Managing Menopause Amid Controversy

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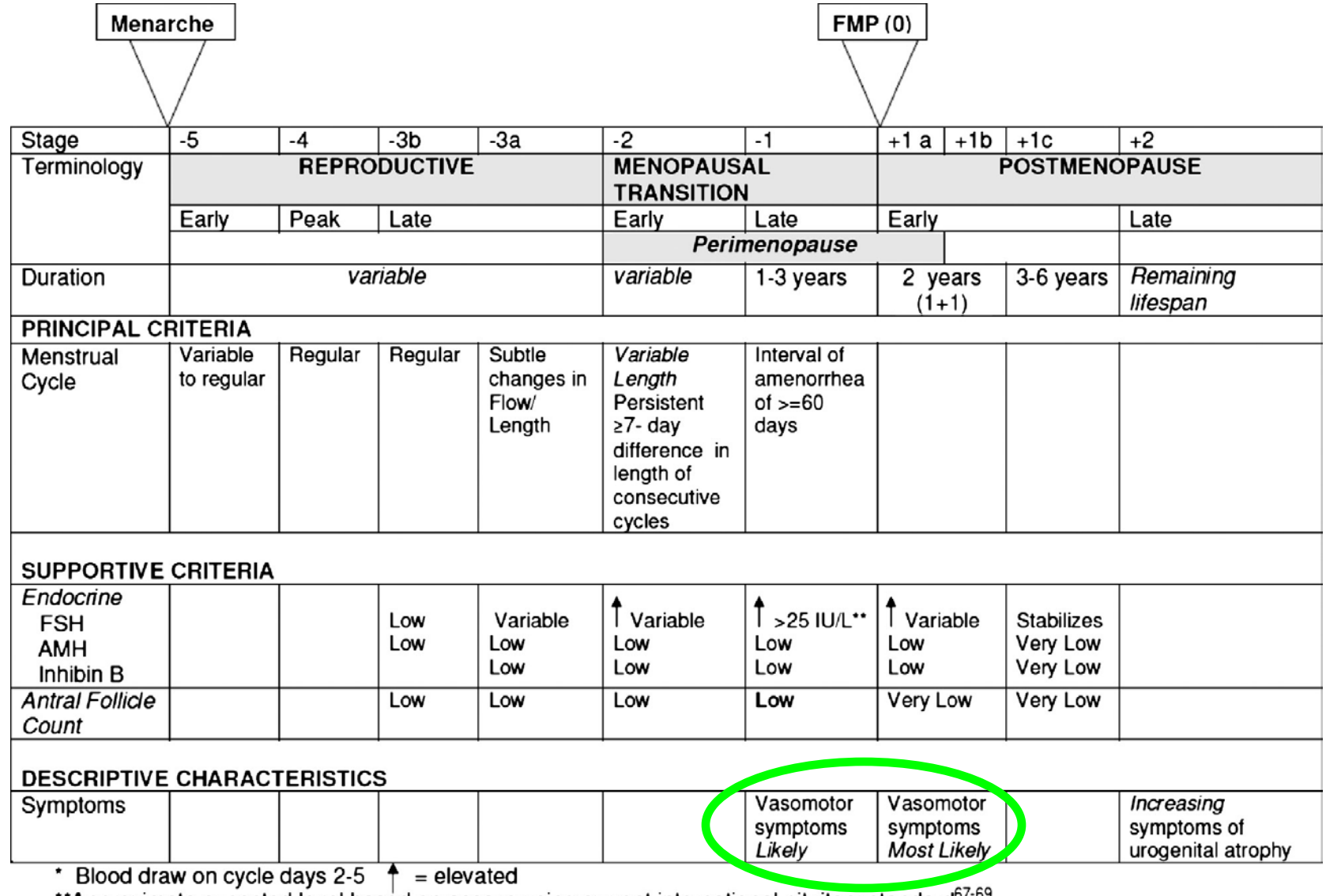
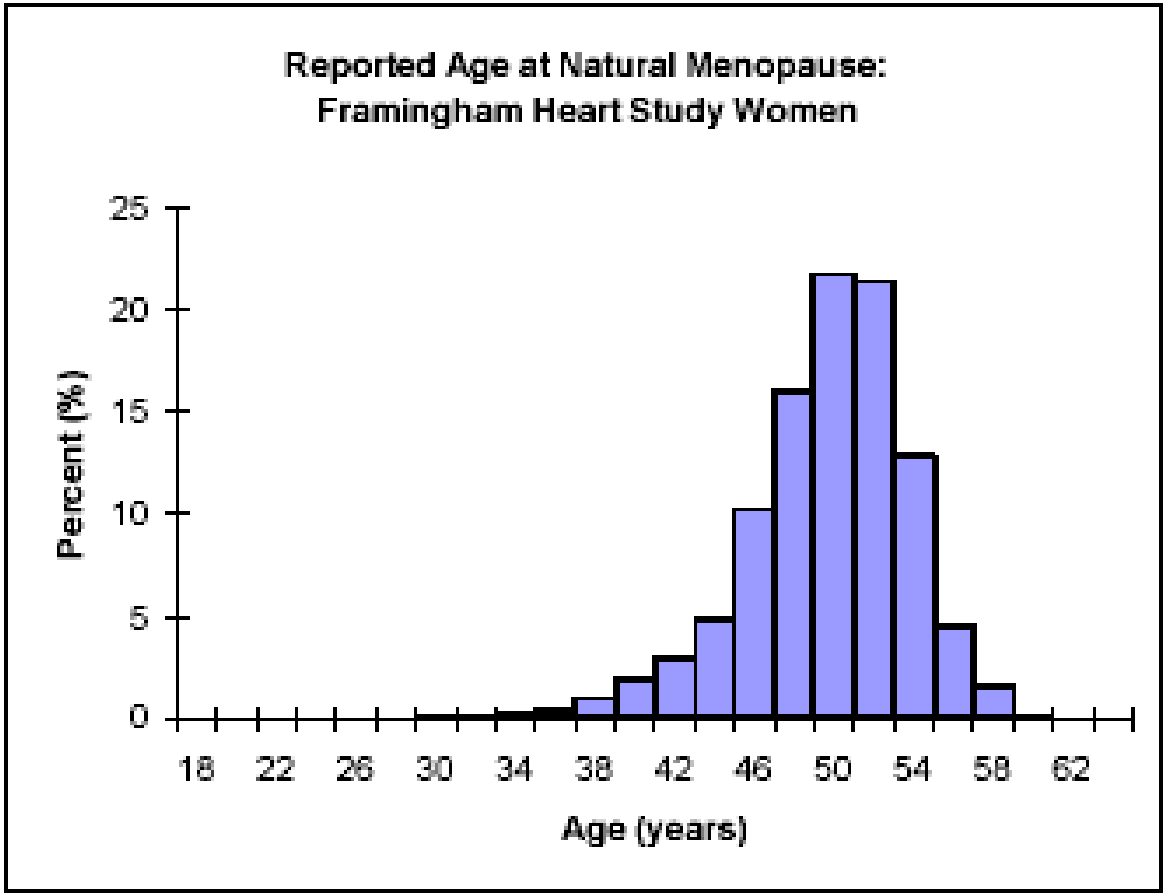
Agenda

- Epidemiology, stages, natural hx
- Managing
  - Vasomotor, urinary, mood sx
  - Reproductive issues
    - Contraception
    - Sex
- The swinging pendulum of evidence

Stages of Reproductive Aging



Epidemiology

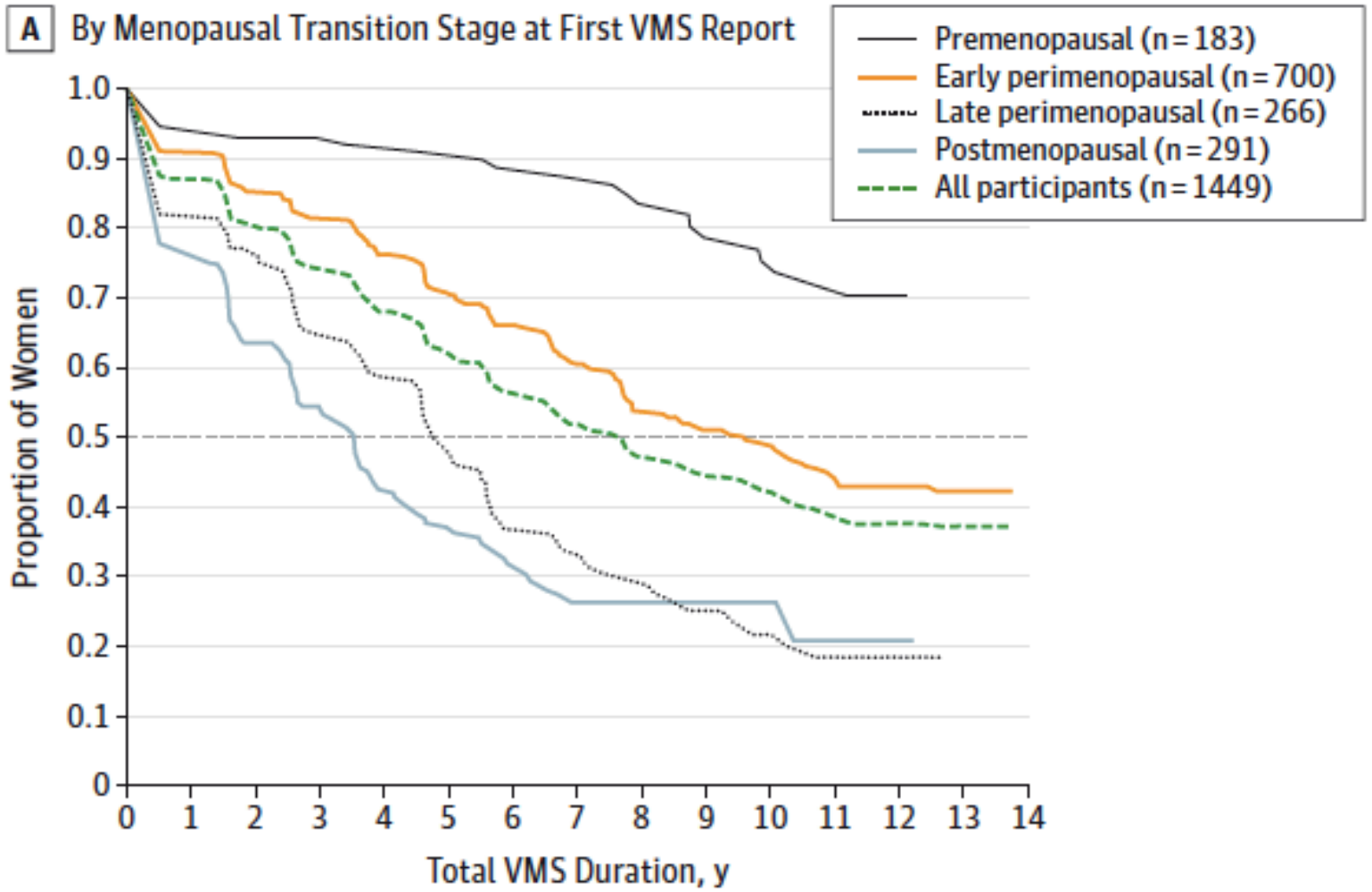


Murabito *J Clin Endocrinol Metab* 2005

Epidemiology

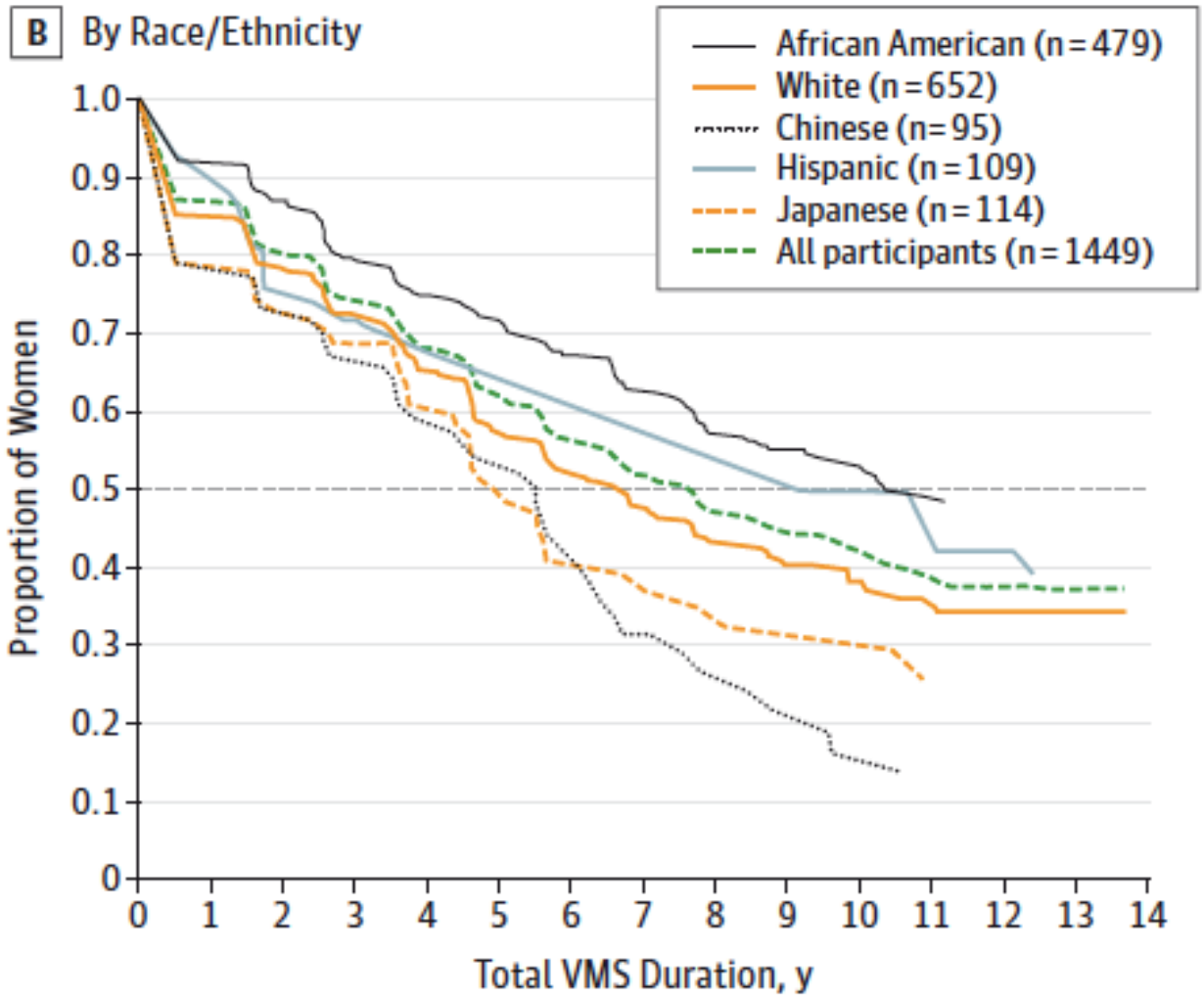
- Mean age 52, 5% age < 40
  - If age <40, Primary Ovarian Insufficiency
- Smokers earlier menopause with worse sx
- Later in OCP users, parous women
- Family history strongest predictor
- Vasomotor symptoms present ~80%
- New information on duration…

Vasomotor Sx



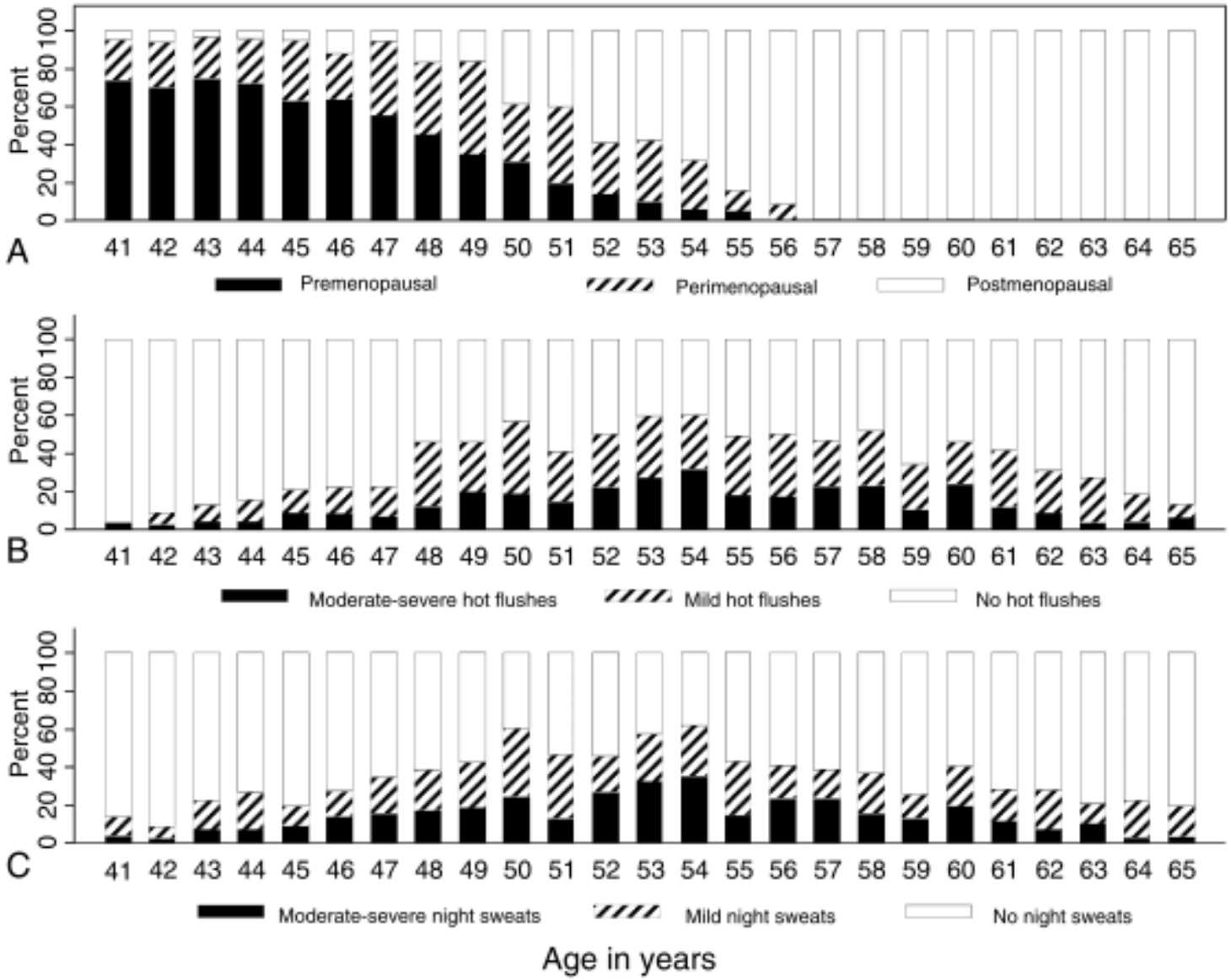
SWAN study Avis, JAMA Int Med 2015

Vasomotor Duration by Race



SWAN study Avis, JAMA Int Med 2015

Gartoulla Menopause 2015



Hot Flash Symptom Reduction

	Drug	Placebo
Estrogen	95%	20-40%
Progesterone	80-90%	
Venlafaxine 75 -150 mg qd	61%	27%
Desvenlafaxine 100 mg qd	64%	51%
Fluoxetine 20 mg qd	50%	36%
Paroxetine 12.5-25 mg qd	65%	38%
Citalopram 20 mg	55%	23%
Escitalopram 10-20 mg	55%	36%

Hot Flash Symptom Reduction

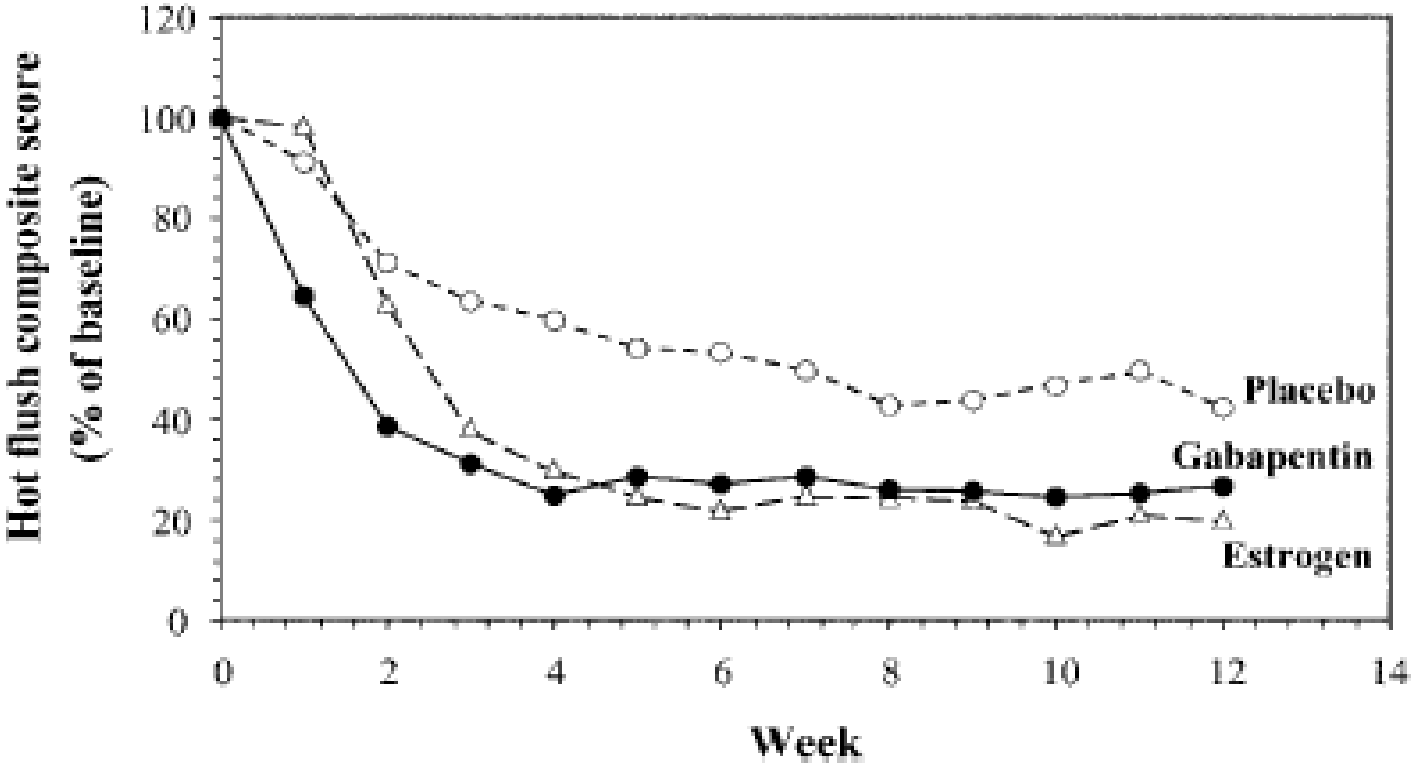
	Drug	Placebo
Gabapentin 300 mg tid	54%	31%
Clonidine 0.1-0.2 bid	30-40%	
Methyldopa 250-1000 mg	65%	38%

Only FDA approved non-hormonal:
Paroxetine 7.5 mg qhs (Brisdelle)

Other Treatments

- Soy
  - Diet, isolated soy protein, soy extract tablets
  - No benefit in most RCTs
  - ?Risk of endometrial hyperplasia
- Black Cohosh (Remifemin) 20 mg bid
  - Trials mixed

Gabapentin vs estrogen?



Gabapentin titrated to 2400 mg over 12 days
Estrogen = Premarin 0.625 mg

Reddy *Obstet Gynecol* 2006;108:41

HT Contraindications

- Undiagnosed vaginal bleeding
- Breast cancer
- Endometrial cancer
- Thromboembolic disease
- Liver disease
- CVA/MI

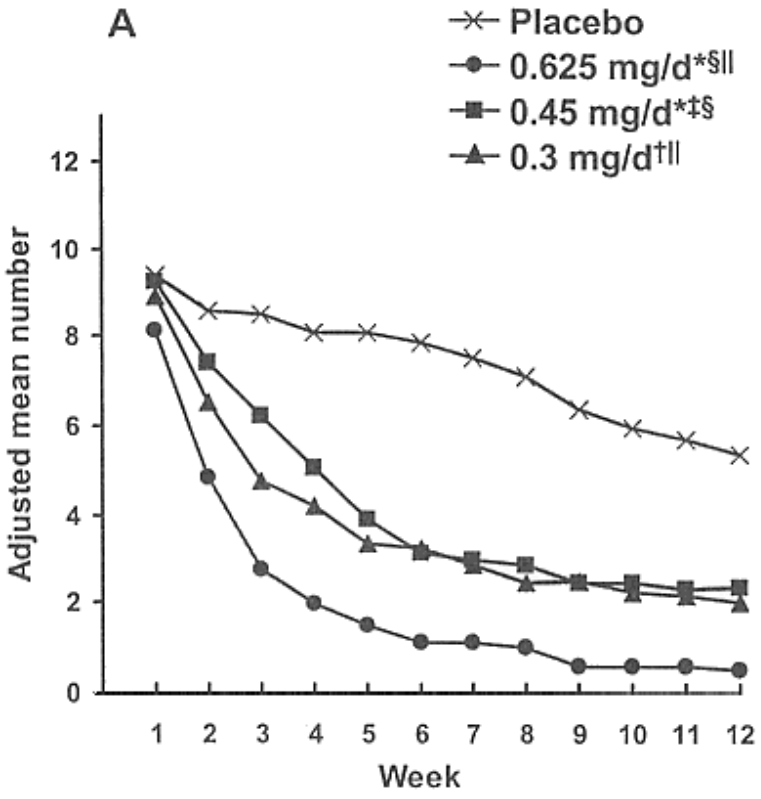
HT Risks

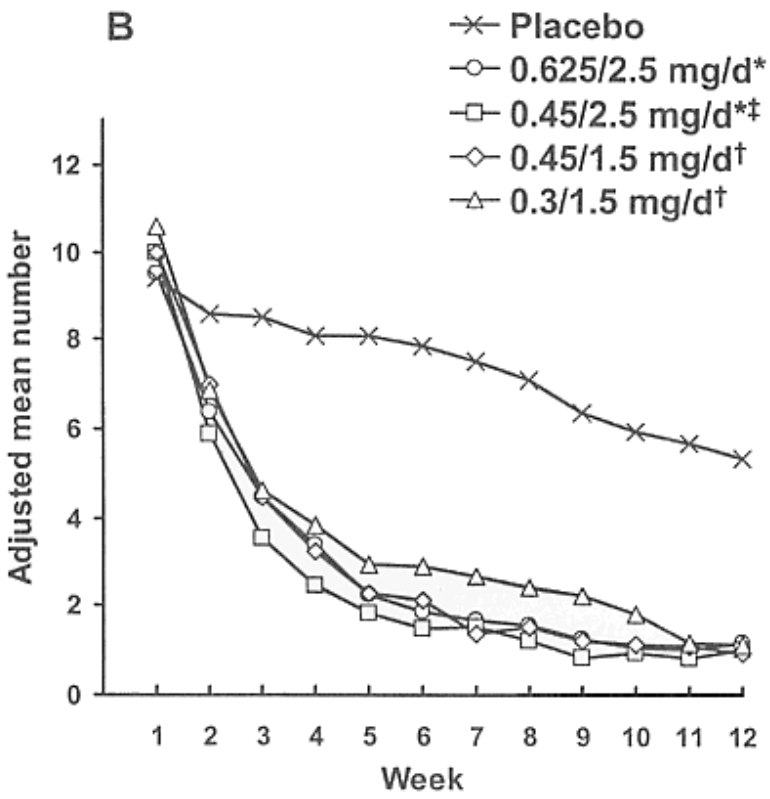
- DVT/PE
  - Highest risk in first year
- Gall stones (oral HRT)
- Coronary artery disease
- Stroke
- Breast cancer
  - Most data suggests risk with >4 years

Starting HT

- Which estrogen?
- Dose
- Is progestin needed?
  - No if hysterectomy; yes if uterus intact
- Oral versus transdermal?
- Duration

Lowest Effective Dose: Hot Flashes





Utian. Lower HRT doses. *Fertil Steril* 2001

Oral Estrogen Options

Drug	Dose	Cost
Premarin (CEE)	0.625 mg	$85
Estropipate (estrone deriv)	0.625 mg	$6-14
Estradiol	1 mg	$5

Cost for 1 month supply

Medventive Pharmacy

Progestin Options

	Continuous Dose	Cost	Cyclic Dose	Cost
Medroxyprogesterone acetate (MPA)	2.5 mg PO 5.0 mg PO	$4	5-10 mg for 10-14 days	
Norethindrone (off label)	5.0 mg PO	$58		
Prometrium (Micronized Progesterone)			100 mg bid or 200 mg qd	$48

Medventive Pharmacy

Oral Combinations

Brand	Estrogen	Progestin	Cost
Prempro	CEE 0.625 mg	Daily MPA 2.5 or 5 mg	$124
	CEE 0.45 mg	Daily MPA 1.5 mg	
	CEE 0.3 mg	Daily MPA 1.5 mg	
Premphase	CEE 0.625 mg	Cyclic MPA 5 mg d 14-28	$124
Fem HRT	EE2 5 mcg	Daily norethindrone 1 mg	$70
Femhrt low	EE2 2.5 mg	Daily norethindrone 0.5mg	$83
Activella	Estradiol 1 mg Estradiol 0.5 mg	Daily norethindrone 0.5 mg Daily norethindrone 0.1 mg	$62
Prefest	Estradiol 1 mg	3 days on 3 days off norgestimate 0.09 mg	$119
Angeliq	Estradiol 1 mg	Drospirenone 0.5 mg	$120
Duavee	CEE 0.45 mg	Bazedoxifene 20 mg	$134

Transdermal Estrogen

- Estradiol patch standard dose 0.025 - 0.1 mg/day
- Must use progesterone in women with uterus
- Avoids first pass hepatic metabolism
- Lower risk cholelithiasis (RR 1.74 oral vs 1.17 transdermal)
- Attenuated rise in HDL levels
- No increase in triglycerides
- ? Lower risk thromboembolic disease

HT and Venous Thromboembolism

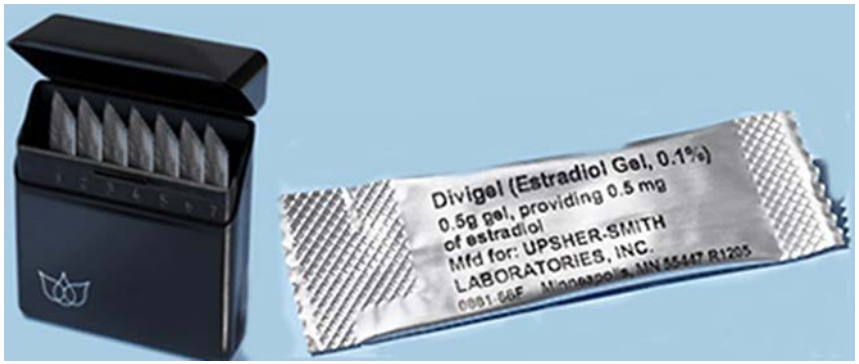
	OR (95%CI) (1)	OR (95%CI) (2)
Oral therapy	4.2 (1.5-11.6)	2.5 (1.9-3.4)
Transdermal	0.9 (0.4-2.1)	1.2 (0.9-1.7)

(1) Case control study Circulation 2007;115:840-845
(2) Meta Analysis BMJ 2008;336(7665)

VTE Risk

- Oral therapy increases resistance to activated Protein C
- Claims analysis transdermal vs oral estrogen 0.67 adjusted risk of VTE/PE
- ACOG opinion April 2013
  - Consider possible thrombosis sparing properties of transdermal estrogen
- But, no difference in KEEPS RCT of Prempro versus transdermal

Other Topicals



Evamist

Non-oral Estrogen Options

Drug	Equivalent Dose	Cost
Estradiol patch	0.05-0.1 mg qd	$40-53
Estrasorb (estradiol gel)	0.05 mg qd in 2 pouches	$68
EstroGel (estradiol gel)	1.25 g	$103
Evamist	1.53 mg	$109
Femring (vaginal estradiol)	0.05 or 0.1 mg qd	$275

Cost for 1 month supply (Femring 3 months)

Patch Combinations

Brand	Estrogen	Progestin	Cost
Combipatch	Estradiol 0.05 mg	Daily norethindrone 0.14 or 0.25 mg	$64
Climara Pro	Estradiol 0.045 mg	Levonorgestrel 0.015 mg	$113

Medventive Pharmacy

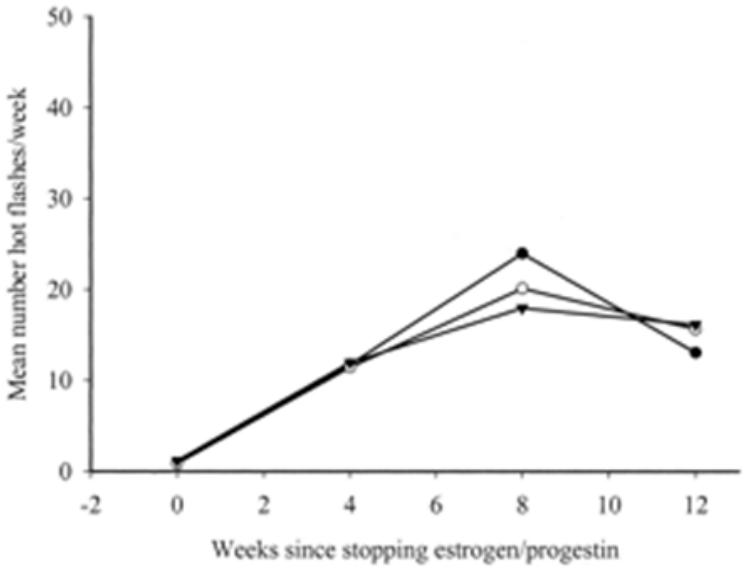
“Bioidentical HT?”

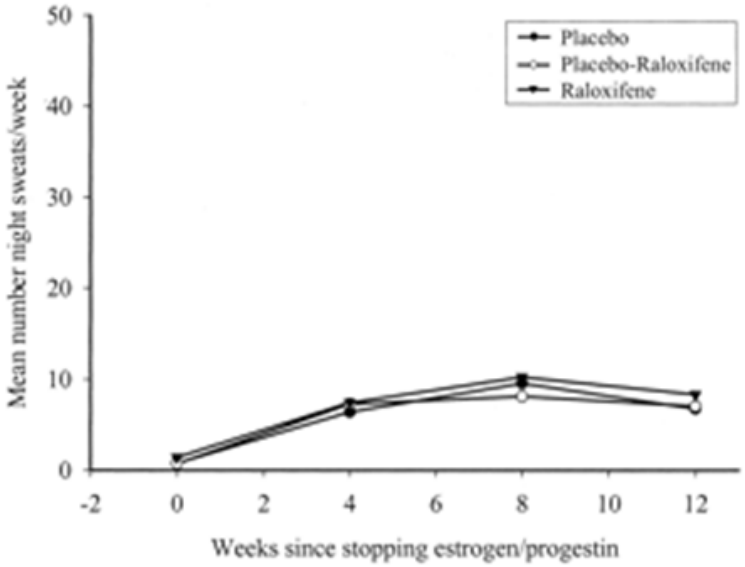
- Compounding pharmacies
- Individualized estrogen, progesterone, testosterone dosing
- No evidence of greater safety
- Risk of dose variability

Stopping HT

- Minimize treatment duration
- Rebound vasomotor symptoms common with abrupt stop
- Tapering
  - Gradual dose reduction:
    - 0.625 mg – 0.3 mg - 0.15 mg
  - Skipping doses
    - 6 days/week, 5 days, 4 days…

Vasomotor symptoms when HT is stopped





Gordon *Ob Gyn* 2004

Mood Disorders

- Increase in risk of major depression and depressive symptoms
  - Increased in perimenopause leading up to final menstrual period after which risk declines
  - SWAN study up to 24% had major depression
  - More common with past history of depression and PMS
  - May correlate with fluctuating hormone levels
- Hot flashes frequently disrupt sleep
- Progestins can exacerbate

Genitourinary Syndrome of Menopause (GSM)

- Worsens over time unlike vasomotor sx
  - Vaginal dryness (75%)
  - Dyspareunia (38%)
  - Urinary frequency, urgency, dysuria
  - Recurrent UTIs (single trial 1993 reduced with topical estrogen)
  - Incontinence (worsens with systemic HT)
- May improve with increased intercourse

Extra narrow speculum

Treating Urogenital Symptoms

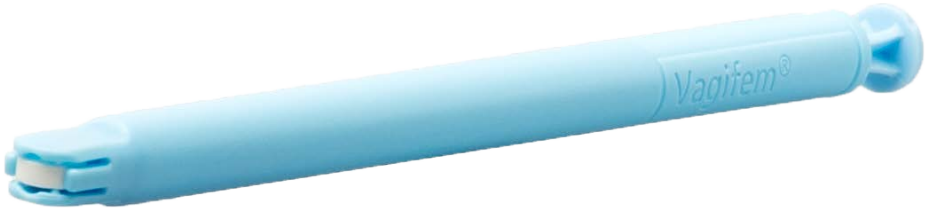
- Vaginal bioadhesive moisturizers (i.e. Replens)
- Topical vaginal estrogen
  - Increases superficial and intermediate cells
  - Normalizes (lowers) vaginal pH
  - Slight increase serum estrogen
    - Consider surveillance or periodic progesterone in long term high dose users
  - Minimum effective dose -- often 1 - 3 times/week
  - Available as cream, tablets, vaginal ring
- Systemic estrogen only if used for other indications
- New SERM Ospemifene

Which vaginal estrogen?

Brand	Type	Ingredient	Initiation	Maintenance	Cost
Premarin	Cream	0.625 mg CEE/g	0.5-2 g/d	Twice/week	$189/tube
Estrace	Cream	0.1 mg estradiol/g	2-4 g/d for 2 wks	1 g 1-3 times/wk	$158/tube
Estring	Ring	2 mg estradiol (7.5 mcg qd)	1 ring q 3 months	same	$239/ring $80/mo
Vagifem	Tablet	10 mcg estradiol	1 tab qd for 2 wks	2 tab/wk	$78 for 8 tabs

Medventive Pharmacy

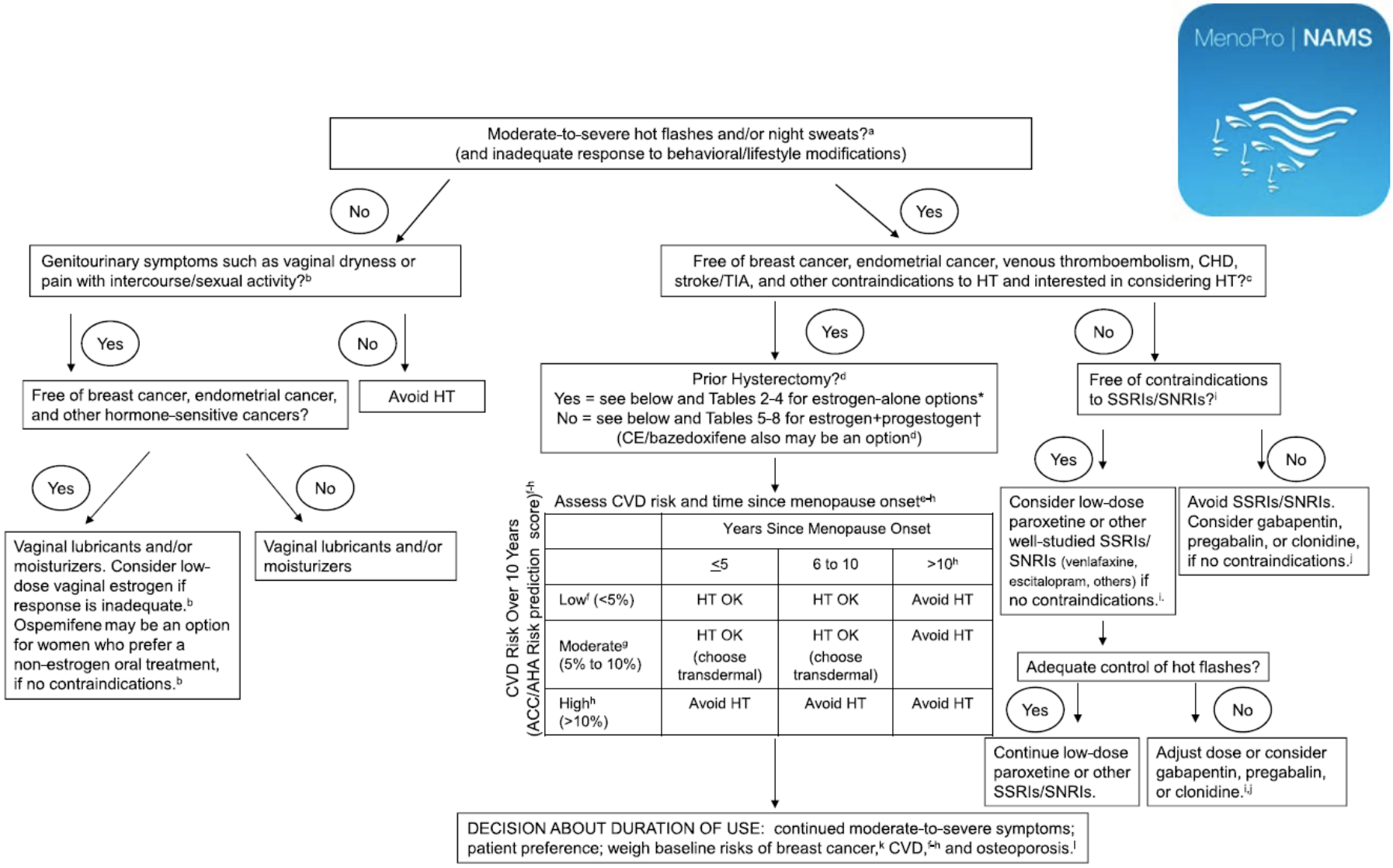
How are they administered?



Ospemifene

- SERM agonist vaginal epithelium, bone, endometrium
- FDA approved Feb 2013 as Osphena
- ? Effect on breast
- Increased risk of VTE
- ~$160/month

NAMS Algorithm and App

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MENOPAUSAL
PRE-MENOPAUSAL
THOUGHT TO BE DONE WITH MENOPAUSE AND PREGNANT
search ID: cwln1098

Unintended Pregnancies

Age	Pregnancies	% births unintended
<15	21,000	98
15-19	769,000	82
20-24	1,716,000	64
25-29	1,751,000	41
30-34	1,334,000	33
35-39	832,000	28
≥40	235,000	48

2006 US data; Finer, Contraception 2011

Contraception…

- Contraception until 1 year without menses
- None contraindicated except OCP (or patch, ring) in smokers
- Caution with natural family planning
- Consider IUD
  - Mirena (progestin release for 5 years)
  - Copper T380 (10 years per IUD)

When is it Safe to Stop Contraceptive?

Method	Recommendations
Non-hormonal	Can stop 2 years after FMP if <50, 1 year if >50
Progestin only pill, implant, IUD	Can stop at 55 and assume menopausal; If <55 if FSH >30 twice 6 weeks apart can stop 1 year later
Depo-provera, combination hormonal	Cannot assess when menopausal by FSH Stop at 50 and switch to other method

July 2010 Royal College of Obstetricians & Gynecologists
Contraception for Women Aged >40 Years

Sexual Dysfunction - Taxonomy

- Hypoactive sexual desire disorder
- Sexual arousal disorder
- Orgasmic disorder
- Dyspareunia
- Vaginismus

Hypoactive sexual desire disorder

- Testosterone
  - Transdermal 300 ug vs placebo increased satisfying sexual episodes (SSE) over 4 wks (2.1 vs 0.5)
  - Lowers HDL, may increase breast cancer
- Flibanserin (serotonin agonist/antagonist)
  - 100 mg qhs
  - “Female Viagra” but completely different mechanism
  - Approved 8/2015 only for premenopausal women
  - Trial postmenopause increased SSE 1.0 vs 0.5 4 weeks

Shifren *NEJM* 2000, Shifren *Menopause,* 2006, Davis *NEJM* 2008

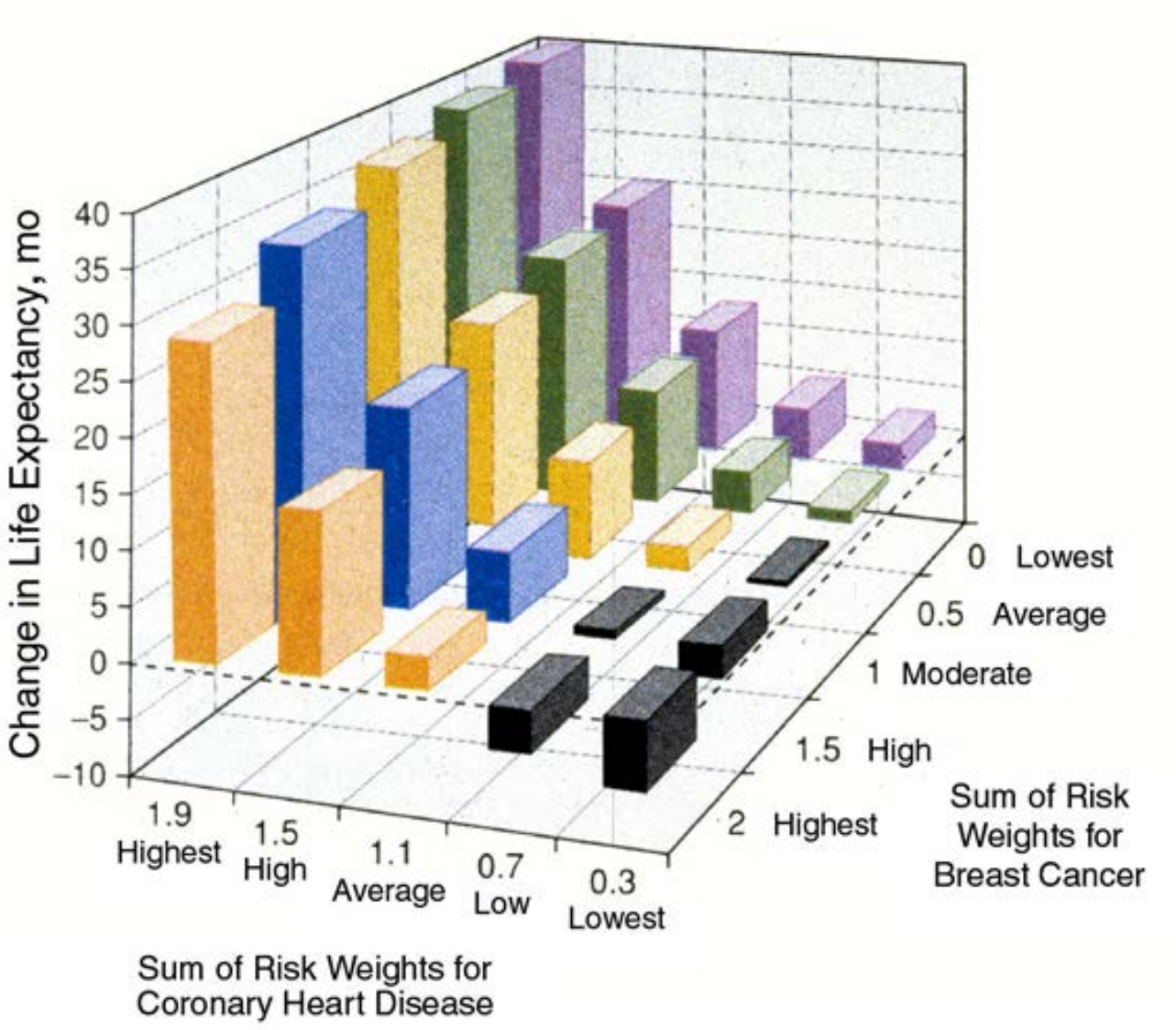
Prescribing Testosterone

- FDA did not approve patch in 2004
- Avoid if breast, uterine cancer; CV, liver disease
- Prescribing options
  - Off label small amounts of male preparation
  - Compounding pharmacy
- Monitoring
  - Testosterone levels, LFTs
- Efficacy (sexual frequency, desire, satisfaction)
- Adverse effects (hirsutism, acne)

HRT and Prevention in the 90s

	Lifetime probability	Probability of death	Mean age of onset
Coronary disease	46%	31%	74 yrs
Breast cancer	10%	3%	69 yrs
Hip fracture	15%	1.5%	79 yrs
Endometrial cancer	2.6%	0.3%	68 yrs

Lifetime probability of disease in 50 yo woman (*Grady D. Ann Int Med 1992; 11:1016*.)



Col et. al. JAMA 1997;277:1140-1147.

Women's Health Initiative

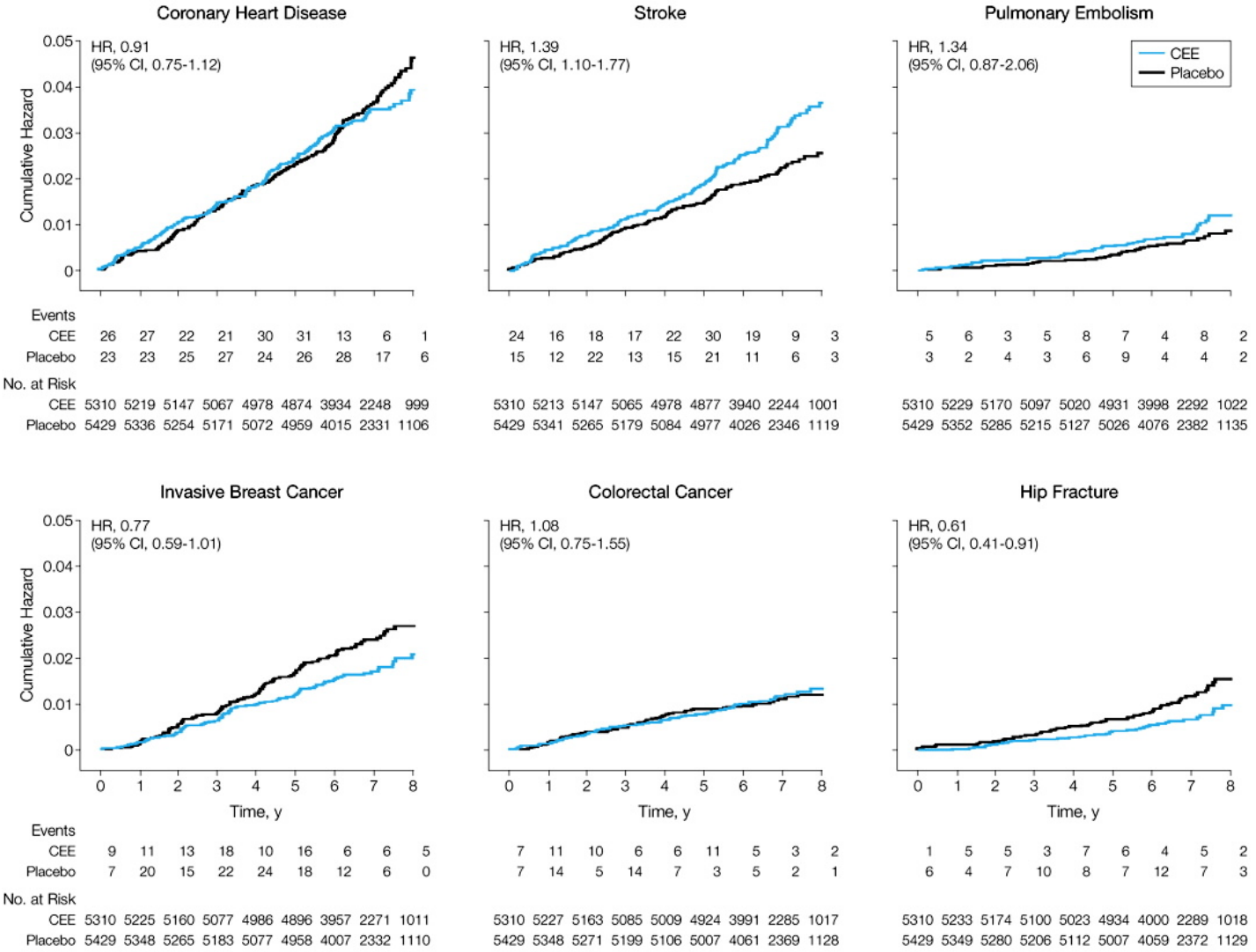
- Multi-center RCT
- Age 50-79 (mean 63)
- 16,608 women in EPT arm
  - Prempro 0.625 mg CEE 2.5 mg MPA
  - Terminated early 2002 (planned 2005)
- 10,739 women s/p hysterectomy
  - 0.625 mg CEE
  - Terminated early 2004

WHI Excess Risk

- 7 more women/10,000 person years with CHD
- 8 more women/10,000 person-years with stroke
- 8 more women/10,000 person-years with PE
- 8 more women/10,000 person-years with breast CA
- 6 fewer women/10,000 person-years with colon CA
- 5 fewer women/10,000 person-years with hip fx

JAMA 2002;288:321-333

WHI Estrogen Only



JAMA 2004;291:1701.

WHI Update 2013

	Combination E+P	Estrogen only
CAD	Increased in trial, neutral in f/u	Neutral
Breast CA	Increased risk	Decreased risk (HR 0.79)
CVA	Increased in trial, neutral in f/u	Increased in trial, neutral in f/u
PE	Increased in trial, neutral in f/u	Increased in trial, neutral in f/u
Colon CA	Decreased in trial, neutral in F/U	Neutral
Endometrial CA	Neutral in trial, decreased in f/u	N/A
Hip fracture	Decreased risk	Decreased risk

JAMA 2013

The Timing Hypothesis

	Started >10 yrs after	Started > 10 yrs after
Death	0.70 (0.52-0.95)	1.06 (0.95-1.18)
Coronary heart dis	0.52 (0.29-0.96)	1.07 (0.96-1.20)
Stroke	1.37 (0.80-2.34)	1.21 (1.06-1.38)
VTE	1.74 (1.11-2.73)	1.96 (1.37-2.80)

Cochrane 2015:

HT and Breast Cancer

- Prolonged endogenous estrogen exposure increases risk
- Progestin likely confers additional risk
- Continuous progestin likely safer than cyclic progestin
- 7% decline in breast cancer incidence likely linked to declining HT prescribing

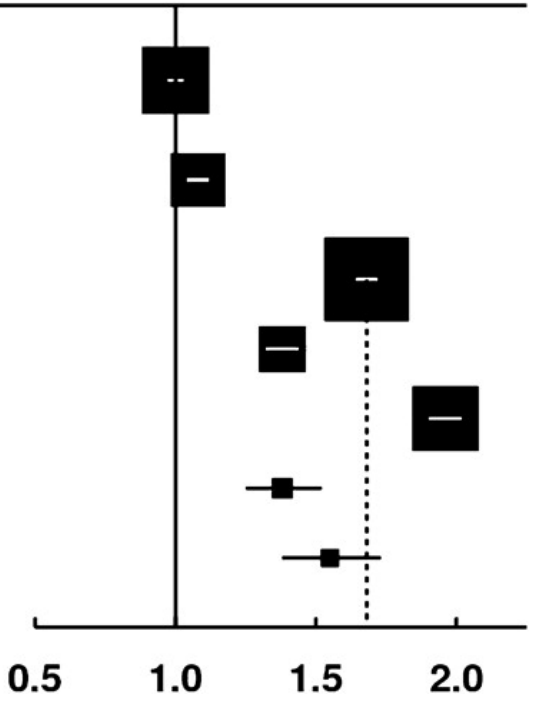
WHI and Breast Cancer

- Women on estrogen/progestin had:
  - Greater risk of breast cancer (HR 1.24)
  - Larger tumors
  - More likely node positive (25.9 vs. 15.8%)
  - Greater risk of regional and distant metastases (25.4% vs. 16%)
  - Higher mortality
  - Greater risk of abnormal mammograms requiring follow-up

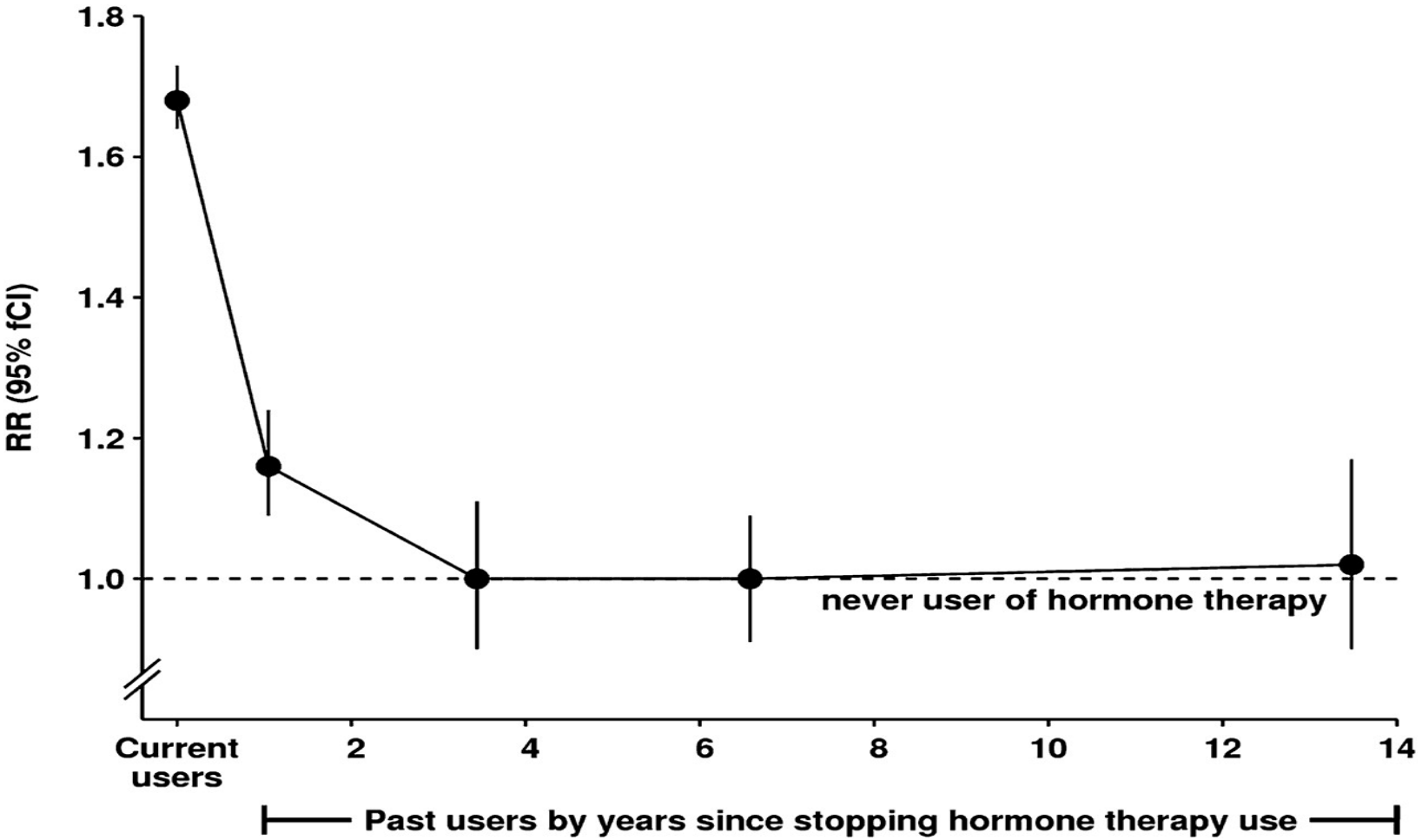
Chlebowski RT et al. *JAMA* 2003, 2010

Breast Cancer and HT: Million Women Study

Last reported use of hormone therapy	Years of hormone therapy use*	No. Cases†/ Population (1000s)	RR (95% fCI)
Never user	-	**6127/513.3**	**1.00 (0.97 to 1.03)**
Past user	**3.7**	**2525/221.1**	**1.08 (1.04 to 1.12)**
Current user	**7.2**	**7107/394.7**	**1.68 (1.64 to 1.72)**
Estrogen-only	8.0	2131/151.0	1.38 (1.32 to 1.44)
Estrogen + progestin	6.8	4292/200.6	1.96 (1.90 to 2.02)
Tibolone	7.0	383/23.7	1.38 (1.25 to 1.52)
Other/unknown	7.4	301/19.3	1.55 (1.38 to 1.73)



Past Users in Million Women Study



Beral V et al. JNCI J Natl Cancer Inst 2011;103:296-305

Breast Cancer Patients

- Non-hormonal treatments for vasomotor symptoms
- Try non-hormonal treatments first for urogenital symptoms
- Consider vaginal estrogen in consultation with oncology

Raloxifene

- Selective estrogen receptor modulator (SERM)
- Increases bone density at spine, hip and total body; somewhat less effect than HRT or alendronate
- Decreased risk vertebral fractures 0.7 RR
- No risk of endometrial hyperplasia or cancer
- Decreased risk of breast cancer with RR of 0.24
  - Risk reduction only for ER positive breast cancer
  - Risk reduction related to endogenous estrogen levels
- Lowers LDL cholesterol but not CAD risk
- Increased risk of thromboembolism RR 2.1-3.1
- Hot flashes are major side effect

Breast Cancer Chemoprophylaxis

- 5 yrs tamoxifen vs raloxifene in STAR trial; ~20,000 high risk women
- Lower risk breast cancer with both but tamoxifen superior; similar risk fracture
- Lower risk endometrial cancer and hyperplasia, VTE, cataracts with raloxifene
- ASCO recommends discussion of chemoprophylaxis if Gail risk >1.66 or LCIS
- USPSTF recommends if Gail risk >3.0

Vogel *JAMA* 2006;295:2727

Selective Estrogen Receptor Modulators

	Indication	Breast	Uterus	Vagina	Bone	VTE
Tamoxifen	Breast CA prevention	-	+	neutral	+	RR 2.0
Raloxifene	Breast CA prevention	-	neutral	neutral	+	RR 2.0
Ospemifene	Atrophic vaginitis	?	weakly +	+	+	
Bazedoxifene	Uterine protection	?-	-		+	

National Guidelines

	For symptoms	Prevention
USPSTF 2012		No; excludes surgical menopause <50
NAMS	Acceptable <60 2012 Extends to >65 2015	Prevention of fractures started before age 60
ACP 2014	Lowest effective dose 2-3 years	
ACOG 2014	Lowest effective dose for shortest period	
Cochrane 2015		Little if any benefit overall; increase in risk of stroke, VTE

The bottom lines…

- Don't use HT for 1º or 2º prevention
- Can use HT for vasomotor sx
  - Lowest dose (estradiol 0.5 mg), shortest period
  - Use progestin if uterus present
  - Breast cancer correlates with years of HT
- Ask about sex life, urination, mood
  - Only 7% of menopausal patients reported being asked about sex life in Revive study
- Assess risks for cardiovascular disease, osteoporosis, breast cancer
- Consider breast cancer chemoprophylaxis if high risk

Unanswered Questions

- Is quarterly cycling with progesterone or progestin IUD as safe for endometrium as monthly cycling?
  - probably but not proven
- Is progesterone required for endometrial protection with very low dose estrogen?
  - No guidance on lowest estrogen dose that would not require progestin
- Is estradiol safer than conjugated equine estrogen?
- Is topical safer than oral estrogen?
  - Maybe, but we await full data from KEEPS Trial

Your Questions?

Ovulation in perimenopause

- SWAN (Study of Woman Across the nation)
- 804 women age 42-52 with at least 1 period past 3 months

Menstrual cycle length	anovulatory cycles
<21 days	44%
21-35 days	8%
>35 days	65%

Van Voorhis, Obstet Gynecol 2008

Vaginal Estrogen and Systemic Absorption

Preparation	Released dose	Serum Estradiol Levels
Estring	7.5 ug released qd	5-10 pg/ml
Vagifem	10 ug	3-11 pg/ml
Estrace	200 ug	80 pg/ml
Women on aromatase inhibitors		3-7 pg/ml
Women on no meds		Generally <10 pg/ml

North American Menopause Society 2013