

Does Adjuvant Bisphosphonate in Early Breast Cancer Modify the Natural Course of the Disease? A Meta-Analysis of Randomized Controlled Trials

Davide Mauri, MD;^{a,b} Antonis Valachis, MD;^{b,c} Nikolaos P. Polyzos, MD;^b Lamprini Tsali, MD;^b Dimitris Mavroudis, MD, PhD;^c Vassilis Georgoulas, MD, PhD;^c and Giovanni Casazza, PhD;^d
Lamia, Greece; Crete, Heraklion, Greece; Milan, Italy

Key Words

Bisphosphonate, early breast cancer, survival, metastases, disease recurrences, distant relapse, zoledronic acid, pamidronate, risedronate, clodronate

Abstract

To address whether the use of bisphosphonates in the adjuvant setting of breast cancer might have any effect on the natural course of the disease, a meta-analysis was conducted of published and unpublished randomized controlled trials found in PubMed, the Cochrane Central Register of Controlled Trials, the ISI Web of Knowledge, and abstracts of major international conferences up to January 2009. All trials that randomized patients with primary breast cancer to undergo adjuvant treatment with any bisphosphonate versus non-use were considered eligible. Analysis included data from 13 eligible trials involving 6886 patients randomized to treatment with bisphosphonates ($n = 3414$) or either placebo or no treatment ($n = 3472$). Compared with no use, adjuvant breast cancer treatment with bisphosphonates did not reduce the overall number of deaths (odds ratio [OR], 0.708; 95% CI, 0.482–1.041; $P = .079$), bone metastases (OR, 0.925; 95% CI, 0.768–1.114; $P = .413$), overall disease recurrences (OR, 0.843;

95% CI, 0.602–1.181; $P = .321$), distant relapse (OR, 0.896; 95% CI, 0.674–1.192; $P = .453$), visceral recurrences (OR, 1.051; 95% CI, 0.686–1.609; $P = .820$), or local relapses (OR, 1.056; 95% CI, 0.750–1.487; $P = .756$). No significant heterogeneity was observed among the trials except for estimates of deaths and disease recurrences ($P = .034$ and $P = .016$, respectively). In subgroup analyses, use of zoledronic acid was associated with a statistically significant lower risk for disease recurrence (OR, 0.675; 95% CI, 0.479–0.952; $P = .025$). However, these results should be interpreted with caution because the statistical significance for this association was weak and might be attributed to chance from multi-test analyses. Use of zoledronic acid was not associated with any significant difference in death (OR, 0.642; 95% CI, 0.388–1.063) and bone metastasis rates (OR, 0.661; 95% CI, 0.379–1.151). Currently available evidence does not support the hypothesis that use of bisphosphonates in adjuvant treatment of early breast cancer will alter the natural course of the disease. Nonetheless, a nonsignificant trend seems to exist for better outcomes in patients undergoing bisphosphonate treatment. Until further evidence from new clinical trials becomes available, adjuvant bisphosphonates should not be recommended routinely. (*JNCCN* 2010;8:279–286)

Preclinical studies show that bisphosphonates may have antitumor activity in addition to their ability to reduce osteoclast-mediated bone resorption.¹ These effects include prevention of tumor cell adhesion to bone and consequently prevention of bone metastasis,^{2–4} induction of tumor cell apoptosis,⁵ antagonism of growth factors,⁶ and antiangiogenic effects.⁷ Bisphosphonates have also shown synergistic antitumor effects in combination with chemotherapy in breast cancer models.⁸

Many randomized controlled trials have evaluated the role of bisphosphonates in the adjuvant setting of

From the ^aDepartment of Medical Oncology, General Hospital of Lamia, Lamia, Greece; ^bPanhellenic Association for Continual Medical Research (PACMeR), Lamia, Greece; ^cDepartment of Medical Oncology, University General Hospital of Heraklion, Crete, Heraklion, Greece; and ^dInstitute of Medical Statistic and Biometry, G.A. Maccacaro, University of Milan, Milan, Italy.

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Correspondence: Davide Mauri, MD, Daravelia 23, Roditsa-Lamias, TK 35100 Lamia, Greece. E-mail: dvd.mauri@gmail.com

breast cancer and have shown a beneficial effect on bone loss prevention.⁹ However, the overall clinical impact of bisphosphonates on the disease status of patients with early breast cancer is still unclear and controversial.^{10–12}

Considering the notable accumulation of randomized trials, the authors performed a meta-analysis of these to address whether the use of bisphosphonates in the adjuvant setting of breast cancer might have any effect on the natural course of the disease. Most specifically, they investigated for any beneficial effects on overall survival, prevention of disease recurrences, and occurrence of bone metastases.

Materials and Methods

Identification of Randomized Trials

The investigators searched PubMed, Cochrane Central Register of Controlled Trials, and ISI Web of Knowledge and collected all prospective randomised trials published as formal papers in peer-reviewed journals or as abstracts in the proceedings of major international congresses (ASCO Annual Meeting, San Antonio Breast Cancer Symposium, the European Cancer Conference) up to January 2009. No language or year restrictions were set. The following searching algorithm was used: [early OR adjuvant] AND [breast OR mammary] AND [tumour OR malign* OR carcinom* OR cancer] AND [bisphosphonates OR bisphosphonates OR clodronate OR pamidronate OR zoledronic acid OR ibandronate]. The reference lists of all studies included in the meta-analysis were examined for other relevant articles missed by the electronic searches.

Eligibility Criteria

Eligibility and exclusion criteria were prespecified. The analysis included all controlled trials that randomized patients with primary breast cancer to undergo adjuvant treatment with any or no bisphosphonate treatment. Trials fulfilling these criteria were considered eligible irrespective of the study sample size and the type and dosage of bisphosphonate used. Nonrandomized studies were considered ineligible.

When multiple records were related to the same study, end point data was extracted from the report with the longest follow-up (largest number of events) to avoid duplication of information in the meta-analysis calculations.

Data Extraction and Outcomes

Information recorded from each eligible trial included author names; journal; year of publication; number of centers involved; number of patients randomly assigned and analyzed per arm; years of patient enrollment; patient age; country of origin; tumor stage; menopausal status; hormonal receptor status; the exact regimens used; and dose and schedule and any additional treatments given to both arms. Study design items such as randomization mode, allocation concealment, and withdrawal descriptions were further recorded.

Two investigators extracted the relevant data, and consensus was reached on all outcomes. Authors of the original trials were contacted to identify any missing information for outcomes.

Primary outcome of this study was to evaluate whether the adjuvant use of bisphosphonates in breast cancer might have any effect on overall survival, disease recurrences, and occurrence of bone metastases compared with nonuse.

Furthermore, the investigators pooled estimates for distant metastases, visceral recurrences, and occurrence rate of locoregional relapses. Considering that treatment outcomes may vary among different types of bisphosphonates, the investigators performed subgroup analyses for deaths, disease recurrences, and bone metastases according to the bisphosphonate used (zoledronic acid/clodronate/pamidronate/risedronate).

Statistical Analysis

The number of events (deaths, disease recurrences, and bone metastases) and the number of nonevents in treated and control groups were retrieved from each primary study and 2x2 tables were constructed. Odds ratios (OR) of events for treated patients with respect to those who were not and the 95% CIs were calculated.

X² test was used to assess heterogeneity between studies (significance level set at 0.1). In the absence of heterogeneity, pooled estimates of ORs with their 95% CIs were calculated using the Mantel-Haenszel method. In the presence of heterogeneity, the DerSimonian and Laird random effects method was used to pool primary studies estimates. Statistical software STATA 8.0 (Stata Corporation, College Station, Texas) was used for statistical analysis.

Results

Eligible Studies

Literature search identified 21 potentially eligible trials^{10–30} evaluating the adjuvant use of bisphosphonates compared with no use. Most of the trials were designed to analyze safety data and the impact of bisphosphonates on bone loss;^{14–27,29} data suitable for our analyses could be retrieved from only 13 studies.^{10–12,21–30}

A flow chart indicating the identification of randomized controlled trials for inclusion in the meta-analysis is reported in Figure 1.

Characteristics of Trials

Table 1 presents the characteristics of the 13 trials that met the eligibility criteria for this study; 6 studies used the bisphosphonate zoledronic acid,^{11,21,22,25–27} 4 trials used clodronate,^{12,28–30} 2 trials used pamidronate,^{10,23} and 1 used risedronate.²⁴

Among these trials, 3 were double-blinded,^{23,24,30} 3 described in detail the mode of randomization,^{23,25,30} 2 reported allocation concealment,^{25,30} and 9 trials reported withdrawal description.^{10–12,21,22,24,25,28,29}

An intent-to-treat analysis was performed in all but 1 trial.²⁹

Outcomes

Meta-analysis included data on 511 deaths from 9 trials (5736 patients),^{11,12,21–24,27,28,30} 675 disease recurrences from 11 trials (5631 patients),^{11,12,21–28,30} and 545 bone metastases from 8 trials (5571 patients).^{10–12,21,23,27,28,30} Although the primary investigators were contacted, additional data could not be retrieved.

Pooled results showed no statistical significant differences with the use of bisphosphonates in early breast cancer versus nonuse for the overall number of deaths (summary OR, 0.708; 95% CI, 0.482–1.041; $P = .079$), disease recurrences (summary OR, 0.843; 95% CI, 0.602–1.181; $P = .321$), and bone metastases (summary OR, 0.925; 95% CI, 0.768–1.114; $P = .413$; Figure 2). A statistically significant heterogeneity was seen among trials in estimates for deaths and disease recurrences ($P = .034$ and $P = .016$ for

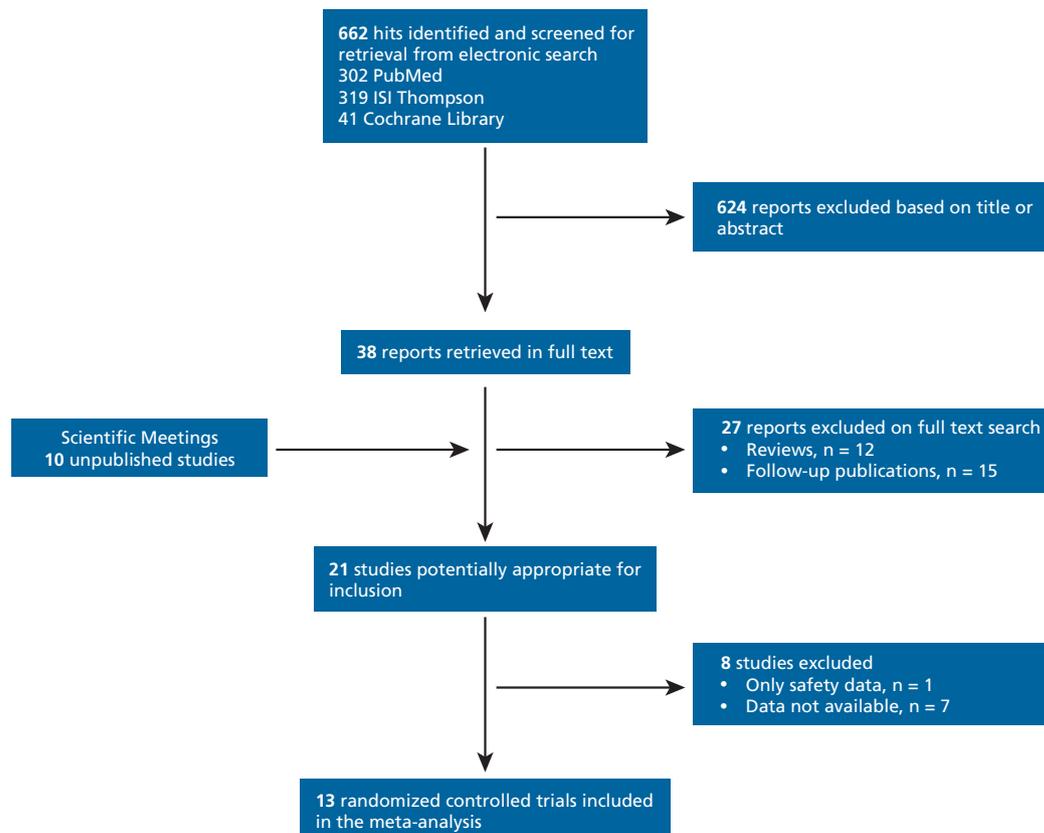


Figure 1 Flowchart diagram of study selection.

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Table 1 Characteristics of Eligible Trials

Study	Year	Intervention	Dosage of Treatment	Duration (y)	Number of Patients	Follow-Up (mo)	Reporting Modality
Kristensen et al. ¹⁰	2008	Pamidronate No treatment	150 mg orally twice daily	4	460 493	NA	Peer-reviewed manuscript
Gnant et al. ¹¹ (ABCSCG-12)	2009	Zoledronic acid No treatment	4 mg IV every 6 mo	3	899 904	47.8	Peer-reviewed manuscript
Diel et al. ¹²	2008	Clodronate No treatment	1600 mg daily	2	157 145	103	Peer-reviewed manuscript
Brufsky et al. ²¹ (Z-FAST)	2007	Upfront zoledronic acid Delayed zoledronic acid	4 mg IV every 6 mo	5	300 300	36 (Survival data retrieved from 12 mo ³⁴)	Conference abstract and peer-reviewed manuscript
Eidtmann et al. ²² (ZO-FAST)	2008	Upfront zoledronic acid Delayed zoledronic acid	4 mg IV every 6 mo	5	532 533	36 (Survival data retrieved from 24 mo ³⁵)	Conference abstracts
Fuleihan et al. ²³	2005	Pamidronate Placebo	60 mg IV every 3 mo	1	21 19	22.8 +/- 9.6 (mean) 24 +/- 9.6	Peer-reviewed manuscript
Delmas et al. ²⁴	1997	Risedronate Placebo	30 mg daily for 2 wk followed by 10 wk without drug	2	27 26	36	Peer-reviewed manuscript
Hershmann et al. ²⁵	2008	Zoledronic acid Placebo	4 mg every 6 mo	1	50 53	12	Peer-reviewed manuscript
Tevaarwerk et al. ²⁶	2007	Zoledronic acid No treatment	4 mg IV every 12 wk	1	26 23	12	Conference abstract
Schenk et al. ²⁷ (EZO-FAST)	2007	Upfront zoledronic acid Delayed zoledronic acid	4 mg IV every 6 mo	5	252 270	12	Conference abstract
Saarto et al. ²⁸	2004	Clodronate Placebo	1600 mg orally daily	3	139 143	120	Peer-reviewed manuscript
Vehmanen et al. ²⁹	2004	Clodronate No treatment	1500 mg intermittent IV for 7 consecutive cycles	NA	21 24	12	Peer-reviewed manuscript
Powles et al. ³⁰	2006	Clodronate Placebo	1600 mg orally daily	2	530 539	66	Peer-reviewed manuscript

Abbreviations: IV, intravenously; NA, not available.

Note: For 2 trials (Brufsky et al.²¹ and Eidtmann et al.²²), survival data could not be retrieved from the last publication. Survival data were thereafter extracted from previous reports.^{34,35}

heterogeneity, for deaths and disease recurrences, respectively). No statistically significant differences between study heterogeneity was observed for bone metastases.

Adjuvant treatment with bisphosphonates compared with no use was not associated with any statistically significant differences between arms for

type of recurrences, including distant metastases (7 trials, 4618 patients; OR, 0.896; 95% CI, 0.674–1.192; $P = .453$),^{11,12,21,23,27,28,30} visceral recurrences (4 trials, 1693 patients; OR, 1.051; 95% CI, 0.686–1.609; $P = .820$),^{12,23,28,30} and local relapses (5 trials, 4276 patients; OR, 1.056; 95% CI, 0.750–1.487; $P = .756$).^{11,21,27,28,30} No significant between-study

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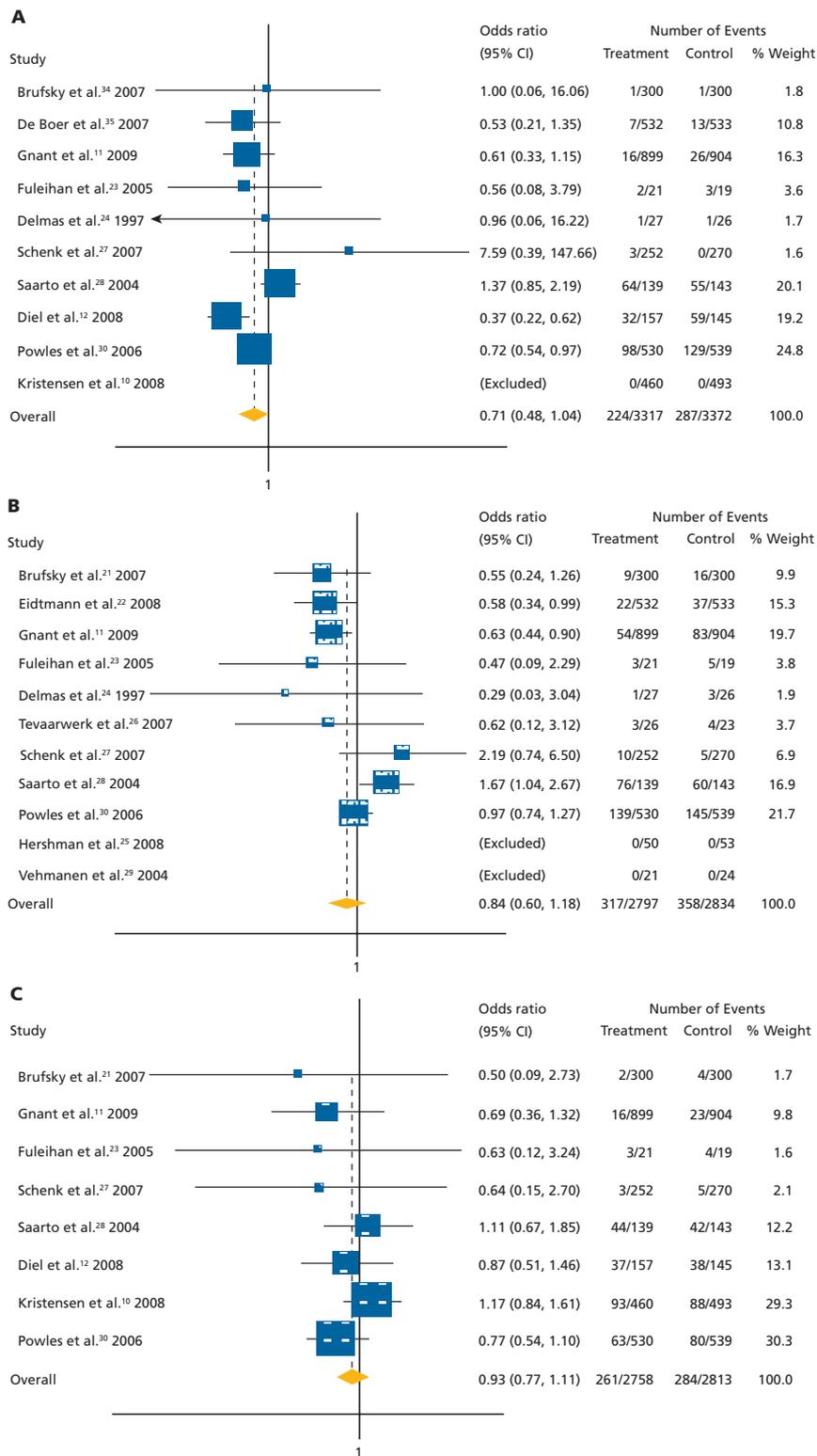


Figure 2 Forest plots of overall survival (A), disease recurrences (B), and bone metastases (C) between bisphosphonates and control group. Squares represent odds ratios and the size of the square is proportional to the trial size. Error bars represent 95% CIs. Kristensen et al.¹⁰ was excluded from overall survival analysis, and Hershman et al.²⁵ and Vehmanen et al.²⁹ were excluded from disease recurrences analysis because there were no events in both groups. For all figures, values < 1 indicate that bisphosphonate use has a beneficial effect in outcome.

heterogeneity was observed.

Subgroup analyses for disease recurrences according to the type of bisphosphonate used showed a statistically significant lower risk for disease recurrences with zoledronic acid (6 trials, OR, 0.675; 95% CI, 0.479–0.952; $P = .025$).^{11,21,22,25–27} Use of zoledronic acid was not associated with any significant difference in death rate (OR, 0.642; 95% CI, 0.388–1.063) or bone metastasis rate (OR, 0.661; 95% CI, 0.379–1.151; Table 2).

Discussion

This meta-analysis showed no significant differences in terms of overall survival, overall disease recurrence, distant and visceral relapses, local relapses, and bone metastases rates for the use or nonuse of bisphosphonates in the adjuvant treatment of early breast cancer. Therefore, the currently available randomized evidence does not support the hypothesis that use of adjuvant bisphosphonates may alter the natural course of breast cancer. Nonetheless, because a positive but nonsignificant trend was seen favoring bisphosphonates use for reduction in death rate (OR, 0.708; 95% CI, 0.482–1.041), further randomized studies are needed before the use of bisphosphonates in the adjuvant setting of breast cancer can be definitively supported or discouraged. Results of the ongoing phase III studies (NSABP B-34, AZURE, and SWOG 0307) will likely be crucial for better defining these issues in the next future.

Of interest, when different bisphosphonates agents were considered, the investigators noted that the use of zoledronic acid may be of benefit in decreasing the number of disease recurrences. However, these results should be interpreted cautiously because the statistical significance for this association was not adequately strong (OR, 0.675; 95% CI, 0.479–0.952; $P = .025$) and may be largely attributed to chance because of multitest analyses (1/21 analyses = 4.7%). Moreover, the observed decrease in the number of disease recurrences was not associated with a decrease in the occurrence of bone metastases. Conversely, the trend for overall survival improvement (OR, 0.642; 95% CI, 0.388–1.063; $P = .085$) noted in the zoledronic acid arm was far from reaching statistical significance. Studies with longer follow-up are needed before firm conclusions for survival setting can be made.

Overall, this meta-analysis is consistent with an earlier one by Ha and Li³¹ that examined the potential benefit of adjuvant oral clodronate in patients with early breast cancer. However, data from this early meta-analysis were feeble and unlikely to detect small differences between the arms because the study was relatively underpowered (only 3 trials were included involving 1653 patients and reflecting low number of events).³¹ Another limitation of the meta-analysis by Ha and Li³¹ was that the results could not be extrapolated to bisphosphonates other than clodronate.³¹

Therefore, this more recent meta-analysis is the first to present solid data on the use of bisphospho-

Table 2 Subgroup Meta-Analyses by Type of Bisphosphonates: Estimates of Effect in 23 Comparisons

Outcome	Bisphosphonate	Number of Studies	Number of Patients	OR (95% CI)	P Value
Death	Zoledronic acid	4	3990	0.642 (0.388–1.063)	.085
	Clodronate	3	1653	0.721 (0.384–1.351)	.307
	Pamidronate	2	993	0.561 (0.083–3.787)	.553
	Risedronate	1	53	0.926 (0.057–16.223)	.978
Disease recurrence	Zoledronic acid	6	4142	0.675 (0.479–0.952)	.025
	Clodronate	3	1396	1.226 (0.720–2.085)	.453
	Pamidronate	1	40	0.476 (0.095–2.295)	.348
	Risedronate	1	53	0.295 (0.029–3.036)	.305
Bone metastasis	Zoledronic acid	3	2925	0.661 (0.379–1.151)	.144
	Clodronate	3	1653	0.871 (0.676–1.122)	.286
	Pamidronate	2	993	1.139 (0.829–1.565)	.422

Abbreviations: CI, confidence interval; OR, odds ratio.

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nates in the adjuvant treatment of early breast cancer.

Several limitations must be considered when interpreting these results. First, this meta-analysis is based on published data and a meta-analysis of individual level data might define more clearly treatment benefits.³² Second, many trials identified were reported in abstract form only, making complete data difficult to extract for analyses. Third, small time-dependent differences may have been lost in these analyses because most of the included studies did not report hazard ratios for overall and disease-free survival; therefore, this meta-analysis was mainly based on OR statistics.³³ Finally, 7 studies were excluded from survival analysis because no survival data could be retrieved. Furthermore, all studies but one¹⁰ either were small or had short follow-up, and were therefore unlikely to invalidate the conclusions. Likewise, the large study by Kristensen et al.¹⁰ was unlikely to change the results because no overall survival differences were reported between the arms.

Allowing for these caveats, this meta-analysis showed that currently available randomized evidence does not support the hypothesis that using bisphosphonates in adjuvant treatment of early breast cancer likely alters the natural course of the disease, because it does not affect overall survival or disease relapse and does not prevent bone metastases. Nonetheless, patients undergoing bisphosphonate treatment seem to show a nonsignificant trend toward better outcomes. Until further evidence from new clinical trials becomes available, adjuvant bisphosphonates should not be routinely recommended as agents that may potentially alter the course of breast cancer when administered in the adjuvant setting.

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All authors had full access to all data in the study

and take responsibility for the integrity of the data and accuracy of the data analysis.

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