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ORIGINAL RESEARCH

Efficacy of Dexrazoxane in Preventing Anthracycline Cardiotoxicity in Breast Cancer

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ABSTRACT

OBJECTIVES The authors performed a systematic review and meta-analysis of randomized and nonrandomized trials on the efficacy of dexrazoxane in patients with breast cancer who were treated with anthracyclines with or without trastuzumab.

BACKGROUND Breast cancer treatment with anthracyclines and trastuzumab is associated with an increased risk of cardiotoxicity. Among the various strategies to reduce the risk of cardiotoxicity, dexrazoxane is an option for primary prevention, but it is seldom used in clinical practice.

METHODS Online databases were searched from January 1990 up to March 1, 2019, for clinical trials on the use of dexrazoxane for the prevention of cardiotoxicity in patients with breast cancer receiving anthracyclines with or without trastuzumab. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model meta-analysis.

RESULTS Seven randomized trials and 2 retrospective trials with a total of 2,177 patients were included. Dexrazoxane reduced the risk of clinical heart failure (RR: 0.19; 95% CI: 0.09 to 0.40; $p < 0.001$) and cardiac events (RR: 0.36; 95% CI: 0.27 to 0.49; $p < 0.001$) irrespective of previous exposure to anthracyclines. The rate of a partial or complete oncological response, overall survival, and progression-free survival were not affected by dexrazoxane.

CONCLUSIONS Dexrazoxane reduced the risk of clinical heart failure and cardiac events in patients with breast cancer undergoing anthracycline chemotherapy with or without trastuzumab and did not significantly impact cancer outcomes. However, the quality of available evidence is low, and further randomized trials are warranted before the systematic implementation of this therapy in clinical practice. (J Am Coll Cardiol CardioOnc 2019;1:68–79) © 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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Breast cancer (BC) is the leading cause of cancer death in women (1). Significant progress has been made in both diagnostics and treatment improving survival. Cardiotoxicity (CTX) is a significant problem during or after BC treatment due to radiotherapy (2,3), estrogen deprivation (4), cytotoxic chemotherapy (5), or related to targeted therapies, especially anti-human epidermal growth factor 2 (HER2) agents (6).

Among the commonly used cytotoxic drugs, anthracyclines (ANTs) are the main cardiotoxic chemotherapy responsible for acute and chronic cardiac damage (7). Acute damage related to ANTs appears to be a consequence of acute myocyte dysfunction and death and clinically manifests as arrhythmias, acute left ventricular dysfunction, and rarely as acute myocarditis. Conversely, chronic damage occurs months or years after treatment and can be either diagnosed clinically through heart failure symptoms or detected asymptomatically with echocardiography (8). In the myocardium, ANT metabolites bind to ferric cation (Fe3+) releasing free radicals, resulting in alteration in permeability and the induction of apoptosis (9). ANTs may also inhibit cardiac topoisomerase IIβ, causing double-stranded DNA breaks and activating death pathways (10). ANT administration is associated with dose-dependent cardiac dysfunction, although many additional factors influence risk including age, pre-existing cardiovascular disease (11–14), and additional cancer therapies. For example, among targeted BC therapies, trastuzumab, a humanized monoclonal antibody targeting HER2, may lead to cardiomyopathy, especially when associated with ANT or taxanes (15–18).

SEE PAGE 80

Dexrazoxane (DEX) might exert a protective effect against ANT-induced CTX (19–21). The proposed mechanisms of DEX include its ability to act as a strong iron chelator and to displace iron from ANTs via its active metabolite (ADR-925) (22). In addition, DEX prevents complex formation between topoisomerase IIβ and ANT, reducing CTX (23). Despite clinical evidence of cardioprotection and the recommendations of cardiology societies (24–27), its use as a cardioprotective agent is limited. DEX was approved by the U.S. Food and Drug Administration in 1995 for use as a cardioprotective agent in patients with metastatic or advanced BC who have reached a cumulative ANT dose of 300 mg/m^2 and are continuing to receive doxorubicin (28). In addition, the American Society of Clinical Oncology recommends considering DEX as one of the possible strategies to avoid CTX during the administration of high-dose ANTs in adult cancer (29).

There are concerns that DEX could mitigate the antitumor activity of ANT in BC patients and increase secondary malignancies in studies in childhood lymphoma and leukemia after DEX use (30). These controversial data led to the limited use of DEX in clinical practice. However, in 2017, the European Medical Agency concluded that DEX should not be contraindicated in children at the highest risk of CTX (31). The European Medical Agency found no data indicating that DEX was associated with an increase in second primary malignancies, interfered with chemotherapy, or increased the risk of early death in children (32–34). In addition, none of the systematic reviews have evaluated the cardioprotective effect of DEX exclusively in BC patients treated with ANT with or without trastuzumab.

The aim of this study was to provide the first comprehensive systematic review and meta-analysis incorporating studies that evaluated the cardioprotective efficacy of DEX exclusively in BC patients treated with ANT with or without trastuzumab in both early and metastatic settings.

ABBREVIATIONS AND ACRONYMS

ANT = anthracycline
BC = breast cancer
CI = confidence interval
CTX = cardiotoxicity
DEX = dexrazoxane
HER2 = anti-human epidermal growth factor 2
HR = hazard ratio
RR = risk ratio

METHODS

The present systematic review was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (35,36) and the Cochrane Handbook for Systematic Reviews of Interventions (37). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist is provided in Supplemental Table 1. This systematic review was registered in the PROSPERO database (CRD42017077462).

SEARCH STRATEGY. Two investigators (A.V.S.M. and A.P.) independently searched MEDLINE (access through PubMed), Cochrane Central Register of Controlled Trials, and Embase from January 1990 up

from Clinigen Group, Pfizer, Novartis, Servier, Amgen, Takeda, Roche, Eli Lilly, Eisai, Bristol-Myers Squibb, Ferring Pharmaceuticals, and Boehringer Ingelheim. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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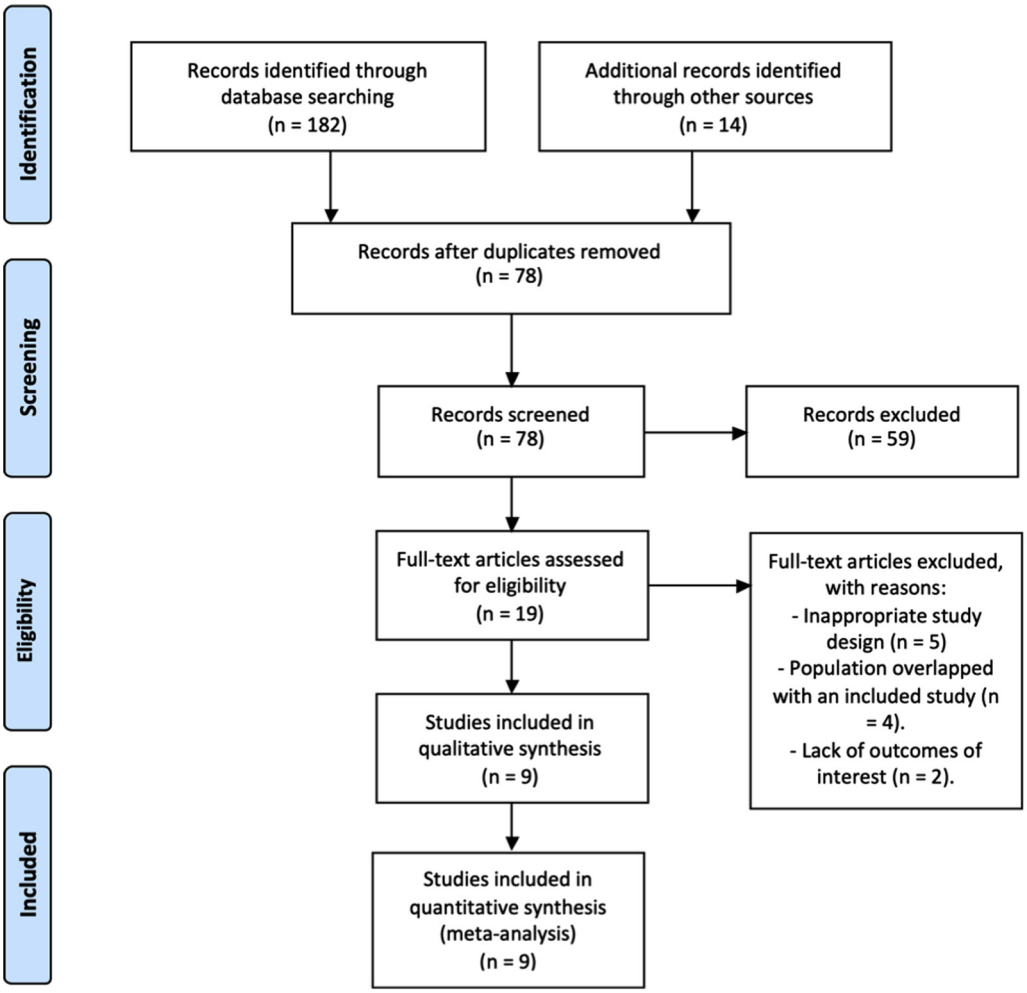
FIGURE 1 Flow Diagram for the Selection of Studies



A flow diagram of the studies screened, assessed for eligibility, and included in the review, with reasons for exclusions.

to March 1, 2019. The search strategy for PubMed is available in the Supplemental Appendix.

STUDY SELECTION. After the identification of all relevant studies, 2 authors (A.V.S.M. and A.P.) independently performed study selection, and discrepancies were resolved by consensus. Eligible studies met the following PICOS criteria: 1) Population: all-stage BC patients undergoing ANT-based chemotherapy; 2) Intervention: DEX; 3) Comparison intervention: placebo or any treatment; 4) Outcome: clinical heart failure (CHF) or cardiac event; and 5) Study design: randomized controlled trial (RCT) or observational trial. Exclusion criteria were pediatric studies and studies with overlapping populations. Eligible studies also had to contain complete data regarding the outcomes under evaluation in the meta-analysis.

The primary outcome was the development of symptomatic CHF (expressed as clinical heart failure according to study definition) or a cardiac event (expressed as subclinical heart failure defined as histopathological abnormal findings in endomyocardial biopsy, ventricular function abnormalities [assessed by echocardiography or radionuclide ventriculography], or hospital admission due to cardiac causes). We accepted each study's definition of subclinical CTX, considering that it was plausible and sufficiently comparable to be pooled (Supplemental Table 2).

Secondary outcomes were interference in oncologic treatment associated with DEX exposure, such

TABLE 1 Characteristics of the Included Studies

First Author (Ref. #)	Chemotherapy Regimen	Design	Population/ Previous Anthracycline Yes/No	N	Dose of Dexrazoxane or Dose Ratio of Dexrazoxane to Anthracycline	Control	Trastuzumab	Follow-Up	Mean or Median Cumulative Dose of Anthracycline* in mg/m^2 (Range) in Each Group if Available
Randomized controlled trials									
Lopez et al. (45)	High-dose epirubicin	Single center	Advanced and metastatic BC/No	92	DEX 1,000 mg/m^2	No therapy	No	NM	Control: 489 mg/m^2 DEX: 533 mg/m^2
Marty et al. (41)	Doxorubicin or epirubicin-based chemotherapy	Multicenter	Advanced and metastatic BC/Yes	164	20:1 DEX:DOX dose ratio or 10:1 DEX:EPI	No therapy	No	5 yrs	Control: 608 mg/m^2 (244-900 mg/m^2) DEX: 669 mg/m^2 (247-936 mg/m^2)
Speyer et al. (42)	5-fluorouracil, doxorubicin, cyclophosphamide (FAC)	Multicenter	Advanced and metastatic BC/No	150	20:1 DEX:DOX	No therapy	No	5 yrs	Control: 407.4 mg/m^2 (25-950 mg/m^2) DEX:558 mg/m^2 (50-2,150 mg/m^2)
Sun et al. (43)	Epirubicin and cyclophosphamide	Single center	Early-stage BC with concurrent type 2 diabetes mellitus/No	80	10:1 DEX:EPI	Placebo	No	126 days	In both groups: 266 mg/m^2
Swain et al. (44)	FAC	Multicenter	Advanced and metastatic BC/No	349	10:1 DEX:DOX	Placebo	No	3 yrs	<100-2,700 mg/m^2 anthracycline cumulative dose in each group; NM
Swain et al. (44)	FAC	Multicenter	Advanced and metastatic BC/No	185	10:1 DEX:DOX dose ratio	Placebo	No	3 yrs	<100-1,750 mg/m^2 anthracycline cumulative dose in each group; NM
Venturini et al. (20)	5-flourouracil, epirubicin, and cyclophosphamide) or high-dose epirubicin	Multicenter	Advanced and metastatic BC/Yes	160	10:1 DEX:EPI dose ratio	No therapy	No	NM	Control: 488 mg/m^2 (66-667 mg/m^2) DEX: 390 mg/m^2 (33-800 mg/m^2)
Retrospective trials									
Kim et al. (46)	Doxorubicin, cyclophosphamide, taxol, and trastuzumab	Single center	Early-stage BC/No	175	10:1 DEX:DOX dose ratio	No therapy	Yes	32.3 months	In both groups: 240 mg/m^2
Tahover et al. (47)	Doxorubicin and cyclophosphamide	Single center	Nonmetastatic BC/No	822	10:1 DEX:DOX dose ratio	No therapy	Yes	7 yrs	In both groups: 420 mg/m^2

*The epirubicin dose was converted to a doxorubicin-equivalent dose: 50 mg doxorubicin = 90 mg epirubicin.
BC = breast cancer; DEX = dexrazoxane; DOX = doxorubicin; Epi = epirubicin; NM = not mentioned.

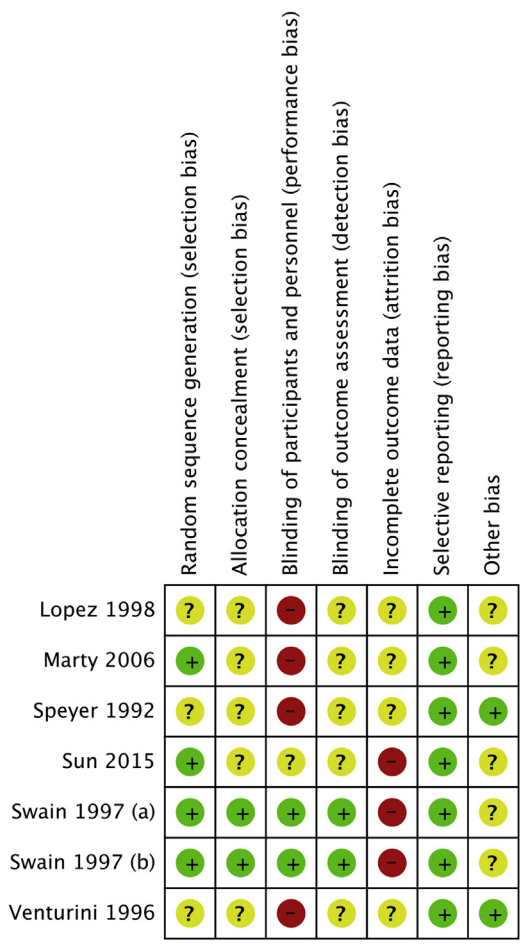
as the oncologic response rate, overall survival, and progression-free survival.

Studies evaluating other types of tumors or in which the outcomes in the BC group could not be assessed separately, case-control studies, studies in children, studies in which the use of DEX did not have a comparator group (placebo or no treatment), literature reviews, studies in animals, pharmacokinetic studies, pharmacoeconomic studies, case reports, and studies in which the outcomes of interest were not assessed were excluded from the analysis (Supplemental Table 3).

DATA EXTRACTION. After the literature search, data from eligible studies were independently extracted by 2 authors (A.V.S.M. and A.P.) using standardized forms. Patients' characteristics, treatment, regimens, outcomes of interest, and follow-up period were systematically collected by 2 investigators (A.V.S.M. and A.P.). Divergences were resolved by consensus.

STUDY QUALITY ASSESSMENT (RISK OF BIAS). Two independent reviewers (A.V.S.M. and A.P.) assessed the quality of the included trials. For nonrandomized trials, the Good Research for Comparative Effectiveness checklist was used (38,39) (Supplemental Table 4). For randomized controlled trials, we used the Cochrane Collaboration Group methods (37). Eventual divergences were resolved by consensus. We rated the potential risk of bias by applying a rating of "low," "high," or "unclear" to each study (Supplemental Figures 1 and 2).

FIGURE 2 Risk of Bias Summary



Authors' judgments about the risk of bias in each included randomized trial. **Green symbol with** + = low risk of bias; **yellow symbol with question mark** = unknown; **red symbol with** – = high risk of bias.

STATISTICAL ANALYSIS. We calculated the risk ratio (RR) with the 95% confidence interval (CI) for dichotomous variables. We reported the p value for the comparison between the groups, and a p value ≤0.05 was considered statistically significant. Heterogeneity between trials was explored by the chi-square test with significance set at a p value ≤0.10 and quantified with inconsistency measure (I^2). The random-effects model was applied because significant heterogeneity (in populations, interventions, and settings) was anticipated; we used τ^2 to quantify between-study variance. We performed publication bias plots for the overall primary outcomes (Supplemental Figures 2 and 3). We did not test publication bias because fewer than 10 trials were included in the analysis (37). The analysis was performed on an intention-to-treat basis whenever possible, as reported by the original studies. For overall survival and progression-free survival data, we applied the generic inverse variance function to combine logs of hazard ratios (HRs). We extracted the HR with 95% CI, and we obtained the log HR and standard deviation from the Kaplan-Meier curves using the Parmar method when HR was not presented (40). A prespecified subgroup analysis was performed hypothesizing that patients with previous exposure to ANT would have had greater benefit from DEX. Post hoc subgroup analyses were performed to assess possible differences in the effect estimates between randomized and retrospective trials and between patients with early or advanced/metastatic cancer. Post hoc sensitivity analysis comparing random- and fixed-effects models was performed (Supplemental Table 5).

We used the software Review Manager (RevMan [Computer program], Version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) or Comprehensive Meta-Analysis software (Version 3.3.070, Biostat, Englewood, New Jersey).

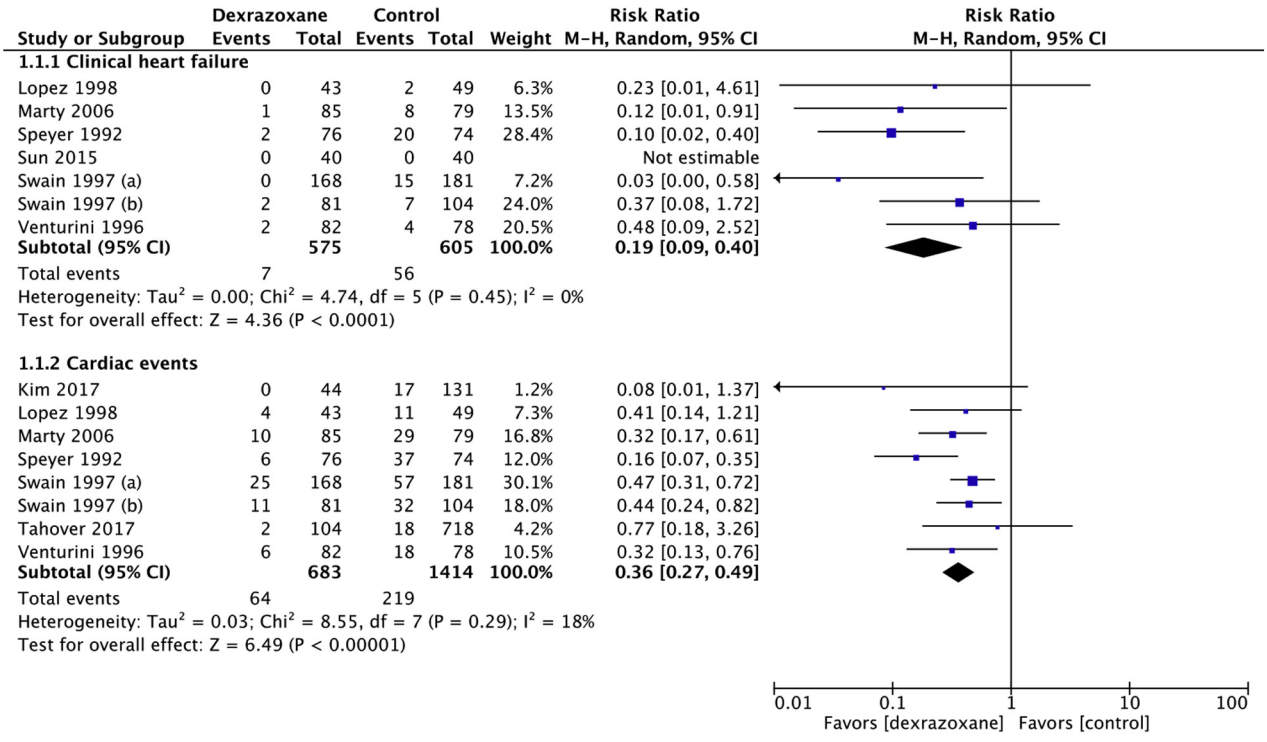
RESULTS

SEARCH RESULTS. A total of 196 publications were selected from the initial search, and a total of 188 records were excluded (**Figure 1**). Finally, 7 randomized trials (20,41-45) and 2 retrospective cohorts (46,47), all evaluating BC patients, were included in the systematic review and the meta-analysis. One article reported the results of 2 randomized trials (44). Major exclusions (articles excluded [19,21,48-56] with reasons) are reported in Supplemental Table 3.

STUDY CHARACTERISTICS. The characteristics of the 9 studies are reported in **Table 1**. We included a total of 2,177 female patients with metastatic/advanced BC (5 trials and 1,100 patients), nonmetastatic BC (1 trial and 822 patients), or early-stage BC (2 trials and 255 patients). All patients received doxorubicin or epirubicin as ANT-based chemotherapy. The average cumulative dose of ANTs ranged from 240 mg/m^2 to 713 mg/m^2, and the dose ratio of DEX to ANT was 10:1 or 20:1. Trastuzumab was part of the treatment only in the 2 retrospective cohorts included.

No randomized trials were judged as low risk of bias in all bias domains. Three trials had low risk of bias in the randomization process, 1 in allocation concealment, 1 in double blinding and blinding of outcome assessor, and 6 in selective reporting. All trials had at least 1 domain at high risk of bias (**Figure 2**, Supplemental Figure 1). The retrospective

FIGURE 3 Forest Plot for the Effect of DEX on the Risk of Clinical Heart Failure and Cardiac Events in BC Patients Treated With ANTs



Dexrazoxane (DEX) therapy reduced the risk of cardiac outcomes in patients receiving anthracycline (ANT)-based chemotherapy. CI = confidence interval; df = degree of freedom; M-H = Mantel-Haenszel.

cohort studies were considered to be of moderate quality (Supplemental Table 4).

CARDIAC TOXICITY. DEX therapy was associated with a lower risk of CHF compared with the control in patients receiving ANT-based chemotherapy alone (7 of 575 [1.22%] with DEX vs. 56 of 605 [9.26%] with control; RR: 0.19; 95% CI: 0.09 to 0.40; $p < 0.001$), with only RCTs reporting these data (**Figure 3**).

Cardiac events were also lower in patients allocated to DEX when compared with the control (64 of 683 [9.4%] with DEX vs. 219 of 1,414 [15.5%] with the control; RR: 0.36; 95% CI: 0.27 to 0.49; $p < 0.001$). The effect estimate was similar when limiting the analysis to RCTs (RR: 0.36; 95% CI: 0.26 to 0.49; $p < 0.001$) or retrospective studies (RR: 0.33; 95% CI: 0.03 to 3.39; $p = 0.35$) (**Figure 3**).

In 2 of 9 studies (20,41), patients had already received ANT-based chemotherapy months or years previously. Among these patients who were re-exposed to ANT, DEX possibly reduced the risk of CHF (RR: 0.27; 95% CI: 0.07 to 1.07; $p = 0.06$) and the risk of cardiac events (RR: 0.32; 95% CI: 0.19 to 0.54; $p < 0.001$). The benefit of adding DEX to ANT treatment was also consistent in the subgroup of patients who were exposed to ANT for the first time. The risk of CHF was significantly reduced (RR: 0.15; 95% CI: 0.06 to 0.39; $p < 0.001$) as well the risk of cardiac events (RR: 0.37; 95% CI: 0.24 to 0.58; $p < 0.001$) (**Table 2**).

The funnel plots addressing publication bias for the overall primary outcomes are reported in Supplemental Figures 2 and 3. In sensitivity analysis, results were similar when a fixed-effects model was used (Supplemental Table 5).

ONCOLOGIC OUTCOMES AND OVERALL SURVIVAL. In 5 randomized trials, the partial and complete response rates were assessed at different follow-up intervals. Similar results were noted in groups exposed or not to DEX (complete response rate [RR: 1.10; 95% CI: 0.75 to 1.61; $p = 0.62$] and partial response rate [RR: 0.88; 95% CI: 0.75 to 1.02; $p = 0.10$]). Stable disease was reported in only 3 randomized trials, and similar results were noted between groups (RR: 0.92; 95% CI: 0.70 to 1.20; $p = 0.54$) (**Figure 4**).

TABLE 2 Subgroup Analyses

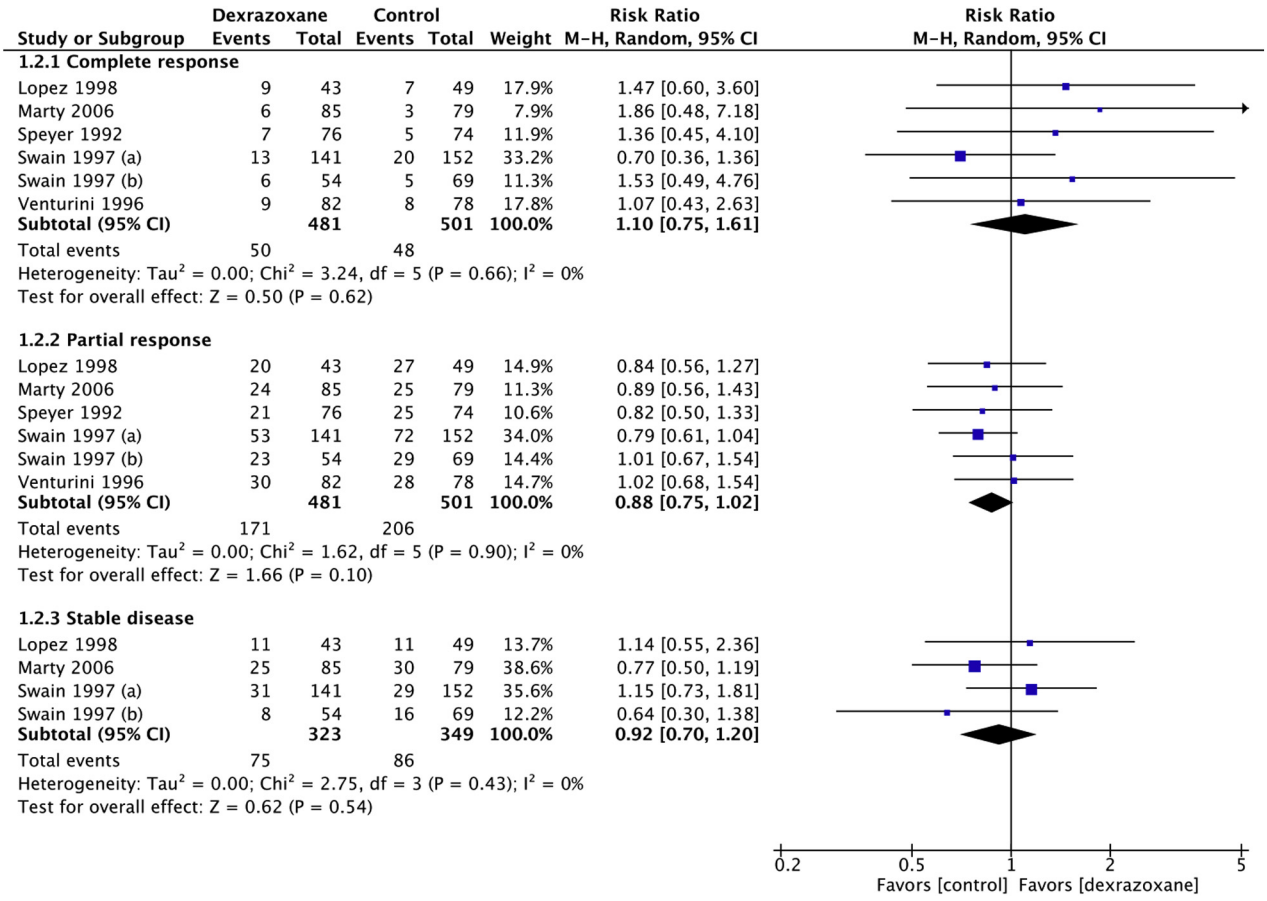
Outcome	Analysis	Number of Trials	Effect Estimate (95% CI)	p Value	p Value Between Groups
Clinical heart failure	Primary analysis	7	RR: 0.19 (0.09-0.40)	<0.001	
	RCTs	7	RR: 0.19 (0.09-0.40)	<0.001	NA
	Retrospective trials	0	–	–	
	Previous ANT	2	RR: 0.27 (0.07-1.07)	0.06	0.51
	No previous ANT	5	RR: 0.15 (0.06-0.39)	<0.001	
	Early BC	1	Not estimable	–	NA
	Advanced/metastatic BC	6	RR: 0.19 (0.09-0.40)	<0.001	
Cardiac events	Primary analysis	8	RR: 0.36 (0.27-0.49)	<0.001	
	RCTs	6	RR: 0.36 (0.26-0.49)	<0.001	0.95
	Retrospective trials	2	RR: 0.33 (0.03-3.39)	0.35	
	Previous ANT	2	RR: 0.32 (0.19-0.54)	<0.001	0.67
	No previous ANT	6	RR: 0.37 (0.24-0.58)	<0.001	
	Early BC	1	RR: 0.08 (0.01-1.37)	0.08	0.30
	Advanced/metastatic BC	7	RR: 0.37 (0.27-0.50)	<0.001	
Complete response	Primary analysis	6	RR: 1.10 (0.75-1.61)	0.62	
	RCTs	6	RR: 1.10 (0.75-1.61)	0.62	NA
	Retrospective trials	0	–	–	
	Previous ANT	2	RR: 1.27 (0.60-2.68)	0.53	0.67
	No previous ANT	4	RR: 1.05 (0.67-1.63)	0.83	
	Early BC	0	–	–	NA
	Advanced/metastatic BC	6	RR: 1.10 (0.75-1.61)	0.62	
Partial response	Primary analysis	6	RR: 0.88 (0.75-1.02)	0.10	
	RCTs	6	RR: 0.88 (0.75, 1.02)	0.10	NA
	Retrospective trials	0	–	–	
	Previous ANT	2	RR: 0.96 (0.71-1.31)	0.81	0.49
	No previous ANT	4	RR: 0.85 (0.70-1.02)	0.07	
	Early BC	0	–	–	NA
	Advanced/metastatic BC	6	RR: 0.88 (0.75-1.02)	0.10	
Stable disease	Primary analysis	4	RR: 0.92 (0.70-1.20)		
	RCTs	4	RR: 0.92 (0.70-1.20)	0.54	NA
	Retrospective trials	0	–	–	
	Previous ANT	1	RR: 0.77 (0.50-1.19)	0.25	0.33
	No previous ANT	3	RR: 1.02 (0.73-1.44)	0.90	
	Early BC	0	–	–	NA
	Advanced/metastatic BC	4	RR: 0.92 (0.70-1.20)	0.54	
Progression-free survival	Primary analysis	5	HR:0.97 (0.75-1.24)	0.81	
	RCTs	5	HR:0.97 (0.75-1.24)	0.81	NA
	Retrospective trials	–	–	–	
	Previous ANT	2	HR:0.68 (0.49-0.94)	0.02	0.007
	No previous ANT	3	HR: 1.13 (0.95-1.34)	0.17	
	Early BC	–	–	–	NA
	Advanced/metastatic BC	5	HR: 0.97 (0.75-1.24)	0.81	
Overall survival	Primary analysis	6	HR: 1.01 (0.86-1.17)	0.92	
	RCTs	5	HR: 1.04 (0.88-1.22)	0.65	0.20
	Retrospective trials	1	HR: 0.71 (0.41-1.24)	0.23	
	Previous ANT	2	HR: 1.06 (0.73-1.54)	0.75	0.76
	No previous ANT	4	HR: 1.00 (0.84-1.18)	0.97	
	Early BC	1	HR: 1.04 (0.88-1.22)	0.23	0.20
	Advanced/metastatic BC	5	HR: 0.71 (0.41-1.24)	0.65	

ANT = anthracycline; BC = breast cancer; CI = confidence interval; HR = hazard ratio; RR = relative risk; NA = not applicable; RCT = randomized clinical trial.

Overall survival was also similar between groups (HR: 1.01; 95% CI: 0.86 to 1.17; p = 0.91) (Figure 5). No subgroup effects were found when stratifying the trials according to previous ANT exposure (Table 2).

Progression-free survival was similar between the groups (HR: 0.97; 95% CI: 0.76 to 1.25; p = 0.81) (Figure 5). However, in the subgroup of studies including patients with more advanced disease

FIGURE 4 Forest Plot for the Effect of DEX on Oncological Response in BC Patients Treated With ANTs



Oncological outcomes were similar in groups exposed or not exposed to dexrazoxane. Abbreviations as in Figure 3.

re-exposed to ANT chemotherapy, the use of DEX was associated with a decreased risk of disease progression (HR: 0.68; 95% CI: 0.49 to 0.94; p = 0.02). In the subgroup of studies without previous exposure to ANT, DEX was associated with no significant difference on progression-free survival (HR: 1.13; 95% CI: 0.95 to 1.34; p = 0.17) (Table 2).

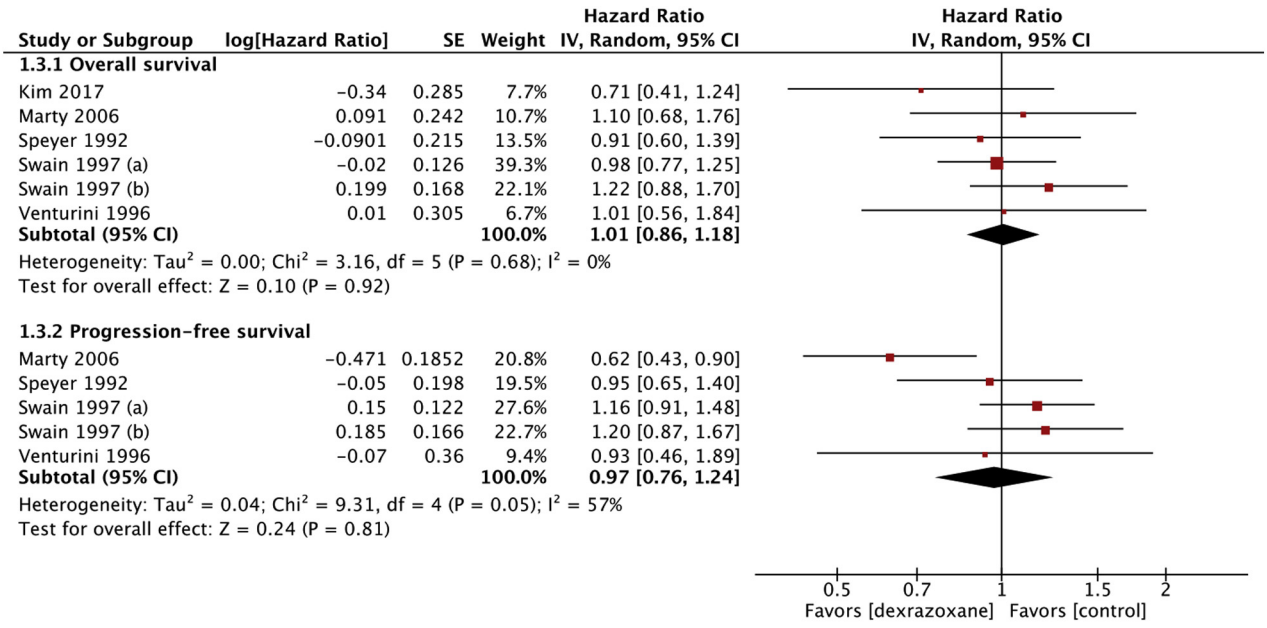
DISCUSSION

Our review is the first and largest meta-analysis performed to date to explore the potential of DEX in the prevention of cardiotoxicity in BC patients exposed to ANT. In our systematic review and meta-analysis including patients with both early and advanced/metastatic BC exposed to ANT, we observed a lower rate of clinical heart failure and cardiac events in patients receiving DEX compared with controls without a detrimental effect on the oncological response (Central Illustration).

This study adds to the existing data an analysis of 2,177 BC patients exposed to anthracycline analyzing cardiovascular outcomes. Previous studies included both adult and pediatric populations (33,57,58), which limited the interpretation of the cardioprotective effect in BC patients.

An important question is whether cardioprotective drugs reduce the antitumor efficacy of ANT and thereby compromise oncology treatment and affect survival (59). A previous systematic review including several types of tumors in adults and children suggested that patients treated with DEX might have a reduced response rate (60). However, an update of the same meta-analysis did not confirm these findings (33), and our results are aligned to the contemporary data, which show DEX does not compromise cancer treatment.

FIGURE 5 Forest Plot for the Effect of DEX on the Overall Survival and Progression-Free Survival



Overall survival and progression free-survival were similar between the groups. IV = inverse variance; other abbreviations as in Figure 3.

For many years, trastuzumab-related CTX was considered to be predominantly temporary and reversible with drug interruption or discontinuation. More recent data partially modified this assumption (61,62), reporting a non-negligible incidence of long-term CTX. A large, retrospective study of Chen et al. (63) reported on 45,537 elderly women with early BC have a higher risk of heart failure or cardiomyopathy in those who received trastuzumab after ANT therapy.

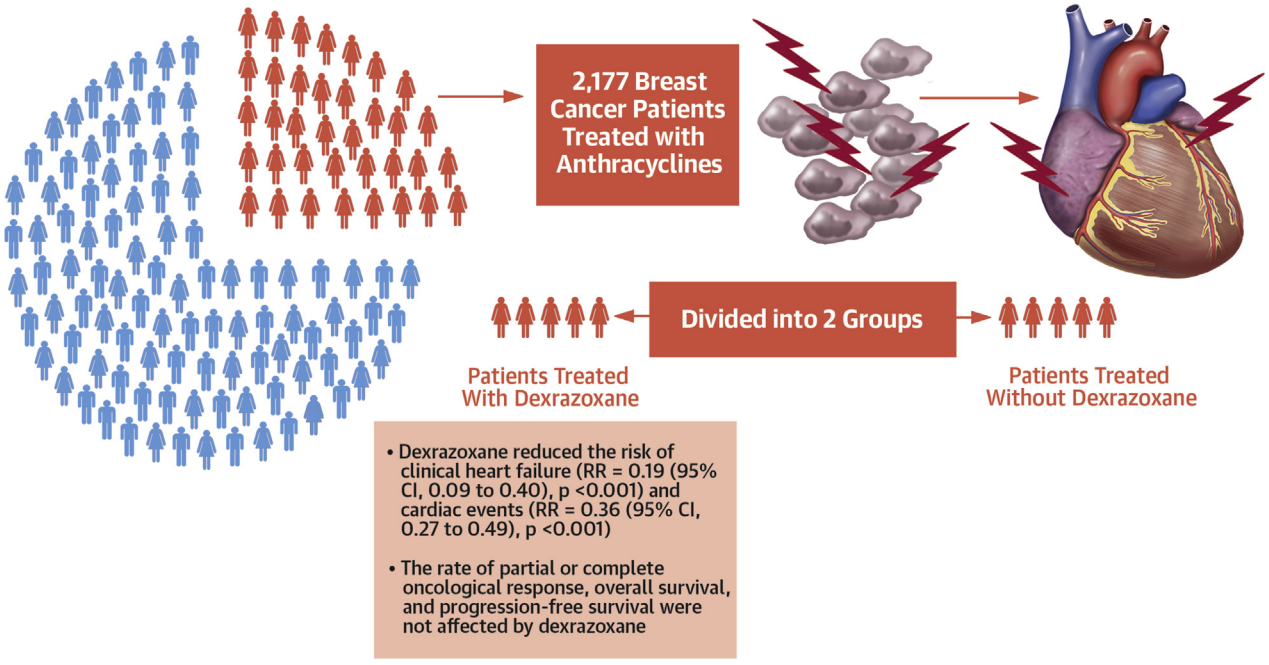
A significant reduction in the occurrence of cardiac events when DEX was added to the ANT-based chemotherapy in BC patients was confirmed by our analysis. Regarding BC patients exposed to both ANT and trastuzumab, the cardioprotective effect of DEX was similar, but it is important to acknowledge that evidence comes from 2 retrospective studies and that prospective RCTs are lacking.

Pharmacological prevention of CTX is not widely used. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers (13,64–66) have been tested as an option for primary prevention, but the level of existing evidence is not sufficiently strong to indicate these treatments routinely for BC patients treated with ANT and/or trastuzumab (67). Our study reinforces DEX as an effective cardioprotective agent in BC patients receiving ANT-based chemotherapy, and it is the only present option for primary prevention in this population.

When we analyzed the studied subgroups, we did not find any difference suggesting a higher cardioprotective effect of DEX in a specific subpopulation of BC patients. Nonetheless, most evidence is of low quality to allow definite recommendations. An assessment of the methodological quality of the studies included in this review was performed using the Cochrane "risk of bias" tool (37) for assessing the risk of bias in each included RCT. We found that no randomized trials were judged as low risk of bias in all bias domains. The domains with more studies classified as high risk of bias were "performance bias" due to knowledge of the allocated interventions by participants and personnel during the studies and "attrition bias" due to the amount, nature, or handling of incomplete outcome data. Future high-quality RCTs should be performed on DEX in BC patients avoiding all potential source of bias, which could compromise the reliability of their results.

Uncertainty regarding oncological outcomes has also limited DEX prescribing (59). In the present meta-analysis, we found no difference between the DEX and control groups regarding the oncological response rate and survival, suggesting no influence of DEX on ANT-anticancer activity in the BC populations studied.

CENTRAL ILLUSTRATION **Dexrazoxane in Breast Cancer Patients Under Anthracycline-Based Chemotherapy**



Macedo, A.V.S. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):68–79.

The present systematic review was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (35,36) and the Cochrane Handbook for Systematic Reviews of Interventions (37). We identified, in a universe of breast cancer patients evaluated in clinical studies **(blue and red people)**, the population included in this review **(red people)**. Studies analyzing the cardioprotective effect of dexrazoxane in breast cancer patients treated with anthracyclines were selected for meta-analysis. In 9 studies with a total of 2,177 breast cancer patients, dexrazoxane reduced the risk of heart failure and cardiac events without a significantly impact in cancer outcomes.

When assessing the meta-analysis data concerning progression-free survival, we found a substantial statistical heterogeneity and a large prediction interval for HR. As part of a possible explanation for this heterogeneity, we found a favorable effect for the use of DEX in the BC patient subgroup previously treated with ANT, with higher rate of progression-free survival. These findings should be considered with caution and hypothesis generating. In addition, it should be noted that some studies in preclinical models showed that DEX has an intrinsic antitumor activity and that its use can enhance the benefit of ANT, potentially also contributing to its therapeutic effect (68).

STUDY LIMITATIONS. We highlight several limitations of our study. We relied on the reporting of CTX and/or clinical cardiac events, and there may be some patients with subclinical CTX who are not included. The definitions of CTX and cardiac events also vary widely between the studies included, and none reported cardiac biomarkers to detect CTX. We did not assess the impact of the use of DEX in combination with ANT on hematologic toxicities. The clinical significance of this excess of hematologic toxicity could impact antitumor efficacy. We believe that this is unlikely because there were no adverse effects on these parameters in our review.

CONCLUSIONS

DEX reduced the risk of clinical heart failure and cardiac events in BC patients undergoing ANT chemotherapy with or without trastuzumab and did not significantly impact cancer outcomes. Nonetheless, due to the low quality of the actual evidence available, further randomized trials are warranted before the systematic implementation of this therapy for primary cardioprotection.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients treated for both early and advanced/metastatic breast cancer exposed to anthracyclines, dexrazoxane reduces the occurrence of clinical heart failure and cardiac events without a detrimental effect on oncological outcomes.

TRANSLATIONAL OUTLOOK: Future, large-scale randomized trials are needed to establish the effects of dexrazoxane in breast cancer patients receiving anthracyclines with or without trastuzumab on both cardiovascular and oncological outcomes.

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KEY WORDS cardiomyopathy, cardioprotection, cardiotoxicity, dexrazoxane, doxorubicin, heart failure, meta-analysis, survivorship, trastuzumab

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