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Patient-reported outcomes with anastrozole versus tamoxifen for postmenopausal patients with ductal carcinoma in situ treated with lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial

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Contributors

PAG designed the study, did the literature search, interpreted data, and wrote the report. RSC and TBJ designed the study, collected, analysed, and interpreted data, and revised the report. RGM designed the study and collected and interpreted data. JPC and EPM designed the study, collected and interpreted data, and wrote the report. LAV, PWW, and MEC collected data and revised the report. KSA designed the study, recruited patients, and revised the report. AMB and GSS collected and analysed data, and wrote the report. HMG designed the study, collected and analysed data, recruited patients, and revised the report. JOH and NW designed the study and revised the report. LF collected, analysed, and interpreted data, and revised the report. KS recruited patients and collected data. TFW recruited patients and revised the report. TES collected data, recruited patients, and revised the report. All authors approved the final report.

Declaration of interests

MEC has received research support from Novartis, fees from Biotheranostics for participation on an advisory board, and fees from Roche and Abbvie. All other authors declare no competing interests.

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Summary

Background—The NSABP B-35 trial compared 5 years of treatment with anastrozole versus tamoxifen for reducing subsequent occurrence of breast cancer in postmenopausal patients with ductal carcinoma in situ. This report assesses the effect of these drugs on quality of life and symptoms.

Methods—The study was done at 333 hospitals in North America. Postmenopausal women with hormone-positive ductal carcinoma in situ treated by lumpectomy with clear resection margins and whole breast irradiation were randomly assigned to receive either tamoxifen (20 mg/day) or anastrazole (1 mg/day) for 5 years, stratified by age (<60 years *vs* ≥60 years). Patients and investigators were masked to treatment allocation. Patients completed questionnaires at baseline and every 6 months thereafter for 6 years. The primary outcomes were SF-12 physical and mental health component scale scores, and vasomotor symptoms (as per the BCPT symptom scale). Secondary outcomes were vaginal symptoms and sexual functioning. Exploratory outcomes were musculoskeletal pain, bladder symptoms, gynaecological symptoms, cognitive symptoms, weight problems, vitality, and depression. We did the analyses by intention to treat, including patients who completed questionnaires at baseline and at least once during follow-up. This study is registered with ClinicalTrials.gov, NCT00053898.

Findings—Between Jan 6, 2003, and June 15, 2006, 3104 patients were enrolled in the study, of whom 1193 were included in the quality-of-life substudy: 601 assigned to tamoxifen and 592 assigned to anastrozole. We detected no significant difference between treatment groups for: physical health scores (mean severity score 46.72 for tamoxifen *vs* 45.85 for anastrozole; p=0.20), mental health scores (52.38 *vs* 51.48; p=0.38), energy and fatigue (58.34 *vs* 57.54; p=0.86), or symptoms of depression (6.19 *vs* 6.39; p=0.46) over 5 years. Vasomotor symptoms (1.33 *vs* 1·17; p=0.011), difficulty with bladder control (0.96 *vs* 0.80; p=0.0002), and gynaecological symptoms (0.29 *vs* 0.18; p<0.0001) were significantly more severe in the tamoxifen group than in the anastrozole group. Musculoskeletal pain (1.50 *vs* 1.72; p=0.0006) and vaginal symptoms (0.76 *vs* 0.86; p=0.035) were significantly worse in the anastrozole group than in the tamoxifen group. Sexual functioning did not differ significantly between the two treatments (43.65 *vs* 45.29; p=0.56). Younger age was significantly associated with more severe vasomotor symptoms (mean severity score 1.45 for age <60 years *vs* 0.65 for age ≥60 years; p=0.0006), vaginal symptoms (0.98 *vs* 0.65; p<0.0001), weight problems (1.32 *vs* 1·02; p<0.0001), and gynaecological symptoms (0.26 *vs* 0.22; p=0.014).

Interpretation—Given the similar efficacy of tamoxifen and anastrozole for women older than age 60 years, decisions about treatment should be informed by the risk for serious adverse health effects and the symptoms associated with each drug. For women younger than 60 years old, treatment decisions might be driven by efficacy (favouring anastrozole); however, if the side-effects of anastrozole are intolerable, then switching to tamoxifen is a good alternative.

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Introduction

Ductal carcinoma in situ is a non-invasive form of breast cancer accounting for approximately 20% of new breast cancer cases in the USA in 2015, representing more than 60 000 women.[1] Controversy exists regarding whether ductal carcinoma in situ is a true neoplasm; however, local treatment generally includes surgery (mastectomy or lumpectomy), with radiotherapy to the whole or partial breast after lumpectomy, or in some cases simple excision only.[2] A series of clinical trials[3–5] done by the National Surgical Adjuvant Breast and Bowel Project (NSABP) established that endocrine treatment with tamoxifen reduces the risk of invasive breast cancer or recurrent ductal carcinoma in situ after breast-conserving treatment. Adjuvant endocrine treatment of ductal carcinoma in situ was introduced when breast-conserving treatment and adjuvant therapy were being applied to the management of invasive breast cancer. Increasingly, adjuvant endocrine treatment for ductal carcinoma in situ is thought of as breast cancer prevention, because ductal carcinoma in situ is rarely lethal.[6] Minimising the harms and maximising the benefits of treatment for ductal carcinoma in situ are crucial.[7,8] When the NSABP B-35 trial was being designed, the ATAC trial[9] suggested that anastrozole, an aromatase inhibitor, might be more effective (providing better disease-free survival) and less toxic (lower risk of thromboembolic complications and uterine cancer) than was tamoxifen for postmenopausal women with hormone-receptor-positive invasive breast cancer. The quality-of-life results from the ATAC trial were not reported until several years later.[10,11]

The primary objective of the NSABP B-35 trial was to compare the effect of 5 years of treatment with tamoxifen versus anastrozole for the prevention of subsequent breast cancer (local, regional, and distant recurrences, and contralateral breast cancer) in postmenopausal women with ductal carcinoma in situ. The primary results of the trial[12] showed a small but statistically significant benefit from 5 years of anastrozole in women who were younger than age 60 years when treatment was initiated. Quality of life and other patient-reported outcomes were an integral component of the trial, building on the previous trials.[13–16] This report details the quality-of-life findings from the NSABP B-35 study.

Methods

Study design and participants

NSABP B-35 was a phase 3 trial designed to compare anastrozole (1 mg/day) with tamoxifen (20 mg/day), each given for 5 years, for the prevention of subsequent breast cancer following lumpectomy with radiotherapy in postmenopausal women with ductal carcinoma in situ. A secondary objective was to assess quality of life and symptoms in a

subgroup of patients, which is the focus of this report. The study was done at 333 hospitals or hospital consortia in Canada, Mexico, and the USA.

We enrolled postmenopausal women with ductal carcinoma in situ or mixed ductal carcinoma in situ and lobular carcinoma in situ with oestrogen receptor positive or progesterone receptor positive disease, with no invasive component. Participants had to have undergone a lumpectomy with clear margins and negative nodes (if a biopsy sample was taken), followed by whole breast irradiation and no systemic treatment. Patients requiring a mastectomy or those who had had any cancer within 5 years before randomisation were ineligible, except for those who had had carcinoma in situ of the cervix, carcinoma in situ of the colon, melanoma in situ, or basal cell or squamous cell carcinoma of the skin. Patients receiving raloxifene or any other selective oestrogen receptor modulator, or any sex hormone treatment were ineligible. Patients with a history of thromboembolic disease, cerebrovascular accident or transient ischaemic attack, uncontrolled hypertension, uncontrolled diabetes, or uncontrolled atrial fibrillation were also ineligible.

All participants who spoke English, French, or Spanish were expected to participate in the quality-of-life study until the accrual goal was met. Exceptions were made if a patient refused to complete the baseline questionnaire or did not read or write in one of the three languages.

The study was approved by the institutional review boards of participating centres, and all participants provided written informed consent.

Randomisation and masking

Patients were randomly assigned centrally (1:1) with minimisation to either anastrozole or tamoxifen, stratified by age (<60 years *vs* ≥60 years). Patients and investigators were masked to treatment allocation.

Procedures

The quality-of-life questionnaire was completed at baseline (before the start of study drug), and every 6 months thereafter up to 5 years of treatment, plus 1 year after treatment completion. This report includes data from only the 5-year period when patients were taking treatment.

This study used a similar design as the BCPT and STAR prevention trials, with some refinements to study instruments that had since become available.[14,16,17] The questionnaires were: the Medical Outcomes Study-Short Form 12 (SF-12)[18] physical and mental health component scales to measure physical and mental health; the four-item SF-36 Vitality Scale[19] to measure energy and fatigue; a shortened version of the BCPT symptom checklist;[14,20,21] a shortened ten-item version of the Center for Epidemiologic Studies Depression Scale (CES-D) to measure symptoms of depression;[22,23] the four-item Medical Outcomes Study (MOS) Sexual Problems Scale to measure sexual functioning;[24] and an 11-point overall health rating scale, where 0 indicates being in the worst imaginable health and 10 indicates being in the best imaginable health.

Patients who had a breast cancer recurrence or second primary cancer were not expected to continue quality-of-life assessments. Patients who discontinued protocol treatment for other reasons were expected to continue assessments on schedule. If a patient declined to complete a scheduled quality-of-life assessment, or if the questionnaire was not completed for another reason, a missing data form was submitted by the institution instead.

Outcomes

The objectives of the quality-of-life study were to determine whether quality of life and symptoms differ in patients receiving anastrozole and those receiving tamoxifen; to assess differences in health states between patients receiving anastrozole and tamoxifen; and to assess the additional value of including a Q-TWiST analysis when evaluating the outcomes of the study. Only the first objective is addressed in this report.

The primary outcomes were SF-12 physical and mental health component scale scores, and vasomotor symptoms measured by the BCPT symptom scale. We postulated no differences between the two treatments for physical and mental health; however, we postulated that hot flushes would be more common in anastrozole-treated patients than in tamoxifen-treated patients aged younger than than 60 years.

Secondary outcomes were related to vaginal symptoms and sexual functioning. We postulated that vaginal dryness and pain with intercourse would be more common in patients receiving anastrozole than in those receiving tamoxifen. We also postulated that sexual functioning would be significantly worse in the anastrozole group than in the tamoxifen group. Prespecified exploratory outcomes were other symptoms (musculoskeletal pain, bladder symptoms, gynaecological symptoms, cognitive symptoms, weight problems) as well as vitality and depression.

Statistical analysis

We aimed to accrue at least 1150 patients, anticipating that this would yield at least 1000 evaluable patients who completed both the baseline and at least one set of followup questionnaires. 1000 patients would provide 91% power to detect a difference between treatment groups in mean SF-12 physical or mental scale score of 1.25 with an α of 0.0125. We also calculated that the power for the other quality-of-life endpoints was at least 80% to detect a difference between treatment groups that was equal to one-quarter of the standard deviation expected for the endpoint mean.

To compare the SF-12 physical and mental health component scales between treatment groups, we calculated the change from baseline, averaged over ten timepoints during the 5 years of treatment. The primary comparison was a test of difference in means over time between treatments based on the *t* distribution. We normalised each scale to have a mean of 50 (in the general population), a standard deviation of 10, and range of 0–100. Higher scores indicate better health. We used mixed models to test for a treatment difference in physical and mental health component scores over time. The models included parameters for treatment, timepoint, age group (<60 years, ≥60 years), baseline score, and the interaction

between treatment and timepoint. The p values for the mixed models were based on Wald's test.

To assess symptoms, we used a version of the BCPT symptom checklist with refinements[20,21] to psychometric properties subsequent to the writing of our protocol in 2002. These changes led to more robust reporting of symptom severity in the STAR trial.[16] We report individual symptom severity distributions at baseline and 6 months for each group for hot flushes, vaginal dryness, pain with intercourse, joint pain, and muscle stiffness; however, the main analyses focus on the seven subscale severity scores from the symptom checklist:[20,21] vasomotor symptoms (hot flushes and night sweats), musculoskeletal pain (joint pain, muscle stiffness, and general aches and pains), vaginal symptoms (vaginal dryness and pain with intercourse), bladder control symptoms (difficulty when laughing or crying and difficulty at other times), cognitive symptoms (forgetfulness, difficulty concentrating, and easily distracted), weight problems (weight gain and unhappy with appearance of body), and gynaecological symptoms (vaginal discharge, vaginal bleeding or spotting, and genital itching or irritation). Patients assessed how bothered they had been by each symptom or problem in the past 4 weeks and scored as follows: 0=not at all, 1=slightly, 2=moderately, 3=quite a bit, 4=extremely. We calculated the severity of the subscale scores as the mean of the non-missing items comprising each scale. If more than half the items were missing, then the score was also considered missing. For each subscale, we plotted the mean scores over time by treatment group as well as stratified by age group. We used mixed models for repeated measures analysis adjusted for timepoint, age group, baseline scores, and the interaction between treatment and timepoint to test for significance of treatment for each subscale.

We used mixed models for repeated measures analysis to test for treatment differences in the MOS Vitality score (for energy or fatigue), the ten-item CES-D score (for depression), and the MOS sexual functioning scale (for sexual function). The shortened version of the CES-D is scored by calculating the sum of the points for all ten items. If more than two items were missing, then the score was considered missing. A higher score on the CES-D indicates a greater risk of depression, with scores of 10 or greater indicating clinically important symptoms of depression. For analyses of sexual functioning symptoms, we first assessed each of the four items individually and then combined them into a total score.[24] Previous validation of the questions suggested that most women without a partner or who had not had sexual intercourse in the given interval responded "not a problem" rather than "not applicable". The scale is designed to include women without sexual experience, so "not applicable" responses were recoded as "not a problem", as recommended by the developers of the scale.[24] The scale score was calculated as the average across the four non-missing items and then transformed to a 0–100 scale, with a higher score indicating greater sexual functioning symptoms.

All analyses followed the intention-to-treat principle and included patients who completed the questionnaire at baseline and at least one follow-up point during treatment. All assessments were based on a two-sided test with α of 0.05. We did the analyses with SAS (version 9.4).

Role of the funding source

The funders had no role in the design of the study, collection, analysis, or interpretation of data, or the writing of the report. PAG and RSC had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 6, 2003, and June 15, 2006, we enrolled 3104 patients into the NSABP B-35 study. Accrual to the quality-of-life study closed on Dec 28, 2004, at which time 1275 patients had been enrolled. 1223 women provided baseline questionnaires (figure 1). 1193 participants had at least one follow-up assessment and were included in the quality-of-life analysis: 601 in the tamoxifen group and 592 in the anastrozole group (table 1). Similar proportions of patients in each group completed the questionnaire over the 5-year study period (figure 1).

For the SF-12 physical health component, mean severity score was 46.72 in the tamoxifen group versus 45.85 in the anastrozole group; the *t* test for the difference between means was not significant (p=0.38). For the SF-12 mental health component, mean severity score was 52.38 versus 51.48. The *t* test for the difference between means for mental health was also not significant (p=0.93).

In the mixed model, there was no significant difference between treatment groups (p=0.20) or the interaction between treatment and timepoint (p=0.21) for the physical health component (figure 2A). Likewise, for the mental health component, the mixed model showed no significant difference between treatment groups (p=0.38) or the interaction between treatment and timepoint (p=0.27; figure 2B).

For the pain with intercourse question, 13% of responses were missing (717 of 5379 in the tamoxifen group, 670 of 5296 in the anastrozole group). For all other symptom questions, around 1% of data were missing.

The distributions of symptom severity were much the same in each group at baseline and there were only modest differences at 6 months (table 2). To provide greater precision in assessing the comparative severity of symptoms in the two treatment groups, we used the more refined subscales of the checklist for longitudinal comparisons.

For the symptom subscales, severity scores for vasomotor symptoms (mean score 1.33 in the tamoxifen group *vs* 1.17 in the anastrozole group; p=0.011), difficulty with bladder control (0.96 *vs* 0.80; p=0.0002), and gynaecological symptoms (0.29 *vs* 0·18; p<0.0001) were significantly greater (worse) in the tamoxifen group than in the anastrozole group (figure 3). The severities of musculoskeletal pain (1.50 *vs* 1.72; p=0.0006) and vaginal symptoms (0.76 *vs* 0.86; p=0.035) were significantly greater in the anastrozole group than in the tamoxifen group (figure 3). We detected no significant difference between treatment groups for cognitive symptoms (0.89 *vs* 0.92; p=0.72) and weight problems (1.15 *vs* 1.17; p=0.48; figure 3, appendix p 1).

There was a significant treatment-by-time interaction for the vasomotor symptoms and musculoskeletal pain subscales. The difference between treatment groups varied over time for vasomotor symptoms, with significant effects at 6 months (mean score 1.18 in the tamoxifen group *vs* 1.51 in the anastrozole group; p<0.0001), 12 months (1.65 *vs* 1·41; p=0.0007), 30 months (1.30 *vs* 1.10; p=0.0085), and 36 months (1.24 *vs* 1·09; p=0.0444). For musculo skeletal pain, the treatment effect was significant at 6 months (1.39 vs 1·74; p<0.0001), 12 months (1·49 vs 1·82; p<0.0001), and 24 months (1.49 *vs* 1·77; p=0.0008).

When adjusted for treatment, younger age was significantly associated with increased vasomotor symptom severity (mean score 1.46 for age <60 years *vs* 1.06 for age ≥60 years; p=0.0006), vaginal symptoms (0.98 *vs* 0.65; p<0.0001), weight problems (1.32 *vs* 1.02; p<0.0001), and gynaecological symptoms (0.26 *vs* 0.22; p=0.014; figure 4, appendix p 2). There were no significant interactions between treatment group and age group for any other subscales.

In a mixed model containing treatment, time, age (<60 years, ≥60 years), baseline vitality score, and the interaction between treatment and time, mean SF-36 Vitality scores did not differ significantly between treatment groups (mean score 58.34 in the tamoxifen group *vs* 57.54 in the anastrozole group; p=0.86), and vitality scores did not decrease with time (appendix pp 1, 4).

The proportion of patients with a CES-D score of 10 or greater was not significantly different between treatment groups at any timepoints (appendix p 3). In a mixed model containing treatment, time, age (<60 years, ≥60 years), baseline CES-D score, and the interaction between treatment and time, there was no significant difference between treatment groups (mean score 6.19 in the tamoxifen group *vs* 6.39 in the anastrozole group; p=0.46; appendix pp 1, 4), and there was no increase in symptoms over time.

Across all timepoints and for all questions, the percentage of answers missing for the sexual functioning items ranged from 10% to 18%, and 24–34% of answers were not applicable. In a mixed model containing treatment, time, age (<60 years, ≥60 years), baseline score, and the interaction between treatment and time, there was no significant difference between treatment groups for mean sexual functioning scale scores (mean score 43.65 for the tamoxifen group *vs* 45.29 in the anastrozole group; p=0.56; appendix pp 1, 5).

Discussion

When the NSABP B-35 protocol was developed, most data for the efficacy and tolerability of anastrozole compared with tamoxifen came from studies of women with advanced breast cancer.[25,26] These studies did not include patient-reported outcomes, and adverse events were reported by investigators, including the occurrence of some predefined adverse events. Hot flushes were slightly greater with anastrozole compared with tamoxifen (38% *vs* 28%) in one study,[26] but not different in another study (20% for both treatments)[25] and lower in the ATAC trial (34% *vs* 40%).[9] In all these studies, hot flushes were substantially less common than reported by patients in the NSABP P-1 study,[14] in which 76% of patients aged 50–59 years and 50% of women older than 60 years reported hot flushes at 6 months.

Furthermore, there was no assessment of quality of life or sexual functioning in these trials. For women with ductal carcinoma in situ taking endocrine treatment for prevention of invasive breast cancer, both these domains were considered to be important by clinicians, patients, regulators, and patient advocates.[8] Because anastrozole completely suppresses oestrogen in postmenopausal women, we postulated that its effects on menopausal symptoms and sexual functioning would be substantially greater than those of tamoxifen. The need for rigorous examination of these outcomes was the rationale for the NASBP B-35 quality-of-life study.

Our primary hypotheses about the effect of treatments on quality of life were confirmed, in that there were no statistically significant differences in physical or mental health outcomes between treatments. Physical and mental health scores were stable over the 5-year period of assessment. Our protocol-defined hypothesis regarding hot flushes was not confirmed, in that patients treated with tamoxifen had significantly more severe vasomotor symptoms than those treated with anastrozole; however, as we predicted, age younger than 60 years was associated with greater severity.

With regard to our secondary hypotheses related to sexual health, we found that vaginal symptoms (pain with intercourse, vaginal dryness) were significantly worse among patients treated with anastrozole than in those treated with tamoxifen. When controlled for treatment, the severity of symptoms was greater in patients younger than age 60 years. We detected no difference in sexual functioning between the two treatments.

Our findings with regard to other symptoms often associated with endocrine treatments of breast cancer (bladder control, gynaecological symptoms, musculo-skeletal symptoms, cognitive symptoms, and weight gain) were similar to the results from other studies[10,11] of tamoxifen and anastrozole for patients with invasive breast cancer.

Since the NSABP B-35 trial, two reports from the ATAC quality-of-life study have become available.[10,11] The initial report with 2-year follow-up showed that those who received anastrozole reported significantly fewer cold sweats and vaginal discharge yet more vaginal dryness, painful intercourse, and loss of sexual interest compared with those who received tamoxifen.[10] Consistent with the 2-year analysis, in the 5-year follow-up from the trial,[11] there were differences between treatment groups for patient-reported side-effects: diarrhoea (3% with anastrozole *vs* 1% with tamoxifen), vaginal dryness (19% *vs* 9%), diminished libido (34% *vs* 26%), and dyspareunia (17% *vs* 8%); however, vaginal discharge was less common with anastrozole (1% *vs* 5%). We recorded similar patterns in our study with respect to vaginal and gynaecological symptoms, although direct comparison with ATAC is not possible because of differences in method of measurement and scales. The ATAC trials showed no detrimental effect of either treatment on quality of life after treatment for women with early stage invasive breast cancer.

A limitation of this study was that participants were volunteers, who are usually healthier than the general population of patients with ductal carcinoma in situ, which is supported by the high physical health scores we recorded. Symptoms in patients with greater comorbidity

might be different. In addition, we assessed group data in these analyses, which might not reflect the experience of specific individuals.

We conclude that both tamoxifen and anastrozole have little effect on physical and mental health, although there are troublesome symptoms with each drug. Given the lack of difference in efficacy between tamoxifen and anastrozole for women older than age 60 years, decisions regarding treatment choice should be informed by the risk for serious adverse health effects (thromboembolism, uterine cancer, bone loss) and the pattern of symptoms associated with each medication. Symptoms are generally of lower severity in this age group, and the choice of treatment should be based on patient values and preferences, as well as the drug's tolerability. For women younger than 60 years of age, who tend to have a significantly longer breast cancer-free interval with anastrozole than with tamoxifen, symptoms (vasomotor symptoms, vaginal symptoms, weight problems, gynaecological symptoms) are generally more severe than in older women, with tamoxifen causing more vasomotor symptoms and anastrozole causing more vaginal symptoms. Decision making for patients in this age group might be driven by the NSABP B-35 efficacy findings; however, if the side-effects of treatment with anastrozole are intolerable, then switching to tamoxifen is a good alternative.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

When the NSABP B-35 trial was designed in 2002, the standard of care for patients with ductal carcinoma in situ was 5 years of adjuvant tamoxifen. In 2002, the ATAC trial suggested that anastrozole improved disease-free survival and had a more favourable toxic effects profile than did tamoxifen in postmenopausal women with invasive breast cancer. Quality-of-life data from the ATAC study were not available when we designed the NSABP B-35 trial.

Added value of this study

Both tamoxifen and anastrozole had little effect on physical and mental wellbeing, depression, or vitality, although there were some troublesome symptoms with each drug. Our results concur with subsequent data from the ATAC trial showing tamoxifen is associated with increased vasomotor symptoms and gynaecological symptoms compared with anastrozole, whereas patients taking anastrozole are more likely than those taking tamoxifen to have musculoskeletal complaints and vaginal symptoms. The severity of some symptoms (vasomotor symptoms, vaginal symptoms, weight problems, and gynaecological symptoms) was significantly worse in women younger than age 60 years than in older women.

Implications of all the available evidence

Our findings enable clinicians to have comprehensive discussions with patients about the benefits and harms of treatment with either tamoxifen or anastrozole for ductal carcinoma in situ. Given the lack of difference in efficacy between tamoxifen and anastrozole for women older than age 60 years, decisions about treatment should be informed by the risk for serious adverse health effects (thromboembolism, uterine cancer, bone loss) and the pattern of symptoms associated with each drug. For women younger than 60 years old, who tend to have a significantly longer breast cancer-free interval with anastrozole, the severity of some symptoms (ie, vasomotor symptoms, vaginal symptoms, weight problems, gynaecological symptoms) is greater than in older women, with tamoxifen causing more vasomotor symptoms, and anastrozole causing more vaginal symptoms. Decision making in this age group might be driven by the efficacy findings; however, if the side-effects of anastrozole treatment are intolerable, then switching to tamoxifen is a good alternative with a different side-effect profile.

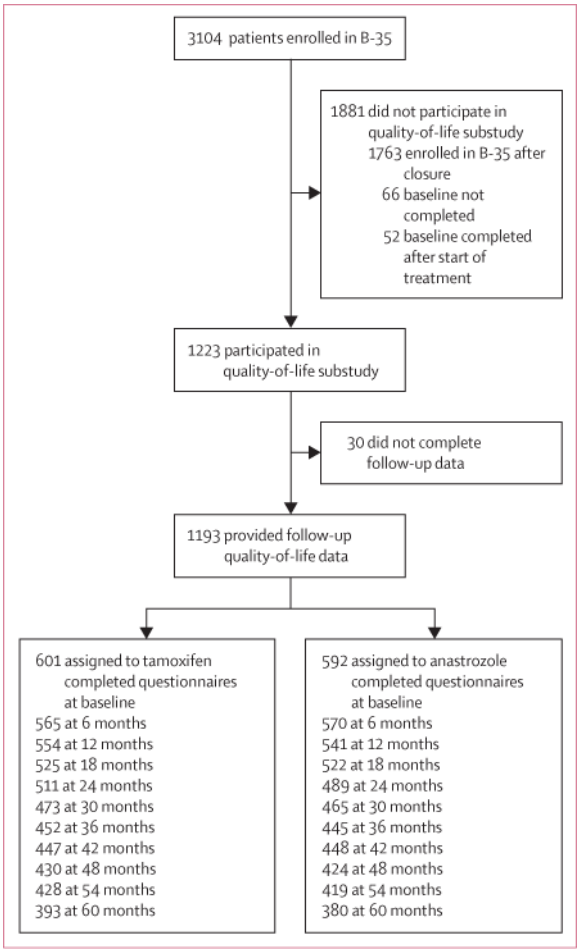

Figure 1.
Trial profile for the quality-of-life substudy

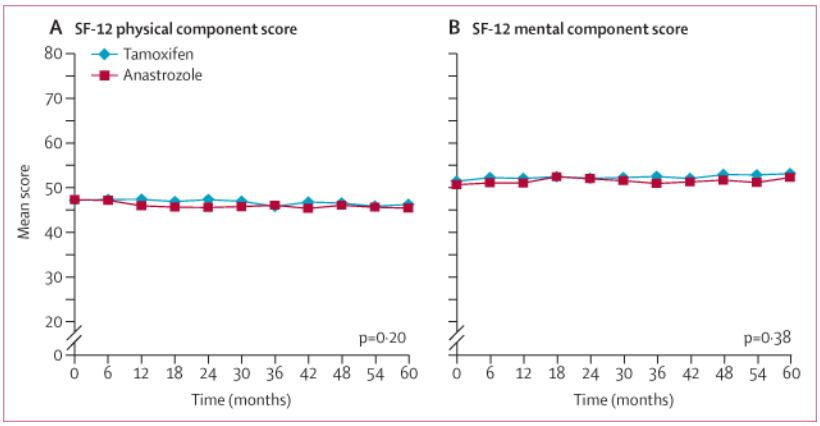

Figure 2. Mean SF-12 score

For (A) the physical component and (B) the mental component.

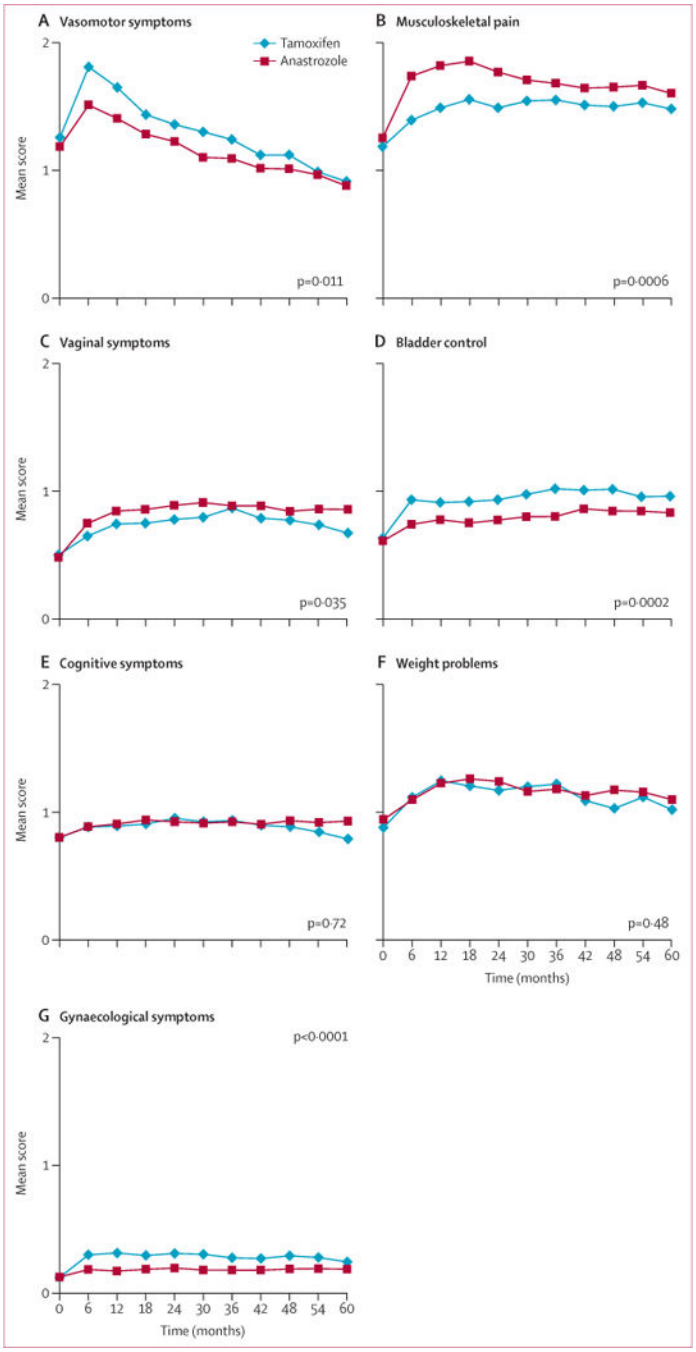

Figure 3. Mean BCPT subscale scores

For (A) vasomotor symptoms, (B) musculoskeletal pain, (C) vaginal symptoms, (D) bladder control, (E) cognitive symptoms, (F) weight problems, and (G) gynaecological symptoms.

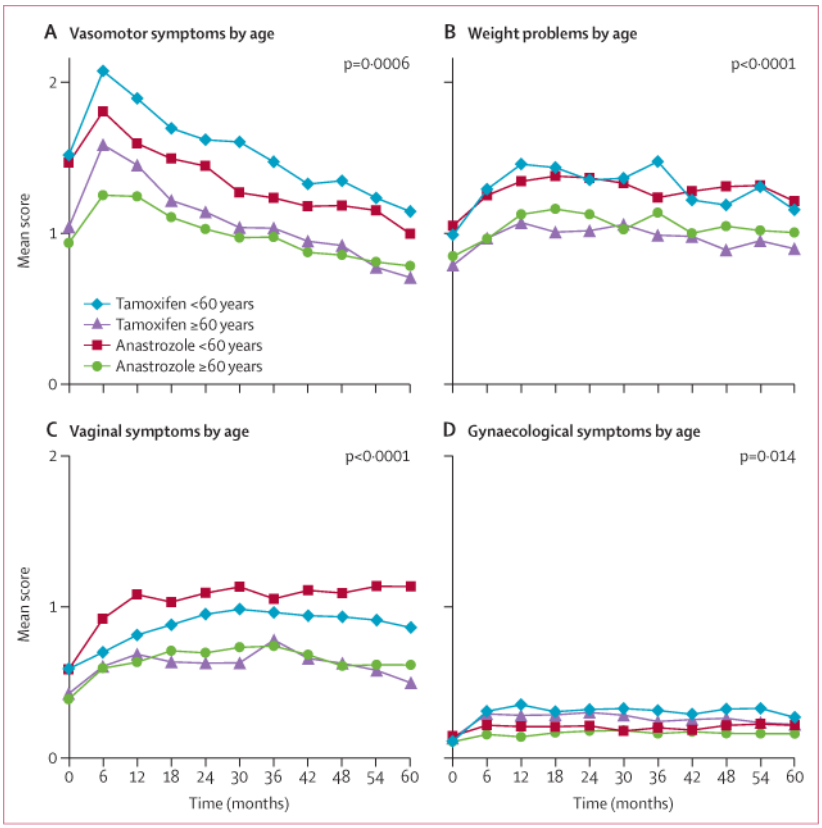

Figure 4. Mean BCPT subscale scores by age and treatment group

For (A) vasomotor symptoms, (B) weight problems, (C) vaginal symptoms, and (D) gynaecological symptoms. Shows only those subscales for which age had a significant effect (p values are for the effect of age adjusted by treatment).

Table 1

Baseline characteristics for all patients in the quality-of-life analysis

	Tamoxifen group (n=601)	Anastrozole group (n=592)
Age (years)		
<60	278 (46%)	282 (48%)
≥60	323 (54%)	310 (52%)
Race		
White	529 (88%)	516 (87%)
Black	47 (8%)	55 (9%)
Pacific Islander	2 (<1%)	2 (<1%)
Asian	16 (3%)	12 (2%)
Native American or Alaskan	0 (0%)	1 (<1%)
Multiracial	4 (1%)	1 (<1%)
Unknown	3 (<1%)	5 (1%)
Ethnicity		
Non-Hispanic	553 (92%)	538 (91%)
Hispanic or Latino	14 (2%)	23 (4%)
Unknown	34 (6%)	31 (5%)
Tumour evident on mammogram		
Unknown	0 (0%)	1 (<1%)
No	25 (4%)	13 (2%)
Yes	576 (96%)	578 (98%)
Comedo necrosis		
Unknown	38 (6%)	37 (6%)
Absent	318 (53%)	293 (49%)
Present	245 (41%)	262 (44%)
Tumour palpable		
Unknown	0 (0%)	1 (<1%)
No	534 (89%)	550 (93%)
Yes	67 (11%)	41 (7%)
Pathological tumour size (cm)		
Unknown	244 (41%)	248 (42%)
<1.0	209 (35%)	205 (35%)
>1.0	148 (25%)	139 (23%)
Nuclear grade		

	Tamoxifen group (n=601)	Anastrozole group (n=592)
Unknown	13 (2%)	22 (4%)
Low	133 (22%)	125 (21%)
Intermediate	249 (41%)	253 (43%)
High	206 (34%)	192 (32%)
Body-mass index (kg/m²)		
<25.0	162 (27%)	140 (24%)
25.0–29.9	200 (33%)	194 (33%)
≥30.0	239 (40%)	258 (44%)

Table 2

Severity of main symptoms of interest

	At baseline		At 6 months	
	Tamoxifen group	Anastrozole group	Tamoxifen group	Anastrozole group
Hot flushes (age <60 years)				
1–4	204/599 (34%)	210/587 (36%)	233/560 (42%)	233/565 (41%)
2–4	142/599 (24%)	144/587 (25%)	186/560 (33%)	184/565 (33%)
3–4	88/599 (15%)	89/587 (15%)	127/560 (23%)	114/565 (20%)
Hot flushes (age ≥60 years)				
1–4	172/599 (29%)	155/587 (26%)	219/560 (39%)	191/565 (34%)
2–4	119/599 (20%)	98/587 (17%)	159/560 (28%)	141/565 (25%)
3–4	73/599 (12%)	50/587 (9%)	110/560 (20%)	82/565 (15%)
Vaginal dryness				
1–4	197/591 (33%)	187/586 (32%)	214/557 (38%)	245/560 (44%)
2–4	113/591 (19%)	102/586 (17%)	126/557 (23%)	147/560 (26%)
3–4	59/591 (10%)	51/586 (9%)	70/557 (13%)	90/560 (16%)
Pain with intercourse				
1–4	109/554 (20%)	102/555 (18%)	126/515 (24%)	132/520 (25%)
2–4	51/554 (9%)	50/555 (9%)	72/515 (14%)	83/520 (16%)
3–4	22/554 (4%)	30/555 (5%)	40/515 (8%)	48/520 (9%)
Joint pain				
1–4	397/600 (66%)	412/590 (70%)	407/561 (73%)	459/568 (81%)
2–4	216/600 (36%)	225/590 (38%)	256/561 (46%)	324/568 (57%)
3–4	89/600 (15%)	113/590 (19%)	132/561 (24%)	181/568 (32%)
Muscle stiffness				
1–4	385/600 (64%)	377/590 (64%)	385/565 (68%)	441/567 (78%)
2–4	172/600 (29%)	177/590 (30%)	218/565 (39%)	287/567 (51%)
3–4	75/600 (13%)	80/590 (14%)	103/565 (18%)	161/567 (28%)

Data are n/N (%). 1–4=at least slightly bothersome, 2–4=at least moderately bothersome, 3–4=at least quite a bit bothersome.