

Efficacy and Safety of Different Bisphosphonates for Bone Loss Prevention in Kidney Transplant Recipients: A Network Meta-Analysis of Randomized Controlled Trials

Yan Yang¹, Shi Qiu², Xi Tang¹, Xin-Rui Li¹, Ling-Hui Deng³, Qiang Wei², Ping Fu¹

¹Division of Nephrology, Kidney Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

²Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

³Department of Neurology, Stroke Clinical Research Unit, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

Abstract

Background: Mineral and bone disorder is one of the severe complications in kidney transplant recipients (KTRs). Previous studies showed that bisphosphonates had favorable effects on bone mineral density (BMD). We sought to compare different bisphosphonate regimens and rank their strategies.

Methods: We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to April 01, 2017, for randomized controlled trials (RCTs) comparing bisphosphonate treatments in adult KTRs. The primary outcome was BMD change. We executed the tool recommended by the Cochrane Collaboration to evaluate the risk of bias. We performed pairwise meta-analyses using random effects models and network meta-analysis (NMA) using Bayesian models and assessed the quality of evidence.

Results: A total of 21 RCTs (1332 participants) comparing 6 bisphosphonate regimens were included. All bisphosphonates showed a significantly increased percentage change in BMD at the lumbar spine compared to calcium except clodronate. Pamidronate with calcium and Vitamin D analogs showed improved BMD in comparison to clodronate with calcium (mean difference [MD], 9.84; 95% credibility interval [CrI], 1.06–19.70). The combination of calcium and Vitamin D analogs had a significantly lower influence than adding either pamidronate or alendronate (MD, 6.34; 95% CrI, 2.59–11.01 and MD, 6.16; 95% CrI, 0.54–13.24, respectively). In terms of percentage BMD change at the femoral neck, both pamidronate and ibandronate combined with calcium demonstrated a remarkable gain compared with calcium (MD, 7.02; 95% CrI, 0.30–13.29 and MD, 7.30; 95% CrI, 0.32–14.22, respectively). The combination of ibandronate with calcium displayed a significant increase in absolute BMD compared to any other treatments and was ranked best.

Conclusions: Our NMA suggested that new-generation bisphosphonates such as ibandronate were more favorable in KTRs to improve BMD. However, the conclusion should be treated with caution due to indirect comparisons.

Key words: Bisphosphonates; Bone Mineral Density; Kidney Transplant Recipients; Network Meta-Analysis

INTRODUCTION

Currently, an increasing number of people are suffering from chronic kidney disease that could progress to end-stage renal disease (ESRD). According to the latest United States Renal Data System Annual Data Report,^[1] more than 660,000 Americans are afflicted with ESRD. Of these ESRD patients, over 193,000 underwent kidney transplantation (KT). Furthermore, mineral and bone disorders after KT increase fracture risk and contribute to cardiovascular disease, thereby impacting patient quality of life and long-term survival. Naylor *et al.*^[2] reported that the 5-year cumulative incidence of fractures ranges from 0.85% to 27% after a successful KT.

Furthermore, bone loss can also impose financial burdens by increasing patient morbidity and mortality.^[3] Hence, prevention and treatment of bone loss are of great importance to the care of post-kidney transplant recipients (KTRs).

Address for correspondence: Prof. Ping Fu,

Division of Nephrology, Kidney Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China
E-Mail: fupinghx@163.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2018 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Received: 11-01-2018 **Edited by:** Yuan-Yuan Ji

How to cite this article: Yang Y, Qiu S, Tang X, Li XR, Deng LH, Wei Q, Fu P. Efficacy and Safety of Different Bisphosphonates for Bone Loss Prevention in Kidney Transplant Recipients: A Network Meta-Analysis of Randomized Controlled Trials. *Chin Med J* 2018;131:818-28.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.228252

The etiology of bone disorders after KT is multifactorial with nearly all of KTRs suffering from preexisting bone disorders.^[4] However, new bone disorders may also emerge following immunosuppressive treatment. Corticosteroid therapy, a main contributor, can decrease bone mass by inhibiting osteoblasts and stimulating osteoclasts.^[5] Calcineurin inhibitors and patient immobility lead to bone loss as well.^[6] Bisphosphonates are common antiresorptive agents employed against osteoporosis. The mechanism of action for bisphosphonates involves binding to bone mineral, which directly suppresses osteoclast activity and consequently reduces fracture risk.^[7] Previous studies^[8,9] have shown that bisphosphonate therapy is an effective treatment for postmenopausal women with osteoporosis and glucocorticoid-induced osteoporosis. However, it remains unclear whether bisphosphonate treatment regimens are beneficial for KTRs because of the potential for nephrotoxicity and development of adynamic bone disease.^[10]

Several meta-analyses^[11,12] have demonstrated that bisphosphonates have favorable effects on bone mineral density (BMD), but questionable effects on the risk of fracture. Moreover, it is unknown that which subclasses of bisphosphonates are more favorable in terms of prevention and treatment of post-KT bone disease. In addition, the results of these trials only compared all bisphosphonate treatments with either Vitamin D analogs or calcium (or both). Only a few head-to-head randomized trials of different bisphosphonates have been conducted.^[13,14] Therefore, it is difficult to evaluate the relative added value among various bisphosphonates classes. To obtain the estimates of relative treatment effects for all possible comparisons, we conducted a network meta-analysis (NMA). The present NMA seeks to systematically review the literature and determine the relative efficacy and safety of bisphosphonate therapies for treating bone loss after KT.

METHODS

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement extension for NMAs.^[15]

Data sources and searches

To compare the tolerability and efficacy of different bisphosphonates in KTRs, a comprehensive search of the literature published up to April 01, 2017, was performed in the following databases: PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The reference lists of retrieved publications as well as relevant meta-analyses in the discipline were manually checked. We also searched international trial registries for trials in progress. The full-search parameters for each database are outlined in Supplement 1. Two independent investigators (YY and SQ) initially screened the citation titles and abstracts.

Study selection

Our preliminary search encompassed all RCTs comparing bisphosphonate-treated and control groups of KTRs. Studies

that met the following criteria were finally involved: (1) trials were conducted in a homogenous group of *de novo* adult KTRs; (2) at least one of the interventions compared in the trial was bisphosphonate treatment and the protocol was listed clearly in the article; (3) the publication was a full-text original article; and (4) at least one trial outcome was of interest for our NMA. Citations were excluded for the following reasons: non-English text, review article, intervention, or study design. Studies accepting recipients of combined transplants including kidney, such as kidney-pancreas transplantation, were also excluded. If duplicate studies from identical authors were found, the reports were grouped together and only the publication with the most complete data was used. Any discrepancies in the study inclusion were resolved by consulting the senior authors (XT and QW).

Data extraction and quality assessment

The independent reviewers (YY and SQ) used a standardized form to extract information from each eligible study. Data regarding study-, patient-, and treatment-related characteristics and outcomes were extracted simultaneously. Attempts were made to obtain missing data from the first or corresponding authors of such studies. We assessed the validity of the NMA through a qualitative appraisal of study designs and methods. We executed the tool recommended by the Cochrane Collaboration to evaluate the risk of bias.^[16]

Outcomes

The primary outcomes were the changes in BMD (percentage change and absolute change [in g/cm²]) at the lumbar spine and the femoral neck after successful KTs. The secondary outcomes were overall fractures (both vertebral and nonvertebral fractures), all-cause mortality, graft loss, acute renal rejection, and adverse events. Only fractures that occurred after the subjects entered the study and during the reported follow-up time were used to calculate fracture incidence. The fracture events were identified by radiography. If the fracture site was not mentioned, it was regarded as a nonvertebral fracture. Graft loss was regarded as renal failure, which also included a doubling of the baseline serum creatinine level and undergoing transplantation or dialysis again. We used data from the longest complete follow-up when the outcomes of different follow-up intervals were reported. When investigators published more than one report addressing the same population, the most comprehensive report was included.

Data synthesis and statistical analysis

We initially performed a pairwise meta-analysis using a random-effects model.^[17] Results were expressed as odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous variables (fracture, all-cause mortality, graft loss, acute renal rejection, and adverse events) and as the mean difference (MD) for continuous outcomes (percentage change and absolute change in BMD). The level of statistical significance was set at $P < 0.05$ and all statistical tests were two sided. The statistical heterogeneity of the studies was

evaluated by the Cochran's Q test and the I^2 statistic. $P \leq 0.05$ for the Q test or an $I^2 > 50\%$ was suggestive of substantial study heterogeneity.

We performed fixed-effects Bayesian NMAs for indirect and mixed comparisons using Markov chain Monte Carlo methods in WinBUGS version 1.4.3 (MRC Biostatistics Unit).^[18] A Bayesian fixed-effects framework was deemed appropriate because of the limited number of studies supporting each edge in the network.^[18,19] We report the resultant effect as MD or OR with corresponding 95% credibility intervals (CrIs), which are the Bayesian analog of 95% CIs. We estimated the relative ranking probability of each strategy and obtained the hierarchy of competing interventions using rankograms and the surface under the cumulative ranking curve (SUCRA).^[20] The SUCRA index ranges between 0 (or 0%) and 1 (or 100%), where the treatments with the highest and lowest SUCRA are considered to be the best and worst treatments, respectively.

To assess the presence of inconsistency, we employed the node-splitting method, excluding one direct comparison at a time and estimating the indirect treatment effect for the excluded comparison. To check the assumption of consistency in the entire network, the design-by-treatment model was conducted.^[19] We then performed sensitivity analysis to explore important network inconsistencies.

Quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology was performed to rate the quality of the evidence.^[21] In this approach, direct evidence from the RCTs starts at high quality and can be downgraded based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and publication bias to levels of moderate, low, and relatively low quality.^[22]

RESULTS

Study characteristics

Of the 864 citations identified through our search strategy, 23 publications reporting 21 randomized controlled trials (RCTs)^[4,13,14,23-42] were included in this NMA. The PRISMA^[15] flowchart depicting the electronic searching process is presented in Figure 1. The trials comparing six different bisphosphonates were published between October 1998 and March 2015. Table 1 provides characteristics of the 21 RCTs involving 1332 participants and additional details are summarized in Supplement Table 1. Of these, seven studies^[14,25,28,29,31,41,42] excluded patients who were diagnosed with diabetes mellitus. Most of the RCTs included both sexes, except two studies^[31,38] which only included male patients. The number of patients allocated to each treatment ranged from 8 to 66. The duration of patient follow-up ranged from 6 months to 4 years after the first administration.

With the exception of one RCT,^[38] all patients in the included trials received co-intervention including calcium,^[4,29,31-33,36,37,39,41] Vitamin D analogs,^[24] or both.

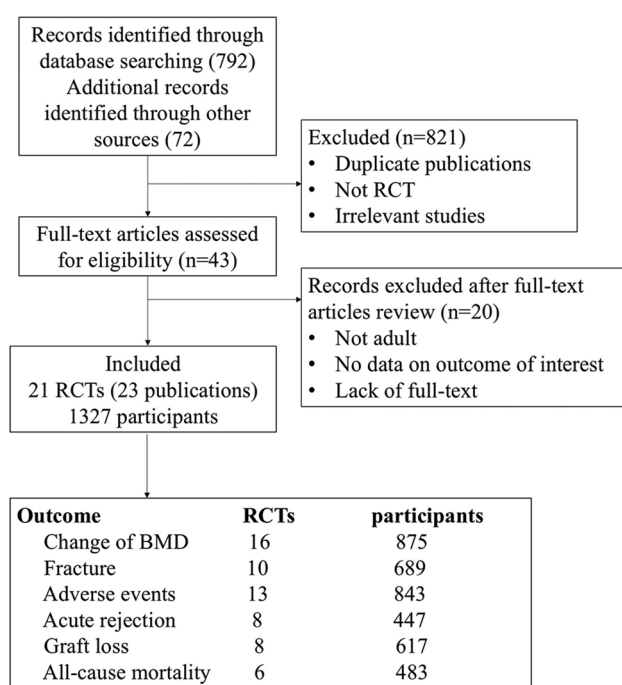


Figure 1: Flowchart of study identification and selection procedure.

As expected, most studies compared bisphosphonates with Vitamin D analogs (cholecalciferol, alfacalcidol, and calcitriol) or placebo treatment. Only two RCTs^[13,14] directly compared two different bisphosphonates. Bisphosphonate interventions encompassed alendronate,^[13,28-31,33,40,41] pamidronate,^[13,26,27,34,35,37,38] zoledronic acid,^[4,32] ibandronate,^[14,23,36] risedronate,^[14,24,25,42] and clodronate.^[39] Pamidronate and zoledronic acid were administered intravenously, while clodronate, alendronate, and risedronate were given orally. Ibandronate was given intravenously in two studies and orally in the other studies. The network geometries for the primary outcome of this NMA are provided in Figure 2.

Risk of bias assessment result

The results from the risk of bias assessment are provided in Supplement Figure 1 and Supplement Table 2. In general, details regarding trial methodology were unsatisfactory or incomplete for the majority of the studies. Overall, there were 6 (26%) studies regarded as having high risk of bias. Only 10 (43%) studies performed randomized sequence generation adequately. Furthermore, the risk of bias for concealment of treatment allocation was high or unclear in 14 (61%) studies. Only 4 (17%) studies explicitly reported the blinding of participants and investigators, whereas the remaining studies were at high or unclear risk in this regard. The investigators attempted to blind outcome assessors in 6 (26%) studies, 3 studies did not make an effort to blind assessors, and the remaining studies were unclear. Comparison-adjusted funnel plots show no evidence of asymmetry.

Pairwise meta-analysis

The results of the NMA and direct pairwise meta-analysis are summarized in Supplement Table 3. In terms of absolute

Table 1: Characteristics of enrolled studies

Studies	Follow-up	Country	Number of patients	Male/female	Intervention	n	Co-intervention	Immunosuppression
Smerud <i>et al.</i> , 2012 ^[23]	12 months	Norway	129	99/30	Ibandronate Placebo	66 63	Calcium + calcitriol	Corticosteroids, MMF, CsA or FK506
Coco <i>et al.</i> , 2012 ^[24]	12 months	USA	42	27/15	Risedronate Placebo	20 22	Calcitriol (with or without calcium)	Corticosteroids, MMF, FK506
Omidvar <i>et al.</i> , 2011 ^[13]	6 months	Iran	40	27/13	Pamidronate Alendronate	20 20	Calcium + calcitriol	Corticosteroids, MMF, CsA
Torregrosa <i>et al.</i> , 2010 ^[25]	12 months	Spain	101	67/34	Risedronate No treatment	52 49	Calcium + Vitamin D	Corticosteroids, FK506 with or without MMF
Torregrosa <i>et al.</i> , 2011 ^[26]	12 months	Spain	39	26/13	Pamidronate Placebo	24 15	Calcium + cholecalciferol	Corticosteroids, MMF, CsA
Walsh <i>et al.</i> , 2009 ^[27]	24 months	UK	125	69/24	Pamidronate No treatment	65 60	Calcium + Vitamin D	Corticosteroids, CsA
Lan <i>et al.</i> , 2008 ^[28]	6 months	China	46	19/27	Alendronate No treatment	23 23	Calcium + calcitriol	Corticosteroids, MMF, CsA
Trabulus <i>et al.</i> , 2008 ^[29]	12 months	Turkey	64	40/19	Alendronate Alfacalcidol Alendronate + alfacalcidol No treatment	13 25 17 9	Calcium	Corticosteroids, AZA or MMF, CsA or FK506
Nayak <i>et al.</i> , 2007 ^[30]	6 months	India	50	NA	Alendronate No treatment	27 23	Calcium + Vitamin D	Not mentioned
El-Agroudy <i>et al.</i> , 2005 ^[31]	12 months	Egypt	60	60/0	Alendronate Alfacalcidol Calcitonin No treatment	15 15 15 15	Calcium	Corticosteroids, CsA
Schwarz <i>et al.</i> , 2004 ^[32]	36 months	Austria	20	NA	Zoledronic acid Placebo	9 10	Calcium	Corticosteroids, MMF, CsA
Jeffery <i>et al.</i> , 2003 ^[33]	12 months	Canada	117	71/26	Alendronate Calcitriol	57 60	Calcium	Corticosteroids, CsA, AZA or MMF
Coco <i>et al.</i> , 2003 ^[34]	12 months	USA	72	31/28	Pamidronate No treatment	36 36	Calcium + calcitriol	Corticosteroids, CsA or FK506
Fan <i>et al.</i> , 2003 ^[35]	48 months	UK	17	17/0	Pamidronate Placebo	9 8	No treatment	Corticosteroids, AZA, CsA
Haas <i>et al.</i> , 2003 ^[4]	6 months	Austria	20	12/8	Zoledronic acid Placebo	10 10	Calcium	Corticosteroids, MMF, CsA
Grotz <i>et al.</i> , 2001 ^[36]	12 months	Germany	80	48/24	Ibandronate No treatment	36 36	Calcium	Corticosteroids, MMF, CsA
Nam <i>et al.</i> , 2000 ^[37]	6 months	Korea	50	29/21	Pamidronate Calcitriol No treatment	15 15 20	Calcium	Not mentioned
Fan <i>et al.</i> , 2000 ^[38]	12 months	UK	26	26/0	Pamidronate Placebo	14 12	No treatment	Corticosteroids, AZA, CsA
Grotz <i>et al.</i> , 1998 ^[39]	12 months	Germany	46	29/17	Clodronate Calcitonin No treatment	15 16 15	Calcium	Corticosteroids, CsA
Giannini <i>et al.</i> , 2001 ^[40]	12 months	Italy	40	27/13	Alendronate No treatment	20 20	Calcium + calcitriol	Corticosteroids, CsA with or without AZA
Koc <i>et al.</i> , 2002 ^[41]	12 months	Turkey	24	17/7	Alendronate Calcitriol No treatment	8 8 8	Calcium	Corticosteroids, AZA, CsA
Torregrosa <i>et al.</i> , 2007 ^[42]	12 months	Spain	84	42/42	Risedronate No treatment	39 45	Calcium + Vitamin D	Corticosteroids, CsA or FK506, with or without MMF
Sánchez-Escuredo <i>et al.</i> , 2015 ^[14]	12 months	Spain	77	11/58	Ibandronate Risedronate	38 39	Calcium + Vitamin D	Corticosteroids, MMF, CsA or FK506 or mTOR inhibitor

MMF: Mycophenolate mofetil; CsA: Cyclosporine; FK506: Tacrolimus; AZA: Azathioprine; mTOR: Mammalian target of rapamycin.

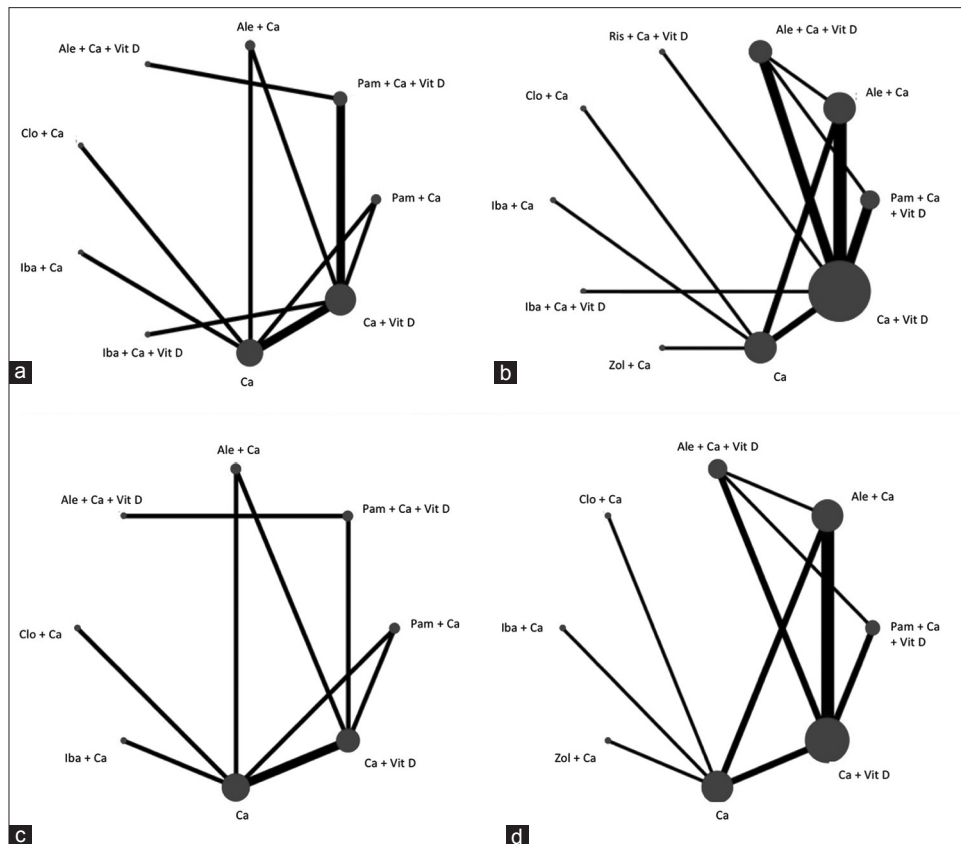


Figure 2: Network of eligible comparisons for primary outcome. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size). (a) Percentage change of BMD at lumbar spine. (b) Absolute change of BMD at lumbar spine. (c) Percentage change of BMD at femoral neck. (d) Absolute change of BMD at femoral neck. Pam: Pamidronate; Ale: Alendronate; Clo: Clodronate; Iba: Ibandronate; Zol: Zoledronic acid; Ris: Risedronate; Ca: Calcium; Vit D: Vitamin D analogs; BMD: Bone mineral density.

femoral change at the longest follow-up, alendronate combined with calcium was significantly better than calcium alone (MD, 1.15; 95% CI, 0.251–2.049). Alendronate with calcium and Vitamin D analogs was associated with a pronounced improvement in absolute femoral change compared to the combination of calcium and Vitamin D analogs (MD, 0.881; 95% CI, 0.430–1.332). Calcium with Vitamin D analogs was significantly better than solely calcium (MD 0.742; 95% CI, 0.141–1.344). When considering absolute change at the lumbar spine for the longest follow-up, only the combination of alendronate, calcium, and Vitamin D analogs was associated with a marginal improvement compared to calcium and Vitamin D analogs (MD, 0.345; 95% CI, 0.002–0.687). Treatments with calcium alone displayed significantly lower percentage change in BMD at the lumbar spine than with combining calcium and Vitamin D analogs (MD, –2.728; 95% CI, –3.511––1.945).

Network meta-analysis primary outcome

Change of bone mineral density at the lumbar spine

Eight RCTs involving 490 adults evaluated the percentage change in BMD at the lumbar spine. The staircase diagrams show the MDs and ranks for the treatment comparisons based on SUCRA. We observed that pamidronate combined

with calcium and Vitamin D analogs was associated with marked improvement compared to the combination of clodronate and calcium [Figure 3a; MD, 9.84; 95% CrI, 1.06–19.70]. All bisphosphonates were significantly better than calcium alone except clodronate (MD, 2.85; 95% CrI, –3.78–10.36). Use of solely calcium showed less improvement than combinatorial treatments of calcium with Vitamin D analogs (MD, –6.35; 95% CrI, –10.67––2.68). However, the addition of either pamidronate or alendronate displayed a notable improvement compared to calcium and Vitamin D (MD, 6.34; 95% CrI, 2.59–11.01 and MD, 6.16; 95% CrI, 0.54–13.24, respectively). The SUCRA values for the regimens were 79%, 72%, 70%, 68%, 66%, 61%, 52%, 31%, and 22% for pamidronate with calcium and Vitamin D analogs, alendronate with calcium and Vitamin D analogs, pamidronate with calcium, ibandronate with calcium and Vitamin D analogs, ibandronate with calcium, clodronate with calcium, alendronate with calcium, calcium alone, and calcium with Vitamin D analogs, respectively.

When measuring in absolute terms, the results from 15 trials (825 patients) at the longest complete follow-up (ranging from 6 months to 24 months) were less impressive [Figure 3b]. Zoledronic acid and calcium outperformed calcium alone (MD, 0.06; 95% CrI,

0.00–0.12). Pamidronate or alendronate combined with calcium and Vitamin D analogs displayed significant improvement over calcium with or without Vitamin D analogs (MD, 0.05; 95% CrI, 0.02–0.08; MD, 0.12; 95% CrI, 0.01–0.22; MD, 0.04; 95% CrI, 0.01–0.08; and MD, 0.11; 95% CrI, 0.00–0.22, respectively). No differences were observed between other groups. Pamidronate combined with calcium and Vitamin D analogs had the highest SUCRA value (77%), then alendronate plus calcium and Vitamin D (64%), zoledronic acid and calcium (61%), alendronate and calcium (60%), ibandronate with calcium and Vitamin D analogs (59%), risedronate plus calcium and Vitamin D analogs (53%), ibandronate with calcium (48%), clodronate with calcium (42%), calcium plus Vitamin D analogs (35%), and calcium only (20%).

Change of bone mineral density at the femoral neck

Six trials including a total of 308 participants provided data for comparisons of percentage change in BMD at the femoral neck. The ranking of interventions is presented in Figure 4a. Only pamidronate or ibandronate combined with calcium demonstrated a significant gain in BMD compared

to calcium (MD, 7.02; 95% CrI, 0.30–13.29 and MD, 7.30; 95% CrI, 0.32–14.22, respectively). The SUCRA values for each of the treatment formulations were as follows: pamidronate with calcium (90%), pamidronate with calcium and Vitamin D analogs (82%), calcium plus Vitamin D analogs (80%), ibandronate with calcium (50%), alendronate plus calcium (46%), alendronate with calcium and Vitamin D analogs (27%), clodronate plus calcium (22%), and solely calcium (3%).

The absolute change in BMD at the femoral neck was analyzed using data from 11 trials (545 patients). Ibandronate with calcium treatment appeared to be advantageous over any other methods [Figure 4b]. Alendronate and calcium with or without Vitamin D analogs showed greater beneficial effects on the BMD than calcium alone (MD, 0.11; 95% CrI, 0.02–0.19 and MD, 0.18; 95% CrI, 0.13–0.31, respectively). Ibandronate plus calcium had the highest SUCRA value (92%), followed by alendronate combined with calcium and Vitamin D analogs (86%), alendronate with calcium (75%), pamidronate with calcium and Vitamin D analogs (51%), calcium with Vitamin D analogs (42%),

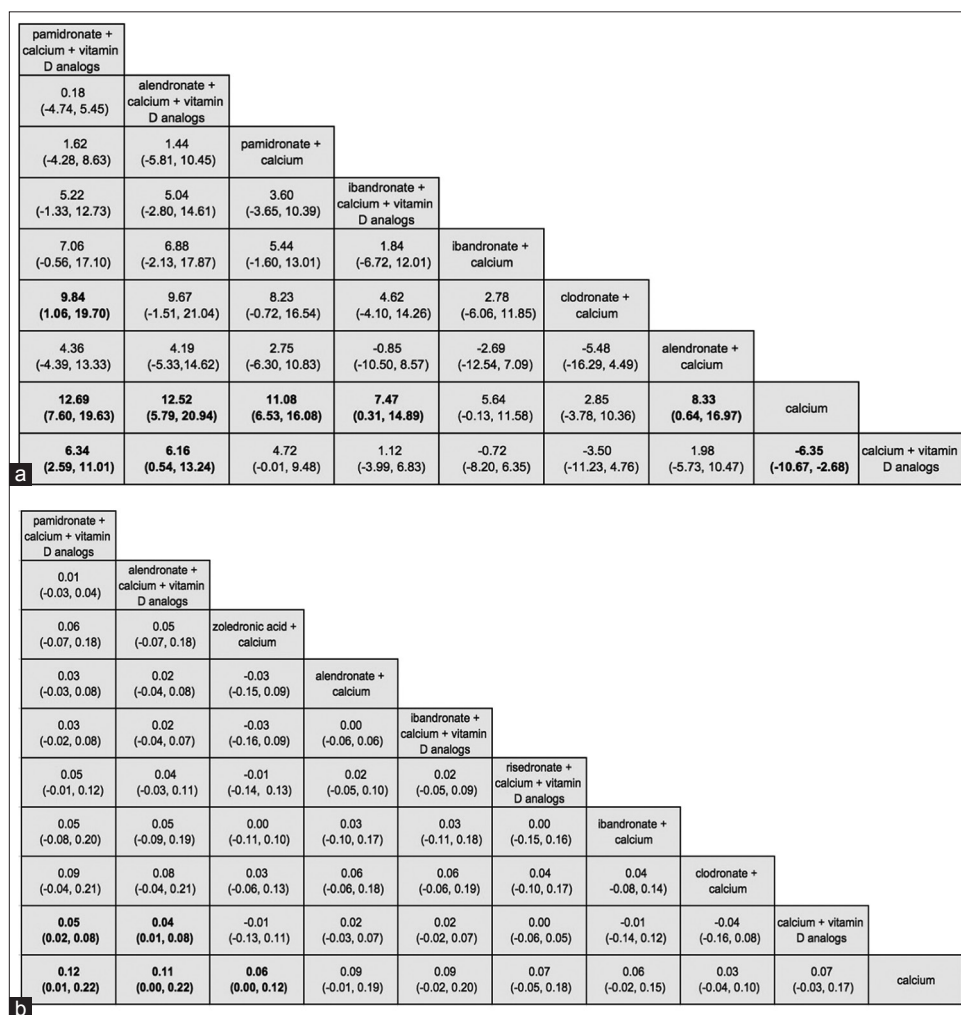


Figure 3: Summary mean difference and 95% credible intervals from network meta-analysis of change of BMD at the lumbar spine. The results of the plots are read from top to bottom and left to right. Significant results are in bold. (a) Percentage change; (b) absolute change. BMD: Bone mineral density.

clodronate plus calcium (28%), zoledronic acid with calcium (21%), and calcium only (6%).

Network meta-analysis: Secondary outcomes

All treatments have uncertain effects on all-cause mortality and graft loss metrics. We did not observe significant differences in the incidences of fractures, including both vertebral and nonvertebral fractures, between the different therapies. No significant differences were detected in the risks of adverse events. Similarly, there were no statistical differences in the number of biopsy-proven acute rejections among different bisphosphonates. Network of included studies for secondary outcomes is shown in Supplement Figure 2. Further details of the secondary outcome analyses are presented in Supplement Table 4.

Network consistency

We did not find any evidence of small study effects based on funnel plot asymmetry, but the number of studies included in each comparison was small. There was no evidence of inconsistency in the NMA when we applied the node-splitting approach [Supplement Figure 3]. The total residual deviance for the outcomes of percentage change (32.22, df = 36) and absolute change (43.86, df = 45) of the BMD at the lumbar spine as well as the percentage change (29.68, df = 28) and absolute change (26.03, df = 28) of the BMD at the femoral

neck implied a good model fit. Convergence of chains was verified qualitatively through examining single-trace plots and inspecting the Brooks–Gelman–Rubin diagnostic statistic for values around 1.^[43]

Sensitivity analysis

To investigate the different assumptions regarding the potential relationship between time and treatment effect, Bayesian NMAs were repeated using the absolute change of the BMD at the 12-month follow-up period. We observed that the combination of pamidronate with calcium and Vitamin D analogs was significantly more favorable than that of risedronate with calcium and Vitamin D analogs at the lumbar spine [Supplement Table 5a; MD, 0.05; 95% CrI 0.00–0.14]. At the femoral neck, only ibandronate with calcium showed a significant advantage over any other treatments [Supplement Table 5b]. When restricting to the first treatment at different times after KT, no significant differences were detected for absolute BMD change at either the lumbar spine or the femoral neck [Supplement Tables 6a and 6b]. When restricting to different modes of administration, oral alendronate and calcium with or without Vitamin D analogs showed improvement in absolute BMD compared to calcium alone at the femoral neck (MD, 0.18; 95% CrI, 0.02–0.33 and

pamidronate + calcium									
-1.18 (-10.41, 8.15)	pamidronate + calcium + vitamin D analogs								
3.33 (-3.40, 9.59)	4.50 (-2.83, 11.36)	calcium + vitamin D analogs							
-0.28 (-9.65, 9.43)	0.90 (-11.29, 12.01)	-3.61 (-13.00, 5.87)	ibandronate + calcium						
-0.11 (-15.22, 14.17)	1.06 (-15.77, 16.80)	-3.44 (-18.18, 10.72)	0.17 (-14.20, 14.32)	alendronate + calcium					
-0.65 (-11.79, 10.73)	0.53 (-6.16, 7.07)	-3.97 (-13.56, 5.74)	-0.37 (-13.18, 13.44)	-0.53 (-16.38, 17.42)	alendronate + calcium + vitamin D analogs				
7.23 (-3.03, 16.84)	8.40 (-4.16, 20.32)	3.90 (-6.17, 13.77)	7.51 (-2.56, 17.66)	7.34 (-7.33, 22.87)	7.87 (-6.53, 22.32)	clodronate + calcium			
7.02 (0.30, 13.29)	8.20 (-1.14, 17.66)	3.70 (-2.97, 10.27)	7.30 (0.32, 14.22)	7.14 (-5.64, 20.60)	7.67 (-3.82, 19.57)	-0.20 (-7.98, 7.19)	calcium		
a									
ibandronate + calcium									
0.54 (0.34, 0.73)	alendronate + calcium + vitamin D analogs								
0.60 (0.44, 0.76)	0.07 (-0.06, 0.18)	alendronate + calcium							
0.63 (0.39, 0.83)	0.09 (-0.08, 0.23)	0.02 (-0.13, 0.16)	pamidronate + calcium + vitamin D analogs						
0.64 (0.47, 0.80)	0.10 (-0.01, 0.21)	0.04 (-0.03, 0.10)	0.01 (-0.10, 0.15)	calcium + vitamin D analogs					
0.70 (0.51, 0.89)	0.17 (-0.05, 0.36)	0.10 (-0.08, 0.27)	0.08 (-0.14, 0.29)	0.06 (-0.13, 0.23)	clodronate + calcium				
0.71 (0.52, 0.91)	0.17 (-0.03, 0.36)	0.10 (-0.07, 0.28)	0.08 (-0.12, 0.32)	0.07 (-0.10, 0.24)	0.00 (-0.20, 0.21)	zoledronic acid + calcium			
0.71 (0.58, 0.84)	0.18 (0.03, 0.31)	0.11 (0.02, 0.19)	0.09 (-0.07, 0.27)	0.07 (-0.03, 0.16)	0.01 (-0.12, 0.16)	0.01 (-0.14, 0.16)	calcium		
b									

Figure 4: Summary mean difference and 95% credible intervals from network meta-analysis of change of BMD at the femoral neck. The results of the plots are read from top to bottom and left to right. Significant results are in bold. (a) Percentage change; (b) absolute change. BMD: Bone mineral density.

MD, 0.11; 95% CrI, 0.02–0.20, respectively). The sensitivity analysis results when restricting to immunosuppression regimens found comparable results with the NMA of absolute BMD change at the femoral neck. We excluded three RCTs that only gave corticosteroids and cyclosporine. Ibandronate and calcium was also better than calcium alone or calcium combined with alendronate, Vitamin D analogs, or zoledronic acid (MD, 0.63; 95% CrI, 0.17–1.09; MD, 0.71; 95% CrI, 0.29–1.10; MD, 0.68; 95% CrI, 0.08–0.13; and MD, 0.70; 95% CrI, 0.13–1.15, respectively). We adjusted the results of the primary outcome by excluding 4 (25%) trials that met the criteria for having a high risk of bias. Overall, the results were similar to those of the full analysis, but the statistical power was compromised because of the reduced sample size.

Quality of evidence

In general, there was no serious risk of bias, indirectness, inconsistency, or publication bias for any of the direct comparisons. In several comparisons, there was serious imprecision in the summary estimate because the 95% CrI crossed unity. According to the GRADE, we had high confidence in estimates supporting the additional use of bisphosphonates and moderate confidence in estimates supporting the use of alendronate in combination with calcium or Vitamin D analogs for increasing the absolute change in BMD at both the lumbar spine and the femoral neck. There was low confidence in estimates supporting the superiority of using ibandronate with calcium in terms of the absolute change of the BMD at the femoral neck. Conceptually, there was no significant intransitivity. The GRADE quality of evidence supported the use of each treatment for the primary outcome [Supplement Table 3].

DISCUSSION

Until recently, therapeutic options for preventing or treating bone loss of KTRs were controversial. The Kidney Disease Improving Global Outcomes (KDIGO) guideline^[44] states that “bisphosphonates be considered for low BMD patients with stable graft function,” but it was derived from very low-quality evidence. Furthermore, it is still unknown that whether certain treatment regimens are more effective than others. Therefore, we performed indirect and direct comparisons between several bisphosphonate treatments for bone mineral disorders in a NMA. To the best of our knowledge, it is the first NMA to evaluate efficacy and safety of different bisphosphonates in KTRs.

In our study, nearly each bisphosphonate assessed was superior to calcium treatment with regard to percentage change of the BMD at the lumbar spine. It is consistent with previous meta-analyses^[12,45] that indicated bisphosphonates are more effective than calcium with respect to improvement of the BMD at the lumbar spine. When measuring percentage change of the BMD at the femoral neck, only addition of pamidronate or ibandronate offered significant improvement over calcium alone. This result was less prominent than

previous studies^[12,45] because we divided bisphosphonates into subclasses and took co-interventions into account. The improvement of the BMD in the appendicular skeleton was less impressive than in the axial skeleton, but that results from the fact that trabecular bone (predominantly present in the lumbar spine) is more active and responds faster than cortical bone (mainly present in the femoral neck).^[31]

However, the differences between certain bisphosphonate treatments were not evident. It was surprising that ibandronate with calcium was superior to all other regimens investigated in terms of absolute change at the femoral neck. Ibandronate has previously been approved for postmenopausal osteoporosis in the US.^[46] *In vitro* studies^[47] have demonstrated that nitrogen-containing bisphosphonates (alendronate, pamidronate, ibandronate, zoledronate, and risedronate) showed an approximately 10,000-fold greater potency than nonnitrogen-containing drugs (clodronate and etidronate). Yet, the evidence for use of ibandronate was low because only 36 patients in a single trial had treatments of ibandronate with calcium. A simulation study^[48] suggested that the probability of being the best may be biased in favor of treatments with a smaller number of studies.

Corticosteroids and calcineurin inhibitors which may affect bone disorders are the cornerstones of immunosuppression after KT.^[5,6] When including RCTs where patients used more than three immunosuppressive drugs, the sensitivity analysis results were comparable at the femoral neck. A retrospective study^[49] had confirmed the correlation between cumulative corticosteroid dose and bone damage after KT. However, modern immunosuppression therapy with reduced corticosteroids exposure may explain why we could not detect a significant difference at the lumbar spine. If we only included trials with a 12-month follow-up period, pamidronate would be favored over risedronate at the lumbar spine. Since this result was derived from indirect comparisons, we had low confidence supporting this result. One study^[36] gave the first administration immediately before KT, while some other studies^[28-30,33,39,41] gave it after 6 months, when the renal function was stable. We divided the RCTs into two groups according to whether the initial treatment was within 6 months of KT. The included RCTs varied in initial treatment time and lacked direct comparisons and hence finding the differences was difficult.

We found no significant differences between the treatments for secondary outcomes. We did not examine whether co-intervention modified the effects of secondary outcomes, because previous studies^[11,12,50] did not elucidate significant differences in adverse events risk, fracture rates, or other secondary outcomes between treatment of Vitamin D analogs with calcium or calcium alone. In addition, the included RCTs did not provide sufficient data to make a polygonal network configuration, while there were no significant differences in secondary outcomes in the RCTs themselves. Addition of bisphosphonates did not increase the adverse events risk or cause renal deterioration. These findings suggest that bisphosphonates are well tolerated in KTRs.

We found that bisphosphonates showed a beneficial effect on BMD, but without a decrease in fracture rate. A previous meta-analysis^[45] arrived at the same result. Due to low fracture event incidences, small sample sizes, and short follow-up duration in the analyzed studies, the ability of this review to perceive a statistically significant difference in fracture rates was limited. In addition, occult fractures were appraised by radiography in only a few studies. Since adynamic bone disease may occur after bisphosphonate exposure,^[51] improvement of BMD is impossible to translate into improved bone histology. Therefore, bone-turnover biomarkers and clinical findings should be interpreted together with BMD. The KDIGO guideline^[44] recommends that bone biopsy is reasonable to guide treatment in the first 12 months after transplant, but it was not graded due to a lack of evidence. Furthermore, bone biopsies were not frequently performed, as most centers lacked the expertise to properly process and analyze bone biopsy specimens. Moreover, bone biopsy is an invasive procedure that is poorly tolerated in patients. Until recently, Naylor *et al.*^[52] suggested the Fracture Risk Assessment Tool, while Luckman *et al.*^[53] validated the use of the spine trabecular bone score for KTRs to predict fracture risk. Consequently, all of the included RCTs used BMD as a surrogate marker, despite it being a suboptimal measurement to reflect pathological bone changes and predict fracture risk. Future trials need to find more specific measurements for detecting mineral and bone disorders in KTRs.

Our analysis is strengthened by broad inclusion criteria and a comprehensive search to maximize available data in this field. This NMA updates the previous meta-analysis and performs sensitivity analyses to demonstrate the robustness of estimates. Furthermore, though the authors expressed BMD results using different units, such as g/cm², Z-score, T-score, we only included RCTs that used g/cm² to express BMD results to standardize the each comparison. We also only included RCTs that investigated adult patients to minimize potential bias and offer more reliable evidence. Moreover, to expand on previous meta-analyses,^[12,45] we took co-intervention (calcium and Vitamin D analogs) into account when we examined the effects of bisphosphonates on BMD.

However, several limitations of our analysis need consideration. First, the omission of important methodological details in the RCTs makes the internal validity difficult to assess. Second, the association between BMD metrics and fracture risk in KTRs is controversial. The short intervention durations and follow-up times in the majority of the included RCTs as well as the different times for initiation of treatment all limit the ability of this NMA to form a conclusion on bisphosphonates and fracture incidence. Moreover, the patients' characteristics, the baseline data of BMD, and the bisphosphonates regimen (dosage, route, timing, and administration duration) differ among the included studies. These factors may potentially influence the calculation of BMD in the RCTs. In addition, most direct comparisons

were based on evidence from a single trial, and almost all treatment comparisons were derived from indirect evidence alone. Finally, the sample size of each treatment was very small, which must be considered when making inferences from our study findings.

Looking forward, more correlative measurements than BMD are needed to reflect pathological bone changes in KTRs. Furthermore, since the efficacy of bisphosphonates can be compromised by poor adherence,^[54] we need to find an optimal protocol with compliance improvement and better economic benefits. Therefore, high-quality RCTs that compare different bisphosphonates directly with adequate sample sizes and sufficient follow-up time are required to determine the effect of bisphosphonates on fracture incidence.

In conclusion, our NMA suggests that new-generation bisphosphonates such as ibandronate are more favorable in KTRs to improve BMD at the lumbar spine and femoral neck. However, risk of fracture was not reduced by bisphosphonate treatment regimens. Bisphosphonate therapy was well-tolerated in KTRs without an increase in adverse events or graft loss. Because most results were derived from indirect comparisons with small populations, clinicians should take all known safety information and compliance of patients into account when using bisphosphonates. Additional head-to-head trials are needed to support our findings and find an optimal treatment option for KTRs.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Acknowledgments

The authors acknowledge Ian Charles Tobias for reviewing the manuscript. Prof. Yi Li and Martina Fu from the Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA, made a great contribution to proofread and revise the manuscript. The authors really appreciate their kindness and contribution.

Financial support and sponsorship

This study was supported by a grant from the National Natural Science Foundation of China (No. 81570668).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Saran R, Li Y, Robinson B, Abbott KC, Agodoa LY, Ayanian J, *et al.* US renal data system 2015 annual data report: Epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2016;67 3 Suppl 1:Svii, S1-305. doi: 10.1053/j.ajkd.2015.12.014.
2. Naylor KL, Li AH, Lam NN, Hodsman AB, Jamal SA, Garg AX, *et al.* Fracture risk in kidney transplant recipients: A systematic review. *Transplantation* 2013;95:1461-70. doi: 10.1097/TP.0b013e31828eead8.
3. Shahidi S, Ashrafi F, Mohammadi M, Moeinzadeh F, Atapour A. Low-dose pamidronate for treatment of early bone loss following kidney transplantation: A randomized controlled trial. *Iran J Kidney Dis* 2015;9:50-5.
4. Haas M, Leko-Mohr Z, Roschger P, Kletzmayer J, Schwarz C,

- Mitterbauer C, *et al*. Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int* 2003;63:1130-6. doi: 10.1046/j.1523-1755.2003.00816.x.
5. Alshayeb HM, Josephson MA, Sprague SM. CKD-mineral and bone disorder management in kidney transplant recipients. *Am J Kidney Dis* 2013;61:310-25. doi: 10.1053/j.ajkd.2012.07.022.
 6. Sprague SM, Josephson MA. Bone disease after kidney transplantation. *Semin Nephrol* 2004;24:82-90. doi: 10.1053/j.semnephrol.2003.08.012.
 7. Reszka AA, Rodan GA. Mechanism of action of bisphosphonates. *Curr Osteoporos Rep* 2003;1:45-52. doi: 10.1007/s11914-003-0008-5.
 8. Adachi JD, Bensen WG, Brown J, Hanley D, Hodsman A, Josse R, *et al*. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;337:382-7. doi: 10.1056/NEJM199708073370603.
 9. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2008;19:23-57. doi: 10.1007/s00198-008-0560-z.
 10. Perazella MA, Markowitz GS. Bisphosphonate nephrotoxicity. *Kidney Int* 2008;74:1385-93. doi: 10.1038/ki.2008.356.
 11. Palmer SC, McGregor DO, Strippoli GF. Interventions for preventing bone disease in kidney transplant recipients. *Cochrane Database Syst Rev* 2007;18:CD005015. doi: 10.1002/14651858.CD005015.pub2.
 12. Versele EB, Van Laecke S, Dhondt AW, Verbeke F, Vanholder R, Van Biesen W, *et al*. Bisphosphonates for preventing bone disease in kidney transplant recipients: A meta-analysis of randomized controlled trials. *Transpl Int* 2016;29:153-64. doi: 10.1111/tri.12691.
 13. Omidvar B, Ghorbani A, Shahbazian H, Beladi Mousavi SS, Shariat Nabavi SJ, Alasti M, *et al*. Comparison of alendronate and pamidronate on bone loss in kidney transplant patients for the first 6 months of transplantation. *Iran J Kidney Dis* 2011;5:420-4.
 14. Sánchez-Escuredo A, Fuster D, Rubello D, Muxi A, Ramos A, Campos F, *et al*. Monthly ibandronate versus weekly risedronate treatment for low bone mineral density in stable renal transplant patients. *Nucl Med Commun* 2015;36:815-8. doi: 10.1097/MNM.0000000000000316.
 15. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med* 2015;162:777-84. doi: 10.7326/M14-2385.
 16. Higgins G, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. Updated March, 2011. London: The Cochrane Collaboration; 2011.
 17. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015;45:139-45. doi: 10.1016/j.cct.2015.09.002.
 18. Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;17:279-301. doi: 10.1177/0962280207080643.
 19. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR, *et al*. Consistency and inconsistency in network meta-analysis: Concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98-110. doi: 10.1002/jrsm.1044.
 20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60. doi: 10.1136/bmj.327.7414.557.
 21. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi: 10.1136/bmj.39489.470347.AD.
 22. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;9:e99682. doi: 10.1371/journal.pone.0099682.
 23. Smerud KT, Dolgos S, Olsen IC, Åsberg A, Sagedal S, Reisæter AV, *et al*. A 1-year randomized, double-blind, placebo-controlled study of intravenous ibandronate on bone loss following renal transplantation. *Am J Transplant* 2012;12:3316-25. doi: 10.1111/j.1600-6143.2012.04233.x.
 24. Coco M, Pullman J, Cohen HW, Lee S, Shapiro C, Solorzano C, *et al*. Effect of risedronate on bone in renal transplant recipients. *J Am Soc Nephrol* 2012;23:1426-37. doi: 10.1681/ASN.2011060623.
 25. Torregrosa JV, Fuster D, Gentil MA, Marcen R, Guirado L, Zarraga S, *et al*. Open-label trial: Effect of weekly risedronate immediately after transplantation in kidney recipients. *Transplantation* 2010;89:1476-81. doi: 10.1097/TP.0b013e3181dc13d0.
 26. Torregrosa JV, Fuster D, Monegal A, Gentil MA, Bravo J, Guirado L, *et al*. Efficacy of low doses of pamidronate in osteopenic patients administered in the early post-renal transplant. *Osteoporos Int* 2011;22:281-7. doi: 10.1007/s00198-010-1197-2.
 27. Walsh SB, Altmann P, Pattison J, Wilkie M, Yaqoob MM, Dudley C, *et al*. Effect of pamidronate on bone loss after kidney transplantation: A randomized trial. *Am J Kidney Dis* 2009;53:856-65. doi: 10.1053/j.ajkd.2008.11.036.
 28. Lan G, Peng L, Xie X, Peng F, Wang Y, Yu S, *et al*. Alendronate is effective to treat bone loss in renal transplantation recipients. *Transplant Proc* 2008;40:3496-8. doi: 10.1016/j.transproceed.2008.09.034.
 29. Trabulus S, Altıparmak MR, Apaydin S, Serdengeçti K, Sariyar M. Treatment of renal transplant recipients with low bone mineral density: A randomized prospective trial of alendronate, alfacalcidol, and alendronate combined with alfacalcidol. *Transplant Proc* 2008;40:160-6. doi: 10.1016/j.transproceed.2007.12.001.
 30. Nayak B, Guleria S, Varma M, Tandon N, Aggarwal S, Bhowmick D, *et al*. Effect of bisphosphonates on bone mineral density after renal transplantation as assessed by bone mineral densitometry. *Transplant Proc* 2007;39:750-2. doi: 10.1016/j.transproceed.2007.01.065.
 31. El-Agroudy AE, El-Husseini AA, El-Sayed M, Mohsen T, Ghoneim MA. A prospective randomized study for prevention of postrenal transplantation bone loss. *Kidney Int* 2005;67:2039-45. doi: 10.1111/j.1523-1755.2005.00306.x.
 32. Schwarz C, Mitterbauer C, Heinze G, Woloszczuk W, Haas M, Oberbauer R, *et al*. Nonsustained effect of short-term bisphosphonate therapy on bone turnover three years after renal transplantation. *Kidney Int* 2004;65:304-9. doi: 10.1111/j.1523-1755.2004.00369.x.
 33. Jeffery JR, Leslie WD, Karpinski ME, Nickerson PW, Rush DN. Prevalence and treatment of decreased bone density in renal transplant recipients: A randomized prospective trial of calcitriol versus alendronate. *Transplantation* 2003;76:1498-502. doi: 10.1097/01.TP.0000092523.30277.13.
 34. Coco M, Glicklich D, Faugere MC, Burris L, Bogner I, Durkin P, *et al*. Prevention of bone loss in renal transplant recipients: A prospective, randomized trial of intravenous pamidronate. *J Am Soc Nephrol* 2003;14:2669-76. doi: 10.1097/01.ASN.0000087092.53894.80.
 35. Fan SL, Kumar S, Cunningham J. Long-term effects on bone mineral density of pamidronate given at the time of renal transplantation. *Kidney Int* 2003;63:2275-9. doi: 10.1046/j.1523-1755.2003.00012.x.
 36. Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M, *et al*. Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 2001;12:1530-7.
 37. Nam JH, Moon JI, Chung SS, Kim SI, Park KI, Song YD, *et al*. Pamidronate and calcitriol trial for the prevention of early bone loss after renal transplantation. *Transplant Proc* 2000;32:1876. doi: 10.1016/S0041-1345(00)01898-4.
 38. Fan SL, Almond MK, Ball E, Evans K, Cunningham J. Pamidronate therapy as prevention of bone loss following renal transplantation. *Kidney Int* 2000;57:684-90. doi: 10.1046/j.1523-1755.2000.00890.x.
 39. Grotz WH, Rump LC, Niessen A, Schmidt-Gayk H, Reichelt A, Kirste G, *et al*. Treatment of osteopenia and osteoporosis after kidney transplantation. *Transplantation* 1998;66:1004-8. doi: 10.1097/00007890-199810270-00007.
 40. Giannini S, D'Angelo A, Carraro G, Nobile M, Rigotti P, Bonfante L, *et al*. Alendronate prevents further bone loss in renal transplant recipients. *J Bone Miner Res* 2001;16:2111-7. doi: 10.1359/jbmr.2001.16.11.2111.
 41. Koc M, Tuglular S, Arikian H, Ozener C, Akoglu E. Alendronate increases bone mineral density in long-term renal transplant recipients. *Transplant Proc* 2002;34:2111-3. doi: 10.1016/S0041-1345(02)02872-5.
 42. Torregrosa JV, Fuster D, Pedrosa S, Diekmann F, Campistol JM, Rubí S, *et al*. Weekly risedronate in kidney transplant patients with

- osteopenia. *Transpl Int* 2007;20:708-11. doi: 10.1111/j.1432-2277.2007.00501.x.
43. Gelman A, Rubin D B. Inference from iterative simulation using multiple sequences. *Stat Sci* 1992;7:457-72. doi: 10.1214/ss/1177011136.
 44. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, *et al.* Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: What's changed and why it matters. *Kidney Int* 2017;92:26-36. doi: 10.1016/j.kint.2017.04.006.
 45. Kan SL, Ning GZ, Chen LX, Zhou Y, Sun JC, Feng SQ, *et al.* Efficacy and safety of bisphosphonates for low bone mineral density after kidney transplantation: A Meta-analysis. *Medicine (Baltimore)* 2016;95:e2679. doi: 10.1097/MD.0000000000002679.
 46. Frampton JE, Perry CM. Ibandronate: A review of its use in the management of postmenopausal osteoporosis. *Drugs* 2008;68:2683-707. doi: 10.2165/0003495-200868180-00011.
 47. Russell RG, Rogers MJ. Bisphosphonates: From the laboratory to the clinic and back again. *Bone* 1999;25:97-106. doi: 10.1016/S8756-3282(99)00116-7.
 48. Kibret T, Richer D, Beyene J. Bias in identification of the best treatment in a Bayesian network meta-analysis for binary outcome: A simulation study. *Clin Epidemiol* 2014;6:451-60. doi: 10.2147/CLEP.S69660.
 49. Gregorini M, Sileno G, Pattonieri EF, Corradetti V, Abelli M, Ticozzelli E, *et al.* Understanding bone damage after kidney transplantation: A Retrospective monocentric cross sectional analysis. *Transplant Proc* 2017;49:650-7. doi: 10.1016/j.transproceed.2017.02.023.
 50. Palmer SC, Strippoli GF, McGregor DO. Interventions for preventing bone disease in kidney transplant recipients: A systematic review of randomized controlled trials. *Am J Kidney Dis* 2005;45:638-49. doi: 10.1053/j.ajkd.2004.12.007.
 51. Cruz EA, Lugon JR, Jorgetti V, Draibe SA, Carvalho AB. Histologic evolution of bone disease 6 months after successful kidney transplantation. *Am J Kidney Dis* 2004;44:747-56. doi: 10.1053/j.ajkd.2004.06.022.
 52. Naylor KL, Leslie WD, Hodsman AB, Rush DN, Garg AX. FRAX predicts fracture risk in kidney transplant recipients. *Transplantation* 2014;97:940-5. doi: 10.1097/01.TP.0000438200.84154.1a.
 53. Luckman M, Hans D, Cortez N, Nishiyama KK, Agarawal S, Zhang C, *et al.* Spine trabecular bone score as an indicator of bone microarchitecture at the peripheral skeleton in kidney transplant recipients. *Clin J Am Soc Nephrol* 2017;12:644-52. doi: 10.2215/CJN.09850916.
 54. Cotté FE, Fardellone P, Mercier F, Gaudin AF, Roux C. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. *Osteoporos Int* 2010;21:145-55. doi: 10.1007/s00198-009-0930-1.

不同的二磷酸盐对预防肾移植术后骨质丢失的有效性 及安全性：随机对照实验的网状Meta分析

摘要

背景：骨质代谢紊乱是肾移植术后患者的常见并发症，已有研究表明，二磷酸盐能增加肾移植患者的骨密度，而具体的用药方案尚不明确。本研究旨在通过网络Meta系统评价不同的二磷酸盐对肾移植患者的疗效及安全性的影响。

方法：系统性检索PubMed, Embase, Cochrane Library数据库中有关成年人肾移植术后使用二磷酸盐的随机对照试验的英文文献，检索时限从建库至2017年4月。主要结果为骨密度的变化。通过Cochrane系统评价手册评估文献质量。采用随机效应模型进行成对meta分析，贝叶斯模型进行网状meta分析，并对证据级别进行评估。

结果：本文共纳入21个随机对照试验，包括6种不同的二磷酸盐，共计1332名患者。腰椎骨密度：评估相对变化，除了氯膦酸盐，其余各组均优于单用钙剂（MD, 2.85; 95% CrI, -3.78 to 10.36）。与钙剂联合维生素D相比，加用帕米膦酸盐或阿仑膦酸盐组更优（MD, 6.34; 95% CrI, 2.59 to 11.01; MD, 6.16; 95% CrI, 0.54 to 13.24）。帕米膦酸盐组优于氯膦酸盐组（MD, 9.84; 95% CrI, 1.06-19.70）。评估绝对变化，唑来膦酸盐联合钙剂优于单用钙剂组（MD, 0.06; 95% CrI, 0.00 to 0.12）。股骨颈骨密度：与单用钙剂相比，帕米膦酸盐或伊班膦酸盐联合钙剂组对提高BMD相对变化更有利（MD, 7.02; 95% CrI, 0.30 to 13.29; MD, 7.30; 95% CrI, 0.32 to 14.22）。评估绝对变化，伊班膦酸盐联合钙剂组最优，排名第一。

结论：网状meta结果显示新一代的二磷酸盐如伊班膦酸盐对提高肾移植术后患者的骨密度更有优势。然而由于此结论大多由间接比较得出，需临床医生谨慎对待。

Supplement 1: Search algorithms

- #1 MeSH descriptor: (Kidney Transplantation) explode all trees
- #2 kidney transplant*
- #3 renal transplant*
- #4 #1 or #2 or #3
- #5 MeSH descriptor: (Disphosphonates) explode all trees
- #6 alendron*
- #7 clodron*
- #8 etidron*
- #9 ibandron*
- #10 Incadron*
- #11 Medron*
- #12 Olpadron*
- #13 Pamidron*
- #14 Risedron*
- #15 Tiludron*
- #16 Zoledron*
- #17 bisphosphonat*
- #18 disphosphonat*
- #19 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
- #20 #4 and #19

Supplement Table 1: Treatment characteristics of included studies

Study	Intervention	Administration	Co-intervention
Smerud <i>et al.</i> , 2012 ^[23]	Ibandronate Placebo	3 mg i.v (every 3 months)	PO calcium 500 mg twice daily + calcitriol 0.25 mcg daily
Coco <i>et al.</i> , 2012 ^[24]	Risedronate Placebo	35 mg p.o (weekly)	PO calcitriol 0.25 µg daily (with or without calcium)
Omidvar <i>et al.</i> , 2011 ^[13]	Pamidronate Alendronate	90 mg i.v (starting from the 3rd week of transplantation for 3 months) 70 mg p.o (weekly for 3 months)	PO calcium + calcitriol
Torregrosa <i>et al.</i> , 2010 ^[25]	Risedronate No treatment	35 mg p.o (weekly)	PO calcium 1.5 g daily + Vitamin D 400 IU daily
Torregrosa <i>et al.</i> , 2011 ^[26]	Pamidronate Placebo	30 mg i.v (between day 7 and 10 after KT and 3 months post-KT)	PO calcium 1 g daily + cholecalciferol 800 IU daily
Walsh <i>et al.</i> , 2009 ^[27]	Pamidronate No treatment	1 mg/kg i.v (perioperatively and at month 1, 4, 8, 12)	PO calcium 500 mg daily + Vitamin D 400 IU daily
Lan <i>et al.</i> , 2008 ^[28]	Alendronate No treatment	70 mg p.o (weekly)	PO calcium 800 mg daily + calcitriol 0.25 µg daily
Trabulus <i>et al.</i> , 2008 ^[29]	Alendronate Alfacalcidol No treatment	10 mg p.o (daily) 0.5 µg p.o (daily) Alendronate + alfacalcidol	PO calcium 1 g daily
Nayak <i>et al.</i> , 2007 ^[30]	Alendronate No treatment	35 mg p.o (weekly)	PO calcium 1 g daily + Vitamin D
El-Agroudy <i>et al.</i> , 2005 ^[31]	Alendronate Alfacalcidol Calcitonin No treatment	5 mg p.o (daily) 0.5 µg p.o (daily) 100 µl intranasally (p.o.d and stopped for 1 month every 3 months)	PO calcium 500 mg daily
Schwarz <i>et al.</i> , 2004 ^[32]	Zoledronic acid Placebo	4 mg i.v (week 2, month 3)	PO calcium 1 g daily
Jeffery <i>et al.</i> , 2003 ^[33]	Alendronate Calcitriol	10 mg p.o (daily) 0.25 µg p.o (daily)	PO calcium 500 mg daily
Coco <i>et al.</i> , 2003 ^[34]	Pamidronate No treatment	60 mg i.v (<48 h after KT, 30 mg i.v. at months 1, 2, 3, 6)	PO calcium + calcitriol
Fan <i>et al.</i> , 2003 ^[35]	Pamidronate Placebo	0.5 mg/kg i.v (preoperatively and at month 1)	No treatment
Haas <i>et al.</i> , 2003 ^[4]	Zoledronic acid Placebo	4 mg i.v (week 2, month 3)	PO calcium 1 g daily
Grotz <i>et al.</i> , 2001 ^[36]	Ibandronate No treatment	1 mg i.v just before KTX, 2 mg i.v at month 3, 6, 9	PO calcium 500 mg daily
Nam <i>et al.</i> , 2000 ^[37]	Pamidronate Calcitriol No treatment	30 mg i.v (every 4 weeks) 0.5 µg p.o (daily)	PO calcium 500 mg daily
Fan <i>et al.</i> , 2000 ^[38]	Pamidronate Placebo	0.5 mg/kg i.v (preoperatively and at month 1)	No treatment
Grotz <i>et al.</i> , 1998 ^[39]	Clodronate Calcitonin No treatment	800 mg p.o (daily) for 14 days, each followed by 75 days without treatment 100 IU intranasally twice a day	PO calcium 500 mg daily
Giannini <i>et al.</i> , 2001 ^[40]	Alendronate No treatment	10 mg p.o (daily)	PO calcium 500 mg daily + calcitriol 0.5 µg daily
Koc <i>et al.</i> , 2002 ^[41]	Alendronate Calcitriol No treatment	10 mg p.o (daily) 0.5 µg p.o (daily)	PO calcium 1 g daily
Torregrosa <i>et al.</i> , 2007 ^[42]	Risedronate No treatment	35 mg p.o (weekly)	PO calcium 2.5 g daily + Vitamin D
Sánchez-Escuredo <i>et al.</i> , 2015 ^[14]	Ibandronate Risedronate	150 mg p.o (monthly) 35 mg p.o (weekly)	PO calcium 2.5 g daily + Vitamin D 800 IU

i.v: Intravenous; p.o and PO: Peros; p.o.d: Per other day; KT: Kidney transplantation.

Supplement Table 2: Risk of bias assessments within studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Risk of bias
Smerud <i>et al.</i> , 2012 ^[23]	+	+	+	+	+	+	-	Low
Coco <i>et al.</i> , 2012 ^[24]	+	+	+	+	+	+	+	Low
Omidvar <i>et al.</i> , 2011 ^[13]	?	?	-	?	+	+	+	High
Torregrosa <i>et al.</i> , 2010 ^[25]	+	+	-	?	+	+	+	Moderate
Torregrosa <i>et al.</i> , 2011 ^[26]	+	?	+	+	+	+	-	Moderate
Walsh <i>et al.</i> , 2009 ^[27]	+	+	-	+	+	+	-	Moderate
Lan <i>et al.</i> , 2008 ^[28]	?	?	?	?	+	+	+	Moderate
Trabulus <i>et al.</i> , 2008 ^[29]	?	?	-	-	+	+	+	High
Nayak <i>et al.</i> , 2007 ^[30]	?	?	?	?	+	+	+	Moderate
El-Agroudy <i>et al.</i> , 2005 ^[31]	+	+	+	-	+	+	+	Low
Schwarz <i>et al.</i> , 2004 ^[32]	?	?	-	+	+	+	-	High
Jeffery <i>et al.</i> , 2003 ^[33]	+	+	-	-	+	+	+	Moderate
Coco <i>et al.</i> , 2003 ^[34]	+	+	?	?	+	+	+	Low
Fan <i>et al.</i> , 2003 ^[35]	?	-	?	?	+	+	+	High
Haas <i>et al.</i> , 2003 ^[4]	?	?	-	+	+	+	-	High
Grotz <i>et al.</i> , 2001 ^[36]	?	?	-	?	+	+	+	High
Nam <i>et al.</i> , 2000 ^[37]	?	?	?	?	+	-	+	High
Fan <i>et al.</i> , 2000 ^[38]	?	-	?	?	+	+	+	High
Grotz <i>et al.</i> , 1998 ^[39]	+	+	?	?	+	+	+	Low
Giannini <i>et al.</i> , 2001 ^[40]	+	?	?	?	+	+	+	Moderate
Koc <i>et al.</i> , 2002 ^[41]	?	+	?	?	+	+	+	Moderate
Torregrosa <i>et al.</i> , 2007 ^[42]	?	?	?	?	+	+	+	Moderate
Sánchez-Escuredo <i>et al.</i> , 2015 ^[14]	?	-	-	?	+	+	+	High

We used an updated “risk of bias” tool from the Cochrane Collaboration recommends. This tool addresses seven specific bias domains including methods for generating the random sequence, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incompleteness of outcome data, and selective outcome reporting. Each item is adjudicated within each study and the results are represented in a risk of bias table. We considered allocation concealment adequate if the investigators responsible for patient selection were unable to suspect before allocation which treatment was next. We considered blinding of patients adequate if interventions were described as indistinguishable, or if double-dummy technique was used. We considered blinding of therapists adequate if it was explicitly mentioned in the text that therapists were blinded. We considered statistical analyses to be adequate if all randomized patients were included in the analysis according to the intention-to-treat principle. We considered incomplete outcome data if it excluded at least one of the randomly assigned patients from the analysis. ?: Unclear risk of bias; +: Low risk of bias; -: High risk of bias.

Supplement Table 3: Results of NMA and direct pairwise meta-analysis for change of BMD

Comparisons	Number of events (participants)	Pairwise meta-analysis MDs (95% CI)	Network meta-analysis MDs (95% CrI)	Heterogeneity I ² (%)	Cochran's Q (P)	Quality of evidence
Percentage change at lumbar spine						
Pamidronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	2 (152)	37.821 (-35.383, 111.024)	6.34 (2.59, 11.01)	99.10	0.000	⊕ low
Calcium versus calcium + Vitamin D analogs	2 (51)	-2.728 (-3.511, -1.945)	-6.35 (-10.67, -2.68)	0.00	0.373	⊕⊕⊕ moderate
Absolute change at lumbar spine						
Pamidronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	3 (181)	2.286 (-0.572, 5.144)	0.05 (0.02, 0.08)	97.70	0.000	⊕ low
Alendronate + calcium versus calcium + Vitamin D analogs	4 (176)	0.191 (-0.108, 0.489)	0.02 (-0.03, 0.07)	0.00	0.866	⊕⊕⊕ moderate
Alendronate + calcium versus calcium	2 (46)	0.577 (-0.014, 1.168)	0.09 (-0.01, 0.19)	0.00	0.728	⊕⊕⊕ moderate
Alendronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	3 (134)	0.345 (0.002, 0.687)	0.04 (0.01, 0.08)	0.00	0.956	⊕⊕⊕ moderate
Calcium versus calcium + Vitamin D analogs	2 (46)	-0.403 (-0.987, 0.182)	-0.07 (-0.17, 0.03)	0.00	0.960	⊕⊕⊕ moderate
Percentage change at femoral neck						
Calcium versus calcium + Vitamin D analogs	2 (51)	-1.427 (-2.873, 0.020)	-3.70 (-10.27, 2.97)	79.30	0.028	⊕⊕ low
Absolute change at femoral neck						
Pamidronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	2 (122)	0.028 (-0.331, 0.387)	0.01 (-0.10, 0.15)	0.00	0.756	⊕⊕⊕ moderate
Alendronate + calcium versus calcium + Vitamin D analogs	4 (176)	0.348 (-0.076, 0.772)	0.04 (-0.03, 0.10)	38.10	0.184	⊕⊕⊕ moderate
Alendronate + calcium versus calcium	2 (46)	1.150 (0.251, 2.049)	0.11 (0.02, 0.19)	48.10	0.165	⊕⊕⊕ moderate
Alendronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	2 (84)	0.881 (0.430, 1.332)	0.10 (-0.01, 0.21)	0.00	0.382	⊕⊕ low
Calcium versus calcium + Vitamin D analogs	2 (46)	-0.742 (-1.344, -0.141)	-0.07 (-0.16, 0.03)	0.00	0.403	⊕⊕ low
Absolute change at lumbar spine 12-month follow-up						
Pamidronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	2 (88)	3.466 (-2.485, 9.416)	0.05 (0.01, 0.10)	98.40	0.000	⊕ low
Alendronate + calcium versus calcium + Vitamin D analogs	4 (176)	0.191 (-0.108, 0.489)	0.04 (0.00, 0.09)	0.00	0.866	⊕⊕ low
Alendronate + calcium versus calcium	2 (46)	0.577 (-0.014, 1.168)	0.07 (-0.04, 0.18)	0.00	0.728	⊕⊕⊕ moderate
Calcium versus calcium + Vitamin D analogs	2 (46)	-0.403 (-0.987, 0.182)	-0.03 (-0.14, 0.08)	0.00	0.960	⊕⊕⊕ moderate
Absolute change at femoral neck 12-month follow-up						
Alendronate+calcium versus calcium + Vitamin D analogs	4 (176)	0.348 (-0.076, 0.772)	0.04 (-0.07, 0.16)	38.10	0.148	⊕⊕⊕ moderate
Alendronate + calcium versus calcium	2 (46)	1.150 (0.251, 2.049)	0.11 (-0.04, 0.27)	48.10	0.165	⊕⊕ low
Calcium versus calcium + Vitamin D analogs	2 (46)	-0.742 (-1.344, -0.141)	-0.07 (-0.24, 0.08)	0.00	0.403	⊕⊕ low

Comparing evidence from the Network meta-analysis with evidence obtained from the only possible pairwise meta-analysis conducted. All MD in bold are statistically significant. CIs: Confidence intervals; CrI: Credible interval. Using GRADE to rate quality of evidence from a network meta-analysis involved several steps: First, we rated quality of evidence for direct comparisons; second, we rated quality of evidence for indirect estimates (starting at the lowest rating of the two pairwise direct estimates that contribute as first-order loops to the indirect estimate, which can be rated down further for imprecision or intransitivity), and then third, rating the quality of evidence for the network combining direct and indirect estimates. In this step, if direct and indirect estimates from second-order comparisons are similar, the higher of the ratings was assigned to the network meta-analysis estimates. NMA: Network meta-analysis; BMD: Bone mineral density; MDs: Mean differences. ⊕ means meet the GRADE criteria, the more ⊕ means the quality of evidence was higher.

Supplement Table 4: Network meta-analysis of secondary outcomes

A. Adverse events					
Clodronate					
0.65 (0.01, 30.30)	Alendronate				
0.55 (0.01, 25.68)	0.86 (0.12, 5.14)	Pamidronate			
0.38 (0.01, 12.76)	0.58 (0.14, 2.38)	0.68 (0.14, 3.80)	Control		
0.29 (0.00, 18.12)	0.44 (0.04, 5.40)	0.51 (0.05, 8.18)	0.75 (0.11, 6.16)	Risedronate	
0.19 (0.00, 10.60)	0.29 (0.04, 3.23)	0.34 (0.04, 4.48)	0.51 (0.10, 3.19)	0.67 (0.09, 5.37)	Ibandronate
B. Fracture incidences					
Zoledronic acid					
0.77 (0.07, 8.89)	Control				
0.74 (0.04, 13.84)	1.01 (0.19, 5.07)	Ibandronate			
0.70 (0.05, 11.46)	0.94 (0.31, 3.31)	0.98 (0.13, 7.27)	Risedronate		
0.47 (0.03, 8.05)	0.62 (0.18, 2.33)	0.62 (0.09, 5.27)	0.66 (0.11, 4.11)	Pamidronate	
0.27 (0.00, 13.51)	0.40 (0.01, 8.92)	0.39 (0.01, 12.94)	0.42 (0.01, 11.05)	0.64 (0.01, 20.45)	Clodronate
C. Vertebral fracture incidences					
Zoledronic acid					
0.92 (0.06, 12.86)	Control				
0.91 (0.03, 25.66)	0.98 (0.14, 7.11)	Ibandronate			
0.88 (0.04, 18.15)	0.93 (0.25, 4.28)	0.92 (0.09, 11.64)	Risedronate		
0.56 (0.01, 21.66)	0.57 (0.03, 8.46)	0.61 (0.02, 16.49)	0.63 (0.02, 11.72)	Pamidronate	
D. Nonvertebral fracture incidences					
Control					
0.99 (0.04, 23.04)	Ibandronate				
0.57 (0.08, 5.17)	0.61 (0.01, 26.83)	Pamidronate			
0.37 (0.01, 12.52)	0.35 (0.00, 37.25)	0.61 (0.01, 34.30)	Clodronate		
E. All-cause mortality					
Pamidronate					
0.35 (0.00, 57.04)	Alendronate				
0.14 (0.00, 3.33)	0.41 (0.01, 11.30)	Control			
0.05 (0.00, 6.23)	0.14 (0.00, 18.90)	0.38 (0.01, 11.12)	Clodronate		
0.05 (0.00, 5.27)	0.13 (0.00, 16.76)	0.36 (0.01, 10.45)	0.93 (0.01, 207.30)	Risedronate	
0.06 (0.00, 2.13)	0.17 (0.00, 7.26)	0.43 (0.05, 2.80)	1.10 (0.02, 104.81)	1.16 (0.02, 81.58)	Ibandronate
F. Graft loss					
Alendronate					
0.38 (0.01, 19.44)	Risedronate				
0.34 (0.01, 9.83)	0.89 (0.12, 5.14)	Control			
0.29 (0.01, 13.14)	0.75 (0.05, 9.52)	0.83 (0.14, 5.16)	Pamidronate		
0.28 (0.01, 14.25)	0.72 (0.06, 10.51)	0.80 (0.16, 5.88)	0.95 (0.08, 14.31)	Ibandronate	
0.05 (0.00, 6.96)	0.15 (0.00, 6.00)	0.18 (0.00, 4.33)	0.21 (0.00, 7.97)	0.21 (0.00, 7.37)	Clodronate
G. Biopsy-proven acute rejections					
Alendronate					
0.59 (0.13, 2.86)	Control				
0.30 (0.01, 6.56)	0.53 (0.03, 7.21)	Zoledronic acid			
0.32 (0.05, 2.24)	0.56 (0.18, 1.73)	1.04 (0.06, 27.70)	Pamidronate		
0.27 (0.04, 1.94)	0.47 (0.13, 1.44)	0.87 (0.05, 21.42)	0.82 (0.15, 4.29)	Ibandronate	

Summary *OR* and 95% *CrIs* from network meta-analysis of secondary outcomes. Comparisons should be read from left to right. The response rate and remission rate estimate is located at the intersection of the column-defining treatment and the row-defining treatment. An *OR* value below 1 favors the column-defining treatment. To obtain *ORs* for comparisons in the opposing direction, reciprocals should be taken. Significant results are in bold. *ORs*: Odds ratios; *CrIs*: Credible intervals.

Supplement Table 5a: Subgroup analysis of league tables of absolute change of BMD at lumbar spine for 12-month follow-up from analysis

Pamidronate + calcium + Vitamin D analogs									
0.00 (-0.11, 0.11)	Alendronate + calcium + Vitamin D analogs								
0.01 (-0.06, 0.09)	0.02 (-0.09, 0.11)	Alendronate + calcium							
0.03 (-0.06, 0.11)	0.03 (-0.07, 0.15)	0.02 (-0.06, 0.10)	Ibandronate + calcium + Vitamin D analogs						
0.01 (-0.14, 0.16)	0.02 (-0.14, 0.19)	0.00 (-0.13, 0.15)	-0.01 (-0.18, 0.13)	Ibandronate + calcium					
0.05 (0.00, 0.14)	0.06 (-0.06, 0.17)	0.04 (-0.05, 0.13)	0.02 (-0.07, 0.12)	0.04 (-0.13, 0.20)	Risedronate + calcium + Vitamin D analogs				
0.05 (0.01, 0.10)	0.05 (-0.04, 0.15)	0.04 (0.00, 0.09)	0.02 (-0.04, 0.08)	0.04 (-0.10, 0.19)	0.00 (-0.07, 0.07)	Calcium + Vitamin D analog			
0.04 (-0.39, 0.52)	0.06 (-0.41, 0.54)	0.04 (-0.41, 0.50)	0.02 (-0.42, 0.49)	0.03 (-0.43, 0.49)	0.00 (-0.45, 0.48)	0.00 (-0.44, 0.46)	Clodronate + calcium		
0.08 (-0.04, 0.19)	0.09 (-0.05, 0.23)	0.07 (-0.04, 0.18)	0.05 (-0.07, 0.17)	0.07 (0.00, 0.16)	0.03 (-0.10, 0.16)	0.03 (-0.08, 0.14)	0.03 (-0.43, 0.49)	Calcium	

For each comparison, the random effects model MD and 95% CrIs are provided. The results of the plots are read from top to bottom and left to right. Significant results are in bold. MD: Mean difference; BMD: Bone mineral density; CrIs: Credible intervals.

Supplement Table 5b: Subgroup analysis of league tables of absolute change of BMD at femoral neck for 12-month follow-up from analysis

Ibandronate + calcium						
0.53 (0.20, 0.85)	Alendronate + calcium + Vitamin D analogs					
0.61 (0.35, 0.90)	0.08 (-0.11, 0.29)	Alendronate + calcium				
0.65 (0.37, 0.94)	0.12 (-0.07, 0.35)	0.04 (-0.07, 0.16)	Calcium + Vitamin D analogs			
0.66 (0.33, 0.99)	0.14 (-0.18, 0.46)	0.06 (-0.19, 0.31)	0.02 (-0.20, 0.23)	Pamidronate + calcium + Vitamin D analogs		
0.70 (0.42, 1.02)	0.18 (-0.14, 0.50)	0.10 (-0.16, 0.37)	0.06 (-0.24, 0.32)	0.04 (-0.30, 0.40)	Clodronate + calcium	
0.72 (0.51, 0.93)	0.19 (-0.05, 0.44)	0.11 (-0.04, 0.27)	0.07 (-0.08, 0.24)	0.05 (-0.22, 0.34)	0.01 (-0.21, 0.23)	Calcium

For each comparison, the random effects model MD and 95% CrIs are provided. The results of the plots are read from top to bottom and left to right. Significant results are in bold. MD: Mean difference, CrIs: Credible intervals; BMD: Bone mineral density.

Supplement Table 6a: Subgroup analysis and sensitivity analysis of absolute change of BMD at lumbar spine

Treatment comparison	MD (95% CrI)					
	Overall	Treatment time after kidney transplantation		Modes of administration		Immunosuppression regime
		Before 6 months	After 6 months	i.v	PO	
Pamidronate + calcium + Vitamin D analogs versus alendronate + calcium + Vitamin D analogs	0.01 (-0.03, 0.04)	-0.03 (-1.21, 0.80)	-	-0.03 (-1.23, 1.00)	-	0.01 (-0.06, 0.09)
Pamidronate + calcium + Vitamin D analogs versus zoledronic acid + calcium	0.06 (-0.07, 0.18)	0.12 (-1.23, 1.69)	-	0.24 (-0.56, 1.05)	-	0.04 (-0.15, 0.22)
Pamidronate + calcium + Vitamin D analogs versus alendronate + calcium	0.03 (-0.03, 0.08)	-0.06 (-1.26, 0.98)	-	-	-	0.03 (-0.07, 0.13)
Pamidronate + calcium + Vitamin D analogs versus ibandronate + calcium + Vitamin D	0.03 (-0.02, 0.08)	0.05 (-1.08, 1.34)	-	0.00 (-0.01, 0.01)	-	0.03 (-0.08, 0.16)
Pamidronate + calcium + Vitamin D analogs versus risedronate + calcium + Vitamin D analogs	0.05 (-0.01, 0.12)	0.04 (-1.13, 1.16)	-	-	-	0.05 (-0.07, 0.18)

Contd...

Supplement Table 6a: Contd...

Treatment comparison	MD (95% CrI)					
	Overall	Treatment time after kidney transplantation		Modes of administration		Immunosuppression regime
		Before 6 months	After 6 months	i.v	PO	
Pamidronate + calcium + Vitamin D analogs versus ibandronate + calcium	0.05 (-0.08, 0.20)	-	-	0.24 (-0.56, 1.06)	-	0.04 (-0.14, 0.23)
Pamidronate + calcium + Vitamin D analogs versus clodronate + calcium	0.09 (-0.04, 0.21)	-	-	-	-	-
Pamidronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	0.05 (0.02, 0.08)	0.07 (-0.59, 0.64)	-	0.07 (-0.59, 0.84)	-	0.05 (-0.03, 0.14)
Pamidronate + calcium + Vitamin D analogs versus calcium	0.12 (0.01, 0.22)	0.15 (-1.16, 1.14)	-	0.24 (-0.56, 1.05)	-	0.10 (-0.07, 0.28)
Alendronate + calcium + Vitamin D analogs versus zoledronic acid + calcium	0.05 (-0.07, 0.18)	0.16 (-1.38, 2.21)	-	0.24 (-0.56, 1.05)	-	0.03 (-0.14, 0.19)
Alendronate + calcium + Vitamin D analogs versus alendronate + calcium	0.02 (-0.04, 0.08)	-0.03 (-1.38, 1.60)	0.02 (-0.05, 0.10)	-	-0.01 (-0.04, 0.04)	0.02 (-0.06, 0.11)
Alendronate + calcium + Vitamin D analogs versus ibandronate + calcium + Vitamin D	0.02 (-0.04, 0.07)	0.09 (-1.37, 2.00)	-	0.03 (-1.75, 1.84)	-	0.02 (-0.09, 0.12)
Alendronate + calcium + Vitamin D analogs versus risedronate + calcium + Vitamin D analogs	0.04 (-0.03, 0.11)	0.07 (-1.30, 1.72)	-	-	0.14 (-0.77, 1.77)	0.04 (-0.06, 0.15)
Alendronate + calcium + Vitamin D analogs versus ibandronate + calcium	0.05 (-0.09, 0.19)	-	-	0.24 (-0.56, 1.05)	-	0.03 (-0.15, 0.21)

Contd...

Supplement Table 6a: Contd...

Treatment comparison	MD (95% CrI)					
	Overall	Treatment time after kidney transplantation		Modes of administration		Immunosuppression regime
		Before 6 months	After 6 months	i.v	PO	
Alendronate + calcium + Vitamin D analogs versus clodronate + calcium	0.08 (-0.04, 0.21)	-	0.06 (-0.12, 0.25)	-	0.15 (-0.77, 1.79)	-
Alendronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	0.04 (0.01, 0.08)	0.10 (-0.10, 1.47)	0.04 (-0.02, 0.09)	0.10 (-1.16, 1.60)	0.05 (-4.91, 5.00)	0.04 (-0.02, 0.11)
Alendronate + calcium + Vitamin D analogs versus calcium	0.11 (0.00, 0.22)	0.18 (-1.27, 1.45)	0.09 (-0.07, 0.24)	0.24 (-0.56, 1.05)	0.15 (-0.76, 1.79)	0.09 (-0.07, 0.25)
Zoledronic acid + calcium versus alendronate + calcium	-0.03 (-0.15, 0.09)	-0.18 (-1.62, 1.09)	-	-	-	-0.01 (-0.16, 0.16)
Zoledronic acid + calcium versus ibandronate + calcium + Vitamin D analogs	-0.03 (-0.16, 0.09)	-0.07 (-1.94, 1.49)	-	-0.24 (-1.06, 0.56)	-	-0.01 (-0.18, 0.17)
Zoledronic acid + calcium versus risedronate + calcium + Vitamin D analogs	-0.01 (-0.14, 0.13)	-0.09 (-1.93, 1.59)	-	-	-	0.01 (-0.16, 0.20)
Zoledronic acid + calcium versus ibandronate + calcium	0.00 (-0.11, 0.10)	-	-	0.03 (-1.23, 1.69)	-	0.00 (-0.12, 0.13)
Zoledronic acid + calcium versus clodronate + calcium	0.03 (-0.06, 0.13)	-	-	-	-	-
Zoledronic acid + calcium versus calcium + Vitamin D analogs	-0.01 (-0.13, 0.11)	-0.06 (-1.54, 1.16)	-	-0.24 (-1.05, 0.56)	-	0.01 (-0.16, 0.17)
Zoledronic acid + calcium versus calcium	0.06 (0.00, 0.12)	0.03 (-1.37, 1.00)	-	0.08 (-0.87, 1.42)	-	0.06 (-0.02, 0.14)

Contd...

Supplement Table 6a: Contd...

Treatment comparison	MD (95% CrI)					
	Overall	Treatment time after kidney transplantation		Modes of administration		Immunosuppression regime
		Before 6 months	After 6 months	i.v	PO	
Alendronate + calcium versus ibandronate + calcium + Vitamin D analogs	0.00 (-0.06, 0.06)	0.11 (-1.22, 1.78)	-	-	-	-0.01 (-0.11, 0.09)
Alendronate + calcium versus risedronate + calcium + Vitamin D analogs	0.02 (-0.05, 0.10)	0.10 (-1.27, 1.82)	-	-	0.14 (-0.77, 1.78)	0.02 (-0.08, 0.12)
Alendronate + calcium versus ibandronate + calcium	0.03 (-0.10, 0.17)	-	-	-	-	0.01 (-0.17, 0.18)
Alendronate + calcium versus clodronate + calcium	0.06 (-0.06, 0.18)	-	0.04 (-0.13, 0.22)	-	0.15 (-0.77, 1.79)	-
Alendronate + calcium versus calcium + Vitamin D analogs	0.02 (-0.03, 0.07)	0.13 (-0.83, 1.33)	0.02 (-0.04, 0.07)	-	0.05 (-2.59, 2.97)	0.02 (-0.04, 0.08)
Alendronate + calcium versus calcium	0.09 (-0.01, 0.19)	0.21 (-0.85, 1, 17)	0.07 (-0.07, 0.22)	-	0.15 (-0.77, 1.78)	0.07 (-0.08, 0.20)
Ibandronate + calcium + Vitamin D analogs versus risedronate + calcium + Vitamin D analogs	0.02 (-0.05, 0.09)	-0.01 (-1.45, 1.21)	-	-	-	0.02 (-0.08, 0.15)
Ibandronate + calcium + Vitamin D analogs versus ibandronate + calcium	0.03 (-0.11, 0.18)	-	-	0.24 (-0.56, 1.06)	-	0.01 (-0.17, 0.21)
Ibandronate + calcium + Vitamin D analogs versus clodronate + calcium	0.06 (-0.06, 0.19)	-	-	-	-	-
Ibandronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	0.02 (-0.02, 0.07)	0.01 (-0.97, 0.94)	-	0.07 (-0.85, 1.28)	-	0.02 (-0.05, 0.11)

Contd...

Supplement Table 6a: Contd...

Treatment comparison	MD (95% CrI)					
	Overall	Treatment time after kidney transplantation		Modes of administration		Immunosuppression regime
		Before 6 months	After 6 months	i.v	PO	
Ibandronate + Calcium + Vitamin D analogs versus calcium	0.09 (-0.02, 0.20)	0.10 (-1.47, 1.18)	-	0.24 (-0.56, 1.06)	-	0.07 (-0.09, 0.23)
Risedronate + calcium + Vitamin D analogs versus ibandronate + calcium	0.00 (-0.15, 0.16)	-	-	-	-	-0.01 (-0.20, 0.19)
Risedronate + calcium + Vitamin D analogs versus clodronate + calcium	0.04 (-0.10, 0.17)	-	-	-	0.75 (-4.58, 7.05)	-
Risedronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	0.00 (-0.06, 0.05)	0.03 (-0.88, 1.04)	-	-	-0.13 (-0.76, 1.77)	0.00 (-0.09, 0.08)
Risedronate + calcium + Vitamin D analogs versus calcium	0.07 (-0.05, 0.18)	0.11 (-1.47, 1.31)	-	-	0.73 (-3.56, 4.94)	0.05 (-0.11, 0.21)
Ibandronate + calcium versus clodronate + calcium	0.04 (-0.08, 0.14)	-	-	-	-	-
Ibandronate + calcium versus calcium + Vitamin D analogs	-0.01 (-0.14, 0.12)	-	-	-0.24 (-1.05, 0.56)	-	0.01 (-0.17, 0.19)
Ibandronate + calcium versus calcium	0.06 (-0.02, 0.15)	-	-	0.05 (-1.08, 1.25)	-	0.06 (-0.04, 0.16)
Clodronate + calcium versus calcium + Vitamin D analogs	-0.04 (-0.16, 0.08)	-	-0.02 (-0.20, 0.15)	-	-0.14 (-1.79, 0.77)	-
Clodronate + calcium versus calcium	0.03 (-0.04, 0.10)	-	0.03 (-0.07, 0.12)	-	-0.03 (-4.72, 4.11)	-
Calcium + Vitamin D analogs versus calcium	0.07 (-0.03, 0.17)	0.08 (-1.07, 0.96)	0.05 (-0.09, 0.20)	0.24 (-0.57, 1.05)	0.15 (-0.76, 1.79)	0.05 (-0.10, 0.20)

i.v: Intravenous; PO: Peros; Immunosuppression regimen included >3 drugs that contained corticosteroid, calcineurin inhibitors (cyclosporine or tacrolimus). Significant results are in bold. CrI: Credible interval; BMD: Bone mineral density; MD: Mean difference. -: No enough data to provide information about the results.

Supplement Table 6b: Subgroup analysis and sensitivity analysis of absolute change of BMD at femoral neck

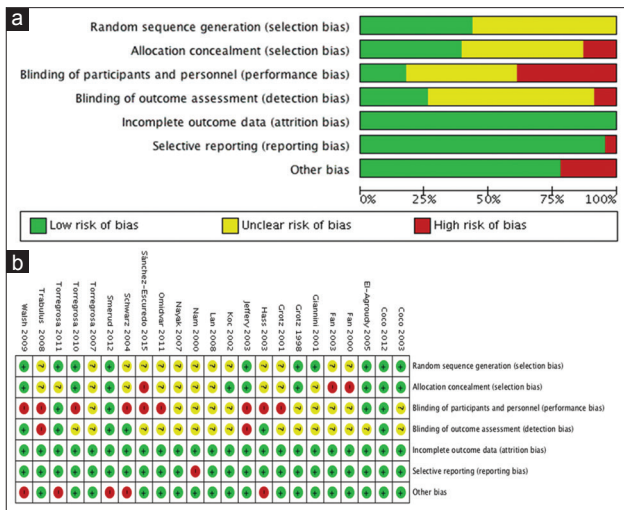
Treatment comparison	MD (95% CrI)					
	Overall	Treatment time after kidney transplantation		Modes of administration		Immunosuppression regime
		Before 6 months	After 6 months	i.v	PO	
Ibandronate + calcium versus alendronate+ calcium+ Vitamin D analogs	0.54 (0.34, 0.73)	–	–	–0.14 (–1.77, 0.77)	–	0.59 (–0.03, 1.07)
Ibandronate + calcium versus alendronate + calcium	0.60 (0.44, 0.76)	–	–	–	–	0.63 (0.17, 1.09)
Ibandronate + calcium versus pamidronate + calcium + Vitamin D analogs	0.63 (0.39, 0.83)	–	–	–0.14 (–1.78, 0.77)	–	0.66 (–0.02, 1.12)
Ibandronate + calcium versus calcium + Vitamin D analogs	0.64 (0.47, 0.80)	–	–	–0.13 (–0.77, 1.77)	–	0.68 (0.08, 1.13)
Ibandronate + calcium versus clodronate + calcium	0.70 (0.51, 0.89)	–	–	–	–	–
Ibandronate + calcium versus zoledronic acid + calcium	0.71 (0.52, 0.91)	–	–	0.75 (–4.58, 7.05)	–	0.70 (0.13, 1.15)
Ibandronate + calcium versus calcium	0.71 (0.58, 0.84)	–	–	0.73 (–3.56, 4.94)	–	0.71 (0.29, 1.10)
Alendronate + calcium + Vitamin D analogs versus alendronate + calcium	0.07 (–0.06, 0.18)	0.06 (–5.42, 5.47)	0.08 (–0.13, 0.28)	–	0.07 (0.06, –0.19)	0.04 (–0.22, 0.32)
Alendronate + calcium + Vitamin D analogs versus pamidronate + calcium + Vitamin D analogs	0.09 (–0.08, 0.23)	–0.02 (–3.57, 3.42)	–	–0.01 (–3.80, 3.77)	–	0.07 (–0.27, 0.31)
Alendronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	0.10 (–0.01, 0.21)	0.07 (–3.98, 4.28)	0.11 (–0.08, 0.32)	0.05 (–4.91, 5.00)	0.12 (–0.01, 0.23)	0.09 (–0.15, 0.30)
Alendronate + calcium + Vitamin D analogs versus clodronate + calcium	0.17 (–0.05, 0.36)	–	0.14 (–0.20, 0.46)	–	0.18 (–0.02, 0.39)	–
Alendronate + calcium + Vitamin D analogs versus zoledronic acid + calcium	0.17 (–0.03, 0.36)	0.22 (–5.93, 7.83)	–	0.15 (–0.77, 1.79)	–	0.12 (–0.39, 0.69)
Alendronate + calcium + Vitamin D analogs versus calcium	0.18 (0.03, 0.31)	0.19 (–4.88, 5.79)	0.15 (–0.14, 0.41)	0.15 (–0.76, 1.79)	0.18 (0.02, 0.33)	0.13 (–0.27, 0.46)
Alendronate + calcium versus pamidronate + calcium + Vitamin D analogs	0.02 (–0.13, 0.16)	–0.08 (–5.00, 4.34)	–	–	–	0.02 (–0.35, 0.35)
Alendronate + calcium versus calcium + Vitamin D analogs	0.04 (–0.03, 0.10)	0.01 (–3.87, 3.89)	0.03 (–0.10, 0.17)	–	0.04 (–0.03, 0.11)	0.05 (–0.21, 0.23)
Alendronate + calcium versus clodronate + calcium	0.10 (–0.08, 0.27)	–	0.06 (–0.30, 0.37)	–	0.10 (–0.05, 0.30)	–

Contd...

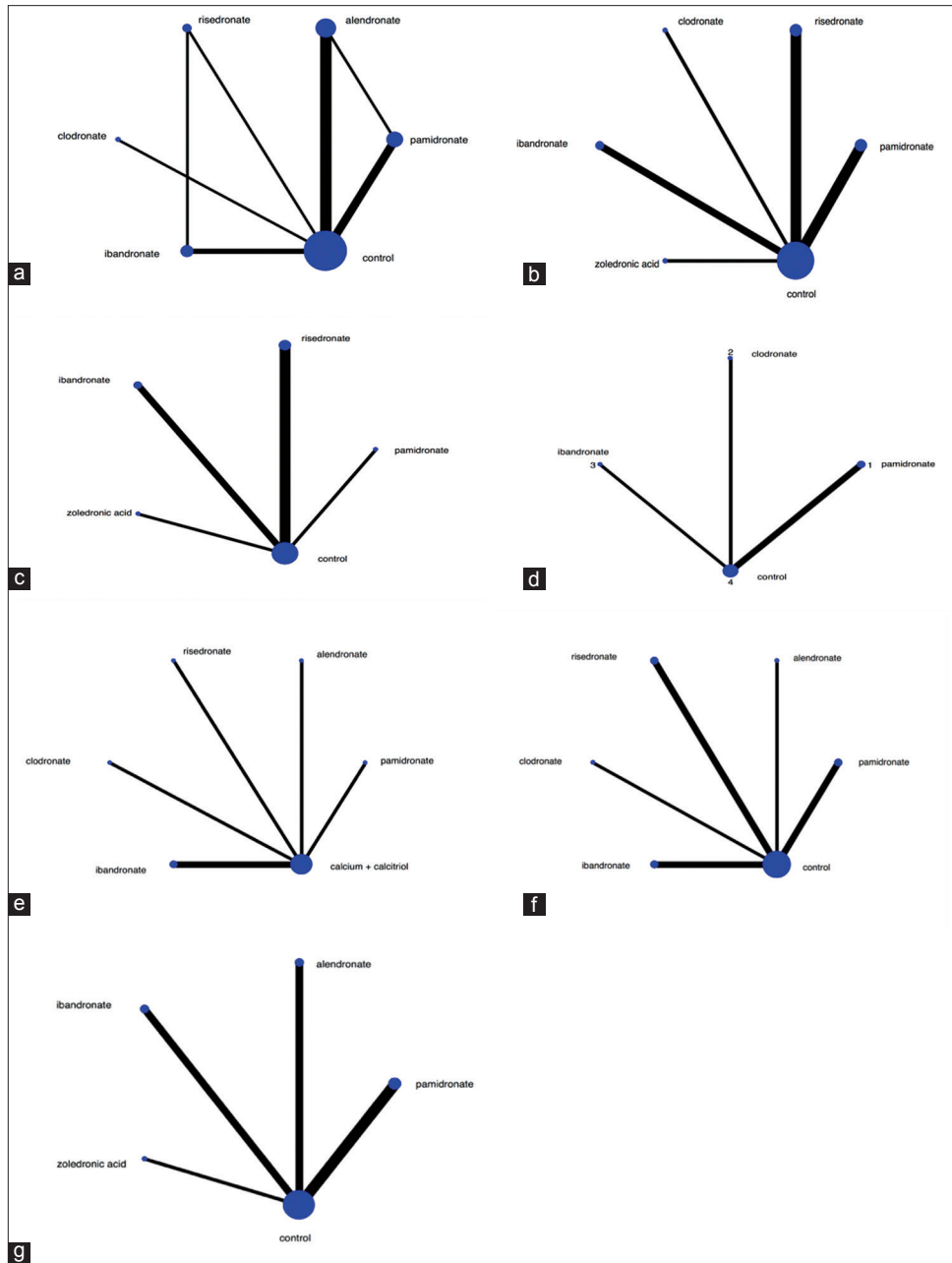
Supplement Table 6b: Contd...

Treatment comparison	MD (95% CrI)					
	Overall	Treatment time after kidney transplantation		Modes of administration		Immunosuppression regime
		Before 6 months	After 6 months	i.v	PO	
Alendronate + calcium versus zoledronic acid + calcium	0.10 (-0.07, 0.28)	0.17 (-5.95, 6.16)	-	-	-	0.07 (-0.42, 0.55)
Alendronate + calcium versus calcium	0.11 (0.02, 0.19)	0.14 (-3.74, 4.02)	0.07 (-0.16, 0.29)	-	0.11 (0.02, 0.20)	0.08 (-0.26, 0.40)
Pamidronate + calcium + Vitamin D analogs versus calcium + Vitamin D analogs	0.01 (-0.10, 0.15)	0.09 (-2.33, 2.53)	-	0.05 (-2.59, 2.97)	-	0.03 (-0.24, 0.32)
Pamidronate + calcium + Vitamin D analogs versus clodronate + calcium	0.08 (-0.14, 0.29)	-	-	-	-	-
Pamidronate + calcium + Vitamin D analogs versus zoledronic acid + calcium	0.08 (-0.12, 0.32)	0.25 (-5.11, 6.92)	-	0.15 (-0.77, 1.79)	-	0.05 (-0.47, 0.64)
Pamidronate + calcium + Vitamin D analogs versus calcium	0.09 (-0.07, 0.27)	0.22 (-4.01, 4.69)	-	0.15 (-0.77, 1.78)	-	0.06 (-0.32, 0.53)
Calcium + Vitamin D analogs versus clodronate + calcium	0.06 (-0.13, 0.23)	-	0.03 (-0.31, 0.33)	-	0.06 (-0.11, 0.25)	-
Calcium + Vitamin D analogs versus zoledronic acid + calcium	0.07 (-0.10, 0.24)	0.15 (-4.95, 5.60)	-	0.15 (-0.77, 1.79)	-	0.02 (-0.41, 0.52)
Calcium + Vitamin D analogs versus calcium	0.07 (-0.03, 0.16)	0.12 (-3.26, 3.75)	0.04 (-0.19, 0.27)	0.15 (-0.76, 1.79)	0.07 (-0.04, 0.18)	0.03 (-0.25, 0.38)
Clodronate + calcium versus zoledronic acid + calcium	0.00 (-0.20, 0.21)	-	-	-	-	-
Clodronate + calcium versus calcium	0.01 (-0.12, 0.16)	-	0.01 (-0.22, 0.25)	-	0.01 (-0.15, 0.15)	-
Zoledronic acid + calcium versus calcium	0.01 (-0.14, 0.16)	-0.03 (-3.62, 3.71)	-	-0.03 (-4.72, 4.11)	-	0.01 (-0.35, 0.37)

i.v: Intravenous; PO: Peros; Immunosuppression regimen included >3 drugs that contained corticosteroid, calcineurin inhibitors (cyclosporine or tacrolimus). Significant results are in bold. CrI: Credible interval; BMD: Bone mineral density; MD: Mean difference. -: No enough data to provide information about the results.



Supplement Figure 1: Risk of bias assessments within studies. (a) Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies. (b) Study-level risk of bias.



Supplement Figure 2: Network of eligible comparisons for secondary outcome. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every circle is proportional to the number of randomly assigned participants (sample size). (a) Adverse events; (b) fracture incidence; (c) vertebral fracture; (d) nonvertebral fracture; (e) all-cause mortality; (f) graft loss; (g) biopsy-proven acute rejections.

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z	
A H *	-5.769255	25.05985	-6.774585	20.00138	1.00533	32.06321	0.975	25.05018
A I *	-2.563544	24.95737	-11.21673	17.4862	8.653182	30.47359	0.776	24.95325
B D *	-.2133201	23.74655	-55.36471	85.46285	55.15139	88.70061	0.534	23.74444
B I *	-36.02907	17.2143	-1.176584	38.67755	-34.85248	42.34845	0.411	23.80042
C H *	-1.318893	25.15489	3.329878	55.36452	-4.648772	60.81162	0.939	25.14897
C I *	-.2054372	25.12221	-13.27946	54.19543	13.07402	59.73481	0.827	25.11721
E H *	-.4856563	24.12881	-14.96325	82.65079	14.47759	86.10089	0.866	24.12585
F H *	-.9614769	24.12912	-14.90127	82.65297	13.9398	86.10301	0.871	24.12783
G I *	-1.744896	24.12027	-18.55869	81.5191	16.81379	85.01268	0.843	24.11933
H I *	2.159753	16.97997	-18.28519	34.43813	20.44494	38.39629	0.594	24.00795

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z	
A C	-.0859614	1.663161	-1.801615	1.342879	1.715653	2.137622	0.422	1.63279
A J	-2.16596	.9801924	-.4106777	1.866659	-1.755282	2.108652	0.405	1.630488
B C	.1802161	1.73705	.6085808	1.442595	-.4283647	2.258037	0.850	1.695543
B I *	-.5937328	1.24029	-.6642396	3.128802	.0705068	3.365334	0.983	1.697032
B J *	-.1835183	.8667822	-1.075499	3.612642	.8919806	3.712905	0.810	1.693381
C J	-.3412173	.9702303	-1.663893	1.707983	1.322675	1.963887	0.501	1.652704
D J *	-5.12e-12	1.612828	-3.566307	63.32801	3.566307	63.34847	0.955	1.582959
E I *	-.3095424	1.626716	-4.307224	63.36473	3.997681	63.38568	0.950	1.583078
F I *	-.3731209	1.600851	-4.3178	63.36383	3.944679	63.38405	0.950	1.583077
G J *	-.2961707	1.592835	-3.559204	63.32814	3.263033	63.34818	0.959	1.582955
H I *	-1.180928	1.658851	-4.31631	63.36465	3.135382	63.38636	0.961	1.583068
I J *	.39682	1.238675	.2137218	3.103794	.1830982	3.341082	0.956	1.69554

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z	
A G *	-4.548277	.5875633	-.9790372	1.191363	-3.56924	1.325672	0.007	3.90e-06
A H *	-2.139416	.4289505	-5.662741	1.37699	3.523325	1.324134	0.008	.000018
B D *	-.9855372	1.210017	4.141716	63.36566	-5.127253	63.37722	0.936	1.162053
B H *	-.4456806	1.181912	-3.420274	28.33836	2.974593	28.36299	0.916	1.163088
C G *	-.6995741	.5132254	-4.263558	1.21649	3.563984	1.328166	0.007	8.13e-06
C H *	-.0785767	.500169	3.482279	1.232586	-3.560856	1.328066	0.007	3.47e-07
E G *	.0441404	1.219027	-8.109737	63.32502	8.153878	63.33683	0.898	1.160987
F G *	-1.209782	1.189243	-8.106388	63.32412	6.896606	63.33528	0.913	1.160975
G H *	1.534661	.8858494	.2000113	31.65574	1.33465	31.66813	0.966	1.161006

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P> z	
A C	-.004	.1507671	.0921654	.0660976	-.0961654	.1646196	0.559	.0304778
A H	.006274	.0582058	-.0887295	.1528527	.0950035	.1635187	0.561	.0304734
B C	.0498816	.0641973	.0454584	.0506198	.0044233	.0820438	0.957	.0354574
B G *	-.1140029	.0378727	-.0776903	.0962496	-.0363126	.1048336	0.729	.0340074
B H *	-.0378427	.0244178	.0932812	.1230581	-.1311238	.1237942	0.290	.0287184
C H	-.0911216	.0315277	.0164275	.0939538	-.107549	.0967735	0.266	.0276649
D G *	-.009	.0531921	-.159492	7.573643	.150492	7.573822	0.984	.0292756
E G *	-.714	.0456954	-.1596602	9.368078	-.5543398	9.368163	0.953	.0292752
F G *	-.01	.0579404	-.1598098	6.958218	.1498098	6.958333	0.983	.029276
G H *	.0679606	.0380004	.1042458	.0972523	-.0362852	.1047844	0.729	.0340002

Supplement Figure 3: Network consistency of primary outcomes. (a) Network consistency of percentage change of BMD at lumbar spine. A: Pamidronate + calcium; B: Pamidronate + calcium + Vitamin D analogs; C: Alendronate + calcium; D: Alendronate + calcium + Vitamin D analogs; E: Clodronate + calcium; F: Ibandronate + calcium; G: Ibandronate + calcium + Vitamin D analogs; H: Calcium; I: Calcium + Vitamin D analogs. (b) Network consistency of absolute change of BMD at lumbar spine. A: Pamidronate + calcium + Vitamin D analogs; B: Alendronate + calcium; C: Alendronate + calcium + Vitamin D analogs; D: Risedronate + calcium + Vitamin D analogs; E: Clodronate + calcium; F: Ibandronate + calcium; G: Ibandronate + calcium + Vitamin D analogs; H: Zoledronic acid + calcium; I: Calcium; J: Calcium + Vitamin D analogs. (c) Network consistency of percentage change of BMD at femoral neck. A: Pamidronate + calcium; B: Pamidronate + calcium + Vitamin D analogs; C: Alendronate + calcium; D: Alendronate + calcium + Vitamin D analogs; E: Clodronate + calcium; F: Ibandronate + calcium; G: Calcium; H: Calcium + Vitamin D analogs. (d) Network consistency of absolute change of BMD at femoral neck. A: Pamidronate + calcium + Vitamin D analogs; B: Alendronate + calcium; C: Alendronate + calcium + Vitamin D analogs; D: Clodronate + calcium; E: Ibandronate + calcium; F: Zoledronic acid + calcium; G: Calcium; H: Calcium + Vitamin D analogs. BMD: Bone mineral density. * means it was direct evidence.