Congestive heart failure risk in patients with breast cancer treated with bevacizumab
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CRD summary
The review concluded that treatment with bevacizumab was associated with an increased risk of severe congestive heart failure in patients with metastatic breast cancer. Due to potential limitations arising from the review process and uncertainties about the quality of included trials, the reliability of this conclusion is unclear.

Authors' objectives
To evaluate the risk of congestive heart failure in patients with breast cancer treated with bevacizumab.

Searching
PubMed (from January 1966 to March 2010) and Web of Science were searched for publications in English; search terms were reported. Abstracts and virtual meeting presentations of conferences of the American Society of Clinical Oncology between January 2004 and March 2010; abstracts of the San Antonio Breast Cancer Symposium from 2007 to 2009 were also searched. Package inserts for bevacizumab (commercial name, Avastin) were handsearched.

Study selection
Phase II and phase III randomised controlled trials (RCTs) of bevacizumab in patients with metastatic breast cancer were eligible for inclusion. Trials had to assign patients to treatment with bevacizumab in only one of the arms and have adequate reporting of safety profile data. Trials that reported analyses of subgroups alone or combined analysis were excluded.

The primary outcome was congestive heart failure; the other eligible outcome was progression-free survival. Events considered to be congestive heart failure events included left ventricular ejection fraction decline or dysfunction; congestive heart failure (not specified); and cardiomyopathy. Only adverse events of grade 3 or higher (using National Cancer Institute toxicity criteria) were included, since trials rarely reported all-grade or low-grade congestive heart failure.

All included trials used concomitant chemotherapy with bevacizumab in intervention and control groups. The concomitant chemotherapy included capecitabine, taxanes (including docetaxel and paclitaxel) and anthracycline (where reported). Most of the trials reported congestive heart failure events with no specific descriptions. All the patients in the trials had metastatic breast cancer, with adequate organ function, coagulation and haematological function. All trials excluded patients with uncontrolled hypertension, clinically significant congestive heart failure, cerebrovascular or peripheral vascular disease, unstable angina, or a recent history of myocardial infarction. All trials allowed the inclusion of patients with prior treatment with anthracycline. Two trials included patients with human epidermal growth factor receptor-2-positive disease (range 7.5 to 26.3% in treatment arms). Median patient age ranged from 51 to 56 years in different patient groups (where reported).

The authors did not report how many reviewers performed study selection.

Assessment of study quality
A formal methodological quality assessment was not performed, but some relevant data was reported to differentiate between double-blind and open-label trials.

Data extraction
Three reviewers independently extracted data according to the PRISMA statement, with discrepancies resolved by consensus. The numbers of congestive heart failure events were extracted to calculate relative risks (RRs) and 95% confidence intervals (CI). For trials where no adverse events were reported in a treatment or control arm, 0.5 was added to calculate the relative risk and variance. For trials with separate treatment arms for low-dose and high-dose bevacizumab, the two treatment arms were combined for the overall analysis.
Methods of synthesis
Relative risks were pooled using a fixed-effect model if no significant heterogeneity was found; a random-effects model (DerSimonian-Laird) was used if there was significant heterogeneity. Between trial heterogeneity was determined using the Q and I^2 (where I^2 over 50% indicated substantial heterogeneity).

Dose response was investigated by separating trials with low dose (2.5mg/kg/week) and high dose (5mg/kg/week) bevacizumab and also by performing a meta-regression analysis related to dose. The influence of concomitant chemotherapy was also evaluated for taxanes, capecitabine, and anthracyclines. Sensitivity analyses were performed for full publications and conference presentations and stratified by study quality.

Publication bias was assessed using the method of Begg and Egger et al, and visually using funnel plots.

Results of the review
Five RCTs were identified (n=3,841 patients, range 462 to 1,237; 3,784 patients were included in the analysis). All the trials were randomised multi-centre phase III trials. Three trials were placebo-controlled double-blind and two trials were open-label. Median follow-up ranged from 15.6 to 43.5 months in individual patient groups (where reported).

There was a significantly higher risk of developing high-grade congestive heart failure in patients who received bevacizumab than in those who did not (RR 4.74, 95% CI 1.84 to 12.19; I^2=0.0%; five RCTs). High-grade congestive heart failure incidence rates were 1.6% (95% CI 1.0 to 2.6%) in bevacizumab patients and 0.4% (95% CI 0.2% to 1.0%) in control group or placebo-treated patients.

There was no significant difference in risk between high-dose bevacizumab (RR 4.46, 95% CI 1.70 to 11.73; five RCTs) and low-dose bevacizumab (RR 6.53, 95% CI 0.34 to 125.7; one RCT), or when high-dose bevacizumab was directly compared with low-dose bevacizumab.

There were no significant differences in risk of high-grade congestive heart failure between treatments with different concomitant therapies with bevacizumab, including taxanes (RR 5.42, 95% CI 1.25 to 23.52; three RCTs), capecitabine (RR 2.77, 95% CI 0.78 to 9.88; two RCTs), and anthracycline (RR 6.22, 95% CI 0.35 to 109.4; one RCT).

Sensitivity analyses found similar results for risk of congestive heart failure for open-label trials versus placebo-controlled double-blind studies and for published trials versus those presented at conferences.

There was no evidence for publication bias.

Authors' conclusions
The use of bevacizumab was associated with an increased risk of serious congestive heart failure in patients with metastatic breast cancer.

CRD commentary
The review addressed a well-defined question for participants, interventions, study design and relevant outcomes. Relevant databases were searched. Only studies published in English and only a limited search was made for unpublished studies, so some relevant studies may have been missed. However, publication bias was assessed and was not identified, although only five trials were found. Although data extraction was carried out with efforts to reduce error and bias, it was not clear whether this process applied to other aspects of the review process.

A formal quality assessment was not made and little relevant data was reported to enable an assessment of trial quality. Some relevant trial details were reported, but further details would have been useful, such as drug regimes or disease duration. Statistical heterogeneity was assessed. The statistical method used for the meta-analysis may not have been appropriate since the drug regimes were so different and definitions of congestive heart failure varied between trials. The authors did not summarise the results for progression-free survival. Also, it should be borne in mind that bevacizumab was given as an adjunctive therapy using a variety of concomitant treatments.

Potential limitations arising from the review process and some uncertainties about the quality of the included trials
imply that the reliability of the authors' conclusion is unclear.

Implications of the review for practice and research

Practice: The authors recommended that, in patients with observed cardiac toxicity related to treatment with bevacizumab, bevacizumab treatment should be held back and the patient referred rapidly to a cardiac specialist. Patients receiving bevacizumab should be monitored to offer an early intervention and optimise the balance between oncological clinical benefit and life-threatening adverse events.

Research: The authors recommended that future studies should assess low-grade congestive heart failure/left ventricular dysfunction with bevacizumab treatment, which may be asymptomatic, and the long-term effect of this toxicity on cardiac outcomes.

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