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ORIGINAL RESEARCH

Randomized, Placebo-Controlled, Triple-Blind Clinical Trial of Ivabradine for the Prevention of Cardiac Dysfunction During Anthracycline-Based Cancer Therapy

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BACKGROUND: Cancer therapy–related cardiac dysfunction frequently occurs in patients receiving anthracycline. Ivabradine reduces heart rate without affecting contractility and showed anti-inflammatory, antioxidant, and antiapoptotic effects in experimental cardiotoxicity models. This study aims to evaluate the effect of ivabradine on cancer therapy–related cardiac dysfunction in patients with lymphoma or sarcoma treated with anthracycline.

METHODS: In a randomized, triple-blind trial, patients starting anthracycline therapy received either ivabradine 5 mg twice daily or placebo until 30 days after completing treatment. The primary outcome was the incidence of cardiotoxicity measured as a ≥10% relative reduction in global longitudinal strain at 12 months from baseline. Secondary outcomes included 12-month clinical outcomes, a ≥10% decrease in the left ventricular ejection fraction to <55%, diastolic dysfunction, and troponin T and N-terminal pro-B-type natriuretic peptide levels.

RESULTS: This study enrolled 107 patients (51 in the ivabradine group and 56 in the placebo group). The median dose of anthracycline was 300 mg/m^2 (250–300 mg/m^2) in both groups. Cardiotoxicity measured as a ≥10% relative reduction in global longitudinal strain at 12 months was reached in 57% versus 50% in the ivabradine and placebo groups (odds ratio, 1.32 [95% CI, 0.61–2.83]; *P*=0.477). Fewer patients in the ivabradine group than in the placebo group had troponin T levels ≥14 ng/L (16 [39.0%] versus 23 [62.2%]; *P*=0.041) at 6 months, with this difference not maintained at the 12-month follow-up. In addition, there were no differences in the other secondary outcomes.

CONCLUSIONS: A fixed 10 mg/day dose of ivabradine does not protect patients with cancer against anthracycline cardiotoxicity.

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Key Words: anthracycline ■ cardiac dysfunction ■ cardiotoxicity ■ ivabradine ■ prevention

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CLINICAL PERSPECTIVES

What Is New?

- This study is the first randomized, triple-blind, placebo-controlled trial to evaluate ivabradine for the prevention of anthracycline-induced cardiotoxicity. Contrary to expectations based on preclinical models, ivabradine did not reduce the incidence of cardiac dysfunction, as assessed by global longitudinal strain, in patients undergoing anthracycline-based cancer therapy.

What Are the Clinical Implications?

- The findings suggest that ivabradine at a fixed dose of 10 mg/d does not provide sufficient cardioprotection in patients receiving anthracyclines for lymphoma or sarcoma. Given the high prevalence of subclinical cardiac dysfunction in this population, alternative strategies, including more individualized heart rate control, or other cardioprotective agents, should be explored. The results highlight the need for further research into tailored approaches for preventing chemotherapy-induced cardiotoxicity, particularly in high-risk patients.

Nonstandard Abbreviations and Acronyms

BEAUTIFUL	Ivabradine for Patients With Stable Coronary Artery Disease and Left-Ventricular Systolic Dysfunction
CECCY	Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity
CTRCD	cancer therapy–related cardiac dysfunction
GLS	global longitudinal strain
HR	heart rate
IPAC	Ivabradine for the Prevention of Cardiac Dysfunction During Anthracycline-Based Cancer Therapy
PRADA	Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy
SHIFT	Ivabradine and Outcomes in Chronic Heart Failure
STOP-CA	Atorvastatin for Anthracycline-Associated Cardiac Dysfunction

While effective at targeting and destroying cancer cells, chemotherapy can also have unintended detrimental effects on the cardiovascular system.[1] These include an increased risk of heart failure (HF), hypertension, arrhythmias, myocardial ischemia, and thromboembolism. These issues are often referred to as cancer therapy–related cardiovascular dysfunction (CTRCD) or cardiotoxicity.[2]

Anthracyclines are highly effective in treating various cancers, including breast cancer and hematologic malignancies, but are highly likely to compromise the cardiovascular system. The risk of CTRCD from anthracycline is dose related, with higher cumulative doses increasing the risk of cardiac damage, which primarily causes myocardial injury and HF.[3] However, even low doses of anthracycline can still be risky, particularly for vulnerable groups such as older individuals or those with preexisting heart disease. Anthracycline-induced cardiotoxicity is complex and involves oxidative stress, DNA damage, and disruption of cardiomyocyte metabolism.[4]

Randomized studies have not shown consistent effects of β blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in the prevention of anthracycline cardiotoxicity.[5] Mineralocorticoid receptor antagonists, such as spironolactone and eplerenone, have demonstrated efficacy in reducing myocardial remodeling and oxidative stress associated with anthracycline use. Statins, known for their pleiotropic effects, including anti-inflammatory and antioxidant properties, have also shown promise in mitigating chemotherapy-induced cardiac damage. Moreover, dexrazoxane, an iron chelator, has been widely used for its ability to prevent anthracycline-induced free radical generation and lipid peroxidation, thereby reducing the risk of cardiotoxicity.[6–9]

An elevated heart rate (HR) in patients with cancer serves as a biomarker of neurohumoral activation, of sympathetic nervous system stimulation, related to atherosclerotic progression and cardiac dysfunction.[10] Anker et al reported that an HR ≥75 bpm was associated with an increased mortality rate in solid neoplasms.[11] In preclinical models, ivabradine, a selective HR-lowering agent, effectively mitigated the increase in heart weight—a finding commonly associated with anthracycline-induced cardiotoxicity. The mechanisms underlying anthracycline-induced cardiotoxicity include lipid peroxidation and reduced enzymatic activity of critical antioxidant systems, such as superoxide dismutase and catalase. Notably, ivabradine has been shown to restore superoxide dismutase and catalase activity, potentially improving cellular resilience against oxidative stress. Additionally, while anthracyclines elevate glutathione peroxidase levels as a compensatory

response, ivabradine has demonstrated the ability to normalize this excessive antioxidant activity.[12] There is little clinical evidence to suggest that ivabradine significantly affects cardiac inotropy, though experimental studies have proposed potential mechanisms, including modulation of sarcoplasmic reticulum Ca^{2+} transit via calmodulin-dependent protein kinase II activation.[13]

These findings underscore the potential of ivabradine not only to counteract neurohumoral activation but also to restore oxidative balance, thereby suggesting a multifaceted mechanism for its cardioprotective effects. By incorporating this evidence, this randomized clinical trial aims to address a critical gap in the understanding of ivabradine's utility in preventing chemotherapy-induced cardiotoxicity in patients undergoing anthracycline-based cancer therapy.

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request (clinical trials registration NCT03650205; https://clinicaltrials.gov/study/NCT03650205?cond=NCT03650205&rank=1).

Study Population

The IPAC (Ivabradine for the Prevention of Cardiac Dysfunction During Anthracycline-Based Cancer Therapy) trial was a triple-blind, randomized, placebo-controlled study conducted at the Instituto do Câncer do Estado de São Paulo and at the Instituto do Coração (InCor), Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Brazil, after approval by the Research Ethics Committee. Consecutive patients with lymphoma or sarcoma slated for anthracycline chemotherapy were assessed for eligibility. Patients were recruited in outpatient clinics. The participants were informed, provided consent, signed up for the study, and were registered on ClinicalTrials.gov (NCT03650205). Funding was provided by the Sao Paulo Research Foundation.

The exclusion criteria were an inability to assess left ventricular (LV) function, prior chemotherapy with anthracycline or radiation, HF symptoms, existing cardiomyopathy, coronary or valve disease, atrial fibrillation, bradycardia, chronic renal disease, a positive test result indicating SARS-CoV-2 infection, and allergy/contraindication to ivabradine.

Study Design

Eligible patients were enrolled and randomly assigned to receive either ivabradine 5 mg twice daily or placebo, starting with chemotherapy initiation and continuing through the anthracycline regimen until 30 days after therapy. Randomization was performed via a computer system, with data held by an independent research pharmacy. Ivabradine was carefully encapsulated so that it was visually indistinguishable from the placebo. The participants, health care professionals, data managers, and statisticians were blinded to the treatment assignments.

Study Procedures

The enrolled patients underwent medical evaluation; laboratory assessments, including cardiac biomarkers (cardiac troponin T and NT-proBNP [N-terminal pro-B-type natriuretic peptide]); ECG; transthoracic echocardiogram featuring myocardial global longitudinal strain (GLS) measurements; and 24-hour Holter monitoring at baseline (before the initiation of chemotherapy). For patients who met the eligibility criteria, randomization was performed, and the medication (ivabradine or placebo) was initiated on the first day of chemotherapy.

A standard global tool for assessing health and quality of life and analyzing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EuroQol-5 Dimension-3 Level questionnaire) was administered at baseline and after chemotherapy.

Sequential laboratory testing, ECG assessments, and transthoracic echocardiogram examinations of the strains were conducted at 3, 6, and 12 months following the initiation of chemotherapy. At the 3- and 6-month marks, all patients were still undergoing chemotherapy, which provide a uniform context for evaluating early cardiac changes. Holter monitoring was also performed at the conclusion of the treatment. An overview of the study procedures is provided in Figure 1. Transthoracic echocardiogram was conducted using a commercially available system with digital ultrasonic equipment (Vivid 9; GE Healthcare, Milwaukee, WI), and all measurements adhered to the recommendations provided by the American Society of Echocardiography.[14]

The left ventricular ejection fraction (LVEF) was measured by Simpson's method via apical 4- and 2-chamber views. Myocardial GLS analysis was performed via semiautomated speckle tracking, covering the whole LV from 3 apical views for the assessment of cardiac cycle tissue deformation. The endocardial border of the LV was manually traced at end-systole and autoadjusted to include the full myocardium.[15,16]

The diastolic function evaluation included an assessment of the mitral inflow E/A pattern, E/A ratio, E velocity deceleration time, annular tissue Doppler curves (e′/a′), and E/e′ ratio. Additional echocardiographic parameters that were assessed via Doppler echocardiography included the left atrial diameter and

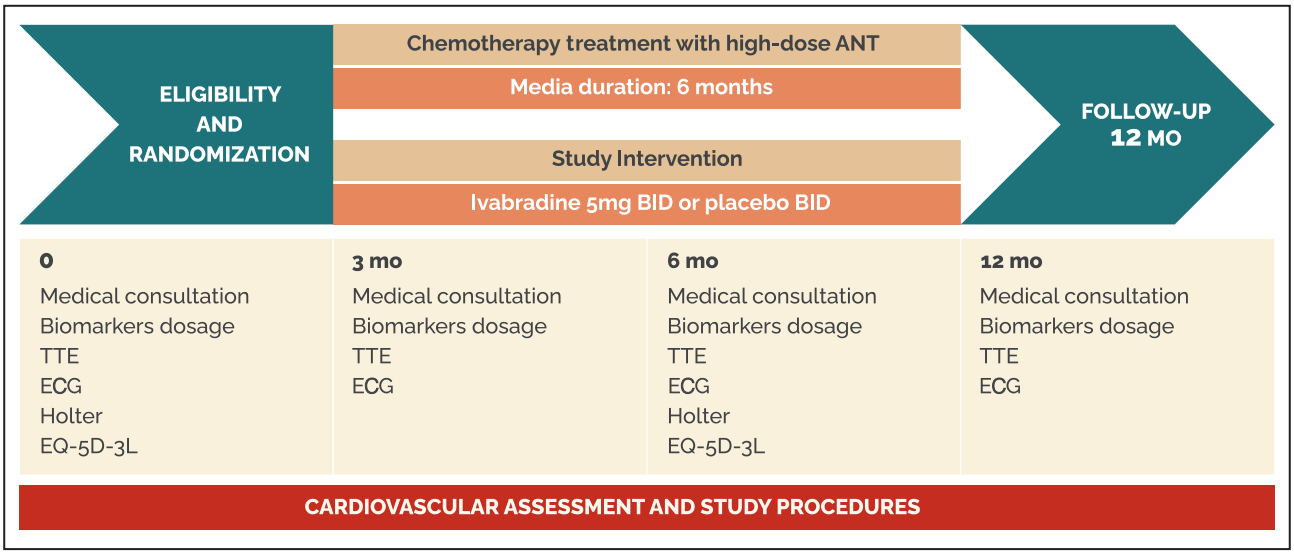

Figure 1. Study procedures and assessment timeline.
The timeline and key medical assessments conducted at baseline (0 months), during the chemotherapy treatment phase with high-dose anthracycline (3 and 6 months), and during the 12-month follow-up after intervention are summarized. The schedule included medical consultations, biomarker dosages, transthoracic echocardiogram, ECG, Holter monitoring, and EQ-5D-3L assessments at each designated time point (0, 3, 6, and 12 months). ANT indicates anthracycline; BID, twice daily; EQ-5D-3L: EuroQol-5 Dimension-3 Level; and TTE, transthoracic echocardiogram.

volume, interventricular septal diameter, posterior wall thickness, LV end-diastolic diameter, LV end-systolic diameter, and mitral inflow.[17] Two experienced and board-certified echocardiographers performed the exams. Diagnosing LV diastolic dysfunction involves evaluating the E/e′ ratio, e′ wave velocity, indexed left atrial volume, and tricuspid regurgitation velocity. Normal diastolic function is defined by alterations in <50% of these criteria; diastolic dysfunction, by alterations in >50% of the criteria; and indeterminate diastolic function, by alterations in exactly 50% of the criteria. Diastolic function was evaluated using Doppler echocardiography, with a focus on mitral inflow velocities. Grade I diastolic dysfunction, indicative of impaired relaxation, was defined by an E/A ratio of <0.8 and a peak E-wave velocity ≤50 cm/s. Grade II diastolic dysfunction was identified when the E/A ratio ranged from 0.8 to 2.0, along with supportive findings suggestive of elevated left atrial pressure. These included an average E/e′ ratio >14, a left atrial volume index >34 mL/m^2, and a peak tricuspid regurgitation velocity >2.8 m/s. Grade III diastolic dysfunction, indicative of restrictive filling, was diagnosed when the E/A ratio was ≥2.0. Supportive findings of significantly elevated left atrial pressure in grade III included a markedly increased E/e′ ratio, an enlarged left atrial volume index, and an elevated peak tricuspid regurgitation velocity.

The classification of dysfunction as grade I or II depends on the number of positive or negative criteria, whereas a split evaluation results in an indeterminate classification.[18]

Arrhythmia was diagnosed when any of the following conditions were present: ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, atrial fibrillation, atrial flutter, atrial tachycardia, supraventricular tachycardia, atrioventricular block, conduction disorder, or sick sinus syndrome.[19] Arrhythmias were identified through surface 12-lead ECGs performed at baseline and during scheduled follow-up visits and also through Holter monitoring at baseline, midtreatment, and at the conclusion of the treatment period. We also measured various 24-hour Holter parameters to evaluate HR variability and autonomic function at baseline and at 12 months. These included (1) minimum HR: the lowest recorded HR during the 24-hour monitoring period, reflecting parasympathetic tone and resting cardiac activity; (2) mean HR: the average HR over the 24-hour period, providing a general indicator of overall cardiac workload and rhythm stability, and (3) maximum HR: the highest recorded HR during the monitoring period, reflecting sympathetic activation and response to physical or emotional stress.

Ultrasensitive troponin T was measured via an advanced electrochemiluminescence method. In this assay, troponin T antibodies are labeled with ruthenium complexes that emit light when activated by an electrical impulse. The threshold for abnormal troponin T levels was set at ≥14 ng/L, which is consistent with current clinical guidelines, to ensure relevance to the patient population.[20]

The measurement of NT-proBNP levels was carried out via a highly sensitive and specific microparticle

immunoassay method that uses chemiluminescence. The chemiluminescent reaction emits light proportionally to the NT-proBNP concentration present. For clinical relevance, a reference value of up to 125 pg/mL was established, which is considered the upper limit of normal for NT-proBNP levels and aids in the interpretation of the assay results in the context of cardiac function and potential heart failure.[21] A significant increase in biomarkers was considered if there was a ≥20% increase from baseline, an NT-proBNP level >125 pg/mL, or a troponin T level ≥14 ng/L during 12 months.

Participants were instructed to fast for at least 8 hours before sample collection to minimize the influence of postprandial metabolic changes on biomarker levels. Samples were drawn in the morning to control for diurnal variations. Blood samples for biomarkers were collected immediately before each chemotherapy cycle and at 3, 6, and 12 months after therapy completion.

A participant could withdraw from the trial if any of the following conditions were met, according to the safety monitoring committee: (1) development of severe or life-threatening adverse events related to the study drug; (2) requirement for interventions, such as initiation of cardioprotective therapies (β blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers); (3) participant withdrawal of consent for any reason; and (4) clinical judgment of the investigator indicating that continued participation would compromise the participant's health.

Study Outcomes

The primary outcome was to assess the incidence of cardiotoxicity measured as a ≥10% relative reduction in GLS at 12 months from baseline.[22,23]

The secondary outcomes were a combined end point of all-cause death, acute myocardial infarction, symptomatic CTRCD, and arrhythmias at 12 months; a reduction in LVEF of at least 10%, resulting in an LVEF <55% and a change in diastolic dysfunction at 12 months; the quantification of troponin T and NT-proBNP levels at 3, 6, and 12 months; and a change in GLS at 180 days. We also analyzed the adverse effects of treatment at 12 months.

Statistical Analysis

The initial sample size was calculated with an expected incidence of cardiotoxicity of 50% with the use of anthracycline and an expected reduction to 25% with ivabradine.[24] With a statistical significance level of 95% and to achieve 90% statistical power with a 2-sided Fisher exact test, 160 patients (80 in each arm) were needed. Owing to recruitment challenges, mainly caused by pandemics, the sample size was revised. We adjusted for 80% power, keeping the same end points and hypothesis, and the required number of patients was recalculated to 100 to detect a reduction in the proportion of patients with cardiotoxicity from 50% to 25%.

Descriptive statistics were used for the distribution of variables; continuous variables are summarized herein as the means±SDs or as medians with interquartile ranges, and categorical variables are summarized as counts and percentages. All the statistical analyses were performed on intention to treat. Continuous variables were compared via *t* tests or Mann–Whitney *U* tests, and categorical variables were compared via the Pearson χ^2, Fisher exact, or likelihood ratio test. Variables measured at multiple time points were evaluated via repeated-measures ANOVA or the Mann–Whitney *U* test and Wilcoxon signed-rank test. For the analysis of categorical outcomes, differences between groups and odds ratios (ORs) were calculated, along with their respective 95% CIs.

The statistical analysis was conducted via SPSS version 25.0 (Statistical Package for the Social Sciences; IBM, Armonk, NY), and *P* values <0.05 were considered significant.

RESULTS

Patient Characteristics

Between January 2019 and May 2022, a total of 270 patients with a diagnosis of lymphoma or sarcoma were screened. We randomized 107 patients to receive ivabradine (n=51) or placebo (n=56) for the intention-to-treat analysis (Figure 2).

The baseline characteristics were well balanced between the groups (Table 1). Most patients had lymphoma, and the median anthracycline dose was 300 mg/m^2 (250–300 mg/m^2) in both groups.

Outcomes

Primary Outcome

A reduction in GLS of at least 10% at the 12-month follow-up was observed in 29 patients (57%) in the ivabradine group and in 28 patients (50%) in the placebo group (OR, 1.32 [95% CI, 0.61–2.83]; *P*=0.47; Table 2). At 3, 6, and 12 months of follow-up, there was a significant reduction in GLS compared with baseline in both groups (*P*=0.034, *P*<0.001, and *P*<0.001), but there was no significant difference between the ivabradine and placebo groups (Figure 3).

Secondary Outcomes

No significant difference in the occurrence of clinical complications at 12 months was detected between the ivabradine and placebo groups (11.8% versus 17.9%; OR, 0.61 [95% CI, 0.21–1.83]; *P*=0.37; Table 2).

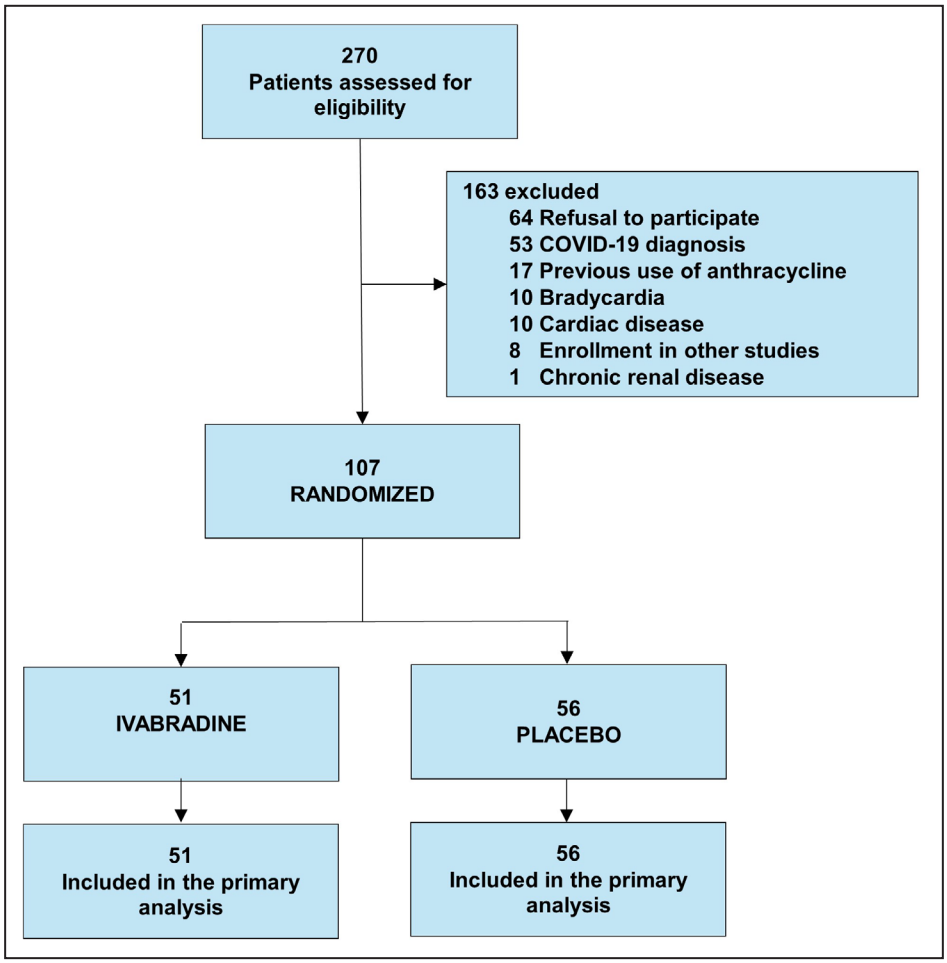

Figure 2. Study flowchart.
Depiction of the participant allocation from the initial assessment to the completion of analysis within the study arms.

Compared with the placebo group, the ivabradine group had 5 deaths (9.8%), whereas the placebo group had 7 deaths (12.5%) (OR, 0.76 [95% CI, 0.23–2.57]; *P*=0.65). In the ivabradine group, 3 deaths were attributed to disease progression, 1 to sepsis, and 1 to pulmonary embolism. In the placebo group, 4 deaths were due to disease progression, 1 to sepsis, 1 to gastrointestinal bleeding, and 1 sudden death of indeterminate cause.

When temporal variations in NT-proBNP levels were considered, there were no statistically significant differences between the studied groups over the 12 months of follow-up (Table 2 and Figure 4A). The comparison of baseline levels with those at 3 months after intervention revealed a significant reduction only in the placebo group (*P*=0.042), whereas in the ivabradine group, the change was not statistically significant (*P*=0.36) (Table 2 and Figure 4A).

In the ivabradine and placebo groups, the median high-sensitivity troponin T levels at 3 and 6 months were greater than those at baseline. However, there was no difference between the groups in the troponin T values at any time point (Table 2 and Figure 4B). At 6 months of evaluation, a smaller proportion of patients in the ivabradine group had troponin T levels ≥14 ng/L (16 [39.0%] versus 23 [62.2%]; *P*=0.041; Table 2).

The number of patients with a >10% decrease in LVEF to <55% was 3 (5.9%) in the ivabradine group and 4 (7.1%) in the placebo group (OR, 0.81 [95% CI, 0.17–3.82]; *P*=1.00; Table 2). The incidence of diastolic dysfunction was greater at 12 months than at baseline in the ivabradine and placebo groups, but there was no significant difference between the groups (17.5% versus 7.8% in the ivabradine group and 22.5% versus 7.1% in the placebo group; *P*=0.73; Table 2).

There was no significant difference between the groups regarding the HR at 3, 6, and 12 months (*P*=0.21). However, a reduction in HR was observed in both the ivabradine and placebo groups at 3, 6, and 12 months compared with baseline. The minimum, mean, and maximum HRs measured via 24-hour Holter monitoring showed no significant differences between the groups at baseline or after 12 months (Table 3).

Table 1. Baseline and Demographic Characteristics of the Patients

Variable	Ivabradine (n=51)	Placebo (n=56)
Sex, n (%)		
Female sex	18 (35.3)	28 (50.0)
Male sex	33 (64.7)	28 (50)
Age, y, median (IQR)	49 (32–59)	39 (26–60)
Race, n (%)		
White	37 (72.5)	45 (80.4)
Black	3 (5.9)	4 (7.1)
Multracial	11 (21.6)	7 (12.5)
Smoking, n (%)		
Former smoker	13 (25.5)	6 (10.7)
Current smoker	7 (13.7)	9 (16.1)
Alcohol consumption, n (%)		
Social/sporadic	17 (33.3)	20 (35.7)
Daily	4 (7.8)	3 (5.4)
Sedentary lifestyle, n (%)	34 (66.7)	35 (62.5)
Diabetes, n (%)	4 (7.8)	5 (8.9)
Hypertension, n (%)	13 (25.5)	9 (16.4)
Dyslipidemia, n (%)	4 (8.0)	3 (5.4)
HFA-ICOS, n (%)		
Low	13 (25.5)	14 (25)
Moderate	34 (66.7)	38 (67.9)
High	4 (7.8)	4 (7.1)
Diagnosis, n (%)		
Diffuse NHL	23 (45.1)	23 (41.1)
Follicular NHL	7 (13.7)	6 (10.7)
HL	18 (35.3)	26 (46.4)
Sarcoma	3 (5.9)	1 (1.8)
Anthracycline dose* (mg/m^2), median (IQR)	300 (250–300)	300 (250–300)

The risk level according to therapy is calculated as follows: low risk: no risk factors or 1 medium risk factor; moderate risk: medium risk factor points totaling 2–4 (eg, 1 medium risk factor or 2 medium risk factors); high risk: ≥1 high risk factor or medium risk factors points totaling ≥5; very high risk: ≥1 very high-risk factor. HL indicates Hodgkin lymphoma; HFA-ICOS, Heart Failure Association of the European Society of Cardiology Cardio-Oncology Study Group in collaboration with the International Cardio-Oncology Society.[44] IQR indicates interquartile range; and NHL, non-Hodgkin lymphoma.

*Doxorubicin.

Ivabradine use was not associated with an increased rate of adverse events. Phosphenes were diagnosed in 3.9% of the patients receiving ivabradine and 1.8% of the patients receiving placebo, whereas bradycardia was diagnosed in 3.9% of the patients receiving ivabradine but in none of the patients receiving placebo (P=0.17). Figure 5 shows the main outcomes of ivabradine treatment in anthracycline-treated patients.

The EuroQol-5 Dimension-3 Level assessment was not different between ivabradine and placebo groups in the baseline (OR, 0.74 [95% CI, 0.61–1.00] versus 0.74 [95% CI, 0.58–0.79]; P=0.63) and 12-month evaluations (OR, 0.74 [95% CI, 0.58–0.79] versus 0.79 [95% CI, 0.61–0.85]; P=0.157).

DISCUSSION

In patients with lymphoma or sarcoma receiving high-dose anthracycline, ivabradine at a fixed dosage of 10 mg/d did not prevent CTRCD. This study, the first randomized triple-blind trial to evaluate ivabradine in this context, demonstrated no significant reduction in the primary outcome of incidence of cardiotoxicity measured as a ≥10% decline in GLS over 12 months or in key secondary outcomes such as LVEF reduction or major clinical complications. Although ivabradine was associated with a reduction in the proportion of patients with elevated cardiac troponin T levels at 6 months, the clinical implications of this finding should be interpreted with caution due to the absence of sustained effects on other cardiac parameters.

In 2006, Cardinale et al[25] reported anthracycline-induced LV dysfunction in patients receiving an average of 335 mg/m^2 doxorubicin, and the LVEF decreased from 62.8% to 48.3% in the placebo group over 12 months. On the other hand, patients receiving enalapril during anthracycline maintained their LVEF and experienced no clinical complications. Those with elevated troponin levels throughout treatment had a more pronounced and persistent decrease in LVEF.

A few clinical trials have since evaluated the effectiveness of β blockers, neurohormonal antagonists, and atorvastatin in preventing anthracycline-related cardiovascular dysfunction.[6–8,26–35] In most studies, neither a high prevalence of cardiovascular dysfunction nor benefits of pharmacological interventions were observed. Earlier trials with lower anthracycline doses, such as PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) and CECCY (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity), did not demonstrate protective effects of metoprolol and carvedilol against cardiotoxicity.[26,36]

The IPAC trial investigated the potential of ivabradine to mitigate GLS decline in patients receiving high doses of anthracyclines. The prevalence of mild CTRCD, characterized by significant reductions in GLS without overt systolic dysfunction, was notably high in our study population. Nearly half of the patients in both the ivabradine and placebo groups experienced this decline, which underscores the subclinical but prevalent nature of cardiac injury in patients treated with anthracyclines. This finding aligns with previous literature suggesting that CTRCD often manifests as early myocardial strain abnormalities before measurable declines in LVEF occur.[14,23] Recognizing these early changes is critical for timely intervention to mitigate

Table 2. Outcomes of the Study

Variable	Ivabradine (n=51)	Placebo (n=56)	*P* value	OR (95% CI)
Primary outcome, n (%)				
GLS reduction ≥10% at 12 mo from baseline	29 (57)	28 (50)	0.47§	1.32 (0.61–2.83)
Secondary outcomes, n (%)				
GLS reduction ≥10% at 6 mo	21 (41.2)	21 (37.5)	0.70§	1.17 (0.54–2.54)
Composite outcome at 12 mo	6 (11.8)	10 (17.9)	0.37§	0.61 (0.21–1.83)
Myocardial infarction	1 (2.0)	0 (0)	0.47¶	…
Symptomatic CTRCD	1 (2.0)	3 (5.4)	0.62¶	0.35 (0.04–3.51)
Arrhythmias	0 (0)	0 (0)	…	…
Death*	5 (9.8)	7 (12.5)	0.65§	0.76 (0.23–2.57)
LVEF (%), Simpson (reduction ≥10%) and LVEF <55% at 12 mo	3 (5.9)	4 (7.1)	1.00‖	0.81 (0.17–3.82)
LVEF (%), Simpson			0.70#	
0	62.2±4.3	61.35±4.36	0.44**	
3 mo	61.73±3.64	60.32±6.24		0.24‡‡
6 mo	60.30±4.36	59.53±4.73		0.008‡‡
12 mo	60.23±4.21	60.65±5.74		0.06‡‡
Diastolic dysfunction				
0	4 (7.8)	4 (7.1)	1.00¶	1.11 (0.26–4.67)
12 mo	41 (82.0)	46 (82.1)	0.57§	0.73 (0.24–2.20)
P (0×12 mo)	0.102‡	0.059‡		
NT-proBNP, pg/dL, median (IQR)				
0	109 (52–240)	101 (51–251)	0.87††	
3 mo	68 (39–180)	53 (27–236)	0.43††	
6 mo	99 (41–218)	108 (34–231)	0.83††	
12 mo	122 (48–164)	89 (43–166)	0.56††	
0×3 mo	0.364‡	0.042‡		
0×6 mo	0.886‡	0.449‡		
0×12 mo	0.388‡	0.234‡		
Troponin T, ng/L, median (IQR)				
0	7 (5–12)	6 (3–10)	0.07††	
3 mo	11 (7–17)	10 (7–15)	0.38††	
6 mo	12 (9–20)	20 (10–31)	0.22††	
12 mo	8 (5–12)	6 (5–11)	0.50††	
0×3 mo	<0.001‡	<0.001‡		
0×6 mo	<0.001‡	<0.001‡		
0×12 mo	<0.696‡	<0.094‡		
Troponin T ≥14 ng/L				
0	5 (10.0)	7 (13.5)	0.58‡	0.76 (0.23–2.57)
3 mo	17 (37.8)	15 (31.9)	0.55‡	1.30 (0.55–3.06)
6 mo	16 (39.0)	23 (62.2)	0.041‡	0.39 (0.16–0.97)
12 mo	2 (6.5)	3 (9.7)	1.00¶	0.64 (0.10–4.15)
Increase of biomarkers†				
NT-proBNP	35 (72.9)	33 (64.7)	0.38‡	1.46 (0.62–3.46)
Troponin T	42 (85.7)	43 (82.7)	0.68‡	1.26 (0.43–3.68)

CTCRD indicates cancer therapy–related cardiovascular dysfunction; GLS, global longitudinal strain; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and OR, odds ratio.

*All-cause deaths.

†Significant increase of biomarkers was diagnosed if there was a ≥20% increase from baseline, or NT-proBNP level>125 pg/mL, or a troponin T level≥14 ng/L.

‡Wilcoxon signed-rank test. Analysis of variance for repeated measures.

§Pearson's χ^2 test.

‖Likelihood ratio test.

¶Fisher's exact test.

#Interaction group×time.

**Comparison between groups (at all times).

††Mann–Whitney test.

‡‡Comparison with baseline (0).

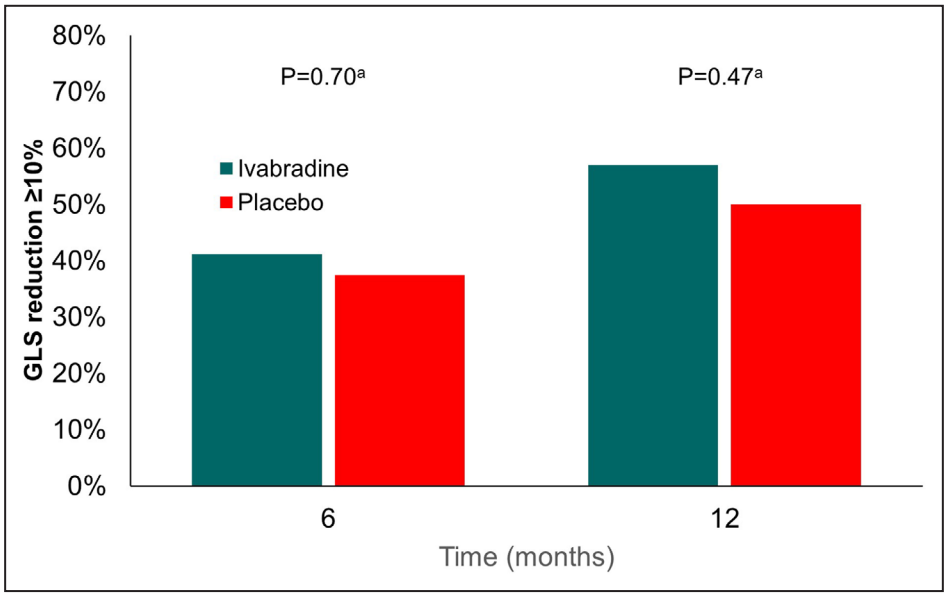

Figure 3. Global longitudinal strain of the left ventricle during the study.
GLS at 3, 6, and 12 months after randomization in comparison with baseline. GLS indicates global longitudinal strain. a. Pearson's chi-square test.

progression to symptomatic heart failure. We excluded patients with breast cancer due to the confounding effect of adjuvant therapies, such as HER2-targeted treatments, which are known to have cardiotoxic effects and might complicate the interpretation of results specific to anthracycline-related cardiotoxicity. In addition, we planned to include only patients receiving high-dose anthracycline, such as patients with lymphoma and sarcoma.

The hypothesis was that ivabradine would prevent anthracycline cardiotoxicity by reducing the HR and inducing antioxidant and antiapoptotic effects. However, ivabradine did not prevent cardiotoxicity, which was defined as a decline in GLS after 6 months. In a pilot study published in 2022 with patients with preserved LVEF and HR ≥75 bpm, ivabradine did not alter the diastolic function or B-type natriuretic peptide levels but significantly improved the GLS.[37]

The association between GLS and HR has been previously reported. Peverill et al[38] showed that GLS in patients with preserved LVEF was independently and inversely related to HR, and Kraigher-Krainer et al[39] demonstrated that worse GLS values were directly associated with higher HRs in patients with preserved LVEF. This informed the study's primary end point choice on the basis of the mechanism of action of ivabradine. These findings also provide a theoretical foundation for using ivabradine, which selectively reduces HR, as a strategy to mitigate GLS decline related to anthracycline.

Over 12 months of follow-up, patients who received anthracycline had a significant reduction in HR, but ivabradine did not increase this reduction in HR. This finding may have been due to the fixed dose of 5 mg twice daily in this study, without any titration to higher doses. Another possibility is that inhibitors and inducers of cytochrome P450 3A4 may interact with ivabradine hydrochloride in patients with cancer, potentially influencing the metabolism and pharmacokinetics of this drug to a clinically significant extent. We ensured reliable adherence in our study, as evidenced by the meticulous pill counting conducted at each visit. Thus, in this trial, we did not observe the expected reduction in HR with ivabradine, which might explain the neutral effects of the drug on anthracycline cardiotoxicity.

In the BEAUTIFUL (Ivabradine for Patients With Stable Coronary Artery Disease and Left-Ventricular Systolic Dysfunction) study, ivabradine did not reduce death or hospitalization in patients with stable coronary artery disease and an LVEF <40%. However, a subgroup analysis revealed reduced hospitalizations for myocardial infarction and decreased need for revascularization in patients with a baseline HR of <70 bpm.[40] The SHIFT (Ivabradine and Outcomes in Chronic Heart Failure) study with 6558 patients with HF with an LVEF <35% revealed that ivabradine, titrated up to 7.5 mg twice daily, reduced the HR, leading to fewer hospitalizations and HF-related deaths.[41] In both studies, ivabradine was effective in patients with established systolic dysfunction, indicating the benefits of HR control in such patients. The ineffectiveness of ivabradine in our study might have stemmed from its preventive rather than therapeutic use.

In this study, ivabradine was well tolerated but did not effectively prevent GLS decline, a decreased LVEF, or clinical complications in anthracycline-treated

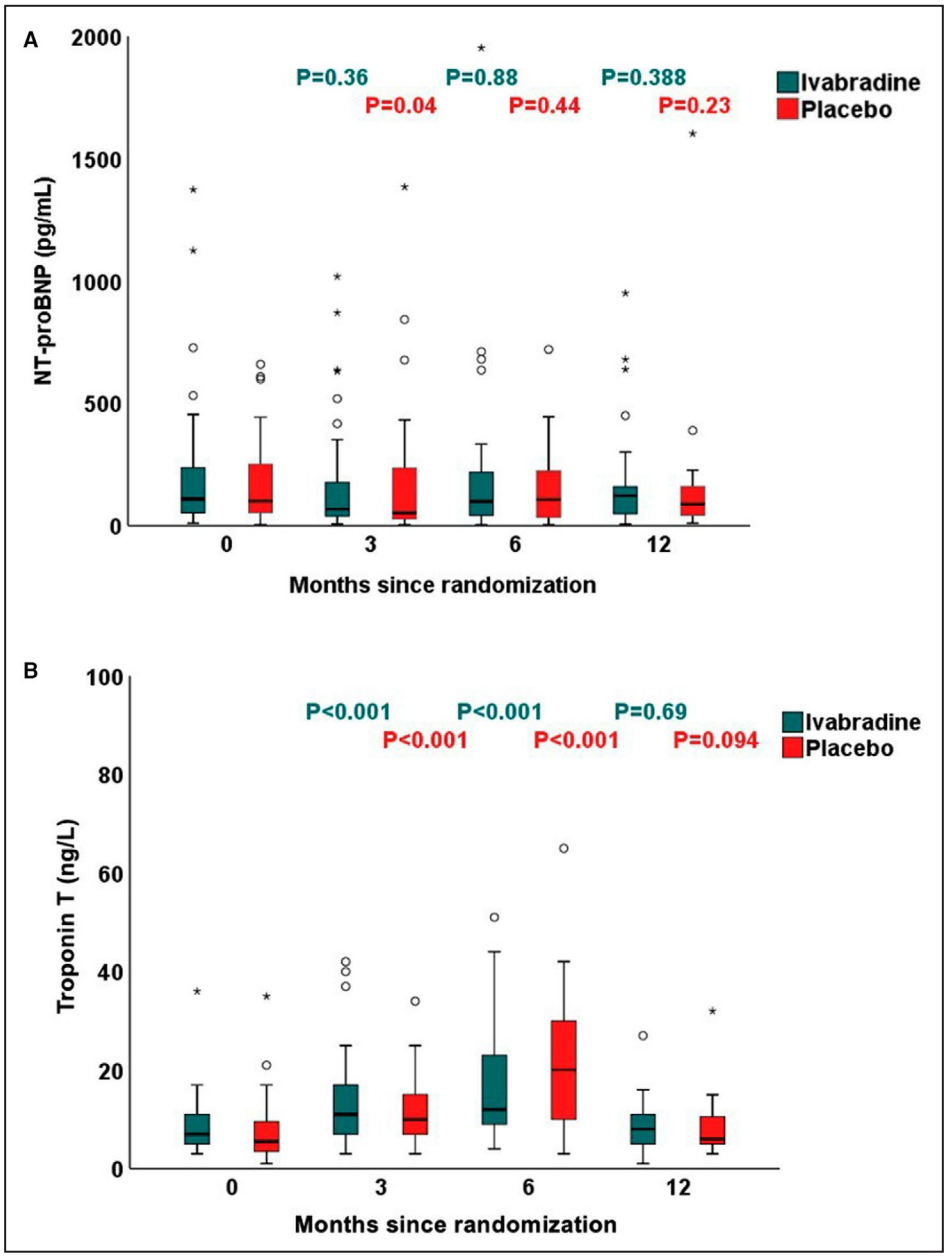

Figure 4. Cardiac biomarkers during the study.
A, NT-proBNP; (**B**) troponin T. *P*: Wilcoxon signed-rank test (comparison within groups at the baseline value). NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

patients, likely because of insufficient HR reduction. In 2023, Neilan et al[8] published the STOP-CA (Atorvastatin for Anthracycline-Associated Cardiac Dysfunction) trial, which evaluated the efficacy of atorvastatin in preventing a decrease in LVEF in lymphoma patients. Over 12 months, a >10% decrease in LVEF to <55% was detected in 22% of the patients receiving placebo, whereas a 9% decrease in LVEF was detected in the atorvastatin-treated group. The protective effect of ivabradine in vitro may be related to its anti-inflammatory, antioxidative, and antiapoptotic mechanisms. In the IPAC trial, while there was no significant reduction in the LVEF or decrease in the GLS, lower troponin release suggested that ivabradine may reduce myocardial injury (as indicated by troponin levels) but might not effectively prevent LV systolic dysfunction in patients with cancer.

The systolic blood pressure trend at 12 months showed a modest increase in both groups, with a more notable change in the ivabradine group. However, the difference between groups did not reach statistical significance. This increase may suggest a hemodynamic adaptation, particularly in the context of the study population undergoing anthracycline therapy and

Table 3. Hemodynamic Parameters of the Patients

Variable	Ivabradine (n=51)	Placebo (n=56)	*P* value
Systolic blood pressure, mm Hg			0.522*
0	114.54±29.84	120.33±17.20	0.163†
3 mo	114.17±23.79	121.37±16.50	0.91‡
6 mo	120.00±16.59	121.60±17.37	0.17‡
12 months	121.34±14.34	123.42±14.69	0.05‡
Diastolic blood pressure, mm Hg			0.311*
0	75.66±11.41	75.51±9.04	0.143†
3 mo	72.46±11.02	75.65±10.13	0.25‡
6 mo	74.22±8.26	78.67±10.37	0.47‡
12 mo	76.66±7.82	78.26±8.94	0.11‡
HR, bpm			0.212*
0	89.93±16.4	93.63±19.46	0.152†
3 mo	80.20±13.41	87.05±14.46	<0.001‡
6 mo	80.37±14.27	84.70±15.52	<0.001‡
12 mo	81.68±16.83	81.12±13.5	<0.001‡
Holter parameters			
Minimum HR, bpm			
0	57.18±11.35	61.21±13.23	0.36§
6 mo	53.80±5.98	55.67±8.85	0.11‖
Maximum HR, bpm			
0	135.48±20.01	135.76±21.79	0.90§
6 mo	133.20±20.16	134.00±22.24	0.89‖
Mean HR, bpm			
0	85.61±13.91	94.33±21.96	0.64‖
6 mo	82.09±15.08	88.48±22.09	0.07‖

HR indicates heart rate. Analysis of variance for repeated measures.
*Interaction group×time.
†Comparison between groups.
‡Comparison with baseline.
§Friedman test.
‖Mann–Whitney test.

potentially recovering from treatment-related impacts on vascular tone.

The findings of El-Naggar et al[42] provide valuable insights into the potential cardioprotective mechanisms of ivabradine. In their experimental models, ivabradine was shown to reduce baroreflex-mediated bradycardia, normalize reflex tachycardia, and preserve myocardial structure, underscoring the role of HR modulation in its protective effects. In our study, however, patients treated with anthracyclines experienced a natural reduction in HR over time, regardless of whether they received ivabradine or placebo. This lack of significant anthracycline-induced tachycardia may have attenuated the potential HR-dependent benefits of ivabradine, such as the attenuation of myocardial injury and strain. These observations suggest that future studies should consider enrolling patients with elevated baseline HR or documented anthracycline-induced tachycardia to better evaluate the efficacy of ivabradine in such contexts. By targeting populations more likely to exhibit HR-related cardiotoxicity, future trials may better elucidate ivabradine's potential benefits.

The transient reduction in troponin levels observed at 6 months suggests a potential early myocardial protective effect of ivabradine, likely attributable to its anti-inflammatory and antioxidant properties. However, this effect was not sustained at 12 months, potentially due to compensatory physiological mechanisms or progressive anthracycline-induced cardiac damage exceeding the protective threshold of ivabradine. By 6 months, patients may have reached a cumulative anthracycline dose sufficient to induce myocardial stress, while still below the level for irreversible injury, explaining the observed reduction in troponin levels. At 12 months, the cumulative dose and chronic oxidative stress likely outweighed ivabradine's protective effects. Additionally, the fixed 10 mg/d dose, without titration to individual HR or myocardial stress markers, may have been insufficient for long-term protection. In an open-label trial, Čiburienė et al[43] demonstrated no significant echocardiographic benefit of ivabradine but observed a reduction in troponin I levels and improvements in global constructive work and global work index at 6 months. These findings align partially with our observation of reduced troponin T levels at 6 months, suggesting a potential protective effect of ivabradine on myocardial injury markers, albeit without sustained echocardiographic benefits.

Our investigation has limitations. First, owing to its single-center design, it may not represent all patient demographics, despite being the first triple-blind study to test ivabradine for cardiotoxicity. The study population, classified as low to moderate risk according to the Heart Failure Association guidelines, might have influenced the observed outcomes, potentially limiting the ability to detect significant benefits of the intervention in higher-risk patients. Second, the fixed ivabradine dose of 10 mg/d was not titrated, resulting in a failure to reduce the patient HR. This limitation could have hindered the ability to assess the effectiveness of ivabradine accurately in this study. Future studies should carefully consider patient selection, focusing on individuals with elevated baseline HR or documented anthracycline-induced tachycardia, to better evaluate the efficacy of HR-dependent cardioprotective interventions like ivabradine.

Third, we conducted a 12-month follow-up analysis of patients to assess clinical outcomes, enabling the detection of differences between groups in later stages of the follow-up period. The fourth limitation of our study is the focus on GLS reduction as the primary outcome, without incorporating symptomatic CTRCD into the analysis. Including symptomatic CTRCD in future studies would provide a more comprehensive evaluation of clinical outcomes. We acknowledge this

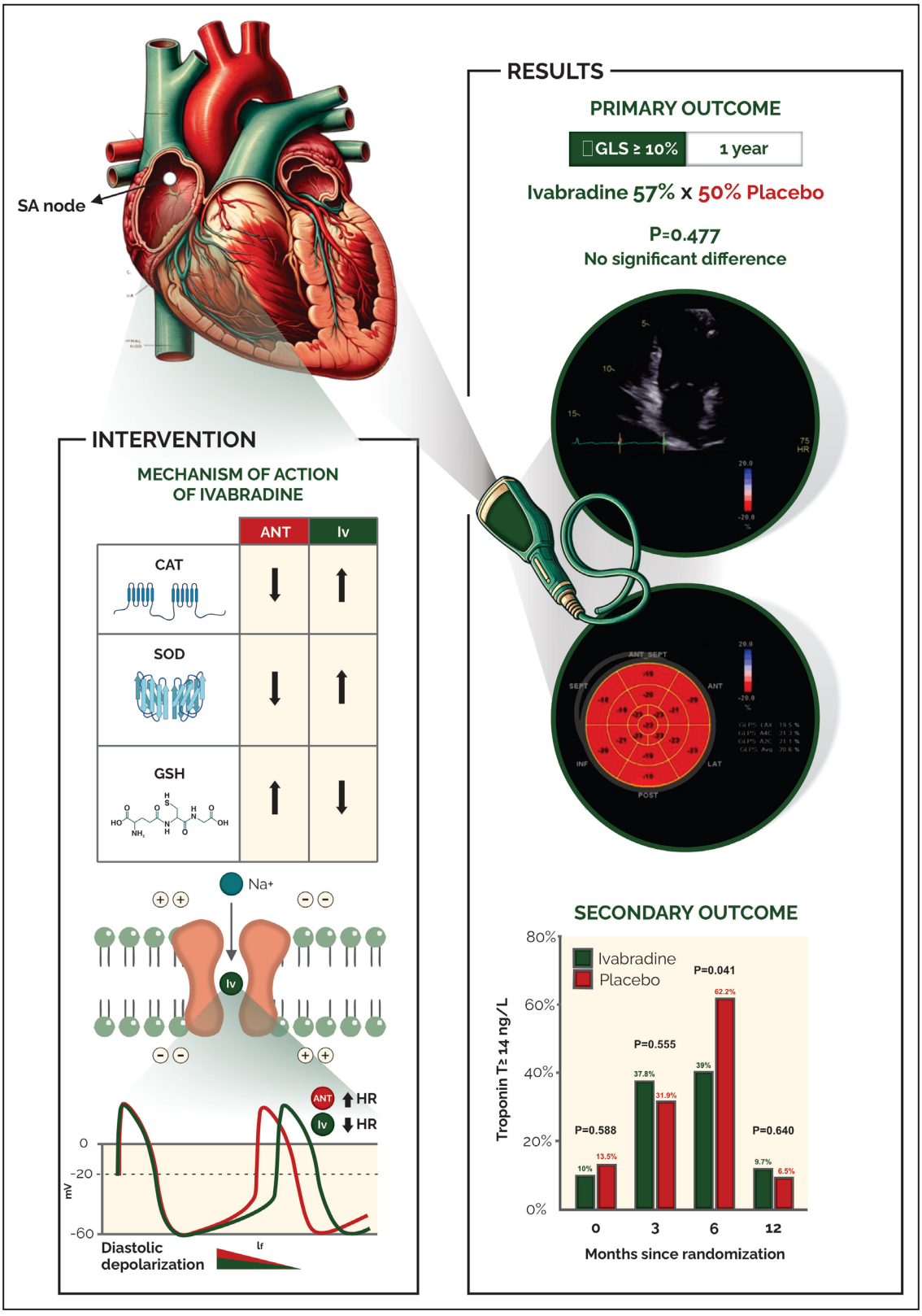

Figure 5. Ivabradine treatment to prevent anthracycline-induced cardiotoxicity.
The diagram provides a schematic representation of the mechanism of action of ivabradine at the cellular level. Ivabradine treatment in patients with lymphoma or sarcoma treated with anthracycline did not prevent the decline in global longitudinal strain at 12 months. ANT indicates anthracycline; CAT, catalase; GLS, global longitudinal strain; GSH, glutathione; HR, heart rate; If, funny current; Iv, ivabradine; SA, sinoatrial; and SOD, superoxide dismutase.

as a limitation and propose it as a key area for future research. Novel studies should further explore the mechanistic relationship between HR modulation and GLS in cardiotoxicity, particularly in the context of targeted interventions like ivabradine. The fifth limitation of our study was the assessment of diastolic dysfunction in only 2 time points (baseline and 12-month). This restricted the ability to capture transient or subclinical changes in diastolic function, which may have provided additional insights into the early cardiac effects of anthracycline-induced cardiotoxicity.

Finally, one of the primary limitations of this trial pertains to its power. The sample size was calculated on the basis of an anticipated incidence of cardiotoxicity of 50% with the use of anthracycline and an optimistic expectation of reducing this incidence to 25% with the introduction of ivabradine. Previous studies evaluating cardioprotective agents, such as β blockers, angiotensin-converting enzyme inhibitors, and statins, have demonstrated varying degrees of reduction in cardiotoxicity, ranging from 15% to 35% depending on the population and methodology. While this expectation underpinned the trial design, it inherently limited the ability to detect more modest effects of ivabradine in this study.

Our results highlight the utility of GLS and cardiac troponin T monitoring for the early detection of CTRCD. GLS, a sensitive echocardiographic parameter for subclinical myocardial dysfunction, showed significant reductions over the study period in both treatment arms. This finding reinforces the importance of myocardial strain imaging as recommended in the 2022 European Society of Cardiology guidelines for cardio-oncology.[2] Similarly, elevated cardiac troponin T levels, observed in a significant proportion of patients at various time points, further underscore the utility of biomarkers as adjuncts to imaging in the comprehensive assessment of CTRCD risk.

In conclusion, ivabradine at a fixed 10-mg/d dose, did not have a definitive protective effect against cardiotoxicity in patients with cancer receiving anthracycline therapy as initially hypothesized. However, intriguing observations regarding the potential of ivabradine to reduce myocardial injury by reducing troponin levels might be explored in future trials.

ARTICLE INFORMATION

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Disclosures

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