

Cardioprotective Effects of Low-Dose Bisoprolol Against Anthracycline-Induced Subclinical Cardiotoxicity in Breast Cancer: A Triple-Blind Randomized Controlled Trial Using Advanced Echocardiographic Parameters

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What's Known

- Anthracycline chemotherapy, despite improving breast cancer survival, is associated with dose-dependent cardiotoxicity that may lead to heart failure.
- Beta-blockers, especially carvedilol, indicated cardioprotective effects. However, evidence regarding bisoprolol remains scarce, and most studies have relied solely on ejection fraction.

What's New

- This triple-blind randomized controlled trial demonstrated that low-dose bisoprolol preserved left and right ventricular function during anthracycline-based chemotherapy.
- Using advanced echocardiographic parameters, the study revealed early cardioprotective effects of bisoprolol beyond conventional ejection fraction, addressing a significant gap in cardio-oncology research.

Abstract

Background: Anthracyclines are cornerstone agents in breast cancer chemotherapy. However, they can cause dose-dependent cardiotoxicity, potentially impairing long-term cardiac function. Beta-blockers have demonstrated cardioprotective effects. However, evidence regarding bisoprolol, particularly using comprehensive echocardiographic evaluations, remains limited. This study aimed to evaluate the cardioprotective effects of low-dose bisoprolol against anthracycline-induced subclinical cardiac dysfunction in patients with breast cancer.

Methods: This triple-blind, randomized controlled trial was conducted in Isfahan, Iran, between January and December 2023. Eligible women with locally advanced breast cancer receiving anthracycline-based chemotherapy were randomized to bisoprolol (2.5 mg/day) or a placebo. Cardiac function was assessed at baseline, mid-treatment, and the end of treatment during a 6-month follow-up period. The evaluated echocardiographic parameters included left ventricular ejection fraction (LVEF), left ventricular end-diastolic and end-systolic dimensions (LVEDD, LVESD), left ventricular end-diastolic volume (LVEDV), global longitudinal strain (GLS), and tricuspid annular systolic excursion (TAPSE). Statistical analyses were performed using SPSS software (version 25.0). Continuous variables were analyzed using paired or independent-samples *t* tests, and categorical variables were analyzed using the Chi square test. Statistical significance was defined as $P < 0.05$.

Results: A total of 50 patients completed the trial (25 in the bisoprolol group and 25 in the placebo group). LVEF remained stable in both groups. Compared with the placebo group, bisoprolol demonstrated significantly more favorable structural and functional changes, including a reduction in LVEDD (mean change = -0.172 cm; 95% CI = -0.343 to -0.001 ; $P = 0.049$), LVESD (mean change = -0.156 cm; 95% CI = -0.295 to -0.017 ; $P = 0.029$), and LVEDV (mean change = -7.920 mL; 95% CI = -15.174 to -0.666 ; $P = 0.033$); improved GLS (mean change = 0.974 ; 95% CI = 0.083 to 1.865 ; $P = 0.033$); and better preserved TAPSE (mean change = 0.168 cm; 95% CI = 0.101 to 0.234 ; $P < 0.001$).

Conclusion: Prophylactic bisoprolol might attenuate early subclinical cardiotoxicity in patients with breast cancer receiving anthracyclines, primarily through the stabilization of LVEDV and a more favorable GLS trajectory.

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Keywords • Bisoprolol • Anthracycline • Cardiotoxicity • Breast neoplasms • Echocardiography

Introduction

Breast cancer is the most frequently diagnosed cancer worldwide. According to GLOBOCAN 2020 data, it accounted for approximately 2.3 million new cases (11.7% of new cancer cases). Furthermore, an estimated 685,000 women died from breast cancer in 2020, representing 16% of all cancer-related deaths in women.^{1, 2} Recently, cancer mortality has decreased significantly due to earlier diagnosis and the development of novel therapeutic modalities.³ Although many new-generation regimens have been developed, anthracyclines remain central components of breast cancer chemotherapy, reducing breast cancer-related mortality by up to 38%.³

However, despite improved cancer-free survival, complications of these therapies, particularly due to cardiac dysfunction, pose notable clinical challenges regarding long-term morbidity and mortality.^{3, 4} Anthracycline-induced cardiotoxicity (AIC) is a chronic, dose-dependent adverse effect that reduces left ventricular ejection fraction (LVEF) and may lead to cardiomyopathy, and in severe cases, heart failure (HF).^{5, 6} This cardiotoxicity is of significant clinical concern, as cardiovascular disease has become the leading cause of non-cancer-related mortality among breast cancer survivors.^{7, 8} This reality poses a significant therapeutic dilemma for oncologists, who must balance the oncologic efficacy of anthracyclines against their potential to cause lasting cardiac injury. In some cases, cardiotoxicity necessitates modification or discontinuation of potentially life-saving chemotherapy regimens.⁹

To address this issue, cardioprotective interventions are gaining increasing attention. Conventional strategies include limiting anthracycline dose, identifying high-risk patients, and early monitoring of cardiac function.¹⁰ In addition, pharmacologic prophylaxis has been explored as a means of mitigating cardiotoxic risk.¹¹ Among these agents, beta-blockers, which have long been used in HF management, have demonstrated efficacy in preventing ventricular remodeling, reducing oxidative stress, and attenuating sympathetic overactivity, thus potentially offering cardioprotection during chemotherapy.^{12, 13}

A variety of beta-blockers, such as metoprolol, atenolol, carvedilol, bisoprolol, and nebivolol, have been studied in this context.^{12, 14} Among these, carvedilol has received substantial attention, partly due to its antioxidant and anti-remodeling properties.¹⁵ Nevertheless, bisoprolol, a highly beta-1 selective agent with favorable tolerability, has also emerged as a

potential prophylactic option in cardio-oncology. In a randomized trial, prophylactic bisoprolol was associated with attenuation of anthracycline-related declines in LVEF and global longitudinal strain (GLS) compared with placebo.^{16, 17}

Despite these promising observations, there is a paucity of high-quality randomized trials specifically evaluating the cardioprotective role of bisoprolol in patients with breast cancer undergoing anthracycline therapy, particularly those utilizing comprehensive echocardiographic assessments. Previous studies have often relied on LVEF as the primary outcome, which might overlook early subclinical changes.^{16, 17} Therefore, in this study, we aimed to assess the cardioprotective effect of bisoprolol using a broad array of echocardiographic parameters, including left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic volume (LVEDV), GLS, tricuspid annular systolic excursion (TAPSE), and LVEF, to provide a more detailed evaluation of myocardial structural and functional integrity. We hypothesized that bisoprolol, when administered prophylactically during chemotherapy, could mitigate anthracycline-induced cardiotoxicity and preserve both left and right ventricular function in patients with breast cancer.

Materials and Methods

Study Design and Setting

This was a triple blind, randomized controlled trial conducted in Isfahan, Iran, between January and December 2023. Patients were consecutively recruited from the Oncology and Hematology Outpatient Clinics at Shariati Hospital, Isfahan, Iran. All patients were provided with oral and written information and provided their written informed consent prior to enrollment. The study protocol was approved by the Ethics Committee of Islamic Azad University, Najafabad Branch (code: IR.IAU.NAJAFABAD.REC.1400.058) and registered at the Iranian Registry of Clinical Trials (IRCT ID: IRCT20130701013828N8; Trial ID: 57932).

Population Selection

Inclusion criteria were adult female patients aged 18 to 70 years with newly diagnosed, histopathologically confirmed locally advanced breast cancer (Stage II or III), scheduled for anthracycline-based chemotherapy, and with a baseline LVEF $\geq 55\%$. To minimize selection bias, consecutive sampling was used. Each day, the research team screened all newly presenting patients using clinic records and admission lists.

A structured screening form was completed to document demographic data, tumor characteristics, and planned chemotherapy regimen. Subsequently, a multidisciplinary team of oncologists and cardiologists reviewed each candidate to confirm eligibility based on predefined criteria.

Exclusion criteria included a history of cardiovascular disease (ischemic heart disease, HF, or arrhythmias), diabetes mellitus, chronic hypertension, or chronic kidney disease; previous exposure to chest radiotherapy or any form of chemotherapy; ongoing or planned use of beta-blockers for other medical indications; and any contraindication to bisoprolol administration, including acute decompensated HF, symptomatic bradycardia, or severe asthma. After confirmation of eligibility, detailed study information was provided, written informed consent was obtained, and baseline assessments, including physical examination and echocardiography, were performed. Randomization was carried out by blinded operators. Participant flow throughout the study is presented in the CONSORT diagram (figure 1).

Randomization

Participants were randomized 1:1 to bisoprolol or placebo using a computer-generated block randomization sequence with a fixed block size ($n=4$) to maintain balanced group allocation. The randomization list was generated by an independent statistician using a random-number generator (SPSS software, version 25.0; IBM Corp., Armonk, NY, USA) and was not accessible to the investigators. The statistician encoded the allocation list and provided the treatment codes directly to the study pharmacist, who was responsible for preparing identical medication packages. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes (SNOSE), which were opened only after eligibility confirmation.

Blinding Method

Patients were treated with medication that was prepared and packaged by an independent pharmacist, who was not involved in patient recruitment, treatment administration, or data analysis. Each package was identical in appearance, size, color, and labeling, regardless

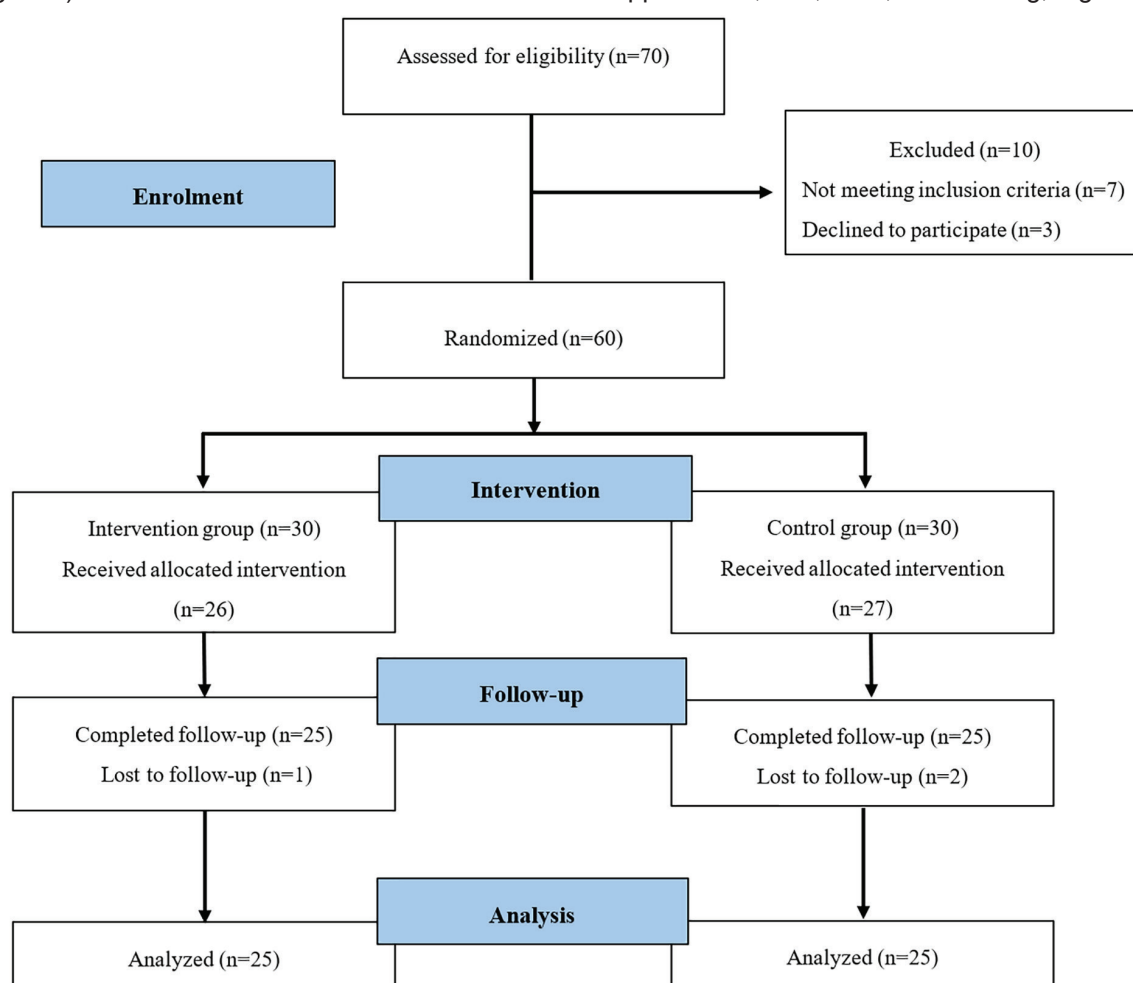


Figure 1: The CONSORT flow diagram shows the patient enrollment, randomization, intervention, follow-up, and analysis.

of whether it contained bisoprolol or placebo, to maintain effective blinding.

The study was conducted in a triple-blind manner: patients, clinical investigators responsible for patient management, and data analysts were all blinded to treatment allocation throughout the study period. Vital signs were monitored at each visit, and adverse events were managed per protocol without unblinding.

Study Treatment

All patients received in-hospital and outpatient chemotherapy according to our institution's protocols. The regimens were as follows: cyclophosphamide (500-600 mg/m²)+epirubicin (75-CEF 100 mg/m²)+5-FU (500–600 mg/m²) (CEF regimen), or adriamycin (60 mg/m²)+cyclophosphamide (600 mg/m²) (AC regimen). All chemotherapy agents were administered as locally available commercial preparations and were identical between the two study groups. The intervention group received 2.5 mg of bisoprolol daily (manufactured by Abidi Pharmaceutical Co., Tehran, Iran, under the trade name of Betalco; n=25) and the control group received 2.5 mg of placebo daily (manufactured from pharmaceutical-grade microcrystalline cellulose provided by Abidi Pharmaceutical Co., Tehran, Iran; n=25). Placebo tablets were matched to the active drug for appearance, shape, weight, thickness, and color, and were packaged by an independent pharmacist to maintain blinding. The study drug was initiated orally at a dose of 2.5 mg for 7 consecutive days prior to chemotherapy. In the control group, placebo was also started 7 days before chemotherapy. Both bisoprolol and placebo were continued for 6 months.

Vital signs, including blood pressure and heart rate, were monitored before each chemotherapy cycle and monthly thereafter. If symptomatic bradycardia (heart rate<50 bpm) or hypotension (systolic BP<90 mmHg) occurred, the study drug was temporarily discontinued and permanently withdrawn upon recurrence.

Safety Monitoring

Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0).¹⁸ In case of serious adverse events (Grade≥3), the safety committee was consulted, and emergency unblinding was permitted if necessary for patient safety.

Echocardiographic Assessments

Patients underwent transthoracic echocardiography at baseline, mid-treatment (at 3 months after chemotherapy initiation,

approximately halfway through the anthracycline course), and end-of-treatment (at 6 months). If a reduction in LVEF ≥10% from baseline to a value <50% occurred, or if clinical signs of HF were observed, the study drug was stopped and guideline-directed medical therapy (GDMT), including initiation of angiotensin-converting enzyme inhibitors and beta-blockers (e.g., carvedilol), was started under cardio-oncology supervision. During follow-up, no participant met these criteria. Consequently, no patient required discontinuation of the study drug and initiation of GDMT.

Outcomes

The primary outcome of the study was the change in LVEF from baseline to following six cycles of chemotherapy. LVEF was measured using Simpson's biplane method according to the guidelines of the American Society of Echocardiography. Secondary outcomes included the incidence of a ≥10% absolute reduction in LVEF to below 50%, the development of clinically overt HF classified by the New York Heart Association (NYHA) functional classification, changes in LVEDD and LVESD, changes in LVEDV, changes in myocardial deformation assessed by GLS, and changes in right ventricular systolic function evaluated by TAPSE. Echocardiographic studies were performed using the EPIC 7 ultrasound machine (Philips Medical Systems, Andover, MA, USA). All images were digitally stored and later analyzed offline directly on the echocardiography machine. All echocardiographic measurements were independently analyzed by an experienced echocardiography fellow.

Sample Size

The sample size was estimated to detect a clinically relevant 5-percentage-point difference in LVEF between the intervention and control groups. Based on previous cardio-oncology trials, a standard deviation (SD) of 5%, a two-sided α of 0.05, and 90% statistical power were assumed.¹⁶ Using the two-sample comparison of means formula, the minimum required sample size was calculated as 21 participants per group. Since patients receiving anthracycline chemotherapy commonly experience treatment discontinuation due to toxicity, clinical progression, withdrawal of consent, or loss to follow-up, an anticipated attrition rate of approximately 30% was incorporated. After adjustment for expected attrition, the target enrollment increased to 30 patients per group (total=60), ensuring that the final analyzable sample would meet the minimum powered requirement. To reach

the target randomized sample of 60 patients, approximately 70 individuals were screened, accounting for the typical 10-20% exclusion rate observed during eligibility assessment in cardio-oncology trials.¹⁹ Reasons for pre-randomization exclusion include baseline cardiac abnormalities, previous chemotherapy exposure, or declining participation. Due to feasibility constraints and recruitment limitations during the study period, 25 participants per group (total=50) were ultimately enrolled and completed post-chemotherapy evaluation. This final sample size remained sufficient to preserve the statistical power requirement after accounting for observed attrition.

Statistical Analysis

All statistical analyses were performed using the SPSS software (version 25.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as numbers and percentages for categorical data, and mean $\pm$ SD and range for numerical data. Within-group analyses were assessed using paired *t* tests. Normality assumptions for paired differences were evaluated using the Shapiro–Wilk test. When data met normality criteria, mean differences and 95% confidence intervals were reported. Multiple imputation was prespecified in the statistical analysis plan to address potential missing data. However, in the present study, no missing data were observed in either primary or secondary outcome variables. Therefore, multiple imputation was not required, and all analyses were performed using complete cases only. No adjustments for multiple comparisons were applied, given the exploratory nature of secondary outcomes. Analyses were primarily conducted based on the intention-to-treat principle, including all randomized patients

according to their assigned groups. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 50 female patients were enrolled and randomized equally to two groups ($n=25$ per group). The overall mean age was 47.7 ± 9.7 years, ranging from 31 to 69 years. The mean age in the bisoprolol group was 48.2 ± 9.4 years, while in the control group it was 47.3 ± 10.1 years, with no statistically significant difference between the groups.

Comparison of Left Ventricular End-Diastolic Dimensions Between and Within Groups

At baseline and mid-treatment, LVEDD values were comparable between the groups, with no significant differences. However, at the final measurement (LVEDD3), the bisoprolol group exhibited a significantly lower mean value than the control group ($P=0.049$). Within-group comparisons demonstrated significant differences between LVEDD1 and LVEDD2 ($P=0.028$) and between LVEDD2 and LVEDD3 ($P=0.001$), whereas no significant difference was observed between LVEDD1 and LVEDD3. In the control group, all pairwise comparisons revealed statistically significant increases over time (table 1).

Comparison of Left Ventricular End-Systolic Dimensions Between and Within Groups

As shown in table 2, no significant differences were found between the groups at baseline left ventricular end-systolic dimensions (LVESD1) or mid-treatment (LVESD2). However, at the final evaluation (LVESD3), the bisoprolol group showed significantly lower values than the control group ($P=0.029$).

Table 1: Comparison of LVEDD between and within groups at three time points

Group	Comparison	LVEDD (mean $\pm$ SD)	P value
Between-group	Baseline (LVEDD1)	Bisoprolol: 4.552 ± 0.301 cm Control: 4.524 ± 0.216 cm	0.708
	Mid-treatment (LVEDD2)	Bisoprolol: 4.700 ± 0.285 cm Control: 4.600 ± 0.206 cm	0.162
	Final (LVEDD3)	Bisoprolol: 4.520 ± 0.389 cm Control: 4.692 ± 0.157 cm	0.049 *
Bisoprolol	LVEDD1 vs. LVEDD2	4.552 ± 0.301 vs. 4.700 ± 0.285	0.028 *
	LVEDD2 vs. LVEDD3	4.700 ± 0.285 vs. 4.520 ± 0.389	0.001 *
	LVEDD1 vs. LVEDD3	4.552 ± 0.301 vs. 4.520 ± 0.389	0.649
Control	LVEDD1 vs. LVEDD2	4.524 ± 0.216 vs. 4.600 ± 0.206	0.004 *
	LVEDD2 vs. LVEDD3	4.600 ± 0.206 vs. 4.692 ± 0.157	0.005 *
	LVEDD1 vs. LVEDD3	4.524 ± 0.216 vs. 4.692 ± 0.157	<0.001 *

Between-group comparisons were analyzed using independent-sample *t* tests, and within-group comparisons were assessed using paired-sample *t* tests. Data are presented as mean $\pm$ SD. Echocardiographic measures are presented as absolute values.

* $P<0.05$ was considered statistically significant. LVEDD: Left ventricular end-diastolic diameter

Table 2: Comparison of LVESD between and within groups at three time points

Group	Comparison	LVESD (mean±SD)	P value
Between-group	Baseline (LVESD1)	Bisoprolol: 3.500±0.304 cm	0.508
		Control: 3.448±0.243 cm	
	Mid-treatment (LVESD2)	Bisoprolol: 3.512±0.248 cm	0.898
		Control: 3.520±0.184 cm	
	Final (LVESD3)	Bisoprolol: 3.480±0.317 cm	0.029*
		Control: 3.636±0.122 cm	
Bisoprolol	LVESD1 vs. LVESD2	3.500±0.304 vs. 3.512±0.248	0.740
	LVESD2 vs. LVESD3	3.512±0.248 vs. 3.480±0.317	0.256
	LVESD1 vs. LVESD3	3.500±0.304 vs. 3.480±0.317	0.619
Control	LVESD1 vs. LVESD2	3.448±0.243 vs. 3.520±0.184	0.039*
	LVESD2 vs. LVESD3	3.520±0.184 vs. 3.636±0.122	0.002*
	LVESD1 vs. LVESD3	3.448±0.243 vs. 3.636±0.122	0.001*

Between-group comparisons were analyzed using independent-sample *t* tests, and within-group comparisons were assessed using paired-sample *t* tests. Data are presented as mean±SD. Echocardiographic measures are presented as absolute values.

*P<0.05 was considered statistically significant. LVESD: Left ventricular end-systolic diameter

Within-group comparisons indicated no significant differences across time in the bisoprolol group. In contrast, the control group showed statistically significant progressive increases in LVESD values across all pairwise comparisons.

Comparison of Left Ventricular End-Diastolic Volume Between and Within Groups

As presented in table 3, there were no statistically significant differences between the two groups at LVEDV1 or LVEDV2. However, at the final measurement (LVEDV3), the bisoprolol group had significantly lower values than the control group (P=0.033). Within-group analysis showed that in the bisoprolol group, LVEDV decreased significantly from LVEDV2 to LVEDV3 (P=0.002), with no significant changes observed from LVEDV1 to LVEDV2 or from LVEDV1 to LVEDV3. In the control group, LVEDV increased significantly from LVEDV2 to LVEDV3 (P<0.001) and from LVEDV1 to LVEDV3 (P<0.001), with a non-significant trend from LVEDV1 to LVEDV2.

Comparison of Left Ventricular Ejection Fraction Between and Within Groups

Table 4 demonstrates that no statistically significant differences were found in LVEF between the two groups at baseline (LVEF1), mid-treatment (LVEF2), or the final evaluation (LVEF3). Within-group comparisons indicated that LVEF values remained stable over time in both the bisoprolol and control groups, with no statistically significant differences.

Comparison of Global Longitudinal Strain Between and Within Groups

As shown in table 5, no significant differences were observed in GLS1 or GLS2 between the groups. However, at the final assessment (GLS3), the bisoprolol group exhibited a significantly better strain value than the control group (P=0.033).

Within-group analysis revealed a significant improvement from GLS2 to GLS3 in the bisoprolol group (P=0.042). The control group showed significant changes from GLS1 to GLS2 (P=0.013) and from GLS1 to GLS3 (P<0.001).

Table 3: Comparison of LVEDV between and within groups at three time points

Group	Comparison	LVEDV (mean±SD)	P value
Between-group	Baseline (LVEDV1)	Bisoprolol: 67.40±13.04 cc	0.810
		Control: 68.20±10.19 cc	
	Mid-treatment (LVEDV2)	Bisoprolol: 68.20±14.20 cc	0.619
		Control: 69.92±9.60 cc	
	Final (LVEDV3)	Bisoprolol: 66.56±14.49 cc	0.033*
		Control: 74.48±10.66 cc	
Bisoprolol	LVEDV1 vs. LVEDV2	67.40±13.04 vs. 68.20±14.21	0.374
	LVEDV2 vs. LVEDV3	68.20±14.21 vs. 66.96±14.49	0.002*
	LVEDV1 vs. LVEDV3	67.40±13.04 vs. 66.96±14.49	0.459
Control	LVEDV1 vs. LVEDV2	68.20±10.19 vs. 69.92±9.60	0.060
	LVEDV2 vs. LVEDV3	69.92±9.60 vs. 74.48±10.66	<0.001*
	LVEDV1 vs. LVEDV3	68.20±10.19 vs. 74.48±10.66	<0.001*

Between-group comparisons were analyzed using independent-samples *t* tests, and within-group comparisons were assessed using paired-samples *t* tests. Data are presented as mean±SD. Echocardiographic measures are presented as absolute values. *P<0.05 was considered statistically significant. LVEDV: Left ventricular end-diastolic volume

Table 4: Comparison of LVEF between and within groups at three time points

Group	Comparison	LVEF (mean±SD)	P value
Between-group	Baseline (LVEF1)	Bisoprolol: 59.20±1.87%	0.720
		Control: 59.00±2.04%	
	Mid-treatment (LVEF2)	Bisoprolol: 59.00±2.50%	<0.999
		Control: 59.00±2.04%	
	Final (LVEF3)	Bisoprolol: 59.20±2.36%	0.731
		Control: 59.40±1.65%	
Bisoprolol	LVEF1 vs. LVEF2	59.20±1.87 vs. 59.00±2.50	0.574
	LVEF2 vs. LVEF3	59.00±2.50 vs. 59.20±2.36	0.327
	LVEF1 vs. LVEF3	59.20±1.87 vs. 59.20±2.36	<0.999
Control	LVEF1 vs. LVEF2	59.00±2.04 vs. 59.00±2.04	<0.999
	LVEF2 vs. LVEF3	59.00±2.04 vs. 59.40±1.65	0.161
	LVEF1 vs. LVEF3	59.00±2.04 vs. 59.40±1.65	0.161

Between-group comparisons were analyzed using independent-samples *t* tests, and within-group comparisons were assessed using paired-samples *t* tests. Data are presented as mean±SD. Echocardiographic measures are presented as absolute values. *P<0.05 was considered statistically significant. LVEF: Left ventricular ejection fraction

Table 5: Comparison of GLS between and within groups at three time points

Group	Comparison	GLS (mean±SD)	P value
Between-group	Baseline (GLS1)	Bisoprolol: -18.24±2.18	0.424
		Control: -18.77±2.44	
	Mid-treatment (GLS2)	Bisoprolol: -17.78±1.85	0.677
		Control: -17.60±1.25	
	Final (GLS3)	Bisoprolol: -18.12±1.69	0.033*
		Control: -17.15±1.42	
Bisoprolol	GLS1 vs. GLS2	-18.24±2.18 vs. -17.78±1.85	0.111
	GLS2 vs. GLS3	-17.78±1.85 vs. -18.12±1.69	0.042*
	GLS1 vs. GLS3	-18.24±2.18 vs. -18.12±1.69	0.730
Control	GLS1 vs. GLS2	-18.77±2.44 vs. -17.60±1.25	0.013*
	GLS2 vs. GLS3	-17.60±1.25 vs. -17.15±1.42	0.072
	GLS1 vs. GLS3	-18.77±2.44 vs. -17.15±1.42	<0.001*

Between-group comparisons were analyzed using independent-samples *t* tests, and within-group comparisons were assessed using paired-samples *t* tests. Data are presented as mean±SD. Echocardiographic measures are presented as absolute values. P<0.05 was considered statistically significant. GLS: Global longitudinal strain

Table 6: Comparison of TAPSE between and within groups at three time points

Group	Comparison	TAPSE (mean±SD)	P value
Between-group	Baseline (TAPSE1)	Bisoprolol: 2.10±0.16 cm	0.598
		Control: 2.12±0.15 cm	
	Mid-treatment (TAPSE2)	Bisoprolol: 2.06±0.15 cm	0.907
		Control: 2.06±0.07 cm	
	Final (TAPSE3)	Bisoprolol: 2.11±0.11 cm	<0.001 *
		Control: 1.94±0.12 cm	
Bisoprolol	TAPSE1 vs. TAPSE2	2.10±0.16 vs. 2.06±0.15	0.382
	TAPSE2 vs. TAPSE3	2.06±0.15 vs. 2.11±0.11	0.202
	TAPSE1 vs. TAPSE3	2.10±0.16 vs. 2.11±0.11	0.664
Control	TAPSE1 vs. TAPSE2	2.12±0.15 vs. 2.06±0.07	0.040*
	TAPSE2 vs. TAPSE3	2.06±0.07 vs. 1.94±0.12	<0.001*
	TAPSE1 vs. TAPSE3	2.12±0.15 vs. 1.94±0.12	<0.001*

Between-group comparisons were analyzed using independent-sample *t* tests, and within-group comparisons were assessed using paired-sample *t* tests. Data are presented as mean±SD. Echocardiographic measures are presented as absolute values. *P<0.05 was considered statistically significant. TAPSE: Tricuspid annular plane systolic excursion

Comparison of Tricuspid Annular Systolic Excursion Between and Within Groups

As detailed in table 6, TAPSE values at baseline (TAPSE1) and mid-treatment (TAPSE2) did not differ significantly between the two groups. However, at the final evaluation (TAPSE3), the

bisoprolol group exhibited a significantly higher value than the control group (P<0.001).

Within-group comparisons showed no significant changes over time in the bisoprolol group, whereas the control group demonstrated significant declines from TAPSE1 to TAPSE2

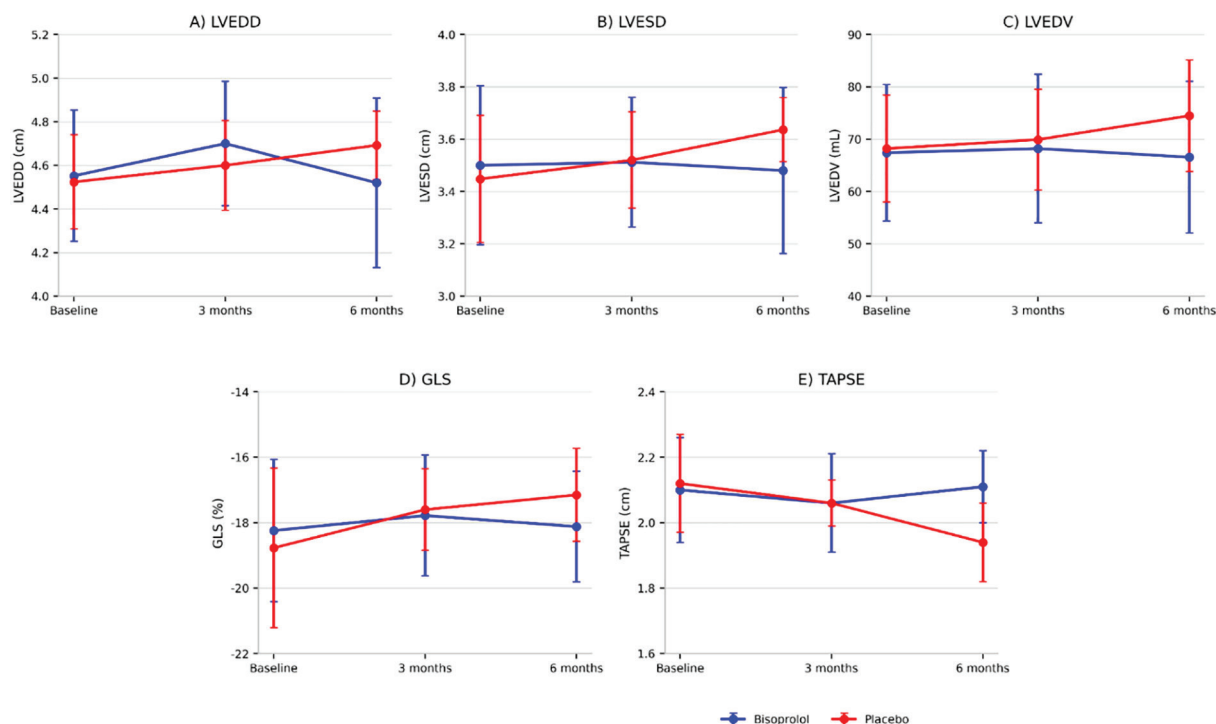


Figure 2: This figure shows longitudinal changes in echocardiographic parameters in the bisoprolol and placebo groups at baseline, 3 months, and 6 months: (A) LVEDD, (B) LVESD, (C) LVEDV, (D) GLS, and (E) TAPSE. Data are presented as mean±SD. Blue line indicates bisoprolol, and red line indicates placebo. LVEDD/LVESD/TAPSE are expressed in cm, LVEDV in mL, and GLS in %. LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LVEDV: Left ventricular end-diastolic volume; GLS: Global longitudinal strain; TAPSE: Tricuspid annular plane systolic excursion

($P=0.040$), TAPSE2 to TAPSE3 ($P<0.001$), and TAPSE1 to TAPSE3 ($P<0.001$). A visual summary of the longitudinal comparison of echocardiographic parameters is presented in figure 2.

Discussion

In this randomized controlled trial of female patients with breast cancer undergoing anthracycline-based chemotherapy, low-dose bisoprolol was associated with significant preservation of cardiac structure and function over time. While LVEF remained stable in both groups, the bisoprolol group showed significantly lower LVEDD, LVESD, and LVEDV at the final follow-up, improved GLS, and stable TAPSE than the declines in the control group. These findings supported the early initiation of bisoprolol for the prevention of anthracycline-induced cardiotoxicity and highlighted the need for preventive cardio-oncology strategies.

LVEDD is a sensitive echocardiographic index for detecting early geometric changes in the left ventricle, which often precede overt systolic dysfunction, especially in the context of anthracycline-induced cardiotoxicity.²⁰ In this study, LVEDD was significantly lower in the bisoprolol group than the placebo group at 6 months. Nevertheless, the absolute

between-group difference was small (≈ 2 mm), which may fall within routine echocardiographic measurement variability and may not represent a clinically meaningful change. Previous studies showed that anthracycline exposure was associated with progressive myocardial remodeling and dilation, reflected by increased LVEDD over time.^{21, 22} Our findings were broadly consistent with earlier reports, and a meta-analysis suggested beta-blockers, particularly carvedilol, might attenuate chemotherapy-related increases in LVEDD.^{14, 23} However, given the small magnitude, this finding should be interpreted cautiously and considered supportive rather than definitive.

LVESD is a key echocardiographic parameter that reflects systolic chamber size and indirectly indicates contractile function, with increases typically signaling progressive ventricular dysfunction.²⁴ Previous studies emphasized the importance of LVESD as an early marker of subclinical systolic impairment during chemotherapy.^{21, 24} We observed statistically lower LVESD at final follow-up in the bisoprolol group than the placebo group. However, the absolute difference was small (2 mm), making its clinical impact uncertain in this short-term setting. Clinically, limiting LVESD progression is crucial given its association with later EF decline and HF.²⁴ Accordingly, although the direction

of effect is potentially favorable, larger trials with longer follow-up are required to determine whether such small early differences translate into meaningful clinical benefit.

LVEDV is a critical indicator of ventricular filling and compliance, and elevations in LVEDV often reflect early subclinical remodeling, particularly in patients exposed to anthracyclines.²⁵ In this study, LVEDV remained essentially unchanged in the bisoprolol group, whereas patients in the placebo group experienced a progressive increase over time, resulting in significantly higher LVEDV at the final follow-up in those not receiving bisoprolol, which was consistent with the volumetric expansion associated with anthracycline-induced cardiotoxicity.²⁵ These findings were in agreement with previous studies, such as meta-analyses by Shah and others, which demonstrated that beta-blockers attenuate left ventricular dilation and preserve cardiac geometry in patients undergoing chemotherapy.¹⁴ Stabilizing LVEDV might counter maladaptive volumetric expansion, reducing long-term HF risk.²⁶⁻²⁸

LVEF is a widely used measure of left ventricular systolic function in cardio-oncology,²⁹ while in this study, LVEF remained stable across all time points in both the bisoprolol and control groups, with no statistically significant differences observed. Previous meta-analyses reported preserved LVEF in patients treated with beta-blockers despite anthracycline exposure, highlighting the limited sensitivity of LVEF in detecting early subclinical cardiotoxicity.^{14, 30, 31} While the preservation of LVEF might imply intact systolic function, it must be interpreted with caution since LVEF typically decreases only after considerable myocardial injury has occurred.³² Thus, favorable GLS and volume changes might better capture bisoprolol's benefit even when LVEF appears stable.³³

GLS has been identified as a sensitive echocardiographic marker for subclinical myocardial dysfunction at an early stage, particularly in patients undergoing anthracycline-based chemotherapy.³⁴ In the present study, the divergence in GLS trajectories between the groups (improvement with bisoprolol versus worsening with placebo) represented one of the most clinically meaningful signals of early cardioprotection. These findings were consistent with previous research, which demonstrated the superiority of GLS over LVEF in early detection of cardiotoxicity and guiding intervention.^{35, 36} The U-shaped pattern observed in the bisoprolol group, with an initial non-significant decline followed by recovery, might reflect early myocardial adaptation mitigated by

beta-blockade. However, this interpretation remains exploratory.³⁷

TAPSE is an important echocardiographic index for assessing right ventricular (RV) systolic function, which can be impacted by anthracycline-induced cardiotoxicity, though it is often underexplored compared with LV function.³⁸ However, similar to LVEDD and LVESD, the absolute difference was small (2 mm). Thus, the clinical relevance of this finding was uncertain over 6 months. These findings were in agreement with previous observations, which reported RV dysfunction following anthracycline therapy.^{39, 40} However, because TAPSE is load-dependent and reflects only a single component of RV mechanics, it should not be considered a comprehensive indicator of global RV performance.³⁸ Thus, the between-group differences in TAPSE should be interpreted cautiously.

The strengths of this study were the triple-blind randomized design, standardized chemotherapy regimens, and the application of advanced echocardiographic parameters in addition to conventional indices for detection of early cardiac alterations. The three-point longitudinal evaluation enabled tracking of dynamic remodeling processes. However, limitations included a small sample size, a short follow-up period, restriction to female patients with breast cancer, the lack of comparison with other cardioprotective agents, a fixed low bisoprolol dose, potential interobserver variability in echocardiographic assessment, and the unavailability of body surface area-indexed parameters. These factors might affect generalizability and precision. Future work should confirm the cardioprotective effects of bisoprolol in large, multicenter, diverse cohorts with long-term follow-up, conduct head-to-head comparisons with other agents, and optimize dosing regimens.

Conclusion

This triple-blind trial suggested that low-dose bisoprolol during anthracycline chemotherapy in patients with breast cancer might mitigate early subclinical cardiotoxicity. LVEF remained stable in both groups. However, LVEDV was essentially preserved, and GLS evolved more favorably with bisoprolol, whereas LVEDV increased and GLS worsened in the placebo group. In contrast, the statistically significant changes in LVEDD, LVESD, and TAPSE were small and of uncertain clinical relevance. Larger, long-term studies are required to confirm its role in routine cardio-oncology care.

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Authors' Contribution

A.M: Coceptualization, study design, data interpretation, drafting and reviewing the manuscript; ZS.T: Dat gathering and drafting the manuscript, A.E: Data interpretation, drafting and reviewing the manuscript; HR.M: Data interpretation, drafting and reviewing the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of AI

We acknowledge the use of ChatGPT (OpenAI) (version 5.4) for language polishing and paraphrasing during manuscript preparation; all content was reviewed, verified, and approved by the authors, who take full responsibility for the integrity and accuracy of the work.

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References

- 1 Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. Lyon: International Agency for Research on Cancer; 2020.
- 2 Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131:1981-8. doi: 10.1161/CIRCULATIONAHA.114.013777. PubMed PMID: 25948538.
- 3 Jasra S, Anampa J. Anthracycline Use for Early Stage Breast Cancer in the Modern Era: a Review. *Curr Treat Options Oncol*. 2018;19:30. doi: 10.1007/s11864-018-0547-8. PubMed PMID: 29752560.
- 4 Sobczuk P, Czerwinska M, Kleibert M, Cudnoch-Jedrzejewska A. Anthracycline-induced cardiotoxicity and renin-angiotensin-aldosterone system-from molecular mechanisms to therapeutic applications. *Heart Fail Rev*. 2022;27:295-319. doi: 10.1007/s10741-020-09977-1. PubMed PMID: 32472524; PubMed Central PMCID: PMC8739307.
- 5 Gulati M, Mulvagh SL. The connection between the breast and heart in a woman: Breast cancer and cardiovascular disease. *Clin Cardiol*. 2018;41:253-7. doi: 10.1002/clc.22886. PubMed PMID: 29446841; PubMed Central PMCID: PMC6489752.
- 6 Dhir AA, Sawant SP. Cardiac morbidity & mortality in patients with breast cancer: A review. *Indian J Med Res*. 2021;154:199-209. doi: 10.4103/ijmr.IJMR_879_20. PubMed PMID: 35295010; PubMed Central PMCID: PMC9131763.
- 7 Li C, Dai H, Guo X, Zhou L, Jiang M. Comprehensive review of non-invasive-treatment-related cardiovascular toxicity in breast cancer. *iScience*. 2025;28:111759. doi: 10.1016/j.isci.2025.111759. PubMed PMID: 40207253; PubMed Central PMCID: PMC11980005.
- 8 Cousin L, Roper N, Nolan TS. Cardio-Oncology Health Disparities: Social Determinants of Health and Care for Black Breast Cancer Survivors. *Clin J Oncol Nurs*. 2021;25:36-41. doi: 10.1188/21.CJON.S1.36-41. PubMed PMID: 34533529; PubMed Central PMCID: PMC8560214.
- 9 Cho H, Lee S, Sim SH, Park IH, Lee KS, Kwak MH, et al. Cumulative incidence of chemotherapy-induced cardiotoxicity during a 2-year follow-up period in breast cancer patients. *Breast Cancer Res Treat*. 2020;182:333-43. doi: 10.1007/s10549-020-05703-5. PubMed PMID: 32468335.
- 10 Fabiani I, Chianca M, Cipolla CM, Cardinale DM. Anthracycline-induced cardiomyopathy: risk prediction, prevention and treatment. *Nat Rev Cardiol*. 2025;22:551-63. doi: 10.1038/s41569-025-01126-1. PubMed PMID: 39875555.
- 11 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. [2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure].

- Kardiol Pol. 2016;74:1037-147. doi: 10.5603/KP.2016.0141. PubMed PMID: 27748494.
- 12 Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol.* 2020;31:171-90. doi: 10.1016/j.annonc.2019.10.023. PubMed PMID: 31959335; PubMed Central PMCID: PMC8019325.
 - 13 Blanter JB, Frishman WH. The Preventive Role of Angiotensin Converting Enzyme Inhibitors/Angiotensin-II Receptor Blockers and beta-Adrenergic Blockers in Anthracycline- and Trastuzumab-Induced Cardiotoxicity. *Cardiol Rev.* 2019;27:256-9. doi: 10.1097/CRD.0000000000000252. PubMed PMID: 31008768.
 - 14 Shah P, Garriss R, Abboud R, Vasudev R, Patel H, Doshi R, et al. Meta-Analysis Comparing Usefulness of Beta Blockers to Preserve Left Ventricular Function During Anthracycline Therapy. *Am J Cardiol.* 2019;124:789-94. doi: 10.1016/j.amjcard.2019.05.046. PubMed PMID: 31307662.
 - 15 Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR, Jr., das Dores Cruz F, Goncalves Brandao SM, Rigaud VOC, et al. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. *J Am Coll Cardiol.* 2018;71:2281-90. doi: 10.1016/j.jacc.2018.02.049. PubMed PMID: 29540327.
 - 16 Wihandono A, Azhar Y, Abdurahman M, Hidayat S. The Role of Lisinopril and Bisoprolol to Prevent Anthracycline Induced Cardiotoxicity in Locally Advanced Breast Cancer Patients. *Asian Pac J Cancer Prev.* 2021;22:2847-53. doi: 10.31557/APJCP.2021.22.9.2847. PubMed PMID: 34582653; PubMed Central PMCID: PMC8850900.
 - 17 Livi L, Barletta G, Martella F, Saieva C, Desideri I, Bacci C, et al. Cardioprotective Strategy for Patients With Nonmetastatic Breast Cancer Who Are Receiving an Anthracycline-Based Chemotherapy: A Randomized Clinical Trial. *JAMA Oncol.* 2021;7:1544-9. doi: 10.1001/jamaoncol.2021.3395. PubMed PMID: 34436523; PubMed Central PMCID: PMC8391772.
 - 18 National Cancer Institute. Common terminology criteria for adverse events (CTCAE) version 5.0. Bethesda (MD): NCI; 2017.
 - 19 Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. *J Natl Cancer Inst.* 2019;111:245-55. doi: 10.1093/jnci/djy221. PubMed PMID: 30856272; PubMed Central PMCID: PMC6410951.
 - 20 Zhao R, Shu F, Zhang C, Song F, Xu Y, Guo Y, et al. Early Detection and Prediction of Anthracycline-Induced Right Ventricular Cardiotoxicity by 3-Dimensional Echocardiography. *JACC CardioOncol.* 2020;2:13-22. doi: 10.1016/j.jacc.2020.01.007. PubMed PMID: 34396205; PubMed Central PMCID: PMC8352081.
 - 21 Moghadam AA, Fazaeli SH, Kamandi M. Left Ventricular Function and Echocardiographic Parameters in Patients Undergoing Chemotherapy With 5-Fluorouracil, Anthracycline, Taxotere, and Herceptin: Prospective Cohort Study. *Health Sci Rep.* 2025;8:e71031. doi: 10.1002/hsr.2.71031. PubMed PMID: 40735261; PubMed Central PMCID: PMC12301501.
 - 22 Nguyen KL, Hu P, Ennis DB, Shao J, Pham KA, Chen JJ. Cardiac MRI: a Translational Imaging Tool for Characterizing Anthracycline-Induced Myocardial Remodeling. *Curr Oncol Rep.* 2016;18:48. doi: 10.1007/s11912-016-0533-x. PubMed PMID: 27292153; PubMed Central PMCID: PMC6509051.
 - 23 Huang S, Zhao Q, Yang ZG, Diao KY, He Y, Shi K, et al. Protective role of beta-blockers in chemotherapy-induced cardiotoxicity: a systematic review and meta-analysis of carvedilol. *Heart Fail Rev.* 2019;24:325-33. doi: 10.1007/s10741-018-9755-3. PubMed PMID: 30523513; PubMed Central PMCID: PMC6476829.
 - 24 Sandamali JAN, Hewawasam RP, Fernando M, Jayatilaka K, Madurawe RD, Sathananthan PP, et al. Anthracycline-Induced Cardiotoxicity in Breast Cancer Patients from Southern Sri Lanka: An Echocardiographic Analysis. *Biomed Res Int.* 2020;2020:1847159. doi: 10.1155/2020/1847159. PubMed PMID: 33274195; PubMed Central PMCID: PMC7683106.
 - 25 Jordan JH, Sukpraphrute B, Melendez GC, Jolly MP, D'Agostino RB, Jr., Hundley WG. Early Myocardial Strain Changes During Potentially Cardiotoxic Chemotherapy May Occur as a Result of Reductions in Left Ventricular End-Diastolic Volume: The Need to Interpret Left Ventricular Strain With Volumes. *Circulation.* 2017;135:2575-7. doi: 10.1161/CIRCULATIONAHA.117.027930. PubMed PMID: 28630272; PubMed Central PMCID: PMC5508602.
 - 26 de Groote P, Delour P, Lamblin N, Dagorn J, Verkindere C, Tison E, et al. Effects of bisoprolol in patients with stable

- congestive heart failure. *Ann Cardiol Angeiol* (Paris). 2004;53:167-70. doi: 10.1016/j.ancard.2004.03.003. PubMed PMID: 15369311.
- 27 Ni Y, Wang T, Zhuo X, Song B, Zhang J, Wei F, et al. Bisoprolol reversed small conductance calcium-activated potassium channel (SK) remodeling in a volume-overload rat model. *Mol Cell Biochem*. 2013;384:95-103. doi: 10.1007/s11010-013-1785-5. PubMed PMID: 23975505.
- 28 Wang X, Zhao XZ, Wang XW, Cao LY, Lu B, Wang ZH, et al. Effect of levosimendan on ventricular remodelling in patients with left ventricular systolic dysfunction: a meta-analysis. *ESC Heart Fail*. 2024;11:1352-76. doi: 10.1002/ehf2.14714. PubMed PMID: 38419326; PubMed Central PMCID: PMC11098670.
- 29 Stone JR, Kanneganti R, Abbasi M, Akhtari M. Monitoring for Chemotherapy-Related Cardiotoxicity in the Form of Left Ventricular Systolic Dysfunction: A Review of Current Recommendations. *JCO Oncol Pract*. 2021;17:228-36. doi: 10.1200/OP.20.00924. PubMed PMID: 33689453.
- 30 Attar A, Behnagh AK, Hosseini M, Amanollahi F, Shafiekhani P, Kabir A. Beta-Blockers for Primary Prevention of Anthracycline-Induced Cardiac Toxicity: An Updated Meta-Analysis of Randomized Clinical Trials. *Cardiovasc Ther*. 2022;2022:8367444. doi: 10.1155/2022/8367444. PubMed PMID: 36687509; PubMed Central PMCID: PMC9818032.
- 31 Jeyaprakash P, Sangha S, Low G, Yu C, Pathan F, Negishi K. Prophylaxis to Prevent Cardiotoxicity in Patients Receiving Anthracycline for Breast Cancer: A Combined Bayesian and Frequentist Network Meta-Analysis of Randomised Controlled Trials. *Heart Lung Circ*. 2024;33:710-20. doi: 10.1016/j.hlc.2023.11.004. PubMed PMID: 38184425.
- 32 Sutton NR, Li S, Thomas L, Wang TY, de Lemos JA, Enriquez JR, et al. The association of left ventricular ejection fraction with clinical outcomes after myocardial infarction: Findings from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With the Guidelines (GWTG) Medicare-linked database. *Am Heart J*. 2016;178:65-73. doi: 10.1016/j.ahj.2016.05.003. PubMed PMID: 27502853.
- 33 Cocco LD, Chiapparini AF, Saffi MAL, Leiria TLL. Global Longitudinal Strain for the Early Detection of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis. *Clin Oncol (R Coll Radiol)*. 2022;34:514-25. doi: 10.1016/j.clon.2022.05.001. PubMed PMID: 35637075.
- 34 Marwick TH. Global Longitudinal Strain Monitoring to Guide Cardioprotective Medications During Anthracycline Treatment. *Curr Oncol Rep*. 2022;24:687-94. doi: 10.1007/s11912-022-01242-y. PubMed PMID: 35239105; PubMed Central PMCID: PMC9054886.
- 35 Stolojanu C, Steflea R, Micsescu-Olah AM, Alexandra I, Popoiu A, Doros G. Combined Utility of Speckle Tracking Echocardiography and Cardiac Biomarkers for Early Detection of Anthracycline-Induced Cardiotoxicity in Pediatric Oncology Patients. *Biomedicines*. 2024;12. doi: 10.3390/biomedicines12122849. PubMed PMID: 39767755; PubMed Central PMCID: PMC11673503.
- 36 Gonzalez-Manzanares R, Castillo JC, Molina JR, Ruiz-Ortiz M, Mesa D, Ojeda S, et al. Automated Global Longitudinal Strain Assessment in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. *Cancers (Basel)*. 2022;14. doi: 10.3390/cancers14061513. PubMed PMID: 35326663; PubMed Central PMCID: PMC8946759.
- 37 Yurdam FS, Gurses E. Myocardial bridge and beta blockers: effect on left ventricular strain parameters. *Acta Cardiol*. 2023;78:623-9. doi: 10.1080/00015385.2023.2209421. PubMed PMID: 37171374.
- 38 Aloia E, Cameli M, D'Ascenzi F, Sciacaluga C, Mondillo S. TAPSE: An old but useful tool in different diseases. *Int J Cardiol*. 2016;225:177-83. doi: 10.1016/j.ijcard.2016.10.009. PubMed PMID: 27728861.
- 39 Abdar Esfahani M, Mokarian F, Karimipناه M. Alterations in the echocardiographic variables of the right ventricle in asymptomatic patients with breast cancer during anthracycline chemotherapy. *Postgrad Med J*. 2017;93:271-4. doi: 10.1136/postgradmedj-2016-134286. PubMed PMID: 27651497.
- 40 Hu HM, Zhang XL, Zhang WL, Huang DS, Du ZD. Detection of Subclinical Anthracyclines' Cardiotoxicity in Children with Solid Tumor. *Chin Med J (Engl)*. 2018;131:1450-6. doi: 10.4103/0366-6999.233950. PubMed PMID: 29893362; PubMed Central PMCID: PMC6006810.