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ORIGINAL REPORT

Congestive Heart Failure Risk in Patients With Breast Cancer Treated With Bevacizumab

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A B S T R A C T

Purpose
Bevacizumab is a treatment option in patients with metastatic breast cancer. Congestive heart failure (CHF) has been reported, although the overall incidence and relative risk (RR) of this complication remains unclear. We performed an up-to-date, comprehensive meta-analysis to determine the risk of serious CHF in patients with breast cancer receiving bevacizumab.

Methods
The databases of Medline were searched for articles from 1966 to March 2010. Abstracts presented at the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium meetings were also searched for relevant clinical trials. Eligible studies include randomized trials with bevacizumab in patients with breast cancer. Adequate reporting of safety profile data was required for inclusion. Statistical analyses were conducted to calculate the summary incidence, RR, and 95% CIs by using random-effects models.

Results
A total of 3,784 patients were included. Overall incidence results for high-grade CHF in bevacizumab- and placebo-treated patients were 1.6% (95% CI, 1.0% to 2.6%) and 0.4% (95% CI, 0.2% to 1.0%), respectively. The RR of CHF in bevacizumab-treated patients was 4.74 (95% CI, 1.66 to 11.18; $P = .001$) compared with placebo-treated ones. In subgroup analyses, there were no significant differences in CHF incidence or risk between patients treated with low-dose (2.5 mg/kg) versus high-dose (5 mg/kg) bevacizumab or among patients treated with different chemotherapy regimens. No evidence of publication bias was observed.

Conclusion
This is the first comprehensive report to show that bevacizumab is associated with an increased risk of significant heart failure in patients with breast cancer.

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INTRODUCTION

In recent years, systemic therapy targeting vascular endothelial growth factor (VEGF) and its receptors has proven to be a successful strategy in patients with cancer. Bevacizumab is a widely used anti-VEGF monoclonal antibody targeting the VEGF ligand. It has been to shown to improve clinical outcomes in several malignancies, including advanced breast cancer, colorectal cancer, non–small-cell lung cancer, high-grade gliomas, and renal cell cancer, and it is currently approved by the US Food and Drug Administration for the treatment of these malignancies.[1]

The use of VEGF-targeted agents, including bevacizumab, is associated with class-effect adverse events, including hypertension, proteinuria, impaired wound healing, bleeding, and arterial and venous thromboembolism.[2-9]

The VEGF pathway is also thought to have an important role in cardiac physiology: mice lacking the VEGF gene have thinned myocardial walls and depressed basal contractile function.[10] In addition, VEGF-overexpressing mesenchymal stem cells may have a cardioprotective effect in the myocardium.[11] These data implicate a critical role for VEGF in coordinated tissue growth and angiogenesis in the heart and suggest that blocking this pathway may lead to a disruption in cardiac remodeling and consequently induce heart failure.

Congestive heart failure (CHF) associated with bevacizumab has been sporadically reported in several trials of bevacizumab in advanced solid tumors. This topic is of special importance in patients with

breast cancer, who may have prior or current exposure to known cardiotoxic agents, including anthracyclines and/or trastuzumab.[12] In this report, using a meta-analysis design, we sought to investigate the incidence and risk of CHF in an up-to-date meta-analysis of randomized, controlled trials of bevacizumab in patients with metastatic breast cancer.

PATIENTS AND METHODS

Selection of Studies

We reviewed PubMed citations from January 1966 to March 2010. The search criteria included only randomized trials published in the English language and the keywords bevacizumab (as well as its commercial name, Avastin) and breast cancer or *adenocarcinoma* of the breast. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (ASCO; http://www.asco.org/ASCO) conferences that took place between January 2004 and March 2010. We also searched the San Antonio Breast Cancer Symposium (SABCS; http://www.sabcs.org) abstracts between 2007 and 2009. When more than one publication was identified from the same clinical trial, we used the most recent or complete report of that trial. An independent search using the citation database Web of Science (developed by the Institute for Scientific Information) also was performed to ensure that no clinical trials were missed. The most recent package insert was also accessed to identify relevant information.

Data Extraction and Clinical End Points

Data abstraction was conducted independently by three investigators (T.K.C., F.A.B.S., and G.R.A.) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[13] and any discrepancies among reviewers were resolved by consensus. For each study, we extracted the following information: first author's name, year of publication, trial phase, underlying malignancy, number of enrolled patients, treatment arms, number of CHF events in experimental and control arms, median age, median follow-up, median treatment duration, median progression-free survival, bevacizumab dose, and reported CHF event.

The following adverse outcomes were considered as CHF events and were included in the analyses: left ventricular ejection fraction (LVEF) decline or dysfunction, CHF (not specified), and cardiomyopathy. Only the adverse events of grade 3 or higher (serious) according to the National Cancer Institute common toxicity criteria (NCI-CTC, version 2 or 3; http://ctep.cancer.gov), were included in the analysis, as trials rarely report all-grade or low-grade CHF. Trials that met the following criteria were included in our analysis: randomized, phase II, phase III, patients assigned to treatment with bevacizumab in only one of the arms, and adequate safety profile data available for CHF.

Statistical Analysis

For the calculation of incidence, the number of patients with CHF events and the number of patients treated with bevacizumab were extracted from the safety profile of selected clinical trials. The proportion of patients with those adverse outcomes and 95% CIs were derived from each trial. We also calculated relative risks (RRs) and CIs of CHF events in patients assigned to bevacizumab versus controls in the same trial. For studies reporting zero CHF events in a treatment or control arm, we applied a classic half-integer continuity correction to calculate the RR and variance.

Statistical heterogeneity among trials included in the meta-analysis was assessed by using the Cochran Q statistic, and inconsistency was quantified with the I^2 statistic ($100\% \times [Q - df] \div Q$) that estimates the percentage of total variation across studies due to heterogeneity rather than chance.[14] We considered an I^2 value of greater than 50% as indicative of substantial heterogeneity. When substantial heterogeneity was not observed, the pooled estimate calculated on the basis of the fixed-effects model was reported by using inverse variance method. When substantial heterogeneity was observed, the pooled estimate calculated on the basis of the random-effects model was reported by using the DerSimonian and Laird method that considers both within-study and between-study variations.[15] For studies with separate treatment arms evaluating low-dose or high-dose bevacizumab, we combined the two treatment arms for the overall analysis.[16]

We also examined a possible dose-response relationship between bevacizumab therapy and CHF events by additionally dividing bevacizumab trials into low dose (2.5 mg/kg/wk) and high dose (5 mg/kg/wk). To evaluate the influence of concomitant chemotherapy with bevacizumab, we also calculated the incidence and RR for patients treated with taxanes, capecitabine, and anthracyclines. To test for variation in risk estimates by bevacizumab dose, we conducted a meta-regression analysis. Finally, publication bias was evaluated through funnel plots (ie, plots of study results against precision) and with the Begg's and Egger's tests.[17,18] A two-tailed P value of less than .05 was considered statistically significant. All statistical analyses were performed by using Stata/SE version 11.0 software (Stata Corp, College Station, TX).

RESULTS

Population Characteristics

Our initial search yielded a total of 60 bevacizumab studies: 49 abstracts from PubMed and 11 from ASCO or SABCS meetings. After evaluating each study, 48 were initially excluded. Subsequently, we carefully screened each one of the remaining 12 trials and excluded an additional six trials for being duplicates, subgroup analyses only, or combined analyses. Six remaining trials were thoroughly evaluated, and only one did not report a detailed cardiac safety profile and thus was eliminated.[19] Finally, a total of five trials were selected for inclusion in the meta-analysis.[16,20-23] A detailed selection process is represented in Figure 1.

The baseline characteristics of each trial are listed in Table 1. Concomitant chemotherapeutic agents examined with bevacizumab included fluoropyrimidines, anthracyclines, and taxanes.

A total of 3,784 patients were available for the meta-analysis. All selected trials included metastatic patients with breast cancer, with adequate organ function, coagulation, and hematologic function. All included trials typically excluded patients with uncontrolled hypertension, clinically significant congestive heart failure, cerebrovascular disease or peripheral vascular disease, and unstable angina or recent history of myocardial infarction. All trials allowed inclusion of patients with prior anthracycline, but only one trial treated patients with concomitant anthracycline.[22] Only two trials allowed the inclusion of patients with human epidermal growth factor receptor 2 (HER2)–positive disease, both requiring prior treatment with trastuzumab, although only a small proportion of patients were HER2 positive on these two trials.[20,21] The most treatment-related reported Cardiotoxicity event was CHF, without additional clinical description.

Incidence of CHF

Among the 2,366 patients that received bevacizumab, 36 presented with high-grade CHF. By using a random-effects model for this analysis (heterogeneity test: $Q = 8.04$; $P = .090$; $I^2 = 50.2\%$), the overall incidence of high-grade CHF was 1.6% (95% CI, 1.0% to 2.6%). For the control group or placebo-treated group, there were four CHF events among 1,418 patients, which conferred an incidence of 0.4% (95% CI, 0.2% to 1.0%; heterogeneity test: $Q = 2.11$; $P = .715$; $I^2 = 0.0\%$; Table 2).

RR of CHF

We determined the overall RR of high-grade CHF from the five randomized, controlled trials. The overall RR of developing high-grade CHF with bevacizumab was 4.74 (95% CI, 1.84 to 12.19; $P = .001$) compared with patients who did not receive bevacizumab.

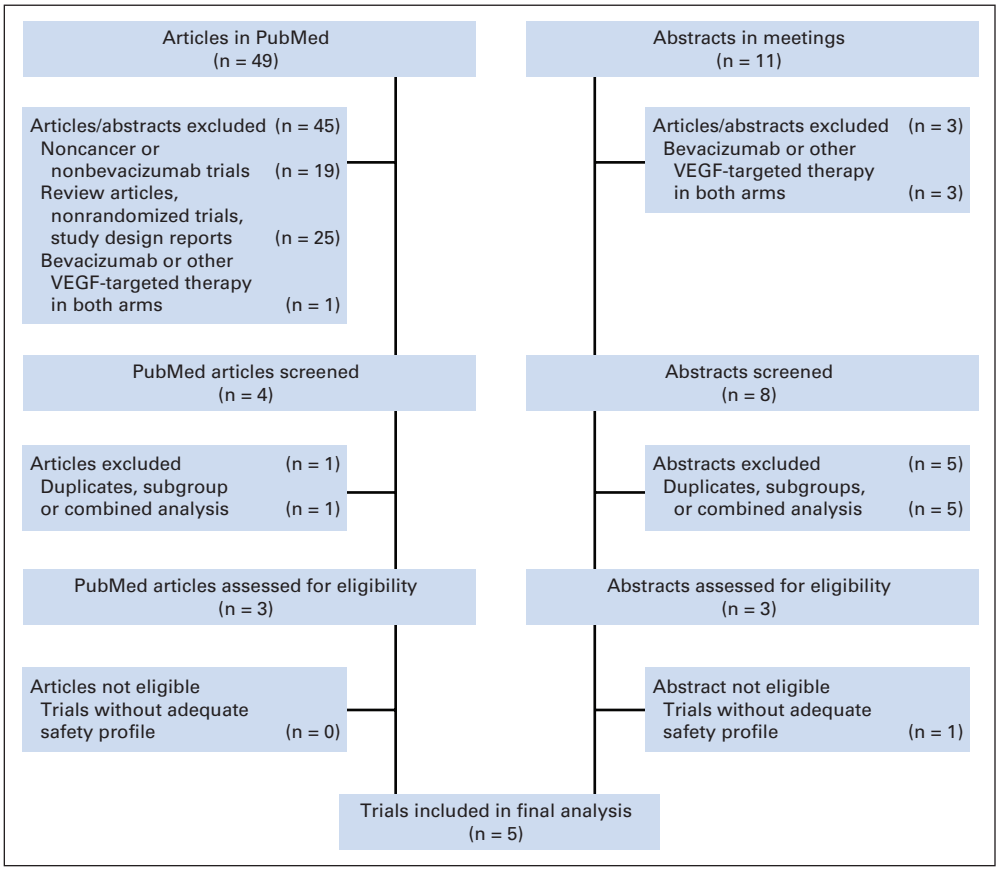

Fig 1. Selection process for randomized controlled trials included in the meta-analysis. VEGF, vascular endothelial growth factor.

No significant heterogeneity among the included trials was observed ($Q = 0.60$; $P = .963$; $I^2 = 0.0\%$; Fig 2).

Influence of Bevacizumab Dose

There are two approved doses for bevacizumab, 2.5 mg/wk (low dose) and 5.0 mg/wk (high dose). Therefore, we attempted to look at the incidence and RR stratified by bevacizumab dose. Five trials randomly assigned patients to high-dose bevacizumab (n = 3,534) and one study to low-dose bevacizumab (n = 486; Table 2). The incidence rates of CHF were 1.9% (95% CI, 1.3% to 2.5%) and 1.2% (95% CI, 0.4% to 3.7%) for the high and low doses, respectively. The overall RRs for the high and low doses were 4.46 (95% CI, 1.70 to 11.73) and 6.53 (95% CI, 0.34 to 125.7). When directly comparing the incidence of CHF with high- versus low-dose bevacizumab, no significant difference was found ($P = .48$). Similarly, when comparing the RRs of CHF for high- versus low-dose bevacizumab, we did not observe a statistically significant difference ($P = .81$).

Influence of Concomitant Chemotherapy

The concomitant chemotherapies administered were taxanes,[16,20,21] capecitabine,[20,22] or anthracyclines,[22] and the incidences of high-grade CHF were 1.7% (95% CI 1.0% to 2.7%), 1.9% (95% CI, 0.6% to 5.4%), and 2.8% (95% CI, 1.3% to 6.2%), respectively. The RRs for patients treated with taxanes, capecitabine, and anthracyclines were 5.42 (95% CI, 1.25 to 23.52), 2.77 (95% CI, 0.78 to 9.88), and 6.22 (95% CI, 0.35 to 109.4), respectively. There was not any statistically significant differences between the different chemotherapies on the incidence ($P = .51$) or RR ($P = .75$) of CHF (Table 2).

Quality of the Study

All trials included in the meta-analysis were randomized, multicenter, phase III trials.[16,20-23] Three trials were placebo-controlled and double-blinded studies,[16,22,23] whereas the remaining two trials were open-label studies.[20,21] Two trials have only been presented in abstract form to date, but we had access to full presentation slides from ASCO and SABCS virtual meetings.[22,23] The patients were stratified according to the type of report. We observed RRs of 4.25 (95% CI, 1.35 to 13.40; $P = .014$) and 5.94 (95% CI, 1.13 to 31.37; $P = .036$) for published studies and for trials presented in meeting, respectively. Additionally, patients from open-label trials had an RR of 4.45 (95% CI, 1.28 to 15.47; $P = .019$), whereas patients from placebo-controlled, double-blind studies had an RR of 5.16 (95% CI, 1.21 to 21.99; $P = .027$). For a quality analysis purpose, we attempted to quantify the magnitude of potential differences in RR by those factors by conducting a random-effects meta-regression, and we found that those factors did not seem to affect overall RR (all $P > .70$).

Publication Bias

No evidence of publication bias was detected for the incidence or RR of CHF in bevacizumab-treated patients with breast cancer by either the Egger's or the Begg's test (for incidence: Egger's $P = .29$, and Begg's $P = .46$;for RR: Egger's $P = .84$, Begg's $P > .99$).

DISCUSSION

To our knowledge, this is the first large report to show a significant increase in the risk of CHF in bevacizumab-treated patients with

Table 1. Baseline Demographic and Clinical Characteristics of the Trials Included in the Final Analysis

Study and Treatment Arm	Phase	No. of Patients Enrolled	Prior Anthracycline Exposure per Treatment Arm (%)	Proportion of HER2-Positive Patients (%)[a]	Median Follow-Up (months)	Age (years) Median	Age (years) Range	Median Treatment Duration (months)	Median PFS (months)	No. of Patients for Analysis	No. of CHF Events	Reported Events
Miller 2005[20] [b]	III	462			NR			NR				CHF, cardiomyopathy
Capecitabine + BEV HD			100	26.3		51	29-78		4.86	229	7	
Capecitabine			100	20.4		52	30-77		4.17	215	2	
Miller 2007[21] [c]	III	722										CHF
Paclitaxel + BEV HD			39.2	7.5	41.6	56	29-84	7.1	11.8	365	8[d]	
Paclitaxel			40.8	10.1	43.5	55	27-85	5.1	5.9	346	1	
Robert 2009[22] [e]	III	1,237	Prior anthracyclines allowed[f]	HER-2 positive patients not eligible		NR		NR				Left ventricular systolic dysfunction
Capecitabine + BEV HD					15.6				8.6	404	4	
Capecitabine + placebo					15.6				5.7	201	1	
Taxane + BEV HD					19.2				9.2	203	4	
Taxane + placebo					19.2				8.2	102	0	
Anthracycline + BEV HD					19.2				9.2	210	6	
Anthracycline + placebo					19.2				7.9	100	0	
Miles 2010[16] [g]	III	736		HER-2 positive patients not eligible	25[h]			NR				CHF
Docetaxel + BEV LD			53%			54	26-83		9.0	250	3	
Docetaxel + BEV HD			55%			55	27-76		10.1	247	0	
Docetaxel + placebo			55%			55	29-83		8.2	233	0	
Brufsky 2009[23] [i]	III	684	Prior anthracyclines allowed	HER-2 positive patients not eligible	NR			NR				Left ventricular systolic dysfunction
Chemotherapy + BEV HD						55	25-86		7.2	458	4	
Chemotherapy + placebo						55	23-90		5.1	221	0	

NOTE. All trials evaluated a metastatic breast cancer population. High-dose bevacizumab was 5.0 mg/kg/wk; low-dose bevacizumab was 2.5 mg/kg/wk.
Abbreviations: HER2, human epidermal growth factor receptor 2; CHF, congestive heart failure; BEV, bevacizumab; HD, high dose; NR, not reported; LD, low dose.
[a]Patients with HER2-positive disease received prior treatment with trastuzumab.
[b]Dosing for Miller 2005[20]: capecitabine 2,500 mg/m^2/day.
[c]Dosing for Miller 2007[21]: paclitaxel 90 mg/m^2 weekly on day 1 for 3 of 4 weeks.
[d]Data retrieved from the drug package insert.
[e]Dosing for Robert 2009[22]: capecitabine 1,000 mg/m^2 twice daily for 14 days; taxane (docetaxel 75 or 100 mg/m^2 every 3 weeks or protein-bound paclitaxel 260 mg/m^2 every 3 weeks); anthracycline-based chemotherapy (ie, adriamycin + cyclophosphamide; epirubicin + cyclophosphamide; fluorouracil, adriamycin, cyclophosphamide; fluorouracil, epirubicin, cyclophosphamide).
[f]Patients treated with capecitabine or taxane were allowed to have received prior treatment with anthracyclines.
[g]Dosing for Miles 2010[16]: docetaxel 100 mg/m^2 every 3 weeks.
[h]Median follow-up reported for the entire cohort.
[i]Dosing for Brufsky 2009[23]: Investigator choice of chemotherapy between taxane (ie, paclitaxel 90 mg/m^2/wk for 3 of 4 weeks; paclitaxel 175 mg/m^2, nab-paclitaxel 260 mg/m^2, or docetaxel 75-100 mg/m^2 every 3 weeks), gemcitabine (1,250 mg/m^2 on days 1 and 8 every 3 weeks), capecitabine (2,000 mg/m^2 on days 1-14 every 3 weeks), or vinorelbine (30 mg/m^2/wk every 3 weeks). No incidence of CHF per chemotherapy was reported.

metastatic breast cancer. The overall incidence of clinically significant (ie, high-grade) CHF was 1.6%. Despite the reasonably low absolute incidence, our results show an overall increase of almost five-fold in the CHF risk of bevacizumab-treated patients when compared with controls. Patients with metastatic breast cancer may be at an especially increased risk of CHF because of prior or concomitant exposure to other cardiotoxic medications in the adjuvant or metastatic settings.

Stratified analyses were done to evaluate subgroups with potentially higher incidence of CHF. No differences were found between high and low doses of bevacizumab, which suggests that the low dose may be already reaching the saturation level to promote cardiac function impairment. Similarly, no differences were found among the chemotherapy subgroups stratified according to the concomitant chemotherapy used. However, caution should be taken when analyzing these subgroups because of the limited sample size, and this remains a hypothesis-generating analysis.

Congestive heart failure has been reported with other VEGF-targeted therapies, such as the VEGF receptor antagonists sorafenib

Table 2. Incidence and RR of High-Grade CHF for the Patients With Breast Cancer Who Were Treated With Bevacizumab, Stratified by Bevacizumab Dose and Concomitant Chemotherapy

Treatment	No. of Trials	Bevacizumab Arm: No. of Patients CHF	Bevacizumab Arm: No. of Patients Total	Bevacizumab Arm: Incidence (%)	Bevacizumab Arm: 95% CI	Placebo/Control Arm: No. of Patients CHF	Placebo/Control Arm: No. of Patients Total	Placebo/Control Arm: Incidence (%)	Placebo/Control Arm: 95% CI	Bevacizumab-Related CHF: RR	Bevacizumab-Related CHF: 95% CI
Overall	5	36	2,366	1.6%	1.0 to 2.6	4	1,418	0.4*	0.2 to 1.0	4.74†	1.84 to 12.19
Bevacizumab											
Low dose: 2.5 mg/kg/wk	1	3	250	1.2	0.4 to 3.7	0	233	0.2	0 to 3.3	6.53	0.34 to 125.7
High dose: 5.0 mg/kg/wk	5	33	2,116			4	1,418	0.4	0.2 to 1.0	4.46	1.70 to 11.73
Concomitant chemotherapy											
Taxanes	3	15	1,065	1.7	1.0 to 2.7	1	581	0.3	0.1 to 1.2	5.42	1.25 to 23.52
Capecitabine	2	11	633	1.9	0.6 to 4.3	3	416	0.8	0.2 to 2.3	2.77	0.78 to 9.88
Anthracycline	1	6	210	2.8	1.3 to 6.2	0	100	0.5	0 to 7.4	6.22	0.35 to 109.4

NOTE. *P* value for difference in RRs of low-dose versus high-dose for CHF events = .81. *P* value for difference in RRs of taxanes versus capecitabine and anthracycline for CHF events = .75.
Abbreviations: RR, relative risk; CHF, congestive heart failure.
*Heterogeneity test: Q = 8.04, $P = .090$, $I^2 = 50.2$.
†$P = .001$; heterogeneity test: Q = 0.60, $P = .963$, $I^2 = 0.0\%$.

and sunitinib. A prospective evaluation of 74 patients with renal cell cancer receiving sorafenib or sunitinib with detailed cardiovascular monitoring observed a 34% incidence of cardiac toxicity; half were symptomatic, with significant decreases in LVEF in 12% of patients. Other important cardiac toxicities (eg, arrhythmias, ECG changes, cardiac enzymes elevations, acute coronary artery syndrome) were also seen, with cardiac enzymes elevations in up to 23% of patients and ECG changes in 16%.[24] A retrospective review of 75 patients receiving sunitinib for advanced gastrointestinal stromal cell tumors in phase I/II clinical trials demonstrated 11% of patients with a clinically significant cardiac event, including 19% with decreases in LVEF of ≥ 15% and 8% who developed symptomatic CHF.[25] A single-center analysis of patients receiving sunitinib for renal cell cancer or gastrointestinal stromal tumor described 15% with symptomatic CHF; importantly, cardiac function appeared to improve with discontinuation of sunitinib and introduction of CHF medication.[26]

Despite the size of our analysis, there are several limitations to this study. Data were abstracted from published/presented clinical trial results; therefore, individual patient information was not available. Therefore, establishment of risk factors for the development of CHF, including prior exposure to cardiotoxic agents, or of potentially contributing comorbid conditions, including prior cardiovascular disease, is not possible in this analysis. Reassuringly, in the ATHENA study of bevacizumab and taxane-based breast cancer therapy in greater than 2,000 patients, a low rate of grades 3 to 4 CHF (0.4%) has been observed in a community-based setting, in which a higher prevalence of cardiac risk factors might be anticipated.[27] However, it is important to point out that these expanded access programs are usually not designed to capture rare events, so the incidence of CHF could have been underestimated. Bevacizumab treatment has also been associated with a significant increase in the risk of hypertension and arterial thromboembolic events (ATEs).[4,8] Therefore, an increase in the risk of CHF may have been secondary to an increased incidence of hypertension and/or ATE. However, we could not correlate the incidence of CHF with secondary hypertension or ATE, as neither the causality nor association was reported in any trial. It is also important to note that death, significant disability from high-grade CHF, and timing of CHF were not captured in the studies analyzed; therefore, the impact of bevacizumab on these aspects cannot be determined. These are typical shortcomings inherent to meta-analyses of literature-based studies, and only individual patient data will be able to answer these questions and establish clinical risk factors for

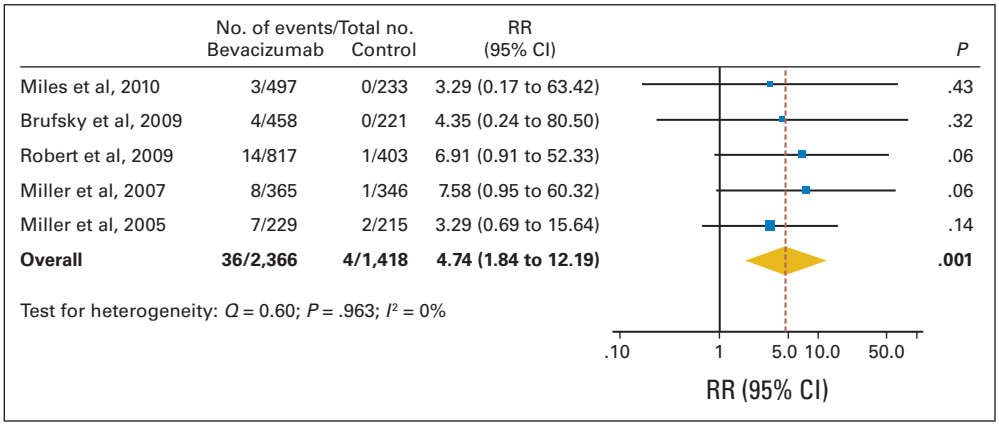

Fig 2. Relative risk of high-grade congestive heart failure events associated with bevacizumab versus control among patients with breast cancer. RR, relative risk.

bevacizumab-induced CHF. Nevertheless, meta-analyses from individual patient data can also carry significant bias, as data are only available to limited numbers of research groups and for only a few types of studies that have high public health priority; consequently, few opportunities exist for pooled analyses.

The majority of randomized data with bevacizumab in breast cancer examines patients with metastatic disease, and there is limited information about the incidence of CHF in the adjuvant setting. Additionally, the vast majority of patients in the five randomized metastatic breast cancer studies were HER2 negative. Data on bevacizumab cardiotoxicity with concurrent or prior trastuzumab exposure are limited, although preliminary results of a pilot phase II study of concurrent bevacizumab and trastuzumab in metastatic disease suggested no significant increase in rates of CHF.[28] Several large, ongoing, randomized studies in the adjuvant setting, including Eastern Cooperative Oncology Group study ECOG 5103 and BETH (bevacizumab and trastuzumab adjuvant therapy in HER2-positive breast cancer), contain careful cardiac monitoring protocols and will provide extensive additional data on the safety of bevacizumab combinations in patients receiving adjuvant therapy.

Guidelines for the management of cardiac events in patients treated with bevacizumab are not well defined. Experience with the VEGF receptor antagonists suggests related cardiac toxicities may be reversible on withdrawal of those agents and/or initiation of cardiovascular treatment and that the VEGF receptor tyrosine kinase inhibitors can be safely resumed, sometimes with a lower dose.[24,26] It is not known if this treatment paradigm applies to bevacizumab-treated patients, as the pharmacokinetics of bevacizumab are different and the half-life (approximately 21 days) is prolonged. It is recommended, however, that, in patients with observed cardiac toxicity related to bevacizumab exposure, bevacizumab is held, and the patient is referred expediently to a cardiac specialist.

It is important to note that the majority of examined trials did not report the incidence of low-grade CHF/left ventricular dysfunction, typically considered to be asymptomatic. However, asymptomatic cardiac dysfunction portends a poor prognosis, with progression to symptomatic heart failure at a rate of 9.7% per year, and has a 3-year mortality rate of 16% in the absence of medical treatment.[29] This type of risk may be of greatest relevance in earlier-stage breast cancer settings, as the safety of adjuvant bevacizumab exposure in breast cancer survivors is unknown. Preliminary cardiac assessment greater than 1 year after completing adjuvant bevacizumab suggests no delayed signal of additional cardiac events.[30] However, capturing asymptomatic toxicity and the long-term effect of this toxicity on risk of future cardiac outcomes is of great importance in the ongoing evaluation of bevacizumab.

In conclusion, the use of the bevacizumab increases the risk of serious CHF in patients with metastatic breast cancer. Although the overall incidence remains low, the RR is significant. Physicians and investigators should be aware of this adverse effect and should monitor patients receiving bevacizumab closely to offer early intervention and to optimize the balance between oncologic clinical benefit and life-threatening adverse events.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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