

·Meta分析·

双膦酸盐治疗骨质疏松症与总死亡率相关性的meta分析

张亚玲¹ 王琳¹ 王敬贤² 何新霞¹

【摘要】目的 系统评价临床随机对照试验是否能够证明双膦酸盐类药物的应用与骨质疏松症患者的死亡率降低相关。**方法** 依据Meta分析要求,对CBM、CNKI、MEDLINE、PubMed、Springer、Embase、万方、维普、Cochrane Library、中国科技论文统计与分析网、专利数据库等进行检索,严格评价纳入以双膦酸盐药物作为主要干预措施治疗骨质疏松症的临床随机对照实验研究文献,并收录有效的相关的数据资料,检索年限从建库至2020年5月。采用NOS文献质量评价标准对符合纳入排除标准的文献进行质量评价。采用RR值及其95%可信区间评估关联强度。根据是否存在异质性,采用固定效应模型合并效应量,并根据单因素敏感性分析法进行敏感性分析。**结果** 最终纳入21篇文献,受试者共42 849例,双膦酸盐组患者22 605例,死亡855例,安慰剂组20 244例,死亡880例。双膦酸盐治疗骨质疏松症与总死亡率相关性的为 $RR=0.949$ (95% CI : 0.866, 1.040, $P=0.264$)。阿仑膦酸盐治疗骨质疏松症与总死亡率相关性的为 $RR=0.996$ (95% CI : 0.705, 1.407, $P=0.982$), 伊班膦酸盐为 $RR=0.802$ (95% CI : 0.496, 1.298, $P=0.369$), 利塞膦酸盐为 $RR=0.915$ (95% CI : 0.757, 1.105, $P=0.354$), 唑来膦酸盐为 $RR=0.898$ (95% CI : 0.770, 1.047, $P=0.168$), 尚未发现双膦酸盐治疗骨质疏松症与总死亡率的关联性。**结论** 经meta分析发现双膦酸盐治疗骨质疏松症患者的总死亡率未见明显降低。

【关键词】 骨质疏松症; 双膦酸盐; 总死亡率

The relationship between bisphosphonates and total mortality in patients with osteoporosis: A Meta-Analysis Zhang Yaling¹, Wang Lin¹, Wang Jingxian², He Xinxia¹. ¹Department of general practice medicine, ²Department of joint sports medicine, Hengshui people's Hospital, Hengshui 053000, China
Corresponding author: Zhang Yaling, Email: 1741349569@qq.com

【Abstract】 Objective To systematically evaluate whether clinical randomized controlled trials can demonstrate that bisphosphonates, especially zoledronic acid, are associated with reduced mortality in patients with osteoporosis. **Methods** According to the requirements of meta-analysis, CBM, CNKI, MEDLINE, PubMed, Springer, EMBASE, Wanfang, VIP and Cochrane were analyzed Library, China Science and Technology Papers Statistics and analysis network, patent database, etc. were searched to strictly evaluate the included clinical randomized controlled trials with bisphosphonates as the main intervention measures in the treatment of osteoporosis, and included effective related data. The retrieval period was from the establishment of the database to may 2020. The NOS standard was used to evaluate the quality of the literatures that met the inclusion and exclusion criteria. RR and its 95% confidence interval were used to evaluate the association strength. According to the existence of heterogeneity, the fixed effect model was used to merge the effect amount, and the single factor sensitivity analysis method was used to analyze the sensitivity. **Results** A total of 21 articles including 42, 849 subjects, 22, 605 patients in the bisphosphonate group, 855 patients died, 20, 244 patients in the placebo group and 880 deaths in the placebo group were analyzed. The correlation between bisphosphonate therapy and total mortality was 0.949 (95% CI : 0.866, 1.040, $P=0.264$). The correlation between alendronate and total mortality was 0.996 (95% CI : 0.705, 1.407, $P=0.982$), ibandronate was $RR=0.802$ (95% CI : 0.496, 1.298, $P=0.369$), risedronate was $RR=0.915$ (95% CI : 0.757, 1.105, $P=0.354$) and zoledronate was $RR=0.898$ (95% CI : 0.770, 1.047, $P=0.168$). There was no association between bisphos-

phonate therapy and total mortality. **Conclusion** The meta-analysis showed that bisphosphonates did not reduce the overall mortality of patients with osteoporosis.

【Key words】 Osteoporosis; Bisphosphonates; Total mortality

骨质疏松症(osteoporosis, OP)是最常见的骨科疾病,目前我国存在骨量减少的患者已超过2亿,骨质疏松症患者已近7000万,其中50岁以上女性患病率约为20.7%,男性约14.4%,60岁以上人群的患病率则更高^[1]。骨质疏松症的特征为骨密度和骨质量下降,骨量减少,骨微结构破坏,造成脆性增加,从而容易发生骨折的全身性骨病^[2]。美国国立卫生研究院(National Institutes of Health, NIH)于2001年将其定义为以骨质量下降和骨折风险增加为主要特征的骨髓疾病^[3]。双膦酸盐(bisphosphonates)是目前临床上应用最为广泛的治疗骨质疏松症药物,其特征是能特异的与骨质中的羟磷灰石结合,抑制破骨细胞活性,从而抑制骨质吸收^[4]。

目前用于防治骨质疏松症的双膦酸盐药物,主要代表性药物包括阿仑膦酸钠、利塞膦酸钠、伊班膦酸钠、唑来膦酸钠、依替膦酸二钠和氯膦酸二钠等^[4-12]。大量文献报道双膦酸盐类药物的安全性良好,其应用可使骨质疏松症患者的死亡率降低10%^[13]。但目前缺少与安慰剂的对比研究。如果能够明确证实双膦酸盐类药物能够减少骨质疏松症患者的骨折发生机会,并有效降低死亡率。那该药物值得在临床上广泛应用,不管患者有无骨折风险。因此本文对所有临床安慰剂随机对照试验进行总结,分析双膦酸盐类药物与死亡率的关系。

资料与方法

一、一般资料

我们系统地检索了CBM、CNKI、Embase、PubMed、Springer、Science Direct、万方、维普、Cochrane Library、中国科技论文统计与分析网、专利数据库等中英文数据库,以“双膦酸”、“阿仑膦酸钠”、“唑来膦酸钠”、“利塞膦酸钠”、“伊班膦酸钠”、“依替膦酸二钠”、“氯膦酸二钠”、“骨质疏松症”为中文检索词,以“bisphosphonate”、“alendronate”、“zoledronate”、“risedronate”、“ibandronate”、“etidronate”、“clodronate”、“osteoporosis”为英文检索词,进行主题、题名、关键词检索。本研究由两名研究人员独立进行检索,以确保检索结果的严谨全面。死亡率由一名

研究人员计算,文章由另外一名研究人员书写。

二、纳入与排除标准

纳入标准:(1)符合RCT试验要求,随机双盲安慰剂临床试验的中英文文献;(2)采用双膦酸盐药物治疗;(3)使用以批准剂量的药物治疗骨质疏松症;治疗时间 ≥ 1 年;(4)建库至今发表的文献。

排除标准:(1)非随机和安慰剂对照组;(2)不以双膦酸盐为主要干预措施;(3)数据不全;(4)临床综述或动物实验。

研究排除了(1)癌症患者;(2)如果是重复出版物只选取最终完整的试验结果报告;(3)接受皮质类固醇或雌激素治疗的患者。

三、文献质量评估

由两名研究人员独立对纳入文献进行meta分析,如在分析过程中遇到分歧,则共同商议决定或交由非本课题组的高年资医师共同裁定。将纳入的所有文献严格按照(Newcastle-Ottawa Scale, NOS)偏倚风险评估标准进行评估,本文仅纳入中等以上文章。

四、统计学方法

采用Stata 15.1进行Meta分析。通过 I^2 值检验不同研究之间的异质性,当 $I^2 < 50\%$ 时,采用固定效应模型(fixed effect)。通过去除某些研究进行敏感性分析,制作漏斗图来评估发表偏倚。二分类变量采用相对危险度(relative risk, RR)及95%可信区间(confidence interval, CI)表示。检验水准 α 值取双侧0.05。

结 果

一、文献检索结果

参照以上meta分析的检索方法在相关数据库进行文献检索,根据关键词初步筛查出1 527篇,严格纳入排除标准后去除不合格文献1 489篇,初步纳入38篇,精读文献后,排除随访时间短、非安慰剂对照等文献,最终纳入21篇^[14-34],具体流程见图1。

二、纳入文献的基本特征

最终纳入的21篇文献中,受试者共42 849例,其中双膦酸盐组患者22 605例,死亡855例,安慰剂组20 244例,死亡880例,其NOS评分均大于5分,见表1。

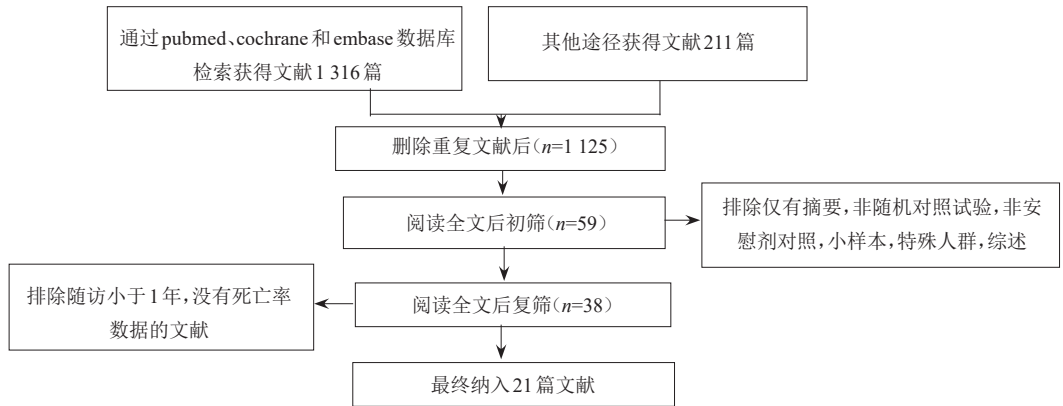


图1 纳入文献流程图

表1 纳入文献特征表

编号	第一作者	发表年份	药物	用药时间,年	治疗组		安慰剂组		年龄	评分
					死亡	全部	死亡	全部		
1	Liberman ^[14]	1995	阿仑膦酸盐	3	3	579	2	397	64(45~80)	7
2	Black ^[15]	1996	阿仑膦酸盐	3	24	1 022	21	1 005	71(55~81)	8
3	Ravn ^[16]	1996	伊班膦酸盐	1	1	150	40	2 218	68(54~81)	9
4	Cummings ^[17]	1998	阿仑膦酸盐	4.5	37	2 214	0	280	65(≤85)	7
5	Harris ^[18]	1999	利塞膦酸盐	3	15	813	249	2 796	80(≥75)	9
6	Reginster ^[19]	2000	利塞膦酸盐	3	11	407	1	30	65(<75)	6
7	McClung ^[20]	2001	利塞膦酸盐	3	167	3 104	10	975	69(55~80)	8
8	Chesnut ^[21]	2004	伊班膦酸盐	3	19	1 954	13	949	67(55~76)	8
9	Recker ^[22]	2004	伊班膦酸盐	3	23	1 911	0	83	54(45~60)	6
10	McCloskey ^[23]	2007	氯膦酸盐	3	264	2 796	3	63	51(NA)	6
11	Välimäki ^[24]	2007	利塞膦酸盐	2	0	115	16	815	69(≤85)	7
12	Black ^[25]	2007	唑来膦酸盐	3	130	3 862	17	407	71(≤85)	7
13	Lyles ^[26]	2007	唑来膦酸盐	1.9	101	1 054	178	3 134	78(70~100)	9
14	Yan ^[27]	2009	阿仑膦酸盐	1	0	280	0	55	66(NA)	6
15	McClung ^[28]	2009	伊班膦酸盐	1	0	77	3	93	61(36~84)	6
16	Boonen ^[29]	2009	利塞膦酸盐	2	2	191	112	3 852	73(65~89)	9
17	Smerud ^[30]	2012	伊班膦酸盐	1	0	66	141	1 057	75(≥50)	7
18	Boonen ^[31]	2012	唑来膦酸盐	2	15	588	18	611	NA(50~85)	7
19	Greenspan ^[32]	2015	唑来膦酸盐	2	14	89	12	92	85(≥65)	6
20	Nakamura ^[33]	2017	唑来膦酸盐	2	2	333	3	332	74(65~89)	7
21	Reid ^[34]	2018	唑来膦酸盐	6	27	1 000	41	1 000	71(>65)	8

注:NA表示没有获取数据

三、结局指标分析

(一)总死亡率的分析结果

纳入文献中有21篇文献进行总死亡率统计(见图2),图中分析显示 $Chi^2=15.93, I^2=0\%, P=0.529>0.1$,提示所纳入文献具有同质性,采取固定效应模型进行分析,并进行效应量合并, $RR=0.949, 95\% CI$

$(0.866, 1.040), Z=1.120, P=0.264$,结果显示其差异无统计学意义。

(二)发表偏倚

分析安慰剂组与双膦酸盐组总有效率在治疗膝关节骨性关节炎的发表偏倚上,Begg's检验中 $Pr>|Z|=0.173>0.05$ 提示不存在偏倚情况,见图3。

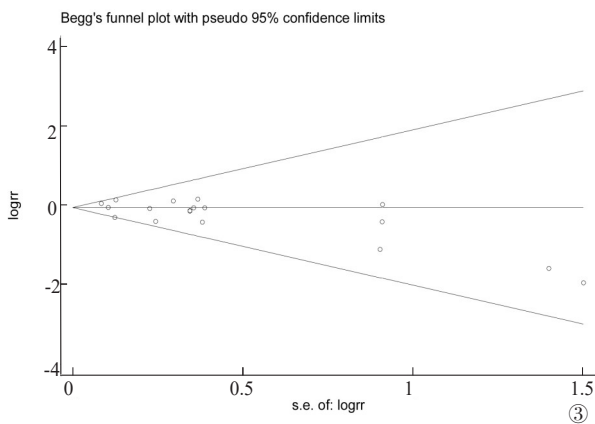
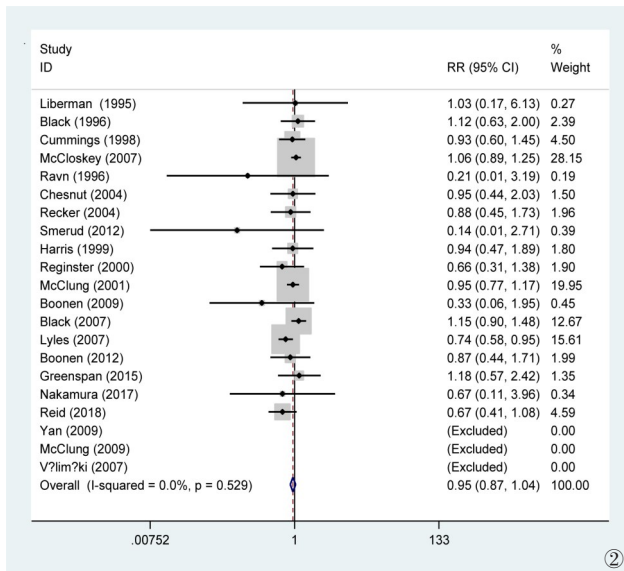


图2 双磷酸盐治疗骨质疏松症与总死亡率相关性的meta分析森林图 图3 双磷酸盐治疗骨质疏松症与总死亡率相关性的发表偏倚漏斗图

(三)敏感性分析

采用逐一排除每项研究的方法进行敏感性分析,合并其余研究的RR值,双磷酸盐治疗骨质疏松症与患者总死亡率相关性的结果如图4,结果提示逐一排除每项研究后,合并的其余研究均比较稳定,说明此次Meta分析的结果较为可靠。

四、亚组分析

仅对4篇阿仑膦酸盐进行总死亡率统计(见图5),图中分析显示 $Chi^2=2.26$, $I^2=0\%$, $P=0.878>0.1$,提示所纳入文献具有同质性,采取固定效应模型进行分析,并进行效应量合并, $RR=0.996$, $95\% CI (0.705, 1.407)$, $Z=0.02$, $P=0.982$,结果显示其差异无统计学意义。仅对5篇伊班膦酸盐进行总死亡率统计(见图6),图中分析显示 $Chi^2=2.52$, $I^2=0\%$, $P=0.471>0.1$,提示所纳入文献具有同质性,采取固定

效应模型进行分析,并进行效应量合并, $RR=0.802$, $95\% CI (0.496, 1.298)$, $Z=0.90$, $P=0.369$,结果显示其差异无统计学意义。仅对5篇利塞膦酸盐进行总死亡率统计(见图7),图中分析显示 $Chi^2=2.16$, $I^2=0\%$, $P=0.541>0.1$,提示所纳入文献具有同质性,采取固定效应模型进行分析,并进行效应量合并, $RR=0.915$, $95\% CI (0.757, 1.105)$, $Z=0.93$, $P=0.354$,结果显示其差异无统计学意义。仅对6篇唑来膦酸盐进行总死亡率统计(见图8),图中分析显示 $Chi^2=8.35$, $I^2=40.1\%$, $P=0.138>0.1$,提示所纳入文献具有同质性,采取固定效应模型进行分析,并进行效应量合并, $RR=0.898$, $95\% CI (0.770, 1.047)$, $Z=1.38$, $P=0.168$,结果显示其差异无统计学意义。

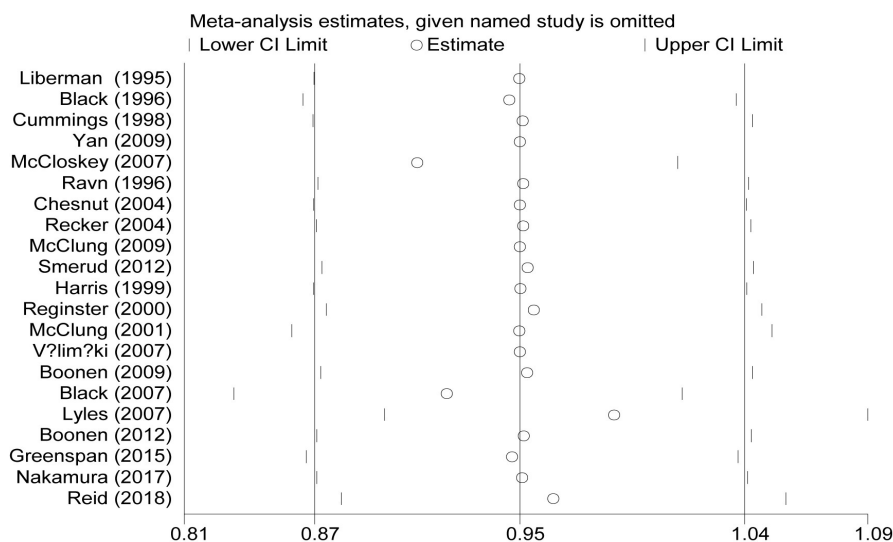
讨 论

一、骨质疏松症的特点

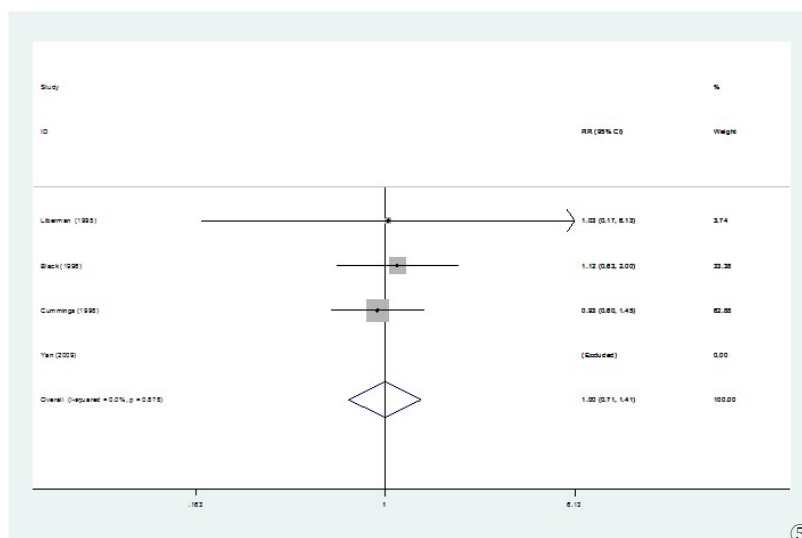
骨质疏松症是一种与年龄增长相关的骨骼系统疾病,随着年龄的增长,其发病率逐渐增高^[35-36]。我国老年人口(≥ 60 岁)达2.02亿,是世界上老年人口最多的国家,约占全世界老年人口总数的20%。众所周知,骨质疏松症易导致骨质疏松性骨折^[39-43]。据统计,2010年我国的骨质疏松性骨折患者约233万例,其中髌部骨折36万,椎体骨折1万,其他骨质疏松性骨折86万,我国为此支出的医疗费用高达649亿元。据推测,至2050年,我国骨质疏松性骨折患者将达到599万例,相应的医疗支出亦高达1745亿元^[44]。骨质疏松骨折的发生显著增加了我国老年患者的死亡率,据统计老年骨质疏松性髌部骨折患者的1年内死亡率高达26%^[45]。因此,有效治疗老年骨质疏松症可降低我国老年患者死亡率,实施老年骨质疏松规范化治疗、加强预防,提高我国老年骨质疏松症的临床诊疗水平,对于保障我国老年人群健康、改善生活质量、减轻家庭和社会负担具有重要意义,但我国目前老年骨质疏松症的诊疗现状并不理想。

二、双磷酸盐治疗骨质疏松症

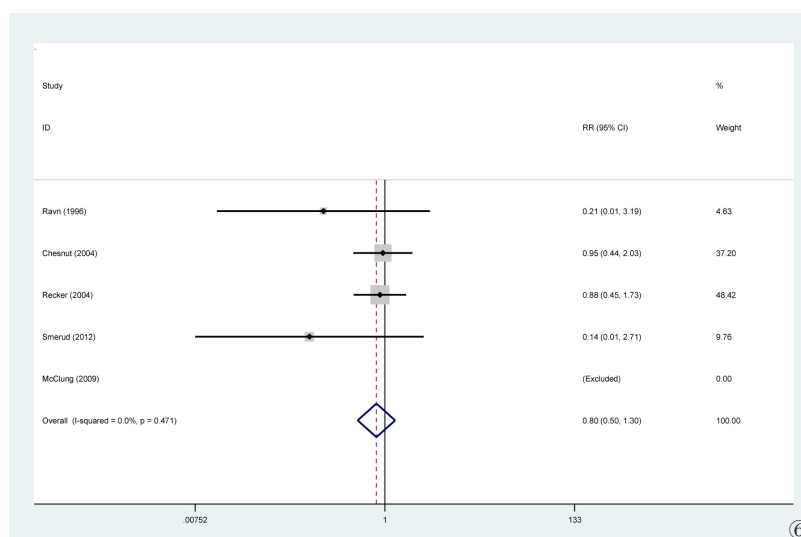
双磷酸类为当前最为常用的抗骨质疏松症药物,大量研究表明该药可有效降低骨质疏松性骨折的风险,提高患者股骨颈、腰椎和全髌骨密度,进而降低骨质疏松骨折的发生风险^[36,45]。2017年《巴西风湿病协会》指出:双磷酸盐类药物可显著升高男性患者的骨密度,降低男性脆性骨折的发生风险,减少绝经后女性骨质疏松症患者的椎骨、非椎骨和髌部



④



⑤



⑥

图4 双磷酸盐治疗骨质疏松症与患者总死亡率相关性的敏感性分析图 图5 阿仑膦酸盐治疗骨质疏松症与总死亡率相关性的森林图 图6 伊班膦酸盐总死亡率的森林图

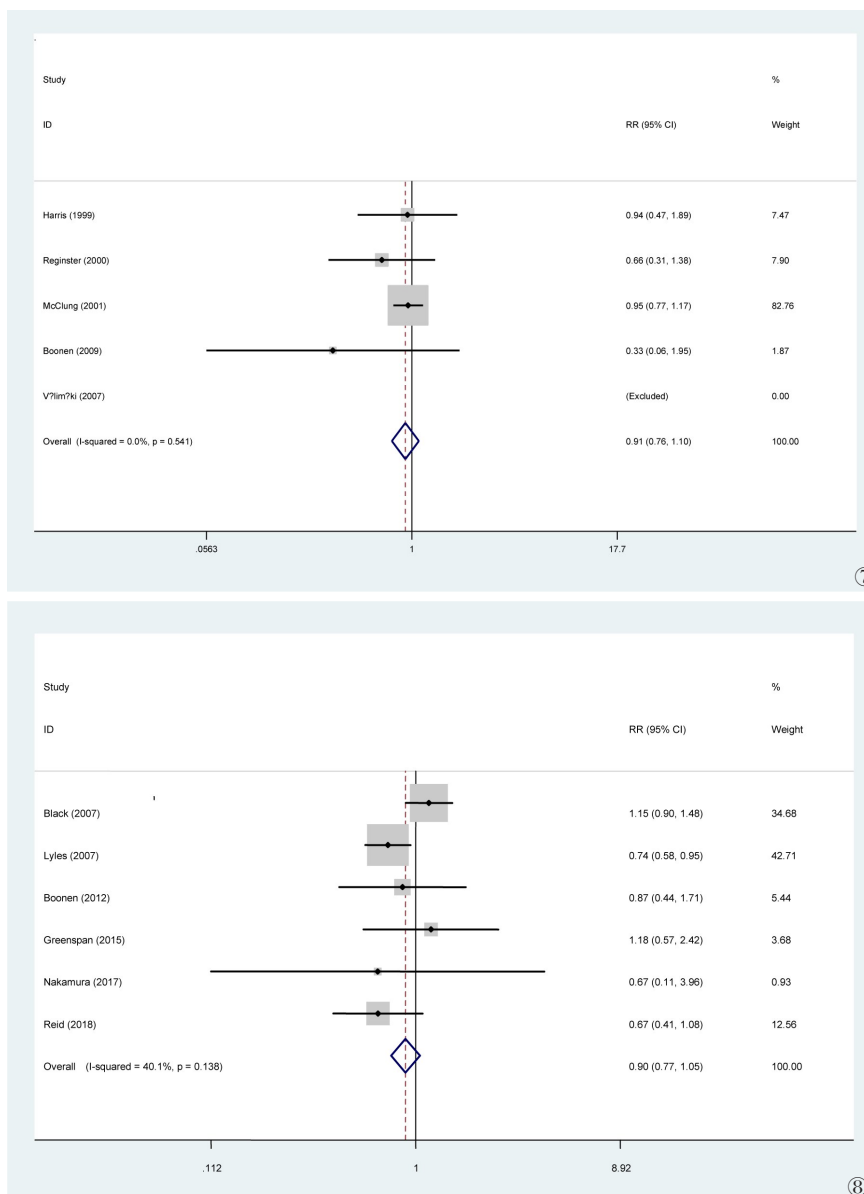


图7 利塞膦酸盐治疗骨质疏松症与总死亡率相关性的森林图 图8 唑来膦酸盐治疗骨质疏松症与总死亡率相关性的森林图

骨折发生率,推荐为绝经后骨质疏松的一线用药^[46]。2016年《美国临床内分泌学家协会和美国内分泌学学会》指出髌骨、椎体、非椎体等高风险骨质疏松性骨折患者,可将双膦酸盐类药物作为治疗骨质疏松症和预防脆性骨折的首选用药^[47]。但也有很多研究发现长时间使用双膦酸盐类药物会增加非典型性骨折的风险,并建议在长时间服用此类药物后,重新评估病情,以便及时更换,防止长时间使用该类药物带来的骨折风险^[48-50]。目前尚缺乏双膦酸盐治疗骨质疏松症与总死亡率的相关性研究^[51],本研究得出双膦酸盐治疗骨质疏松症患者未见其总死亡率显著降低,包括阿仑膦酸盐、伊班膦酸盐、利塞膦酸盐和唑

来膦酸盐。诸多研究表明,并非所有患者服用双膦酸盐所带来的收益均大于风险,长期应用双膦酸盐药物后需要重新进行评估^[52-53]。近年来,关于长期使用双膦酸盐药物所致的非典型骨折等严重不良后果的报道备受关注。2014年新英格兰杂志发表的一项队列研究分析了55岁以上股骨干骨折患者的X线片5342例,其中172例患者出现非典型骨折,而女性发生非典型骨折的风险是男性的3倍,且女性的非典型骨折风险随着用药时间的延长逐渐升高,连续使用4年后的相对风险增高达126倍^[52]。其原因可能是长期服用双膦酸盐后,患者的骨表面发生持续性沉积,增加了非典型骨折的风险^[52-53]。此外,

长期服用阿仑膦酸可能并发下颌骨坏死^[54-56],且长期服用双膦酸类抗骨质疏松药物或许不能显著降低骨质疏松症患者的总死亡率。

三、本研究的局限性与发展

本研究存在以下不足之处,首先本研究的观察时间最低为1年,死亡率的获取需要长时间随访,观察时间过短可能会引入选择偏差;第二,其他抗骨质疏松症的药物在此项研究中未被考虑进来,为该研究的全面评估带来一定的局限性;第三,本文虽然对所有文献严格依照纳入排除标准进行细致筛选,尽力排除可能造成整体异质性的文献,但由于纳入的文献中无法对骨质疏松分级、性别等情况进行细致划分,可能存在一定的异质性,经全面的发表偏倚评估和敏感性分析后,提示本研究结果较为可靠。总之,本研究双膦酸盐治疗骨质疏松症与患者总死亡率无相关性,双膦酸盐类药物并不能降低患者的总死亡率。尚需进一步长时间、大样本的前瞻性随机对照研究进行深入分析。

参 考 文 献

- 1 中国健康促进基金会骨质疏松防治中国白皮书编委会骨质疏松症中国白皮书[J]. 中华健康管理学杂志, 3: 148-154.
- 2 Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis [J]. Am J Med, 1993, 94: 646-650.
- 3 NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: Highlights of the Conference [J]. South Med J, 2001, 94: 569-573.
- 4 Russell RG, Watts NB, Ebetino FH, et al. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy [J]. OsteoporosInt, 2008, 19(6): 733-759.
- 5 Russell RG. Bisphosphonates: the first 40 years [J]. Bone, 2011, 49(1): 2-19.
- 6 Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women [J]. N Engl J Med, 2004, 350(12): 1189-1199.
- 7 Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture [J]. N Engl J Med, 2007, 357(18): 1799-1809.
- 8 McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group [J]. N Engl J Med, 2001, 344(5): 333-340.
- 9 Chesnut CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis [J]. J Bone Miner Res, 2004, 19(8): 1241-1249.
- 10 Harris ST, Watts NB, Jackson RD, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy [J]. Am J Med, 1993, 95(6): 557-567.
- 11 Gu JM, Wang L, Lin H, et al. The efficacy and safety of weekly 35-mg risedronate dosing regimen for Chinese postmenopausal women with osteoporosis or osteopenia: 1-year data [J]. ActaPharmacol Sin, 2015, 36(7): 841-846.
- 12 Zhang ZL, Liao EY, Xia WB, et al. Alendronate sodium/vitamin D3 combination tablet versus calcitriol for osteoporosis in Chinese postmenopausal women: a 6-month, randomized, open-label, active-comparator-controlled study with a 6-month extension [J]. OsteoporosInt, 2015, 26(9): 2365-2374.
- 13 Kranenburg G, Bartstra JW, Weijmans M, et al. Bisphosphonates for cardiovascular risk reduction: A systematic review and meta-analysis [J]. Atherosclerosis, 2016, 252: 106-115.
- 14 Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group [J]. N Engl J Med, 1995, 333(22): 1437-1443.
- 15 Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group [J]. Lancet, 1996, 348(9041): 1535-1541.
- 16 Ravn P, Clemmesen B, Riis BJ, et al. The effect on bone mass and bone markers of different doses of ibandronate: a new bisphosphonate for prevention and treatment of postmenopausal osteoporosis: a 1-year, randomized, double-blind, placebo-controlled dose-finding study [J]. Bone, 1996, 19(5): 527-533.
- 17 Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial [J]. JAMA, 1998, 280(24): 2077-2082.
- 18 Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group [J]. JAMA, 1999, 282(14): 1344-1352.
- 19 Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group [J]. OsteoporosInt, 2000, 11(1): 83-91.
- 20 McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group [J]. N Engl J Med. 2001, 344(5): 333-340.
- 21 Chesnut CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis [J]. J Bone Miner Res, 2004, 19(8): 1241-1249.
- 22 Recker R, Stakkestad JA, Chesnut CH, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal anti-fracture efficacy in postmenopausal osteoporosis [J]. Bone, 2004, 34(5): 890-899.
- 23 McCloskey EV, Beneton M, Charlesworth D, et al. Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study [J]. J Bone Miner Res, 2007, 22(1): 135-141.
- 24 Valimaki MJ, Farrerons-Minguella J, Halse J, et al. Effects of risedronate 5 mg/d on bone mineral density and bone turnover markers in late-postmenopausal women with osteopenia: a multinational, 24-month, randomized, double-blind, placebo-controlled, parallel-

- group, phase III trial [J]. ClinTher, 2007, 29(9): 1937-1949.
- 25 Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis [J]. N Engl J Med, 2007, 356(18): 1809-1822.
- 26 Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture [J]. N Engl J Med, 2007, 357(18): 1799-1809.
- 27 Yan Y, Wang W, Zhu H, et al. The efficacy and tolerability of once-weekly alendronate 70 mg on bone mineral density and bone turnover markers in postmenopausal Chinese women with osteoporosis [J]. J Bone Miner Metab, 2009, 27(4): 471-478.
- 28 McClung MR, Bolognese MA, Sedarati F, et al. Efficacy and safety of monthly oral ibandronate in the prevention of postmenopausal bone loss [J]. Bone, 2009, 44(3): 418-422.
- 29 Boonen S, Orwoll ES, Wenderoth D, et al. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study [J]. J Bone Miner Res, 2009, 24(4): 719-725.
- 30 Smerud KT, Dolgos S, Olsen IC, et al. A 1-year randomized, double-blind, placebo-controlled study of intravenous ibandronate on bone loss following renal transplantation [J]. Am J Transplant, 2012, 12(12): 3316-3325.
- 31 Boonen S, Reginster JY, Kaufman JM, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis [J]. N Engl J Med, 2012, 367(18): 1714-1723.
- 32 Greenspan SL, Perera S, Ferchak MA, et al. Efficacy and safety of single-dose zoledronic acid for osteoporosis in frail elderly women: a randomized clinical trial [J]. JAMA Intern Med, 2015, 175(6): 913-921.
- 33 Nakamura T, Fukunaga M, Nakano T, et al. Efficacy and safety of once-yearly zoledronic acid in Japanese patients with primary osteoporosis: two-year results from a randomized placebo-controlled double-blind study (ZOledroNate treatment in Efficacy to osteoporosis; ZONE study) [J]. OsteoporosInt, 2017, 28(1): 389-398.
- 34 Reid IR, Horne AM, Mihov B, et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia [J]. N Engl J Med, 2018, 379(25): 2407-2416.
- 35 Serio B, Paolino S, Casabella A, et al. Osteoporosis in the elderly [J]. Aging ClinExp Res, 2013, 25(Suppl 1): S27-29.
- 36 马晓龙, 刘强, 吴斗, 等. 骨质疏松显微骨折早期发生发展过程的实验研究 [J/CD]. 中华老年骨科与康复电子杂志, 2016, 2(3): 129-135.
- 37 中华人民共和国国家统计局. 中国统计年鉴 [M]. 北京: 中国统计出版社, 2015.
- 38 邱贵兴. 老年骨质疏松性骨折的治疗策略 [J]. 中华老年骨科与康复电子杂志, 2015, 1(1): 1-5.
- 39 Abrahamsen B, van Staa T, Ariely R, et al. Excess mortality following hip fracture: a systematic epidemiological review [J]. OsteoporosInt, 2009, 20(10): 1633-1650.
- 40 邵佳申, 刘勃, 李佳, 等. 2010至2011年河北省老年股骨转子间骨折的流行病学特征分析 [J/CD]. 中华老年骨科与康复电子杂志, 2018, 4(6): 352-355.
- 41 李佳, 刘勃, 刘松, 等. 中国中西部地区2010至2011年60岁以上股骨颈骨折流行病学对比[J/CD]. 中华老年骨科与康复电子杂志, 2018, 4(1): 38-42.
- 42 刘松, 李佳, 李石伦, 等. 中国华北和华东地区2010至2011年老年股骨转子间骨折流行病学对比分析[J/CD]. 中华老年骨科与康复电子杂志, 2018, 4(1): 43-47.
- 43 刘松, 陈伟, 朱燕宾, 等. 中国东北和西北地区2010—2011年老年髋部骨折的流行病学对比[J/CD]. 中华老年骨科与康复电子杂志, 2017, 3(3): 172-176.
- 44 Si L, Winzenberg TM, Jiang Q, et al. Projection of osteoporosis-related fractures and costs in China: 2010-2050 [J]. OsteoporosInt, 2015, 26(7): 1929-1937.
- 45 Davidson CW, Merrilees MJ, Wilkinson TJ, et al. Hip fracture mortality and morbidity--can we do better? [J]. N Z Med J, 2001, 114(1136): 329-332.
- 46 Loures MAR, Zerbini CAF, Danowski JS, et al. Guidelines of the Brazilian Society of Rheumatology for the diagnosis and treatment of osteoporosis in men [J]. Rev Bras ReumatolEngl Ed, 2017, 57(Suppl 2): 497-514.
- 47 Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016 [J]. EndocrPract, 2016, 22(Suppl 4): 1-42.
- 48 宋会平, 张柳. 阿仑膦酸钠治疗老年女性严重骨质疏松症患者的疗效分析[J/CD]. 中华老年骨科与康复电子杂志, 2016, 2(3): 141-145.
- 49 Yeap SS, Hew FL, Lee JK, et al. The Malaysian Clinical Guidance on the management of postmenopausal osteoporosis, 2012: a summary [J]. Int J Rheum Dis, 2013, 16(1): 30-40.
- 50 Lee S, Yin RV, Hirpara H, et al. Increased risk for atypical fractures associated with bisphosphonate use [J]. FamPract, 2015, 32(3): 276-281.
- 51 Cremers S, Papapoulos S. Pharmacology of bisphosphonates [J]. Bone, 2011, 49(1): 42-49.
- 52 Schilcher J, Koeppen V, Aspenberg P, et al. Risk of atypical femoral fracture during and after bisphosphonate use [J]. N Engl J Med, 2014, 371(10): 974-976.
- 53 李玉洁, 朱志伟, 刘忠厚. 2014年骨质疏松领域进展回顾--美国骨矿盐研究学会(ASBMR)年会精粹(2014, 休斯顿) [J]. 中国骨质疏松杂志, 2015, 21(4): 379-394.
- 54 Borromeo GL, Brand C, Clement JG, et al. A large case-control study reveals a positive association between bisphosphonate use and delayed dental healing and osteonecrosis of the jaw [J]. J Bone Miner Res, 2014, 29(6): 1363-1368.
- 55 Lin TC, Yang CY, Kao Yang YH, et al. Incidence and risk of osteonecrosis of the jaw among the Taiwan osteoporosis population [J]. OsteoporosInt, 2014, 25(5): 1503-1511.
- 56 Chiu WY, Chien JY, Yang WS, et al. The risk of osteonecrosis of the Jaws in Taiwanese osteoporotic patients treated with oral alendronate or raloxifene [J]. J ClinEndocrinolMetab, 2014, 99(8): 2729-2735.

(收稿日期:2020-07-25)

(本文编辑:吕红芝)

张亚玲, 王琳, 王敬贤, 等. 双膦酸盐治疗骨质疏松症与总死亡率相关性的meta分析 [J/CD]. 中华老年骨科与康复电子杂志, 2020, 6(5): 304-311.