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1	A systematic review and meta-analysis of beta-blockers and renin-
2	angiotensin system inhibitors for preventing left ventricular
3	dysfunction due to anthracyclines or trastuzumab in patients with
4	breast cancer.
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30	

1 Abstract

2 Aims:

Trastuzumab and anthracyclines, often used in the treatment of breast cancer, may impair myocardial function, and reduce left ventricular ejection fraction (LVEF), potentially causing heart failure. Randomized controlled trials (RCTs) have evaluated the effects of beta-blockers (BBs), angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEI) on trastuzumab and anthracycline associated cardiotoxicity. We report a meta-analysis of these RCTs in patients with breast cancer.

9 Methods and Results:

10 The primary analysis was on the effect of BBs and ACEI/ARBs on LVEF in patients treated with 11 either trastuzumab or anthracyclines. A secondary analysis was done investigating the effect of BBs 12 or ACEI/ARBs on LVEF in trastuzumab and anthracycline treatments. Only RCTs were included 13 using the search term "ARBs, ACEIs, BBs, anthracyclines, trastuzumab and breast cancer" in 14 PubMed, EMBASE and CENTRAL up to March 31, 2021. A meta-analysis was conducted to 15 estimate the mean difference (MD) in LVEF between intervention and placebo groups at follow-up. 16 17 A total of 9 RCTs (N = 1362) were included in the analysis. All patients were women. BBs and 18 ACEI/ARBs were both shown to attenuate the decline in LVEF during trastuzumab and anthracycline 19 treatments (MD 2.4; 95% confidence interval [CI] 0.3 to 4.5 and MD 1.5; 95% CI -0.6 to 3.7). 20 Compared to placebo, LVEF was significantly higher in patients assigned to BB or ACEI/ARB on 21 trastuzumab (MD 2.3; 95% CI 0.0 to 4.6) but not on anthracyclines (MD 1.9; 95% CI -0.5 to 4.5). 22 **Conclusion:** 23 Both BB and ACEI/ARB therapies were associated with preservation of LVEF during trastuzumab

24 and anthracycline-containing regimens as compared to placebo, suggesting both to be beneficial.

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3	Keywords: Left ventricular ejection fraction, breast cancer, trastuzumab, anthracyclines, prevention,
4	cardiotoxicity, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-
5	blockers.
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- 1 Introduction

3	Breast cancer is the most common form of cancer in women. ¹ Apart from surgery and radiotherapy,
4	systemic chemotherapy, and immunotherapy, including anthracyclines and trastuzumab, are
5	recommended to try to eradicate residual tumour cells. Anthracyclines and trastuzumab can have off-
6	target effects, including negative effects on cardiac function. ² Patients with breast cancer expressing
7	human epidermal growth factor receptor 2 (HER2) typically receive both anthracyclines and
8	trastuzumab (a monoclonal antibody that blocks HER2 receptors), in a sequential manner.
9	Detrimental effects of trastuzumab and anthracyclines on left ventricular systolic function, including a
10	reduction in left ventricular ejection fraction (LVEF), have been found in clinical practice. ³
11	
12	In order to prevent cardiotoxicity, evidence-based treatments for heart failure with reduced ejection
13	fraction (HFrEF) have been prescribed concomitantly with cancer treatments containing
14	anthracyclines and trastuzumab. ⁴ Thus far, published reviews of cardiotoxicity associated with
15	anthracyclines and trastuzumab therapies for breast cancer patients have rarely included meta-
16	analyses of existing randomized controlled trials (RCTs) evaluating distinct versus indistinct blockade
17	of the sympathetic and/or renin-angiotensin system despite the low numbers of participants in existing
18	trials. Therefore, we performed a meta-analysis investigating the treatment effect of angiotensin-
19	converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs) and beta-blockers (BBs)
20	on LVEF during either anthracycline or trastuzumab regimens in patients with no pre-existing heart
21	failure (HF).
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1 Methods

We followed the PRISMA guidelines for reporting meta-analysis (see supplementary material).⁵ The
target was RCTs assessing LVEF before and after treatment with either anthracyclines or
trastuzumab, concomitantly with either mono- or combination therapy with an ARB or ACEI or BB
versus placebo.

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7 Search methods

PubMed was queried through the search term "ACE inhibitors, angiotensin receptor blockers, betablockers, anthracyclines, trastuzumab and breast cancer". EMBASE and CENTRAL were searched for additional RCTs. Studies were identified and included from database inception to March 31, 2021. All titles and abstracts were investigated for randomization to intervention versus placebo. All potentially relevant articles were read in full. Moreover, we reviewed previous systematic reviews, guidelines, or statements from cardiovascular society meetings for references to any RCTs not found in our own search results. The searching process was restricted to two of the authors (CL and TN).

15 Study and data collection

16 Studies for inclusion were RCTs randomising to ACEI or ARBs or BBs or both as compared with

17 placebo. Furthermore, studies had to contain information on LVEF in percent (%) before and after

18 breast cancer treatment. Measurement of LVEF could have been performed by either

19 echocardiography, magnetic resonance imaging (MRI) or multi-gated acquisition (MUGA) scan.

20 Non-randomized studies were excluded. Further exclusion criteria were previous HF.

21 Baseline characteristics including age, gender, type and duration of medical breast cancer treatment,

22 duration of BB and ACEI/ARB treatment, radiotherapy before, during or after the trial, other medical

23 breast cancer therapy prescribed before or after the study drug, LVEF at baseline, type of LVEF

24 measurement, LVEF as a primary outcome and observation time were gathered.

25 Study selection was made independently by two reviewers (CL and TN). In case of disagreement,

26 consensus was reached by the reviewers.

1 Risk of bias assessment

- 2 The Cochrane collaboration tool was applied to assess internal validity of the selected studies through
- 3 assessment of risk of bias.⁶ The categories were sequence generation, allocation concealment,
- 4 blinding, incomplete outcome data and selective outcome reporting. An estimate of risk of bias was
- 5 conducted by two independent reviewers (CL and TN) reaching consensus in case of disagreement.
- 6 The risk of bias was categorized as 'low' or 'high'; unclear was systematically classified as high risk.

7 **Outcomes**

- 8 Our primary outcomes were the distinct effects of BBs and ACEI/ARBs on LVEF during either
- 9 trastuzumab or anthracycline treatments.

Secondary outcomes were the effect of either BBs or ACEI/ARBs on LVEF during anthracycline and
 trastuzumab treatments.

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13 Statistics

- 14 Continuous data were calculated as means (standard deviations [SDs]) where discrete data were
- 15 presented as percentages.
- 16 Means of LVEF after chemotherapy were applied in calculating functional differences between the
- 17 intervention groups. Meta-analyses estimated the pooled mean difference (MD) of LVEF at the
- 18 follow-up time and associated 95% confidence intervals (CIs) between the group randomised to either
- 19 BB or ACEI/ARB treatment versus a control group receiving placebo. Overall, a random effect model
- 20 was undertaken translating moderate to high heterogeneity due to the double-sided nature of
- 21 ACEI/ARBs, BBs, anthracyclines and trastuzumab in the analysis. The effects sizes of the individual
- 22 studies were pooled by inverse variance weighting through the DerSimonian-Laird (DL) estimate and
- 23 displayed through forest plots. Test statistics and CIs were adjusted according to the Hartung and
- 24 Knapp method.⁷ The 95% CIs were defined as the mean±1.96*standard error (SE) in a normal

1	distribution. The SD was the SE* \sqrt{N} , where N was number of participants. If follow-up LVEF was
2	reported indirectly as a MD, we approximated follow-up LVEF and associated SD. LVEF was
3	calculated as the sum of baseline LVEF and the MD. The SD of follow-up LVEF was substituted by
4	the baseline SD of LVEF when missing (only the Guglin study). Heterogeneity was calculated as I ² . ⁸
5	Meta-regressions were undertaken through univariate analysis with the above-described baseline
6	characteristics from the studies. Heterogeneity was assumed at least moderate in the primary
7	outcomes due to the double-sidedness of breast cancer and HF preventive treatments.
8	A reference analysis was performed as a sensitivity assessment including all the selected studies
9	without distinguishing between medical breast cancer or preventive HF treatment. This was
10	prespecified to investigate linear associations between the MD of LVEF and anthracycline,
11	trastuzumab, BBs and ACEI/ARBs. Finally, meta-analyses estimating the standardized mean
12	differences (SMDs) were undertaken to adjust for potential measurements differences between
13	echocardiography, MUGA and MRI of the heart. The package Meta in R statistics was applied in the
14	data synthesis.9
15	Results
16	Studies included vs excluded
17	A total of 237 studies were found in our preliminary search in PubMed, EMBASE and CENTRAL.

18 Among these, a total of 9 fulfilled our inclusion criteria (Table 1 and Supplementary material).¹⁰⁻¹⁸ We 19 did not find supplementary studies from our search in guidelines and statements from cardiovascular 20 society meetings.

21

22 **Characteristics**

23 A total of 1362 patients were included in the analysis, and all were women. Mean age varied from

- 24 40.8 to 53.6 years between the studies. Overall, the RCT populations were without previous
- 25 cardiovascular disease since it was part of their exclusion criteria. The baseline LVEF means varied
- 26 between 59.5% and 66.0%. Three studies had a factorial design and randomized the experimental

1	group to either ACEI/ARBs, BBs or both at the same time. ^{10, 11, 15} Five studies randomized solely to
2	BBs versus placebo, and only one RCT allocated patients to ACEI/ARBs and a placebo group,
3	respectively. ^{12-14, 16, 17} A total of three studies examined the preventive effect of HF treatments with
4	trastuzumab versus six with anthracycline treatments.
5	The duration of chemotherapy ranged between 63 and 365 days. In addition to these, between 0 and
6	65.1% of patients received radiotherapy as part of their post-surgical treatments and all patients,
7	except for one trial, received other biological and chemotherapeutic agents in addition to trastuzumab
8	or anthracyclines. ¹⁸
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10	Primary and secondary outcomes
11	ACEI/ARB therapy irrespective of concomitant anthracycline or trastuzumab therapy resulted in a
12	non-significantly higher LVEF compared to placebo (MD 1.5; $\frac{95\%}{2}$ CI 0.2 to 2.9; $P=0.11$; $I^2=52\%$)
13	(Figure 1A). In contrast, BB therapy preserved LVEF significantly better compared with placebo (MD
14	2.4; 95% CI 0.3 to 4.5; $P=0.033$; $I^2 = 82\%$) (Figure 1B).
15	
16	As a secondary outcome, ACEI/ARB or BB therapy preserved LVEF compared with placebo (MD
17	1.9; 95% CI -0.5 to 4.2; P=0.096; $I^2 = 77\%$) although non-significantly during anthracycline therapy
18	(Figure 2A). Furthermore, during trastuzumab therapy we also found preservation of LVEF with
19	ACEI/ARBs or BBs (MD 2.3, 95% CI 0.0 to 4.6; $\mathbf{P}=0.046$; $\mathbf{I}^2 = 72\%$) as compared with placebo
20	(Figure 2B).
21	
22	Sensitivity analysis
23	Irrespective of cancer therapies, those randomized to active treatment had better preservation of

- 24 LVEF compared to those assigned to placebo (MD 2.0; 95% CI 0.7 to 3.4; P=0.007; I² = 75%)
- 25 (Supplementary material). The decline in LVEF was similar whether trastuzumab or anthracycline
- 26 was the background breast cancer treatment (P=0.38) (Table 2). Potential LVEF protection was similar
- 27 for ACEI/ARBs and BBs (P=0.57). Whether LVEF was a primary outcome or not did not influence

the MD (P=0.65), nor did the imaging modality. Meta-analyses using SMDs were similar to the MD
 models (Supplementary material).

3

4 Risk of bias

A total of 6 out of 9 studies were assessed to have high risk of bias in the randomization process and in their blinding of both participants and investigators (Supplementary material).^{12-14,16-18} The overall trend among these assessments was lack of clear description of methods. A single study was stated to be patient-blinded only.¹⁴ Attrition bias was high in <u>four</u> of the studies due to substantial numbers of patients not completing the study protocol without known impact on the study outcome. In general, other biases were assessed as high when incomplete description of the methodology existed, and attrition bias was suspicious.

12

13 Discussion

14 Our meta-analysis of 9 RCTs showed a protective effect of ACEI/ARBs and BBs on LVEF during

15 breast cancer treatments with anthracyclines and trastuzumab as compared with placebo (Graphical

16 abstract).

17 Issues in our analysis were the great variety among the RCTs of supplementary breast cancer

18 treatments, such as radiotherapy and cardiotoxic drugs before or after anthracycline and trastuzumab

19 regimens. Moreover, the hemodynamic side-effects of ACEI/ARBs and BBs leading to hypotension,

20 tiredness and dizziness will be discussed in the following.

21

22 The beneficial effects of ACEI/ARBs and BBs on LVEF decrease were demonstrated in our analysis.

23 These results are equally reproduced in observational data with LVEF preservative effects of

24 ACEI/ARBs and BBs in anthracycline and trastuzumab induced cardiotoxicity. Up to 10% of patients

25 treated with anthracyclines and trastuzumab succumb to cardiotoxicity.¹⁹ Experimental studies with

26 animal models have also demonstrated efficacy of ACEI/ARBs and BBs on preservation of LVEF

27 during exposure to potentially cardiotoxic breast cancer treatments.²⁰A meta-analysis investigating

28 neurohormonal therapies in cancer patients receiving chemotherapy found similar significant

1 beneficial effects favouring ACEI/ARBs and BBs in sensitivity analyses of breast cancer, and 2 anthracycline treatment.²¹ Preventive therapy including ACEI/ARBs and BBs to preserve the LVEF 3 during both chemotherapeutic and biological breast cancer treatment therefore seems feasible. 4 The secondary outcome distinguishing between anthracycline and trastuzumab treatment in women 5 with breast cancer but not the type of preventive drug established similar LVEF preservative effects as 6 compared to the primary outcomes. 7 Combinatorial results from factorial designs were not included in the analysis. If both intervention 8 drugs were effective independently, this suggests that ACEI/ARBs and BBs may be prescribed 9 concomitantly, although the latter is based on HFrEF according to the HF guidelines.²² The factorial 10 designed studies supported this as none of them showed interaction. 11 Although ACEI/ARBs and BBs may be prescribed together with anthracycline and trastuzumab 12 therapy, their optimal dose remains unknown. Preventive drug doses in the included RCTs were often 13 lower than target doses for HFrEF treatment indicating that up-titration was not achieved. This 14 suggests that lower drug doses than recommended in HFrEF guidelines preserved LVEF in breast 15 cancer patients. The optimal combination of ACEI/ARBs and BBs remains unknown. 16 Heterogeneity was moderate to high overall. Factors explaining the differences between the RCTs 17 were not established through meta-regressions. In contrast to real-life studies suggesting a larger 18 cardiotoxic profile of anthracyclines as compared with trastuzumab, the latter predominantly causing 19 temporary LVEF decrease, meta-regressions were not able to show LVEF differences between anthracycline and trastuzumab treatments²³ (Table 2). By the same token, there were no difference in 20 21 efficacy comparisons of ACEI/ARBs and BBs in the meta-regressions. This is despite their different 22 mechanism of action on the heart through afterload reduction from vasodilation and reduced oxidative 23 stress from sympathetic nerve stimulation, respectively.²⁴ The overall small MDs in the LVEF over 24 the follow-up time could be calculated as an absolute LVEF difference up to 2.4% between 25 intervention and placebo (Figure 1B). On the long-term perspective, a gradual decline in heart 26 function without protective LVEF drugs is suspected. Clinical cases of severe LVEF deterioration 27 many years after anthracycline and trastuzumab administrations support a "gradual decline" theory.²⁵

From our meta-regression results no priority of ACEI/ARBs as compared with BBs was found in the
 prevention of LVEF decrease in patients undergoing breast cancer treatment.

3 The outcomes show benefits of ACEI/ARBs and BBs although the antecedents were non-significant. 4 Implications could be administration of both preventive HF drugs from the beginning in breast cancer 5 patients receiving anthracycline and trastuzumab. Nevertheless, caution should be exercised when 6 combined with anthracyclines and trastuzumab. For example, nausea and fever induced by breast 7 cancer treatments may be exacerbated by hypotension from the preventive drugs. This could even lead 8 to renal impairment. To avoid such hemodynamic side-effects, a general recommendation is to pause 9 ACEI/ARBs and BBs during a sick day.²⁶ As an isolated pharmacological mediator, ACEI/ARBs and 10 BBs should not cause hemodynamic imbalance even in patients without cardiovascular disease.²⁷ The 11 lower therapeutic dose from the RCTs compared with conventional HFrEF treatments does also 12 reduce the risk of side-effects. The 2016 ESC position paper on cancer treatments and 13 cardiotoxicities indicates that preventive HF therapy should be restricted to ACEI/ARBs and BBs; 14 further research is required to define the feasibility of employing other HF drugs.²⁸ This is currently 15 being investigated in the PRADA II study.²⁹ 16 One virtue of well conducted meta-analyses is they may justify class A evidence in guidelines 17 depending on predefined endpoints. Moreover, our results were limited to patients treated for breast 18 cancer, which eliminated gender differences and reduced the variation in study protocols. The latter 19 was although substantial in the selected studies. 20 It could be a downside that the outcomes of ACEI/ARBs and anthracyclines were not statistically 21 significant. Broader CIs were expected due to the Hartung-Knapp approach and fully qualified due to 22 the uncertain heterogeneity present among the RCTs.⁷ However, in analyses with five or fewer 23 studies, the amount of uncertainty may be overestimated. Supporting the lack of statistical 24 significance is that none of the included RCTs were based on a mechanistic model. This means that 25 neither ACEI/ARBs or BBs were targeted directly to influence cardiotoxic metabolites from 26 anthracyclines or trastuzumab. Instead, they were targeted to alter the physiology of the heart to a

- 27 more favourable environment against cardiotoxity. Therefore, significant outcomes can be hard to
- 28 achieve. The statistical trend towards LVEF protection from ACEI/ARBs and BBs was highlighted by

1 that all analyses were statistically significant when the DL estimate was unadjusted by the Hartung-

2 Knapp approach (not reported).

3 A real caveat of our study was the great variation between RCT results and the lack of baseline 4 characteristics to explain this in our meta-regressions. We presume this variation may largely have 5 been due to differences in study protocols with respect to additional breast cancer drugs administered, 6 beside anthracyclines and trastuzumab. Inconsistent reporting of left versus right-sided thoracic 7 radiotherapy could have influenced our effect sizes, but presumably in a consistent way. The double 8 sidedness of two HF preventive and two breast cancer treatments in our analysis could be a drawback 9 and may have presumably contributed to the moderate to high statistical heterogeneity in our analysis 10 due to distinct mechanism of action of the four drugs. The significant heterogeneity among the studies 11 made funnel plots inappropriate to assess publication bias.³⁰ We do not interpret the substantial 12 heterogeneity of the included RCTs to be linked to the fact that they did not all apply the same left 13 ventricular measurement at follow-up as their primary outcome. It is an issue in published medical 14 science that data manipulations lead to false conclusions, but in our case, we think this was not 15 existing. This is due to the integration of LVEF and additional functional measurements during the 16 same imaging sessions of the heart. A priori, the mode of LVEF measurement could cause 17 measurement error, but the comparison between modes was neutral in the meta-regression. It was 18 equally a weakness that the follow-up periods of the RCTs were not long-term based since diagnosis 19 of HF in some patients first appears decades after their breast cancer treatments.

20

21 Conclusion

BBs but not ACEI/ARBs were found to preserve LVEF significantly and more effectively than
placebo in breast cancer patients receiving adjuvant trastuzumab and/or anthracyclines. Despite
heterogeneity in effect sizes, only positive associations between LVEF and the interventional drugs
were found. Our results therefore may suggest prescription of either ACEI/ARBs or BBs during
trastuzumab and/or anthracycline therapy in patients undergoing breast cancer treatments. It remains

1	to	be seen what the modest mean preservative LVEF effects (max 2.4%) from ACEI/ARBs and BBs
2	n	nean in the long term.
3	A	cknowledgement: none
4	C	Conflict of interest: See attached word file.
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4	Figure legends
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7	Graphical abstract: Breast cancer treatment trajectory and protective effects of ACEI/ARBs
8	and BBs. ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, BB
9	beta-blocker, MD mean difference.
10	Fig1. Primary outcome. Meta-analysis of the impact of concomitant treatment with (A) angiotensin-
11	converting enzyme inhibitors/angiotensin receptor blockers or (B) beta-blockers compared to placebo
12	on left ventricular ejection fraction in patients treated with anthracyclines or trastuzumab. anth
13	denotes anthracyclines, biso bisoprolol, cand candesartan, carv carvedilol, CI confidence interval, diff
14	difference, lisi lisinopril, MD mean difference, meto metoprolol, nebi nebivolol, peri perindopril, tras
15	trastuzumab.
16	Fig 2. Secondary outcome. Meta-analysis of patients treated with (A) anthracyclines or (B)
17	trastuzumab with the impact on left ventricular ejection fraction through concomitant treatment with
18	angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or beta-blockers compared to
19	placebo. In the PRADA study (Gulati_2016) a total of 22% received trastuzumab. Anth denotes
20	anthracyclines, biso bisoprolol, cand candesartan, carv carvedilol, CI confidence interval, diff
21	difference, lisi lisinopril, MD mean difference, meto metoprolol, nebi nebivolol, peri perindopril, tras
22	trastuzumab.
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 Table 1. Baseline characteristics of the selected randomized controlled trials.

Characteristics	Guglin ¹⁰	Avila ¹³	Nabati ¹⁴	Pituskin ¹¹	Beheshti ¹⁷	Boekhout ¹²	Gulati ¹⁵	Elitok ¹⁸	Kaya ¹⁶
Publication year	2019	2018	2017	2017	2016	2016	2016	2014	2013
No. patients	468	192	81	94	70	206	126	80	45
Age, years	51.0	51.9	47.3	51.3	40.8	49.0	50.8	53.6	51.0
Female sex, %	100	100	100	100	100	100	100	100	100
Trastzumab ¹	yes	no	no	yes	no	yes	no	no	no
Anthrazycline ¹	no	yes	yes	no	yes	no	yes	yes	yes
Duration of anti-cancer therapy,									
days	365	63	105	365	63	365	70	180	NA
BB	yes	yes	yes	yes	yes	no	yes	yes	yes
ACEI or ARB	yes	no	no	yes	no	yes	yes	no	no
Duration of ACEI/ARB or BB,									
days	365	140	180	365	83	546	427	180	180
Observation time, days	730	168	180	365	83	644	427	180	180
LVEF at baseline, %	62.6	65	59.9	61.7	60.2	61	62.9	65.5	66
Radiotherapy, %	NA	0	0	41.5	NA	52	65.1	NA	26.7
Other cancer treatments ² , %	40	100	100	100	100	100	<mark>100</mark> *	0	100
LVEF as primary outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
	Echo,					Echo,			
Type of LVEF measurement	MUGA	Echo	Echo	MRI	Echo	MUGA	MRI	Echo	Echo

¹Primary study drug, which was either anthracycline or trastuzumab.

²Supplementary breast cancer treatments (e.g. cyclophosphamide, anthracycline and trastuzumab) administered before, or after the study drug.

*The population of patients treated with trastuzumab in addition to anthracyclines was 22%.

BB Beta-blocker, ACEI Angiotensin-converting enzyme inhibitor, ARB Angiotensin receptor blocker, LVEF left ventricular ejection fraction, MRI magnetic resonance imaging, MUGA multi-gated acquisition, NA not available

 Table 2. Meta-regressions of all the studies.

Variable	Coefficient	SE	P-value
Sample size	<mark>-0.003</mark>	<mark>0.004</mark>	<mark>0.46</mark>
Age	<mark>-0.06</mark>	0.21	<mark>0.78</mark>
Trastuzumab or anthracyclines	<mark>0.49</mark>	<mark>1.31</mark>	<mark>0.71</mark>
Duration of anti-cancer therapy	<mark><0.001</mark>	<mark>0.005</mark>	<mark>0.98</mark>
BB or ACEI/ARB	<mark>0.79</mark>	<mark>1.36</mark>	<mark>0.57</mark>
Duration of BB or ACEI/ARB	<mark>-0.004</mark>	<mark>0.005</mark>	<mark>0.42</mark>
Observation time	<mark>-0.002</mark>	<mark>0.003</mark>	<mark>0.48</mark>
LVEF at baseline	<mark>-0.17</mark>	<mark>0.36</mark>	<mark>0.65</mark>
Radiotherapy	<mark>-0.04</mark>	<mark>0.04</mark>	<mark>0.35</mark>
Other anti-cancer treatments			
including anthracyclines	0.01	0.02	<mark>0.61</mark>
LVEF as a primary outcome	<mark>0.89</mark>	<mark>1.36</mark>	<mark>0.52</mark>
Type of LVEF measurement	<mark>-0.23</mark>	<mark>0.77</mark>	<mark>0.77</mark>

SE Standard error, BB Beta-blocker, ACEI Angiotensin-converting enzyme inhibitor, ARB Angiotensin receptor blocker, LVEF left ventricular ejection fraction.