Post Menopausal Hot Flashes

Medical Insights – Market Opportunity

Tro Kalayjian
Physician
Chimera Research Group

Outline

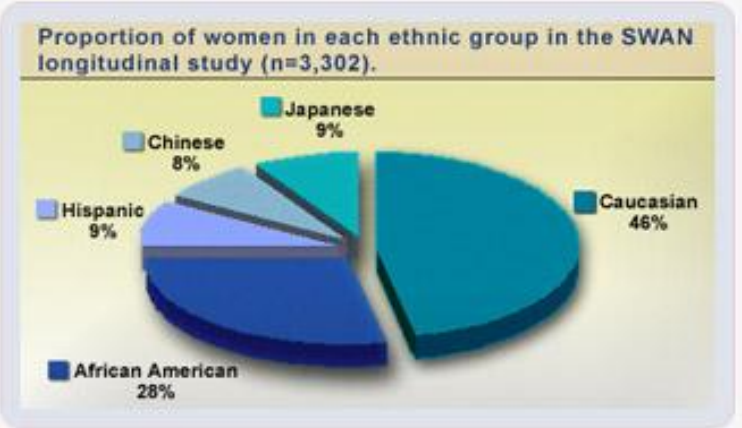
- Introduction & Presentation
- Epidemiology
- Comorbidities
- Pathophysiology
- Women's Health Initiative
- Treatments
- OTC Products
- Pipeline

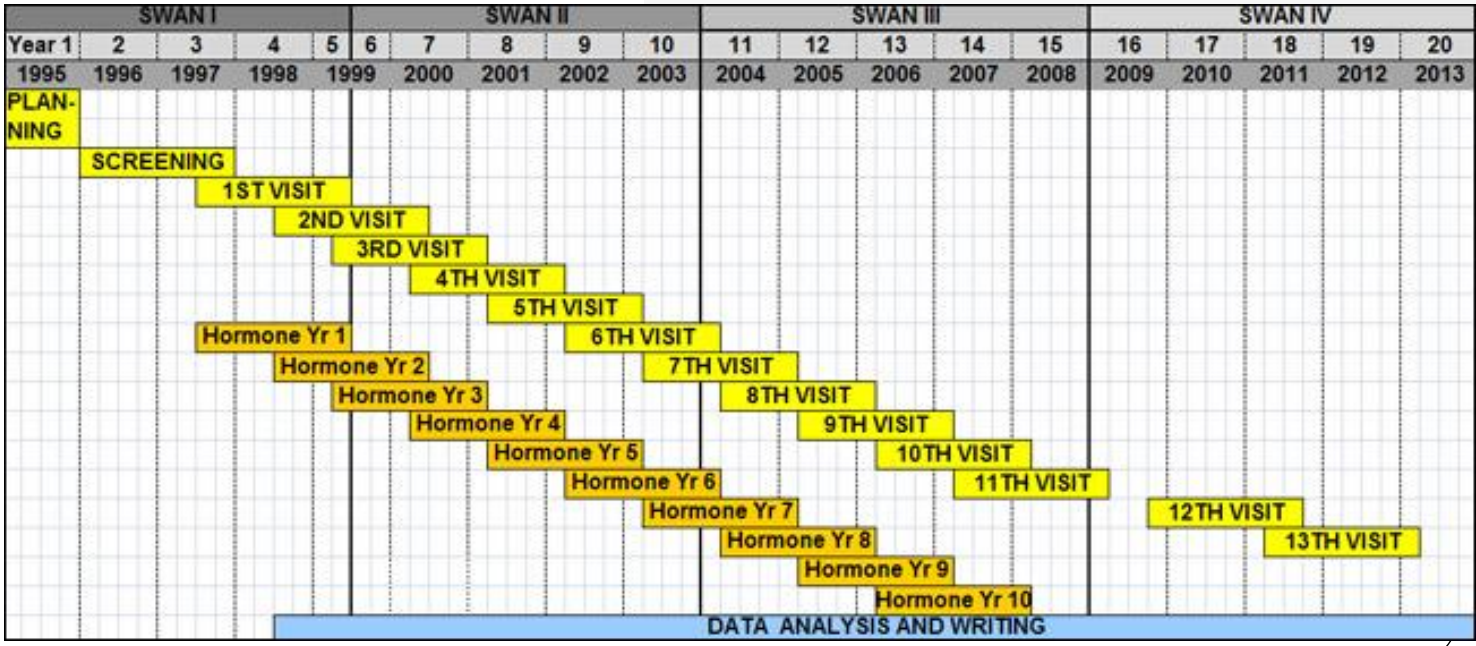
Introduction & Clinical Presentation

- Hot flashes typically occur in 75% of menopausal women in the US
- A sudden sensation of heat
  - Location: Typically start in the face and upper chest
  - Radiation: can spread to the neck, upper back and become generalized
  - Duration: Typically lasts between 2 and 4 minutes
  - Associated Symptoms: profuse perspiration and occasionally palpitations
  - Often followed by chills and shivering
- Begin in late menopausal transition and early post menopausal periods
- Occur several times in a day, can occur up to 1 per hour
- Often cause arousal from sleep, leading to sleep disturbances

Epidemiology - SWAN

- Study of Women's health Across the Nation
  - longitudinal epidemiologic study
  - Enrolled in 1994-1997
  - n=3302
  - Still ongoing





Epidemiology & Risk Factors

- 14-51% of women experience hot flashes before perimenopause*
- 36-55% of women experience hot flashes during perimenopause*
- 30-80% of women experience hot flashes after menopause*
- 12-15% of women still experience hot flashes in the 7th decade*
- <9% of women still experience hot flashes in the 8th decade*
  - * From systemic analysis that included SWAN and other studies
- 80% of women who have hot flashes will have them for more than 1 year
- Japanese & Asian women report hot flashes less than Caucasians
- African Americans report hot flashes more often than Caucasians
- Obese women, those with higher BMI, have increased hot flashes
- Smoking is associated with increased hot flashes
- Decreased physical activity associated with increased hot flashes

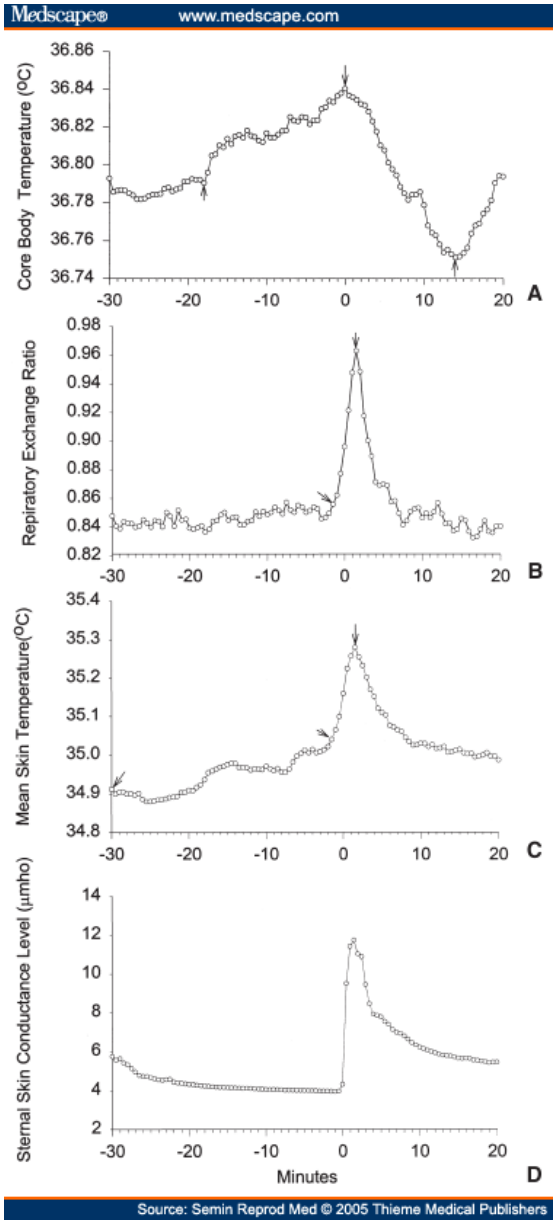
Combordities

- Sleep disturbance
  - Hot flashes are associated with arousal from sleep and chronic insomnia
  - Polysomnography studies have shown that hot flashes typically occur in the first four hour of sleep
  - REM sleep, typically the latter four hours of sleep suppress hot flashes, arousals, and awakenings.

- Depression
  - Perimenopausal/Postmenopausal women with hot flashes are more likely to be clinically depressed

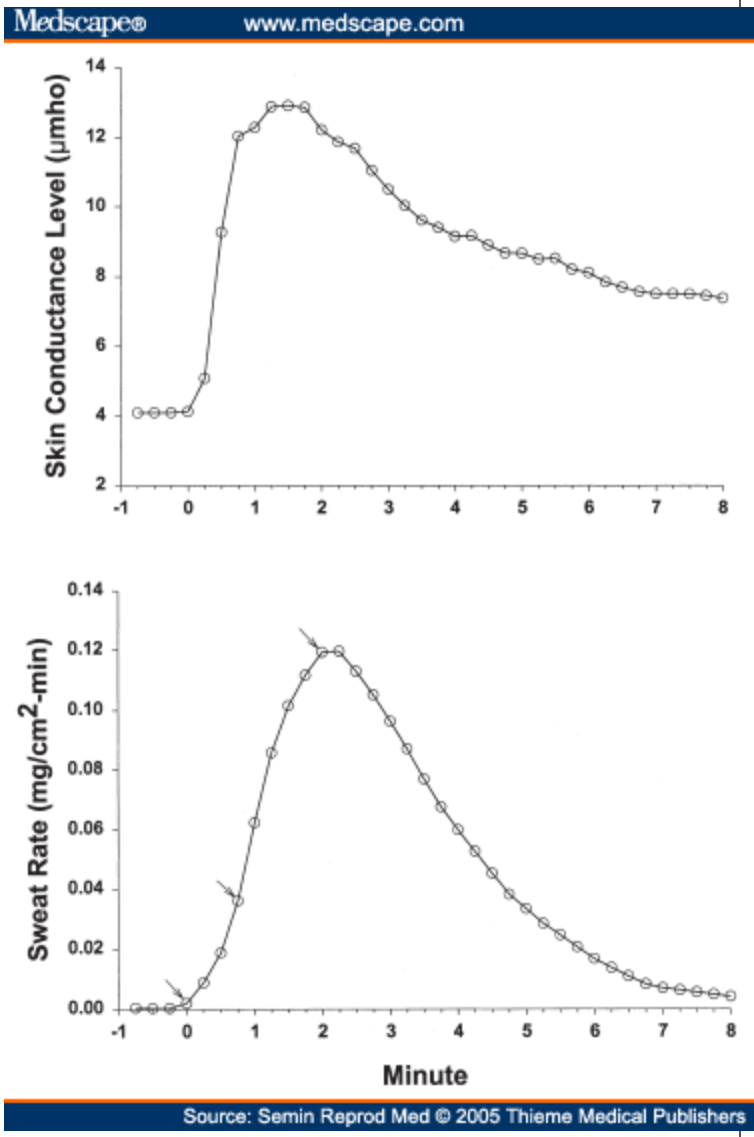
Pathophysiology

- Thermoregulatory dysfunction, initiated at the level of the hypothalamus by estrogen withdrawal.
- Post menopausal women have a decreased thermoneutral zone.
- Radiotelemetry pills have shown elevations in Tc preceding the majority of hot flashes (75-86%)
- Core body temperatures are typically increased at the onset of a hot flash and falls below after it, indicative of rapid heat dissipation.



Pathophysiology

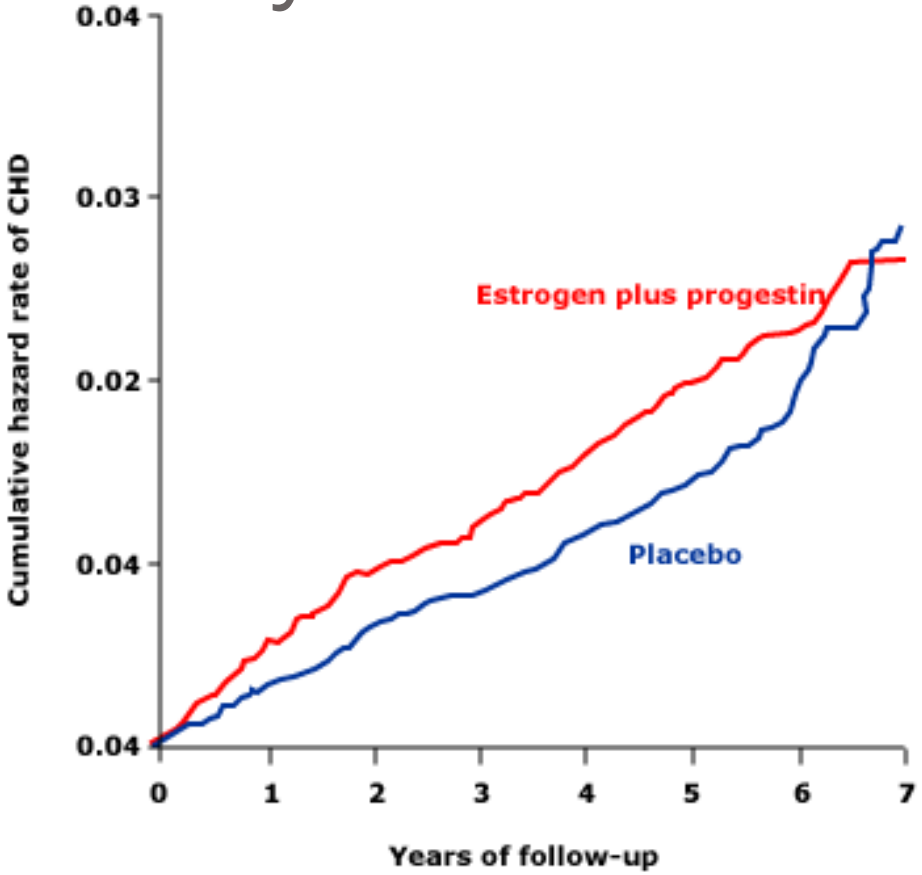
- Peripheral vasodilatation demonstrated by increased skin temperature and blood flow occurs during hot flashes.
- Skin Conductance an indirect measure of sweat rate increases during 90% of hot flashes
- Modest increases in heart rate also precede the hot flash, typically 7-15bpm



Women's Health Initiative

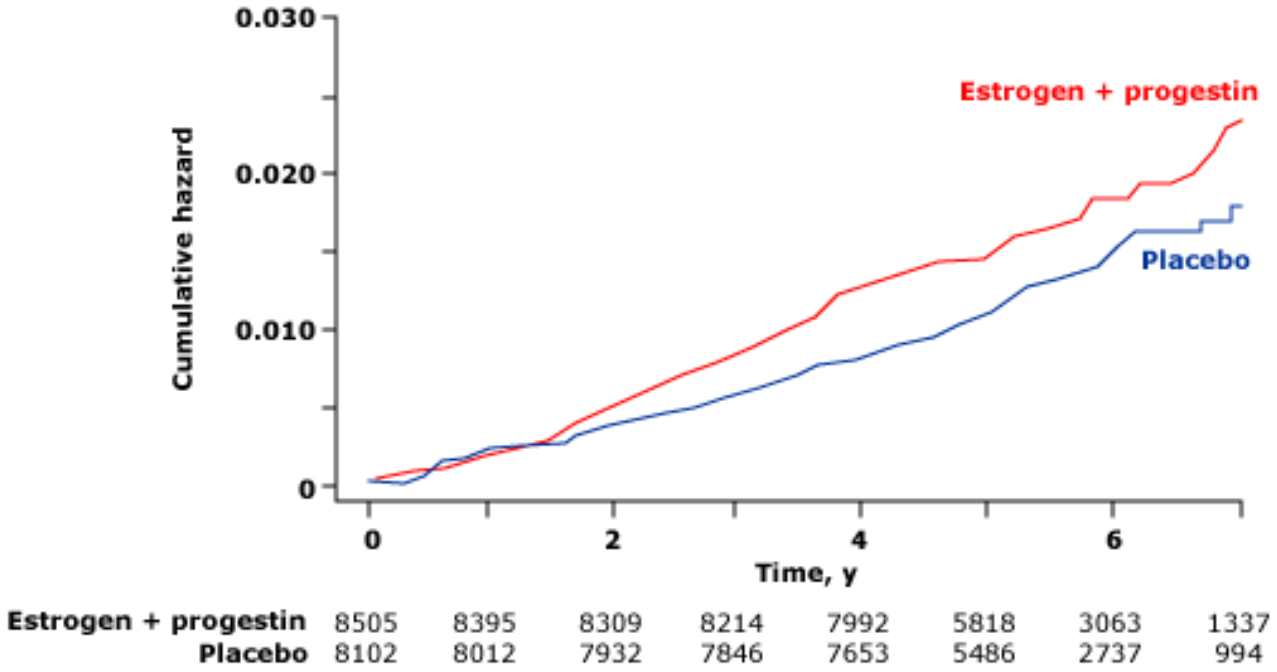
- The Women's Health Initiative (WHI)
  - Two hormone trials (unopposed estrogen & combined estrogen-progestin)
  - Healthy postmenopausal women ages 50 to 79
  - Scheduled to be completed in 2005.
  - The goal of the study was to determine whether estrogen alone or in combination with progestin would reduce the risk of cardiovascular events.
  - The WHI was not designed to study the effects of postmenopausal hormone therapy on menopausal symptoms.
- Discontinued early
  - Combined estrogen-progestin arm, 16,000 women, was discontinued early in July 2002 because of an increased risk of breast cancer, CHD, stroke, and venous thromboembolism over an average follow-up of 5.2 years.
  - Unopposed Estrogen arm, 11,000 women, was discontinued early in February of 2004 due to increased risk of stroke.

Coronary Heart Disease



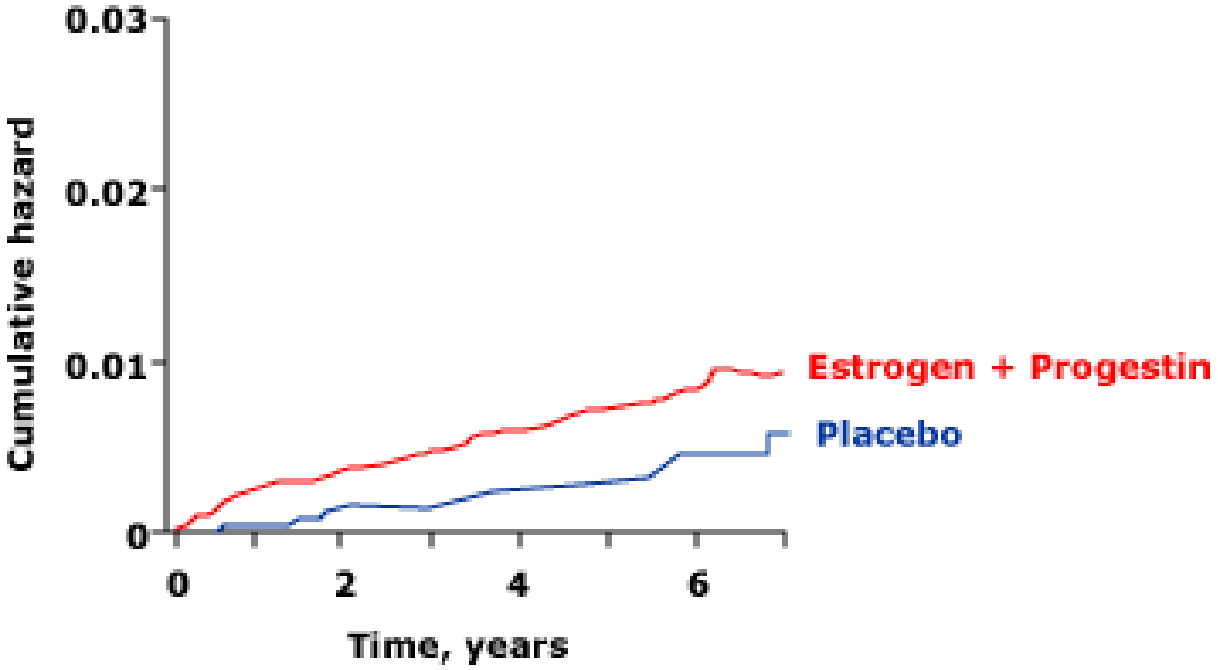
In the Women's Health Initiative, combined estrogen-progestin therapy was associated with a significant increase in coronary events. CHD included nonfatal myocardial infarction and death due to CHD. The overall hazard ratio for CHD was 1.24 (nominal 95 percent confidence interval, 1.00 to 1.54). *Data from Manson, JE, Hsia, J, Johnson, KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349:523.*

Stroke



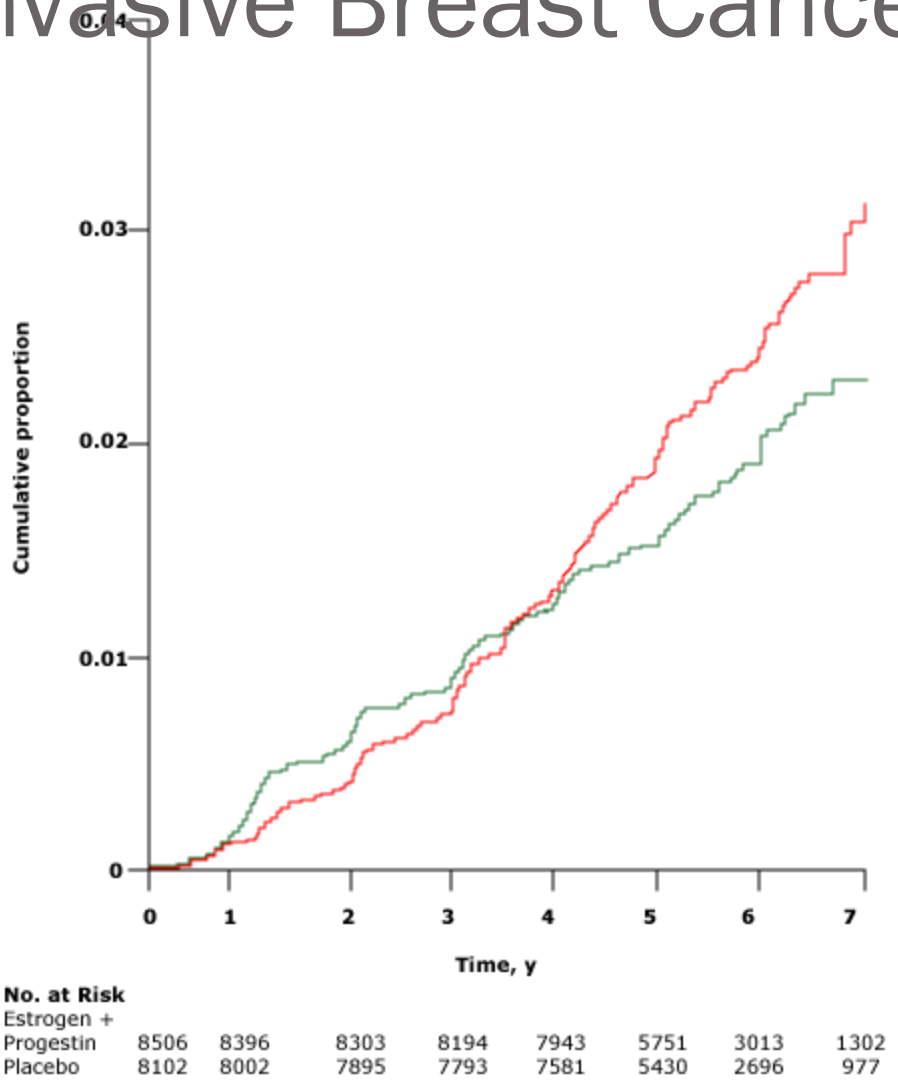
In the Women's Health Initiative, combined estrogen-progestin therapy was associated with a significant increase in stroke when compared with placebo. The intention-to-treat hazard ratio was 1.31, 95 percent CI 1.02 to 1.68. *Data from Wassertheil-Smoller, S, Hendrix, S, Limacher, M, et al. Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women: The Women's Health Initiative: A Randomized Trial. JAMA 2003; 289:2673.*

Pulmonary Embolism



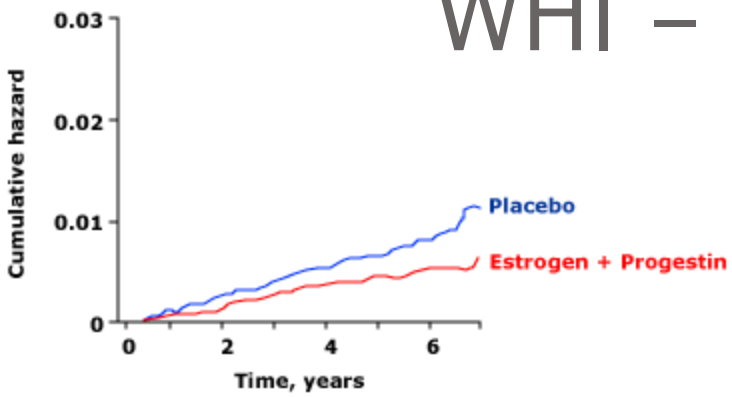
In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with a significant increase in pulmonary embolism (8 more pulmonary emboli per 10,000 person years, HR 2.13, unadjusted 95 percent CI 1.39 to 3.25). *Data from Risks and benefits of estrogen and progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321.*

Invasive Breast Cancer

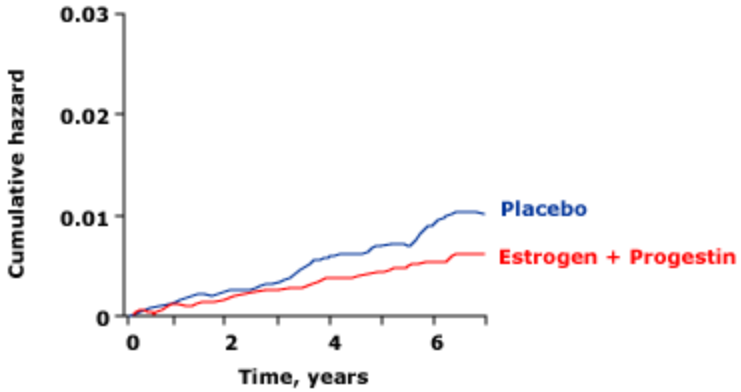


In the Women's Health Initiative, combined estrogen-progestin replacement therapy (red) was associated with a significant increase in invasive breast cancer (HR 1.24, unadjusted 95 percent CI 1.01 to 1.54) when compared with placebo (green). *Data from Chlebowski, RT, Hendrix, SL, Langer, RD, et al. Risks and benefits of estrogen and progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2003; 289:3243.*

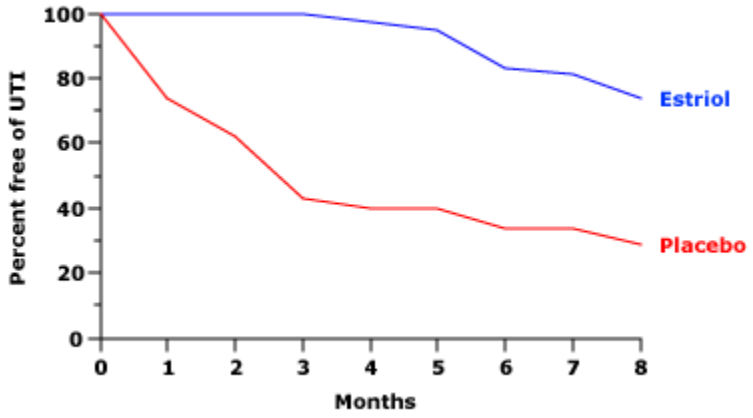
WHI – Benefits to HRT



In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with significant *reduction in hip fracture* (5 fewer hip fractures per 10,000 person-years, HR 0.7, unadjusted 95 percent CI 0.4 to 1.0). *Data from Risks and benefits of estrogen and progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321.*



In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with a significant reduction in the cumulative hazard of *invasive colorectal cancer* (hazard ratio 0.56, unadjusted 95 percent CI 0.38 to 0.81). *Data from: Estrogen and progestin and colorectal cancer in postmenopausal women. N Engl J Med 2004; 350:991.*



The effect of intravaginal estriol or placebo on the incidence of urinary tract infection in postmenopausal women with recurrent urinary tract infections. Estrogen therapy was associated with a much greater likelihood of *remaining free of infection*. *Data from Raz, R, Stamm,WE, N Engl J Med 1993; 329:753.*

Treatments

- Estrogen Therapy – currently recommended for short-term management of moderate-to-severe vasomotor flushes
- Most effective treatment therapy is estrogen, despite poor adverse events
- NAMS guidelines: "Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable for women who initiate HT close to menopause but decreases in older women and with time since menopause in previously untreated women."
- FDA, NAMS, ACOG all agree that the lowest dose possible should be used.
- Alternative treatment options needed

Estrogen Therapy

- 1 mg micronized 17-beta-estradiol
- 50 mcg/day transdermal 17-beta-estradiol
- 0.625 mg conjugated equine estrogens
- 1.25 mg piperazine estrone sulfate

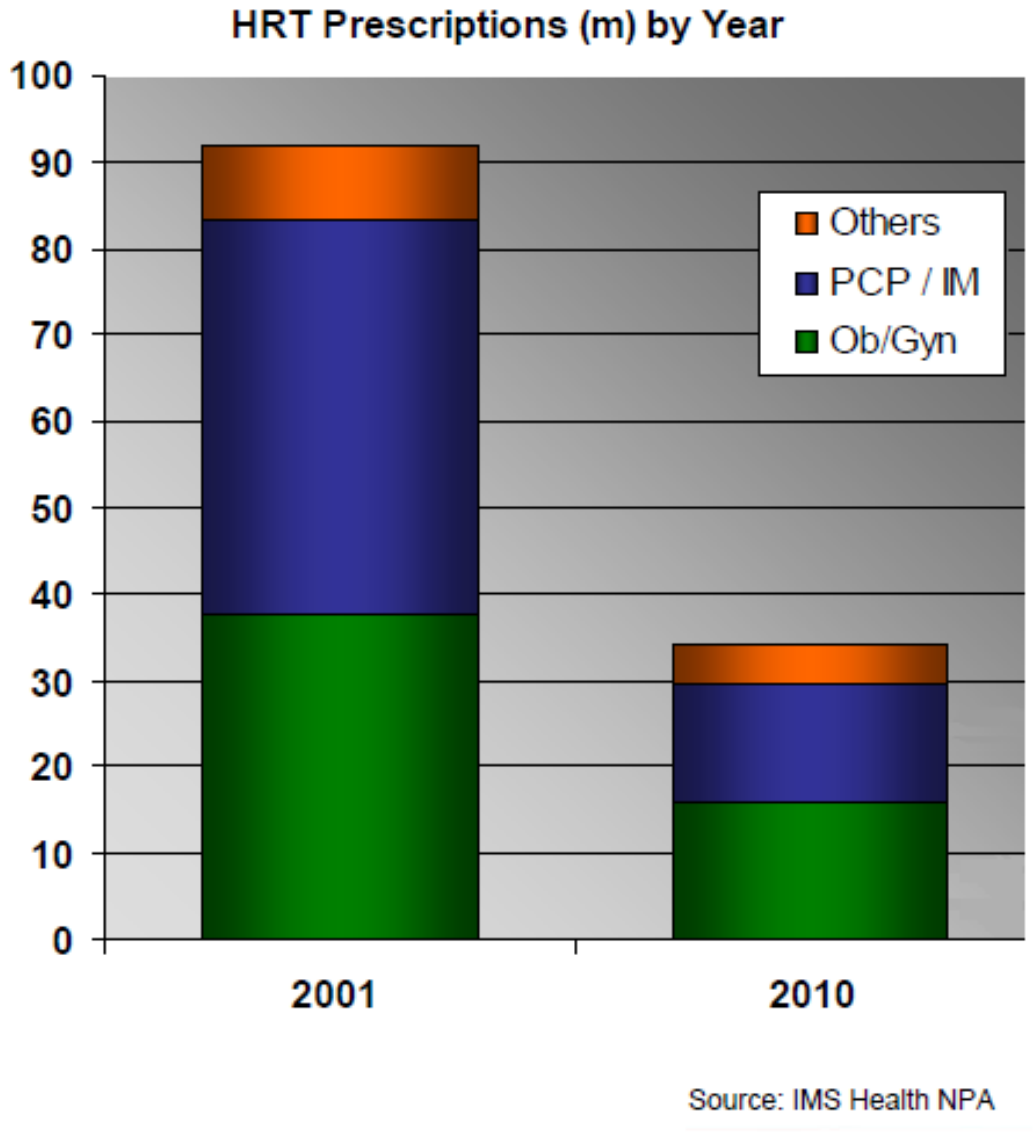
Elestrin – transdermal – lowest dose approved by FDA

0.0125mg estradiol

Estrogen Black Box Warnings

- Endometrial Cancer
- DVT/PE
- Coronary Heart Disease
- Stroke
- Invasive Breast Cancer
- Dementia
- Gallbladder disease
- Hypercalcemia
- Retinal Vascular Thrombosis

Treatment void after WHI



Source: IMS Health NPA

OTC market

- Lack of FDA approved non-hormonal treatment options has become a boon for snake oil
- There is currently a $2 Billion dollar OTC market for post menopausal hot flash treatments.
- No OTC therapy has been proven to be effective
- ACOG, NAMS, FDA do not recommend the use of OTC or "natural" hormones, black cohosh, red clover, soy
- 351 patient DB PC RT demonstrated Black Cohosh no better than placebo - http://annals.highwire.org/content/145/12/869.short
- 189 patient DB Treatment control RT demonstrated that Black Cohosh and Red Clover were less effective than placebo
  - Geller SE et al. Menopause 2009 Jul 15
  - Maki PM et al. Menopause 2009 Jul 31

Other ineffective therapies

- Exercise – raises core temperature and causes more hot flashes
- Acupuncture – has performed no better than sham accupuncture
- Relaxation – equivocal data

Some evidence of efficacy

- Weight loss – basically decreased insulation lower core temperature
- Smoking Cessation
- Paced Respiration

Off Label Use

- Placebo has been shown to decrease the severity and frequency of hot flashes by up to 62% (29-62% across several large recent phase II-III trials)
- Gabapentin – most widely studied product, several large Phase III trials have been conducted in the last 7 years. Typically decreases hot flashes by 2 over placebo per day, and decreases severity by 2 points per day.
  - http://jama.ama-assn.org/content/295/17/2057.full?sid=bc5cc5e0-b34a-47d6-8dd5-21aa803d3eff
  - http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9MjgxNDJ8Q2hpbGRJRD0tMXxUeXBlPTM=&t=1
- Desvenlexafine – same efficacy profile as Gabapentin
- Clonidien – not efficacious in all trials

Pipeline

- CRL issues for Pristiq in September 2011, an extended release desvenlexafine formulation
- Large Phase III trial results pending in mid October for Serada, an extended release gabapentin formulation
- Large Phase III trial results pending in mid October for Mesafem, an extended release paroxetine formulation
- Large Phase III trial ongoing for Bazedoxifene/conjugated-estrogens, a combination SERM and CE, shown to have no effect on uterus.
- Large Phase III trial initiated for Menerba, a 50g botanical preparation, MOA is selective estrogen beta receptor modulation, no side effects seen to date in any animal or human trial.

Comments or Questions

- Email: Contact@ChimeraResearchGroup.com