Surrogate threshold effect: a novel approach for potential approval of new osteoporosis treatments using change in BMD. Study-level analysis from the FNIH Bone Quality Project

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For the FNIH Bone Quality Project

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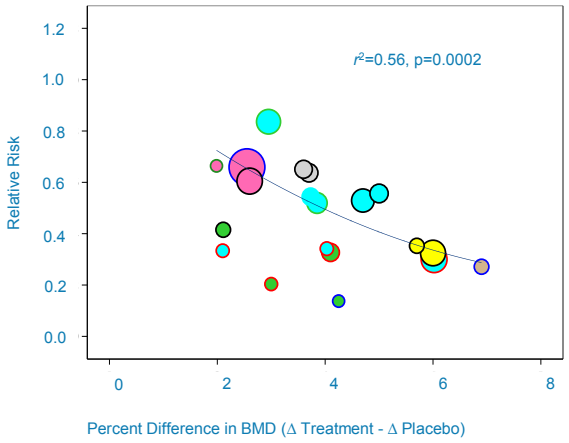
Background

- Change in dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD)
  - May be a useful surrogate for fracture endpoints
  - Could enable much smaller and shorter clinical trials for new drug approvals in osteoporosis
- The difference in the change in total hip BMD between active and placebo groups is strongly related to fracture risk reduction with osteoporosis treatments (1)
- What BMD increase would predict a fracture benefit?
  - Such knowledge could allow us to develop a new regulatory pathway for approval of new osteoporosis treatments

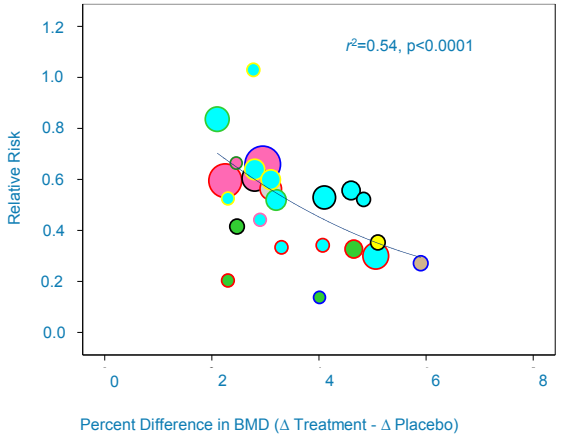
1. Bouxsein M, et al, J Bone Miner Res. 2019 Apr;34(4):632-642

Change in BMD is related to vertebral fracture risk reduction

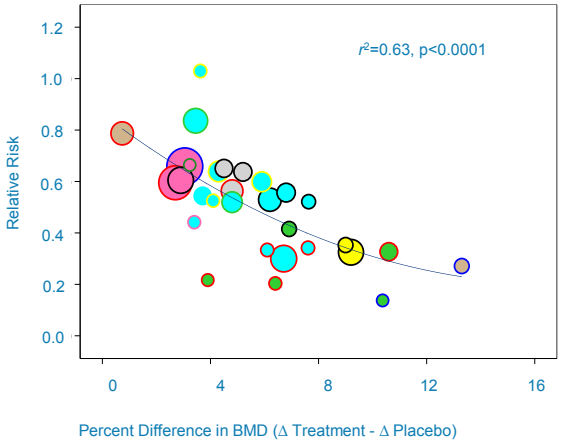
Total Hip BMD

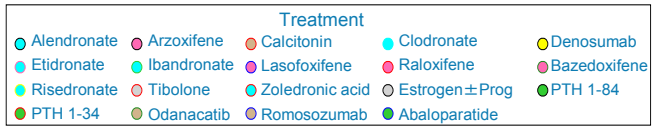


Femoral Neck BMD



Lumbar Spine BMD

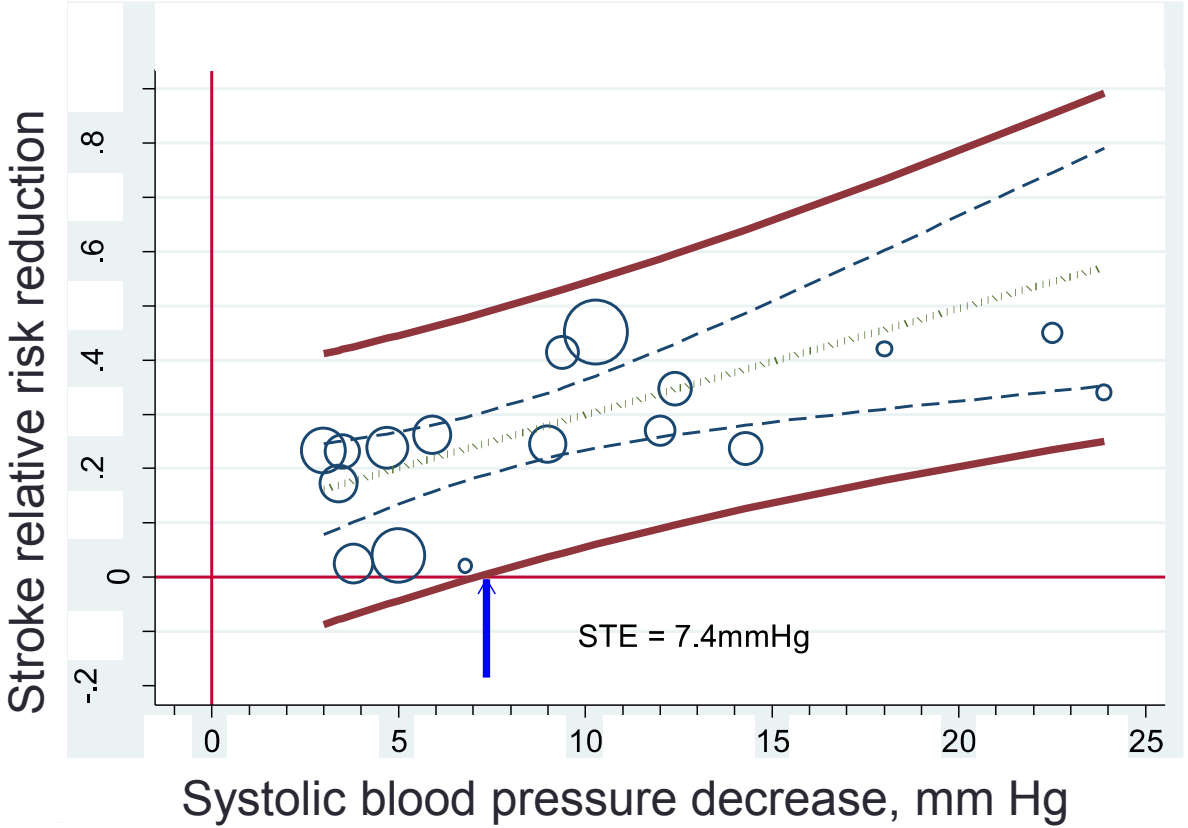




Bouxsein ML et al, J Bone Miner Res. 2019 Apr;34(4):632-642.

Surrogate Threshold Effect (STE)

- The level of the marker that would predict an improvement in a disease outcome with 95% certainty
- Example: systolic blood pressure change and stroke risk on treatment



Population

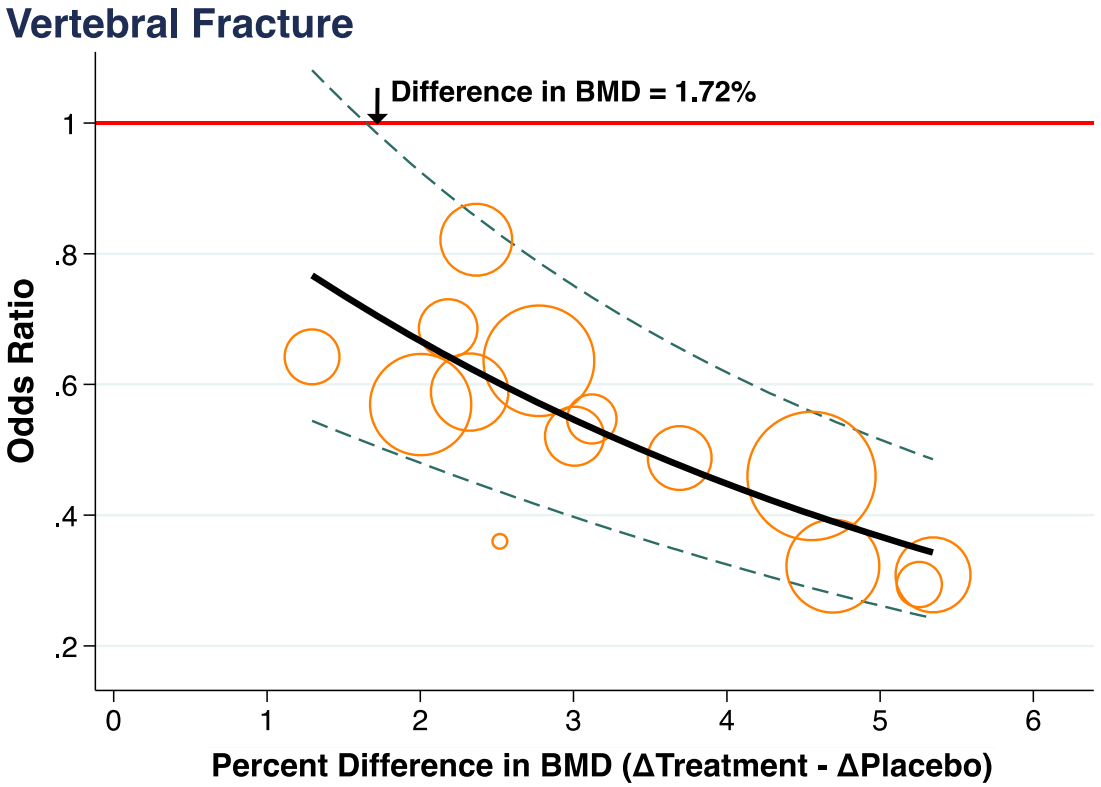
- Data from study participants
  - collected as part of the FNIH Bone Quality project
  - a public-private partnership, which compiled IPD from over 150,000 participants in all major clinical trials of osteoporosis therapies, including DXA BMD and fracture outcomes
- The current analyses reflect data from 61,415 study participants with 2-year BMD from 16 osteoporosis trials
  - 9 bisphosphonate; 4 SERM; 1 teriparatide; 1 denosumab; 1 odanacatib

Methods

- Meta-regression using
  - baseline and follow-up BMD results
  - incident fractures from each study
- Assessment of the relationship between
  - the treatment-related difference in total hip BMD changes (percent difference, active minus placebo at 24 months)
  - to the observed fracture risk reduction in each study
- We fit a linear regression to the logarithm of the relative risks and estimated the 95% confidence interval and prediction limits
- The surrogate threshold was defined as the point where the prediction limits crossed the relative risk of fracture of unity

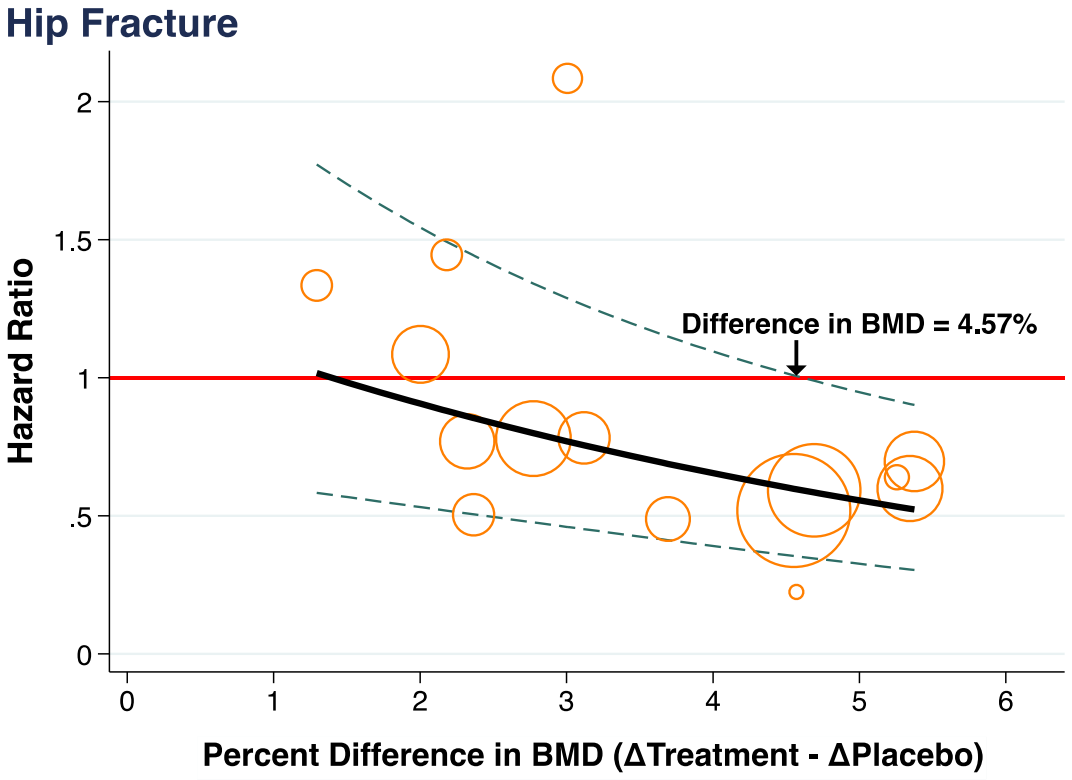
Total Hip BMD difference and fracture reduction - 1

- Arrow indicates the minimum BMD difference predicting significant fracture reduction in a future trial



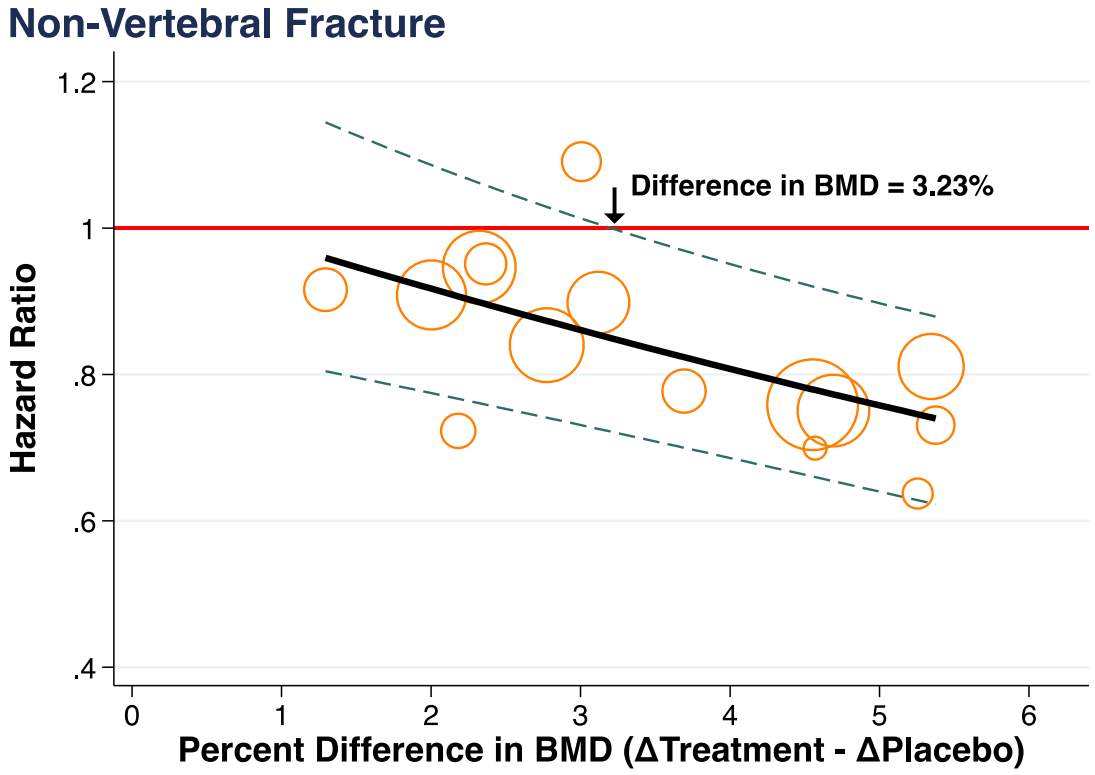
Total Hip BMD difference and fracture reduction - 2

- Arrow indicates the minimum BMD difference predicting significant fracture reduction in a future trial



Total Hip BMD difference and fracture reduction - 3

- Arrow indicates the minimum BMD difference predicting significant fracture reduction in a future trial



- Application of thresholds to completed clinical trials

Study name	Study drug	THBMD	VFx	Hip Fx	NV Fx
BZA PHASE 3	Bazedoxifene	1.3	*	ns	ns
MORE	Raloxifene	2.0	**	ns	ns
VERT-NORTH AMERICA	Risedronate	2.2	*	ns	*
GENERATIONS	Arzoxifene	2.3	**	ns	ns
IBAN IV	Ibandronate (i.v.)	2.4	ns	ns	ns
MEN'S STUDY	Alendronate	2.5		N/A	N/A
PEARL	Lasofoxifene	2.8	**	ns	*
BONE	Ibandronate (oral)	3.0	**	ns	ns
FIT CLINICAL FRACTURE	Alendronate	3.1	**	ns	ns
FIT VERTEBRAL FRACTURE	Alendronate	3.7	**	ns	ns
LOFT	Odanacatib	4.6	**	**	**
ALN PHASE 3	Alendronate	4.6	N/A	ns	ns
HORIZON 2301	Zoledronic acid (i.v.)	4.7	**	**	**
FRX PREVENTION TRIAL	PTH(1-34) (SQ)	5.3	**	ns	*
FREEDOM	Denosumab (SQ)	5.4	**	*	*
HORIZON 2310	Zoledronic acid (i.v.)	5.4	N/A	ns	*

VFx, 1.7%

Non-VFx, 3.2%

Hip Fx, 4.6%

Trials sorted by 2-year difference in THBMD.

Fracture reduction
ns, not significant
N/A, not available
* $p<0.05$, ** $p<0.01$

Strengths and Limitations

- Strengths
  - Application of approach used for other surrogate endpoints
  - Large study
  - Access to individual patient data allows study of 2-year BMD and consistent fracture definition
- Weaknesses
  - The approach depends on the power of the underlying studies
- Further analyses
  - Use of clinically meaningful reduction (e.g. 20%)
  - Use of different time windows, different levels of confidence

Conclusions

- Conclusions
  - This analysis identifies the BMD increases that would predict a fracture benefit
- Discussion
  - The results may be helpful to regulatory agencies if they adopt total hip BMD as a surrogate for fracture risk reduction in clinical trials of new osteoporosis drugs
  - Why are the BMD increases not the same for all fracture types?
    - The drugs may work preferentially on the trabecular bone of the spine

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Reserve Slide: Total Hip, Femoral Neck, Lumbar Spine BMD difference and fracture reduction

Fracture type	Total Hip	Femoral Neck	Lumbar Spine
Vertebral	1.72	1.93	2.62
Hip	4.57	3.79	6.20
Non-vertebral	3.23	2.95	4.94