Extending the duration of endocrine treatment for early breast cancer: patient-level meta-analysis of 12 randomised trials of aromatase inhibitors in 22 031 postmenopausal women already treated with at least 5 years of endocrine therapy

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background In postmenopausal women with oestrogen receptor-positive early breast cancer, 5 years of adjuvant tamoxifen substantially reduces 15-year recurrence and mortality; aromatase inhibitor treatment (AIT) is even more effective. We assess the effects of further AIT among women recurrence-free after at least 5 years of endocrine therapy.

Methods We conducted individual patient data meta-analyses of 12 randomised trials, including 22 031 women who had completed at least 5 years of tamoxifen, AIT, or tamoxifen then AIT, comparing subsequent AIT versus no further adjuvant therapy. Primary outcomes were recurrence of invasive breast cancer (local, distant, or new contralateral), breast cancer mortality, mortality from other causes, and all-cause mortality. Intention-to-treat analyses (irrespective of allocation adherence and stratified by age, nodal status, and trial, and censored at death from unrelated causes) yielded event rate ratios (RRs).

Findings Allocation to AIT versus no further treatment reduced recurrence rates by 27% (RR 0·73 [95% CI 0·67–0·80], p<0·0001). This reduction was greater after previous tamoxifen alone than after some previous AIT, and greater in trials of 5 years of AIT versus no further AIT than in trials of 2–3 years of AIT versus no further AIT. After some previous AIT, allocation to 5 further years of AIT (with median 8·1 years [IQR 6·0–10·0] follow-up after trial treatments diverged) reduced both recurrence (RR 0·71 [0·61–0·81], p<0·0001; risk from year 5 to year 15 after diagnosis 11·6% *vs* 15·2%) and distant recurrence (RR 0·73 [0·61–0·88], p=0·0010; 6·6% *vs* 8·6%); breast cancer mortality was reduced non-significantly (RR 0·90 [0·70–1·15], p=0·40; 4·4% *vs* 5·0%). Tumour characteristics had no definite effects on the proportional recurrence reductions from year 5 to year 15, so the absolute recurrence reduction with 10 years *vs* 5 years AIT was greater for node-positive (risk 16·3% *vs* 20·1%) than for node-negative disease (9·1% *vs* 11·8%). Allocation to 5 further years of AIT increased 5-year bone fracture risk (RR 1·35 [1·13–1·61], p=0·0009; 4·6% *vs* 3·4%). Non-adherence to allocated treatment was widespread (39·0% further AIT *vs* 37·6% placebo in the placebo-controlled trials).

Interpretation Allocation to 5 further years of AIT reduced subsequent distant recurrence rates by about a quarter despite substantial non-adherence. Longer follow-up would have been needed to help assess directly any effects on mortality.

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Introduction

In postmenopausal women with recently diagnosed oestrogen receptor (ER)-positive early breast cancer, allocation to 5 years of adjuvant endocrine therapy, despite imperfect adherence, proportionally reduces breast cancer recurrence rates during the first 10 years by about 40% for tamoxifen and 50% for aromatase inhibitor treatment (AIT), with little further gain thereafter.[1–3] The corresponding proportional reductions in breast cancer mortality rates are about 30% and 40%, and continue beyond year 10. Even after completion of 5 years of endocrine therapy, however, a substantial recurrence risk persists for many years.[4] Extending tamoxifen treatment to 10 years somewhat reduces this risk, but can cause endometrial cancer or pulmonary embolism.[5,6] Using AIT to extend endocrine therapy beyond year 5 also reduces the risk of recurrence, but oestrogen deprivation can cause vasomotor symptoms, musculoskeletal symptoms, osteoporosis, or fractures.[3,7–11]

Among women who had already received 5 years of adjuvant tamoxifen, trials that compared further AIT versus no further endocrine treatment have reported

Research in context

Evidence before this study

Most postmenopausal women with early-stage breast cancer have oestrogen receptor (ER)-positive disease. After any surgery, chemotherapy, or radiotherapy, 5 years of endocrine treatment with tamoxifen or, more effectively, aromatase inhibitor treatment (AIT) substantially reduces their 15-year risk of death from breast cancer. Despite this, an appreciable risk of recurrence and death remains. Trials have studied adding further years of AIT after at least 5 years of previous endocrine treatment, but current guidelines differ on optimal AIT duration, due partly to uncertainties about effects on breast cancer outcomes that could be resolved by meta-analyses of individual patient-level data from all trials. The Early Breast Cancer Trialists' Collaborative Group's network of trialists (and regular database searches up to Sept 30, 2024, including MEDLINE, Embase, the Cochrane Library, and meeting abstracts) identified 12 such trials, all now closed.

Added value of this study

This meta-analysis, involving the more than 22 000 eligible women from 12 trials, summarises the randomised evidence on benefits and risks of 2–3 further years of AIT versus no further AIT or of 5 further years of AIT versus no further AIT for postmenopausal women who had already received at least 5 years of tamoxifen, AIT, or tamoxifen then AIT. After previous tamoxifen alone, AIT immediately halved recurrence rates, an effect greater than that seen in the trials of further tamoxifen, reinforcing the greater efficacy of AIT. Even after some previous AIT, further AIT further reduced recurrence. Reductions were more definite, and appeared greater, in trials of 5 years versus no further AIT than in trials of 2–3 years versus no further AIT. In the placebo-controlled trials of 5 years versus no further AIT, there were substantial, but similar, levels of non-adherence in both the AIT and the placebo groups, suggesting most women discontinued for reasons not directly due to AIT. Despite this non-adherence, allocation to 5 further years reduced rates of subsequent recurrence and distant recurrence by about a quarter, with narrow CIs. More evidence is needed to assess eventual effects on breast cancer mortality. No excess of cardiovascular, or other, mortality was seen.

Implications of all the available evidence

Despite substantial non-adherence, among women who have already completed 5 years of adjuvant AIT, allocation to 5 further years of AIT significantly reduces the risk of distant recurrence over the next decade. Substantially greater adherence should increase both the benefits and the side-effects of treatment. If further AIT reduces breast cancer mortality as well as distant recurrence then, for individual patients, the absolute effects on survival will depend on the remaining risk of death from the original tumour (which largely depends on nodal status) and on the life expectancy that would remain without breast cancer (which is greater for younger women than older women).

See Online for appendix

fewer recurrences but no significant reduction in breast cancer mortality,[9–11] perhaps because many participants in the two largest such trials switched from placebo to AIT soon after early findings were published. For women who had already received 5 years of adjuvant AIT, reports from the trials of then continuing versus stopping AIT were promising but inconclusive. Thus, irrespective of the drugs used during the first 5 years of endocrine therapy, uncertainties remain about whether prolonging treatment beyond year 5 is worthwhile. To help clarify the benefits and risks, we review all the trials among women who had already received at least 5 years of previous endocrine therapy that randomly allocated giving further AIT versus giving no further adjuvant treatment. Information is reviewed on outcome by allocated treatment (by intention-to-treat meta-analyses) and contextualised based upon adherence to allocated treatment (to help assess the likely effects of actually taking AIT for some years versus no further endocrine treatment).

Methods

Study design and participants

Methods of identifying trials, data collection, checking, analysis, and presentation are as in previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reports,[1,12,13] and conform with PRISMA guidelines.[14] The statistical analysis plan (SAP) agreed before data collection began (appendix pp 50–57) involves all trials starting before Jan 1, 2010, that randomly assigned postmenopausal women with ER-positive early breast cancer who had already taken at least 5 years of endocrine therapy to some additional years of AIT versus no further adjuvant treatment. Some trials included women recorded as having had ER-negative, progesterone receptor (PR)-positive tumours, but the SAP excluded these women due to uncertainty about their benefits from any endocrine therapy.[1]

Trial groups provided individual patient-level data on randomisation date, allocated treatment, type and duration of previous endocrine therapy, age, BMI, tumour diameter, grade, histology, axillary lymph node involvement, ER, PR, and HER2 status; follow-up duration; dates of any loco-regional, contralateral, or distant breast cancer recurrence; details of any other second primary cancer; dates of any bone fracture; and date and underlying cause of death.

Outcomes

Protocol-specified primary outcomes were recurrence of invasive breast cancer (local, distant, or new contralateral), breast cancer mortality, mortality from other causes, and all-cause mortality. Time to first distant recurrence

(ignoring any other recurrences) was an important secondary outcome, and is used to analyse breast cancer mortality by log-rank subtraction. Other secondary outcomes were bone fractures, cardiovascular deaths, and site-specific second primary cancers.

Statistical analysis

Forest plots and Kaplan–Meier graphs describe the separate trials and their combined results, and subgroup analyses help explore whether the proportional risk reductions produced by treatment depend strongly on patient or tumour characteristics. Statistical methods are as in previous EBCTCG reports[1,2,12,13] and in the SAP (appendix pp 50–57). Follow-up of breast cancer outcomes is censored at death from an unrelated cause, so Kaplan–Meier graphs yield breast cancer recurrence risks in the hypothetical absence of deaths from other causes. Competing-risk analyses could allow for how other deaths curtail any treatment benefits but would confuse effects on breast cancer outcomes with consequences of mortality from other causes. Time-to-first-event analyses, stratified by age, nodal status, year of follow-up, and trial, give the log-rank observed minus expected (O−E) statistic and its variance V. These yield not only a significance test but also the first-event rate ratio, RR, and its confidence interval (using the one-step estimate $\log_e$ RR=[O−E]/V with

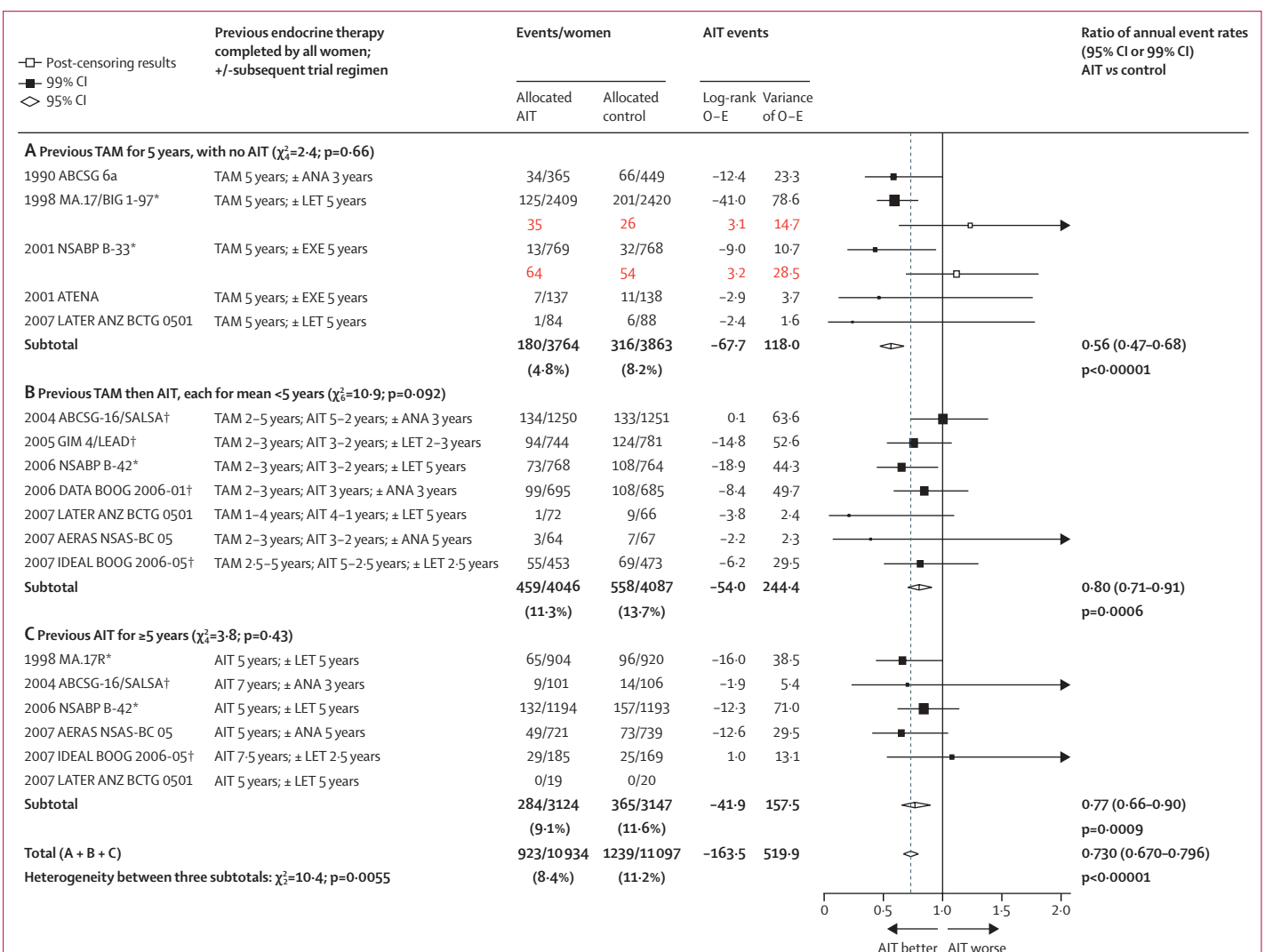
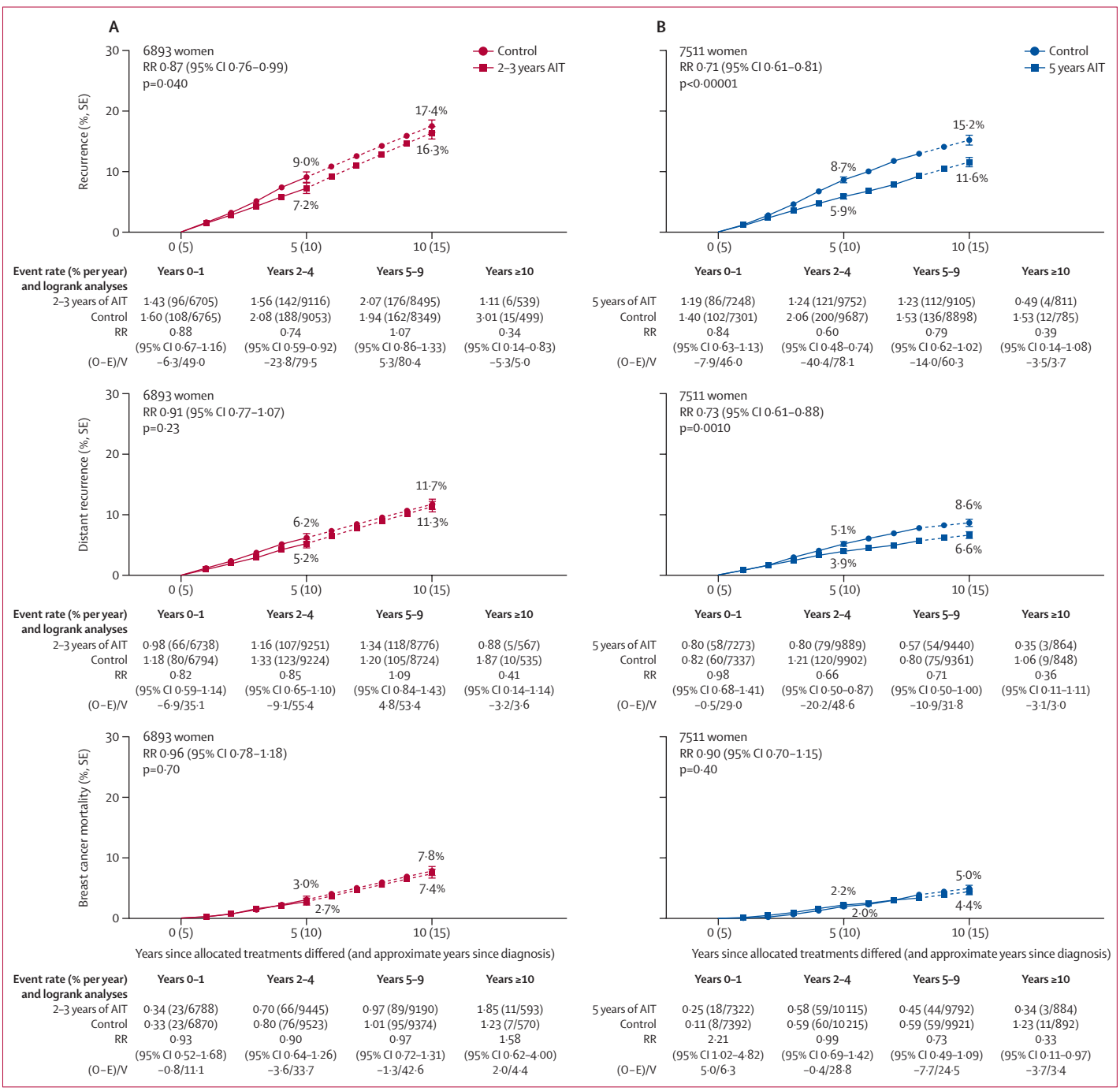


Figure 1: **Recurrence in trials of 2–3 further years of AIT versus no further AIT or of 5 further years of AIT versus no further AIT in women who had already completed at least 5 years of previous endocrine therapy**

For each trial, figure shows year started, study name, previous endocrine therapy, randomised treatment comparison, log-rank statistics, and recurrence RR (local, distant, or new contralateral invasive disease. AIT=aromatase inhibitor treatment. ANA=anastrozole. E=expected. EXE=exemestane. LET=letrozole. O=observed. TAM=tamoxifen. *Placebo-controlled trial. †Landmark analysis, excluding events before scheduled treatment divergence (appendix pp 8–11). All analyses exclude women with recurrence already diagnosed when the allocated treatments first differed. MA.17 and NSABP B-33 results were censored on Jan 1, 2005, due to crossover; post-censoring results (red font) were ignored in all analyses. Due to this censoring, median follow-up duration was only 3·4 years in (A), but 8 years in (B) and in (C). Some participants in MA.17R had received TAM for 5 years before their 5 years of previous AIT, and some participants in ABCSG 6a had received aminoglutethimide with their first 2 years of TAM.

variance 1/V). For overall results 95% CIs are given. Results for subgroups and individual trials are not unduly emphasised, and for them 99% CIs are given. χ^2 tests for heterogeneity or, where appropriate, trend compare RRs in different subgroups. Median (IQR) follow-up duration (among women who would have been survivors) was from Kaplan–Meier graphs of time to follow-up cessation. All p values are two-sided.

Breast cancer mortality RRs are estimated by subtracting the log-rank statistics (O – E and V) for



Event rate (% per year) and logrank analyses	Years 0–1	Years 2–4	Years 5–9	Years ≥10
2–3 years of AIT	1·43 (96/6705)	1·56 (142/9116)	2·07 (176/8495)	1·11 (6/539)
Control	1·60 (108/6765)	2·08 (188/9053)	1·94 (162/8349)	3·01 (15/499)
RR	0·88 (95% CI 0·67–1·16)	0·74 (95% CI 0·59–0·92)	1·07 (95% CI 0·86–1·33)	0·34 (95% CI 0·14–0·83)
(O–E)/V	−6·3/49·0	−23·8/79·5	5·3/80·4	−5·3/5·0

Event rate (% per year) and logrank analyses	Years 0–1	Years 2–4	Years 5–9	Years ≥10
5 years of AIT	1·19 (86/7248)	1·24 (121/9752)	1·23 (112/9105)	0·49 (4/811)
Control	1·40 (102/7301)	2·06 (200/9687)	1·53 (136/8898)	1·53 (12/785)
RR	0·84 (95% CI 0·63–1·13)	0·60 (95% CI 0·48–0·74)	0·79 (95% CI 0·62–1·02)	0·39 (95% CI 0·14–1·08)
(O–E)/V	−7·9/46·0	−40·4/78·1	−14·0/60·3	−3·5/3·7

Event rate (% per year) and logrank analyses	Years 0–1	Years 2–4	Years 5–9	Years ≥10
2–3 years of AIT	0·98 (66/6738)	1·16 (107/9251)	1·34 (118/8776)	0·88 (5/567)
Control	1·18 (80/6794)	1·33 (123/9224)	1·20 (105/8724)	1·87 (10/535)
RR	0·82 (95% CI 0·59–1·14)	0·85 (95% CI 0·65–1·10)	1·09 (95% CI 0·84–1·43)	0·41 (95% CI 0·14–1·14)
(O–E)/V	−6·9/35·1	−9·1/55·4	4·8/53·4	−3·2/3·6

Event rate (% per year) and logrank analyses	Years 0–1	Years 2–4	Years 5–9	Years ≥10
5 years of AIT	0·80 (58/7273)	0·80 (79/9889)	0·57 (54/9440)	0·35 (3/864)
Control	0·82 (60/7337)	1·21 (120/9902)	0·80 (75/9361)	1·06 (9/848)
RR	0·98 (95% CI 0·68–1·41)	0·66 (95% CI 0·50–0·87)	0·71 (95% CI 0·50–1·00)	0·36 (95% CI 0·11–1·11)
(O–E)/V	−0·5/29·0	−20·2/48·6	−10·9/31·8	−3·1/3·0

Event rate (% per year) and logrank analyses	Years 0–1	Years 2–4	Years 5–9	Years ≥10
2–3 years of AIT	0·34 (23/6788)	0·70 (66/9445)	0·97 (89/9190)	1·85 (11/593)
Control	0·33 (23/6870)	0·80 (76/9523)	1·01 (95/9374)	1·23 (7/570)
RR	0·93 (95% CI 0·52–1·68)	0·90 (95% CI 0·64–1·26)	0·97 (95% CI 0·72–1·31)	1·58 (95% CI 0·62–4·00)
(O–E)/V	−0·8/11·1	−3·6/33·7	−1·3/42·6	2·0/4·4

Event rate (% per year) and logrank analyses	Years 0–1	Years 2–4	Years 5–9	Years ≥10
5 years of AIT	0·25 (18/7322)	0·58 (59/10 115)	0·45 (44/9792)	0·34 (3/884)
Control	0·11 (8/7392)	0·59 (60/10 215)	0·59 (59/9921)	1·23 (11/892)
RR	2·21 (95% CI 1·02–4·82)	0·99 (95% CI 0·69–1·42)	0·73 (95% CI 0·49–1·09)	0·33 (95% CI 0·11–0·97)
(O–E)/V	5·0/6·3	−0·4/28·8	−7·7/24·5	−3·7/3·4

Figure 2: **Effects on any recurrence, distant recurrence, and breast cancer mortality in the trials of 2–3 further years of AIT versus no further AIT or of 5 further years of AIT versus no further AIT following some previous AIT**

(A) 2–3 further years of AIT versus no further AIT. (B) 5 further years of AIT versus no further AIT. Results are smoothed (broken lines) after year 5 in (A) and year 8 in (B).AIT=aromatase inhibitor treatment. E=expected. O=observed. RR=rate ratio. V=variance.

mortality without distant recurrence from those for overall mortality (log-rank subtraction). This avoids having to determine which deaths after distant recurrence were from breast cancer without inappropriately assuming all were, and use of distant recurrence improves on the original plan to use any recurrence. In-house FORTRAN programmes were used.

Four trials[15–18] randomly assigned women well before the allocated treatments diverged and hence gave the same AIT for some years after randomisation. For these trials a landmark analysis was used that excluded women who had had a recurrence, second primary cancer, or died before the scheduled treatment divergence, or had stopped treatment more than 3 months before that time. Sensitivity analyses (appendix pp 8–11, 32–33) included all women.

In two trials of 5 years of AIT among women who had already received 5 years of tamoxifen, interim results led to widespread switching from placebo to AIT.[9,11,19] One was unblinded in October, 2003, with median follow-up only 2·4 years, with patients on placebo then offered AIT; 1579 (61%) of 2594 patients crossed over before 2005.[9,19] Following these preliminary results, patients on placebo in the other trial were also offered AIT and 344 (44%) of 779 crossed over, most before 2005.[11] In the present analyses, results for both are censored from Jan 1, 2005, which limits the evidence from this dataset. Sensitivity analyses examine the effects of this widespread switching from placebo to active treatment (appendix pp 34–40).

Role of the funding source

Funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

All 12 eligible trials provided data.[9–11,15–24] Their designs and patient characteristics are given in the appendix (pp 4–7). These trials enrolled 25 100 women between Dec 15, 1995, and May 21, 2014, of whom 22 031 are included in the analyses. As prespecified, analyses excluded 364 women with unknown tumour ER status, 656 with ER-negative disease, and 2049 in four trials[15–18] who did not reach the landmark time when treatment schedules diverged (appendix p 3). In these four trials, numbers of excluded women and events differed little by treatment allocation, and these exclusions made no material difference to the overall results (appendix pp 8–11, 32–33).

Median age was 63 years (IQR 56–69), and 10 038 (45·6%) of 22 031 participants had nodal involvement. HER2 status was known for 7676 (34·8%) of 22 031 tumours, with 857 (11·2%) of 7676 being HER2-positive. Trial treatment generally began when, or soon after, previous endocrine therapy ended, although some trials allowed up to 24 intervening months (appendix p 4). Four trials compared AIT versus placebo and eight versus open control. Aromatase inhibitors were letrozole (six trials), anastrozole (four trials), and exemestane (two trials). Meta-analyses of the randomised comparisons between aromatase inhibitors found no evidence of differing effects on outcomes (appendix pp 46–49).

For each trial, figure 1 shows year started, study name, previous endocrine therapy, randomised treatment comparison, log-rank statistics, and recurrence RR (local, distant, or new contralateral invasive disease, with each given separately in the appendix pp 12–14). For the two trials with widespread crossover from placebo to AIT, black and white squares show analyses of events before and after the censoring date. Combining information from all trials (by summing the log-rank statistics for an information-weighted average over all trials and time periods), allocation to AIT versus no further treatment reduced recurrence rates by about a quarter (RR 0·73 [95% CI 0·67–0·80], p<0·0001).

Trials are grouped by previous endocrine therapy: previous tamoxifen for 5 years with no AIT; previous tamoxifen then AIT, each for a mean of fewer than 5 years; or previous AIT for at least 5 years. The treatment effect was significantly greater in women who had previously received only tamoxifen than in women who were already taking AIT (heterogeneity: χ^2_2=10·4, p=0·0055), so subsequent analyses are subdivided by previous treatment (only tamoxifen, or some previous AIT). In women who had previously received only tamoxifen, allocation to AIT almost halved recurrence during years 0–4 (RR 0·56 [95% CI 0·46–0·67], p<0·0001), but the early widespread crossover in the two largest such trials meant there was little follow-up thereafter, meaning longer-term effects could not be assessed (appendix p 18).

In the trials among women who had previously received AIT, follow-up was considerably longer (median 8·1 years, IQR 6·0–10·0). Figure 2 shows the risk of any recurrence, distant recurrence, and breast cancer

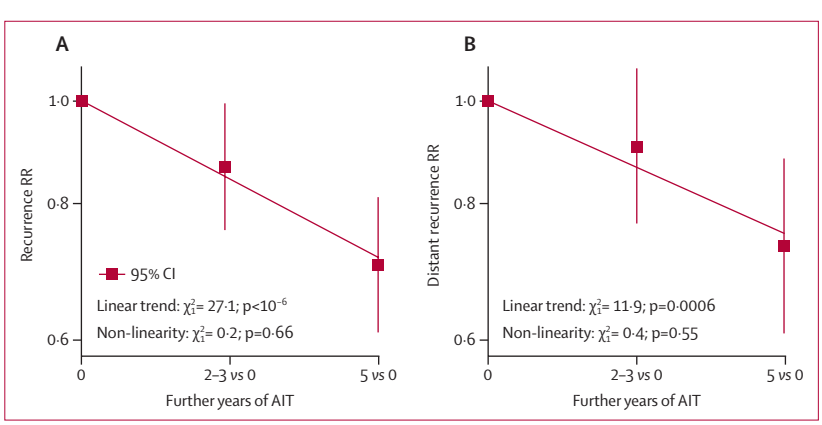


Figure 3: **Effect of further AIT duration on recurrence or distant recurrence RR in the trials of 2–3 further years of AIT versus no further AIT or of 5 further years of AIT versus no further AIT following some previous AIT**
(A) Any recurrence. (B) Distant recurrence. In the placebo-controlled trials of 5 further years of AIT versus no further AIT (n=5743), non-adherence was 39·0% for AIT versus 37·6% for placebo. AIT=aromatase inhibitor treatment. RR=rate ratio.

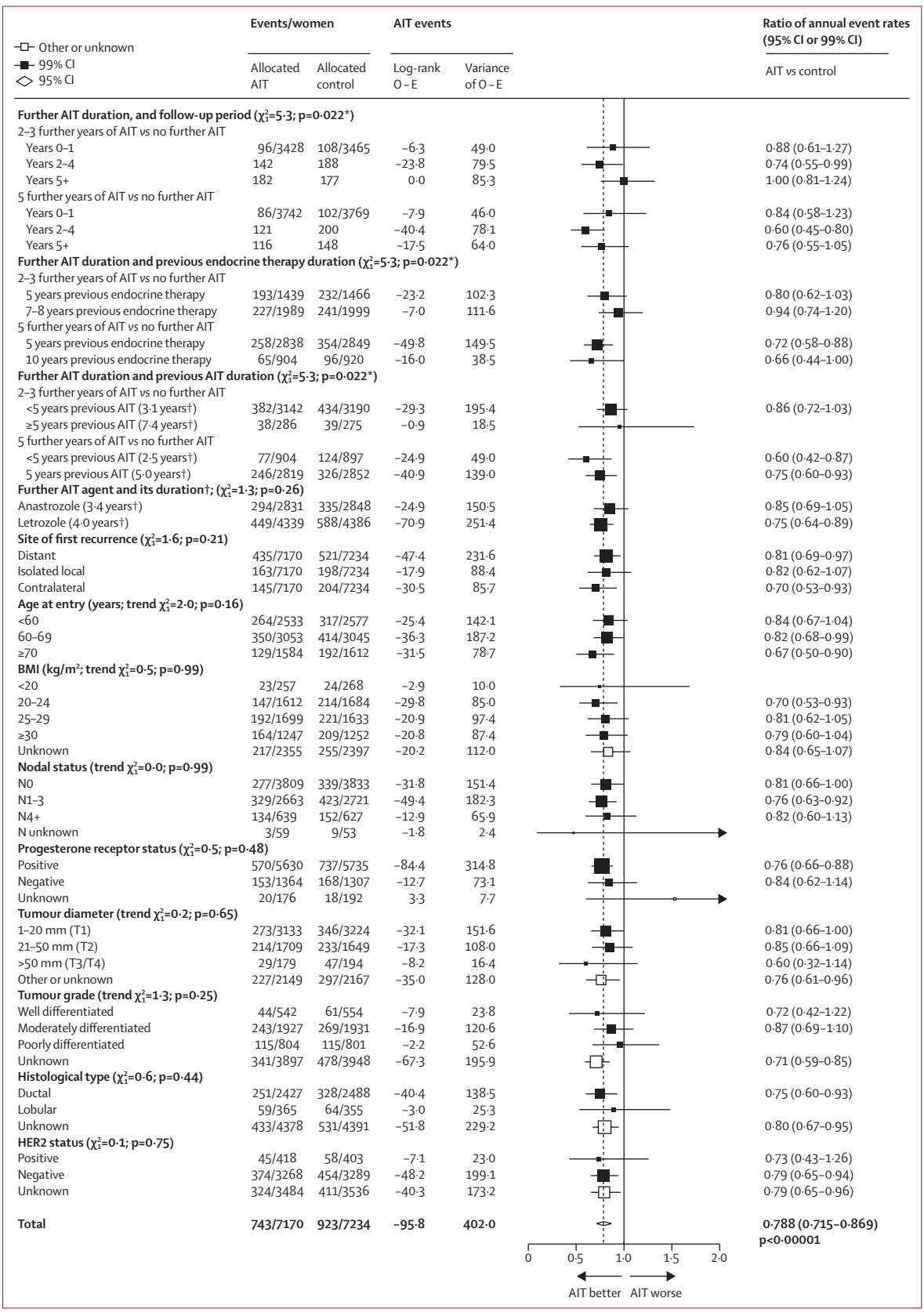


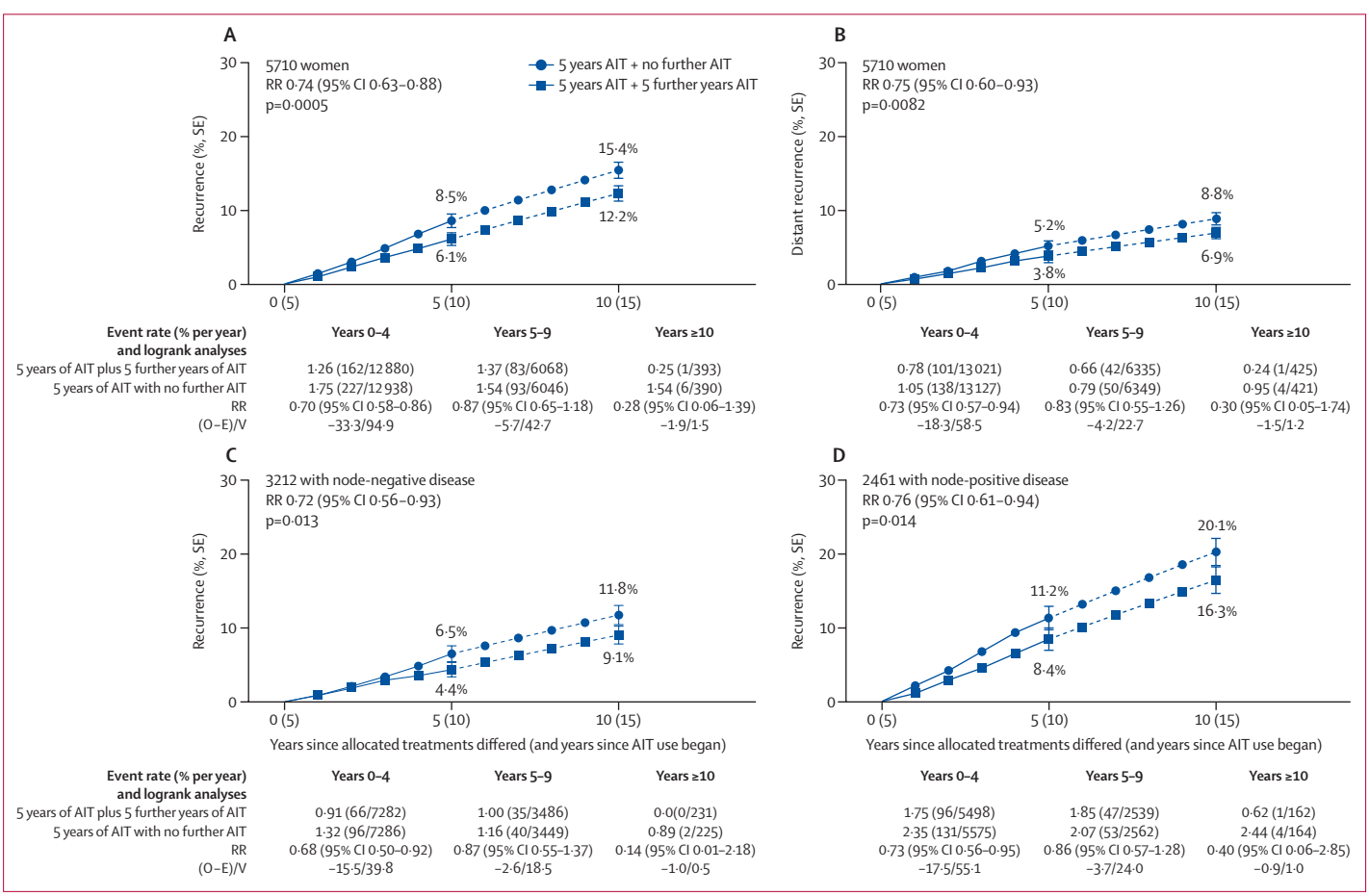
Figure 4: **Subgroup analyses of effects on any recurrence in the trials of 2–3 further years of AIT versus no further AIT or of 5 further years of AIT versus no further AIT following some previous AIT**

AIT=aromatase inhibitor treatment. E=expected. O=observed. RR=rate ratio. *Comparing RRs in trials of 2–3 further years of AIT versus no further AIT against RRs in trials of 5 further years of AIT versus no further AIT, ignoring years 0–1 of follow-up. †Weighted mean duration of AIT. Unknown results do not contribute to heterogeneity or trend tests.

mortality by scheduled duration of further AIT. Treatment effects appeared greater, and were more definite, with 5 further years of AIT than with only 2–3 further years of AIT with a highly significant, and approximately linear, relationship between the duration of further AIT and the effect on recurrence (linear trend for 0, 2·5, and 5 further years: χ^2_1=27·1, p<0·00001; non-linearity: χ^2_1=0·2, p=0·66, figure 3). In the hypothetical absence of deaths from other causes, the risks comparing 5 further years of AIT with control during the decade after treatment divergence were 11·6% versus 15·2% (RR 0·71 [0·61–0·81], p<0·00001, figure 2B) for any recurrence and 6·6% versus 8·6% (RR 0·73 [0·61–0·88], p=0·0010) for distant recurrence, but the reduction in breast cancer mortality was only 4·4% versus 5·0% (RR 0·90 [0·70–1·15], p=0·40). All-cause mortality was not significantly reduced (RR 0·99 [0·86–1·14], p=0·89, appendix p 20).

Figure 4 shows, for trials with some previous AIT, subgroup analyses of recurrence, with p values for interaction (unadjusted for the number of analyses). Similar subgroup analyses for distant recurrence and for breast cancer mortality are available (appendix pp 21–22), but involve smaller numbers. The recurrence reduction appeared chiefly during years 2–4 after treatments diverged and endured for longer with 5 further years of AIT than only 2–3 further years (figure 4). There was no good evidence of differential treatment effect by duration of either previous endocrine treatment or previous AIT (figure 4). There was no significant heterogeneity by type of AIT (letrozole or anastrozole), or site of first recurrence (distant [the commonest], local, or contralateral). There was insufficient data for subgroup analyses by chemotherapy or Ki-67, and no difference in the proportional reductions by age, or BMI, or original tumour size, grade, histological type, PR status, HER2 status, or nodal status.

In current practice, many postmenopausal women are offered initial adjuvant treatment with 5 years of AIT. Figure 5 shows the effect of five further years of AIT, compared to no further adjuvant treatment, in the 5710 women from four trials who had already received



Event rate (% per year) and logrank analyses	Years 0–4	Years 5–9	Years ≥10
5 years of AIT plus 5 further years of AIT	1·26 (162/12 880)	1·37 (83/6068)	0·25 (1/393)
5 years of AIT with no further AIT	1·75 (227/12 938)	1·54 (93/6046)	1·54 (6/390)
RR	0·70 (95% CI 0·58–0·86)	0·87 (95% CI 0·65–1·18)	0·28 (95% CI 0·06–1·39)
(O–E)/V	−33·3/94·9	−5·7/42·7	−1·9/1·5

	Years 0–4	Years 5–9	Years ≥10
	0·78 (101/13 021)	0·66 (42/6335)	0·24 (1/425)
	1·05 (138/13 127)	0·79 (50/6349)	0·95 (4/421)
	0·73 (95% CI 0·57–0·94)	0·83 (95% CI 0·55–1·26)	0·30 (95% CI 0·05–1·74)
	−18·3/58·5	−4·2/22·7	−1·5/1·2

Event rate (% per year) and logrank analyses	Years 0–4	Years 5–9	Years ≥10
5 years of AIT plus 5 further years of AIT	0·91 (66/7282)	1·00 (35/3486)	0·0 (0/231)
5 years of AIT with no further AIT	1·32 (96/7286)	1·16 (40/3449)	0·89 (2/225)
RR	0·68 (95% CI 0·50–0·92)	0·87 (95% CI 0·55–1·37)	0·14 (95% CI 0·01–2·18)
(O–E)/V	−15·5/39·8	−2·6/18·5	−1·0/0·5

	Years 0–4	Years 5–9	Years ≥10
	1·75 (96/5498)	1·85 (47/2539)	0·62 (1/162)
	2·35 (131/5575)	2·07 (53/2562)	2·44 (4/164)
	0·73 (95% CI 0·56–0·95)	0·86 (95% CI 0·57–1·28)	0·40 (95% CI 0·06–2·85)
	−17·5/55·1	−3·7/24·0	−0·9/1·0

Figure 5: **Effects on recurrence and distant recurrence in the trials of 5 further years of AIT versus no further AIT in women who had already completed 5 years of previous AIT (total of 10 years *vs* 5 years of AIT)**

Results are smoothed (broken lines) from year 5 since allocated treatments differed (year 10 after AIT began). (A) Any recurrence. (B) Distant recurrence. (C) Any recurrence after node-negative disease. (D) Any recurrence after node-positive disease. AIT=aromatase inhibitor treatment. E=expected. O=observed. RR=rate ratio. V=variance.

5 years of adjuvant AIT (ie, 10 years *vs* 5 years of AIT in total). With median follow-up of 7·1 years (IQR 5·8–9·9), the risks during the decade after treatment divergence were 12·2% versus 15·4% (RR 0·74 [0·63–0·88], p=0·0005) for any recurrence and 6·9% versus 8·8% (RR 0·75 [0·60–0·93], p=0·0082) for distant recurrence, but only 4·3% versus 4·7% for breast cancer mortality (RR 0·92 [0·68–1·23], p=0·55, appendix p 23). The proportional recurrence reduction was consistent in node-positive and node-negative disease, so the absolute reduction appeared somewhat greater for node-positive disease. For all trials analysed together, the largest absolute benefits were in the few women with four or more involved nodes (appendix p 24).

Including all 12 trials, numbers of non-breast cancer deaths without distant recurrence were similar for women allocated AIT (584 [5·3%] of 10 934) and control (602 [5·4%] of 11 097; appendix pp 16, 25). Mortality without any record of distant recurrence was not related to nodal status or tumour size, suggesting few such deaths involved misclassified breast cancer events (appendix p 26). To help consider 10-year reductions in breast cancer outcomes in the context of life expectancy, estimated 10-year survival in the absence of any breast cancer recurrence, combining all trials, was subdivided by age (appendix p 27). It was 96% for younger than 60 years (mean 54), 90% for ages 60–69 years (mean 64) and 69% for ages 70 years or older (mean 75).

The incidence of endometrial cancer (defined as any uterine cancer except cervix cancer) was low: 37 (0·3%) of 10 934 women allocated AIT versus 52 (0·5%) of 11 097 allocated control (p=0·12, appendix p 31). For women who had received some AIT in their previous endocrine therapy, figure 6 shows non-breast-cancer outcomes after treatment divergence. There was no difference in mortality from cardiovascular disease (68 *vs* 70 deaths, with little data available on non-fatal vascular events) or all non-breast-cancer causes, but there was a definite increase in bone fracture incidence. For women with some previous AIT, 5 further years increased the reported 5-year bone fracture risk from 3·4% to 4·6% (RR 1·35 [1·13–1·61], p=0·0009; appendix pp 28–30). Not all trials reported fractures completely after trial treatment ended, so the absolute incidence, especially after year 5, might be underestimated. Individual patient-level information on other toxicities and on quality of life was not available. Most trials monitored toxicity only during or shortly after the scheduled treatment periods. The toxicities reported in each of the trial publications showed excess vasomotor and musculoskeletal symptoms but no differences in hypercholesterolaemia, hypertension, cardiovascular

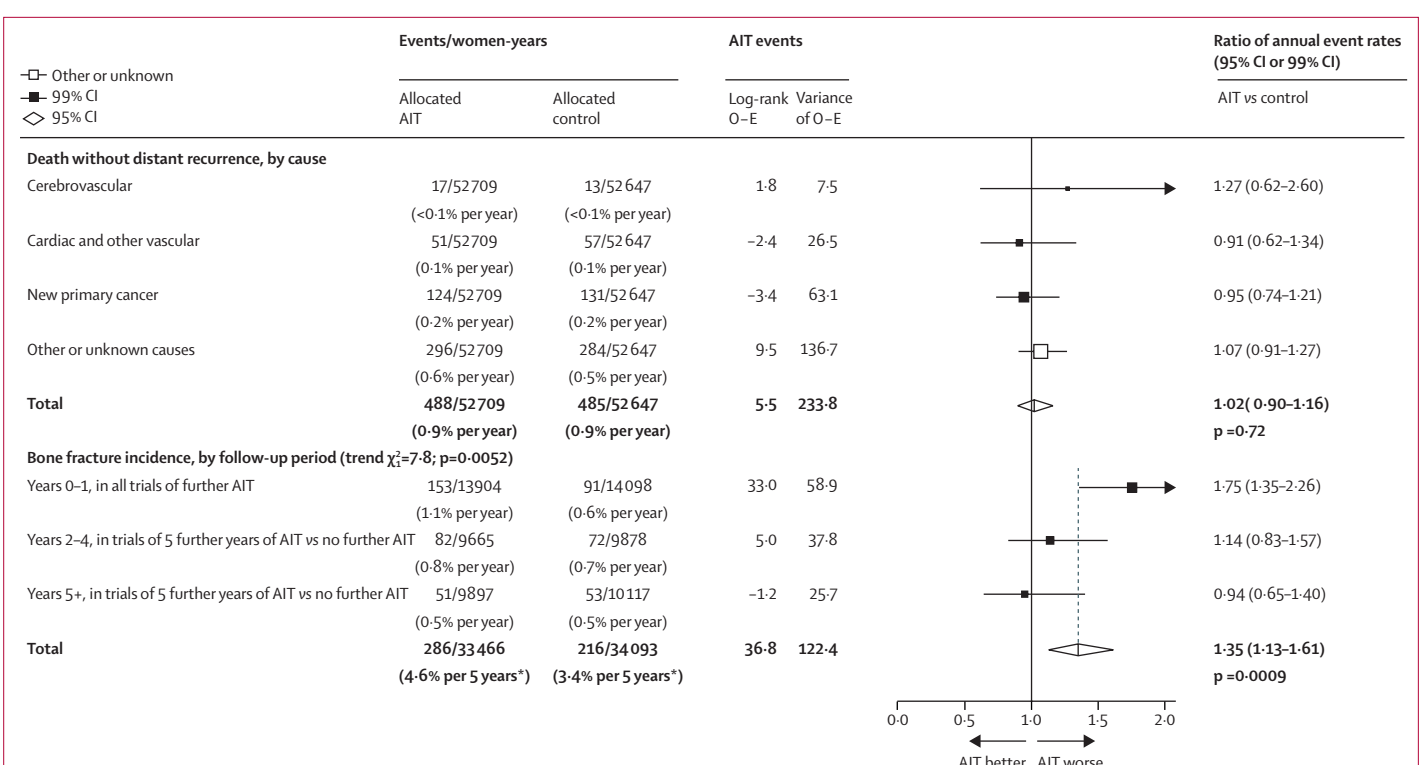


Figure 6: **Effects of AIT allocation on non-breast cancer mortality and on bone fractures in the trials of 2–3 further years of AIT versus no further AIT or of 5 further years of AIT versus no further AIT following some previous AIT**

AIT=aromatase inhibitor treatment. E=expected. O=observed. Trials of 2–3 years of further AIT versus no further AIT generally stopped systematic monitoring for bone fractures at the end of the scheduled treatment period, and these trials are excluded from the analyses of bone fractures during years 2–4 and 5 or later. *From Kaplan–Meier graph of bone fractures (appendix p 29).

events, or thromboembolic events (appendix pp 43–45). In the two placebo-controlled trials of 5 further years of AIT among women already on AIT, 1138 (39·0%) of 2918 versus 1098 (37·6%) of 2923 became non-adherent to their random allocation, including 241 (8·3%) of 2918 discontinuations in the AIT group versus 175 (6·0%) of 2923 discontinuations in the placebo group attributed to adverse events and 897 (30·7%) of 2918 for AIT versus 923 (31·6%) of 2923 for placebo attributed to other reasons, mostly during the first year.[21,22] In the non-placebo-controlled trials discontinuation was likewise substantial among women allocated further AIT (appendix p 42), but those trials had open-label control groups, potentially biasing symptom reporting.

Discussion

For postmenopausal women with ER-positive early breast cancer, previous meta-analyses had shown that 5 years of tamoxifen substantially reduces breast cancer recurrence and mortality throughout the first and into the second decade after diagnosis, and that 5 years of AIT is somewhat more effective.[1,2] This report assesses the effects of using AIT to continue endocrine therapy after year 5, considering analyses by allocated treatment in the light of reported information on adherence.

After 5 years of tamoxifen alone, trials of switching to AIT (*vs* no further endocrine therapy) show the subsequent recurrence rate is immediately halved. This effect is much greater than that of continuing versus stopping tamoxifen[5,6] and provides strong independent confirmation of the directly randomised evidence[2] of greater efficacy of AIT. The effect was so striking that women allocated placebo in the placebo-controlled trials were offered crossover to AIT,[9,11,19] limiting median follow-up to only 3·4 years for this comparison. Hence, it is not known how long these recurrence reductions would persist, how much they owed to the data-dependent stopping of the largest such trial, or what the long-term effects would be on breast cancer mortality.

Among women already receiving AIT, some further years of AIT reduces recurrence rates, and the apparent size of this reduction is supported by the trials of only 2–3 further years appearing to produce only about half the effect of 5 further years (figures 3, 4A). A limitation of these analyses is that, with hindsight, the trials of 5 further years of AIT versus no further AIT were, even in aggregate, under-powered for mortality, while for recurrence those of only 2–3 further years could not reliably determine on their own whether 7 years differs from 5 years, or 10 years differs from 7 years, although it is implausible that all the effect of 5 further years of AIT versus no further AIT derives from the first 2–3 years of treatment.

Nowadays AIT is recommended for all or part of the initial 5 years of endocrine treatment, but guidelines differ on whether, or for whom, to recommend further treatment. The rest of this Discussion focuses on trials of 5 further years of AIT versus no further AIT in women already receiving AIT.

Allocation to 5 further years of AIT reduced the rates of further recurrence, and further distant recurrence, by about a quarter, with no apparent increase in mortality from other causes. There was no evidence that the previous duration of endocrine treatment or AIT affected the benefit of further AIT on recurrence, and combining all 4 trials of 10 years of AIT versus 5 years of AIT (ie, of allocation to 5 further years of AIT *vs* no further AIT in women already prescribed AIT throughout the previous 5 years) also gave a reduction of about a quarter in any recurrence and in distant recurrence. In the placebo-controlled trials of 5 further years of AIT versus no further AIT, 8% of AIT-allocated versus 6% of placebo-allocated women discontinued due to adverse events and 31% of AIT-allocated versus 32% of placebo-allocated women discontinued for other reasons, many within the first year after randomisation. Analysis by allocated treatment therefore underestimates the benefits, and the side-effects, that could have been seen with substantially better adherence. These might involve recurrence reductions of about one-third rather than a quarter, and 5-year excess fracture risks of 2% rather than 1·2%.

The reduction in further recurrence with 5 further years of AIT might not yield a corresponding reduction in breast cancer mortality, but previous meta-analyses[1,2] of the trials of 5 initial years of endocrine treatment versus no endocrine treatment showed that the proportional reduction in 10-year risk was about two-thirds as great for breast cancer mortality as for recurrence. This suggests that the definite reduction in distant recurrence in the present meta-analyses of the trials of 5 further years of AIT versus no further AIT might also eventually correspond to some reduction in breast cancer mortality. Ignoring non-adherence, in the present meta-analysis of 5 further years versus no further AIT the distant recurrence RR is 0·73, a proportional reduction of 27%. Using the estimate from previous meta-analyses to convert reductions in distant recurrence to breast cancer mortality, this would equate to an RR of about 0·82, compatible with the observed breast cancer mortality RR of 0·90 (with 95% CI 0·70–1·15).

The absolute further recurrence reduction from 5 further years of AIT appeared greater for women with node-positive than node-negative disease, but limitations of trial size and follow-up duration mean subgroup analyses are not statistically stable. There was, however, no convincingly significant variation with any recorded patient or tumour characteristics in the proportional effects of further AIT on breast cancer outcomes.

If proportional benefits are similar in most circumstances, absolute benefits will depend on the absolute breast cancer risk, and on life expectancy if cured. Without mortality from breast cancer, however, the large majority of participants younger than 70 years (and two-thirds of older ones) in these trials would still

have been alive 10 years later, so reductions in 10-year distant recurrence risk are relevant despite any competing risks. The eventual benefit from any reduction in breast cancer mortality would, however, be substantially greater for younger than for older women because of their longer life expectancy.

No significant effects were observed on other cancers or on non-breast-cancer mortality. In particular, there was no excess cardiovascular mortality with 5 further years of AIT, but this was based on only 68 versus 70 vascular deaths. Follow-up in these trials was for only a few years after treatment ended, so longer-term effects cannot be excluded. Information on non-fatal vascular events was not sought for the present meta-analyses, but in the published data from these trials and those of AIT for breast cancer prevention[25,26] there was no effect on myocardial infarction, stroke, or thromboembolism (appendix p 43). Also, there was no excess vascular mortality in meta-analyses of 5-year treatment with AIT versus tamoxifen (RR 0·96; 95% CI 0·78–1·19)[2] or of tamoxifen versus control (RR 0·98; 0·77–1·25).[1] These results are consistent with a Danish cohort study of over 30 000 post-menopausal women with early breast cancer that concluded that AIT had no clinically relevant effect on ischaemic cardiotoxicity.[27] However, this contrasts with published data meta-analyses[28–30] that reported an increased risk of cardiovascular events with AIT, perhaps largely due to inclusion of an unpublished safety assessment from the IDEAL study that recorded "palpitations" as cardiac disorders (appendix p 43). Reliable reports of four major trials[31–34] showed no good evidence of hazard. Meta-analyses of individual patient data for non-fatal cardiovascular events would overcome methodological concerns about the published data meta-analyses.

For women already taking AIT, those allocated 5 further years had an absolute 1·2% excess 5-year incidence of reported bone fracture (4·6% *vs* 3·4%), although some trials may have somewhat under-reported fractures. Hence, the excess 5-year incidence of fractures with actual use of 5 further years of AIT might be about 2% rather than 1·2%. There was no evidence that any excess incidence continued after year 5 of further treatment. Monitoring of bone density varied and protection by bisphosphonates was generally permitted. Patient-level information was not available on symptomatic side-effects or quality of life, which are best assessed with placebo control.

In the placebo-controlled trials, as in clinical practice, many women discontinued treatment, but almost as many did so with placebo as with AIT. Strategies to support women taking long-term AIT and manage any symptoms reported (many of which may not actually be due to the AIT, even if they are symptoms that AIT can cause) might substantially improve adherence, and hence breast cancer outcomes. AIT is generally administered at a fixed daily dose, and intermittent treatment might be as effective,[35] but further well-designed randomised trials are required to evaluate this.

This meta-analysis has reliably shown that allocation to five further years of AIT reduces by about one-quarter the distant recurrence rate during that further treatment, with no apparent rebound afterwards or increase in mortality from other causes. The proportional reduction in breast cancer mortality is less certain, due partly to non-adherence to allocated treatment and limited follow-up duration.

Women who have been taking AIT will know their individual experience of symptomatic side-effects, and physicians can assess bone density. Decisions about further AIT should balance absolute benefits and risks, and the absolute benefit from the reduction in distant recurrence depends on prognostic factors for subsequent recurrence, and on the use of other treatments, eg, CDK 4/6 inhibitors, as well as adherence. Outcomes in ER-positive early breast cancer continue to improve for various reasons,[36] reducing the expected absolute benefit from further AIT. Nevertheless, for women who have already had about 5 years of adjuvant AIT, the quantitative finding that 5 further years reduces any remaining risk of distant recurrence by about a quarter can usefully inform current and future decisions.

Contributors

JBr, RB, RG, and RKH designed and carried out the analyses. RB, RG, and RKH accessed and verified the data. JBr, RB, RG, RP, and RKH drafted the report and all other writing committee members contributed to revising it. Interim analyses were presented and discussed at steering committee meetings. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) secretariat (G Beake, R Berry, C Boddington, R Bradley, J Braybrooke, M Clarke, C Davies, L Davies, D Dodwell, F Duane, V Evans, J Gay, L Gettins, J Godwin, R Gray, R K Hills, F Holt, S James, A Kerr, H Liu, Z Liu, E MacKinnon, G Mannu, P McGale, T McHugh, P Morris, M Nakahara, H Pan, R Peto, S Read, E Straiton, C Taylor, and H Taylor) was responsible for maintaining collaboration, identifying trials, and obtaining and checking datasets.

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Data sharing

All datasets provided to the EBCTCG remain the property of the trial groups sending them, to whom data sharing requests should be made. The EBCTCG data sharing policy is available at https://www.ctsu.ox.ac.uk/research/the-early-breast-cancer-trialists-collaborative-group-ebctcg/data-policy-for-the-early-breast-cancer-trialists2019-collaborative-group-ebctcg.

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