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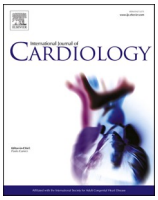

Statins as preventive therapy for anthracycline cardiotoxicity: a meta-analysis of randomized controlled trials

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ABSTRACT

Background: Cardiotoxicity occurs in 5–20% of cancer patients who receive anthracyclines. The aim of this study was to pool all the randomized controlled trials (RCTs) investigating the cardio-protective role of statins in patients treated with anthracyclines.

Methods: PubMed and Scopus electronic databases were scanned for eligible studies up to May 3rd, 2023. A total of 5 RCTs with 808 patients were included. Efficacy endpoints were the rate of anthracycline-mediated cardiotoxicity, the incidence of hospitalization for heart failure (HF), left ventricular ejection fraction (LVEF) value after anthracycline treatment, and ΔLVEF calculated as the difference in LVEF before and after anthracycline therapy. Safety endpoints [i.e., the incidence of muscle pain and serious adverse events (SAE)] were also assessed.

Results: On pooled analysis, the statin-treated group had a lower incidence of cardiotoxicity compared to the placebo group [risk ratio (RR) 0.52, 95% confidence Interval (CI) 0.33–0.83, $P = 0.01$; $I^2 = 0\%$], as well as higher mean LVEF [Mean difference (MD) 1.88, 95% CI 0.66–3.1, $P < 0.01$; $I^2 = 57.3\%$)] and a more favorable ΔLVEF during follow-up (MD 2.38, 95% CI -0.03 – +4.79, $P = 0.05$; $I^2 = 99\%$), despite no significant difference in terms of hospitalization for HF and rate of adverse events. Of note, severe heterogeneity affected the analyses for both LVEF and ΔLVEF.

Conclusions: The current meta-analysis of all RCTs conducted so far shows an overall beneficial effect of statins on the risk of anthracyclines-induced cardiotoxicity and LVEF preservation. No difference was observed in the rate of HF hospitalization. More powered RCTs are needed to fully investigate the impact of statins on prognosis in patients receiving anthracyclines therapy.

1. Introduction

As the survival of cancer patients continues to increase, the short and long-term cardiovascular complications of chemotherapy are a major concern. Since its discovery in the 1960s, anthracyclines persist as a cornerstone in oncology for several types of cancer. However, cancer therapy-related cardiac dysfunction (CTRCD) is a side effect that currently limits the net clinical benefit of this treatment [1]. Since therapies that consistently and unequivocally have been shown to prevent this severe complication are lacking, there is an unmet need for effective therapies preventing CTRCD [1]. A variety of mechanisms, such as increased superoxide anion free radicals, apoptosis, and mitochondrial dysfunction, are implicated in CTRCD. The current European guidelines on cardio-oncology recommend the use of neuro-hormonal therapies (i.e., beta-blockers and renin–angiotensin–aldosterone system blockers) and statins for primary prevention in patients treated with anthracyclines and at high and very high-risk for cardiovascular toxicity (class of recommendation IIa, level of evidence B) [1]. Specifically, statins have been tested in various phase II-randomized controlled trials (RCTs) as preventive treatments for CTRCD, given their anti-oxidant and

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anti-inflammatory pleiotropic effects [2–6]. Nonetheless, they have led to conflicting results, due to the small sample size of individual RCTs and to inter-study differences in the baseline characteristics of patients, in the dosage and type of statin therapy, in the duration and cumulative dose of chemotherapy, and in the definition of endpoints. The purpose of this meta-analysis was to pool all RCTs investigating statins as a modality to mitigate cardiotoxicity among cancer survivors treated with anthracyclines, gathering evidence on their efficacy.

2. Methods

We carried out a systematic review of the available publications according to the current PRISMA guidelines to perform meta-analyses of RCTs [7]. The adopted PRISMA checklist is depicted in Supplementary Table S1. The PRISMA flowchart depicting the process of inclusion of the selected studies is reported in Supplementary Table S2. The study protocol was registered within the PROSPERO International Prospective Register of Systematic Reviews with the following ID: CRD42023408633.

2.1. Search strategy and selection criteria

PubMed and Scopus were searched from inception until May 3rd, 2023 to identify relevant studies using the following keywords and their MeSH terms: "statin", "anthracyclines", "anthracycline-induced", "cardiotoxicity", "chemotherapy-induced", "doxorubicin", "cardiomyopathy", and "left ventricular ejection fraction". Full electronic search strategy is reported in Supplementary Method S1. Studies were included if: 1) they were RCTs, 2) included patients with any type of cancer, 3) patients received anthracyclines as a chemotherapeutic agent, and 4) statin therapy was used during cancer treatment. Two independent investigators reviewed the studies (RL and GC) to determine whether they met the inclusion criteria. Conflicts were revolved by consensus.

2.2. Data extraction and quality assessment

Data were extracted by two co-authors (RL and EB) using a standardized worksheet. Baseline demographics and clinical characteristics of the population included were extracted. Furthermore, data on the cumulative dosage of anthracycline therapy, type and dosage of statins, mean follow-up time, cancer type, and imaging technique for outcome measure were also collected for subsequent sensitivity analyses and meta-regressions. The risk of bias assessment was conducted using the RoB2 (revised tool for assessing risk of bias in randomized trials 2.0) scale [8].

2.3. Study endpoints

Efficacy endpoints comprehended the following: the rate of anthracycline-mediated cardiotoxicity, the rate of hospitalization for heart failure (HF), left ventricular ejection fraction (LVEF) at the end of treatment with anthracycline, and the ΔLVEF between pre- and post-anthracycline therapy. Further details on efficacy endpoints' definitions are available in Supplementary Method S2. The occurrence of muscle pain and serious adverse events (SAE) were considered as safety endpoints. Further details on the definition of SAE are available in Supplementary Method S2.

2.4. Statistical analysis

For inferential purposes, a random-effect model was used (restricted maximum likelihood). Risk Ratio (RR) with 95% confidence intervals (CI) for discrete variables, mean difference (MD) for continuous variables and *P* values were used as the summary statistics. Publication bias was assessed by funnel plot visual examination and Egger's test. The meta-analysis was performed using Stata 17 (64 bit; StataCorp, College Station, TX). Heterogeneity across studies was assessed with Cochran's Q method and I^2 testing. A threshold of $P < 0.10$ was used to define the presence of heterogeneity for the Q test. I^2 was considered substantial when it was >50%. If substantial heterogeneity was detected, a Galbraith plot was generated to graphically depict the principal outliners. We performed meta-regressions to explore the potential impact of the following covariates on outcomes: mean age, percentage of male patients, low-density lipoprotein (LDL) levels after statin therapy, cumulative dosage of anthracycline therapy, and mean follow-up time. The various subtypes of anthracyclines do not exhibit the same level of cardiotoxicity. Therefore, when an anthracycline other than doxorubicin was used, its dosage was converted to an isoequivalent dose, using doxorubicin as a reference (1). Leave-one-out sensitivity analyses were performed removing studies with a high cardiovascular-risk population, a statin treatment adherence of <90%, and the use of rosuvastatin instead of atorvastatin. A subgroup analysis was also performed comparing different imaging techniques (cardiac magnetic resonance, CMR or echocardiography).

3. Results

Out of 2535 potentially relevant articles initially screened, 5 met the inclusion criteria and were included in the meta-analysis, with a total population of 808 patients, 401 in the statin-treated group vs. 407 in the placebo group [2–6]. Median follow-up was 10 months (range 2,4–24 months). 398 patients received a diagnosis of lymphoma and 388 had breast cancer. The statin used was atorvastatin at a dosage of 40 milligrams (mg) in all RCTs, with the exception of one study in which rosuvastatin 20 mg was employed. Further details on the population enrolled and the studies' characteristics are summarized in Table 1. Supplementary Table S2 shows the risk of bias of the included studies according to the Rob2 scale.

3.1. Efficacy endpoints

The statin-treated group had a lower incidence of cardiotoxicity compared to the placebo group (RR 0.52, 95% CI 0.33–0.83, $P = 0.01$; $I^2 = 0\%$), (Fig. 1a). No significant difference was found between the two groups in terms of hospitalization for HF during the available follow-up (RR 0.48, 95% CI 0.18–1.26, $P = 0.98$; $I^2 = 0\%$), (Fig. 1b). No publication biases were found by funnel plot visual examination and Egger's tests for the above endpoints, (Supplementary Fig. S1). Furthermore, the statin-treated group had a higher mean LVEF at the end of anthracycline treatment (MD 1.88, 95% CI 0.66–3.1, $P < 0.01$; $I^2 = 57.3\%$), (Fig. 1c). A more favorable ΔLVEF between follow-up and baseline measurements was also observed in the statin-treated group, with a *P* value on the edge of significance (MD 2.38, 95% CI -0.03 – +4.79, $P = 0.05$; $I^2 = 99\%$), (Fig. 1d). However, severe heterogeneity affected the pooled analyses for both LVEF and ΔLVEF. By Galbraith plot visual examination, the studies of Neilan et al. and Hundley et al. resulted as the principal outliners (Supplementary fig. S2). Publication bias was identified for both ΔLVEF and LVEF pooled analyses, through funnel plot visual examination (Supplementary fig. S3). On a subgroup analysis according to the diagnostic method employed (i.e., CMR or echocardiography), the statin-treated group was favored in terms of ΔLVEF in both CMR (MD 0.64, 95% CI 0.05–1.24, $P = 0.03$; $I^2 = 96\%$) and echocardiography (MD 6.04, 95% CI 2.23–9.86, $P < 0.01$; $I^2 = 61\%$) subgroups (P of interaction = 0.01), (Supplementary fig. S4).

3.2. Safety endpoints

No significant difference was observed between the statin-treated group and the control group in any of the safety endpoints (RR 1.31, 95% CI 0.78–2.20, $P = 0.3$; $I^2 = 0\%$) (RR 0.79, 95% CI 0.37–1.67, $P = 0.53$; $I^2 = 0\%$), respectively (Supplementary fig. S5).

Table 1
Main features of the included RCTs.

Author, year	Acar, 2011	Nabati, 2019	Hundley, 2022	Neilan, 2022	Thavendiranathan, 2023
Study design	RCT, un-blinded	RCT, single-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded
Sample size, n	40	77	279	300	112
Comparison group	Control	Placebo	Placebo	Placebo	Placebo
Tumor type n, (%)	-Lymphoma: 23 (58); -Multiple myeloma: 6 (15); -Leukaemia: 11 (27)	-Breast cancer: 77 (100)	-Breast cancer: 237 (85); -Lymphoma: 42 (15)	-Lymphoma: 300 (100)	-Breast cancer: 74 (66); -Lymphoma: 25 (22); -Leukaemia: 3 (3); -Sarcoma: 7 (6); -Thymoma: 3 (3)
Follow up, days	180	180	720	360	72
Statin, dose mg	Atorvastatin, 40	Rosuvastatin, 20	Atorvastatin, 40	Atorvastatin, 40	Atorvastatin, 40
Statin adherence, n (%)	40 (100)	75 (94.7)	153 (54.7)	270 (90)	109 (97)
Anthracycline cumulative dosage mg/m^2, (SD)	482.5 (3.8)	338.6 (40.8)	240 (N.A.)	264 (N.A.)	247.7 (52.3)
Age ys, (SD)	53 (15.9)	49 (11.05)	49 (12)	50 (N.A.)	57 (13.5)
Male n, (%)	17 (42.5)	0 (0)	23 (8.2)	52 (17.7)	25 (22.3)
Baseline risk of cardiotoxicity	Low	Low	Low	Low	High
Pre-existing CV disease, n (%)	0 (0)	0 (0)	0 (0)	N.A.	45 (40.2)
Hypertension, n (%)	N.A.	0 (0)	N.A.	N.A.	29 (25.9)
Diabetes, n (%)	N.A.	12 (15.6)	0 (0)	N.A.	7 (6.3)
Dyslipidaemia, n (%)	N.A.	18 (23.4)	0 (0)	N.A.	5 (4.5)
Baseline LDL, mg/dL (SD)	N.A.	N.A.	111 (29) in statin, 112 (26) in placebo	N.A.	111.76 (34.4) in statin, in 114.8 (36.7) placebo
LDL at the end of treatment, mg/dL (SD)	N.A.	126.7 (37.1) in statin, 82.4 (30.2) in placebo	89 (38) in statin, 110 (34) in placebo	N.A.	66.9 (26.68) in statin, 112.5 (33.6) in placebo
Definition of CTRCD	reduction in LVEF to <50%	reduction in LVEF to <45%	reduction in LVEF to <50%	reduction in LVEF >10%	reduction in LVEF >10%
LVEF assessment method	Echo	Echo	CMR	CMR	CMR
Incidence of CRTCD, n (%), *p* value*	1 (5%) in statin, 5 (25%) in control, $p = 0.18$	4 (11%) in statin, 6 (15%) in placebo, $p = 0.963$	4 (2.8%) in statin, 7 (5%) in placebo, $p > 0.05$	14 (9%) in statin, 33 (22%) in placebo, $\mathbf{p = 0.002}$	3 (4%) in statin, 5 (4%) in placebo, $p \geq 0.99$
LVEF, % (SD) statin:					
-Baseline	61.3 (7.9)	55.05 (4.84)	62.6 (6.4)	63 (4)	60.2 (5.4)
-Post	62.6 (9.3)	53.5 (6.68)	57.7 (5.6)	59 (0.5)	57.3 (5.8)
-Difference	1.3 (3.8)	−1.5 (6.56)	3.2 (0.7)	−4.1 (0.5)	−2.9 (1.25)
LVEF, % (SD) placebo:					
Baseline	62.9 (7)	55.1 (5.9)	61.7 (5.5)	63 (4)	59.2 (6.6)
Post	55 (9.5)	49.9 (6.57)	57.4 (6.8)	57 (0.4)	55.9 (7.4)
Difference	−7.9 (8)	−5.1 (5.68)	3.3 (0.6)	−5.4 (0.5)	−3.4 (1.25)
p value†	$\mathbf{p < 0.001}$	$\mathbf{p = 0.012}$	$p = 0.93$	$\mathbf{p = 0.04}$	$p = 0.34$

Studies characteristics.
Abbreviations: CMR, cardiac magnetic resonance; CTRCD, cancer therapy-related cardiac dysfunction; CV, cardiovascular disease; dL, decilitre; Echo, echocardiogram; LDL, low-density lipoprotein; m, metrum; LVEF, left ventricular ejection fraction; mg, milligram; N.A., not available; RCT, randomized controlled trial; SD, standard deviation; years, ys
* P value for intergroup comparison in the incidence of CRTCD.
† P value for intergroup comparison (i.e., statin versus placebo/control) in LVEF mean difference before and after treatment.

3.3. Sensitivity analyses and meta-regressions

At meta-regressions, none of the following covariates was associated with the effect size for the endpoints of interest: LDL after statin treatment, age, and sex. (Supplementary fig. S6–7). Conversely, a positive association between the magnitude of the statin-related protective effect and the cumulative dosage of anthracycline therapy was found on ΔLVEF and final LVEF ($p < 0.01$ and $p < 0.01$, respectively) (Supplementary fig. S7). Furthermore, the mean follow-up time was found positively associated to the magnitude of the final LVEF difference between the statin group and the placebo group, favouring the former ($p = 0.026$) These findings may explain at least part of the heterogeneity of these two endpoints. On leave-one-out sensitivity analyses, the removal of the study by Neilan et al. affected the significance for both cardiotoxicity and LVEF analyses (Supplementary fig. S8–9). Several studies removal affected the significance for ΔLVEF (Supplementary fig. S9).

4. Discussion

The current meta-analysis, encompassing 808 cancer patients from 5 RCTs, shows a beneficial effect of statins in preventing left ventricular dysfunction after anthracyclines treatment, evidenced by both lower incidence of cardiotoxicity and smaller mean change in LVEF in statin-treated patients compared to placebo, despite no difference in the occurrence of HF hospitalization *(Graphical abstract)*. Of note, dexrazoxane is the only medication approved to prevent chemotherapy-induced cardiotoxicity in patients with high and very high CTRCD risk [1]. However, concerns related to reduced cancer-specific survival and risk of secondary cancers have been raised, limiting its use in clinical practice. Undoubtedly, there is a pathophysiological rationale behind the protective effect of statins in individuals receiving cardiotoxic chemotherapeutic drugs deriving from their effects [9]. To date, only retrospective observational studies in humans and randomized studies in animal models showed that statins may reduce all-cause mortality and incident HF in anthracyclines-treated subjects [9]. Conversely, statins have not shown clinical benefit in patients with pre-existing HF [10,11]. Therefore, solid evidence from randomized human trials, which

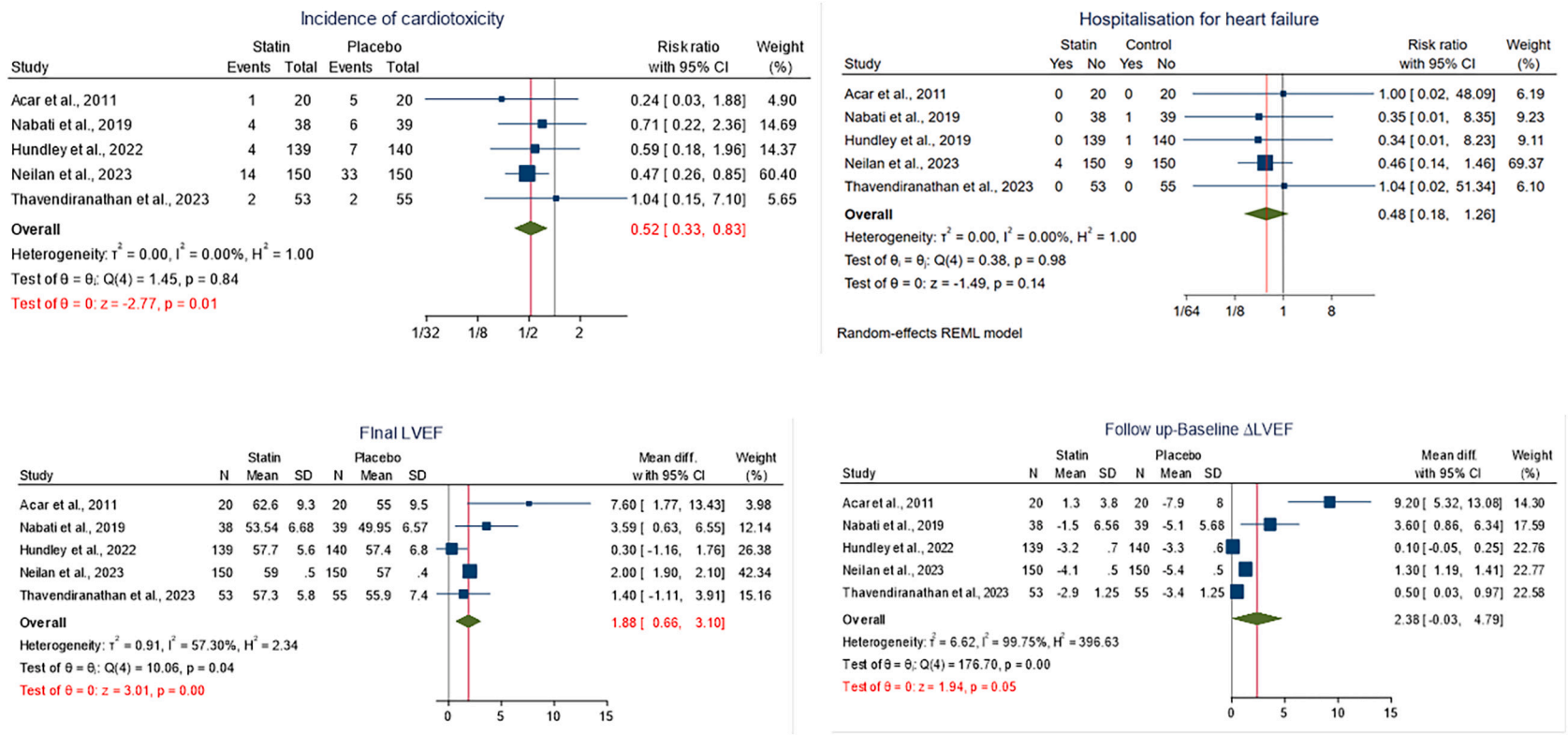

Fig. 1. Forest plot for the incidence of cardiotoxicity (1a), incidence of heart failure (1b) final LVEF (1c), follow up-baseline ΔLVEF (1d). The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% confidence intervals (CIs). The open diamond represents the pooled relative risk, and its width represents its 95% CI. Abbreviations: CI: confidence interval; LVEF, left ventricular ejection fraction.

demonstrates a benefit on hard clinical endpoints, is still lacking.

4.1. Statin dosage and intensity

Several types of statins exist, and each is available at different dosages [12]. According to the degree of LDL reduction expected, three different statin regimens have been currently identified (i.e., high-intensity, moderate intensity, and low intensity) [12]. In addition to their pleiotropic effects, the protective action of statins against CTRCD might depend on their lipid-lowering properties, by reducing the progression of atherosclerosis, accelerated by the concomitant radiotherapy and/or chemotherapy treatment [13,14]. Dixon et al. showed that the excess late mortality among survivors of childhood cancer is mainly ascribed to the early onset of common causes of death found in the middle-aged population, including heart and cerebrovascular disease, suggesting that targeting conventional cardiovascular risk factors may play a role in preventing cardiotoxicity. [15]. In this meta-analysis, the statins used are atorvastatin 40 mg and rosuvastatin 20 mg, both belonging to the high-intensity therapeutic regimen, with the highest theoretical degree of LDL reduction. On leave-one sensitivity analyses, the removal of the study by Nabati et al, which is the only one that employed rosuvastatin, did not affect the results for any of the efficacy endpoints [3] (Supplementary Figs. S8, S9). Therefore, both high-intensity regimens (i.e., atorvastatin 40 mg and rosuvastatin 20 mg) seem to be equally effective in preventing CTRCD. Other statin regimens with different intensity have not been investigated in this specific clinical setting. At meta-regression analyses, LDL levels after treatment do not appear to influence the effect of statins on efficacy endpoints. In conclusion, statin effect in preventing CTRCD seems to be independent of the cholesterol reduction achieved at the end of treatment.

4.2. Statin effect according to the baseline cardiotoxicity risk

ESC guidelines on cardio-oncology recommend cardiovascular toxicity risk assessment before anticancer therapy [1]. Although several risk scores have been published, the most commonly accepted score is the HFA-ICOS [16]. It comprises the presence of cardiovascular risk factors, a previous cardiovascular disease, a previous cancer, and a previous exposure to chemotherapy or mediastinal radiotherapy, resulting in the classification of patients into four risk classes [1,16]. In this meta-analysis, only the study by Thavendiranathan et al included patients at high or very high risk of cardiotoxicity, whether all the other RCTs excluded deliberately patients with any of the aforementioned risk factors, resulting in a low-risk population [6]. On leave-one analysis, the removal of Thavendiranathan et al does not affect the beneficial results of statins for any of the efficacy endpoints (Supplementary Figs. S8, S9). On the contrary, according to the results by Thavendiranathan et al, statins do not prevent the cardiotoxic effect of anthracyclines in patients at high or very high risk for cardiotoxicity. In summary, the protective effect of statins seems to be greater in low-risk patients and is blunted in high-risk patients.

4.3. Statin effect according to cumulative dosage of anthracyclines

In the case of patients for whom anthracycline chemotherapy is planned, an additional risk factor for cardiotoxicity is the expected cumulative dose of anthracyclines [17]. At meta-regression analyses, cumulative dose of anthracyclines was positively correlated to the effect size for ΔLVEF and LVEF. Therefore, the protective effect of statins seems greater in patients exposed to higher cumulative anthracycline dosage. Nevertheless, whether it translates into a benefit on hard clinical endpoints needs to be demonstrated by further RCTs.

4.4. Follow-up time and therapeutic adherence

CTRCD may occur several years after anthracycline treatment [18–20]. Caballero et al. showed that most cases of CTRCD occur after the first few months from the end of anthracycline treatment [18]. In this meta-analysis, only two RCTs (i.e., Hundley et al. and Neilan et al). have a follow-up of >6 months [4,5]. However, 36% of patients in the study by Hundley et al. had missing primary outcomes at long term follow-up [4]. This may explain partly why Hundley et al. is one of the outliners and why the removal of this study reinforces the results for the echocardiographic outcomes. In contrast, Neilan et al. has the longest follow-up after Hundley et al [4,5] . This may underpin why the removal of this study in leave one-out analyses weakens the beneficial effect of statins for each of the efficacy endpoints. Therefore, a short follow-up may not detect some of the cases of CTRCD, underestimating the beneficial effect of statins. This hypothesis is also supported by the results of the meta-regression, according to which as the average follow-up time increases, the statin group is favored over placebo. Further RCTs with longer follow-up durations are needed to confirm these findings. Finally, an additional source of heterogeneity may be represented by therapeutic adherence. All RCTs, except Hundley et al., exhibited a therapeutic adherence above 90%. Its low therapeutic adherence, amounting to 54% of patients, could therefore explain the neutral results of statins in this RCT.

4.5. Safety of statin therapy

A typical issue with primary prevention strategies is that some patients are treated unnecessarily, as only a certain percentage develops the complication of chemotherapy treatment. Therefore, ensuring the security of statin treatment is a key concern. In this meta-analysis, statins have been proven to be safe, as statin-treated patients do not exhibit an increased incidence of adverse side effects, defined either as SAE or muscle pain. This result is not unexpected, as the safety of statins has been extensively demonstrated over the years, although in other clinical settings [21]. Of note, the SAMSON study demonstrated that 90% of statin-related adverse symptoms can be attributed to the nocebo effect, as they were equally elicited by placebo in 90% of patients [22].

4.6. Limitations

Some limitations should be carefully noted. First, the adopted definition of cardiotoxicity varies slightly among the 5 included RCTs (Table 1 and Supplementary method S2), partially reducing the robustness of the pooled result. This reflects the considerable degree of heterogeneity among the different definitions proposed over the years, which has resulted in inconsistencies in diagnosis and has hindered efforts to generate an evidence base for clinical practice [23]. In order to solve this issue and address the need to harmonize the different definitions, current ESC guidelines coined the term CTRCD, capturing the wide range of possible presentations. It comprises both a symptomatic form, which includes patients who develop symptoms and signs of HF, and an asymptomatic form, diagnosed through instrumental and laboratory tests [1]. Subsequent RCTs should then adhere to this new definition to ensure uniformity and reproducibility of results. Second, since the included studies were designed for surrogate endpoints, our pooled analysis is still underpowered to detect significant differences in both hard clinical endpoints and safety endpoints. Third, CTRCD is not uniform but varies greatly depending on age of the population treated, baseline cardiovascular risk profile, history of heart disease, including impaired LVEF before chemotherapy, drug dose and length of follow-up. Although several sensitivity analyses and meta-regressions have been performed, they may be still underpowered, because of small sample sizes and the absence of individual studies designed to detect differences in subgroups. Thus, a careful evaluation of the preventive effect of statins in the different subgroups of patients and under various circumstances is needed. Although the cardio-protective effect of statins appears to be independent of LDL levels, this finding is limited by the small sample size of RCTs included. Therefore it remains unclear

whether to initiate statin therapy when there is no clear cardiovascular indication by LDL levels. Fourth, using EF and its change as the primary endpoint may not be appropriate if it is assumed that the predominant cardio-protective mechanism of statins remains slowing the progression of atherosclerotic disease. Furthermore, the short follow-up of RCTs conducted so far is unlikely to highlight this kind of statins effect in cancer patients. Finally, the included RCTs diverged in some aspects, such as study design, tumor type, cumulative anthracycline dose, imaging method (echocardiography or MRI), and duration of follow-up. Nevertheless, the influence of some of these sources of heterogeneity on endpoints was evaluated in further sensitivity analyses and in meta-regressions.

5. Conclusions

Statins represent a promise in mitigating CTRCD. Undoubtedly, larger RCTs with adequate follow-up are required to evaluate the impact of statins alone or in combination with the most recent guided-directed medical therapy [i.e. *sodium-glucose cotransporter 2 inhibitors (*SGLT2i)] on prognosis in patients receiving anthracyclines therapy.

Author contribution

R.L. and D.D.A. had a role in conceptualization and writing - original draft. R.L. and E.B. had a role in formal analysis. M.G., G.C., M.M., and G.P. had a role in writing- review & editing.

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Declaration of Competing Interest

M.G. declares that he has received consulting fees or honoraria from Terumo, outside the present work. The other authors have no conflicts of interest to declare for the present work.

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Nothing to declare.

Appendix A. Supplementary data

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