FACULTAD DE MEDICINA HUMANA
SECCIÓN DE POSGRADO

PROTECTIVE ROLE OF CARVEDILOL TO PREVENT LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN PATIENTS UNDER CHEMOTHERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

PRESENTED BY
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THESIS

TO THE ACADEMIC DEGREE OF MASTER OF MEDICAL RESEARCH

LIMA – PERÚ

2018

USMP
UNIVERSIDAD DE
SAN MARTIN DE PORRES

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JURY

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To my husband, daughter and son who accompanied me through this trip with patience, solidarity and joy

To my colleagues, who were a source of motivation, enthusiasm and curiosity

ACKNOWLEDGMENTS

To my advisers Jorge Leite, PhD and Sandra Carvalho, PhD that answered my concerns with strict methodological respect.

To Tomás Galvez, MD, Ms that allowed this thesis to end with high academy level and generosity.

To Diogo Bugano, MD that was a generous source of answers for unexpected statistical issues.

To my colleague and friend Pablo Alvarez, MD, Associate Professor of Internal Medicine and Coordinator of UMIC (Heart Failure Multi-approach Unit), who worked with me through all the process of searching and interpreting results with a high academy sense of relevance.

CONTENT

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RESUMEN

Algunos tratamientos oncológicos pueden causar alteraciones cardiovasculares pese a lograr tratamientos exitosos de la enfermedad maligna. Se evaluó el rol del carvedilol para prevenir el deterioro de la función sistólica del ventrículo izquierdo en pacientes bajo quimioterapia.

Se trata de una revisión sistemática y metanálisis de ensayos clínicos aleatorizados. Se realizó una búsqueda en Pubmed, Embase, Cochrane , Scielo y clinicaltrials.gov; se incluyeron trabajos que evaluaron y compararon la diferencia en la fracción de eyección del ventrículo izquierdo (antes y después de recibir quimioterapia) entre pacientes con y sin carvedilol. El tamaño del efecto es expresado como la diferencia estandarizada (d) y la diferencia de medias entre grupos con su intervalo de confianza 95%.

Resultó que 9749 manuscritos fueron identificados; se incluyeron cuatro estudios con un total de 343 pacientes adultos, 86.9% de sexo femenino, con fracción de eyección del ventrículo izquierdo normal y sin historia previa de insuficiencia cardíaca. El grupo bajo tratamiento con carvedilol mostró una caída menor aunque no significativa de la fracción de eyección del ventrículo izquierdo que el grupo control (d= -0.501 [-1.372, 0,371]; p = 0.260; siendo la diferencia de la reducción de fracción de eyección del ventrículo izquierdo pre-postquimioterapia entre ambos grupos = -0.71% [-1,88, 0,575]); pero la fracción de eyección del ventrículo izquierdo final fue mayor en el grupo carvedilol (d= 0,361 [0,146, 0,575]; p = 0,001; el tamaño del efecto fue = 1.73 %[0,74,2,72].

En conclusión, el carvedilol solo o combinado, se asocia a una mayor fracción de eyección del ventrículo izquierdo, pero no a un menor descenso de la misma al finalizar la quimioterapia.

Palabras claves: Antagonistas de receptores adrenérgicos beta; quimioterapia; cardiotoxicidad.

SUMMARY

Cardiovascular toxicity related to cancer therapy may cause significant morbidity and limitation of long term survival after successful treatment. We evaluated the role of carvedilol for prevention of chemotherapy related left ventricular systolic dysfunction.

A systematic review and meta-analysis of randomized clinical trials was performed through Pubmed, Embase, Cochrane , Scielo and clinicaltrials.gov. Trials that evaluated the difference of left ventricular ejection fraction before and after chemotherapy in patients with and without carvedilol, were included. Effect size is expressed as mean, mean difference, standardized mean difference, with 95% confidence interval.

It turned out that 9749 manuscripts were screened. Four studies evaluating 343 adult patients, 86.88% female, with normal ejection fraction and no past history of heart failure, under anthracyclines treatment, were included. There was a non-significant minor reduction of left ventricular ejection fraction in active group (d= -0.501 [-1.372, 0.371]; p = 0.260; difference of left ventricular ejection fraction reduction, mean difference= -0.71%[-1.88, 0.46]); but left ventricular ejection fraction after chemotherapy was better in carvedilol group (d=0.361 [0.146,0.575]; p = 0.006; left ventricular ejection fraction difference = 1.73%[0.74, 2.72].

In conclusions, therapy with carvedilol alone or plus other cardio-protective treatments is associated with a better left ventricular ejection fraction, but not a significant minor reduction after chemotherapy treatment.

Keywords: Adrenergic beta antagonists; chemotherapy; cardiotoxicity.

INTRODUCTION

Cancer is the leading cause of mortality in developed countries and the second leading cause of mortality in developing countries[1]. The prognosis of patients with cancer has improved remarkably over the past years. The introduction of new chemotherapeutic and antineoplastic drugs and the use of more dose-intensive regimens have increased the cure and remission of several types of cancer, and, in some cases, has converted cancer into a chronic disease. However, these treatments are associated to several significant adverse events, such as cardiac toxicity, especially when associated to high doses and long-term use of these therapies[2].

For instance, anthracycline´s effect over cardiac function is a well-known adverse effect, with a potentially irreversible deterioration of the cardiac function. This effect, among other causes, is dose-dependent[2]. Besides that, several other drugs used in the treatment of hematologic malignancies, breast cancer and many other oncological pathologies; even at standard doses, may induce acute and chronic cardiac toxicity through a diversity of mechanisms including endothelial toxicity and direct myocyte injury[3]. Long-term cardiac toxicity and systolic dysfunction may affect patients' survival even in asymptomatic patients as left ventricular systolic dysfunction might limit patients' treatment options and their long-term survival[4].
Therefore, in 2009 a cardio-oncology medical specialization was created in order to increase the knowledge about cardiac toxicity mechanisms and therapeutic options; clinical practice guides were elaborated and clinical information summarized. A novel impulse was created to deep knowledge regarding early systolic function diagnosis through new echocardiographic technics and the specific use of some potentially cardioprotective agents.

Studies have shown that beta blockers (mainly carvedilol, bisoprolol, metoprolol XR and nevibolol) have a protective effect over the left ventricle decreased systolic dysfunction from further dilatation and loss of systolic function in ischemic and non-ischemic cardiopathy[5, 6, 7], but their role in oncology stage preventing new systolic dysfunction is not well defined. Carvedilol is the only beta blocker with antioxidant

action, this singularity may explain its beneficial effect in chemotherapy cardio-toxicity. Few drugs have demonstrated effective protection against left ventricle deterioration under chemotherapy and carvedilol is one of them; it is also one of the most used pharmacological treatment, due to its cardio-protective function. Carvedilol is relatively inexpensive and well tolerated. Large randomized trials and meta-analysis have established its efficiency for other stages of systolic dysfunction[8]. International guidelines about cardio toxicity recommend carvedilol in patients who experience a decrease in left ventricular ejection fraction greater than 10% and less or equal than 50% regardless symptoms[9].

However, little evidence is available and the exact effect size of carvedilol in preserving left ventricular systolic function (LVSF) in patients with no previous systolic dysfunction and under chemotherapy is not well defined. Few small clinical trials[10-17] evaluate LVSF after chemotherapy under carvedilol and no meta-analysis focused on carvedilol´s effect has been published.

The general objective of this research is to investigate the effect of carvedilol´s cardio-protective role in patients under chemotherapy. The specific objective is to compare LVSF deterioration after onset of chemotherapy in patients under carvedilol vs. no specific cardio-protective treatment or placebo. The p*rimary outcome* is Difference between pre and post chemotherapy in LVSF parameters, any of the following: left ventricular ejection fraction (LVEF), left ventricle´s shortening fraction, left ventricle´s global strain. If LVEF was available, it was preferred for first analysis; regardless pooled effect through different LVSF measurements was additionally done. The *secondary outcome is* LVSF after chemotherapy (LVEF if available was preferred for a first global analysis and LVSF through other measurements was also tested).

Cardio-toxicity due to chemotherapy is an emerging problem. Different mechanisms of cardiac damage are recognized as leading to systolic dysfunction; some are reversible, but others are not. Heart failure is a pathology with great mortality (even higher than cancer in some stages). To prevent systolic dysfunction and heart failure is an issue of great concern all over the world.

Carvedilol, as it was explained, is a well-known beta blocker, relatively inexpensive and well tolerated. Its efficacy, although well known in other stages of established systolic dysfunction, is not well defined in preserving systolic function in cardiac-toxicity stage. Some observational studies[18] and few small clinical trials[10-15] suggest efficacy of carvedilol in preventing systolic dysfunction. A meta-analysis could be a good tool to obtain a bigger and more powered sample to establish the exact effect size; and at the same time is a good tool to compare and interpret differences or heterogeneity in effect through studies. This information can guide future research and can also provide level of evidence for the clinical use of carvedilol.

The project is the development of a systematic review and a meta-analysis of randomized clinical trials and the research question is: Is carvedilol (alone or associated with other cardio-protective pharmacologic treatments) effective in preventing LVSF deterioration in patients under chemotherapy with at least 1 month of follow-up, compared with placebo or no cardio-protective treatment?

Relevant studies were searched in PubMed, EMBASE, Cochrane and Scielo; ongoing studies were searched in clinicaltrials.gov and a hand search for grey literature was performed and those studies which follow inclusion criteria will be included.

CHAPTER I: THEORETICAL BASES

1.1 Background research

Cardiovascular toxicity is a potential short- and long-term complication of various anticancer therapies. Cancer should be treated in an integral way and even though new therapies have improved oncologic patient´s survival, there is great awareness about adverse effects of antineoplastic agents. Cardiac toxicity is a well-known serious potential adverse effect. Heart failure and cardiac systolic dysfunction regardless the stage, have an important compromise of survival and sometimes it can be worse than some oncologic disease[9].

There are two main mechanism involved in cardiac toxicity regarding chemotherapy, one is irreversible (type I) and the other is potentially reversible (type II).Type I damage is classically described due to anthracyclines and the mechanism involved is cell loss; meanwhile type II damage (trastuzumab and other monoclonal antibodies and targeted agents are the best known) involves mitochondrial dysfunction and protein alterations [19].

A common presentation in both types of cardiac damages is systolic dysfunction and heart failure. Therefore, great effort has been developed detecting cardiac dysfunction in patients under chemotherapy or candidates to receive it. The relevance of this detection is that systolic dysfunction may forbid, interrupt, change or delay anticancer therapy and at the same time compromise survival independently from cancer[9]. Even though still under discussion, international guidelines defined cardio toxicity and recommend the indication of specific cardiac protecting treatment when ejection fraction decreases more than 10% and less or equal than 50% regardless symptoms[9].

As a consequence of previous concepts, patients who are under chemotherapy or have received chemotherapy are considered at high risk for the development of heart failure, and clinical guidelines indicate these patients are in stage A of heart failure as patients with hypertension or diabetes [20].

LVEF is the most used LVSF parameter in clinical practice and clinical trials; even though systolic function may be measured through different methods with advantages and disadvantages for each one (example: myocardial strain, s wave peak through tissular Doppler, shortening fraction, etc). Different treatments have demonstrated to improve LVEF and at the same time improve survival and functional class in the stage of systolic dysfunction in ischemic and non-ischemic cardiomyopathy [5, 6, 7]; but few small trials have been performed to test prevention of systolic dysfunction in oncologic patients[10-17, 21, 22, 23] .

There are meta- analysis that show the cardio protective effect of angiotensine converting enzyme inhibitors (ACEI) and beta-blockers in these patients [24-25]. Recently a meta-analysis of randomized clinical trials (RCT) including 317 patients regarding beta-blockers as a group (bisoproolol, carvedilol, nevibolol) about cardio-protective effect on chemotherapy stage, showed not only prevention of systolic dysfunction but also a beneficial effect on survival[25].

We must highlight that the effect of beta blockers on systolic function is not a class effect as it is ACEI´s and angiotensine´s receptors antagonist´s effect. Large clinical trials and meta-analysis have shown carvedilol is useful to improve LVEF and to improve survival in heart failure and systolic dysfunction stages [7,26,27,28] but, as it was explained, the evidence about its cardio-protected primary prevention effect on chemotherapy stage is small and no meta-analysis was still published.

1.2 Theoretical bases

Under this title, we will describe brief theoretical bases about mechanisms of chemotherapy in cardiac damage; mechanisms of carvedilol cardiac protection and antioxidant effect, bases of LVSF assessment and theoretical bases of meta-analysis.

Type I and II cardiac damage

As it was mentioned, cardiac damage and heart failure are one of the most serious adverse effects of systemic cancer therapy[9].

Type I damage: Anthracyclines and others as the non-anthracycline analogue mitoxantrone are among the most effective anticancer agents. Data from endomyocardial biopsy and troponin I measurements suggest that myocyte injury may occur early after anthracycline exposure. However, clinical manifestation may not become apparent for months or years after the initial chemotherapy exposure[29,30].

Early cardiac adverse effects are typically reversible and self-limiting and include dysrhythmia, repolarization changes in the electrocardiogram, pericarditis, and myocarditis; meanwhile, late anthracycline cardiotoxicity is characterized by cardiomyopathy and systolic heart failure. Patients treated with anthracyclines are five times more likely to develop chronic heart failure or reduced LVEF compared with those treated with a non-anthracycline chemotherapy[31].

The pathophysiology of this late cardiotoxicity is cell loss through necrosis or apoptosis and its effects are irreversible. Although many variables are related with individual response (age, genetic predisposition, arterial hypertension, previous or concurrent mediastinal radiation therapy, and combination with alkylating or antimicrotubule chemotherapeutics); damage is dose dependent and patients without other risks factors tolerate cumulative doses of doxorubicin of up to 300 mg/m^2 [32].

Type II damage: Other new anticancer drugs lead to cardiac damage through a different mechanism. This group of drugs is the “targeted drugs” against HER2/ erbB2- and vascular endothelial growth factor signaling pathways. They were recently introduced in the treatment of breast cancer and other oncological pathologies. Trastuzumab, a monoclonal antibody against HER2, has proved to prolong survival in breast cancer and gastric cancer patients; and two

observational studies found higher incidence of heart failure in patients treated with trastuzumab and anthracyclines than with anthracyclines alone[33,34].

The pathophysiology of type II cardiac damage is cellular dysfunction (mythocondrial and protein dysfunction), which leads to temporary myocardial dysfunction, vasospastic angina and reversible hypertension. However reversible cardiac damage can be serious and lead to death. Besides that, it is thought that trastuzumab may act as a modulator of anthracycline toxicity when administered during a period of myocyte vulnerability following anthracycline exposure; no major cardiac toxicity is found in patients receiving trastuzumab without previous or concomitant anthracyclines[35].

Protective effect of carvedilol

Seicean et al. (2013) evaluated in an observational study the incidence of heart failure in patients under trastuzumab and/or anthracyclines treatment and assessed the effect of incidental β-blocker use on new heart failure and non-cardiac mortality during a median of follow up of 3 years. The use of β-blocker resulted in a significant reduction of the incidence of symptomatic heart failure (hazard ratio: 0,2: 95% CI 0.1-0.7)[18].

There are no published data assessing the effect of prophylactic β-blocker on trastuzumab-induced cardiomyopathy. However, there are at least 5 studies assessing carvedilol[14,15,16], metoprolol[31] and nevibolol[34] alone to prevent anthracycline-induced cardiomyopathy and at least two meta-analysis that assessed the cardioprotective effect of β-blockers as a group on this stage. These studies suggested a beneficial effect of β-blockers, although with great heterogeneity. This aspect and others regarding some preclinical studies suggest that not all β-blockers are the same; particularly in oncologic patients, β-blockers effects would not be a class effect. Related to general heart failure stage, the /a β-blocker effect is also heterogeneous, and it is related with the inhibition of the sympathetic tone regarding the neuro-hormonal theory of heart failure[24,25].

In animals exposed to anthracyclines, β1 activation seems to be cardio toxic, meanwhile β2 activation is cardio protective and this last effect could be related with an activation of pro-survival kinases and a decrease in intracellular calcium, attenuating mythocondrial dysfunction seen in chemotherapy treatment[36].

This suggests a better cardio protection in β1 selective β-blockers, even though this is opposite to results of mortality in a cancer registry [37].

Carvedilol is a non-selective β-blocker and a α1 adrenergic antagonist with antioxidant properties[38]. Its cardio protective effect in systolic dysfunction is related with the β1-blocker action and the α1 antagonism which resulted in a cardiac frequency control, vasodilatation and energetic saving. Nonetheless, the antioxidant activity rather than β-blocker action of carvedilol seems the most promising in chemotherapy cardio-protection. A study that compared carvedilol with atenolol (β1 selective blocker with no antioxidant effect) showed that carvedilol but not atenolol prevented mitochondrial damage and reduced histopathologic changes associated with doxorubicin cardiotoxicity[39].

Furthermore, in some tumor cells carvedilol increases cytotoxicity of doxorubicine turning it into a theoretically ideal drug for cardio-protection since it does not diminish the antineoplastic activity of anthracyclines[40]. The cardio-protective effect of carvedilol under trastuzumab treatment is still less known and an ongoing study will evaluate the effect of carvedilol associated with lisinopril in women with HER2 positive breast cancer (NCT01009918).

Left ventricular systolic function assessment

LVSF is of great relevance in cardiology since it is the most important prognostic factor regarding cardiologic diseases [41].

LVEF is the most widely used parameter for LVSF assessment and it is the one used in almost all big cardiology trials. Nonetheless, LVEF is not the only nor the best way to evaluate LVSF. LVEF is related with the contractile function itself but also depends on pre and afterload. Therefore, changes in loading

conditions may result in changes in LVEF without reflecting a modification in contractility. LVEF can be assessed through various methods from subjective evaluation to different quantitative methods by echocardiography, magnetic resonance or cardiac tomography; LVEF evaluated through Simpson´s biplane method is the method recommended by the American Society of Echocardiography and most used in clinical trials. LVEF evaluated through magnetic resonance is the nowadays gold-standard, being comparable with LVEF evaluated through 3D echocardiography[42].

Recently, new echocardiographic technology introduced new ways for the evaluation of systolic function (strain and strain rate) that demonstrated to be reproducible, accurate, less related with charge conditions and more sensitive to early changes in systolic function [43].

Bases of systematic review and meta-analysis

Systematic review gives the possibility of a more objective review of the topic regarding a specific question, with pre-established rules to search for studies and to define which one will be included or excluded from analysis with a final statistical synthesis of data (meta-analysis). Regarding the topic in question, available results seem to be promising, but the research process is slow and erratic and may be helped with a synthesis of results that can guide new primary studies and strengthen or modify current clinical practice[44].

1.3 Definitions of basic terms

The objective of this research is to review the topic of carvedilol as an effective protector of cardiac systolic function in patients treated with chemotherapeutic agents and to obtain a pooled effect regarding available results.

Research question: See section I, delimitation of the study.

Design: systematic review and study-level meta-analysis.

Chemotherapy: any antineoplastic drug with known potential cardio toxicity. Cardiac damage should be classified regarding mechanism in type I or type II damage.

Active treatment: The drug used for treatment of the disease, in this case: carvedilol.

Outcome: LVSF. Difference in LVSF before and after chemotherapy and LVSF after chemotherapy will be compared. The following parameters for evaluating LVSF will be considered: LVEF, left ventricle´s shortening fraction, left ventricle´s global strain. If LVEF was available, it was preferred to diminish variability in LVSF evaluation.

Comparison: the outcome obtained in the group under carvedilol treatment will be compared with a placebo or no specific cardio-protective treatment group.

Heterogeneity among included studies was tested to a better qualification of results and to a better selection between random or fixed effect of the pooled effect.

Heterogeneity: the potential variation of the true effect size from study to study. Heterogeneity was identified and quantified through I^2 statistics that reflects the proportion of the observed variance that reflects real differences in effect size. According with Higgins et al. values on the order of less than 25%, 25%-75% and more than 75% will be considered as low, moderate and high heterogeneity respectively[46].

- **Inclusion of studies:** RCTs which evaluated systolic function with and without treatment with carvedilol (alone or associated with other potential cardio-protective agents) in patients under chemotherapy.
- Evaluation of bias will be done regarding Jadad score[45], including studies with a Jadad score ≥ 3.
- **Exclusion of studies:** Patients with previous systolic dysfunction or heart failure symptoms.

CHAPTER II: HYPOTHESIS AND VARIABLES

2.1 Operationalization of the variables

Hypothesis	Variables	Type	Subtype	Scale	Possible Values
The hypothesis tested was that carvedilol is effective in preventing LVSF deterioration in patients under chemotherapeutic agents' treatment. Género	Active treatment:	Qualitative		Nominal	Carvedilol with or without another pharmacological cardioprotective agent.
	Comparison treatment:	Qualitative		Nominal	Placebo treatment or no cardio-protective treatment.
	Oncological treatment: Chemotherapy with potential cardio-toxic action.	Qualitative		Nominal	Anthracyclines or preponderant type I damage and trastuzumab or similar with preponderant type II damage.
	LVSF: It was searched through: LVEF, left ventricular´s shortening fraction, left ventricular´s global strain. To compare LVSF between active and placebo/no treatment groups standardized mean difference was calculated as not all studies use the same parameter 50, and mean difference was also calculated when LVEF was	Quantitative	Continuous	Ratio (razon)	Percentage

	the only used.				
	The difference of LVSF before and after chemotherapy was the main outcome and LVSF after chemotherapy was the secondary outcome.	Quantitative	Continuous	Ratio (razon)	Negative or positive number
	Difference and SD (standard deviation) of the difference of LVSF was registered if available and if not it was calculated for each group as follow 51:	Quantitative	Continuous	Ratio (razon)	Negative or positive number plus its SD
	Difference of means: μ pre - μ pos-chemotherapy	Quantitative	Continuous	Ratio (razon)	Negative or positive number
	SD of difference of means: =√(〖SEM pre ch〗^2 +-〖SEM pos ch〗^2) Where SEM (standard error of the mean) pre ch =SD pre ch/√sample size	Quantitative	Continuous	Ratio (razon)	Negative or positive number

CHAPTER III: METHODOLOGY

3.1 Type and design

The present was a systematic review and meta-analysis of RCT focused on the effect of carvedilol in preserving LVSF in patients under cardio-toxic chemotherapy.

The objective was to obtain a pooled effect and to define through it a more powerful result than the obtained through single studies. Trials regarding this topic are few and small; additionally, due to ethical issues exposed by the Institutional Review Boards to develop double-blinding studies, many of them do not achieve a Jadad score of 3. The outcome selected (LVEF mainly measured through LVEF) is an excellent surrogate outcome [47].

Research design

Systematic Review and Meta-analysis as a method have the same advantages as they allow a comprehensive search of available data regarding a focus question (our research question). A meta-analysis uses a statistical synthesis of the results from multiple studies to increase power and improve estimates of the size of the effect and/or compare them when results disagree. A meta-analysis produces a weighted average of the included study results with some advantages as the possibility to generalize to a larger population and to increase the statistical power to detect an effect. Inconsistency of results across studies can be quantified and analyzed, and publication bias can be investigated. On the other hand, a meta-analysis has problems and limitations, and the accuracy of results must be weighted with the quality of the studies as potential sources of bias. It is a discussion which studies are worthy to be included in meta-analysis and how to qualify them.

This meta-analysis has some important limitations to be addressed and to take in consideration at time of analysis of results:

The small number of studies included with a small number of total subjects.

High heterogeneity among studies we dealt with and tried to explain at least partially.

3.2 Sampling design

Population

We did a comprehensive search of all available data with the objective of obtaining not a sample of relevant studies but the whole relevant population of studies.

The searching was done as complete as possible minimizing bias. For that reason, more than two important data bases were searched, without language or another filter, up to April 15th, 2016. Relevant studies were sought in PubMed, EMBASE, Cochrane and Scielo and a hand search for grey literature and references of included articles; unpublished and ongoing studies was searched in clinicaltrials.gov. Studies which follow inclusion criteria were included.

As written key words were in English, but no language filter was used to diminish bias; as a consequence, any foreign language could be found and hand searching, text comprehension and authors communication was a limitation in some situations.

Two independent researchers performed the search, to exclude irrelevant reports and to identify duplicate reports from the same study. Differences were solved by consensus.

Search keywords were at first: (carvedilol or beta blockers) and (chemotherapy or cardiac toxicity) and (systolic dysfunction or systolic function or heart failure); but finally a more extended search was performed (carvedilol OR beta blocker*) and (chemotherapy OR cardiac toxicity OR anthracycline OR trastuzumab) and (systolic dysfunction OR systolic function OR heart failure OR ejection fraction OR strain).

Sample Size

The sample size was the consequence of the search and was not previously established.

3.3 Data collection techniques

Strategy of selection of studies:

Studies considered for this review were RCTs and for eligibility criteria and quality assessment a Jadad score ≥ 3 was required.

Eligibility criteria for the patient´s population: children and adults under new onset chemotherapy and absence of previous heart failure symptoms or left ventricular systolic dysfunction (LVEF ≥ 50%).

Eligibility criteria for each intervention and comparator: Carvedilol regardless doses (with or without an additional cardio-protective drug) vs placebo or no cardio-protective treatment.

Outcomes information

Primary outcome: the difference between pre and post chemotherapy in LVSF parameters, any of the following: left ventricular ejection fraction (LVEF), left ventricle´s shortening fraction, left ventricle´s global strain. If LVEF was available, it was preferred for first analysis; regardless pooled effect through different LVSF measurements was additionally done.

Secondary outcome: LVSF after chemotherapy (LVEF if available was preferred for a first global analysis and LVSF through other measurements was also tested).

Details of subgroups

a. Subgroups regarding treatment: carvedilol alone vs carvedilol plus another possible active treatment.
b. Subgroups regarding LVSF evaluation: LVEF vs. strain.

Search methods for identification of studies

See section III, population. Flow chart of retrieved studies was performed regarding PRISMA recommendations [48].

Inclusion of studies

- RCT on pharmacological prevention of LVSF deterioration, in patients under new onset chemotherapy compared with placebo or no cardio-protective treatment.
- The studies were sought by two researchers and, during the process, irrelevant reports and multiple reports identified from the same study were removed.
- Analysis of concordance between researchers was performed regarding studies selection and qualification.
- The identification of studies was through key words search.
- Screening: After duplicates were removed, studies were screened by title and abstract, looking for relevant studies regardless study design about cardio-protective role of carvedilol and beta blockers in patients under chemotherapy.
- Eligibility: Selected relevant studies were looked for eligibility criteria through full text lecture (RCT, testing carvedilol in patients under chemotherapy, systolic function available as an outcome). Other designs but RCT were removed.
- Included studies: Studies with inclusion criteria were included for qualitative analysis and those with enough quality (Jadad score ≥ 3) were included in statistical analysis.

- From all the included studies, baseline data: number of subjects in each group, children/adult's population, type and doses of chemotherapy, carvedilol doses, presence or absence of additional cardio-protective treatment in active group (type); LVSF function pre and post chemotherapy and its difference and time of follow-up were registered.

3.4 Processing and data analysis

Excel´s sheet with collected data was exported to STATA 13 for statistical analysis.

Pooled effects were obtained through random and fixed effect model, although random effect was preferred regarding heterogeneity. Results are shown through a forest plot.

It was expected a pooled effect with a negative standardized mean difference (d) of the difference between pre and post chemotherapy to affirm that carvedilol shows an effective cardio-protective role (expressing a significant less reduction of systolic function in carvedilol group vs no cardio-protective/placebo group). Cohen´s d and its confident interval was calculated to estimate the effect size.

At the same time a positive standardized mean difference (d) of LVSF after chemotherapy was expected to affirm the same conclusion (expressing a significant better/major last systolic function in carvedilol group).

The pooled effect through last LVSF may be more sensitive as it depends on a direct measurement than on the result of the difference of two measurements with its own variability each.

A sensitivity analysis for primary and secondary outcome was also performed testing the difference of LVSF and LVSF after chemotherapy with other measures not LVEF if available; and another sensitivity analysis for primary outcome through the single omission of each study.

Additional analysis: Not enough power was obtained to perform a meta-regression analysis. Sub-group analysis comparing the effect size evaluated through LVEF vs strain was done, subgroup analysis comparing carvedilol alone effect vs carvedilol and other cardioprotective treatment was also done.

Publication bias, other sources of bias and quality assessment:

Analysis of publication bias is an issue at time of developing meta-analysis. The most used method to address publication bias, the funnel plot is not recommended for less than 10 studies, and other methods are not well powered to detect publication bias. We ran Begged and Eger´s test looking for a p value > 0.1 but we are still aware of publication bias. A special effort was developed to look after non-published and grey literature.

We think that language bias affects results, even though search was performed without language filter and help to understand some foreign language articles was required.

At time of publication checklist and all PRISMA recommendations were considered [48,49,50,51].

3.4 Ethical aspects

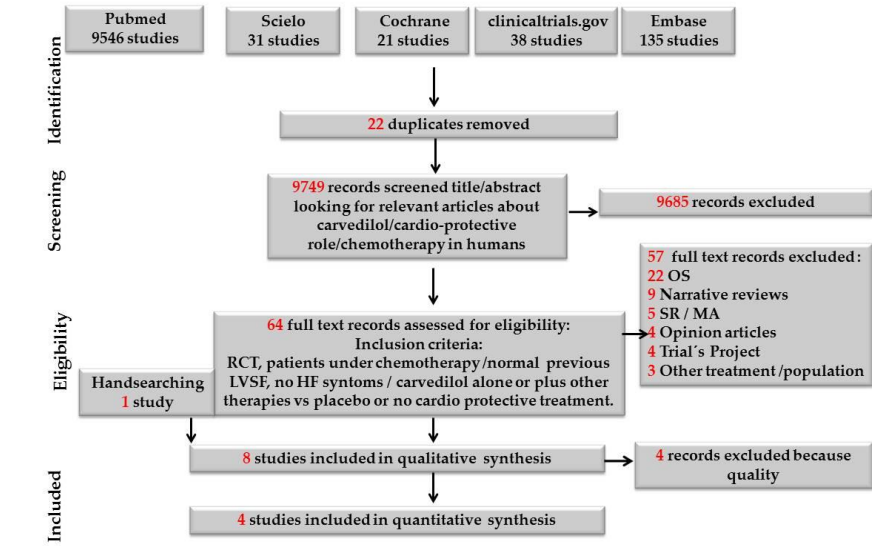
Meta-analysis is finally an observational study of previously reported studies; in this case RCTs. Ethical issues about meta-analysis are related with the proper protection of human subjects in included clinical trials. RCTs should be developed regarding IRB recommendations and with adequate informed consent from subjects.

CHAPTER IV: RESULTS

A total of 9771 studies were identified through data bases search, 22 duplicates were removed and 9749 of them were screened through title and abstract; of these, only 64 were selected for eligibility; at last 7 studies plus one (obtained after hand-searching and follow up of references of the 64 selected studies) were finally included in qualitative synthesis. Finally, 4 studies with a total of 343 adult patients, 86.88% female, were included for quantitative synthesis regarding quality evaluation. Number and reasons of exclusion in every step are shown in **figure 1**.

Few randomized controlled trials were found with carvedilol as active treatment alone or in combination with other cardio-protective treatment. Additional cardio-protective treatments, when present, were enalapril, candesartan and trimetazidine. Only one study was double blinded and only 3 studies reported placebo use for control group.

Figure 1: Flow chart studies selection



Regarding PubMed searching and evaluating strategy, the concordance between searchers was for screening stage, kappa index 0, 6 CI95% (0.46-0.75); for elegibility stage and Jadad score kappa index 1.

Selected studies characteristics, population, intervention, time of follow-up, outcomes and bias evaluation are shown in **tables 1a and 1b**.

Table 1a: Characteristics of selected studies.

Study Author, Journal, Year	***Population***	***Chemo***	***Active / control treatment***	***Follow-up (months)***
Kalay, JACC, 2006	Any malignancy/adults	ANT	Carvedilol 25 mg Placebo	6
Salehi, Am Heart Hosp J, 2011	Breast Cancer-Lymphoma/adults	ANT	Carvedilol 12.5 / 25 mg Placebo	4
El-Shitany, J Card Fail, 2012	Acute Leukemia/ Children	ANT	Carvedilol 12.5 mg no protective treatment	1
Bosch JACC 2013	Malignant hemopathies/ adults	ANT *	Carvedilol 25-50 mg and Enalapril 10 mg no protective treatment	6
Liu Ch Oncology J 2013	Breast cancer/ adults , female	ANT	Carvedilol 10 mg and Candesartan 5 mg no protective treatment	6
Elitok Cardiol J 2014	Breast cancer/ Adults, female	ANT	Carvedilol 12.5 no protective treatment	6
Tashakori Cardiology 2016	Breast cancer/ Adults, female	ANT	Carvedilol 6.25 Placebo	3
Zhang Ch J Gen Pract 2016	Breast cancer/ Adults, female	ANT	Carvedilol 25-50 mg and Trimetazidine 60 mg no protective treatment	4

Studies included in statistical analysis (Bosch 2013, Elitok 2014, Zhang 2016 and Tashakori 2016) included 343 patients, with no heart failure history and normal LVEF; all of them adults, all of them received anthracycline treatment, 86.88% female and most of them with breast cancer as cause of chemotherapy.

No statistical differences were found between carvedilol and control group in the difference of LVEF pre-after chemotherapy (primary outcome) d= -0.501 CI 95% -

1.372 -0.371; p 0.260); but LVEF after chemotherapy (secondary outcome) was significantly better in the carvedilol group (d= 0.361 CI95% 0.146-0.575; p 0.001). **Tables 2a and 3a, figures 2 and 3.** Effect sizes shown through mean differences are shown in **tables 2b and 3b.** Studies that tested carvedilol alone and evaluate systolic function through myocardial strain (Tashakori and Elitok) are shown at the top of the forest plots and those that associated another treatment to carvedilol and do not evaluate systolic function in an additional way than LVEF (Zhang and Bosch) are shown at the bottom (figures 2 and 3).

Study	***Randomisation***	***Blinding***	***Follow-up***	***Jadad scale***
Kalay, JACC, 2006[13]	Yes Not specified	Single-blinding Placebo use	Yes	2
Salehi, Am Heart Hosp J, 2011[14]	Yes Not specified	Not specified. Placebo use	Yes	2
El-Shitany, J Card Fail, 2012[10]	Yes Not specified	No	No	1
Bosch JACC 2013[12]	Yes Stratified, block randomisation, software generated, centralized	Open label Imagine analysis blinded	Yes	3
Liu Ch Oncology J 2013[11]	Yes Not specified	No	Yes	2
Elitok Cardiol J 2014[15]	Yes Software generated sequence	No	Yes	3
Tashakori Cardiology 2016[16]	Yes Block randomisation	Yes Double-blinding, placebo use	Yes	5
Zhang Ch J Gen Pract 2016[17]	Yes Table for random number	No	Yes	3

Table 2a: Primary Outcome meta-analysis of the difference of LVEF pre-post chemotherapy.

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z_value	p_value	No. of studies
Fixed	-0.529	-0.752	-0.305	-4.632	0.000	4
Random	-0.501	-1.372	0.371	-1.126	0.260	

Test for heterogeneity: Q= 45.480 on 3 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance = 0.739

I^2= 93.4% (high heterogeneity)

Figure 2: Primary Outcome random effect forest plot of difference pre-post chemotherapy LVEF.

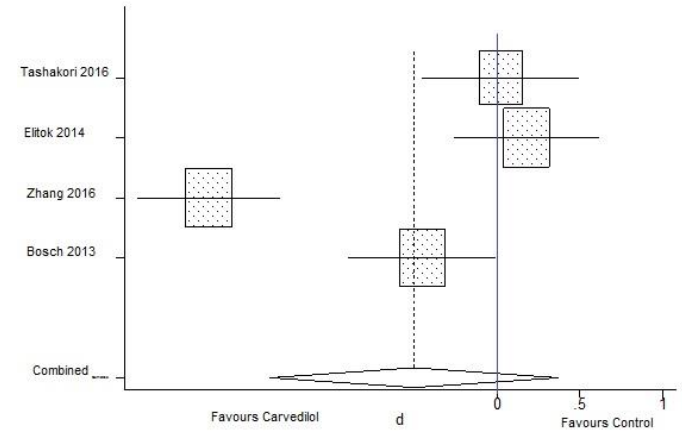


Table 2b : Primary outcome with effect size shown as mean difference and not standard mean difference. All outcome values express LVEF.

Study	Carvedilol			Control		Weight	Mean difference
	Mean %	SD %	Total	Mean % Total	SD %		Random , 95% CI %
Tashakori 2016	0.25	1.79	30	0.22 49	0.91	28.6%	0.03 [-0.67, 0.73]
Elitok 2014	1.90	1.26	40	1.70 40	0.97	30.1%	0.20 [-0.29, 0.69]
Zhang 2016	3.31	0.85	58	4.79 56	0.85	31.1%	-1.48 [-1.79, -1.17]
Bosch 2013	0.17	6.84	42	3.28 37	6.85	10.2%	-3.11 [-6.14, -0.08]
Total (95% CI)	**170**			**173**		**100.0%**	**-0.71 [-1.88, 0.46]**

Table 3a: Secondary outcome, meta-analysis of LVEF after chemotherapy.

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z_value	p_value	No. of studies
Fixed	0.361	0.146	0.575	3.301	0.001	4
Random	0.361	0.146	0.575	3.301	0.001	

Test for heterogeneity: Q= 1.060 on 3 degrees of freedom (p= 0.787)
Moment-based estimate of between studies variance = 0.000

I^2= 0% low heterogeneity

Figure 3: Secondary outcome, fixed and random effect forest plot of LVEF after chemotherapy.

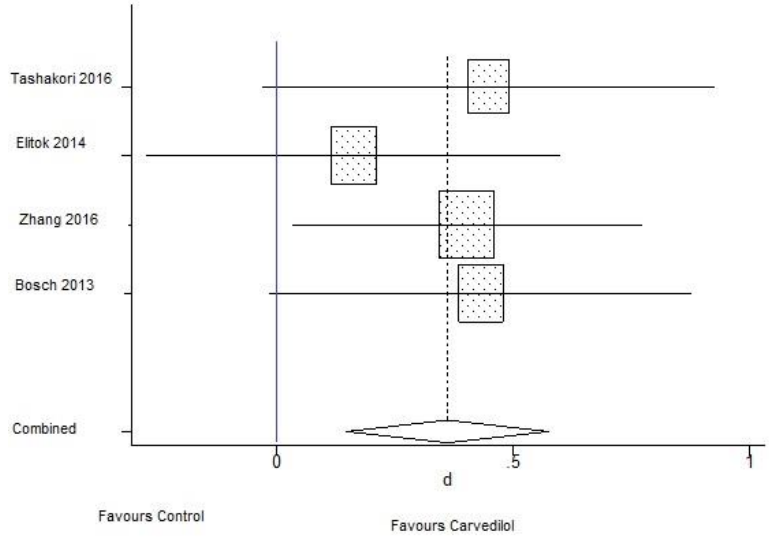


Table 3b : Secondary outcome with effect size shown as mean difference and not standard mean difference. All outcome values express LVEF. p= 0.0005, I^2= 0%

Study	Carvedilol			Control		Weight	Mean difference
	Mean %	SD %	Total	Mean %	SD % Total		Random , 95% CI %
Tashakori 2016	61.1	3.4	30	59.3	4.3 49	29.9%	1.80 [-0.00,3.60]
Elitok 2014	64.1	5.1	40	63.3	4.8 40	20.7%	0.80 [-1.37,2.97]
Zhang 2016	62.4	4.8	58	60.4	4.8 56	31.4%	2.00 [0.24, 3.76]
Bosch 2013	61.5	5.1	42	59.3	5.4 37	18.0%	2.20 [-0.13, 4.53]
Total (95% CI)			**170**		**173**	**100.0%**	**1.73 [0.74, 2.72]**

We calculated to strengthen the last outcome, a pooled LVEF pre chemotherapy and found no significant difference between active and control group with a mean difference of 1.04 that favors control group and CI 95% [-0.06, 2.14]; p=0.06 and I^2 20%.

Regarding subgroup analysis, carvedilol as active cardioprotective drug seems better when tested in combination with other cardioprotective treatments (table 4a); but we must highlight that carvedilol dosis was 6.25 mg vs 25-50 mg in the latter. When we took into consideration only those studies with strain and LVEF available, and we compared within groups effects strain shows a significant and major d (table 4b).

Table 4a: Subgroup analysis, difference of LVEF pre and after chemotherapy, carvedilol studies (Tashakori and Elitok) vs carvedilol plus other treatment (Bosch and Zhang). Random effect of mean difference.

Subgroups	***Mean difference***	***CI 95%***	***p***	**I^2**
Carvedilol alone	0.14	-0.26,0.55	0.48	0%
Carvedilol and other	-1.57	-2.31,-0.83	<0.0001	9%

***Table 4b*: Post hoc analysis: Intragroup analysis, difference of LVSF pre and after chemotherapy only strain groups (Tashakori and Elitok) ; strain vs LVEF. Random effect of standarized mean difference.**

Elitok and Tashakori	***D***	***CI 95%***	***p***	***I^2***
Strain	-2.01	-4.58 ,0.56	0.13	97%
LVEF	0.10	-0.22, 0.43	0.52	0%

We ran Begged and Eger´s test to evaluate publication bias and both of them showed a p value > 0.1 (Table 5).

Table 5: Publication bias tests.

```
Begg's Test

  adj. Kendall's Score (P-Q) =       2
         Std. Dev. of Score =    2.94
          Number of Studies =       4
                          z  =    0.68
                    Pr > |z| =   0.497
                          z  =    0.34 (continuity corrected)
                    Pr > |z| =   0.734 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-13.38619	13.22405	-1.01	0.418	-70.28469	43.5123
bias	56.36753	57.94063	0.97	0.433	-192.9309	305.6659

As sensitivity analysis we performed same primary outcome but including myocardial strain instead of LVEF when available, and what we found is a significative better result that favors carvedilol group d= -1.538 CI95% -2.627 , -0.449; p 0.006 (**table 6, figure7**); and when this is tested with our secondary outcome , the result remains significant and favors carvedilol group with a major LVSF in active group (**table7, figure8**).Regarding primary outcome sensitivity analysis, omitting one study each time what reveals is no significant differences with effects not significant for any result and, in most cases, with wider confident intervals (**figure 9**).

Table 6: Sensitivity analysis: meta- analysis of the difference pre-post chemotherapy LVSF (including strain in two studies-Tashakori and Elitok).

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z_value	p_value	No. of studies
Fixed	-1.303	-1.548	-1.058	-10.430	0.000	4
Random	-1.538	-2.627	-0.449	-2.768	0.006	

```
Test for heterogeneity: Q= 57.347 on 3 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance =  1.165
```

I^2=94.8%

Figure 7: Sensitivity analysis: Random effect forest plot of difference of LVSF (including strain in two studies- Tashakori and Elitok).

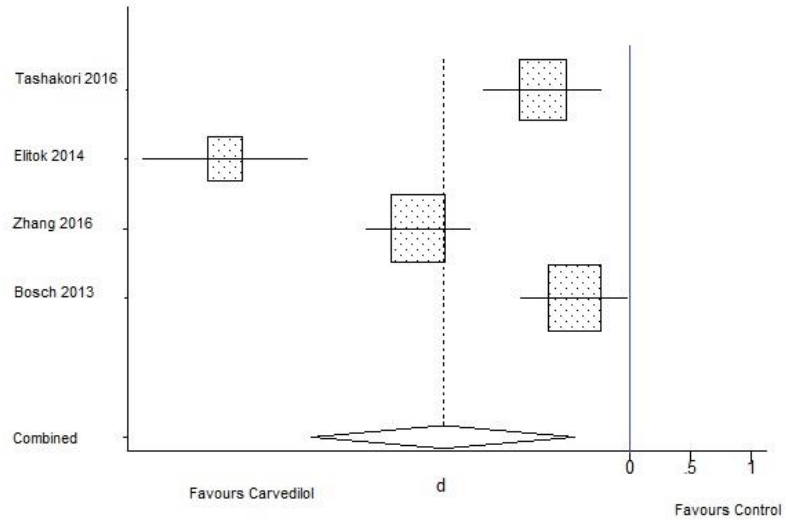


Table 7: Sensitivity analysis: meta- analysis of LVSF after chemotherapy (including strain in two studies- Tashakori and Elitok).

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z_value	p_value	No. of studies
Fixed	0.436	0.220	0.652	3.961	0.000	4
Random	0.436	0.137	0.734	2.860	0.004	

Test for heterogeneity: Q= 5.658 on 3 degrees of freedom (p= 0.130)
Moment-based estimate of between studies variance = 0.044

I^2=46.9%

Figure 8: Sensitivity analysis: random effect forest plot of LVSF after chemotherapy (including strain in two studies- Tashakori and Elitok).

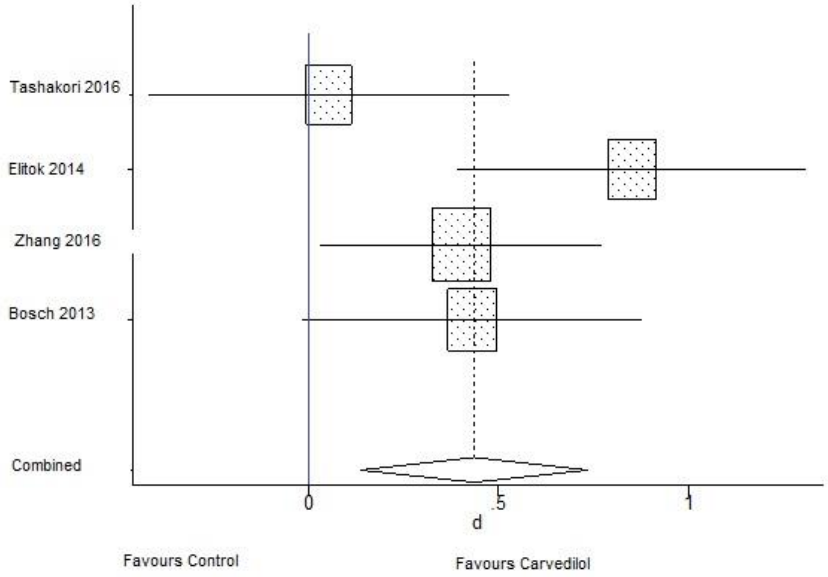
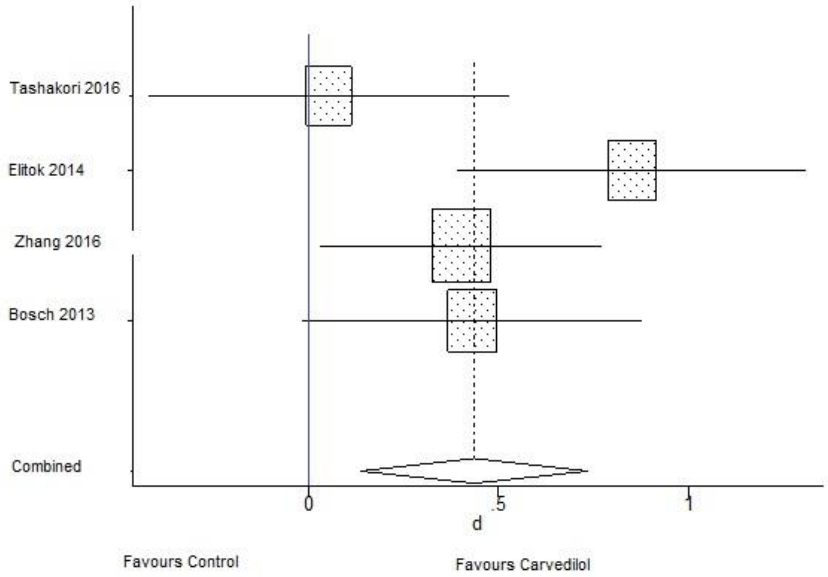


Figure 8: Sensitivity analysis: random effect forest plot of LVSF after chemotherapy (including strain in two studies- Tashakori and Elitok).



CHAPTER V: DISCUSSION

The present is the first published meta-analysis of RCT about the effect of carvedilol in preserving left ventricular ejection fraction in patients under anthracyclines. It is a small meta-analysis with 4 studies included and 343 patients. Results show a non-significant effect when testing the magnitude of LVEF reduction between carvedilol active group vs control group, but a significantly higher final LVEF after chemotherapy in the carvedilol group.

This study reflects the concern of physicians over the last years, of preventing rather than treating LVSF deterioration when onset of chemotherapy is installed in patients with previous LVSF deterioration [52].

Although there is little evidence regarding this topic, previous meta-analysis that tested β blockers and angiotensin antagonists in patients under chemotherapy had also shown an improved final LVEF in the active group [24], and a recent meta-analysis of RCT that included 5 studies and 317 patients and tested β blockers as a group in the/a same stage showed a significant decrease of ejection fraction in the control group and a significant all-cause mortality benefit in the β blockers group [25]. Due to the small sample size, low immediate mortality risk patients included (most of them breast cancer female) and short follow up, this study was not powered to test clinical outcomes.

Our meta-analysis and others regarding this topic showed high heterogeneity among studies effect. In our opinion, this is easy to understand as different malignant pathologies are included, different doses and types of chemotherapy (although anthracyclines were almost the only tested) and different types, plans and doses of cardio-protected agents were used. Regarding our results, although high heterogeneity was found when testing primary outcome, no heterogeneity resulted when testing secondary outcome. This seems very interesting as our meta-analysis included a majority of adults female with breast cancer treated with anthracyclines, treated with carvedilol alone or with an additional cardio-protected agent and besides that LVEF is the most validated way of testing LVSF with a known and low

inter and intra evaluator variability, even though differences on heterogeneity between both outcomes remains unexplained.

Subgroups analysis showed a significant major effect when carvedilol is combined with another cardio-protected effect. This is not surprising, as in heart failure stage effective treatments (β blockers, ACEI, angiotensin antagonist, and aldosterone antagonists) potentiate each other. But trimetazidine is not a proved treatment in heart failure stage. Trimetazidine has a metabolic and anti-oxidant effect that can be useful in patients under chemotherapy adding benefit with carvedilol, which has similar properties [9]. Although more used in ischemic heart disease to treat angor, trimetazidine has previously shown in small studies to improve LVSF in patients with ischemic heart disease [53,54, 55]. But, it is also relevant that the carvedilol dosis was not the same between those studies that tested carvedilol alone and also evaluate systolic function through strain and those studies that combined carvedilol and evaluate systolic function through LVEF. The first used low doses and the last standard doses; so major effect may be related also with carvedilol doses expressing optimal doses for cardio-protection.

Although significant, the magnitude of the effect regarding secondary outcome is modest with a difference in the final evaluation of LVEF of 1.73%; but clinical relevance of that effect is highlighted as LVEF is one of the most remarkable prognostic factors in heart failure [56] and also in most of cardiologic pathologies. In fact, it is interesting to remember that patients under chemotherapy are in a stage A of heart failure with a higher risk of developing heart failure symptoms than normal population and that the identification of asymptomatic left ventricular systolic dysfunction positions this patient in a B stage of heart failure [57].

Besides that, heart failure has worse vital prognosis than most known cancers; regarding our population, particularly in women, heart failure has more mortality than breast cancer [58], so great efforts should be done in women with breast cancer to avoid a second and worse pathology. This is a good enough justification in favor of the clinical use of carvedilol as cardio-protective agent, even more taking into consideration it has not serious and also easy to control secondary effects (bradycardia, hypotension, bronchospasm) besides a low cost. Manrique´s meta-

analysis[25] that tested β-blockers in general found a bigger although still modest effect size (5.17% of LVEF bigger in active group), subgroup analysis regarding each β-blocker effect would be interesting as it is remarkable that β-blockers´ effects seem not to be comparable, some β-blockers as atenolol have not shown a cardio-protected effect in this stage[59]. Tashakori et al.[16] related the cardio-protected effect of carvedilol against anthracyclines not with its β-blocker effect but with antioxidant effect and suppression of free-radical oxygen species production through the inhibition of exogenous nicotinamide adenine dinucleotide dehydrogenase (NADH-D); and maybe this effect is potentiated by trimatizidine regarding Zhang et al.[17] results.

A paragraph is needed about different ways to measure LVSF. As mentioned, LVEF is the most widely used echocardiographic parameter both in clinical practice and in large research studies, although it is highly dependent on cardiac loading conditions. Studies with new echocardiographic techniques as strain and strain rate have shown that global left-ventricular longitudinal strain is a good predictor of early systolic dysfunction [60,61] and Stoodley et al.[62] reported a 10% of reduction in longitudinal strain in half of the patients immediately after anthracyclines treatment, without left ventricular ejection fraction deterioration. Chemotherapy is in fact, the clinical stage where left-ventricular longitudinal strain is best validated and its measure to monitor LVSF has an ongoing recommendation. It seems logical that the inclusion of a more sensitive parameter as strain in meta-analysis synthesis, it improves the capacity to detect differences between groups expressing a major effect size as happened when we compare strain vs LVEF in available studies.

The main limitation of this meta-analysis is the low number of studies and patients included; some of the studies included are phase 2 studies; that explains the low number of subjects and also the outcomes selected- outcomes, although closely related with clinical outcomes, that are surrogate ones. Subgroup analysis must be taken with caution as no more than two studies were included in each subgroup. High heterogeneity was found, and it was partially unexplained. All studies included were about patients under anthracyclines treatment, no data about trastuzumab and other chemotherapeutic agents was available.

CONCLUSION

Although not significantly, carvedilol can help to prevent LVEF deterioration in patients under anthracyclines and this effect seems bigger and significant when associated with other cardio-protective treatments or/and with higher doses of carvedilol. Therapy with carvedilol seems to be associated with a better final LVEF in patients undergoing chemotherapy with anthracyclines.

RECOMMENDATIONS

Results are good enough to justify further research on this topic. Long-term and larger high quality RCT are required to determine the implication of the use of carvedilol on LVSF and other clinical outcomes as mortality and HF symptoms, to be able to change clinical practice.

SOURCES OF INFORMATION

1. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva: World Health Organization; 2008.
2. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity by chemotherapy: targeted agents and radiotherapy: ESMO Clinical Pactice guidelines. Annals of Oncology 2012; 23 Supplement 7:vii155-vii166
3. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353:1673-1684.
4. Lipshultz SE, Sallan SE. Cardiovascular abnormalities in long-term survivors of childhood malignancy.J Clin Oncol. 1993;11:1199–1203.
5. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–2007.
6. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study (CIBIS II): a randomized trial. Lancet. 1999;353:9–13.
7. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure. Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. Circulation 2002; 106:2194 – 9.
8. Wali R, Iyengar M, Beck G, et al. Efficacy and Safety of Carvedilol in Treatment of Heart Failure with Chronic Kidney Disease: A Meta-Analysis of Randomized Trials Circ Heart Fail. 2011;4:18-26, published online before print October 29 2010
9. Cardiotoxicity of therapeuthics agents and radiotherapy related heart disease. ESMO Clinical Practice Guidelines. Annals of Oncology 2012;23s:155-66
10. El Shitany NA, Tolba OA, El-Shanshory MR, et al. Protective effect of carvedilol on Adriamycin left-induced left ventricular dysfunction in children with acute lymphoblastic leukemia. J Card Fail 2012;18:607-13
11. Liu L, Liu ZZ, Liu YY, et al. Preventive effect of low dose carvedilol combined with candesartan on the cardiotoxicity of anthracyline drugs in the ajuvant chemotherapy of breast cancer. Zhongua Zhong Liu Za Zhi 2013;35:936-40

12. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy induced left ventricular systolic dysfunction in patients with malignant hemopathies. JACC 201;61:2355-62
13. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline induced-cardiomyopathy. JACC 2006;48:2258-62
14. Salehi R, Zamani B, Esfehani A, et al. Protective effect of carvedilol in cardiomyopathy caused by anthracyclines in patients suffering from breast cancer and lymphoma. Am Heart Hosp J. 2011;9(2):95-8
15. Elitok A, Cizgisi A, Kilic L, et al. Effect of carvedilol on silent anthraciclyne-induced cardiotoxicity assessed by strain imaging: a prospective randomized controlled study with six month follow-up. Cardiology Journal 2014;21(5):509-15
16. Tashakori Beheshti A, Mostafavi Toroghi H, Hosseini G, et al. Carvedilol Administration Can Prevent Doxorubicin-Induced Cardiotoxicity: A Double-Blind Randomized Trial. *Cardiology*. 2016;134(1):47-53.
17. Zhang SW, Zhang XX, Shi ZC, et al. Heart protective effect of carvedilol combined with trimetazidine on breast cancer patients receiving anthracycline. Chinese General Practice 2016, (19)7:794-798
18. Seicean S, Seicean A, Alan N, et al. Cardioprotective Effect of Beta-Adrenoceptor Blockade in Breast Cancer Patients Undergoing Chemotherapy: A Follow-Up Study of Heart Failure. *Circ Heart Fail*. 2013;(icl).
19. Suter TM, Ewer MS. Cancer drugs and the heart: Importance and management. Eur Heart J. 2013;34(15):1102-1111. doi:10.1093/eurheartj/ehs181.
20. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):e240-e327.
21. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol 2004;22:820–8.
22. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006;114:2474–81.

23. Georgakopoulos P, Roussou P, Matsakas E, et al. Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. Am J Hematol 2010;85:894–6.
24. Yun S, Vincelette N, Abraham I. Cardioprotective role of β-blockers and angiotensin antagonists in early-onset anthracyclines-induced cardiotoxicity in adult patients: a systematic review and meta-analysis. Postgrad Med J 2015;0:1–7. doi:10.1136/postgradmedj-2015-133535
25. Manrique CR, Spinetto PV, Tiwari N, et al. Protective Effect of Beta-Blockers on Chemotherapy Induced Cardiomyopathy: a Meta-Analysis of Prospective Studies.(abstract) *J Am Coll Cardiol*. 2016; 67(13):1529.
26. Packer M, Bristow M, Cohn J, et al. for the US Carvedilol Group. The effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. N Engl J Med 1996; 334:1349-55
27. Australia/New Zealand Heart Failure Research Collaborative Group. Randomized placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischemic heart disease. Lancet 1997;349:375-80
28. Heidenreich P, Lee T, Massie B. Effect of beta blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. JACC 1997; 30:27-34
29. Cardinale D, Sandri MT, Martinoni A, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol 2002;13:710–715.
30. Ewer MS, Ali MK, Mackay B, et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol 1984;2:112–117.
31. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer 2010;10:337.
32. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869–2879.

33. Slamon D, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–792.
34. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol 2010;7:564–575.
35. Kaya MG, Ozkan M, Gunebakmaz O, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol 2013;167:2306–10.
36. Fajardo G, Zhao M, Berry G, et al. Beta2-adrenergic receptors mediate cardioprotection through crosstalk with mitochondrial cell death pathways. J Mol Cell Cardiol. 2011;51:781–789.
37. Barron TI, Connolly RM, Sharp L, et al. Beta blockers and breast cancer mortality: a population-based study. J Clin Oncol. 2011;29:2635–2644.
38. Nohria A. -Adrenergic Blockade for Anthracycline- and Trastuzumab-Induced Cardiotoxicity: Is Prevention Better Than Cure? *Circ Hear Fail*. 2013;6(3):358-361.
39. Oliveira PJ, Bjork JA, Santos MS, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. Toxicol Appl Pharmacol. 2004;200:159–168.
40. Jonsson O, Behnam-Motlagh P, Persson M, et al. Increase in doxorubicin cytotoxicity by carvedilol inhibition of P-glycoprotein activity. Biochem Pharmacol. 1999;58:1801–1806.
41. J.J.V. McMurray, S. Adamopoulos, S.D. Anker, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESCEur Heart J, 33 (2012), pp. 1787–1847
42. Lang RM, Badano LP, Mor-avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults : An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14.

43. Kraigher-Krainer E, Shah A, Gupta D, et al. Impaired Systolic Function by Strain Imaging in Heart Failure with Preserved Ejection Fraction. J Am Coll Cardiol. 2014;63(5):447-456.
44. Borenstein M, Hedges L, Higgins J and Rothstein H. Preface in: Introduction to Meta-Analysis. 2009;xxi-xxviii. John Wiley and Sons.Ltd. ISBN 978-0-470-05724-7.
45. Jadad, A. R., Moore, R. A., Carroll, D., et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials. 1996; 17 (1): 1–12.
46. Higgins J, Thompson S, Deeks J, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;(327):557-60.
47. Anand IS, Florea VG, Fisher L. Surrogate end points in heart failure. *J Am Coll Cardiol*. 2002;39(9):1414-1421.
48. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777.
49. Borenstein M, Hedges L, Higgins J and Rothstein H. Effect sizes based on means. Chapter 4 in: Introduction to Meta-Analysis. 2009:21-32 Editorial Wiley
50. Online Statistics Education: A Multimedia Course of Study (http://onlinestatbook.com/). Project Leader:David M. Lane, Rice University.
51. Moher D, Liberati A, Tezlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Plosmedicine 2009; 9(7):e1000097
52. Huang C, Zhang X, Ramil JM, et al. Juvenile exposure to anthracyclines impairs cardiac progenitor cell function and vascularization resulting in greater susceptibility to stress-induced myocardial injury in adult mice. Circulation 2010;121:675–83.
53. Sellier P, Broustet JP. Assessment of anti-ischemic and antianginal effect at trough plasma concentration and safety of trimetazidine MR 35 mg in patients with stable angina pectoris: a multicenter, double-blind, placebo-controlled study. Am J Cardiovasc Drugs. 2003;3:361–369.
54. Kowalski J, Banach M, Barylski M, et al. Carvedilol modifies antioxidant status of patients with stable angina. Cell Mol Biol Lett.2008;13:230–239.

55. Brottier L, Barat JL, Combe C, et al. Therapeutic value of a cardioprotective agent in patients with severe ischaemic cardiomyopathy. Eur Heart J. 1990;11:207–212.
56. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model Prediction of Survival in Heart Failure. 2006.
57. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and Prognostic Significance of Heart Application of the American College of Cardiology / American Heart Association Heart Failure Staging Criteria in the Community. 2007.
58. Stewart S, Macintyre K, Hole DJ, et al. More " malignant " than cancer ? Five-year survival following a first admission for heart failure. 2001:315-322.
59. Machado V, Cabral A, Monteiro P, et al. Providencia LA: Carvedilol as a protector against the cardiotoxicity induced by anthracyclines (doxorubicin). Rev Port Cardiol 2008; 27: 1277–1296.Brown J, Jenkins C, Marwick TH. Use of myocardial strain to assess global left ventricular function: a comparison with cardiac magnetic resonance and 3-dimensional echocardiography. Am Heart J. 2009;157:102-5.
60. Feigenbaum H, Mastouri R, Sawada S. A practical approach to using strain echocardiography to evaluate the left ventricle. Circ J. 2012;76:1550-5.
61. Stoodley PW, Richards DA, Hui R et al. Two-dimensional myocardial strain imaging detects changes in left ventricular systolic function immediately after anthracycline chemotherapy. Eur J Echocardiogr, 2011; 12: 945–952.

ANNEX

Data Collection Sheets

Studies	Pablo	Lucía	Final	Full-text	Elegibility Lucía	Design				
Tashakori cardiology 2016	1	1	1	0	1	RCT			1	1
Yun Postgrad Med J. 2015	1	1	1	1	0	MA			1	1
Tan Compr Physiol. 2015	1	1	1	0		Review			1	1
Elitok Cardiol J. 2014	1	1	1	1	1	RCT			1	1
Nolan Intern Med J. 2014	0	1	1	1	0	Review			1	1
Magnano Curr Treat Options Cardiovasc Med. 2014	0	1	1	1	0	Review			1	1
Schlitt Dtsch Arztebl Int. 2014	0	1	1	1	0	Review			1	1
Lipshultz Curr Opin Cardiol. 2014	0	1	1	1	0	Review			0	0
Negishi Eur Heart J Cardiovasc Imaging. 2014	0	1	1	1	0	OS	Indice Kappa	0,6 IC (0.46-0.75)	0	0
Gulati Tidsskr Nor Laegeforen. 2013	0	1	1	1	0	Review	screening	bueno	0	0
Golwala J Am Coll Cardiol. 2013	0	1	1	1	0	Letter			0	0
Spallarossa J Am Coll Cardiol. 2013	0	1	1	1	0	Letter			0	0
Bosch J Am Coll Cardiol. 2013	1	1	1	1	1	RCT	indice kappa		0	0
Kalam Eur J Cancer. 2013	0	1	1	1	0	MA	Elegibility		0	0
Cardinale Semin Oncol. 2013	0	1	1	1	0	Review			0	0

Seicean Circ Heart Fail. 2013	0	1	1	1	0	OS	0	0
Farolfi Heart. 2013	0	1	1	1	0	OS	0	0
Colombo Future Cardiol. 2013	0	1	1	0		Review	0	0
Liu Zhonghua Zhong Liu Za Zhi. 2013	1	1	1	0	1	RCT	0	0
El-Shitany J Card Fail. 2012	1	1	1	1	1	RCT	0	0
Heck Cardiology. 2012	0	1	1	1	0	Project	0	0
Tarantini . Ann Oncol. 2012	1	1	1	1	0	OS	0	0
Oliva Oncologist. 2012	1	1	1	1	0	OS	0	0
Shaikh Curr Heart Fail Rep. 2012	1	1	1	1	0	Review	0	0
Hantson Clin Toxicol (Phila). 2012	1	0	1	1	0	Review	0	0
Salehi Am Heart Hosp J. 2011	1	1	1	1	1	RCT	0	0
Zeglinski Exp Clin Cardiol. 2011	1	1	1	1	0	Review	0	0
Bosch J Card Fail. 2011	1	1	1	1	0	Project	0	0
Pituskin Cancer. 2011	1	0	1	1	0	Project	0	0
Bernstein Prog Pediatr Cardiol. 2011	1	0	1	1	0	Review	0	0
Pereira Curr Pharm Des. 2011	1	1	1	1	0	Review	0	0
van Dalen Cochrane Database Syst Rev. 2011	1	1	1	1	0	SR	0	0
Kurihara J Artif Organs. 2011	1	0	1	1	0	CR	0	0
Hong Clin Cardiol. 2010	1	1	1	1	0	Review	0	0

Pancholia Indian Heart J. 2010	1	0	1	1	0	Letter	0	0
Chopra Indian Heart J. 2010	1	0	1	0		Letter	0	0
Yoon J Am Coll Cardiol. 2010	1	1	1	1	0	OS	0	0
Georgakopoulos Am J Hematol. 2010	1	1	1	1	0	MA	0	0
Cardinale J Clin Oncol. 2010	1	1	1	1	0	RCT Include Low EF	0	0
Dabrowski Kardiol Pol. 2010	0	1	0	999	999		0	0
Roul Presse Med. 2009	0	1	1	1	0	Review	0	0
Shakir J Clin Med Res. 2009	0	1	1	1	0	Review	0	0
Cardinale Curr Treat Options Cardiovasc Med. 2008	0	1	1	1	0	Review	0	0
Kalay J Am Coll Cardiol. 2006	1	1	1	1	1	RCT	0	0
Tallaj J Heart Lung Transplant. 2005	1	0	1	1	0	OS	0	0
Carreira Cardiovasc Hematol Disord Drug Targets. 2006	0	1	0	999	999		0	0
Bader J Heart Lung Transplant. 2005	1	0	0	999	999		0	0
Tabet Int J Cardiol. 2006	1	0	1	1	0	CR	0	0
Iarussi Paediatr Drugs. 2005	1	0	1	1	0	Review	0	0
Mukai Intern Med. 2004	1	1	1	1	0	cases serie	0	0
Simpson Clin J Oncol Nurs. 2004	1	0	1	1	0	Review	0	0

Keefe Semin Oncol. 2001	1	1	1	0		Narrative review	0	0
Noori J Card Fail. 2000	1	0	0	999	999		0	0
Fazio Clin Cardiol. 1998	0	1	1	1	0	Case Report	0	0
Feuerstein Am J Cardiol. 1997	0	1	0	999	999		0	0
Okamoto Japanese 1995	1	1	1	0		Case Report	0	0
	35	44	51		7			

Population	Active Trea	Follow-up	N	n Carvedilo	n Control	LVSF after ch	LVSF after ch	Difference c	Difference o	Jadad		
Adult/Children							Control Group		Control grou	Score		
Chemotherapy type												
Adults; AN	Carvedilol	3 months	70	30	40	61.06±3.39**	59.30±4.29	0.25±0.85	0.11±0.95	5		
						18.67 ±5.01*	18.40 ±4.91	0.39±4.5	2.77±2.09			
Adults; AN	Carvedilol	6 months	80	40	40	64.10± 5.10*	63.30±4.80	1.9±1.26	1.7±0.97	3		
						20.1± 5.3	16.0±4.3	0.10±0.98	3.3±0.94			
Adults; che	Carvedilol	6 months	79	42	37	61.50 ± 5.11*	59.24±15.38	0.17±1.1	3.11±1.2	3		
Children; A	Carvedilol	36 days	50	25	25	39.46 ± 6.28*	33.50± 6.24	´-5.47±1.56	6.5±1.55	1		
						19.3 6± 1.96*	15.1 6± 1.769	´-1.86±0.70	3.55±0.68			
Adults; AN	Carvedilol	6 months	40	20	20	57.50 ± 2.57*	45.95±3.68	16.85±1.00	26.30±1.08	2		
Adults; CH	Carvedilol	4 months	66	44	22	54.98 ± 2.16*	53.94± 3.80	5.77±0.40	4.62±1.13	1		
Adults; AN	Carvedilol	6 months	50	25	25	68.9 ± 8.00**	52.3± 7.3	1.7±2.26	17.4±2.06	2		
Adults; AN	Carvedilol	4 months	114	58	56	62.38±4.81*	60.44±4.84	3.31±0.85	4.79±0.85	3	Hand searching	
						* FA						
						**EF						
						***Sseptal						
						****SLG						