7th Annual Vivian W. Pinn Symposium

Menopausal Hormone Therapy: 30 Years of Lessons from the WHI

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Faculty/Presenter Disclosure

I have no financial conflicts of interest related to this presentation.

Hormone Therapy and Health Outcomes
(One Size Does Not Fit All)

"things should be as simple as possible, but not any simpler."

A. Einstein

Objectives

- Review the goal of the WHI: to assess the benefit:risk profile of menopausal hormone therapy (HT) when used for chronic disease prevention (not to evaluate its role for menopausal symptom management).
- Describe recent findings from WHI and other randomized trials of HT on clinical event outcomes.
- Describe patient characteristics, including age, time since menopause, underlying risk factor status, and biomarker levels, that modify health outcomes on HT.
- Address the role of recent research in improving clinical decision making for hormonal vs non-hormonal therapy.

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Menopause Management — Getting Clinical Care Back on Track

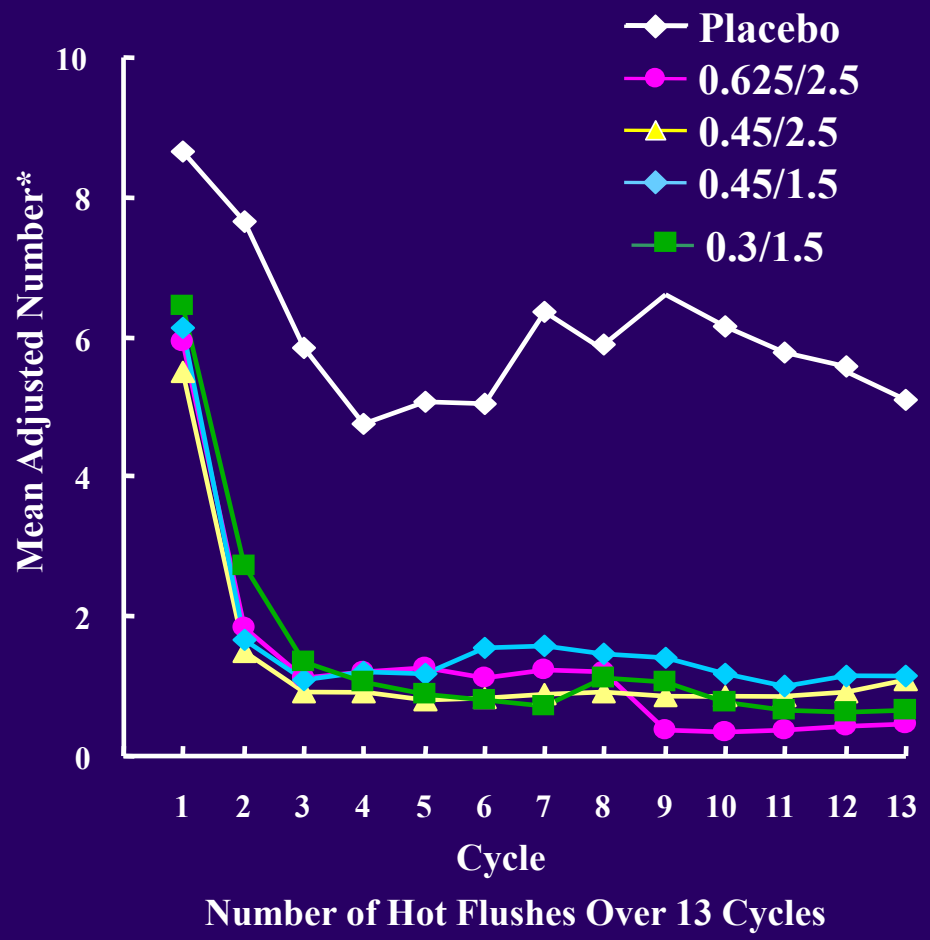
JoAnn E. Manson, M.D., Dr.P.H., and Andrew M. Kaunitz, M.D.

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

>75% of peri/post-menopausal women have hot flashes/night sweats (20% mod-severe symptoms). Impact on sleep/QOL/work productivity.

HT is the most effective treatment for vasomotor symptoms.

Number of Hot Flushes with Estrogen/Progestin (CEE+MPA of different doses) vs. Placebo



Source: Utian W, et al. *Fertil Steril* 2001; 75:1065.

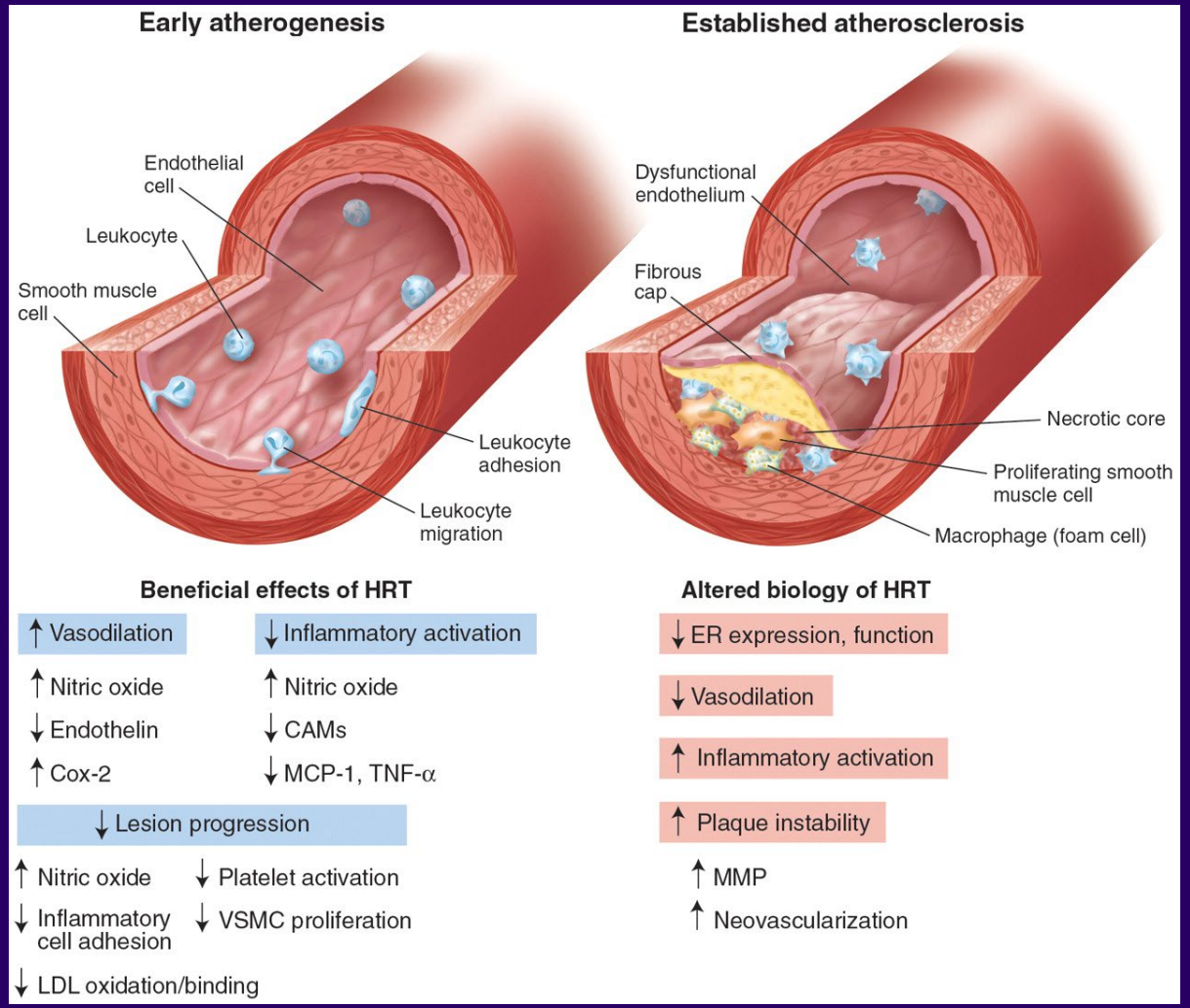
Non-Hormonal Medications: Efficacy for Hot Flashes

Medication	Dose	Reduction in Frequency
Paroxetine*	7.5 – 25 mg	↓ 40 – 50%
Venlafaxine	75 – 150 mg	↓ 40%
Escitalopram	10 – 20 mg	↓ 30 – 40%
Gabapentin	900 – 2400 mg	↓ 40 – 50%

* *Only FDA-approved nonhormonal prescription medication for treatment of hot flashes.*

Source: Stuenkel CA, et al. *JCEM* 2015; 100:3975-4011.

Hypothesis: Differential Effects of Estrogen on Early and Later Stages of Atherosclerotic Disease



Source: Mendelsohn ME and Karas RH. *Science* 2005; 308:1583.

HT and Coronary Heart Disease (CHD): Meta-Analysis of Observational Studies

- **Based on more than 40 observational studies of HT and CHD, the summary relative risks for CHD were 40-50% lower among current users of HT compared to never users ($p<0.001$).**

  (HT was increasingly being prescribed for prevention of CHD, stroke, cognitive decline, and other chronic diseases in the 1980-1990s -- across all menopausal age groups.)

From: Grodstein F, Stampfer MJ. *Prog Cardiovasc Dis* 1995; 38:199.

Key Differences Between the WHI and Observational Studies of Hormone Therapy (HT)

	WHI	Observational Studies
Age at HT initiation (mean)	63 yrs	52 yrs
Time since menopause (mean)	≥12 yrs	1-3 yrs
Health Status	RCT (randomized groups similar)	Users tend to be healthier than nonusers

Randomized Trials of HT and CVD

Secondary Prevention:

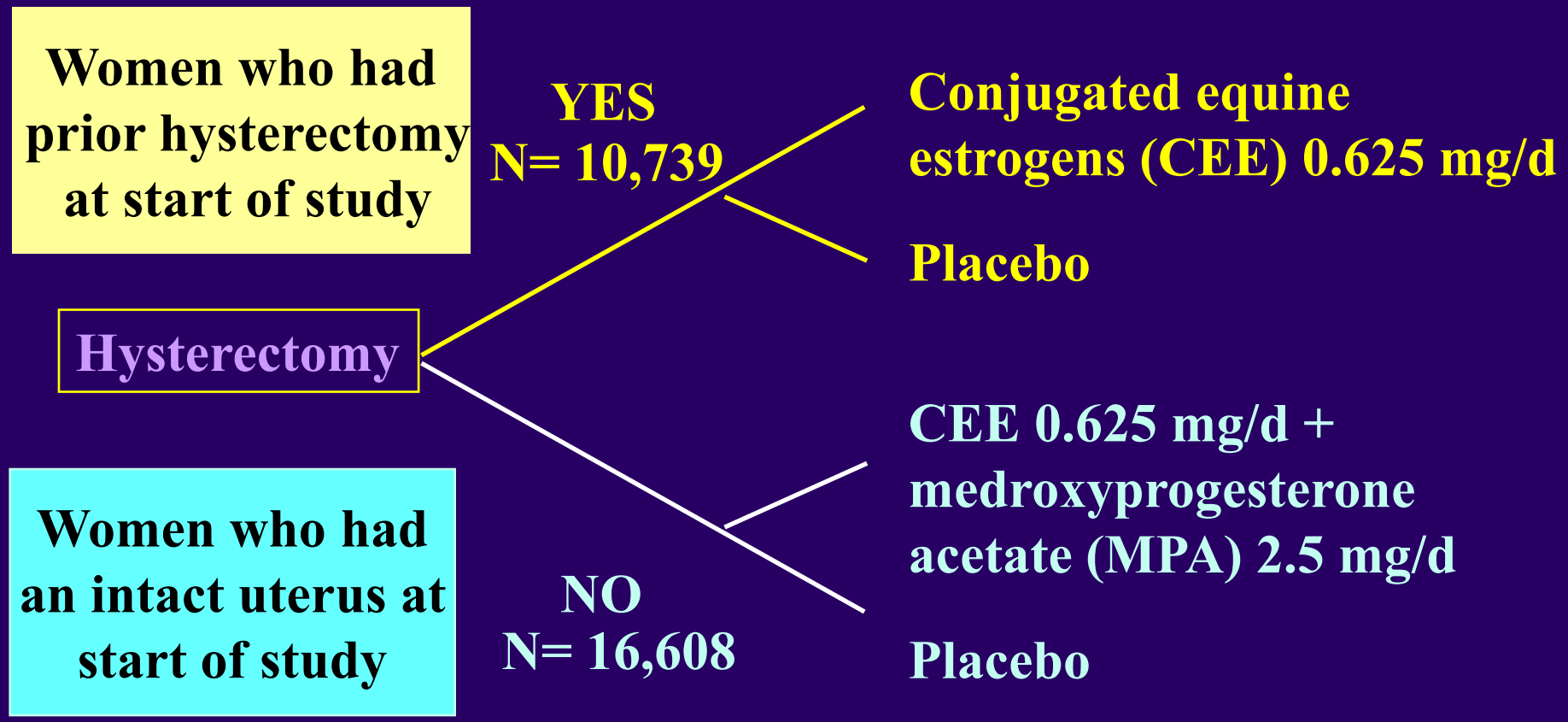
- Heart and Estrogen/Progestin Replacement Study (HERS)
- Estrogen Replacement and Atherosclerosis Trial (ERA)
- Papworth HRT Atherosclerosis Study*
- Women's Estrogen for Stroke Trial (WEST)†
- Estrogen in the Prevention of ReInfarction Trial (ESPRIT)†
- Women's Angiographic Vitamin and Estrogen (WAVE) Trial

Primary Prevention:

- Women's Health Initiative (WHI)
  - Estrogen+Progestin Trial
  - Estrogen-Alone Trial

CEE±MPA except: *transdermal estradiol±NETA, †oral estradiol

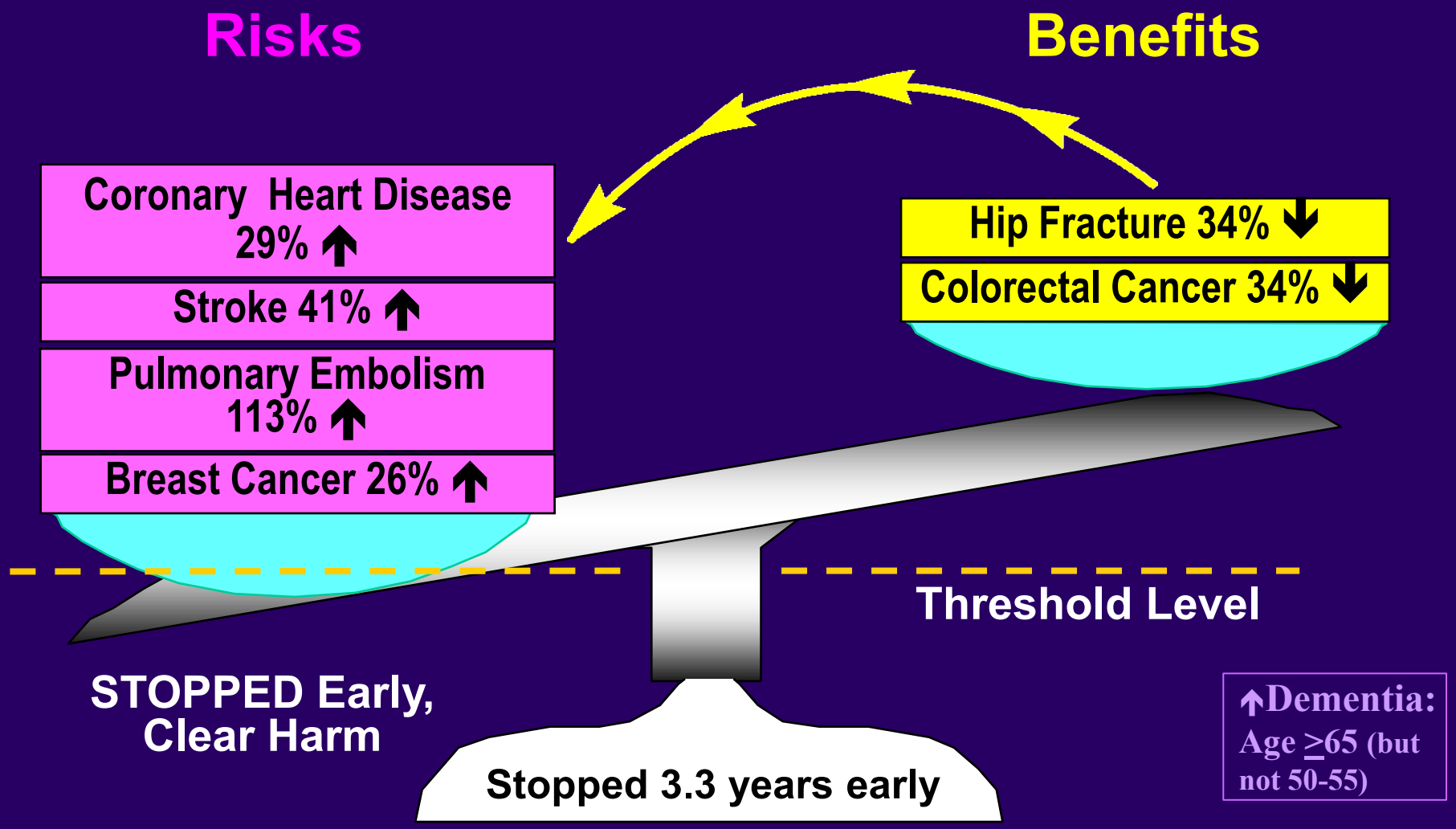
Women's Health Initiative (WHI), Ages 50-79 Hormone Program Design



These were the most common HT formulations at the time and used in most observational studies.

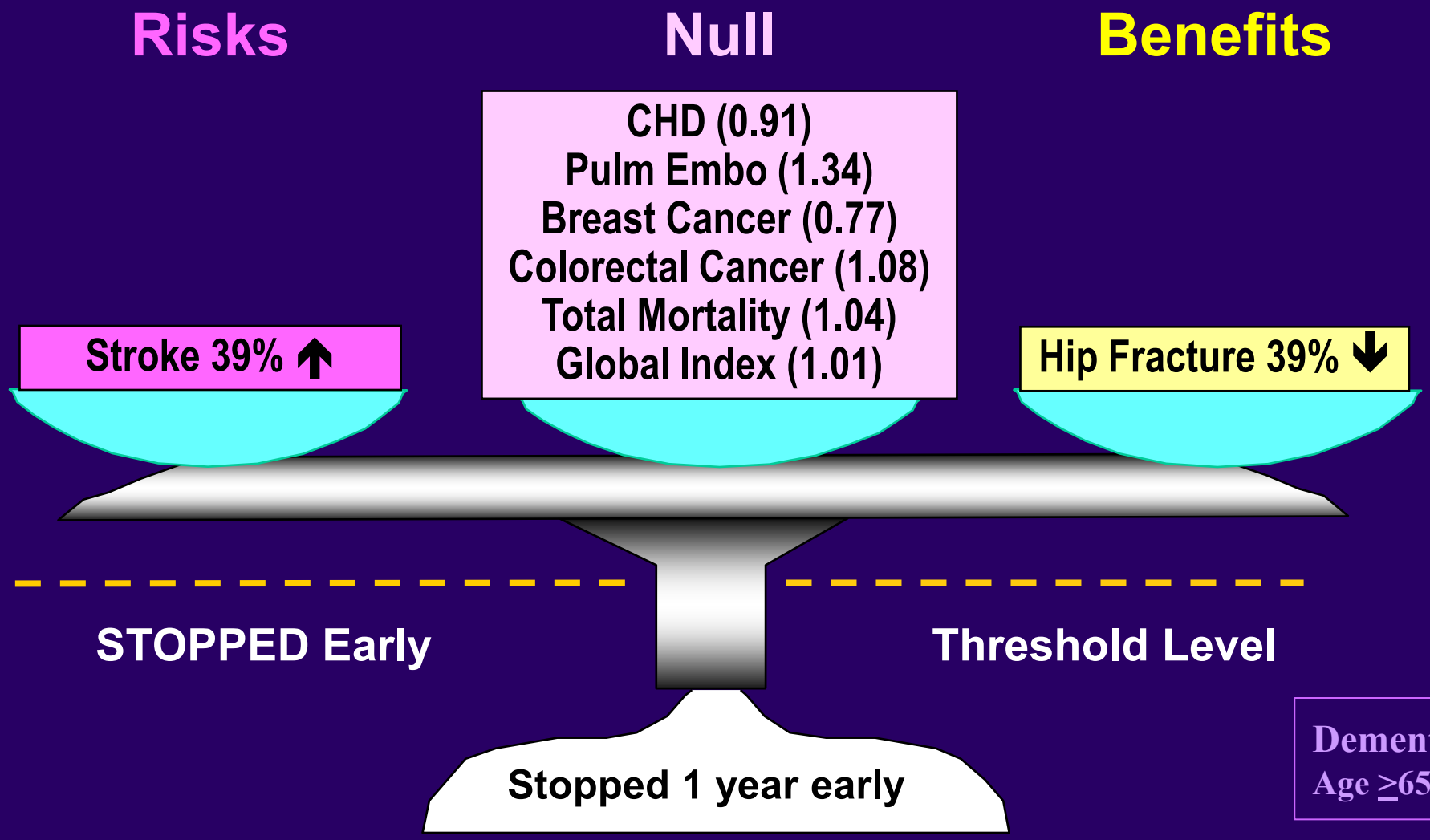
WHI Estrogen+Progestin Trial Findings, July 2002

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



Adapted from: Writing Group for the Women's Health Initiative. *JAMA* 2002;288:321.

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



Dementia: borderline ↑
Age ≥65 (but not 50-55)

Source: *JAMA* 2004; 291:1701.

Research

Original Investigation

Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Poststopping Phases of the Women's Health Initiative Randomized Trials

JoAnn E. Manson, MD, DrPH; Rowan T. Chlebowski, MD, PhD; Marcia L. Stefanick, PhD; Aaron K. Aragaki, MS; Jacques E. Rossouw, MD; Ross L. Prentice, PhD; Garnet Anderson, PhD; Barbara V. Howard, PhD; Cynthia A. Thomson, PhD, RD; Andrea Z. LaCroix, PhD; Jean Wactawski-Wende, PhD; Rebecca D. Jackson, MD; Marian Limacher, MD; Karen L. Margolis, MD, MPH; Sylvia Wassertheil-Smoller, PhD; Shirley A. Beresford, PhD; Jane A. Cauley, DrPH; Charles B. Eaton, MD, MS; Margery Gass, MD, NCMP; Judith Hsia, MD; Karen C. Johnson, MD, MPH; Charles Kooperberg, PhD; Lewis H. Kuller, MD, DrPH; Cora E. Lewis, MD, MSPH; Simin Liu, MD, ScD; Lisa W. Martin, MD; Judith K. Ockene, PhD; Mary Jo O'Sullivan, MD; Lynda H. Powell, PhD; Michael S. Simon, MD, MPH; Linda Van Horn, PhD, RD; Mara Z. Vitolins, DrPH, RD; Robert B. Wallace, MD, MSc

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00000611

JAMA. 2013;310(13):1353-1368. doi:10.1001/jama.2013.278040

Editorial page 1349

Author Video Interview at jama.com

Supplemental content at jama.com

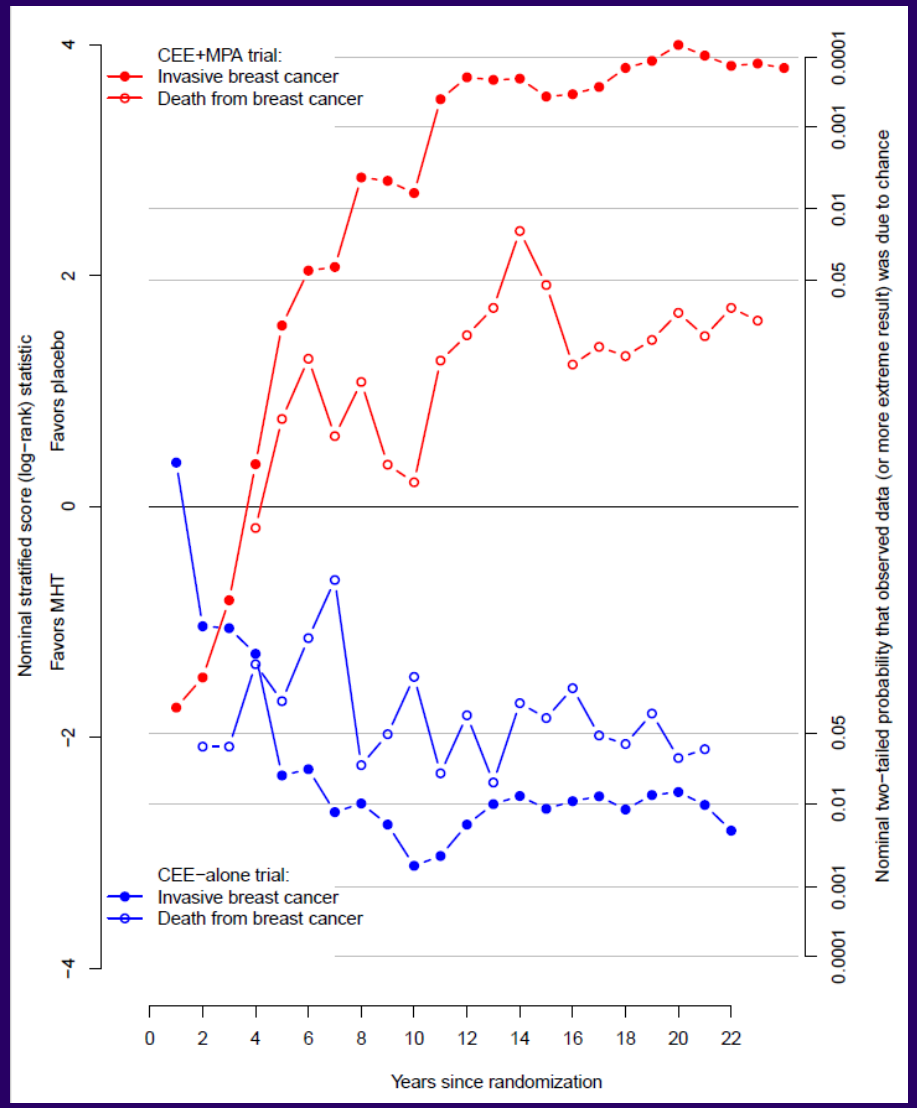
Manson JE, Chlebowski RT, Stefanick ML, et al. *JAMA* 2013.

WHI HT Trials: Summary of Results for Primary and Other Major Endpoints by Study Phase (13 yr f/u)

Major Endpoints	Intervention		Post-Intervention	
	CEE+MPA	CEE Alone	CEE+MPA	CEE Alone
CHD	0	0	0	0
Breast cancer	↑	↓	↑	↓
Stroke	↑	↑	0	0
PE	↑	0	0	0
Colorectal cancer	↓	0	0	0
Endometrial cancer	0	NA	↓	NA
Hip fracture	↓	↓	0	0
All-cause mortality	0	0	0	0
Global index	↑	0	0	0

Source: Manson, Chlebowski, Stefanick, et al. *JAMA* 2013;310:1358-68.

WHI: HT and Breast Cancer Incidence and Mortality



CEE + MPA

Incidence: HR=1.28 (1.13-1.45)

Mortality: HR=1.35 (0.94-1.95)

CEE Alone

Incidence: HR=0.78 (0.65-0.93)

Mortality: HR=0.60 (0.37-0.97)

Source: Chlebowski RT, et al. JAMA 2020

WHI Hormone Therapy Trials: Absolute Risks (cases per 10,000 person-years) for Outcomes in the Estrogen-Progestin and Estrogen-Alone Trials, by Age Group

Source: Manson JE, Chlebowski RT, Stefanick ML, et al. *JAMA* 2013.

WHI: Health Outcomes

- In both trial, HRs were similar by age for most health outcomes, including stroke, venous thrombosis/pulmonary embolism, breast cancer, and other cancers.

BUT

- Much lower absolute risks in younger, compared to older, women.

WHI Estrogen-Alone Trial: MI and Total Mortality According to Age at Randomization

	Total MI	Total Mortality
Age Group	HR (95% CI)	HR (95% CI)
50-59	0.55 (0.31-1.00)	0.70 (0.46-1.09)
60-69	0.95 (0.69-1.30)	1.01 (0.79-1.29)
70-79	1.24 (0.88-1.75)	1.21 (0.95-1.56)
P, trend by age	0.02†	0.04†

MI = myocardial infarction
† p, trend by age group

Source: Manson JE, Chlebowski RT, Stefanick ML, et al. *JAMA* 2013.

Estrogen+Progestin Therapy and Risk of MI in WHI: Results According to Age and Time Since Menopause

Age	HR	Time since Menopause Onset	HR
50-59	1.32	<10 yrs	0.91
60-69	1.05	10-19 yrs	1.16
70-79	1.46*	≥20 yrs	1.99*
P, trend	0.55	P, trend	0.01†

* P-value <0.05

† P for trend by yrs since menopause onset=0.01

Source: Manson JE, Chlebowski RT, Stefanick ML, et al. *JAMA* 2013.

Early vs. Late Intervention Trial with Estradiol (ELITE) Design

Participants: 643 healthy recently postmenopausal women without CVD or diabetes.

Study design: Randomized treatment (oral estradiol, placebo) x time since menopause (<6 years, ≥10 years).

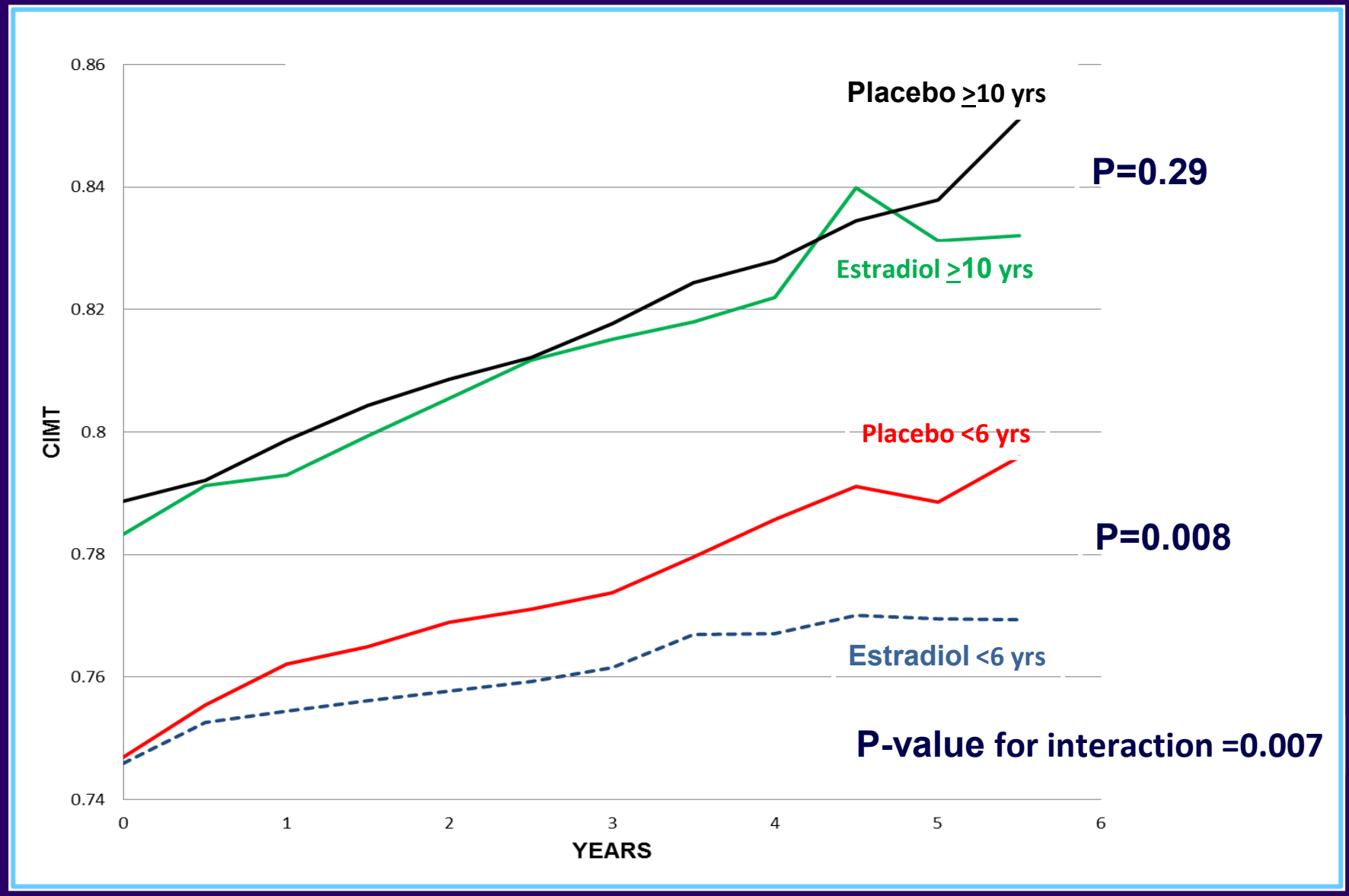
Intervention: Oral micronized 17β-estradiol 1 mg/d (+ vaginal micronized progesterone gel x 12 days/mo in women with a uterus).

Placebos

Outcomes: Primary: rate of change in Carotid IMT, up to 6 yrs.

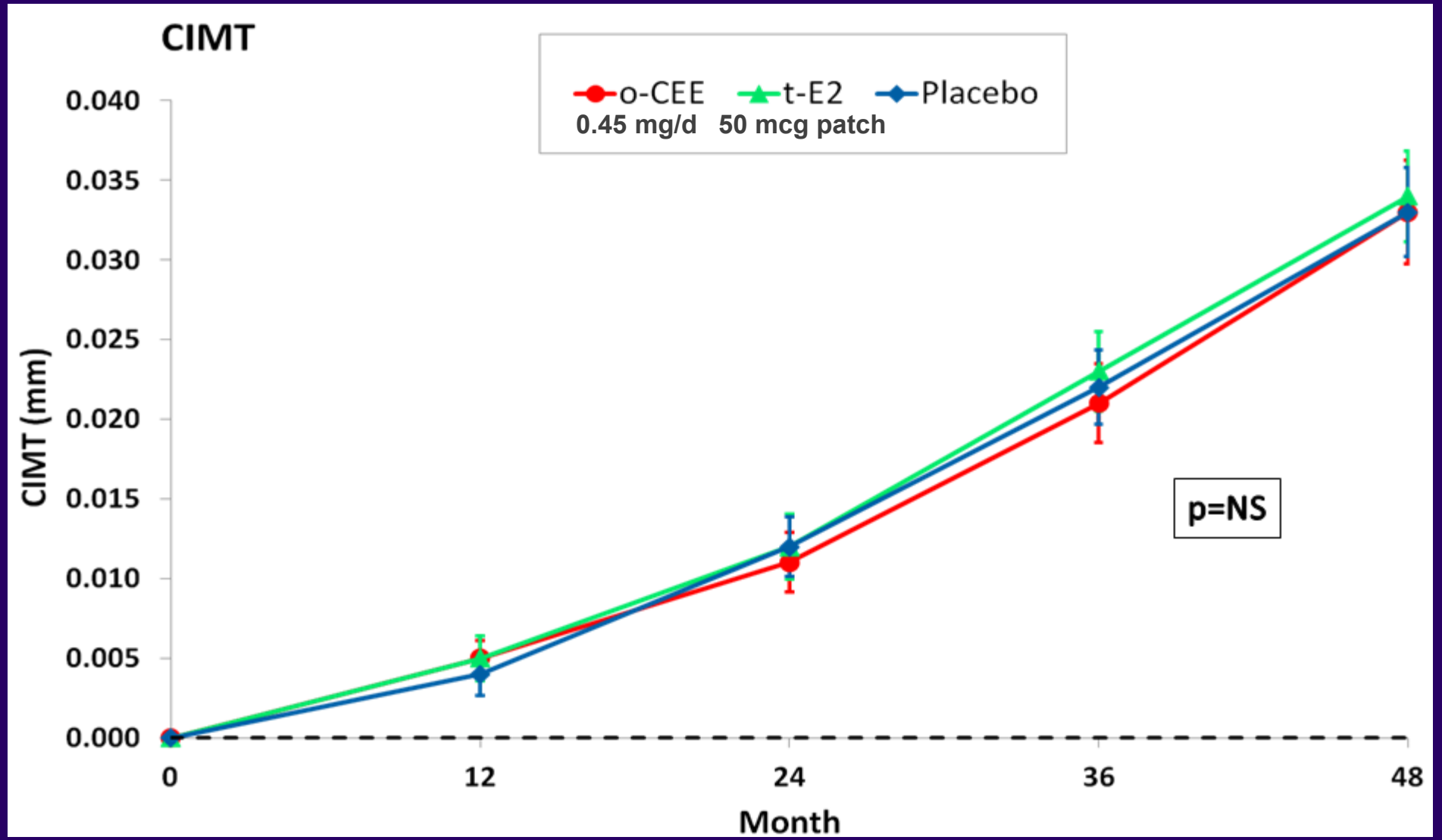
Source: Hodis H, et al. *N Engl J Med* 2016.

ELITE:
Carotid IMT by Treatment and Time Since Menopause



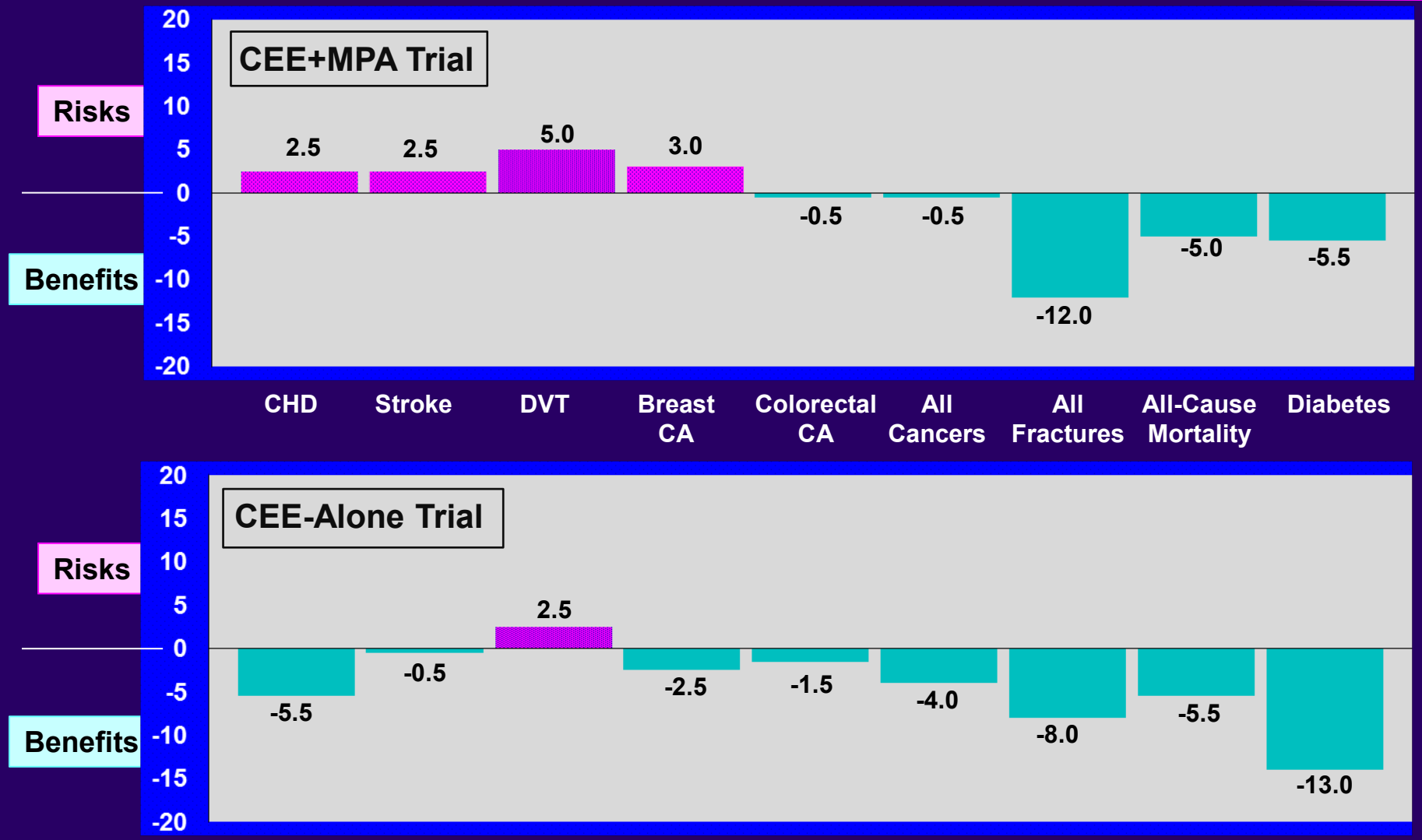
Source: Hodis H, et al. *N Engl J Med* 2016.

The Kronos Early Estrogen Prevention Study (KEEPS)
Changes in Imaging Endpoints, CIMT



Source: Harman SM, et al. *Ann Intern Med* 2014.

Benefits and Risks of HT in Women Aged 50-59 in the WHI HT Trials (per 1000 women over 5 years)



Source: Manson JE, Kaunitz AM. *New Engl J Med* 2016; 374:803-806.

Absolute Risks (Cases per 1000 Women Over 5 Years) by Age Group in the WHI HT Trials

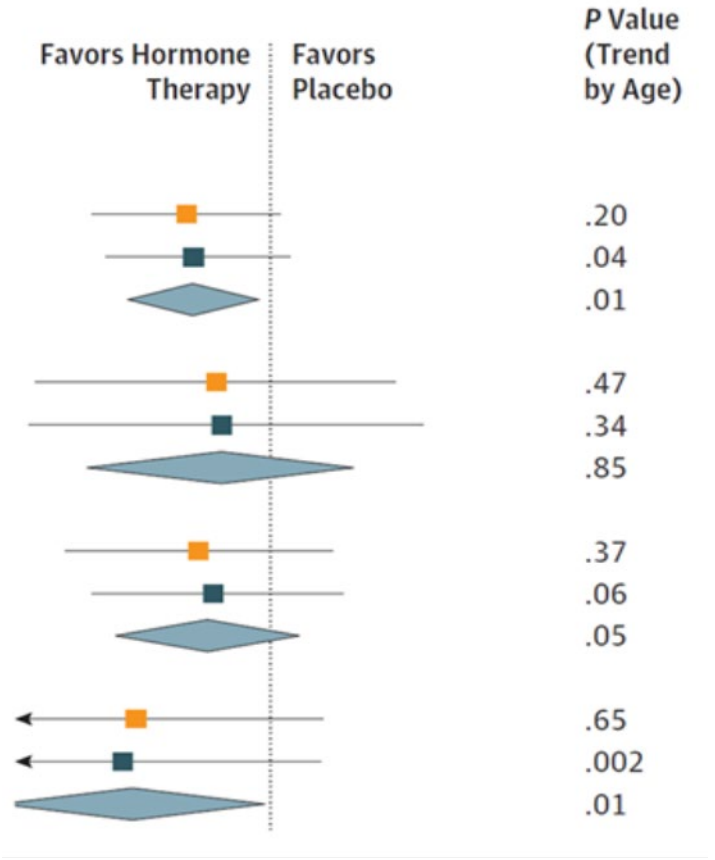
	E+P Trial			E-Alone Trial		
	50-59	60-69	70-79	50-59	60-69	70-79
Total mortality	-5	+2	+2	-6	0	+13
Global Index†	+6	+11	+19	-10	-1	+25

†Global index is a composite outcome of CHD, stroke, pulm embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, and mortality.

Source: Manson, Chlebowski, Stefanick, et al. *JAMA* 2013;310:1358-68.

Mortality Outcomes During the Intervention Phase According to 10-Year Age Groups: Age 50-59

Outcome by Age	HR (95% CI)	*P* Value (Trend by Age)
Age 50-59 y		
All-cause mortality		
CEE plus MPA vs placebo	0.67 (0.43-1.04)	.20
CEE alone vs placebo	0.71 (0.46-1.09)	.04
Pooled trials	0.69 (0.51-0.94)	.01
CVD mortality		
CEE plus MPA vs placebo	0.77 (0.33-1.79)	.47
CEE alone vs placebo	0.81 (0.32-2.04)	.34
Pooled trials	0.79 (0.42-1.47)	.85
Cancer mortality		
CEE plus MPA vs placebo	0.71 (0.38-1.33)	.37
CEE alone vs placebo	0.78 (0.43-1.40)	.06
Pooled trials	0.74 (0.48-1.14)	.05
Other mortality		
CEE plus MPA vs placebo	0.53 (0.22-1.27)	.65
CEE alone vs placebo	0.51 (0.20-1.26)	.002
Pooled trials	0.52 (0.28-0.97)	.01

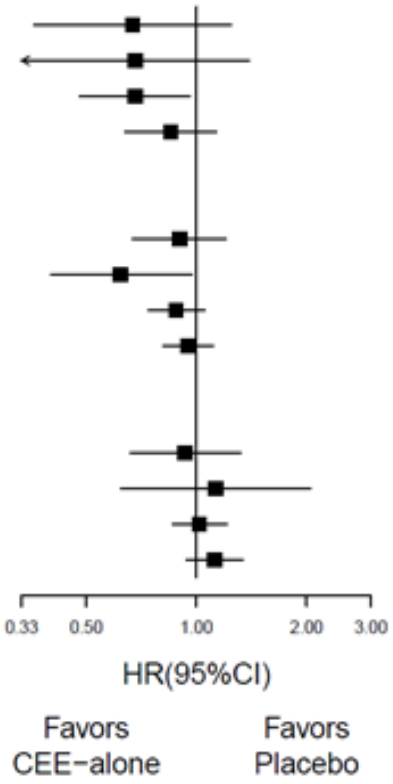


Source: Manson JE, Aragaki AK, Rossouw JE, et al. *JAMA* 2017;318:927-938.

Health Outcomes in the Women's Health Initiative Estrogen-Alone Trial, according to Bilateral Oophorectomy (BSO) Status and Age at Study Entry, 18-Year Cumulative Follow-up: Women with BSO

Bilateral Oophorectomy (N=4,049)

Cumulative follow-up Health outcomes	# of events (%*) CEE-alone	 Placebo	Diff/ 10K PY†	HR(95%CI)	P, trend by age‡
Age group 50–59 y	**(N = 530)**	**(N = 599)**			
Coronary heart disease	17(0.22)	28(0.33)	−11	0.67 (0.36, 1.24)	0.44
Invasive breast cancer	12(0.16)	21(0.25)	−9	0.68 (0.33, 1.39)	0.23
All-cause mortality	53(0.56)	84(0.79)	−24	0.68 (0.48, 0.96)	0.034
Global index	88(1.19)	115(1.40)	−20	0.85 (0.64, 1.13)	0.072
Age group 60–69 y	**(N = 909)**	**(N = 996)**			
Coronary heart disease	84(0.69)	99(0.75)	−6	0.90 (0.67, 1.20)	
Invasive breast cancer	30(0.24)	53(0.40)	−16	0.62 (0.40, 0.97)	
All-cause mortality	225(1.50)	280(1.71)	−21	0.88 (0.74, 1.05)	
Global index	302(2.62)	334(2.71)	−9	0.95 (0.81, 1.11)	
Age group 70–79 y	**(N = 499)**	**(N = 516)**			
Coronary heart disease	61(1.07)	71(1.15)	−7	0.93 (0.66, 1.32)	
Invasive breast cancer	22(0.38)	21(0.34)	5	1.13 (0.62, 2.05)	
All-cause mortality	262(3.65)	284(3.65)	0	1.02 (0.86, 1.21)	
Global index	257(4.99)	252(4.43)	57	1.12 (0.94, 1.34)	

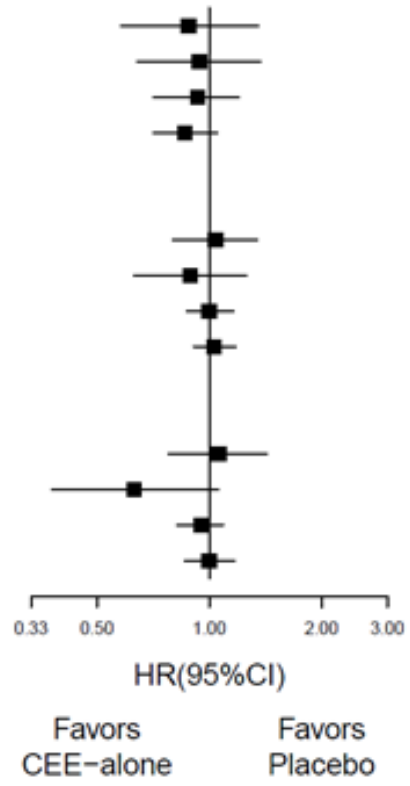


Source: Manson JE et al., *Ann Intern Med* 2019; 171:406-414.

Health Outcomes in the Women's Health Initiative Estrogen-Alone Trial, according to Bilateral Oophorectomy Status and Age at Study Entry, 18-Year Cumulative Follow-up: Women with Conserved Ovaries

No Bilateral Oophorectomy (N=5,890)

Cumulative follow-up	# of events (%*) CEE-alone	Placebo	Diff/ 10K PY†	HR(95%CI)	P, trend by age‡
Health outcomes					
Age group 50–59 y	**(N = 1,024)**	**(N = 984)**			
Coronary heart disease	42(0.28)	44(0.31)	−3	0.88 (0.58, 1.35)	0.55
Invasive breast cancer	53(0.36)	53(0.38)	−2	0.94 (0.64, 1.37)	0.27
All-cause mortality	111(0.61)	115(0.65)	−5	0.93 (0.71, 1.20)	0.91
Global index	188(1.31)	202(1.51)	−20	0.86 (0.71, 1.05)	0.32
Age group 60–69 y	**(N = 1,289)**	**(N = 1,288)**			
Coronary heart disease	120(0.70)	121(0.69)	1	1.04 (0.80, 1.34)	
Invasive breast cancer	61(0.35)	69(0.39)	−4	0.89 (0.63, 1.26)	
All-cause mortality	363(1.72)	364(1.72)	0	1.00 (0.87, 1.16)	
Global index	442(2.77)	449(2.75)	2	1.03 (0.91, 1.18)	
Age group 70–79 y	**(N = 660)**	**(N = 645)**			
Coronary heart disease	89(1.13)	82(1.07)	5	1.06 (0.78, 1.43)	
Invasive breast cancer	24(0.30)	36(0.47)	−17	0.63 (0.38, 1.06)	
All-cause mortality	358(3.69)	364(3.88)	−19	0.95 (0.82, 1.09)	
Global index	326(4.50)	318(4.55)	−4	1.00 (0.86, 1.17)	



Source: Manson JE et al., *Ann Intern Med* 2019; 171:406-414.

CHD Risk Associated with E+P or E-Alone (pooled) According to Baseline Biomarker Status in the WHI

	OR (95% CI) for HT Treatment Effect	*P* value for Interaction
LDL chol (mg/dl)		
<130	0.66 (0.34-1.27)	0.03
≥130	1.46 (1.02-2.10)	
LDL/HDL Ratio*		
<2.5	0.60 (0.34-1.06)	0.002
≥2.5	1.73 (1.18-2.53)	
Metabolic Syndrome†		
No	0.97 (0.58-1.61)	0.032
Yes	2.26 (1.26-4.07)	

*Similar results with total chol/HDL ratio (p-value=0.01). Statins attenuate risk.
†Meeting ≥3 criteria for ATP definition of MetS.

Sources: Bray PF, et al. *Am J Cardiol* 2008; Wild RA, et al. *Menopause* 2013.

Transdermal Therapy and Low-Dose Regimens: Advantages over Oral/Conventional?

- Less effect on:
  - Clotting factors
  - Triglycerides
  - C-reactive protein
  - Blood pressure

* But no large-scale randomized trials assessing relative safety or clinical events (predominately observational data)*

Are Lower Doses Safer?

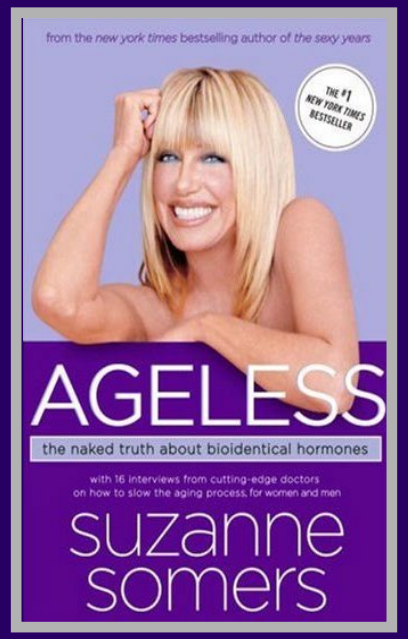
- **Blood Pressure:** No effect on BP with low-dose o-CEE or t-E2 in KEEPS, compared to ↑ SBP with 0.625 mg o-CEE or E+P in WHI.
- **Stroke:** In the Nurses' Health Study, the risk of stroke was not increased for women taking 0.3 mg CE (RR 0.93); the 0.625 mg dose was associated with risks similar to WHI.[1]
- **MI:** In a Danish National Registry, no associations were found with estrogen dose.[2]

1. Grodstein F. *Arch Intern Med* 2008;168:861-6.
2. Lokkegaard E. *Eur Heart J* 2008;29:2660-8.

Compounded Bioidentical Market Has Exploded to Fill a Vacuum

- Prescriptions for compounded "bioidentical" hormones have skyrocketed.
- Developed into a billion dollar industry of products neither tested nor FDA regulated.
- Believed by millions of women to be safer and more effective than FDA-approved HT.

(no package insert or black box warning)



Approach to Initiating Menopausal Hormone Therapy

- **Vasomotor Symptom Assessment**

  Confirm that hot flashes and/or night sweats are adversely affecting sleep, daytime functioning, or quality of life.

- **Risk Factor Assessment (contraindications, CVD risk, breast cancer risk, fracture risk, etc.**

- **Menopausal Hormone Therapy Initiation or Consider Non-Hormonal Options**

Recommend	Consider with Caution	Avoid
Age <60 years and Menopause onset within 10 years and Low risk of breast cancer and cardiovascular disease	Age ≥ 60 years ••••••••••••OR•••••••••••• Menopause onset >10 years prior ••••••••••••OR•••••••••••• Moderate risk of breast cancer Or cardiovascular disease	High risk of breast cancer or cardiovascular disease ••••••••••••OR•••••••••••• Age ≥60 years or menopause onset >10 years prior and Moderate risk of breast cancer or cardiovascular disease

Source: Shifren JL, Crandall CJ, Manson JE. *JAMA* 2019;321:2458-2459.

Consider Transdermal

- Obesity/Metabolic Syndrome
- Diabetes
- Hypertriglyceridemia
- Higher risk of thrombosis
- Low libido (less effect on SHBG)
- Migraines (without aura)
- Gallbladder or liver disease

Source: Pinkerton JV. *N Engl J Med* 2020.

Conclusions

- Hormone therapy continues to have an important clinical role in the management of menopausal symptoms (not refuted by WHI).
- Current evidence does not support the use of HT for the prevention of CVD or other chronic diseases (due to increased risk of VTE and stroke/breast CA [E+P] in all age groups).
- The best candidates for systemic HT are recently menopausal and symptomatic women in generally good health (low absolute risks and greater QOL benefits).
- Risk stratification and a personalized approach to decision making is recommended, with shared decision making with the patient.
- Additional studies of different HT formulations, doses, routes of delivery, and of non-hormonal options are needed.

Thanks to the Participants, Investigators, and Staff of WHI and other Research Studies

Thank you!

(Email: jmanson@bwh.harvard.edu)