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RANDOMIZED-CONTROLLED TRIAL

Cardioprotection Using Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy

3-Year Results of the SUCCOUR Trial

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ABSTRACT

BACKGROUND Global longitudinal strain (GLS) can predict cancer therapeutics–related cardiac dysfunction and guide initiation of cardioprotection (CPT).

OBJECTIVES In this study, the authors sought to determine whether echocardiography GLS-guided CPT provides less cardiac dysfunction in survivors of potentially cardiotoxic chemotherapy, compared with usual care at 3 years.

METHODS In this international multicenter prospective randomized controlled trial, patients were enrolled from 28 international sites. All patients treated with anthracyclines with another risk factor for heart failure were randomly allocated to GLS-guided (>12% relative reduction in GLS) or ejection fraction (EF)-guided (>10% absolute reduction of EF to <55%) CPT. The primary end point was the change in 3-dimensional (3D) EF (ΔEF) from baseline to 3 years.

RESULTS Among 331 patients enrolled, 255 (77%, age 54 ± 12 years, 95% women) completed 3-year follow-up (123 in the EF-guided group and 132 in the GLS-guided group). Most had breast cancer (n = 236; 93%), and anthracycline followed by trastuzumab was the most common chemotherapy regimen (84%). Although 67 (26%) had hypertension and 32 (13%) had diabetes mellitus, left ventricular function was normal at baseline (EF: 59% ± 6%, GLS: 20.7% ± 2.3%). CPT was administered in 18 patients (14.6%) in the EF-guided group and 41 (31%) in the GLS-guided group ($P = 0.03$). Most patients showed recovery in EF and GLS after chemotherapy; 3-year ΔEF was −0.03% ± 7.9% in the EF-guided group and −0.02% ± 6.5% in the GLS-guided ($P = 0.99$) group; respective 3-year EFs were 58% ± 6% and 59% ± 5% ($P = 0.06$). At 3 years, 17 patients (5%) had cancer therapeutics–related cardiac dysfunction (11 in the EF-guided group and 6 in the GLS guided group; $P = 0.16$); 1 patient in each group was admitted for heart failure.

CONCLUSIONS Among patients taking potentially cardiotoxic chemotherapy for cancer, the 3-year data showed improvement of LV dysfunction compared with 1 year, with no difference in ΔEF between GLS- and EF-guided CPT. (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes [SUCCOUR]; ACTRN12614000341628) (J Am Coll Cardiol Img 2023;16:269–278) © 2023 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin receptor blocker

CPT = cardioprotective therapy

CTRCD = cancer therapy-related cardiac dysfunction

EF = ejection fraction

GLS = global longitudinal strain

HF = heart failure

LV = left ventricular

LVEF = left ventricular ejection fraction

Risk of left ventricular (LV) dysfunction and heart failure (HF) during cancer chemotherapy arises from the underlying risk of the patient, the nature of the cancer, and the type of chemotherapy. Multiple therapies used in cancer treatment are potentially cardiotoxic, and much effort is directed toward surveillance during cancer chemotherapy.[1] Left ventricular ejection fraction (LVEF), most commonly assessed by echocardiography, is the common factor among the many guidelines designed to facilitate surveillance.[2] However, the measurement of LVEF presents a number of challenges related to image quality, assumptions regarding LV geometry, and insensitivity to minor change, caused by broad confidence intervals.[3] Two-dimensional (2D) strain is an automated and quantitative technique for the measurement of global long-axis function from grayscale images. 2D global longitudinal strain (GLS) may help the clinician to recognize evidence of abnormal function in a chemotherapy patient and has been incorporated in international guidelines as a standard approach to assessing cardiac function responses to chemotherapy.[2,4] The use of GLS is particularly helpful when the LVEF is borderline (50%-59%).[5]

Previous observational studies have suggested that myocardial strain identifies LV dysfunction earlier than conventional echocardiographic measures in patients treated with chemotherapy,[6] thereby allowing the initiation of cardioprotective therapy to preserve LV function. The SUCCOUR (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes; ACTRN12614000341628) trial was designed to confirm these results in a randomized trial.[7] The 1-year results showed no difference in the change in LVEF between ejection fraction (EF)- and GLS-guided groups, with the 3% EF reduction being within the margin of error of 3-dimensional (3D) EF.[8] Nonetheless, GLS was more frequently abnormal than EF and led to the initiation of cardioprotective therapy, which was associated with a less frequent reduction of LVEF by >10%, to below the normal range. The purpose of the present report was to address the primary hypothesis of the trial that GLS-guided therapy leads to less change in 3D LVEF at 3 years.

METHODS

DESIGN. The SUCCOUR trial involved 28 centers from Australia, Asia, Europe, Canada, and the United States from January 2014 to December 2019. The design has been published previously.[7] In brief, patients treated for cancer with anthracyclines were eligible for recruitment if they had another risk factor for LV dysfunction, including more than 2 traditional HF risk factors (age >65 years, type 2 diabetes mellitus, hypertension, previous cardiac injury), other cardiotoxic agents (eg, trastuzumab, sunitinib), or high anthracycline dose (>450 mg/m^2). Patients with pre-existing HF or LV dysfunction (LVEF <50%), significant (more than moderate) valve disease, conditions incompatible with the initiation of cardioprotective therapy (eg, current therapy with or intolerance to beta-blockers and angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs], systolic blood pressure <110 mm Hg, heart rate <60 beats/min), inadequate echocardiographic images, and <12 months oncologic life expectancy were excluded. The computerized randomization process allocated patients 1:1 to EF-guided (usual care) or GLS-guided therapy. The study was approved by the research ethics

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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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committees for each site, and all patients provided informed consent. The previously published 1-year interim analysis of our data was approved by an independent data safety and monitoring board.[8]

CLINICAL DATA. Standard demographic and clinical data were gathered at baseline, including information on HF risk factors, comorbid diseases, cancer history, and medical therapy

ECHOCARDIOGRAPHY. Patients underwent baseline echocardiography before exposure to the main risk for cardiotoxicity, that is, at the start of anthracycline therapy (in the presence of cardiac risk factors) or before adjunctive therapy (eg, trastuzumab) or high-dose anthracycline. Images were obtained at baseline and every 3 months in the first year, and then at 24 and 36 months. Those with evidence of cancer therapeutics-related cardiac dysfunction (CTRCD) in the first year underwent echocardiography at 18 months as well. In addition to standard echocardiography, all patients had 3 to 5 cardiac cycles acquired in 4-, 3-, and 2-chamber apical views at a frame rate of 50 to 70 frames per second and stored digitally in raw data format. In addition to apical 2D images, LV full-volume 3D acquisitions were obtained at all stages. LV volumes and EF were quantified by means of the biplane Simpson method, and 3D LVQ (EchoPAC, GE Medical Systems). 2D-LVEF was used by the sites and core laboratory when 3D-LVEF could not be reliably measured.

Strain analyses were performed using speckle tracking (EchoPAC) with a model of the entire LV (the 3 apical views). Because the design sought to mimic local decision making regarding the detection of LV dysfunction, all images were measured at the participating centers, which undertook a calibration exercise to ensure consistent measurement.[9] However, all images were also transferred to a core laboratory to enable blinded analysis of LV outcome measures. In particular, GLS images obtained in patients in the EF-guided arm were not performed at the site, but were measured at the core laboratory.

CARDIOPROTECTIVE THERAPY. Patients were started on an ACEI followed by a beta-blocker if there was evidence of CTRCD, and these decisions were made locally at each site. In the EF-guided arm, CPT was triggered by a symptomatic drop of >5% or asymptomatic drop of >10% in LVEF to <55%, preferentially measured by 3D-LVEF. In the GLS-guided group, CPT was triggered by a ≥12% reduction ([baseline GLS − current GLS]/baseline GLS) in GLS. Once treatment was initiated, doses were up-titrated every 2 weeks until the maximal dose was achieved or intolerable side-effects developed. Treatment was continued throughout the first year, and patients were encouraged to continue on CPT thereafter.

OUTCOMES. The primary outcome was the difference in the change in 3D-LVEF from baseline to 3 years between GLS- and EF-guided groups, as determined by a blinded core laboratory analysis. 3D-EF was used preferentially, with 2D-EF using the biplane Simpson rule if 3D was not feasible—with the same modality compared at baseline and follow-up. The secondary outcomes at 3 years were the numbers meeting criteria for CTRCD, final LVEF, differences in GLS between baseline and 3-year follow-up, and clinical HF. When patients dropped out before the 3-year follow-up, the last available echocardiogram was used for analysis.

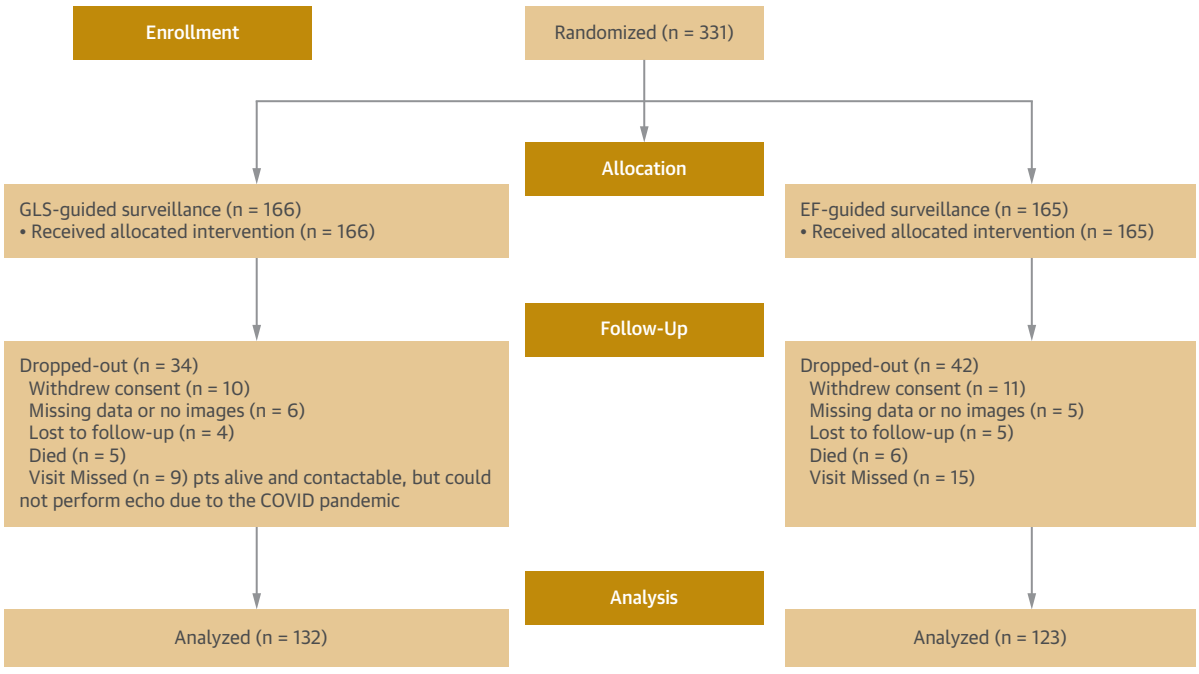
STATISTICAL ANALYSIS. Risk was evaluated after trial completion, using the recent position statement of the Heart Failure Association of the European Society of Cardiology (ESC), from the perspective of patients about to start treatment with anthracycline therapy.[10] Patients were classified as low risk (<2%) in the presence of a single 1-point medium risk factor (positive biomarkers, risk factors [hypertension, diabetes mellitus, chronic kidney disease], and lifestyle factors [smoking, obesity]). Medium risk (2%-9%) was identified with multiple 1-point or 1 or more 2-point risks (age 65-79 years or borderline EF [50%-54%]). High risk (10%-19%) was identified in the presence of 1 or more high-risk factors (previous myocardial infarction, revascularization, previous anthracyclines or radiotherapy, severe valvular disease, age >80 years, or abnormal LV function [EF <50%]) or multiple medium-risk factors (>5 points). Very high risk (>20%) was identified in the presence of preexisting HF or cardiomyopathy.

Baseline characteristics in the GLS- and EF-guided patients were compared with the use of an unpaired *t*-test or Fisher's exact test as appropriate. An intention to treat analysis was used for the outcome analyses. A paired *t*-test was used to assess change in LVEF or GLS from baseline to 3 years. The proportion of patients developing CTRCD in each group was compared by means of Fisher's exact test. Statistical significance was defined as $P \leq 0.05$.

RESULTS

PATIENT CHARACTERISTICS. Of the 331 eligible patients, 166 were randomized to GLS-guided and 165 to EF-guided intervention (Figure 1). At 1 year, 307 (93%, 153 in the EF-guided arm and 154 in the GLS-guided

FIGURE 1 Patient Allocation and Drop-Out



EF = ejection fraction; GLS = global longitudinal strain; pts = patients.

arm) completed follow-up. At 3 years, 255 (77% of the original group) had follow-up echocardiography; this group did not differ significantly from the full group who underwent 1-year imaging (Supplemental Table 1). Of these 255 followed to 3 years, 123 were in the EF-guided group and 132 in the GLS-guided group. Comparison of baseline clinical characteristics between the 2 groups is provided in **Table 1**. Patients were an average 54 ± 12 years of age (range 23-82 years), and 95% were women. HF risk factors were prevalent: 67 (26%) had hypertension and 32 (13%) had diabetes mellitus. On the basis of anthracycline therapy, all would have been considered to be at high risk; the risk level before anthracycline therapy was moderate or higher in 172 (67%).

Most patients had breast cancer (n = 236; 93%), with the remainder having hematological malignancies. All patients received anthracycline based chemotherapy, and 214 (84%) received subsequent therapy with trastuzumab. The median doxorubicin equivalent dose was 209 mg/m^2 (IQR: 200-241 mg/m^2). A total of 169 patients received chest radiation therapy.

INITIATION OF CARDIOPROTECTION. At baseline, there were no significant differences in LVEF or GLS between the 2 arms (**Figure 2**). In total, CPT was administered in 18 patients (14.6%) in the EF-guided group and 41 (31%) in the GLS-guided group ($P = 0.03$), including 6 patients who were taking 1 CPT at baseline. Most of these patients received both ACEI/ARB and beta-blocker. There were 5 patients who ceased medication before the 3-year visit, most commonly because of resolution of LV impairment (Supplemental Table 2). As in the original series, there were no differences in the maximal doses of ACEI/ARB or BB achieved between the 2 arms; the most frequent explanation for not being treated to target dose was inability to further up-titrate medications owing to hypotension or bradycardia. None of the patients had serious adverse events related to initiation of cardiac medications.

EVOLUTION OF LV FUNCTION. The mean follow-up duration after enrollment was 2.9 ± 0.4 years. The EF and GLS measurements at baseline and 1 and 3 years are summarized in **Figure 2**. Although the average EF and GLS showed a small deterioration at 1 year, the mean EF and GLS returned to baseline in both arms. The 3-year change in EF was −0.03% ± 7.9% in the EF-guided group and −0.02% ± 6.5% in the GLS-guided group ($P = 0.99$). Similar proportions

of patients were identified as showing CTRCD at 1 and 3 years in the EF-guided patients (11% and 9%, respectively) and in the GLS-guided patients (both 5%) (Table 2). The development of LV dysfunction (EF <55% or GLS >−18%) increased at 1 year and decreased at 3 years (Table 2). Although reduction of EF to <55% and EF criteria for CTRCD were uncommon (<10%) at 3 years, abnormal GLS (>−18%) and a >12% decrement of GLS from baseline were more frequent (>20%).

When patients who satisfied criteria for cardioprotection in the 2 arms were compared (n = 41 in the GLS-guided group and n = 18 in the EF-guided group), although change in EF was not significantly different after 3 years (−2.4% ± 9.7% vs −0.4% ± 7.3% respectively; $P = 0.38$), the final EF was lower in the EF-guided group (54% ± 8% vs 59% ± 6%; $P = 0.02$). The evolution of EF in the GLS- and EF-guided groups dichotomized by initiation of cardioprotective therapy is shown in the Central Illustration.

There were 2 patients with clinical HF requiring hospital admission during the 3-year follow-up (1 in each group). The patient in the EF-guided group continued to have asymptomatic CTRCD at the end of 3 years, whereas the patient in the GLS-guided arm had both reduced EF and GLS at 3 months but both EF and GLS recovered at 3 years.

ASSOCIATION WITH CLINICAL RISK. Table 3 explores the association of baseline risk with EF-based CTRCD. Overall, about one-third on the cohort were designated low risk before being administered anthracycline, of whom CTRCD developed in 6% at 1 year and in 7% at 3 years. In contrast, patients classified clinically as high risk had an overall 11% prevalence of CTRCD at 3 years. The difference in LVEF between baseline and 3 years was not predicted by the expected clinical variables (age, doxorubicin-equivalent dose, systolic blood pressure, diabetes mellitus) or treatment group (Supplemental Table 3).

TABLE 1 Patient Characteristics

	EF-Guided (n = 123)	GLS-Guided (n = 132)	*P* Value
Demographics			
Age, y	54 ± 12	54 ± 12	0.87
Female	116 (94)	127 (96)	0.47
Race			0.36
European	79 (64)	84(63)	
East Asian	28 (22)	36 (27)	
South Asian	11 (9)	5 (4)	
Other	5 (4)	6 (5)	
Risk factors			
Diabetes	21 (17)	11 (8)	0.04
Hypertension	34 (28)	33 (25)	0.63
Dyslipidemia	34 (28)	22 (17)	0.03
Smoking	35 (28)	38 (29)	0.95
BMI, kg/m^2	26 ± 5	25 ± 5	0.46
Obesity (BMI ≥30 kg/m^2)	23 (19)	19 (14)	0.35
Previous cardiovascular disease	9 (7)	12 (9)	0.61
Risk level			
High/very high	29 (23)	25 (18)	0.67
Moderate	56 (46)	62 (50)	
Low	38 (31)	44 (33)	
Baseline medical therapy			
Beta-blocker	5 (4)	7 (5)	0.64
ACEI or ARB	18 (15)	17 (13)	0.68
Statin	24 (20)	13 (10)	0.03
Observations			
Systolic blood pressure, mm Hg	130 ± 32	127 ± 16	0.40
Diastolic blood pressure, mm Hg	75 ± 10	76 ± 10	0.45
Heart rate, beats/min	78 ± 13	76 ± 12	0.27
Cancer history			
Breast cancer	112 (91)	124 (94)	0.38
Hematologic malignancy	11 (9)	8 (6)	
Anthracycline + herceptin therapy	98 (80)	115 (87)	0.11
Cumulative doxorubicin-equivalent dose, mg/m^2	223 ± 124	218 ± 72	0.67
EF			
Baseline, %	58 ± 6	59 ± 6	0.09
Baseline <50%	9 (7)	4 (3)	0.24
Baseline 50%-55%	30 (25)	29 (22)	
Baseline >55%	84 (68)	99 (75)	
GLS			
Baseline, %	20 ± 2	21 ± 2	0.18
Baseline >18%	107 (87)	120 (91)	0.57
Baseline 16%-18%	11 (9)	9 (7)	
Baseline <16%	5 (4)	3 (2)	

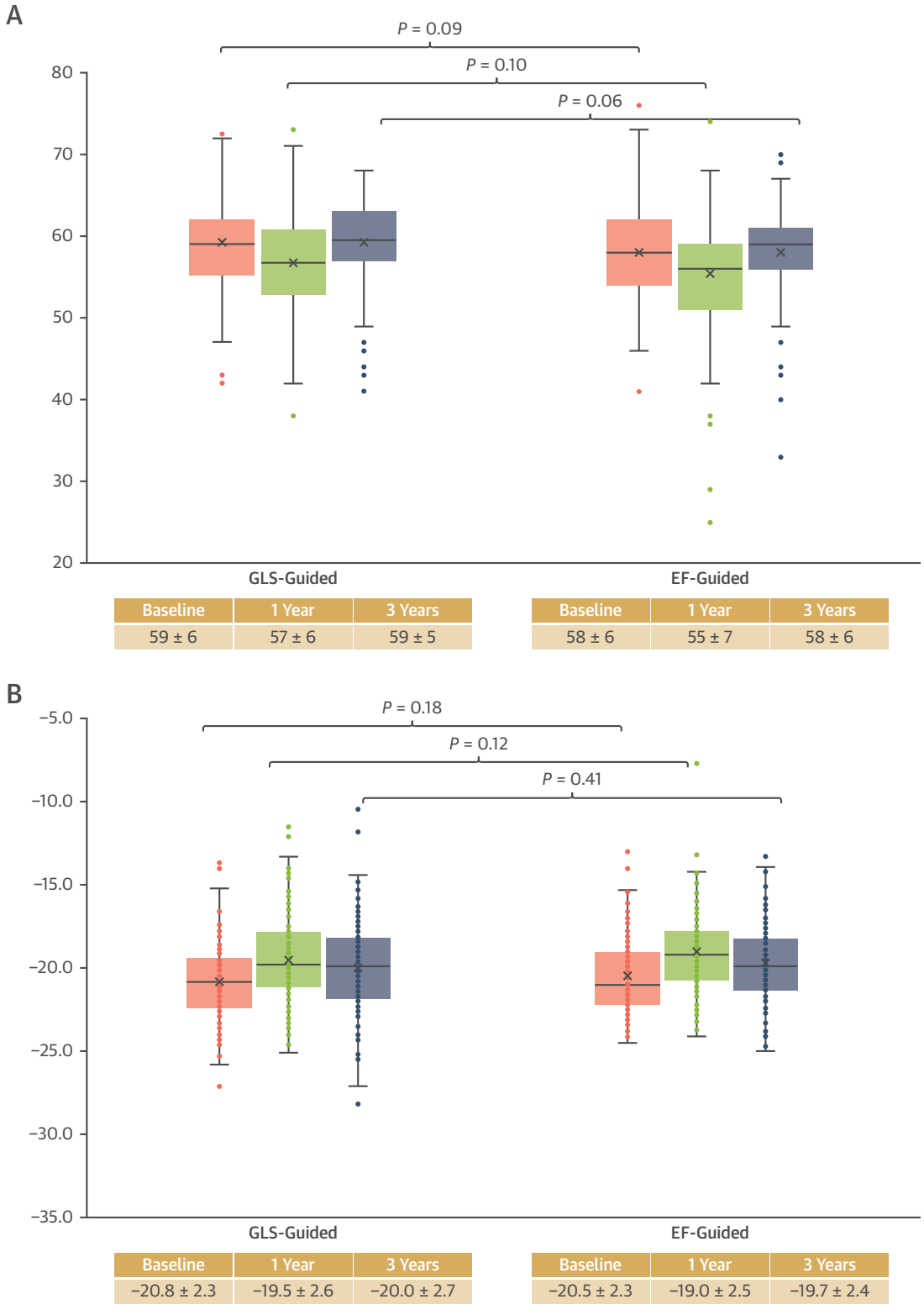
Values are mean ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; EF = ejection fraction; GLS = global longitudinal strain.

DISCUSSION

The results of this study showed a minimal difference in EF between the current standard of EF-guided CPT, and GLS-guided CPT at 3-year follow-up. However, more importantly, there was no net change in EF in either group over 3 years. This is not reflective of a problem unique to EF, as the change in GLS over the same timeframe was similarly small. A meaningful change of EF occurred in 9% of participants in the EF arm and 5% in the GLS arm, although more showed a change in GLS (albeit mainly in the normal range). These results prompt questions about how broadly to apply the current follow-up guidelines for potential CTRCD. From a Bayesian standpoint, the low probability of developing significant LV dysfunction makes it very challenging to develop an appropriate screening process. Under these circumstances, a strategy to identify a subgroup at increased risk may be the best way to formulate a screening process.

FIGURE 2 **Baseline and 1- and 3-Year Assessment of Left Ventricular Function in GLS-and EF-Guided Groups**



Baseline	1 Year	3 Years
59 ± 6	57 ± 6	59 ± 5

Baseline	1 Year	3 Years
58 ± 6	55 ± 7	58 ± 6

Baseline	1 Year	3 Years
−20.8 ± 2.3	−19.5 ± 2.6	−20.0 ± 2.7

Baseline	1 Year	3 Years
−20.5 ± 2.3	−19.0 ± 2.5	−19.7 ± 2.4

Left ventricular function is assessed by **(A)** ejection fraction (EF) and **(B)** global longitudinal strain (GLS).

TABLE 2 Responses to EF- and GLS-Guided Management

	EF-Guided (n = 123)				GLS-Guided (n = 132)			
	Baseline	1 y	3 y	*P* Value	Baseline	1 y	3 y	*P* Value
EF <55%	33 (27)	47 (38)	15 (12)	<0.0001[a]	20 (15)	47 (36)	13 (10)	<0.0001[a]
CTRCD-EF	-	13 (11)	11 (9)	0.67[b]	-	7 (5)	6 (5)	0.78[b]
GLS >-18%	17 (14)	35 (29)	27 (22)	0.02[a]	11 (8)	33 (25)	29 (22)	<0.0001[a]
CTRCD-GLS	-	39 (32)	24 (20)	0.03[b]	-	25 (19)	29 (22)	0.54[b]

Values are n (%). All categories of left ventricular function showed a deterioration at 1 year with subsequent recovery at 3 years; this was most marked with criteria based on the lower limit of normal EF. *P* values for comparison of [a]trend and [b]1 vs 3 years.

CTRCD = cancer therapy-related cardiac dysfunction; other abbreviations as in Table 1.

CARDIOPROTECTION STRATEGIES. The prevention of CTRCD is based around avoidance of potentially toxic therapies, the provision of CPT to stabilize LV dysfunction, and, in some (rare) instances, altering or even stopping the culprit chemotherapeutic agent. In relation to prevention, although the use of anthracyclines is avoided whenever possible, they are effective for a number of cancers.[11] Moreover, the problem is not limited to anthracyclines, and the number of potentially cardiotoxic agents is increasing.[12] Altering chemotherapy is a very undesirable means of controlling this problem, as it is often associated with worse cancer outcomes.[13] Therefore, cardioprotective therapy is central to the problem of controlling CTRCD.

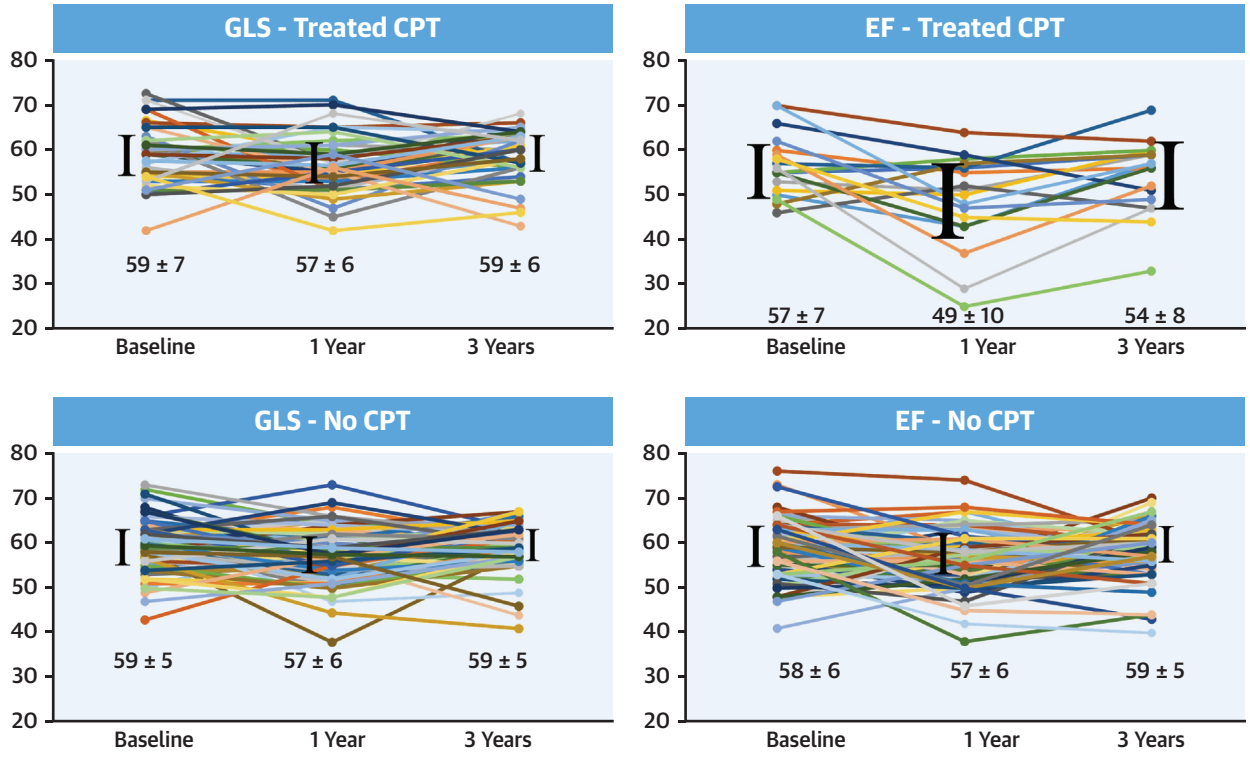
Antagonists to the renin-angiotensin and adrenergic pathways have been shown to be effective in preventing the development and progression of LV dysfunction in patients at risk of HF in a variety of circumstances.[14] Both observational studies and randomized trials have shown their benefits in the prevention of HF in patients on chemotherapy, with a typical finding of a 5%-10% reduction of EF in the control groups.[15] Randomized studies such as PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy),[16] MANTICORE (Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research),[17] and OVERCOME (Prevention of Left Ventricular Dysfunction With Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies)[18] have shown that use of beta-adrenoceptor blockade and/or renin-angiotensin inhibitors and antagonists can avert this EF reduction.

The universal use of cardioprotection in patients at risk of CTRCD would be effective for the prevention of dysfunction, but even the most sensitive indicators of LV dysfunction show that it does not develop in 80% of cases. Therefore, a majority of patients would be exposed to potentially detrimental side-effects (including hypotension) without receiving benefit. In a decision-analytic model, it has been shown that uniform use of CPT is less effective and more costly than an effective surveillance program in women with breast cancer.[19] The approach investigated in the SUCCOUR trial[7] was to provide more targeted use of CPT based on repeated surveillance. Delays between the recognition of myocardial injury and the initiation of CPT may be responsible for worsening LV function.[20] Provision of regular surveillance and cardioprotection to all patients in this study may explain the favorable outcome.

In a surveillance strategy, the reliability of the relevant test is of pivotal importance. Although EF is recommended in most guidelines, the utility of 2D echocardiography is constrained by test-retest variability, which is up to 10%. The use of 3D-EF is more reliable,[3] and recommended in many guidelines, but is highly dependent on image quality and is sometimes not feasible. Myocardial strain is a reproducible parameter which has been shown to detect relatively minor changes of LV function and proposed to be more effective than EF in a number of observational studies.[6] The SUCCOUR trial has been the first randomized comparison of GLS and 3D-EF surveillance, with the 12-month results showing no significant difference in change of EF between these tests, largely reflecting the minor (~3%) overall change in LVEF.[8] Nonetheless, the development of a meaningful reduction of LV function to beneath the normal range was reduced by the GLS-based approach. At 1 year, there were 20 patients in the EF-guided group and 45 in the GLS-guided group who were started on CPT. Despite the loss to follow-up, a similar proportion were treated in the 3-year results reported in this study: 18 patients (14.6%) in the EF-guided arm and 41 (31%) in the GLS-guided arm ($P = 0.03$). In the 3-year follow-up, the EF change from baseline was minimal overall.

ASSESSMENT OF HF RISK IN PATIENTS ON ANTHRACYCLINES. The risk of HF in patients subjected to chemotherapy relates to the nature of

CENTRAL ILLUSTRATION **Evolution of EF in the GLS- and EF-Guided Groups**



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Groups are subdivided according to intention to treat. CPT = cardioprotective therapy; EF = ejection fraction; GLS = global longitudinal strain.

chemotherapy, other cardiac toxic stimuli, and the underlying HF risk of the patient. The main stimulus to the development of LV dysfunction in this study was exposure to anthracyclines, with less impact from trastuzumab and other agents. Although there is an anthracycline dose-effect, the development of CTRCD is idiosyncratic, and the exposure of many patients to low or intermediate doses means that this risk is hard to ignore in any patient on anthracyclines.[10] The effects of trastuzumab on LV function are less frequent now that it is used sequentially rather than concurrently with anthracycline therapy. Radiation is another potent contributor to the development of CTRCD. However, the underlying HF risk of the patient may be greatest source of variability.

Age is probably the most important factor for the development of HF, and it influences the association of CTRCD with different cancer types. The present study predominantly involved middle-aged women with breast cancer, which alone may explain the low

TABLE 3 **Development of EF-Based CTRCD at Different Clinical Risk Levels**

	All (n = 255)			EF-Guided (n = 123)			GLS-Guided (n = 132)		
	n	1 y	3 y	n	1 y	3 y	n	1 y	3 y
Low	82	6 (7)	4 (6)	38	4 (11)	4 (13)	44	2 (5)	0 (0)
Moderate	118	8 (7)	8 (8)	56	4 (7)	4 (7)	62	4 (6)	4 (8)
High	55	3 (5)	5 (11)	29	3 (14)	3 (15)	26	0 (0)	2 (8)
P value		0.91	0.59		0.81	0.53		1.00	0.09

Values are n (%). The observed 3-year risks showed a small (but nonsignificant) gradation between risk groups.
Abbreviations as in Tables 1 and 2.

likelihood of CTRCD. In contrast, anthracyclines are widely used in the treatment of hematologic malignancies, and such patients tend to be 10 to 20 years older and therefore inherently at higher risk of LV dysfunction. In addition to age, the most common HF risks are hypertension, diabetes, coronary artery disease, and coronary artery disease risk factors, including hyperlipidemia and smoking.[10] Lifestyle factors, including alcohol intake,[21] lack of dietary fruit and vegetables, overweight and obesity, inactivity, and psychologic stress, are also prevalent HF risk factors in cancer populations.[22]

Ideally, to minimize the risk of false positive results, screening would be undertaken in people with at least intermediate risk of developing CTRCD. In fact, the guidelines do not advocate a selective approach to screening, which is understandable because the risk tools for calculating overall HF risk are rudimentary. The risk calculator used in this study was based on expert opinion from the Heart Failure Association of the ESC.[10] It is important that although that position statement proposed that patients at medium or higher risk be recommended for cardio-oncology review, it recommended that surveillance be extended according to national guidelines, which do not advocate the alignment of screening with risk level. Indeed, the calculated risk from the ESC position statement was not very useful in this study, with actual 3-year CTRCD showing a small increment between those at estimated low, intermediate, and high risks. Perhaps more potent adjustment for age in the algorithm could provide a more effective baseline risk assessment that could increase the efficiency of imaging surveillance.

It is possible that additional steps could be undertaken to improve risk assessment. The use of pharmacogenomics may facilitate identification of patients who are likely to develop CTRCD, although not all potential markers have proven to be effective.[23] The use of biomarkers, such as troponin and natriuretic peptides may facilitate the selection of patients for imaging, but the reliability of these markers has been questioned.[24] The assessment of myocardial work[25] or tissue characterization with cardiac magnetic resonance[26] may provide a more sensitive and specific imaging marker, but better tests are unlikely to overcome the Bayesian challenge of low baseline risk.

STUDY LIMITATIONS. This study used 3-year EF as the reference standard, based on the acknowledged predictive value of EF. Nonetheless, alternative functional metrics, such as exercise capacity, are even stronger predictors of outcome. Yu et al[27] have shown that individuals with CTRCD have a lower functional capacity after 5 years compared with those with preserved LV function. Unfortunately, functional capacity was not measured in this study.

CONCLUSIONS

The results of this study show that a GLS-based strategy for early detection and treatment of CTRCD was not superior to an EF-based strategy. Rather than being a problem of imaging, these results reflect the low probability of developing LV dysfunction in the overall group and suggest that a more selective strategy for imaging surveillance is warranted.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Current guidelines propose the use of EF for surveillance of LV function during anthracycline-based chemotherapy. Because of the limits of reproducibility of 2D echocardiography, GLS has been proposed as an alternative parameter. In this study, both EF- and GLS-guided cardioprotection led to a low frequency of abnormal EF at 3 years.

TRANSLATIONAL OUTLOOK: More reliable approaches are needed for the identification of pretest risk among patients undergoing surveillance of LV function during chemotherapy.

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KEY WORDS cancer therapy-related cardiac dysfunction, cardioprotective therapy, global longitudinal strain, heart failure

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

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