Validation of the Surrogate Threshold Effect for Change in Bone Mineral Density as a Surrogate Endpoint for Fracture Outcomes: The FNIH-ASBMR SABRE Project

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ABSTRACT
The surrogate threshold effect (STE) is defined as the minimum treatment effect on a surrogate that is reliably predictive of a treatment effect on the clinical outcome. It provides a framework for implementing a clinical trial with a surrogate endpoint. The aim of this study was to update our previous analysis by validating the STE for change in total hip (TH) BMD as a surrogate for fracture risk reduction; the novelty of this study was this validation. To do so, we used individual patient data from 61,415 participants in 16 RCTs that evaluated bisphosphonates (nine trials), selective estrogen receptor modulators (four trials), denosumab (one trial), odanacatib (one trial), and teriparatide (one trial) to estimate trial-specific treatment effects on TH BMD and all, vertebral, hip, and nonvertebral fractures. We then conducted a random effects meta-regression of the log relative fracture risk reduction against 24-month change in TH BMD, and computed the STE as the intersection of the upper 95% prediction limit of this regression with the line of no fracture reduction. We validated the STE by checking whether the number of fractures in each trial provided 80% power and determining what proportion of trials with BMD changes ≥ STE reported significant reductions in fracture risk. We applied this analysis to (i) the trials on which we estimated the STE; and (ii) trials on which we did not estimate the STE. We found that the STEs for all, vertebral, hip, and nonvertebral fractures were 1.83%, 1.42%, 3.18%, and 2.13%, respectively. Among trials used to estimate STE, 27 of 28 were adequately powered, showed BMD effects exceeding the STE, and showed significant reductions in fracture risk. Among the validation set of 11 trials, 10 met these criteria. Thus STE differs by fracture type and has been validated in trials not used to develop the approach. © 2021 The Authors. Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: BONE MINERAL DENSITY; FRACTURE; SURROGATE; BISPHOSPHONATES; SELECTIVE ESTROGEN RECEPTOR MODULATORS

Introduction
Surrogate endpoints such as low-density lipoprotein (LDL) cholesterol and blood pressure help accelerate drug development. In the field of osteoporosis, we have proposed that change in bone mineral density (BMD) of the total hip could be a surrogate outcome for fracture risk reduction,1 a proposal that has been made by others.2 There are several approaches to implementing surrogate endpoints in trials,3 but one of the most promising is the surrogate threshold effect (STE).4

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The surrogate threshold effect (STE) is defined as the change in the level of a marker that would predict any improvement in a disease outcome with 95% certainty. For example, a statin-related decrease of at least 1.4 mmol/L (54 mg/dL) or more in LDL cholesterol identified a reduction in cardiovascular mortality and a decrease in systolic blood pressure of 7.4 mm Hg or more predicts a reduction in the risk of stroke.

In the Foundation for the National Institutes of Health (FNH)-ASBMR Study to Advance BMD as a Regulatory Endpoint (SABRE) project we obtained a unique dataset of individual patient data from randomized, placebo-controlled trials. Using this dataset, we previously conducted a meta regression of the association between treatment-related changes in BMD and fracture risk reduction. We also calculated the STE, namely the change in BMD that would predict a significant reduction in fracture.

The purpose of the current study is to compute the STE for different magnitudes of minimum fracture risk reduction ranging from 0% to 50%. We also tested the STE against the trials we used in the meta regression to determine whether the claims for fracture risk would have been supported. Finally, we wanted to test the application of the STE in trials not used in the meta regression to further validate the STE method.

### Subjects and Methods

As described, we did a systematic search of published literature to identify randomized controlled trials (RCTs) of osteoporosis drugs with fracture as the outcome. We checked databases including PubMed, Embase, and Cochrane for publications.

#### Table 1. Validation of STE Estimates in trials used for the derivation of STE

| Study number used in Fig. 1 | Study name | Drug | TH BMD (%) | All Fx (>1.83%) | Vertebral Fx (>1.42%) | Hip Fx (>3.18%) | Nonvertebral Fx (>2.13%) |
|-----------------------------|------------|------|------------|----------------|-----------------------|----------------|--------------------------|
| 1                           | BZA PHASE 3(12) | Bazedoxifene | 1.29 | 0.74 | 0.57 |
| 2                           | MORE(13) | Raloxifene | 2.00 | 0.74 | 0.57 |
| 3                           | VERT-NORTH AMERICA(14) | Risedronate | 2.18 | 0.85 | 0.59 |
| 4                           | GENERATIONS(15) | Arzoxifene | 2.32 | 0.85 | 0.59 |
| 5                           | IBAN IV(16) | Ibandronate (iv) | 2.37 | 0.85 | 0.59 |
| 6                           | MEN’S Study(17) | Alendronate | 2.52 | 0.74 | 0.64 |
| 7                           | PEARL(18) | Lasofoxifene | 2.77 | 0.74 | 0.64 |
| 8                           | BONE(19) | Ibandronate (oral) | 3.01 | 0.79 | 0.52 |
| 9                           | FIT CLINICAL FRACTURE(20) | Alendronate | 3.12 | 0.85 | 0.55 |
| 10                          | FIT VERTEBRAL FRACTURE(21) | Alendronate | 3.69 | 0.65 | 0.49 |
| 11                          | LOFT(22) | Odanacatib | 4.56 | 0.60 | 0.46 | 0.52 | 0.76 |
| 12                          | ALN PHASE 3(23) | Alendronate | 4.57 | 0.55 | 0.32 | 0.59 | 0.75 |
| 13                          | HORIZON 2301(24) | Zoledronic acid (iv) | 4.69 | 0.55 | 0.32 | 0.59 | 0.75 |
| 14                          | FRX PREVENTION TRIAL(25) | Teriparatide (SQ) | 5.26 | 0.46 | 0.29 | 0.52 | 0.76 |
| 15                          | FREEDOM(26) | Denosumab (SQ) | 5.35 | 0.59 | 0.31 | 0.52 | 0.76 |
| 16                          | HORIZON 2310(26) | Zoledronic acid (iv) | 5.38 | 0.65 | 0.49 | 0.52 | 0.76 |

### Table 2. Estimates of Change in Total Hip BMD at 24 Months on Treatment

| Minimum fracture risk reduction | STE (% difference in TH BMD between active and placebo) |
|--------------------------------|------------------------------------------------------|
|                                | All fractures | Vertebral fracture | Hip fracture | Nonvertebral fracture |
| Any                            | 1.8 | 1.4 | 3.2 | 2.1 |
| >10%                           | 2.7 | 1.9 | 3.7 | 3.5 |
| >20%                           | 3.8 | 2.4 | 4.5 | 6.2 |
| >30%                           | 5.1 | 3.0 | 5.8 | — |
| >40%                           | 3.7 | — | — | — |
| >50%                           | 4.6 | — | — | — |

STE for any reduction in the four categories of fracture. STEs for different minimal treatment effects ranging from 10% to 50% are shown. The cells left blank indicate those estimates where the 95% confidence interval upper bound exceeded 10%.

STE = surrogate threshold effect.
between 1985 and 2018 in English using the search terms “fracture, BMD, bone mineral density and required RCT or synonyms.” We excluded small studies and studies of patients with certain conditions (eg, glucocorticoid-induced osteoporosis). Strontium ranelate can artifically increase BMD, which alters calcium hydroxyapatite in bone, so we excluded such trials. We attempted to collect from trial sponsors the following: complete data files, individual patient data, and study documentation. We included trials of approved osteoporosis medications, as well as trials of drugs for which approval was not sought or received. We used a standardized template including uniform fracture definitions and standardized BMD conversions. Some studies were not included in the FNIH-SABRE databases because the sponsor was unable or unwilling to provide the data.

We created standardized fracture definitions across all trials. We excluded fractures due to major trauma, by which we meant trauma sufficient to cause a fracture in a young, healthy person. However, we included all fractures reported when trauma information was not available. We included all nonvertebral fractures without exclusion except for one study in which the category of fragility fractures had excluded more than half of nonvertebral fractures due to trauma. For vertebral fractures, we used the individual study definitions based on comparing baseline with follow-up lateral spinal radiographs. Vertebral fracture definition was based on quantitative morphometry, semiquantitative assessment, or a combination of these criteria. We added a fourth category of fracture to this study that was not in our previous study, namely “all fractures.” This is the composite of nonvertebral and clinical or morphometric vertebral fractures.

**Statistical analysis**

We used Cox proportional hazard models for time to all, hip, and nonvertebral fractures with the hazard ratio (HR) as the measure of fracture reduction in order to estimate the effect of treatment within each study. We used logistic regression with the odds ratio (OR) as the measure of fracture reduction for vertebral fractures, where the time to event was unknown. All analyses were by intention-to-treat. The association between treatment and fracture risk (eg, OR or HR) that we calculated differed from the original published results in some studies, for various reasons (eg, use of a different fracture definition, exclusion of trauma, or updates to the final dataset after publication).

We conducted study-level analyses where the unit of analysis is the study and not the individual. We plotted ORs or HRs against the between-group difference in percentage change in BMD.

**Fig 1.** Relationship between difference in the change in total hip BMD between active and placebo groups at 24 months and the hazard or odds ratio of all, vertebral, hip and nonvertebral fractures. The red horizontal line is the ratio of 1 (no treatment effect) and the STE is the point where the upper 95% prediction limits intersects this line; eg, 1.83% for the all fracture outcome. The class of drugs is indicated in the legend. For each trial, the point estimates and 95% confidence intervals for relative risks are given and the numbers 1–16 relate to the studies listed in Table 1.
Validation of STE Estimates in Trials Not Used for the Derivation of STEs

| Study                          | Active treatment | Control treatment | BMD change at 24 months (active-control, %) | Relative risk (odds ratio or hazard ratio) |
|-------------------------------|------------------|-------------------|--------------------------------------------|------------------------------------------|
|                               |                  |                   |                                             | All Fx | Vertebral Fx | Hip Fx | Nonvertebral Fx |
| Reganister and colleagues (2001) | Tiludronate      | PBO               | 0.80                                       |        |              |       |
| Chesnut and colleagues (2000)  | Calcitonin       | PBO               | 0.70                                       |        |              |       |
| Greenspan and colleagues (2007) | PTH (1-84)       | PBO               | 2.11                                       | 0.42   |              |       |
| Watts and colleagues (1990)    | Etidronate       | PBO               | 2.90                                       |        |              |       |
| McCloskey and colleagues (2004) | Clodronate       | PBO               | 3.00                                       | 0.54   |              |       |
| Reid and colleagues (2018)     | Zoledronate      | PBO               | 3.30                                       | 0.63   | 0.45         | 0.66  |
| Miller and colleagues (2016)   | Abaloparatide    | PBO               | 4.25                                       | 0.14   |              |       |
| Riggs and colleagues (1990)    | Sodium fluoride  | PBO               | 4.50                                       | 3.20   |              |       |
| Saag and colleagues (2017)     | Romosozumab→ALN  | ALN→ALN           | 3.70                                       | 0.73   | 0.52         |       |
| Cosman and colleagues (2016)   | Romosozumab→Dmab | PBO→Dmab          | 5.90                                       | 0.67   | 0.25         |       |

We estimated the number of subjects with fracture needed for 80% power based on the reported hazard ratio of fracture risk. We then identified studies which did not reach at least 80% power (gray). Of the remainder, we did not have data on some (yellow) but in those for which we had data, we checked whether the change in total hip BMD between active and placebo at 24 months exceeded the STE and, if so, whether the trial showed a nominally significant reduction in fracture risk (p < 0.05). If the STE was exceeded and the trial was significant, the result is shown in green; if the STE was exceeded and the trial was not significant the result is shown in red. The numbers in the first four columns are observed relative risk of fracture (all p < 0.05). We took change in total hip at 2 years but there were some exceptions such as abaloparatide, which was 18 months total hip BMD; with clodronate there was a measurement of BMD at 3 years so we had to interpolate; sodium fluoride, etidronate, which had 2-year femoral neck BMD; and tiludronate and calcitonin, which had 2-year lumbar spine BMD.

ALN = alendronate; Dmab = denosumab; PBO = placebo; STE = surrogate threshold effect.

Results

Estimating the STE

Change in total hip BMD at 24 months, required for the STE analysis, was available for 61,415 participants. The number of participants used in each analysis depended on the specific fracture type (e.g., "all," vertebral, hip, or nonvertebral fractures). Mean net differences (% change in active minus % change in placebo groups) in total hip BMD ranged from 1.3% to 5.4% across the studies.

We included 16 trials; these enrolled mostly women (exceptions are the MENS study and HORIZON 2310[20] [about 25% men]). The drugs tested in these trials included alendronate,[14,17,21] denosumab,[2] etidronate,[20] and clodronate.[21]
We identified the STE estimates for change in total hip at 24 months for four different fracture locations. The choice of the threshold would be taken by the regulator, eg, US Food and Drug Administration, and the study sponsor. For the validation of the approach, we have taken the 95% prediction limits and we have taken any significant fracture risk reduction (requiring no minimal fracture risk reduction). It may be more rigorous to choose a minimal fracture risk reduction such as 30% for vertebral fracture, because many of our licensed drugs reduce fracture risk by more than this and so a lower reduction may not be clinically important.

We found that in most cases (37/39), a significant fracture reduction was observed when the BMD change exceeded the STE threshold. Importantly, this concordance between STE threshold and fracture reduction was seen both in studies that were included and those that were not included in the meta-regression used to establish the STE, providing robust evidence for the validity of the STE approach.

There were only two studies that were not concordant. The first was a trial using a dose of intravenous ibandronate (70 mg) that was lower than the licensed dose (0.5 and 1 mg as compared to the licensed dose of 3 mg every 3 months). The study was adequately powered to detect a decrease in vertebral fractures, but not other fractures. There are two possible explanations. This could be a false negative—we would not expect all 40 studies to be concordant when we are using a p value of 0.05 as our nominal level of significance. Alternatively, the explanation may lie in the inconsistent decrease in bone turnover markers. Although the total hip BMD increase (2.4%) was greater than the STE for vertebral fracture (1.4%), the bone turnover markers were only intermittently suppressed by the 3-monthly injection; the serum and urinary cross-linked C-telopeptide (CTX) were only about 10% below the placebo response 3 months after injection.

The second was a trial of sodium fluoride, which had sufficient power to detect a decrease in nonvertebral fracture (which actually increased). Sodium fluoride is known to impair bone mineralization in biopsies from humans and minipigs and to reduce structural and material strength in chickens, rats, rabbits, and minipigs. Nowadays, the preclinical program as well as bone biopsies taken during phase 3 would identify such a problem. Moreover, our proposal to use BMD as a surrogate endpoint in future clinical trials would require preclinical evidence of the expected positive association between bone mass and strength.

Precisely how to use the STE to gain regulatory approval for a new drug in osteoporosis remains under discussion. However, one option would be to use the STE method to identify “efficacy thresholds” for a future placebo-controlled trial of a new non-osteoporosis drug that would predict a significant fracture reduction. Results presented here indicate that a different “efficacy threshold” of total hip BMD change (eg, % change: active – placebo) is needed for each fracture type and that, as expected, higher changes in BMD are required for greater fracture reductions. Thus, a new anti-osteoporosis drug could be approved based on a placebo-controlled trial that exhibited a total hip BMD increase that exceeded these thresholds, and perhaps, depending on the magnitude of BMD change, with a statement in the drug label indicating which fracture-specific thresholds were met. Alternatively, for simplicity, the BMD threshold for all different fracture types could be used. Finally, we have few studies of active comparators and so the application to such trials needs further work.

In conclusion, these results provide strong support for using the STE approach in the application of change in TH BMD as a surrogate marker for identifying likely fracture benefits for future clinical trials of osteoporosis treatment.

Disclosures

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Authors’ roles: RE study design, data compilation, drafting, interpretation and revision of manuscript, review of manuscript. DCB, DMB, MB: study design, drafting, interpretation and revision of manuscript, review of manuscript. EV: statistical analysis and interpretation, creation of figures, revision of manuscript. LYL: statistical analysis and interpretation; creation of figures and tables; revision and review of manuscript. IP, AC, SK, JAC, BM: revision and review of manuscript. CEM: statistical analysis and interpretation, review of manuscript.

Peer Review

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Data Availability Statement

Data Sharing Statement As stated above, all study data were acquired by requesting IPD from study sponsors. An overarching data use agreement was created between all parties and individual data use agreements were created between individual study sponsors, FNIH and UCSF. Per the data sharing agreements that we have with each sponsor, the data can be used for surrogate marker analyses including any surrogate qualification processes with regulatory authorities. However, other uses of the data are restricted by this agreement and UCSF is not allowed to share the data.

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