

-10 years after WHI- Hormone Therapy and Bone Mineral Density

이 동 옥

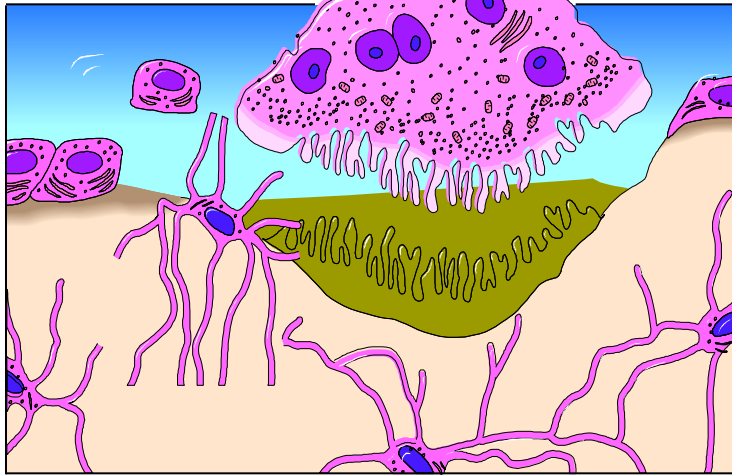
국립암센터

암예방검진센터

자궁암센터 / 폐경클리닉

Treatment objectives

Osteoclast

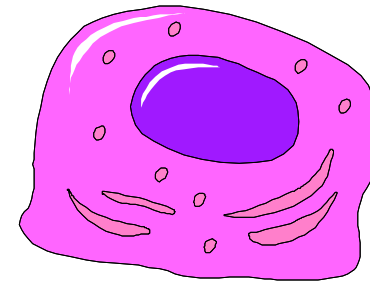


Inhibition of resorption

- HRT
- SERM/Raloxifene
- Calcitonin
- Bisphosphonates

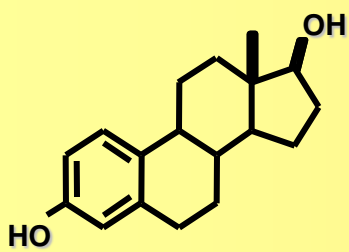
Strontium ranelate

Osteoblast



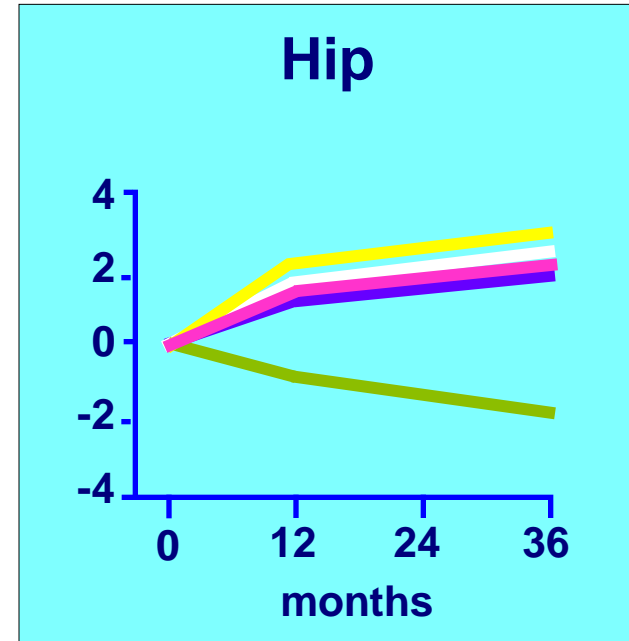
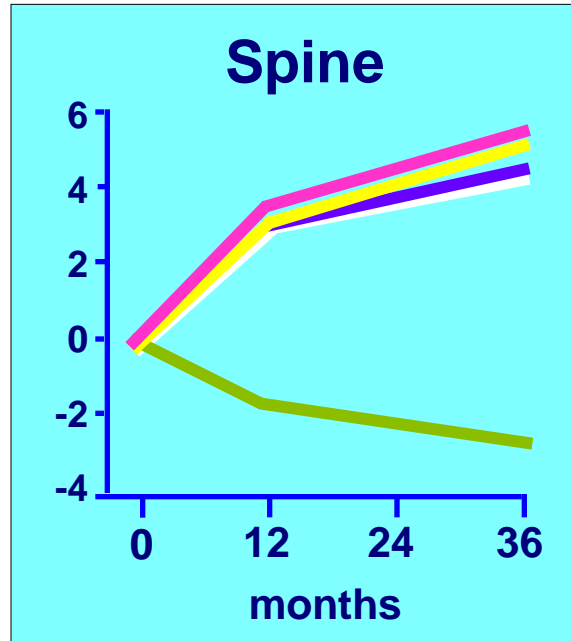
Stimulation of formation

Parathyroid hormone (PTH)

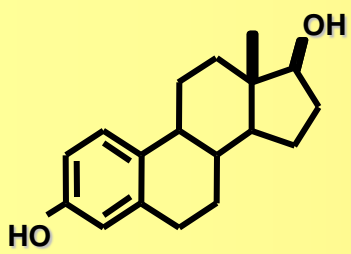


Effect of Hormone Replacement Therapy on BMD: the PEPI Trial

% change from baseline n:875

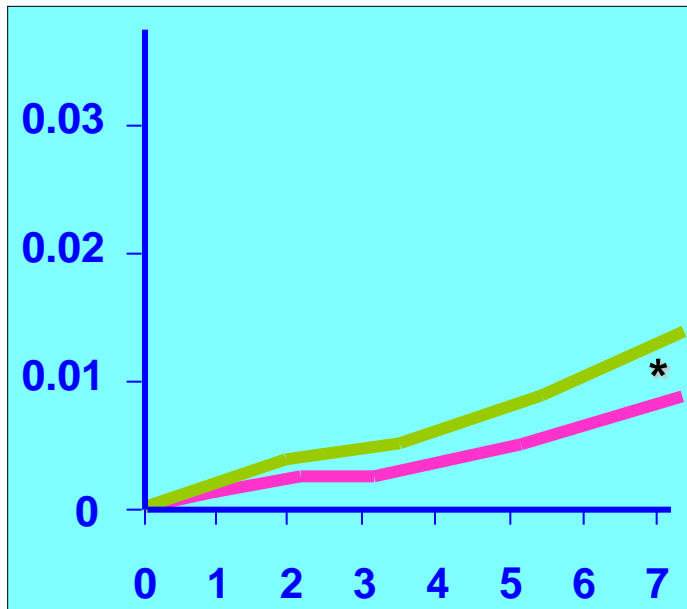


- Placebo
- CEE-MP-cyc
- CEE-MPA-cont
- CEE-MPA-cyc
- CEE

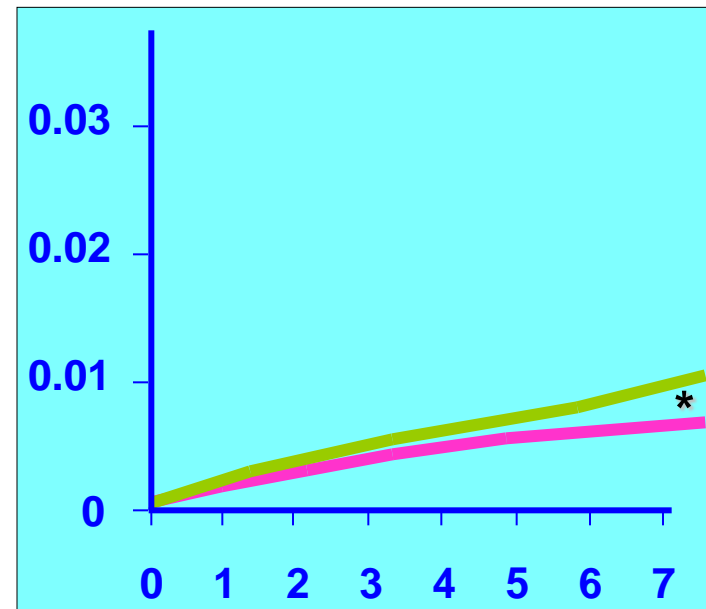


Effect of Hormone Replacement Therapy on fractures

Cumulative hazard of **vertebral** fractures



Cumulative hazard of **hip** fractures



● Estrogen+progestin ● Placebo

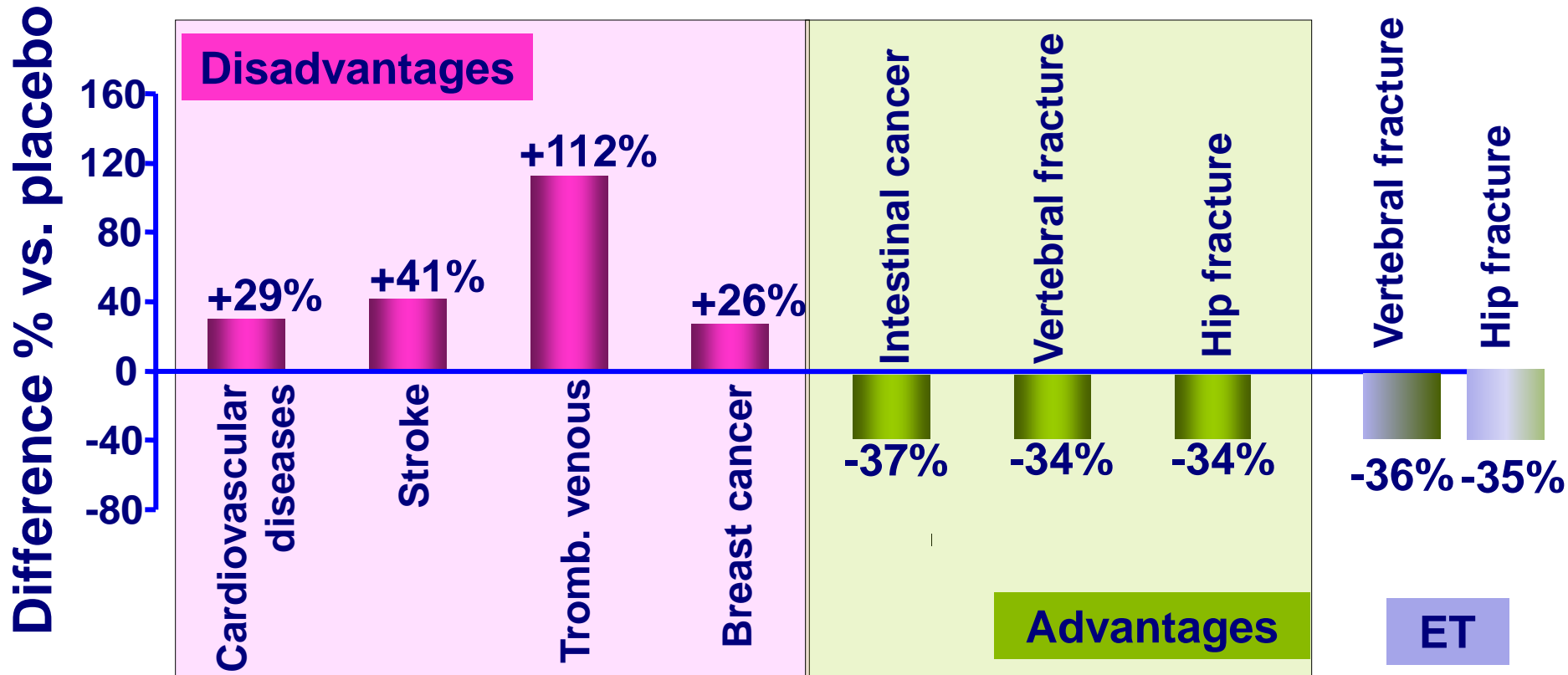
Time (years)

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WHI - First randomized, controlled trial in women (50-79 years) treated with HRT

6700 women with 5.2 years of follow-up

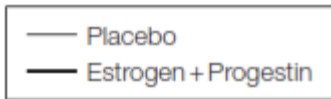


EPT arm – baseline characteristics

- 16,608 women, aged 50-79 (mean 63 yrs), for 5.2 yrs
- Healthy postmenopausal women, 44% were > 65yrs
- Mean F/U time in the sensitivity analysis: 3.7 yrs
- Baseline characteristics

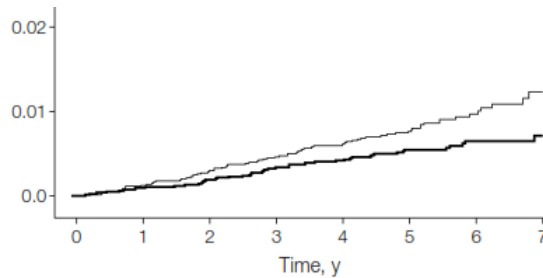
	EPT arm	Placebo	P value
Spine BMD, g/cm ²	0.94±0.16	0.95±0.16	0.87
Spine BMD, T-score	-1.30±1.39	-1.26±1.42	0.87
Osteoporosis	4%	6%	
Summary Fx risk score			
0-2 (low)	2393±34.5	2350±34.4	0.93
3-5 (moderate)	2691±42.7	2910±42.6	
>5 (high)	1575±22.7	1571±23.0	

EPT arm – fracture prevention



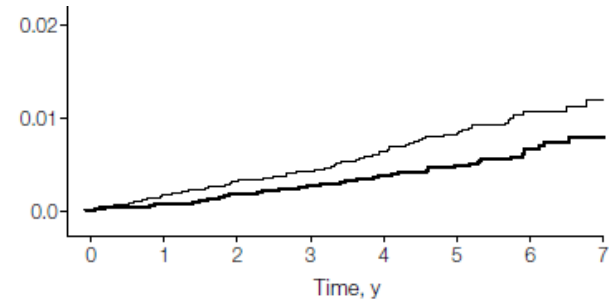
Hip fracture

HR, 0.67 (95% CI, 0.47-0.96)



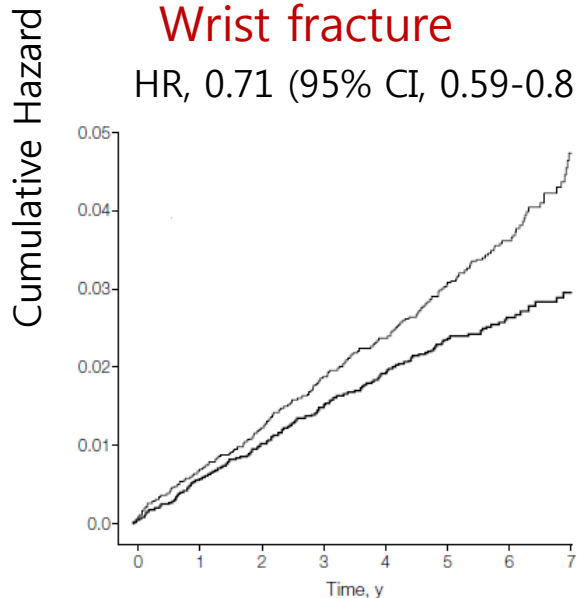
Vertebral fracture

HR, 0.65 (95% CI, 0.46-0.92)



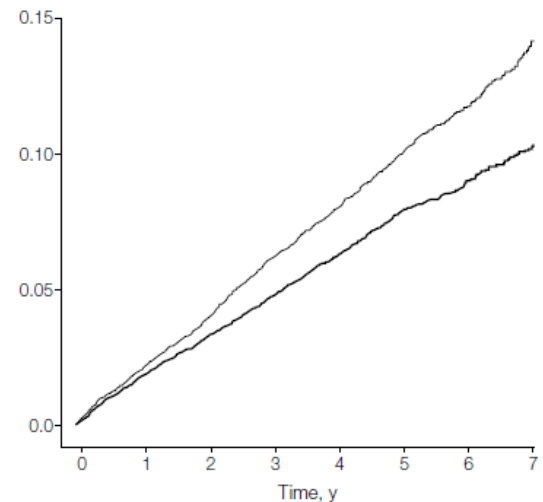
Wrist fracture

HR, 0.71 (95% CI, 0.59-0.85)



Total fracture

HR, 0.76 (95% CI, 0.69-0.83)



EPT arm – subgroup analysis

HR of hip Fx by randomization assignment and stratification

outcomes	EPT arm (n=8506) No. (%)	Placebo (n=8102) No. (%)	HR (95% CI)	P value
Total Ca intake at baseline, mg/d				
<600	15 (0.13)	14 (0.13)	0.94 (0.45-1.96)	0.02
600-1200	24 (0.13)	25 (0.14)	0.91 (0.52-1.59)	
>1200	13 (0.08)	31 (0.20)	0.40 (0.21-0.76)	

No difference when stratified by age, smoking, fall, Fx Hx, past use of HT, parental Fx Hx, years since MP, summary Fx risk score

EPT arm – What's important?

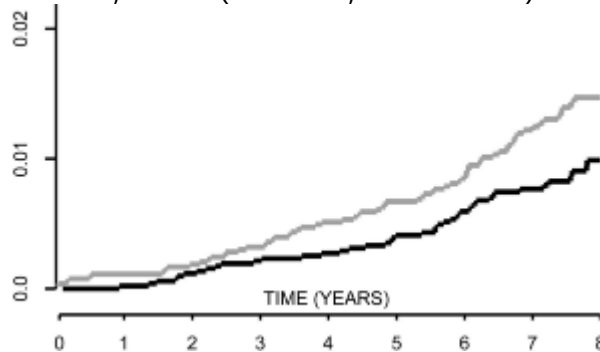
- Healthy, relatively young postmenopausal women
- Hip Fx rate were about 50% lower than expected for a similar age-matched cohort.
- Only 4% of EPT group and 6% of placebo group had osteoporosis by WHO criteria.
- 골다공증 치료제는 대개 골다공증이 심한 환자가 많이 포함될수록 골절예방률이 높게 나타남
- 비스포스포네이트의 경우 골감소증 환자에서는 골절예방률이 입증되지 않음
- WHI 연구의 경우 많은 수의 환자를 상대로 하여 충분한 power를 가짐
- 하지만 Global index 분석에서는 net benefit이 없었음

ET arm – fracture prevention

— CEE
— PLACEBO

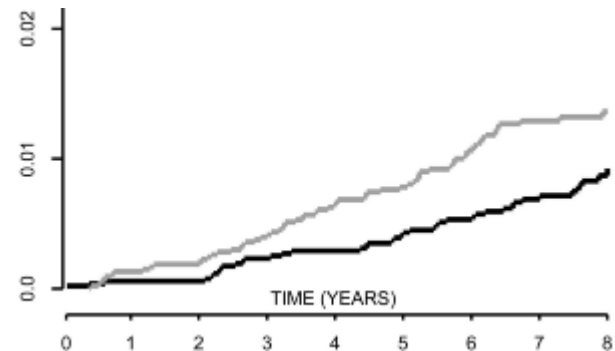
Hip fracture

HR, 0.65 (95% CI, 0.45-0.94)



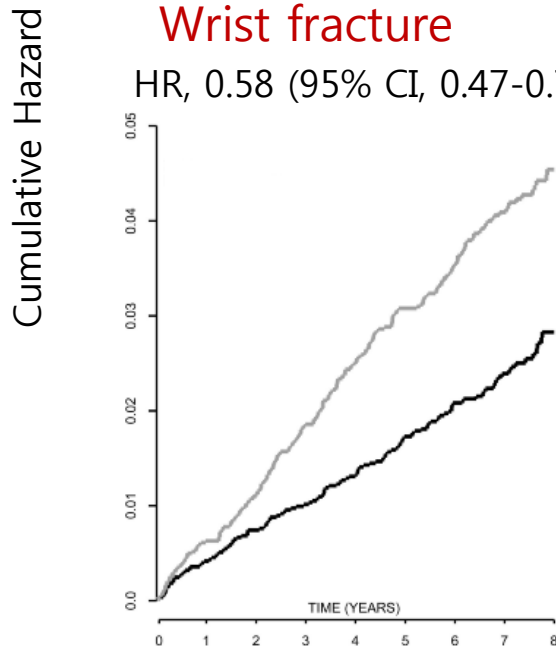
Vertebral fracture

HR, 0.64 (95% CI, 0.44-0.93)



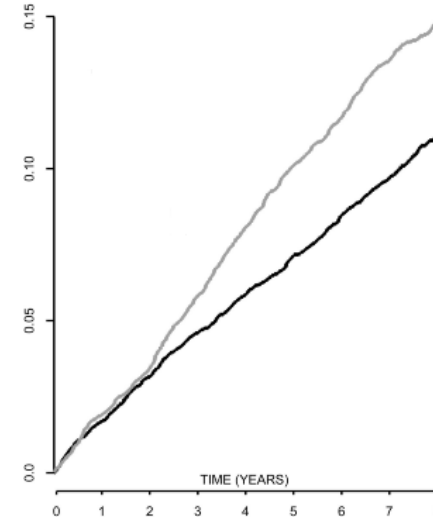
Wrist fracture

HR, 0.58 (95% CI, 0.47-0.72)



Total fracture

HR, 0.71 (95% CI, 0.64-0.80)



Cumulative Hazard

ET only arm – fracture prevention

- 50-79 years of age with hysterectomy
- f/u for average 7.1yrs
- Only 5.7% met the WHO criteria for osteoporosis (T score \leq -2.5)
- Women with low risk for Fx

- The first RCT of ET alone to show fracture prevention in a cohort of MP women not specifically selected by the risk for Fx
- EPT and ET showed similar effect for hip and total fracture.
- But even in women at the highest risk for Fx, the global index was balanced, with no evidence of overall benefit or risk noted.

Benefits / Risks of hormone therapy

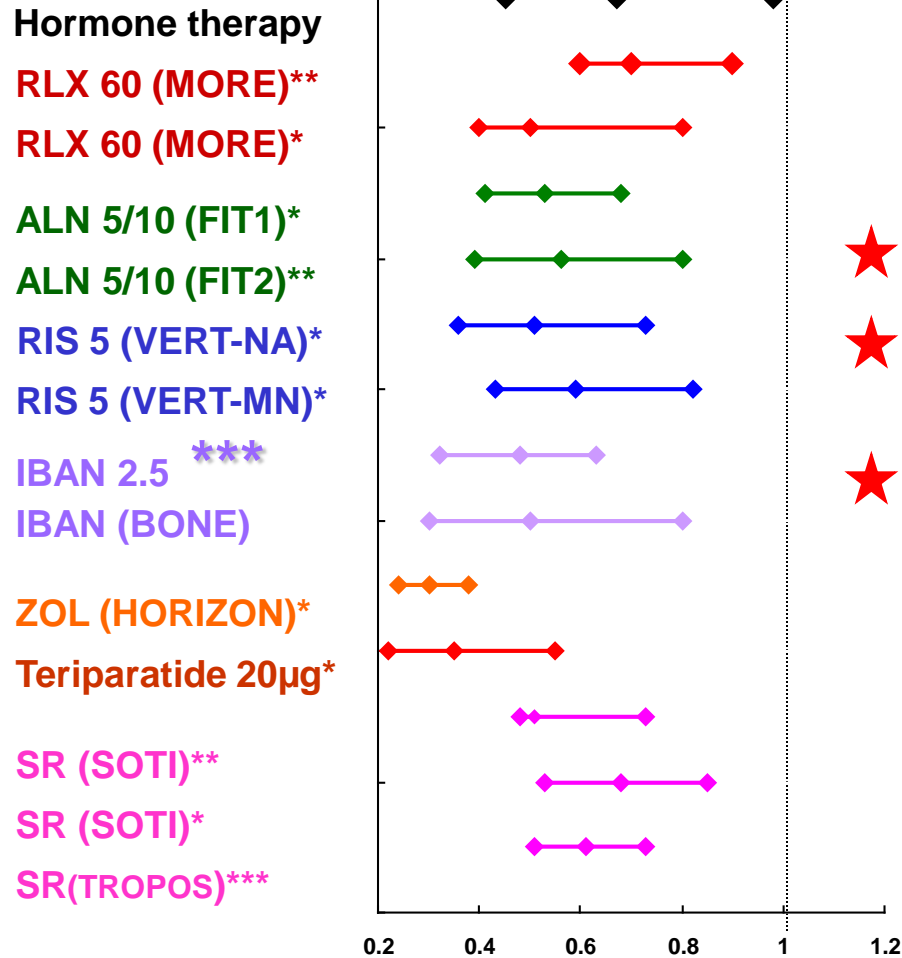
Degree of evidence	Benefits	Risks
Strong	Relief of vasomotor Sx Prevention of bone loss	Vaginal bleeding Breast tenderness Deep vein thrombosis Pul. Embolism Stroke
Moderate	Prevention of Fx	Breast cancer after long-term use (EPT)
Weak	1° prevention of heart dis. Cognitive function Alzheimer's ds.	Ovarian cancer after long-term use (ET)

 **First choice** in early menopausal women **with menopausal Sx**

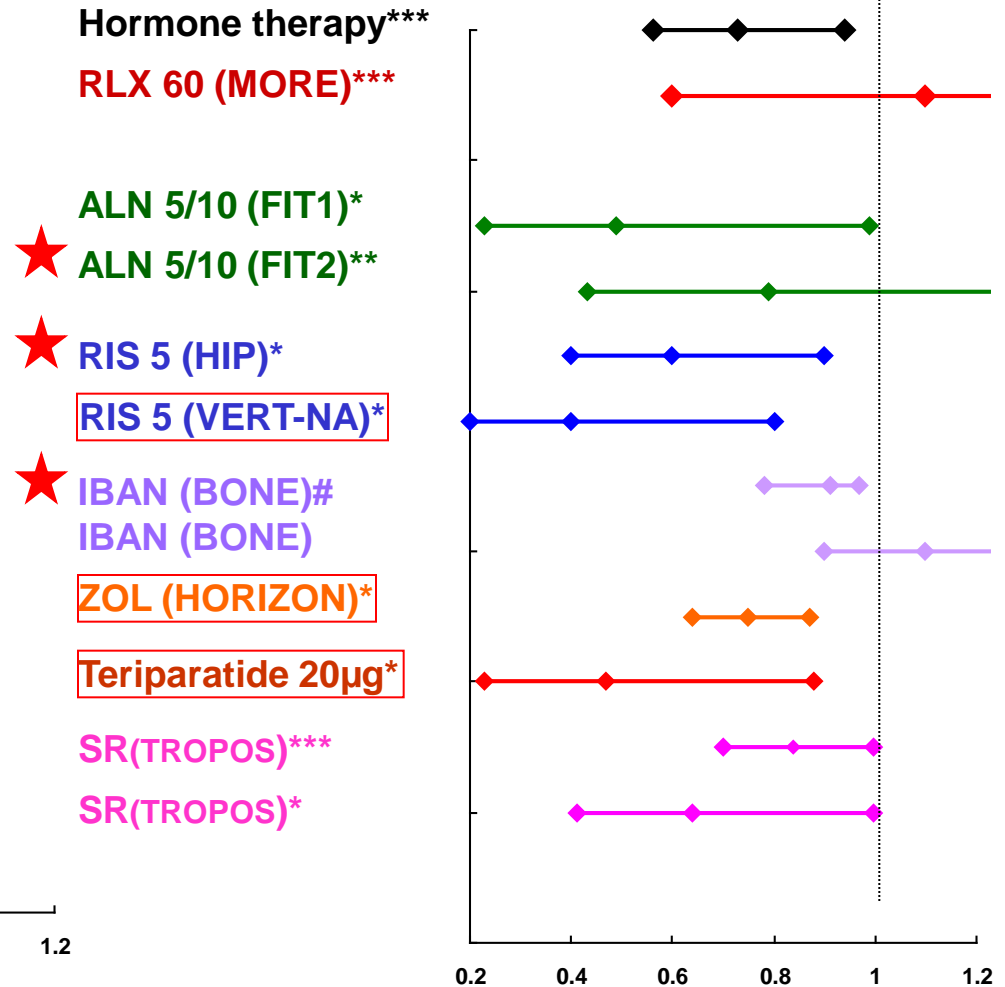
Delmas PD, 2002, Lancet

Antifracture efficacy of antiosteoporotic agents

Incident *vertebral* fractures



Incident *Hip* fractures



* with prev vert Fx(s) ** without prev vert Fx
 # FN BMD<-3.0

*** with or without prev vert Fx

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Other studies from WHI (1)

- A modest association between laxative use and increase in the risk of falls but not for fractures (HR, 1.06, 95% CI 1.03-1.10 for any laxative use)

Haring B, 2013, BMC Geriatr

- Estrogen-alone use in postmenopausal women results in a modest but sustained reduction in the frequency of joint pain.

Chlebowski RT, 2013, Menopause

- Antiepileptic drugs are associated with total Fx (HR 1.44, 95% CI 1.30-1.61), hip Fx (HR 1.51, 95% CI 1.05-2.17) and ≥ 2 falls (HR 1.62, 95% CI 1.50-1.74) but not with baseline BMC or changes in BMD.

Carbone LD, J Bone Miner Res, 2010

- A low-fat and increased fruit, vegetable, and grain diet intervention modestly reduced the risk of multiple falls (HR 0.87) and slightly lowered hip BMD but did not change the risk of Fx.

McTiernan A, Am J Clin Nutr, 2009

Other studies from WHI (2)

- Moderate to severe pelvic organ prolapse is related to low bone mass in postMP women. – suboptimal collagen status?

Pal L, Menopause, 2008

- ET is cost-effective for the prevention of Fx. in women with hysterectomy irrespective of prior Fx status. In women with an intact uterus, EPT was cost-effective in those with a prior vertebral Fx.

Lekander I, Bone, 2008

- Statin use did not improve Fx risk or BMD.

LaCroix AZ, Ann Intern Med, 2003

- Increased fracture risk in patients with RA and OA

	HR for any Fx	HR for hip Fx
Osteoarthritis	1.09 (1.05-1.13)	N.S.
Rheumatoid arthritis	1.49 (1.26-1.75)	3.03 (2.03-4.51)

Wright NC, J Rheumatol, 2011

Other studies from WHI (3)

- In a multivariate Cox proportional hazards model, the hazard ratios (95%CI) for incident breast cancer were 1.35 (1.05–1.73) for high Gail score ($\geq 1.67\%$), and 1.25 (1.11–1.40) for each unit of increase in total hip BMD T-score.

Chen Z, Cancer, 2008

- Femur geometry derived from hip DXA using hip structural analysis (HAS): benefits on femur geometry were observed as early as 1yr after Tx. HT led to favorable changes in femur geometry.

Chen Z, JBMR, 2008

- The effect of HT on fracture reduction is independent of estradiol and SHBG levels.

Cauley JA, Osteoporos Int, 2010

Other studies from WHI (4)

- Elevated levels of inflammatory markers for all three investigated cytokine-soluble receptors (IL-6SR, TNF SR1, TNF SR2) were associated with an increased risk of hip Fx.

Barbour KE, JBMR, 2012

- PM White women with mild renal dysfunction are at an increased risk of nonvertebral Fx. – chronic inflammation?

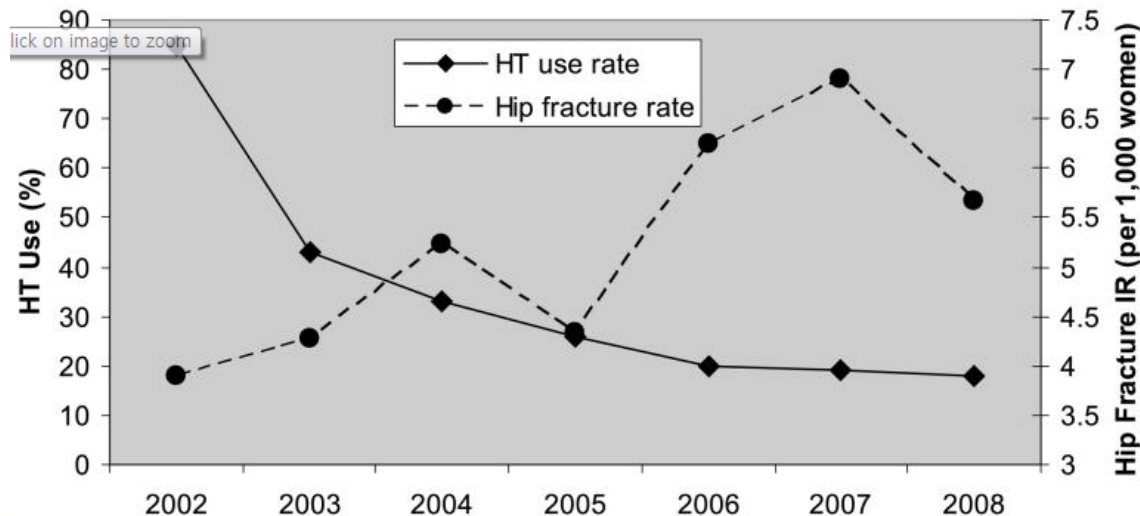
Ensrud KE, Osteoporos Int, 2012

- Clinical risk factors for Fx: in Asian women, older age, positive Fx Hx, > 2 falls, parity were independently associated with a 15-65% increased Fx, yrs since MP, education, Wt, Ht, daily caffeine intake, smoking, corticosteroid use > 2yrs, sedatives, arthritis, depression were not associated.
- Women with ≥ 8 risk factors had 2 fold higher rate of Fx.
- Asian women, MV-adjusted HR for Fx: 0.66 (0.59-0.74)

연구발표 후 반응의 변화

- 골절률 감소를 확인한 것은 획기적이거나 부작용을 감안할 때 특별히 골다공증 치료만을 위해서 권고하기는 어려움. 당시 비스포스포네이트가 골절예방효과를 보이며 상대적으로 부작용이 적다고 생각되었기 때문
- 이후 비스포스포네이트의 장기간 사용시 부작용이 대두됨
- WHI 연구 발표 이후 호르몬 처방율의 급격한 감소와 폐경 여성에서 급격한 골절을 증가가 관찰됨

Islam S, Menopause, 2009



NAMS, 2012

- ...HT may be considered in younger women at high risk for fracture...

- HT seems to be the only proven effective option for the primary prevention of postMP osteoporosis.

Palacios S, BMC Women's Health, 2008

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Low dose HT or other regimen

- 위약군에 비해 유의한 BMD의 차이를 입증

- 0.25mg/d of 17 β -estradiol with or without P4

Prestwood KM, JAMA, 2003

- 0.014mg/d of estrogen without P4

Ettinger B, Obstet Gynecol, 2004

- Transdermal 17 β -estradiol patch delivering 0.1mg estradiol/d

Lufkin EG, Ann Intern Med, 1992

- Not proven anti-fracture efficacy

- Optimal dose for bone health is not determined.

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Tibolone (Livial®)

- 🌈 Increased BMD in early/ elderly postmenopausal women
- 🌈 33% of fracture risk reduction in Million Women's Study

LIFT trial

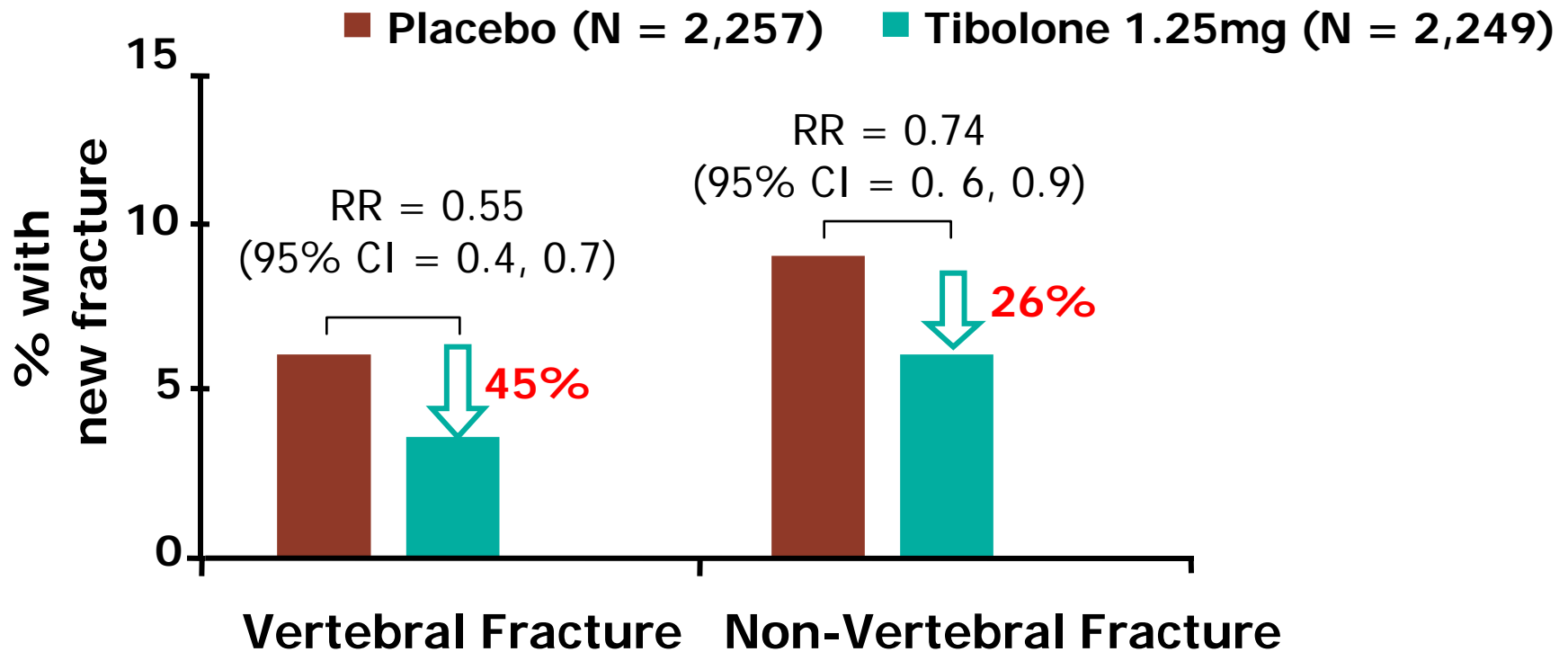
- 🌈 Tibolone 1.25mg in 4,538 women, mean age 68 yrs
- 🌈 Total hip or spine BMD ≤ -2.5 /or/ < 2.0 with vertebral fracture
- 🌈 50% lower vertebral fracture rate during 2.75 yrs
- 🌈 Premature closure due to increased risk of stroke

Ettinger B, 2007, Maturitas

LIFT:

Fracture Incidence

Tibolone reduces the risk of vertebral and non-vertebral fractures³

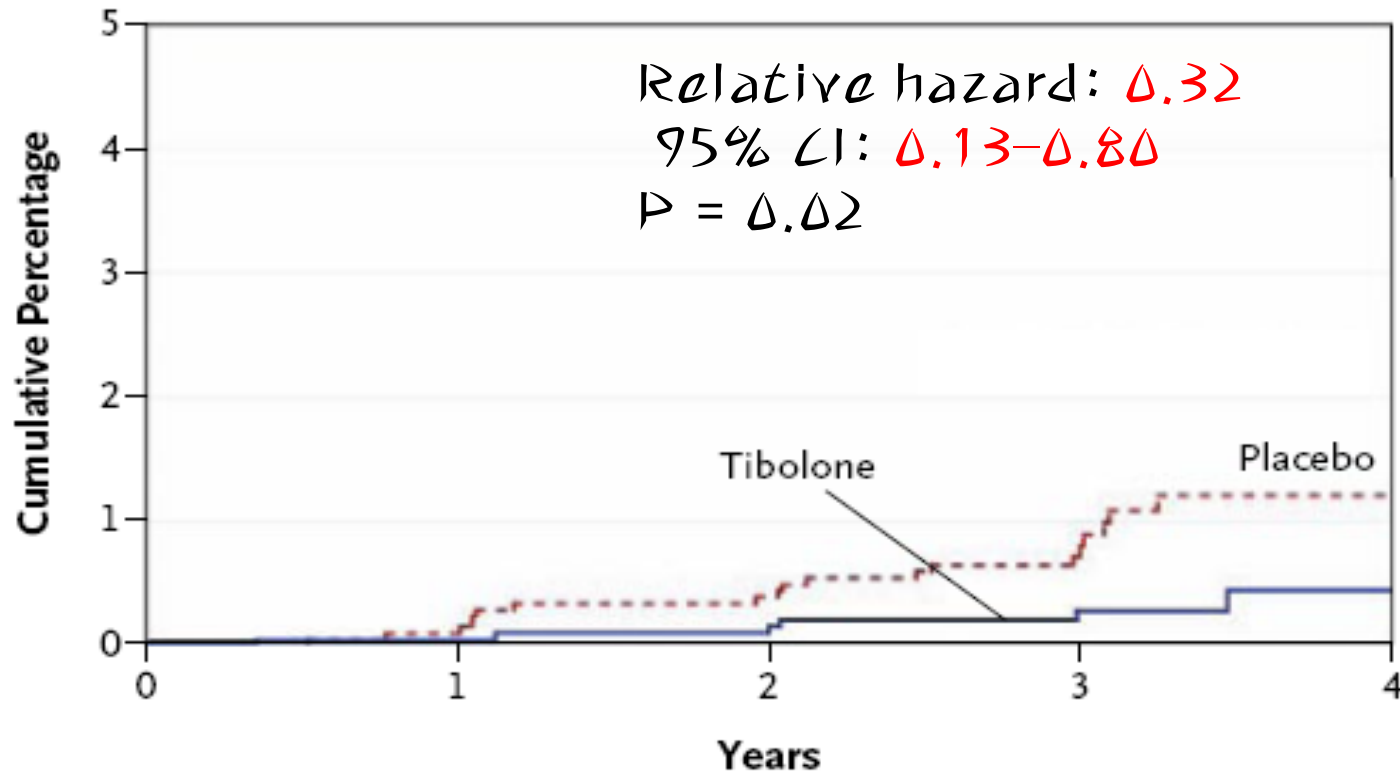


Mean duration of treatment: 34 months

LIFT:

Breast Cancer Risk

Tibolone *does not increase* breast cancer risk in older osteoporotic women with no history of breast cancer⁴



Anti-fracture efficacy

from placebo controlled randomized trials

Drug	Vertebral fractures	Non-vertebral fractures (hip)
Alendronate	+ + +	+ +
Risedronate	+ + +	+ +
Calcitonin (nasal)	+	0
HRT	+ +	+
Raloxifene	+ + +	0
PTH	+ + +	+ +
Strontium ranelate	+ + +	+

Thank you for your attention...