Breast Cancer Research and Treatment (2019) 174:357–363
https://doi.org/10.1007/s10549-018-05114-7

REVIEW

The clinical utility of baseline cardiac assessments prior to adjuvant anthracycline chemotherapy in breast cancer: a systematic review and meta-analysis

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Received: 24 September 2018 / Accepted: 20 December 2018 / Published online: 2 January 2019

Abstract

Background Cardiac assessment with multi-gated acquisition scan (MUGA) or echocardiography (ECHO) is commonly employed prior to adjuvant anthracycline-based chemotherapy (AA). However, the clinical utility of routine baseline cardiac assessments prior to AA for early-stage breast cancer (EBC) is unknown.

Objectives To determine: (i) the clinical utility of routine baseline cardiac assessments prior to AA for EBC and (ii) identify patients in whom baseline cardiac assessments may not be warranted.

Methods A systematic review of the literature was conducted to identify all relevant studies that met predefined criteria. The clinical utility was defined by: (i) the rates of abnormal baseline left ventricular ejection fraction (LVEF) and (ii) the rates of change in chemotherapy decisions prompted by baseline LVEF results.

Results Eight studies met our criteria, of whom six ($n = 2545$) reported rates of abnormal LVEF and six ($n = 1713$) reported rates of change in chemotherapy decision. Overall, 2.5% (95% CI 2.0–4.0%) of patients had abnormal baseline LVEF and 1.6% (95% CI 1.0–3.0%) had a change in chemotherapy decision. In subset analyses, the underlying imaging modality (ECHO vs. MUGA) or inclusion of patients with metastatic disease (YES vs. NO) did not significantly affect these rates. There were no consistently identified underlying predictors of abnormal baseline LVEF across studies.

Conclusions Routine baseline cardiac assessments prior to AA in all EBC patients have low yield and infrequently affect clinical management. Future studies should further examine potential predictors of abnormal cardiac functions in an attempt to identify low risk patients in whom routine baseline LVEF assessment may not be warranted and prevent delay in chemotherapy administration.

Keywords Breast cancer · Anthracyclines · Cardiotoxicity · Routine · Screening

Abbreviations

MUGA	Multi-gated acquisition scan
ECHO	Echocardiography
AA	Adjuvant anthracycline chemotherapy
EBC	Early-stage breast cancer
LVEF	Left ventricular ejection fraction
mBC	Metastatic breast cancer

Introduction

Adjuvant anthracyclines (AA) in breast cancer have been associated with improvements in disease-free survival [1] and overall survival [2, 3] in comparison to their non-anthracycline counterparts. However, anthracyclines are also associated with recognized cardio-toxicity risks particularly in the setting of higher cumulative doses, underlying

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-018-05114-7) contains supplementary material, which is available to authorized users.

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cardiovascular risk factors, previous irradiation and co-administration of other potentially cardio-toxic drugs (e.g., trastuzumab) [4–7].

In an attempt to mitigate potential cardiovascular complications, baseline cardiac assessments with multi-gated acquisition scan (MUGA) or echocardiography (ECHO) are commonly utilized as screening tools in clinical practice prior to the initiation of AA. In fact, many practice guidelines recommend routinely obtaining a baseline left ventricular ejection fraction (LVEF) assessments in all patients prior to anthracycline treatments, regardless of anticipated anthracycline dose, underlying malignancy or patient characteristics [8–10]. However, the clinical utility of routine baseline LVEF assessments prior to AA for all patients with early-stage breast cancer (EBC) who are not being considered for concomitant anti-Her-2 therapy is currently unknown. These routine studies may entail unnecessary costs, prompt additional visits or referrals, delay treatment onset, and, could potentially elicit an unwarranted change from the recommended anthracycline-based regimen to a non-cardiotoxic, less efficacious one.

The overall goal of this systematic review and meta-analysis is to examine the clinical utility of routine baseline LVEF assessments prior to AA in EBC with Her-2-negative disease, and potentially identify patients in whom baseline cardiac assessments may not be warranted. Our primary aims were to determine: (i) the rate of abnormal baseline LVEF and (ii) the rate of change in chemotherapy decisions prompted by baseline LVEF results. Our secondary aim was to examine independent predictors of abnormal baseline LVEF results in an attempt to identify a subset of low-risk patients for whom baseline LVEF assessments may be unwarranted.

Methods

Search strategy

We conducted a date unrestricted electronic search of the literature on June 18th, 2017, through three electronic databases: EMBASE, MEDLINE and Web of Science. The electronic search strategy in EMBASE was built using the following keywords/search terms and concepts: 'breast cancer' OR 'breast adenocarcinoma' OR 'breast carcinoma' OR 'breast tumor' OR 'breast cancer'/exp OR 'breast adenocarcinoma'/exp OR 'breast carcinoma'/exp OR 'breast tumor'/exp *AND* 'adjuvant chemotherapy'/exp OR 'adjuvant chemotherapy' OR 'anthracycline'/exp OR 'anthracycline' OR 'doxorubicin'/exp OR 'doxorubicin' OR 'epirubicin'/exp OR 'epirubicin' OR 'adjuvant'/exp OR 'adjuvant' OR 'chemotherapy'/exp OR 'chemotherapy' *AND* 'echocardiography' OR 'radionuclide ventriculography' OR 'echocardiography'/exp OR 'radionuclide ventriculography'/exp OR 'muga' OR 'multi-gated acquisition scan' OR 'multi-gated acquisition scan' OR 'multi-gated acquisition scan'. Similar electronic search strategies were used in MEDLINE and Web of Science. A backward search through the reference lists of identified studies was also conducted to look for other relevant studies.

Study selection

The study selection process was performed in two steps, as per standard recommendation for systematic review conduct [11]. First, the title and abstracts of all citations were screened to exclude all duplicate and irrelevant studies. Second, the studies deemed potentially relevant by this screening process were then examined by full text review by two team members (PO and TY). Discrepancies were resolved by consensus.

Eligible studies were identified based on a number of predetermined inclusion criteria; (i) study design: observational studies, (ii) publication language: English, (iii) study population: EBC patients considered for AA, (iv) intervention: baseline LVEF assessment by MUGA and / or Echo and (v) outcomes: the rates of abnormal baseline LVEF and / or the rates of change in chemotherapy decisions prompted by baseline LVEF results. As such, clinical trials, and studies exclusively involving Her-2/neu positive or metastatic breast cancer (mBC) patients were excluded. Thus, studies that included both EBC and mBC, as well Her-2/neu-positive and -negative patients, were included.

Data abstraction

The study characteristics extracted included publication year, publication type (journal article vs. conference abstract), study design (prospective vs. retrospective, cohort vs. case control), study origin (country), study setting (centre vs. population), cardiac assessment modality (MUGA vs. ECHO vs. MIXED), sample size, patient age (median and range), the proportions of Her-2/neu-positive and / or mBC patients included in the study, and underlying predictors of cardiac toxicity (e.g., underlying cardiovascular risk factors) when reported. The rates of abnormal baseline LVEF and / or change in chemotherapy decisions prompted by baseline LVEF results were abstracted and computed when feasible.

Evidence synthesis

We conducted a meta-analysis to determine overall estimated rates of abnormal baseline LVEF and of change in chemotherapy decisions prompted by baseline LVEF results. Event rates with 95% confidence intervals were calculated using random-effects models. Heterogeneity among studies

was explored using the Cochran's Q statistic with $p < 0.1$ indicating significant heterogeneity. I^2 was used to assess the percentage of total variance attributed to heterogeneity between studies. Sub-group analyses for the primary outcomes were conducted according to imaging modality (MUGA vs. ECHO vs. MIXED), type of publication (journal article vs. conference abstract) and inclusion of mBC patients (yes vs. no).

Results

Selected studies

Of 1401 non-duplicate citations identified, 339 studies were selected for full text review (Supplemental Fig. 1). Of these, 333 were excluded for not meeting our inclusion criteria of study design ($n = 62$), publication language ($n = 12$), population ($n = 118$), intervention ($n = 43$), and outcome ($n = 98$) criteria. Conversely, six met our pre-determined inclusion/exclusion criteria [12–17] and two more were identified through a backward literature search [18, 19].

Study characteristics

Study characteristics are summarized in Table 1. Of the eight studies included, six ($n = 2545$) reported rates of abnormal baseline LVEF, six ($n = 1713$) reported rates of change in chemotherapy decision change prompted by baseline LVEF results, and four ($n = 1080$) reported both outcomes.

Rate of abnormal baseline LVEF and change in chemotherapy decision

The overall estimated rate of abnormal baseline LVEF across studies was 2.5% (95% CI 2.0–4.0%) (Fig. 1). The rate of abnormal baseline LVEF was 2% (95% CI 1.0–3.0%) in patients who had their LVEF assessed by MUGA and 4.4% (95% CI 3.0–6.0%) in those assessed by ECHO (Fig. 1b). In studies that excluded mBC patients, the rate of abnormal baseline LVEF was 2.0% (95% CI 1.0–4.0) (Fig. 1b). There was no correlation between median age and rate of abnormal baseline LVEF by meta-regression analysis (Supplemental Fig. 2). Overall, the estimated rate of change in chemotherapy decision prompted by baseline LVEF results was 1.6% (95% CI 1.0–3.0%) (Fig. 2a). In studies that excluded mBC patients, this rate was 1.1% (95% CI 0.0–3.0%) (Fig. 2b). Finally, in studies that reported both rates of abnormal baseline LVEF and change in chemotherapy decision ($n = 1,080$), 7 of the 20 patients with abnormal baseline LVEF results (35%) had their chemotherapy regimen changed accordingly.

Predictors of abnormal LVEF

Two studies reported a non-statistically significant trend to higher prevalence of underlying cardiovascular risk factors (smoking, hypertension, dyslipidemia and diabetes) in patients with abnormal vs. normal baseline LVEF [15, 16]. As well, in the study by Jeyakumar et al., all four patients with abnormal baseline LVEF were smokers and older than 65 years of age [14]. Finally, Peddi et al. showed that smoking, hypertension, and family history of coronary artery

Table 1 Included studies are described

Study	Year	Type	Country	Modality	Sample size	Age	Abnormal LVEF	Change in decision	Her-2+	Metastatic breast cancer
Sabel et al.	2001	Journal	USA	MUGA	62	51	Y	Y	NR	N
McIlroy et al.	2004	Abstract	UK	MUGA	151	55	N	Y	NR	Y
Jeyakumar et al.	2012	Journal	CAN	MUGA	198	62	Y	Y	Y	N
Abu-Khalaf et al.	2013	Abstract	USA	MUGA	702	51	Y	N	NR	NR
Mina et al.	2015	Journal	LEBANON	ECHO	220	NR	Y	Y	Y	N
Peddi et al.	2016	Abstract	USA	ECHO	482	52	N	Y	NR	NR
Truong et al.	2016	Journal	USA	MIXED	600	48	Y	Y	Y	N
Yoon et al.	2016	Journal	KOREA	ECHO	763	56	Y	N	Y	Y

Type of study is expressed as conference abstract or journal article. Modality describes imaging modality utilized to assess baseline LVEF, either by echocardiography (ECHO), multi-gated acquisition scan (MUGA), or both (MIXED)

Abnormal LVEF describes studies that included data on abnormal baseline LVEF, Yes (Y) or No (N). Abnormal LVEF was defined as < 49% [12], < 50% [14, 15, 18] and < 55% [17]. Change in chemotherapy decision describes studies that reported data on this outcome, Yes (Y) or No (N). Four studies reported the proportion of Her2 (+) patients. These were 10% [14], 24% [15], 34% [16] and 74% [17]. Two studies included patients with mBC: one of which did not report the proportion [13] and the other reported a proportion of 10% [17]

N sample size. Age is expressed in median years. *NR* not reported

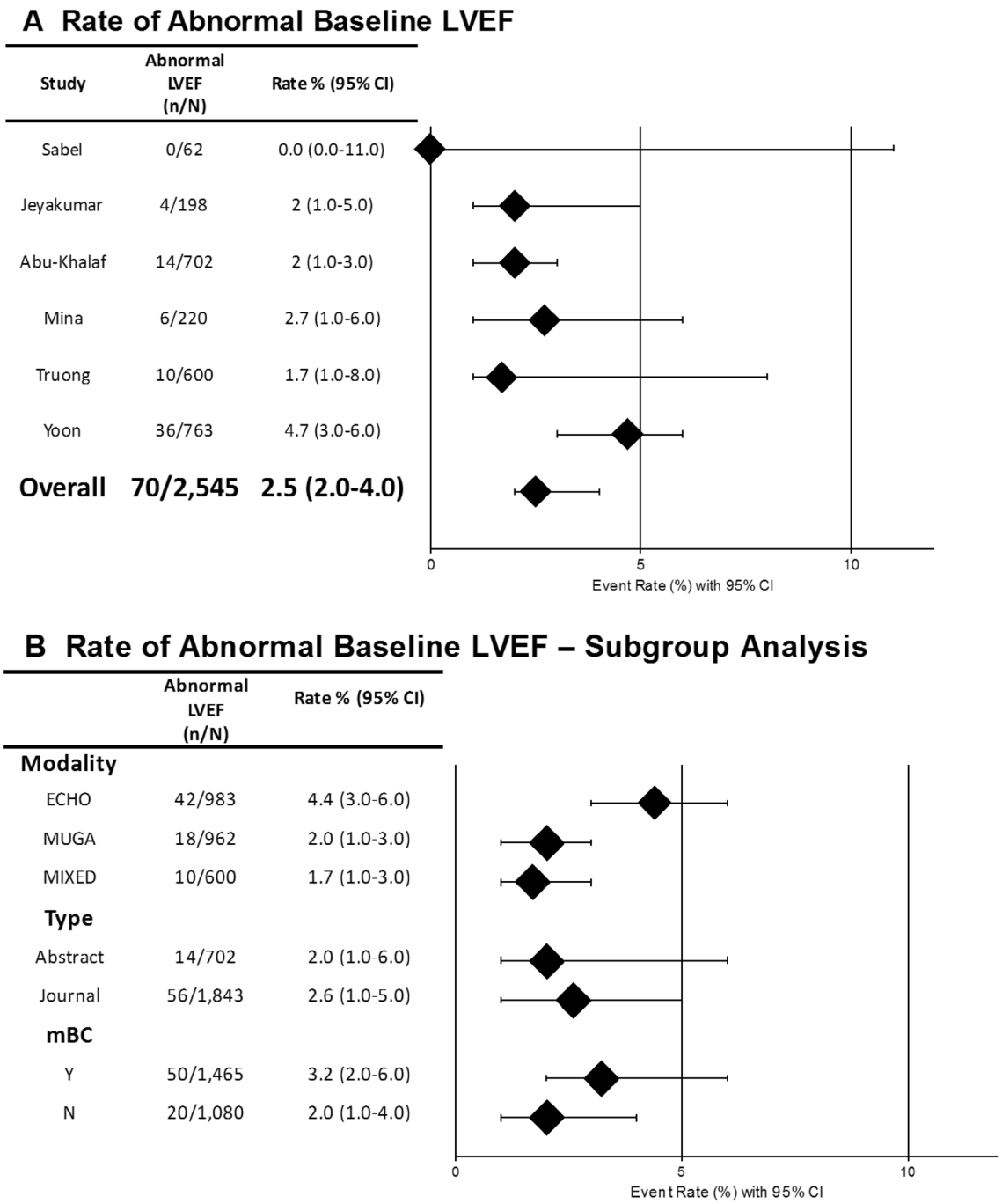

Fig. 1 Rate of abnormal baseline LVEF (**a**). The rate is determined by the number of events (abnormal baseline LVEF = *n*)/the number of baseline LVEF assessments (*N*). The overall abnormal baseline LVEF rate is estimated with a 95% confidence interval using a random-effects statistical model. The *Q*-value for heterogeneity among studies is 15.128 with *p*-value 0.010. Studies are sub-grouped by LVEF determination modality (ECHO vs. MUGA vs. MIXED) publication type (Abstract vs. Journal) and inclusion of mBC patients (yes vs. no) (**b**)

disease correlated with abnormal baseline LVEF by logistic regression [19].

Discussion

The clinical utility of routine baseline LVEF assessments prior to AA in all patients with EBC is uncertain. In this systematic-review and meta-analysis, a small proportion of

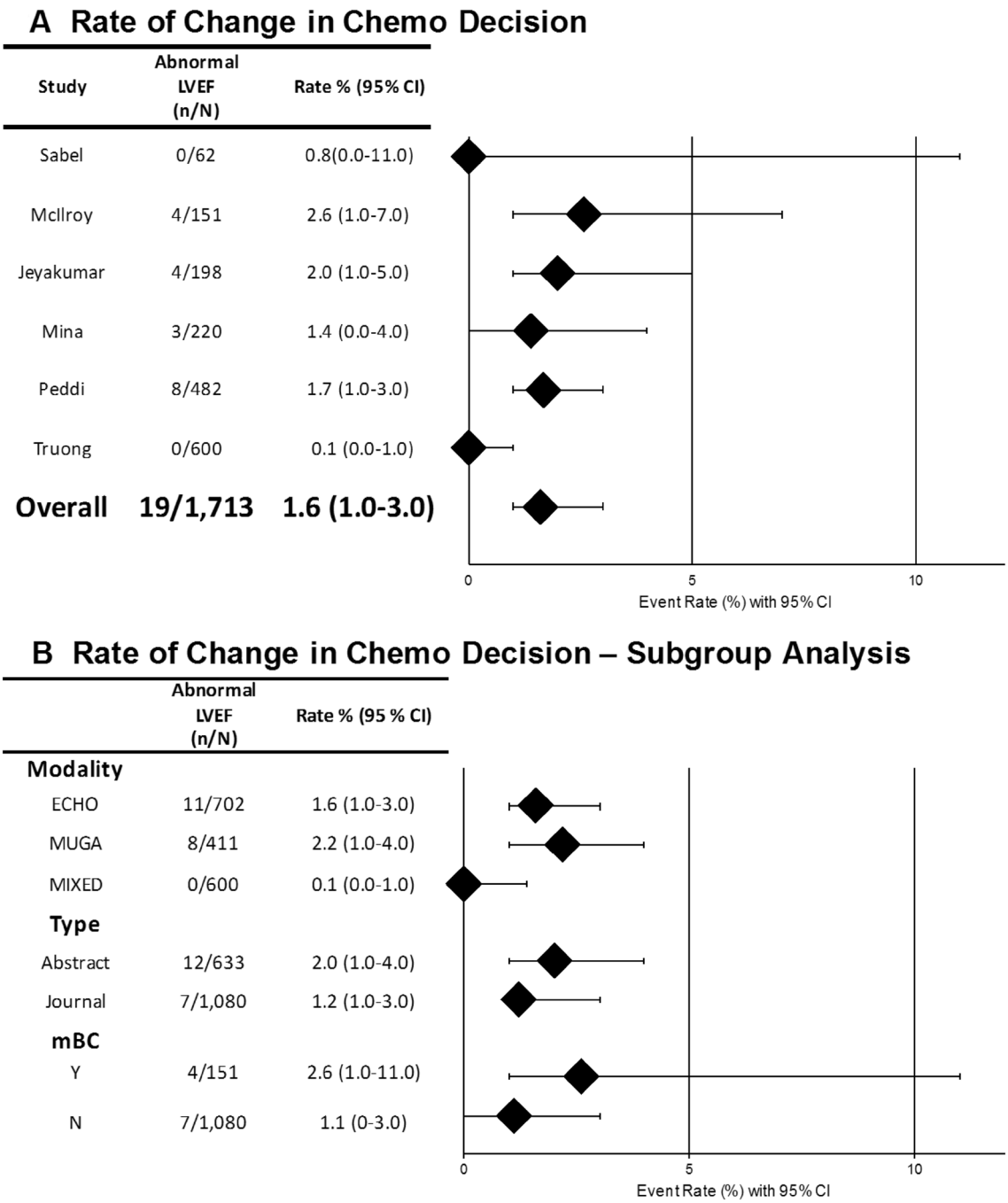

Fig. 2 Rate of chemotherapy decision change (**a**). The rate is determined by the number of events (changes in chemotherapy decision = *n*)/number of baseline LVEF assessments (*N*). Overall change in chemotherapy decision event rate is estimated with a 95% confidence interval using a random-effects statistical model. The *Q*-value for heterogeneity is 5.962, I^2 is 16.132 with *p*-value 0.310. Studies are sub-grouped by LVEF determination modality (ECHO vs. MUGA vs. MIXED), publication type (Abstract vs. Journal) & inclusion of mBC patients (yes vs. no) (**b**)

patients (2.5%, 95% CI 2.0–4.0%) had abnormal baseline LVEF and even fewer (1.6%, 95% 1.0–3.0%) had a change in chemotherapy decisions accordingly. When adjusted for studies that included only EBC patients, these rates were still very low; 2.0% (95% 1.0–4.0%) and 1.1% (95% CI 1.0–3.0%), respectively. These estimates should be examined within the context of a number of caveats, including the lack of long-term data regarding patient outcomes, ongoing "Choosing Wisely" Campaigns and yet-to-be conducted cost-effectiveness analysis.

Routine baseline cardiac assessments prior to AA are often conducted for a number of reasons. Most commonly, the goal is to identify patients with low/abnormal LVEF who are considered at high-risk for AA cardio-toxicity, and thus often offered non-anthracycline-based chemotherapy [8–10]. More recently, baseline cardiac assessments, in conjunction with underlying cardiovascular risk factors, are also conducted to identify patients at high risk for anthracycline cardio-toxicity in whom cardio-protective interventions (e.g., exercise or pharmacologic interventions) could be employed prior to or concurrent with AA to minimize the cardiotoxicity risks [20–22]. Finally, routine baseline cardiac assessments are also warranted in patients in whom serial cardiac assessments are planned, including those with Her-2 positive diseases undergoing trastuzumab-based therapy. The results of this systematic review and meta-analysis are, therefore, applicable to centres where baseline cardiac assessments are only implemented to identify patients with low/abnormal LVEF in whom AA would not be considered.

The observed higher rate of abnormal baseline LVEF compared with the rate of change in chemotherapy decisions prompted by baseline LVEF results raises the possibility that decision to proceed with anthracycline chemotherapy may also be influenced by other factors. However, inconsistencies in risk factor reporting across studies made these variables unamenable to meta-analysis. Still, data from individual studies suggest that underlying patient characteristics (i.e., cardiovascular risk factors) could potentially identify patients at low/high risk of an abnormal baseline LVEF. As such, a risk-based approach for LVEF assessments prior to AA could be considered, whereby EBC patients with low cardiovascular risk could forego baseline LVEF assessments whereas high-risk patients would be ineligible for anthracyclines, thus not requiring a baseline LVEF assessment. In patients with moderate cardiovascular risk, baseline LVEF assessment would be warranted to further risk stratify and determine appropriateness for anthracyclines.

This study has limitations. First, systematic reviews carry the potential for publication bias, which we attempted to minimize by also including conference abstracts in our analysis. Nonetheless, the lack of detailed results in the studies presented as abstracts alone was a limitation. However, subset analysis (Figs. 1b, 2b) according to publication type (journal vs. abstract) showed no difference in the primary outcomes. Second, only one study reported data on the incidence of future heart failure in relation to baseline LVEF results, which prevents us from making any conclusions on this potentially impactful outcome. Third, our results primarily apply to a specific population of EBC patients and cannot be generalized to all patients with mBC who may have higher cardio-toxic risks. Lastly, the studies we identified utilized various imaging modalities (MUGA and/or ECHO) for the baseline assessments of cardiac function. These modalities have different characteristics and varying sensitivities and specificities for abnormal cardiac function. The rate of abnormal baseline LVEF in this meta-analysis was 2% (95% CI 1.0–3.0%) in patients who had their LVEF assessed by MUGA vs. and 4.4% in those assessed by ECHO (95% CI 3.0–6.0%).

In conclusion, routine baseline cardiac assessments prior to AA in all EBC patients have low yield and infrequently affect clinical management. However, our systematic review could not identify a subset of patients in whom baseline LVEF assessments could be safely omitted. Further studies should attempt to better identify patients for whom cardiac imaging prior to AA is more likely to change chemotherapy decisions. This could prevent unnecessary delays to adjuvant chemotherapy for a high proportion of patients with EBC, in addition to potentially being a more cost-effective approach.

Funding This study did not receive any funding.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human and Animal Rights Statement This article does not contain any studies with human participants or animals performed by any of the authors.

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