Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis.
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CRD summary
The authors concluded that, compared with additional tamoxifen endocrine therapy, aromatase inhibitors reduced the risks of venous thrombosis and endometrial cancer, but increased the risks of bone fractures and developing cardiovascular disease in postmenopausal women with early-stage breast cancer. Given some reporting limitations plus possible error and bias in the review process, the reliability of these conclusions is uncertain.

Authors' objectives
To evaluate and compare serious and/or life-threatening adverse events arising from different adjuvant endocrine therapies in postmenopausal women with early-stage breast cancer.

Searching
MEDLINE and EMBASE were searched for articles in English from 1996 up to 2010. Search terms were reported. The conference proceedings of the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium were scanned from 2000 to 2009. Published articles and conference abstracts were included the meta-analysis.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared the toxicity profiles of aromatase inhibitors versus tamoxifen as initial adjuvant treatment in postmenopausal women with early-stage breast cancer. Eligible trials had to give treatment for no longer than five years.

Most trials were industry-sponsored. Women with any hormone receptor status were included; their average age ranged from 59.9 years to 64.5 years. Radiotherapy and chemotherapy were reported as previous adjuvant therapies in most trials. Six pre-specified adverse events were analysed: cardiovascular disease (including myocardial infarction, angina, and cardiac failure); cerebrovascular disease (including cerebrovascular accident and transient ischaemic attack); venous thrombosis (any episode); any bone fracture; endometrial carcinoma alone; and other invasive secondary cancers (excluding endometrial carcinoma and contralateral breast cancer). All grades of hypercholesterolaemia were assessed. Hot flushes or arthralgia were excluded. Tamoxifen (20mg or 30mg) was compared with the one of three aromatase inhibitors: anastrozole (1mg), exemestane (25mg), or letrozole (2.5mg). The proportion of women with tumour size over 2cm ranged from 22% to 52%; the proportion of node positive women ranged from 26% to 100%.

The authors did not state how many reviewers carried out study selection.

Assessment of study quality
The authors did not state whether they assessed trial quality.

Data extraction
Intention-to-treat data were extracted to calculate of odds ratios (OR) and 95% confidence intervals (CI) for the outcomes of interest.

Two reviewers extracted the data. Discrepancies were resolved by consensus.

Methods of synthesis
Separate meta-analyses were conducted for three subgroups: women who received five years of aromatase inhibitor treatment versus five years of tamoxifen (up-front treatment with aromatase inhibitor versus tamoxifen); women who received tamoxifen for two to three years followed by an aromatase inhibitor for two to three years versus five years of tamoxifen (switching versus tamoxifen); and women who received tamoxifen for two to three years followed by an aromatase inhibitor for two to three years versus five years of an aromatase inhibitor (switching versus aromatase inhibitor). Pooled analysis of all three cohorts was also conducted.
A fixed-effect model was used and weighted by sample size and intra-trial heterogeneity. Statistical heterogeneity was assessed using the $X^2$ test.

Absolute risks were calculated, along with the number needed to harm (NNH) associated with one adverse event.

Sensitivity analysis was conducted for the switching versus tamoxifen subgroup to adjust for better survival in the aromatase inhibitor group versus tamoxifen group (an adjustment for absolute difference in overall mortality of 2.2% was carried out).

**Results of the review**
Seven trials (30,023 patients) were included in the review. The median follow-up ranged from 28 to 100 months.

Pooled analysis of all three cohorts showed that longer duration of aromatase inhibitor use significantly increased the risk of cardiovascular disease (OR 1.26, 95% CI 1.10 to 1.43; seven trials; NNH=132) and bone fractures (OR 1.47, 95% CI 1.34 to 1.61, six trials; NNH=46).

The risk of venous thrombosis (OR 0.55, 95% CI 0.46 to 0.64; six trials; NNH=79) and endometrial carcinoma (OR 0.34, 95% CI 0.22 to 0.53; six trials; NNH=258) were significantly reduced with longer duration of aromatase inhibitor use. Subgroup analysis showed no significant difference between longer duration aromatase inhibitors versus switching from tamoxifen to aromatase inhibitors for these two outcomes.

There was a non-statistically significant increased risk of death without breast cancer recurrence in the analysis of treatment with five years of aromatase inhibitors versus five years of tamoxifen alone or switching from tamoxifen to an aromatase inhibitor. No differences were observed between the treatment strategies in terms of cerebrovascular disease and other second cancers.

There was no statistically significant heterogeneity. Sensitivity analysis did not alter the main findings.

Further results were reported in the review.

**Authors’ conclusions**
Compared with tamoxifen, aromatase inhibitors in postmenopausal women with early-stage breast cancer decreased the odds of venous thrombosis and endometrial carcinoma, but increased the odds of developing cardiovascular disease and bone fractures.

**CRD commentary**
The review question was clear. Inclusion criteria were specified in sufficient detail to allow replication. The search strategy included relevant sources of published and unpublished material, but language bias could not be ruled out. The extent to which attempts were made to minimise error and bias in the selection of studies was unclear.

The absence of any reported quality assessment of trials precluded interpretation of their reliability. Trial details were presented. The chosen method of synthesis appeared to be appropriate in the absence of statistical heterogeneity.

Given some reporting limitations, and possible error/bias in the review process, the extent to which the authors’ conclusions are reliable is uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that switching from tamoxifen to aromatase inhibitors reduced toxicity and was likely to be the best balance between efficacy and toxicity. Oncologists should consider the toxicity profiles of different endocrine therapies for breast cancer according to baseline health status. Specific consideration should be given to patients with pre-existing heart disease or related risk factors.

**Research:** The authors stated that future trials should, in addition to efficacy, report data on rare and potentially serious toxicities.

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