Screening and Treatment Decisions in Osteoporosis: Current Controversies and State of the Evidence

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Division of General Internal Medicine
Division of Epidemiology and Community Health
Case

• 57 year old woman comes in to establish care
• Possible to do list: Osteoporosis screening?
  – 5’5”, 120 lbs
  – Smokes 1 pack/day
  – No other risk factors
Current Controversies

• Who to screen for osteoporosis?
• How often to screen?
• Who to treat?
• What to treat with?
• How long to treat?
Expanding Disease Definitions

• Traditionally, a disease was a condition a patient experienced directly, but diseases are increasingly being defined more broadly
  – Eg. Diabetes, hypertension, chronic kidney disease
  – Eg. Early detection due to screening: breast cancer, coronary artery disease, osteoporosis, others

• Implications of expanding disease definition
  – Some patients may benefit from treatment they would have otherwise not received
  – More patients exposed to potential harms of treatment
  – As # of patients grows, market for treatment expanded
Definition of Osteoporosis

- Systemic skeletal disease characterized by low bone mass and microarchitectural deterioration in bone tissue, leading to enhanced bone fragility and increased fracture risk
Scope of the problem

- Estimated 10 million adults in U.S. over age of 50 have osteoporosis
- About 1.5 million/year osteoporotic-related fractures in U.S.
- Due to aging of the population, estimated that number of hip fractures will double/triple by 2020-2025.
- Cost to the U.S. healthcare system of osteoporosis-related fractures estimated at $18 billion in 2010.
Diagnosis of Osteoporosis

- Presence of low-impact or fragility fracture
  - Fracture that occurs in the absence of trauma – i.e., falling from a standing height (e.g., vertebral compression fracture, hip fracture)
- Bone mineral density (BMD) below specified level
Bone Mineral Density

• Bone mineral content divided by area or volume of bone estimates bone mineral density (BMD)

• High correlation between BMD and force needed to break a bone
BMD by Dual Energy X-ray Absorptiometry (DXA)

• Amount of x-ray energy absorbed by calcium in a section of bone reflects the bone mineral content

• Provides measure of BMD at multiple skeletal sites (hip, spine, forearm, whole body)

• High precision and predictive value for fracture
BMD Scores

• Densitometry results are reported as T-scores and Z-scores

• **Z-score:** patient’s BMD compared to age & gender-matched mean BMD. Z is the number of SDs below or above the mean BMD for people of same age

• **T-score:** patient’s BMD compared to mean BMD in young adults. T is the number of SDs below or above the mean BMD for young adults
Spine: L1-L4

BMD gm/cm²

Score

20  40  60  80  100

Age

T = -2.0  Z = -0.5

T = 1.320  Z = 1.200  T = 1.080  Z = 0.960  T = 0.840  Z = 0.720  T = 0.0  Z = +1.0  T = -1.0  Z = 0.0  T = -2.0  Z = -1.0  T = -3.0  Z = -2.0  T = -4.0
Use of BMD to Identify Postmenopausal Osteoporosis

• **Normal**: BMD within 1 SD of a “young, normal” female (T at or above −1)

• **Osteopenia**: BMD between 1 and 2.5 SD below that of a “young, normal” female (T between −1 and −2.5);
  – **Mild** (T −1.01 to −1.49),
  – **Moderate** (T −1.50 to −1.99)
  – **Advanced** (T −2.00 to −2.49)

• **Osteoporosis**: BMD 2.5 SD or more below that of a “young, normal” female (T at or below −2.5)
How to screen for osteoporosis

• Involves:
  – Measurement of Bone Mineral Density
    • Dual Energy X-ray Absorptiometry (DXA)
  – Assessment of risk factors for fracture
    • Assessment of risk factors that are independent of BMD is important for fracture prediction (most fractures occur in patients without osteoporosis by BMD)
Risk factors independent of BMD

- Advanced age
- Previous fracture
- Long-term glucocorticoid use
- Low body weight (less than 57 kg [127 lbs])
- Parental history of hip fracture
- Cigarette smoking
- Excess alcohol intake
Limitations of T-score based definition of osteoporosis

• These thresholds are useful as diagnostic categories

• However, the relation between BMD and risk of fracture is continuous – there is no absolute cutoff value.
  – For each 1 S.D. decrease in BMD at the hip, there is 2.6-fold increase in risk of hip fracture

• At least half all fractures occur in individuals with osteopenia
Fracture Rate and the Number of Women with Fractures According to Peripheral Bone Mineral Density (BMD).

BMD Score and 10-year Fracture Risk

Used with permission from McClung MR. Bone 2006;38(2 suppl):S13-S17.
Absolute Fracture Risk

• Likelihood of fractures over a given period of time (fracture probability over a 10-year interval)
• Depends on age, gender, BMD, and these other risk factors that independently increase risk for fracture
• Development of models to estimate absolute fracture risk
• Process similar to that used in development of Framingham Risk Score, an indicator of absolute risk of CVD
FRAX Risk Assessment Tool

• Web-based risk assessment tool using clinical risk factors with and without femoral neck BMD to enhance fracture prediction
• Estimates an individual’s 10-year probability of:
  — hip fracture
  — major osteoporotic fracture (hip, clinical vertebral, humerus, or forearm)
FRAX®

• Can be used for an untreated patient (men and women) between ages 40-90
• Based on data collected from large prospective observational studies
• Some controversy about the fracture risk models
  — Uncertain whether this is more accurate in predicting risk than simpler models incorporating age and BMD
FRAX – Example #1

• 65 year old woman
• Caucasian
• 5’ 5”
• 150 lbs
• Non-smoker, no personal history of fracture or maternal history of hip fracture
• No other risk factors for osteoporosis
• Risk calculated without BMD measurement
FRAX Calculation Tool - Result

Questionnaire:
1. Age (between 40-90 years) or Date of birth
   Age: 65
   Date of birth: Y: [ ] M: [ ] D: [ ]
2. Sex
   Male [ ] Female [ ]
3. Weight (kg) 68.04
4. Height (cm) 165.1
5. Previous fracture
   No [ ] Yes [ ]
6. Parent fractured hip
   No [ ] Yes [ ]
7. Current smoking
   No [ ] Yes [ ]
8. Glucocorticoids
   No [ ] Yes [ ]
9. Rheumatoid arthritis
   No [ ] Yes [ ]
10. Secondary osteoporosis
    No [ ] Yes [ ]
11. Alcohol 3 or more units per day
    No [ ] Yes [ ]
12. Femoral neck BMD (g/cm²)
    Select DXA [ ]

BMI 25.0
The ten year probability of fracture (%)
without BMD
- Major osteoporotic 9.3
- Hip fracture 1.2
Our case

- 57 year old woman, Caucasian
- 5’ 5”; 120 lbs
- Current smoker

Would you refer her for DXA for screening?
Who should be tested?

- All U.S. guidelines recommend testing women \(\geq 65\) years of age; based on data from observational cohort studies and RCTS of interventions
- Demonstrate strong association between BMD and risk of hip fracture in older women (65 years and older)
- Supported by cost effective analyses
Screening recommendations for postmenopausal women

<table>
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<th>AACE</th>
<th>AAFP</th>
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<tbody>
<tr>
<td>Women 65 years and older</td>
<td>X</td>
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<tr>
<td>Younger post-menopausal women</td>
<td>If estimated fracture risk ≥ 9.3%/10 yrs; fragility fx</td>
<td>“With risk factors” or fragility fx</td>
<td>“With risk factors” or fragility fx</td>
<td>Age ≥60 years “With risk factors”</td>
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Screening rates

• Room for improvement in screening rates in women 65 years and older
  – Remains underutilized
• Low rates of BMD testing after a fracture
  – In 2009, 20% of women in Medicare HMOs received DXAs or treatment for osteoporosis within 6 months of a fracture.
  – In fee-for-service Medicare, an estimated 37% of women tested or treated after a fracture.
Women Aged 50-64 Years

- Low prevalence of osteoporosis in younger postmenopausal women
• Younger women’s 10-year fracture risk is lower for a given BMD
• No data are available on the benefit of osteoporosis treatment beginning at age 50-59 and continuing over 3-4 decades
• Early treatment leads to prolonged duration of use – increased risk of net harm
• Over-treating younger women when fracture risk is low leaves them with fewer options in their 70s, when hip fracture risk increases
Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 57

2. Sex
   Male

3. Weight (kg)
   54.43

4. Height (cm)
   165.1

5. Previous fracture
   No

6. Parent fractured hip
   No

7. Current smoking
   No

8. Glucocorticoids
   No

9. Rheumatoid arthritis
   No

10. Secondary osteoporosis
    No

11. Alcohol 3 or more units per day
    No

12. Femoral neck BMD (g/cm²)
    Select DXA

BMI 20.0
The ten year probability of fracture (%)

without BMD

- Major osteoporotic: 7.2%
- Hip fracture: 1.2%
Screening in men?
## Screening recommendations for men

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<td>Men</td>
<td>Insufficient evidence to recommend screening (2011)</td>
<td>Men &gt; 70; Men 50-70 when risk factors present; recommend use of male specific T scores</td>
<td>Men &gt; 70; Men 50-70 with risk factors; recommend use of male specific T scores</td>
<td>Men &gt; 70; Men 50-70 with risk factors;</td>
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Osteoporosis in men

- Mean BMD higher in men vs. women at all ages
- Age-specific prevalence of osteoporosis and incident fracture rates are lower among men.
- Similar age-adjusted absolute fracture risk in men and women with same absolute BMD level.
Diagnosis of osteoporosis in men

• Diagnostic cutoff values for osteoporosis in men less well defined than for women.
• WHO recommends same diagnostic criteria as for women: BMD 2.5 or more SDs below the mean for referent group of young healthy females.
• Other organizations (NOF, Endocrine Society) recommend that T-scores in men be calculated using the young male normal reference.
Osteoporosis in Men Study (MrOS): Proportion of Men Identified as Osteoporotic

- **OP by NOF (but not WHO) criteria**: 7.2%
- **OP by WHO criteria**: 2.2%
Screening in men

- Fragility fracture
- Long term glucocorticoid use
- Androgen deprivation therapy
- Hypogonadism
- Primary hyperparathyroidism
- Loss of 1.5 inch height
- Radiographic osteopenia
Who to treat?

- Individuals with a clinical fragility fracture
  - Hip fracture
  - Vertebral compression fracture
- Women with osteoporosis by DXA
  - T-score $\leq -2.5$ at hip or spine
Treatment options

- Bisphosphonates
- Selective estrogen receptor modulators (SERMs)
- Recombinant PTH - I-34 (teriparatide)
- Denosumab
- Calcitonin
- Estrogen
Bisphosphonates

- Potently inhibit osteoclastic bone resorption
- Increase BMD
- Reduce fracture risk
- 10 year + safety data
- Persist in bone long term
- Because inhibit bone resorption by suppressing osteoclastic activity, concern that prolonged therapy can lead to oversuppression of bone turnover (frozen bone) and increased skeletal fragility
Bisphosphonates

- Bisphosphonates generally considered first line option due to longterm safety data, cost
- Controversy about how long to treat with bisphosphonates
  - Concept of frozen bone
  - Osteonecrosis of the jaw (ONJ)
  - Atypical femur fractures
  - Consideration of drug holiday after 5-10 years
Selective estrogen receptor modulators (Raloxifene)

- Competitively inhibit estrogen binding to estrogen receptors
- Have mixed agonist and antagonist activity at estrogen receptors, depending on the target issue – in bone, act as agonists
- Increase BMD
- Reduce risk of vertebral fractures
- Have not been shown to reduce risk of hip fracture
Recombinant PTH (teriparatide)

- Stimulates preosteoblasts to mature into boneforming osteoblasts
- Stimulates bone formation
- Bone formation peaks after 6-9 months
- BMD changes level off about 18 months
- Potential risk of carcinogenicity – osteosarcoma
- Approved for only two years of use
Denosumab

- Monoclonal antibody to the receptor activity of RANKL, an osteoclastic differentiating factor.
- Inhibits osteoclastic formation, decreasing bone resorption
- Increases BMD
- Reduces fracture risk in postmenopausal women with osteoporosis
- 5 year follow up data
- RANKL also functions in immune system - concern about infectious and neoplastic complications
What About Patients with Osteopenia (T-score > −2.5)?

• Focus is on identifying patients with osteopenia who have a higher risk of fracture and treating them
• Use of FRAX to predict fracture risk
• Argument: if at higher risk of fracture, more benefit in reducing fracture risk
National Osteoporosis Foundation Treatment Guidelines

- For those with osteopenia, treat based on 10-year risk
  - ≥20% 10-year risk of major osteoporotic fractures
  - ≥3% 10-year risk of hip fracture
NOF Treatment Guidelines

• Problem: No RCT using this approach
• In fact, there are no RCTS of treating osteopenia, only post-hoc analyses
• Controversial - based on cost-effectiveness analyses which assume:
  – 35% reduction of major fracture with treatment;
  – no adverse effects;
  – generic bisphosphonate costs
Fracture Intervention Trial (FIT)

• Randomized, double-blind placebo-controlled trial
• Alendronate vs. placebo
• Postmenopausal women aged 54 to 81
• BMD at femoral neck < 0.68 gm/cm² (equivalent to T-score < −1.6)
• Stratified on presence or absence of vertebral fractures
• Followed for four years for risk of clinical fractures, new vertebral deformities on x-rays, and BMD
From: Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures: Results From the Fracture Intervention Trial

HR 0.86 (14% relative risk reduction); p=0.07
1.8% absolute risk reduction
<table>
<thead>
<tr>
<th>T Score of Bone Marrow Density*</th>
<th>Clinical Fractures</th>
<th>Vertebral Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo, No. (%)</td>
<td>Alendronate, No. (%)</td>
</tr>
<tr>
<td>&lt;−2.5</td>
<td>159 (19.6)</td>
<td>107 (13.1)</td>
</tr>
<tr>
<td>−2.5 to −2.0</td>
<td>87 (12.3)</td>
<td>92 (12.7)</td>
</tr>
<tr>
<td>−2.0 to −1.6</td>
<td>66 (9.5)</td>
<td>73 (10.9)</td>
</tr>
</tbody>
</table>

*T scores correspond to femoral neck bone mineral density in SDs below the bone density of young white women using data from the Third National Health and Nutrition Examination Survey.12
†RH indicates relative hazard; CI, confidence interval.
RH in Low vs. High BMD

- Alendronate (FIT)
- Alendronate (FOSIT)
- Ibandronate
- Risedronate
- Estrogen
- Bazedoxifene
- Raloxifene
- PTH (1-84)
- Denosumab

Relative Hazard

0.1 1 10

Favors Treatment 
Favors Placebo
Debate

• Treat those fragility fracture or T-scores ≤ -2.5
  – strength of the evidence is high

• Treat based on absolute fracture risk
  – Strength of the evidence is weaker
  – RCT of intervention based on absolute fracture risk needed
Applying NOF Recommendations: Study of Osteoporotic Fractures (SOF)

• Application of these guidelines resulted in treatment of:
  – 72% of women over age 65
  – 93% of women over age 75

Donaldson MG et al. J Bone Miner Res 2011; 26:1767-1773
Treating men
Drug Treatment in Men: Guidelines (NOF 2010, Endocrine Society 2012):

- History of hip or vertebral (radiographic or clinical) fracture
- **Male** specific BMD T score ≤ −2.5 at femoral neck, total hip or lumbar spine
- Male specific BMD T score between −1.0 and −2.5 with FRAX 10-yr probabilities of ≥3% for hip fracture or ≥20% for major osteoporotic fracture
Proportion of Men > 65 Identified as Eligible for Drug Treatment to Prevent Fracture (MrOS)

- No OP, "High" Fx Risk (n=936) - 15.9%
- OP by NOF (but not WHO) criteria (n=422) - 7.2%
- OP by WHO criteria (n=130) - 2.2%
Expanding Disease Definitions in Osteoporosis

1. Introduction of screening tests has allowed identification of osteoporosis when previously would have been unrecognized.

2. Evolving focus on absolute fracture risk rather than strict definition of osteoporosis (T-score < -2.5 or fragility fracture)
   - Appropriately draws attention to fracture risk, the outcome of interest
Absolute fracture risk

• Treatment decisions based on absolute fracture risk result in a great expansion of pool of candidates for treatment.

• May be premature given current state of evidence – need for RCT of treatment based on absolute fracture risk.
Expanding Disease Definitions in Osteoporosis

3. In men, controversy over definition of osteoporosis:
   – How osteoporosis defined significantly impacts percentage of older men recommended for treatment
Summary

• Screen women over age 65
• Remains uncertain who to screen in the 50-64 year old population
• Treatment most clearly effective the lower the BMD
• Treatment of patients with osteopenia has not been rigorously tested.
• Definition of osteoporosis in men controversial
• Paucity of evidence to guide screening and treatment decisions in men
How long to treat?
How Long to Treat?

- FIT Longterm Extension Trial (FLEX)
- Women randomized to alendronate in FIT were subsequently randomized to either continue alendronate for an additional five years or to placebo
From: Effects of Continuing or Stopping Alendronate After 5 Years of Treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial

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JAMA. 2006;296(24):2927-2938
Date of download: 8/23/2012
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Nonvertebral Fractures

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<tr>
<th>Time to First Fracture, mo</th>
<th>Alendronate (Pooled)</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
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<tr>
<td>24</td>
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<td>36</td>
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<td>48</td>
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<tr>
<td>60</td>
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<tr>
<td>72</td>
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</table>

RR, 1.00 (95% CI, 0.76-1.32)

Clinical Vertebral Fractures

<table>
<thead>
<tr>
<th>Time to First Fracture, mo</th>
<th>RR, 0.45 (95% CI, 0.24-0.86)</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>12</td>
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No. at Risk

<table>
<thead>
<tr>
<th>Placebo</th>
<th>437</th>
<th>421</th>
<th>410</th>
<th>396</th>
<th>373</th>
<th>355</th>
</tr>
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<tbody>
<tr>
<td>Alendronate</td>
<td>662</td>
<td>642</td>
<td>619</td>
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Table 3. Incidence of Fracture by Treatment Group

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<tr>
<th>Fractures</th>
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<th>Pooled Alendronate, No. (%)</th>
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<td>(n = 662)</td>
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<td>Vertebral</td>
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<td>Clinical</td>
<td>23 (5.3)</td>
<td>16 (2.4)</td>
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<tr>
<td>Morphometric</td>
<td>46 (11.3)</td>
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<td>0.86 (0.60-1.22)</td>
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<tr>
<td>Clinical</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>93 (21.3)</td>
<td>132 (19.9)</td>
<td>0.93 (0.71-1.21)</td>
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<tr>
<td>Nonspine</td>
<td>83 (19.0)</td>
<td>125 (18.9)</td>
<td>1.00 (0.76-1.32)</td>
</tr>
<tr>
<td>Hip</td>
<td>13 (3.0)</td>
<td>20 (3.0)</td>
<td>1.02 (0.51-2.10)</td>
</tr>
<tr>
<td>Forearm</td>
<td>19 (4.3)</td>
<td>31 (4.7)</td>
<td>1.09 (0.62-1.96)</td>
</tr>
</tbody>
</table>

*Adjusted for clinic and stratum.
FLEX results

• These results sometimes stated as “55% reduction in risk of clinical vertebral fractures” with continuation of alendronate for additional 5 years.
• NNT to prevent one clinical vertebral fracture: treat 35 women for 5 additional years
• No effect on reduction of non-spine fractures (hip, forearm, others)
• No effect on reduction of morphometric vertebral fractures
• What if this patient was 65 years old, with same characteristics?
• Would you treat her?
• FRAX calculation of 10 year risk:
  – Major osteoporotic fracture: 11%
  – Hip fracture: 3.2%
Number Of DXA Tests Per 1,000 Medicare Fee-For-Service Beneficiaries, 1996–2010.
Unadjusted Cumulative Incidence of Osteoporosis According to Baseline T-Score Range

How Long to Treat?

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- **Alendronate (Pooled)**
- **Placebo**

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<td>20 (3.0)</td>
<td>1.02 (0.51-2.10)</td>
</tr>
<tr>
<td>Forearm</td>
<td>19 (4.3)</td>
<td>31 (4.7)</td>
<td>1.09 (0.62-1.96)</td>
</tr>
</tbody>
</table>

*Adjusted for clinic and stratum.
FLEX results

• These results sometimes stated as “55% reduction in risk of clinical vertebral fractures” with continuation of alendronate for additional 5 years.
• NNT to prevent one clinical vertebral fracture: treat 35 women for 5 additional years
• No effect on reduction of non-spine fractures (hip, forearm, others)
• No effect on reduction of morphometric vertebral fractures
Observed 10-year Probability of Major Osteoporotic Fracture According to Definition and Fracture Risk

<table>
<thead>
<tr>
<th>Category</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP by WHO criteria</td>
<td>30.00</td>
</tr>
<tr>
<td>OP by NOF (but not WHO) criteria</td>
<td>17.50</td>
</tr>
<tr>
<td>No OP – “High” Fx Risk</td>
<td>12.00</td>
</tr>
<tr>
<td>No OP – “Low” Fx Risk</td>
<td>4.80</td>
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</tbody>
</table>