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OHSU HEALTH SYSTEM
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary

Secondary fragility fracture prevention after osteoporotic hip fractures with Zoledronic Acid

BACKGROUND

Hip fractures are highly prevalent in older adults (Melton 1993; Chevalley 2007) and contribute to significant morbidity and mortality in this age group (Autier 2000; Cauley 2000; Kado 1999; Vestergaard 2007; Magaziner 1997; Hannan 2001). The goal of osteoporosis management is to prevent osteoporotic fractures, but for those who have had sustained an osteoporotic fracture, it is more urgent to prevent secondary fracture (Shi 2019). Patients with previous fractures lose significant bone and muscle mass (Fox 200). Hip fracture is a strong risk factor for subsequent non-hip skeletal fractures in the elderly population. It is not only a marker of prevalent osteoporosis but also a precipitant of functional and bone density decline, which further increases fall and fracture risk. (Colon-Emeric 2003). Furthermore, patients with an osteoporotic fracture are at increased risk of morbidity and mortality compared to those patients without fractures (Shi 2019; Su 2014; Yoo 2015; Fraser 2011; Willson 2015; Sale 2014).

Bisphosphonates are well-studied antiresorptive medications that are widely approved and recommended as a first line choice for osteoporosis in post-menopausal women and older populations. A meta-analysis (Jansen 2011) comparing the efficacy of bisphosphonates showed a relative risk (RR) of 0.30 (95% Confidence Interval 0.23-0.37) for zoledronic acid relative to placebo, an RR of 0.55 (0.41-0.76) relative to alendronate, an RR of 0.50 (0.36-0.70) relative to risedronate, and an RR of 0.58 (0.37-0.92) relative to ibandronate. Regarding hip fractures, there is a 47% probability that zoledronic acid shows the greatest risk reduction, followed by alendronate (36%) and risedronate (11%). Overall, there was a 94% probability that zoledronic acid showed the greatest reduction in any fracture. Several high-quality RCTs have demonstrated the efficacy of individual bisphosphonates for secondary fracture prevention, but few sufficient comparisons have been carried out due to a lack of large-scale direct trials (Shi 2019). This evidence review will evaluate the use of zoledronic acid in preventing secondary fragility fractures in patients with osteoporotic hip fractures.

ASK THE QUESTION

Question 1: For hospitalized older adults over 50 with an acute osteoporotic hip fracture, does zoledronic acid reduce the risk of additional fragility fracture compared to alendronate (or a similar oral bisphosphonate) or placebo?

Question 2: For hospitalized older adults over 50 with an acute osteoporotic hip fracture, does zoledronic acid reduce **the risk of dying at 1 year** compared to alendronate (or a similar oral bisphosphonate) or placebo?

Question 3: Is zoledronic acid after an acute osteoporotic fracture more **cost effective** than alendronate (or a similar oral bisphosphonate)?

Question 4: What effect does zoledronic acid given shortly after an acute osteoporotic fracture have on **fracture healing**?

SEARCH FOR EVIDENCE

Appendix C

CRITICALLY ANALYZE THE EVIDENCE

Question 1: For hospitalized older adults over 50 with an acute osteoporotic hip fracture, does zoledronic acid reduce the risk of additional fragility fracture compared to alendronate (or a similar oral bisphosphonate) or placebo?

Secondary Fractures

Three systematic reviews were found comparing the effect of zoledronic acid compared to other bisphosphonates. One systematic review (Jin 2019) investigated the efficacy of current medication therapies on preventing secondary osteoporotic vertebral compression fracture (OVCF) through systematic literature review and meta-analysis of RCTs. Study found the effectiveness in reducing OVCF of zoledronate (Relative Risk, RR: 0.34; 95% CI, 0.17–0.69, p = 0.003), alendronate (RR: 0.54; 95% CI: 0.43–0.68; p < 0.0001) and risedronate (RR:0.61; 95% CI: 0.51–0.73; p < 0.0001. Another systematic review (Shi 2019) assessed the efficacies of the five most commonly used bisphosphonates (alendronate, ibandronate, risedronate, zoledronate, and etidronate) for the secondary prevention of osteoporotic fractures via an integrated analysis of all available direct and indirect evidence in a Bayesian network meta-analysis. The rank probability plot and the SUCRA calculation results suggested that alendronate was the best intervention (14.6%) for secondary prevention of vertebral fractures, followed by zoledronate (15.3%) and etidronate (22.1%). Lastly, another systematic review (Saito 2017) found zoledronic acid significantly reduces the secondary vertebral fracture (RR 0.53; 95% CI 0.32 – 0.91).

There is **moderate quality evidence for the use of zoledronic acid for secondary fractures in comparison with other bisphosphonates.**

New Hip Fractures

One systematic review (Shi 2019) assessed the efficacies of the five most commonly used bisphosphonates (alendronate, ibandronate, risedronate, zoledronate, and etidronate) for the secondary prevention of osteoporotic fractures via an integrated analysis of all available direct and indirect evidence in a Bayesian network meta-analysis. For the incidence of new hip fractures, alendronate was associated with the lowest incidence (18.5%), followed by zoledronate (43.1%) and risedronate (52.5%).

There is **low quality evidence the alendronate is associated with lower incidence for new hip fractures, followed by zoledronic acid.**

New non-vertebral fractures

Three studies were found comparing zoledronic acids effect on new non-vertebral fractures. One systematic review (Jin 2019) assessed the efficacies of the five most commonly used bisphosphonates (alendronate, ibandronate, risedronate, zoledronate, and etidronate) for the secondary prevention of osteoporotic fractures via an integrated analysis of all available direct and indirect evidence in a Bayesian network meta-analysis. Zoledronate ranked lowest (16.6%) regarding the incidence of new nonvertebral nonhip fractures, followed by risedronate (23.8%) and alendronate (44.1%). Another systematic review (Shi 2019) investigated the efficacy of current medication therapies on preventing secondary osteoporotic vertebral compression fracture (OVCF) through systematic literature review and meta-analysis of RCTs. Zoledronate could significantly decrease event ratio of non-vertebral fractures (RR, 0.54; 95% CI, 0.32–0.91; p = 0.02). Lastly, another systematic review (Saito 2017) found zoledronic acid significantly reduces the incidence of non-vertebral fracture (RR 0.74; 95% CI 0.56 – 0.98).

There is **moderate quality evidence for the use of zoledronic acid for new non-vertebral fractures in comparison with other bisphosphonates.**

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Secondary Fractures

Quality (certainty) of evidence for: (outcome) ☐High ☒ Moderate ☐ Low ☐ Very Low					
Risk of Bias across studies: ☐ High ☐ Medium ☒ Low		**Low Quality Rating if:** ☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) – *patient populations varied between studies* ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Jin, Y.-Z., et al. Year Published: 2019 Location: Seoul National University, South Korea Journal: *BMC musculoskeletal disorders*	To investigate the efficacy of current medication therapies on preventing secondary osteoporotic vertebral compression fracture (OVCF) through systematic literature review and meta-analysis of randomized controlled trials (RCTs)	**Size:** 41 studies **Inclusion Criteria**: Study involved patients with osteoporosis, RCTs published in English that investigated the efficacy of currently approved medications for patients with OVCF, studies that included osteoporosis patients without distinguishing their fracture history were included if the data of the participants with prevalent fractures was adequately presented. **Exclusion Criteria**: Studies that recruited patients with traumatic vertebral fracture, secondary osteoporosis, or did not report results in dichotomous data (i.e., patient-years, etc.)	**Type:** Systematic Review	**Results:** Effectiveness in reducing OVCF of zoledronate (Relative Risk, RR: 0.34; 95% CI, 0.17–0.69, p = 0.003), alendronate (RR: 0.54; 95% CI: 0.43–0.68; p < 0.0001), risedronate (RR: 0.61; 95% CI: 0.51–0.73; p < 0.0001), etidronate (RR, 0.50; 95% CI, 0.29–0.87, p < 0.01), ibandronate (RR: 0.52; 95% CI: 0.38–0.71; p < 0.0001), parathyroid hormone (RR: 0.31; 95% CI: 0.23–0.41; p < 0.0001), denosumab (RR, 0.41; 95% CI, 0.29–0.57; p < 0.0001) and selective estrogen receptor modulators (Raloxifene, RR: 0.58; 95% CI: 0.44–0.76; p < 0.0001; Bazedoxifene, RR: 0.66; 95% CI: 0.53–0.82; p = 0.0002) in preventing secondary fractures. **One study was included in meta-analysis for zoledronate that used placebo as control.*	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

Author: Shi, L. et al. Year Published: 2019 Location: Journal: *BioMed Research International*	To assess the efficacies of the five most commonly used bisphosphonates (alendronate, ibandronate, risedronate, zoledronate, and etidronate) for the secondary prevention of osteoporotic fractures via an integrated analysis of all available direct and indirect evidence in a Bayesian network meta-analysis	**Size:** 13 papers, involving 11,822 patients with osteoporotic fractures **Inclusion Criteria**: (1) designed as a RCT; (2) included postmenopausal women or men over 50 years with existing osteoporotic fractures; (3) included a comparison between at least one of the five bisphosphonates, including alendronate, ibandronate, risedronate, zoledronate, and etidronate, with placebo or another of the investigated bisphosphonates; (4) reported clinical outcomes including new vertebral fractures, new hip fractures, or new nonvertebral nonhip fractures, with new vertebral fractures defined as the primary outcome, and new nonvertebral fractures defined as a secondary outcome; (5) provided sufficient and qualified data that could be extracted from original academic studies; and (5) had a treatment duration of at least 24 months. **Exclusion Criteria**: (1) the patients did not have osteoporotic fractures; (2) the study was not a RCT or a conference abstract or paper, case report, observational study, reviews or duplicated paper; (3) sufficient and qualified data were unavailable; (4) the treatment duration was less than 24 months; and (5) included patients with secondary osteoporosis (glucocorticoid-induced osteoporosis, etc.).	**Type:** Systematic Review	**Results:** In network meta-analyses, significant differences were found between placebo and any one of the five bisphosphonates for new vertebral fractures. The **rank probability plot and the SUCRA calculation results suggested that alendronate was the best intervention (14.6%) for secondary prevention of vertebral fractures, followed by zoledronate (15.3%) and etidronate (22.1%).** **Whether allocation concealment was conducted properly was unclear in 12 studies. Also, a high risk of incomplete outcome data bias was observed because the method of last-observation was carried out for the missing data in some studies.*	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

Author: Saito, T., et al. Year Published: 2017 Location: University of Michigan Journal: *Osteoporosis International*	To analyze the effectiveness of individual osteoporotic drugs in preventing subsequent fractures	**Size:** 1 study; 2111 participants **Inclusion Criteria**: RCTs including participants who had one or more primary fractures and were at high risk for a secondary fracture.	**Type:** Systematic Review	**Results:** Zoledronic acid significantly reduces the secondary vertebral fracture (RR 0.53; 95% CI 0.32 – 0.91).	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

References:

1. Jin, Y.-Z., et al. (2019). "Effect of medications on prevention of secondary osteoporotic vertebral compression fracture, non-vertebral fracture, and discontinuation due to adverse events: a meta-analysis of randomized controlled trials." BMC musculoskeletal disorders **20**(1): 399.
2. Shi, L., et al. (2019). "Bisphosphonates for Secondary Prevention of Osteoporotic Fractures: A Bayesian Network Meta-Analysis of Randomized Controlled Trials." BioMed Research International **2019**: 2594149.
3. Saito, T., et al. (2017). "Effectiveness of anti-osteoporotic drugs to prevent secondary fragility fractures: systematic review and meta-analysis." Osteoporosis International **28**(12): 3289-3300.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
New Hip Fractures

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Low Quality Rating if:**	**Other Considerations:**
☐ High ☒ Medium ☐ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) – *No consistency statistical included for new hip fractures* ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Shi, L. et al. Year Published: 2019 Location: Journal: *BioMed Research International*	To assess the efficacies of the five most commonly used bisphosphonates (alendronate, ibandronate, risedronate, zoledronate, and etidronate) for the secondary prevention of	**Size:** 13 papers, involving 11,822 patients with osteoporotic fractures **Inclusion Criteria**: (1) designed as a RCT; (2)	**Type:** Systematic Review	**Results:** In terms of the incidence of new hip fractures, alendronate was associated with the lowest incidence (18.5%), followed by	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or

	osteoporotic fractures via an integrated analysis of all available direct and indirect evidence in a Bayesian network meta-analysis	included postmenopausal women or men over 50 years with existing osteoporotic fractures; (3) included a comparison between at least one of the five bisphosphonates, including alendronate, ibandronate, risedronate, zoledronate, and etidronate, with placebo or another of the investigated bisphosphonates; (4) reported clinical outcomes including new vertebral fractures, new hip fractures, or new nonvertebral nonhip fractures, with new vertebral fractures defined as the primary outcome, and new nonvertebral fractures defined as a secondary outcome; (5) provided sufficient and qualified data that could be extracted from original academic studies; and (5) had a treatment duration of at least 24 months. **Exclusion Criteria**: (1) the patients did not have osteoporotic fractures; (2) the study was not a RCT or a conference abstract or paper, case report, observational study, reviews or duplicated paper; (3) sufficient and qualified data were unavailable; (4) the treatment duration was less than 24 months; and (5) included patients with secondary osteoporosis (glucocorticoid-induced osteoporosis, etc.).		zoledronate (43.1%) and risedronate (52.5%). **Whether allocation concealment was conducted properly was unclear in 12 studies. Also, a high risk of incomplete outcome data bias was observed because the method of last-observation was carried out for the missing data in some studies.*	exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

References:

1. Shi, L., et al. (2019). "Bisphosphonates for Secondary Prevention of Osteoporotic Fractures: A Bayesian Network Meta-Analysis of Randomized Controlled Trials." BioMed Research International **2019**: 2594149.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
New Nonvertebral Fractures

Quality (certainty) of evidence for: (outcome) ☐High ☒ Moderate ☐ Low ☐ Very Low					
Risk of Bias across studies: ☐ High ☐ Medium ☒ Low		**Low Quality Rating if:** ☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) – *Populations varied between studies* ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Shi, L. et al. Year Published: 2019 Location: Journal: *BioMed Research International*	To assess the efficacies of the five most commonly used bisphosphonates (alendronate, ibandronate, risedronate, zoledronate, and etidronate) for the secondary prevention of osteoporotic fractures via an integrated analysis of all available direct and indirect evidence in a Bayesian network meta-analysis	**Size:** 13 papers, involving 11,822 patients with osteoporotic fractures **Inclusion Criteria**: (1) designed as a RCT; (2) included postmenopausal women or men over 50 years with existing osteoporotic fractures; (3) included a comparison between at least one of the five bisphosphonates, including alendronate, ibandronate, risedronate, zoledronate, and etidronate, with placebo or another of the investigated bisphosphonates; (4) reported clinical outcomes including new vertebral fractures, new hip fractures, or new nonvertebral nonhip fractures, with new vertebral fractures defined as the primary outcome, and new nonvertebral fractures defined as a secondary outcome; (5) provided sufficient and qualified data that could be	**Type:** Systematic Review	**Results:** Zoledronate ranked lowest (16.6%) regarding the incidence of new nonvertebral nonhip fractures, followed by risedronate (23.8%) and alendronate (44.1%). **Whether allocation concealment was conducted properly was unclear in 12 studies. Also, a high risk of incomplete outcome data bias was observed because the method of last-observation was carried out for the missing data in some studies.*	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

		extracted from original academic studies; and (5) had a treatment duration of at least 24 months. **Exclusion Criteria**: (1) the patients did not have osteoporotic fractures; (2) the study was not a RCT or a conference abstract or paper, case report, observational study, reviews or duplicated paper; (3) sufficient and qualified data were unavailable; (4) the treatment duration was less than 24 months; and (5) included patients with secondary osteoporosis (glucocorticoid-induced osteoporosis, etc.).			
Author: Jin, Y.-Z., et al. Year Published: 2019 Location: Seoul National University, South Korea Journal: *BMC musculoskeletal disorders*	To investigate the efficacy of current medication therapies on preventing secondary (OVCF) through systematic literature review and meta-analysis of randomized controlled trials (RCTs)	**Size:** 41 studies **Inclusion Criteria**: Study involved patients with osteoporosis, RCTs published in English that investigated the efficacy of currently approved medications for patients with OVCF, studies that included osteoporosis patients without distinguishing their fracture history were included if the data of the participants with prevalent fractures was adequately presented. **Exclusion Criteria**: Studies that recruited patients with traumatic vertebral fracture, secondary osteoporosis, or did not report results in dichotomous data (i.e., patient-years, etc.)	**Type:** Systematic Review	**Results:** Zoledronate could significantly decrease event ratio of non-vertebral fractures (RR, 0.54; 95% CI, 0.32–0.91; p = 0.02) **One study was included in meta-analysis for zoledronate that used placebo as control.*	**Study Limitations:** ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised ☐ Inappropriate pooled analysis
Author: Saito, T., et al. Year Published: 2017 Location: University of Michigan Journal: *Osteoporosis International*	To analyze the effectiveness of individual osteoporotic drugs in preventing subsequent fractures	**Size:** 1 study; 2111 participants **Inclusion Criteria**: RCTs including participants who had one or more primary fractures and were at high risk for a	**Type:** Systematic Review	**Results:** Zoledronic acid significantly reduces the incidence of non-vertebral fracture (RR 0.74; 95% CI 0.56 – 0.98).	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive

		secondary fracture.			☒ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

References:

1. Jin, Y.-Z., et al. (2019). "Effect of medications on prevention of secondary osteoporotic vertebral compression fracture, non-vertebral fracture, and discontinuation due to adverse events: a meta-analysis of randomized controlled trials." BMC musculoskeletal disorders **20**(1): 399.
2. Saito, T., et al. (2017). "Effectiveness of anti-osteoporotic drugs to prevent secondary fragility fractures: systematic review and meta-analysis." Osteoporosis International **28**(12): 3289-3300.
3. Shi, L., et al. (2019). "Bisphosphonates for Secondary Prevention of Osteoporotic Fractures: A Bayesian Network Meta-Analysis of Randomized Controlled Trials." BioMed Research International **2019**: 2594149.

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

Question 2:

For hospitalized older adults over 50 with an acute osteoporotic hip fracture, does zoledronic acid reduce the risk of dying at 1 year compared to alendronate (or a similar oral bisphosphonate) or placebo?

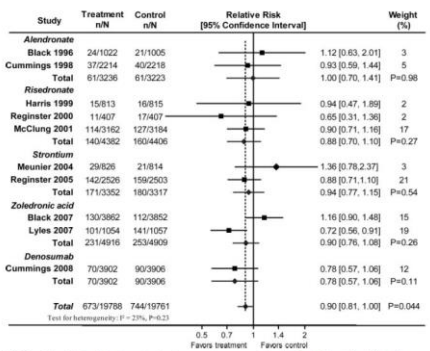
One systematic review (Bollard 2010) conducted a meta-analysis of placebo-controlled randomized trials to determine whether effective osteoporosis treatment reduces mortality. The meta-analysis included two studies testing the efficacy of zoledronic acid and its effect on mortality. One first RCT (Lyles 2007) included all patients who had undergone repair of a hip fracture and were unable or unwilling to take an oral bisphosphonate. Patients were ambulatory before the hip fracture and had both legs. Study found that 101 of 1054 patients in the zoledronic acid group (9.6%) and 141 of 1057 patients in the placebo group (13.3%) died, a reduction of 28% in deaths from any cause in the zoledronic acid group (P = 0.01). The second RCT (Black 2007) included postmenopausal women between the ages of 65 and 89 years; a bone mineral density T score of −2.5 or less at the femoral neck, with or without evidence of existing vertebral fracture, or a T score of −1.5 or less, with radiologic evidence of at least two mild vertebral fractures or one moderate vertebral fracture. Study found 130 deaths (3.4%) in group receiving zoledronic acid and 112 deaths (2.9%) in the group receiving placebo. Therefore, Bollard's meta-analysis when combining both studies found that Zoledronic acid had a relative risk of 0.90 (95% CI 0.76 – 1.08). In comparison to other bisphosphonates, Alendronate had a RR of 1.00 (95% CI 0.70 – 1.41) and Risendronate had a RR of 0.88 (95% CI 0.70 – 1.10),

There is **low quality evidence that mortality rates are similar or lower when using zoledronic acid compared to other bisphosphonates**. Individual RCTS reported a large loss to follow-up during study period. Also, the body of evidence is inconsistent between individual studies, and imprecise due to lack of events.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Mortality

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Low Quality Rating if:**	**Other Considerations:**
☐ High ☒ Medium ☐ Low	☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Bolland, M.J., et al. Year Published: 2010 Location: University of Auckland Journal: *The Journal of clinical endocrinology and metabolism*	To conduct meta-analysis of placebo-controlled randomized trials to determine whether effective osteoporosis treatment reduces mortality	**Size:** 8 studies **Inclusion Criteria**: 1) randomized, double-blind, placebo controlled trials analyzed by intention-to-treat; 2) trials of agents with proven vertebral and nonvertebral antifracture efficacy; 3) trials using agents at the currently approved dosage for treatment of osteoporosis; 4) mean age of trial participants at baseline above 50 yr; 5) number of deaths in study greater than 10; 6) trial population of men, women, or both; and 7) trial duration longer than 1 yr. **Exclusion Criteria**: 1) trials of estrogen and selective estrogen receptor modulators (such as raloxifene, bazedoxifene, and lasofoxifene) because of their effects on multiple systems and outcomes such as heart	**Type:** Systematic Review	**Results:** Zoledronic acid RR 0.90 (95% CI 0.76 – 1.08)  FIG. 3. The effect of treatment of osteoporosis on mortality in 10 studies included in the secondary analysis, grouped by individual agents. The two alendronate studies were not included in the primary analysis because the treatment dose was 5 mg/d for part of the study, which is not the approved dose.	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

		attack, stroke, colon cancer, breast cancer, and venous thromboembolism that might obscure any effects on mortality from effective osteoporosis treatment; 2) duplicate publications, with the largest study otherwise conforming to the inclusion and exclusion criteria included in analyses; 3) trials in which most subjects had a major systemic pathology other than osteoporosis, such as malignancy; 4) trials in which subjects had secondary osteoporosis such as glucocorticoid-induced osteoporosis; and 5) trials in which subjects did not have osteoporosis.			
Author: Lyles, K.W., et al. Year Published: 2007 Location: UCSF Journal: *New England Journal of Medicine*	To test the efficacy and safety of zoledronic acid (at a dose of 5 mg) administered intravenously once yearly for the prevention of new clinical fractures in women and men who had undergone recent surgical repair of a hip fracture.	**Size:** 2127 patients; 1065 in the intervention group and 1062 in the control group. **Inclusion Criteria**: All patients had undergone repair of a hip fracture and were unable or unwilling to take an oral bisphosphonate. Patients were ambulatory before the hip fracture and had both legs. **Exclusion Criteria**: Previous hypersensitivity to a bisphosphonate, a potential for pregnancy, a calculated creatinine clearance of less than 30 ml per minute, a corrected serum calcium level of more than 11.0 mg per deciliter (2.8 mmol per li ter) or less than 8.0 mg per deciliter (2.0 mmol per liter), active cancer, metabolic bone disease other than osteoporosis, and a life expectancy of less than 6 months in the investigator's	**Type:** RCT **Intervention**: Yearly intravenous zoledronic acid (at a dose of 5 mg) **Comparator**: Placebo The infusions were first administered within 90 days after surgical repair of a hip fracture. All patients (mean age, 74.5 years) received supplemental vitamin D and calcium. The median follow-up was 1.9 years. The primary end point was a new clinical fracture.	**Results:** 101 of 1054 patients in the zoledronic acid group (9.6%) and 141 of 1057 patients in the placebo group (13.3%) died, a reduction of 28% in deaths from any cause in the zoledronic acid group (P = 0.01).	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unclear allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

		judgment.			
Author: Black D.M., et al. Year Published: 2007 Location: UCSF Journal: *New England Journal of Medicine*	Annual infusions of zoledronic acid (5 mg) for 3 years were evaluated to determine whether they reduced the risk of vertebral, hip, and other types of fracture.	**Size:** 3889 patients **Inclusion Criteria**: Postmenopausal women between the ages of 65 and 89 years; a bone mineral density T score of −2.5 or less at the femoral neck, with or without evidence of existing vertebral fracture, or a T score of −1.5 or less, with radiologic evidence of at least two mild vertebral fractures or one moderate vertebral fracture. Previous use of oral bisphosphonates was allowed, with the duration of the washout period dependent on previous use (e.g., previous use of ≥48 weeks required 2 years of washout). Concomitant use of the following osteoporosis medications was allowed at baseline and during follow-up: hormone therapy, raloxifene, calcitonin, tibolone, tamoxifen, dehydroepiandrosterone, ipriflavone, and medroxyprogesterone. **Exclusion Criteria**: Any previous use of parathyroid hormone or sodium fluoride, use of anabolic steroids or growth hormone within 6 months before trial entry or oral or intravenous systemic corticosteroids within 12 months, and any previous use of strontium. Patients with a serum calcium level of more than 2.75 mmol per liter or less than 2.00 mmol per liter were ineligible, as were patients with a calculated creatinine clearance of less than 30.0 ml per minute at	**Type:** RCT **Intervention**: Single 15-minute infusion of zoledronic acid (5 mg) **Comparator**: Placebo At 12 months, and at 24 months; the patients were followed until 36 months. Primary end points were new vertebral fracture (in patients not taking concomitant osteoporosis medications) and hip fracture (in all patients). Secondary end points included bone mineral density, bone turnover markers, and safety outcomes	**Results:** 130 deaths (3.4%) in group receiving zoledronic acid and 112 deaths (2.9%) in the group receiving placebo.	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unclear allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

		either of two baseline visits or urine dipstick results of more than 2+ for protein, without evidence of contamination or bacteriuria.			

References:

1. Black, D. M., et al. (2007). "Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis." The New England journal of medicine **356**(18): 1809-1822.
2. Bolland, M. J., et al. (2010). "Effect of osteoporosis treatment on mortality: a meta-analysis." The Journal of clinical endocrinology and metabolism **95**(3): 1174-1181.
3. Lyles, K. W., et al. (2007). "Zoledronic acid and clinical fractures and mortality after hip fracture." The New England journal of medicine **357**(18): 1799-1809.

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

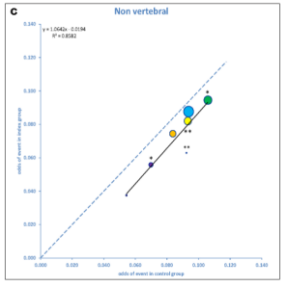
Question 3:

Is zoledronic acid after an acute osteoporotic fracture more cost effective than alendronate (or a similar oral bisphosphonate)?

One study was found focusing on cost-effectiveness in the United States. Modeling studies from outside the United States were not included in this review, due to the fact that cost of care and pharmaceuticals vary between each country. One economic evaluation (Albert and Reddy 2017) assessed the cost efficacy of available regimens for therapy of osteoporosis as defined as the cost time's number need to treat to prevent one fracture. Evaluation focused on postmenopausal women and did not include male participants in analysis. Study found zoledronic acid to be less expensive or comparable in cost to other osteoporosis therapies.

There is **low quality evidence that zoledronic acid is costs effective compared to other bisphosphonates**. Evidence is indirect because economic evaluation limited scope to postmenopausal women.

BODY OF EVIDENCE APPRAISAL TABLE FOR: Cost-effectiveness		
Quality (certainty) of evidence for: (outcome) ☐High ☐ Moderate ☒ Low ☐ Very Low		
Risk of Bias across studies: ☐ High ☒ Medium ☐ Low	**Low Quality Rating if:** ☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☒ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention,*	**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)*

		comparison, or outcome) ☐ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Albert, S.G. and S. Reddy Year Published: 2017 Location: Saint Louis University School of Medicine Journal: *Endocrine practice*	To assess the cost efficacy of available regimens for therapy of osteoporosis as defined as the cost time's number need to treat to prevent one fracture.	**Size:** 43 RCTs; 71,809 postmenopausal women **Inclusion Criteria**: RCTs, trials of anti-osteoporotic drugs versus a comparator	**Type:** Systematic Review	**Results:** Trials were similar in recruitment age (mean ± SD, 67.3 ± 8.1 years) and follow-up duration (25.5 ± 12.6 months). Cost comparisons were evaluated for a treatment strategy assuming generic alendronate as first-line therapy. Denosumab and teriparatide showed benefits in vertebral fracture reduction over alendronate at incremental costs respectively of $46,000 and $455,000 per fracture prevented. **Zoledronate, recently released as a generic, would be either less expensive or comparable in cost.** None of the alternate medicines were statistically better in preventing hip fractures.  Fig. 3. L'Abbe plots of odds of fracture events of drug compared with placebo for (A) vertebral fractures, (B) hip fractures, and (C) nonvertebral fractures. The size of the circle is related to the number in the study population. The dashed line of identity refers to no effect of the study drug compared with placebo. Study drugs are alendronate (green), risedronate (yellow), ibandronate (red), raloxifene (light blue), denosumab (purple), teriparatide (dark blue), and zoledronate (orange). *$P \leq .05$, **$P \leq .001$ compared with placebo.	Study Limitations = ☐ None ***Economic Evaluation*** ☐ The research question is not clearly stated ☐ The perspective of interest is not clear (ie., societal, patient, health system, payer) ☒ The source(s) of effectiveness estimates are not clearly stated ☐ The primary outcome measures are not clearly stated ☐ The methods for the estimation of quantities and unit costs are not described

References:

1. Albert, S. G. and S. Reddy (2017). "CLINICAL EVALUATION OF COST EFFICACY OF DRUGS FOR TREATMENT OF OSTEOPOROSIS: A META-ANALYSIS." Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **23**(7): 841-856.

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

Question 4: What effect does zoledronic acid given shortly after an acute osteoporotic fracture have on fracture healing?

Delayed Healing

One RCT (Colon-Emeric 2011) was found determine whether the timing of zoledronic infusion affected the risk of delayed hip fracture healing. Men and women aged >/= 50 years were randomized up to 90 days following surgical procedure of a low-trauma hip fracture. The overall incidence of delayed healing was 3.2% (ZOL) and 2.7% (placebo; odds ratio [OR], 1.17; 95% confidence interval [CI], 0.72-1.90; p = 0.61). Logistic regression models revealed no association between ZOL and delayed healing even after adjusting for other risk factors (OR, 1.21; 95% CI, 0.74-1.99; p = 0.44).

There is **low quality evidence that that is no association between zoledronic acid and delayed healing**. Evidence is imprecise due to few events reported.

Bone Density

Three studies were found examining zoledronic acid's effect on bone density. One RCT (Colon-Emeric 2011) was conducted to determine whether the timing of zoledronic infusion affected the risk of delayed hip fracture healing. Patients were randomized within 90 days of a low-trauma hip fracture to receive either once-yearly ZOL or placebo. After 12 months of treatment, the bone density of the treatment group was not significantly different than that before treatment. After 24 months, the improvement in bone density in the treatment group was better than that in the control group. One retrospective cohort study (Craig 2011) compared the safety and effectiveness of intravenous zoledronic acid (ZOL) and oral alendronate (ALN) in osteoporotic patients following a low trauma fracture. Lumbar spine bone mass densit (BMD) (L2–L4) improved 5.6% in the ZOL group (P < 0.001) and 5.5% in the ALN group (P < 0.001). Total hip BMD improved 2% in the ZOL group (P < 0.01) and 2.5% in the ALN group (P < 0.001). There was no significant difference in BMD change between the groups. One secondary analysis (Magaziner 2014) of the HORIZON Recurrent Fracture Trial determined the effect of zoledronic acid (ZOL) on total hip (TH) and femoral neck (FN) BMD in subgroups with low-trauma hip fracture. Percentage change from baseline in TH and FN BMD at months 12 and 24 was greater (p < 0.05) in ZOL-treated patients compared with placebo in most subgroups.

There is **moderate quality evidence that zoledronic acid improves bone mass density after fracture**.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Delayed Healing

Quality (certainty) of evidence for: (outcome)
☐High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Low Quality Rating if:**	**Other Considerations:**
☐ High ☐ Medium ☒ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - *Unknown* ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Colon-Emeric, C., et al. Year Published: 2011 Location: Duke University Medical Center Journal: *Osteoporosis international*	To determine whether the timing of ZOL infusion affected the risk of delayed hip fracture healing	**Size:** 2,127 **Inclusion Criteria**: Men and women aged >/= 50 years were randomized up to 90 days following surgical procedure of a low-trauma hip fracture. All patients were ambulatory with or without an assistive device prior to the hip fracture, and were unwilling or unable to take an oral bisphosphonate. Patients with previous use of bisphosphonates or teriparatide were enrolled after a washout period that was determined based on their pre-existing usage. **Exclusion Criteria**: Patients were excluded if they were taking oral corticosteroids, had active malignancies, or had a prior lower extremity amputation.	**Type:** RCT **Methods**: Patients were randomized within 90 days of a low-trauma hip fracture to receive either once-yearly ZOL (n = 1,065) or placebo (n = 1,062). Clinical symptoms of delayed hip fracture healing were sought at randomization, 6 months and 12 months after fracture; if present, a central adjudication committee blinded to treatment assignment reviewed radiographs and clinical records.	**Results: The overall incidence of delayed healing was 3.2% (ZOL) and 2.7% (placebo; odds ratio [OR], 1.17; 95% confidence interval [CI], 0.72-1.90; p = 0.61). Logistic regression models revealed no association between ZOL and delayed healing even after adjusting for other risk factors (OR, 1.21; 95% CI, 0.74-1.99; p = 0.44).** There was no interaction by timing of infusion, and nonunion rates were similar even when ZOL was given within 2 weeks of hip fracture repair. NSAID use was significantly associated with delayed fracture healing (OR, 2.55; 95% CI, 1.49-4.39; p < 0.001).	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unclear allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Bone Density

Quality (certainty) of evidence for: (outcome)
☐ High
☒ Moderate
☐ Low
☐ Very Low

Risk of Bias across studies:
☐ High
☐ Medium
☒ Low

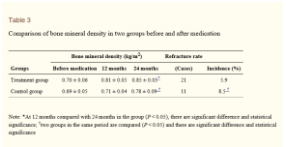
Low Quality Rating if:
☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) -

☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

☐ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*

Other Considerations:
Lower Quality Rating if:
☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)*

Increase Quality Rating if:
☐ Large effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	Aim of Study	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Author: Liu, Z., et al. Year Published: 2019 Location: The Second Affiliated Hospital of Zhejiang Chinese Medical University Journal: *Orthopaedic surgery*	To observe the effect of zoledronic acid on the reduction of acute bone loss and fracture rate in elderly postoperative patients with intertrochanteric fracture.	**Size:** 482 patients; 353 in treatment group and 129 in control group **Inclusion Criteria**: (i) bone mineral density value determined by dual energy X ray T < −2.5 or T < − 1.0 and past history of brittle fracture; (ii) no serious liver and renal dysfunction; (iii) no caltrate and calciferol allergy history, confirmed and with informed consent provided for diagnosis and treatment; and (iv) the occurrence of senile osteoporotic femoral intervertebral fracture with low energy fracture, 2 weeks after surgical treatment. **Exclusion Criteria**: (i) past history: (3 months before treatment) used estrogen, glucocorticoid, and other drugs that may affect bone metabolism; (ii) there were	**Type:** RCT **Intervention**: Treated with 100 mL/5 mg of zoledronic acid injection in 1 week after operation, as well as orally taken 600 mg/d of calcium carbonate and active vitamin D3 400 IU/d. **Comparator**: Given the same dose of calcium carbonate and active vitamin D3 orally.	**Results:** **After 12 months of treatment, the bone density of the treatment group was not significantly different than that before treatment. After 24 months, the improvement in bone density in the treatment group was better than that in the control group.** There was a significant difference between the groups ($P < 0.05$), and the rate of refracture in the treatment group was lower than that of the control group ($P < 0.01$). 	**Study Limitations:** ☐ None ***RCTs*** ☒ Lack of blinding ☐ Lack of allocation concealment ☒ Unclear allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☐ Difference in important prognostic factors at baseline

		thyroid or parathyroid diseases, or adrenal and gonadal endocrine diseases; (iii) secondary osteoporosis; (iv) patients allergic to zoledronic acid or inability to use zoledronic acid; (v) patients with serious Alzheimer's disease are not suitable for treatment and evaluation of therapeutic effects; and (vi) severe hypocalcemia.			
Author: Craig, S.J., et al. Year Published: 2011 Location: Sydney, Australia Journal: *Internal Medicine Journal*	To compare the safety and effectiveness of intravenous zoledronic acid (ZOL) and oral alendronate (ALN) in osteoporotic patients following a low trauma fracture.	**Size:** 169 **Inclusion Criteria**: Patients with a documented low-trauma fracture (radiological evidence and history of minimal trauma) who were treated with either ZOL or ALN for at least 12 months, and who had a bone mass density (BMD) scan at the time of fracture and at least 12 months later. **Exclusion Criteria**: Prior history of oral bisphosphonate use longer than 3 weeks, prior history of intravenous bisphosphonate use, hypogonadism, hyperparathyroidism, prior glucocorticoid or hormonal therapy exposure, or had less than 90% reported compliance with oral medication regimens.	**Type:** Retrospective Cohort Study **Methods:** Patients were treated with either an infusion of 4 mg ZOL or ALN 70 mg weekly. The outcomes measures were change in BMD after 12 months of treatment with either bisphosphonate, or new osteoporotic fractures.	**Results:** Lumbar spine BMD (L2–L4) improved 5.6% in the ZOL group ($P < 0.001$) and 5.5% in the ALN group ($P < 0.001$). **Total hip BMD improved 2% in the ZOL group ($P < 0.01$) and 2.5% in the ALN group ($P < 0.001$). There was no significant difference in BMD change between the groups.** There were no serious adverse reactions in either group.	**Study Limitations:** ☐ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Author: Magaziner, J.S., et al. Year Published: 2014 Location: University of Maryland Journal: *Journal of bone and mineral research*	A post hoc analysis of the HORIZON Recurrent Fracture Trial was done to determine the effect of zoledronic acid (ZOL) on total hip (TH) and femoral neck (FN) BMD in subgroups with low-trauma hip fracture.	**Size:** 2127 patients **Inclusion Criteria**: Men and women aged >/= 50 years within 90 days after operation for a minimal-trauma hip fracture (ie, a fall from standing height or lower). Patients were enrolled from24 countries across North America, South America, and Europe and were from a variety of cultural,	**Type:** Secondary analysis of RCT **Intervention**: ZOL intravenously over 15 minutes within 90 days after operation for a hip fracture and every 12 months thereafter for up to 3 years **Comparator**: Placebo	**Results: Percentage change from baseline in TH and FN BMD at months 12 and 24 was greater ($p < 0.05$) in ZOL-treated patients compared with placebo in most subgroups**. Treatment-by-subgroup interactions ($p < 0.05$) indicated that a greater effect on BMD was observed for TH BMD at month 12 in females, in patients in the	**Study Limitations:** ☒ None **Non-Randomized Studies** ☐ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

		ethnic, and racial groups. **Exclusion Criteria**: Previous hypersensitivity to a bisphosphonate, a calculated creatinine clearance of <30 mL/min, a serum calcium level of >11.0 mg/dL (2.8mmol/L), or a corrected serum calcium level of <8 mg/dL (2mmol/L) at screening and/or randomization, active cancer, metabolic bone disease other than osteoporosis, and a life expectancy of less than 6 months		lower tertile body mass index at baseline (<=22.6 kg/m(2)), and in patients with baseline FN BMD T-score of <= -2.5; for FN BMD in patients who received ZOL for >6 weeks post-surgery; and for TH and FN BMD in patients with a history of one or more prior fractures. All interactions were limited to the first 12 months after treatment with none observed for the 24-month comparisons.	

References:

1. Craig, S. J., et al. (2011). "Intravenous zoledronic acid and oral alendronate in patients with a low trauma fracture: experience from an osteoporosis clinic." Internal Medicine Journal **41**(2): 186-190.
2. Liu, Z., et al. (2019). "Study on Zoledronic Acid Reducing Acute Bone Loss and Fracture Rates in Elderly Postoperative Patients with Intertrochanteric Fractures." Orthopaedic surgery **11**(3): 380-385.
3. Magaziner, J. S., et al. (2014). "Subgroup variations in bone mineral density response to zoledronic acid after hip fracture." Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research **29**(12): 2545-2551.

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

Guideline Recommendations

The **2019 Endocrine Society** clinical practice guideline for the pharmacologic management of osteoporosis in postmenopausal women recommended the following:

Bisphosphonates

1. In postmenopausal women at high risk of fractures, we recommend initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) to reduce fracture risk. **(**1|⊕⊕⊕⊕**)**

   Technical Remark: Ibandronate is not recommended to reduce nonvertebral or hip fracture risk.
2. In postmenopausal women with osteoporosis who are taking bisphosphonates, we recommend that fracture risk be reassessed after 3 to 5 years, and women who remain at high risk of fractures should continue therapy, whereas those who are at low-to-moderate risk of fractures should be considered for a "bisphosphonate holiday." **(**1|⊕⊕⊖⊖**)**

   Technical Remark: A bisphosphonate holiday is operationally defined as a temporary discontinuation of bisphosphonate for up to 5 years. This period may be longer depending on the bone mineral density and clinical circumstances of the individual patient. The evidence is stronger for retention of benefits during a holiday for alendronate and zoledronic acid where there are randomized extension trials. A shorter reassessment period of 3 years is more appropriate for annual intravenous zoledronic acid (5 mg) based on evidence from research control trials showing residual effects after 3 years of annual use. Once a bisphosphonate holiday is initiated, reassess fracture risk at 2- to 4-year intervals and consider reinitiating osteoporosis therapy earlier than the 5-year suggested maximum if there is a significant decline in bone mineral density, an intervening fracture, or other factors that alter the clinical risk status.

2018 French Guideline recommendation on the management of postmenopausal osteoporosis

- In hip fracture patients, zoledronic acid should be considered for the first-line treatment as the only drug for which evidence of anti-fracture efficacy exists in this population **(grade A)**.

- In patients with severe fractures and very low BMD values (T-score ≤ −3) injectable drugs can be used to achieve the BMD target (T-score > −2.5 or −2 at the hip) by the end of the course of treatment; options include zoledronic acid, denosumab (inpatients with intolerance or unresponsiveness to bisphos-phonates), and teriparatide (reimbursed for patients with at least two vertebral fractures) followed by an anti-resorptive agent **(consensus of experts)**.

The 2017 Clinical Practice Guideline Update from the American College of Physicians: Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women recommended:

- **Recommendation 1**: ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (**Grade: strong recommendation; high-quality evidence**)

- **Recommendation 2**: ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years. (**Grade: weak recommendation; low-quality evidence**)

- **Recommendation 3**: ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (**Grade: weak recommendation; low-quality evidence**)

- **Recommendation 4**: ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women. (**Grade: weak recommendation; low quality evidence**)

- **Recommendation 5**: ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (**Grade: strong recommendation; moderate-quality evidence**)

- **Recommendation 6**: ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at a high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (**Grade: weak recommendation; low-quality evidence**)

ACP meta-analysis found High-quality evidence that bisphosphonates, including alendronate, risedronate, and zoledronic acid, reduce vertebral, nonvertebral, and hip fractures compared with placebo in postmenopausal osteoporotic women. Moderate-quality evidence showed that zoledronic acid reduces radiographic vertebral fractures in osteoporotic men.

The 2016 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis

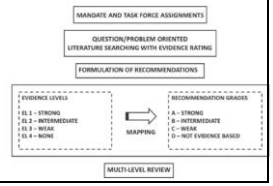
- Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, risedronate, zoledronic acid, and denosumab are appropriate as initial therapy for most patients at high risk of fracture **(Grade A; BEL 1)**.

- Teriparatide, denosumab, or zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at especially high fracture risk **(Grade A; BEL 1)**.

References:

1. Briot, K., et al. (2018). "2018 update of French recommendations on the management of postmenopausal osteoporosis." Joint Bone Spine **85**(5): 519-530.
2. Camacho, P. M., et al. (2016). "AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS — 2016--EXECUTIVE SUMMARY." **22**(9): 1111-1118.
3. Eastell, R., et al. (2019). "Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline." Journal of Clinical Endocrinology & Metabolism **104**(5): 1595-1622.
4. Qaseem, A., et al. (2017). "Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians." **166**(11): 818-839.

Guideline Evidence Evaluation Systems

		French Guideline 2018	ACP 2017	AACE/ACE 2016
Evidence Evaluation	Grading of Recommendations Assessment, Development and Evaluation (GRADE) Classification of Guideline Recommendations	French National Authority for Health (HAS) evidence criteria	Evidence was graded according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.	

Guideline Ratings

Guideline Issuer and Date	ES 2019	French 2018	ACP 2017	AACE/ACE 2016
1. Transparency	A	A	A	A
2. Conflict of interest	A	B	A	B
3. Development group	A	A	B	B
4. Systematic Review	A	B	A	A
5. Supporting evidence	A	A	A	A
6. Recommendations	A	A	A	A
7. External Review	A	B	A	A
8. Currency and updates	A	A	A	B

See appendix B for full description of the Trustworthy Guideline grading system.

REFERENCES

1. Albert, S. G. and S. Reddy (2017). "CLINICAL EVALUATION OF COST EFFICACY OF DRUGS FOR TREATMENT OF OSTEOPOROSIS: A META-ANALYSIS." Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **23**(7): 841-856.
2. Autier P, Haentjens P, Bentin J et al. Costs induced by hip fractures: A pro-spective controlled study in Belgium. Belgian Hip Fracture Study Group Osteoporos Int 2000;11:373–380.
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Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:
Who wrote the initial draft
How the committee voted on or otherwise approved recommendations
Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:
Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.
Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded

B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers’ stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst’s discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated

Appendix C. Search Strategy

C1 - Database: Ovid MEDLINE(R) ALL <1946 to May 06, 2020>

Search Strategy:

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1 exp Osteoporotic Fractures/ (5469)
2 exp Hip/ (11823)
3 exp Hip Fractures/ (23705)
4 femur head/ or femur neck/ (15497)
5 2 or 3 or 4 (46977)
6 1 and 5 (1292)
7 exp Osteoporosis/ (55277)
8 exp Fractures, Bone/ (182521)
9 5 and 7 and 8 (3392)
10 6 or 9 (4146)
11 ((osteoporo* or (bone* adj3 (loss* or lose or losing or loses lost or densit*))) adj10 ((hip or hips or ((femur* or femoral) adj3 neck*)) adj7 (fractur* or break* or broke*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4378)
12 10 or 11 (6600)
13 exp Zoledronic Acid/ (3389)
14 (zoledron* or reclast).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5266)
15 13 or 14 (5266)
16 12 and 15 (119)
17 7 and 8 (15878)
18 1 or 17 (18769)
19 14 and 18 (297)
20 5 and 14 (105)
21 19 or 20 (344)
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