Hormone Replacement Therapy and Stroke

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Disclosures

- none

Objectives

1. Discuss the risk of stroke associated with the use of hormone replacement therapy (HRT)

2. Discuss the evidence of stroke risk based on a summary of primary and secondary prevention studies

3. Discuss the role of other factors that may affect the effects of menopausal hormone therapy

Menopause and HRT

Background

- The risk of stroke in women increases after menopause
- Despite some inconsistencies, earlier age of menopause is associated with higher risk of stroke
- The main physiological change after menopause is reduced estrogen levels (there may also be other factors at play such as increase vascular risk factors after menopause)

Menopause and HRT

- High premenopausal estrogen believed to be protective against stroke and cardiac disease
- HRT is an attempt to replace estrogen levels that are depleted after menopause
- Observational studies reported benefit in reducing risk of cardiac disease (50% reduction), inconsistent results in stroke prevention
- Prescribed widely in 1990s for treatment of vasomotor symptoms and to reduce risk of chronic disease including cardiovascular disease
- Evidence followed…

HERS (Heart Estrogen-Progestin Replacement Study)

- Secondary prevention study (2763 women with previous coronary artery disease) treated with combination of estrogen and progesterone vs placebo

- No benefit associated with HRT over the entire follow-up period (6.8 years)

- Increased risk of coronary events during the first year, nonsignificant increase in stroke risk

Simon JA et al. Circulation 2001; 103:638-642

WEST (Women Estrogen Stroke Trial)

- 664 women with previous ischemic stroke or TIA treated with estradiol vs placebo (mean age 71 years)

- No difference in overall stroke rate but
  - increased risk of stroke in the first 6 months
  - trend to increase in fatal stroke
  - more severe nonfatal strokes

Viscoli CM et al. NEJM 2001;345:1243-1249

Women's Health Initiative

- Primary prevention study of *healthy* women launched in 1991
- Two parallel RCTs of estrogen alone (in women with prior hysterectomy) or combination with progesterone
- To determine if there were benefits in reducing chronic disease including cardiovascular disease
- Enrolled between 1993-1998

Women's Health Initiative

- Estrogen and progesterone trial was stopped in 2002 because health risks exceeded benefits
- 16 608 healthy women (mean age 63 years)
- Trial stopped early at 5.2 years instead of planned 8.5 years because of increased risk of
  - **invasive breast cancer**
  - **coronary artery disease**
  - **stroke**
  - **pulmonary embolism**

Writing Group for the Women's Health Initiative Investigators, JAMA 2002;288:321-333

Women's Health Initiative

- Results were independent of race or age (applicable to all healthy women)
- Hazards ratio
  - CHD 1.29
  - Stroke 1.41
  - Venous thrombosis 2.11
  - Invasive breast cancer 1.26
  - Hip fracture 0.66
  - Colorectal cancer 0.63

Women's Health Initiative

- Estrogen only study of 10 739 women was stopped in 2004

- Hazards ratio
  - CHD 0.91 (non-significant increase in the first year with modest benefit with longer use)
  - Breast cancer 0.77
  - **PE 1.34**
  - **Stroke 1.39**
  - Colorectal cancer 1.08
  - Hip fracture 0.61

- Overall increased risk of stroke and decreased risk of hip fracture and did not affect CHD

  Non significant reduction in breast cancer requires additional investigation

Anderson GL et al. JAMA 2004;29:1701-

WHI Extended Post-intervention Follow-up

- After intervention ended, patients in the 2 trials were followed until September 2010 (info on 80% of patients)

- Hazards ratio (combination, estrogen alone)
  - **CHD (1.09, 0.94**)
  - **Invasive breast cancer (1.28, 0.79)**
  - **Stroke (1.26, 1.15)**
  - Colorectal cancer (neutral in both groups)
  - Hip fracture (risk reduction attenuated post intervention but significant benefit persisted in combination arm)

Manson et al. JAMA 2013; 310: 1353-1368

WHI Extended Postintervention Follow-up

- Based on subgroup analysis, suggestion that age and time since onset of menopause may be factors in outcome
  - Risk of coronary artery disease increased with age and time from menopause
  - Increased risk of breast cancer in patients treated closer to menopause

Factors related to risk of stroke

- Formulation
  - In the WHI both groups treated with estrogen alone or estrogen and progesterone had increased risk of stroke
  - oral versus transdermal formulations of estrogen

- Timing hypothesis – effects of hormone therapy on atherosclerosis depend on timing of initiation of therapy relative to menopause

Early versus Later Intervention with Estradiol (ELITE) Trial

- 643 healthy postmenopausal women stratified according to time after menopause
- early (<6 years) or late (≥ 10 years)
- received oral estrogen +/- progesterone gel or placebo
- Primary outcome was rate of change of carotid intima-media thickness (marker of subclinical atherosclerosis)
- Secondary outcome was coronary atherosclerosis

Hodis et al. NEJM 2016;374:1221-1231

ELITE

- 643 patients were followed for 5 years
  - Early menopause:
    - Placebo 0.0078 mm
    - Estrogen 0.0044 mm
  - Late menopause:
    - Placebo 0.0088 mm
    - Estrogen 0.0100 mm

- Early menopause group had less progression of subclinical carotid atherosclerosis with estrogen compared with late menopause group (no differences in cardiac group)

- No difference in serious adverse events but this was a smaller study

KEEPS Study

- Kronos Early Estrogen Prevention Study
  - Women 42-58 years
  - Hormone replacement in early perimenopausal period (within 3 years of last period)
  - Randomized to oral estrogen, transdermal estrogen in combination with progesterone and placebo
  - Estrogen had no significant effect on carotid intimal thickness progression
  - Lower dose of estrogen compared with ELITE study

Harman et al. Annals of Internal Medicine 2014; 161:249-260

Timing of HRT

- The results are mixed on potential benefits of estrogen in carotid intima-media thickness

- The differences in carotid intima-media thickness does not translate in clinical outcome and reduced risk of stroke

Formulation

- Case control study of 15 710 cases of stroke in a UK General Practice Registry of 6 million patients between 1987-2006 with 60 000 matched control women 50-79 years
- Oral estrogen was associated with significantly increased stroke risk (rate ratio 1.28)
- Transdermal estrogen was not associated with increased stroke risk (rate ratio 0.95)
- Higher stroke rate with higher doses of estrogen

Renoux C et al. BMJ 2010; 340:c2519

Formulation – Danish Study

- Cohort of women identified by linking 5 in Danish national registries linkages regarding HRT exposure and stroke incidence
- aged 51-70 yrs
- between 1995-2010

Lokkegaard E et al. Stroke 2017;48:2266-2269

Formulation – Danish study

- 980 003 women, 20 199 suffered stroke
- Oral estrogen associated with increased relative rate stroke
  - Oral estrogen alone ***1.29***
  - Oral estrogen and progesterone ***1.18***
  - Transdermal estrogen ***0.82***
  - Vaginal estrogen ***0.64***

Lokkegaard E et al. Stroke 2017;48:2266-2269

Formulation

- Transdermal route may avoid first pass through liver and the production of clotting factors

What about progesterone

- Findings were replicated in a third study from France with OR of 1.58 in oral estrogen users and 0.83 in transdermal estrogen users
- Increased risk with higher doses of estrogen
- No association between stroke and use of progesterone

Canonico M et al. Stroke 2016: 47:1734-41

Take home points

- There is documented association between the use of oral estrogen and stroke
- Estrogen and progesterone also associated with increase risk of breast cancer (risk higher if treatment begins at earlier age)
- Limited evidence that estrogen may reduce subclinical atherosclerotic disease and should not be prescribed for this reason

Take home points

- There may be a role for the use of HRT to manage vasomotor symptoms of menopause but there are uncertainties
  - *How long:* Duration unclear (not addressed in literature)
  - *When*: More benefits and less harm for cardiovascular outcome if given at younger age
  - *What formulation:* Transdermal and vaginal formulations may have a better safety profile

Take home points

- Evidence from the WHI applies to healthy women
- Previous secondary prevention studies did not show benefit but we should exercise caution in prescribing HRT to women with previous cardiovascular diseases

Questions