Menopausal Hormone Therapy:
Risks & Benefits - Making Sense of the LATEST Data & Evidence

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Formerly Naval Hospital
San Diego, CA

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Disclosure

I have no financial interests or relationships to disclose.

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Additional Disclosure

In this topic, I will use the terms "woman/en" or "patient(s)" as they are used in the studies presented.

Please adapt your own verbiage to consider the specific counseling needs of your transgender and gender diverse individuals.

- I do not consider menopause to be a disease or disorder
- I am neither pro or con MHT, I am pro-individual-informed-patient-choice

3

Learning Objectives

- Identify the latest data, evidence, and professional society recommendations, for prescribing menopausal hormone therapy, and non- hormonal alternatives to women with moderate to severe menopausal symptoms.
- Describe and discuss the potential risks, benefits, and FDA-approved indications, for menopausal hormone therapy
- Describe and discuss the current evidence-based prescribing recommendations for menopausal hormone therapy, in a language that can be readily shared in patient-based discussions.

4

Terminology

- Vasomotor symptoms (VMS)– "hot flashes"
- MHT – menopausal hormone therapy
  a collective term for ET and EPT
  - ET - estrogen (alone) therapy
  - EPT - combined estrogen-progestogen therapy
- Progestogen – a collective term for progesterone and progestins

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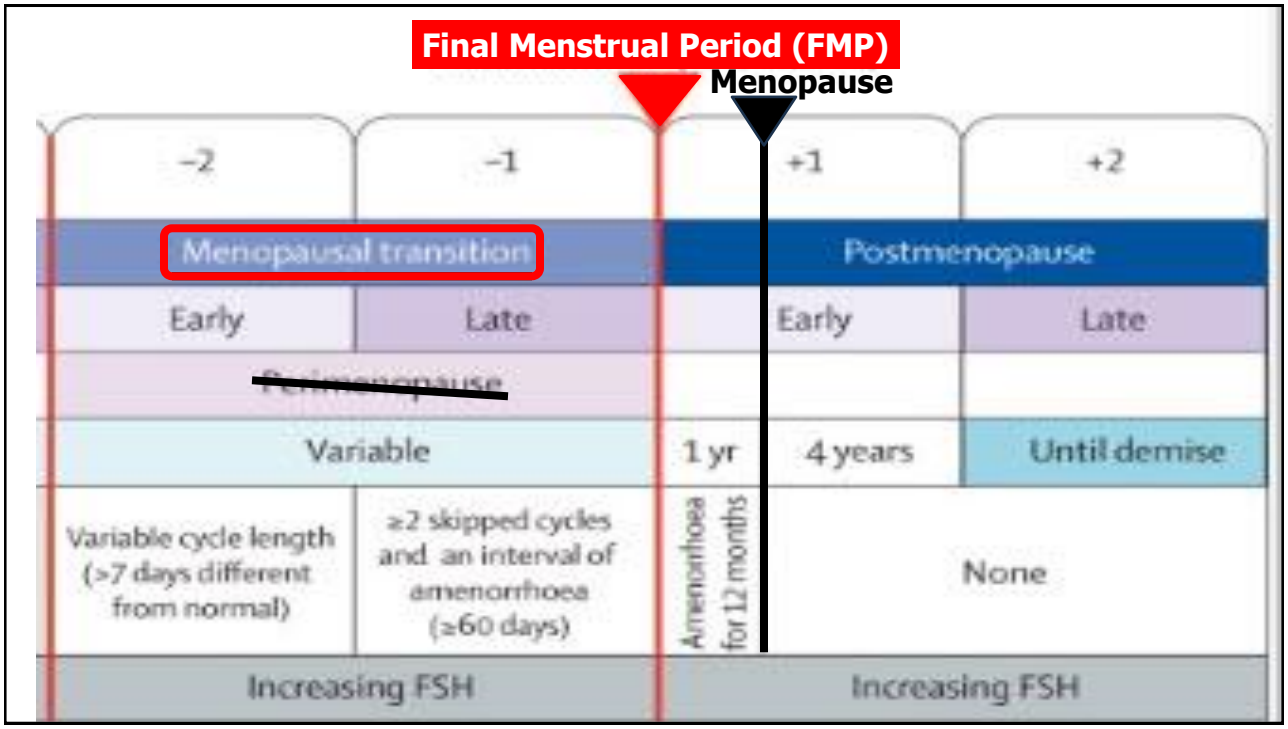

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FDA-approved Indications for Menopausal Hormone Therapy

HRT is approved by the U.S. Food and Drug Administration to:

- treat hot flashes
- prevent bone loss
- treat vaginal dryness and vaginal atrophy
- treat premature low estrogen levels

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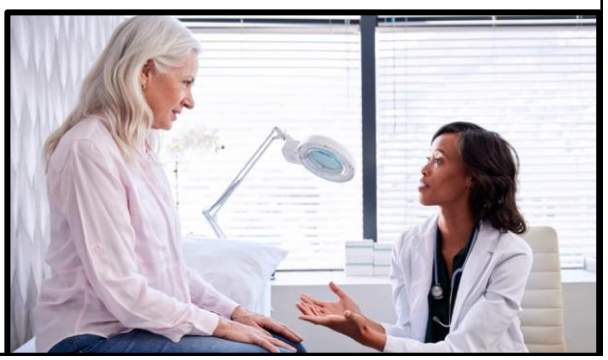

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Grade of Recommendation	Level of Evidence	Type of Study
A	1a	Systematic review of (homogeneous) randomized controlled trials
A	1b	Individual randomized controlled trials (with narrow confidence intervals)
B	2a	Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects
B	2b	Individual cohort study / low-quality randomized control studies
B	3a	Systematic review of (homogeneous) case-control studies
B	3b	Individual case-control studies
C	4	Case series, low-quality cohort or case-control studies
D	5	Expert opinions based on non-systematic reviews of results or mechanistic studies

9

Plourd's Pledge

- **MY PLEDGE TO YOU:**

I promise you an up-to-date,
Cutting edge,
Clinically-relevant
With some practical prescribing pearls

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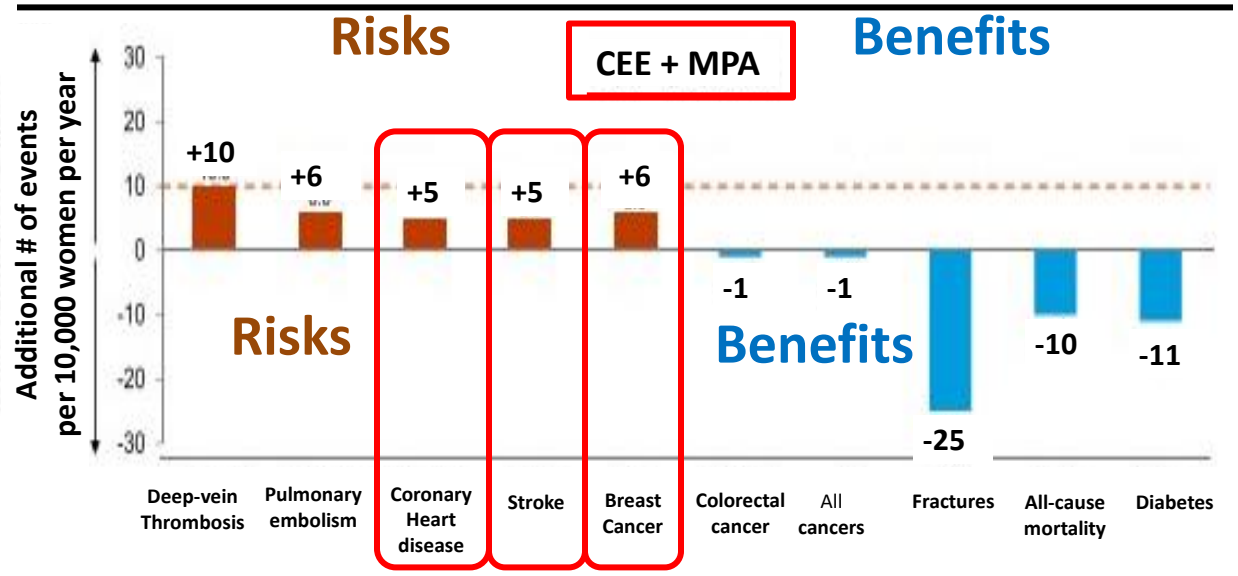
The Original Data (Results) from the W.H.I. **2002**



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NEWS RELEASES

Media Advisory Wednesday, May 1, 2024

Researchers review findings and clinical messages from the Women's Health Initiative 30 years after launch

Data from influential study underscore the importance of personalized and shared decision-making to support the health of postmenopausal women.

What

A new review in *JAMA* highlights key findings and clinical messages from the Women's Health Initiative (WHI), the largest women's health study in the United States. The WHI is supported by the National Institutes of Health's National Heart, Lung, and Blood Institute

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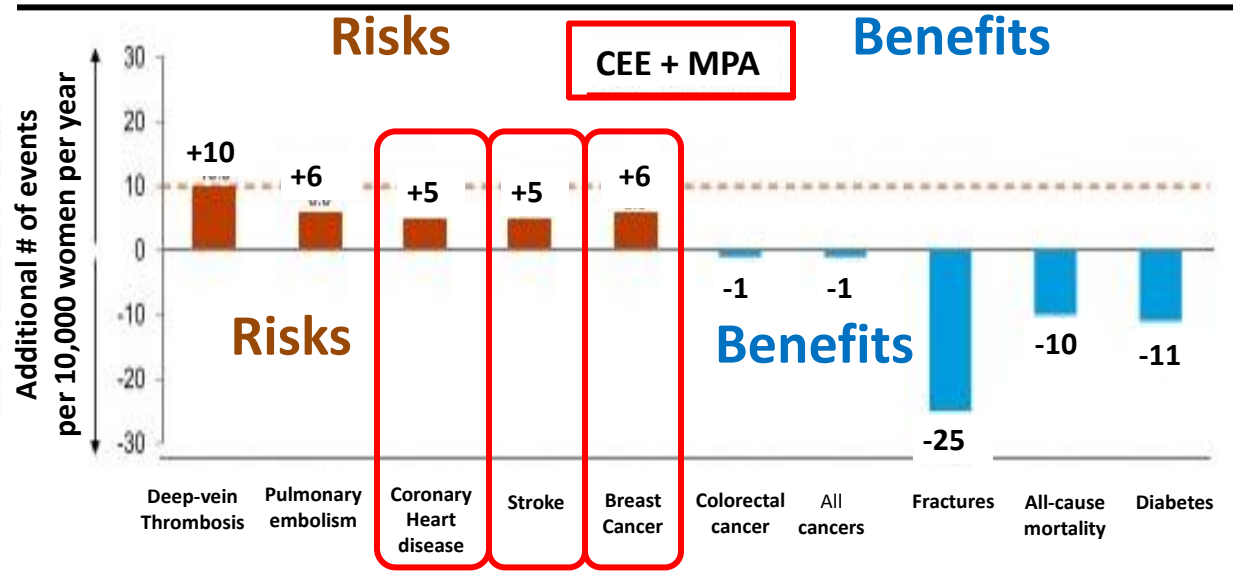

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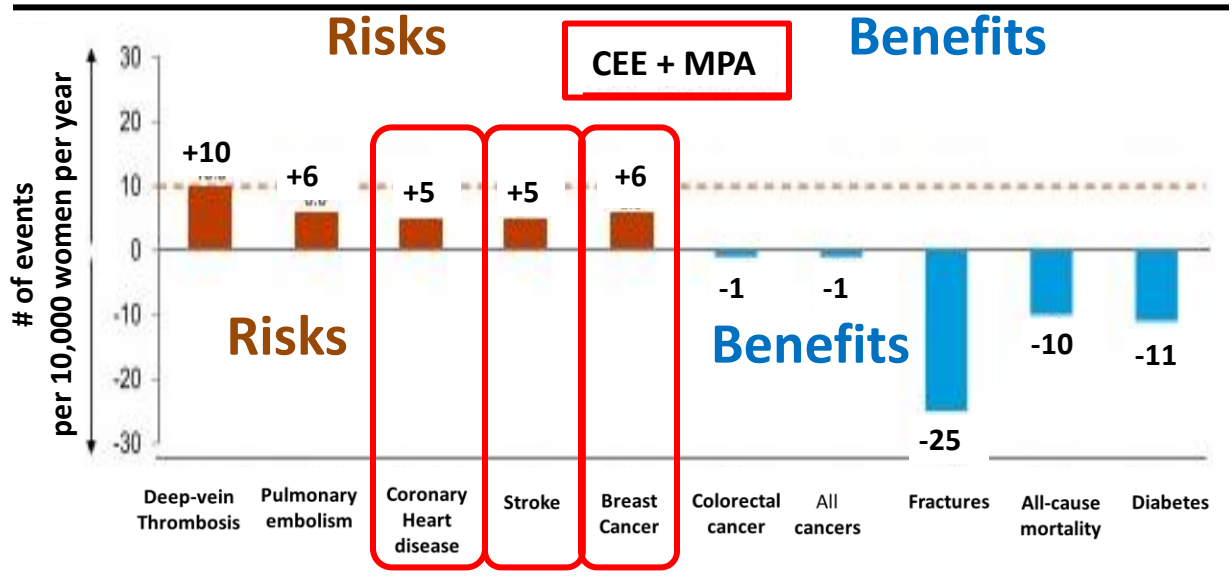

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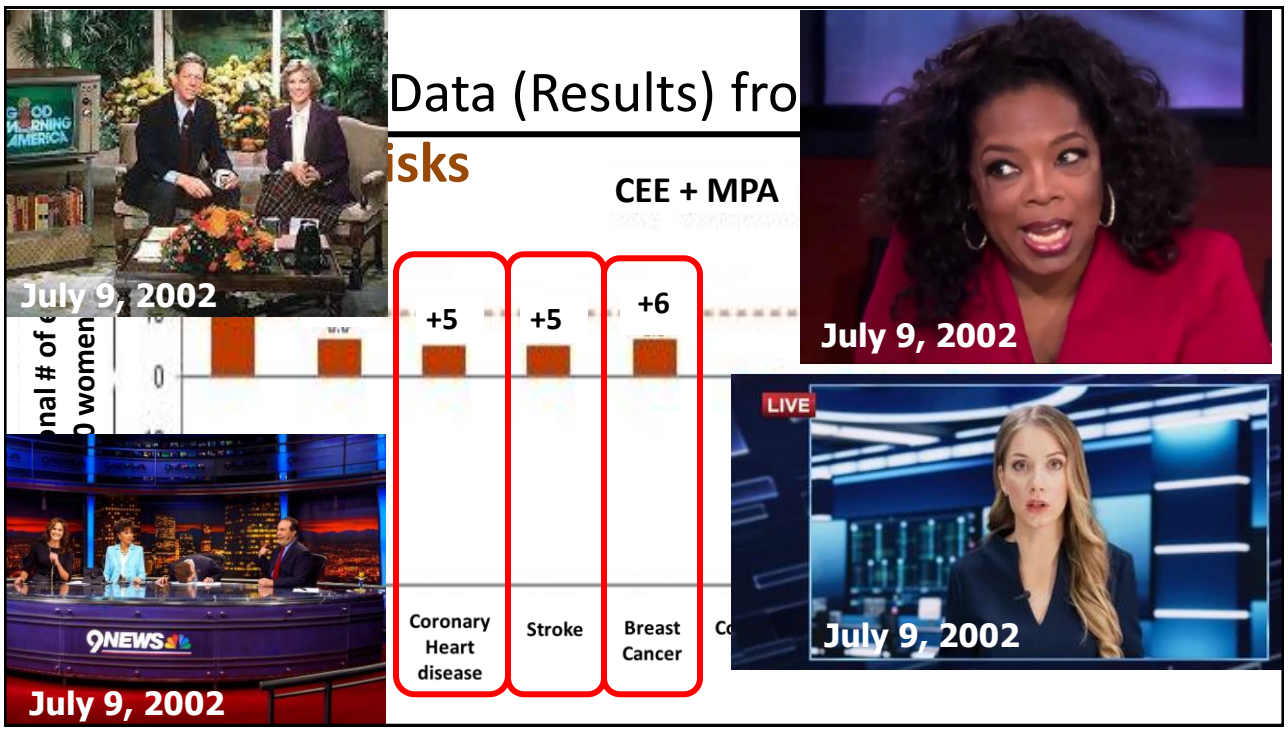

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Women's Health Initiative (WHI): Preliminary Results With CEE/MPA in 2002

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.

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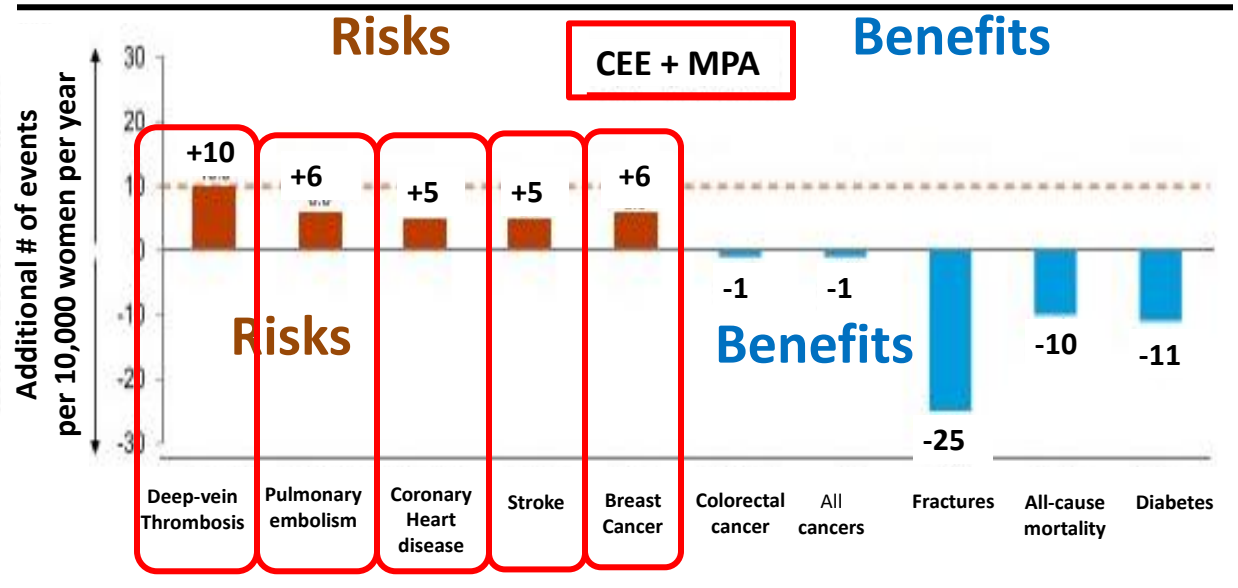

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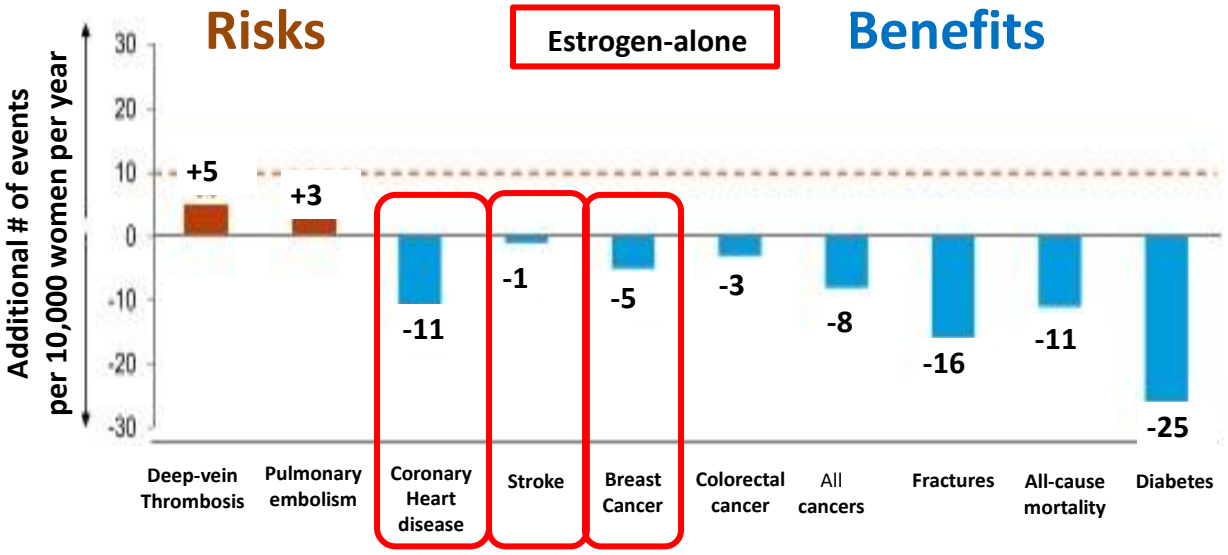
Later Data (Estrogen-alone Results) from the W.H.I. 2006



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Data (Results) fro isks

CEE + MPA

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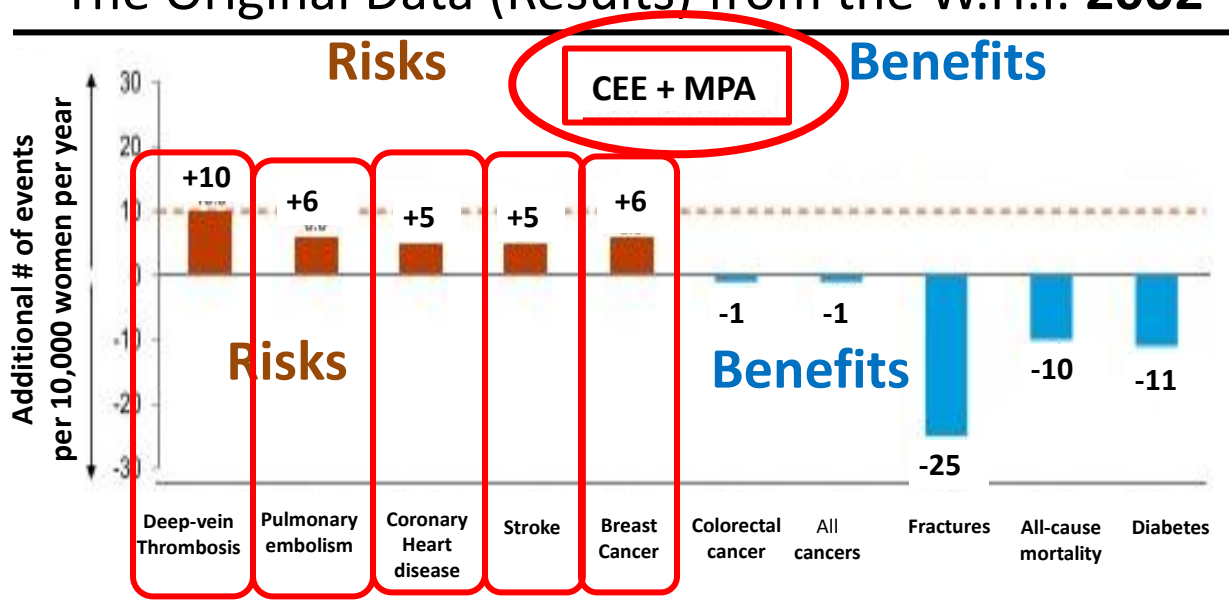

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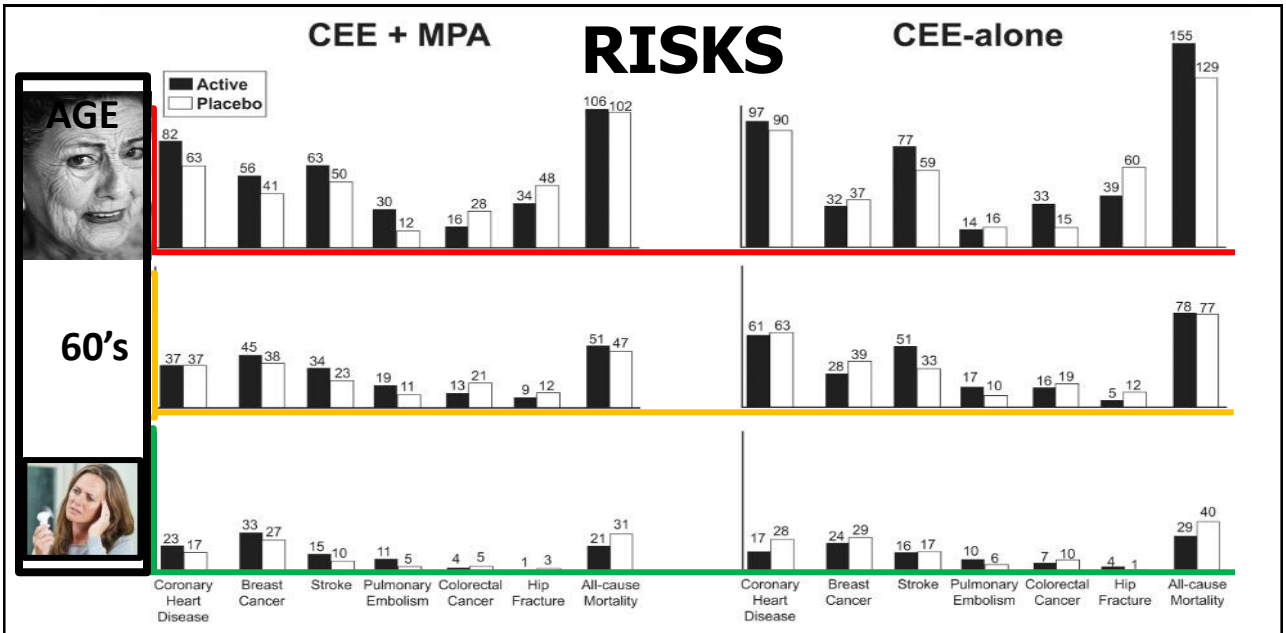

Cho L. Circulation. 2023; 147 (7) https://doi.org/10.1161.122.061559

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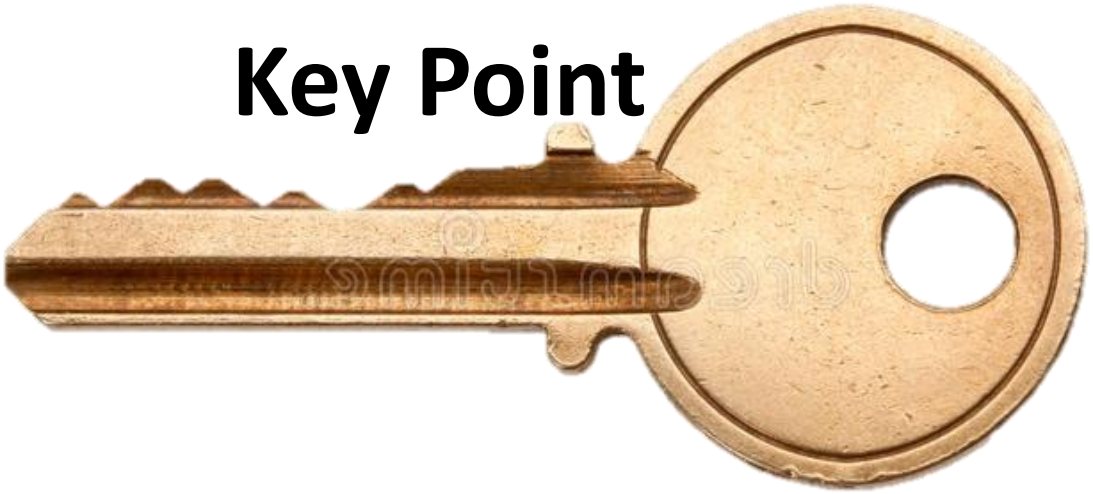
Key Point



Regarding the data on MHT for women, when we talk about the ages of the women on HT, we are referring to their

age of INITIATION of HT

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NAMS Hormone Therapy Position Statement

Key points

- For healthy symptomatic women aged younger than 60 years or within 10 years of menopause onset, the favorable effects of hormone therapy on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke. (Level I)
- Hormone therapy is not government approved for primary or secondary cardioprotection. (Level I)
- Personal and familial risk of CVD, stroke, VTE, and breast cancer should be considered when initiating hormone therapy.

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Women's Health Initiative (WHI): Preliminary Results With CEE/MPA in 2002

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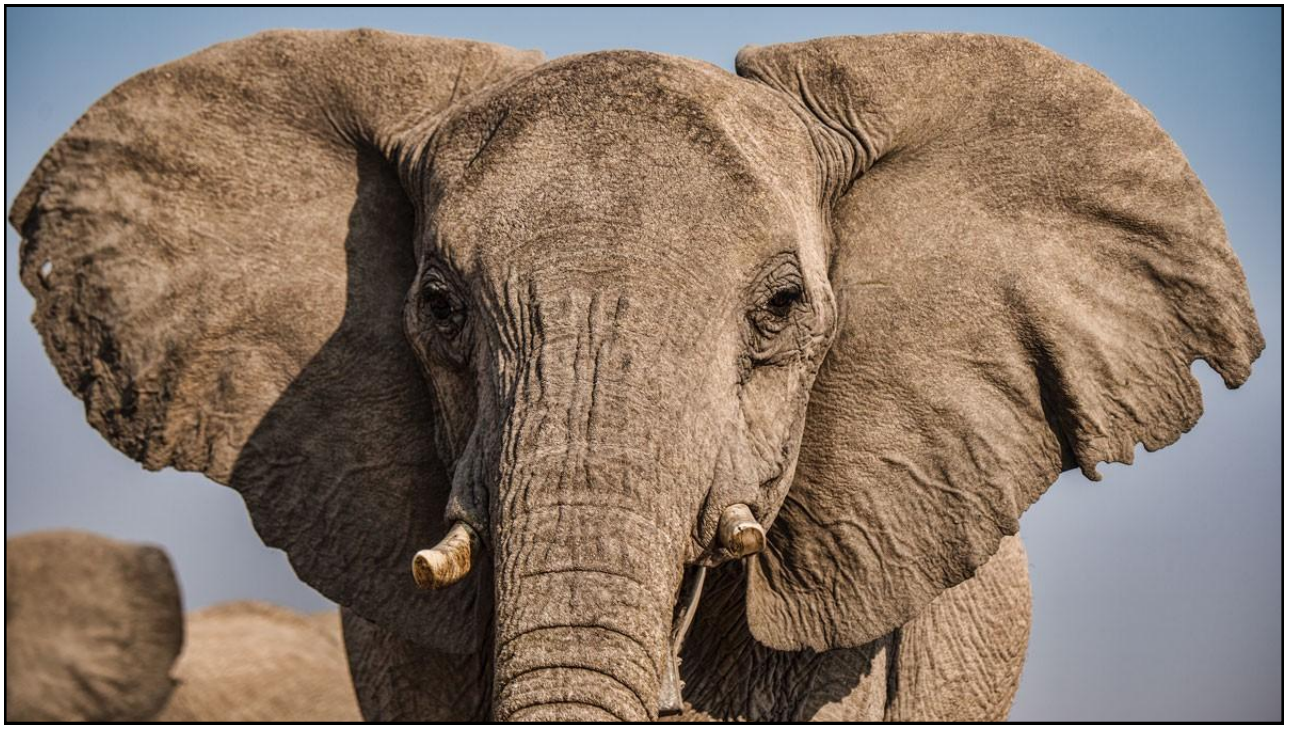

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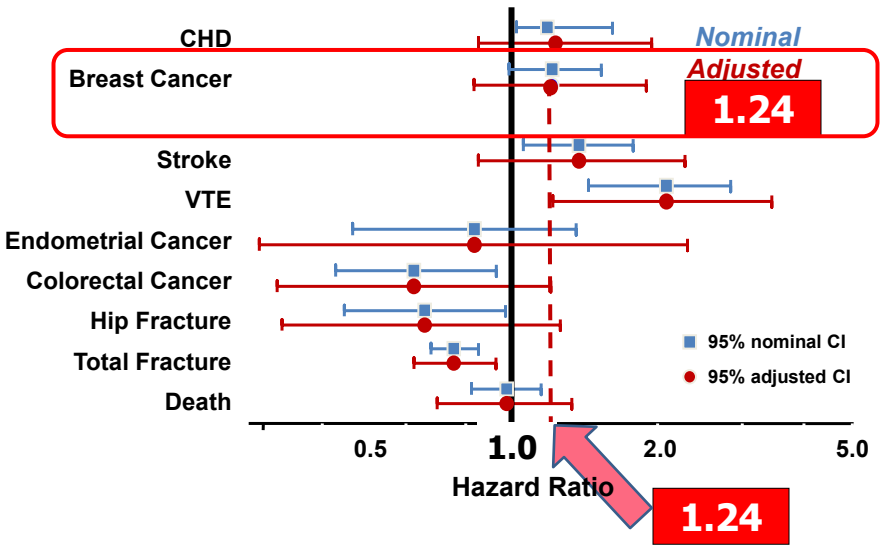

Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.

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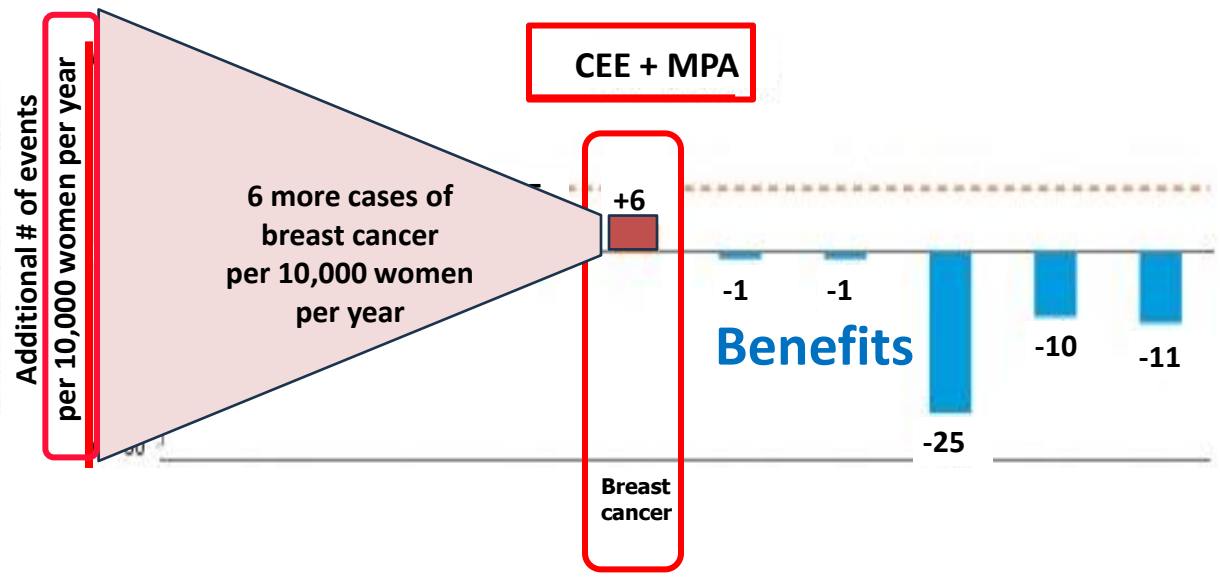
ANNUALIZED RISK of Breast CA from the W.H.I. 2002



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RISKS of ET / EPT In Perspective - Breast

- The risk of breast CA was increased by 24% in the **EPT** arm vs. placebo
  - Background rate of breast CA :
    - **22** cases/10k women/yr. → Add 24% to that → **28** cases/10k/yr.
    - **6** / 10,000 = **0.06% attributable risk per year**

- **There was no increase in risk with ET alone**

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Whoa Whoa!

- How can I quote a background risk of breast cancer of only 22/10,000 women per year ???
- We all know the rate of breast cancer is 1 in 8, women

[redacted]

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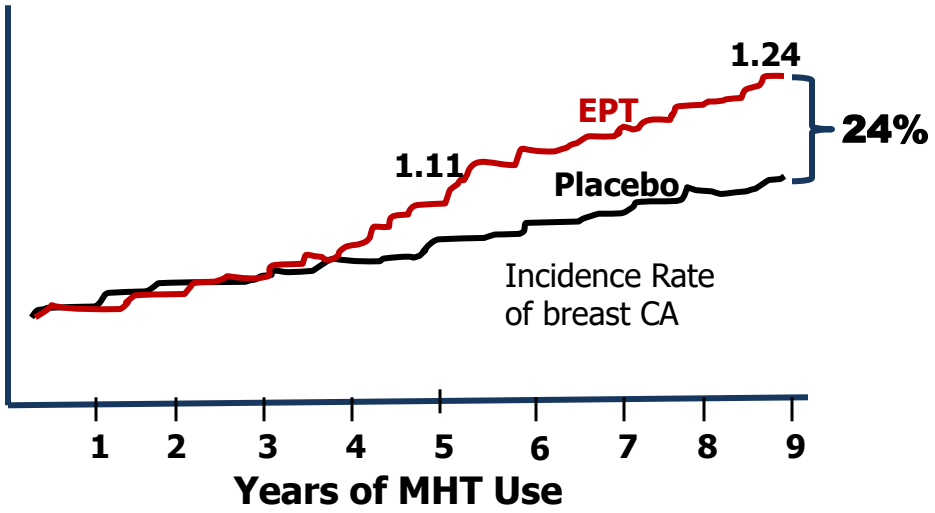
W.H.I. Data: Breast CA & HT (CEE + MPA) – Kaplan-Meier Curves



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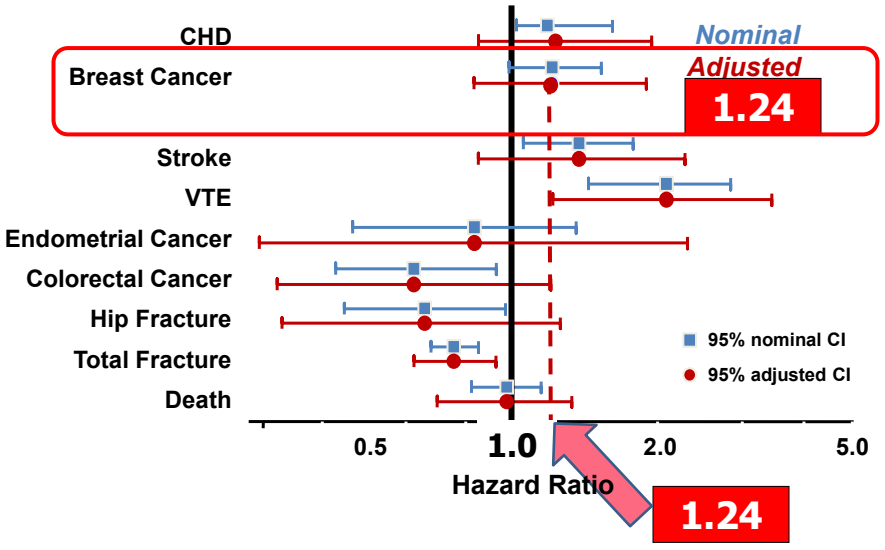

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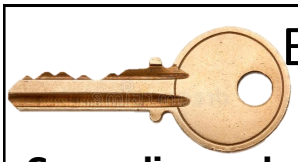
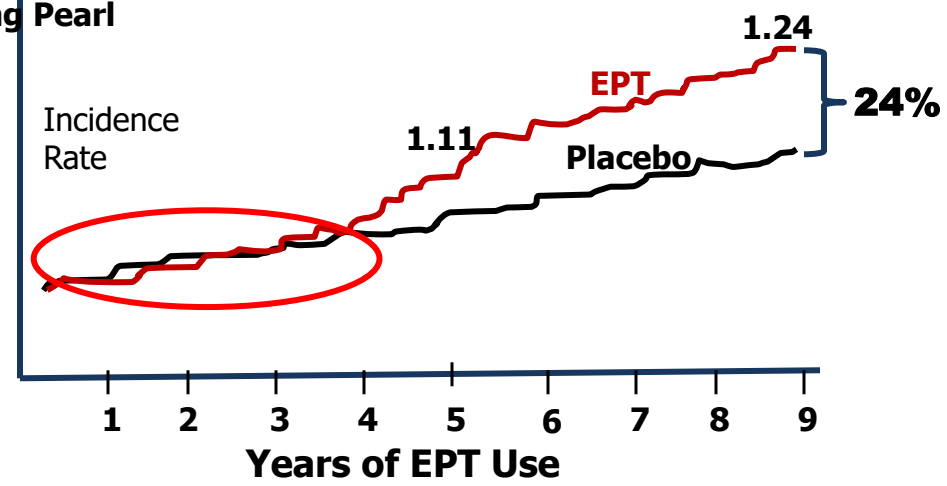


Counseling and Prescribing Pearl



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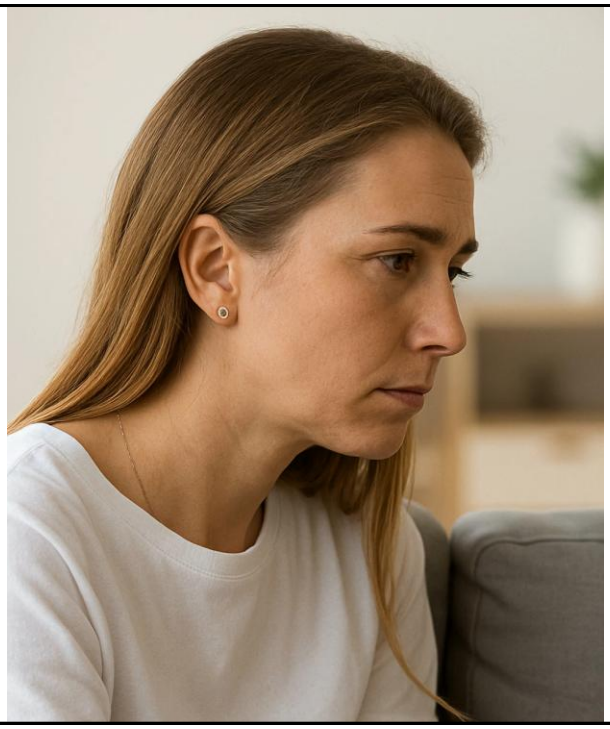

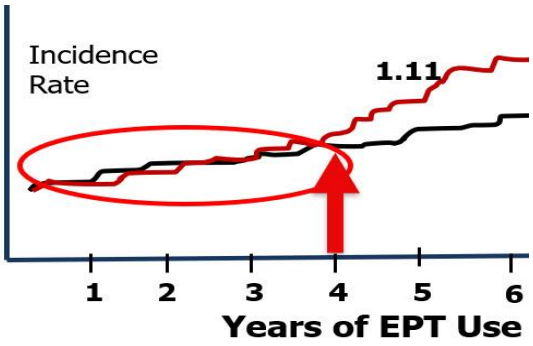

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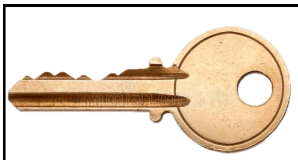

Prescribing Pearl

- Systemic MHT is not advisable in breast cancer survivors, particularly those taking an aromatase inhibitor
  - This even applies to local vaginal estrogens
    - Absorbed to small but measurable degrees
- MHT may be considered for these patients with severe VMS refractory to non hormonal alternatives – individualized shared decision-making; and in concert with their oncologist.

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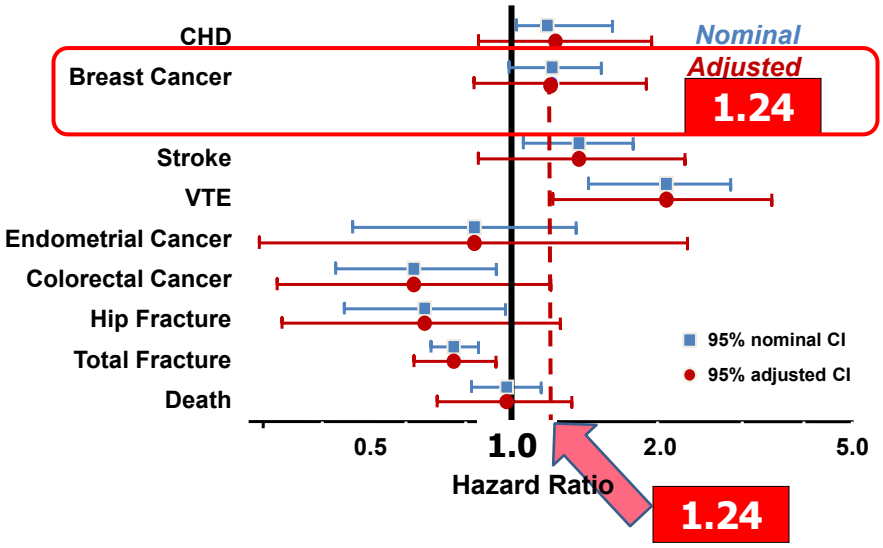
Women's Health Initiative (WHI): Preliminary Results with CEE/MPA in 2002



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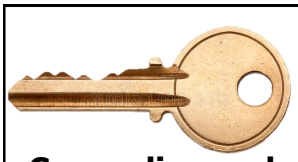
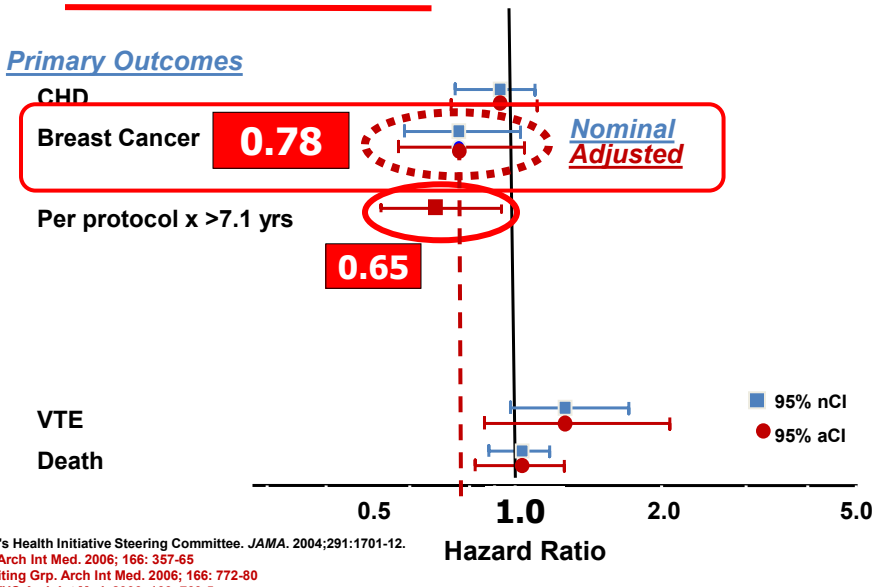


Counseling and Prescribing Pearl

WHI CEE Alone in 2006: Results



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Black WHS Arch Int Med. 2006; 166: 760-5
Stefanick ML. JAMA 2006; 295(14): 1647-57
Salpeter S. J Gen Int Med. 2004; 19: 791-804

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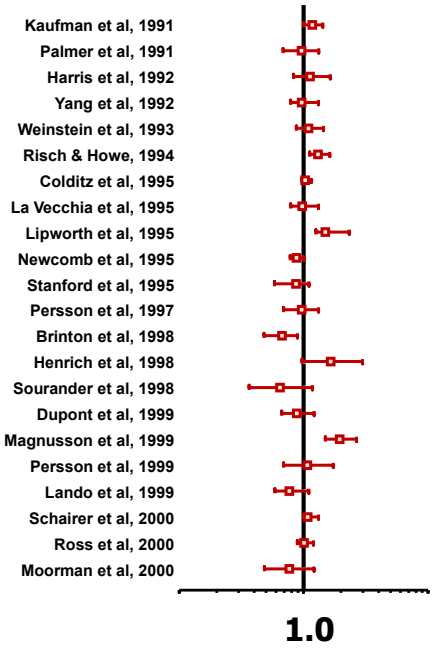
Risk Estimates for Incident Breast Cancer

Ever-users

compared with never-users of ET (Estrogen ALONE)

22 Studies



Bush TL, et al. *Obstet Gynecol.* 2001;98:498-508.

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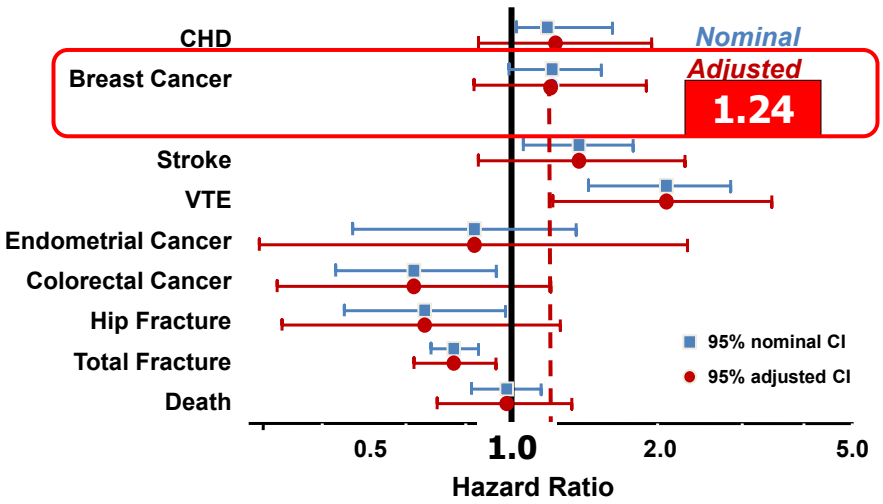
Women's Health Initiative (WHI): with CEE/MPA



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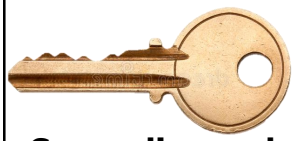
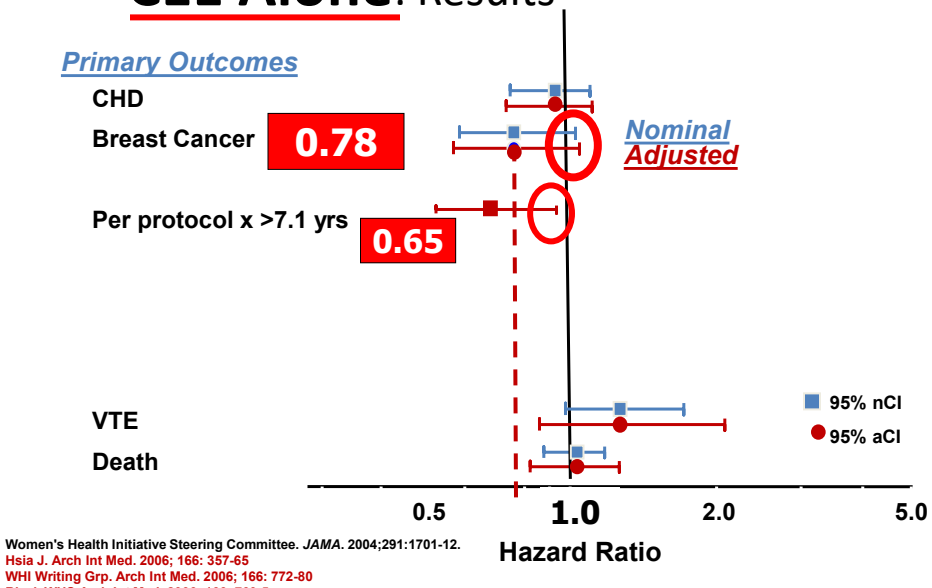


Counseling and Prescribing Pearl

CEE Alone: Results



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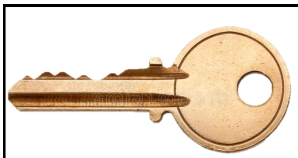

An "Ah-HAH Moment"

Maybe it's the
medroxyprogesterone acetate,
not the estrogen,
that is causing the breast CA

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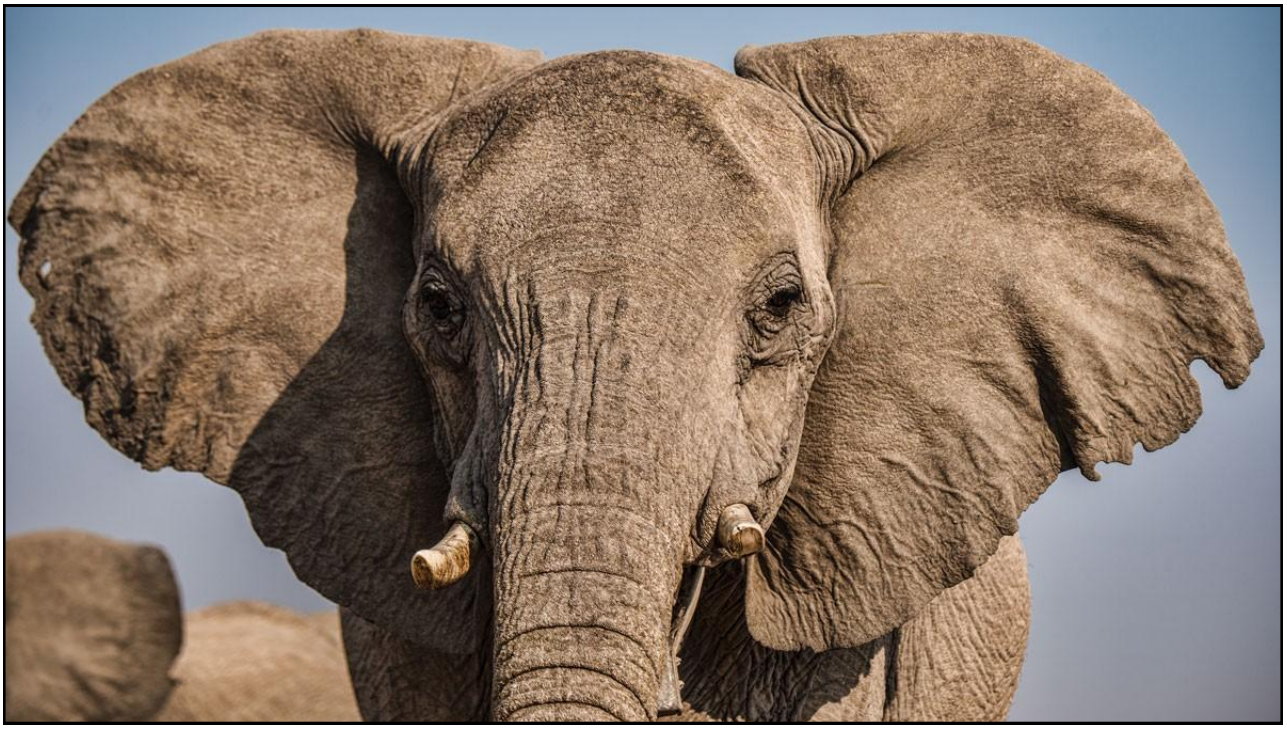

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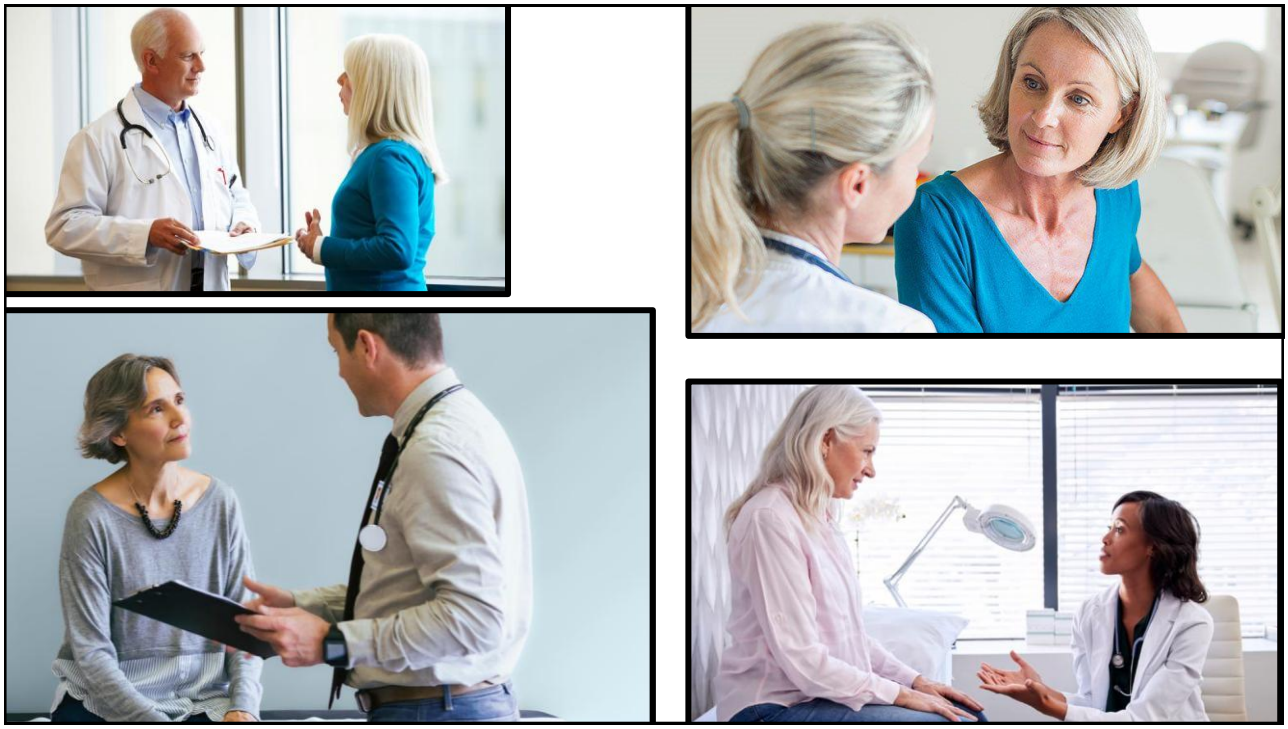

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23 Years Later – 2025
>30 Peer-reviewed Studies

- ☺ Overwhelming evidence supports the safety , and favorable benefit/risk of HT for most recently menopausal women
  - Combo EPT or ET alone
- ☹ Yet many providers remain reluctant to prescribe HT at all, or limit it to 5 years, or D/C, **arbitrarily**, at age 65
  - Patients are suffering decreased QOL
  - resorting to unproven and unregulated "bioidenticals"

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NAMS 2022 Hormone Therapy Position Statement

Discontinuation… or Not

Key points

- The safety profile of hormone therapy is most favorable when initiated in healthy women aged younger than 60 years or within 10 years of menopause onset, so initiation of hormone therapy by menopausal women aged older than 60 years requires careful consideration of individual benefits and risks. (Level I)
- Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of CVD and breast cancer with persistent VMS or at elevated risk of fracture for whom other therapies are not appropriate. (Level III)
- Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone interventions, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer. (Level III)
- Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years. (Level III)

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Bullet Points – 2025
The Good News ☺

- **ET / EPT is the most effective Rx for moderate-to-severe VMS (vasomotor symptoms)**
- **ET (local therapy) is the optimal Rx for vaginal atrophy**
- **ET / EPT offers a 2^0 benefit of preventing osteoporosis AND FRACTURES**
- **Early initiation of HT (at <60 y/o)- 39% reduction in all-cause mortality (with E+P); (30% reduction with E alone)**

SUMMARY STATEMENT: Initiating MHT by <60 (or <10 yrs after menopause)- the benefits to a healthy symptomatic woman, without a contraindication, outweigh the risks.

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Bullet Points – 2025
The Bad News ☹

- **ET / EPT does not provide 1^0 or 2^0 CV protection; it carries potential harm when initiated after age 60—65**
- **EPT (but not ET alone) increases the risk of breast CA**
- ET / EPT initiated after 65 y/o **increases** the risk of cognitive decline
  - **HT should not be considered for the prevention of dementia**
- **MHT should not be considered for the prevention of CV disease, osteoporosis, or dementia.**

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Current FDA-approved Indications for ET / EPT

- 1. The treatment of moderate-to-severe vasomotor symptoms associated with menopause
- 2. The treatment of genitourinary symptoms of menopause (GSM)
- 3. The prevention of postmenopausal osteoporosis
- 4. The treatment of premature low estrogen levels*

*new in 2022

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NOT Indications for MHT

- Primary prevention of
  - Cardiovascular disease
  - Osteoporosis
  - Dementia

(Previously thought to be benefits- and may still be, but the risks likely outweigh these benefits)

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How We Can Best Help Our Patients Suffering from Any One, or More, of the Current Indications for Hormone Therapy

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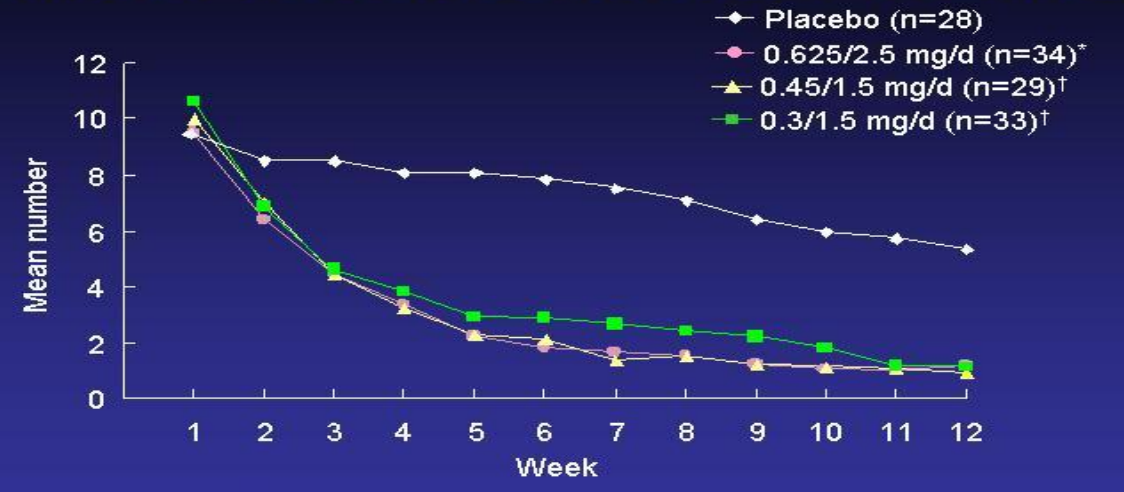
Women's HOPE Study: Number of Hot Flashes Over 12 Weeks With CEE/MPA



Mean hot flashes at baseline = 12.3 (range, 11.3-13.8).
• Significant effect with all doses maintained at cycle 13.
Utian WH, et al. Fertil Steril. 2001;75:1065-1079.

*P<0.05 by week 2 compared to placebo.
†P<0.05 by week 3 compared to placebo.

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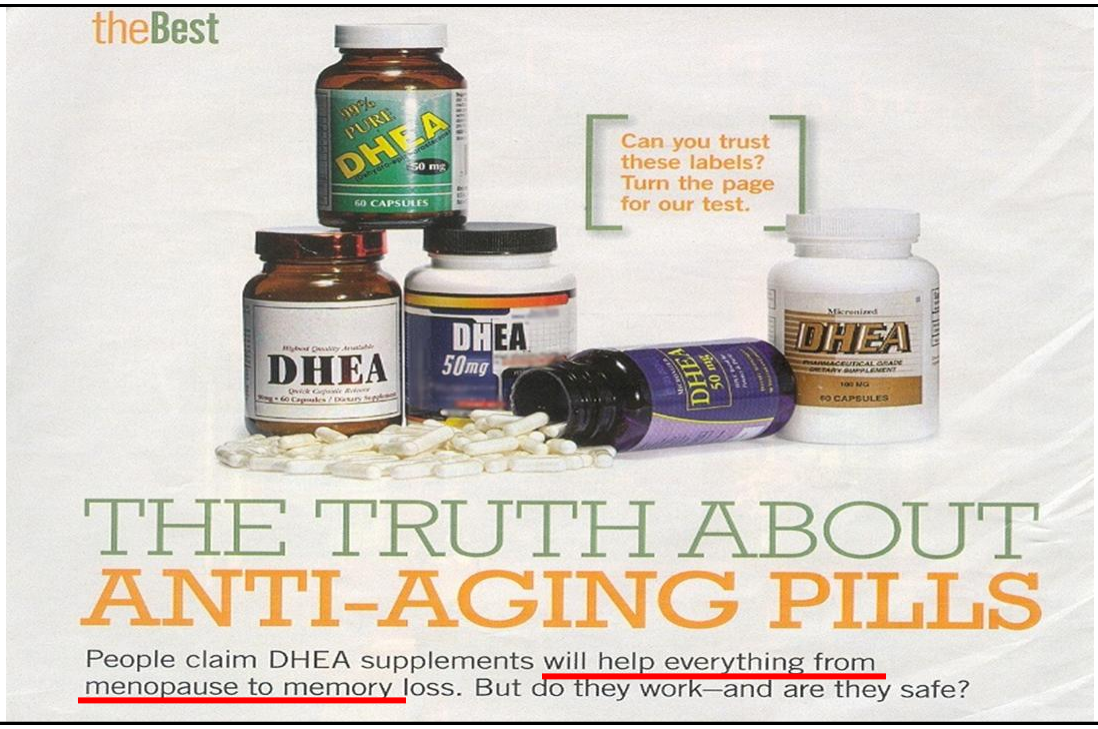
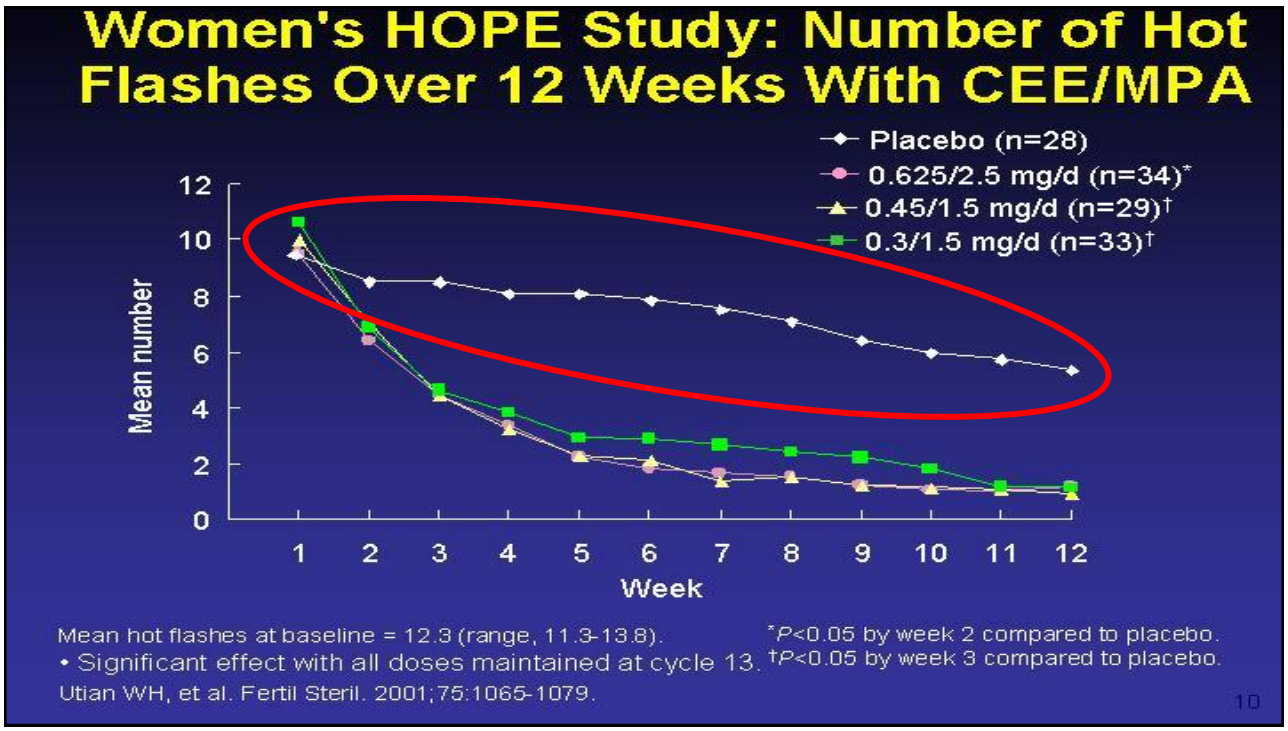

theBest
Can you trust these labels? Turn the page for our test.
DHEA
50mg
60 CAPSULES
THE TRUTH ABOUT
ANTI-AGING PILLS
People claim DHEA supplements will help everything from menopause to memory loss. But do they work—and are they safe?

59


Women's HOPE Study: Number of Hot Flashes Over 12 Weeks With CEE/MPA
Placebo (n=28)
0.625/2.5 mg/d (n=34)*
0.45/1.5 mg/d (n=29)†
0.3/1.5 mg/d (n=33)†
Mean number
Week
Mean hot flashes at baseline = 12.3 (range, 11.3-13.8).
• Significant effect with all doses maintained at cycle 13.
*P<0.05 by week 2 compared to placebo.
†P<0.05 by week 3 compared to placebo.
Utian WH, et al. Fertil Steril. 2001;75:1065-1079.
10

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Progestin Component to MHT

- Only ONE purpose: to protect her endometrium
- BUT…

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Other Means (Beside MPA) Available to Protect Her Endometrium

- Norethindrone (NET)
- Norethindrone acetate (NETA)
- Norgestrel / levonorgestrel
- Bazedoxifene (a SERM)
- Micronized progesterone (bioidentical)

Lowest risks;
Least side effects
(but somnolence)

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Ways to Avoid Medroxyprogesterone Acetate

- Oral micronized progesterone
  - 200 mg po qd x 12 d/mo
  - 100 mg po qd
- Vaginal progesterone – expen$ive
  - (45 mg daily; 100 mg qod) from days 1-12 of each calendar month with estrogens taken continuously
- LNG-IUS – 52 mg
  - Extensive experience in Europe (approved for 5 yrs of endometrial protection)
  - NOT yet FDA-approved in U.S. for this indication

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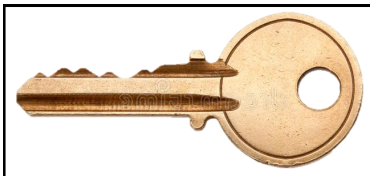

Prescribing Pearls

Q: Which is the preferred regimen for a woman with her uterus intact– continuous combined, or cyclic combined MHT?

A. For women in menopausal transition or early menopause- cyclic combined regimen (or low-dose OCP's) preferred: 80-90% will have regular monthly withdrawal bleeds, but less unscheduled bleeding

B. For women >3 years after their FMP- continuous combined: induces amenorrhea in most women; BTB is less likely to occur >3 years after the FMP. (may "forgive" the first 6 months of Rx)

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The First FDA-approved TRULY- BIOIDENTICAL Combination

FDA-approved for VMS Oct. 29, 2018

- **17-β-estradiol & progesterone** ("natural hormones")
  - **1.0 mg. & 100 mg.** vs. 0.5 & 50 vs. 0.25 & 50 vs. placebo
- N = 1, 835 postmenopausal women with VMS
- 12 months of follow up
  - The "REPLENISH" Trial

- VMS frequency and severity decreased significantly
  - dose-response-related response
- 0 cases of endometrial hyperplasia
  - Lobo RA. Obstet Gynecol. 2019; 132(1): 161-70

65

Recommended (or Not) Alternative Rx Products for Hot Flashes

- SSRI's / SNRI's – very good evidence (10 PCRT's)
  - Paroxetine (used for MDD, since 2005)
    7.5 mg – **FDA-approved**: June, 2013
    But write Rx for 10 mg (insurance won't cover 7.5mg)
  - Venlafaxine ER/desvenlafaxine ER – Off label
  - Citalopram/ escitalopram – Off label
- Gabapentin – (3 PCRT's) very good evidence esp. for nocturnal VMS
- Clonidine (TTS-1, TTS-2, TTS-3)– weak evidence
- Oxybutynin- weak evidence
- Testosterone, sertraline, fluoxetine - No benefit

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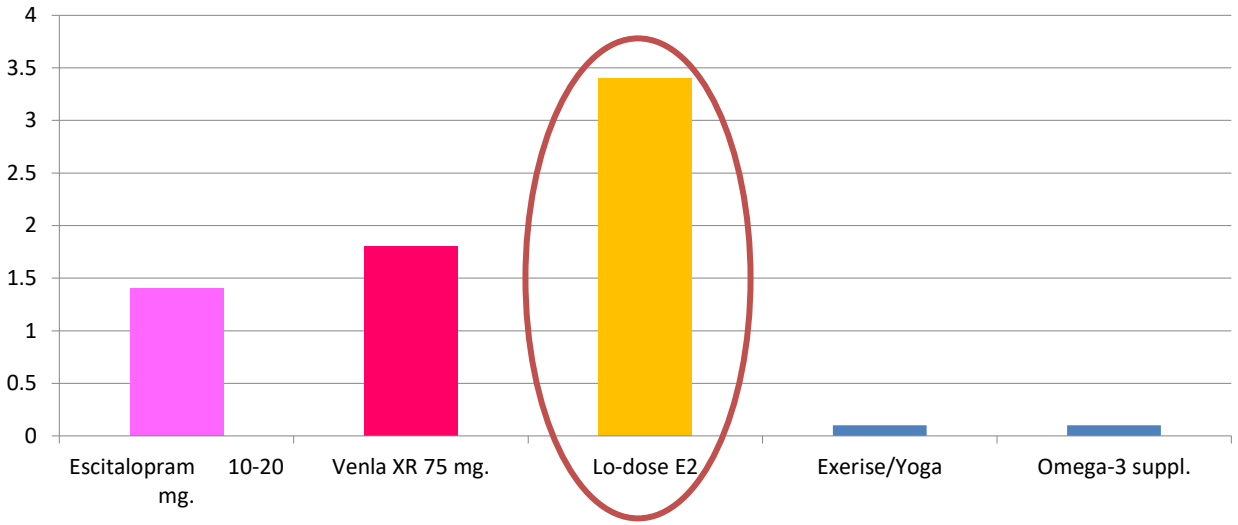
Comparative Pooled Analysis

reduction in VMS/wk



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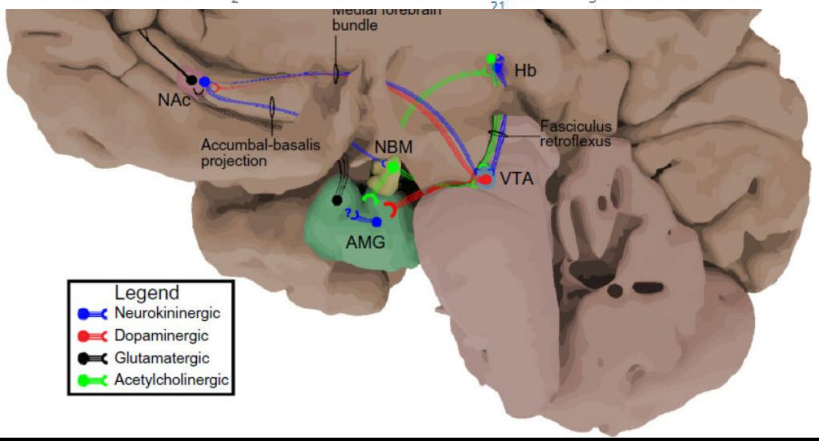
Basic neurokinin pharmacology

The ensuing era of neurokinin research revolved around the characterization of two more human neurokinins and their receptors. In 1983, neurokinin A and neurokinin B (NKA and NKB, respectively) were discovered and characterized, putting them in the same family as SP (the tachykinin family[16]) based on similar $-CO_2$ terminal sequences.[17] By 1984, all three neurokinin receptors had been proposed,[18] followed by the permanent nomenclature: neurokinin-1 receptor (NK_1R), neurokinin-2 receptor (NK_2R), and neurokinin-3 receptor (NK_3R) in 1986.[19] Each ligand can bind and activate each receptor; however, they all have their preference owing to a graded affinity: SP preferentially activates NK_1R, NKA preferentially activates NK_2R, and NKB preferentially activates NK_3R (Table 1).[20] Cellular



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NON-HORMONAL: Fezolinetant
a Neurokinin-3 Receptor (NK3R) Antagonist
FDA-approved- May, 2023

- It inhibits abnormal firing of neurons in the thermoregulatory centers (endogenous estrogen did the same prior to menopause)
- Phase 3 study 12-month RCT completed
  - The SKYLIGHT-4 Study*: n=1,830 45 mg vs 30 mg vs placebo qd
- Both doses were more effective than placebo*

  *PLACEBO achieved a 45% reduction (vs. 59% and 64% for 30 and 45mg)
  - Transaminase elevations (a class effect; <2%) were reversible upon DC'ing – FDA requires checking liver enzymes at baseline & q3 mos x 3

*Neal-Perry G. Obstet & Gynecol. 2023; 141: 737-47

70

Elinzanetant

- The first DUAL NK-1 and NK-3 receptor antagonist
  - Fezolinetant is only and NK-3 receptor antagonist
- NDA – accepted by the FDA on October 9, 2024
- FDA-approved - July 26, 2025

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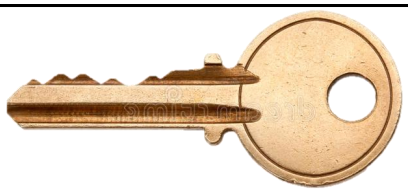

General Guidelines

- Although systemic HT is the gold standard for treating VMS, it is strongly discouraged in breast CA survivors (esp. with recent cancer)
- Generally avoid all estrogens, even vaginal, in women who are on, or who have recently been on, an aromatase inhibitor (consider SSRI's, SNRI's; gabapentin, fezolinetant)

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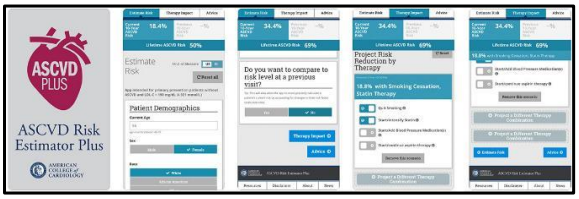
General Guidelines

- Individualize your counseling and prescribing of MHT by calculating, with the patient, her cardiovascular risk (ACC's ASCVD-Plus App) and breast CA risk (e.g. NCI (Gail Model) bcrisktool.cancer.gov, IBIS (Tyrer-Cuzick), Rosner-Colditz, SAS macro)



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General Guidelines

- For your reference: Equivalent dosing

CEE 0.625 mg =
1 mg po 17-ß-estradiol (orally) =
0.05 mg 17-ß-estradiol transdermal =
5 mcg of EE (ethinyl estradiol) – in birth control pills

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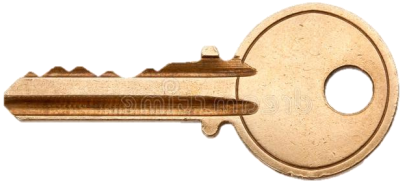

Prescribing Pearls

Q: What to do for a woman with elevated ACC ASCVD risk and/or elevated breast cancer risk?

A: If moderate risk of CVD (5--10% 10-year risk)- transdermal estrogen is preferred over oral.

A: If severe risk of CVD (>10% 10-year-risk) and/or moderate or high risk of breast cancer (1.67--5% 5-year risk, or >5%) – nonhormonal therapies are preferred.

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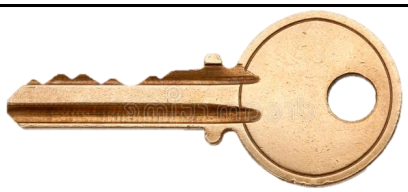

Prescribing Pearls

Q: What to do for a woman with persistent VMS after 5 years, and/or after age 60/65, and you and/or she are not comfortable continuing with MHT any longer?

A: Wean (taper) off of MHT, and crossover to …

1. gabapentin – esp. if sleep disorder, nocturnal VMS
2. an SSRI/SNRI – esp. if any mood disorder

   venlafaxine, citalopram, paroxetine (but not if she's taking tamoxifen); not fluoxetine or sertraline.
3. fezolinetant / elinzanetant

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What If She Doesn't Respond to Multiple Therapies? Consider the DDx of Her Night Sweats or Hot Flashes:

- Tuberculosis
- Anxiety / panic disorders
- Common blushing
- Hyperthyroidism
- Fever/infection
- Carcinomas
- Carcinoid syndrome
- Pheochromocytoma
- Medications
- Hypoglycemia
- Diabetes insipidus
- Autonomic dysreflexia
- Chronic fatigue
- Lymphomas
- Mastocytosis
- Rosacea
- Sleep apnea
- Idiopathic hyperhydrosis

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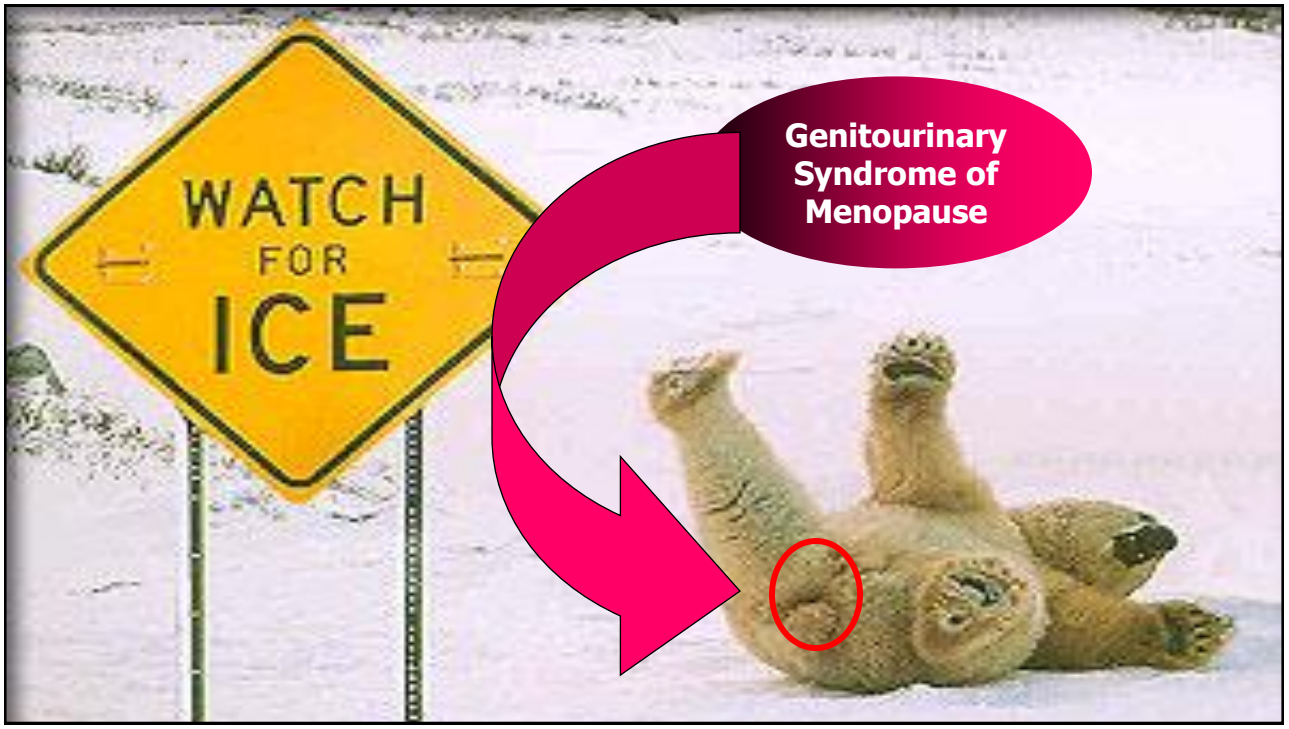

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Genitourinary Syndrome of Menopause

Lubricants

Moisturizers

80

NAMS Hormone Therapy Position Statement

For GSM

Genitourinary symptoms both local & systemic

Hormone therapy has been shown in RCTs to effectively treat symptoms of vulvovaginal atrophy (VVA).[45,46] Hormone therapy is FDA approved to treat moderate to severe symptoms of VVA and dyspareunia because of menopause but with the preference for low-dose vaginal therapy if solely prescribed for vulvar or vaginal symptoms.

Two vaginal therapies, vaginal ET and vaginal dehydroepiandrosterone (DHEA), have been FDA approved for treatment of moderate to severe dyspareunia, a symptom of VVA resulting from menopause. One oral therapy (a SERM) has FDA approval as well.

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Prescribing Pearls

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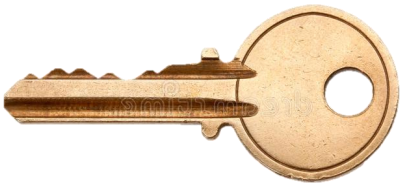
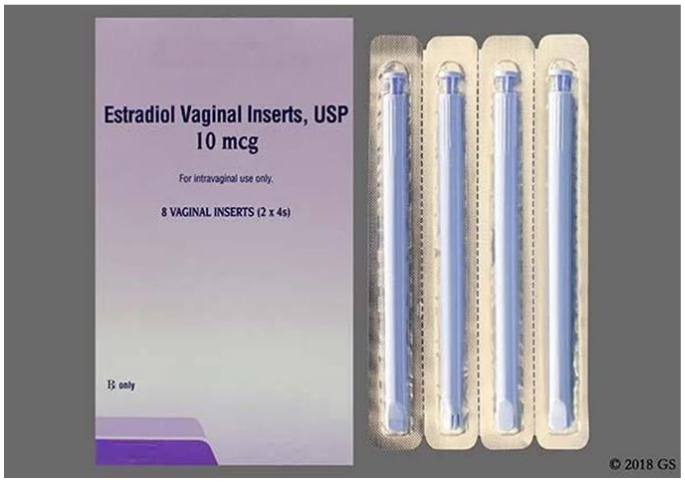


Prescribing Pearls



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HRT-1 Vaginal Ring – 28 Day Release Period

Investigational Use Only Not Yet FDA-approved

- **17-β-estradiol & progesterone**
- Released through an EVA ring (the same as the contraceptive vaginal ring material)
- Investigational (not yet FDA-approved)
- Phase 1 / 2 clinical trial
  - N = 50 women; f/u = 12 weeks
  - Significantly reduced hot flashes, improved vaginal pH, dyspareunia

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Vaginal DHEA

FDA-approved in 2016

- Prasterone (AKA: DHEA - dehydroepiandrosterone)
  - Intravaginal insert 6.5 mg PV qhs (inconvenient daily regimen)
- ***Clinical role?: Breast CA survivors on aromatase inhibitors (AI's)***
  - *(has not been tested in women with breast CA)*
  - *FDA-indication: dyspareunia (it also reverses vaginal atrophy; improves urinary symptoms)*
  - ***Absorption is minimal***
  - ~~***Prasterone does NOT increase [E_2]***~~
- *DHEA occurs naturally in wild yams, soy*

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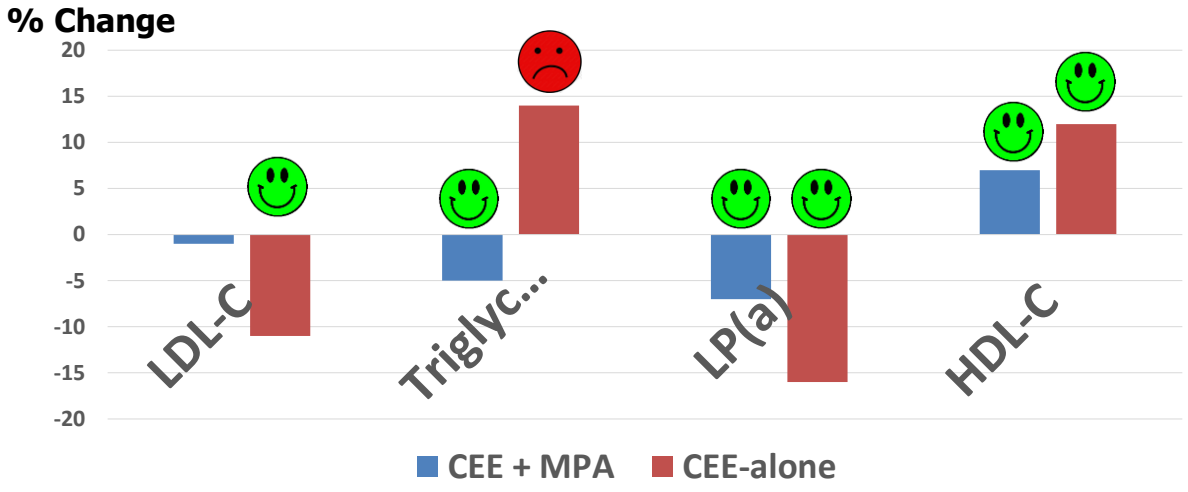
Estrogen and Cardiovascular Disease

86

WHI: a 20-year Follow-up on Cardiovascular Biomarkers in 2600 Women



Nudy M. Obstet & Gynecol. 2025; 145: 357-67

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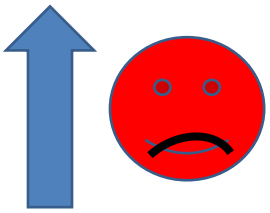
It May Not Be What You Take,

But Where You Put It

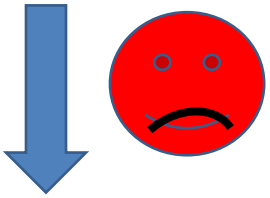
88

Metabolic Effects of **ORAL** Estrogens

- **Increased** Endogenous **Procoagulants**
  - CRP
  - TG's
  - Clotting factors
  - Prothrombin factors



- **Decreased** Endogenous **Anticoagulants**
  - AT-III, Protein C, Protein S, etc.



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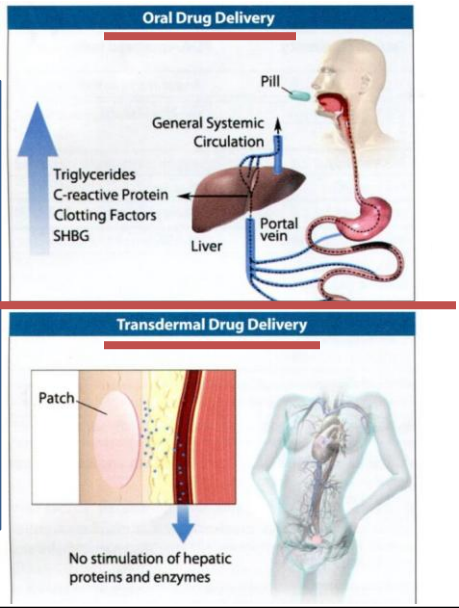
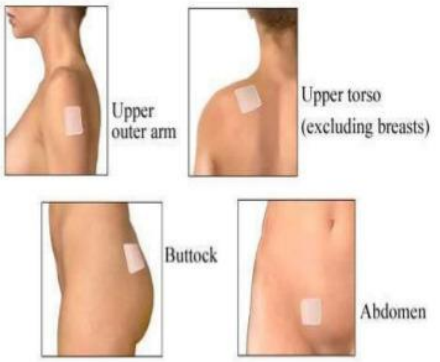
Transdermal vs. Oral E_2

This Makes a HUGE Difference Clinically (VTE Risk)





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Advantages of Transdermal Over Oral Estrogen

- 1. Better absorption (bypasses liver / intestinal variables)
- 2. Better steady state levels (no daily peaks)
- 3. Lower risk of VTE than with oral
- 4. Lower risk of stroke than with oral
- 5. Lower risk of gallbladder disease than with oral
- 6. Less negative impact on triglycerides
- 7. Lower rate of estradiol-to-estrone conversion (?lower CA risk to breast & endometrium?)
- 8. All patches contain estradiol (no conjugated equine estrogens)

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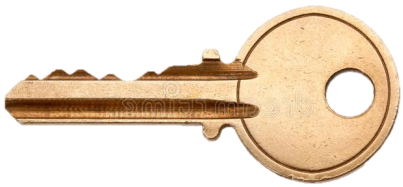

Prescribing Pearls

- Avoid prescribing <u>oral</u> estrogens to women with:
  - Hypertriglyceridemia
  - Active gall bladder disease
  - Known thrombophilia or other hypercoagulability disorder
  - ?? migraines with aura

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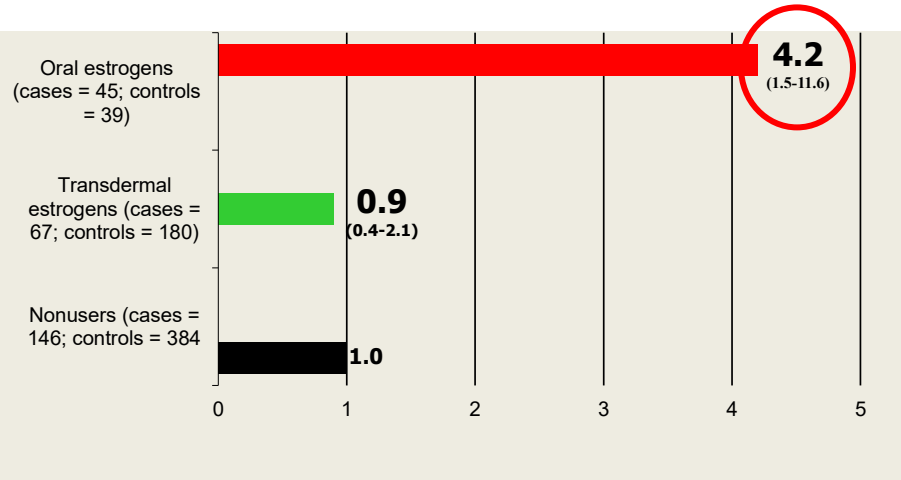
VTE: Oral vs Transdermal & Venous Thromboembolic Events ESTHER Study



Straczek C, et al. *Circulation.* 2005.

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Bioidenticals??

BEWARE: this is a marketing term

- Some patients resort to custom compounding pharmacies - some are good; others not so good
- We have bioidenticals that are FDA-approved
  - Estradiol
  - Progesterone
- Non-hormonal alternatives FDA-Approved
  - Paroxetine
  - Not approved for hot flashes, but are effective:
    - Venlafaxine, escitalopram, gabapentin, pregabalin

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NAMS 2022 Hormone Therapy Position Statement

Compounded BHT

Key points

- Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks. (Level I)
- Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed. (Level II/III)
- Shared decision-making is important, but patient preference alone should not be used to justify the use of compounded bioidentical hormone preparations, particularly when government-regulated bioidentical hormone preparations are available. (Level III)
- Situations in which compounded bioidentical hormones could be considered include allergies to ingredients in a government-approved formulation or dosages not available in government-approved products. (Level III)

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Take-Home SUMMARY POINTS

- Hormone therapy initiated at age <60, or <10 years after menopause, confers a favorable risk-benefit ratio for most women
- There should be NO arbitrary limit on the maximum age or duration of ET/EPT use (1/3 of women experience VMS x >10 years
- The most effective regimen for hot flashes is systemic estrogen
- (transdermal preferred); local estrogen is best for vulvovaginal symptoms
- Estrogen-alone does not increase breast cancer risk

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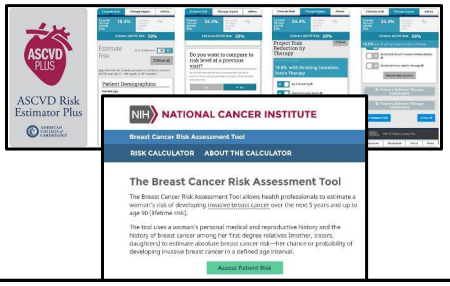
More Take-Home SUMMARY POINTS

- There are many FDA-approved bioidentical formulations available to women:
  - (containing **17-β-estradiol and/or progesterone)**
- Since many patients seek "customized care", you can prudently tailor your counseling and prescribing to their individual risks:
  - ACC's ASCVD-Plus Risk calculator
  - NCI's breast CA risk assessment tool



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Dos and Don'ts THESE are the "Don'ts"

- What MHT is NOT indicated for:
  - Prevention of CV disease, osteoporosis*, dementia
    - *Albeit FDA-approved for this indication

  - Don't prescribe/administer Depot-estrogen (e.g. injections/subQ pellets)
    - These cause an initial dangerously-high (thrombogenic) level (a "surge effect")
  - Don't prescribe/administer custom compounded formulations ("bioidenticals")

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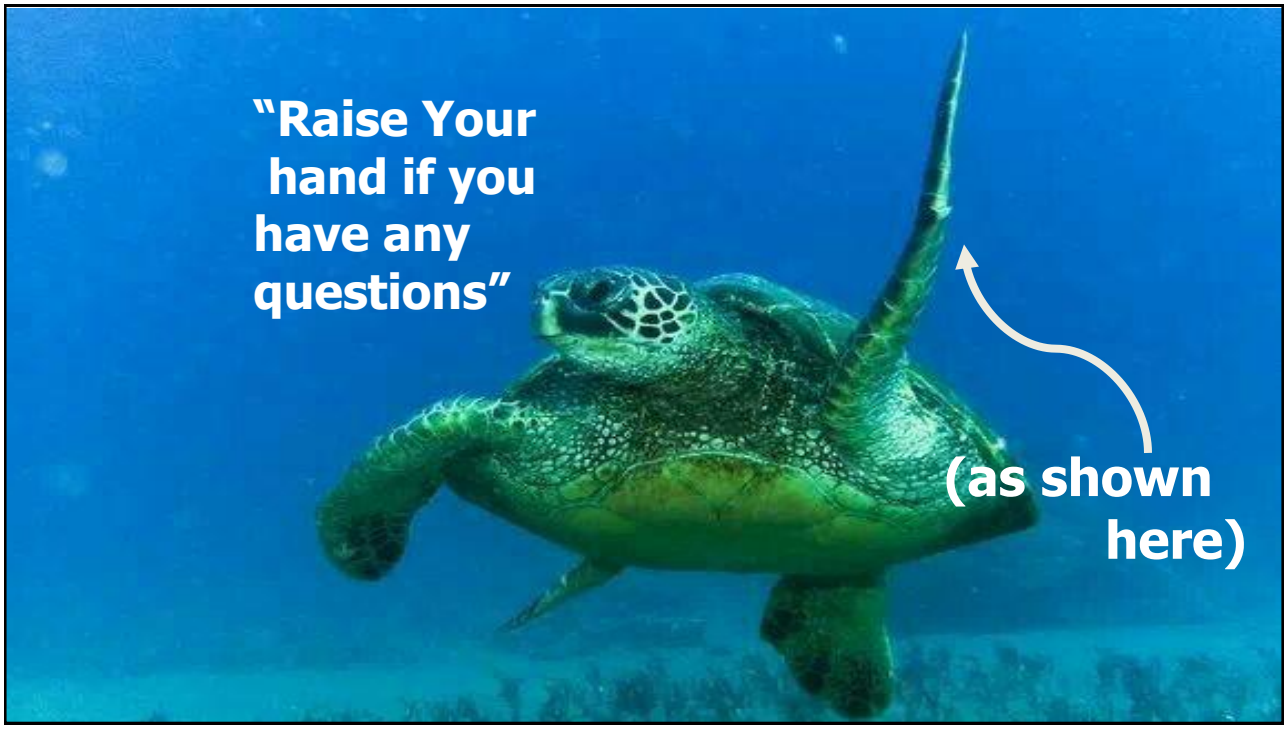

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Menopausal Hormone Therapy:
Risks & Benefits - Making Sense of the LATEST Data & Evidence

David M. Plourd, MD, FACOG
Staff Obstetrician & Gynecologist & Obstetric Hospitalist
Formerly Naval Hospital
San Diego, CA

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