

골다공증약제의 올바른 사용과 유해성 관리

김 범 택
아주의대 가정의학과

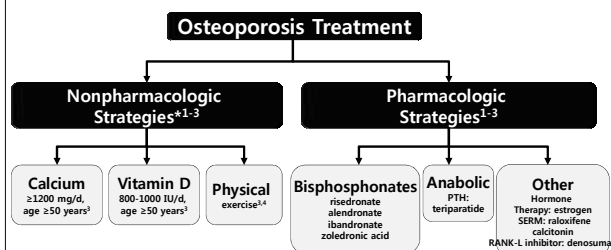
강의 내용

- ◆ Principles of Osteoporosis Treatment
- ◆ Factors to consider for osteoporosis medications
- ◆ Adverse effects of osteoporosis medications
- ◆ Give the Best you have



Principles of Osteoporosis Treatment

Osteoporosis Treatment Strategies



SERM=selective estrogen receptor modulator; RANK-L=RANK ligand.

*Including supplements if necessary.

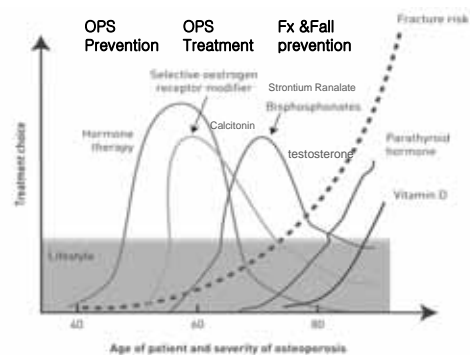
1. NIH, JAMA. 2001;285:785-795.

2. AACE. Endocr Pract. 2003;9:S44-S64.

3. NOF. Clinician's Guide to Prevention and Treatment of Osteoporosis. NOF; 2010.

4. US DHHS. Bone Health and Osteoporosis: A Report of the Surgeon General. Office of the Surgeon General; 2004.

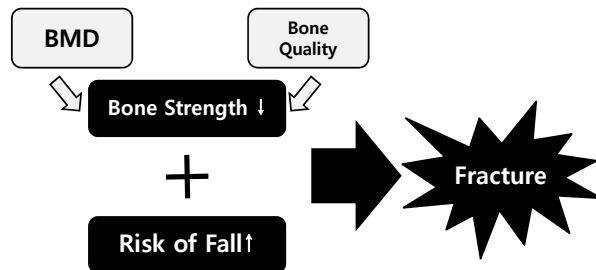
What options do we have?



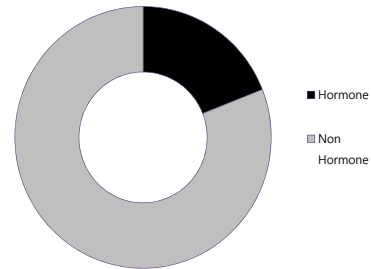
Nguyen TV *et al. Med J Aust* 2004; 180: S18-22.



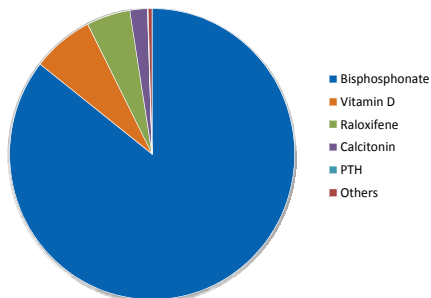
How fracture occurs



HRT vs. Non-HRT



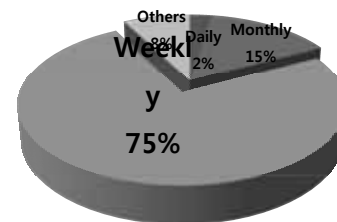
Bisphosphonates Rule !



J Korean Soc Menopause. 2010 Dec;16(3):170-175

The Most Commonly Prescribed BPs

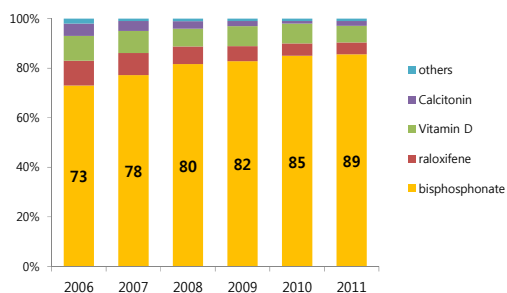
Total Prescriptions for Traditional Bisphosphonates, %*



2011 2Q IMS data

Osteoporosis Treatment (Korea data)

Bisphosphonate ~ 89%



Why Bisphosphonates ?

- Interval of medication
- Low cost
- Safety

BRONJ and Atypical fracture



골다공증을 치료하는 의사의 어려움



Factors to consider for
osteoporosis medications

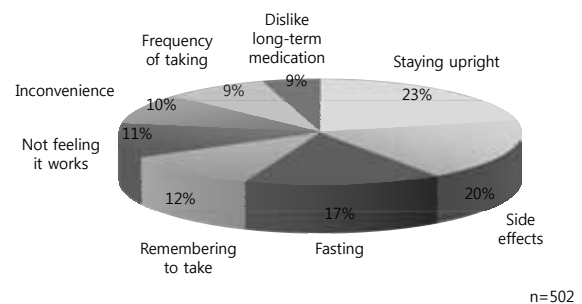
When Should We Stoooooop?



Long Term Treatment



Why Pts Stop?



IOF, 2005
http://www.osteofound.org/publications/pdf/adherence_gap_report.pdf

Ideal OPS medication

	Easy	to Take
	Greatest	Efficacy
The	Long-term	Prevention
	Least	Adverse Effects
	Reasonable	Cost

Adverse effects of osteoporosis medications

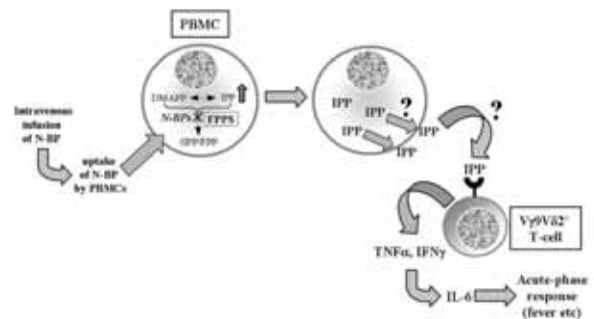
Are BPs Safe?

Short term vs. Long term

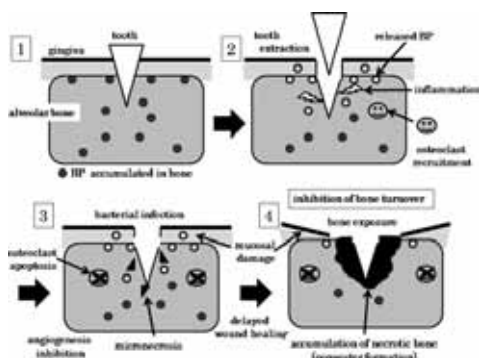
- Acute phase reaction
- Upper GI trouble
- Musculoskeletal pain
- Hypocalcemia
- Ocular inflammation
- Skin reactions
- BRONJ
- Atypical Fracture
- Renal Toxicity
- Atrial Fibrillation(?)
- Esophageal cancer(?)

Drugs. 2011;71(6):791-814

Flu like reaction (Acute phase reaction)

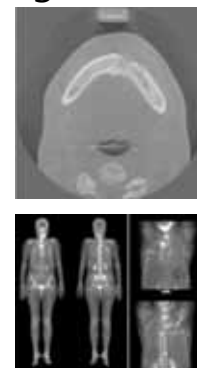


Pathophysiology of BRONJ



BRONJ diagnosis

- No X-ray
- CT
- MRI
- Bone Scan

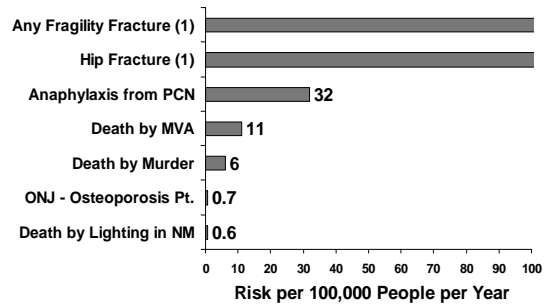


Stage of BRONJ

At risk category	No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates
Stage 0	Nonspecific clinical findings and symptoms such as jaw pain or osteodermosis but no clinical evidence of exposed bone
Stage 1	Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage
Stage 3	Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border or sinus floor

Ann N Y Acad Sci. 2011 Feb;1218:38-46

ONJ Comparative Risks



[M. Lewiecki 2007]

Renal Toxicity

• Restrain of Use when

- Risedronate : CCR < 30 mL/min
- Ibandronate : CCR < 30 mL/min
- Alendronate : CCR < 35 mL/min
- Zoledronate : CCR < 35 mL/min



Manufacturer's instructions

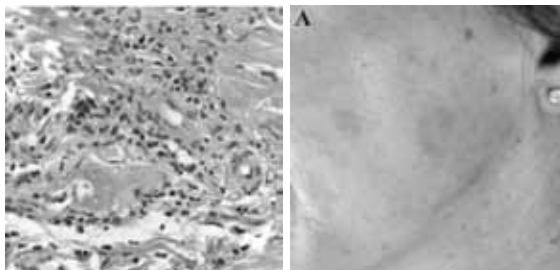
Ocular inflammation

- Iritis, Uveitis, Scleritis
- Ocular pain & photo sensitivity
- Variable duration



Mayo Clin Proc. 2009;84(7):632-8

Ibandronate related dermatitis



Eur J Dermatol. 2011;21(4):591-4

	Duration of Bisphosphonate Therapy			
	Transient, <100 days	Short-term Use, 100 days to 3 years	Intermediate Use, 3 to 5 Years	Long-Term Use, ≥5 Years
No. (%) of patients				
Case (n = 9723)	817 (8.4)	5567 (57.5)	2436 (25.1)	881 (9.1)
Control (n = 48564)	3434 (7.1)	27066 (55.8)	13148 (27.1)	4896 (10.1)
Odds Ratio (95% CI)				
Crude	1.0 [Reference]	0.87 (0.80-0.94)	0.72 (0.65-0.79)	0.65 (0.58-0.74)
Adjusted ^a	1.0 [Reference]	0.93 (0.81-1.07)	0.86 (0.73-1.00)	0.76 (0.63-0.93)

	Duration of Bisphosphonate Therapy			
	Transient, <100 days	Short-term Use, 100 days to 3 years	Intermediate Use, 3 to 5 Years	Long-Term Use, ≥5 Years
No. (%) of patients				
Case (n = 716)	42 (5.9)	349 (48.7)	204 (28.5)	121 (16.9)
Control (n = 3580)	218 (6.1)	1832 (51.2)	1070 (29.9)	460 (12.9)
Odds Ratio (95% CI)				
Crude	1.0 [Reference]	1.00 (0.70-1.43)	1.08 (0.73-1.59)	1.74 (1.11-2.73)
Adjusted ^a	1.0 [Reference]	0.90 (0.48-1.68)	1.59 (0.80-3.15)	2.74 (1.25-6.02)

JAMA. 2011 Feb 23;305(8):783-9.



Atypical Fracture



Diagnostic Criteria

Characteristics	Sensitivity (%)	Specificity (%)	Accuracy (%)
Reader 1			
Focal lateral cortical thickening	100 (18/18)	89.5 (17/19)	94.7 (35/38)
Transverse fracture	89.5 (17/19)	84.2 (16/19)	86.8 (33/38)
Medial spike	79.0 (15/19)	73.7 (14/19)	76.3 (29/38)
Comminution	73.7 (14/19)	73.7 (14/19)	73.7 (28/38)
Reader 2			
Focal lateral cortical thickening	100 (18/18)	88.4 (17/19)	94.2 (32/38)
Transverse fracture	89.5 (17/19)	79.0 (15/19)	84.2 (32/38)
Medial spike	73.7 (14/19)	73.7 (14/19)	73.7 (28/38)
Comminution	79.0 (15/19)	83.2 (12/19)	71.1 (27/38)
Reader 3			
Focal lateral cortical thickening	94.7 (18/19)	89.5 (17/19)	92.1 (35/38)
Transverse fracture	94.7 (18/19)	79.0 (15/19)	86.8 (33/38)
Medial spike	84.2 (16/19)	84.2 (16/19)	84.2 (32/38)
Comminution	79.0 (15/19)	79.0 (15/19)	79.0 (30/38)

AJR Am J Roentgenol. 2011;197(4):954-60

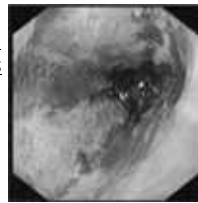
Erosive esophagitis

Most common reason for patient intolerance to oral BPs

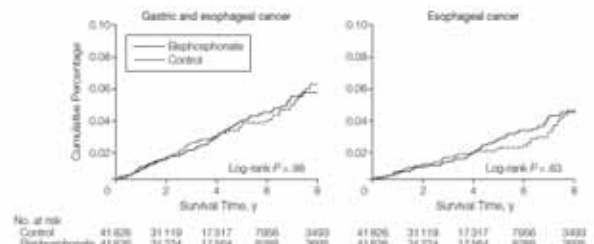
Resulting from failure to maintain an upright posture for 30 to 60 minutes after ingesting medication with a full glass of water

IV BPs

: not associated with increase in GI events

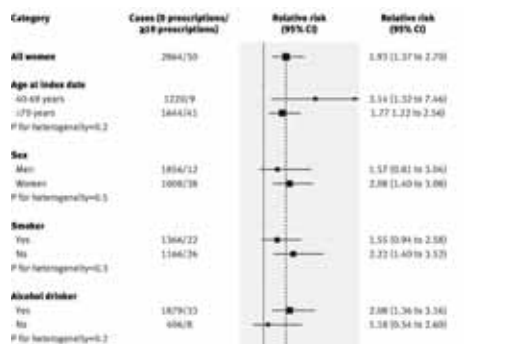


BPs and Esophageal cancer



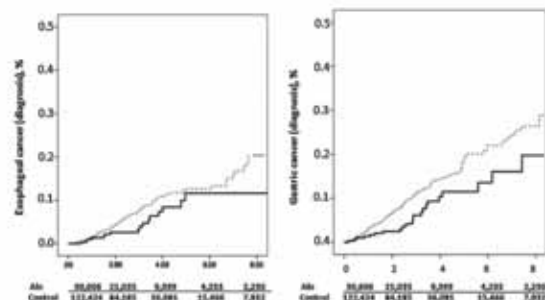
JAMA. 2010 ;304(6):657-63.

BPs and Esophageal cancer



Green J et al. BMJ 2010;341:bmj.c4444

Alendronate and UGI cancers



J Bone Miner Res. 2011 Nov 23. doi: 10.1002/jbmr.1481. Epub

Alendronate and UGI cancers

	No. of prescriptions	Crude		Adjusted	
		OR	95% CI	OR	95% CI
Esophageal cancer	Any	0.75	(0.46-1.22)	0.71	(0.43-1.19)
	1	2.12	(0.86-5.22)	1.96	(0.79-4.89)
	2-9	0.85	(0.34-2.08)	0.81	(0.32-2.04)
	10+	0.53	(0.27-1.05)	0.51	(0.25-1.02)
Gastric cancer	Any	0.58	(0.37-0.91) ^a	0.61	(0.39-0.97) ^a
	1	1.06	(0.39-2.88)	1.15	(0.42-3.13)
	2-9	0.91	(0.44-1.85)	0.99	(0.48-2.05)
	10+	0.40	(0.21-0.75) ^a	0.42	(0.22-0.81) ^a
Combined outcome	Any	0.61	(0.44-0.84) ^a	0.63	(0.45-0.87) ^a
	1	1.32	(0.68-2.57)	1.36	(0.70-2.67)
	2-9	0.86	(0.50-1.47)	0.90	(0.52-1.56)
	10+	0.42	(0.27-0.66) ^a	0.44	(0.27-0.69) ^a

J Bone Miner Res. 2011 Nov 23. doi: 10.1002/jbmr.1481. Epub

Alternatives

- Change Dose and Route
- Change medication
- Drug Holidays

Alternative Drugs

- SERM
- Denosumab
- Teriperatide
- Strontium Ranelate
- HRT

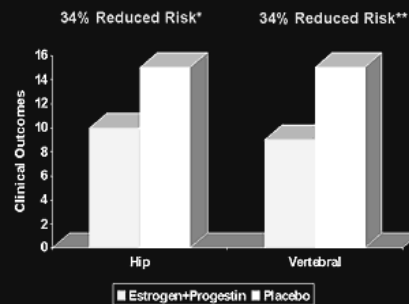
Holiday for BPs

- Efficacy
 - Residual in Bone
 - Over suppression
 - Slow recovery of bone turnover
- Adverse Effect
 - BRONJ
 - Atypical Fracture
 - Esophageal cancer



Give the Best you have

WHI Estrogen+Progestin Trial Study Results - Fractures



*Hip Fractures: HR 0.66; Nominal 95% CI (0.45-0.98), Adjusted 95% CI (0.33-1.33)
 **Vertebral Fractures: HR 0.66; Nominal 95% CI (0.44-0.98), Adjusted 95% CI (0.32-1.34)
 Writing Group for the Women's Health Initiative. JAMA. 2002;288:321-333.



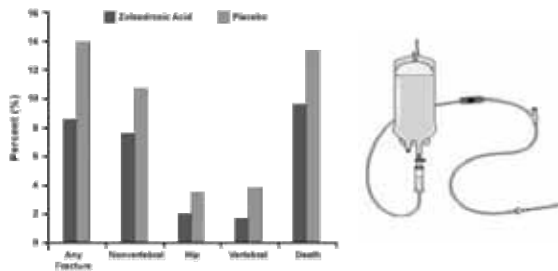
Evidence Summary — Hazard of HRT

Clinical Event	HERS E+P	WHI E+P	WHI E only
CHD event	0.99	1.29	0.91
Stroke	1.23	1.41	1.39
DVT	2.79	2.13	1.34
Breast Ca	1.30	1.26	0.77
Colon Ca	0.69	0.63	1.08
Hip Fx	1.10	0.66	0.61
Death	1.08	0.98	1.04

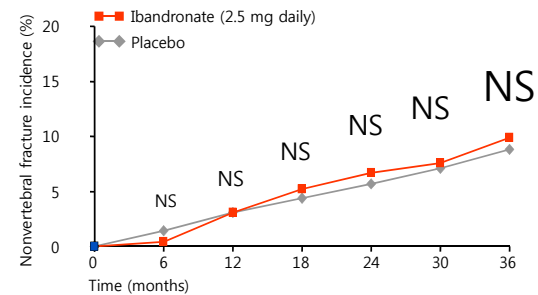
HRT: Pros and Cons

- Pros
 - Excellent control of vasomotor symptom
 - Reduced incidence of:
 - Colon Cancer
 - Osteoporosis
 - ? Type 2 DM
 - ? UTI
 - ? Depression
 - Preservation of joints, teeth, skin
- Cons
 - CHD: doesn't help, might hurt
 - Increased risk of stroke and DVT
 - Increased rates of breast Ca
 - Increased GB disease
 - Increased rates of lupus
 - Vaginal bleeding or endometrial cancer

Intravenous bisphosphonates - ZLD

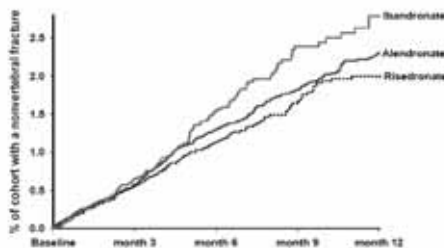


Lack of Evidence for Non-Vertebral Fracture Risk Reduction With Ibandronate in BONE Trial Population



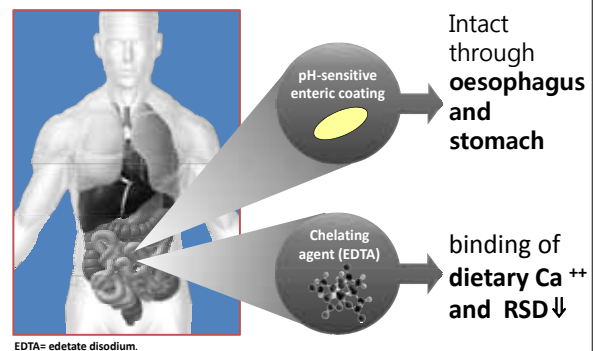
Chesnut et al., J Bone Miner Res 2004; 19: 1241-1249

REAL (IBN addition) study Non-vertebral fracture



Patients at risk (fracture events)					
Alendronate	21619 (0)	21489 (126)	12794 (253)	8436 (308)	5319 (343)
Risedronate	12219 (0)	12147 (68)	6743 (123)	4198 (162)	2449 (164)
Ibandronate	1000 (0)	7799 (291)	3008 (395)	2113 (202)	1146 (120)

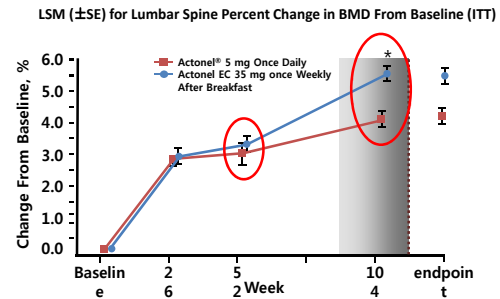
Enteric Coating Risedronate minimised interaction with food



Benefits of Risedronate EC

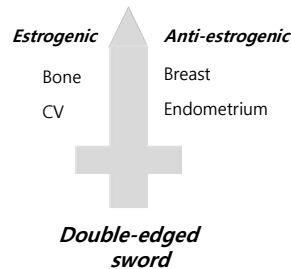
- **Before, during or after** breakfast
- **Reliable efficacy** with or without food

Enteric Coating Risedronate and Lumbar Spine BMD

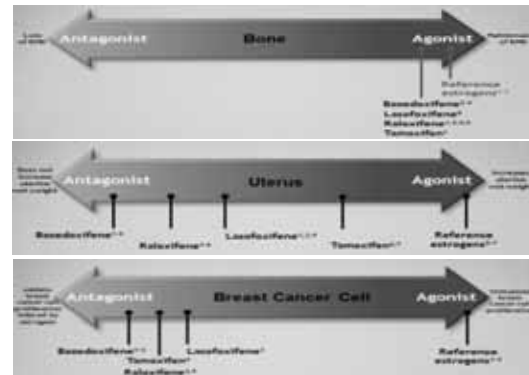


Concept of a SERM

*S*elective
*E*strogen
*R*eceptor
*M*odulator



Spectrum of SERM effects



Agonist/Antagonist Activities Differ among Tissues in SERM

	Bone	Uterus	Breast
Estradiol	++	++	++
Tamoxifen	+	+	-
Raloxifene	+	-	-
Bazedoxifene	++	-	-

+ agonist
- antagonist

When Is It A Good Idea to Prescribe SERM?

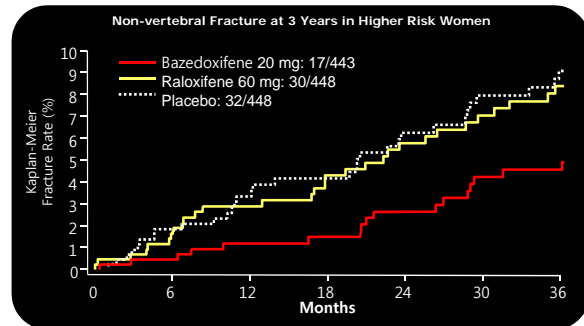
1. Early treatment of osteoporosis
2. Switching after Bisphosphonates
3. Consolidation of benefit after PTH
4. Synergic effect of combination PTH



Disadvantages of SERM

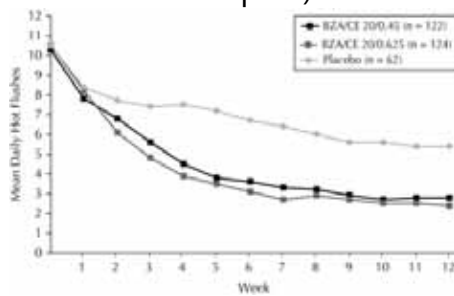
- Increased risk of thromboembolic events
- Doesn't treat post-menopausal Sx.
- Hot flashes
- No effect on HDL
- Leg cramps
- Daily oral intake
- Men

Bazedoxifene and Nonvertebral Fracture



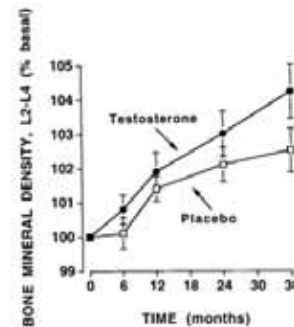
*Femoral neck T-score ≤ -3.0 or ≥ 1 moderate or multiple mild vertebral fracture(s); N=1,772.

TSEC(Tissue Selective Estrogen Complex)



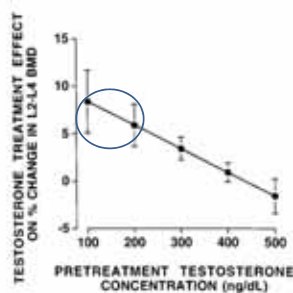
Menopause, 16 (2009), pp. 1116-1124

Testosterone replacement and BMD



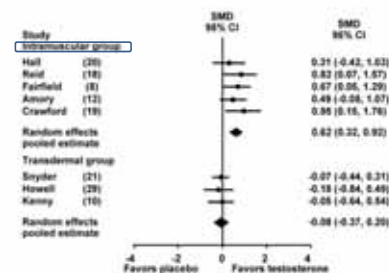
J Clin Endocrinol Metab84:1966-1972, 1999

Who can get a benefit ?

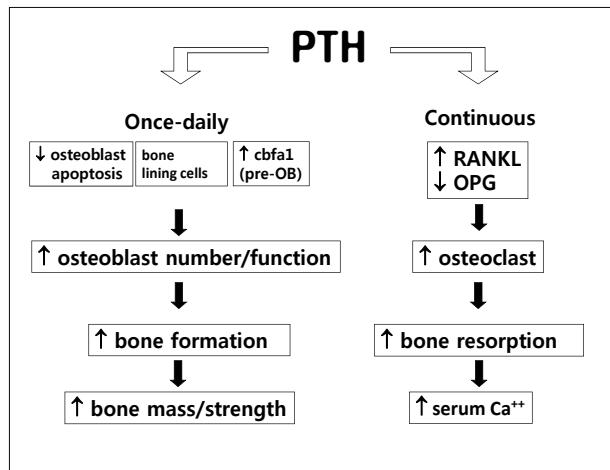


J Clin Endocrinol Metab84:1966-1972, 1999

Mode of Delivery



J Clin Endocrinol Metab, June 2006, 91(6):2011-2016



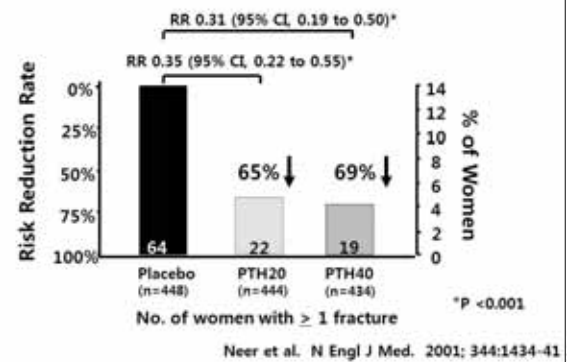
Disadvantages of PTH

- Expensive price
- Injection – pain
- Daily administration
- Patient education
- Short term use – less than 2 years
- Sarcomatogenesis (?)
- Few additional benefits

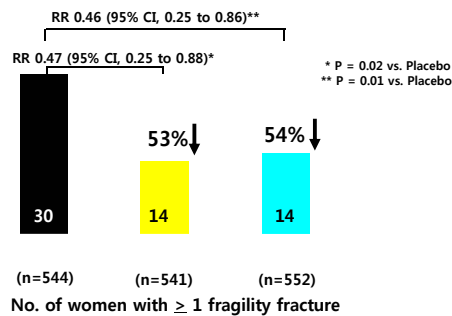
When Is It A Good Idea to Prescribe PTH?

1. Need for strong anti-fracture efficacy
2. Non-responders to conventional treatment
3. Bisphosphonates-induced bone remodeling suppression
4. Osteoporosis with severe back pain

Effect of Teriparatide on the Risk of New Vertebral Fractures

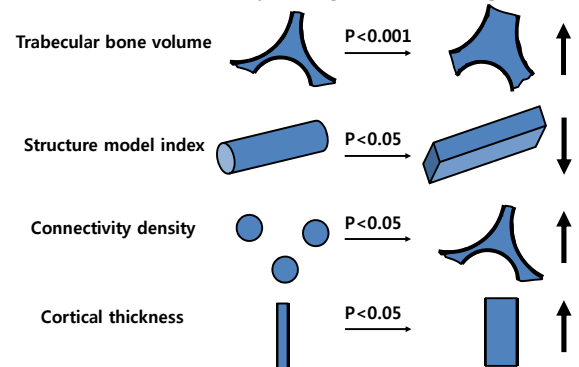


Effect of Teriparatide on the Risk of Non-Vertebral Fractures

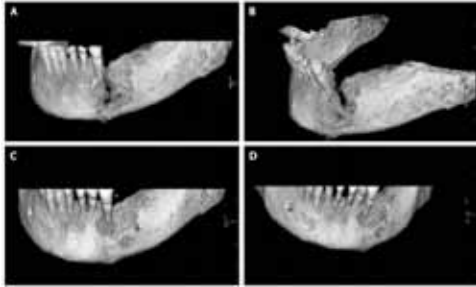


Structural Indices

Quantitative analysis-Significant changes



Teriperatide for BRONJ



N Engl J Med. 2010;363(25):2473-4

Take Home Messages

1. HRT는 좋은 치료제이나 장기간 사용은 어렵다.
2. Bisphosphonate는 효과는 좋으나 부작용에 대한 대책을 세워야 한다.
3. SERM은 효과는 약하나 부작용이 적고 유방암 예방의 장점이 있다.
4. Testosterone은 골밀도에 대한 효과는 좋으나 골절에 대한 연구가 없다.
5. PTH는 효과가 확실하고 부작용도 적은편이나 투여법과 비용의 문제가 있다.

AACE 2010 treatment guidelines

	Drugs
1 st line	Alendronate, Risedronate, Zoledronate, Denosumab
2 nd line	PTH
2 nd or 3 rd line	SERM
Last line	Calcitonin
Special consideration	PTH

Take Home Message!

**Lift Up
Your
Scale !**

