Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial

*The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group**

Summary

Background Little data exist on whether efficacy benefits or side-effects persist after 5 years of adjuvant treatment with an aromatase inhibitor. We aimed to study long-term outcomes in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial that compares anastrozole with tamoxifen after a median follow-up of 100 months.

Methods We analysed postmenopausal women with localised invasive breast cancer. The primary endpoint disease-free survival (DFS), and the secondary endpoints time to recurrence (TTR), incidence of new contralateral breast cancer (CLBC), time to distant recurrence (TTDR), overall survival (OS), and death after recurrence were assessed in the total population (intention to treat; ITT: anastrozole, n=3125; tamoxifen, n=3116; total 6241) and the hormone-receptor-positive subpopulation, the clinically important subgroup for which endocrine treatment is now known to be effective (84% of ITT: anastrozole, n=2618; tamoxifen, n=2598; total 5216). After treatment completion, fractures and serious adverse events continued to be collected blindly (safety population: anastrozole, n=3092; tamoxifen, n=3094; total 6186). This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN18233230.

Findings At a median follow-up of 100 months (range 0–126), DFS, TTR, TTDR, and CLBC were improved significantly in the ITT and hormone-receptor-positive populations. For hormone-receptor-positive patients: DFS hazard ratio (HR) 0·85 (95% CI 0·76–0·94), p=0·003; TTR HR 0·76 (0·67–0·87), p=0·0001; TTDR HR 0·84 (0·72–0·97), p=0·022; and CLBC HR 0·60 (0·42–0·85), p=0·004. Absolute differences in time to recurrence increased over time (TTR 2·8% [anastrozole 9·7% *vs* tamoxifen 12·5%] at 5 years and 4·8% [anastrozole 17·0% *vs* tamoxifen 21·8%] at 9 years) and recurrence rates remained significantly lower on anastrozole compared with tamoxifen after treatment completion (HR 0·75 [0·61–0·94], p=0·01). The fewer deaths after recurrence (anastrozole 245 *vs* tamoxifen 269) was not significant (HR 0·90 [0·75–1·07], p=0·2), and no effect was noted for OS (anastrozole 472 *vs* tamoxifen 477) HR 0·97 [0·86–1·11], p=0·7). Fracture rates were higher in patients receiving anastrozole than in those receiving tamoxifen during active treatment (number [annual rate]: 375 [2·93%] *vs* 234 [1·90%]; incidence rate ratio [IRR] 1·55 [1·31–1·83], p<0·0001), but were not different after treatment was completed (off treatment: 146 [1·56%] *vs* 143 [1·51%]; IRR 1·03 [0·81–1·31], p=0·79). We did not note any significant difference in risk of cardiovascular morbidity or mortality between anastrozole and tamoxifen treatment groups.

Interpretation These data show long-term safety findings and establish clearly the long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant treatment for postmenopausal women with hormone-sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after 5 years of adjuvant treatment with anastrozole compared with tamoxifen.

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Introduction

Breast cancer is the most common type of cancer in women and the most frequent cause of cancer-related death; the number of women diagnosed with breast cancer worldwide in 2002 was 1·15 million and about 410 000 women died as a result of breast cancer.[1] In developed countries, around 75% of all breast cancers occur in postmenopausal women, of which about 80% are hormone-receptor positive.[2] Until recently, tamoxifen has been the endocrine treatment of choice for post-menopausal women with hormone-receptor-positive early breast cancer. Tumour recurrence and mortality in women with hormone-receptor-positive breast cancer are significantly decreased by the use of 5 years of adjuvant tamoxifen, both in the presence and absence of chemotherapy.[3] Nonetheless, yearly recurrence rates remain above 2% long term and more than 30% of women develop recurrent disease within 15 years. Additionally, a small proportion of women have serious side-effects, including increased incidence of endometrial cancer, and thromboembolism and cerebrovascular events.[3–7]

Data from clinical trials comparing third-generation aromatase inhibitors with tamoxifen[8–10] have confirmed that aromatase inhibitors offer significant efficacy and tolerability advantages over tamoxifen during the treatment phase. Aromatase inhibitors are now recommended as adjuvant treatment for post-menopausal women with hormone-receptor-positive early breast cancer.[11,12] However, several questions

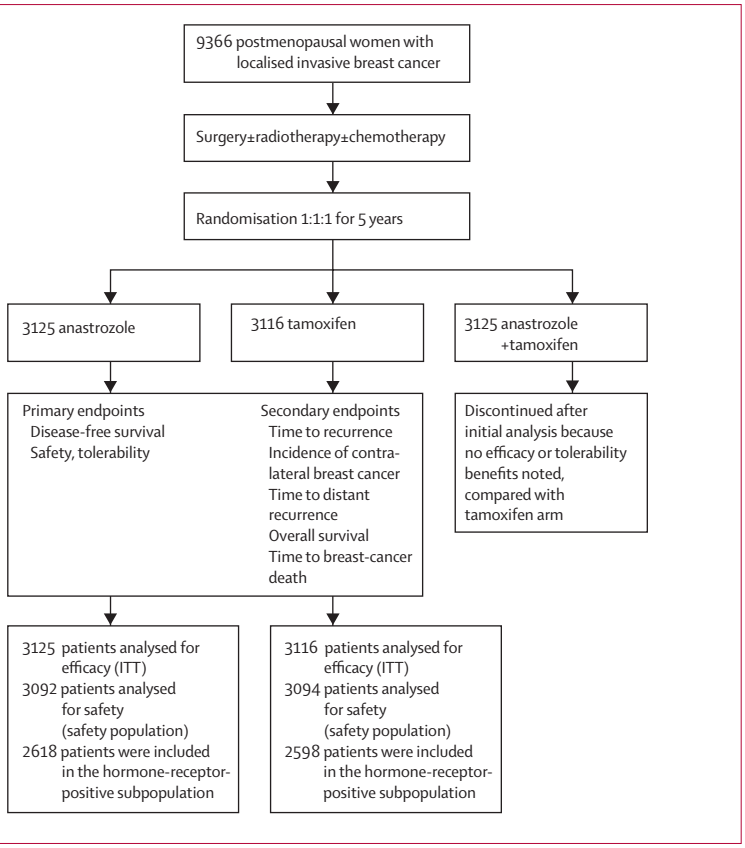

Figure 1: **Trial profile**
ITT=intention-to-treat.

remain unanswered, including the extent to which treatment benefits and side-effects continue after treatment is completed, the most appropriate duration of treatment, and the relative benefits of initial treatment with aromatase inhibitors versus sequencing after 2 years of tamoxifen.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was undertaken to compare the efficacy and safety data of the third-generation, oral, non-steroidal aromatase inhibitor anastrozole (Arimidex; AstraZeneca, Macclesfield, UK) against tamoxifen (Nolvadex; AstraZeneca) for 5 years as initial adjuvant hormonal treatment in postmenopausal women with hormone-receptor-positive early breast cancer.[13] Previous analyses of findings from the ATAC trial showed that anastrozole significantly prolonged disease-free survival (DFS) and time to recurrence (TTR).[8,13,14] Additionally, anastrozole treatment was associated with significantly fewer serious adverse events than tamoxifen, including fewer occurrences of thromboembolism, ischaemic cerebrovascular events, and endometrial cancer, but increased numbers of fractures on treatment.[15] The 68-month follow-up analysis suggested that the efficacy benefits extended for at least 1 year beyond the completion of treatment at 5 years.[8]

This report presents updated data from the ATAC trial at a 100-month median follow-up and is the longest follow-up to date after 5 years of upfront treatment with aromatase inhibitors.

Methods

Patients and procedures

The ATAC trial was undertaken by methods previously described (figure 1).[13] The combination treatment was discontinued after the initial analysis because it showed no efficacy or tolerability benefits over tamoxifen alone. Patients who received combination treatment were unblinded and not followed up; therefore, comparable long-term data are not available for this group. For the two monotherapy arms, follow-up after treatment included scheduled annual visits and quarterly reminders and requests for missed appointments, including letter and telephone call, and email requests were made to non-responders to minimise patient loss.

Statistical analysis

For the data presented here, efficacy and safety analyses were done by use of methodology previously described.[13,15] The primary endpoint was DFS, defined as the time from randomisation to the earliest occurrence of local or distant recurrence, new primary breast cancer, or death from any cause. Secondary endpoints were TTR, which included new contralateral tumours, but not deaths from non-breast-cancer causes before recurrence, incidence of new contralateral tumours, time to distant recurrence (TTDR, defined as the time between randomisation and the first report of distant recurrence, censoring at deaths without recurrence), and overall survival (OS). For safety analyses, only patients who started with their allocated treatment were included (safety population) and they were censored at local or distant recurrence. Hazard ratios (HR) and 95% CI were based on the partial likelihood for Cox's proportional hazards model without adjustment for covariates.[16] All time-to-event curves were truncated at 9 years' follow-up, but HR include all events until database cutoff (March 31, 2007). Hazard rate curves for time to recurrence in hormone-receptor-positive patients were smoothed with an Epanechinikov kernel with bandwidth chosen by cross validation (STATA 9.0 sts graph command).[17] To allow for a 1-year smoothing interval, smoothed hazard plots were truncated at 8·5 years (last interval 8–9 years). Optimum bandwidth was about 12 months.

Efficacy analyses were based on the intention-to-treat population (3125 patients in the anastrozole group *vs* 3116 in the tamoxifen group) and also on the predefined hormone-receptor-positive subpopulation (2618 patients in the anastrozole group and 2598 in the tamoxifen group). Women with known hormone-receptor-positive tumour status (defined as oestrogen-receptor-positive or progesterone-receptor-positive, or both, according to local laboratory standards) were predefined as a clinically

important subgroup for all efficacy endpoint analyses, and we now know that benefits from endocrine treatment are confined to this group.

Safety analyses were based on treatment first received in all randomised patients (anastrozole n=3092; tamoxifen n=3094). As previously described,[15] adverse events were recorded during the treatment period as prespecified adverse events or spontaneously reported events, or both, subsequently categorised according to Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) terms.[18] At each visit, investigators were required to ask patients whether they had had any adverse events and to record events on the trial case-report forms. All adverse events occurring while a patient was receiving treatment, and up to 14 days after the study treatment had ended, were recorded (on treatment). After treatment (14 days after treatment termination), all fracture episodes (a fracture episode comprised one or more fractures on the same day) and serious adverse events continued to be recorded up to the time of recurrence or death (off treatment). Recording of adverse events included a description of the event, date of onset and resolution, event intensity (mild, moderate, or severe), whether the event was serious, event outcome, whether the treating physician regarded the event to be treatment-related, and any action taken (eg, further treatment or diagnostic tests). Consistent with good clinical practice definitions, serious adverse events were defined as death, a life-threatening event, an event that caused or extended long-term hospital care, an event that caused disability or incapacity, or an event that needed medical intervention to prevent permanent impairment or damage. Serious adverse events were analysed on an individual (per) patient basis and reported as odds ratios (OR), except for fractures where patients could have multiple events and these are reported as incidence rate ratios (IRR). Women on the ATAC trial were provided with blinded medication for a maximum of 5 years. Blinding was maintained beyond the completion of treatment and hence further treatment or switching between primary treatments beyond the 5-year completion date was not likely to occur. All additional medications were recorded during the drug treatment period, but not after treatment completion. However, because the study was blinded, the use of additional medications was probably similar for both arms. All p values were two-sided. The ATAC trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN18233230.

Role of the funding source

The study was developed by the new studies working party of the Cancer Research UK Breast Cancer Trials Group before a sponsor was identified. The management of the trial has subsequently been coordinated by the international steering committee with funding and organisational support from the trial sponsor, AstraZeneca.

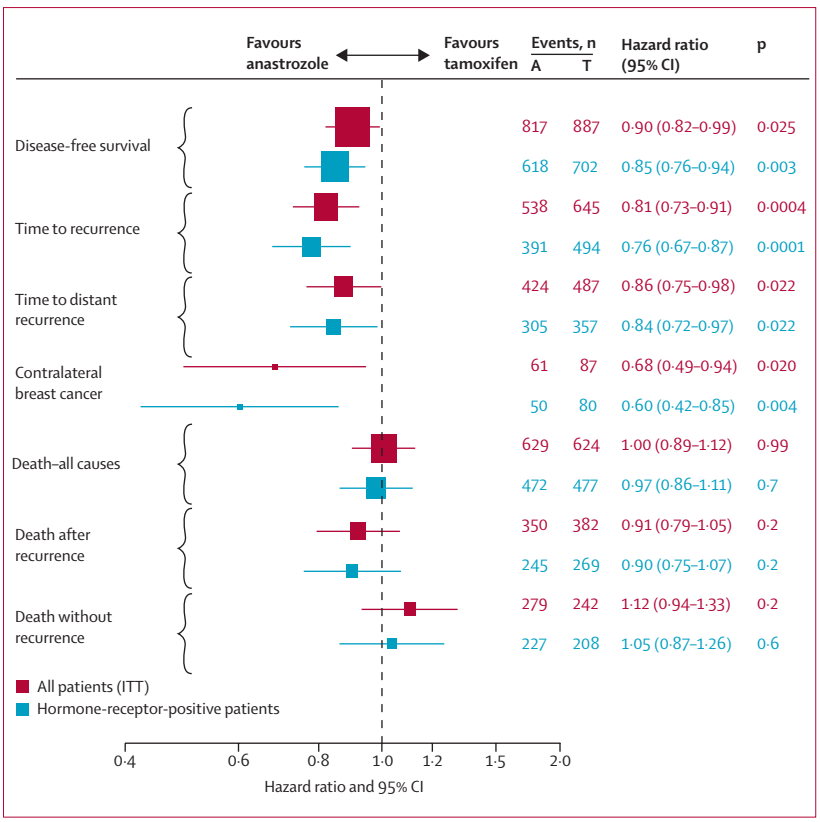

Figure 2: **Efficacy endpoints for all patients and hormone-receptor-positive patients**
A=anastrozole. T=tamoxifen. ITT=intention-to-treat.

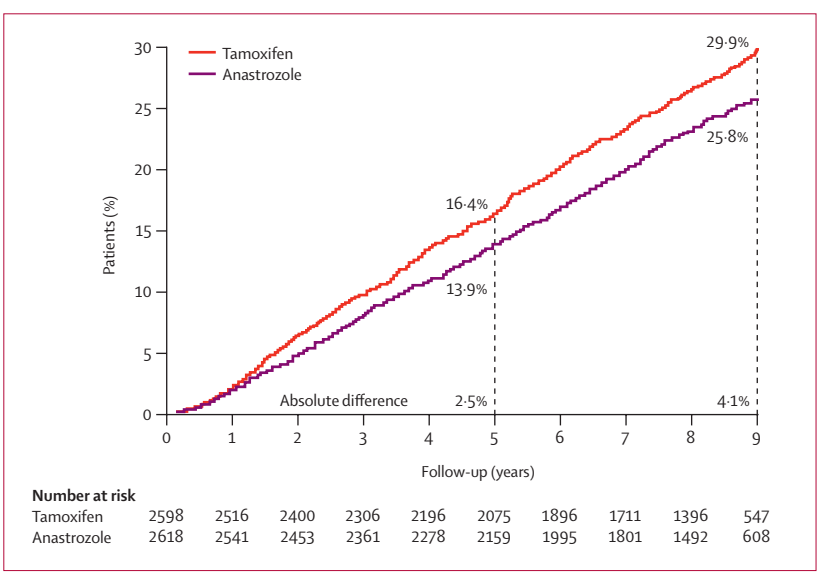

Figure 3: **Kaplan-Meier prevalence curves for disease-free survival (DFS) in hormone-receptor-positive patients**

The independent statistician (JC) had full access to the data, and was responsible for providing regular information to the independent data monitoring committee. The sponsor had access to all data except the

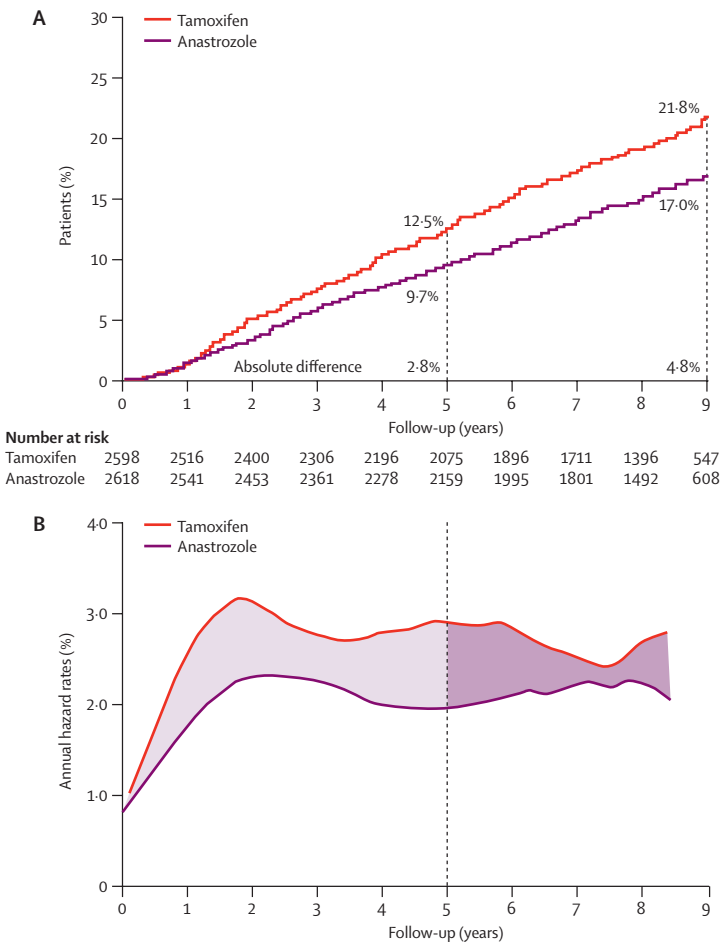

***Figure 4*: Curves for time to recurrence (TTR) in hormone-receptor-positive patients**
(A) Kaplan-Meier prevalence curves and (B) smoothed hazard rate curves for time to recurrence. Plots are smoothed with an Epanechinikov kernel with bandwidth chosen by cross validation.

randomisation codes until unblinding. The writing and steering committees were responsible for data interpretation, writing of the report, and the decision to submit for publication. Complete Medical Communications (Macclesfield, UK)—who were funded by the sponsor—provided assistance with the design and construction of the tables and figures. The sponsor was represented in a minority on the steering committee.

Results

See Online for webtable

Median follow-up for this extended analysis was 100 months (range 0–126). This follow-up included a total of 46 202 women-years of follow-up for patients receiving monotherapy; a 38% increase in years of follow-up over the last analysis (median follow-up of 68 months). The mean (SD) duration of treatment for patients receiving anastrozole was 4·11 years (1·65) compared with 3·97 years (1·71) for tamoxifen, and we noted a high reported compliance to randomised treatment (percentage of allocated treatment received before recurrence: anastrozole 88% (12 559 women-years of treatment), tamoxifen 87% (12 113 women-years of treatment). Mean (SD) age was 64 years (9) at study entry and 72 years (9) for the survivors at the time of this analysis. Figure 2 shows the HR and 95% CI for the major endpoints for all randomised patients and the clinically important hormone-receptor-positive subgroup, which comprised 84% of all randomised patients. For the primary endpoint, DFS, the previously reported benefit for the anastrozole group[8] was maintained after treatment was completed (hormone-receptor-positive subgroup HR 0·85 [95% CI 0·76–0·94], p=0·003; figure 3). For other endpoints, similar HR to those in the previous report were also maintained, and showed significantly lower recurrence and occurrences of new contralateral breast cancer (CLBC) for anastrozole compared with tamoxifen. Of particular note was the effect on distant recurrence, which was now significant overall in the intention-to-treat (ITT) population (HR 0·86 [0·75–0·98], p=0·022) and in the hormone-receptor-positive subgroup (HR 0·84 [0·72–0·97], p=0·022) compared with the previous analysis where it was only significant in the ITT population.[8] In the hormone-receptor-negative subgroup, DFS (HR 1·02 [0·78–1·33], p=0·9) and recurrence (HR 0·96 [0·71–1·29], p=0·8) were not affected. Deaths after recurrence for all patients were 350 (anastrozole) and 382 (tamoxifen; HR 0·91 [0·79–1·05], p=0·2), and for the hormone-receptor-positive subgroup were 245 (anastrozole) and 269 (tamoxifen; HR 0·90 [0·75–1·07], p=0·2; figure 2). No statistically significant difference was noted for OS (for the ITT population: anastrozole, 629 deaths; tamoxifen, 624 deaths; HR 1·00 [0·89–1·12], p=0·99).

Figure 4 shows that the lower recurrence rate for anastrozole compared with those on tamoxifen was maintained after treatment was completed, especially for the hormone-receptor-positive population where the absolute benefit of 2·8% (anastrozole, n=245 events; tamoxifen, n=312 events; HR 0·77 [0·65–0·91], p=0·002) at 5 years increased to 4·8% at 9 years (anastrozole, n=391 events, tamoxifen, n=494 events; HR 0·76 [0·67–0·87], p=0·0001). This finding is also shown clearly as annual hazard rates for recurrence remained lower on anastrozole compared with tamoxifen throughout the entire follow-up period (figure 4B). After 5 years, for the hormone-receptor-positive patient population, we noted 146 events in 2159 (7%) at-risk patients who received anastrozole and 182 events in 2075 (9%) at-risk patients who received tamoxifen (HR 0·75 [0·61–0·94], p=0·01). This finding shows that the carryover benefit after treatment completion with anastrozole is larger than that known to exist after tamoxifen.[3] The distant recurrence rates also continued to diverge with increasing follow-up time, being 1·3% lower for anastrozole compared with tamoxifen at year 5 and 2·4% lower at year 9 (figure 5). The occurrence of

isolated contralateral tumours as a first event was significantly lower with anastrozole compared with tamoxifen (hormone-receptor-positive patients: HR 0·60 [0·42–0·85], p=0·004; figure 6). The HR for recurrence favoured anastrozole for all subgroups based on baseline and treatment characteristics (figure 7). There was no significant heterogeneity across these treatment subgroups, except for the small subgroup of oestrogen-receptor-positive and progesterone-receptor-negative patients for whom the benefit in favour of anastrozole was larger than for the oestrogen-receptor-positive and progesterone-receptor-positive subgroup (p=0·001 for heterogeneity between these subgroups). This finding, according to progesterone-receptor status, was not noted in the only other similar adjuvant trial.[9]

Deaths without recurrence were higher in patients receiving anastrozole, although not significantly so, and no specific cause of death was significantly raised (table 1). Occurrences of any serious adverse events were similar in both treatment arms, but treatment-related serious adverse events were lower in those receiving anastrozole compared with those receiving tamoxifen during treatment and similar after treatment completion; this finding led to a lower overall prevalence (202 *vs* 341, OR 0·57 [0·47–0·68], p<0·0001; table 2). In particular, myocardial infarctions were similar in the two treatment arms, both during treatment and after its completion when they were only captured as serious events (table 2). Fewer cerebrovascular accidents were noted in patients receiving anastrozole during treatment (20 *vs* 34, OR 0·59 [0·32–1·05], p=0·056), but not afterwards (22 *vs* 20, OR 1·10 [0·57–2·13], p=0·75) for those events reported as serious.

Table 3 shows occurrence of new non-breast primary cancers before recurrence. We did not note a significant difference overall, but the occurrence of endometrial cancer remained significantly lower in patients treated with anastrozole (five events) than with tamoxifen (24 events; OR 0·21 [0·06–0·56], p=0·0004). Although other differences were noted (fewer occurrences of lung and colorectal cancer with tamoxifen and fewer occurrences of ovarian cancer and melanoma on anastrozole), we did not expect any differences in specific cancers by treatment arm, except for endometrial cancer. Only the difference between groups in the numbers of patients with endometrial cancer was significant after a Bonferroni correction for multiple comparisons.

Predefined side-effects during treatment (or within 14 days of treatment cessation) were similar to those published previously[8] in that 5740 of 6241 (92%) patients had completed treatment by that time (webtable). However, fracture data continued to be monitored in a blinded manner after treatment cessation. Figure 8 shows that although fracture rates were increased on anastrozole during treatment (IRR 1·55 [1·31–1·83], p<0·0001), as reported previously,[8,13,14] no excess was noted after the 5-year treatment period (IRR 1·03

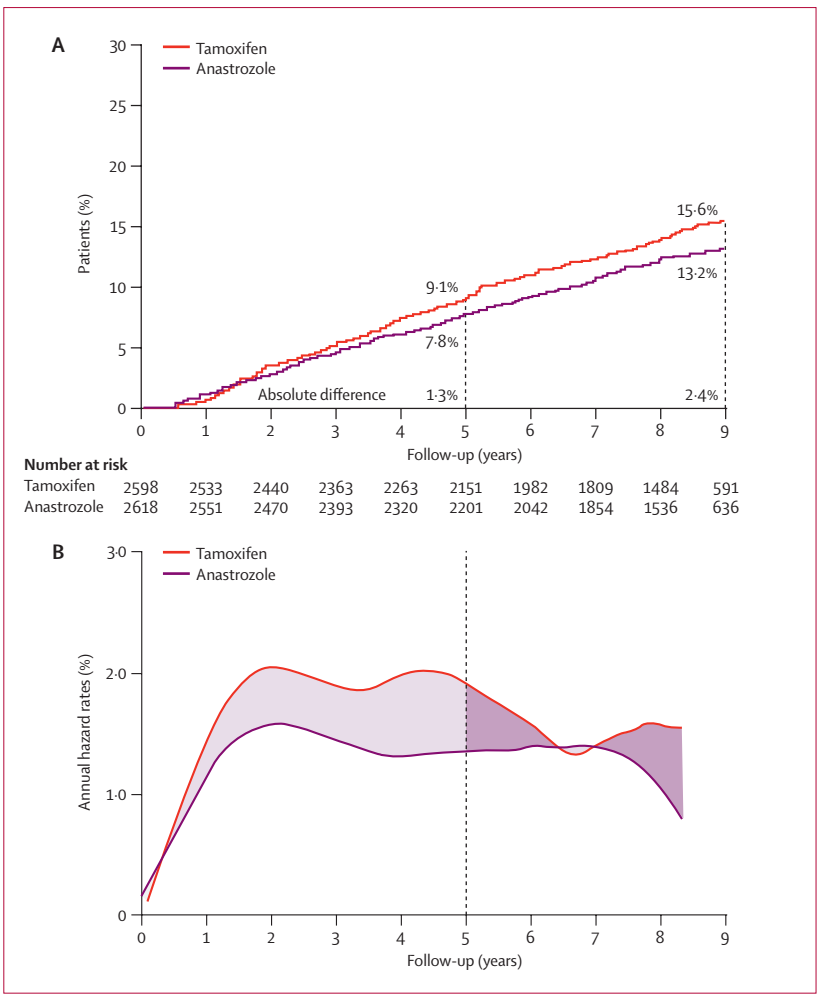

***Figure 5*: Curves for time to distant recurrence in hormone-receptor-positive patients**
(A) Kaplan-Meier prevalence curves and (B) smoothed hazard rate curves for time to distant recurrence. Plots are smoothed with an Epanechinikov kernel with bandwidth chosen by cross validation.

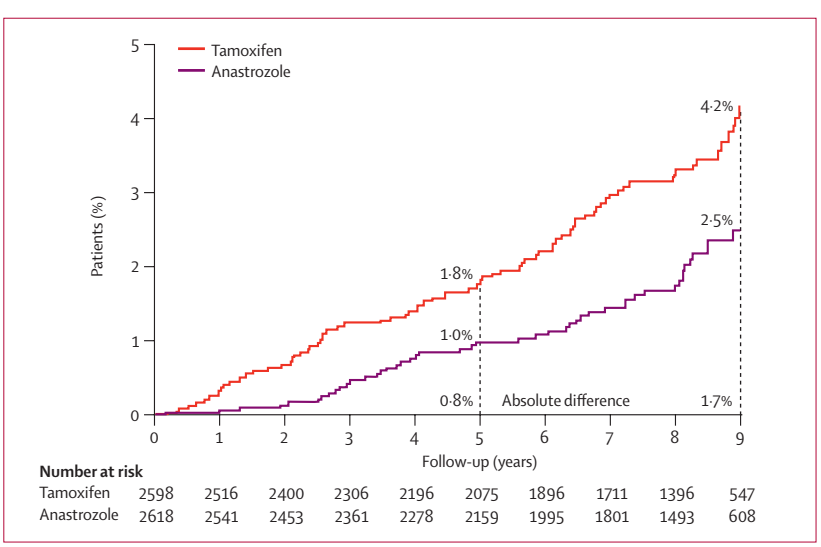

***Figure 6*: Kaplan-Meier prevalence curves for contralateral breast cancer in hormone-receptor-positive patients**

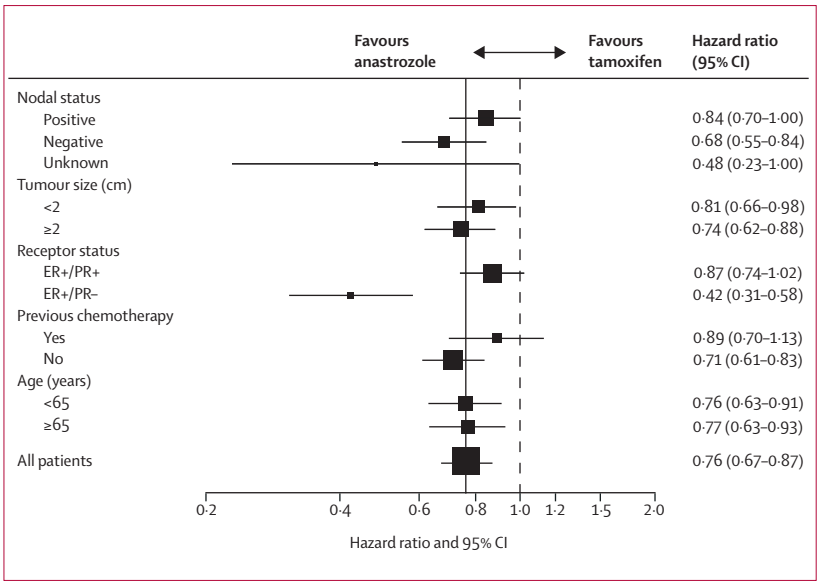

***Figure 7*: Analysis of time to recurrence for anastrozole versus tamoxifen according to baseline and treatment characteristics in the hormone-receptor-positive population**
ER=oestrogen receptor. PR=progesterone receptor.

	Anastrozole (n=3125)	Tamoxifen (n=3116)
Total deaths	629 (20)	624 (20)
Deaths after recurrence	350 (11)	382 (12)
Deaths without recurrence	279 (9)	242 (8)
Cardiovascular	67 (2)	66 (2)
Cerebrovascular	25 (0·8)	29 (0·9)
Second primary non-breast cancers	84 (3)	60 (2)
Other	103 (3)	87 (3)

Data are patients, n (%).

***Table 1*: Deaths in the anastrozole and tamoxifen treatment groups according to randomised treatment (intention-to-treat population)**

	On treatment		Off treatment	
	Anastrozole	Tamoxifen	Anastrozole	Tamoxifen
Women-years of follow-up	12 781	12 331	9351	9448
All serious adverse events	1054 (8·25)	1125 (9·12)	356 (3·81)	339 (3·59)
Treatment-related serious adverse events*	153 (1·20)	284 (2·30)	49 (0·52)	57 (0·60)
Endometrial cancer	4 (0·03)	12 (0·10)	1 (0·01)	12 (0·13)
Myocardial infarction	34 (0·27)	33 (0·27)	26 (0·28)	28 (0·30)
Cerebrovascular accident	20 (0·16)	34 (0·28)	22 (0·24)	20 (0·21)
Fracture episodes†	375 (2·93)	234 (1·90)	146 (1·56)	143 (1·51)

Numbers refer to patients with an event, except for fracture episodes for which patients could have more than one episode. Patients with an "on treatment" event were not at risk of an "off treatment" event, except for fracture episodes. *Judged by the investigator. †A fracture episode comprised one or more fractures on the same day based on reports of adverse events and serious adverse events.

***Table 2*: Serious adverse events on and off treatment before recurrence for the safety population: number (and annual rate)**

[0·81–1·31], p=0·79). Virtually identical findings were recorded if the number of patients with fractures was used for logistic regression rather than the number of episodes (data not shown). Overall, hip fractures were rare in both treatment groups (49 [1·6%] anastrozole *vs* 42 [1·4%] tamoxifen) and there was no statistically significant difference (OR 1·17 [0·75–1·82], p=0·46).

Discussion

The findings of this report extend the previously reported superior efficacy of anastrozole over tamoxifen at 68 months of follow-up[8] to 100 months. We also show a carryover benefit for recurrence in the hormone-receptor-positive population, which is larger than that previously shown for tamoxifen.[3] The difference in recurrence rates has continued to increase, and the smoothed hazard plots show clearly that lower recurrence rates are maintained with anastrozole, even after treatment has been completed. For the clinically relevant hormone-receptor-positive subgroup, the difference in recurrence increased from 2·8% after 5 years to 4·8% after 9 years, showing the long-term benefit of starting treatment with anastrozole. This finding is important because a carryover effect for 5 years of tamoxifen on recurrence rates in years 5–9 (of about two-thirds the size of that achieved during active treatment) has previously been reported.[3] The additional significant reduction in recurrence noted with anastrozole versus tamoxifen after treatment completion shows that anastrozole decreases recurrence by 50% (HR=0·75×0·67) in the post-treatment period compared with no treatment.

The subgroups predefined for analysis, based on clinicopathological and treatment parameters, showed an advantage for anastrozole as initial adjuvant endocrine treatment (figure 7). In the small subgroup of oestrogen-receptor-positive and progesterone-receptor-negative patients (19% of oestrogen-receptor-positive patients), the benefit seems to be even greater. However, this finding has not been confirmed in another study with letrozole[19] or in a subset of patients from whom tissue was able to be collected for translational research studies.[20]

At this 100-month median follow-up, a 30% increase in the number of distant recurrences was noted overall since the last analysis at 68 months (911 events *vs* 699 events). The benefit on distant recurrence of anastrozole compared with tamoxifen has been maintained with a similar HR to that reported previously,[8] both for all randomised patients and for the hormone-receptor-positive subgroup (figure 2). Deaths after recurrence were decreased by 9% (anastrozole, n=350; tamoxifen, n=382) overall and by 10% (anastrozole, n=245; tamoxifen, n=269) in the hormone-receptor-positive subgroup; these differences were not significant. Since we recorded only 732 deaths after recurrence compared with 911 distant recurrences (and 1183 recurrences at any site), further follow-up is needed to ascertain if the lower breast-cancer mortality rate for

	Anastrozole (n=3092)	Tamoxifen (n=3094)
Total	292 (9)	288 (9)
Head and neck	12 (0·4)	5 (0·2)
Upper gastrointestinal	8 (0·3)	6 (0·2)
Colorectal	56 (2)	36 (1)
Lung	42 (1)	24 (0·8)
Skin (non-melanoma)	96 (3)	107 (3)
Melanoma	8 (0·3)	18 (0·6)
Ovary	12 (0·4)	26 (0·8)
Endometrium*	5 (0·2)	24 (0·8)
Cervix	2 (0·1)	6 (0·2)
Kidney or bladder	17 (0·5)	15 (0·5)
Leukaemia, lymphoma, or myeloma	22 (0·7)	19 (0·6)
Other	37 (1·2)	32 (1)

Data are patients, n (%). *Includes uterine cancers not specified as cervix.

Table 3: **New primary cancers at non-breast cancer sites before recurrence (safety population)**

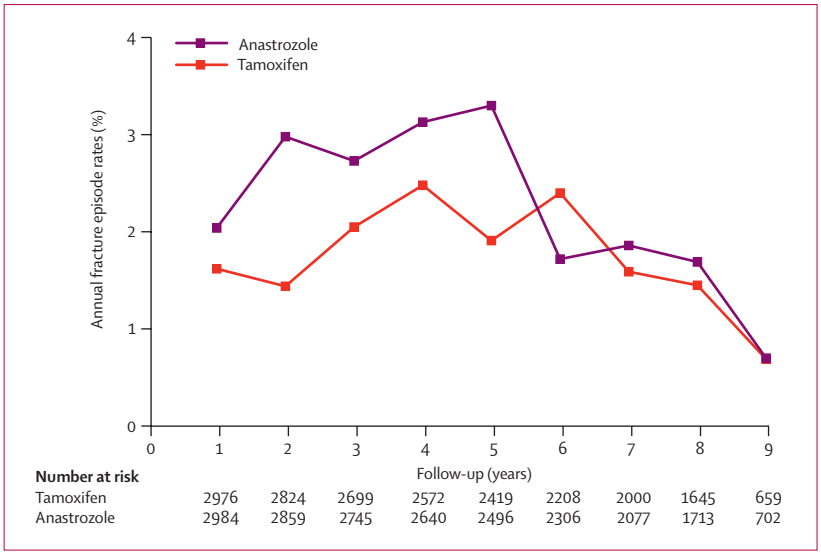

Figure 8: **Fracture episode* rates throughout the study**
*A fracture episode comprised one or more fractures on the same day. Fractures occurring after recurrence are not included because patients were censored after recurrence and fractures were not recorded.

anastrozole will become statistically significant when more events are recorded. Furthermore, as all types of recurrence (local, contralateral, or distant) have important implications for long-term survival, future analysis is awaited with interest. This analysis is currently planned for 2010, when all patients will be more than 10 years past their date of randomisation.

No differences were noted in OS. This observation might be partly because of an excess (not significant) of deaths from other causes without a previous recurrence, which were a major component of OS (about 44% in the anastrozole group and 39% in the tamoxifen group of the total deaths [table 1] were non-breast-cancer deaths). In a report on non-breast cancer deaths, findings showed that for at least 10 years after diagnosis for women aged 50 years and over who had node-negative, oestrogen-receptor-positive primary breast cancer treated with adjuvant tamoxifen, competing non-breast-cancer causes of deaths comprised most of the deaths.[21]

In the current ATAC analysis, no specific cause of death was increased significantly in patients assigned to anastrozole, and the non-significant excess of deaths from other causes was probably due to chance. In particular, we did not note an increase in deaths from heart disease, nor any excess of incident myocardial infarction (fatal and non-fatal combined). This finding is reassuring, especially since concerns of a potential increased incidence of serious cardiovascular events with other aromatase inhibitors have been raised.[6,9,10]

For this analysis, the mean age at last follow-up was 72 years. Risk of serious comorbidities increases with age. Therefore, deaths from causes other than breast cancer were a major component for OS. This effect was partially compensated for by studying deaths after recurrence. Although these deaths have previously been labelled as "breast-cancer deaths" in previous ATAC reports and elsewhere,[3] they also include deaths from non-breast-cancer causes, thus some dilution of the true mortality from breast cancer exists. Such a definition is a pragmatic one because, for many patients, identification of the cause of death in those who have recurred is difficult. However, the significant decrease in distant recurrence seen in ATAC for anastrozole is likely to lead to a real decrease in breast-cancer deaths, as has been reported in the tamoxifen overview[3] and most adjuvant trials.

The safety profile for anastrozole established at 68 months' median follow-up[8,15] has been confirmed. The increased yearly fracture episode rate noted during treatment (2·93% *vs* 1·90%, a 55% relative increase) did not continue into the post-treatment follow-up period, where the rate on anastrozole was very similar to that with tamoxifen (IRR 1·03, non significant). Therefore, by contrast to the effect on breast-cancer recurrence of anastrozole and tamoxifen, which extend substantially beyond the cessation of treatment, the increase in fracture rates with anastrozole seems to be associated only with the active treatment period and does not continue after its completion (figure 8). Fracture rates were lower in the post-treatment period for both treatments, most probably due to the under-reporting of fractures at this time. However, since both patients and clinicians remained blinded to treatment allocation in most cases, reporting bias was unlikely, and the relative incidences should not be affected. Throughout the study, hip fractures were little affected by anastrozole (1·6% of patients) compared with tamoxifen (1·4% of patients). As reported previously in a substudy of this trial, anastrozole was associated with a 6–7% bone loss during active treatment, although no patients with normal bone at baseline developed osteoporosis after 5 years' treatment.[22,23]

Bisphosphonate use was very low in this trial (ever-use on treatment: anastrozole, 311 of 3125 [10%] patients; and tamoxifen, 213 of 3116 [7%] patients). However, evidence is increasing that patients with low bone-mineral density at the start of treatment can be identified and managed according to evolving clinical guidelines.[24,25]

The numbers of treatment-related serious adverse events remained lower with anastrozole than with tamoxifen for the entire follow-up period, and were significantly lower during treatment and similar after treatment completion. In particular, occurrences of endometrial cancer were much lower in both periods for anastrozole. Ovarian cancer and melanoma were also lower with anastrozole and lung and colorectal cancer higher, but these were not prespecified outcomes and were not significant after correction for multiple comparisons. The only difference in new primary cancer occurrences that was significant, after a Bonferroni correction for multiple comparisons, was the lower number of endometrial cancers noted with anastrozole treatment. Since tamoxifen is known to increase the incidence of endometrial cancer,[26] this difference is not surprising, and could be a result of either protection from lowered oestrogen concentrations or the increase associated with tamoxifen, or both. Other differences, (lower ovarian cancer and melanoma occurrences with anastrozole, and lower colorectal and lung cancer occurrences with tamoxifen, none significant after Bonferroni correction for multiple comparisons) might have resulted from random variations or could be real. As the other studies of aromatase inhibitors mature, a review of additional data might help clarify these observations.

Treatment with tamoxifen might be associated with an increased risk of cerebrovascular accidents.[5] In our previous reports, all cerebrovascular events occurring during treatment were significantly higher on tamoxifen compared with anastrozole in ATAC, and this is little changed in the current report (91 *vs* 64, OR 1·44 [95% CI 1·04–1·99], p=0·03; webtable). Cerebrovascular accidents were also increased during treatment, but this was not statistically significant (p=0·056; table 2) and no difference was reported after treatment completion, suggesting that any effect of tamoxifen on these events occurs only during treatment.

Other side-effects were only recorded during active treatment and 14 days thereafter. Consequently, these side-effects were little changed from our previous report,[15] where fewer occurrences of hot flushes, gynaecological symptoms, hysterectomy and venous thromboembolic occurrences, and more occurrences of arthralgia, other joint symptoms, and carpal tunnel syndrome, were noted with anastrozole than with tamoxifen.

The current analysis, at a median follow-up of 100 months, extends and strengthens the evidence for the use of 5 years of anastrozole as initial adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive breast cancer.

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JFF took part in the trial management and data interpretation, and chairs the writing and steering committees. JC is an independent statistician and was responsible for the statistical analysis, and participated in trial design and data interpretation. AB, MB, AH, and JST participated in the analysis and interpretation of data. JST was chair of the new studies working party of the Cancer Research UK Breast Cancer Group for 10 years before the initiation of the ATAC trial and took part in the trial design. All contributors took part in writing the report, and saw and approved the final version.

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Conflicts of interest

AB has received research grants, travel awards, and honoraria from AstraZeneca. JFF, MB, AH, and JST have received honoraria and appeared on speakers' bureaus for AstraZeneca. JC is statistical consultant to, and has received research funds from, AstraZeneca.

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