New Horizons in the Management of Vasomotor Symptoms

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Patient and Provider Voice Initial Survey Results -

March 2021

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About the Paired Survey and This Report

- Designed to elucidate care gaps in VMS
  - Assessed provider perspective on QoL, treatment, and rationale
  - Used a modified version of the same questions for patients (edited to meet patient health literacy needs)
  - Compared the discrepancies to identify needs and gaps
- 209 patient respondents; 96 ob-gyn respondents
- This report contains survey response charts with cohort comparison not yet completed

Physician Survey Results

Physician Overview

Sample of **96** respondents

Who see ~6 patients per day with whom menopause symptoms are discussed

Which translates to an estimated

~11,520

interventions monthly by respondents

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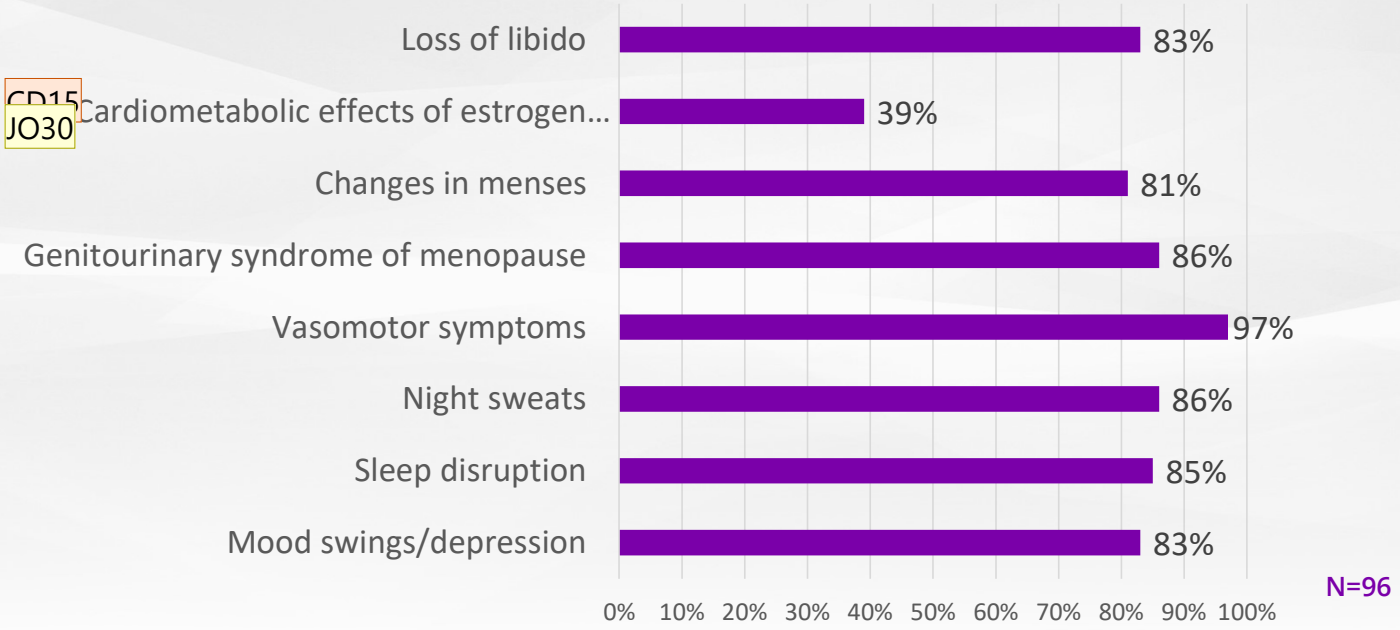
Patient Symptom Counseling

About which symptoms or conditions associated with menopause do you routinely counsel your patients?



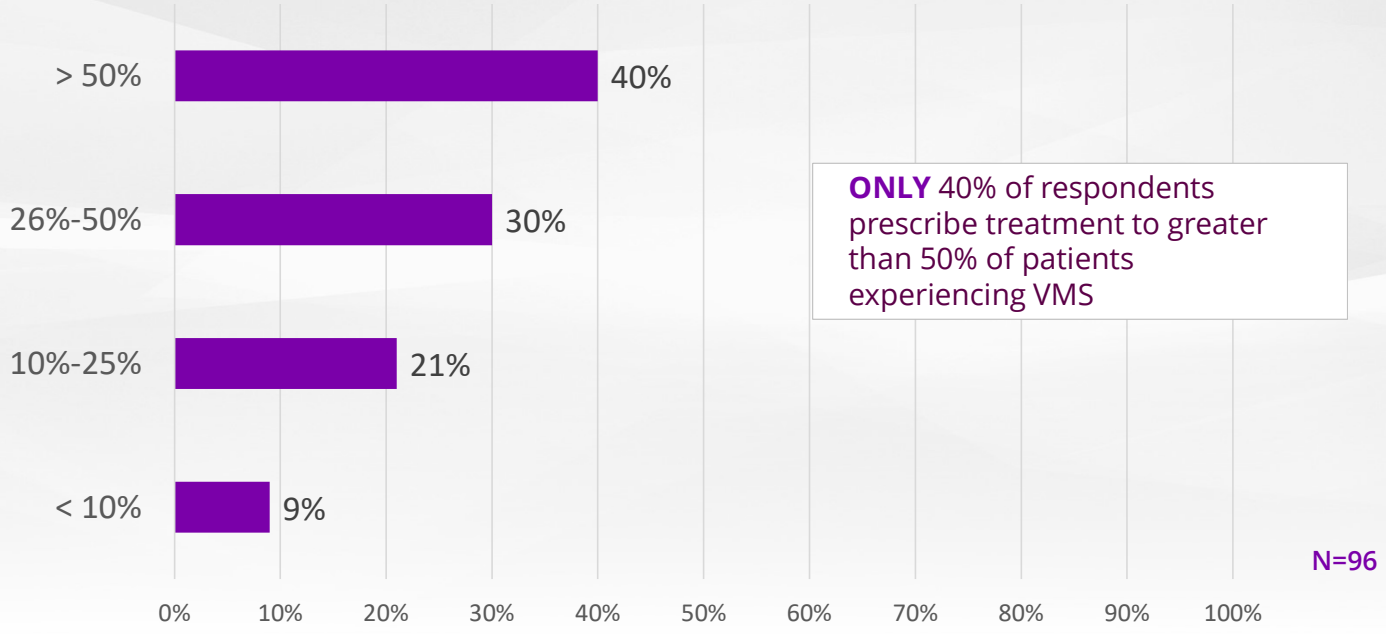
Slide 5

CD15 Is there more to this option that can be shown to avoid "..."?
Cindy Davidson, 4/15/2021

JO30 Sue: The rest of the text is embedded in the slide if you look at the data that underlies the chart
Judy Orvos, 4/15/2021

Prescribing Treatment for VMS

For what percentage of your menopausal patients with vasomotor symptoms (VMS) do you prescribe treatment?



ONLY 40% of respondents prescribe treatment to greater than 50% of patients experiencing VMS

N=96

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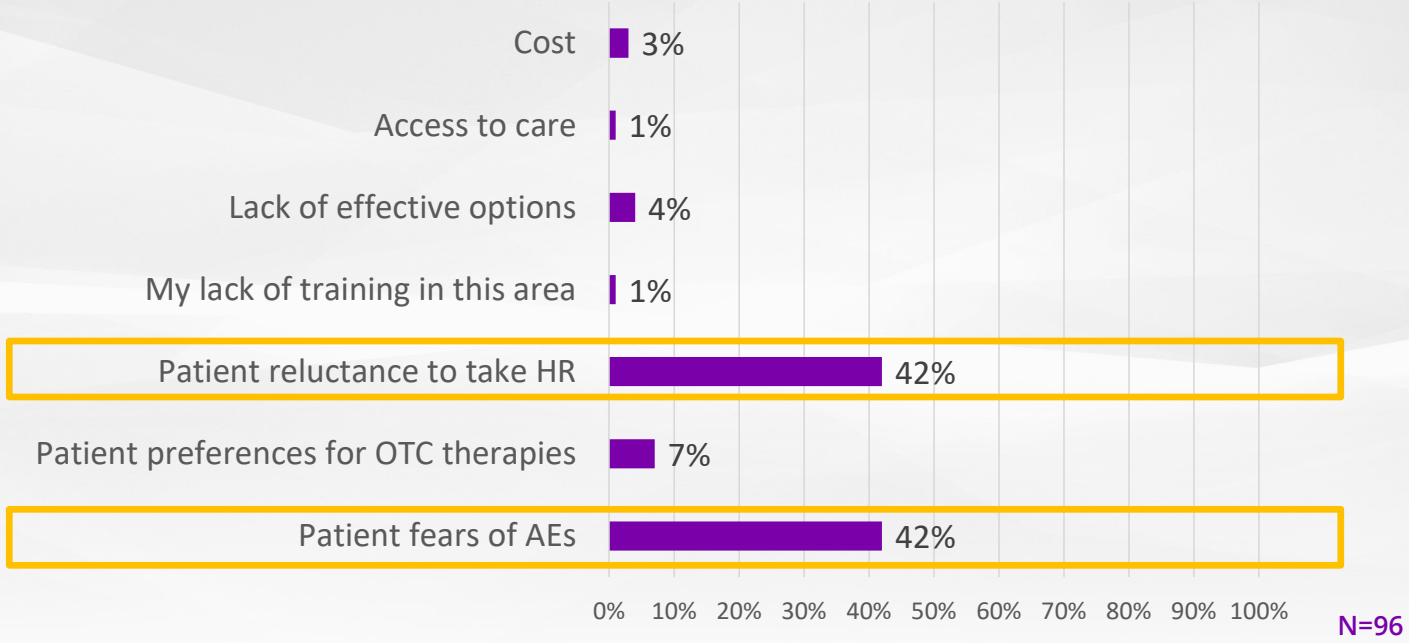
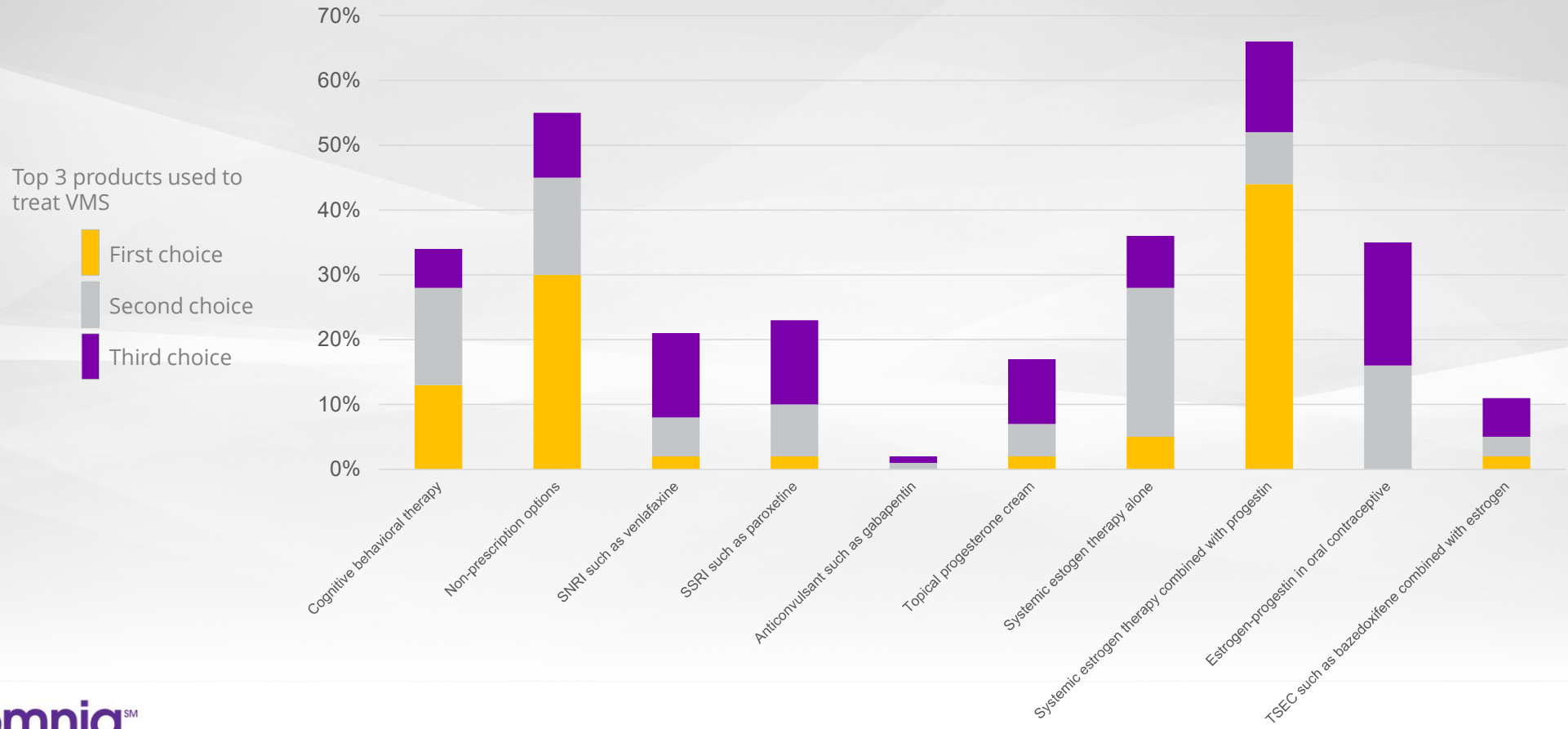
Barriers to VMS Treatment

What are the most important barriers to treatment of vasomotor symptoms (VMS) in your menopausal patients?



Preferred Products for Treatment of VMS



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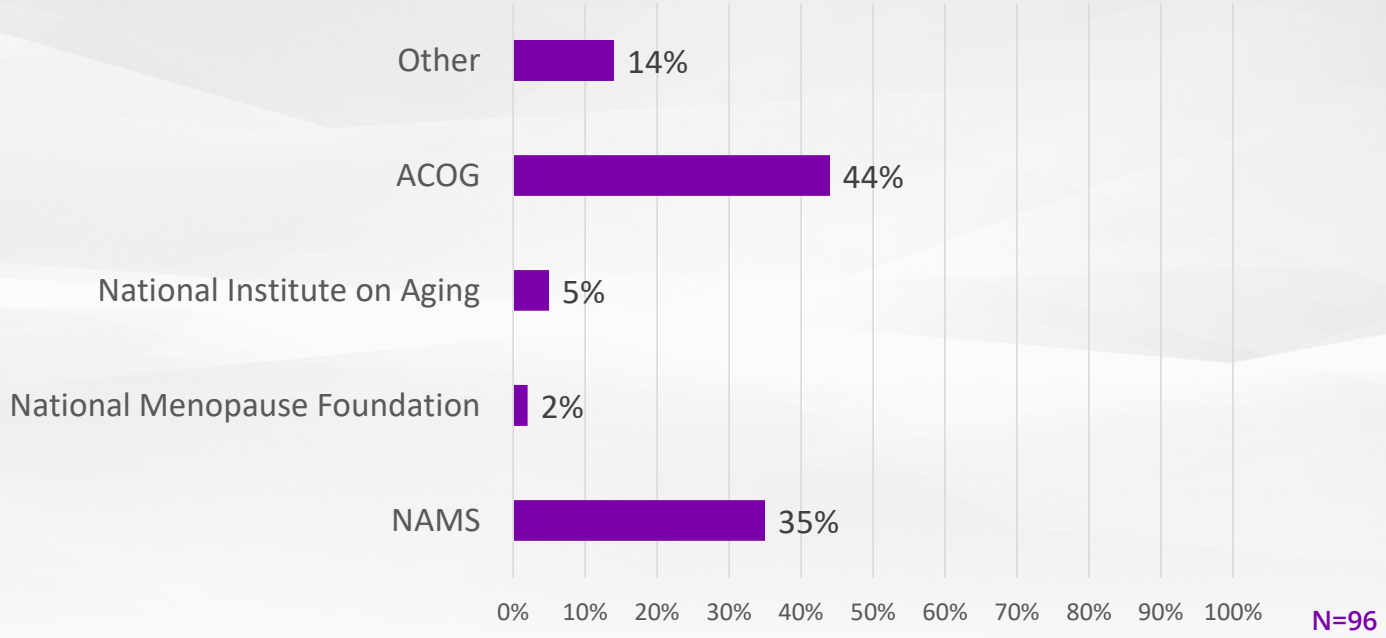
Sources of Patient Resources

What resources do you suggest to your patients for additional information about perimenopause/menopause?



Patient Survey Results

Patient Overview

Sample of **209** respondents who experience peri- or post-menopausal symptoms

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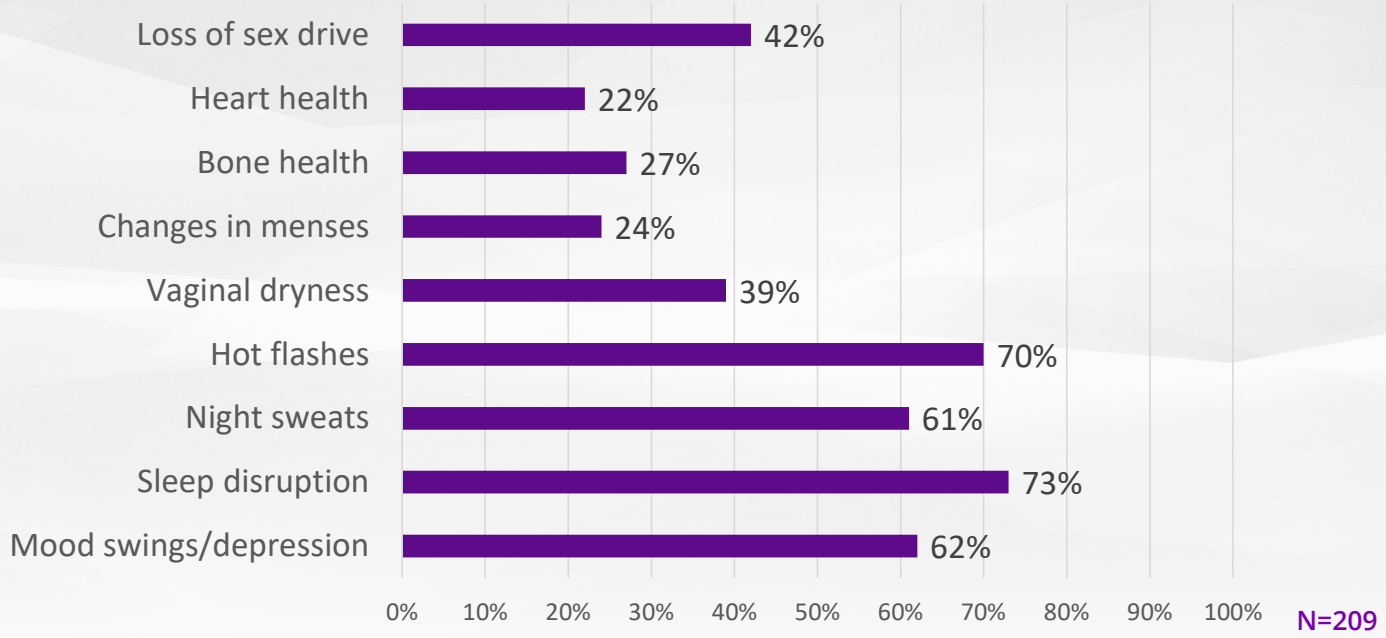
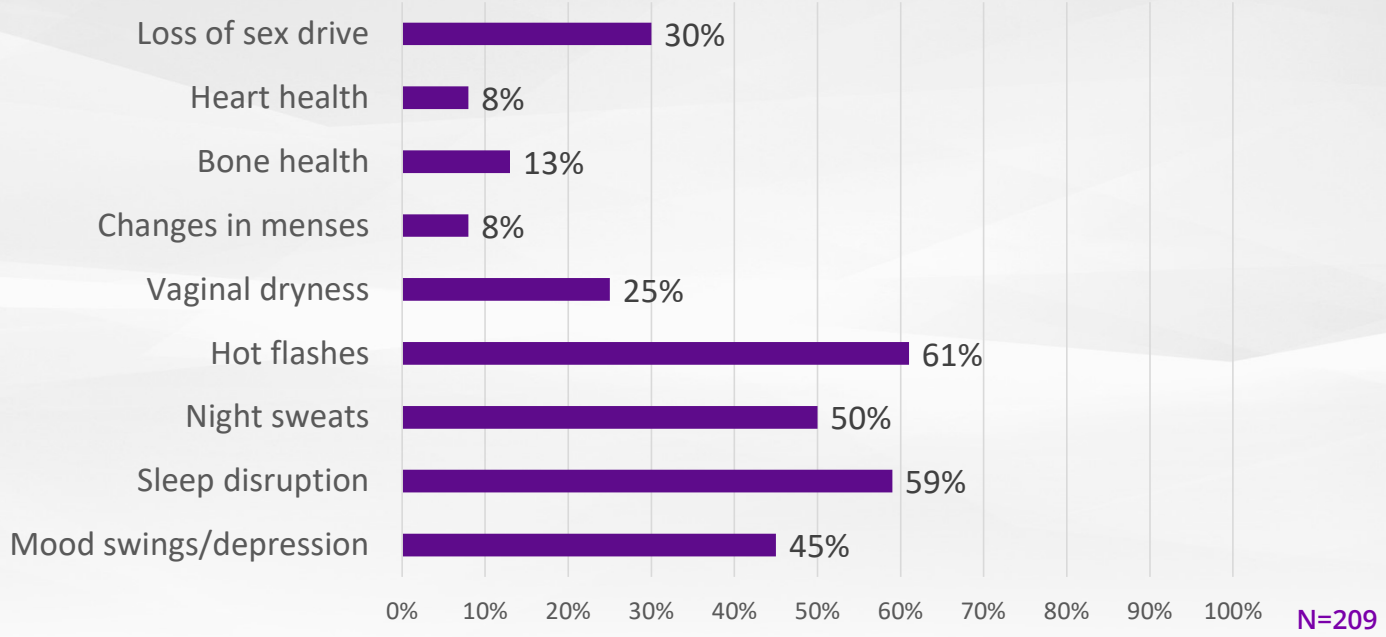
Symptom Discussions

Which symptoms or conditions associated with menopause do you talk to your doctor about?



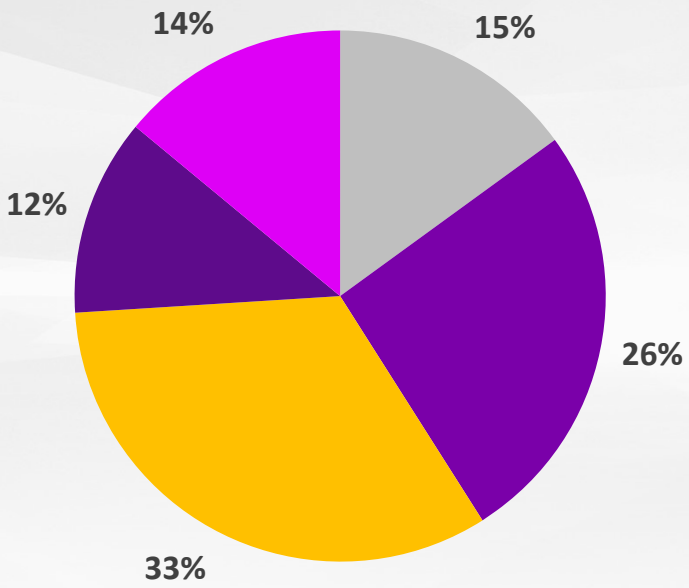
Symptom Effects

Which symptoms or conditions associated with menopause bother you the most? (Top 3)



Prescription Treatment for Symptoms

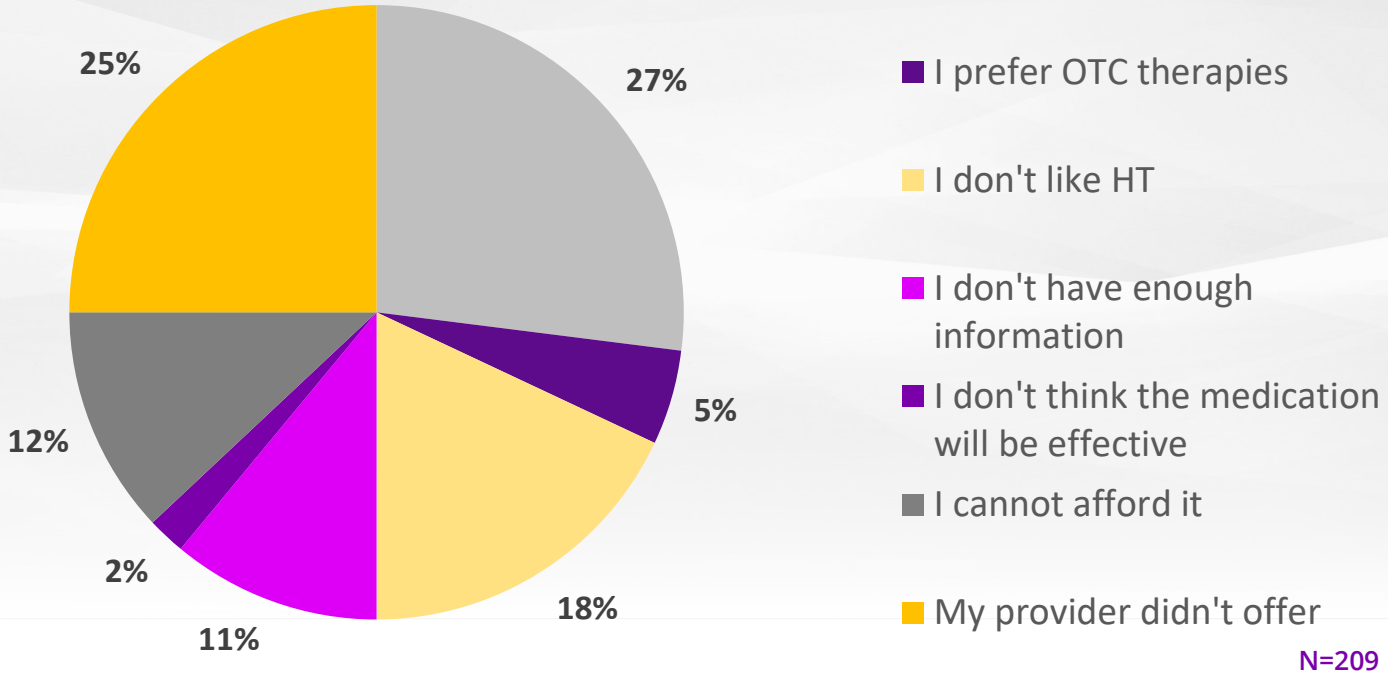
Has your doctor prescribed medication for your menopause symptoms?



N=209

Rationale for Not Taking Prescription Treatment for Symptoms

If you don’t take a prescription medication for your menopause symptoms, why not?



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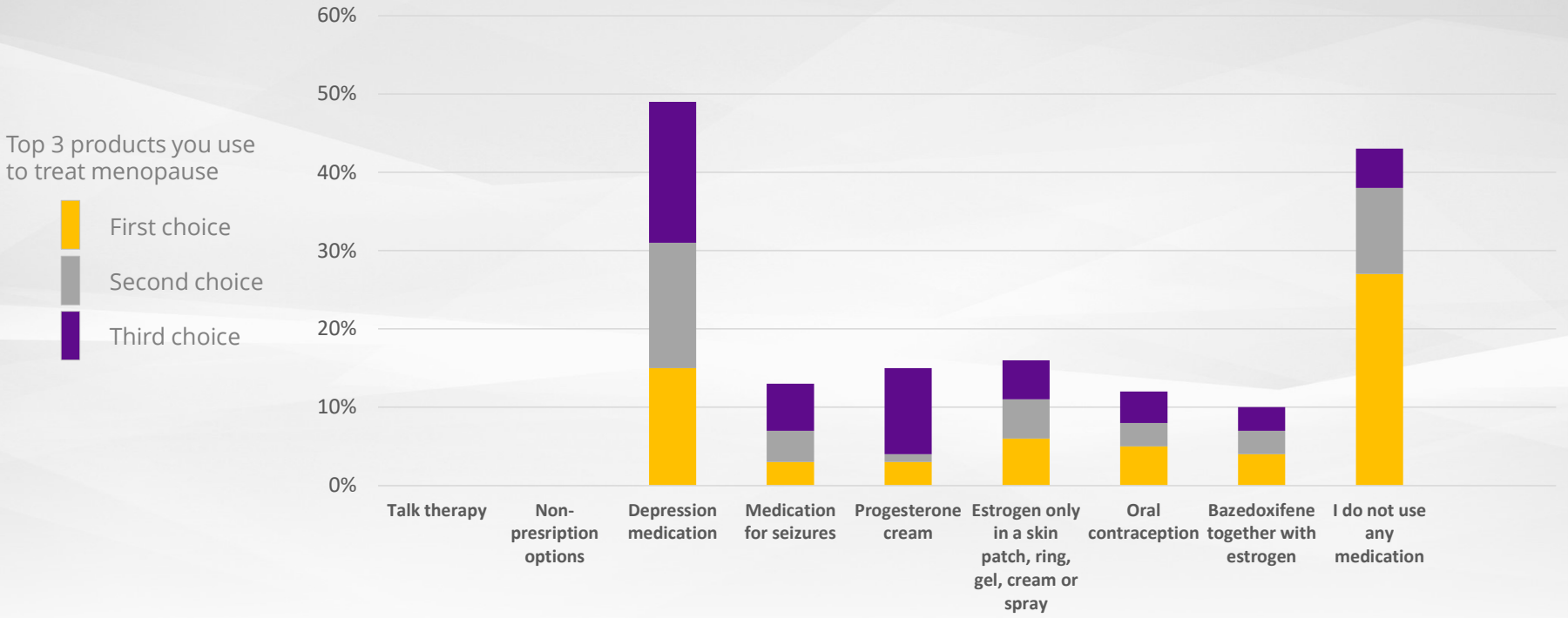
Preferred Products for Treatment of Symptoms



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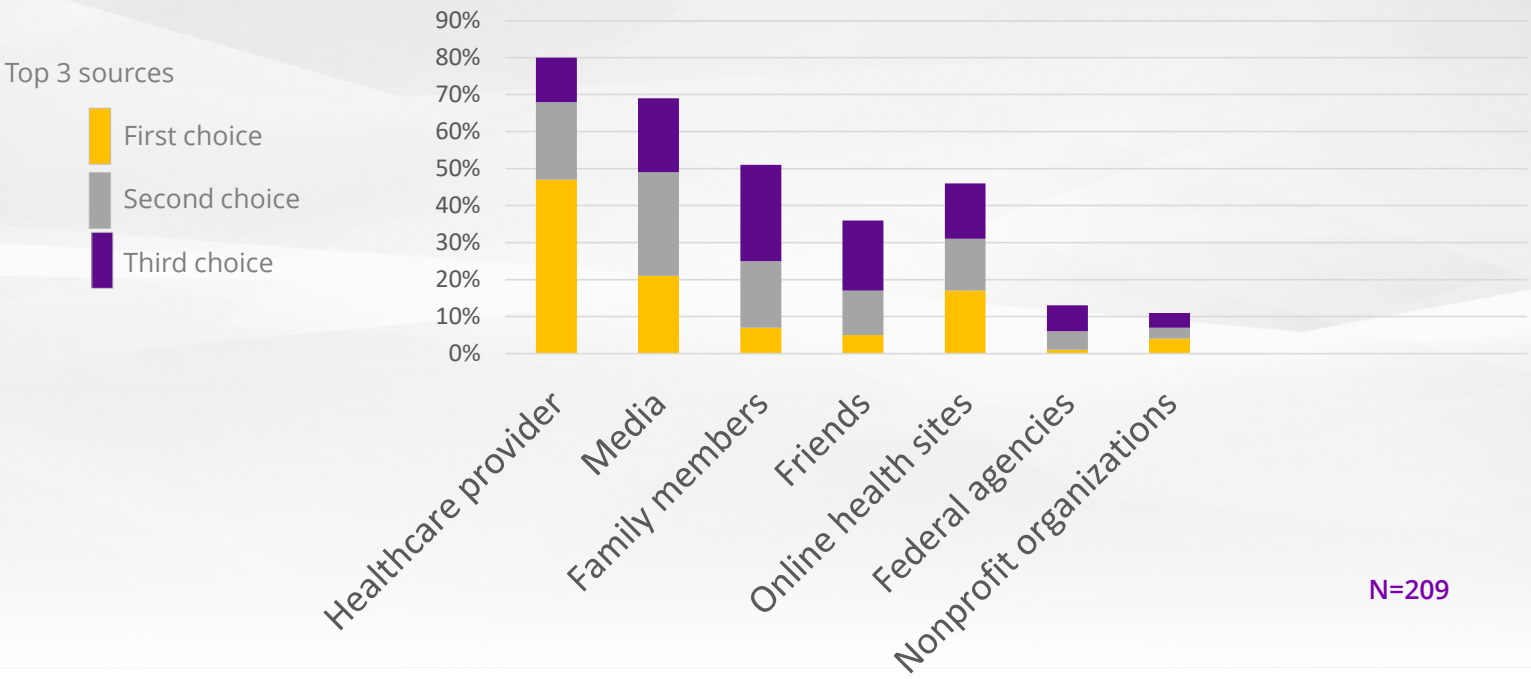
Sources of Information

What are your main sources for information about perimenopause/menopause?



N=209

Natural History of Hot Flashes

Transition stage	% Affected	Author
Premenopause	20% to 45%	Gold et al. 2006
Premenopause to early perimenopause	25% to 55%	Gold et al. 2006
Early to late perimenopause	50% to 80%	Gold et al./Politi et al. 2008
Late perimenopause to postmenopause	35% to 75%	Gold et al./Politi et al.
Late postmenopause (>5 yr)	16% to 44%	Barnabei et al./Politi et al.

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

The Burden of VMS

- Prevalence: 65% to 79% of women (N = 4,402)
- 7% to 9% with 7+ moderate to severe VMS daily
- In quality-of-life study (N = 2,703), hot flashes negatively affected:
  - Sleep (82%)
  - Concentration (69%)
  - Mood (68%)
  - Energy levels (63%)
  - Work (46%)
  - Social activities (44%)

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

How Many Women Seek Treatment for Symptoms?

- Population-based survey of women aged 40 to 65 (N = 3,135)
- 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***

Williams R. *Maturitas*. 2007;58(4):348-358.

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.

Hot Flashes Last Longer Than Previously Believed

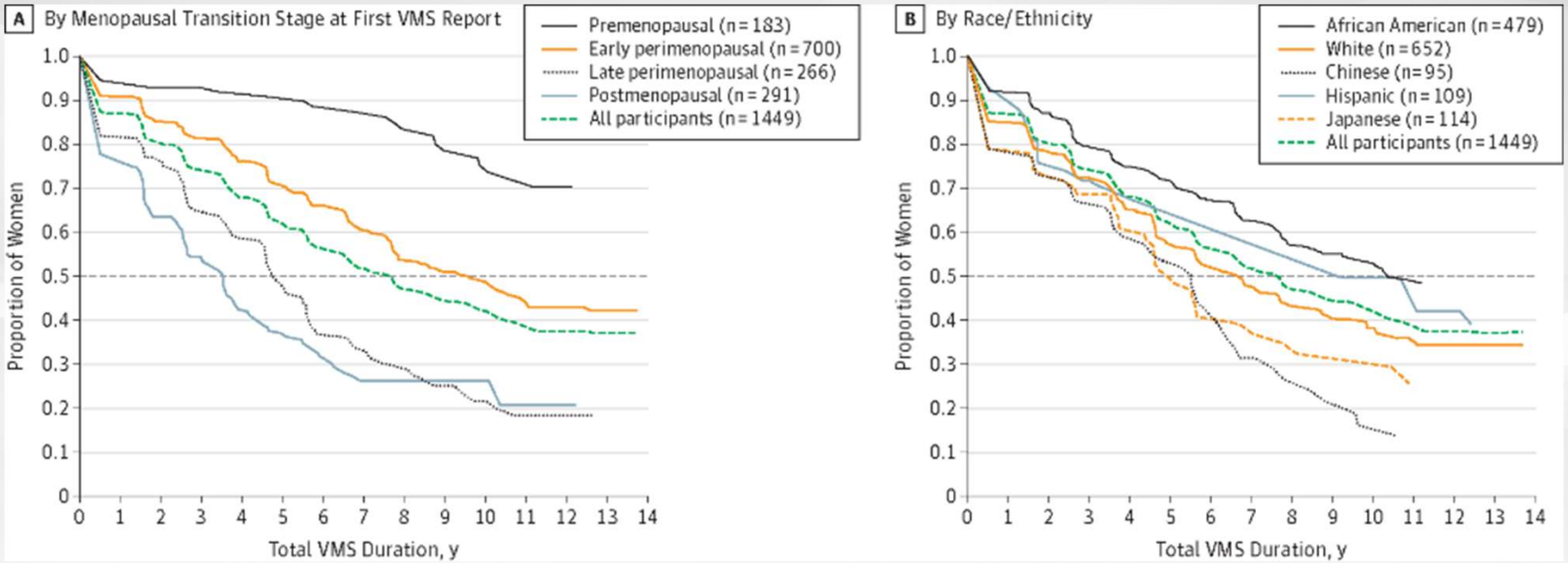
- 3,302 women from 7 US sites, followed for 17 years
- Median total VMS duration: 7.4 years
- >50% of women had duration >7 years of frequent VMS*
- >50% of women had >4 years post-FMP persistence of frequent VMS

*≥6 days over the past 2 weeks.

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

The JAMA Network

Total Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition



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

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Hormone Therapy:
Risks and Benefits of Traditional Treatments

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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.

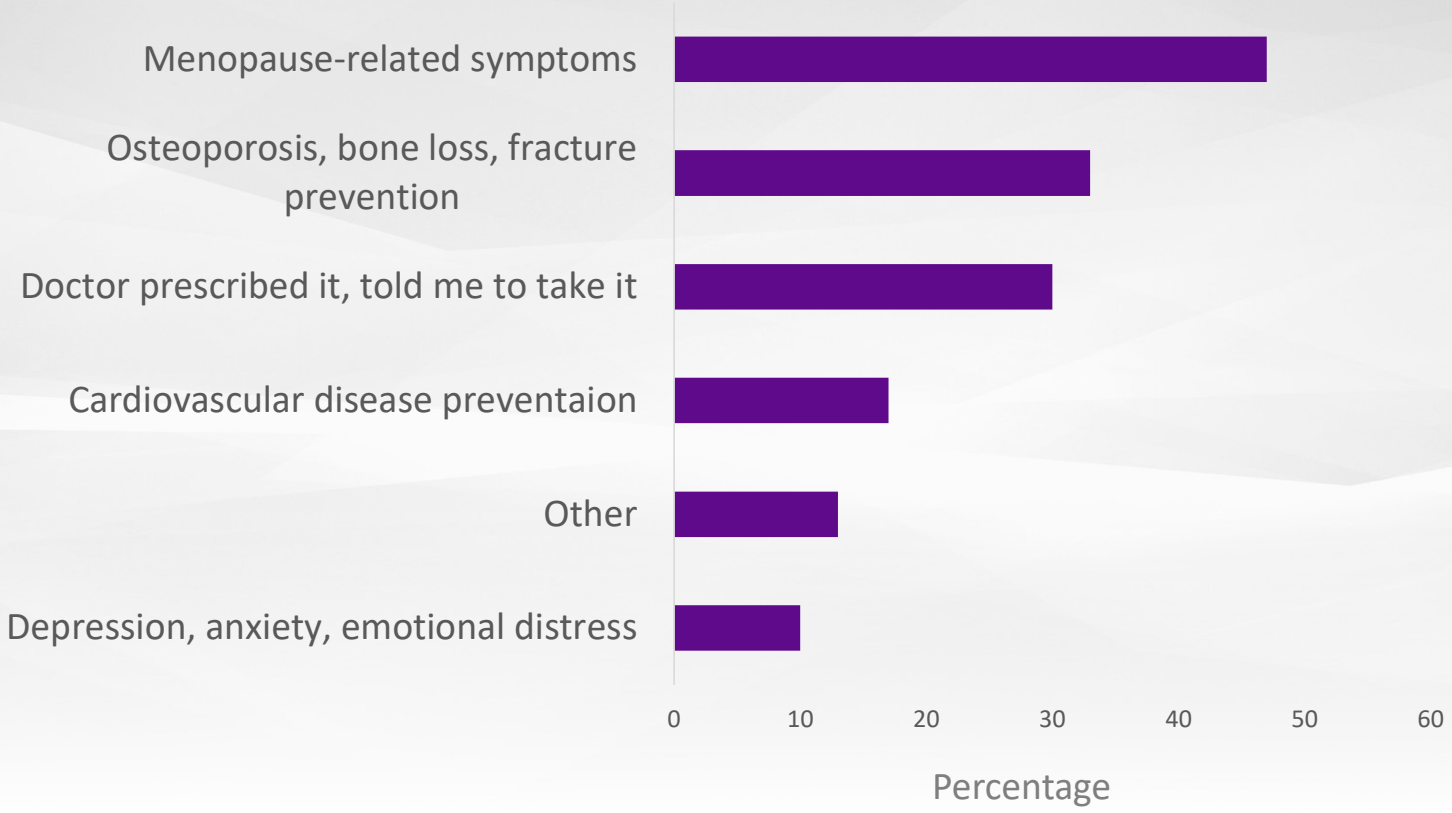
Discussion

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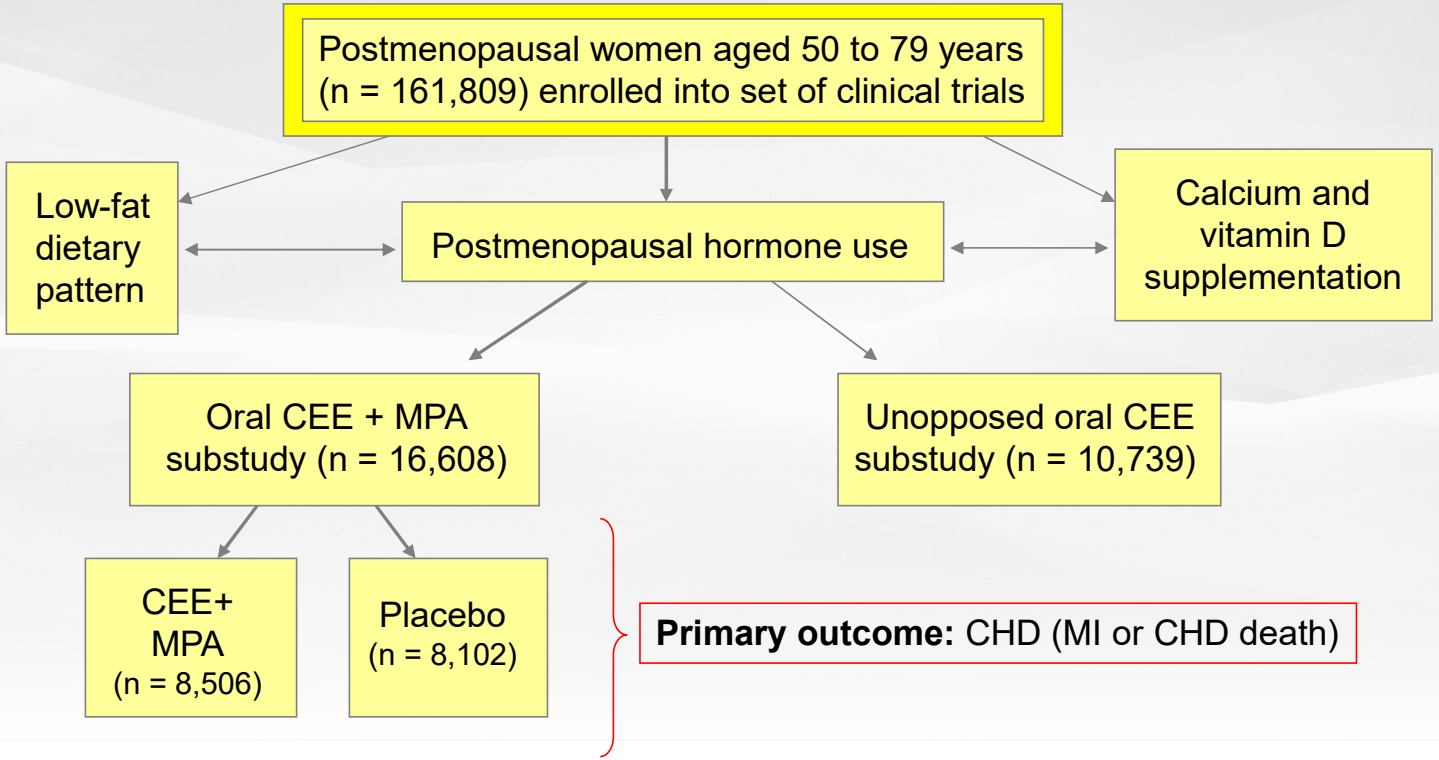
Women's Health Initiative (WHI): Study Design and Objectives



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

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

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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.

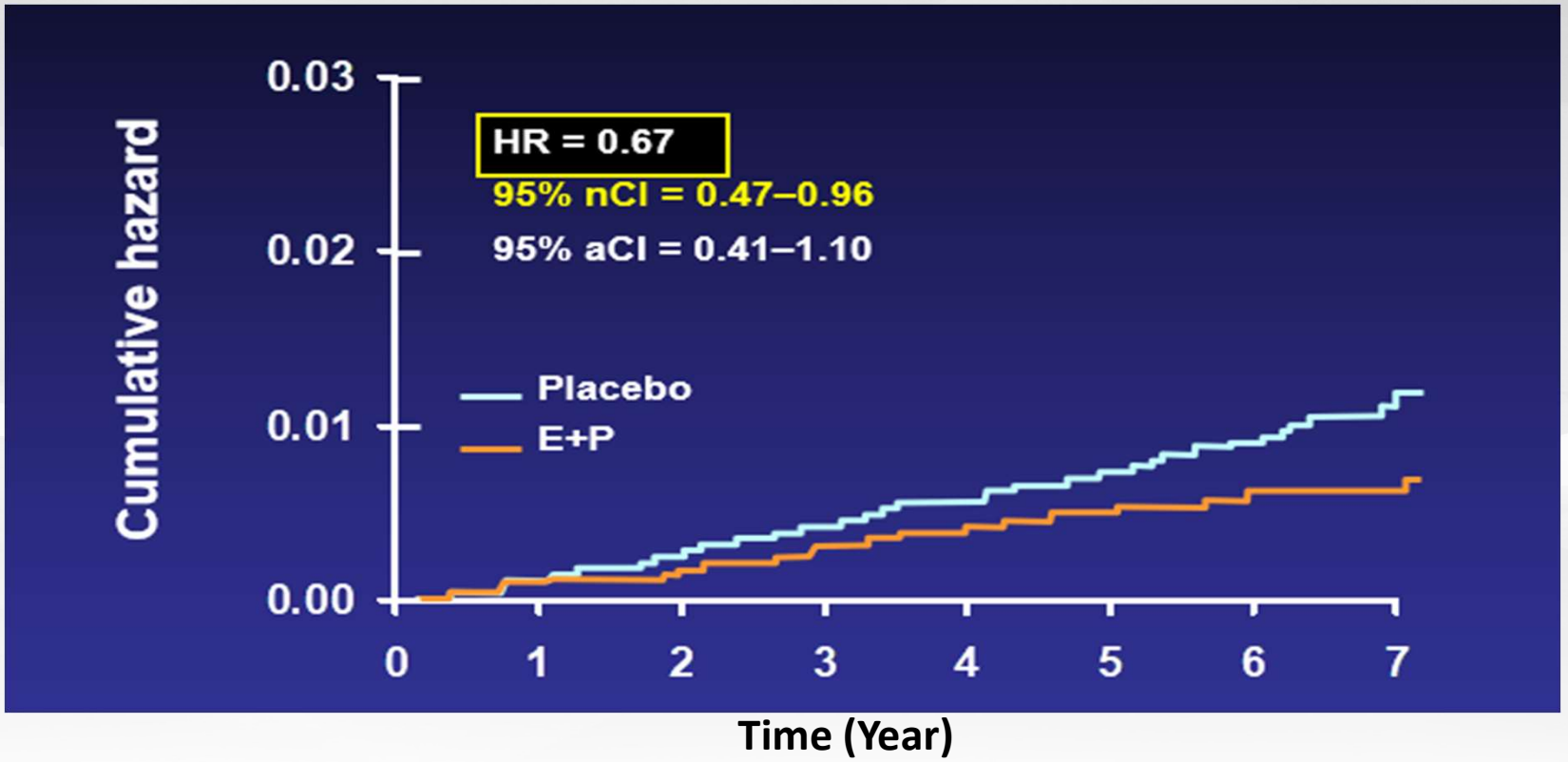
WHI

- Average age = 63
- Excluded women with menopausal symptoms
- Did not consider “disease latency”

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*

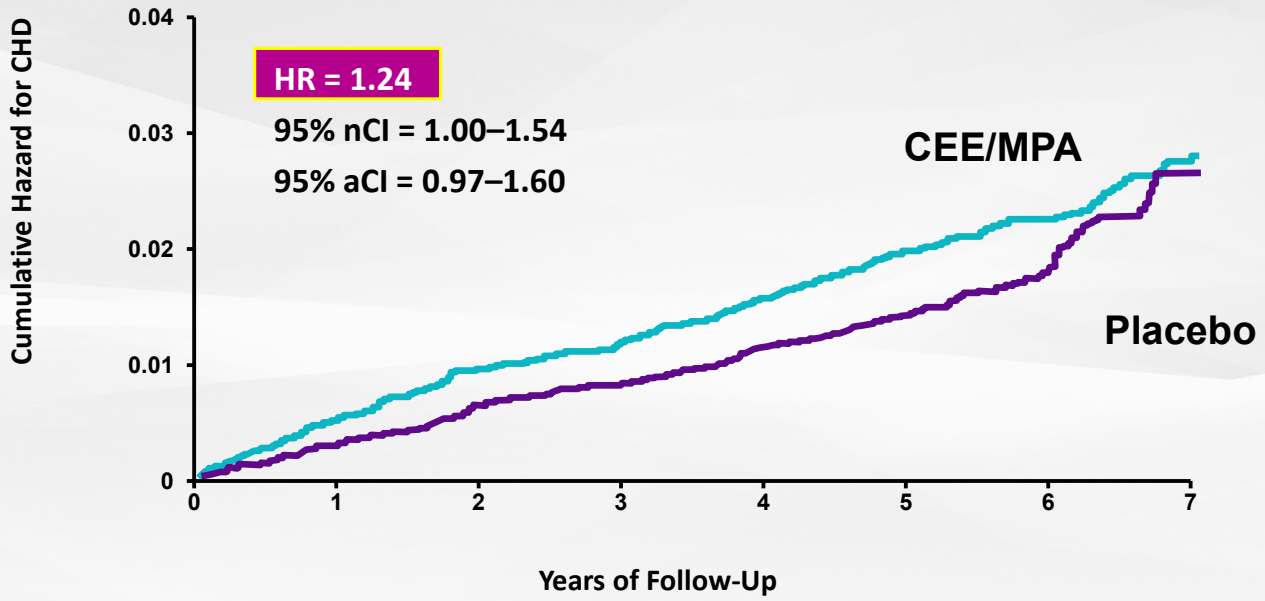
Nurses' Health Study (NHS), 1976–2000

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



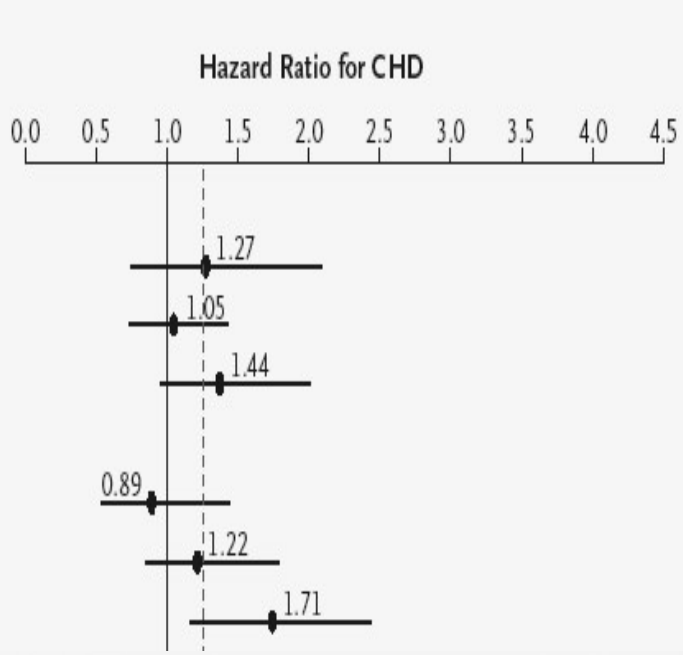
Includes 9 silent MIs

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

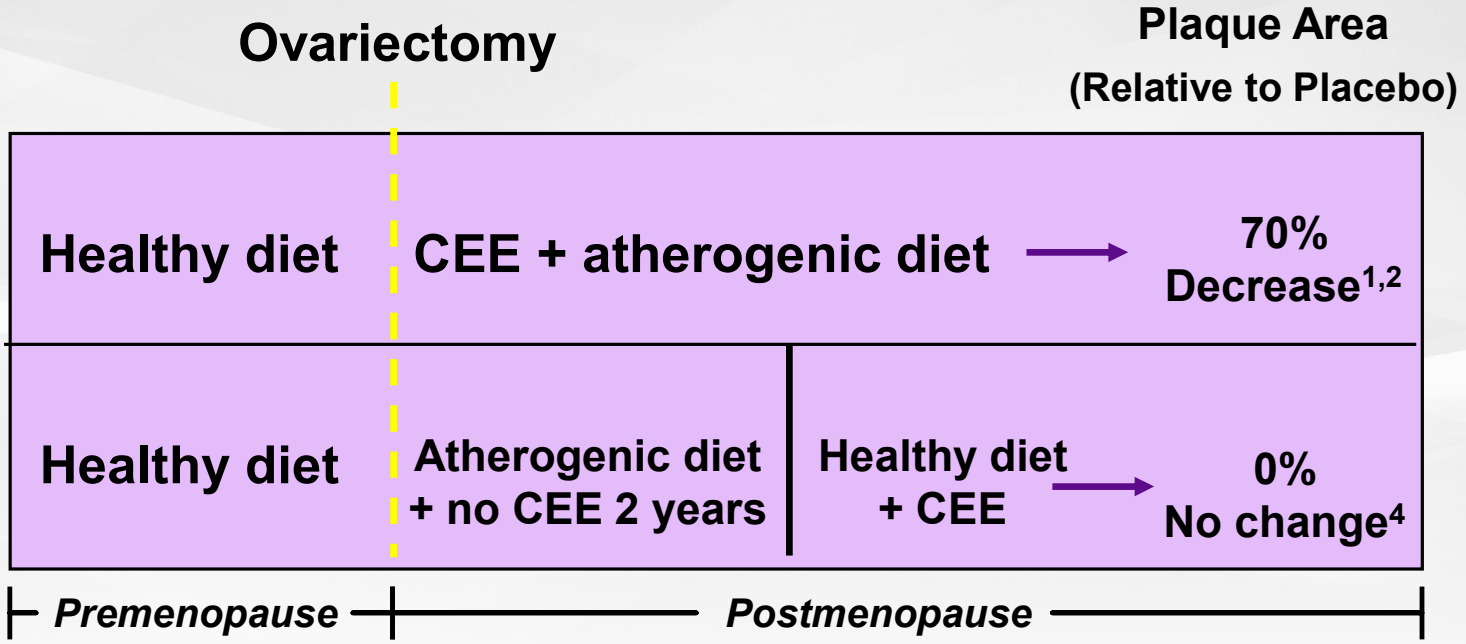
Manson JE, et al. *N Engl J Med*. 2003;349(6):523-534.

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)	



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.

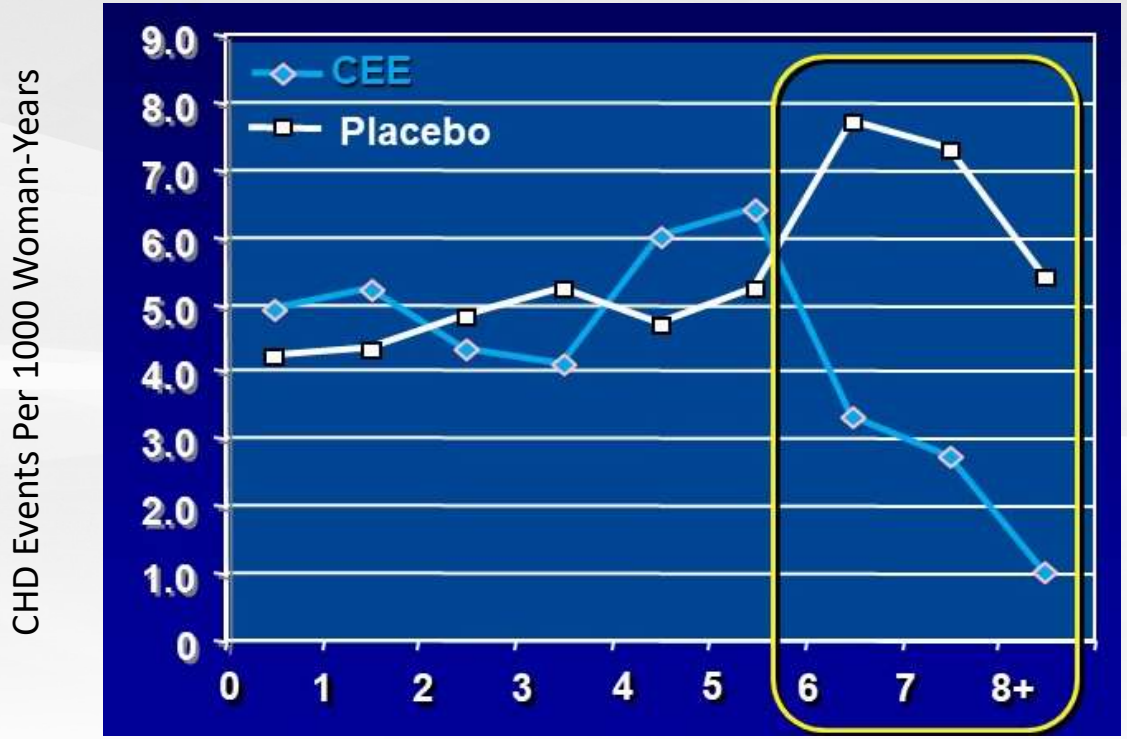
†Acute coronary syndrome includes myocardial infarction and hospitalized angina.

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

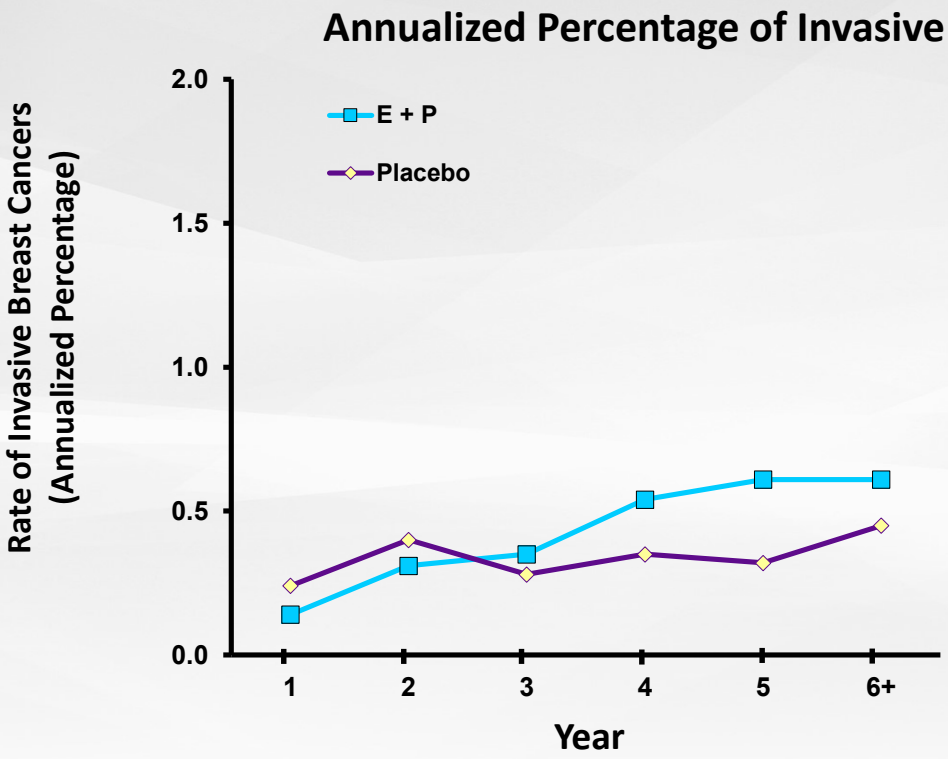


Hazard ratio 0.4

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

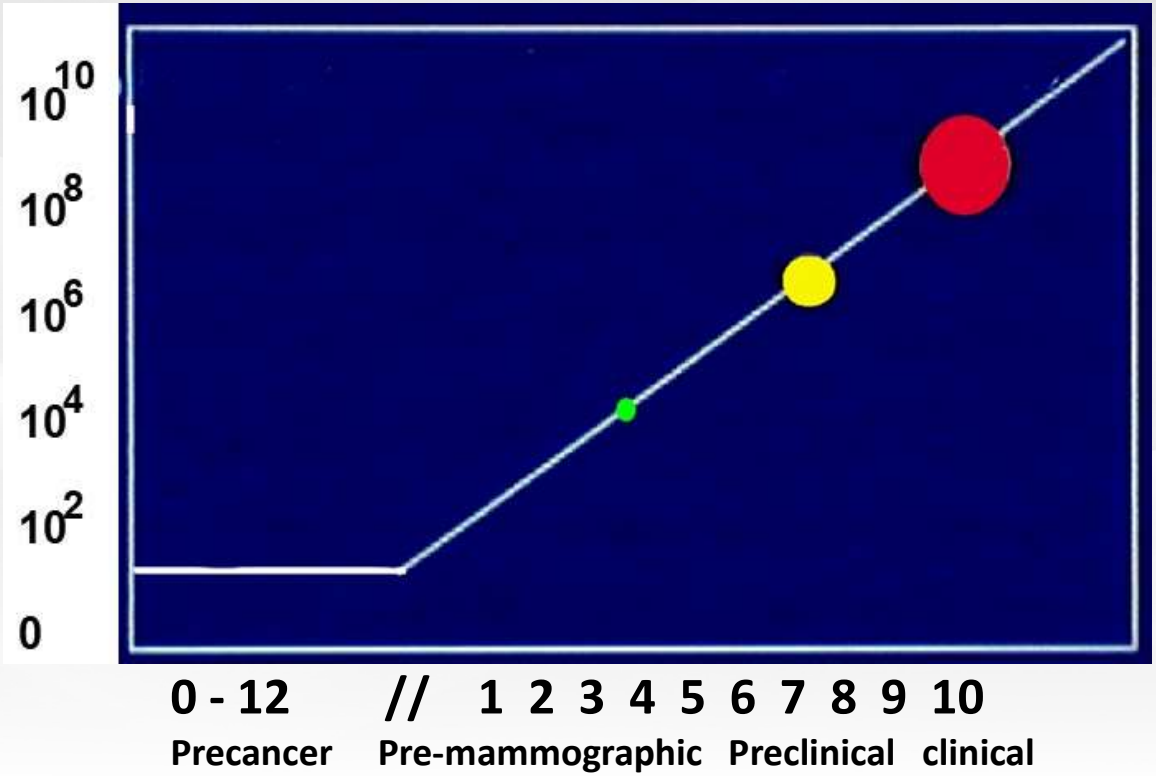


Year	Risk Ratio
1	0.60
2	0.77
3	1.26
4	1.54
5	1.99
6+	1.35

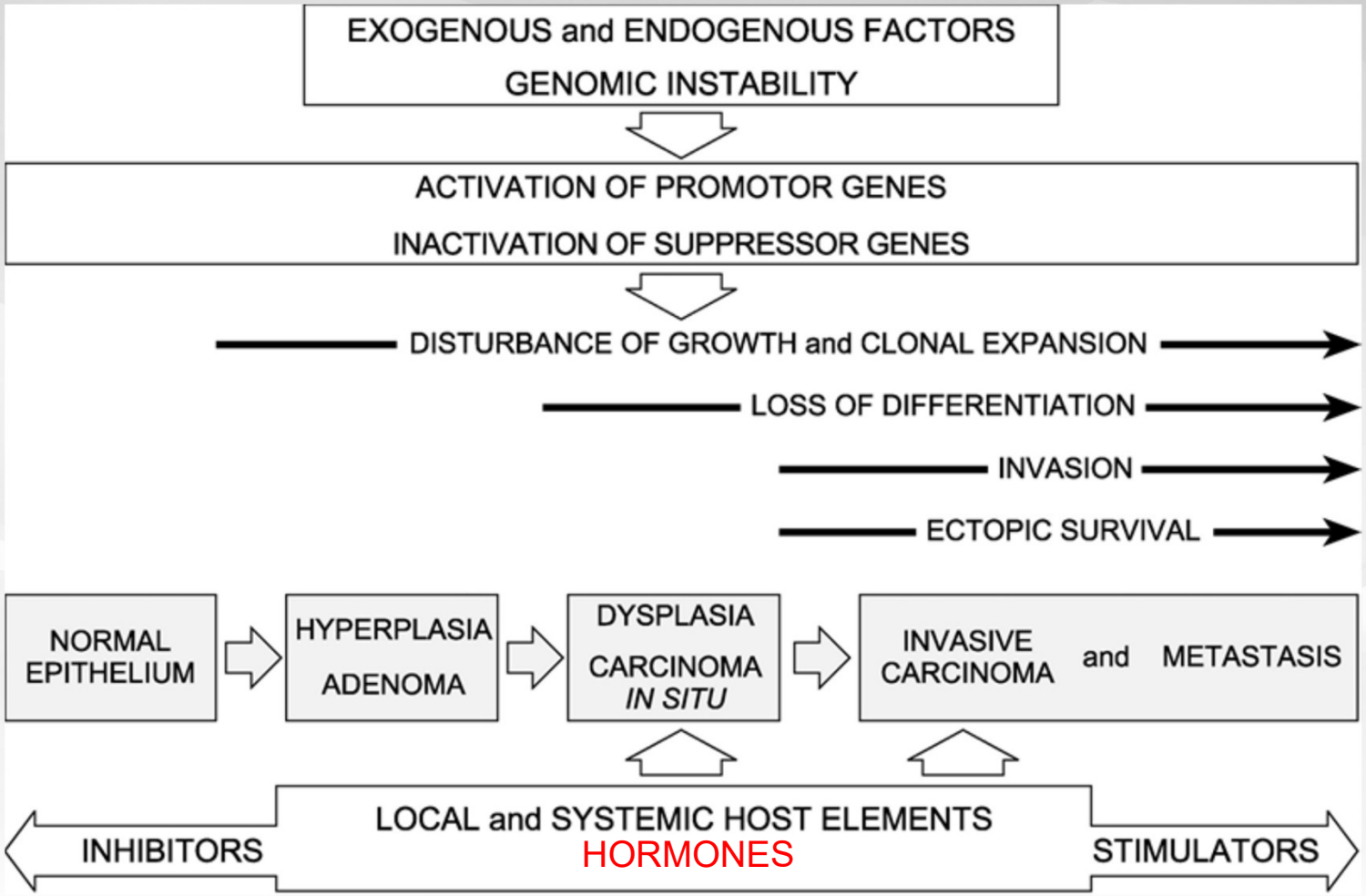
- *Overall: Estrogen plus progestin in subjects with and without prior HT.
- Chlebowski RT, et al. *JAMA*. 2003;289(24):3243-3253.

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

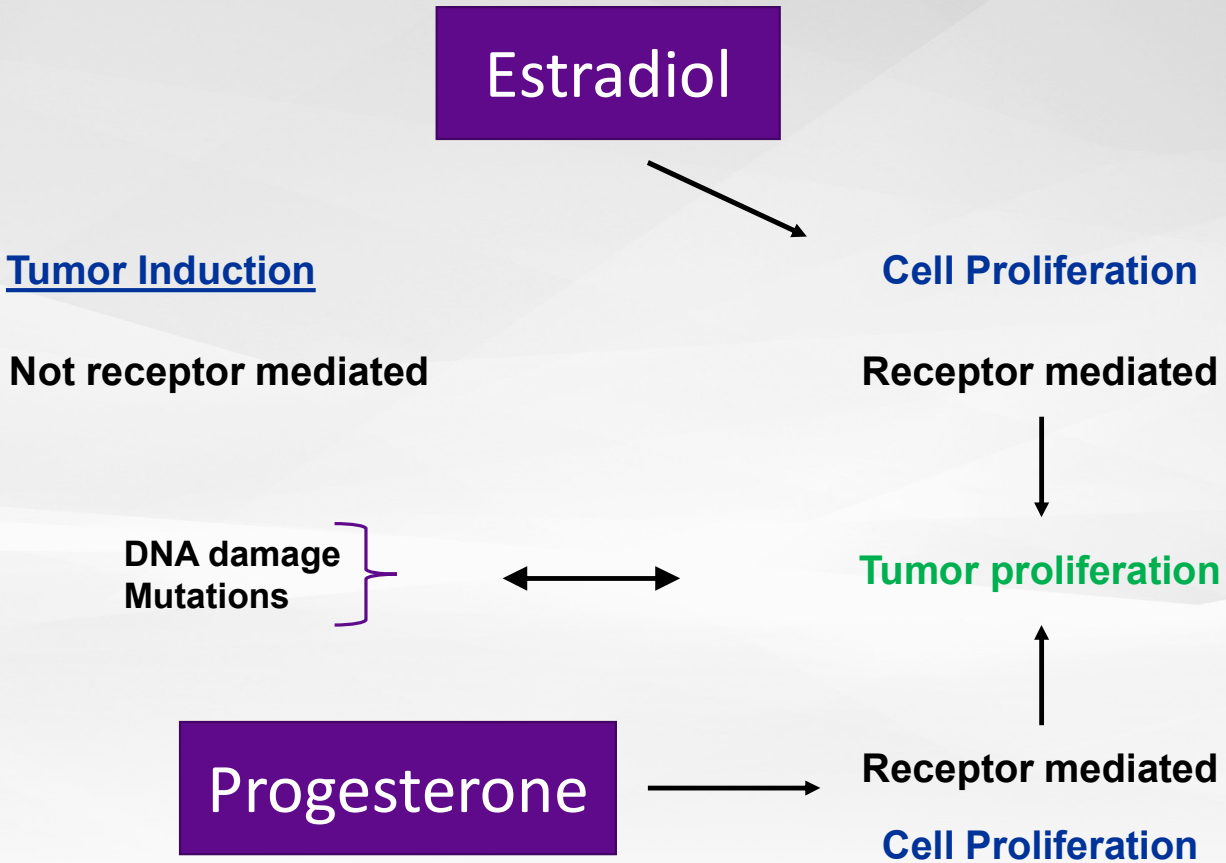
Time Course for Breast Cancer Development



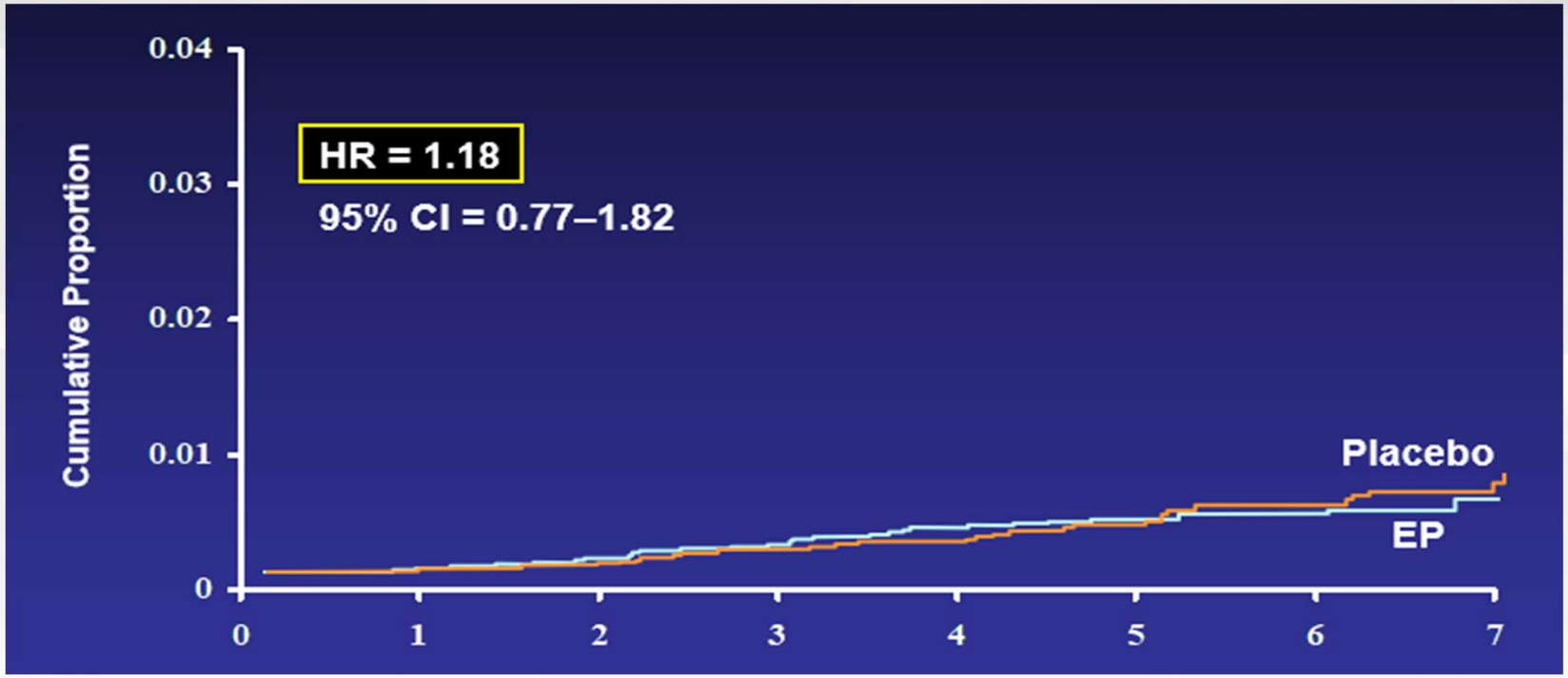
- Tan KHX, et al. *Br J Cancer*. 2013;109(8):2035-2043.



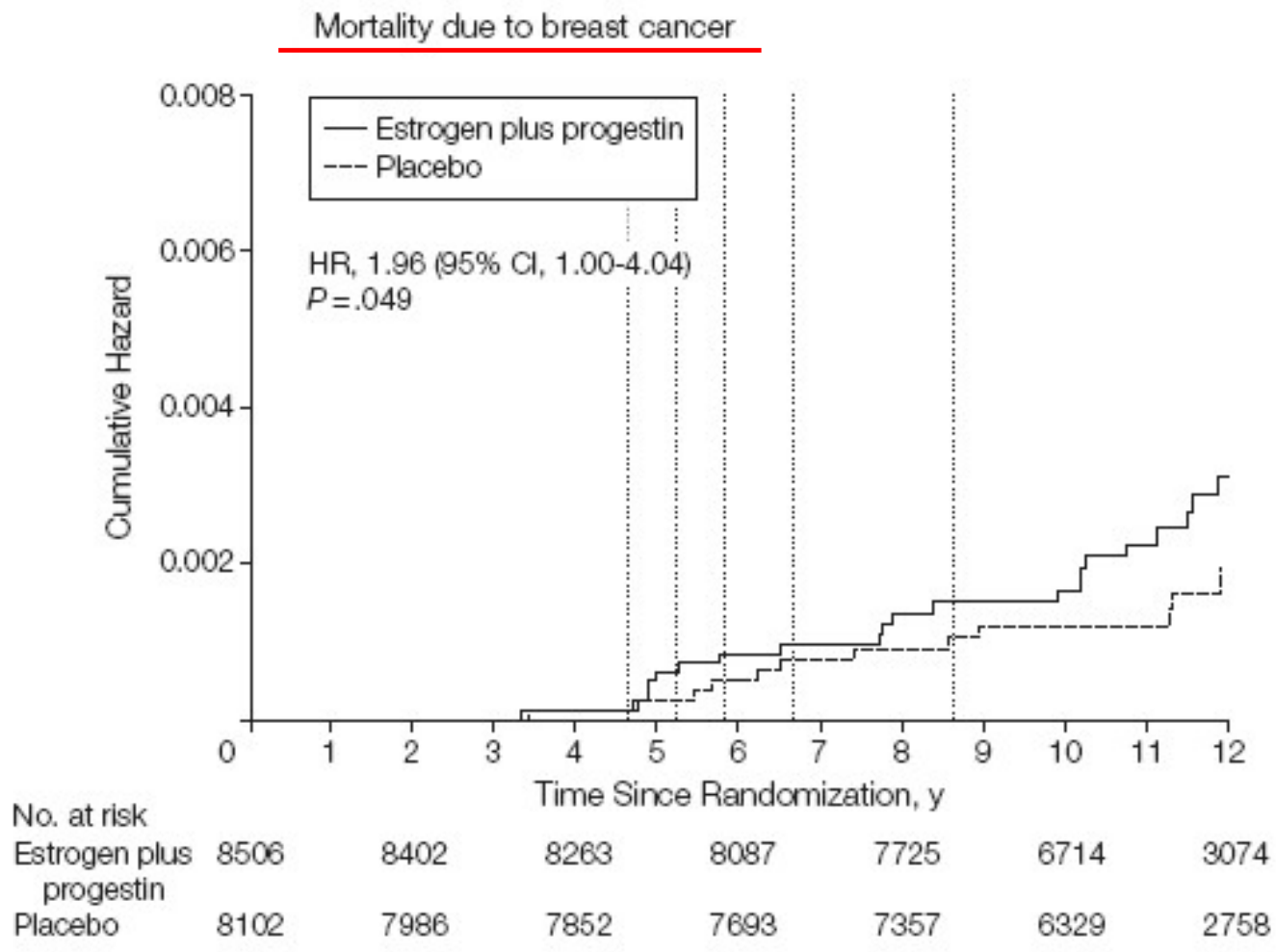
Modified from Mareel M, Leroy A. *Physiol Rev*. 2003;83(2):337-376.


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

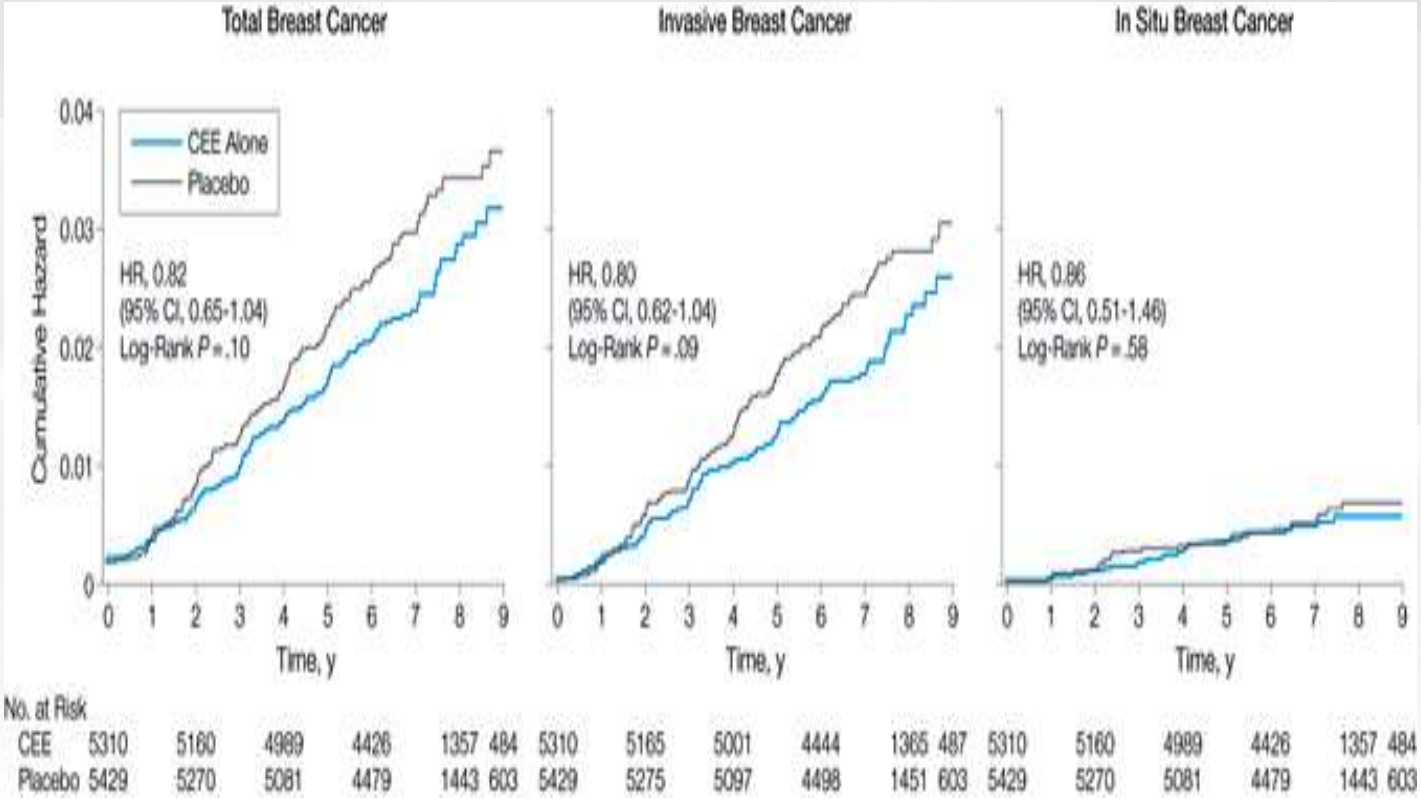


Chlebowski RT, et al. *JAMA*. 2003;289(24):3243-3253.



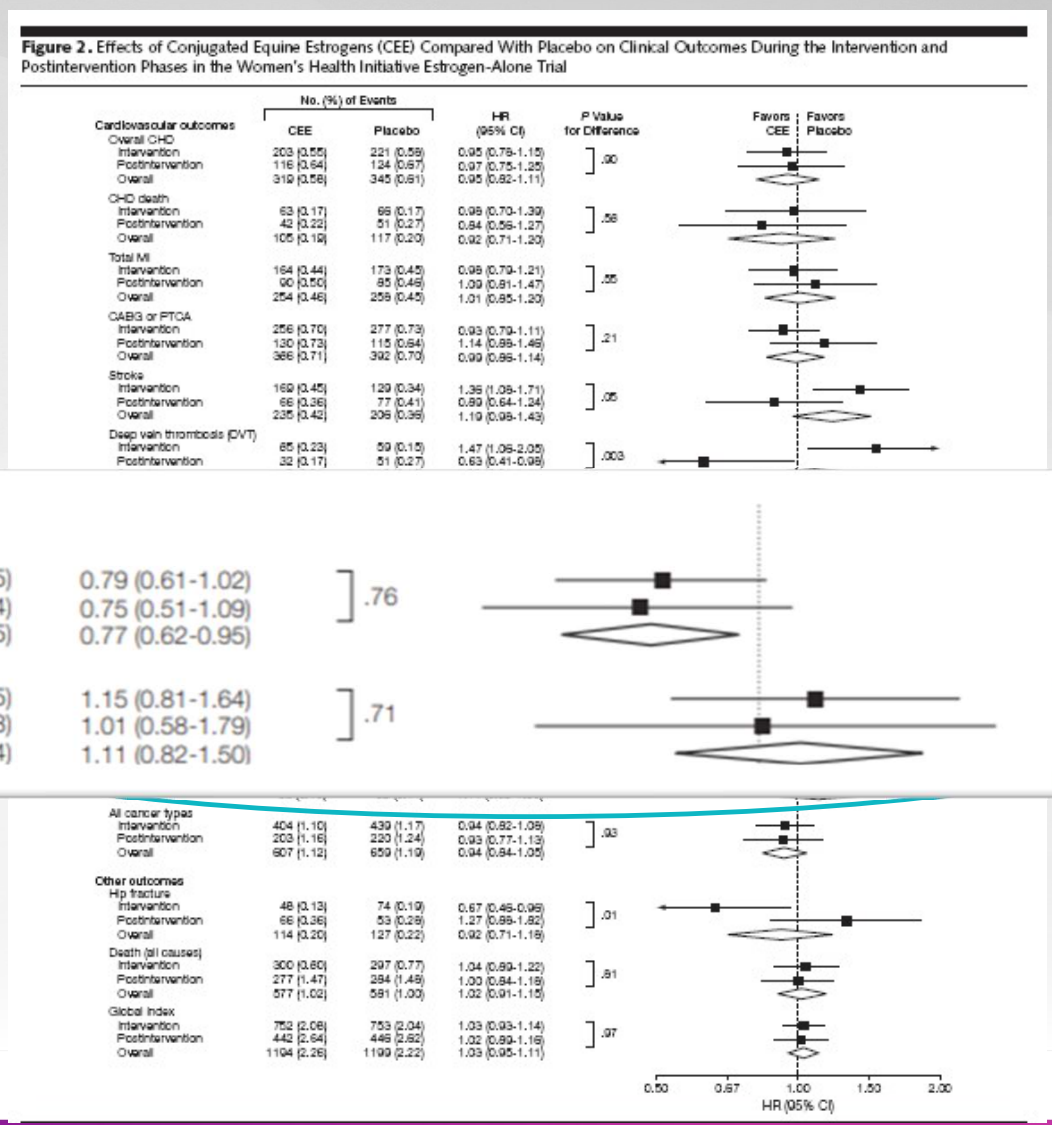
Chlebowski RT, et al. *JAMA*. 2010;304(15):1684-1692.

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



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

WHI E-Alone Post-Intervention Study

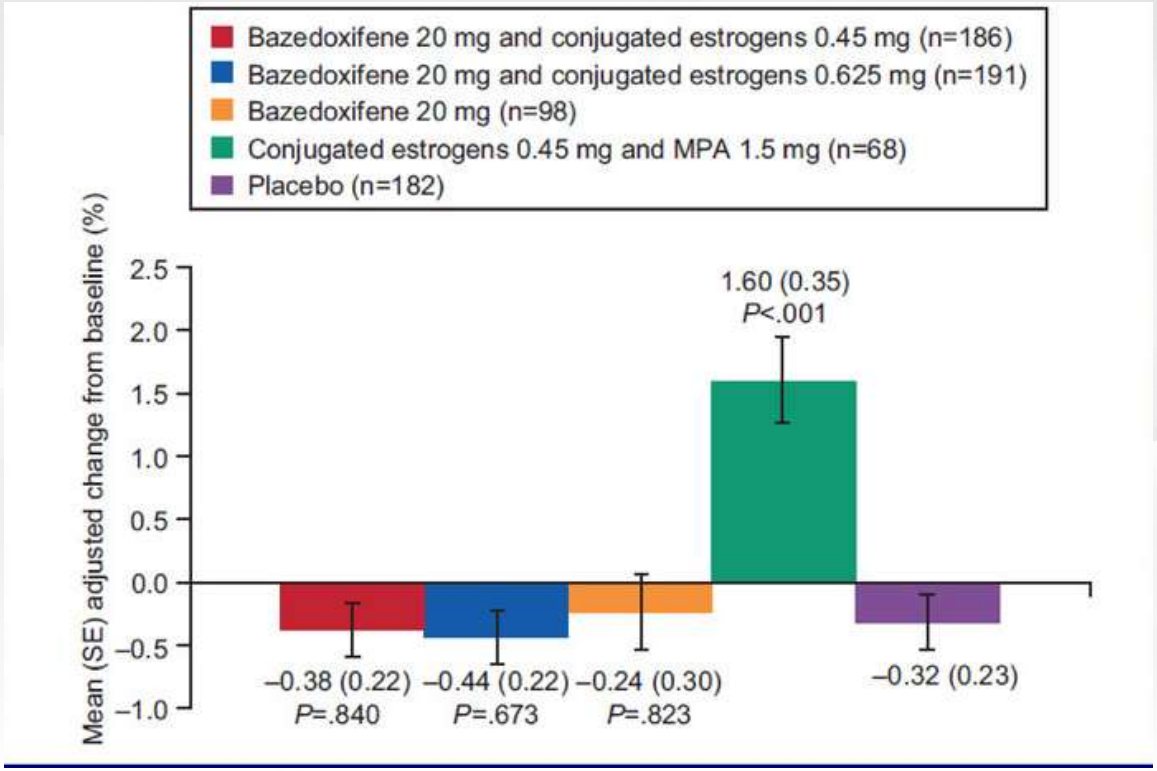


LaCroix AZ, et al. *JAMA*. 2011;305(13):1305-1314.

Tissue-Selective Estrogen Complex: TSEC

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

Breast Density Effects of Bazedoxifene-Conjugated Estrogens



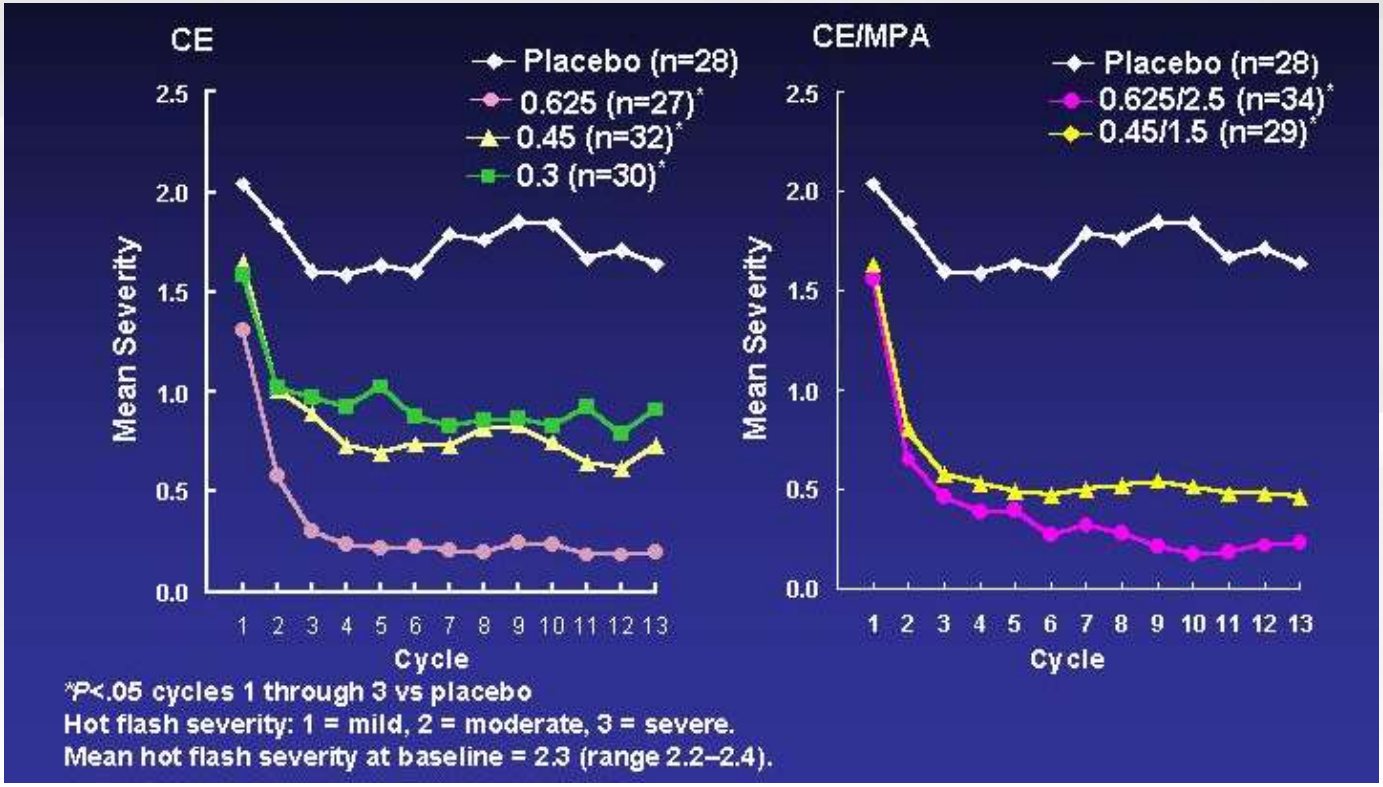
Pinkerton JV, et al. *Obstet Gynecol.* 2013;121(5):959-968. 1-year trial.

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



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 the menopausal transition
- Estrogen with SERMS or local progestins may eliminate the breast cancer risks associated with progestins
- The ability to treat vasomotor symptoms using nonhormonal therapies will allow wider use, even in those who are hesitant to use hormones or who have increased risk

Nonhormonal Alternatives

- Gabapentin 100 to 900 mg
- SSRI/SNRIs—only one FDA-approved (paroxetine mesylate)
- Clonidine 0.1- to 0.3-mg weekly patch
- Oxybutynin 2.5 to 5 mg bid

ACOG Practice Bulletin 141: Management of Menopausal Symptoms. *Obstet Gynecol*. 2014;123(1):202-216. Johnson ED, et al. *Pharm Pract (Granada)*. 2011;9(3):117-121. Leon-Ferre RA, et al. Abstract GS6-02: A randomized, double-blind, placebo-controlled trial of oxybutynin (Oxy) for hot flashes (HF): (ACCRU study SC-1603). *Cancer Res*. 2019;79(4 Suppl).

Gabapentin

- Approved as anti-seizure medication
- Wide dose range: 100 to 2,400 mg/day
- May take at night to relieve night sweats
- Divided doses up to tid—hot flash studies typically start at 100 mg tid

Reddy SY, et al. *Obstet Gynecol*. 2006;108(1):41-48.
Loprinzi CL, et al. *J Clin Oncol*. 2009;27(17):2831-2837.

Gabapentin Side Effects

- Drowsiness
- Dizziness
- Fatigue
- Dry mouth
- Constipation
- Serious side effects: sudden mood change, ecchymoses, respiratory depression

Neurontin. Package insert. Pfizer. 2017. Accessed March 27, 2021.
https://www.accessdata.fda.gov/drugsatfda_ docs/label/2017/020235s064_020882s047_021129s046lbl.pdf

Gabapentin: Empirical Advice

- Start slowly
- 100 mg qhs
- Increase in 100-mg increments, up-titrate to full-day dosing as needed
- Relief should occur within days of administration
- If it's not working, consider pushing dose

SNRI/SSRIs

- First noted to be effective in women with breast cancer on tamoxifen and aromatase inhibitor therapy (Loprinzi)
- Applied to healthy women without cancer in RCTs
- Rationale to combine RCTs seems sound
- Is a hot flash in a cancer patient different from a hot flash in a woman taking a GnRH agonist or a naturally menopausal woman?

Loprinzi CL, et al. *J Clin Oncol*. 2009;27(17):2831-2837.

SNRI/SSRIs with Medical Evidence

- Venlafaxine
- Paroxetine
- Fluoxetine
- Sertraline
- Bupropion
- Desvenlafaxine

Grindler N, et al. In: *Comprehensive Toxicology*. 3rd ed. Elsevier; 2018:381-389. doi:10.1016/B978-0-12-801238-3.02160-7

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.

SNRIs: Administration

- Start at lowest dose
- Relief should occur within 1 week
- Common side effects:
  - Anxiousness OR lethargy—adjust time of daily dosing
  - Nausea and weight loss
  - Constipation or other GI side effects
  - “Loopiness,” dry mouth, memory loss (short term)
  - Sexual side effects

The National Institute of Mental Health. Mental Health Medications. Transforming the understanding and treatment of mental illnesses. October 2016. Accessed March 28, 2021. https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml#part_149856

Paroxetine

- May inactivate active tamoxifen metabolite
- Interference with antihormone chemotherapy in women with breast cancer taking tamoxifen
- Less of an issue with common use of aromatase inhibitors

Tamoxifen and CYP 2D6 inhibitors: caution. *Prescrire Int*. 2011;20(118):182-184.

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

SNRI/SSRIs: Other Considerations

- If change or discontinuation occurs:
  - MUST TAPER MEDICATIONS
  - Reduce dose slowly
  - Severe side effects: headache, dysphoria possible

Harvard Health Publishing. How to taper off your antidepressant. Harvard Women's Health Watch. November 2010. Updated January 29, 2020. Accessed March 28, 2021. https://www.health.harvard.edu/diseases-and-conditions/how-to-taper-off-your-antidepressant

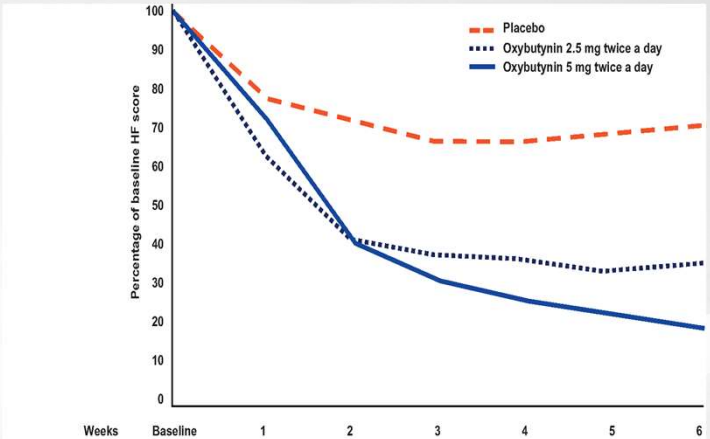
Clonidine

- Alpha-adrenergic antagonist
- Centrally acting
- Start low, increase slowly (0.1-mg transdermal patch)
- Side effects:
  - Postural hypotension
  - Dizziness
  - Depression
  - Dry mouth
  - Nocturia

NIH US National Library of Medicine. Label: Clonidine Transdermal System-Clonidine Patch. DailyMed. Updated October 31, 2015. Accessed March 28, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=99a59495-2a48-4276-bbe3-cdd55a45aba4

Oxybutynin

- 5 to 10 mg per day vs PBO bid randomly given to 150 postmenopausal women x 6 weeks
- Mean age 57 +/- 8.2 yr, 65% received tamoxifen or aromatase inhibitor
- Both doses significantly decreased HF frequency and severity
- More dry mouth, difficulty urinating, and abdominal pain in oxybutynin groups



Weeks	Baseline	1	2	3	4	5	6
Placebo	38	38	38	37	35	35	35
Oxybutynin 2.5 mg twice a day	40	40	38	36	35	35	34
Oxybutynin 5 mg twice a day	35	35	34	32	32	31	31

Leon-Ferre RA, et al. *JNCI Cancer Spect*. 2019;4(1):pkz088.

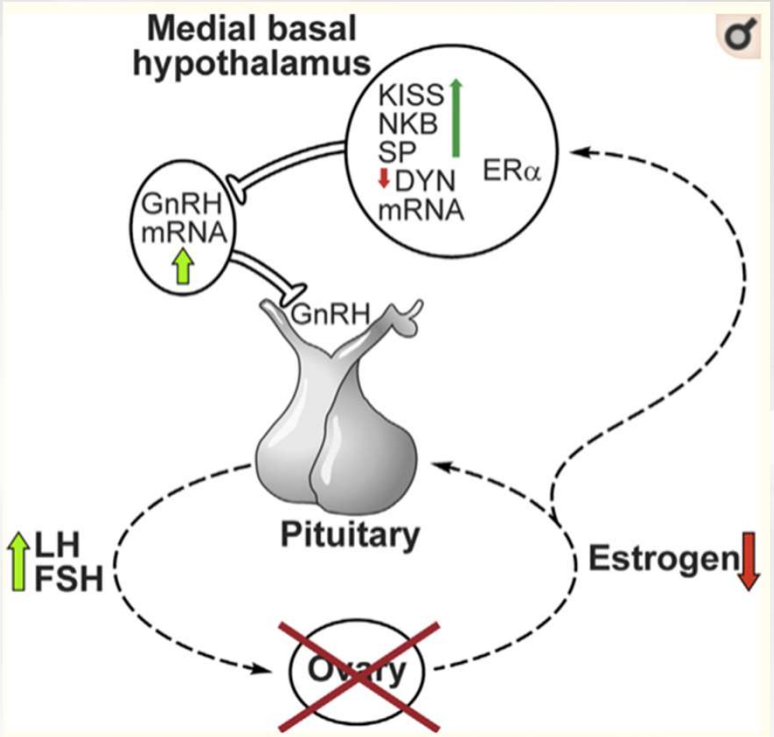
New Option in Clinical Trials: NK3R Antagonists

- KNDy neurons (kisspeptin, neurokinin, dynorphin) in the hypothalamus noted to be vastly increased in the brains of animals and humans post-oophorectomy
- Blockade of NK3R with antibody reduced coolness-seeking behavior in oophorectomized mice
- Blockade of the neurokinin-3 receptor abolishes hot flashes

Mittleman-Smith MA, et al. *Proc Natl Acad Sci*. 2012;109(48):19846-19851. Depypere H, et al. *J Clin Endocrinol Metab*. 2019;104(12):5893-5905.

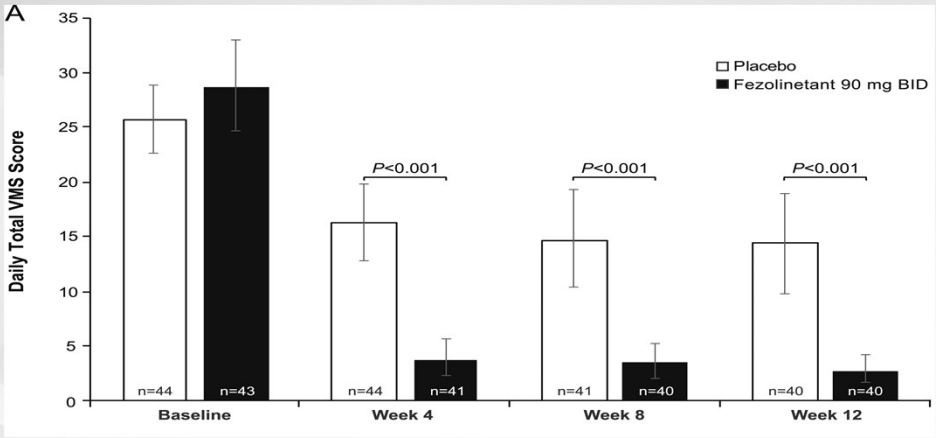
KNDy Neuron Circuitry

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

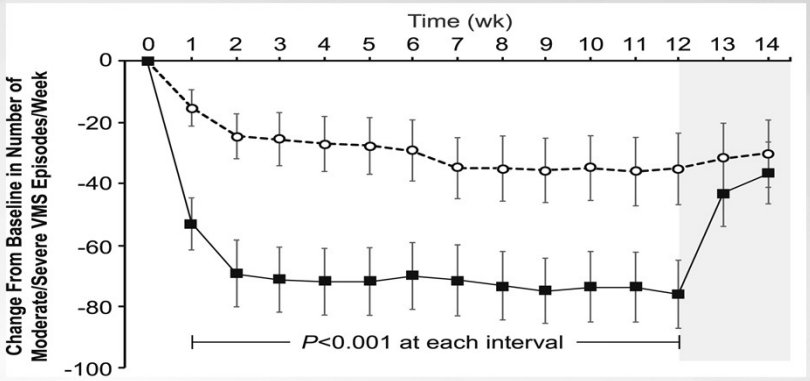


Rance NE, et al. *Front Neuroendocrinol*. 2013;34(3):211-227.

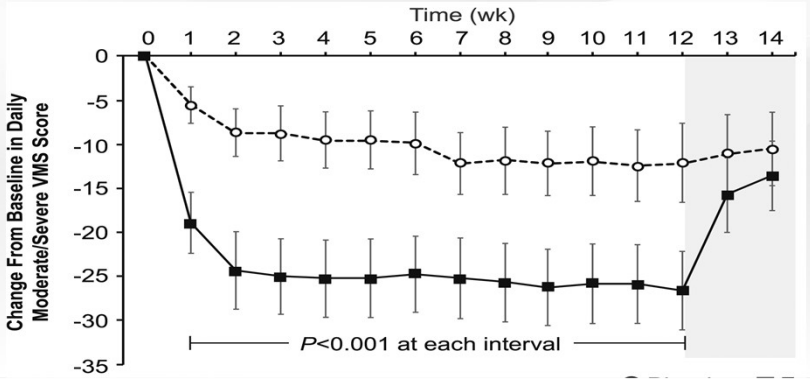
Effect of Fezolinetant on VMS Over Time



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



(B) Frequency



(C) Moderate/severe VMS score

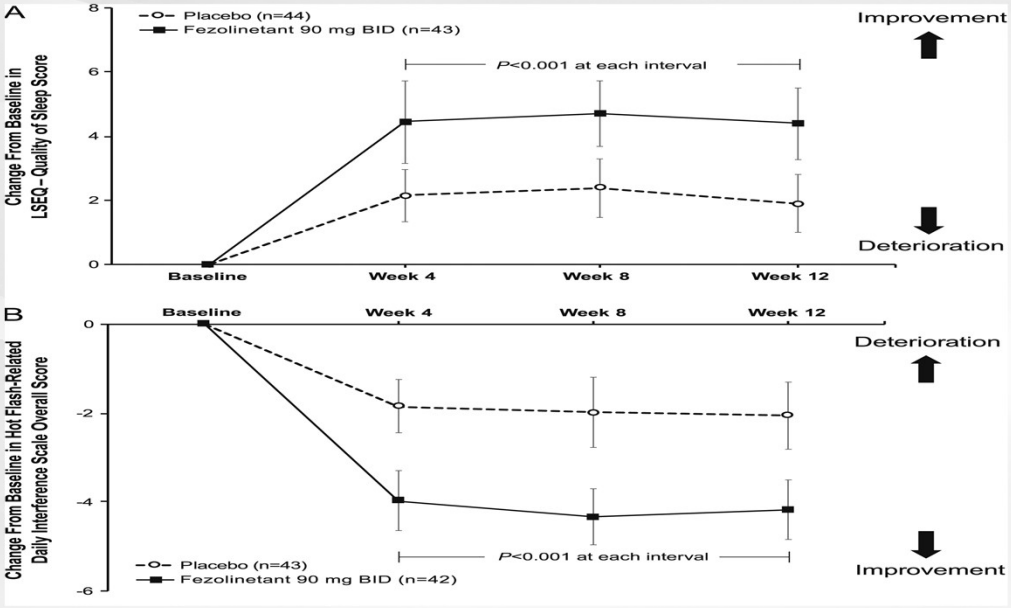
Placebo Fezolinetant 90 mg BID

OXFORD UNIVERSITY PRESS
ENDOCRINE SOCIETY

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

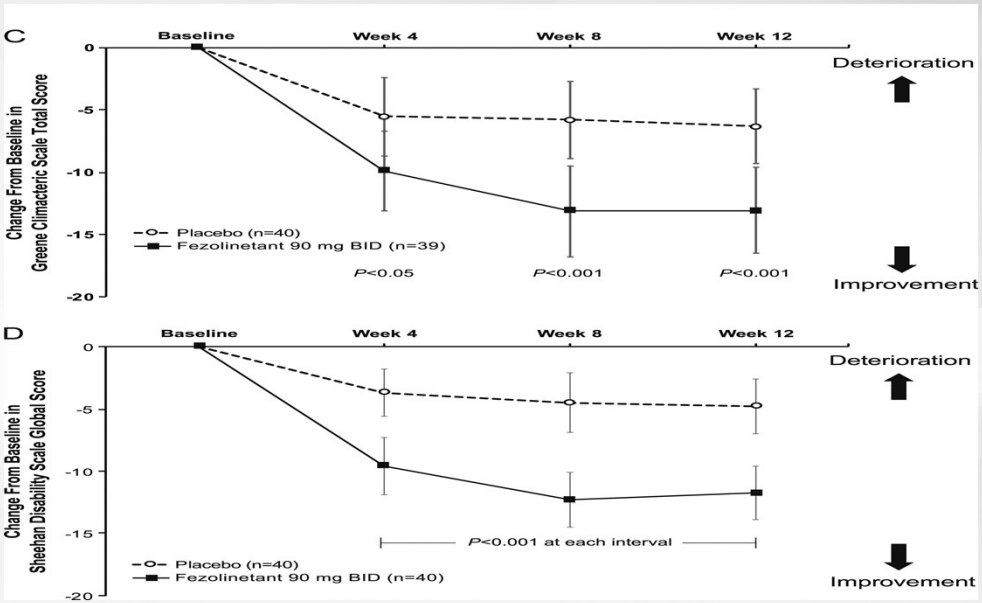
Effect of Fezolinetant on Quality-of-Life Measures

(A) SLEEP: LSEQ



(B) HFRDIS

(C) Greene Climacteric Scale

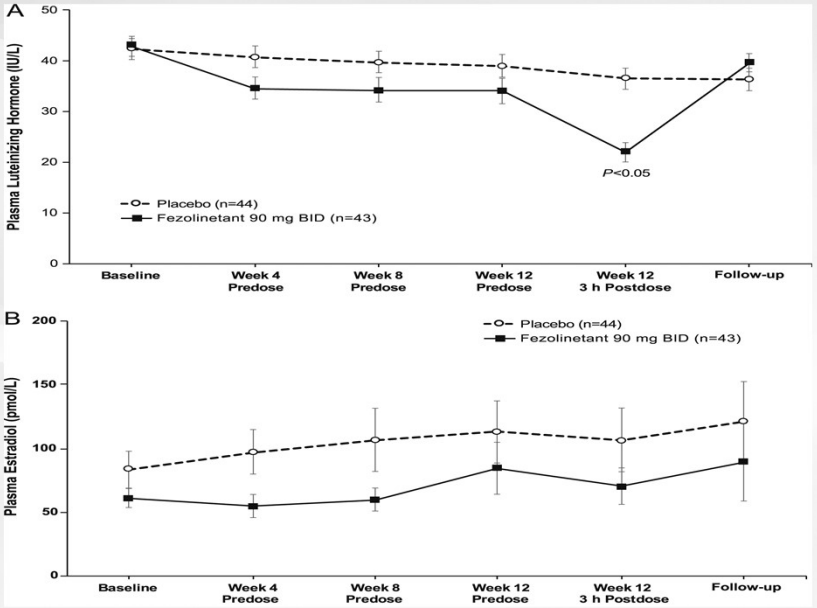


(D) Sheehan Disability Scale

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

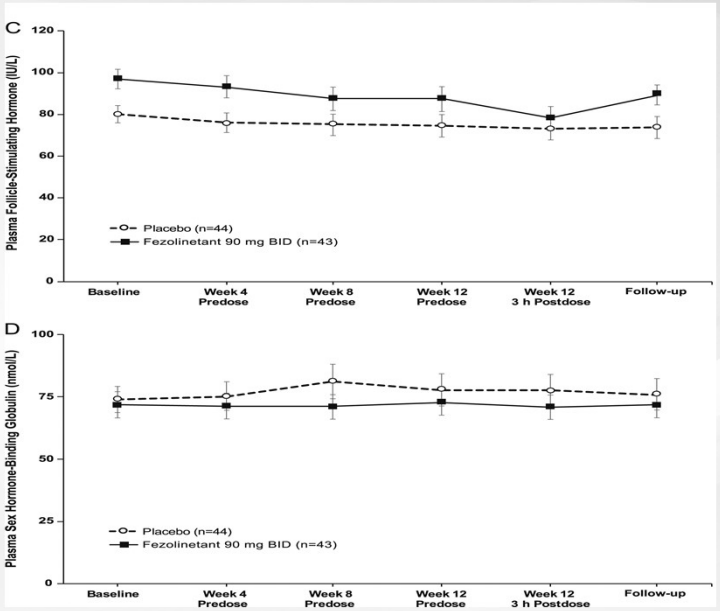
Effect of Fezolinetant on Plasma Hormones

(A) LH



(B) Estradiol

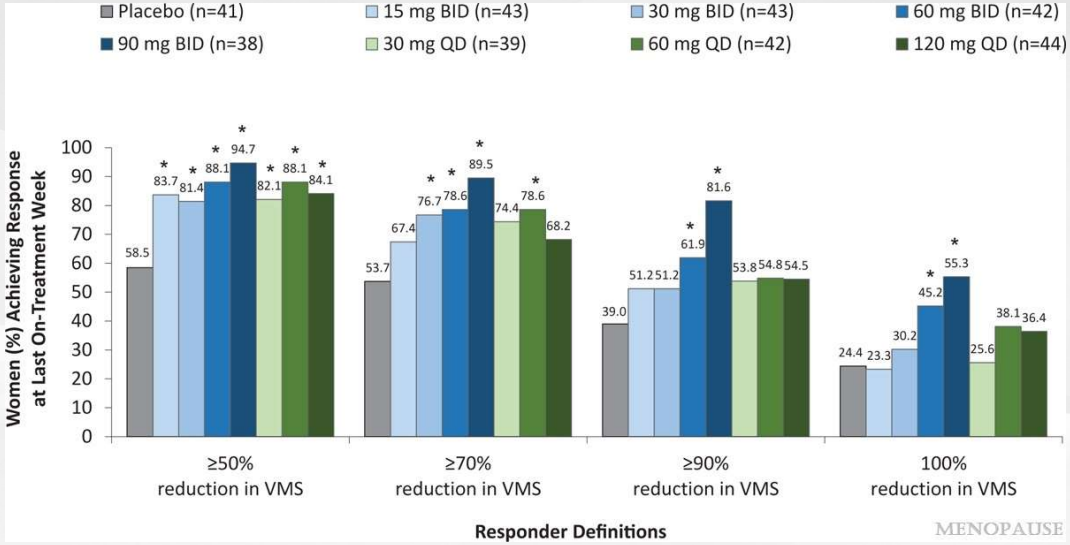
(C) FSH



(D) SHBG

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

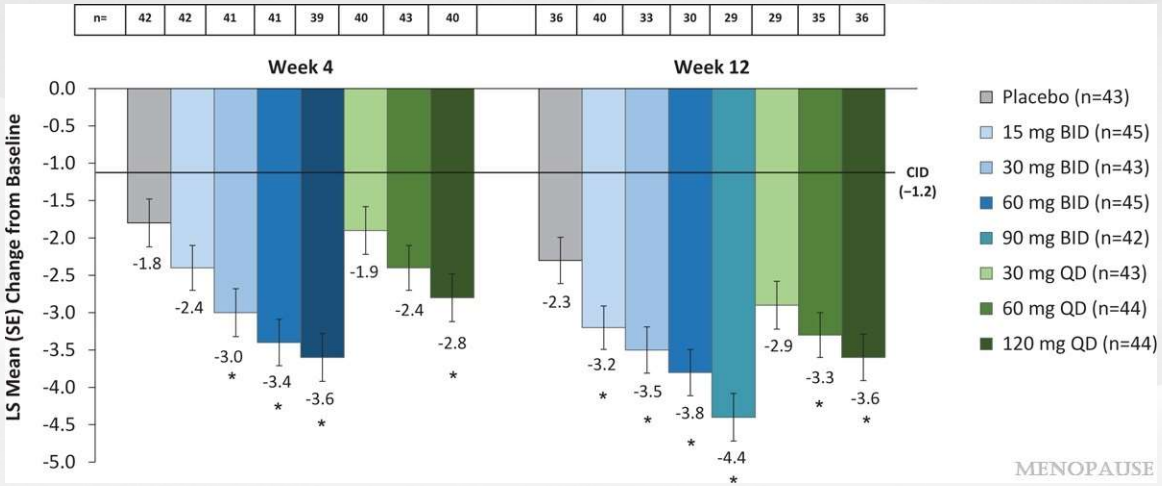
Reduction in Moderate/Severe VMS Frequency at Last On-Treatment Week (VESTA)



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.

Change from Baseline—MENQOL Vasomotor Function Domain Score



Change from baseline in MENQoL vasomotor function domain score. LS means and SEs are from a mixed model for repeated measurements with change from baseline as the dependent variable and the treatment group, visit, and smoking status as factors and baseline measurement as a covariate as well as interaction of treatment by week and an interaction of baseline measurement by week. Baseline values on the VMS function domain ranged from 1 to 8 with a mean score of 6.9 (SD 1.1). Reductions from baseline indicate improvement. The CID was derived by Bushmakin et al. $*P < 0.05$ for paired comparisons of fezolinetant versus placebo at last on-treatment week, with no adjustments for multiplicity. CID, clinically important difference; LS, least squares; MENQoL, menopause-specific quality of life questionnaire; SE, standard error; VMS, vasomotor symptoms.

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

Prescription Nonhormonals for VMS: 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
- These compounds appear to have superior efficacy in early clinical trials compared to all other nonhormonals
- A highly effective nonhormonal treatment for hot flashes would be a welcome addition to the clinical armamentarium for menopausal medicine!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