APPROACH TO THE MENOPAUSAL PATIENT & CURRENT MANAGEMENT of Menopausal Symptoms

MOA AUTUMN CONFERENCE

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DISCLOSURES

- NOTHING TO DISCLOSE RELATIVE TO THIS PRESENTATION
- NO STOCK IN PHARM

LEARNING OBJECTIVES

- Understand the **impact and duration** of menopausal symptoms on women, as well as morbidities associated with post-menopause
- Understand **treatment options** for Management of Menopausal Symptoms
- Understand the "**timing hypothesis**" relative to the timing of initiation of hormone therapy, and potential cardiac risks or benefits
- Understand the **risks and benefits** of various treatment options and individualization of therapy based on a women's risk-benefit ratio

Goals

- **Discuss/Understand** role of HRT (HT, ET)
  - For whom, how long
  - Systemic? Oral vs Transdermal
  - Which Progestin?
  - Bioidentical?
- **Discuss** risks and benefits: *relative to menopause & treatment*
  - Heart
  - Breast
  - Bone
  - Genito-Urinary
- **Discuss** "critical window" hypothesis
- **Discuss** how do you help the patient decide? (SHARED DECISION MAKING)
- **Discuss**:How do you educate your patient beyond the media-hype?
- **Become familiar** with **MenoPro** (NAMS) app

GOALS

Educate Clinicians & Eliminate Fear

- Since early 2000s , the Practice and Art of HT for post menopausal care has been abandoned or minimized.
- We as leaders in women's health need to;
  - understand the **evidence**,
  - **individualize** therapy, and
  - understand possible **treatment options**, and
  - provide our female patients with **tools** to assist in understanding.

meno pro app (FREE)

- North American Menopause Society (NAMS)
- **To help clinician & patient work together to personalize treatment decisions on the basis of a your personal preferences (hormone vs nonhormone options), taking into account patient medical history and risk factor status**
- Facilitates shared decision making
- The ***MenoPro* app**
  - Calculate patient **10-year risk of heart disease** and **stroke**
  - **Has links** to online tools that assess your risk of **breast cancer** and **osteoporosis/ fracture**.
  - AIDS IN DECISION FOR HT OR ALTERNATIVES

Meno Pro app

*MenoPro was developed in collaboration with **NAMS** and includes links to NAMS education materials, including a downloadable MenoNote on behavioral and lifestyle modifications to reduce hot flashes, and information pages on*

- *the pros and cons of hormone versus nonhormone therapy options,*
- *a discussion of pill versus patch therapy, and*
- *information on treatment options for vaginal dryness and pain with sexual activities,*

--with links to tables with information about different medications. These pages can be printed out or directly accessed from your phone or tablet.

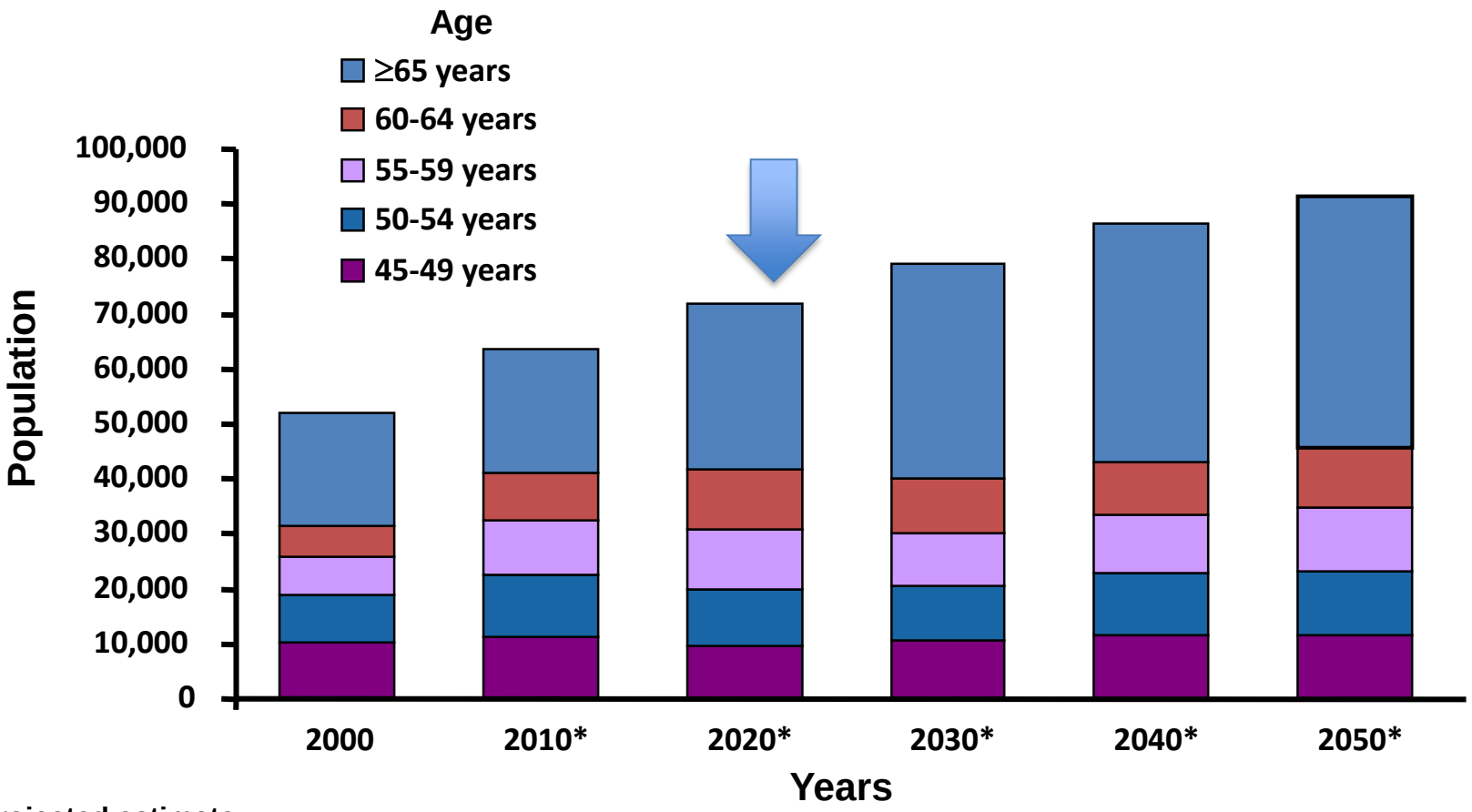
- **Helps make informed choices about managing menopause symptoms.**
- ***MenoPro* contains no advertising and was developed without any industry or pharmaceutical company support.**

meno pro


one for clinicians and one for women/patients, to support shared decision making.
Are you a Health Care Provider or Woman/Patient?
Health Care Provider
Woman/ Patient


Paper about the App/Algorithm
Breast Cancer Risk Score
FRAX Score
2017 NAMS Position Stateme…
Clinical Guidelines
Feedback

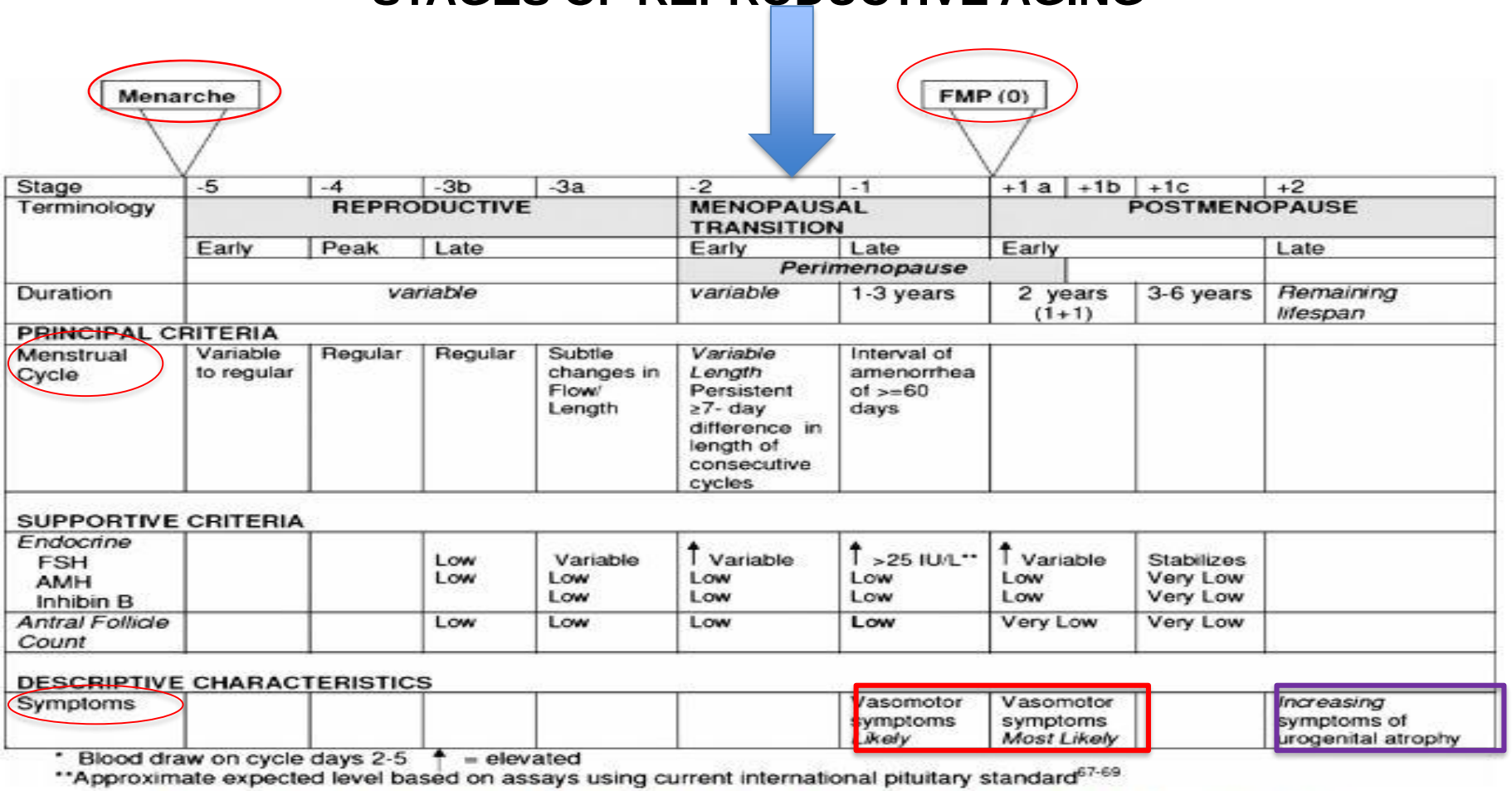
Number of Postmenopausal Women in the United States Is Continually Increasing



*Projected estimate.
US Census Bureau. *Statistical Abstract of the United States*. 2000:15.
US Census Bureau. National population projections. Available at: http://www.census.gov/population/www/projections/natsum-T3.html. Accessed January 3, 2002.

[Data from US Census Bureau]

STAGES OF REPRODUCTIVE AGING



Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable	↑ Variable	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B				Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated

**Approximate expected level based on assays using current international pituitary standard[67-69]

FIG. 2. The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.

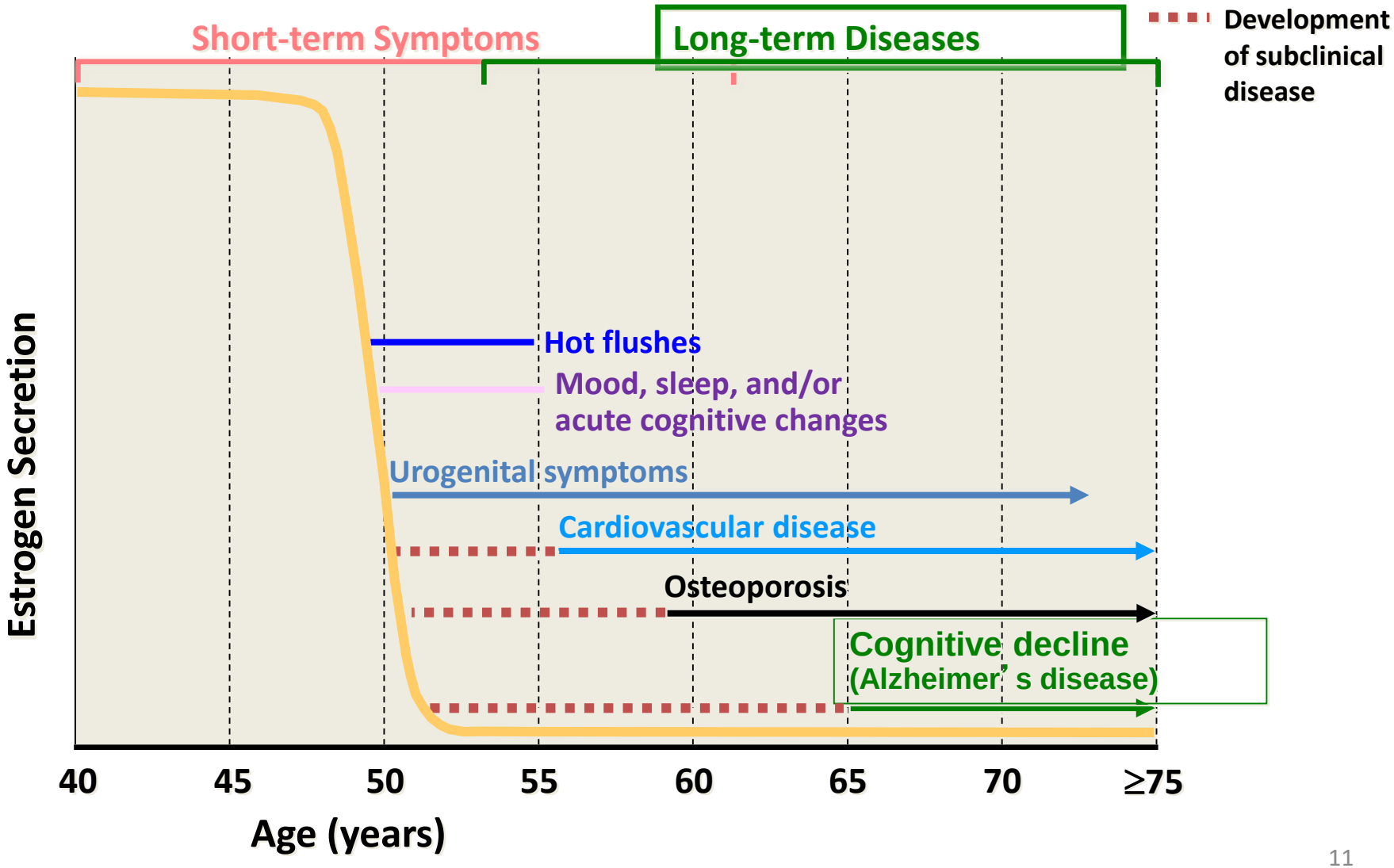
4 *Menopause, Vol. 19, No. 4, 2012*

WWW.MENOPAUSE.ORG

STAGES:

REPRODUCTIVE PERIOD → MENOPAUSAL TRANSITION (PERIMENOPAUSE) → MENOPAUSE/POSTMENOPAUSE

Estrogen Loss and Manifestations of Health Risks Over Time



Patient: 'HF'

52 year old Caucasian female, G4 P 3013, presents with c/o Hot Flashes and Night Sweats, with increasing severity over past 6 months.

FDLMP : 9 months ago. Increased spacing between periods over past 2-3 years.

Medical History:

- Tobacco, 25 pack year history. Quit: 1 year ago
- Etoh: 4-6 glasses wine /week
- Hyperlipidemia (controlled with Statin)

PMH: no major problems PSH: NONE

Vitals: BMI : 30 BP: 134/88.

Exam: normal

Case 'HF': Management Options?

- Where is she in the stages of reproductive aging?
- What therapy would you offer her?
- What are options of management?
- How would you counsel her?
- Does she have any contraindications to HT ?
- Is she a candidate for HT?
- What if there is a family history of breast carcinoma?

FACTORS TO CONSIDER

SYMPTOMS & SIGNS OF MENOPAUSE

Menstrual Cycle Alterations

- ***Beginning at approx age 40*** a woman may notice shortening or lengthening of her cycles
- The luteal phase remains constant (13-14 days) whereas the follicular phase changes
- *Frequency of ovulation decreases* from 13-14 times per year to 11-12 times per year
  - With advancing reproductive age, ovulation frequency may decrease to 3-4 times/year
- ***average age menopause = 51.7 years***
- ***duration of symptoms? 7-10 years +***

Menopause Review

- Average age of menopause: 50-52
- Age Range : 45-56
- Earlier onset with:
  - Smoking, lower SE status, malnutrition, maternal hx of early menopause
- Duration: 10 years +/- average

SYMPTOMS & SIGNS OF MENOPAUSE
Hot flushes and Vasomotor Instability

- ***Hot flushes*** are the 1st physical manifestation of decreasing ovarian function and estrogen production. It is a symptom of **vasomotor instability**
  - Hallmark sign of perimenopause
- **Hot flushes** = recurrent, transient episodes of flushing, perspiration, and a sensation ranging from warmth to intense heat on the upper body and face, sometimes followed by chills
  - **Night sweats** = when they occur during sleep and are associated with perspiration
  - Typically last less than 3 minutes
  - Resolve with **hormone therapy (HT)** in 3-6 weeks

SYMPTOMS & SIGNS OF MENOPAUSE

Sleep Disturbances

- **Latent phase of sleep** (time required to fall asleep) is lengthened and the actual period of sleep is shortened
- One of the most common and disabling effects of menopause

SYMPTOMS & SIGNS OF MENOPAUSE

Mood Changes

- Depression
- Apathy
- Crying spells
- These symptoms may be related to menopause, **sleep disturbances**, or both

HORMONE THERAPY--TIMELINE:

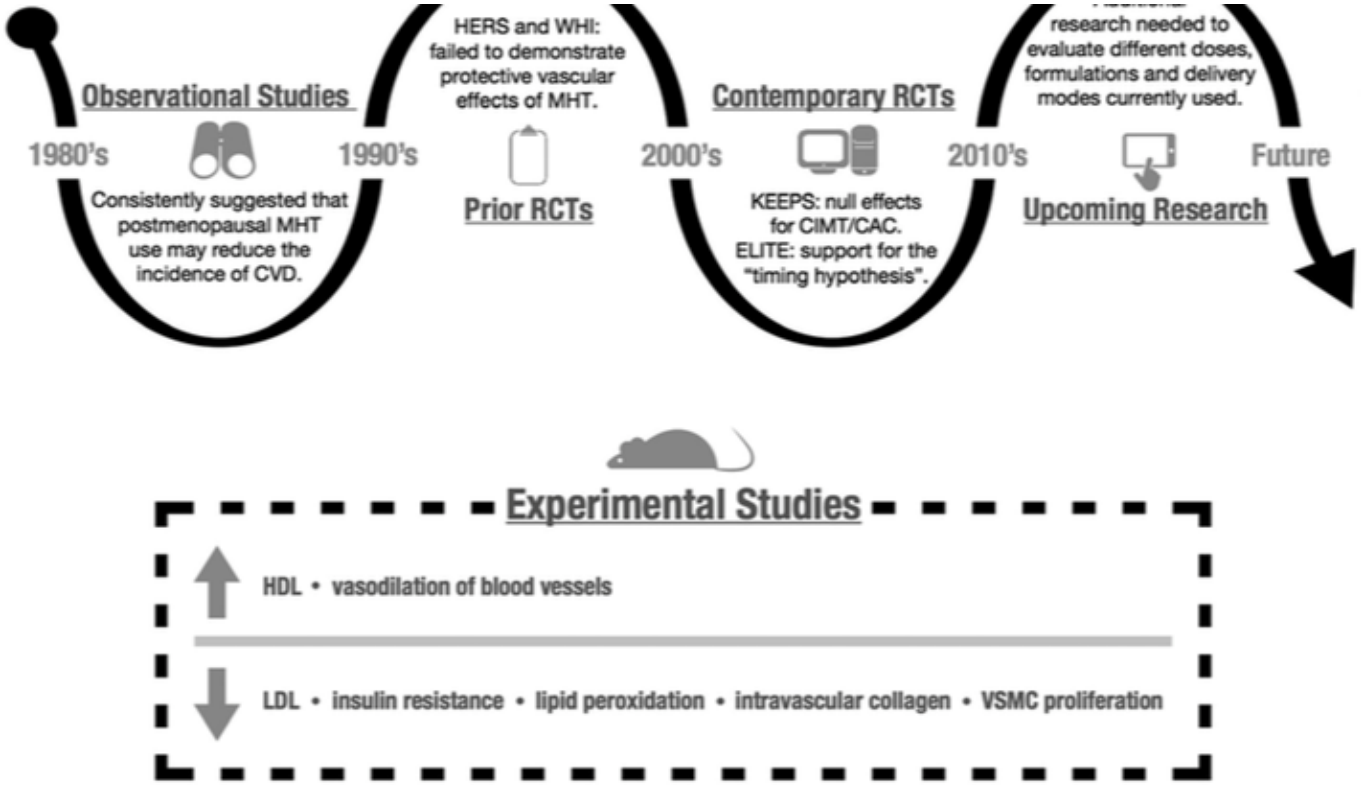


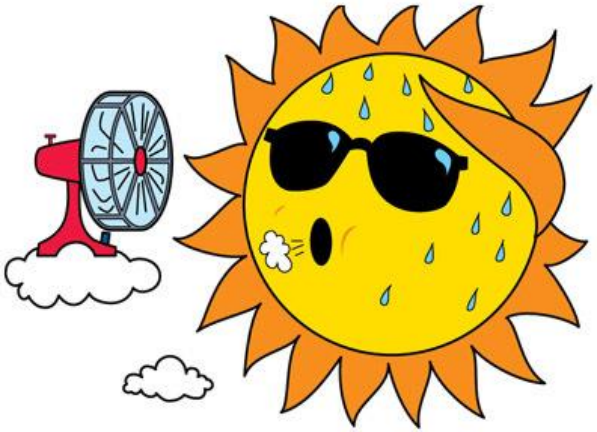
Figure 3. Menopausal hormone therapy timeline. Experimental studies have consistently demonstrated beneficial physiological effects of estrogen on the vascular endothelium at the cellular and molecular level. This long-standing observation led to a hypothesis that estrogens were cardioprotective, which was initially supported by retrospective and prospective observational studies, followed by disappointment from Heart Estrogen/Progestin Replacement Study (HERS), Women's Health Initiative (WHI), and other randomized clinical trials (RCTs) that failed to demonstrate reduced risks of clinical cardiovascular disease (CVD) events with menopausal hormone

Hormone Therapy---2000

Prevailing View:

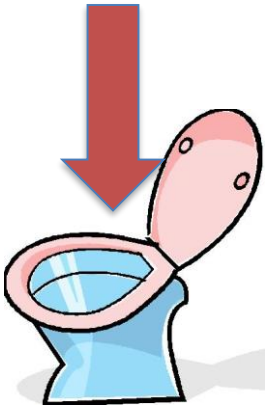
- HT was a low-risk intervention
- Immediate value for symptom relief
- Probably conferred long term protection against the major chronic diseases post menopausal

What happened on a HOT SUMMER night in 2002??



WHI E-P ARM:
discontinued due to reported risks and released to media before published or notification to physicians

CEE/MPA RX



WHI

- WHAT DID WHI TELL US?
- EPT
- ET
- **Quick review of WHI**
- **Important to understand & demystify findings**
- **Much Consternation over how decision was made to stop and release information**

Review: The evidence base for HRT: what can we believe. R.D Langer, Climacteric, 2017. vol 20, #2, 91-96

Hormone therapy: Women's Health Initiative

- Large RCT to determine if hormones prevent **heart disease**, **breast** and colorectal **cancer**, and osteoporotic fractures in postmenopausal women
- Enrolled women ages **50-79** **(average age 63)**
- One arm of trial (11,000 women)—continuous, combined E-P vs placebo
- Other arm (16,000 women)—estrogen only
- Was scheduled to be completed in 2005, but both arms terminated early
- **Prescriptions for HT decreased by approx. 38% in the first year post-WHI**

TABLE 1. WHI E+P and WHI-E and selected health events Initial data, non abjudicated

Health Event	Absolute Risk per 10,000 Women/Year		Absolute Benefit per 10,000 Women/Year	
90% > age 60	WHI E+P	WHI-E	WHI E+P	WHI-E
Breast cancer	8	—	—	7
Colorectal cancer	—	1	7	—
Coronary heart disease	6	—	—	5
Hip fracture	—	—	5	6
New-onset diabetes	—	—	15	14
Pulmonary embolism	—	3	NS	NS
Stroke	7	12	—	—
Total fractures	—	—	47	56
Venous thromboembolism	18	7	—	—

NS= not significant. Cauley JA, et al. *JAMA.* 2003;290:1729-1738; Chlebowski RT, et al. *N Engl J Med.* 2004;350:991-1004; Chlebowski RT, et al. *JAMA.* 2003;289:3243-3253; Manson JE, et al. *N Engl J Med.* 2003;349:523-534; Wassertheil-Smoller S, et al. *JAMA.* 2003; 289:2673-2684; Margolis KL, et al. *Diabetologia.* 2004;47:1176-1187; Writing Group for the Women's Health Initiative Investigators. *JAMA.* 2002;288:321-333; Women's Health Initiative Steering Committee. *JAMA.* 2004;291:1701-1712.

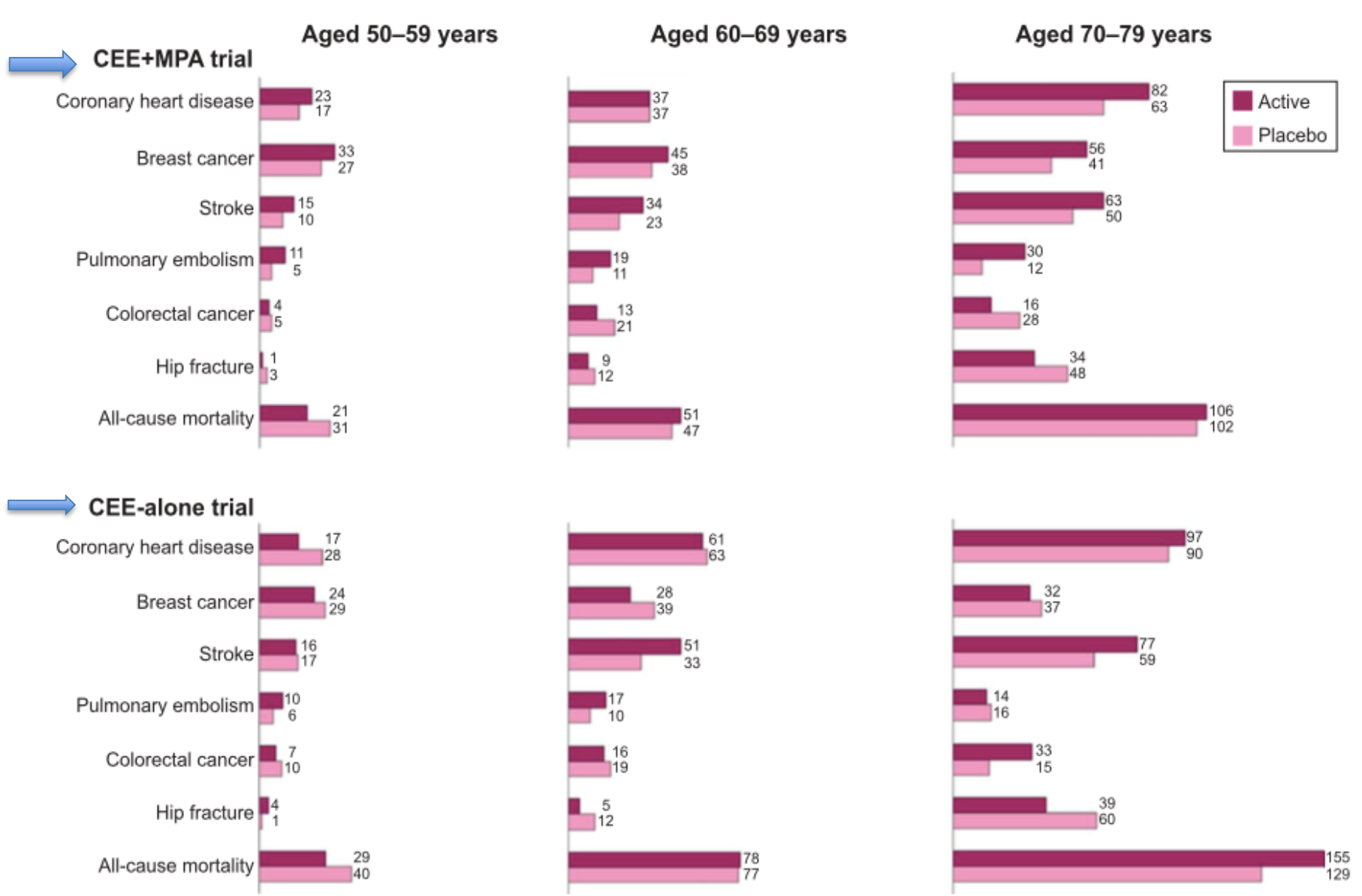


Fig. 1. Women's Health Initiative hormone therapy trials: absolute risks (cases per 10,000 person-years) for outcomes in the intervention phases of the estrogen–progestin and estrogen-alone trials by age group. CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate. Modified from Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310:1353–68.

Kaunitz and Manson. Management of Menopausal Symptoms. Obstet Gynecol 2015.

WHI: Limitations and Criticisms

- Older population (**mean age 63**)
- Heavier women (**BMI>30**)
- 50% pts were current or past **smokers-tobacco**
- Only one route of administration
- Only one formulation of estrogen and progestogen (***HIGHER DOSE*—*CEE,.625MG &MPA, 2.5MG***)
- Should **NOT** be extrapolated to pts with premature ovarian failure OR premenopausal oophorectomy
- **High crossover** (from intention to treat), & **dropout** rates

WHI: Limitations and Criticisms

- **Conclusions---** were **not stratified** by age/decade or time since menopause
- ***Reanalysis of data*** suggests that HT/ET in younger postmenopausal women may not be as detrimental, and in fact, benefits > risks
- Many experts called for studies to evaluate hormone therapy in **newly menopausal women**
- Large observational studies (such as ***Nurses' Health Study***) did not corroborate some of WHI findings

REEVALUATING WHI
Where do we stand in 2018?

- In **2012**, NAMS, ASRM, Endocrine Society prepared a statement summarizing WHI and expert recommendations :
- *"Systemic hormone therapy is an acceptable option for relatively young and healthy women who are bothered by moderate to severe menopausal symptoms."*
- ***Women up to age 59 or within 10 years of menopause (greatest benefit, minimal risk)***
- Consider her **quality-of-life priorities** and **risk factors**: age, time since menopause, risk of VTE, stroke, and breast cancer
- **Counsel and Individualize treatment**

REEVALUATING WHI
Where do we stand in 2018?

- **Estrogen plus progestogen** (progestin or progesterone) therapy in women with a uterus to prevent endometrial hyperplasia/cancer
- **Local estrogen therapy** for women with vaginal dryness, discomfort with intercourse
- *Lowest dose of hormone for the shortest amount of time to manage menopausal symptoms*
- Risk of VTE is increased with E+P or E alone, but the risk is rare in women ages 50-59
  - ***may be* less in transdermal vs oral**
- **Risk of breast cancer** increased with 5 years or more with continuous E+P (not with E alone in WHI)

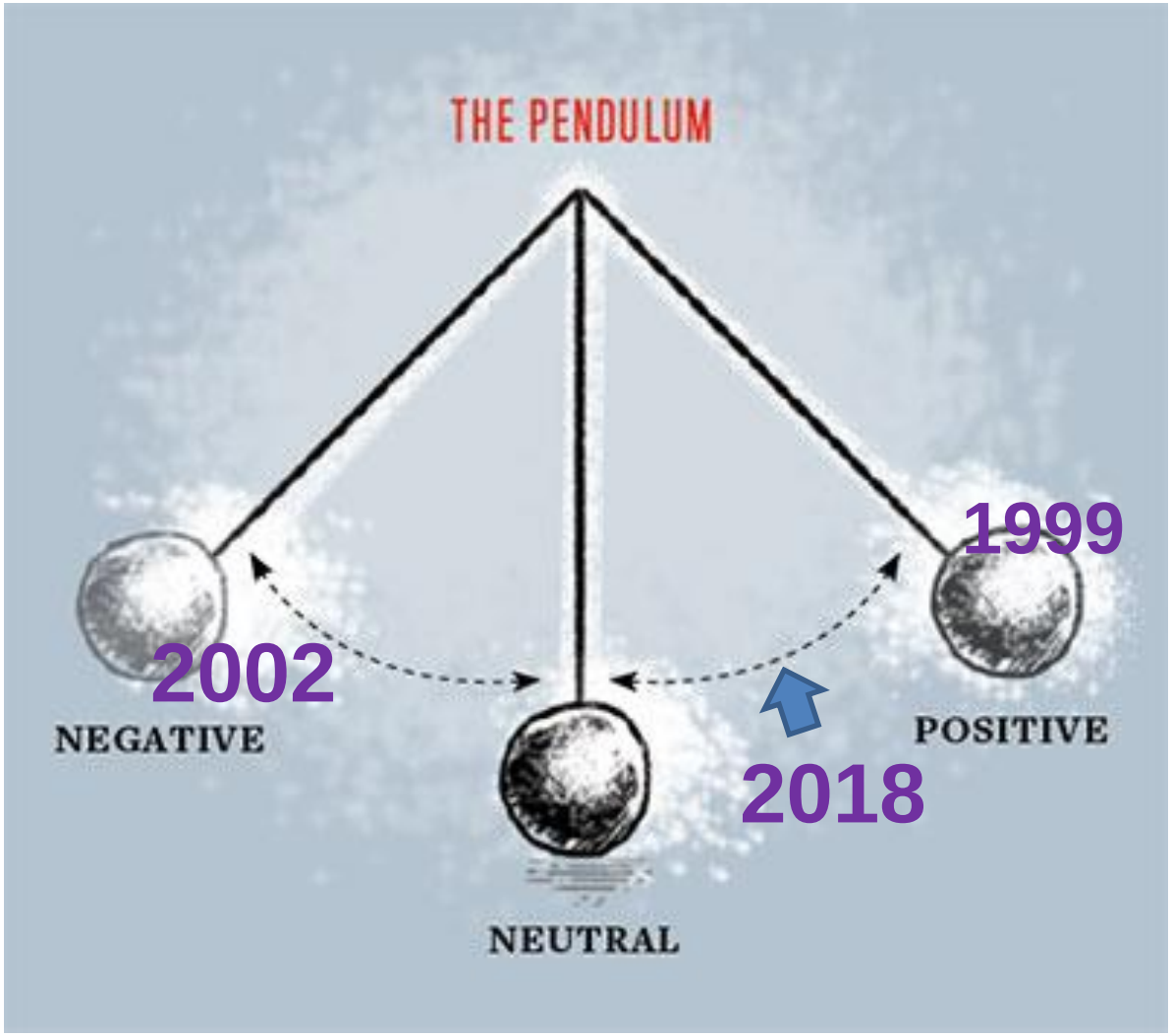
What are the FDA indications for HT?

?

Management of Menopause

- **FDA Approved indications for HT**
  - Vasomotor menopausal symptoms
  - Prevention & tx of osteopenia/osteoporosis
    - Proven reduction in fractures
  - Vulvar-vaginal atrophy

HORMONE THERAPY IN 2018



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GOLD STANDARD FOR HOT FLASHES

ESTROGEN

- REVIEW CURRENT EVIDENCE
- ALTERNATIVES ??
- COMPARE EFFICACY
- CONTROVERSIES??

Therapeutic Goals

- Maintain **quality** of life
- Treat the most **bothersome symptoms** for the patient
- **Individualize therapy** based on patient's medical history, risk factors and desire for type of treatment

HOW DOES THIS DIFFER FROM 1995?, 2003?

Hormone Therapy

WHAT ARE THE **BENEFITS**??

WHAT ARE THE **RISKS**??

WHAT ARE THE ***QUALITY OF LIFE*** ISSUES???

Hormone Therapy

- **3 Major Benefits**:
  - Relieve vasomotor symptoms
  - Alleviate vulvar/vaginal atrophy
    - May have an effect on sexual function
  - Reduction in postmenopausal osteoporotic fractures

Potential Risks

We will discuss

- Coronary heart disease (???)---risk, benefit ,or neutral?
- Breast cancer:(EPT, ET)?
- Stroke
- VTE/Pulmonary embolism
- Endometrial cancer (ET)

Remember our patient: poor Ms 'HF'

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FDLMP : 9 months ago. Increased spacing between periods over past 2-3 years.

Medical History:

- *Tobacco, 25 pack year history. Quit: 1 year ago*
- *Etoh: 4-6 glasses wine /week*
- *Hyperlipidemia (controlled with Statin)*

PMH: no major problems PSH: NONE

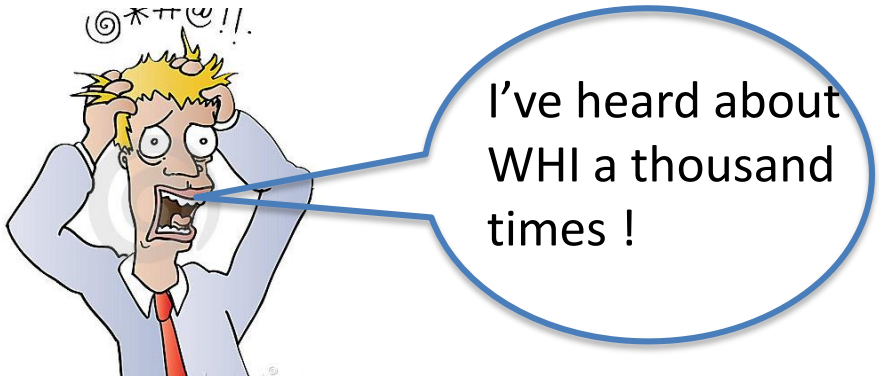
Vitals: BMI : 30 BP: 134/88. Exam: normal

DOES SHE HAVE CONTRAINDICATIONS TO THERAPY??

- ***ABSOLUTE or RELATIVE ??***

“HF” MANAGEMENT OPTIONS

- Where is she in the stages of reproductive aging?
- How would you counsel her?
- Does she have any contraindications to HT ?
- Is she a candidate for HT?
- What if there is a family history of breast carcinoma?



- **What therapy options would you offer her?**
- **Hormonal vs non-hormonal??**
- **What about the WHI?**

Summary of ---- Management OPTIONS

- **LIFESTYLE MODIFICATIONS** *(next SLIDE) –1st step*
- **NONHORMONE** Rx --prescription treatment
  - Clonidine ??
  - SSRI (Paroxetine, 7.5 mg) FDA approved.
  - Other SSRI or SNRI (not FDA approved)
  - Gabapentin
- **HORMONE THERAPY (*FDA Approved*):**
  [Transdermal, Transvaginal, Oral]
  - **HT (estrogen and progesterone/progestin)**
  - **ET: (estrogen only)**
  - **FDA APPROVED BIOIDENTIAL (ESTRADIOL, micronized Progesterone)**
  - **SERM (ESTROGEN AGONIST/ANTAGONIST)**
  - **Bioidentical Hormone Therapy , FDA approved and regulated**
- **COMPOUNDED 'BIOIDENTICAL' HT**
  - (NOT *FDA Approved*)

Nonhormonal Treatment for vasomotor symptoms

- **Mind-Body approaches**
  - Cognitive-behavioral therapy
  - ? Hypnosis
  - Mindfulness-based stress reduction
  - Yoga, exercise, (*DATA DOES NOT SUPPORT)*
- **Weight Loss?**
  - Overweight vs normal weight
- **Soy:** variable
- **Herbal remedies**: (Data DOES NOT SUPPORT)

Contraindications?

- DOES SHE HAVE CONTRAINDICATIONS?

- Absolute
- Relative

WHAT ARE THE CONTRAINDICATIONS TO HT?

Contraindications to Hormone Therapy

- Undiagnosed abnormal genital bleeding
- Known or suspected **estrogen-dependent neoplasia** except in appropriately selected patients
- Active deep vein thrombosis, pulmonary embolism, or a history of these conditions or known thrombophilia
- Active or recent arterial **thromboembolic disease** (stroke, myocardial infarction)
- Liver dysfunction or liver disease
- Known or suspected pregnancy
- Hypersensitivity to hormone therapy preparations

- **RELATIVE CONTRAINDICAITONS/risks:**
  - High Triglycerides (>400 mg/dl) (transdermal may be prefered)
  - Elevated risk of breast cancer (5 yr risk > 5%)--**controversial**

Hormone Therapy

2018

- Safest to use in newly menopausal women up to age 59 and within 10 years of menopause
- Weigh risks/benefits **age 60-69**, (ok to continue if benefits > risks)
  - **Do not need to STOP at age 65** (ACOG)--*individualize*
- *Lowest effective dose for the shortest amount of time???*
  - Low-dose and ultra-low systemic doses of estrogen assoc with better adverse effect profile
- Counsel regarding all options
- Weigh overall risks and benefits

WHI-----*unintended* effects of

- In 16 years since publication of WHI, use of **HT has decreased markedly worldwide**, and prevalence of use has remained low.
- WHI has resulted in millions of women receiving no treatment and consequently experiencing reduced quality of life
- WHI results inappropriately led to d/c HT **in all age groups** (re: younger women etc)
  - **WHI Acting Director: "the adverse effects of E & P applied to all women, irrespective of age, ethnicity, or prior disease status"**

PERCEPTIONS

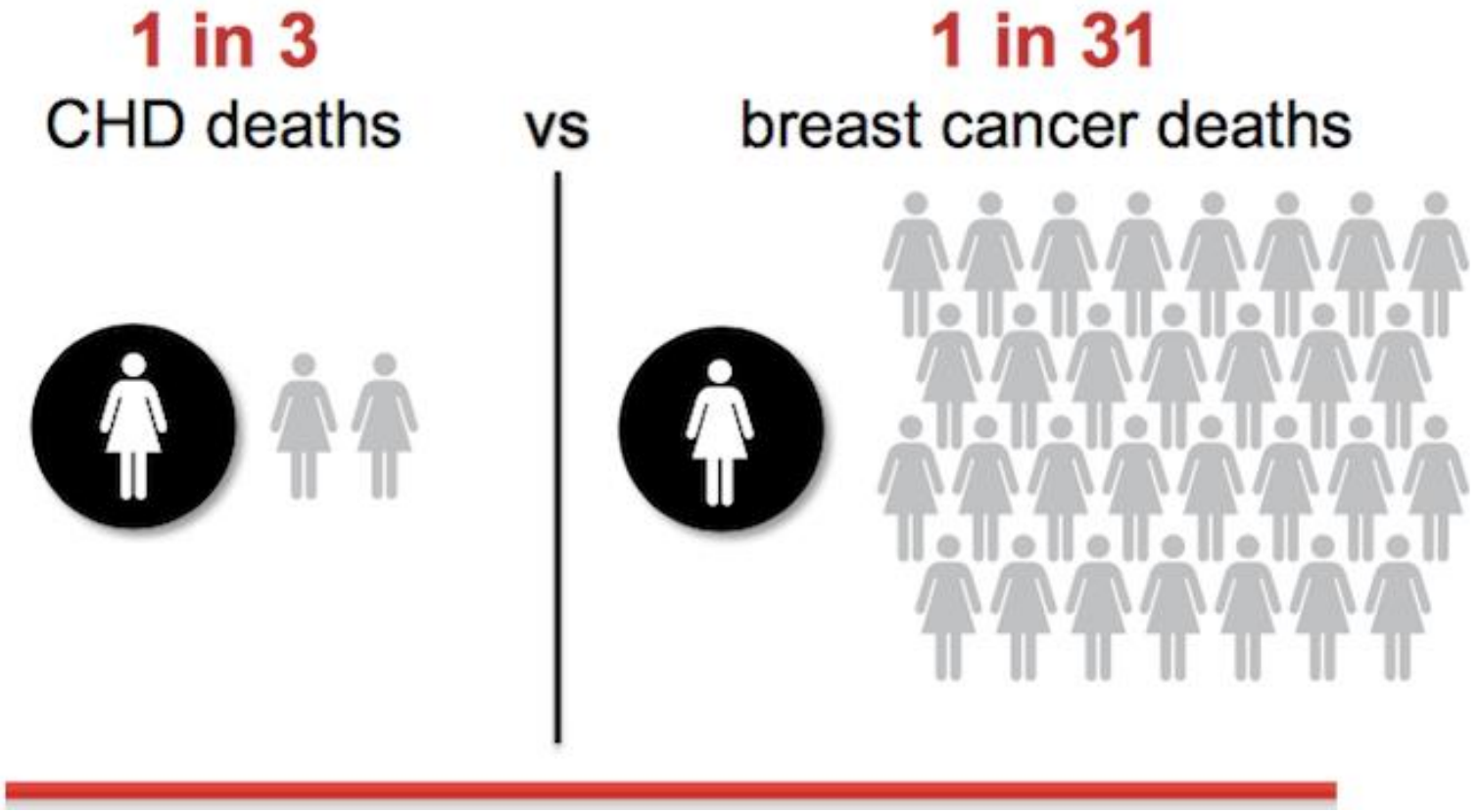
- What do many women believe is #1 cause of death after Menopause?
- What is the greatest cause of death in this group?
- What is the greatest risk of HT?

HORMONE THERAPY

- **GREATEST RISK**: **DVT/PE**
- **GREATEST PERCEIVED RISK**: **BREAST CANCER**
  - WHI data
    - EP THERAPY: < 1/1000 added RISK, BUT PRESENT
    - ET THERAPY: REDUCED RISK PER WHI

    - **NO LONG TERM** DATA BEYOND WHI
- #1 cause of death post menopausal: **HEART**

DEATH RATES: CHD vs Breast Cancer



FORMS OF ET, EPT

- **TRANSDERMAL: (& transvaginal)**
  - Observational data (Europe) suggests lower risk of VTE/PE
  - Avoids 1st pass through liver = ***decrease thrombogenic effect***
  - Especially consider in high risk groups such as obesity, and age > 60
- **ORAL**
  - **CEE*** (most widely studied), **Estradiol** (E-2) may be lower risk for thrombosis.

* **CONJUGATED** EQUINE **ESTROGEN**, also, Plant derived

Some estrogen products

Drug and US brand name	Available strengths
Estrogen preparations and doses for the management of vasomotor symptoms	
Oral estradiol*	
Estrace¶	0.5, 1, 2 mg
Oral esterified estrogen*	
Menest	0.3, 0.625, 1.25, 2.5 mg
Oral estropipate	
Ortho-Est¶	0.75, 1.5, 3 mg estropipate (equivalent to 0.625, 1.25, 2.5 mg conjugated equine estrogen)
Oral conjugated equine estrogen (CEE)*	
Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg
Oral conjugated synthetic estrogens (A and B)*	
A: Cenestin	0.3, 0.45, 0.625, 0.9 mg
B: Enjuvia	0.3, 0.45, 0.9, 1.25 mg
Oral estrogen-progestin combinations	
Prempro$^{\Delta}$	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45/1.5 mg, 0.625/2.5 mg, 0.625/5 mg
Prefest	1 mg estradiol/0.09 mg norgestimate (cyclic)
Activella, Mimvey¶	0.5 mg estradiol/0.1 mg norethindrone acetate, 1 mg/0.5 mg
FemHRT	2.5 mcg ethinyl estradiol/0.5 mg norethindrone acetate
Jinteli	5 mcg ethinyl estradiol/1 mg norethindrone acetate
Angeliq	0.5 mg estradiol/0.25 mg drospirenone, 1 mg/0.5 mg
Oral conjugated equine estrogens and bazedoxifene	
Duavee	0.45 mg CEE/20 mg bazedoxifene

Drug and US brand name	Available strengths
Estradiol patches*	
Alora (twice weekly)	0.025, 0.05, 0.075, 0.1 mg per day
Minivelle (twice weekly)	0.0375, 0.05, 0.075, 0.1 mg per day
Vivelle-Dot (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Climara¶ (weekly)	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg per day
Menostar (weekly)	0.014 mg per day
Estrogen-progestin patches	
Combi-Patch (twice weekly)	0.05 mg estradiol/0.14 mg norethindrone, 0.05 mg/0.25 mg per day
Climara Pro (weekly)	0.045 mg estradiol/0.015 mg levonorgestrel per day
Gel*	
EstroGel 0.06 percent	0.75 mg estradiol per pump
Elestrin 0.06 percent	0.52 mg estradiol per pump
Divigel 0.1 percent	0.25, 0.5, 1 mg estradiol per pouch
Emulsion*	
Estrasorb	0.025 mg estradiol per pouch
Topical spray*	
EvaMist	1.53 mg estradiol per spray
Intravaginal rings*	
Femring	0.05 mg estradiol per day over three months, 0.1 mg estradiol per day over three months
Vaginal estrogen preparations for treatment of genitourinary atrophy (inadequate dose to relieve vasomotor symptoms)	
Vaginal ring	
Estring	7.5 mcg estradiol per day, released over three months
Vaginal tablet	
Vagifem	10 mcg estradiol per tablet
Vaginal cream	
Estrace 0.01 percent	0.1 mg estradiol per gram cream
Premarin	0.625 mg CEE per gram cream

FDA-approved bioidentical hormones for Menopausal symptoms

Type/source	Brand name(s)	Preparations	Bioidentical?
Estrogens			
Estradiol	Estrace, Gynodiol, Innofem	Pill	Yes*
	Estrace	Vaginal cream+	Yes
	Alora, Climara, Esclim, Estraderm, FemPatch, Menostar, Vivelle, generic	Transdermal patch	Yes
	Estrogel, Elestrin, Divigel	Topical gel	Yes
	Evamist	Topical spray	Yes
	Estring	Vaginal ring+	Yes
Estradiol acetate	Femring	Vaginal ring	Yes++
Estradiol hemihydrate	Vagifem	Vaginal tablet+	Yes
	Estrasorb	Topical lotion	Yes

FDA-approved bioidentical hormones for Menopausal symptoms

Progesterone	Prometrium	Pill	Yes
	Crinone 4%	Vaginal gel	Yes
Combined hormones			
Estradiol and norethindrone acetate	Combipatch	Patch	The estradiol is bioidentical but not the progestin.
Estradiol and norgestimate	Prefest	Pill	The estradiol is bioidentical but not the progestin.
Estradiol and levonorgestrel	Climara Pro	Patch	The estradiol is bioidentical but not the progestin.

* Bioidentical estradiol until ingested and converted in the liver to estrone.
+ For vaginal symptoms only.
++ Converts to bioidentical estradiol in the bloodstream.

equivalency

Oral: 0.625 mg CEE = 1 mg Ethinyl Estradiol (approximate)

Progestins/Progesterone

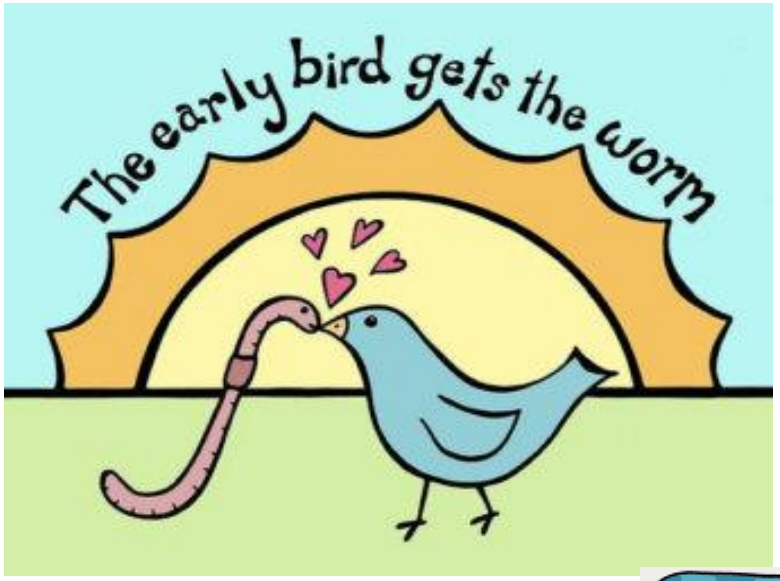
- **Progestins: continuous or sequential**
  - **Medroxyprogesterone** (MPA) 2.5-10 mg
  - CEE 0.3 and 0.45 have 1.25 mg MPA
  - CEE .625 has 2.5 mg MPA
  - **Norethindrone acetate**: 5-10 mg

  - **Micronized Progesterone**: 100-200 mg
    - Continuous: 100 mg/day
    - Sequential: 200 mg/day (10-12 days per month)

  - **Levonorgestrel (progestin) IUD** (**NOT FDA APPROVED**)

Timing Hypothesis

What is it?



FEMALE REPRODUCTIVE AGING

- Effects on CVD/Heart Disease
- Premenopausal Women are relatively protected against CVD
- Sex gap narrows after menopause
- Female Steroid Hormones –Estrogens-- believed to be cardioprotective
  - Cohort studies and retrospective studies supported HT
    - **NURSES HEALTH STUDY**
  - Brought into question by RCT of Primary and Secondary Prevention
    - STUDIES:
      - » **PEPI**
      - » **HERS**
      - » **WHI**

ESTROGEN

BENEFICIAL PHYSIOLOGIC EFFECTS OF ESTROGEN ON THE VASCULAR ENDOTHELIUM

- Cellular Level
- Molecular Level
- Animal Studies
- Beneficial effects on Lipids & insulin-resistance biomarkers

HORMONE THERAPY

- **TIMING HYPOTHESIS**:
  - TIMING OF INITIATION OF HT IMPORTANT
  - **EARLY:** PROTECTIVE
  - **LATE:** INCREASED RISK OF CV MORBIDITY

- HT MAY INCREASE RISK FOR CAD WHEN INITIATED LATER IN LIFE, AFTER PLAQUE ALREADY PRESENT IN CORONARY ARTERIES
- YOUNGER AGE, CARDIOPROTECTIVE (AGE 50-59)

Testing of the timing hypothesis was first carried out in the cynomolgus monkey model[37]. After bilateral oophorectomy, monkeys treated immediately with CEE showed a 70% reduction in coronary atherosclerosis at necropsy compared with placebo-treated monkeys. However, monkeys who had the same treatment after a delay of 2 years showed no changes in coronary atherosclerosis[37,39]. This delay in the monkey model of 2 years was thought to correspond to ≥6 years in humans.

93 % SAME DNA (Cynomolgus monkey –Human)

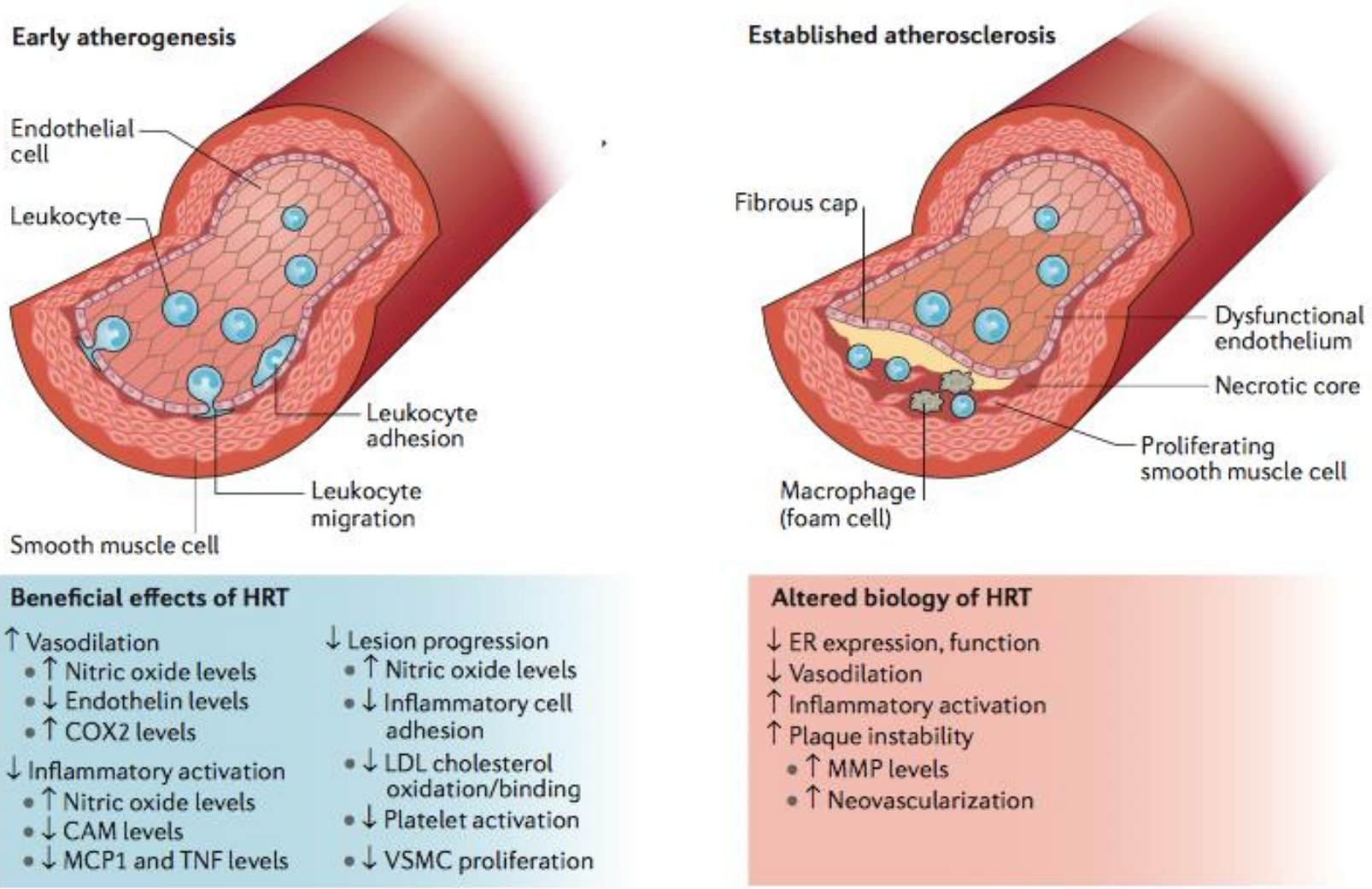


Figure 2 | **Coronary vessels in atherosclerosis.** Left panel depicts coronary vessels in a young woman with early atherosclerosis. Right panel depicts coronary vessels in an older (aged >65 years) woman with established atherosclerosis. Various effects of hormone-replacement therapy (HRT) on the vessels in the two stages of atherosclerosis are shown, with benefit in young arteries and altered biology in old arteries. CAMs, cell adhesion molecules; COX2, cyclooxygenase 2; ER, oestrogen receptor; MCP1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; TNF, tumour necrosis factor; VSMC, vascular smooth muscle cell. Permission obtained from the American Association for the Advancement of Science © Mendelsohn, M. E. & Karas, R. H. *Science* **308**, 1583–1587 (2005).

Relative safety of HT?

*WHAT ABOUT …..***Breast Cancer**

HOW COUNSEL ON RISKS OF BREAST CANCER

EPT: less than 1/1000 women per year (WHI)

ET: decrease

RELATIVE RISKS OF BREAST CANCER

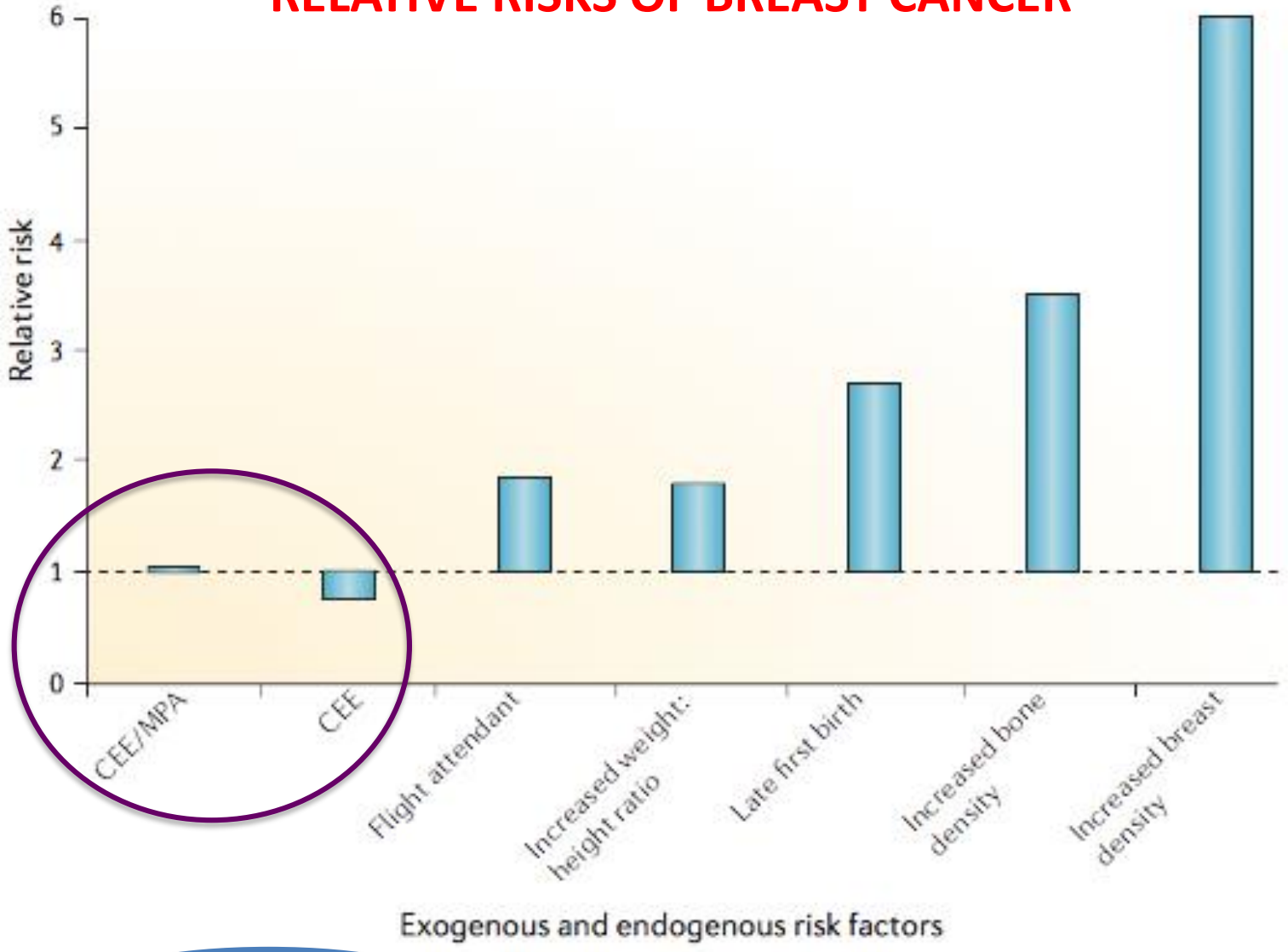


Figure 3 | **Breast cancer risk.** Relative risks of breast cancer associated with treatment with conjugated equine oestrogens (CEE) alone or with medroxyprogesterone acetate (MPA), occupational exposures and endogenous risks. Data obtained from elsewhere[19,25,81,82].

FAQ's --Systemic HT: YES OR NO ?

- Is Smoking (tobacco) is a contraindication to the use of menopausal hormone therapy??
- BMI > 35, > 40 etc ???
- ? Carriers of BRCA1 or BRCA2 with no personal history of breast cancer
- Endometriosis?
- DVT?
- Personal Hx of Breast Cancer?

NEW Patient: 'Surgical Menopause'

- Patient had BSO at age 36 for benign condition, (endometriosis, chronic PID, bilateral teratoma etc.)
- HT:? How long?
- Evidence ?
  - WHI did not address this population

Case # 2

- A 63 year old female comes to your office with chief complaint of **dyspareunia**. She has been divorced and recently become sexually active again in a new relationship after 10 years of abstinence. She also reports **vaginal dryness and occasional pruritus.**
  - On physical exam, she has significant discomfort with the bimanual exam and you note pale pink, thin vaginal epithelium.

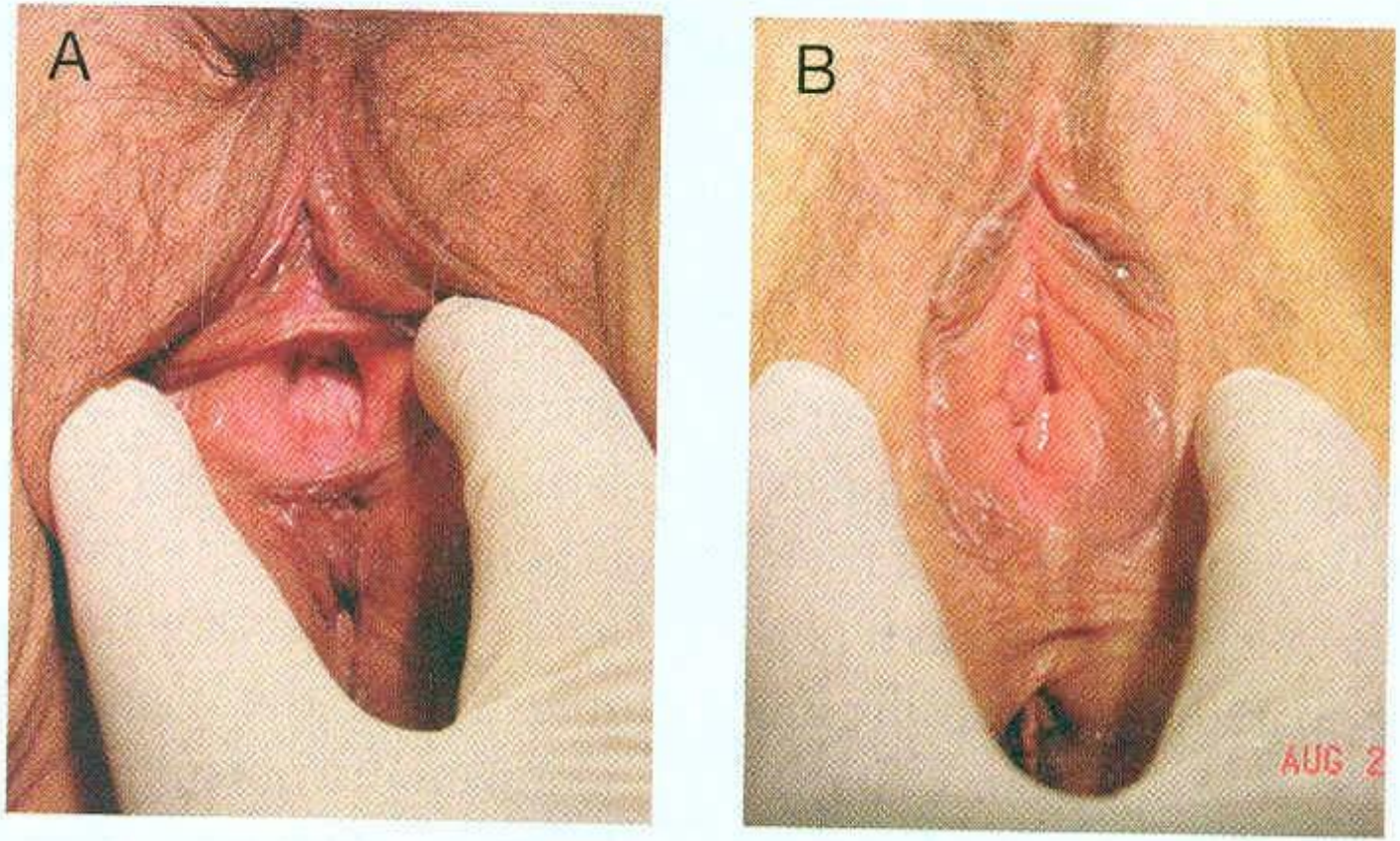


Figure 5. Comparison of two sexually active 65-year-old women (both P 2002). Patient A discontinued estrogen therapy 3 years previously while Patient B remained on therapy.

Vulvovaginal Atrophy

- A.k.a. **genitourinary syndrome of menopause**
- Typically occurs in 10-40% of older women
- Progressive and less likely to resolve without intervention
- Has a significant impact on a woman's sexual health and quality of life.
- REVIVE, largest survey of US women (0ver 3,000 participants), found that only 7% of women with VVA reported their symptoms to their physician

NAMS position statement (p 889)

The Physiologic Changes: Genitourinary Syndrome of Menopause

- **Structural---ATROPHY**
  - Reduced collagen content, elastin, hyalinization
  - Thinning of epithelium
- **Physiologic**
  - Reduced blood flow
  - **Decreased lubrication**
  - **Decreased flexibility/elasticity** of vaginal vault
  - Increased vaginal pH

Non-Hormonal Treatment 'GUSM'

- **Vaginal moisturizers**- applied a few times weekly
  - Replens, Me Again, Vagisil, Feminine Moist, Feminease, K-Y Silk-E

- **Vaginal lubricants**-applied prior to intercourse
  - Water-soluble- Astroglide, Slippery Stuff, K-Y jelly
  - Silicone-based- Pjur Eros, ID Millinium
  - Oil-based- Elegance

- **Sexual activity**
  - Use it or lose it.

- **Vaginal dilators**
  - Set of graduated sizes, instructions on use taught by physician or pelvic PT.
  - Consider topical estrogen prior to use

Estrogen therapy

- **Most effective** for moderate to severe VVA **TOPICAL**
- Restoration of normally acidic vaginal pH and microflora, thickening of the epithelium, increased vaginal secretions and decreased vaginal dryness.
- **Reduction of OAB symptoms**. Not indicated for stress or urge incontinence as prior studies have not shown benefit with use.
- **Contraindications**- caution in women with or at increased risk for estrogen-dependent tumors. Controversial in women with breast cancer

- *??Progestin therapy? NEEDED??? (No)*
- *Monitor endometrium??? (No)*
- *Evaluate if bleeding (Endometrial stripe, EMB)*

Low-dose Vaginal Estrogen Therapy

- Defined as concentrations less than 50 mcg or 0.3 mg conjungated estrogens
- Typically have similar estradiol levels as those not taking exogenous estrogen, however, systemic effects are possible but not likely
- Dose and duration may vary. Trials have not followed women treated with vaginal estrogen beyond a year

Vaginal estrogen treatments
Vagifem- 10 mcg tab, insert daily for 2 weeks, then twice weekly thereafter
Estring- 7.5 mcg silastic ring inserted vaginally, for 90 days
Premarin- 0.3 mg/0.5 g cream- considered “low dose” at this concentration

High-dose estrogen therapy

- **Femring**- 50-100 mcg- considered **systemic** and also indicated for treatment of vasomotor symptoms

- **Conjugated estrogens-** Premarin- 0.625 mg/1 g cream
  - Cyclic regimen: daily for 21 days and off for 7 days
  - Continuous: daily for 1-2 weeks, then twice weekly

- **Estrace-** 100 mcg/1 g cream- 2-4 g daily for 1-2 weeks, then gradually reduce to half the initial dose for a similar period. Maintenance dose of 1 g, 1-3 times weekly

Serum estrogen levels with local treatments

	Premenopausal women	Postmenopausal women
Serum estrogen level	40-600 pg/mL	< 30 pg/mL

Estrogen	Serum concentration
Vagifem 10 mcg tab	3-11 pg/mL
Estring 7.5 mcg ring	5-10 pg/mL
Premarin 0.625 mg cream	Unknown, as there are > 200 compounds, come estrogenic and others antiestrogenic. Serum concentration does not correlate with activity level
Estrace 100 mcg cream	40 pg/mL

Risks of Estrogen Therapy

- Higher serum estrogen concentrations lower serum gonadotropic concentrations and may induce endometrial proliferation. **Progestins** are recommended as adjunct therapy with any "high dose" estrogen treatments.
- **Progestins** are given for 10-12 consecutive days per month OR continuous OR progestin IUD

Progestins
Medroxyprogesterone 10 mg
Norethindrone acetate 5-10 mg
Micronized progestertone 200 g

Estrogen Agonist and Antagonists

Selective estrogen receptor modulators

- **Ospemifene (Osphena)-** FDA approval for treatment of moderate to severe **dyspareunia**
  - Estrogen agonist in the vagina, without clinically significant estrogenic effect on the endometrium or breast.
  - Recommended for women who cannot or prefer not to use a vaginal product
  - Disadvantages (compared to vaginal estrogen) include need for daily use and systemic side-effects such as hot flashes and potential risk of thromboembolism.
  - Safety of Osphena has not been demonstrated in women with a prior history of or increased risk of breast cancer or in women with increased risk of VTE.
  - Causes reduction in bone turnover
- **Raloxifene and Tamoxifen** not FDA approved for tx dyspareunia

SUMMARY

- For healthy symptomatic women **age younger than 60 (or within 10 years of menopause onset)**, the more favorable effects of HT on CHD and all-cause mortality should be considered against potential rare risks (> 1/10,000 and < 1/1000 per year) of breast cancer, VTE, and stroke. HT is not FDA indicated for primary or secondary cardioprotection.

- "lowest dose for shorted period of time" may be inadequate or harmful for some women".

- A more fitting concept is suggested (NAMS): **"appropriate dose,duration, regimen, and route of administration"**

- **Individualization with shared decision making remains key, with periodic reevaluation to determine an individual woman's benefit-risk profile.**

Evidence base for HT*: what can we believe

"IT IS TIME TO GET PAST THE MISINFORMATION & HYSTERIA GENERATED BY THE HIGHLY IRREGULAR CIRCUMSTANCES OF THE WHI AND STOP DENYING POTENTIAL BENEFITS (control of vasomotor symptom, prevention of fractures, prevention of CHD) to women who have indications & may be helped**. HRT is appropriate for symptomatic women within 10 years of menopause who have no major contraindication"**

"Good evidence from over 50 years of observational studies and clinical trials suggests that the benefits outweigh the risks for most women when started early".

*RD Langer, Climacteric, 2017: Vol 20, #2, 91-96

International Menopause Society

Updated recommendations

FURTHER INFORMATION AVAILABLE AT THEIR WEB SITE.

Cardiovascular disease

Key points

- In women under age 60 and recently postmenopausal with no evidence of cardiovascular disease, the initiation of estrogen-alone therapy reduces coronary heart disease (CHD) and all-cause mortality [A]
- Data on daily continuous combined estrogen–progestin are less robust but other combined therapy regimens appear to be protective as shown in Danish and Finnish studies [A]
- **Recent meta-analyses and WHI 13-year follow-up data all show a consistent reduction in all-cause mortality for MHT users** [A]
- It is not recommended to initiate MHT beyond age 60 years solely for primary prevention of CHD [A]

International Menopause Society: 2016 IMS Recommendations:

Climacteric: 2016; 19, 109-150

Venous thromboembolism

Key points

- A careful assessment of personal and family history of venous thromboembolism (VTE) is essential before prescribing MHT ☑
- Oral estrogen is contraindicated in women with a personal history of VTE [A]
- Transdermal estrogen should be first choice in obese women with VMS [B]
- VTE risk increases with age and with thrombophilic disorders ☑
- The risk of VTE increases with oral MHT but is rare below age 60 ☑
- Observational studies and biological plausibility point to a lower risk with low-dose transdermal therapy ☑
- Some progestogens may be associated with a greater VTE risk [C]
- The incidence of VTE is less frequent amongst Asian women [C]
- Population screening for thrombophilia is not indicated prior to MHT use [C]

International Menopause Society: 2016 IMS Recommendations: Climacteric: 2016; 19, 109-150

Breast cancer

Key points

- The risk of breast cancer associated with MHT in women over 50 is complex
- The increased risk is primarily associated with the addition of a synthetic progestogen to estrogen therapy and to duration of use [B]
- The risk may be lower with micronized progesterone or dydrogesterone [C]
- The MHT attributable risk is small and decreases when treatment stops [B]
- There is a lack of safety data supporting MHT use in breast cancer survivors
- Breast cancer risk should be evaluated before MHT prescription [D]
- Any possible increased risk associated with MHT may be decreased by selecting women with lower baseline risk including low breast density and by providing education on preventive lifestyle measures (reducing weight, reducing alcohol intake, increasing physical activity) [D]

International Menopause Society: 2016 IMS Recommendations: Climacteric: 2016; 19, 109-150

Endometrial safety and bleeding

Key points

- Postmenopausal bleeding is 'cancer until proven otherwise'. 1–14% of women with postmenopausal bleeding will have endometrial cancer
- Blind endometrial sampling is an appropriate first-line investigation [B]
- Unopposed estrogen therapy is associated with a dose and duration-related increased risk of endometrial cancer [A]
- Endometrial protection requires an adequate dose and duration of progestogen [A]
- For doses of estradiol of 2 mg/50 μg, an adequate dose of micronized progesterone appears to be 200 mg for 10–14 days per month or 100 mg daily for continuous therapy [B]
- Higher doses of progesterone may be required for higher estradiol doses or in women with high body mass index ☑

International Menopause Society: 2016 IMS Recommendations: Climacteric: 2016; 19, 109-150

Complementary and bioidentical therapies

Key points

- Complementary therapies have limited evidence of efficacy and are not regulated by medicines agencies [B]
- Cognitive behavioral therapy, mindfulness training, acupuncture, hypnosis and stellate ganglion blockade may be useful techniques to consider when treating VMS [A]
- Prescribing **compounded bioidentical hormone therapy (BHT)** is not recommended due to lack of evidence of efficacy, lack of quality control and lack of regulatory oversight [B]
- The use of serum or salivary hormone levels is not recommended to assist in the management of MHT [B]

International Menopause Society: 2016 IMS Recommendations: Climacteric: 2016; 19, 109-150

Pharmacological treatments for VMS

Key points

- SSRIs and SNRIs such as venlafaxine, desvenlafaxine, paroxetine, escitalopram and citalopram are effective in reducing VMS in postmenopausal women [A]
- Paroxetine should be avoided in women receiving tamoxifen [A]
- Gabapentin is effective in reducing VMS in higher doses but has more side-effects than the SNRIs/SSRIs [B]

International Menopause Society: 2016 IMS Recommendations: Climacteric: 2016; 19, 109-150

Vulvovaginal atrophy

Key points

- Be proactive in order to encourage patients to disclose symptoms of vulvovaginal atrophy (VVA) and to seek treatment where appropriate [A]
- Treatment is best started early and needs to be continued to maintain benefits [B]
- The principles of treatment are restoration of urogenital physiology and alleviation of symptoms
- When VVA is the sole symptom, local estrogen therapy is preferred [B]
- Local estrogen therapy minimizes systemic absorption and serum estradiol levels are not above the normal range (< 20 pg/ml) for postmenopausal women [B]
- **Additional progestogen is not required** [B]
- There are limited data on the use of topical estrogens in women with hormone-dependent cancers [D]

International Menopause Society: 2016 IMS Recommendations: Climacteric: 2016; 19, 109-150

VVA in Women with Breast Cancer

- VVA symptoms are a common complaint in women with breast cancer, particularly those on endocrine treatments (aromatase inhibitors or tamoxifen).
- **First line treatment** is non-hormonal
- Few data regarding safety of vaginal estrogen therapy are available.
- **Estrogen therapy** should NOT be used in women using aromatase inhibitor therapy for breast cancer
- It is reasonable to prescribe **low-dose vaginal estrogen** in women taking tamoxifen only after discussion with her oncologist.
- **Vaginal testosterone** is under investigation and has not been shown to increase serum estrogen. It's efficacy is questionable

References:

- **North American menopause Society**:
  - www.menopause.org
    - Position statements on
      - HT
      - Non-hormonal therapy
      - GUSM (VVA)
      - Meno Pro app
- **Management of Menopausal Symptoms**: Kaunitz & Manson. Ob&Gyn: vol 126, #4, Oct.2015
- **An Update on HT in postmenopausal women**: Am J Physio heart Circ Physiol 313: H1013-1021, 2017
- **Hormone replacement therapy: current thinking**. Roger A Lobo. Columbia Univ., www.nature.com/nrendo, April 2017.volume 13. 220-231.
- **Review: The evidence base for HRT: what can we believe. R.D Langer, Climacteric, 2017. vol 20, #2, 91-96**