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ORIGINAL RESEARCH

Efficacy of Neurohormonal Therapies in Preventing Cardiotoxicity in Patients With Cancer Undergoing Chemotherapy

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ABSTRACT

OBJECTIVES This study sought to assess the effects of neurohormonal therapies in preventing cardiotoxicity in patients receiving chemotherapy.

BACKGROUND Various cardioprotective approaches have been evaluated to prevent chemotherapy-related cardiotoxicity; however, their overall utility remains uncertain.

METHODS This meta-analysis included randomized clinical trials of adult patients that underwent chemotherapy and neurohormonal therapies (β-blockers, mineralocorticoid receptor antagonists, or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) versus placebo with follow-up ≥4 weeks. The primary outcome was change in left ventricular ejection fraction (LVEF) from baseline to the end of the trial. Other outcomes of interest were measures of LV size, strain, and diastolic function. Pooled estimates for each outcome were reported as standardized mean difference and weighted mean difference between the neurohormonal therapy and placebo groups using random effects models.

RESULTS We included 17 trials, collectively enrolling 1,984 participants. In pooled analysis, neurohormonal therapy (vs. placebo) was associated with significantly higher LVEF on follow-up (standardized mean difference: +1.04 [95% confidence interval (CI): 0.57 to 1.50]) but with significant heterogeneity in the pooled estimate ($I^2 = 96\%$). Compared with placebo-treated patients, those randomized to neurohormonal therapies experienced a 3.96% (95% CI: 2.90 to 5.02) less decline in LVEF estimated by weighted mean difference, but with significant heterogeneity ($I^2 = 98\%$). There was a trend toward lower adverse clinical events with neurohormonal therapy (vs. placebo) that did not meet statistical significance (risk ratio: 0.80 [95% CI: 0.53 to 1.20]; $I^2 = 71\%$).

CONCLUSIONS Neurohormonal therapies are associated with higher LVEF in follow-up among cancer patients receiving chemotherapy, although absolute changes in LVEF are small and may be within inter-test variability. Furthermore, significant heterogeneity is observed in the treatment effects across studies highlighting the need for larger trials of cardioprotective strategies. (J Am Coll Cardiol CardioOnc 2019;1:54–65) © 2019 The Authors. 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 development and use of targeted cancer therapies has improved survival in many cancers. Indeed, in the past 25 years, overall 5-year cancer survival has improved from 49% to 69% (1). Unfortunately, many of these life-saving therapies are associated with increased risk of cardiotoxicity (2-5). In anthracycline-treated patients, the incidence of significant cardiotoxicity and clinical heart failure (HF) has been reported to be as high as 5% to 10% depending on the dose and duration of exposure (6). However, the incidence of left ventricular (LV) dysfunction is reported up to 16% in adult breast cancer survivors (6) and 27% in childhood cancer survivors (7). Among trastuzumab-treated patients, 2% develop symptomatic HF and 34% develop asymptomatic LV dysfunction (8).

As increasing evidence emerges pertaining to the long-term cardiotoxic effects of chemotherapy, there is renewed interest among clinicians to further explore the role of cardioprotective therapies to minimize treatment-emergent cardiovascular adverse effects. In this regard, various cardioprotective approaches have been evaluated to prevent the development of chemotherapy-related cardiotoxicity and HF, with mixed results (2-4). In light of recently completed trials (9) and relatively modest-sized sample sizes, we conducted an updated meta-analysis to assess the effects of neurohormonal therapies in preventing cardiotoxicity in patients with exposure to chemotherapy.

METHODS

SEARCH STRATEGY. A trial-level meta-analysis of randomized clinical trials examining the effects of neurohormonal therapies to reduce cardiotoxicity in patients receiving chemotherapy was performed, and the findings are reported per the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (10). We performed a search of the MEDLINE, EMBASE, Cochrane CENTRAL, ClinicalTrials.gov, and ICTRP databases for randomized clinical trials and included studies that were published from inception of these databases to March 2018 (see the Supplemental Appendix for search strategy). In addition, references from trials, review articles, and editorials were manually reviewed to identify any trials missed with the above search strategy.

STUDY SELECTION AND QUALITY ASSESSMENT. All publications were screened by title and abstracts by 2 independent reviewers (A.Q. and A.G.) for potential inclusion. The following inclusion criteria were required to be eligible for the meta-analysis: 1) adult participants ≥18 years of age; 2) prospective randomized clinical trial design; 3) randomization to neurohormonal therapy versus placebo; 4) assessment of LV ejection fraction (LVEF) at baseline and at the end of treatment; 5) study follow-up of 4 weeks or more; and 6) type of chemotherapy and cancer reported. Studies were excluded for the following reasons: 1) follow-up shorter than 4 weeks; 2) publication in a language other than English; 3) incomplete assessment of LVEF; or 4) animal studies. All discrepancies regarding trial inclusion were settled by the senior author (A.P.). Study quality was assessed independently by 2 reviewers (A.Q. and A.P.) using Jadad's 5-point scale (11). The characteristics assessed were randomization (0-2 points), double blinding (0-2 points), and description of withdrawals or dropouts (0-1 point). All included studies had a Jadad quality score of ≥3, denoting acceptable quality.

DATA EXTRACTION AND OUTCOMES MEASURES. Data were independently extracted from each trial by

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitors

ARB = angiotensin II receptor blockers

CI = confidence interval

HF = heart failure

I² = inconsistency index

LV = left ventricular

LVEF = left ventricular ejection fraction

LVEDD = left ventricular end-diastolic dimension

LVESD = left ventricular end-systolic dimension

MRI = magnetic resonance imaging

MRA = mineralocorticoid receptor antagonists

RAAS = renin-angiotensin-aldosterone system

SMD = standardized mean difference

WMD = weighted mean difference

TABLE 1 Baseline Clinical Characteristics of the Participants Across the Included Trials

First Author (Year) (Ref. #)	Therapeutic Intervention	Sample Size Control/Therapy	Age (yrs) Control/Therapy	Women (%) Control/Therapy	HTN (%) Control/Therapy	DM (%) Control/Therapy	Breast Cancer (%) Control/Therapy
Akpek et al. (2015) (17)	Spironolactone	40/43	50.6/50	100/100	NA/NA	NA/NA	100/100
Avila et al. (2018) (9)	Carvedilol	96/96	52.9/50.8	100/100	9.3/9.1	5.2/4.1	100/100
Bosch et al. (2013) (18)	Enalapril + carvedilol	45/45	50.9/49.7	47/40	18/13	2/7	0/0
Boekhout et al. (2016) (19)	Candesartan	104/106	51/50	100/100	11/13	3/3	100/100
Cadeddu et al. (2010) (20)	Telmisartan	24/25	53/52.9	25/24	NA/NA	NA/NA	42/32
Cardinale et al. (2006) (21)*	Enalapril	58/56	44/47	67/60	7/5	2/2	26/25
Elitok et al. (2014) (22)	Carvedilol	40/40	52.9/54.3	100/100	NA/NA	NA/NA	100/100
Georgakopoulos et al. (2010) (23)	Metoprolol/enalapril	40/42/43	49.1/51/47.4	47/48/49	15/24/33	15/24/7	0/0/0
Gulati et al. (2016) (24)	Candesartan + metoprolol/ candesartan alone/ metoprolol alone	30/32/32/32	50/51.7/50.5/50.8	100/100/100/100	3.3/15.6/6.3/0.0	0.0/3.1/3.1/0.0	100/100/100/100
Janbabai et al. (2017) (25)	Enalapril	35/34	47.1/47.8	88.6/97.1	11.4/17.6	14.3/8.8	85.7/88.2
Jhorawat et al. (2016) (26)	Carvedilol	27/27	38.7/43.9	33.3/14.8	NA/NA	NA/NA	0/0
Kaya et al. (2013) (27)	Nebivolol	18/27	50.5/51.4	100/100	22/22	11/7	100/100
Kalay et al. (2006) (28)	Carvedilol	25/25	49.0/46.8	84/88	NA/NA	NA/NA	64/72
Pituskin et al. (2017) (29)	Perindopril/bisoprolol	33/31/30	50/53/51	100/100/100	6/0/7	3/10/0	100/100/100
Salehi et al. (2011) (30)	Carvedilol	22/22	43.5/43.5	64/77	NA/NA	NA/NA	59/73
Nabati et al (2017) (32)	Carvedilol	45/46	47.1/47.6	100/100	12.5/26/8	12.5/7.3	100/100
Guglin et al (2019) (31)	Carvedilol/ lisinopril	154/156/158	51.1/51.6/50.6	100/100/100	5.2/6.4/3.8	3.2/2.6/1.3	100/100/100

TABLE 1 Continued

First Author (Year) (Ref. #)	% Anthracycline Control/Therapy	Maximum Daily Dose of Study Therapy	% of Guideline-Recommended Target Dosing for Chronic HFrEF (33-35)	Clinical Endpoint Reported	Follow-Up Period
Akpek et al. (2015) (17)	100/100	25 mg	50	-	24 weeks
Avila et al. (2018) (9)	100/100	50 mg	100	Mortality, HF, arrhythmia, or significant (>10%) decline in EF	24 weeks
Bosch et al. (2013) (18)	40/40	20 mg + 50 mg	50/100	Mortality, HF, or final EF <45%	24 weeks
Boekhout et al. (2016) (19)	100/100	32 mg	100	Significant LV dysfunction (>15% decline or <45% on follow-up)	26 weeks
Cadeddu et al. (2010) (20)	100/100	40 mg	50	-	28 days
Cardinale et al. (2006) (21)*	56/47	20 mg	50	Mortality, arrhythmia, HF, acute pulmonary edema	12 months
Elitok et al. (2014) (22)	100/100	12.5 mg	25	-	24 weeks
Georgakopoulos et al. (2010) (23)	100/100/100	88.8 mg/11 mg	44.4/27.5	Clinical HF or significant decline in LV function	12 months
Gulati et al. (2016) (24)	100/100/ 100/100	32 mg+100 mg/ 32 mg/ 100 mg	100/50	-	10–61 weeks
Janbabai et al. (2017) (25)	100/100	10 mg	25	-	24 weeks
Jhorawat et al. (2016) (26)	100/100	12.5 mg	25	Mortality or EF <50% on follow-up	24 weeks
Kaya et al. (2013) (27)	100/100	5 mg	50	-	24 weeks
Kalay et al. (2006) (28)	100/100	12.5 mg	25	Mortality, clinical HF or EF decline <50%	24 weeks
Pituskin et al. (2017) (29)	33/13/23	8 mg/10 mg	50/100	Significant LV dysfunction (>10% decline to <53% on follow-up)	52 weeks
Salehi et al. (2011) (30)	100/100	25 mg	50	-	16 weeks
Nabati et al (2017) (32)	100/100	12.5 mg	25	-	24 weeks
Guglin et al (2019) (31)	40.2/39.1/41.8	10 mg/10 mg	20/25	Significant decline in LV function (> 10% decline in patients with EF >50% or >5% decline in those whose EF decreases to <50%)	2 yrs

*Enrolled high-risk patients who experienced an increase in troponin I after high-dose chemotherapy.

DM = diabetes mellitus; EF = ejection fraction; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricular; NA = not available.

2 authors (A.Q. and A.P.) using a structured data collection form. The following data were collected from each trial: year of publication, sample size, inclusion and exclusion criteria, baseline characteristics of enrolled patients, details of chemotherapy, description of cancer, intervention and comparison arms, duration of follow-up, clinical outcomes, imaging modality used for assessment of LVEF, and echocardiographic data. Studies with more than 2 comparisons (e.g., angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers [ACEI/ARB] vs. placebo and β-blockers vs. placebo) were

treated as 2 different studies for this meta-analysis. Any disagreements between reviewers were discussed and resolved by consensus.

The primary clinical outcome was change in LVEF from baseline to the end of trial. Secondary outcomes were rates of major adverse clinical events and changes in echocardiographic parameters, such as change in LV systolic longitudinal strain, LV end-systolic dimension (LVESD), LV end-diastolic dimension (LVEDD), E/A ratio, and E/e′. Major clinical endpoints, as reported across the studies (Table 1), were also pooled together to evaluate how the cardioprotective therapies may modify the risk of adverse clinical outcomes. The clinical endpoints assessed across the included studies were composite of HF, significant LV dysfunction, or mortality.

STATISTICAL ANALYSIS. Mean ± SD and the proportion of patients experiencing outcomes were extracted for continuous and dichotomous outcomes, respectively. The comparison between neurohormonal therapy and placebo groups is presented as mean difference with 95% confidence intervals (CIs) for continuous outcomes and risk ratio with 95% CIs for dichotomous data. Random-effects meta-analysis using the DerSimonian and Laird method was used given significant heterogeneity was observed across most tested outcomes (12). A random-effects model was chosen to account for heterogeneity across studies that was considered to be related to the clinical diversity in the study population across trials with the goal to determine the average intervention effect. We analyzed differences in changes in echocardiographic parameters between the neurohormonal therapy and placebo groups. Standard deviation for the change in continuous variables from baseline to trial completion was ascertained using correlation coefficients, a method that has been previously described (13). Pooled estimates for each outcome are reported as standardized mean difference (SMD) with 95% CIs between the neurohormonal therapy and placebo groups to account for the differences in imaging modalities across studies (echocardiogram vs. cardiac magnetic resonance imaging [MRI]). Weighted mean differences (WMD) with 95% CIs were also calculated for clinical relevance. Treatment effects were also compared in prespecified stratification by type of imaging modality (echocardiogram or cardiac MRI) used to account for variability in accuracy/precision of these tests in evaluating LV structure and function (14). We performed the following sensitivity analyses to examine the heterogeneity in the effects of neurohormonal therapy versus placebo on LVEF: 1) trials evaluating

ACEI/ARB or mineralocorticoid receptor antagonists (MRA) only; 2) trials evaluating β-blockers only; 3) trials evaluating anthracyclines for chemotherapy; and 4) trials only enrolling patients with breast cancer.

We assessed the extent of variability across the trials attributable to heterogeneity beyond chance by estimating the I^2 statistics; $I^2 > 50\%$ denotes significant heterogeneity (15). Publication bias was assessed using funnel plot and Egger's regression intercept (16). SMD and standard error of SMD were plotted on a funnel plot to assess symmetry of treatment effects across studies. In case of significant publication bias, Duval and Tweedie trim and fill method using a linear estimator was used to account for publication bias and derive corrected estimates based on random-effects meta-analytic point using Comprehensive Meta-analysis, version 2. All other computations were performed using Stata version 14.1 (StataCorp, College Station, Texas). A 2-tailed p value <0.05 was considered significant.

RESULTS

STUDY SELECTION AND BASELINE CHARACTERISTICS. The Preferred Reporting Items for Systematic reviews and Meta-Analyses diagram for the study selection is shown in Figure 1. The final meta-analysis included 1,984 participants from 17 published studies (9,17-32). Ten studies were performed in Europe, 4 in Asia, and 3 in North and South America. Study-level baseline clinical characteristics are presented in Table 1. Mean age ranged from 38.7 to 53 years, and 9 studies composed cohorts of all female participants. Additionally, all studies included a proportion of patients with either co-existing diabetes mellitus and/or hypertension. Most therapeutic comparisons were conducted in patients with a primary diagnosis of breast cancer (n = 14) mostly treated with anthracyclines and less frequently with human epidermal growth factor receptor 2 antagonists alone or combination anthracycline + human epidermal growth factor receptor 2 antagonist therapy. With respect to neurohormonal therapies, β-blockers and ACEI/ARB/MRA were used in 12 studies and 10 studies, respectively. Five studies evaluated both β-blockers with ACEI/ARB/MRA. Maximal daily doses of neurohormonal therapies across trials represented 25% to 100% of guideline-recommended (33-35) target doses for the management of stage C chronic heart failure with reduced ejection fraction. Baseline LV structural and functional characteristics are summarized in Table 2. Median baseline LVEF was reported in all studies, which ranged from 59% to 71%; however, LVEDD

(ranging from 3.9 to 4.9 cm) and E/A ratios (ranging from 0.83 to 1.31) were only reported in 7 and 10 studies, respectively.

EFFECTS ON LVEF AND OTHER ENDPOINTS. Follow-up periods ranged from 4 weeks to 2 years across trials. Follow-up LV structural and functional characteristics are presented in **Table 3**. In random-effects pooled analysis, patients receiving neurohormonal therapy had higher LVEF on follow-up when compared with placebo-treated patients, regardless of choice of imaging modality (SMD: +1.04: 95% CI: 0.57 to 1.50; I^2 = 96%; p < 0.001) (Supplemental Figure 1). Similar findings were noted on meta-analysis using WMD (+3.96: 95% CI: 2.90 to 5.02; p < 0.001) (**Figure 2**); **Table 4**. Moreover, we observed presence of significant publication bias (asymmetry on funnel plot and p < 0.001 for Egger's test) (Supplement Figure 2). Corrected estimates for LVEF changes in patients receiving neurohormonal therapy versus placebo using trim and fill methods revealed consistent findings: SMD +1.32 (95% CI: 0.80 to 1:85); p < 0.001.

For other outcomes of interest, compared with the control group, patients randomized to neurohormonal therapy had better (more negative) LV peak systolic longitudinal strain (SMD: -0.43; 95% CI: -0.69 to -0.16; I^2 = 25.8; p = 0.257). There were no significant differences in the changes in LVESD (SMD: -0.40; 95% CI: -0.90 to 0.10), LVEDD (SMD: -0.32; 95% CI: -0.71 to 0.007), and measures of diastolic function (E/e′ SMD: -0.18; 95% CI: -0.70 to 0.35 and E/A SMD: 0.18: 95% CI: -0.07 to 0.42) from baseline to follow-up between the neurohormonal versus the control group. Finally, there was a trend toward lower likelihood of adverse clinical endpoints with neurohormonal therapy compared with placebo, but this did not reach statistical significance (risk ratio 0.80; 95% CI: 0.53 to 1.20; I^2 = 71%). We observed considerable heterogeneity across the pooled studies for each study outcome, except for LV peak systolic longitudinal strain.

SENSITIVITY ANALYSIS. In sensitivity analysis examining trials comparing ACEI/ARB/MRA agents versus placebo only, the neurohormonal therapy group had higher LVEF during follow-up when compared with control group (SMD: +1.30; 95% CI: 0.57 to 2.04; I^2 = 96.4%) (Supplemental Figure 3). Likewise, a similar treatment effect was observed in trials evaluating β-blockers only (SMD: +0.85; 95% CI: 0.20 to 1.50; I^2 = 96%), in trials that enrolled patients treated with anthracycline-based chemotherapy (SMD: +1.36; 95% CI: 0.63 to 2.10; I^2 = 96.6%), and in trials enrolling only patients with breast cancer
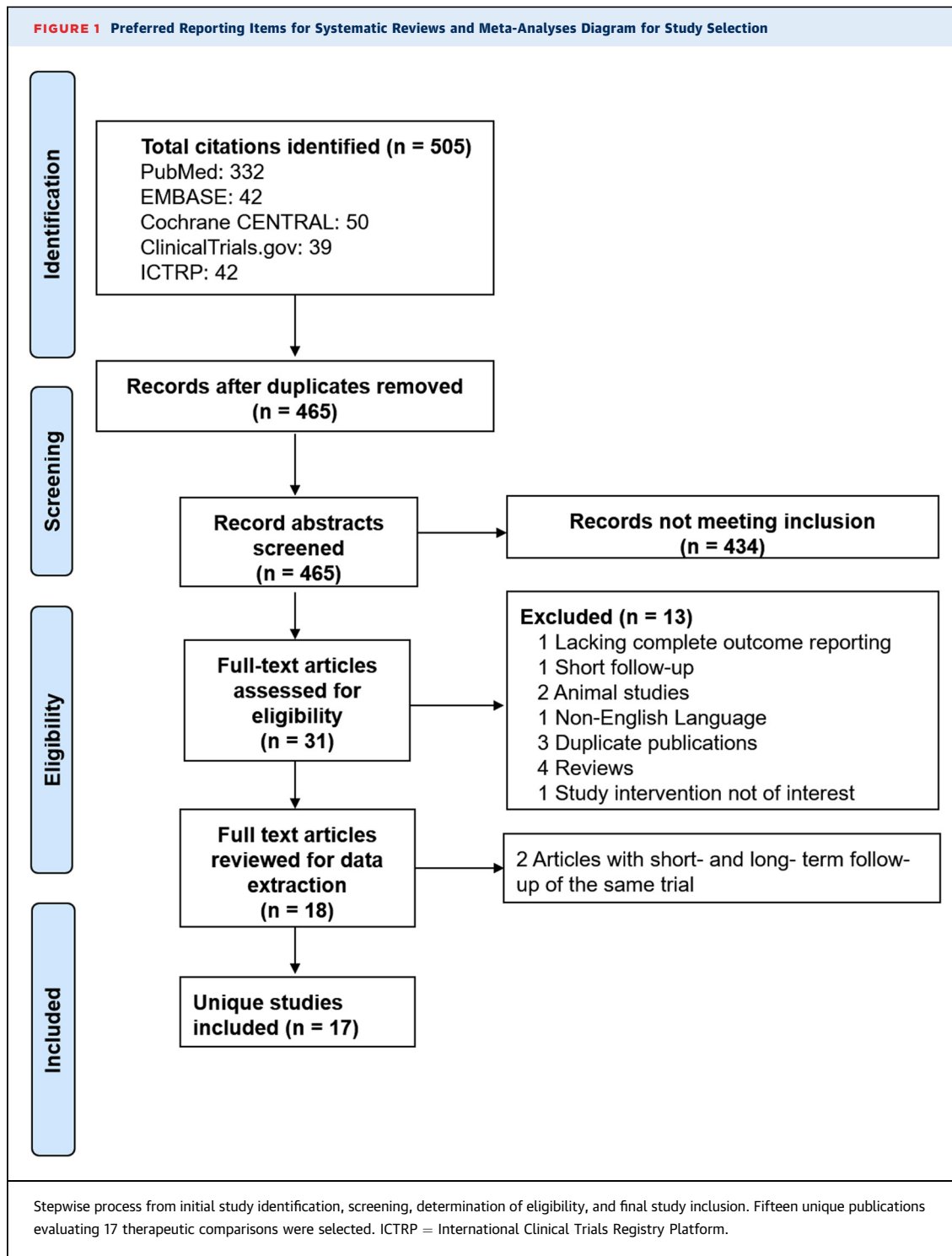
(SMD: +1.10; 95% CI: 0.49 to 1.72; I^2 = 96.9%), but this sensitivity analyses did not attenuate the large degree of heterogeneity (Supplemental Figure 4). Similar findings were noted on meta-analysis using WMD (p < 0.001 for all comparisons).

DISCUSSION

In this comprehensive and updated meta-analysis of cancer patients with recent chemotherapy across 17 studies, we identified a significant benefit to the use of neurohormonal therapy with higher LVEF and better LV strain on follow-up and no changes in other LV parameters in patients receiving chemotherapy (**Central Illustration**). The absolute benefit in attenuating declines in LVEF was estimated as small (<5% difference) and may be within inter-test variability of its measurement (36). These modest treatment effects on LVEF were consistently observed in trials examining strategies with renin-angiotensin-aldosterone-system (RAAS) inhibitors and β-blockers and in the large subgroup of trials examining exclusively breast cancer patients and patients receiving anthracycline-based chemotherapy. Additionally, there were numerically fewer major adverse clinical events in the neurohormonal therapy arm compared with placebo, although this did not reach statistical significance. However, interpretation of these findings needs to be contextualized in the background of significant heterogeneity across included studies and potential for publication bias as negative or neutral trials may not have been published.

CURRENT LANDSCAPE OF CARDIOPROTECTIVE STRATEGIES. The recognition of the cardiotoxic potential with various chemotherapeutic agents, including anthracyclines and trastuzumab, formed the basis for establishment of "cardio-oncology," an emerging area in clinical medicine and scientific discovery (37). In the current era, targeted cancer therapies have resulted in overall improvement in patient outcomes, life expectancy, and disease prognosis. Because older patients with greater burden of cardiovascular risk factors are exposed to potentially cardiotoxic chemotherapy regimens, cardiovascular disease prevention represents a central element in cancer management. As such, various cardioprotective approaches have been evaluated in a number of relatively small studies, introducing imprecision in effect size estimates and challenges to generalizability and application in clinical practice.

Recognizing this variability and the important gap in evidence, we conducted this study with an intention to provide a more global estimate of the overall benefits (or lack thereof) of current strategies of

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagram for Study Selection

Stepwise process from initial study identification, screening, determination of eligibility, and final study inclusion. Fifteen unique publications evaluating 17 therapeutic comparisons were selected. ICTRP = International Clinical Trials Registry Platform.

cardioprotection, specifically examining neurohormonal therapies. In this updated meta-analysis, the quality of reporting and availability of data regarding treatment-related changes in LVEF were high across studies. Importantly, there was significant evidence

of publication bias such that many of smaller identified experiences demonstrating cardioprotective benefits may have been selectively published. In addition, despite use of random effects models, we observed significant heterogeneity in treatment

TABLE 2 Baseline Left Ventricular Structure and Function Parameters

First Author (Year) (Ref. #)	Therapeutic Intervention	Control/Therapy					
		EF (%)	LVEDD (cm)	LVESD (cm)	E/A Ratio	E/e′ Ratio	Strain
Akpek et al. (2015) (17)*†	Spironolactone	67.7 ± 6.3/ 67.0 ± 6.1	4.6 ± 0.5/ 4.6 ± 0.4	2.9 ± 0.4/ 2.9 ± 0.3	1.29 ± 0.32/ 1.31 ± 0.37	8.3 ± 2.1/ 8.3 ± 1.6	-
Avila et al. (2018) (9)*†	Carvedilol	65.2 ± 3.6/ 64.8 ± 4.7	-	-	-	-	-
Bosch et al. (2013) (18)*†	Enalapril + carvedilol	62.6 ± 5.4/ 61.7 ± 5.1	-	-	-	-	-
Boekhout et al. (2016) (19)*	Candesartan	61 ± 6.6/ 60 ± 6.6	-	-	-	-	-
Cadeddu et al. (2010) (20)*†	Telmisartan	66 ± 5.0/ 66 ± 7.0	-	-	1.13 ± 0.14/ 0.96 ± 0.12	-	−20.9 ± 2.0/ −22.8 ± 1.5
Cardinale et al. (2006) (21)*†	Enalapril	62.8 ± 3.4/ 61.9 ± 2.9	-	-	-	-	-
Elitok et al. (2014) (22)*†	Carvedilol	65 ± 4.5/ 66 ± 6.1	4.4 ± 0.3/ 4.5 ± 0.4	2.8 ± 0.5/ 2.8 ± 0.4	1.1 ± 0.3/ 1.2 ± 0.4	-	−19.2 ± 4.1/ −20.2 ± 3.2
Georgakopoulos et al. (2010) (23)*	Metoprolol/enalapril	67.6 ± 7.1/ 67.7 ± 5.0/ 65.2 ± 7.1	4.8 ± 0.6/ 4.7 ± 0.5/ 4.9 ± 0.4	-	1 ± 0.4/ 1.1 ± 0.4/ 1.1 ± 0.4	-	-
Gulati et al. (2016) (24)‡	Candesartan + metoprolol/ candesartan alone/ metoprolol alone	62.8 ± 4.1/ 62.1 ± 5.0/ 62.5 ± 5.3/ 63.2 ± 4.4	-	-	-	7.4 ± 1.9/ 7.4 ± 2.1/ 7.1 ± 1.9/ 7.1 ± 2.1	-
Janbabai et al. (2017) (25)*†	Enalapril	59.6 ± 5.7/ 59.4 ± 7.0	-	-	1.09 ± 0.33/ 1.07 ± 0.00	6.4 ± 1.2/ 7.7 ± 1.2	-
Jhorawat et al. (2016) (26)*	Carvedilol	67.6 ± 6.0/ 63.2 ± 7.2	4.7 ± 6.0/ 4.6 ± 7.7	2.8 ± 5.5/ 2.9 ± 6.8	1.2 ± 0.5/ 1.4 ± 1.2	-	-
Kaya et al. (2013) (27)*†	Nebivolol	66.6 ± 5.5/ 65.6 ± 4.8	4.7 ± 0.4/ 4.7 ± 0.4	3.0 ± 0.3/ 3.0 ± 0.4	0.98 ± 0.22/ 1.01 ± 0.31	-	-
Kalay et al. (2006) (28)*	Carvedilol	69.7 ± 7.3/ 70.6 ± 8.0	4.6 ± 0.5/ 4.8 ± 0.5	3.0 ± 0.5/ 3.1 ± 0.5	1.0 ± 0.2 ± / 1.1 ± 0.2	-	-
Pituskin et al. (2017) (29)‡	Perindopril/Bisoprolol	61 ± 5.0/ 62 ± 5.0/ 62 ± 5.0	-	-	-	-	-
Salehi et al. (2011) (30)*†	Carvedilol	58.6 ± 3.6/ 61 ± 7.1	4.1 ± 0.6/ 3.9 ± 0.3	3.0 ± 0.4/ 2.7 ± 0.3	0.99 ± 0.45/ 0.83 ± 0.17	-	-
Nabati et al. (2017) (32)*†	Carvedilol	61.1 ± 5.0 / 58.7 ± 4.7	-	-	1.08 ± 0.32/ 1.01 ± 0.26	6.3 ± 1.2/ 6.9 ± 1.6	-
Guglin et al. (2019) (31)*	Carvedilol/lisinopril	62.2 ± 6.1 / 62.5 ± 6.6/ 63 ± 6.2	-	-	-	-	-

*EF measurement modality reported as 2-dimensional echocardiography. †EF measurement methodology (Simpson's rule) according to the American Society of Echocardiography guidelines, if reported. ‡EF measurement modality reported as magnetic resonance imaging.

LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; other abbreviations as in Table 1.

effects for all clinically relevant endpoints, potentially reflecting variation in study population, underlying malignancy, neurohormonal therapy, and imaging modality. Importantly, all identified studies were small in size, with only 2 randomizing >100 in each arm (19), and many were restricted to single-center experiences. Specific examination of studies applying more precise measures of LVEF using cardiac MRI attenuated, but did not eliminate this observed heterogeneity. Although our study does suggest a potential role of cardioprotective therapy, including with use of RAAS inhibitors and β-blockers, the degree of heterogeneity does limit the interpretability of pooled effect estimates.

FUTURE CLINICAL TRIALS OF CARDIOPROTECTIVE STRATEGIES. The degree of heterogeneity across these small, predominantly single-centered experiences (with attendant local biases) highlight the imperative for large, multicenter randomized clinical trials powered for adjudicated and meaningful clinical outcomes. Most contemporary clinical trials have been restricted to assessing effects of concomitant use of cardioprotective medical therapies on short-term changes in LVEF. Indeed, surrogate markers of cardiotoxicity (including LVEF) are subject to significant variability, may recover in a proportion of patients, and may not reliably reflect health status. Unfortunately, it is uncertain whether favorable

TABLE 3 Follow-Up Left Ventricular Structure and Function Parameters

First Author (Year) (Ref. #)	Therapeutic Intervention	Control/Therapy					
		EF (%)	LVEDD (cm)	LVESD (cm)	E/A Ratio	E/e Ratio	Strain
Akpek et al. (2015) [17]	Spironolactone	53.6 ± 6.8/ 65.7 ± 7.4	5.2 ± 0.4/ 4.9 ± 0.4	3.6 ± 0.5/ 3.1 ± 0.3	0.97 ± 0.33/ 1.19 ± 0.39	9.3 ± 2.8/ 8.5 ± 2.6	-
Avila et al. (2018) [9]	Carvedilol	63.9 ± 5.2/ 63.9 ± 3.8	-	-	-	-	-
Bosch et al. (2013) [18]	Enalapril + carvedilol	59.3 ± 1.65/ 61.5 ± 4.9	-	-	-	-	-
Boekhout et al. (2016) [19]	Candesartan	59 ± 10.3/ 59 ± 5.9	-	-	-	-	-
Cadeddu et al. (2010) [20]	Telmisartan	67 ± 6.0/ 68 ± 6.0	-	-	1.06 ± 0.12/ 0.87 ± 0.08	-	-20.8 ± 2.1/ -21.2 ± 1.9
Cardinale et al. (2006) [21]	Enalapril	48.3 ± 9.3/ 62.4 ± 3.5	-	-	-	-	-
Elitok et al. (2014) [22]	Carvedilol	63.3 ± 4.8/ 64.1 ± 5.1	4.4 ± 0.4/ 4.5 ± 0.3	2.8 ± 0.5/ 2.8 ± 0.4	1.09 ± 0.4/ 1.17 ± 0.3	-	-16.0 ± 0.4± / -20.1 ± 5.3
Georgakopoulos et al. (2010) [23]	Metoprolol/ enalapril	66.6 ± 6.7/ 63.3 ± 7.4/ 63.9 ± 7.5	4.8 ± 0.5/ 4.9 ± 0.4/ 5.0 ± 0.5	3 ± 0.4/ 3.2 ± 0.4/ 3.2 ± 0.5	1.0 ± 0.4/ 1.1 ± 0.4/ 1.0 ± 0.4	-	-
Gulati et al. (2016) [24]	Candesartan + metoprolol/ candesartan alone/ metoprolol alone	61 ± 1.8/ 61.4 ± 1.8/ 61 ± 1.8/ 60.6 ± 1.8	-	-	-	7.2 ± 0.7/ 7.6 ± 0.7/ 7.2 ± 0.7/ 7.6 ± 0.7	-
Janbabai et al. (2017) [25]	Enalapril	46.3 ± 7.0/ 59.9 ± 7.8	-	-	0.98 ± 0.3/ 0.98 ± 0.3	7.4 ± 2.0/ 7.1 ± 2.6	-
Jhorawat et al. (2016) [26]	Carvedilol	60.8 ± 11.3/ 63.9 ± 8.6	4.9 ± 0.6/ 4.8 ± 0.5	3.1 ± 0.7 ±/ 3.0 ± 0.6	1.28 ± 0.5/ 1.18 ± 0.5	-	-
Kaya et al. (2013) [27]	Nebivolol	57.5 ± 5.6/ 63.8 ± 3.9	5.2 ± 0.5/ 4.7 ± 0.4	3.3 ± 0.5/ 3.1 ± 0.4	0.84 ± 0.23/ 1.11 ± 0.30	-	-
Kalay et al. (2006) [28]	Carvedilol	52.3 ± 5.0/ 69.7 ± 5.0	5.1 ± 0.6/ 4.7 ± 0.4	3.8 ± 0.5/ 3.2 ± 0.6	0.87 ± 0.2/ 0.98 ± 0.2	-	-
Pituskin et al. (2017) [29]	Perindopril/bisoprolol	56 ± 4.0/ 59 ± 6.0/ 61 ± 4.0	-	-	-	-	-
Salehi et al. (2011) [30]	Carvedilol	53.9 ± 3.8/ 56.8 ± 6.2	4.6 ± 0.6/ 4.1 ± 0.4	3.2 ± 0.4/ 2.9 ± 0.4	0.86 ± 0.33/ 0.81 ± 0.17	-	-
Nabati et al. (2017) [32]	Carvedilol	51.7 ± 6.0/ 57.4 ± 7.5	-	-	0.96 ± 0.28/ 0.92 ± 0.25	7.2 ± 1.9/ 6.8 ± 1.5	
Guglin et al. (2019) [31]	Carvedilol/lisinopril	59.5/ ± 0.7/ 59.3 ± 0.7/ 60.7 ± 0.7					

Abbreviations as in **Table 2**.

short-term effects on this surrogate marker reliably translates to long-term benefits with respect to cardiovascular outcomes, especially when the estimated absolute benefits in LVEF appear to be within inter-test variability of its measurement [36].

Innovative trials in progress or that have recently completed will continue to expand the scope and understanding of cardioprotective strategies. The CECCY (Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity) trial, the largest clinical trial of β-blockers in cardioprotection, failed to demonstrate significant impact on LVEF reduction with carvedilol, but did suggest effects on troponin levels [9]. Longer term follow-up and evaluation of higher risk populations may facilitate greater power to detect meaningful effects on clinical outcomes. Trials enrolling cohorts with enriched risk profiles (for instance with positive cardiac biomarkers) [21] have the potential to identify patients who stand to benefit the most from cardioprotective strategies. The Cardio-Oncology Breast Cancer Study (NCT02571894) and Cardiotoxicity of Cancer Therapy (NCT01173341) trials are examining long-term cardiovascular effects of chemotherapy over 8-10 years. The Prevention of Anthracycline-Induced Cardiotoxicity (NCT01968200) trial is varying the timing of application cardioprotective therapy (either routinely concurrent to chemotherapy or selectively after presentation of signs of cardiotoxicity).
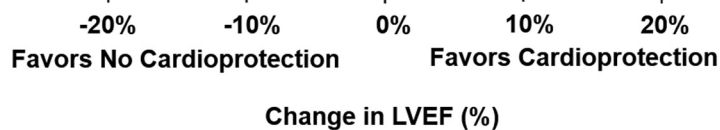
Ongoing and future clinical trials should incorporate dedicated clinical endpoint committees to adjudicate clinical HF events [38]. Given the broader

FIGURE 2   Treatment Effects on Changes in LVEF

Pooled effects of neurohormonal therapies versus placebo on changes in LVEF from baseline to follow-up. Data are presented here as pooled weighted differences. LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging.
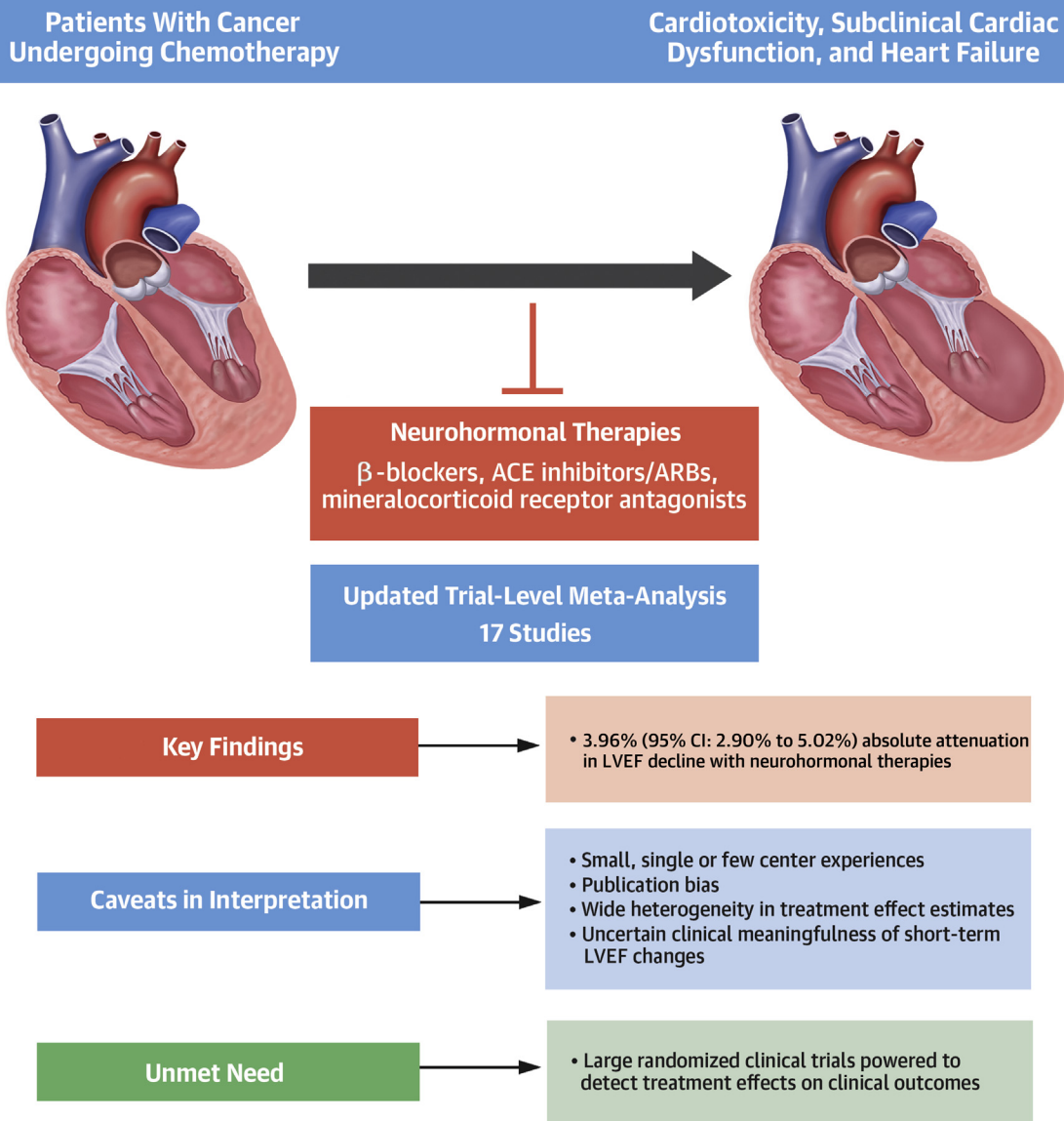
TABLE 4   Pooled Effects of Neurohormonal Therapies on Changes in LV Structure and Function

Outcome of Interest	No. of Studies Pooled	SMD (95% CI) Between Intervention and Control Arm for Change From Baseline	I²; p Value	Pooled Mean Differences (95% CI) Between Intervention and Control Arm for Change From Baseline*	I²; p Value
LV ejection fraction (%)	17	1.04 (0.57 to 1.50)	96%; <0.001	3.96 (2.90 to 5.02)	98%; <0.001
LV peak systolic longitudinal strain	3	−0.43 (−0.69 to −0.16)	26%; 0.257	−0.76 (−1.48 to −0.03)	68%; 0.023
LVESD (cm)	7	−0.40 (−0.90 to 0.10)	87%; 0.001	−0.19 (−0.42 to −0.04)	88%; <0.001
LVEDD (cm)	7	−0.32 (−0.71 to 0.07)	79%; 0.001	−0.19 (−0.42 to −0.04)	88%; <0.001
E/e′	4	−0.18 (−0.70 to 0.35)	88%; 0.001	−0.39 (−1.23 to 0.44)	89%; <0.001
E/A	10	0.18 (−0.07 to 0.42)	62%; 0.005	0.05 (−0.01 to 0.11)	60%; 0.005

Studies with more than 2 different comparator arms (e.g., ACEI/ARB vs. control and β-blockers vs. control) were treated as 2 different studies for the meta-analysis. *Weights were determined using random-effects models.

CI = confidence interval; SMD = standardized mean difference; other abbreviations as in **Tables 1 and 2**.

CENTRAL ILLUSTRATION Are Neurohormonal Therapies Beneficial in Preventing Cardiotoxicity in Patients Receiving Chemotherapy?

Patients With Cancer Undergoing Chemotherapy

Cardiotoxicity, Subclinical Cardiac Dysfunction, and Heart Failure

Neurohormonal Therapies

β-blockers, ACE inhibitors/ARBs, mineralocorticoid receptor antagonists

Updated Trial-Level Meta-Analysis 17 Studies

Key Findings
- 3.96% (95% CI: 2.90% to 5.02%) absolute attenuation in LVEF decline with neurohormonal therapies

Caveats in Interpretation
- Small, single or few center experiences
- Publication bias
- Wide heterogeneity in treatment effect estimates
- Uncertain clinical meaningfulness of short-term LVEF changes

Unmet Need
- Large randomized clinical trials powered to detect treatment effects on clinical outcomes

Vaduganathan, M. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):54–65.

In this updated meta-analysis of 17 studies enrolling patients receiving chemotherapy, randomization to neurohormonal therapy compared with placebo resulted in higher LVEF on follow-up with a small but statistically significant treatment effect. Small sample sizes, publication bias, and significant heterogeneity all limit clinical interpretability of these findings. Future trials of cardioprotective strategies adequately powered to detect clinical outcomes are needed. CI = confidential interval; HF = heart failure; LVEF = left ventricular ejection fraction.

range of potential cardiovascular effects of evolving cancer therapies, other than cardiomyopathy, evaluation of therapies beyond RAAS inhibitors and β-blockers are needed in this space. For instance, the PREVENT (Preventing Anthracycline Cardiovascular Toxicity With Statins) trial is evaluating the role of atorvastatin in attenuating anthracycline-related cardiotoxicity. Furthermore, trials will need to

determine if effective detection and potential treatment of cardiotoxicity may prevent dose reduction or interruption of necessary cancer therapies.

STUDY LIMITATIONS. Our meta-analysis has several important limitations. This trial-level meta-analysis relied on reported values in published reports; we lacked access to patient-level data. Most studies evaluated LVEF using standard echocardiography, and few included advanced imaging modalities to provide more precise characterization of LV structure and function. Changes in LVEF, as a continuous measure, may vary by baseline measurement, which was not consistently reported across studies. Beyond LVEF measurements, other reported endpoints, including clinical outcomes, were subject to significant missingness. Moreover, the long-term clinical significance of an echocardiographic endpoint in the cardio-oncology population remains unknown. This meta-analysis did not account for the dose of cancer therapy. The limited sample sizes across trials precluded detailed subgroup analyses by cardiovascular risk. Measures of safety or tolerability were not reported in standardized fashion across trials to facilitate pooling. Finally, many of the studies in this meta-analysis involved cardioprotection following treatment with anthracyclines. These results probably do not extend to many novel cancer therapies, such as cancer immunotherapies, where the mechanism of cardiotoxicity is different (39).

CONCLUSIONS

In this study-level pooled analysis, we observed a significant, but small, benefit of neurohormonal therapies in reducing decline in LV systolic function among patients undergoing chemotherapy. However, owing to the substantial heterogeneity across the 15 modest-sized studies and potential for publication bias in this updated meta-analysis, our study findings are not sufficient to recommend routine use of RAAS inhibitors or β-blockers as cardioprotective strategies in patients undergoing cardiotoxic chemotherapy (predominantly with anthracycline-based regimens). There is an enduring need for future, adequately powered randomized clinical trials to test the effects of cardioprotective therapies on both cardiovascular and cancer outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients receiving chemotherapy, there may be a modest benefit of neurohormonal therapies in attenuating declines in LVEF, with absolute benefits estimated to be less than 5%. Substantial heterogeneity and possible publication bias among existing trials limit our ability to recommend routine use of these agents to reduce cardiotoxicity.

TRANSLATIONAL OUTLOOK: Large, adequately powered randomized clinical trials are needed to determine the efficacy and safety of cardioprotective therapies in lowering the risk of chemotherapy-related cardiotoxicity and improving clinical outcomes.

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