

REVIEW

Beta-blockers in early-stage breast cancer: a systematic review and meta-analysis

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Background: Preclinical and retrospective studies suggest that beta-blockers are active against breast cancer. We carried out a systematic review and meta-analysis to assess the impact of beta-blockers on the outcomes of patients with early-stage breast cancer.

Methods: A systematic literature search was performed to identify studies comparing outcomes of patients with early-stage breast cancer according to beta-blocker use (yes versus no). The primary endpoint was recurrence-free survival (RFS), defined as the occurrence of breast cancer recurrence or death. Secondary objectives were pathologic complete response (pCR), breast cancer recurrence, breast cancer-specific mortality and overall survival (OS). Hazard ratios (HRs) or odds ratios (ORs) and 95% confidence intervals (CIs) were extracted from each study and a pooled analysis with the random-effect model was conducted. The Higgins' *I*-squared test was used to quantify heterogeneity. Egger's test was applied to assess publication bias. All *P* values were two-sided and considered significant if ≤ 0.05 .

Results: Overall, 13 studies were included as follows: RFS (6), pCR (2), breast cancer recurrence (6), breast cancer-specific mortality (7) and OS (5). The use of beta-blockers was associated with a significant RFS improvement in the overall population ($N = 21\ 570$; HR 0.73; 95% CI, 0.56-0.96; $P = 0.025$) and in patients with triple-negative disease ($N = 1212$; HR 0.53; 95% CI, 0.35-0.81; $P = 0.003$). No significant differences in terms of pCR ($N = 1554$; OR 0.77; 95% CI, 0.44-1.36; $P = 0.371$), breast cancer recurrence ($N = 37\ 957$; OR 0.66; 95% CI, 0.42-1.03; $P = 0.065$), breast cancer-specific mortality ($N = 64\ 830$; HR 0.77; 95% CI, 0.56-1.08; $P = 0.130$) or OS ($N = 103\ 065$; HR 1.03; 95% CI, 0.87-1.23; $P = 0.692$) were observed according to beta-blocker use.

Discussion: In this meta-analysis, beta-blocker use was associated with a longer RFS in patients with early-stage breast cancer, with a more pronounced effect observed in those with triple-negative disease. Beta-blockers arise as an interesting option to be explored in prospective studies for patients with early-stage breast cancer.

Key words: breast cancer, early stage, beta-blocker, recurrence

INTRODUCTION

Breast cancer is the most frequent malignancy and the leading cause of cancer deaths in women worldwide.¹ The vast majority of patients with newly diagnosed breast cancer present with early-stage disease (no evidence of distant metastases), being thus candidates to receive treatments with curative intention.² Although current standard-of-care treatments for early-stage breast cancer yield excellent long-term results, unfortunately a large

number of patients still experience recurrences, and thus efforts to improve the outcomes of this population are needed.³

In preclinical studies, stress and adrenergic activation stimulate proliferation, invasion and migration of breast cancer cells, and this effect can be effectively inhibited by beta-blockers.⁴⁻⁶ Moreover, the inhibition of adrenergic stimulation by beta-blockers may present a direct cytotoxic activity against cancer cells.^{7,8} Beta-blockers can also stimulate the production of inflammatory cytokines, induce lymphocyte infiltration and inhibit angiogenesis in the tumoral stroma, effects that may enhance the activity of anticancer treatments.⁹⁻¹¹ The evidence of preclinical activity against breast cancer, combined with the low cost and the manageable safety profile of beta-blockers generate interest in the repurposing of these drugs as an attempt to optimize the treatment of patients with breast cancer.¹²

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Some retrospective studies suggest that the use of beta-blockers is associated with a favorable prognosis in patients with breast cancer.^{13,14} Meta-analyses assessing the impact of beta-blocker use in patients with breast cancer provide conflicting results so far. However, as these meta-analyses pooled studies that included patients with advanced and early-stage disease, the effects of beta-blockers on the outcomes of those with early-stage breast cancer remain unclear.¹⁵⁻¹⁷

The early disease may be the most adequate setting to evaluate the real impact of beta-blockers on patients with breast cancer, since patient outcomes in this scenario are not influenced by potential subsequent lines of treatment, as it occurs in those with advanced disease.^{18,19} In this regard, we carried out a systematic review and meta-analysis to assess the impact of beta-blockers on the outcomes of patients with early-stage breast cancer.

MATERIALS AND METHODS

The present study is a quantitative synthesis and meta-analysis based on published or publically available data from studies that reported outcomes of patients with early-stage breast cancer according to beta-blocker use (yes versus no).

Objectives and endpoints

The primary objective was to compare the outcomes of patients with early-stage breast cancer who received beta-blockers versus those who did not. The primary endpoint was recurrence-free survival (RFS), defined as the occurrence of either a breast cancer recurrence (local, regional or distant) or death, whichever occurred first.

Subgroup analyses were planned to assess RFS according to beta-blocker use per breast cancer subtype [triple-negative, human epidermal growth factor receptor 2 (HER2)-positive and luminal] and beta-blocker class (non-selective and β 1-selective).

Secondary objectives were to assess pathologic complete response (pCR), breast cancer recurrence, breast cancer-specific mortality and overall survival (OS) according to beta-blocker use.

Data sources and search strategy

A literature search in PubMed, Embase, the Cochrane Library and conference proceedings from major Oncology Conferences [American Society of Medical Oncology, European Society for Medical Oncology (ESMO), San Antonio Breast Cancer Symposium and ESMO Breast] was performed with no date restriction up to 31 October 2020. The search strategy was developed using the Patient, Intervention, Comparator and Outcome (PICO) framework and comprised keywords related to 'breast cancer', 'beta-blocker' and 'recurrence'.²⁰ The detailed search strategy used in one database (PubMed) is provided as [Supplementary material](https://doi.org/10.1016/j.esmooop.2021.100066), available at <https://doi.org/10.1016/j.esmooop.2021.100066>.

Two reviewers (RC and EA) independently evaluated the titles and the abstracts of the identified studies and reviewed the search results to apply eligibility criteria; one additional author (EdA) was invited to solve any potential discrepancies. Cross-referencing from relevant studies and review articles on the topic was carried out to confirm that all eligible studies were included. This meta-analysis was conducted and reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines for systematic reviews (specifications provided as [Supplementary material](https://doi.org/10.1016/j.esmooop.2021.100066), available at <https://doi.org/10.1016/j.esmooop.2021.100066>), and registered before its initiation in the PROSPERO database (registration number CRD42020201743; full protocol available on the website).²¹

Selection of the articles

Eligible studies had to meet the following criteria: had published, presented, or otherwise publically available data; reported patient outcomes for at least one of the endpoints of this meta-analysis according to beta-blocker use (yes versus no); included only patients with early-stage breast cancer (or reported data for this subgroup of patients separately from those with advanced disease).

The definition of RFS was incorporated from each study, as long as both breast cancer recurrence and death were part of this endpoint. The definition of beta-blocker use was incorporated from each study, with no restriction according to beta-blocker class, timing or duration of administration.

Studies for which insufficient or no results were available at the time of the literature search, those including only patients with advanced breast cancer, those in which the effects of beta-blocker use were analyzed together with other medications (such as statins or antihypertensives), those with insufficient data regarding beta-blocker use or patient outcomes, and those not published in English were excluded.

Statistical analysis

For the primary objective and its respective subgroup analyses, and for the secondary objectives OS and breast cancer-specific mortality, hazard ratios (HRs) were extracted from each study for the comparison between patients who received beta-blockers versus those who did not.

For the secondary objectives pCR and breast cancer recurrence, odds ratios (ORs) were extracted from each study (whenever available), or calculated according to the number of events occurring in patients who received beta-blocker versus those who did not.

For each HR or OR estimate, 95% confidence intervals (CIs) were computed. Pooled HRs and ORs using the random-effects model were computed with the method of DerSimonian and Laird. The Higgins' I^2 index was computed to obtain a quantitative measure of the degree of inconsistency in the results of the included studies. To assess whether the pooled HRs or OR estimates were stable or strongly dependent on one or few studies, sensitivity

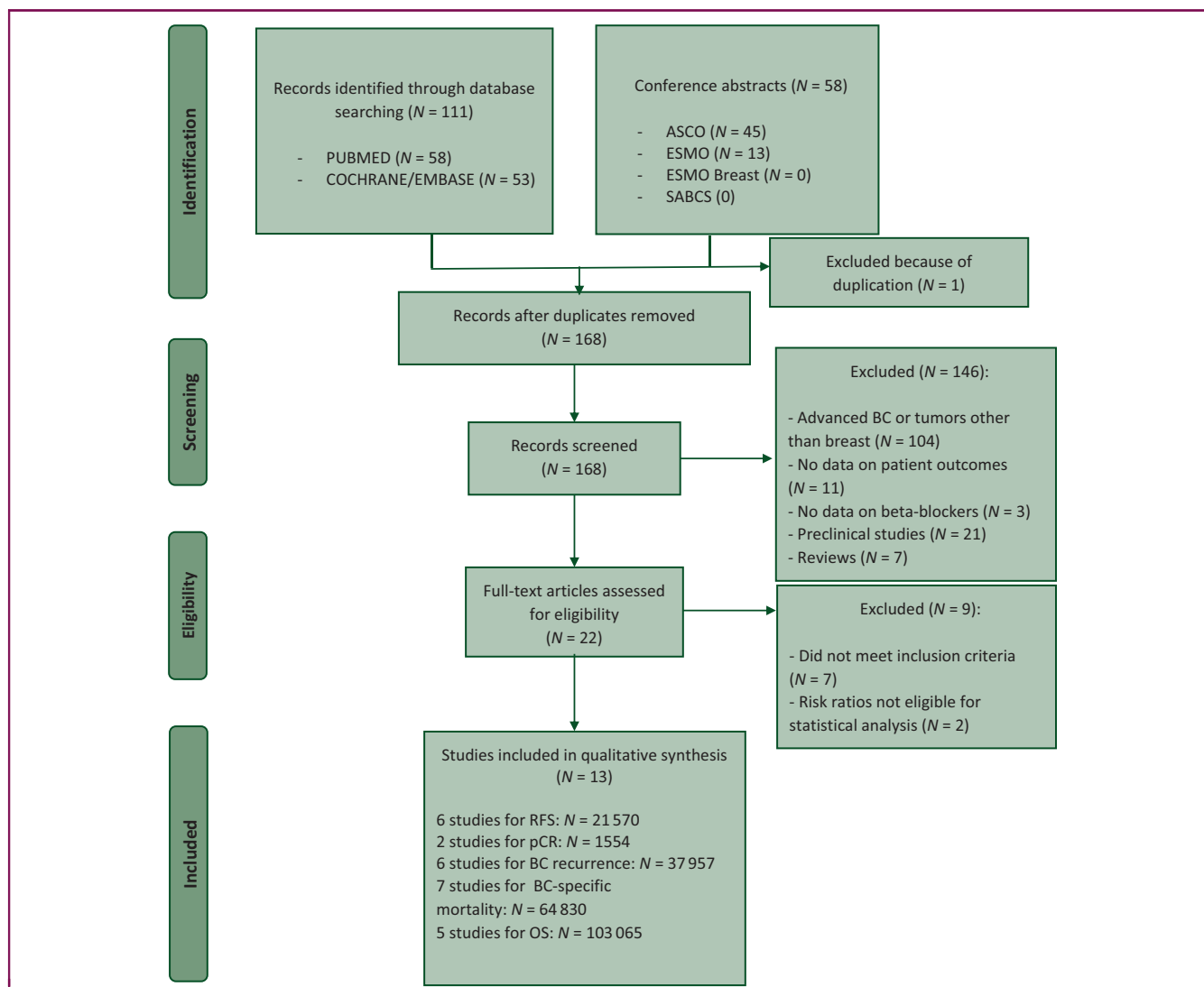


Figure 1. PRISMA chart of study selection for the meta-analysis.

ASCO, American Society of Medical Oncology; BC, breast cancer; ESMO, European Society for Medical Oncology; pCR, pathologic complete response; OS, overall survival; RFS, recurrence-free survival; SABCS, San Antonio Breast Cancer Symposium.

analyses were conducted by interactively recalculating the pooled HR or OR estimates after exclusion of each single study. Egger's test was applied to assess the occurrence of publication bias. All reported *P* values were two-sided and considered significant if ≤ 0.05 . All statistical analyses and the generation of forest plots were conducted using Stata Software Version 13.1 (Stata-Corp LP, College Station, TX). The Newcastle-Ottawa Scale was employed to assess the quality of the data obtained and the risk of bias in each study (Supplementary Tables S1 and S2, available at <https://doi.org/10.1016/j.esmooop.2021.100066>).

RESULTS

From the 169 records initially identified, 168 remained after duplicate removal and were screened, with 146 being excluded for the following reasons: 104 included patients with advanced breast cancer or tumors other than breast cancer, 21 were preclinical studies, 11 did not report patient outcomes, 7 were reviews, and 3 did not report data on

beta-blockers. The remaining 22 records were fully assessed for eligibility, with 7 being excluded for not meeting eligibility criteria and 2 for reporting risk ratios discrepant from the remaining studies for that same endpoint. Overall, 13 studies were included: 6 for RFS; 2 for pCR; 6 for breast cancer recurrence; 7 for breast cancer-specific mortality; and 5 for OS.^{13,14,22-32} The PRISMA chart of study selection is provided in Figure 1. The characteristics of each study included are presented in Supplementary Table S3, available at <https://doi.org/10.1016/j.esmooop.2021.100066>.

The study by Barron et al²² had two separate cohorts of patients ('propranolol' and 'atenolol') eligible for the breast cancer-specific mortality analysis, and thus data from this study were extracted and reported as two independent studies.

RFS according to beta-blocker use—overall population

With data available from six studies (N = 21 570), beta-blocker use was significantly associated with improved

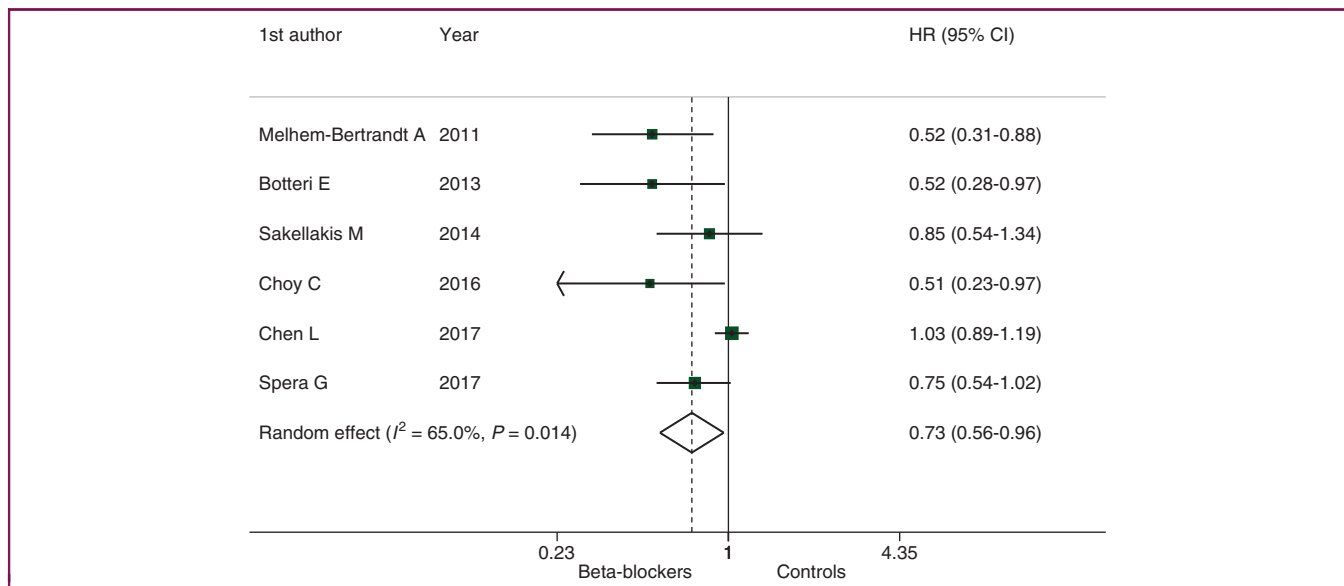


Figure 2. RFS according to beta-blocker use in patients with early-stage breast cancer ($N = 21\ 570$). CI, confidence interval; HR, hazard ratio.

RFS (HR 0.73; 95% CI, 0.56-0.96; $P = 0.025$) in patients with early-stage breast cancer. Egger's test suggested the occurrence of publication bias ($P = 0.005$) and significant heterogeneity was observed in this analysis ($I^2 = 65\%$, $P_{\text{heterogeneity}} = 0.014$; Figure 2). In sensitivity analysis, heterogeneity was eliminated and the association between beta-blocker use and improved RFS remained statistically significant (HR 0.67; 95% CI, 0.55-0.83; $P < 0.001$; $I^2 = 0$, $P_{\text{heterogeneity}} = 0.458$) after the exclusion of one study (Chen et al.³¹; Supplementary Table S4, available at <https://doi.org/10.1016/j.esmooop.2021.100066>).

RFS according to beta-blocker use—per breast cancer subtype

Data were not available in the studies included to allow the assessment of RFS according to beta-blocker use in patients with HER2-positive and luminal breast cancer subtypes.

With data available from three studies ($N = 1212$), beta-blocker use was significantly associated with improved RFS (HR 0.53; 95% CI, 0.35-0.81; $P = 0.003$) in patients with triple-negative early-stage breast cancer. Egger's test did not suggest the occurrence of publication bias ($P = 0.385$) and no significant heterogeneity was observed in this analysis ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.436$; Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmooop.2021.100066>). Sensitivity analysis is provided as Supplementary Table S5, available at <https://doi.org/10.1016/j.esmooop.2021.100066>.

RFS according to beta-blocker use—per beta-blocker class

Two studies reported RFS according to beta-blocker class, with a total of 3847 patients who received non-selective beta-blockers and 8220 who received β 1-selective beta-blockers.

No significant RFS difference was observed according to non-selective (HR 1.01; 95% CI, 0.87-1.17; $P = 0.902$) or β 1-

selective beta-blocker use (HR 0.97; 95% CI, 0.87-1.08; $P = 0.599$) in patients with early-stage breast cancer. No significant heterogeneity was observed in these analyses ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.795$, Supplementary Figure S2A, available at <https://doi.org/10.1016/j.esmooop.2021.100066>; and $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.319$, Supplementary Figure S2B, available at <https://doi.org/10.1016/j.esmooop.2021.100066>, respectively).

pCR

Two studies reported pCR rates according to beta-blocker use ($N = 1554$). With a total of 251 events observed, no significant difference in terms of pCR was observed according to beta-blocker use (OR 0.77; 95% CI, 0.44-1.36; $P = 0.371$) in patients with early-stage breast cancer. No significant heterogeneity was observed in this analysis ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.558$, Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmooop.2021.100066>).

Breast cancer recurrence

With data available from six studies ($N = 37\ 957$), no significant difference in terms of breast cancer recurrence was observed according to beta-blocker use (OR 0.66; 95% CI, 0.42-1.03; $P = 0.065$) in patients with early-stage breast cancer. Egger's test did not suggest the occurrence of publication bias ($P = 0.887$), although significant heterogeneity was observed in sensitivity analysis ($I^2 = 93.5\%$, $P_{\text{heterogeneity}} < 0.001$; Figure 3). After the exclusion of one study (Chen et al.³¹), heterogeneity was eliminated and beta-blocker use was significantly associated with a lower likelihood of breast cancer recurrence (OR 0.59; 95% CI, 0.48-0.73; $P < 0.001$; Supplementary Table S6, available at <https://doi.org/10.1016/j.esmooop.2021.100066>).

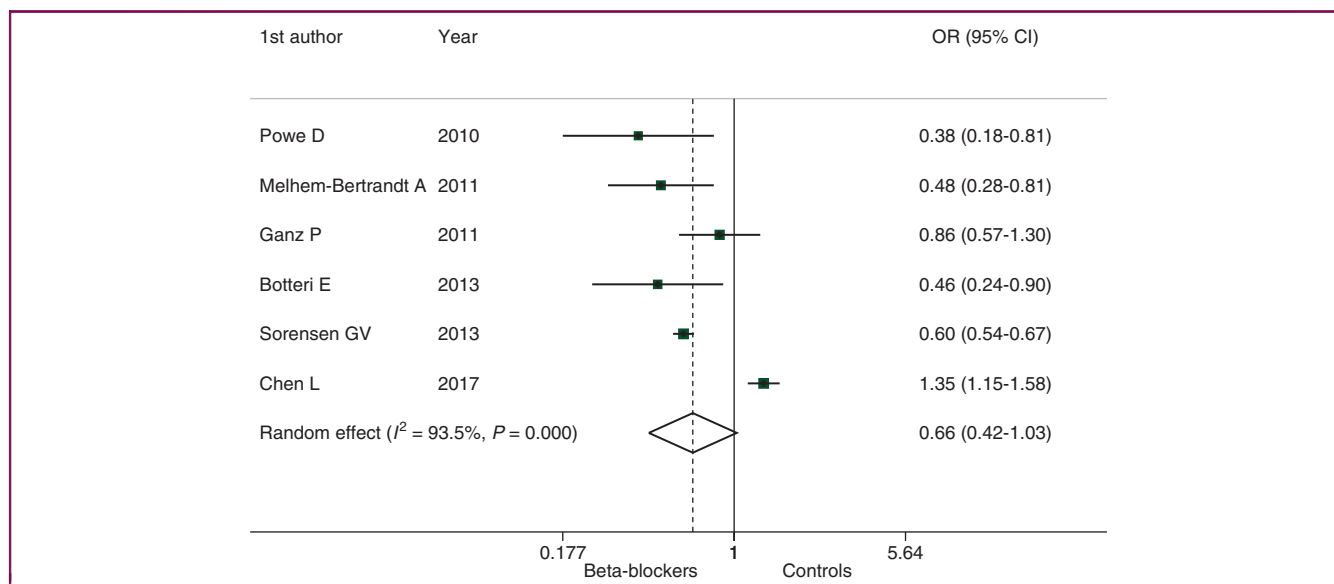


Figure 3. Breast cancer recurrence according to beta-blocker use in patients with early-stage breast cancer ($N = 37\,957$). CI, confidence interval; OR, odds ratio.

Breast cancer-specific mortality

With data available from seven studies ($N = 64\,830$), no significant difference in terms of breast cancer-specific mortality was observed according to beta-blocker use (HR 0.77; 95% CI, 0.56-1.08; $P = 0.130$) in patients with early-stage breast cancer. Egger's test suggested the occurrence of publication bias ($P = 0.002$), and significant heterogeneity was observed in this analysis ($I^2 = 75.1\%$, $P_{\text{heterogeneity}} < 0.001$; Figure 4). In sensitivity analysis, the exclusion of each study individually did not eliminate heterogeneity. After the exclusion of one study (Chen et al.³¹), beta-blocker use was significantly associated with a lower likelihood of breast cancer-specific mortality (OR 0.67; 95% CI, 0.46-0.98; $P = 0.039$; Supplementary Table S7, available at <https://doi.org/10.1016/j.esmooop.2021.100066>).

OS

With data available from five studies ($N = 103\,065$), no significant difference in terms of OS was observed according to beta-blocker use (HR 1.03; 95% CI, 0.87-1.23; $P = 0.692$) in patients with early-stage breast cancer. No significant heterogeneity was observed in this analysis ($I^2 = 29.9\%$, $P_{\text{heterogeneity}} = 0.222$; Figure 5). Egger's test did not suggest publication bias ($P = 0.404$). In sensitivity analysis, after the exclusion of one study (Melhem-Bertrandt et al.²³), beta-blocker use was associated with worse OS (HR 1.11; 95% CI, 1.02-1.22; $P = 0.020$; Supplementary Table S8, available at <https://doi.org/10.1016/j.esmooop.2021.100066>).

DISCUSSION

Although no prospective data support the administration of beta-blockers to patients with breast cancer, this class of drugs has shown interesting signs of activity in preclinical studies, and retrospective series suggest a potential favorable prognostic effect associated with the administration of

beta-blockers for patients with breast cancer.^{5,7,9,10,13,14} By pooling data from 13 studies that included more than 103 000 patients with early-stage breast cancer, this meta-analysis showed a significant association between the use of beta-blockers and an improvement in terms of RFS. Interestingly, in the subgroup of patients with triple-negative disease, in whom recurrences occur more frequently, a more pronounced RFS benefit was observed in those who received beta-blockers.

A trend for a favorable impact of beta-blockers in breast cancer recurrences and breast cancer-specific survival was also observed, whereas no effect on pCR or OS was demonstrated. Interestingly, when excluding the study by Chen et al.,³¹ significant heterogeneity was eliminated from the RFS and breast cancer recurrence analyses, whereas the associations between beta-blocker use and a lower likelihood of breast cancer recurrence and breast cancer-specific mortality became statistically significant. In the study by Chen et al.,³¹ only patients with stage I and II breast cancer were included. Since these patients present a favorable prognosis in comparison with those with stage III disease, the effects of an intervention that aims to prevent recurrences—such as beta-blockers—could become less evident in a lower-risk population. Furthermore, beta-blocker exposure in this study was defined as 'ever use after cancer', and thus some of these patients may have received beta-blockers after breast cancer treatment, which is curative in the vast majority of these individuals.^{3,31} Also in the study by Chen et al.,³¹ although efficacy analyses were adjusted for prognostic factors, important variables such as body mass index and HER2 status were not included in the model, so an imbalance between groups in terms of these prognostic variables may have impacted its results.^{31,33-35}

Around 90% of patients with breast cancer present with early-stage disease, and the vast majority of these individuals will be cured with currently available standard

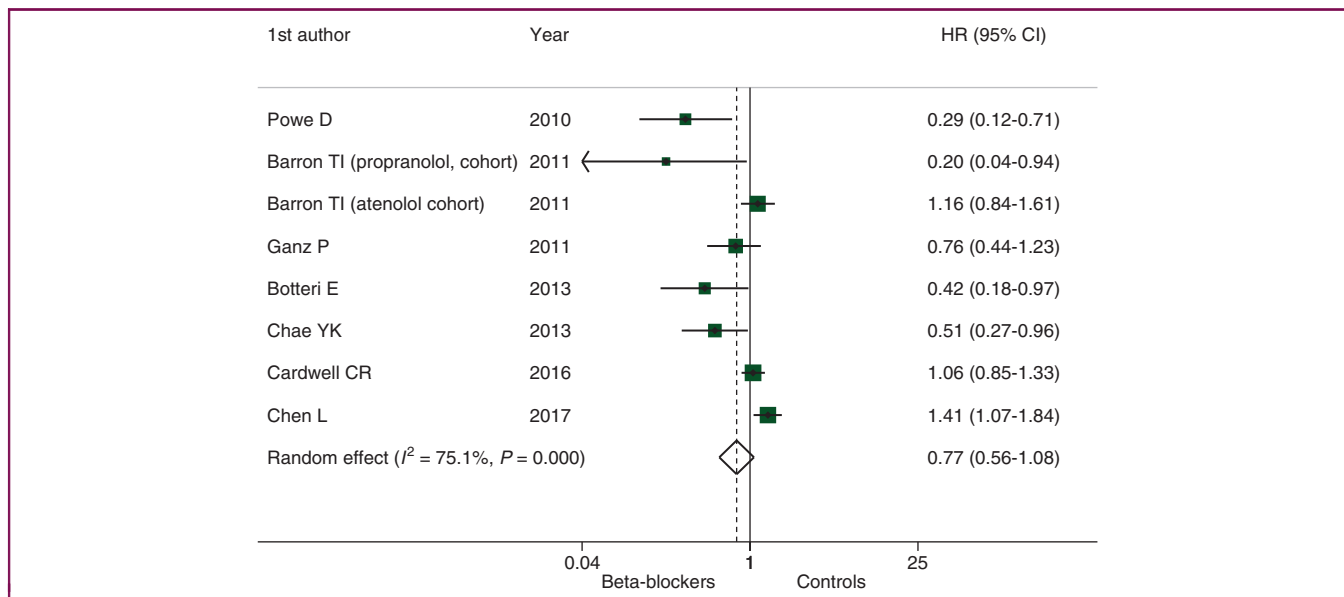


Figure 4. Breast cancer-specific mortality according to beta-blocker use in patients with early-stage breast cancer (N = 64 830). CI, confidence interval; HR, hazard ratio.

treatments.³ Despite being highly effective, treatment of early-stage breast cancer is associated with a non-negligible risk of adverse events that may compromise a patient’s quality of life.^{36,37} Moreover, the costs of incorporating novel treatments into the therapeutic arsenal of breast cancer present a heavy burden for health care systems worldwide.³⁸⁻⁴⁰ Therefore, it is essential to develop alternatives to optimize patient outcomes and minimize not only clinical but also financial toxicities. The whole process of drug development ‘from bench to bed’ is dispendious and resource-consuming, and it leads to drug approval in only around 10% of the cases.^{12,41} In this regard, repurposing of drugs that are already in use for other indications arises as an attractive strategy to improve cancer treatment

spending less time and resources, due to the possibility of expediting the drug development process by starting it at more advanced phases.⁴² The results of the present meta-analysis support preclinical data and findings from previous studies, underscoring the potential of beta-blockers as an interesting class of drugs to be repositioned and evaluated as part of the treatment of patients with early-stage breast cancer.^{8,10,13,14}

Previous meta-analyses present conflicting results on the effects of beta-blockers in patients with breast cancer.¹⁵⁻¹⁷ Notably, the inclusion of patients with advanced breast cancer—who typically receive several lines of treatment that impact their OS—together with those with early-stage disease render the interpretation of these data challenging.

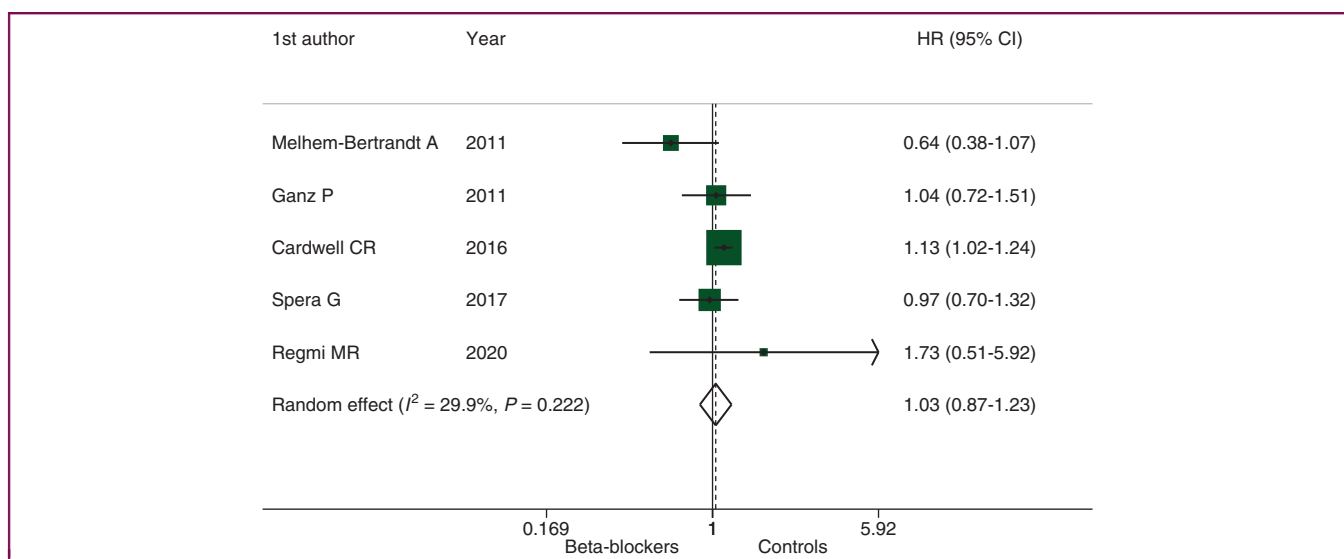


Figure 5. OS according to beta-blocker use in patients with early stage breast cancer (N = 103 065). CI, confidence interval; HR, hazard ratio.

Since the vast majority of patients with breast cancer present with early-stage disease, and considering the physical and psychological burden that a disease recurrence represents for these individuals, the benefit of a novel intervention such as beta-blockers would be more relevant for patients if it could be demonstrated in the early-stage disease setting.^{3,43} Indeed, the use of alternative endpoints such as RFS, invasive disease-free survival and pCR has been widely adopted in contemporary breast cancer trials to estimate the benefit of novel therapies, as an attempt to refine the evaluation of treatment benefit for patients with early-stage breast cancer without relying only on OS as an endpoint.^{44,45} By including only patients with early-stage disease, this meta-analysis provides a comprehensive evaluation of the effect of beta-blockers in this population, with our results suggesting that beta-blockers may be beneficial in terms of preventing recurrences.

In preclinical studies, beta-blockers inhibit angiogenesis, stimulate T-cell recruitment, increase the production of pro-inflammatory cytokines and induce immune activation, which ultimately leads to an inhibition of cancer proliferation and metastases.^{4,5,7-10} Notably, these effects seem of particular interest for patients with triple-negative breast cancer, which is considered the most 'immunogenic' breast cancer subtype, in which the benefit of immune checkpoint inhibitors has been initially demonstrated, being also the subgroup of patients who may derive some benefit from the addition of angiogenesis inhibitors to chemotherapy.⁴⁶⁻⁴⁸ Despite the limited number of studies included, the benefit of beta-blockers in patients with triple-negative disease in our subgroup analyses was more pronounced than the one observed in the overall population, building a rationale for further investigating this class of drugs, for example, in combination with immunotherapy in future studies for patients with triple-negative breast cancer.

Beta-blockers can be classified according to their affinity for the different beta-adrenergic receptors as β 1-selective and non-selective.⁴⁹ Some preclinical studies suggest that specifically the β 2-adrenergic receptor activation may modulate angiogenesis, proliferation and invasion.^{4,50} Moreover, in preclinical models of breast cancer, a significant cross-talk between β 2-adrenergic receptor and HER2 has been demonstrated, with β 2-adrenergic activation mediating resistance to HER2-blockade.⁵¹⁻⁵³ Accordingly, non-selective beta-blockers with activity against β 2-adrenergic receptors, such as propranolol, can block these effects, inhibit cancer growth and restore sensitivity to HER2-blockade.⁵¹⁻⁵³ Our subgroup analyses did not show any significant effect of beta-blockers in RFS per beta-blocker class. Notably, the limited number of studies included in these analyses precludes definitive conclusions regarding potential differences between the effects of distinct beta-blockers in patients with early-stage breast cancer, and this remains an interesting point to be clarified.

In addition to the provoking preclinical rationale supporting its activity against breast cancer, the favorable safety profile, the low cost and the fact that beta-blockers have been used in clinical practice for a long time to treat

cardiovascular diseases, the results of this meta-analysis bring an additional piece of evidence to motivate further studies to explore the benefits of beta-blockers for patients with early-stage breast cancer.^{4,8-10,54,55} Some ongoing trials aim to address this question (NCT01847001; NCT00502684), although the lack of interest from clinicians and sponsors in drug repurposing remains a barrier to patient recruitment, as evidenced by the early termination of one of such studies (NCT02596867) due to poor accrual. A promising niche to evaluate beta-blockers would be the subgroup of patients with triple-negative disease, who present unfavorable outcomes with the currently available standard treatments, but are also more likely to benefit from immunotherapy, a strategy that could be further evaluated in combination with beta-blockers to explore the potential immunomodulatory effects of these drugs.^{7,9,50} Biomarkers may also help in the identification of patients who benefit from beta-blockers and guide patient selection for future studies. As an example, our group previously demonstrated that a high expression of the β 2-adrenergic receptor gene (*ADRB2*)—which might occur as a result of beta-blocker use—may be associated with a favorable prognosis and also predict trastuzumab benefit in patients with HER2-positive early-stage breast cancer.^{11,56}

Some limitations need to be considered when interpreting our findings. This meta-analysis was not based on individual patient data, and all studies included were retrospective or exploratory analyses, increasing the chances of bias and/or missing data. Each study had its own definition of 'beta-blocker use', and thus the duration and the timing of beta-blocker exposure were not homogeneous. Indeed, in some studies patients with any previous beta-blocker exposure were included, whereas to assess any potential synergy between beta-blockers and anticancer treatments, ideally both medications should have been administered concomitantly. Missing data limited the sample size of subgroup and secondary objective analyses, and precluded some planned assessments such as the evaluation of beta-blocker effects in patients with HER2-positive and luminal tumors. Evaluation of beta-blocker toxicities—which is a critical endpoint for patients receiving treatment with curative intention—was not possible because these data were not available in the included studies, although the safety profile of these medications is well described in the medical literature.^{49,54} Despite the aforementioned limitations, this meta-analysis generates updated data that allows a comprehensive assessment of the effects of beta-blockers on the outcomes of patients with early-stage breast cancer.

In conclusion, the results of this meta-analysis showed that the use of beta-blockers was associated with improved RFS in patients with early-stage breast cancer, with a more pronounced association being observed in those with triple-negative disease. A trend favoring beta-blocker use was also observed in terms of preventing breast cancer recurrences and breast cancer specific mortality, whereas no effect on OS was demonstrated. Beta-blockers arise as a promising, safe, low-cost and widely available option to be

combined with standard and experimental treatments for patients with early-stage breast cancer in prospective studies.

FUNDING

None declared.

DISCLOSURE

RC has received speaker honoraria from Boehringer Ingelheim, AstraZeneca and Janssen, and travel grants from AstraZeneca and Pfizer, none related to the present work. EdA has received honoraria from Roche-Genentech, Libbs, Seattle Genetics, Novartis, Pierre Fabre; research grant from Roche-Genentech, AstraZeneca, GlaxoSmithKline/Novartis, Servier (to the institution), and travel grants from Roche-Genentech and GlaxoSmithKline, none related to the present work. All the other authors declare no conflicts of interest.

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