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Review Article

Safety of the cathepsin K inhibitor odanacatib in postmenopausal women with osteopenia or osteoporosis: a meta-analysis

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Abstract: Cathepsin K, a cysteine protease expressed in osteoclasts, degrades type 1 collagen. Odanacatib selectively and reversibly inhibited cathepsin K and rapidly decreased bone resorption in preclinical and clinical studies. By searching the PubMed, Embase, OVID and Science Direct databases, we conducted a meta-analysis to examine the safety of odanacatib in postmenopausal women with osteoporosis. Studies were pooled, and the relative risk (RR) and its corresponding 95% confidence interval (CI) were calculated. Version 12.0 STATA software was used for statistical analysis. Six relevant articles were included for this meta-analysis study. We observed that the incidence of fracture in postmenopausal women treatment with odanacatib is significantly lower than that with placebo (RR=0.34, 95% CI=0.16-0.71, $P_{heterogeneity}$<0.750, I^2=0%), however, there was no significant difference in the incidence of AEs, SAEs, discontinuations due to AEs and skin AEs. In conclusion, compared to placebo, odanacatib treatment significantly reduced the risk of relative fracture, however, there was no difference between the safety of odanacatib and placebo. Odanacatib is a valuable new option for the treatment of postmenopausal osteoporosis in women and may be used as a first-line treatment in future.

Keywords: Odanacatib, osteoporosis, meta-analysis, randomized controlled trials

Introduction

Menopause is associated with decreased estrogen levels and subsequent change in bone density [1]. This relationship is the result of bone remodeling imbalance, which occurs with aging and menopause. Bone loss that follows this imbalance, leading to a change in bone structure and a reduction in bone mineral density (BMD) [2, 3]. Osteoporosis is a significant and increasingly important clinical conditions. An estimated 30% of all postmenopausal women in the United States and Europe have osteoporosis, the prevalence of this situation is expected to increase as the world population ages, lead to increased health care costs [4]. With the ageing of population aging, China was experiencing a growing epidemic of osteoporosis. About one third of the women aged 60-69 years and half of those aged 70 years or over have osteoporosis [5].

Cathepsin K is a key enzyme expressed predominantly in osteoclasts, which involved in the degradation of organic bone matrix. Inhibiting bone resorption found in animal models and human deficient for cathepsin K has identified this enzyme as a suitable target, intervention for small molecules with potential as a therapeutic agent in the treatment of osteoporosis [6]. Odanacatib (ODN) is a non-basic selected cathepsin K inhibitor with good pharmacokinetic parameters such as long half-life, minimal in vitro metabolism, as well as oral bioavailability. In preclinical studies, ovary removal of monkeys and rabbits by ODN showed significantly inhibited bone resorption markers along with increase of bone mineral density (BMD) [7, 8]. The effects of ODN treatment in comparison with those of other antiresorptive agents (e.g. bisphosphonates and denosumab) were significant differences. ODN showed specific effects on trabecular versus cortical bone formation, resulting in significant increases in cortical thickness and periosteal bone formation in ovary removal of monkeys whereas trabecular bone formation was reduced [7, 8].

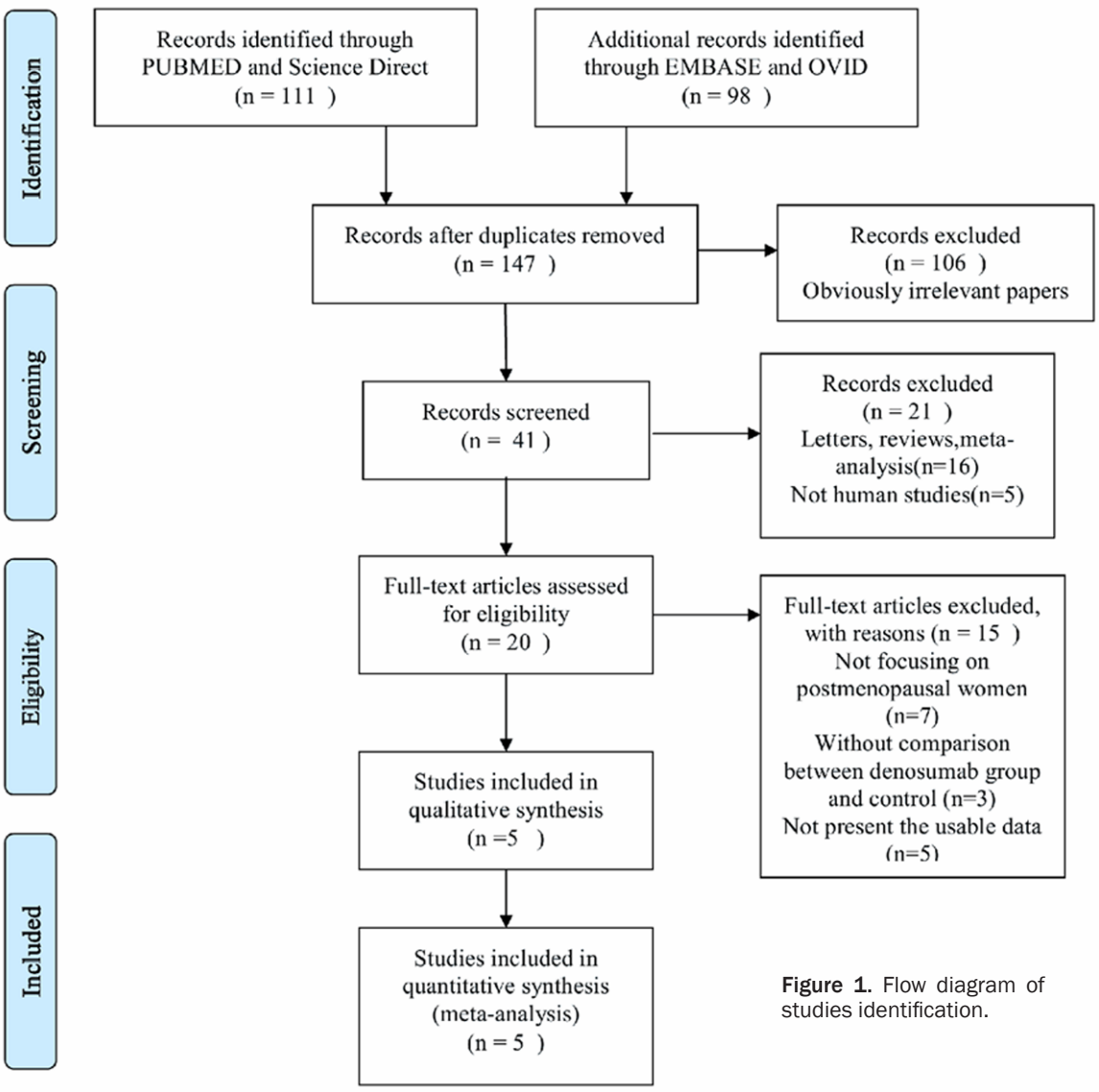


Figure 1. Flow diagram of studies identification.

In recent years, several randomized controlled trials (RCTs) have been conducted to evaluate the safety of ODN in the treatment of postmenopausal osteoporosis in women [9-13]. However, the results were not consistent. Therefore, the safety of ODN for the treatment of postmenopausal osteoporosis in women should be systematically evaluated. Here in this study, we performed a meta-analysis of eligible studies to assess the safety of ODN in postmenopausal women with osteoporosis.

Materials and methods

Search strategy

PubMed, Embase, OVID, Science Direct databases were searched for RCTs using the following terms and their combinations: 1) odanacatib, 2) osteopenia or osteoporosis, and 3) postmenopausal women. And the last research was updated on Nov. 2015. All searched studies were screened and their references were retrieved to obtain other related articles. Then we downloaded the relevant papers and further screened to identify potentially eligible studies.

Selection criteria

The inclusion criteria included: 1) eligibility is limited to randomized controlled trials (RCT) in postmenopausal women with osteoporosis; 2) study compared the safety of odanacatib in treatment of osteoporosis. The exclusion criteria included: 1) clinical cases; 2) literature revi-

Table 1. Characteristics of randomized controlled trials included in this meta-analysis

Authors/ year of publication	Drug, dose and No randomized		Duration (months)	Safety
	Odanacatib	Placebo		
Bone/2010 [9]	50 mg (n=78)	N=83	24	Total AEs, SAEs, Discontinuations due to AEs, Skin AEs
Eisman/2011 [10]	50 mg (n=97)	N=92	36	Total AEs, SAEs, Discontinuations due to AEs, Skin AEs
Langdahl/2012 [11]	50 mg (n=100)	N=41	60	Total AEs, SAEs, Discontinuations due to AEs, Skin AEs
Bonnick/2013 [12]	50 mg (n=122)	N=121	24	Total AEs, SAEs, Discontinuations due to AEs, Skin AEs, incidence of fracture
Brixen/2013 [13]	50 mg (n=109)	N=105	24	Skin AEs, incidence of fracture

Total AEs: Total Adverse events; SAEs: Serious Adverse events; NA: Not available.

ews; 3) commentaries; 4) letters to the editor; 5) experimental studies.

Data extraction

All the available data were extracted from each study by two investigators independently according to the inclusion criteria listed above. The safety outcomes included: (1) Adverse events (AEs); (2) Serious adverse events (SAEs); (3) Skin AEs; (4) Discontinuations due to AEs; (5) Fractures.

Statistical analysis

All results summarized using STATA Software (version 12, StataCorp, College Station, TX). We calculated the risk ratio (RR) and 95% confidence intervals for dichotomous data. Preliminary analysis using a fixed effect model (Mantel-Haenszel method), if there are study heterogeneity (P<0.1), using a random effects model. By Begg's funnel plot and Egger's test to assess publication bias visually evaluated symmetry (P<0.05 was considered statistically significant).

Results

Characteristics of the studies

There were 147 papers relevant to the search words. Subsequently, 106 irrelevant articles were excluded. The remaining articles were systematically reviewed, and 20 articles qualified for full-text reading. After full-text reading, 15 articles were deemed unsuitable and were therefore excluded, and 5 articles were identified to be included for qualitative analysis. Finally, 5 studies composed of 948 osteoporosis patients were incorporated into the current meta-analysis. The flow chart of selection of studies and reasons for exclusion is presented in **Figure 1**. The main characteristics of the eligible studies were shown in **Table 1**.

Quantitative synthesis

The five studies were included in the meta-analysis of adverse events.

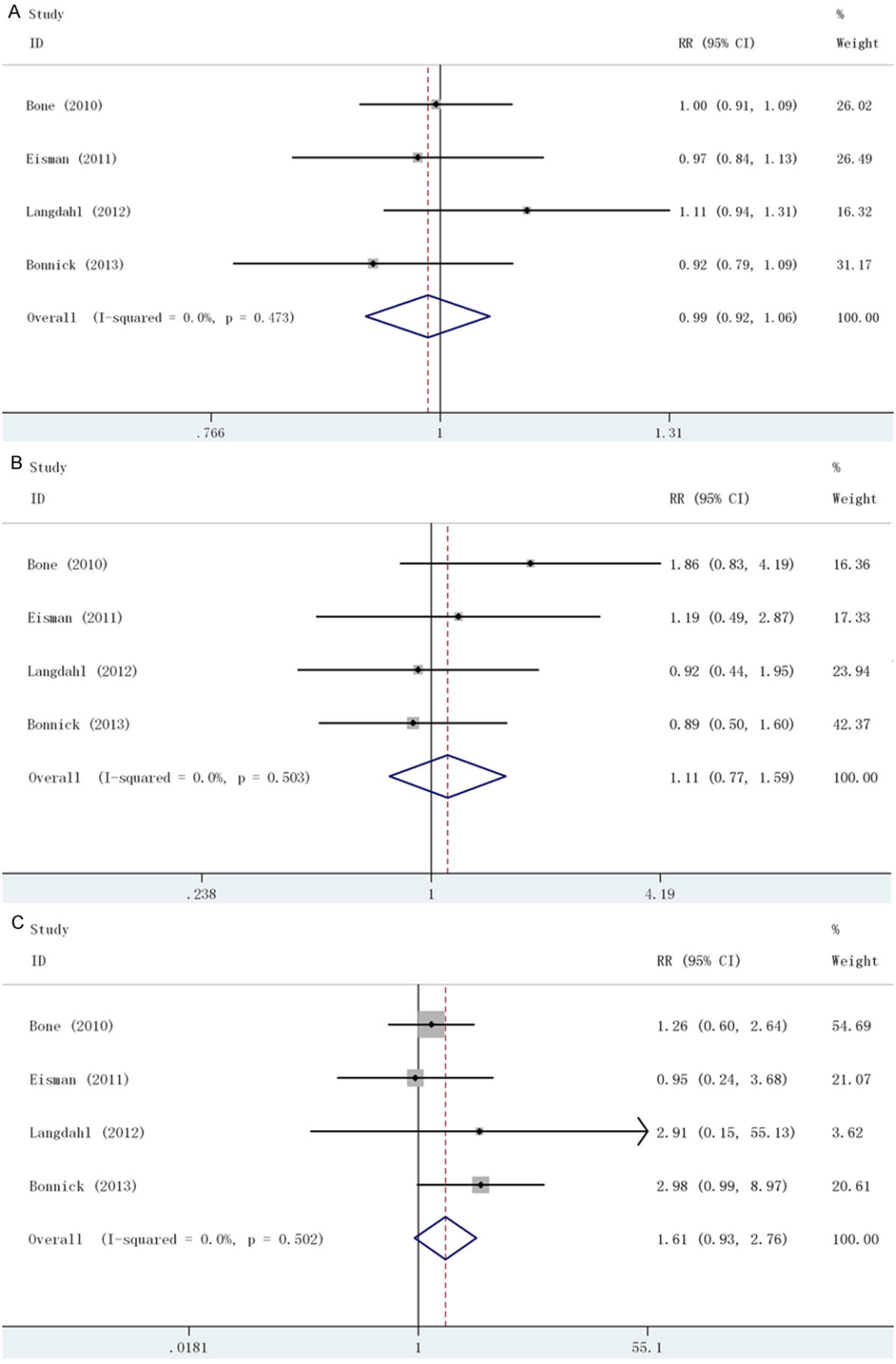
Adverse events (AEs): This outcome was reported in 4 trials, all comparing odanacatib to placebo. There was no heterogeneity between the study (P=0.473, I^2=0%), the fixed effect model was used. There was no significant difference in the incidence of adverse events (RR=0.99, 95% CI: 0.92~1.06), as shown in **Figure 2A**.

Serious adverse events (SAEs): This outcome was reported in four trials, all comparing odanacatib to placebo. There was no heterogeneity between the study (P=0.503, I^2=0%), the fixed effect model was used. There was no significant difference in the incidence of serious AEs (RR=1.11, 95% CI: 0.77~1.59), as shown in **Figure 2B**.

Discontinuations due to AEs: This outcome was reported in 4 trials, all comparing odanacatib to placebo. There was no heterogeneity between the study (P=0.502, I^2=0%), the fixed effect model was used. There was no significant difference in the incidence of discontinuations due to AEs (RR=1.61, 95% CI: 0.93~2.76), as shown in **Figure 2C**.

Skin AEs: This outcome was reported in five trials, all comparing odanacatib to placebo. There was no heterogeneity between the study (P=0.586, I^2=0%), the fixed effect model was used. However, there was significant difference in the incidence of skin AEs (RR=0.86, 95% CI: 0.64~1.16), as shown in **Figure 2D**.

Fractures: This outcome was reported in two trials, all comparing odanacatib to placebo. There was no heterogeneity between the study (P=0.750, I^2=0%), the fixed effect model was used. However, there was significant difference in the incidence of fractures (RR=0.34, 95% CI: 0.16~0.71), as shown in **Figure 2E**.


A
Study
ID
RR (95% CI)
%
Weight
Bone (2010)
1.00 (0.91, 1.09)
26.02
Eisman (2011)
0.97 (0.84, 1.13)
26.49
Langdahl (2012)
1.11 (0.94, 1.31)
16.32
Bonnick (2013)
0.92 (0.79, 1.09)
31.17
Overall (I-squared = 0.0%, p = 0.473)
0.99 (0.92, 1.06)
100.00
.766
1
1.31
B
Study
ID
RR (95% CI)
%
Weight
Bone (2010)
1.86 (0.83, 4.19)
16.36
Eisman (2011)
1.19 (0.49, 2.87)
17.33
Langdahl (2012)
0.92 (0.44, 1.95)
23.94
Bonnick (2013)
0.89 (0.50, 1.60)
42.37
Overall (I-squared = 0.0%, p = 0.503)
1.11 (0.77, 1.59)
100.00
.238
1
4.19
C
Study
ID
RR (95% CI)
%
Weight
Bone (2010)
1.26 (0.60, 2.64)
54.69
Eisman (2011)
0.95 (0.24, 3.68)
21.07
Langdahl (2012)
2.91 (0.15, 55.13)
3.62
Bonnick (2013)
2.98 (0.99, 8.97)
20.61
Overall (I-squared = 0.0%, p = 0.502)
1.61 (0.93, 2.76)
100.00
.0181
1
55.1

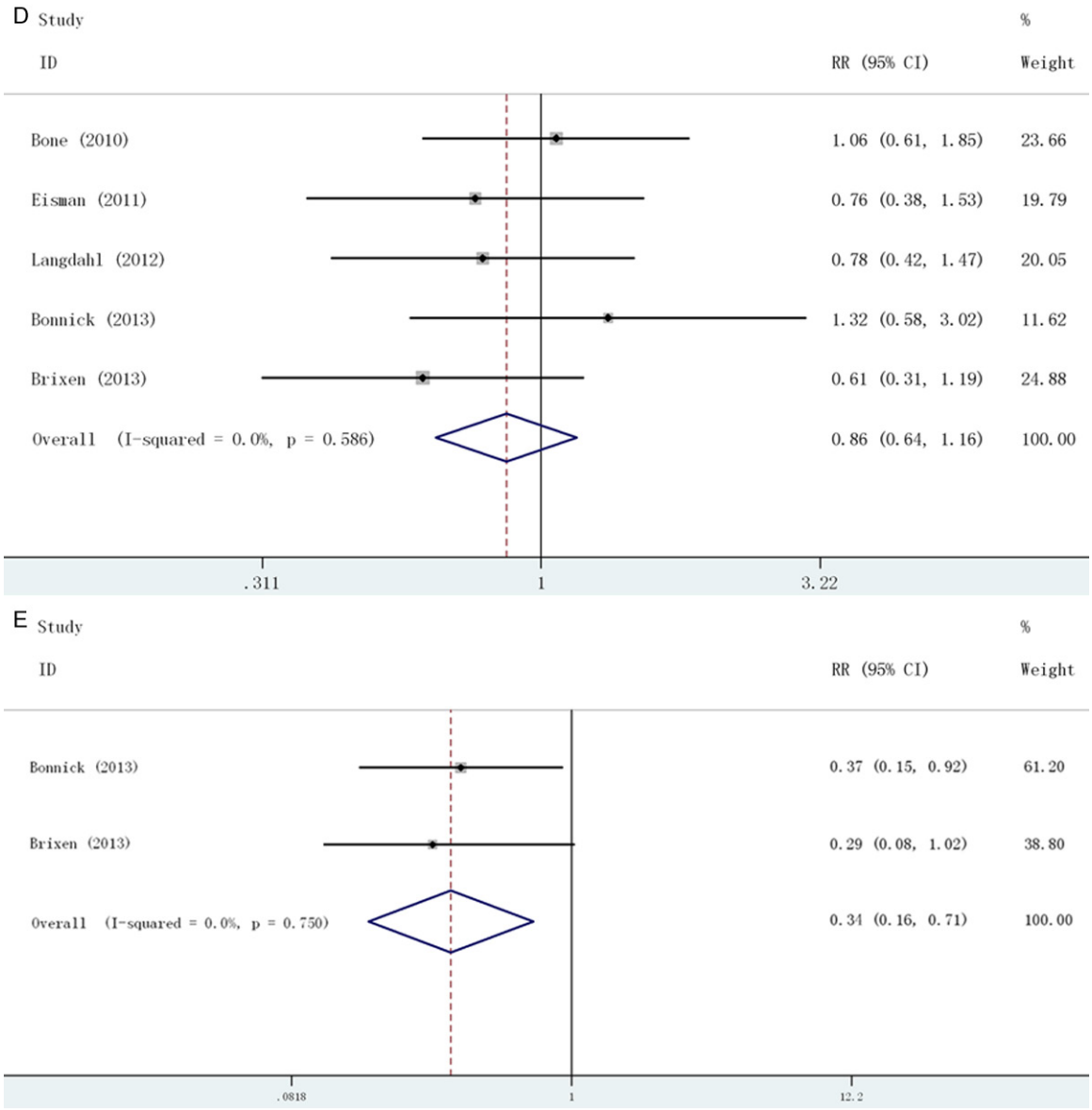


Figure 2. Adverse effects of treatment in randomised controlled trials of odanacatib versus placebo. A. Adverse events (AEs); B. Serious adverse events (SAEs); C. Discontinuations due to AEs; D. Skin AEs; E. Fractures.

Publication bias

Finally, the Egger's regression test showed no evidence of asymmetrical distribution in the funnel plot in incidence of adverse events (Begg's test *P*=1.000; Egger's test *P*=0.924) and incidence of skin AEs (Begg's test *P*=1.000; Egger's test *P*=0.895) (**Figure 3**).

Discussion

WHO determines the osteoporosis as a major public health problem, due to its high prevalence and the consequences of osteoporotic fracture [14]. In a particularly high risk of osteoporosis after menopause, women lack of estrogen usually has a high rate of bone remodeling and bone absorption than bone formation. The result is bone loss, bone fragility and increased risk of fractures [15]. Good method can be used in the measurement of bone mineral density in clinical practice now [16], the assessment of fracture risk [17], and treatment of patients with drug preparation, appropriate to reduce their risk of fractures [18].

Odanacatib is a specific inhibition of cathepsin K, is secreted by the cells broken bone and

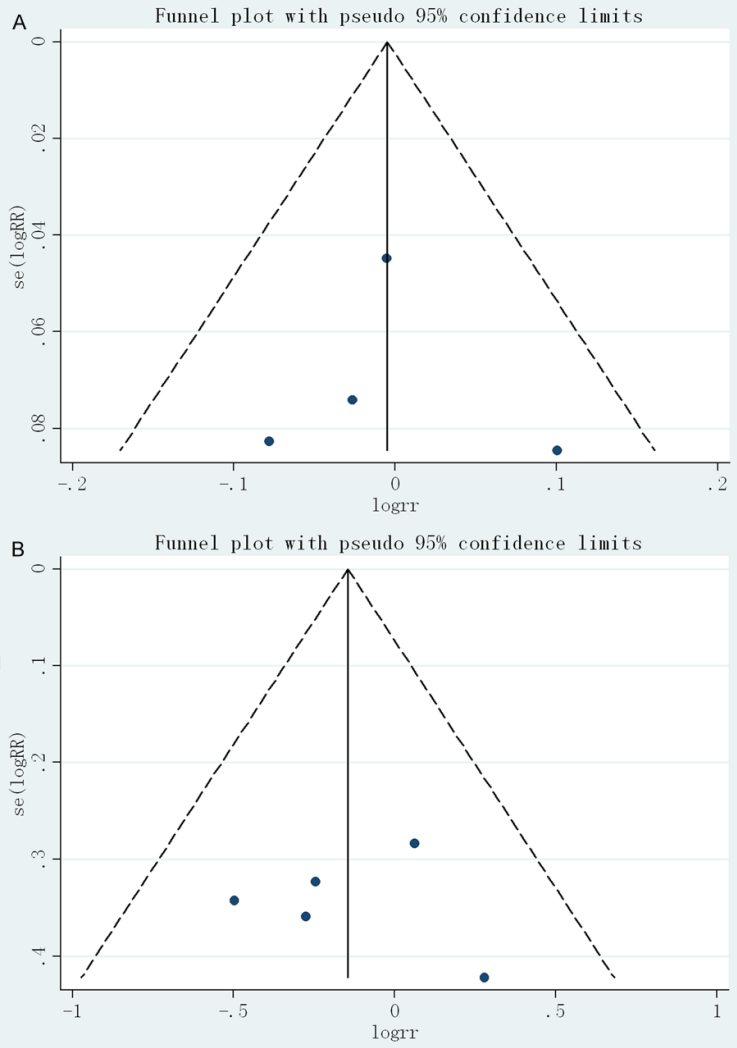


Figure 3. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. A. Incidence of adverse events; B. Incidence of skin AEs.

bone type I collagen degradation enzymes. Increase bone mineral density in the spine and hip after effects, withdrawal immediately reversible [11]. Preliminary data, in the United States Society for Bone and Mineral Research (ASBMR) 2014, showed a significant reduction in the risk of vertebral, non-vertebral and hip fractures [19]. The results of this meta-analysis including 5 RCTs indicate that treatment of postmenopausal women with odanacatib is associated with reduced the risk of relative fracture as compared with those that received placebo and adverse event rates during treatment period were similar between groups. These results indicate that odanacatib can cause a significant reduction in relative fracture risk in the odanacatib compared with the placebo group.

Odanacatib is a cathepsin K inhibitor extensively studied in clinical trials and is the sole remaining agent in clinical development. In preclinical studies, the use of CATK inhibitors in ovariectomized rabbits and monkeys induced dose-dependent reduction of bone resorption in trabecular and cortical sites and preservation of areal BMD [20-24]. Odanacatib treatment increased the number of osteoclast when assessed by histomorphometry, and elevated serum levels of tartrate resistant acid phosphatase 5b (TRAP5b). The effects of CatK inhibition on bone formation are more complex. Like other resorption inhibitors, balicatib and odanacatib inhibit trabecular bone formation in ovariectomized monkeys. In the 2 phase of the placebo controlled clinical trial, postmenopausal women with low BMD received odanacatib at a dose ranging from 3 to 50 mg per week [9]. More than 24 months of treatment, observed a dose-dependent increase in the lumbar spine and femoral neck bone mineral density. At the highest dose (50 mg odanacatib weekly), BMD increased 5.7% and 4.1% at the lumbar spine and hip, respectively, versus placebo. The effects of treatment with odanacatib on the incidence of fracture is being assessed in an international, phase 3 placebo-controlled study in more than 16,000 postmenopausal women with osteoporosis [19]. According to the results of a pre-planned interim analysis, this study was recently stop early because of "powerful effectiveness". After a average duration of therapy of approximately 3 years, it was recently reported that odanacatib significantly reduced the incidence of vertebral, non-vertebral and hip fractures [25].

Several limitations in this meta-analysis should be addressed. First, our study may be impaired, to extract the raw data from including research. Secondly, the language can also introduce a bias. Specifically, we select only the English lan-

guage and exclude other qualified researchers. A third of a potential limitation is that the assessment data sets were considered too little for visual or statistical examination of publication bias, and the potential presence of such bias could not be determined. Therefore, we hypothesized that publication bias might be present.

In conclusion, compared to placebo, odanacatib treatment significantly reduced the risk of relative fracture, however, there was no difference between the safety of odanacatib and placebo. Odanacatib is a valuable new option for the treatment of postmenopausal osteoporosis in women and may be used as a first-line treatment in future. However, due to the existence of the unstable factors, furthermore studies need to be done to verify the result of this study.

Disclosure of conflict of interest

None.

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References

[1] Zallone A. Direct and indirect estrogen actions on osteoblasts and osteoclasts. Ann N Y Acad Sci 2006; 1068: 173-179.

[2] Office of the Surgeon General (US). Bone health and osteoporosis: a report of the Surgeon General. Office of the Surgeon General (US), MD, U S A www.ncbi.nlm.nih.gov/books.

[3] Rosen CJ. The cellular and clinical parameters of anabolic therapy for osteoporosis. Crit Rev Eukaryot Gene Expr 2003; 13: 25-38.

[4] National Osteoporosis Foundation. America's bone health: the state of osteoporosis and low bone mass in our nation, 2002. Available at http://nof.org/advocacy/prevalence/index.htm; accessed September 23, 2009.

[5] Zhang ZQ, Ho SC, Chen ZQ, Zhang CX and Chen YM. Reference values of bone mineral density and prevalence of osteoporosis in Chinese adults. Osteoporos Int 2014; 25: 497-507.

[6] Le TD, Leung AT and Langdahl B. Cathepsin K inhibition: a new mechanism for the treatment of osteoporosis. Calcif Tissue Int 2016; 98: 381-397.

[7] Schultz TC, Valenzano JP, Verzella JL and Umland EM. Odanacatib: an emerging novel treatment alternative for postmenopausal osteoporosis. Womens Health (Lond) 2015; 11: 805-814.

[8] Chapurlat RD. Odanacatib: a review of its potential in the management of osteoporosis in postmenopausal women. Ther Adv Musculoskelet Dis 2015; 7: 103-109.

[9] Bone HG, McClung MR, Roux C, Recker RR, Eisman JA, Verbruggen N, Hustad CM, DaSilva C, Santora AC and Ince BA. Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. J Bone Miner Res 2010; 25: 937-947.

[10] Eisman JA, Bone HG, Hosking DJ, McClung MR, Reid IR, Rizzoli R, Resch H, Verbruggen N, Hustad CM, DaSilva C, Petrovic R, Santora AC, Ince BA and Lombardi A. Odanacatib in the treatment of postmenopausal women with low bone mineral density: three-year continued therapy and resolution of effect. J Bone Miner Res 2011; 26: 242-51.

[11] Langdahl B, Binkley N, Bone H, Gilchrist N, Resch H and Rodriguez Portales J. Odanacatib in the treatment of postmenopausal women with low bone mineral density: five years of continued therapy in a phase 2 study. J Bone Miner Res 2012; 27: 2251-8.

[12] Bonnick S, De Villiers T, Odio A, Palacios S, Chapurlat R, DaSilva C, Scott BB, Le Bailly De Tilleghem C, Leung AT and Gurner D. Effects of odanacatib on BMD and safety in the treatment of osteoporosis in postmenopausal women previously treated with alendronate: a randomized placebo-controlled trial. J Clin Endocrinol Metab 2013; 98: 4727-35.

[13] Brixen K, Chapurlat R, Cheung AM, Keaveny TM, Fuerst T, Engelke K, Recker R, Dardzinski B, Verbruggen N, Ather S, Rosenberg E and de Papp AE. Bone density, turnover, and estimated strength in postmenopausal women treated with odanacatib: a randomized trial. J Clin Endocrinol Metab 2013; 98: 571-80.

[14] Kanis JA, on behalf of the world health organization scientific group. Assessment of osteoporosis at the primary health-care level (world health organization collaborating centre for metabolic bone diseases, university of sheffield, UK, 2008).

[15] Felsenberg D and Boonen S. The bone quality framework: determinants of bone strength and their interrelationships, and implications for osteoporosis management. Clin Ther 2005; 27: 1-11.

[16] Lewiecki EM. Update on bone density testing. Curr Osteoporos Rep 2005; 3: 136-42.

[17] World Health Organization. FRAX WHO Fracture Risk Assessment Tool [online] http://www.shef.ac.uk/FRAX/.

[18] MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, Carter J, Tringale C, Valentine D, Johnsen B and Grossman J. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med 2008; 148: 197-213.

[19] Bone HG, Dempster DW, Eisman JA, Greenspan SL, McClung MR, Nakamura T, Papapoulos S, Shih WJ, Rybak-Feiglin A, Santora AC, Verbruggen N, Leung AT and Lombardi A. Odanacatib for the treatment of postmenopausal osteoporosis: development history and design and participant characteristics of LOFT, the long-term odanacatib fracture trial. Osteoporos Int 2015; 26: 699-712.

[20] Stroup GB, Kumar S and Jerome CP. Treatment with a potent cathepsin K inhibitor preserves cortical and trabecular bone mass in ovariectomized monkeys. Calcif Tissue Int 2009; 85: 344-55.

[21] Jerome C, Missbach M and Gamse R. Balicatib, a cathepsin K inhibitor, stimulates periosteal bone formation in monkeys. Osteoporos Int 2011; 22: 3001-11.

[22] Masarachia PJ, Pennypacker BL, Pickarski M, Scott KR, Wesolowski GA, Smith SY, Samadfam R, Goetzmann JE, Scott BB, Kimmel DB and Duong LT. Odanacatib reduces bone turnover and increases bone mass in the lumbar spine of skeletally mature ovariectomized rhesus monkeys. J Bone Miner Res 2012; 27: 509-523.

[23] Pennypacker BL, Duong LT, Cusick TE, Masarachia PJ, Gentile MA, Gauthier JY, Black WC, Scott BB, Samadfam R, Smith SY and Kimmel DB. Cathepsin K inhibitors prevent bone loss in estrogen-deficient rabbits. J Bone Miner Res 2011; 26: 252-262.

[24] Cusick T, Chen CM, Pennypacker BL, Pickarski M, Kimmel DB, Scott BB and Duong LT. Odanacatib treatment increases hip bone mass and cortical thickness by preserving endocortical bone formation and stimulating periosteal bone formation in the ovariectomized adult rhesus monkey. J Bone Miner Res 2012; 27: 524-537.

[25] Bone HG, Dempster DW, Eisman JA, Greenspan SL, McClung MR, Nakamura T, Papapoulos S, Shih WJ, Rybak-Feiglin A, Santora AC, Verbruggen N, Leung AT and Lombardi A. Odanacatib anti-fracture efficacy and safety in postmenopausal women with osteoporosis: results from the phase III long-term odanacatib fracture trial. Arthritis Rheumatol 2014; 66: S987.