New Horizons in Managing Menopause:

Managed Care Considerations for Improved Outcomes

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Health Impact and Prevalence of Menopause

Gary Owens, MD

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Menopause is often associated with the following comorbidities: hypertension, osteoporosis, and depression.

How much annual healthcare spending is directly attributed to menopause with these comorbidities?

a) $7.5 billion annually
b) $10.2 billion annually
c) $18 billion annually
d) $22.5 billion annually
e) None of the above

Menopause Definition and Overview

The worldwide prevalence of menopause is estimated to be about **50 million cases** annually. Worldwide, menopause naturally occurs in women between **49 to 52 years** of age on average.

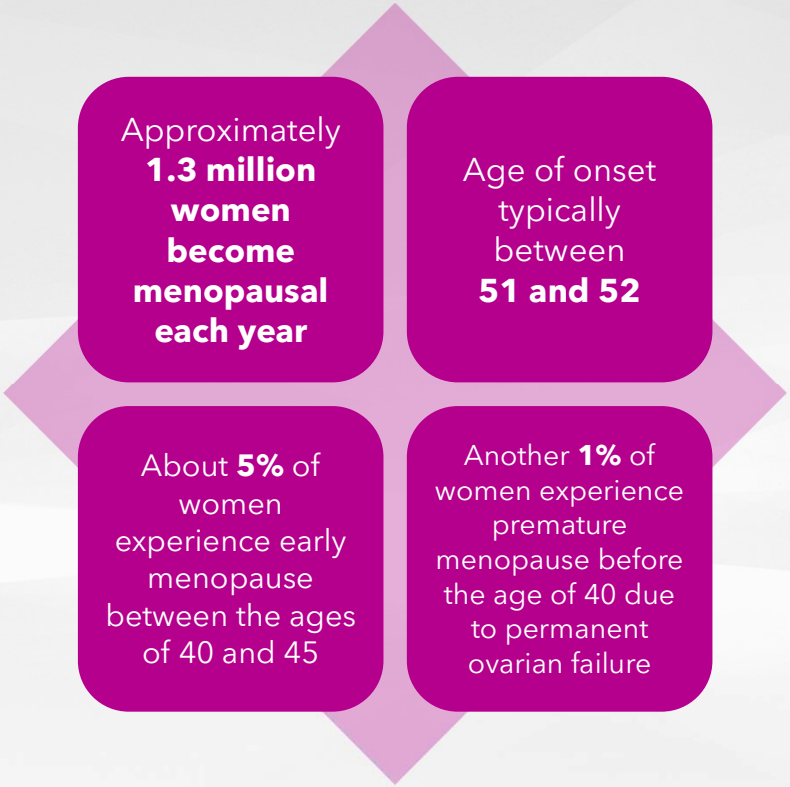
Menopausal transition begins, on average, 4 years before the final menstrual period and includes a number of physiologic changes that may affect a woman's QoL.

Virtually all women experience menstrual irregularity and hormonal fluctuations prior to clinical menopause; up to **80% develop hot flashes** (the most common menopausal symptom), but only a relatively **small percent seek medical attention** for them.

Taffe JR, Dennerstein L. Menstrual patterns leading to the final menstrual period. *Menopause*. 2002;9(1):32-40.

Miro F, Parker SW, Aspinall LJ, et al. Origins and consequences of the elongation of the human menstrual cycle during the menopausal transition: the FREEDOM Study. *J Clin Endocrinol Metab*. 2004;89(10):4910-4915.

US Statistics on Menopause



United States

Peacock K, Ketvertis KM. Menopause [Updated 2022 Feb 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507826/

Common Symptoms of Menopause

- Common symptoms include:
  - Irregular menstrual cycles and marked hormonal fluctuations
  - **Vasomotor symptoms—hot flashes are the most frequent symptom**
  - Frequent sleep disturbances
  - Mood symptoms (depression is common)
  - Vaginal dryness
- Changes in lipids and bone loss begin to occur:
  - Implications for long-term health and need for additional management

Miro F, Parker SW, Aspinall LJ, et al. Origins and consequences of the elongation of the human menstrual cycle during the menopausal transition: the FREEDOM Study. *J Clin Endocrinol Metab*. 2004;89(10):4910-4915.

Timing of Onset, Race/Ethnicity, and Other Factors Influence VMS Duration

- Median duration of VMS for African American women:
  - 10.1 years
- VMS that start in pre- or early perimenopause last longer!
  - Median 11.8 years
- Predictors of long duration:
  - Younger age at onset, smoking, high BMI, worse overall symptoms, stress
- VMS that start post menopause:
  - Median duration 3.4 years
- Predictors of short duration:
  - Japanese or Chinese heritage, being married or partnered, less financial stress, and more social support

Avis NE. *JAMA Intern Med*. 2015;175(4):531-539.

Burden of VMS

- Prevalence
  - 65% to 79% of women*
  - 7% to 9% with 7+ moderate to severe VMS daily
- In QoL study†, hot flashes negatively affected
  - Sleep (82%)
  - Concentration (69%)
  - Mood (68%)
  - Energy levels (63%)
  - Work (46%)
  - Social activities (44%)

*N = 4,402; †N = 2,703

Williams RE, et al. *Climacteric*. 2008;11(1):32-43. Williams RE, et al. *Maturitas*. 2009;62(2):153-159.

Natural History of Hot Flashes

Transition stage	% Affected
Premenopause[1]	20% to 45%
Premenopause to early perimenopause[1]	25% to 55%
Early to late perimenopause[1,2]	50% to 80%
Late perimenopause to postmenopause[1,2]	35% to 75%
Late postmenopause (>5 yr)[2, 3]	16% to 44%

1. Gold EB, et al. *Am J Pub Health.* 2006;96(7):1226-1235. 2. Politi MC, et al. *J Gen Intern Med.* 2008;23(9):1507-1513.
3. Barnabei VM, et al. *Obstet Gynecol.* 2002;100(6):1209-1218.

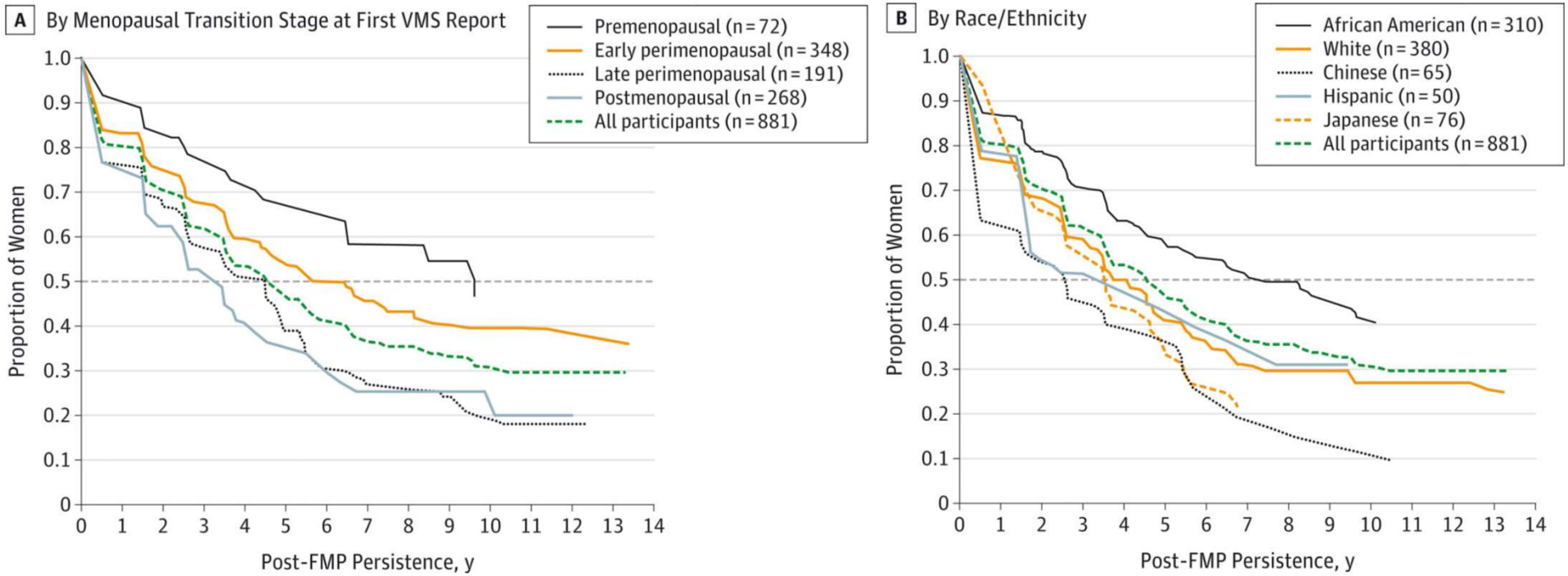
Hot Flashes Last Longer Than Previously Believed

- 3,302 women from 7 US sites, followed for 17 years
  - Median total VMS duration: 7.4 years
  - >50% of women had duration >7 years of frequent VMS*
  - >50% of women had >4 years post-FMP persistence of frequent VMS

*≥6 days over the past 2 weeks.

Avis NE. *JAMA Intern Med*. 2015;175(4):531-539.

Total Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition



JAMA Network™

Avis NE, et al. *JAMA Intern Med*. 2015;175(4):531-539.

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How Many Women Seek Treatment for Symptoms?

- Population-based survey of women aged 40 to 65
- 60% sought care for symptoms
- Most common symptom: hot flashes
  - 34% used hormone therapy
  - 12% used complementary and alternative medicine
  - 16% used both
  - ***That leaves 38% of women untreated***

*N = 3,135

Williams RE, et al. *Maturitas*. 2007;58(4):348-358.

Menopause Unmet Needs

- Clinically understudied
- Education about menopause journey and being a self-advocate is empowering
- Many clinicians lack training and familiarity with patient needs and symptoms
  - Even when symptoms addressed, there is underutilization of…
    - > hormone therapy for hot flashes (low-dose vaginal estrogen for vaginal dryness and its consequences)
    - > antidepressants for mood disorders
    - > nonhormonal medications for related conditions
    - > behavioral strategies for related symptoms and health conditions
- Research about pathophysiology and epidemiology across diverse populations and the efficacy of treatments for symptom management is needed

Society for Women's Healthcare Research. It's Time for a Mood Change on Menopause. February 3, 2021. Accessed February 22, 2022.

Increased Economic Burden of Menopause: Cost of Co-Morbidities and Impact on Productivity

2005 Study of 4,116 women with menopausal symptoms compared to 4,695 without

Significant findings:

- Decreased quality of life
- Increased work impairment
- Higher healthcare resource utilization
- Depression, anxiety, and joint stiffness
  - Strongest association with health outcomes and resource utilization

2016 study on women of low socioeconomic status showed:

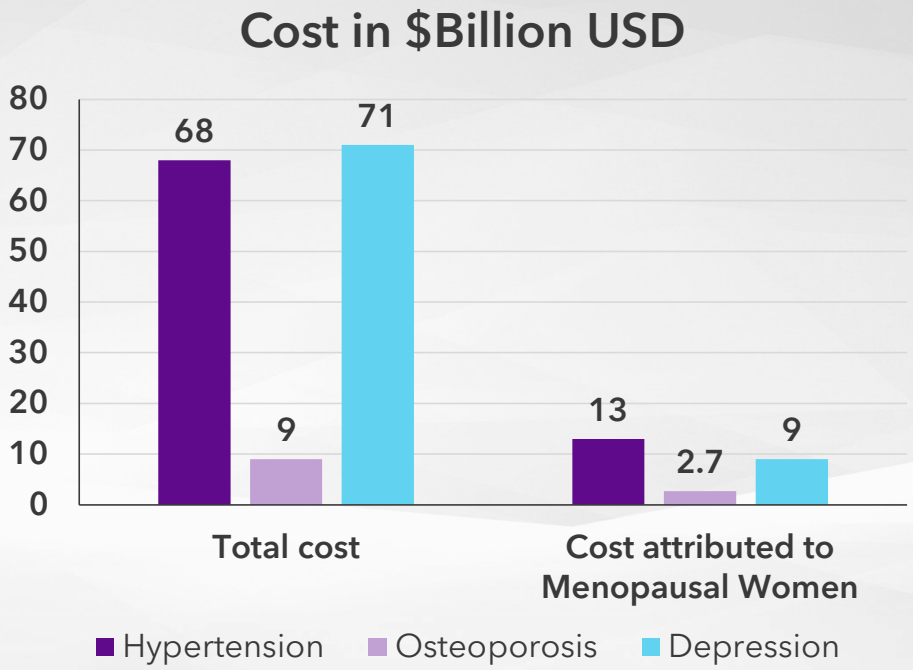
- Patients with menopausal symptoms more likely to have depression and anxiety
- Resulted in higher healthcare costs ($7,237 vs $6,739, $P < 0.001$) and healthcare utilization for the 6-month follow-up period

Whiteley J, et al. *J Womens Health (Larchmt)*. 2013;22(11):983-990. Keshishian A, et al. *Expert Rev Pharmacoecon Outcomes Res*. 2016;16(2):305-313.

Societal and Work Implications

American employers may experience **$770 in productivity losses** per menopausal woman/year

Substantial health costs can be attributed to menopause—nearly **$18 billion annually for common comorbidities**



Elektra Health. The Menopause Care Gap is Costing You Serious Money. February 21, 2020. Accessed February 24, 2022.

Summary

- Menopause and symptoms affect 1.3 million women/year in US
- Symptoms are frequent and often have a major impact on QoL, work productivity, health outcomes, and **ultimately healthcare cost**
- Women often don't seek treatment
  - Undertreated when they do seek care
- Unmet needs include
  - More clinical research
  - Better patient education
  - Better clinician education on use of effective treatments (eg, hormonal and nonhormonal treatments and behavioral health strategies)

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Menopause Pathophysiology

Anita Nelson, MD

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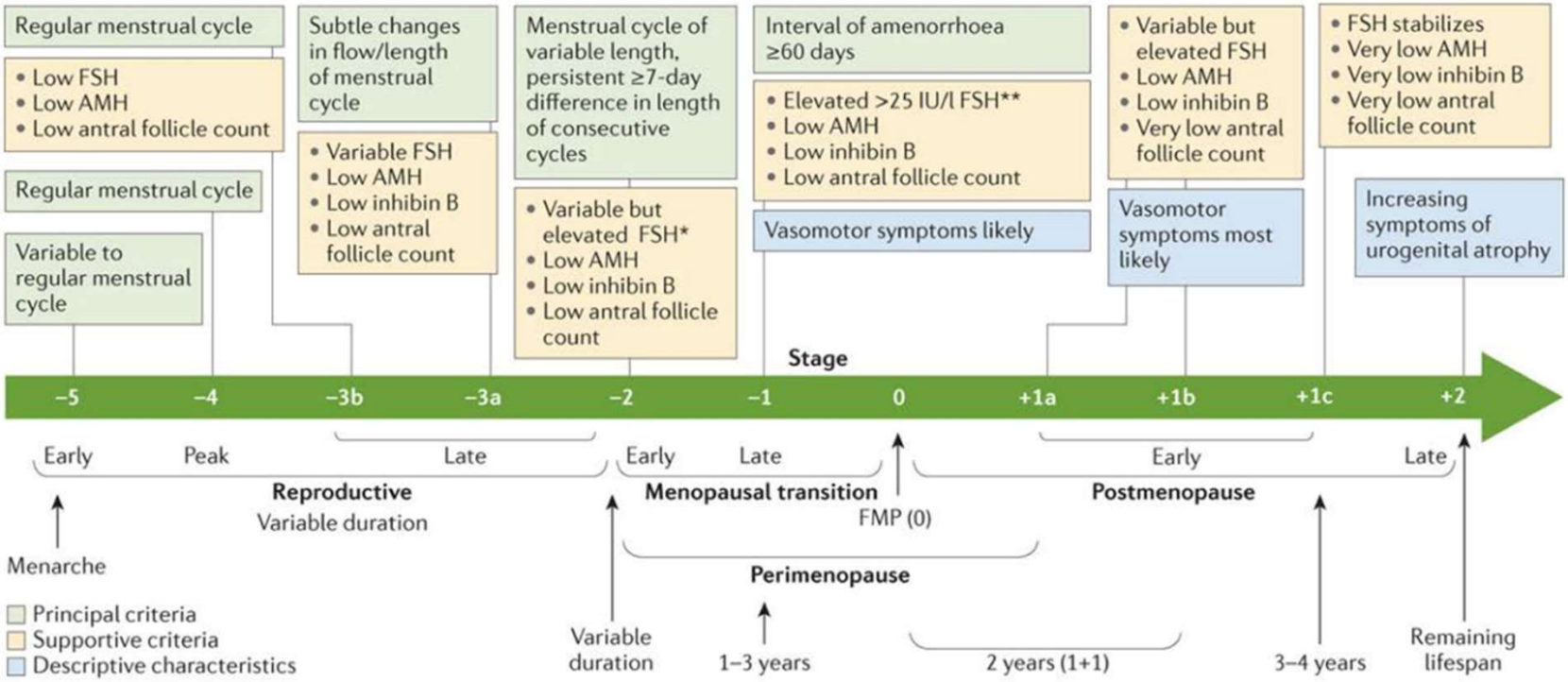
Which of the following best explains how the loss of estrogen is responsible for vasomotor symptoms in menopausal women?

a) The thermoregulatory zone expands with the loss of estrogen
b) The GnRH pulse generator in the hypothalamus excites the adjacent temperature control center
c) High levels of FSH cause vasodilatation and sweating
d) The lack of follicles reduces blood flow to the brain

STRAW +10 Staging for Reproductive Age in Women



El Khoudary SR, et al. *Circulation.* 2020;142(25):e506-e532.

Menopause or Something Else?

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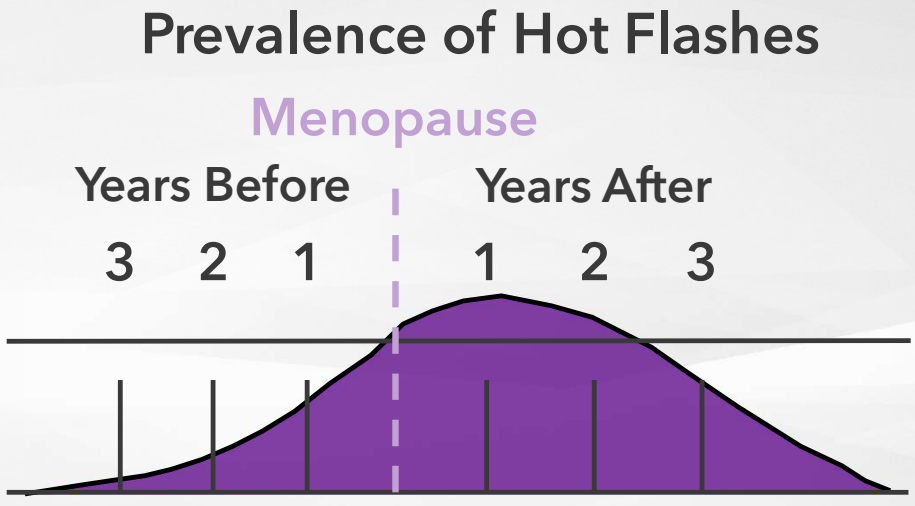
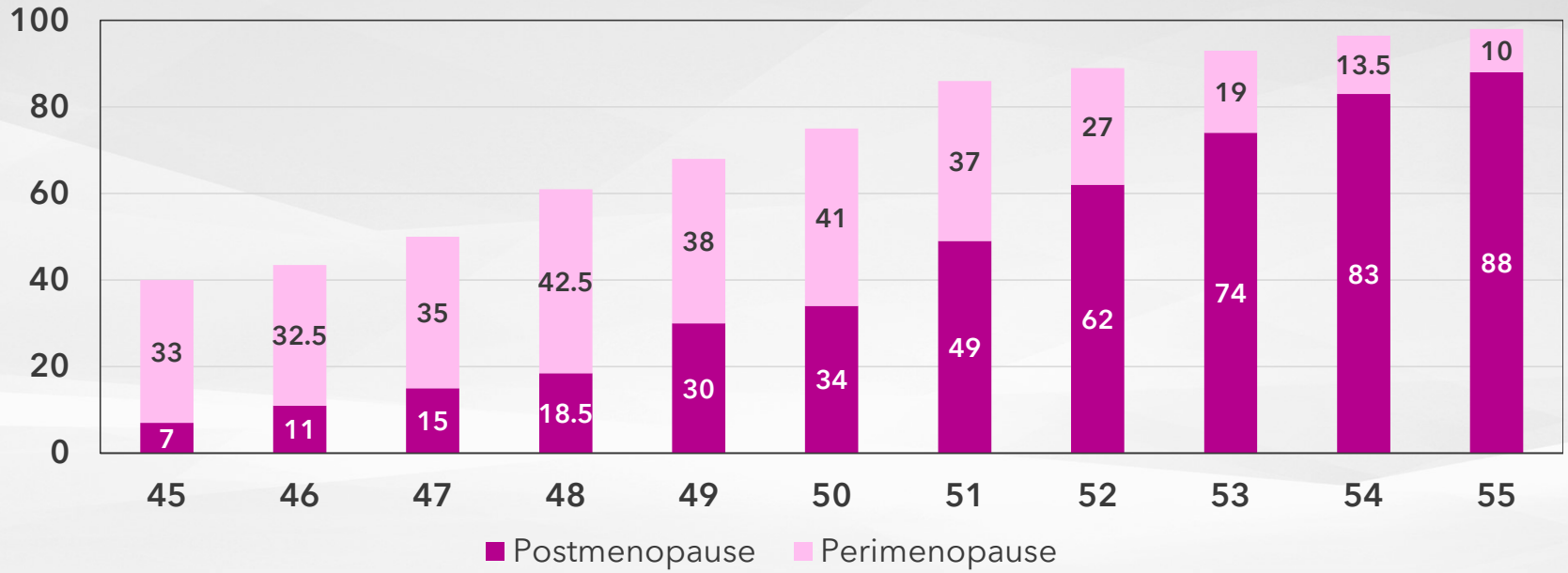
Vasomotor Symptoms: Prevalence

- >75% of women report hot flashes within the 2-year period surrounding their menopause
- Primary reason women seek medical treatment
- 25% remain symptomatic for >5 years



Kronenberg F. *Ann N Y Acad Sci.* 1990;592:52-86.

Percentage of Women at Perimenopause and Postmenopause by Age



- Median age of onset for perimenopause was 47.5 years
- Median age of onset for menopause was 51.3 years

McKinlay SM, et al. *Maturitas*. 1992;14(2):103-115.

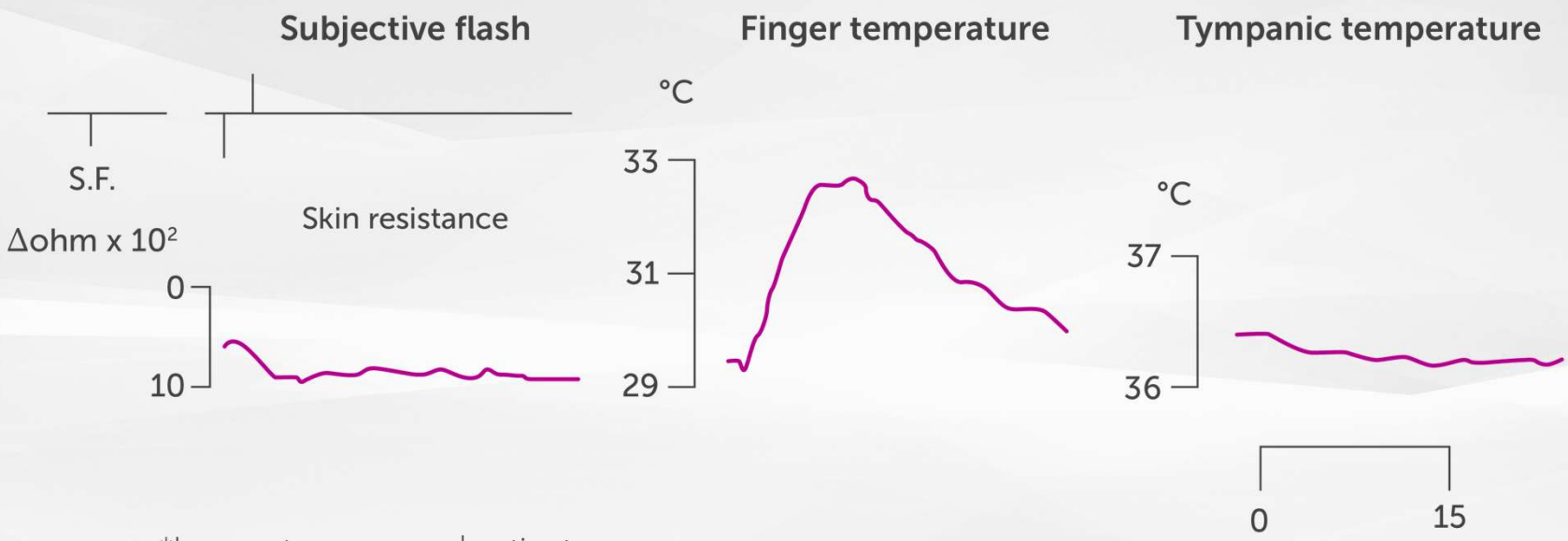
Vasomotor Symptom Complex

- Heart rate increases
- Respiratory rate increases
- Sudden sensation of warmth
- Flush begins in thorax and neck and extends to face and down arms
- Profuse perspiration follows in same area
- Women can perceive flash before any of the characteristic changes can be measured
- Nonspecific complaints that result from sleep disruption and interruption:
  - Irritability, anxiety, nervousness, depression, fatigue, forgetfulness, and inability to concentrate

Physiologic Changes with Hot Flashes

- Hot flash perceived duration: 2.7 minutes
  - Physiologic changes: 20-30 minutes
- Without any premonitory signs:
  - Finger temperature increases 7.5° F
  - Pulse rate increases 9-20 BPM
  - Skin conduction increases

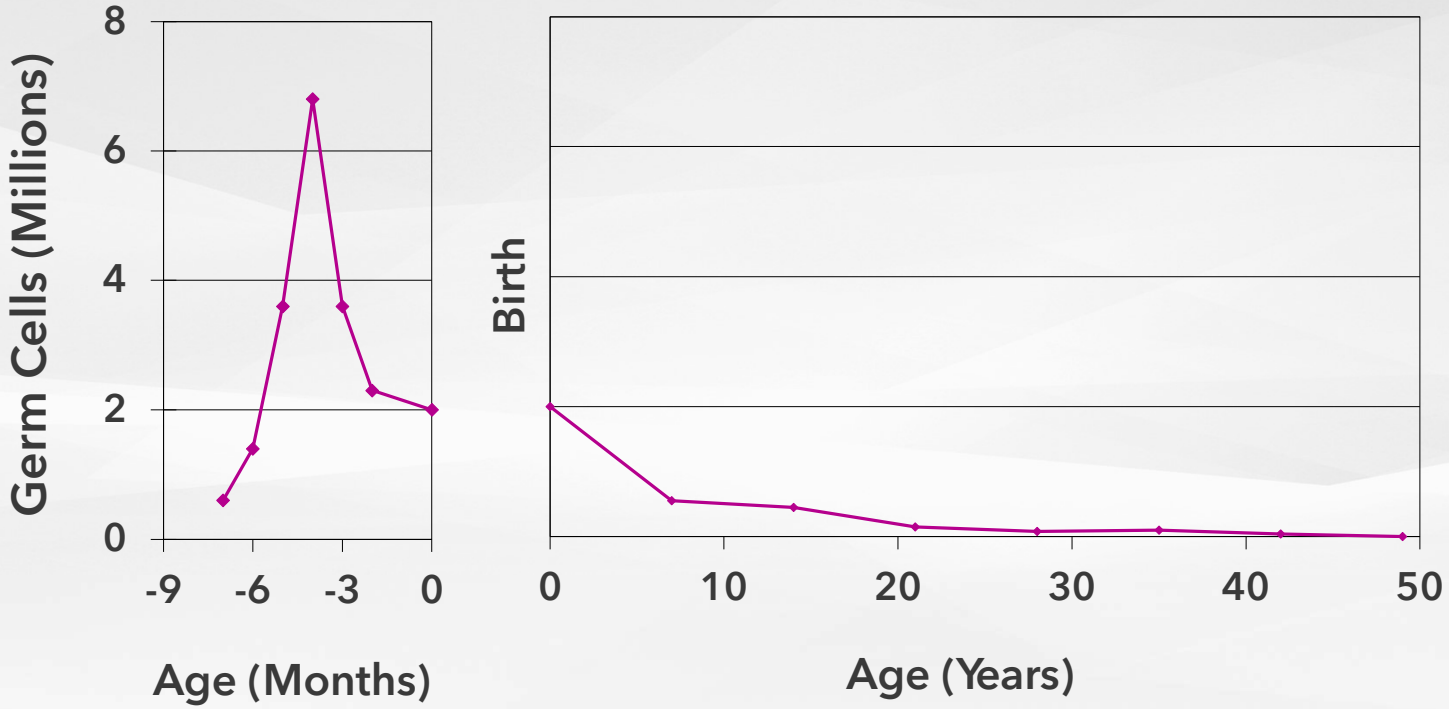
Finger and Core Temperatures and Skin Resistance During Hot Flash Episode*



*In a postmenopausal patient

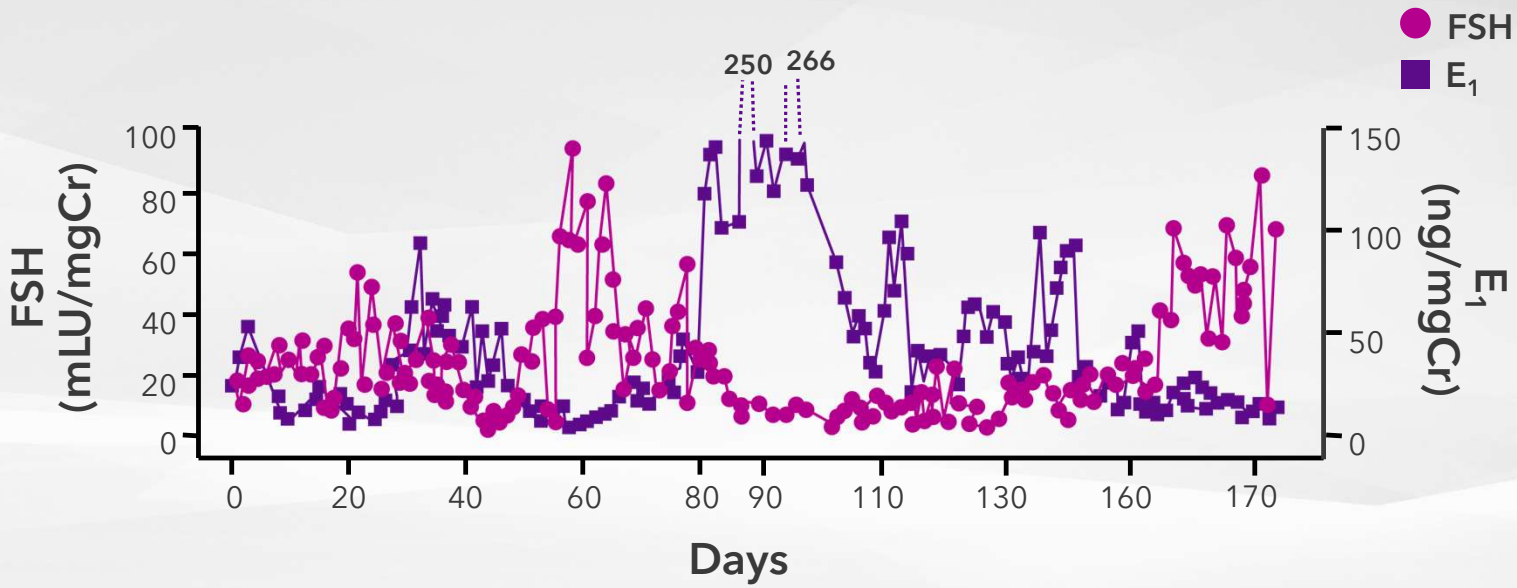
Tataryn IV, et al. *Obstet Gynecol.* 1981;57(3):340-344.

Changes in Total Number of Oocytes (Follicles) in the Human Ovaries During Aging



Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. 7th ed. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2005.

FSH and E_1 Variability in a Perimenopausal Woman



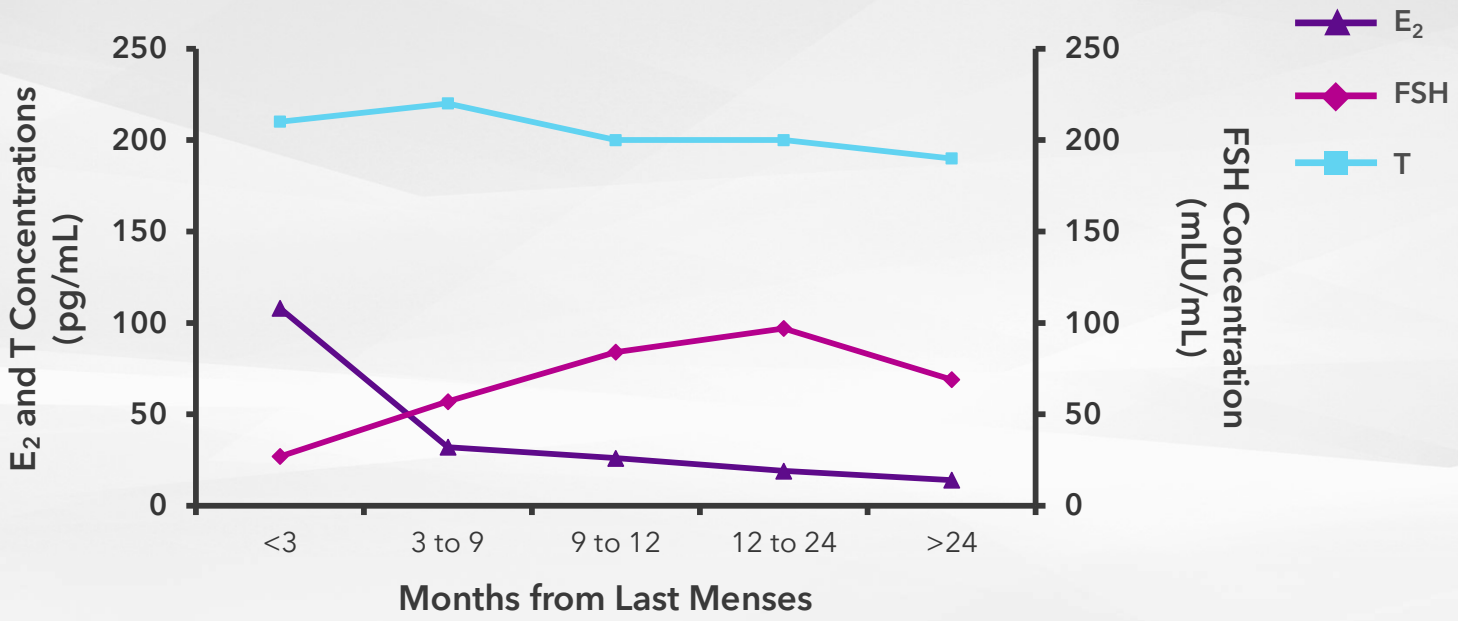
FSH variability makes diagnosing menopause using a single FSH value unreliable. Estrogen variability may account for perimenopausal menstrual irregularities.

Santoro N, et al. *J Clin Endocrinol Metab*. 1996;81(4):1495-1501.
Prior JC. *Endocr Rev*. 1998;19(4):397-428.

Endocrinology of Menopause

- Ovarian event
  - Depletion of number of follicles
  - Decreased sensitivity of the few remaining follicles
- Gonadotrophins elevated
  - FSH increases more than LH
- Ovarian secretion of estrogens decreases

Hormonal Changes in Perimenopausal and Postmenopausal Women After Last Menses



Mean concentrations of estradiol (E_2), FSH, and testosterone (T) stratified by months from last menses

Longcope C, et al. *Maturitas*. 1986;8(3):189-196.

Putting the Pieces Together: Reproductive Years Versus Menopause

- Ventral hypothalamus sends pulses of GnRH to the pituitary to stimulate release of hormones (FSH and LH) to direct ovaries to make hormones
- Hypothalamus and pituitary monitor serum estrogen levels and adjust stimulation to match what is needed next in the cycle
- In menopause, there are few responsive follicles; estrogen levels are low
- Hypothalamus and pituitary go into overdrive trying to stimulate ovaries
  - GnRH pulses intensify and FSH and LH levels rise

Menopause Neuroendocrinology: Animal Model

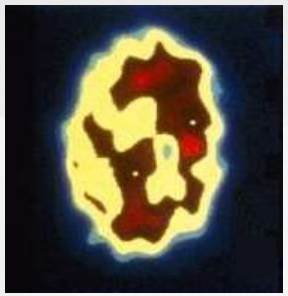
- Hypothesis: Neuroendocrine axis controls transition from regular to irregular cycles, but ovary determines cessation of cycles
  - Transplantation of old ovaries into reproductive-aged, previously oophorectomized animals results in follicular development and ovulation
  - Grafting young ovaries into old animals does not restore cycling

Another Piece of the Puzzle: How Does That Cause Hot Flashes?

- Ventral hypothalamus (GnRH pulse generator) is adjacent to thermoregulation center
  - Small temperature variations stay within "thermoregulatory zone" and are well tolerated
  - Over the limits, trigger whole body responses
- GnRH pulses can trigger rise in the set point for body temperature
  - If temperature rises above "thermoregulatory zone," body tries to cool down using mechanisms to break a fever
    - > Diverting blood from warm core to periphery
    - > Dilating peripheral blood vessels (flushing)
    - > Perspiring to radiate off heat

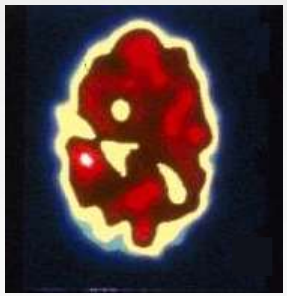
Cerebral and Peripheral Blood Flow During a Flash & Euestrogenism

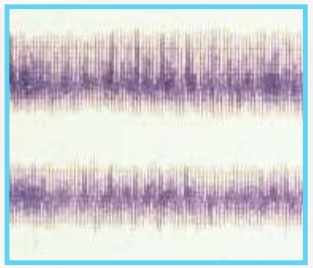
During a Flash

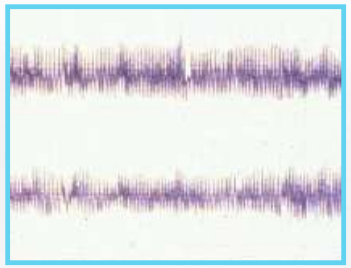


mL/100g/min

Euestrogenism







Where Does This Leave Us?

- Why do some women have hot flashes and others do not?
  - Differences in the width of their thermoregulatory zones
- This helps us understand why some agents help reduce hot flash frequency
  - Both estrogen and SSRI/SNRIs broaden the thermoregulatory zone
  - A new target for therapies?
- **But what controls the GnRH pulse generator?**

Different Hot Flash-Related Thermoregulatory Thresholds

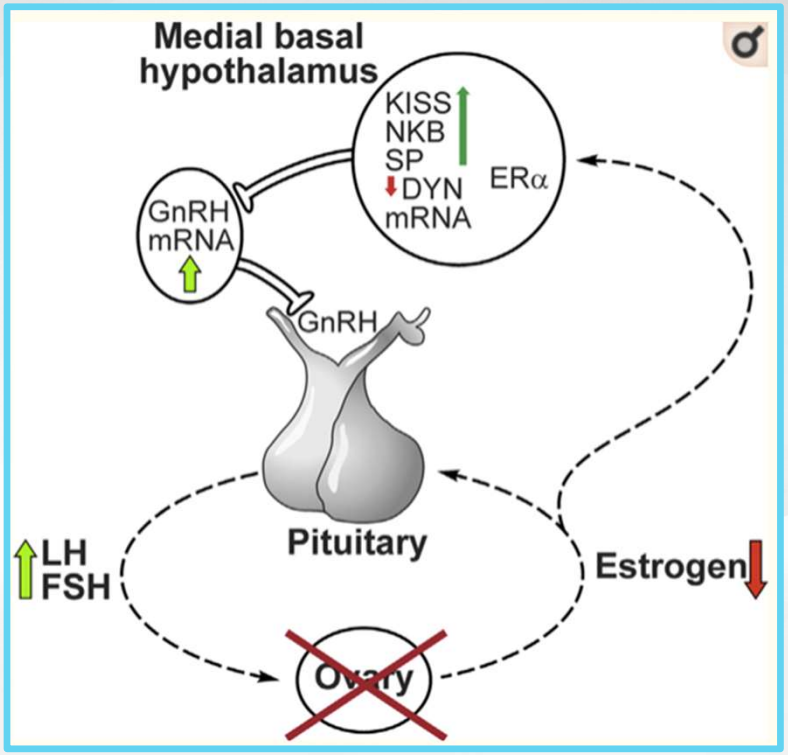
	Symptomatic Women	Asymptomatic Women	*P* Value
T_c sweat threshold (°C)	36.88 ± 0.06	37.42 ± 0.06	0.001
Basal rectal (°C)	36.82 ± 0.09	37.12 ± 0.07	0.023
Maximum sweat rate ($mg/cm^2/min$)	0.200 ± 0.015	0.128 ± 0.020	0.0001

No difference in BMI, E2, P4, or skin fold thickness

Freedman RR, et al. *Menopause*. 2005;12(2):156-159.

KNDy Neuron Circuitry

- VMS caused by a loss of thermoregulatory control coincident with the altered KNDy signaling triggered by menopause
- KNDy neurons are stimulated by NKB and inhibited by estrogen
- As estrogen declines
  - Activity of KNDy neurons changes activity in brain regions these neurons innervate
  - Impacts thermoregulation from median preoptic nucleus

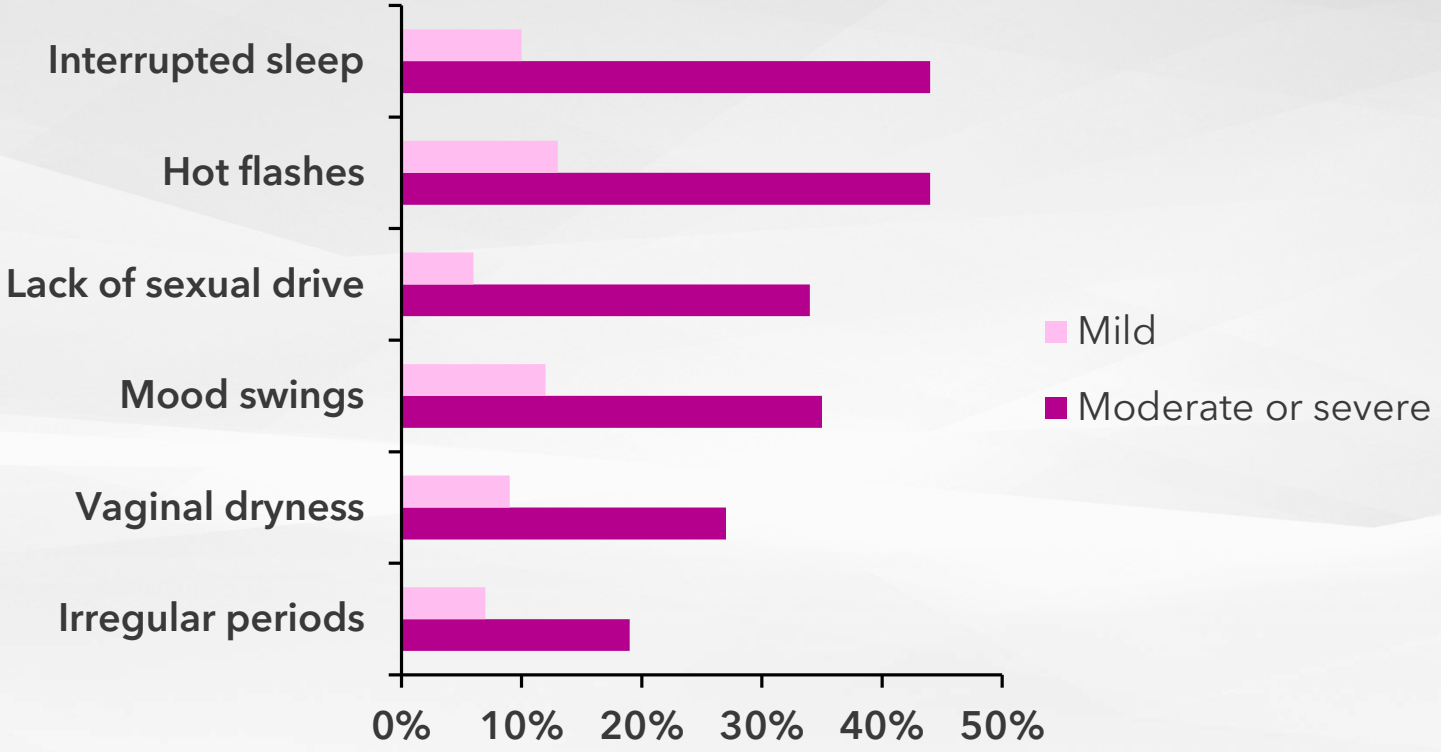


Rance NE, et al. *Front Neuroendocrinol*. 2013;34(3):211-227.

Vasomotor Symptoms: Impacts and Causes

- Decreased sleep quality
- Difficulty concentrating
- Irritability
- Reduced Quality of Life (QoL)
- Poor health status
- With decreasing estrogen, the thermoregulation zone narrows
  - Temperature excursions outside that zone perpetuate symptoms

Percentage of Women Currently Experiencing Menopause Symptoms



http://www.endo-society.org/endo_news/2012/upload/Endocrine-News-November-2012.pdf

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Longer-Term Health Risks

- As women age and estrogen levels fall, risk is increased from
  - Genitourinary syndrome of menopause
  - Osteoporosis
  - Cardiovascular disease
  - Cognitive decline
- Questions: After 20 years. . .
  - Which of these menopausal changes can hormone therapy (HT) treat?
  - What are the risks of postmenopausal HT?

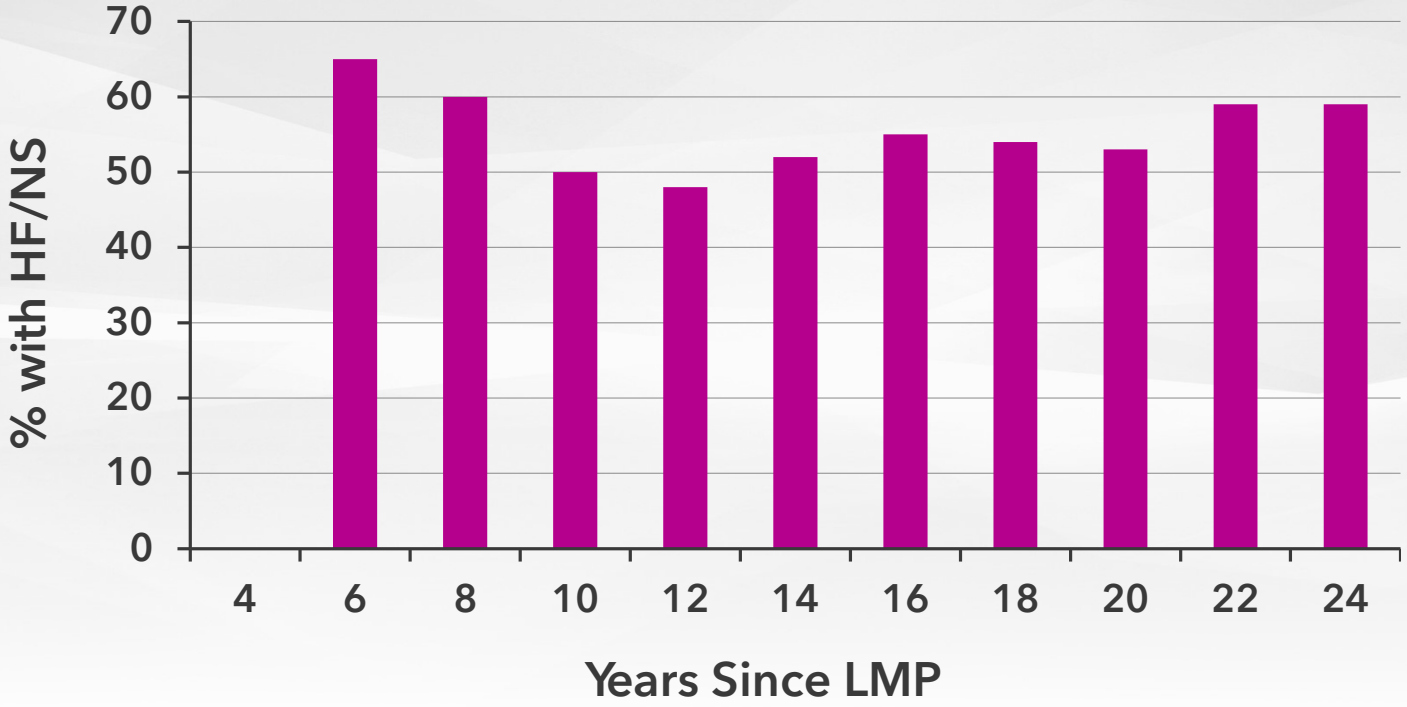
How Long, Oh Lord?

	Median Duration (years)
All women	10.20
Hot flashes started	
Entry to transition	11.57
Early in transition	7.25
Late transition	3.84

Duration of moderate to severe hot flashes

Freeman EW, et al. *Obstet Gynecol*. 2011;117(5):1095-1104.

Hot Flashes: Prevalence, Frequency, and Intensity in Older Postmenopausal Women



Hunter MS, et al. *BJOG*. 2011;119(1):40-50.

Duration of VMS: SWAN[1]

- 1,449 symptomatic women
- Median total years VMS **7.4**
- Median years persist after LMP **4.5**
- Early symptoms duration **> 11.8 (years)**
- African American women longer **10.1 (years)**
- Lower BMI: symptoms last longer[2]

1. Avis NE, et al. *JAMA Intern Med*. 2015;175(4):531-539.
2. Freeman EW, et al. *Obstet Gynecol*. 2011;117(5):1095-1104.

Evolutionary Advantage of Menopause to Homo Sapiens

- In other animals, females reproduce until death
  - Females come into estrus only when infant self-sustaining
- Historically, only a minority of human women survived to menopause, but some did
- Impact of available grandparents (male or female)
  - Shortened interval between pregnancies possible → increased fertility

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Risks and Benefits of Hormonal Therapies

Jeffrey Dunn, PharmD, MBA

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Which is NOT an outcome of WHI?

a) Increase in breast cancer
b) Decrease in MI, cerebrovascular accident, and VT
c) Decrease in bone fractures
d) Decrease in colon cancer

Menopause: Issues

- This is more than QoL
  - But difficult for payers to measure
- Current drugs are generic
  - Most have limitations
  - New drugs are in pipeline

Imperative that we understand disease and how we can help appropriately manage and appropriately evaluate new drugs

Taylor HS, Manson JE. *J Clin Endocrinol Metab*. 2011;96(2):255-264.

Menopause: HRT Benefits

- Improvement in or elimination of hot flashes
- Improved sleep patterns
- Improved blood flow to vulva and vagina
- Improved sexual function
- Protection from osteoporosis and fractures
- Increased collagen content and skin thickness

Taylor HS, Manson JE. *J Clin Endocrinol Metab*. 2011;96(2):255-264.

Menopause Health Risks

- Breast cancer
- Cardiovascular disease

Taylor HS, Manson JE. *J Clin Endocrinol Metab*. 2011;96(2):255-264.

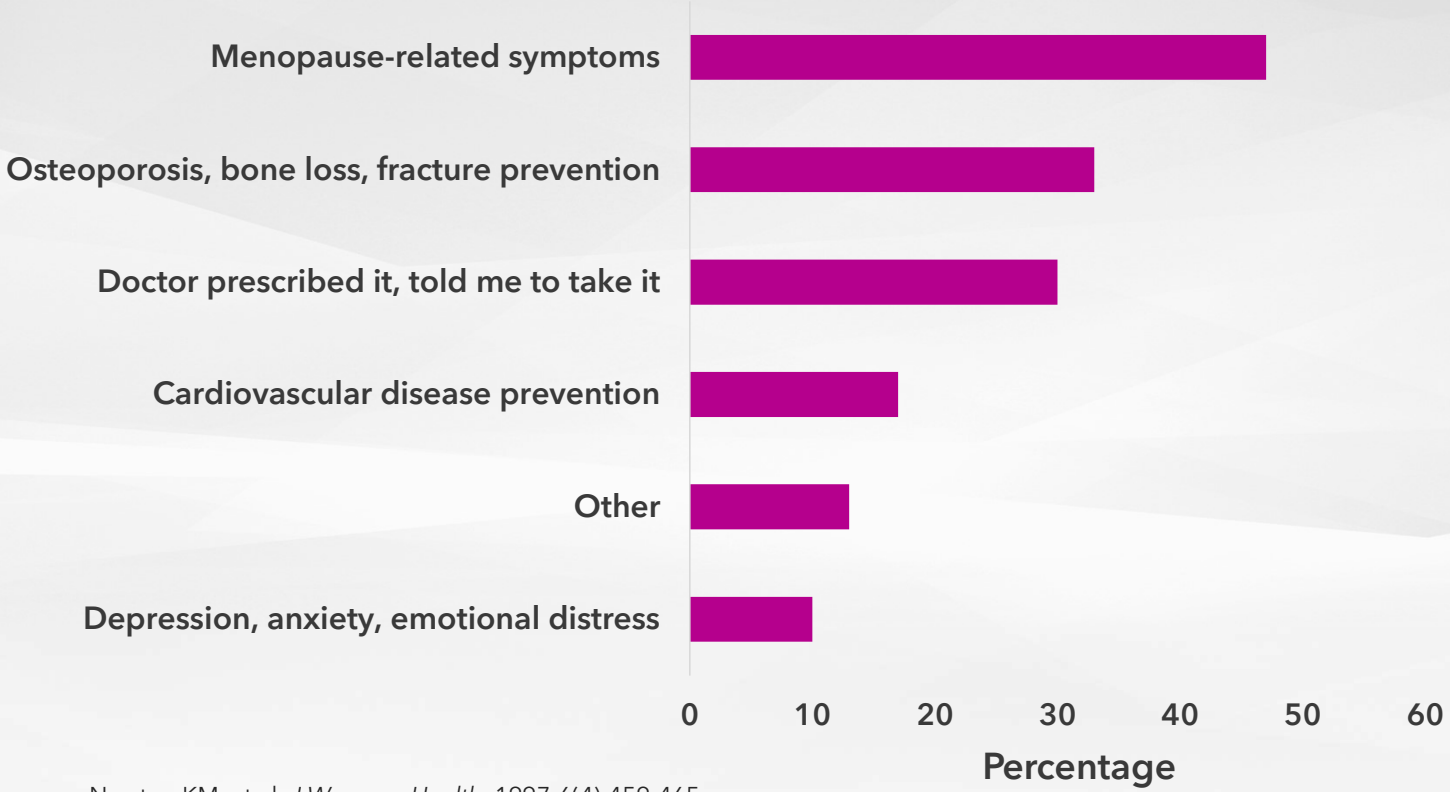
Discussion

Balancing the needs with the risks

- Cardiovascular disease
- Breast cancer

Is hormone therapy safe, and if so, how much and for how long?

Women's Reasons for Initiating or Continuing ERT/HRT



Newton KM, et al. *J Womens Health*. 1997;6(4):459-465.

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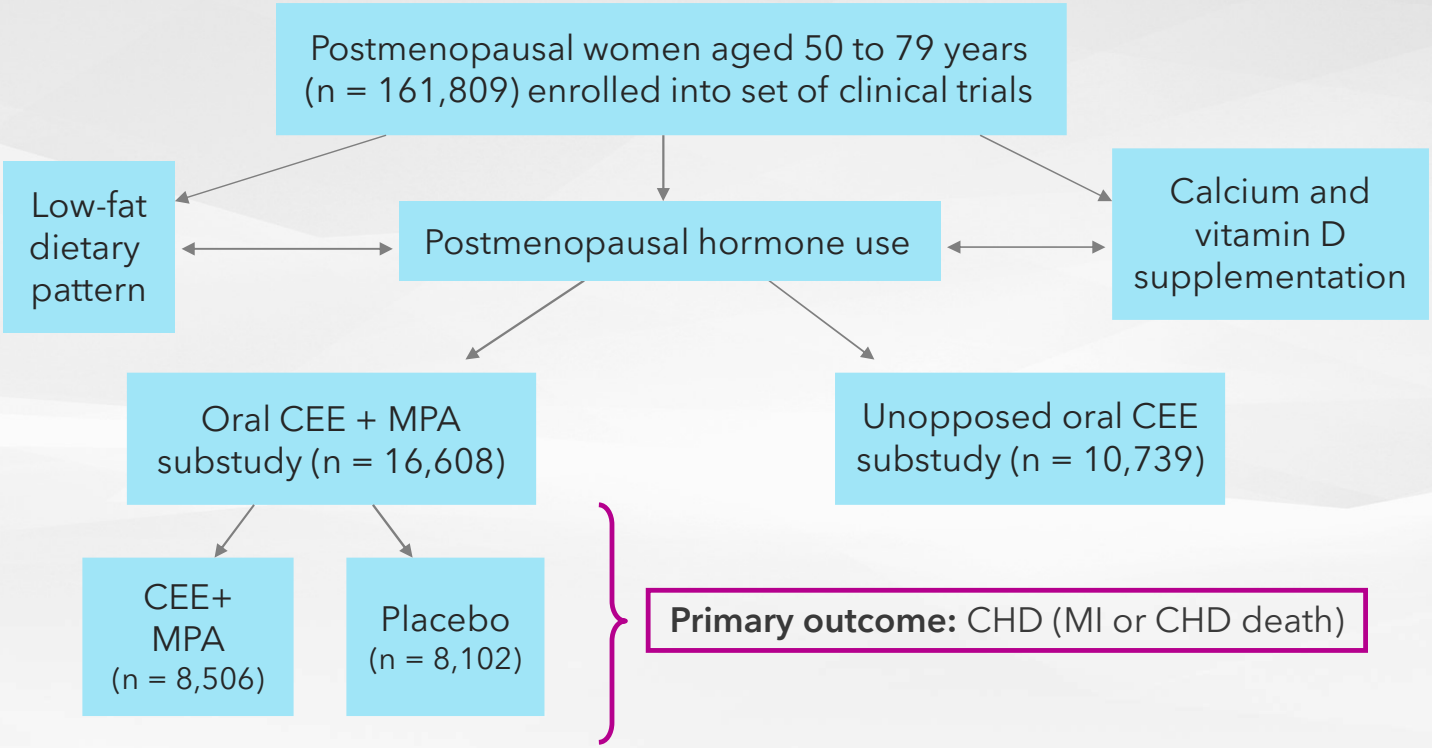
Women's Health Initiative (WHI): Study Design and Objectives



Women's Health Initiative Investigators. *JAMA*. 2002;288(3):321-333.

WHI E+P Background

Design	Randomized, double-blind, placebo-controlled trial of HT[1]
Inclusion criteria	Postmenopausal women 50–79 years of age (mean age: ~63 years) with an intact uterus[1]
Randomization	Women (N = 16,608) were randomized at 40 clinical centers in the US to conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) 0.625 mg/2.5 mg/day (n = 8,506) or placebo (n = 8,102)[1]
Outcomes	Primary efficacy outcome: CHD[1] Primary safety outcome: invasive breast cancer[1]
Other outcomes	Hip fracture; other cardiovascular diseases; endometrial, colorectal and other cancers; and other fractures[1]
Trial termination	Stopped after 5.2 years with follow-up through 5.6 years with final adjudicated data released after publication of initial trial results[2-8]

1. Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-333. 2. Manson JE, et al. *N Engl J Med*. 2003;349:523-534. 3. Chlebowski RT, et al. *JAMA*. 2003;289:3243-3253. 4. Wassertheil-Smoller S, et al. *JAMA*. 2003;289:2673-2684. 5. Cushman M, et al. *JAMA*. 2004;292:1573-1580. 6. Chlebowski RT, et al. *N Engl J Med*. 2004;350:991-1004. 7. Cauley JA, et al. *JAMA*. 2003;290:1729-1738. 8. Anderson GL, et al. *JAMA*. 2003;290:1739-1748.

WHI E-Alone Background

Design	Prospective, randomized, double-blind, placebo-controlled trial of ET
Inclusion criteria	Postmenopausal women 50–79 years of age (mean age: 63.6 years) with prior hysterectomy
Randomization	Women (N = 10,739) were randomized at 40 clinical centers in the US to CE 0.625 mg/day (n = 5,310) or placebo (n = 5,429)
Outcomes	Primary efficacy outcome: CHD Primary safety outcome: invasive breast cancer
Other outcomes	Hip and other fractures, other cardiovascular diseases, colorectal and other cancers
Trial termination	Stopped after 6.8 years because: ▪ Estrogen alone did not appear to affect risk of heart disease ▪ Risk of stroke increased ▪ Lack of effects on heart disease and breast cancer would not likely change if the trial continued

Women's Health Initiative Steering Committee. *JAMA*. 2004;291(14):1701-1712.

WHI E+P: Relative and Absolute Benefits and Risks

	Relative risk or benefit			Absolute increased risk or benefit	
				Per 10,000 women per year	
Event	Overall HR	95% CI Nominal	95% CI Adjusted	Risk	Benefit
CHD[1]	1.24	1.00–1.54	0.97–1.60	6	
Breast cancer[2]	1.24	1.01–1.54	0.97–1.59	8	
Strokes[3]	1.31	1.02–1.68	0.93–1.84	7	
VTE[4]	2.06	1.58–2.82	1.26–3.55	18	
Colorectal cancer[5]	0.63	0.43–0.92	0.32–1.24		6
Hip fractures[6]	0.67	0.47–0.96	0.41–1.10		5
Total fractures[6]	0.76	0.69–0.83	0.54-0.92		47

1. Manson JE, et al. *N Engl J Med*. 2003;349:523-534. 2. Chlebowski RT, et al. *JAMA*. 2003;289:3243-3253. 3. Wassertheil-Smoller S, et al. *JAMA*. 2003;289:2673-2684. 4. Cushman M, et al. *JAMA*. 2004;292:1573-1580. 5. Chlebowski RT, et al. *N Engl J Med*. 2004;350:991-1004. 6. Cauley JA, et al. *JAMA*. 2003;290:1729-1738.

WHI Estrogen Alone

Outcome	HR	Nominal CI	Adjusted CI
CHD[1]*	0.95	0.79–1.16	0.76–1.19
Stroke[2]	1.39	1.10-1.77	0.97-1.99
Breast Ca[2]	0.77	0.59-1.01	0.57-1.06
Total Fx[2]	0.70	0.63-0.79	**0.59-0.83**

*Final, centrally adjudicated data.

1. Hsia J, et al. *Arch Intern Med*. 2006;166(3):357-365. 2. Women's Health Initiative Steering Committee. *JAMA*. 2004; 291(14):1701-1712.

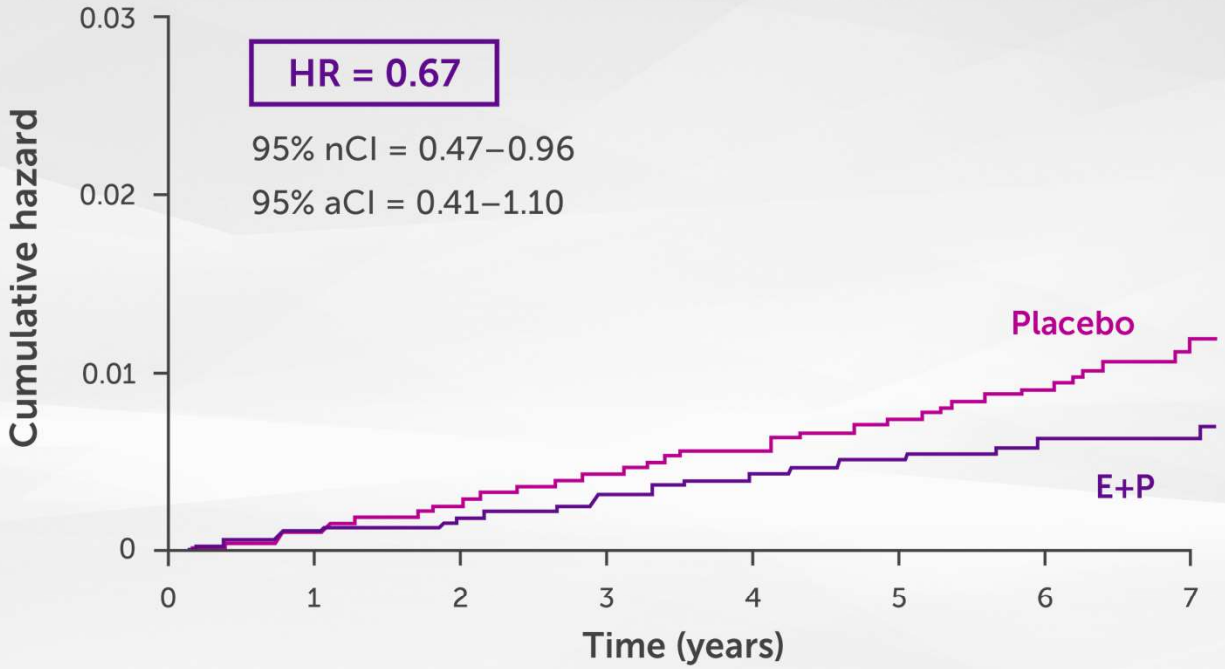
WHI

- Average age = 63
- Excluded women with menopausal symptoms
- Did not consider “disease latency”
  - Inception
  - Detection
  - Subclinical disease
  - Clinical event
  - Potential for intervention
  - Time lag for results of Rx

Disease Latency

- Inception
- Detection
- Subclinical disease
- Clinical event
- Potential for intervention
- Time lag for results of Rx

WHI E+P: Hip Fracture



Kaplan-Meier estimate

Cauley JA, et al. *JAMA*. 2003;290(13):1729-1738.

Factors That Influence Heart Disease

- Genetics
- Diet
- Exercise
- Smoking
- Diabetes
- Hypertension
- Hyperlipidemia

Effect of Estrogen on Risk for CHD*

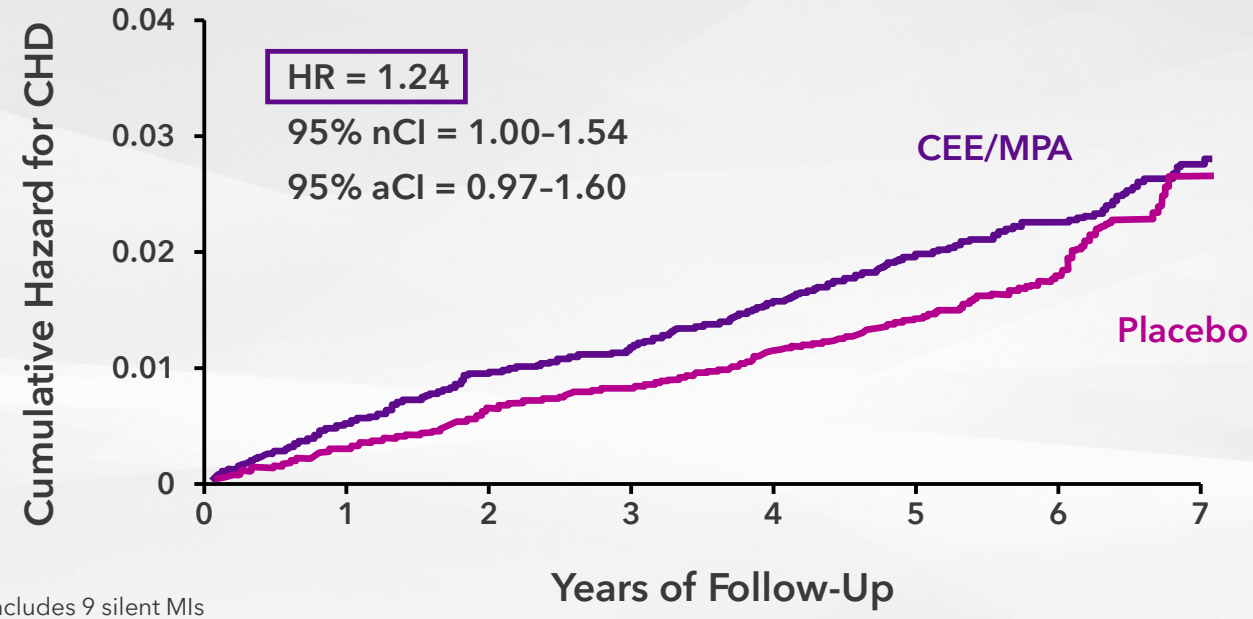
Nurses' Health Study (NHS), 1976–2000

Hormone Use	Person-years of follow-up	Cases (n)	Multivariate-adjusted RR (95% CI)
0.3 mg	26,690	32	0.74 (0.52–1.06)
0.625 mg	188,102	195	0.70 (0.59–0.83)
1.25 mg +	50,453	56	0.80 (0.60–1.06)

RR, relative risk for current vs never-users.
***Analyses combine use of estrogen alone and estrogen plus progestin.**

Grodstein F, et al. *J Women's Health*. 2006;15(1):35-44.

WHI E+P: Risk of CHD



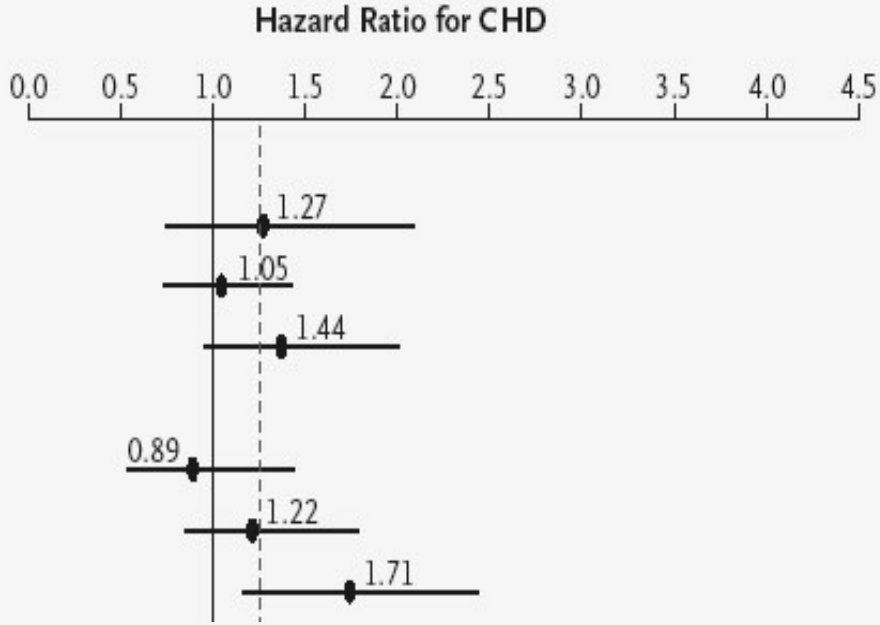
Includes 9 silent MIs

Kaplan-Meier estimate
aCI, adjusted confidence interval; HR, hazard ratio; nCI, nominal confidence interval.

Manson JE, et al. *N Engl J Med*. 2003;349(6):523-534.

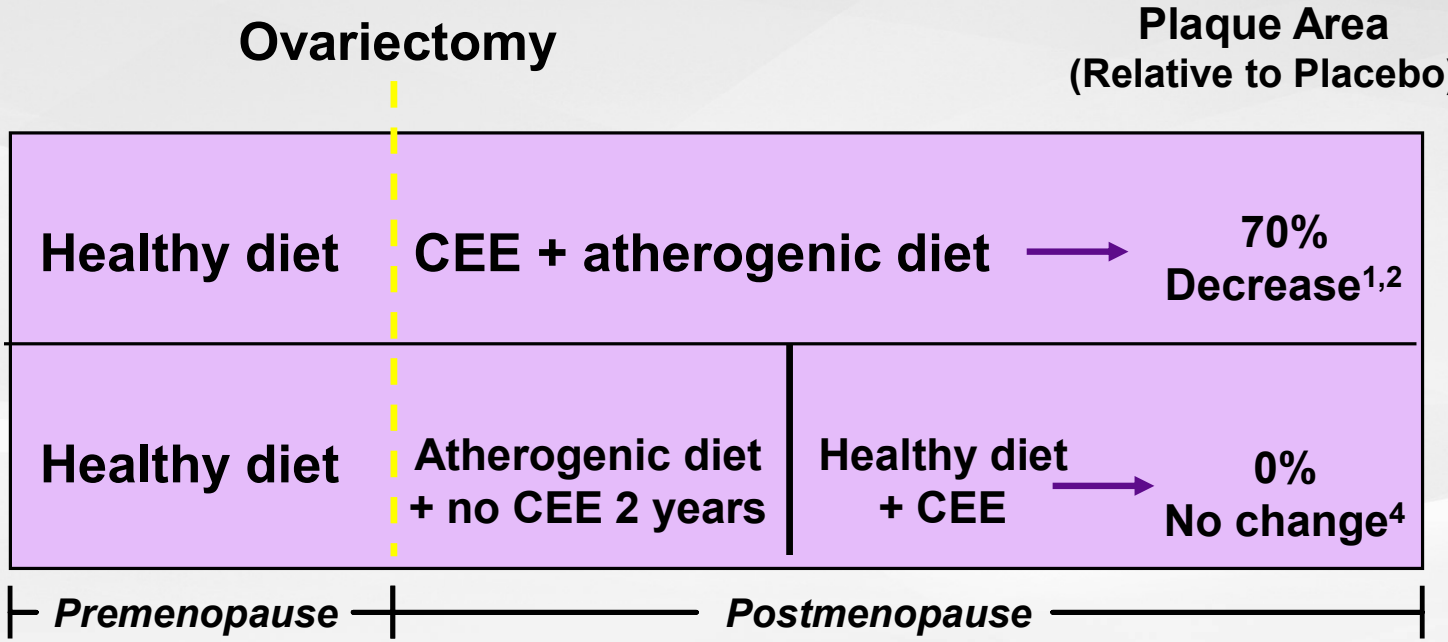
WHI: CHD and HT

Subgroup	Estrogen-plus-Progestin Group	Placebo Group	P value for Interaction
	No. of cases of CHD (annualized percentage)		
Age			0.36
50–59 yr	37 (0.22)	27 (0.17)	
60–69 yr	75 (0.35)	68 (0.34)	
70–79 yr	76 (0.78)	52 (0.55)	
Years since menopause			0.33
<10	31 (0.19)	34 (0.22)	
10–19	63 (0.38)	51 (0.32)	
≥20	74 (0.75)	44 (0.46)	



Manson JE, et al. *N Engl J Med*. 2003;349(6):523-534.

Importance of Timing of Intervention on the Effect of Estrogens on Atherogenesis in Nonhuman Primates



1. Clarkson TB, et al. *J Clin Endocrinol Metab*. 1998;83(3):721-726.
2. Adams MR, et al. *Arterioscler Thromb Vasc Biol*. 1997;17(1):217-221.
3. Clarkson TB, et al. *J Clin Endocrinol Metab*. 2001;86(1):41-47.
4. Williams JK, et al. *Arterioscler Thromb Vasc Biol*. 1995;15(7):827-836.

Coronary Events with CEE or Placebo by Age at Baseline in WHI

Table 2. Coronary Events With CEE or Placebo by Age at Baseline

	No. of Cases (Annualized %) by Age at Baseline, y									
	50-59			60-69			70-79			
Coronary Event	CEE (n = 1637)	Placebo (n = 1673)	HR (95% CI)	CEE (n = 2387)	Placebo (n = 2465)	HR (95% CI)	CEE (n = 1286)	Placebo (n = 1291)	HR (95% CI)	*P* Value for Interaction
CHD (MI or coronary death)	21 (0.17)	34 (0.27)	0.63 (0.36-1.08)	96 (0.57)	106 (0.61)	0.94 (0.71-1.24)	84 (0.96)	77 (0.86)	1.11 (0.82-1.52)	.07
CABG or PCI	29 (0.24)	52 (0.42)	0.55 (0.35-0.86)	129 (0.77)	130 (0.75)	0.99 (0.78-1.27)	95 (1.08)	94 (1.06)	1.04 (0.78-1.39)	.09
Hospitalized angina	42 (0.35)	51 (0.41)	0.81 (0.54-1.22)	125 (0.75)	122 (0.71)	1.06 (0.82-1.36)	98 (1.12)	89 (1.00)	1.10 (0.82-1.46)	.37
Confirmed angina*	21 (0.17)	35 (0.28)	0.59 (0.34-1.02)	80 (0.48)	80 (0.46)	1.03 (0.76-1.41)	62 (0.71)	56 (0.63)	1.12 (0.78-1.60)	.18
Acute coronary syndrome†	56 (0.46)	73 (0.59)	0.76 (0.54-1.08)	185 (1.11)	187 (1.08)	1.01 (0.82-1.24)	154 (1.76)	141 (1.58)	1.10 (0.87-1.38)	.18
MI, coronary death, CABG, and PCI	42 (0.35)	65 (0.52)	0.66 (0.44-0.97)	177 (1.06)	177 (1.02)	1.02 (0.83-1.25)	137 (1.56)	130 (1.46)	1.08 (0.85-1.38)	.09
MI, coronary death, CABG, PCI, and hospitalized angina	65 (0.54)	84 (0.68)	0.78 (0.56-1.07)	225 (1.35)	228 (1.32)	1.01 (0.84-1.21)	176 (2.01)	164 (1.84)	1.08 (0.87-1.34)	.13
MI, coronary death, CABG, PCI, and confirmed angina	46 (0.38)	70 (0.56)	0.66 (0.45-0.96)	186 (1.11)	194 (1.12)	0.98 (0.80-1.20)	148 (1.69)	141 (1.58)	1.05 (0.84-1.33)	.11

Abbreviations: CABG, coronary artery bypass grafting; CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, nominal confidence interval; HR, nominal hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Confirmed angina requires hospitalization for angina with confirmatory stress test or obstructive coronary disease by angiography.

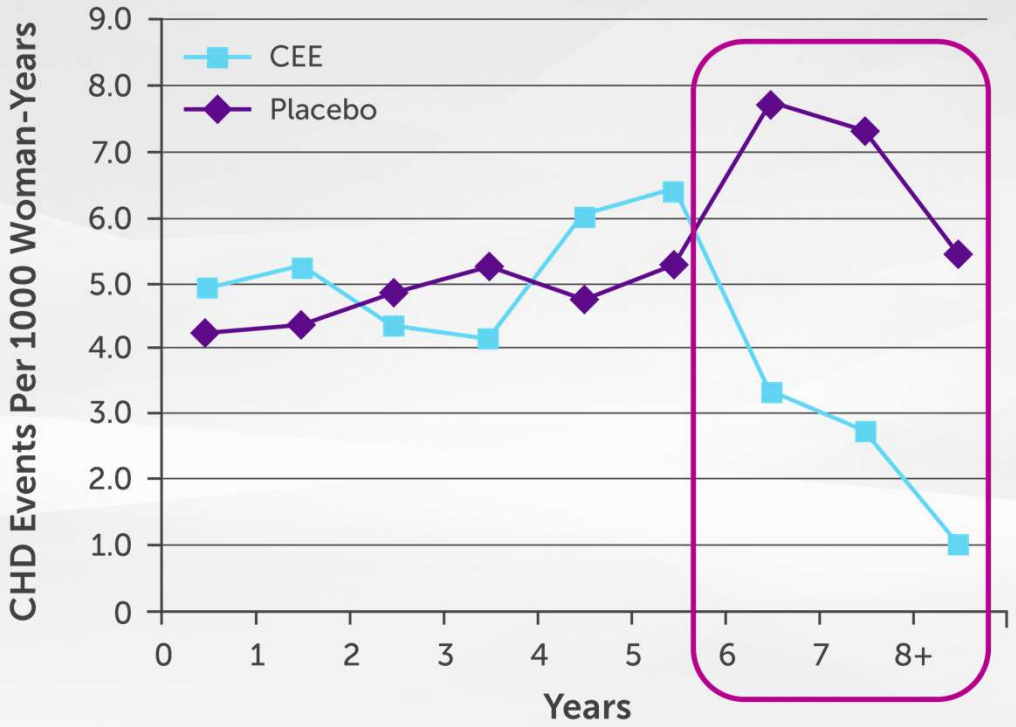
†Acute coronary syndrome includes myocardial infarction and hospitalized angina.

Hsia J, et al. *Arch Intern Med.* 2006;166(3):357-365.

WHI: Estrogen-Alone Cardiovascular Outcomes, Ages 50–59

	CEE	Placebo	HR
MI, coronary death, CABG, PCI, and confirmed angina	46 (0.38)	70 (0.56)	0.66 (0.45-0.96)

Annual CHD Event Rates per 1,000 by Year in the WHI E-Only Arm: Potential Long-Term Benefit



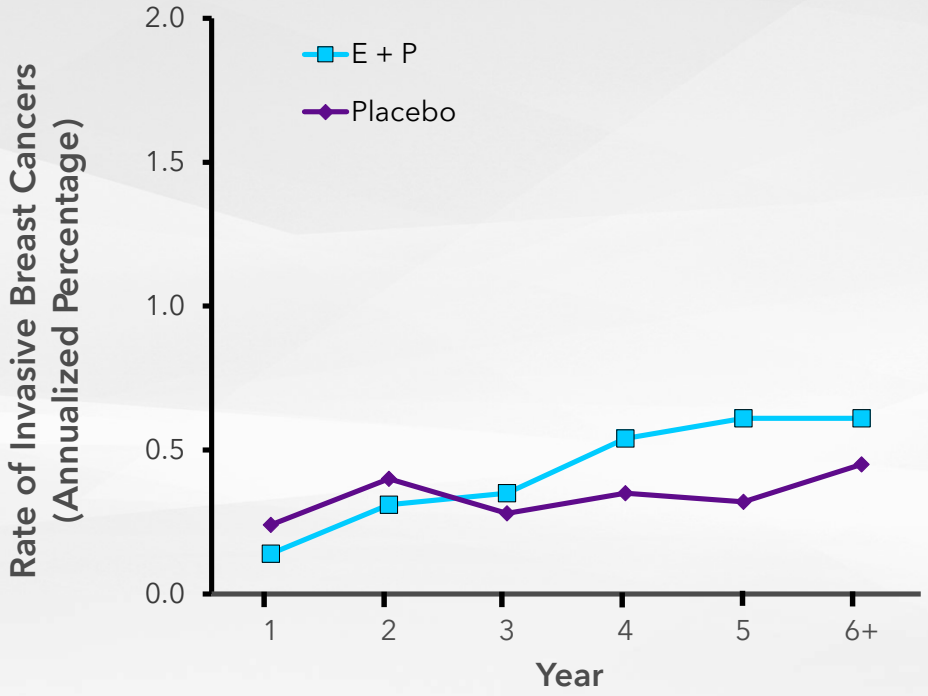
Hazard ratio 0.4

Modified from Women's Health Initiative Steering Committee. *JAMA*. 2004;291(14):1701-1712.

Estrogens/Progestins Are Not Highly Effective in Preventing Cardiovascular Disease and May Carry Short-Term Risk, Especially in Older Menopausal Women

WHI Results

Annualized Percentage of Invasive Breast Cancers*



Year	Risk Ratio
1	0.60
2	0.77
3	1.26
4	1.54
5	1.99
6+	1.35

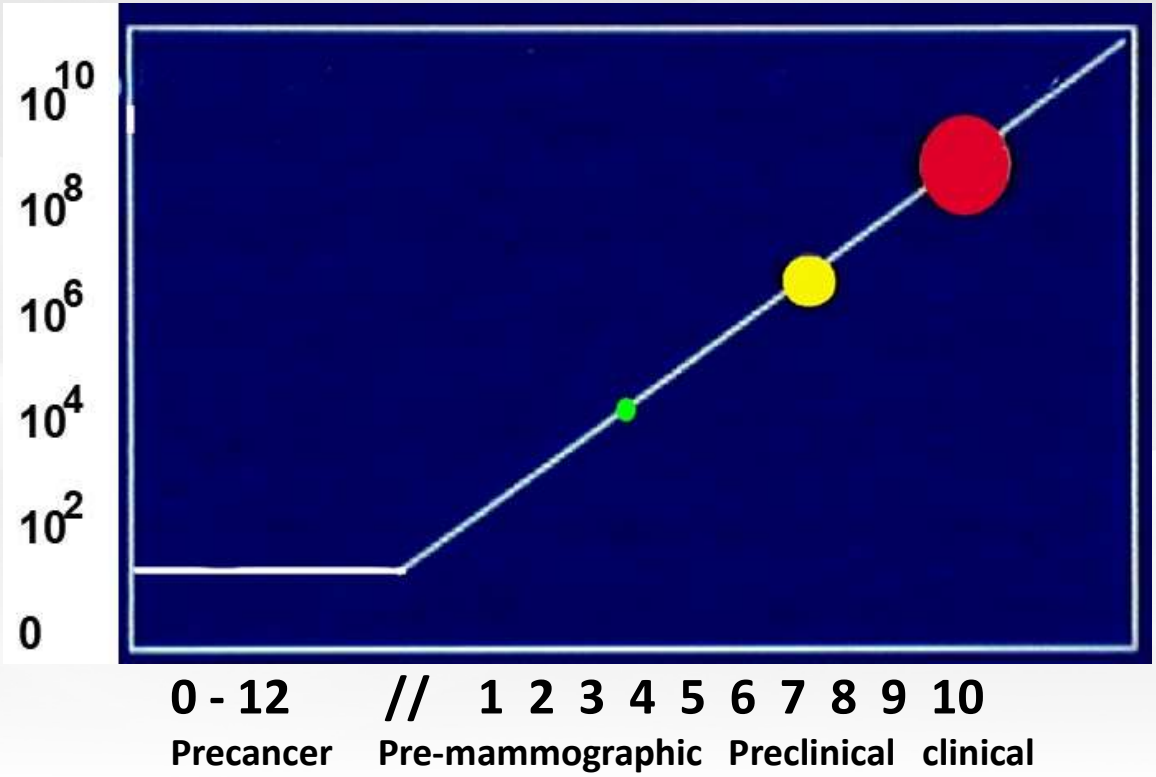
*Overall: Estrogen plus progestin in subjects with and without prior HT.

Chlebowski RT, et al. *JAMA*. 2003;289(24):3243-3253.

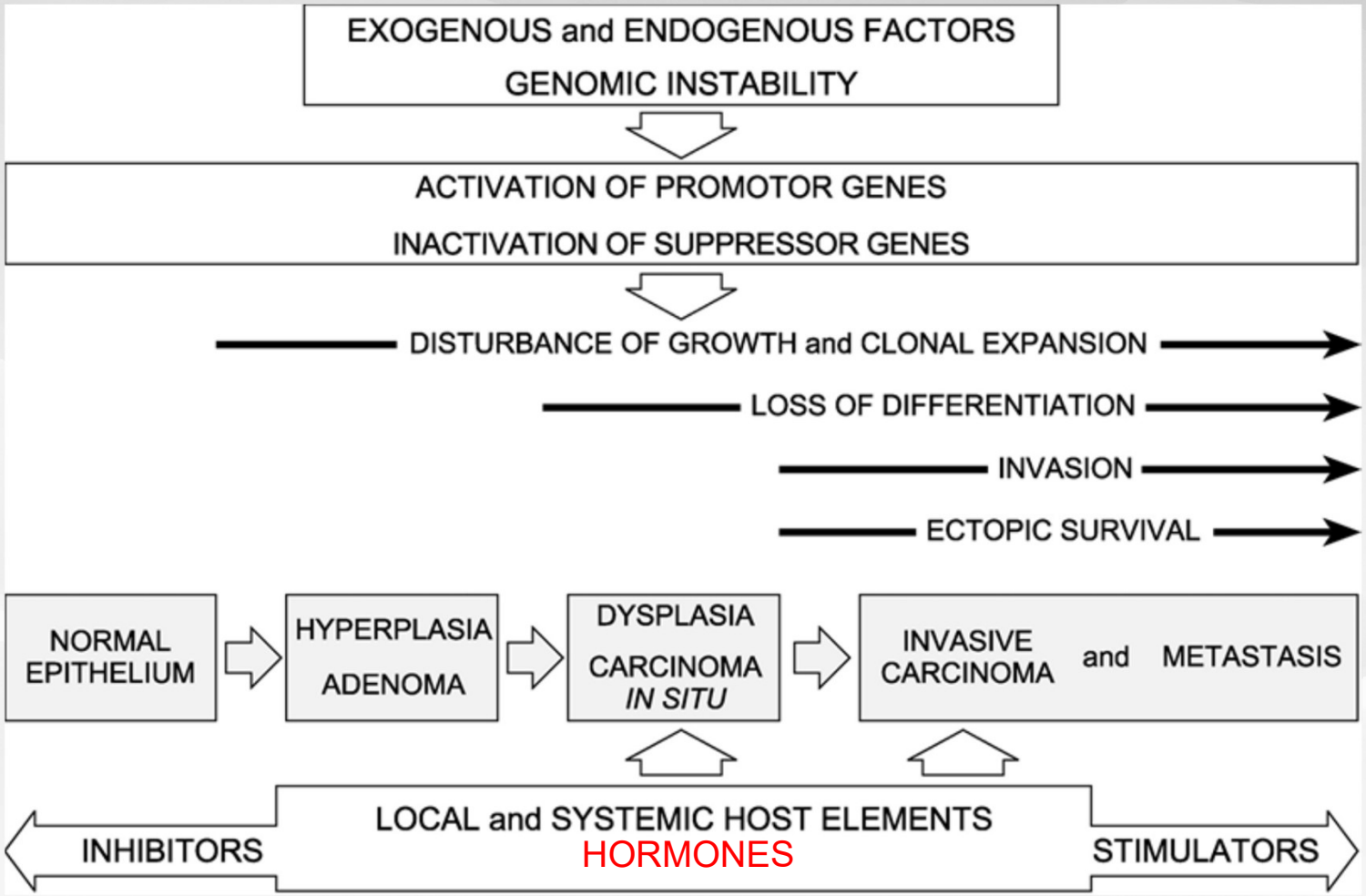
Increased Risk of Breast Cancer Detection Is Not the Same as Breast Cancer Mortality or Causality

omnia℠ EDUCATION

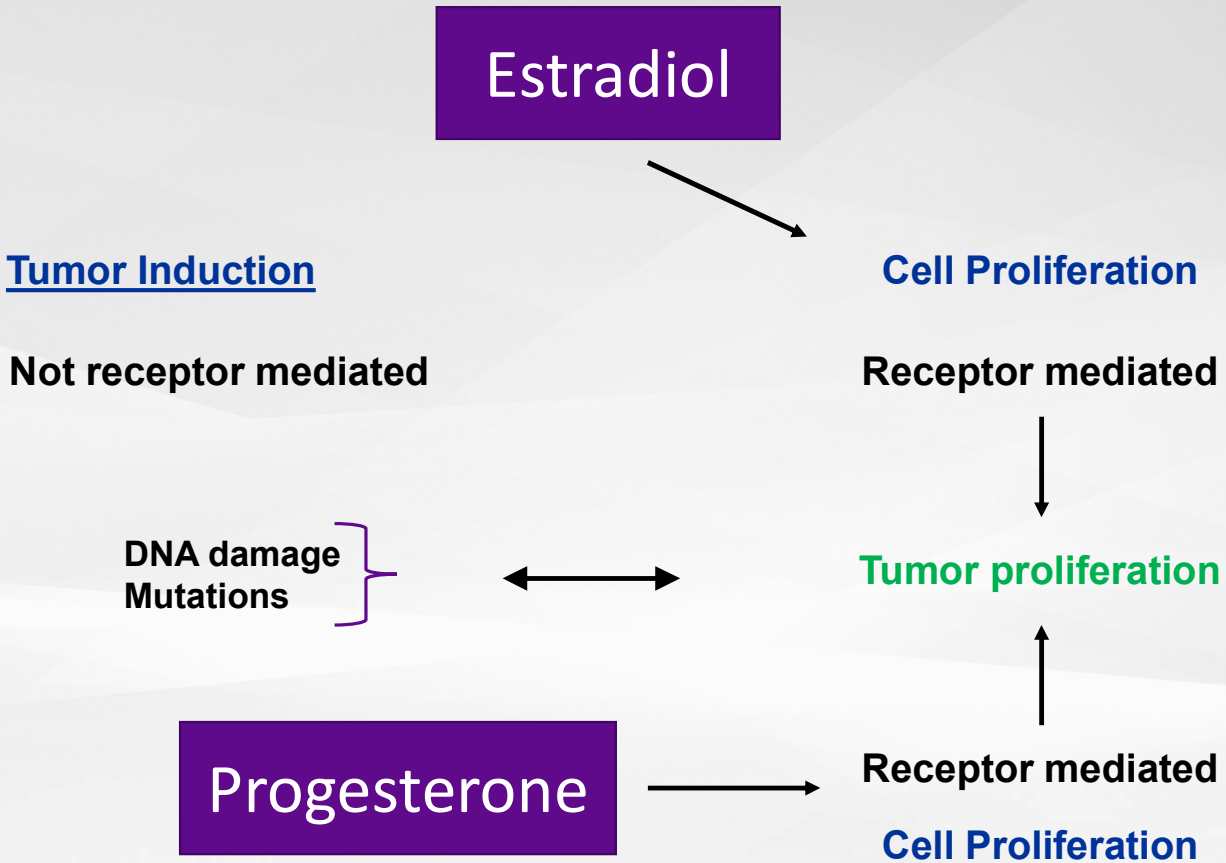
Time Course for Breast Cancer Development



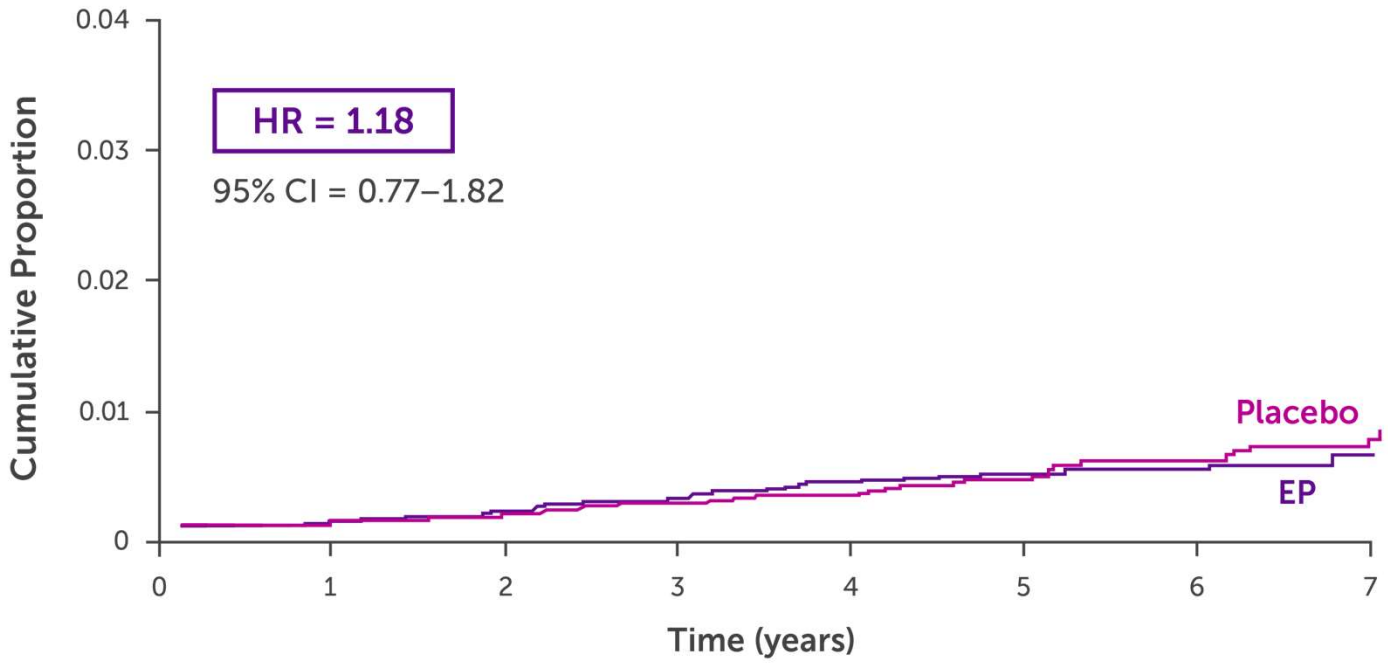
Tan KHX, et al. *Br J Cancer*. 2013;109(8):2035-2043.



Modified from Mareel M, Leroy A. *Physiol Rev*. 2003;83(2):337-376.

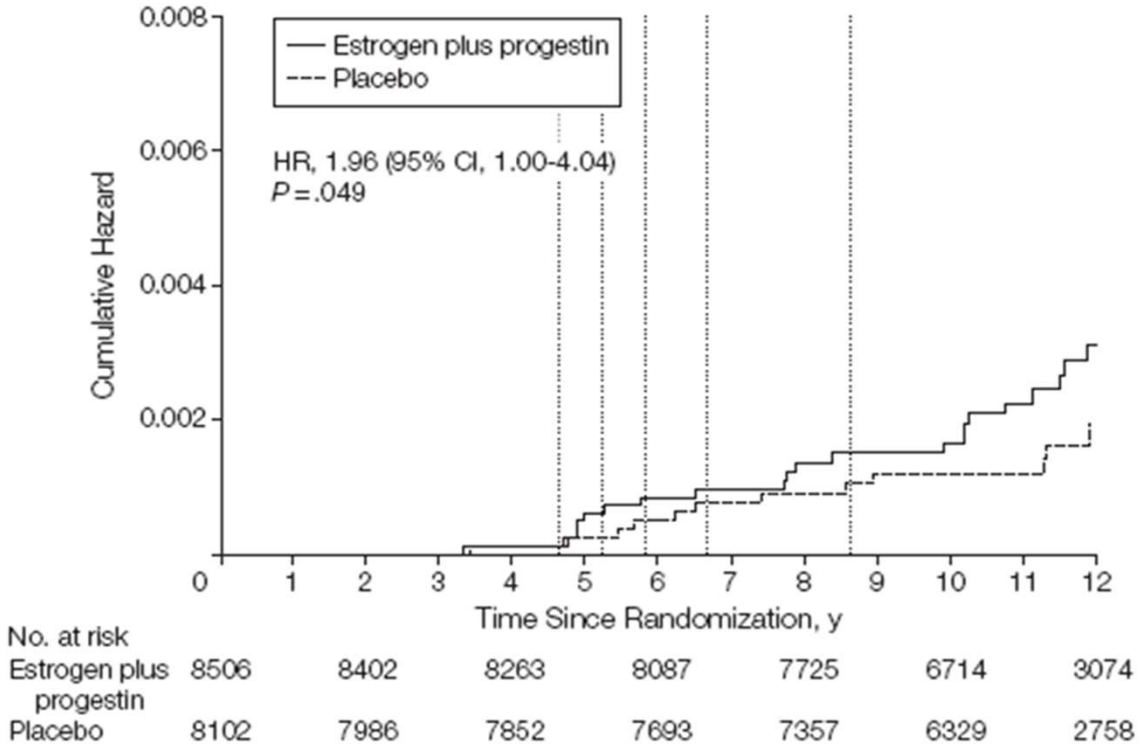

Estradiol
Tumor Induction
Not receptor mediated
Cell Proliferation
Receptor mediated
DNA damage
Mutations
Tumor proliferation
Progesterone
Receptor mediated
Cell Proliferation

WHI E+P Trial: No Effect of E+P on Risk of In Situ Breast Cancer



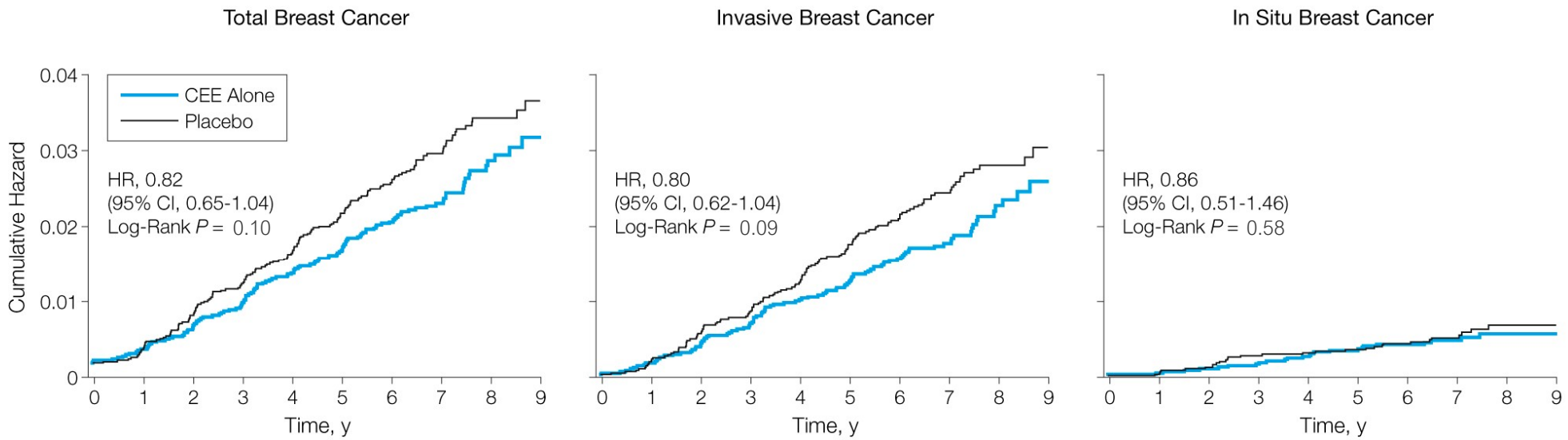
Chlebowski RT, et al. *JAMA*. 2003;289(24):3243-3253.

Mortality Due to Breast Cancer



Chlebowski RT, et al. *JAMA*. 2010;304(15):1684-1692.

Cumulative Hazard for Total, Invasive, and In Situ Breast Cancer



No. at Risk

CEE	5310	5160	4989	4426	1357	484	5310	5165	5001	4444	1365	487	5310	5160	4989	4426	1357	484
Placebo	5429	5270	5081	4479	1443	603	5429	5275	5097	4498	1451	603	5429	5270	5081	4479	1443	603

Stefanick ML, et al. *JAMA*. 2006;295(14):1647-1657.

WHI E-Alone Post-Intervention Study

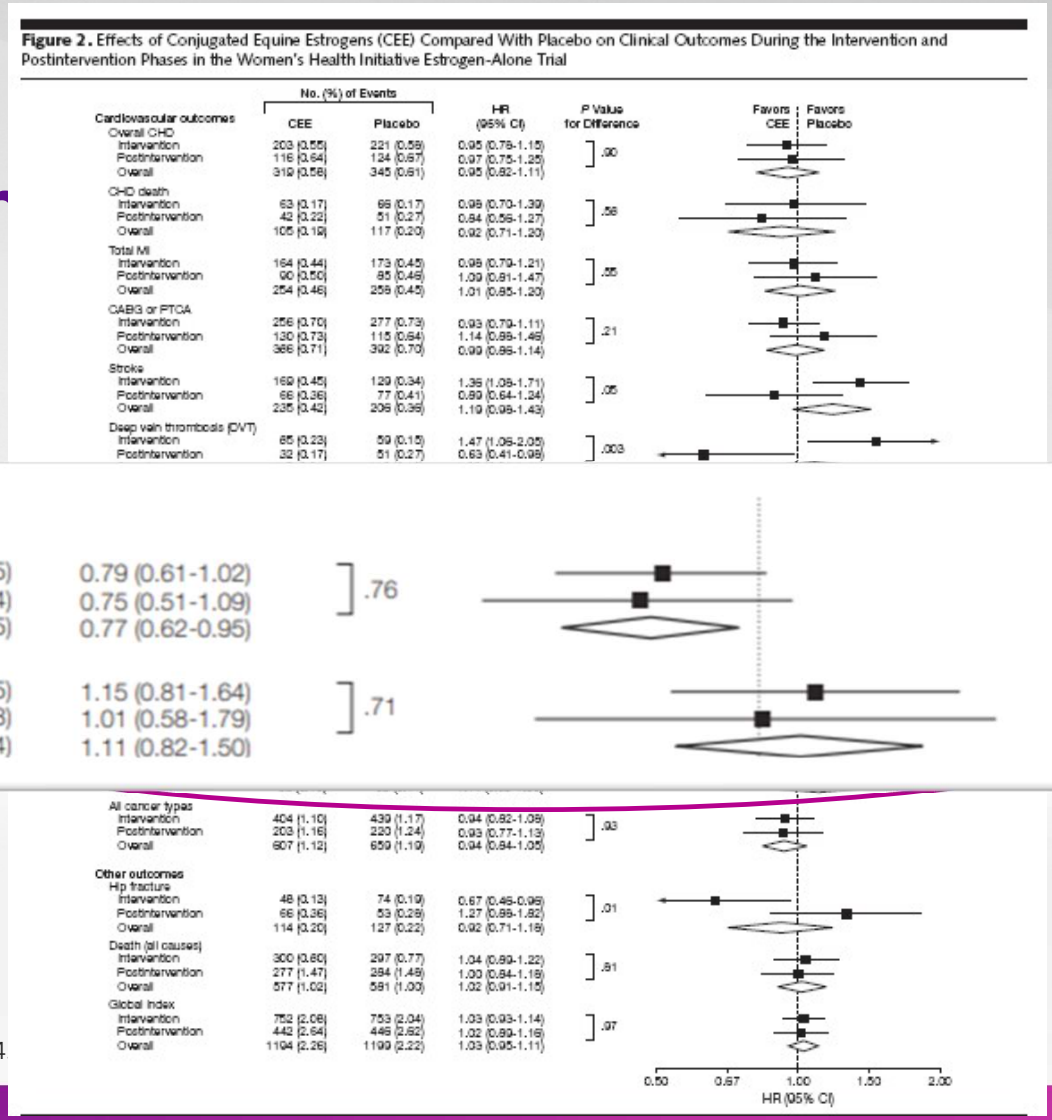


Figure 2. Effects of Conjugated Equine Estrogens (CEE) Compared With Placebo on Clinical Outcomes During the Intervention and Postintervention Phases in the Women's Health Initiative Estrogen-Alone Trial

	No. (%) of Events		HR (95% CI)	P Value for Difference
	CEE	Placebo		
Cardiovascular outcomes				
Overall CHD				
Intervention	203 (0.55)	221 (0.59)	0.95 (0.78-1.15)	.90
Postintervention	116 (0.64)	124 (0.67)	0.97 (0.75-1.25)	
Overall	319 (0.58)	345 (0.61)	0.95 (0.82-1.11)	
CHD death				
Intervention	63 (0.17)	66 (0.17)	0.98 (0.70-1.39)	.56
Postintervention	42 (0.22)	51 (0.27)	0.84 (0.56-1.27)	
Overall	105 (0.19)	117 (0.20)	0.92 (0.71-1.20)	
Total MI				
Intervention	164 (0.44)	173 (0.45)	0.98 (0.79-1.21)	.85
Postintervention	90 (0.50)	85 (0.46)	1.09 (0.81-1.47)	
Overall	254 (0.46)	258 (0.45)	1.01 (0.85-1.20)	
CABG or PTCA				
Intervention	256 (0.70)	277 (0.73)	0.93 (0.79-1.11)	.21
Postintervention	130 (0.73)	115 (0.64)	1.14 (0.88-1.46)	
Overall	386 (0.71)	392 (0.70)	0.99 (0.86-1.14)	
Stroke				
Intervention	169 (0.45)	129 (0.34)	1.35 (1.08-1.71)	.05
Postintervention	66 (0.36)	77 (0.41)	0.89 (0.64-1.24)	
Overall	235 (0.42)	206 (0.36)	1.19 (0.98-1.43)	
Deep vein thrombosis (DVT)				
Intervention	65 (0.23)	39 (0.15)	1.47 (1.05-2.05)	.003
Postintervention	32 (0.17)	51 (0.27)	0.63 (0.41-0.98)	
Cancer				
Invasive breast cancer				
Intervention	104 (0.28)	135 (0.35)	0.79 (0.61-1.02)	.76
Postintervention	47 (0.26)	64 (0.34)	0.75 (0.51-1.09)	
Overall	151 (0.27)	199 (0.35)	0.77 (0.62-0.95)	
Colorectal cancer				
Intervention	65 (0.17)	58 (0.15)	1.15 (0.81-1.64)	.71
Postintervention	24 (0.13)	24 (0.13)	1.01 (0.58-1.79)	
Overall	89 (0.16)	82 (0.14)	1.11 (0.82-1.50)	
All cancer types				
Intervention	404 (1.10)	439 (1.17)	0.94 (0.82-1.08)	.93
Postintervention	203 (1.16)	220 (1.24)	0.93 (0.77-1.13)	
Overall	607 (1.12)	659 (1.19)	0.94 (0.84-1.05)	
Other outcomes				
Hip fracture				
Intervention	48 (0.13)	74 (0.19)	0.67 (0.46-0.96)	.01
Postintervention	66 (0.36)	53 (0.28)	1.27 (0.88-1.82)	
Overall	114 (0.20)	127 (0.22)	0.92 (0.71-1.18)	
Death (all causes)				
Intervention	300 (0.80)	297 (0.77)	1.04 (0.89-1.22)	.91
Postintervention	277 (1.47)	284 (1.48)	1.00 (0.84-1.18)	
Overall	577 (1.02)	581 (1.00)	1.02 (0.91-1.15)	
Global index				
Intervention	752 (2.06)	753 (2.04)	1.03 (0.93-1.14)	.97
Postintervention	442 (2.64)	446 (2.62)	1.02 (0.89-1.16)	
Overall	1194 (2.26)	1199 (2.22)	1.03 (0.95-1.11)	

Favors CEE | Favors Placebo

0.50 0.67 1.00 1.50 2.00

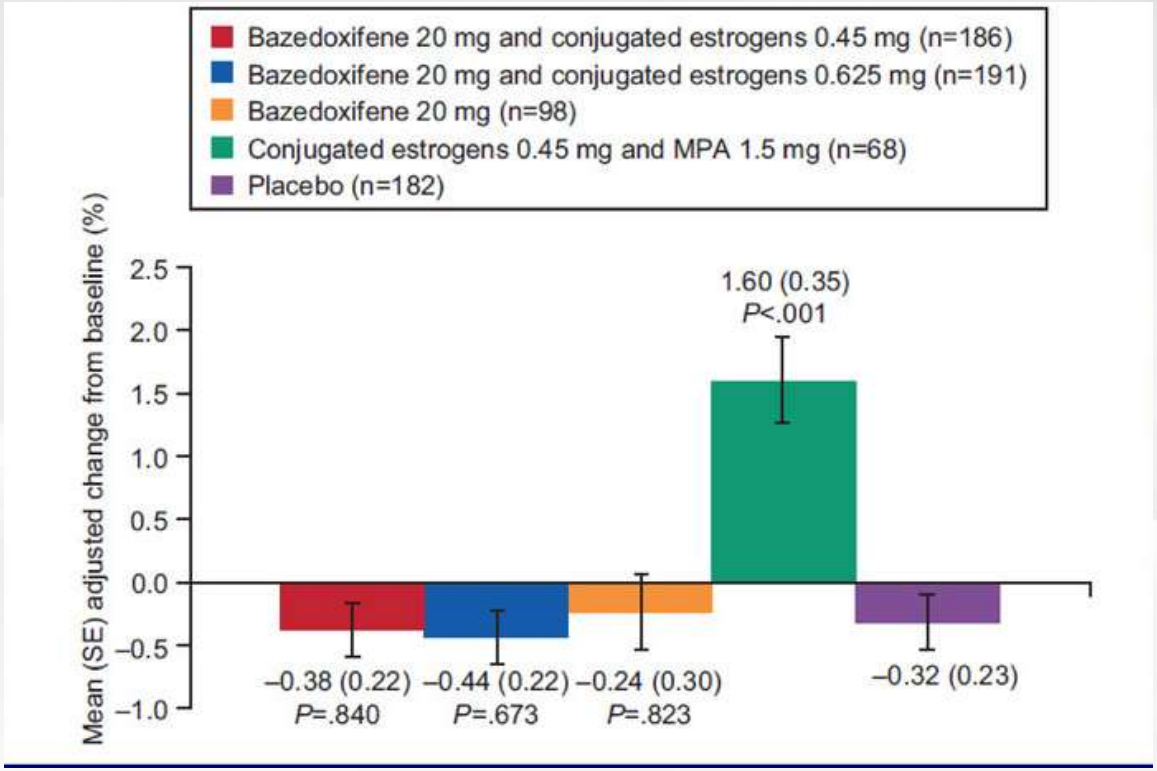
HR (95% CI)

LaCroix AZ, et al. *JAMA*. 2011;305(13):1305-1314

Tissue-Selective Estrogen Complex: TSEC

- Replacing the progestin with a uterine- and breast-specific antiestrogen

Breast Density Effects of Bazedoxifene-Conjugated Estrogens



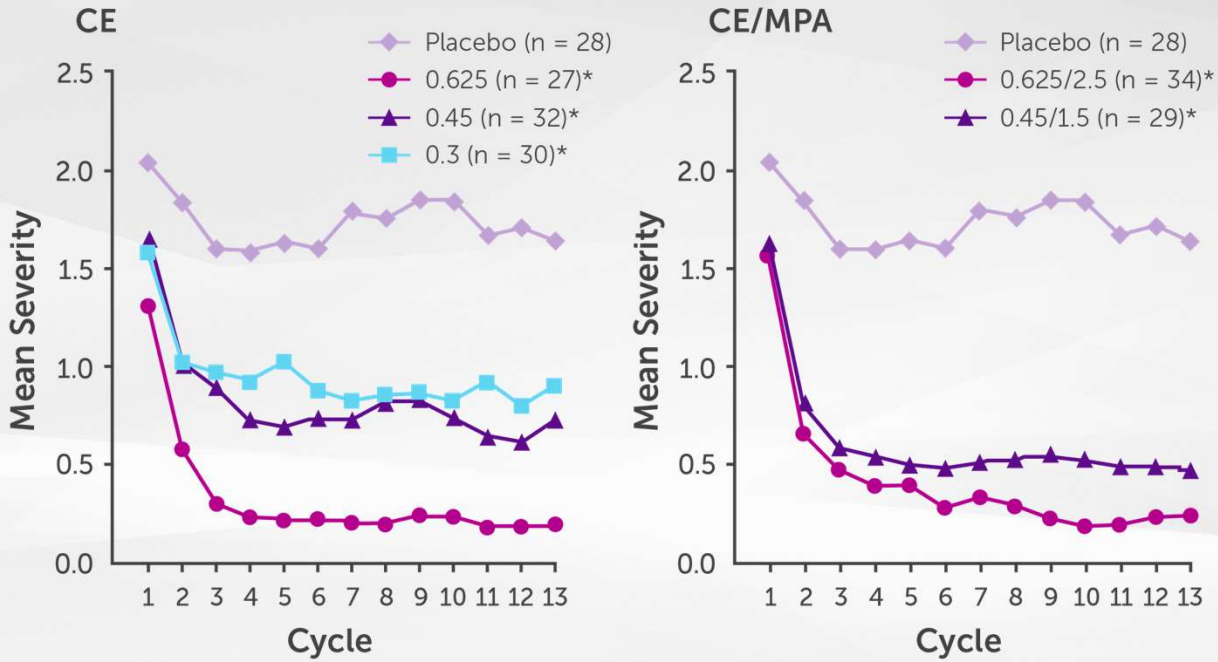
Pinkerton JV, et al. *Obstet Gynecol*. 2013;121(5):959-968. 1-year trial.

Low Dose for a Short Time:

- What is the lowest effective dose?
- What is the shortest duration?

Women's HOPE Study

Severity of Hot Flashes Over 13 Cycles



*$P < 0.05$ cycles 1 through 3 vs placebo
Hot flash severity: 1 = mild, 2 = moderate, 3 = severe.
Mean hot flash severity at baseline = 2.3 (range 2.2-2.4).

Utian WH, et al. *Fertil Steril*. 2001;75(6):1065-1079.

Improvements

- Transdermal
- Estrogen with a local progestin
- SERMS
- Estrogen combined with a SERM or SPRM without progestin

Conclusions

- ET/HT can be appropriate therapy for many women, especially early in menopausal transition
- Estrogen with SERMS or local progestins may eliminate breast cancer risks associated with progestins
- Patients who are hormone-hesitant or are at increased risk may benefit from nonhormonal therapies for vasomotor symptoms

Which is NOT an outcome of WHI?

a) Increase in breast cancer
b) Decrease in MI, cerebrovascular accident, and VT
c) Decrease in bone fractures
d) Decrease in colon cancer

New Horizons and Emerging Data for Nonhormonals

Anita Nelson, MD

omnia℠ EDUCATION

The new NK3 receptor antagonist provides which of the following advantages over other nonhormonal treatments for hot flashes?

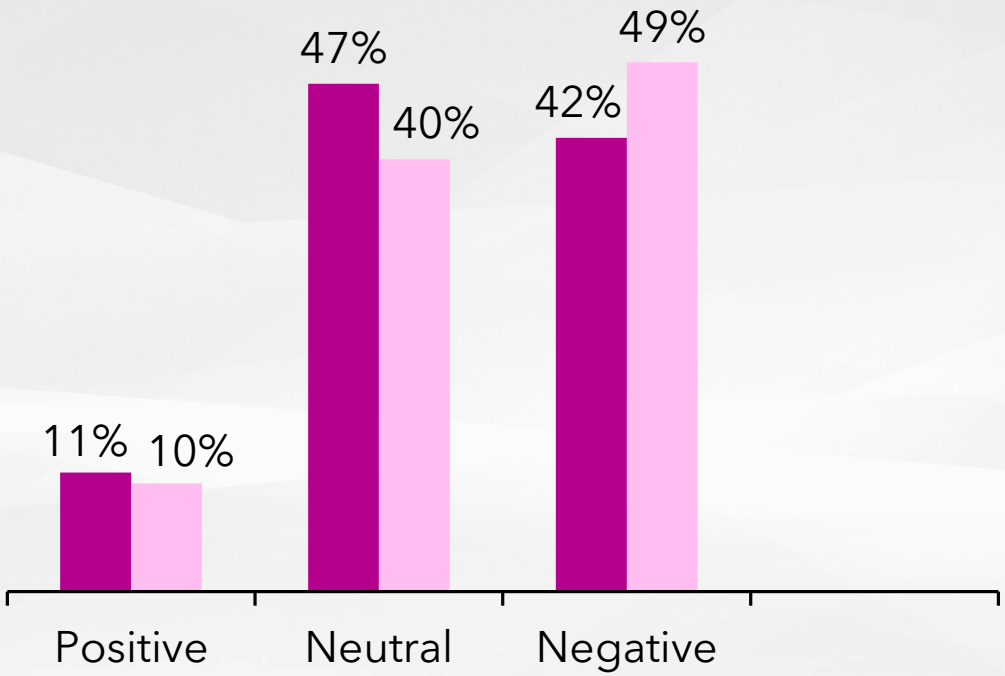
a) It has no adverse interactions with SSRIs used in breast cancer treatment
b) It specifically targets the GnRH pulse generator
c) It blocks receptors on the pituitary that signal adequate estrogen in the circulation
d) It may have additional health benefits like bone protection and vaginal lubrication

Menopause Relief: What Are Women Using?

Treatment	% Who Used	% Helped a Lot
Prescription medication	36%	63%
Black cohosh	22%	21%
Over-the-counter medication	35%	18%
Multivitamins	35%	9%
Calcium supplements	34%	6%

Consumer Reports National Research Center. 2010 Annual Questionnaire.

Impression of Hormone Therapy



http://www.endo-society.org/endo_news/2012/upload/Endocrine-News-November-2012.pdf

Nonpharmacologic Therapies: NAMS

- Lifestyle adaptation: reconsidered
  - Layered clothing
  - Paced respiration
- Other
  - Cognitive behavioral therapy
    - > Does not reduce frequency of hot flashes
    - > Helps women cope with symptoms
  - Hypnotherapy
    - > 74% vs 17% fewer hot flashes
    - > 80% vs 15% reduced severity scores
  - Potential other options
    - > Weight loss, stellate ganglion block
    - > Mindfulness-based stress reduction, S-equol soy

Jacob JA. *JAMA.* 2016;315(1):14-16.

VMS: *Nonhormonal* Therapies

	% treated pts with >50% ↓HF	% placebo patients with >50% ↓HF
Venlafaxine 75 mg	54% - 70%	30%
Paroxetine 10mg	50% - 76%	35% - 57%
Sertraline	40% - 56%	21% - 41%
Escitalopram	55%	36%
Gabapentin	46% - 84%	27% - 47%

On horizon: Neurokinin 3 receptor antagonist

SNRI/SSRIs: Mode of Action

- Narrowing the "thermoregulatory zone"
  - Women with hot flashes have low tolerance for temperature variation
    - > Too high: sweating/hot flashes
    - > Too low: shivering
  - Effective treatments widen the tolerance zone
- Functioning at the motor end plate
- Other CNS function
- CNS mechanisms of hot flashes not known

Freedman RR, et al. *Am J Obstet Gynecol*. 1999;181(1):66-70.

Vasomotor Symptoms: FDA-Approved Product

- Paroxetine (Brisdelle®) 7.5 mg
- Reduced hot flashes in two 12-week studies
  - 57%-59% reduction
- Placebo at 12 weeks
  - 40%-48% reduction
- Side effects: headaches, fatigue, nausea, reduced sex drive, possible bone loss
- Appropriate for women who want/need no hormones

SNRIs: Desvenlafaxine/Venlafaxine

- Similar molecular structure (desvenlafaxine is an enantiomer of venlafaxine)
- Effective at low dose range for depression
- Effective within days
- Venlafaxine 37.5 to 75 mg/day
- Desvenlafaxine single dose (50 mg)

Pristiq Extended-Release. Prescribing information. Wyeth Pharmaceuticals; 2018. Accessed March 28, 2021. http://labeling.pfizer.com/showlabeling.aspx?id=100

Effexor XR (venlafaxine). Prescribing information. Wyeth Pharmaceuticals; 2018. Accessed March 28, 2021. http://labeling.pfizer.com/showlabeling.aspx?id=100

Clinical Pearls SSRI/SNRIs

- Response is rapid – easily within 1 week
  - Start with low dose
  - Watch for side effects: anxiety or lethargy, GI problems, "loopiness," sexual side effects
- Always taper slowly when stopping therapy
  - Side effects with rapid stopping
    - > Headaches, dysphoria, depression
- Paroxetine – do not mix with tamoxifen given for breast cancer

Pearls for Other Nonhormonal Options for VMS

- Gabapentin 100-2400 mg/day (start low)
  - May take at night to relieve night sweats
  - Rapid response
  - Mood changes, respiratory, depression, fatigue, dizziness

Pearls for Other Nonhormonal Options for VMS

- Clonidine 0.1 to 0.3 mg weekly patch
  - Start low
  - Warn about postural hypotension
- Oxybutynin 2.5 to 5.0 mg twice daily
  - Or 5 to 10 mg daily
    - > Side effects: dry mouth, difficulty urinating

Nonprescription Therapies That Are No Better Than Placebo for VMS

- Black cohosh (liver toxicity)
- Dong quai
- Evening primrose oil
- Flaxseed
- N-3 fatty acids
- Ginseng
- Red clover
- Vitamin E

Pinkerton JV et al. *N Engl J Med.* 2020;382(5):446-55.

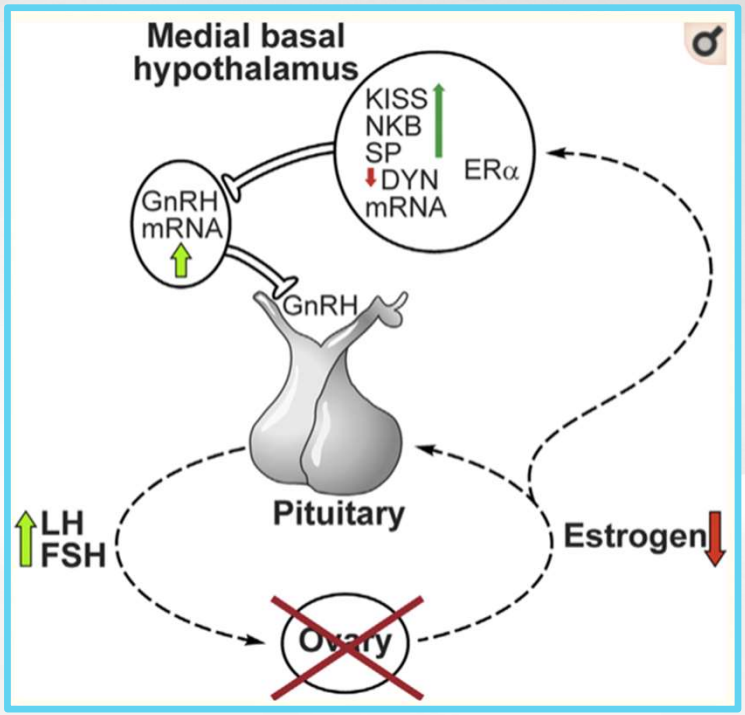
New Nonhormonal Option for VMS in Clinical Trials

- KNDy neurons (Kisspeptin, neurokinin, dynorphin) in hypothalamus upstream of ventral hypothalamus
- Blockage of neurokinin 3 receptor abolishes hot flashes
- New drug fezolinetant dosing studies showed
  - ~70% reduction in frequency of hot flashes
  - 25% reduction in VMS score

1. Depypere H, et al. *J Clin Endocrinol Metab*. 2019;104(12):5893-5905.
2. Santoro N, et al. *Menopause*. 2020;27(12):1350-1356.

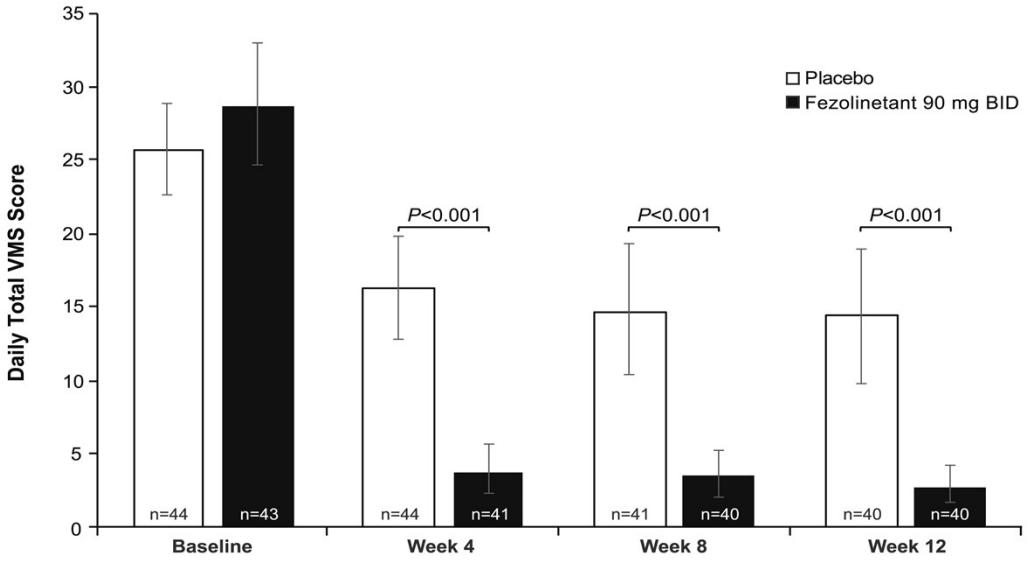
KNDy Neuron Circuitry

- KNDy neurons proliferate with ovarian ablation
- Specific blockade of the NK3 receptor on KNDy neurons abolishes hot flashes

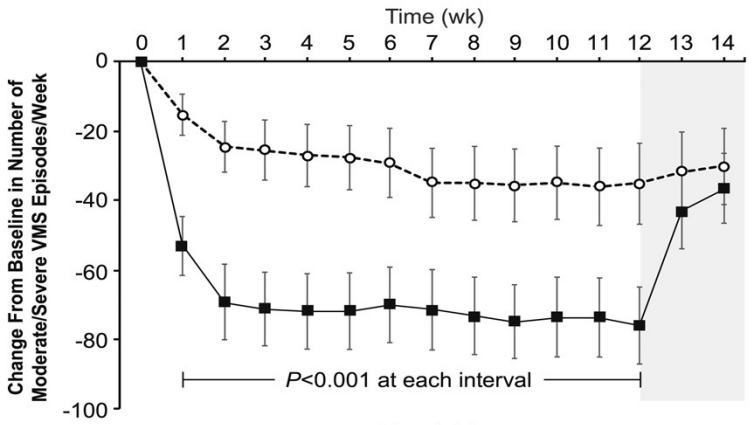


Rance NE, et al. *Front Neuroendocrinol*. 2013;34(3):211-227.

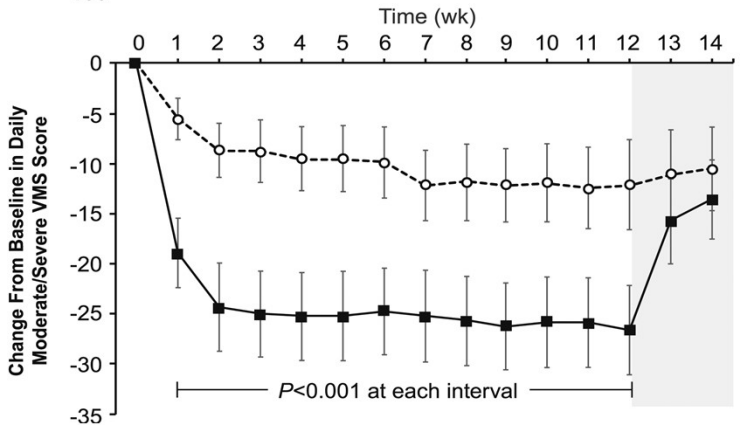
Effect of Fezolinetant on VMS Over Time



(A) Daily total VMS score during week 4 and week 12



(B) Frequency



(C) Moderate/ severe VMS score

Depypere H, et al. *J Clin Endocrinol Metab*. 2019;104(12):5893-5905.

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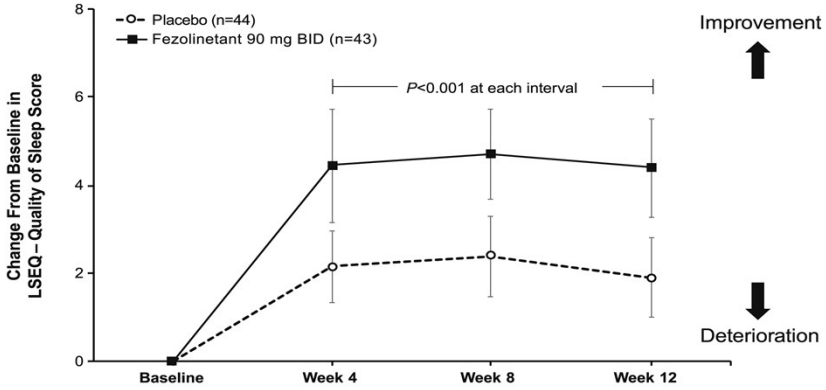
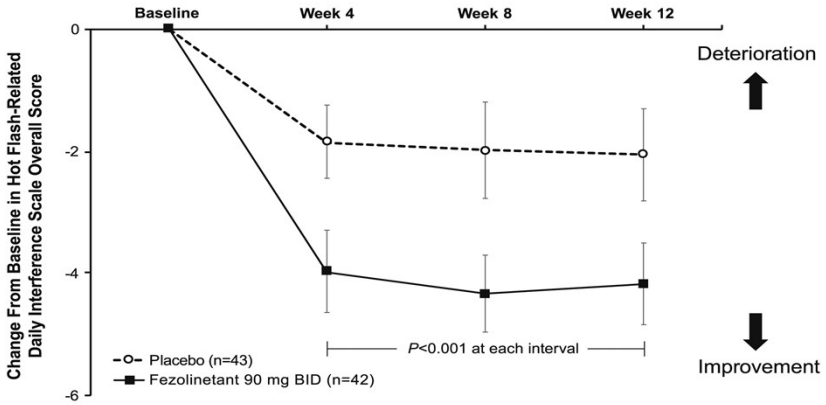
Effect of Fezolinetant on Quality of Life Measures

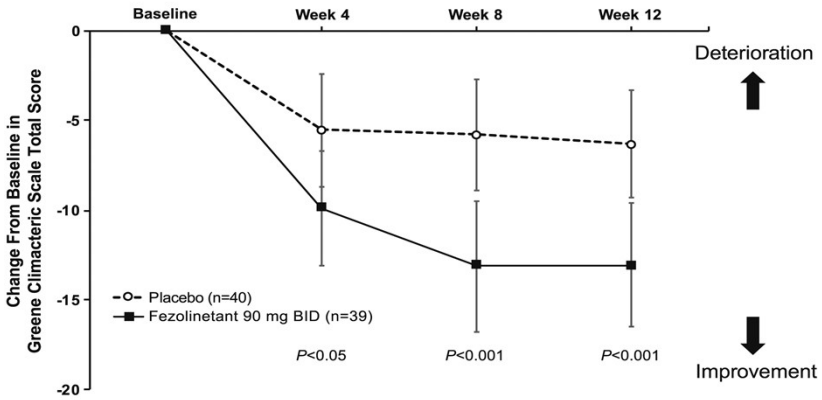
(A) SLEEP: LSEQ



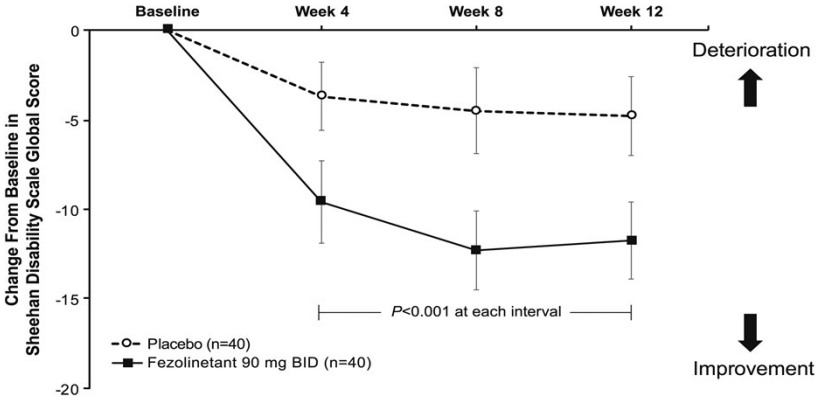
(B) HFRDIS



(C) Greene Climacteric Scale



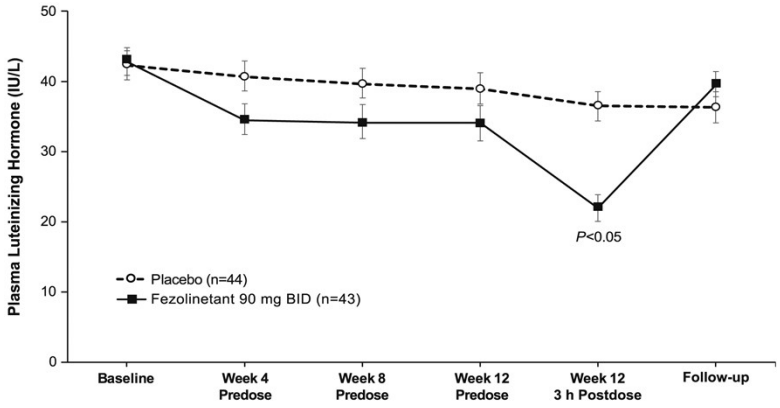
(D) Sheehan Disability Scale



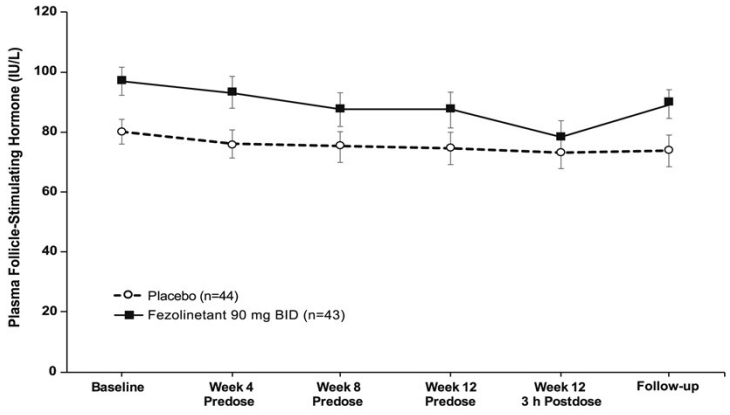
Depypere H, et al. *J Clin Endocrinol Metab*. 2019;104(12):5893-5905.

Effect of Fezolinetant on Plasma Hormones

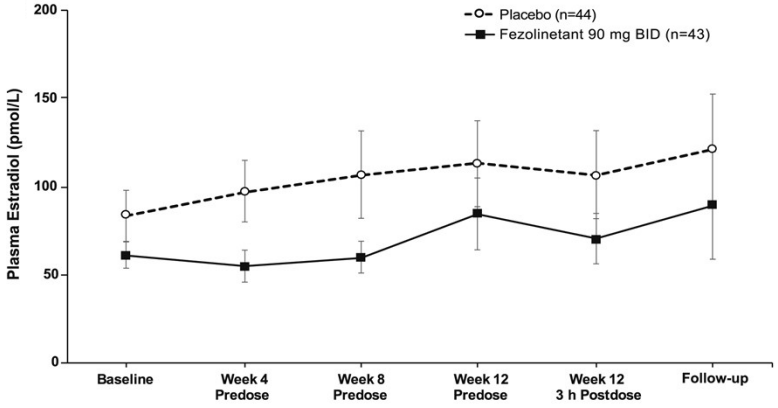
(A)
LH



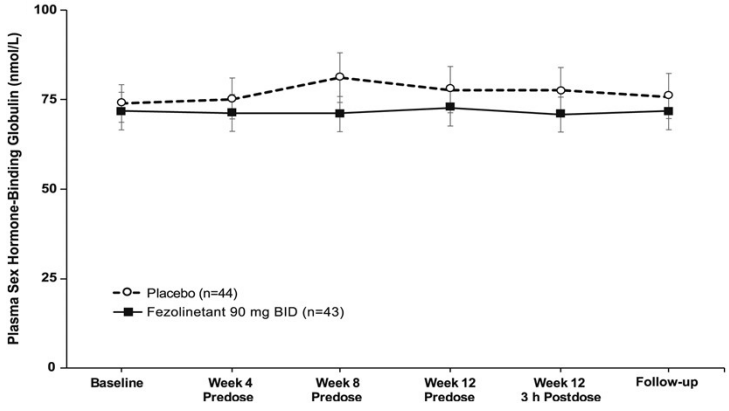
(C)
FSH



(B)
Estradiol



(D)
SHBG



Depypere H, et al. *J Clin Endocrinol Metab*. 2019;104(12):5893-5905.

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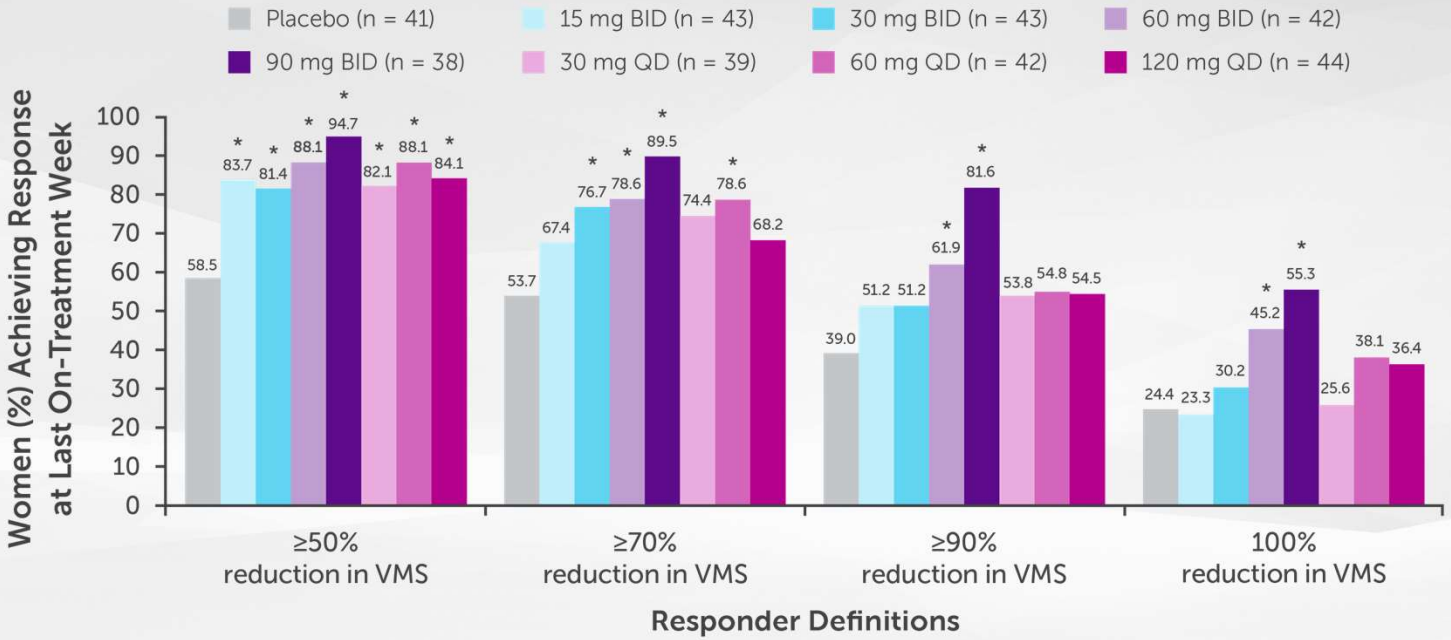
Reduction in Moderate/Severe VMS Frequency at Last On-Treatment Week (VESTA)



Responder analyses for reduction in moderate or severe VMS frequency at last on-treatment week. The last on-treatment week was defined as the last 7 days of treatment. $*P<0.05$ for paired comparisons of fezolinetant versus placebo at last on-treatment week, with no adjustments for multiplicity.

Santoro N, et al. *Menopause*. 2020;27(12):1350-1356.

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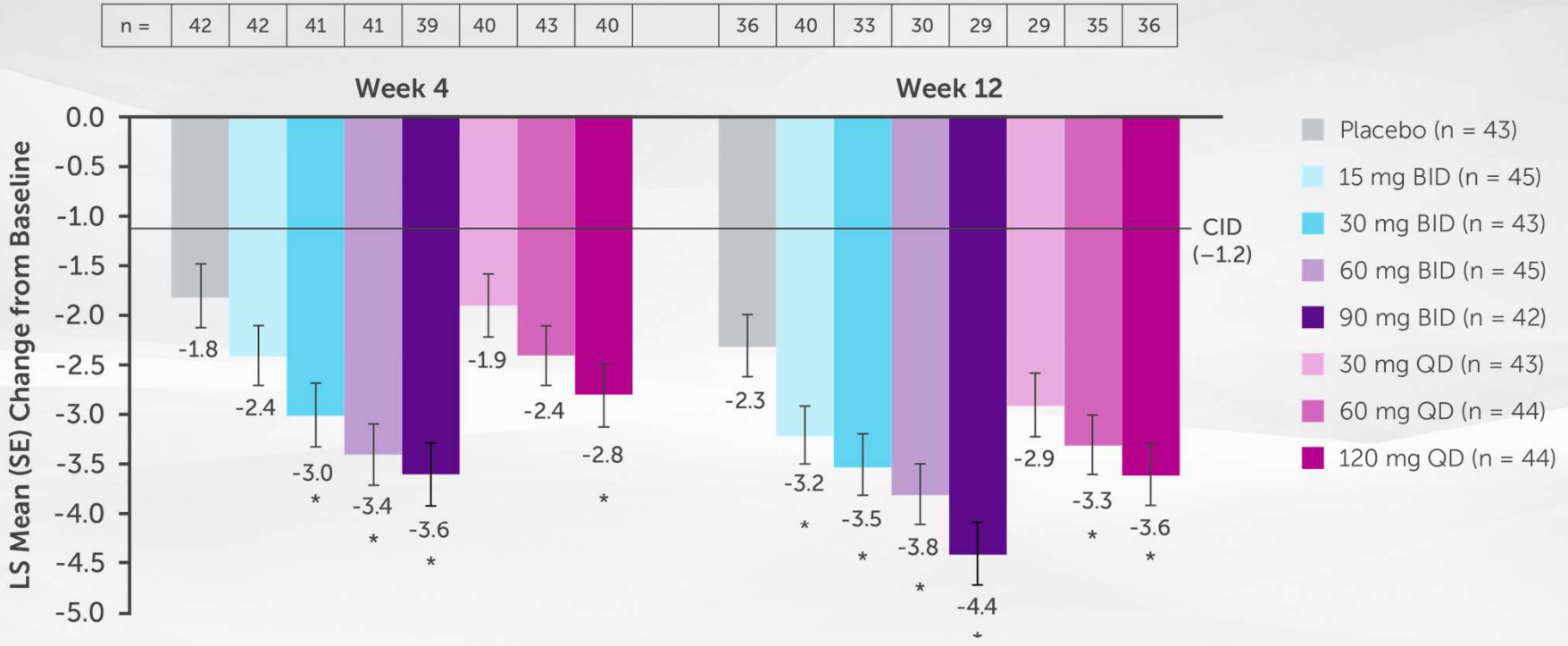
Change from Baseline–MENQOL Vasomotor Function Domain Score



Santoro N, et al. *Menopause*. 2020;27(12):1350-1356.

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Prescription Nonhormonal Drugs for Vasomotor Symptoms: Summary

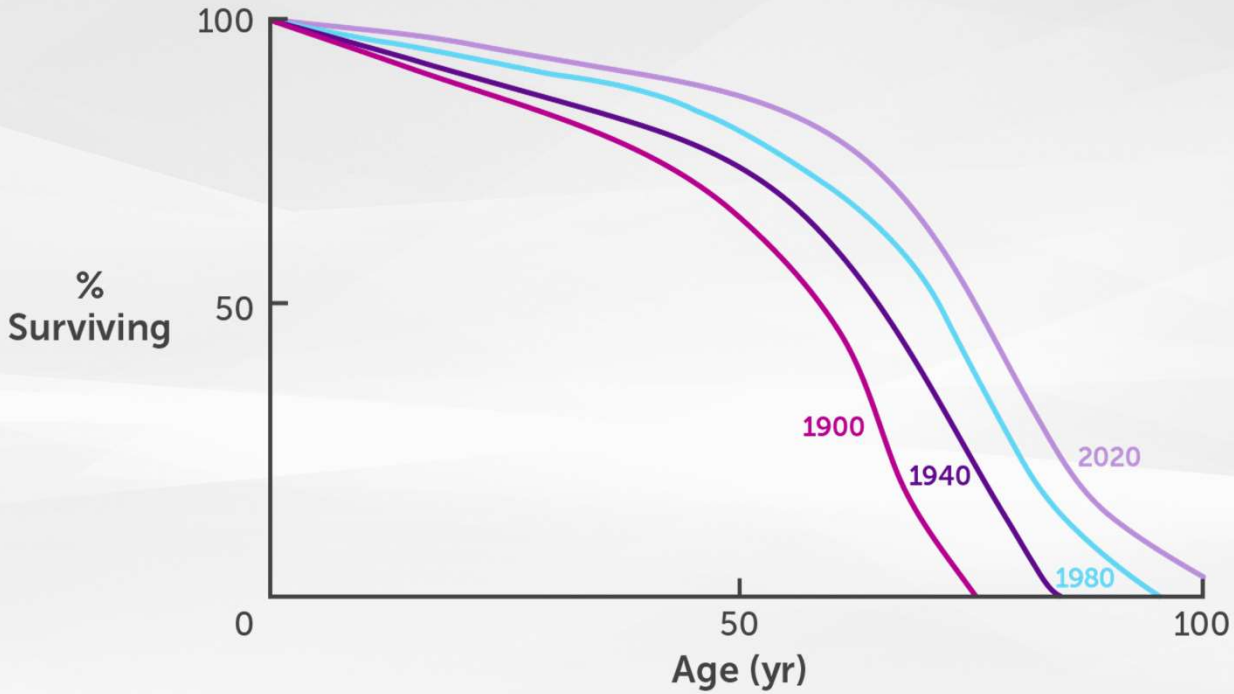
- Alternatives exist with a reasonable track record of efficacy and safety
- SNRI/SSRI drugs used in hundreds to thousands of women
- Gabapentin in hundreds
- Clonidine reported in a hundred
- Oxybutynin in hundreds
- Typical efficacy one-half that of estrogen, just edging placebo

New Agents for VMS

- Targeting of the NK3 receptor is a highly specific treatment that may address vasomotor symptoms at their origin
- In early clinical trials, superior efficacy compared to all other nonhormonals
- Highly effective nonhormonal treatment for hot flashes would be a welcome addition to the clinical armamentarium for menopausal medicine!

STAY TUNED!

Common Misconception About Change in Life Expectancy



Fries JF, Crapo LM. *Vitality and Aging*. W.H. Freeman; 1981.

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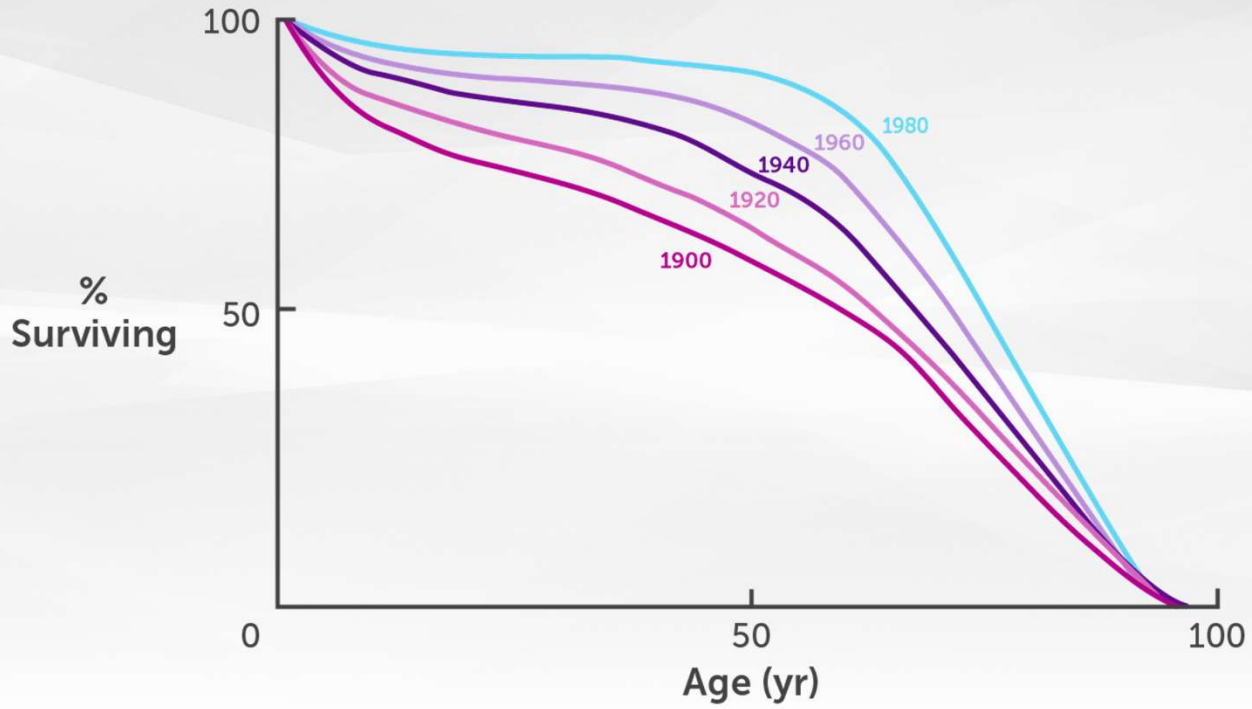
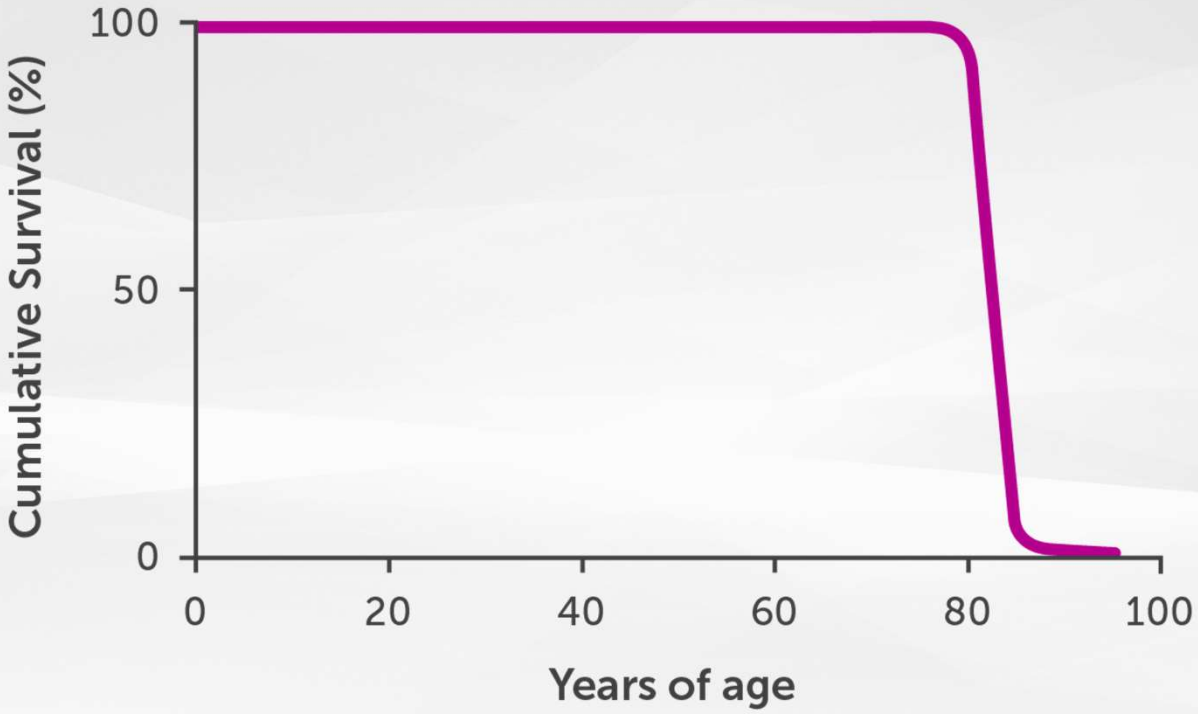
Human Survival Curves: US, 1900-1980



Fries JF, Crapo LM. *Vitality and Aging*. W.H. Freeman; 1981.

The Rectangular Survival Curve



The new NK3 receptor antagonist provides which of the following advantages over other nonhormonal treatments for hot flashes?

a) It has no adverse interactions with SSRIs used in breast cancer treatment.
b) It specifically targets the GnRH pulse generator
c) It blocks receptors on the pituitary that signal adequate estrogen in the circulation
d) It may have additional health benefits like bone protection and vaginal lubrication

Please submit questions for lightning round

- Bullet 1
  - Bullet 2
    - Bullet 3
      - Bullet 4
        - Bullet 5

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