Osteoporosis: recent advances in risk assessment and management

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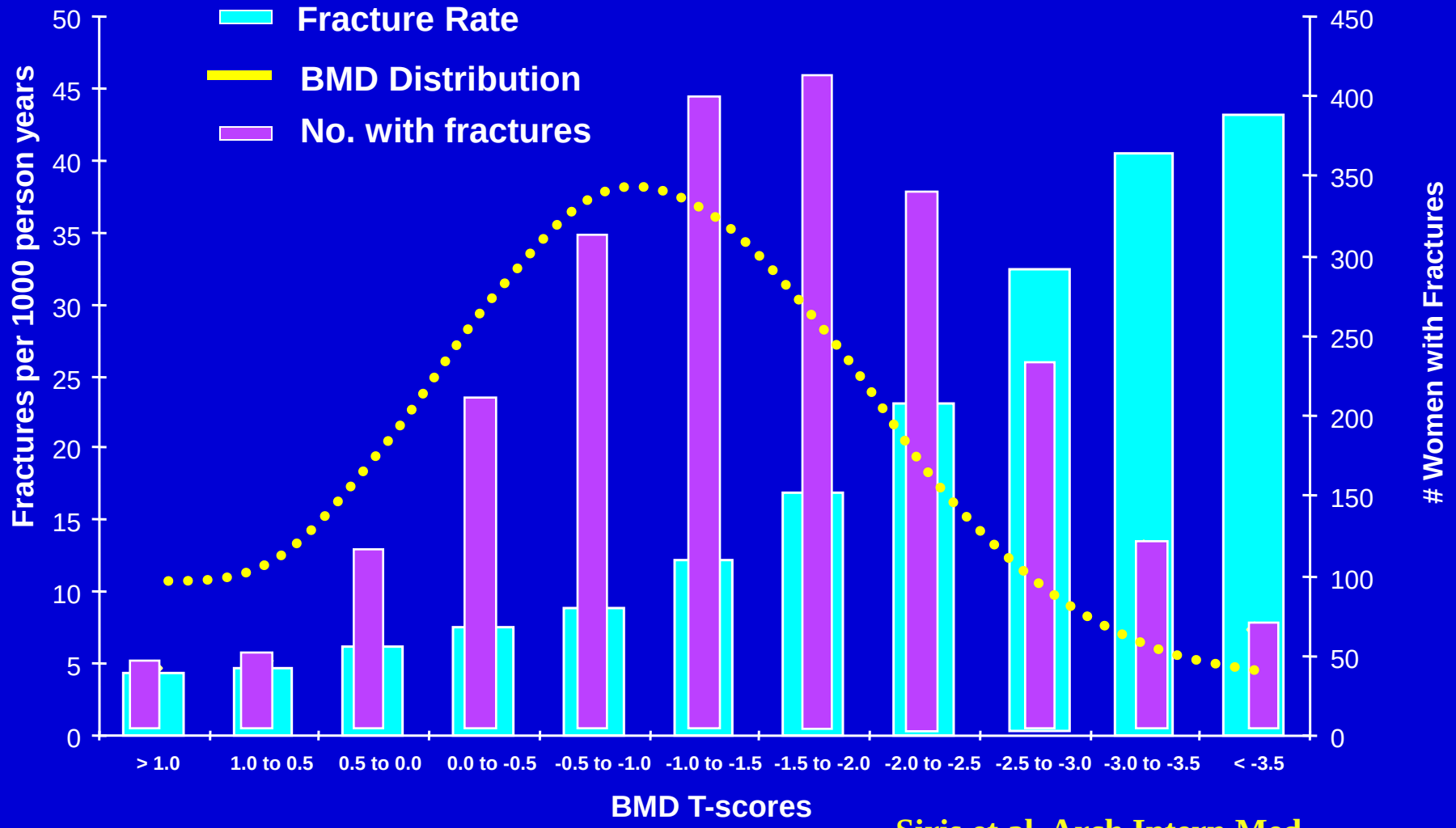
Diagnosis of osteoporosis: measurement of bone mineral density by dual energy X-ray absorptiometry (DXA)

- High specificity but low sensitivity for predicting fracture
- Over 50% of fractures in postmenopausal women occur at T-scores above -2.5
- Prediction of fracture risk improved by addition of clinical risk factors that act independently of BMD

Fracture rates, population BMD distribution and number of women with fractures



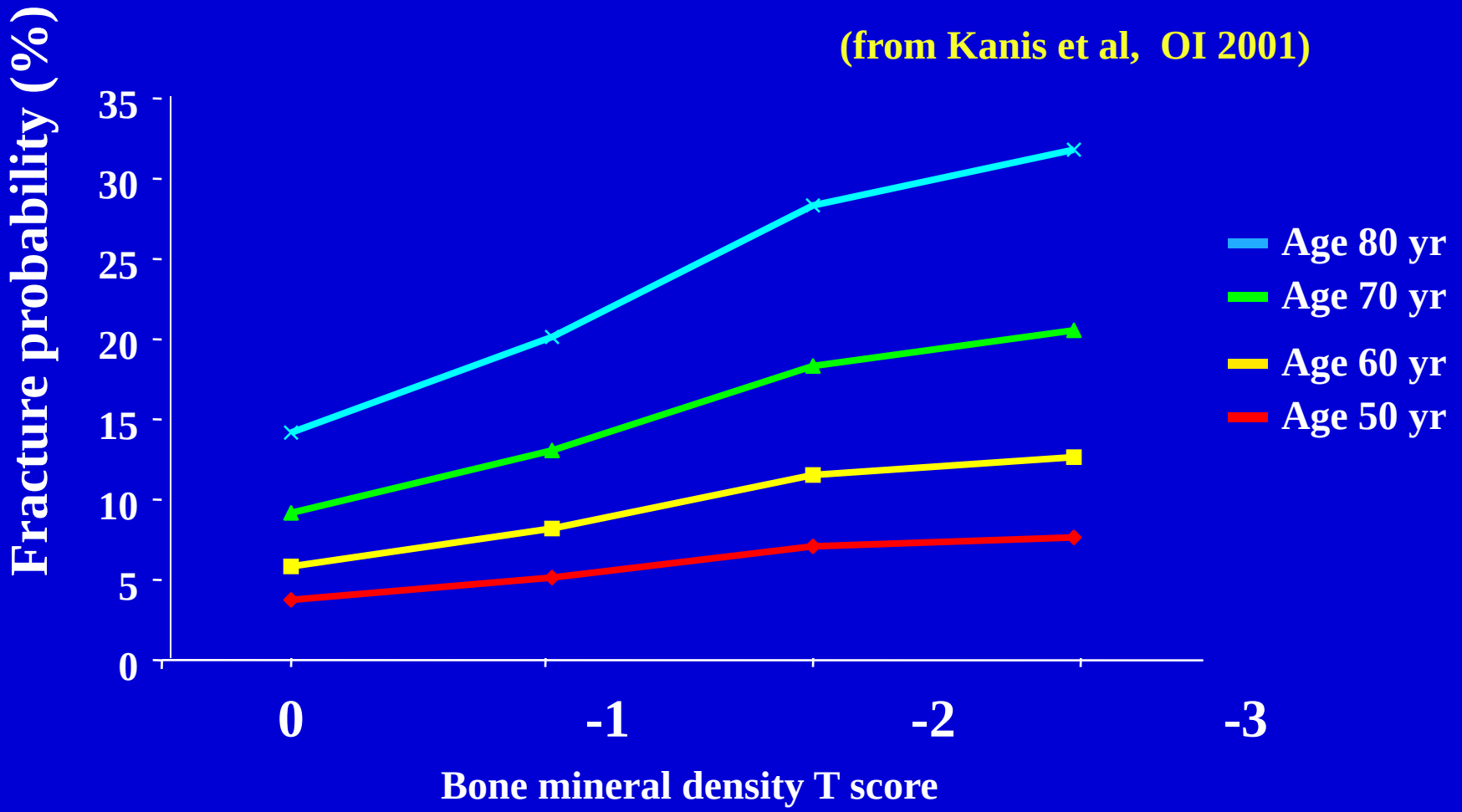
Siris et al, Arch Intern Med 2004,164:1108

Clinical risk factors that are partially independent of BMD

- Prior fragility fracture
- Increased age
- Low BMI
- Family history of fracture
- Glucocorticoid therapy
- Smoking
- Alcohol abuse
- Some forms of secondary osteoporosis
- Falls

Effect of age on 10-year fracture probability according to BMD T score in women

(from Kanis et al, OI 2001)



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: 55 Date of birth: Y: M: D:

2. Sex Male Female

3. Weight (kg) 65

4. Height (cm) 165

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

Clear Calculate

BMI 23.9

The ten year probability of fracture (%)

without BMD

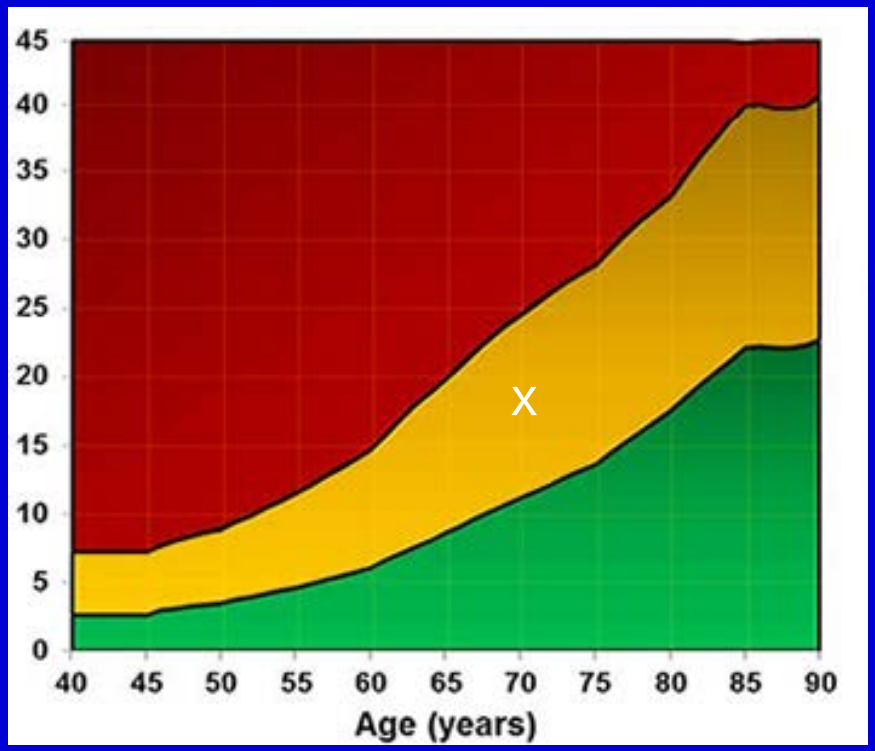
Major osteoporotic	9.6
Hip fracture	1.5

View NOGG Guidance

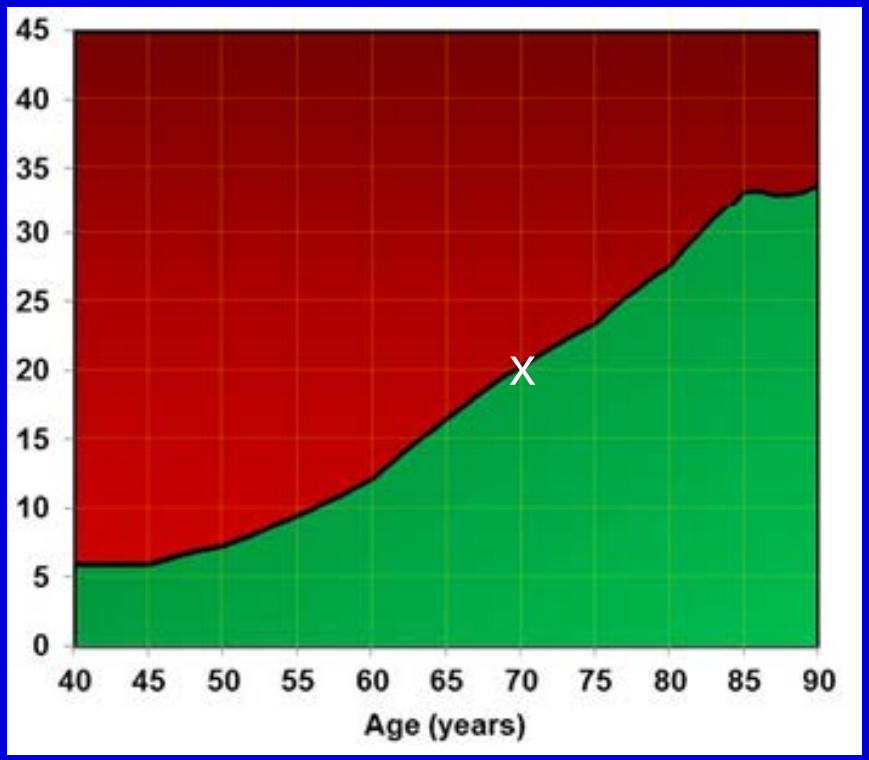
NOGG intervention thresholds

10 yr major osteoporotic fracture probability

FRAX - BMD



FRAX + BMD

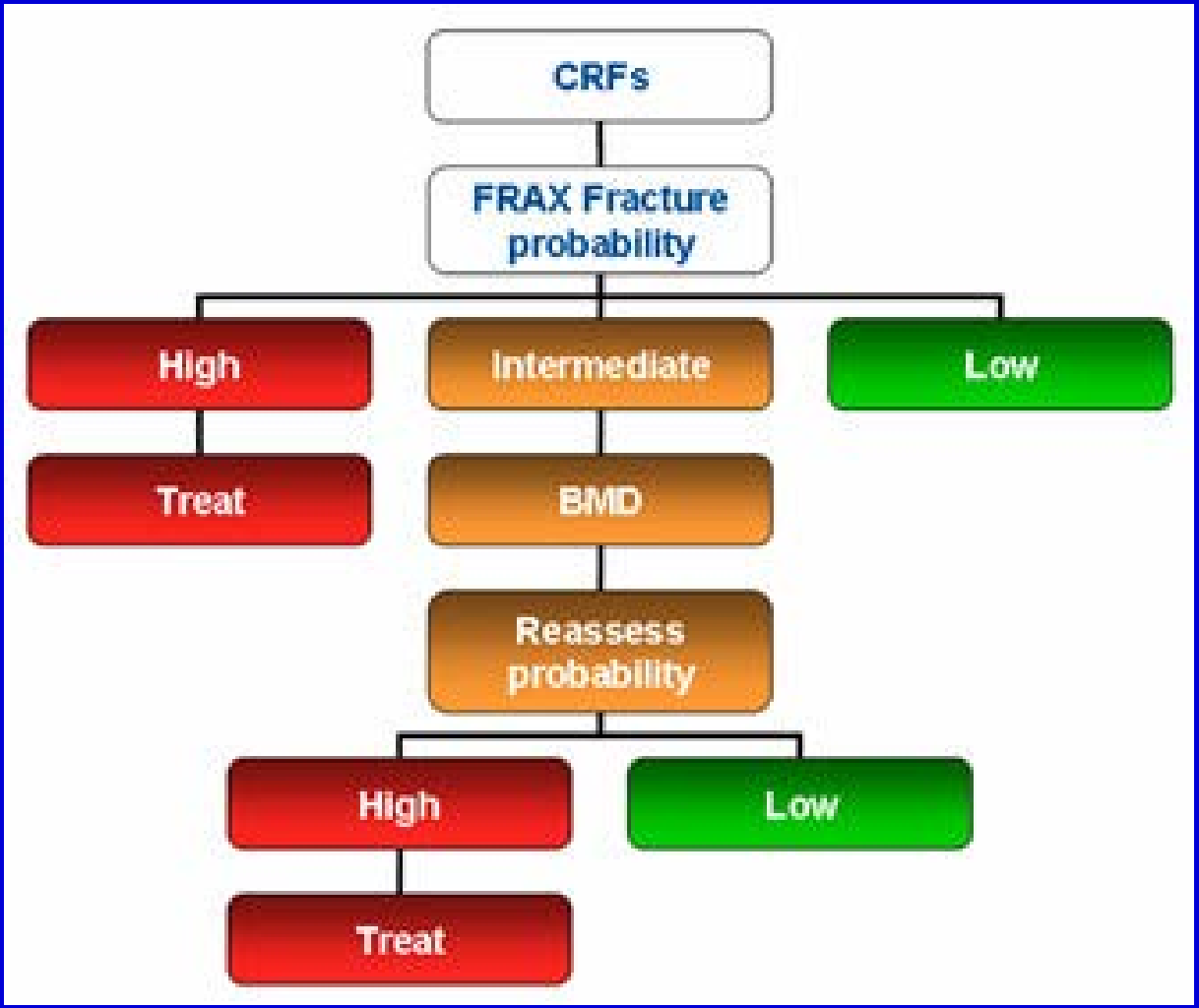


70 yr old woman, BMI 24.5, previous fracture

FN T-score -2.2

www.shef.ac.uk/FRAX/NOGG

Management algorithm for fracture risk assessment



www.shef.ac.uk/NOGG/

NICE guidance on assessment of fracture risk (CG 146): August 2012

- Consider assessment
  - in women aged ≥65 and men aged ≥75 yrs
  - In younger women and men with risk factors

- Estimate absolute fracture risk using FRAX or Qfracture,

- Consider BMD:
  - If fracture probability is close to intervention threshold
  - In individuals aged <40 yrs with strong risk factors
  - Prior to treatment with e.g. aromatase inhibitors, androgen deprivation therapy

- Take into account possible underestimation of fracture risk if multiple fractures, high dose glucocorticoids etc

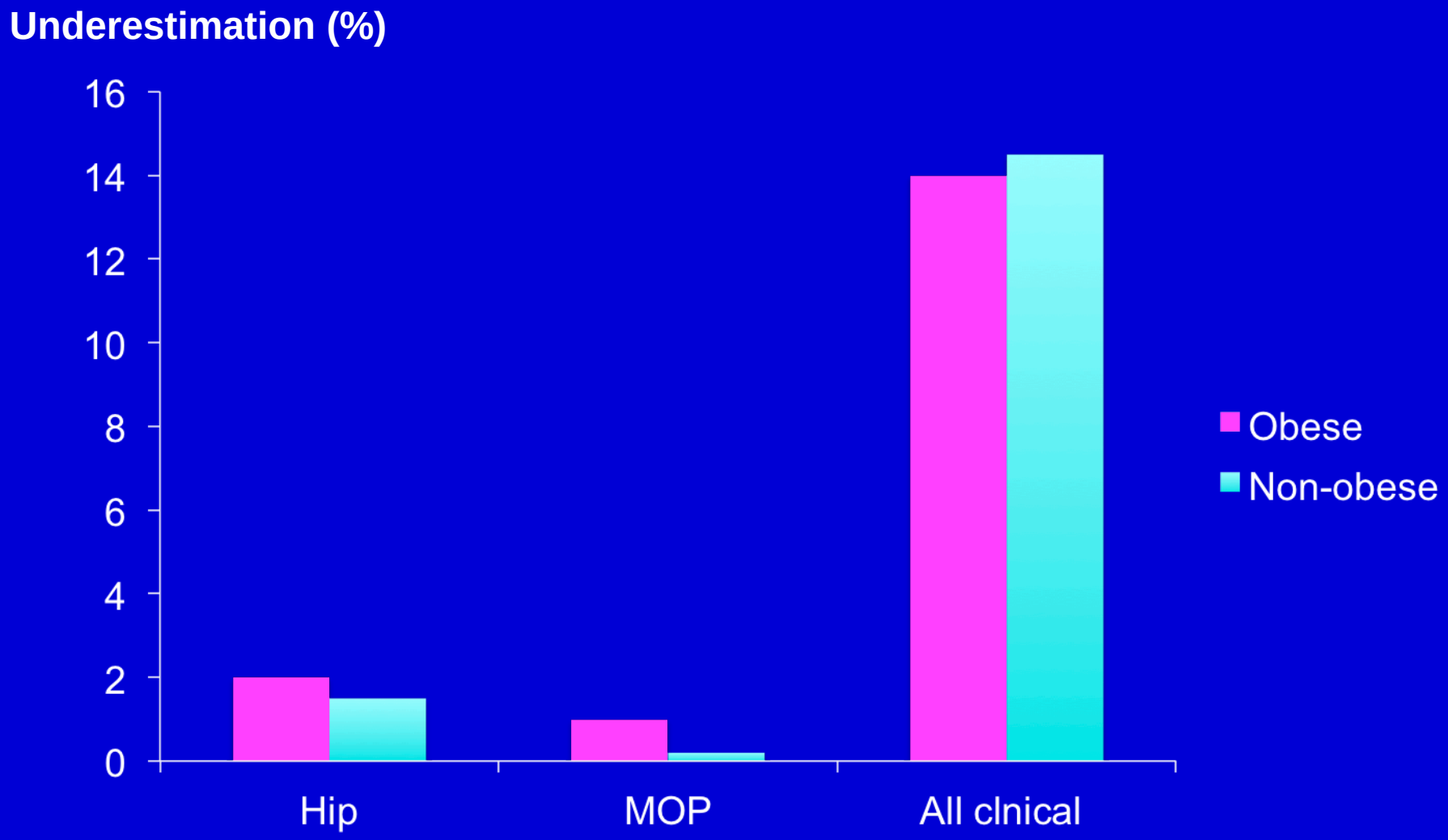
Comparison of FRAX and Qfracture

	FRAX	QFracture
Age range	40-90	30-99
Derivation	Cohort studies (international)	General practice data (UK)
Output	10 yr fracture probability	1-10 yr cumulative fracture incidence
Fractures included	Hip, major osteoporotic fracture (hip, wrist, humerus, spine)	Hip, major osteoporotic fracture (hip, wrist, humerus, spine)
Clinical risk factors (CRFs)	7	21
Dose-response for CRFs	No	Yes, for smoking and alcohol
Inclusion of BMD	Yes	No
Inclusion of falls	No	Yes

Shared limitations of FRAX and QFracture

- Lack of dose-response e.g. glucocorticoids, previous fracture
- Risk may be underestimated if vertebral fracture assessment not conducted at baseline
- Output is limited to 4 fracture sites
- Only applicable to treatment-naïve individuals
- Interaction between fracture probability and treatment response uncertain

Predicted vs observed fracture incidence using FRAX + BMD in the SOF cohort



Premaor et al, JBMR 2013

Treatment options for osteoporosis

Anti-resorptive

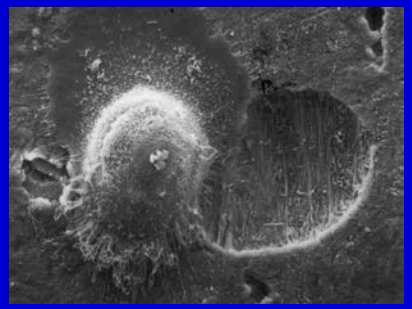
Anabolic

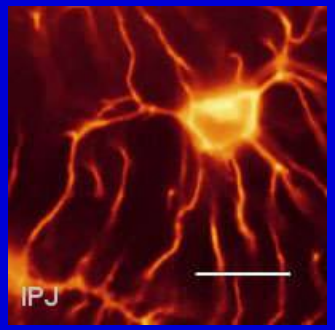
Bone material properties

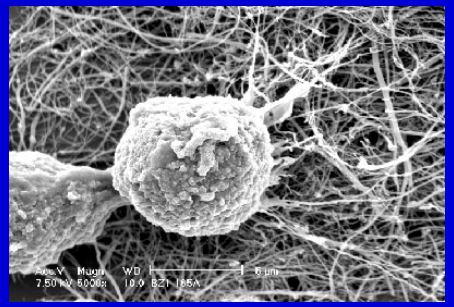
Denosumab Bisphosphonates
HRT
Raloxifene

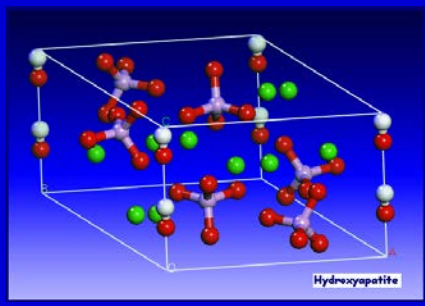
PTH peptides

Strontium ranelate









Efficacy of approved pharmacological interventions for osteoporosis

Intervention	Vertebral (30-70% reduction)	Non-vertebral (15-20% reduction)	Hip (≥ 40% reduction)
Alendronate*	+	+	+
Ibandronate	+	+**	-
Risedronate*	+	+	+
Zoledronate*	+	+	+
Denosumab*	+	+	+
HRT	+	+	+
Raloxifene	+	-	-
Strontium ranelate*	+	+	+**
Teriparatide*	+	+	-

* also approved in men

** post hoc anaysis

Dosing regimens of drugs used in the treatment of osteoporosis

Oral

- Once daily
  - Raloxifene
  - Strontium ranelate
- Once weekly
  - Alendronate
  - Risedronate
- Once monthly
  - Ibandronate

Parenteral

- Once daily
  - Teriparatide (sc)
- Once 3 monthly
  - Ibandronate (iv)
- Once 6 monthly
  - Denosumab (sc)
- Once yearly
  - Zoledronic acid (iv)

Challenges in the treatment of osteoporosis

- Under-treatment of high risk patients
- Low treatment adherence
- Low efficacy against non-vertebral non-hip fractures

History of NICE guidance on prevention of fragility fractures

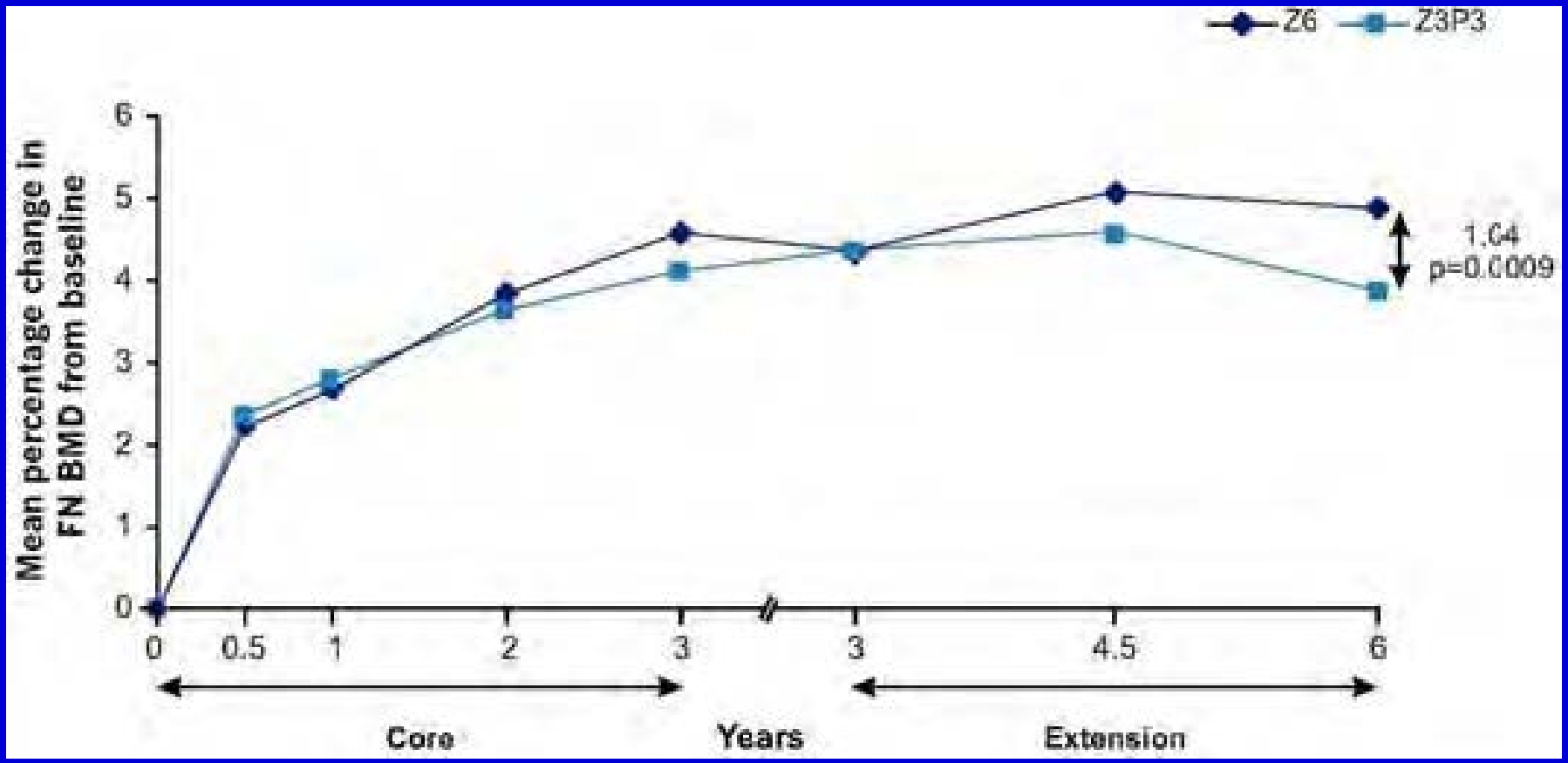
- 2008: TA 160 and 161 – etidronate, alendronate, risedronate, raloxifene, strontium ranelate, teriparatide
- 2010: TA 204 – denosumab
- 2014: update (suspended June 2015)

- No guidance for men
- Glucocorticoid-induced osteoporosis not included
- Zoledronic acid not included
- Intervention thresholds based wholly or mainly on BMD T-scores
- Cost-effectiveness analyses are outdated

Issues relevant to the duration of bisphosphonate therapy

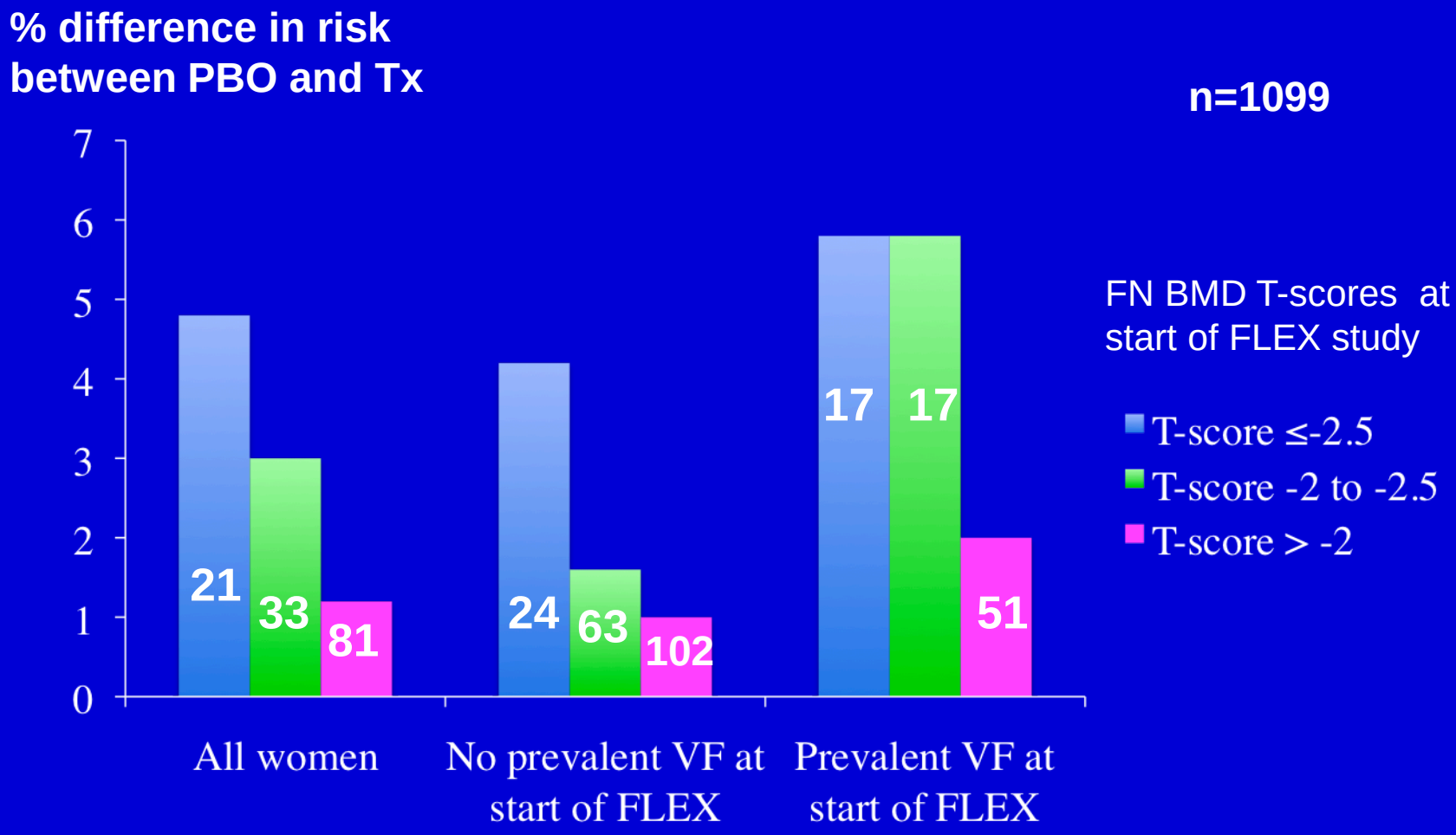
- How long does fracture protection persist with treatment?
- Does fracture protection persist after withdrawal of treatment or does fracture risk increase after treatment is stopped?
- What are the potential adverse effects of long-term therapy?

Effects of continued versus discontinued zoledronic acid therapy over 6 years



Black et al, JBMR 2012;27:243-54

Differences in 5-yr risk of clinical vertebral fracture according to BMD and prevalent vertebral fracture in FLEX



From Black et al, NEJM 2012

Osteonecrosis of the jaw: clinical definition and incidence

- Exposed bone in maxillofacial region for ≥ 8 weeks in the absence of radiation
- Oncology patients: incidence of 1-2% with zoledronate or denosumab treatment
- Osteoporosis patients: 1/10,000- 1/100,000 person yrs of BP exposure, a few cases also described with denosumab
- Can occur in treatment-naïve patients

Atypical femoral fractures

- Comprise 1% of all femoral fractures
- Increase with duration of bisphosphonate therapy
- Also reported with denosumab treatment
- Can occur in treatment-naïve patients

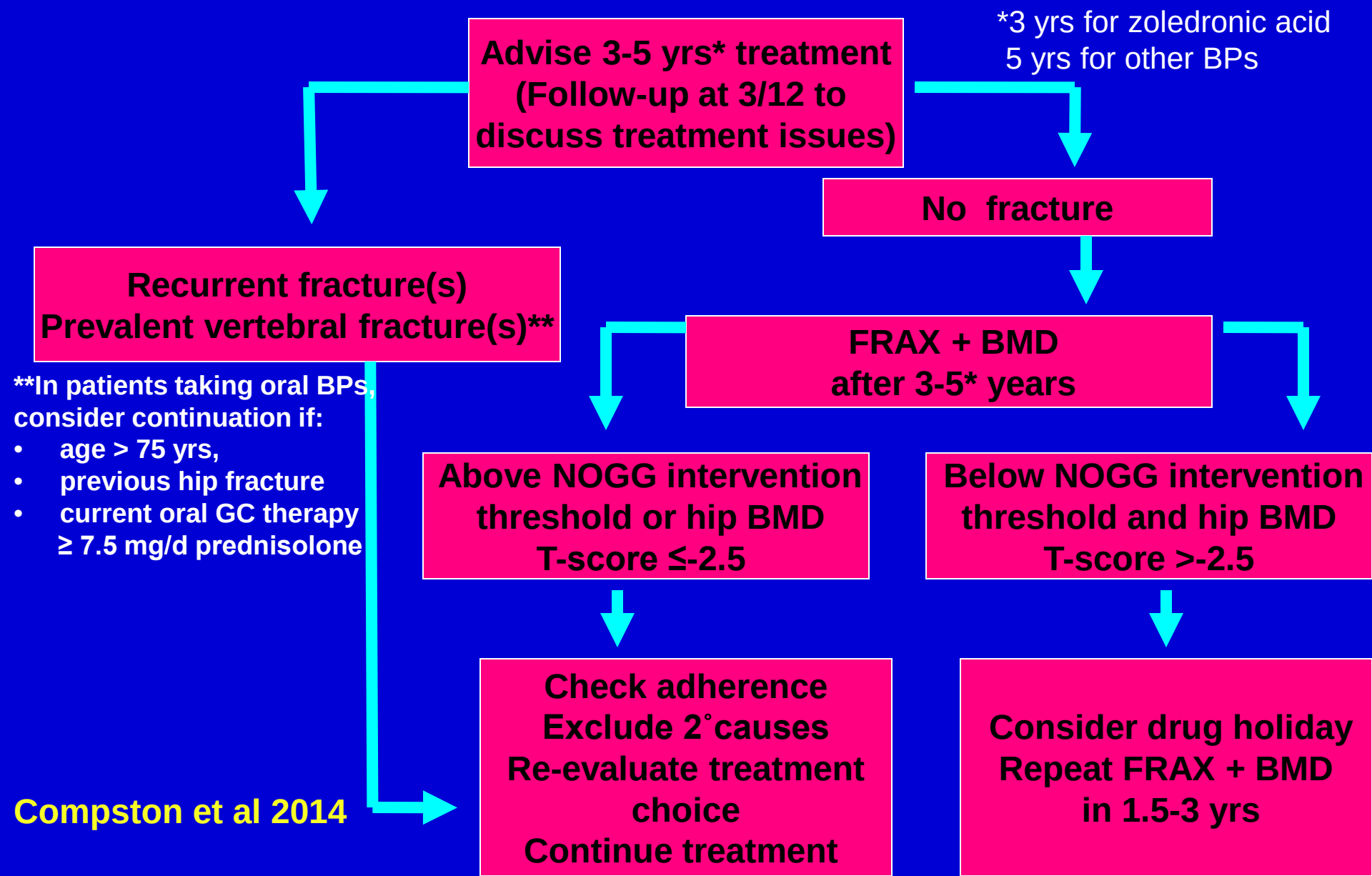
Benefit/risk ratio of bisphosphonate therapy for osteoporosis

Fractures prevented/caused per 100,000 patients for up to 5 yr BP therapy	
Hip	175
Spine	1470
Wrist	945
Atypical fracture	16

Total of 162 fractures prevented/AFF caused

ASBMR Task Force JBMR 2016

Bisphosphonates: NOGG algorithm for long-term treatment monitoring



Compston et al 2014

New treatments on the horizon

	Odanacatib 3 yr, Phase 3	Romosozumab 12 mo, Phase 2	Abaloparatide 18 mo, Phase 3
Mechanism of action	Cathepsin K inhibitor	Anti-sclerostin antibody	PTHrP peptide
Mode of administration	Once weekly, oral	Monthly or 3-monthly, sc	Daily, sc injection
Effect on BMD	Spine ↑ 7.9% Hip ↑ 5.8%	Spine ↑ 11.3 Hip ↑ 4.1	Spine ↑ 6.7% Hip ↑ 3.1% (6 weeks)
Effect on fracture	54%/72% ↓ morphometric and clinical vert 23% ↓ non-vert 47% ↓ hip	Awaited	86% ↓ vertebral 43% ↓ non-vert 45% ↓ clinical

Summary and conclusions

- Addition of clinical risk factors to BMD significantly improves fracture risk assessment
- Intervention thresholds, expressed in terms of fracture probability, should be clinically appropriate and cost-effective
- A range of effective pharmacological interventions is available in postmenopausal women and older men
- Drug holidays may be appropriate in some bisphosphonate treated individuals after 3-5 years of treatment