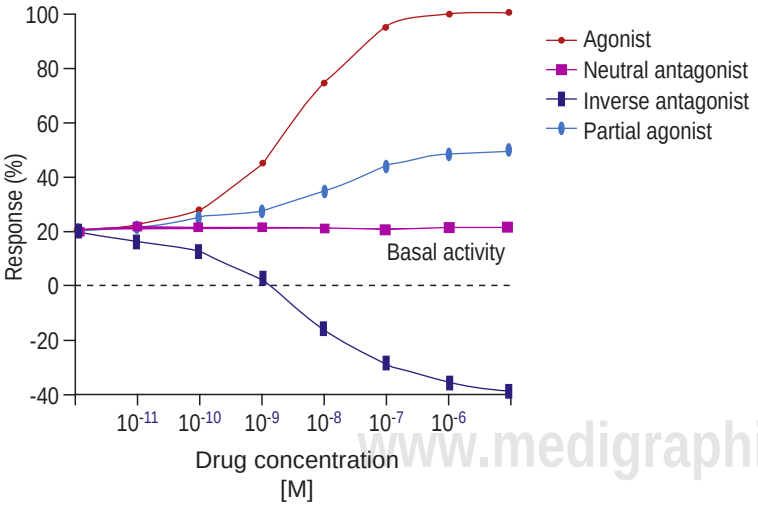

Figure 3: Dose-response curve based on their activity in the beta-adrenergic receptor. Agonist: isoproterenol and epinephrine. Partial agonist: formoterol. Neutral antagonist: alprenolol. Inverse agonist: propranolol and carvedilol (Modified from: Ferguson SSG, Feldman RD. β-Adrenoceptors as molecular targets in the treatment of hypertension. Can J Cardiol [Internet]. 2014; 30 (5): S3-S8).[12]

CONCLUSION

Based on the information described, the knowledge of the interactions and affinity between a drug and a receptor in its different states becomes relevant. Highlighting the importance of knowing parameters such as potency, efficacy, dosage and types of agonism (partial, full, inverse), antagonism (competitive and noncompetitive) or allosteric modulator.

The pharmacological approach to explain the action of drugs together with what is learned during clinical practice, can make the difference between success or failure in therapeutics.

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Original Research

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Severe pericardial effusion etiologies

Etiologías del derrame pericárdico severo

Ricardo Arango-Moreno,* Ana G Múnera-Echeverri,‡ María Clara Gaviria-Aguilar,§ Mateo Mejía-Zuluaga,* Laura Duque-González,* Mauricio Duque-Ramírez¶

Keywords:
Severe pericardial effusion, etiology, developing countries.

Palabras clave:
Derrame pericárdico severo, etiología, país en desarrollo.

ABSTRACT

Introduction: The etiology of pericardial effusion is highly variable around the world. The present study describes the clinical features and etiologies of severe pericardial effusion in a series of cases treated at a third-level hospital in Medellín, Colombia. **Material and methods:** Retrospective case series based on clinical records. All patients treated between 2006 and 2018 with severe pericardial effusion requiring intervention for pericardial fluid drainage were included. The exclusion criteria were the absence of more than 50% of the data in the clinical history and the recurrence of the pericardial effusion after its first drainage. Etiology, indications for pericardial drainage and patient comorbidities are described. **Results:** 48 patients were included, 50% men with a mean age of 52.4 years (SD 17.5). Non-infectious etiologies were the most common causes of severe pericardial effusion (66.7%), followed by idiopathic (20.8%) and infectious causes (12.5%), being tuberculosis the most important. The main indication for pericardial drainage was to determine its etiology (58.0%) and the most relevant comorbidity was hypertension (40.0%). **Conclusions:** The main causes of severe pericardial effusion were non-infectious, unlike previous reports from developing countries where infectious diseases are considered the most common. Although, the frequency of idiopathic etiology was lower than that reported in other series, it continues to be a representative number of patients in which the etiology cannot be established.

RESUMEN

Introducción: *La etiología del derrame pericárdico es altamente variable en diferentes regiones del mundo. Este estudio describe las características clínicas y la etiología del derrame pericárdico severo en una serie de casos atendidos en un hospital de tercer nivel de la ciudad de Medellín, Colombia.* ***Material y métodos:*** *Serie de casos retrospectiva basada en registros clínicos. Se incluyeron todos los pacientes atendidos entre 2006 y 2018 que presentaron derrame pericárdico severo y requirieron intervención para extracción del líquido pericárdico. Los criterios de exclusión fueron la ausencia de más de 50% de los datos en la historia clínica. Para el análisis únicamente se tuvo en cuenta el primer derrame pericárdico y no la recurrencia de éste. Se describen etiología, indicación de drenaje y comorbilidades de los pacientes.* ***Resultados:*** *Se incluyeron 48 pacientes, 50% hombres, edad media 52.4 años (DE 17.5). Las etiologías no infecciosas fueron las más frecuentes (66.7%), seguidas por derrames pericárdicos idiopáticos (20.8%) y etiologías infecciosas (12.5%), la mayoría secundarias a tuberculosis. La principal indicación de drenaje fue búsqueda etiológica (58.0%) y la principal comorbilidad fue hipertensión (40.0%).* ***Conclusiones:*** *Las causas no infecciosas fueron las más comunes, contrario a lo reportado en otras series para países en vía de desarrollo donde las causas infecciosas son las más frecuentes. Aunque la etiología idiopática fue inferior a las reportadas en otras series, continúa siendo un número representativo de pacientes en los que no se logra establecer la etiología.*

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INTRODUCTION

Pericardial effusion (PE) is the abnormal accumulation of fluid in the space between the two layers of the pericardium. It is an increasingly common condition, due to the advance in diagnostic images that allow its identification.[1]

Multiple diseases can cause pericardial effusion, however, only in a minority of cases an accurate diagnosis can be made. Recent advances in diagnostic techniques (microbiology, for example) and newer imaging methods, have allowed to establish with greater precision its etiology.[2]

Etiologies imply great variations according to regions, they are not the same in developed countries as in developing countries. In the former, the majority are considered idiopathic or secondary to cancer, whereas in developing countries infectious etiologies, especially tuberculosis, are the main causes and represent

more than a half of the cases.[3] Knowing the local epidemiology is essential for clinical practice, physicians will be more confident regarding which etiologies to asses when facing a severe pericardial effusion and making the correct decision between diagnostic and treatment alternatives. Likewise, it is worth asking if the impact of PE secondary to tuberculosis is as great as it is presumed in affected countries or if there are other etiologies with relevant participation.

Prognosis associated with PE depends on the underlying etiology, however, having PE is a marker of severity and in some cases, leading to an ominous outcome.[4-6] PE, specifically in patients with human immunodeficiency virus (HIV) is associated with low survival, 36% at 6 months and 19% at 1 year; due to the antiretroviral therapy and the timely diagnosis and treatment of the effusion, these statistics have been reduced and the paradigm of the disease has changed.[7]

Although in cases of mild PE, a specific treatment is not recommended other than treating the root cause, adequate clinical and imaging follow-up is essential to prevent progression to severe effusion and cardiac tamponade; the most feared complication and with the highest mortality within the spectrum of the disease.[8,9]

There is no history of local studies that establish the different etiologies of severe PE in Colombia. The aim of this study is to describe the main etiologies and comorbidities at a tertiary care hospital in the city of Medellín.

MATERIAL AND METHODS

Retrospective case series, based on clinical records obtained between November 1st, 2006 and December 31st, 2018 from the emergency and hospitalization service of a highly complex hospital in the city of Medellín, where patients are mostly from the public health sector and rural areas. This hospital has the services of internal medicine, cardiology, infectious diseases, general surgery, cardiovascular surgery and intensive care unit.

The included patients were adults older than 18 years who entered the emergency department or hospitalization. All patients had an imaging diagnosis of PE and, its severity was defined by echocardiographic quantification performed by an echocardiography cardiologist. The exclusion criteria were the absence of more than 50% of the data in the clinical history and the recurrence of the pericardial effusion after its first drainage. All the patients required some intervention for pericardial fluid drainage; percutaneously in 26 patients and with surgery (pericardial window) other 22.

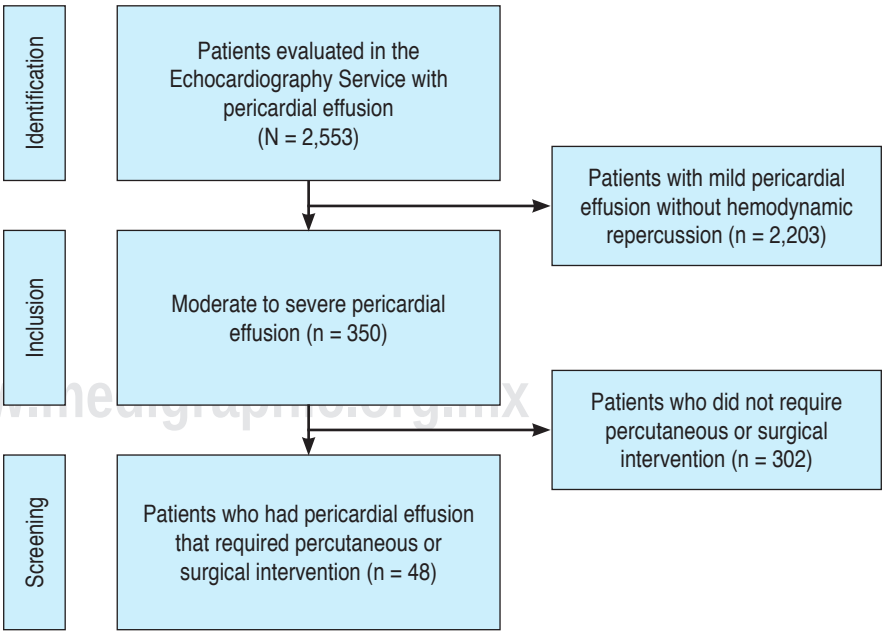

Figure 1:

Flow chart of patient selection.

Table 1: Demographic and clinical characteristics.

Characteristics	Measure %	Number of patients
Men	50.00	24
Age	52.41 ± 17.5 years	48
Comorbidities		
Hypertension	41.00	19
Cancer	31.00	14
Chronic kidney disease	20.00	9
Heart failure	16.00	8
Type 2 diabetes mellitus	14.58	7
Chronic obstructive pulmonary disease	12.50	6
Hypothyroidism	8.33	4
Autoimmune disease	6.25	3
Tuberculosis	6.25	3
HIV	4.17	2
Hyperthyroidism	4.17	2
Substance abuse	2.08	1

HIV = human immunodeficiency virus.

Variables included were patient past medical history, drainage indication, type of drainage intervention and etiology of the PE, if successfully established. Etiologies were classified in two large groups: infectious or non-infectious, with subsequent specific definition by subgroups, according to the 2015 ESC Guidelines for the diagnosis and management of pericardial diseases.[10]

Descriptive analysis was performed with relative and absolute frequencies for the variables studied with the Stata version 12.1 software.

RESULTS

During the study period, 2,553 patients were evaluated for pericardial effusion, 350 compatible with moderate to severe PE; 302 of these patients did not require percutaneous or surgical intervention. The clinical histories of 48 patients with severe pericardial effusion were identified in whom echocardiography and drainage of the pericardial effusion was performed *(Figure 1)*. Of these patients, 50% were men, mean age was 52 ± 17.5 years. The most relevant comorbidities were hypertension (41%), malignancy (31%), chronic kidney disease (20%) and heart failure (16%). Other less frequent were diabetes mellitus, hypothyroidism, HIV infection, tuberculosis, and drug dependence *(Table 1)*.

The main indication for drainage was the need to find an etiology (58%), followed by hemodynamic compromise (23%) and symptoms refractory to medical treatment (19%).

Regarding the etiologies *(Figure 2)*, non-infectious etiologies were the most frequent (66.7%). These included: malignancy (14 cases equivalent to 43.8% of non-infectious causes), postoperative or traumatic (12 cases, 37.5%), chronic kidney disease (2 cases, 6.2%), heart failure (2 cases, 6.2%) and autoimmune disease (2 cases, 6.2%). In 20.8% of the cases, it was not possible to establish a clear underlying cause, therefore, they were established as idiopathic PE or idiopathic pericarditis. Infectious etiologies were the least common (6 cases, 12.5%). Among these, pericardial tuberculosis was the cause in 5 of the 6 cases (83.3%).

DISCUSSION

In this study, we identified that non-infectious etiologies were the most frequent etiologies in patients with severe PE. A significant fraction of these cases were secondary to malignancy, even with a mean age of 50 years, and consequently, patients presented with manifestations of malignant PE. Among the infectious etiologies, the main one was tuberculosis, this is possibly explained because Colombia has an intermediate prevalence for this entity, along with the fact that the institution where this study was carried out is a highly complex center with a large flow of patients presenting with extrapulmonary manifestations of tuberculosis. Pericardial biopsy was required in most patients with pericardial tuberculosis, to optimize the diagnostic performance of the tests used.

According to the published series so far, it is evident that the etiology of PE, especially in moderate to severe cases, varies dramatically when analyzed between developed or developing countries. In the former, most are idiopathic (50%), followed by malignancy

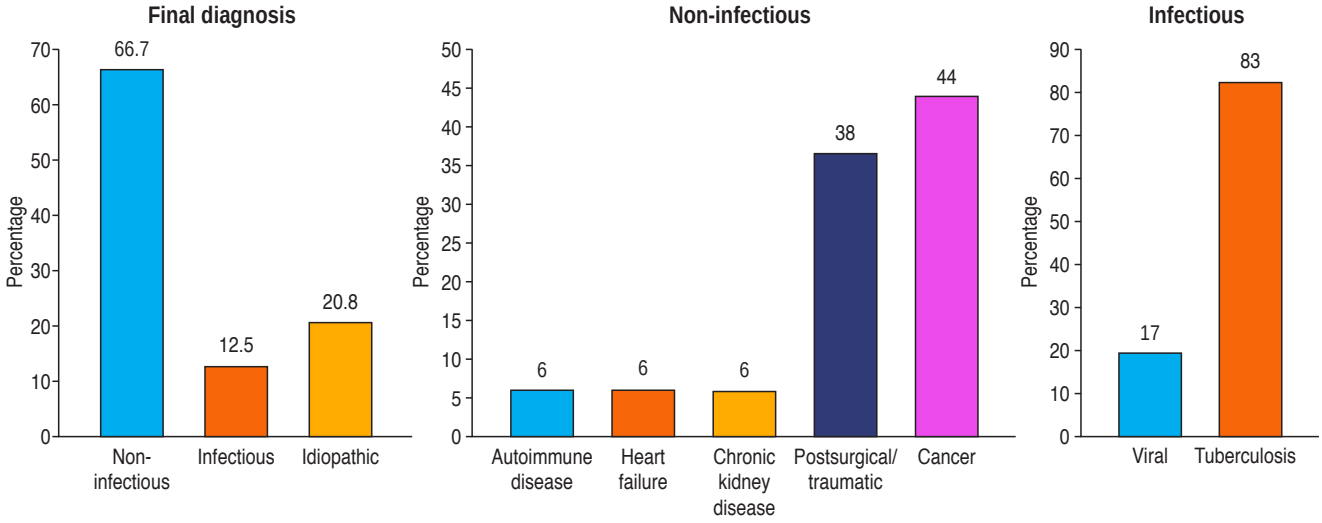

Figure 2: Pericardial effusion etiologies.

(10-25%), pericarditis or infectious (15-30%), iatrogenic (15-20%) and associated with connective tissue diseases (5-15%). In developing countries, more than 60% of the cases are infectious, represented in more than half of the cases by tuberculosis, especially in those regions where this mycobacterium is endemic. It should be noted that HIV infection continues to rise worldwide, increasing the incidence of PE diagnosis related to this condition.[11-15]

Regarding pericarditis with associated pericardial effusion, it is mostly represented by infectious and malignant etiologies with a global distribution of 15-50%, depending on the series reviewed.[11-14] Idiopathic pericarditis, which is presumed to be mostly due to post-viral causes, is the main inflammatory cause of pericardial effusion.[16] The difficulty in diagnosing PE, those considered idiopathic, may be due to the fact that isolating a virus is a complex and difficult task, often requiring a pericardium sample for histological, cytological and/or immunohystological analysis. In the vast majority of cases, clarification of the etiology is not necessary for the management of the patient; furthermore, it would increase costs for the health system and imply invasive and additional procedures or interventions for the patient.[17]

It is important to highlight how progress in the different diagnostic methods (microbiological cultures, polymerase chain reaction, cardiac magnetic resonance imaging) has favored the identification of the underlying cause, making idiopathic etiologies group, to decrease. In this study, idiopathic etiology was 20.8%, while in the world literature it is approximately 50%.[10]

On the other hand, the high ratio of severe pericardial effusion and cardiovascular surgeries should be kept in mind when the patient's postoperative period does not show a favorable evolution. This high prevalence described in the study could be maximized by the fact that the patients were analyzed in a hospital with high-complexity of services such as thoracic and cardiovascular surgery.

Among the study limitations, it is a retrospective study and the research was carried out in a single center, which could disregard other PE etiologies. It should be noted that, in this setting, severe PE drainage procedures are only performed in highly complex hospitals and clinics. On the other hand, the amount of patient data described is not large despite the fact that the medical records reviewed, included more than 10 years, possibly explained by the fact that only patients with severe pericardial effusion with drainage were included, since patients who did not have a study of pericardial fluid were not included. Nevertheless, in Colombia there are no similar reports, as the presented in this study.

CONCLUSIONS

PE is an entity with an important prevalence and associated morbidity and mortality, often with insufficient resources aimed at finding its etiology. In this study, non-infectious causes were the most common, especially those related to traumatic or postsurgical events, making it easier to suspect, timely diagnose, and to intervene. However, infectious (especially pericardial tuberculosis) or idiopathic (possibly post-viral) causes also account for a significant number of cases, a situation that resembles with the reports in world literature. In this study, the idiopathic etiology was lower than that reported in other series, suggesting that an exhaustive and rigorous search has been carried out, which is essential to achieve an adequate diagnostic and therapeutic approach.

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Positioning

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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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Keywords:
Cardiovascular disease, breast cancer, cardiotoxicity, cardiac imaging techniques, cardio-protection.

Palabras clave:
Enfermedad cardiovascular, cáncer de mama, cardiotoxicidad, técnicas de imagen cardiaca, cardioprotección.

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 cardiotóxicos 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 anticancer 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), valvulophaties 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 consensus[14] 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 burden[26] 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 CVD[33] 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 CV[41] 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 atherosclerose 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-Kb,[51] hypoxia inducible factor-1α.[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 limited[55-57] which stimulates cancer.[58] In a succession of events, genetic changes favour the activation of oncogenes (RAS, Myc, RET)

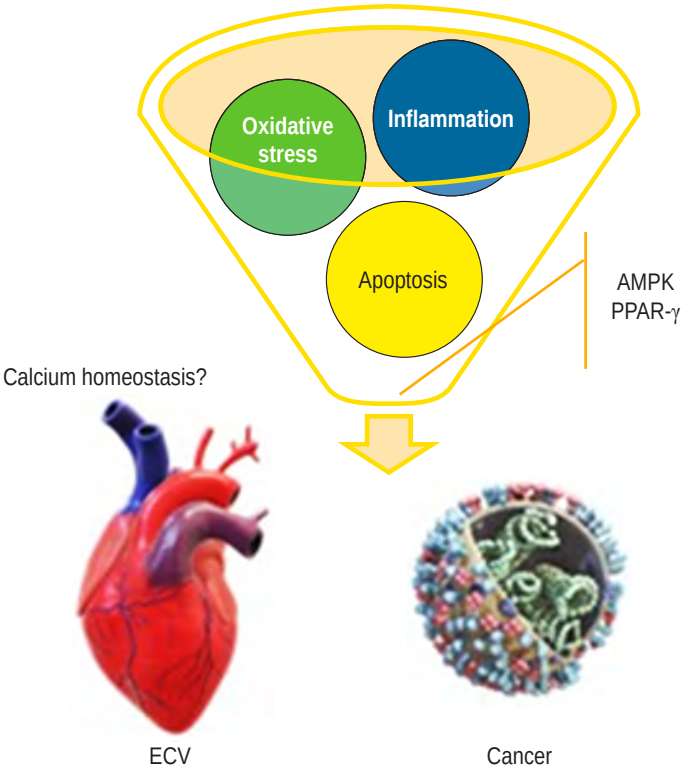


Figure 1: Pathophysiological mechanisms underlying between breast cancer and cardiovascular disease.
Inflammation, oxidative stress and apoptosis are phenomena and conditions AMPK and PPAR-γ inhibiting factors are considered.
Inflammation, oxidative stress and apoptosis are conditioning factors.
AMPK 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, Il1β, 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 oxidation[65] 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 (PTH-rP) 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-?) 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
• 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)	• 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)

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]

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 reversibility[81] 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 identified[76-79] *(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 2α (Top2α) doxorubicin-DNA. Cancer cells have elevated Top2α 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 monotherapy 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 occurs six to 12 month 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

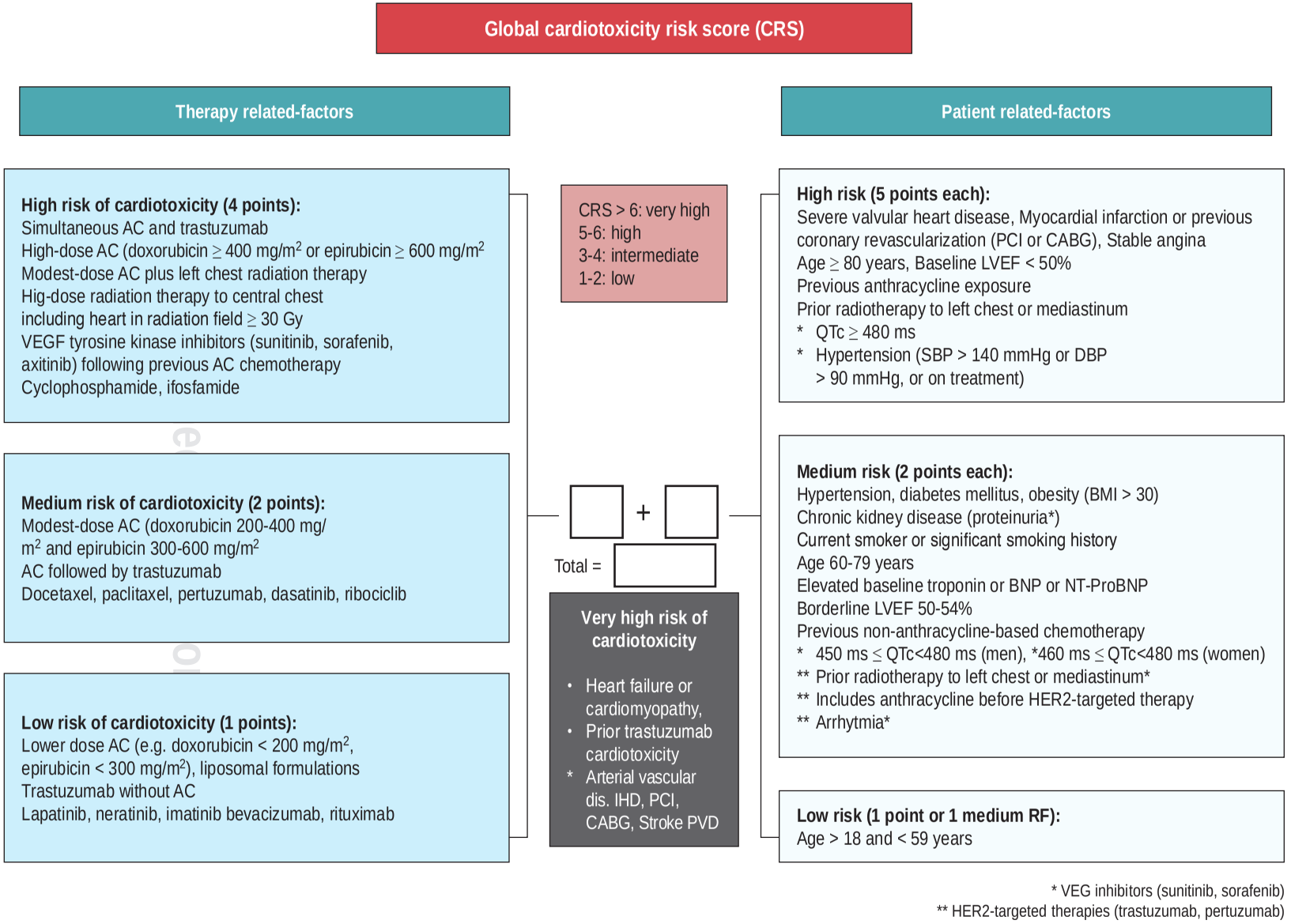


Figure 2: Global cardiotoxicity risk score (CRS).

AC = anthracyclines, VEGF = vascular endothelial growth factor, IHC = 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 ≥ 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 troponins[111] 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/m^2 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 examines 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*	
All patients	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 moths‡	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 2nd or 3rd cycle	3DE/2DE/+GLS • After 3rd 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 echocardiogramis 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/m^2 doxorubicin is equivalent to 420 mg/m^2 epirubin, 400 mg/m^2 daunorubicin and 60 mg/m^2 idarubicin.

¶ 240 mg/m^2 doxonubicin is equivalent to 360 mg/m^2 epirubicin, 320 mg/m^2 daunorabidin and 50 mg/m^2 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/m^2)[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

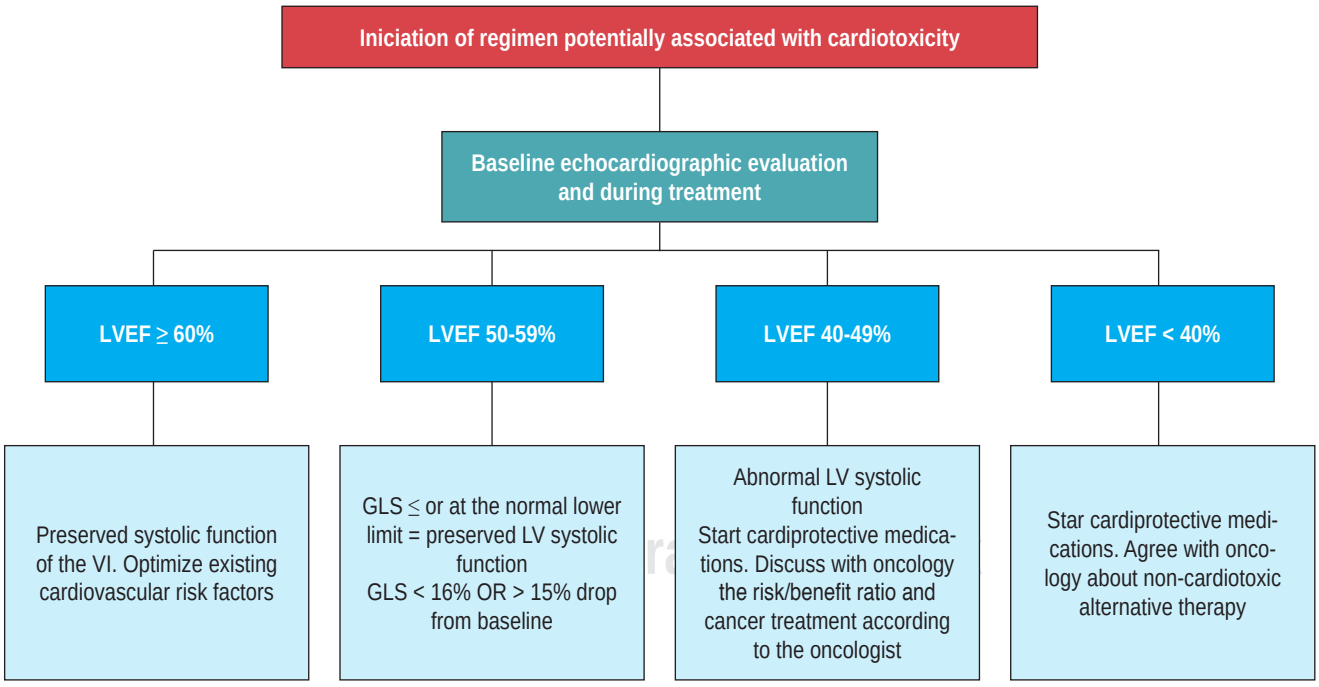


Figure 3: Follow-up algorithm in patients who will receive potentially cardiotoxic therapy.
LVEF = left ventricular ejection fraction, LV = left ventricle, GLS = global longitudinal strain.
Modified from: Plana JC et al.[103]

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]

2. 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 cadiotoxicity	2D-3D echo, CT, CMR
Pericardial disease	Metrotexate, arsenic trioxide, antimetabolites, anti-microtubule 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?

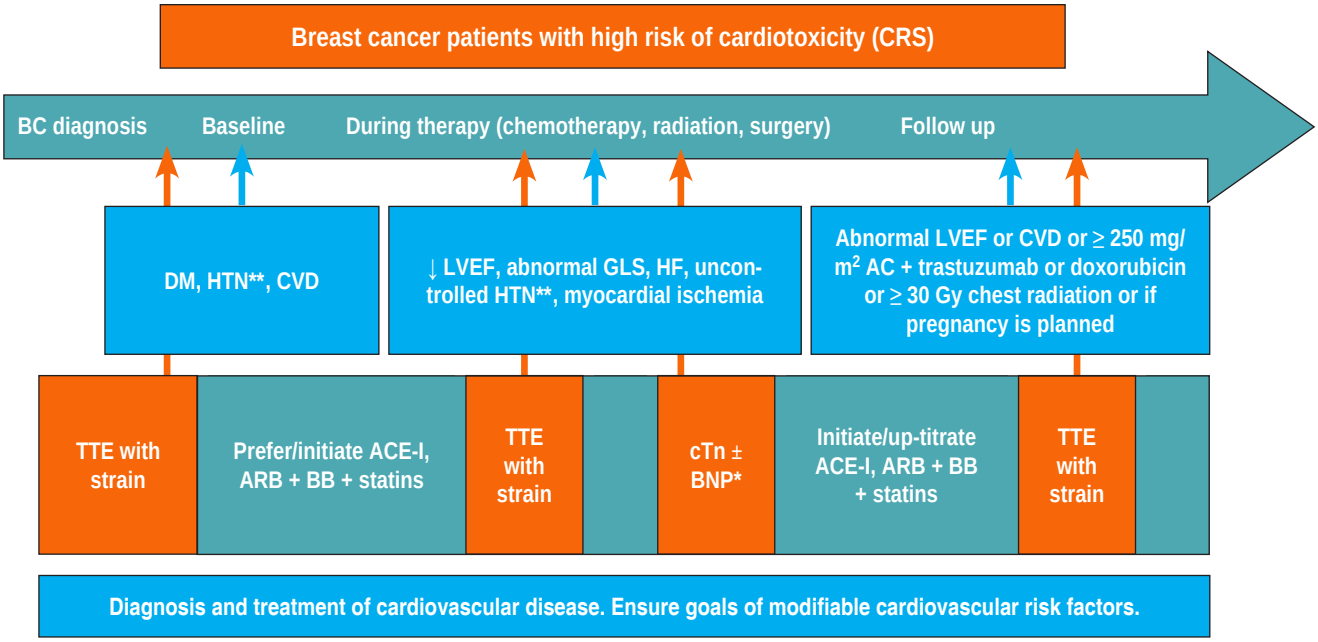
CT prevention begins the identification of high-risk groups *(Figures 2, 3 y 4, Table 4)*,[78,82,83,134] and includes diagnosis, RF control and timely prescription of cardioprotective drugs at the right time,[12,77,82,88] as well as the careful selection of the chemotherapy scheme.[12,16,77]

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/m^2, for cumulative doses of 500 is 16% and 26% for doses of 550 mg/m^2.[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/m^2 and epirubicin 450-600 mg/m^2. 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 ± trstuzumab cycle. ** HTN goal 140/90 mmHg or lower, before VEGF inhibitor initiation (sunitib, sorafenib) if ≥ 200/100 mmHg despite treatment reinforcement, whitdrawal 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 + dexzrazoxane 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 tissues 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 antitumor 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/m^2 of doxorubicin or 540 mg/m^2 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	Retrosp/5y	318	Breast	AC + TZ	BB	No ↑pro-BNP ↓HF
Statins						
Acar 2011	RCT/6m	40	Hematol	AC	Atorvastatin	Do not ↓LVEF
Seicean 2012	Retrosp/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 studies[88] 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 events[160] *(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 TnI and better diastolic function.[165,166] Nevibolol[167] and bisoprolol have some benefit;[165] metoprolol has a neutral effect[162] 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 cardioprotective 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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A minimal tour towards the history of the myocardial infarction

Breve recorrido por la historia del infarto del miocardio

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Keywords:
Myocardial infarction, history of myocardial infarction, heart attack, history of Medicine.

Palabras clave:
Infarto del miocardio, historia del infarto del miocardio, ataque al corazón, historia de la Medicina.

ABSTRACT

Myocardial infarction is one of the significant causes of death in the urban population since the second half of the past century. The current paper describes the discoveries and thinkings concerning coronary disease, from ancient times towards the twentieth century.

RESUMEN

El infarto del miocardio es una de las causas importantes de muerte en la población urbana desde la segunda mitad del siglo pasado. El presente artículo describe los descubrimientos y pensamientos sobre la enfermedad coronaria, desde la antigüedad hasta el siglo XX.

INTRODUCTION

Myocardial infarction is one of the significant causes of death in the urban population since the second half of the last century; however, the clinical description has not changed; it is worth referring the narration of Dr. Ignacio Alvarado, who personally attended the Mexican President, Benito Juárez in his last moments:

«Two hours ago, I had hardly been at his side when the oppression of the heart with which he began transformed into very sharp and sudden pains, those that I saw, those that I guessed in the pallor of his countenance. That man must be suffering the mortal anguish of the one who looks for air to breathe and cannot find it; from the one who feels that the ground on which he leans runs away and fears to fall; from which, in short, he is simultaneously proving what it is to die and continue living. The disease progresses to successive attacks while standing up, then he reclines to avoid collapse, instinctively searching for the blood that he so badly needs into his brain.

Each paroxysm lasts for a variable time, then gradually fades away, then the color returns to its countenance and enters a complete calm; the patient gets up and talks with those of us around him who are indifferent, in all naturalness and without hinting at his sufferings; and it seems that he is already saved, when a new attack returns, and a new relief, and in these alternatives four or five long hours elapse, in which a thousand times we have believed to sing a victory or mourn a death.

It was eleven o'clock in the morning of that mournful day, July 18, when a new, excruciating cramp in his heart forced him to throw himself quickly to the bed; his pulse was no longer moving, his heart was beating weakly; his countenance fell, covering himself with the precursor shadows of death, and in the supreme event I had to go, against my will, to apply a very cruel, but effective remedy: boiling water over the region of the heart...».[1]

The first graphic description of an event of sudden cardiac death corresponds to Horemkenes I (1050 BC), Priest of Ammon, and foreman pyramids construction manager of the Thebes XX Dynasty.[2] Leonardo da Vinci performed the first necropsy after death from coronary origin, in 1506.[3]

The discovery and reading of the Ebers papyrus make manifest the Egyptians' knowledge about heart disease. This papyrus dates back

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more than 1500 years BC, and it is an ancient medical treatise that has, of course, the description and treatment of heart diseases, including coronary heart disease; these include classic symptoms such as chest pain or heaviness and collapse, expressing the nearness of death when a person has a heart condition and has pain in the arms, chest, and side of the heart.[4]

Hippocrates and his followers, between the 5th and 4th centuries BC, related, on a theoretical basis, symptoms such as cooling, blindness, seizures, and loss of speech, with stasis in the blood vessels. The Bible and the Talmud talk about cardiac death, apart from their poetic allusions to the heart.[5]

William Heberden, in 1768, made a fascinating description of his observations in about one hundred of his patients with angina pectoris and sudden death. The narrative is very detailed and includes the characteristics of chest pain in different locations and irradiations, sometimes with paresthesia in the hands; it also states that the pain can appear during the march, mainly uphill but that the movement of a horse or carriage or even swallowing, coughing, defecating or any mental disorder may trigger it. He also mentions that sometimes the subject can wake up with dyspnea and feel compelled to sit down to achieve some improvement and that sometimes he found alterations in the pulse of some of his patients.

Among those almost 100 patients, only three were women and a twelve-year-old boy; the rest were men over fifty years old. It is exciting the description of one of his patients who died suddenly, in whom he opened the chest to find a heart without apparent alterations. Dr. Heberden also clarifies that he could not make any new contribution to the remedies proposed in the classical writings; however, he explains how spirits and opium can control symptoms; it also narrates the case of one of his patients who was cured after sawing wood for half an hour daily and another who obtained spontaneous healing.[6]

A short time later, between 1786 and 1799, Edward Jenner and Caleb Hillier Parry, who were close friends, first described the relationship between angina and cardiac death with coronary sclerosis found in several of their patients. The surgeon John Hunter confirmed this description and wrote Jenner about his paroxysms of chest pain, with the mention that his life was in the hands of any rogue who chose to disturb him; finally, he died suddenly during a discussion in the hospital; his autopsy showed coronary ossification and white plaques inside the left atrium and left ventricle.[7]

One of the first evidence connecting sudden death with the heart and coronary atherosclerosis results from the dramatic end of Bertel Thorvaldsen in 1844; he was a famous Danish sculptor who died in his seat while witnessing the execution of the first movement of Ferdinand Ries's sixth symphony at the Royal Danish Theater. Thorvaldsen's death generated a great dispute between two of the doctors attending him because one of them had performed a bilateral tibial fontanel to cure weakness in both legs. This fontanelle consists of a surgical wound so that the fluids that cause discomfort in the limbs can drain there; it is not clear in the narratives if this problem was due to edema or intermittent claudication, but there was a strong media reaction towards one of the doctors accused of causing the artist's death because he had closed one of the fontanelles.

The sculptor's autopsy clearly describes that the left coronary contained within it numerous plaques of atheroma from one inch of its origin to its bifurcation, that one of those plaques was severely ulcerated and that the atheromatous mass had escaped into the lumen of the artery; this constitutes the first finding of a broken plaque in a person with sudden death.[8]

Rudolf Ludwing Karl Virchow, in 1848, coined the terms «thrombosis» and «embolus» with the meaning we use today. He was a doctor who admirably covered his profession, as an excellent student, teacher of medical legends who would later produce famous publications in various areas, researcher and editor of his magazine and also a significant committed to society and constant annoyance for the German government - refused a duel to the death to the Iron Chancellor, Otto von Bismarck, Otto von Bismarck-. In the same year, he described his famous triad of vascular lumen irregularity, damaged blood flow, and increased coagulability.[9]

Virchow's work in the vascular area was continued and crowned by his extraordinary student Julius Cohnheim, who injected wax emboli into the frog's tongue and demon-

strated the lesions that a hundred years later would be called ischemic necrosis and hemorrhagic infarction.[10]

In the second half of the 19th century, Thomas Lauder Brunton identified effects similar to those observed for centuries with therapeutic bleeding in amyl nitrite, and in 1879, Alfred Murrel used nitroglycerin to mitigate angina pectoris. Nitroglycerin was a homeopathic drug that was first used by Constantine Hering in 1840.[11]

There is a direct line of research from Virchow; Cohnheim, Carl Wiger, Karl Huber and William Osler, published several experiments and observations about the correlation between coronary occlusion and myocardial infarction and angina[12] and soon after, in 1899, Walter Baumgarten and William Porter published their experimental observations of loss of myocardial contractility after coronary occlusion and contractile recovery by restoring circulation with blood without fibrin; they also observed that contractile loss was more significant in the center of ischemia than in the periphery.[13]

John B. Herrick published in 1912 an extensive review of publications about the relationship between heart attack, angina, and coronary artery disease and managed to establish that thrombotic occlusion of the coronary vessels can be fatal but not always. Using his findings, he differentiates between infarction and ischemia, describes the variability of the clinical presentation of the syndrome and explains this variability to extra coronary factors such as blood pressure, previous myocardial status, and aspects of coronary occlusion such as vessel size, location of the occlusion and number of vessels injured. This valuable Herrick publication was the result of reading a previous work published in German by two Russian doctors, Obrastzov and Straschesko.[14]

There was a long delay between Heberden's work and the clinical identification of myocardial infarction until the beginning of the 20th century, with Herrick. These delays had several causes, among them, the belief of the absolute unviability of the coronary occlusion, the significant inconsistency between the symptoms and the pathological findings, the confidence of nineteenth-century doctors in auscultation, the lack of revision of the coronary arteries and the myocardium at autopsy, the gap between pathological and physiological findings and their incorporation into medical practice, the preponderance towards bacteriological research and the lack of diagnostic tools.[15]

After the invention of the electrocardiogram, by Willem Einthoven, it was a resource used for the recognition of arrhythmias that was not very useful because there were no monitors to monitor patients. Still, it was the same Herrick who, together with his assistant, Fred Smith, described electrocardiographic changes during the experimental coronary occlusion. Concepts that in 1932 Charles Wolferth and Francis Wood enriched with the precordial leads.[16]

The treatment of the heart attack did not change much for hundreds of years because there was no efficient therapy that modified the evolution of the patients until the sixties of the last century, confined to absolute bed rest with assisted feeding for a month and a half. Such that survivors faced the risk of apparent complications from prolonged bed stay, particularly infections and thrombus embolism.

The knowledge of ventricular fibrillation is a critical aspect of the care of myocardial infarction well as its diagnosis and treatment. The Ebers papyri recognized ventricular fibrillation, saying that when the heart is sick, it performs its work imperfectly, and the vessels that come from it becomes inactive and unfelt. If the heart trembles, it has little energy and sinks, the disease is advanced, and death is near. Hippocrates also described sudden death for the first time when he said that subjects who suffered frequent and severe fainting without apparent cause died suddenly.[17]

The classic descriptions of ventricular fibrillation were published long before the invention of the electrocardiogram, from Vesalius's appreciation that the hearts of dying animals exhibited worm movements. The same with the experimental achievement of ventricular fibrillation in the work of Carl Ludwig and Hoffa, until the first proposal of this phenomenon as a mechanism of sudden death, by John Mac William, ending the belief that the cause was sudden cardiac arrest in diastole. This publication also changed the name of heart failure to sudden death.[18]

General Electric sponsored research, at various Universities, after several electrocu-

tion accidents due to the change from direct to alternating current, to discover the causes of the lethality of electric current. Then William Kouwenhoven and Guy Knickerbocker started the modern era of cardiopulmonary resuscitation with the implementation of electrical cardioversion and the cardiac massage, later Claud Beck performed the first successful clinical cardioversion by Claud Beck in 1947.[19]

For two decades after these discoveries, the development of closed-chest defibrillators arose from the publications of Bernard Lown –creator of the term cardioversion– and Barouh Berkovits and the introduction of biphasic wave equipment in the Soviet Union by Naum Gurvich, until the development of the 70 kg portable equipment in 1965. The characteristics of these devices made them of little value for clinical application because, apart from the enormous complexity for their management, patients moved for considerable distances in hospitals for reanimation.[20]

These considerations led to one of the crucial moments in the treatment of myocardial infarction, the creation of the coronary units; Eugene Braunwald considers the coronary care unit the essential advance in the treatment of acute myocardial infarction. The concept stems from the need to bring patients vulnerable to lethal arrhythmia together in a single area to shorten the reaction time and reduce the possibility of brain damage; likewise, it requires the training of nursing personnel in the early recognition of acute complications of heart attack and the immediate application of resuscitation maneuvers.

The initial concept of the coronary unit comes simultaneously in 1961 from the ideas of William Dock in the United States and Julian Desmond in England. Both doctors achieved little attention, and Julian had to open the first unit in Australia, but there was no acceptance of this resource in the world until after the death of Clark Gable on the tenth day of an uncomplicated heart attack, treated at the Presbyterian Hospital in Hollywood; the press provoked the reaction and the creation of the first well-equipped coronary unit in Kansas City.[21] In Mexico, there was a sequence for creating units for post-surgical care, and Dr. Enrique Parás Chavero established the first coronary unit at the Spanish Hospital in 1968.[22]

Despite the knowledge concerning thrombosis and necrosis for more than a century, it took a long period of controversy during the second half of the twentieth century about thrombosis as cause or effect during the myocardial infarction. It was the single paper from Marcus DeWood et al,[23] which constitutes significant therapeutic changes: 1. It showed to the world that it is feasible the cardiac catheterization during the acute myocardial infarction in an era when it was considered lethal, 2. It confirmed the almost constant presence of coronary thrombosis, 3. It confirmed the open artery theory, with the first experience of thrombus retrieval A significant development came later, with many trials for thrombolysis and catheter-based treatments for acute myocardial infarction. Our country had the possible first experience of primary angioplasty, included in the Spanish Hospital's initial patients' series experience.[24] I want to conclude with something that I commented to my professor during my early trainee as a cardiology resident about what we can expect from the future diagnostic and therapeutic approaches; he asked me to remember that we see beyond because we are over the shoulders of giants.

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http://dodd.cmcvellore.ac.in/ftext/free%20e-journalR.htm

Mercyhurst University. Hammermill Library. Erie, Pennsylvania
http://services.trueserials.com/CJDB/MERCYHURST/browse

Memorial University of Newfoundland, Canada
http://www.library.mun.ca/copyright/index_new.php?showAll=1&page=1

Journals for free
http://www.journals4free.com/

Google Books
http://www.google.com.mx/books?id=w0GaAAAAIAAJ&lr=&hl=en&redir_esc=y

Research Institute of Molecular Pathology (IMP)/ Institute of Molecular Biotechnology (IMBA) Electronic Journals Library, Viena, Austria
http://cores.imp.ac.at/max-perutz-library/journals/details/?tx_ezbfe_pi3%5Bjournal_id%5D=15597&cHash=ce986bc3bc6d621dbca9ddbfea98424b

Scielo México
http://www.scielo.org.mx

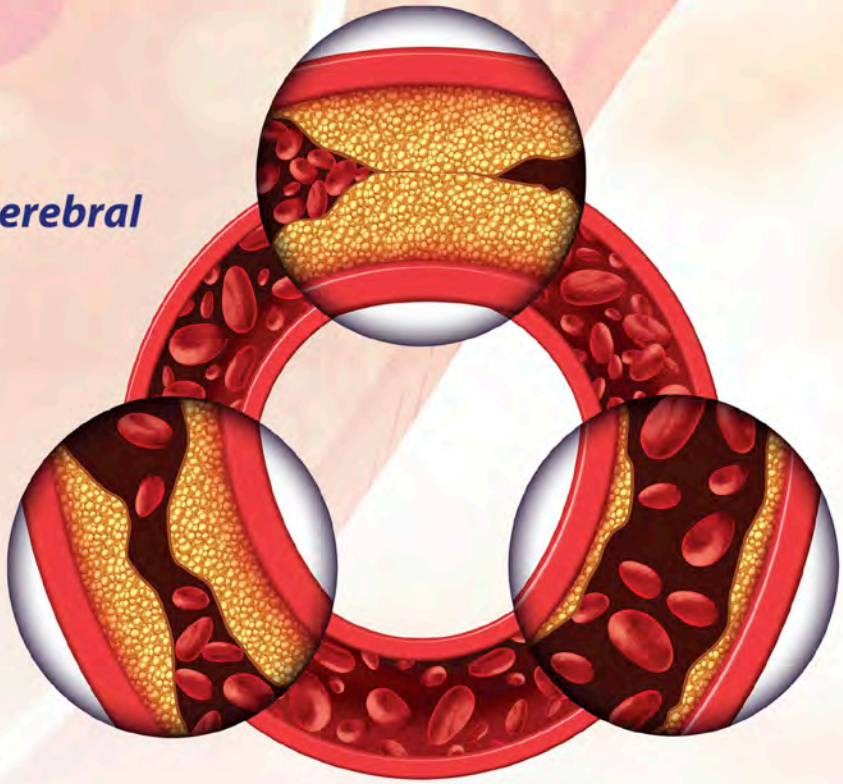
Gantena

(Rosuvastatina)

Controla eficazmente

Las **enfermedades cardiovasculares** siguen siendo la **primera causa de muerte en el mundo** y el factor común de estas entidades es la elevación del **colesterol LDL**.

- ***Infarto al miocardio***
- ***Accidente vascular cerebral***
- ***Coronariopatía***



Estudios clínicos en pacientes con factores de riesgo cardiovascular alto, sugieren que mientras mayor sea la **disminución de los niveles de colesterol LDL**, menor será el riesgo de presentar enfermedades cardiovasculares.

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Cetus

Senosiain®

Sies®

HIDROSMINA

- La hidrosmina, en la insuficiencia venosa periférica, adecúa el flujo sanguíneo de retorno
- Regula el proceso filtración-absorción a nivel de la unidad microcirculatoria y aumenta la resistencia del capilar

INDICACIONES :

- Várices
- Hemorroides
- Edema del embarazo

SIES-01A/ter-09
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OK EN HIPERTENSIÓN

Porque la **hipertensión** es un problema de salud global que daña órganos blanco y que tiene como consecuencia:

- Insuficiencia cardiaca
- Daño renal
- Retinopatía
- Demencia vascular

OKSEN Es la cápsula de contenido líquido que da el **OK en hipertensión**

+ Telmisartán Hidroclorotiazida

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IPAL

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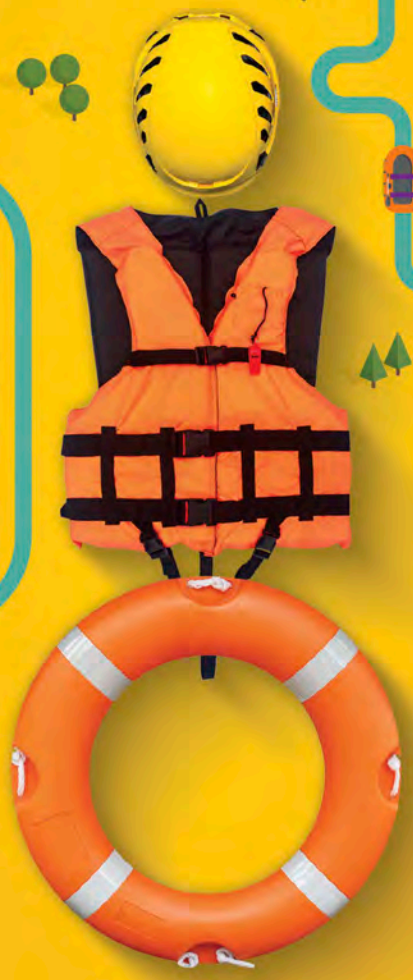
Flujo continuo

En el **manejo y prevención** de eventos **aterotrombóticos**

SALVA VIDAS



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Senosiain

Evipress®

Protección cardiovascular contínua

Evipress de 10 a 20 mg/día asegura:

- Selectividad vascular
- Acción gradual y sostenida
- Control adecuado de la PA, aún en pacientes con factores de riesgo
- Adecuado perfil de seguridad
- Menor incidencia de edema

PROTEGE TU CORAZÓN

Con una toma al día Evipress®

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