Title

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Brief Report

Statins for Primary Prevention of Anthracycline Chemotherapy-Related Cardiac Dysfunction: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Anthracyclines are widely used chemotherapeutic agents for treating cancers such as breast cancer, lymphoma, leukemia, and others. The cardiotoxicity associated with anthracyclines is reported in up to 18% of patients, and it can result in clinical heart failure and reduced health-related quality of life.[1]

Statins may have a role in the primary prevention of anthracycline chemotherapy-related cardiac dysfunction (CTRCD) due to their pleiotropic, antioxidative, and anti-inflammatory effects.[2] The 2022 European Society of Cardiology (ESC) Cardio-Oncology guidelines recommend that statins should be considered for the primary prevention of CTRCD in adult patients with cancer at high and/or very high risk of cardiotoxicity (Class IIa, Level of Evidence B).[2] However, this weak recommendation is based on only 2 randomized controlled clinical trials (RCTs)[3,4] (n=117) of patients on anthracycline chemotherapy and is primarily grounded on observational data. In the last year, 3 sentinel RCTs[5–7] comprising 691 patients have been conducted to investigate this subject, but they have shown conflicting results. Therefore, in this systematic review and meta-analysis, we examined the totality and strength of evidence behind the role of statins in the primary prevention of anthracycline CTRCD.

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The meta-analysis protocol was registered on PROSPERO: CRD42023428082 on May 31, 2023.

A systematic database search of EMBASE/Ovid, PubMed/MEDLINE, SCOPUS, *ClinicalTrials.gov*, and the Cochrane Library from inception till May 2023 using the search terms "statin", "anthracyclines", "doxorubicin", "daunorubicin", "epirubicin", "idarubicin", "trastuzumab", "cardiotoxicity", "cancer" was performed. In addition, we manually reviewed the bibliography of included studies to identify other potential trials of interest.

The primary outcome was the development of anthracycline CTRCD using the study level definitions that included: (1) incident heart failure diagnosis, or (2) cardiotoxicity defined as a reduction in LV ejection fraction of >10% to <55% without symptoms of heart failure, or >5% drop to <55% with symptoms, or reduction in left ventricular ejection fraction (LVEF) to <50% (Table 1). The secondary outcome was the mean change in LVEF, defined as the difference between the final LVEF and the initial LVEF before statin use. The Mantel-Haenszel method was used to calculate the pooled risk ratio (RR) with a 95% confidence interval (CI). For the mean change in the LVEF, the mean difference with the corresponding standard deviation (SD) was extracted and pooled to generate a weighted mean difference (WMD). The random-effects model approach accounted for heterogeneity across the studies included. The proportion of total variability in the estimates was summarized with the I^2 index. Heterogeneity was considered high when I^2>50%. Statistical analysis was performed using the Review Manager (Version 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The Cochrane risk of bias assessment tool was used to assess the quality of studies. We also rated the certainty of evidence (COE) using the grading of recommendations assessment, development, and evaluation (GRADE) approach (https://gdt.gradepro.org/app/), as high, intermediate, low, or very low (Table 1). The outcomes were compared between statin vs. no statin as the control group.

A total of 5 RCTs comprising 808 patients (statin=401, control=407) were identified through a comprehensive database searching of 1,289 studies and were included in our analysis.[3–7] The mean age of patients included in the meta-analysis was 50.3 years; with 71.8% females and a mean

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See page 66 for Declaration of Competing Interest.

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Table 1
Characteristics of included randomized controlled trials and grading of recommendations assessment, development, and evaluation (GRADE) chart for the certainty of the evidence for the efficacy of statins in attenuating cardiotoxicity in cancer patients receiving anthracycline-based chemotherapy.

Characteristics of Included Randomized Controlled Trials

Study	Sample size (n) (statin/placebo)	Type of cancer (%)	Age (years)	Female (%)	Statin	Imaging modality	Primary endpoint	Definition of CTRCD	Cumulative anthracycline dose (mg/m^2)	Trastuzumab (%)	Radiation therapy (%)	Diabetes (%)	HLD (%)	Other cardiac medications (%)	Follow-up (months)
Acar et al. 2011	20/20	Non-Hodgkin lymphoma (60/55), multiple myeloma (10/20), leukemia (30/25)	54/53	60/55	Atorvastatin 40 mg/day	TTE	Impairment in left ventricular systolic function, (LVEF) of <50%.	The decline in the LVEF to < 50%	Doxorubicin-261/251	0/0	-	-	-	-	6
Nabati et al. 2019	38/39	Breast cancer (100/100)	48/51	100/100	Rosuvastatin 20 mg/day	TTE	Changes in the LVEF and the global longitudinal strain after completion of chemotherapy when compared with the baseline values.	The decline in the LVEF to < 45%	Doxorubicin-339/338	6/4	0/0	17.9/13.2	20.5/26.3	-	6
Hundley et al. 2022	139/140	Breast cancer [Stage I-III] (85.6/85.0) and lymphoma [Stage I-IV] (14.4/15.0)	48/49	93/91	Atorvastatin 40 mg/day	CMR	Difference in 24-month LVEF between placebo and treatment groups	The decline in the LVEF to < 50%	Doxorubicin-240/240	4/7	56/59	-	-	14.4/20.0	24
Neilan et al. 2023	150/150	Hodgkin (25/29), non-Hodgkin lymphoma (T cell [6/3], B cell [69/68])	50/49	45/49	Atorvastatin 40 mg/day	TTE or CMR	The decline in the LVEF of ≥ 10% to < 55%.	The decline in the LVEF of ≥ 10% to < 55%	Doxorubicin-300/300	0/0	8/14	-	-	22.0/18.0	12
Thavendiranathan et al. 2023	54/58	Breast cancer (Stage I [14/11], Stage II [66/61], Stage III [20/29]), lymphoma (23/21), leukemia (2/3), sarcoma (6/7), thymoma (6/3)	55/59	72/83	Atorvastatin 40 mg/day	CMR	Change in the LVEF at the end of anthracycline-based treatment.	The decline in the LVEF of > 10% to < 53%	Doxorubicin- 242/243	0/0	-	6.0/7.0	4.0/5.0	13.0/12.0	2.5

GRADE Chart for the Certainty of the Evidence

Outcome	Study Results & Measurements	Absolute Effect Estimates		Certainty of Evidence
		Control	Statin	(Quality of Evidence)
Incidence of CTRCD	Relative risk: 0.46 (CI 95% 0.29 - 0.74) Based on data from 808 participants in 5 studies [a]	130 per 1000	60 per 1000 Difference: 70 fewer per 1000 (CI 95% 92 fewer - 34 fewer)	High
Change in LVEF	Based on data from 808 participants in 5 studies [b]		Difference: MD 2.38 higher (CI 95% 0.28 higher - 4.48 higher)	Moderate Due to serious inconsistency [c]

[a] Systematic review with included studies: Hundley et al. 2022, Nabati et al. 2019, Acar et al. 2011, Neilan et al. 2023, Thavendiranathan et al. 2023 **Baseline/comparator** Control arm of reference used for intervention.

[b] Systematic review with included studies: Thavendiranathan et al. 2023, Neilan et al. 2023, Nabati et al. 2019, Hundley et al. 2022, Acar et al. 2011 **Baseline/comparator** Control arm of reference used for intervention.

[c] **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:87%.

Abbreviations: CMR = cardiac magnetic resonance imaging; CTRCD = cancer therapy-related cardiotoxicity; CI = confidence interval; HLD = hyperlipidemia; LVEF = left ventricular ejection fraction; MD = mean difference; TTE = transthoracic echocardiogram.

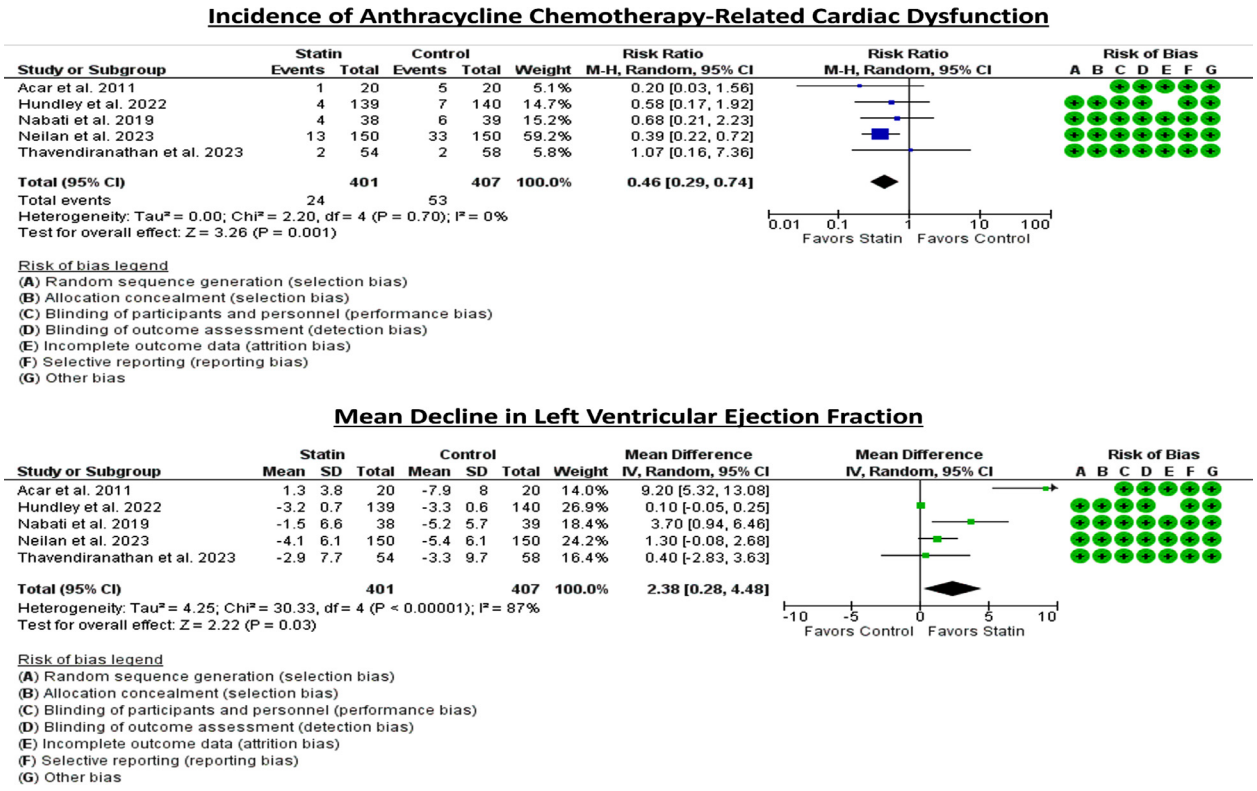

Figure 1. Forest plot for incidence of cancer therapy-related cardiotoxicity and mean change in left ventricular ejection fraction in patients receiving statin versus control for primary prevention of anthracycline chemotherapy related cardiac dysfunction.

follow-up of 10 months. The characteristics of included patient populations are reported in Table 1. Only 21 patients were on concurrent Trastuzumab and anthracycline therapy, with 10 and 11 randomized to statin and control group, respectively.

In patients undergoing anthracycline chemotherapy, a total of 24 (6.0%) out of 401 patients receiving statins developed cardiotoxicity, as compared with 53 (13.0%) out of 407 patients in the control group. The pooled estimate showed a statistically significant lower risk of developing anthracycline CTRCD with statin use vs. control (RR: 0.46; 95% CI: 0.29 to 0.74; p<0.001; I^2=0%) *(COE: high certainty)* (Figure 1).

The mean decline in LVEF was also significantly lower in patients receiving statin as compared to control (WMD: 2.38; 95% CI: 0.28 to 4.48; p=0.03; I^2=87%) *(COE: moderate certainty)* (Figure 1). Subgroup analysis was also performed based on the type of imaging modality used. In patients undergoing LVEF measurements using transthoracic echocardiogram (TTE), statins were associated with a significantly lower decline in mean LVEF as compared to control (WMD: 6.27; 95% CI: 0.89 to 11.65; p=0.02; I^2=80%), whereas no significant difference was observed in patients undergoing LVEF measurements using cardiac MRI (WMD: 0.10; 95% CI: −0.05 to 0.25; p=0.20; I^2=0%), test for subgroup differences (p=0.02).

In this meta-analysis of 5 RCTs comprising 808 patients, we compared the efficacy of statins vs. control for the primary prevention of anthracycline CTRCD. Our major findings include the following: (1)High certainty evidence shows that statins were associated with a 54% relative risk reduction in the incidence of anthracycline CTRCD; (2) Moderate certainty evidence shows that statins were associated with a significantly lower decline in the mean LVEF in patients undergoing anthracycline chemotherapy.

Our results provide evidence to support modifications of the recently published ESC guidelines on the use of statins in primary prevention of CTRCD. Our results are significant as they are based on high-quality evidence from multiple RCTs and provide a solid evidence base for formulating future clinical practice guidelines on this subject. There are certain limitations in the current ESC Cardio-Oncology guidelines on statin use for the primary prevention of CTRCD. First, the current guidelines are not specific to patients undergoing anthracycline chemotherapy whereas our data provides evidence specific to anthracycline CTRCD. Second, due to reliance on observational data and only 2 RCTs on the anthracycline chemotherapy population, the resulting recommendation is Class IIa (weight of evidence/opinion is in favor of usefulness/efficacy) and level of evidence B (data derived from a single RCT or large non-randomized studies). Our meta-analysis is based on pooled data from additional 3 high-quality RCTs and it provides robust evidence to explore updating the guidelines to Class IIa with Level of Evidence A (data derived from multiple randomized trials or meta-analyses).

A decreased LVEF at baseline or decline during chemotherapy is associated with a poor outcome. Anthracycline-induced cardiomyocyte cell death is likely mediated through caspase-3-related apoptotic pathways activated by p53 and/or TNF-signaling.[8] It usually begins with myocyte injury, progresses to silent LV systolic dysfunction, and

eventually becomes symptomatic and irreversible.[8] Statins exhibit anti-inflammatory as well as anti-fibrotic properties and interfere with the 2 main mechanisms involved in anthracycline- cardiotoxicity by preventing the generation of reactive oxygen species (ROS) and preventing DNA damage through topoisomerase II inhibition.[8] In addition, statins may also sensitize certain tumor entities to chemotherapeutics, thus improving the efficacy of the anthracycline regimen while protecting normal cells.[8]

Our meta-analysis findings should be interpreted in the context of its limitations. First, this is a study-level analysis as aggregate data was extracted from original publications and we did not have access to patient-level data. Additionally, all the included RCTs focused on anthracycline-based chemotherapy and so we could not evaluate the efficacy of statins in preventing trastuzumab-related cardiotoxicity.

In conclusion, this meta-analysis of RCTs suggests that in patients undergoing anthracycline chemotherapy, statins are associated with a statistically significant lower risk of developing anthracycline CTRCD. Future studies with larger sample sizes and extended follow-up duration are needed to further validate these findings.

Declaration of Competing Interest

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