



*O*teomark NTx

Bone therapy monitoring

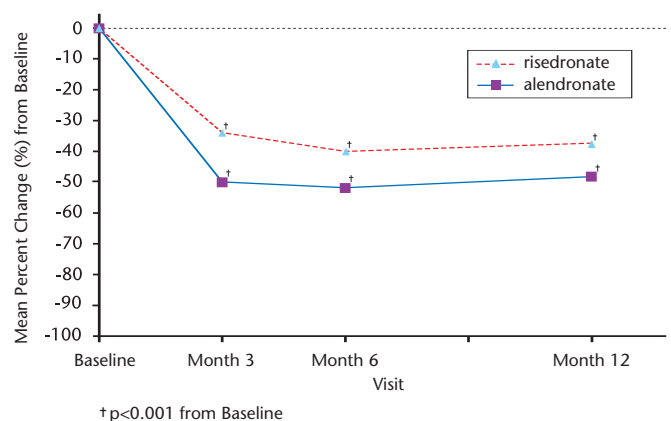
### Monitoring Osteoporosis Therapy

- Inhibition of bone resorption can be detected as early as 3 months.
- Reducing levels of bone resorption markers to the lower half of the premenopausal reference range is optimal for fracture reduction.

Fracture prevention is the aim of osteoporosis therapy, however a decrease in the fracture rate cannot be used to monitor treatment effectiveness and a surrogate marker needs to be used. Serial Bone Mineral Density (BMD) measurements can be used to monitor current antiresorptive therapies (bisphosphonates, raloxifene and HRT), although the association of increase in BMD with reduction in fracture rate varies depending upon the treatment. In order to detect a treatment induced increase in BMD, measurements must be spaced at least 2 years apart. Bone resorption markers can also be used to determine whether the therapy is working. Cross-linked N-telopeptide of type 1 collagen (NTx) is a specific indicator of bone resorption and can be measured in urine or in serum (uNTx, sNTx). Reductions in bone resorption marker levels associated with significant BMD increase and fracture risk reduction vary dependent upon marker and therapy and can be detected as early as 3 months following commencement of treatment (Figure 1)<sup>1-4</sup>.

A decrease of 40% in uNTx is associated with maximal response in fracture risk reduction for patients taking risedronate<sup>1</sup>. Recent findings from the IMPACT study support the theory that reducing the levels of bone turnover markers to a level within the lower half of the premenopausal reference range is optimal for fracture risk reduction<sup>5</sup>. Bisphosphonate treated osteoporotic women from 171 centres in 21 countries were followed for 1 year and results from 1317 patients were included in the analysis. A significant relationship was observed between the probability of a new fracture and uNTx, with thresholds of 26.4 and 29.8 nmol BCE/mmol at week 10 and week 22 respectively giving best performance.

**Figure 1.** Mean change in NTx as % of baseline for patients taking alendronate or risedronate. (Data in Rosen CJ et al<sup>4</sup>.) Urine NTx corrected for Creatinine (Cr) - nmol bone collagen equivalents/mmol of Cr.



## Poor Adherence is Common

- Less than 50% of patients adhere with current bisphosphonate therapy regimens.

Adherence with (or compliance to) a medication regimen is generally defined as the extent to which patients take medication as prescribed by their healthcare providers and expressed as a percentage of prescribed doses taken over a specified period. The terms adherence and compliance are often used interchangeably, however adherence is the preferred term<sup>6</sup>. Persistence is defined as continuing to take medication with non-persistence (stopping treatment permanently) being the most extreme form of non-adherence<sup>7</sup>.

Monitoring of individuals allows the identification of poor responders. The most common cause of a poor response is poor adherence. Recent studies have shown that less than half of osteoporosis patients are adherent with current bisphosphonate therapy regimens. Only one-third (33.3%) of

women over 50 years old and prescribed daily bisphosphonates, and just less than half (44.8%) on weekly bisphosphonate therapy, had adequate adherence<sup>a,8</sup>. In a separate study<sup>9</sup>, based on women over 45 years old newly prescribed a once weekly or once daily bisphosphonate, only 31.7% of patients on daily therapy and 44.2% on weekly therapy were persistent<sup>b</sup> at the end of 12 months. Even lower persistence values have been reported in the results of a study of over ten thousand women in a managed care organisation. At the end of 12 months persistence<sup>c</sup> rates were 23%, 19.4% and 16.2% for alendronate, risedronate and raloxifene respectively<sup>10</sup>. These recent findings on patient adherence are supported by earlier work showing that poor adherence and persistency to treatment are common among osteoporosis patients<sup>11-13</sup>.

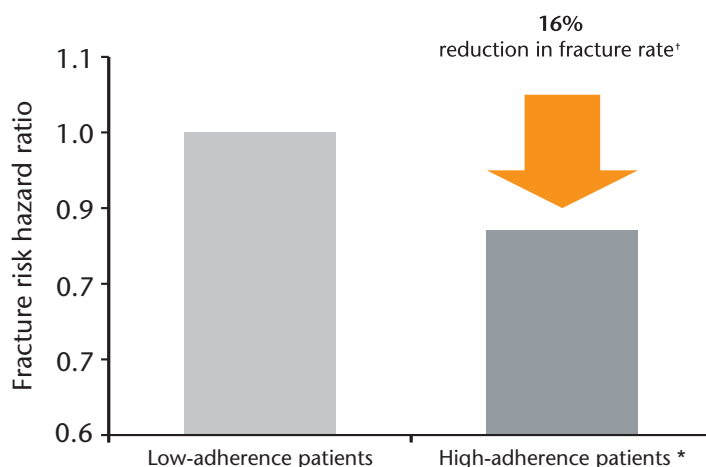
## Patients Who Adhere Have a Decreased Risk of Fracture

- Non-adherent patients have a 26% increased risk of fracture compared to adherent patients.
- Better adherence could result in 390,000 fewer fractures each year.

A number of studies have highlighted the clinical risk of poor adherence. A three year study compared clinical outcomes in 1,041 osteoporosis patients categorised as either consistent or inconsistent<sup>d</sup> users of bisphosphonates<sup>14</sup>. In consistent users lumbar spine BMD increased significantly from baseline after one, two and three years. Inconsistent users showed no significant improvement until the third year, when a modest gain occurred. There was a trend of a 27% greater 10 year fracture risk in inconsistent users (not significant). A positive relationship between adherence and spine BMD was demonstrated in a study of 176 women taking anti-osteoporotic treatments<sup>12</sup>. A recent study has examined the relationship between adherence with bisphosphonate therapy and fracture risk<sup>15</sup>. The two year study of 6,825 women, over 45 years old and with postmenopausal osteoporosis, showed that women who adhered<sup>e</sup> significantly reduced their risk of fracture by 26% compared to those who were non-adherent. Extrapolation of these results to

the entire US population could result in as many as 390,000 fewer fractures each year. These findings are supported by further studies that show a link between adherence and fracture rate (Figure 2)<sup>13,16</sup>.

Figure 2. Patients who adhere experience a lower fracture rate. (Data in Caro JJ et al.<sup>16</sup>)



\* High adherence = drug available to cover  $\geq 80\%$  of time  
†  $p = 0.005$  vs low adherence patients

<sup>a</sup> Based on prescription data and defined as a medical possession ratio, MPR, of at least 80% over a 12 month period.  
<sup>b</sup> Based on prescription data. Non-persistent following a lapse of > 30 days after completion of previous refill.

<sup>c</sup> Defined as continuous therapy on the same drug with 45 day therapy gap.  
<sup>d</sup> Discontinued therapy early or self-reported taking the medication less than 80% of the time.

<sup>e</sup> Based on medical and pharmaceutical claims data. Adherence defined as drug being available 80 percent or more of the time.



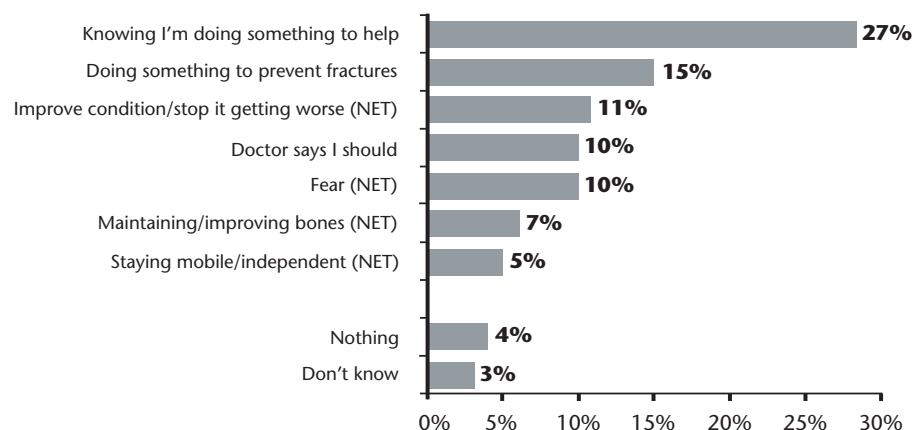
## Why Don't Patients Adhere?

- 60% of patients believe that focusing on the positive outcomes of treatment provided the greatest motivation for continuing with therapy.
- 27% believe fracture risk is the same whether they adhere or not.
- 34% of women are unaware of the benefits of their medication.

A recent European survey has provided some insight as to why women are discontinuing therapy too early to get the full benefit<sup>17</sup>. The study questioned 502 women aged over 60 years with postmenopausal osteoporosis and 500 physicians. The study reveals that one in three women (34%) interviewed either did not know the benefits of their medication or wrongly thought there were no benefits at all. Over a quarter of women (27%) felt their risk of fracture was the same regardless of whether they took the treatment or not.

The drawbacks of treatment identified by the women were mainly related to inconvenience and side effects. Sixty percent (60%) of patients felt that focusing on the positive outcomes of treatment provided the greatest motivation for continuing their therapy (Figure 3) whilst 41% of physicians surveyed focused on negative motivators. Providing patients with positive encouragement and reasons for staying on therapy may provide greater motivation for patients than focussing on the negative outcomes of poor adherence.

Figure 3. Factors motivating women to stay on their osteoporosis treatment. (Data in IPSOS Health Survey<sup>17</sup>.)





## Patient Monitoring May Improve Adherence

- Patients with a positive uNTx response were 92% more likely to adhere to therapy than those with usual care.

Monitoring patients on therapy allows the identification of a poor response and a common cause is poor adherence. The positive message obtained from monitoring may improve long-term compliance. The impact of monitoring 74 healthy osteopenic postmenopausal women on compliance has been assessed<sup>7</sup>. The women were randomised into three groups; usual care (no monitoring), nurse-monitored (predefined interview), and marker-monitored (nurse plus feedback on changes in uNTx). The study showed a significant 57% increased adherence<sup>f</sup> to therapy in the monitoring groups compared to usual care, and increased adherence in turn increased the effectiveness of the therapy. Subjects in the marker-monitoring group, who were informed they had a good response to therapy, were 92% more likely to adhere to therapy compared with usual care and 18% more likely to adhere compared to the nurse-monitored group. Data from the IMPACT study showed increased persistence in those patients receiving a positive message based on bone resorption marker monitoring (including uNTx)<sup>18</sup>. The study also showed that adherence is an important correlate with achievement of better outcomes in terms of bone resorption marker levels and BMD and that poor adherence should be considered in those patients who have not responded<sup>19</sup>.

<sup>f</sup>Data from electronic cap monitoring. Persistence defined as taking tablets for more than 7 days out of the previous 14 days.

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The logo for Osteomark NTx features the word "Osteomark" in a black, handwritten-style font, with "NTx" in a similar but slightly more formal font. To the left of the text is a decorative graphic consisting of a vertical line of blue dots of varying sizes, with some dots appearing to trail off to the left, suggesting movement or a signal.A decorative graphic consisting of a series of grey circles of varying sizes, arranged in a roughly vertical line that curves slightly to the right. The circles are semi-transparent and overlap slightly.

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