1.

Comparison of BMD Changes and Bone Formation Marker Levels 3 Years After Bisphosphonate Discontinuation: FLEX and HORIZON-PFT Extension I Trials.

Kim TY; Bauer DC; McNabb BL; Schafer AL; Cosman F; Black DM; Eastell R.

Journal of Bone & Mineral Research. 34(5):810-816, 2019 May.
[Journal Article]
UI: 30536713

An ASBMR Task Force recommends a drug holiday for certain women treated for >=5 years with oral alendronate or >=3 years with intravenous zoledronic acid, with reassessment 2 to 3 years later. It is not known whether changes in bone mineral density (BMD) or bone turnover markers differ after oral or intravenous therapy. Our goal was to compare changes in BMD and procollagen type I N propeptide (PINP) after oral or intravenous bisphosphonate use. In the Fracture Intervention Trial Long-term Extension (FLEX), women who received a mean 5 years of alendronate were randomized to placebo or continued treatment. In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial Extension I (HORIZON-PFT E1), women who received 3 years of zoledronic acid were randomized to placebo or continued treatment. We examined the proportion of participants with BMD loss or PINP gain >= least significant change (LSC) and those whose values exceeded a threshold (T-score <=-2.5 or PINP >=36.0 ng/mL, a premenopausal median value). After 3 years of placebo, the FLEX group had greater mean total hip BMD decreases (-2.3% versus -1.2% in the HORIZON-PFT E1 group, p < 0.01) and greater rises in PINP (+11.6 ng/mL versus +6.7 ng/mL, p < 0.01). There was a greater proportion of individuals in FLEX with total hip BMD loss and PINP increases that exceeded LSC, and PINP values >=36.0 ng/mL. In contrast, there were small changes in the proportion of women with femoral neck T-scores <=-2.5 in both groups. In conclusion, 3 years after bisphosphonate discontinuation, a considerable proportion of former alendronate and zoledronic acid users had meaningful declines in total hip BMD and elevations in PINP. Despite a longer treatment course, alendronate may have a more rapid offset of drug effect than zoledronic acid. © 2018 American Society for Bone and Mineral Research.

Version ID
1

Status
In-Data-Review
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Year of Publication
2019

2.

Insights into the bisphosphonate holiday: a preliminary FTIRI study.
Boskey AL; Spevak L; Ma Y; Wang H; Bauer DC; Black DM; Schwartz AV.
Osteoporosis International. 29(3):699-705, 2018 03.
[Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, N.I.H., Extramural. Research Support, Non-U.S. Gov't]

UI: 29204959

Bone composition evaluated by FTIRI analysis of iliac crest biopsies from post-menopausal women treated with alendronate for 10 years, continuously or alendronate for 5 years, followed by a 5-year alendronate-holiday, only differed with the discontinued biopsies having increased cortical crystallinity and heterogeneity of acid phosphate substitution and decreased trabecular crystallinity heterogeneity.

INTRODUCTION: Bisphosphonates (BP) are the most commonly used and effective drugs to prevent fragility fractures; however, concerns exist that prolonged use may lead to adverse events. Recent recommendations suggest consideration of a BP "holiday" in individuals taking long-term BP therapy not at high risk of fracture. Data supporting or refuting this recommendation based on bone quality are limited. We hypothesized that a "holiday" of 5 years would cause no major bone compositional changes.

METHODS: We analyzed the 31 available biopsies from the FLEX-Long-term Extension of FIT (Fracture Intervention Trial) using Fourier transform infrared imaging (FTIRI). Biopsies from two groups of post-menopausal women, a "Continuously treated group" (N = 16) receiving alendronate for ~ 10 years and a "Discontinued group" (N = 15), alendronate treated for 5 years taking no antiresorptive medication during the following 5 years. Iliac crest bone biopsies were provided at 10 years.

RESULTS: Key FTIRI parameters, mineral-to-matrix ratio, carbonate-to-phosphate ratio, acid phosphate substitution, and collagen cross-link ratio as well as heterogeneity of these parameters were similar for Continuously treated and Discontinued groups in age-adjusted models. The Discontinued group had 2% greater cortical crystallinity ($p = 0.01$), 31% greater cortical acid phosphate heterogeneity ($p = 0.02$), and 24% lower trabecular crystallinity heterogeneity ($p = 0.02$).

CONCLUSIONS: Discontinuation of alendronate for 5 years did not affect key FTIRI parameters, supporting the hypothesis that discontinuation would have little impact on bone composition. Modest differences were observed in three parameters that are not likely to affect bone mechanical properties. These preliminary data suggest that a 5-year BP holiday is not harmful to bone composition.

Version ID

1

Status

MEDLINE

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Year of Publication
2018

3.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016.
Camacho PM; Petak SM; Binkley N; Clarke BL; Harris ST; Hurley DL; Kleerekoper M; Lewiecki EM; Miller PD; Narula HS; Pessah-Pollack R; Tangpricha V; Wimalawansa SJ; Watts NB.
Endocrine Practice. 22(Suppl 4):1-42, 2016 Sep 02.
[Journal Article. Practice Guideline]
UI: 27662240
ABBREVIATIONS: AACE = American Association of Clinical Endocrinologists AFF = atypical femur fracture ASBMR = American Society for Bone and Mineral Research BEL = best evidence level BMD = bone mineral density BTM = bone turnover marker CBC = complete blood count CI = confidence interval DXA = dual-energy X-ray absorptiometry EL = evidence level FDA = U.S. Food and Drug Administration FLEX = Fracture Intervention Trial (FIT) Long-term Extension FRAX = Fracture Risk Assessment Tool GFR = glomerular filtration rate GI = gastrointestinal HORIZON = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly IOF = International Osteoporosis Foundation ISCD = International Society for Clinical Densitometry IU = international units IV = intravenous LSC = least significant change NBHA = National Bone Health Alliance NOF = National Osteoporosis Foundation 25(OH)D = 25-hydroxy vitamin D ONJ = osteonecrosis of the jaw PINP = serum carboxy-terminal propeptide of type I collagen PTH = parathyroid hormone R = recommendation RANK = receptor activator of nuclear factor kappa-B

RANKL = receptor activator of nuclear factor kappa-B ligand RCT = randomized controlled trial RR = relative risk S-CTX = serum C-terminal telopeptide SQ = subcutaneous VFA = vertebral fracture assessment WHO = World Health Organization.

Version ID

1

Status

MEDLINE

Authors Full Name

Camacho, Pauline M; Petak, Steven M; Binkley, Neil; Clarke, Bart L; Harris, Steven T; Hurley, Daniel L; Kleerekoper, Michael; Lewiecki, E Michael; Miller, Paul D; Narula, Harmeet S; Pessah-Pollack, Rachel; Tangpricha, Vin; Wimalawansa, Sunil J; Watts, Nelson B.

Year of Publication

2016

4.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016--EXECUTIVE SUMMARY.

Camacho PM; Petak SM; Binkley N; Clarke BL; Harris ST; Hurley DL; Kleerekoper M; Lewiecki EM; Miller PD; Narula HS; Pessah-Pollack R; Tangpricha V; Wimalawansa SJ; Watts NB.

Endocrine Practice. 22(9):1111-8, 2016 Sep.

[Journal Article. Practice Guideline]

UI: 27643923

ABBREVIATIONS: AACE = American Association of Clinical Endocrinologists AFF = atypical femur fracture ASBMR = American Society for Bone and Mineral Research BEL = best evidence level BMD = bone mineral density BTM = bone turnover marker CBC = complete blood count CI = confidence interval DXA = dual-energy X-ray absorptiometry EL = evidence level FDA = U.S. Food and Drug Administration FLEX = Fracture Intervention Trial (FIT) Long-term Extension FRAX() = Fracture Risk Assessment Tool GFR = glomerular filtration rate GI = gastrointestinal HORIZON = Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly IOF = International Osteoporosis Foundation ISCD = International Society for Clinical Densitometry IU = international units IV = intravenous LSC = least significant change NBHA = National Bone Health

Alliance NOF = National Osteoporosis Foundation 25(OH)D = 25-hydroxy vitamin D ONJ = osteonecrosis of the jaw PINP = serum carboxy-terminal propeptide of type I collagen PTH = parathyroid hormone R = recommendation RANK = receptor activator of nuclear factor kappa-B RANKL = receptor activator of nuclear factor kappa-B ligand RCT = randomized controlled trial RR = relative risk S-CTX = serum C-terminal telopeptide SQ = subcutaneous VFA = vertebral fracture assessment WHO = World Health Organization.

Version ID

1

Status

MEDLINE

Authors Full Name

Camacho, Pauline M; Petak, Steven M; Binkley, Neil; Clarke, Bart L; Harris, Steven T; Hurley, Daniel L; Kleerekoper, Michael; Lewiecki, E Michael; Miller, Paul D; Narula, Harmeet S; Pessah-Pollack, Rachel; Tangpricha, Vin; Wimalawansa, Sunil J; Watts, Nelson B.

Comments

Erratum in (EIN)

Year of Publication

2016

5.

Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. [Review]

Adler RA; El-Hajj Fuleihan G; Bauer DC; Camacho PM; Clarke BL; Clines GA; Compston JE; Drake MT; Edwards BJ; Favus MJ; Greenspan SL; McKinney R Jr; Pignolo RJ; Sellmeyer DE.

Journal of Bone & Mineral Research. 31(1):16-35, 2016 Jan.

[Journal Article. Review]

UI: 26350171

Bisphosphonates (BPs) are the most commonly used medications for osteoporosis. This ASBMR report provides guidance on BP therapy duration with a risk-benefit perspective. Two trials provided evidence for long-term BP use. In the Fracture Intervention Trial Long-term Extension (FLEX), postmenopausal women receiving alendronate for 10 years had fewer clinical vertebral fractures than those switched to placebo after 5 years. In the HORIZON extension, women who

received 6 annual infusions of zoledronic acid had fewer morphometric vertebral fractures compared with those switched to placebo after 3 years. Low hip T-score, between -2 and -2.5 in FLEX and below -2.5 in HORIZON extension, predicted a beneficial response to continued therapy. Hence, the Task Force suggests that after 5 years of oral BP or 3 years of intravenous BP, reassessment of risk should be considered. In women at high risk, for example, older women, those with a low hip T-score or high fracture risk score, those with previous major osteoporotic fracture, or who fracture on therapy, continuation of treatment for up to 10 years (oral) or 6 years (intravenous), with periodic evaluation, should be considered. The risk of atypical femoral fracture, but not osteonecrosis of the jaw, clearly increases with BP therapy duration, but such rare events are outweighed by vertebral fracture risk reduction in high-risk patients. For women not at high fracture risk after 3 to 5 years of BP treatment, a drug holiday of 2 to 3 years can be considered. The suggested approach for long-term BP use is based on limited evidence, only for vertebral fracture reduction, in mostly white postmenopausal women, and does not replace the need for clinical judgment. It may be applicable to men and patients with glucocorticoid-induced osteoporosis, with some adaptations. It is unlikely that future trials will provide data for formulating definitive recommendations. © 2015 American Society for Bone and Mineral Research.

Version ID
1
Status
MEDLINE
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Comments
Erratum in (EIN)
Year of Publication
2016

6.

A model of BMD changes after alendronate discontinuation to guide postalendronate BMD monitoring.
McNabb B; Vittinghoff E; Eastell R; Schwartz AV; Bauer DC; Ensrud K; Barrett-Connor E; Black DM.
Journal of Clinical Endocrinology & Metabolism. 99(11):4094-100, 2014 Nov.
[Journal Article. Randomized Controlled Trial. Research Support, Non-U.S. Gov't. Research Support, U.S. Gov't, Non-P.H.S.]
UI: 25127011
CONTEXT: Women stopping alendronate are commonly monitored with serial bone mineral density (BMD) measurements, yet no information exists on how frequently or for whom these measurements should be performed.
OBJECTIVE: The objective of the study was to develop a tool to guide post-alendronate BMD monitoring.
DESIGN: A predictive model was constructed to estimate the time until a given percentage of women's BMD T-scores drop below a given threshold that indicates a management change (such as retreatment) would be considered. This model was then used to estimate the time it would take for groups of women defined by their baseline BMDs to drop below the given threshold.
SETTING: Data were derived from the Fracture Intervention Trial Long Term Extension (FLEX), the largest multicenter clinical trial of its type to date.
PARTICIPANTS: Four hundred four women who had received an average of 5.1 years of alendronate during the Fracture Intervention Trial and were subsequently observed for 5

treatment-free years (on placebo) during the FLEX trial were used to estimate the change in BMD over time.
RESULTS: If a management change such as alendronate reinitiation would be considered when BMD T-score drops below -2.5, the model shows that women with total hip BMD greater than -1.9 T-scores at the time of alendronate discontinuation have less than a 20% probability that at follow-up, monitoring BMD will be below the threshold within 5 years. The model performed similarly, and results are provided over a range of management change thresholds from -1.75 to -3 T-scores.
CONCLUSIONS: Using the tool developed in this analysis, it is possible to estimate when BMD repeat measurement after alendronate discontinuation could potentially be useful. Measuring BMD within 5 years after alendronate discontinuation is unlikely to change management for women with total hip BMD 0.6 T-scores above a prespecified retreatment threshold within the range of -1.75 to -3 T-scores.
Version ID
1
Status
MEDLINE
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Year of Publication
2014

7.

Effect of bisphosphonate use on risk of postmenopausal breast cancer: results from the randomized clinical trials of alendronate and zoledronic acid.
Hue TF; Cummings SR; Cauley JA; Bauer DC; Ensrud KE; Barrett-Connor E; Black DM.
JAMA Internal Medicine. 174(10):1550-7, 2014 Oct.
[Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't]
UI: 25111880
IMPORTANCE: Studies have shown that bisphosphonates may have antitumor and antimetastatic properties. Recently, observational studies have suggested a possible protective effect of bisphosphonates on breast cancer, but the effect of bisphosphonate use on risk of breast cancer has not been tested in randomized trials.
OBJECTIVE: To assess the relationship of postmenopausal breast cancer incidence and bisphosphonate use using data from 2 randomized (1:1), double-blind, placebo-controlled trials.
DESIGN, SETTING, AND PARTICIPANTS: The Fracture Intervention Trial (FIT) randomly assigned 6459 women aged 55 to 81 years to alendronate or placebo for a mean follow-up of 3.8 years. The Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) randomly assigned 7765 women aged 65 to 89 years to annual intravenous zoledronic acid or placebo for a mean follow-up of 2.8 years. Data were collected at clinical centers in the United States (FIT and HORIZON-PFT) and in Asia and the Pacific, Europe, North America, and South America (HORIZON-PFT). Women, in either study, with recurrent breast cancer or who reported a history of breast cancer were excluded from analyses. In each trial, a blinded review was conducted of each cancer adverse event report to verify incident invasive breast cancer cases. The primary analysis compared events in the active vs placebo group using a log-rank test.
INTERVENTION: Alendronate vs placebo (FIT) or zoledronic acid vs placebo (HORIZON-PFT).
MAIN OUTCOMES AND MEASURES: Hazard ratio for incident breast cancer in the bisphosphonate treatment group compared to the placebo group.
RESULTS: There was no significant difference in the rate of breast cancer in FIT: 1.5% (n = 46) in the placebo group and 1.8% (n = 57) in the alendronate group (hazard ratio [HR], 1.24 [95% CI, 0.84-1.83]). In HORIZON-PFT, there was also no significant difference: 0.8% (n = 29) in the placebo group and 0.9% (n = 33) in the zoledronic acid group (HR, 1.15 [95% CI, 0.70-1.89]). There was also no significant difference when the data from FIT and HORIZON-PFT were pooled (HR, 1.20 [95% CI, 0.89-1.63]).

CONCLUSIONS AND RELEVANCE: These 2 randomized clinical trials do not support the findings from observational research. Contrary to the results from observational studies, we found that 3 to 4 years of bisphosphonate treatment did not decrease the risk of invasive postmenopausal breast cancer.
TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00049829 (HORIZON-PFT).
Version ID
1
Status
MEDLINE
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Comments
Comment in (CIN) Comment in (CIN)
Erratum in (EIN)
Year of Publication
2014

8.

Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study.
Bauer DC; Schwartz A; Palermo L; Cauley J; Hochberg M; Santora A; Cummings SR; Black DM.
JAMA Internal Medicine. 174(7):1126-34, 2014 Jul.
[Journal Article. Randomized Controlled Trial. Research Support, Non-U.S. Gov't]
UI: 24798675

IMPORTANCE: Discontinuation of bisphosphonate therapy after 3 to 5 years is increasingly considered, but methods to monitor fracture risk after discontinuation have not been established.
OBJECTIVE: To test methods of predicting fracture risk among women who have discontinued alendronate therapy after 4 to 5 years.
DESIGN, SETTING, AND PARTICIPANTS: The prospective Fracture Intervention Trial Long-term Extension (FLEX) study randomized postmenopausal women aged 61 to 86 years previously treated with 4 to 5 years of alendronate therapy to 5 more years of alendronate or placebo from 1998 through 2003; the present analysis includes only the placebo group. Hip and spine dual-energy x-ray absorptiometry (DXA) were measured when placebo was begun (FLEX baseline) and after 1 to 3 years of follow-up. Two biochemical markers of bone turnover, urinary type 1 collagen cross-linked N-telopeptide (NTX) and serum bone-specific alkaline phosphatase (BAP), were measured at FLEX baseline and after 1 and 3 years.
MAIN OUTCOMES AND MEASURES: Symptomatic spine and nonspine fractures occurring after the follow-up measurement of DXA or bone turnover.
RESULTS: During 5 years of placebo, 94 of 437 women (22%) experienced 1 or more symptomatic fractures; 82 had fractures after 1 year. One-year changes in hip DXA, NTX, and BAP were not related to subsequent fracture risk, but older age and lower hip DXA at time of discontinuation were significantly related to increased fracture risk (lowest tertile of baseline femoral neck DXA vs other 2 tertiles relative hazard ratio, 2.17 [95% CI, 1.38-3.41]; total hip DXA relative hazard ratio, 1.87 [95% CI, 1.20-2.92]).
CONCLUSIONS AND RELEVANCE: Among postmenopausal women who discontinue alendronate therapy after 4 to 5 years, age and hip BMD at discontinuation predict clinical fractures during the subsequent 5 years. Follow-up measurements of DXA 1 year after discontinuation and of BAP or NTX 1 to 2 years after discontinuation are not associated with fracture risk and cannot be recommended.
TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00398931.

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1
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MEDLINE
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Comments

Comment in (CIN)

Year of Publication

2014

9.

BMD changes and predictors of increased bone loss in postmenopausal women after a 5-year course of alendronate.

McNabb BL; Vittinghoff E; Schwartz AV; Eastell R; Bauer DC; Ensrud K; Rosenberg E; Santora A; Barrett-Connor E; Black DM.

Journal of Bone & Mineral Research. 28(6):1319-27, 2013 Jun.

[Journal Article. Randomized Controlled Trial]

UI: 23408577

Management of women discontinuing bisphosphonates after 3 to 5 years of treatment is controversial. Little is known about how much bone mineral density (BMD) is lost after discontinuation or whether there are risk factors for greater rates of bone loss post-

discontinuation. We report patterns of change in BMD and prediction models for the changes in BMD in postmenopausal women during a 5-year treatment-free period after alendronate (ALN) therapy. We studied 406 women enrolled in the Fracture Intervention Trial (FIT) who had taken ALN for a mean of 5 years and were then enrolled in the placebo arm of the FIT Long-Term Extension (FLEX) trial for an additional 5 years, describing 5-year percent changes in total hip, femoral neck, and lumbar spine BMD over the treatment-free period. Prediction models of 5-year percent changes in BMD considered all linear combinations of candidate risk factors for bone loss such as BMD at the start of the treatment-free period, the change in BMD on ALN, age, and fracture history. Serum for three markers of bone turnover was available in 76 women, and these bone turnover markers were included as candidate predictors for these 76 women. Mean 5-year BMD changes were -3.6% at the total hip, -1.7% at the femoral neck, and 1.3% at the lumbar spine. Five-year BMD losses of >5% were experienced by 29% of subjects at the total hip, 11% of subjects at the femoral neck, and 1% of subjects at the lumbar spine. Several risk factors such as age and BMI were associated with greater bone loss, but no models based on these risk factors predicted bone loss rates. Although about one-third of women who discontinued ALN after 5 years experienced >5% bone loss at the total hip, predicting which women will lose at a higher rate was not possible.

Version ID

1

Status

MEDLINE

Authors Full Name

McNabb, Brian Louis; Vittinghoff, Eric; Schwartz, Ann V; Eastell, Richard; Bauer, Douglas C; Ensrud, Kristine; Rosenberg, Elizabeth; Santora, Arthur; Barrett-Connor, Elizabeth; Black, Dennis M.

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Year of Publication

2013

10.

Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur.
Black DM; Kelly MP; Genant HK; Palermo L; Eastell R; Bucci-Rechtweg C; Cauley J; Leung PC; Boonen S; Santora A; de Papp A; Bauer DC; Fracture Intervention Trial Steering Committee; HORIZON Pivotal Fracture Trial Steering Committee.
New England Journal of Medicine. 362(19):1761-71, 2010 May 13.
[Journal Article. Research Support, Non-U.S. Gov't]
UI: 20335571
Available at Baycrest library; check holdings list for details
BACKGROUND: A number of recent case reports and series have identified a subgroup of atypical fractures of the femoral shaft associated with bisphosphonate use. A population-based study did not support this association. Such a relationship has not been examined in randomized trials.
METHODS: We performed secondary analyses using the results of three large, randomized bisphosphonate trials: the Fracture Intervention Trial (FIT), the FIT Long-Term Extension (FLEX) trial, and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (PFT). We reviewed fracture records and radiographs (when available) from all hip and femur fractures to identify those below the lesser trochanter and above the distal metaphyseal flare (subtrochanteric and diaphyseal femur fractures) and to assess atypical features. We calculated the relative hazards for subtrochanteric and diaphyseal fractures for each study.
RESULTS: We reviewed 284 records for hip or femur fractures among 14,195 women in these trials. A total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient-years. As compared with placebo, the relative hazard was 1.03 (95% confidence interval [CI], 0.06 to 16.46) for alendronate use in the FIT trial, 1.50 (95% CI, 0.25 to 9.00) for zoledronic acid use in the HORIZON-PFT trial, and 1.33 (95% CI, 0.12 to 14.67) for continued alendronate use in the FLEX trial. Although increases in risk were not significant, confidence intervals were wide.
CONCLUSIONS: The occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare, even among women who had been treated with bisphosphonates for as long as 10 years. There was no significant increase in risk associated with bisphosphonate use, but the study was underpowered for definitive conclusions.

Version ID
1
Status
MEDLINE

Authors Full Name
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Comments
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2010

11.

Estimating long-term effects of treatment from placebo-controlled trials with an extension period, using virtual twins.
Vittinghoff E; McCulloch CE; Woo C; Cummings SR.
Statistics in Medicine. 29(10):1127-36, 2010 May 10.
[Journal Article. Research Support, Non-U.S. Gov't]
UI: 20209478
The best information about the benefits of long-term treatment is obtained from a long-term placebo-controlled trial. However, once efficacy has been demonstrated in relatively brief trials, it may not be possible to conduct long-term placebo-controlled trials, for ethical or practical reasons. This paper presents a method for estimating long-term effects of a treatment from a placebo-controlled trial in which some participants originally randomized to active-treatment volunteer to continue on treatment during an extension study, but follow-up of participants originally assigned to placebo ends with the trial, or they are crossed over to active treatment during the extension. We propose using data from the trial to project the outcomes for a 'virtual twin' for each active-treatment volunteer under the counterfactual placebo condition, and using

bootstrap methods for inference. The proposed method is validated using simulation, and applied to data from the Fracture Intervention Trial and its extension, FLEX.
Version ID
1
Status
MEDLINE
Authors Full Name
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Year of Publication
2010

12.

Efficacy of continued alendronate for fractures in women with and without prevalent vertebral fracture: the FLEX trial.
Schwartz AV; Bauer DC; Cummings SR; Cauley JA; Ensrud KE; Palermo L; Wallace RB; Hochberg MC; Feldstein AC; Lombardi A; Black DM; FLEX Research Group.
Journal of Bone & Mineral Research. 25(5):976-82, 2010 May.
[Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't]
UI: 20200926
In the Fracture Intervention Trial (FIT) Long Term Extension (FLEX) Trial, 10 years of alendronate (ALN) did not significantly reduce the risk of nonvertebral fractures (NVFs) compared with 5 years of ALN. Continuing ALN reduced the risk of clinical but not morphometric vertebral fractures regardless of baseline vertebral fracture status. In previous studies, ALN efficacy for NVF prevention in women without prevalent vertebral fracture was limited to those with femoral neck (FN) T-scores of -2.5 or less. To determine whether the effect of long-term ALN on fracture differs by vertebral fracture status and femoral neck (FN) T-score, we performed a post hoc analysis using FLEX data, a randomized, double-blind, placebo-controlled trial among 1099 postmenopausal women originally randomized to ALN in the FIT with mean ALN use of 5 years.

In the FLEX Trial, women were randomized to placebo (40%) or ALN 5 mg/day (30%) or ALN 10 mg/day (30%) for an additional 5 years. Among women without vertebral fracture at FLEX baseline (n = 720), continuation of ALN reduced NVF in women with FLEX baseline FN T-scores of -2.5 or less [relative risk (RR) = 0.50, 95% confidence interval (CI) 0.26-0.96] but not with T-scores of greater than -2.5 and -2 or less (RR 0.79, 95% CI 0.37-1.66) or with T-scores of greater than -2 (RR 1.41, 95% CI 0.75-2.66; p for interaction = .019). Continuing ALN for 10 years instead of stopping after 5 years reduces NVF risk in women without prevalent vertebral fracture whose FN T-scores, achieved after 5 years of ALN, are -2.5 or less but does not reduce risk of NVF in women whose T-scores are greater than -2.

Version ID

1

Status

MEDLINE

Authors Full Name

Schwartz, Ann V; Bauer, Douglas C; Cummings, Steven R; Cauley, Jane A; Ensrud, Kristine E; Palermo, Lisa; Wallace, Robert B; Hochberg, Marc C; Feldstein, Adrianne C; Lombardi, Antonio; Black, Dennis M; FLEX Research Group.

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Year of Publication

2010

13.

Mineralization density distribution of postmenopausal osteoporotic bone is restored to normal after long-term alendronate treatment: qBEI and sSAXS data from the fracture intervention trial long-term extension (FLEX).

Roschger P; Lombardi A; Misof BM; Maier G; Fratzl-Zelman N; Fratzl P; Klaushofer K.

Journal of Bone & Mineral Research. 25(1):48-55, 2010 Jan.

[Journal Article. Randomized Controlled Trial. Research Support, Non-U.S. Gov't]

UI: 19580465

Long-term treatment studies showed that the therapeutic effects of alendronate (ALN) were sustained over a 10-year treatment period. However, data on the effects on intrinsic bone material properties by long-term reduction of bone turnover are still sparse. We analyzed transiliacal bone biopsies of a subgroup of 30 Fracture Intervention Trial Long-Term Extension (FLEX) participants (n = 6 were treated for 10 years with ALN at dose of 10 mg/day, n = 10 were treated for 10 years with ALN at dose of 5 mg/day, and n = 14 were treated for 5 years with ALN plus a further 5 years with placebo) by quantitative backscattered electron imaging (qBEI) and scanning small-angle X-ray scattering (sSAXS) to determine the bone mineralization density distribution (BMDD) and the mineral particle thickness parameter T. BMDD data from these FLEX participants were compared with those from a previously published healthy population (n = 52). Compared with 5 years of ALN plus 5 years of placebo 10 years of ALN treatment (independent of the dose given) did not produce any difference in any of the BMDD parameters: The weighted mean (Ca(mean)), the typical calcium concentration (Ca(peak)), the heterogeneity of mineralization (Ca(width)), the percentage of low-mineralized bone areas (Ca(low)), and the portion of highly mineralized areas (Ca(high)) were not different for the patients who continued ALN from those who stopped ALN after 5 years. Moreover, no significant differences for any of the BMDD parameters between the FLEX participants and the healthy population could be observed. In none of the investigated cases were abnormally high mineralization or changes in mineral particle thickness observed (Ca(high) and T were both in the normal range). The findings of this study support the recommendation that antiresorptive treatment with ALN should be maintained for 5 years. Even with longer treatment durations of up to 10 years, though, no negative effects on bone matrix mineralization were observed.

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1
Status
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Authors Full Name
Roschger, P; Lombardi, A; Misof, B M; Maier, G; Fratzl-Zelman, N; Fratzl, P; Klaushofer, K.
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Year of Publication
2010

14.

Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial.
Black DM; Schwartz AV; Ensrud KE; Cauley JA; Levis S; Quandt SA; Satterfield S; Wallace RB; Bauer DC; Palermo L; Wehren LE; Lombardi A; Santora AC; Cummings SR; FLEX Research Group.
JAMA. 296(24):2927-38, 2006 Dec 27.
[Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't]
UI: 17190893
Available at Baycrest library; check holdings list for details
CONTEXT: The optimal duration of treatment of women with postmenopausal osteoporosis is uncertain.
OBJECTIVE: To compare the effects of discontinuing alendronate treatment after 5 years vs continuing for 10 years.
DESIGN AND SETTING: Randomized, double-blind trial conducted at 10 US clinical centers that participated in the Fracture Intervention Trial (FIT).
PARTICIPANTS: One thousand ninety-nine postmenopausal women who had been randomized to alendronate in FIT, with a mean of 5 years of prior alendronate treatment.
INTERVENTION: Randomization to alendronate, 5 mg/d (n = 329) or 10 mg/d (n = 333), or placebo (n = 437) for 5 years (1998-2003).
MAIN OUTCOME MEASURES: The primary outcome measure was total hip bone mineral density (BMD); secondary measures were BMD at other sites and biochemical markers of bone remodeling. An exploratory outcome measure was fracture incidence.
RESULTS: Compared with continuing alendronate, switching to placebo for 5 years resulted in declines in BMD at the total hip (-2.4%; 95% confidence interval [CI], -2.9% to -1.8%; P<.001) and spine (-3.7%; 95% CI, -4.5% to -3.0%; P<.001), but mean levels remained at or above pretreatment levels 10 years earlier. Similarly, those discontinuing alendronate had increased serum markers of bone turnover compared with continuing alendronate: 55.6% (P<.001) for C-telopeptide of type 1 collagen, 59.5% (P < .001) for serum n = propeptide of type 1 collagen, and 28.1% (P<.001) for bone-specific alkaline phosphatase, but after 5 years without therapy, bone marker levels remained somewhat below pretreatment levels 10 years earlier. After 5 years, the cumulative risk of nonvertebral fractures (RR, 1.00; 95% CI, 0.76-1.32) was not significantly different between those continuing (19%) and discontinuing (18.9%) alendronate. Among those

who continued, there was a significantly lower risk of clinically recognized vertebral fractures (5.3% for placebo and 2.4% for alendronate; RR, 0.45; 95% CI, 0.24-0.85) but no significant reduction in morphometric vertebral fractures (11.3% for placebo and 9.8% for alendronate; RR, 0.86; 95% CI, 0.60-1.22). A small sample of 18 transilial bone biopsies did not show any qualitative abnormalities, with bone turnover (double labeling) seen in all specimens.
CONCLUSIONS: Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.
TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT 00398931.
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1
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Authors Full Name
Black, Dennis M; Schwartz, Ann V; Ensrud, Kristine E; Cauley, Jane A; Levis, Silvina; Quandt, Sara A; Satterfield, Suzanne; Wallace, Robert B; Bauer, Douglas C; Palermo, Lisa; Wehren, Lois E; Lombardi, Antonio; Santora, Arthur C; Cummings, Steven R; FLEX Research Group.
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2006

15.

Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension.
Ensrud KE; Barrett-Connor EL; Schwartz A; Santora AC; Bauer DC; Suryawanshi S; Feldstein A; Haskell WL; Hochberg MC; Torner JC; Lombardi A; Black DM; Fracture Intervention Trial Long-Term Extension Research Group.
Journal of Bone & Mineral Research. 19(8):1259-69, 2004 Aug.
[Clinical Trial. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't]
UI: 15231012
UNLABELLED: To determine the effects of continuation versus discontinuation of alendronate on BMD and markers of bone turnover, we conducted an extension trial in which 1099 older women who received alendronate in the FIT were re-randomized to alendronate or placebo. Compared with women who stopped alendronate, those continuing alendronate for 3 years maintained a higher BMD and greater reduction of bone turnover, showing benefit of continued treatment. However, among women who discontinued alendronate and took placebo in the extension, BMD remained higher, and reduction in bone turnover was greater than values at FIT baseline, showing persistence of alendronate's effects on bone.
INTRODUCTION: Prior trials including the Fracture Intervention Trial (FIT) have found that therapy with alendronate increases BMD and decreases fracture risk for up to 4 years in postmenopausal women with low BMD. However, it is uncertain whether further therapy with alendronate results in preservation or further gains in BMD and if skeletal effects of alendronate continue after treatment is stopped.
MATERIALS AND METHODS: We conducted a follow-up placebo-controlled extension trial to FIT (FIT long-term extension [FLEX]) in which 1099 women 60-86 years of age who were assigned to alendronate in FIT with an average duration of use of 5 years were re-randomized for an additional 5 years to alendronate or placebo. The results of a preplanned interim analysis at 3 years are reported herein. Participants were re-randomized to alendronate 10 mg/day (30%), alendronate 5 mg/day (30%), or placebo (40%). All participants were encouraged to take a calcium (500 mg/day) and vitamin D (250 IU/day) supplement. The primary outcome was change in total hip BMD. Secondary endpoints included change in lumbar spine BMD and change in markers of bone turnover (bone-specific alkaline phosphatase and urinary type I collagen cross-linked N-telopeptide).
RESULTS: Among the women who had prior alendronate therapy in FIT, further therapy with alendronate (5 and 10 mg groups combined) for 3 years compared with placebo maintained BMD

at the hip (2.0% difference; 95% CI, 1.6-2.5%) and further increased BMD at the spine (2.5% difference; 95% CI, 1.9-3. 1%). Markers of bone turnover increased among women discontinuing alendronate, whereas they remained stable in women continuing alendronate. Cumulative increases in BMD at the hip and spine and reductions in bone turnover from 8.6 years earlier at FIT baseline were greater for women continuing alendronate compared with those discontinuing alendronate. However, among women discontinuing alendronate and taking placebo in the extension, BMD remained higher and reduction in bone turnover was greater than values at FIT baseline.

CONCLUSIONS: Compared with women who stopped alendronate after an average of 5 years, those continuing alendronate maintained a higher BMD and greater reduction of bone turnover, showing benefit of continued alendronate treatment on BMD and bone turnover. On discontinuation of alendronate therapy, rates of change in BMD at the hip and spine resumed at the background rate, but discontinuation did not result in either accelerated bone loss or a marked increase in bone turnover, showing persistence of alendronate's effects on bone. Data on the effect of continuation versus discontinuation on fracture risk are needed before making definitive recommendations regarding the optimal length of alendronate treatment.

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1

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