NWOOA Fall Conference 2020

Hormonal and Nonhormonal Therapy: Where we are in 2020

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Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 7, pp. 728-753
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Position Statement

The 2017 hormone therapy position statement of The North American Menopause Society

Menopause: The Journal of The North American Menopause Society
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Position Statement

Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society

The 2017 NAMS Hormone Therapy Position Statement has been endorsed by

- Academy of Women's Health
- American Association of Clinical Endocrinologists
- American Association of Nurse Practitioners
- American Medical Women's Association
- American Society for Reproductive Medicine
- Asociación Mexicana para el Estudio del Climaterio
- Association of Reproductive Health Professionals
- Australasian Menopause Society
- Chinese Menopause Society
- Colegio Mexicano de Especialistas en Ginecologia y Obstetricia
- Czech Menopause and Andropause Society
- Dominican Menopause Society
- European Menopause and Andropause Society
- German Menopause Society
- Groupe d'études de la ménopause et du vieillissement Hormonal
- HealthyWomen
- Indian Menopause Society
- International Menopause Society
- International Osteoporosis Foundation
- International Society for the Study of Women's Sexual Health
- Israeli Menopause Society
- Japan Society of Menopause and Women's Health
- Korean Society of Menopause
- Menopause Research Society of Singapore
- National Association of Nurse Practitioners in Women's Health
- SIGMA Canadian Menopause Society
- SOBRAC and FEBRASGO
- Società Italiana della Menopausa
- Society of Obstetricians and Gynaecologists of Canada
- South African Menopause Society
- Taiwanese Menopause Society
- Thai Menopause Society

The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool, June 2017. The British Menopause Society supports this Position Statement.

A Decade After the WHI: The Experts Do Agree

- All acknowledge that hormone therapy has an important role in managing symptoms for women during the menopausal transition and in early menopause

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FDA-approved indications for hormone therapy

- First-line therapy for relief of vasomotor symptoms in appropriate candidates
- To prevent bone loss and reduce fractures in postmenopausal women at elevated risk of osteoporosis or fractures
- For women with hypogonadism, primary ovarian insufficiency, or premature surgical menopause without contraindication, hormone therapy is recommended for health benefits until the average age of menopause
- Low-dose vaginal estrogen therapy is recommended first line for isolated genitourinary syndrome of menopause to treat symptoms of vulvovaginal atrophy

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

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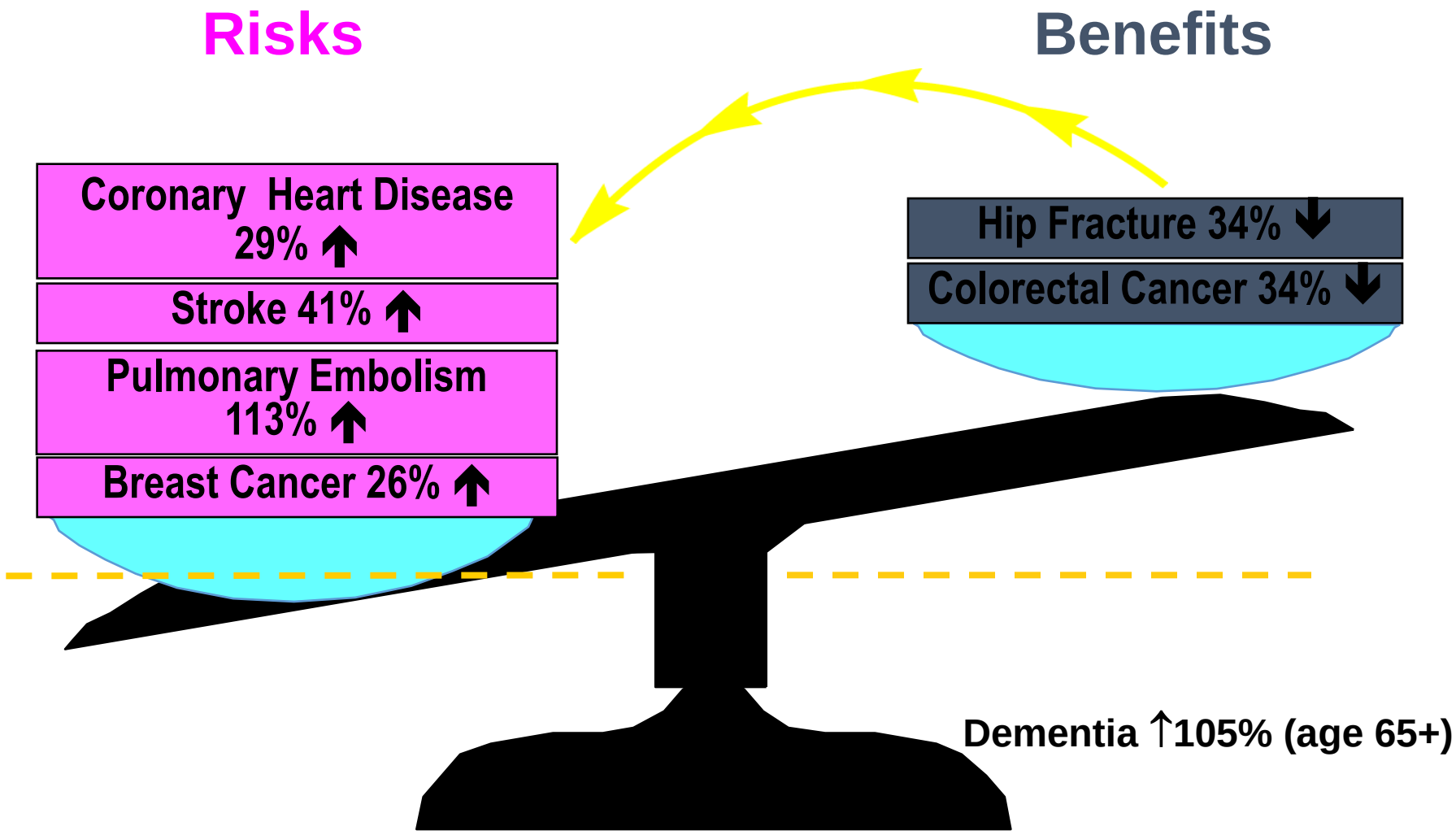
WHI Estrogen+Progestin Trial Findings, July 2002

(N=16,608; mean age 63 yrs; mean follow-up 5.2 yrs)



WHI EPT Results 2002

Health Event	RR of EPT (Prempro)	Increase in Absolute Risk Per 10,000 Women	Increase in Absolute Benefit Per 10,000 Women
CHD	1.29	7 (30 vs. 37)	
Stroke	1.41	8 (21 vs. 29)	
Breast Cancer	1.26	8 (30 vs. 38)	
VTE	2.11	18 (16 vs. 34)	
Colon Cancer	0.63		6 (15 vs. 10)
Hip Fracture	0.76		5 (16 vs. 10)
Total		41	11

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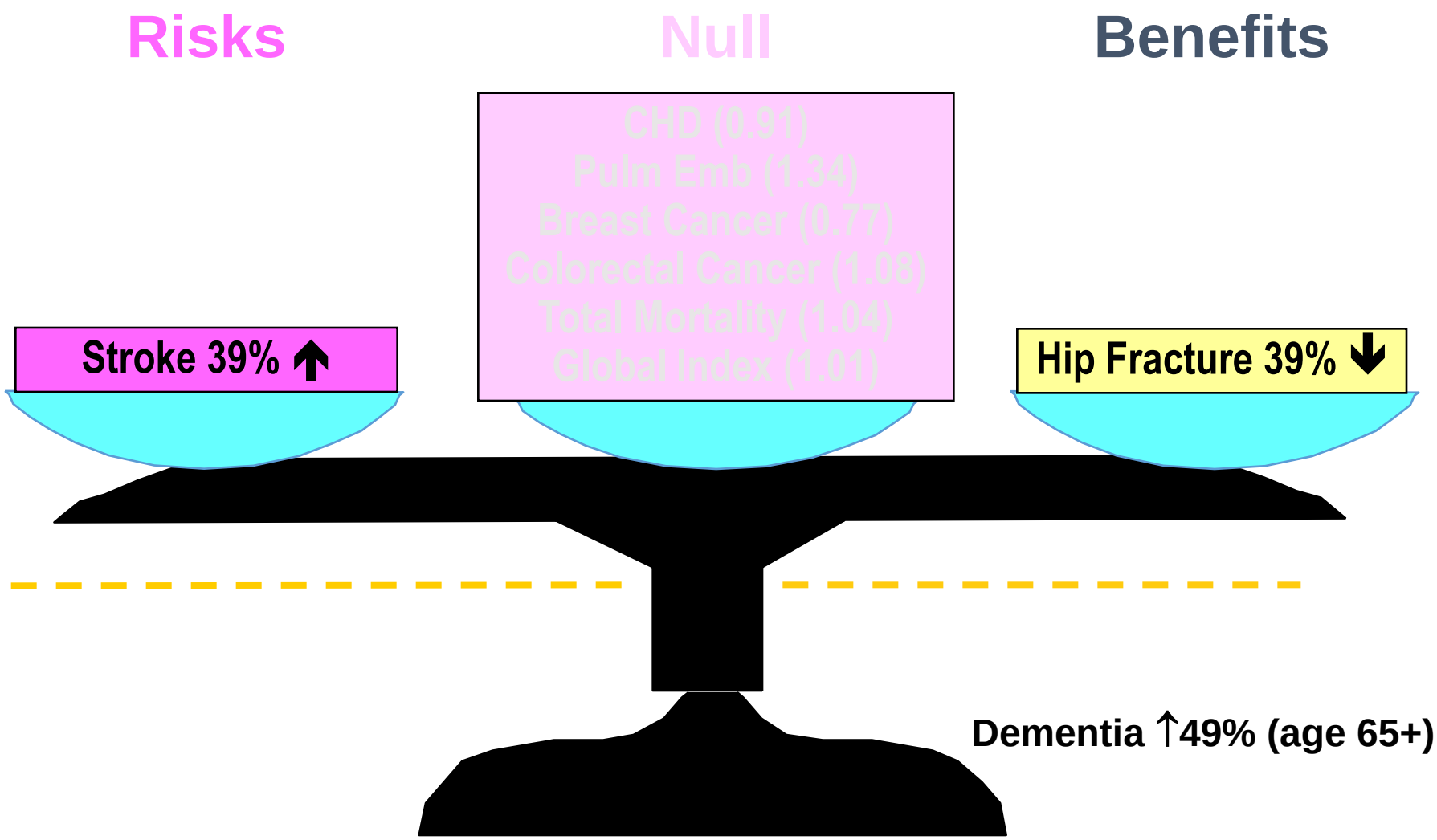
WHI Estrogen-Alone and Health Outcomes
(N=10,739; mean age 63.6 yrs; mean follow-up 6.8 yrs)



WHI EPT: Results 2004

Health Event	RR of ET (Premarin)	Increase in Absolute Risk Per 10,000 Women	Increase in Absolute Benefit Per 10,000 Women
CHD	0.91		5 (54 vs. 49)
Stroke	1.39	12 (32 vs. 44)	
Breast Cancer	0.77		7 (33 vs. 26)
VTE	1.34	7 (21 vs. 28)	
Colon Cancer	1.08	1 (16 vs. 17)	
Hip Fracture	0.61		6 (17 vs. 11)
Total		20	18

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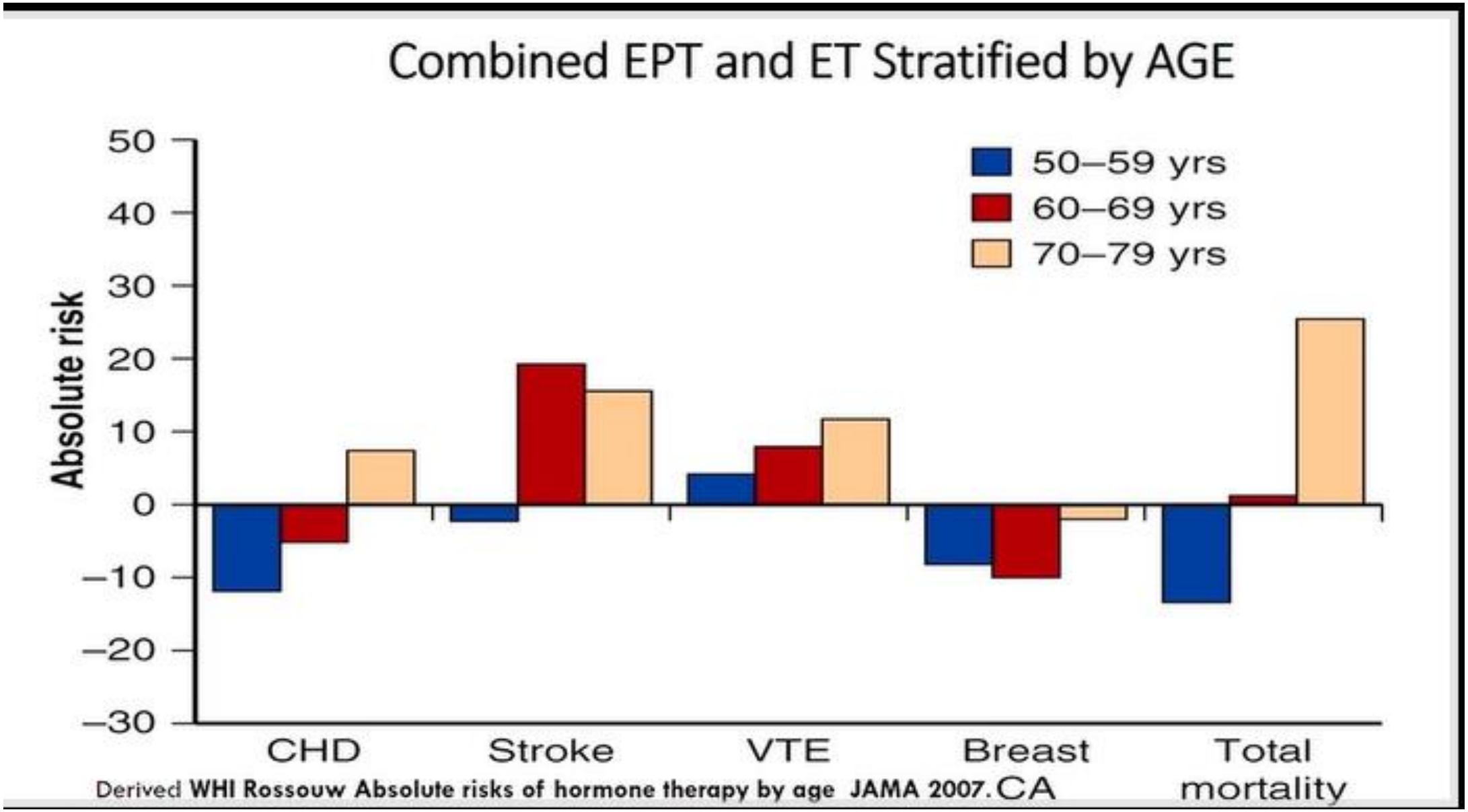
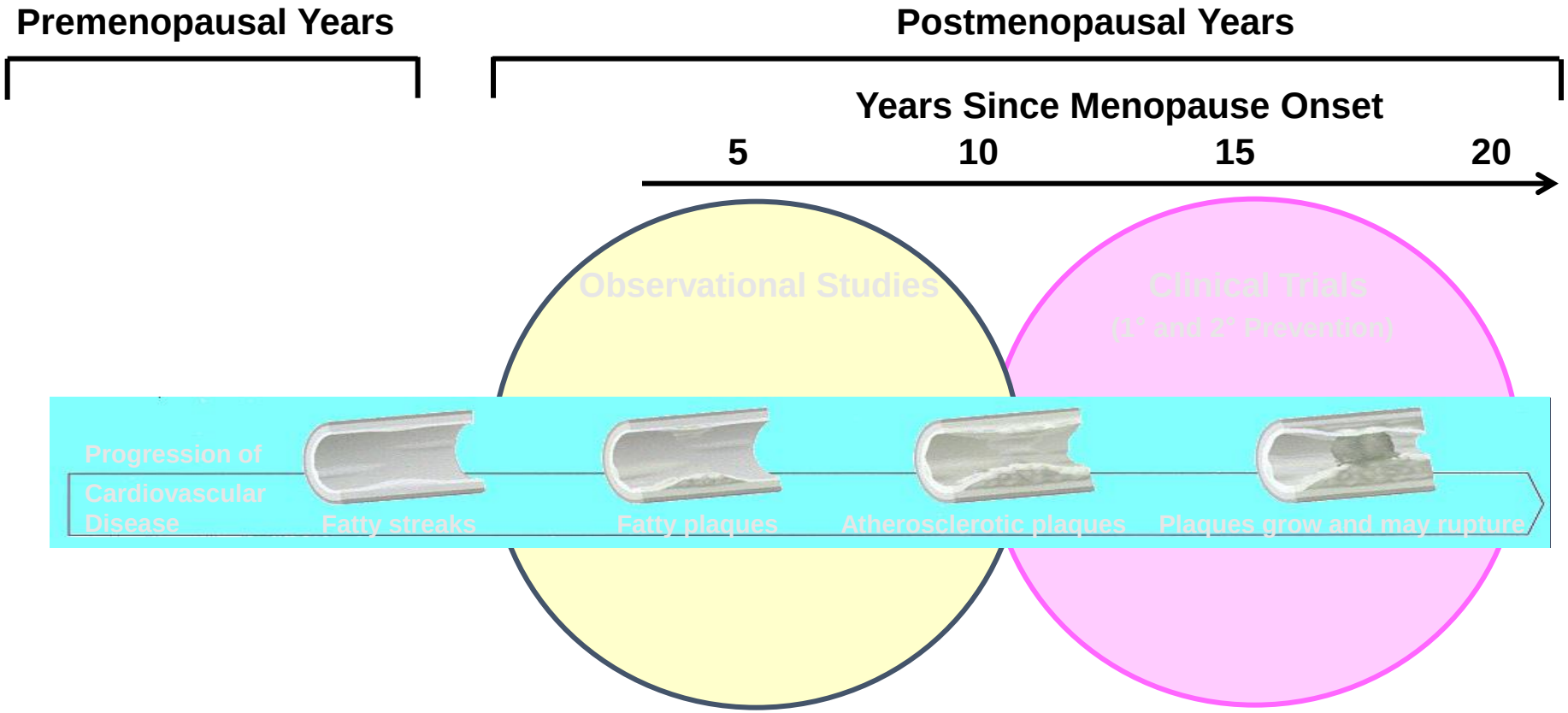

Combined EPT and ET Stratified by AGE
50–59 yrs
60–69 yrs
70–79 yrs
Absolute risk
50
40
30
20
10
0
–10
–20
–30
CHD
Stroke
VTE
Breast
Total mortality
Derived WHI Rossouw Absolute risks of hormone therapy by age JAMA 2007. CA

Timing of Hormone Therapy Initiation in Relation to Stage of Atherosclerosis: Observational Studies vs Clinical Trials



Favorable Lipid and Endothelial Effects of Estrogen Predominate

Favorable Influence of Initiating Exogenous Estrogens

Prothrombotic and Proinflammatory Effects of Estrogen Predominate
(plaque rupture, thrombo-occlusion)

Adverse Influence of Initiating Exogenous Estrogens

From: J Manson, et al. *Menopause* 2006.

Age and time since menopause onset: *timing hypothesis*

- **The effects of hormone therapy (HT) on coronary heart disease (CHD) may vary depending on a woman's age and time since menopause onset**
- **Data show reduced CHD in women who initiate HT aged younger than 60 years and/or within 10 years of menopause onset**
- **There is concern of increased risk of CHD in women who initiate HT more than 10 or 20 years from menopause onset**

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):728-753.

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Trials of hormone therapy and coronary heart disease

- **Meta-analysis of randomized, controlled trials (Boardman HM, et al. *Cochrane Database Syst Rev*. 2015.)**
  - **Hormone therapy initiated fewer than 10 years after menopause onset in postmenopausal women reduced coronary heart disease**
    - **Relative risk (RR), 0.52; 95% confidence interval (CI), 0.29-0.96**
  - **Significant increased risk of venous thromboembolism**
    - **RR, 1.74; 95% CI, 1.11-2.73**
  - **Death was significantly reduced**
    - **RR, 0.70; 95% CI, 0.52-0.95**

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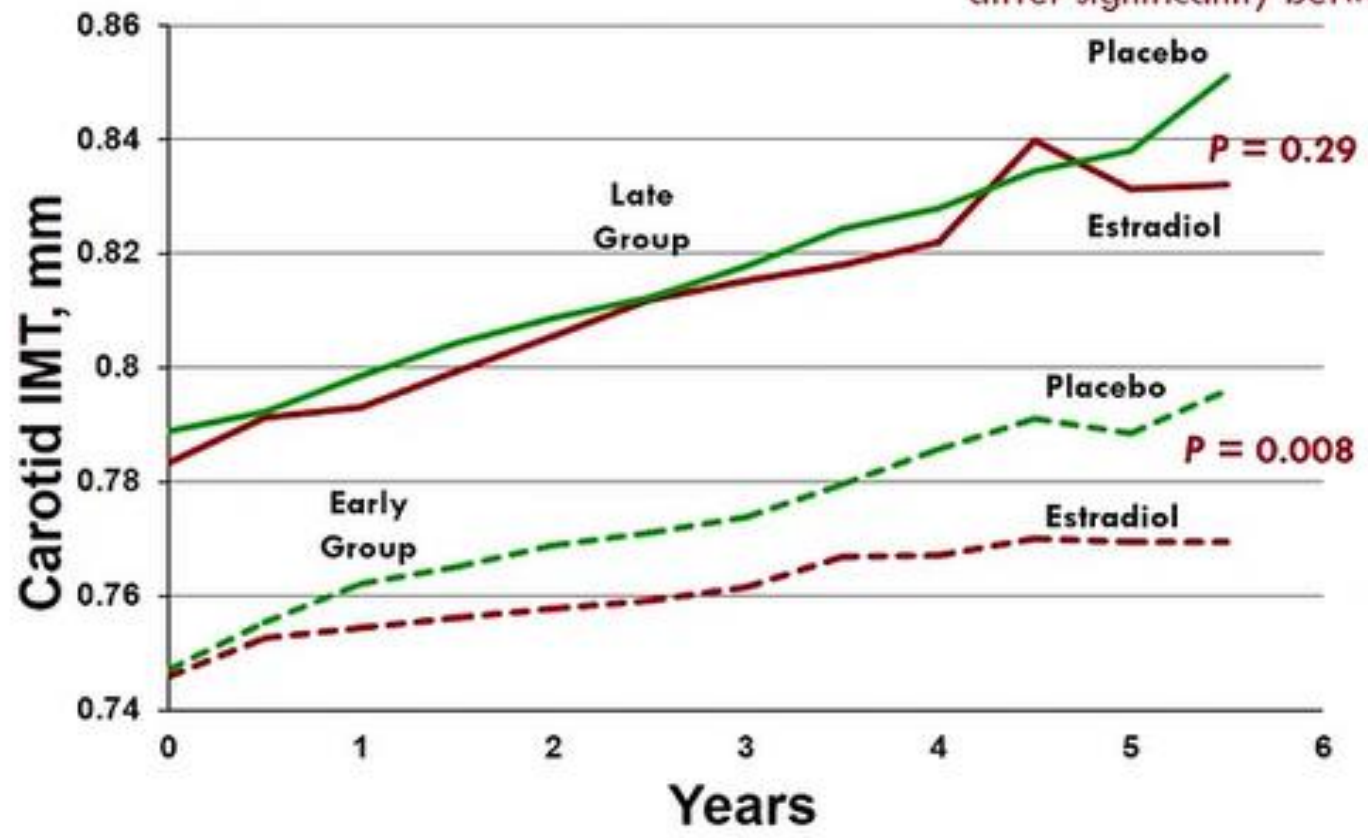
ELITE: E2 and subclinical atherosclerosis

In the early-postmenopause stratum, mean 5-year CIMT significantly lower in the estradiol group than placebo (P=0.04)
In the late-postmenopause stratum, mean 5-year CIMT did not differ significantly between estradiol and placebo groups



Hodis et al, *NEJM* 2016:347:1221

Transdermal hormone therapy

- **Based on observational data only, the use of lower doses and transdermal therapy appears to be associated with lower venous thromboembolic and stroke risk**
- **But . . . the lack of comparative randomized control trial data limits recommendations**

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Most Recent 2019- NOT RCT

RISK VTE: Adjusted odds ratios for different types of hormone therapy (HT) and different doses of oestrogen

- Risk VTE with Oral Estrogen alone-
  - conjugated estrogen had more risk than Estradiol
  - 9/10,000 women-years
- Risk VTE with Oral E+P
  - Conjugated estrogen + MPA (0.625/2.5)- most common
  - 18/10,000 women-years
- No increased risk with Transdermal-patches
  - odds ratio of 0.93 (P = .07)
- No increased risk with vaginal Estrogen
- Risk ↑ with Age and BMI

Yana Vinogradova et al. BMJ 2019;364:bmj

Consider Use of Transdermal Estrogen

First line therapy for VMS

Underlying medical conditions

- Higher risk of VTE (DVT or PE)
- High triglyceride levels
- Gall bladder disease
- Hypertension
- Metabolic syndrome/Fatty Liver

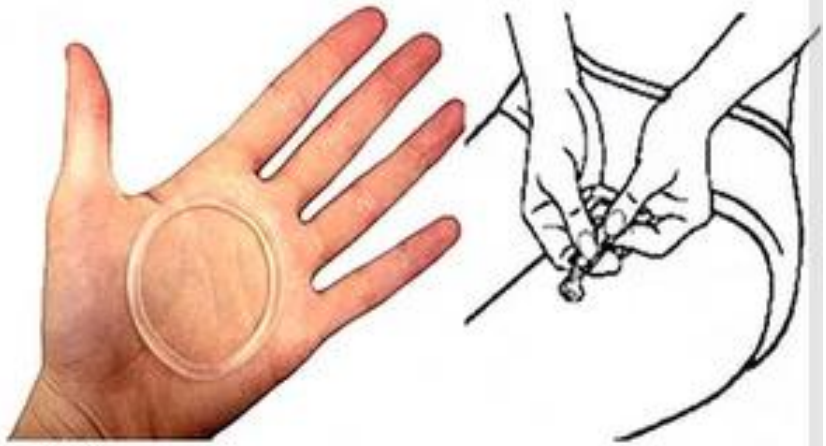
Need for "steady state" drug release

- Daily mood swings
- Migraine headaches
- Patients who do shift work OR travel

Inability to use oral tablets

- GERD/reflux on oral estrogen
- Noncompliance with taking daily pill

- **Decreased Libido and sexual arousal**
  - On oral estrogen and /or smoking
  - Increased SHBG



Endometrial protection

- For systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination conjugated equine estrogen with bazedoxifene (Level I)
- Progestogen therapy is not recommended with low-dose vaginal estrogen—1-year safety data
- Appropriate evaluation of the endometrium should be performed for vaginal bleeding (Level I)

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Hormone therapy and cognition

- Hormone therapy (HT) is not recommended for preventing or treating cognitive function or dementia
- Conjugated equine estrogen + medroxyprogesterone acetate initiated in women aged older than 65 years in the Women's Health Initiative Memory Study showed a rare increased risk for dementia
- Estrogen therapy may have positive cognitive benefits if initiated early after surgical menopause
- HT in the early postmenopause neutral on cognitive function
- Tentative support (observational studies) available for critical window hypothesis of HT in Alzheimer disease prevention

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Concerns about compounded bioidentical hormone therapy

- **Unique concerns about safety surround use of compounded bioidentical hormone therapy**
  - **Lack of regulation and monitoring**
  - **Possibility of overdosing or underdosing**
  - **Lack of scientific efficacy and safety data**
  - **Lack of a label outlining risks**
- **No evidence to support use of routine serum or salivary hormone testing**

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Compounded bioidentical hormone therapy should be avoided

- Prescribers of compounded bioidentical hormone therapy should identify and document the medical indication for compounded hormone therapy over government-approved therapies
- Such indications include allergy or the need for different dosing, formulation, or preparation

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Hormone therapy, the Women's Health Initiative, and breast cancer

- Increased risk of invasive breast cancer after 3 to
  5 years of conjugated equine estrogen 0.625 mg + medroxyprogesterone acetate 2.5 mg therapy
- No increased risk of breast cancer was seen with 7 years conjugated equine estrogen 0.625 mg alone therapy
- Allows for more flexibility in duration of estrogen therapy use in women without a uterus

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Effect of HT on risk of breast cancer: COMPLEX

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- Factors: type of HT, patient risk factors, and duration of Tx
  - Progesterone appears to have less risk of breast cancer
- WHI- very low excess risk (<1/1000) of breast cancer for patient taking combination therapy (CEE 0.625/MPA 2.5
  - similar to placebo for nonprior users of HT
  - 7 fewer breast cancer/100,000 conjugated estrogen
- DOPS- no increase risk breast cancer
- Collab Group et al Observational meta-analysis, increased EPT>ET and increasing with increasing duration of use
- NHS- increased risk ET alone by 15 yrs, significant after 20 years

NAMS 2017 HT PS

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:
  - **Significant ↓ risk breast cancer: 0.79**

JE Manson, et al. JAMA October 2, 2013

JAMA

EPT and Elevated Risk of Breast Cancer

- **What does an 1.28 HR breast cancer mean?**
  - <1 additional case per 1,000 EPT users annually can be attributed to HT (WHI)
  - HR with EPT slightly higher than that seen
    - one daily glass of wine or being sedentary
    - less than HR with 2 daily glasses
    - (Nurses Health Study)

JE Manson, et al. 2013

WY Chen, et al. 2011

Hormone therapy and family history of breast cancer

- Observational evidence shows use of hormone therapy does not alter risk for breast cancer in women with a family history of breast cancer
- Family history is one risk among many that should be assessed when counseling women on the use of hormone therapy (Level II)

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Hormone therapy and early menopause and primary ovarian insufficiency

- Data regarding hormone therapy in women aged older than 50 years should not be extrapolated to younger postmenopausal women
- Observational studies suggest benefits outweigh risks on bone, heart, cognition, vulvovaginal atrophy/ genitourinary syndrome of menopause, sexual function, and mood
- Hormone therapy recommended until at least median age of menopause (52 y)
- Younger women may require higher doses for symptom relief or protection against bone loss

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Hormone therapy and *BRCA* after oophorectomy

- **Limited observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women with a family history of breast cancer or in women after oophorectomy for *BRCA 1* or *2* gene mutation**

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Hormone therapy and prolonged duration

- Longer durations of therapy should be for documented indications such as persistent vasomotor symptoms or bone loss, with shared decision making and periodic reevaluation
- Good-quality information is lacking about prolonged duration with lower doses or transdermal products in women who initiate hormone therapy at younger ages or closer to menopause for risk of coronary heart disease or breast cancer
  - Risk may increase with longer durations of use or with age
- Recent observational data are positive
  - Finnish database (less coronary heart disease, no increased breast cancer)
  - May include healthy-user bias

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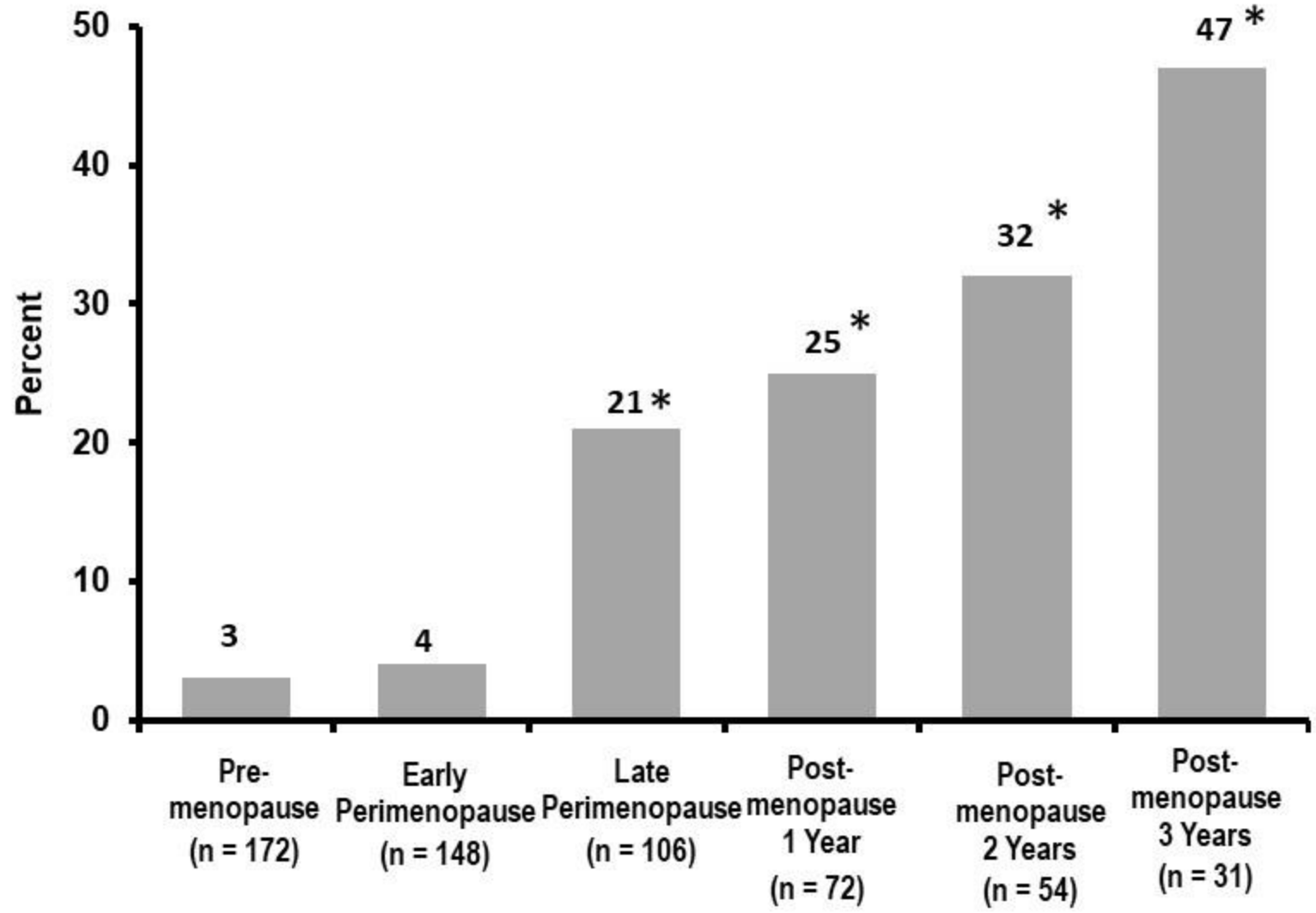
Increase in Vaginal Dryness with Aging and Years Beyond Menopause



*Dryness increased significantly in late perimenopause and postmenopause ($P < .001$)

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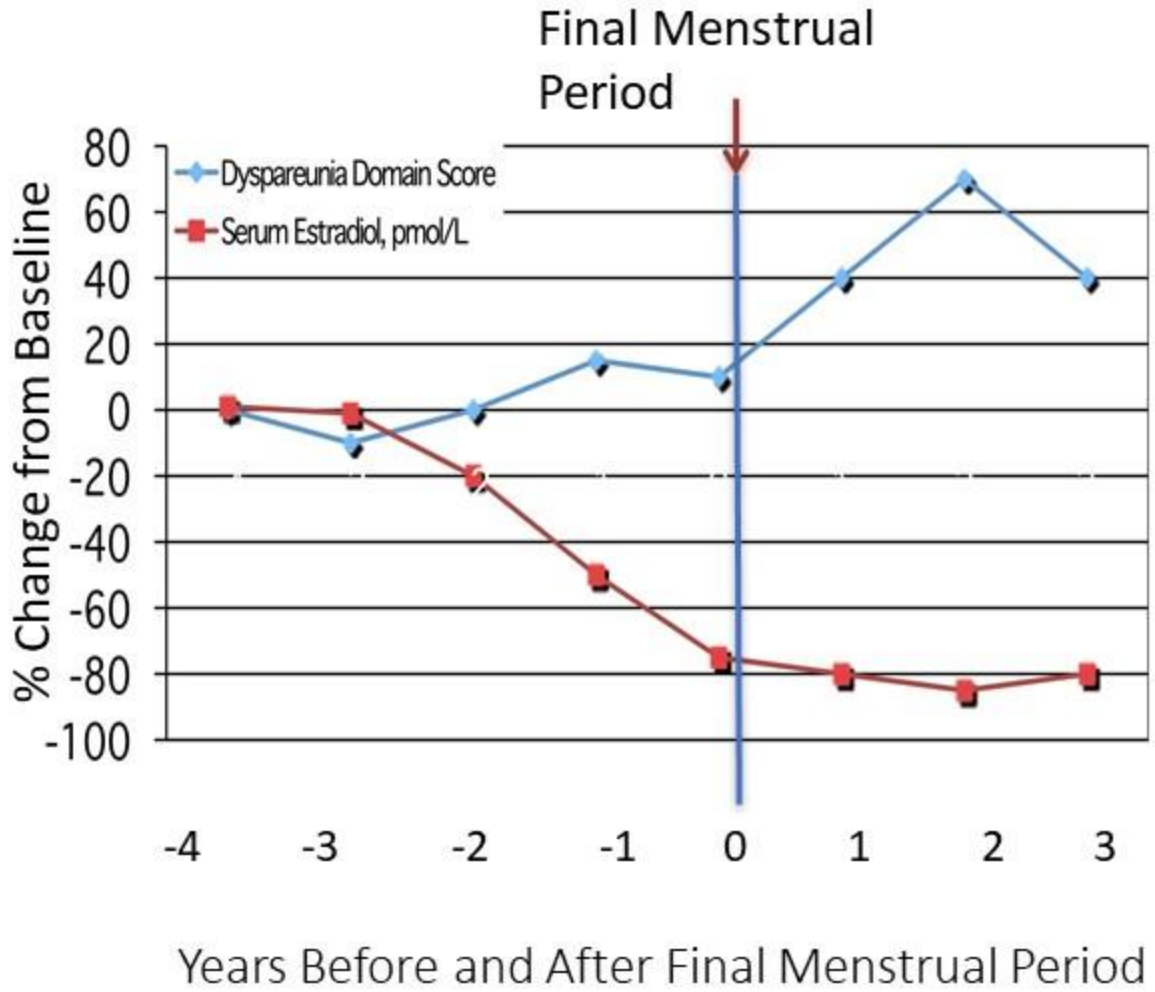
Estrogen Decline and Dyspareunia



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Hormone therapy and bothersome genitourinary syndrome of menopause (vulvovaginal atrophy)

- Low-dose vaginal estrogen effective and safe for treatment of vulvovaginal atrophy, with minimal systemic absorption
- Advised when estrogen therapy is considered only for symptoms of the genitourinary syndrome of menopause (vulvovaginal atrophy)
- Nonestrogen alternatives approved for dyspareunia include ospemifene and intravaginal dehydroepiandrosterone

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Low-dose vaginal estrogen and survivors of breast cancer with bothersome genitourinary syndrome of menopause

- **Low-dose vaginal estrogen therapy (ET)**
  - **Minimal systemic absorption**
    - **Blood levels in postmenopause range**
  - **Based on limited data, minimal risk for recurrence of breast cancer (Level II)**
- **For survivors of breast cancer with bothersome genitourinary syndrome of menopause symptoms, low-dose vaginal ET may be an option**
  - **After a failed trial of nonhormone therapies**
  - **In consultation with an oncologist**
  - **Concern even with low-dose vaginal ET for women on aromatase inhibitors because of suppressed estradiol levels (Level III)**

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The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

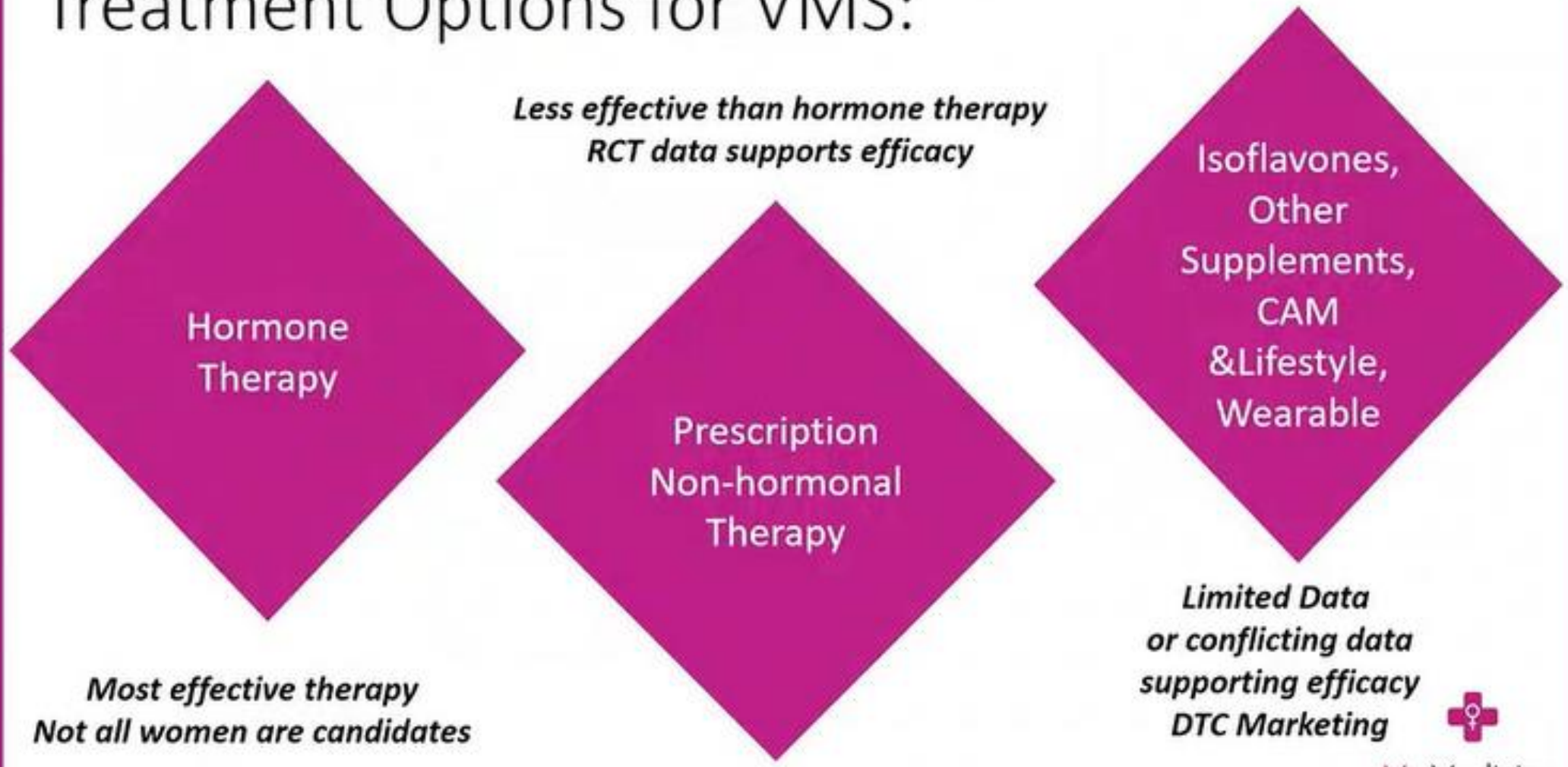
Number 659 • March 2016
Reaffirmed 2018

Committee on Gynecologic Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Member contributors included Ruth Farrell, MD. *This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer

Treatment Options for VMS:



Ms.Medicine

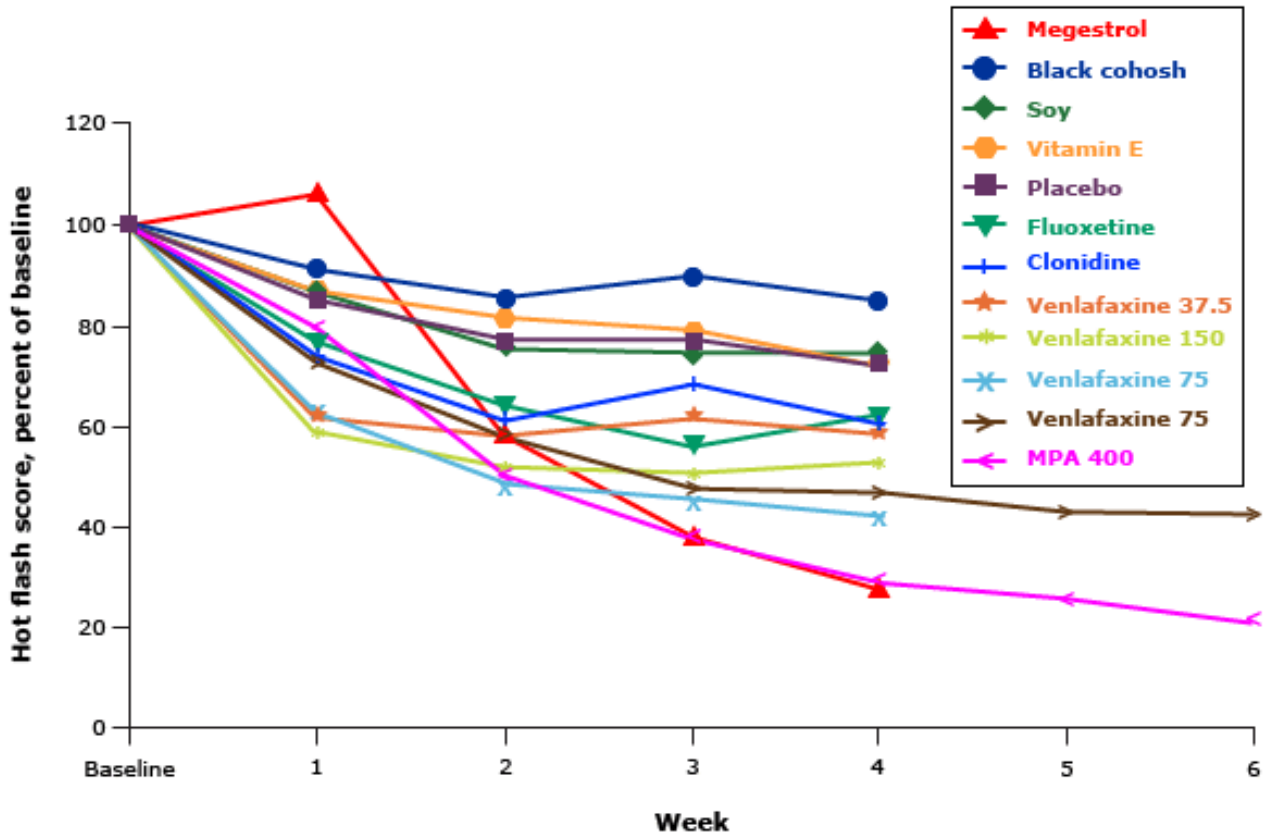
Paroxetine Mesylate 7.5 mg (Brisdelle)

- First and only nonhormonal medication approved by the FDA (2013) to treat moderate to severe VMS
- SSRI; Low dose compared to typical antidepressant doses
- RCT 1184 menopausal women with median 10 hot flushes per day. At 12 weeks:
  - Placebo reduction 3.9 hot flushes per day
  - Paroxetine mesylate reduction 5.6 hot flushes per day
- RCT in 80 gyne cancer survivors reduced VMS frequency and severity
- **Sustained benefit in reducing VMS and improving sleep, and well tolerated**
- No impact on weight or libido
- Potent CYP26 inhibitor; avoid use in patient on Tamoxifen

Simon JA et al Menopause 2013;20 (10): 1027-1035
Capriglione *GynecolOncol*2016

Ms.Medicine

Therapies hot flashes



Hot flash score changes from baseline for a series of eight randomized, placebo-controlled trials, plus a trial in which women were randomized to venlafaxine (75 mg/day) versus a single dose (400 mg) of intramuscular medroxyprogesterone acetate. Six week data shown for the latter trial.

Reproduced with permission from: Loprinzi CL, Barton DL, Sloan JA, et al. Mayo Clinic and North Central Cancer Treatment Group hot flash studies: a 20-year experience. Menopause 2008; 15:655.

Gabapentin

- Large RCT's shows efficacy in reducing VMS (doses 600-2400mg)
- AE: dizziness, sedation, lethargy
- Particularly good for patients with sleep disturbance
- Start 100 mg qhs; titrate to 300 mg qhs and if needed increase to 300mg bid/tid and increase to 600 tid if needed
- Combination with a SSRI or SSNRI- no added benefit
- No inhibition of CYP2D6. First choice for VMS treatment in non depressed patients on tamoxifen

Reddy SY et al Obstet Gynecol. 2006;108 (1);41-48
Loprinzi et al J Clin Oncol. 2010; 28 (4): 641-647 Desmarais, JE Maturitas 67 (2010) 296-308

Oxybutynin

- Antimuscarinic, anticholinergic agent, FDA approved for OAB
- 2 RCT in women with VMS to date; Other studies in men on androgen deprivation
- Simon et al (2016)
  - Oxybutinin ER 15 mg vs placebo
  - Improved VMS frequency and severity
  - Oxybutynin 73% compared to placebo 26.1% “much better”
- Leon-Ferre et al (Presented SABC Dec 2018, submitted)
  - Oxybutynin 5 mg, 2.5 mg, vs placebo
  - VMS reduction 75% 5 mg, 60% 2.5 mg, 30% placebo

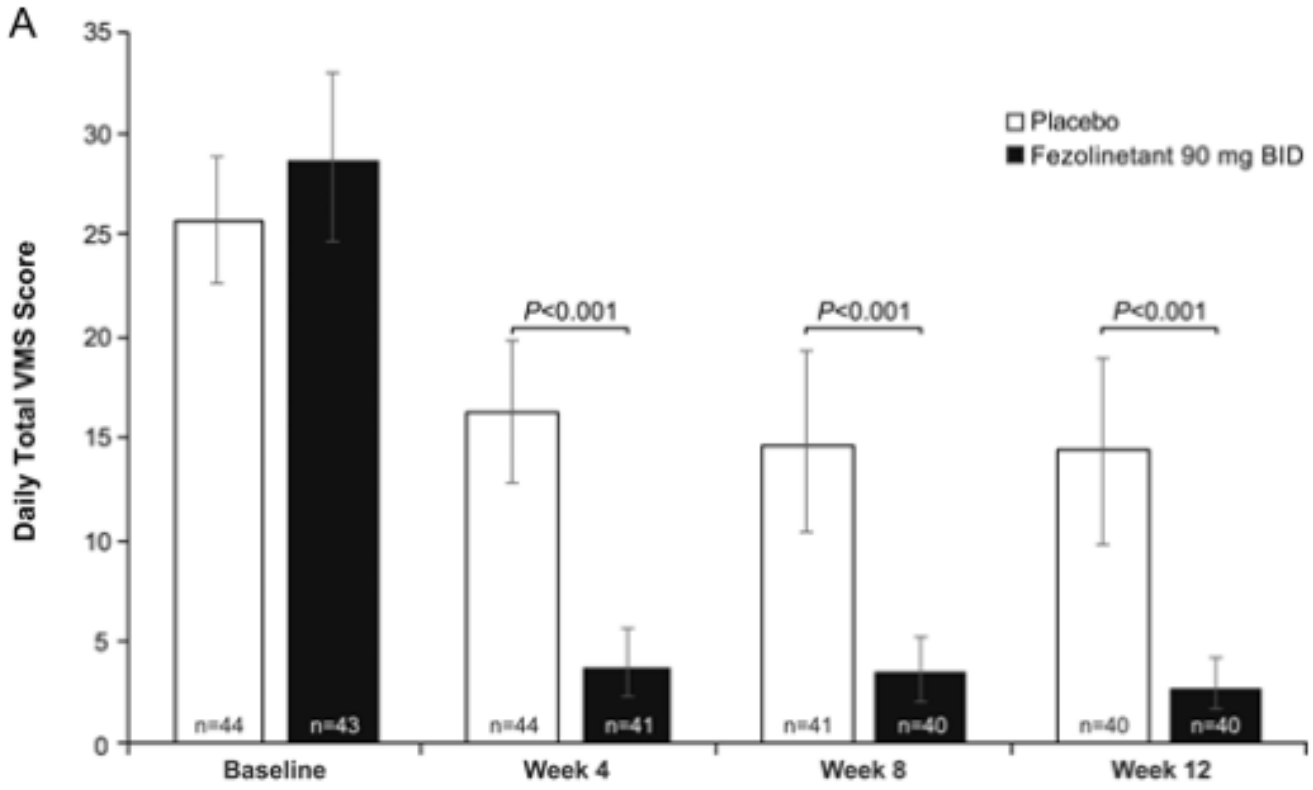
Simon JA et al. Menopause.2016;23(11):1214-1221.
Leon-Ferre et al. Presented SABC December 2018

In Development: Neurokinin 3 Receptor Antagonists

- Kisspeptin-neurokinin B (NKB) neurons are a key link between the hypothalamic GnRH axis and vasomotor symptoms
- NK3 receptor antagonists blocks NKB signaling
- One small proof of concept phase 2 RCT of oral NK3 receptor antagonist in 28 women with VMS
- Placebo vs MLE4901 40 mg bid for 4 weeks
- Results:
  - 73% reduction in VMS with MLE4901 compared to 28% placebo
  - 41% reduction in VMS severity relative to placebo
- 3/28 women developed increased LFT's

Prague et al. Lancet.2017.doi.org/10.1016/S0140-6736(17)30823-1

Figure 2.



The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 12, December 2019, Pages 5893–5905, https://doi.org/10.1210/jc.2019-00677

Thank

you