

UPDATES IN MENOPAUSE: CARDIOVASCULAR RISK

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10/1/2024

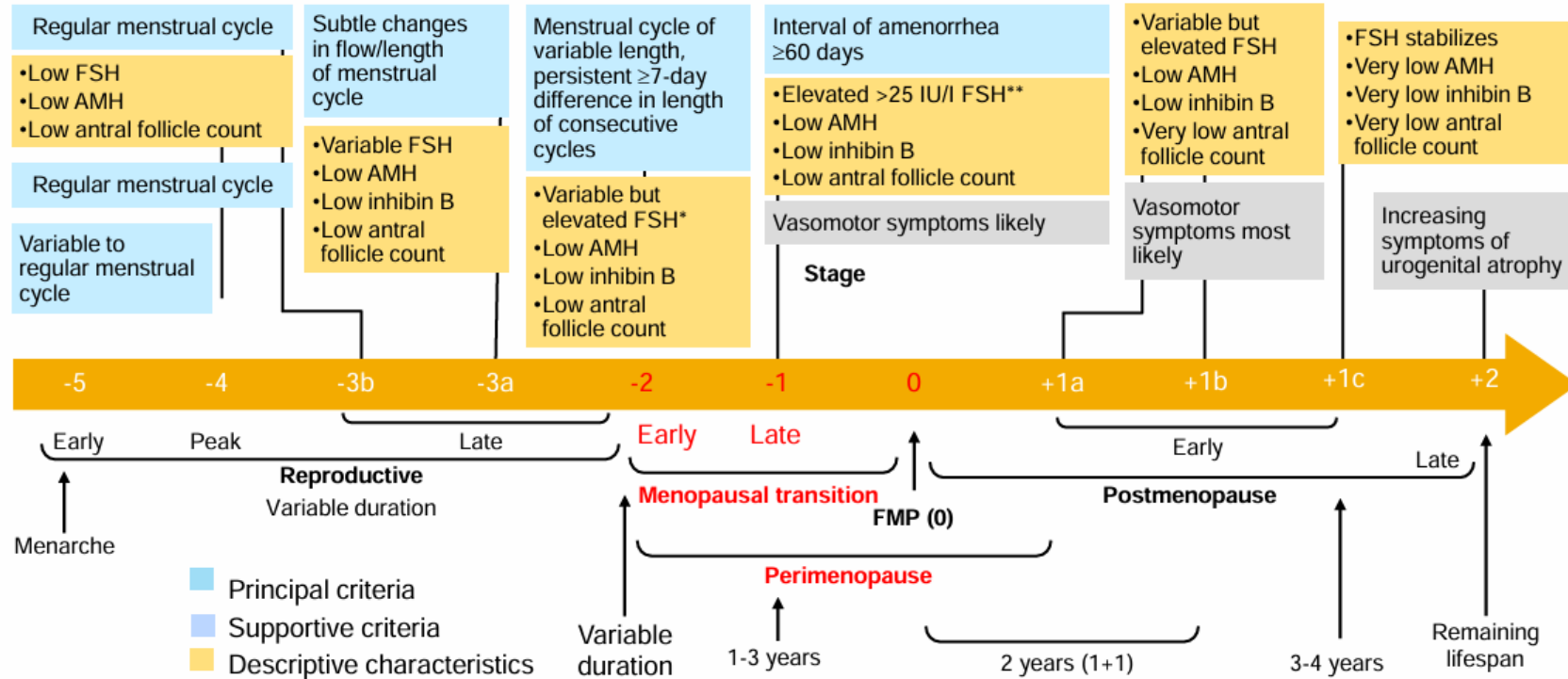
LEARNING OBJECTIVES

- 1. Review the cardiovascular and safety data of hormone therapy and contrast with historical data
- 2. Discuss how risk varies with type of estrogen and progestogen therapy, including MHT vs OCP
- 3. Discuss use of ASCVD and CAC score in menopausal women
- 4. Consider the innumerable ways that menopause affects health and wellness for women

I HAVE NO DISCLOSURES

MENOPAUSE DEFINED

THE STAGES OF REPRODUCTIVE AGE WORKSHOP (STRAW) +10 STAGING SYSTEM FOR REPRODUCTIVE AGE IN WOMEN



STRAW defined 7 stages ranging from the onset of menstrual cycles at menarche and the reproductive age to the perimenopausal and postmenopausal phases. Principal (menstrual cycle), supportive (biochemical and imaging), and descriptive (symptoms) criteria are used to characterize the phases. AMH indicates anti-Müllerian hormone; FMP, final menstrual period; and FSH, follicle-stimulating hormone. *Blood drawn on cycle days 2 to 5. **Approximate expected level based on assays using current international pituitary standard.

SYMPTOMS OF MENOPAUSE

- Anxiety
- Brain fog
- Depression
- Headaches/migraines
- Weight gain
- Period changes
- Skin/hair/nail changes
- Sleep issues
- Fatigue
- Heart palpitations
- Hot flashes
- Night sweats
- Joint pain
- Low libido
- Painful sex
- Incontinence
- UTIs

MHT

- Preferred term is MHT for menopausal hormone therapy
- In the past, we used “HRT” or hormone replacement therapy
 - This implied something was “missing” or abnormal
 - Replacing estrogen in POI = HRT
- Early estrogens were available in the 1900s, popularized in 1930 and 40s when ethinyl estradiol identified
- OCPs generally have MORE estrogen than MHT
 - However, often a good option in perimenopause
- PREMARIN approved in 1942 in USA
 - Still the only “natural” estrogen
 - Premarin is CEE- >10 different estrogens
 - NO progesterone

WHI: WOMEN'S HEALTH INITIATIVE

- Funded by NIH
 - largest women's study ever! >161K women
- Original trial had 3 parts
 1. Clinical trial: 64,000 women (50-79) RCT of drug vs placebo
 2. Observational study: 100,000 women
 3. Community prevention study
- Primary outcome: MHT as prevention of CVD, fractures
- Safety: monitor for increased breast cancer, endometrial cancer, blood clots, and dementia
- Other arms evaluated Calcium and D for prevention of fracture, dietary patterns in colorectal and breast CA risk

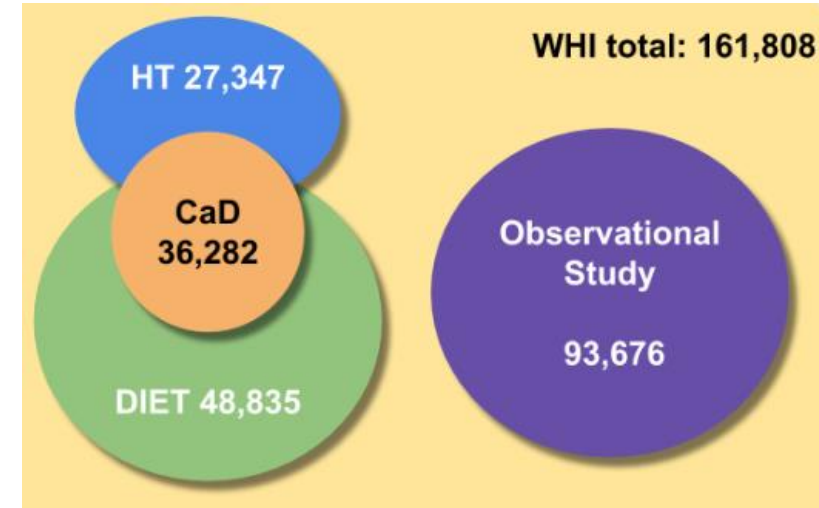
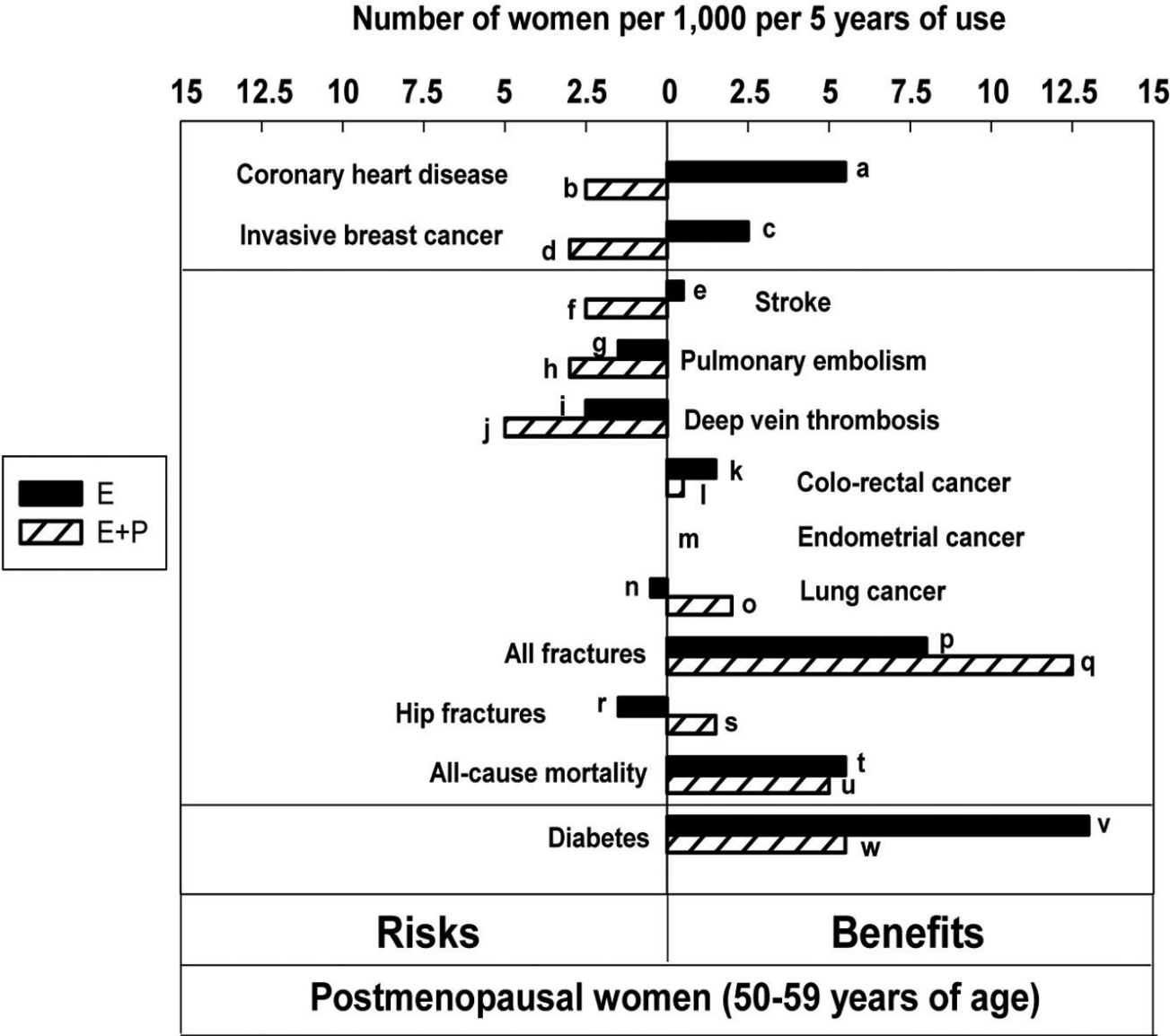
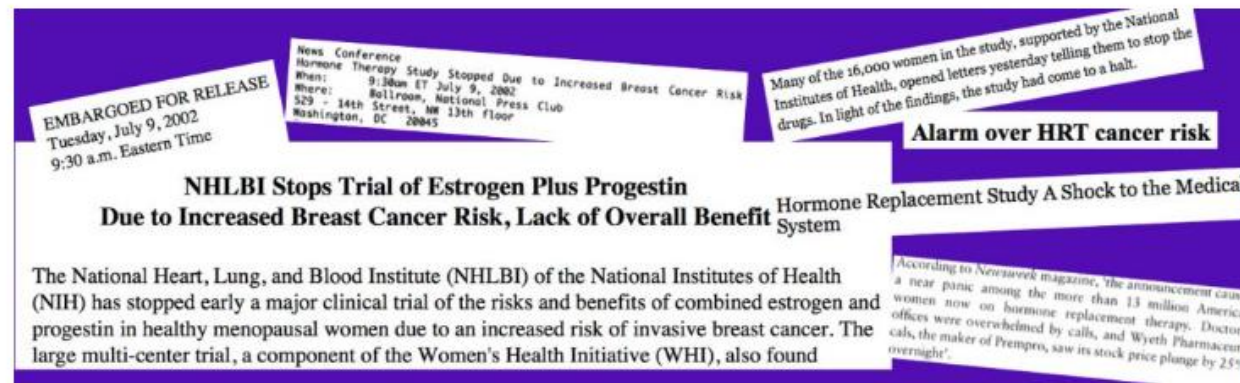


FIGURE 3. UPDATED SUMMARY OF THE EFFECTS OF ORALLY ADMINISTERED CEE ALONE OR COMBINED WITH MPA IN WOMEN AGES 50–59 ...





The drama of NIH's 2002 announcement that the estrogen plus progestin trial had been stopped early.

THE WHI & THE AFTERMATH

- The WHI was stopped early because it did not meet the primary outcomes
 - MHT for PREVENTION of CVD
 - Increased risk of stroke and breast cancer seen
- A press conference was held
 - EVERYONE stopped prescribing MHT
 - Women were told, “only for hot flashes” and for <5y
- However, there have been many sub-analyses
 - The average age of participants was 63 (leading to the “timing” hypothesis)
 - Women with VMS excluded
 - The use of CEE and MPA contribute (vs newer meds)

THE MHT RENAISSANCE & RISE OF CHARLATANS



SOCIAL MEDIA & THE RENAISSANCE

- This cannot be a GYN issue, all of us need to take responsibility for prescribing hormones
 - There are 10 FM & IM physicians for each OBGYN nationally
 - 50% of adults are female
- In the last few years, new evidence has lead to a “renaissance” of MHT
 - TikTokers claim all women should be on hormones, it is the “fountain of youth”
 - Influencers tout hormones, vitamins, testosterone pellets, vaginal steaming, and various other treatments



RED FLAGS OF INFLUENCERS

- There has been an explosion of menopause information on TikTok, with unfortunately LOTS of misinformation
- Lack of trust in the medical community, long waits for all care
- “I did my research”
 - Search engines are optimized for popularity, not scientific validity
 - Expensive up-front consultations
 - Selling supplements
 - Financial relationships (sponsored by pharma)
 - “gaslighting” and the true reality that women have historically been dismissed by medical professionals
 - Not a physician (chiropractors, others talking outside their scope)
 - They routinely recommend compounded hormones or pellets
 - They recommend routine lab draws



NAMS POSITION STATEMENT

The 2022 hormone therapy position statement of The North American Menopause Society

1. Vasomotor symptoms
2. Premature hypoestrogenism (POI, oophorectomy)
3. Genitourinary symptoms (GSM)
 - Vaginal preferred (FDA approved topical E and DHEA)
4. Prevention of bone loss

COMPOUNDED MEDICATIONS

- By definition are non-FDA approved.
- Often combine estradiol, estrone, DHEA, testosterone, estriol, progesterone based on prescription, mixed together in a specialized pharmacy.
- Often nonstandard application methods such as subdermal pellet, implant, or troches.
- Some prescribers use saliva, serum, urine testing to guide levels, which is not recommended due to unreliability
- Dearth of safety and efficacy data
- Issues with sterility, presence of impurities



1. VASOMOTOR SYMPTOMS

- Hot flashes negatively impact QoL and are linked with higher CV risk (SWAN)
- No drug works as well as E to improve VMS
- Symptom frequency reduced by 75%, as well as severity
- Lower doses (<0.5mg estradiol, 0.025mg estradiol patch) take 6-8 weeks
 - 0.014 patch works for VMS, but only FDA approved for osteoporosis prevention

2. PREMATURE HYPOESTROGENISM

- Premature menopause <40
 - Early menopause 40-45
- Causes can be genetic, autoimmune, toxic, metabolic, and iatrogenic (chemo, radiation, and surgery)
- Women with OI are at risk for AE
 - The earlier the BO, the higher the risk of CVD (7x higher for women <35)
 - Decreased QoL, Increased risk of fracture, CVD, Heart failure, DM, and increased mortality
 - Decreased persistent VMS, loss of fertility, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, increased risk of dementia, ophthalmic conditions, and depression (some is related to E deficiency, but also evidence of aging/shortened telomeres)
- HRT is recommended until age 52 minimum

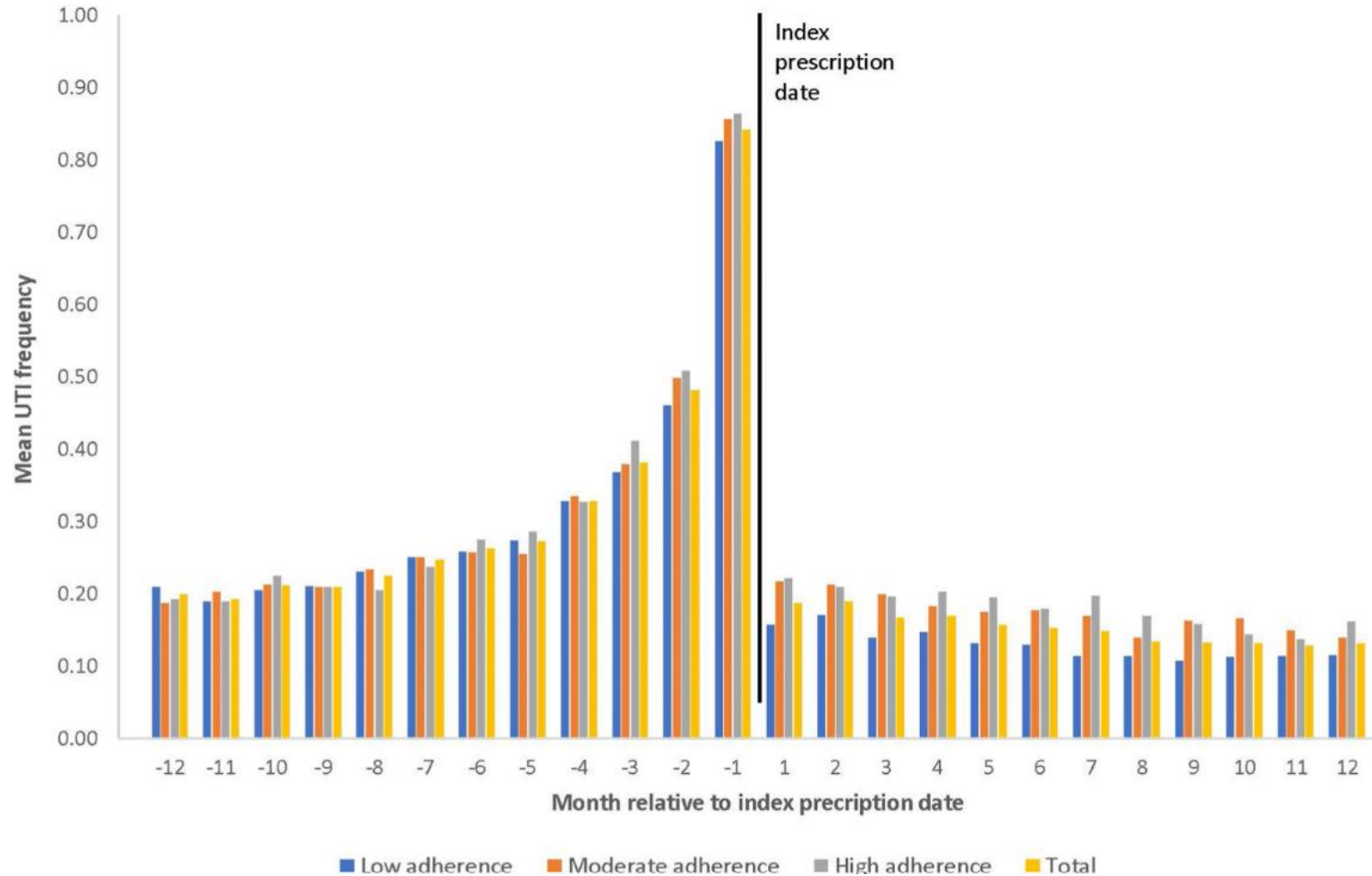
3. GENITOURINARY SYMPTOMS

- Estrogen deficiency causes changes to labia, vagina, urethra, bladder-including VVA
- Symptoms may include dryness, burning, irritation, pain with intercourse, urinary symptoms, frequent UTI, dysuria.
- Vaginal preparations do not differ in efficacy
 - Creams, tablets, softgel insert, vaginal ring
 - Insert into lower 1/3 of vagina (exc ring)
- ET increases vascularity around the urethra and bladder neck and ↓ frequency of detrusor contractions. ↓ incontinence
 - No evidence ET prevents pelvic organ prolapse

LOCAL HORMONAL OPTIONS

Brand names	Estrace	Imvexxy, yuvafem, vagifem	Intrarosa	Premarin	E-string
Mode	Cream	Insert/tablet	insert	Cream	Ring
Dose	0.01 mg/g estradiol	10mcg estradiol	6.5mg DHEA	0.625mg/g CEE	0.075mcg/d estradiol
Directions	1g nightly x 2 weeks, then 1g twice weekly	1 insert every night x 2 weeks, then 2x weekly	1 insert nightly	1g nightly x 2 weeks, then 1g twice weekly	Insert ring every 3 months
Pros/cons	-can be messy -can be moisturizing -Base can be irritating to some	Yuvaferm and Vagiferf come with applicators	-only androgen option -can be messy -can be moisturizing -helps vestibule	-can be messy -alcohol base can be irritating to some	‘Set it and forget it’

MEAN UTI FREQUENCY IN 12 MONTHS BEFORE AND AFTER VAGINAL ESTROGEN PRESCRIPTION



American Journal of Obstetrics and
Gynecology

Volume 229, Issue 2, August 2023, Pages 143.e1-143.e9



Original Research

Gynecology

Efficacy of vaginal estrogen for recurrent urinary tract infection prevention in hypoestrogenic women

The results of this study were presented at the 2022 scientific meeting of the American Urogynecologic Society and the International Urogynecological Association, Austin, TX, June 14–18, 2022.

Jasmine Tan-Kim MD, MAS ^a, Nemi M. Shah MD ^{a,b}, Duy Do PhD ^c,
Shawn A. Menefee MD ^a

Low adherence defined as no further refills after the index vaginal estrogen prescription. Moderate adherence defined as 1 refill after index prescription. High adherence defined as ≥ 2 refills after index prescription.

KIRK KORKORIAN
SCHOOL OF MEDICINE | UNLV

4. OSTEOPOROSIS

NAMS POSITION STATEMENT

Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society

- If we don't check, how can we treat?
- Screen women >65
- Who to screen early?
- Aged 50 and older with risk factors
 - Weight less than 127lbs or BMI <21
 - History of hip fracture in a parent
 - Current smoker
 - After discontinuation of estrogen
 - Those with medical conditions that might affect bone

NAMS POSITION STATEMENT

TABLE 3. *Common or important medications and medical conditions that can adversely affect bone health*

Medications	
Medications causing bone loss	
Aromatase inhibitors	Glucocorticoids for >3 mo
Thyroid hormone in excess	Immunosuppressive agents (eg, cyclosporine)
Gonadotropin-releasing hormone agonists or antagonists	Some anticonvulsants (eg, phenytoin)
Cytotoxic agents	Intramuscular medroxyprogesterone
Medications associated with increased fracture risk	
Proton pump inhibitors	Thiazolidinediones
SGLT2-inhibitors	Insulin with hypoglycemia
Selective serotonin-reuptake inhibitors	Selective norepinephrine-reuptake inhibitors
Medical conditions	
Genetic disorders	
Osteogenesis imperfecta	Hypophosphatasia
Thalassemia	Hemochromatosis
Endocrinopathies	
Gonadal insufficiency (primary and secondary)	Type 1 and type 2 diabetes mellitus
Hyperthyroidism	Primary hyperparathyroidism
Hypercortisolism, including Cushing syndrome	
Nutritional disorders	
Eating disorders	Obesity
Disorders of calcium balance	
Vitamin D deficiency	Hypercalciuria
Gastrointestinal diseases	
Malabsorption syndromes (eg, celiac disease)	Inflammatory bowel disease
Gastrectomy	Chronic liver disease
Other disorders and conditions	
Chronic renal disease	Systemic mastocytosis
Rheumatologic diseases (eg, rheumatoid arthritis)	Hematologic malignancies (eg, leukemia, multiple myeloma)
Frailty	Neuromuscular or visual impairment

SGLT2, sodium glucose cotransporter 2.

Cosman F, et al⁴; Camacho PM, et al.⁷

HOW TO TREAT WITH ESTROGEN

Method	Patch	Gel packet (Divigel)	Gel pump (Estrogel)	Ring (Femring)	Spray (Evamist)	Oral (Estrace)
Pros	Generic available; cheap; usually good absorption; many doses	Generic available; many doses	Dose flexibility without needing new product	Set it and forget it - 90 day ring; systemic AND local therapy	Dose flexibility without needing new product	Generic available; cheap
Cons	Local adhesive reactions are possible	Some do not absorb very well	Brand only (Estrogel)	Brand only (Femring); only 2 doses; sometimes need to supplement	Brand only (Evamist)	Higher blood clot risk; raises SHBG - bad for sexual health
Pharmacy	Any	Any	Any	Transition or any	Any	Any
Prior Auth?	Usually no	Usually no	Usually no	Yes, sometimes	Usually no	Usually no

CARDIOVASCULAR DISEASE

MENOPAUSE: AN OPPORTUNITY FOR PREVENTION

- Women develop heart disease a decade later than men
- Menopause transition is a period of accelerated CV risk
- In the US, 6000 women enter menopause every day
- The average lifespan for a woman in the US is 81, meaning half their life is spent in the post-menopause era



TIMING HYPOTHESIS



- Timing hypothesis
 - Early introduction of E beneficial, late is harmful
 - When to stop? Assess risk yearly
- Heart disease is the #1 cause of death for all Americans, including women, including women with breast CA!
- WHI showed CV risk is LOWER in women who started MHT within 10 years of menopause
 - Lots of large scale data from WHI and HERS (Heart E/P Replacement Study)

ESTROGEN & CV RISK- PRIMARY PREVENTION

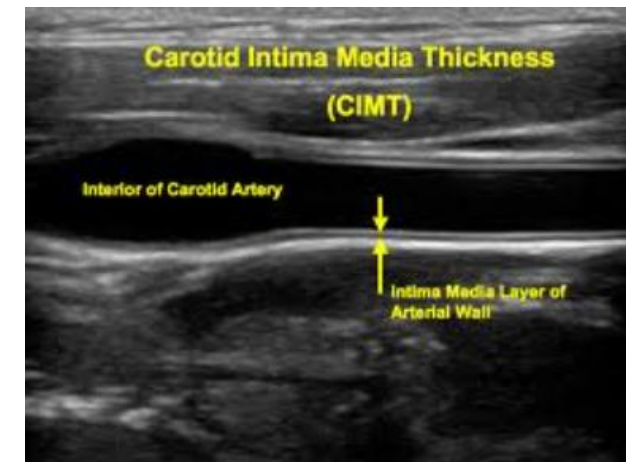


- Estrogen was always thought to be cardioprotective based on animal models and effects on lipids
- Lipids: E ↑ triglycerides, but improves TC, HDL and LDL
 - Transdermal E has no effect on cholesterol (good or bad)

- Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med*. 1991;325(17):1196-1204. doi:10.1056/NEJM199110243251702
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- WHI: Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333. doi:10.1001/jama.288.3.321

SECONDARY PREVENTION

- HERS 2763 women with KNOWN CVD, average age 67, randomized to CEE $\pm$ MPA or placebo.
 - Despite improvements in lipids, there was no difference in nonfatal MI or death from IHD during the 4y FU
 - However, an 50% increase in recurrent MI was noted in the treatment group during the first year
 - HERS II followed same group additional 3y, no evidence of CV protection
- ERA invasive angiography trial (mean age 63) with coronary artery stenosis $>30\%$ at baseline. At 3y, there was no change in luminal diameter between CEE $\pm$ MPA vs placebo)
- WAVE: women (mean age 65) with confirmed coronary artery stenosis to CEE $\pm$ MPA, vitamin C & vitamin E vs placebo. No benefit, possible harm.



PROGESTOGENS

- Prior to WHI there seemed to be no difference between progestogens
- WHI showed CV benefit in those on CEE alone, but ↑risk in those CEE & MPA
- There are no large scale RCTs evaluating progestogens, all data is observational
 - Risk of DVT MPA > MP (2010 French E3N), norethindrone > MP (ESTHER)
- Transdermal E no VTE risk
- Recommend MP (micronized progesterone) over MPA (medroxyprogesterone)

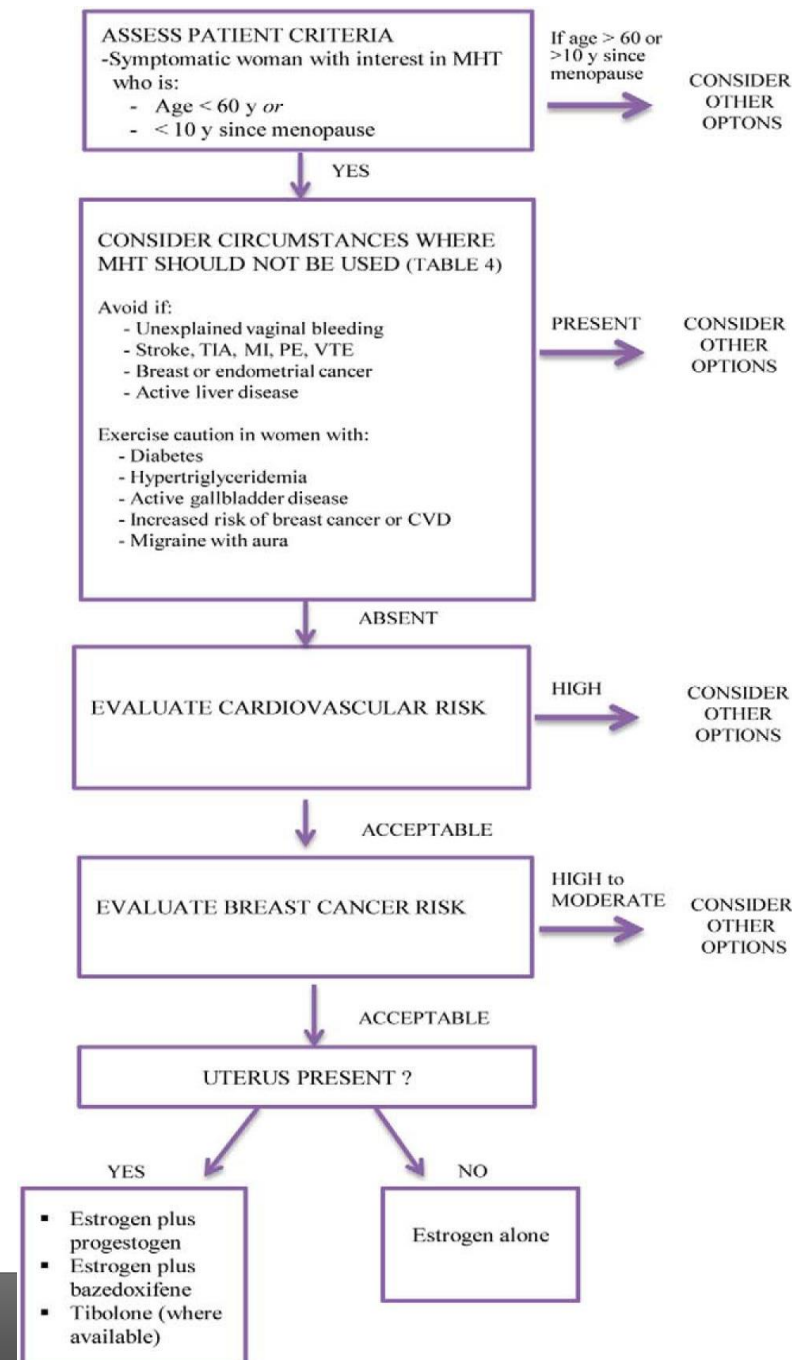


ROUTE OF DELIVERY

- There are no large-scale RCTs evaluating PO vs transdermal
- Oral estrogens undergo first-pass hepatic metabolism
 - Oral $\uparrow$ coagulation factors, $\uparrow$ CRP, $\uparrow$ TG, $\uparrow$ dose requirements since liver converts to estrone, resulting in increased concentration of E in the liver sinusoids
- Current guidelines (Endocrine society, NAMS, ACOG) recommend transdermal for intermediate ASCVD patients or those with $\uparrow$ VTE & ASCVD risk



FIGURE 2. APPROACH TO THE PATIENT WITH VMS CONTEMPLATING MHT. TIA, TRANSIENT ISCHEMIC ATTACK.



Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

Cynthia A Stuenkel¹, Susan R Davis¹, Anne Gompel¹, Mary Ann Lumsden¹, M Hassan Murad¹,
JoAnn V Pinkerton¹, Richard J Santen¹

Evaluating CVD Risk in Women Contemplating MHT

10-y CVD Risk	Years Since Menopause Onset	
	<5 y	6 to 10 y
Low (<5%)	MHT ok	MHT ok
Moderate (5–10%)	MHT ok (choose transdermal)	MHT ok (choose transdermal)
High (>10%) ^a	Avoid MHT	Avoid MHT

NON-HORMONAL TREATMENT

Non-hormonal options and their efficacy in the treatment of VMS.

Medication	Efficacy in Reducing HF Frequency vs. placebo
★ Paroxetine salt (7.5–25 mg)	40–50%
Escitalopram 10–20 mg	30–45%
Citalopram 10–20 mg	45–47%
Venlafaxine 75–100 mg	25–55%
Desvenlafaxine 100–150 mg	60–70%
Gabapentin 900–2400 mg	40–45%
Oxybutynin	25%
Clonidine	20–35%

2022 Jul;161:1-6. doi:

10.1016/j.maturitas.2022.01.016. Epub 2022

Jan 29

★ Fezolinetant: NEW approved 2023, 61% fewer hot flashes compared to placebo

- Neurokinin 3 receptor antagonist (NK3- aka KNDY neurons)

★ FDA approved for VMS

CONCLUSIONS

- More physicians should treat women with MHT
 - Vaginal estrogen for everyone!
- Systemic therapy indicated for POI, prevention of osteoporosis, and vasomotor symptoms
 - Local (& systemic) therapy indicated for GSM
- Personalized approach to prescribing MHT
- Recommend transdermal E as much as possible, micronized progesterone over MPA
- Evaluate CV risk using ASCVD calculator
- Evaluate annually to determine when risk outweighs benefit

REFERENCES

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- Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnika V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med*. 1991;325(17):1196-1204. doi:10.1056/NEJM199110243251702
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Secondary prevention

- HERS: Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998;280(7):605-613. doi:10.1001/jama.280.7.605
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