Update and ~~Controversies~~ on Hormone Therapy

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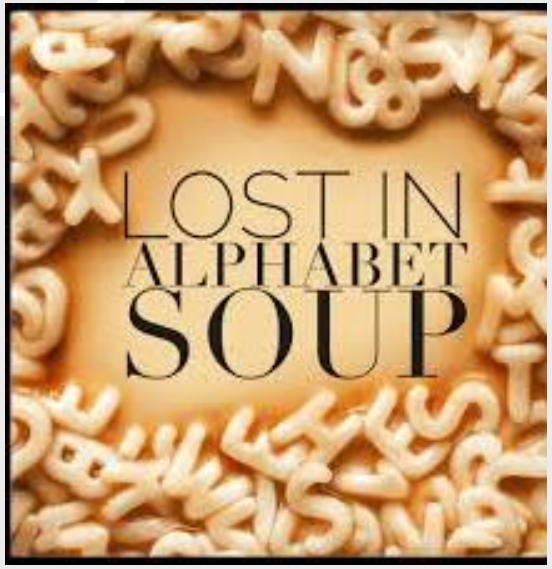
Objectives

- Overview data surrounding hormone therapy
- Identify individualized hormonal treatment options for women with vasomotor symptoms
- Identify individualized treatments for Genitourinary syndrome of menopause (GSM)

Shorthand for abbreviations

HT	• Hormone therapy
E+P	• Estrogen + progesterone • Needed for women with uterus
E2	• Estradiol • “bioidentical”: naturally produced in the body
CEE	• Conjugated equine estrogen (CEE/MPA = Prempro®)
MPA	• Medroxyprogesterone acetate (Provera®)
GMS	• Genitourinary syndrome of menopause • Previously referred to as vulvovaginal atrophy



Case 1: Marion

54yo with worsening hot flashes (now 6-7/day) and often wakes at night drenched in sweat; feels fatigued and irritable most of the time, “miserable”

PMH: HTN on HCTZ
SHx: quit tob 13yrs ago, +EtOH 3-5/wk
FHx: Mom had MI age 58
Gyne: No menses x1yr, normal prior; ++vaginal dryness

She is interested hearing about the safety of hormones…how should we counsel?

Menopause

Clinical Diagnosis: >45, no menses x1y

- No need for testing hormone levels
- Symptoms persist longer than previously thought
  - —median 7.4 years post-menopause
  - Menstrual changes
  - Vasomotor symptoms—75% will experience
  - Genitourinary symptoms—progressive

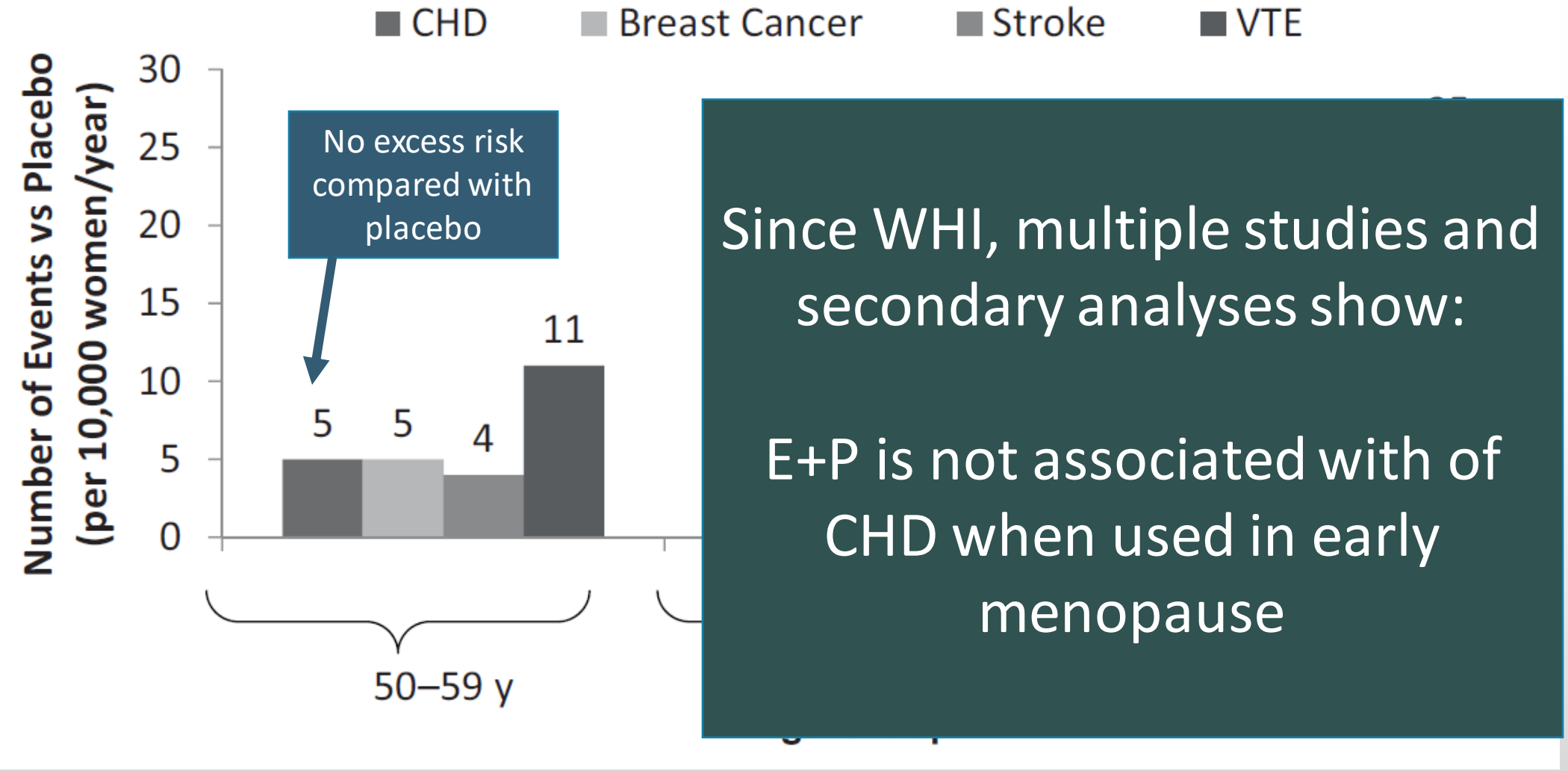
SWAN, JAMA Intern Med 2015

WHI Results—RCT of hormones on primary prevention of disease

	Trial ran 5.6y		Trial ran 7.2y	
	E+P vs. Placebo	**Hazard Ratio**	**E only vs. Placebo**	**Hazard Ratio**
CHD	164 vs 122	1.29	177 vs 199	0.91
Stroke	127 vs 85	1.41	158 vs 118	1.39
DVT/PE	151 vs 67	2.13	101 vs 78	1.33
Breast CA	166 vs 124	1.26	94 vs 124	0.77
Colon CA	45 vs 67	0.63	61 vs 58	1.08
Hip Fracture	44 vs 62	0.66	38 vs 64	0.61
Death	231 vs 218	0.98	291 vs 289	1.04

Rossouw et al, 2002; Anderson et al, 2004.

WHI E+P—absolute risks by age



Since WHI, multiple studies and secondary analyses show:

E+P is not associated with of CHD when used in early menopause

Rossouw, et al. JAMA. 2007

Gurney EP, et al. J Ster Biochem. 2014

HT and Long-term CV Mortality

- Women from WHI were followed for ~18 years
- HT was not associated with risk of cardiovascular mortality during a follow-up

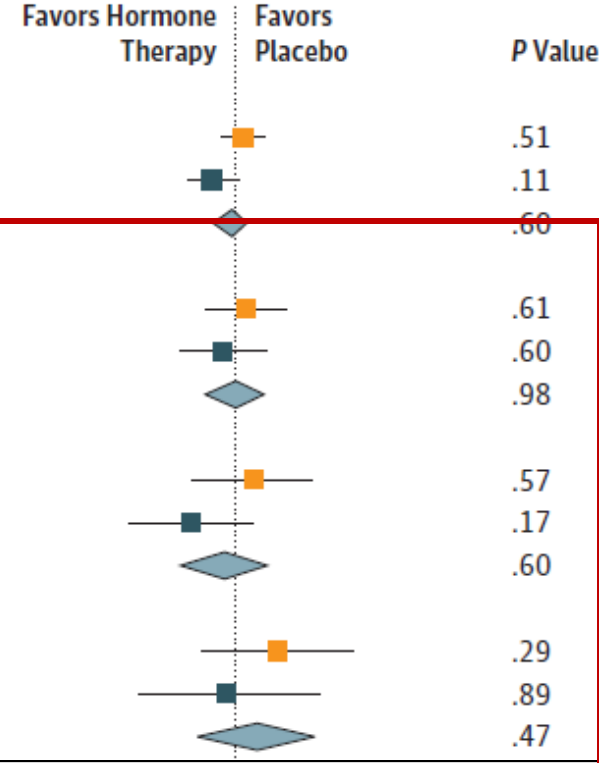
Recall amount of time women on hormones during WHI:

- CEE/MPA 5.6 years
- CEE alone 7.2 years

CEE/MPA aged 50-59: no sig risk

CEE alone: no excess risk

End Points	No. of Deaths, Annualized Rates (%) Hormone Therapy	Placebo	HR (95% CI)	*P* Value
All-cause mortality				
CEE plus MPA vs placebo	2244 (1.58)	2110 (1.57)	1.02 (0.96-1.08)	.51
CEE alone vs placebo	1505 (1.73)	1630 (1.83)	0.94 (0.88-1.01)	.11
Pooled trials			0.99 (0.94-1.03)	.60
CVD mortality[a]				
CEE plus MPA vs placebo	688 (0.49)	644 (0.48)	1.03 (0.92-1.15)	.61
CEE alone vs placebo	547 (0.63)	577 (0.65)	0.97 (0.86-1.09)	.60
Pooled trials			1.00 (0.92-1.08)	.98
CHD mortality				
CEE plus MPA vs placebo	310 (0.22)	285 (0.21)	1.05 (0.89-1.23)	.57
CEE alone vs placebo	240 (0.28)	277 (0.31)	0.89 (0.75-1.05)	.17
Pooled trials			0.97 (0.86-1.09)	.60
Stroke mortality				
CEE plus MPA vs placebo	188 (0.13)	161 (0.12)	1.12 (0.91-1.38)	.29
CEE alone vs placebo	126 (0.14)	132 (0.15)	0.98 (0.77-1.26)	.89
Pooled trials			1.06 (0.90-1.24)	.47



Manson, et al. *JAMA*. 2017

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This patient can be offered hormones
-no increased CV risk in first 10 years of menopause

Case 2: Eleanor

50yo with terrible hot flashes, feeling extremely irritable and is often short-tempered with her colleagues.

PMH: Hypothyroid, G3P2—first birth @32yo
PSH: Hysterectomy for fibroids
SHx: ~2 drinks/month
FHx: maternal aunt with breast cancer age 58
Gyne: Last period was 11 months ago

She is interested hearing about the safety of hormones…how should we counsel?

Menopause, Hormones, and Breast Cancer

Women with a *personal* history of breast cancer are NOT candidates for hormones

Hormones and Breast Cancer

- Women at high risk for breast cancer are not optimal candidates for systemic HT for hot flashes
- http://www.cancer.gov/bcrisktool
  - >1.7% is considered high risk for breast cancer
  - **This patient is not at high risk**

In WHI:

- E+P increased breast CA after 5 yrs
- E alone had no increased risk

- Some effect on breast cancer risk from progestin
  - Does type matter?

Use of HT and Risk of Breast Cancer: UK Primary Care databases

Large case control studies from a primay care database

- In women aged 50–59 who used HT for ≥5 years
  - E+P: attributable risk = 15/10,000 woman-years
  - ET: attributable risk = 3/10,000 woman-years

- E+P users → risks were similar regardless of type of progesterone or estrogen
  - Also regardless of dose or route (oral vs. transdermal)

- Vaginal estrogen was not associated with risk

Taken together with WHI, this study clarifies that most of the excess risk for breast cancer seen with HT relates to E+P

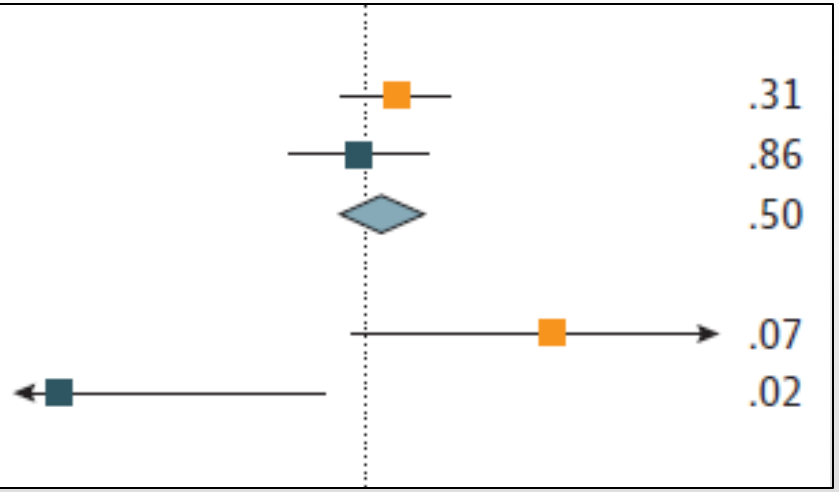
Vinogradova et al. BMJ 2020.

HT and Long-term Breast Cancer Mortality

- Women from WHI were followed for ~18 years
- HT was not associated with risk of *cancer* mortality

  Recall amount of time women on hormones during WHI:
  - CEE/MPA 5.6 years
  - CEE alone 7.2 years

Cancer mortality				
CEE plus MPA vs placebo	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
Breast cancer mortality				
CEE plus MPA vs placebo	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			NR[b]	



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This patient can be offered hormones and only needs estrogen

-Breast cancer risk increases particularly after 5 years, risk is tiny for estrogen alone

Case 3: Cynthia

53yo with extreme mood lability, her depression was previously well controlled. Terrible night sweats interrupting her sleep.

PMH: Depression, G4P3—first birth @26yo, no complications with her pregnancies
SHx: n/a
FHx: Father had a blood clot, she is concerned
Gyne: Last period was 2 years ago

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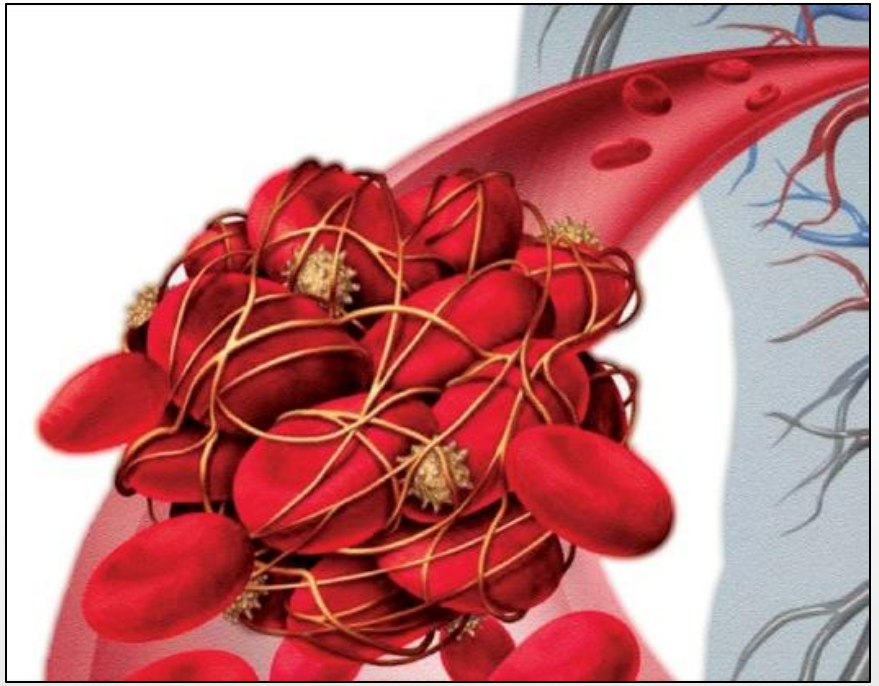
Menopause, Hormones, and VTE



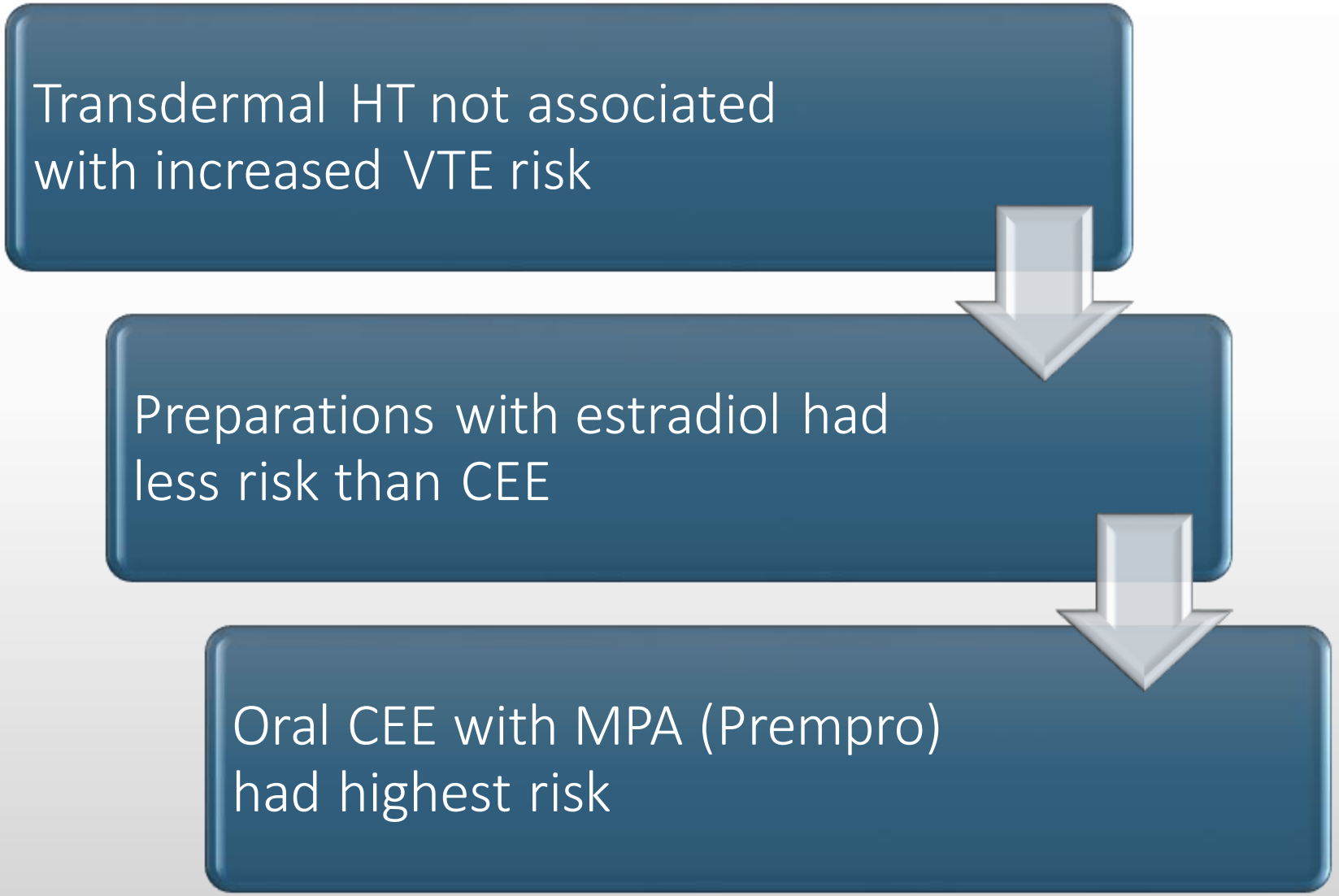
Women with a *personal* history of VTE are NOT candidates for hormones

Hormones and VTE

- Association between hormones and VTE
  - Rates vary with type of hormone
- Overall ~2x risk of VTE, but depends on type
  - Oral CEE > Oral estradiol > transdermal estradiol
    - No risk of clot seen with transdermal estradiol
  - >1000 women on hormones to see 1 VTE
    - NNH oral estrogen: 1076

Vinogradova, et al. BMJ 2019.

Choosing the type of HT according to VTE Risk



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This patient can be offered hormones

-Transdermal hormones would be the safest option

Implications and Weighing Risks…

Heart

- Studies provide reassurance about the safety of HT if started early in menopause: not harmful, suggests may slow the progression of atherosclerosis

Breast Cancer

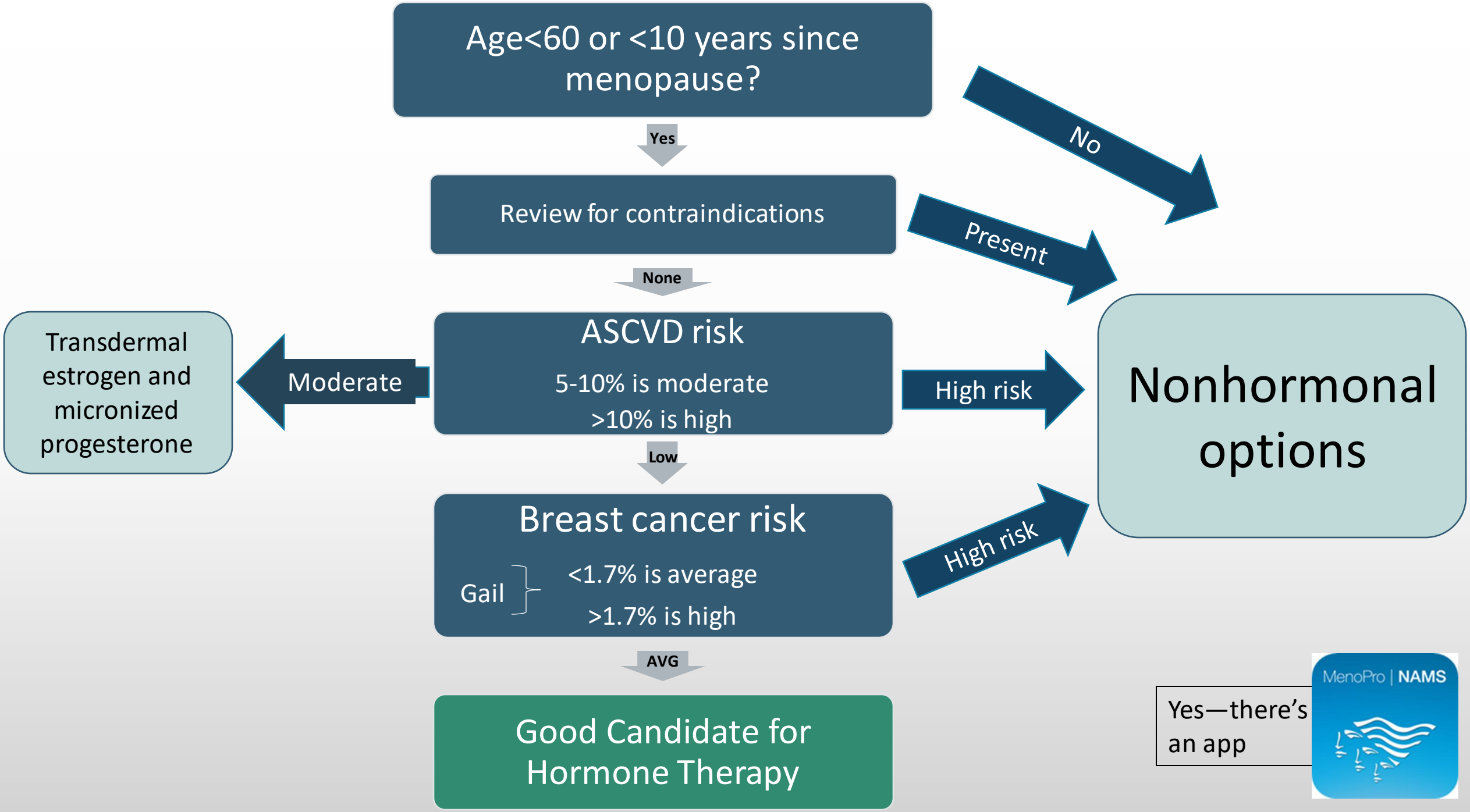
- E+P <5 years, absolute cancer risk is low ≈ 1 alcoholic drink/day
- E+P >5 years, cancer risk starts to increase ≈ 2 alcoholic drink/day
- E alone—tiny (or no) increased risk

VTE

- **Oral hormones** have a small risk for clot
  - CEE/MPA: ~5 clots seen in 1000 women on hormones for 5 yrs
  - E2 with micronized progesterone had lowest risk
- **Transdermal** E2 had no observed risk

Individualized decision should be based on risks for CVD, breast cancer, and quality of life

Refining choice of hormone therapy based on risks


Age<60 or <10 years since menopause?
Yes
No
Review for contraindications
Present
None
Transdermal estrogen and micronized progesterone
Moderate
ASCVD risk
5-10% is moderate
>10% is high
High risk
Nonhormonal options
Low
Breast cancer risk
Gail
<1.7% is average
>1.7% is high
High risk
AVG
Good Candidate for Hormone Therapy
Yes—there's an app
MenoPro | NAMS

Hormonal Therapy

My general approach when using hormones:

Transdermal estrogen

- Generally start 50mcg
- Start low, adjust up for symptoms
  - Option: oral E2

Micronized progesterone

- 100mg daily
  - Option: MPA 2.5mg daily

Or a Combo patch

Continuous regimen

- Typically amenorrheic
  - Consider cyclic early menopause

Ultimately cost drives choices… hormones are $$

Case 4: Vivian

62yo with dyspareunia and incontinence

PMHx: HTN, h/o stroke, diabetes, obesity

A1c today 7.2

Are there safety concerns for vaginal estrogen?

Vaginal Estrogen Use and Chronic Disease Risk --is it safe?

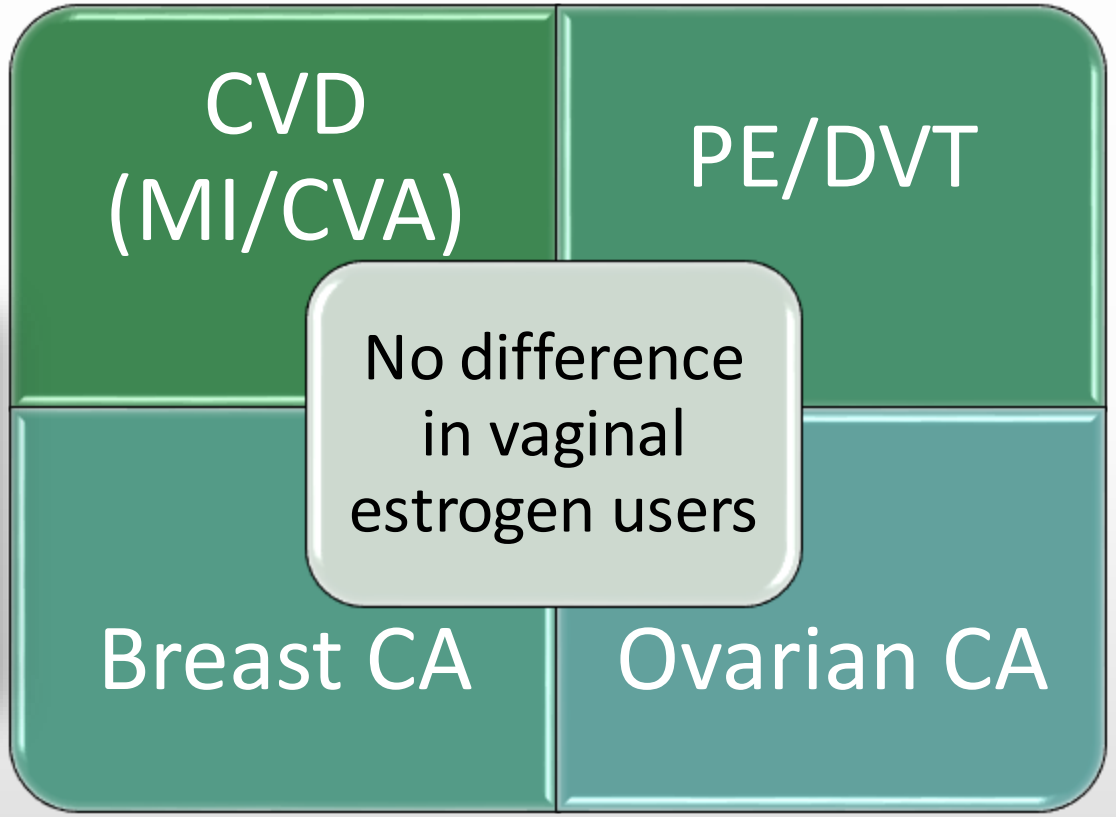
FDA black-box warning:

Risk of endometrial and breast cancer, cardiovascular disease, and probable dementia

Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 6, pp. 603-610
DOI: 10.1097/GME.0000000000001284

Vaginal estrogen use and chronic disease risk in the Nurses' Health Study

Shilpa N. Bhupathiraju, PhD,[1,2] Francine Grodstein, ScD,[1,3] Meir J. Stampfer, MD, DrPH,[1,2,3,4] Walter C. Willett, MD, DrPH,[1,2,3] Carolyn J. Crandall, MD, MS,[5] Jan L. Shifren, MD,[6] and JoAnn E. Manson, MD, DrPH[1,3,4]



Menopause, 2018

GSM: Vaginal Hormone Comparison

	Estrogen				DHEA
	Cream	Ring	Tablet		
Dose	0.5-1g	~7.5mcg qd	10 mcg	4mcg	6.5mg
Frequency	2-3x/wk	q 3mo	2-3x/wk		Nightly
Safety	No reports endometrial CA	No endometrial proliferation at 1yr	No reports endometrial CA		No impact on endometrium
Comments	Can achieve serum E2 in premenopausal range	$$$	Serum E2 level in menopausal range	$$$	Local conversion to estrogen
Length of use	Can be used indefinitely				?

Estrace
Premarin

Estring

Vagifem

Imvexxy

Prasterone
(Intrarosa)

No need for progesterone when used vaginally


WHAT'S NEW?

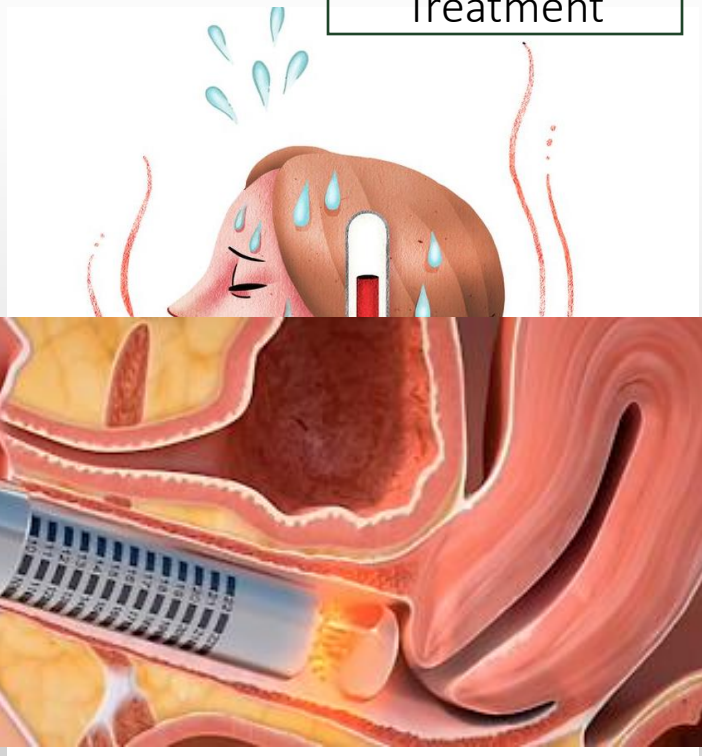
- Estrogen without progesterone?
  - Conjugated estrogen with bazedoxifene—Duavee™
    + Estrogen effects for vasomotor symptoms
    - Estrogen effect at breast/uterus
    - FDA approved for hot flashes, prevention of osteoporosis

SERM

New Systemic Treatment

New GSM Treatment

- Ospemifene
  - Oral SERM—targeting vaginal tissues
  - Reduces vaginal pain associated with sexual intercourse
  - Hot flushes were the most common AE



- MonaLisa Touch: fractionated CO2 laser
  - Promote blood flow, healthy tissue growth
    - Short term benefits, no long term studies
  - Not FDA approved for GSM

Summary: Hormones for Menopause Symptoms

Hormonal

Gold standard for vasomotor sx

No increase CV risk when started within 10y of menopause

Breast cancer risk increases at 5y

- Lowest effective dose, continuously
- Must use progesterone if uterus
- Ideally use transdermal

GSM

- **Screen** and treat!
- Vaginal estrogen or moisturizer
  - Vaginal estrogen cream/tablet most affordable
    2-3d/week only