**When to Use Menopausal Hormone Therapy: Does It Still Have a Role**

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**Disclosures (Last 12 months)**

- Consultant
  - AstraZeneca
  - Health Diagnostic Labs

- Lecture Bureau
  - AstraZeneca
  - Merck

**Associations with Menopause**

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**EARLY Symptoms**

- Hot flushes
- Insomnia
- Irritability
- Mood disturbances

**INTERMEDIATE Physical changes**

- Vaginal atrophy
- Stress (urinary) incontinence
- Skin atrophy

**LATE Diseases**

- Osteoporosis
- Cardiovascular disease
- Dementia of the Alzheimer’s type
- Cancers
Recommendation: The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women and against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade D recommendation)."
CV Aspects of Estrogen Use in Peri and Early Menopause

Women’s Health Initiative Observational Study (WHI-OS)

- Early VMS were not associated with increased CVD risk
- Rather, early VMS were associated with decreased risk of stroke, total CVD events, and all-cause mortality
- Late VMS were associated with increased CHD risk and all-cause mortality
- The predictive value of VMS for clinical CVD events may vary with the onset of VMS at different stages of menopause

10 years of follow-up of over 60,000 postmenopausal women

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Quality of Life

- Although no HT product has government approval for enhancing QOL, use of HT can result in an improvement in health-related QOL (HQOL) in symptomatic women through the alleviation of symptoms
- There is no clear evidence that HT improves HQOL in asymptomatic women

Menopause 2012;19:257-271

American Association of Clinical Endocrinology 2011 Position Statement Position Statement on Diagnosis and Treatment of Menopause

FDA Indications for Estrogen

- Treatment of moderate to severe vasomotor symptoms (such as hot flashes and night sweats) associated with menopause
- This indication has not changed as a result of recently published studies that have questioned the safety of estrogen treatment of chronic conditions in postmenopausal women
- Estrogen-containing products are the most effective approved therapies for these symptoms

Endocrine Practice 2011;17 (Suppl 6) 1-25
American Association of Clinical Endocrinology
2011 Position Statement on Diagnosis and Treatment of Menopause

- FDA Indications for Estrogen
  - Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (such as dryness, itching, and burning) associated with menopause
  - When estrogen is prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal preparations should be considered

Endocrine Practice 2011;17 (Suppl 6) 1-25

American Association of Clinical Endocrinology
2011 Position Statement on Diagnosis and Treatment of Menopause

- FDA Indications for Estrogen
  - Prevention of postmenopausal osteoporosis
  - When MHT is being prescribed solely for the prevention of postmenopausal osteoporosis, approved nonestrogen treatments should be carefully considered
  - Estrogens and combined E+P products should be considered only in women with substantial risk of osteoporosis that outweighs the potential drug-related risks

Endocrine Practice 2011;17 (Suppl 6) 1-25

North American Menopause Society
2012 Hormone Therapy Position Statement

- Progestogen
  - The primary menopause-related indication for progestogen use is to negate the increased risk of endometrial cancer from systemic ET use
  - All women with an intact uterus who use systemic ET should also be prescribed adequate progestogen
  - With occasional exceptions (e.g., history of extensive endometriosis), postmenopausal women without a uterus should not be prescribed a progestogen with systemic ET

Menopause 2012;19:257-271
American Association of Clinical Endocrinology
2011 Position Statement on Diagnosis and Treatment of Menopause

**FDA Contraindications for Estrogen**

- Current, past, or suspected breast cancer
- Known or suspected estrogen-sensitive malignant conditions
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)

*Endocrine Practice 2011;17 (Suppl 6) 1-26*

American Association of Clinical Endocrinology
2011 Position Statement on Diagnosis and Treatment of Menopause

**FDA Contraindications for Estrogen**

- Active or recent arterial thromboembolic disease (angina, myocardial infarction)
- Untreated hypertension
- Active liver disease
- Known hypersensitivity to the active substances of MHT or to any of the excipients
- Porphyria cutanea tarda (absolute contraindication)

*Endocrine Practice 2011;17 (Suppl 6) 1-26*

American Association of Clinical Endocrinology
2011 Position Statement on Diagnosis and Treatment of Menopause

**Menopausal Hormone Therapy**

- The dose of estrogen should be the lowest amount necessary to provide relief from symptoms or bone protection, with consideration for the patient’s age (that is, reducing the dose with advancing age)
- Until the risk of any one product is clearly understood on the basis of scientific studies, each woman and her physician should choose the best MHT for her individually

*Endocrine Practice 2011;17 (Suppl 6) 1-26*
Prevalence and Incidence of Hormone Therapy by Formulation Since The Women's Health Initiative (WHI)

Overall prescribing of hormone therapy continued to decline during the past decade, suggesting a long-term impact of the Women’s Health Initiative findings and during this same time, treatment regimens shifted to favor vaginal and lower-dose oral formulations.

Steinkellner AR et al. Menopause 2012;19:616-621

American Association of Clinical Endocrinology
2011 Position Statement Position Statement on Diagnosis and Treatment of Menopause

Estrogen Therapies

► Transdermal administration of estrogen is preferred in certain clinical situations, such as in women with hypertension, hypertriglyceridemia, and increased risk for cholelithiasis and possibly to reduce the risk of thromboembolic disease.

► Although most authorities believe there is an absolute contraindication to the use of estrogen in women with a previous history of thromboembolic disease or in women with thrombogenic mutations, recent evidence suggests that transdermal administration of estrogen may be safe in those situations.

Endocrine Practice 2011:17 (Suppl 6) 1-25

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Menopausal Hormone Products Available in USA and Canada

ORAL
- Conjugate estrogen
- Synthetic conjugated estrogen
- Esterified estrogen
- 17β-estradiol
- Estradiol acetate
- Estrone
- Vaginal cream

PROGESTOGENS
- Medroxyprogesterone acetate
- Norethindrone
- Norethindrone acetate
- Megestrol acetate
- Progesterone (oral or vaginal)
- Levonorgestrel (IUD)
- Megestrol acetate

COMBINATION PRODUCTS
- Oral continuous-cyclic
- Oral intermittent-combined
- Transdermal continuous-combined
- Transdermal continuous-sequence (Canada)
- Patch
- Gel
- Emulsion
- Spray
- Vaginal cream
- Vaginal ring

Estrogen Therapies
Systemic review of RDBCT of menopausal women with at least 7 hot flashes per day and/or 50 per week: all used estrogen formulations below the equivalent dose of 0.05 mg of 17β-estradiol

Results were divided into 3 groups by decreasing estrogen doses:
- 0.037-0.045, 0.20-0.29 and 0.003-0.125
- Mean decrease in hot flashes was 9.36, 7.91 & 7.07 respectively
- Mean decrease in placebo groups was 5.07
- In the 8/9 trials estrogen vs placebo was < 0.05

There is strong evidence that low-dose transdermal estrogen at any dose is more effective than placebo in decreasing the daily number of moderate to severe hot flashes

Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use

In one RCT, tapering the dose of HT for 1 month and abruptly discontinuing HT had a similar impact on vasomotor symptoms

The decision to continue HT should be individualized based on the severity of symptoms and current benefit-risk ratio considerations

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Discontinuation of HT Use

- Vasomotor symptoms have an approximately 50% chance of recurring when HT is discontinued, independent of age and duration of use
- In one RCT, tapering the dose of HT for 1 month and abruptly discontinuing HT had a similar impact on vasomotor symptoms
- The decision to continue HT should be individualized based on the severity of symptoms and current benefit-risk ratio considerations
Heart and Estrogen/Progestin Replacement Study (HERS): Incidence of Nonfatal MI and CHD Death

Women with a documented history of coronary heart disease (CHD) at baseline

Those who reported vasomotor symptoms (16% of study) were 9 times more likely to experience CHD events during the first year of hormone therapy compared with women without VMS

Stuenkel C. Menopause 2011;18:593-595

CEE – MPA vs placebo

Hulley, et al. JAMA 1998; 280, 605-613

Heart and Estrogen/Progestin Replacement Study (HERS): Statin Use

Cumulative incidence of primary events (CHD death and nonfatal MI) according to baseline statin therapy and HRT treatment assignment

HRT use resulted in a significant increase in early risk for primary events in women not on statins but not in statin users.

Postrandomization statin use showed no effect of HRT on risk for the primary outcome


Heart and Estrogen/Progestin Replacement Study (HERS): Lp(a)

In the subgroup with lipoprotein(a) above the median, the hormone group tended to have fewer events than did the placebo group after a lag time of 1.5 years

On the contrary, for those with lipoprotein(a) levels below the median, the placebo group seemed to fare better for 2 to 3 years, and the 1-year value was P=.03, which suggests an unfavorable early hormone effect

CV Aspects of Estrogen Use in Peri and Early Menopause

**HT and Risk of CVD by Age & Years Since Menopause: The Women’s Health Initiative (WHI)**

Secondary analysis of both arms of the the Women’s Health Initiative (WHI) of 10,739 menopausal women who had undergone a hysterectomy randomized to CEE and 16,608 postmenopausal women who had not had a hysterectomy on CEE/MPA.

Women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion for statistical significance.

A similar non-significant trend was observed for total mortality but the risk of stroke was elevated regardless of years since menopause.

*Rossouw J et al. JAMA. 2007;297:1465-1477*

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**EDITORIAL**

Checking the pulse of the menopausal hot flash: feeling the heat and saving the beat

► A truly provocative finding of the WHI combined analysis was the revelation that *older women* (age, ≥ 70 y) who reported hot flashes (6% of patients) and were assigned to hormone therapy, experienced a 5-fold increased risk of cardiovascular events compared with symptomatic women assigned to placebo.

*Cynthia A. Stuenkel. Menopause 2011;18:593-595*

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**2010 Executive Summary: Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement**

**Coronary Heart Disease**

► Basic science, animal models, and observational studies support the hypothesis that MHT may prevent atherosclerosis and reduce CHD events. Level of evidence: B

► More recent subgroup analyses suggest that the lack of benefit or increase in CHD risk observed in the overall analysis of the WHI resulted from harmful effects of MHT in older women starting therapy many years after onset from menopause, a subgroup that contributed to a large percentage of events recorded in the WHI. Level of evidence: B

*Level B: likely to remain unchanged but with a lesser level of certainty*
CV Aspects of Estrogen Use in Peri and Early Menopause

Women's Health Initiative (WHI)

Coronary heart disease events in the Women’s Health Initiative hormone trials; effect modification by metabolic syndrome:
A nested case-control study within the Women’s Health Initiative randomized clinical trials

► Metabolic syndrome modified risk in those with CHD
► Women without Metabolic Syndrome had no increased risk with HT
► CHD risk was increased by 2.26; 95% CI 1.26-4.07) in HT users
► Results similar in EPT and ET trials
► CHD risk stratification is recommended before initiating HT

Kronos Early Estrogen Prevention Study (KEEPS)

► Objective: To assess atherosclerosis progression and CVD risk factors after Menopausal Hormone Therapy (MHT) initiated in early menopause in a randomized, controlled trial
► Participants: Healthy menopausal women aged 42 to 58 years between 6 and 36 months from last menses without prior CVD events who had a coronary artery calcium (CAC) score less than 50 Agatston units and had not received estrogen or lipid-lowering therapy for at least 90 days
► Intervention: Oral conjugated equine estrogens (o-CEE), 0.45 mg/d, or transdermal 17β-estradiol (t-E2), 50 mcg/d, each with 200 mg of oral progesterone for 12 days per month, or placebo for 48 months
► Measurements: Primary end point was annual change in carotid artery intima-media thickness (CIMT) and secondary end points included changes in markers of CVD risk

► The CAC score increased in only 3.0% and 1.5% fewer women receiving o-CEE and t-E2, respectively, compared with placebo
► When only women with a measurable baseline CAC score (1 Agatston unit) were considered, CAC progressed in 19% in the o-CEE group, 22% in the t-E2 group, and 26% in the placebo group with respective differences of 7 and 4 percentage points in this subgroup
► KEEPS had power to detect with confidence only on the order of a 50% difference


Thomas Dayspring MD, FACP
Kronos Early Estrogen Prevention Study (KEEPS)

- No changes in blood pressure were observed with o-CEE or t-E2
- LDL-C and HDL-C levels improved
- Levels of C-reactive protein and sex hormone-binding globulin but not interleukin-6 increased with o-CEE
- Insulin resistance decreased with t-E2
- Serious adverse events did not differ by treatment

Four years of early MHT did not affect progression of atherosclerosis despite improving some markers of CVD risk


Early versus Late Intervention Trial with Estradiol (ELITE)

- A 6 year, CIMT 2X2 double blind, placebo-controlled trial of 634 healthy menopausal women without CVD or diabetes randomized according to their time since menopause
- < 6 years, n = 271 or > 10 years, n = 372
- Women with a median interquartile range of 3.5 (1.9-5.0) and 14.3 (11.4-18.6) years since menopause received oral 17β estradiol 1 mg with vaginal micronized progesterone gel 4% (45 gm) 10 days per month in those with intact uterus vs placebos

Hodis et al. AHA Abstract 13283 Circulation 2014;130:A13283

Early versus Late Intervention Trial with Estradiol (ELITE)

- Rate of CIMT progression was significantly reduced with hormone therapy relative to placebo in the early but not the late postmenopausal group (p for interaction = 0.007)

Conclusion

The results of ELITE support the cumulative literature that suggests when HT is initiated at the time of menopause or early (within 6 years) after menopause that there is a significant reduction in CVD relative to no effect when initiated late (>10 years) after menopause

Hodis et al. AHA Abstract 13283 Circulation 2014;130:A13283
This finding may account for the absence of coronary protection conferred by estrogen in the randomized hormone trials. 

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CVD Conclusions  

► HT is currently not recommended for coronary protection in women of any age  
► Initiation of HT by women ages 50 to 59 years or by those within 10 years of menopause to treat typical menopausal symptoms does not seem to increase the risk of CHD events  
► There is emerging evidence that the initiation of ET in early postmenopause may reduce coronary artery disease and CHD risk.
10,101 postmenopausal women (mean age, 67.5 years) with CHD or multiple risk factors for CHD to 60 mg of raloxifene daily or placebo and followed them for a median of 5.6 years. The two primary outcomes were coronary events (i.e., death from coronary causes, myocardial infarction, or hospitalization or an acute coronary syndrome) and invasive breast cancer.

Raloxifene had no significant effect on the risk of primary coronary events (533 vs. 533 events)


Among the 3 prespecified age subgroups (≤ 65, 65 to < 70, and ≥70), the interaction P value was 0.29, hardly suggesting a difference by age. The authors changed their age breakdown to match those in the Women’s Health Initiative randomized trials. The estimated effect size is considerably greater in the subgroup < 65 (hazard ratio = 0.59) than it is in the subgroup > 65 (hazard ratio = 0.84) and very much greater than in the subgroup of women 10 years postmenopause (hazard ratio = 0.94).

► In women randomized in the WHI within 5 years of menopause, there were three additional strokes per 10,000 women per year of EPT, which is not statistically significant

► The excess risk of stroke in this age group observed in the WHI studies would fall into the rare-risk category
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Conclusions

Venous Thromboembolism

- MHT increases VTE risk approximately 2-fold. The VTE risk with MHT is multiplicative with baseline risk factors including age, higher BMI, thrombophilias, surgery, and immobilization. Level of evidence: A
- Based on observational, but not RCT, data, transdermal estrogen does not increase VTE risk. Level of evidence: C
- Raloxifene increases the incidence of venothrombotic episodes

*Level A: likely to remain unchanged  C: Tentative

J Clin Endocrinol Metab, July 2010, 95(Suppl 1):S1–S66

North American Menopause Society 2012 Hormone Therapy Position Statement

SUMMARY

- The benefit-risk profile is essential for every woman considering any HT regimen
- A woman’s interest in using HT will vary depending on her individual situation, particularly the severity of her menopausal symptoms and their effect on her QOL
- The absolute risks known to date for use of HT in healthy women ages 50 to 59 years are low
- In contrast, long-term HT or HT initiation in older women is associated with greater risks

Menopause 2012;19:257-271

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Menopause 2012;19:257-271
CONCLUSION
Leading medical societies devoted to the care of menopausal women agree that the decision to initiate hormone therapy should be for the indication of treatment of menopause-related symptoms.
Although research is ongoing and these recommendations may be modified over time, there is no question that hormone therapy has an important role in managing symptoms for women during the menopausal transition and in early menopause.