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The efficacy of zoledronic acid in breast cancer adjuvant therapy: A meta-analysis of randomised controlled trials

Tingting Yan [a,b,c], *Wenjin Yin* [a,b,c], *Qiong Zhou* [a,b], *Liheng Zhou* [a,b], *Yiwei Jiang* [a,b], *Yueyao Du* [a,b], *Zhimin Shao* [a,b], *Jinsong Lu* [a,b,*]

[a] *Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China*
[b] *Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China*

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ABSTRACT

Background: The effect of zoledronic acid in breast cancer adjuvant therapy concerning improvement of patient survival has yet to be confirmed. We performed a meta-analysis of published and unpublished randomised controlled trials with the aim of accurate evaluation between clinical outcome and the association of the addition of zoledronic acid to adjuvant therapy.

Methods: We searched PubMed (from 1966 to present) and online abstracts from the proceeding Annual Meetings of the American Society of Clinical Oncology (ASCO) (years 1992–2010) and online abstracts from San Antonio Breast Cancer Symposium (years 2004–2010). A total of five eligible studies including 3676 subjects and 3678 controls met our search criteria and were evaluated. Random and fixed-effects meta-analytical models were used where indicated, and between-study heterogeneity was assessed. The primary study end-points were the disease free survival (DFS). Secondary end-points were overall survival (OS), distant or loco-regional recurrence free survival and bone metastasis free survival.

Findings: Compared with the control arm, adjuvant breast cancer treatment with zoledronic acid did not significantly improve overall survival, disease free survival, bone metastasis free survival, distant and locoregional recurrence free survival. However, in the postmenopausal subgroup, the addition of zoledronic acid to standard therapy could significantly improve DFS (relative risk (RR) = 0.763, 95% confidence interval (CI) 0.658–0.884, $p < 0.001$) and reduce the risk of distant (RR = 0.744, 95% CI 0.611–0.906, $p = 0.003$) and locoregional recurrence (RR = 0.508, 95% CI 0.340–0.760, $p = 0.001$).

Interpretation: Adjuvant zoledronic acid did not significantly improve the prognosis of breast cancer patients. Due to the highly variable definitions of menopause utilised in different studies, we hypothesise that zoledronic acid may have a potential effect on postmenopausal patients. Additional studies are needed to evaluate the value of adjuvant treatment of zoledronic acid in premenopausal counterparts, differing disease stages and various pathological types of breast cancer.

* *Corresponding author at:* Department of Breast Surgery, Fudan University Shanghai Cancer Center, 399 Ling-Ling Road, Shanghai 200032, China. Tel.: +86 (21) 64175590/8710; fax: +86 (21) 64438653.
E-mail address: lujjss@yahoo.com.cn (J. Lu).
[c] These authors contributed equally to this work.
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1. Introduction

Breast cancer is the most common cancer in women and remains the second leading cause of cancer death among women worldwide.[1] Although major advances in cancer and adjuvant therapies for breast cancer have been achieved over the past 60 years, a substantial number of patients experience disease relapse. As the disease progresses, approximately 70% of all metastatic breast cancer patients develop bone metastasis, which in turn increases the risk of fracture through osteoclast-mediated destruction of the surrounding bone,[2] and is the cause of considerable morbidity. The median survival after first relapse in the bone is 20 months.[3] In addition to the effect of cancer on bone metabolism, cancer treatment induced bone loss (CTIBL) is a critical problem that includes hypoestrogenism secondary to gonadotropin-releasing hormone antagonists in premenopausal women or aromatase inhibitors in postmenopausal women.[4–7] Therefore, the treatment of both bone loss and bone metastasis is of great importance in order to improve quality of life and extend survival for breast cancer patients.

Bisphosphonates (BPs), as potent inhibitors of osteoclast-mediated bone resorption, have demonstrated proven clinical utility for the treatment of both postmenopausal osteoporosis[8] and bone metastasis.[9] The third-generation bisphosphonate zoledronic acid, characterised by an imidazole ring containing two nitrogen atoms, is the most potent of the available nitrogen containing BPs (N-BPs).[10] The Health Outcomes and Reduced Incidence with Zoledronic Acid One Yearly Pivotal Fracture Trial (HORIZON) showed that a single infusion of intravenous zoledronic acid could significantly improve bone density and reduce the risk of bone fractures in postmenopausal women with osteoporosis.[11] Additionally, multiple clinical trials have demonstrated that zoledronic acid effectively prevents CTIBL and increases bone mineral density (BMD) above baseline levels.[12–15]

Interestingly, the true effect of zoledronic acid seems to have a wider spectrum. Preclinical data have revealed a direct anti-tumour role for zoledronic acid which may act through the inhibition of tumour cell adhesion, invasion and proliferation as well as acting to induce apoptosis in multiple human tumour cell lines.[16] However, no such effect has been observed in thousands of breast cancer patients. Recently, several randomised controlled trials[17–19] have been reported on adjuvant zoledronic acid treatment, although the results were somewhat controversial. The Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG 12) and Zometa-Femara Adjuvant Synergy Trial (ZO-FAST) were in concordance regarding the addition of zoledronic acid to adjuvant endocrine therapy, which significantly improved the disease-free survival (DFS) of breast cancer patients,[20] whereas Coleman and colleagues[18,20] reported on the AZURE (Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer) trial at the 33th SABCS (San Antonio Breast Cancer Symposium) last December that adjuvant use of zoledronic acid failed to improve DFS. In the neoadjuvant subgroup of the AZURE, the addition of zoledronic acid to neoadjuvant chemotherapy could significantly reduce the residual invasive tumour size at surgery ($p = 0.006$); however, there was no significant difference in pathological complete response (pCR) ($p = 0.146$).[21] Thus, we performed a meta-analysis in order to obtain a more precise understanding of the role of zoledronic acid in the adjuvant therapy for breast cancer patients.

2. Methods

2.1. Publication search

The electronic database PubMed (from 1966 to the present) and online abstracts from the proceeding Annual Meetings of the American Society of Clinical Oncology (ASCO) (years 1992–2010) and online abstracts from SABCS (years 2004–2010) were searched by investigators. The following algorithm was used to perform the search: 'adjuvant', 'breast cancer', and 'zoledronic acid' or 'zometa'. The citation list associated with all the studies retrieved in the search was used to identify other potentially relevant publications. Review articles were also scanned to find additional eligible studies. The final search was updated on the 13th December, 2010. The search results were then screened according to the following inclusion criteria: (a) phase III prospective randomised trial, (b) zoledronic acid used in the adjuvant setting for breast cancer, (c) inclusion of sufficient data to allow for the estimation of a relative risk (RR) with a 95% confidence interval (95% confidence interval (CI)) of DFS and OS and (d) English language publications. If multiple publications of the same trial were retrieved, or if there was a case overlap between publications, only the most recent publication (the most informative) was included. Non-randomised studies were excluded, as were letters to the editor, reviews, abstracts containing insufficient detail to meet the inclusion criteria, articles published in a book and papers published in a language other than English.

2.2. Data extraction

The following data were collected from each of the included studies: first authors' surname, year of publications, number of patients randomly assigned and analysed per arm, menopausal status, the exact regimens used and the corresponding doses and schedules. We also recorded the median duration of follow-up. The outcome measures were based on the intention-to-treat analysis (ITT). Two of the authors of the present study (T.T.Y. and W.J.Y.) independently and carefully extracted the information indicated from all eligible publications. All discrepancies were addressed by a third author (J.S.L.) until a consensus was achieved on every single item. The primary study end-points were the DFS. Secondary end-points were OS, distant or loco-regional recurrence free survival and bone metastasis free survival.

2.3. Statistical analysis

Relative risk with a 95% confidence interval (95% CI) was used to estimate the value of zoledronic acid in breast cancer adjuvant therapy. The heterogeneity assumption was calculated using the chi-square based Q-test ($p < 0.10$ was considered significant)[22] or the I-square statistic to examine the extent of between-study heterogeneity (considered large for I^2 values

of 50–74% and very large for I^2 values of 75% and higher).[23] Data were combined according to both the fixed-effects model (Mantel–Haenszel's method) and random-effects (DerSimonian and Laird's method) model.

Funnel plots and Egger's tests were performed to investigate a potential publication bias. Sensitivity analyses were used to estimate the influence of individual studies on the summary effect. Statistical software STATA 10.0 (Stata Corporation, College Station, TX, United States of America (USA)) was used for statistical analysis. All *P*-values are two-sided.

3. Results

3.1. Description of eligible studies

Based on the search strategy, a total of five trials containing 7354 breast cancer patients were deemed eligible according to the inclusion criteria for the present analysis. All the studies were multicentre prospective clinical trials. Among these trials, the patients of Z-FAST, ZO-FAST and E-ZO-FAST trials[18,19,24] were postmenopausal women with hormone-responsive early breast cancer, whereas the ABCSG-12 trial[20] included premenopausal women with endocrine-responsive early breast cancer treated with ovarian suppression goserelin who were thus considered to be postmenopausal patients for the purposes of the analysis. The AZURE trial[25] enrolled both postmenopausal and non-postmenopausal breast cancer patients, and subgroup analysis was performed according to pre-specified menopause state. However, menopause was defined as more than five years post-menopause, which was different from other trials such as Z-FAST, ZO-FAST and E-ZO-FAST.

Z-FAST, ZO-FAST and E-ZO-FAST trials[18,19,24] delayed the use of zoledronic acid in the patients control arm when (1) post-baseline spine or hip *T*-score decreased to below –2.0; (2) a non-traumatic clinical fracture occurred; or (3) an asymptomatic fracture was discovered at the month-36 scheduled visit.[14] In contrast, the control arms of the ABCSG-12 and AZURE trials[20,25] were not treated with zoledronic acid. The characteristics of all studies included in the meta-analysis are shown in Table 1.

3.2. Impact of zoledronic acid on breast cancer in the adjuvant setting

This meta-analysis demonstrated that adjuvant use of zoledronic acid was not statistically significantly associated with improved overall survival (OS) (pooled RR = 0.900, 95% CI 0.608–1.334, $p = 0.601$, random-effect, significant studies heterogeneity *I*-squared = 53.1%, $p = 0.092$) (Fig. 1A); DFS (pooled RR = 0.851, 95% CI 0.651–1.113, $p = 0.239$, random-effect, significant studies heterogeneity *I*-squared = 67.3%, $p = 0.054$) (Fig. 1B); bone metastasis free survival (BMFS) (pooled RR = 0.833, 95% CI 0.672–1.032, $p = 0.094$, fixed-effect, no studies heterogeneity *I*-squared = 0.0%, $p = 0.580$) (Fig. 1C). E-ZO-FAST trial did not provide data regarding locoregional recurrence and distant recurrence data, thus we used the other four studies for meta-analyses. Moreover, no differences were observed in locoregional recurrence (pooled RR = 0.631, 95% CI 0.342–1.165, $p = 0.141$, random-effect, significant studies heterogeneity *I*-squared = 56.4%, $p = 0.192$) (Fig. 1D); distant recurrence (pooled RR = 0.917, 95% CI 0.799–1.053, $p = 0.221$, fixed-effect, no significant studies heterogeneity *I*-squared = 48.9%, $p = 0.118$) between the treatment and control arm. (Fig. 1E).

3.3. Subgroup analyses

According to menopausal status, all study subjects were categorised according to two subgroups: postmenopausal and

Table 1 – Characteristics of studies included for the meta-analysis.

Author (trial)	Year	Patients per arm	Regimen	Dosage of zoledronic acid (ZOL)	Combination therapy	Duration (years)	Median follow-up (months)
Coleman (Z-FAST)	2009	300 300	Immediate ZOL Delayed ZOL	4 mg IV every 6 months	Letrozol	5	54
Coleman (ZO-FAST)	2009	532 533	Immediate ZOL Delayed ZOL	4 mg IV every 6 months	Letrozol	5	48
LLombarto (E-ZO-FAST)	2009	263 264	Immediate ZOL Delayed ZOL	4 mg IV every 6 months	Letrozol	5	36
Gnant (The Austrian Breast and Colorectal Cancer Study Group Trial 12)	2010	900 903	ZOL No treatment	4 mg IV every 6 months	tamoxifen or Anastrozole	3	62
Coleman (Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer)	2010	1861 1678	ZOL No treatment	4 mg IV every 3–4 weeks for 6 doses, then 3 monthly × 8 and 6 monthly × 5	Standard treatment	5	59

Standard treatment: patients received adjuvant or neoadjuvant therapy according the guideline.

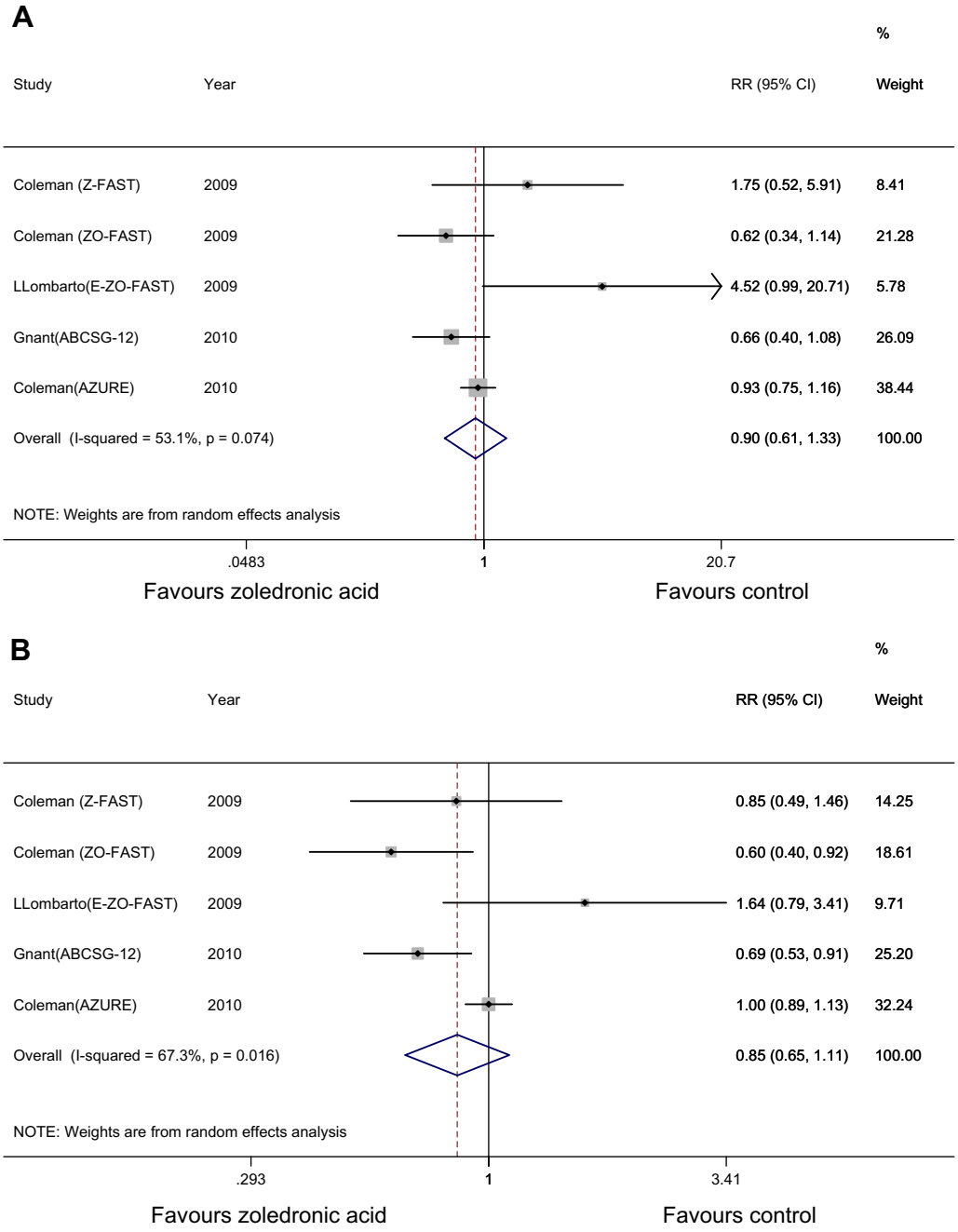

Fig. 1 – Forest plot from meta-analysis of overall survival (OS) (A), disease free survival (DFS) (B), bone metastasis free survival (C), loco-regional recurrence free survival (D) and distant recurrence free survival (E) for the adjuvant use of zoledronic acid as compared to control arm.

non-postmenopausal. The adjuvant use of zoledronic acid significantly improved DFS in postmenopausal patients (pooled RR = 0.763, 95% CI 0.658–0.884, $p < 0.001$, fixed-effect, significant studies heterogeneity I-squared = 34.4%, $p = 0.192$) (Fig. 2A), locoregional (pooled RR = 0.508, 95% CI 0·340–0.760, $p = 0.001$, fixed-effect, significant studies heterogeneity I-squared = 0.0%, $p = 0.614$) (Fig. 2B) and distant recurrence free survival (pooled RR = 0.744, 95% CI 0.611–0.906, $p = 0.003$, fixed-effect, significant studies heterogeneity I-squared = 0.0%, $p = 0.603$) (Fig. 2C). However, there was no significant improvement of OS (pooled RR = 0.811, 95% CI 0.552–1.192, $p = 0.286$, random-effect, significant studies heterogeneity I-squared = 49.7%, $p = 0.093$) (Fig. 2D) and BMFS (pooled RR = 0.798, 95% CI 0.586–1.085, $p = 0.149$, fixed-effect, significant studies heterogeneity I-squared = 0.0%, $p = 0.595$) compared to the control arm (Fig. 2E).

3.4. *Publication bias and sensitivity analysis*

The funnel plots and Egger's tests were performed to evaluate the publication bias of included studies. No publication bias was evident in the meta-analysis aside from analysis of dis-

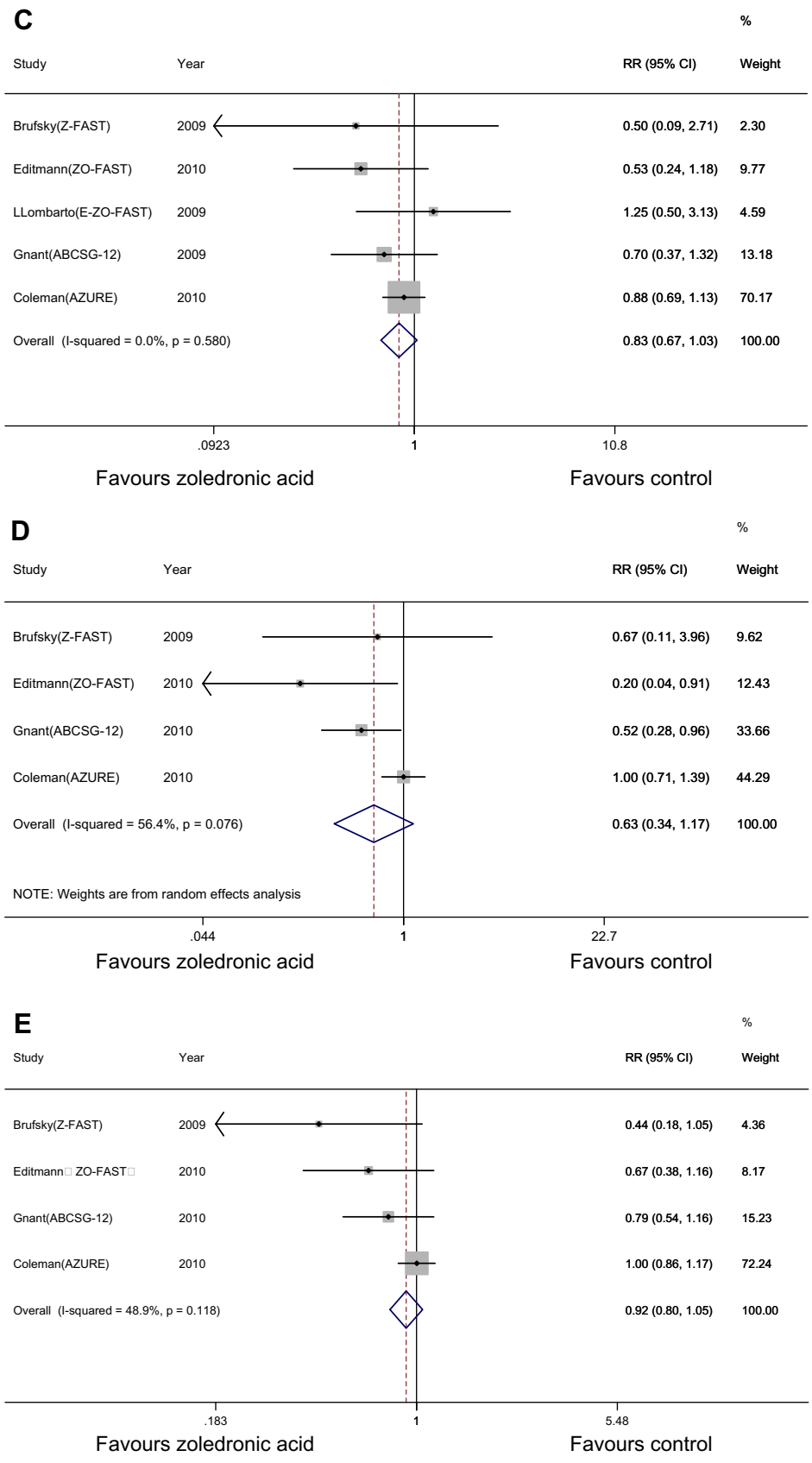

Fig. 1. *(continued)*

tant recurrence in the whole study populations ($t = -24.02$, $p = 0.002$). Therefore, we performed an influence analysis to estimate the influence of individual studies on the summary effect. The meta-analysis was not dominated by any single

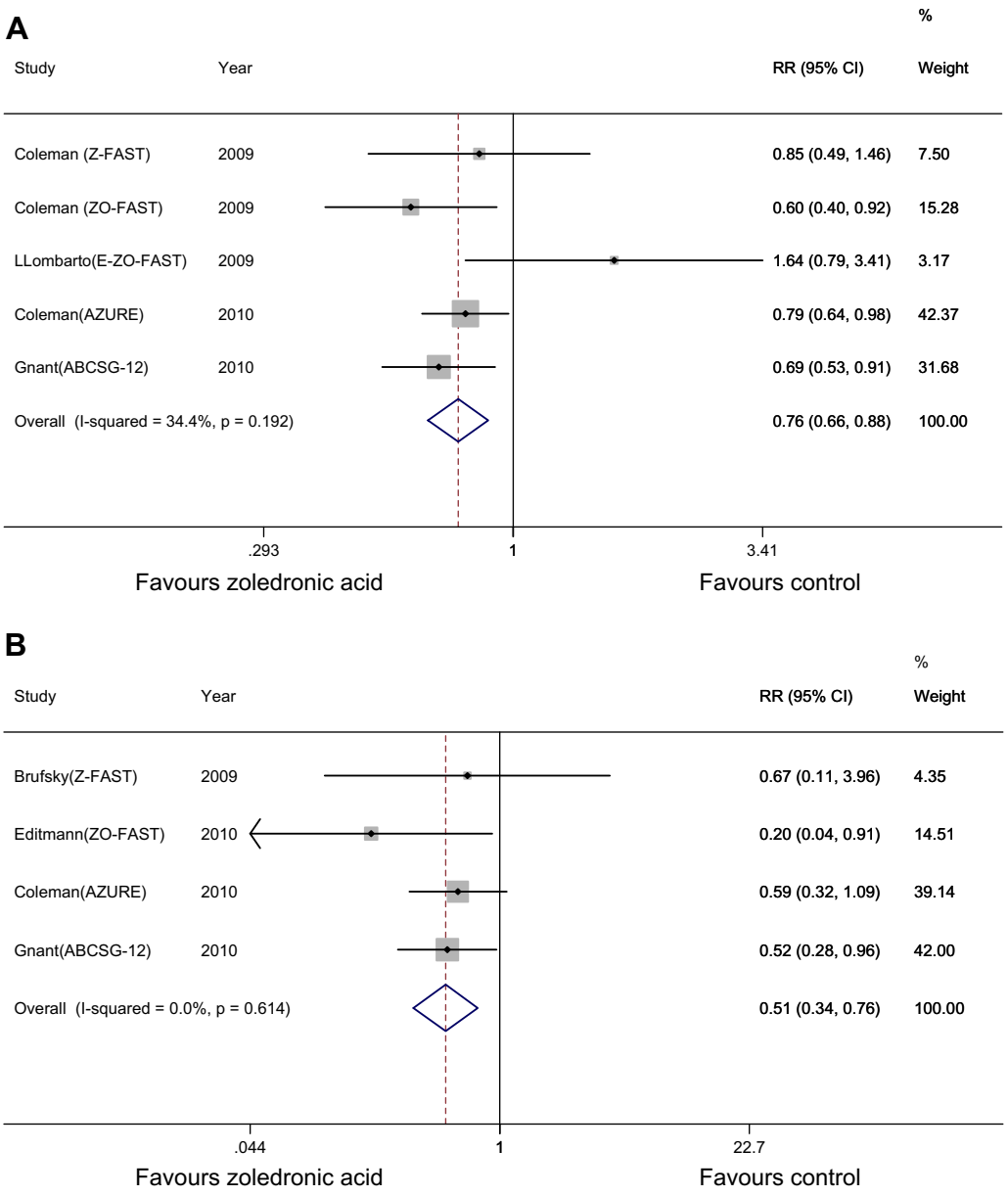

Fig. 2 – Forest plot from meta-analysis of disease free survival (DFS) (A), loco-regional recurrence free survival (B), distant recurrence free survival (C), overall survival (OS) (D) and bone metastasis free survival (E) for the adjuvant use of zoledronic acid as compared to control arm in postmenopausal patients.

study, and omission of any particular study exhibited no impact on the summary effect (Figures not shown).

4. Discussion

This meta-analysis indicated that zoledronic acid did not significantly improve the prognosis of breast cancer patients. Subgroup analysis suggested that adjuvant use of zoledronic acid could significantly improve DFS and reduced the risk of locoregional and distant recurrence in postmenopausal breast cancer patients. Due to the highly variable definition of menopause, we hypothesise that zoledronic acid potentially exhibits an effect in postmenopausal women. No effect was observed for the non-postmenopausal subjects without ovarian suppression. To the best of our knowledge, the present meta-analysis is the largest and up-to-date study to address whether the use of zoledronic acid in the adjuvant setting impacts the prognosis of breast cancer patients.

An extensive body of preclinical and clinical evidence has revealed that zoledronic acid exhibits direct and indirect anti-tumour effect. It has been previously demonstrated that zoledronic acid inhibits breast cancer cell lines growth[26] and prolongs survival in an animal breast cancer model,[27] and moreover zoledronic acid has been shown to enhance the anti-tumour effects of chemotherapeutic drugs both *in vitro* and *in vivo*.[28–31] Recently, a phase II randomised clinical trial testing the ability of zoledronic acid to eliminate disseminated tumour cells (DTCs) from the bone marrow in stage

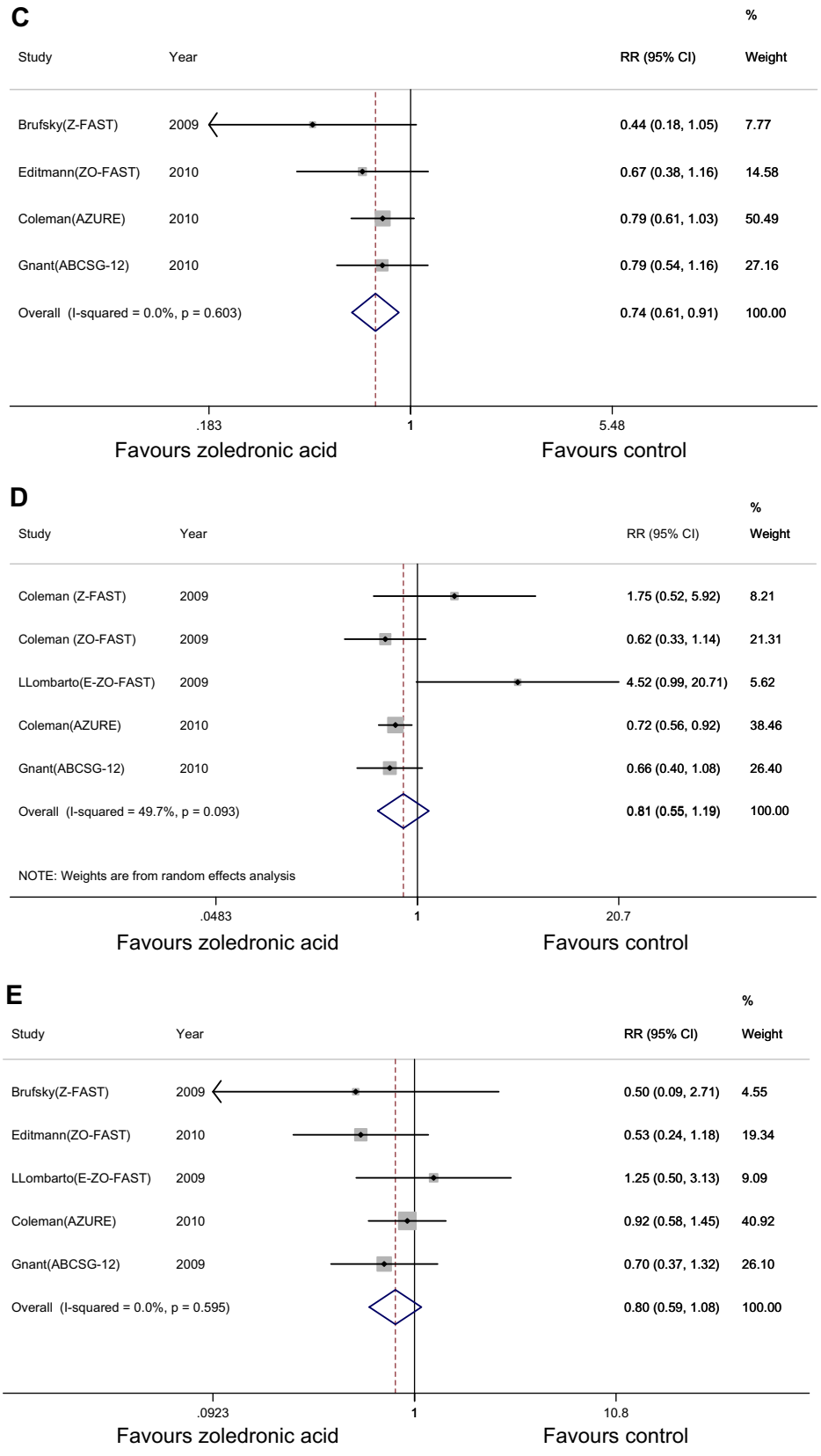

Fig. 2. *(continued)*

II–III newly diagnosed breast cancer patients was reported. The patients receiving zoledronic acid exhibited decreased detectable DTCs compared to patients who did not receive zoledronic acid with marginal statistical significance

($P = 0.054$).[32] Taken together, these reports suggest that a potential anti-tumour effect for zoledronic acid therapy in this subgroup analysis and indicate that there may be a significant benefit from zoledronic acid treatment regarding the prognosis of postmenopausal patients.

This meta analysis indicates that use of zoledronic acid as an adjuvant therapy does not improve DFS in a broad population of stage II/III breast cancer subjects. A highly significant heterogeneity of effect by menopausal status was observed in this study, however, the underlying mechanism is unclear and further research is needed. Using cell culture conditions that mimic the postmenopausal state, Neville-Webbe et al. determined that a synergistic interaction exists between zoledronic acid and letrozole for induction of apoptosis in breast cancer cells *in vitro*.[33] In concordance with our meta-analysis results, this potentially indicates that zoledronic acid may execute a significant anti-tumour effect in the low oestrogen microenvironment or in conjunction with anti-oestrogen endocrine therapy, and therefore postmenopausal patients are perhaps the most suitable females for treatment with zoledronic acid. Subgroup analysis of non-postmenopausal subjects in the AZURE trial demonstrated that the addition of zoledronic acid to standard treatment did not improve the prognosis for breast cancer patients. On the other hand, premenopausal patients with ovarian function suppression with goserelin in the ABCSG 12 trial indicated that zoledronic acid did improve DFS. This clinical evidence is potentially due to the low oestrogen microenvironment that perhaps enhances the effect of zoledronic acid. However, only AZURE trial provided not postmenopausal data, and more clinical trials are needed that focus on premenopausal patients without ovarian suppression in order to evaluate the value of the adjuvant use of zoledronic acid, particularly in oestrogen-responsive early stages of breast cancer.

There are certain limitations to the present meta-analysis. Firstly, some current follow-up data from such trials as AZURE and ABCSG 12 trial were reported only in conference abstracts, and therefore it is difficult to extract the complete, detailed data for this analysis until publication in a peer-reviewed journal. Although there were pre-specified subgroup analyses of menopause in the AZURE trial, the lack of data on subgroups of hormone receptor (ER/PR) status and adjuvant endocrine therapy, made it almost impossible for us to analyse the interaction between the effect of zoledronic acid and these parameters, particularly in the adjuvant endocrine therapy subgroup. All of the trials focused on ER/PR positive patients treated with different adjuvant endocrine therapy with the exception of AZURE trial, which enrolled both ER positive and negative patients. Secondly, some of the patients in the control group were those treated with delayed zoledronic acid, and therefore the effect of zoledronic acid might be underestimated in the treatment group. Thirdly, in the AZURE trial postmenopause was defined as $\geqslant 5$ years since or age > 60 years, and this does not reflect the commonly used definition of postmenopause. However, the survival outcome was unclear for patients with less than five years postmenopause. Fourthly, the use of gonadotropin-releasing hormone (GnRH) analogues made the patients in ABCSG 12 transiently postmenopausal. Nonetheless, part of the patients would restore menses after stopping use of GnRH analogues. Fifthly, the Z-series of trials were designed to access changes in BMD as a primary end-point, but not DFS. And the E-ZO-FAST trial had a large number of patients lost to follow up. Finally, these five clinical trials included in this meta-analysis utilised different methodology, did not use double-blindness, had no standard methodology for the measurement of relapse and had no standardised starting point. Any of these limitations could potentially affect the final results to a varying degree. Thus, this meta-analysis could be viewed as a hypothesis-generating study. Further prospective, randomised and double-blinded clinical trials are warranted to define the role of zoledronic acid in the adjuvant setting for breast cancer patients.

In summary, adjuvant treatment of zoledronic acid did not improve the prognosis of breast cancer patients. Due to the highly variable definition of menopause utilised in these five clinical trials, we hypothesise that zoledronic acid potentially has an effect on postmenopausal breast cancer patients. Although the exact mechanism has not been elucidated the addition of zoledronic acid to standard adjuvant therapy could improve breast cancer prognosis in postmenopausal patients. Further clinical research is required to clearly define the role of zoledronic acid in breast cancer patients, particularly in postmenopausal endocrine responsive breast cancer patients treated with aromatase inhibitors and premenopausal endocrine responsive breast cancer patients treated with ovarian suppression.

Contributors

T.T.Y. and W.J.Y. took part in the literature review, data extraction and analysis and writing of the manuscript. L.H.Z. took part in the literature review, data extraction and analysis and writing of the manuscript, Y.W.J. took part in the data analysis and interpretation, and provided scientific advice. Q.Z. and Y.Y.D. took part in conceptualisation, data interpretation. Z.M.S. took part in data interpretation and writing of the manuscript. J.S.L. took part in conceptualisation, data analysis and interpretation and writing of the manuscript, and provided scientific advice. All authors were involved in the decision to submit for publication.

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Conflict of interest statement

None declared.

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