

## Hormone Replacement Therapy in Menopause: Evidence and Current Recommendations for Use

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- I have no disclosures

## Educational Objectives

- Basic understanding of menopause and hormonal therapies
- Acknowledge the history of hormone use
- Understand key points about:
  - The Women's Health Initiative (WHI)
    - The Women's Health Initiative Memory Study (WHIMS)
  - Kronos Early Estrogen Prevention Study (KEEPS)
  - Early versus Late Intervention Trial with Estradiol (ELITE)
- Review current recommendations for hormone replacement therapy (HRT)



## A Case to Ponder

- Ms. D is a 53 yo woman presenting with bothersome hot flashes
- Her LMP was 12/2016
- The hot flashes occur a few times weekly and at anytime
- She also complains of fatigue, mood changes and sleep disturbance
- She denies active liver disease, breast cancer, CVA, CVD, DVT, GB disease (s/p cholecystectomy), hypertriglyceridemia, migraine with auras
- **What treatment options are you thinking of?**

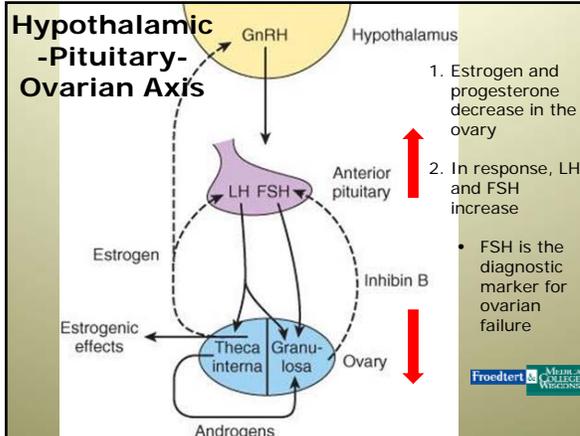


## Overview of Menopause

- All women experience menopause
- Each one does so in a unique way
- Average age of menopause in the US is 51 years old
- Definition of menopause: the *final* menstrual period resulting from the permanent decline in gonadal hormone levels confirmed by 12 months of amenorrhea in women with a uterus



Menopause Practice A Clinician's Guide 5<sup>th</sup> ed



### Symptoms of Menopause

(may or may not be caused by menopause)

- **Hot flashes**
  - Experienced by up to 75% of women
  - Heat spreads over the body, particularly the upper body and face
  - Lasts from 1-5 minutes
  - Can occur infrequently (monthly, weekly) or frequently (hourly)
- Genitourinary syndrome of menopause (GSM)
- Decreased sexual desire
- Depressed mood, anxiety, stress and a decreased sense of well-being (most do not report this)
- Sleep disturbances
- Headaches
- Decreased cognition



### Hormone Replacement Therapy (HRT)

**Estrogens**



**Progestogens**






### Fact

- Estrogen causes proliferative effects on the endometrium
- Use of *unopposed* estrogen in women with an intact uterus is NOT recommended
- Progesterone (or a SERM) must be used



### Estrogen Therapy

some common formulations and doses (mg)

Conjugated Equine Estrogen (CEE)	0.3, 0.45, 0.625, 0.9, 1.25
- Isolated from the urine of pregnant mares	
- On the market for 65+ years	
Synthetic conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25
Micronized 17beta-estradiol	0.5, 1.0, 2.0
17beta-estradiol matrix patch	0.014, 0.025, 0.0375, 0.05, 0.075, 0.1

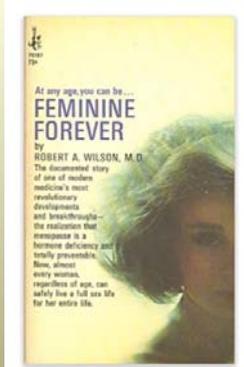
### Progestogen Therapy

some common formulations and doses (mg)

Medroxyprogesterone acetate (MPA)	2.5, 5, 10
Micronized progesterone (in peanut oil)	100, 200
Progesterone vaginal gel	45, 90



- In **1898**, German doctors fed fresh cow ovaries to a young woman suffering from severe hot flashes after having her ovaries removed
- By the **1960s**, pharmaceutical companies and doctors were promoting hormones as a way for women to stay "feminine forever"
- Trend to start HRT in older women for prevention of chronic disease, including heart disease and dementia





The Fountain of Youth by Eduard Veith (1900)



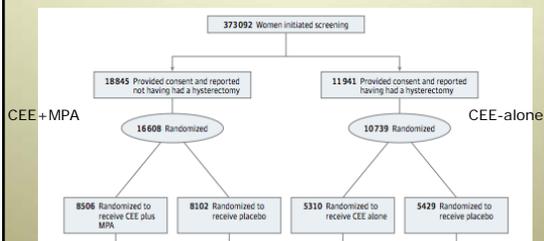
## WHI



- In the **1990s**, the WHI, a \$625 million study was started in the US to examine the risks and benefits of menopause hormones
- Funded by the The National Heart, Lung, and Blood Institute
  - Wyeth-Ayerst Research provided the study medication (active and placebo)
- It is comprised of several trials including Estrogen Plus Progestin and Estrogen-alone Trials
  - **Will HRT reduce cardiovascular events in mostly healthy postmenopausal women?**



## WHI



## WHI : CEE +MPA

- Oral conjugated equine estrogen (CEE) 0.625 mg/d and medroxyprogesterone (MPA) 2.5 mg/d
- Average age 63
- 74% never used hormones before
- Mean follow-up: 5.2 years



## WHI : Shocking Results

- In **2000**, participants given information indicating increases in MI, stroke and PE/DVT had been observed, but the risks and benefits remained uncertain
- In **2002**, MI, stroke and PE/DVT risk persisted, but within study boundaries
  - However, **HARM** from breast cancer crossed the designated boundary



## WHI Makes HEADLINES

### Study Is Halted Over Rise Seen In Cancer Risk

By GINA KOLATA JULY 9, 2002

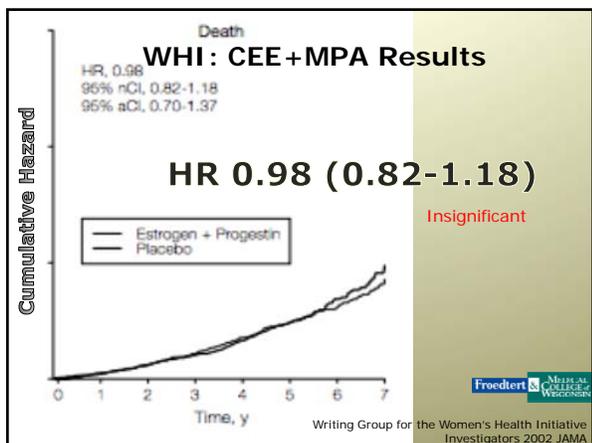
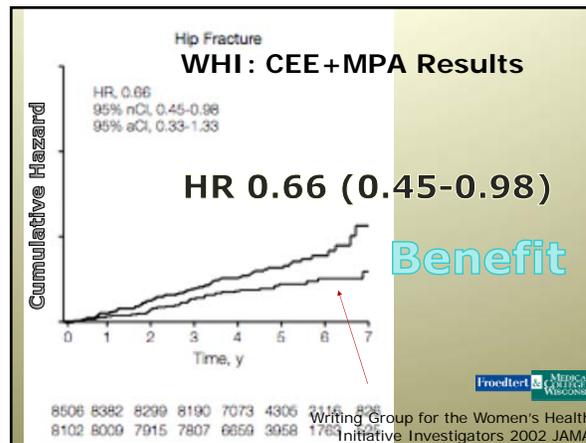
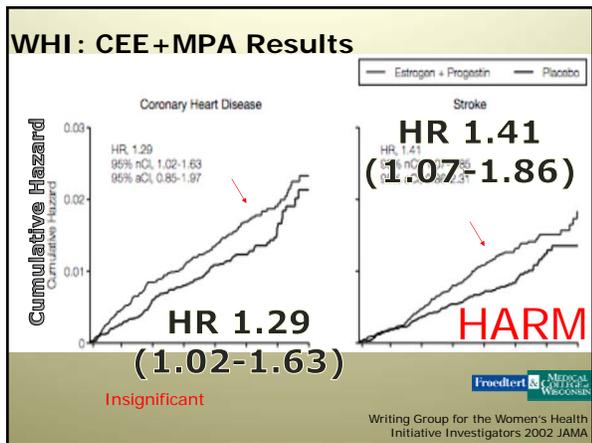
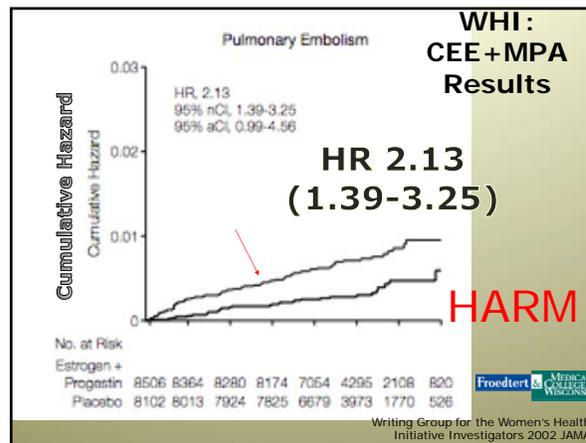
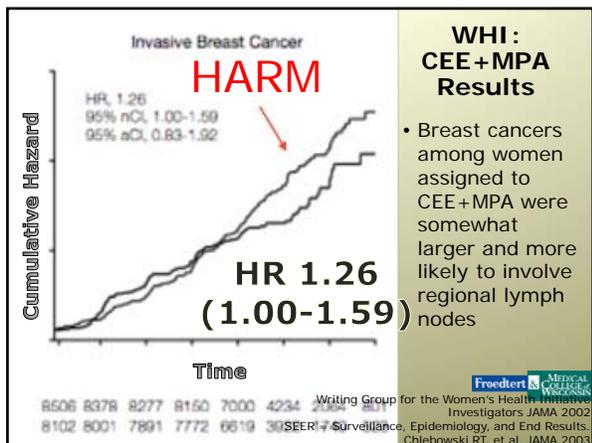
**Hormone replacement therapy study halted**  
 Increased risk of breast cancer a factor, government says

August 14, 2002 Posted: 11:56 AM EDT (1986 GMT)

### Hormone Replacement Study A Shock to the Medical System

By GINA KOLATA WITH MELISSA PETERSON JULY 10, 2002





- ### WHI: CEE+MPA Characteristics
- 10.5% current smokers
  - 40% past smokers
  - 36% treated for hypertension
  - 7% were on a statin
  - 90% had children
  - 16% had a female relative with breast cancer
  - 64% had a Gail model 5-year risk of breast cancer of 1-2
  - **There were NO substantial differences between the hormone and placebo groups at baseline**
- Writing Group for the Women's Health Initiative Investigators 2002 JAMA  
Froedtert & Medical College of Wisconsin

### WHI: CEE+MPA Take Away

- Health risks exceeded benefits from use of estrogen+progestin for an average of 5.2 years
- This regimen should NOT be initiated or continued for primary prevention of coronary heart disease

Froedtert & MEDICAL COLLEGE OF WISCONSIN

### WHI: CEE-alone Details

- 11,000 women participated
- Oral CEE 0.625 mg/d
- Average age 64
- 52% never used hormones before
- Mean follow-up: 6.8 years

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Anderson GL et al. JAMA 2004

### WHI: CEE-alone

- In 2004, the NIH terminated the CEE-alone intervention phase

**Estrogen Study Stopped Early Because of Slight Stroke Risk**

By DENISE GRADY | MARCH 8, 2004

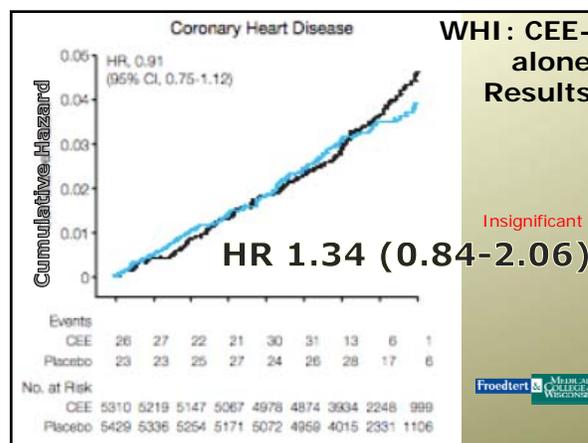
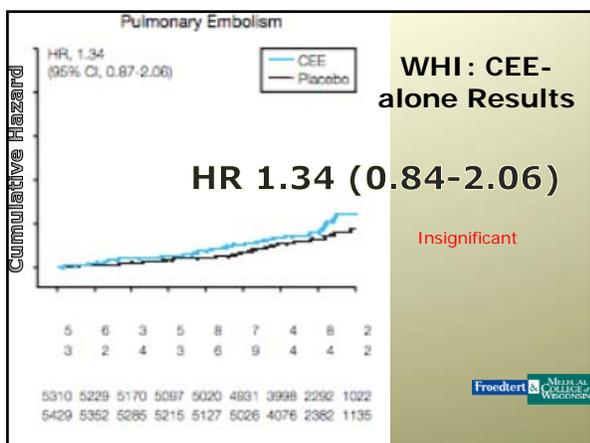
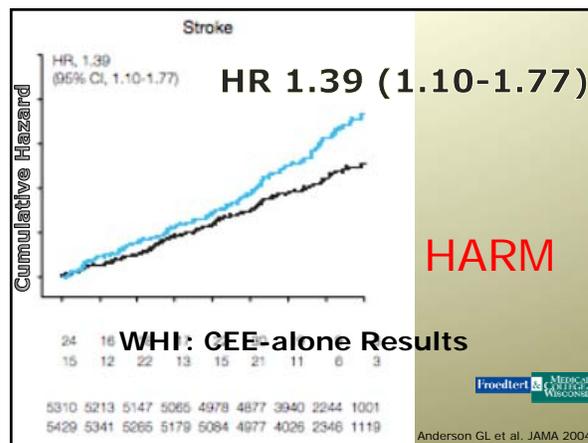
**HEALTH**

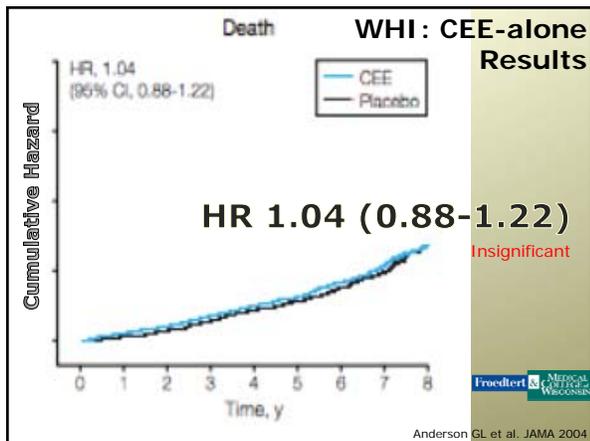
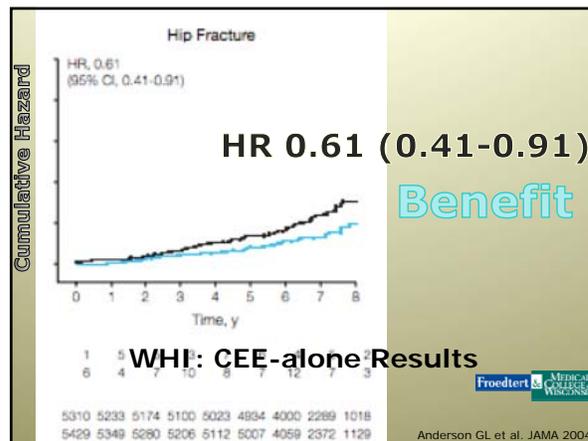
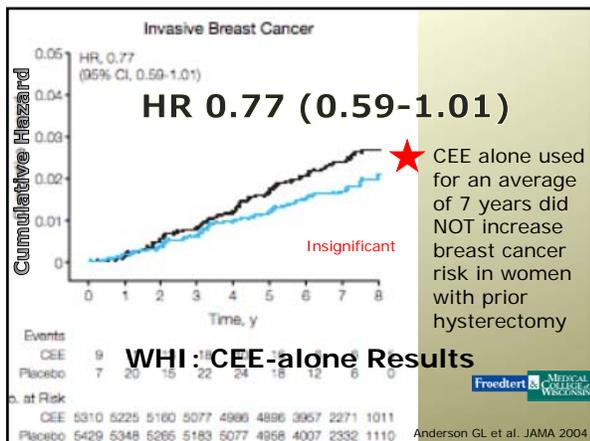
**Study finds estrogen alone is risky, too**

Feds halt trial, citing no heart disease benefit

From Saundra Young and Christy Feig  
CNN  
Tuesday, March 2, 2004 Posted: 10:12 AM EST (1512 GMT)

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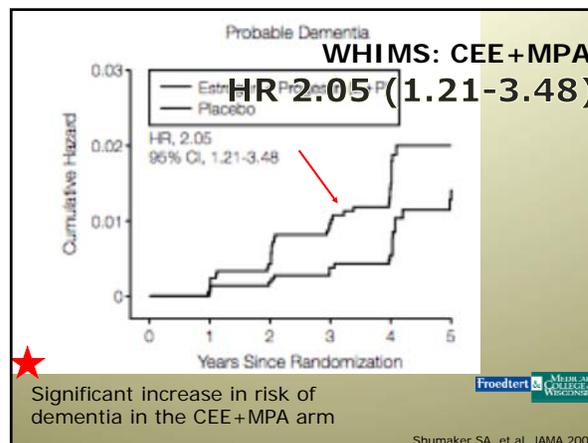
**WHI: CEE-alone Take Away**

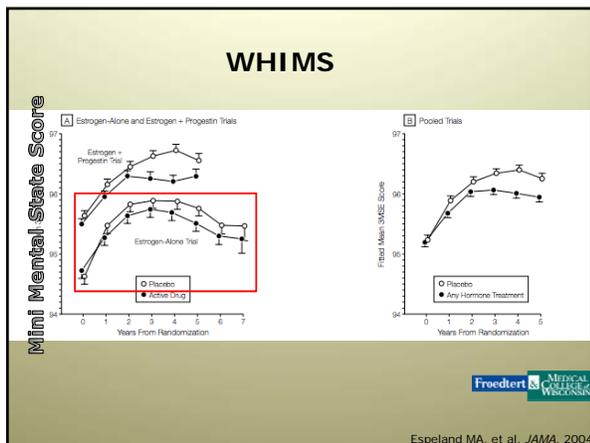
- The use of CEE increases the risk of stroke in postmenopausal women with prior hysterectomy over an average of 6.8 years
- CEE should NOT be recommended for chronic disease prevention in postmenopausal women

**WHIMS**

- Ancillary study of the WHI
- Participants were all aged 65 years old
- Used the Modified Mini-Mental State Examination

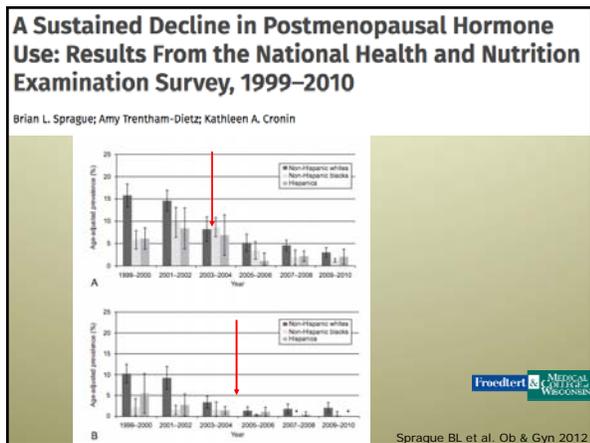
Espeland MA, et al. JAMA 2004





### WHI : Shocking Results

- Prior to publication of WHI, at least 40% of postmenopausal women in the US were using HRT
- Hormones became evil
- Women were deprived of HRT for any cause



### WHI : A Closer Look

- Only one form and strength of estrogen used
- One form and strength of progestin used
- Oral preparations only
- Most women were >10 years past menopause
- NOT designed to address the benefits of hormones for symptomatic women

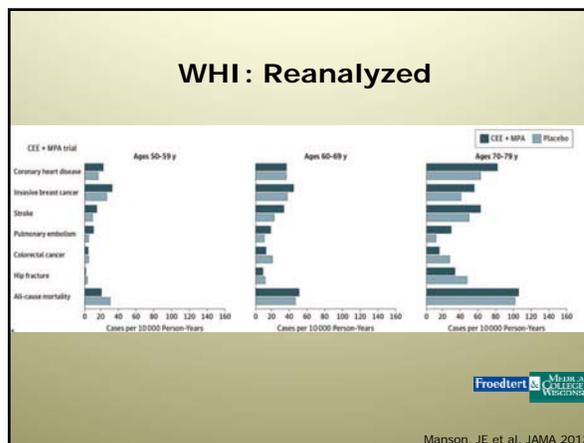
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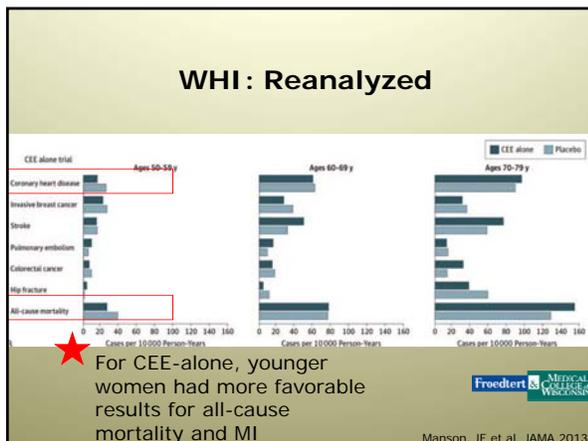
### WHI : Reanalyzed

- Results were re-synthesized
- Analyses were stratified by age and time since menopause

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Manson, JE et al. JAMA 2013





### WHI Reanalysis: Take Away

- A more favorable risk-to-benefit ratio seen in *younger* women
  - especially in the CEE-alone group
- Findings from the intervention and extended post-intervention follow-up of the 2 WHI hormone therapy trials do NOT support use of this therapy for chronic disease prevention

### Long-Term Effects on Cognitive Function of Postmenopausal Hormone Therapy Prescribed to Women Aged 50 to 55 Years

Mark A. Espeland, PhD; Sally A. Shumaker, PhD; Iris Leng, PhD; JoAnn E. Manson, MD, DrPH; Candice M. Brown, PhD; Erin S. LeBlanc, MD, PhD; Leslie Vaughan, PhD; Jennifer Robinson, MD, MPH; Stephen R. Rapp, PhD; Joseph S. Goveas, MD; Dorothy Lane, MD, MPH; Jean Wactawski-Wende, PhD; Marcia L. Stefanick, PhD; Wenjun Li, PhD; Susan M. Resnick, PhD; for the WHIMSY Study Group

- Women aged 50-55 years during trial **WHIMSY**
- Cognitive testing conducted an average 7.2 years after trials ended
- Mean age 67.2
- Conclusion: HRT administered to women earlier in menopause does NOT seem to convey long-term adverse consequences for cognitive function

JAMA Intern Med. 2013

### WHIMSY: A Critical Window?

- Does the effects of HRT on cognition vary depending on a woman's age and time since menopause?

Hodis HN, et al. NEJM 2016

### Rebuilding Confidence: KEEPS

- In 2012, the **Kronos Early Estrogen Prevention Study (KEEPS)** trial was discussed at the North American Menopause Society
- 727 women **within 3 years** of menopause
- Average age 52
- Followed for 4 years

Barker, C. Women's Health 2013

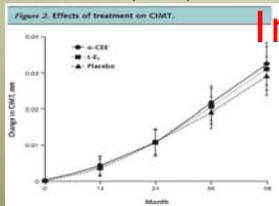
### Rebuilding Confidence: KEEPS

- Oral CEE 0.45 mg/d
- Micronized progesterone (Prometrium) 200 mg for 12 days/m
- Transdermal estradiol patch 50 mcg/d
- Micronized progesterone (Prometrium) 200 mg for 12 days/m

Barker, C. Women's Health 2013

### Rebuilding Confidence: KEEPS

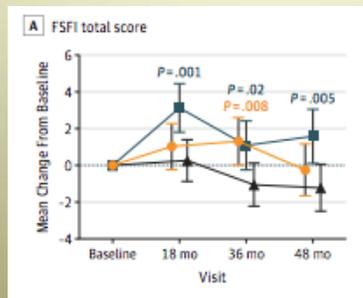
- Primary endpoint: annual change in carotid artery intima-media thickness (CIMT)



Insignificant

Barker, C. Women's Health 2013  
Harman SM, et al. Ann Intern Med 2014  
PLoS Medicine 2015; 12(6): e1001833

### Rebuilding Confidence: KEEPS



- Improvement in sexual function

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Taylor, HS, et al. JAMA 2017

### Rebuilding Confidence: KEEPS

- Women in each hormone group did not differ from women receiving placebo on five cognitive outcomes
- Significant reduction in vasomotor symptoms
- Improvement in bone mineral density



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Barker, C. Women's Health 2013

### WHI vs. KEEPS

#### WHI

- Mean age 63 years
- Average 12 years past the onset of menopause
- Oral CEE 0.625 mg/d
- MPA 2.5 mg/d

#### KEEPS

- Mean age 52 years
- All within 3 years after their final menstrual period
- Oral CEE 0.45 mg/d
- Transdermal estradiol
- Cyclical micronized progesterone
- Much smaller study

Barker, C. Women's Health 2013

#### ORIGINAL ARTICLE

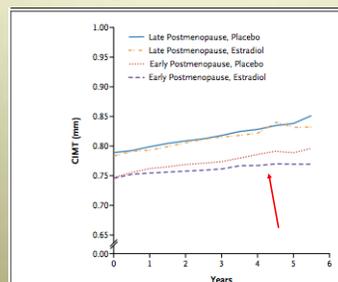
### Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol

Howard N. Hodis, M.D., Wendy J. Mack, Ph.D., Victor W. Henderson, M.D., Donna Shoup, M.D., Matthew J. Budoff, M.D., Juliana Hwang-Levine, Pharm.D., Yanjie Li, M.D., Mei Feng, M.D., Laurie Dunlap, M.S., Naoko Kono, M.P.H., Frank Z. Stanczyk, Ph.D., Robert H. Sotzer, M.S., and Stanley R. Azem, Ph.D., for the ELITE Research Group  
N Engl J Med 2016; 374:1221-1231 | March 31, 2016 | DOI: 10.1056/NEJMoa1502041

- 234 postmenopausal women **within 6 years of menopause**
- 333 postmenopausal women **10+ years past menopause**
- Mean age 55 years
- Mean age 64 years
- Oral estradiol 1 mg/d
- Cyclic micronized progesterone 45 mg/d as a vaginal gel
- Follow-up: median 5 years

Hodis HN, et al. NEJM 2016

### Rebuilding Confidence: ELITE



No. of Participants	643	533	522	515	424	295	56
With CIMT data	0	106	119	128	215	345	382
Who completed or discontinued study	0	4	2	0	4	3	5
Without CIMT data	0	4	2	0	4	3	5

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Hodis HN, et al. NEJM 2016

### Rebuilding Confidence: ELITE-Cog

- Cognition outcomes at 2.5 and 5 years
- Primary outcome: verbal memory
- Secondary outcomes: Global cognition and executive function
- Estradiol neither benefited nor harmed *regardless of time since menopause*

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Henderson, VW et al. Proc Natl Acad Sci USA 2013

### The Timing Hypothesis: ELITE

The effects of HRT on heart disease may vary depending on a woman's age and time since menopause



HRT neither benefited nor harmed cognition *regardless of time since menopause*



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Hodis HN, et al. NEJM 2016

PERSONAL HEALTH

### Rethinking the Use of Hormones to Ease Menopause Symptoms

BY JANE E. BRODY AUGUST 29, 2016 6:45 AM



**Principal Investigators of 2002 WHI Study Reverse Findings - HRT vindicated in new JAMA article**

PHOTO: GETTY IMAGES

### Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality

The Women's Health Initiative Randomized Trials

JaAnn E. Manson, MD, DrPH<sup>1</sup>, Aaron K. Aragaki, MD<sup>2</sup>, Jacques E. Rossouw, MD<sup>3</sup>, et al.

- Observational, 18-year follow-up of the WHI
- Data available for >98% of participants
- All-cause mortality was 27.1% in the hormone therapy group vs 27.6% in the placebo group



Froedtert & MEDICAL COLLEGE OF WISCONSIN

JAMA 2017

### What does this mean?

CEE+MPA for ~6 years and CEE alone for ~7 years

Is **NOT** associated with risk of:

- All-cause
- Cardiovascular or
- Cancer mortality

(although there are risks, we don't see death!!)



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JAMA 2017

### Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality

The Women's Health Initiative Randomized Trials

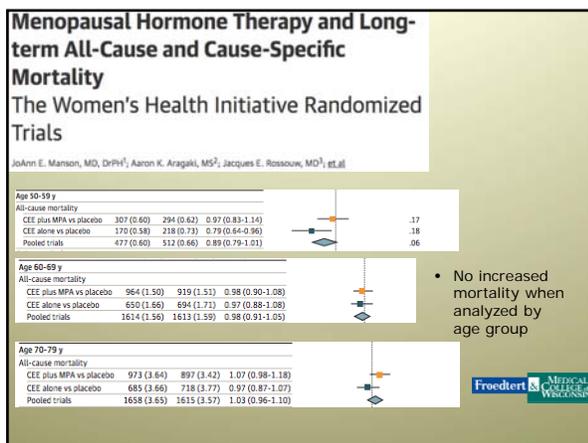
JaAnn E. Manson, MD, DrPH<sup>1</sup>, Aaron K. Aragaki, MD<sup>2</sup>, Jacques E. Rossouw, MD<sup>3</sup>, et al.

	CEE plus MPA vs placebo	CEE alone vs placebo	Relative Risk (95% CI)	P-value
<b>Cancer mortality</b>	706 (0.50)	638 (0.47)	1.06 (0.95-1.18)	.31
CEE alone vs placebo	424 (0.49)	439 (0.49)	0.99 (0.86-1.13)	.86
Pooled trials			1.03 (0.95-1.12)	.50
<b>Breast cancer mortality</b>	61 (0.043)	40 (0.030)	1.44 (0.97-2.15)	.07
CEE alone vs placebo	22 (0.025)	41 (0.046)	0.55 (0.33-0.92)	.02
Pooled trials			0.87	
<b>Colorectal cancer mortality</b>	53 (0.037)	50 (0.037)	1.01 (0.69-1.49)	.96
CEE alone vs placebo	47 (0.054)	40 (0.043)	1.21 (0.79-1.84)	.38
Pooled trials			1.10 (0.82-1.46)	.53
<b>Other known cancer mortality</b>	548 (0.39)	521 (0.39)	1.00 (0.89-1.13)	.94
CEE alone vs placebo	336 (0.39)	345 (0.39)	1.00 (0.86-1.16)	.96
Pooled trials			1.00 (0.91-1.10)	.98
<b>Other mortality</b>	850 (0.60)	828 (0.61)	0.99 (0.90-1.08)	.77
CEE alone vs placebo	534 (0.61)	614 (0.69)	0.89 (0.79-1.00)	.05
Pooled trials			0.95 (0.88-1.02)	.14
<b>Alzheimer's or dementia mortality</b>	223 (0.16)	233 (0.17)	0.93 (0.77-1.11)	.42
CEE alone	127 (0.15)	175 (0.20)	0.74 (0.59-0.94)	.01
Pooled trials			0.85 (0.74-0.98)	.03

Lower risk of death with HRT | Higher risk of death with HRT

- Decreased mortality from breast cancer in CEE-alone group
- Decreased mortality from Alzheimer's in CEE-alone group

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- ### FDA-approved Indications for HRT
- First-line therapy for vasomotor symptoms
  - Prevent bone loss and reduce fractures
  - For women with hypogonadism, primary ovarian insufficiency or premature surgical menopause until the average age of menopause
  - Genitourinary symptoms
- Froedtert & MEDICAL COLLEGE OF WISCONSIN
- The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.*

- ### Contraindications for HRT
- Unexplained vaginal bleeding
  - Severe active liver disease
  - Prior estrogen-sensitive breast or endometrial cancer
  - Stroke
  - Thromboembolic disease
  - Hypertriglyceridemia
  - Pregnancy
  - Hypersensitivity
  - Heart disease\*\*
  - Dementia\*\*
- Froedtert & MEDICAL COLLEGE OF WISCONSIN
- The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.*

- ### Changing the Conversation
- Recommendation from NAMS
- 
- **“For women who are aged younger than 60 years or within 10 years of menopause and have no contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and in those at elevated risk for bone loss or fracture”**
  - Treatment should be individualized
  - Periodic reevaluation is necessary
- Froedtert & MEDICAL COLLEGE OF WISCONSIN
- The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.*

- ### The 2017 NAMS Hormone Therapy Position Statement has been endorsed by:
- Academy of Women's Health
  - American Association of Clinical Endocrinologists
  - American Medical Women's Association
  - American Society for Reproductive Medicine
  - Association of Reproductive Health Professionals
  - International Society for the Study of Women's Sexual Health
  - The American College of Obstetricians and Gynecologists
  - International Osteoporosis Foundation...
- Froedtert & MEDICAL COLLEGE OF WISCONSIN

## Changing the Conversation



- “Appropriate hormone therapy to meet treatment objectives”
- Lowest most effective dose
- Lack of good quality information about prolonged duration of use
  - Decisions regarding whether to continue HRT beyond age 60 should be individualized

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

## Final Thoughts: Breast Cancer

- The effect of HRT on breast cancer risk may depend on:
  - Type of hormone
    - Less risk with estrogen alone
    - Is it the progesterone?

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### Risk of Breast Cancer by Type of Menopausal Hormone Therapy: a Case-Control Study among Post-Menopausal Women in France

Emilie Cordina-Duverger<sup>1,2</sup>, Thérèse Truong<sup>1,2</sup>, Antoinette Anger<sup>1,2</sup>, Marie Sanchez<sup>1,2</sup>, Patrick Arveux<sup>1</sup>, Pierre Kerbrat<sup>1</sup>, Pascal Guénel<sup>1,2\*</sup>

Odds ratios for breast cancer among current users of combined MHT by type of treatment and duration of use.

	Any duration				Duration < 4 years				Duration ≥ 4 years			
	Cases	Controls	OR <sup>a</sup>	95% CI	Cases	Controls	OR <sup>a</sup>	95% CI	Cases	Controls	OR <sup>a</sup>	95% CI
<b>Never MHT use</b>	311	357	1	ref.	311	357	1	ref.	311	357	1	ref.
Estrogen + natural progesterone	25	34	0.80	[0.44-1.43]	10	17	0.69	[0.29-1.68]	14	17	0.79	[0.37-1.71]
Estrogen + synthetic progestagen	67	48	1.72	[1.11-2.65]	11	14	1.17	[0.48-2.86]	55	34	2.07	[1.26-3.39]
<i>By type of synthetic progestagen</i>												
Estrogen + Progesterone Der.	55	43	1.57	[0.99-2.49]	10	13	1.02	[0.40-2.58]	45	30	1.92	[1.13-3.27]
Estrogen + Testosterone Der.	11	5	3.35	[1.07-10.4]	4	4	1.64	[0.38-7.15]	7	1	9.47	[1.09-82.4]
<i>By regimen</i>												
Continuous	9	5	2.52	[0.77-8.32]	3	2	2.41	[0.36-16.1]	6	3	2.70	[0.60-12.2]
Sequential	56	40	1.75	[1.09-2.79]	11	10	1.40	[0.54-3.65]	45	30	2.06	[1.18-3.41]

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- Observational study suggesting the risk of breast cancer may be less with micronized progesterone

PLOS ONE 2013

## Bazedoxifene

- SERM
- Combined with CEE 0.45 mg to form a tissue-selective estrogen complex
- Provides endometrial protection without the need for a progestogen
- Approved for treatment of hot flashes and the prevention of bone loss in postmenopausal women with an intact uterus
- Longer studies are needed to assess VTE risk

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## Final Thoughts: DVT/PE, MI, Stroke

- Timing Hypothesis from ELITE:
  - HRT initiated < 10 years after menopause safer
- !Risk of DVT/PE
  - ?Less risk with non-oral preparation

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## Oral vs Transdermal Estrogen and Thromboembolic Complications (OR and 95% CI)

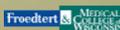
Study Publication	Oral estrogen	Transdermal estrogen
Scarabin, et al (1)	3.5 (1.8-6.8)	0.9 (0.5-1.6)
Canonic, et al (2)	4.2 (1.5-11.6)	0.9 (0.4-2.1)

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1. Lancet, 2003  
2. Circulation, 2007

## Compounded Bioidentical HRT

- Why **NOT** use it:
  - LACK of regulation and monitoring
  - Real possibility of overdosing or underdosing
  - LACK of scientific efficacy and safety data
  - LACK of a label outlining risks
  - Possible presence of impurities or lack of sterility
- When to use it:
  - Allergy
  - Need for different dosing, formulation or preparation



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

## Non-Hormonal Therapies

- SSRIs/SNRIs
  - Venlafaxine
  - Paroxetine
- Gabapentin
- Pregabalin
- Clonidine



## Back to the case...

- Ms. D was prescribed:
- Estradiol patch .05 mg and micronized progesterone 200 mg 12 days monthly



## Take Home Points

- WHI does deserve credit for stopping the common practice of prescribing HRT to prevent chronic disease
- The WHI is not generalizable
- HRT is the *most* effective first line treatment available for the common symptoms of menopause
- Hormones are NOT exclusively evil and may make a HUGE difference in a woman's quality of life (But, it's not a simple therapy and a lot of discourse needs to take place)



## Questions for consideration

- Is there a risk of breast cancer on CEE-bazedoxifene? (since there is no progesterone)
- How long can women safely stay on CEE-bazedoxifene?
- How long can women safely stay on HRT?
- How does estrogen impact diabetes (suggestions that insulin resistance is reduced)?



## Thank You!

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### The Seven Stages of Menopause

