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Published in:
Lancet

Document Version:
Publisher's PDF, also known as Version of record

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Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*

Summary

Background Bisphosphonates have profound effects on bone physiology, and could modify the process of metastasis. We undertook collaborative meta-analyses to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer.

Methods We sought individual patient data from all unconfounded trials in early breast cancer that randomised between bisphosphonate and control. Primary outcomes were recurrence, distant recurrence, and breast cancer mortality. Primary subgroup investigations were site of first distant recurrence (bone or other), menopausal status (postmenopausal [combining natural and artificial] or not), and bisphosphonate class (aminobisphosphonate [eg, zoledronic acid, ibandronate, pamidronate] or other [ie, clodronate]). Intention-to-treat log-rank methods yielded bisphosphonate versus control first-event rate ratios (RRs).

Findings We received data on 18 766 women (18 206 [97%] in trials of 2–5 years of bisphosphonate) with median follow-up 5·6 woman-years, 3453 first recurrences, and 2106 subsequent deaths. Overall, the reductions in recurrence (RR 0·94, 95% CI 0·87–1·01; 2p=0·08), distant recurrence (0·92, 0·85–0·99; 2p=0·03), and breast cancer mortality (0·91, 0·83–0·99; 2p=0·04) were of only borderline significance, but the reduction in bone recurrence was more definite (0·83, 0·73–0·94; 2p=0·004). Among premenopausal women, treatment had no apparent effect on any outcome, but among 11 767 postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002), distant recurrence (0·82, 0·74–0·92; 2p=0·0003), bone recurrence (0·72, 0·60–0·86; 2p=0·0002), and breast cancer mortality (0·82, 0·73–0·93; 2p=0·002). Even for bone recurrence, however, the heterogeneity of benefit was barely significant by menopausal status (2p=0·06 for trend with menopausal status) or age (2p=0·03), and it was non-significant by bisphosphonate class, treatment schedule, oestrogen receptor status, nodes, tumour grade, or concomitant chemotherapy. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR 0·85, 95% CI 0·75–0·97; 2p=0·02).

Interpretation Adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival, but there is definite benefit only in women who were postmenopausal when treatment began.

Funding Cancer Research UK, Medical Research Council.

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Introduction Circulating tumour cells can be attracted to surfaces within the bone where they can displace haemopoietic stem cells and bind to the osteoblastic niche.1 These disseminated malignant cells can remain quiescent for years. Then, for reasons that are not well understood, they can exit this dormant state, start to proliferate, and establish macro-metastases in the bone or elsewhere.2 Bisphosphonates have profound effects on osteoclasts, and affect T-cell function, so could also be effective as adjuvant treatments, particularly in preventing or delaying bone recurrence.3,4 For this reason, and because bisphosphonates can be added to the aromatase inhibitor treatment of postmenopausal breast cancer to restrict adverse skeletal effects of oestrogen deprivation, reliable evidence is needed about the effects of bisphosphonates on breast cancer outcomes.

Improvements in bone-metastasis-free survival, disease-free survival, and overall survival in women with early breast cancer have been reported in some adjuvant trials of oral clodronate5,6 or of intravenous zoledronic acid.7,8 However, in other trials of adjuvant bisphosphonates no significant benefits were seen in analyses that included all randomised patients, although both planned and exploratory subset analyses suggested benefits either in postmenopausal women or in older women.9,10 This led to the hypothesis11–13 that treatment is of benefit only in patients with low concentrations of reproductive hormones (ie, those who are postmenopausal or undergoing ovarian suppression therapy).14,15 To help clarify whether adjuvant bisphosphonates reduce the risk of bone and other metastases, and whether menopausal status affects efficacy, we undertook collaborative...
meta-analyses of all unconfounded randomised trials that compared breast cancer outcomes in those allocated adjuvant bisphosphonate versus those who were not.

**Methods**

**Identification of studies and collection of data**

The methods of identifying trials, seeking collaboration, data collection, collation, checking, and presentation are as in previous Early Breast Cancer Trials’ Collaborative Group (EBCTCG) reports. Trials were eligible if they began before 2008 and randomly assigned women between a bisphosphonate of any type, dose, and schedule versus a control group (open label or placebo) with no bisphosphonate, all other treatments being similar in both groups. Information was sought during 2012–14 for each individual patient on date of randomisation, allocated treatment, age, menopausal status, tumour diameter, grade, spread to locoregional lymph nodes, HER2 and oestrogen and progesterone receptor (ER/PR) status, dates and sites of any breast cancer recurrence, other second primary cancer, bone fracture, and the date and cause of death.

The main definitions and analysis methods are those used in previous EBCTCG reports, but with some amendments that reflect the potential effect of bisphosphonates on bone metastases (appendix).

**Outcomes**

The pre-defined coprimary endpoints were any recurrence of breast cancer (distant, locoregional, or new primary in the contralateral breast); distant recurrence, ignoring any previous locoregional or contralateral recurrence; and breast cancer mortality (estimated by log-rank subtraction, as in previous EBCTCG reports).

Secondary outcomes were all-cause mortality; death without recurrence; bone recurrence as the first distant recurrence (with or without concurrent other recurrence); other first (extraskeletal) distant recurrence (with all analyses of distant recurrence ignoring any previous locoregional or contralateral recurrence); locoregional recurrence as first event (ipsilateral breast, chest wall, or locoregional lymph nodes); contralateral new primary breast cancer as first event; and any bone fractures.

**Statistical analyses**

Time-to-event analyses were stratified by age, ER status, nodal status, and trial. Within each stratum, they compared all those allocated bisphosphonate versus all those allocated control, regardless of treatment compliance (yielding intention-to-treat analyses). Log-rank statistics were used to assess the effects (bisphosphonate vs control) on various outcomes, and, for each, to estimate first-event rate ratios (RRs) and their CIs. We did statistical analyses using EBCTCG in-house Fortran programs.

Pre-specified primary subgroup investigations were of site of first distant recurrence (bone, other), menopausal status (premenopausal, perimenopausal, postmenopausal [natural or induced, either potentially reversibly, using luteinising hormone-releasing hormone analogues, or permanently by oophorectomy]) or, if menopausal status was unavailable, years of age, grouped as <45, 45–54, ≥55 years), and class of bisphosphonate (aminobisphosphonate [zoledronic acid, ibandronate, pamidronate, risedronate, alendronate], other [clodronate]). Exploratory investigations were undertaken of potential interactions between treatment efficacy and ER status, nodal status, histological grade, use or not of adjuvant chemotherapy, and follow-up period. If appropriate, tests comparing effects in different subgroups were for trend rather than heterogeneity.

We pre-specified that comparisons of treatment efficacy within subgroups would exclude local and contralateral recurrence if the prior hypothesis that bisphosphonates would reduce distant but not local or contralateral recurrence was established from analyses of the overall results in all randomised patients. As bone recurrence was the only type of recurrence significantly reduced by bisphosphonates we used this instead as the primary endpoint for subgroup comparisons, but the appendix includes subgroup analyses for any distant recurrence. Because the ABCSG-12 and AZURE trials helped generate the hypothesis of the relevance of menopausal status to the effects of treatment, we provide sensitivity analyses of this hypothesis that treated these trials as hypothesis-generating, with the remaining trials hypothesis-testing. The policy on data sharing from this study is available online.

### Table: Numbers of unconfounded randomised trials of an adjuvant bisphosphonate identified, and numbers with data received, by duration and type of bisphosphonate treatment

<table>
<thead>
<tr>
<th>Duration of Treatment</th>
<th>Any aminobisphosphonate</th>
<th>1 year aminobisphosphonate</th>
<th>2–5 years of treatment</th>
<th>3–5 years aminobisphosphonate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials (n)</td>
<td>Patients (n)</td>
<td>Trials (n)</td>
<td>Patients (n)</td>
</tr>
<tr>
<td>Up to 1 year of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year clodronate</td>
<td>2</td>
<td>120</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>&lt;1 year aminobisphosphonate</td>
<td>2</td>
<td>208</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>1 year aminobisphosphonate</td>
<td>7</td>
<td>1088</td>
<td>3</td>
<td>448</td>
</tr>
<tr>
<td>Total for ≤1 year of treatment</td>
<td>11</td>
<td>1416</td>
<td>5</td>
<td>560</td>
</tr>
<tr>
<td>2–5 years of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years clodronate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5 years clodronate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years aminobisphosphonate</td>
<td>10</td>
<td>351</td>
<td>1</td>
<td>1069</td>
</tr>
<tr>
<td>3–5 years aminobisphosphonate</td>
<td>12</td>
<td>11901</td>
<td>9</td>
<td>9711</td>
</tr>
<tr>
<td>Total for 2–5 years of treatment</td>
<td>27</td>
<td>20611</td>
<td>21</td>
<td>18206</td>
</tr>
<tr>
<td>Any clodronate regimen</td>
<td>7</td>
<td>5167</td>
<td>2</td>
<td>5053</td>
</tr>
<tr>
<td>Any aminobisphosphonate</td>
<td>31</td>
<td>16860</td>
<td>21</td>
<td>13737</td>
</tr>
<tr>
<td>Total, all regimens</td>
<td>38</td>
<td>22027</td>
<td>26</td>
<td>18766</td>
</tr>
</tbody>
</table>

*Number of patients with data received as a percentage of all randomised patients in identified studies. Mean scheduled treatment duration (weighted in proportion to numbers of patients with data received). Includes two trials (2116 patients) still in progress; excluding these, the total with data received is 94%. The aminobisphosphonates in these trials were zoledronic acid (9290 patients with data received, 3582 recurrences [41% of all recurrences]), ibandronate (3072 patients, 380 recurrences [11%]), pamidronate (953 patients, 473 recurrences [14%]), risedronate (395 patients, 13 recurrences [2.4%]), and alendronate (no trials with data received); the only non-aminobisphosphonate in these trials was clodronate (5053 patients, 1005 [29%] recurrences).
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 writing committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Individual patient datasets were provided for 26 trials with 18,766 participants, 97% of all 19,291 women in the 32 completed trials that recorded recurrence data (table, appendix). In four other trials (620 women) recurrence was not recorded, and from the two ongoing trials (2,116 women) outcome data cannot yet be provided. Mean scheduled treatment duration was 3.4 years; 18,206 (97%) of 18,766 participants were in trials of 2–5 years of treatment.

Median follow-up was 5.6 woman-years (IQR 3.7–8.0). 3,453 women had a recurrence, after which 2,106 died. Recurrence rates were slightly lower with than without bisphosphonates, but this was not significant in analyses that included all 18,766 women (RR 0.94, 95% CI 0.87–1.01; 2p=0.08; figure 1). However, there was a borderline significant reduction in the risk of distant recurrence, ignoring any previous local or contralateral recurrence, after which 2,106 women died.

Figure 1: Recurrence by site and breast cancer mortality in 24 trials of bisphosphonate versus no bisphosphonate (control)

Kaplan-Meier graphs showing effects of treatment allocation on 10-year outcomes in all 18,766 patients. (A) Any recurrence. (B) Distant recurrence. (C) Bone recurrence. (D) Breast cancer mortality. O–E=observed minus expected. V=variance of O–E. RR=rate ratio (exp\[{O–E}/V\]). Error bars are SE.
<table>
<thead>
<tr>
<th>Category</th>
<th>Events/women</th>
<th>Bisphosphonate events</th>
<th>Ratio of annual event rates</th>
<th>Rate ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Allocated</td>
<td>Log-rank O–E</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bisphosphonate</td>
<td>control</td>
<td>Variance of O–E</td>
<td></td>
</tr>
<tr>
<td>(a) Age, years (trend χ²=0.9; 2p=0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>164/2475 (6·6%)</td>
<td>151/2141 (7·1%)</td>
<td>0.3</td>
<td>71.3</td>
</tr>
<tr>
<td>45–54</td>
<td>152/3532 (4·3%)</td>
<td>173/3224 (5·4%)</td>
<td>14·2</td>
<td>74.3</td>
</tr>
<tr>
<td>55–69</td>
<td>168/3314 (5·1%)</td>
<td>196/3022 (6·5%)</td>
<td>25·1</td>
<td>84.4</td>
</tr>
<tr>
<td>≥70</td>
<td>131/531 (2·4%)</td>
<td>22/521 (4·2%)</td>
<td>-5.1</td>
<td>7.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age unknown</th>
<th>0/0 (0.0%)</th>
<th>0/2 (0.0%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(b) Menopausal status (trend χ²=3·5; 2p=0.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>217/3396 (6·6%)</td>
<td>212/2875 (7·4%)</td>
<td>7.9</td>
<td>96.4</td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>28/461 (6·1%)</td>
<td>19/357 (5·2%)</td>
<td>2.0</td>
<td>8.8</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>252/6099 (4·1%)</td>
<td>331/5668 (5·5%)</td>
<td>-22.1</td>
<td>128.0</td>
</tr>
<tr>
<td>(c) ER status (trend χ²=0.6; 2p=0.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER negative</td>
<td>107/964 (5·4%)</td>
<td>135/1684 (8·0%)</td>
<td>-15.7</td>
<td>56.4</td>
</tr>
<tr>
<td>ER unknown</td>
<td>42/637 (6·6%)</td>
<td>47/690 (6·8%)</td>
<td>1.2</td>
<td>20.9</td>
</tr>
<tr>
<td>ER positive</td>
<td>348/7255 (4·8%)</td>
<td>360/6636 (5·5%)</td>
<td>-26.9</td>
<td>169.1</td>
</tr>
<tr>
<td>(d) Nodal status (trend χ²=0.5; 2p=0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0/N=</td>
<td>70/2638 (2·7%)</td>
<td>68/2631 (2·6%)</td>
<td>0.6</td>
<td>32.3</td>
</tr>
<tr>
<td>N1–3</td>
<td>225/4323 (5·2%)</td>
<td>231/3352 (6·9%)</td>
<td>-24.0</td>
<td>104.1</td>
</tr>
<tr>
<td>N4+</td>
<td>160/1205 (13·3%)</td>
<td>183/1190 (15·4%)</td>
<td>-14.3</td>
<td>76.1</td>
</tr>
<tr>
<td>N other/unknown</td>
<td>42/1690 (2·5%)</td>
<td>60/1273 (3·1%)</td>
<td>-6.9</td>
<td>24.6</td>
</tr>
<tr>
<td>(e) Tumour grade (trend χ²=0.4; 2p=0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>24/877 (2·7%)</td>
<td>26/793 (3·3%)</td>
<td>-1.6</td>
<td>10.9</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>296/1667 (5·3%)</td>
<td>203/3249 (6·2%)</td>
<td>-11.7</td>
<td>94.4</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>156/2801 (5·6%)</td>
<td>174/2316 (7·5%)</td>
<td>-17.6</td>
<td>76.8</td>
</tr>
<tr>
<td>Grade unknown</td>
<td>121/3511 (3·8%)</td>
<td>139/2542 (5·5%)</td>
<td>-4.4</td>
<td>61.4</td>
</tr>
<tr>
<td>(f) Bisphosphonate type (trend χ²=0.3; 2p=0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>139/2514 (5·5%)</td>
<td>165/2539 (6·5%)</td>
<td>-16.7</td>
<td>67.5</td>
</tr>
<tr>
<td>Aminobisphosphonate</td>
<td>358/7342 (4·9%)</td>
<td>377/6371 (5·9%)</td>
<td>-21.1</td>
<td>169.7</td>
</tr>
<tr>
<td>(g) Bisphosphonate (trend χ²=9·5; 2p=0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clodronate</td>
<td>139/2514 (5·5%)</td>
<td>165/2539 (6·5%)</td>
<td>-16.7</td>
<td>67.5</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>200/4642 (4·3%)</td>
<td>250/4648 (5·4%)</td>
<td>-24.1</td>
<td>108.7</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>80/460 (17·4%)</td>
<td>76/493 (15·4%)</td>
<td>5.1</td>
<td>33.1</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>78/2040 (3·8%)</td>
<td>49/1032 (4·7%)</td>
<td>-8.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Risedronate</td>
<td>0/0 (0.0%)</td>
<td>2/198 (1·0%)</td>
<td>-0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Alendronate (no data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(h) Bisphosphonate dose (trend χ²=0.4; 2p=0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More intensive</td>
<td>434/7040 (6·2%)</td>
<td>457/6089 (7·5%)</td>
<td>-34.5</td>
<td>201.7</td>
</tr>
<tr>
<td>Low intensity</td>
<td>63/2816 (2·2%)</td>
<td>85/2821 (3·0%)</td>
<td>-10.1</td>
<td>35.5</td>
</tr>
<tr>
<td>(i) Bisphosphonate duration (trend χ²=2·2; 2p=0.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>47/777 (1·4%)</td>
<td>4/283 (1·4%)</td>
<td>0.8</td>
<td>17.1</td>
</tr>
<tr>
<td>2 years</td>
<td>169/2083 (5·5%)</td>
<td>154/2091 (7·1%)</td>
<td>-18.5</td>
<td>68.6</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>234/4598 (5·0%)</td>
<td>384/6536 (5·5%)</td>
<td>-26.9</td>
<td>166.9</td>
</tr>
<tr>
<td>(j) Chemotherapy (trend χ²=0.3; 2p=0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>391/1615 (2·4%)</td>
<td>53/1616 (3·3%)</td>
<td>-6.3</td>
<td>21.0</td>
</tr>
<tr>
<td>Presence</td>
<td>458/8240 (5·6%)</td>
<td>489/7294 (6·7%)</td>
<td>-38.3</td>
<td>216.2</td>
</tr>
<tr>
<td>(k) Follow-up period, years (trend χ²=2·5; 2p=0.11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>373/9586 (18·8%)</td>
<td>204/8910 (2·3%)</td>
<td>-25.0</td>
<td>85.0</td>
</tr>
<tr>
<td>2–4</td>
<td>218/8445 (2·6%)</td>
<td>237/7609 (3·1%)</td>
<td>-20.0</td>
<td>104.6</td>
</tr>
<tr>
<td>5–9</td>
<td>104/5721 (1·8%)</td>
<td>99/5814 (1·8%)</td>
<td>0.8</td>
<td>46.8</td>
</tr>
<tr>
<td>≥10</td>
<td>2/706 (0·3%)</td>
<td>2/758 (0·3%)</td>
<td>-0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>(χ²=0·6; 2p=0·4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>497/9856 (5·0%)</td>
<td>542/8910 (6·1%)</td>
<td>-44.6</td>
<td>237.1</td>
</tr>
</tbody>
</table>

Figure 2: Multiple subgroup analyses of effects on bone recurrence in trials of bisphosphonate versus no bisphosphonate (control)

Results are plotted as black squares with horizontal lines that denote 95% rather than 95% CIs to allow for multiple hypothesis testing. Total is plotted as a white diamond that denotes 95% CI. ER—oestrogen receptor. O–E—observed minus expected.
breast recurrence (10-year risk 20·4% bisphosphonate vs 21·8% control; RR 0·92, 95% CI 0·83–0·99; 2p=0·03; figure 1), whereas there was no significant effect on the incidence of local recurrence as first event (RR 1·10, 0·94–1·28; 2p=0·25; appendix) or of contralateral breast cancer as first event (RR 0·96, 0·74–1·25; 2p=0·79). The greater efficacy of bisphosphonates in preventing distant recurrence than in preventing other (local or contralateral) breast cancer recurrence was significant (test for interaction 2p=0·01).

The effect on distant recurrence was mainly because of a reduction in bone recurrence (10-year risk 7·8% vs 9·0%; RR 0·83, 95% CI 0·73–0·94; 2p=0·004; figure 1). There was significantly (p=0·04) greater bone recurrence on other first distant recurrence than on other first distant recurrence (RR 0·98, 95% CI 0·89–1·08; 2p=0·69; appendix), although this apparent lack of efficacy could be partly because delay of bone recurrence with bisphosphonate in a woman who would otherwise have had both bone and other distant recurrence allowed the other recurrence to be the first event.

Breast cancer mortality was borderline significantly lower in patients allocated bisphosphonate than control (10-year risk 16·6% vs 18·4%; RR 0·91, 95% CI 0·83–0·99; 2p=0·04; figure 1), and all-cause mortality was similarly reduced (10-year risk 20·8% vs 22·3%; RR 0·92, 0·85–1·00; 2p=0·06; appendix). Of 2607 deaths from any cause, 501 (19%) were in recurrence-free women; this non-breast cancer mortality appeared to be unaffected by the treatment allocation (RR 0·99, 95% CI 0·82–1·19; 2p=0·91). We did many subgroup analyses to investigate the effects of bisphosphonates on any recurrence, distant recurrence, bone recurrence, and breast cancer mortality (appendix). In the overall analyses, among all 18 766 women, the clearest evidence of effect of bisphosphonates was, as anticipated, on bone recurrence, so the most informative subgroup analyses should relate to this endpoint (figure 2). The efficacy of bisphosphonates in reducing bone recurrence appeared to be greater in older women (2p=0·03 for trend with age in treatment effect) or, similarly, in postmenopausal women (2p=0·06 for trend with menopausal status). As menopausal status and age are closely correlated, we cannot determine reliably which is more relevant (appendix). Among the 4616 women younger than 45 years, bone recurrence appeared to be unaffected by the treatment allocation (RR 1·00, 95% CI 0·79–1·26; 2p=0·97), but among the 7388 women 55 years or older there was a highly significant treatment effect (RR 0·72, 0·59–0·88; 2p=0·002). Sensitivity analyses of the possible relevance of age and menopausal status that omitted the hypothesis-generating ABCSG-121 and AZURE11,14 studies still showed significant (2p=0·004) benefit only in postmenopausal women (appendix). As was the case for bone recurrence, the reductions in any distant recurrence with bisphosphonate were also significantly greater in older women (2p=0·003 for trend with age) and postmenopausal women (2p=0·01).

None of the other subgroup analyses of bone recurrence in figure 2 revealed any significant evidence of heterogeneity of benefit by tumour type (or for other breast cancer outcomes; appendix). Although the benefit appeared somewhat larger in ER-negative than ER-positive disease and in node-positive than node-negative tumours, this apparent heterogeneity of treatment effect did not approach significance and could be a chance finding.

Likewise, there was no significant heterogeneity between the apparent effects on bone recurrence of the different bisphosphonate regimens tested in these trials. For this outcome, the benefits of the non-aminobisphosphonate (clodronate, n=5053) and of the two most widely tested aminobisphosphonates (zoledronic acid, n=9290, and ibandronate, n=3072) appeared similar, but there was no apparent benefit in the smaller oral pamidronate group (n=953).

For bone recurrence, the benefits appeared to be similar in trials of low-intensity anti-osteoporosis schedules (eg, 6-monthly intravenous zoledronic acid) and in trials of more intensive schedules such as those approved for use in metastatic bone disease (eg, monthly zoledronic acid, daily oral ibandronate, or daily oral clodronate). Likewise, the average effect appeared similar in trials that tested different durations of treatment (trials of 2 years bisphosphonate vs none: RR 0·76, 95% CI 0·60–0·97; 2p=0·026; trials of 3–5 years bisphosphonate vs none: RR 0·85, 0·73–0·99; 2p=0·037; figure 2), and in the presence or absence of chemotherapy. There were significant reductions in bone recurrence during years 0–1 and years 2–4 after randomisation but there appeared to be no further reduction thereafter. Again, though, this decrease in treatment effect over time was not significant (trend 2p=0·11), perhaps because there is thus far only limited follow-up after the first 5 years.

The 10-year disease outcomes for premenopausal and postmenopausal women separately are summarised in figure 3 and the appendix. In premenopausal women, treatment appeared to have little effect on bone metastases or breast cancer mortality, whereas in postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002; appendix), distant recurrence (RR 0·82, 0·74–0·92; 2p=0·0003; appendix), bone recurrence (RR 0·72, 0·60–0·86; 2p=0·0002), and breast cancer mortality (RR 0·82, 0·73–0·93; 2p=0·002). In both menopausal subgroups, rates of first distant recurrence at sites other than bone appeared to be unaffected by treatment. In the postmenopausal subgroup, for bone recurrence the absolute gain from treatment was 2·2% (95% CI 0·6–3·8) (10-year risks 6·6% vs 8·8%; RR 0·72, 95% CI 0·60–0·86; 2p=0·002), whereas for breast cancer mortality the absolute gain was 3·3% (95% CI 0·8–5·7) (10-year risks 14·7% vs 18·4%; RR 0·92, 95% CI 0·85–0·99; 2p=0·03; figure 3).
Figure 3: Main outcomes in premenopausal (excluding perimenopausal) and in postmenopausal women in trials of bisphosphonate versus no bisphosphonate (control). Kaplan-Meier graphs showing the effects of treatment allocation on 10-year breast cancer outcomes. (A) Premenopausal and (B) postmenopausal bone recurrence. (C) Premenopausal and (D) postmenopausal distant recurrence outside the bone. (E) Premenopausal and (F) postmenopausal breast cancer mortality. O-E observed minus expected. V-variance of O-E. RR=rate ratio (exp(O–E)/V). Error bars are SE.
all be restricted to postmenopausal women (appendix). In
postmenopausal women, there was significant (p=0.01)
heterogeneity between agents in the reductions in bone
recurrence, explained by the apparent lack of benefit from
pamidronate. The clodronate results did appear somewhat
more promising than the aminobisphosphonate results
but this difference was not significant for distant
recurrence or for bone recurrence, and was of only
borderline significance for breast cancer mortality, even
though the reduction in postmenopausal breast cancer
mortality was significant with clodronate but not with the
aggregate of all aminobisphosphonate regimens.

Information on fractures was available from only
13 341 (71%) of 18 766 women. Among them, 422 (6.3%) of
6649 bisphosphonate-allocated patients had a fracture
reported, as against 487 (7.3%) of 6692 control patients
(RR 0.85, 95% CI 0.75–0.97; 2p=0.02; appendix), and the
5-year fracture risk was reduced from 6.3% to 5.1%, with
little effect in years 0–1 and most of the gain in years 2–4.
After year 5 there appeared to be little further gain, but in
both groups the absolute rates after year 5 were lower than
in years 0–4, perhaps reflecting incomplete ascertainment.

Discussion

Taking all women together, regardless of menopausal
status, this collaborative meta-analysis of individual
patient data from 18 766 women randomised in trials of
adjuvant bisphosphonates found a highly significant
reduction only in bone recurrence, and not in other
breast cancer outcomes. Subgroup analyses suggested
benefit just in postmenopausal women, among whom
there were highly significant reductions not only in bone
recurrence but also in any distant recurrence (bone or
other), breast cancer mortality, and overall mortality.

Neither in the overall results nor in the results just
among postmenopausal women, however, was there any
significant effect on distant recurrence at extra-osseous
sites, on locoregional recurrence, or on the incidence of
contralateral breast cancer. The lack of effect on new
contralateral breast cancers is consistent with findings of
the large FIT and HORIZON-PFT fracture prevention
trials,29 but contrasts with reports from epidemiological
studies that breast cancer incidence is reduced in
postmenopausal women taking bisphosphonates for
osteoporosis.10,12 Thus, the randomised evidence provides
no support for the use of bisphosphonates as a breast
cancer chemoprevention strategy.

Though the statistical significance of the apparent
interaction between menopausal status and treatment
efficacy is not extreme, greater benefit for postmenopausal
women had been hypothesised to explain the apparent
discordance between the ABCSG-121 and AZURE11,14 trial
results. Sensitivity analyses that excluded these two
hypothesis-generating datasets only marginally weakened
the evidence of an interaction with menopausal status,
and the benefit was still significant in the remaining
postmenopausal women.

Moreover, there is some preclinical evidence that
reproductive hormones can inhibit bisphosphonate
efficacy against cancer cells in the bone. The effects of
zoledronic acid (100 μg/kg weekly) on the growth of
disseminated MDA-231 breast cancer cells in bone were
compared in ovariectomised mice (modelling the
postmenopausal setting) and in sham-operated mice
(modelling the premenopausal setting). Zoledronic acid
decreased the number of detectable tumours in bone only
in the ovariectomised animals.29 Likewise, in a prostate
cancer mouse model the ability of disseminated tumour
cells in the bone to form detectable tumours was inhibited
by zoledronic acid only in castrated mice, not in sham-
operated mice.24

The effects on bone recurrence emphasise the potential
importance of host microenvironment factors to
metastasis. Further studies are needed to clarify why
menopausal status should importantly affect the response
to bisphosphonates. The complex interactions between
reproductive hormones, tumour biology, bone cell
function, and bone marrow stem cells could well change
as patients progress from the premenopausal setting,
where oestradiol and inhibin are of major importance in
bones, to the postmenopausal setting, where activin and
other members of the TGF-β superfamily become the
main regulators of bone cell metabolism.25 A clearer
understanding of some of the other mechanisms involved
in the development of bone metastasis is now emerging,
although how these relate to menopausal status and
reproductive hormones remains unknown.26

Other than the apparent effect of menopausal status or,
similarly, age on treatment efficacy, the proportional
reductions in bone recurrence and breast cancer mortality
with treatment did not depend significantly on other
patient or clinico pathological primary tumour character-
istics, including ER status, axillary lymph node involve-
ment, and tumour grade. Similar reductions were seen in
the presence and absence of chemotherapy, suggesting
that the benefits of bisphosphonates are approximately
additive to those of chemotherapy, and vice versa.

As subgroup analyses can yield erratic results, it is
difficult to determine from them whether different
bisphosphonate regimens have different effects. The
endpoint that should yield the most reliable subgroup
analyses is bone recurrence. Both for all women and for
postmenopausal women, subgroup analyses of bone
recurrence suggested similar effects of oral clodronate
and of the aggregate of all aminobisphosphonate
regimens (mainly intravenous zoledronic acid). Likewise,
they suggested no significant heterogeneity in efficacy
between the different aminobisphosphonates, though no
benefit was seen with oral pamidronate (which could be
real, as oral pamidronate is poorly absorbed, has little
effect on bone resorption biomarkers or the underlying
metastatic bone disease, and failed to show efficacy in
myeloma27,28). Numbers were insufficient to assess the
efficacy of the standard treatments for osteoporosis, oral
risedronate or alendronate, as therapy for early breast cancer. Subgroup analyses based instead on breast cancer mortality suggested a greater effect with clodronate than with aminobisphosphonates. However, as the two drugs appeared to have similar effects on bone recurrence, their apparently different effects on breast cancer mortality could be a chance finding.

Much more reliable comparisons of different bisphosphonate regimens will emerge from ongoing trials that compare them directly. The SWOG0307 trial (NCT00127205) comparing clodronate versus zoledronic acid versus ibandronate in 5400 patients has completed recruitment and addresses the choice of agent; the SUCCESS trial (NCT02181100) comparing 5 years versus 2 years of zoledronic acid in 3800 patients has also completed recruitment and addresses duration. Similarly, results from two ongoing trials (HOBOE-premenopausal [NCT00412022] and TEAM-IIb [ISRCTN17633610]), plus longer follow-up of the trials included in this meta-analysis, will eventually provide better evidence on any effect of bisphosphonates in premenopausal women, and will provide more stable estimates of the 10-year outcomes in postmenopausal women.

Consistent with the known effects on bone mineral density and quality, the use of adjuvant bisphosphonates was associated with a small reduction in fracture incidence. Although not highly significant, it can be accepted as real because of evidence of fracture reduction in other types of patient. There was no apparent effect of adjuvant bisphosphonates on non-breast cancer mortality. Major adverse events with bisphosphonates are uncommon, but can include impaired renal function and osteonecrosis of the jaw. From the data provided, we were unable to assess the incidence of osteonecrosis of the jaw, but previous reports suggest it ranges from under 1% with clodronate, ibandronate, or 6-monthly zoledronic acid to about 2% with more intensive zoledronic acid schedules.

These trials have shown that some years of adjuvant bisphosphonate treatment can reduce breast cancer recurrence rates in bone and improve breast cancer survival, but have provided clear evidence of benefit only in women who are postmenopausal (natural or induced) at the time bisphosphonates are started. The use of bisphosphonates in breast cancer is mainly to reduce bone loss and risk of fracture in postmenopausal women with ER-positive disease treated with aromatase inhibitors. Our results show that such bisphosphonate treatment can, in addition, provide oncological benefit, and suggest that adjuvant bisphosphonates should be considered in a broader range of postmenopausal women.

**Contributors**

Analyses were planned by R Coleman, R Gray, T Powles, A Paterson, M Grant, J Bergh, K I Pritchard, J Bliss, and D Cameron, and undertaken by R Bradley, R Gray, H Pan, and R Peto in Oxford. R Coleman, R Gray, T Powles, and A Paterson drafted the report and revised it with advice from all writing committee members. The EBCTCG secretariat (R Bradley, J Burrett, M Clarke, C Davies, F Duane, V Evans, L Gettins, J Godwin, R Gray, H Liu, P McGale, E MacKinnon, T McHugh, S James, P Morris, H Pan, R Peto, S Read, C Taylor,  Y Wang, Z Wang) identified trials, obtained datasets, and had full access to them.

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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 Trials’ Collaborative Group Secretariat. EBCCTG is funded by Cancer Research UK and UK Medical Research Council grants to the CTSU. SA reports grants from National Institutes of Health (U10 CA069974 and U10 CA69651), during the conduct of the study. JB reports that Karolinska University Hospital and Karolinska Institutet have received payments for academic clinical studies and research grants for molecular biological studies and PET studies from Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche, and Sanofi-Aventis; he was Swedish principal investigator (PI) for an adjuvant bisphosphonate study for which oral pamidronate was provided free-of-charge (this formulation is not licensed); he is also Swedish PI for the ongoing ABCSG-18 adjuvant denosumab study (the drug was provided free-of-charge); he reports no personal payments in the past 3 years. DC reports support from Novartis to attend the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium conferences, outside the submitted work. RC reports personal fees from Novartis (for expert testimony), outside the submitted work. MG reports grants and personal fees from Novartis and personal fees from Amgen, during the conduct of the study; outside the submitted work he has received grants and personal fees from Novartis, Roche, and GlaxoSmithKline, grants from Sanofi-Aventis, Pfizer, and Smith Medical, and personal fees from AstraZeneca, Nanosting Technologies, and Accelsiors, JG reports grants from Novartis, Amgen, and Roche, outside the submitted work. VM reports grants and personal fees from Amgen and Roche, grants from Novartis, and personal fees from Celgene, outside the submitted work. KIP reports grants and personal fees from AstraZeneca, Pfizer, Roche, Novartis, and Eisai, and personal fees from Amgen and GlaxoSmithKline, outside the submitted work. JBL, RB, ID, VE, RG, HP, AP, RP, TP, and GvM declare no competing interests.

Acknowledgments
We thank the tens of thousands of women who took part in the trials, the many staff in trial centres and participating clinics who helped conduct the trials, and the trials who shared their data. Funding for individual trials was chiefly from manufacturers (see trial publications) but no commercial funding was sought or used by the secretariat. Funding for the EBCCTG secretariat is through the direct support from Cancer Research UK and the UK Medical Research Council, to the Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, UK.

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