Menopause and Hormone Therapy

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No Disclosures
Objectives

- Define menopause and review the clinical issues related to menopause
- Outline the indications and contraindications for hormone therapy (HT) use in postmenopausal (PM) women
- Provide an overview of the evidence as it relates to risks and benefits of HT use in PM women
- Become familiar with the timing hypothesis
- Be able to clinically apply a tailored approach to HT in your PM patient
Menopause

- Permanent cessation of menses
- Loss of ovarian follicular function with age
- Definition:
  - 12 months of amenorrhea (no pathological cause)
  - Natural vs. induced
  - No reliable independent biological marker
- Average age 51.2 yrs (range 40-58)
- Reproductive aging continuum STRAW
  - Early and late menopausal transition
  - Early and late postmenopause
  - Early menopause ≤ 45 yrs
  - Premature menopause < 40 yrs
Clinical issues during the Peri- and Postmenopausal

- Abnormal menses
- Sleep disturbance (38%)
  - Late perimenopause (45.4%)
  - Surgical menopause (47.6%)
- Hot Flashes
- Memory and concentration
- Mood changes (10%)
- Genitourinary symptoms (50%)
- Change in sexual function
- Weight gain
- Bone loss/osteoporosis
Vasomotor Symptoms

- The “Hot Flash”: sensation of heat or warmth with or without sweating

- Affect three quarters of women during peri/post menopause

- Median total duration 7.4 years (SWAN study) (African American women 10.1 years)

- 15-20% severe (interfere with daily activities)

- Women with mod-severe hot flashes average duration 10.2 yrs (Penn Ovarian Aging Study)
### VMS Treatment Options

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% Reduction of VMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone Therapy</strong></td>
<td>&gt; 90</td>
</tr>
<tr>
<td><strong>Venlafaxine</strong></td>
<td>60-75</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>50-60</td>
</tr>
<tr>
<td><strong>SSRI’s (fluoxetine, sertraline, paroxetine)</strong></td>
<td>50</td>
</tr>
<tr>
<td><strong>Vitamin E/Soy</strong></td>
<td>25</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>20-50</td>
</tr>
</tbody>
</table>

FDA-Approved Indications for Hormone Therapy

- Treatment of moderate to severe vasomotor symptoms
- Treatment of genitourinary syndrome of menopause
- Prevention of osteoporosis
Contraindications

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active or h/o VTE
- Active or recent (within past year) arterial thromboembolic disease (eg AMI, CVA)
- Liver dysfunction or disease
- Known or suspected pregnancy
- Known hypersensitivity to ingredients
Types of Hormone Therapy

- Bioidentical - compounds that have the same chemical and molecular structure as hormones that are produced in the body

- Oral

- Transdermal (patch, gel, spray)

- Vaginal (cream, ring, tablet)
Government Approved Hormone Therapy Products

<table>
<thead>
<tr>
<th>Hormone Therapy Formulations</th>
<th>Non-Patch Topical formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral tablets</strong></td>
<td></td>
</tr>
<tr>
<td>Conjugated equine estrogens (CEE)</td>
<td>Estrasorb™ (estrogen) ¹</td>
</tr>
<tr>
<td>Premarin® ¹,²</td>
<td>Estrogel™ (topical daily estrogen gel) ¹</td>
</tr>
<tr>
<td>Prempro™ ¹,²</td>
<td></td>
</tr>
<tr>
<td>Low Dose Prempro™ ¹,²</td>
<td></td>
</tr>
<tr>
<td><strong>Conjugated synthetic estrogens</strong></td>
<td></td>
</tr>
<tr>
<td>Cenestin® ¹</td>
<td></td>
</tr>
<tr>
<td><strong>17β-estradiol. (E₂)</strong></td>
<td></td>
</tr>
<tr>
<td>Micronized oral tablets</td>
<td></td>
</tr>
<tr>
<td>Estrace® ¹,²</td>
<td>Activella® (norethindrone acetate) ¹,²</td>
</tr>
<tr>
<td>Menest® ¹,²</td>
<td>Prefest™ (norgestimate acetate) ¹,²</td>
</tr>
<tr>
<td><strong>Transdermal patches</strong></td>
<td></td>
</tr>
<tr>
<td>Alora® ¹,²</td>
<td>CombiPatch® (estradiol combined with norethindrone acetate) ¹</td>
</tr>
<tr>
<td>Climara® ¹,²</td>
<td>ClimaraPro® (levonorgestrel) ¹</td>
</tr>
<tr>
<td>Estraderm® ¹,²</td>
<td></td>
</tr>
<tr>
<td>Vivelle® ¹,²</td>
<td></td>
</tr>
<tr>
<td>Esclim® ¹,²</td>
<td></td>
</tr>
<tr>
<td>Vivelle-Dot® ¹,²</td>
<td></td>
</tr>
<tr>
<td>Menostar® ¹,²</td>
<td></td>
</tr>
</tbody>
</table>

1- Systemic vasomotor symptom relief
2- Bone protection: specifically approved for osteoporosis prevention
The Women’s Health Initiative

- Randomized Controlled Trial of US postmenopausal women age 50-79
  - Average age 64 yrs
  - Average time since menopause 12 yrs
- Hysterectomized Arm: CEE 0.625mg/day or placebo - 5.6 years intervention
- Non-hysterectomized Arm: CEE 0.625mg+MPA 2.5mg/day or placebo - 7.2 years intervention
The Women’s Health Initiative

Limitations

• **CEE:**
  • More racially diverse
  • More distant from menopause
  • More likely had prior HT use (47.8% vs 36.2% EPT arm)
  • Less favorable CV profile
  • Average BMI higher (27.5 vs 29.2)

• **Detection bias:**
  • CEE+MPA: 44.4% unblinded during active therapy (placebo 6.8%)
  • CEE: 1.9% (placebo 1.6%)

Danish Osteoporosis Study

- First randomized controlled trial of recently menopausal women

- Average age 50 (45-58); time since menopause 7 months

- Hysterectomized arm: 2mg oral estradiol or placebo

- Non-hysterectomized arm: 2 mg oral estradiol + 1 mg norethisterone (NETA) or placebo

- Intervention stopped after 11 yrs following adverse outcomes of WHI

Benefits of HT: Bone Health

- WHI

- CEE+MPA:
  - Stat sig decreased risk of vertebral and non vertebral fractures (HR 0.76, CI 0.69-0.83)
  - Mean increase total hip BMD 3.7% after 3 yrs (p<.001)
  - Combined arms by end of trial
    - 33% overall reduction in hip fracture (HR 0.67, CI 0.46-0.96)

Cauley et al. JAMA 2003
Benefits of HT: Bone Health

- Large observational study that followed initial HT users over 6.5 years
- Those who stopped HT were at a 55% greater risk of hip fracture compared to women who continued HT
- The protective effects of HT disappeared as early as 2 years after cessation of treatment

Benefits of HT:
Bone Health

- **DOPS (Both arms):**
  - Significant reduction overall fracture risk  
    RR 0.61 (CI 0.39-0.97)
  - Significant reduction forearm fractures  
    RR 0.24 (CI 0.009-0.69)
Benefits of HT: Mortality

- Meta-analysis (Salpeter, et al)
  - 8 obs trials and 19 RCT
  - Younger women (avg age 54) on HT (vs non HT users)
  - 28% reduction in total mortality (RR 0.78, CI 0.52-0.96)
- WHI: 30% NS reduction in overall mortality HT use < 60
  - CEE (RR 0.71, CI 0.46-1.11)
  - CEE+MPA (RR 0.69, CI 0.44-1.07)
- DOPS: 34% NS reduction in overall mortality HT use
  - RR 0.66 (CI 0.41-1.08) after 16 yrs follow up
- Cost effective analysis (Salpeter et al)
  - Modeled 15 yrs of HT use (initiated age 50) vs no use
  - Gain of 1.49 QALY
  - Incremental cost of $2438 per QALY gained
Benefits/Risks of HT: CHD

- Observational studies:
  - 30-50% lower CV risk
- Observational studies vs Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Clinical Trials</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age or age range</td>
<td>&gt;63</td>
<td>30-55</td>
</tr>
<tr>
<td>Menopausal symptoms</td>
<td>excluded</td>
<td>predominant</td>
</tr>
<tr>
<td>Time since menopause</td>
<td>&gt;10</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>&lt;7</td>
<td>&gt;10-40</td>
</tr>
<tr>
<td>Average BMI</td>
<td>28.5</td>
<td>25.1</td>
</tr>
</tbody>
</table>

Benefits/Risks of HT: CHD

- **RCT**: Risk of CHD (CV death and nonfatal MI) dependent on age and time since LMP

- **Meta-analysis** of 23 RCT’s (excludes WHI)
  - Mean duration of HT use 4.8 yrs

<table>
<thead>
<tr>
<th>Overall</th>
<th>Age &lt; 60 yrs and &lt; 10 yrs since menopause</th>
<th>Age &gt; 60 yrs and &gt; 10 yrs since menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 0.99</td>
<td>OR 0.68</td>
<td>OR 1.03</td>
</tr>
<tr>
<td>CI 0.88-1.11</td>
<td>CI 0.48-0.96</td>
<td>CI 0.91-1.16</td>
</tr>
</tbody>
</table>

Salpeter et al, Gen Int Med Apr 2006
**Benefits/Risks of HT: CHD**

- **Secondary Analysis of WHI (Rossouw, et al 2007)**
- **Overall Risk of CHD: HR 1.07 (CI 0.92-1.23)**

<table>
<thead>
<tr>
<th>Within 10 years of menopause</th>
<th>HR 0.76 CI 0.50-1.16</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19 years since menopause</td>
<td>HR 1.10 CI 0.84-1.45</td>
</tr>
<tr>
<td>20 + years since menopause</td>
<td>HR 1.28 CI 1.03-1.58</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 50-59</th>
<th>HR 0.93 CI 0.65-1.33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 60-69</td>
<td>HR 0.98 CI 0.79-1.21</td>
</tr>
<tr>
<td>Age ≥ 70</td>
<td>HR 1.26 CI 1.00-1.59</td>
</tr>
</tbody>
</table>
Benefits/Risks of HT: CHD

- DOPS (Scheirbeck, et al)
- Composite end point: CV death, nonfatal MI and heart failure

<table>
<thead>
<tr>
<th>11 years of HT use</th>
<th>16 years follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 0.48</td>
<td>HR 0.61</td>
</tr>
<tr>
<td>CI 0.26-0.87</td>
<td>CI 0.39-0.94</td>
</tr>
</tbody>
</table>
Timing Hypothesis

The "timing hypothesis" posits that there is a differential effect on atherosclerosis and clinical events according to when postmenopausal HRT is initiated in relation to menopause.

**KEEPS Trial - 2014**

- Four year prospective RCT designed to assess risk of atherosclerosis progression with earlier menopause initiation of HT
- Largest/longest duration RCT comparing oral and transdermal HT to placebo
- Primary outcome: change in CIMT
- Secondary outcome: change in CAC
- Treatment groups:
  - Lower dose oral HT (CEE 0.45mg daily + cyclical micronized progesterone)
  - Transdermal HT (estradiol 50 mcg/week with cyclical micronized progesterone)
KEEPS Outcomes

• After 48 months, similar increases in CIMT and CAC scores across all three groups
• No statistically significant differences between treatment and placebo
• No sig differences between oral and transdermal in terms of stroke and VTE risk (underpowered)
• Oral HT more favorable changes in lipid profile
• Transdermal HT more favorable changes on glycemic effects
Risks of HT: Stroke

- **WHI**
  - Age stratified results, no increased risk for women age 50-59
  - Overall HT use: HR 1.32 (CI 1.12-1.56)
  - CEE: HR 1.35 (CI 1.07-1.70)
  - CEE+MPA: HR 1.37 (CI 1.07-1.76)

- **HERS**
  - RR 1.23 (CI 0.89-1.70)

- **WEST**
  - RR 1.10 (CI 0.80-1.60)

- **DOPS**
  - 10 yr intervention HR 0.77 (0.35-1.70)
  - 16 yr follow up HR 0.89 (0.48-1.65)
### Risk of Stroke - NHS
Confirmed cases of CVA

RR of CVA for entire HT cohort was 1.4

<table>
<thead>
<tr>
<th>AGE</th>
<th>Attributable Risk</th>
<th>Risk per 10,0000 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>50-54</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>55-59</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>60-64</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>65+</td>
<td>7.2</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Grodstein et al, JAMA 2008
Risks of HT: Venous Thromboembolism (VTE)

- **WHI:**
  - **PE:** CEE+MPA HR 1.98 (CI 1.36-2.87); CEE 1.35 (CI 0.89-2.05)
  - **DVT:** CEE+MPA HR 1.87 (CI 1.37-2.54); CEE 1.48 (CI 1.06-2.07)
- Increased risk (2X) within first 1-2 years of use
- Risk quickly returns to baseline after discontinuation
- Risk modified by:
  - Age (younger=lower risk)
  - BMI $\geq 30$, risk was 3X
VTE Risks: ESTHER Study

- Multi-center case-control trial in France 1999-2006
- Designed to look at different HT formulations, routes of delivery and risk of VTE
- 17 B estradiol, 26-29% transdermal

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonuse</td>
<td>146</td>
<td>384</td>
<td>1</td>
</tr>
<tr>
<td>Oral Estrogen Use</td>
<td>45</td>
<td>39</td>
<td>4.2 (1.5-11.6)</td>
</tr>
<tr>
<td>Transdermal Estrogen Use</td>
<td>67</td>
<td>180</td>
<td>0.9 (0.4-2.1)</td>
</tr>
</tbody>
</table>

Risks of HT: Breast Cancer

- WHI:
  - CEE+MPA saw increased risk after 3-5 yrs of use
  - CEE alone lower risk that became significant after long term follow up
  - Risk was lower for those without prior HT exposure (HR 1.06)
  - Risk significantly decreased following 3 years of cessation of CEE+MPA
  - CEE+MPA small increased risk of long term breast cancer mortality (2 breast cancer deaths per 10,000 years of use)

- WHI Intervention phase:
  - CEE 0.79 (0.61-1.02) (6 fewer cases/10,000)
  - CEE+MPA 1.24 (1.10-1.53) (8 cases/10,000)

- WHI 13 yrs culmatative follow up:
  - CEE 0.80 (0.58-1.11) (7 fewer)
  - CEE+MPA 1.32 (1.08-1.61) (9 cases /10,000)
## Risks of HT: Breast Cancer

### Nurses Health Study
Risk of invasive breast cancer according to duration of ET use per protocol (screened and unscreened):

<table>
<thead>
<tr>
<th>Current Duration of Use</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt; 5 yrs</td>
<td>0.96 (0.75-1.22)</td>
</tr>
<tr>
<td>5-9.9 yrs</td>
<td>0.90 (0.73-1.12)</td>
</tr>
<tr>
<td>10-14.9 yrs</td>
<td>1.06 (0.87-1.30)</td>
</tr>
<tr>
<td>15-19.9 yrs</td>
<td>1.18 (0.95-1.48)</td>
</tr>
<tr>
<td>20+ yrs</td>
<td>1.42 (1.13-1.77)*</td>
</tr>
</tbody>
</table>

# Breast Cancer Risk and Alcohol Intake

<table>
<thead>
<tr>
<th>Weekly Intake</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 glasses wine</td>
<td>1.06</td>
</tr>
<tr>
<td>3-6</td>
<td>1.15</td>
</tr>
<tr>
<td>6-13</td>
<td>1.22</td>
</tr>
<tr>
<td>13-19</td>
<td>1.20</td>
</tr>
<tr>
<td>19+</td>
<td>1.51</td>
</tr>
<tr>
<td>per 10 gm increase</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Chen W, et al. JAMA 2011
## Magnitude of Risk
(absolute excess risk/10,000 years use)

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET (7.2)</th>
<th>EPT (5.6)</th>
<th>ET (13)</th>
<th>EPT (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Ca</strong></td>
<td>-7</td>
<td>9*</td>
<td>-7*</td>
<td>9*</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td>-3</td>
<td>6</td>
<td>-4</td>
<td>3</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>11*</td>
<td>9*</td>
<td>5</td>
<td>5*</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td>4</td>
<td>9*</td>
<td>2</td>
<td>4*</td>
</tr>
<tr>
<td><strong>Colorectal C</strong></td>
<td>2</td>
<td>-6*</td>
<td>2</td>
<td>-3</td>
</tr>
<tr>
<td><strong>Endometrial Cancer</strong></td>
<td>NA</td>
<td>-1</td>
<td>NA</td>
<td>-3</td>
</tr>
<tr>
<td><strong>Hip fractures</strong></td>
<td>-6*</td>
<td>-6*</td>
<td>-2</td>
<td>-5*</td>
</tr>
<tr>
<td><strong>All Cause Mortality</strong></td>
<td>3</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td><strong>Global Index</strong></td>
<td>4</td>
<td>20*</td>
<td>1</td>
<td>12*</td>
</tr>
<tr>
<td><strong>CV deaths</strong></td>
<td>27</td>
<td>19</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td><strong>CancerDeath Deaths</strong></td>
<td>-1</td>
<td>3</td>
<td>-2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Lung Ca</strong></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Ovarian CA</strong></td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td><strong>All Fracture</strong></td>
<td>-61*</td>
<td>-51*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Manson et al October 2013
Classification of Frequency of Drug Reactions (WHO)

Very common: >1/10 (>10%)

Common: >1/100 and <1/10 (>1% and <10%)

Uncommon: >1/1,000 and <1/100 (>0.1% and <1%)

Rare: >1/10,000 and <1/1,000 (0.01% and <0.1%)

Very rare <1/10,000 (<0.01%)

Hodis et al. Menopause 2007
Genitourinary Syndrome of Menopause (GSM)

- Newer terminology encompasses both genital and urinary symptoms related to low estrogen levels
- Diagnosis clinical, not otherwise accounted for by alternative diagnosis
- Symptoms:
  - Genital dryness
  - Decreased lubrication with sexual activity
  - Discomfort or pain with sexual activity
  - Post-coital bleeding
  - Decreased arousal, orgasm, desire
  - Irritation/Burning/Itching of vulva or vagina
  - Dysuria
  - Urinary frequency/urgency
Benefits of HT: GSM

• ET is the most effective treatment of moderate to severe symptoms of vulvar and vaginal atrophy
• May help symptoms of urge incontinence
• (Systemic HT may worsen stress incontinence)
• Decrease frequency of recurrent UTI’s

NAMS position statement. Menopause 2012
Benefits of HT: GSM

• Many systemic HT products and all local vaginal ET products FDA approved

• Low-dose systemic regimens may be inadequate
  • May require addition of low-dose local ET

• When ET is considered solely for treatment of vaginal atrophy, local vaginal ET is recommended

• Progestogen is generally not indicated
  • Clinical trial data supporting endometrial safety beyond 1 year are lacking

NAMS position statement. Menopause 2012
Benefits of HT: Quality of Life

- HT can improve health-related QOL through mood elevation and decreased menopause symptoms

- Not a treatment for major depressive disorder

NAMS position statement. *Menopause* 2012
Lack of Benefit of HT: Cognition

- HT not recommended at any age for the sole or primary indication of preventing cognitive aging or dementia
- Postmenopausal women older than 65 years
  - Clinical trials HT does not improve memory/cognition abilities
  - EPT is harmful for memory
- Observational studies HT use associated with lower risk of Alzheimer’s
  - More likely to be ET users

NAMS position statement. *Menopause* 2012
Benefits of HT: Decreased Risk of DM

- Decreased risk of new diagnosis of Type 2 DM
- Not FDA-approved for Type 2 DM prevention

- WHI EPT arm:
  - 21% reduction (HR, 0.79; 95% CI, 0.67-0.93) in the incidence of T2DM requiring treatment
  - 15 fewer cases per 10,000 women per year of therapy
Is your patient a candidate for systemic HT?

- Is she having moderate-severe vasomotor symptoms (interfere with daily activities, impair QOL and/or interrupted sleep)

- Does she have contraindications

- What is her age and time since menopause

- Does she have a uterus

- Assess CVD, breast cancer and OP risk
MenoPro

- Appropriate for women age 45 and older with menopausal symptoms
- Can be used for women who have had removal of both ovaries regardless of age
- Patients should try lifestyle modifications for at least 3 months before using algorithm
- Discourages use of HT if >10 yrs from menopause, 10 yr CVD risk $\geq 10\%$
Duration of Treatment: NAMS Recommendation

- Lowest dose of HT should be used for the shortest duration to manage menopausal symptoms

- Women age 60-65, 42% continue to experience VMS

- Extended duration of HT use might be appropriate in symptomatic women or for the prevention of OP if alternative therapies are not tolerated

- Long term use: limited data on CHD risk; small but stat sig increased risk of stroke and breast ca
Women Age 65 years and Older

- The use of HT should be individualized and not discontinued solely based on age
- HT may be appropriate for some women 65 years of age and older:
  - Benefit of treatment of hot flashes outweighs the risks
  - Risk of fragility fracture and cannot use alternative treatments for OP prevention

NAMS Statement, Utian
Primary Ovarian Insufficiency
NAMS recommendations

- Estrogen containing product is advised (unless contraindications)
- Oral contraceptive or HT dose
- Goals: preserve bone health, manage VMS
- Duration: through average age of menopause
- Periodic reassessment

NAMS Position Statement on Hormone Therapy, 2012
Clinical Pearls

- HT is the most effective treatment for VMS and GSM
- HT if effective for prevention of OP and fragility fracture
- Benefits more likely to outweigh risks when initiated < 60 yrs of age and within 10 yrs of menopause
- Patients taking HT should be evaluated annually to assess need for ongoing therapy
- Discussion of HT use should include absolute risk
- Shared decision making: patients may elect to continue HT if risks outweigh benefits
- Long term use associated small but significantly increased risk of stroke and breast cancer
Thank You!!
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Every life deserves world class care.