Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

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

Summary

Background The optimal ways of using aromatase inhibitors or tamoxifen as endocrine treatment for early breast cancer remains uncertain.

Methods We undertook meta-analyses of individual data on 31 920 postmenopausal women with oestrogen-receptor-positive early breast cancer in the randomised trials of 5 years of aromatase inhibitor versus 5 years of tamoxifen; of 5 years of aromatase inhibitor versus 2–3 years of tamoxifen then aromatase inhibitor to year 5; and of 2–3 years of tamoxifen then aromatase inhibitor to year 5 versus 5 years of tamoxifen. Primary outcomes were any recurrence of breast cancer, breast cancer mortality, death without recurrence, and all-cause mortality. Intention-to-treat log-rank analyses, stratified by age, nodal status, and trial, yielded aromatase inhibitor versus tamoxifen first-event rate ratios (RRs).

Findings In the comparison of 5 years of aromatase inhibitor versus 5 years of tamoxifen, recurrence RRs favoured aromatase inhibitors significantly during years 0–1 (RR 0·64, 95% CI 0·52–0·78) and 2–4 (RR 0·80, 0·68–0·93), and non-significantly thereafter. 10-year breast cancer mortality was lower with aromatase inhibitors than tamoxifen (12·1% *vs* 14·2%; RR 0·85, 0·75–0·96; 2p=0·009). In the comparison of 5 years of aromatase inhibitor versus 2–3 years of tamoxifen then aromatase inhibitor to year 5, recurrence RRs favoured aromatase inhibitors significantly during years 0–1 (RR 0·74, 0·62–0·89) but not while both groups received aromatase inhibitors during years 2–4, or thereafter; overall in these trials, there were fewer recurrences with 5 years of aromatase inhibitors than with tamoxifen then aromatase inhibitors (RR 0·90, 0·81–0·99; 2p=0·045), though the breast cancer mortality reduction was not significant (RR 0·89, 0·78–1·03; 2p=0·11). In the comparison of 2–3 years of tamoxifen then aromatase inhibitor to year 5 versus 5 years of tamoxifen, recurrence RRs favoured aromatase inhibitors significantly during years 2–4 (RR 0·56, 0·46–0·67) but not subsequently, and 10-year breast cancer mortality was lower with switching to aromatase inhibitors than with remaining on tamoxifen (8·7% *vs* 10·1%; 2p=0·015). Aggregating all three types of comparison, recurrence RRs favoured aromatase inhibitors during periods when treatments differed (RR 0·70, 0·64–0·77), but not significantly thereafter (RR 0·93, 0·86–1·01; 2p=0·08). Breast cancer mortality was reduced both while treatments differed (RR 0·79, 0·67–0·92), and subsequently (RR 0·89, 0·81–0·99), and for all periods combined (RR 0·86, 0·80–0·94; 2p=0·0005). All-cause mortality was also reduced (RR 0·88, 0·82–0·94; 2p=0·0003). RRs differed little by age, body-mass index, stage, grade, progesterone receptor status, or HER2 status. There were fewer endometrial cancers with aromatase inhibitors than tamoxifen (10-year incidence 0·4% *vs* 1·2%; RR 0·33, 0·21–0·51) but more bone fractures (5-year risk 8·2% *vs* 5·5%; RR 1·42, 1·28–1·57); non-breast-cancer mortality was similar.

Interpretation Aromatase inhibitors reduce recurrence rates by about 30% (proportionately) compared with tamoxifen while treatments differ, but not thereafter. 5 years of an aromatase inhibitor reduces 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen, hence by about 40% (proportionately) compared with no endocrine treatment.

Funding Cancer Research UK, Medical Research Council.

Lancet 2015; 386: 1341–52

Published Online
July 24, 2015
http://dx.doi.org/10.1016/S0140-6736(15)61074-1

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Introduction

Treatment for 5 years with the selective oestrogen receptor (ER) modulator tamoxifen reduces recurrence rates in ER-positive early breast cancer by about half during treatment and about one-third in the subsequent 5 years, and reduces breast cancer mortality by almost one-third throughout the first 15 years.[1] Further reductions in breast cancer mortality during years 10–14 are achieved by extending tamoxifen treatment to 10 years.[2,3] In postmenopausal women only, aromatase inhibitors can greatly reduce oestrogen concentrations, hence avoiding stimulation of ER-positive breast cancer cells. Aromatase inhibitors, given either for 5 years or for 2–3 years after 2–3 years of tamoxifen, produce greater reductions in recurrence than 5 years of tamoxifen alone,[4] but the effect on breast cancer mortality, and the optimal way to schedule aromatase inhibitors and tamoxifen in the treatment of early breast cancer, remain uncertain.

American Society of Clinical Oncology (ASCO) clinical practice guidelines reflect this, recommending that postmenopausal women with early ER-positive breast cancer be offered either tamoxifen for 10 years, an aromatase inhibitor for 5 years, tamoxifen initially for 5 years followed by an aromatase inhibitor for up to a further 5 years, or tamoxifen for 2–3 years followed by an aromatase inhibitor for up to a further 5 years.[5] To help clarify the relative benefits of aromatase inhibitors and tamoxifen and the effect of different scheduling during 5 years of endocrine therapy, we undertook collaborative meta-analyses of individual patient data from the trials of aromatase inhibitors versus tamoxifen.

Methods

Identification of studies and collection of data

Trial identification, data checking, analysis, and involvement of trialists are as described in previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reports.[1,6,7] Eligible trials began by 2005 and randomised postmenopausal women with ER-positive early breast cancer between 5 years of an aromatase inhibitor versus 5 years of tamoxifen (comparison A); 5 years of aromatase inhibitor versus 2–3 years of tamoxifen, then aromatase inhibitor to year 5 (comparison B); 2–3 years of tamoxifen, then aromatase inhibitor to year 5 versus 5 years of tamoxifen (comparison C); 5 years of aromatase inhibitor versus 2 years of aromatase inhibitor, then tamoxifen to year 5 (comparison D); or 2 years of aromatase inhibitor, then tamoxifen to year 5 versus 5 years of tamoxifen (comparison E). Separate analyses are provided for each of these comparisons (A–E), then results from some of them are combined.

For the **CTSU policy on data sharing** see http://www.ctsu.ox.ac.uk/research/data-access-policies/data-access-and-sharing-policy/view

See Online for appendix

Information was sought during 2012–14 for each individual patient on randomisation date, allocated treatment, age, menopausal status, body-mass index (BMI), tumour diameter, grade, spread to locoregional lymph nodes, ER, progesterone receptor (PR), and HER2 receptor status, and dates of any locoregional, contralateral, or distant breast cancer recurrence, other second primary cancer, bone fractures, death, and cause of death.

Outcomes

The primary outcomes were any recurrence of breast cancer (distant, locoregional, or new primary in the contralateral breast); breast cancer mortality; death without recurrence; and all-cause mortality. Secondary outcomes were incidence and site of second primary cancers, and bone fracture. Prespecified primary subgroup investigations were of site of recurrence, age, nodal status, PR status, histological grade, and follow-up period.

Statistical analyses

Statistical methods (stratified log-rank statistics, Kaplan-Meier graphs) are described elsewhere.[1,6,7] Time-to-event analyses were stratified by age, nodal status, and trial. Within each stratum, they compared all those allocated aromatase inhibitor versus all those allocated tamoxifen, regardless of treatment compliance (yielding intention-to-treat analyses). Log-rank statistics were used to assess the effects (aromatase inhibitor *vs* tamoxifen) on various outcomes, and, for each, to estimate first-event-rate ratios (RRs) and their CIs. If a log-rank statistic (o−e) has variance v, then, defining $z=(o-e)/\sqrt{v}$ and $b=(o-e)/v$, b has variance 1/v and the event RR (newer treatment *vs* control) is estimated as exp(b) with SE=(RR−1)/z. CIs for RR are derived from those for b (by normal approximations). 2p indicates two-sided significance. The breast cancer mortality rate in each year is the overall mortality rate among all women minus that among women of similar age without recurrence. Breast cancer mortality RRs are estimated from the corresponding log-rank analyses of mortality with recurrence (obtained by subtracting log-rank analyses of mortality without recurrence [ie, censored at recurrence] from those of overall mortality). Analyses used EBCTCG Fortran programs. The policy on data sharing from this study is available online.

Role of the funding source

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

Results

Individual patient datasets were provided for nine trials,[8–16] including 35 129 (98%) of the 35 718 women randomised between aromatase inhibitor and tamoxifen as part of about 5 years of adjuvant endocrine treatment (appendix). This report is restricted to the 31 920 (91%) with ER-positive tumours of these 35 129 patients. All were randomised evenly between aromatase inhibitor and tamoxifen, though one trial (BIG 1-98[8]) included a four-way randomisation that contributes data to all five comparisons (A–E); the aggregated analyses avoid double counting its results. When reports emerged that patients on tamoxifen had their recurrence risk reduced by switching after 2–3 years to an aromatase inhibitor, crossover to an aromatase inhibitor from the tamoxifen-only group was systematically offered in two trials (BIG 1-98,[8] 25% [619/2459] crossover; ABCSG-8,[9] 18% [341/1949] crossover). In eight trials, compliance was similar in both groups, but in TEAM[10] 56% (2698/4814) of those allocated tamoxifen then aromatase inhibitor versus 30% (1438/4852) of those allocated only aromatase inhibitor discontinued treatment prematurely.

In comparison A (5 years of aromatase inhibitor *vs* 5 years of tamoxifen: two trials, n=9885), recurrence and mortality were both significantly reduced (figure 1). The numbers with recurrence were 827 in the aromatase inhibitor group versus 964 in the tamoxifen group ($p<0·00001$), with separately significant reductions during years 0–1 after surgery (RR 0·64, 95% CI

0·52–0·78) and during years 2–4 (RR 0·80, 0·68–0·93), but no significant further effect after the scheduled treatment period, and little follow-up beyond year 10. The 10-year recurrence risk was 19·1% in the aromatase inhibitor group versus 22·7% in the tamoxifen group (difference 3·6%, 95% CI 1·7–5·4). Distant recurrence (RR 0·86, 95% CI 0·77–0·96; 2p=0·007), local recurrence (RR 0·74, 0·58–0·95; 2p=0·020), and contralateral recurrence (RR 0·62, 0·48–0·80; 2p=0·0003) were all reduced (appendix). Breast cancer mortality was also reduced (RR 0·85, 95% CI 0·75–0·96; 2p=0·009), as was all-cause mortality (936 *vs* 1000 deaths; RR 0·89, 0·81–0·97; 2p=0·010), even though half the deaths were from non-breast cancer causes that are little affected by treatment.

In comparison B (5 years of aromatase inhibitor *vs* 2–3 years of tamoxifen then aromatase inhibitor to year 5: three trials, n=12 779), recurrence was significantly reduced only during years 0–1 (RR 0·74, 95% CI 0·62–0·89; 2p=0·002), ie, when the treatments differed, and was similar during years 2–4 (RR 0·99, 0·85–1·15), when both groups were receiving an aromatase inhibitor (figure 2). There was no significant further effect after year 5, but little follow-up beyond year 7. Perhaps because the period during which the treatments differed lasted only half as long as in comparison A, the absolute reductions in recurrence and mortality appeared smaller. The total numbers with recurrence were 705 in the aromatase inhibitor group versus 765 in the tamoxifen group (2p=0·045). Although breast cancer mortality appeared somewhat reduced (RR 0·89, 95% CI 0·78–1·03; 2p=0·11), this was not significant, and nor were the effects on other mortality or all-cause mortality.

In comparison C (2–3 years of tamoxifen then aromatase inhibitor to year 5 *vs* 5 years of tamoxifen: six trials, n=11798), recurrence and mortality were both significantly reduced (figure 3). Four trials did not randomise until after 2 years of tamoxifen, but two randomised at year 0; for comparability with the other four, only patients who completed 2 years of tamoxifen without recurrence or a second primary are included, but sensitivity analyses (appendix) show this exclusion made little difference. Starting from when treatments diverged, the numbers with recurrence were 753 in the aromatase inhibitor group versus 863 in the tamoxifen group (2p=0·0001). Allocation to an aromatase inhibitor reduced the recurrence rate during years 2–4 (RR 0·56, 95% CI 0·46–0·67; p<0·0001), with no significant further effect on recurrence after the treatment period, and little follow-up beyond year 10. The 10-year recurrence risk was 17·0% in the aromatase inhibitor group versus 19·0% in the tamoxifen group (difference 2·0, 95% CI 0·2–3·8). Distant recurrence (RR 0·86, 95% CI 0·77–0·97; 2p=0·02), and contralateral recurrence (RR 0·67, 0·51–0·87; 2p=0·002) were both reduced (appendix). Breast cancer mortality was also reduced (RR 0·84, 95% CI 0·72–0·96; 2p=0·015), as was all-cause mortality (639 *vs* 764 deaths; RR 0·82, 0·73–0·91; 2p=0·0002), helped by what might have been a chance reduction in non-breast cancer mortality.

The recurrence results already described for comparisons A–C are summarised in the appendix, using black squares for periods when the treatments differed (aromatase inhibitor in one group *vs* tamoxifen in the other) and open squares for periods when they did not. It also gives the comparisons D and E, which both derive from BIG 1-98.[8] Comparison D was restricted to the 2558 women who were recurrence free and still on treatment after 2 years of aromatase inhibitor. Although they suggest no apparent gain from continuing to take an aromatase inhibitor rather than switching to tamoxifen after 2 years, the CIs were wide. Comparison E included 3060 women; the proportional recurrence reduction during years 0–1 (when the treatments differed) was similar to that in earlier comparisons, and the apparent fluctuations in the recurrence RR during the period when the treatments no longer differed could well be chance.

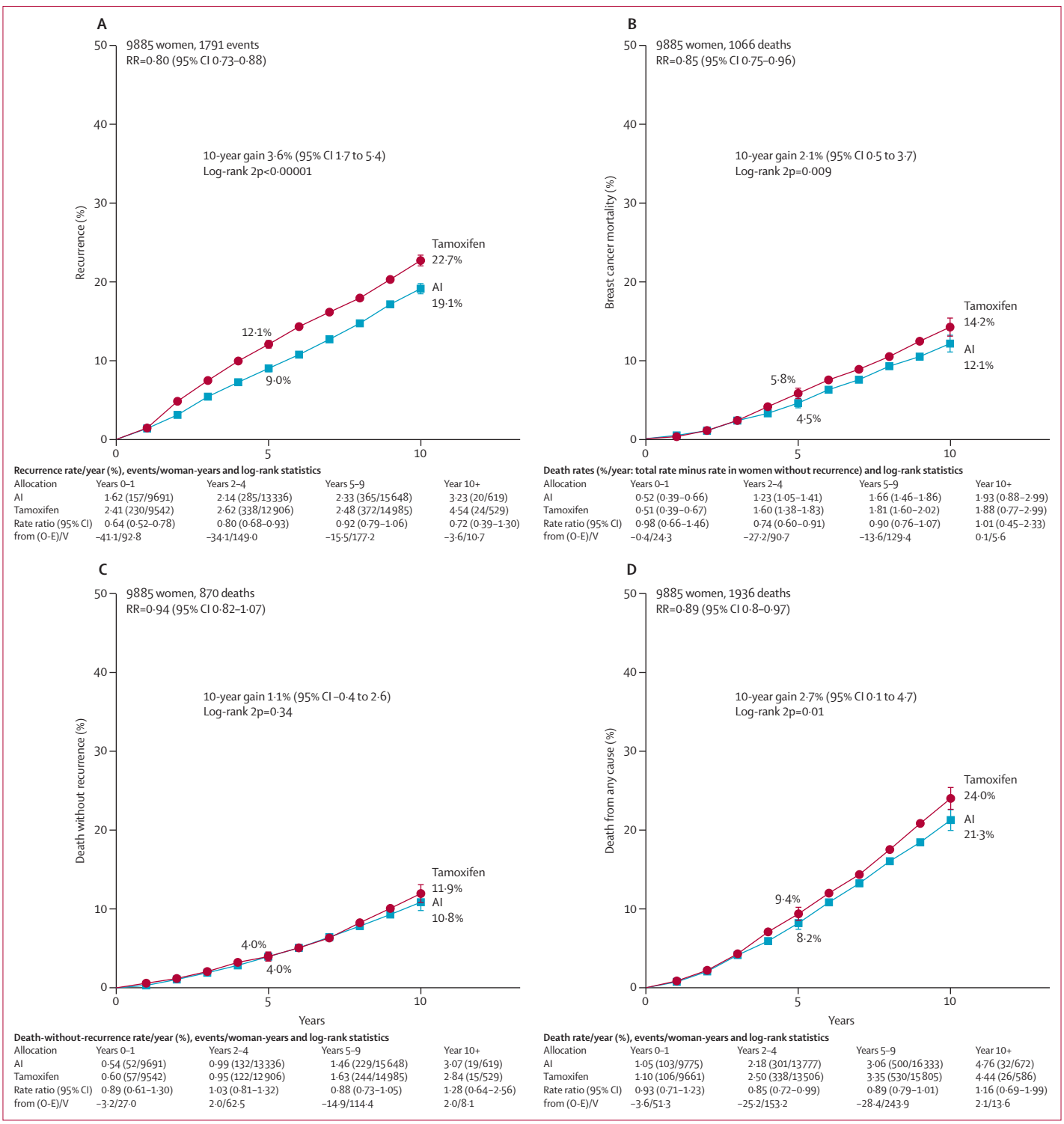
In each of comparisons A–C there was significant benefit only when treatments differed and not when they were the same in both groups. This pattern is even clearer when results from all five comparisons are aggregated by time period (figure 4). Recurrence RRs favoured aromatase inhibitors during periods when treatments differed (RR 0·70, 95% CI 0·64–0·77), but not significantly thereafter (RR 0·93, 0·86–1·01; 2p=0·08). The recurrence rate was about 30% lower with an aromatase inhibitor than with tamoxifen in years 0–1 (RR 0·70, 95% CI 0·61–0·80; 2p<0·0001), and in years 2–4 (RR 0·71, 0·62–0·80; 2p<0·0001). Combining trials where treatments differed only during years 0–1 and not during years 2–4, there was no reduction in recurrence during years 2–4 (RR 1·03, 95% CI 0·87–1·22). There was little further effect during years 5–9 when no further treatment was scheduled (RR 0·92, 95% CI 0·83–1·01), and little follow-up beyond year 10.

Breast cancer mortality was reduced both while treatments differed (RR 0·79, 95% CI 0·67–0·92), and subsequently (RR 0·89, 0·81–0·99), and for all periods combined (RR 0·86, 0·80–0·94; p=0·0005; appendix). All-cause mortality was likewise reduced (RR 0·90, 95% CI 0·84–0·95; 2p=0·0005).

To enhance statistical power, the main subgroup analyses of recurrence are restricted to the periods when aromatase inhibitor was directly compared with tamoxifen (figure 5). The first such analyses compare the six components from previous figures that contribute to this: the recurrence RRs during years 0–1 were, as expected, similar in comparisons A, B, and E, but the recurrence RRs during years 2–4 appeared somewhat more extreme after 2–3 years of previous tamoxifen (RR 0·56, 95% CI 0·46–0·67) than after 2–3 years of aromatase inhibitor versus tamoxifen (RR 0·83, 0·69–1·00), or after 2 years of aromatase inhibitor (RR 1·08, 0·70–1·68).

Figure 5 subdivides the aggregated result from the periods when treatments differed by aromatase

inhibitor drug, site of first recurrence, entry age, BMI, and tumour characteristics: PR status, nodal status, tumour diameter, tumour grade, and HER2 status (available for only one-third of patients). The recurrence RRs were similar with different aromatase inhibitors (each p<0·0001), with local recurrence, contralateral



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13336)	2·33 (365/15648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12906)	2·48 (372/14985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	–41·1/92·8	–34·1/149·0	–15·5/177·2	–3·6/10·7

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	0·52 (0·39–0·66)	1·23 (1·05–1·41)	1·66 (1·46–1·86)	1·93 (0·88–2·99)
Tamoxifen	0·51 (0·39–0·67)	1·60 (1·38–1·83)	1·81 (1·60–2·02)	1·88 (0·77–2·99)
Rate ratio (95% CI)	0·98 (0·66–1·46)	0·74 (0·60–0·91)	0·90 (0·76–1·07)	1·01 (0·45–2·33)
from (O-E)/V	–0·4/24·3	–27·2/90·7	–13·6/129·4	0·1/5·6

Death-without-recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	0·54 (52/9691)	0·99 (132/13336)	1·46 (229/15648)	3·07 (19/619)
Tamoxifen	0·60 (57/9542)	0·95 (122/12906)	1·63 (244/14985)	2·84 (15/529)
Rate ratio (95% CI)	0·89 (0·61–1·30)	1·03 (0·81–1·32)	0·88 (0·73–1·05)	1·28 (0·64–2·56)
from (O-E)/V	–3·2/27·0	2·0/62·5	–14·9/114·4	2·0/8·1

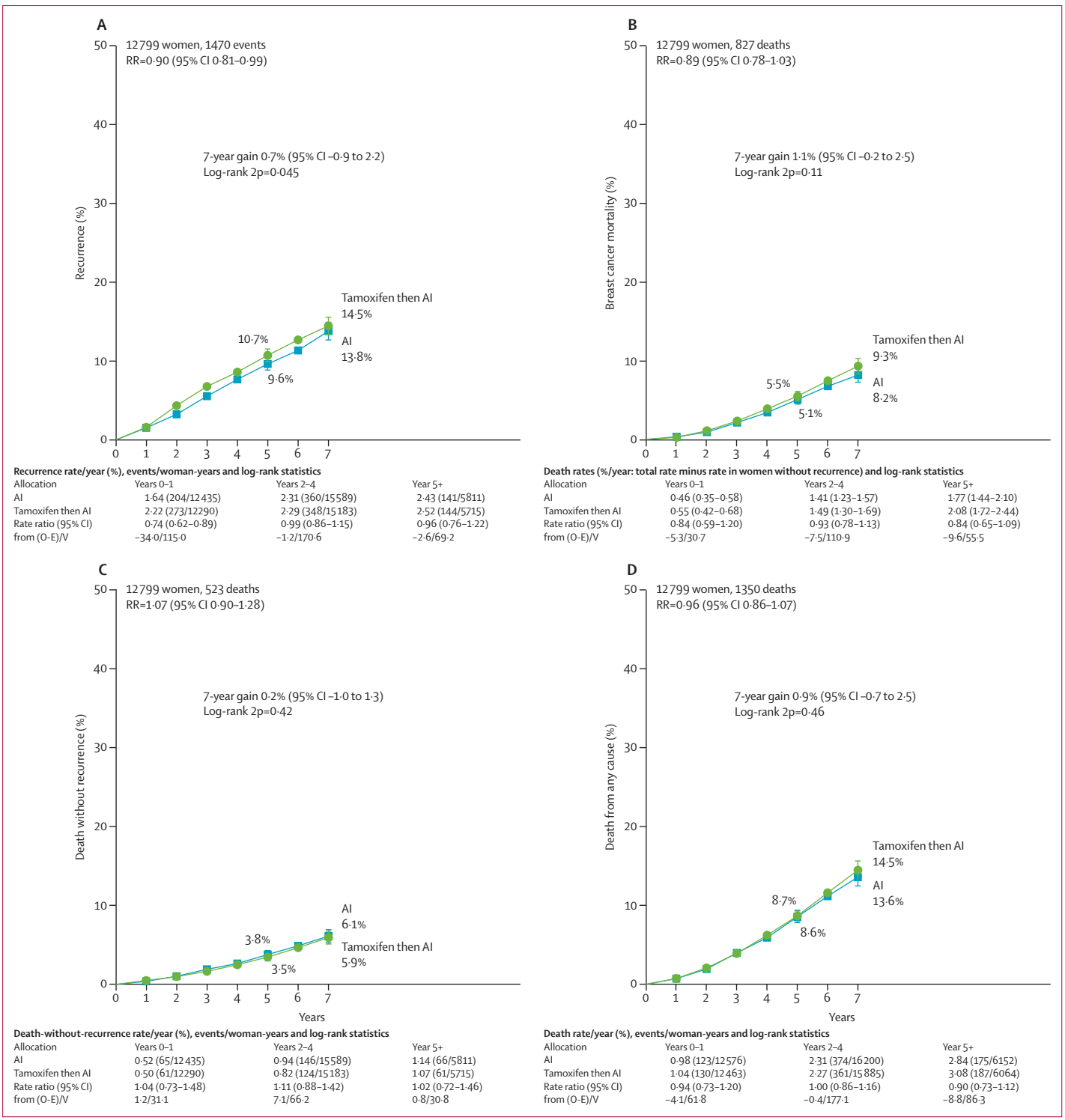
Death rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·05 (103/9775)	2·18 (301/13777)	3·06 (500/16333)	4·76 (32/672)
Tamoxifen	1·10 (106/9661)	2·50 (338/13506)	3·35 (530/15805)	4·44 (26/586)
Rate ratio (95% CI)	0·93 (0·71–1·23)	0·85 (0·72–0·99)	0·89 (0·79–1·01)	1·16 (0·69–1·99)
from (O-E)/V	–3·6/51·3	–25·2/153·2	–28·4/243·9	2·1/13·6

Figure 1: **5 years of aromatase inhibitor versus 5 years of tamoxifen**

(A) Recurrence, (B) breast cancer mortality, (C) death without recurrence, and (D) death from any cause. RR=rate ratio (with 95% CI). AI=aromatase inhibitor. O–E=observed minus expected. V=variance of O–E.

breast cancer, and distant recurrence all substantially reduced by aromatase inhibitor compared with tamoxifen. In the aggregated data, the RRs while treatments differed appeared similar in every subgroup, suggesting that age, BMI, and tumour characteristics cannot usefully predict the RR.



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12 435)	2·31 (360/15 589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12 290)	2·29 (348/15 183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	−34·0/115·0	−1·2/170·6	−2·6/69·2

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	0·46 (0·35–0·58)	1·41 (1·23–1·57)	1·77 (1·44–2·10)
Tamoxifen then AI	0·55 (0·42–0·68)	1·49 (1·30–1·69)	2·08 (1·72–2·44)
Rate ratio (95% CI)	0·84 (0·59–1·20)	0·93 (0·78–1·13)	0·84 (0·65–1·09)
from (O-E)/V	−5·3/30·7	−7·5/110·9	−9·6/55·5

Death-without-recurrence rate/year (%), events/woman-years and log-rank statistics

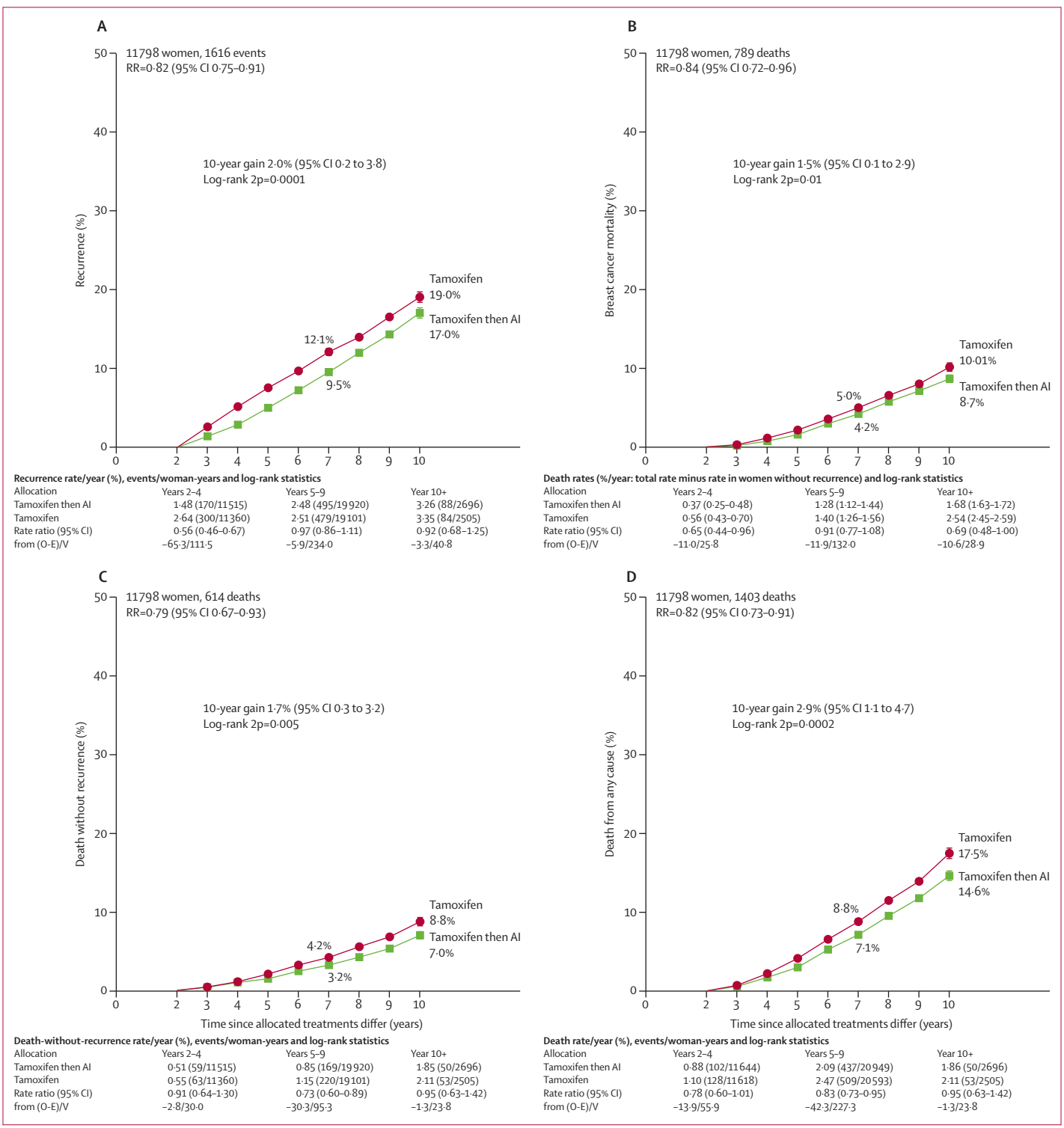
Allocation	Years 0–1	Years 2–4	Year 5+
AI	0·52 (65/12 435)	0·94 (146/15 589)	1·14 (66/5811)
Tamoxifen then AI	0·50 (61/12 290)	0·82 (124/15 183)	1·07 (61/5715)
Rate ratio (95% CI)	1·04 (0·73–1·48)	1·11 (0·88–1·42)	1·02 (0·72–1·46)
from (O-E)/V	1·2/31·1	7·1/66·2	0·8/30·8

Death rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Year 5+
AI	0·98 (123/12 576)	2·31 (374/16 200)	2·84 (175/6152)
Tamoxifen then AI	1·04 (130/12 463)	2·27 (361/15 885)	3·08 (187/6064)
Rate ratio (95% CI)	0·94 (0·73–1·20)	1·00 (0·86–1·16)	0·90 (0·73–1·12)
from (O-E)/V	−4·1/61·8	−0·4/177·1	−8·8/86·3

Figure 2: **5 years of aromatase inhibitor versus tamoxifen to years 2–3 then aromatase inhibitor to year 5**
(A) Recurrence, (B) breast cancer mortality, (C) death without recurrence, and (D) death from any cause. RR=rate ratio. AI=aromatase inhibitor. O–E=observed minus expected. V=variance of O–E.

Tumour characteristics were, however, importantly predictive of the absolute risk of recurrence, and hence of the absolute effect on breast cancer outcomes of giving an aromatase inhibitor rather than tamoxifen (appendix). For example, in the aggregate of the trials that contribute to the black squares in figure 4, the



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	1·48 (170/11515)	2·48 (495/19920)	3·26 (88/2696)
Tamoxifen	2·64 (300/11360)	2·51 (479/19101)	3·35 (84/2505)
Rate ratio (95% CI)	0·56 (0·46–0·67)	0·97 (0·86–1·11)	0·92 (0·68–1·25)
from (O-E)/V	−65·3/111·5	−5·9/234·0	−3·3/40·8

Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	0·37 (0·25–0·48)	1·28 (1·12–1·44)	1·68 (1·63–1·72)
Tamoxifen	0·56 (0·43–0·70)	1·40 (1·26–1·56)	2·54 (2·45–2·59)
Rate ratio (95% CI)	0·65 (0·44–0·96)	0·91 (0·77–1·08)	0·69 (0·48–1·00)
from (O-E)/V	−11·0/25·8	−11·9/132·0	−10·6/28·9

Death-without-recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	0·51 (59/11515)	0·85 (169/19920)	1·85 (50/2696)
Tamoxifen	0·55 (63/11360)	1·15 (220/19101)	2·11 (53/2505)
Rate ratio (95% CI)	0·91 (0·64–1·30)	0·73 (0·60–0·89)	0·95 (0·63–1·42)
from (O-E)/V	−2·8/30·0	−30·3/95·3	−1·3/23·8

Death rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	0·88 (102/11644)	2·09 (437/20949)	1·86 (50/2696)
Tamoxifen	1·10 (128/11618)	2·47 (509/20593)	2·11 (53/2505)
Rate ratio (95% CI)	0·78 (0·60–1·01)	0·83 (0·73–0·95)	0·95 (0·63–1·42)
from (O-E)/V	−13·9/55·9	−42·3/227·3	−1·3/23·8

Figure 3: **Tamoxifen to years 2–3 then aromatase inhibitor to year 5 versus 5 years of tamoxifen: events in women alive and free of recurrence when treatments diverged**
(A) Recurrence, (B) breast cancer mortality, (C) death without recurrence, and (D) death from any cause. RR=rate ratio. AI=aromatase inhibitor. O–E=observed minus expected. V=variance of O–E.

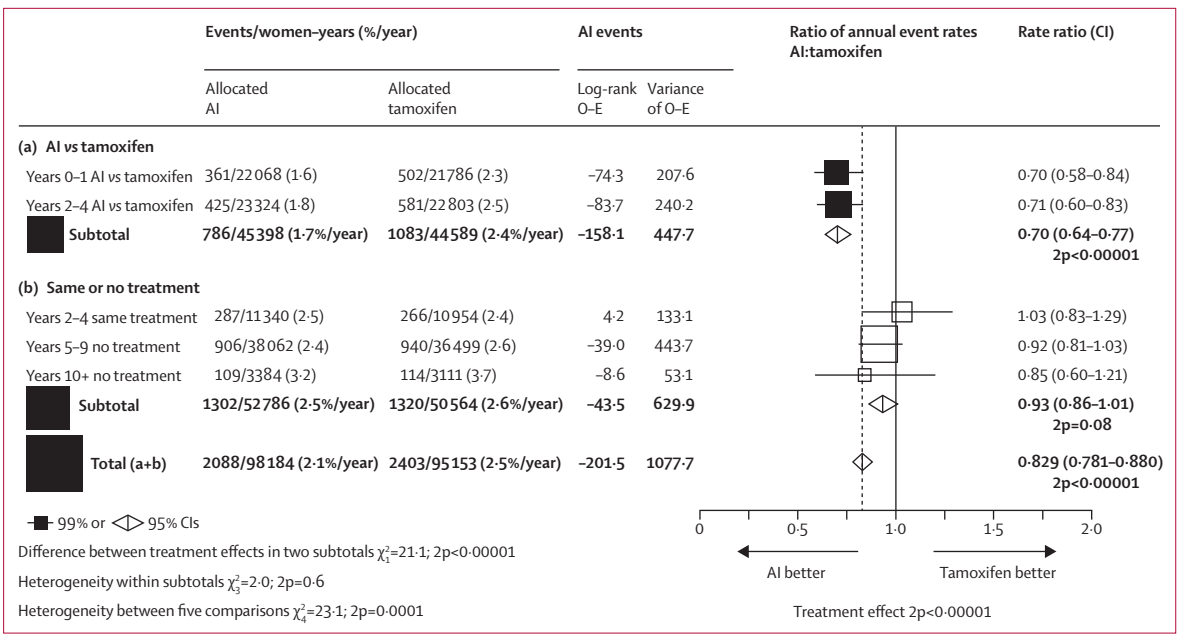


Figure 4: **Recurrence reductions by time since surgery, combining data from different comparisons of aromatase inhibitor (AI) versus tamoxifen treatment as part of 5 years of endocrine therapy**

Black squares show periods when the protocol specified that one group should receive an aromatase inhibitor and the other should receive tamoxifen; open squares show periods when the treatments should have been the same in both groups. *Aggregated totals are adjusted to avoid double counting of events in the four-way randomisation in BIG 1-98. AI=aromatase inhibitor. O–E=observed minus expected.

overall Kaplan-Meier estimate of the 5-year recurrence risk was reduced by 2·5% (7·3% *vs* 9·8%, appendix). But, in this same data set, the 5-year recurrence risks for women with N0, N1–3, and N4+ disease were reduced by 1·2%, 3·7%, and 6·4%, respectively.

Similar sets of subgroup analyses for each separate category of comparisons A–E are in the appendix, but with so many subgroup analyses the apparent findings should be interpreted cautiously, as striking false-positive and false-negative results can easily arise just by chance. For example, the hypothesis from ATAC[15] of a more extreme recurrence RR in ER-positive PR-negative than in ER-positive PR-positive disease is not supported by evidence from other trials (figure 5, appendix). Likewise, the hypothesis from comparison C of equivalent efficacy of aromatase inhibitors and tamoxifen in node-negative disease is not supported by evidence from the other comparisons. Such patterns might be due mainly to chance.

Results for cause-specific mortality, second cancer incidence, and bone fracture before any breast cancer recurrence are in the appendix. There was a significant reduction in mortality without recurrence in comparison C (tamoxifen then aromatase inhibitor *vs* tamoxifen alone) that was not explained by any particular cause and is unlikely to be due to misclassified breast cancer deaths (partly because the non-breast-cancer mortality rates were sharply age-related whereas breast cancer mortality rates were similar in all age groups).

There were fewer uterine cancers and more bone fractures with aromatase inhibitors than with tamoxifen. Aggregating the five comparisons, the 10-year incidence of endometrial cancer (defined as any uterine cancer except cervix cancer) was 0·4% in the aromatase inhibitor group versus 1·2% in the tamoxifen group (absolute difference 0·8%, 95% CI 0·6–1·0; p<0·0001), including five versus nine deaths. The proportional decrease in endometrial cancer incidence with aromatase inhibitors (RR 0·33, 0·21–0·51) was approximately independent of age and persisted for some years after treatment ended. As endometrial cancer increases with age, the absolute excess with tamoxifen was 0·7% (95% CI 0·5–0·9) at ages 55–69 and 1·4% (95% CI 0·5–2·4) at older ages (appendix). There was no significant effect on any other type of cancer (except for contralateral breast cancer).

The incidence of bone fractures was increased among aromatase-inhibitor-allocated patients during years 0–4 (RR 1·42, 95% CI 1·28–1·57; p<0·0001), and remained significantly higher through years 5–9 (RR 1·29, 1·09–1·53; 2p=0·003) despite fractures being monitored less reliably after the 5-year treatment period. The 5-year fracture risk was 8·2% in the aromatase inhibitor group versus 5·5% in the tamoxifen group (absolute excess 2·7%, 95% CI 1·7–3·7). Again, the proportional increase appeared approximately independent of age and the absolute incidence increased with age. Hence, among women of age younger than 55, 55–69, and older than 70 years at randomisation, the absolute excess risks (aromatase inhibitor *vs* tamoxifen) of having a fracture

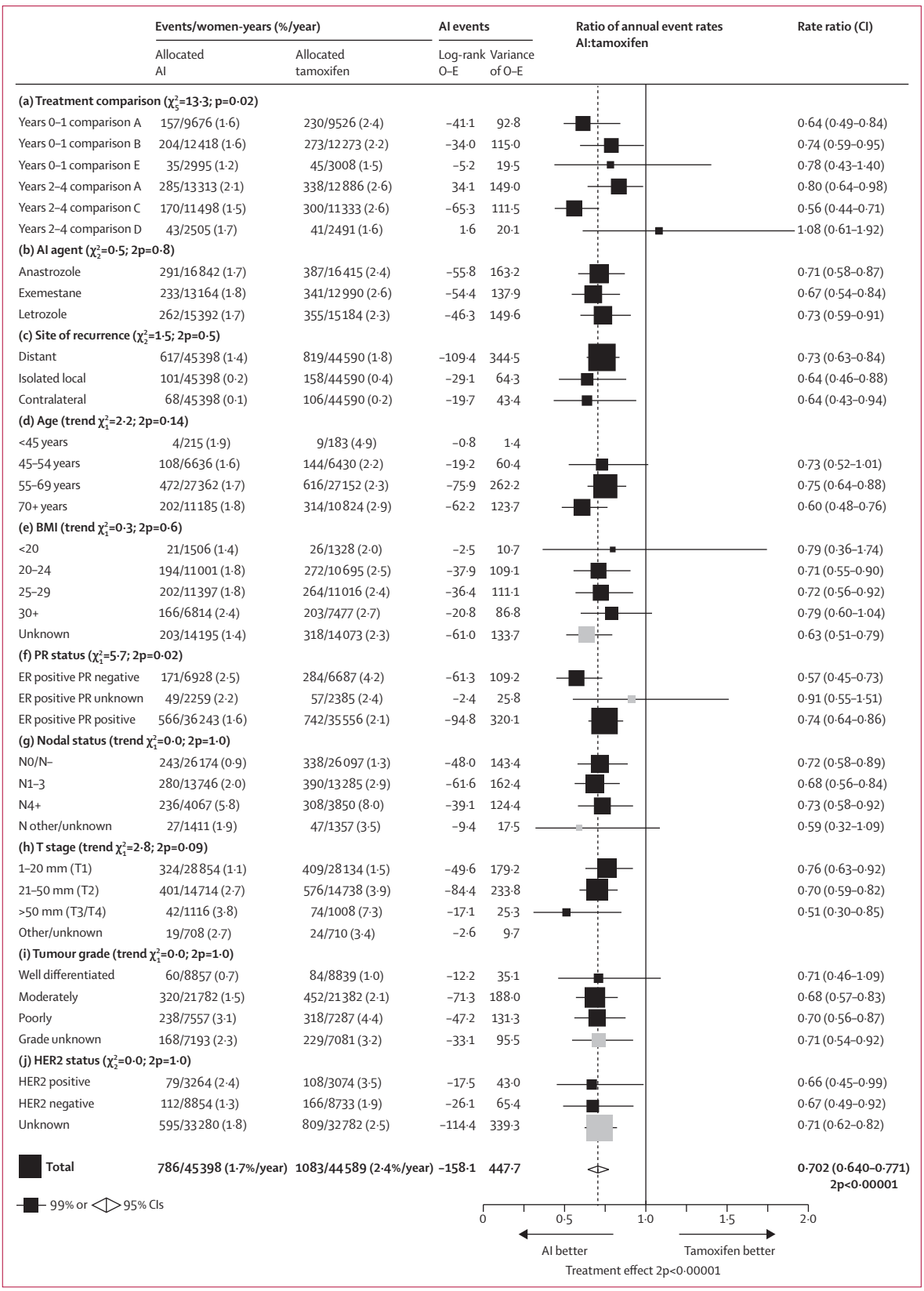


Figure 5: **Subgroup analyses of recurrence risk reductions combining data from five comparisons of aromatase inhibitors versus tamoxifen including only data during periods when treatments differed**

Grey squares show unknown status within the subgroup. Results are plotted as black squares with horizontal lines that denote 99% rather than 95% CIs to allow for multiple hypothesis testing. Total is plotted as a white diamond that denotes 95% CI. AI=aromatase inhibitor. O–E=observed minus expected. Comparison A=5 years of aromatase inhibitor versus 5 years of tamoxifen. Comparison B=5 years of aromatase inhibitors versus 2–3 years of tamoxifen, then aromatase inhibitor to year 5. Comparison C=2–3 years of tamoxifen, then aromatase inhibitor to year 5 versus 5 years of tamoxifen. Comparison D=5 years of aromatase inhibitor versus 2 years of aromatase inhibitor, then tamoxifen to year 5. Comparison E=2 years of aromatase inhibitor, then tamoxifen to year 5 versus 5 years of tamoxifen. ER=oestrogen receptor. PR=progesterone receptor.

	5 years of tamoxifen *vs* none: EBCTCG previous meta-analysis[1] (n=10 645)		5 years of aromatase inhibitor *vs* 5 years of tamoxifen: present meta-analyses* (n=34 882)		5 years of aromatase inhibitor *vs* none: estimated effects (product of two RRs†)	
	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
Breast cancer recurrence						
During years 0–4	0·53 (0·48–0·57)	2p<0·0001	0·70 (0·64–0·77)	2p<0·0001	0·37 (0·33–0·42)	2p<0·0001
During years 5–9	0·68 (0·60–0·78)	2p<0·0001	0·92 (0·83–1·01)	2p=0·082	0·63 (0·53–0·74)	2p<0·0001
Breast cancer mortality						
During years 0–4	0·71 (0·62–0·80)	2p<0·0001	0·79 (0·67–0·92)	2p=0·002	0·56 (0·46–0·68)	2p<0·0001
During years 5–9	0·66 (0·58–0·75)	2p=0·0001	0·91 (0·80–1·02)	2p=0·12	0·60 (0·50–0·72)	2p<0·0001

EBCTCG=Early Breast Cancer Trialists' Collaborative Group. RR=rate ratio. *Estimated from the aggregated data (appendix). †Estimated rate ratio for 5 years of aromatase inhibitor *vs* none (RR_3) is obtained by direct multiplication of the rate ratio for 5 years of tamoxifen *vs* none (RR_1) by the rate ratio for 5 years of aromatase inhibitor *vs* 5 years of tamoxifen (RR_2) estimated from the aggregated data; 95% confidence limits for RR_3 are $\exp[(o-e)_1/v_1 + (o-e)_2/v_2) - 1{\cdot}96\sqrt{(1/v_1 + 1/v_2)}]$ and $\exp[(o-e)_1/v_1 + (o-e)_2/v_2) + 1{\cdot}96\sqrt{(1/v_1 + 1/v_2)}]$, respectively, where (o−e) and v are the observed minus expected statistics and their variances for the comparisons of 5 years of tamoxifen *vs* none and 5 years of aromatase inhibitor *vs* 5 years of tamoxifen (estimated from aggregated data from trials contributing to subtotal (a) in figure 4).

Table: **Estimation of the effect of 5 years of an aromatase inhibitor versus no endocrine treatment**

within 5 years were, respectively, about 1%, 2%, and 4% (appendix). Differences in vascular mortality, aromatase inhibitor versus tamoxifen, were not significant: thromboembolic, 14 versus 19 deaths; cerebrovascular, 44 versus 52 deaths; and cardiac, 137 versus 128 deaths.

Discussion

Individual trials have already shown reduced recurrence rates with aromatase inhibitor compared with tamoxifen but none has shown in intention-to-treat analyses that breast cancer mortality is reduced, nor did previous meta-analyses.[4] Now, with longer follow-up, the present meta-analyses establish that breast cancer mortality and all-cause mortality are also reduced, better characterise time-dependent effects on recurrence, and allow informative investigation of differential efficacy within subgroups and of uncommon adverse events.

There was a fairly consistent pattern of substantial recurrence reductions during periods when one group was receiving an aromatase inhibitor and the other tamoxifen, but little further reduction during subsequent periods when both groups were receiving the same endocrine treatment or after scheduled endocrine treatment had ended in both groups. However, this finding should not be interpreted as aromatase inhibitors not having the carry-over benefits of tamoxifen,[1] rather that 5 years of endocrine therapy that includes an aromatase inhibitor reduces recurrence by about one-third during years 5–9, as does 5 years of tamoxifen.

The most extreme recurrence reduction appeared to be in comparison C in which, after 2 years of tamoxifen, an aromatase inhibitor was compared with tamoxifen during years 2–4. This result is not explained by differences in efficacy between different aromatase inhibitors, as indirect comparisons in figure 5, and direct randomised comparisons,[16] show little difference between drugs. It has been hypothesised that the superiority of aromatase inhibitors over tamoxifen is greater after previous exposure to tamoxifen,[17] and the larger recurrence reductions reported in years 5–9 in trials of aromatase inhibitor versus no further treatment[18–20] after 5 years of tamoxifen than in trials of 10 versus 5 years of tamoxifen[2,3] provide some support for this. However, the directly randomised findings in comparison B do not show any effect of the type of endocrine therapy during years 0–1 on the efficacy of treatment during years 2–4, so the apparent heterogeneity of benefit from indirect comparisons could be largely chance.

In comparison E, after an initial 2–3 years of an aromatase inhibitor there appeared to be no benefit from continuing an aromatase inhibitor to 5 years rather than switching to tamoxifen, but this result was based on one trial with few events. Hence, it remains uncertain whether, after 2–3 years of an aromatase inhibitor, any loss of benefit occurs from switching to tamoxifen—reassuringly for women who do not tolerate aromatase inhibitors. Results of ongoing trials comparing different durations of aromatase inhibitor treatment will determine whether, as with tamoxifen, longer is better.[2,3,21]

The reduction in breast cancer mortality with aromatase inhibitor compared with tamoxifen is only slight, as expected in an already relatively good-prognosis population, but persists during years 0–4 and 5–9, significantly reducing 10-year breast cancer mortality. Overall 10-year mortality was also significantly reduced, even though about half the deaths were not due to breast cancer. Non-breast cancer death rates were similar with aromatase inhibitor and tamoxifen except that, after 2–3 years of tamoxifen, there appeared to be fewer such deaths with an aromatase inhibitor than with continuing tamoxifen. This finding was unexpected, not explained by any one cause, and not replicated in the other comparisons. Though likely to be a chance finding, it is reassuring for the safety of aromatase inhibitors.

Bone fractures are a concern with aromatase inhibitors, though the absolute excess of about 0·5% per year might be partly explained by a bone-protective effect of

tamoxifen.[22] Practitioners need to be aware of this complication as monitoring bone health and using bisphosphonates if indicated can reduce risk.[23] The lower endometrial cancer incidence with aromatase inhibitor than tamoxifen of around 0·1% per year partly counterbalances the increased fracture risk.

With full compliance, the benefit of aromatase inhibitors over tamoxifen would probably have been somewhat greater than in our intention-to-treat analyses, as in addition to the usual levels of dropout in long-term trials, which might affect both groups similarly, substantial crossover of patients from tamoxifen to an aromatase inhibitor occurred in two trials,[8,9] following reports that switching to an aromatase inhibitor after 2–3 years of tamoxifen reduces recurrence compared with continuing tamoxifen.[11] The intention-to-treat analyses presented throughout this report take no account of dropouts or crossovers, so they underestimate the superiority of aromatase inhibitor over tamoxifen for breast cancer endpoints. Subsequent publications will investigate various analytic approaches (eg, as applied to BIG 1-98[24]) to estimate the aromatase inhibitor effect that would be seen with full compliance.

Among the postmenopausal women in these trials there were no significant differences in the RR by age. Trials of aromatase inhibitors versus tamoxifen in premenopausal women treated with an ovarian suppressant[25,26] were not included. Although age is not an independent correlate of distant recurrence or treatment efficacy, it is a major determinant of the life expectancy gain from avoiding distant recurrence. As subgroup analyses pooling data from all trials did not identify any patient or tumour characteristic that strongly predicted the RR, the key quantitative findings likely to be generalisable to future patients[27] are the proportional risk reductions of around 30% in recurrence during the aromatase inhibitor versus tamoxifen comparison periods, and the proportional reduction of about 15% in the breast cancer mortality rate during the first decade.

We can infer from the present results the proportional reductions that would be achieved with 5 years of aromatase inhibitor compared with no adjuvant endocrine therapy (table). Treatment with tamoxifen for 5 years reduces recurrence by about half during years 0–4 and one-third during years 5–9, and reduces the breast cancer mortality rate by about 30% throughout the first decade and beyond.[1] Therefore, 5 years of an aromatase inhibitor compared with no endocrine therapy would reduce breast cancer recurrence by about two-thirds during treatment and by about one-third during years 5–9, and would reduce the breast cancer mortality rate by around 40% throughout the first decade, and perhaps beyond. Though these proportional reductions in risk are approximately independent of nodal status, tumour grade, diameter, PR, and HER2 status, these prognostic factors substantially affect the absolute risk with no endocrine treatment, and hence substantially affect the absolute reduction in that risk produced by aromatase inhibitors.

Finally, the trials that involve starting endocrine treatment with an aromatase inhibitor rather than with tamoxifen collectively show a highly significant 30% recurrence reduction during years 0–1. The trials comparing 5 years of aromatase inhibitor with a switching strategy of 2–3 years of tamoxifen then aromatase inhibitor to year 5 provide no indication that this recurrence reduction during years 0–1 will later be lost, and it is likely that it would eventually translate into a slight survival improvement. However, in the 2014 ASCO guidelines on endocrine treatment of postmenopausal women with ER-positive early breast cancer, three of the four recommended options start with tamoxifen;[5] a review seems appropriate.

Contributors

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Declaration of interests

Clinical Trial Service Unit (CTSU) staff policy excludes honoraria or consultancy fees for any member of the Early Breast Cancer Trialists' Collaborative Group Secretariat. EBCTCG is funded by Cancer Research UK and UK Medical Research Council grants to the CTSU. JB reports grants, personal fees, and non-financial support from Pfizer during the conduct of the study; outside the submitted work she reports grants from Pfizer, GlaxoSmithKline, Novartis, AstraZeneca, Clovis, and Janssen-Cilag. RCC reports financial and non-financial support from Pfizer to Imperial College, London during the conduct of the study; outside the submitted work he has received personal fees (speaker fees) from Pfizer. JC reports grants from AstraZeneca, outside the submitted work. MD reports grants from Pfizer, Novartis, and AstraZeneca, and personal fees from Pfizer and AstraZeneca, outside the submitted work. PD reports grants and non-financial support from Agendia and Sividon, grants from Nanostring Technologies, personal fees and travel support from AstraZeneca, personal fees from Pfizer and TEVA-ratiopharm, and travel support from Novartis, outside the submitted work. JFF reports grants from National Health & Medical Research Council, during the conduct of the study. MG reports grants and personal fees from Novartis, Roche, and GlaxoSmithKline, grants from Sanofi-Aventis, Pfizer, and Smith Medical, and personal fees from AstraZeneca, Nanostring Technologies, and Accelsiors, outside the submitted work. LK reports funding from Pfizer for the IES study. FP reports grants and non-financial support from AstraZeneca and non-financial support from Novartis, during the conduct of the study. BT reports grants, personal fees, and compensation received by the hospital for research work from Novartis, grants and personal fees from AstraZeneca, and grants from OSKK, during the conduct of the study, outside the submitted work, contracts for clinical research and honoraria for other services were received by the hospital from Novartis, AstraZeneca, and Pfizer; BT also holds stock in Novartis. TA, FB, RB, AC, CD, RG, JI, MK, HP, RP, DR, and CvdV declare no competing interests.

Acknowledgments

We thank the 35 000 women who took part in the trials, the many staff in trial centres and participating clinics who helped conduct the trials, the trialists who shared their data, and the Clinical Trial Service Unit, which has long hosted this collaboration.

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