Welcome!

FLS Bone Health ECHO® TeleECHO Clinic

We will be recording this TeleECHO Clinic for educational and quality improvement purposes.

Please type in your name, location, and email address in the chat.

Some helpful tips:

Please mute your microphone when not speaking

Position webcam effectively

Communicate clearly during clinic:

- Speak clearly
- Use chat function

Project ECHO's goal is to protect patient privacy

To help Project ECHO accomplish that goal, please only display or say information that doesn't identify a patient or that cannot be linked to a patient.

References:

For a complete list of protected information under HIPAA, please visit www.hipaa.com

Common HIPAA Identifier Slip-Ups and Easy Ways to Protect Patient Privacy

1st – **Names:** Please do not refer to a patient's *first/middle/last name* or use any *initials*, etc. Instead please use the *ECHO ID*.

2nd – **Locations:** Please do not identify a patient's *county, city or town*. Instead please use only the patient's *state* if you must or the *ECHO ID*.

3rd – **Dates:** Please do not use any dates (like *birthdates*, etc.) that are linked to a patient. Instead please use only the patient's *age* (unless > 89)

4th – **Employment:** Please do not identify a patient's *employer*, work *location* or *occupation*. Instead please use the *ECHO ID*.

5th – **Other Common Identifiers:** Do not identify patient's *family* members, *friends, co-workers, numbers, e-mails*, etc.

NOF Staff Disclosures

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Clinical review of hormone therapy in prevention and treatment of osteoporosis

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Disclosures

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- Radius Health- consultant
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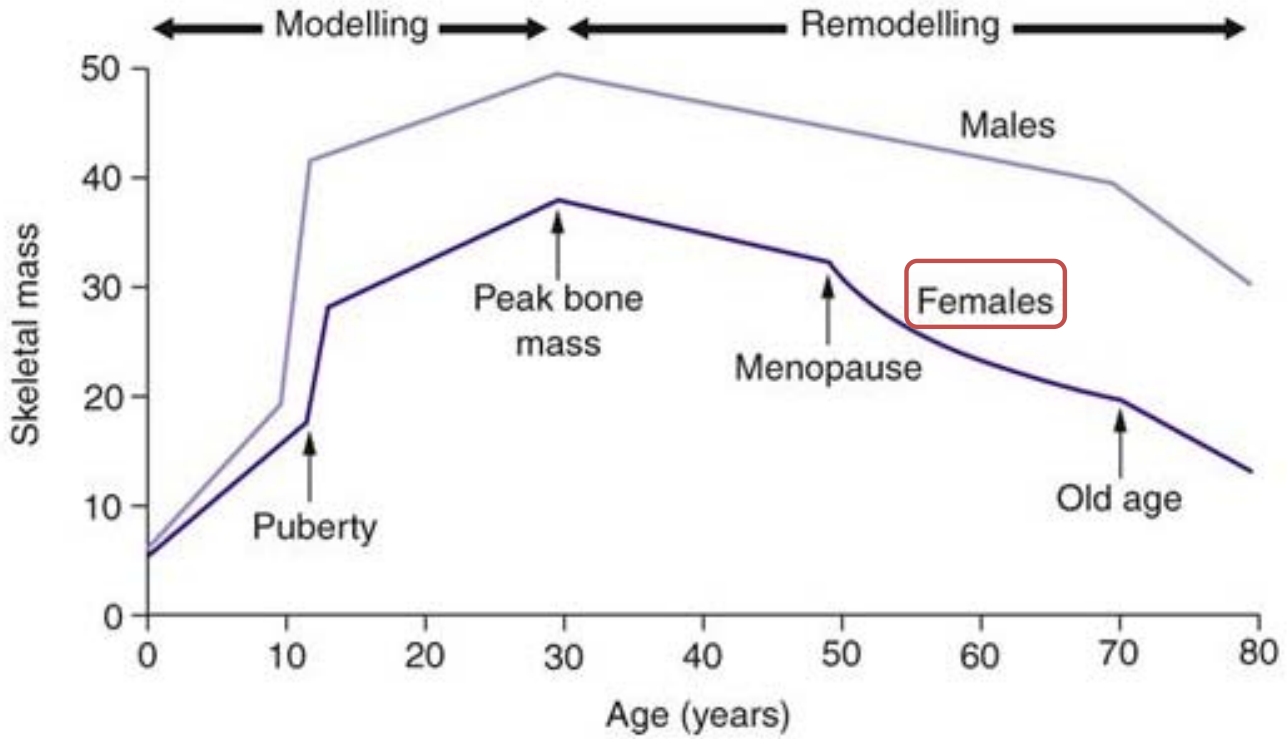
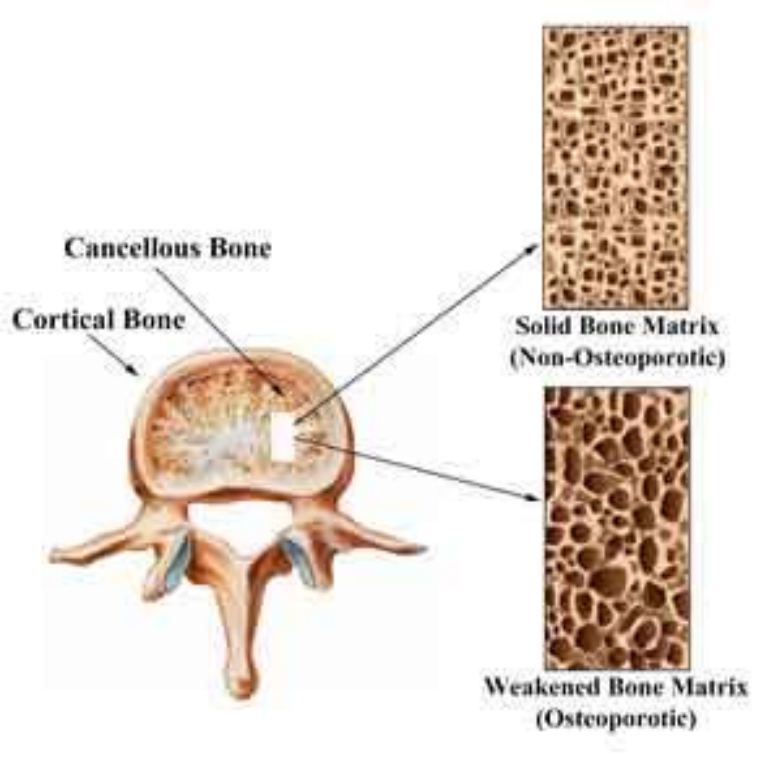
Objectives

- 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

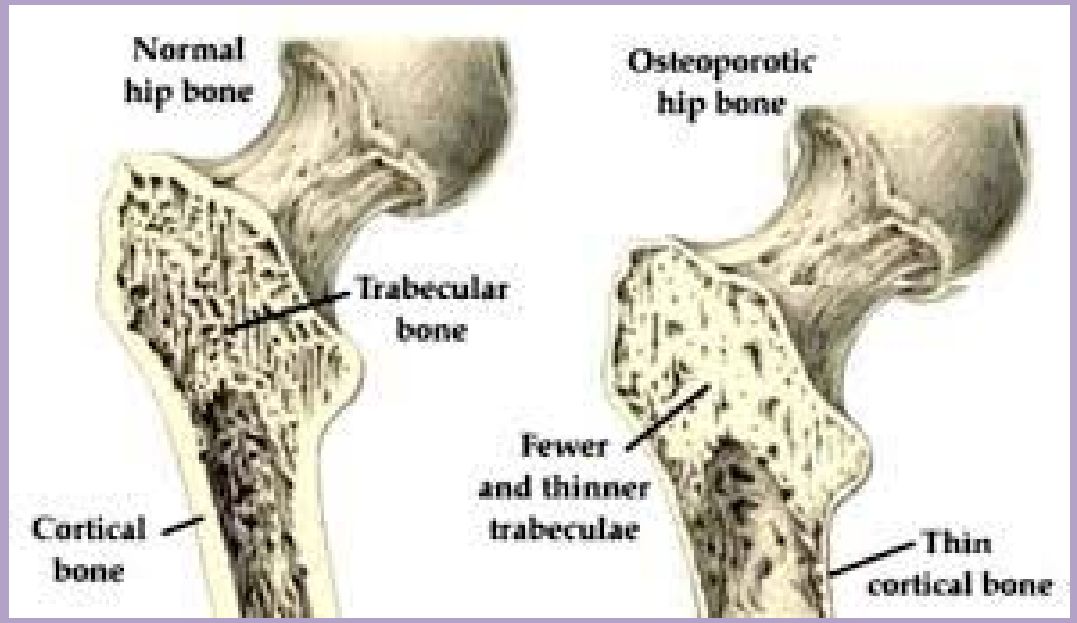
Changes in bone density over the lifetime



Types of bone



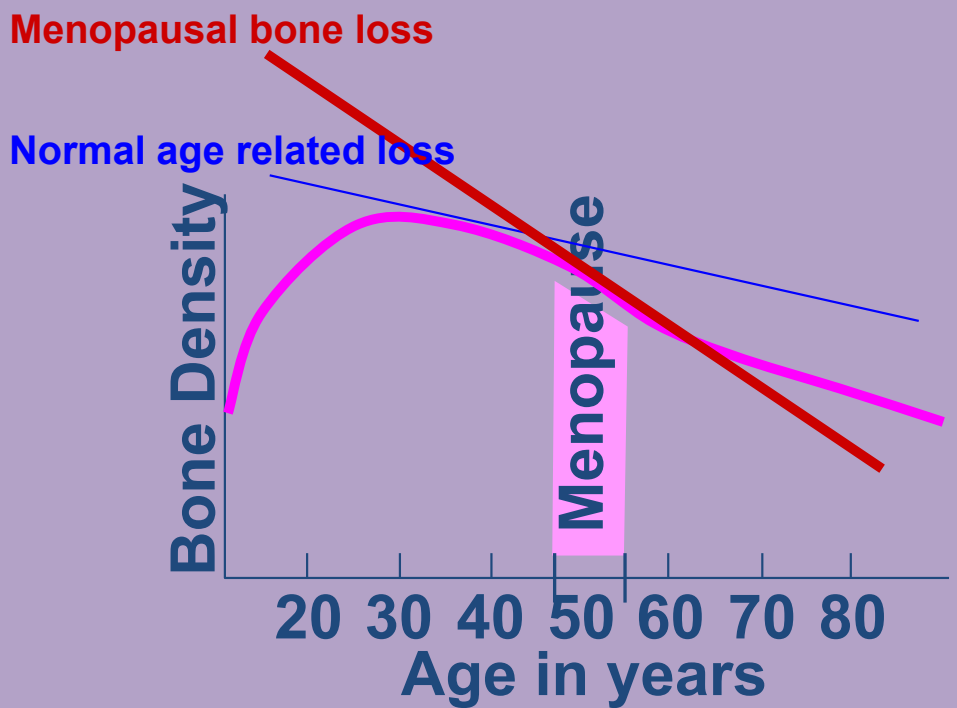
Vertebral spine:
trabecular (cancellous) > cortical



Hip (femur):
cortical > trabecular

Menopausal bone loss

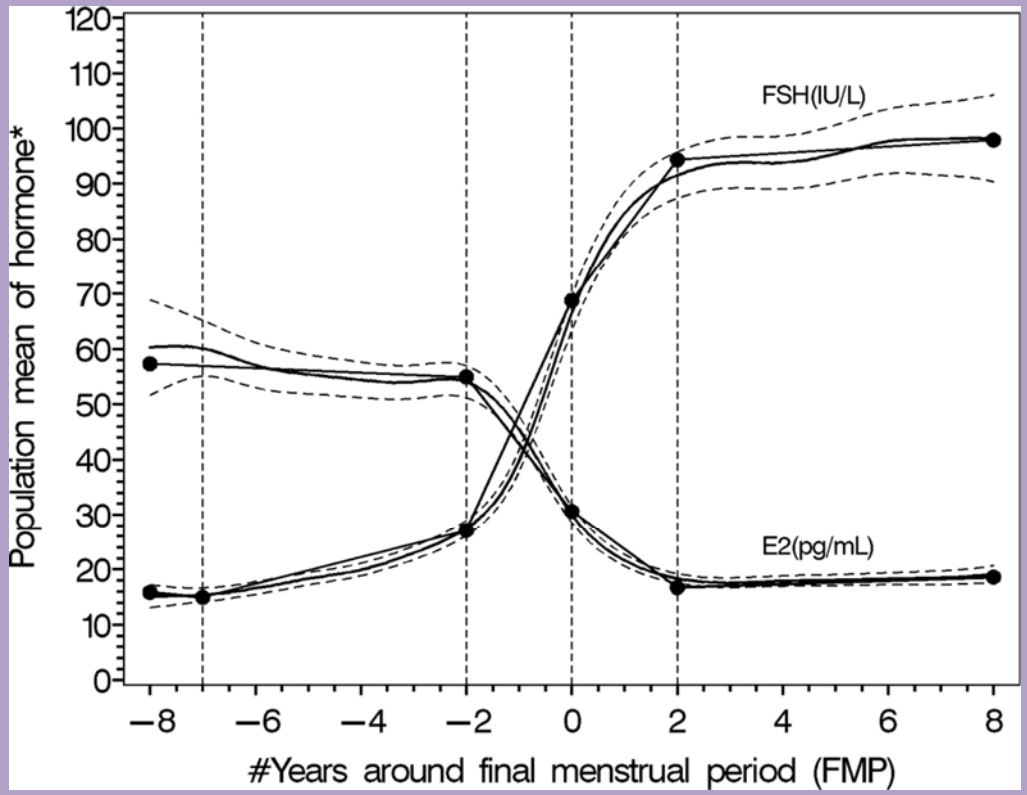
- Accelerated bone loss associated with menopause
- Loss at spine-rate of 3%/yr for about 5 years =15% BMD loss
- Loss at hip-rate of 0.5%/yr- additional 5% across menopause transition



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

Physiology of the Menopause Transition

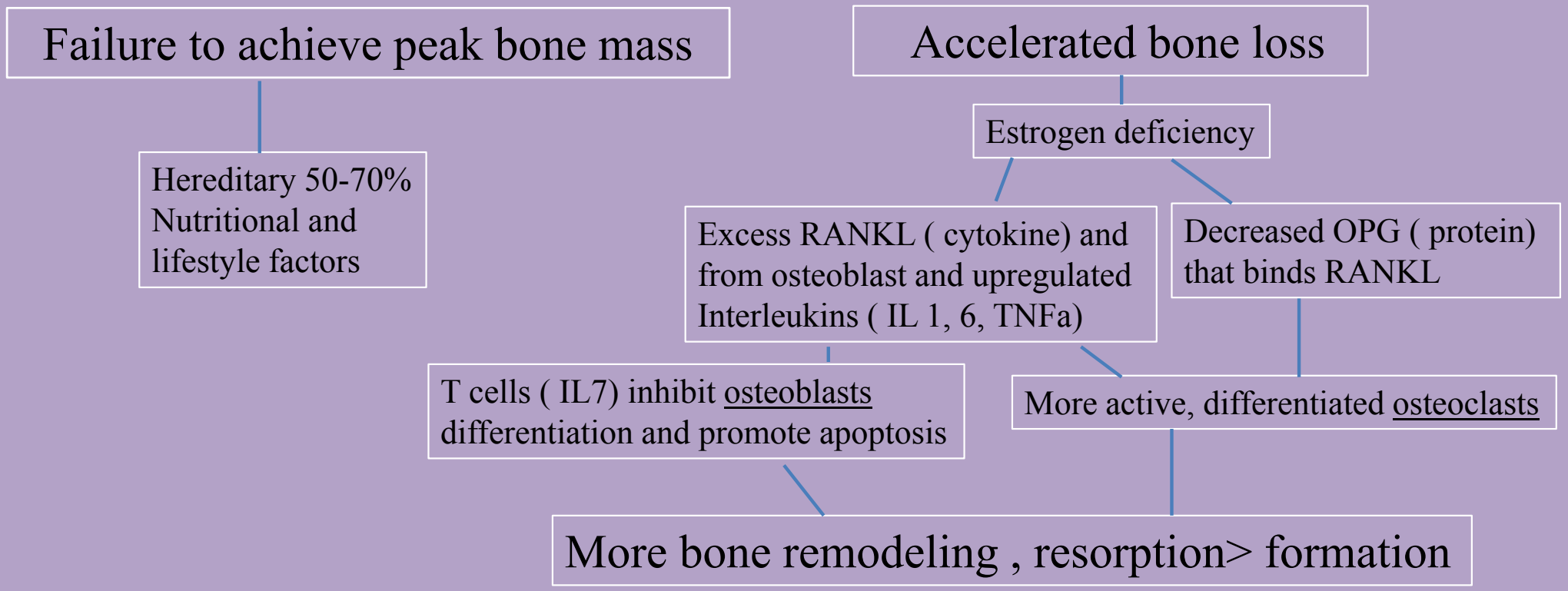
- **Changes in estradiol and FSH during the menopause transition (SWAN)**



Burger HC, et al. *J Clin Endocrinol Metab*. 1999;84(11):4025-4030;
Harlow SD, et al. *Menopause*. 2012;19(4):387-395.
Figure reproduced with permission from Randolph JF Jr, et al. *J Clin Endocrinol Metab*. 2011;96(3):746-754.

***The y axis is unitless. The units of hormone are marked in the corresponding curves.**

Menopausal Bone loss explained



Clinical case 1: Claire

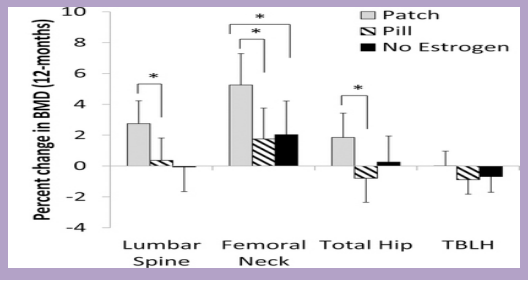
Claire is a 38 yo with history of hypothyroid. During a work up for infertility and amenorrhea was found to have unexplained premature ovarian insufficiency (POI) with FSH > 60 IU/L and estradiol < 15 pg/ml. Her BMI is 25, she is a non- smoker. Her 25 hydroxy D is 35 ng/ml and she takes a MVI with calcium. 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?

CHC vs. HRT?

- Comparative study 119 women with POI (average age 30 yrs) on various HT regimen[1]
  - COC with ethinyl estradiol (EE) 30 µg and levonorgestrel
  - Low-dose estrogen plus progestin therapy (EPT, conjugated equine estrogen [CEE] 0.625 mg with medroxyprogesterone acetate OR estradiol 1.0 mg with norethindrone acetate);
  - High-dose estrogen plus progestin (CEE 1.25 mg or estradiol 2.0 mg combined with the same progestins).
  - Results: COC or high dose EPT increased lumbar spine BMD after 2 yrs
- Other studies: Scotish study; RCT 18 women with POI (mean age 27)[2]
  - Transdermal estradiol 100-150 ug (LS BMD ↑0.17) VS. 30 ug ethinyl estradiol/norethindrone (LB BMD ↑ 0.07) after 1 yr. Bone formation markers (BSAP, P1NP) slightly increased for HRT group
- RCT In 121 oligio-amenorrheic females (normal body weight) (mean age 20)[3]
  - 100 mcg transdermal 17B estradiol VS. COC (30 ug estradiol/desogestrel) increases LS & FN BMD



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

2Crofton PM et al. Clin Endocrinol (Oxf). 2010;73:707-714

3 Ackerman et a. Br J Sports Med. 2019;53:229-236

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
- 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..**

Transitioning From Hormone Contraception to HT

- Individualization is required
- May continue contraception until typical age of menopause (52 y) or mid-50s, when women will likely reach menopause (90% by 55 y)
- Can transition from OCs to HT if still symptomatic
- As low-dose OCs have higher hormone levels than HT, hot flashes may reappear transiently

Curtis KM, et al. *MMWR Recomm Rep*. 2016;65(4):1-66; Kaunitz AM. *N Engl J Med*. 2008;358(12): 1262-1270.

Clinical Case 2. Donna

Donna is a 53 yo woman present 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?

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 related to bone health

- 1940s: Dr. Fuller Albright, 5 postmenopausal patients using estrogens: DES and estradiol benzoate IM

(Spinal x-rays bones more calcified, decreased calcium and phosphorus excretion, stimulated bone formation)

- 1942: FDA approved Diethylstilbestrol (DES) conjugated equine estrogens (CEE)
- 1972 FDA declares estrogen therapies probably effective at preventing osteoporosis
- 1984 NIH concensus estrogens best way to prevent bone loss
- 1994 FDA approves HT for prevention and treatment of OP
- 2002 FDA After WHI data removes HT indication for treatment of OP

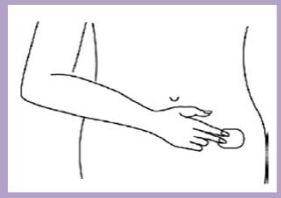
ET and EPT Hormone Therapy Definitions

- 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 (SERM)
  - 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

Routes of ET Administration

- Oral (estradiol E2, conjugated equine estrogen, conjugated estrogen)

- 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.

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

- Synthetic Progestins
  - Synthetic products with progesterone-like activity
  - Classified into two groups based on structure
  - Chemical structure similar to progesterone
    - Medroxyprogesterone acetate (MPA) is the most commonly used and studied in the United States for endometrial protection
    - Others: Norethindrone acetate
    - Off label use: 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

- Hormones that are chemically identical to the hormones produced by the ovaries during the reproductive years
- The term also is used for *custom-compounded* HT by compounding pharmacies
  - These products are not FDA approved
- *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

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.

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

Bioidenticals: 2020 NASEM Recommendations

- In July 2020 **the National Academy of Sciences, Engineering, and Medicine (NASEM) issued a report that** assessed the clinical utility of compounded bioidentical hormone therapy (cBHT). **Recommendations included:**
  - **Restricting the use of cBHT to certain situations, such as to people 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**

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.**

What's the evidence for 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 GL, Limacher M, Assaf AR et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health Initiative randomized controlled trial. JAMA 291:1701-1712,2004.
2. J.A.Cauley et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the women's health Initiative randomized controlled trial. JAMA 290 (13) 2891-2897.2003.
3. R.D.Jackson et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J bone Miner Res 21 (6) (2006) 817-828.
4. D.J.Torgerson, S.E bell-Syer. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA 285. June 22 (2001) 2891-2897.

Progestogen effect on bone?

- PEPI trial , 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 plus MPA 10 mg/d for 12 d/mo;
  - (4) CEE, 0.625 mg/d plus MPA, 2.5 mg/d daily; or
  - (5) CEE, 0.625 mg/d plus micronized progesterone (MP), 200 mg/d for 12 d/m

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

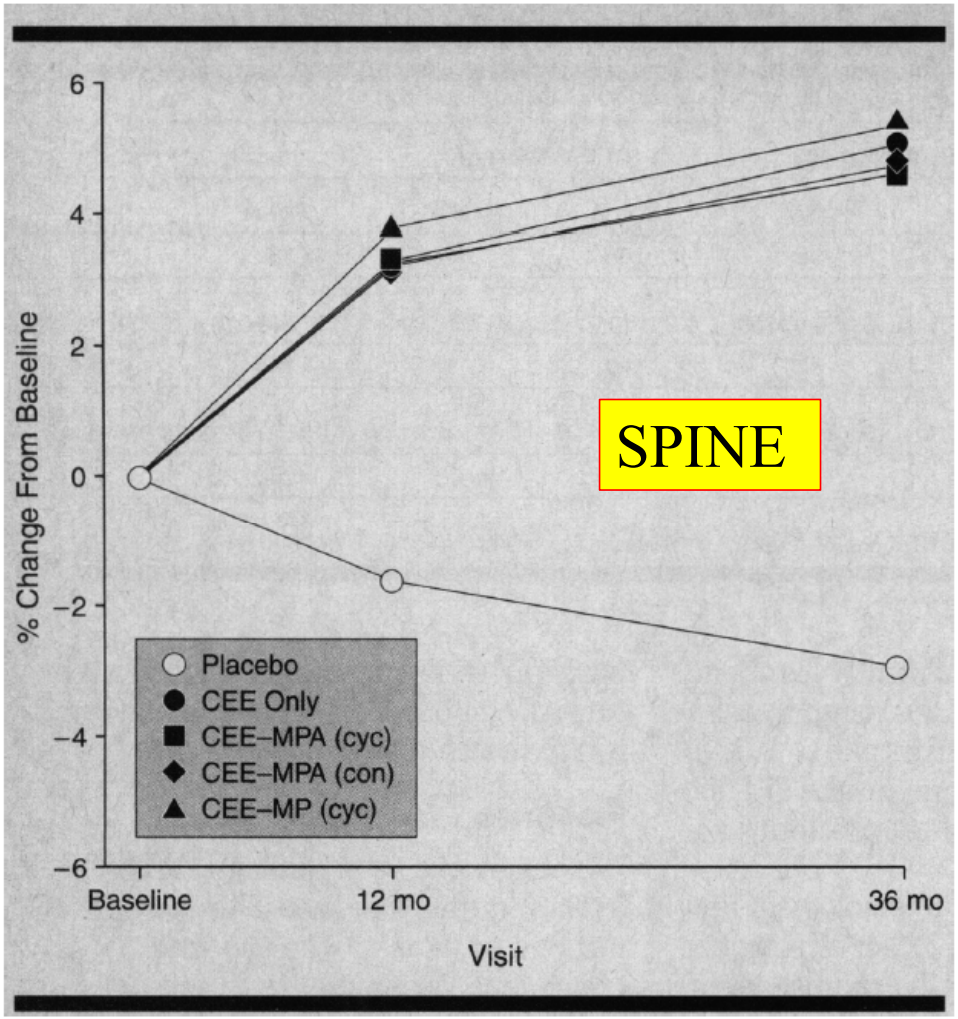


Figure 1.—Unadjusted mean percent change in bone mineral density in the spine by treatment assignment and visit: adherent PEPI participants only. See Table 1 footnotes for explanation of treatment groups and definitions.

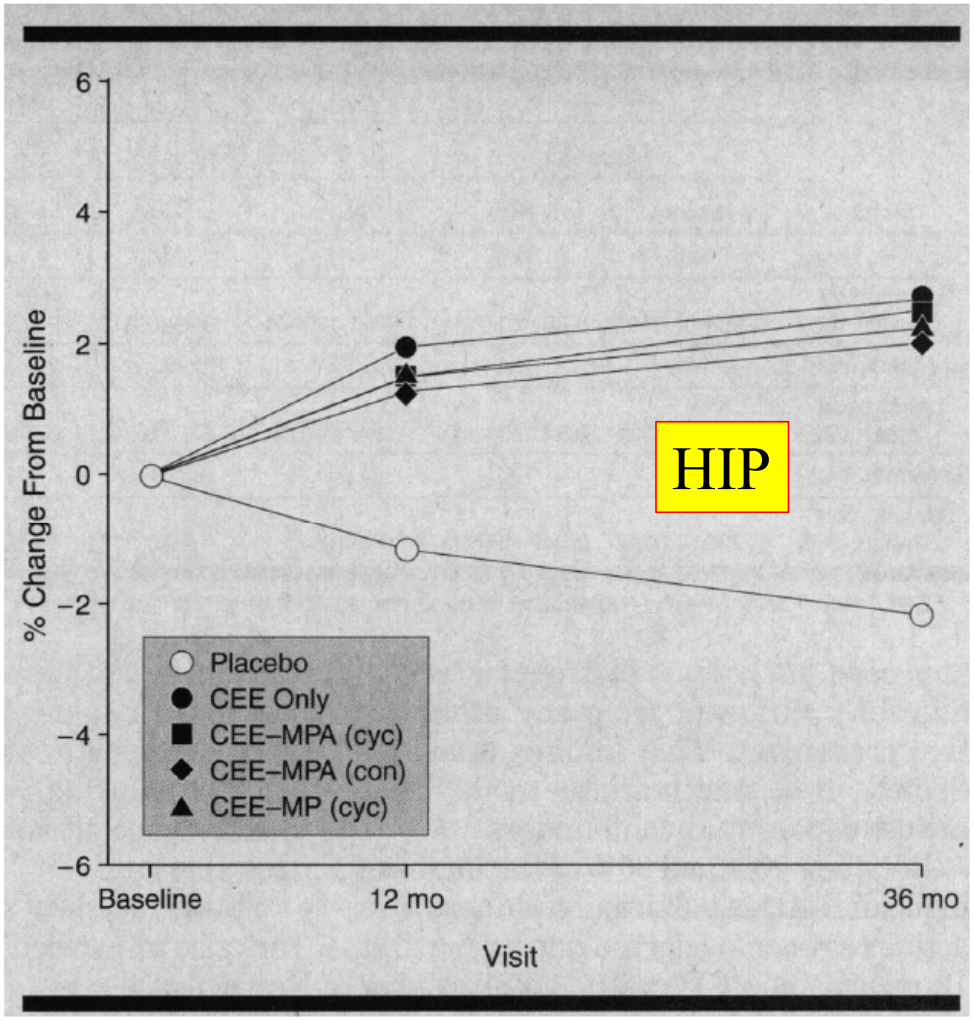


Figure 2.—Unadjusted mean percent change in bone mineral density in the hip by treatment assignment and visit: adherent PEPI participants only. See Table 1 footnotes for explanation of the treatment groups and definitions.

PEPI conclusions

- BMD increase greatest within first 12 mos
- No added benefit of EPT over Estrogen alone
- Women in CEE+MPA continuous group had ↑ 5% LS BMD vs. ↑ 3.8% in other groups after 3 years . Women in active HRT groups increased hip BMD (average 2.3%) no significant difference b/t groups.
- Older women (age 55-64yr) AND greater time since menopause, women with low initial BMD, no previous hormone use gained significantly more bone than younger women (age 45-54 yr) , women with higher initial BMD, and those who had used hormones previously.
- YOUNGER women in placebo groups (lost most BMD in spine and hip) than older women taking placebo
- No difference in fracture rates across groups

How low can you go?

- Does estrogen (estradiol) 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 protection dissipates→ without increase risk in rebound fracture

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

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 and CEE (TSEC) combination is available in the United States for treatment of VMS and prevention of osteoporosis (SMART trials)
    - Increased BMD *** , 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.

Risk vs. Benefit of HT

- Timing hypothesis
  - There may be 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
  - Heart attack risk increased during the first year of EPT in older 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 a more favorable all-cause mortality and fewer Mis

- Early Estrogen Prevention Study and the Early Versus Late Intervention Trial (ELITE) With Estradiol also showed safety of HT use initiated early in menopause

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.

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 CEE 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.

Revisit Clinical Case 2. Donna

Donna is a 53 yo woman present 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.

Treatment: combination estrogen/norethrindone patch 2x/wk, calcium and vitamin D discussion, assess symptoms after 3 months and repeat DXA in 2 years.

Clinical Case 3. Eileen

Eileen is a 64 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 current DXA shows her spine T score is -1.5 with degenerative changes , FN -2.7 and total hip -2.5. At age 60 she had a Colles wrist fracture from a fall. 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
3. Stop HT and switch to more potent anti-resorptives , manage VMS with non – hormonal options
4. Continue HT and consider adding osteo-anabolic agent

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)
- Abaloparatide (PTHrP)

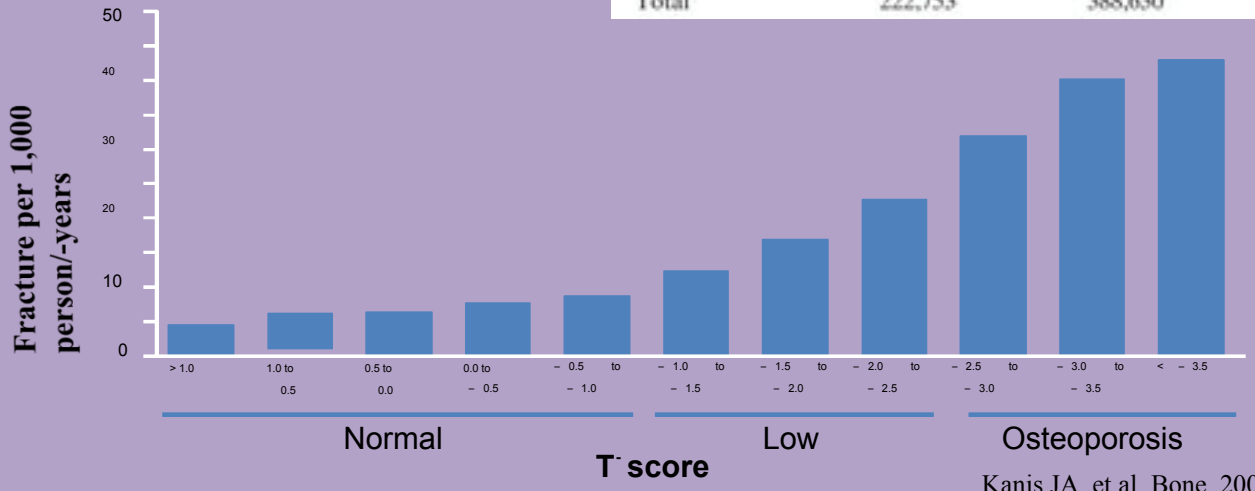
DUAL ANABOLIC/ ANTIRESORPTIVE

- Romosozumab

Strongest risk factor 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.

Revisit Clinical Case 3. Eileen

Eileen is a 64 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 current DXA shows her spine T score is -1.5 with degenerative changes , FN -2.7 and total hip -2.5. At age 60 she had a Colles wrist fracture from a fall. 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
3. Stop HT and switch to more potent anti-resorptives , manage VMS with non – hormonal options
4. Continue HT and consider adding osteo-anabolic agent (such as teriparatide, abaloparatide or romosozumab)

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