Global Scientific JOURNALS

GSJ: Volume 11, Issue 11, November 2023, Online: ISSN 2320-9186
www.globalscientificjournal.com

CARDIOTOXICITY INDUCED BY TYROSINE KINASE INHIBITORS

Badr I. Alrufaiq, Mashan L Abdullah , Hani A Al-suwayeh

Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Kingdom of Saudi Arabia
Mashan L Abdullah,Hani A Al-suwayeh
King Abdullah International,Medical Research Center, P.O. Box 2457, Riyadh, 11451, Kingdom of Saudi Arabia.
Department of Pharmacology and Toxicology, College of Pharmacology, King Saud University, P.O. Box 2457, Riyadh, 11451, Kingdom of Saudi Arabia.

alrufaiqba@ngha.med.sa

KeyWords

Beta blocker (BB), cardiotoxicity, Trastuzumab, angiotensin receptor blockers (ARBs), Trastuzumab induced cardiotoxicity (TIC), Angiotensin-converting enzyme (ACEI) inhibitors.

ABSTRACT

Prevents cardiovascular toxicity caused by trastuzumab in breast cancer patients treatment, after treatment interruption. The effectiveness of administration of beta blockers , angiotensin receptor blockers and angiotensin converting enzyme inhibitors during trastuzumab chemotherapy in preventing cardiotoxicity evaluated by recent randomized controlled trial (RCT). Prevents cardiovascular toxicity caused by trastuzumab in breast cancer patients, after treatment interruption. The efficacy of administration of beta blockers , angiotensin receptor blockers and angiotensin converting enzyme inhibitors evaluated by recent randomized controlled trial (RCT) during the treatment with trastuzumabin preventing cardiovascular diseases. This preventing treatment did not decrease cardiotoxicity occur in compared to controls (Odds Ratios OR = 0.90, 92% CI 0.64–1.86, p = 0.85).Comes about comparable for , angiotensin receptor blockers, angiotensin converting enzyme inhibitors and beta-blockers. The treatment with , angiotensin receptor blockers, angiotensin converting enzyme inhibitors driven a critical, increment in LVEF patients compared to the placebo treatment gather. As it were two thinks about detailed less probability of suspension of trastuzumab treatment. More satisfactorily fueled RCTs are required to decide the adequacy of schedule prophylactic treatment.

INTRODUCTIN

Breast cancer is the most commonly indicated cancers in females [1, 2] . An estimated 15 to 25% of human breast cancers overexpress an oncogene growth factor molecule called human epidermal receptor 2 (HER-2), that is associated with malignancy[3, 4]. This“HER-2 positive” cancers can be treated with biologic drug calledtrastuzumab[1, 5]. The administration of trastuzumab has leading to a 40–50% relative overall survival has been improved, and these patients could expect a 10 year survival rate of up to 90% [6, 7]. The most important advers effects of trastuzumab is cardiotoxicity, that is the main reason for discontinuation of trastuzumab[1, 8, 9]. Cardiotoxicity is defined as decrease in left ventricular ejection fraction (LVEF) or present cardiotoxicity caused disturbance in heart function [10].The presence of cardiac toxicity due

to trastuzumab can range from 7 to 10% of treated patients[5, 11],However, no symptoms can be predicted with certainty. These numbers may vary clinically depending the cohorts diseases and follow-up methods. Current guidelines recommend reassessing left ventricular ejection fraction LVEF every 2 months whiletrastuzumab treatment using echocardiographic or clinical signs to detect cardiac toxicity and guideing continuation of treatment[1, 8].

According meta-analyses and *the European Society of Cardiology (ESC).* 2022. guidelines[12] for treating the cardiotoxicity, Except dexrazoxane, most studies and drugs remain angiotensin II receptor blocker (ARBs), beta blockers and angiotensin converting enzyme inhibitors (ACEIs)[6, 13]. A small, different studies shown that neurohormonal inhibitors make the onset of cardiotoxicity delayed in patients receiving chemotherapy such as anthracyclines or human epidermal receptor 4 inhibitors , growth factor receptor 2 inhibitors [10]. The ability of these drugs to treat HFrEF may prevent cardiotoxicity without stopping chemotherapy by administration of Beta Blockers, angiotensin converting enzyme inhibitorsand ARBs in breast cancer patients, even before heart attack [14]. This mannerwilldecrease secondary progression of HFrEF before clinical examinationsand between echocardiographic detection. The most meta-analyses focused on the prevention of cardiovascular disease in breast cancer womanwho receiving manyvarieties of chemotherapy[5, 8, 15]. Therefore, they evaluated cardioprophylaxis in breast cancer woman who receiving mixed chemotherapy anthracycline and trastuzumab). NO body focusedon (HER2) positive patients receiving trastuzumab. Thetwo reasons for paucity of publications on cardiovascular disease preventioncaused bytrastuzumab. The first reason may be the over use of anthracyclines and the second reason is very small number of patients in the study.

Many systematic review suggested to fill this gap by evaluating the effect ACE inhibitors, ARBs and Beta Blokers on the presence of cardiotoxicity iin patients who trastuzumab recipients without prior HF and breast cancer[5, 12].

The mainobjectin thesystematic review was to assess cardiovascular effect by summarizing the cardioprotective effect of drugs (BB, ACEI, or ARB) compared with in effective drugplacebo in patients with HER2positive breast cancer receiving trastuzumabtreatment and not HF index at the beginning treatment. Secondary objectives were to compare ACE inhibitors, ARBs and BBs for cardiovascular disease protection by counting of number of patients who discontinued trastuzumab.the changes in LVEF and global longitudinal strain (GLS) after 2 months of treating and the changes in serologica cardiac biomarkers. the objectives were achieved by comparing the patients who taking single or combined cardioprotective drugs with those who did notplacebo[8].

Materials and Methods

The systematic review and meta-analysis was conducted based on the PICO framework and PRISMA 2020 guidelines [16]. RCTs, observational studies, SRs and MAs were studied. Papers presented at conferences and papers in abstract format were excluded.MEDLINE—PubMed, EMBASE, and the Cochrane Library were searched in English from 2000 to 2022 using a set of keywords. A literature review of systematic reviews and meta-analysis was performed.

Search Strategy, Inclusion Criteria and Results

The database review process (MEDLINE—PubMed, EMBASE and the Cochrane Library) included studies from 1990 to January 2023. Reference lists cited in systematic reviews and meta-analyses based on the same or similar topics were examined.The search strategy was performed in individual databases using many keywords. Examplescardiotoxicity, cardiac dysfunction, chemotherapy, primary prevention, prophylaxis, cardioprotective drugs,cardioprotective drug, cancer, breast cancer,trastuzumab, HER2positive cancer, Beta blockers, Angiotensin receptor blockers and Angiotensin conversion Enzyme inhibitors. Anycombination fromtwo or more keywords used with cardiotoxicity and prevention being mandatory in the search. The search strategy need filters to include results of studies conducted in English as the studies mentioned above.

The patient intervention compared with outcome result was used to made the inclusion criteria. Our Inclusion criteria were many studiesin women with (HER2 positive) breast cancer disease with normal ejection

fraction and GLS at baselinewithout clinical symptoms and symptoms of HF. All patients have the same age of the group. There is no patient received a less studied cardioprotective regimen before trastuzumabtreatment. The most patientsfollowed-up for2 months. Methods for comparing drugs, drug and placebo, drug and drug, combination and placebo.Theooutcomesresistance, ineffectiveness, the side effects of the used cardioprotectivedrugsmust be explained . The mainly result is heart disease. This is defined as a fall in LVEF of more than 10% from baseline or a fall in LVEF of less than 50% from baseline [2]. Secondary outcomes of interest were the number of patients who discontinued trastuzumab treatment, changes in measured echocardiographic parameters (LVEF, GLS), and observed changes in serum biomarkers during follow-up.

Data Collection and Extraction

Studies were identified and assessed for inclusion by two independent authors (N.K. and K.G.) using the search strategy mentioned above.The systematic review was performed independently by two authors and included only RCTs. Discrepancies that arose between the two investigators were resolved by a third reviewer (D.F.) who acted as a referee after an extensive review of the data. Data extracted included information on the study, the method, the population, intervention and outcome results. Data were taken from 2002 to May2023. Outcomes included mainly primary prevention the cardiovascular toxicity associated with HER2 positive patients receiving trastuzumab treatment . The paper selected based on the main title, abstract and Methodology. Then, we studied well full text in the papers and selected the studies that appropriate to inclusion criteria. In every article, we identify key points related to the study results. Pre-specified attribute data for the eeffect of the Primary prevention of heart disease and what isthe cardiotoxicity?And Whether the medications for HER2 positive patients was trastuzumabchemotherapy alone orin combination withtrastuzumab and other chemotherapy drugs was reported in the statistical analysis. The Trastuzumab group, the cardioprotective regimen and the dose at which this drug was used, the characteristics of the study population, the Procedure; type of measurements and clinical trials performed on patients, duration of trastuzumab chemotherapy, duration of follow-up.

Quality Assessment

The think about quality was surveyed utilizing the GRADE score. The GRADE criteria were connected to the generally examination of our results in arrange to grade the certainty of prove. Six spaces of the GRADE criteria were considered: arbitrary grouping era, allotment concealment, blinding, result information, announcing predisposition and other inclinations or biases. Bias predisposition was outlined in a plot additionally evaluated using Egger's scale which graphically shown the probability of bias for assumptions.Inthe studies gotten the ultimate review scale as: high, Moderate and low. Exceptionally low evaluated thinks about avoided from our meta-analysis. Chance of population and bias risk were freely surveyed by the two authors(N.K. and K.G.) using the Cochrane risk-of-bias (RoB2) tool [5, 17]. Disagreements were resolved by the third referee.

Statistical Analysis

All analyzes were performed using a random effects model as inRevMan version 5.5.2 statistical tools. The main outcomes of interest were cardiac work function assessed by detect LVEF or GLS,the discontinuation of HER2 trastuzumabtreatment, and the changes in cardiac serological biomarkers. For different outcomes (number of patients with discontinuation of HER2 therapy and cardiotoxicity), the difference was expressed at the odds ratio with 99%, confidence interval (CI) parameters and continued, respectively, the mean and 90% CI. Results changes in FEVI and GLS.The random effects model Mantel-Haenszel (M-H) was used for random outcomes and the random effects modelinverse variable was used for detect the outcomes.

To make sure that data collection in consistency, many studies showing results in consistent with the of cardiotoxicity, LVEF was measured during completion of treatment, and discontinuation of HER2 treatment and 3-month follow-up were appropriate considerations. The choice of randomeffects models considered as priority due to the heterogeneity between the studies (e.g., many populations and other chemotherapy regimens). Variation detected visually. Forest plots and measures I2. I2 was interpreted based on the

recommendations of the Cochrane journal [18, 19]. A p value <0.05 was considered probable for heterogeneity, indicating significant differences. A twosided p-value <0.05 with no adjust the coefficient was considered as statistically significant. Clip and fill filters when the output was bad.A subgroup analysis stratified by drug type (ACEI, ARA, BB) and combination therapy was also performed.

Results and Discussion

Search Results

ManySearches included EMBASE(n =280), MEDLINE (n =70) and the Library of Cochrane (n =318) identified 2,293 relevant studies. According to the diagram as in Figure 1, the totalstudies 674 excluded during screening due to duplicate the records. thestudies remaining 1172 excluded during screening of the titles, abstracts and methodology because they were not relevant to the topic studied in this systematic review. All papers from the remaining 347 studies were retrieved for review.There are also 339 studies. Discarded due to poor design and/or incorrect population. None of the experiments found an additive search strategy. Theinstallation, selection andidentificationprocess as shown Figure 1.

Finally,8 studies in the systematic review and 6 studies in the meta-analysis performed. Two studies ([7, 20]) notapplied the meta-analysis. howeverwell designed RCTs in this studies, the results of this studies did not take in consadration HER2 positive womansufferingcardiotoxicity and changes at LVEF and GLS parameters. ten RCTs studies from a total of 1556 patients with HER2 breast cancerreceiving with trastuzumabchemotheraby were included in the analysis.

The probability of bias inthis studies were detected using the RoB2 tool [21]. Five from the eight studies were shown low risk of bias and the three studies remaningwere arranged as either low or high probability of bias. manycharacteristicsof this study are shown as in (Table1).Most of the studies included trastuzumabtreatment for HER2 positive breast cancer patient. The main purpose to included four RCTs to assess the primary outcome. ([3, 13, 22, 23])this studies were included to assess secondary outcomes.

Study and Patient Characteristics

The included articles, five studied the effects of beta-blockers, one studied the effects of ARBs, two studied the effects of ACE inhibitors, and none studied the effects of combination therapy. In all studies, patients were not previously treated with ACE inhibitors, ARBs, or BBs. Seven studies included non-metastatic breast cancer and one study ([11, 24]) applies thetrastuzumab adjuvant treatmet or used as preventing treatment for metastatic breast cancer. This studies ([2, 4, 21, 25, 26]) included HER2 positive breast cancer patients. Confirmed that trastuzumabinduced cardiotoxicity was based on GLS detected by LVEF, echocardiography (3D or 4D), CMR or MUGA. Seven studies used echocardiography. While one study [27] used only CMR parameters for detection. [28] and [29] this studies used MUGA modality and echocardiography.

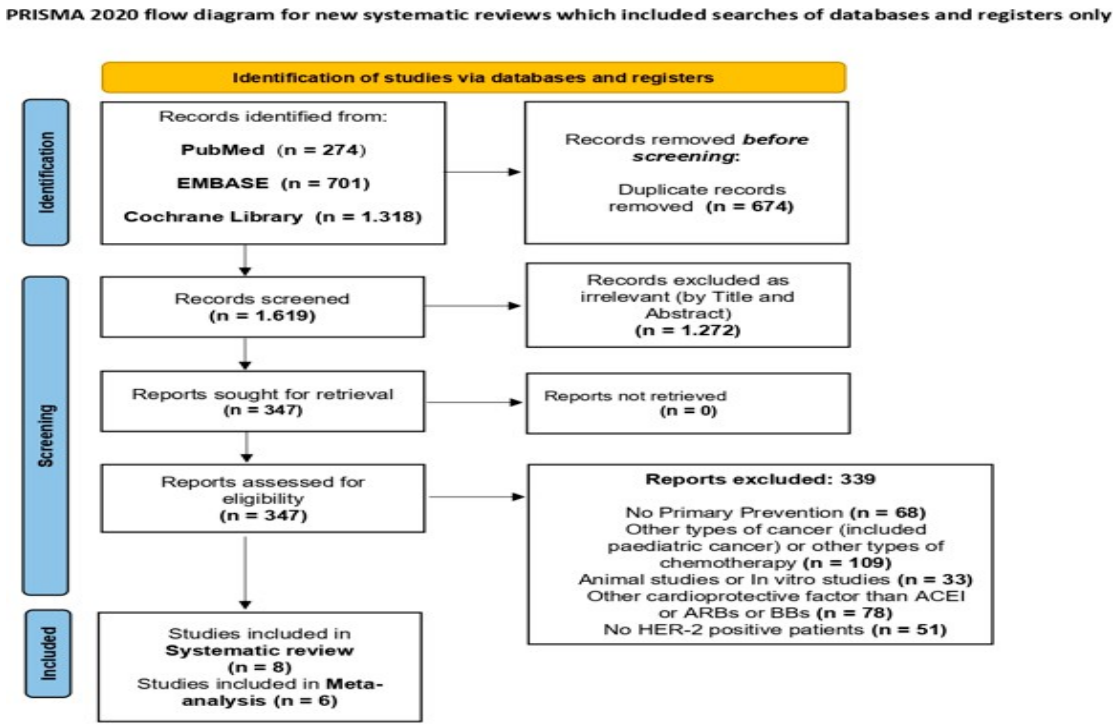

Figure 1: Flow chart for study retrieval and selection. PRISMA 2020.http://www.prisma-statement.org/,accessed on 30 April 2023.

Unfortunately, the dosefor prophylactic medication varied between studies. There were several dose differences between subgroups, some of which varied during the study. Therefore, there is high heterogeneity and it is not possible to compare and evaluate the dosage of each drug between studies[30].

Primary and Secondary Outcomes

The average follow-up time for patients is 3 to 24 months. It is known that 3-month cycles of trastuzumab treatment are required to suppress cardiovascular disease. Therefore, the risk of cardiovascular disease remains constant in each 3-month cycle. Four studies ([10, 15, 31, 32]) eight hundred and twenty-eight patients with information on the first episode of cardiotoxicity were included. The effect of drug administration was not shown significant preventing cardiotoxicity in compared with control patient where (OR = 0.95, 97% - CI: 0.55 to 1.55 - p = 0.75). Treatment with Beta Blocker, ACEI amdARA did not reduce the probability of cardiovascular disease compared with that take placebo (OR = 0.95, 95% -CI: 0.20 to 3.55, p = 0.91)and(OR = 0,79,95% -IC: 0,54 to 1,80 -p= 0,75). two studies stopped using of trastuzumab treatment as secondary prevention ([33, 34]). The beta-blockers treantmenthas been shown that the risk of discontinuation trastuzumab reduce compared with ACE inhibitors. Unfortunately, due to the small number of studies, we were unable to perform an analysis and obtain results Conclusions on the cardioprotective efficacy associated totrastuzumab resistance.Many studies involving 770 patients that assess the cardioprotective effects of many drugs based on LVEF measurements . The high level LVEF from baseline was greater in patients that treated with ACEI/ARA significantly (MD 2.90%, 95%, CI: 1.50% to 3.50%, p<0.0001), and was less extensive after administration of Beta Blocker (MD 1.20%, 95% CI: 0.15 to 3.10%,p = 0.01).the significant difference shown as (I2 = 75%, p=0.0001), due to the change in beta-blockers study (I2 = 90%, p = 0.0001). after contiousfollow-up, the patients that treated with ACEI, ARA and Beta Bloker had higher LVEF than the control patient (1.91%, 95% CI: 0),(50~2,92%, p=0,001).The evaluation the quality of the courses was carried out using the GRADE scale score. The most studies are characterized by a Moderateto low peobability of bias. No material risk studies were found. Serum biomarkers of troponin-T and brain natriuretic peptide (pro-BNP) levels detected in three studies for assessment thecardiotoxicity

Table 1. Characteristics and main findings of included studies.

Study ID	Type of Study	Sample Size	Age, Years	Hormonal Receptors Positive	Trastuzumab without Previous Use of Anthracyclines	Adjuvant Trastuzumab	Cardio Protective Agent	Dose of Medication	Type of Baseline Measurements	Duration of Follow-Up	Serum Biomarkers
Lee et al., 2021 [32]	Double-blind, placebo-controlled RCT	174	Median age 48 years	132	..	64	Bisoprolol, Ramipril, or both	5 mg Bisoprolol and/or 5 mg of Ramipril	Standard and 3D echocardiography	24 months	No
Gulati et al., 2016 [33]	Double-blind, placebo-controlled RCT	120	Mean age 50.7 years	..	..	28	Candesartan cilexetil and Metoprolol succinate	Starting dose for candesartan cilexetil was 8 mg and for metoprolol succinate 50 mg, target dose 32 and 100 mg, respectively	CMR and Echocardiography	No follow-up information beyond the adjuvant therapy period	Cardiac troponin I and B-type natriuretic peptide (BNP)
Eskandhoo et al., 2021 [34]	Simple RCT	60	Mean age 47 years	60 non-metastatic Her-2 positive patients	..	60	Carvedilol	The dose has been increased in a three-week period to reach 12.5 mg twice a day and continued until the end of therapy	Echocardiography	12 months	No
Gaglia et al., 2019 [35]	Double-blind, placebo-controlled RCT	468	Mean age 51 years	468 HER-2 positive	279	468	Lisinopril, Carvedilol	10 mg once daily	MUGA	12 months	Troponin I and B-type natriuretic peptide (BNP)
Pituskin et al., 2017 [36]	Double-blind, placebo-controlled RCT	94	Mean age 51.3 years	94 HER-2 positive	..	94	Perindopril, Bisoprolol	Daily target doses of Perindopril 8 mg, Bisoprolol 10 mg after was initiated with Perindopril 2 mg daily and Bisoprolol 2.5 mg daily.	CMR	24 months	No
Boekhout et al., 2016 [37]	Double-blind, placebo-controlled RCT	206	Mean age 49.5 years	206 HER-2 positive	..	206	Candesartan	32 mg daily	Echocardiography or MUGA	The median follow-up was 23 months	NT-proBNP and hs-TnT
Farahani et al., 2019 [38]	Open-label RCT	71	Mean age 57 years	71 HER-2 positive	..	71	Carvedilol	6.25 mg twice a day, and 6.25 mg was added to each serving every week to the maximum tolerated dose (12.5 ± 3.125 mg twice a day)	2DSTE	3 months	No
Shenafelt et al., 2019 [39]	Double-blind, usual care-controlled RCT	65	Mean age 46.5 years	65 HER-2 positive	..	65	Carvedilol	6.25 mg twice daily	Echocardiography	3 months	No
8		1256			279	1056					

Abbreviations: 2DSTE, 2D speckle-tracking echocardiography; MUGA, Echocardiography and multi-gated acquisition; CMR, cardiac magnetic resonance.

disease. Two studies ([35, 36]) did not demonstrate an association between biomarker changes and cardiotoxicity. Another study ([37]) reported only cardiac biomarkers with no effect. Of course, no statistical analysis can be performed on these biomarkers.

The systematic review present seven RCTs assessting the beta-blockers, ACE inhibitors, cardioprotectiveefficacy of and ARBs in breast cancer female thattaking potentially cardiotoxictreatment with trastuzuma drug. According tocardiotoxicity as variable, our systematic review did not show that the aforementioned drugs used as treatment with active drugs could reduce the probabilityof trastuzumab produce cardiotoxicity in cancer patients. where Administration of an ACEI/ARA during trastuzumab chemotherapy prevented the decrease in left ventricular ejection fraction measurements.There was weak evidence prove that the relation of ACEI/ARA and BB with reduced trastuzumab treatment toxicity. Several previous studies have evaluated breast cancer prevention. These groups initially takinganthracyclines, but some subgroups taking monotherapy or in combination totrastuzumab treatment. according the high use of trastuzumab therapy clinically, for knowledge, this is the unique systematic review that avoids confounding and focuses only on the prevention of trastuzumab causecardiotoxicity.theadverse effects of other chemotherapy drugs, Compared with previous analyses,the RCTs of breast cancer patients who takingtrastuzumab monotherapy withcardioprotective drugs. Due to this reason, manyclinical trial well-designed excluded [38], because the SAFE study is not good in the area of the small number of HER2-positive patients. From the point of view of methodological, the assessment of cardiotoxicity by a dichotomous parameter or change in LVEF as continuous parameter. The second strength of the current systematic review was the detection of LVEF measures to minimize the effect of variability between the study [39].This systematic review aimed to determine whether the administration of cardioprotectivemedications and treatment with trastuzumab has a clinical benefit in patients without prior disease. The response is important because of the most of the patients treated with the combination withanthracycline and trastuzumabthat developed heart failure (27%), symptomatic heart failure (16%). [40]. The addition of trastuzumab to chemotherapy significantly increased survival and increased the risk of cardiovascular disease. These results need to be confirmed in other groups to calculate the probability of cardiovascular disease accurately with trastuzumab drug in breast cancer woman. In a systematic review, prophylaxis with ACE inhibitors, ARBs or beta-blockers did not reduce cardiovascular toxicity. Heart disease is better for, In the analysis,the prophylaxis group (OR =0.95,99%, CI: 0.75: 1.56, p=0.75), but did not reach significance difference statistical.

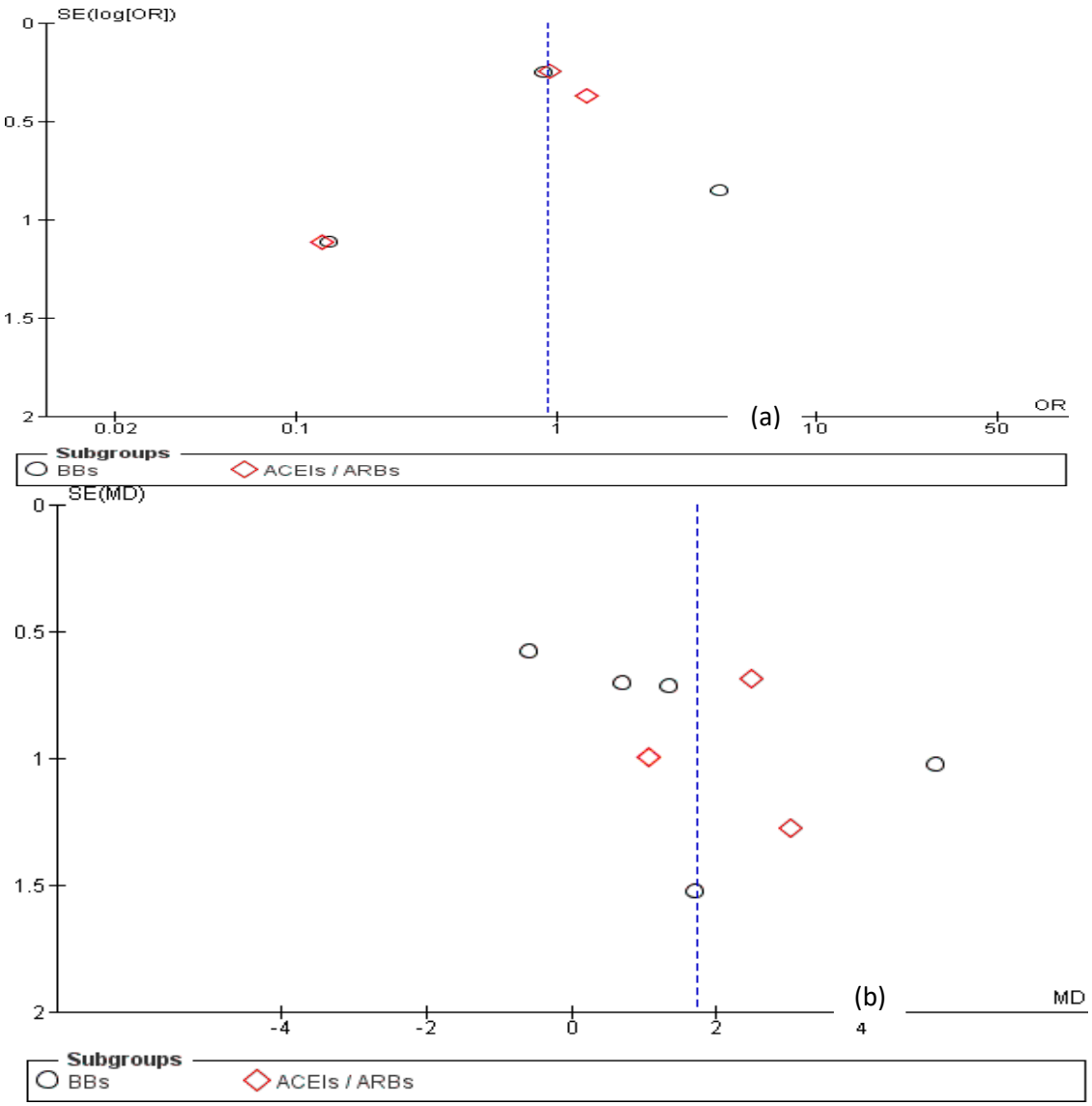

Figure 2:Funnel plot to visualize the publication and other bias: (a) The asymmetric funnel plot indicates publication bias regarding the number of patients who experienced cardiotoxicity between the control and intervention group; (b) the asymmetric funnel plot indicates publication bias regarding the changes in LVEF between the control and intervention group.

There was hypothesis suggest that ARB/ACEI and/or BB prophylaxis may reduce cardiovascular events present and should be the undergofor appropriate RCT. Furthermore, this systematic review did not differentiate whether one of agents that mentioned above is the most effective in preventingtrastuzumab caused cardiotoxicity.[41].

the important outcome of the systematic review of six RCT was that prophylactic effect ARB/ACEI was associated significantly with a small LVEF compared to placebo. From point of view clinically, increasing in LVEF after combinationthe treatment of trastuzumab and ACEI,BRA appears within the normal range of many repeated LVEF readings (MD = 2.01, 95% CI 1.30% : 2.18%, p < 0.0001), LVEF was seemed very higher at 1.50%.

Therefore, the present evidence is unclear whether the use of AECIs/ARBs as prophylactic can prevent trastuzumab caused cardiotoxicity by preventing echocardiographic deterioration of left ventricular function. Other studies validate the measurement of LVEF can used as an indicator of cardiovascular disease prevention[42].

The three RCT showed a 60% reduction in trastuzumab discontinuation when given with ARB/ACEI and/or BB. Trastuzumab discontinuation represents the other side of the coin: heart failure. Therefore, more RCTs are

needed to incorporate this indication clinically. this case, the significance of ARB/ACEI over BB did not observe in the final results. No structural analysis was included in the analysis[41, 43]. This suggests that ACEIs/ARAs and BBs may be prescribed concurrently with trastuzumab treatment, although the optimal regimen is unclear. It was not possible to draw conclusions about the prescribed doses of these drugs for preventive treatment. Our meta-analysis did not confound patients' risk of developing cardiovascular disease. Therefore, the current evidence for early treatment of high-risk patients cannot be provenaccording to 2022 ESC guidelines [44] and American Society of Clinical Oncology Clinical Practice Guideline. 2017[42].

Many biomarkers used to indicate cardiac damage, such as troponin T and natriuretic peptide (NT-proBNP), are useful as early markers of heart disease. Assessment of these cardiac biomarkers is an important part of monitoring patients receiving trastuzumab chemotherapy. This is because it shows signs of heart failure before it is detected on echocardiography. Thereby, several prospective studies[45, 46] have used these cardiac biomarkers as surrogate markers of cardiovascular toxicity, but the results have been controversial. this systematic reviewevaluation the effect of ACEI,ARB or BetaBlocker on biomarkers which mentioned the above. There there studies were available for assessment[39].

The primary prevention of heart toxicityassociated with chemotherapy was under study for more data , with more and advanced clinical trials. Invitrotrialson animal models have uncovered unique pathophysiological mechanisms and shown perfect results for clinically meaningful therapeutic interventions,[47]We highlight the important role of antioxidant enzymes in prevention of trastuzumab caused cardiotoxicity. They significantly notice that changes in heart tissue, including cell destruction,inflammatory necrosis, and increase in inflammatory mediators and cardiac biomarker enzymes in mice treated with trastuzumab. This study present the effect of oxidative stress and reduced antioxidant enzymes in trastuzumab caused cardiotoxicity. Therefore, confirm the drugs Cardiovascular measures are needed for heart failure. Although the study showed improved prevention of cardiovascular disease with the patients takinganthracyclines, the outcome may not apply to patients takingtrastuzumab medications because of small studies and many pathophysiological mechanisms. The effective prophylactic medicine may require goodselection for the patients with chronic diseases. For example, ACE inhibitors/ARBs may be more effective in people with high blood pressure. patient, BB for patients with previous cancer. Applying these criteria can be helpful Patients who require treatment and a preventive approach. Further studies are needed the important ofneurohormonal inhibitory agent such as ARNI or SGLT2 that may be more effective in preventing trastuzumab-induced heart failure in patients[42, 48].

This systematic review has several limitations. First, the heterogeneity of studies needmanyitems of cardiotoxicity, effects or lack of databaes, and before used and contrary database on anthracyclines. howeverthere no patient had a heart attack at normal condition, the frequency of anthracycline exposure varied. from 25% ([43]) to 100% ([49]), This raises the question of whether trastuzumab treatment has additiveeffects on cardiac function or can be applied alone. The present criteria proposed by scientific community and mantstudies that only reported changes in LVEF were used for the assessment of cardiovascular disease. however, the authors of thid two selected RCT did not respond to the data submission and these studies were excluded from the systematic review. Finally, ratings of variability are less reliable.

We will perform a systematic review with less than 15 studies. The asymmetric curve plot Figure 2, shows the mean reading in relation to the number of patients with heart disease between the control and intervention groups and the variation in LVEF between the control and intervention groups[50].

Conclusions

In a meta-analysis of six randomized trials, prophylactic use of ARB/IECA or BB did not reduce the risk of trastuzumab-induced cancer in patients with advanced lung cancer. Less strong evidence has shown a positive benefit in maintaining LVEF, and systematic reviews have shown that trastuzumab is less likely to be discontinued. Future clinical trials focused on primary prevention of cardiovascular toxicity and new treatments for cardiotoxicity are needed to evaluate .

According to cardio oncology. Biomarker analysis and new imaging techniques can support early recognition of the onset of heart disease, which can aid in personalized treatment.

Funding: This investigate was supported by the inside investigate extend of the College of Cyprus IAT 128/2020.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable.

Conflicts of Interest: No conflict of interest.

References:

1. Zhu, X., K. Stergiopoulos, and S.J.A.o. Wu, *Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis.* 2009. **48**(1): p. 9-17.
2. Romond, E.H., et al., *Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2–positive breast cancer.* 2012. **30**(31): p. 3792.
3. Zamorano, J.L., et al., *2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC).* 2016. **37**(36): p. 2768-2801.
4. Yarden, Y. and M.X.J.N.r.M.c.b. Sliwkowski, *Untangling the ErbB signalling network.* 2001. **2**(2): p. 127-137.
5. Yap, T.A., C.P. Carden, and S.B.J.N.R.C. Kaye, *Beyond chemotherapy: targeted therapies in ovarian cancer.* 2009. **9**(3): p. 167-181.
6. Yang, B. and T.J.J.o.A.T. Papoian, *Preclinical approaches to assess potential kinase inhibitor-induced cardiac toxicity: Past, present and future.* 2018. **38**(6): p. 790-800.
7. Yang, B. and T.J.J.o.A.T. Papoian, *Tyrosine kinase inhibitor (TKI)-induced cardiotoxicity: approaches to narrow the gaps between preclinical safety evaluation and clinical outcome.* 2012. **32**(12): p. 945-951.
8. Vaidya, T., et al., *Systems pharmacological analysis of mitochondrial cardiotoxicity induced by selected tyrosine kinase inhibitors.* 2018. **45**: p. 401-418.
9. Tromp, J., et al., *Cardio-oncology: progress in diagnosis and treatment of cardiac dysfunction.* 2017. **101**(4): p. 481-90.
10. Tocchetti, C.G., et al., *From molecular mechanisms to clinical management of antineoplastic drug-induced cardiovascular toxicity: a translational overview.* 2019. **30**(18): p. 2110-2153.
11. Stupp, R.J.N.E.J.M., *European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* 2005. **352**: p. 987-996.
12. Starling, N., et al., *Role of erlotinib in the management of pancreatic cancer.* 2006. **2**(4): p. 435-445.
13. Seidman, A., et al., *Cardiac dysfunction in the trastuzumab clinical trials experience.* 2002. **20**(5): p. 1215-1221.
14. Schmidinger, M., et al., *Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma.* 2007.

15. Schlessinger, J.J.S., *Common and distinct elements in cellular signaling via EGF and FGF receptors.* 2004. **306**(5701): p. 1506-1507.
16. Russell, S.D., et al., *Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials.* 2010. **28**(21): p. 3416-3421.
17. Okwuosa, T.M. and A.J.J.o.t.A.C.o.C. Barac, *Burgeoning cardio-oncology programs: challenges and opportunities for early career cardiologists/faculty directors.* 2015. **66**(10): p. 1193-1197.
18. Motzer, R.J., et al., *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* 2007. **356**(2): p. 115-124.
19. Moslehi, J.J.J.N.E.J.o.M., *Cardiovascular toxic effects of targeted cancer therapies.* 2016. **375**(15): p. 1457-1467.
20. Ky, C.J.J.C.O., *Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry.* 2005. **23**: p. 1803-1810.
21. Lee, C.K., et al., *Impact of EGFR inhibitor in non–small cell lung cancer on progression-free and overall survival: a meta-analysis.* 2013. **105**(9): p. 595-605.
22. Koch, S., et al., *Signal transduction by vascular endothelial growth factor receptors.* 2011. **437**(2): p. 169-183.
23. Kloth, J., et al., *Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors.* 2015. **112**(6): p. 1011-1016.
24. Kerkela, R., et al., *Sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase.* 2009. **2**(1): p. 15-25.
25. Kenigsberg, B., V. Jain, and A.J.H.F.C. Barac, *Cardio-oncology related to heart failure: epidermal growth factor receptor target-based therapy.* 2017. **13**(2): p. 297-309.
26. Kamba, T. and D.J.B.j.o.c. McDonald, *Mechanisms of adverse effects of anti-VEGF therapy for cancer.* 2007. **96**(12): p. 1788-1795.
27. Jain, D., et al., *Cardiac complications of cancer therapy: pathophysiology, identification, prevention, treatment, and future directions.* 2017. **19**: p. 1-12.
28. Izzedine, H., et al., *Management of hypertension in angiogenesis inhibitor-treated patients.* 2009. **20**(5): p. 807-815.
29. Imai, K. and A.J.N.R.C. Takaoka, *Comparing antibody and small-molecule therapies for cancer.* 2006. **6**(9): p. 714-727.
30. Herrmann, J., et al., *Vascular toxicities of cancer therapies: the old and the new–an evolving avenue.* 2016. **133**(13): p. 1272-1289.
31. Hahn, V.S., D.J. Lenihan, and B.J.J.o.t.A.H.A. Ky, *Cancer therapy–induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies.* 2014. **3**(2): p. e000665.
32. Guo, Y., et al., *Interleukin-6 signaling pathway in targeted therapy for cancer.* 2012. **38**(7): p. 904-910.
33. Force, T. and K.L.J.N.r.D.d. Kolaja, *Cardiotoxicity of kinase inhibitors: the prediction and translation of preclinical models to clinical outcomes.* 2011. **10**(2): p. 111-126.
34. Ferrara, N., H.-P. Gerber, and J.J.N.m. LeCouter, *The biology of VEGF and its receptors.* 2003. **9**(6): p. 669-676.
35. Escudier, B., et al., *Sorafenib in advanced clear-cell renal-cell carcinoma.* 2007. **356**(2): p. 125-134.
36. Earp 3rd, H.S., et al., *The EGF receptor family--multiple roles in proliferation, differentiation, and neoplasia with an emphasis on HER4.* 2003. **114**: p. 315.
37. Dong, J. and H.J.F.i.c.m. Chen, *Cardiotoxicity of anticancer therapeutics.* 2018. **5**: p. 9.
38. Di Lisi, D., et al., *Anticancer therapy-induced vascular toxicity: VEGF inhibition and beyond.* 2017. **227**: p. 11-17.

39. Cheng, H. and T.J.C.r. Force, *Molecular mechanisms of cardiovascular toxicity of targeted cancer therapeutics.* 2010. **106**(1): p. 21-34.
40. Dempsey, K.S.J.C.C.N.C.o.N.A., *Chemotherapy-induced cardiotoxicity in women.* 2008. **20**(3): p. 343-350.
41. Avelar, E., C.R. Strickland, and G.J.C.t.o.i.c.m. Rosito, *Role of imaging in cardio-oncology.* 2017. **19**(6): p. 46.
42. Armenian, S.H., et al., *Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline.* 2017. **35**(8): p. 893-911.
43. Burden, S. and Y.J.N. Yarden, *Neuregulins and their receptors: a versatile signaling module in organogenesis and oncogenesis.* 1997. **18**(6): p. 847-855.
44. Lyon, A.R., et al., *2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC).* 2022. **43**(41): p. 4229-4361.
45. Damrongwatanasuk, R. and M.G.J.C.t.o.i.c.m. Fradley, *Cardiovascular complications of targeted therapies for chronic myeloid leukemia.* 2017. **19**: p. 1-13.
46. Chu, T.F., et al., *Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib.* 2007. **370**(9604): p. 2011-2019.
47. Cardinale, D., et al., *Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy.* 2000. **36**(2): p. 517-522.
48. Agus, D.B., et al., *Efficacy and safety of single-agent pertuzumab (rhuMAb 2C4), a human epidermal growth factor receptor dimerization inhibitor, in castration-resistant prostate cancer after progression from taxane-based therapy.* 2007. **25**(6): p. 675-681.
49. Bonner, J.A., et al., *Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.* 2006. **354**(6): p. 567-578.
50. Abdel-Qadir, H., et al., *Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis.* 2017. **53**: p. 120-127.