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The Journal of Clinical Oncology

ISSN 3064-7002

Research Article

Efficacy Of Statins In Preventing Anthracycline-Induced Cardiotoxicity In Individuals With Breast Cancer: A Systematic Review And Meta-Analysis.

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Abstract

Introduction: Anthracyclines are standard chemotherapeutic agents for breast cancer but may cause dose-dependent, irreversible myocardial damage (class I cardiotoxicity) via reactive oxygen species (ROS), potentially leading to dilated cardiomyopathy and heart failure. Statins, through their pleiotropic effects, reduce oxidative stress and inflammation, offering cardioprotection. This meta-analysis evaluates the impact of statins on cardiac dysfunction, LVEF, LVESV, LVEDV, and LA diameter in women with breast cancer receiving anthracycline-based chemotherapy.

Methods: PubMed, Google Scholar, and Cochrane Library were searched through February 11, 2025, for randomized controlled trials and propensity-matched observational studies comparing statins with placebo in breast cancer patients on anthracyclines. Outcomes included changes in cardiac dysfunction, LVEF, LVESV, LVEDV, and LA diameter. A review manager was used to analyze data as mean differences with 95% confidence intervals (CI).

Results: A total of 428 patients were included; 180 (42%) in the statin group and 248 (58%) in the placebo group. Statin users had a significantly lower risk of cardiac dysfunction (RR=0.41 [95% CI: 0.23–0.72], P=0.02, I^2=0%). They also had reduced LVEF decline (MD= -3.42 [CI: -5.10 to -1.73], P<0.0001, I^2=20%) and two-chamber LVESV (MD= -4.87 [CI: -7.64 to -2.10], P=0.0006, I^2=0%). No significant changes were seen in LA diameter or LVEDV/ LVESV across other views.

Conclusion: Statins significantly reduce early cardiac dysfunction risk by 59% in breast cancer patients receiving anthracyclines. Benefits were observed in LVEF and LVESV, though limited by small sample size and data variability

Keywords : *Anthracyclines, Cardiotoxicity, Statins, Cardio-Protective Effect, Left Ventricular Ejection Fraction.*

INTRODUCTION

Anthracyclines have revolutionized cancer therapy, offering curative potential for malignancies such as breast cancer, lymphoma, and leukemia. However, their clinical benefits are limited by a well-recognized adverse effect: cardiotoxicity (1). Through the inhibition of topoisomerase II and intercalation into DNA, anthracyclines generate reactive oxygen species and iron-mediated free radicals, leading to oxidative stress, mitochondrial damage, and ultimately, myocyte injury. This process results in dose-dependent cardiac dysfunction, which can develop during treatment or manifest months to years later [(2). With improving cancer survival rates, particularly among breast cancer patients, the long-term cardiotoxic effects associated with anthracycline-based chemotherapy have emerged as a growing concern requiring targeted clinical attention. Several pharmacologic strategies have been investigated to reduce anthracycline-induced cardiotoxicity. Agents such as ACE inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers have shown some benefit in preserving left ventricular function, although their effectiveness remains inconsistent across studies. Recently, statins have gained attention for their potential cardioprotective properties. In addition to their lipid-lowering effects, statins have anti-inflammatory, antioxidative, and endothelial-stabilizing effects that may counteract the mechanisms responsible for anthracycline-induced myocardial injury. Preliminary studies,

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Received: 07-July-2025, Manuscript No. TJOCO-4970 **; Editor Assigned:** 09-July-2025 **; Reviewed:** 11-Aug-2025, QC No. TJOCO-4970 **; Published:** 24-Oct-2025, **DOI:** 10.52338/tjoco.2025.4970
Citation: Ridda Khattak. Efficacy Of Statins In Preventing Anthracycline-Induced Cardiotoxicity In Individuals With Breast Cancer: A Systematic Review And Meta-Analysis. The Journal of Clinical Oncology. 2025 October; 13(1). doi: 10.52338/tjoco.2025.4970.
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including randomized controlled trials and observational cohorts, suggest that statins may reduce cardiac dysfunction and preserve left ventricular ejection fraction (LVEF) during chemotherapy (3).

Despite growing interest, the current evidence regarding statin use in this context remains inconclusive. To date, no comprehensive meta-analysis has synthesized findings specifically in breast cancer patients receiving anthracycline-based chemotherapy. Existing studies differ in design, sample size, outcome measures, and follow-up periods, making it difficult to establish standardized clinical recommendations. Additionally, it is not well understood which patient subgroups may benefit the most from statin therapy in this context.

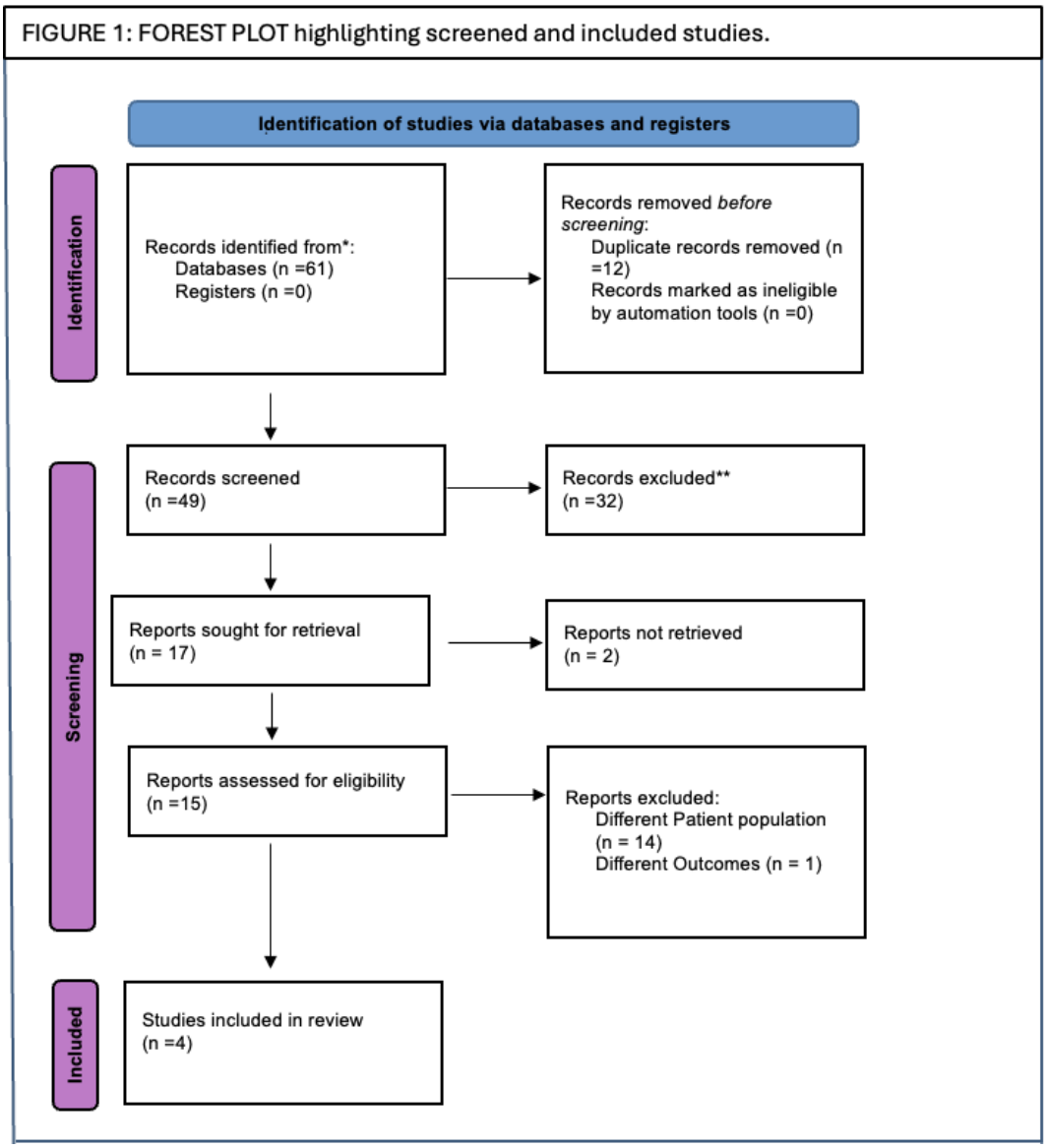
Our meta-analysis seeks to fill this gap by assessing and integrating the current body of research on statin use in prevention of anthracycline induced cardiotoxicity. Key outcomes include decreased risk of cardiotoxicity and improvement in left ventricular ejection fraction (LVEF). These findings may offer more robust evidence to inform clinical decision-making and support the implementation of statins as a preventive intervention in the field of cardio-oncology.

METHODS

Protocol and registration

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (**figure 1**), which outlines minimum standards for reporting systematic reviews and meta-analyses (4). The protocol for this meta-analysis was registered and published with PROSPERO (CRD420251046463).

Figure 1. PRISMA diagram highlighting identification of studies.



Search Strategy and Data Sources

A comprehensive literature search was conducted in PubMed, Google Scholar and the Cochrane Library for studies published from inception to February 2025, using the search string: ("Cancer" OR "Breast Cancer" OR "HER-2-positive breast cancer") AND ("Anthracycline" OR "Doxorubicin" OR "epirubicin") AND ("Cardiotoxicity" OR "heart failure" OR "Cardiac dysfunction") AND ("Statin" OR "HMG-CoA reductase inhibitor"). We also searched ClinicalTrials.gov for completed RCTs. Reference lists of included studies and relevant systematic reviews were manually screened to identify additional eligible studies.

Eligibility Criteria and Study Selection

Studies were included if they focused on adult breast cancer patients receiving anthracycline-based chemotherapy and assessed the use of statins before or during treatment. The primary outcome of interest was the incidence of cardiac dysfunction, defined as a decline in left ventricular ejection fraction (LVEF) by 10% or more, or the development of heart failure. Secondary outcomes included changes in left ventricular ejection fraction (LVEF), 2 chamber left ventricular end diastolic volume (LVEDV), 4 chamber LVEDV, 2 chamber left ventricular end systolic volume (LVESV), 4 chamber left ventricular end systolic volume (LVESV) and left atrium (LA) diameter. Eligible study designs included randomized controlled trials (RCTs), prospective or retrospective cohort studies, and case-control studies. Studies were excluded if they were animal studies, case reports, reviews, lacked a non-statin control group, or did not provide quantitative data on cardiotoxicity outcomes.

Data Extraction

The articles retrieved from the systematic search were exported to the EndNote Reference Library software and de-duplicated separately by two reviewers. The same two reviewers then carefully assessed the remaining articles and screened the titles, abstracts, and full texts of identified studies to determine eligibility. A standardized data extraction form was used to collect relevant information, including study characteristics such as author, year, study design, and sample size, as well as patient demographics, cancer stage, cardiovascular risk factors, and details regarding the statin type, dose, and duration (**Tables 1 and 2**). Additionally, data on the anthracycline regimen, cumulative dose, cardiac function parameters including baseline and post-treatment LVEF, biomarkers, and cardiovascular events such as cardiotoxicity. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer. (**Table 1 and 2**).

Table 1. Baseline characteristics of included studies.

Author	Country	Study Design	Sample Size Study/Control	Side of Cancer	Intervention	Control
Seicean 2012	USA	Cohort study	628 (67/561)	-	Statin	No statin
Nabatti 2019	Iran	Randomized control trial	77 (38/39)	R-43 (55.8%) L-34 (44%)	20 mg rosuvastatin	Placebo
Kettana 2024	Egypt	Randomized control trial	53 (26/27)	R-23 (43.4%) L-27 (50.9%)	20 mg rosuvastatin	Placebo
Mohamed 2024	Iran	Randomized Control trial	100 (50/50)	-	40 mg atorvastatin	Placebo

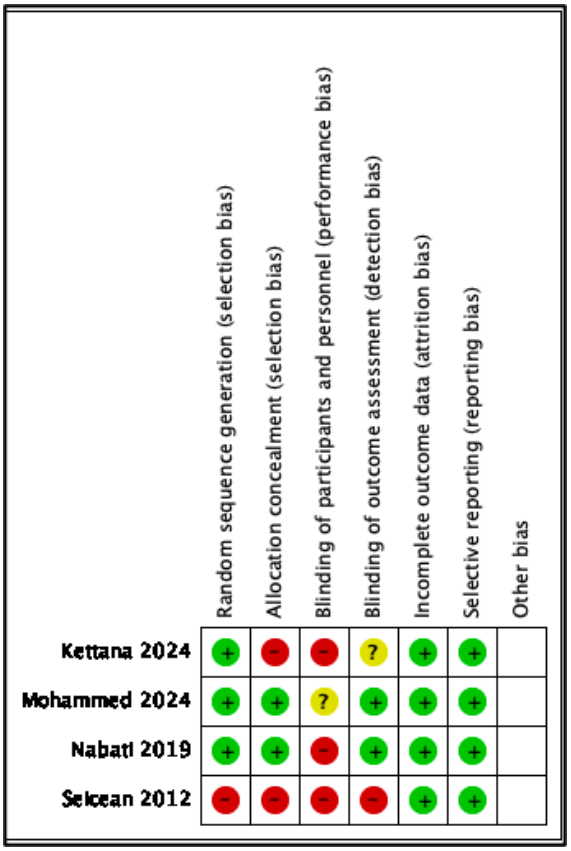
Table 2. Baseline Characteristics of Included Patient Population.

	Mohammad-2024		Kettana-2024		Seicena-2012		Nabati -2019	
	Study	Control	Study	Control	Study	Control	Study	Control
Mean Age (Years)	47.84+/-9.16	49.80+/-10.51	47.92+/- 9.14	49.72+/-9.51	61.3+/-8.9	50.3+/-10.43	47.47 (9.70)	50.74 (12.44)
Body Surface Area(m^2)	1.83+/-0.21	1.82+/-0.15	1.75±0.11	1.71±0.11	-	-	1.80+/-0.22	1.80+/-0.19
Diabetes Mellitus (N,%)	15 (30.0%)	14(28.0%)	5 (20%)	6 (24%)	17 (25.4%)	15 (2.7%)	5 (13.2%)	7 (17.9)
Hypertension (n,%)	16 (32.0%)	13 (26.0%)	7 (28%)	6 (24%)	74 (13.2%)	35 (50.8%)	-	-
Total Anthracyclinedose	437.67+/-54.70	433.48+/-36.66	-	-	404 ±150	413 ± 151	339.44+/-39.00	337.83+/-42.60
Anti HER-2 therapies	21 (42.0%)	23 (46.0%)	-	-	8 (11.9%)		-	-

Risk of Bias Assessment

Two of the reviewers independently assessed the risk of bias for all eligible trials using the Cochrane risk of bias tool for RCTs and ROBINS-I for the non-randomized studies of intervention (**Figure 2**) (5–7). Any discrepancies were discussed and resolved through a third reviewer. Methodological components of the studies were assessed and classified as high-risk, low-risk, or some concerns of bias. Any discrepancies were discussed and clarified with other authors to make a final recommendation.

Figure 2. Risk of Bias.



Statistical Analysis

All statistical analyses were conducted using Review Manager (RevMan, Version 5.4.1). Data from the included studies were pooled, and for the primary outcome, risk ratios (RRs) with corresponding 95% confidence intervals (CIs) were calculated. For secondary outcomes, mean differences (MDs) with 95% CIs were used to assess continuous variables. A random-effects model was applied to account for anticipated variability across studies. To visually present the meta-analysis results, forest plots were generated. Due to the inclusion of fewer than ten studies, publication bias could not be assessed using a funnel plot. Similarly, meta-regression and subgroup analyses were not feasible given the limited number of studies. Statistical heterogeneity was evaluated using Higgins' I^2 statistic, with a threshold of 50% or lower considered acceptable (8). A p-value of less than 0.05 was considered statistically significant.

Certainty of Evidence Assessment

For evaluation of the certainty of the evidence, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used, and the quality of evidence of the pooled estimates was judged as high, moderate, low, or very low according to the GRADE Working Group (Supplementary table 3) (9,10).

Ethical Considerations

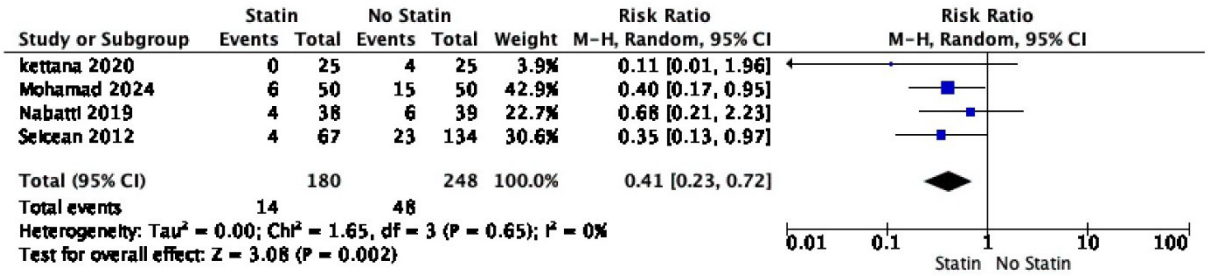
As this study was based on previously published data, institutional review board (IRB) approval and patient consent were not indicated.

RESULTS

This meta-analysis included a total of 428 women with diagnosis of breast cancer and on anthracycline therapy. Of these 180 (42%) were included in the treatment (statin arm) and 248 (58%) were in the control (placebo arm).

Pooled analysis identified that patients on statins had a significant risk reduction of cardiac dysfunction RR=0.41 [95% CI=0.23 to 0.72], P=0.02, I^2=0%) (**Figure 3**). Furthermore, these patients had experienced lower reductions of LVEF when compared to the patients who were taking anthracycline therapy and placebo (MD= -3.42 [95% CI= -5.10 to -1.73], P<0.0001, I^2=20%) (**Figure 4**). It was also found that 2-chamber LVESV was reduced in patients who were on anthracycline therapy and statins (MD= -4.87 [95% CI= -7.64 to -2.10], P=0.0006, I^2=0%) (**Figure 5**).

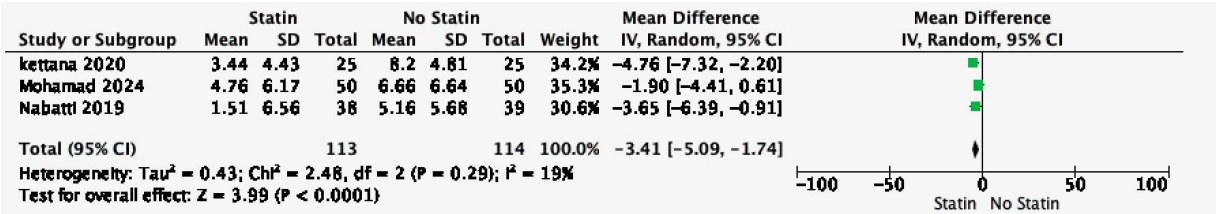
Figure 3. Forest plot comparison of cardiotoxicity.



Caption

Forest plot of comparison: 1 Cardiotoxicity, outcome: 1.1 Cardiotoxicity.

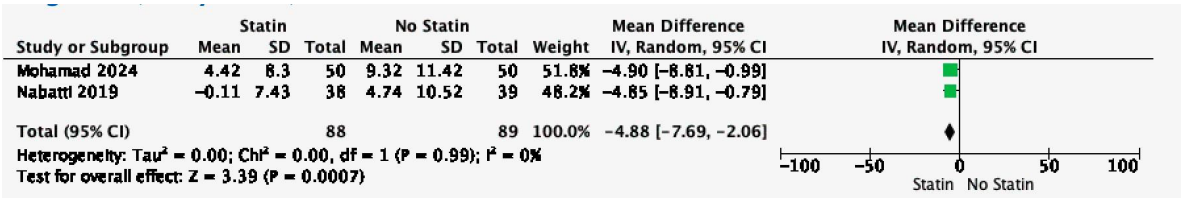
Figure 4. Forest plot comparison of LVEF.



Caption

Forest plot of comparison: 2 LVEF, outcome: 2.1 LVEF.

Figure 5. Forest plot comparison of 2-chamber LVESV

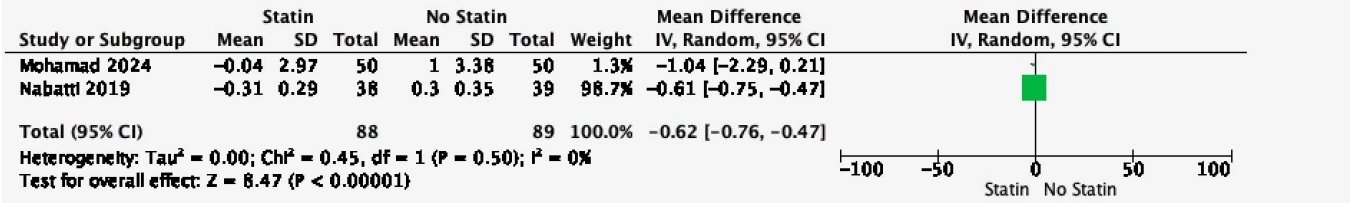


Caption

Forest plot of comparison: 3 2 chamber LVESV, outcome: 3.1 2 chamber LVESHV.

It should be further noted that there was no significant difference in other cardiac parameters such as LA diameter (MD=0.78 [95% CI= -1.37 to 2.93], P=0.48, I^2=97%), 2-chamber LVEDV (MD= -0.51 [95% CI= -2.05 to 1.03], P=0.52, I^2=0%), 4-chamber LVEDV (MD= -0.68 [95% CI= -4.95 to 3.58], P=0.75, I^2=0%), and 4-chamber LVESV (MD= 1.32 [95% CI= -6.53 to 9.18], P=0.74, I^2=92%) (**Figures 6, 7, 8 and 9**).

Figure 6. Forest plot comparison of LA diameter.



Caption

Forest plot of comparison: 7 LA diameter, outcome: 7.1 LA diameter.

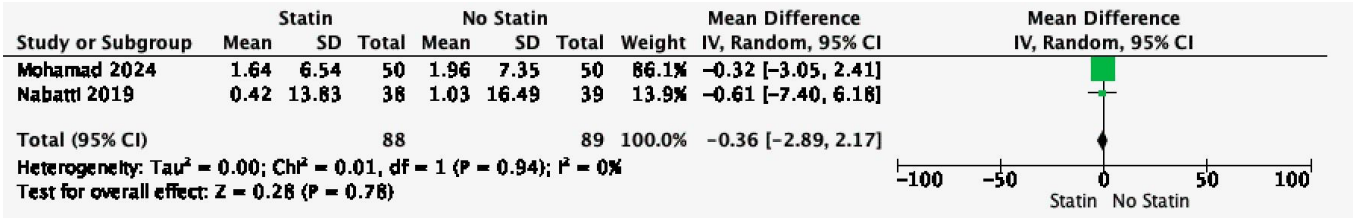
Figure 7. Forest plot comparison of 2-chamber LVEDV.



Caption

Forest plot of comparison: 5 2 Chamber LVEDV, outcome: 5.1 2 Chamber LVEDV.

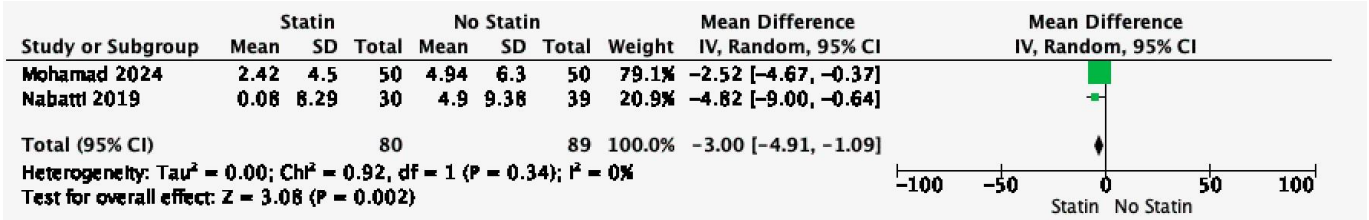
Figure 8. Forest plot comparison of 4-chamber LVEDV.



Caption

Forest plot of comparison: 6 4 Chamber LVEDV, outcome: 6.1 4 chamber LVEDV.

Figure 9. Forest plot comparison of 4-chamber LVESV.



Caption

Forest plot of comparison: 4 4 chamber LVESV, outcome: 4.1 4 Chamber LVESV.

DISCUSSION

This meta-analysis provides compelling evidence to support the potential therapeutic role of statins in mitigating anthracycline-induced cardiotoxicity in breast cancer patients receiving anthracyclines, with a 59% relative risk reduction observed across included studies. Although anthracyclines remain among the most effective chemotherapeutic agents, their clinical utility is limited by well-established dose-dependent cardiotoxicity; this can result in irreversible myocardial injury and progressive heart failure (11). The cardioprotective effect of statins likely stems from their pleiotropic properties—including antioxidant,

anti-inflammatory, endothelial-stabilizing, antifibrotic, and immunomodulatory actions—which may attenuate the cardiac insults associated with anthracycline therapy (12).

Specifically, statins reduce reactive oxygen species (ROS) generation, a major contributor to anthracycline-mediated myocardial apoptosis. This is done by enhancing the expression of antioxidant enzymes like superoxide dismutase (SOD) and catalase while suppressing NADPH oxidase activity (13). Additionally, statins enhance endothelial function by increasing endothelial nitric oxide synthase (eNOS) expression and nitric oxide (NO) bioavailability, potentially improving myocardial perfusion while simultaneously reducing ischemic injury during chemotherapy (14). Furthermore, dampening inflammatory pathways—through inhibition of NF-κB and suppression of cytokines such as TNF-α, IL-1β, and IL-6—statins may prevent inflammatory cardiac remodeling, a hallmark of anthracycline-induced cardiotoxicity. These multifaceted mechanisms support the observed reduction in cardiotoxicity and suggest that statins may offer a comprehensive protective strategy for patients undergoing chemotherapy. Our analysis further demonstrated that statin therapy is associated with a significantly smaller decline in left ventricular ejection fraction (LVEF), indicating preservation of systolic function. Even subclinical declines in LVEF, though within normal clinical limits, are strong predictors of future heart failure and adverse cardiovascular outcomes in cancer survivors. In a seminal study by Cardinale et al. (2015), subclinical reductions in LVEF were shown to strongly predict later development of overt heart failure and cardiovascular mortality in anthracycline-treated patients (15). This underscores the clinical importance of maintaining myocardial function during treatment. The LVEF preservation noted among statin users may result from a combination of mitochondrial protection and improved cellular energetics due to reduced oxidative stress, as well as enhanced endothelial function and decreased vascular inflammation. Statins' inhibition of maladaptive inflammatory pathways and cardiac fibrosis—such as downregulation of TGF-β and connective tissue growth factor (CTGF)—may further help maintain myocardial compliance and contractility, directly supporting preserved LVEF. These cardioprotective mechanisms align with the observed smaller decline in LVEF and suggest a tangible clinical benefit in statin-treated patients.

In addition, our findings demonstrate that statins significantly reduce left ventricular end-systolic volume (LVESV), a marker of myocardial contractility and ventricular remodeling. Reductions in LVESV suggest better preservation of cardiac structure and reduced progression toward systolic heart failure. This supports the hypothesis that statins not only prevent functional decline but also protect against adverse ventricular remodeling commonly induced by anthracyclines. Mechanistically, this effect may be attributed to statins' antifibrotic properties which inhibit interstitial fibrosis and maladaptive hypertrophy, particularly through suppression of TGF-β signaling. By limiting cardiac fibrosis and maintaining ventricular compliance, statins may prevent increases in LVESV, thereby preserving overall systolic performance. Additionally, statins' anti-inflammatory effects may reduce myocardial edema and tissue injury, contributing to structural stability of the ventricle.

While our meta-analysis supports the cardioprotective potential of statins in the context of anthracycline-induced cardiotoxicity, not all cardiac parameters demonstrated significant improvements. Specifically, left atrial (LA) diameter and left ventricular end-diastolic volume (LVEDV) did not differ significantly between the statin and placebo groups. This is in keeping with the current literature which has demonstrated inconclusive evidence for the efficacy of statins in this regard. For instance, the PREVENT trial, a multicenter study assessing the efficacy of atorvastatin in 279 patients undergoing doxorubicin treatment, found no significant difference in the decline of left ventricular ejection fraction (LVEF) between the atorvastatin and placebo groups (16) This suggests that although statins may offer theoretical protective benefits, they may not necessarily translate into clinically meaningful outcomes as they relate to improvements in long-term systolic function (16). Conversely, Nabati et al. (2019) demonstrated the cardioprotective potential of rosuvastatin in a randomized trial involving 89 breast cancer patients receiving anthracyclines (17). Here, the rosuvastatin group maintained stable LVEF, while the placebo group experienced a significant decline. Similarly, a subsequent randomized trial by Mohamed et al. (2023) reported that atorvastatin significantly reduced the incidence of chemotherapy-related cardiac dysfunction (CTRCD), with only 12% of patients in the atorvastatin group developing CTRCD compared to 30% in the placebo group (18).

The variability in outcomes across these studies may be attributed, at least in part, to differences in sample size, variations in statin type and dosing, patient populations, and the lack of a standardized study protocol. These inconsistencies highlight the complexity of the issue and underscore the pressing need for larger, well-designed, and standardized trials to more definitively determine the role of statins in preventing anthracycline-induced cardiotoxicity.

LIMITATIONS AND CONSIDERATIONS

Despite promising results, several limitations must be acknowledged. First, the relatively small sample size of 428 patients may limit the generalizability of the findings. Second, variability in the reporting of cardiac parameters, particularly with respect to left atrial (LA) diameter and left ventricular end-diastolic volume (LVEDV), limits the ability to draw definitive

conclusions regarding these parameters. Substantial heterogeneity observed in certain measurements, such as four-chamber LVESV (I2=92%), reflects objective differences in study methodologies and patient populations, which may have influenced the overall results.

Additionally, while statins' anti-inflammatory and antioxidant properties are well-established, their ability to prevent late-onset cardiotoxicity remains uncertain and warrants additional research (Wu et al., 2023). Future research should aim to standardize the measurement of cardiac outcomes, determine the optimal timing and dosing of statins, and explore their impact on other chemotherapy regimens beyond anthracyclines (19).

Furthermore, this meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as illustrated in Figure 1. The study selection and data extraction process adhered to systematic review methodologies to ensure accuracy and reliability in data synthesis.

CONCLUSION

The findings from this meta-analysis support further research regarding the potential role of statins in cardio-oncology protocols for breast cancer patients undergoing anthracycline therapy. Statins may significantly reduce the risk of chemotherapy-induced cardiotoxicity by preserving crucial cardiac parameters such as LVEF and LVESV. They offer a feasible and cost-effective approach to reducing the long-term cardiovascular burden in these patients. Given their established safety and accessibility, statins could be easily integrated into clinical practice, especially for patients at high risk of cardiotoxicity.

However, to establish statins as a standard cardioprotective strategy in oncology care, larger randomized controlled trials with extended follow-up are critical. These studies should assess long-term cardiovascular outcomes and efficacy across various chemotherapy regimens to fully elucidate the clinical utility of statin therapy in preventing cancer treatment-related cardiac dysfunction.

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