European Review for Medical and Pharmacological Sciences 2021; 25: 1564-1573

Zoledronic acid and fracture risk: a meta-analysis of 12 randomized controlled trials

B. HE[1], J.-Q. ZHAO[2], M.-Z. ZHANG[1], Z.-X. QUAN[1]

[1]Department of Orthopedics, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[2]Department of Infectious Diseases, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Bin He and Jinqiu Zhao contributed equally to this work

Abstract. – OBJECTIVE: Zoledronic acid is widely used in patients with osteoporosis, and this meta-analysis aims to explore the influence of zoledronic acid on fracture risk and mortality in patients with osteoporosis or osteopenia.

MATERIALS AND METHODS: We searched PubMed, Google Scholar, and Cochrane Library for randomized clinical trials comparing zoledronic acid with control intervention (i.e., placebo or nothing) for osteoporosis or osteopenia. The fracture and mortality were estimated using the random-effect model.

RESULTS: 12 randomized trials were included in this meta-analysis. Compared to control intervention, zoledronic acid was associated with significantly reduced incidence of fracture at the follow-up of 12 months, 24 months, 36 months and 72 months. In addition, zoledronic acid could remarkably reduce mortality at 12 months and 24 months than control intervention but revealed no influence on mortality at 36 months or 72 months. In terms of adverse events, zoledronic acid might result in the increase in serious atrial fibrillation and death from stroke than control intervention.

CONCLUSIONS: Zoledronic acid is beneficial to reduce the incidence of fracture, while its benefits to reduce the mortality are only observed at the follow-up time of 24 months.

Key Words:
Zoledronic acid, Fracture, Mortality, Meta-analysis.

Abbreviations
Bone Mineral Density (BMD); Risk Ratio (RR); Confidence Intervals (CI); Randomized Controlled Trials (RCTs).

Introduction

Primary osteoporosis occurs frequently in elderly patients, especially postmenopausal women[1-4]. Osteoporosis is characterized by reduced bone quality and bone mass[5-7]. The most serious consequence of osteoporosis is brittle fractures, which results in substantially reduced quality of life and increased mortality rate[8-11]. Many preventive and therapeutic drugs have been developed to reduce the serious consequences of osteoporosis[12-15].

Zoledronic acid is the third generation of bisphosphonate to treat osteoporosis by promoting osteoclast apoptosis and inhibiting bone resorption[16-18]. It is preferred over oral bisphosphonates because of the intravenous injection at the interval of 1 year[19]. In the HORIZON Recurrent Fracture Trial involving 1,065 patients, intravenous zoledronic acid at a dose of 5 mg yearly was associated with the reduction in new clinical fractures and improved survival[20].

A total of 3, 889 patients with postmenopausal osteoporosis were included in the HORIZON Pivotal Fracture Trial, and once-yearly infusion of zoledronic acid was documented to significantly improve bone mineral density (BMD) and reduce the risk of fracture but demonstrated no evident reduction in mortality[21]. In the frail elderly women with osteoporosis, zoledronic acid was associated with improved BMD over 2 years, but non-significant difference of fracture and mortality rates were observed between zoledronic acid and control intervention[22].

Numerous randomized trials have explored zoledronic acid for the treatment of osteoporosis[18,22-24], but the effect of zoledronic acid on fracture risk and mortality has not been well established. Therefore, we performed this meta-analysis to examine the effect of zoledronic acid *vs.* control intervention on long-term fracture and mortality.

Materials and Methods

Study Selection and Data Collection

This systematic review and meta-analysis were performed based on the guidance of the Preferred

Corresponding Author: Zhengxue Quan, MD; e-mail: quanzx18@126.com

Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions[25,26].

We have searched PubMed, Google Scholar, and Cochrane Library up to February 19, 2020, and used the search terms including "zoledronic acid", or "zoledronate", and "fracture" or "mortality", and "random". Two researchers (BH and JQZ) independently identified randomized trials comparing zoledronic acid with placebo (or nothing) in patients with osteoporosis or osteopenia. The studies involving cancer were excluded. Reference lists from potentially relevant articles were checked to ensure that no studies were missed. The quality of individual trials was evaluated using the Cochrane Collaboration's tool[27]. Ethical approval and patient consent were not required because this was a meta-analysis of previously published studies.

Outcome Measures

To allow the consistent definition of follow-up among trials, the duration of follow-up was calculated from the day of intravenous infusion of zoledronic acid. The incidence of fracture and mortality were estimated by the subgroup of different follow-up time periods.

We prespecified subgroup analysis for total adverse events according to any adverse events, serious events, serious atrial fibrillation, serious stroke, death from stroke, myocardial infarction, and death from cardiovascular causes.

Statistical Analysis

A team consisting of three authors (BH, JQZ, and MZZ) performed the statistical analyses. We assessed risk ratio (RR) with 95% confidence intervals (CI) for all dichotomous outcomes. Heterogeneity was evaluated using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity[28]. The random-effects model was used for all meta-analysis. We searched for potential sources of heterogeneity when encountering significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate *via* omitting one study in turn or performing the subgroup analysis.

Discrete data of fracture were presented as frequencies and were compared with χ^2 tests between vertebral fracture and non-vertebral fracture, between female and male patients. *p*-value <0.05 was considered to have statistical significance. All statistical analyses were done with Review Manager Version 5.3 or SPSS software, version 21 (IBM, Armonk, NY, USA).

Role of the Funding Source

The funder of the study (BH) participated in study design, data collection, data analysis, data interpretation or writing of the report.

Results

Literature Search, Study Characteristics and Quality Assessment

The flowchart of the search and selection results were shown in Figure 1. 886 potentially relevant articles were identified initially, and 12 studies involving 14,395 patients were finally included in this study[18,20-24,29-34]. When assessing the full-articles, we removed three secondary articles of HORIZON Recurrent Fracture Trial and HORIZON Pivotal Fracture Trial[35-37] and three articles with no available data[38-40]. In the continued study of HORIZON-Pivotal Fracture Trial, two articles comparing Z6 (continues use of 5 mg zoledronic acid yearly for 6 years) with Z3P3 (continues use of 5 mg zoledronic acid yearly for 3 years plus continues use of placebo for additional 3 years) or Z9 with Z6P3 were excluded in order to avoid the effect of previous zoledronic acid on the outcomes[41,42].

Among the 12 trials included, 11 trials reported an intravenous infusion of zoledronic acid (5 mg) once a year[20-24,29-34], while the remaining trial reported an intravenous infusion of zoledronic acid (5 mg) once every 18 months for 4 times[18]. In the control intervention, patients in two randomized controlled trials (RCTs) received no drug for intravenous infusion[23,29], while patients in other included RCT received intravenous placebo[18,20-22,24,30-34]. All patients were female in five studies[18,21,22,29,31] or male in one study[24]. Baseline, fracture history, surgical history and inclusion criteria for the patients were shown in Table I. All trials were generally considered to have high quality according to criteria, despite some bias in allocation concealment and blinding of investigators and patients in two trials[23,29] (Figure 2).

Fracture

Among the included RCTs, several studies reported the fracture incidence at the follow-up of 12 months[24,29], 24 months[20,22-24,31], 36 months[21] and 72 months[18]. In Figure 3, zoledronic acid was associated with significantly reduced incidence of fracture at the follow-up of 12 months (RR=0.28; 95% CI=0.11 to 0.71; *p*=0.008), 24 months (RR=0.65; 95% CI=0.49 to 0.87; *p*=0.004), 36 months

Table I. Characteristics of included studies.

No.	Author	Zoledronic acid group						Control group						Region	Included patients	Follow-up (month)
		Number	Age (years)	Female/ Male (n)	Body-mass index (kg/m²)	Fracture history and type (yes/no, n)	Methods	Number	Age(years)	Female/ Male (n)	Body-mass index (kg/m²)	Fracture history and type (yes/no, n)	Methods			
1	Zhang et al[29]	50	64.60 ± 6.70	50/0	26.13 ± 1.81	Vertebral fracture (50/0)	An intravenous infusion of zoledronic acid (5 mg) after percutaneous kyphoplasty	51	63.98 ± 7.51	50/0	26.15±2.23	Vertebral fracture (51/0)	nothing	China	Postmenopausal women with T-score of -2.5 or less, isolated compression fracture of single vertebral body of T12 or L1 within 2 weeks	12
2	Liu et al[23]	353	75.41 ±12.54	_	23.54±8.24	Hip fracture (353/0)	An intravenous infusion of zoledronic acid (5 mg) within 1 week after the fracture	129	73.25±13.75	_	22.26±9.55	Hip fracture (129/0)	nothing	China	Patients with senile osteoporotic femoral intertrochanteric fracture and internal fixation, T < −2.5 or T < − 1.0 and past history of brittle fracture	24
3	Reid et al[18]	1000	71±5.0	1000/0	26.8±4.6	Fracture (364/636)	Four infusions of either zoledronate at a dose of 5 mg (zoledronate group) at 18-month intervals	1000	71±5.1	1000/0	26.9±4.7	Fracture (374/626)	placebo	European, Maori, Pacific Islander, East Asian, Indian, Other	Women (65 years of age or older) with osteopenia, T score of −1.0 to −2.5	72
4	Cengiz et al[30]	48	76.79 (mean)	32/24	_	Hip fracture (48/0)	5 mg of zoledronic acid via 30 min-intravenous infusion in postoperative week 2	38	80.28 (mean)	38/20	_	Hip fracture (38/0)	placebo	Turkey	Elderly patients (65 years or above) with intertrochanteric femoral fractures who underwent surgical osteosynthesis	12
5	Greenspan et al[22]	89	85.4±0.6	89/0	28.2±0.6	Vertebral fracture (46/43)	An intravenous infusion of zoledronic acid (5 mg) yearly	92	85.5±0.5	92/0	26.9±0.5	Vertebral fracture (38/54)	placebo	USA	Frail women 65 years or older, either a history of vertebral or hip fracture or a measured BMD below the treatment cutoff for osteoporosis	24
6	Bai et al[31]	242	56.50±6.83	242/0	23.44±0.32	Vertebral fracture (149/93)	An intravenous infusion of zoledronic acid (5 mg) yearly	241	57.15±6.34	241/0	23.73±0.46	Vertebral fracture (144/97)	placebo	China	Postmenopausal osteoporosis T-score ≤ 2.5or T-score ≤1.5 with radiological diagnosis of two or more vertebral fractures	24
7	Boonen et al[32]	588	66 (50–85), median (range)	0/588	_	Vertebral fracture (183/405)	An intravenous infusion of zoledronic acid (5 mg) yearly	611	66(50–85), median(range)	0/611	_	Vertebral fracture (201/410)	placebo	Africa, Latin America, Europe, Oceania	Men with primary osteoporosis or osteoporosis associated with low testosterone levels, T score of −1.5 or less and one to three prevalent vertebral fractures of mild or moderate grade	24
8	Boonen et al[44]	248	72.5±10.3	_	24.4±4.1	Hip fracture (248/0)	A single infusion of zoledronic acid (5 mg) yearly, first administered within 90 days after surgical repair of a hip fracture	260	72.6±10.4	_	24.9±4.2	Hip fracture (260/0)	placebo	Western Europe, Eastern Europe, North America, Latin America	Patients in HORIZON Recurrent Fracture Trial	24
9	Colón-Emeric et al[45]	1057	172 (<65)/305 (65-74)//440 (75-84)/137 (≥85)	810/244	79 (<19)/502(19–25)/441(>25)	Hip fracture (1057/0)	A single infusion of zoledronic acid (5 mg) yearly, first administered within 90 days after surgical repair of a hip fracture	1054	191(<65)/268 (65-74)//447 (75-84)/151(≥85)	796/61	72 (<19)/506 (19–25)/ 450(>25)	Hip fracture (1054/0)	Placebo	Western Europe, Eastern Europe, North America, Latin America	Patients in HORIZON Recurrent Fracture Trial	24
10	Boonen et al[34]	2731(<75 years)	69.2±3.7	_	25.1±4.4	Vertebral fracture (1406/971)	A single infusion of zoledronic acid (5 mg) yearly	2736	69.1±3.7	_	25.4±4.4	Vertebral fracture (1462/946)	Placebo	Western Europe, Eastern Europe, North America or Oceania, Latin America, Asia	Patients in HORIZON Pivotal Fracture Trial and HORIZON Recurrent Fracture Trial	36
		1961(≥75 years)	79.3 3.7	_	25.1 4.3	Vertebral fracture (1010/486)		1927	79.6 3.7	_	25.2 4.2	Vertebral fracture (1015/437)				
11	Lyles et al [20]	1065	74.4±9.48	817/248	24.7±4.4	Hip fracture (1065/0)	A single infusion of zoledronic acid (5 mg) yearly, first administered within 90 days after surgical repair of a hip fracture	1062	74.6±9.86	802/260	24.8±4.5	Hip fracture (1062/0)	Placebo	Western Europe, Eastern Europe, North America, Latin America	HORIZON Recurrent Fracture Trial: men and women 50 years of age or older, within 90 days after surgical repair of a hip fracture sustained with minimal trauma	24
12	Black et al[21]	3875	1140 (<70)/1238(70–74)/1497(≥75)	3875/0	25.1±4.3	Vertebral fracture (2416/1457)	A single 15-minute infusion of zoledronic acid (5 mg) yearly	3861	1174 (<70)/1235(70–74)/1452(≥75)	1174/0	25.4±4.3	Vertebral fracture (2477/1383)	placebo	Western Europe, Eastern Europe, North America or Oceania, Latin America, Asia	HORIZON Pivotal Fracture Trial: postmenopausal women, T score of −2.5 or less at the femoral neck, or a T score of −1.5 or less, with radiologic evidence of at least two mild vertebral fractures or one moderate vertebral fracture	36

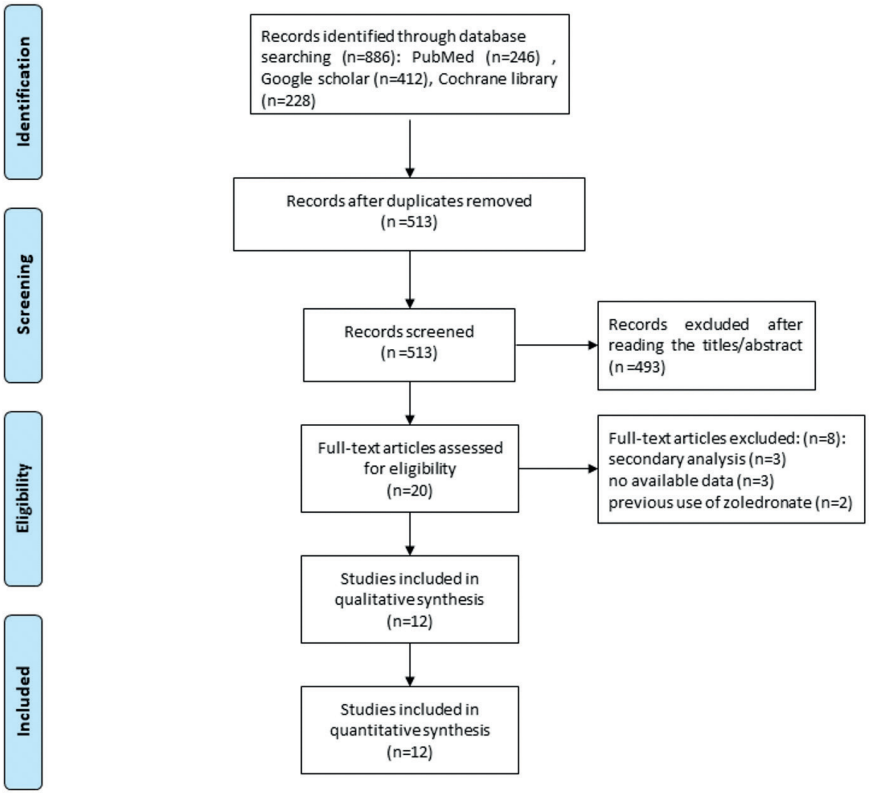

Figure 1. Flow diagram of study searching and selection process.

(RR=0.67; 95% CI=0.59 to 0.77; $p<0.00001$) and 72 months (RR=0.76; 95% CI=0.63 to 0.92; $p=0.004$).

In addition, three included trials reported the vertebral fracture and non-vertebral fracture at 24 months[20,22,31]. 33 cases with vertebral fracture were compared with 119 cases with non-vertebral fracture after zoledronic acid treatment, while 57 cases for vertebral fracture were compared to 169 cases for non-vertebral fracture in control intervention. Therefore, zoledronic acid showed similar effect on the reduction of vertebral fracture and non-vertebral fracture ($\chi^2=0.617$, $p=0.432$).

Considering the effect of sex, four included trials reported the fracture incidence in female or male patients at 24 months[22,24,31,32]. There were 136 cases of fracture in female patients and 25 cases of fracture in male patients after zoledronic acid treatment, which were compared to 206 cases of fracture in female patients and 48 cases of fracture in male patients after control intervention. Therefore, the sex also revealed no influence on the efficacy of zoledronic acid to reduce fracture incidence ($\chi^2=0.772$, $p=0.380$).

Sensitivity Analysis

There was low or even no heterogeneity for the fracture, and thus we did not perform the analysis via omitting one study or subgroup analysis to detect the heterogeneity.

Mortality

Six included studies reported the mortality at the follow-up of 12 months[30], 24 months[20,22,24], 36 months[21] and 72 months[18]. Compared to control intervention, zoledronic acid could substantially decrease the mortality at 12 months (RR=0.41; 95% CI=0.20 to 0.86; $p=0.02$) and 24 months (RR=0.76; 95% CI=0.62 to 0.95; $p=0.02$) but showed no evident effect on mortality at 36 months (RR=1.16; 95% CI=0.90 to 1.48; $p=0.25$) or 72 months (RR=0.66; 95% CI=0.41 to 1.06; $p=0.09$; Figure 4).

Adverse Events

In order to analyze the influence of zoledronic acid on adverse events, two additional RCTs comparing Z6 with Z3P3 or Z9 with Z6P3 were included[41,42], because previous use of zoledronic

acid may have no effect or compromise the effect of certain adverse events on the pooling results. The results found that zoledronic acid was still associated with significantly increased serious atrial fibrillation (RR=1.62; 95% CI=1.02 to 2.57; p=0.04) and death from stroke (RR=1.82; 95% CI=1.01 to 3.27; p=0.04) than control intervention. There was no statistical difference of adverse events (RR=1.05; 95% CI=1.0 to 1.10; p=0.06), serious event (RR=0.98; 95% CI=0.93 to 1.03; p=0.39), serious stroke (RR=1.18; 95% CI=0.88 to 1.58; p=0.28), myocardial infarction (RR=0.82; 95% CI=0.54 to 1.26; p=0.37) or death from cardiovascular causes (RR=1.05; 95% CI=0.59 to 1.85; p=0.87; Figure 5) between two groups.

Discussion

This meta-analysis of 12 randomized trials involved 14,395 patients to compare zoledronic acid with control intervention on fracture risk and mortality. We found that the incidence of 6-year total fracture was significantly lower after zoledronic acid than that after control intervention. The preventive effect of zoledronic acid on vertebral fracture was similar to that on non-vertebral fracture (p=0.432).

Over the follow-up of 2 years, annual infusions of zoledronic acid significantly reduced the risk of new morphometric vertebral fractures by 67% among men with osteoporosis[24], which resembled that reported in postmenopausal women with osteoporosis (relative reduction in the risk of vertebral fracture, 71% at 2 years)[21]. Among the included patients with fracture, the most of included patients were female (136 cases for female *vs.* 25 cases for male at 24 months). Our meta-analysis also confirmed that sex showed no evident impact on the preventive effect of zoledronic acid to reduce fracture (p=0.380), indicating that the potential of zoledronic acid in decreasing fracture

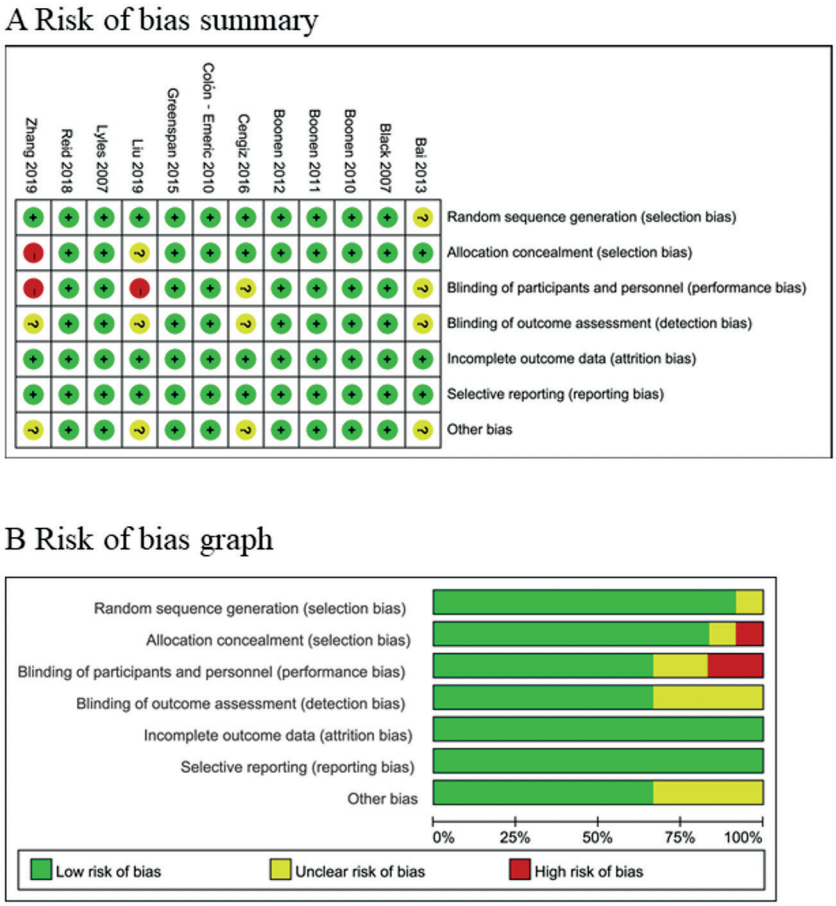

Figure 2. Risk of bias assessment. **A**, Authors' judgments about each risk of bias item for each included study. **B**, Authors' judgments about each risk of bias item presented as percentages across all included studies.

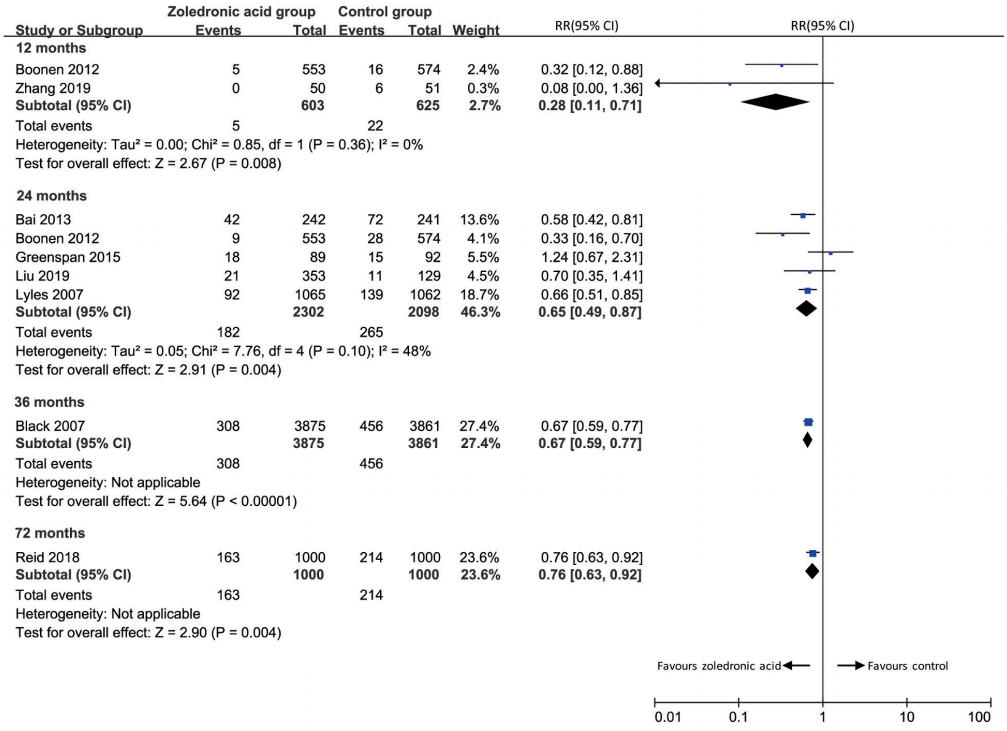

Figure 3. Fracture after zoledronic acid *vs.* control intervention by subgroup. RR=risk ratio. CI=confidence interval.

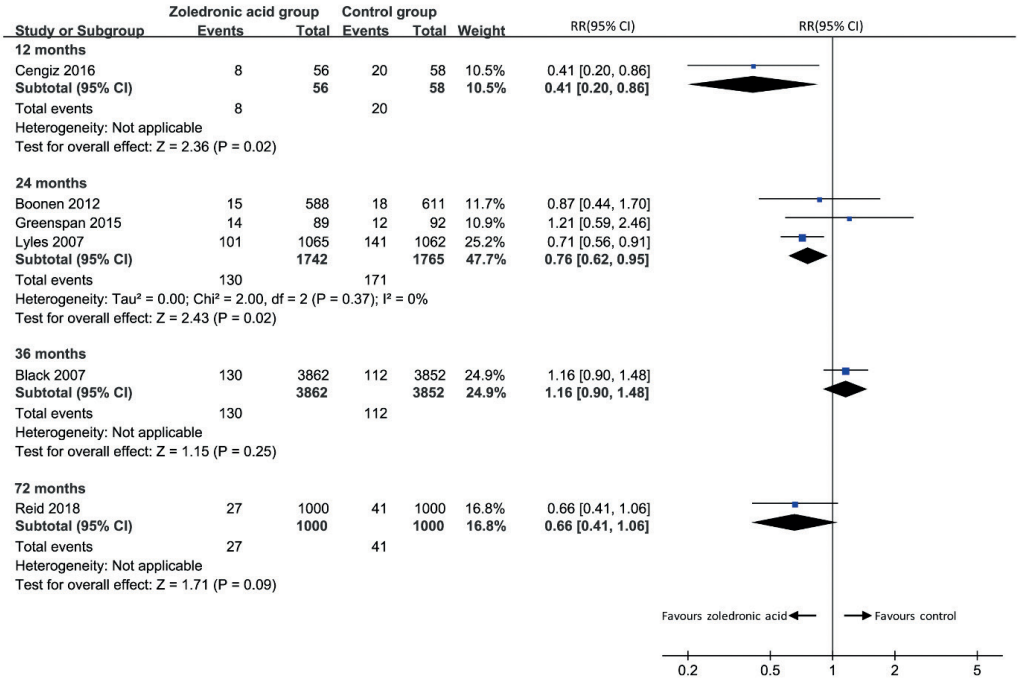

Figure 4. Mortality after zoledronic acid *vs.* control intervention by subgroup. RR=risk ratio. CI=confidence interval.

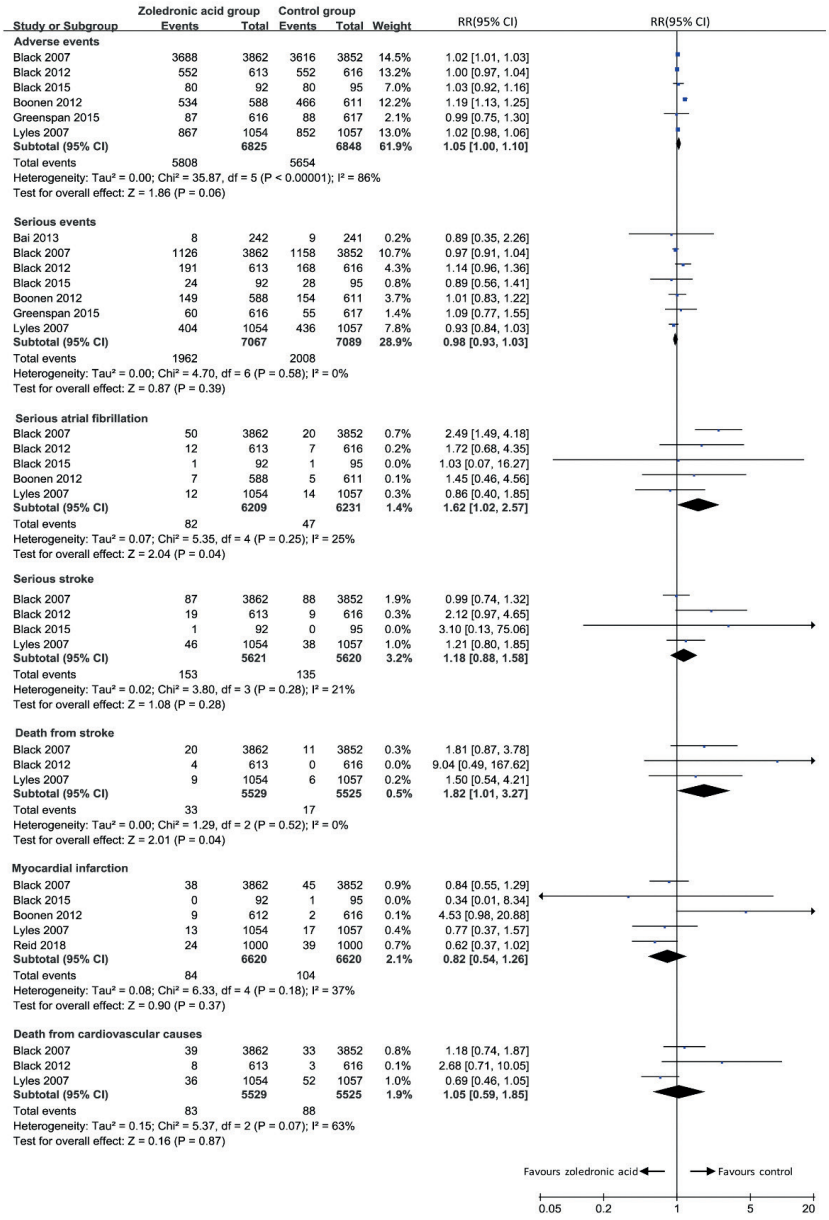

Figure 5. Adverse events after zoledronic acid vs. control intervention by subgroup. RR=risk ratio. CI=confidence interval.

may be independent of menopausal status. Zoledronic acid was reported to reduce bone loss and fracture through causing the apoptosis of osteoclasts and inhibition of bone resorption mediated by osteoclasts[43].

The relative benefits of zoledronic acid *vs.* control intervention in terms of mortality were highly debated. In one multicenter, double-blind, placebo-controlled trial involving 1,199 male patients with osteoporosis, intravenous infusion of zoledronic acid at the dose of 5 mg yearly led to similar incidence of death as compared with placebo (15 deaths/total 588 cases *vs.* 18 deaths/total 611 cases, respectively; $p>0.05$) over a period of 24 months[24]. However, this meta-analysis confirmed that significant benefit of zoledronic acid to reduce mortality was seen within the follow-up of 24 months, but after that there was no evident benefit to reduce mortality after zoledronic acid treatment.

It is unreasonable that zoledronic acid is able to notably reduce the incidence of fracture including vertebral fracture and non-vertebral fracture, but only shows significant benefit to reduce mortality

within 24 months. For instance, hip fractures were associated with increased morbidity, functional decline, and death in older adults[44]. Therefore, two reasons may explain this inconsistency. First, only two RCTs reported the mortality after using zoledronic acid for 36 months[21] or 72 months[18], which may produce some bias. Second, zoledronic acid may increase some serious adverse events that improve the mortality of patients. This pooled analysis reveals that zoledronic acid led to the substantial increase in serious atrial fibrillation (p=0.04) and death from stroke (p=0.04). It was well known that osteonecrosis of the jaw was a detrimental side effect of the long-term administration of bisphosphonates[45]. However, no cases with osteonecrosis of the jaw were reported in three included RCTs[18,20,24]. Another included RCT reported two cases of potential osteonecrosis of the jaw (one in the placebo group and one in the zoledronic-acid group)[21]. These suggested that zoledronic acid may have no evident effect on the incidence of osteonecrosis of the jaw.

The main strength of this meta-analysis is that we are able to identify clinically relevant differences in total fracture and mortality between zoledronic acid and control intervention. Nevertheless, this study has several potential limitations. First, all the included trials assume clinical equipoise between zoledronic acid and control intervention, but they have different and specific inclusion and exclusion criteria, which may result in some heterogeneity for the pooling results. Second, two included studies show evident bias in allocation concealment, and blinding of investigators and patients[23,29]. Third, the follow-up time in 12 included RCTs is not continuous and sufficient, such as only two RCTs reporting the mortality after using zoledronic acid for 36 months[21] or 72 months[18]. Fourth, we are unable to do the subgroup analysis according to some important factors such as age range, smoker and menopausal status. Fifth, relatively small patient samples are involved in several included trials, which may have some effect on the pooling results. Sixth, zoledronic acid is generally administered by intravenous infusion at the dose of 5 mg yearly, but only one included trial involves zoledronic acid at the dose of 5 mg once every 18 months for 4 times[18].

Conclusions

We show that the incidence of fracture is significantly reduced by zoledronic acid, and only the beneficial effect of 24 month-mortality is seen after using zoledronic acid.

Ethics Approval and Consent to Participate

These were not required because this is a meta-analysis of previously studies..

Consent for Publication

All authors approved for the publication..

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

Bin He was funded by the Foundation of The First Affiliated Hospital of Chongqing Medical University (PYJJ2018-13) and Natural Science Foundation of Chongqing (cstc2019jcyj-msxmX0836). Bin He participated in the design, collection, analysis, interpretation of data and writing of this study.

Authors' Contributions

BH, JQZ and ZXQ designed the trial concept and protocol. BH, JQZ and MZZ searched the databases, collected and reviewed the data. BH, JQZ, MZZ and ZXQ conducted data quality. BH and JQZ drafted the manuscript. BH and ZXQ revised and approved the final version of the manuscript the final manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

References

1) Kendler DL, Marin F, Zerbini CA, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet 2018; 391: 230-240.
2) Tsai JN, Lee H, David NL, Eastell R, Leder BZ. Combination denosumab and high dose teriparatide for postmenopausal osteoporosis (DATA-HD): a randomised, controlled phase 4 trial. Lancet Diabetes Endocrinol 2019; 7: 767-775.
3) McClung MR, O'Donoghue ML, Papapoulos SE, Bone H, Langdahl B, Saag KG, Reid IR, Kiel DP, Cavallari I, Bonaca MP. Odanacatib for the treatment of postmenopausal osteoporosis: results of

the LOFT multicentre, randomised, double-blind, placebo-controlled trial and LOFT extension study. Lancet Diabetes Endocrinol 2019; 7: 899-911.
4) Black DM, Rosen CJ. Postmenopausal osteoporosis. N Engl J Med 2016; 374: 254-262.
5) Sugimoto T, Shiraki M, Nakano T, Kishimoto H, Ito M, Fukunaga M, Sone T, Hagino H, Miki T, Nishizawa Y. A randomized, double-blind, placebo-controlled study of once weekly elcatonin in primary postmenopausal osteoporosis. Curr Med Res Opin 2019; 35: 447-454.
6) Komar C, Ahmed M, Chen A, Richwine H, Zia N, Nazar A, Bauer L. Advancing methods of assessing bone quality to expand screening for osteoporosis. J Am Osteopath Assoc 2019; 119: 147-154.
7) Ulivieri FM, Caudarella R, Camisasca M, Cabrini DM, Merli I, Messina C, Piodi LP. Assessment of bone quality in osteoporosis treatment with bone anabolic agents: really something new? Curr Rheumatol Rev 2018; 14: 53-61.
8) Nakamura Y, Nakano M, Suzuki T, Sato J, Shiraki M. Two adipocytokines, leptin and adiponectin, independently predict osteoporotic fracture risk at different bone sites in postmenopausal women. Bone 2020; 137: 115404.
9) Khosla S. Personalising osteoporosis treatment for patients at high risk of fracture. Lancet Diabetes Endocrinol 2019; 7: 739-741.
10) Shane E. Improving fracture risk assessment in older adults. Lancet Diabetes Endocrinol 2019; 7: 5-7.
11) Ruggiero C, Bonamassa L, Pelini L, Prioletta I, Cianferotti L, Metozzi A, Benvenuti E, Brandi G, Guazzini A, Santoro G. Early post-surgical cognitive dysfunction is a risk factor for mortality among hip fracture hospitalized older persons. Osteoporos Int 2017; 28: 667-675.
12) Abtahi S, Driessen JH, Vestergaard P, van den Bergh J, Boonen A, de Vries F, Burden AM. Secular trends in major osteoporotic fractures among 50+ adults in Denmark between 1995 and 2010. Arch Osteoporos 2018; 13: 91.
13) Real J, Galindo G, Galván L, Lafarga MA, Rodrigo MD, Ortega M. Use of oral bisphosphonates in primary prevention of fractures in postmenopausal women: a population-based cohort study. PLoS One 2015; 10: e0118178
14) Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. Lancet Diabetes Endocrinol 2017; 5: 898-907.
15) Sugimoto T, Shiraki M, Fukunaga M, Hagino H, Sone T, Nakano T, Kishimoto H, Ito M, Yoshikawa H, Kishida M. 24-month open-label teriparatide once-weekly efficacy research trial examining bone mineral density in subjects with primary osteoporosis and high fracture risk. Adv Ther 2017; 34: 1727-1740.
16) Miller P, Pannacciulli N, Brown J, Czerwinski E, Nedergaard B, Bolognese M, Malouf J, Bone H, Reginster J-Y, Singer A. Denosumab or zoledronic acid in postmenopausal women with osteoporosis previously treated with oral bisphosphonates. J Clin Endocrinol Metab 2016; 101: 3163-3170.
17) Lozano MJF, Sánchez-Fidalgo S. Adherence and preference of intravenous zoledronic acid for osteoporosis versus other bisphosphonates. Eur J Hosp Pharm 2019; 26: 4-9.
18) Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wong S, Wiessing KR, Bolland MJ, Bastin S, Gamble GD. Fracture prevention with zoledronate in older women with osteopenia. N Engl J Med 2018; 379: 2407-2416.
19) McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, Zhou W, Adera M, Davis J. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. Bone 2007; 41: 122-128.
20) Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007; 357: 1799-17809.
21) Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356: 1809-1822.
22) Greenspan SL, Perera S, Ferchak MA, Nace DA, Resnick NM. Efficacy and safety of single-dose zoledronic acid for osteoporosis in frail elderly women: a randomized clinical trial. JAMA Intern Med 2015; 175: 913-921.
23) Liu Z, Li Cw, Mao Yf, Liu K, Liang Bc, Wu Lg, Shi Xl. Study on zoledronic acid reducing acute bone loss and fracture rates in elderly postoperative patients with intertrochanteric fractures. Orthop Surg 2019; 11: 380-385.
24) Boonen S, Reginster J-Y, Kaufman J-M, Lippuner K, Zanchetta J, Langdahl B, Rizzoli R, Lipschitz S, Dimai HP, Witvrouw R. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med 2012; 367: 1714-1723.
25) Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535.
26) Higgins JPT. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. The cochrane collaboration 2011.
27) Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
28) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
29) Zhang J, Zhang T, Xu X, Cai Q, Zhao D. Zoledronic acid combined with percutaneous kyphoplasty in the treatment of osteoporotic compression fracture in a single T12 or L1 vertebral body in postmenopausal women. Osteoporos Int 2019; 30: 1475-1480.
30) Cengiz Ö, Polat G, Karademir G, Tunç OD, Erdil M, Tuncay I, Şen C. Effects of Zoledronate on mortality and morbidity after surgical treatment of hip fractures. Adv Orthop 2016; 2016: 3703482.

31) Bai H, Jing D, Guo A, Yin S. Randomized controlled trial of zoledronic acid for treatment of osteoporosis in women. J Int Med Res 2013; 41: 697-704.
32) Boonen S, Orwoll E, Magaziner J, Colón-Emeric CS, Adachi JD, Bucci-Rechtweg C, Haentjens P, Kaufman JM, Rizzoli R, Vanderschueren D. Once-yearly zoledronic acid in older men compared with women with recent hip fracture. J Am Geriatr Soc 2011; 59: 2084-2090.
33) Colón-Emeric CS, Mesenbrink P, Lyles KW, Pieper CF, Boonen S, Delmas P, Eriksen EF, Magaziner J. Potential mediators of the mortality reduction with zoledronic acid after hip fracture. J Bone Miner Res 2010; 25: 91-97.
34) Boonen S, Black DM, Colón-Emeric CS, Eastell R, Magaziner JS, Eriksen EF, Mesenbrink P, Haentjens P, Lyles KW. Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. J Am Geriatr Soc 2010; 58: 292-299.
35) Prieto-Alhambra D, Judge A, Arden NK, Cooper C, Lyles K, Javaid MK. Fracture prevention in patients with cognitive impairment presenting with a hip fracture: secondary analysis of data from the HORIZON Recurrent Fracture Trial. Osteoporos Int 2014; 25: 77-83.
36) Hwang JS, Chin LS, Chen JF, Yang TS, Chen PQ, Tsai KS, Leung PC. The effects of intravenous zoledronic acid in Chinese women with postmenopausal osteoporosis. J Bone Miner Metab 2011; 29: 328-333.
37) Cauley JA, Black D, Boonen S, Cummings SR, Mesenbrink P, Palermo L, Man Z, Hadji P, Reid IR, Group HPF. Once-yearly zoledronic acid and days of disability, bed rest, and back pain: randomized, controlled HORIZON pivotal fracture trial. J Bone Miner Res 2011; 26: 984-992.
38) Akehurst R, Brereton N, Ariely R, Lusa T, Groot M, Foss P, Boonen S. The cost effectiveness of zoledronic acid 5 mg for the management of postmenopausal osteoporosis in women with prior fractures: evidence from Finland, Norway and the Netherlands. J Med Econ 2011; 14: 53-64.
39) Adachi JD, Lyles K, Colón-Emeric C, Boonen S, Pieper C, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore K. Zoledronic acid results in better health-related quality of life following hip fracture: the HORIZON–recurrent fracture trial. Osteoporos Int 2011; 22: 2539-2549.
40) Eriksen EF, Lyles KW, Colón-Emeric CS, Pieper CF, Magaziner JS, Adachi JD, Hyldstrup L, Recknor C, Nordsletten L, Lavecchia C. Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture. J Bone Miner Res 2009; 24: 1308-1313.
41) Black DM, Reid IR, Cauley JA, Cosman F, Leung PC, Lakatos P, Lippuner K, Cummings SR, Hue TF, Mukhopadhyay A. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2015; 30: 934-944.
42) Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, Cummings SR, Hue TF, Lippuner K, Lakatos P. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2012; 27: 243-254.
43) Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY, on behalf of the Scientific Advisory Board of the European Society for C, Economic Aspects of O, Osteoarthritis, the Committee of Scientific Advisors of the International Osteoporosis F. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2013; 24: 23-57.
44) Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. Osteoporos Int 2004; 15: 87-94.
45) Colón-Emeric C, Kuchibhatla M, Pieper C, Hawkes W, Fredman L, Magaziner J, Zimmerman S, Lyles KW. Zoledronic acid promotes TLR-4-mediated M1 macrophage polarization in bisphosphonate-related osteonecrosis of the jaw. FASEB J 2019; 33: 5208-5219.