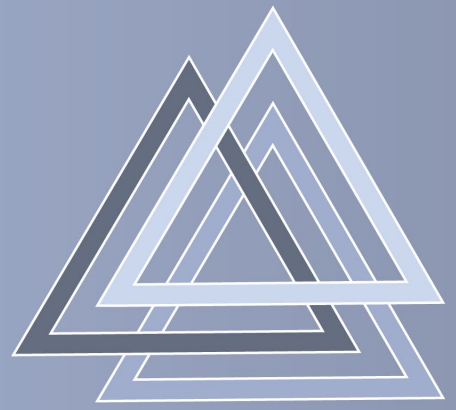


SAAOG

Annual Meeting • 2024

January 20-23 • The Cloister at Sea Island

Treating Menopausal Symptoms Without Fear: An Evidence-Based Strategy

Andrew M. Kaunitz MD, FACOG, NCMP
Tenured Professor and Associate Chair
Department of Obstetrics and Gynecology
University of Florida College of Medicine - Jacksonville

Medical Director, and Director of Menopause & GYN Ultrasound Services

UF Southside Women's Health Specialists

Andrew M. Kaunitz, M.D.
Menopause-related Disclosures

Clinical Trials

(Funding to University of Florida Research Foundation):

- Bayer
- Mylan

Royalties

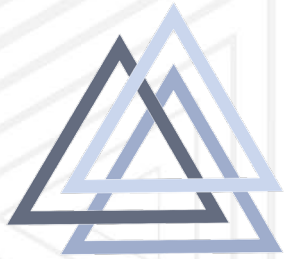
- UpToDate

Menopause Society

- *Menopause* Editorial Board
- 2020 GSM Position Statement writing group member

Off-label Use

- I will mention off-label use of levonorgestrel IUD for endometrial protection in women using systemic estrogen therapy



Abbreviations

- HT = hormone therapy
- ET = estrogen therapy
- CE = conjugated equine estrogen, E2=estradiol
- EPT = combination estrogen-progestin therapy
- VMS= vasomotor symptoms
- CHD= coronary heart disease
- VTE= venous thromboembolism

= Women's Health Initiative (WHI)

= Menopause Society (formerly known as NAMS)

Safety of Systemic Hormone Therapy

- Our patients will likely spend more than one third of their lifespan as menopausal women…

Safety of Systemic Hormone Therapy

Learning Objectives I

- Briefly review menopausal vasomotor symptoms
- Describe evidence regarding the safety of oral conjugated estrogen with or without medroxyprogesterone
  - breast cancer
  - coronary heart disease
  - venous thromboembolism (VTE)
- Review risk of VTE with oral vs. transdermal estrogen
- Review risk of invasive breast cancer with synthetic progestins vs. progesterone

Learning Objectives II:

- Discuss practical issues related to initiating systemic menopausal hormone therapy
- Detail a recent study assessing safety of vaginal estrogen in breast cancer survivors
- Review a new non-hormonal treatment for menopausal symptoms

Up to date clinicians can change the conversation, providing evidence-based guidance, thereby helping our patients make good choices regarding HT

Vasomotor Symptoms (VMS)

- Spontaneous sensations of warmth, usually felt on chest, neck and face
  - 'hot flashes' , 'hot flushes' or 'night sweats'
  - often associated with perspiration, palpitations and anxiety
  - may impair quality of life
- Variable in frequency, duration and severity
  - usually < 5 minutes

- Can be triggered by warm environments, hot drinks, emotional stress
- **VMS: Most common reason women seek care at time of menopausal transition**

Prevalence and Timing of VMS

- Experienced by > 50% of menopausal women
- Substantial increase in frequency and severity during menopausal transition (perimenopause)
- For some women, VMS persist 6 months to several years, with ↓ frequency and intensity over time
  - **Mean duration bothersome VMS >10 years**
    - **Sobering observation for symptomatic women**
    - **Important for decision making re treatment**
- VMS may be associated with negative cardiovascular and cognitive outcomes

EW Freeman, et al. Obstet Gynecol 2011 HD Nelson. Lancet 2008
RC Thurston, et al. Neurol 2023

Treatment of VMS: Hormone Therapy

- Appropriate when VMS
  - Disrupt daytime activities and/or sleep
  - Impair quality of life
- Estrogen used for many decades used to treat VMS
  - most effective treatment
    - numerous randomized, placebo-controlled trials
    - ~75% reduction in VMS frequency
    - significant reduction in VMS severity
    - oral and transdermal estrogen have similar efficacy
- Progestin therapy, including DMPA and megestrol also effective in treating VMS

Hormone Therapy

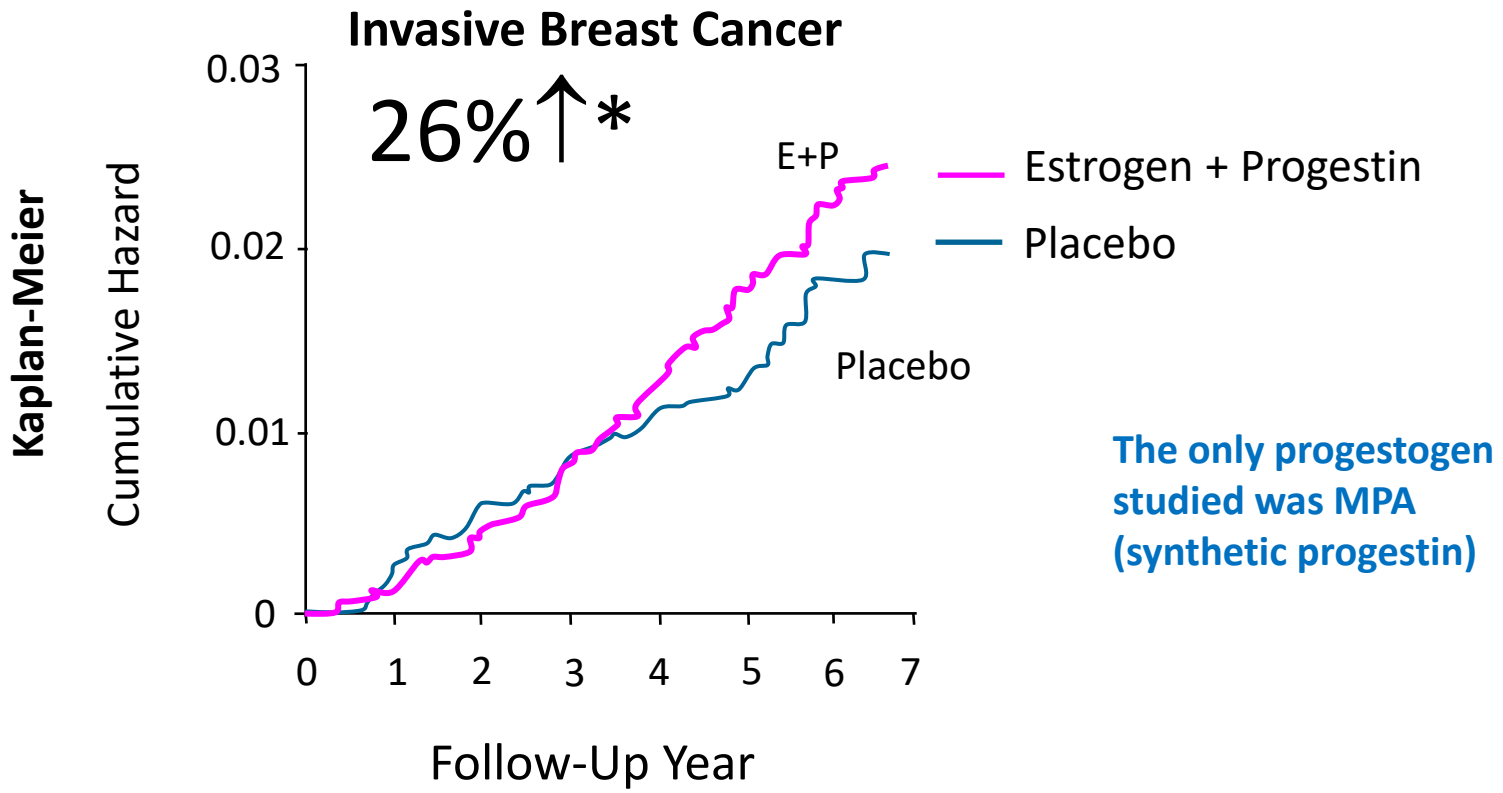
- Clear
  - VMS: most common indication for HT
  - HT's efficacy in treating VMS well-established
- Controversial
  - Our understanding of HT's safety….

WHI: Women's Health Initiative

- NIH-sponsored multicenter, double-blind, placebo-controlled trial of women **age 50-79 years at baseline**, designed to assess HT's impact on cardiovascular disease
- **Mean age at screening 63-64 years**
- Planned 10-year trial; stopped early
  - Oral CE/Medroxyprogesterone acetate (MPA) v. placebo: N ~ **17,000** , stopped Summer '02, mean follow-up 5.2 years
  - Oral CE v. placebo: N ~ **11,000** , stopped Spring '04, mean follow-up 6.8 years

Writing Group WHI. JAMA 2002
WHI Steering Committee. JAMA 2004

EPT: Breast Cancer

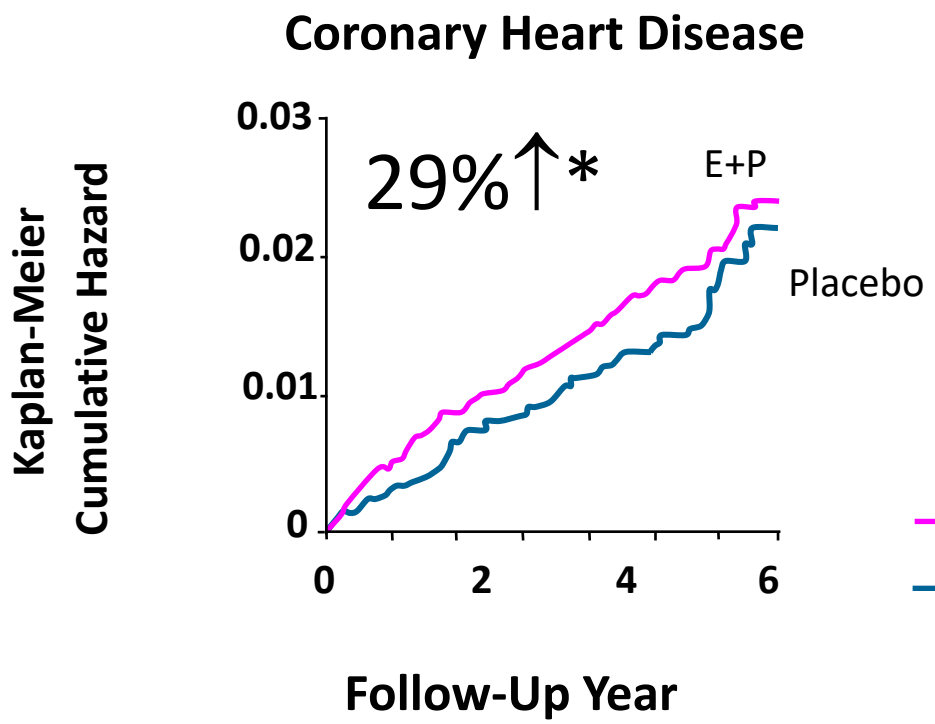


The only progestogen studied was MPA (synthetic progestin)

*95% nominal CI Hazard Ratio = **1.26 (1.00-1.59)**

Adapted from: Writing Group WHI. JAMA 2002

EPT: Coronary Heart Disease (CHD)



-Initially, no age-stratified analysis presented…

Estrogen + Progestin

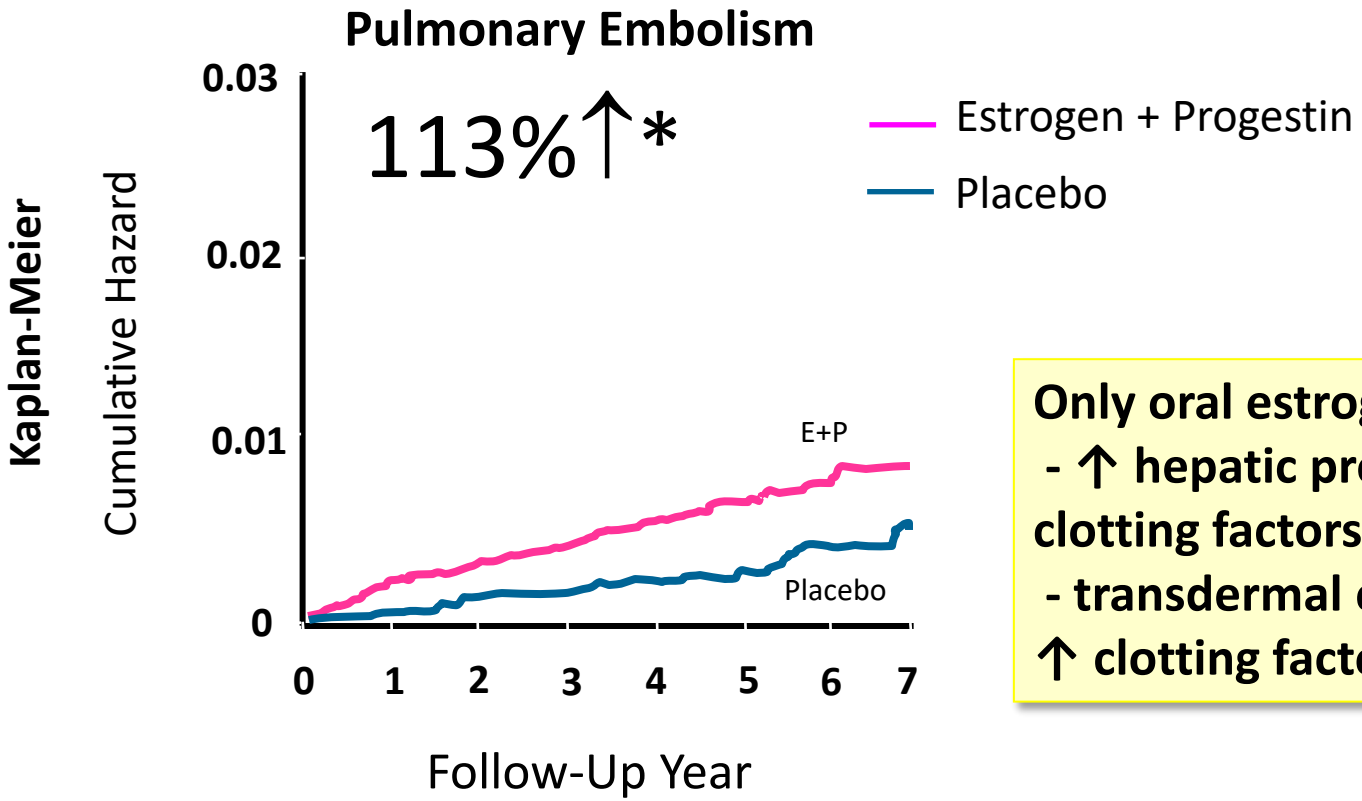
Placebo

Hazard Ratio = **1.29**

*Statistically significant based on 95% nominal CI on Hazard Ratios

Adapted from: Writing Group WHI. JAMA 2002

EPT: Pulmonary Embolism

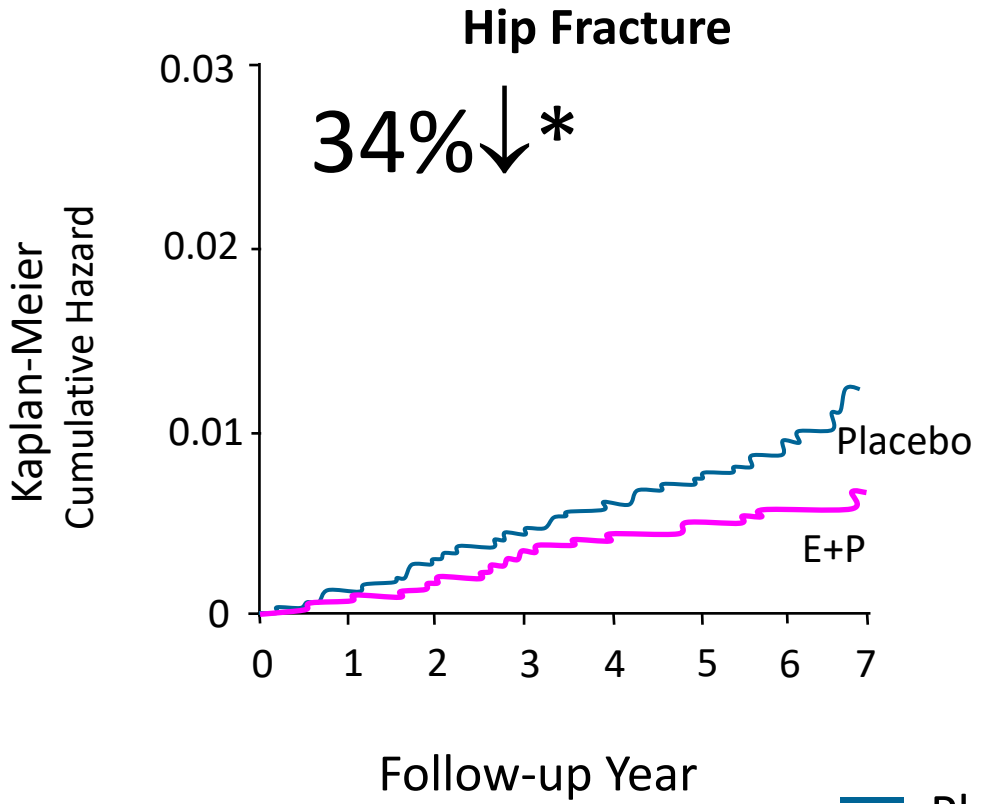


Only oral estrogen used in WHI
- ↑ hepatic production of clotting factors
- transdermal estradiol does <u>not</u> ↑ clotting factors

*95% nominal CI Hazard Ratio = **2.13 (1.39-3.25)**

Writing Group WHI. JAMA 2002

Standard Dose EPT Prevents Fractures

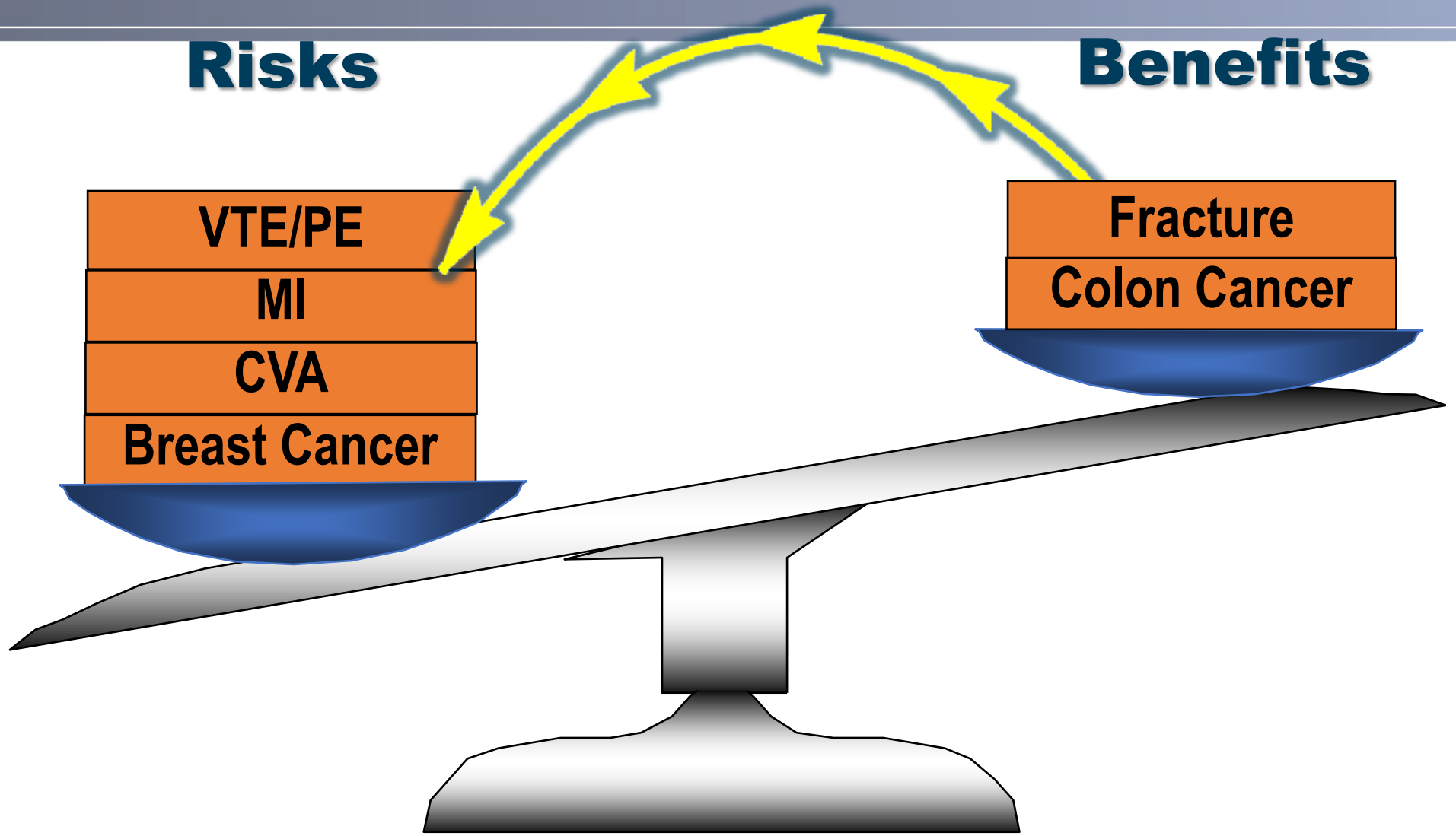


EPT also reduced risk colorectal cancer by 37%

*Statistically significant based on 95% nominal CI on Hazard Ratios

Adapted from: Writing Group WHI. JAMA 2002

WHI EPT Study: Findings at Early Interruption Summer 2002



Adapted from: Writing Group WHI. JAMA 2002

WHI ET Initial Findings: Summary as of 2004

- ET component of study also stopped early
  - after 6.8 years of follow-up
- ET **not** found to significantly impact risk of breast cancer, CHD, PE, or colorectal cancer
  - significant reduction in hip fracture risk
- Overall safety of ET appears greater than EPT
- 2004 findings received less attention than 2002 report

WHI Steering Committee. JAMA 2004

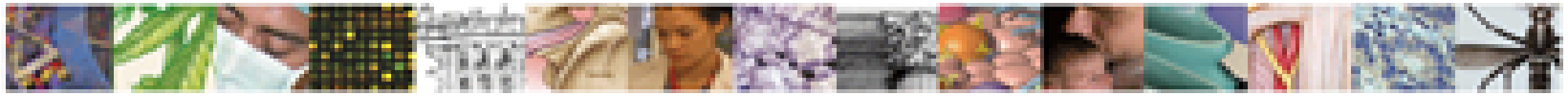
WHI's Impact on Use of HT in US Women

- Since 2002, use of HT has decreased substantially
- Many clinicians, including OB/GYNs, remain reluctant to treat women with bothersome menopausal symptoms

Many symptomatic women not treated…

PI Jewett, et al. Obstet Gynecol 2014

The NEW ENGLAND JOURNAL of MEDICINE



Perspective

Menopause Management — Getting Clinical Care Back on Track

JoAnn E. Manson, M.D., Dr.P.H., and Andrew M. Kaunitz, M.D.

N Engl J Med 2016; 374:803-806 | March 3, 2016 | DOI: 10.1056/NEJMp1514242

WHI: 13,18, and 20-Year Follow-up: EPT and ET…

JAMA®
The Journal of the American Medical Association

JE Manson, et al. 2013, 2017 RT Chlebowski, et al. 2020

Risk of Breast Cancer @13 Years Cumulative f/u in Participants OVERALL (all ages at randomization)

- EPT Hazard Ratios (HRs):
  - **Persistent, significant but modest ↑ risk breast cancer: 1.28**

- ET Hazard Ratios:
  - **WHI: Persistent, significant but modest ↓ risk breast cancer: 0.79**
  - **Smaller RCTs: no elevated risk of breast cancer with CEE or estradiol ET**

JAMA® The Journal of the American Medical Association

Menopause The Journal of The North American Menopause Society

JE Manson, et al. JAMA October 2, 2013 K Pan, … RT Chlebowski. Menopause 2022

EPT and Elevated Risk of Incident Breast Cancer

- **What does an 1.28 HR for breast cancer mean?**
  - <1 additional case per 1,000 EPT users annually can be attributed to HT (WHI)
    - Per WHO: 'rare'
  - Breast cancer common with or without use of HT
    - Only 1 in 5 breast cancers occurring in women using EPT can be attributed to HT (WHI)

JE Manson, et al. 2013

JAMA® The Journal of the American Medical Association

Breast Cancer Incidence and Mortality with 20+ Years Median Cumulative f/u*

- EPT Hazard Ratios (HRs):
  - Persistent significant ↑ risk <u>incident</u> breast cancer**:**

    HR 1.28
  - Breast cancer <u>mortality</u> not significantly ↑ed**:** HR 1.35
- ET Hazard Ratios:
  - Significantly lower <u>incidence</u> of breast cancer: **HR 0.78**
  - Significantly lower <u>mortality</u> from breast cancer: **HR 0.60**

***Statistically significant HRs bolded**

JAMA®
The Journal of the American Medical Association

RT Chlebowski, et al. JAMA 2020

Risk of All-cause Mortality @18 Years Cumulative f/u in Participants OVERALL (all ages at randomization)

- With EPT (HR 1.02) and ET (HR 0.94), **all-cause mortality** similar with HT and placebo
  - Mortality from CVD and Cancer (all types) similar with HT and placebo
- Above findings refer to all participants (mean age at screening 63-64 years)

WHI recruited women age 50-79 years--
Age stratified results…

JE Manson, et al. JAMA September 2017

JAMA® The Journal of the American Medical Association

All-cause Pooled (EPT+ET) Mortality Hazard Ratios at 18 Years Cumulative f/u Stratified by Age at Randomization

70-79 years
1.03

60-69 years
0.98

50-59 years
0.89

Risks ⇧ with age at randomization

JE Manson, et al. JAMA September 2017

JAMA®
The Journal of the American Medical Association

HT, CHD and the 'Timing Hypothesis'

- If initiated **early** in the menopausal transition, HT does not increase coronary heart disease risk
  - May reduce morbidity/mortality if initiated early
  - **'Early':** Age 50-59 years, or < 10 years after menopause onset
  - If initiated later, HT increases CHD risk
- Timing hypothesis may also apply to type II diabetes and dementia

J Hsia. Arch Int Med 2006
JE Rossouw. JAMA 2007
RI Pereira, et al. JCEM 2015
JE Manson. N Eng J Med 2007
S Toh. Annals Int Med 2010
B Imtiaz. Neurology 2017
Stram DO. Menopause 2011
HN Hodis,. N Engl J Med 2016
MA Allison, JE Manson. Editorial. Menopause 2011
P Tuomikoski. Obstet Gynecol 2014

Treatment of Menopausal Symptoms: Practical Issues

- Transdermal vs. oral ET, and risk of VTE
  - Monitoring estradiol levels
- Use of synthetic vs. natural progesterone in women with an intact uterus
- One clinician's approach to HT initiation,

Risk of VTE: Is Transdermal Estrogen Safer than Oral?

- No randomized trial data comparing benefits and risks
  - 8 observational studies: VTE risk increased with oral, but not with transdermal ET
- Given consistency and biologic plausibility of observational data, we should counsel patients: **transdermal estrogen safer re risk of VTE**
- Transdermal route particularly appropriate when obesity or other risk factors for VTE present
  - Appropriate also for women with hypertriglyceridemia

PY Scarabin. Lancet 2003 M Canonico. Arterioscler Thromb Vasc Biol 2010 A Bergendal. Menopause 2016 JA Simon . Menopause 2016
C Renoux. J Thromb Haemost 2010 C Renoux,. BMJ 2010
L Laliberté. Menopause 2011 RE Roach. J Thromb Haemost 2012 **Y Vinogradova. BMJ 2019**

Another Advantage of Transdermal Estrogen: Monitoring Estradiol Levels

- Unlike treating diabetes, lipid and thyroid disorders, routine monitoring of hormone levels not useful when Rxing HT
  - Monitoring, however, useful if bothersome VMS persist despite increasing dose of estrogen
  - Serum estrogen levels fluctuate with oral estrogen administration; monitoring levels not useful
  - Relatively stable estradiol levels with transdermal administration
    - If monitoring, target estradiol levels: 40-100 pg/ml
    - Younger patients often need higher doses/levels

AM Kaunitz. Menopause 2012

Risk of Breast Cancer: Is Bioidentical Progesterone Safer than MPA or NETA?

- No randomized trial data has compared safety of progesterone with progestins medroxyprogesterone acetate or norethindrone acetate
- However, two observational studies provide reassurance re progesterone
  - 2022 large case-control study (>43,000 breast cancer cases) based on UK Family Practice data
    - E+ progestin (mostly MPA): **RR 1.28** (relative risk similar to WHI findings)
    - E+ progesterone: RR **0.99** (risk ~identical to that of non-users)
- Findings from this large UK study similar to those from an earlier smaller French cohort study (< 1,000 case of breast cancer)

From perspective of breast cancer risk, progesterone appears to be safest progestogen

HA Abenheim, et al. Obstet Gynecol 2022 A Fournier, et al. Int J Cancer 2005 JV Pinkerton, C Wilson, AM Kaunitz. Menopause 2022

Initiating HT in Symptomatic Young/Recently Menopausal women: Evidence-based statements (I)

'Script' examples: *'HT is highly effective in treatment of symptoms and prevention of osteoporosis, including fractures…'*

- **Uterus absent:** *'estrogen therapy does not impact risk of breast cancer'*
- **Oral ET:** *'Oral ET increases risk of blood clots, similar to what is seen with younger women using oral contraceptives.'*
- **Uterus present, E+Progesterone:** *'EPT does not appear to impact risk of breast cancer'*
- **Uterus present, E+Progestin:** *'After 3-5 years of use, EPT slightly increases risk of being diagnosed with breast cancer, underscoring the importance of continuing regular mammograms.'*

Initiating HT in Symptomatic Young/Recently Menopausal women: One Clinician's Approach (II)

- Start HT using standard dose of estrogen*
  - **Oral estradiol (E2) 1 mg; Oral conjugated equine estrogen (CE) 0.625 mg**
  - **Transdermal (TD) E2 0.0375 mg-0.05 mg patch**
    - For overweight/obese women, smokers and other women with ↑ risk VTE/CVD, consider TDE2
- After VMS have resolved for several years on initial dose of estrogen, encourage trial of lower dose
  - If VMS or loss of sense of wellbeing occur on the lower dose, patients can resume prior higher dose

***Some clinicians start with lower doses**

AM Kaunitz. Clin Obstet Gynecol 2018 Cho, Kaunitz, Faubion, et al. Circulation 2023

Genitourinary Syndrome of Menopause in Breast Cancer Survivors

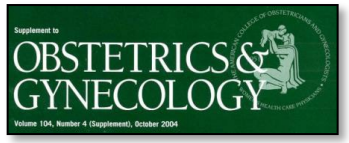
- More than 3.8 million BC survivors reside in US
- GSM: major impact on sexuality/QOL among menopausal women
- Breast cancer associated with several GSM risk factors:
  - Chemotherapy-induced ovarian insufficiency
  - Surgical removal of the ovaries (premenopausal women)
  - Adjuvant endocrine therapies
    - GnRH agonists sometimes used in premenopausal patients
    - Aromatase inhibitors (AIs) often used in menopausal patients

FDA list all estrogens as contraindicated in women with a personal history of breast cancer…

2023 US Retrospective Cohort Study Assessing Safety of Vaginal Estrogen Use in Breast Cancer Survivors

- Among some 42,000 women diagnosed with GSM after breast cancer, 5% had used vaginal ET
- No significant differences were noted in recurrence-free survival between the vaginal estrogen and no estrogen groups
  - Among women with estrogen-receptor positive tumors, risk of breast cancer recurrence similar between vaginal ET users and non-users
  - However, concomitant use of vaginal estrogen and aromatase inhibitors associated with a higher risk of breast cancer recurrence than use of vaginal estrogen alone

P Agrawal, et al. *Obstet Gynecol* Sept 2023



Fezolinetant 45 mg tabs (Veozah): Selective Neurokinin 3 (NK3) Antagonist

- Declines in estrogen at menopause leads to increased signaling at kisspeptin/neurokinin B/dynorphin neurons in the hypothalamic thermoregulatory center with resultant increases in hot flashes
- Fezolinetant binds to and blocks activity of NK3 receptor
- In pivotal phase 3 trials, 64% reduction in mean daily VMS from baseline seen at 12 weeks for fezolinetant vs. 45% reduction with placebo

S Lederman, et al. Lancet 2023
JV Pinkerton,…AM Kaunitz. J Clin Endocrinol Metab 2023

Fezolinetant 45 mg tabs (Veozah): Hepatic Safety Issues

- In pivotal trials, ↑s in aminotransferase (ALT) and/or aspartate aminotransferase (AST) were noted and described as asymptomatic, isolated, intermittent, or transient
  - LFT ↑s to more than 3 times the upper limit of normal occurred in 6 of 583 participants taking placebo, and 12 of 589 taking fezolinetant 45 mg
  - LFT levels returned to baseline during treatment or after discontinuation

Package label: Fezolinetant should not be started if baseline LFTs equal to or exceed 2 times the upper limit of normal. LFTs should be repeated every 3 months for the first 9 months and then if symptoms suggest liver injury

JV Pinkerton,…AM Kaunitz J Clin Endocrinol Metab 2023

Fezolinetant 45 mg tabs (Veozah): Cost Issues

- Fezolinetant: very expensive
- Insurance coverage varies…

Treating Menopausal Symptoms without Fear

- Transdermal ET minimizes/eliminates elevated risk of VTE with oral route
- Regarding breast cancer
  - Estrogen-only therapy does not increase risk
  - Using progesterone reduces or eliminates increased risk with synthetic progestins…
- In selected well-counselled breast cancer survivors, off-label use of vaginal estrogen may safely improve sexual function and quality of life
- A new nonhormonal medication effectively treats VMS

Conclusions: Systemic Menopausal Hormone Therapy

- Well informed clinicians can change the conversation, *removing fear from discussions re HT*, and help women make sound, evidence-based choices regarding treatment of menopausal symptoms

Pinkerton JV. Clin Obstet Gynecol 2018

Additional Information

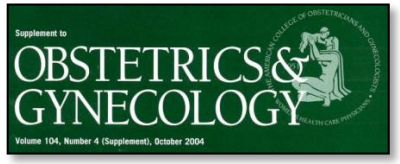
Clinical Expert Series

CME

Management of Menopausal Symptoms

Andrew M. Kaunitz, MD, and JoAnn E. Manson, MD, DrPH

Obstet Gynecol October 2015; 126: 859–876



The 2022 Hormone Therapy Position Statement of the Menopause Society.
Available at no charge: Menopause.org

Thank you!

UF UNIVERSITY of FLORIDA