REVIEW ARTICLE

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Effects of Bazedoxifene on Bone Mineral Density and Fracture in Post-Menopausal Osteoporotic Women: a Systematic Review and Meta-Analysis

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Abstract

Bazedoxifene (BZA) is a selective estrogen receptor modulator that reduces the risk of fracture and improves bone mineral density in post-menopausal women with osteoporosis. The aim of the present systematic review and meta-analysis was to investigate effects of BZA on bone mineral density (BMD) and fracture in post-menopausal osteoporotic women. We searched PubMed, Cochrane Central Register of Controlled Trials, Web of Sciences, Embase, and Scopus from until November 30, 2016. All randomized controlled trials that compared the effects of BZA on BMD and the incidence of vertebral and non-vertebral fractures in post-menopausal osteoporotic women compared with a control group were eligible for inclusion. Meta-analyses were conducted to calculate relative risk (RR) with 95% confidence interval (CI) for the association of BZA and vertebral and non-vertebral fractures compared with placebo. Nine randomized clinical trials met our inclusion criteria. Studies results showed that BZA significantly improves BMD, although we were not able to pool the results. Meta-analysis showed that the pooled effect of BZD on vertebral fracture was protective and significant (RR = 0.63; 95% CI 0.48, 0.83; $P = 0.001$). But pooled results did not show any association between taking BZD and the incidence of non-vertebral fracture (RR = 0.97; 95% CI 0.83, 1.13; $P = 0.683$). Evidence suggests that bazedoxifene is generally effective and safe in preventing bone loss and vertebral fracture in post-menopausal women with osteoporosis.

Keywords Bazedoxifene · Bone mineral density · Post-menopausal osteoporosis · Bone fracture

Introduction

Osteoporosis is a silent disease but its impacts are serious in public health [1–3]. There are approximately 200 million people with this disease in the world [3]. In the USA, an estimated two million osteoporotic fractures occur annually, resulting in more than half a million hospitalizations [1] and in the EU, it was estimated that in 2010, 6.6% of men and 22.1% of women aged over 50 years had osteoporosis, and that 3.5 million fractures occurred [4].

In post-menopausal women (PM), the level of endogenous estrogen decreases and leads to osteoporosis [5]. The characteristics of post-menopausal osteoporosis are low BMD and deterioration of bone structure, which is associated with an increased risk of hip, vertebral and non-vertebral fractures [6].

Bisphosphonates, hormone therapy, parathyroid hormone, denosumab, strontium ranelate (outside the USA), and selective estrogen receptor modulators (SERMs) are therapies currently used to treat and prevent osteoporosis [7, 8]. Each of these treatments has its unique benefits and complications and may not be appropriate for all women [8].

SERMs are a class of compounds that interact with estrogen receptors (ERs) and exert agonist or antagonist effects on ERs in a tissue-specific manner. Tamoxifen, a first-generation SERM, is able to maintain BMD in post-menopausal women. Raloxifene, a second-generation SERM, was used to prevent post-menopausal osteoporosis [9, 10]. BZD is a third-

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generation SERM that has been approved for the prevention and treatment of osteoporosis in post-menopausal women at increased risk for fractures [8, 11, 12].

There are several multicenter, national, and international randomized clinical trials (RCTs) that were conducted to show BZA effects post-menopausal osteoporosis in women. Our purpose was to systematically review the literature regarding the effect of BZA on BMD and the incidence of vertebral and non-vertebral fractures in post-menopausal osteoporotic women.

Methods

Databases and Search Strategy

We performed a literature search in PubMed, Cochrane Central Register of Controlled Trials, Web of Sciences, Embase, and Scopus from the 6th to 30th of November 2016. The search terms used are listed in Table 1.

Eligibility Criteria

Inclusion criteria included a focus on RCTs comparing the effects of BZA on BMD and the incidence of vertebral and non-vertebral fractures in post-menopausal osteoporotic women compared with a control group. We excluded narrative review articles, animal studies, and human cell and tissue culture studies. Also, irrelevant outcome measures, duplicate papers about the same study, and secondary analysis of previous trials were our exclusion criteria.

Study Selection

Two authors (MK and HM) reviewed the search results separately to find potentially eligible studies. The publications were sorted by titles and abstracts, and eligible studies were selected for full-text review. During this stage, all the irrelevant studies and duplicates were excluded (Fig. 1). Then, they independently assessed each of the selected articles for inclusion in the study using the inclusion and exclusion criteria previously mentioned.

Data Extraction

Data were extracted independently by two authors (MK and HM) and any discrepancies that arose were solved by a third author (NK). The following information was extracted: RCTs phase (II, III), age of participants, sample size, a summary of inclusion/exclusion criteria, years since menopause, types of interventions in active and control group, study duration, incidence of vertebral and non-vertebral fractures, mean percent change in lumbar spine BMD, and adverse events.

Quality Assessment

The methodological quality of the studies was assessed according to the standardized form of the CONSORT 2010 statement for randomized controlled trials (www.consort-statement.org) [13] by MK and HM independently.
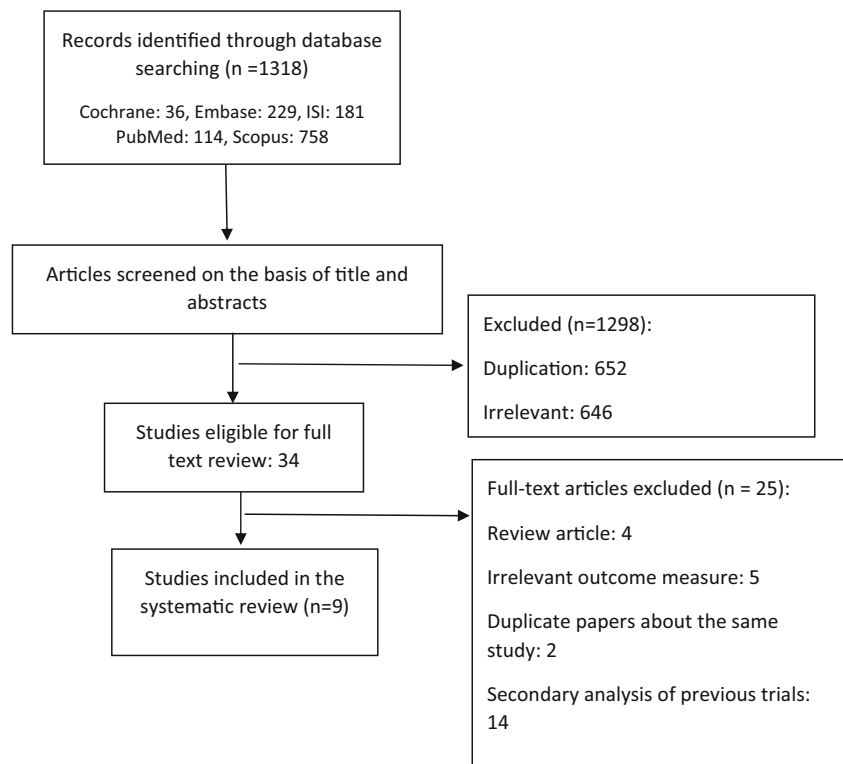
Statistical Analysis

Due to different intervention and the different measure for mean percent change in lumbar spine BMD, we only reported each study result and did not report pooled mean percent change in BMD. Relative risk (RRs) with 95% confidence intervals (CIs) estimated for the association of BZA and vertebral and non-vertebral fractures compared with placebo were pooled. Adverse events data were also summarized with RRs.

Heterogeneity between studies was assessed using both the I^2 statistic with a cutoff of $\geq 50\%$ and the χ^2 test with a P value < 0.10, to define a significant degree of heterogeneity. Also, in order to investigate the existence of publication bias, we used the Egger regression asymmetric test with 10% significant levels. Stata 14 (StataCorp, College Station, TX) was used for all the analyses and graphics. A two-sided P value ≤ 0.05 was considered statistically significant, if not otherwise specified.

Table 1 Search strategy

1	bazedoxifene acetate OR duavee OR conjugated estrogens OR Bazedoxifene
2	"bone mass" OR "bone density" OR mineralization OR bone demineralization OR "pathologic bone demineralization" OR BMD OR Bone Density Conservation agents OR "Bone Resorption" OR "metabolic bone disease "OR "bone loss" OR "bone quality" OR "bone strength" OR "bone mineral density" OR "bone mineral content" OR "Osteoclastic Bone Loss" OR "metabolic bone disease "
3	fracture OR "bone fracture" OR "bones broken" OR "fragility fracture" OR "fragile bone"
4	Postmenopausal Osteoporosis OR Post-Menopausal Osteoporosis OR Postmenopausal Bone Loss OR Perimenopausal Bone Loss OR Osteoporosis OR Post-Traumatic Osteoporosis OR Senile Osteoporosis OR Involution Osteoporosis OR Age-Related Osteoporosis OR Age Related Osteoporosis OR Age-Related Bone Loss OR Age Related Bone Loss OR Prevention of osteoporosis OR Treatment of osteoporosis
5	1 AND 2 AND 3 AND 4

Fig. 1 Flow diagram of studies
identified for the systematic
review

Records identified through database
searching (n =1318)

Cochrane: 36, Embase: 229, ISI: 181
PubMed: 114, Scopus: 758

Articles screened on the basis of title and
abstracts

Excluded (n=1298):

Duplication: 652

Irrelevant: 646

Studies eligible for full
text review: 34

Full-text articles excluded (n = 25):

Review article: 4

Irrelevant outcome measure: 5

Duplicate papers about the same
study: 2

Secondary analysis of previous trials:
14

Studies included in the
systematic review (n=9)

Results

A total of 1318 articles were retrieved from five scientific
databases (Cochrane Central Register of Controlled Trials,
Embase, ISI Web of Sciences, PubMed, and Scopus). These
papers were screened on the basis of title and abstract, and
1298 were excluded because they were irrelevant or dupli-
cates. Thirty-four studies were eligible for full-text review.
Twenty-five of these were subsequently excluded according
to the criteria (Fig. 1). Finally, nine studies were selected for
the systematic review of mean percent change in lumbar spine
BMD [7, 11, 14–20]. Four of these studies reported incidence
of vertebral and non-vertebral fracture compared with place-
bo, and they were included in the meta-analysis [7, 11, 14, 19].
One study was a phase II clinical trial [14], and to describe the
long-term efficacy and safety of BZD, Silverman et al. con-
tinued the RCT on healthy post-menopausal women with os-
teoporosis for up to 7 years and reported findings in three
papers [7, 11, 19]. Table 2 outlines the main study
characteristics.

BMD

All of nine studies assessed BMD of the lumbar spine chang-
ing after taking BZA 20 mg compared with the control group.
Furthermore, in three studies BZD was taken with conjugated
estrogens (CEs) [15, 17, 18]. Study results showed that BZA
significantly improves BMD [7, 11, 14–20], even in Lindsay

et al.'s study, BMD increased significantly more in BZA/CE
groups compared with controls [15]. In studies that women
had been treated with only BZD [7, 11, 14, 16, 19, 20], mean
percent change of lumbar spine BMD from baseline was
greater than those that women had been treated with BZD/
CE [15, 17, 18]. In three studies, women took BZD 40 mg
[14, 16, 19], and in Lindsay et al.'s study, they took BZD 40/
CE [15]. According to study results, both BZD doses 20 and
40 mg had a similar effect on BMD. Efficacy information is
summarized in Table 3.

Vertebral and Non-Vertebral Fracture

Only four studies reported the efficacy of BZD 20 mg/day on
the incidence of vertebral and non-vertebral fracture. We esti-
mated the RR for each study. In all of the four studies, RR of
BZD on vertebral fracture was protective and significant.
Also, pooling under a fixed-effects model showed a signifi-
cant association (RR = 0.63; 95% CI 0.48, 0.83; $P = 0.001$)
(Fig. 2), with no evidence of statistical heterogeneity across
studies ($I^2 = 0.0\%$; $P = 0.798$). In order to find an estimation
about publication bias, a Begg's funnel plot was drawn and the
result showed a no significant publication bias (Egger test, $t = -0.33$, $P = 0.772$).

Non-vertebral osteoporosis- related fractures were defined
as fractures that were sustained after minimal or low-impact
trauma, such as falling from standing height [19]. We ob-
served no association between taking BZD 20 mg/kg and

Table 2 Extracted data from original studies

Author	Types of participants	Years since menopause	Age (mean)	Sample size	No. of centers/countries	Types of interventions	Control group	Study duration	Outcome
Itabashi et al. [14]	Postmenopausal women, with an intact uterus, 85 years of age or younger	2	63.43	375 subjects; 311 completed	17 sites in Japan	BZA 20 or 40 mg/day	Placebo	2 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral and non-vertebral fractures
Silverman et al. [19]	Healthy postmenopausal women between the ages of 55 and 85 years with osteoporosis	2	66.40	7492 subjects; 4991 completed	206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the USA	BZA 20 or 40 mg/day	RLX 60 mg/day or placebo	3 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral and non-vertebral fractures
Silverman et al. [7]	Women who completed the 3-year multicenter outpatient core study.	2	68.97	3146 subjects; 2503 completed	206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the USA	BZA 20 and 40 mg/day	Placebo	2 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral and non-vertebral fractures
Palacios [11]	Women who completed extension I	2	65.7	1530 subjects; 1301 completed	206 sites in Asia-Pacific countries, Canada, Europe, Latin America, South Africa, and the USA	BZA 20 mg/day	Placebo	2 years	Change from baseline in BMD of the lumbar spine, incidence of vertebral, and non-vertebral fractures
Xu et al. [20]	healthy women, 45 years or older without osteoporosis	1	57.24	487 subjects; 450 completed	China, South Korea, and Taiwan	BZA 20 mg/day	Placebo	6 months	Change from baseline in BMD of the lumbar spine
Miller et al. [16]	healthy women 45 years of age and older	1	57.6	1583 subjects; 1113 completed	101 site in Canada, Europe, and the USA	BZA 20 or 40 mg/day	RLX 60 mg or placebo	2 years	Change from baseline in BMD of the lumbar spine relative to placebo
Lindsay et al. [15]	healthy postmenopausal women aged 40–75 years with an intact uterus	1–5 & more than 5	58.52	3397 subjects; 2315 completed	94 sites in the United States, Europe, and Brazil	BZA (20 or 40 mg/day) each with CE (0.625 or 0.45 mg/day)	RLX 60 mg/day or placebo	2 years	Change from baseline in BMD of the lumbar spine
Mirkin et al. [17]	postmenopausal women aged 40–65 years with an intact uterus	1	54.42	1061 subjects; 850 completed	62 sites in the USA and two sites in Argentina	BZA 20 mg/day and CE 0.45 mg/day or BZA 20 mg/day and CE 0.625 mg/day	CE 0.45 mg/day and MPA 1.5 mg/day or placebo	1 year	Change from baseline in BMD of the lumbar spine
Pinkerton et al. [18]	healthy postmenopausal women aged 40–65 years with an intact uterus	1	54.15	590 subjects; 512 completed	166 sites in the United States, Europe, Australia, New Zealand, Argentina, Chile, Colombia, and Mexico	BZA 20 mg/day and CE 0.45 mg/day or BZA 20 and 0.625 mg/day, BZA 20 mg/day	CE 0.45 mg/day and MPA 1.5 mg/day or placebo	1 year	Change from baseline in BMD of the lumbar spine

Table 3 Mean percent change of lumbar spine BMD from baseline

Author		BZA 20 mg	%SE	BZA 40 mg	%SE	CE 0.45 mg and MPA 1.5 mg	%SE	Placebo	%SE
Itabashi et al. [14]		2.43	0.35	2.74	0.36	–	–	− 0.65	0.35
Silverman et al. [19]		2.21	0.16	2.38	0.16	–	–	0.88	0.16
Silverman et al. [7]		2.16	–	2.08[a]	–	–	–	1.46	–
Palacios et al. [11]		2.73	0.51	2.95[a]	0.39	–	–	2.19	0.49
Miller et al. [16]		1.41[b]	1.65	1.49[b]	1.64	–	–	–	–
Xu et al. [20]		0.41	0.09	–	–	–	–	−0.32	0.1
Lindsay et al. [15]	More than 5 years since menopause[c]	1.04[d]	0.25	0.57[d]	0.24	–	–	−1.08	0.25
		0.94[e]	0.25	0.51[e]	0.25				
	1–5 years since menopause[c]	0.55[d]	0.29	0.77[d]	0.29	–	–	−1.41	0.28
		1.01[e]	0.28	0.62[e]	0.28				
Mirkin et al. [17]		0.80[d]	0.24	–	–	2.22	0.37	−1.56	0.35
		0.80[e]	0.24						
Pinkerton et al. [18]		0.07	0.40	–	–	1.30	0.39	−1.28	0.28
		0.6[d]	0.27						
		0.24[e]	0.29						

[a] The group received BZA 40 mg in the first 3 years of study (Silverman et al. 2008) and received BZA 20 mg in this study

[b] Change from baseline in BMD of the lumbar spine relative to placebo

[c] Annual percent change

[d] BZA + CEs 0.625 mg

[e] BZA + CEs 0.45 mg

the incidence of non-vertebral fracture (RR = 0.97; 95% CI 0.83, 1.13; $P = 0.683$) in fixed model results (Fig. 3), and there was no significant heterogeneity across studies ($I^2 = 0.0\%$; $P = 0.846$). Also, we assessed publication bias. There was no publication bias according to the Egger test and Begg's funnel plot in evaluating the effect BZD 20 mg/day on non-vertebral fracture (Egger test, $t = 0.14$, $P = 0.903$).

Averse Events

Seven articles contained safety data and the number of patients with AEs or any AE, and the number of patients with serious AEs or most common AEs were reviewed [8, 14, 16, 19, 20]. Meanwhile, Palacios et al. [11] reported AEs up to 7 years and contains AEs of Silverman et al. studies [7, 19] as
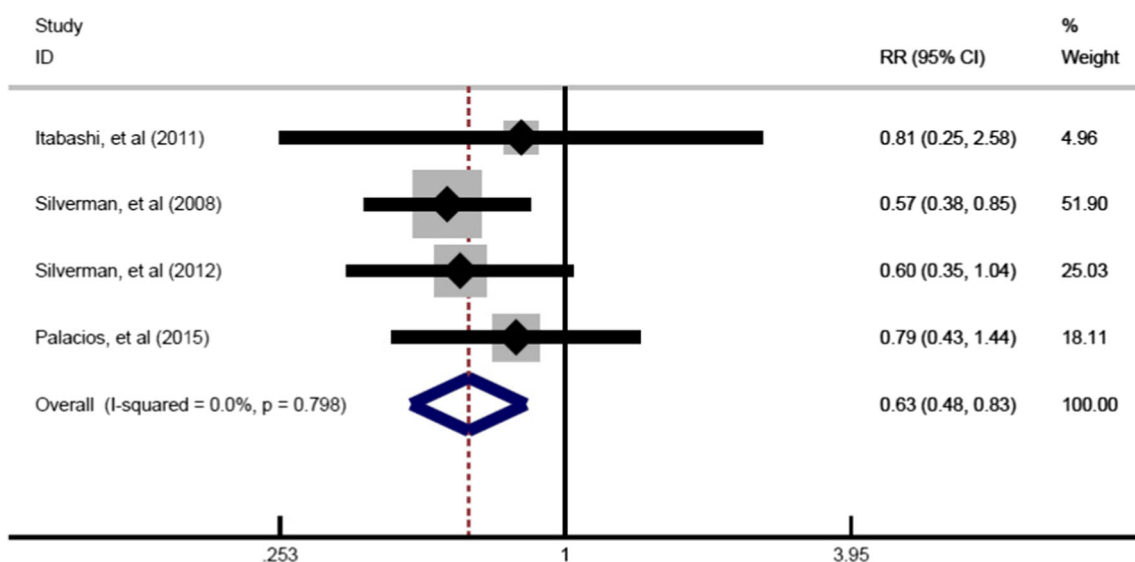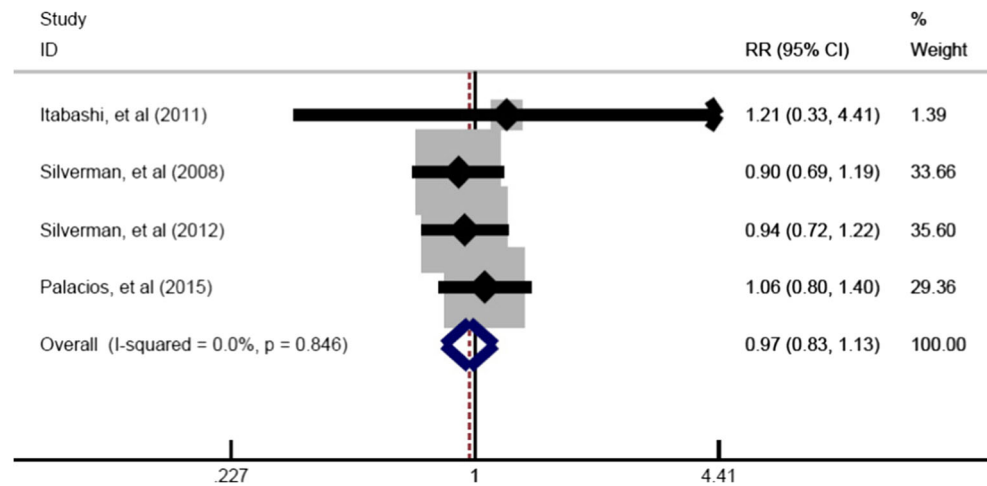

Fig. 2 Forest plot of the association between BZD 20 mg/day and vertebral fracture. The center of each square indicates the relative risk of the study, and the horizontal lines indicate 95% CIs. The diamond indicates pooled estimates

Fig. 3 Forest plot of the association between BZD 20 mg/day and non-vertebral fracture. The center of each square indicates the relative risk of the study, and the horizontal lines indicate 95% CIs. The diamond indicates pooled estimates

Study ID	RR (95% CI)	% Weight
Itabashi, et al (2011)	1.21 (0.33, 4.41)	1.39
Silverman, et al (2008)	0.90 (0.69, 1.19)	33.66
Silverman, et al (2012)	0.94 (0.72, 1.22)	35.60
Palacios, et al (2015)	1.06 (0.80, 1.40)	29.36
Overall (I-squared = 0.0%, p = 0.846)	0.97 (0.83, 1.13)	100.00

well. Two studies were removed from the meta-analysis because their interventions were different (CE and BZD together). Therefore, we used 4 studies for the meta-analysis of BZD 20 mg/day and AEs. Table 4 shows the adverse effects in detail. Side effects such as endometrial carcinoma and hyperplasia, vaginal hemorrhage, breast cancer, myocardial infarction, stroke, and hot flushes were evaluated in these studies. In the BZD 20 mg/day group compared with placebo group, incidence of infectious and parasitic disease, headache, endometrial disorder, endometrial carcinoma, and hyperplasia decreased significantly, but the incidence of deep vein thrombosis, venous thromboembolism, and hot flushes increased significantly. As well as in the BZD 40 mg/day group, the risk of infectious and parasitic disease, arthralgia, and hot flushes increased significantly in comparison to the placebo group.

As shown in Fig. 4, there was no association between taking BZD 20 mg/day and incidence of any AE ($RR_{fixed\ effect}$ = 1.00; 95% CI 0.98, 1.02; P = 0.683). Heterogeneity across these studies was low (I^2 = 22.7%; P = 0.275). In Fig. 5, pooled RRs show no association between BZD 20 mg/day and serious AEs ($RR_{fixed\ effect}$ = 1.00; 95% CI 0.98, 1.02; P = 0.683) either.

Discussion

Immediately after the menopause, bone mass decreases and increased bone turnover is associated with increased bone loss and the risk of fractures. This led to the use of estrogen therapy which was shown to prevent bone loss at menopause and to reduce the risk of important fragility fractures [21, 22]. Due to the adverse effects of estrogen in extra-skeletal organs, SERMs has been considered for treating osteoporosis in both sexes. SERMs contain non-steroidal synthetic compounds that have been developed to retain the beneficial effects of estrogens while eliminating unwanted side effects [21, 23]. This group includes raloxifene, arzoxifene, tamoxifene,

lasofoxifene, and bazedoxifene [21–23]. Bazedoxifene acetate, the first of the third-generation SERMs, is chemically distinct SERM that was developed using stringent preclinical screening parameters, including favorable effects on the skeleton and lipid metabolism and demonstrable breast and uterine safety [16, 24]. BZA is available for the treatment of post-menopausal women at risk for, or presenting with, osteoporosis in Europe, Korea, and Japan [11, 12].

Due to its favorable preclinical effects, BZA has been selected to combine CE resulting in CE/BZA as a new progestin-free hormone therapy option for alleviating estrogen deficiency symptoms in post-menopausal women [12]. This treatment has shown the reduction of the incidence of serious adverse effect such as s myocardial infarction, cystic or fibrocystic breast diseases, venous thromboembolism, and back pain [15, 17, 18]. Also BZD/CE approved in the United States for the treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of post-menopausal osteoporosis, and in the European Union for the treatment of estrogen deficiency symptoms in post-menopausal women with a uterus for whom treatment with progestin-containing therapy is not appropriate [25].

The objective of this study was to compare the efficacy of BZD versus placebo in terms of lumbar spine BMD improvement and prevention of vertebral and non-vertebral fracture in the post-menopausal women with an intact uterus. We also summarized the adverse events of BZD.

In this systematic review, studies showed that the BZD is effective on lumbar spine BMD improvement in healthy post-menopausal women. Even in three studies which the treatment group had taken BZD with CE, lumbar spine BMD increased from baseline compared to the placebo group [15, 17, 18]. Studies showed that the efficacy of BZA remained after 5 and 7 years of treatment. [7, 11, 19] Calcium and vitamin D supplementation may have contributed to this increase [11] as well. The increase in BMD with BZD and BZA/CE can be due to the decrease in bone turnover and bone loss as

Table 4 Incidence and relative risk of adverse reaction with BZA

Adverse events	BZD 20 mg/day			BZD 40 mg/day			BZD 20 mg/day + CE 0.45			BZD 20 mg/day + CE 0.625			Placebo
	No. of trials	Number/total (%)	Relative risk (95% CI)	No. of trials	Number/total (%)	Relative risk (95% CI)	No. of trials	Number/total (%)	Relative risk (95% CI)	No. of trials	Number/total (%)	Relative risk (95% CI)	Number/total (%)
Any AE	5	4441/5544 (80.1)	0.870 (0.856, 0.885)	2	427/459 (93.0)	1.011 (0.984, 1.038)	2	715/806 (88.1)	0.964 (0.938, 0.99)	2	725/823 (88.09)	0.957 (0.931, 0.983)	2964/3220 (92.05)
Any serious AE	5	1030/5544 (18.5)	1.096 (0.997, 1.204)	2	42/459 (9.1)	0.54 (0.4, 0.727)	2	31/806 (3.8)	0.227 (0.159, 0.323)	2	28/823 (3.4)	0.201 (0.138, 0.291)	546/3220 (16.95)
Any treatment emergent AEs	3	647/1643 (39.3)	0.494 (0.463, 0.528)	1	292/319 (91.5)	1.149 (1.1, 1.201)	2	673/806 (83.5)	1.048 (1.005, 1.093)	2	685/823 (83.2)	1.045 (1.002, 1.09)	346/1195 (79.66)
Death	3	52/4310 (1.2)	1.714 (1.026, 2.864)	1	3/319 (0.9)	1.336 (0.399, 4.471)	2	0/806 (0.0)	0.086 (0.005, 1.419)	2	0/823 (0.0)	0.084 (0.005, 1.389)	346/2841 (0.703)
Discontinuations due to AEs	4	783/4453 (17.5)	1.216 (1.092, 1.355)	2	70/459 (15.2)	1.055 (0.836, 1.331)	2	64/806 (7.9)	0.549 (0.427, 0.706)	2	58/823 (7.0)	0.487 (0.375, 0.634)	446/2981 (14.45)
Infectious and parasitic disease	2	142/1234 (11.5)	0.352 (0.285, 0.435)	1	85/140 (60.7)	1.856 (1.525, 2.259)	0	—	—	—	—	—	246/379 (32.71)
Arthralgia	2	35/1234 (2.8)	0.597 (0.342, 1.042)	1	16/140 (11.4)	2.406 (1.263, 4.586)	0	—	—	—	—	—	246/379 (4.749)
Back pain	2	51/373 (13.6)	1.105 (0.794, 1.537)	1	21/140 (15.0)	1.212 (0.775, 1.895)	1	43/445 (9.7)	0.781 (0.548, 1.112)	1	58/474 (12.2)	0.989 (0.718, 1.361)	246/614 (12.37)
Leg cramps	3	573/5171 (11.0)	1.119 (0.970, 1.291)	1	38/319 (11.9)	1.203 (0.872, 1.659)	0	—	—	—	—	—	346/2434 (9.901)
Headache	3	72/1464 (4.9)	0.356 (0.269, 0.471)	1	13/140 (9.3)	0.671 (0.39, 1.157)	1	59/445 (13.2)	0.958 (0.717, 1.282)	1	75/474 (15.8)	1.144 (0.876, 1.494)	346/853 (13.83)
Endometrial disorder	1	3/1091 (0.3)	0.164 (0.037, 0.729)	0	—	—	0	—	—	—	—	—	146/239 (1.673)
Endometrial carcinoma/-hyperplasia	3	7/4992 (0.1)	0.353 (0.132, 0.946)	1	0/140 (0.0)	0	0	—	—	—	—	—	346/2264 (0.397)
Ovarian cyst	2	3/1464 (0.2)	0.350 (0.088, 1.397)	1	0/140 (0.0)	0	2	4/806 (0.5)	0.848 (0.24, 2.994)	2	6/823 (0.7)	1.245 (0.403, 3.847)	246/1025 (0.585)
Vaginal hemorrhage	3	54/4131 (1.3)	0.760 (0.511, 1.130)	1	0/140 (0.0)	0	1	11/445 (2.5)	1.437 (0.747, 2.764)	1	5/474 (1.1)	0.613 (0.244, 1.54)	346/2499 (1.720)
Breast cancer	3	24/4131 (0.6)	1.117 (0.570, 2.189)	1	0/140 (0.0)	0	1	2/445 (0.4)	0.864 (0.196, 3.815)	1	0/474 (0.0)	0	346/2499 (0.520)
Cystic or fibrocystic breast disease	2	44/3901 (1.1)	0.708 (0.456, 1.100)	1	5/140 (3.6)	2.242 (0.892, 5.633)	1	3/361 (0.8)	0.522 (0.161, 1.687)	1	1/349 (0.3)	0.18 (0.025, 1.309)	246/2197 (1.593)
Breast pain	3	120/5222 (2.3)	0.925 (0.690, 1.241)	1	2/140 (1.3)	0.575 (0.142, 2.323)	1	15/445 (3.4)	1.357 (0.783, 2.353)	1	13/474 (2.4)	1.104 (0.615, 1.983)	346/2738 (2.483)
Pulmonary embolus	2	7/4080 (0.2)	0.941 (0.276, 3.213)	1	1/319 (0.3)	1.72 (0.193, 15.342)	0	—	—	—	—	—	246/2195 (0.182)

Table 4 (continued)

| Adverse events	BZD 20 mg/day			BZD 40 mg/day			BZD 20 mg/day + CE 0.45			BZD 20 mg/day + CE 0.625			Placebo
	No. of trials	Number/total (%)	Relative risk (95% CI)	No. of trials	Number/total (%)	Relative risk (95% CI)	No. of trials	Number/total (%)	Relative risk (95% CI)	No. of trials	Number/total (%)	Relative risk (95% CI)	Number/total (%)
Myocardial ischemia	1	27/3758 (0.7)	1.042 (0.539, 2.014)	0	–	–	0	–	–	–	–	–	146/1885 (0.689)
Myocardial infarction	5	24/5544 (0.4)	0.942 (0.488, 1.819)	2	1/459 (0.2)	0.474 (0.063, 3.598)	1	1/445 (0.2)	0.489 (0.064, 3.711)	1	0/474 (0.0)	0.221 (0.013, 3.704)	546/3048 (0.459)
Ischemic stroke	1	28/3758 (0.7)	1.080 (0.561, 2.081)	0	–	–	0	–	–	–	–	–	146/1885 (0.689)
Hemorrhagic stroke	2	5/4080 (0.1)	0.538 (0.156, 1.856)	1	0/319 (0.0)	0	0	–	–	–	–	–	246/2195 (0.227)
Indeterminate stroke	1	9/3758 (0.2)	2.257 (0.488, 10.436)	0	–	–	0	–	–	–	–	–	146/1885 (0.106)
TIA	1	19/3758 (0.5)	2.383 (0.812, 6.993)	0	–	–	0	–	–	–	–	–	146/1885 (0.212)
DVT	2	22/4080 (0.5)	2.959 (1.021, 8.576)	1	0/319 (0.0)	0	0	–	–	–	–	–	246/2195 (0.182)
Retinal vein thrombosis	2	4/4080 (0.1)	0.717 (0.161, 3.202)	1	0/319 (0.0)	0	0	–	–	–	–	–	246/2195 (0.136)
Hot flushes	4	584/5314 (10.9)	1.572 (1.339, 1.845)	2	77/459 (16.8)	2.399 (1.873, 3.073)	0	–	–	–	–	–	446/2574 (6.993)
VTE	3	32/4131 (0.8)	2.069 (1.019, 4.202)	1	0/140 (0.0)	0	2	2/806 (0.2)	0.663 (0.146, 3.019)	2	0/823 (0.0)	0.154 (0.009, 2.632)	346/2671 (0.374)
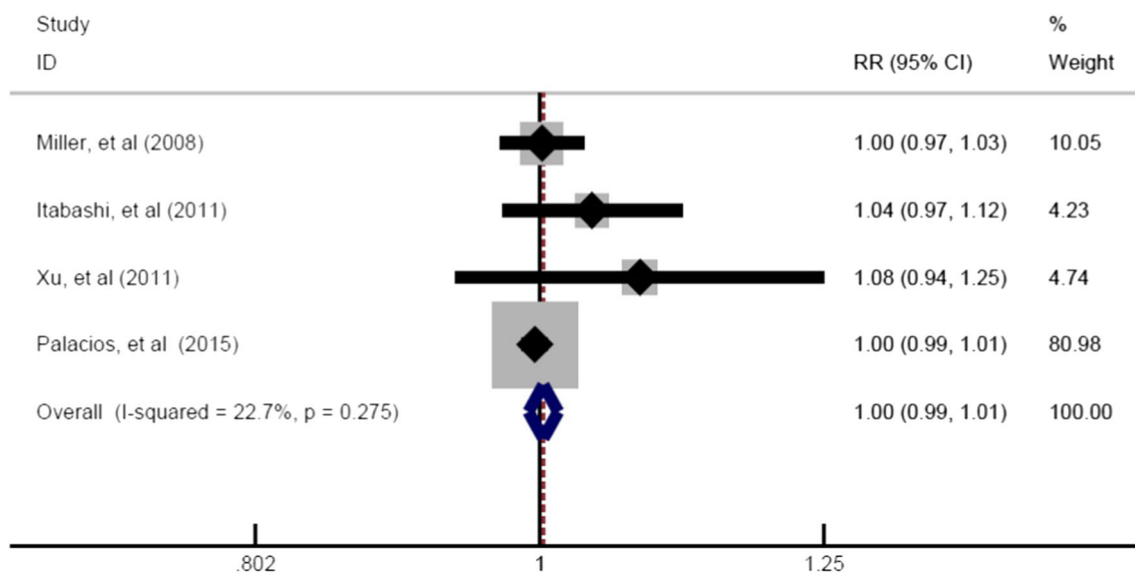
Fig. 4 Pooled relative risk of any AEs associated with BZD 20 mg/day

demonstrated by a significant decrease in osteocalcin and C-telopeptide plasma levels versus the baseline and placebo group levels [15, 26].

Another important result of this review was the assessment of the efficacy of BZD in preventing vertebral and non-vertebral fractures. Meta-analysis results showed significant reductions in the relative risks of vertebral fractures. After treatment with BZD 20 mg/day, the overall risk of vertebral fracture was around 30%. But BZA had no effect on the incidence of non-vertebral fractures. Even in a higher-risk subpopulation, there were 30% reductions in the risk of non-vertebral fracture at 7 years versus placebo, but they were not statistically significant [11]. Our findings are consistent with other meta-analysis that reported the vertebral fractures relative risk reduction for BZD was − 0.23 versus ibandronate,

− 0.17 versus alendronate, and − 0.06 versus risedronate. They concluded that bazedoxifene is comparable to bisphosphonates in the overall post-menopausal osteoporosis (PMO) population and is at least as effective as bisphosphonates for preventing vertebral fractures among higher-risk PMO patients [6].

Changes in BMD have been shown to predict improvements in fracture risk reduction [7, 27], because reductions in bone turnover and/or improvements in bone properties/microarchitecture have been contribute to enhanced bone strength with osteoporosis treatments [11, 23, 28]. Significant reductions in bone turnover markers were seen after taking BZD [7, 14, 16, 18–20]. According to expert opinion, BZD could be considered as a second-line therapy for women < 65–70 years of age, where other drug such as
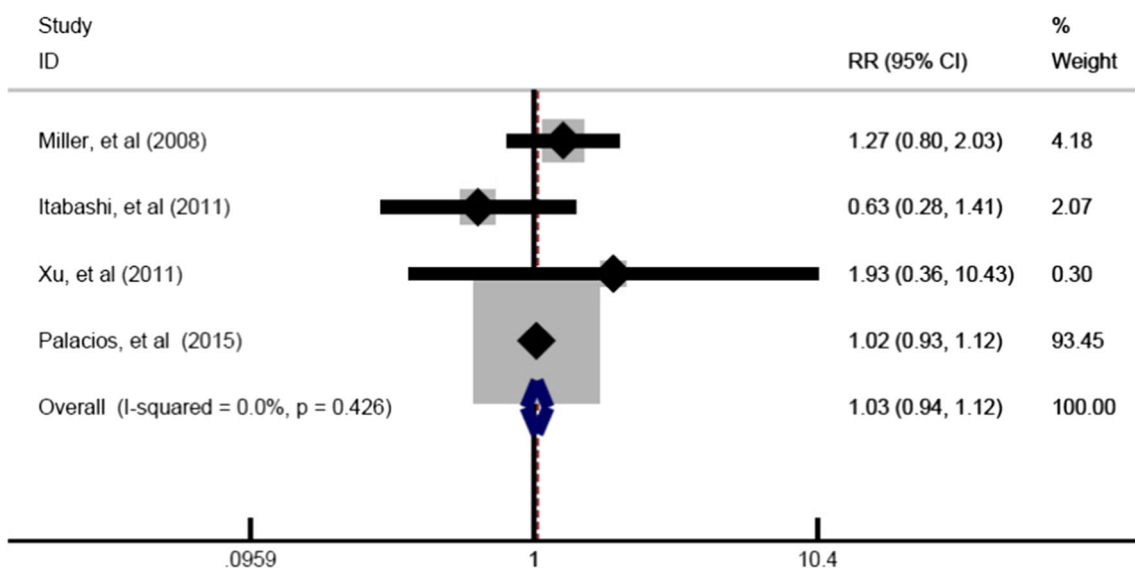

Fig. 5 Pooled relative risk of serious AEs associated with BZD 20 mg/day

bisphosphonates are contraindicated or not well tolerated [24, 29]. Furthermore, bazedoxifene could also have its place as a first-line therapy for younger post-menopausal patients in the management of menopause and prevention of osteoporosis [24].

We also assessed publication bias with the Egger test, Begg's funnel plots, and trim tests. There was no evidence of small study effects (publication bias) according to visual inspection of the funnel plots and the Egger test.

The meta-analyses did not show any significant association between AEs and BZD 20 mg/day versus the placebo group. Also, in two studies in which the treatment group had taken CE and BZA, the treatment was safe and well tolerated [17, 18]. The overall rates of AEs, serious AEs, and discontinuations due to AEs were similar among the bazedoxifene and placebo groups. According to results of RCTs, BZA treatment showed no evidence of breast or endometrial stimulation. The incidence of endometrial carcinoma was significantly lower in the BZA group compared with the placebo group at 7 and at 5 years. The incidence of breast carcinoma was low and similar for BZA and placebo at 7 years [7, 11].

Conclusions

In summary, these results suggest that bazedoxifene is a safe and effective therapy for post-menopausal women with an intact uterus, seeking treatment for post-menopausal symptoms and prevention of bone loss. It significantly improves lumbar spine BMD, reduces incidence of vertebral fracture, and is well tolerated in post-menopausal women with osteoporosis.

Compliance with Ethical Standards

Conflict of Interest   The authors declare that they have no conflict of interest.

Ethical Approval   The article does not contain any studies with human or animal subjects performed by any of the authors.

Informed Consent   The article does not contain any studies with human subjects performed by any of the authors.

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