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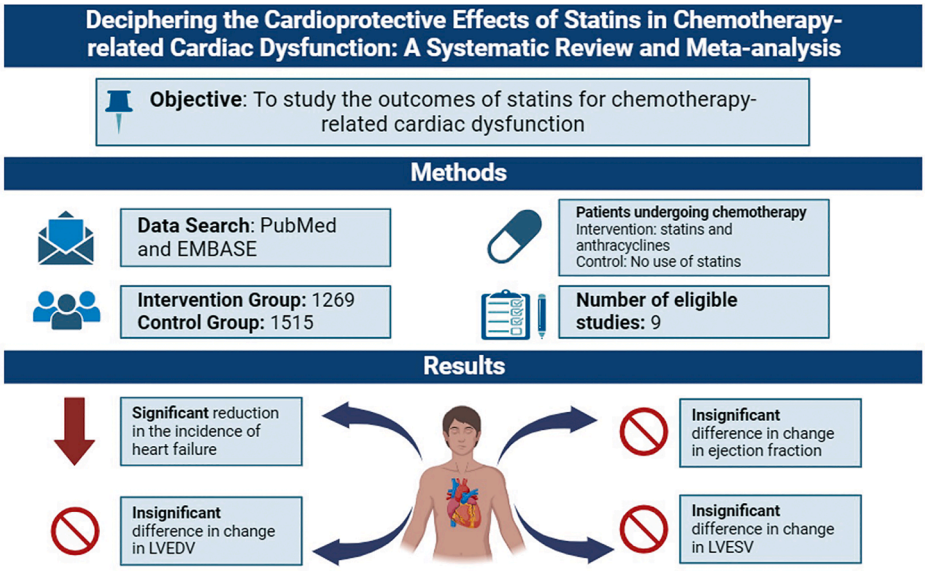
Original Research

Deciphering the cardioprotective effects of statins in anthracycline-related cardiac dysfunction: A systematic review and meta-analysis

Mubashar Karamat [a], Bilal Hussain [b], Munis Mahboob Ahmed [c], Mohammad Hamza [d], Junaid Mir [e], Ayedh Alamri [f], Aimen Shafiq [g], Yasar Sattar [h], Muhammad Zia Khan [h], Harshith Thyagaturu [h], Karthik Gonuguntla [h], Birjesh D Patel [h,*]

[a] Department of Internal Medicine, Ascension Saint Francis Hospital, Evanston, IL, USA
[b] Division of Cardiovascular Health and Disease, University of Cincinnati, Cincinnati, OH, USA
[c] Department of Internal Medicine, Springfield Regional Medical Center, OH
[d] Department of Internal Medicine, Albany Medical Center, Albany, NY
[e] Department of Internal Medicine, University of Missouri, Columbia, MO, USA.
[f] Department of Cardiovascular Department, Tufts Medical Center, Boston, USA
[g] Department of Internal Medicine, Dow University of Health Sciences, Pakistan
[h] Department of Cardiology, West Virginia University, Morgantown, WV, USA

GRAPHICAL ABSTRACT



* Corresponding author at: Cardiology Department, West Virginia University, Morgantown, WV, Address: 1 Medical Center Dr, Morgantown, WV 26506, USA.
E-mail address: brijesh.patel@wvumedicine.org (B.D. Patel).

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ABSTRACT

Background: Cancer induced chronic inflammation and cancer drugs effects on the vascular system can lead to rapidly progressing atherosclerotic burden. Statins drugs are known to reduce atherosclerotic plaque burden and inflammation. We studied outcomes of statins for anthracycline-related cardiac dysfunction (ARCD).
Methods: We conducted an online systematic search on PubMed and Embase to identify studies assessing statins' role in alleviating ARCD. We selected 9 studies that had patients with ARCD and use of statins. We primarily focused on outcomes including incidence of heart failure (HF), mean changes in left ventricular ejection fraction (LVEF), end-diastolic volume (LVEDV), and end-systolic volume (LVESV) from baseline. Odds ratios (OR) were calculated using a random effect model in *R-statistics*.
Results: Among 9 studies with a total of 2784 patients we noticed a significant reduction in the incidence of HF among patients administered statins, with an OR of 0.52 (95 % CI 0.37-0.74, $p < 0.0003$), indicating a substantial protective effect. However, the mean changes in EF, LVEDV, and LVESV from baseline, represented by *Hedges's g* of 1.09 (95 % CI -0.40 to 2.57, $p = 0.15$), 0.91 (95 % CI -1.69 to 3.51, $p = 0.47$), and 1.32 (95 % CI -2.30 to 4.94, $p = 0.49$) respectively, were not statistically significant. (Figure 1).
Conclusion: Our meta-analysis confirms statins' effectiveness in reducing risk of ARCD. However, their influence on EF, LVEDV, and LVESV remains uncertain, warranting further study.

1. Introduction

Cancer is among the top causes of death worldwide, with increasing incidence and mortality rates. One of the principal treatments include chemotherapies which help in increasing survival of cancer patients, however, that comes at the expense of side effects, mainly cardiac toxicities. The adverse effects of chemotherapy on the heart are a spectrum that includes coronary artery disease (CAD), acute coronary syndrome (ACS), congestive heart failure (CHF) and pericardial effusion [1]. Multiple chemotherapy agents were found to have cardiac adverse events, such as anthracyclines, HER-2 receptor blockers, antimetabolites, tyrosine kinase inhibitors, and Immunotherapy with checkpoint inhibitors [1]. Anthracycline agents such as doxorubicin are among the therapeutic options for many cancers. Multiple mechanisms have been implicated in causing cardiotoxicity due to anthracyclines. Cardiotoxicity can be acute or chronic. Acute toxicity manifests as myopericarditis with reversible left ventricle (LV) dysfunction shortly after initial administration. More importantly, chronic cardiotoxicity can progress from asymptomatic LV dysfunction to overt CHF. Among the risk factors for toxicity from anthracyclines, total cumulative dose is the most substantial. Other risk factors include older age, female gender, hypertension, mediastinal radiation, preexisting cardiovascular disease, and use of another cardiotoxic agent [1,2].

Antimetabolites such as 5-fluorouracil and HER-2 receptor blockers such as Trastuzumab have also been implicated in causing cardiotoxicity. Trastuzumab, a monoclonal antibody targeting HER-2 receptor, results in apoptosis and cell death. Trastuzumab cardiotoxicity is reversible upon discontinuation. 5-fluorouracil can cause vasospasm, which can lead to myocardial infarction and death, and other adverse events such as CHF, CAD, and pericardial effusion [1]. A summary of the various cardiac side effects associated with different chemotherapy agents is presented in Table 1. Effective cardio-protection can mitigate these risks, improve life quality by preventing debilitating symptoms, and reduce healthcare costs associated with managing chemotherapy-induced cardiotoxicity.

Hyperlipidemia is a well-known modifiable risk factor for atherosclerosis cardiovascular disease (ASCVD). The guidelines recommended starting lipid-lowering agents in high-risk patients which is associated with significant risk reduction of ASCVD [3,4]. Data shows that using statins as primary prevention in patients on chemotherapies can lower chemotherapies-related cardiotoxicity. However, this is still not well-studied. Statins were included in the European Society of cardiology guidelines as class IIa indication based on some observational studies, to be given to patients at high risk of cardiotoxicity as primary prevention of chemotherapy-related cardiac dysfunction [3,4]. The aim of this meta-analysis is to report the aggregated effect of statins in lowering the risk for anthracycline cardiotoxicity.

2. Methods

We have documented our search strategy and meta-analysis in accordance with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR-2 (A Methodological Quality Assessment of Systematic Reviews-2). The associated checklists from these guidelines can be referenced in **Supplemental S1** and **Supplemental S2** [5,6]. The criteria for inclusion in our meta-analysis consisted of: 1) Patients diagnosed with cancer on anthracyclines, 2) Patients treated with statin in the experimental group and no statin in the control group. Patients who were not on anthracyclines were excluded. Case reports, clinical spotlights, and review articles were not included in our study selection.

Using PRISMA guidelines, a comprehensive literature search was

Table 1
Summary of the various cardiac side effects associated with different chemotherapy agents.

Agents	Examples	Associated Cardiac Complications
Anthracyclines	Doxorubicin, Epirubicin	Cardiac dysfunction, Heart failure, Myocardial ischemia, Myocarditis, Pericarditis, Ventricular arrhythmias
HER-2 Receptor Blockers	Trastuzumab	Cardiac dysfunction, Heart failure, Myocardial ischemia, Left ventricular dysfunction, Reversible cardiomyopathy
Antimetabolites	5-Fluorouracil, Methotrexate	Coronary vasospasm, Myocardial infarction, Pericardial effusion, Congestive heart failure (CHF), Coronary artery disease (CAD), QT prolongation
Alkylating Agents	Cyclophosphamide	Myocarditis, Pericardial effusion, Heart failure, Atrial fibrillation, QT prolongation, Hypertension
Platinum-Based Agents	Cisplatin, Carboplatin	Hypertension, Myocardial ischemia, Thrombosis, Ventricular arrhythmias, Acute coronary syndrome (ACS)
Tyrosine Kinase Inhibitors	Imatinib, Sorafenib	Hypertension, Thrombosis, Heart failure, Myocardial ischemia, Left ventricular dysfunction, QT prolongation
Immunotherapy (e.g., Checkpoint Inhibitors)	Pembrolizumab, Nivolumab	Myocarditis, Myocardial ischemia, Heart failure, Ventricular arrhythmias, Pericardial disease, Autoimmune myocarditis

carried out on the MEDLINE Portal, encompassing EMBASE Classic and PubMed. Our focus was on trials and observational studies that met our inclusion criteria. This search covered the entire time frame from the start of the databases up to August 2023. Search strategies incorporated both MeSH terms and specific keywords, applying Boolean Operators "OR" and "AND", with terms such as: "Cancer", "Chemotherapy", "Anthracyclines" "Cardiac Dysfunction", "Statins'', "Heart Failure (HF)", and "Ejection Fraction". Details of the search strategy are included in the **Supplemental S3.**

2.1. Study selection

We shortlisted studies for inclusion based on whether they were randomized clinical trials (RCTs), pilot trials, retrospective or prospective studies, and if they matched our inclusion criteria. The articles underwent an independent screening by MH and MK. Full-text articles that cleared the initial screening were then subjected to a deeper review for pertinent outcomes. Furthermore, by employing backward snowballing, we delved into the references of articles to unearth any overlooked studies of interest. YS took on the task of verifying the data from the screening process.

2.2. Data collection and statistical analysis

The baseline characteristic and data were exported to Microsoft Excel and were arranged in baseline characteristics, in binary outcome format for discrete variables and continuous outcome format for continuous variables. From the studies in our dataset, we extracted and presented mean values, standard deviations (SD), and other relevant statistics that revolve around baseline conditions and patient demographics. The analytical engine driving our computations was the *CRAN-R* software, known for its proficiency in delivering aggregate effect sizes. We relied on the *meta-bin* module and combined it with the Mantel-Haenszel random-effects approach for deducing the Odds Ratio (OR), adhering to a significance benchmark of $p < 0.05$. For continuous outcomes, we turned to the *meta-cont* module, working in tandem with the Inverse-variance method, aiming for a consolidated standard mean difference (SMD). Our cumulative effect testing was articulated through a z-score, mirroring the nuances of a 95 % confidence bracket. Using the Higgins I-squared (I2) tool, we could gauge the extent of statistical disparity across studies. Values of $\leq$ 50 % denoted low heterogeneity, 50-75 % signified moderate heterogeneity, and values $\geq$75 % represented high heterogeneity [7]. In compliance with the Cochrane Handbook for Systematic Reviews of Interventions, we opted not to include a funnel plot for publication bias assessment in our meta-analysis. This decision adheres to the recommendation of avoiding funnel plots in analyses with fewer than 10 studies, which applies to our study [8]. To wrap up, the credibility of our pooled studies was upheld by applying the renowned Cochrane Risk of Bias [9] for randomized studies and the Newcastle-Ottawa Scale [10] for observational studies.

3. Results

From an initial retrieval of 265 articles, 27 were identified as duplicates and subsequently removed. This yielded 238 articles for the primary screening. Following a rigorous assessment, 219 articles were excluded based on predefined criteria. The ensuing detailed assessment of the 19 potentially relevant studies culminated in the selection of 9

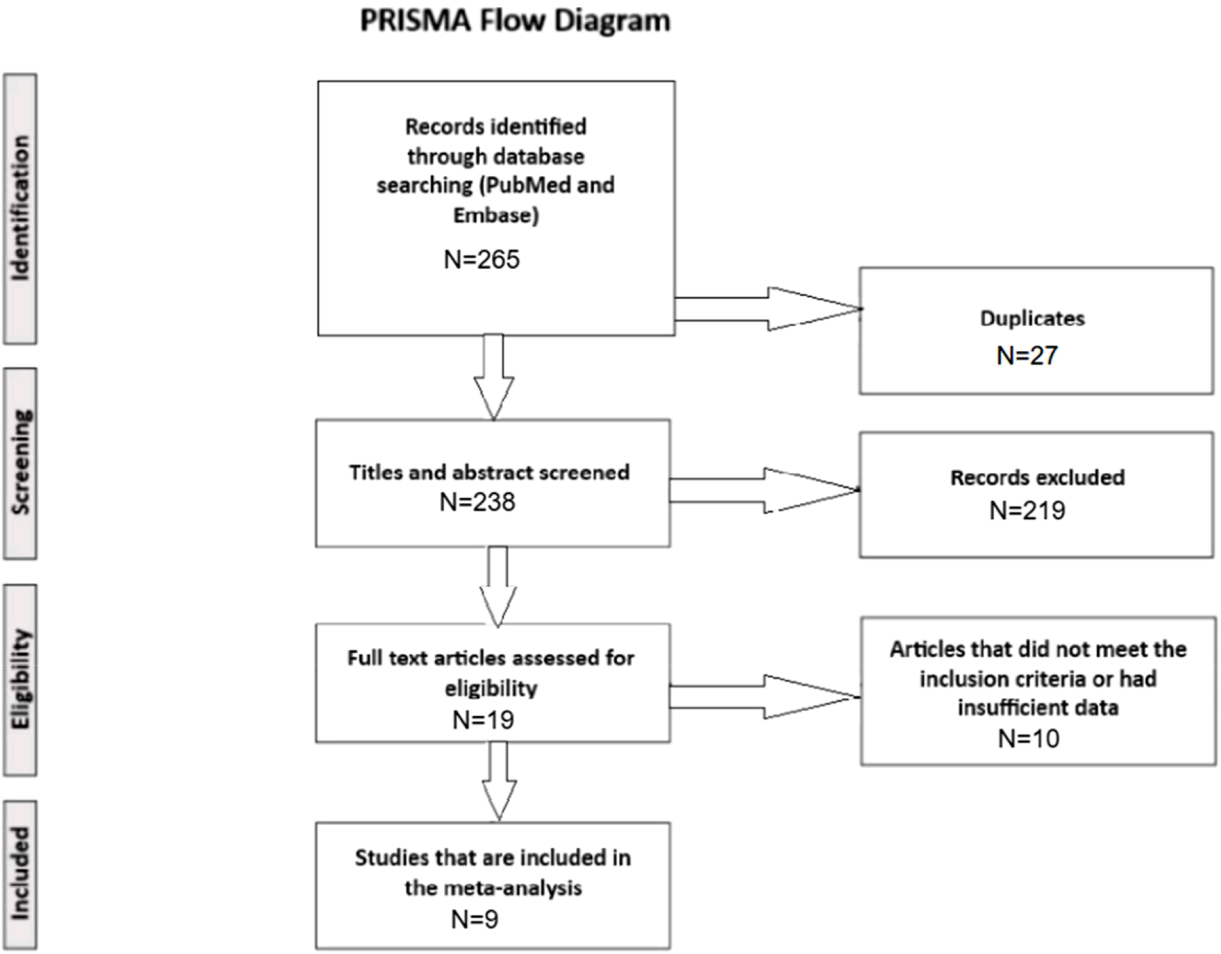

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow of the search strategy for systematic review and meta-analysis.

articles deemed suitable for our meta-analysis. The flow of study selection is delineated in Fig. 1.

The 9 incorporated studies (5 randomized controlled trials and 4 observational studies) represented a cumulative population of 2784 cancer patients undergoing chemotherapy. Within this experimental group, 1269 patients were administered statins, while the control group consisted of 1515 patients not on statin therapy. Characteristics of included studies are shown in Table 2. The baseline characteristics of both groups, derived from the incorporated studies, are systematically presented in Table 3.

4. Primary outcome

Of the 9 studies, 7 provided data on the incidence of heart failure. The pooled analysis indicated that statin therapy was associated with a substantial reduction in heart failure incidence among the chemotherapy patients. The observed odds ratio was 0.52 (95 % CI: 0.37-0.74; $p < 0.0003$). The detailed meta-analysis results for this outcome can be found in Fig. 2.

5. Secondary outcomes

In the meta-analysis, secondary outcomes (Fig. 3) did not show significant differences between statin and non-statin groups. The pooled Hedges's g for the change in Ejection Fraction (EF) from baseline was reported as 1.09 (SMD: 1.09; 95 % CI: -0.40 to 2.57), lacking statistical significance ($p = 0.15$). For the change in Left Ventricular End Diastolic Volume (LVEDV) from baseline, the Hedges's g was 0.91 (SMD: 0.91; 95 % CI: -1.69 to 3.51), which was similarly non-significant ($p = 0.47$). The change in Left Ventricular End Systolic Volume (LVESV) from baseline also showed no statistical significance, with a Hedges's g of 1.32 (SMD: 1.32; 95 % CI: -2.30 to 4.94; $p = 0.49$) (Fig. 4).

6. Discussion

We conducted a thorough review and analysis to evaluate statins as a protective measure for the heart in patients with cancer undergoing anthracycline chemotherapy, known for its heart-related risks. Our findings revealed a noteworthy decrease in the incidence of heart failure among patients taking statins compared to the other group. However, there weren't significant statistical changes observed in the metrics like left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV). Our study contributes to the existing knowledge, primarily focusing on the potential benefits of statins and cancer patients on anthracyclines, amalgamating observational studies, and randomized clinical trials.

The small GTPase RAS regulates DNA Damage Response (DDR) in tumor development and progression. DNA double-strand breaks (DSBs), documented with topoisomerase inhibitors like anthracyclines, are potent activators of DDR [11]. Not only does it enhance the effectiveness of anticancer drugs, it also reduces their harmful effects on normal tissue. Targeting Ras signaling, potentially through HMG-CoA reductase inhibitors (statins), could widen the therapeutic window for anticancer treatments by depleting the cellular pool of isoprene precursor molecules necessary for Ras function [12].

The severity of the cardiotoxicity greatly influences the safety and effectiveness of anthracyclines, impacting how well a patient tolerates it. The extensive comparison within our meta-analysis involved a meticulous assessment of data from five randomized clinical trials and four observational studies, with the bulk of the data stemming from Neilan et al (STOP-CA) (CI -0.39-0.08) [13] and Hundley et al.(PREVENT) (CI -044-0.01) [14] trials. This meticulous comparison allowed us to discern critical insights regarding the efficacy of statins in mitigating chemotherapy-induced cardiotoxicity.

Cardiovascular imaging plays a pivotal role in pinpointing individuals with concealed left ventricular dysfunction. Among these imaging modalities, the transthoracic echocardiogram stands out as the preferred technique for initial risk assessment. It offers a quantitative evaluation of the left ventricle's ejection fraction., serving as a crucial tool not only for baseline risk stratification but also for continuous monitoring during treatment and long-term follow-up. Importantly, existing definitions of chemotherapy-induced cardiotoxicity hinge upon the decline in the left ventricular ejection fraction, making this imaging method particularly significant in his context. Analytical methodologies, like the hedges G method, were instrumental in quantifying the differences across studies, offering a standardized means to compare varying outcomes.

Building upon the existing literature, the 2022 European Society of Cardiology guidelines provided a class IIa recommendation for statins use in primary prevention against cancer therapy-related cardiovascular toxicity among the high and very high-risk patient groups. This recommendation was drawn from retrospective observational studies and small randomized control trials [15,16,17]. To further scrutinize these studies we aim to dissect their findings, explore any existing

Table 2
Characteristics of included studies.

Study	Year	Type of study	Country	Cancer type	Chemotherapy agent	Statin	Follow up period	Statin group (n)	Control group (n)
Abdel-Qadir et al.	2021	Retrospective Cohort Study	Canada	Breast Cancer	Anthracyclines	Atorvastatin 40mg, Rosuvastatin, Simvastatin Pravastatin	10 years	666	666
Acar et al.	2011	Randomized Controlled Trial	US	HL, MM, Leukemia	Adramicin, Idarubicin	Atorvastatin 40mg	6 months	20	20
Chotenimikhun et al.	2015	Prospective Cohort Study	US	Breast Cancer, Leukemia, Lymphomas	Anthracyclines	40±5 mg of Atorvastatin or Simvastatin	6 months	14	37
Hundley et al.	2022	Randomized Controlled Trial	US	Breast Cancer, Lymphoma	Doxorubicin	Atorvastatin 40mg	24 months	122	126
Nabati et al.	2019	Randomized Controlled Trial	Iran	Breast Cancer	Doxorubicin	Rosuvastatin 20mg	6 months	38	39
Seicean et al.	2012	Retrospective Cohort Study	US	Breast Cancer	Anthracyclines	Unspecified	2.5 years	67	134
Tase et al.	2014	Retrospective Cohort Study	Romania	Gastric Cancer	Epirubicin	Unspecified	2.5 years	144	288
Neilan et al.	2023	Randomized Controlled Trial (STOP-CA Trial)	US/ Canada	Lymphoma	Anthracyclines	Atorvastatin 40mg	12 months	150	150
Thavendiranathan et al.	2023	Randomized Controlled Trial	Canada	Breast Cancer	Anthracyclines	Atorvastatin 40mg	4 weeks	54	58

Table 3
Baseline characteristics of patients on statin treatment vs non-treatment in included studies.

Characteristic	Group	Abdel-Qadir et al.	Acar et al.	Chotenimikhun et al.	Hundley et al.	Nabati et al.	Seicean et al.	Tase et al.	Neilan et al.	Thavendiranathan et al.
Age (mean, SD)	Statin	69 ± 1	53.7 ±14.2	62 ± 2	48.5 ± 12.5	47.74 ± 9.7	61.2 ± 9		50 17	55.2 13.7
	Control	69 ± 0.8	52.6 ± 17.6	43 ± 2	49.4 ± 11.5	50.74 ± 12.44	60.1 ± 8.5		49 16	58.6 13.4
Female (%)	Statin		60	57.2	92.8				45	72
	Control		55	67.6	90.7				49	83
White Ethnicity (%)	Statin				82.7		65.7		90	67
	Control				82.9		67.2		87	79
Black Ethnicity (%)	Statin				11.5				3	4
	Control				15.7				3	3
Asian Ethnicity (%)	Statin				1.4				3	24
	Control				0.7				5	16
BMI (Mean, SD)	Statin			30.7 ± 1.6	29 ± 6.4		30.2 ± 5.2		28 62	
	Control			27.7 ± 1.1	31 ± 7.4		30.5 ± 7.6		28 6.1	
CCI (Mean, SD)	Statin	1 ± 1					7 ± 1			
	Control	0 ± 1					6.6 ± 1.3			
Hypertension (%)	Statin	76.1		86			47.8		9	
	Control	79.6		27			20.9		13	20
IHD/CAD (%)	Statin	8.1		14			7.5			31
	Control	6.6		3			0.8			
MI (%)	Statin	<0.9 %		7						
	Control	<0.9 %		3						
Atrial Fibrillation (%)	Statin	4.2								
	Control	3.8								
Diabetes Mellitus (%)	Statin	23.3		50		13.2			0	6
	Control	23		5		17.9			1	7
CKD (%)	Statin	2.7								
	Control	2.7								
COPD (%)	Statin	17.1								
	Control	16.8								
Hyperlipidemia (%)	Statin			100		26.3				4
	Control			5		20.5				5
Smoking (%)	Statin			64			35.8		19	46
	Control			38			33.6		21	45
Sleep Apnea (%)	Statin								3	
	Control								5	
LVEF (%)	Statin		61.3 ± 7.9	56.6 ± 1.4		55.1 ± 4.84	58.2 ± 7.6		62.9 ± 4.5	60.2 ± 5.4
	Control		62.9 ± 7	57.5 ± 1.4		55.1 ± 5.1	59.1 ± 4.2		62.5 ± 4.9	59.2 ± 55
LDL (mg/dL)	Statin				111 ± 29					52.02 16.02
	Control				112 ± 26					53.46 17.1
HDL (mg/dL)	Statin				59 ± 18					24.7 8.1
	Control				57 ± 14					25.6 7.6
Triglycerides (mg/dL)	Statin				112 ± 52					28.9 15.3
	Control				127 ± 92					26.8 21.4
Cholesterol (mg/dL)	Statin				192 ± 41					90 21.9
	Control				195 ± 32					92.3 19.1
Troponin (ng/mL)	Statin				0.03 ± 0.2					
	Control				0.01 ± 0.0					
CRP (mg/L)	Statin				7.2 ± 20.1					
	Control				9 ± 16.7					
TNF-a (pg/mL)	Statin				1.46 ± 1.3					
	Control				1.73 ± 2.4					
Breast Cancer Stage 1 (%)	Statin	16.4								14
	Control	16.7								11
Breast Cancer Stage 2 (%)	Statin	51.8								66
	Control	50.9								61
Breast Cancer Stage 3 (%)	Statin	31.8								20
	Control	32.4								29
Beta Blockers (%)	Statin	20.4		50	14.4 % (statin) 20 % (control)		38.8		5	6
	Control	21.6		8			17.2		2	3
CCB (%)	Statin			29					3	
	Control			3					3	
ARB (%)	Statin	54.5		29					5 % (statin) 7 % (control)	6

(*continued on next page*)

Table 3 (*continued*)

Characteristic	Group	Abdel-Qadir et al.	Acar et al.	Chotenimikhun et al.	Hundley et al.	Nabati et al.	Seicean et al.	Tase et al.	Neilan et al.	Thavendiranathan et al.
	Control	54.2		0						7
ACE-I (%)	Statin			43			38.8			6
	Control			11			14.9			10
Non-statin LLA (%)	Statin	5								
	Control	5.1								
Diuretics (%)	Statin			50						
	Control			3						
Insulin (%)	Statin						10.5			
	Control						3.7			
Cyclophosphamide (%)	Statin		80	64						
	Control		85	81						
Tamoxifen (%)	Statin			0						
	Control			3						
Trastuzumab (%)	Statin			14	2.9	15.8	11.9			
	Control			14	5	10.3	17.2			
Taxane (%)	Statin					18.4				
	Control					12.8				

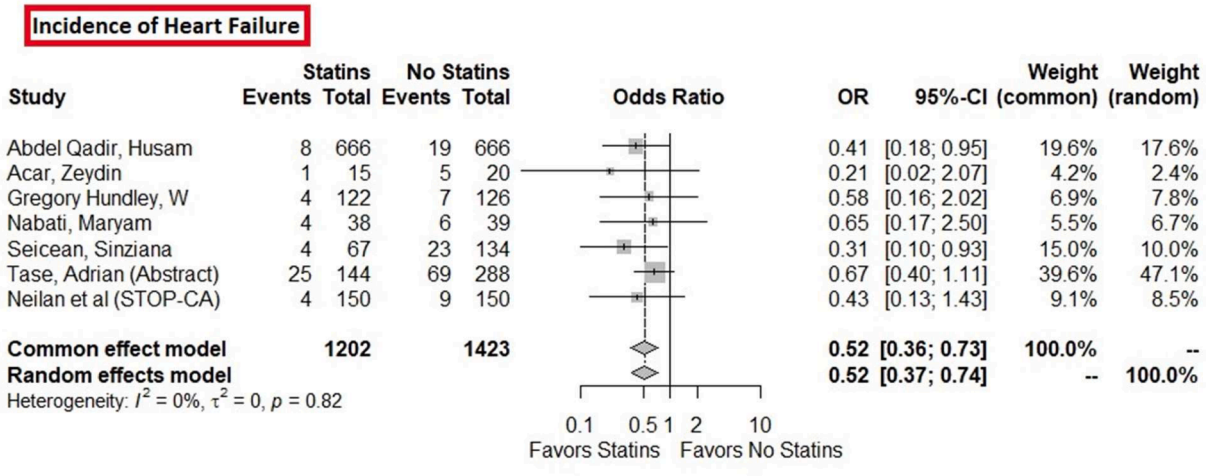

Fig. 2. Incidence of heart failure in patients on statin treatment vs non-treatment.

correlations, and examine both positive and negative outcomes.

The PREVENT, SPARE-HF, and STOP-CA trials collectively showed that atorvastatin reduces the decline in heart function associated with anthracycline treatment in cancer patients. While all three trials found that fewer patients on atorvastatin experienced significant heart function decline compared to placebo, they differed in patient populations and outcomes. The PREVENT trial, which involved breast cancer and lymphoma patients, and the SPARE-HF trial, focusing on high-risk patients, both highlighted a reduction in heart function decline with atorvastatin [18]. However, in the STOP-CA trial, which involved a different patient cohort, the decline was more pronounced in the placebo group after 12 months, underscoring the variation in results across different patient populations. However, a single-blind placebo-controlled study by Nabati in Iraq (2019) reported a different outcome, showing a negative change in ejection fraction (-1.62) among statin users, contrasting with the positive results from the other trials. This discrepancy may be attributed to demographic and geographic variations in the study population [15].

Acar 2011 and Nabati 2019 are the two randomized controlled trials that randomly assigned participants to either statin or placebo in a one-to-one ratio [15,19]: the incidence of cardiotoxicity was not significant in the randomized clinical trials. The median dose of anthracyclines was around 300 mg/m2 in the STOP CA trial compared to 240 mg/m2 for the rest of the RCTs. The PREVENT and SPARE trials lacked the necessary power to identify significant differences in the ejection fractions when comparing statin therapy against a placebo. This inadequacy stemmed from a high dropout rate of 36 % in the PREVENT trial and a modest sample size of around 112 participants in the SPARE trial. Conversely, the STOP-CA trial boasted a larger sample size of around 300 participants and achieved a completion rate exceeding 95 %.

In STOP-CA, the primary focus was on the proportion of each study group experiencing a 10 % or more decline in LVEF as the primary endpoint. However, some studies have opted for the absolute difference in LVEF decline instead [14,20,21]. Comparing the entire cohort revealed only a slight 1.3 % difference in LVEF at 12 months between groups. This suggests that for a portion of the anthracycline population, atorvastatin might offer limited benefit.

Considering the alternative option of FDA-approved dexrazoxane in the market; which is approved for just breast cancer patients and associated with secondary malignancies, statins emerge as a comparatively less risky approach to potentially reduce the risk of chemotherapy-related cardiac issues and subsequent cancer mortality [22].

As we delve deeper into the mechanisms of chemical damage caused by anticancer treatments, we uncover opportunities for developing more cardio-protective drugs. Statins, among others, have shown promise in this regard. Studies have also explored medications like angiotensin-converting enzyme inhibitors (ACEIs) and beta blockers such as carvedilol. In a recent clinical trial (NCT01009918), 468 participants were

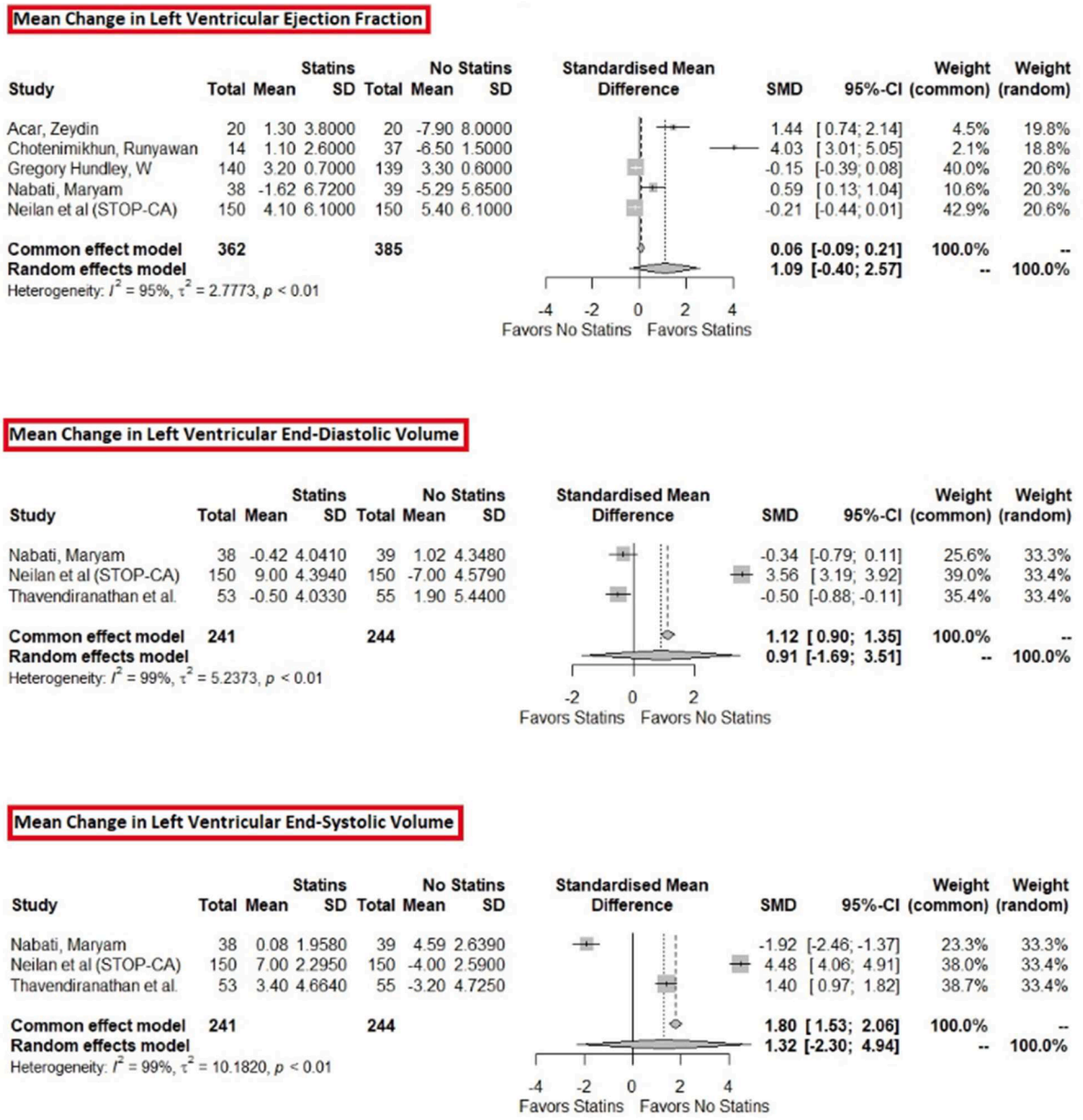

Fig. 3. Secondary outcomes of patients on statin treatment vs non-treatment.

randomly assigned to receive lisinopril, carvedilol, or a placebo. Results indicated improved cardiotoxicity-free survival in both the lisinopril (hazard ratio HR 0.53) and carvedilol (HR 0.49) groups compared to placebo [23]. Recent studies have highlighted the emergence of additional cardio-protective medications, notably SGLT-2 inhibitors, showing promising effects. In patients with cancer and diabetes mellitus (DM), the use of SGLT2 inhibitors was linked to a reduced rate of cardiac events following anthracycline therapy [24,25].

6.1. Limitations

The major limitation posed for this analysis is the small sample sizes in various individual randomized controlled trials and observational studies. However, challenges persist in ensuring effective randomization due to the small sample sizes in the analyzed randomized control trials. Observational studies, although adjusted for multiple risk factors, may still have committed confounders like race influencing their outcomes. Despite these limitations, the status shows promise in mitigating anthracycline-induced cardiotoxic effects, potentially aiding medical oncologists in devising long-term management plans for cancer patients.

When examining the use of statins in these scenarios, it's worth noting that most studies have concentrated on high-intensity statins, primarily due to their heightened anti-inflammatory effects. Consequently, attempting to generalize the outcomes of this meta-analysis to encompass other, less potent statins might not be prudent or appropriate, given the disparity in their efficacy profiles. This meta-analysis also could not assess variations in outcomes by sex or race, as the individual studies did not provide disaggregated data for these demographics.

The included studies did not specify whether patients were on GLP-1 agonists or SGLT-2 inhibitors. These medications are known for their cardioprotective effects, which could influence the outcomes of cardiac function and heart failure incidence. The absence of data on these medications represents a limitation of our meta-analysis. Future studies should consider including this information to better understand the potential impact of these agents on cardiotoxicity outcomes in patients undergoing chemotherapy.

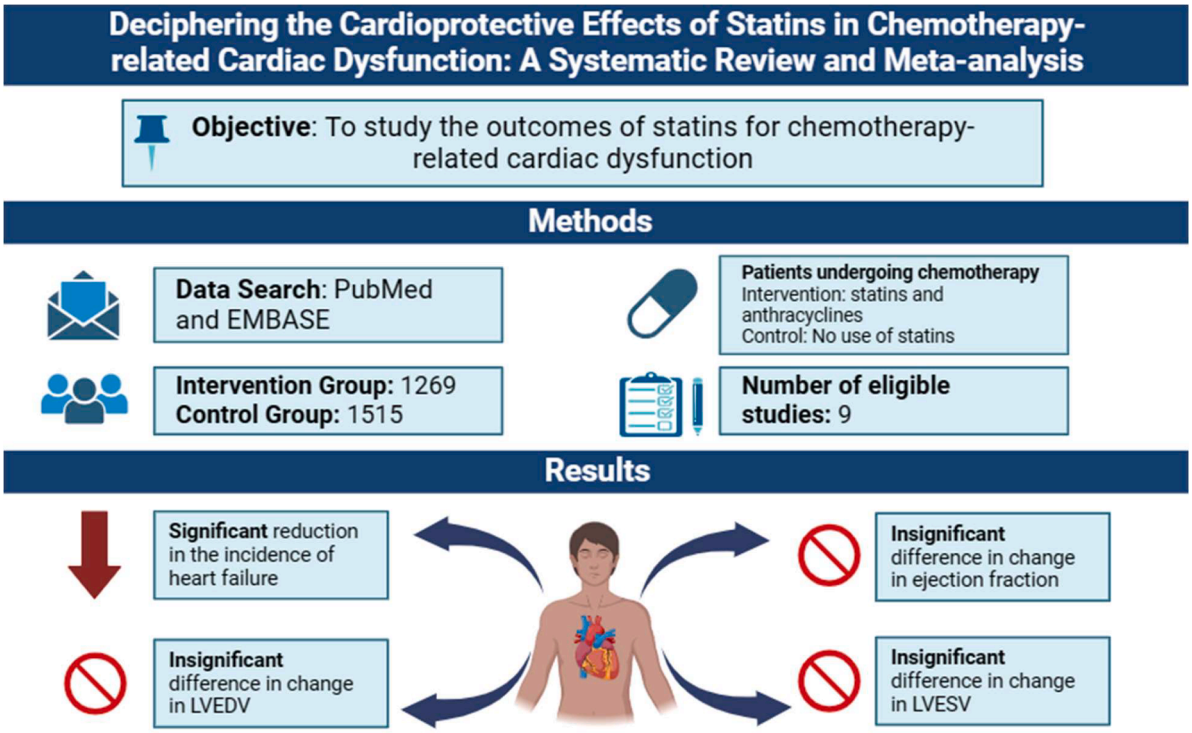

Fig. 4. Central illustration of outcomes of statin treatment vs non-treatment in chemotherapy-related cardiac dysfunction.

7. Conclusion

In conclusion, while our study shows statins reducing the incidence of heart failure in cancer patients on anthracyclines, further studies are crucial for a conclusive understanding. A nuanced analysis considering different statins, cancer types, and specific cardioprotective effects in terms of EF, LVESV, LV EDV changes is necessary for comprehensive insights. Universal endorsement of statins as a cardioprotective agent requires more stratified studies, considering factors like drug types, dosages, cancer types, and chemotherapy variation to better comprehend their effects on our target population.

8. Disclosures

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Authorship contributions

Mubashar Karamat (Screening, data collection, and management).
Bilal Hussain (Screening and manuscript writing).
Munis Mahboob Ahmed (Manuscript writing).
Mohammad Hamza (Screening and data analysis).
Junaid Mir (Quality check).
Ayedh Alamri (Manuscript writing).
Aimen Shafiq (Illustrations).
Yasar Sattar (Conception, design, supervision).
Muhammad Zia Khan (Data collection).
Harshith Thyagaturu (Supplementary file).
Karthik Gonuguntla (Supplementary file).
Birjesh D Patel (Conception, design, supervision).

Ethics statement

This study did not require Institutional Review Board (IRB) approval as it involved a meta-analysis of previously published data.

Author agreement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

CRediT authorship contribution statement

Mubashar Karamat: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Bilal Hussain:** Writing – review & editing, Validation, Methodology, Data curation, Conceptualization. **Munis Mahboob Ahmed:** Writing – review & editing, Writing – original draft. **Mohammad Hamza:** Writing – review & editing, Methodology, Formal analysis. **Junaid Mir:** Writing – review & editing. **Ayedh Alamri:** Writing – original draft. **Aimen Shafiq:** Writing – original draft. **Yasar Sattar:** Writing – review & editing, Supervision, Conceptualization. **Muhammad Zia Khan:** Writing – review & editing. **Harshith Thyagaturu:** Writing – review &

editing. **Karthik Gonuguntla:** Writing – review & editing. **Birjesh D Patel:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100874.

References

[1] Jain D, Aronow W. Cardiotoxicity of cancer chemotherapy in clinical practice. Hosp Pract 2019;47:6–15.

[2] Levis BE, Binkley PF, Shapiro CL. Cardiotoxic effects of anthracycline-based therapy: what is the evidence and what are the potential harms? Lancet Oncol 2017;18:e445–56.

[3] Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation 2019;140:e563–95.

[4] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation 2019;139:e1082–143.

[5] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. Mar 29PMID: 33782057; PMCID: PMC8005924.

[6] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008. https://doi.org/10.1136/bmj.j4008. Sep 21PMID: 28935701; PMCID: PMC5833365.

[7] Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009;172(1):137–59. https://doi.org/10.1111/j.1467-985X.2008.00552.x. JanPMID: 19381330; PMCID: PMC2667312.

[8] Julian P.T. Higgins JT, Jacqueline Chandler, Miranda Cumpston, Tianjing Li, Matthew J. Page, Vivian A. Welch. Cochrane handbook for systematic reviews of interventions, Second Edition.

[9] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898. Aug 28PMID: 31462531.

[10] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5. https://doi.org/10.1007/s10654-010-9491-z. SepEpub 2010 Jul 22. PMID: 20652370.

[11] Nitiss JL. DNA topoisomerases in cancer chemotherapy: using enzymes to generate selective DNA damage. Curr Opin Investig Drugs 2002;3(10):1512–6. Oct; PMID: 12431029.

[12] Pommier Y, Sun Y, Huang SN, Nitiss JL. Roles of eukaryotic topoisomerases in transcription, replication, and genomic stability. Annu Rev Pharmacol Toxicol 2016;56:103–21. https://doi.org/10.1146/annurev.pharmtox.45.120403.095748.

[13] Neilan TG, Quinaglia T, Onoue T, et al. Atorvastatin for anthracycline-associated cardiac dysfunction: the STOP-CA randomized clinical trial. JAMA 2023;330:528–36.

[14] Hundley WG, Jr D'Agostino R, Crotts T, et al. Statins and left ventricular ejection fraction following doxorubicin treatment. NEJM Evid 2022. Aug 18:[ePub ahead of print].

[15] Nabati M, Janbabai G, Esmailian J, Yazdani J. Effect of Rosuvastatin in Preventing Chemotherapy-Induced Cardiotoxicity in Women With Breast Cancer: A Randomized, Single-Blind, Placebo-Controlled Trial. J Cardiovasc Pharmacol Ther 2019;24(3):233–41. https://doi.org/10.1177/1074248418821721. MayEpub 2019 Jan 2. PMID: 30599756.

[16] Calvillo-Argüelles O, Abdel-Qadir H, Michalowska M, et al. Cardioprotective effect of statins in patients with HER2-positive breast cancer receiving trastuzumab therapy. Can J Cardiol 2019;35:153–9.

[17] Abdel-Qadir H, Bobrowski D, Zhou L, et al. Statin exposure and risk of heart failure after anthracycline- or trastuzumab-based chemotherapy for early breast cancer: a propensity score–matched cohort study. J Am Heart Assoc 2021. Jan 19.

[18] Thavendiranathan P, Houbois C, Marwick TH, et al. Statins to prevent early cardiac dysfunction in cancer patients at increased cardiotoxicity risk receiving anthracyclines. Eur Heart J Cardiovasc Pharmacother 2023. Apr 29.

[19] Acar Z, Kale A, Turgut M, Demircan S, Durna K, Demir S, Meriç M, Ağaç MT. Efficiency of atorvastatin in the protection of anthracycline-induced cardiomyopathy. J Am Coll Cardiol 2011;58(9):988–9. https://doi.org/10.1016/j.jacc.2011.05.025. Aug 23PMID: 21851890.

[20] Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left ventricular dysfunction with enalapril and carvedilol in patients submitted to intensive chemotherapy for the treatment of malignant hemopathies). J Am Coll Cardiol 2013;61(23):2355–62. https://doi.org/10.1016/j.jacc.2013.02.072.

[21] Gulati G, Heck SL, Ree AH, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 2016;37(21):1671–80. https://doi.org/10.1093/eurheartj/ehw022.

[22] Cvetković RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. Drugs 2005;65(7):1005–24. https://doi.org/10.2165/00003495-200565070-00008.

[23] 23 Guglin M, Krischer J, Tamura R, et al. Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer. J Am Coll Cardiol 2019;73(22):2859–68. https://doi.org/10.1016/j.jacc.2019.03.495.

[24] Gongora CA, Drobni ZD, Quinaglia Araujo Costa Silva T, et al. Sodium-glucose Co-transporter-2 inhibitors and cardiac outcomes among patients treated with anthracyclines. JACC Heart Fail 2022;10(8):559–67. https://doi.org/10.1016/j.jchf.2022.03.006.

[25] 25 Avula V, Sharma G, Kosiborod MN, et al. SGLT2 inhibitor use and risk of clinical events in patients with cancer therapy-related cardiac dysfunction. JACC Heart Fail 2024;12(1):67–78. https://doi.org/10.1016/j.jchf.2023.08.026.