Cardiol Ther (2025) 14:141–159
https://doi.org/10.1007/s40119-025-00401-z

ORIGINAL RESEARCH

ACEi and ARBs as Primary Prevention of Cancer Therapy-Related Cardiomyopathy in Patients Undergoing Chemotherapy with Anthracyclines: A Systematic Review and Meta-Analysis

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Received: December 11, 2024 / Accepted: February 11, 2025 / Published online: March 16, 2025

ABSTRACT

Introduction: Anthracyclines treat a myriad of malignancies; however, they are known to lead to cancer therapy-related cardiomyopathy (CTRC). Randomized controlled trials (RCTs) evaluating the role of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) in primary prevention of CTRC have yielded mixed results.

Methods: A systematic search of MEDLINE, Cochrane, and Scopus databases was performed to identify RCTs that evaluated outcomes in patients receiving anthracyclines and ACEi or ARBs versus control. The primary outcome was occurrence of CTRC. All data were pooled using a random-effects model.

Results: The final analysis included 10 RCTs, with 1049 patients assessed. The weighted follow-up period was 16.8 months. The average age was 43.2 years and 90% were female. Breast cancer (80%) and lymphomas (13%) were the most common malignancies. There was no statistically significant difference between the groups with regards to occurrence of CTRC (16% vs 24%; risk ratio (RR) 0.67, 95% confidence interval (CI) [0.31, 1.45]). Compared with control, ACEi/ARBs were associated with favorable absolute changes in left ventricular ejection fraction (LVEF) (standardized mean difference (SMD) +1.20%, 95% CI [0.40, 2.00]), left ventricular end-diastolic volume (SMD −0.36 mL, 95% CI [−0.66, −0.06]), and left ventricular end-systolic volume (SMD −1.04 mL, 95% CI [−1.79, −0.29]). There was also a lower risk of arrhythmias in the ACEi/ARBs group compared to control (1.6% vs 8.0%; RR 0.30, 95% CI [0.10, 0.94]), but no difference in all-cause mortality (2.8% vs 3.2%; RR 0.82, 95% CI

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40119-025-00401-z.

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[0.26, 2.61]), or heart failure (1.2% vs 7.1%; RR 0.40, 95% CI [0.03, 4.54]).
Conclusions: ACEi/ARBs therapy was not associated with a reduction in CTRC among patients with cancer receiving anthracyclines. However, there were favorable changes in LVEF and left ventricular remodeling with ACEi/ARBs therapy. Further large-scale studies are needed to better understand the potential role of ACEi/ARBs in preventing long-term cardiotoxicity.

Keywords: Cancer therapy-related cardiomyopathy; Angiotensin converting enzyme inhibitors; Angiotensin receptor blockers; Ejection fraction; Anthracyclines; Cardiotoxicity

Key Summary Points
Anthracyclines are used to treat malignancies but are associated with cancer therapy-related cardiomyopathy (CTRC).
Contemporary data has yielded mixed results on the benefits of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) in prevention of CTRC.
This meta-analysis demonstrated that ACEi/ARBs therapy was not associated with a reduction in CTRC among patients with cancer receiving anthracyclines.
This meta-analysis also demonstrated favorable changes in absolute values of left ventricular (LV) ejection fraction and LV remodeling with ACEi/ARBs.

INTRODUCTION

Anthracycline-based chemotherapy regimens treat a myriad of malignancies, including carcinomas, leukemias, lymphomas, and sarcomas [1]. However, they are well known to lead to cancer therapy-related cardiomyopathy (CTRC) [2]. Patients with higher cumulative doses of anthracyclines, preexisting cardiovascular disease, age ≥ 60 years, Black race, prior exposure to anthracyclines or chest radiation are risk factors for developing CTRC [1, 2].

Neurohormonal antagonists such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) have been established as treatment pathways for heart failure [2]. Interest has been directed towards evaluating the potential role of ACEi and ARBs in prevention of CTRC [3]. Randomized controlled trials (RCTs) have shown mixed results on the benefit of ACEi/ARBs in this patient population. Some RCTs [4–7] have demonstrated the efficacy of ACEi or ARBs in prevention of CTRC; while other RCTs [8, 9] have failed to demonstrate similar benefit. Initial results from the PRADA trial (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) suggested potential benefit for candesartan in prevention of decline in left ventricular ejection fraction (LVEF) among patients with breast cancer receiving adjuvant anthracycline-containing chemotherapy [10]. However, extended follow-up results from PRADA showed no sustained benefit with candesartan in preserving LVEF [11]. Importantly, the current RCTs were underpowered to detect efficacy of ACEi and ARBs in prevention of CTRC. Hence, we conducted a systematic review and meta-analysis of RCTs that evaluated the efficacy of ACEi and ARBs in prevention of CTRC.

METHODS

Search Strategy and Data Sources

A systematic search of MEDLINE, Cochrane, and Scopus databases was performed through September 2024 to identify RCTs that evaluated outcomes in patients receiving anthracycline-based chemotherapy and ACEi/ARBs as primary prevention of CTRC. The search terms were constructed in the aforementioned

databases as follows: Population—"Cancer", OR "Anthracycline" OR "Chemotherapy", Condition—"Cardiotoxicity", OR "Ejection fraction", Intervention—"Angiotensin converting enzyme inhibitors", OR "Angiotensin receptor blockers". The Boolean operator "AND" was used to combine terms related to population, condition, and intervention. No language restrictions were imposed. Further screening of ClinicalTrials.gov was performed to identify any relevant RCTs not retrieved through the primary search. Our meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12] (Supplemental Table 1). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Selection Criteria

We included RCTs that compared the outcomes with ACEi or ARBs versus control in preventing CTRC. We excluded non-randomized trials, as well as RCTs that assessed a combination of beta blockers with ACEi or ARBs or a combination of other neurohormonal antagonists with ACEi or ARBs.

Data Extraction

Studies were independently confirmed by three independent authors (W.H., R.T., A.D.). The following data elements were extracted: study design, baseline characteristics and demographics of study population, intervention strategies, and clinical outcomes. Discrepancies among investigators were resolved by consensus.

Outcomes

The primary outcome was the occurrence of CTRC among patients receiving ACEi or ARBs versus control. Secondary outcomes included the absolute change in LVEF, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), as well as occurrence of arrhythmias, all-cause mortality, and heart failure. Outcomes were adopted as defined by the studies included in our analysis (Supplemental Table 2).

Assessment of Quality of Evidence

The quality of the included RCTs was evaluated by three investigators (W.H., R.T., A.D.) utilizing the Cochrane Risk of Bias 2 (RoB 2) assessment tool in RevMan [13] (Cochrane Collaboration, Oxford, UK). Criteria included in the assessment were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Accordingly, RCTs were classified into low risk, unclear risk, or high risk of bias. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) analysis was conducted for certainty assessment of all outcomes utilizing the GRADEpro Software [14].

Statistical Analysis

The analysis was performed using intention-to-treat model. Data were pooled primarily using a random-effects model because of anticipated heterogeneity among included RCTs. Heterogeneity was assessed via chi-squared and Higgin's I^2 statistics [15, 16]. Summary estimates for categorical variables were reported as risk ratios (RR). Summary estimates for continuous variables were reported as standardized mean difference (SMD). Effect estimates for continuous outcomes were derived by utilizing validated methods as detailed by the Cochrane Handbook for Systematic Reviews of Interventions [17]. P values were considered significant if < 0.05. RevMan [13] (Cochrane Collaboration, Oxford, UK) was utilized to perform statistical analysis.

Subgroup analysis was performed for the primary outcome by assessing ACEi and ARBs as separate subgroups. Stepwise sensitivity analyses was conducted by excluding each study at a time to evaluate sources of heterogeneity among heterogenous outcomes. Sensitivity analyses were performed for the primary outcome by excluding the RCT contributing the most to heterogeneity, exclusion of RCTs with the highest risk of bias, exclusion of RCTs with follow-up time being < 12 months, and including RCTs that only evaluated patients with breast cancer.

A trial sequential analysis was conducted for the primary outcome of CTRC with calculation of the required information size based on an estimated relative risk reduction of 21% and estimated incidence in the control arm of 46%. These values were based upon the largest, high-quality RCT on this topic. This analysis was performed using an alpha value of 5% and power of 80%.

RESULTS

Search Results and Study Characteristics

The study flowsheet is outlined in Fig. 1. From our systematic search, 525 records were identified with 490 records screened after removing duplicates. After exclusion of records that did not meet our inclusion or exclusion criteria, 23 full-text articles were assessed for eligibility. From the 23 articles, 13 full-text articles were excluded as they were non-randomized trials or studied pharmacologic agents other than ACEi or ARBs. The final analysis included 10 RCTs with 1049 patients

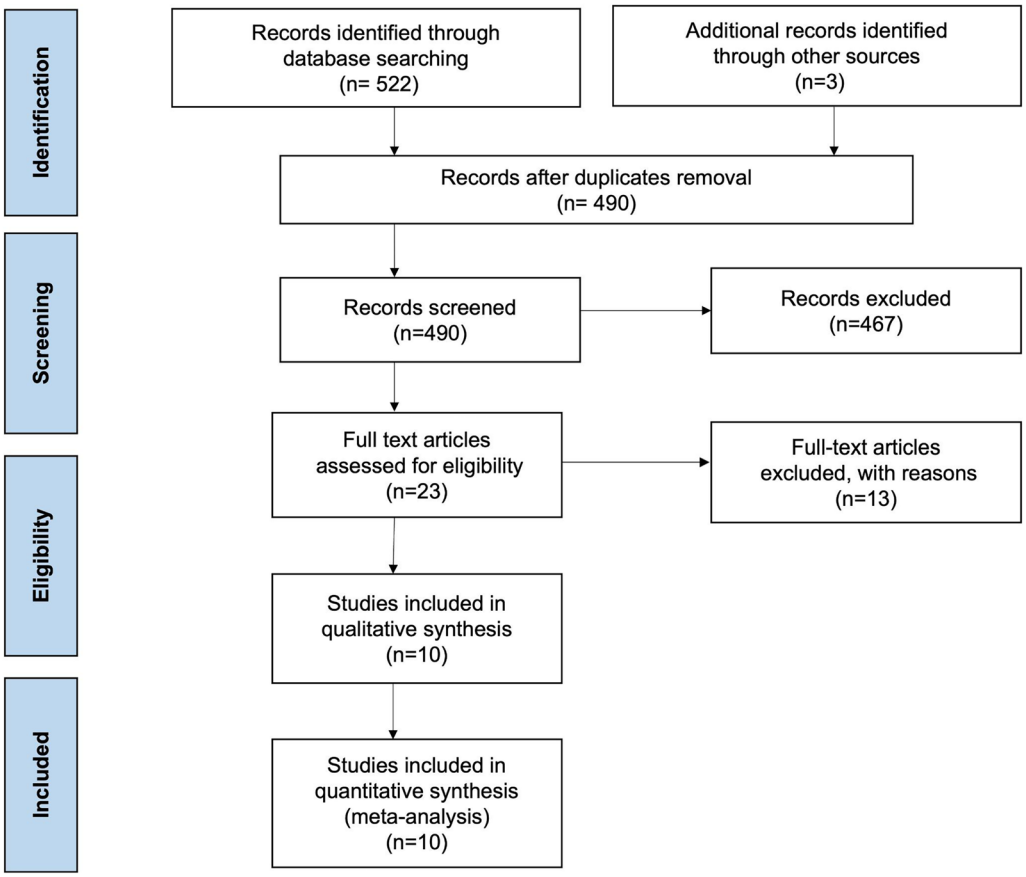

Fig. 1 Study flowsheet

assessed. The weighted follow-up period was 16.8 months. The RCTs were conducted in geographically diverse populations, including Italian [4, 5], Iranian [6], American [7], Dutch [8], Canadian [9], Norwegian [11], Greek [18], Polish [19], and Korean [20] patient populations. Common anthracyclines utilized included doxorubicin, epirubicin, and idarubicin. Six RCTs assessed ACEi [4, 6, 7, 9, 18, 19] and four RCTs assessed ARBs [5, 8, 11, 20]. Six RCTs solely assessed patients with breast cancer [7–9, 11, 19, 20] while one exclusively assessed patients with lymphoma [18], and three assessed a mix of malignancies [4–6]. A summary of the RCTs can be found in Table 1.

Baseline Characteristics

A total of 1049 patients were assessed: 548 in the ACEi/ARBs group and 501 in the control group. Cumulatively, the average age was 43.2 years and 90% of the study population were female. Breast cancer (80%) and lymphomas (13%) were the most common malignancies. Mean baseline LVEF in the ACEi/ARBs group was 62.7 ± 5.13 compared to 63.1 ± 6.34 in the control group. Full details regarding the baseline characteristics of the population studied can be found in Table 2. Two [5, 20] of the ten RCTs had a high risk of bias with regards to allocation concealment and blinding of participants and personnel (Supplemental Fig. 1).

Outcomes and Analysis

There was no statistically significant difference between the study groups with regards to the primary outcome of CTRC (16% vs 24%; RR 0.67, 95% confidence interval (CI) [0.31, 1.45], $P=0.31$, $I^2=76\%$, high certainty) (Fig. 2). Similar results were obtained on sensitivity analyses excluding the RCT contributing the most to heterogeneity; (RR 0.86, 95% CI [0.44, 1.66], $P=0.65$, $I^2=69\%$), excluding RCTs with high risk of bias; (RR 0.75, 95% CI [0.33, 1.72], $P=0.50$, $I^2=78\%$), excluding RCTs with follow-up time < 12 months; (RR 0.78, 95% CI [0.36, 1.70], $P=0.53$, $I^2=77\%$), and by including RCTs that solely assessed patients with breast cancer; (RR 0.71, 95% CI [0.43, 1.17], $P=0.18$, $I^2=43\%$) (Supplemental Fig. 2). Subgroup analysis showed no interaction according to ACEi versus ARBs for occurrence of CTRC; $P_{\text{Interaction}}=0.78$ (Supplemental Fig. 3).

Regarding secondary outcomes, the ACEi/ARBs group had a favorable change in LVEF compared with control; SMD +1.20%, 95% CI [0.40, 2.00], $P=0.003$, $I^2=97\%$, low certainty (Fig. 3a). Additionally, patients on ACEi/ARBs had a favorable change in LVEDV (SMD −0.36 mL, 95% CI [−0.66, −0.06], $P=0.02$, $I^2=41\%$, moderate certainty) (Fig. 3b), and LVESV (SMD −1.04 mL, 95% CI [−1.79, −0.29], $P=0.006$, $I^2=89\%$, moderate certainty) (Fig. 3c). There was also a lower risk of arrhythmias in the ACEi/ARBs group compared to control; 1.6% vs 8.0%; RR 0.30, 95% CI [0.10, 0.94], $P=0.04$, $I^2=0\%$, low certainty (Fig. 4a). On the other hand, there was no difference between the treatment and control group for all-cause mortality; 2.8% vs 3.2%; RR 0.82, 95% CI [0.26, 2.61], $P=0.74$, $I^2=0\%$, high certainty (Fig. 4b) or heart failure; 1.2% vs 7.1%; RR 0.40, 95% CI [0.03, 4.54], $P=0.46$, $I^2=64\%$, low certainty (Fig. 4c). The summary of findings table regarding the certainty assessment can be found in Supplemental Table 3.

Trial sequential analysis was conducted for the primary outcome of CTRC using random effects model. The required information size (RIS) was calculated on the basis of an estimated incidence in the control group of 46%. A relative risk reduction of 21% was evaluated using an alpha value of 5% and power of 80%. Given the heterogeneity in the primary outcome, diversity adjustment was used for the RIS. The cumulative Z-score curve suggested a potential benefit with ACEi/ARBs, as well as a benefit for further RCTs (Supplementary Fig. 4).

DISCUSSION

In this meta-analysis of ten RCTs, including 1049 patients, we evaluated the efficacy and safety of ACEi/ARBs in primary prevention of CTRC with anthracyclines. The principal findings of our meta-analysis were the following: (1) there

Table 1 Summary of RCTs included in the meta-analysis

Trial	Trial timeline	Study design	Geographic location	Type of cancer	Anthracycline utilized	Treatment group	Control group	Major inclusion criteria	Primary outcome	Longest follow-up
Cardinale 2006 [4]	1/1/2002–12/31/2004	RCT	Italy	AML, breast, Ewing's sarcoma, Hodgkin's lymphoma, myeloma, NHL	Idarubicin and epirubicin	ACEi; enalapril	No treatment	Patients with advanced or primary resistant breast cancer, AML, relapsed poor prognosis Hodgkin's lymphoma, high-grade NHL, myeloma, Ewing's sarcoma	Occurrence of cardiotoxicity defined as absolute decrease > 10% in resting LVEF associated with a decline < 50%	12 months
Georgakopoulos 2010 [18]	4/2003–6/2008	RCT	Greece	Lymphoma	Doxorubicin	ACEI; enalapril	No treatment	Age > 18 years ECOG PS of 0 or 1 Serum bilirubin < 2.0 mg/dL Serum creatinine < 2.0 mg/dL Normal sinus rhythm LVEF > 50% Fraction shortening > 25% before chemotherapy	Occurrence of doxorubicin-induced clinical or subclinical cardiotoxicity in patients with lymphoma during first year of chemotherapy	31 months

Table 1 continued

Trial	Trial timeline	Study design	Geographic location	Type of cancer	Anthracycline utilized	Treatment group	Control group	Major inclusion criteria	Primary outcome	Longest follow-up
Dessi 2013 [5]	09/2008–10/2009	RCT	Italy	Breast, endometrial, NHL, non-small cell lung cancer, ovarian, salivary gland	Epirubicin	ARB; telmisartan	Placebo	Age 18–70 years Normal blood pressure range Echocardiographic LVEF ≥ 55% Normal strain rate (range 1.7–2.1 cm/s) ECOG PS 0–2 Normal hepatic and renal function No medications known to interfere with inflammatory and oxidative stress parameters such as NSAIDs, aspirin, COX-2 inhibitors	Systolic function (assessed by strain rate)	18 months
Boekhout 2016 [8]	10/2007–10/2011	RCT	Netherlands	Breast	Doxorubicin and epirubicin	ARB; candesartan	Placebo	Women aged ≥ 18 years Early-stage HER2-positive breast cancer Completion of anthracycline-based adjuvant treatment LVEF at least 50% measured by echocardiography or multiple gate acquisition radionuclide imaging Creatinine clearance > 50 mL/min TSH between 0.5 and 3.9 MU/L or thyroid hormone free thyroxine between 8 and 26 pmol/L SBP between 100 and 180 mmHg and DBP between 60 and 100 mmHg First trastuzumab infusion received at least 3 weeks after day 1 of the last anthracycline infusion	Decline in LVEF > 15% or decrease < 45%	92 weeks

Table 1 continued

Trial	Trial timeline	Study design	Geographic location	Type of cancer	Anthracycline utilized	Treatment group	Control group	Major inclusion criteria	Primary outcome	Longest follow-up
Janabai 2017 [6]	2012–2014	RCT	Iran	Breast, Wilms tumor, lung cancer, bone sarcoma, Hodgkin's lymphoma	Doxorubicin	ACEi; enalapril	Placebo	Aged 21–74 years ECOG PS 2 Normal sinus rhythm Preserved LVEF at baseline echocardiography Newly diagnosed malignancy Adequate hematological, hepatic, and renal function	Change from baseline LVEF by echocardiography 6 months post-chemotherapy	6 months
Pituskin 2017 [9]	10/2011–6/2014	RCT	Canada	Breast	Doxorubicin and epirubicin	ACEi; perindopril	Placebo	Patients > 18 years with newly diagnosed HER2-overexpressing early breast cancer (stage I to IIIA) Planned adjuvant treatment with trastuzumab	LVEDVi on cardiac MRI from baseline to completion of trastuzumab	12 months

Table 1 continued

Trial	Trial timeline	Study design	Geographic location	Type of cancer	Anthracycline utilized	Treatment group	Control group	Major inclusion criteria	Primary outcome	Longest follow-up
Guglin 2019 [7]	2010–2018	RCT	USA	Breast	Unspecified	ACEi; lisinopril	Placebo	Men and women ≥ 18 years with HER2-positive breast cancer scheduled to receive neoadjuvant or adjuvant trastuzumab (anthracycline-containing regimens permitted) LVEF ≥ 50% by MUGA scan or echocardiogram Adequate renal function Sitting SBP > 90 mmHg Pulse ≥ 60/minute Not pregnant or breastfeeding Female patients of childbearing potential, who are sexually active, must have a negative pregnancy test before starting the study Both men and women must be willing to use effective contraception during the study	Rate of cardiotoxicity	12 months

Table 1 continued

Trial	Trial timeline	Study design	Geographic location	Type of cancer	Anthracycline utilized	Treatment group	Control group	Major inclusion criteria	Primary outcome	Longest follow-up
Slowik 2020 [19]	2014–2017	RCT	Poland	Breast	Doxorubicin and epirubicin	ACEi; ramipril	Non-specified standard of care (except treatment of HTN without an ACEi)	Consecutive women with stages I–III breast cancer who underwent breast surgery and were referred for adjuvant anthracycline therapy	Increase in levels of troponin I or NTproBNP or both and a decrease in LVEF below lower limit	12 months
Heck 2021 [11]	9/15/2011–9/11/2014	RCT	Norway	Breast	Epirubicin	ARB; candesartan	Placebo	Adult women aged 18–70 years LVEF ≥ 50% Normal kidney function No serious comorbidities Scheduled for adjuvant anthracycline therapy after surgery	Change in LVEF assessed by CMR from baseline to extended follow-up	23 months
Lee 2021 [20]	12/2013–11/2017	RCT	Korea	Breast	Doxorubicin	ARB; candesartan	No treatment	Female sex, age > 18 years Breast cancer with indications for adjuvant or neoadjuvant doxorubicin chemotherapy (either adriamycin-cyclophosphamide "AC" or adriamycin- docetaxel "AT" chemotherapy only) Normal LVEF ≥ 50%	Early (at 6 months) and late (at 12 months) doxorubicin-induced cardiotoxicity	12 months

ACEI angiotensin converting enzyme inhibitor, *AML* acute myeloid leukemia, *ARB* angiotensin receptor blocker, *CMR* cardiovascular magnetic resonance imaging, *COX-2* cyclooxygenase-2, *ECOG* Eastern Cooperative Oncology Group, *HER2* human epidermal growth factor receptor 2, *HTN* hypertension, *LVEF* left ventricular ejection fraction, *MUGA* multi-gated acquisition scan, *NHL* non-Hodgkin's lymphoma, *NSAIDs* non-steroidal anti-inflammatory drugs, *RCT* randomized controlled trial, *ROS* reactive oxygen species, *SBP* systolic blood pressure, *TSH* thyroid stimulating hormone

Table 2 Baseline characteristics of the study population

Trial	ACEi/ARBs sample size	Control sample size	Mean age ACEi/ARBs	Mean age control	Female ACEi/ARBs	Female control	Female ACEi/ARBs	Female control	HTN ACEi/ARBs	HTN control	DM ACEi/ARBs	DM control	HLD ACEi/ARBs
	n	*n*	Years	Years	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Cardinale 2006 [4]	56	58	47	44	33 (59)	39 (67)	N/A	N/A	3 (5)	4 (7)	1 (2)	1 (2)	2 (4)
Georgakopoulos 2010 [18]	42	40	47.4	49.1	20 (48)	19 (48)	25.6	25.1	14 (33)	6 (15)	3 (7)	6 (15)	11 (26)
Dessi 2013 [5]	25	24	52.9	53	19 (76)	18 (75)	N/A	N/A	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Boekhout 2016 [8]	103	103	50	51	103 (100)	103 (100)	N/A	N/A	14 (13)	11 (11)	3 (3)	3 (3)	4 (4)
Janabai 2017 [6]	34	35	47.76	47.06	33 (97)	31 (89)	N/A	N/A	6 (17.6)	4 (11.4)	3 (8.8)	5 (14.3)	4 (11.8)
Pituskin 2017 [9]	33	30	50	51	33 (100)	30 (100)	29.4	26.1	2 (6)	2 (7)	1 (3)	0 (0)	1 (3)
Guglin 2019 [7]	65	60	50.58	51.11	65 (100)	60 (100)	28.01	29.03	N/A	N/A	N/A	N/A	N/A
Slowik 2020 [19]	48	48	45	45	48 (100)	48 (100)	24.3	23.74	6 (12)	7 (13.8)	0 (0)	0 (0)	N/A
Heck 2021 [11]	60	60	51	51	60 (100)	60 (100)	25	26.5	6 (10)	2 (3)	1 (2)	2 (3)	N/A
Lee 2021 [20]	82	43	47.8	48.5	82 (100)	43 (100)	22.7	23.1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cumulative	548	501	41.7	44.9	496 (90.5)	451 (90)	25.4	25.8	51 (10.6)	36 (8.2)	12 (2.5)	17 (3.9)	22 (6.3)

Table 2 continued

Trial	HLD control	History of smoking ACEi/ARBs	History of smoking control	Breast cancer ACEi/ARBs	Breast cancer control	Hodgkin's lymphoma ACEi/ARBs	Hodgkin's lymphoma control	NHL ACEi/ARBs	NHL control	Other cancer ACEi/ARBs	Other cancer control	Baseline LVEF (%) ACEi/ARBs	Baseline LVEF (%) control
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	Mean ± SD	Mean ± SD
Cardinale 2006 [4]	2 (3)	N/A	N/A	14 (25)	15 (26)	5 (9)	5 (9)	19 (34)	20 (34)	18 (32)	18 (31)	62 ± 3	63 ± 3
Georgakopoulos 2010 [18]	10 (25)	20 (47)	16 (40)	0 (0)	0 (0)	19 (44)	20 (50)	24 (56)	20 (50)	0 (0)	0 (0)	65.2 ± 7.1	67.6 ± 7.1
Dessi 2013 [5]	N/A	N/A	N/A	8 (32)	10 (42)	N/A	N/A	1 (4)	2 (8)	16 (64)	12 (50)	66 ± 7	66 ± 5
Boekhout 2016 [8]	5 (5)	N/A	N/A	103 (100)	103 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	60 ± 6.67	61 ± 6.67
Janabai 2017 [6]	3 (8.6)	N/A	N/A	30 (88.2)	30 (85.7)	4 (11.8)	2 (5.7)	N/A	N/A	0 (0)	3 (8.6)	59.39 ± 6.95	59.61 ± 5.70
Pituskin 2017 [9]	0 (0)	16 (48)	15 (50)	33 (100)	30 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	62 ± 5	61 ± 5
Guglin 2019 [7]	N/A	N/A	N/A	65 (100)	60 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	62.97 ± 6.18	62.24 ± 6.09

Table 2 continued

Trial	HLD control	History of smoking ACEi/ARBs	History of smoking control	Breast cancer ACEi/ARBs	Breast cancer control	Hodgkin's lymphoma ACEi/ARBs	Hodgkin's lymphoma control	NHL ACEi/ARBs	NHL control	Other cancer ACEi/ARBs	Other cancer control	Baseline LVEF (%) ACEi/ARBs	Baseline LVEF (%) control
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	Mean ± SD	Mean ± SD
Slowik 2020 [19]	N/A	12 (24.2)	12 (24.1)	48 (100)	48 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	67 ± 3.7	65 ± 3.7
Heck 2021 [11]	N/A	12 (20)	9 (15)	60 (100)	60 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	62.2 ± 4.45	62.7 ± 4.45
Lee 2021 [20]	0 (0)	N/A	N/A	82 (100)	43 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	64.5 ± 1.11	64.5 ± 2.89
Cumulative	20 (6.5)	60 (32.8)	52 (29.2)	443 (80.8)	399 (79.6)	28 (5.3)	27 (5.6)	44 (8.5)	42 (9)	34 (6.2)	33 (6.5)	62.7 ± 5.13	63.1 ± 6.34

ACEi angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *BMI* body mass index, *DM* diabetes mellitus, *HTN* hypertension, *HLD* hyperlipidemia, *LVEF* left ventricular ejection fraction, *NHL* non-Hodgkin's lymphoma, *N/A* Not Applicable

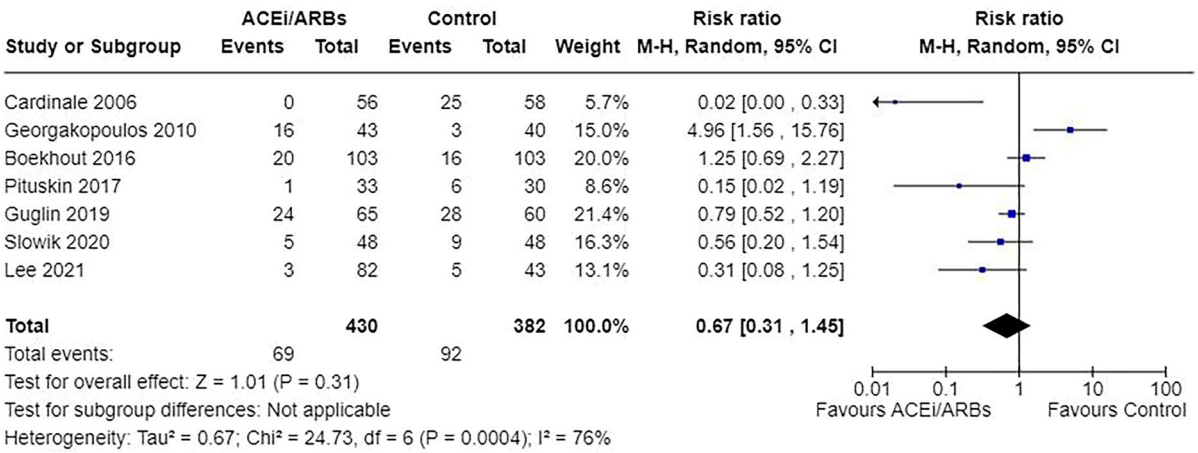

Fig. 2 Forest plot for the occurrence of cancer therapy-related cardiomyopathy among study groups

was no statistically significant difference in the primary outcome of CTRC among the ACEi/ARBs versus the control group; (2) the ACEi/ARBs group was associated with favorable changes in absolute values of LVEF, LVEDV, and LVESV compared with the control group; (3) there were no differences among both study groups in all-cause mortality, and heart failure.

Currently, the American Society of Clinical Oncology guidelines published in 2017, which includes experts from both the oncology and cardiology fields, concluded that there is not enough data to support the routine use of ACEi or ARBs in the prevention of chemotherapy-induced cardiotoxicity [21]. Additionally, the American College of Cardiology/American Heart Association [2] 2022 heart failure guidelines do not recommend the routine use of ACEi or ARBs in the prevention of CTRC. Such recommendations were based on the lack of adequately powered randomized studies with long-term outcomes [21]. Since the publication of the guidelines, there have been more recent RCTs aiming to assess the efficacy of ACEi/ARBs in primary prevention of CTRC [6, 7, 9, 11, 19, 20]. In the current meta-analysis, we have included the totality of available randomized data evaluating the use of ACEi/ARBs in prevention of CTRC. Our results showed that the use of ACEi/ARBs could result in lower absolute change in LVEF after chemotherapy compared with control; however, such benefit failed to provide a meaningful reduction in the incidence of CTRC.

Our favorable findings on absolute change in LVEF and left ventricular remodeling without statistically significant difference in CTRC seem paradoxical; however, they can be explained by a few factors. One potential explanation could be that the aggregate data from the RCTs lacked the power to detect a statistically significant difference in regards to CTRC, and that a large sample size is needed to uncover a true difference. Additionally, it is possible that certain patient subgroups derive higher benefit from ACEi/ARBs preventive treatment, such as subgroups according to the type of cancer or patient comorbidities. We attempted to explore these patients subgroups in our exploratory analyses; however, these were underpowered analyses and did not yield significant differences. Most of the included RCTs had relatively similar definitions for CTRC, except for the cutoff for LVEF. For example, Boekhout et al. [8] defined CTRC as decline in LVEF < 45% while Pituskin et al. [9] defined it as < 53% (Supplementary Table 2). This difference in definitions could partly explain our findings on the primary outcome. However, the difference observed in our analysis regarding LVEF, LVEDV, and LVESV may not be large enough to prevent toxicity and subsequent CTRC. Finally, a dose-dependent preventive effect of ACEi/ARBs is plausible; however, we had insufficient data to verify such a hypothesis.

The results of individual RCTs on the role of ACEi/ARBs in prevention of CTRC were mixed. For example, Cardinale et al. [4] assessed 114

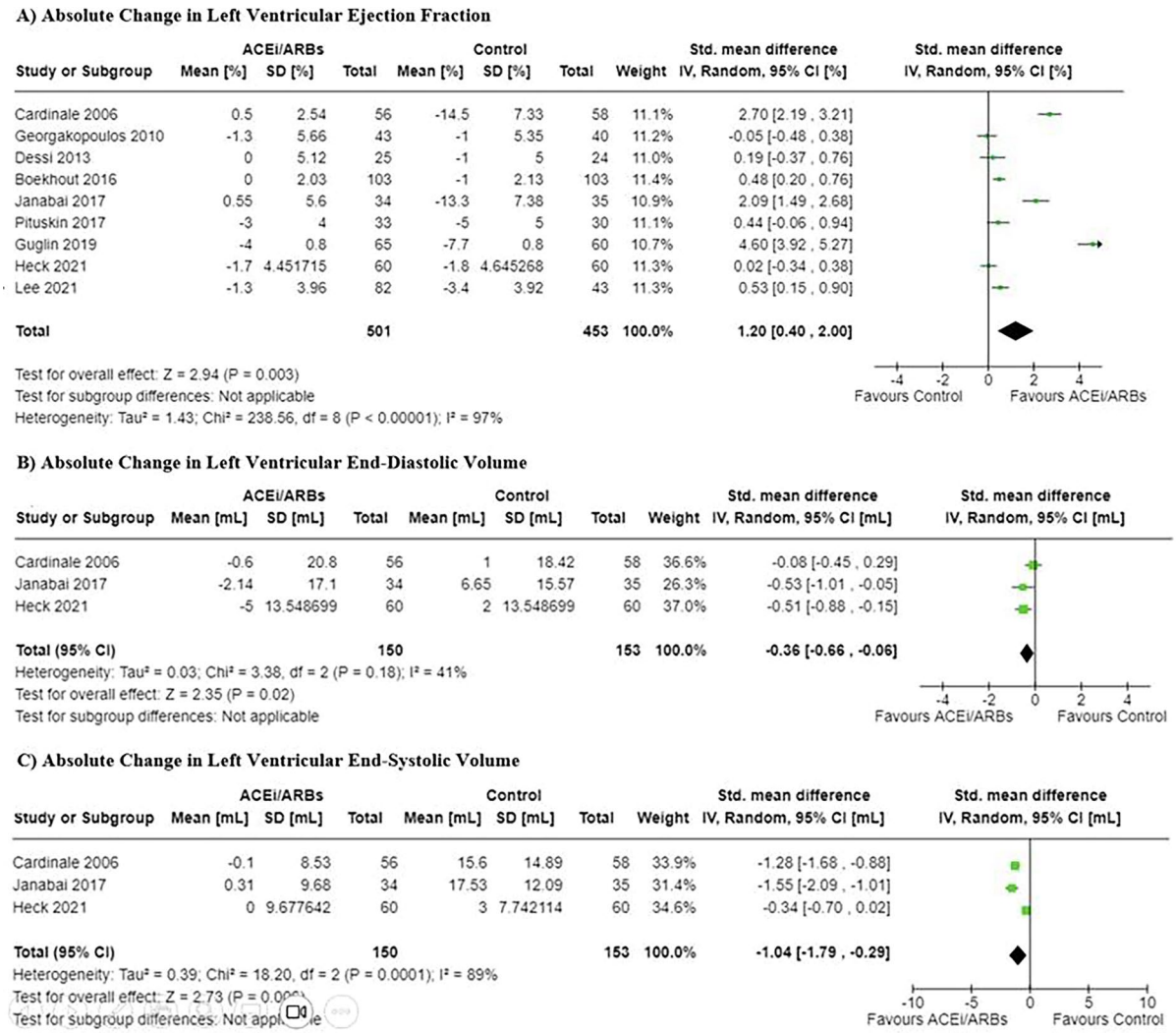

Fig. 3 Forest plots for the absolute change in **a** left ventricular ejection fraction, **b** left ventricular end-diastolic volume, and **c** left ventricular end-systolic volume among study groups

patients with a mix of malignancies with 56 patients receiving enalapril. They demonstrated that control subjects had statistically significant reductions in LVEF and increases in LVEDV and LVESV compared to patients on ACEi/ARBs [4]. On the other hand, Boekhout et al. in their RCT of 210 women with early-stage breast cancer with 103 patients receiving candesartan did not demonstrate protection against a decrease in LVEF in patients receiving anthracyclines [8].

In the initial PRADA trial of 130 female patients with breast cancer receiving adjuvant chemotherapy, with 32 assigned to the candesartan-metoprolol group and 33 assigned to the candesartan-placebo group, results demonstrated that candesartan provided protection against early decline in global LVEF [10]. At 2-year follow-up, the prevention of decline in LVEF was not appreciated in the candesartan group and a modest reduction in LVEDV and perseveration of global longitudinal strain were appreciated [11]. In the MANTICORE 101-Breast trial, 33 HER2-positive patients with early breast cancer received anthracyclines and perindopril. Perindopril was protective against decline in LVEF, but not against left ventricular

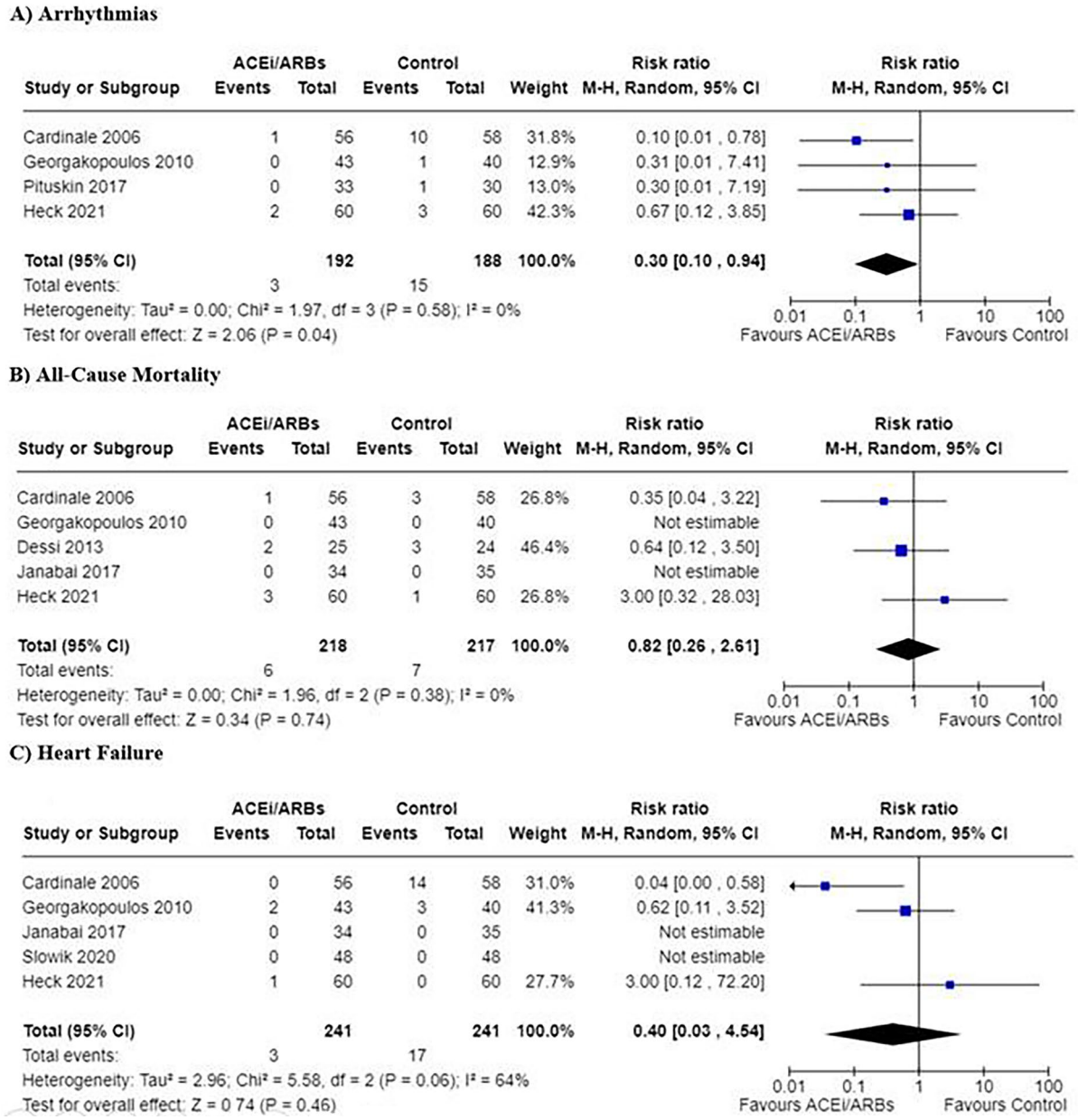

Fig. 4 Forest plots for the risk of **a** arrhythmias, **b** all-cause mortality, and **c** heart failure among study groups

remodeling [9]. On the other hand, Slowik et al. assessed 96 women with low-risk breast cancer receiving anthracycline therapy, with 48 on ramipril, and did not demonstrate prevention in decline of LVEF at 1-year follow-up [19]. Lee et al. [20] in their RCT of 195 patients, 82 of whom received candesartan, demonstrated a reduced incidence of early doxorubicin-induced subclinical cardiotoxicity. The candesartan group also showed a reduced decrease in LVEF [20].

Bench studies have proposed several mechanisms that could mediate a potential beneficial role for ACEi/ARBs in the prevention of CTRC. It has been proposed that ARBs demonstrate antioxidant properties through their regulation of angiotensin II subtype I and angiotensin II subtype II receptors [22].

ARBs have also demonstrated the potential to stimulate superoxide dismutase, which inhibits crucial reactive oxygen species [22]. In a rat model, lisinopril was shown to prevent doxorubicin-mediated myocyte reduction by blocking or decreasing mRNA for angiotensin II subtype I receptor and atrial natriuretic peptide [23]. In another study, also using a rat model with doxorubicin, enalapril was found to prevent mitochondrial dysfunction [24].

Overall, our analysis is the largest meta-analysis focusing on RCTs assessing ACEi and ARBs as primary prevention of CTRC. While we did not find significant differences in the primary outcome of CTRC, the favorable findings on the absolute change in LVEF, LVEDV, and LVESV, and lower risk of arrhythmias with ACEi/ARBs suggest a remaining potential benefit for ACEI/ARBs in patients receiving anthracyclines. Future trials should include larger sample sizes, standardized definitions for CTRC, and stratified randomization by cancer type and patient risk factors to ensure adequate power and clarity in subgroup benefits. Extended follow-up, dose–response analysis, and additional cardiac imaging/biomarkers will provide better insights into long-term effects and optimal dosing. Including comparator arms with other cardioprotective agents and assessing patient-centered outcomes will further clarify ACEi/ARBs effectiveness in preventing chemotherapy-induced cardiotoxicity.

Our analysis should be viewed in the context of a few limitations. First, there was a considerable degree of heterogeneity among several of the study outcomes. However, we conducted sensitivity analysis to explore the sources of heterogeneity among the primary outcome. Second, many of the secondary outcomes were only reported by a portion of the included studies; therefore, these specific outcomes could have been underpowered to detect a significant finding. Third, included studies utilized different anthracyclines and had patients with different types of cancers. An attempt to control for this phenomenon was done with sensitivity analysis regarding the primary outcome; however, there was no change in the effect on the primary outcome. Lastly, the lack of patient-level data precluded further granular analyses.

CONCLUSION

ACEi/ARBs therapy was not associated with a reduction in CTRC among patients with cancer receiving anthracyclines. However, there were favorable changes in absolute values of LVEF and LV remodeling with ACEi/ARBs. Further large-scale studies are needed to better understand the potential role of ACEi/ARBs in preventing long-term cardiotoxicity.

Author Contributions. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Wissam Harmouch, Ravi Thakker, Alexander Dang, and Ayman Elbadawi. The first draft of the manuscript was written by Wissam Harmouch, Ravi Thakker, Alexander Dang, Abdelazeem Mohamed Etewa, Krishna Suthar and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding. No funding or sponsorship was provided for this work or the publication of this article.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Ravi Thakker is an Editorial Board member of *Cardiology and Therapy*. Ravi Thakker was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Wissam Harmouch, Alexander Dang, Abdelazeem Mohamed Etewa, Krishna Suthar, Salim Hayek, Wissam Khalife, and Ayman Elbadawi have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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