Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Cardiotoxic Effect of Modern Anthracycline Dosing on Left Ventricular Ejection Fraction: A Systematic Review and Meta-Analysis of Placebo Arms From Randomized Controlled Trials

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BACKGROUND: Anthracyclines are a key chemotherapeutic agent used against hematological and solid organ malignancies. However, their benefits in cancer survival are limited by cumulative, dose-related cardiotoxicity. The impact of anthracyclines on left ventricular ejection fraction (LVEF), in the era of modern chemotherapy regimens, remains unclear.

METHODS AND RESULTS: Three databases (CENTRAL, MEDLINE, and SCOPUS) were systematically searched for randomized trials evaluating cardioprotective agents against placebo, in preventing cardiotoxicity. Echocardiography or magnetic resonance measured LVEF pre- and post-anthracycline-based chemotherapy was abstracted from placebo trial arms. The key terms included "anthracycline," "cardiotoxicity" and "randomized." A doxorubicin equivalent anthracycline dose metric was calculated to compare different anthracyclines. A random-effects model was used to pool mean difference in LVEF after anthracycline. Meta-regressions were calculated to identify variation sources. We included 660 patients from 19 trials. The weighted mean baseline LVEF across studies was 62.6%, and follow-up LVEF assessment was performed at 6 months. The pooled mean decline in LVEF among placebo arms was 5.4% (95% CI, 3.5%–7.3%) with a doxorubicin equivalent anthracycline dose of 385 mg/m^2. Meta-regression analysis showed no significant difference in LVEF against doxorubicin equivalent anthracycline dose as continuous (P=0.29) or against published cut-offs for cardiotoxicity (250 mg/m^2, P=0.21; 360 mg/m^2, P=0.40; and 400 mg/m^2, P=0.66). The differences in mean LVEF were not associated with sex, adjunct chemotherapy, or cancer type.

CONCLUSIONS: The magnitude of LVEF impairment post-anthracycline therapy appears less than previously described with modern dosing regimens. This may improve the accuracy of power calculation for future clinical trials assessing the role of cardioprotective therapy.

Key Words: anthracyclines ■ cardio-oncology ■ cardiotoxicity ■ left ventricular ejection fraction ■ meta-analysis

Anthracyclines have remained a key chemotherapeutic agent for the past 5 decades in the treatment of breast and hematological malignancies.[1] As survivorship from cancer improves with earlier detection and improved treatment strategies, clinicians are now increasingly challenged by the manifestation of anthracycline-induced cardiotoxicity. The American Society of Echocardiography defines cardiotoxicity as a 10% reduction in left ventricular ejection fraction (LVEF) <53%.[2]

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018802

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Our systematic review and meta-analysis pools left ventricular ejection fraction data from the placebo arms of randomized controlled trials to establish the cardiotoxic effects of modern anthracycline regimens for the first time.
- After performing our literature search, we identified 660 patients from 19 relevant trials.
- We found that even in placebo groups with no cardioprotective therapy, the pooled mean difference in left ventricular ejection fraction was only 5.40% (95% CI, 3.5%–7.3%), much less than previously described.

What Are the Clinical Implications?

- Our review will assist clinicians in educating patients receiving modern anthracycline-based chemotherapy on the overall risks of cardiotoxicity.
- It will also provide important baseline placebo data for future studies evaluating the role of cardioprotective agents in anthracycline-based cardiotoxicity.
- Future studies will be able to use our pooled mean data to assist with sample size calculation during trial design.

Nonstandard Abbreviations and Acronyms

CTRCD	cancer therapeutics related cardiac dysfunction
EAD	equivalent anthracycline dose

Anthracyclines can induce left ventricular dysfunction, which typically causes a chronic, irreversible cardiomyopathy.[3] Clinical studies have identified risk factors for anthracycline cardiotoxicity such as cumulative anthracycline dose, infusion rates, and pre-existing heart failure.[2] Since the discovery of anthracycline-induced cancer therapeutics–related cardiac dysfunction (CTRCD), clinicians have sought to minimize toxicity by modifying chemotherapy protocols to limit the cumulative anthracycline dose, and by monitoring cardiac function more closely.[3] The potential for cardioprotective drugs to further minimize cardiotoxicity before anthracycline administration, has been an area of intense research over the past 2 decades.[4–6] Multiple randomized controlled trials (RCTs) have been performed to find a suitable agent, however some of these trials have failed to show a statistically significant benefit with drugs such as beta-blockers and angiotensin-converting enzyme inhibitors.[7–9]

The rates of cardiac failure and cardiotoxicity reported in the literature are based on data published >30 years ago, ranging broadly from 7% to 65%.[10–12] However, little is known about the degree of LVEF decline caused by anthracyclines in the era of modern chemotherapy protocols. We hypothesized that the reasons for the negative results in some RCTs could be because of an overestimation of anticipated LVEF decline in sample size calculations, as modern dosing regimens may cause less cardiotoxicity than what was seen 20 to 30 years ago.[7,9,13] Thus, we aimed to elucidate the pooled mean of LVEF decline amongst the cancer population in "placebo" groups of RCTs which investigate cardioprotective agents.

METHODS

The authors declare that all supporting data are available within the article and its supplementary files.

Literature Search

We performed a systematic review of literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to identify RCTs where the effects of potential cardioprotective agents, on anthracycline-induced cardiotoxicity, were observed.[14] The search strategy was designed to address our aim, and we followed a structured Patient-Intervention-Comparison-Outcome (PICO) format to define our inclusion criteria. The population of interest were patients with any malignancy who required anthracycline-based chemotherapy. We focused on the placebo arms of eligible trials, so that only patients who did not receive any cardioprotective intervention were included. Our primary outcome was the change in LVEF from baseline to post anthracycline-based chemotherapy with either transthoracic echocardiography, or via cardiac magnetic resonance imaging. We searched PUBMED, SCOPUS, CENTRAL (Cochrane database (Cochrane Central Register of Controlled Trials), and Cochrane Database of Systematic Reviews from database inception until the search date (April 2, 2019) to identify eligible RCTs. Key MeSH terms that were used included "cardio-protective," "cardiotoxicity," "CTRCD," "anthracyclines," and "RCT." Our search strategies for all included databases are provided in Table S1. We also performed manual searches of reference lists from relevant systematic reviews and guidelines and incorporated additional relevant studies into our overall search.

Study Selection

Databases were searched by 2 independent reviewers (P.J. and S.S.), and pertinent articles were screened by title, abstract, and full-text. Disputes between the 2 reviewers were resolved by a third, senior author (K.N.). Articles were excluded if only animal or pediatric data were reported, or if LVEF was not assessed with validated measures such as LVEF biplane in accordance with echocardiography guidelines as well as cardiac magnetic resonance imaging. Only full-text published articles were included, and studies were excluded if patients in the placebo arm had received anthracycline-based therapy before baseline echocardiographic assessment to avoid measuring preexisting cardiotoxicity.

Data Extraction

Patient characteristics such as sample size, age, sex, and cancer type were extracted into an electronic data-entry form. Cancer therapy protocols including anthracycline type, anthracycline dose, and adjunctive trastuzumab use were also obtained to include in our analysis. We used conversion factors described in the European Society of Cardiology consensus statement to standardize anthracycline types into a single measure termed doxorubicin equivalent anthracycline dose (EAD).[2] This allowed idarubicin and epirubicin doses to be scaled to doxorubicin dose with scaling factors of 0.53 and 0.7, respectively. LVEF pre- and post-chemotherapy, along with corresponding SDs, were also included to ascertain the mean difference in unadjusted LVEF after anthracycline administration. If SDs were not available in the main or supplementary text, they were derived from statistical significance tests or CIs reported for the difference in mean LVEF. Available outcome data for symptomatic heart failure, hospitalization, and death rates were also extracted for patients in placebo arms. E-mails were also sent to the corresponding authors to obtain raw data and further statistical information where available.

Statistical Analysis

Data were meta-analyzed with R statistical software version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) with the "metafor" package.[15] A random-effects model was used as primary analytical method to pool the mean difference between LVEF measurement pre- and post-anthracycline therapy in the placebo arms of these trials. We chose the random-effects model as primary because we assumed that the effects being estimated in the different studies are not identical but follow some distribution. More precisely, we assumed that LVEF reduction attributable to anthracycline cardiotoxicity varies from study to study and the true LVEF reduction for these RCTs would be distributed around a mean. A fixed-effects model was also used as sensitivity analysis. The 95% CIs were also calculated for the mean difference ejection fraction. To determine if there was any difference in LVEF decline amongst more modern RCTs, we performed a subset analysis to examine trials performed since 2010.

Findings were considered statistically significant if $P<0.05$. Pre-specified meta-regression was performed to determine if anthracycline dose, expressed as either a continuous or categorical variable, caused a statistically significant impact on outcome as well as for potential confounders such as, the proportion of female, adjunct chemotherapy, and cancer type. Heterogeneity between studies was assessed using the Cochrane test statistic and I^2. Other key variables such as sex, cancer type, and adjunct chemotherapy were also compared against mean LVEF change with meta-regression analysis. We used the Cochrane Risk of Bias Tool version 2 on all included studies and plotted outcomes as either "low," "unclear," or "high" across the 5 primary domains.

We hypothesized that RCTs evaluating cardioprotective agents may be underpowered to detect a statistically significant LVEF decline in the age of modern chemotherapy. To evaluate this, we aimed to tabulate the sample sizes required for future RCTs to demonstrate statistically significant findings. To achieve this, the pooled mean LVEF decline obtained from our meta-analysis, along with the associated SD from the random-effects model, were entered into the Vanderbilt statistical power calculator.[16] We used a 2-sided alpha of 0.05 with 80% and 90% power across all studies.

RESULTS

We identified 19 RCTs relevant to our analysis after performing a literature search in accordance with the PRISMA guidelines, shown in Figure 1. Baseline characteristics for each included trial are summarized in Table 1.[17–32] A total of 660 patients were included from the placebo arms of these 19 trials, and 85% of these patients were female. The mean age was 50.6 years. We found differences in treated malignancy between the included trials, with 12 of the trials focusing on breast cancer, 4 on hematological malignancy, and 3 on a combination of both. Nine of the trials used doxorubicin exclusively, while 6 used only epirubicin. The remaining 6 trials had patients who had received different anthracycline agents within the same placebo arm. With regards to anthracycline dosing, the mean doxorubicin EAD

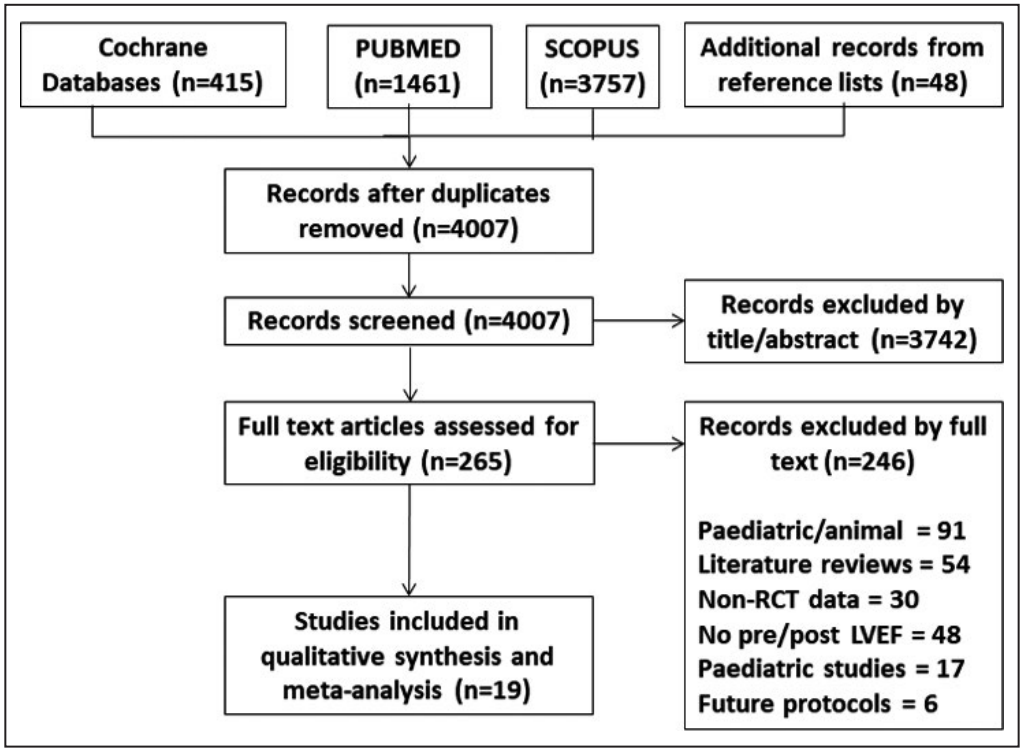

Figure 1. PRISMA flowchart of literature search.
Literature search was performed by 2 independent reviewers from database inception until April 2, 2019. LVEF indicates left ventricular ejection fraction; RCT, randomized controlled trial.

was 385 mg/m^2 as adjusted for body surface area. Patients were followed up for an average duration of 6 months across the 19 included trials. Three of the trials used cardiac magnetic resonance as their main imaging modality,[21,27,29] while the others used LVEF measured with transthoracic echocardiography bi-plane method of disks.

LVEF measures, pre- and post-chemotherapy for each included trial, are shown in Table 2. We performed a meta-analysis of the pooled mean difference in LVEF pre- and post-anthracycline–based chemotherapy, as shown in Figure 2. Using a random-effects model, the overall reduction in pooled mean LVEF post-chemotherapy in the placebo arms of included RCTs was 5.4% (95% CI, 3.5%–7.3%). The fixed-effects model had a lower 95% CI of 3.4%, which was similar to the random-effects model. Of note, there was significant heterogeneity between included studies, with an I^2 statistic of 92%. Our subset analysis of modern trials performed within the past 10 years is illustrated in Figure 3. This showed an LVEF reduction of 5.62% (95% CI, 3.59%–7.68%) using the random-effects model, which was similar to our initial analysis.

We tabulated outcome data for symptomatic heart failure, hospitalization rates and death in Table S2. There was a clear paucity of reported data for clinical outcomes across all studies, and definitions of CTRCD varied significantly between studied RCTs. As a result, further statistical analysis on these outcomes was not performed.

Based on our pooled estimates of LVEF decline, we performed several sample size estimations, assuming a hypothetical situation with a perfect agent which can completely prevent LVEF decline (Table 3). After using the Vanderbilt calculator, required sample sizes per arm ranged between 50 and 1136. Of note, these sample sizes are larger than the majority of RCTs included in our meta-analysis.

We performed a meta-regression analysis which showed no significant difference in LVEF decline against doxorubicin EAD when measured as a continuous variable (P=0.29). There was also no significant difference when doxorubicin EAD was measured as a categorical variable using cut-offs of 250 mg/m^2 (P=0.21), 360 mg/m^2 (P=0.40), and 400 mg/m^2 (P=0.66). These thresholds have been previously published as potential limits above which significant increases in cardiotoxicity have been observed.[33,34] A graphical representation of our meta-regression analysis against doxorubicin EAD is shown in Figure 4. There was significant heterogeneity in the equivalent anthracycline dose administered between studies. Separate meta-regression analyses were also performed against sex (ie, proportion of female, P=0.69), cancer type (P=0.36), and adjunct chemotherapeutic agents (P=0.51). No statistically significant impacts of these variables on the mean change in LVEF were found.

Table 1. Baseline Characteristics of Included Trials

Trial	Y	Sample Size	Mean Age	% Female	Follow-Up (mo)	Cancer Type	Anthracycline Agent	EAD (mg/m^2)
Massidda et al[17]	1997	10	50.7	100	6	Breast	Epirubicin	252
Lopez et al[18]	1998	62	55	76	6	Mixed	Epirubicin	616
Georgakopoulos et al[19]	2010	40	49	53	31	Hematology	Doxorubicin	388
Acar et al[20]	2011	20	53	55	6	Hematology	Doxorubicin or Idarubicin	251
Salehi et al[13]	2011	22	44	64	4	Mixed	Doxorubicin or Epirubicin	540
Bosch et al[21]	2013	37	51	47	6	Haematology	Doxorubicin	241
Kaya et al[22]	2013	18	51	100	6	Breast	Doxorubicin or Epirubicin	348
Liu et al[23]	2013	20	54	100	6	Breast	Doxorubicin	…
Elitok et al[24]	2014	40	53	100	6	Breast	Doxorubicin	523
Akpek et al[25]	2015	40	51	100	6	Breast	Doxorubicin or Epirubicin	509
Cadeddu et al[26]	2016	24	53	75	6	Mixed	Epirubicin	280
Gulati et al[27]	2016	30	51	100	6	Breast	Epirubicin	283
Jhorawat et al[28]	2016	27	39	33	6	Hematology	Doxorubicin	253
Pituskin et al[29]	2016	30	51	100	11	Breast	Doxorubicin	643
Janbabai et al[30]	2017	35	47	89	6	Mixed	Doxorubicin	367
Nabati et al[31]	2017	40	47	100	6	Breast	Doxorubicin	360
Avila et al[7]	2018	96	53	100	6	Breast	Doxorubicin	240
Cochera et al[8]	2018	30	52	100	6	Breast	Doxorubicin	519
Nabati et al[32]	2019	39	48	100	6	Breast	Doxorubicin	338

EAD indicates equivalent anthracycline dose standardized to doxorubicin; and Mixed, both breast cancer and hematological malignancies.

Table 2. Left Ventricular Ejection Fraction Pre- and Post-Anthracycline Chemotherapy in Placebo Arms

Trial	Y	Pre-LVEF (%)	Post-LVEF (%)	Mean Change LVEF (%)	95% Lower CI	95% Lower CI
Massidda et al[17]	1997	56.00	57.00	1.00	–1.17	3.17
Lopez et al[18]	1998	65.00	56.76	–8.24	–11.01	–5.47
Georgakopoulos et al[19]	2010	67.60	66.60	–1.00	–4.03	2.03
Acar et al[20]	2011	62.90	55.00	–7.90	–13.07	–2.73
Salehi et al[13]	2011	58.56	53.94	–4.62	–6.81	–2.43
Bosch et al[21]	2013	62.59	59.31	–3.28	–5.73	–0.83
Kaya et al[22]	2013	66.60	57.50	–9.10	–12.73	–5.47
Liu et al[23]	2013	57.00	45.95	–11.05	–13.82	–8.28
Elitok et al[24]	2014	66.00	64.10	–1.90	–4.36	0.56
Akpek et al[25]	2015	67.70	53.60	–14.10	–16.97	–11.23
Cadeddu et al[26]	2016	66.00	66.00	0.00	–2.83	2.83
Gulati et al[27]	2016	63.10	60.30	–2.80	–5.11	–0.49
Jhorawat et al[28]	2016	67.56	60.82	–6.74	–11.56	–1.92
Pituskin et al[29]	2016	61.00	56.00	–5.00	–7.29	–2.71
Janbabai et al[30]	2017	59.61	46.31	–13.30	–16.30	–10.30
Nabati et al[31]	2017	61.13	51.67	–9.46	–11.88	–7.04
Avila et al[7]	2018	65.20	63.90	–1.30	–2.57	–0.03
Cochera et al[8]	2018	61.00	60.00	–1.00	–2.29	0.29
Nabati et al[32]	2019	55.10	49.95	–5.15	–7.76	–2.54

LVEF indicates left ventricular ejection fraction.

Risk of Bias Assessment

Using the Cochrane Risk of Bias V2 tool, articles were evaluated across 5 primary domains. Of note there was significant overall bias amongst 60% of individual studies, with only 20% having an overall low risk of bias. Key areas of concern were insufficient details about blinding of sonographers when LVEF was being assessed, as well as a lack of clear information about the blinding process. Only 4 of the included trials reported sufficient detail about allocation concealment to minimize the risk of selection bias occurring. A summary of the overall risk of bias assessment is shown in Figure 5. A breakdown of risk of bias assessment by individual study is included in Figures S1 and S2.

DISCUSSION

The accurate estimation of the degree of LVEF decline from modern anthracycline regimens is crucial, as it affects clinical practice, informed consent, and trial design (ie, sample size calculation). Our analysis showed that the mean LVEF reduction in patients from the RCT placebo arm exposed to anthracycline chemotherapy appears to be around 5.4% but could be as small as 3.4% based on lower limit of 95% CI. In meta-regression analysis, none of sex, cancer type, adjunct chemotherapy, and anthracycline dose was associated with the variability in LVEF decline.

To our knowledge, this is the first systematic review and meta-analysis that has quantitatively assessed the magnitude of LVEF decline in the era of modern anthracycline-based chemotherapy. While previous studies have examined the incidence of clinical heart failure and subclinical cardiotoxicity, there have not been any randomized trials designed to quantitatively assess magnitude of LVEF reduction in patients exposed to anthracycline agents.[5,6] Small studies have reported a higher LVEF reduction of 9% to 17% post anthracycline exposure without cardio-protection, however, these were performed over 15 years ago.[18,35] Our pooled mean LVEF decline of 5.4% is less than previously described, and may not manifest as heart failure clinically.

A common finding with our analysis and recent systematic reviews of cardioprotective agents is the marked heterogeneity in frequency and degree of cardiotoxicity among RCTs exploring CTRCD. A recent meta-analysis evaluating cardioprotective agents demonstrated that the incidence of heart failure with anthracyclines reported in the literature is ≈3.1% (95% CI, 1.9%–4.6%; I^2, 93.6%), and that the frequency of LVEF reduction was seen in ≈13.8% (95% CI, 10.4%–17.7%; I^2,=95.3%) of patients.[36] Of note, this data were heterogeneous with high Cochrane test statistic and I^2, and significant differences in treatment protocols. There were also marked variations in the baseline standards of care between placebo arms of the included

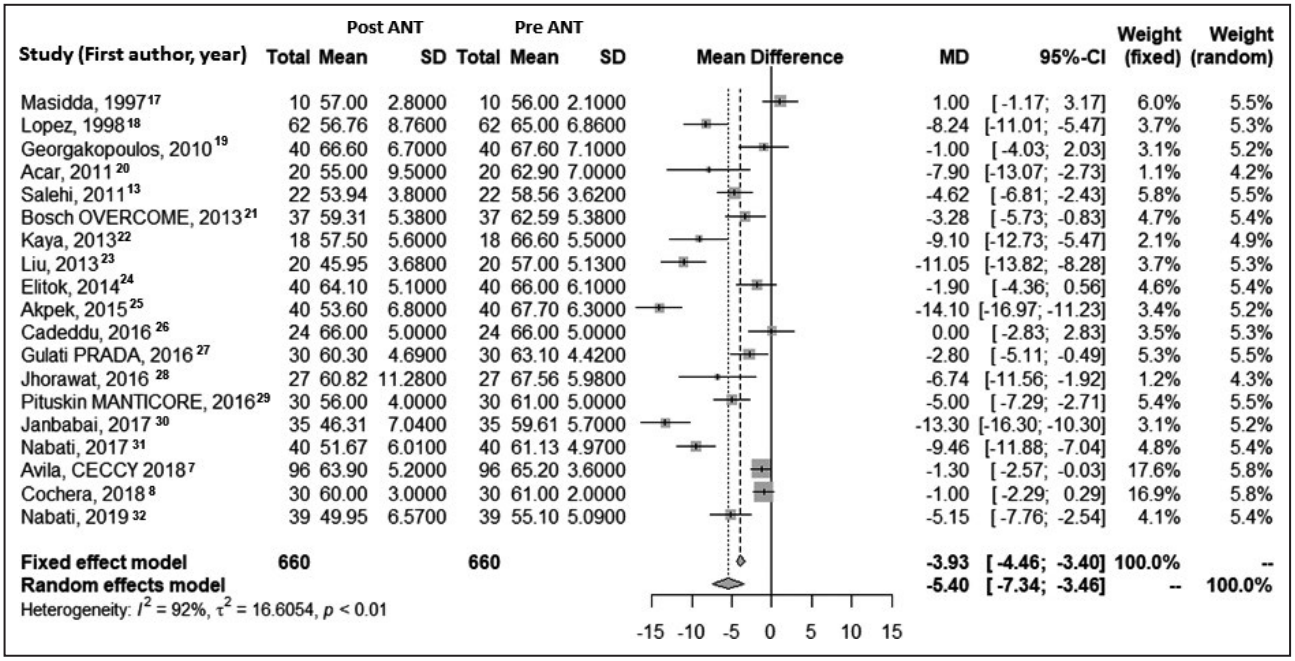

Figure 2. Meta-analysis of left ventricular ejection fraction mean difference pre- and post-anthracycline chemotherapy. The fixed-effects model assumes that the left ventricular ejection fraction decline in one study is the same as the values of the other studies, where the differences are only from sampling error. A random-effects model assumes that the left ventricular ejection fraction declines are not identical but follow some distribution. We reported left ventricular ejection fraction decline using the random-effects model (ie, 5.4 percentage point declines) as our primary end point to provide a conservative estimate of the magnitude of cardiotoxicity, and the fixed-effects model as secondary (3.9 percentage point declines). ANT indicates anthracycline; CECCY, Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity; MANTICORE, Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research; MD, mean difference; OVERCOME, Prevention of Left Ventricular Dysfunction with Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies; and PRADA, Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy.

trials. Part of this heterogeneity could be the variability in clinical manifestation of heart failure, as well as how susceptible different population subgroups may be to CTRCD. There may be underlying genetic factors that make certain subgroups more susceptible, as in-vitro work has identified possible genes such as ABCC1 that may play a role in cardiotoxicity.[37] A better understanding of the underlying mechanisms driving cardiotoxicity may help to explain the variations in LVEF decline between different populations.

This analysis emphasizes the importance of accurate sample size calculations performed when designing trials that examine cardioprotective agents. Historically, adequate sample size in cardioprotection RCTs has been determined using the expected incidence of heart failure or CTRCD. However, this relies on LVEF being considered a dichotomous variable, where the change is over or under 10%, in accordance with the definition. Importantly, most RCTs studying cardioprotective agents also evaluate LVEF as a continuous variable, and as such the expected magnitude of LVEF decline could be considered when calculating statistical power.[7,9,13,24] Despite this, that amongst our 22 included trials, only 4 performed sample size calculations with mean LVEF estimates.[21,25,29,38] The calculations were based on in-house pilot studies with marked variability ranging from 5% to 17%.[25,38]

Regarding the outcome of these trials, 6 of the included did not show a statistically significant difference in LVEF change between the treatment and placebo groups.[7,8,13,21,24,26] Of these, only 3 trials reported their sample size calculations, as shown in Table 3.[7,21,24] Only 1 trial used LVEF as a continuous variable for the sample size calculation,[21] whilst another used estimated cardiotoxicity incidence rather than mean LVEF change.[7] Therefore, there might have been a type II error among the RCTs with non-significant results, where much larger sample sizes would have shown positive findings. If larger sample sizes are not feasible, future trials may require alternate strategies such as studying higher risk populations.

One of the strengths of our analysis is the focus on only RCT patients, as the methodology is typically performed at high quality to assess patient outcomes in a controlled setting. Our findings from the above analysis when compared with the Table 3

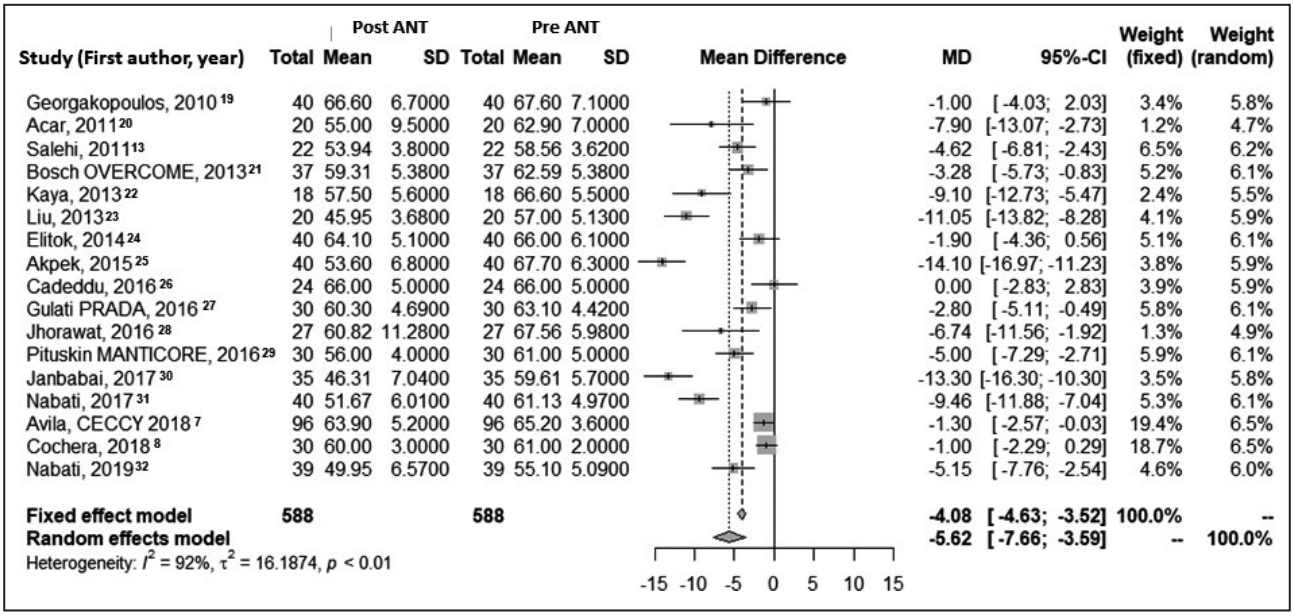

Figure 3. Meta-analysis of left ventricular ejection fraction mean difference pre- and post-anthracycline chemotherapy for modern trials performed since 2010.
ANT indicates anthracycline; CECCY indicates Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity; MANTICORE, Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research; MD, mean difference; OVERCOME, Prevention of Left Ventricular Dysfunction with Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies; and PRADA, Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy.

calculations show that some of the cardioprotection RCTs performed to date may have been underpowered to detect a statistically significant difference in LVEF between treatment and placebo groups. This suggests that there is the potential for type II statistical error in some of the cardioqprotective trials which have already been performed. Future studies should consider this when performing power calculation, and investigators may need to recruit larger sample sizes to minimize the chance of Type II error occurring.

Table 3. Sample Size Calculations Based on This Meta-Analysis

Estimated Mean Decline in LVEF		Power Required for Trial	Sample Size Per Trial Arm
Random-effects model Point estimate	5.4%	80%	349
		90%	467
Random-effects model Lower 95% CI	3.46%	80%	849
		90%	1136
Fixed-effects model Point estimate	3.93%	80%	50
		90%	66
Fixed-effects model Lower 95% CI	3.4%	80%	66
		90%	88

SDs calculated using 95% CIs. Fixed-effect model SD=6.93%. Random effects model SD=25.43. Sample size calculations performed based on independent t test using Vanderbilt power size calculator.[16] LVEF indicates left ventricular ejection fraction.

Study Limitations

Several factors merit consideration in the interpretation of our results. First, like all meta-analyses, this work is limited by variations in the original studies and publication bias, although we followed standard approaches

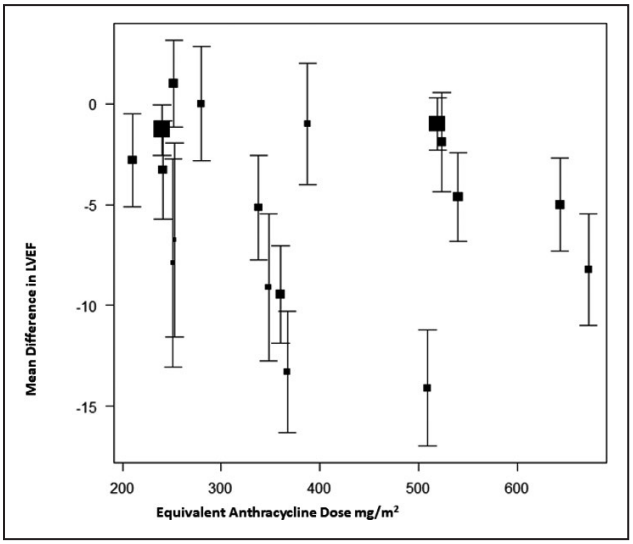

Figure 4. Meta-regression of left ventricular ejection fraction against equivalent anthracycline dose.
There is marked heterogeneity in anthracycline doses between studies. There does not appear to be a clear correlation between left ventricular ejection fraction mean difference, and doxorubicin EAD. LVEF indicates left ventricular ejection fraction.

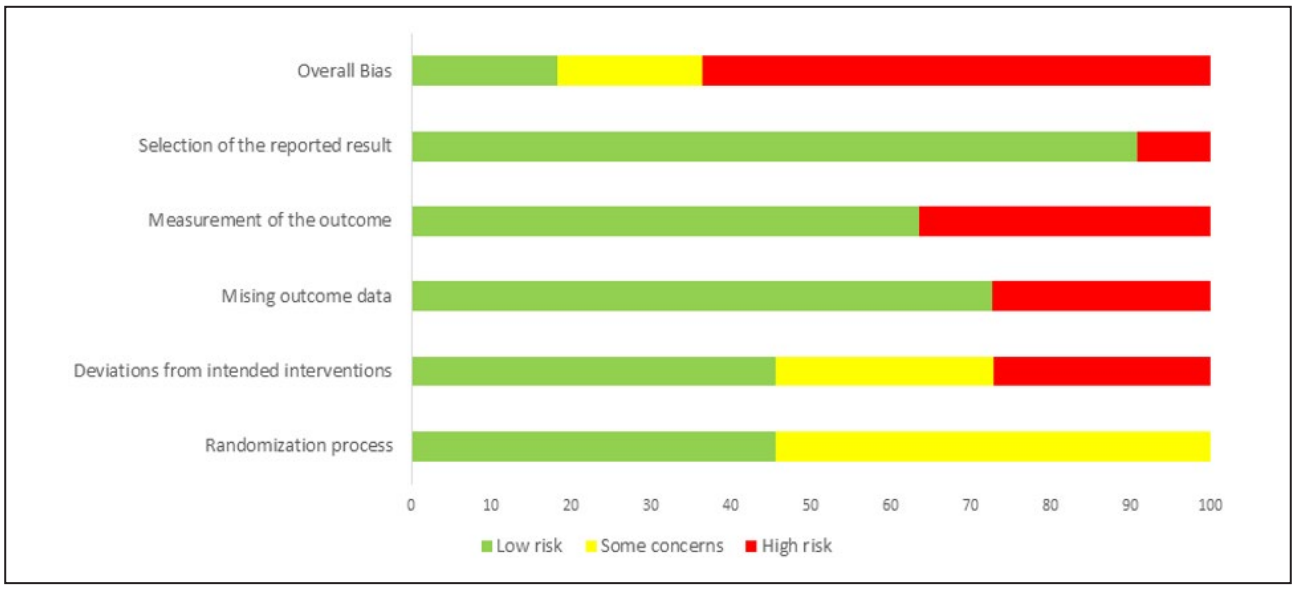

Figure 5. Summary of risk of assessment bias, as assessed by the Cochrane risk of bias assessment tool.
There was an overall bias of 60% across all studies.

to detect this. We could not perform individual patient data meta-analysis although we contacted the corresponding authors. This did not allow us to extensively explore the underlying reasons for such marked heterogeneity between studies beyond the standard approaches including meta-regression analysis.

Our Cochrane Risk of Bias assessment showed significant bias in up to 60% of the RCTs in our meta-analysis. This was contributed to by limited descriptions of outcome assessment in the methodology sections of included trials, as well as a lack of LVEF data for patients who passed away before repeat cardiac imaging. As shown in Figures S1 and S2, the majority of outcome assessment bias is amongst the trials conducted from 2011 to 2013.[13,20,22,23] These trials predominantly reported their primary outcome dichotomously as the incidence of cardiomyopathy, eg, LVEF <50%, rather than LVEF decline as a continuous variable. The high risk of bias we calculated using the Cochrane Risk of Bias tool was attributed to the missing data in their defined primary outcome. However LVEF measurements were consistently reported amongst these studies, with lower risk of measurement bias, and this is the data we used for our analysis.

Next, the studied population in the majority of the included RCTs were females undergoing chemotherapy for breast cancer. This limits the external validity of our review to male patients, and to patients with non-breast cancer malignancies receiving anthracyclines. Considering that our reviewed trials were also highly heterogeneous, the results need to be interpreted in this context. Also, there are also significant temporal variations of cardiotoxicity onset, from 1 week up to 20 years after anthracycline administration, which are independent of established risk factors of cumulative dose and pre-existing cardiac disease.[39]

The majority of RCTs do not have follow-up beyond 6 months, and as a result the long-term LVEF reduction may have been underestimated. Studies using more sensitive measures of cardiac function such as myocardial strain have shown that subclinical changes can develop well before changes in LVEF occur.[40] There are currently large RCTs underway evaluating the role of cardioprotection in preventing cardiotoxicity (using) myocardial strain as outcome of changes (instead of LVEF), and these may provide important insights.[41]

CONCLUSIONS

The magnitude of LVEF impairment caused by modern anthracycline regimens is less than previously described. This has important implications in sample size calculation estimates for future clinical trial design assessing the role of cardioprotective therapy. The small magnitude of LVEF reduction with known its inherent variability, LVEF may not be the best marker for detecting cardiotoxicity. Further research is needed into more sensitive ways monitoring CTRCD, such as myocardial strain imaging or troponin assays.

ARTICLE INFORMATION

Received August 4, 2020; accepted January 14, 2021.

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Sources of Funding

None.

Disclosures

Dr. Negishi is supported by a Fellowship (Award Reference No.101868) from the National Heart Foundation of Australia, which had no role in the preparation of this manuscript.

Supplementary Material

Tables S1–S2
Figures S1–S2

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Supplemental Material

Table S1. Search Strategies for each database.

Database	Search String	Results
SCOPUS	1. "randomized controlled trial " OR "controlled clinical trial" OR randomized OR placebo OR randomly OR trial OR rct 2. preventative OR prevention OR preventing OR cardioprotective OR protective OR prophylactic 3. cardiotoxicity OR "Cardiac toxicity" OR "chemotherapy related cardiomyopathy" OR "cancer treatment-related cardiac dysfunction" OR CTRCD OR anthracycline OR doxorubicin OR epirubicin OR Idarubicin OR daunorubicin 4. #1 AND #2 AND #3 5. #4 Limited to exact keyword "Human" **6.** # 5 Limited to Article or Review	3757
PUBMED	"randomized controlled trial " OR "controlled clinical trial" OR randomised OR randomized OR placebo OR randomly OR trial OR rct **AND** preventative OR prevention OR preventing OR cardioprotective OR protective OR prophylactic **AND** cardiotoxicity OR "Cardiac toxicity" OR "chemotherapy related cardiomyopathy" OR "cancer treatment-related cardiac dysfunction" OR CTRCD OR anthracycline OR doxorubicin OR epirubicin OR Idarubicin OR daunorubicin	1461

	Limit to Humans	
COCHRANE	"randomized controlled trial " OR "controlled clinical trial" OR randomised OR randomized OR placebo OR randomly OR trial OR rct **AND** preventative OR prevention OR preventing OR cardioprotective OR protective OR prophylactic **AND** cardiotoxicity OR "Cardiac toxicity" OR "chemotherapy related cardiomyopathy" OR “cancer treatment-related cardiac dysfunction” OR CTRCD OR anthracycline OR doxorubicin OR epirubicin OR Idarubicin OR daunorubicin	415

Table S2. Summary of adverse events amongst included studies.

Trial	Year	Sample size	Symptomatic Heart Failure	Hospitalisation	Death
Massidda[17]	1997	10	NR	NR	NR
Lopez[18]	1998	62	11 (17.7%)	NR	NR
Georgakopoulos[19]	2010	40	3 (7.5%)	NR	NR
Acar[20]	2011	20	NR	NR	NR
Salehi[13]	2011	22	NR	NR	NR
Bosch[21]	2013	37	7 (19%)	NR	8 (24.4%)*
Kaya[22]	2013	18	0	0	0
Liu[23]	2013	20	NR	NR	NR
Elitok[24]	2014	40	0	0	0
Akpek[25]	2015	40	NR	NR	NR
Cadeddu[26]	2016	24	NR	NR	NR
Gulati[27]	2016	30	0	NR	NR
Jhorawat[28]	2016	27	NR	NR	5 (18.5%)#
Pituskin[29]	2016	30	NR	NR	NR
Janbabai[30]	2017	35	NR	NR	NR
Nabati[31]	2017	40	0	NR	0
Avila[7]	2018	96	1 (1%)	NR	2 (2.1%)
Cochera[8]	2018	30	NR	NR	0
Nabati[32]	2019	39	1 (2.6%)	1 (2.6%)	1 (2.6%)

NR – Not Reported, *All of these deaths were described as non-cardiac, secondary to either sepsis or cancer progression, #Cause of death unknown.

Figure S1. Risk of bias for individual studies that used an intention to treat analysis.

Trial ID	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Massida[17]	5.5	Low Risk	High Risk	High Risk	Low Risk	Low Risk	High Risk
Bosch[21]	5.4	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	High Risk
Akpek[25]	5.2	Some Concerns	Some Concerns	Low Risk	High Risk	Low Risk	High Risk
Cadeddu[26]	5.3	Some Concerns	Low Risk	Low Risk	High Risk	High Risk	High Risk
Pituskin[29]	5.5	Low Risk	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns
Janbabai[30]	5.2	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns
Nabati[31]	5.4	Some Concerns	High Risk	High Risk	Low Risk	Low Risk	High Risk
Avila[7]	5.8	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Cochera[8]	5.8	Some Concerns	Some Concerns	Low Risk	High Risk	Low Risk	High Risk

Figure S2. Risk of bias for individual studies that used a pre-protocol analysis.

Trial ID	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Lopez[18]	5.3	High Risk	Some Concerns	Low Risk	High Risk	Low Risk	High Risk
Georgakopoulos[19]	5.2	Some Concerns	High Risk	High Risk	Low Risk	Some Concerns	High Risk
Acar[20]	4.2	Some Concerns	High Risk	High Risk	Low Risk	Low Risk	High Risk
Salehi[13]	5.5	Some Concerns	High Risk	High Risk	High Risk	Some Concerns	High Risk
Kaya[22]	4.9	Some Concerns	High Risk	High Risk	Low Risk	Low Risk	High Risk
Liu[23]	5.3	Some Concerns	High Risk	High Risk	Low Risk	High Risk	High Risk
Elitok[24]	5.4	Low Risk	High Risk	Low Risk	High Risk	Low Risk	High Risk
Gulati[27]	5.5	Low Risk	Some Concerns	Low Risk	Low Risk	Low Risk	Some Concerns
Jhorawat[28]	4.3	High Risk	High Risk	High Risk	Low Risk	Some Concerns	High Risk
Nabati[32]	5.4	Some Concerns	High Risk	Low Risk	Low Risk	Low Risk	High Risk