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SYSTEMATIC REVIEW

Is dyslipidemia a risk factor for trastuzumab-induced cardiotoxicity in breast cancer patients? A systematic review and meta-analysis

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Breast cancer;
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Abstract
Introduction: Breast cancer patients undergoing trastuzumab therapy have greater risk of cardiovascular disease. Risk factors for this effect have been proposed. However, the role of dyslipidemia is not completely understood. This systematic review aimed to explore the role of dyslipidemia in trastuzumab-induced cardiotoxicity.
Methods: The investigators searched MEDLINE, Scopus, and Web of Science up to October 25, 2020. A random-effects model was used to determine pooled estimates of the results. The primary endpoint was trastuzumab-induced cardiotoxicity in patients with and without dyslipidemia.
Results: A total of 39 studies were selected for inclusion in our systematic review assessing 21 079 patients. One study demonstrated a statistically significant association between dyslipidemia and cardiotoxicity (OR=2.28, 95% CI 1.22–4.26, p=0.01). In all other studies, no such association was observed. Twenty-one studies including 6135 patients were eligible for meta-analysis. In this meta-analysis of unadjusted data, dyslipidemia was significantly associated with cardiotoxicity (OR=1.25, 95% CI 1.01–1.53, p=0.04, I^2=0%), however, a subgroup analysis of studies reporting adjusted measures did not demonstrate a significant association (OR=0.89, 95% CI 0.73–1.10, p=0.28, I^2=0%).

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Conclusion: This systematic review and meta-analysis did not demonstrate a significant association between dyslipidemia alone and the development of cardiotoxicity. In the absence of other relevant cardiovascular risk factors, review of lipid profile may not be obligatory, and management of patients could be performed without referral for cardio-oncology assessment. Further investigation of risk factors for trastuzumab-induced cardiotoxicity is required to confirm these results.

PALAVRAS-CHAVE
Cancro da mama;
Cardiotoxicidade;
Quimioterapia;
Trastuzumab;
Dislipidemia

É a dislipidemia um fator de risco para cardiotoxicidade do trastuzumab em pacientes com cancro da mama? Uma revisão sistemática e meta-análise

Resumo
Introdução: Pacientes com cancro da mama sob tratamento com trastuzumab apresentam maior risco de doença cardiovascular. Fatores de risco têm sido propostos. No entanto, o papel da dislipidemia não é completamente conhecido. Esta revisão sistemática destinou-se a explorar o papel da dislipidemia na cardiotoxicidade induzida por trastuzumab.
Métodos: Os investigadores pesquisaram publicações na MEDLINE, Scopus e Web of Science até 25 de outubro de 2020. Um modelo de efeitos aleatórios foi utilizado para determinar as estimativas combinadas dos resultados. A variável de resultado primária foi a cardiotoxicidade induzida por trastuzumab em pacientes com e sem dislipidemia.
Resultados: Foram selecionados 39 estudos para inclusão na nossa revisão sistemática, avaliando 21.079 pacientes. Um estudo demonstrou associação significativa entre dislipidemia e cardiotoxicidade (OR=2,28, 95% CI=1,22-4,26, p=0,01). Em todos os restantes não foram observadas semelhantes associações. Foram elegíveis 21 estudos para a meta-análise incluindo 6135 pacientes. Na meta-análise de dados não ajustados a dislipidemia esteve associada significativamente a cardiotoxicidade (OR=1,25, 95% CI=1,01-1,53, p=0,04, I^2=0%). No entanto, a análise de subgrupos de estudos que reportaram as medidas ajustadas não demonstrou uma associação significativa (OR=0,89, 95% CI=0,73-1,10, p=0,28, I^2=0%).
Conclusão: Esta revisão sistemática e meta-análise não demonstrou uma associação significativa entre dislipidemia isolada e o desenvolvimento de cardiotoxicidade. Na ausência de outros fatores de risco cardiovasculares relevantes, a análise do perfil lipídico nestes pacientes pode não ser obrigatória e a vigilância poderá ser realizada sem referenciação para avaliação por cardio-oncologia. Investigação adicional sobre fatores de risco para cardiotoxicidade induzida por trastuzumab é necessária para confirmar estes resultados.

Introduction

Treatment of breast cancer has progressed greatly due to advances in systemic therapies, and survival rates have increased.[1] Trastuzumab is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER-2)/neu oncogene. It is used in combination with chemotherapy in metastatic and (neo)adjuvant settings in breast cancer, demonstrating improvement in survival outcomes and clinical benefit compared to chemotherapy alone.[2,3]

Trastuzumab therapy causes an increase in lifetime risk of heart failure (HF),[4] the incidence of which is higher when combined with anthracyclines.[5,6] Although rare (5% in the NSABP B-31 trial and 2.5% in the HERA trial),[7] this has important prognostic implications.

In contrast to the well-recognized effect of anthracyclines,[8] which have been the focus of research on cancer therapy-related cardiac dysfunction, trastuzumab-induced cardiotoxicity (TIC) is still the subject of debate,[9] as it appears not to be dose-dependent, and discontinuation of treatment can often reverse the condition.[10,11]

Although current guidelines encourage modification of cardiovascular risk factors for patients in this setting,[12] the real incidence of TIC, especially in breast cancer patients, is still largely unknown.[13]

Several potential risk factors for TIC have been proposed. However, their real weight and role as independent predictors are still debated.[13]

Dyslipidemia is a known risk factor for cardiovascular disease.[14] However, the actual susceptibility for TIC of patients with dyslipidemia is not well documented and to

our knowledge, there has to date been no systematic review assessing this link.

This systematic review and meta-analysis aimed to explore whether dyslipidemia could be used as a predictor for the development of TIC in breast cancer patients and to quantify its impact.

Methods

The PRISMA guidelines were followed for the systematic review design.[15,16] Patients and the public were not involved in this review.

Search strategy

Three electronic databases were searched (MEDLINE, Scopus, and ISI Web of Science) to identify potentially eligible articles using a pre-defined search strategy (Appendix A).

The search encompassed all articles from inception to October 25, 2020.

This process resulted in 857 articles in the MEDLINE database, 1048 articles in ISI Web of Science, and 840 in Scopus (Figure 1). A further 19 articles were later identified, mainly through manual searches and citations.

Eligibility criteria

We considered only human studies assessing the effects of HER-2 directed agents in breast cancer patients undergoing chemotherapy and reporting on independent risk factors. This strategy ensured that articles that did not mention dyslipidemia in their title or abstract due to non-significant results were included. The included studies assessed the impact of risk factors for cardiotoxicity, analyzing at least two study arms, comparing either patients with cardiotoxicity to those without or patients with a given factor to those without. Subsequently, the studies were screened for the role of dyslipidemia in the development of TIC.

Our primary outcome was cardiotoxicity, defined according to the criteria used in the HERA trial[17] as symptomatic (e.g. HF and/or dyspnea, and/or referral to a cardiologist) or asymptomatic (e.g. decline in left ventricular ejection fraction [LVEF] >10% from baseline or LVEF <50%). We did not, however, exclude articles that diverged slightly from this definition for the qualitative and quantitative synthesis.

Secondary outcomes consisted of symptomatic cardiotoxicity, discontinuation of trastuzumab due to cardiac causes, recovery of cardiac function after a cardiac event and reintroduction of therapy after discontinuation.

Exclusion criteria

We excluded (1) studies that mainly focused on anthracycline effects rather than trastuzumab; (2) studies that analyzed outcomes in a pediatric population; (3) non-human studies; (4) studies that followed patients for less than six months; and (5) guidelines, systematic reviews and meta-analyses, case reports, editorials, letters, and/or review articles with no original data.

No articles were excluded based on population size, publication date, or language.

Study selection

After removal of duplicates, two reviewers (JFP and MMC) independently screened the articles at title/abstract level according to the predefined inclusion and exclusion criteria. Afterward, the two reviewers (JFP and MMC) independently analyzed the full texts of studies not previously excluded using the same inclusion and exclusion criteria. Disagreements were resolved by consensus with a third reviewer (CDS) serving as final arbitrator. Efforts were made to contact investigators in order to obtain publications not accessible by other means.

Data extraction

Two reviewers (JFP and MMC) independently analyzed the full texts that had met the inclusion criteria and extracted data into a pre-established spreadsheet.

The full text of short-listed articles was systematically appraised for the following items: first author, year of publication, nationality, study setting, study design, number of patients with breast cancer, number of patients treated with anthracyclines and/or trastuzumab, duration of follow-up, patients' median age and age at diagnosis, method of LVEF assessment, and number of patients developing or not developing cardiotoxicity (or number of patients with and without a given cardiovascular risk factor).

Quality assessment and risk of bias

The risk of bias was assessed at the study level according to the method used by Haffar et al.,[18] given that for the most part, the studies included are observational. This method was also used to classify sub-analyses of randomized controlled trials (RCTs) since the primary subject of these studies was not the effect of dyslipidemia. Two reviewers (JFP and MMC) independently analyzed the studies. Any disagreements were resolved by consensus.

Statistical analysis

Review Manager® (version 5.4.1)[19] was used for statistical analysis and to derive forest plots.

Summary measures and synthesis of results

The frequency of a given risk factor was assessed using absolute and relative frequencies. If these were not present, they were calculated.

Odds ratios (ORs) were used as a summary measure. The precision of effect sizes was measured using 95% confidence intervals (CIs) and corresponding p-values for both. We chose the OR since relative estimates are more comparable than absolute effects between studies with different designs, populations, and lengths of follow-up.[20]

The Cochran Q test (I^2)[21,22] was used to assess heterogeneity and statistical inconsistency. Small study effects

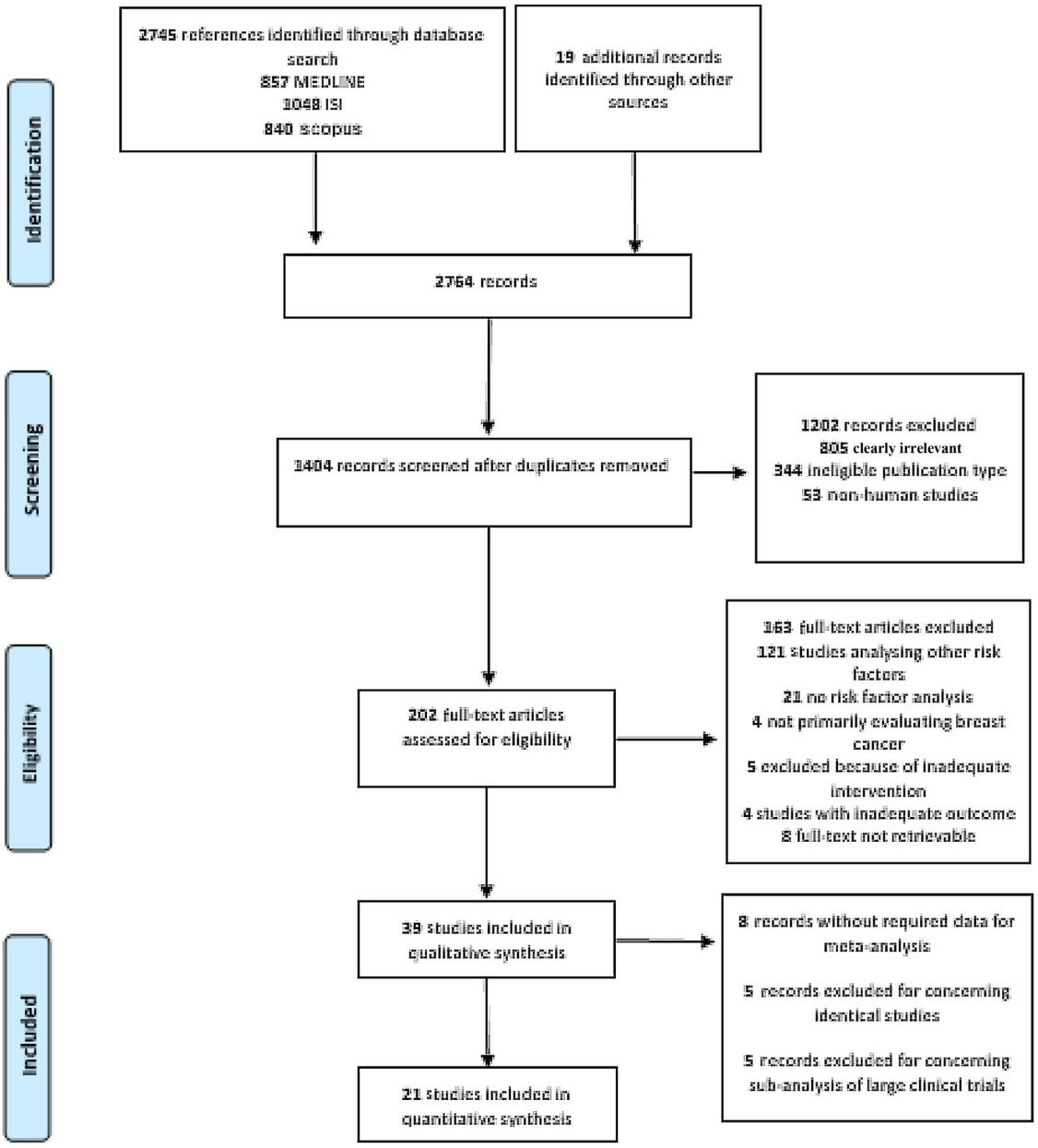

Figure 1 Flowchart of study selection using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to illustrate the study selection process.

and reporting bias were explored with a visual inspection of asymmetry in funnel plots.[23] We classified heterogeneity as 0%, signifying absence of detected heterogeneity; 0–10%, indicating low heterogeneity; 10–50%, indicating moderate heterogeneity; and over 50%, indicating high heterogeneity.

A random-effects model was used to pool data owing to the anticipated heterogeneity in the included trials. In fact, adjusted indirect comparisons that use a fixed-effects model tend to underestimate the standard errors of pooled estimates.[24]

To better understand the specific effect of dyslipidemia alone as a risk factor for cardiotoxicity, we also performed a pre-planned subgroup analysis involving only studies reporting the most adjusted measures.

Results

General characteristics of the included studies

The search returned 2745 records, of which 1407 remained after removal of duplicates. After title and abstract screening, followed by full-text appraisal, 39 articles matched our eligibility criteria and were included in our systematic review.[25–63] Afterward, 18 records were excluded from the meta-analysis because of data duplication (n=5), missing data (n=8) or being sub-analyses of large RCTs (n=5), and were thus not suitable for use in pooled estimates in conjunction with observational studies. Hence, 21 studies were further examined by meta-analysis (Figure 1).

Table 1 Main features of the included studies.

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Abd Alghafar et al.[25]	Retrospective	2020	146	HER-2 BC all stages	Anthracyclines »1-year adjuvant trastuzumab (when possible) In MBC, trastuzumab continued beyond progression AC (doxorubicin plus cyclophosphamide) or FEC or other chemo regimen; Palliative, adjuvant, neoadjuvant, pseudoadjuvant trastuzumab	24%	67%	100%	32 (21.92%)	LVEF drop >10% or LVEF <50% or symptomatic HF	Dyslipidemia: Calculated OR=0.68 CI (0.25–1.81) p=0.44
Abdel-Razaq et al.[26]	Retrospective	2019	146	BC all stages	Adjuvant/neoadjuvant or palliative trastuzumab With or without anthracy-cline/taxanes/endocrine therapy	21.9%	32.9%	100%	30 (20.5%)	LVEF drop ≥10% or a drop to LVEF <50% or symptomatic HF even without decline in LVEF	Dyslipidemia: Calculated OR=1.12 (0.43–2.88) p=0.8335 Multivariate OR=0.45 CI (0.11–1.93) p=0.23
Aldiab[27]	Retrospective	2010	98	HER-2 BC	Adjuvant trastuzumab after TAC (docetaxol, cyclophosphamide, F-FU) or AC (doxorubicin, cyclophosphamide) followed by taxotere	11.2%	89%	100%	24 (24%)	LVEF drop >10% or a drop to LVEF <50%	Insufficient data

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Ayres et al.[28]	Retrospective	2015	79	HER-2 EBC	Pre-treatment »1-year trastuzumab Adjuvant/neoadjuvant chemotherapy ECT or FEC or FEC+T or other ECT (epirubicin plus cyclophosphamide plus docetaxel), FEC (fluorouracil plus epirubicin plus cyclophosphamide), FEC+T (fluorouracil plus epirubicin plus cyclophosphamide plus docetaxel)	32.9%	91.1%	100%	7 (8.9%)	LVEF drop ≥10% or to <50% at any time or symptomatic HF	Hypercholesterolemia: Calculated OR=1.60 CI (0.33–7.73) p=0.56 Crude OR=1.6 CI (0.3–7.7) Multivariate OR 0.7 CI (0.1–4.3)
Baron et al.[29]	Retrospective	2014	76	HER-2 all stages	Pre-treatment+(1-year trastuzumab) with or without prior anthracycline Adjuvant or palliative	28%	58%	100%	14 (18%)	≥16% decrease in LVEF or ≥10% decrease in LVEF to <50%.	Hyperlipidemia: Calculated OR 1.84 CI (0.52–6.43) p=0.34
Ben Kridis et al.[30]	Prospective	2020	50	HER-2 BC including metastatic	With/without anthracycline »taxane and trastuzumab Neoadjuvant, adjuvant or palliative	14%	76%	100%	6 (12%)	Asymptomatic decrease in LVEF of 10–15% from baseline to a below <50% or a decrease >15% of the LV LMS (peak systolic left ventricular longitudinal myocardial strain)	Hyperlipidemia: Calculated OR=0.38 CI (0.02–7.58) p=0.53 Adjusted OR=0.91 (0.74–1) p=0.67
Bergamini et al.[31]	Retrospective	2016	227	HER-2 EBC or locally advanced (stages I–IIIC)	Adjuvant/neoadjuvant trastuzumab with or without anthracyclines and/or taxanes	17.62%	50%	100%	33 (14%)	LVEF drop to <50% or >10% with or without signs and/or symptoms of HF	Hypercholesterolemia: Calculated OR=0.81 CI (0.29–2.249) p=0.69 Univariate OR=0.81 CI (0.29–2.24) p=NA

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Bergamini et al.[32]	Retrospective	2018	90	HER-2 EBC or locally advanced (stages I–IIIC)	Adjuvant/ neoadjuvant trastuzumab with or without anthracyclines and/or taxanes	21.1%	50%	100%	16 (17.8%)	LVEF drop to <50% or >10% with or without signs and/or symptoms of HF	Hypercholesterolemia: Calculated OR=0.21 CI (0.02–1.69) p=0.14
Blancas et al.[33]	Retrospective	2020	66	HER-2 all stages	Trastuzumab: neoadju-vant/adjuvant/both With or without anthracyclines and/or taxanes or other drugs	27.3%	87.9% no total	100%	29 (43.9%)	Asymptomatic drop in baseline LVEF ≤10% with a final value <50%, or any drop in LVEF accompanied by signs or symptoms of CHF or other cardiac symptom suggestive of CT	Hypercholesterolemia: Calculated OR=1.91 CI (0.88–4.12) p=0.10
Bonifazi et al.[34]	Retrospective	2013	2046	EBC	Adjuvant trastuzumab+ chemotherapy Yes 1845 (90.2) Adjuvant/ neoadjuvant/ undefined	2.6%	Insufficient data	100%	285 (14%)	ICD-9 code referring to possibly drug-induced cardiac disease in the main diagnosis (hospitalization)	Dyslipidemia: Calculated OR=2.28 CI (1.22–4.26) p<0.01
Eiger et al.[35]	Post-hoc analysis of the ALTTO trial*	2020	4190	HER-2 EBC	Adjuvant trastuzumab Trastuzumab vs. Trastuzumab+L (apatinib)	8.6% total* (7.9%) of patient in T+L arm vs. 197 (9.3%) in T arm	95% vs. 95%	100%	339 (8%)	Asymptomatic CE (cardiac event)=asymptomatic significant LVEF drop, defined as an absolute decline of at least 10 percentage points from baseline and to below 50% symptomatic CE=NYHA class II, III or IV HF associated with a significant LVEF drop. Cardiac death: death due to CHF, myocardial infarction or documented arrhythmia, or probable cardiac death within 24 h of a CE	Hypercholesterolemia: Calculated OR=0.99 CI (0.66–1.46) p=0.94 Adjusted OR=0.99 CI (0.66–1.46) p=0.94 Multivariate OR=0.90 CI (0.60–1.36) p=0.63

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Farolfi et al.[36]	Retrospective	2013	179	HER-2 EBC	Adjuvant trastuzumab with or without anthracycline and/or taxane	44%	90%	100%	16 (9%)	LVEF drop ≥15% or a drop to LVEF<50%	Hypercholesterolemia: Calculated OR=0.76 CI (0.26–2.19) p=0.61 Univariate OR=0.76 CI (0.26–2.19) p=0.61
Fried et al.[37]	Retrospective	2013	124	HER-2 EBC	Adjuvant or neoadjuvant treatment Anthracycline cyclophosphamide (AC), followed by taxol+trastuzumab (TH) OR taxotere, carboplatin, and trastuzumab (TCH) OR cyclophosphamide, anthracycline and fluouracil (CAF)	7%	90%	100%	12 (10%)	LVEF drop >10%	Insufficient data
Ganz et al.[38]	Post-hoc analysis of NSABP B-31*	2017	407 complete LVEF assess-ments: 110 in the control group and 297 in the trastuzumab group	HER-2 EBC	AC→P vs. AC→PH (trastuzumab) AC, doxorubicin and cyclophosphamide; H, trastuzumab; P, paclitaxel	3.7%	100%	72.2% of total	28/313 (eligible, con-sented) (9%)	LVEF drop >10% to a value <50% along with patient-reported outcomes	Hyperlipidemia: Calculated OR=2.89 CI (1.41–5.91) p=<0.01 Multivariable model for predicting low DASI score (<43) – baseline elevated lipid profile medication use: OR=1.92 CI 0.85–4.36 p=0.12
Gong et al.[39]	Retrospective	2016	3134	EBC	Adjuvant trastuzumab with or without anthracycline/taxane	9.3% events compo-site	78.9%	100%	55 (1.75%)	Composite endpoints: hospitaliza-tion/emergency room visit for HF or death	Dyslipidemia Various composite outcomes – composite of HF event or death: adjusted HR 0.65 CI (0.21–1.99) p=0.45

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Grazziotin et al.[40]	Prospective	2017	109	EBC or MBC	Adjuvant or palliative trastuzumab With or without anthracy-cline/taxane/hormone therapy	53.2%	8.3%	100%	17 (15.6%)	(1) LVEF drop ≥10%, (2) drop to <50% or (3) trastuzumab discontinuation without significant decrease in LVEF, due to important symptoms or signs of HF The secondary outcomes were hospitalization rate, emergency-seeking rate and trastuzumab discontinuation due to CT	Dyslipidemia: Calculated OR=0.76 CI (0.27–2.12) p=0.61 Univariate HR 1.47 CI (0.74–2.93) p=0.27
Guglin et al.[41]	Retrospective	2019	118 (adju-vant) 38 (metastatic) 156 (com-bined group)	HER-2 BC	>1-Year trastuzumab	48% total* 33.1% percent of adjuvant group vs. 34.2% com-bined group	93.2% adjuvant group 36.8% metastatic group	100%	12 (10.2%)	Time to development of cardiomyopathy (decline of LVEF by ≥10%, decline of LVEF to <50%, symptoms and physical signs of HF)	Dyslipidemia Calculated OR for EF<50 in adjuvant=0.56 CI (0.07–4.59) RR segregated for cardiomyopathy, LVEF <50, LVEF drop >10, HF symptoms=1.00 p=0.98; 0.57 p=0.84; 1.22 p=0.74, N/A p=0.60
Gunaldi et al.[42]	Retrospective	2016	111	Metastatic and non-metastatic BC	Adjuvant or palliative trastuzumab	16.21%	91.9%	100%	25 (22.52)	LVEF drop to <50% or drop >10% or any indication of HF	Hyperlipidemia (LVEF): Calculated OR=2.65 CI (0.90–7.79) p=0.08

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Kaboré et al.[43]	Prospective	2019	929	EBC	Anthracycline and/or trastuzumab	3.2%	93%	43%	92 (9.9%)	Reduction in LVEF >10% to LVEF<50%	Dyslipidemia: Calculated OR=2.47 CI (0.98–6.23) p=0.06 Univariate OR=2.46 CI (0.97–6.23) p=0.05
Kosalka et al.[44]	Retrospective	2019	243	HER-2 BC all stages	Trastuzumab with or without previous anthracycline	13.6% hospital-izatio	76.3	100%	28 (11.5%)	Asymptomatic drop in LVEF of more than 10% to <53%, or cardiac hospitalization	Insufficient data
Matos et al.[45]	Prospective	2016	92	HER-2 BC	Anthracycline+ adjuvant 1-year trastuzumab+ taxane concomitantly when indicated	23.9%	100%	100%	9 (9.8%)	Clinical signs and/or symptoms of HF or a drop in LVEF $\geq$10% in asymptomatic patients	Insufficient data
Piotrowski et al.[46]	Prospective	2012	253	HER-2 BC, no metasta-sis	AC (anthracycline cyclophos-phamide)/FEC (fluorouracil plus epirubicin plus cyclophosphamide)/ docetaxel/ endocrine when indicated Adjuvant trastuzumab for 1 year	20.6%	Insufficient data	100%	87 (34.4%)	(1) LVEF drop >15% (2) LVEF drop of 10% and below 50%, (3) any symptoms or signs of HF.	Hypercholesterolemia: Calculated OR=0.91 CI (0.48–1.74) p=0.77 OR=1.03 CI (0.53–2.01) p=0.93

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Piotrowski et al.[47]	Prospective	2013	253	HER-2 BC, no metastasis	AC (anthracycline cyclophosphamide)/ FEC (fluorouracil plus epirubicin plus cyclophosphamide)/ docetaxel/ endocrine when indicated Adjuvant trastuzumab for 1 year	31.7%	Insufficient data	100%	87 (34.4%)	(1) Left ventricular size (left ventricular end diastolic volume index, and left ventricular end systolic volume index), (2) LVEF, (3) left ventricular mass and structure, (4) left atrial size	Hypercholesterolemia: Multivariate OR= Hypercholesterolemia (i) changes after 6-month follow-up ≥SD of baseline value in at least one echo parameter (model I); (ii) changes after 6-month follow-up ≥2 SD of baseline value in at least one echo parameter (model II) I OR=0.76 CI (0.31–1.84) p=0.54 II OR=1.49 CI (0.70–3.19) p=0.31
Romond et al.[48]	Post-hoc analysis of NSABP B-31*	2012	944 trastuzumab arm and 743 in control arm	HER-2 BC, no metastasis	AC+trastuzumab with at least 1 dose of post-AC therapy	5% total* 4.0% trastuzumab vs. 1.3% control arm	100%	Arm with vs. arm without	70 (7.5%)	Time to cardiac toxicity A CE was defined as a definite or probable cardiac death or congestive HF manifested by dyspnea with normal activity or at rest and associated with an absolute decrease in LVEF of >10 percentage points from baseline to a value less than 55% or a decrease of more than 5% to a value below the lower limit of normal	Lipid medication: p=0.61 HR=0.69 CI (0.17–2.86) Calculated OR=0.69 CI (0.16–2.94) p=0.62

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Rossi et al.[49]	Retrospective	2016	681	MBC	Palliative	4.7%	Insufficient data	100%	90 (13.2%)	Hospitalization for one of the following conditions: myocardial infarction/ischemia, HF, rhythm disorders, or other cardiac disease after the first trastuzumab administration	Insufficient data
Russo et al.[50]	Retrospective	2012	499	HER-2 EBC	Adjuvant trastuzumab	26%	88%	100%	75 (15%)	Experience of at least one episode of CT	Dyslipidemia
Russo et al.[51]	Retrospective	2014	499	EBC	Previously treated with chemotherapy (anthracyclines, cyclophosphamide, taxanes, 5-fluorouracil, neoadjuvant)+trastuzumab (18 doses)	26.6%	88%	100%	75 (15%)	Onset of congestive HF	Dyslipidemia: Calculated OR=1.90 CI (0.60–6.10) p=0.28
Sato et al.[52]	Retrospective	2019	119	BC	Trastuzumab every 3 weeks with or without previous anthracycline	10.8%	60.5%	100%	24 (20%)	Overt HF or ≥10% LVEF drop to LVEF <55% in asymptomatic patients.	Dyslipidemia: Calculated OR=0.69 CI (0.14–3.36) p=0.65 Univariate OR=0.672 CI (0.16–2.89) p=0.59
Serrano et al.[53]	Retrospective	2012	45	Early or advanced BC	>1 dose trastuzumab-based regimen	17.8%	40%	100%	13 (28.9%)	Onset of symptomatic CT (drop ≥10% resulting in a final LVEF <50% or absolute drop >20%)	Dyslipidemia: Calculated OR=2.23 CI (0.55–9.02) p=0.26 Univariate p=0.25 Multivariate p=0.76

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Suter et al.[54]	Post-hoc analysis of HERA trial*	2007	1693 1678 used in trastu-zumab safety analysis	HER-2 BC early stage invasive	1 vs. 2 years of trastuzumab every 3 weeks	3.04% vs. 0.53%	100%	94%	74(4.4)	Disease-free survival and cardiac adverse event	Hyperlipidemia: Calculated OR=0.3525 CI (0.05–2.58) p=0.30 Difference in incidence=−2.39 CI (−5.87 to 1.09)
Tan-Chiu et al.[55]	Post-hoc analysis of NSABP B-31*	2005	814	HER-2 node-positive BC	Doxorubicin and cyclophosphamide (AC) followed by paclitaxel vs. AC followed by paclitaxel plus 52 weeks of trastuzumab	0.6% control vs. 3.6% trastuzumab	100%	Arm with vs. arm without	60 (7.4%)	Time to cardiac event	Elevated fasting lipid profile medications: Calculated OR CI (0.41–0.06) p=0.39 Elevated fasting lipid profile medications: Relative risk=0.44 CI (0.06–3.2) p=0.52
Tang et al.[56]	Retrospective	2017	160	HER-2 EBC	Adjuvant trastuzumab	21.3%	48.1%	100%	25 (15.6%)	Symptomatic HF or asymptomatic [decline in LVEF by ≥10% or LVEF ≤50%]	Hyperlipidemia: Calculated OR=1.21 CI (0.44–3.31) p=0.71
Tarantini et al.[57]	Retrospective	2012	499	EBC treated with trastuzumab	Adjuvant trastuzumab	27%	87%	100%	75 (15%)	Time to cardiac dysfunction LVEF/HF	Dyslipidemia (LVEF) Calculated OR 1.17 CI (0.68–2.01) p=0.57
Tarantini et al.[58]	Retrospective	2012	499	EBC treated with trastuzumab	Adjuvant trastuzumab	27%	87%	100%	75 (15%)	Drop of LVEF classified into five grades	Insufficient data

Table 1 (*Continued*)

Study	Design	*Year*	Sample size	Type of BC	Setting	CT rate	AC use rate	T use rate	DLP rate, n (%)	CT definition	DLP role
Ürun et al.[59]	Prospective	2015	52	HER-2 EBC+MBC	Trastuzumab either single-agent or combined with chemotherapy agents	9.6%	75%	100%	6 (11.5%)	Symptomatic HF or LVEF drop >10%	Hyperlipidemia: Calculated OR=0.58 CI (0.03–11.78) p=0.72
Vicente et al.[60]	Retrospective	2009	61	HER-2 BC	Adjuvant trastuzumab (excluding neoadjuvant)	32.8%	Insufficient data	100%	Insufficient data	LVEF <50% or ≥10% LVEF drop	Insufficient data
Wadhwa et al.[61]	Retrospective	2009	152	HER-2 BC	Adjuvant trastuzumab after FEC or AC AC adriamycin, cyclophophamide.	23.7%	100%	100%	20 (13.2%)	Onset of cardiac dysfunction (decline of 10% in LVEF)	Hyperlipidemia: Calculated OR=0.53 CI (0.15–1.92) p=0.33
Yoon et al.[62]	Retrospective	2016	712	BC all stages	Neoadjuvant/adjuvant anthracycline based, taxane-based, or combined regimens followed by adjuvant trastuzumab in some cases	11.5%	68%	15,7%	Not specified	LVEF <55% or LVEF drop >10%	Low triglyceride level: RR=0.995 CI (0.99–1.00) p=0.11
Yu et al.[63]	Retrospective	2015	573	HER-2 EBC	Adjuvant trastuzumab with or without previous adjuvant anthracyclines	16.1%	81.5%	100%	125 (21.8%)	LVEF drop ≥16% or LVEF drop of ≥10% to <55% with or without symptoms of HF	Hyperlipidemia: Calculated OR=1.15 CI (0.68–1.95) p=0.60 OR=1.15 CI (0.68–1.95) p=0.595

»: followed by; AC: doxorubicin plus cyclophosphamide; AC rate: anthracycline use rate; BC: breast cancer; CT: cardiotoxicity; CE: cardiac event; CI: confidence interval; DASI: Duke Activity Status Index; DLP: dyslipidemia; EBC: early breast cancer; echo: echocardiographic; FEC: 5-fluorouracil plus epirubicin plus cyclophosphamide; HF: heart failure; HR: hazard ratio; ICD-9: International Classification of Diseases, Ninth Revision; LVEF: left ventricular ejection fraction; MBC: metastatic breast cancer; NYHA: New York Heart Association functional class; OR: odds ratio; RR: risk ratio; SD: standard deviation; T: trastuzumab.

* Studies that analyzed risk factor data in databases provided by large randomized clinical trials. Data were collected referring specifically to dyslipidemia.

Table 1 summarizes the characteristics of the included studies.

Of the 39 articles included in the qualitative analysis, most were Italian[31–36,49–51,57,58] (n=9) or American[29,38,41,48,54,55,63] (n=7), and all were published between 2005[55] and 2020.[25,30,33,35] The shortest follow-up time was six months[47,61] and the longest was 9.5 years.[33] Seven studies were prospective and observational,[30,43,45–47,59] 27 were retrospective and observational,[29,31–34,36,37,39,41,42,44,49–53,56–58,60–63] and five were subanalyses of large trials[35,38,48,54,55] (of the ALTTO trial,[35] NSABP B-31,[38,48,55] and HERA.[54] The studies included a total of 21 079 patients (17 998 excluding those based on the same population[32,38,46,48,50,51,57]), with ages ranging from 20[27] to 92[53] years, and one study focused on the elderly population.[53] No mentions of male patients were found. The median sample size was 179 patients, ranging from 45[53] to 4190.[35]

Patients were treated in both (neo)adjuvant and palliative settings. Only 11 studies did not analyze HER-2 confirmed breast cancer.[26,34,39,40,42,43,49,51,52,58,62] Some studies had higher rates of anthracycline use and lower rates of trastuzumab therapy. This was most evident in Kaboré et al.[43] (43% patients treated with trastuzumab) and Yoon et al.[32] (15.7%). We tried to keep this bias to a minimum by excluding three articles in which trastuzumab use was less than 5% and were therefore judged to have inadequate intervention. These characteristics and other several variations in the treatment for adjuvant/neoadjuvant therapy, dosing, and regimen are further described in Table 1.

Dyslipidemia

The definition of dyslipidemia was similar between studies. Alghafar et al.[25] and Farolfi et al.[36] defined it as total plasma cholesterol >5.2 mmol/l or use of lipid-lowering medications, while Ganz et al.,[38] Romond et al.[48] and Tan-Chiu et al.[55] used only lipid medications as the marker for dyslipidemia. Matos et al.[45] defined dyslipidemia as a combination of low-density lipoprotein cholesterol >3 mmol or total cholesterol >5 mmol/l. Piotrowski et al.,[47] Russo et al.[50,51] and Tarantini et al.[57] defined dyslipidemia as total serum cholesterol >190 mg/dl or lipid-lowering therapy or triglycerides >150 mg/dl. Bonifazi et al.[34] used International Classification of Diseases, Ninth Revision (ICD-9) codes to identify patients diagnosed with dyslipidemia.

In our systematic review, after excluding articles dealing with the same populations,[32,38,46,48,50,51,57] lacking information on dyslipidemia prevalence,[60,62] and large subanalyses of RCTs,[35,38,48,54,55] we found the overall prevalence of dyslipidemia to be 11.32%, ranging between studies from 1.75%[39] to 43.9%.[33] In the meta-analysis this figure was 15.84% and in RCTs only, it was 7.01%.

Trastuzumab-induced cardiotoxicity

Most studies included in this systematic review defined cardiotoxicity as a ≤10–16% decline in LVEF, a decline in LVEF to <50–55%, or patients exhibiting signs and symptoms of heart failure.[25–33,35–38,40–46,48–63] All these studies used either echocardiography or multigated acquisition (MUGA) scan as a tool to serially assess LVEF. However, outcome definitions and assessment of results differed widely between different studies, with a vast array of descriptive terminology being used. Bonifazi et al.[34] defined the primary outcome as ICD-9 code reports referring to possibly drug-induced cardiac hospitalization in the main diagnosis, while Gong et al.[39] and Rossi et al.[49] defined it as hospitalizations due to cardiac events, and it was defined as use of medication in Ganz et al.,[38] Romond et al.,[48] and Tan-Chiu et al.[55] We also included other studies in which there were slight variations in the percentages of LVEF decrease[29,36,44,46,62,63] (Table 1), such as asymptomatic cardiotoxicity defined as LVEF drop ≥16%[29,63] or LVEF drop ≥15%,[36,46] or for symptomatic cardiotoxicity, LVEF drop ≥10% to LVEF <55%[62,63] or LVEF <53%.[44]

A detailed characterization of cardiotoxicity-related parameters is presented in Table 2. In this systematic review, excluding RCTs,[35,38,48,54,55] we found the overall incidence of TIC to be 11.94%, with 5.59% of patients presenting symptoms of heart failure. Performing the same calculation only for RCTs, we found these values to be 9.18% and 2.4%, respectively. In the primary meta-analysis, the cardiotoxicity rate was 13.55%.

In observational studies that provided data concerning discontinuation of trastuzumab, 11.13% of 3808 patients discontinued treatment temporarily or permanently due to cardiac complications. The figure was 6.61% when only RCTs were considered.

Furthermore, in studies that provided data concerning recovery of cardiac function after trastuzumab discontinuation, recovery was observed in 72.12% of patients discontinuing trastuzumab due to cardiac reasons.

Also, in studies reporting reintroduction of trastuzumab after discontinuation, we observed that 43.65% presented significant recovery of cardiac function that enabled continuation of therapy.

Association between dyslipidemia and trastuzumab-induced cardiotoxicity

Six of the included studies[28,31,36,43,52,53] presented univariate estimations of ORs concerning the role of dyslipidemia in trastuzumab-induced cardiotoxicity, while another six presented multivariate data.[26,28,35,38,47,53] In all other studies, we calculated ORs based on demographic data found in the reports.

Of the latter studies, only Bonifazi et al.[34] found a significant association (OR=2.28, 95% CI 1.22–4.26, p=0.01). The study's original summary measure was the hazard ratio (HR). This study identified the rate of severe cardiac adverse events among 2046 women treated with trastuzumab for early breast cancer, through a record linkage between health care databases and searches for records concerning ICD-9 codes referring to cardiac events and cardiovascular risk factors. A cumulative risk of cardiotoxicity was then estimated using the Kaplan-Meier method over a follow-up of three years. The predictors found were age and history of cardiac disease.

Other studies were close to the significance threshold. Gunaldi et al.[42] retrospectively assessed a sample of 111 women, however, a significant association between hyperlipidemia and LVEF decrease was not found (OR=2.65, 95%

Table 2 Characterization of cardiotoxicity events.

Study	Reintroduction of trastuzumab	Recovery	Discontinuation of trastuzumab due to CT	Cardiac death	CT rate	DLP patients	DLP rate	*CT*	Symptomatic CT	Total patients treated with trastuzumab
Abd Alghafar et al.[25]	13	22	29	1	24%	32	21.92%	35	15	146
Abdel-Razaq et al.[26]	No data	No data	No data	No data	21.90%	30	20.5%	32	24	146
Aldiab[27]	No data	No data	11	0	11.20%	24	24%	11	5	98
Ayres et al.[28]	No data	No data	13	No data	32.9%	7	8.9%	26	12	79
Baron et al.[29]	4	12	17	No data	28%	14	18.00%	21	1	76
Ben Kridis et al.[30]	3	No data	7	0	14%	6	12.00%	7	2	50
Bergamini et al.[31]	No data	No data	No data	No data	17.62%	33	14.00%	40	5	227
Blancas et al.[33]	No data	No data	No data	No data	27.30%	29	43.9%	18	12	66
Bonifazi et al.[34]	No data	No data	No data	2	2.60%	285	14.00%	53[a]	28[b]	2046
Farolfi et al.[36]	24	24	30	No data	44%	16	9.00%	78[c]	4	179
Fried et al.[37]	5	5	9	No data	22.4%	12	10.00%	26	4	124
Gong et al.[39]	No data	No data	No data	No data	9.3% composite HF/death events composite[a]	55	1.75%	291	291[d]	3134
Grazziotin et al.[40]	22		34	1	53.20%	17	15.6%	58	10	109
Guglin et al.[41]	11		23	1	48% total 33.1% of adjuvant group vs. 34.2% combined group	12	10.2%	39	11	118
Gunaldi et al.[42]	7	7	18	No data	16.21%	25	22.52%	18	9	111
Kaboré et al.[43]	No data	No data	No data	No data	3.20%	92	9.9%	29	No data	929
Kosalka et al.[44]	No data	No data	No data	No data	13.6%	28	11.5%	33[e]	33	243

Table 2 (*Continued*)

Study	Reintroduction of trastuzumab	Recovery	Discontinuation of trastuzumab due to CT	Cardiac death	CT rate	DLP patients	DLP rate	*CT*	Symptomatic CT	Total patients treated with trastuzumab
Matos et al.[45]	No data	No data	0	0	23.90%	9	9.8%	22	0	92
Piotrowski et al.[46]	13	33	52		20.60%	87	34.4%	52	9[f]	253
Rossi et al.[49]	No data	No data	No data	Unspecified cardiac death	4.7%	90	13.2%	32[g]	32	681
Sato et al.[52]		13	13	0	10.80%	24	20.00%	13	2	119
Serrano et al.[53]	5	11	12	No data	17.80%	13	28.9%	12	4	45
Tang et al.[56]			6	No data	21.3%	25	15.6%	34	7	160
Tarantini et al.[58]	13	13	24	0	27%	75	15.00%	133	15	499
Ürun et al.[59]		3	5	No data	9.60%	6	11.5%	5	2	52
Vicente et al.[60]	7	9	14	0	32.8%	No data	No data	19	12	61
Wadhwa et al.[61]	4	20	36	No data	23.70%	20	13.2%	36	5	152
Yoon et al.[62]		9	14	Unspecified cardiac death	11.50%	No data	No data	82	59	712
Yu et al.[63]	27	57	57	No data	16.10%	125	21.8%	92	18	573

CT: cardiotoxicity; DLP: dyslipidemia; HF: heart failure.

The table does not include studies in which different analyses of the same samples were performed.[32,38,46,48,50,51,57]

[a] Hospitalizations due to cardiac events.

[b] Heart failure.

[c] Cardiac events: four cases of heart failure (New York Heart Association class III or above).

[d] Refers to composite heart failure/death in both columns, since information on asymptomatic cardiotoxicity was not provided.

[e] Refers to cardiac hospitalizations in both columns.

[f] Six severe, symptomatic heart failure, one left bundle branch block, two negative T waves V1-6 on the electrocardiogram.

[g] Refers to cardiac hospitalizations in both columns.

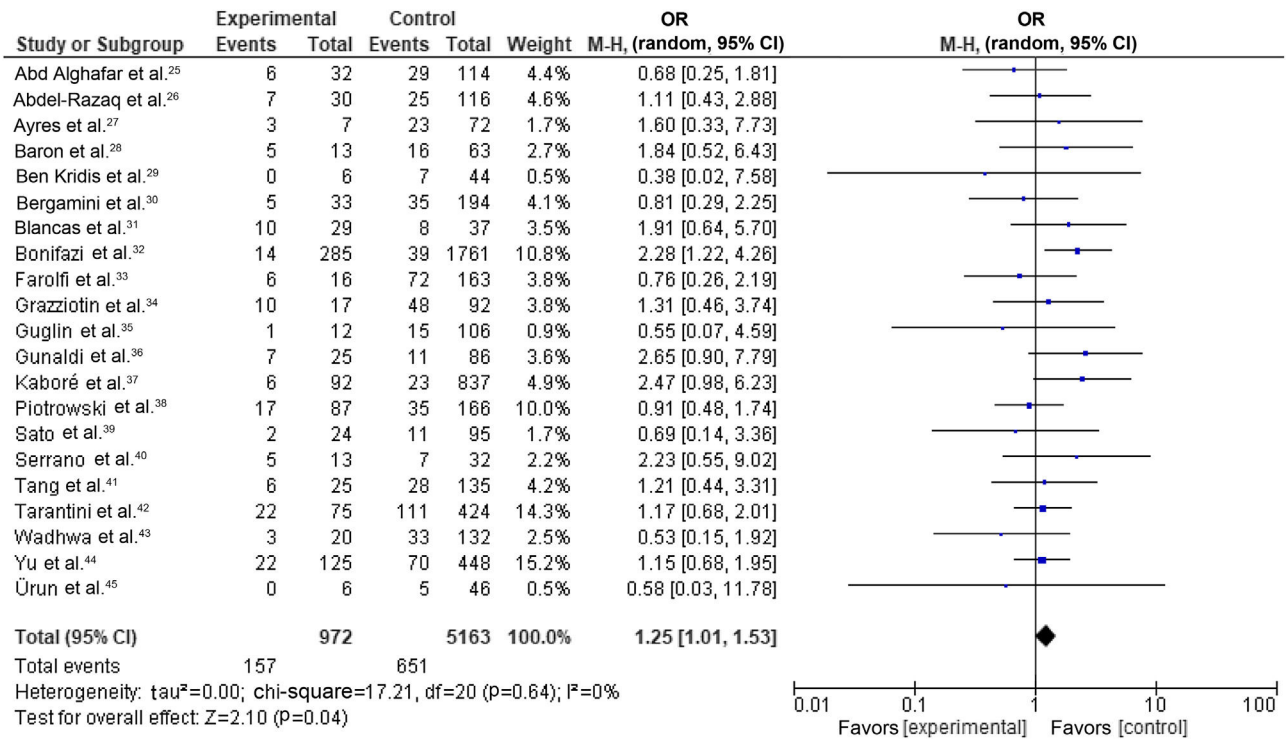

Figure 2 Forest plot representing the effect on cardiotoxicity of dyslipidemia compared with the absence of a diagnosis of dyslipidemia in trastuzumab-based breast cancer treatment (odds ratio with 95% confidence interval, random effects meta-analysis). CI: confidence interval; OR: odds ratio; SE: standard error.

CI 0.90–7.79, p=0.08). Kaboré et al.[43] used prospective data in a French national multicenter study aiming to examine the association of body mass index (BMI) and cardiotoxicity defined as a decrease in LVEF in a total of 929 patients. In multivariate analysis, obesity was independently associated with cardiotoxicity. However, no significant association was found for dyslipidemia on univariate analysis (OR=2.46, 95% CI 0.97–6.23, p=0.05). This proximity to significance may also be in part explained by the low rates of trastuzumab use (43%).

Furthermore, studies that performed subanalyses of large RCTs,[35,38,48,54,55] including studies reporting multivariate measures,[35,38] did not observe such an association either: OR=0.90, 95% CI 0.60–1.36, p=0.63 as observed in Eiger et al.[35] and OR=1.92, 95% CI 0.85–4.36, p=0.12 for the association between baseline elevated lipid profile medication use and low Duke Activity Index Status score in Ganz et al.[38]

Other studies were not included in the meta-analysis because of unavailability of data to calculate OR. These studies used other summary measures such as risk ratio (RR)[41,55,62] or HR,[39,40,48] however, they also failed to find an association. Of note that one of these studies performed rigorous adjustments for HR.[39]

Our random-effects meta-analysis encompassed 21 studies[5,25,26,28–31,33,34,36,40–43,46,53,56,58,59,61,63] and included 6135 patients. The prevalence of dyslipidemia was 15.84%. The pooled estimate for the OR of cardiotoxicity for individuals with dyslipidemia undergoing trastuzumab treatment for breast cancer was 1.25 (95% CI 1.01–1.53, p=0.04, I^2=0%) (Figure 2).

We also performed a subgroup analysis by selecting only studies reporting the most adjusted results,[26,28,30] which resulted in a pooled estimate for the OR of cardiotoxicity for individuals with dyslipidemia undergoing trastuzumab treatment for breast cancer of 0.89 (95% CI 0.73–1.10, p=0.28, I^2=0%) (Figure 3). However, one study[30] demonstrated a disproportionate weight in the pooled result, but it did cause significant heterogeneity.

Heterogeneity and risk of bias

There were no significant differences between individual studies in the magnitude of the association between dyslipidemia and cardiotoxicity in our primary meta-analysis, as indicated by the statistical test for heterogeneity (tau^2=0.00; chi-square=17.21, df=20 [p=0.64]; I^2=0%).

However, across studies, the treatment was heterogeneous due to the use of different regimens (Table 1), which makes it difficult to define the effect specifically caused by dyslipidemia in the setting of trastuzumab therapy.

The quality of the studies and the risk of bias were assessed at the study level using the method of Haffar et al.[18] Overall, we judged 13 studies to be of moderate quality, 12[27,29,33,36,40–42,44,52,53,59,61] due to incomplete exclusion of pre-existing LVEF impairment and one due to lack of specification of the tool used for outcome assessment.[34] One study was deemed to be of low quality[49] because of failure to collect diagnosis details and unclear diagnostic method. The results of this assessment are shown in Table 3.

Publication bias and small-study effects were assessed for all collected variables, as demonstrated by the funnel

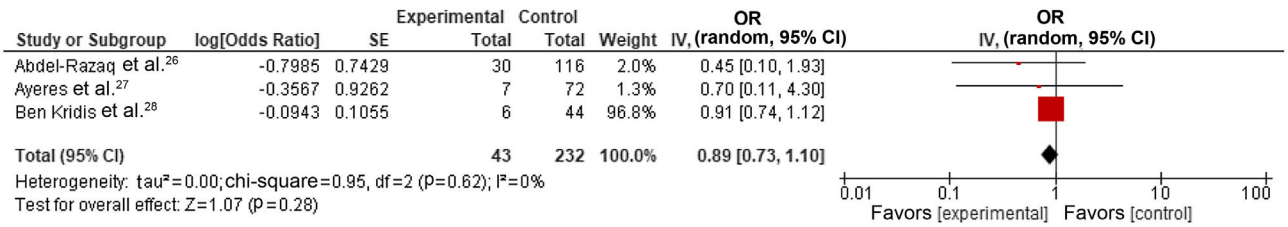

Figure 3 Forest plot representing the effect on cardiotoxicity of dyslipidemia compared with the absence of a diagnosis of dyslipidemia in trastuzumab-based breast cancer treatment only in studies reporting adjusted data (odds ratio with 95% confidence interval, random effects meta-analysis). CI: confidence interval; OR: odds ratio; SE: standard error.

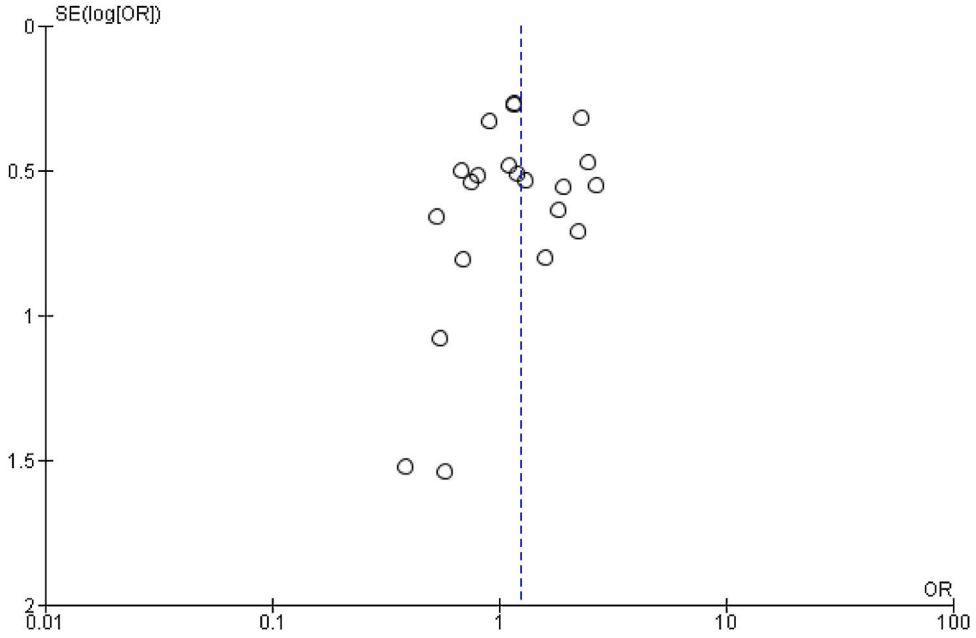

Figure 4 Funnel plot of included studies. OR: odds ratio; SE: standard error.

plot of data from the 21 studies included in the meta-analysis of raw ORs, which was asymmetrical (Figure 4). These data indicate that included studies with small sample sizes appear to underestimate the effect of dyslipidemia.

Discussion

To our knowledge, this is the most comprehensive and up-to-date systematic review and meta-analysis studying the effect of dyslipidemia on TIC. Overall, most studies (38 out of 39), adjusted or otherwise, did not observe an association between dyslipidemia and cardiac events. The quantitative analysis using random-effects model meta-analysis of raw demographic data yielded an OR of 1.25 (95% CI 1.01–1.53, p=0.04, I^2=0%). However, subgroup analysis using only the most adjusted measures failed to observe this association (OR=0.89, 95% CI 0.73–1.10, p=0.28, I^2=0%).

Is dyslipidemia a predictor of trastuzumab-induced cardiotoxicity?

Despite the existence of a plethora of studies on the mechanisms and characteristics of TIC, there remains ambiguity concerning robust clinical predictors for this complication. The systematic review by Jawa et al.[13] identified hypertension, diabetes, age, and previous anthracycline use as risk factors for a cardiac event, but failed to prove other associations with known risk factors, including dyslipidemia. Attempts have also been made to develop risk scores that will predict rates of heart failure and cardiotoxicity to enable appropriate monitoring in this group,[48,64] considering such factors as baseline LVEF,[48] age,[48,64] adjuvant chemotherapy, coronary artery disease, atrial fibrillation or flutter, diabetes, hypertension, and renal failure.[65]

Dyslipidemia is linked with heart failure and coronary heart disease in the general population.[14] There have been several animal and human studies that point to the beneficial effect of statins in the context of TIC,[66–68] and a study has shown that rats fed a high-lipid diet are more sensitive to anthracycline-induced cardiotoxicity.[65] We therefore hypothesized that dyslipidemia may play a role in TIC. A previous meta-analysis[13] failed to show such an association; however, most of the literature had been based on small samples and there was a lack of studies presenting formal multivariate adjustment, hence the need for an up-to-date and comprehensive systematic review on this topic.

Table 3 Assessment of article quality according to the method used by Haffar et al.[18]

Study	Did the patients represent the whole experience of the medical center?	Was the diagnosis correctly made?	Were other important diagnoses excluded?	Were all important data cited in the report?	Was the outcome correctly ascertained?	Overall quality assessment
Abd Alghafar et al.[25]	Yes	Yes	Yes	Yes	Yes	Good
Abdel-Razaq et al.[26]	Yes	Yes[a]	Yes	Yes	Yes	Good
Aldiab[27]	Yes	Yes[a]	No	Insufficient data to calculate OR	Yes	Moderate
Ayres et al.[28]	Yes	Yes[a]	Yes	Yes	Yes	Good
Baron et al.[29]	Yes	Yes[a]	No	Yes	Yes	Moderate
Ben Kridis et al.[30]	Yes	Yes[a]	Yes	Yes	Yes	Good
Bergamini et al.[31]	Yes	Yes[a]	Yes	Yes	Yes	Good
Bergamini et al.[32]	Yes	Yes[a]	Yes	Yes	Yes	Good
Blancas et al.[33]	Yes	Yes[a]	No	Yes	Yes	Moderate
Bonifazi et al.[34]	Yes	Yes	Yes	Yes	No	Moderate
Eiger et al.[35]	Yes	Yes[a]	Yes	Yes	Yes	Good
Farolfi et al.[36]	Yes	Yes	No	Yes	Yes	Moderate
Fried et al.[37]	Yes	Yes[a]	Yes	Insufficient data to calculate OR	Yes	Good
Ganz et al.[38]	Yes	Yes	Yes	Yes	Yes	Good
Gong et al.[39]	Yes	Yes[a]	Yes	Insufficient data to calculate OR	Yes	Good
Grazziotin et al.[40]	Yes	Yes[a]	No	Yes	Yes	Moderate
Guglin et al.[41]	Yes	Yes[a]	No	Yes	Yes	Moderate
Gunaldi et al.[42]	Yes	Yes[a]	No	Yes	Yes	Moderate
Kabore et al.[43]	Yes	Yes[a]	Yes	Yes	Yes	Good
Kosalka et al.[44]	Yes	Yes[a]	No	Insufficient data to calculate OR	Yes	Moderate
Matos et al.[45]	Yes	Yes	Yes	Insufficient data to calculate OR	Yes	Good
Piotrowski et al.[46]	Yes	Yes	Yes	Yes	Yes	Good
Piotrowski et al.[47]	Yes	Yes	Yes	Yes	Yes	Good
Romond et al.[48]	Yes	Yes	Yes	Yes	Yes	Good
Rossi et al.[49]	Yes	Yes[a]	Yes	No+insufficient data to calculate OR	No	Low
Russo et al.[50]	Yes	Yes	Yes	Yes	Yes	Good
Russo et al.[51]	Yes	Yes	Yes	Yes	Yes	Good
Sato et al.[52]	Yes	Yes[a]	No	Yes	Yes	Moderate
Serrano et al.[53]	Yes	Yes[a]	No	Yes	Yes	Moderate
Suter et al.[54]	Yes	Yes[a]	Yes	Yes	Yes	Good
Tan-Chiu et al.[55]	Yes	Yes	Yes	Yes	Yes	Good
Tang et al.[56]	Yes	Yes[a]	Yes	Yes	Yes	Good
Tarantini et al.[57]	Yes	Yes	Yes	Yes	Yes	Good
Tarantini et al.[58]	Yes	Yes	Yes	Yes	Yes	Good
Ürun et al.[59]	Yes	Yes[a]	No	Yes	Yes	Moderate
Vicente et al.[60]	Yes	Yes[a]	Yes	Insufficient data to calculate OR	Yes	Good
Wadhwa et al.[61]	Yes	Yes[a]	No	Yes	Yes	Moderate
Yoon et al.[62]	Yes	Yes[a]	Yes	Insufficient data to calculate OR	Yes	Good
Yu et al.[63]	Yes	Yes[a]	Yes	Yes	Yes	Good

OR: odds ratio.
[a]Not specified, probably adequate.

This systematic review was planned and designed to assess the association between dyslipidemia and TIC in breast cancer patients and included 39 studies found by a systematic search regarding this topic.

We found the overall prevalence in this systematic review of dyslipidemia in observational studies to be 11.32%, ranging between studies from 1.75%[39] to 43.9%.[33] This wide range may be explained because a large proportion of patients excluded in our primary analysis were in subanalyses of data from large RCTs,[35,38,48,54,55] in which the dyslipidemia prevalence was 7.01%. These trials included relatively healthier and younger patients. Consequently, there is a risk that it may inadequately represent the real-world breast cancer population, who may present with a higher prevalence of risk factors, including dyslipidemia. Indeed, a major research concern in oncology is the lack of information on elderly populations.[69] This question was addressed in a study included in our review that included a population with a median age of 75.9 years[53] and that presented a higher prevalence of dyslipidemia (28.9%) than most included studies.

We documented a significant rate of TIC in this population, around 12.0% in the overall review of observation studies, which is consistent with previously reported data.[13,70] A recent pooled analysis of adjuvant trials investigated the incidence of TIC and its impact on treatment completion.[70] The incidence of symptomatic heart failure in our meta-analysis was 3.18%, which was slightly higher than the figure reported by these authors (2.3%). This suggests that cardiotoxicity may be more frequent outside clinical trials, as observed in recent retrospective cohorts.[4]

In the qualitative and quantitative synthesis of the data, only one study, Bonifazi et al.,[34] showed a clear association between dyslipidemia and trastuzumab-induced cardiotoxicity (OR=2.28, 95% CI 1.22–4.26, p=0.01). This study had the third largest sample size (2046 patients); however, ICD codes were used for both identification of patients diagnosed with dyslipidemia and the incidence of cardiac events (defined as hospitalization). Hence, we judged this study to be at moderate risk of bias for our meta-analysis, and thus the results in the meta-analysis of unadjusted measures may be overestimated due to the weight of this study. Other studies appear to suggest an association; however, in none did it achieve statistical significance.[33,42,43] These findings are further supported by the absence of association found in our subgroup analysis, which only took into consideration adjusted measures. However, it is of note that studies were also unclear about their methods of adjustment, with only Ayres et al.[28] specifying that their adjustments controlled for age and BMI.

In our meta-analysis, an association of dyslipidemia with TIC was observed in the pooled data from raw ORs in observational studies. This association was not supported by a subgroup analysis of studies reporting the most adjusted measures. This suggests that the role of dyslipidemia may merit further attention, since it is a condition that often exists in interplay with other comorbidities in a synergistic interaction. Indeed, obesity,[35,42,43,59,71] diabetes,[13,35,59,65] and hypertension[13,30,38,42,47,49] are factors reported to be associated with TIC, which suggests that metabolic syndrome as a whole could be linked to this complication. A study by Kosalka et al.[44] found that, compared with any risk factor alone, the combination of two or three comorbidities (such as diabetes, dyslipidemia, and obesity) is associated with a significant increase in the incidence of symptomatic cancer therapy-related cardiotoxicity.

Strengths and limitations

This systematic review was conducted according to the PRISMA guidelines.[15,16] Data selection was rigorous, and the analysis was thorough. We were also conservative in our analysis, as undefined data were not considered and the most precise and adjusted measures were extracted for a subgroup analysis.

However, this study has all the limitations inherent to systematic reviews and meta-analyses, particularly of observational studies. Overall, we judged thirteen studies to be of moderate quality[27,29,33,34,36,40–42,52,53,59,61] and one of low quality.[49] There is considerable heterogeneity between the included studies concerning sample size, therapeutic regimens, cancer stages and molecular profiles, patient demographics, and inclusion/exclusion criteria and follow-up in each study.

The fact that advanced cancer predisposes to further doses of treatment should be taken into consideration, since it may enhance the risk for cardiac harm and consequently overestimate the incidence of cardiotoxicity. Furthermore, different imaging modalities were used, particularly MUGA scans as opposed to echocardiography, which is currently considered the preferred imaging modality for surveillance.[72] We should also bear in mind that there is still no clear consensus on the correct definition of cardiotoxicity, hence our outcome aggregates subclinical and clinical cardiotoxicity as a single endpoint. This highlights the need to create a universally acceptable definition of cardiotoxicity in this setting that could be uniformly used in future trials.

Although we tried to minimize the risk of selection bias by performing a wider initial search for all possible risk factors for TIC, the studies included were not specifically designed to address this question and the definitions of dyslipidemia were not always stated and differed between studies. This led to bias in data collection, as we were only able to extract data from studies in which the authors considered dyslipidemia to be a relevant factor.

Clinical relevance

Although our systematic review and meta-analysis found an association between dyslipidemia and cardiotoxicity in a pooled estimation of unadjusted data, the same did not apply for the meta-analysis of multivariate measures. Hence, in the absence of other relevant cardiovascular risk factors, routine review of these patients' lipid profile may not be as important as previously thought. Also, breast cancer patients who are candidates for trastuzumab therapy and who present isolated dyslipidemia should probably not be considered at high risk for the development of cardiotoxicity and can be managed in the same way as patients with no dyslipidemia, without referral for cardio-oncology assessment.

Conclusion

TIC is responsible for a significant burden in breast cancer treatment, causing an increase in morbidity and mortality. Although there is concern about the role of dyslipidemia in TIC, our study was not able to provide conclusive evidence to identify dyslipidemia as a risk factor for TIC. These findings, however, should not be taken as definitive, as the data are insufficient and extracted from observational studies at risk of various biases.

As such, a low-bias, adequately powered RCT designed to clarify this question and additional systematic reviews on the topic of the real predictive value of cardiovascular risk factors in the development of TIC would be of significant scientific and clinical value.

Even so, this review may provide valuable support for stratifying the risk for this effect, and help to manage and avoid adverse outcomes in these patients, particularly if integrated into a system to predict the risk of this complication in each patient. These questions and the role of other specific factors should be addressed in future studies.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A

Queries used in the electronic database search

Our search was performed using the following queries:

MEDLINE:

((''trastuzumab''[MeSH Terms] OR ''trastuzumab''[Title/ Abstract] OR ''pertuzumab''[Title/ Abstract] OR ''lapatinib''[Title/ Abstract] OR ''neratinib''[Title/ Abstract]) AND (''cardiotoxicity''[MeSH Terms] OR ''cardiotox*''[Title/ Abstract] OR (''cardiac''[Title/ Abstract] AND ''toxi*''[Title/ Abstract]) OR ''LVEF''[Title/ Abstract] OR ''cardiomyopathy''[Title/ Abstract])) NOT (animal[mh] NOT human [mh]) NOT ((Review[pt]) OR (meta-analysis[pt]) OR (practice-guideline[pt]))

Scopus:

(TITLE-ABS (*trastuzumab*) OR TITLE-ABS (*pertuzumab*) OR TITLE-ABS (*lapatinib*) OR TITLE-ABS (*neratinib*)) AND (TITLE-ABS (*cardiotoxicity*) OR TITLE-ABS (*cardiotox**) OR (TITLE-ABS (*cardiac*) AND TITLE-ABS (*toxi**)) OR TITLE-ABS (*lvef*) OR TITLE-ABS (*cardiomyopathy*)) AND NOT (TITLE-ABS (*animal*) AND NOT TITLE-ABS (*human*)) AND (LIMIT-TO (DOCTYPE, ''*ar*''))

Web of Science:

TS=(trastuzumab OR pertuzumab OR lapatinib OR neratinib) AND TS= (cardiotoxicity OR cardiotox* OR (cardiac AND toxicity) OR Cardiomyopathy OR LVEF) NOT TS=(animal NOT human) Refined by: DOCUMENT TYPES: (ARTICLE)

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