# Clinical review of hormone therapy in prevention and treatment of osteoporosis

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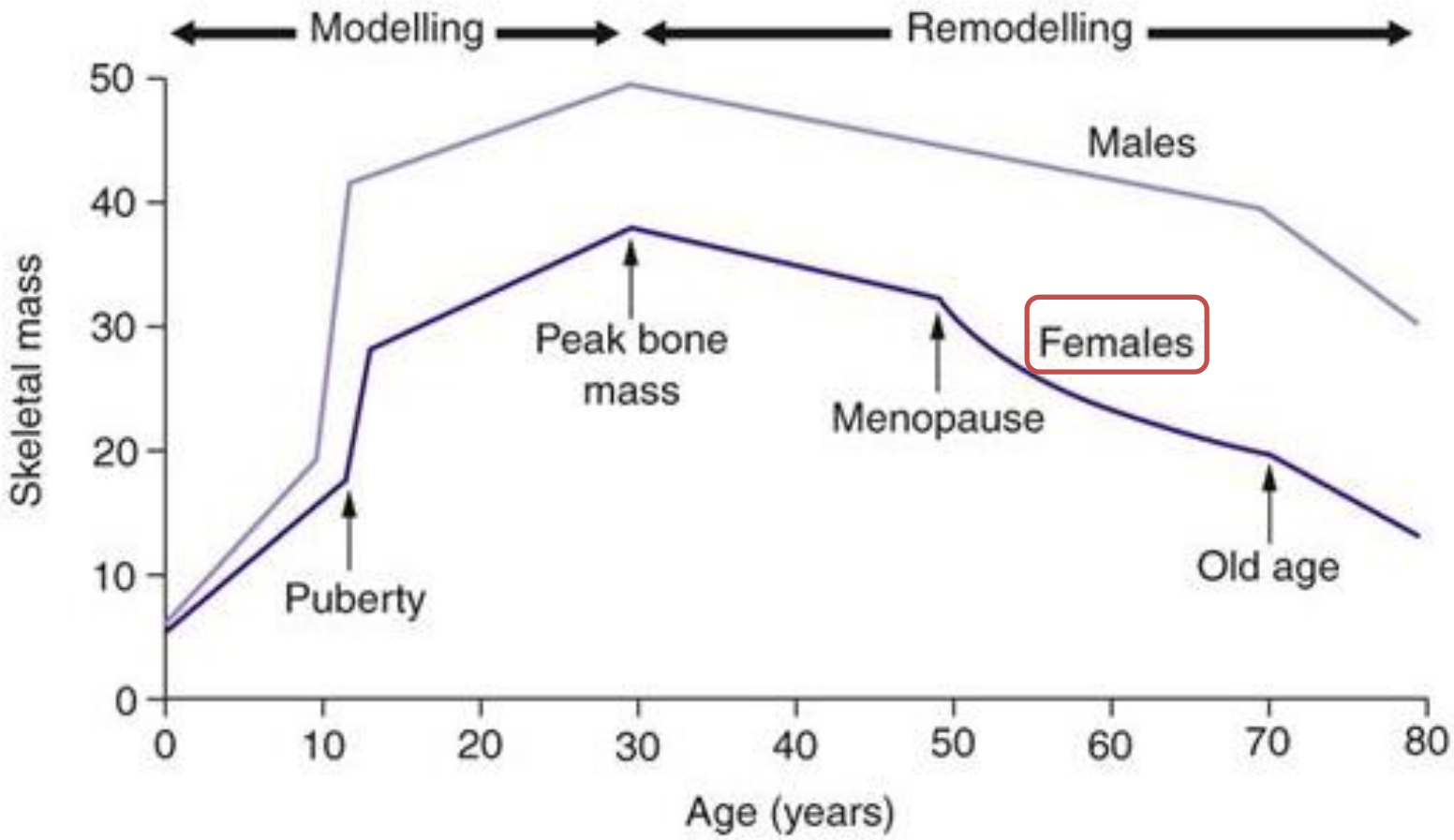
# Disclosures

- Amgen- speaker bureau, consultant
- Radius Health- consultant
- Credits: Select NAMS Menopause A-Z slide deck (co-author)

# Objectives

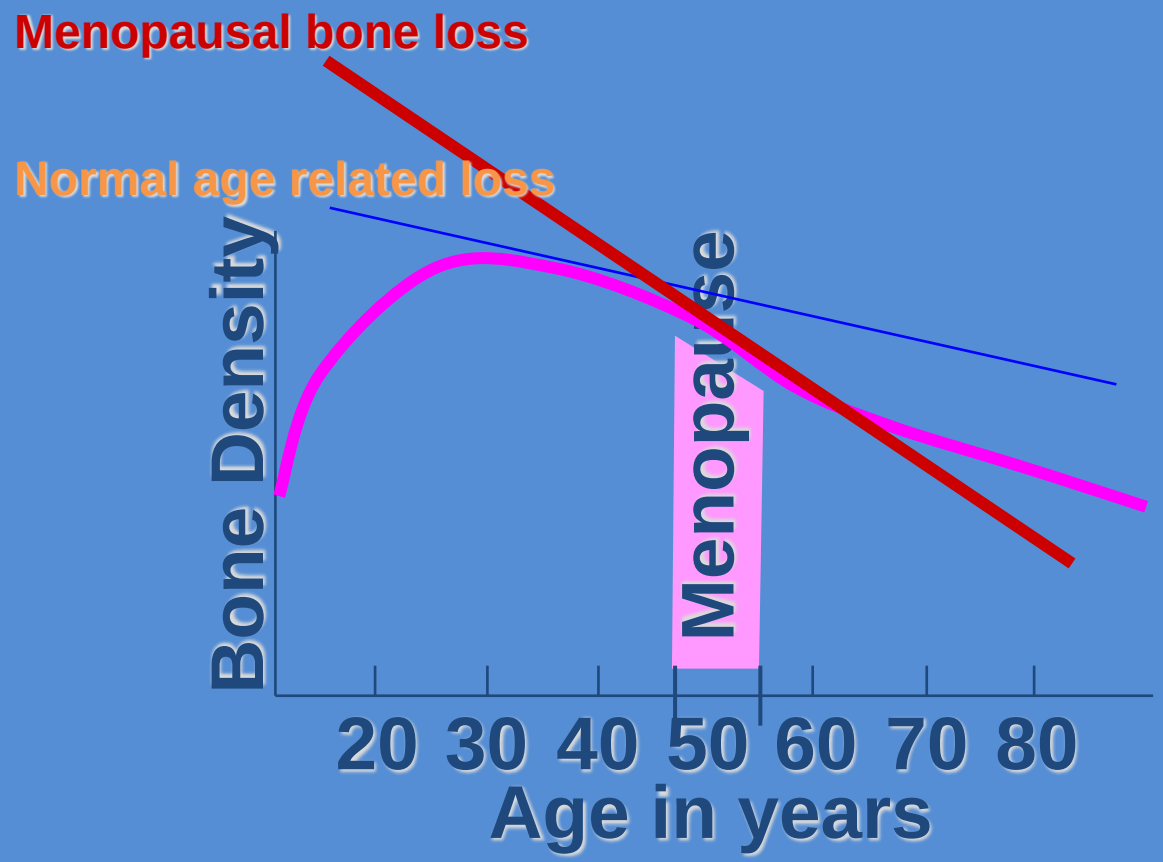
- Why is menopause such a critical time for bone loss?
- Management of POI and early menopausal bone loss
- What doses and formulations of HT prevent and treat osteoporosis
- HT in relation to other OP therapies
- Questions

# Changes in bone density over the lifetime

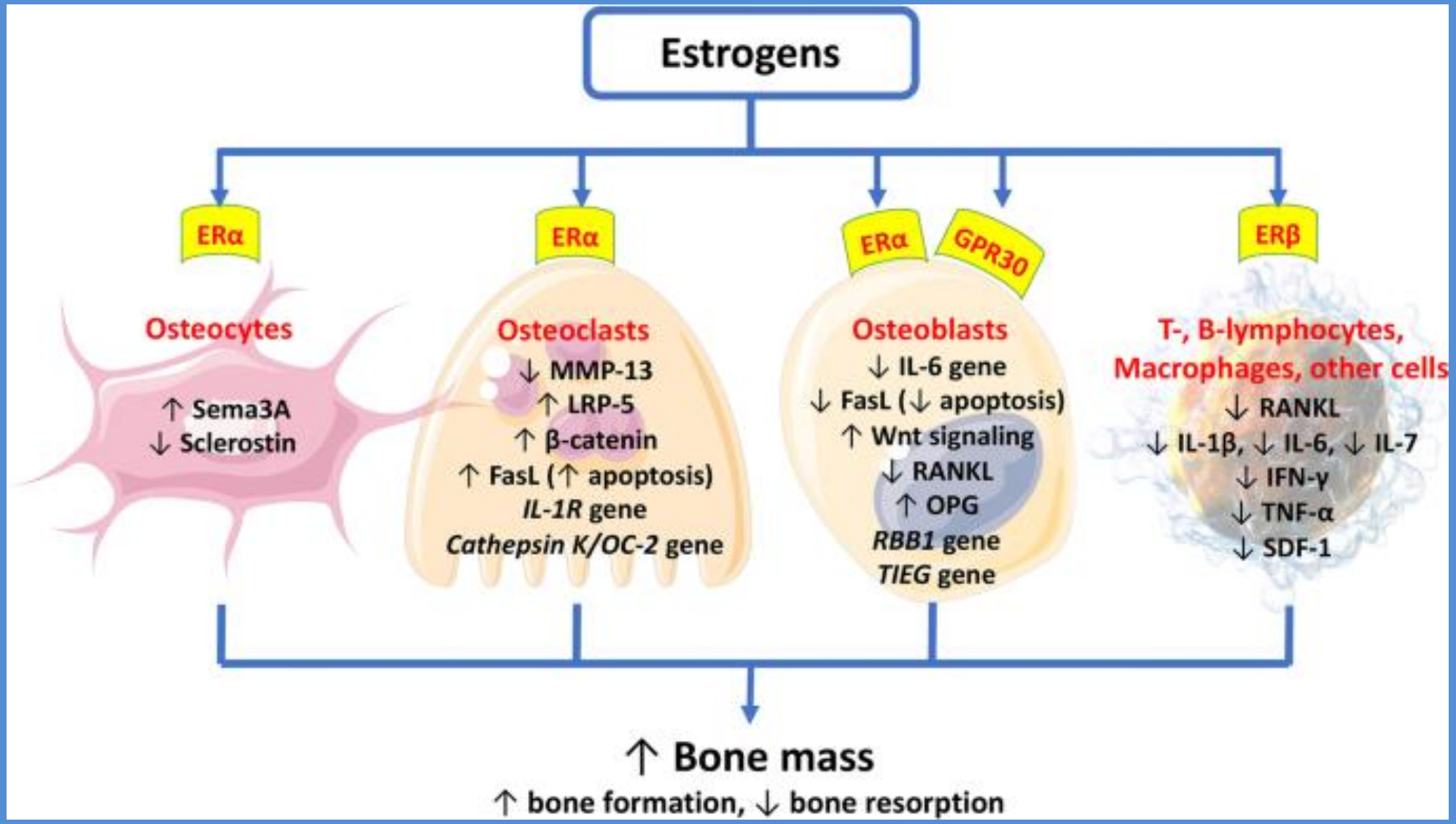


# Menopausal bone loss

- Accelerated bone loss associated with menopause
- Loss at spine-rate of 3%/yr for about 5 years =15% BMD loss
- Loss at hip-rate of 0.5%/yr- additional 5% across menopause transition




Caplan GA,et al. J R Soc Med. 1994. 87:200-202.
Tannenbaum C, et al. 2002. J of Clin Endocrinology and Metabolism 87:4431-4437


Estrogens
ERα
ERα
ERα
GPR30
ERβ
Osteocytes
↑ Sema3A
↓ Sclerostin
Osteoclasts
↓ MMP-13
↑ LRP-5
↑ β-catenin
↑ FasL (↑ apoptosis)
IL-1R gene
Cathepsin K/OC-2 gene
Osteoblasts
↓ IL-6 gene
↓ FasL (↓ apoptosis)
↑ Wnt signaling
↓ RANKL
↑ OPG
RBB1 gene
TIEG gene
T-, B-lymphocytes,
Macrophages, other cells
↓ RANKL
↓ IL-1β, ↓ IL-6, ↓ IL-7
↓ IFN-γ
↓ TNF-α
↓ SDF-1
↑ Bone mass
↑ bone formation, ↓ bone resorption

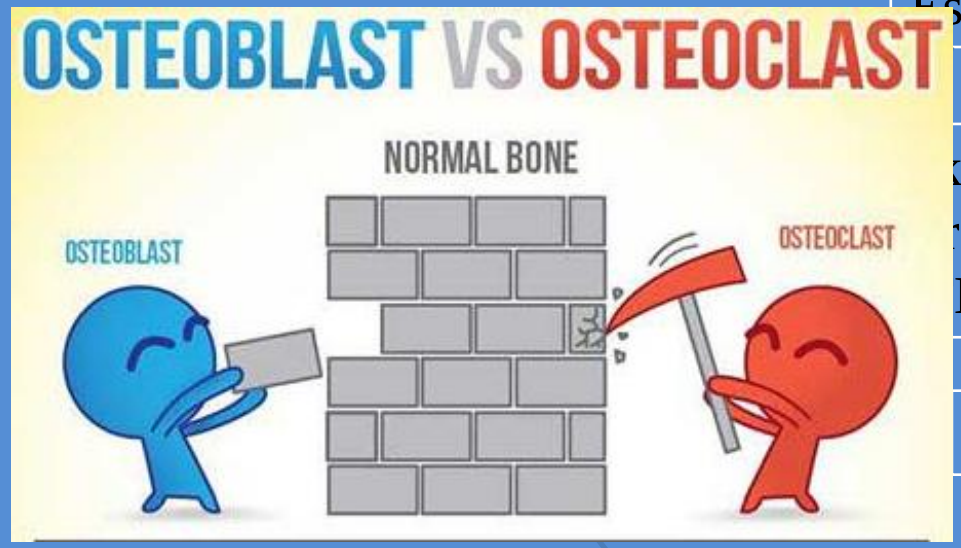
# Menopausal Bone loss explained

Failure to achieve peak bone mass

Hereditary factors 50-70%
Nutritional and
lifestyle factors

Accelerated bone loss

Estrogen deficiency




kine) and
regulated
NFa)

Decreased OPG ( protein) that binds RANKL

More active, differentiated osteoclasts

More bone remodeling , resorption> formation

Increase PTH
senstitivity

Decreased GI calcium absorption and excess renal calcium excretion

# Hormone Therapy ( HT) Definitions

- Estrogen therapy (ET)
  - Unopposed estrogen for postmenopausal women who have undergone hysterectomy or in ultra low doses for women with vaginal symptoms regardless of presence of uterus
- Estrogen-progestogen therapy (EPT)
  - For postmenopausal women with a uterus
  - Progestogen reduces the risk of endometrial adenocarcinoma because of unopposed estrogen
- Estrogen agonist/antagonist therapy (formerly SERM)
- Conjugated estrogen + bazedoxifene
  - For postmenopausal women with a uterus who prefer a progestogen-free option
  - Estrogen antagonist/agonist has a similar effect to progestogen on the uterine lining

# Clinical case 1: Claire

Claire is a 38 yo with history of hypothyroid. During a work up for infertility and amenorrhea > 2 yrs was found to have unexplained premature ovarian insufficiency (POI) with FSH > 60 IU/L and estradiol < 15 pg/ml on 2 separate blood draws 6 mos apart. Her BMI is 25, she is a non- smoker. Her 25 hydroxy D is 35 ng/ml and she takes a MVI with calcium. You obtain a baseline DXA.

T –score shows -1.8 at spine ( Z score -1.1) and T score -0.9 at hip (Z score -1.0).

How would you counsel Claire on her DXA results? Would you start hormone therapy or hormonal contraception?

Treatment: High dose HRT or continuous COC's, repeat DXA in 1-2 yrs.

# CHC vs. HRT?

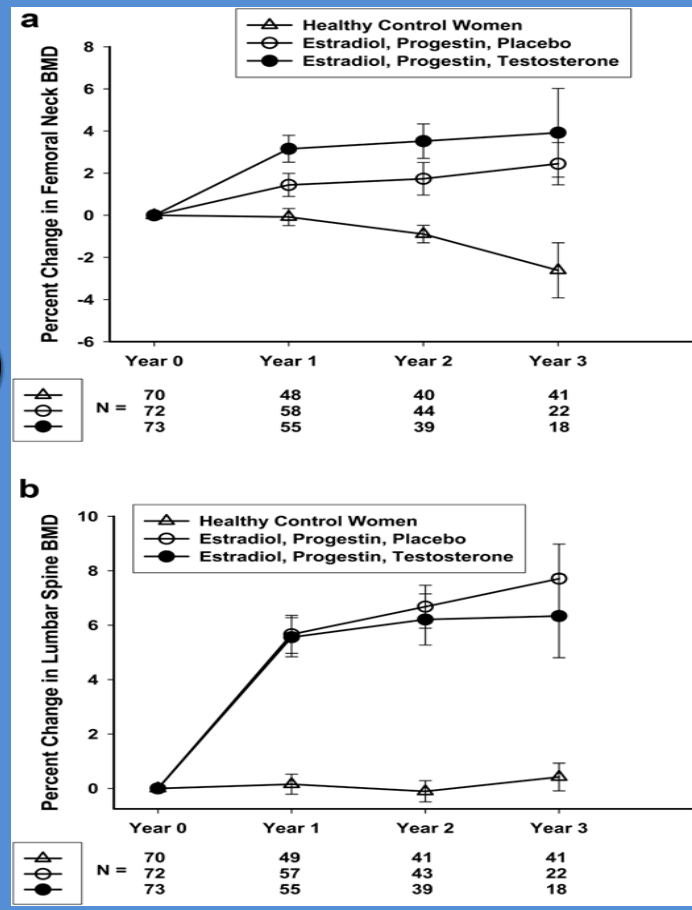
- Comparative study 119 women with POI ( mean age 30 yrs) on various HT regimens[1]
  - `COC: ethinyl estradiol (EE) 30 µg and levonorgestrel ( continuous use)
  - Low-dose EPT: conjugated equine estrogen [CEE] 0.625 mg with medroxyprogesterone acetate OR estradiol 1.0 mg with norethindrone acetate
  - High-dose EPT: CEE 1.25 mg or estradiol 2.0 mg combined with the same progestins.
- Results: Lumbar spine BMD increased COC ( 2.5% ) or high dose EPT (1.8%) after 2 yrs, total femur increased COC ( 2.4%) and high dose EPT (0.9%)

1 Carvalho et al. Menopause. 2020;27:1110-1116.

# CHC vs. HRT?

- NIH 3 yr RCT[1] 215 women with POI ( mean age 33) on transdermal E2 100 ug/day with MPA 10 mg 12d/mo[2] versus healthy controls

- Other studies: RCT 18 women with POI ( mean age 27)[2]
- Transdermal estradiol 100-150 ug/cyclic vaginal progestin ( LS BMD ↑0.17)
  VS. 30 ug ethinyl estradiol/norethindrone (LB BMD ↑ 0.07) after 1 yr,
  No change in FN BMD.
- Women with female triad ( anorexia, amenorrhea, low BMD)
  – recommend transdermal estrogen

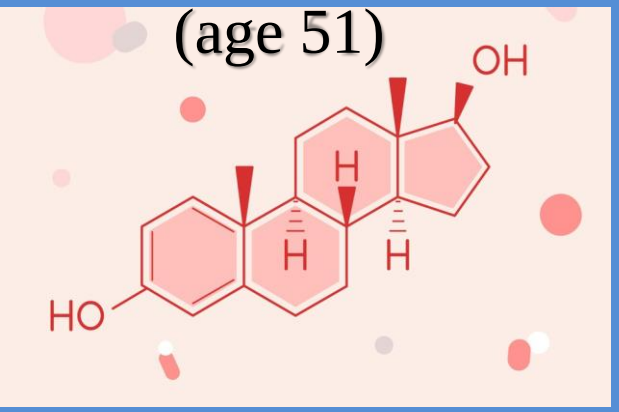



1 Popat VB et al JCEM 2014; 99: 3418-3426
2Crofton PM et al. Clin Endocrinol (Oxf). 2010;73:707-714

# Management of POI

Standard of care is physiologic estrogen and progestin treatment

- Estrogen: 100 µg transdermal estradiol patch, or 1.25 mg conjugated equine estrogens (CEE), or 2 mg of estradiol orally
- If uterus is present, cyclical progestins should be added ≥12 days/month
- Combined hormone contraception ( OCPS, patch, ring)  or transdermal estradiol-progestin systems are alternatives
- Goal estradiol level 100 pg/ml
- Recommended duration of therapy is at least until the natural age of menopause (age 51)




**European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI; Webber L, et al. *Hum Reprod*. 2016;31(5):926-937..**

# Clinical Case 2. Donna

Donna is a 53 yo woman presents to review recent BMD results. Her baseline DXA showed T score -2.4 at spine, -2.0 left FN and -1.9 at total hip ( Z scores normal) FRAX score: 1.9/8% Her FMP was 2 years ago. She is a non smoker, drinks 5 glasses of wine/wk, plays tennis 3x/wk, BMI 23. Her mother had history of hip fracture in her 70s. Since menopause she has experienced hot flashes that disturb sleep most nights, and has tried various herbs and OTC to manage unsuccessfully.

How do you counsel Donna on her treatment options?

# Clinical Case 2. Donna

Treatment options:

EPT ( estrogen/progestogen therapy)

- Combination transdermal estrogen/progestogen patch (NETA)
- Oral estradiol/NETA
- Transdermal estrogen/MP

CEE/Bazodoxifene

Calcium and vitamin D discussion, assess symptoms after 3 months and repeat DXA in 2 years.

**FDA-approved drugs for preventing and treating osteoporosis**

| Generic Name | Brand Name | Dosing Method | Dosing Interval | Postmenopausal Osteoporosis | | Glucocorticoid-Induced Osteoporosis | | Osteoporosis In Men |
|---|---|---|---|---|---|---|---|---|
| | | | | **Prevention** | Treatment | Prevention | Treatment | Treatment |
| **Estrogen** | Many | Various (oral, transdermal) | Various | **Yes** | No | No | No | No |
| **Alendronate** | Fosamax | Pill, liquid | Daily, Weekly | **Yes** | Yes | No | Yes | Yes |
| **Ibandronate** | Boniva | Pill | Monthly | Yes | Yes | No | No | No |
| **Ibandronate** | Boniva | Intravenous injection | 3-Monthly | No | Yes | No | No | No |
| **Risedronate** | Actonel Atelvia | Pill | Daily, Weekly, Monthly | **Yes** | Yes | Yes | Yes | Yes |
| **Zoledronate** | Reclast | Intravenous injection | Yearly (or every Other year- Prevention) | **Yes** | Yes | Yes | Yes | Yes |
| **Raloxifene** | Evista | Pill | Daily | **Yes** | Yes | No | No | No |
| **Denusomab** | Prolia | Subcutaneous injection | Every 6 month by HCP | No | Yes | No | Yes | Yes |
| **Teriparatide** | Forteo (anabolic) | Subcutaneous injection | Daily for up to 2 years (self) | No | Yes | No | Yes | Yes |
| **Abaloparatide** | Tymlos (anabolic) | Subcutaneous injection | Daily for up to 18 mos (self) | No | Yes | No | No | No |
| **Romosozumab** | Evenity (dual anabolic/ anti-resorptive) | 12 monthly Subcutaneous injections by HCP | Monthly for 1 year | No | Yes | No | No | No |

# History of estrogen therapy and bone health

- 1940s: Dr. Fuller Albright, 5 postmenopausal patients using estrogens: DES and estradiol benzoate IM
- 1942: FDA approved Diethylstilbestrol (DES) conjugated equine estrogens(CEE)
- 1972 FDA declares estrogen therapies probably effective at preventing osteoporosis
- 1984 NIH consensus estrogens best way to prevent bone loss
- 1994 FDA approves HT for prevention and treatment of OP
- 2002 Post WHI, FDA removes HT indication for treatment of OP

# Routes of ET Administration

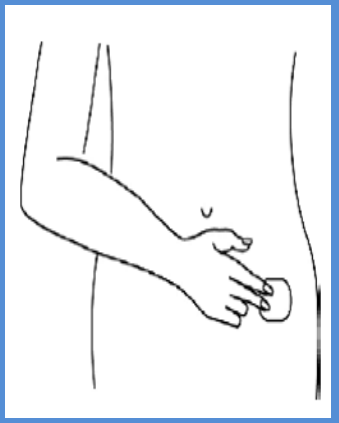
- Oral (estradiol E2, conjugated equine estrogen, conjugated estrogen)
- Vaginal ring
- Transdermal/Topical
  - Patch, gel, spray, and emulsion forms available
  - Not subjected to first-pass hepatic metabolism
  - Associated with more stable serum levels
  - Risk of skin-to-skin transfer of small amounts
  - Some studies have shown increase in VTE and stroke with oral ET but not with transdermal
  - Stroke and VTE events were comparable across oral, transdermal, and placebo groups in the Kronos Early Estrogen Prevention Study (KEEPS)

**Shifren JL, et al. *J Clin Endocrinol Metab*. 2008;93(5):1702-1710; Goodman MP. *J Womens Health (Larchmt)*. 2012;21(2):161-169; Canonico M, et al. *Stroke*. 2016;47(7):1734-174; Laliberte F, et al. *Menopause*. 2011;18(10):1052-1059; Renoux C, et al. *BMJ*. 2010;340:c2519; Santen RJ. *Climacteric*. 2015;18:121-134; Suckling J, et al. *Cochrane Database Syst Rev*. 2006;CD001500.**

# FDA approved available estrogens







# Types of Progestogen Therapy


- **MP ( Micronized progestin)**
  - Compound identical to endogenous progesterone
  - Prometrium is the only FDA-approved bioidentical progestogen
  - Contraindicated in women with peanut allergy
  - Bedtime dosing advised because of sedating effects, 100 mg Qhs or 200 mg, 12 days/month to protect lining of endometrial

- **Synthetic Progestins**
  - Synthetic products with progesterone-like activity
    - Medroxyprogesterone acetate (MPA) is the most commonly used and studied in the US for endometrial protection
    - Others: Norethindrone acetate, levonorgestrel , drosperinone, dienogest
    - Off label use in US ( approved in Europe): Levonorgestrel or progestin containing IUD

Schussler P, et al. *Psychoneuroendorinology*. 2008;33(8):1124-1131. Montplaisir J, et al. *Menopause*. 2001;8(1):10-16.

# Bioidentical Hormone Therapy

- Chemically identical to the hormones produced by the ovaries during the reproductive years
- ***Bioidentical hormone therapy*** is a marketing term not recognized by FDA
- Several FDA-approved bioidentical hormone preparations on the market (eg, estradiol pills, patches, gels, sprays, vaginal ring) and oral micronized progesterone
- ***Custom-compounded* HT** by compounding pharmacies
  - These products are not FDA approved
  - Concerns about safety, active ingredients



**Bio-identicals: Sorting Myths From Facts [FDA Consumer Update]. January 9, 2008. Simon JA, et al. Proceedings from the Postgraduate Course presented prior to the 17th Annual Meeting of The North American Menopause Society. Nashville, TN: October 11, 2006.**

# Bioidenticals: 2020 NASEM Recommendations

- Restricting the use of cBHT to certain situations (with allergies, unavailable doses in FDA-approved products, or testosterone for women with sexual dysfunction)
- Improved education for prescribers and pharmacists who market, prescribe, compound, and dispense cBHT preparations
- Expanding and improving oversight and review of compounding pharmacies
- Collecting and disclosing information on conflicts of interest
- The evidence base on the safety, effectiveness, and use of cBHT preparations should be strengthened and expanded
- Patient preference is not reason alone to use these products

NAMS practice pearl ( Dec 2020)

https://www.menopause.org/docs/default-source/professional/nams-practice-pearl-cbht.pdf

Editorial ( Oct 2020)

https://www.contemporaryobgyn.net/view/stand-firm-with-science

**National Academies of Sciences, Engineering, and Medicine. *The Clinical Utility of Compounded Bioidentical Hormone Therapy: A Review of Safety, Effectiveness, and Use*. Washington, DC: The National Academies Press; 2020.**

# Indications for HT

- Vasomotor symptoms ( hot flashes, night sweats)
  - Affect 60-80% women during menopause transition
  - Median duration 7-10 yrs
  - Associated with sleep disturbance, cognitive function, depressive symptoms
  - Correlation between VMS and CVD risk AND low bone density
- Genito-urinary syndrome of menopause ( GSM) formerly vulvo-vaginal atrophy
- Prevention of osteoporosis /fractures

**Crandall CJ, et al. *J Clin Endocrinol Metab*. 2015;100(2):524-534**

# Contraindications to HT

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer, except in appropriately selected patients being treated with oncology involvement
- Suspected estrogen-dependent neoplasia
- Active or history of deep vein thrombosis, pulmonary embolism
- Active or recent (within the past year) arterial thromboembolic disease ( MI or CVA)
- Liver dysfunction or disease
- Known or suspected pregnancy
- Known hypersensitivity to ET or EPT

# Women's Health Initiative (WHI) in a nutshell

- Randomized controlled primary prevention trial with endpoints of CHD, nonfatal MI, CHD death
- PMO women ( average age 63 yrs and 12 yrs since menopause transition)
- 2 arms:

  16K EPT ( CEE 0.625 + MPA 2.5 mg) vs placebo x 5 yrs ( halt for increase breast cancer)

  11K hysterectomized women ET ( CEE) vs placebo x 7 yrs ( halt for stroke)
- To date: both cohorts followed for 18 yrs

# Risk vs. Benefit of HT (Heart)

- Timing hypothesis
  - Less risk associated with HT use and potential coronary heart disease (CHD) benefit if initiated closer to the time of menopause
  - In contrast, HT use initiated further from menopause may be harmful

- Evidence from the WHI
  - Absolute risk of CHD was lower in younger, recently postmenopausal women
  - Use of HT within 10 y of the onset of menopause was associated with a lower CHD risk than if it was started ≥20 y from LMP
  - Women aged 50-59 y in the ET arm had decreased all-cause mortality and fewer MI's

Rossouw JE, et al. *JAMA*. 2007;297(13):1465-1477. Manson JE, et al. *JAMA*. 2013;310(13)1353-1368. Manson JE, et al. *JAMA*. 2017;318(10):927-938. Harman SM, et al. *Ann Intern Med*. 2014;161(4):249-260. Hodis HN, et al. *N Engl J Med*. 2016;374(13):1221-1231.

# Risk vs. Benefit of HT (Heart)

American Heart Association/American College of Cardiology
Dec 2020 updated guidelines:

- Changes in body fat deposition, metabolic syndrome, lipids ( increased LDL) and narrowing arteries/vascular health associated with menopausal transition.
- Sleep disturbance and depressive symptoms related to hormonal fluctuations and associated with increased risk of cardiovascular disease.
- Women presenting with severe hot flashes have more subclinical atherosclerosis and cardiovascular risk factors.
- Summary: CHD prevention strategies, may include FDA approved HT in appropriate patients may be considered part of prevention strategies alongside aggressive lifestyle modification

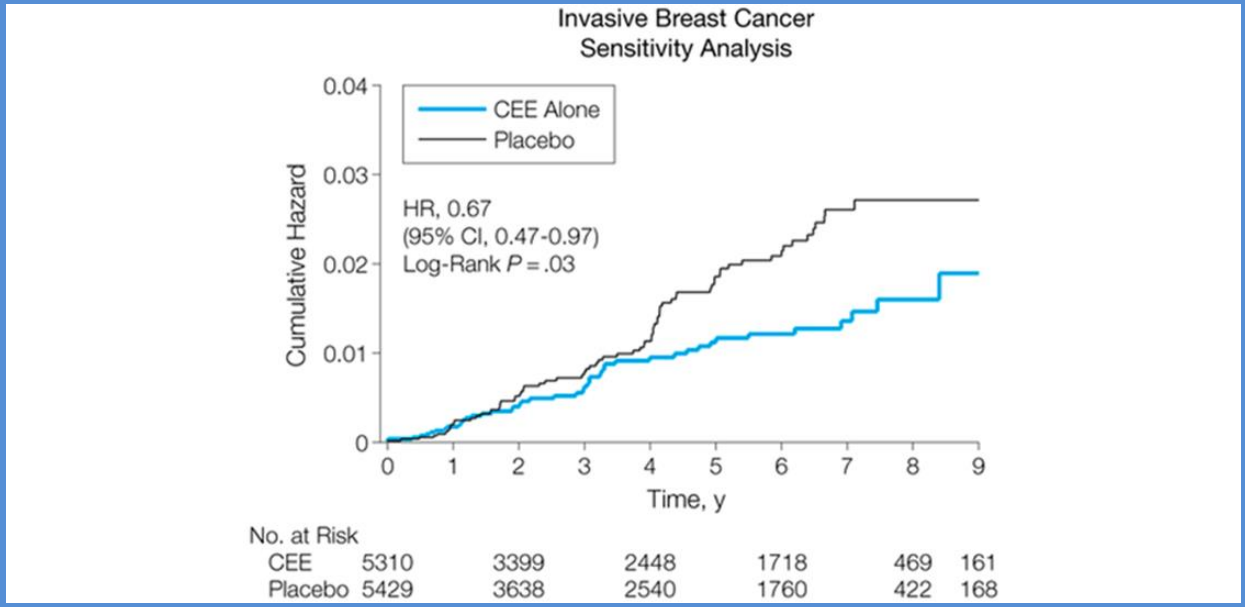
Khoudary, SR et al. Circulation. 2020;142;506–532.

# Risk vs. Benefit ( Breast)

Estrogen alone[1]

NO increased risk after 7.1 yrs ( WHI)[1]

18 year follow up[2]: 21 % reduction in breast cancer ( and 45% reduction in BC mortality ) persisted and 32 % reduction in ALL cause mortality in women age 50-59 yrs




Stefanick ML *JAMA* 2006;295:1647-57;
Manson JE JAMA 2017; 318: 927-938

# Risk vs. Benefit ( Breast)

EPT[1] CEE and MPA

- Increase risk of breast cancer seen after 3-5 yrs
- 24% increased risk of invasive breast cancer. RR of 1.24 ( CI 1.11-1.48) with E+MPA
- 13 yr WHI follow up: Increase risk of breast cancer persisted ( HR 1.28, CI 1.11- 1.48)
- RR of 1.66 ( CI 1.58-1.75) with E+ NETA ( Million Women Study[2])
- Comparative risk: 30% increased risk of invasive breast cancer

  RR 1.29 ( CI 1.22-1.36)[3] for PM women BMI > 30

Absolute risk: 9 breast cancers diagnosed for every 10,000 women on EPT for 1 yr

1Manson et al. JAMA 2013; 310:1353-1368

2 Beral et al. Lancet 2003; 362: 419-427.

3 Reeves et al. BMJ 2007; 335 ( 7630) 1134.

# Risk vs Benefit ( Breast)

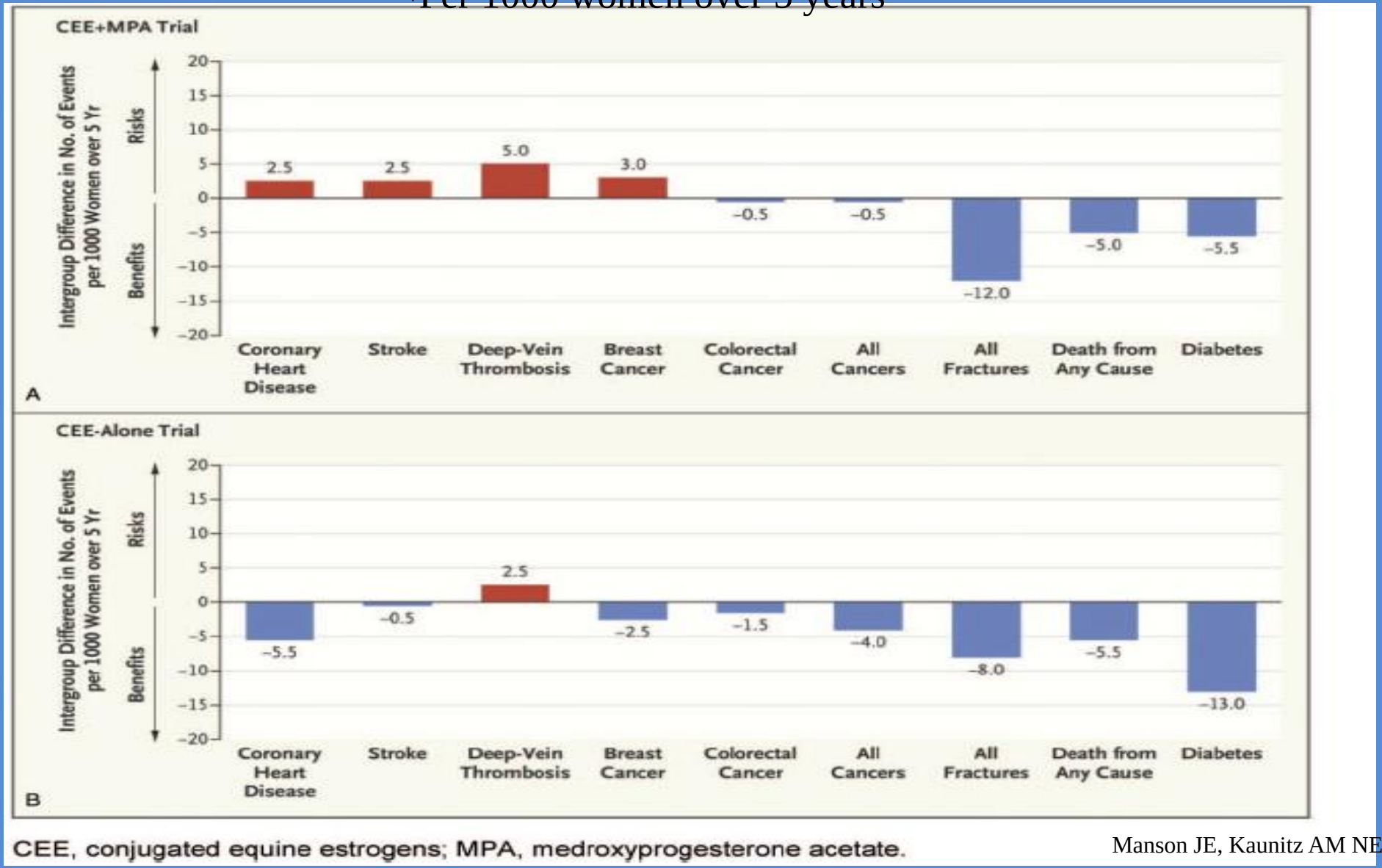
- Analysis from French prospective cohort study[1] ( 78, 353 women)
  - No increased risk of invasive breast cancer in users of MP ( prometrium) 5 yrs; HR 1.13 ( CI 0.99- 1.29)
  - < 1 breast cancer per 1000 women per year of use
- MP mammographic density mixed results ( no change or slight increase)
- Animal ( monkey) data on breast epithelial cell proliferation[2]( Ki67 expression) significant higher in E+ MPA vs. E+ MP ( 200 mg /day)

1Fournier A, Berrino F, Clavel-Chapelon F. Uneqresults from the E3N cohort study. Breast Cancer Res Treat 2008; 107: 103-111.

2 Wood et al. Breast Cancer Res Treat 2007, 101 (2) 125-134.

# Benefits vs. Risk for women age 50-59 yrs

*Per 1000 women over 5 years




CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

Manson JE, Kaunitz AM NEJM 2016; 374:803-806

**TABLE 4.** *Approach to initiating menopausal hormone therapy*

**1 Vasomotor symptom assessment**

Confirm that hot flashes and/or night sweats are adversely affecting sleep, daytime functioning, or quality of life.

**2 Risk factor assessment**

Confirm that there are no absolute contraindications to menopausal hormone therapy

- Breast, endometrial, or other estrogen-dependent cancer
- Cardiovascular disease (heart disease, stroke, transient ischemic attack)
- Active liver disease
- Undiagnosed vaginal bleeding

**3 Menopausal hormone therapy initiation**

| RECOMMEND | CONSIDER WITH CAUTION | AVOID |
|---|---|---|
| Age <60 y | Age ≥ 60 y | High risk of breast cancer |
| AND | ••••••••••••••••OR•••••••••••••••• | or cardiovascular disease |
| Menopause onset within 10 y | Menopause onset >10 y prior | ••••••••••••••••OR•••••••••••••••• |
| AND | ••••••••••••••••OR•••••••••••••••• | Age ≥60 y or menopause onset >10 y prior |
| Low risk of breast cancer and cardiovascular disease | Moderate risk of breast cancer or cardiovascular disease | and Moderate risk of breast cancer or cardiovascular disease |

Adapted from Shifren JL, et al. *JAMA* 2019;321:2458-2459.[45] Copyright © 2019 American Medical Society. Used with permission.

# NAMS position statement on HT use

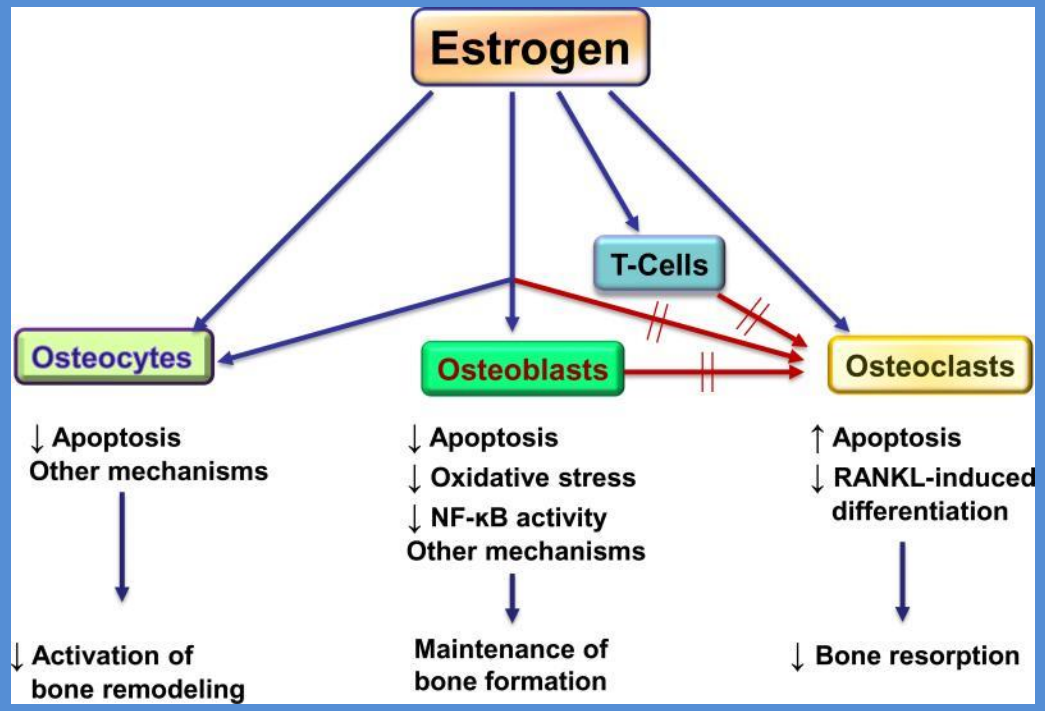
- ✓ Individualize HT type, dose, formulation, route of administration, and duration of use, to maximize benefits and minimize risks, with periodic reevaluation of continuing or discontinuing HT.

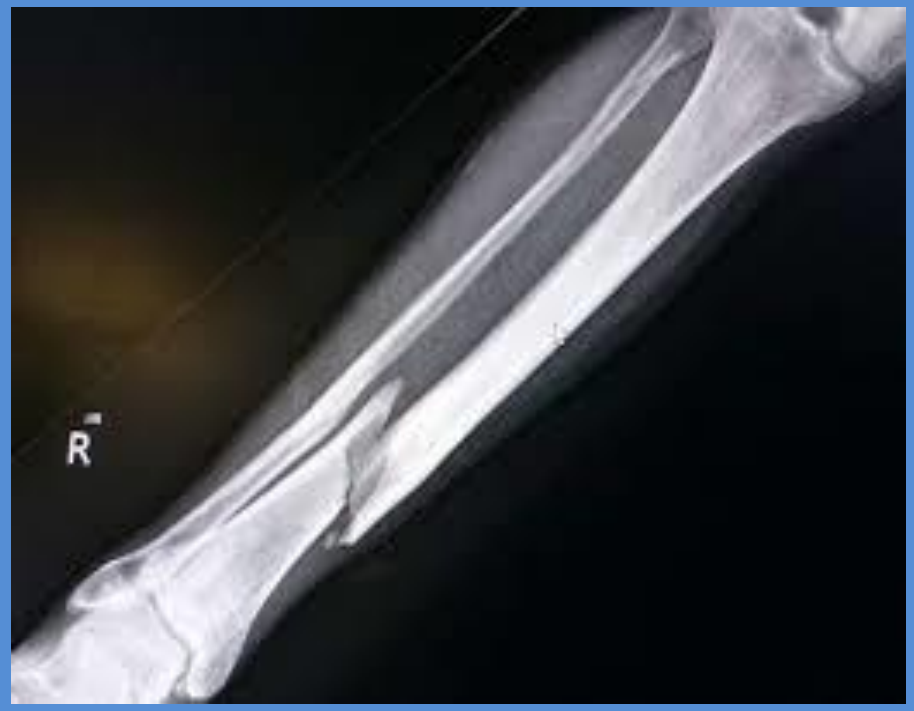
- ✓ For women with VMS aged younger than 60 years or who are within 10 years of menopause onset, HT (ET, EPT, or CE combined with bazedoxifene) is probably the most appropriate bone-active therapy in the absence of contraindications.

- ✓ When alternate osteoporosis therapies are not appropriate or cause AEs, the extended use of HT is an option for women who are at high risk of osteoporotic fracture.

2017 HT Position Statement Menopause 018;24(7):728-753.

# HT and Fracture reduction



# What's the evidence for HT and fracture reduction

## WHI ( Women's Health Initiative)[1,2,3]

- In the WHI, HT ( EPT and E alone) reduced the risk of hip fracture by **33-40%. ( P< 0.03)**
- Vertebral fractures reduced by 30-40%
- After 3 years LS BMD ↑4.6% and ↑ 3.6% in total hip

## Million Women Study[4]

- HT users 38% reduced risk of fracture vs. non user ( no difference based on formulation, route of administration)

- A meta-analysis of 22 trials of estrogen for the prevention of fractures[5]
  - 33 % reduction in non-vertebral fractures in women under age 60
  - 12 % reduction in women over 60.


1 Anderson et al .JAMA 2004 ; 291; 1701-1712.
2 JA Cauley et al. JAMA 2003 ; 290 (13) 2891-2897
3 RD Jackson JBMR 2006 21 (6) 817-828.
4 Beral et al. Lancet 2003; 362: 419-427.
5 DJ Torgerson et al. JAMA 2001 285

# Progestogen effect on bone?

- Progesterone receptors on osteoblasts and intracellular
- MPA 10 mg/day OR NETA (0.25-1 mg) + estradiol increased BMD more estradiol alone [1]
- NETA 1- 5 mg beneficial effect on BMD[2]
- MPA alone – BMD results mixed (pre-menopausal women)
- PEPI trial[3] , 3 yr RCT of 875 postmenopausal women aged 45-64 years
- Treatments were
  - (1) placebo;
  - (2) conjugated equine estrogens (CEE), 0.625 mg/d;
  - (3) CEE, 0.625 mg/d + MPA 10 mg/d for 12 d/mo;
  - (4) CEE, 0.625 mg/d +MPA, 2.5 mg/d daily; or
  - (5) CEE, 0.625 mg/d + MP 200 mg/d for 12 d/m

1Greenwald et al. Menopause 2005; 12 : 741-748.
*2 Speroff et al. JAMA.* 1996;276(17):1397-1403
*3 Writing group of the PEPi trial. JAMA.* 1996;276(17):1389-1396

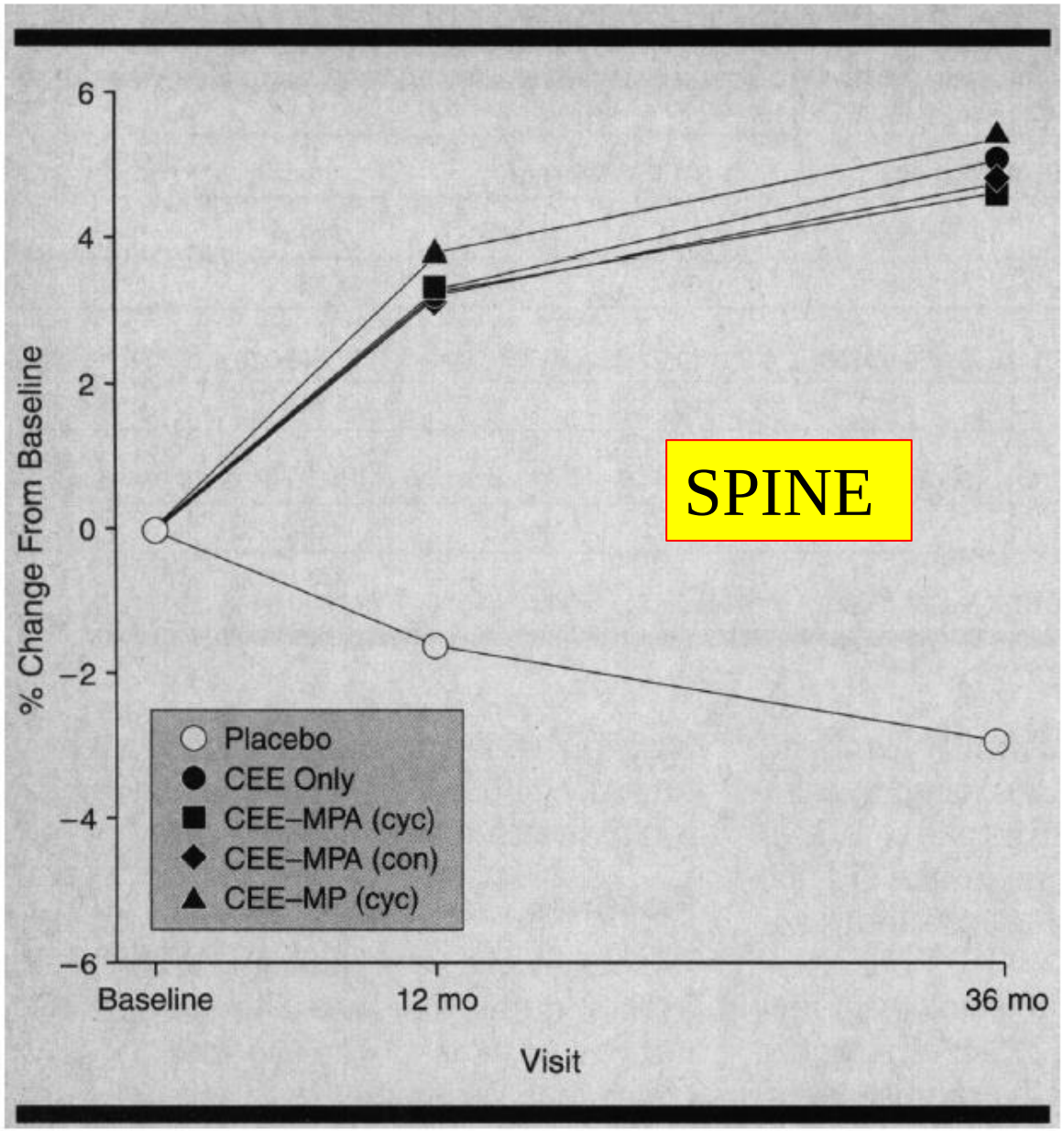



Figure 1.—Unadjusted mean percent change in bone mineral density in the spine by treatment assignment and visit: adherent PEPI participants only. See Table 1 footnotes for explanation of treatment groups and definitions.

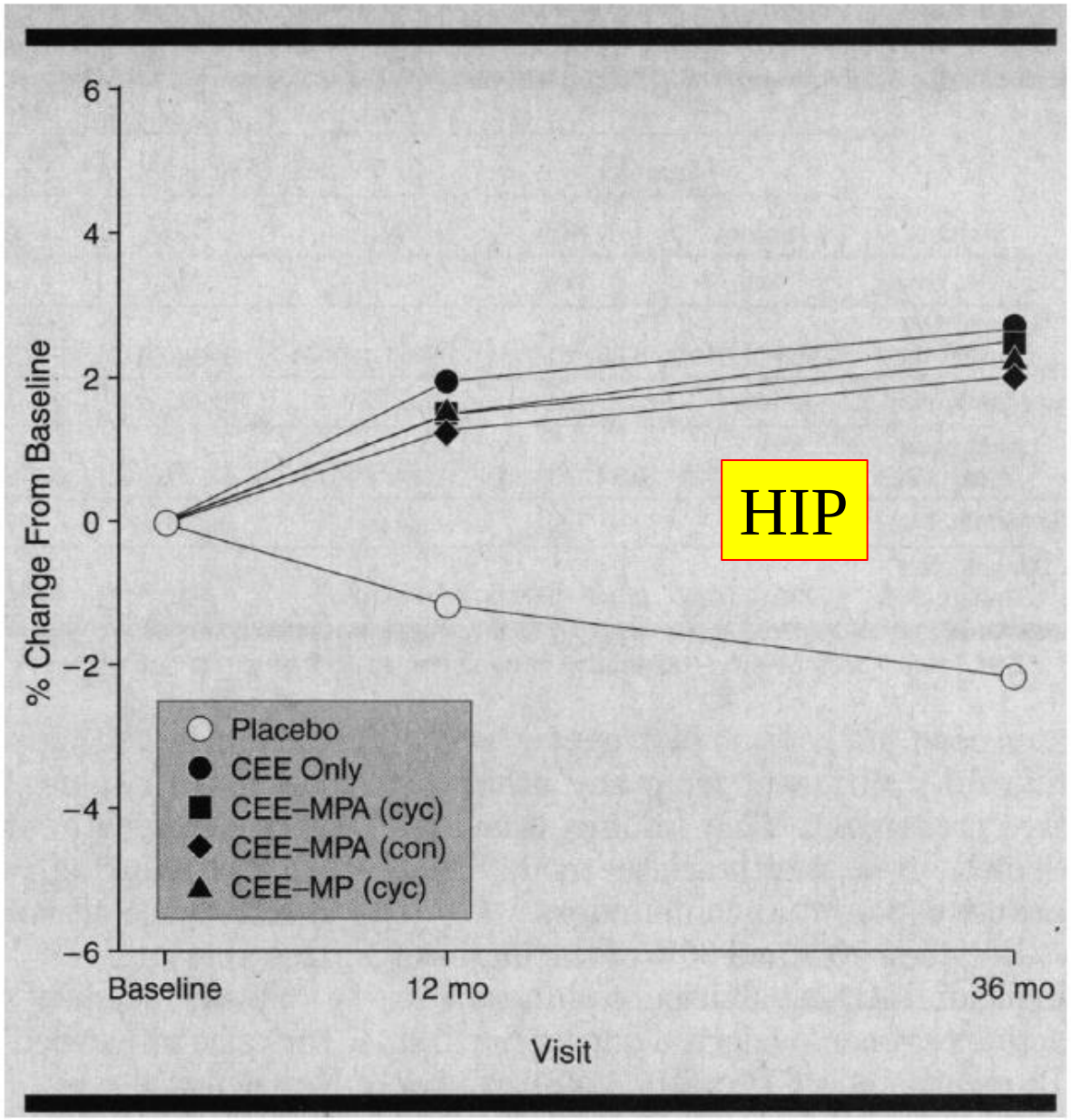



Figure 2.—Unadjusted mean percent change in bone mineral density in the hip by treatment assignment and visit: adherent PEPI participants only. See Table 1 footnotes for explanation of the treatment groups and definitions.

# PEPI conclusions

- BMD increase greatest within first 12 mos on HT
- No added benefit of EPT over Estrogen alone in this trial
- Women in active HT increase spine BMD ( 3.5-5%) and hip BMD (average 1.8%) vs placebo. No significant difference b/t groups.
- No difference of fractures rates across groups

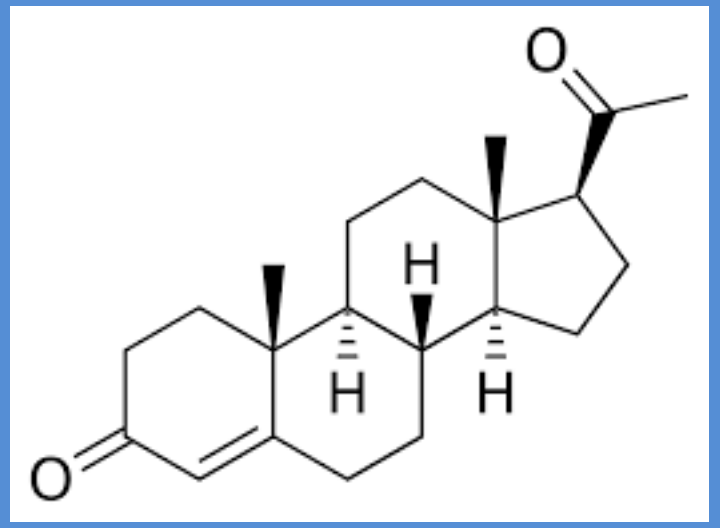
Other interesting findings:

- Women age 45-54 yrs taking placebo groups ( age 45-54 yrs) lost most BMD in spine &hip than women 54-65 yr on placebo
- Older women ( age 55-64yr) , greater time since menopause, women with low initial BMD , no previous hormone use gained significantly more BMD than younger women on HT

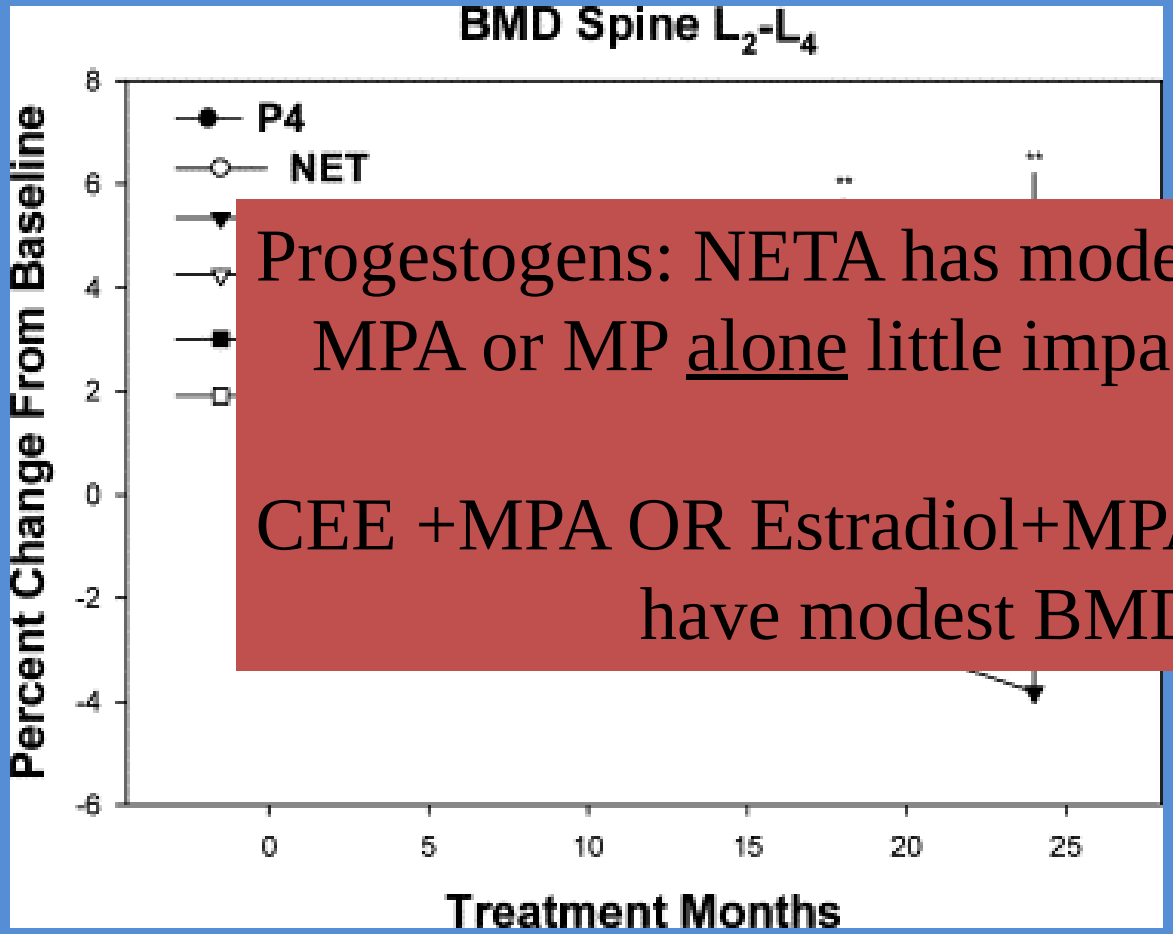
Writing group of the PEPi trial. JAMA. 1996;276(17):1389-1396

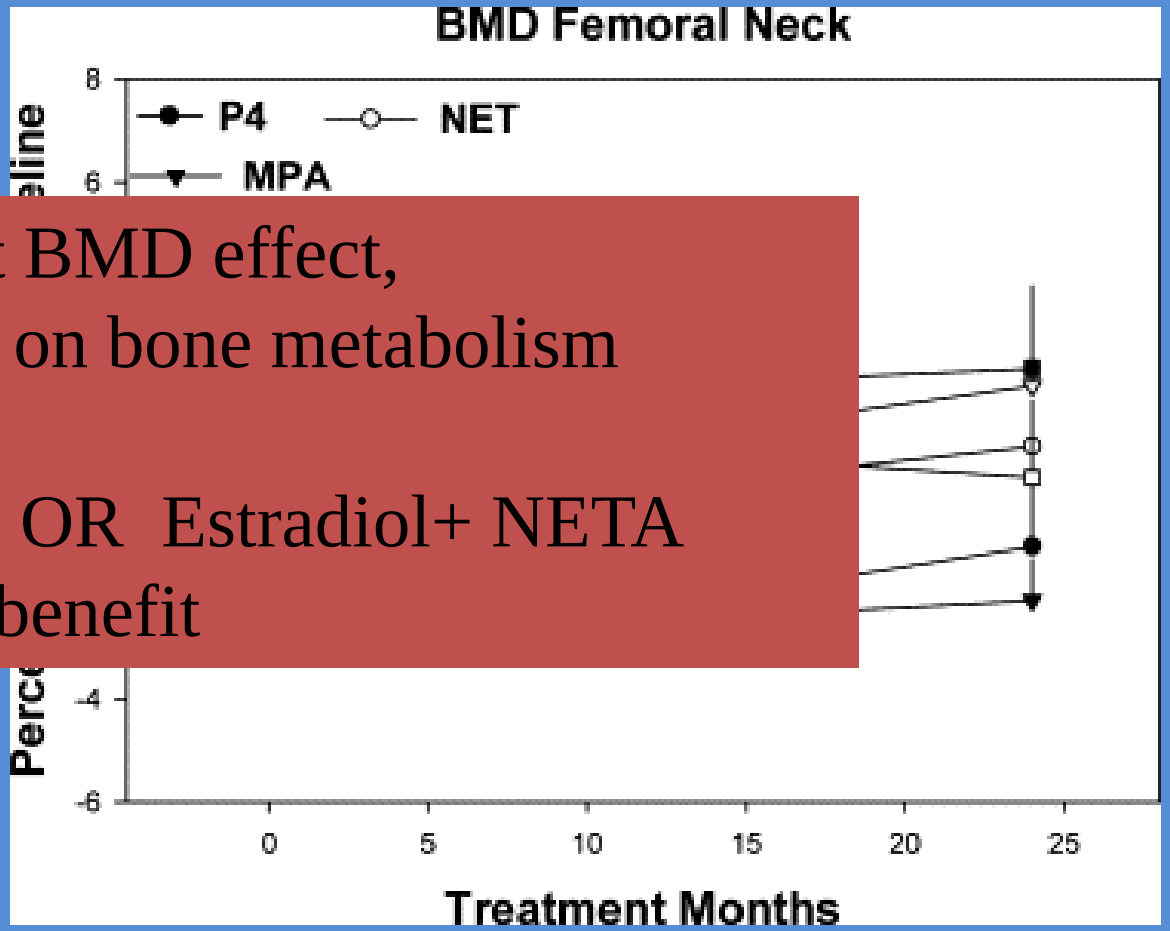
# Progestogen effect on bone?

- 2 yr prospective randomized , DB, placebo control 132 PM women
- 6 treatment groups: 3 different types of Progestogens : MP 300 mg/day, MPA 10 mg/day, NETA 1 mg/day, E2 1mg/day + MPA 10 mg/day and placebo




Liu et al . AJOG 2005 1316-1324




Progestogens: NETA has modest BMD effect,
MPA or MP alone little impact on bone metabolism

CEE +MPA OR Estradiol+MPA OR Estradiol+ NETA
have modest BMD benefit

Lumbar spine BMD increased 2-4% in E2 alone or E2 + MPA 10 md/day
FN E2 or E2+ MPA trend to increase BMD ( NS)

Liu et al . AJOG 2005 1316-1324

## PHARMACOKINETIC AND PHARMACOLOGIC VARIATION BETWEEN DIFFERENT ESTROGEN PRODUCTS

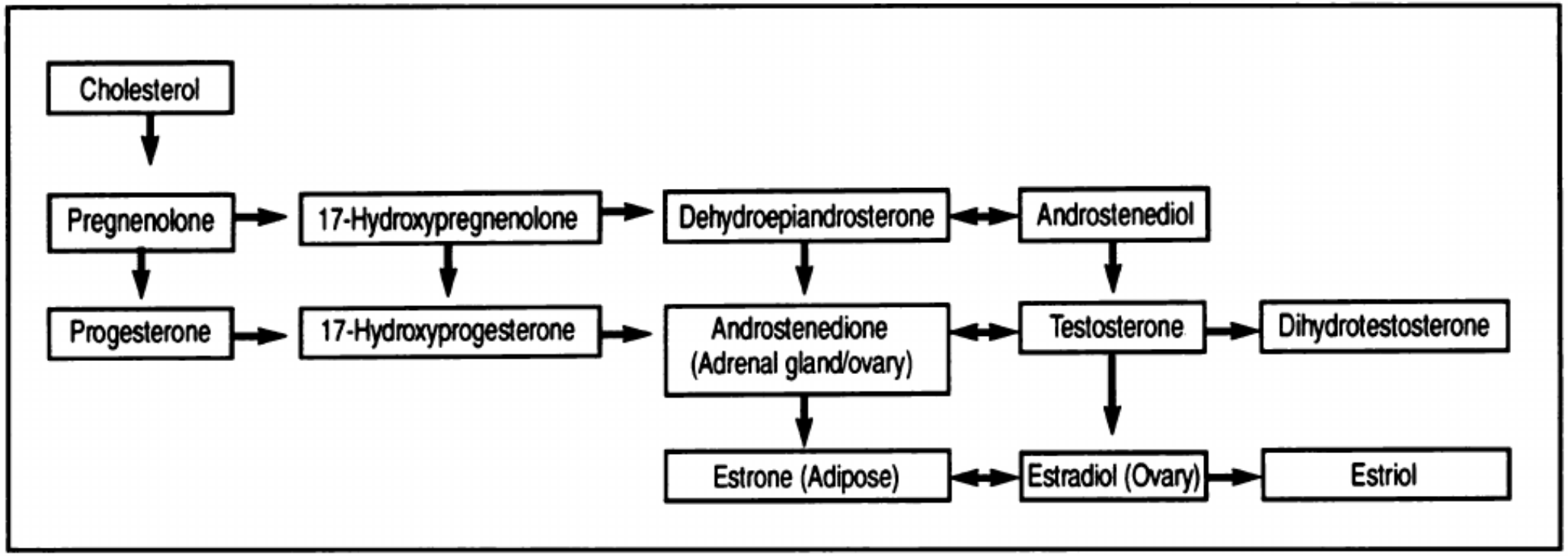



*Figure 1. General scheme for synthesis of androgens and estrogens. Adapted with permission.*[1]

O'Connell et al. J Clini Pharm 1995

# Does estrogen dose matter?

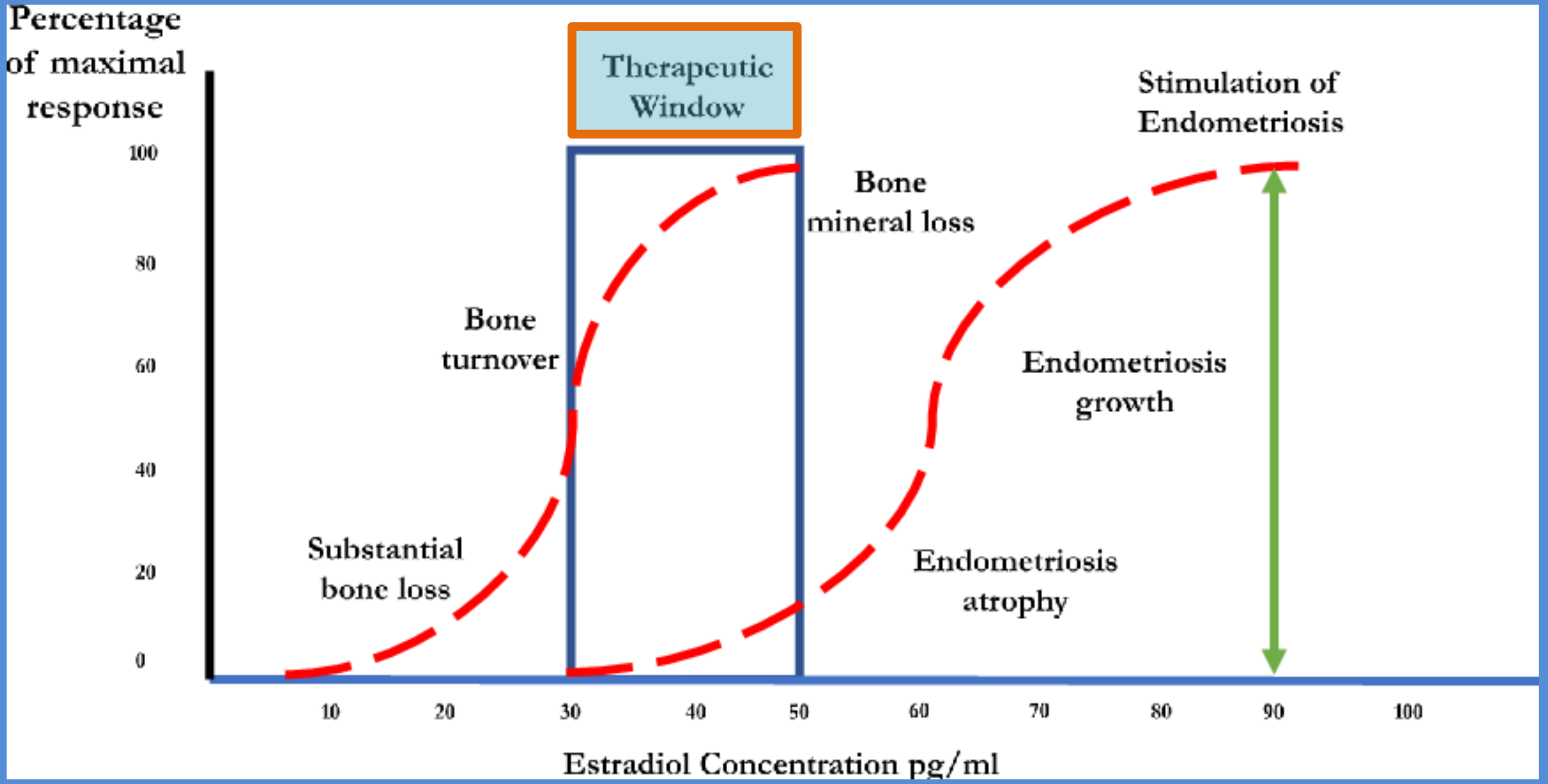
YES: BMD response is dose related

- FDA approved patch: Estradiol 0.014 mg weekly patch for prevention of OP→ NO fracture data. (*use cyclical progestogen q 6 mos in women with intact uterus)
- Low dose: oral CEE 0.3 mg; oral 17β-estradiol ≤ 0.5 mg; or estradiol patch 0.025 mg

➢ After discontinuation of HT, bone mineral density decreases → without increase risk in rebound fracture

Manson et al. JAMA. 2013;310(13):1353-1368

# Estrogen Threshold Hypothesis : Premenopausal women




Barberi et al AmJ Obstet Gynecol 1992 740-745

# Does serum estradiol matter?

- Serum estradiol levels 40-60 pg/ml ( equal to early follicular phase estradiol) prevents BMD loss and decrease urinary calcium excretion and bone turnover markers[1,2]
- Study
  Linear relationship between estrogen dose and BMD response,
  Not necessary to check serum estradiol
  wome
  l)
  vs. 5-25 pg/ml.
- In women with < 5 pg/ml
  - Increase risk vertebral deformities (30% had significant height loss)
  - 2.5 more likely to have hip or vert fracture .
  - BMD lower at spine, radius and femur

1 O'Connell et al. J Clinic Pharm 1995
2 Reginster Claci Tissue Inst 1992 Nov;51(5):340-3
3Odvina et al. JCEM 90 (3) 2005 1294-1301

# Commercially Available SERMs


- Bazedoxifene
  - Third-generation SERM
  - Estrogen agonist on bone
  - Estrogen antagonist on breast and endometrial tissue
  - Approved in Europe and Japan for treatment of osteoporosis
  - Bazedoxifene 20mg and CEE 0.45 mg ( TSEC) combination is available in the United States for treatment of VMS and prevention of osteoporosis ( SMART trials)
    - Increased BMD (2-3% in LS and 1-2% in hip after 2 yrs, no fracture data)

Silverman SL, et al. *J Bone Miner Res*. 2018;23(12):1923-1934; Christiansen C, et al. *BMC Musculosketel Disord*. 2010;11:130; Harvey6 HA, et al. *Breast*. 2006;15(2):142-157. Archer DF, et al. *Fertil Steril*. 2009;92(3):1039-1044. Pinkerton JV, et al. *Obstet Gynecol*. 2013;121(5):959-968. Pinkerton JV, et al. *J Clin Endocrinol Metab*. 2014;99(2):E189-E198. Pickar JH, et al. *Menopause*. 2018;25(9):1033-1045.

# Clinical Case 3. Eileen

Eileen is a 65 yo postmenopausal woman who started HT around the time of menopause, age 52. She has tried to discontinue HT but her VMS recur. Her current HT regimen is: estradiol 0.0375 mg 2x.wk and prometrium 100 mg nightly. Her DXA shows her spine T score is -1.5 with degenerative changes , FN -2.7 and total hip -2.5. She had a wrist fracture after a fall last year. She has no changes in weight, no new medications and is compliant with calcium, vitamin D and weight bearing exercise.

How do you counsel Eileen about OP treatment?

1. Increase her HT dose
2. Continue HT and add bisphosphonates
3. Continue HT and consider adding osteo-anabolic agent

# AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

**High risk/no prior fractures****

- Alendronate, denosumab, risedronate, zoledronate***
- Alternate therapy: Ibandronate, raloxifene

**Very high risk/prior fractures****

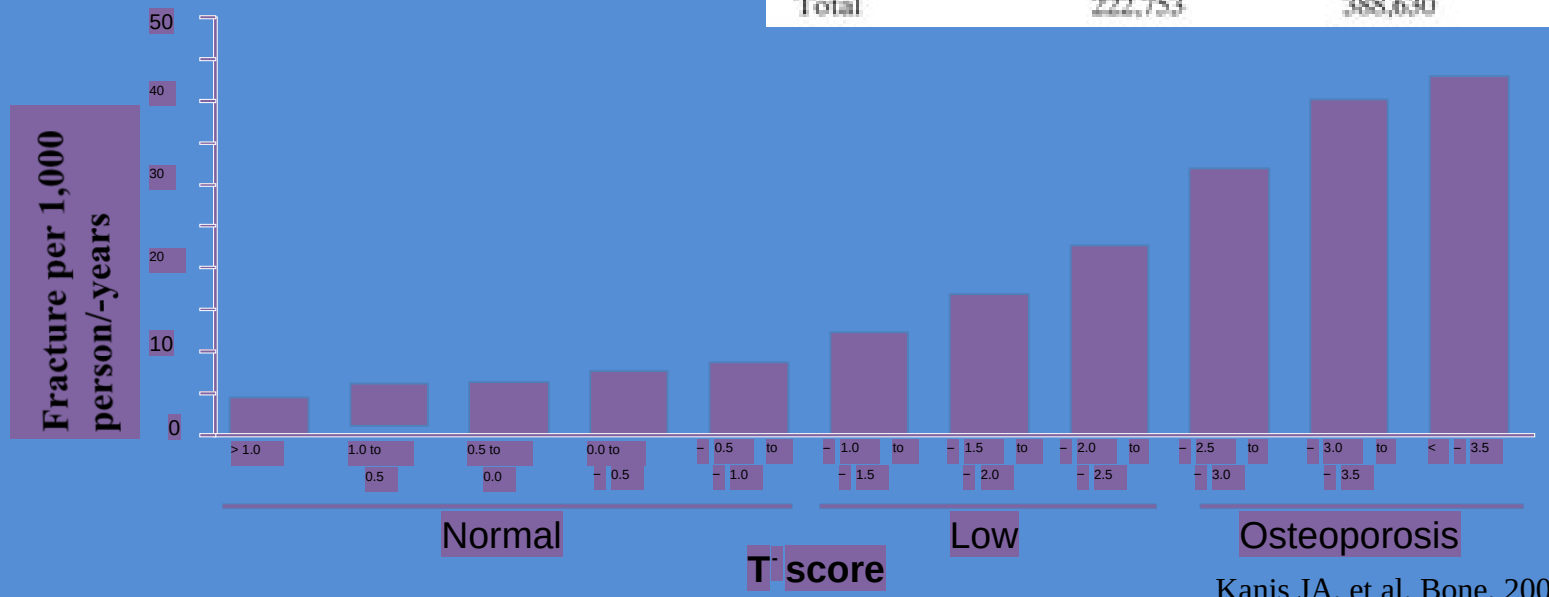
- Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
- Alternate therapy: Alendronate, risedronate

Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2020 update. Endocr Pract. 2020;26(1):1-4

# Strongest risk factors for fracture

- Prior fracture
- Age > 65 years
- T score < -2.5

| Stratum | Number of fractures per fracture type | | | | | |
|---|---|---|---|---|---|---|
| | *Hip* | *Vertebral* | *Wrist* | *Pelvic* | *Other* | *Total* |
| Women | | | | | | |
| Age (years) | | | | | | |
| 50–64 | 13,420 | 57,562 | 136,624 | 5,532 | 159,043 | 372,180 |
| 65–74 | 25,288 | 85,020 | 88,072 | 15,596 | 84,963 | 298,938 |
| 75–84 | 84,274 | 142,892 | 70,317 | 43,059 | 105,394 | 445,937 |
| ≥85 | 99,771 | 103,156 | 31,815 | 38,469 | 65,576 | 338,788 |
| Race | | | | | | |
| White | 201,123 | 347,739 | 285,973 | 88,973 | 366,360 | 1,290,168 |
| Black | 6,995 | 13,838 | 15,030 | 5,004 | 18,057 | 58,923 |
| Hispanic | 8,175 | 15,417 | 15,045 | 5,276 | 17,755 | 61,668 |
| Other | 6,460 | 11,636 | 10,781 | 3,403 | 12,805 | 45,085 |
| Total | 222,753 | 388,630 | 326,828 | 102,655 | 414,976 | 1,455,843 |




Kanis JA, et al. Bone. 2004;285:375-382.. Siris ES, et al. Arch Intern Med. 2004;164:1108-1112.

# Many options to individualize treatment

## ANTIRESORPTIVES

- Hormone therapy (estrogens/progestogens)
- Estrogen Agonists/Antagonists (formerly SERMS i.e: raloxifene or tamoxifen (postmenopause only)
- Tissue-selective estrogen complex (TSEC) i.e: conjugated estrogen/bazedoxifene
- Bisphosphonates (oral, IV)
- Denusomab (SQ)

## OSTEO-ANABOLICS

- Teriparatide (PTH 1-34- SQ)
- Abaloparatide (PTHrP- SQ)

## DUAL ANABOLIC/ ANTIRESORPTIVE

- Romosozumab ( SQ)

# Combination therapy ( HT and Alendronate)

- Greenspan et al, JAMA 2003. RCT, 373 women ( age 65-90yrs) HT ( 0.625mg CEE or CEE/MPA 2.5 mg) or alendronate 10 mg daily OR BOTH followed for 3 yrs[1]
- Results: BMD greater with combination ( 5.9% at hip and 10.4% at LS) vs. monotherapy
- BMD at hip in alendronate vs HT alone 4.2% vs. 3% ( $P < 0.05$)

- Lindsay et al, JCEM 1999. RCT, 428 women on HT ( on average 9 yrs)[2] randomized to add alendronate 10 md daily or placebo. Followed for 1 yrs
- Results: LS BMD greater in combination ( HT+ alendronate 3.6% vs HT+ placebo 1.0%) after 1 yr, no difference in FN BMD
- Adverse events similar , no AFF, no difference in fracture incidence

1Greenspan et al. JAMA 2003; 289 (19): 2525
2 Lindsay et al JCEM 84: 3076-3081

# Combination therapy

Finish study, JCEM 2004 RCT, 90 women ( mean age 71 yr)[1]

- HT ( 2mg estradiol/1mg norethindrone) or alendronate 10 mg or BOTH followed for 2 yrs
- Results : No significant differences in combination group in LS or hip BMD vs. monotherapy
- Reduction in bone markers ( CTX) and PINP less in HT than alendronate group

Take home efficacy: oral BP ( alendronate) + HT ( estrogen: mostly oral conjugated) together may increase BMD at spine (? at hip ) more than monotherapy

NO additional fracture reduction ( limited data)

# Combination therapy: potential concerns

- Suppression bone formation and low bone turnover

(Implications for AFF, ONJ?)

- Duration of therapy and potency and ½ life of bisphosphonates
- JCEM 2005, bone biopsy data 3 women on HT and alendronate 3- 8 yrs. Onset on non spinal/atypical fractures ( 3-5 yrs) combination tx than those on alendronate alone ( 6-8yr) [1]

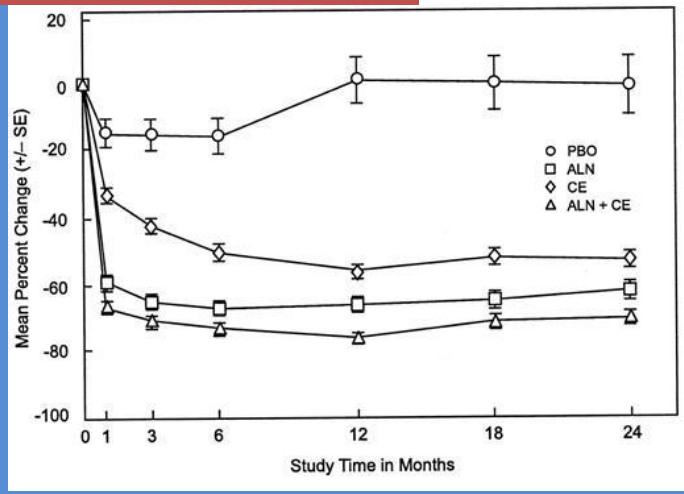
Odvina et al. JCEM vol 90, issue 3 March 2005 1294-1301

# Combination therapy: potential concerns

- Bone et al. JCEM 2000. RCT, 425 women CEE vs. alendronate 10 mg vs. COMBO CEE+ alendronate vs. placebo followed for 2 yrs. [1]
- Results : similar BMD gain in LS in CEE or alendronate
- Combination

Take home safety: Potential for lower bone turnover states in combination ( HT + alendronate) , AE: ONJ/AFF?
Need for better studies

- Bone turnove
- Histomorphometric studies: 92 patients after 18 mos
  - Mineralizing surface on trabecular bone(rate of bone turnover) <u>decreased</u> 90% alendronate, 75% HT and 95% in combination
  - Tetracycline labeling present in all groups (cortical bone)




Bone et al. JCEM 85 (2) 2000 720-726.

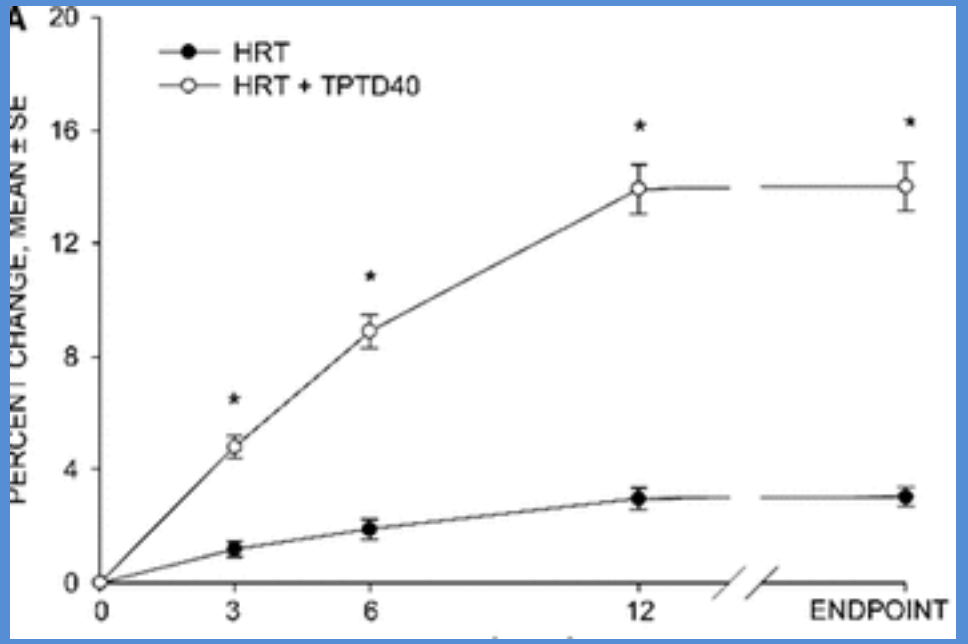
# HT+ osteo-anabolic therapy

- JBMR 2009[1], RCTs 250 women with OP/osteopenia followed for 14 mos

  Teriparatide 40 ug SQ daily + HT OR Placebo SQ + HT

  LS: 14% ( PTH+ HT) vs 3% ( HT)

  HIP: 5.2 (PTH+ HT) vs 1.6% (HT)




- Lindsay et al Lancet 1997[2] , RCT 34 PMO on Teriparatide 25 ug daily + HT vs. HT alone x 3 yrs

  PTH+ HT: LS: 13% HIP: 2.7 %

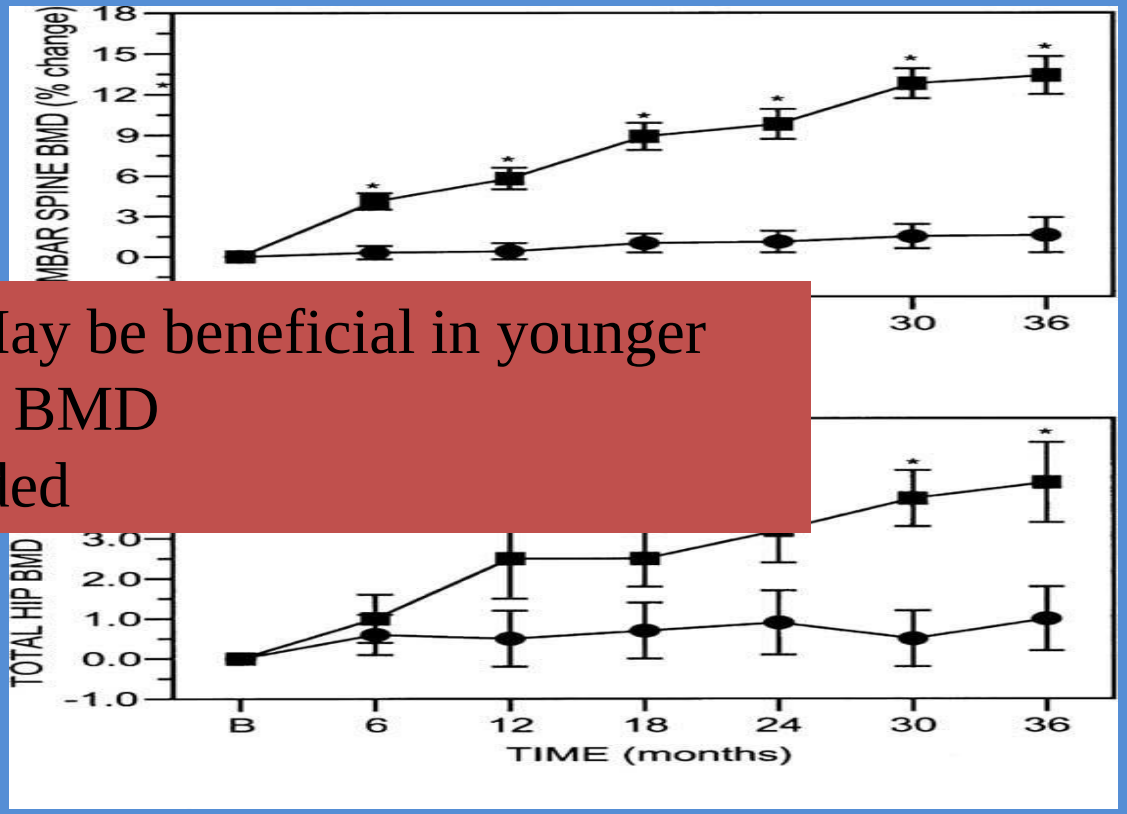
1 Ste-Marie, L et al J Bone Miner Res. 2009 Feb;21(2):283-91.
2 Lindsay et al. Lancet 1997, P550-555

# HT+ osteo-anabolic therapy

- Cosman et al. JBMR 2001[3], RCT 52 women with OP on HT alone vs. HT added Teriparatide 25 ug daily x3 years

  LS: 14% (PTH+ HT)

  Hip: 4% (PTH+HT)




Take home: Effective in small trials. May be beneficial in younger postmenopausal women with very low BMD

More research needed

- ❖ In th
  continuing HT No BMD loss occurred
  at spine and hip
- ❖ PTH+HT: Incidence of vert fractures
  ( 15% decrease in vertebral height measurement)
  decreased 75-100%

Cosman et alJ Bone Miner Re 2001 May;16(5):925-31.

# Revisit Clinical Case 3. Eileen

Eileen is a 65 yo postmenopausal woman who started HT around the time of menopause, age 52. She has tried to discontinue HT but her VMS recur. Her current HT regimen is: estradiol 0.0375 mg 2x.wk and prometrium 100 mg nightly. Her DXA shows her spine T score is -1.5 with degenerative changes , FN -2.7 and total hip

-2.5. She had a wrist fracture from a fall last year. She has no changes in weight, new medications and is compliant with calcium, vitamin D and weight bearing exercise.

In your clinical decision making should you?

1. Increase her HT dose
2. Continue HT and add bisphosphonates (consider treatment duration, monitor bone turnover markers)
3. Continue HT and consider adding osteo-anabolic agent

# Summary

- HT used since 1940s to improve BMD and WHI (RCT) confirmed hip, spine and fracture reductions
- HT mostly anti- resorptive effect on cortical and trabecular bone
- BMD response is dose dependent
- Consider HT in women < age 60 or 10 years since menopause with appropriate indications ( and no contraindications)
- Many effective therapies individualize prevention and treatment of OP and fractures

# Questions?


- Thanks for your attention!

Additional reading:

Rozenberg et al. Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? Osteoporosis International. March 2020.

Manson et al. Invited Review. The Women's Health Initiative trials of menopausal hormone therapy: Lessons learned. Menopause. Vol 27, No. 8. 2020