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POSTER perspectives

Osteoporosis Posters and Abstracts from Atlanta

CME Activity

Overview

Steven T. Harris, MD, provides his perspectives on key posters and abstracts presented on management of patients with osteoporosis.

Content Areas:

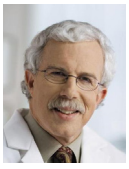
- Long-term effect of bisphosphonates on mortality risk
- Safety and efficacy of the anabolic agents abaloparatide-SC and romosozumab
- Safety and efficacy of the cathepsin K inhibitor odanacatib

Target Audience

Endocrinologists, rheumatologists, primary care physicians, orthopedic surgeons, hospitalists, radiologists, and other health care professionals who manage patients with osteoporosis.

This activity is supported by educational grants from Merck Sharp & Dohme Corp and Radius Health, Inc.

Faculty



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Commentary on 6 posters:

CE/CME Information

Target Audience
This activity was developed for endocrinologists, rheumatologists, primary care physicians, orthopedic surgeons, hospitalists, radiologists, and other health care professionals who manage patients with osteoporosis.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments in the treatment of osteoporosis
- Incorporate evidence-based research into clinical practice

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Steven T. Harris, MD

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The estimated time to complete the activity is 1.5 hours.

This activity was originally released in November, 2016 and is eligible for credit through in November, 2017.

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1 *Safety of odanacatib in postmenopausal women with osteoporosis: 5-year data from the extension of the phase 3 Long-term Odanacatib Fracture Trial (LOFT) [#1156]*

Papapoulos S, et al.

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The next presentation is entitled "Safety of Odanacatib in Postmenopausal Women with Osteoporosis: Five-Year Data from the Extension of Phase 3 Long-Term Odanacatib Fracture Trial," otherwise known as LOFT.

Hi, this is Dr. Steven Harris. I'm clinical professor of medicine at the University of California, San Francisco. I will be discussing “Safety of Odanacatib in Postmenopausal Women with Osteoporosis: Five-year Data from the Extension of the Phase 3 long-term Odanacatib Fracture Trial,” otherwise known by the acronym LOFT. This was presented by Dr. Papapoulos and his colleagues at the American Society of Bone and Mineral Research Annual Meeting held in Atlanta between September 16th and 19th, 2016.

As far as an overall summary is concerned, this presentation reported the results of the extension phase of the Long-Term Odanacatib Fracture Trial showing that the safety and tolerability of odanacatib were maintained out to 5 years. The report provides evidence that the safety and good tolerability associated with odanacatib were maintained over the long-term, however further analysis indicates an increased risk of stroke, prompting the pharmaceutical company developing odanacatib to terminate further clinical investigation of the compound.

If we look at the methods involved in this study, it was a planned, double-blind, extension of LOFT in which patients continued on their originally assigned treatment for up to 5 years. Now, the patients who were recruited into the study were women who were at least 65 years of age who had a bone mineral density T-score of -2.5 or lower at the total hip or femoral neck or alternatively had evidence of radiographic vertebral fracture and had a T-score of -1.5 or lower at the total hip or femoral neck. So, older women with osteoporosis, or at least osteopenia with some evidence of vertebral fracture. They were randomized 1:1 to odanacatib 50 milligrams once a week or placebo and they were given calcium and vitamin D3 as needed.

This is a big clinical undertaking. Twelve thousand two hundred ninety patients actually completed the original study. Eight thousand two hundred fifty-seven entered the extension phase and of those people, 6,047 actually completed that extension. That included 3,432 patients receiving odanacatib and 2,615 receiving matching placebo. Overall, 88.3% of the odanacatib patients experienced at least 1 adverse event compared to 88.2% of the placebo patients. Thirty point three percent of odanacatib patients experienced a serious adverse event compared to 30.4% of placebo patients. There is no obvious imbalance as you might see from those numbers, but it makes perfect sense that in an older population during a multi-year study, there would be a fair number of both adverse events and serious adverse events. Remember, these are simply regulatory definitions. They don't imply causality. They're simply descriptive of what happened to people during the study.

An intention-to-treat analysis showed that a similar percentage of patients in each group died. So, 8.5% of the odanacatib participants died during the project as compared with 8.2% in the placebo group.

If we think about a few key findings here, delayed fracture union occurred in 18 patients in each group. Again, no obvious imbalance. If one looks, however, at femoral shaft fractures, those occurred in 0.3% of the odanacatib patients and 0.1% of the placebo patients so there was an imbalance there. And if one limited that to atypical femoral shaft fractures, that was 0.1% in the odanacatib and 0%, as in none, in the placebo group. There were no cases of osteonecrosis of the jaw, otherwise known as ONJ.

There were, however, a small number of morphea-like skin lesions, 0.2% in the odanacatib compared with less than 0.1% in the placebo group. Most had the onset relatively early in the trial, within the first couple of years and 15 out of 16 improved or fully recovered upon discontinuation of the study medication. Actual systemic sclerosis occurred in less than 0.1% in each group. As far as serious respiratory infection was concerned, 1.6% in the odanacatib group, 1.8% in the placebo group.

Here are my thoughts and analysis of this interesting study.

If we think again about the overall sort of clinical significance of this study, I think it's fair to say that the overall safety profile of odanacatib over that 5-year interval appeared to be very good, but there was a slight increase in femoral shaft fractures and morphea-like skin reactions in those patients who were receiving odanacatib. That's in addition to the increased risk of stroke that was noted in another safety analysis. There's no immediate impact as a consequence on the current state of patient management, in part because this was an investigational medication, but the excess of femoral shaft fractures—admittedly not all of them fit the criteria of atypical femoral fractures—but that increase in femoral shaft fracture really is quite provocative.

It underscores the importance of understanding the pathophysiology of these unusual femoral fractures, whether they're occurring with odanacatib or with the widely used bisphosphonates and denosumab. Again, so-called atypical femoral fracture has been one of the problems that's really bedeviled both the bisphosphonates and denosumab. Even though those atypical femoral fractures appear to be very, very rare, it's interesting that here's yet another compound, odanacatib, that seems to be associated with something very similar to that.

It's obviously disappointing that this very promising oral anabolic agent, it's sometimes referred to actually as a passive anabolic because it seems to inhibit bone resorption while having relatively little effect on bone formation, will not be developed any further because of the documented safety concerns. I think it's really very thought-provoking and troubling. It's obviously challenging to try and understand what the appropriate balance between benefit and risk ought to be for medications in general, and for the osteoporosis medications in particular.

For better or for worse, successful treatment of osteoporosis is marked by the absence of a clinical event, by the absence of fracture, and for most of our patients, for most of us as clinicians, that's not inherently very, as you might say, impactful. That's not a very dramatic endpoint on a day-to-day basis. The fact that we didn't break isn't terribly impressive to us. Now, odanacatib is a novel oral osteoporosis medication with a consistent effect in increasing bone mineral density and reducing fracture risk. Over a period as long as 5 years, which is potentially very important, but it's development has regrettably been halted by the appearance of these relatively rare but notable adverse events. And again, I think it's a challenge for us to try and understand what the appropriate balance between benefit and risk might be, but as best we can tell for the moment, further development of odanacatib is not in fact proceeding.

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2 *Abaloparatide-SC is an effective treatment option for postmenopausal osteoporosis: Review of the number needed to treat compared with teriparatide [#MO0280]*

Lewiecki EM, et al.

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The next presentation is entitled, "Abaloparatide-SC is an Effective Treatment Option for Postmenopausal Osteoporosis: Review of the Number Needed to Treat Compared with Teriparatide."

Hi, this is Dr. Steven Harris, clinical professor of medicine at the University of California, San Francisco. I will be discussing "Abaloparatide-SC is an Effective Treatment Option for Postmenopausal Osteoporosis: Review of the Number Needed to Treat Compared with Teriparatide," presented by Dr. Mike Lewiecki and colleagues at the American Society of Bone and Mineral Research Annual Meeting in Atlanta between September 16th and 19th, 2016.

If one were to simply summarize this presentation, this analysis calculated the number needed to treat using data from the ACTIVE trial which compared 18 months of treatment with abaloparatide-SC—so abaloparatide given subcutaneously each day—compared with teriparatide given subcutaneously each day, compared with placebo, in postmenopausal women with lower risk. In this analysis, the number needed to treat was lower with abaloparatide-SC for vertebral, nonvertebral, clinical, and osteoporotic fractures when compared with treatment with teriparatide. Using historical data in a higher risk population, the number needed to treat with 18 months of abaloparatide-SC was estimated to be approximately 12 for a reduction of the risk in a single vertebral fracture.

Based upon this analysis of the ACTIVE trial, abaloparatide-SC may be a highly effective option for the treatment of osteoporosis in postmenopausal women.

And now here are the comments from Dr. Lewiecki, the lead author of the study.

The 3 most important findings of the study are:

- *Abaloparatide is an investigational synthetic analog of parathyroid hormone-related protein that reduces the risk of vertebral fractures, nonvertebral fractures, and all clinical fractures compared with placebo.*
- *In the study population, the number needed to treat to prevent a vertebral fracture, nonvertebral fracture, clinical fracture, and major osteoporotic fracture was less with abaloparatide-SC than with open-label teriparatide.*

- *In projections of the number needed to treat to prevent a vertebral fracture with abaloparatide-SC, using historical populations similar to those studied with alendronate, zoledronic acid, and denosumab, the number was lower than that observed in the ACTIVE trial.*

Speaking to the impact this study will have, we think abaloparatide-SC is a potentially highly effective agent for the treatment of postmenopausal osteoporosis that may offer advantages over current therapeutic options.

Let's take a look at the methods that were involved in this analysis. So, the ACTIVE trial included abaloparatide-SC, so that's abaloparatide given subcutaneously each day compared with open-label teriparatide and compared with placebo over a period of 18 months, so a year and a half. The patients were between the ages of 49 and 86. The average lumbar spine T-score was -2.9. Twenty-four percent of the study participants had prevalent vertebral fractures, so those are fractures that already are apparent at the baseline of the study. Forty-eight percent had had a non-vertebral fracture within the past 5 years, but 37% had no prior vertebral or nonvertebral fracture. The mean FRAX scores at baseline, FRAX, as you know, is a calculator to estimate fracture risk, were 4.8% for hip fracture and 13.2% for the risk of major osteoporotic fracture over the next 10 years.

When compared to placebo, abaloparatide-SC, so again, subcutaneous injection of abaloparatide each day reduced vertebral fractures by 86%, non-vertebral and all clinical fractures by 43%, and major osteoporotic fractures by 70%. The number needed to treat represents the average number of patients that would need to be treated to prevent one additional fracture.

Now, admittedly, the ACTIVE trial used a relatively low-risk population due to ethical concerns associated with the use of placebo in a frankly osteoporotic population, so the effectiveness of abaloparatide-SC in a higher risk population was estimated using some historical data. So, if one assumes a 10% vertebral fracture incidence over the course of the trial, then there was an 86% reduction of vertebral fracture with abaloparatide-SC. I mean, again, those are the assumptions, 10% vertebral fracture incidence, 86% reduction.

With those underlying assumptions, the number needed to treat over 18 months of therapy for vertebral fracture, it would be abaloparatide-SC, 28, so you would need to treat 28 patients with abaloparatide-SC for 18 months to prevent 1 vertebral fracture. That can be compared with teriparatide where the estimated number to treat would be 30. So, 28 vs 30. For non-vertebral fracture over that same 18-month treatment interval, for abaloparatide-SC it would be 55, for teriparatide, 92. If one were to lump everything together and say the risk of any clinical fracture, abaloparatide-SC, 37, for the number needed to treat over 18 months, compared with teriparatide, 59, and if one limits the analysis to major osteoporotic fractures, abaloparatide-SC, 34, over 18 months compared with teriparatide, 75.

Now, if one goes back and then looks at the higher risk population using those historical data, the number needed to treat for abaloparatide-SC to prevent 1 vertebral fracture, would be approximately 12. So, in a high-risk population, you only need to treat 12 patients with abaloparatide for 18 months to prevent a vertebral fracture.

So, here are a few clinical thoughts and a little bit of musing about the significance of this study. In this study, treatment with abaloparatide-SC for 18 months clearly reduced the risk of both vertebral fracture and nonvertebral fractures as well as the composite endpoint such as clinical fractures in general and major osteoporotic fractures in particular. Interestingly, this ACTIVE trial included a placebo control as well as an active control; patients who were treated with a standard anabolic agent teriparatide. So, the contrast in the active study again was the novel treatment agent, abaloparatide-SC, compared with placebo, but also compared with the, if you will, the usual anabolic treatment teriparatide. So, the NNT, the number needed to treat to prevent 1 fracture over 18 months, was, in fact, lower with abaloparatide treatment than with teriparatide.

There again will be no immediate day-to-day impact on clinical practice because abaloparatide is still an investigational agent, but I'd say that the advent of a novel bone-building agent obviously is very, very interesting. You know, for the past 13 years now, the daily self-administered injection teriparatide, for no longer than 2 years, actually has been the standard bone-building approach and this study actually suggests that the daily self-administered injection of abaloparatide-SC for 18 months may be more effective than treatment with teriparatide over the same treatment interval. I think that the key issues for us, clinically, really are related again to the balancing of risks and benefits. There's obviously extensive clinical experience with the administration of teriparatide over the past 13 years. I think it's fair to say that this novel anabolic agent abaloparatide-SC appears very promising, but the risk and benefits of abaloparatide, and the expense, have to be carefully weighed against the existing treatments that we already have in hand.

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3

Fracture risk reduction with romosozumab: Results of the phase 3 FRAME study (FRActure study in postmenopausal woMen with ostEoporosis) [#1096]

Cosman F, et al.

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The next poster is entitled "Fracture Risk Reduction with Romosozumab. Results of the phase 3 FRAME study." FRAME is an acronym that stands for Fracture Study in Postmenopausal Women with Osteoporosis.

This is Dr. Steve Harris. I'm a clinical professor of medicine at the University of California, San Francisco. I will be discussing "Fracture Risk Reduction with Romosozumab: Results of the Phase 3 FRAME study," presented by Dr. Felicia Cosman and her colleagues at the American Society of Bone and Mineral Research Annual Meeting in Atlanta. The meeting was held between September 16th and 19th of this year.

If we were to simply summarize the results in postmenopausal women with osteoporosis, romosozumab was well tolerated. The risk of vertebral and clinical fractures was reduced when compared with placebo at 12 months and that risk reduction persisted over an additional 12 months despite patients being switched to denosumab after 12 months.

If we think about the importance of this, the persistence of the beneficial effects with romosozumab at 12 months following treatment suggests that romosozumab may be a highly effective treatment for postmenopausal women with osteoporosis.

Let's think about the methods that were involved in this study. It was a randomized, double-blind, placebo-controlled, multicenter study that enrolled postmenopausal women with osteoporosis. Those women were between the ages of 55 and 90. The patients were randomized 1:1 to either placebo or romosozumab given as a single 210 milligram subcutaneous dose once a month for 12 months. Importantly, after 12 months, all of the patients were switched to denosumab given at a dose of 60 milligram subcutaneously every 6 months for the next year. So, it was 1 year of romosozumab followed by 1 year of denosumab.

If we were to think about the key findings, 7,180 women were enrolled; the mean age was 71 years and the mean total hip T-score was -2.5 at 12 months. So at the end of the romosozumab vs placebo comparison, the incidence of vertebral fracture was significantly less with the romosozumab treatment when compared with placebo. There was a 0.5% risk of fracture in the romosozumab group compared with 1.8% in the placebo group for a relative risk reduction of 73%. At 24 months, after everyone had been switched over to denosumab, the incidence of vertebral fracture was significantly less in the romosozumab/denosumab group when compared with the placebo/denosumab group and the relative figures here were 0.6% and 2.5% for a relative risk reduction of 75%. Clinical fracture risk at 12 months was lower with romosozumab; 1.6% vs 2.5% for a relative risk reduction of 36% and non-vertebral fracture instance was similar after 12 and 24 months, although the relative risk reduction was significant, favoring romosozumab, if one looked at the patients enrolled in the study outside of Central and Latin America.

Bone mineral density at 12 months increased with romosozumab vs placebo, 12.7% and 5.8% at the lumbar spine and hip, respectively. Adverse events were generally balanced between the groups except for injection site reactions, which were somewhat more common in the romosozumab group at 5.2% as opposed to placebo with 2.9%. There was 1 case of atypical femoral fracture and there were 2 cases of osteonecrosis of the jaw, otherwise known as ONJ, in the romosozumab group.

Here are my thoughts and analysis of this really very provocative study. The monthly subcutaneous injection of romosozumab for 1 year produced a significant reduction in the risk of new vertebral fractures and a trend toward a reduction in the risk of new non-vertebral fractures. That anti-fracture efficacy was maintained during a second year, in which all of the study participants were treated with denosumab every 6 months. This study really has no immediate impact on the day-to-day clinical practice that we're all engaged in because this is an investigational medication, but there's obviously great interest in the development of novel, anabolic bone-building agents such as romosozumab. Romosozumab is a monoclonal antibody directed against sclerostin and it seems to be a very potent bone-building agent as we've just seen.

If we look into the future just a little bit and sort of anticipate where this is all going, I think it would be fair to say that for many years osteoporosis treatment really has revolved around the use of the so-called antiresorptive agents such as the bisphosphonates. Although those agents are certainly very effective in reducing fracture risk, they work primarily by decreasing bone resorption and, as such, they don't actually build bone.

Now, for some years, teriparatide has been available as an anabolic agent, and I think most of us have had some experience with that over the years. It's very likely over the long term that anabolic agents will be used more widely to build bone, at least for short-term treatment because all of these bone-building agents seem to do their bone-building over a relatively short period with subsequent follow-on therapy with an antiresorptive agent designed to maintain the improvement of bone strength that's been induced by the anabolic agent. I think that the paradigm will probably be to build the bone for 12 months, 18 months, 24 months, something of that sort with the various anabolic agents, and then chase that anabolic treatment with antiresorptive treatment designed to maintain that benefit.

If we sort of ponder what the unresolved issues are though, romosozumab did clearly reduce fracture risk in the study but it did so in a relatively low-risk patient population and in truth, it's not yet obvious whether treatment with a bone-building anabolic agent such as romosozumab will, in fact, be superior to the use of an antiresorptive agent in reducing fracture risk. I think that most people think that it will be, but that's not yet been demonstrated clearly. Whether the novel anabolic agent romosozumab will actually be superior to the existing anabolic agent, teriparatide, has not yet been evaluated.

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4 *Differential effects of odanacatib therapy on markers of bone resorption and formation in postmenopausal women with osteoporosis: A subgroup study of the 5-year data from the extension of the phase 3 Long-term Odanacatib Fracture Trial (LOFT) [#FR0299]*

Duong LT, et al.

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The next presentation is entitled, "Differential Effects of Odanacatib Therapy on Markers of Bone Resorption and Formation in Postmenopausal Women with Osteoporosis, a Sub-Group Study of the 5-Year Data from the Extension of the Phase 3 Long-Term Odanacatib Fracture Trial," otherwise known as LOFT.

Hi, this is Dr. Steven Harris. I'm clinical professor of medicine at the University of California, San Francisco. I will be discussing “Differential Effects of Odanacatib Therapy on Markers of Bone Resorption and Formation in Postmenopausal Women with Osteoporosis: A Subgroup Study of the 5-year Data from the Extension of the Phase 3 Long-Term Odanacatib Fracture Trial,” known by the acronym LOFT. This was presented by Dr. Le Duong and colleagues at the American Society of Bone and Mineral Research Annual Meeting held in Atlanta recently between September 16th and 19th of 2016.

The overall summary holds that the study reported on the changes in bone markers over the 5 years of the Long-Term Odanacatib Fracture Trial. The bone markers showed a persistent effect of odanacatib to inhibit bone resorption—so a decrease in bone resorption—and underscored the unique mechanism mediating collagen processing and bone turnover by odanacatib. These results do provide additional insight into the multiple mechanisms whereby odanacatib reduces bone turnover.

If we think about the methods involved in this analysis, LOFT was a double-blind, placebo-controlled, event-driven phase 3 trial with a planned double-blind extension for up to 5 years of treatment. Patients had archived the serum and urine samples collected at baseline and periodically over the 5 years. Those archived samples were then assayed for markers of bone resorption, targeted engagement, osteoclast number and bone formation.

The key findings included the fact that odanacatib treatment rapidly reduced and maintained the levels of bone resorption markers throughout the 5 years. So, if we get a little bit more particular about this, odanacatib reduced serum C-telopeptides, otherwise known as serum CTX, of type 1 collagen in the first 2 years. This returned to baseline by 4 years, but the finding was different from placebo. Odanacatib increased pyridinoline cross-linked carboxyterminal telopeptide of type I collagen at month 6 extending out to 5 years, indicating cathepsin K inhibition. Serum tartrate-resistant acid phosphatase-5b was unchanged through 12 months, then increased 17% to 30% for month 24 to month 60. The increase in larger C-telopeptides of type I collagen and tartrate-resistant acid phosphatase-5b in the odanacatib group compared to placebo and there's a transient decrease in internal propeptides of type I collagen and bone specific alkaline phosphatase, but those levels then rose back to a level comparable to placebo by month 48 and month 60.

Here are my thoughts and analysis of this interesting study.

So, this is all a bit bewildering and confusing, isn't it? So, if we think about this clinically and try to make some sense out of all this, as a cathepsin K inhibitor, odanacatib has a novel mechanism of action when compared with other osteoporosis therapies. Interestingly, odanacatib treatment does not reduce osteoclasts number, so it's not wiping out the osteoclasts, but rather inhibits osteoclast mediated bone resorption, creating a population of what people have sometimes called frustrated osteoclasts because they're sitting there but they can't actually do what they're intending to do, which is to resorb bone, because cathepsin K inhibits that processing of collagen.

Now, Cath K, as it's often abbreviated, cathepsin K, is important for the processing of collagen breakdown products. Now, as such, it gets very confusing when we try to interpret the usual standard biochemical markers of bone resorption. Over extended treatment, however, it appears that odanacatib has an inhibitory effect upon bone resorption that outstrips an initial inhibitory effect on bone formation as well. So, a decrease in bone resorption that wanes a little bit over time, but an initial inhibition of bone formation as well, that goes away relatively quickly. So, again, odanacatib has sometimes been called a passive anabolic. Not because it's stimulating bone formation, but rather because it's preferentially inhibiting bone resorption with a relatively modest effect on bone formation.

Because odanacatib is not currently available, and may not be anytime soon, this study is nevertheless interesting because it gives us some additional insight into how bone remodeling works and how the various biochemical markers used in clinical practice to assess bone resorption/bone formation might be interpreted. As far as we know, odanacatib really is unique in the way it affects the measurement of these markers of bone resorption.

From my perspective, it's certainly disappointing that the further development of this promising weekly oral anabolic treatment has been halted by safety issues, but the mechanism of action of odanacatib really is fascinating and the fracture risk reduction is really quite striking. It would obviously be of great interest to understand how best to preserve the benefits of this cathepsin K inhibition without incurring the risks apparently associated with odanacatib therapy. The effects of odanacatib on the markers of bone remodeling may be unique, but the findings provide additional impetus for us to find the best combination of biochemical markers to be used in clinical practice to assess bone resorption and bone formation.

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5 *Effect of investigational treatment abaloparatide-SC for prevention of major osteoporotic fracture or any fracture is independent of baseline fracture probability [#MO0281]*

McCloskey EV, et al.

Steven T. Harris, MD
Clinical Professor of Medicine
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San Francisco, California

The next presentation is entitled, "Effective Investigational Treatment with Abaloparatide-SC for Prevention of Major Osteoporotic Fracture or Any Fracture is Independent of Baseline Fracture Probability."

Hi, this is Dr. Steven Harris, I'm clinical professor of medicine at the University of California, San Francisco. I will be discussing "Effective Investigational Treatment with Abaloparatide-SC for Prevention of Major Osteoporotic Fracture or Any Fracture is Independent of Baseline Fracture Probability," as presented by Dr. McCloskey and his colleagues at the American Society of Bone and Mineral Research Annual Meeting in Atlanta, Georgia, between September 16th and 19th of 2016.

To summarize the key findings, accounting for baseline risk factors and using country-specific FRAX models, abaloparatide-SC reduced the 10-year probability of major osteoporotic fracture and any clinical fracture in postmenopausal women irrespective of baseline fracture risk. This reduction in 10-year fracture risk with abaloparatide-SC being independent of baseline fracture risk may simplify the treatment decisions in postmenopausal women.

If we consider the methods involved in this project, postmenopausal women were assessed for baseline clinical risk factors for fracture. Those risk factors included age, body mass index, prior fracture, corticoid use, rheumatoid arthritis, smoking, and a maternal history of hip fracture. Country-specific FRAX models were used to calculate the 10-year probability of any major osteoporotic fracture with or without the incorporation of the femoral neck bone mineral density measurement.

If we consider the key findings, all told, 1,645 women were randomized 1:1 to receive either abaloparatide-SC, so that's the daily subcutaneous administration of abaloparatide-SC or placebo and then followed for up to 2 years. At baseline, the 10-year probability of major osteoporotic fractures, including the bone mineral density data, ranged from 2.3% to 57.5%. Abaloparatide-SC reduced the risk of major osteoporotic fractures by 69% and reduced the risk of any clinical fracture by 43%. Interestingly, the hazard ratios for the effect of abaloparatide-SC on fracture outcome *did not* change significantly with increasing fracture probability. Similar results were found without the inclusion of the bone mineral density data.

If we consider the overall importance of this study, I think it's fair to say that in the active study that abaloparatide-SC was effective in reducing the risk of a variety of fractures.

In assessing the utility of treatment in clinical practice, however, it is really important to understand that the anti-fracture efficacy is present across a variety of baseline fracture risks. Importantly, in this analysis, abaloparatide-SC treatment was effective independent of the severity of the osteoporosis using that FRAX tool to assess baseline fracture risk. I think it's fair to say that conventional osteoporosis treatment still revolves around the use of the so-called antiresorptive agents such as the bisphosphonates. It seems to me that that is unlikely to change anytime soon, but the advent of these novel anabolic bone-building treatments such as abaloparatide-SC really is quite provocative. I do not think that anabolic treatment is likely to supplant antiresorptive treatment in the near future. It would be perfectly appropriate, however, to start to identify a higher risk subgroup of patients who actually would benefit from treatment initiation with an anabolic agent rather than starting with the standard tried and true antiresorptive agents with which we have all become familiar.

When we consider the unanswered questions in this area, I think it's likely that the bisphosphonates will remain the mainstay of osteoporosis treatment because they are effective in reducing fracture risk, they're quite inexpensive, and they're reasonably safe, despite all of the discussion about safety concerns over the past dozen years or so. As we all know, teriparatide is already available as an anabolic bone-building agent and it seems likely now that abaloparatide-SC will be available at some point as well. It will be critical to determine what higher risk subgroup of patients would be best served by starting treatment with an anabolic agent of some type rather than relying upon inexpensive antiresorptive treatment for first-line therapy in everyone.

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6 *The effect of bisphosphonates on all-cause and post-fracture mortality risk in the population-based Canadian Multicentre Osteoporosis Study (CaMOS) [#1007]*

Bliuc D, et al.

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The first presentation that we'll be discussing this morning is "The Effect of Bisphosphonate on All- Cause and Post-Fracture Mortality Risk in the Population-Based Canadian Multicentre Osteoporosis Study."

This is Dr. Steven Harris. I'm a clinical professor of medicine at the University of California, San Francisco. I'll be discussing this poster which is entitled, "The Effect of Bisphosphonate on All-Cause and Post-Fracture Mortality Risk in the Population-Based Canadian Multicentre Osteoporosis Study," also known as CaMos. It was presented at the American Society for Bone and Mineral Research Annual Meeting held recently in Atlanta, Georgia, between September 16th and 19th.

In this prospective study involving men and women followed over 15 years, patients who are currently or previously treated with bisphosphonates had a lower mortality risk. Interestingly, this benefit was observed in patients treated with a nitrogen-containing bisphosphonate such as alendronate and risedronate, but not etidronate, which is a non-nitrogen-containing bisphosphonate. The mortality benefit with nitrogen-containing bisphosphonates appears to be unrelated to a decline in subsequent fractures.

When you think about the importance of this, the study suggests that the nitrogen-containing bisphosphonates may have benefits beyond simply reducing the risk of fracture, including a reduction in mortality risk.

And now, here are the comments from Dr. Bliuc, the lead author of the study:

The 3 most important findings of the study are:

- *Bisphosphonates appear to be associated with a reduction in mortality risk in both women and men with and without fracture.*
- *The association of bisphosphonates with survival benefit was present in amino-bisphosphonates (ie, alendronate and risedronate) but not non-amino-bisphosphonates (ie, etidronate).*

- *The mechanism of mortality risk reduction is not completely understood, but could not be completely explained by a reduction in subsequent fracture risk.*

Speaking to the impact this study will have, we hope that the findings from this study will result in the uptake of anti-resorptive medication following an osteoporotic fracture.

So, if we take a step back and just think about the methods involved in this study, data were collected yearly over 15 years from the Canadian Multicentre Osteoporosis Study. They used a time-dependent Cox model to assess the overall effect of bisphosphonates on mortality risk, and the effects of the individual bisphosphonates on mortality risk were assessed in the fracture cohort using survival data.

This is a very big study because they had 7,689 men and women over the age of 50. Eighty-seven percent of the study subjects were women. Two thousand five hundred forty-one men and women received bisphosphonate therapy, and for a comparator they used 1,265 women who were receiving hormone therapy. When one looks at the mortality risk, the current bisphosphonate users showed a hazard ratio of 0.58. In other words, there appeared to be a 42% reduction in mortality risk. Interestingly, past bisphosphonate users showed a hazard ratio of 0.53 so there was a 47% reduction of mortality, but current hormone therapy users showed a hazard ratio of 1.08, so there was no real effect of current hormone therapy on mortality risk. In men, the mortality risk was rather similar. For current bisphosphonate users, the hazard ratio was 0.70 and for past bisphosphonate users the hazard ratio was 0.49, so there was roughly a 51% reduction in mortality in that latter group.

For the 1,110 women who had fractures, the mortality risks were with alendronate 0.63; that was the hazard ratio. For risedronate, the hazard ratio was 0.48, and for etidronate the hazard ratio was 1.00, showing, again, no effect of the etidronate on overall mortality. Interestingly, the decrease in mortality risk appears to be unrelated to a reduction in the subsequent fractures, with a hazard ratio of 0.90.

Here are my thoughts and analysis of this interesting study.

This was a long-term observational follow-up study and mortality was reduced in both men and women who are both current users of the nitrogen-containing bisphosphonates, such as alendronate and risedronate, as well as past users of bisphosphonates. I think it's fair to say when we think about the impact on patient management, the oral bisphosphonates have long been the mainstay of osteoporosis treatment. Though obviously there's been concern about relatively rare possible complications of such treatment, such as osteonecrosis of the jaw and atypical femoral fractures, and those safety issues really have dominated the discussion in recent years.

From my clinical perspective, it's really encouraging to see some evidence of an additional benefit of treatment above and beyond that afforded by fracture risk reduction. There's been so much negativity about the bisphosphonates that it's actually kind of refreshing to have a positive note injected into the conversation here. It seems likely at this point that the bisphosphonates will continue to play a major role in osteoporosis treatment, in part because the treatment is inherently very inexpensive and it's actually quite reasonably effective in reducing fracture risk. Again, having some additional evidence for benefit beyond the direct skeletal benefit certainly is encouraging and suggests that bisphosphonates will continue to find wide use in the years to come.

It is kind of puzzling though, because if we think a little bit about this, it's not clear by what mechanism bisphosphonates might provide a beneficial effect on mortality. It's strange, but such an effect was seen with intravenous zoledronic acid in the so-called HORIZON Recurrent Fracture trial, but the current longitudinal study didn't include patients who had such intravenous therapy. In other randomized clinical trials of the nitrogen-containing bisphosphonates such as alendronate, risedronate and ibandronate, which was not included in this analysis, there was no apparent benefit on mortality; so I find it curious that the prospective randomized trials didn't consistently see an effect on mortality, whereas this longitudinal study did. It's also kind of puzzling that the beneficial effect of mortality carried over to past users of bisphosphonates, and to my mind, that suggests that there might have been some unrecognized selection bias that influenced the mortality results. Now, it's obviously an issue that requires further thought and investigation, but overall the tone of this poster was certainly encouraging.

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