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ORIGINAL RESEARCH

Prognosis After Withdrawal of Cardioprotective Therapy in Patients With Improved Cancer Therapeutics–Related Cardiac Dysfunction

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ABSTRACT

BACKGROUND The long-term prognosis after the discontinuation of cardioprotective therapy (CPT) in patients with cancer therapeutics-related cardiac dysfunction (CTRCD) that has shown improvement remains unclear.

OBJECTIVES This study aims to assess the prognosis after CPT withdrawal in patients exhibiting improved CTRCD.

METHODS In this retrospective analysis of a single-center prospective cohort study, patients with improved CTRCD, defined as an increase in left ventricular ejection fraction (LVEF) ≥10 percentage points from the time of CTRCD diagnosis, were included. We analyzed their clinical outcomes, which included hospitalization for heart failure or a decrease in LVEF ≥10 percentage points within 2 years after CTRCD improvement, alongside echocardiographic changes.

RESULTS The cohort comprised 134 patients with improved CTRCD. The median follow-up duration after CTRCD diagnosis was 368.3 days (Q1-Q3: 160-536 days). After improvement, 90 patients continued CPT (continued group [CG]) and 44 withdrew CPT (withdrawn group [WG]). Among patients whose baseline LVEF at CTRCD diagnosis ranged from 45% to 55%, the final mean LVEF was comparable between both groups (CG: 64.9% ± 4.4% vs WG: 62.9% ± 4.2%; $P = 0.059$). However, for patients with a baseline LVEF <45%, the final mean LVEF was significantly lower in the WG (CG: 53.3% ± 6.4% vs WG: 48.2% ± 6.9%; $P < 0.001$). The occurrence of composite major clinical events was notably higher in the WG (HR: 3.06; 95% CI: 1.51-7.73; $P = 0.002$).

CONCLUSIONS Patients who withdrew CPT after demonstrating improvement in CTRCD experienced worse clinical outcomes. Notably, a significant decrease in LVEF was observed after CPT withdrawal in patients with a baseline LVEF <45%. (JACC CardioOncol. 2024;6:699-710) © 2024 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CG = control group

CPT = cardioprotective therapy

CTRCD = cancer therapeutics-related cardiac dysfunction

DCM = dilated cardiomyopathy

GLS = global longitudinal strain

HER2 = human epidermal growth factor 2

HF = heart failure

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

WG = withdrawn group

The prevalence of cancer is on the rise, alongside significant advancements in oncologic treatments that have improved mortality rates. As a result, there has been a steady increase in both the number of cancer survivors and the incidence of cardiovascular toxicities related to cancer therapeutics.[1,2] Cancer therapeutics-related cardiac dysfunction (CTRCD) is a manifestation of such cardiovascular toxicities, characterized by heart failure (HF), a decrease in left ventricular (LV) systolic function, and an increase in cardiac biomarkers after cancer treatment. Notably, treatments involving anthracyclines or trastuzumab have been associated with reductions in left ventricular ejection fraction (LVEF) by more than 10% in 10% to 20% of patients.[3,4] CTRCD and subsequent HF may necessitate the discontinuation of anticancer therapies, leading to poor oncologic outcomes.[5] Additionally, among cancer survivors, CTRCD and HF not only diminish quality of life but also increase the risk of major adverse cardiac events.[6-8]

Early identification of CTRCD and initiation of cardioprotective therapy (CPT) are associated with better cardiac function recovery and fewer adverse cardiac events.[9] However, little is known about the optimal strategies for secondary prevention and long-term management of CTRCD. Recent evidence suggests that continuing CPT even after recovery from dilated cardiomyopathy (DCM) is crucial to prevent reductions in LVEF or increases in left ventricular end-diastolic volume (LVEDV).[10] Yet, whether CPT should be continued after the recovery of LV function in CTRCD patients is still unclear. Because of the potential for long-term CPT to significantly raise health care costs, identifying patients who could safely discontinue CPT after effective treatment is of great importance. Consequently, this study aimed to investigate the outcomes after withdrawal of CPT in patients who have shown improvement in CTRCD.

METHODS

ETHICAL APPROVAL. The study protocol received approval from the Institutional Review Board of Chonnam National University Hwasun Hospital in Hwasun, Jeollanam-do, Republic of Korea (Institutional Review Board no. CNUHH-2015-05-092). Conducted in accordance with the Declaration of Helsinki (2013), all participants provided informed consent before inclusion.

STUDY DESIGN AND POPULATION. This prospective cohort study was conducted at Chonnam National University Hwasun Hospital, a tertiary care center specializing in cancer located in Hwasun, Jeollanam-do, Republic of Korea. From March 2015 to April 2022, we identified a total of 277 patients newly diagnosed with CTRCD. Of these, 134 cancer patients with improved LV systolic function were included for analysis (Supplemental Figure 1).

CTRCD was defined as a significant decrease in LVEF after the use of at least 1 cardiotoxic cancer therapeutic agent in the absence of significant coronary artery disease (CAD) as evidenced by coronary imaging. A significant decrease in LVEF was quantified as a reduction of more than 10 percentage points from baseline to an absolute value below 55%. This study did not use changes in LV global longitudinal strain (GLS) values or cardiac biomarkers to define CTRCD. Improvement in CTRCD was specified as an increase in LVEF of at least 10 percentage points from the time of CTRCD diagnosis.

This study included patients exposed to cardiotoxic cancer therapeutic agents such as anthracyclines, human epidermal growth factor 2 (HER2)-targeted therapy, proteasome inhibitors, or vascular endothelial growth factor inhibitors. The cumulative dose of anthracycline was calculated based on the anthracycline equivalence dose, adhering to the cardiovascular toxicity dose ratios recommended by the current European Society of Cardiology guidelines on cardio-oncology.[11] According to the guidelines, doxorubicin was used as a reference drug with a cardiotoxicity dose ratio of 1. The cardiotoxicity dose ratios for other anthracyclines were as follows: epirubicin at 0.8, daunorubicin at 0.6, mitoxantrone at 10.5, and idarubicin at 5.

This study used myocardial single-photon emission computed tomography, computed tomography coronary angiography, or coronary angiography to determine the presence of significant CAD. Significant CAD was defined on single-photon emission computed tomography as perfusion abnormalities indicative of significant CAD, as interpreted by an experienced nuclear medicine physician. In computed tomography coronary angiography or angiography, significant CAD was identified by the presence of more than 50% stenosis of the left main coronary artery or more than 70% stenosis in other coronary arteries. All patients underwent at least 1 of these examinations before confirmatory diagnosis of CTRCD.

The management of each CTRCD patient was left to the discretion of the attending cardio-oncologist, who administered CPT in accordance with the current HF

guidelines. After observing improvements in CTRCD, 44 patients withdrew or reduced their CPT dosage because of various reasons, including patient preference, intolerance to CPT such as symptomatic hypotension, or the attending physician's judgment. For analysis, the population was divided into 2 groups: patients who continued CPT (continued group [CG]) and those who withdrew or downtitrated CPT (withdrawn group [WG]) based on CPT maintenance status after CTRCD improvement.

ECHOCARDIOGRAPHY. Echocardiographic examination was conducted in the left lateral decubitus position using 3 digital echocardiographic systems (1 Vivid E9 and 2 Vivid E95, GE Healthcare). These examinations were performed by 3 experienced sonographers and 2 cardiologists. Images were acquired and interpreted in accordance with the current guidelines and diagnostic criteria by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[12] Both digital cine images and still images were captured and stored in raw format for subsequent off-line analysis. Echocardiography was performed quarterly for the first 6 months after CTRCD diagnosis and subsequently every 6 months for up to 5 years.

LVEDV and left ventricular end-systolic volume were measured from apical 4- and 2-chamber views, whereas LVEF was calculated using the modified biplane Simpson's method in all cases. Left atrial volume was measured at the end-systole using Simpson's method in both apical 4- and 2-chamber views.[13,14] LV peak longitudinal strain was assessed using a 2-dimensional speckle tracking method facilitated by EchoPAC software (GE Medical Systems). For strain analysis, the LV endocardial border was manually defined, and the region of interest width was adjusted to match the LV wall thickness, a process overseen by 2 cardiologists. The left ventricle was then divided into 6 segments, and their longitudinal movements throughout a cardiac cycle were tracked in apical 3-, 4-, and 2-chamber views. The average LV peak longitudinal strain values from these 3 views were used to calculate the GLS.

STUDY OUTCOMES. Clinical characteristics such as demographics, medical history, and cancer types were obtained from patient medical records. The primary endpoint was defined as the occurrence of major clinical events, a composite of hospitalization for HF or a decrease in LVEF by ≥10 percentage points within 2 years after CTRCD improvement. The power calculations indicated that the sample size was sufficient to detect a statistically significant difference in the primary endpoint, with 80% power at a 5% significance level, assuming incidence rates of 27% in the WG and 5% in the CG.

Two cardiologists, completely independent from the conception, design, patient enrollment, and data handling of this study, reviewed hospitalization records for each patient. Hospitalization for HF was defined based on a review of electronic medical records, which included the patient's symptoms, clinical signs, vital signs, 12-lead electrocardiography, laboratory findings, chest x-ray, and echocardiography (if available) at the time of hospitalization. The cardiologists were blinded to other patient data, and their decisions were made in accordance with current HF guidelines. Changes in LVEF or LV GLS after CTRCD improvement based on CPT maintenance status were analyzed. Subgroup analysis was performed based on the baseline LVEF at the time of CTRCD diagnosis and anthracycline use.

STATISTICAL ANALYSIS. Categoric variables are reported as numbers and percentages compared using the chi-square test or the Fisher exact test. Continuous variables are described as mean ± SD for normally distributed data or median value with 25th and 75th percentiles (Q1-Q3) for non-normally distributed data. The Shapiro-Wilk test determined the distribution of the data. Continuous variables were compared using an independent samples Student's *t*-test.

We hypothesized that the effects of CPT continuation or withdrawal on the serial changes in LVEF and LV GLS might vary according to baseline LVEF groups (45%-55% vs <45% and 40%-55% vs <40%) at the time of CTRCD diagnosis. To test the significance of the interaction, a linear mixed model analysis incorporating a 3-way interaction term (CPT continuation/withdrawal, timing of echocardiography, and baseline LVEF group) was conducted. The analysis evaluated changes over time within each group, focusing initially on overall trends and then on differences observed during the improved phase and the final follow-up, with adjustments made for LVEF and LV GLS at the time of CTRCD diagnosis.

Results are presented as least squares mean 95% CIs. Analysis used a first-order autoregressive covariance matrix and a restricted maximum likelihood estimation method. The Kenward-Roger approximation was set as the denominator df. A 2-sided *P* value of <0.05 was considered statistically significant.

To determine the association between CPT withdrawal and major clinical events, we used Kaplan-Meier methods to visualize and compare time-dependent data using the log-rank test. Cox proportional hazards models identified factors

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TABLE 1 Baseline Characteristics

	CG (n = 90)	WG (n = 44)	*P* Value
Demographics			
Age, y	55.3 ± 16.3	52.3 ± 14.8	0.29
Male	17 (18.9)	8 (18.2)	0.92
BMI, kg/m^2	22.4 ± 3.9	21.8 ± 3.8	0.34
Previous cardiovascular history			
Hypertension	43 (47.8)	18 (40.9)	0.45
Diabetes mellitus	19 (21.1)	16 (36.4)	0.059
Dyslipidemia	38 (42.2)	13 (29.5)	0.16
Smoking	9 (10.0)	6 (13.6)	0.57
CPT			
ACEI/ARB	63 (70.0)	33 (75.0)	0.55
ARNI	18 (20.0)	7 (15.9)	0.57
BB	77 (85.6)	36 (81.8)	0.58
MRA	36 (40.0)	13 (29.5)	0.24
Ivabradine	9 (10.0)	4 (9.1)	>0.99
Statin	34 (37.8)	13 (29.5)	0.35
SGLT2i	6 (6.7)	6 (13.6)	0.21
Type of primary cancer			0.53
Breast cancer	67 (74.4)	29 (65.9)	
Malignant lymphoma	11 (12.2)	6 (13.6)	
Multiple myeloma	5 (5.6)	3 (6.8)	
Gastric cancer	1 (1.1)	3 (6.8)	
Acute leukemia	3 (3.3)	2 (4.5)	
Renal cell carcinoma	1 (1.1)	1 (2.3)	
Sarcoma	2 (2.2)	0 (0.0)	
Anticancer therapy			
Administration of anthracycline	49 (54.4)	19 (43.2)	0.22
Cumulative dose of anthracycline, mg/m^2, doxorubicin equivalent	239.2 ± 89.5	280.5 ± 142.0	0.15
HER2-targeted therapy	49 (54.4)	27 (61.4)	0.49
Trastuzumab	38 (42.2)	24 (54.5)	0.18
Trastuzumab + pertuzumab	24 (26.7)	12 (27.3)	0.94
T-DM1	8 (8.9)	10 (22.7)	0.027
VEGF inhibitors	1 (1.1)	1 (2.3)	0.55
Proteasome inhibitors	5 (5.6)	3 (6.8)	0.72
Radiation therapy to the chest	46 (51.1)	21 (47.7)	0.71
Total chest irradiation dose, cGy	4,998.7 ± 661.7	5,243.8 ± 646.6	0.16

Values are mean ± SD or n (%). *P* values are from independent samples Student's *t*-test or the chi-square or Fisher exact test. Before CTRCD diagnosis, some patients were on medications for other indications; ACEIs/ARBs were used by 13 CG patients and 5 WG patients, BBs by CG 5 patients, statins by 26 CG patients and 11 WG patients, and SGLT2is by 2 WG patients. At least 1 CPT medication was taken by 38 CG patients and 15 WG patients, with no significant differences in all variables between the 2 groups.

ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor neprilysin inhibitor; ARB = angiotensin 2 receptor blocker; BB = beta-blocker; BMI = body mass index; CG = continued group; CPT = cardioprotective therapy; HER2 = human epidermal growth factor receptor 2; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium glucose co-transporter 2 inhibitor; T-DM1 = trastuzumab emtansine; VEGF = vascular endothelial growth factor; WG = withdrawn group.

significantly associated with major clinical events. Relevant factors with a *P* value < 0.15 in univariable analysis (including diabetes mellitus, beta-blocker use, statin use, CPT duration without withdrawal, withdrawal of CPT, administration of anthracyclines, and a baseline LVEF <45% or <40%) at CTRCD diagnosis along with clinically significant factors (pre-CTRCD use of ≥1 CPT, radiation therapy to the chest, and LVEF <50% at the improved phase) were entered in the multivariable model. Because of significant multicollinearity (variance inflation factors >10), only 1 of the 2 variables (a baseline LVEF at CTRCD diagnosis <45% or <40%) was selected at a time. Irrelevant factors were removed through a backward selection procedure. The Cox model results are presented as HRs with 95% CIs. The proportional hazards assumption was tested by visual inspection of log-log plots and Schoenfeld residuals. All statistical analyses were performed using SPSS software (version 27.0, IBM Corp).

RESULTS

PATIENT CHARACTERISTICS. Among the 134 patients with improved CTRCD, 90 patients continued CPT (CG), and 44 patients withdrew from CPT for various reasons (WG) (Supplemental Figure 2). In patients with a baseline LVEF ≥45% at CTRCD diagnosis, the primary reason to discontinue CPT was patient preference. Conversely, for those with a baseline LVEF <45%, intolerance to medications was the main reason.

Table 1 shows the baseline characteristics at the time of CTRCD diagnosis, showing general similarity between the 2 groups in demographics, medical history, type of primary cancer, and anticancer therapy. However, the proportion of patients using trastuzumab emtansine was higher in the WG. Breast cancer was the most common primary cancer in both groups.

CPT prescribed from CTRCD diagnosis until improvement of CTRCD is detailed in Table 1. Over 70% of patients received neurohormonal blockade as CPT for CTRCD. After improvement of CTRCD, the same CPT was maintained in the CG, whereas at least 1 CPT was withdrawn or downtitrated in the WG. The median CPT duration without withdrawal after CTRCD improvement was 397.8 days (Q1-Q3: 201-542 days) in the CG and 128.8 days (Q1-Q3: 98-289 days) in the WG.

Anthracyclines were administered to 68 (50.7%) of the patients, with mean cumulative doses of 239.2 ± 89.5 mg/m^2 in the CG and 280.5 ± 142.0 mg/m^2 in the WG, calculated as a doxorubicin equivalent dose. No significant differences were observed in the proportion of patients receiving chest radiation therapy or in the total dose of chest irradiation dose between the 2 groups. The median follow-up duration after CTRCD diagnosis was 368.3 days (Q1-Q3: 160-536 days).

FINDINGS AT THE TIME OF CTRCD DIAGNOSIS. Geometric parameters including LVEDV index and LV end-diastolic dimension were similar in both groups at the time of CTRCD diagnosis (Table 2). The mean

TABLE 2 Baseline Echocardiographic Findings at the Time of CTRCD Diagnosis

	CG (n = 90)	WG (n = 44)	*P* Value
LVEDVI, mL/m^2	59.5 ± 12.6	62.6 ± 13.5	0.11
LVEDD, mm	48.4 ± 7.7	49.2 ± 7.2	0.29
LVEF, %	44.5 ± 8.5	45.5 ± 7.8	0.55
LV GLS, %	−13.3 ± 2.8	−13.6 ± 2.6	0.51
E, cm/s	72.4 ± 11.2	68.2 ± 11.6	0.16
Medial e', cm/s	7.4 ± 1.8	7.6 ± 1.9	0.47
E/e' ratio	9.7 ± 1.4	9.1 ± 1.3	0.26
TR Vmax, m/s	2.7 ± 0.6	2.9 ± 0.6	0.78
LAVI, mL/m^2	33.1 ± 4.5	32.5 ± 4.9	0.26
Moderate or severe VHD	13 (14.4)	4 (9.1)	0.38
Pericardial effusion	3 (3.3)	2 (4.5)	0.66

Values are mean ± SD or n (%). *P* values from independent samples Student's *t*-test or the chi-square or Fisher exact test. The values in the table represent raw values, and they were not derived from a model.

CTRCD = cancer therapeutics-related cardiac dysfunction; E = early diastolic mitral inflow velocity; e' = mitral annular early diastolic velocity; GLS = global longitudinal strain; LAVI = left atrial volume index; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; TR Vmax = maximal velocity of tricuspid regurgitation; VHD = valvular heart disease; other abbreviations as in Table 1.

baseline LVEF was 44.5% ± 8.5% in the CG and 45.5% ± 7.8% in the WG ($P = 0.55$). The mean baseline LV GLS was −13.3% ± 2.8% in the CG and −13.6% ± 2.6% in the WG ($P = 0.51$). Diastolic parameters, such as early diastolic mitral inflow velocity/early diastolic velocity of mitral septal annulus ratio, maximal velocity of tricuspid regurgitation, and left atrial volume index, were also similar in both groups.

CHANGES OF LVEF AND LV GLS. Figures 1 and 2 depict the trajectories of LVEF and LV GLS, respectively. Table 3 details each patient's LVEF or LV GLS at the time of CTRCD diagnosis and at the time of LVEF improvement and the final values during clinical follow-up.

The final mean LVEF was higher in the CG compared with the WG (59.8% ± 7.8% vs 56.5% ± 9.2%, estimated mean effect of CPT withdrawal = −2.12%; 95% CI: −2.90% to −1.34%; $P < 0.001$). The effect of CPT continuation or withdrawal on serial LVEF changes was significantly modified by baseline LVEF groups at the time of CTRCD diagnosis (45%-55% vs <45%; $P < 0.001$).

In patients with a baseline LVEF of 45% to 55%, there were no statistically significant effects between CPT continuation/withdrawal and serial changes in LVEF during the follow-up (final mean LVEF 64.9% ± 4.4% in the CG and 62.9% ± 4.2% in the WG; estimated mean effect of CPT withdrawal = −1.04%; 95% CI: −2.12% to 0.04%; $P = 0.059$). However, in patients with a baseline LVEF <45%, a significant effect was observed, resulting in a lower final mean LVEF in the WG (final mean LVEF 53.3% ± 6.4% in the CG and 48.2% ± 6.9% in the WG; estimated mean effect of CPT withdrawal = −3.50%; 95% CI: −4.52% to −2.47%; $P < 0.001$) (Figure 1).

Dividing the patients using a baseline LVEF threshold <40% vs 40% to 55% did not change the overall trends (Supplemental Figure 3). The final mean LV GLS during clinical follow-up was not significantly different between the CG and the WG. Unlike LVEF, the final mean LV GLS did not show significant differences after subdividing the population according to the baseline LVEF at the time of CTRCD diagnosis (Figure 2, Supplemental Figure 4).

When the population was divided into anthracycline users vs nonusers, the overall longitudinal trends in LVEF or LV GLS changes were consistent with the entire population (Supplemental Figures 5 and 6). Twenty-two patients who received both anthracyclines and HER2-targeted therapy had a similar LVEF during the follow-up period (final mean LVEF 59.0% ± 9.4% in patients with both therapies and 58.6% ± 8.4% in others; $P = 0.28$).

PREDICTORS OF MAJOR CLINICAL EVENTS. Composite major clinical events of hospitalization, comprising HF or a decrease in LVEF ≥10 percentage points after CTRCD improvement, occurred more frequently in the WG within 2 years after CTRCD improvement (HR: 3.06; 95% CI: 1.51-7.73; $P = 0.002$) (Figure 3A). Both hospitalization for HF and a decrease in LVEF ≥10 percentage points were more common in the WG (Figures 3B and 3C). The trajectories of LVEF and LV GLS for patients hospitalized for HF (4 in the CG and 8 in the WG) are illustrated in Supplemental Figure 7.

Table 4 shows the predictors of major clinical events. Multivariable analysis using the Cox proportional hazards model identified the following independent predictors of major clinical events: a medical history of diabetes mellitus, nonuse of a beta-blocker, shorter durations of CPT without withdrawal after CTRCD improvement, withdrawal of CPT, and an anthracycline cumulative dose >240 mg/m^2 (median). A baseline LVEF at CTRCD diagnosis <45% also predicted major clinical events.

When the baseline LVEF at CTRCD diagnosis was set at <40% instead of <45% in the multivariable analysis, the HR for major clinical events was 1.43 (95% CI: 1.03-3.06; $P = 0.025$). CPT types other than beta-blockers or the pre-CTRCD use of ≥1 CPT was not associated with major clinical events.

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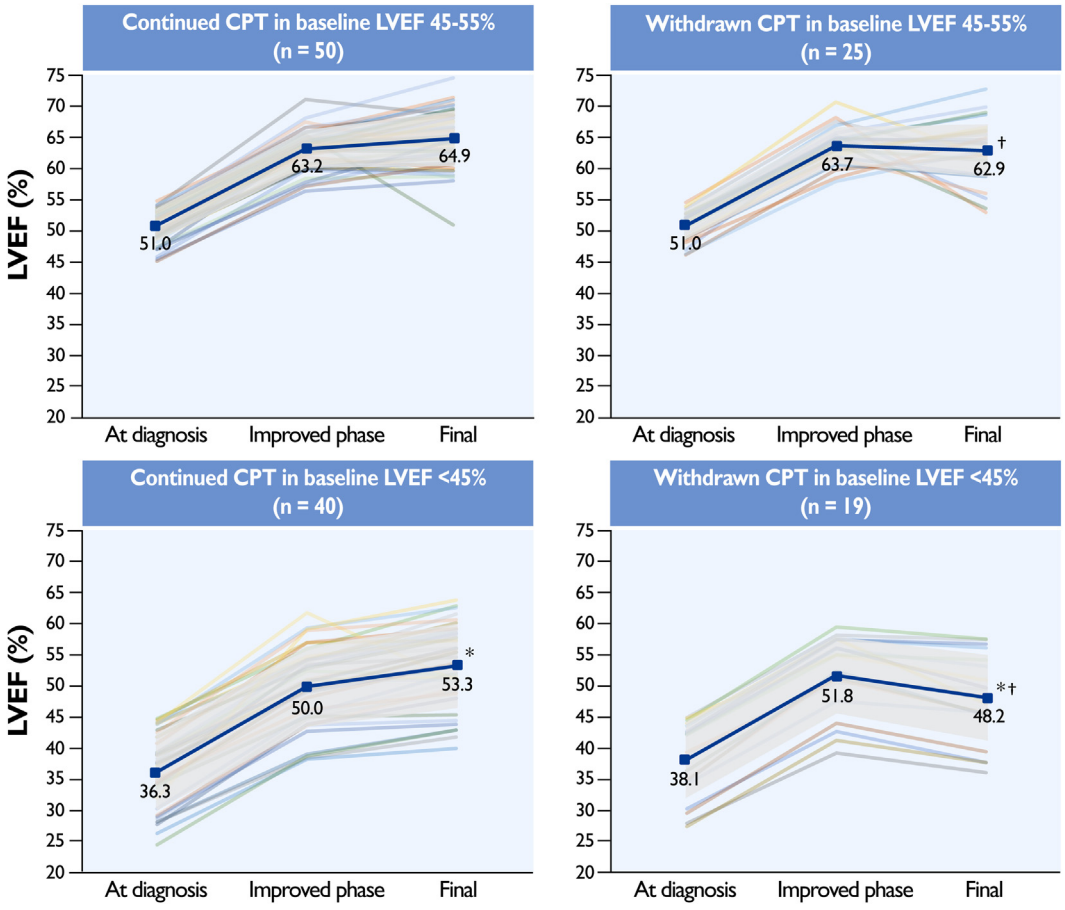
FIGURE 1 Trajectory of LVEF



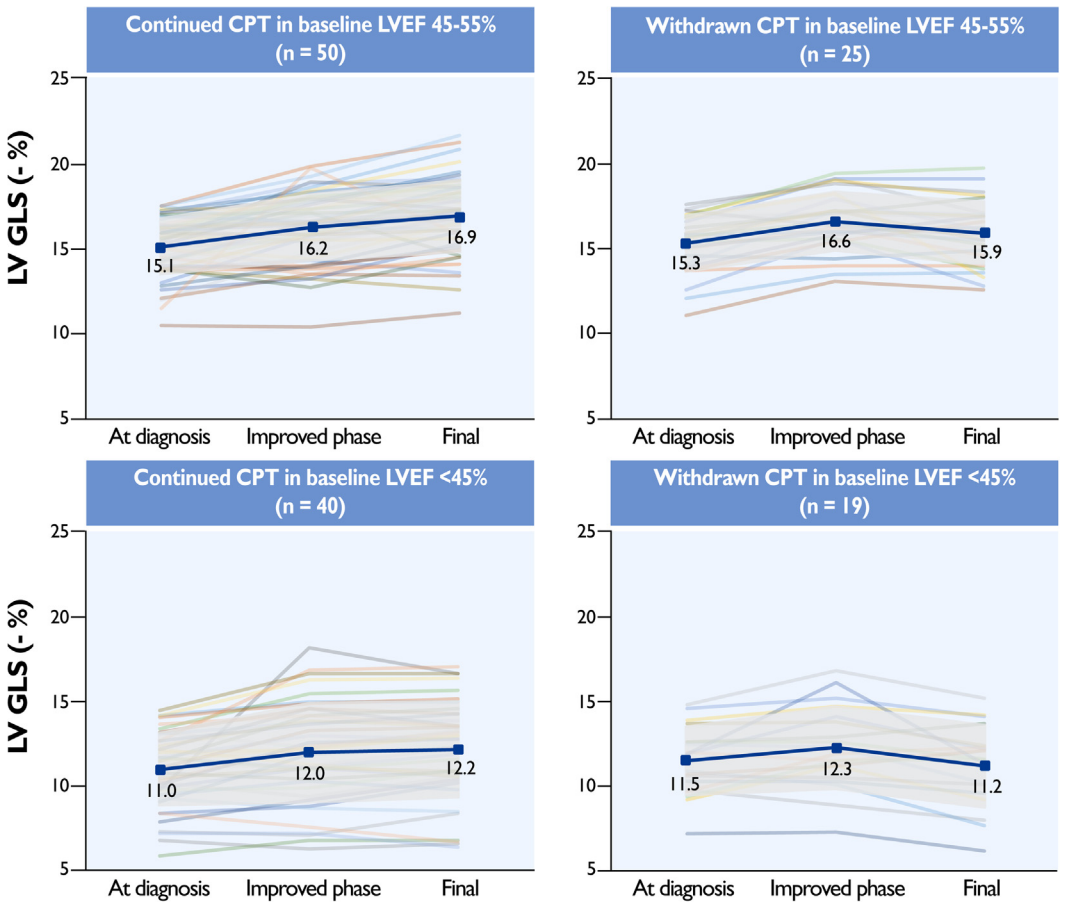
This figure illustrates the changes in left ventricular ejection fraction (LVEF) over time segmented by cardioprotective therapy (CPT) maintenance status and baseline LVEF at the time of cancer therapeutics–related cardiac dysfunction diagnosis. The shaded area represents the 95% CI. Asterisks (*) indicate significant differences in LVEF changes ($P < 0.001$), and the dagger (†) denotes a significant difference ($P = 0.001$).

DISCUSSION

To the best of our knowledge, this is the largest study with the longest follow-up duration to report the impact of CPT withdrawal on clinical outcomes and cardiac functional parameters among cancer patients with recovery of CTRCD. Our findings highlight several clinically important findings. First, patients who withdrew CPT after recovery of CTRCD experienced worse clinical outcomes compared with those who continued therapy. Second, a significant decrease in LVEF was observed among patients with a baseline LVEF <45% at the time of CTRCD diagnosis when CPT was withdrawn after CTRCD improvement. Conversely, patients with a relatively higher baseline LVEF (45%-55%) did not experience a significant reduction in LVEF even after CPT withdrawal (**Central Illustration**).

Little is known about the detailed management strategies of CTRCD. Current cardio-oncology guidelines generally recommend managing cardiovascular disease following established cardiology guidelines.[11] Consequently, the medical management of CTRCD often relies on extrapolation from HF guidelines. However, these guidelines do not specify a duration for maintaining CPT. Reverse remodeling, a biological process that alters cardiac myocyte size and function along with modifications in LV structure and function, does not guarantee myocardial recovery or prevent future HF events.[15] Earlier studies using LV assist devices in advanced HF have shown that, despite successful reverse remodeling, issues such as

FIGURE 2 Trajectory of LV GLS



Depicts the changes in left ventricular (LV) global longitudinal strain (GLS) categorized by the CPT maintenance status and baseline LVEF at the time of cancer therapeutics-related cardiac dysfunction diagnosis. The shaded area indicates the 95% CI. Abbreviations as in Figure 1.

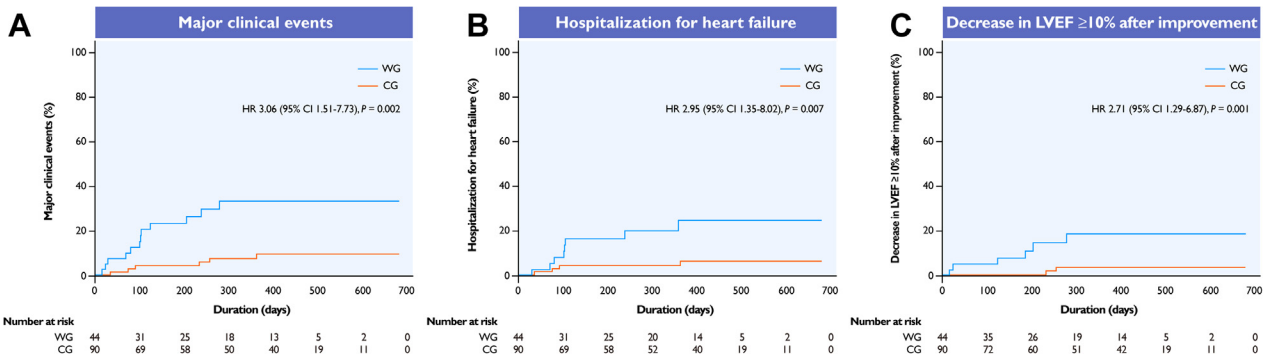
TABLE 3 Changes in LVEF and LV GLS During Clinical Follow-Up

	At CTRCD Diagnosis (Baseline)		Improved Phase		Final	
	CG	WG	CG	WG	CG	WG
LVEF						
All baseline LVEF ranges	44.5 ± 8.5	45.4 ± 7.8	57.3 ± 8.1	58.6 ± 7.5	59.8 ± 7.8[a]	56.5 ± 9.2[a]
Baseline LVEF 45%-55%	51.0 ± 2.6	51.0 ± 2.3	63.2 ± 3.0	63.7 ± 2.9	64.9 ± 4.4	62.9 ± 4.2[b]
Baseline LVEF <45%	36.3 ± 5.9	38.1 ± 6.1	50.0 ± 6.2	51.8 ± 6.2	53.3 ± 6.4[a]	48.2 ± 6.9[a,b]
LV GLS						
All baseline LVEF ranges	13.3 ± 2.8	13.6 ± 2.6	14.3 ± 3.2	14.7 ± 3.0	14.8 ± 3.4	13.9 ± 3.2
Baseline LVEF 45%-55%	15.1 ± 1.7	15.3 ± 1.7	16.2 ± 2.0	16.6 ± 1.8	16.9 ± 2.2	15.9 ± 1.9
Baseline LVEF <45%	11.0 ± 2.2	11.5 ± 2.0	12.0 ± 3.0	12.3 ± 2.4	12.2 ± 2.9	11.2 ± 2.4
Number of patients						
All baseline LVEF ranges	90	44				
Baseline LVEF 45%-55%	50	25				
Baseline LVEF <45%	40	19				

Values are mean ± SD. [a]$P < 0.001$ from linear mixed model. [b]$P = 0.001$ from linear mixed model. The values in the table represent raw values, and they were not derived from a model.

Abbreviations as in Tables 1 and 2.

FIGURE 3 Major Clinical Outcomes



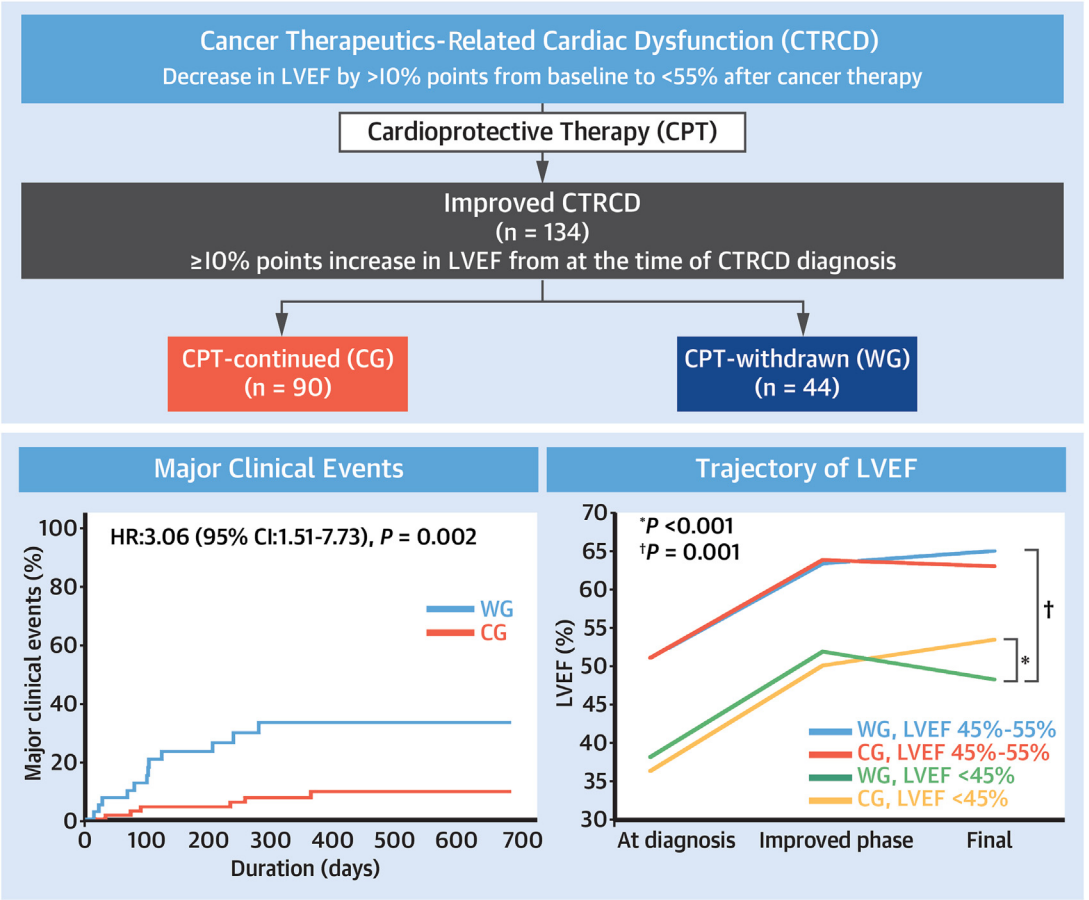
Kaplan-Meier curves illustrate the major clinical events, including hospitalization for heart failure or a decrease in LVEF ≥10 percentage points within 2 years after cancer therapeutics–related cardiac dysfunction improvement. The outcomes are displayed as follows: (A) a composite of hospitalization for heart failure and a decrease in LVEF by ≥10 percentage points, (B) hospitalization for heart failure, and (C) decreased in LVEF by ≥10 percentage points, based on the maintenance status of CPT. CG = control group; WG = withdrawn group; other abbreviations as in Figure 1.

TABLE 4 Predictors of Major Clinical Events

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, /1-year-old increase	1.02 (0.56-1.38)	0.28		
Hypertension	1.07 (0.74-1.58)	0.16		
Diabetes mellitus	1.31 (1.12-2.24)	0.019	1.26 (1.05-2.08)	0.016
Smoking	1.06 (0.66-2.37)	0.51		
CPT				
ACEI/ARB	1.02 (0.36-2.88)	0.97		
ARNI	0.78 (0.26-2.36)	0.65		
BB	0.71 (0.42-0.97)	0.021	0.76 (0.54-0.98)	0.013
MRA	0.80 (0.31-2.07)	0.62		
Ivabradine	0.41 (0.12-1.42)	0.16		
Statin	1.09 (0.79-3.40)	0.11	1.03 (0.62-4.48)	0.27
SGLT2i	0.74 (0.17-3.20)	0.68		
Pre-CTRCD use of ≥1 CPT	0.85 (0.56-4.93)	0.17	0.89 (0.57-5.59)	0.30
CPT duration without withdrawal after CTRCD improvement, /10 days increase	0.93 (0.90-0.97)	<0.001	0.92 (0.88-0.97)	0.001
Withdrawal of CPT	3.06 (1.51-7.73)	0.002	3.13 (1.54-7.69)	0.001
Administration of anthracyclines				
No anthracyclines	1.00 (reference)		1.00 (reference)	
Anthracycline cumulative dose ≤240 mg/m^2, median value	1.03 (0.78-2.72)	0.14	1.04 (0.72-2.81)	0.16
Anthracycline cumulative dose >240 mg/m^2, median value	1.37 (1.05-2.63)	0.010	1.33 (1.02-2.84)	0.012
HER2-targeted therapy	1.07 (0.81-2.32)	0.23		
VEGF inhibitors	2.31 (0.71-9.50)	0.68		
Proteasome inhibitors	1.88 (0.65-7.27)	0.42		
Radiation therapy to the chest	1.17 (0.83-3.09)	0.22	1.11 (0.73-2.85)	0.26
Baseline LVEF at CTRCD diagnosis <45%	1.42 (1.11-3.02)	0.011	1.48 (1.12-3.07)	0.009
Baseline LVEF at CTRCD diagnosis <40%	1.37 (1.05-3.01)	0.020		
LVEF at improved phase <50%	1.09 (0.89-2.14)	0.15	1.12 (0.93-2.61)	0.20
Final LVEF <59.2%, median value	1.06 (0.71-3.52)	0.28		
Moderate or severe VHD	1.36 (0.33-5.80)	0.75		
Pericardial effusion	1.40 (0.49-4.19)	0.59		

VHD = valvular heart disease; other abbreviations as in Tables 1 and 2.

CENTRAL ILLUSTRATION **Cardioprotective Therapy Maintenance and Outcomes**



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In patients with improved cancer therapeutics-related cardiac dysfunction (CTRCD), those who discontinued cardioprotective therapy (CPT) experienced worse clinical outcomes, defined as a composite of hospitalization for heart failure or a decrease in left ventricular ejection fraction (LVEF) ≥10 percentage points within 2 years after CTRCD improvement. A significant decrease in LVEF was observed in patients with a baseline LVEF <45% at the time of CTRCD diagnosis after CPT withdrawal. However, patients with a baseline of LVEF ≥45% did not exhibit a significant decrease in LVEF even after CPT withdrawal. CG = continued group; WG = withdrawn group.

gene dysregulation, impaired maximal myocardial force generation, interactions within the extracellular matrix with other cardiac structures, and LV radius-to-wall thick ratio were not normalized, suggesting possible deterioration of LV function after apparent clinical improvement.[16-19]

In a similar context, the effect of discontinuing HF medication in patients who recovered from DCM was investigated in the open-label, randomized TRED-HF trial (Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy, NCT02859311). The trial found that 44% of patients who stopped HF medication after recovering from DCM experienced a relapse. In contrast, none of the patients who continued HF medication experienced a relapse. However, after 6 months, 96% of these patients attempted to stop taking HF medication, and 36% subsequently relapsed. In the trial, the median LVEF of the subjects at initial diagnosis was as low as 25%. Conversely, a recent small study suggested that in patients with HER2-positive breast cancer and mild CTRCD (LVEF mostly >45%), withdrawing CPT might not lead to worsening cardiac function.[20]

The present study reveals that a baseline LVEF below 45% at CTRCD diagnosis independently is

associated with major clinical events, and patients with such baseline LVEF values experience a significant decrease in LVEF after CPT withdrawal. Therefore, successful CPT leading to reverse cardiac remodeling may not reflect a complete cure, especially in patients with a lower baseline LVEF. Notably, impaired LV GLS was not completely restored even after improvement in LVEF, and the CG did not exhibit better final LV GLS compared with the WG. This phenomenon may indicate an incomplete recovery even in patients with a normalized LVEF. Further investigations into its clinical significance over an extended follow-up duration is warranted.

In a previous retrospective study, 42 patients who had recovered from idiopathic DCM with an LVEF of at least 40% or an increase of 10% or more (mean LVEF at recovery: 53.4% ± 7.6%) were monitored.[21] During follow-up, LV systolic dysfunction recurred in 8 (19.0%) patients, 5 of whom discontinued HF medication after their recovery. Notably, these 8 patients exhibited a significantly lower LVEF at the time of improvement (47.5% ± 7.6% vs 53.9% ± 8.0%). Conversely, another trial involving 22 patients with peripartum cardiomyopathy found that after recovering to LVEF >50%, none experienced a recurrence of LV systolic dysfunction, even after discontinuing HF medication.[22] These contradictory findings suggest that the decisions to discontinue HF medications after recovery should be based on individual prognostic factors, including LVEF, to determine the appropriate timing for withdrawing CPT.

In the present study, patients with a baseline LVEF of 45% to 55% showed LVEF of 63.2% ± 3.0% at the time of CTRCD improvement, which would not warrant further CPT based on current guidelines. Conversely, patients with a baseline LVEF <45% only improved to LVEF of 50.6% ± 6.2%. This suboptimal improvement could potentially lead to a further decrease in LVEF and worse clinical outcomes after CPT withdrawing. However, contrary to our hypothesis, LVEF <50% during the improved phase was not independently associated with major clinical events in this study. This outcome may be attributed to the study's nonrandomized design. Additionally, within the WG, the time between CTRCD improvement and CPT withdrawal varied significantly, and the duration of CPT also likely affected clinical outcomes. This variability also applies to the classes of CPT used.

In the Republic of Korea, several CPTs, such as an angiotensin receptor neprilysin inhibitor or sodium glucose co-transporter 2 inhibitors, are covered by the national health insurance only in patients with LVEF ≤40%. This may mean that CTRCD patients who receive multiple CPTs are at a higher risk of HF. Consequently, a randomized controlled trial is necessary to determine the relationship between LVEF at the time of CTRCD improvement, the particular class of CPT used, and the resulting clinical outcomes.

The reasons for withdrawing CPT were analyzed in the WG. Notably, a significant number of patients with a baseline LVEF ≥45% at the time of CTRCD diagnosis expressed a desire to discontinue CPT. The specific reason to withdraw CPT was unclear because of the lack of detailed data, but it could be hypothesized that these patients experienced fewer symptoms, and, thus, they felt less need to continue CPT. Conversely, medication intolerance was a more common reason for discontinuing CPT among patients with LVEF <45%. Their poorer general health and weaker cardiac function might have led to lower blood pressure, increasing their risk of symptomatic hypotension when using CPT. However, without controlled blood pressure monitoring, this hypothesis remains unproven in this study.

Regardless of the underlying reasons, identifying patients who do not require prolonged CPT after CTRCD improvement could help minimize the potential side effects associated with prolonged CPT use and reduce un-necessary polypharmacy. Several ongoing randomized controlled trials (NCT06183437, NCT05880160, and ANZCTR12621000928819) are investigating the safety of withdrawing CPT after CTRCD improvement. These studies may provide insights into the optimal strategies for continuing CPT in such patients.

STUDY LIMITATIONS. First, it was conducted at a single center and, despite having a larger sample size than previous studies, it remains relatively small. Second, the patient cohort was heterogenous, encompassing various types of cancer and anticancer therapies, which could result in differing genetic predispositions and cardiac adverse effects.

Third, because of the small study population and the lack of a standardized protocol for administering or withdrawing CPT, it is not possible to determine the optimal drug class or dosage from this study's results. Fourth, CTRCD was defined solely by a decrease in LVEF, without considering changes in LV GLS or cardiac biomarkers. This criterion does not align with the current European Society of Cardiology guidelines on cardio-oncology,[11] which might lead to the exclusion of several potential CTRCD cases. Fifth, the incidence of hospitalization for HF might have been underestimated because of insufficient data on the patients' cardiac status.

CONCLUSIONS

Patients who discontinued CPT after showing improvement in CTRCD experienced worse clinical outcomes. Notably, a significant decrease in LVEF was observed in patients with a baseline LVEF <45% at the time of CTRCD diagnosis following CPT withdrawal. In contrast, patients with a higher baseline LVEF (45%-55%) did not exhibit a significant reduction in LVEF after discontinuing CPT. Future research involving a larger sample size, a more homogeneous patient population regarding underlying cancer and anticancer therapy, and standardized protocols for CPT and cardiotoxicity surveillance will be crucial for identifying which patients should continue CPT and which can safely discontinue it after improvement in CTRCD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients who discontinued CPT after improved CTRCD experienced worse clinical outcomes. Notably, there was a significant decrease in LVEF in patients with a baseline LVEF below 45% at the time of CTRCD diagnosis following the withdrawal of CPT. Conversely, patients with a baseline of LVEF ≥45% did not exhibit significant declines in LVEF after stopping CPT.

TRANSLATIONAL OUTLOOK: Further research needs to focus on homogeneous patient groups and standardized CPT and cardiotoxicity surveillance protocols to accurately identify patients who should continue CPT and those who can safely discontinue it after improvements in CTRCD. Additionally, studies should explore epidemiologic, serologic, cardiac functional, or genetic factors that could aid in determining the necessity of continuing CPT.

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KEY WORDS cardiomyopathy, heart failure, outcomes, treatment

APPENDIX For supplemental figures, please see the online version of this paper.