

Assessment for treatment based on FRAX

Dr Eugene Mc Closkey
Reader in Adult Bone Disease,
University of Sheffield



The aim of the clinician in managing osteoporosis

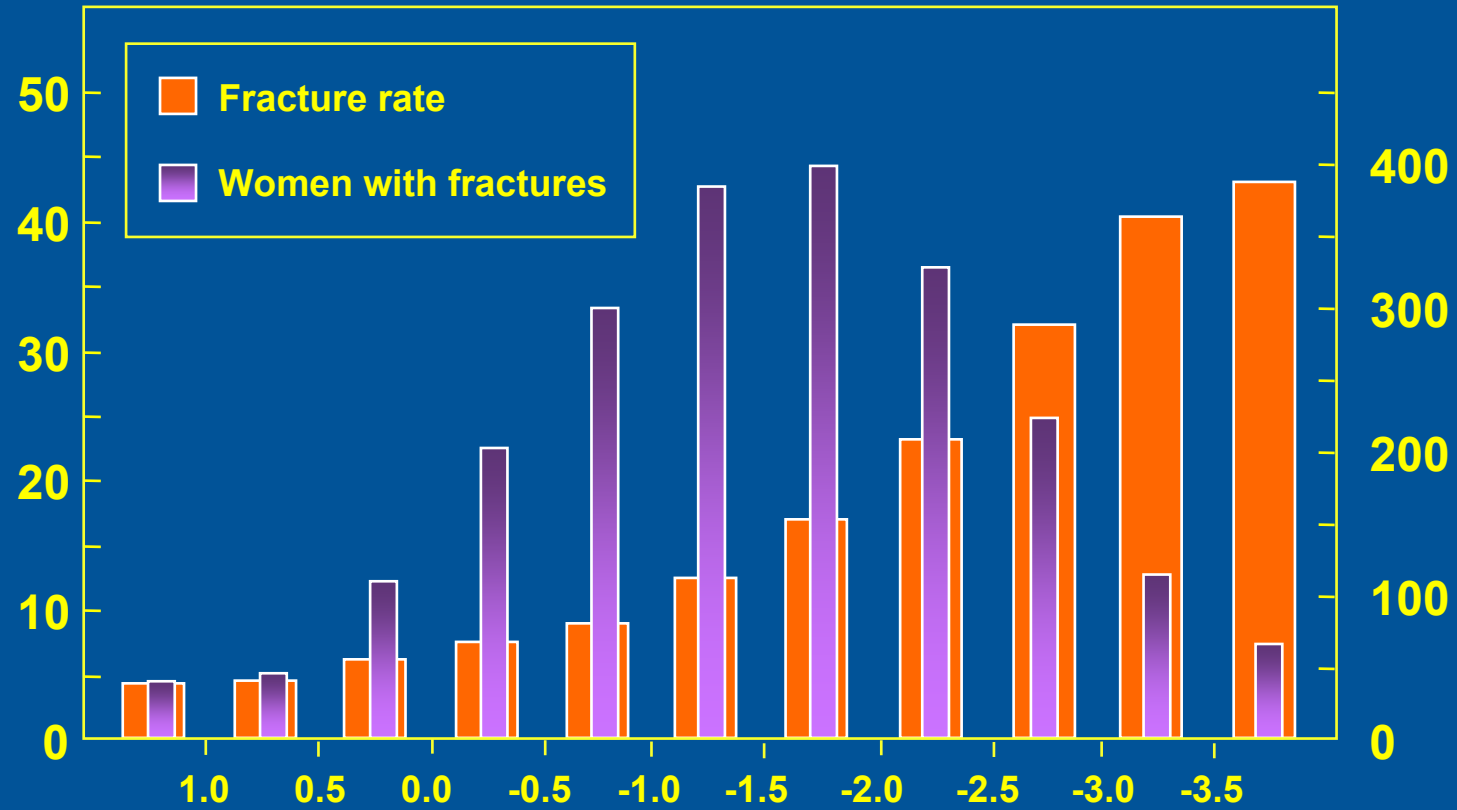
- **TO REDUCE THE INCIDENCE OF FRACTURES**
- To identify patients at increased risk of fracture
- To be able to assess that risk accurately
- To give advice to aid understanding of the disease, the aims of therapy and the choice of therapy
- **Treatment**
 - Lifestyle advice
 - Therapeutic agents



Osteoporotic fracture and BMD

Fractures/1,000 person-years

Number of fractures

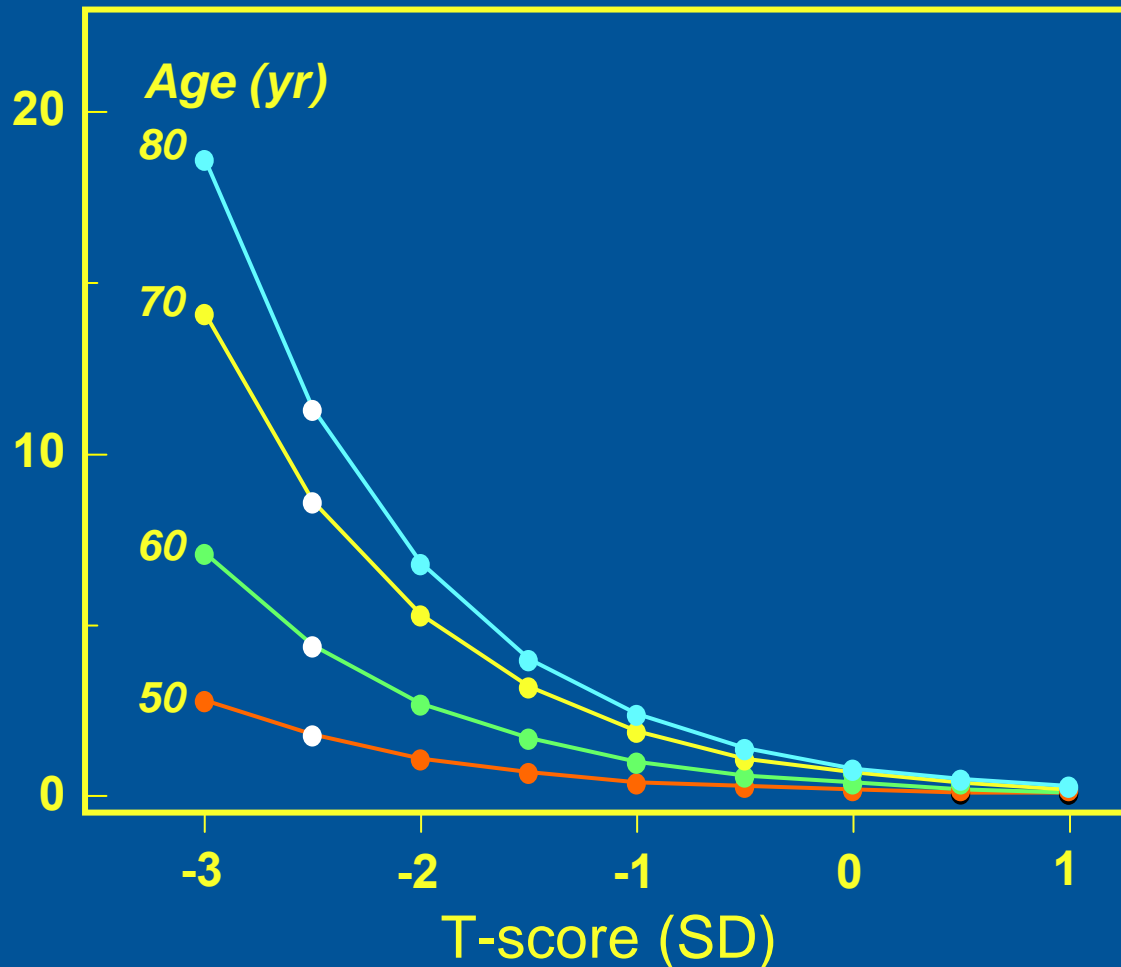


Siris. Surgeon General's Workshop on Osteoporosis and Bone Health, December 2002



Ten year probability of hip fracture in Sweden

Fracture probability (%)



The development of FRAX

- **A two stage process**
 - Determine impact of risk factors on fracture risk and mortality
 - Large multinational cohorts
 - Identification of common risk factors that could be standardised
 - Meta-analyses
 - Superimpose the resulting risk algorithm on the epidemiology of fracture and mortality for each country



FRAX development: Primary cohorts

- **Primary cohorts included baseline and follow-up data from nine prospective, population-based cohorts**
 - Based on the Rotterdam study, EVOS/EPOS, CaMos, Rochester, Sheffield, DOES, AHS and two cohorts from Gothenburg
 - 46,340 men and women (68% women)
 - ~190,000 person/years
 - 4,168 osteoporotic fractures, of which 850 were at the hip

EVOS/EPOS = European Vertebral Osteoporosis Study/European Prospective Osteoporosis Study

CaMos = Canadian Multicentre Osteoporosis Study; DOES = Dubbo Osteoporosis Epidemiology Study

AHS = Adult Health Study

Kanis JA, et al. Osteoporos Int 2007;18:1033–46



FRAX development: Validation data

- **Data was obtained from a further 11 independent, population-based cohorts**
 - Based on the EPIDOS, SOF, two cohorts from the Geelong osteoporosis study in Australia, OPUS, PERF, THIN, the SEMOF study, the Women's Health Initiative (US), plus cohorts from York, UK and Miyama in Japan
 - 230,486 women
 - ~1,200,000 person/years
 - 18,543 osteoporotic fractures, of which 3,360 were at the hip

EPIDOS = Epidemiologie de l'osteoporose study; SOF = Study of Osteoporotic Fractures

PERF = Prospective Epidemiological Risk Factors; OPUS = Osteoporosis Prevention Using Soy

SEMOF = Schweizerische Evaluierung der Messmethode des Osteoporotischen Frakturrisikos

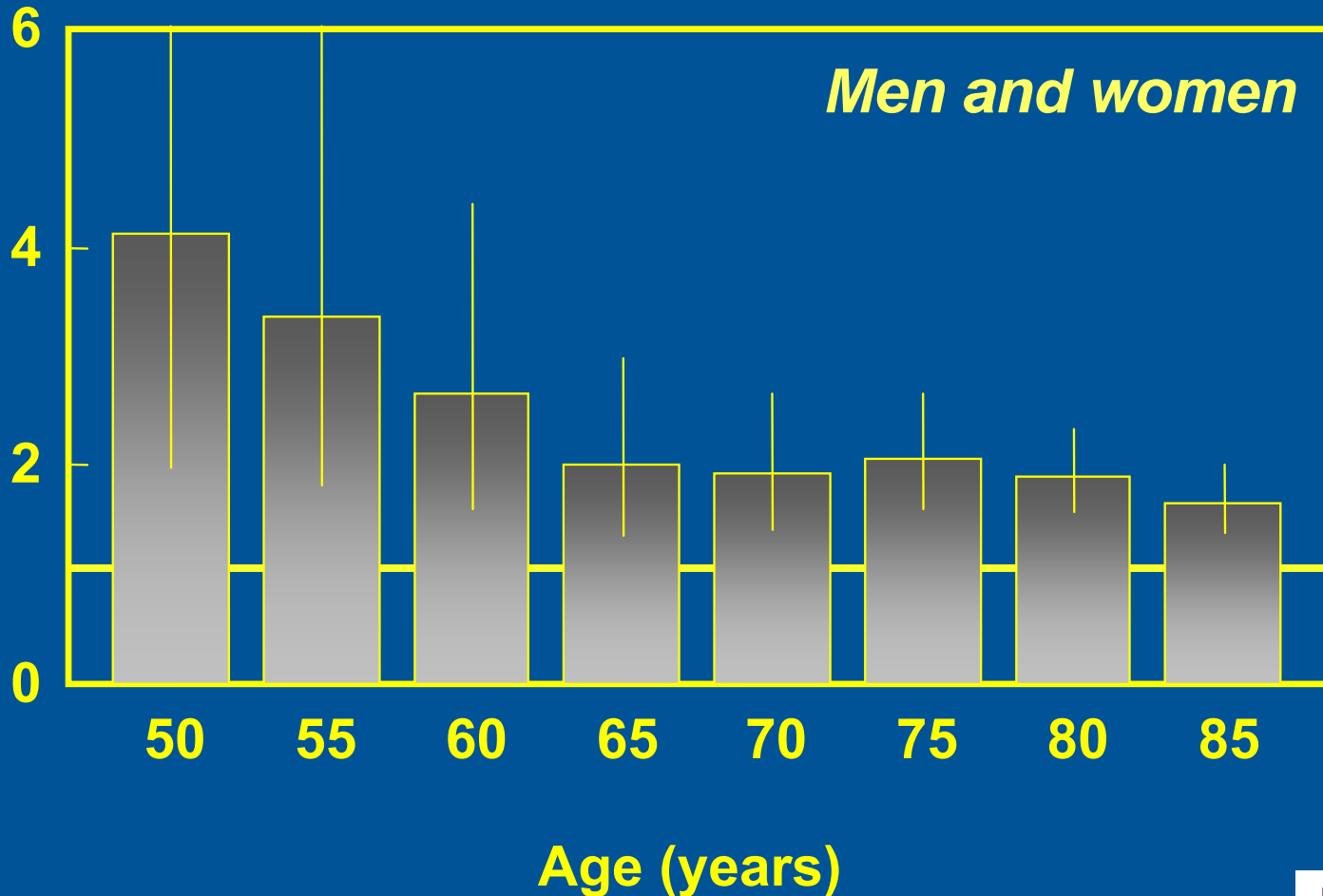
THIN = Health Improvement Network database

Kanis JA, et al. Osteoporos Int 2007;18:1033–46



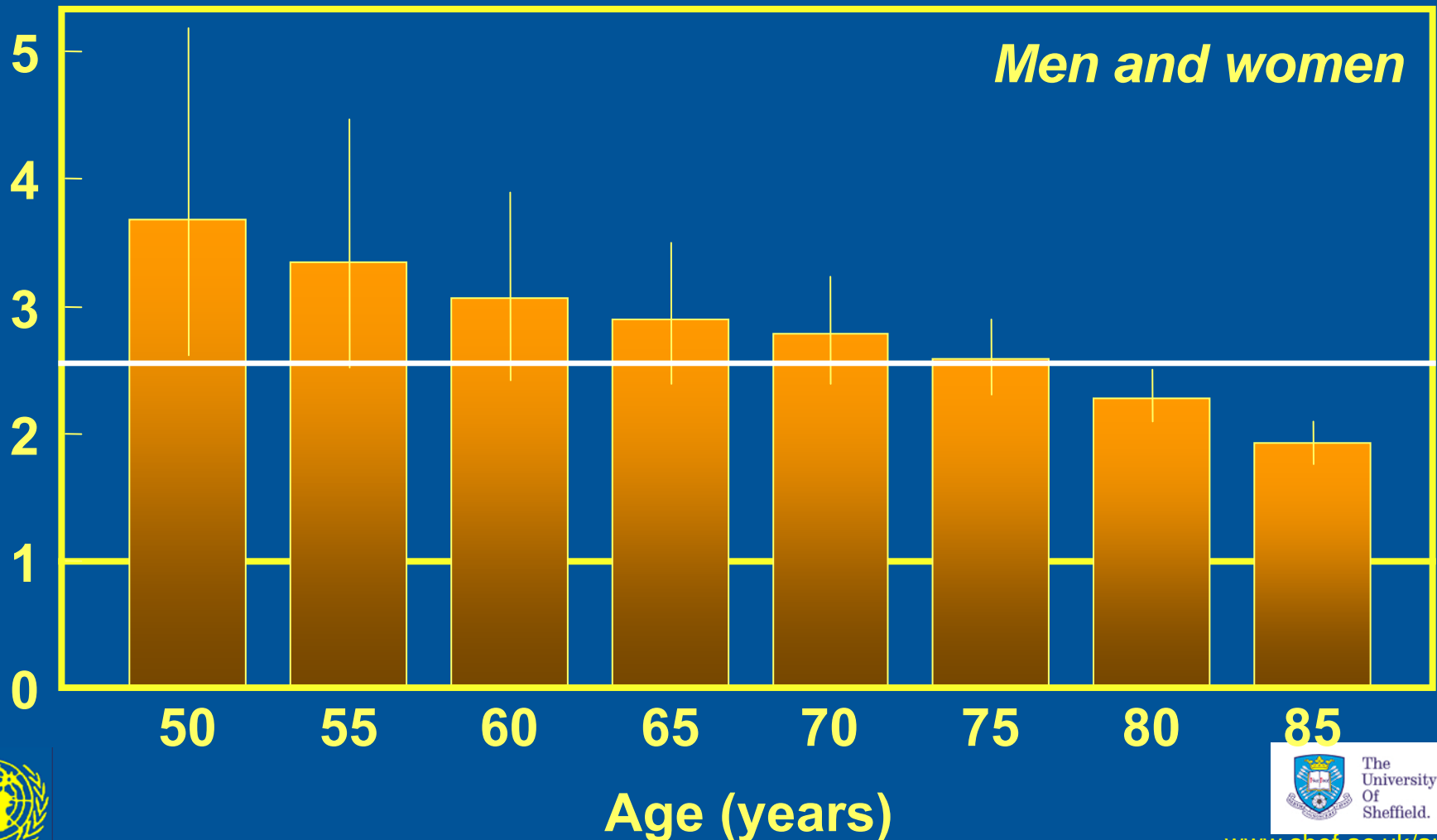
Prior fracture and hip fracture risk

RR



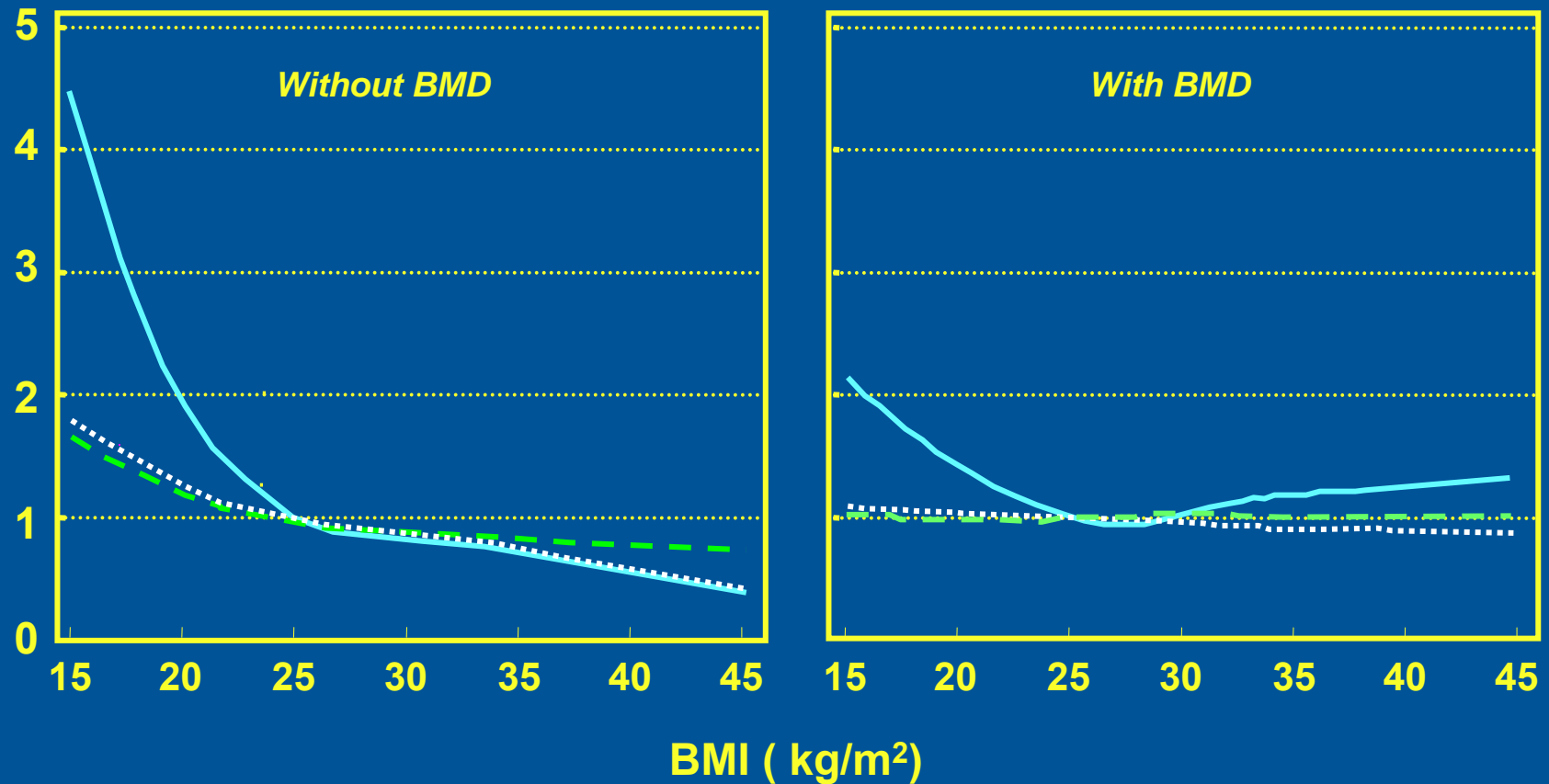
Femoral neck BMD and hip fracture prediction

RR/SD



BMI and fracture risk

RR (vs. BMI = 25)

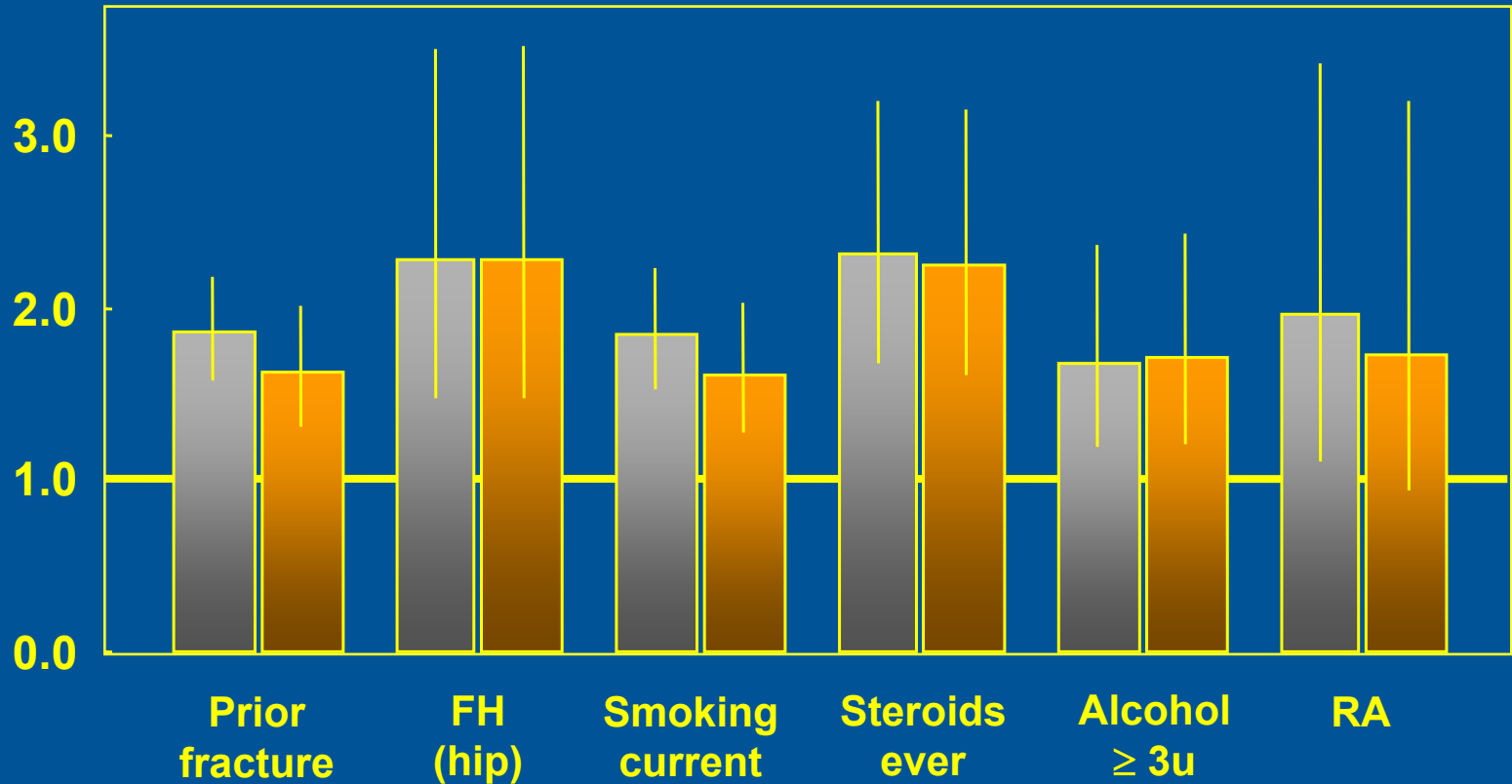


- Any fracture
- Osteoporotic fracture
- Hip fracture

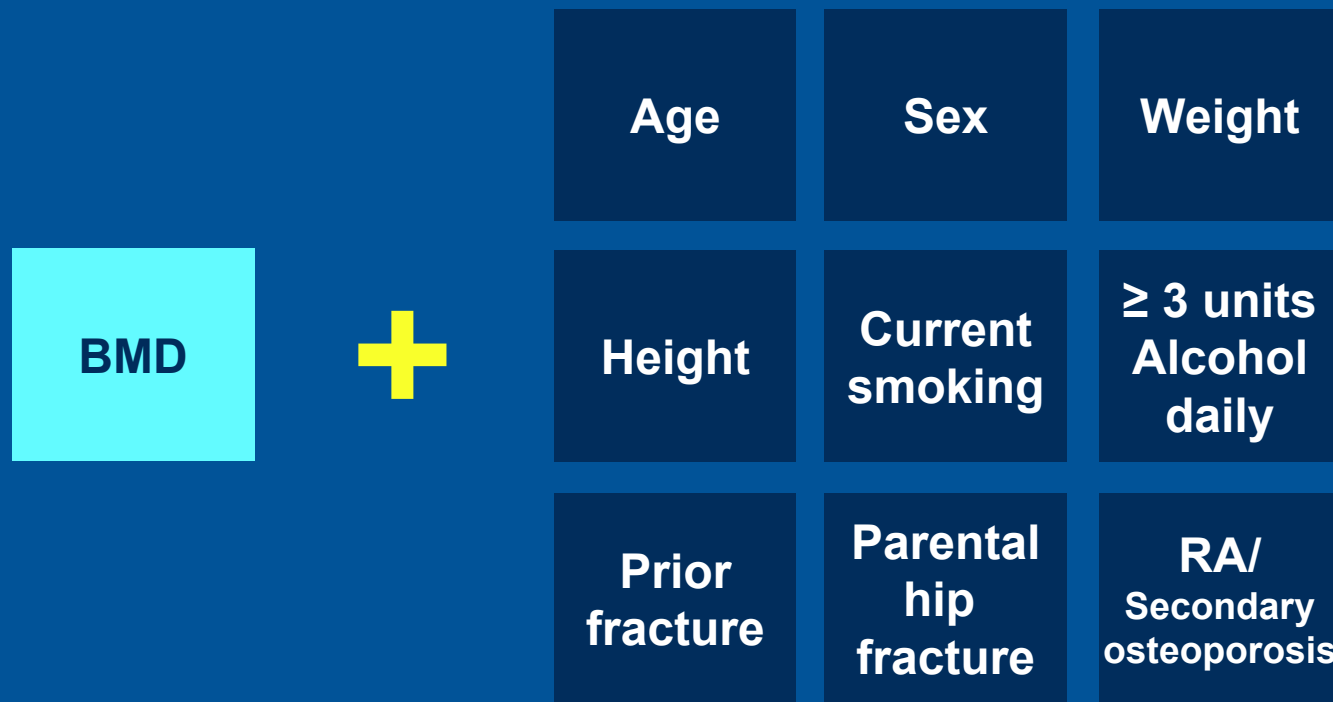


Risk factors for hip fracture in men and women

RR



BMD is one of a number of internationally-validated risk factors for fracture

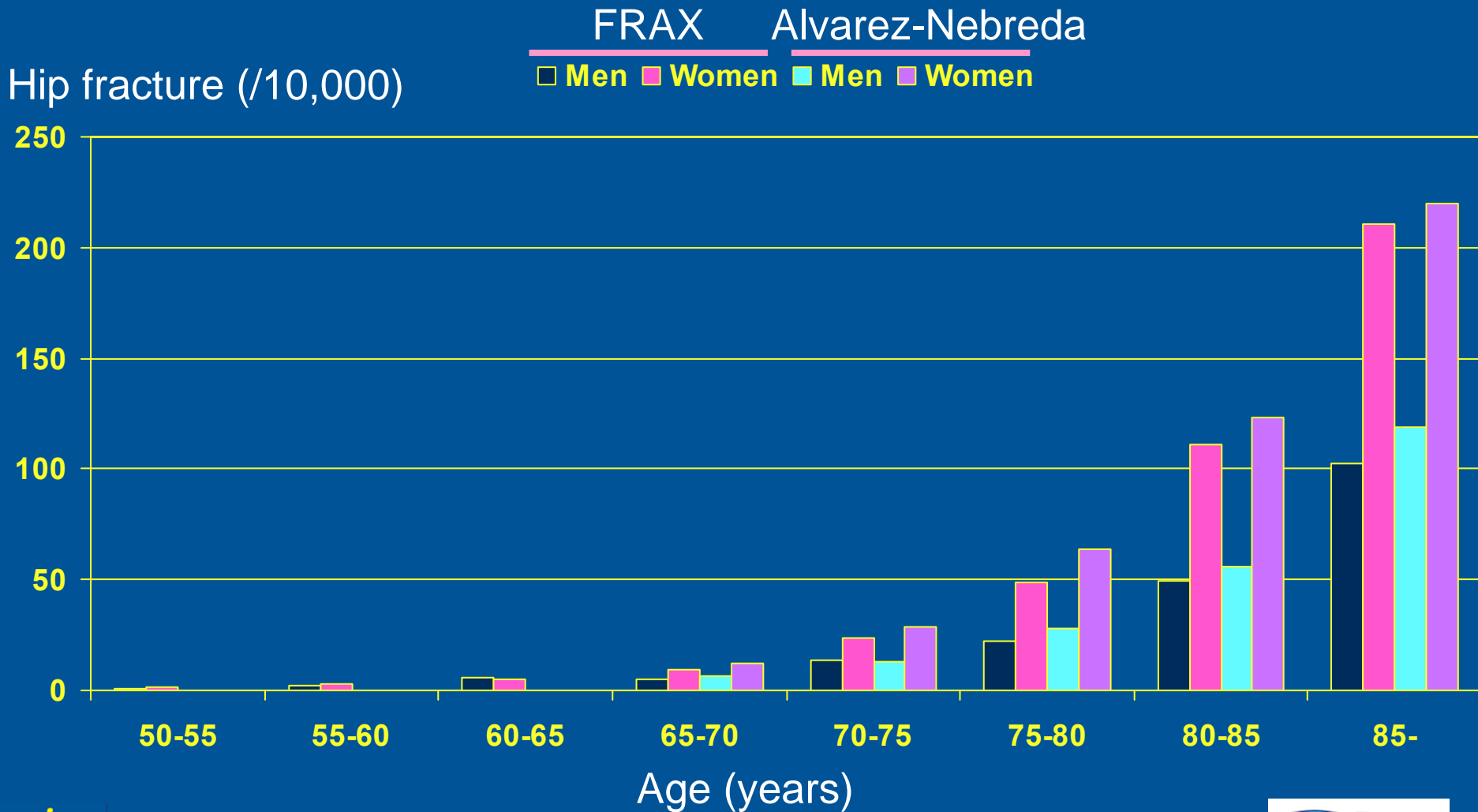


Epidemiology in Spain

- Risk of death from WHO population and mortality data from 1999 in Spain
- Risk of hip fracture is the mean value of:
 - Barcelona 1984, Canaries 1990, Seville/Madrid 1989, Zamora 1991 and Cantabria 2006
- Risk of major osteoporotic fracture is computed from the hip fracture incidence from Spain multiplied with the proportion from Sweden



FRAX data vs. Latest Spanish Data



Characteristics of FRAX[®]

Defines associations between clinical risk factors and fracture risk in multiple data sets world wide


Uses NHANES III femoral neck BMD as reference data in men and women

Provides probability of hip fracture and major osteoporotic fracture (clinical vertebral, hip, forearm, humerus)

Takes account of Nation-specific fracture rates, death rates, and the impact of the risk factors on both



FRAX Version 2.0





FRAX[®] WHO Fracture Risk Assessment Tool

HOME CALCULATION TOOL PAPER CHARTS FAQ REFERENCES Select a Language

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.



Country : UK **Name / ID :** [About the risk factors](#) 

Questionnaire:

1. Age (between 40-90 years) or Date of birth
Age: Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

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:
GE-Lunar
Hologic
Norland
T-Score

Weight Conversion:
pound:

Height Conversion:
inch:



Limitations of FRAX[®]

Does not accommodate all known risk factors

Falls, biochemical markers, QUS etc

Lacks detail on some risk factors

**Dose response effects of glucocorticoids,
smoking, prior fracture etc**

Depends on adequacy of epidemiological information

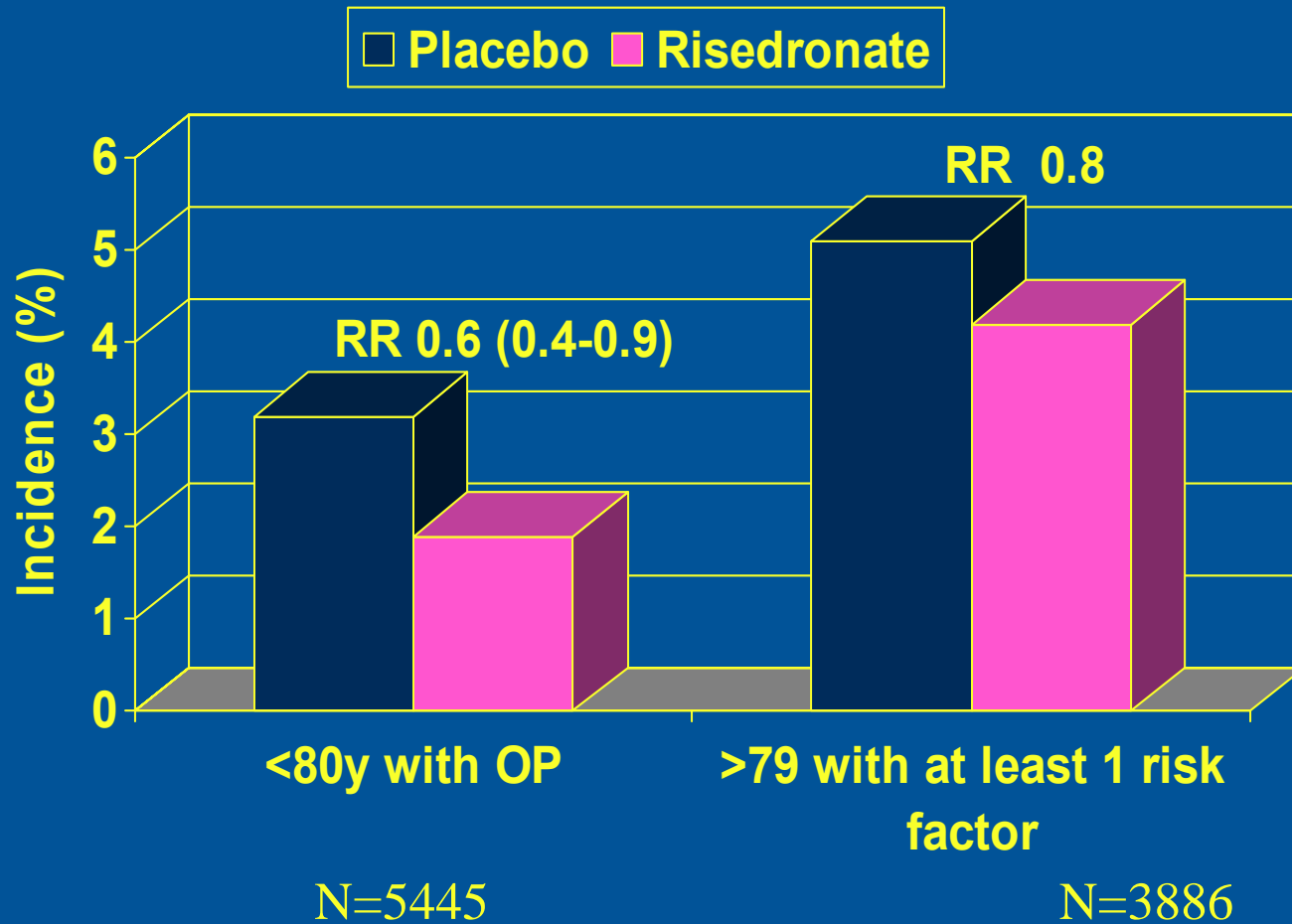
Limited country models available

Model relevant only for untreated patients

Does not replace clinical judgment



Hip Fracture Efficacy in Elderly Women



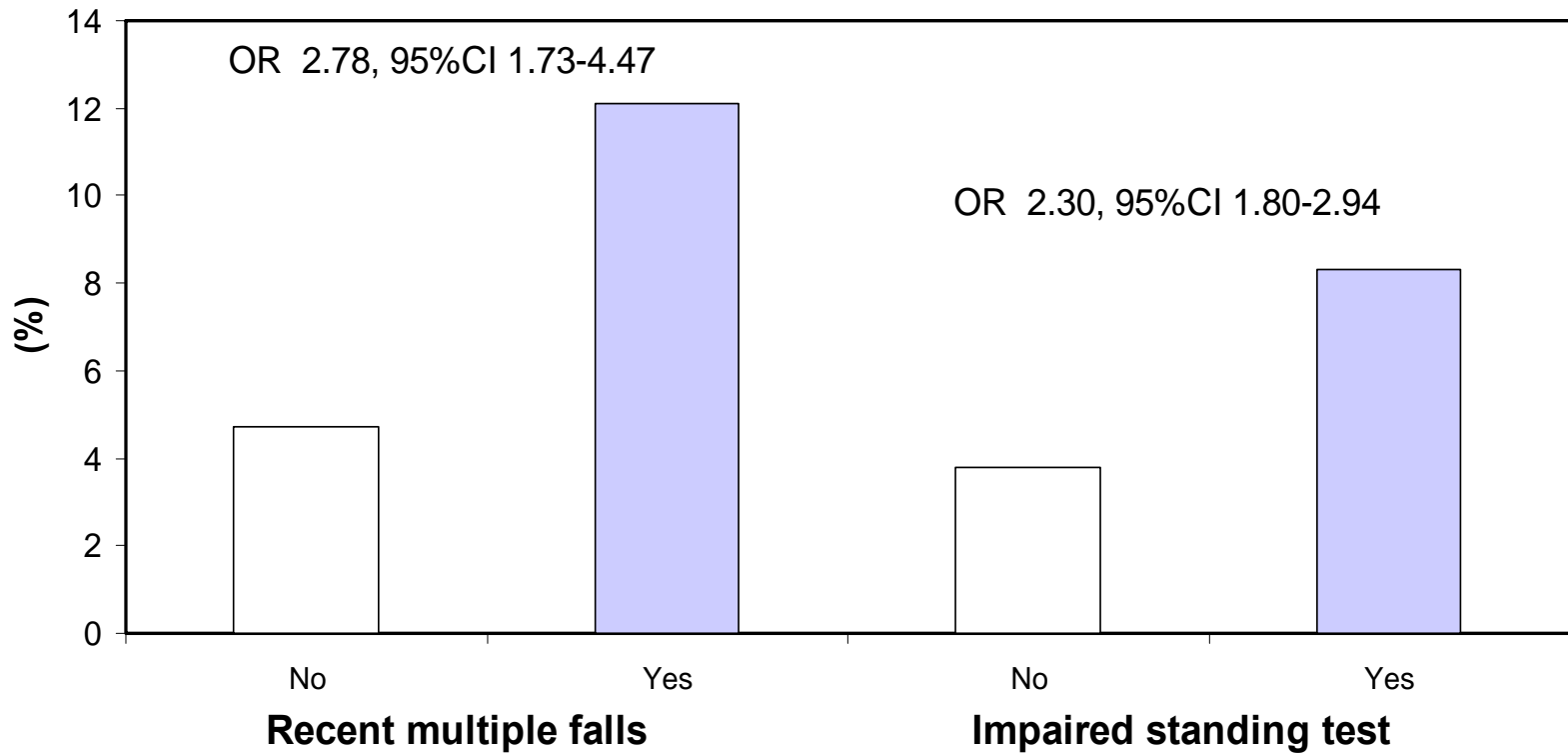
2.5mg, 5mg daily for 3 years

McClung et al NEJM 2001

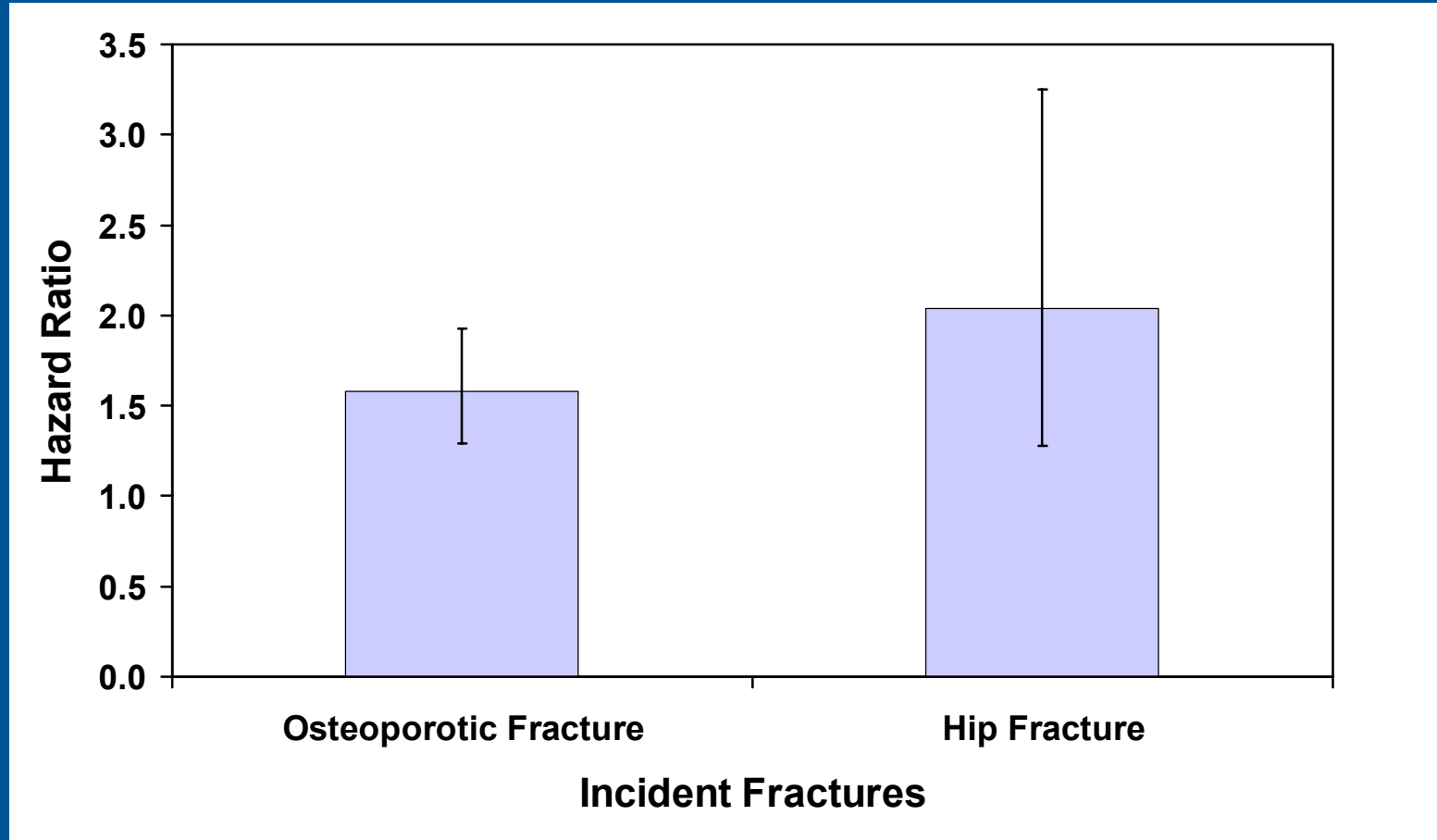


Predicting falls

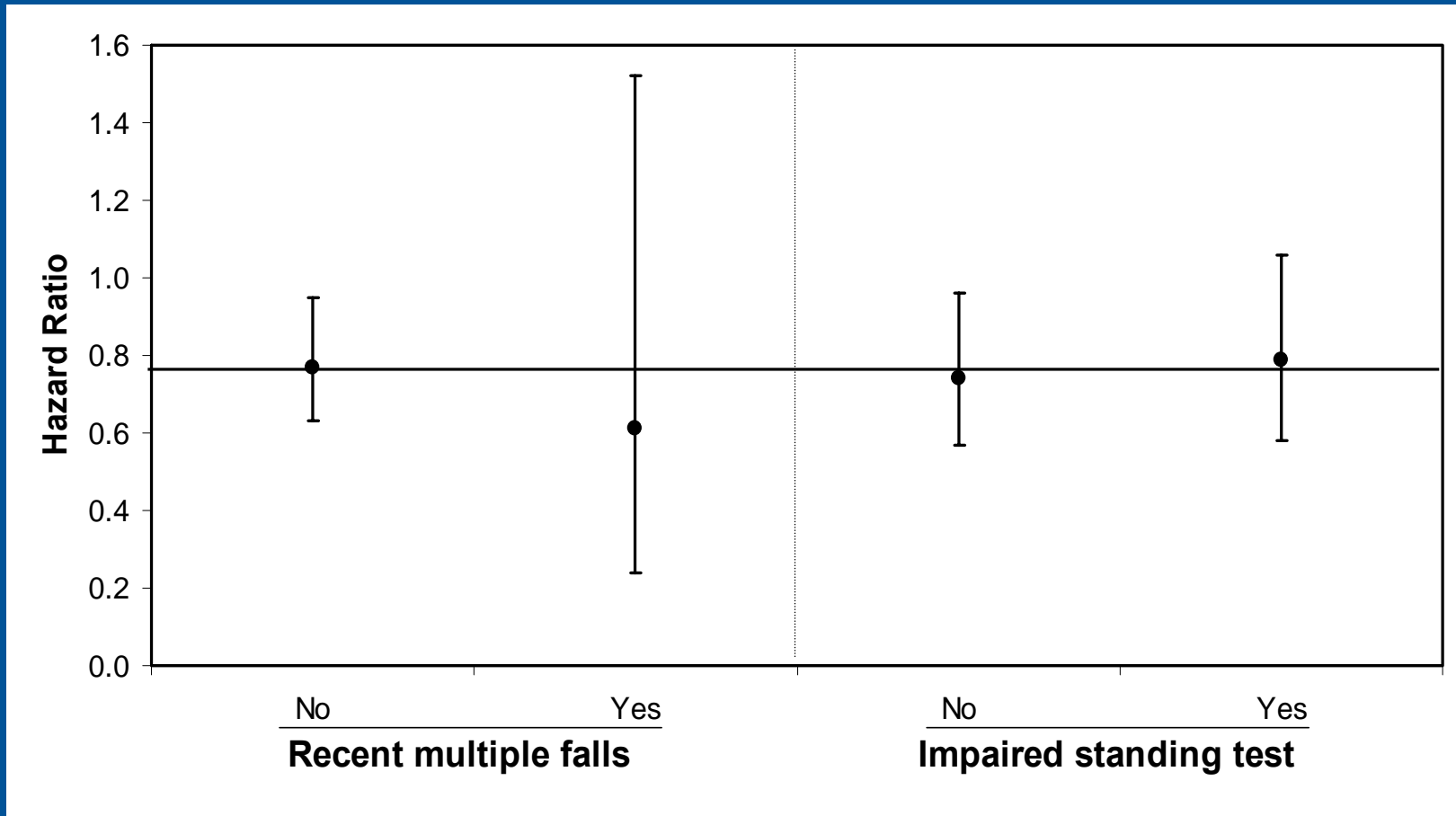
Incidence of serious falls (not associated with fracture)



Association between impaired ability to stand and future fracture risk

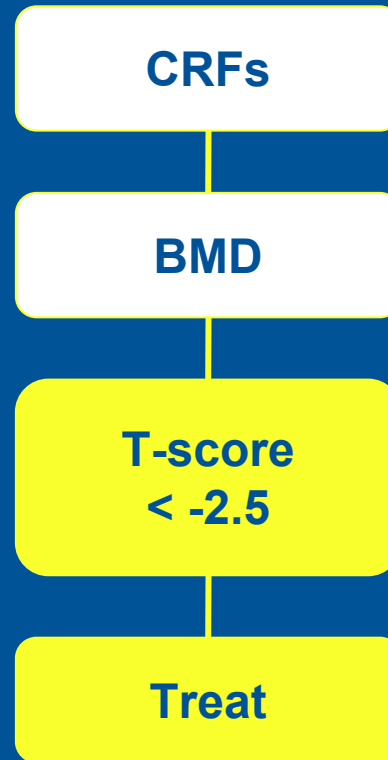


Interaction between falls or impaired ability to stand and the efficacy of clodronate on osteoporotic fracture

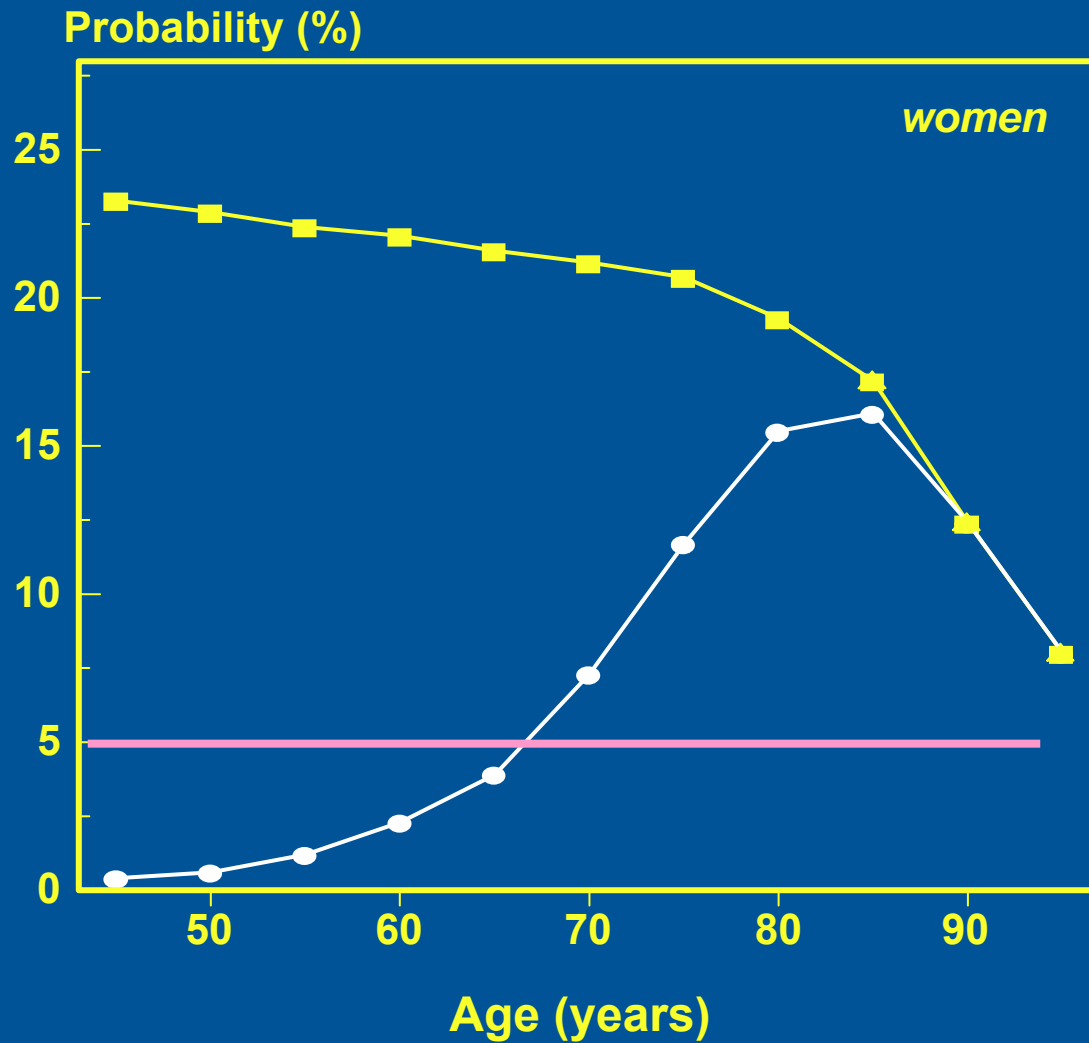


Case Finding Strategies

Royal College of Physicians 1999

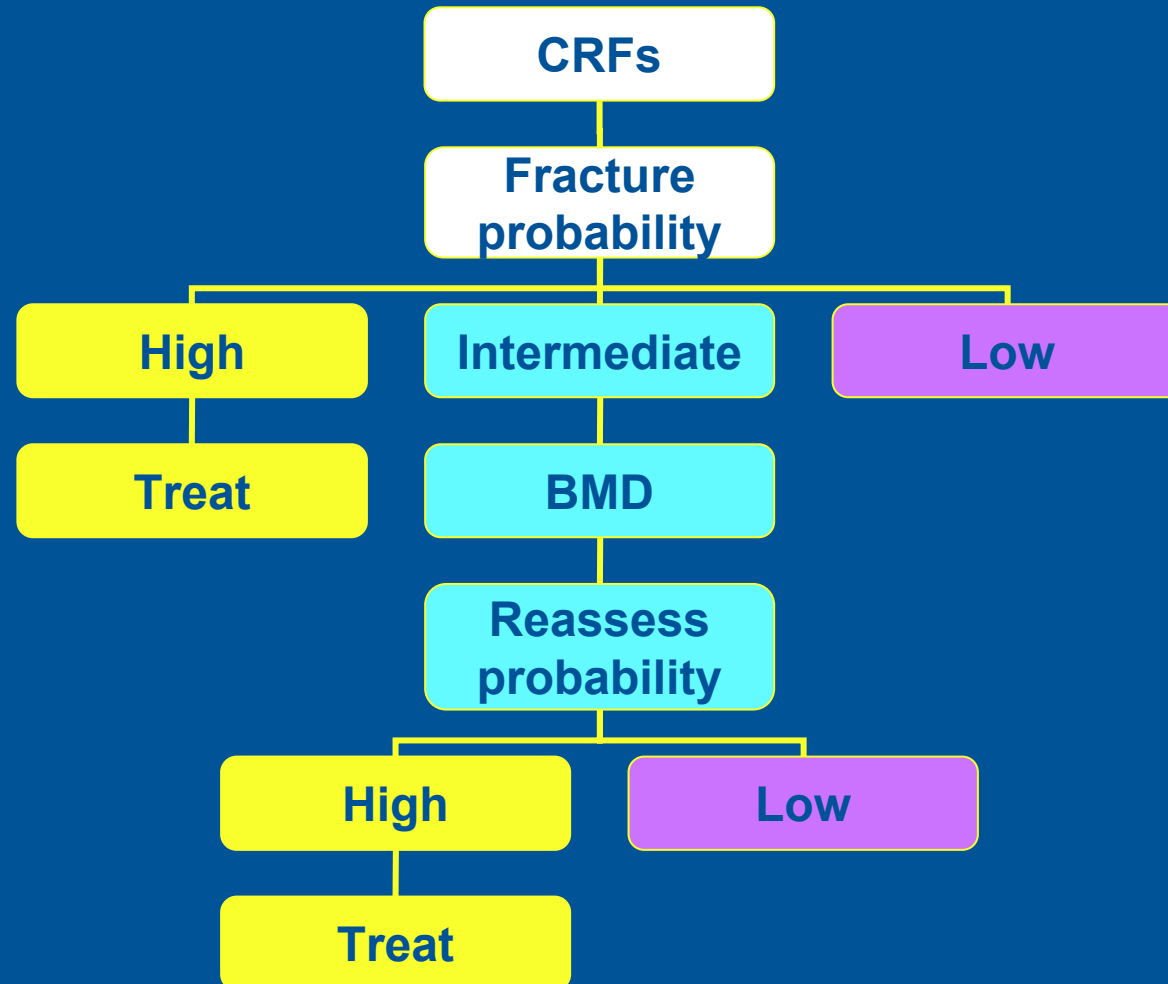


Intervention Thresholds



Case Finding Strategies

National Osteoporosis Guideline Group 2008



National Osteoporosis Guideline Group (NOGG)

Clinical guideline for prevention and treatment

www.shef.ac.uk/NOGG



Osteoporosis Dorset
registered charity no: 1023507



Royal College
of Physicians
Setting higher medical standards

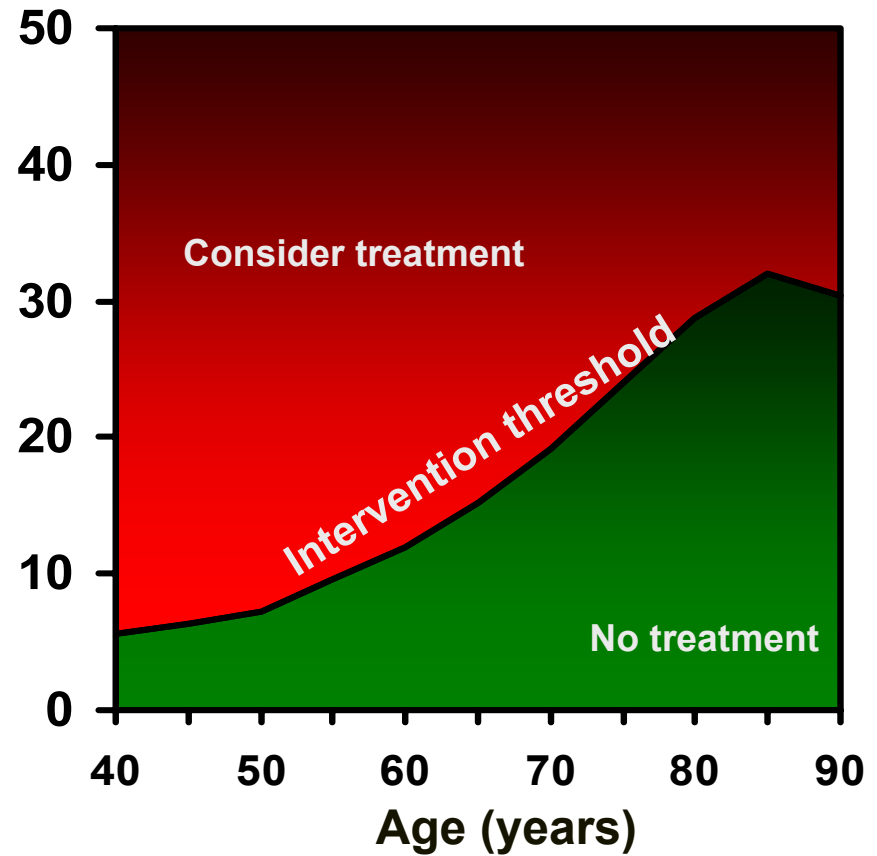
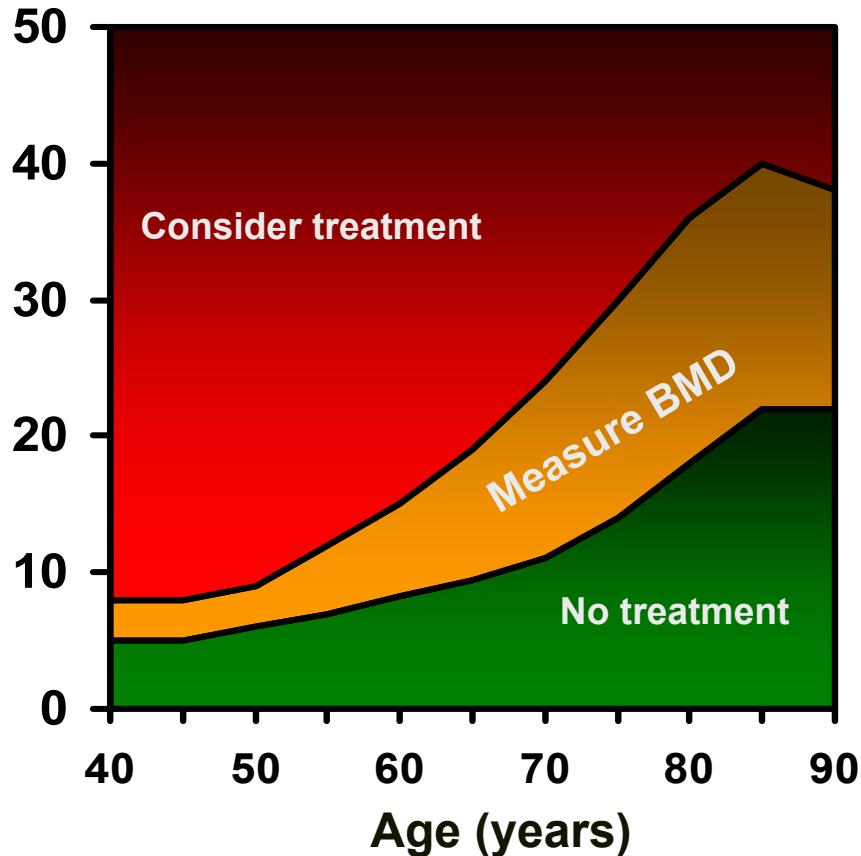


Society for
Endocrinology



Management Charts for Osteoporosis

10 year probability of major osteoporotic fracture (%)



www.shef.ac.uk/FRAX



Weight Conversion:

pound:

[convert](#)

Height Conversion:

inch:

[convert](#)

Country : **UK** Name / ID : [About the risk factors](#)

Questionnaire:

1. Age (between 40-90 years) or Date of birth
Age: Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

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 more units per day No Yes

12. Femoral neck BMD

BMI 23.9

The ten year probability of fracture (%)

without BMD

■ Major osteoporotic	9.6
■ Hip fracture	1.5



NOGG guideline: main recommendations

- Generic alendronate is the first line treatment option in the majority of cases
- In individuals unable to tolerate alendronate or in whom it is contraindicated, other bisphosphonates, strontium ranelate or raloxifene may provide appropriate options
- The use of parathyroid hormone peptides is generally restricted to those at very high risk, particularly for vertebral fractures



www.shef.ac.uk/FRAX



Weight Conversion:

pound:

[convert](#)

Height Conversion:

inch:

[convert](#)

Country : **UK** Name / ID : [About the risk factors](#)

Questionnaire:

1. Age (between 40-90 years) or Date of birth
Age: Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg)

4. Height (cm)

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 more units per day No Yes

12. Femoral neck BMD
 Select

BMI 23.9

The ten year probability of fracture (%)

without BMD

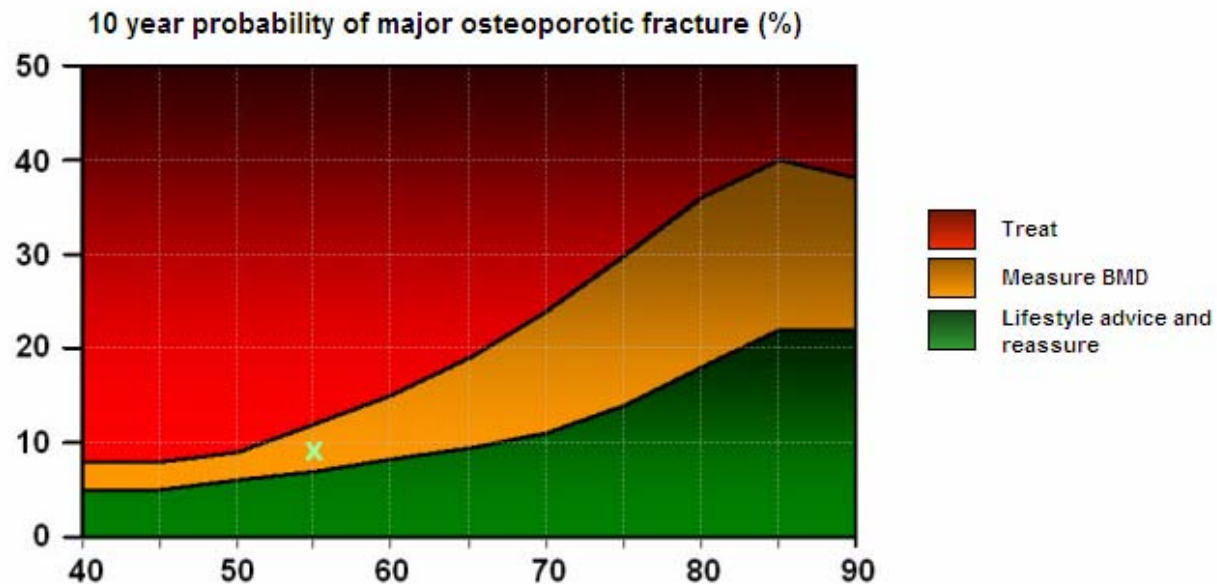
Major osteoporotic	9.6
Hip fracture	1.5



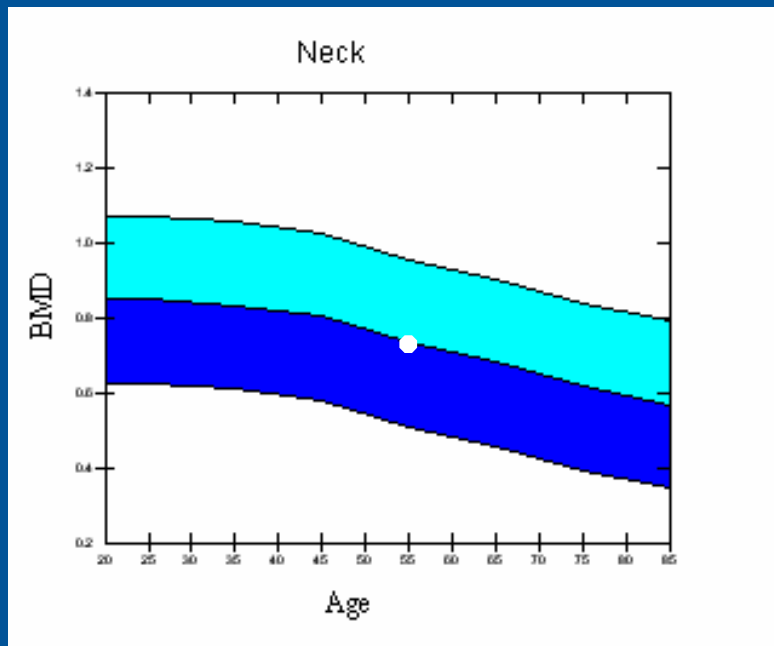
Graphs

[Back to FRAX Home](#) [Back to NOGG Home](#) [Manual Data Entry](#) [FAQ](#) [Download Documents](#)

Assessment threshold - Major fracture



Femoral Neck BMD Scan



BMI 23.9

The ten year probability of fracture (%)



with BMD

Major osteoporotic	8.3
--------------------	-----

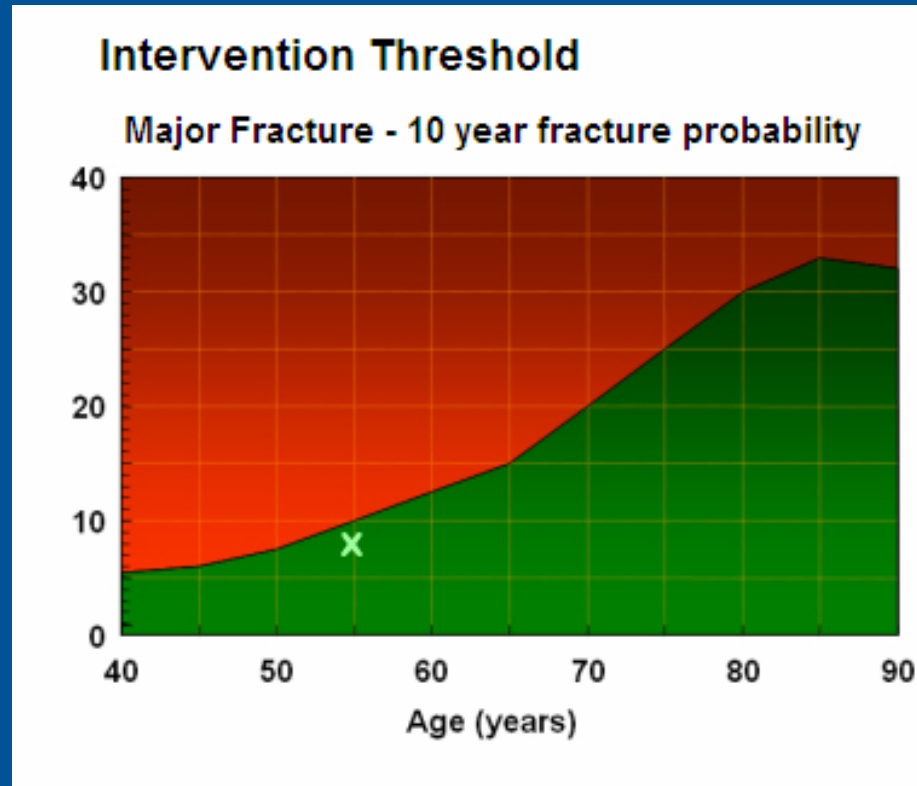
Hip fracture	0.7
--------------	-----

[View NOGG Guidance](#)

T-score = -1.1



Reassess risk and view NOGG advice



T-score = -1.1



Fragility fracture

No fragility fracture

**Postmenopausal women
≥ 75yrs**

**Postmenopausal women
< 75yrs
Or Man >50 yrs**

**Postmenopausal women and men
>50 yrs with ≥ 1CRF**

FRAX® ± BMD

Exclude secondary causes

Treat with alendronate

If not tolerated

**Other bisphosphonates or
strontium ranelate or
raloxifene**

**Ca and vit D supplements
Falls assessment/Rx
Lifestyle advice**

**High fracture
probability**

**Low fracture
probability**

**Reassure
Lifestyle advice**



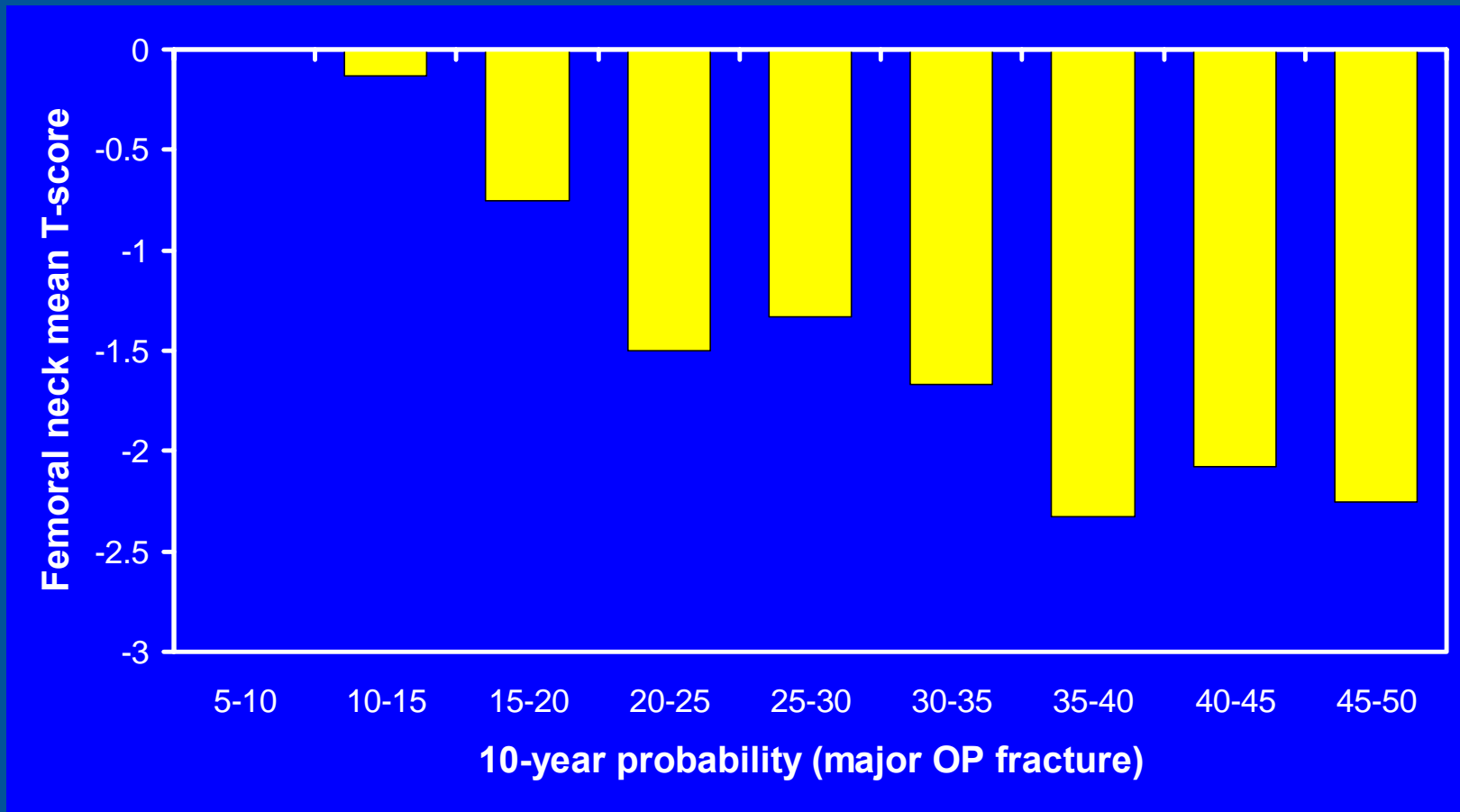
Categorization of risk factors for fracture according to evidence for reversible risk

Grade	Description	Risk factor
A	Validated by use as inclusion criteria in randomized controlled trials	Low BMD (DXA spine or hip) Prior vertebral fracture Long-term glucocorticosteroid treatment Age Postmenopausal status
B	Do not adversely affect fracture outcomes in randomized controlled trials	Low BMD (DXA spine or hip) Family history of fracture Prior non-vertebral fracture Prior vertebral fracture Biochemical markers of bone turnover QUS (at the heel) Smoking Body weight or BMI Age Alcohol intake
C	Untested	Other risk factors
D	Adversely affect intervention outcomes	Risk factors for falling

BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; QUS, quantitative ultrasound; BMI, body mass index.



Fracture probability and BMD*



*In 80 years-old women in Sheffield

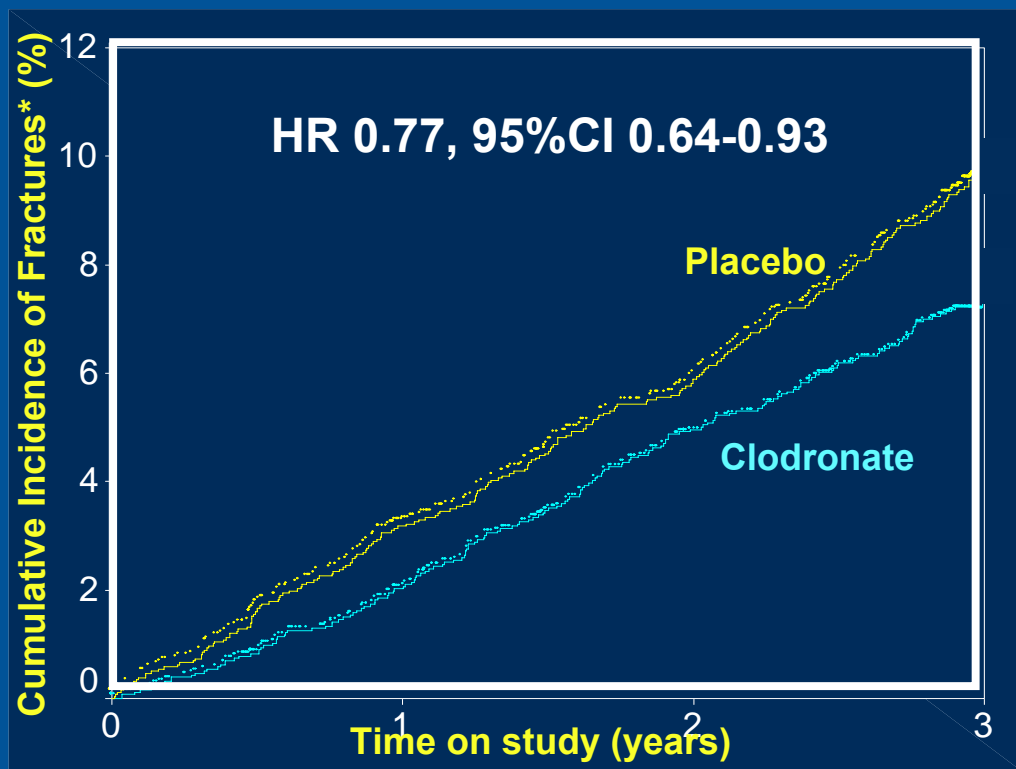


MRC Clodronate Study

Background

- **Aim**

- To determine if patients identified at high risk by the algorithm are responsive to anti-resorptive treatment



- Randomized, double-blind, placebo controlled trial over 3 years
- Women aged at least 75 years unselected for osteoporosis or low BMD
- Clodronate (Bonafos®) 800mg/day or Placebo
- Fractures ascertained at 6-monthly visits and confirmed against source documents or radiographs

* Excludes fractures of the hands, feet, ankle and skull

McCloskey et al, JBMR 2007



Baseline Variables

WHO Fracture Probability Model

- Age
- Sex
- Femoral neck BMD
- Previous fragility fracture after age 50
- Body mass index
- Ever use of glucocorticoids
- Secondary osteoporosis (e.g., rheumatoid arthritis)
- Parental history of hip fracture (Paternal)
- Current cigarette smoking
- Alcohol intake 3 or more units/day



Data not captured at entry



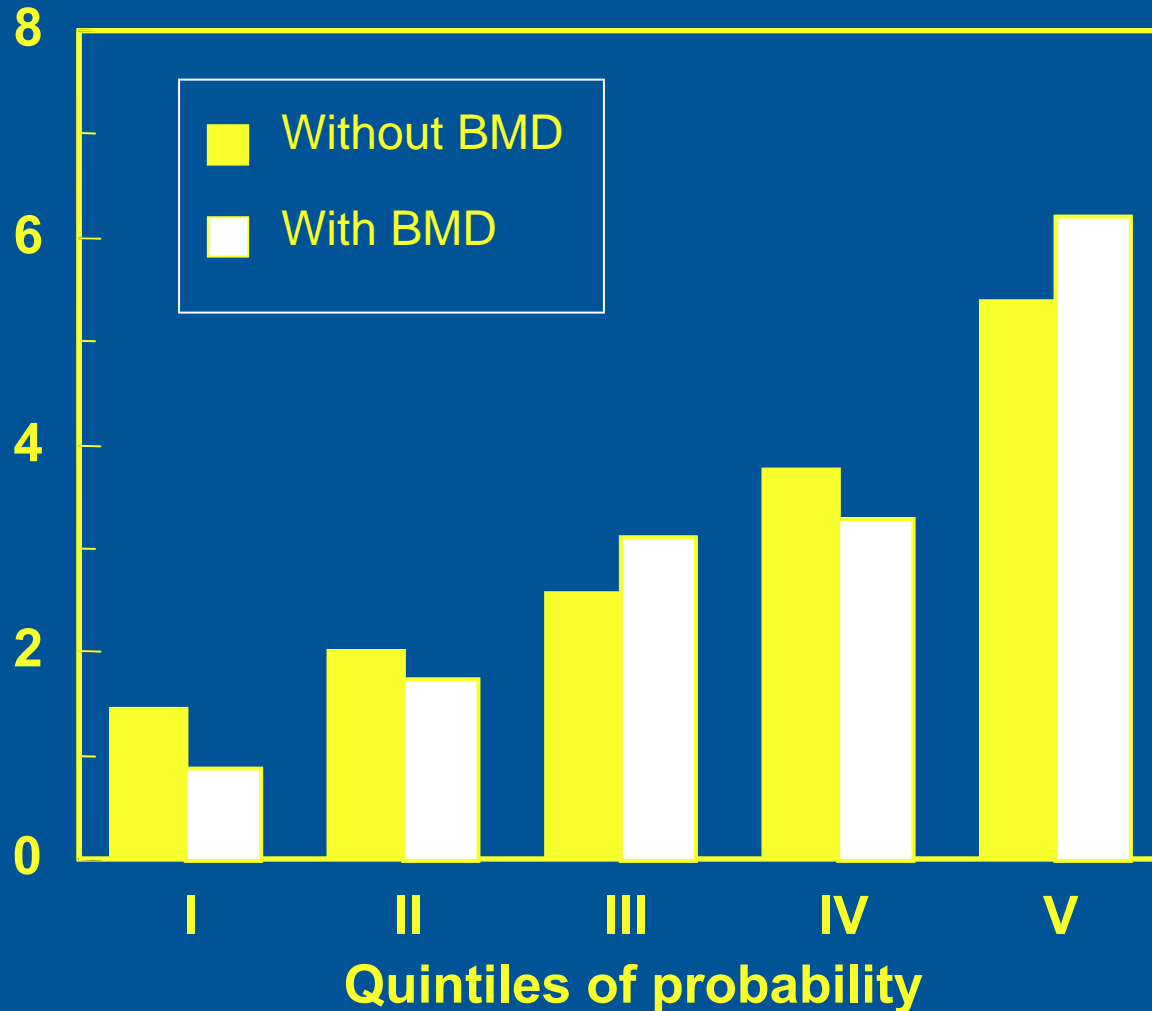
www.shef.ac.uk/aubm

Baseline Characteristics

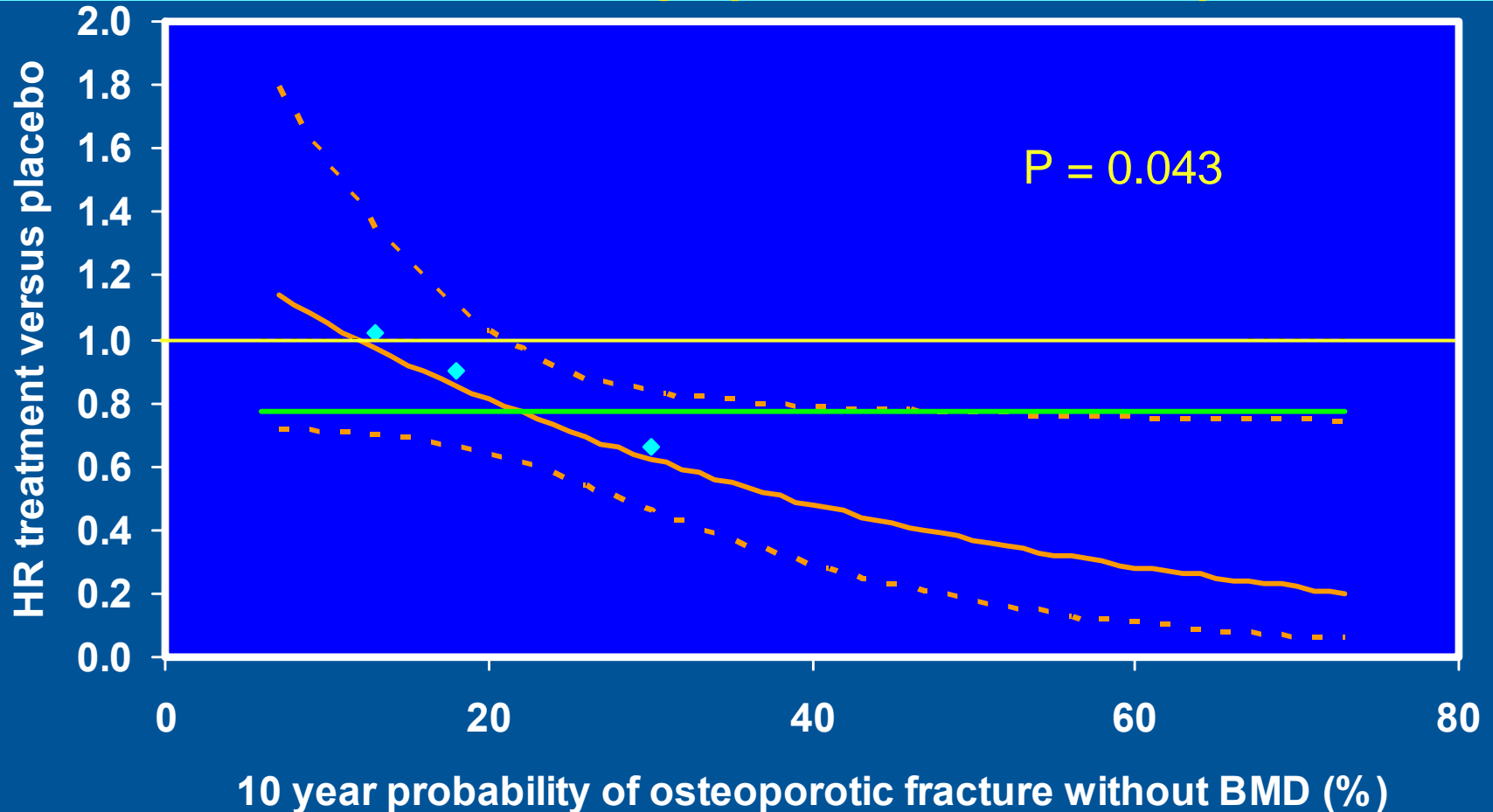
	Clodronate (N=2016)	Placebo (N=1958)
Age (years)	79.8±3.7	79.7±3.7
BMI (kg/m ²)	26.8±4.4	27.0±4.7
Femoral Neck BMD (g/cm ²)	0.65±0.12	0.65±0.12
Femoral neck BMD T-score	-1.74±0.98	-1.72±0.99
Previous fracture (%)	22	24
Family history (%)	5	6
Current smoking (%)	6	6
Corticosteroids (%)	9	10
RA (%)	2	2



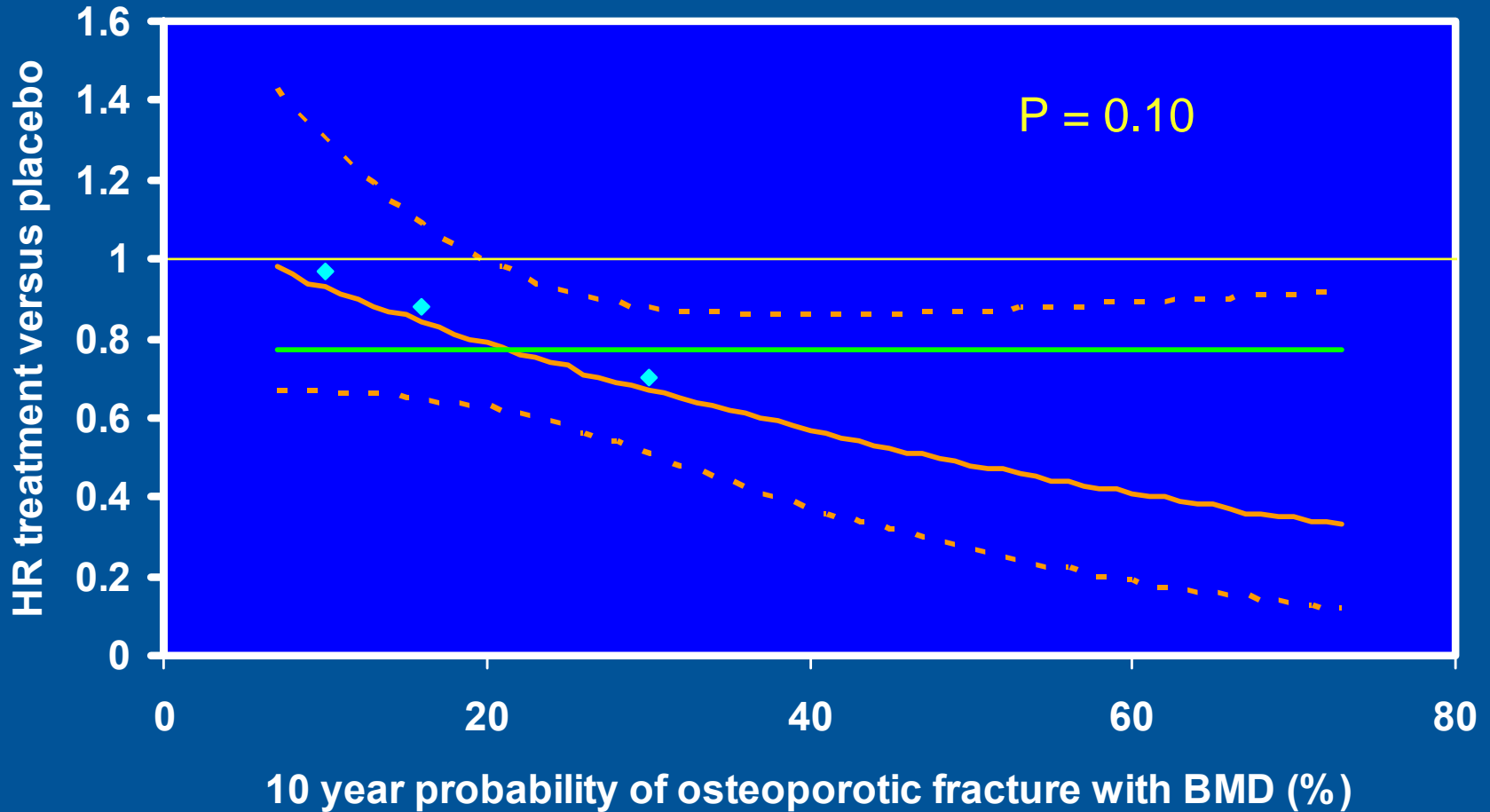
Incidence of osteoporotic fracture and estimated 10-year probability



Interaction between treatment and fracture probability (without BMD)



Interaction between treatment and fracture probability (with BMD)



Bazedoxifene and anti-fracture efficacy

- **Bazedoxifene (BZA)**
 - a novel selective estrogen receptor modulator
 - bone-sparing effects without endometrial or breast stimulation in postmenopausal women
- **Anti-fracture efficacy – Vertebral fracture (primary outcome)**
 - 3-year phase III trial, treatment with bazedoxifene 20mg reduced the risk by 42% relative to placebo in postmenopausal women with osteoporosis.
- **Anti-fracture efficacy – Non-vertebral fracture**
 - in a subsequent post hoc analysis of a subgroup of patients at high risk, bazedoxifene treatment was associated with a significant decrease in non-vertebral fracture.



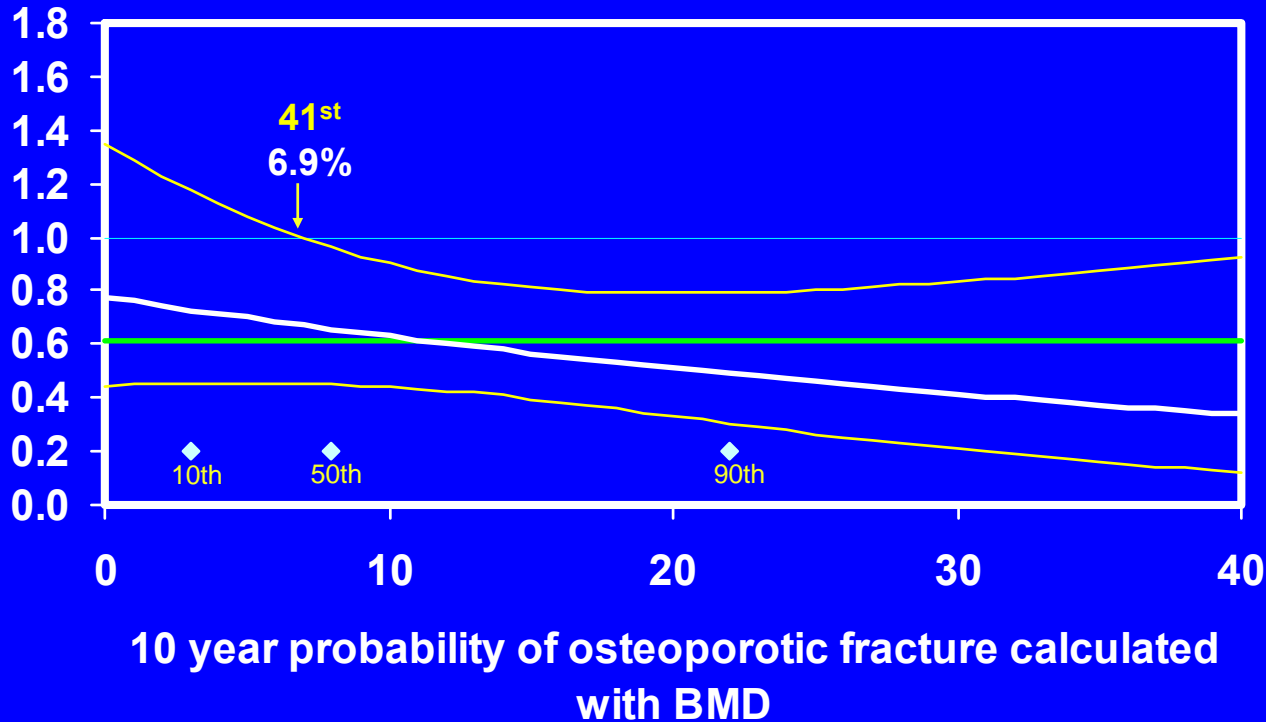
Overall Efficacy

- **Bazedoxifene significantly decreased incident morphometric vertebral fractures by 39%**
 - (HR = 0.61; 95% CI = 0.43-0.86; p = 0.005).
- **Bazedoxifene was associated with a 16% decrease in all clinical fractures**
 - (HR = 0.84; 95% CI = 0.67-1.06; p = 0.14)



Results – Morphometric Vertebral Fractures

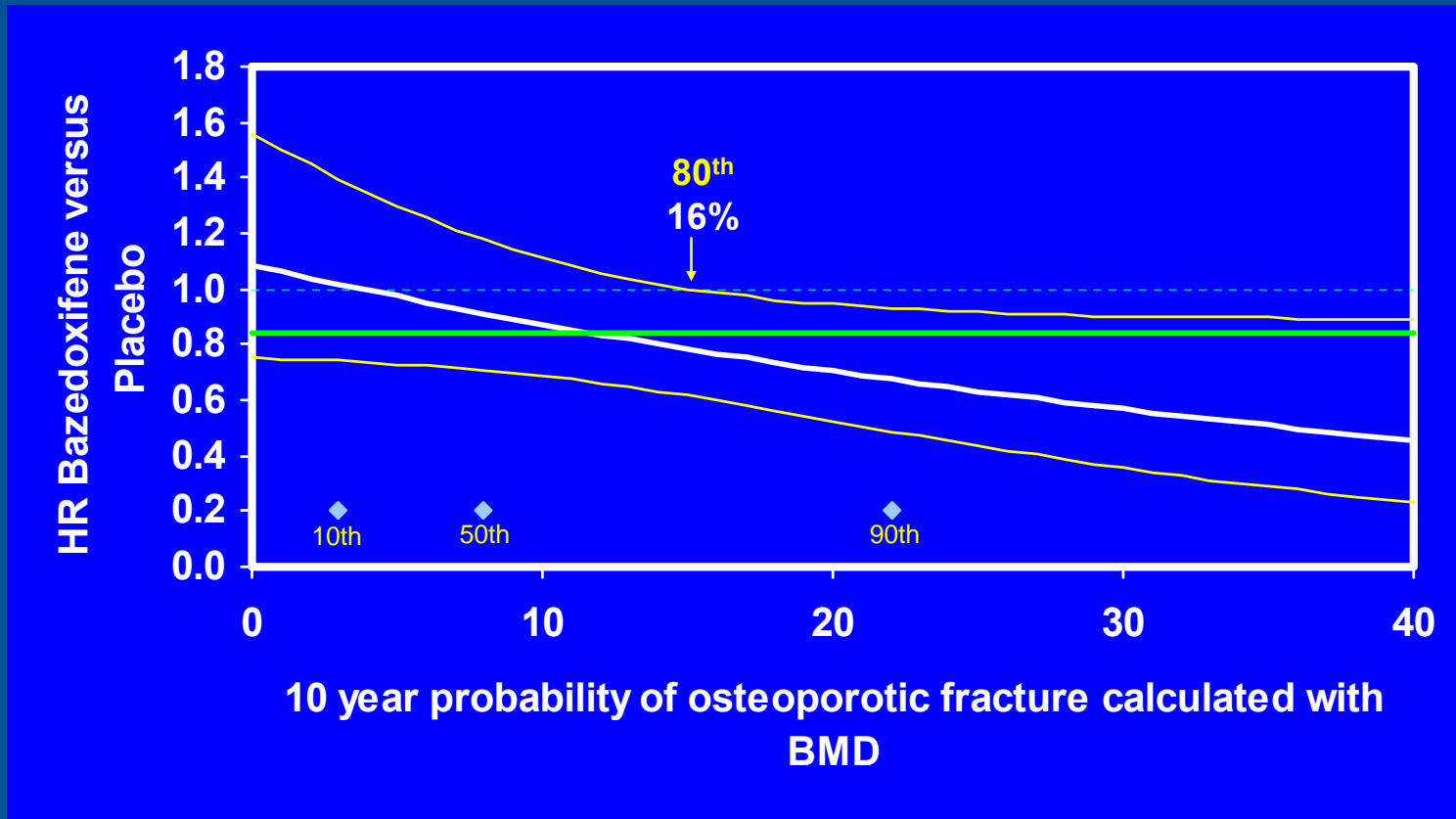
HR Bazedoxifene versus
Placebo



Overall effect



Results – All Clinical Fractures



Overall effect



Efficacy of Bazodoxifene at higher probabilities

Percentile	Morphometric vertebral fractures			Clinical fractures		
	Probability (%)	HR	95% CI	Probability (%)	HR	95% CI
10 th	2.8	0.73	0.45-1.18	2.8	1.02	0.74-1.40
25 th	4.5	0.71	0.45-1.10	4.5	0.98	0.73-1.32
50 th	8.2	0.65	0.45-0.95	8.3	0.91	0.71-1.17
75 th	14.0	0.58	0.41-0.82	14.5	0.80	0.63-1.02
90 th	21.7	0.49	0.31-0.79	22.4	0.68	0.49-0.93



Summary

- **The use of FRAX provides management algorithms for osteoporosis based on estimation of fracture probabilities, rather than BMD alone.**
- **Case-finding to target treatment is a very cost-effective strategy for management of osteoporosis**
- **Management strategies including intervention thresholds will need to be developed within each health care setting.**





The
University
Of
Sheffield.

www.shef.ac.uk/aubm