Historical Background
WHI E+P
ages 50-79
2002

Benefits

Risks

RR 2.05
RR 2.06
RR 1.23
RR 1.26
Average Age 63

Benefits

Risks

RR 1.23

RR 2.05

RR 2.06

RR 1.26
Women make a decision about menopausal hormone therapy shortly after menopause and commonly plan to use for about five years.
Definition of attributable risk

• Calculate underlying risk without MHT
• Determine risk with MHT
• Subtract the underlying risk from risk with MHT
• Express per 1000 patients using MHT for 5 years
CEE alone ages 50-59 with symptoms

Benefits

Risks

# per 1000 women over 5 years
CEE alone ages 50-59
with symptoms

Benefits

Risks

Annals Int Med 9-1-2019

# per 1000 women over 5 years
Where are we today?
“The treatment selected should be tailored to the individual patient”

“A fully informed patient should be empowered to make a decision”
**Approach to Menopause Guideline**

1.0 Definitions/Diagnosis

**Postmenopausal woman**
- < 60 y of age or
- < 10 y since menopause
Late perimenopausal

2.0 Health Considerations for All Women

3.0 VMS
Moderate or severe MHT: Patient interest (−) Contraindications

4.0 VMS
Moderate or severe MHT: Patient declines (+) Contraindications

5.0 VVA/GSM
Therapies:
- Local
- Systemic
Diagnosis of Menopause

- Women with uterus
  - Menopause is a clinical diagnosis based on cessation of menses for at least 12 months
- Women having undergone hysterectomy but not bilateral oophorectomy
  - Elevated FSH levels and estradiol concentrations <20 pg/ml on several occasions support but do not confirm the diagnosis
Approach to Menopause Guideline

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Therapies:
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- Systemic
General Recommendations

- address
  - bone health
  - smoking cessation
  - alcohol use
  - cardiovascular risk assessment and management
  - cancer screening and prevention
“Women without VMS and at significant risk of osteoporosis can discuss merits of MHT for bone preservation”
Approach to Menopause Guideline

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Postmenopausal woman
- < 60 y of age or
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Late peri-menopausal
Analysis of benefit versus risk

- Usual time to decide on MHT is shortly after menopause
- Consider risks and benefits for those 50-59 or < 10 years after menopause onset
- Assume use for 5 years
- Express all risks and benefits as attributable
- Use WHI post-hoc analyses
CEE plus MPA during intervention

Number of women per 1,000 per 5 years of use

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risks</th>
<th>Benefits</th>
</tr>
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<tbody>
<tr>
<td>Coronary heart disease</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0</td>
<td>12.5</td>
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<tr>
<td>All fractures</td>
<td>7.5</td>
<td>7.5</td>
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<tr>
<td>Hip fractures</td>
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<td></td>
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<tr>
<td>All-cause mortality</td>
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<tr>
<td>Diabetes</td>
<td>15</td>
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<tr>
<td>Deep vein thrombosis</td>
<td>12.5</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Colo-rectal cancer</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>0</td>
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Postmenopausal women (50-59 years of age)

Primary End points
Secondary End Points
Self-reported End point
CxEE alone during intervention

Number of women per 1,000 per 5 years of use

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<td></td>
<td></td>
<td>Colo-rectal cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial cancer (N/A)</td>
</tr>
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<td></td>
<td></td>
<td>Lung cancer</td>
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Risks

Benefits

Postmenopausal women (50-59 years of age)
Women’s Health Initiative:  
18 year cumulative follow-up age 50-59

- Overall mortality
  - CEE plus MPA vs placebo         HR 0.97 (0.83-1.14)  
  - CEE alone vs placebo            HR 0.79 (0.64-0.96)  
  - Pooled trials                   HR 0.89 (0.79-1.01)  

- CVD mortality
  - CEE plus MPA vs placebo         HR 0.99 (0.72-1.38)  
  - CEE alone vs placebo            HR 0.97 (0.65-1.44)  
  - Pooled Trials                   HR 0.98 (0.76-1.27)
Women’s Health Initiative: 18 year follow-up

Breast Cancer Mortality
- CEE plus MPA vs placebo HR 1.44 (0.97-2.15)
- CEE alone vs placebo HR 0.55 (0.33-0.92) **
Meta-analysis Conducted in Preparation of Clinical Guideline

- Is transdermal therapy associated with reduced risk of VTE when compared with oral estrogen therapies?
Veno-thrombotic episodes: Risk Ratio oral vs transdermal 1.63 (lower limit 1.40, upper limit 1.9, p<0.001)

Deep venous thromboses: Risk ratio 2.09 (lower limit 1.35, upper limit 3.23, p=0.001)

Conclusion: Low quality evidence from 14 observational studies suggests that compared to transdermal estradiol, oral estrogen therapy may be associated with increased risk of VTE, DVT, and possibly stroke, but not MI.
Does Transdermal estrogen increase risk of VTE?

- E3N study in Europe
- 80,308 postmenopausal women
- Never vs current use HR 1.1 (0.8-1.8)
- Conclusion: Transdermal estrogen probably does not increase risk of VTE but RCT required to confirm (Scientific Statement ES, JCEM 95 (suppl1):S7-66, 2010)
Approach to Patient with VMS
Considering MHT

Assess Patient Criteria
- Symptomatic woman?
  - Age < 60 y or
  - < 10 y since menopause
- Interested in MHT?

If age ≥ 60 y or ≥ 10 y since menopause
CONSIDER OTHER OPTIONS

YES
Approach to Patient with VMS Considering MHT

Consider circumstances where MHT should not be used:

- Contraindications
- Cautions
Contraindications

- No guidelines on MHT have listed contraindications
- Writing group decided to use the USA FDA listing
In general, estrogen therapy, should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of cancer of the breast
- Known or suspected estrogen-dependent neoplasia including endometrial cancer
- Active deep vein thrombosis, pulmonary embolism or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, myocardial infarction), or a history of these conditions
- Known anaphylactic reaction or angioedema in response to any ingredient in the medication‡
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders‡
- Known or suspected pregnancy
Caution should also be exercised in women with:

- Gallbladder disease (oral ET)
- Hypertriglyceridemia (> 400 mg/d) (oral ET)
- Diabetes
- Hypoparathyroidism (risk of hypocalcemia)
- Benign meningioma
- Intermediate or high risk of breast cancer
- High risk of heart disease
- Migraine with aura (oral ET)
- Other conditions §
Approach to Patient with VMS Considering MHT

- **EVALUATE CARDIOVASCULAR RISK**

- **ACCEPTABLE**

- **HIGH** *

- **CONSIDER OTHER OPTIONS**

  * Includes known CHD, CVD, PAD, etc.
Evaluate risk based on risk assessment method validated for your patient population

<table>
<thead>
<tr>
<th>10-yr CVD Risk</th>
<th>Years since Menopause Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 5 y</td>
</tr>
<tr>
<td>Low (&lt;5%)</td>
<td>MHT ok</td>
</tr>
<tr>
<td>Moderate (5 to 10%)</td>
<td>MHT ok (Choose Transdermal)</td>
</tr>
<tr>
<td>High** (&gt;10%)</td>
<td>Avoid MHT</td>
</tr>
</tbody>
</table>

Manson JE et al Menopause 2014
Canadian Cardiovascular Society calculations 2015
www.nrcresearchpress.com/apnm
Approach to Patient with VMS Considering MHT

- EVALUATE BREAST CANCER RISK
  - ACCEPTABLE
  - HIGH to MODERATE *
  - CONSIDER OTHER OPTIONS

* Includes calculated level of risk that would qualify for risk-reducing medications
ID:
Woman's age is 51 years.
Age at menarche was 14 years.
Age at first birth was 24 years.
Age at menopause was 51 years.
Height is 165 m.
Weight is 65 kg.
Woman has never used HRT.

Risk after 10 years is 6.8%.
10 year population risk is 2.6%.
Lifetime risk is 25.8%.
Lifetime population risk is 10.5%.
Probability of a BRCA1 gene is 0.04%.
Probability of a BRCA2 gene is 0.18%.
## Breast Cancer Risk Cutoffs for Counseling before Recommending MHT*

<table>
<thead>
<tr>
<th>Risk Category***</th>
<th>5-Year NCI or IBIS Breast Cancer Risk Assessment</th>
<th>Suggested Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 1.67 %</td>
<td>MHT ok</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.67 - 5 %</td>
<td>Caution†</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 5 %</td>
<td>Avoid</td>
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</table>

* Adapted from: Endocrine Society.
Approach to Patient with VMS Considering MHT

UTERUS PRESENT?

NO ➔ ESTROGEN ALONE

YES ➔

- ESTROGEN \textit{plus} PROGESTOGEN
- ESTROGEN \textit{combined with} BAZEDOXIFENE
- TIBOLONE \textit{where available}
New Therapeutic Approach

- Tissue selective estrogen complex (TSEC)
- Conjugated equine estrogens plus bazedoxifene
- Unique cDNA array signature
- Approved in USA and European Union
Most Developed TSEC

- Eliminates need for progestogen
- Randomized, placebo controlled trials in > 5000 women
- 85% reduction in hot flashes
- Relieves signs and symptoms of vulvo-vaginal atrophy
- Improves bone density
- No increase in endometrial hyperplasia or cancer
- No uterine bleeding
- No increase in VTE (insufficient power of data)
- No increase in cardio-or cerebrovascular disease (insufficient power of data)
- Improves quality of life score (MENQOL) p<0.001
# Approach to Menopause Guideline

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## 4.0 VMS
- Moderate or severe MHT: Patient declines 
  - (+) Contraindications

## 5.0 VVA/GSM
- Therapies: 
  - Local 
  - Systemic
Effects of drug vs placebo-number of hot flushes
Effects of drug vs placebo-composite of severity and number
**Approach to Menopause Guideline**

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Therapies:
- Local
- Systemic
Use vaginal as opposed to systemic estrogen if VVA only indication:

lower systemic estrogen levels result
Other Therapies for VVA

The SERM ospemifene

Effective therapy for relief of Vulvo-vaginal atrophy
Key Take Home Points:
Treatment of Menopausal Symptoms

- MHT is suggested therapy for relief of menopausal symptoms for appropriately selected patients.
- Effective relief of vasomotor symptoms can be achieved with non-hormonal prescription therapies.
- Vaginal and urinary symptoms are undertreated; local estrogen and a systemic SERM therapy are effective.
- Compared to oral estrogen, transdermal estrogen therapy appears to be associated with lower VTE risk.
- Individualize approach to initiation and continuation of MHT.
Unresolved Issues in Treatment of Menopausal Symptoms

- What are the best methods to assess CVD and breast cancer risk prior to MHT?
- Are some MHT preparations, doses, and routes of administration safer than others?
- What duration of MHT is safe?
- What are effects of MHT on prevention?
As the impact of severe menopausal symptoms on quality of life may be substantial, however, there are instances in which a woman with a history of coronary heart disease or breast cancer, for example, will choose to accept a degree of risk that might be considered to outweigh the benefits of MHT.

An accepted philosophy is that a fully informed patient should be empowered to make a decision that best balances benefits to that individual when weighed against potential risks.”
Thank you for your attention