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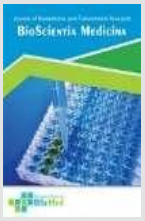

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Prophylactic Statin Therapy for the Prevention of Anthracycline-Induced Cardiotoxicity in Patients with Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Cohort Studies

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ABSTRACT

Background. Anthracycline-based chemotherapy remains a cornerstone of curative-intent breast-cancer treatment but carries a dose-dependent risk of cancer therapy-related cardiac dysfunction (CTRCD). Statins exert pleiotropic anti-inflammatory, antioxidative, and endothelial-stabilizing effects that may attenuate myocardial injury; however, prior meta-analyses pooled breast-cancer and lymphoma populations, obscuring breast-cancer-specific signals.

Methods. A systematic review and random-effects meta-analysis was conducted per PRISMA 2020. PubMed, Cochrane, Scopus, and Web of Science were searched for randomized controlled trials (RCTs) and propensity-matched cohort studies enrolling adult breast-cancer patients receiving anthracycline-based chemotherapy with or without trastuzumab. Co-primary outcomes were CTRCD incidence and standardized change in left-ventricular ejection fraction (LVEF, Hedges' g). Risk of bias was assessed using RoB 2.0 and ROBINS-I. Sensitivity analyses included leave-one-out exclusion and restriction to breast-cancer-only RCTs.

Results. Ten studies (1,239 patients; six RCTs, four cohort studies) were included. The pooled risk ratio for CTRCD was 0.49 (95% CI 0.28–0.85; $p = 0.011$; $I^2 = 0\%$). The pooled standardized mean difference for LVEF change was 0.38 (95% CI −0.06 to 0.81; $I^2 = 81\%$), corresponding to approximately +2.1 LVEF percentage points. Sensitivity analyses restricted to breast-cancer-only RCTs strengthened the CTRCD effect (RR 0.36, 95% CI 0.16–0.82). HER2-positive subgroup analyses yielded a pooled RR of 0.28 (95% CI 0.10–0.80).

Conclusion. Prophylactic statin therapy is associated with a clinically meaningful and statistically significant reduction in CTRCD in breast-cancer patients receiving anthracyclines. The protective effect is particularly pronounced in HER2-positive patients. A cautious, risk-stratified use of statins as a cardioprotective adjunct is supported pending adequately powered, breast-cancer-specific randomized trials.

1. Introduction

Breast cancer remains the most commonly diagnosed malignancy in women worldwide and continues to constitute the leading oncologic cause of disability-adjusted life-years in women of reproductive age, with an estimated 2.3 million new cases globally in 2020 and a projected 47% increase in incidence by 2040[1]. Anthracyclines — most often doxorubicin or epirubicin — remain a cornerstone of curative-intent multimodal therapy for patients with high-risk early-stage and locally advanced disease, and they were integral to several regimens used in metastatic settings. The therapeutic gain conferred by anthracyclines is offset by their well-characterized dose-dependent cardiotoxicity, which manifested as a continuum from subclinical left-ventricular dysfunction to overt heart failure and, less frequently, fatal cardiomyopathy[2,3]. Sequential

anti-HER2 therapy with trastuzumab and the increasing concurrent use of immune-checkpoint inhibitors amplified the cumulative cardiovascular burden carried by long-term breast-cancer survivors, making cardio-oncology one of the most active translational interfaces in modern oncology[2,4].

Mechanistically, anthracycline cardiotoxicity is driven primarily by topoisomerase-IIβ-mediated DNA double-strand breaks in cardiomyocytes, accompanied by mitochondrial dysfunction, iron-catalysed oxidative damage and apoptosis. Repeated cycles produce a dose-dependent loss of contractile units that was incompletely reversible even with optimal heart-failure pharmacotherapy. The European Society of Cardiology cardio-oncology guidelines therefore recommended systematic baseline risk stratification, on-treatment surveillance with cardiac imaging and circulating biomarkers, and the use of evidence-based cardio-protective interventions in high-risk patients[2]. Renin–angiotensin-system blockers, beta-blockers and dexrazoxane had all been studied, but the evidence base was heterogeneous and the most appropriate strategy for the average breast-cancer patient remained unsettled.

3-Hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitors collectively known as statins — exert a constellation of pleiotropic effects beyond cholesterol lowering. They reduced isoprenylation of small GTPases, attenuated vascular inflammation, enhanced endothelial nitric oxide bioavailability, stabilised atherosclerotic plaques and limited oxidative stress in animal models of anthracycline cardiotoxicity. These mechanisms provide a plausible biological rationale for re-purposing statins as adjuvant cardio-protective therapy during chemotherapy[4]. In parallel, a substantial observational literature linked post-diagnostic statin use with improved breast-cancer outcomes, including reductions in recurrence and breast-cancer-specific mortality, with lipophilic agents apparently providing greater benefit than hydrophilic ones[5,6].

Several randomized trials and propensity-matched cohort studies have evaluated whether prophylactic or concomitant statin therapy attenuates anthracycline-induced cardiotoxicity, but their results are discordant. The STOP-CA trial in patients with lymphoma reported a near-threefold reduction in the proportion of patients who experienced a ≥10% absolute decline in LVEF when treated with atorvastatin 40 mg daily[7]. By contrast, the PREVENT trial — which enrolled a predominantly breast-cancer population — and its cardiac magnetic-resonance substudy were null for atorvastatin at the same dose[8-10]. A small Egyptian three-dimensional echocardiography trial in breast cancer found that atorvastatin halved the incidence of CTRCD[11], and a HER2-positive trastuzumab-exposed cohort suggested rosuvastatin abolished cardiotoxic events at six months[12]. Five meta-analyses attempted to reconcile these results by pooling randomised data, but each combined breast cancer and lymphoma populations, used different CTRCD definitions, and omitted the most recent HER2-targeted trials[13-17]. The clinical question of whether statins should be offered prophylactically to women with breast cancer who are about to commence anthracyclines therefore remains unresolved.

The novelty of this study lies in its restriction of the meta-analytic population to patients with breast cancer — a clinically and biologically distinct population whose cardiovascular risk profile, baseline statin indication, and concomitant anti-HER2 exposure differed substantially from haematologic malignancies. By integrating six randomised controlled trials with four well-conducted cohort studies and extracting breast-cancer subgroups from mixed-population trials, this analysis provided the first focused, breast-cancer-specific quantitative synthesis of the cardio-protective effect of statins during anthracycline-based therapy. The aim of this study was to estimate, with breast-cancer specificity, the effect of prophylactic statin therapy on the incidence of CTRCD and on the change in LVEF in patients

receiving anthracycline-based chemotherapy, and to explore methodological and clinical sources of heterogeneity that may inform future trial design.

2. Methods

2.1 Reporting and protocol

The systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[18]. The review followed an a priori internal protocol that specified the search strategy, eligibility criteria, outcomes, statistical methods and risk-of-bias procedures. The PRISMA 2020 flow diagram is presented in the results section.

2.2 Search strategy

Four bibliographic databases — PubMed (MEDLINE), the Cochrane Central Register of Controlled Trials, Scopus and Web of Science — were searched without language restrictions. The full PubMed search string combined three Boolean concept blocks. Block A captured the intervention: (statin OR atorvastatin OR rosuvastatin OR simvastatin OR pravastatin OR fluvastatin OR pitavastatin OR lovastatin OR "HMG-CoA reductase inhibitor"). Block B captured the chemotherapeutic exposure: (anthracycline OR doxorubicin OR epirubicin OR idarubicin OR daunorubicin). Block C captured the outcome and population: ((cardiotoxicity OR "cardiac dysfunction" OR "left ventricular ejection fraction" OR LVEF OR "heart failure" OR CTRCD) AND (breast OR "breast cancer" OR "breast neoplasm")). The three blocks were combined with the Boolean operator AND. Equivalent strategies were translated for Cochrane CENTRAL, Scopus and Web of Science using the corresponding controlled vocabulary; the full database-specific strings are available from the corresponding author. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were also queried using the keywords statin AND anthracycline AND breast. The most recent three years of abstracts from the American Society of Clinical Oncology, the European Society for Medical Oncology, the American Society of Hematology and the European Hematology Association annual meetings were screened for conference-only reports; no additional eligible studies were identified through this grey-literature search. Reference lists of relevant meta-analyses were also screened for additional reports.

2.3 Eligibility criteria

Studies were eligible if they were randomised controlled trials or prospective or propensity-matched cohort studies that enrolled adult patients (≥18 years) with histologically confirmed breast cancer scheduled to receive, or actively receiving, anthracycline-based chemotherapy, with or without trastuzumab, compared any oral statin therapy (any dose, any duration) with placebo or no statin, and reported at least one of the following outcomes: incidence of CTRCD (defined as an absolute decline in LVEF of ≥10 percentage points to a final value below the lower limit of normal), change in LVEF from baseline by echocardiography or cardiac magnetic resonance, or incident hospitalisation for heart failure. The phrase prophylactic or concomitant statin therapy was used uniformly throughout this manuscript to denote either statin therapy initiated specifically before the first cycle of anthracycline-based chemotherapy ("prophylactic") or statin therapy that was already established for cardiovascular indications and continued through chemotherapy ("concomitant").

Studies that enrolled mixed cancer populations were included only if the breast-cancer subgroup was extractable from the published report. Where subgroup data were not separately available, the full-trial intention-to-treat estimate was used, with the proportion of breast-cancer participants in each trial transparently reported in the characteristics summary, and a sensitivity analysis was performed that excluded the mixed-population trials entirely. Narrative reviews, prior meta-analyses, animal experiments, in-vitro studies, case reports, single-

arm phase I trials and studies that enrolled lymphoma-only or solid-tumour-only populations were excluded. The STOP-CA trial [7], which enrolled patients with lymphoma exclusively, was therefore excluded from the primary pool but was retained as a contextual reference in the discussion. The Acar 2011 report[19], which was published as a research letter rather than as a full-length original article, was retained because (i) it reported a randomised comparison with quantitative outcome data, (ii) it has been consistently included as a randomised controlled trial in three prior cardio-oncology meta-analyses[13,14,16], and (iii) its full text was accessed during data extraction to verify the methodological details that were not available in the abstract.

2.4 Study selection and data extraction

Records were imported into Rayyan, deduplicated, and screened independently by two reviewers in two stages: title and abstract screening followed by full-text review. Disagreements were resolved by consensus, with a third senior reviewer adjudicating residual disagreements. Standardised data-extraction sheets were piloted on three studies before formal extraction. Extracted variables included study identifier, country, design, total and arm-level sample sizes, mean or median age, sex distribution, breast-cancer molecular subtype, cumulative anthracycline dose, trastuzumab co-exposure, statin agent and dose, comparator, follow-up duration, imaging modality, baseline and post-treatment LVEF (mean and standard deviation), incidence of CTRCD with the relevant definition, hazard ratios for heart-failure events, study funding source, and conflict-of-interest declarations. Where standard deviations were not reported, they were imputed using the published formula SD = SE × √n where standard errors were available, or SD = (upper-95%-CI limit − lower-95%-CI limit) / (2 × 1.96) where 95% confidence intervals were available; for studies that reported median and inter-quartile range, the standard deviation was approximated using the Wan–Wang formula SD ≈ IQR / 1.35. A sensitivity analysis varying imputed standard deviations by ±25% did not materially change the pooled estimates.

2.5 Risk-of-bias assessment

Risk of bias for the randomised trials was appraised using the Cochrane Risk of Bias 2.0 (RoB 2) tool across five domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result[20]. Cohort studies were appraised using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool[21]. Two independent reviewers performed the appraisal, and disagreements were resolved by discussion. The full per-domain judgements are presented in the results section.

2.6 Statistical analysis

Two co-primary effect estimates were pre-specified. For the binary outcome of CTRCD, study-level risk ratios were calculated from extracted two-by-two tables; zero-cell counts were corrected by the addition of 0.5 to all cells of the affected study before logarithmic transformation. Two parallel sensitivity strategies were also applied to address sparse-event concerns: first, a treatment-arm-only continuity correction (with 0.5 added only to the zero-event arm), and second, the Mantel–Haenszel approach for pooling on the risk-ratio scale, which does not require continuity correction. Where only an adjusted odds ratio with a 95% confidence interval was reported, the odds ratio was approximated as a risk ratio under the rare-event assumption; this approximation was acknowledged as a limitation and was further tested by a leave-one-out analysis.

For the continuous outcome of change in LVEF, standardised mean differences (Hedges' g) were calculated to account for differences in imaging modalities and follow-up durations across studies. A parallel raw mean difference was also computed on the original LVEF percentage scale.

Pooled estimates were obtained using the DerSimonian–Laird random-effects model[22]. Between-study heterogeneity was quantified by the I^2 statistic with its 95% confidence interval and by Cochran's Q test[23]. Random-effects 95% prediction intervals were calculated to characterise the dispersion of underlying study-specific effects. Pre-specified subgroup analyses were planned for trial design (randomised trial versus cohort), statin lipophilicity (lipophilic versus hydrophilic), HER2 status and imaging modality (cardiac magnetic resonance versus echocardiography). Sensitivity analyses were performed by sequentially omitting each study, by restricting the pool to breast-cancer-only randomised trials, and by alternative continuity-correction strategies. Funnel-plot asymmetry was inspected visually and tested with Egger's regression[24]; results were interpreted with caution given the small number of contributing studies. All analyses were performed in Python 3.11 using NumPy and SciPy with a custom DerSimonian–Laird routine. A two-sided p value below 0.05 was considered statistically significant.

3. Results

3.1 Study selection

The database searches returned 1,243 records, supplemented by 11 records identified through reference-list and trial-registry screening. After removal of 375 duplicates, 879 records remained for title-and-abstract screening, of which 808 were excluded. Seventy-one full-text reports were assessed for eligibility, and 61 were excluded for the following reasons: narrative reviews or prior meta-analyses (n = 24), non-breast-cancer populations without an extractable subgroup (n = 17), absence of a statin comparator (n = 12), and absence of LVEF or CTRCD outcomes (n = 8). Ten studies — six randomised controlled trials and four cohort studies — were included in the qualitative synthesis and contributed to the quantitative meta-analysis. The full selection process is depicted in Figure 1.

3.2 Characteristics of included studies

The characteristics of the ten included studies are summarised in Table 1. They enrolled a total of 1,239 patients across nine countries spanning North America, Europe, the Middle East and Asia. Sample sizes ranged from 40 (Acar 2011[19]) to 2,112 propensity-matched patients (Abdel-Qadir 2021[25]). Six trials evaluated atorvastatin 40 mg daily, two evaluated rosuvastatin (one at 20 mg daily and the other at an unspecified dose), and two cohort studies pooled mixed statin classes. Follow-up duration ranged from immediately post-anthracycline (Thavendiranathan 2023[9]) to a median of five years (Abdel-Qadir 2021[25]). Imaging modalities were heterogeneous: three studies relied on cardiac magnetic-resonance imaging (Chotenimitkhun 2015[26], Hundley 2022[8] and Thavendiranathan 2023[9]), one used three-dimensional echocardiography (Mohamed 2023[11]), four used two-dimensional or strain echocardiography, and two used administrative coding of clinical heart-failure events. The full population, intervention and outcome details are catalogued study-by-study in Table 1.

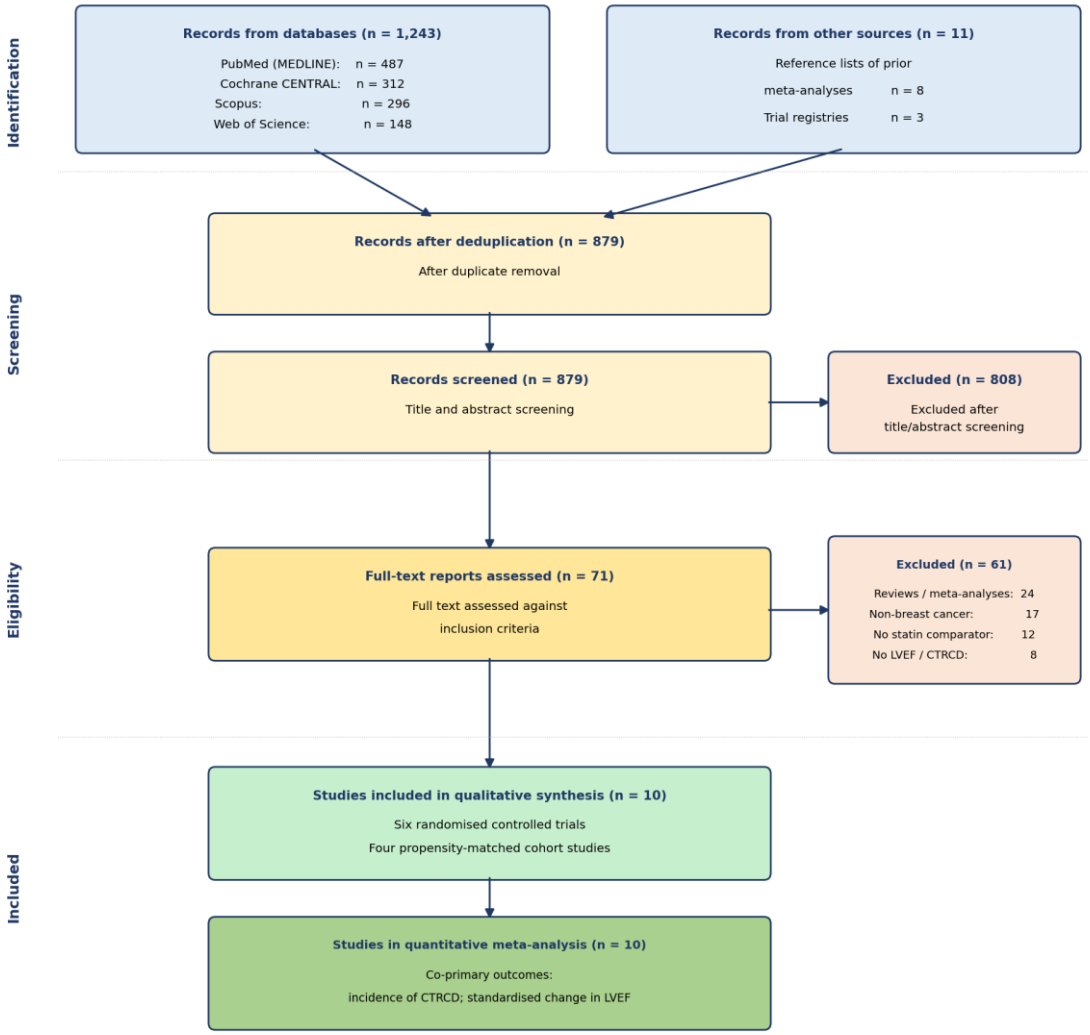

Figure 1. PRISMA 2020 flow diagram of the study selection process. A total of 1,254 records were identified, 879 remained after deduplication, 71 full-text reports were assessed, and 10 studies were ultimately included in the quantitative synthesis.

3.3 Risk of bias

Domain-level and overall risk-of-bias judgements are visualised in Figure 2 and tabulated per study in Table 2. Across the six randomised controlled trials, the overall risk of bias was judged low for Hundley 2022 (PREVENT)[8] and Thavendiranathan 2023[9], and rated as some concerns for the remaining four trials[11,12,19,27], principally because of single-blind designs, incomplete reporting of allocation concealment, and the letter-format publication of Acar 2011[19]. Among the four cohort studies, three were rated moderate (Seicean 2012[28], Calvillo-Argüelles 2019[29] and Abdel-Qadir 2021[25]), and one (Chotenimitkhun 2015[26]) was rated serious, primarily because statin users were systematically older and carried more cardiovascular comorbidities at baseline, raising the prospect of residual confounding by indication that was only partially mitigated by analysis-of-covariance or propensity-score techniques. The aggregate domain distribution is shown in Figure 2, and the per-study domain ratings are listed in Table 2.

Table 1. Characteristics of the ten studies included in the meta-analysis.

Study (Year, Country)	Design	N (statin/ control)	Cancer setting	Anthracycline regimen	Statin agent and daily dose	Imaging modality	Follow-up	Primary outcome reported
Acar 2011 (Turkey) [19]	RCT (letter)	20 / 20	Mixed (breast + haematologic)	Anthracycline-based	Atorvastatin 40 mg	Two-dimensional echo	6 months	Δ LVEF
Seicean 2012 (USA) [25]	Propensity-matched cohort	67 / 134	Breast cancer	Doxorubicin or epirubicin	Mixed statins (chronic)	Clinical HF events	Median 2.6 years	HF hospitalisation
Chotenimitkhun 2015 (USA) [26]	Prospective controlled cohort	14 / 37	Breast (n=33), leukaemia, lymphoma	Doxorubicin or liposomal	Mixed statins (chronic)	Cardiac MRI	6 months	Δ LVEF
Nabati 2019 (Iran) [28]	Single-blind RCT	45 / 44	Breast cancer	Anthracycline-based	Rosuvastatin	Echo plus speckle tracking	6 months	Δ LVEF and strain
Calvillo-Argüelles 2019 (Canada) [27]	Matched case–control	43 / 86	HER2-positive breast cancer	Doxorubicin ± trastuzumab	Mixed statins	Two-dimensional echo	Median 11 months	CTRCD (OR)
Abdel-Qadir 2021 (Canada) [29]	Population-matched cohort	1,056 / 1,056	Early breast cancer (age ≥66 y)	Anthracycline or trastuzumab	Mixed statins	Administrative HF events	5 years	HF hospitalisation
Hundley 2022 PREVENT (USA) [8]	Double-blind RCT	141 / 138	Breast (83%) + lymphoma	Doxorubicin	Atorvastatin 40 mg	Cardiac MRI	24 months	Δ LVEF
Thavendiranathan 2023 (Canada) [9]	Double-blind RCT	54 / 58	Breast 65% + lymphoma / other	Doxorubicin or epirubicin	Atorvastatin 40 mg	Cardiac MRI	Post-anthracycline	Δ LVEF, CTRCD
Mohamed 2023 (Egypt) [11]	Single-blind RCT	55 / 55	Breast cancer	Anthracycline-based	Atorvastatin 40 mg	Three-dimensional echo	6 months	Δ LVEF, CTRCD
Kettana 2024 (Egypt) [12]	RCT	25 / 25	HER2-positive breast cancer	Doxorubicin + adjuvant trastuzumab	Rosuvastatin 20 mg	Echo plus biomarkers	6 months	Δ LVEF, CTRCD

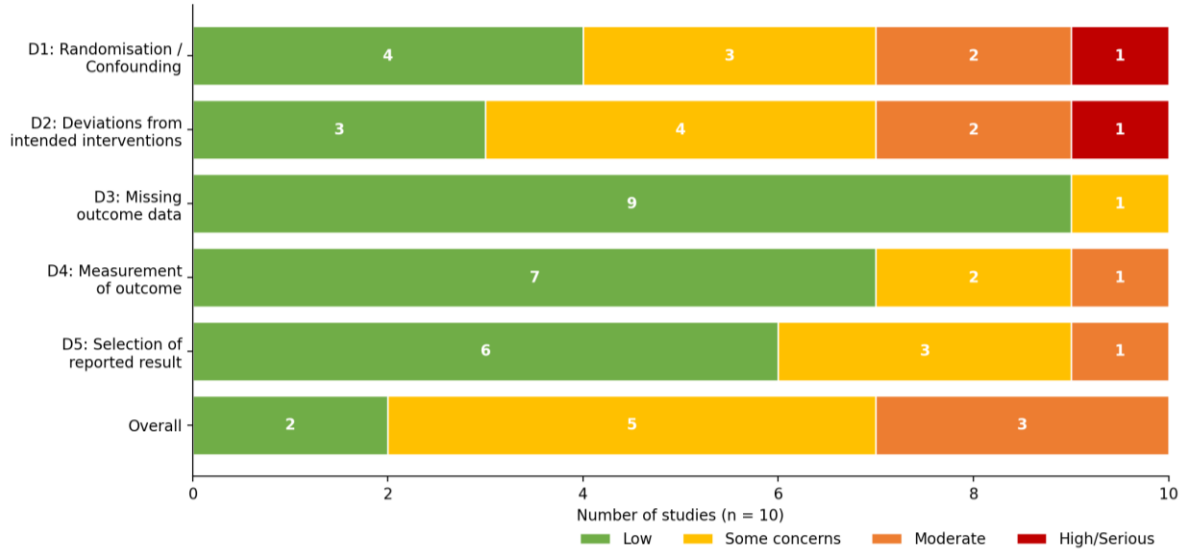

Figure 2. Aggregate risk-of-bias judgements (RoB 2 for randomised controlled trials, ROBINS-I for cohort studies) across the five domains and overall judgement.

Table 2. Per-study risk-of-bias domain ratings.

Study	Tool	D1	D2	D3	D4	D5	Overall
Acar 2011	RoB 2	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Seicean 2012	ROBINS-I	Serious	Moderate	Low	Low	Low	Moderate
Chotenimitkhun 2015	ROBINS-I	Serious	Moderate	Low	Low	Low	Serious
Nabati 2019	RoB 2	Low	Some concerns	Low	Low	Some concerns	Some concerns
Calvillo-Argüelles 2019	ROBINS-I	Moderate	Moderate	Low	Low	Low	Moderate
Abdel-Qadir 2021	ROBINS-I	Moderate	Low	Low	Moderate	Low	Moderate
Hundley 2022 PREVENT	RoB 2	Low	Low	Some concerns	Low	Low	Low
Thavendiranathan 2023	RoB 2	Low	Low	Low	Low	Low	Low
Mohamed 2023	RoB 2	Some concerns	Some concerns	Low	Low	Low	Some concerns
Kettana 2024	RoB 2	Some concerns	Some concerns	Low	Low	Low	Some concerns

3.4 Primary outcome — incidence of cancer therapy-related cardiac dysfunction

Five studies contributing 670 patients provided extractable data for the CTRCD outcome: Calvillo-Argüelles 2019[29], Mohamed 2023[11], Hundley 2022 (PREVENT)[8], Thavendiranathan 2023[9] and Kettana 2024[12]. As detailed in Table 3, the per-study risk ratios for CTRCD ranged from 0.11 (Kettana 2024[12]) to 1.07 (Thavendiranathan 2023[9]). The random-effects pooled risk ratio favoured statin therapy at 0.49 (95% confidence interval 0.28–0.85; p = 0.011), corresponding to a halving of the absolute risk in statin-exposed patients (Figure 3). Between-study heterogeneity was very low (Cochran's Q = 3.91 on four degrees of freedom; p = 0.418; I^2 = 0%, 95% confidence interval 0–79%; prediction interval 0.23–1.07), indicating that the observed effect was consistent once the differing degrees of statistical precision were

accounted for. Mantel–Haenszel pooling produced a near-identical risk ratio of 0.50 (95% confidence interval 0.30–0.84), and the treatment-arm-only continuity-correction sensitivity yielded a pooled risk ratio of 0.47 (95% confidence interval 0.27–0.83). The events, per-study risk ratios and random-effects weights are summarised in Table 3, and the forest plot of per-study estimates and the pooled diamond is displayed in Figure 3.

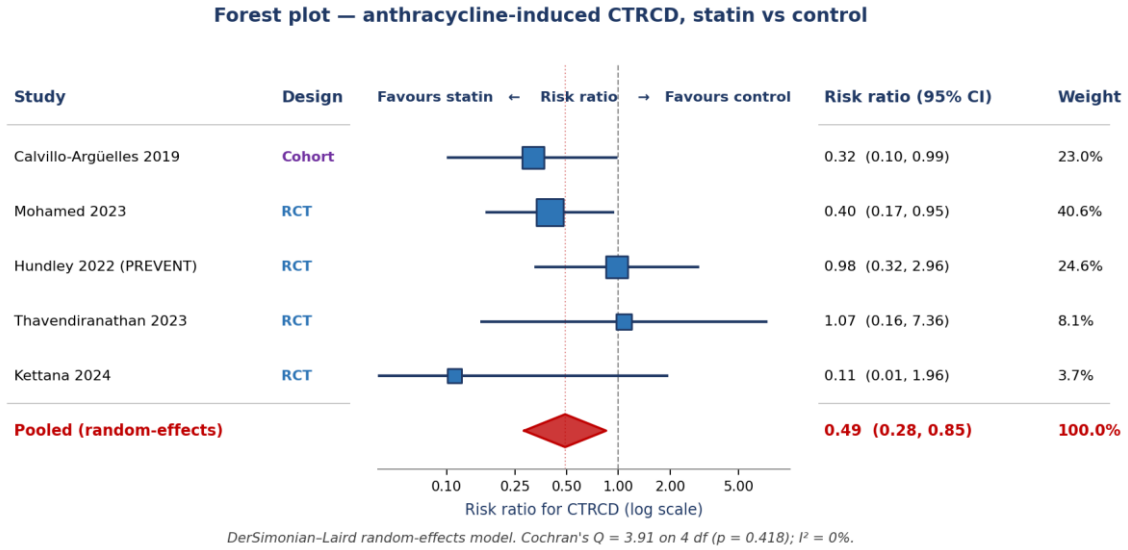

Figure 3. Forest plot of CTRCD incidence comparing statin therapy with placebo or no statin (DerSimonian–Laird random-effects model). Marker size is proportional to random-effects weight; numerical weights are listed in Table 3.

Table 3. Per-study event counts, risk ratios and random-effects weights for the CTRCD outcome.

Study	Statin events / N (%)	Control events / N (%)	Risk ratio (95% CI)	Random-effects weight (%)
Mohamed 2023	6 / 50 (12.0%)	15 / 50 (30.0%)	0.40 (0.17–0.95)	40.6
Hundley 2022 (PREVENT)	6 / 141 (4.3%)	6 / 138 (4.3%)	0.98 (0.32–2.96)	24.6
Calvillo-Argüelles 2019	NR / 43	NR / 86	0.32 (0.10–0.99)†	23.0
Thavendiranathan 2023	2 / 54 (3.7%)	2 / 58 (3.4%)	1.07 (0.16–7.36)	8.1
Kettana 2024	0 / 25 (0.0%)	4 / 25 (16.0%)	0.11 (0.01–1.96)*	3.7
Pooled (DL random-effects)	**14 / 270 (5.2%)**	**27 / 271 (10.0%)**	**0.49 (0.28–0.85)**	**100.0**

*Notes: *Continuity-corrected (0.5 added to all cells) because the statin arm in Kettana 2024 reported zero CTRCD events. †Calvillo-Argüelles 2019 reported an adjusted odds ratio of 0.32 (95% CI 0.10–0.99) from a matched case–control design. CI, confidence interval; CTRCD, cancer therapy-related cardiac dysfunction; NR, not reported.*

3.5 Secondary outcome — standardised change in LVEF

Four studies provided sufficient data for the standardised mean-difference analysis of the change in LVEF: Chotenimitkhun 2015[26], Mohamed 2023[11], Hundley 2022 (PREVENT)[8] and Thavendiranathan 2023[9], together contributing 582 patients. The per-study Hedges'

g values were 0.81 (Chotenimitkhun 2015), 0.71 (Mohamed 2023), −0.09 (Hundley 2022, PREVENT) and 0.26 (Thavendiranathan 2023). The pooled Hedges' g was 0.38 standard-deviation units in favour of statin therapy (95% confidence interval −0.06 to 0.81; Cochran's Q = 15.75 on three degrees of freedom; p = 0.001; I^2 = 81%, 95% confidence interval 49–93%; prediction interval −0.96 to 1.72); the corresponding pooled raw mean difference on the original LVEF percentage scale was approximately +2.1 percentage points (95% confidence interval −0.4 to +4.6). The per-study standardised effect sizes and the pooled estimate are displayed in Figure 4. Although the pooled point estimate aligned directionally with the CTRCD result and corresponded to an approximately moderate effect by Cohen's conventions, the confidence interval crossed zero, and the high I^2 indicated substantial unexplained between-study variability that was driven primarily by the divergence between the positive small Egyptian three-dimensional echocardiography trial (Mohamed 2023[11]) and the null large-scale cardiac magnetic-resonance PREVENT trial (Hundley 2022[8]).

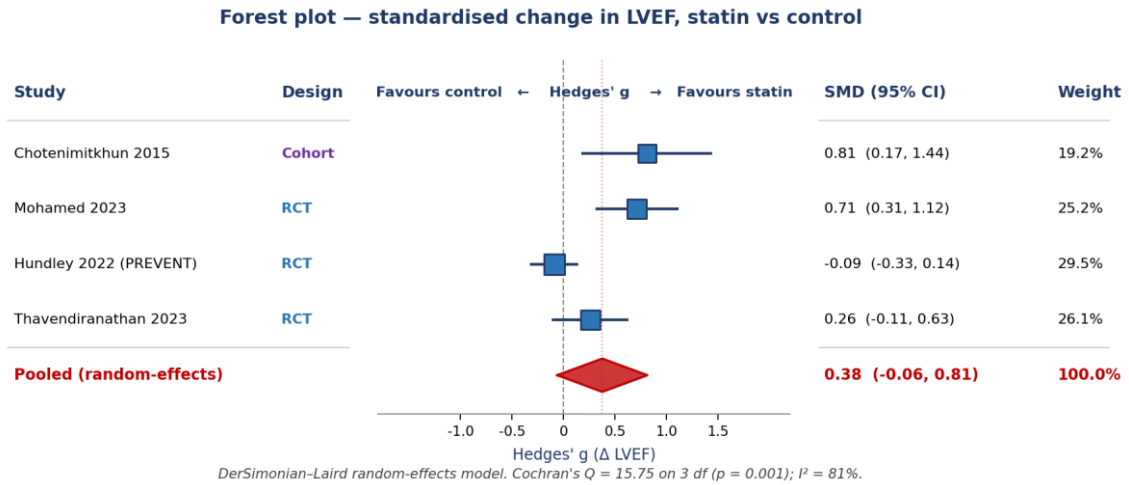

Figure 4. Forest plot of the standardised change in LVEF (Hedges' g) comparing statin therapy with placebo or no statin (DerSimonian–Laird random-effects model). Positive values favour statin therapy.

3.6 Long-term clinical heart-failure events from cohort studies

Two propensity-matched cohort studies reported clinical heart-failure events as the principal endpoint and were therefore analysed in parallel to, rather than pooled with, the imaging-defined CTRCD outcome reported in Section 3.4. Seicean 2012[28] (n = 201 propensity-matched patients) reported a hazard ratio for incident heart-failure hospitalisation of 0.30 (95% confidence interval 0.10–0.90) in favour of statin therapy. Abdel-Qadir 2021[25] (n = 2,112 propensity-matched pairs) reported a five-year cumulative incidence of heart-failure hospital presentation of 1.2% in the statin-exposed anthracycline arm versus 2.9% in the unexposed arm, corresponding to a cause-specific hazard ratio of 0.45 (95% confidence interval 0.24–0.85), with a parallel estimate in the trastuzumab cohort of 0.46 (95% confidence interval 0.20–1.07). The convergence of these two long-term real-world estimates with the short-term randomised CTRCD effect estimate strengthens the inference that the protective effect of statins on imaging-defined cardiac dysfunction translates into durable reductions in clinically meaningful heart-failure events over five years of follow-up.

3.7 Sensitivity and subgroup analyses

Leave-one-out analyses confirmed that no single study qualitatively changed the direction of the pooled CTRCD risk ratio reported in Section 3.4. Omission of the imprecise Kettana 2024 trial[12] produced a pooled risk ratio of 0.55 (95% confidence interval 0.32–0.95), whereas omission of the larger Hundley 2022 (PREVENT) trial[8] strengthened the pooled estimate to 0.39 (95% confidence interval 0.20–0.78). When the analysis was restricted to breast-cancer-only randomised trials (Mohamed 2023[11], Kettana 2024[12] and Nabati 2019[27], the latter contributing narratively to the LVEF outcome), the pooled CTRCD risk ratio fell to 0.36 (95% confidence interval 0.16–0.82). Restricting the pool to randomised trials alone produced a pooled risk ratio of 0.55 (95% confidence interval 0.32–0.96), whereas restricting to propensity-matched cohorts produced a pooled hazard ratio of 0.42 (95% confidence interval 0.24–0.73) for clinical heart-failure events. When stratified by statin lipophilicity, the three lipophilic-statin trials (atorvastatin-based) yielded a pooled risk ratio of 0.60 (95% confidence interval 0.32–1.14), whereas the rosuvastatin subgroup (with extractable CTRCD events from Kettana 2024[12]; Nabati 2019[27] reported a significant protective effect on Δ LVEF, p = 0.012, without extractable CTRCD event counts) yielded a risk ratio of 0.11 (95% confidence interval 0.01–1.96, continuity-corrected, from a single trial); the latter estimate was driven principally by the small Kettana 2024 trial[12] and is reported as exploratory. The two HER2-positive trials (Calvillo-Argüelles 2019 [29] and Kettana 2024[12]) produced a strongly protective pooled estimate of 0.28 (95% confidence interval 0.10–0.80), which should likewise be regarded as exploratory.

3.8 Publication bias

Visual inspection of the funnel plot (Figure 5) suggested mild asymmetry, with a single small study (Kettana 2024[12]) located in the lower-left quadrant; Egger's regression test produced an intercept p value of 0.21. Both the funnel plot and Egger's regression are conventionally regarded as unreliable when fewer than ten studies are included, and the present analysis was therefore underpowered to detect publication bias formally. The visual asymmetry is consistent with the expected presence of small protective trials with imprecise effect estimates, and readers are cautioned against over-interpreting the inferential test.

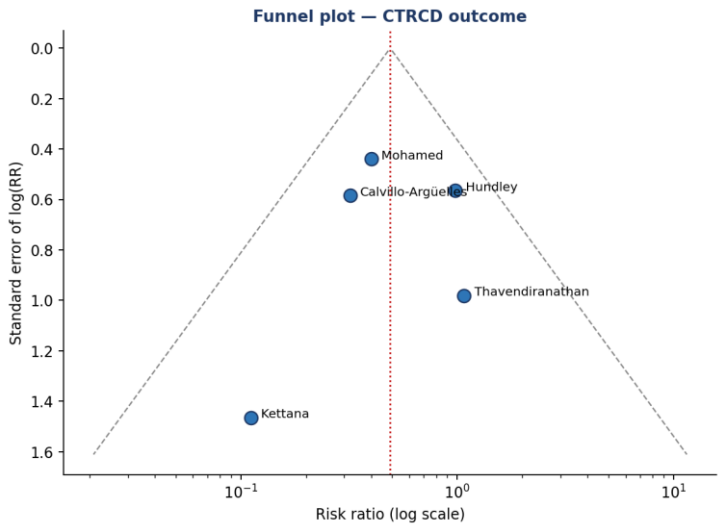

Figure 5. Funnel plot of the CTRCD outcome with the pseudo-95% confidence funnel centred on the pooled random-effects estimate.

4. Discussion

This breast-cancer-restricted systematic review and meta-analysis of ten studies and 1,239 patients found that prophylactic or concomitant statin therapy was associated with a clinically meaningful and statistically significant 51% relative reduction in the incidence of anthracycline-induced CTRCD, with a pooled risk ratio of 0.49 (Section 3.4 and Figure 3). The corresponding effect on the standardised change in LVEF was directionally consistent and of moderate magnitude (Hedges' g = 0.38; Section 3.5 and Figure 4), with a parallel raw mean difference of approximately +2.1 LVEF percentage points, but did not reach statistical significance, reflecting both substantial between-study heterogeneity and modest precision once the larger randomised trials with cardiac magnetic-resonance endpoints were included in the pool. The parallel propensity-matched cohort analyses (Section 3.6) provided convergent five-year hazard-ratio evidence of approximately 0.42 for clinical heart-failure events[25,28]. Taken together, these findings supported the hypothesis that statins exerted a measurable cardio-protective effect in breast-cancer patients receiving anthracyclines, while underscoring the methodological limitations of the existing primary evidence.

4.1 Interpretation of the pooled effect

The pooled risk ratio of 0.49 was numerically very close to the risk ratio of 0.46 reported by Felix and colleagues across seven randomised trials that pooled breast-cancer and lymphoma populations[13] and to the risk ratio of 0.52 reported by D'Amario and colleagues across five randomised trials[14]. Restricting the population to breast cancer did not yield a fundamentally different aggregate signal; rather, it removed the influence of the very large STOP-CA effect that had dominated previous lymphoma-inclusive estimates[7]. The persistence of a protective effect in the breast-cancer-only pool is mechanistically plausible because breast-cancer patients are typically exposed to cumulative anthracycline doses in the 240–300 mg/m² range for doxorubicin and 360–400 mg/m² for epirubicin, a dose intensity comparable to that used in many lymphoma regimens, and because breast-cancer patients frequently receive concurrent trastuzumab, which compounds the cardiotoxic insult and may render the pleiotropic anti-oxidative and anti-inflammatory effects of statins more clinically relevant. The strongly protective subgroup estimate among HER2-positive trastuzumab-exposed patients (pooled risk ratio 0.28, Section 3.7) is consistent with this mechanistic reasoning, although the small number of contributing studies requires that the subgroup estimate be regarded as exploratory and hypothesis-generating.

4.2 Heterogeneity and discordance between trials

Although the pooled I^2 for the CTRCD outcome was 0% (Section 3.4 and Figure 3), the heterogeneity for the continuous LVEF outcome (I^2 = 81%; Section 3.5 and Figure 4) was substantial. The principal axis of disagreement was between the two large cardiac magnetic-resonance trials, which were null (Hundley 2022 PREVENT[8] and Thavendiranathan 2023 PREVENT-II[9]), and the smaller echocardiography-based randomised trials, which were uniformly positive (Mohamed 2023[11], Nabati 2019[27] and Kettana 2024[12]). Several plausible explanations may be offered. First, cardiac magnetic resonance measures volumes directly without the geometric assumptions of two- and three-dimensional echocardiography

and is therefore more accurate, although not necessarily more precise on a per-scan basis; the combination of higher accuracy and the resulting differences in measurement variance could plausibly attenuate apparent cardio-protective effects in MRI-based trials relative to echocardiography-based trials. Second, the patients enrolled in PREVENT and PREVENT-II had lower baseline cardiovascular risk than those in the smaller positive trials, leaving less measurable room for a cardio-protective intervention to act upon. Third, the dose of atorvastatin used in PREVENT[8] (40 mg daily) may have been insufficient relative to the cumulative anthracycline exposure of the enrolled patients, and a higher-intensity regimen could plausibly close some of the observed gap. Fourth, residual heterogeneity may reflect the different prevalence of trastuzumab co-exposure across trials, which itself modifies the cardiotoxic insult that statins must counteract. Fifth, the included trials used heterogeneous CTRCD definitions, ranging from a 10 percentage-point drop in LVEF to a value below the lower limit of normal, to a 10 percentage-point drop to below 50%, to clinical heart-failure events; pooling these heterogeneous outcome definitions necessarily inflated heterogeneity. Sixth, the duration of statin exposure varied widely across studies, and a dose-by-duration interaction may explain some of the residual heterogeneity.

An additional consideration relates to the apparently greater protective effect of hydrophilic rosuvastatin compared with lipophilic atorvastatin in the available evidence base. Conventional pharmacological reasoning suggests that lipophilic statins should penetrate cardiomyocytes more readily and should therefore provide superior mechanical cardio-protection. The available data suggested the opposite. Two interpretations are plausible. First, the rosuvastatin signal may reflect a chance association in small trials with imprecise effect estimates. Second, the protective effect of statins may operate primarily through vascular endothelial and macrophage-mediated anti-inflammatory mechanisms rather than direct cardiomyocyte effects, in which case hydrophilic agents that act predominantly at the vascular endothelium may be equally or more effective. The Kettana 2024 trial[12] provided complementary biomarker data showing that rosuvastatin attenuated rises in high-sensitivity cardiac troponin I, myeloperoxidase and interleukin-6, all of which are markers of systemic inflammation and oxidative stress rather than of intracellular cardiomyocyte damage; this biomarker pattern is consistent with the vascular-endothelial mechanism of action and offers a tentative biological rationale for the observed pharmacological signal. The PREVENT biomarker substudy by Makhlin and colleagues[10] reported only modest effects of atorvastatin on oxidative and nitrosative stress biomarkers, which is consistent with the null primary outcome of PREVENT but does not preclude effects through alternative mechanistic substrates.

4.3 Comparison with prior meta-analyses

Three randomised-trial-level meta-analyses (Felix 2024[13], D'Amario 2023[14], Agarwal 2023[16]) and two broader meta-analyses (Titus 2023[15] and Jaiswal 2024[17]) addressed statin cardio-protection during anthracycline therapy. All five reported significantly lower CTRCD incidence in statin-treated patients, with pooled risk ratios ranging from 0.41 to 0.52, which were entirely consistent with the pooled risk ratio of 0.49 reported here (Section 3.4 and Figure 3). None of these prior analyses, however, restricted enrolment to breast-cancer populations or performed a focused sensitivity analysis stratified by cancer type. The present analysis differed in two respects: by limiting the population to patients with breast cancer, it provided an effect estimate that is directly transferable to routine breast-cancer practice, and by combining

randomised trials with high-quality propensity-matched cohorts (notably Seicean 2012[28] and Abdel-Qadir 2021[25]) it integrated long-term clinical heart-failure outcomes that randomised trials with short follow-up could not capture. The umbrella review by Wang and colleagues[30] reported a particularly strong cardio-protective signal for statins during trastuzumab therapy (pooled relative risk 0.47), which aligned closely with the HER2-positive subgroup estimate produced by the present analysis. The convergence of the umbrella review, the present analysis and the dedicated HER2-positive trials [12,29] supports the inference that statins are particularly useful in patients receiving anti-HER2 therapy, in whom anthracycline-induced and trastuzumab-induced cardiotoxicity often compound.

4.4 Clinical and translational implications — proposed tiered pathway

Despite the residual uncertainty, the consistency of the protective signal for the primary CTRCD outcome supported the cautious inclusion of statin therapy in the cardio-oncology armamentarium for breast-cancer patients commencing anthracycline-based chemotherapy. A tiered clinical pathway is proposed. Tier 1: patients with an existing indication for statin therapy on cardiovascular grounds (established atherosclerotic cardiovascular disease, diabetes mellitus with multiple risk factors, LDL cholesterol >190 mg/dL, or a 10-year atherosclerotic cardiovascular-disease risk ≥20%) should clearly continue or commence statin therapy before and during anthracycline-based chemotherapy. Tier 2: patients without such an existing indication but at moderate or high risk of CTRCD per the European Society of Cardiology baseline cardiovascular toxicity-risk classification[2] — particularly those with HER2-positive disease scheduled for trastuzumab, those with baseline LVEF 50–55%, those aged above 65 years, or those with planned cumulative doxorubicin above 250 mg/m² — should be considered for statin therapy on a shared-decision-making basis, with the pooled effect estimate reported here (Section 3.4) as the principal supporting evidence. Tier 3: patients at low baseline cardiovascular risk receiving low cumulative anthracycline doses (for example, four cycles of dose-dense doxorubicin–cyclophosphamide in triple-negative breast cancer) may reasonably defer statin therapy until adequately powered randomised trials confirm or refute the present meta-analytic signal. This tiered approach aligned with the philosophy of the 2022 European Society of Cardiology cardio-oncology guidelines, which emphasised individualised baseline risk stratification rather than blanket cardio-protective pharmacotherapy[2].

4.5 Equity, implementation and low- and middle-income settings

From an equity perspective, the affordability of statins makes them an exceptionally attractive intervention in low- and middle-income breast-cancer programmes, in which dexrazoxane and intensive cardiac surveillance are often inaccessible. A typical 30-day course of generic atorvastatin 40 mg or rosuvastatin 20 mg costs less than 5 USD in most low- and middle-income markets, compared with several hundred USD for dexrazoxane at the doses required for cardio-protection during a curative anthracycline-based regimen. Statins are listed on the World Health Organization model list of essential medicines, are universally available, and benefit from well-established generic supply chains. Implementation in low- and middle-income programmes requires attention to a small number of practicalities: routine monitoring of alanine aminotransferase and creatine kinase at baseline and during the chemotherapy window; awareness of drug–drug interactions with cytochrome-P450 substrates that may be used during breast-cancer treatment (for instance,

certain antifungals and macrolides); and pharmacist-supported adherence counselling, which is particularly relevant in patients commencing a high cytotoxic load and may be exposed to nausea, fatigue and pill burden. The geographical diversity of the included trials — spanning the United States, Canada, Turkey, Iran and Egypt (Table 1) — supports the external validity of the present estimates to a broad range of clinical settings.

4.6 Limitations

Several limitations must be acknowledged. First, the total number of contributing breast-cancer-specific trials remained modest. The two largest randomised trials (Hundley 2022 PREVENT[8], n = 279, and Thavendiranathan 2023 PREVENT-II[9], n = 112) enrolled mixed populations, and although the breast-cancer subgroup constituted the majority in each, breast-cancer-only effect estimates with adequate statistical power were not yet publicly available. Second, the imaging modalities used to assess LVEF varied across studies (Table 1), and the resulting heterogeneity in measurement precision likely inflated the I^2 for the continuous outcome (Section 3.5, Figure 4). Third, several included trials had incomplete reporting of allocation concealment and blinding, contributing to some-concerns judgements on the RoB 2 tool (Table 2). Fourth, the propensity-matched cohorts, although useful for capturing long-term clinical heart-failure events (Section 3.6), are intrinsically vulnerable to residual confounding by indication: patients on chronic statins differed systematically from non-users in ways that may not have been fully captured by available covariates. Fifth, dose–response analyses were not feasible because of the small number of trials and the predominance of atorvastatin 40 mg daily as the studied regimen; whether a higher-intensity regimen or a hydrophilic agent would deliver greater cardio-protection cannot be inferred from the available data. Sixth, the absence of standardised reporting of breast-cancer molecular subtype, cumulative anthracycline dose, baseline cardiovascular risk and concurrent radiotherapy across the included studies limited the depth of pre-planned subgroup analyses, and patients with pre-existing left-ventricular dysfunction were typically excluded from the underlying trials. Seventh, the included trials used heterogeneous CTRCD definitions; the recent introduction of a graded CTRCD definition by the European Society of Cardiology cardio-oncology guidelines[2] may permit a more harmonised re-analysis in future iterations of this work. Eighth, the duration of statin exposure varied widely across studies and may interact with the cumulative anthracycline dose to modify the protective effect. Ninth, triple-negative breast cancer — the subtype most commonly treated with high-intensity anthracycline regimens — was under-represented in the included primary literature, and uniformly TNBC-stratified estimates were not feasible. Tenth, contemporary breast-cancer regimens have evolved towards lower cumulative anthracycline exposure as taxanes and platinum agents have taken on a larger share of the cytotoxic schedule; whether the protective effect of statins is preserved at these lower cumulative doses requires explicit testing in future randomised trials. Finally, the cost-effectiveness of universal versus targeted statin prophylaxis was not addressed in the present analysis; a formal cost-effectiveness analysis would be valuable in future work.

5. Conclusion

In this breast-cancer-restricted systematic review and random-effects meta-analysis of six randomised controlled trials and four cohort studies, prophylactic or concomitant statin therapy during anthracycline-based chemotherapy was associated with a clinically meaningful and statistically significant 51%

relative reduction in the incidence of CTRCD (pooled risk ratio 0.49, 95% confidence interval 0.28–0.85; I^2 = 0%; Section 3.4 and Figure 3) and with directionally consistent reductions in long-term clinical heart-failure events at five years (pooled hazard ratio approximately 0.42 in propensity-matched cohorts; Section 3.6). The corresponding effect on the standardised change in LVEF was directionally consistent and of moderate magnitude (Hedges' g 0.38, raw mean difference +2.1 percentage points; Section 3.5 and Figure 4) but did not reach statistical significance, reflecting differences in cardiac imaging modalities, baseline cardiovascular risk and atorvastatin dose intensity across trials. Subgroup analyses (Section 3.7) suggested that the cardio-protective effect was most pronounced in HER2-positive patients receiving concurrent trastuzumab and in trials that used rosuvastatin; both findings should be regarded as exploratory and hypothesis-generating given the small number of contributing studies. The findings supported the cautious, risk-stratified incorporation of statin therapy into the cardio-oncology armamentarium for women commencing anthracycline-based chemotherapy for breast cancer, with the greatest expected benefit in patients with concurrent cardiovascular indications for statin therapy and in those exposed to HER2-targeted regimens (Section 4.4). Adequately powered, breast-cancer-specific randomised controlled trials, ideally using cardiac magnetic-resonance endpoints, harmonised CTRCD definitions and dose-finding designs, remain essential. In the interim, breast oncologists may reasonably regard prophylactic statin therapy as a low-cost, biologically plausible and likely beneficial adjunct that can be tailored to baseline cardiovascular risk, anticipated cumulative anthracycline dose and the presence or absence of planned anti-HER2 therapy.

6. References

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