

# Menopause- An Update

## *Management Consensus & Controversies*

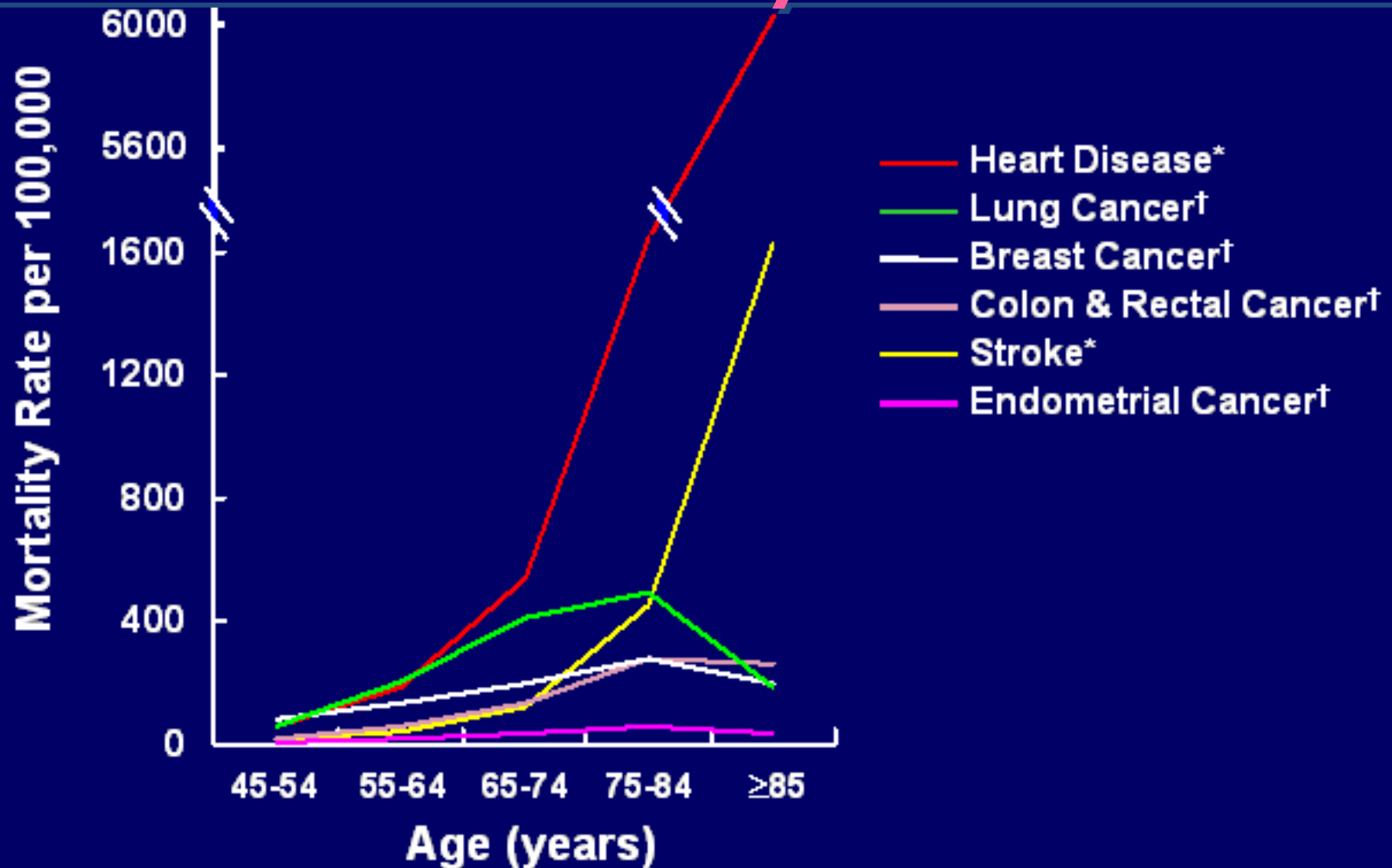
Michel Abou Abdallah, MD.  
Reproductive Endocrinology

# Learning Objectives

**At the conclusion of this presentation, participants should be able to:**

- Appreciate the spectrum of menopause related symptom burden and health concerns
- **Be familiar with the status of menopausal medicine**
- Identify unique needs & risks of women experiencing unnatural menopause (POI, iatrogenic)
- Compare & contrast the efficacy, safety & side effects of available therapies (hormonal & non-hormonal)
- **Individualize risk assessment & Rx strategies**

# Aging Female Population Mortality



\*Mean of years 1995-1998; †1994-1998.

Eberhardt VMS, et al. *Health, United States, 2001*. National Center for Health Statistics, 2001:189,192.

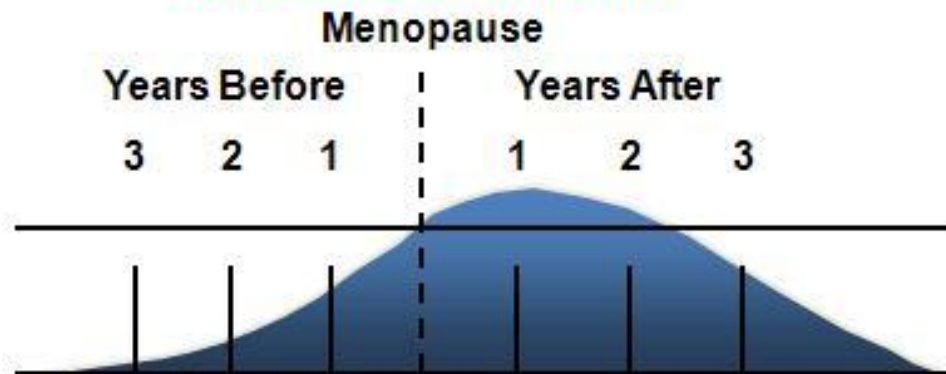
Ries LAG, et al. *SEER Cancer Statistics Review, 1973-1998*. National Cancer Institute, 2001.

# Menopausal Symptom Burden

## Prevalence of Hot Flashes

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

### *Prevalence of Hot Flashes*

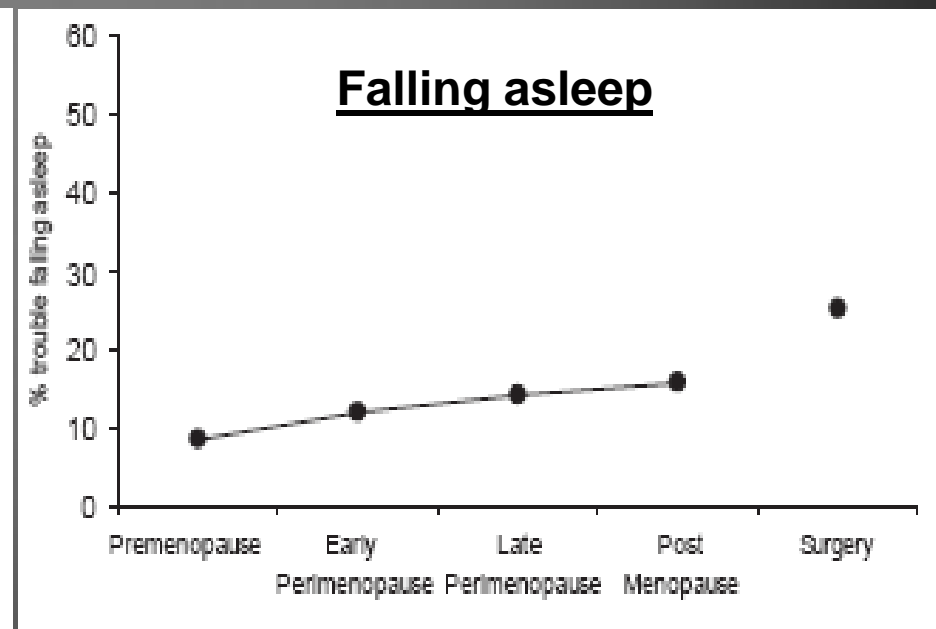
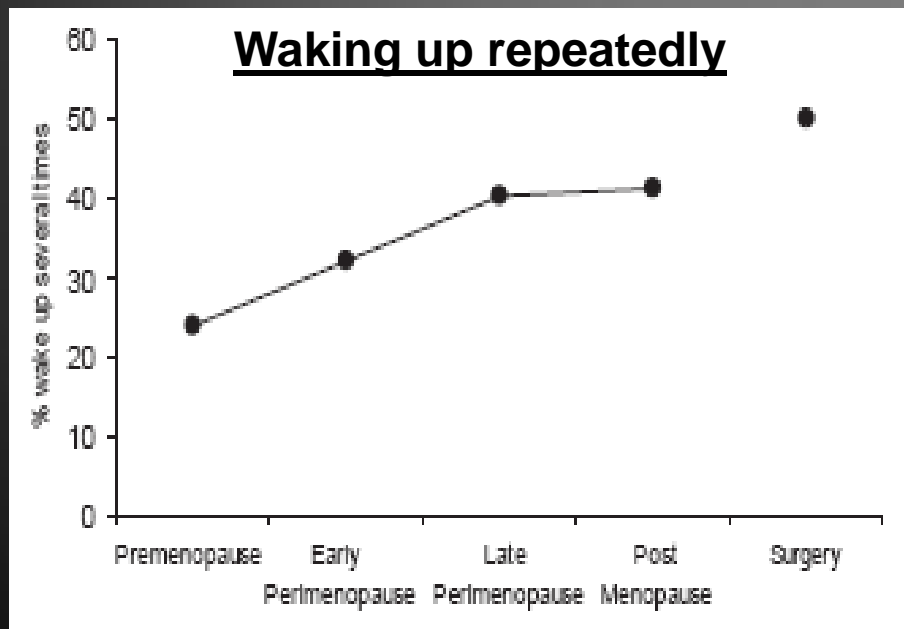
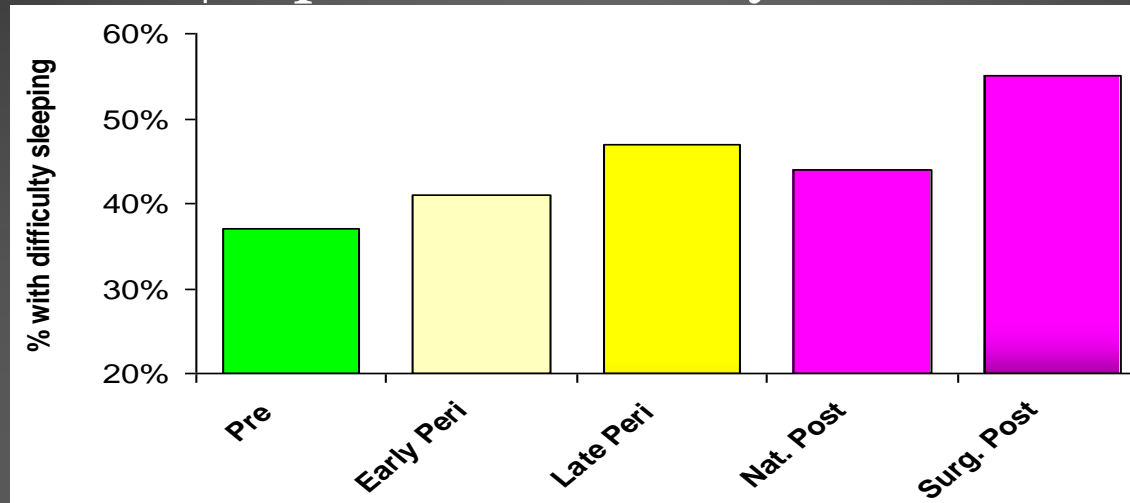


Kronenberg *Ann NY Acad Sci.* 1990;592:52-86.

Gold, *Am J Epi* 2004; 159:1169

# Sleep Disturbance in Peri/Postmenopausal Women

↑ reports of difficulty



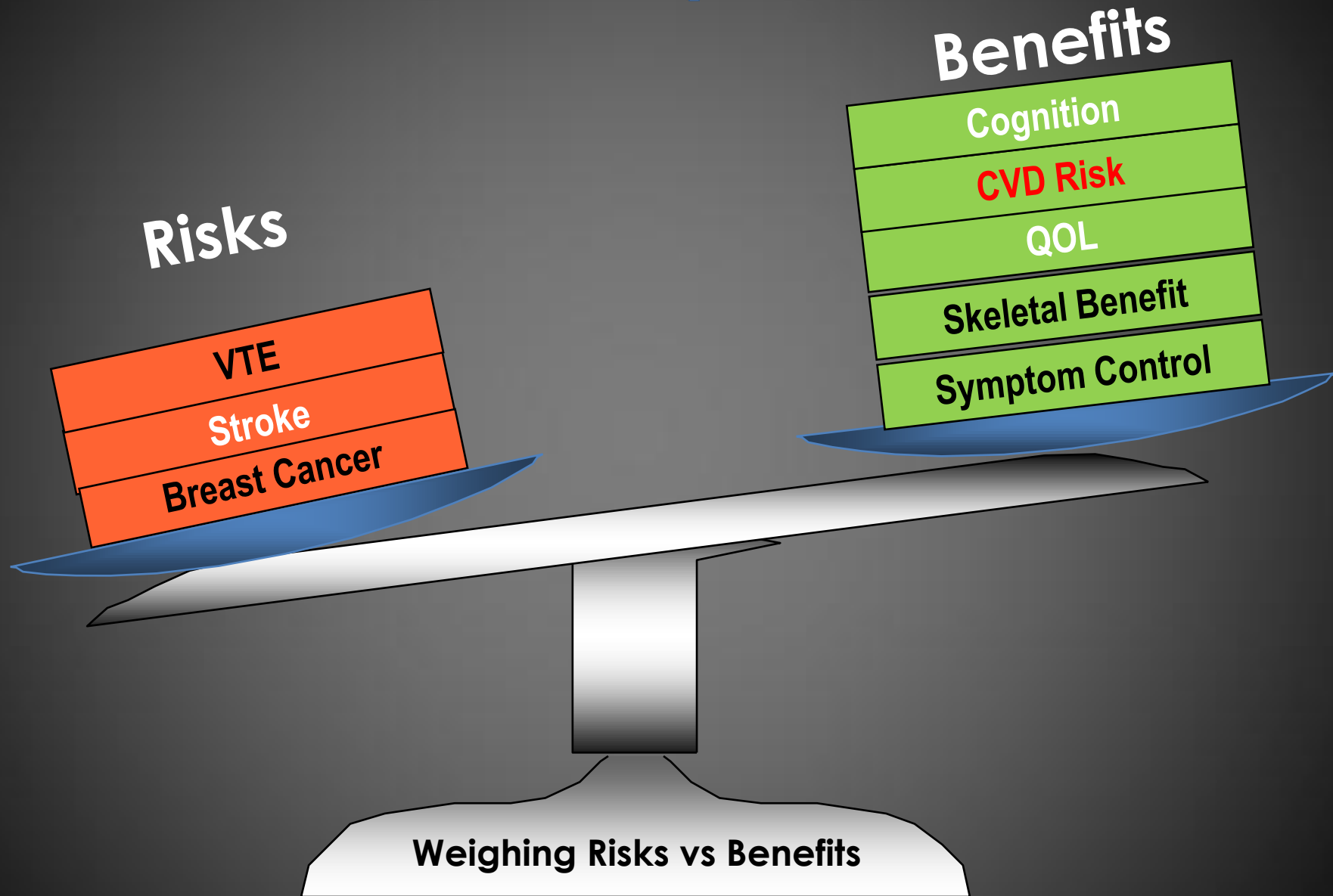
# Reproductive Aging Paradigm

Puberty      Reproductive Yrs      Transition      Postmenopause

	Reproductive Yrs					Transition		Postmenopause	
	-5	-4	-3	-2	-1	0	+1	+2	
<i>Stages:</i>	Reproductive					Menopausal Transition		Postmenopause	
<i>Terminology:</i>	Early	Peak	Late	Early	Late*		Early*	Late	
						Perimenopause			
<i>Duration of Stage:</i>	variable			variable		a	4 yrs	until demise	
<i>Menstrual Cycles:</i>	variable to regular	regular		variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amen x 12 mos	none		
<i>Endocrine:</i>	normal FSH		↑ FSH	↑ FSH			↑ FSH		

\*Stages most likely to be characterized by vasomotor symptoms      ↑ = elevated

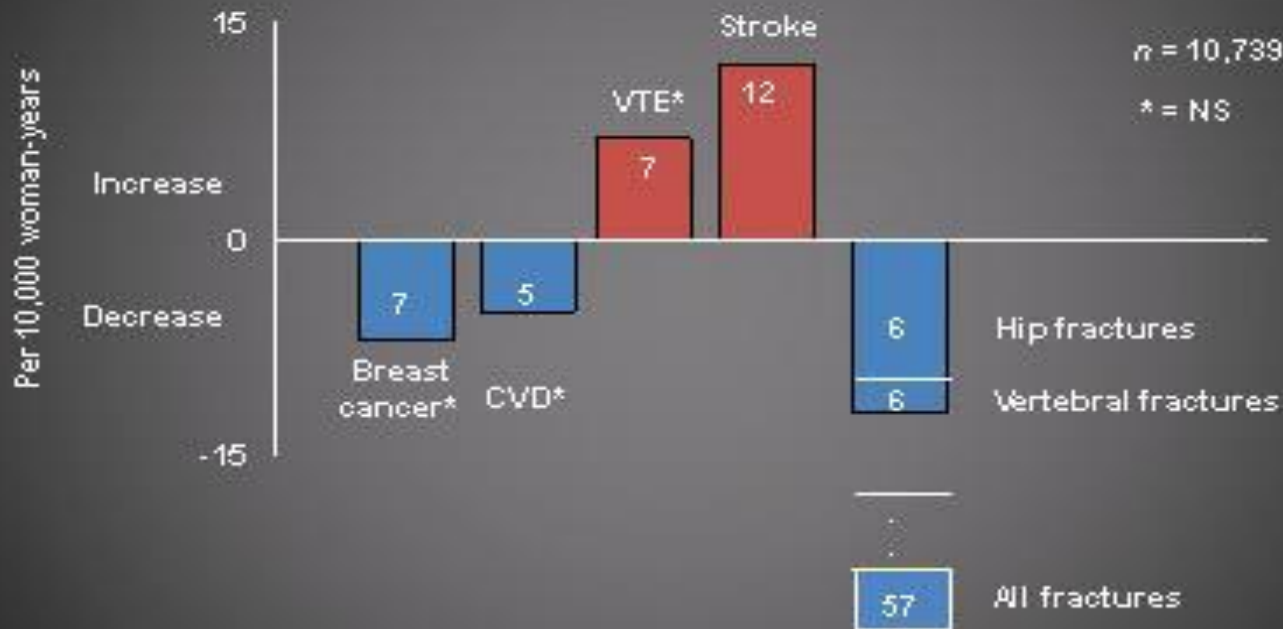
# HT...Pre-WHI Perceptions



Adapted from: Writing Group for the Women's Health Initiative. *JAMA*. 2002;288:321-333.

# WHI Hormone Trials

## Annual Risks & Benefits after 7 years of E alone

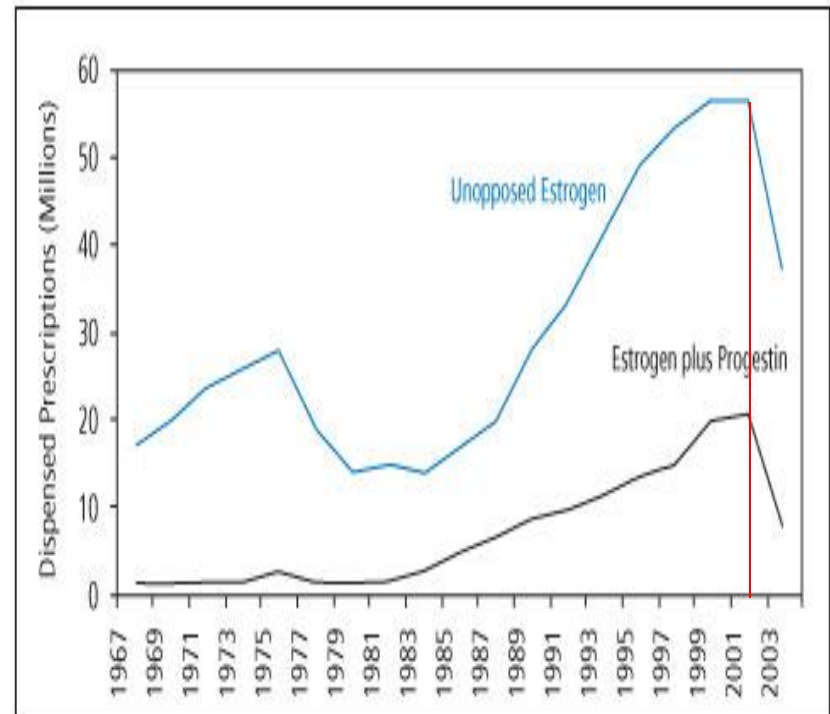


Adapted from *JAMA* 2004;291:1701-12  
MacLennan A, Sturdee D. *Climacteric* 2004



# Menopause Hormone Therapy (MHT)...*lessons learnt from WHI*

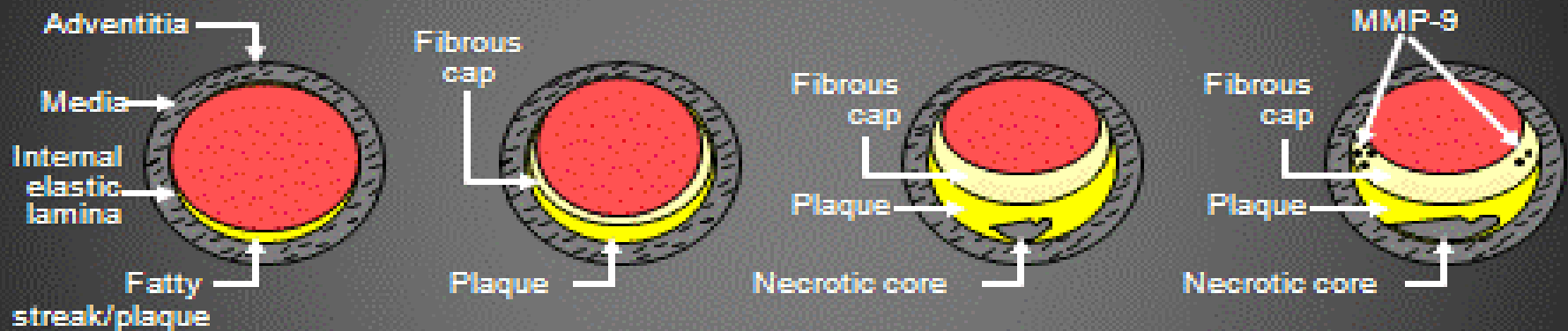
- Is NOT risk free
- NOT cardioprotective
- CAN harm
  - Aged
  - Remote from last menstrual period
  - Overweight/obese
  - Existing pre morbidities



**Figure 1.** Trends in menopausal hormone therapy use in the U.S., 1967–2003. (Adapted from Beral V, et al. 1999 and Hersch AL, et al. 2004)

# Timing Hypothesis

## Relation of years since menopause to progression of atherosclerosis



Years postmenopause % of WHI enrollees	< 5 17%	5 to < 10 19%	10 to < 15 21%	≥ 15 43%

**To compare effects of low dose oral CEE (0.45mg) vs. transdermal estradiol (50 µg/d weekly patch) vs. placebo on surrogates for CVD:**

- 1) Carotid IMT**
- 2) Coronary artery calcium (CAC)**

- 727 women aged 42-59 (mean age, 52.7, within 3 yrs of FMP)**
- Trial Duration = 48 months**
- Multi-center double-blinded placebo-controlled RCT**
- Active Treatment Arms:**
  - *Cyclical micronized P 200 mg/d x 12 days/month vs. placebo***

# Study Design

## Inclusion criteria

- **42-59 years of age at randomization**
- **Final menses  $\leq 3$  years earlier**
- **Good general health**
- **Plasma FSH  $\geq 35$  mIU/ml and/or E2 levels  $< 40$  pg/ml**
- **Normal mammogram within one year before randomization**

## Exclusion criteria

- **Prior h/o CVD or VTE**
- **Use of lipid-lowering med**
- **CAC score  $> 50$**
- **LDL  $> 160$  mg/dl**
- **Triglyceride  $> 400$**
- **Uncontrolled hypertension**
- **Smoking  $> 10$  cigarettes/day**
- **Severe obesity (BMI  $> 35$ )**
- **Use of estrogen/SERM in past 6 mos.**
- **Hysterectomy**
- **Endometrial thickening ( $> 5$  mm) at baseline**
- **Chronic systemic illness**
  - **Renal failure**
  - **Hepatic failure**
  - **Dementia**
  - **Diabetes mellitus**

## Baseline Characteristics\*

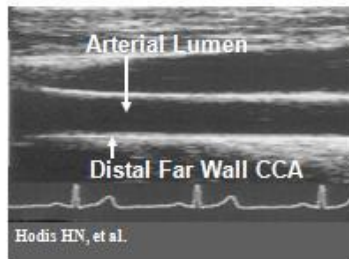
	<u>Mean</u>	<u>SD</u>
<b>Age</b>	<b>52.7</b>	<b>2.6</b>
<b>Yrs since menopause</b>	<b>1.43</b>	<b>0.7</b>
<b>BMI (kg/m<sup>2</sup>)</b>	<b>26.2</b>	<b>4.3</b>
<b>Systolic BP (mm Hg)</b>	<b>119</b>	<b>15</b>
<b>Diastolic BP (mm Hg)</b>	<b>75.0</b>	<b>9.2</b>
<b>Total cholesterol (mg/dl)</b>	<b>208</b>	<b>34</b>
<b>LDL cholesterol (mg/dl)</b>	<b>111</b>	<b>28</b>
<b>HDL cholesterol (mg/dl)<sup>†</sup></b>	<b>72.0</b>	<b>15 (p &lt;0.05)</b>

\* Unless otherwise noted, there were no differences between treatment groups at baseline.

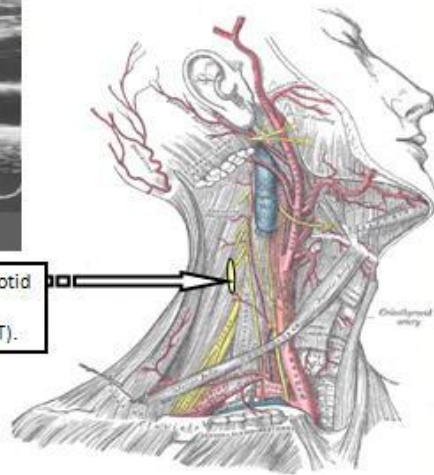
<sup>†</sup> p=0.0497

# Effects of Low Dose Oral vs. Transdermal E on Carotid Intima Thickness in Early Menopause ... KEEPS Trial

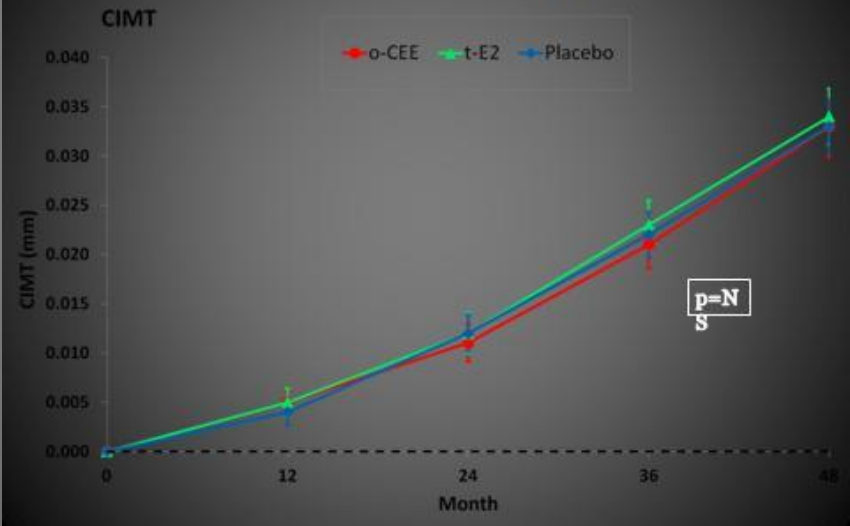
## Ultrasound Measurement of CIMT



Thickness of the common carotid artery intima-media layers measured by ultrasound (CIMT).



## Changes in Imaging Endpoints, CIMT - KEEPS Trial

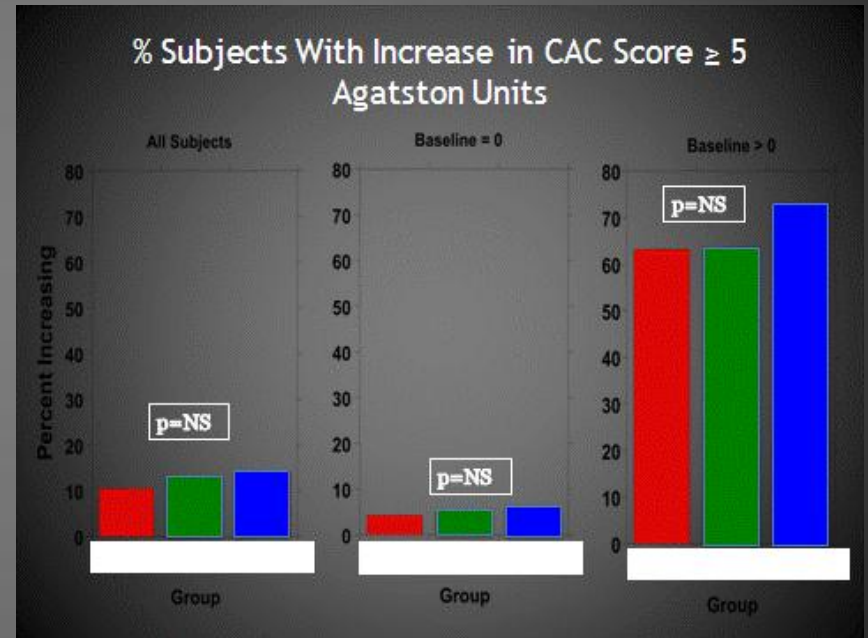
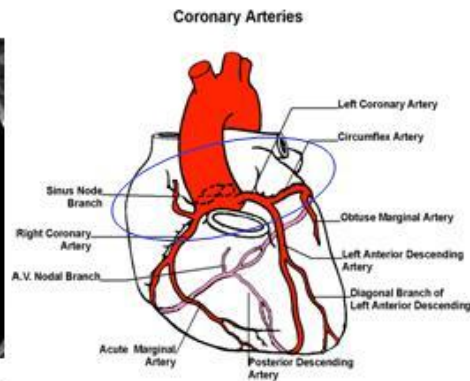


# Effects of Low Dose Oral vs. Transdermal E on Coronary Artery Calcification (CAC) in Early Menopause ...KEEPS Trial

## Coronary Artery Calcium (CAC) by CAT Scan

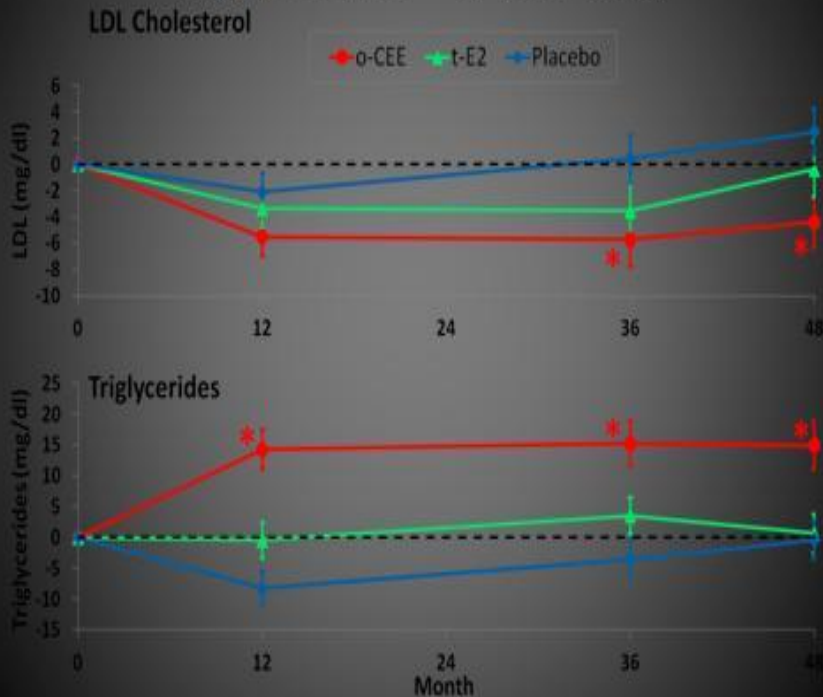


Linear calcification in the left coronary artery in a KEEPS participant, Mayo Clinic

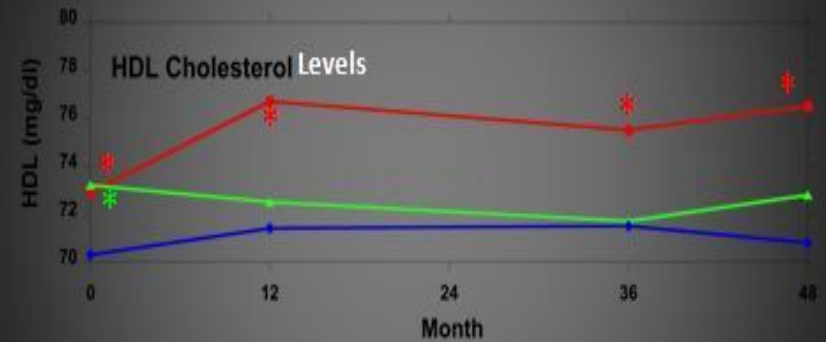


# Effects of Low Dose Oral vs. Transdermal E on CVD Risk in Early Menopause ...KEEPS Trial

## Changes in CVD Risks... LDL & Triglycerides-- KEEPS Trial



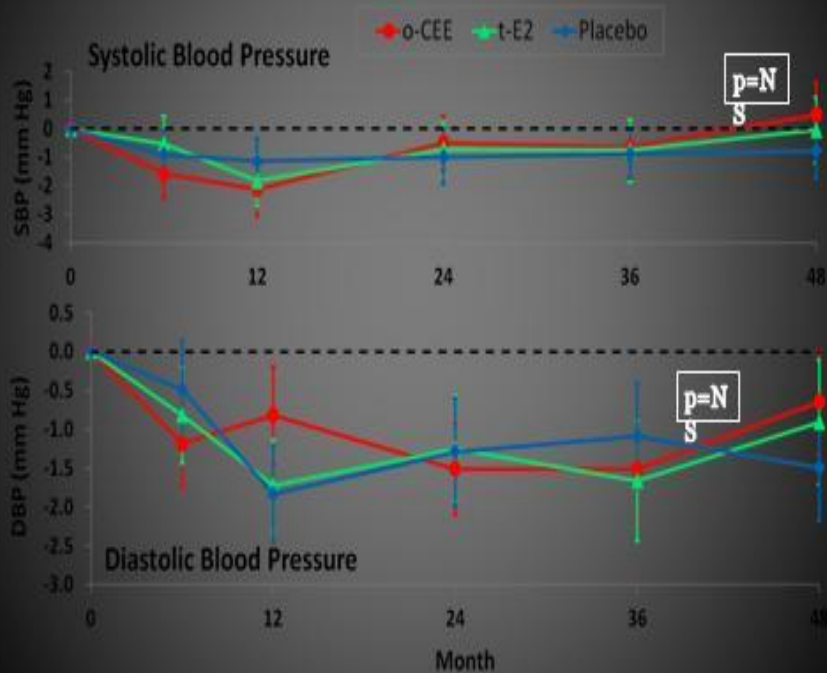
## Changes in Risk Factors, HDL Cholesterol



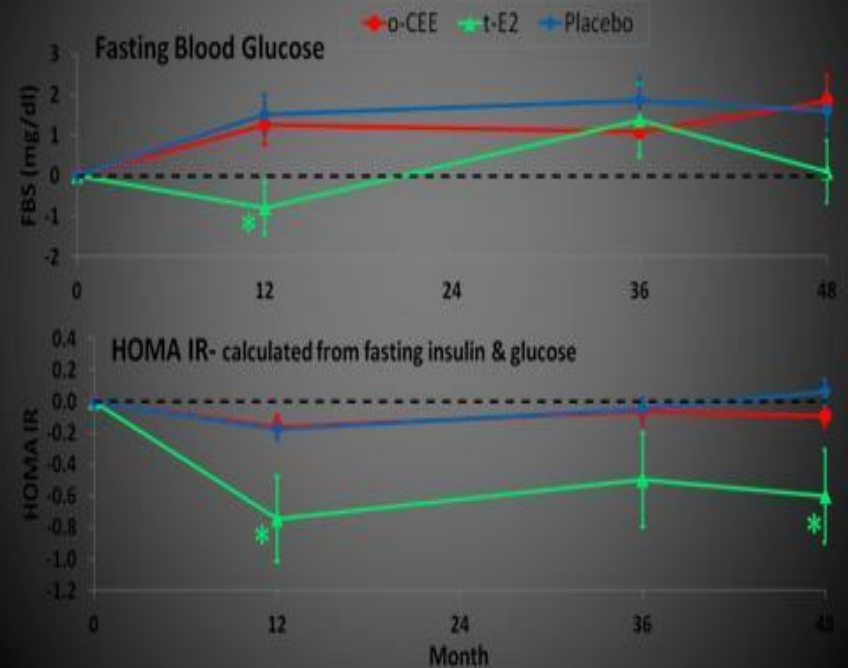


# Effects of Low Dose Oral vs. Transdermal E on CVD Risk in Early Menopause ...KEEPS Trial

## Blood Pressure Changes - KEEPS Trial



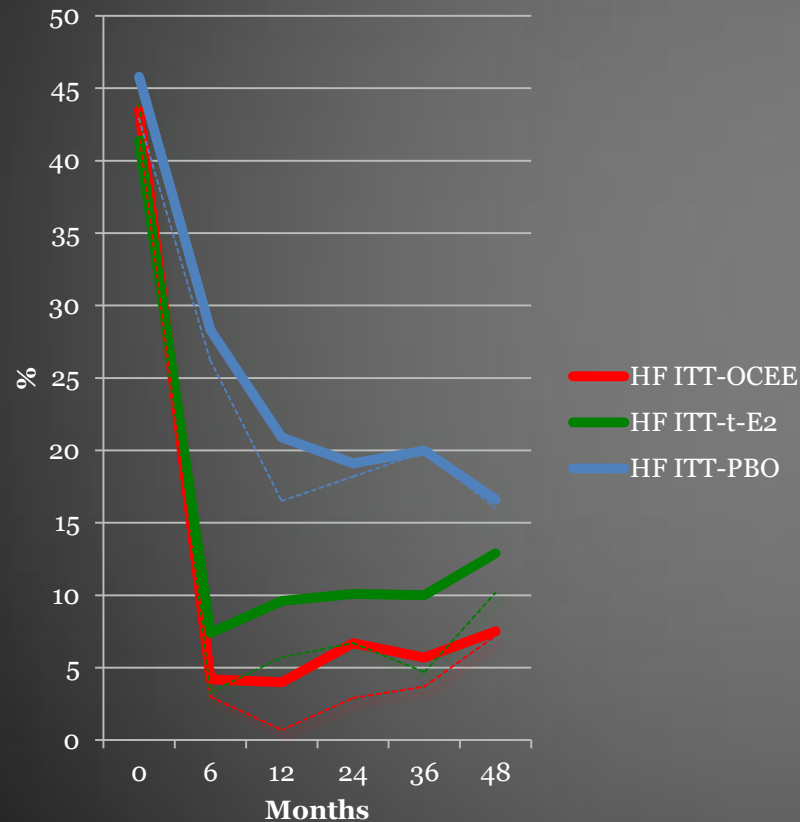
## Changes in Fasting Blood Sugar & Insulin Resistance - KEEPS Trial



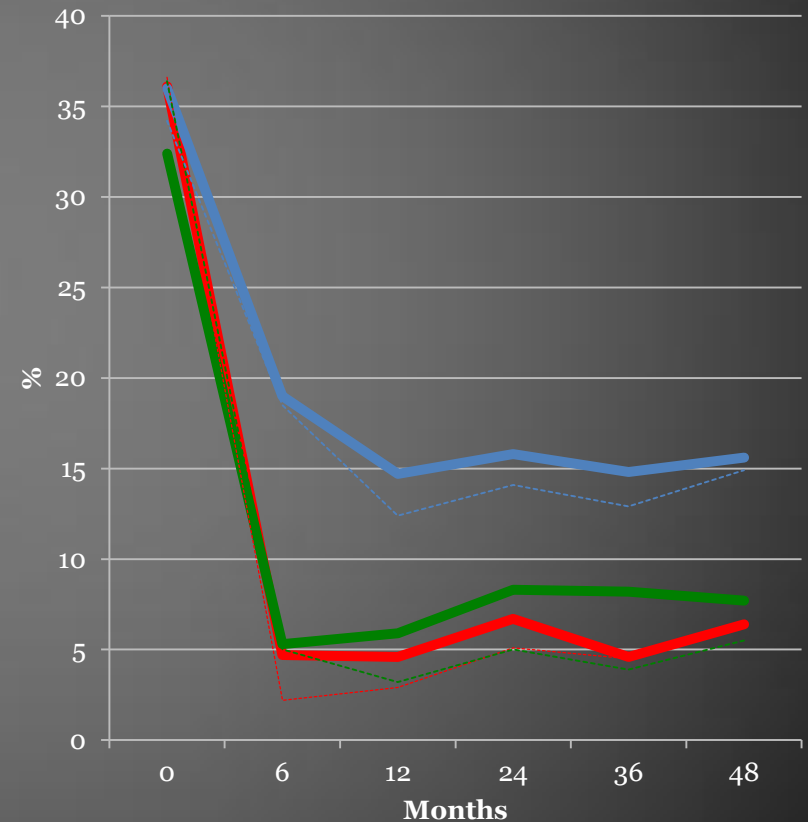
# Placing HT Related Risks in Perspective

# Effects of Low Dose Oral vs. Transdermal E in Early Menopause ...KEEPS Trial

## Hot Flashes



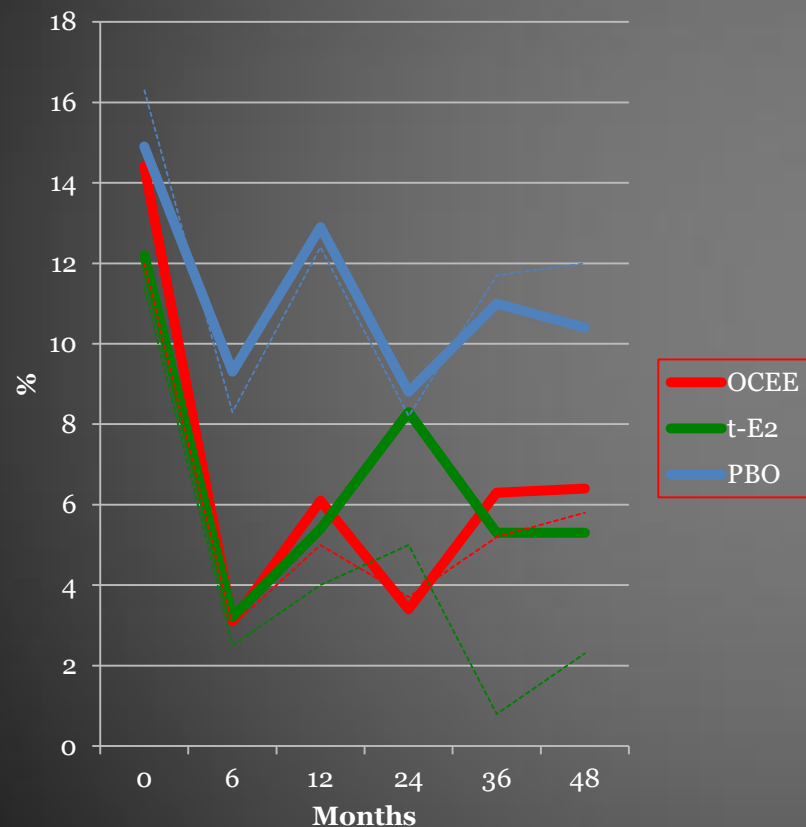
## Night Sweats



727 postmenopausal women within 3 years of final menses, mean age

# Effects of Low Dose Oral vs. Transdermal E in Early Menopause ...KEEPS Trial

## Dyspareunia

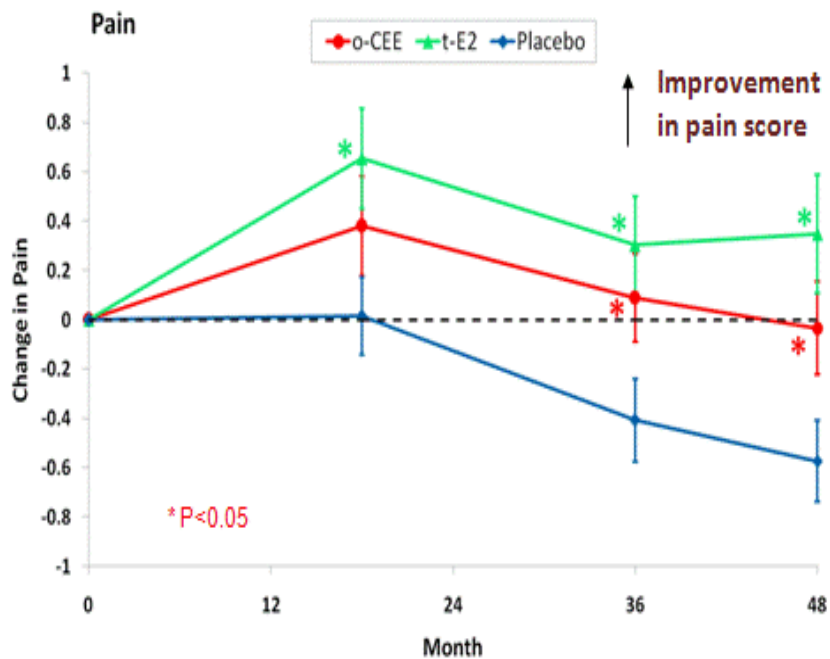


## Vaginal Dryness

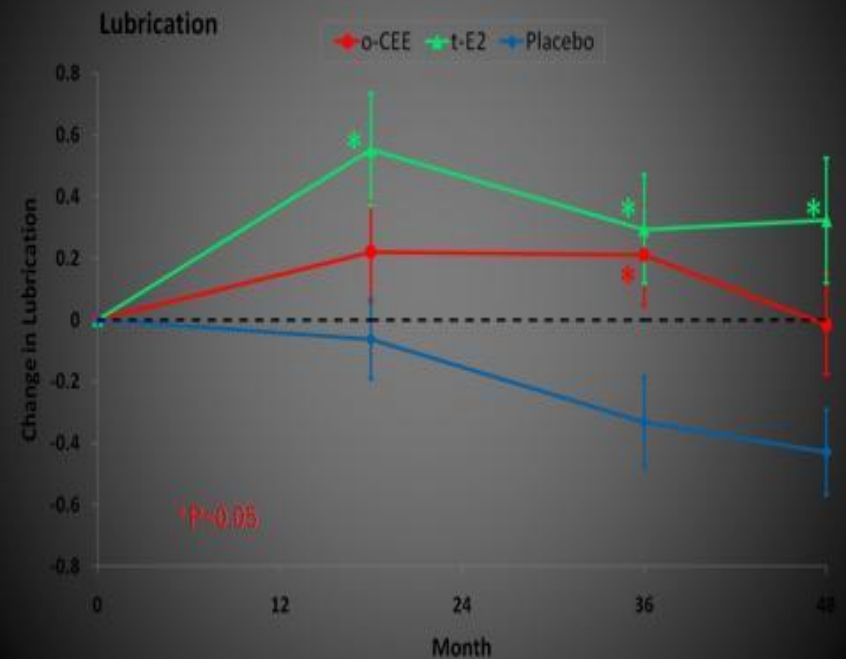


# Effects of Low Dose Oral vs. Transdermal E in Early Menopause Symptoms ...KEEPS Trial

## Female Sexual Function Index, Pain



## Female Sexual Function Index, Lubrication



# MHT & Breast Cancer Risk

## MHT & Breast Ca Risk



OR (95% CI)

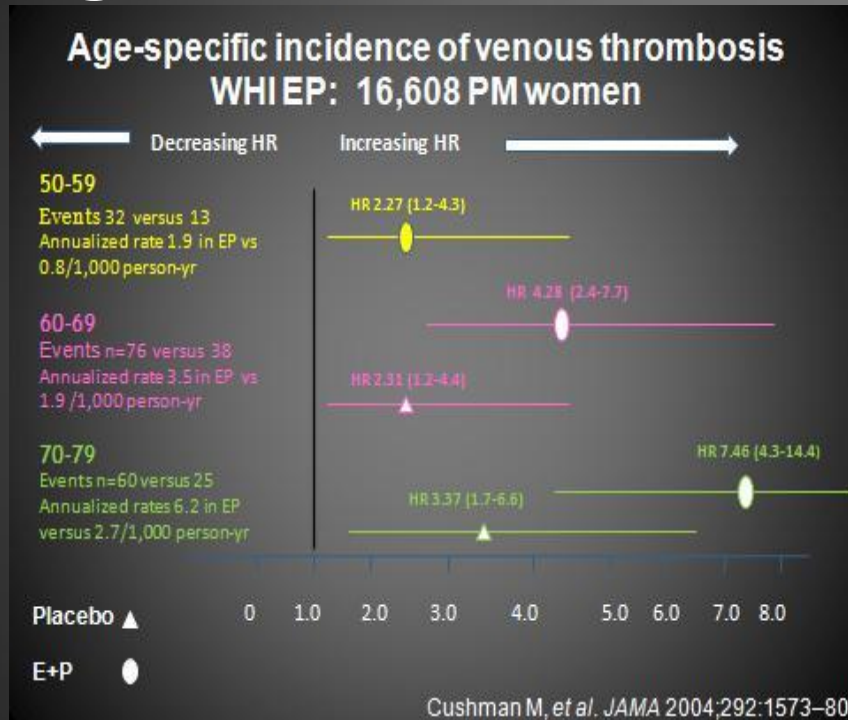
Adapted from Hulley, *JAMA* 1998, Chlebowski, *JAMA* 2002, *JAMA* 2003, Stefanick, *JAMA* 2006

### Current Understanding:

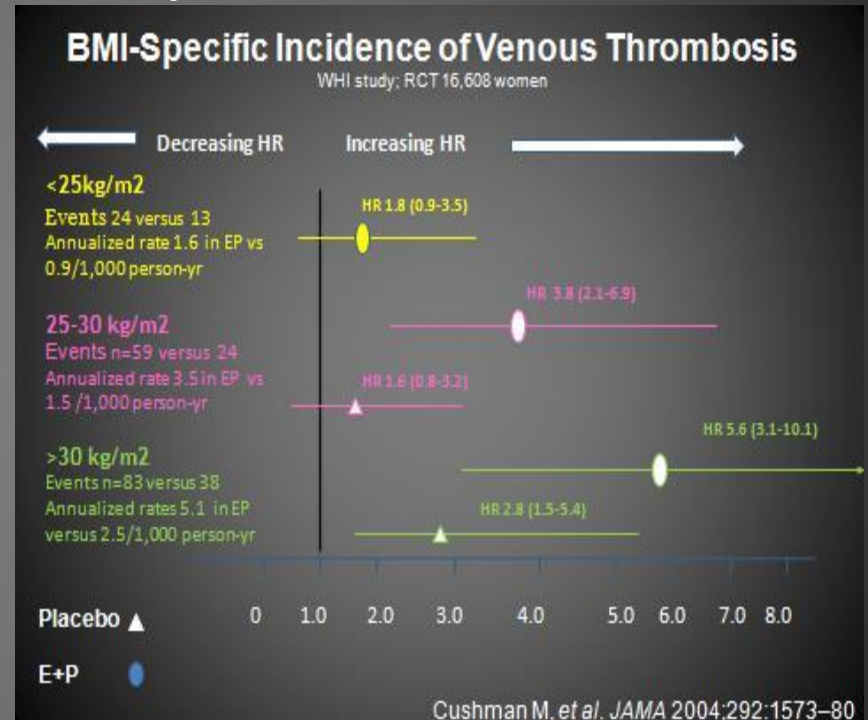
- Estrogen alone Rx in hysterectomized population is deemed relatively safe for breast tissue
- Type of progesterone (natural progesterone preferred over synthetic) and regimen (cyclic preferred over continuous) merit consideration.

# MHT & VTE Risk

## Age



## Body Mass



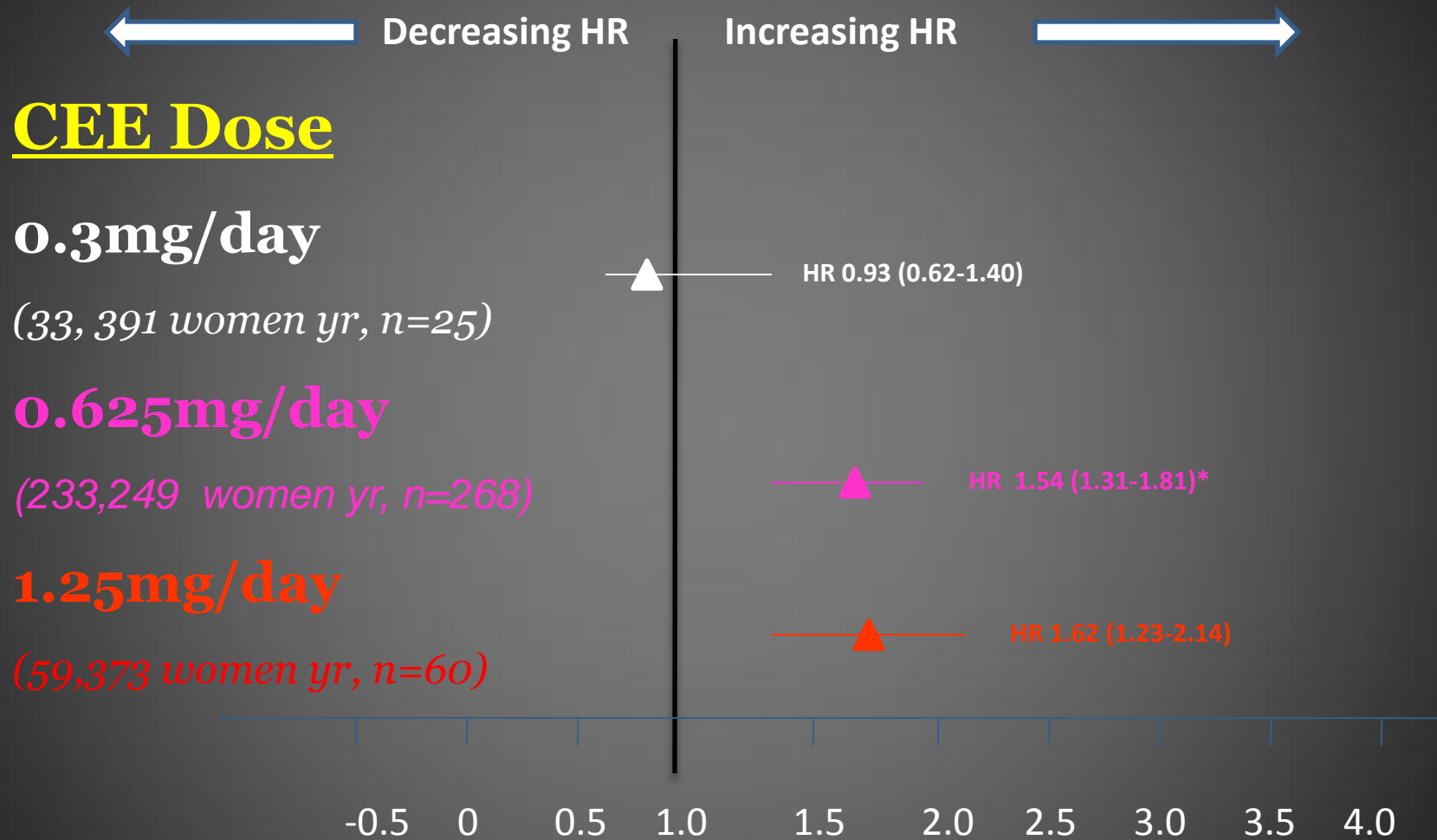
## Current Understanding:

- Advancing age, obesity and individualized profile should be considered when assessing risks for TE in patient being considered for HT



# Stroke Risk & HT in Nurses Health Study (1980-2004)

## Risk for current versus never users by dose of CE



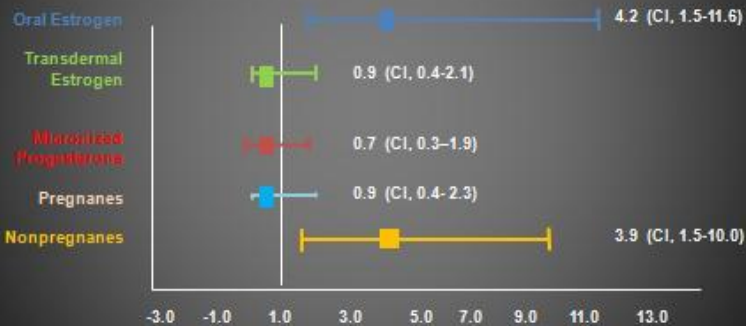


# VTE Risk: *Drug & Route*

## Route of HT & Progestin

## Oral vs. Transdermal E

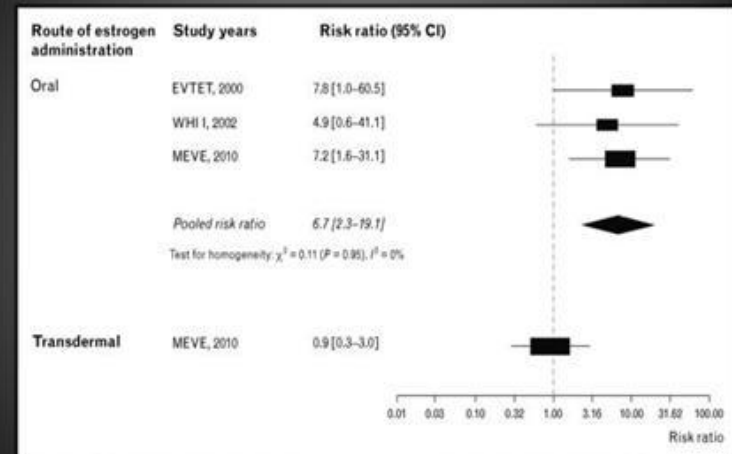
VTE & Relationship to Route of HT & Type of Progestin  
ESTHER Study



Case-control study (271 cases and 610 controls, postmenopausal women 45-70 yrs)

Canonico M, et al. *Circulation* 2007; 115:820-2

Risk of Venous Thrombosis with Oral versus Transdermal Estrogen Therapy among Postmenopausal Women.



Olie V et al. *Current Opinion in Hematology* 2010; 17(5):457-463.

## Current Understanding:

- Choice of progestin (progesterone preferred to synthetic progestins) and both dose & route of E (low dose transdermal preferred over oral route) can confer risk reduction against TE.

# The *art* of medicine must not be a victim to our overzealous pursuit of *evidence based* approach











Therapeutic benefits of HT far exceed purported risks for a substantial proportion of the most symptomatic population, i.e. early menopausal women

It is my/our responsibility to ensure that I/we minimize risks while helping alleviate symptom/s.

# MHT Decision Should Be Based upon Individualized Assessment

**THERE IS NO ROLE OF  
HORMONE THERAPY FOR  
CARDIAC PROTECTION  
OR  
COGNITIVE BENEFIT**

# Future of MHT

Target	E+P	SERM
Breast		
Uterus		
Hot Flush		
Vagina		
Bone		

# Take Home Points

- Management strategies **MUST** be individualized to:
  - address nature and severity of symptoms
  - while maintaining individualized risk/s in perspective
- For early menopausal women, MHT is the **MOST** efficacious of available strategies.
- Non-hormonal therapies **SHOULD** be 1<sup>st</sup> line Rx for symptomatic women who are deemed “at risk” for MHT related adverse effects.
- Estrogen dose reduction, TD administration, choice of progestin & regimen **CAN** offer risk reduction.