

Osteoporosis

The Good, the Bad and the Ugly

Michael Hooper

Clinical Associate Professor, The University of Sydney
Area Head, Bone and Mineral Stream,, Endocrinology, SSWAHS

My Bagage (Conflict of Interest)

- **Michael Hooper has received consulting fees, lecture fees, and/or grant support from Astra Zenica, Eli Lilly, Merck, Novartis, Pfizer, Sanofi Aventis and Servier.**

Some topical key points regarding the treatment of Osteoporosis

New treatments

Missed opportunities

Barriers to treatment – myths

Vitamin D

Osteoporotic Fractures are a Major Risk Factor for Subsequent Fractures

Vertebral fracture: → **Vertebral deformity: 5.4 RR¹**

→ **Hip fracture: 2.8 RR¹**

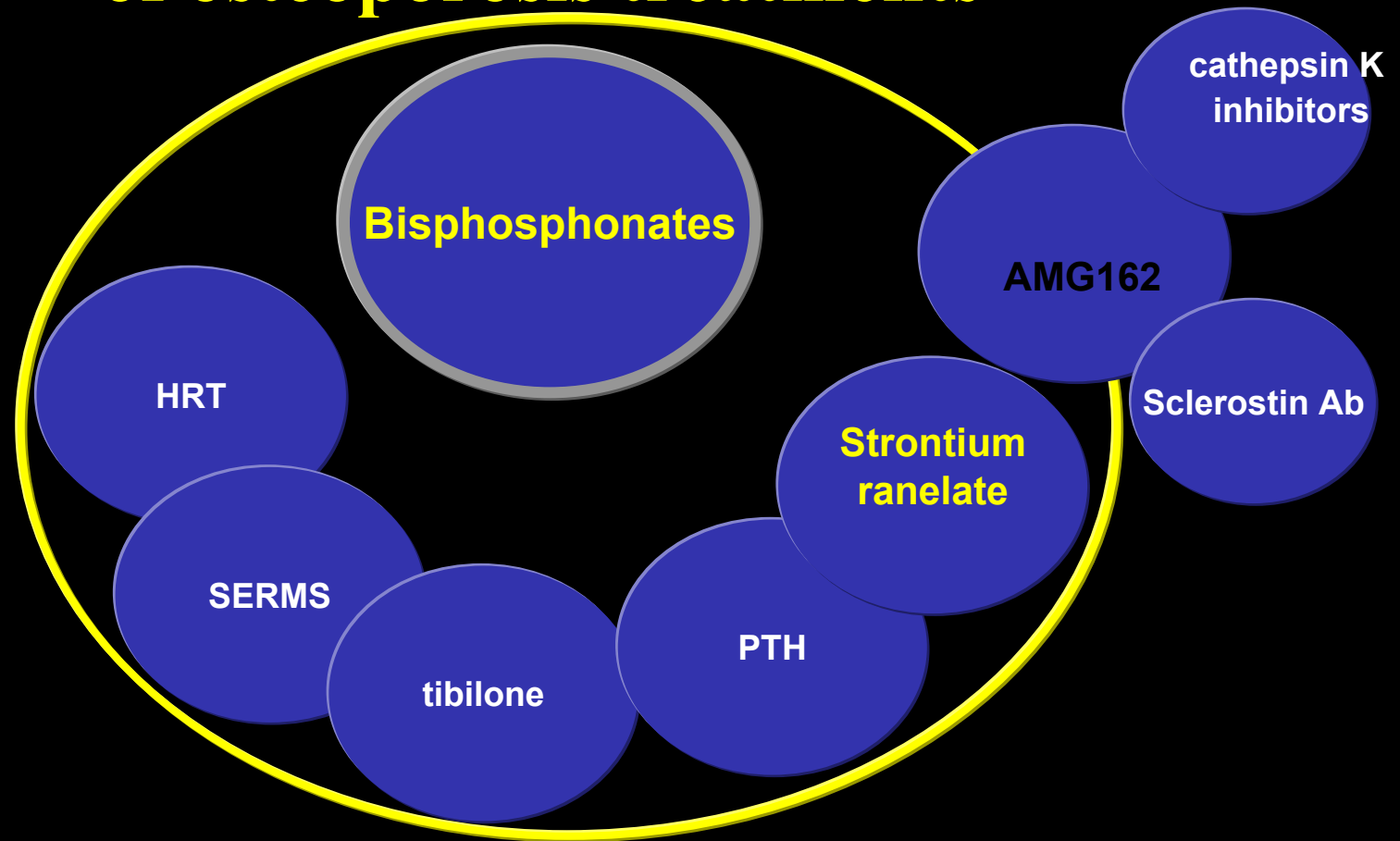
→ **Non-vertebral fracture: 1.9 RR¹**

Colles fracture: → **Hip fracture: 1.6 RR in women over 70²**

Hip fracture: → **17- 21% in 2 years (hip, pelvis, vertebral, etc)³**

But even in Teaching Hospitals most patients fail to have investigations and treatment after their sentinel fracture

Bisphosphonates: still the gold standard of osteoporosis treatments

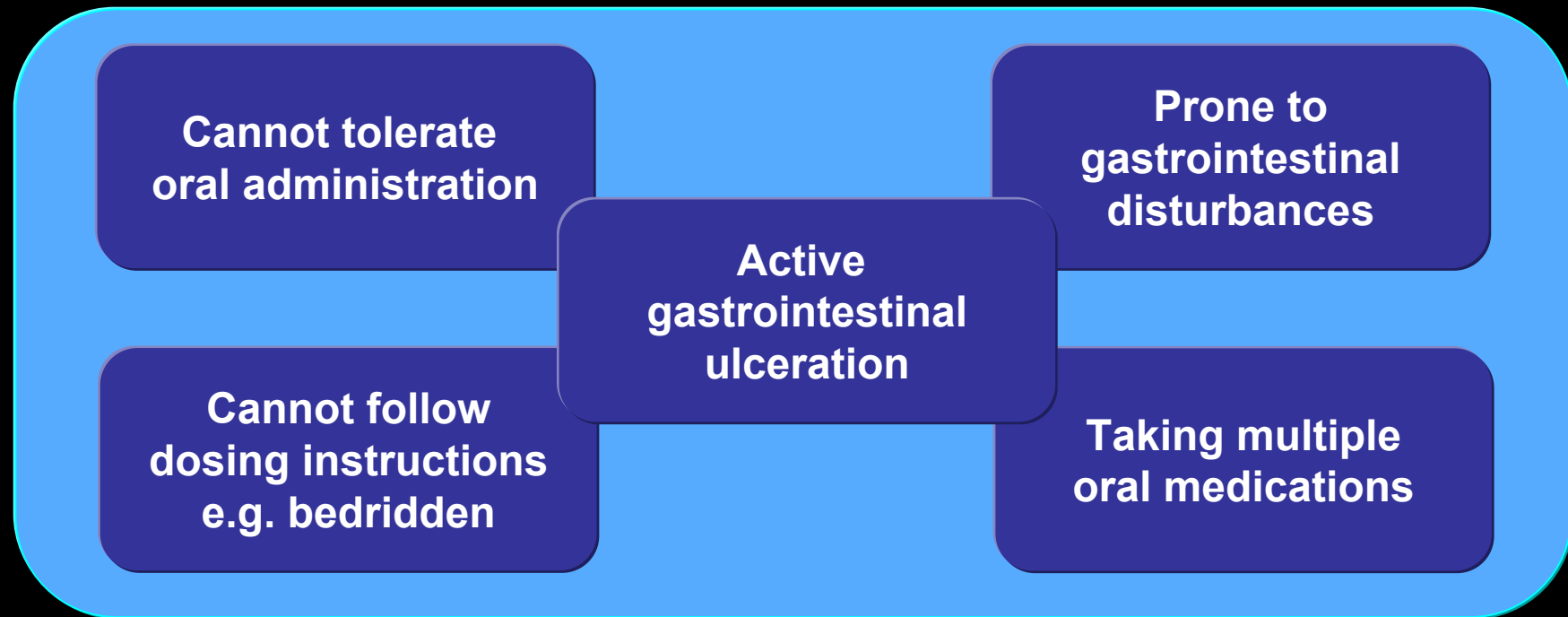


SERMs = selective oestrogen receptor modulators
HRT = hormone replacement therapy

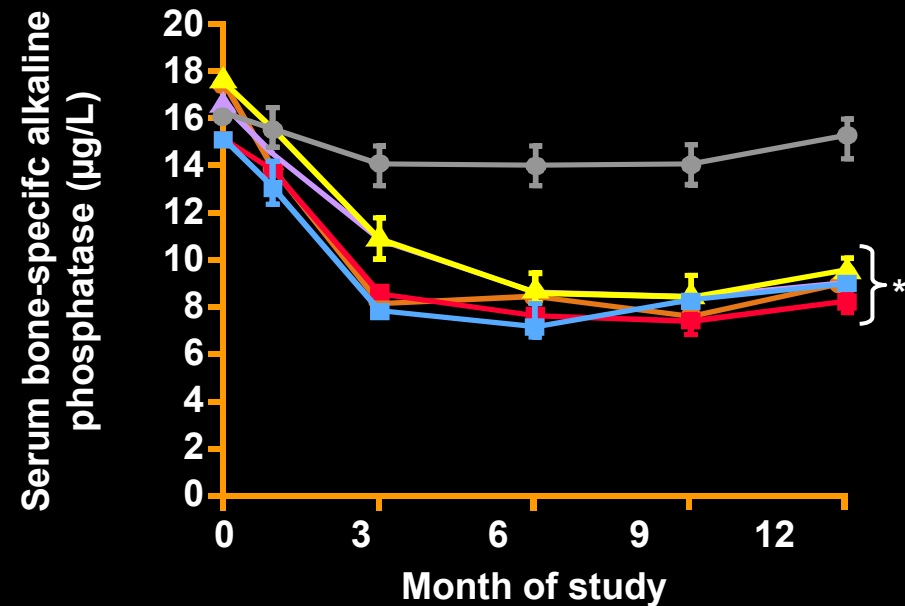
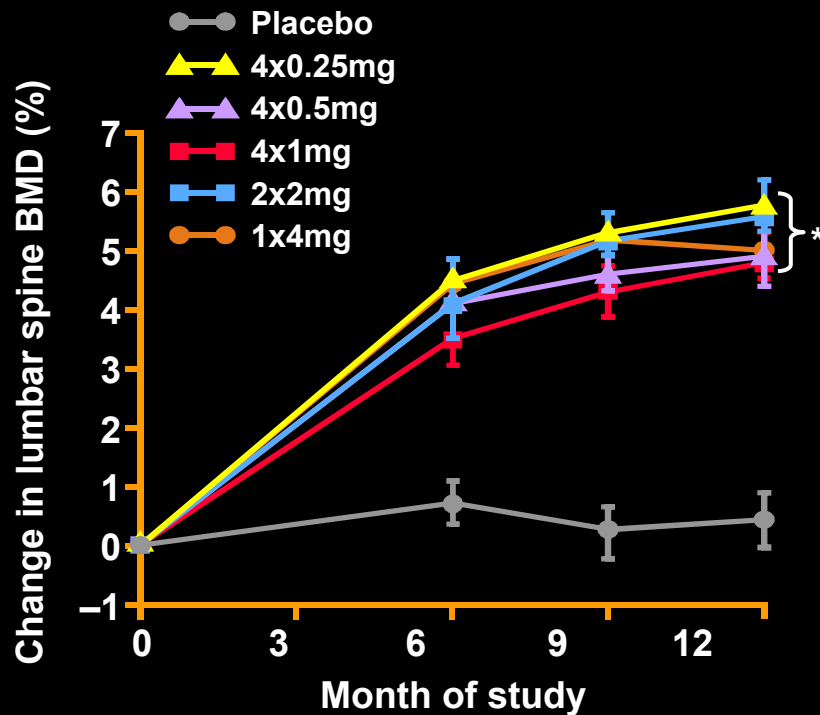
N -Bisphosphonates and osteoporosis

- **N - Bisphosphonates are the standard of care**
- **Consistently demonstrated good efficacy and tolerability**
 - **reduction in fracture risk**
 - **increases in bone mineral density (BMD)**
 - **reductions in biochemical markers of bone turnover**
 - **reduction in mortality**
- **Despite differences between data sets, efficacy is comparable among the available therapies^{1,2}**
- **The main difference is the dosing schedule i.e. oral -daily, weekly, monthly, IV - 3 monthly or yearly**

Previous indication for IV bisphosphonates in osteoporosis



Intravenously administered bisphosphonate infusions: zoledronate¹



*p<0.001 for all treatment regimens relative to placebo

¹Reid IR, et al. N Engl J Med 2002;346:653–61

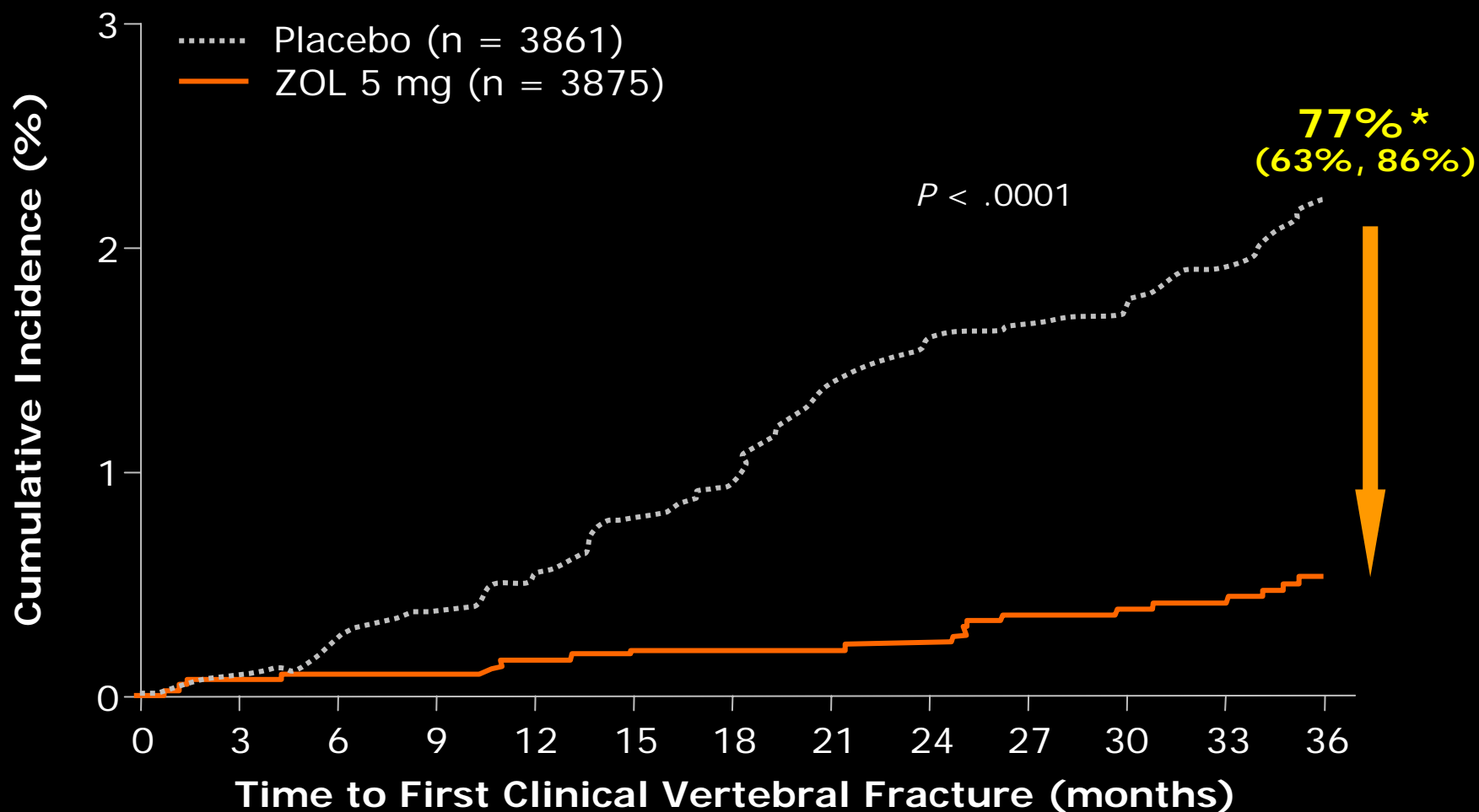
HORIZON Pivotal Fracture Trial (PFT):

- **To evaluate the potential of once yearly zoledronic acid (ZOL) 5 mg to decrease fracture risk in postmenopausal women with osteoporosis**
- **3-year, randomised, double-blind, placebo-controlled clinical trial**
 - **7736 women from 239 clinical centers in 27 countries**
- **Annual infusion of either ZOL 5 mg or placebo**
 - **Calcium 1000–1500 mg/d; vitamin D 400–1200 IU/d**

Study Population

- **Women 65 to 89 years of age**
- **Femoral neck T-score ≤ -2.5 with or without fracture **or** ≤ -1.5 with 2 mild or 1 moderate vertebral fracture**
- **Exclusion if**
 - **Current use of PTH or strontium ranelate**
 - **Failure to meet specified washout periods for previous bisphosphonate (BP) use**
- **Stratum I: no current osteoporosis therapy**
- **Stratum II: SERMs, calcitonin, HT/ET, or tibolone at baseline**

Effect of Zoledronic Acid on Cumulative 3-Year Risk of Clinical Vertebral Fractures (Strata I + II)



*Relative risk reduction vs placebo (95% confidence interval)

Adapted from Black DM, et al. *N Engl J Med.* 2007;356:1809-1822.

Summary

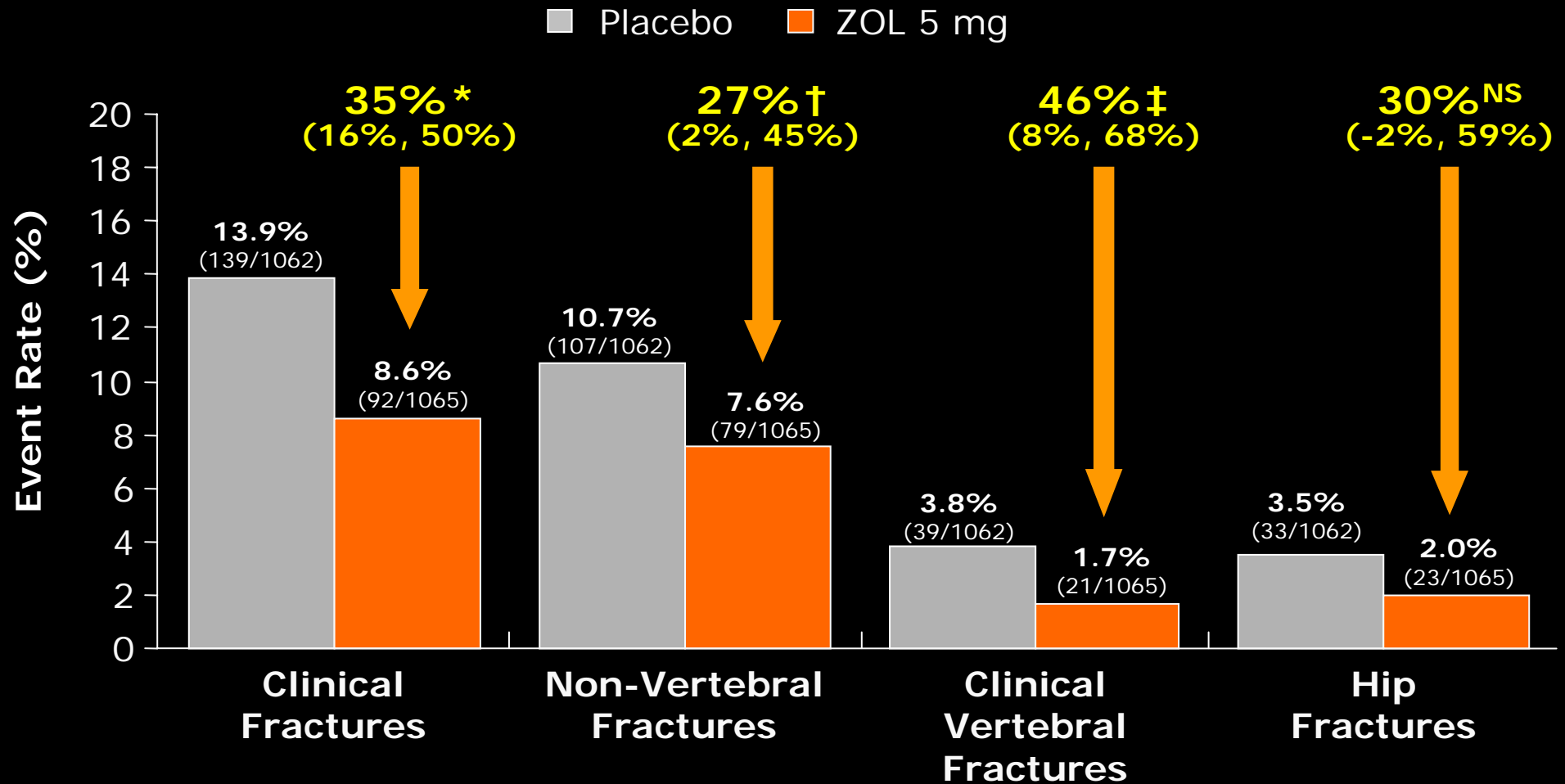
- **In PMO, once yearly infusion of ZOL 5 mg over 3 years significantly reduces¹:**
 - **Vertebral fractures (morphometric 70%, clinical 77%)¹**
 - **Hip fractures (41%)¹**
 - **Non-vertebral fractures (25%)¹**
- **Significantly superior to placebo in increasing or preserving BMD¹**
- **Markers of bone formation and resorption were reduced and maintained within premenopausal reference range over 36 months¹**
- **Generally well tolerated¹**
- **High adherence**

1. Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

HORIZON-Recurrent Fracture Trial

- **Double-blind, placebo-controlled RCT**
 - **2127 men and women, 76% women**
 - **Median age = 76, range 50 – 98**
- **Treatment**
 - **Annual infusion of either ZOL 5 mg or placebo**
 - **Initial dose 2 weeks after Vit D - 3 months after Surgery**
 - **Loading dose of vitamin D 50,000–125,000 IU**
 - **Calcium 1000–1500 mg/d; vitamin D 800–1200 IU/d**

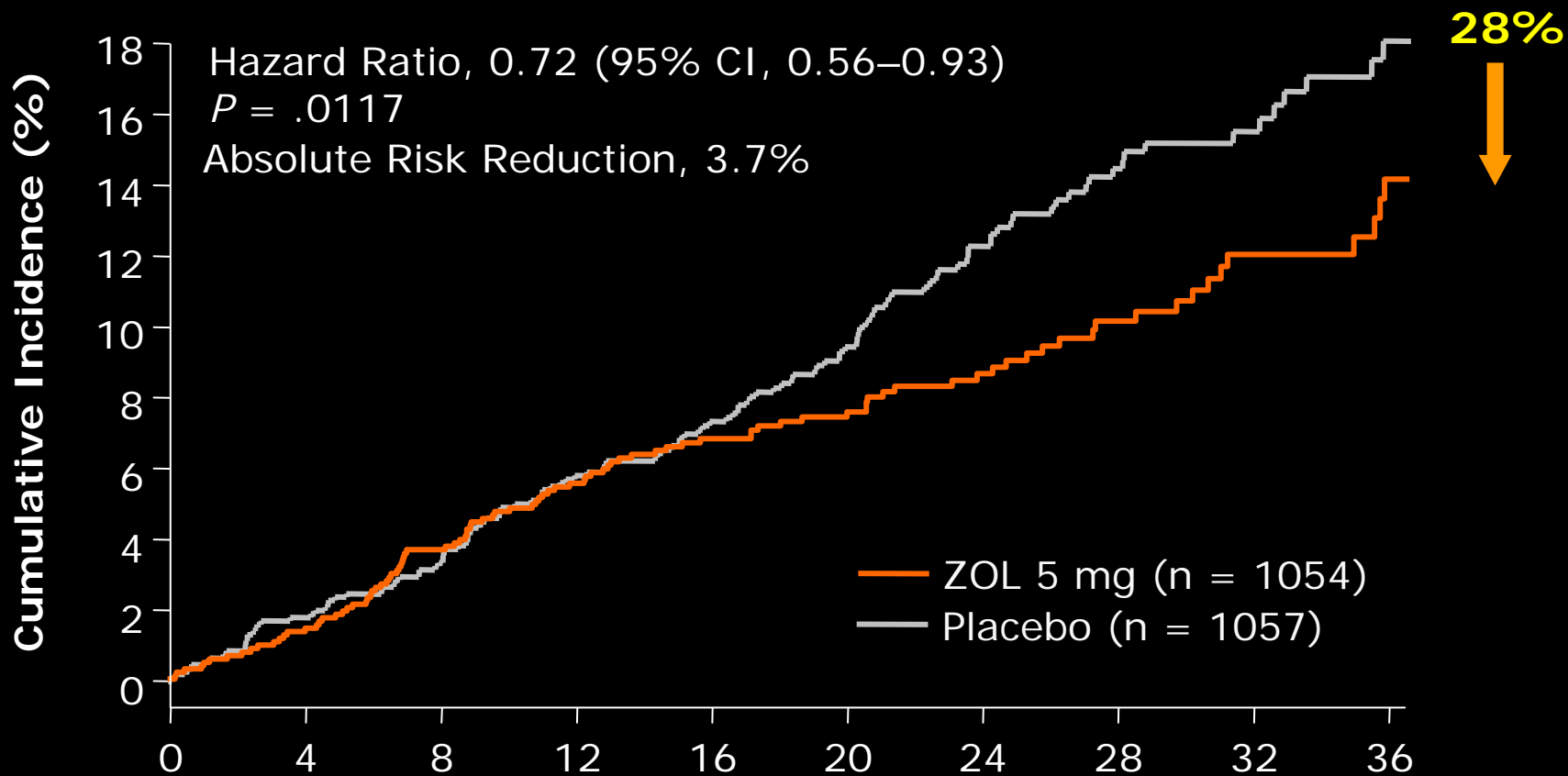
Effect of Zoledronic Acid 5 mg on Risk of Subsequent Fractures Over Time vs placebo



* $P = .0012$; † $P = .0338$; ‡ $P = .0210$, relative risk reduction vs placebo; NS = not significant.
Values above bars are cumulative event rates based on Kaplan-Meier estimates at Month 24.

Lyles KW, et al. N Engl J Med. 2007 Nov 1;357(18):1799-809.

Effect of Zoledronic Acid 5 mg on All-Cause Mortality



No. at Risk

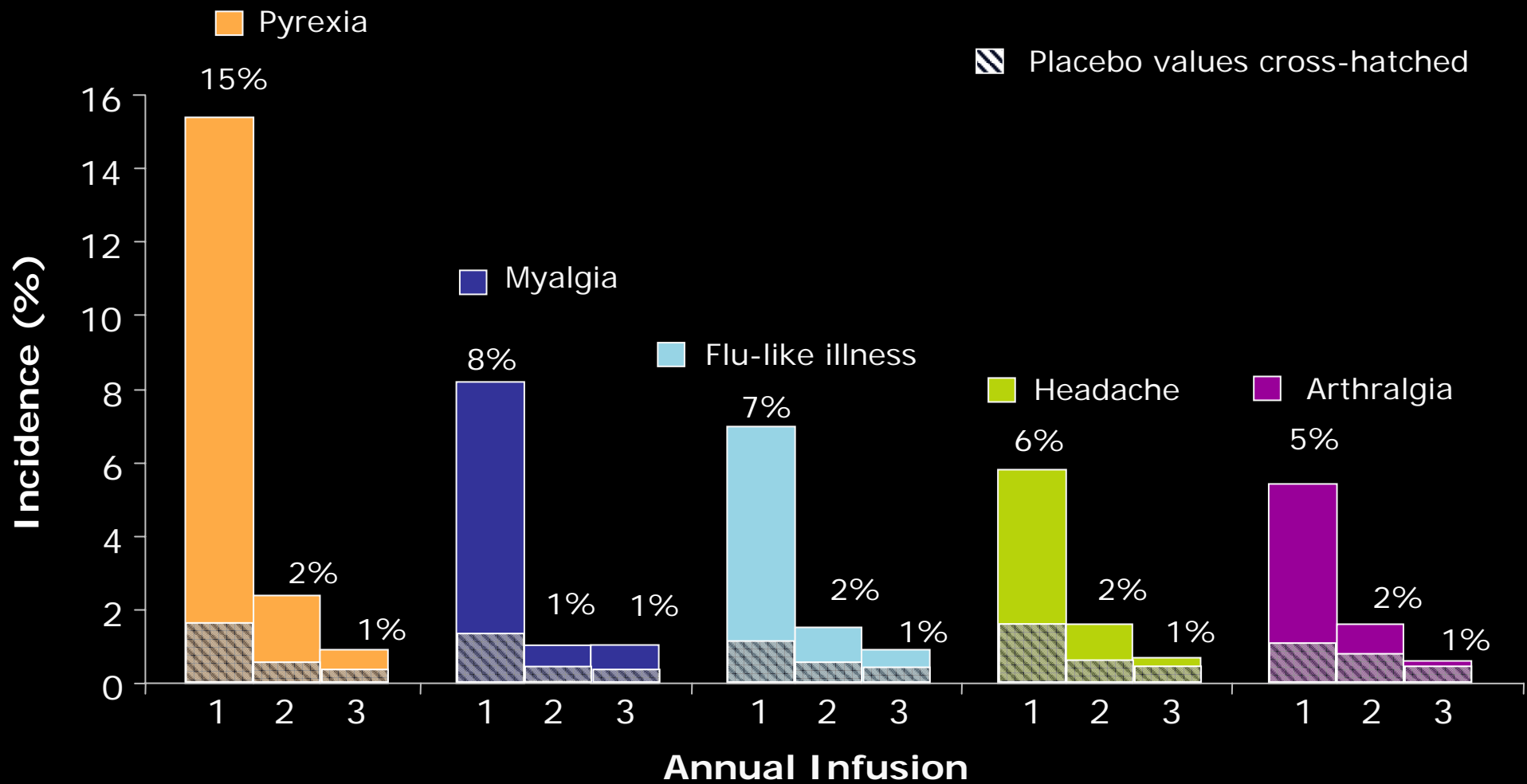
	0	4	8	12	16	20	24	28	32	36
ZOL 5 mg	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

Month

Conclusions

- **ZOL 5 mg within 90 days after a surgical procedure for hip fracture:**
 - **Reduced risk of overall clinical fractures by 35%**
 - **Clinical vertebral fractures by 46%**
 - **Non-vertebral fracture by 27%**
 - **Reduced mortality risk by 28%**
 - **No adverse effects on ONJ, fracture healing, cardiovascular safety, or renal function**

Common ($\geq 5\%$ in ZOL) Post-Dose Symptoms Occurring Within 3 Days After Infusion



Data from Black DM, et al. *N Engl J Med.* 2007;356:1809-1822.

Renal and Cardiac Effects

- **Renal safety**
 - Transient rises in serum creatinine in 1.81% of patients (vs 0.81% placebo) with resolution and all patients redosed
 - Overall, no cumulative impact on renal function
- **Hypocalcaemia** (serum calcium < 2.075 mmol/L)
 - 49/2114 cases (2.3%) 9-11 days after 1st ZOL 5 mg infusion, 2/1663 cases after 2nd (0.1%) or 5/1559 after 3rd (0.3%)
 - All asymptomatic and transient
- **Cardiac safety**
 - Atrial fibrillation AEs 2.4% ZOL 5 mg vs 1.9% placebo
 - ECG study (n = 559) 9-11 days after 3rd infusion:
No differences observed between ZOL 5 mg and placebo

Bone Safety Results

- **Histomorphometry** evaluable in 152 bone biopsies
 - Label seen in all but 1 specimen, indicating ongoing bone remodeling
- **Bone turnover** markers maintained in pre-menopausal reference range over 36 months
- **Fracture healing**
 - Non-union: 2 in ZOL 5 mg, 1 in placebo
- **Avascular necrosis** (hip or knee)
 - 4 in ZOL, 3 in placebo
- **Osteonecrosis of the jaw**
 - No spontaneous AE reports
 - Case searching: 1 case in placebo, 1 case in ZOL
 - Both cases healed with antibiotic therapy and/or debridement

Osteonecrosis of the jaw (ONJ) and bisphosphonate therapy

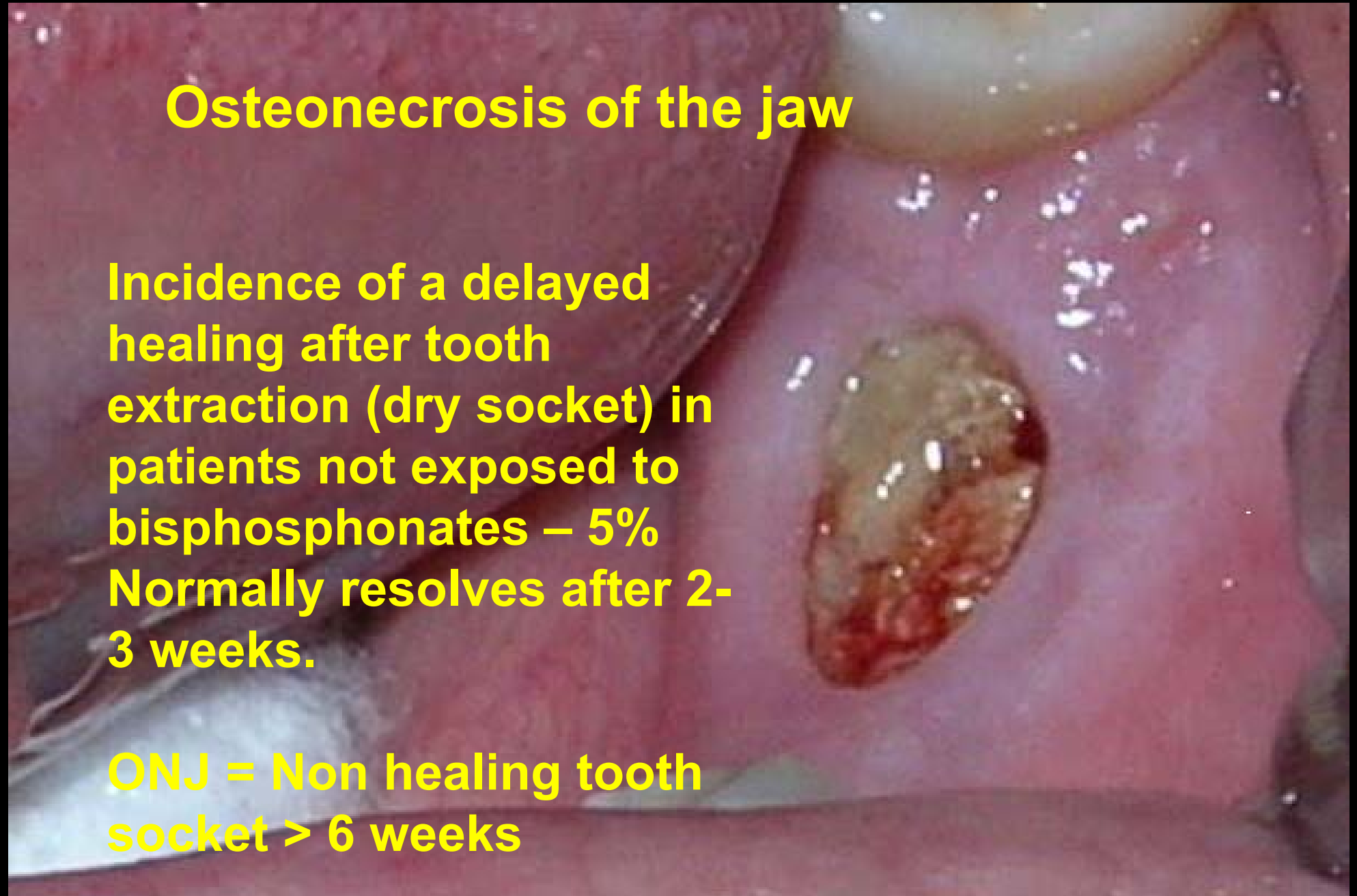
Myths & Questions

- **What is ONJ?**
- **What is the frequency of ONJ?**
- **Are there identifiable risk factors?**
- **What is the appropriate management?**

Osteonecrosis of the jaw

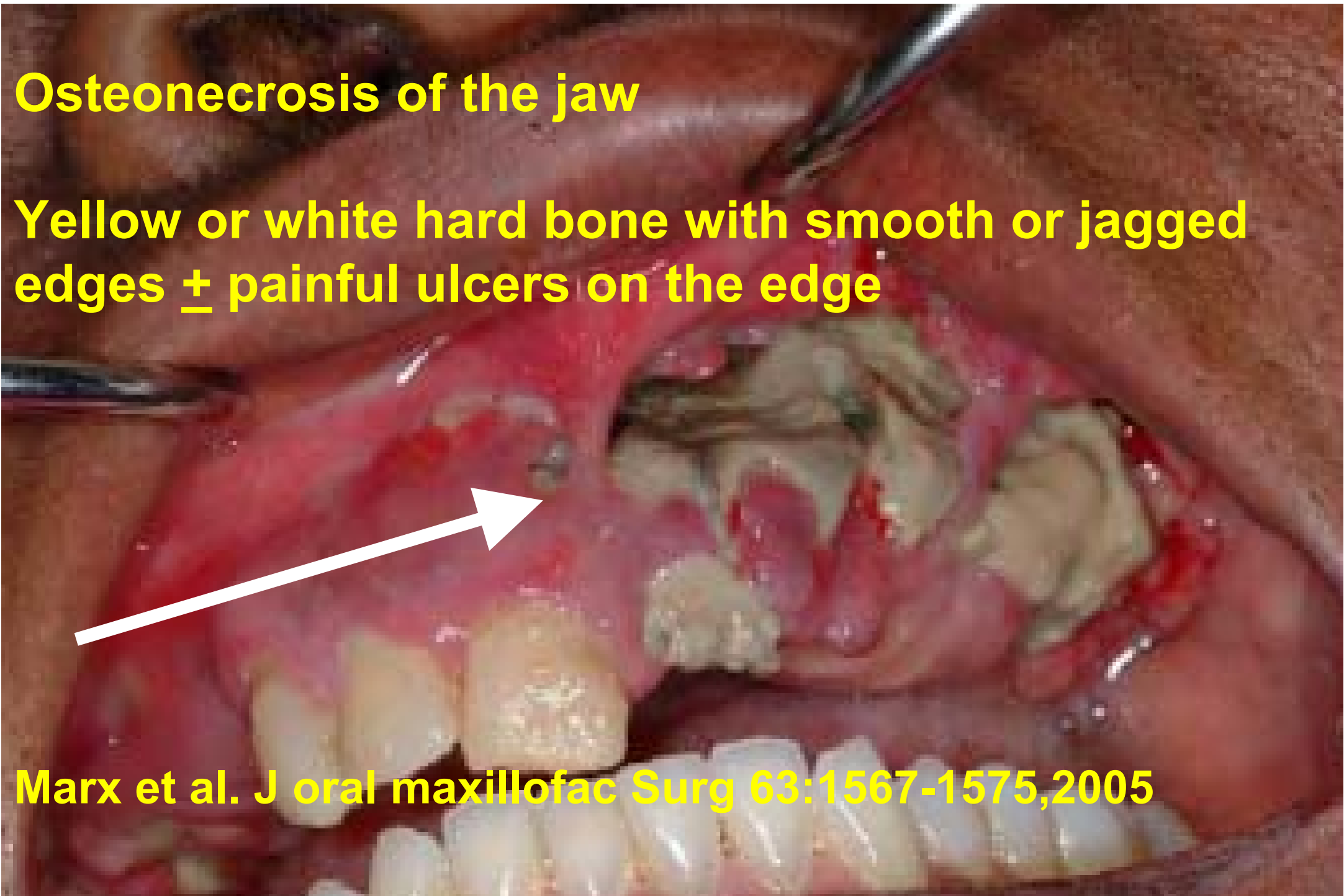
**Incidence of a delayed healing after tooth extraction (dry socket) in patients not exposed to bisphosphonates – 5%
Normally resolves after 2-3 weeks.**

ONJ = Non healing tooth socket > 6 weeks



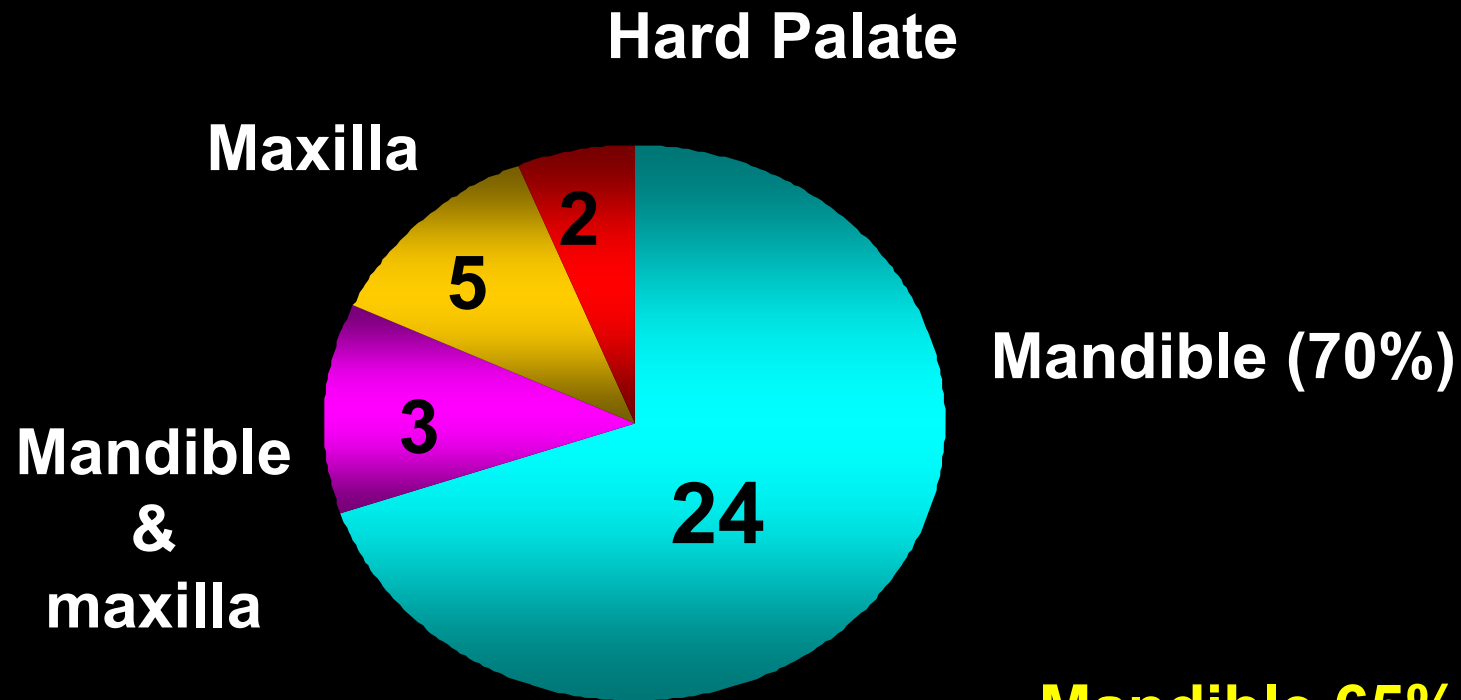
Osteonecrosis of the jaw

Yellow or white hard bone with smooth or jagged edges \pm painful ulcers on the edge



Marx et al. J oral maxillofac Surg 63:1567-1575,2005

Sites of ONJ



MD Anderson Cancer Centre
Hoff 2006

Mandible 65%
maxilla 26%
Both 9%
Woo 2006

ONJ and bisphosphonate therapy

Aetiology and pathogenesis

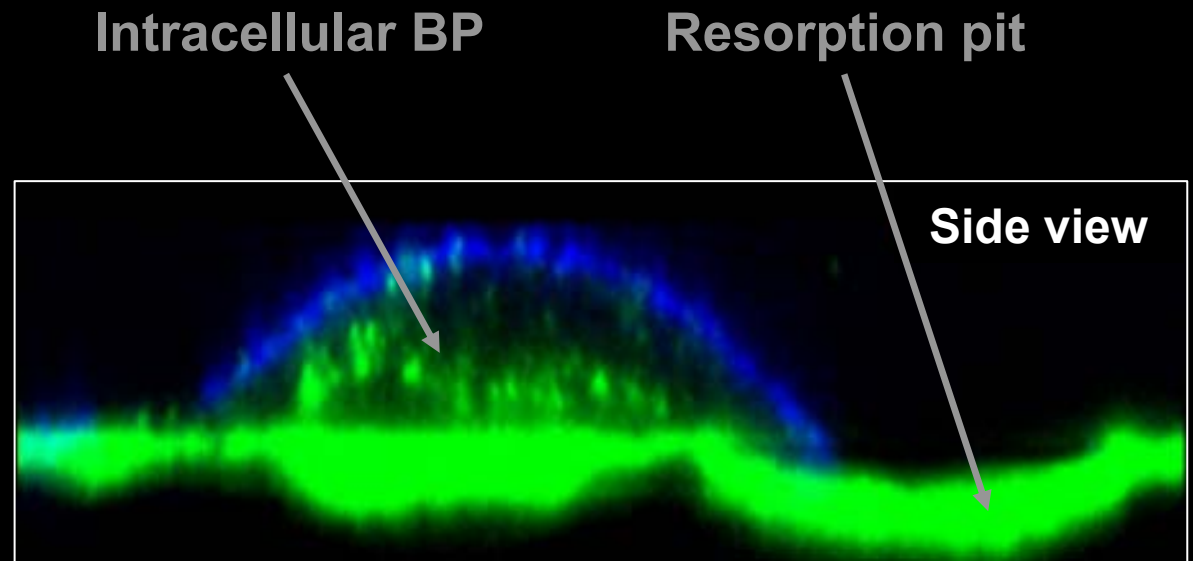
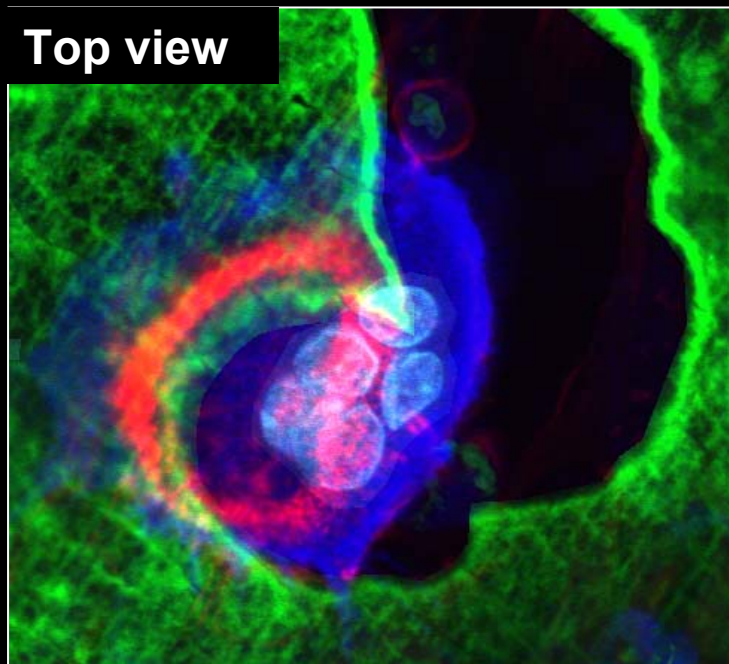
Myth




“lack of repair in hypodynamic bone with accumulation of microdamage leading to necrosis and infection” proposed by Woo, Marx and others

likely pathogenesis

a soft tissue and antiangiogenic effect of bisphosphonates on the overlying thin mucosa and periosteum delaying healing and allowing bone infection and formation of necrotic bone sequestrs.

Bisphosphonates are concentrated at sites of bone resorption



-  Bisphosphonate (bone surface)
-  Osteoclast membrane
-  Cytoskeleton

Courtesy of Dr Fraser Coxon, University of Aberdeen

Osteonecrosis of the jaw (ONJ) and bisphosphonate therapy

Histological findings

The histiological findings are those of necrotic bone, often infection and increased osteoclastic activity but rarely ischaemia or obliteration of regional blood vessels

(Fazzalari, Hellstein, Hoefert....)

ONJ and bisphosphonate therapy

Aetiology and pathogenesis

Myth

ONJ is related to spontaneous osteonecrosis of the hip, knee, talus etc

Fact

bisphosphonates have been successfully used to treat osteonecrosis experimentally in animal models and clinically

(Little, Kim, Agarwala)

Osteonecrosis of the Jaw (ONJ)

Myth

- An impending epidemic of ONJ (Marx, Goss...7.30 report)

Fact

- ONJ is an uncommon event, usually reported in cancer patients with skeletal metastases receiving complex treatment regimens, including IV bisphosphonates
- ONJ reported in a very small number of patients who are receiving bisphosphonates for noncancer indications
- No evidence of ONJ in Paediatric Patients treated with pamidronate – Glorieux 2007

Frequency of ONJ in Cancer

	Univ. of Athens	Univ. of Maryland	Myeloma Foundation	MD Anderson
Breast Cancer	2/70 (2.9%)		13/299 (4.3%)	18/1340 (1.2%)
Multiple Myeloma	11/111 (9.9%)	11/340 (3%)	62/904 (6.9%)	14/550 (2.4%)
Prostate cancer	3/46 (2.9%)			1/185 (0.5%)

Incidence in non-cancer bone disease?

Alendronate post marketing reports

- **Previously no cases have been reported in clinical trials in benign bone disease with alendronate – 17000 patients**
- **? related to its rare occurrence and the relatively small number of patients followed for a long time**
- **Reports of potential ONJ received by MSD to mid 2006**
 - **170 cases from 20 million patient years**
 - **0.7% per 100,000 patient years**
- **German Study: estimated incidence - <1 in 100,000**

J American Den Assoc August 2006

Determinants of ONJ risk

Dental
extraction
or
trauma

Bisphosphonates

IV (Woo 85%)
Aminobisphos.
Duration & Survival
Cumulative dose

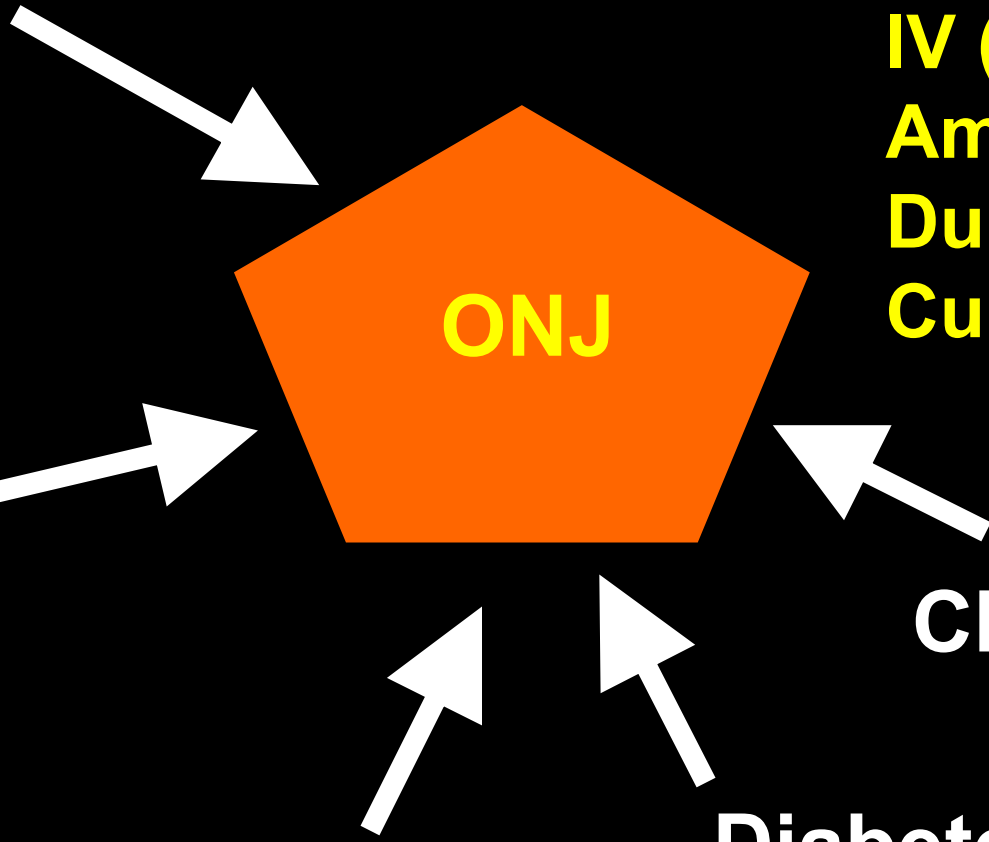
Peridontal
disease

ONJ

Chemotherapy

Corticosteroids

Diabetes

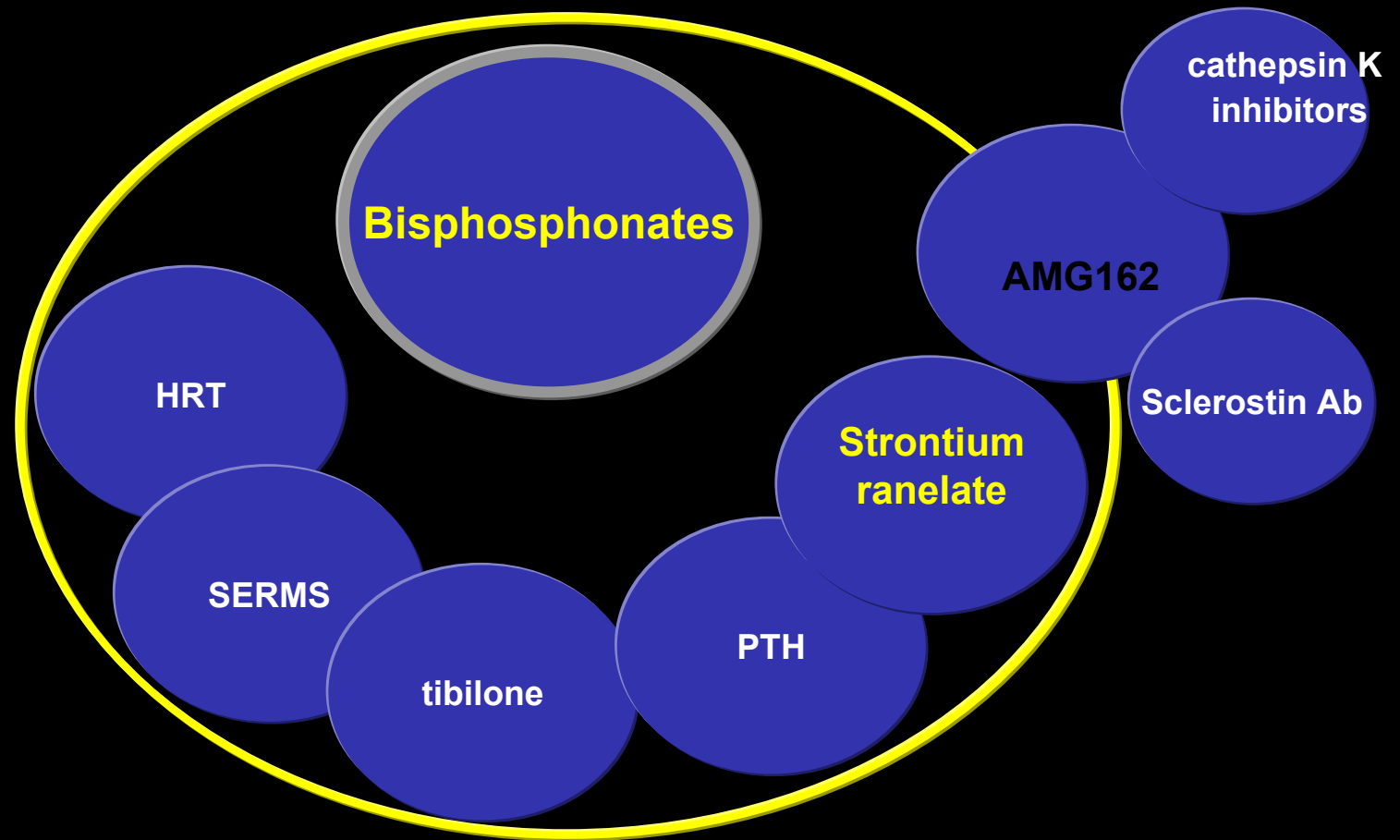


ONJ and bisphosphonate therapy

What is the appropriate management?

- **Before BIS:** eliminate infection and need for future dentoalveolar surgery
- **Already on:** good oral hygiene and regular dental review, if pending extraction consider treatment holiday, antiseptic mouth washes and antibiotics
- **ONJ:** antibiotics, antiseptic mouth rinses, holiday from bisphosphonate, remove loose sequestra, avoid aggressive surgery

Strontium: where does it fit in?



SERMs = selective oestrogen receptor modulators
HRT = hormone replacement therapy

Strontium Ranelate

- **Suppresses the bone resorption and increases bone formation.**
- **Reduces fractures in postmenopausal women.**

What is the evidence?

Bone mass determinants

**Rate of
Bone
Resorption**

**Rate of Bone
Formation**

depends on:
number of new osteoclasts ↓¹²
activity of osteoclasts ↓³
lifespan of osteoclasts

depends on:
number of new osteoblasts
activity of osteoblasts
lifespan of osteoblasts

Coupling

1,2 Mason 2007, Canalis 1996
3,4 Baron 2002, Takahashi 2003

Bone mass determinants

Rate of Bone
Resorption

Rate of
Bone
Formation

depends on:

number of new osteoclasts
activity of osteoclasts
lifespan of osteoclasts

depends on:

number of new osteoblasts ↑
activity of osteoblasts ↑
lifespan of osteoblasts ↑

Mason 2007, Canalis 1996

Coupling

2 major studies have demonstrated efficacy in post-menopausal osteoporosis.

SOTI:

Spinal Osteoporosis Therapeutic Intervention

– vertebral fractures

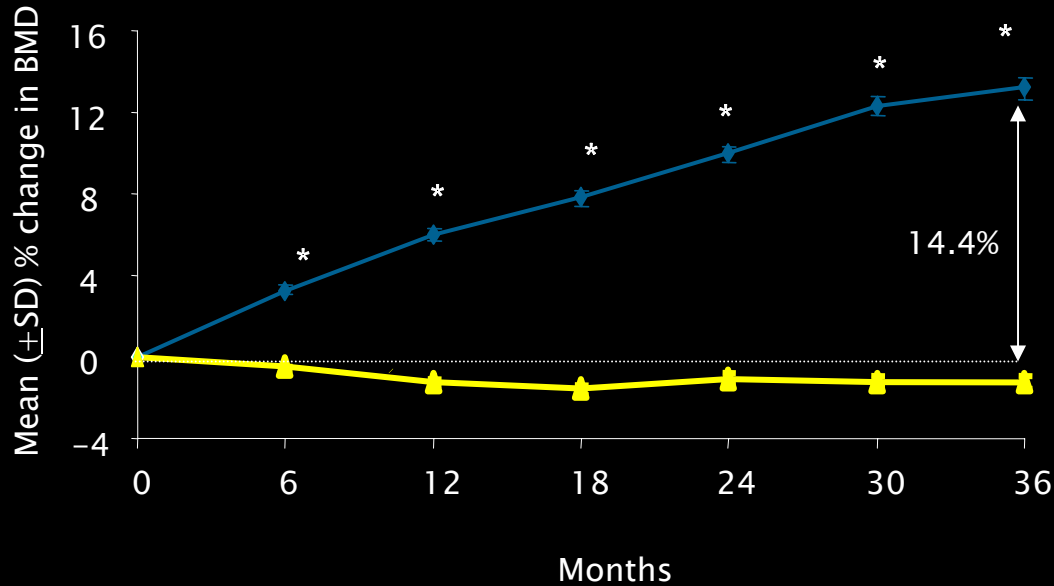
TROPOS:

Treatment Of Peripheral Osteoporosis

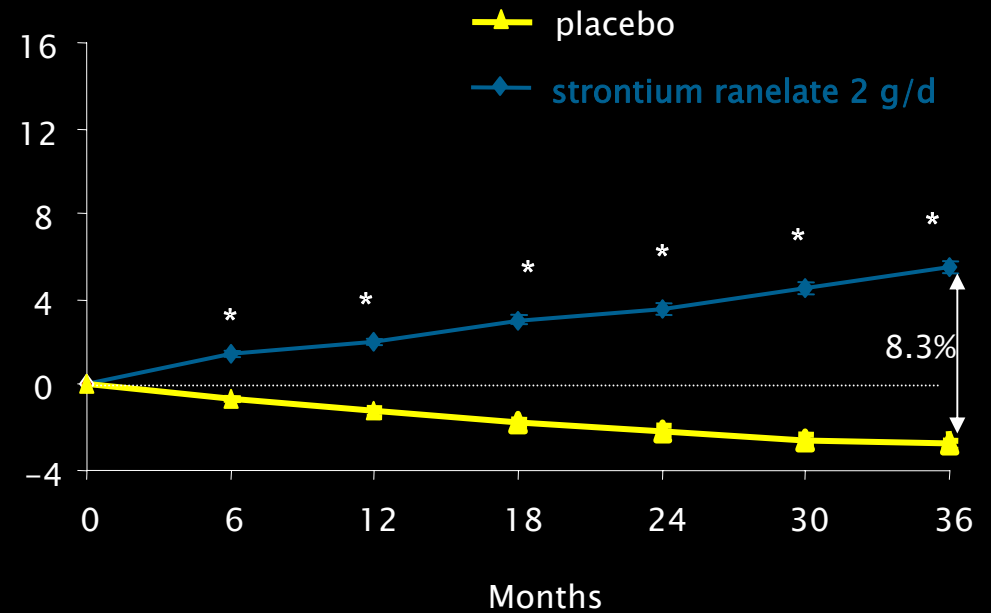
– prevention of peripheral fractures

The higher atomic number of strontium (than calcium) influences BMD. Lumbar BMD is increased 12.7 % from baseline (14.4% c.f. placebo) and femoral neck by 7.2% from baseline (8.3% c.f. placebo) over 3 years.

LUMBAR L2-L4



FEMORAL NECK



*p < 0.001 mean relative change from baseline vs placebo

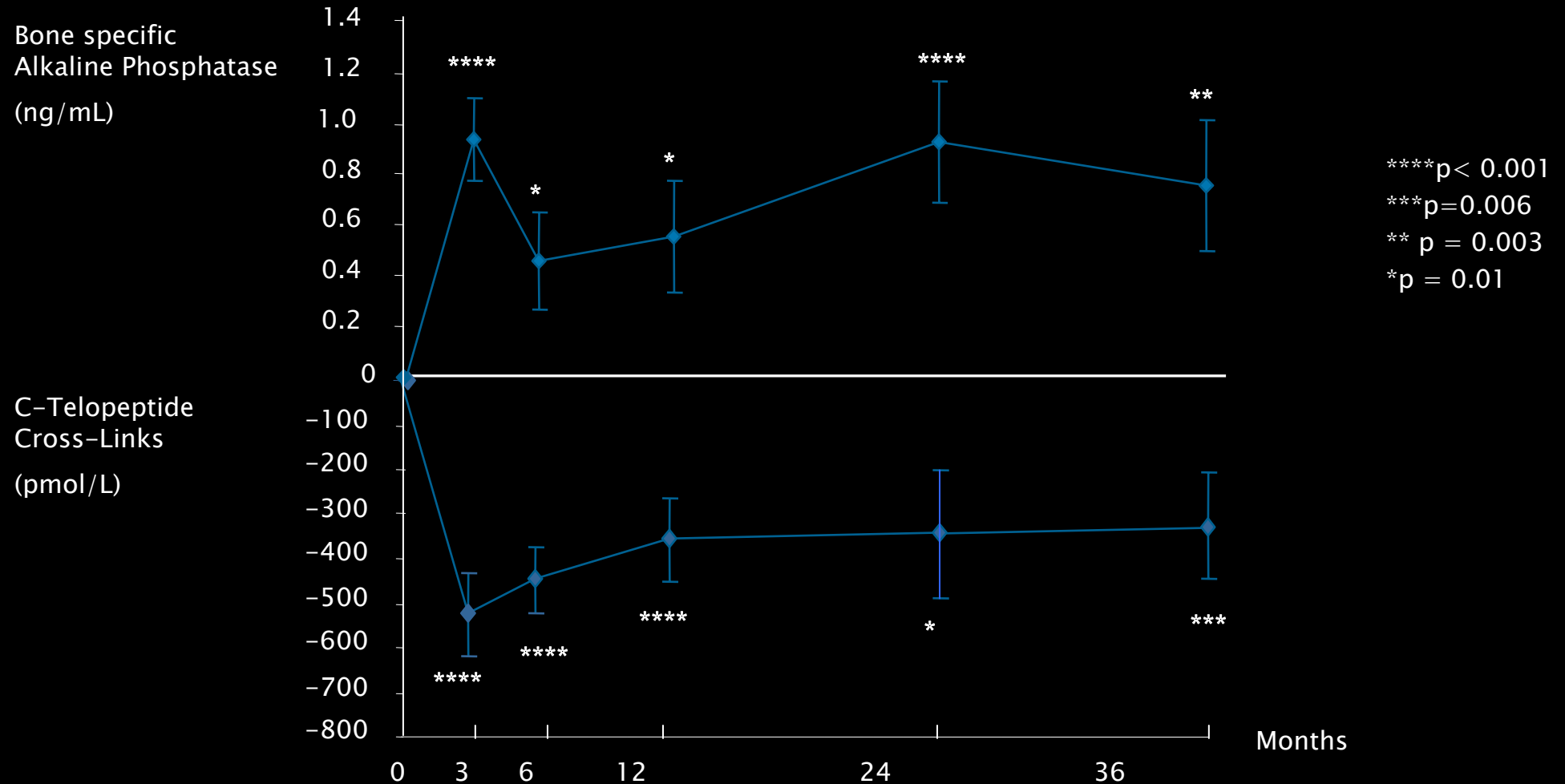
The treatment effect after adjustment for the strontium content of bone was an increase in BMD of 8.1% at the lumbar spine.

Each 1% increase in FN or total hip BMD after 1 (3) years predicts a 3 (4)% decrease in the risk of a new clinical fracture after 3 years.

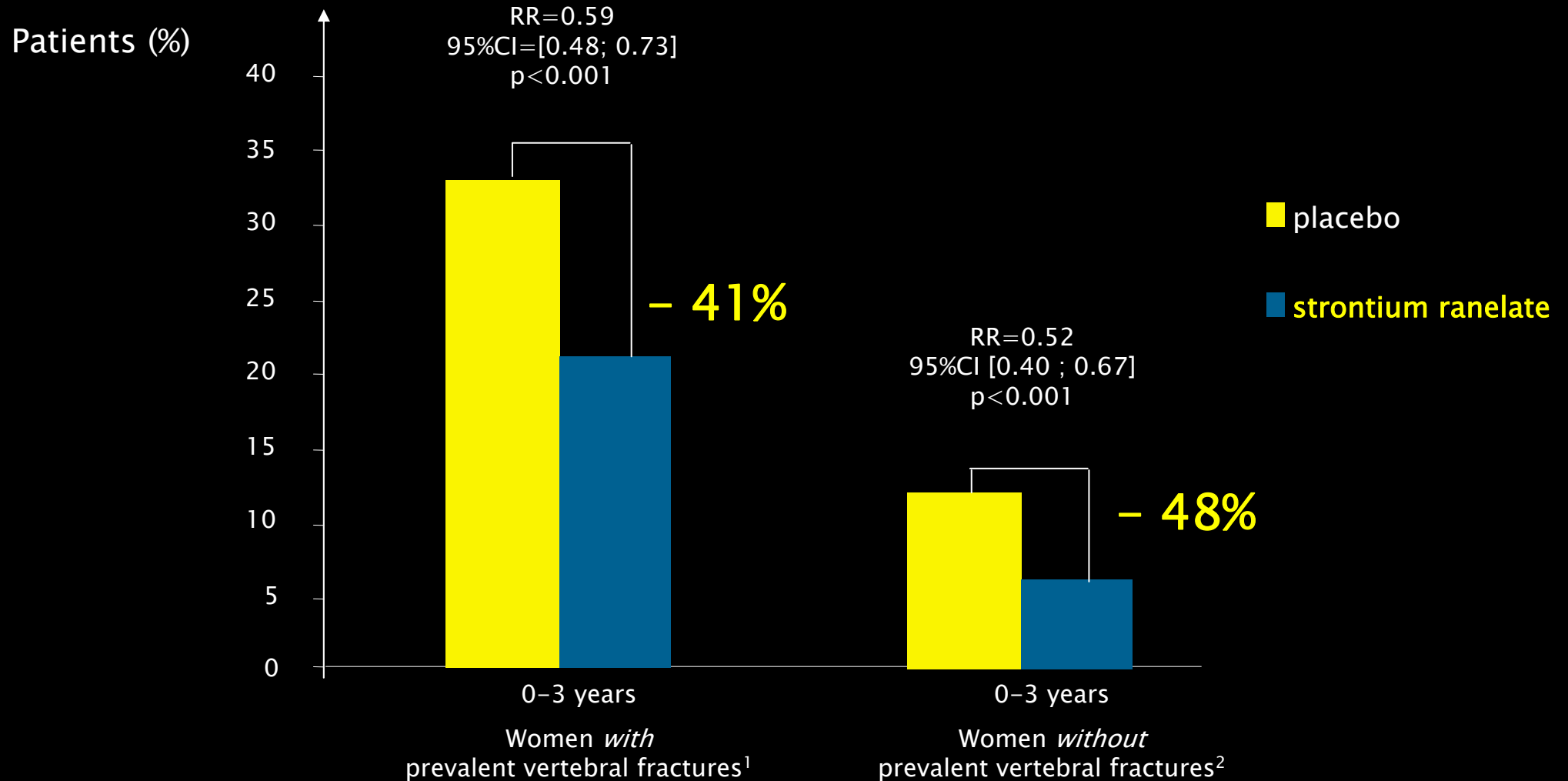
Meunier et al. *NEJM*. 2004;350:459-468

SOTI: bone markers

Difference over time between groups



Reduces vertebral fractures in patients with & without baseline fractures



1. Meunier et al. *NEJM*. 2004;350:459-468

2. Reginster JY. *Osteoporos Int*. 2004;15(Suppl 1):P409SA

TROPOS: peripheral & hip fracture

	Population	Risk reduction	95% CI	
Peripheral fracture	ITT	0.84 16%	0.70:0.995	p=0.04
Hip fracture	per protocol*	0.59 41%	0.37:0.95	p=0.025
	>74, BMD < 2.5	0.64 36%	0.41:0.99	P=0.046

* Population having taken treatment for at least the first 18 months verified by blood strontium levels

Reginster JY. Prevention of nonvertebral fractures. In: *Abstracts - IOF World Congress on Osteoporosis 2004*. Rio de Janeiro: International Osteoporosis Foundation; May 14-18, 2004. Abstract.

SOTI: tolerability

Symptoms	strontium ranelate	placebo	
Diarrhoea	6.1%	3.6%	p=0.02
Nausea	6.5%	4.3%	
Gastritis	3.6%	5.5%	NS

“Diarrhea was the most frequent adverse gastrointestinal event in the strontium ranelate group. However, this effect disappeared after the first three months.”

Osteoporosis Conclusions

A wide choice of effective treatments for osteoporosis

Missed treatment opportunities

Barriers to treatment because of Myths about side effects.