UNIVERSITY OF BIRMINGHAM | IMSR
INSTITUTE OF METABOLISM AND SYSTEMS RESEARCH

Birmingham Health Partners
CEDAM Centre for Endocrinology, Diabetes and Metabolism

Choosing the appropriate bisphosphonate treatment

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Building healthier lives

NHS
University Hospitals Birmingham
NHS Foundation Trust

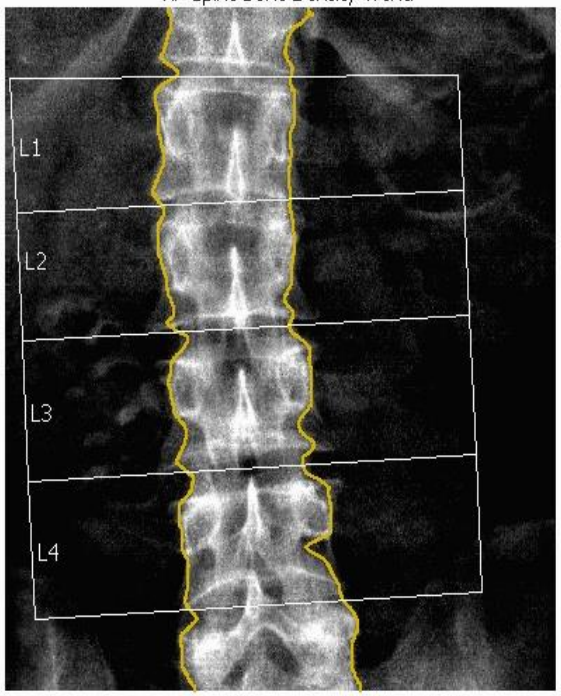
Disclosures

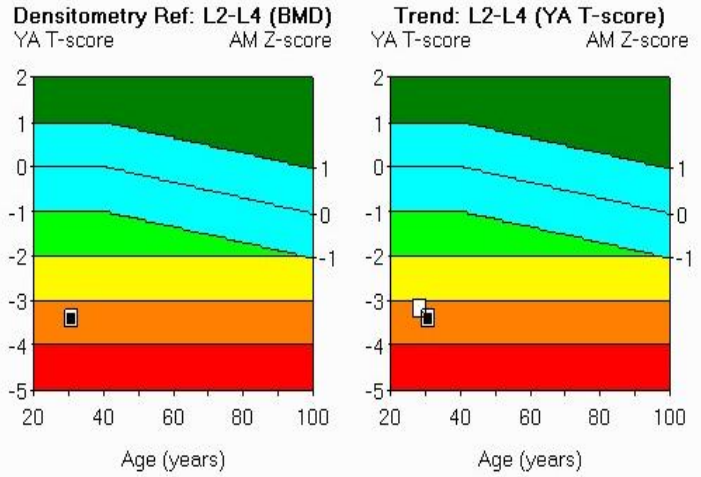
- Member National Osteoporosis Advisory Group (NOGG)

nogg NATIONAL OSTEOPOROSIS GUIDELINE GROUP

- Chair & Trustee, Royal Osteoporosis Society Clinical & Scientific Committee

Royal Osteoporosis Society
Better bone health for everybody





Region	[1] BMD (g/cm²)	[2] Young-Adult T-score	[3] Age-Matched Z-score
L1	0.834	-2.7	-2.7
L2	0.806	-3.6	-3.6
L3	0.823	-3.5	-3.5
L4	0.848	-3.3	-3.3
L1-L2	0.820	-3.2	-3.2
L1-L3	0.821	-3.2	-3.2
L1-L4	0.829	-3.3	-3.3
L2-L3	0.815	-3.5	-3.5
L2-L4	0.827	-3.4	-3.4

Trend: L2-L4

Measured Date	Age (years)	[1] BMD (g/cm²)	Change vs Previous (g/cm²)	Change vs Previous (%)
06/08/2013	31.0	0.827	-0.030 *	-3.5 *
13/04/2011	28.7	0.857	-	-

COMMENTS:

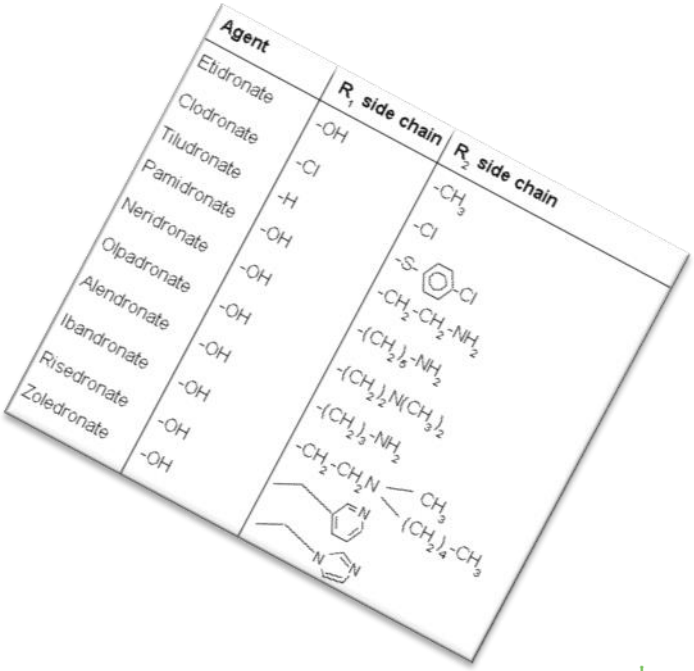
…please commence a bisphosphonate…

Bisphosphonate prescribing in osteoporosis

- ~85% of all active drug prescribing (all formulations)
  - Contraindications
  - Intolerance
  - ‘Escalation’
- Strong data in fracture prevention
- Long track record and familiarity to prescriber
- Cheap
- Poor adherence
- Tolerance
- Uncertainties
  - Duration
  - ‘Complications’
  - Perceptions

Bisphosphonates

- Consider
  - Alendronic acid (ALN)
  - Ibandronic acid (IBN)
  - Risedronic acid (RIS)
  - Zoledronic acid (ZOL)



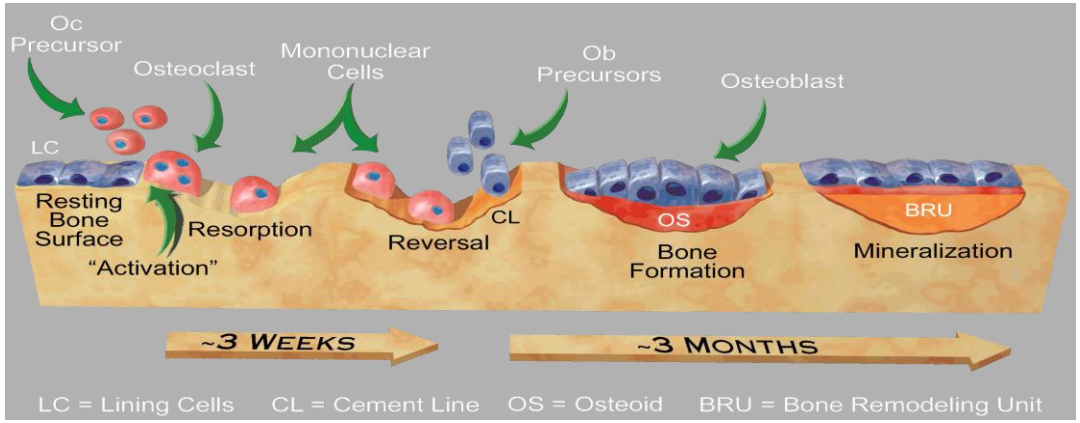
Agent	R_1 side chain	R_2 side chain
Etidronate	-OH	$-CH_3$
Clodronate	-Cl	-Cl
Tiludronate	-H	-S- -Cl
Pamidronate	-OH	$-CH_2-CH_2-NH_2$
Neridronate	-OH	$-(CH_2)_3-NH_2$
Olpadronate	-OH	$-(CH_2)_2N(CH_3)_2$
Alendronate	-OH	$-(CH_2)_3-NH_2$
Ibandronate	-OH	$-CH_2-CH_2N(CH_3)(CH_2)_4-CH_3$
Risedronate	-OH	
Zoledronate	-OH	

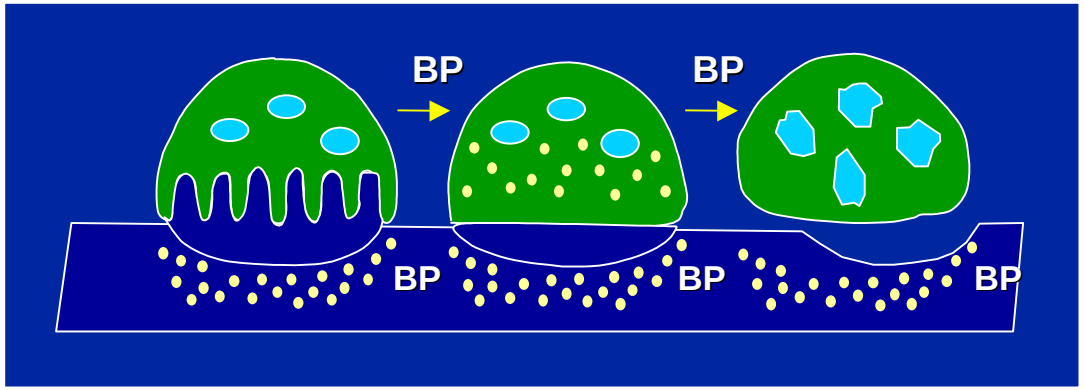
- Not consider
  - Clodronate
  - Etidronate
  - Pamidronate

Pharmacological properties of bisphosphonates

- Low bioavailability (<1%)
- Low systemic exposure
- Food interaction
  - Bioavailability further reduced by ~40%
- Rapid distribution from plasma
- Specific affinity for bone
- Not metabolised, renal excretion
- Minimal systemic toxicity
  - Predominantly limited to upper GI tract

Bone remodelling and bisphosphonate mechanisms of action





Active Osteoclast | **Inactive Osteoclast** | **Apoptotic Osteoclast**

HMG Co-A

↓

Mevalonate

↓

Alendronate ⊣

↓

Farnesyl-PP

↓

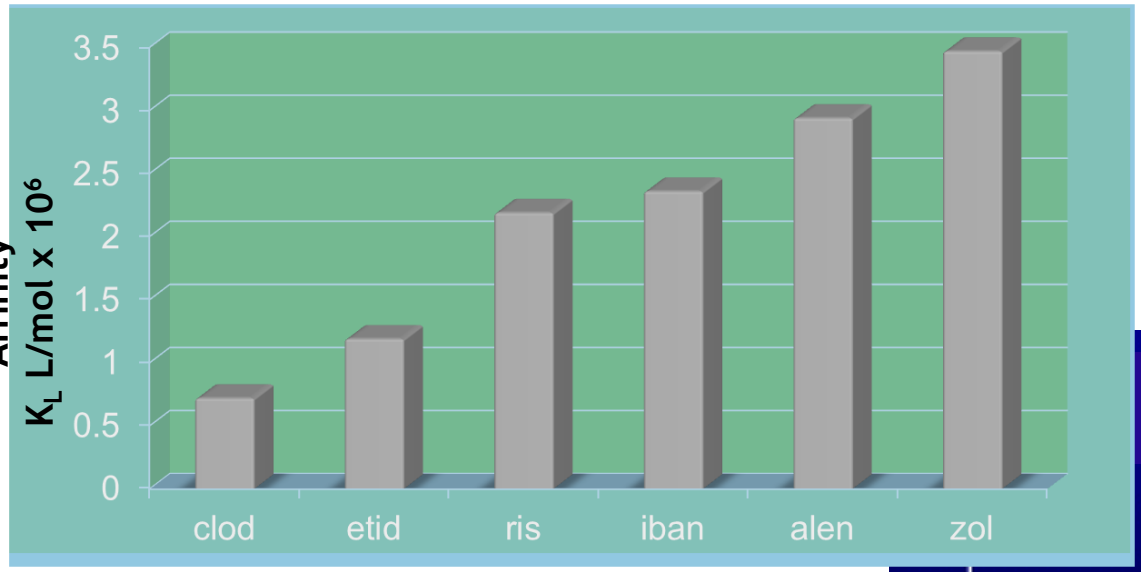
Geranylgeranyl

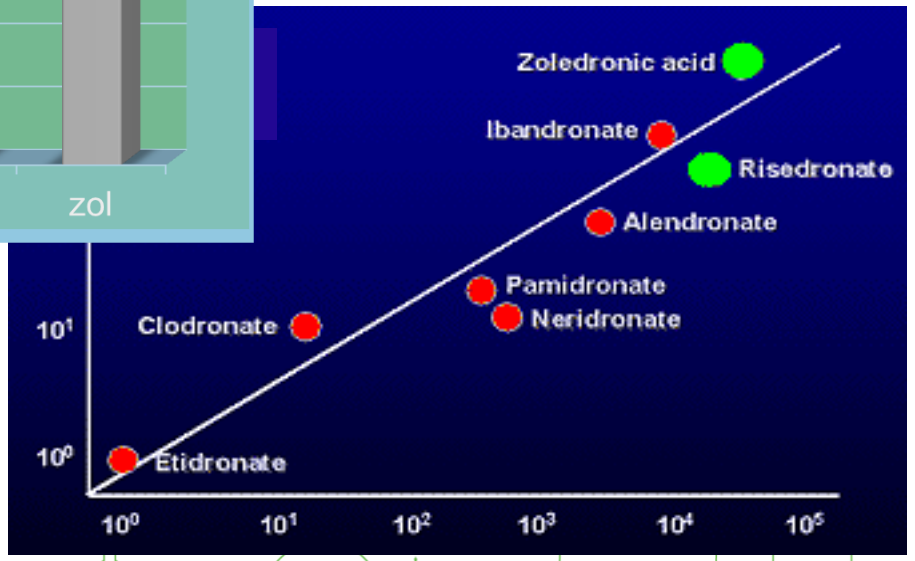
↓

Isoprenylation (Geranylgeranylation)

J Clin Invest. 1996;97:2692.

Bisphosphonate binding affinity and potency





Coleman, 2001; Henneman et al, 2003

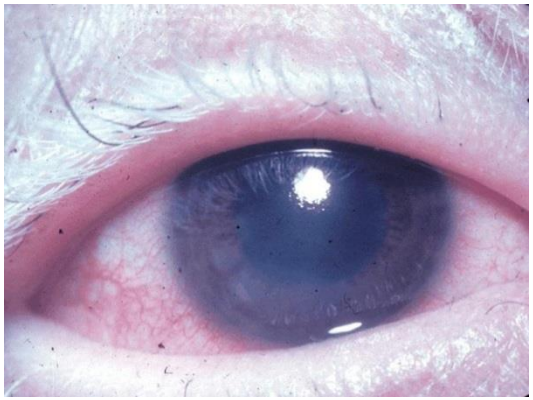
Bisphosphonate *class* considerations MHRA

- Oesophageal reactions (oral)
  - Not oesophageal cancer
- Atrial fibrillation under review
- Osteonecrosis of jaw
- Atypical femoral fractures
- Severe renal impairment

https://www.gov.uk/government/publications/bisphosphonates-use-and-safety/bisphosphonates-use-and-safety

Bisphosphonate side effects – caution about switch in class

- Iritis/uveitis



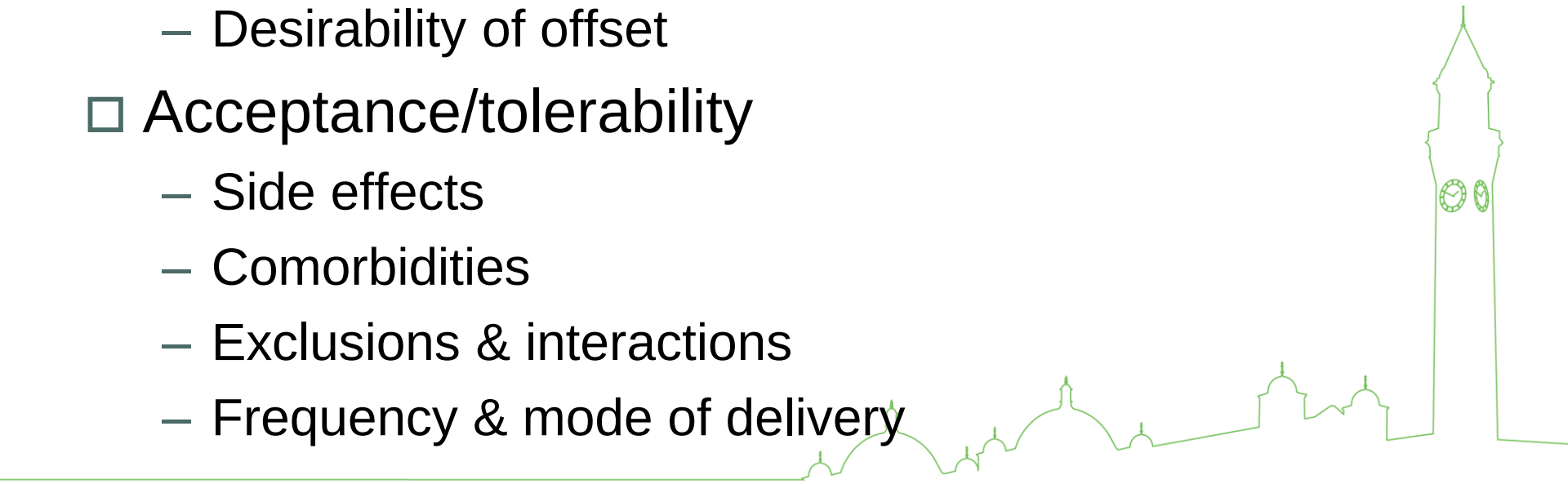
- Severe skeletal pain
- Consider switch to non-bisphosphonate

What are we trying to achieve with osteoporosis pharmacotherapy?

- Improve bone strength
- Minimise fracture risk
- Minimise inconvenience to patients
- Safety and adverse events
- Acceptability
- Dosing frequency, route, palatability
- Improve bone quality
- Provide long-term solution for fracture risk reduction

Practical considerations for pharmacotherapy

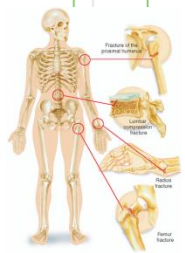
- Efficacy
  - Fracture reduction at all relevant sites
  - Pertinent to age group
  - Speed of onset of action
  - Desirability of offset
- Acceptance/tolerability
  - Side effects
  - Comorbidities
  - Exclusions & interactions
  - Frequency & mode of delivery



Fracture reduction at all relevant sites

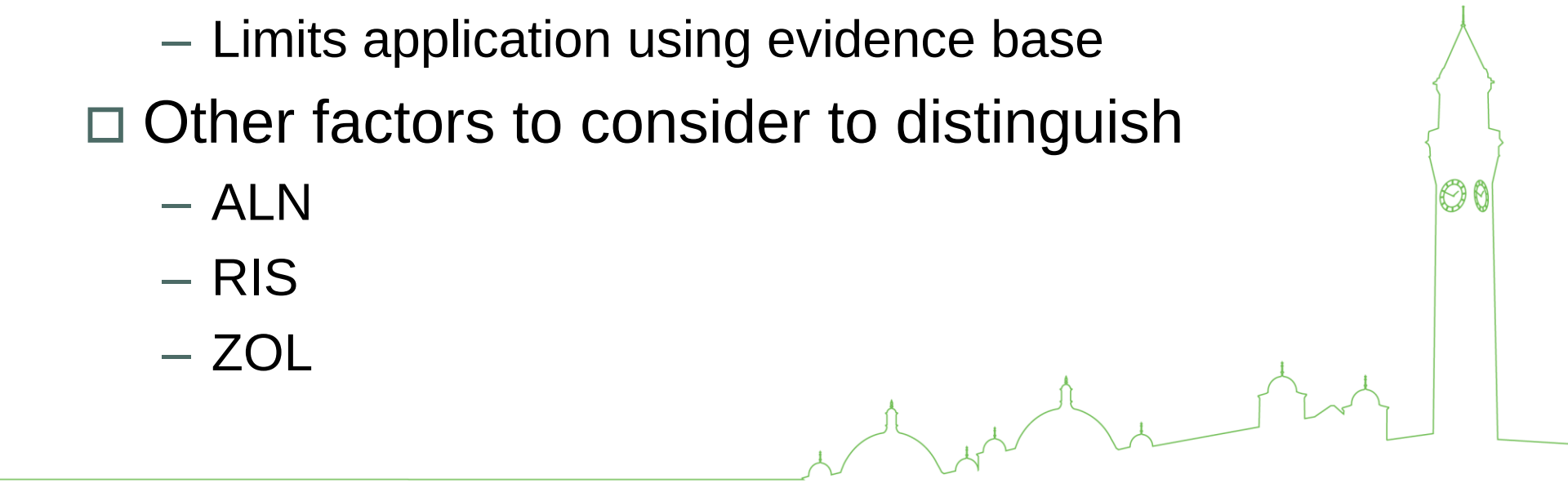
Licensed indications for use (SPC)

Drug	Vertebral #	Hip #	GCIOP	OP men
Alendronate	✔	✔	✔	✔
Risedronate	✔	✔	✔	✔
Ibandronate	✔	✘	✘	✘
Zoledronate	✔	✔	✔	✔
Raloxifene	✔	✘	✘	✘
Strontium ranelate	✔	✔	✘	✘
Teriparatide	✔	✔	✔	✔
Denosumab	✔	✔	✘	✔



Differentiating bisphosphonates

- ALN, RIS and ZOL broadly equivalent fracture data
- IBN no hip fracture data
  - Maybe study design related
  - Limits application using evidence base
- Other factors to consider to distinguish
  - ALN
  - RIS
  - ZOL



Bisphosphonate comparators

	Route	Frequency	Drug cost (£)	Total annual cost (£)	eGFR threshold <(ml/min)
ALN	O	1/52	9.91	61.57	35
IBN	O/IV	1/12 3/12	11.88 31.56	63.54 797.11	30
RIS	O	1/52	9.91	61.57	30
ZOL	IV	12/12	13.24	439.71	35

Fracture data

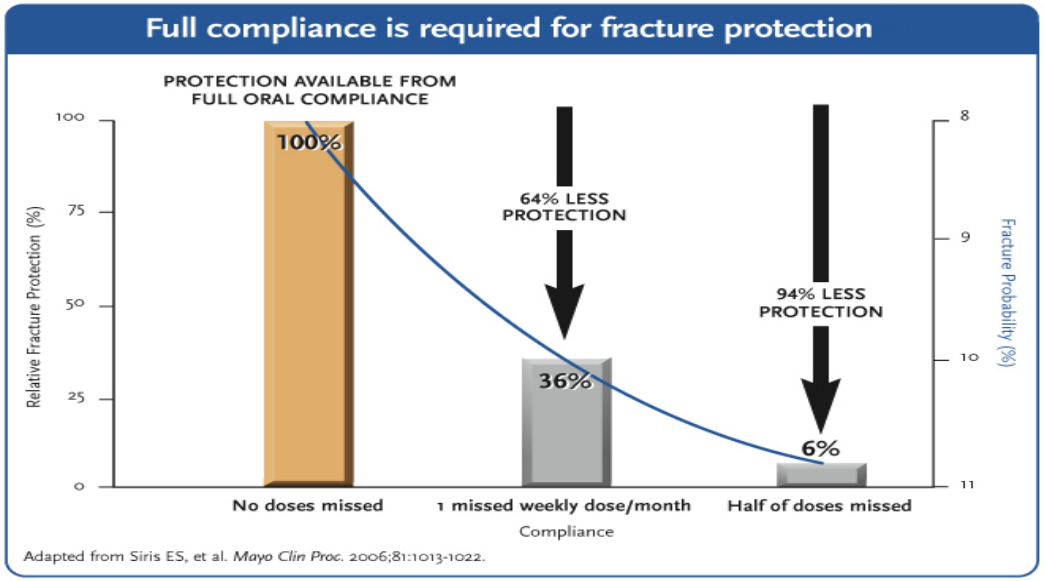
Drug costs based on the National Drug Tariff
Total annual cost = drug + administration + monitoring
NICE MTA costs

Route of administration - clinical

- IV desirable (ZOL)
  - Active upper GI symptoms
  - Anatomical or functional oesophageal pathology
  - Oesophageal varices

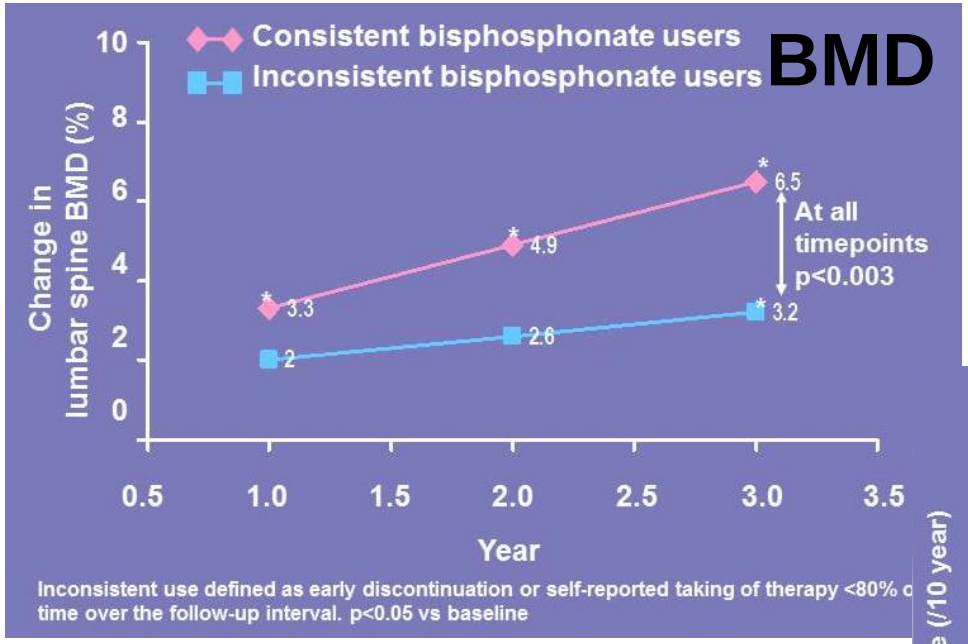
Compliance with oral BPs is poor

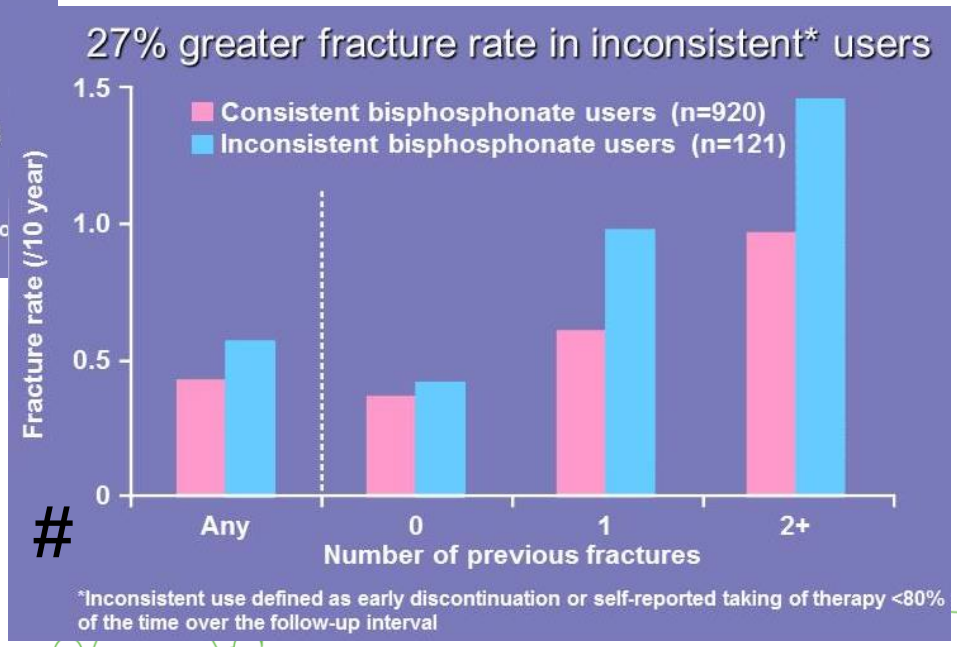
- Approximately 50% of patients are noncompliant within 1 year
- Probability of fracture increases as compliance decreases
- GI intolerability and inconvenient dosing regimens contribute to poor compliance



Siris et al, 2006; Seeman et al, 2007; Cramer & Silverman, 2006

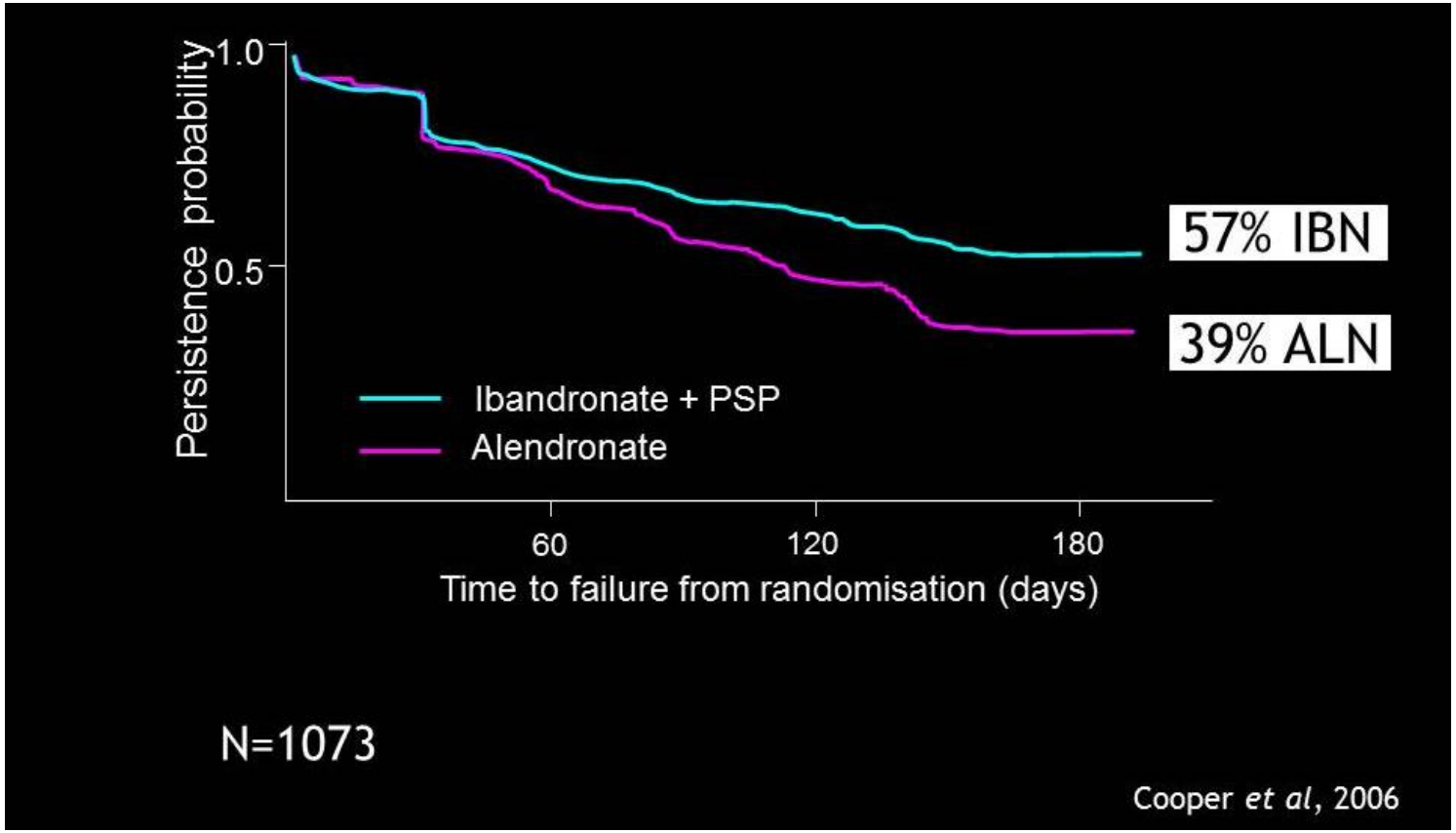
BMD gains impaired and fractures increased with poor adherence





Sebaldt RJ, *et al.*, 2004

Persistence weekly ALN v monthly IBN



Factors contributing to non-adherence

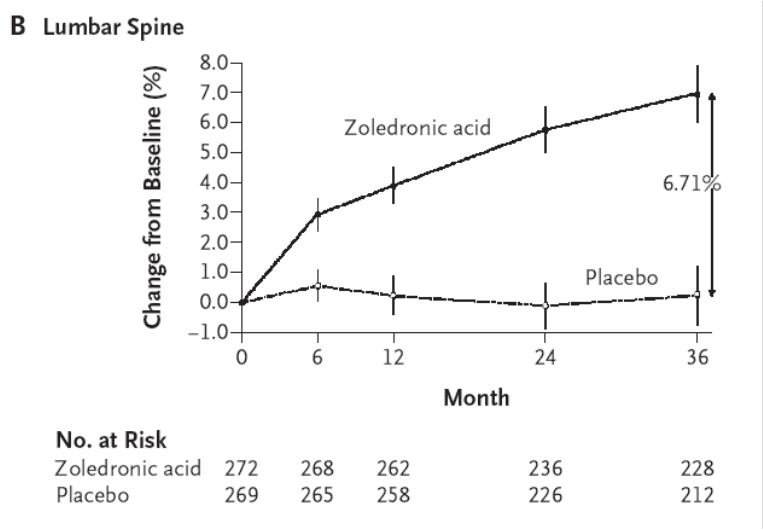
- ‘Silent’ disease
- Failure to perceive benefits of treatment versus drug related side-effects
- Disease chronicity
- Relative ‘importance’ of diseases
  - Should I take my osteoporosis or heart tablets?
- Polypharmacy
- Lack of understanding of what medication is supposed to treat
- Inconvenient dosing regimen

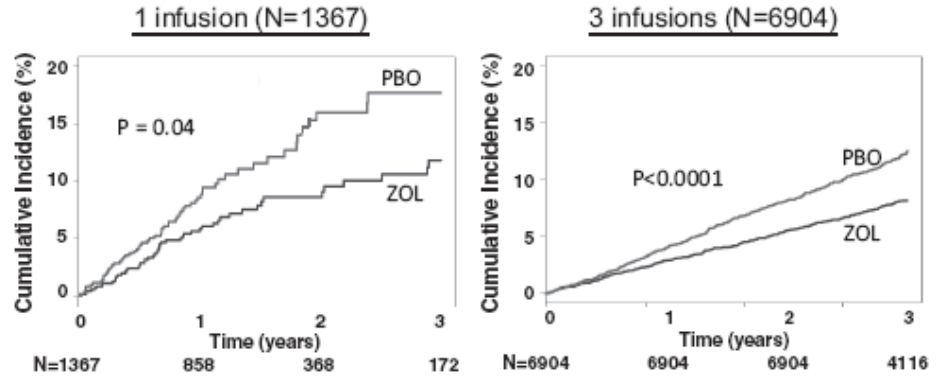
Frequency (and route) of administration

- Approximately 50% noncompliance with oral bisphosphonates at 12/12
- Poor adherence, compliance and persistence
  - Efficacy falls++
  - Cost effectiveness poor
  - Side effects with no benefit
- Polypharmacy
  - Convenience
- Pragmatism
  - Post hip #

Seeman E, et al., 2007

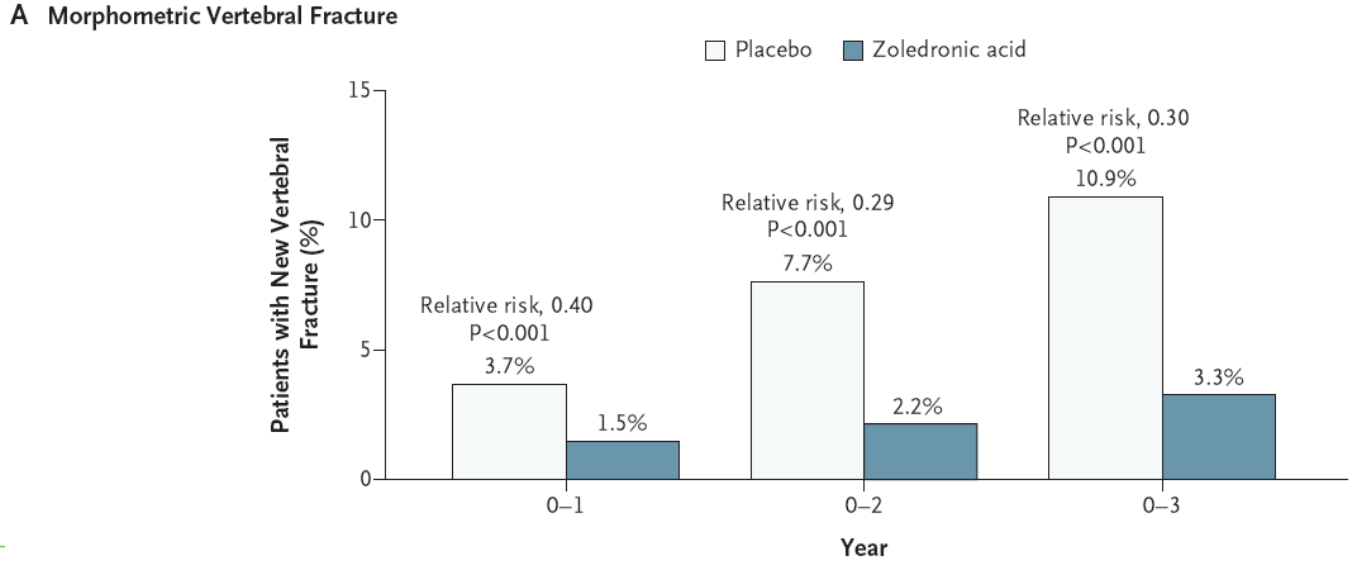
Infrequent administration





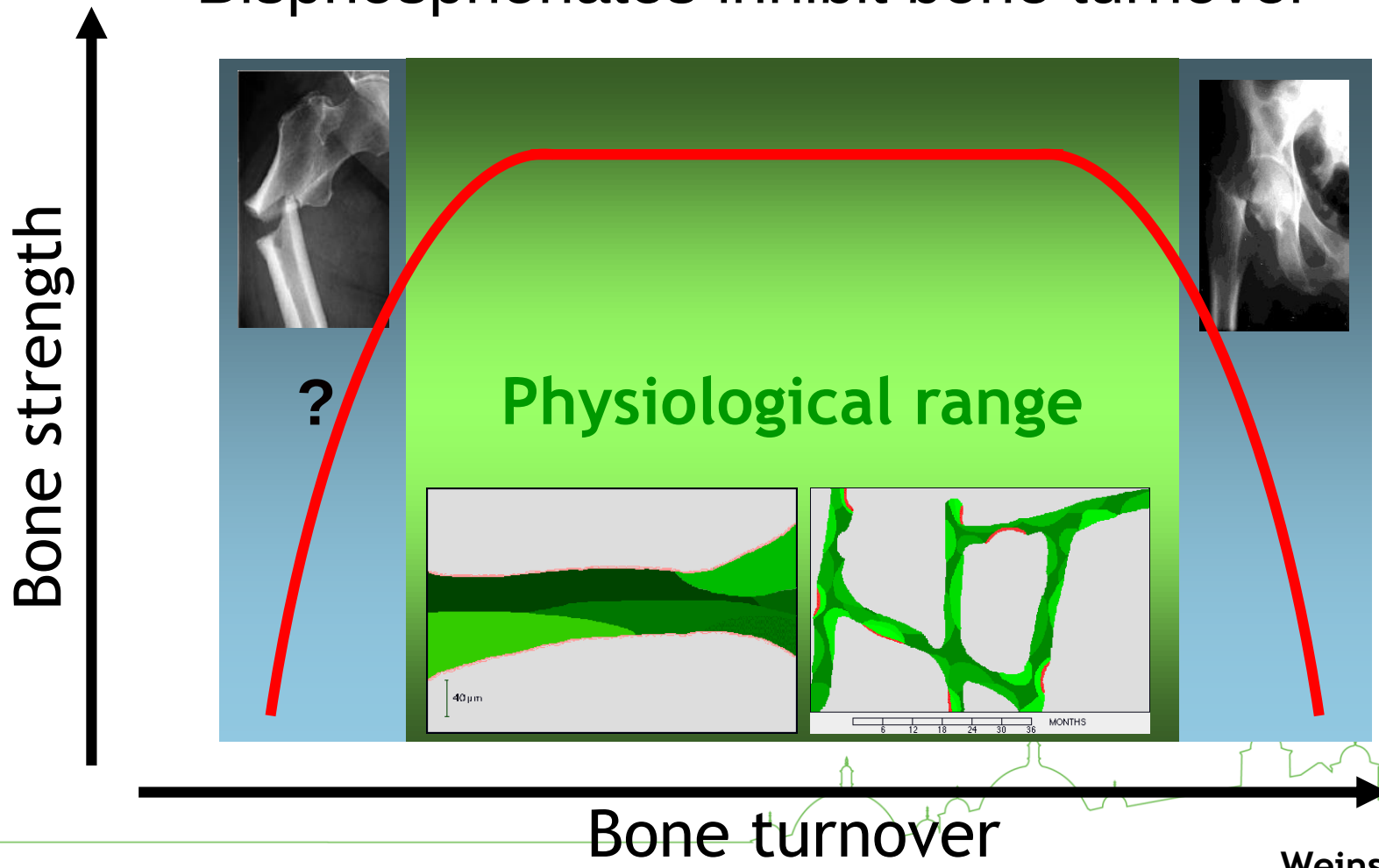
Time	HR	p
3 years	0.68	0.04
2 years	0.64	0.02

Time	HR	p
3 years	0.66	<0.0001
2 years	0.66	<0.0001



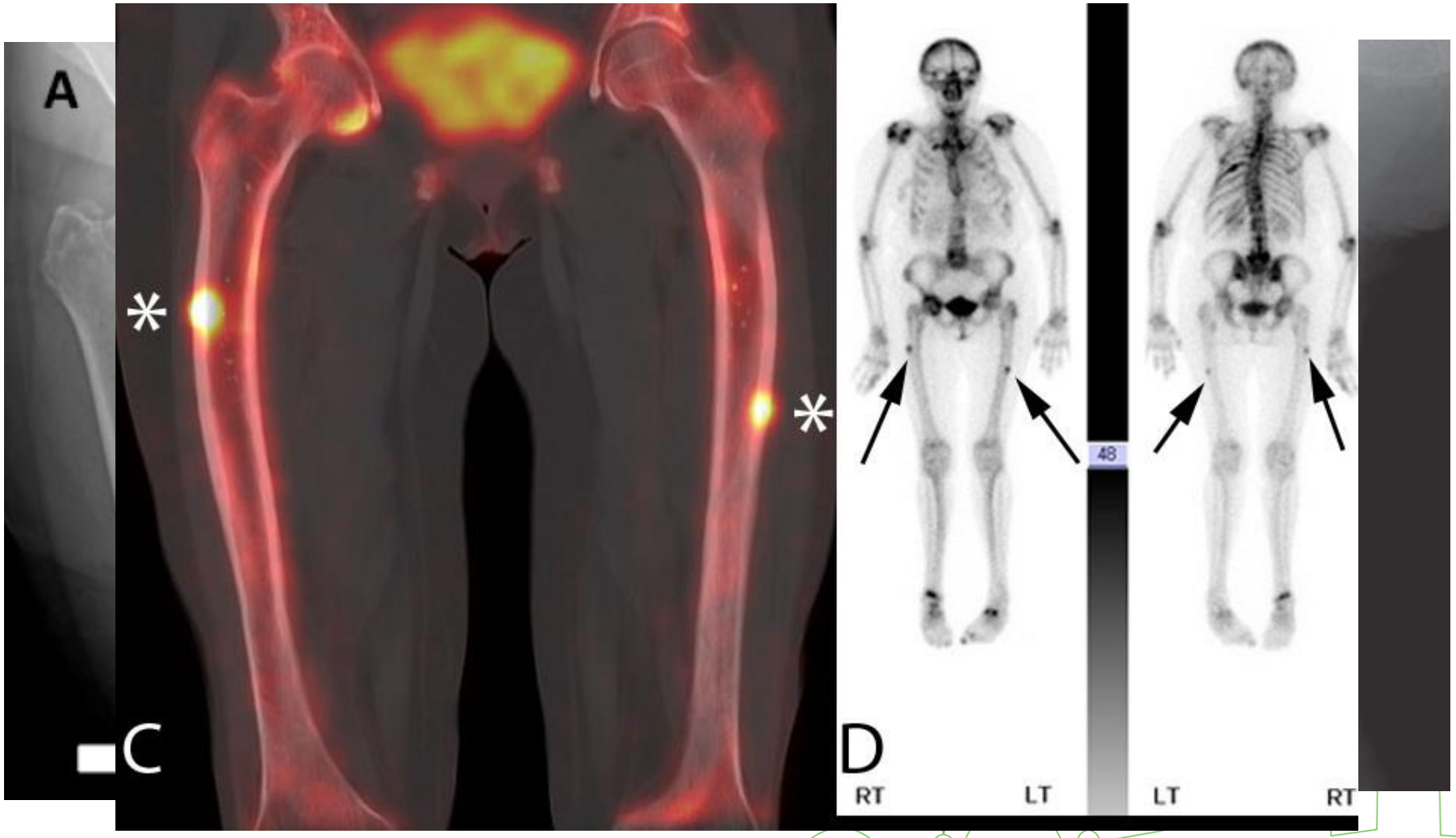
How long to treat with bisphosphonates?

Bisphosphonates inhibit bone turnover



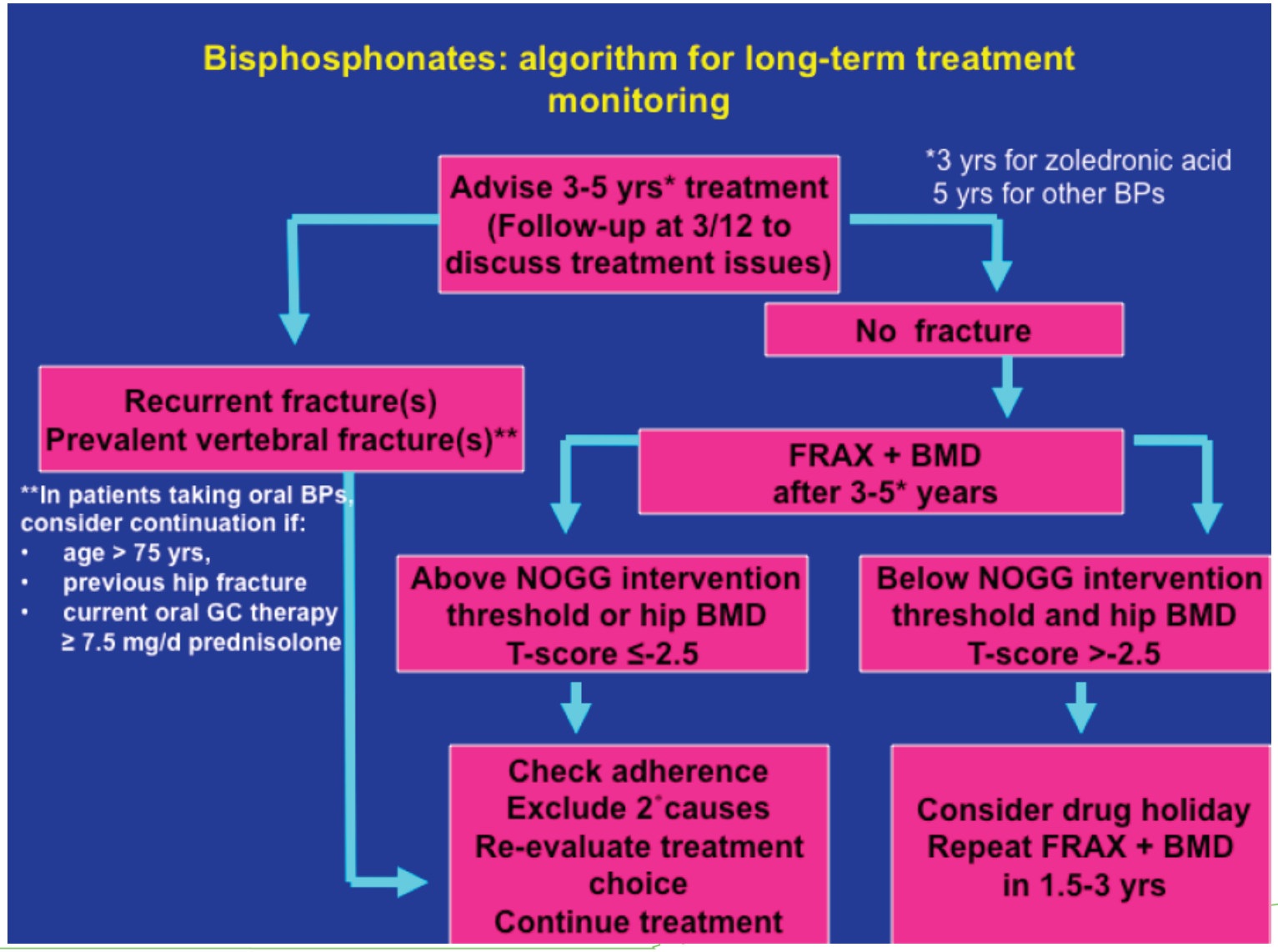
Weinstein, 2000

Duration of action and offset



Manolopoloulos & Gittoes, 2013

How long to treat with bisphosphonates?



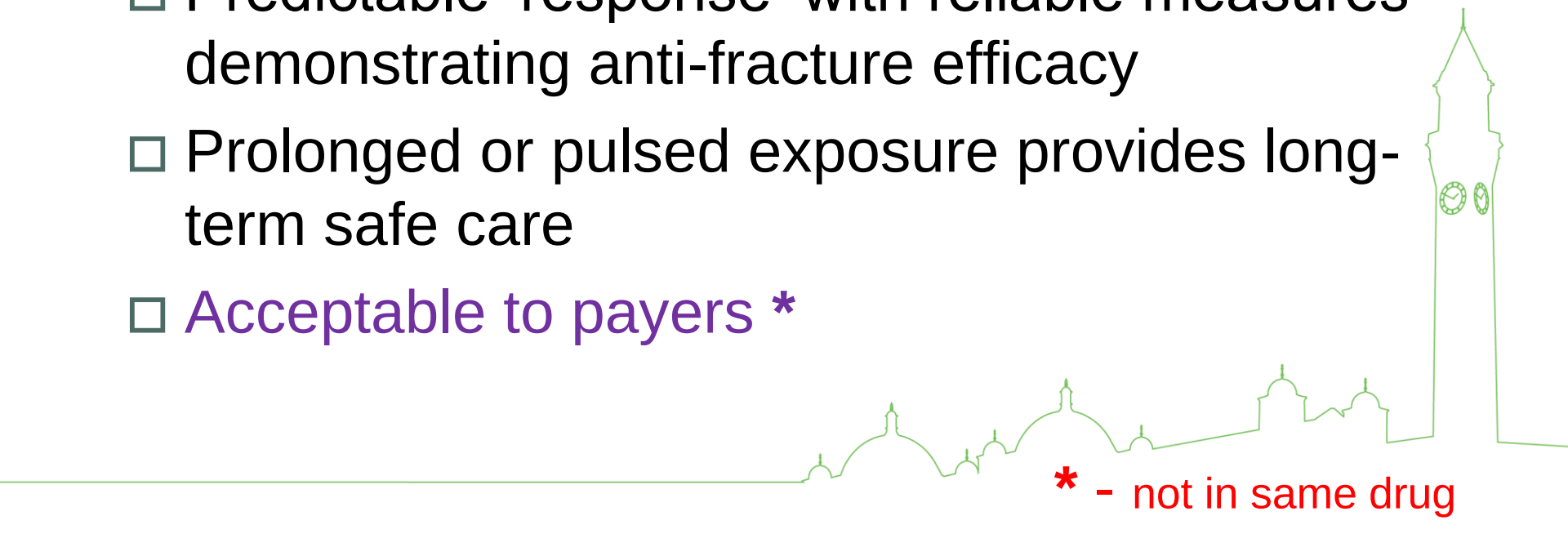
NOGG, 2017

Available bisphosphonates to reduce fracture risk – What's good?

- Highly effective in *high risk groups*
  - Fractures, older, low BMD (T<-2.5)
  - 50%+ anti-fracture efficacy
  - Sustained effect (10 yrs)
- Safe when used appropriately
- Rapid onset of anti-fracture effect
  - 6-12 months
- Multiple treatment options
  - Daily, weekly, monthly, 3/12, 12/12
  - Oral, IV

The ideal osteoporosis drug (BP)

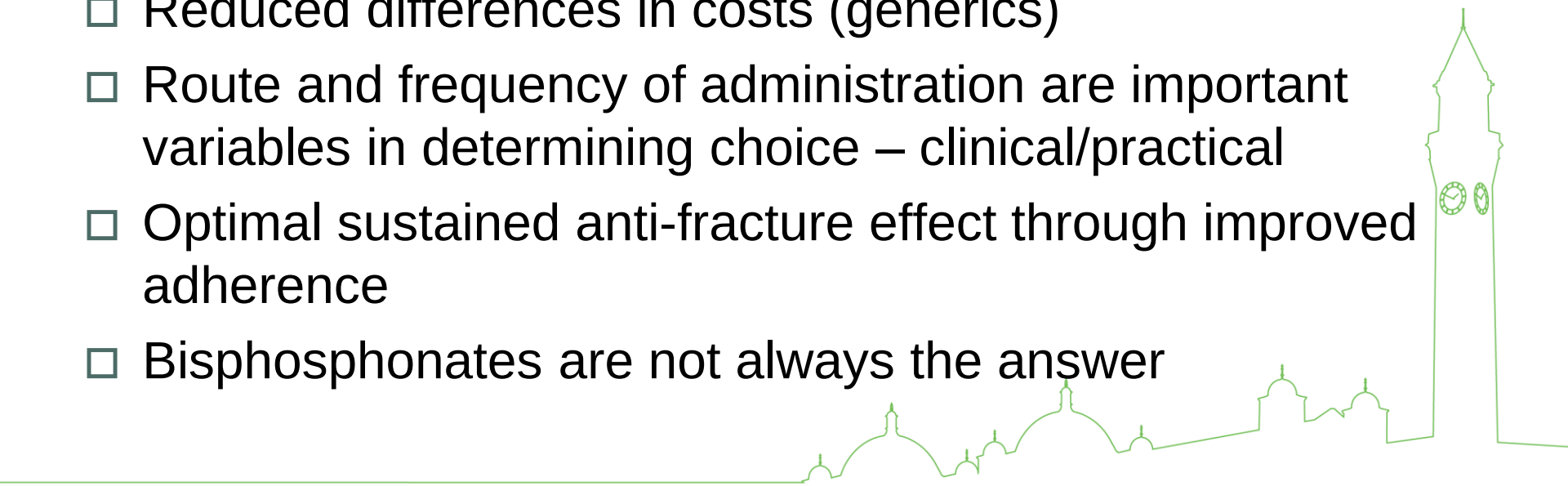
- Reverses pathology of osteoporosis *
- Reduces fracture risk to ‘background’
- Infrequently administered *
- Minimal side effects and inconvenience *
- Predictable ‘response’ with reliable measures demonstrating anti-fracture efficacy
- Prolonged or pulsed exposure provides long-term safe care
- Acceptable to payers *



* - not in same drug

Summary

- Bisphosphonates are appropriately the most prescribed active treatment for osteoporosis
- Most adverse effects are class related
  - Caution switching within class
- Subtle differences in anti-fracture effect
- Reduced differences in costs (generics)
- Route and frequency of administration are important variables in determining choice – clinical/practical
- Optimal sustained anti-fracture effect through improved adherence
- Bisphosphonates are not always the answer



Conclusion

- Be aware of differences between bisphosphonates
- Aim for sustainable anti-fracture efficacy
- Be prepared to switch within class and beyond class to optimise outcomes
- Involve patients in decision making