International Journal of Cardiology and Cardiovascular Diseases

Kundu S, et al., Int J Cardiol Cardiovasc Dis. 2025;5(1):9-19.

Systematic Review

Prophylactic use of ACEIs, ARBs and BBs in anthracycline and trastuzumab induced cardiotoxicity in adult cancer patients: A systematic review

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Received date: August 16, 2025
Accepted date: September 29, 2025

Abstract

Background: Cancer therapy related cardiac dysfunction (CTRCD) poses a significant challenge to the treatment of cancer patients receiving cardiotoxic chemotherapeutic regimen like anthracyclines and human epidermal growth factor receptor 2 (HER2) inhibitors like trastuzumab. This systematic review evaluated the efficacy and safety of conventional heart failure medications—angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and beta-blockers (BBs)—in preventing CTRCD in adults undergoing such therapies.

Method: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, 12 randomized controlled trials (RCTs) involving 1,571 patients were analyzed from PubMed, Scopus and Embase. Primary outcomes included changes in left ventricular ejection fraction (LVEF), biomarkers like Troponin, atrial/brain natriuretic peptide (ANP/BNP) level and electrocardiograph (ECG), before and after chemotherapy. Secondary outcomes included total mortality and development of symptomatic heart failure, either necessitating treatment initiation or hospitalization.

Results: Several studies demonstrated cardioprotective effects after the use of the aforementioned medications. Biomarker-guided approaches using troponin yielded inconsistent results, and combination therapy did not consistently outperform monotherapy. Most interventions were well tolerated, with few adverse events such as bradycardia and hypotension.

Conclusion: Conventional heart failure medications such as ACEIs, ARBs, and BBs may offer selective benefit. However, current evidence is heterogeneous and does not support their routine prophylactic use. Future large-scale, long-term trials with standardized cardiac endpoints and patient-specific risk stratification are essential to guide clinical practice in cardio-oncology.

Keywords: Cancer therapy related cardiac dysfunction, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Beta-blockers, Anthracycline, Trastuzumab, Heart failure

Abbreviations: LV EDV: Left Ventricular End Diastolic Volume; GLS: Global Longitudinal Strain; LV EDD: Left Ventricular End Diastolic Diameter; LV ESD: Left Ventricular End Systolic Diameter; FS: Fractional Shortening; DNA: Deoxyribonucleic Acid; NO: Nitric Oxide; CHOP: Cyclophosphamide Hydroxydauorubicin Oncovin Prednisone; ECOG PS: Eastern Co-operative Oncology Group Performance Status; CMR: Cardiac Magnetic Resonance; SAVE HEART: proSpective registry for prediction And preVEntion of cHEmotherapy-induced cARdiotoxicity in patients with breasT cancer

Introduction

Cancer therapy-related cardiac dysfunction (CTRCD) is a well-recognized complication in oncology and remains a major clinical concern, particularly in patients treated with anthracyclines or human epidermal growth factor receptor 2 (HER2) inhibitors such as trastuzumab. These drugs have transformed cancer outcomes, but their potential for cardiotoxicity can result in permanent

myocardial injury, impaired quality of life, and, in severe cases, premature death [1–3]. Anthracyclines form the backbone of many treatment regimens for both hematologic malignancies and solid tumors, while HER2 inhibitors have become essential in managing aggressive HER2-positive cancers [4–7]. Although their therapeutic targets differ, both can damage the myocardium through mechanisms such as oxidative stress, mitochondrial injury, and disruption of cardiomyocyte signaling (see **Figures 1** and **2**) [5,7–10]. CTRCD is often defined as a drop in left ventricular ejection fraction (LVEF) of at least 10% to a value below 50%. Clinically, it may present with arrhythmias, pericardial effusion, myocardial ischemia, or frank heart failure [11,12]. The onset can be rapid during chemotherapy itself and emerge within the first year after treatment or appear many years later as late-onset cardiomyopathy [13–17].

Recognizing these risks, current cardio-oncology guidelines recommend regular cardiac surveillance and, in high risk patients, prophylactic initiation of conventional heart-failure therapies such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), or beta-blockers (BBs), particularly, in patients with baseline cardiovascular risk factors including hypertension, diabetes or concurrent cardiac diseases and patients receiving high cumulative doses or multiple cardiotoxic chemotherapeutic drugs [18–20]. While these agents are proven in established heart failure, their ability to prevent chemotherapy-related cardiac injury is less certain. The available evidence is limited by small sample sizes, differences in trial endpoints, heterogeneous patient populations and exclusion of high-risk patients from the trials [21–23]. It is still unclear whether one class should be preferred over another for primary prevention, or whether certain patient subgroups gain particular benefit. In this systematic review, through incorporating randomized controlled trials (RCTs) conducted in 2024–25, we present the most up-to-date synthesis of RCTs on prophylactic use of ACEIs, ARBs, and BBs in anthracycline and trastuzumab induced cardiotoxicity in adult cancer patients. In addition to analyzing cardiac outcomes, our review uniquely explores biomarker-guided risk stratification to determine whether high-risk patients may selectively benefit from cardioprotective therapy. By bringing together most comprehensive and recent evidence up to July 2025, we aim to clarify the strength of current data, highlight areas where knowledge remains limited, and help guide both future research and everyday clinical decision-making in cardio-oncology.

Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [24]. The protocol was not registered in PROSPERO due to project timeline constraints.

Literature search

A comprehensive search of PubMed, Scopus, and Embase was performed from database inception to 1st July 2025. Search terms combined controlled vocabulary (MeSH/Emtree) and free-text words related to the intervention, population, and outcomes. The Boolean strategy applied to PubMed was: (Cardioprotective medication) OR

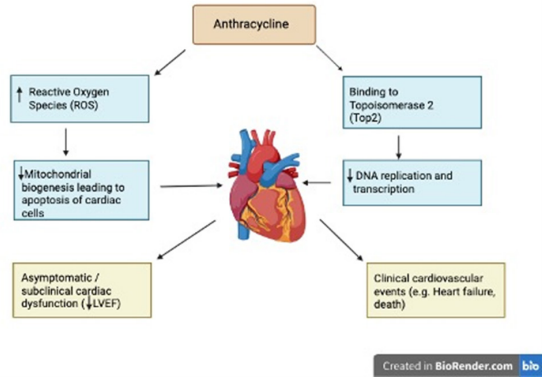

Figure 1.

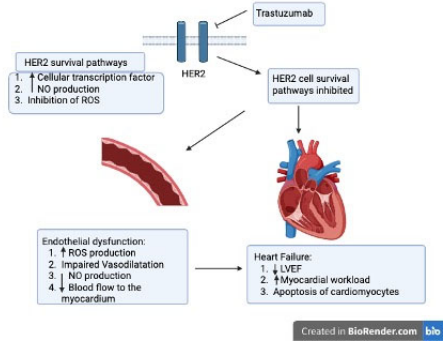

Figure 2.

(ACE inhibitor) OR (Enalapril) OR (ARB) OR (Beta blocker) OR (Carvedilol) OR (Metoprolol)) AND ((Cancer) OR (Lymphoma) OR (Chemotherapy) OR (Doxorubicin) OR (Anthracycline) OR (Trastuzumab) OR (Herceptin)) AND (cardiotoxicity) OR (Heart failure) OR (cardiomyopathy) OR (ejection fraction).

Equivalent search strings were adapted for each database. Manual reference screening of all included studies and relevant reviews was also undertaken to identify additional eligible trials.

Eligibility criteria

We included RCTs and observational studies published in English involving adult cancer patients undergoing anthracycline and/or trastuzumab based chemotherapy and using ACEIs and/or ARBs and/or BBs as cardioprotective medications with at least one quantifiable measure of cardiotoxicity (see **Table 1**). Non-randomized trials, conference abstracts, unpublished studies, non-peer-reviewed data, reviews, editorials and animal studies were excluded. Studies involving pediatric population, adult patients with significant pre-existing cardiac comorbidities and published in non-English language were excluded as well. Additionally, studies using cardioprotective medications other than the medications of interest such as statin or studies reporting only surrogate endpoints without clinical or imaging-based cardiac outcomes were not included in this systematic review.

The initial database search for relevant studies generated a total of 539 articles that met the initial search criteria. Of these, 92 duplicates were removed, leaving 447 records to be screened. Based on our eligibility criteria, four investigators independently performed title-abstract screening of those 447 articles using the Rayyan platform leaving 35 articles. Seven observational studies found during initial search were screened and excluded as they did not meet eligibility criteria. After four researchers' full-text assessment of those 35 articles and conflict resolution by two others, twelve studies were finally included in our systematic review. All other studies were excluded due to either wrong population (n=10), wrong drug (n=10), wrong study design (n=9) or wrong study outcome (n=6) as depicted in **Figure 3**.

Table 1. Inclusion criteria of the studies included in the systematic review.

Particulars	Inclusion Criteria
Study type	Randomized controlled trials (RCTs) and observational studies
Participants	Adult patients (2:18 years) undergoing chemotherapy regimens consisting of anthracyclines and/or trastuzumab
Intervention	Prophylactic or concurrent administration of conventional heart failure medications: o Angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril lisionpril) o Angiotensin receptor blockers (ARBs) (e.g., valsartan, candesartan) o Beta-blockers (e.g., carvedilol, bisoprolol, metoprolol)
Comparison	Placebo or no cardioprotective therapy, in addition to standard chemotherapy
Outcomes	At least one quantifiable measure of cardiotoxicity, such as: · Left ventricular ejection fraction (LVEF) · Serum cardiac biomarkers (troponin, atrial/brain natriuretic peptide [ANP/BNP]) · Electrocardiographic changes (0Tc interval/dispersion) · Incidence of clinical heart failure
Language	Articles published in English

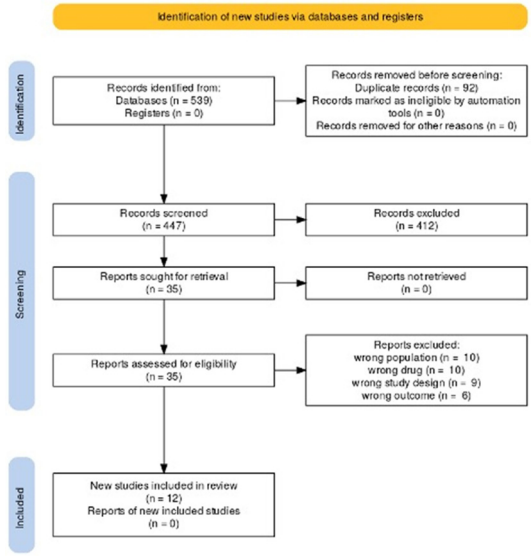

Figure 3.

Data extraction and quality assessment

The construction of the data extraction excel sheet was performed by two reviewers, and four reviewers extracted data independently. Two additional reviewers performed the data revision and second check. The investigators collected the first author, study design, location, number of patients, baseline patient characteristics (age, gender, cancer type), chemotherapy and cardioprotective regimens across study arms. Primary outcomes included change in LVEF (%), cardiac biomarkers such as troponin and ANP/BNP level and electrocardiograph (ECG) changes before and after chemotherapy. Secondary outcomes included total mortality and development of symptomatic heart failure either necessitating treatment initiation or hospitalization. Two reviewers assessed each of the included studies for bias using the Cochrane Risk of Bias 2.0 quality assessment tool and any conflict was resolved by another reviewer [25].

Data synthesis

Due to marked heterogeneity in outcomes a quantitative meta-analysis could not be performed, and findings are presented narratively.

Results

Characteristics of the included studies

The sum of patients included across all twelve studies was 1,571 adults with concomitant cancer treated with chemotherapeutic regimens consisting of anthracyclines and/or trastuzumab. The study characteristics are depicted in **Tables 2** and **3**. ACEIs were studied as either combination or comparison drug to BBs mainly in hematological malignancies. On the other hand, ARBs were studied both as monotherapy and combination and/or comparison to BBs mainly in breast cancer. Both showed mixed results and their effects in preserving LVEF were not consistent across the studies. BBs were more extensively studied among all cardioprotective medications both as monotherapy and combination and/or comparison to ARBs/ACEIs mainly in breast cancer and mixed cancer groups providing strongest evidence of cardioprotection. Increased doses of BBs were not associated with better cardioprotection. Oncology trials of combination therapy produced mixed results. Biomarker-guided risk stratification gave inconclusive reports. All medications were reported to be well tolerated among patients.

Table 2. Summary of the studies included in the systematic review.

Study ID	Design	Location	Duration	Patient number - Intervention - Control	Conclusion
Bosch *et al*., 2013 [30]	Randomized Controlled Trial	Hospital Clinic of Barcelona, Spain	6 months	Total: 90 - Enalapril + carvedilol: 45 - Control: 45	Combined treatment with enalapril and carvedilol may prevent left ventricular systolic dysfunction in patients with malignant hemopathies undergoing intensive chemotherapy, but larger studies are needed to confirm the clinical relevance of this strategy.
Pituskin *et al*., 2011 [34]	Parallel 3-arm, randomized, placebo-controlled, double-blind study	Canada	12 months	Total: 159 - Perindopril: 53 - Bisoprolol: 53 - Control: 53	Perindopril and bisoprolol were well tolerated in patients with human epidermal growth factor receptor 2 (HER2) positive early breast cancer who received trastuzumab and protected against cancer therapy related declines in left ventricular ejection fraction (LVEF), however trastuzumab mediated left ventricular remodeling was not prevented by these pharmacotherapies.
Nakamae *et al*., 2005 [29]	Randomized Controlled Trial	Osaka City University Medical Foundation, Japan	7 days	Total: 40 - Valsartan: 20 - Control: 20	Valsartan significantly prevents changes in cardiac markers associated with acute cyclophosphamide hydroxydauorubicin oncovin prednisone (CHOP) induced cardiotoxicity, except for the elevation in atrial natriuretic peptide (ANP), suggesting a potential role for angiotensin receptor blockers (ARBs) in preventing cardiotoxicity but requiring further research on long-term effects.

Gulati *et al*., 2016 [26]	Randomized, double-blind, placebo-controlled and 2×2 factorial study design	Akershus University Hospital, Norway	10–61 weeks depending on the chemotherapy regimen	Total: 130 - Candesartan + metoprolol: 28 - Candesartan + placebo: 32 - Metoprolol + placebo: 30 - Placebo + placebo: 30	Candesartan significantly alleviates the decline in LVEF associated with adjuvant breast cancer therapy, while metoprolol did not show a short-term beneficial effect, and suggests potential long-term benefits in reducing ventricular dysfunction risk.
Heck *et al*., 2021 [35]	Randomized, 2×2 factorial, placebo-controlled, double-blind clinical trial	Akershus University Hospital, Norway	10–61 weeks	Total: 120 - Candesartan + metoprolol: 30 - Candesartan + placebo: 30 - Metoprolol + placebo: 30 - Placebo + placebo: 30	Candesartan during adjuvant therapy for breast cancer did not prevent reduction in LVEF at 2 years but was associated with modest reduction in left ventricular end diastolic volume (LV EDV) and preserved global longitudinal strain (GLS), suggesting that a broadly administered cardioprotective approach may not be required in most patients with early breast cancer without preexisting cardiovascular disease.
Abuosa *et al*., 2018 [31]	Prospective, randomized, double-blind, placebo-controlled dose-ranging study	King Faisal Cardiac Centre in King Abdulaziz Medical City-Jeddah, Saudi Arabia	6 months	Total: 154 - Placebo: 38 - Carvedilol 6.25 mg: 41 - Carvedilol 12.5 mg: 38 - Carvedilol 25 mg: 37	Carvedilol may prevent deterioration in LVEF in cancer patients treated with doxorubicin, with this effect possibly not being dose-related, and provides further evidence for its protective role against anthracycline-induced cardiomyopathy.
Kalay *et al*., 2006 [36]	Prospective, randomized, single-blind, placebo-controlled study	Erciyes University Medical School, Turkey	6 months	Total: 50 - Carvedilol: 25 - Control: 25	Prophylactic use of carvedilol in patients receiving anthracycline therapy may protect both systolic and diastolic functions of the left ventricle.
Georgakopoulos *et al*., 2010 [27]	Prospective, randomized controlled trial	Greece	36 months	Total: 147 - Metoprolol group: 42 - Enalapril group: 43 - Control group: 40	Metoprolol and enalapril did not significantly reduce the risk of cardiotoxicity in patients treated with doxorubicin, although there was a trend towards lower incidence of heart failure and subclinical cardiotoxicity in the treatment groups, particularly with metoprolol.
Lee *et al*., 2021 [37]	Randomized phase III study Post-hoc analysis of SAVE HEART study	The Catholic University of Korea, Korea	At least 12 months	Total: 238 - Candesartan: 82 - Carvedilol: 70 - Control: 43 - Total randomized: 195	Subclinical cardiotoxicity is prevalent in breast cancer patients without cardiovascular risk treated with doxorubicin, and low-dose candesartan may be effective in preventing early decreases in LVEF, with its protective effect persisting over a year, although further large-scale trials are needed to confirm these findings.

Jung *et al*., 2025 [38]	Single-center, prospective, randomized, open-label Phase I clinical trial	University of Pennsylvania, United States	12 months	Total: 68 - Low risk, nonrandomized: 49 - Elevated risk, usual care: 6 - Elevated risk, carvedilol: 13	This Phase 1 trial demonstrated the feasibility, safety, and tolerability of risk-guided cardioprotection with carvedilol in breast cancer patients and highlighted the need for additional strategies to optimize non-treatment intervention trials, particularly during global health crises.
Avila *et al*., 2018 [39]	Prospective, double-blind, randomized, placebo-controlled study	Heart Failure Department of Heart Institute (InCor) and the Cancer Institute, São Paulo, Brazil	20 weeks	Total: 200 - Carvedilol: 96 - Placebo: 96	Carvedilol did not prevent early onset LVEF reduction but significantly reduced troponin levels and diastolic dysfunction, indicating some protective effects against cardiotoxicity.
Henriksen *et al*., 2023 [28]	Multicenter, prospective, randomized, open-label, blinded end- point trial nested within an observational cohort study	South-East Scotland Research Ethics Committee, United Kingdom	Variable, but it includes the time from randomization to 6 months post-chemotherapy.	Total: 175 - Cardioprotection: 29 - Standard care: 28 -Nonrandomized: 118	The study found no strong evidence that early cardioprotection therapy with combined candesartan and carvedilol prevented decline in LVEF in patients with breast cancer or non-Hodgkin lymphoma, questioning the benefit of current guidelines and highlighting poor tolerance to the therapy.

Table 3. Baseline patient characteristics including cancer types, chemotherapy and cardioprotective regimens.

Study ID	**Patient characteristics**	**Cancer type**	**Chemotherapy regimen**	**Cardioprotective medication**
Bosch *et al*., 2013 [30]	- Age: 18-70 years - Gender: 43% female, 57% male - Baseline left ventricular ejection fraction (LVEF) >50% and in sinus rhythm	Hematological malignancies	Anthracycline based regimen	Enalapril and Carvedilol combination regimen
Pituskin *et al*., 2011 [34]	- Women aged >18 years - No history of heart failure, cardiomyopathy, or uncontrolled hypertension - Baseline LVEF ≥50%	human epidermal growth factor receptor 2 positive (HER2+) breast cancer	Trastuzumab	- Perindopril - Bisoprolol
Nakamae *et al*., 2005 [29]	- Age: 24–70 years (mean 56 years) - Gender: 52.5% female, 47.5% male - ECOG PS: 0 to 1 - Total serum bilirubin <2.0 mg/dL, serum creatinine level <2.0 mg/dL - LVEF >50% - Not pregnant or lactating - No history of chronic or acute heart failure, other cardiac diseases, cirrhosis, uncontrolled diabetes mellitus, cerebral vascular accidents, severe psychopathy, contraindication to angiotensin receptor blockers (ARBs)	Non-Hodgkin lymphoma	Anthracycline based regimen	Valsartan

Gulati *et al*., 2016 [26]	- Women aged 18–70 years - ECOG PS: 0–1 - Serum creatinine <1.6 mg/dL - No symptomatic heart failure, clinically significant coronary artery disease, valvular heart disease, significant arrhythmias, or conduction delays Bradycardia, hypertension - No concurrent use or intolerance to angiotensin-converting enzyme inhibitors (ACEIs), ARBs and beta-blockers (BBs) - Baseline LVEF ≥50% - Not pregnant or breastfeeding	Breast cancer	Anthracycline based regimen	- Candesartan and Metoprolol combination regimen - Candesartan monotherapy - Metoprolol monotherapy
Heck *et al*., 2021 [35]	- Women aged 18–70 years - Cardiovascular risk factors: diabetes (1.7%), hypertension (6.7%) and smoking (17.5%) - Baseline LVEF ≥50% - No serious comorbidities	Breast cancer	Anthracycline based regimen	- Candesartan and Metoprolol combination regimen - Candesartan monotherapy - Metoprolol monotherapy
Abuosa *et al*., 2018 [31]	- Age: >16 years - Gender: 72.7% female, 27.3% male - Cardiovascular risk factors: hypertension (11.7%), diabetes mellitus (17.5%) and dyslipidemia (5.2%) - Baseline LVEF ≥50%	Multiple (mainly breast cancer and non-Hodgkin lymphoma)	Anthracycline based regimen	Carvedilol of different doses
Kalay *et al*., 2006 [36]	- Age: 32.8–60.8 years - Gender: 86% female, 14% male - No history of congestive heart failure, cardiomyopathy of any type, coronary arterial disease, moderate or severe mitral or aortic valve disease, any contraindication to Carvedilol, bundle branch block, thyroid function disorder, or another comorbid disease - Not on ACEIs, ARBs, BBs and diuretics - Baseline LVEF ≥50%	Multiple (mainly breast cancer and lymphoma)	Anthracycline based regimen	Carvedilol
Georgakopoulos *et al*., 2010 [27]	- Age: 49 years on average - Gender: 50% women, 50% men - Cardiovascular risk factors: hypertension (24%), diabetes mellitus (15.2%), hypercholesterolemia (28%), family history of cardiac disease (13.6%), smoking (42.4%) - Baseline LVEF ≥50%	Hodgkin lymphoma and non-Hodgkin lymphoma	Anthracycline based regimen	- Metoprolol - Enalapril
Lee *et al*., 2021 [37]	- Female patients of age over 18 years - No prior history of smoking, coronary artery disease, hypertension, diabetes and dyslipidemia - Baseline LVEF ≥50%	Breast cancer	Anthracycline based regimen	- Candesartan - Carvedilol

Jung *et al*., 2025 [38]	- Women aged ≥18 years - Cardiovascular risk factors: smoking (32%), hypertension (21%), diabetes mellitus (7%), hyperlipidemia (25%), coronary artery disease (12%), arrhythmia (6%) - Not pregnant or lactating - No stage IV breast cancer, contraindications to Carvedilol, no current beta-blocker therapy - Baseline LVEF ≥50%	Breast cancer	Anthracycline and/or trastuzumab therapy	Carvedilol
Avila *et al*., 2018 [39]	- Women aged ≥18 years - Cardiovascular risk factors: hypertension (6.2%), diabetes mellitus (4.7%), hypercholesterolemia under statin treatment (4.2%), any history of smoking (26%) - Baseline LVEF ≥50%	Breast cancer	Anthracycline based regimen	Carvedilol
Henriksen *et al*., 2023 [28]	- Age: >18 years - Gender: 87% female, rest was male - Cardiovascular risk factors: diabetes (2.3%), hypertension (9.1%), coronary disease (2.9%), any history of smoking (39.4%) - Concomitant cardiovascular medication prescription (9.7%) - Baseline LVEF ≥50%	Breast cancer, non-Hodgkin lymphoma	Anthracycline based regimen	Candesartan and carvedilol combination regimen

Risk of bias assessment

The Cochrane Risk of Bias 2.0 RevMan quality assessment tool was used to construct the risk of bias graph and risk of bias summary depicted in **Figure 4**. Most studies were methodologically sound: seven trials had a low risk of bias in all domains. In four trials, there were gaps in reporting, particularly around how randomization was done or how blinding was maintained, so we judged these as having "unclear" risk in at least one area. Only one trial was rated as high risk, mainly because more than 20% of participants were lost to follow-up, and the losses weren't balanced between groups. This raised concerns that the missing data could have influenced the results. Overall, selective reporting did not appear to be a problem. However, differences in how cardiac outcomes were measured—for example, using echocardiography in some trials and cardiac MRI in others and the fact that some outcome assessors were not blinded could have introduced some subtle measurement bias.

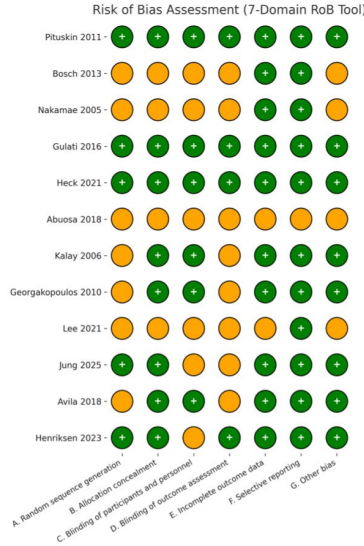

Figure 4.

Discussion

This systematic review evaluates the efficacy and safety of ACEIs, ARBs, BBs, and their combinations in preventing CTRCD in cancer patients receiving anthracycline- and/or trastuzumab-based chemotherapy. It draws data and synthesizes findings from twelve RCTs. The endpoints of these trials predominantly included changes in LVEF and cardiac biomarkers such as cardiac troponins and natriuretic peptides. Current evidence paints a mixed picture: while ACEIs, ARBs, and BBs can help preserve cardiac function in some patients, their benefits are neither consistent nor universal, underscoring the need for targeted rather than routine use. In Gulati *et al.'s* trial, adjuvant breast cancer patients on candesartan showed a smaller LVEF decline after chemotherapy than controls (–0.8% vs –2.6%, p=0.026) [26]. In contrast, Georgakopoulos *et al.* found no significant benefit, with 12-month LVEF changes of –2.4%, –1.3%, and –1.0% in the metoprolol, enalapril, and control groups, respectively [27]. The use of biomarkers, particularly troponin, as a stratification tool for initiating cardioprotective therapy was explored with varying success. For example, in the Cardiac CARE trial of 175 anthracycline-treated cancer patients, troponin levels during chemotherapy were used to classify participants as high- or low-risk for cardiotoxicity [28]. In the trial, the failure to demonstrate a statistically significant difference in CMR measured LVEF changes across all three groups after six months of chemotherapy, challenges the clinical utility of biomarker-guided strategies and further questions if troponin elevations truly predict clinically significant cardiac dysfunction. A significant challenge in interpreting these RCTs lies in the heterogeneity of outcomes assessed. While LVEF remains the most reported endpoint, its insensitivity to early myocardial dysfunction limits its use as a sole measure of cardiotoxicity. Several trials used a multimodal approach, assessing cardiac biomarkers, ECG changes, and imaging measures beyond LVEF. In Nakamae *et al's* trial, outcomes were grouped into three categories: 1) biomarkers (ANP/BNP), 2) echocardiographic parameters (LVEF, LVEDD, LVESD, FS, E/A ratio, deceleration time), and 3) ECG measures (QTc interval and dispersion) [29]. The clinical relevance of these surrogate markers, particularly in the absence of long-term follow-up data on symptomatic heart failure or mortality, remains debatable. The variability in imaging techniques (ECG and CMR), endpoints, and follow-up durations further complicates cross-trial comparisons. Oncology trials of combination therapy have produced mixed results. In Bosch *et al.'s* trial, enalapril plus carvedilol led to a significantly smaller LVEF decline than placebo after six months (–0.17% vs –3.28%, p=0.04) [30]. However, direct comparisons with monotherapy are few; among the 12 RCTs, only the PRADA trial included both combination and monotherapy arms, but group-specific LVEF data were unavailable, preventing such analysis [26].

Chemotherapy regimen and dose-related subgroup analysis was insufficiently explored. Patients receiving higher cumulative anthracycline doses or additional cardiotoxic chemotherapeutic drugs like Trastuzumab may derive greater benefit from cardioprotection, however, no study stratified results by dose intensity or Trastuzumab addition. In all the twelve RCTs reviewed, the medications used for cardioprotection were generally well tolerated among patients. The incidence of adverse effects such as hypotension, bradycardia, or renal dysfunction was low [26,31]. Notably, some trials reported that cardioprotective therapy allowed cancer treatment to proceed without interruptions, potentially improving outcomes by reducing delays or dose reductions related to cardiac issues [32,33]. This review has several limitations. Meta-analysis was not possible due to heterogeneity in outcome measures, limiting the precision of effect estimates. Heterogeneity in anthracycline formulations, unclear cumulative doses and the addition of Trastuzumab or other chemotherapeutic agents likely contributed to inconsistent results across the studies. Additionally, the follow up duration of most RCTs was within 6–12 months over a range of one week to 36 months. This variability affected outcome detection as well. Variability in CTRCD definitions and imaging modalities further hindered data aggregation and interpretation. Most trials had small sample sizes and excluded patients with pre-existing cardiovascular disease or low (<50%) LVEF at baseline limiting external validity of our study since these high-risk groups are common in real-world practice and are most likely to benefit from preventive therapy. Short follow up duration (6–12 months on average) is insufficient to detect late-onset cardiotoxicity, which may manifest years after chemotherapy completion and likely underestimates long-term cardiovascular risk and the potential benefits of cardioprotective therapy.

Future progress in cardio-oncology will require large, well-powered studies with long-term follow-up to assess feasibility, cost-effectiveness, and patient-centered outcomes of cardioprotective strategies. Standardizing CTRCD definitions and monitoring protocols, adopting risk-based patient selection, and integrating multidisciplinary cardio-oncology pathways into cancer centers will be crucial for translating research into practice.

Conclusion

This systematic review highlights both the promise and the limitations of current pharmacologic strategies for preventing chemotherapy-induced cardiotoxicity. While conventional heart failure medications such as ACEIs, ARBs and BBs offer modest protection in select populations, the variability in outcomes underscores the need for individualized, evidence-based approaches. Robust, long-term trials incorporating clinical endpoints and precision risk stratification are essential to inform future guidelines and optimize cardiovascular outcomes in cancer patients.

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