



## Renal safety in patients treated with bisphosphonates for osteoporosis: A review

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Abstract:	<p>Bisphosphonates are widely used for the treatment of osteoporosis and are generally well tolerated. However, the United States Food and Drug Administration safety reports have highlighted the issue of renal safety in bisphosphonate-treated patients. All bisphosphonates carry labeled "warnings" or a contraindication for use in patients with severe renal impairment (creatinine clearance &lt;30 or &lt;35 mL/min). Data from pivotal trials and their extension studies of bisphosphonates approved for the management of osteoporosis were obtained via PubMed, and were reviewed with support from published articles available on PubMed.</p> <p>Renal safety analyses of pivotal trials of oral alendronate, risedronate and ibandronate for postmenopausal osteoporosis showed no short- or long-term effects on renal function. Transient post-infusion increases in serum creatinine have been reported in patients receiving intravenous ibandronate and zoledronic acid, however studies showed that treatment with these agents did not result in long-term renal function deterioration in clinical trial patients with osteoporosis.</p> <p>All bisphosphonate therapies have "warnings" for use in patients with severe renal impairment. Clinical trial results have shown that even in elderly, frail osteoporotic patients with renal impairment, intravenous bisphosphonate therapy administration in accordance with the prescribing information did not result in long-term renal function decline. Physicians should follow guidelines for bisphosphonate therapies administration at all times.</p>

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## Renal safety in patients treated with bisphosphonates for osteoporosis: A review

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## Abstract

Bisphosphonates are widely used for the treatment of osteoporosis and are generally well tolerated. However, the United States Food and Drug Administration safety reports have highlighted the issue of renal safety in bisphosphonate-treated patients. All bisphosphonates carry labeled “warnings” or a contraindication for use in patients with severe renal impairment (creatinine clearance <30 or <35 mL/min).

Data from pivotal trials and their extension studies of bisphosphonates approved for the management of osteoporosis were obtained via PubMed, and were reviewed with support from published articles available on PubMed.

Renal safety analyses of pivotal trials of oral alendronate, risedronate and ibandronate for postmenopausal osteoporosis showed no short- or long-term effects on renal function. Transient post-infusion increases in serum creatinine have been reported in patients receiving intravenous ibandronate and zoledronic acid, however studies showed that treatment with these agents did not result in long-term renal function deterioration in clinical trial patients with osteoporosis.

All bisphosphonate therapies have “warnings” for use in patients with severe renal impairment. Clinical trial results have shown that even in elderly, frail osteoporotic patients with renal impairment, intravenous bisphosphonate therapy administration in accordance with the prescribing information did not result in long-term renal function decline. Physicians should follow guidelines for bisphosphonate therapies administration at all times.

**Key terms:** Bisphosphonates, renal impairment, osteoporosis, zoledronic acid, renal safety.

## Introduction

Osteoporosis is a major public health concern with rising prevalence due to the increasing longevity in many regions.<sup>(1)</sup> A number of pharmacological options are available for the management of osteoporosis. They include bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid), estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene), parathyroid hormone (PTH[1-34], teriparatide) and the RANK ligand inhibitor, denosumab.<sup>(2)</sup> Available in both oral and parenteral preparations, bisphosphonates are widely regarded as the drug class of choice for the prevention of fractures in postmenopausal women.<sup>(1)</sup> This class of drug constitutes the focus of this review.

Bisphosphonates effectively reduce fracture risk and have a high benefit to risk ratio for the treatment of osteoporosis. Bisphosphonates are commonly used in an aged population who often present with concomitant kidney diseases or age-related reductions in estimated glomerular filtration rate (eGFR). Given that bisphosphonates are eliminated from the body through the kidneys, it is important to understand the effect of long-term use of bisphosphonates on renal function. A United States Food and Drug Administration (FDA) safety newsletter reported 24 cases of renal impairment and acute renal failure between April 2007 and February 2009, associated with the use of zoledronic acid 5 mg in patients with osteoporosis.<sup>(3)</sup> A second FDA drug safety communication reported an additional 11 cases of fatal acute renal failure and nine cases of renal injury requiring dialysis after zoledronic acid infusion between March 2009 and April 2011.<sup>(4)</sup> Subsequently, the prescribing information for zoledronic acid 5 mg was revised to include postmarketing surveillance data to reinforce existing warnings regarding renal safety, and to add a statement that zoledronic acid 5 mg is contraindicated in patients with creatinine

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3 clearance (CrCl) <35 mL/min and in those with evidence of acute renal impairment (the FDA  
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5 accepted eGFR calculated by the Cockcroft-Gault formula<sup>(5)</sup> in lieu of a 24-hour urine collection  
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7 for calculation of GFR by CrCl).<sup>(4,6)</sup>  
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12 Due to the mechanism of bisphosphonate excretion via the kidney, and the lack of clinical trial  
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14 data in patients with osteoporosis and severe renal impairment (CrCl <30 mL/min), the oral  
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16 bisphosphonates alendronate, risedronate and ibandronate and the intravenous (IV)  
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18 bisphosphonates ibandronate and zoledronic acid all carry warnings regarding their use in  
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20 patients with CrCl <30 mL/min (risedronate, oral and IV ibandronate) or <35 mL/min  
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22 (alendronate) and recently for zoledronic acid, a “contraindication” for CrCl <35 mL/min.<sup>(6-11)</sup>  
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29 As both osteoporosis and renal insufficiency become more prevalent with age<sup>(12)</sup> and  
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31 bisphosphonates are the most widely prescribed treatment for osteoporosis, it is important for  
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33 physicians to understand the impact of bisphosphonate therapies in osteoporotic patients with  
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35 different levels of renal function. The aim of this review is to examine clinical data regarding  
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37 renal safety in patients with osteoporosis treated with bisphosphonates and to discuss  
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39 considerations for bisphosphonate use in patients who have osteoporosis and CKD (but who do  
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41 not require renal dialysis). Data from pivotal trials (including *post hoc* analyses) and their  
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43 extension studies of approved bisphosphonates were obtained via PubMed, and were reviewed  
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45 and discussed with support from published literature available on PubMed. A comprehensive  
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47 search of postmarketing surveillance data was also performed through the European Medicines  
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49 Agency (EMA) and US FDA websites.  
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## Bisphosphonates and the renal system

Bisphosphonates are stable analogues of the inorganic compound, pyrophosphate, in which the P-O-P backbone of the molecule has been replaced by P-C-P.<sup>(13)</sup> The presence of a carbon atom allows for the attachment of side chains, the modification of which differentiates first- and second-generation bisphosphonates (e.g., clodronate and pamidronate, respectively) from third-generation compounds (e.g., zoledronic acid).<sup>(13)</sup> Third-generation bisphosphonates typically contain a heteroaromatic ring with at least one nitrogen atom as part of their side chains and have improved antiresorptive effect compared with early generations.<sup>(13)</sup> These nitrogen-containing bisphosphonates have improved potency over early generations because their antiresorptive effect is mediated *via* inhibition of the mevalonate pathway, whereas the non-nitrogen-containing bisphosphonates act by interfering with adenosine triphosphate-dependent intracellular pathways.<sup>(14)</sup>

Bisphosphonates are not metabolized. Between 27% and 62% of the drug binds to bone mineral and the rest is excreted via the kidneys, predominantly within hours after administration.<sup>(15,16)</sup>

Renal excretion occurs by both passive glomerular filtration and active transport in renal proximal tubular cells.<sup>(17,18)</sup>

In humans, early use of bisphosphonates to treat hypercalcemia due to malignancy highlighted three cases of renal failure following IV administration of high doses of etidronate and clodronate.<sup>(19)</sup> Such cases of nephrotoxicity may occur secondary to the formation of aggregates within the blood.<sup>(20,21)</sup> Renal impairment such as toxic acute tubular necrosis, tubulointerstitial damage or focal segmental glomerulosclerosis has also been reported following IV



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3 administration of the third-generation bisphosphonate, zoledronic acid, every 3 to 4 weeks in  
4 patients with multiple myeloma or Paget's disease (Table 1).<sup>(22-25)</sup> In contrast to the mechanism  
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6 by which first-generation bisphosphonates lead to renal failure, it is believed that the  
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8 nephrotoxicity that may occur secondary to administration of third-generation bisphosphonates is  
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10 caused – at least in part – by inhibition of the mevalonate pathway.<sup>(12,26)</sup> All reported cases of  
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12 zoledronic acid-associated renal impairment involved the dosing regimen of zoledronic acid 4  
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14 mg once every 3 to 4 weeks, which is higher than the 5 mg once a year dosing for patients with  
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16 osteoporosis.<sup>(27)</sup> Moreover, cancer patients (e.g. patients with multiple myeloma or some  
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18 advanced solid tumors) are known to be at risk of renal failure from compromised kidney  
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20 function and hypercalcemia.<sup>(28-31)</sup>

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29 Clinical data suggest that any potential renal damage associated with IV bisphosphonates may be  
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31 infusion time– or dose-related. In a study comparing zoledronic acid with pamidronate in  
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33 patients with bone lesions secondary to cancer, the dosing schedule of zoledronic acid was  
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35 amended from 4 or 8 mg via a 5-minute infusion once every 3 or 4 weeks, to 4 mg via a 15-  
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37 minute infusion.<sup>(32)</sup> This change was made because of the high incidence of increased serum  
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39 creatinine (SCr) levels among patients receiving zoledronic acid via a 5-minute infusion.<sup>(32)</sup> After  
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41 the amendments, no significant differences in changes in renal function were seen between the  
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43 zoledronic acid 4 mg–treated and the pamidronate 90 mg–treated groups during the 25-month  
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45 treatment period.<sup>(32)</sup> A prostate cancer prevention trial also showed that a slower zoledronic acid  
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47 infusion rate (15 minutes) may improve renal safety compared with a rapid (5 minutes)  
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49 infusion.<sup>(33)</sup>

Concerns about the potential impact on renal function of bisphosphonates led to exclusion of patients above a predefined SCr threshold in earlier studies: SCr >1.27 mg/dL for the Fracture Intervention Trial (FIT) of alendronate<sup>(34)</sup>; SCr >1.1 times the upper limit of normal for the Vertebral Efficacy with Risedronate Therapy MultiNational (VERT-MN) and VERT-North America (VERT-NA) studies of risedronate<sup>(35)</sup>; and SCr >2.4 mg/dL for the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE),<sup>(36)</sup> the Monthly Oral iBandronate in LadiEs (MOBILE) trial<sup>(37)</sup> and the Dosing IntraVenous Administration (DIVA) study of IV ibandronate.<sup>(38)</sup> These early bisphosphonate trials excluded patients on the basis of serum creatinine rather than GFR because, at the time, it was not appreciated that serum creatinine – which is derived from skeletal muscle – is an inadequate means of estimating GFR. More recent clinical trials have used estimated or actual GFR in the study inclusion/exclusion criteria. For example, patients with an estimated CrCl <30 mL/min were excluded from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) clinical trial program of zoledronic acid<sup>(39–41)</sup> and those with an actual GFR <35 mL/min were excluded from the Designed for intravenous (IV) Ibandronate reNal safety Evaluation (DIVINE) study.<sup>(42)</sup>

## **Clinical evidence of the effect of bisphosphonates on renal function in patients treated for osteoporosis**

### *Oral bisphosphonates*

Alendronate was studied in the FIT and the FLEX studies but renal safety data were not specifically discussed in the primary publications of these studies.<sup>(43–46)</sup> However, a *post hoc* analysis of the FIT study of alendronate in women with postmenopausal osteoporosis showed

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3 that alendronate (5 mg/day for 2 years and 10 mg/day for the third year) had no negative effect  
4 on renal function, even in patients with eGFR as low as 15 mL/min (Table 2).<sup>(34)</sup> No differences  
5 were found in bone mineral density (BMD) increases and antifracture efficacy for vertebral and  
6 all clinical fractures by renal function.<sup>(34)</sup> The odds ratio (OR) for clinical fracture after  
7 alendronate therapy was 0.84 (95% confidence interval [CI], 0.45–1.54) in patients with eGFR  
8 <45 mL/min compared with 0.74 (95% CI, 0.61–0.91) in those with moderately reduced or  
9 normal eGFR ( $\geq 45$  mL/min)(interaction  $P=0.72$ ). For spinal fractures, the OR was 1.01 (95% CI,  
10 0.29–3.6) for those with eGFR <45 mL/min and 0.62 (95% CI, 0.36–1.10) for those with  
11 moderately reduced or normal eGFR (interaction  $P=0.49$ ).<sup>(34)</sup>  
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27 For risedronate, renal safety results were not discussed specifically in the VERT-NA study  
28 publication,<sup>(51)</sup> but a retrospective pooled analysis of phase III trials of risedronate 5 mg showed  
29 no significant differences between placebo and risedronate groups in changes from baseline in  
30 SCr at 6, 12 or 24 months (Figure 1).<sup>(35)</sup> The overall incidence of renal function–related adverse  
31 events did not differ statistically or clinically either within or between treatment groups in those  
32 patients with severe (CrCl <30 mL/min; risedronate vs placebo 3% vs 3%; relative risk [RR],  
33 0.80; 95% CI, 0.31–2.04), moderate (CrCl  $\geq 30$ –<50 mL/min; 1% vs 2%; RR, 0.88; 95% CI,  
34 0.53–1.45), or mild (CrCl  $\geq 50$ –<80 mL/min; 1% vs 2%; RR, 0.63; 95% CI, 0.37–1.07) renal  
35 impairment. The incidence of new vertebral fractures in risedronate-treated patients was also  
36 similar ( $P=0.124$ ) across subgroups of patients with different levels of renal impairment (eGFR  
37 using the Cockcroft-Gault formula).<sup>(5,35)</sup> These data demonstrate that the vertebral antifracture  
38 efficacy of risedronate was not affected by these degrees of renal impairment.<sup>(35)</sup> Additionally, a  
39 prospective, randomized trial in women with osteoporosis or osteopenia found no significant  
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3 differences in blood urea nitrogen (BUN), creatinine and eGFR between baseline and 12 months  
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5 for patients receiving risedronate, alendronate or raloxifene.<sup>(47)</sup> Moreover, between baseline and  
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7 12 months, the mean value of serum creatinine remained unchanged and mean eGFR increased  
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9 in all three treatments groups. These results suggest that use of these agents in patients with  
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11 osteoporosis did not cause a change in renal function.<sup>(47)</sup>  
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17 The BONE study of oral ibandronate (2.5 mg daily or 20 mg every other day for 12 doses every  
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19 3 months) in patients with postmenopausal osteoporosis did not report any clinically relevant  
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21 changes in laboratory markers (including renal function tests) for the placebo or ibandronate  
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23 treatment groups over a 3-year period (Table 2).<sup>(36)</sup> Renal safety results were not included in the  
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25 publication of the MOBILE study.<sup>(52)</sup> None of the oral bisphosphonate registration trials included  
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27 patients with an eGFR <15 mL/min, so there are no data on patients with National Kidney  
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29 Foundation (NKF)-defined stage 5 CKD.  
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### 34 35 36 *IV bisphosphonates*

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38 In the randomized, double-blind, 2-year DIVA study, 1395 women with postmenopausal  
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40 osteoporosis received intermittent IV ibandronate (2 mg every 2 months or 3 mg every 3 months)  
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42 or daily oral ibandronate 2.5 mg.<sup>(38,48)</sup> At baseline, CrCl values (estimated using the Cockcroft-  
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44 Gault formula<sup>(5)</sup>) were <90 mL/min in 95.0% of patients and <60 mL/min in 50.5% of  
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46 patients.<sup>(48)</sup> The proportion of patients with a decline in CrCl at any time point was similar  
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48 between the three treatment groups (daily oral ibandronate 2.5 mg, 14.1%; 2 mg every 2 months,  
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50 14.1%; 3 mg every 3 months, 17.3%) and the overall incidence of renal adverse events was low  
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52 and similar across the treatment groups (daily oral ibandronate 2.5 mg, 2%; 2 mg every 2  
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3 months, 3%; 3 mg every 3 months, 2%). No cases of acute renal failure were reported. After 2  
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5 years of treatment, 12 patients experienced clinically relevant changes in SCr but none of these  
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7 cases was considered to be treatment-related.<sup>(48)</sup> The effect of IV ibandronate on renal function  
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9 has also been compared with that of oral alendronate. In the prospective, randomized open-label  
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11 DIVINE study, 801 postmenopausal women considered to be at increased risk for renal disease  
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13 received IV ibandronate (3 mg every 3 months) given by bolus injection or 15-minute infusion,  
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15 or oral alendronate (70 mg/week). The effects of the three therapies on renal function were  
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17 similar (percentage change from baseline in GFR at Month 9: ibandronate bolus, -1.3%  
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19 [standard deviation, 7.14]; ibandronate infusion, -0.5% [7.86]; oral alendronate, -1.6 [5.89]),  
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21 suggesting that injection and slow infusion of ibandronate had similar renal safety profiles.<sup>(42)</sup>  
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30 In the HORIZON-Pivotal Fracture Trial (PFT), 7765 women with postmenopausal osteoporosis  
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32 (mean age, 73 years) were randomized to receive zoledronic acid 5 mg once yearly (IV  
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34 administration over 15 minutes) or placebo for 3 years (Table 2).<sup>(39)</sup> Patients were excluded from  
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36 the trial if they had an estimated CrCl <30 mL/min by the Cockcroft-Gault formula<sup>(5,49)</sup> at  
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38 baseline or urine dipstick results of more than 2+ for protein, without evidence of contamination  
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40 or bacteriuria. A detailed analysis of the safety population showed no association between annual  
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42 infusions of zoledronic acid 5 mg and long-term deterioration of renal function in patients with  
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44 postmenopausal osteoporosis, and a similar frequency of long-term (3-year) changes from  
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46 baseline in renal adverse events, impairments and function in the zoledronic acid- and placebo-  
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48 treated groups (increase in serum creatinine >0.5 mg/100 mL: zoledronic acid, 36/3022 [1.19%];  
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50 placebo, 38/3066 [1.24%];  $P=0.907$ ; estimated CrCl <30 mL/min: zoledronic acid, 97/2994  
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52 [3.24%]; placebo, 96/3035 [3.16%];  $P=0.884$ ).<sup>(49)</sup> A gradual deterioration of renal function with  
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3 time was observed in both the treatment and placebo groups, consistent with age-related renal  
4 deterioration. SCr measurements were taken 9 to 11 days after each infusion (n=5035).<sup>(39)</sup>  
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6 Transient but significant increases in SCr were observed in 12 patients in the zoledronic acid  
7 group after the second infusion, compared with one patient in the placebo group ( $P<0.002$ ;  
8 Figure 2A). The proportion of patients experiencing an increase  $>0.5$  mg/100 mL from pre-  
9 infusion value in the zoledronic acid group was greatest in those with baseline estimated CrCl  
10 between 30–34 mL/min. Follow-up of these patients showed that SCr returned to within 0.5  
11 mg/100 mL of pre-infusion values within 12 months.<sup>(49)</sup> There was also no significant difference  
12 between the zoledronic acid and placebo groups after the first or third infusions (13 vs 6, 8 vs 13,  
13 respectively). In the subsequent extension study, significantly more patients experienced short-  
14 term rises in SCr 9–11 days after infusion in the group that received zoledronic acid for 6 years  
15 than those who received zoledronic acid for 3 years followed by placebo for 3 years (n=18 vs  
16 n=4;  $P=0.002$ ); however, these increases were transient and resolved with no overall long-term  
17 impact on renal function (Figure 2B).<sup>(50,53)</sup> These data demonstrated that three annual infusions  
18 of zoledronic acid have no significant effect on eGFR<sup>(39)</sup> and that any effect on SCr – even in  
19 patients who have received six annual zoledronic acid infusions – is transient.<sup>(39,53)</sup>  
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43 In the HORIZON-Recurrent Fracture Trial (RFT), 2127 men and women who had experienced a  
44 recent, low-trauma hip fracture received zoledronic acid 5 mg once yearly (IV administration  
45 over 15 minutes) or placebo (Table 2).<sup>(40)</sup> SCr levels were measured at baseline and within 4  
46 weeks before each annual infusion of the study drug. Approximately 75% of patients were  
47 female and the average age of the total population was 74 years, an older population than in the  
48 PFT. Coexisting conditions reported by trial participants included: hypertension, coronary artery  
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3 disease, osteoarthritis, previous stroke, depression and diabetes mellitus. Following treatment,  
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5 the incidence of renal adverse events was similar across the zoledronic acid- and placebo-treated  
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7 groups (increase in SCr >0.5 mg/dL, 6.2% vs 5.6%; calculated CrCl <30 mL/min, 8.2% vs  
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9 7.3%).<sup>(40)</sup>

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15 In the HORIZON-Glucocorticoid-Induced Osteoporosis (GIO) study, 833 men and women with  
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17 glucocorticoid-induced osteoporosis were randomized to receive once-yearly zoledronic acid 5  
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19 mg (IV administration over 15–20 minutes) or daily risedronate 5 mg for 1 year (Table 2).<sup>(41)</sup>  
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21 Renal function was assessed by monitoring serum creatinine and calculated CrCl before  
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23 treatment, 9–11 days after treatment had started, and at 3, 6 and 12 months. Patients in this study  
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25 had coexisting conditions, with rheumatoid arthritis the most common (~40%). The numbers of  
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27 patients with a SCr increase >44 µmol/L (zoledronic acid, n=8; placebo, n=6) or CrCl <30  
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29 mL/min (zoledronic acid, n=4; placebo, n=4) after drug administration were comparable between  
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31 the two groups ( $P=1.000$  for both). Adjudicated clinically significant renal events occurred in  
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33 nine patients receiving zoledronic acid and six receiving risedronate. Acute renal failure was  
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35 reported for two patients in the risedronate group and one patient in the zoledronic acid group; all  
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37 cases were considered to be related to underlying diseases.<sup>(41)</sup>  
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46 Adding to data from the HORIZON-PFT, RFT and GIO studies are the results from the  
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48 zoledronic acid male fracture study, in which there were no significant differences in long-term  
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50 parameters of renal function (Table 2).<sup>(54)</sup> As in the HORIZON clinical trial program, patients  
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52 with a baseline eGFR <30 mL/min were excluded from this study.  
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### Postmarketing evidence of the effect of bisphosphonates on renal function

Clinical trials have the advantage that all safety outcomes are recorded, follow-up is good, and the risks of particular adverse events can be calculated. Post-marketing surveillance reports, on the other hand, may reflect the real-world situation in clinical practice, where patients may have more co-morbidities than subjects randomized into clinical trials. Subsequent to the approval of zoledronic acid 5 mg in 2007 for the treatment of postmenopausal osteoporosis, by April 2011, the FDA Adverse Event Reporting System had received 44 evaluable spontaneous post-marketing cases of renal impairment and acute renal failure associated with zoledronic acid 5 mg.<sup>(3,4)</sup> Details of these cases have been reported in full in the FDA reports and are detailed below. More than half of the patients described in the first report (14/24) had underlying medical conditions that may have contributed to their risk of renal impairment or acute renal failure, or had concurrent exposure to known nephrotoxic medications (e.g., nonsteroidal anti-inflammatory drugs). Thirteen cases had documented transient increases in SCr following drug administration. Most patients improved following IV fluid administration or other supportive care. Four patients died from acute renal failure; however, these patients also had other comorbidities (such as chronic diabetic renal disease, chronic pulmonary obstructive disease or hypertension) that may have contributed to death due to acute renal failure.<sup>(3)</sup> These data led to the revision of the prescribing information for zoledronic acid 5 mg in the United States,<sup>(4)</sup> A similar process led to updating of the Summary of Product Characteristics in Europe in response to post-marketing reports.<sup>(55)</sup>

### Discussion



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3 Bisphosphonates, when used in accordance with the prescribing information, have demonstrated  
4 favorable renal safety results in clinical studies in patients with osteoporosis. Although cases of  
5 acute renal failure reported in post-marketing reports are important, there are a number of factors  
6 related to renal function that should be taken into consideration in treating patients with  
7 osteoporosis. Renal function is known to decline with age: the reduction in GFR usually begins  
8 after 30–40 years of age and has the potential to decline at a faster rate after 50–60 years.<sup>(56)</sup> This  
9 decline is associated with structural and functional changes in the kidneys.<sup>(56)</sup> There may also be  
10 differences in the pathophysiology of age-related reductions in GFR compared with reductions in  
11 GFR due to intrinsic renal disease, proteinuria or ongoing kidney damage.<sup>(57)</sup> Recent studies have  
12 indicated that combining proteinuria with eGFR may provide a better predictive model for  
13 progression of chronic kidney disease than assessment of GFR alone.<sup>(58)</sup> In addition, the NKF  
14 classification of chronic kidney disease categorizes eGFR >90 mL/min (up to 110 mL/min) as  
15 Stage 1 and 90–60 mL/min as stage 2, only if the patient also has proteinuria.<sup>(59)</sup> However, data  
16 on proteinuria have not been included in the publications of the pivotal trials of bisphosphonates.  
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39 Regardless of treatment, data from the third National Health Assessment and Nutritional  
40 Examination Survey (NHANES III) indicate that impaired renal function is seen in a high  
41 proportion of both men and women aged  $\geq 20$  years, who have osteoporosis.<sup>(12)</sup> Early CKD (GFR  
42 <60 mL/min) may also be associated with an approximate doubling of the hazard ratio for hip  
43 fractures as compared with patients (age-adjusted) exhibiting normal renal function.<sup>(60-62)</sup> The  
44 reasons why fracture risk appears to be greater in early stages of CKD (eGFR <60 mL/min) are  
45 unknown, but the effect of elevated PTH levels,<sup>(63)</sup> and early phosphorus retention on bone  
46 might, in part, explain the increase in bone resorption or altered bone strength in these  
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3 patients.<sup>(64-66)</sup> In addition, fibroblast growth factor 23, which rises in serum in early CKD before  
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5 PTH increases and is a strong risk factor for all-cause mortality, may impair bone mineralization  
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7 and be an additional factor explaining the greater fracture risk in early CKD.<sup>(67-69)</sup>  
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10 Hypothetically, these are interesting associations since fracture risk reduction as well as  
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12 reduction in all-cause mortality has been observed with bisphosphonates even in an elderly and  
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14 frail population.<sup>(39,54)</sup>  
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19 In patients with severe CKD, clinicians should also be aware of the possibility of adynamic bone  
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21 disease, a low bone turnover bone disease that shares many clinical features with osteoporosis  
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23 such as low bone mass and increased risk of fractures, but is associated with low PTH and low  
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25 bone turnover.<sup>(71-74)</sup> In these cases, further suppression of bone turnover may not be  
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27 recommended, as there is a hypothetical link between lowering bone turnover and increasing  
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29 vascular calcification.<sup>(64,75,76)</sup> Calcium and vitamin D treatment must also be used judiciously  
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31 because they may enhance vascular calcification in these patients who have very low capacity for  
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33 calcium uptake in the bone compartment.<sup>(77)</sup> Given that BMD is poorly correlated with fracture  
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35 risk in patients with stage 4–5 CKD,<sup>(71,78)</sup> measurement of PTH and bone specific alkaline  
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37 phosphatase (BSAP) and/or histomorphometry assessment may be needed in selected patients  
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39 with CKD stage 4–5 (eGFR <30mL/min) in order to discriminate between osteoporosis and  
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41 adynamic bone disease.<sup>(64,79)</sup> A recent comprehensive review of quantitative histomorphometry  
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43 and PTH/BSAP values suggests that combining PTH and BSAP may offer a higher positive  
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45 predictive value for adynamic bone disease than measuring either PTH or low BSAP alone.<sup>(79)</sup>  
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3 Potential management of adynamic bone disease includes reduction of calcium and vitamin D  
4 load to restore parathyroid activity, and prevention of other risk factors known to induce PTH  
5 oversuppression.<sup>(71,77)</sup>  
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12 Data from the NHANES surveys suggest that the prevalence of moderate renal impairment is  
13 underestimated when SCr is used instead of eGFR to screen for CKD.<sup>(80)</sup> Use of eGFR may,  
14 therefore, be of particular importance in older adults who are more likely to have lower  
15 creatinine values due to lower muscle mass or poor protein intake.<sup>(80,81)</sup> Many commercial  
16 laboratory reports automatically report eGFR using the Modification of Diet in Renal Disease  
17 (MDRD) equation.<sup>(82,83)</sup> Both the Cockcroft-Gault formula and the MDRD are accurate, practical  
18 predictors of eGFR but neither has a linear relationship to the most accurate eGFR  
19 measurements, inulin clearance or iodothalamate determinations.<sup>(84)</sup> If either eGFR result needs  
20 clinical confirmation, well-hydrated and carefully collected 24-hour urine for CrCl could be  
21 considered.<sup>(85)</sup> A recently developed Chronic Kidney Disease Epidemiology Collaboration eGFR  
22 equation has been shown to have improved precision, accuracy and mortality risk prediction  
23 compared with MDRD, and is recommended for routine clinical use.<sup>(86-88)</sup>  
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43 Given the prevalence of kidney impairment in patients with osteoporosis, it is critical that  
44 clinicians know which patients are suitable for treatment with specific bisphosphonates.<sup>(89)</sup>  
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48 Although the oral bisphosphonates carry warnings on their use in patients with severe renal  
49 impairment, renal function did not change between treatment and placebo groups in clinical  
50 studies on alendronate, risedronate and oral ibandronate.<sup>(34,35)</sup> A recent retrospective cohort study  
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3 in 122,727 patients aged  $\geq 66$  years with a fragility fracture also found that  
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5 oral bisphosphonate use was not associated with acute kidney injury.<sup>(90)</sup>  
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10 Clinical studies of IV bisphosphonates reported cases of acute and transient increases in SCr  
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12 following drug administration but no long-term impact in kidney function has been reported. For  
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14 zoledronic acid, similar incidences of renal adverse events, impairments and function were  
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16 reported for the zoledronic acid- and placebo-treated groups over the duration of the trials,<sup>(39)</sup>  
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18 even in an older study population and in those who had received IV zoledronic acid for up to 6  
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20 years.<sup>(42)</sup> As none of the patients in the zoledronic acid pivotal studies had biochemical changes  
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22 that could suggest CKD-MBD, it is unknown whether the responses observed in these trials  
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24 would vary in patients with known intrinsic kidney disease or unresolved secondary  
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26 hyperparathyroidism.<sup>(58,91,92)</sup> Although the renal tissue half-life of ibandronate is shorter than  
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28 zoledronic acid (24 vs 150–200 days),<sup>(93)</sup> no data comparing the renal effects of IV ibandronate  
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30 with IV zoledronic acid in a randomized population have been published, and there is no  
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32 scientific evidence establishing any differences on renal effects between these two  
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34 bisphosphonates.  
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43 Clinicians wishing to prescribe bisphosphonates to patients with osteoporosis are advised to  
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45 check their patients' CrCl or eGFR prior to initiating treatment and ensure that they adhere to  
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47 prescribing instructions. We recommend that in patients with marginal eGFR values, a well-  
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49 hydrated 24-hour CrCl should be performed for GFR calculation before clinical management  
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51 decisions are made with regard to bisphosphonate use. For zoledronic acid, IV administration  
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53 should be over a period of no less than 15 minutes and patients must be adequately hydrated  
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3 prior to the infusion. In addition, clinicians should make an assessment of any concomitant  
4 medication that a patient may be taking, with special regard to potentially nephrotoxic therapies.  
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## 10 **Conclusion**

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12 Bisphosphonates – a class of drug that is available in both oral and parenteral preparations – have  
13 historically been associated with a low incidence of renal adverse events. This review of clinical  
14 trial and post-marketing surveillance data has shown that, if used with care and in accordance  
15 with the prescribing information, these agents can be administered to patients with various  
16 degrees of renal impairment, with no long-term decline in renal function. This applies to both  
17 oral and IV bisphosphonates. Clinical trials have shown little evidence of an association between  
18 oral bisphosphonate administration and renal impairment, and these medications are effective in  
19 reducing fracture risk and increasing BMD in patients (*by post hoc* analysis) with eGFR >15  
20 mL/min. Moreover, results from clinical trials of IV bisphosphonates have shown that, even in  
21 elderly osteoporotic patients with existing fracture, administration in accordance with the  
22 prescribing information does not result in long-term renal function decline and is efficacious in  
23 preventing fracture at all skeletal sites over 6 years of administration.  
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43 Although bisphosphonates are generally well tolerated in clinical studies, the low incidence of  
44 renal adverse events has led to the inclusion of “warnings” on the prescribing information of all  
45 bisphosphonates regarding the use of these agents in patients with severe renal impairment (CrCl  
46 <30 or <35 mL/min). For IV zoledronic acid, this warning constitutes a “contraindication” in the  
47 registration labels for patients with eGFR <35 mL/min.<sup>(4)</sup> This contraindication – which does not  
48 alter the positive benefit-to-risk balance for the product<sup>(55)</sup> – is primarily due to the way  
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3 bisphosphonates are excreted from the body, via glomerular filtration and tubular secretion. The  
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6 parenteral formulations of therapies for postmenopausal osteoporosis are invaluable for patients  
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8 intolerant to oral bisphosphonates, patients with pre-existing esophageal disease, and those in  
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10 whom there is uncertainty regarding gastrointestinal absorption. In view of their efficacy in  
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12 preventing osteoporotic fractures, bisphosphonates are clearly beneficial in these patient groups.  
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14 However, as with any drug, it is important that physicians follow the prescribing information for  
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16 administration at all times, in order to maximize the benefit-to-risk ratio associated with  
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18 administration.  
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25 This review has clearly shown that the benefit-to-risk ratio for all bisphosphonates is very  
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27 favorable when they are used according to the label in the right patient populations for the right  
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29 duration, and that IV bisphosphonates – which have an established renal safety profile when used  
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31 according to prescribing information – can even be used in the majority of patients, including  
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33 those who are elderly, as long as their eGFR is  $>35$  mL/min.<sup>(94,95)</sup> These drugs therefore  
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35 constitute an important and effective part of the physician's pharmacological armamentarium.  
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**Authors' roles:**

Data collection: PM and SB. Data analysis: PM, SJ, PE, RE and SB. Data interpretation: PM, SJ, PE, RE and SB. Drafting manuscript: PM and SB. Revising manuscript content: PM, SJ, PE, RE and SB. Approving final version of manuscript: PM, SJ, PE, RE and SB. PM takes responsibility for the integrity of the data analysis.

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## Figure legends

**Figure 1.** Mean (95% confidence interval) difference between the placebo and risedronate 5 mg treatment groups in the percentage change from baseline in serum creatinine at 6, 12, and 24 months and at the endpoint (last post-baseline visit).<sup>(35)</sup> Results were based on the analysis of 9 randomized, double-blind, placebo-controlled, parallel-group, phase III trials of risedronate 5 mg daily treatment. Mean differences are shown for the severe (CrCl, <30 mL/min), moderate (CrCl,  $\geq 30$ –<50 mL/min), and mild (CrCl,  $\geq 50$ –<80 mL/min) renal impairment subgroups. Negative values imply that decreases from baseline in serum creatinine were greater in the risedronate group than in the placebo group. Figure reprinted from Miller and colleagues, with permission from John Wiley and Sons.

CrCl was calculated using the Cockcroft-Gault method.<sup>(5)</sup>

CrCl, creatinine clearance; SCr, serum creatinine.

**Figure. 2(A)** Mean serum creatinine levels in patients with pre- to post- infusion change of >0.5 mg/100 mL from baseline to 36 months in the HORIZON-PFT.<sup>(49)</sup> For each infusion, the patients treated with 5 mg of zoledronic acid showed similar mean serum creatinine levels at 9–11 days post-infusion and also at 12 months post-infusion. Figure reprinted from Boonen and colleagues, with permission from the International Society of Nephrology. **(B)** Mean changes in calculated creatinine clearance from the baseline of the HORIZON-PFT extension study (Year 3 of the HORIZON-PFT trial) to year 6 were comparable for zoledronic acid vs. placebo (safety population).<sup>(50)</sup> Figure reprinted from Miller and colleagues, with permission from Springer.

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3 HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly  
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5 Pivotal Fracture Trial; SE, standard error; Z6, patient group receiving zoledronic acid 5 mg for 6  
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7 years; Z3P3, patient group receiving zoledronic acid 5 mg for 3 years followed by placebo for 3  
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9 years. Conversion factor for SCr from mg/dL to  $\mu\text{mol/L}$  is 88.4.  
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Table 1. Case reports of renal events in patients receiving zoledronic acid<sup>(22-25)</sup>

Patient	Renal-related comorbidities	Bisphosphonate treatment	Clinical presentation and histology
59-year-old male with multiple myeloma <sup>(22)</sup>	Long-standing renal insufficiency	Pamidronate 90 mg monthly for 13 months then switch to zoledronic acid 4 mg monthly	4 months after switching to zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.9 to 4.0 mg/dL</li> <li>• 24-hour urine protein, 1.08 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
73-year-old female with Paget's disease <sup>(22)</sup>	Acute renal failure	Pamidronate 90 mg monthly for 21 months then switch to zoledronic acid 4 mg monthly	After 4 doses of zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from ~1.5 to 3.8 mg/dL</li> <li>• 24-hour urine protein, 2 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
57-year-old female with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg monthly for 2 years and 9 months then switch to zoledronic acid 4 mg monthly	8 months after switching to zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.3 to 2.5 mg/dL</li> <li>• 24-hour urine protein, 194 mg/day to 1.3 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
75-year-old male with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg monthly for 22 months then switch to zoledronic acid 4 mg monthly	By the 4 <sup>th</sup> dose of zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.4 to 1.7 mg/dL (levels continued to increase to 2.6 mg/dL after treatment discontinuation for 2 months)</li> <li>• Urinalysis showed absence of protein</li> <li>• Biopsy revealed toxic ATN</li> </ul>
85-year-old male with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg for 2 doses then switch to zoledronic acid 4 mg monthly	After 3 doses of zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.6 to 3.8 mg/dL</li> <li>• Biopsy revealed toxic ATN</li> </ul> 1 month after zoledronic acid discontinuation <ul style="list-style-type: none"> <li>• SCr reached 5.5 mg/dL</li> </ul>

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			<ul style="list-style-type: none"> <li>• 24-hour urine protein, 1.7 g/day</li> </ul>
66-year-old male with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg monthly for 4 months then switch to zoledronic acid 4 mg monthly	After 4 doses of zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.0 to 2.0 mg/dL</li> <li>• 24-hour urine protein, 2.6 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
65-year-old male with multiple myeloma <sup>(23)</sup>	NR	Zoledronic acid 4 mg (9 doses), 3.3 mg (1 dose)	After 9 doses of zoledronic acid, SCr levels was 2.39 mg/dL Shortly after the 10 <sup>th</sup> dose: <ul style="list-style-type: none"> <li>• SCr levels reached 4.6 mg/dL</li> <li>• Patient reported heavy proteinuria, hypoalbuminemia and acute renal failure with nephrotic syndrome</li> <li>• Biopsy showed focal segmental glomerulosclerosis</li> </ul>
74-year-old male with bone metastases <sup>(24)</sup>	NR	Zoledronic acid 4 mg infused over 15 minutes every 3 or 4 weeks for 14 months	Steady increase in SCr that reached above normal range after 10 months of therapy; increases continued over the subsequent 4 months until treatment discontinuation
72-year-old female with multiple myeloma <sup>(25)</sup>	NR	Zoledronic acid 4 mg monthly	After 5 <sup>th</sup> dose of zoledronic acid, SCr increased from 0.67 to 4.28 mg/dL but subsequently stabilized after 2 weeks at 1.88 mg/dL with CrCl of 23 mL/min
57-year-old male with multiple myeloma <sup>(25)</sup>	NR	Zoledronic acid 4 mg monthly	4 weeks after zoledronic acid administration, SCr increased from 2.49 to 12.22 mg/dL; biopsy showed tubulointerstitial damage

ATN, acute tubular necrosis; CrCl, creatinine clearance; NR, not reported; SCr, serum creatinine.

Conversion factor for SCr from mg/dL to μmol/L is 88.4.

**Table 2.** Clinical evidence of the effect of bisphosphonates on renal function<sup>(34-36,38-41,47-50)</sup>

Study details	Dosage	Renal function effects
<i>Oral bisphosphonates</i>		
FIT subanalysis in women with postmenopausal osteoporosis (n=6438) <sup>(34)</sup>	Alendronate vs. placebo; 3-year follow-up	Small significant increase in SCr from baseline to 3 years in both groups
Risedronate pooled analysis of Phase III studies (n=9883) in women with osteoporosis (91% renal impairment at baseline – subdivided into severe, moderate and mild) <sup>(35)</sup>	Risedronate 5 mg daily or placebo for up to 3 years	No significant difference in SCr changes between placebo and risedronate groups; overall incidence of renal function-related adverse events similar across all renal impairment subgroups
BONE study in women with postmenopausal osteoporosis (n=2946) <sup>(36)</sup>	Oral ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months	No clinically relevant changes in laboratory markers (including renal function tests) reported for placebo or ibandronate groups over 3 years
Postmenopausal women with osteoporosis or osteopenia (n=127) <sup>(47)</sup>	Alendronate 70 mg weekly, risedronate 35 mg weekly or raloxifene 60 mg daily for 12 months	No significant differences in blood urea nitrogen, creatinine and eGFR seen between baseline and 12 months
<i>IV bisphosphonates</i>		
DIVA study in women with postmenopausal osteoporosis (n=1395) <sup>(38,48)</sup>	Intermittent IV ibandronate (2 mg every 2 months or 3 mg every 3 months) or daily oral ibandronate (2.5 mg) for 2 years (only 1-year data are shown)	Low incidence of renal adverse events; no acute renal failure reported; 12 cases of clinically relevant changes in SCr from baseline but none was considered to be treatment-related
HORIZON-PFT: Women with postmenopausal osteoporosis (n=7765) <sup>(39,49)</sup>	Zoledronic acid 5 mg once yearly (IV infusion over 15 minutes) or placebo for 3 years	No significant between-group differences in SCr or CrCl at 3 years; no association between zoledronic acid 5 mg and long-term renal function deterioration; age-related deterioration of renal function over time observed in both zoledronic acid and placebo groups

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HORIZON-RFT: Men and women with low-trauma hip fracture (n=2127) <sup>(40)</sup>	Zoledronic acid 5 mg once yearly (IV infusion over 15 minutes) or placebo	Renal adverse events similar across zoledronic acid 5 mg and placebo groups
HORIZON-GIO: Men and women with glucocorticoid-induced osteoporosis (n=833); Prevention/treatment cohorts <sup>(41)</sup>	Once-yearly zoledronic acid 5 mg (IV infusion over 15–20 minutes) or daily risedronate 5 mg for 1 year	Clinically significant renal events in 2% zoledronic acid patients + 1.4% risedronate patients; 3 cases acute renal failure related to underlying disease
Study in men with osteoporosis (n=1199) <sup>(50)</sup>	Once-yearly zoledronic acid 5 mg (IV infusion over 15–30 minutes)	Increased in SCr >0.5 mg/dL occurred in 2.4% (14/584) patients receiving zoledronic acid, and 3.0% (18/610) patients receiving placebo CrCl < 30 mL/min at any time during the study was reported in 0.5% (3/557) zoledronic acid-treated patients, and 1.6% (9/577) placebo-treated patients; CrCl was calculated using the Cockcroft-Gault formula <sup>(5)</sup>

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; FIT, Fracture Intervention Trial; GIO, Glucocorticoid-induced Osteoporosis; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial; SCr, serum creatinine

Conversion factor for SCr from mg/dL to μmol/L is 88.4.

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## Renal safety in patients treated with bisphosphonates for osteoporosis: A review

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**Abstract**

Bisphosphonates are widely used for the treatment of osteoporosis and are generally well tolerated. However, the United States Food and Drug Administration safety reports have highlighted the issue of renal safety in bisphosphonate-treated patients. All bisphosphonates carry labeled “warnings” or a contraindication for use in patients with severe renal impairment (creatinine clearance <30 or <35 mL/min).

Data from pivotal trials and their extension studies of bisphosphonates approved for the management of osteoporosis were obtained via PubMed, and were reviewed with support from published articles available on PubMed.

Renal safety analyses of pivotal trials of oral alendronate, risedronate and ibandronate for postmenopausal osteoporosis showed no short- or long-term effects on renal function. Transient post-infusion increases in serum creatinine have been reported in patients receiving intravenous ibandronate and zoledronic acid, however studies showed that treatment with these agents did not result in long-term renal function deterioration in clinical trial patients with osteoporosis.

All bisphosphonate therapies have “warnings” for use in patients with severe renal impairment. Clinical trial results have shown that even in elderly, frail osteoporotic patients with renal impairment, intravenous bisphosphonate therapy administration in accordance with the prescribing information did not result in long-term renal function decline. Physicians should follow guidelines for bisphosphonate therapies administration at all times.

**Key terms:** Bisphosphonates, renal impairment, osteoporosis, zoledronic acid, renal safety.



## Introduction

Osteoporosis is a major public health concern with rising prevalence due to the increasing longevity in many regions.<sup>(1)</sup> A number of pharmacological options are available for the management of osteoporosis. They include bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene), parathyroid hormone (PTH[1-34], teriparatide) and the RANK ligand inhibitor, denosumab.<sup>(2)</sup> Available in both oral and parenteral preparations, bisphosphonates are widely regarded as the drug class of choice for the prevention of fractures in postmenopausal women.<sup>(1)</sup> This class of drug constitutes the focus of this review.

Bisphosphonates effectively reduce fracture risk and have a high benefit to risk ratio for the treatment of osteoporosis. Bisphosphonates are commonly used in an aged population who often present with concomitant kidney diseases or age-related reductions in estimated glomerular filtration rate (eGFR). Given that bisphosphonates are eliminated from the body through the kidneys, it is important to understand the effect of long-term use of bisphosphonates on renal function. A United States Food and Drug Administration (FDA) safety newsletter reported 24 cases of renal impairment and acute renal failure between April 2007 and February 2009, associated with the use of zoledronic acid 5 mg in patients with osteoporosis.<sup>(3)</sup> A second FDA drug safety communication reported an additional 11 cases of fatal acute renal failure and nine cases of renal injury requiring dialysis after zoledronic acid infusion between March 2009 and April 2011.<sup>(4)</sup> Subsequently, the prescribing information for zoledronic acid 5 mg was revised to include postmarketing surveillance data to reinforce existing warnings regarding renal safety, and to add a statement that zoledronic acid 5 mg is contraindicated in patients with creatinine

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3 clearance (CrCl) <35 mL/min and in those with evidence of acute renal impairment (the FDA  
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5 accepted eGFR calculated by the Cockcroft-Gault formula<sup>(5)</sup> in lieu of a 24-hour urine collection  
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7 for calculation of GFR by CrCl).<sup>(4,6)</sup>  
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12 Due to the mechanism of bisphosphonate excretion via the kidney, and the lack of clinical trial  
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14 data in patients with osteoporosis and severe renal impairment (CrCl <30 mL/min), the oral  
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16 bisphosphonates alendronate, risedronate and ibandronate and the intravenous (IV)  
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18 bisphosphonates ibandronate and zoledronic acid all carry warnings regarding their use in  
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20 patients with CrCl <30 mL/min (risedronate, oral and IV ibandronate) or <35 mL/min  
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22 (alendronate) and recently for zoledronic acid, a “contraindication” for CrCl <35 mL/min.<sup>(6-11)</sup>  
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29 As both osteoporosis and renal insufficiency become more prevalent with age<sup>(12)</sup> and  
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31 bisphosphonates are the most widely prescribed treatment for osteoporosis, it is important for  
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33 physicians to understand the impact of bisphosphonate therapies in osteoporotic patients with  
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35 different levels of renal function. The aim of this review is to examine clinical data regarding  
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37 renal safety in patients with osteoporosis treated with bisphosphonates and to discuss  
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39 considerations for bisphosphonate use in ~~osteoporotic~~ patients with who have osteoporosis and  
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41 established CKD (but who do not require renal dialysis). Data from pivotal trials (including *post*  
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43 *hoc* analyses) and their extension studies of approved bisphosphonates were obtained via  
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45 PubMed, and were reviewed and discussed with support from published literature available on  
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47 PubMed. A comprehensive search of postmarketing surveillance data was also performed  
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49 through the European Medicines Agency (EMA) and US FDA websites.  
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## Bisphosphonates and the renal system

Bisphosphonates are stable analogues of the inorganic compound, pyrophosphate, in which the P-O-P backbone of the molecule has been replaced by P-C-P.<sup>(13)</sup> The presence of a carbon atom allows for the attachment of side chains, the modification of which differentiates first- and second-generation bisphosphonates (e.g., clodronate and pamidronate, respectively) from third-generation compounds (e.g., zoledronic acid).<sup>(13)</sup> Third-generation bisphosphonates typically contain a heteroaromatic ring with at least one nitrogen atom as part of their side chains and have improved antiresorptive effect compared with early generations.<sup>(13)</sup> These nitrogen-containing bisphosphonates have improved potency over early generations because their antiresorptive effect is mediated *via* inhibition of the mevalonate pathway, whereas the non-nitrogen-containing bisphosphonates act by interfering with adenosine triphosphate-dependent intracellular pathways.<sup>(14)</sup>

Bisphosphonates are not metabolized. Between 27% and 62% of the drug binds to bone mineral and the rest is excreted via the kidneys, predominantly within hours after administration.<sup>(15,16)</sup>

Renal excretion occurs by both passive glomerular filtration and active transport in renal proximal tubular cells.<sup>(17,18)</sup>

In humans, early use of bisphosphonates to treat hypercalcemia due to malignancy highlighted three cases of renal failure following IV administration of high doses of etidronate and clodronate.<sup>(19)</sup> Such cases of nephrotoxicity may occur secondary to the formation of aggregates within the blood.<sup>(20,21)</sup> Renal impairment such as toxic acute tubular necrosis, tubulointerstitial damage or focal segmental glomerulosclerosis has also been reported following IV

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3 administration of the third-generation bisphosphonate, zoledronic acid, every 3 to 4 weeks in  
4 patients with multiple myeloma or Paget's disease (Table 1).<sup>(22-25)</sup> In contrast to the mechanism  
5 by which first-generation bisphosphonates lead to renal failure, it is believed that the  
6 nephrotoxicity that may occur secondary to administration of third-generation bisphosphonates is  
7 caused – at least in part – by inhibition of the mevalonate pathway.<sup>(12,26)</sup> However, a All reported  
8 cases of zoledronic acid-associated renal impairment reported adopted involved the dosing  
9 regimen of zoledronic acid 4 mg once every 3 to 4 weeks, which is higher than the 5 mg once a  
10 year dosing for patients with osteoporosis.<sup>(27)</sup> ~~No case reports of renal failures associating with~~  
11 ~~once yearly zoledronic acid administration for osteoporosis have been published. Moreover,~~  
12 ~~Cancer patients (e.g. patients with multiple myeloma or some advanced solid tumors;) are~~  
13 known to be at risk of renal failure from compromised kidney function<sup>(21,22)</sup> and hypercalcemia.  
14 ~~— a consequence of multiple myeloma and some advanced solid tumors — can precipitate renal~~  
15 ~~dysfunction.~~<sup>(28-31)</sup>

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37 Clinical data suggest that any potential renal damage associated with IV bisphosphonates may be  
38 infusion time– or dose-related. In a study comparing zoledronic acid with pamidronate in  
39 patients with bone lesions secondary to cancer, the dosing schedule of zoledronic acid was  
40 amended from 4 or 8 mg via a 5-minute infusion once every 3 or 4 weeks, to 4 mg via a 15-  
41 minute infusion.<sup>(32)</sup> ~~owing to~~ This change was made because of the high incidence of increased  
42 serum creatinine (SCr) levels among patients receiving zoledronic acid via a 5-minute  
43 infusion.<sup>(32)</sup> After the amendments, no significant differences in changes in renal function were  
44 seen between the zoledronic acid 4 mg–treated and the pamidronate 90 mg–treated groups during  
45 the 25-month treatment period.<sup>(32)</sup> A prostate cancer prevention trial also showed that a slower  
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3 | zoledronic acid infusion rate (15 minutes) may improve renal safety compared with a rapid (5  
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5 minutes) infusion.<sup>(33)</sup>  
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10 Concerns about the potential impact on renal function of bisphosphonates led to exclusion of  
11 patients above a predefined SCr threshold in earlier studies: SCr >1.27 mg/dL for the Fracture  
12 Intervention Trial (FIT) of alendronate<sup>(34)</sup>; SCr >1.1 times the upper limit of normal for the  
13 Vertebral Efficacy with Risedronate Therapy MultiNational (VERT-MN) and VERT-North  
14 America (VERT-NA) studies of risedronate<sup>(35)</sup>; and SCr >2.4 mg/dL for the Oral Ibandronate  
15 Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE),<sup>(36)</sup> the Monthly  
16 Oral iBandronate in LadiEs (MOBILE) trial<sup>(37)</sup> and the Dosing IntraVenous Administration  
17 (DIVA) study of IV ibandronate.<sup>(38)</sup> These early bisphosphonate trials excluded patients on the  
18 basis of serum creatinine rather than GFR because, at the time, it was not appreciated that serum  
19 creatinine – which is derived from skeletal muscle – is an inadequate means of estimating GFR.  
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21 More recent clinical trials have used estimated or actual GFR in the study inclusion/exclusion  
22 criteria. For example, patients with an calculated estimated CrCl <30 mL/min were excluded  
23 from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly  
24 (HORIZON) clinical trial program of zoledronic acid.<sup>(39–41)</sup> and those with an actual GFR <35  
25 mL/min were excluded from the Designed for intravenous (IV) Ibandronate reNal safety  
26 Evaluation (DIVINE) study.<sup>(42)</sup>  
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53 **Clinical evidence of the effect of bisphosphonates on renal function in patients treated for**  
54 **osteoporosis**  
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### Oral bisphosphonates

Alendronate was studied in the FIT and the FLEX studies but renal safety data were not specifically discussed in the primary publications of these studies.<sup>(43–46)</sup> However, a *post hoc* analysis of the FIT study of alendronate in women with postmenopausal osteoporosis, showed that alendronate (5 mg/day for 2 years and 10 mg/day for the third year) had no negative effect on renal function, even in patients with eGFR as low as 15 mL/min (Table 2).<sup>(34)</sup> No differences were found in bone mineral density (BMD) increases and antifracture efficacy for vertebral and all clinical fractures by renal function.<sup>(34)</sup> The odds ratio (OR) for clinical fracture after alendronate therapy was 0.84 (95% confidence interval [CI], 0.45–1.54) in patients with eGFR <45 mL/min compared with 0.74 (95% CI, 0.61–0.91) in those with moderately reduced or normal eGFR ( $\geq 45$  mL/min)(interaction  $P=0.72$ ). For spinal fractures, the OR was 1.01 (95% CI, 0.29–3.6) for those with eGFR <45 mL/min and 0.62 (95% CI, 0.36–1.10) for those with moderately reduced or normal eGFR (interaction  $P=0.49$ ).<sup>(34)</sup>

For risedronate, renal safety results were not discussed specifically in the VERT-NA study publication,<sup>(51)</sup> but a retrospective pooled analysis of phase III trials of risedronate 5 mg showed no significant differences between placebo and risedronate groups in changes from baseline in SCr at 6, 12 or 24 months (Figure 1).<sup>(35)</sup> The overall incidence of renal function–related adverse events did not differ statistically or clinically either within or between treatment groups in those patients with severe (CrCl <30 mL/min; risedronate vs placebo 3% vs 3%; relative risk [RR], 0.80; 95% CI, 0.31–2.04), moderate (CrCl  $\geq 30$ –<50 mL/min; 1% vs 2%; RR, 0.88; 95% CI, 0.53–1.45), or mild (CrCl  $\geq 50$ –<80 mL/min; 1% vs 2%; RR, 0.63; 95% CI, 0.37–1.07) renal impairment. The incidence of new vertebral fractures in risedronate-treated patients was also

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3 similar ( $P=0.124$ ) across subgroups of patients with different levels of renal impairment (eGFR  
4 using the Cockcroft-Gault formula).<sup>(5,35)</sup> These data demonstrate that the vertebral antifracture  
5 efficacy of risedronate was not affected by these degrees of renal impairment.<sup>(35)</sup> Additionally, a  
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8 prospective, randomized trial in women with osteoporosis or osteopenia found no significant  
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11 differences in blood urea nitrogen (BUN), creatinine and eGFR between baseline and 12 months  
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13 for patients receiving risedronate, alendronate or raloxifene.<sup>(47)</sup> Moreover, between baseline and  
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15 12 months, the mean value of serum creatinine remained unchanged and mean eGFR increased  
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17 in all three treatments groups. These results suggesting that use of these agents in patients with  
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20 osteoporosis did not cause a change in renal function.<sup>(47)</sup>  
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27 The BONE study of oral ibandronate (2.5 mg daily or 20 mg every other day for 12 doses every  
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29 3 months) in patients with postmenopausal osteoporosis did not report any clinically relevant  
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31 changes in laboratory markers (including renal function tests) for the placebo or ibandronate  
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33 treatment groups over a 3-year period (Table 2).<sup>(36)</sup> Renal safety results were not included in the  
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35 publication of the MOBILE study.<sup>(52)</sup> None of the oral bisphosphonate registration trials included  
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37 patients with an eGFR <15 mL/min, so there are no data on patients with National Kidney  
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39 Foundation (NKF)-defined stage 5 CKD.  
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#### 46 *IV bisphosphonates*

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48 In the randomized, double-blind, 2-year DIVA study, 1395 women with postmenopausal  
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50 osteoporosis received intermittent IV ibandronate (2 mg every 2 months or 3 mg every 3 months)  
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52 or daily oral ibandronate 2.5 mg.<sup>(38,48)</sup> At baseline, CrCl values (estimated using the Cockcroft-  
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54 Gault formula<sup>(5)</sup>) were <90 mL/min in 95.0% of patients and <60 mL/min in 50.5% of  
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3 patients.<sup>(48)</sup> The proportion of patients with a decline in CrCl at any time point was similar  
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6 between the three treatment groups (daily oral ibandronate 2.5 mg, 14.1%; 2 mg every 2  
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8 months, 14.1%; 3 mg every 3 months, 17.3%). ~~F~~ and the overall incidence of renal adverse  
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10 events was low and similar across the treatment groups (daily oral ibandronate 2.5 mg, 2%; 2 mg  
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12 every 2 months, 3%; 3 mg every 3 months, 2%). No cases of acute renal failure were reported.  
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15 After 2 years of treatment, 12 patients experienced clinically relevant changes in SCr but none of  
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17 these cases was considered to be treatment-related.<sup>(48)</sup> The effect of IV ibandronate on renal  
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19 function has also been compared with that of oral alendronate. In ~~a~~ the prospective, randomized  
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21 open-label DIVINE study ~~in~~, 801 postmenopausal women considered to be at increased risk for  
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23 renal disease, ~~patients~~ received IV ibandronate (3 mg every 3 months) given by bolus injection or  
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25 15-minute infusion, or oral alendronate (70 mg/week). The effects of the three therapies on renal  
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27 function were similar (percentage change from baseline in GFR at Month 9: ibandronate bolus,  
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29 -1.3% [standard deviation, 7.14]; ibandronate infusion, -0.5% [7.86]; oral alendronate, -1.6  
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31 [5.89]), suggesting that injection and slow infusion of ibandronate had ~~a~~ similar renal safety  
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33 profile ~~as a slower infusions~~.<sup>(42)</sup>  
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41 In the HORIZON-Pivotal Fracture Trial (PFT), 7765 women with postmenopausal osteoporosis  
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43 (mean age, 73 years) were randomized to receive zoledronic acid 5 mg once yearly (IV  
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45 administration over 15 minutes) or placebo for 3 years (Table 2).<sup>(39)</sup> Patients were excluded from  
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47 the trial if they had an estimated CrCl <30 mL/min by the Cockcroft-Gault formula<sup>(5,49)</sup> at  
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49 baseline or urine dipstick results of more than 2+ for protein, without evidence of contamination  
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51 or bacteriuria. A detailed analysis of the safety population showed no association between annual  
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53 infusions of zoledronic acid 5 mg and long-term deterioration of renal function in patients with  
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postmenopausal osteoporosis, and a similar frequency of long-term (3-year) changes from baseline in renal adverse events, impairments and function in the zoledronic acid- and placebo-treated groups (increase in serum creatinine >0.5 mg/100 mL: zoledronic acid, 36/3022 [1.19%]; placebo, 38/3066 [1.24%];  $P=0.907$ ; estimated CrCl <30 mL/min: zoledronic acid, 97/2994 [3.24%]; placebo, 96/3035 [3.16%];  $P=0.884$ ).<sup>(49)</sup> A gradual deterioration of renal function with time was observed in both the treatment and placebo groups, consistent with age-related renal deterioration. SCr measurements were taken 9 to 11 days after each infusion (n=5035).<sup>(39)</sup> Transient but significant increases in SCr were observed in 12 patients in the zoledronic acid group after the second infusion, compared with one patient in the placebo group ( $P<0.002$ ; Figure 2A). The proportion of patients experiencing an increase >0.5 mg/100 mL from pre-infusion value in the zoledronic acid group was greatest in those with baseline estimated CrCl between 30–34 mL/min. Follow-up of these patients showed that SCr returned to within 0.5 mg/100 mL of pre-infusion values within 12 months.<sup>(49)</sup> There was also no significant difference between the zoledronic acid group and placebo groups after the first or third infusions (13 vs 6, 8 vs 13, respectively). In the subsequent extension study, significantly more patients experienced short-term rises in SCr 9–11 days after infusion in the group that received zoledronic acid for 6 years than those who received zoledronic acid for 3 years followed by placebo for 3 years (n=18 vs n=4;  $P=0.002$ ); however, these increases were transient and resolved with no overall long-term impact on renal function (Figure 2B).<sup>(50,53)</sup> These data demonstrated that three annual infusions of zoledronic acid have no significant effect on eGFR<sup>(39)</sup> and that any effect on SCr – even in patients who have received six annual zoledronic acid infusions – is transient.<sup>(39,53)</sup>

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3 In the HORIZON-Recurrent Fracture Trial (RFT), 2127 men and women who had experienced a  
4 recent, low-trauma hip fracture received zoledronic acid 5 mg once yearly (IV administration  
5 over 15 minutes) or placebo (Table 2).<sup>(40)</sup> SCr levels were measured at baseline and within 4  
6 weeks before each annual infusion of the study drug. Approximately 75% of patients were  
7 female and the average age of the total population was 74 years, an older population than in the  
8 PFT. Coexisting conditions reported by trial participants included: hypertension, coronary artery  
9 disease, osteoarthritis, previous stroke, depression and diabetes mellitus. Following treatment,  
10 the incidence of renal adverse events was similar across the zoledronic acid- and placebo-treated  
11 groups (increase in SCr >0.5 mg/dL, 6.2% vs 5.6%; calculated CrCl <30 mL/min, 8.2% vs  
12 7.3%).<sup>(40)</sup>

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29 In the HORIZON-Glucocorticoid-Induced Osteoporosis (GIO) study, 833 men and women with  
30 glucocorticoid-induced osteoporosis were randomized to receive once-yearly zoledronic acid 5  
31 mg (IV administration over 15–20 minutes) or daily risedronate 5 mg for 1 year (Table 2).<sup>(41)</sup>  
32 Renal function was assessed by monitoring serum creatinine and calculated CrCl before  
33 treatment, 9–11 days after treatment had started, and at 3, 6 and 12 months. Patients in this study  
34 had coexisting conditions, with rheumatoid arthritis the most common (~40%). The number<sub>s</sub> of  
35 patients with a SCr increase >44 μmol/L (zoledronic acid, n=8; placebo, n=6) or CrCl <30  
36 mL/min (zoledronic acid, n=4; placebo, n=4) after drug administration were comparable between  
37 the two groups ( $P=1.000$  for both). Adjudicated clinically significant renal events occurred in  
38 nine patients receiving zoledronic acid and six receiving risedronate. Acute renal failure was  
39 reported for two patients in the risedronate group and one patient in the zoledronic acid group; all  
40 cases were considered to be related to underlying diseases.<sup>(41)</sup>

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6 Adding to data from the HORIZON-PFT, RFT and GIO studies are the results from the  
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8 zoledronic acid male fracture study, in which there were no significant differences in long-term  
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10 parameters of renal function (Table 2).<sup>(54)</sup> As in the HORIZON clinical trial program, patients  
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12 with a baseline eGFR <30 mL/min were excluded from this study.  
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### 15 16 17 18 **Postmarketing evidence of the effect of bisphosphonates on renal function**

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20 Clinical trials have the advantage that all safety outcomes are recorded, follow-up is good, and  
21  
22 the risks of particular adverse events can be calculated. Post-marketing surveillance reports, on  
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24 the other hand, may reflect the real-world situation in clinical practice, where patients may have  
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26 more co-morbidities than subjects randomized into clinical trials. Subsequent to the approval of  
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28 zoledronic acid 5 mg in 2007 for the treatment of postmenopausal osteoporosis, by April 2011,  
29  
30 the FDA Adverse Event Reporting System had received 44 evaluable spontaneous post-  
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32 marketing cases of renal impairment and acute renal failure associated with zoledronic acid 5  
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34 mg.<sup>(3,4)</sup> Details of these cases have been reported in full in the FDA reports and are detailed  
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36 below. More than half of the patients described in the first report (14/24) had underlying  
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38 medical conditions that may have contributed to their risk of renal impairment or acute renal  
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40 failure, or had concurrent exposure to known nephrotoxic medications (e.g., nonsteroidal anti-  
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42 inflammatory drugs). Thirteen cases had documented transient increases in SCr following drug  
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44 administration. Most patients improved following IV fluid administration or other supportive  
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46 care. Four patients died from acute renal failure; however, these patients also had other  
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48 comorbidities (such as chronic diabetic renal disease, chronic pulmonary obstructive disease or  
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50 hypertension) that may have contributed to death due to acute renal failure.<sup>(3)</sup> These data led to  
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3 the revision of the prescribing information for zoledronic acid 5 mg in the United States,<sup>(4)</sup>. A  
4 similar process led to updating of the Summary of Product Characteristics in Europe in response  
5 to post-marketing reports.<sup>(55)</sup>  
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## 10 11 12 **Discussion**

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15 Bisphosphonates, when used in accordance with the prescribing information, have demonstrated  
16  
17 favorable renal safety results in clinical studies in patients with osteoporosis. ~~Subsequent to the~~  
18 ~~approval of zoledronic acid 5 mg in 2007 for the treatment of postmenopausal osteoporosis, by~~  
19 ~~April 2011, the FDA Adverse Event Reporting System had received 44 evaluable spontaneous~~  
20 ~~postmarketing cases of renal impairment and acute renal failure associated with zoledronic acid 5~~  
21 ~~mg.<sup>(1,2)</sup> Details of these cases have been reported in full in the FDA reports and are detailed~~  
22 ~~below: More than half of the patients described in the first report (14/24) had underlying medical~~  
23 ~~conditions that may have contributed to their risk of renal impairment or acute renal failure, or~~  
24 ~~had concurrent exposure to known nephrotoxic medications (e.g. nonsteroidal anti-inflammatory~~  
25 ~~drugs). Thirteen cases had documented transient increases in SCr following drug administration.~~  
26 ~~Most patients improved following IV fluid administration or other supportive care. Four patients~~  
27 ~~died from acute renal failure; however, these patients also had other comorbidities (such as~~  
28 ~~chronic diabetic renal disease, chronic pulmonary obstructive disease or hypertension) that may~~  
29 ~~have contributed death due to acute renal failure.<sup>(1)</sup>~~  
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51 ~~Whilst~~ Although the cases of acute renal function failure reported above in post-marketing reports  
52 are important ~~for clinicians to be aware of~~, there are a number of factors related to renal function  
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55 that should be taken into consideration in treating patients with osteoporosis. Renal function is  
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3 known to decline with age, ~~with~~ the reduction in GFR usually begins after 30–40 years of age  
4 and has the potential to ~~decline at a faster rate~~ ~~accelerate~~ after 50–60 years.<sup>(56)</sup> This decline is  
5  
6 associated with structural and functional changes in the kidneys.<sup>(56)</sup> There may also be  
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8 differences in the pathophysiology of age-related reductions in GFR compared with reductions in  
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10 GFR due to intrinsic renal disease, proteinuria or ongoing kidney damage.<sup>(57)</sup> Recent studies have  
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12 indicated that combining proteinuria with eGFR may provide a better predictive model for  
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14 progression of chronic kidney disease ~~than assessment of GFR alone~~.<sup>(58)</sup> In addition, the NKF  
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16 classification of chronic kidney disease categorizes eGFR >90 mL/min (up to 110 mL/min) as  
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18 Stage 1 and 90–60 mL/min as stage 2, only if the patient also has proteinuria.<sup>(59)</sup> However, data  
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20 on proteinuria have not been included in the publications of the pivotal trials of bisphosphonates.  
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30 Regardless of treatment, data from the third National Health Assessment and Nutritional  
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32 Examination Survey (NHANES III) indicate that impaired renal function is seen in a high  
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34 proportion of both men and women aged  $\geq 20$  years, who have osteoporosis.<sup>(12)</sup> Early CKD (GFR  
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36 <60 mL/min) may also be associated with an approximate doubling of the hazard ratio for hip  
37  
38 fractures as compared with patients (age-adjusted) exhibiting normal renal function.<sup>(60-62)</sup> The  
39  
40 reasons why fracture risk appears to be greater in early stages of CKD (eGFR <60 mL/min) are  
41  
42 unknown, but the effect of elevated PTH levels,<sup>(63)</sup> and early phosphorus retention on bone  
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44 might, in part, explain the increase in bone resorption or altered bone strength in these  
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46 patients.<sup>(64-66)</sup> In addition, fibroblast growth factor 23, which rises in serum in early CKD before  
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48 PTH increases and is a strong risk factor for all-cause mortality, may impair bone mineralization  
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50 and be an additional factor explaining the greater fracture risk in early CKD.<sup>(67-69)</sup>  
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55 Hypothetically, these are interesting associations since fracture risk reduction as well as  
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3 reduction in all-cause mortality has been observed with bisphosphonates even in an elderly and  
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5 frail population.<sup>(39,54)</sup>  
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10 In patients with severe CKD, clinicians should also be aware of the possibility of adynamic bone  
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12 disease, a low bone turnover bone disease that shares many clinical features with osteoporosis  
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14 such as, low bone mass and increased risk of fractures, but is associated with low PTH and low  
15  
16 bone turnover.<sup>(71-74)</sup> In these cases, further suppression of bone turnover may not be  
17  
18 recommended, as there is a hypothetical ~~may be a~~ link between lowering bone turnover and  
19  
20 increasing vascular calcification.<sup>(64,75,76)</sup> Calcium and vitamin D treatment must also be used  
21  
22 judiciously -because they may enhance vascular calcification in these patients who have very low  
23  
24 capacity ~~of for~~ calcium uptake in the bone compartment.<sup>(77)</sup> Given that BMD ~~are is~~ poorly  
25  
26 correlated with fracture risk in patients with stage 4–5 CKD,<sup>(71,78)</sup> measurement of PTH and  
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28 bone specific alkaline phosphatase (BSAP) measurement and/or histomorphometry assessment  
29  
30 may be needed in selected patients with CKD stage 4–5 (eGFR <30mL/min) in order to  
31  
32 discriminate between osteoporosis and adynamic bone disease.<sup>(64,79)</sup> A recent comprehensive  
33  
34 review of quantitative histomorphometry and PTH/BSAP values suggests that combining PTH  
35  
36 and BSAP may offer a higher positive predictive value for adynamic bone disease than  
37  
38 measuring weither PTH or low BSAP alone.<sup>(79)</sup>  
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46 Potential management of adynamic bone disease includes reduction of calcium and vitamin D  
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48 load to restore parathyroid activity, and prevention of other risk factors known to induce PTH  
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50 oversuppression.<sup>(71,77)</sup>  
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3 Data from the NHANES surveys suggest that the prevalence of moderate renal impairment is  
4 underestimated when SCr is used instead of eGFR to screen for CKD.<sup>(80)</sup> Use of eGFR may,  
5  
6 therefore, be of particular importance in older adults who are more likely to have lower  
7  
8 creatinine values due to lower muscle mass or poor protein intake.<sup>(80,81)</sup> Many commercial  
9  
10 laboratory reports automatically report eGFR using the Modification of Diet in Renal Disease  
11  
12 (MDRD) equation.<sup>(82,83)</sup> Both the Cockcroft-Gault formula and the MDRD are accurate, practical  
13  
14 predictors of eGFR but neither has a linear relationship to the most accurate eGFR  
15  
16 measurements, inulin clearance or iodothalamate determinations.<sup>(84)</sup> If either eGFR result needs  
17  
18 clinical confirmation, well-hydrated and carefully collected 24-hour urine for CrCl could be  
19  
20 considered.<sup>(85)</sup> A recently developed Chronic Kidney Disease Epidemiology Collaboration eGFR  
21  
22 equation has been shown to have improved precision, accuracy and mortality risk prediction  
23  
24 compared with MDRD, and is recommended for routine clinical use.<sup>(86-88)</sup>  
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34 Given the prevalence of kidney impairment in patients with osteoporosis, it is critical that  
35  
36 clinicians know which patients are suitable for treatment with specific bisphosphonates.<sup>(89)</sup>  
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38 Although the oral bisphosphonates carry warnings on their use in patients with severe renal  
39  
40 impairment, renal function did not change between treatment and placebo groups in clinical  
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42 studies on alendronate, risedronate and oral ibandronate.<sup>(34,35)</sup> A recent retrospective cohort study  
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44 in 122,727 patients aged  $\geq 66$  years with a fragility fracture also found that  
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46 oral bisphosphonate use was not associated with acute kidney injury.<sup>(90)</sup>  
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53 Clinical studies of IV bisphosphonates reported cases of acute and transient increases in SCr  
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55 following drug administration but no long-term impact in kidney function has been reported. For  
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3 zoledronic acid, similar incidences of renal adverse events, impairments and function were  
4 reported for the zoledronic acid- and placebo-treated groups over the duration of the trials,<sup>(39)</sup>  
5  
6 even in an older study population and in those who had received IV zoledronic acid for up to 6  
7 years.<sup>(42)</sup> As none of the patients in the zoledronic acid pivotal studies had biochemical changes  
8 that could suggest CKD-MBD, it is unknown whether the responses observed in these trials  
9 would vary in patients with known intrinsic kidney disease or unresolved secondary  
10 hyperparathyroidism.<sup>(58,91,92)</sup> Although the renal tissue half-life of ibandronate is shorter than  
11 zoledronic acid (24 vs 150–200 days),<sup>(93)</sup> no data comparing the renal effects of IV ibandronate  
12 with IV zoledronic acid in a randomized population have been published, and there is no  
13 scientific evidence establishing any differences on renal effects between these two  
14 bisphosphonates.  
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32 Clinicians wishing to prescribe bisphosphonates to patients with osteoporosis are advised to  
33 check their patients' CrCl or eGFR prior to initiating treatment and ensure that they adhere to  
34 prescribing instructions. We recommend that in patients with marginal eGFR values, a well-  
35 hydrated 24-hour CrCl should be performed for GFR calculation before clinical management  
36 decisions are made with regard to bisphosphonate use. For zoledronic acid, IV administration  
37 should be over a period of no less than 15 minutes and patients must be adequately hydrated  
38 prior to the infusion. In addition, clinicians should make an assessment of any concomitant  
39 medication that a patient may be taking, with special regard to potentially nephrotoxic therapies.  
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## 53 Conclusion

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4 Bisphosphonates – a class of drug that is available in both oral and parenteral preparations – have  
5 historically been associated with a low incidence of renal adverse events. This review of clinical  
6 trial and post-marketing surveillance data has shown that, if used with care and in accordance  
7 with the prescribing information, these agents can be administered to patients with various  
8 degrees of renal impairment, with no long-term decline in renal function. This applies to both  
9 oral and IV bisphosphonates. Clinical trials have shown little evidence of an association between  
10 oral bisphosphonate administration and renal impairment, and these medications are effective in  
11 reducing fracture risk and increasing BMD in patients (by *post hoc* analysis) with eGFR >15  
12 mL/min. Moreover, results from clinical trials of IV bisphosphonates have shown that, even in  
13 elderly osteoporotic patients with existing fracture, administration in accordance with the  
14 prescribing information does not result in long-term renal function decline and is efficacious in  
15 preventing fracture at all skeletal sites over 6 years of administration.

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34 Although bisphosphonates are generally well tolerated in clinical studies, the low incidence of  
35 renal adverse events has led to the inclusion of “warnings” on the prescribing information of all  
36 bisphosphonates regarding the use of these agents in patients with severe renal impairment (CrCl  
37 <30 or <35 mL/min). For IV zoledronic acid, this warning constitutes a “contraindication” in the  
38 registration labels for patients with eGFR <35 mL/min.<sup>(4)</sup> This contraindication – which does not  
39 alter the positive benefit-to-risk balance for the product<sup>(55)</sup> – is primarily due to the way  
40 bisphosphonates are excreted from the body, via glomerular filtration and tubular secretion, ~~and~~  
41 ~~to post-marketing reports of acute renal failure and death in a small number of patients. The~~  
42 parenteral formulations of therapies for postmenopausal osteoporosis are invaluable for patients  
43 intolerant to oral bisphosphonates, patients with pre-existing esophageal disease, and those in  
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3 whom there is uncertainty regarding gastrointestinal absorption. In view of their efficacy in  
4 preventing osteoporotic fractures, bisphosphonates are clearly beneficial in these patient groups.  
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6 However, as with any drug, it is important that physicians follow the prescribing information for  
7 administration at all times, in order to maximize the benefit-to-risk ratio associated with  
8 administration.  
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18 This review has clearly shown that the benefit-to-risk ratio for all bisphosphonates is very  
19 favorable when they are used according to the label in the right patient populations for the right  
20 duration, and that IV bisphosphonates – which have an established renal safety profile when used  
21 according to prescribing information – can even be used in the majority of patients, including  
22 those who are elderly, as long as their eGFR is >35 mL/min.<sup>(94,95)</sup> These drugs therefore  
23 constitute an important and effective part of the physician’s pharmacological armamentarium.  
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32 ~~While all bisphosphonates are generally well tolerated in clinical studies, all bisphosphonates~~  
33 ~~have registration “warnings” for use in patients with severe renal impairment (CrCl <30 or <35~~  
34 ~~mL/min). IV zoledronic acid has included a “contraindication” in the registration labels for~~  
35 ~~patients with eGFR <35 mL/min.<sup>(2)</sup> This contraindication is primarily due to the way~~  
36 ~~bisphosphonates are excreted from the body, via glomerular filtration and tubular secretion, and~~  
37 ~~from the post-marketing reports of acute renal failure and deaths in a small number of patients.~~  
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46 ~~There is little evidence that oral bisphosphonates are associated with renal impairment in clinical~~  
47 ~~trials, and these medications are effective in reducing fracture risk and increasing BMD in~~  
48 ~~patients (by *post hoc* analysis) with eGFR >15 mL/min. Results from clinical trials of IV~~  
49 ~~bisphosphonates for osteoporosis have shown that even in elderly patients with existing fracture,~~  
50 ~~administration in accordance with the prescribing information does not result in long-term renal~~  
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3 function decline and is efficacious in preventing fracture at all skeletal sites over 6 years of  
4 administration. The parenteral formulations of therapies for postmenopausal osteoporosis are  
5 invaluable for patients intolerant to oral bisphosphonates, patients with pre-existing esophageal  
6 disease, or in whom there is uncertainty regarding the absorption, given that most oral  
7 bisphosphonates are poorly absorbed in the gastrointestinal tract. In order to maximize this  
8 benefit to risk ratio of bisphosphonates, it is important that physicians follow the registered  
9 guidelines for administration at all times. When used according to the label, IV bisphosphonates  
10 are well tolerated and can even be used in elderly patients whose eGFR is  $>35$  mL/min. The  
11 benefit/risk ratio for all bisphosphonates is very favorable when they are used in the right patient  
12 populations for the right duration.<sup>(85,86)</sup> In the same manner, bisphosphonates have an established  
13 renal safety profile when used according to prescribing information.  
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[This paper is dedicated to the memory of Professor Steven Boonen.](#)

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**Authors' roles:**

Data collection: PM and SB. Data analysis: PM, SJ, PE, RE and SB. Data interpretation: PM, SJ, PE, RE and SB. Drafting manuscript: PM and SB. Revising manuscript content: PM, SJ, PE, RE and SB. Approving final version of manuscript: PM, SJ, PE, RE and SB. PM takes responsibility for the integrity of the data analysis.

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## Figure legends

**Figure 1.** Mean (95% confidence interval) difference between the placebo and risedronate 5 mg treatment groups in the percentage change from baseline in serum creatinine at 6, 12, and 24 months and at the endpoint (last post-baseline visit).<sup>(35)</sup> Results were based on the analysis of 9 randomized, double-blind, placebo-controlled, parallel-group, phase III trials of risedronate 5 mg daily treatment. Mean differences are shown for the severe (CrCl, <30 mL/min), moderate (CrCl,  $\geq 30$ –<50 mL/min), and mild (CrCl,  $\geq 50$ –<80 mL/min) renal impairment subgroups. Negative values imply that decreases from baseline in serum creatinine were greater in the risedronate group than in the placebo group. Figure reprinted from Miller and colleagues, with permission from John Wiley and Sons.

CrCl was calculated using the Cockcroft-Gault method.<sup>(5)</sup>

CrCl, creatinine clearance; SCr, serum creatinine.

**Figure. 2(A)** Mean serum creatinine levels in patients with pre- to post- infusion change of >0.5 mg/100 mL from baseline to 36 months in the HORIZON-PFT.<sup>(49)</sup> For each infusion, the patients treated with 5 mg of zoledronic acid showed similar mean serum creatinine levels at 9–11 days post-infusion and also at 12 months post-infusion. Figure reprinted from Boonen and colleagues, with permission from the International Society of Nephrology. **(B)** Mean changes in calculated creatinine clearance from the baseline of the HORIZON-PFT extension study (Year 3 of the HORIZON-PFT trial) to year 6 were comparable for zoledronic acid vs. placebo (safety population).<sup>(50)</sup> Figure reprinted from Miller and colleagues, with permission from Springer.

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3 HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly  
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5 Pivotal Fracture Trial; SE, standard error; Z6, patient group receiving zoledronic acid 5 mg for 6  
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7 years; Z3P3, patient group receiving zoledronic acid 5 mg for 3 years followed by placebo for 3  
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10 years.  
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13 Conversion factor for SCr from mg/dL to  $\mu\text{mol/L}$  is 88.4.  
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**Table 1. Case reports of renal events in patients receiving zoledronic acid<sup>(22-25)</sup>**

Patient	Renal-related comorbidities	Bisphosphonate treatment	Clinical presentation and histology
59-year-old male with multiple myeloma <sup>(22)</sup>	Long-standing renal insufficiency	Pamidronate 90 mg monthly for 13 months then switch to zoledronic acid 4 mg monthly	4 months after switching to zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.9 to 4.0 mg/dL</li> <li>• 24-hour urine protein, 1.08 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
73-year-old female with Paget's disease <sup>(22)</sup>	Acute renal failure	Pamidronate 90 mg monthly for 21 months then switch to zoledronic acid 4 mg monthly	After 4 doses of zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from ~1.5 to 3.8 mg/dL</li> <li>• 24-hour urine protein, 2 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
57-year-old female with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg monthly for 2 years and 9 months then switch to zoledronic acid 4 mg monthly	8 months after switching to zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.3 to 2.5 mg/dL</li> <li>• 24-hour urine protein, 194 mg/day to 1.3 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
75-year-old male with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg monthly for 22 months then switch to zoledronic acid 4 mg monthly	By the 4 <sup>th</sup> dose of zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.4 to 1.7 mg/dL (levels continued to increase to 2.6 mg/dL after treatment discontinuation for 2 months)</li> <li>• Urinalysis showed absence of protein</li> <li>• Biopsy revealed toxic ATN</li> </ul>
85-year-old male with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg for 2 doses then switch to zoledronic acid 4 mg monthly	After 3 doses of zoledronic acid: <ul style="list-style-type: none"> <li>• SCr increased from 1.6 to 3.8 mg/dL</li> <li>• Biopsy revealed toxic ATN</li> </ul> 1 month after zoledronic acid discontinuation <ul style="list-style-type: none"> <li>• SCr reached 5.5 mg/dL</li> </ul>

			<ul style="list-style-type: none"> <li>• 24-hour urine protein, 1.7 g/day</li> </ul>
66-year-old male with multiple myeloma <sup>(22)</sup>	NR	Pamidronate 90 mg monthly for 4 months then switch to zoledronic acid 4 mg monthly	<p>After 4 doses of zoledronic acid:</p> <ul style="list-style-type: none"> <li>• SCr increased from 1.0 to 2.0 mg/dL</li> <li>• 24-hour urine protein, 2.6 g/day</li> <li>• Biopsy revealed toxic ATN</li> </ul>
65-year-old male with multiple myeloma <sup>(23)</sup>	NR	Zoledronic acid 4 mg (9 doses), 3.3 mg (1 dose)	<p>After 9 doses of zoledronic acid, SCr levels was 2.39 mg/dL</p> <p>Shortly after the 10<sup>th</sup> dose:</p> <ul style="list-style-type: none"> <li>• SCr levels reached 4.6 mg/dL</li> <li>• Patient reported heavy proteinuria, hypoalbuminemia and acute renal failure with nephrotic syndrome</li> <li>• Biopsy showed focal segmental glomerulosclerosis</li> </ul>
74-year-old male with bone metastases <sup>(24)</sup>	NR	Zoledronic acid 4 mg infused over 15 minutes every 3 or 4 weeks for 14 months	Steady increase in SCr that reached above normal range after 10 months of therapy; increases continued over the subsequent 4 months until treatment discontinuation
72-year-old female with multiple myeloma <sup>(25)</sup>	NR	Zoledronic acid 4 mg monthly	After 5 <sup>th</sup> dose of zoledronic acid, SCr increased from 0.67 to 4.28 mg/dL but subsequently stabilized after 2 weeks at 1.88 mg/dL with CrCl of 23 mL/min
57-year-old male with multiple myeloma <sup>(25)</sup>	NR	Zoledronic acid 4 mg monthly	4 weeks after zoledronic acid administration, SCr increased from 2.49 to 12.22 mg/dL; biopsy showed tubulointerstitial damage

ATN, acute tubular necrosis; CrCl, creatinine clearance; NR, not reported; SCr, serum creatinine.

Conversion factor for SCr from mg/dL to  $\mu\text{mol/L}$  is 88.4.

**Table 2.** Clinical evidence of the effect of bisphosphonates on renal function<sup>(34-36,38-41,47-50)</sup>

Study details	Dosage	Renal function effects
<i>Oral bisphosphonates</i>		
FIT subanalysis in women with postmenopausal osteoporosis (n=6438) <sup>(34)</sup>	Alendronate vs. placebo; 3-year follow-up	Small significant increase in SCr from baseline to 3 years in both groups
Risedronate pooled analysis of Phase III studies (n=9883) in women with osteoporosis (91% renal impairment at baseline – subdivided into severe, moderate and mild) <sup>(35)</sup>	Risedronate 5 mg daily or placebo for up to 3 years	No significant difference in SCr changes between placebo and risedronate groups; overall incidence of renal function-related adverse events similar across all renal impairment subgroups
BONE study in women with postmenopausal osteoporosis (n=2946) <sup>(36)</sup>	Oral ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months	No clinically relevant changes in laboratory markers (including renal function tests) reported for placebo or ibandronate groups over 3 years
Postmenopausal women with osteoporosis or osteopenia (n=127) <sup>(47)</sup>	Alendronate 70 mg weekly, risedronate 35 mg weekly or raloxifene 60 mg daily for 12 months	No significant differences in blood urea nitrogen, creatinine and eGFR seen between baseline and 12 months
<i>IV bisphosphonates</i>		
DIVA study in women with postmenopausal osteoporosis (n=1395) <sup>(38,48)</sup>	Intermittent IV ibandronate (2 mg every 2 months or 3 mg every 3 months) or daily oral ibandronate (2.5 mg) for 2 years (only 1-year data are shown)	Low incidence of renal adverse events; no acute renal failure reported; 12 cases of clinically relevant changes in SCr from baseline but none was considered to be treatment-related
HORIZON-PFT: Women with postmenopausal osteoporosis (n=7765) <sup>(39,49)</sup>	Zoledronic acid 5 mg once yearly (IV infusion over 15 minutes) or placebo for 3 years	No significant between-group differences in SCr or CrCl at 3 years. <b>N</b> ; <b>n</b> o association between zoledronic acid 5 mg and long-term renal function deterioration; <b>A</b> ge-related deterioration of renal function over time observed in both zoledronic acid and placebo groups



HORIZON-RFT: Men and women with low-trauma hip fracture (n=2127) <sup>(40)</sup>	Zoledronic acid 5 mg once yearly (IV infusion over 15 minutes) or placebo	Renal adverse events similar across zoledronic acid 5 mg and placebo groups
HORIZON-GIO: Men and women with glucocorticoid-induced osteoporosis (n=833); Prevention/treatment cohorts <sup>(41)</sup>	Once-yearly zoledronic acid 5 mg (IV infusion over 15–20 minutes) or daily risedronate 5 mg for 1 year	Clinically significant renal events in 2% zoledronic acid patients + 1.4% risedronate patients; 3 cases acute renal failure related to underlying disease
Study in men with osteoporosis (n=1199) <sup>(50)</sup>	Once-yearly zoledronic acid 5 mg (IV infusion over 15–30 minutes)	Increased in SCr >0.5 mg/dL occurred in 2.4% (14/584) patients receiving zoledronic acid, and 3.0% (18/610) patients receiving placebo CrCl < 30 mL/min at any time during the study was reported in 0.5% (3/557) zoledronic acid-treated patients, and 1.6% (9/577) placebo-treated patients; CrCl was calculated using the Cockcroft-Gault formula <sup>(5)</sup>

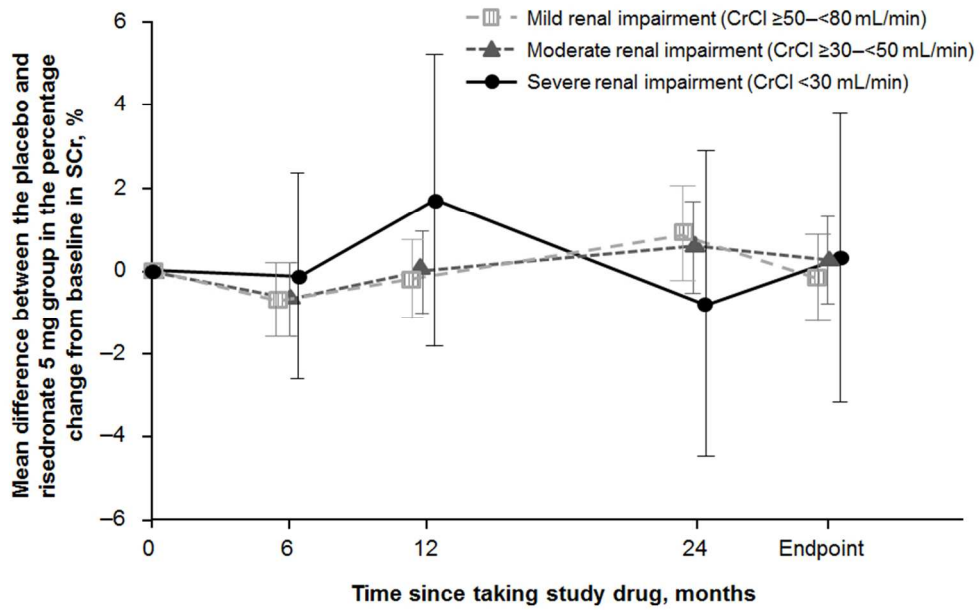
CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; FIT, Fracture Intervention Trial; GIO, Glucocorticoid-induced

Osteoporosis; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial; SCr, serum creatinine

[Conversion factor for SCr from mg/dL to  \$\mu\$ mol/L is 88.4.](#)

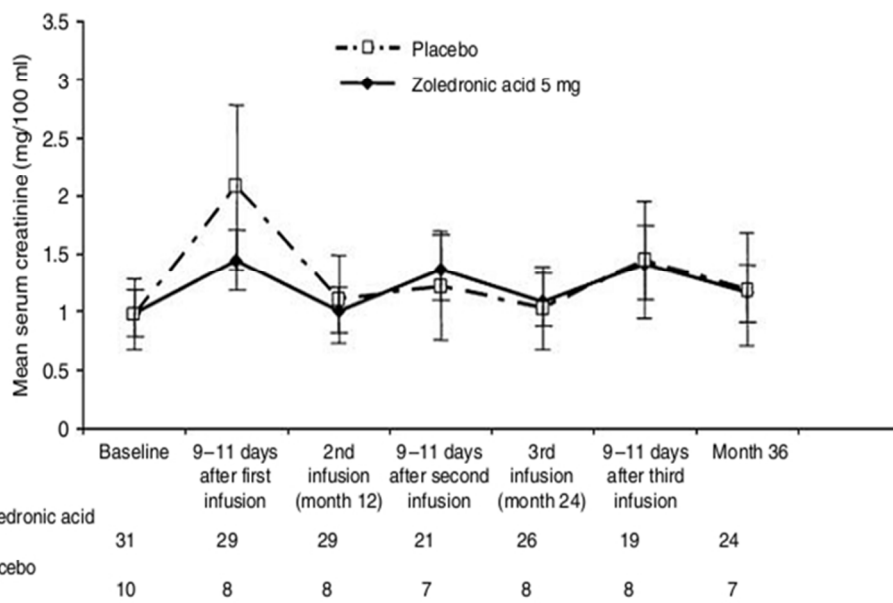
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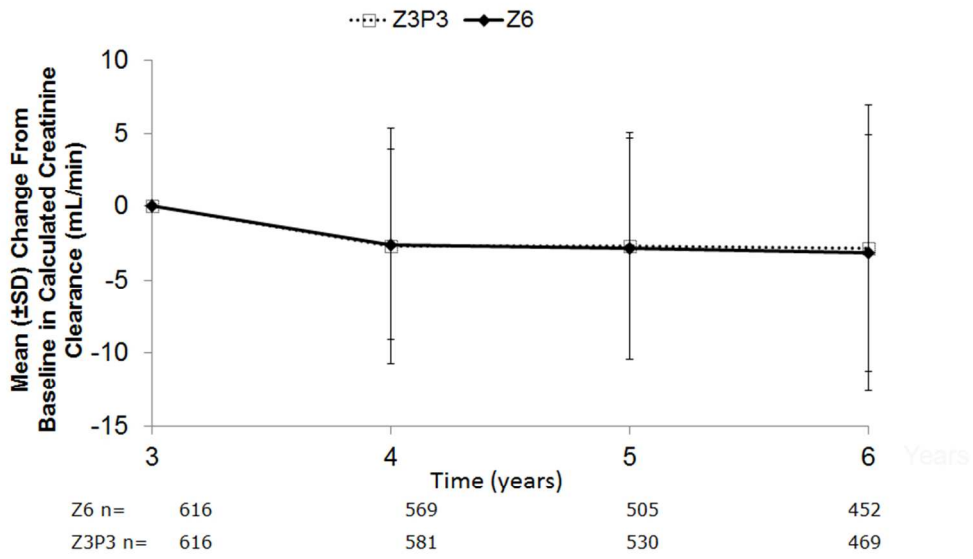
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