



Hormones And Your Heart

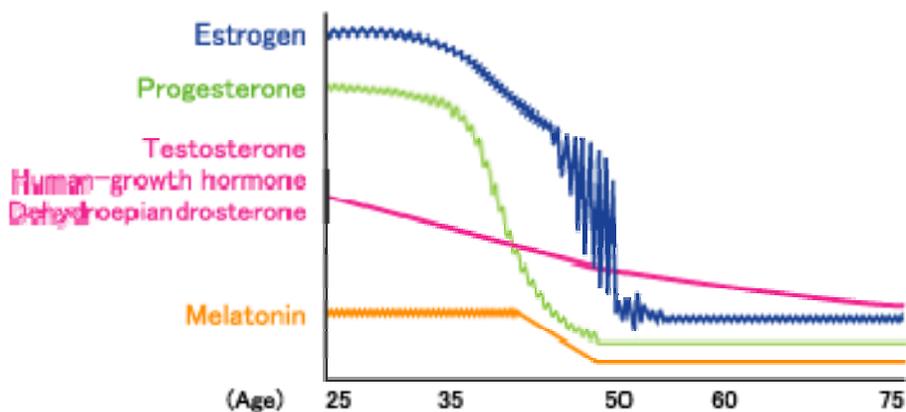
Charles R. Caldwell, MD, FACC
Arkansas Cardiology

Disclosures

I have no relevant relationships with
commercial interests to disclose.

Sex Hormones and Aging

Hormone decreases by aging



Symptoms Associated With Sex Hormone Decline

- Fatigability
 - Weight Gain
 - Muscle Weakness
- Loss of Sexual Desire
- Wrinkles
- Depression
- Joint Pain
- Flabby Skin
- Cold Hands
- Thinning Hair
- Weak Nails
- Predisposition to Illness
- Memory Loss
- Sudden Perspiration
- Urinary Incontinence
- Constipation
- Pain During Intercourse
- Insomnia
- Hot Flashes

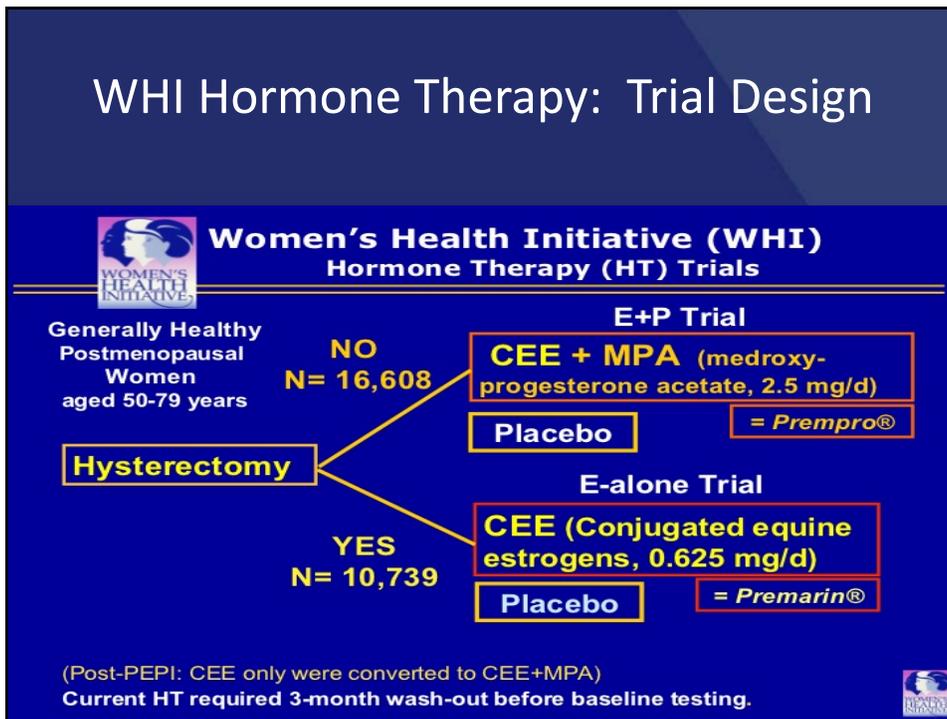
Hormone Replacement in Women

- In the 1990's 40% of women were taking hormone therapy.
 - The question then was not about taking therapy but more about the timing of initiation.
- In 2002, the Women's Health Initiative (WHI) study found that hormone therapy provided no protection against heart disease. Rather, it increased the risk.

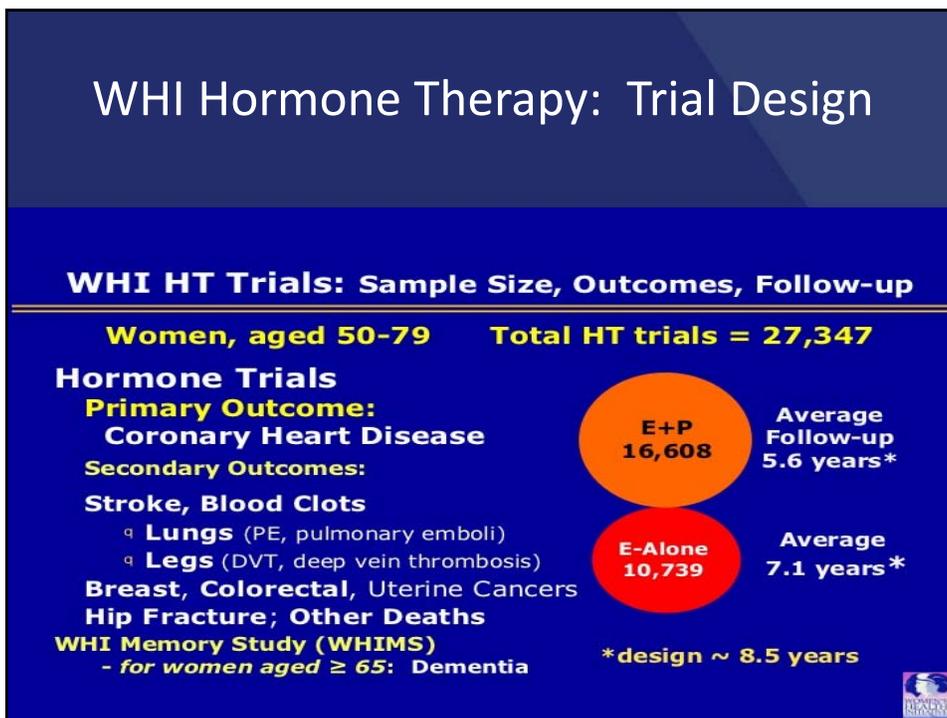
Women's Health Initiative (WHI)

- 27,347 women followed for 9 years in the hormone therapy arm. A dietary arm and calcium supplementation arm were also performed.
- Estrogen-Progestin therapy arm was stopped early at 5.2 years due to adverse findings of increased breast cancer, coronary heart disease, stroke, and pulmonary embolism.

WHI Hormone Therapy: Trial Design

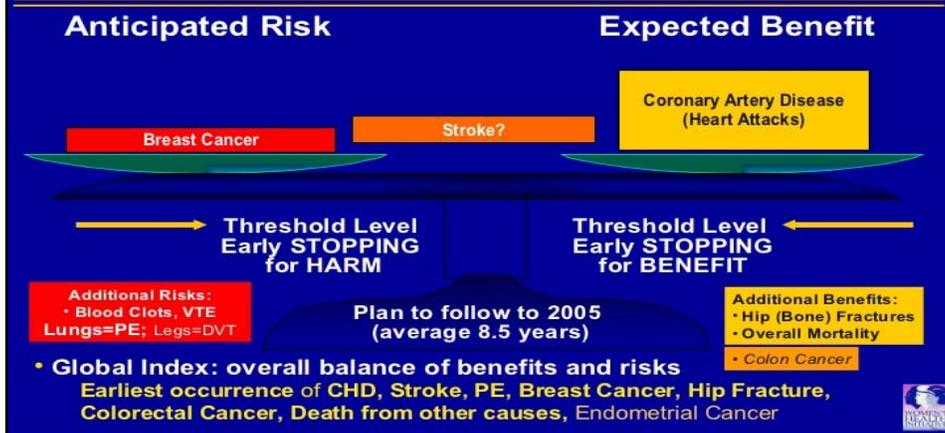


WHI Hormone Therapy: Trial Design



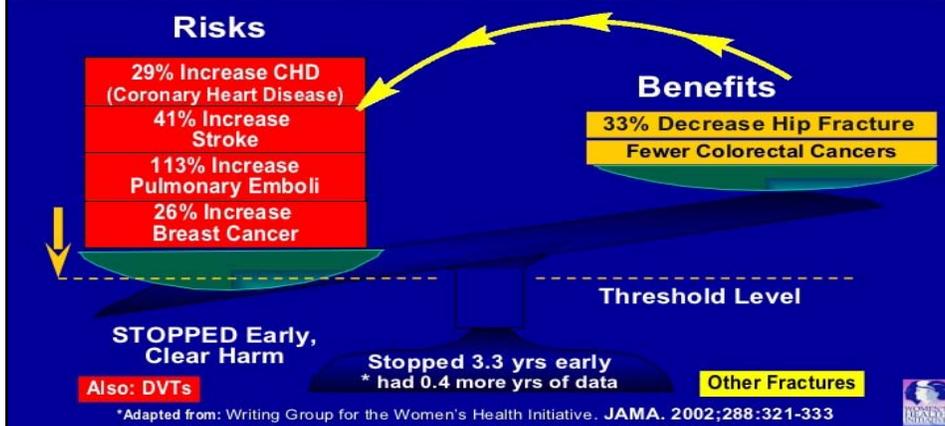
WHI: Risk vs Benefit

WHI Hormone Trials: Baseline Hypotheses



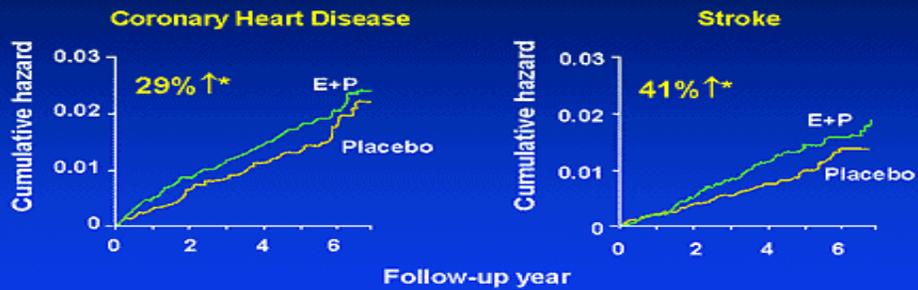
WHI: E+P Stopped Early

WHI E+P Trial: Preliminary* Findings, July 2002 (*aver. 5.2 yrs)



WRI E+ P Risk of CHD and Stroke

WHI HRT Study Kaplan-Meier Estimates of Cumulative Hazards for CHD and Stroke



*Statistically significant based on 95% nominal CI on hazard ratios

Writing Group for the Women's Health Initiative. *JAMA*. 2002;288:321.

WHI: E + P Absolute Risk

WHI E+P Trial: Absolute (annualized) Risk (5.2 Yrs*)

*Preliminary Findings



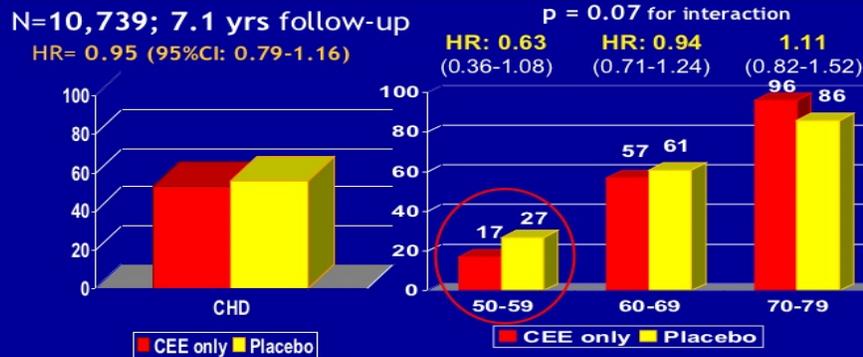
*Statistically significant based on 95% nominal CI on Hazard Ratios

Adapted from: Writing Group for the Women's Health Initiative. *JAMA*. 2002;288:321-333



WHI: Estrogen Alone

WHI E-alone: CORONARY HEART DISEASE (CHD) Total and by Age (Rates per 10,000/year)



Hsia et al Arch Intern Med 2006; 166:357-365.



Women and Hormonal Therapy

- Estrogen + Progesterone: Not recommended
- Estrogen Alone
 - Only after lifestyle modification is tried first. Identify triggers of hot flashes (coffee, alcohol, certain foods)
 - Less risk of DVT in transdermal therapy but not quite as effective as oral therapy.
 - Minimize duration of therapy around menopause. Do not continue into 6th and 7th decade of life.

Hormone Therapy in Men

- Male Menopause: Myth or Fact?
- Limited Data in Men: There is no Men's Health Initiative to guide us
 - WHI Study 27,347
 - Largest Male Hormone Replacement Study is 790 men.
- Initial data on men obtained in trials of men 60+ with diagnosed hypogonadism.
- Based on data showing increased rates of lipid abnormalities, diabetes, and CV disease in patients with true untreated hypogonadism.

Hormone Therapy in Men: Rationale

- Epidemiologic studies strongly support the association of low testosterone concentrations and hypogonadism, with cardiovascular events and all-cause mortality, especially in elderly men.
- However, low testosterone could be a marker of illness and not a causal factor.
- TRT favorably changes many cardiovascular risk factors. It decreases fat mass, increases muscle mass, decreases insulin resistance and can reverse metabolic syndrome.

Male Hormone Replacement Therapy

“Do You Have This Symptom? We Can Help.”

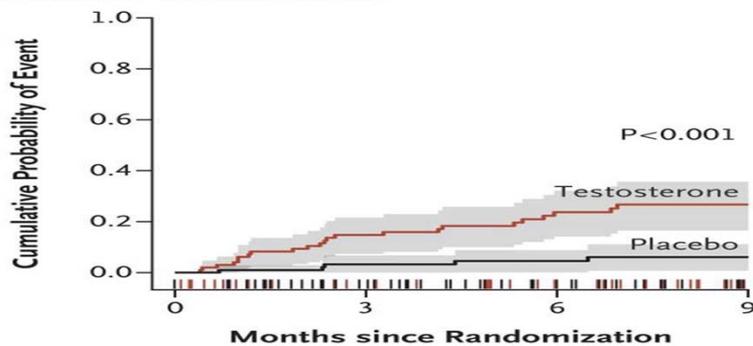
Marketing vs Medicine

- I don't have as much energy as I used to
- I don't feel like I see physical results when I exercise
- I gain weight more easily than I used to
- I seem to have trouble losing weight
- I often feel sad, depressed or frustrated
- I'm easily agitated
- I have a hard time concentrating or staying focused
- I don't have the drive at work I once did
- I sometimes forget things I normally wouldn't
- I don't have the sex drive I used to have
- I don't feel like I'm really living or loving my life the way I could be

Increased CV Events with Testosterone Therapy

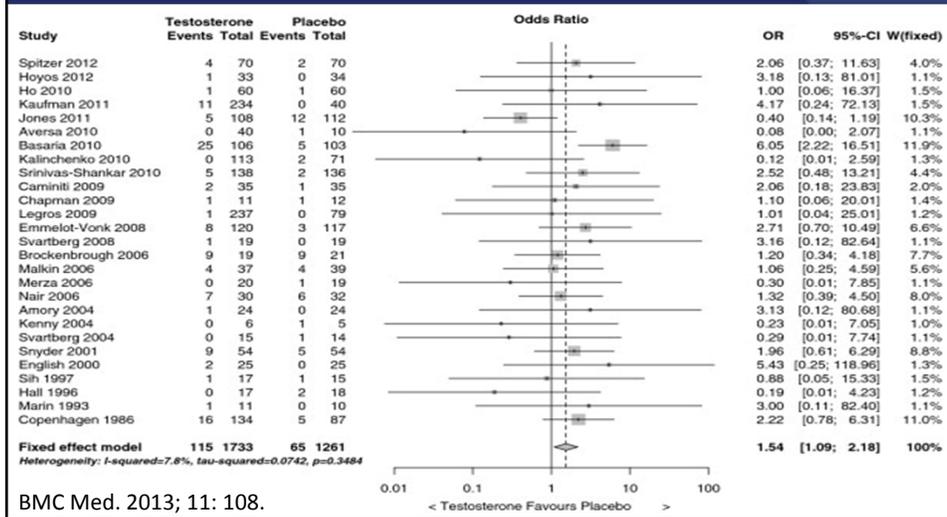
N Engl J Med. 2010 Jul 8;363(2):109-22

A Cardiovascular-Related Events

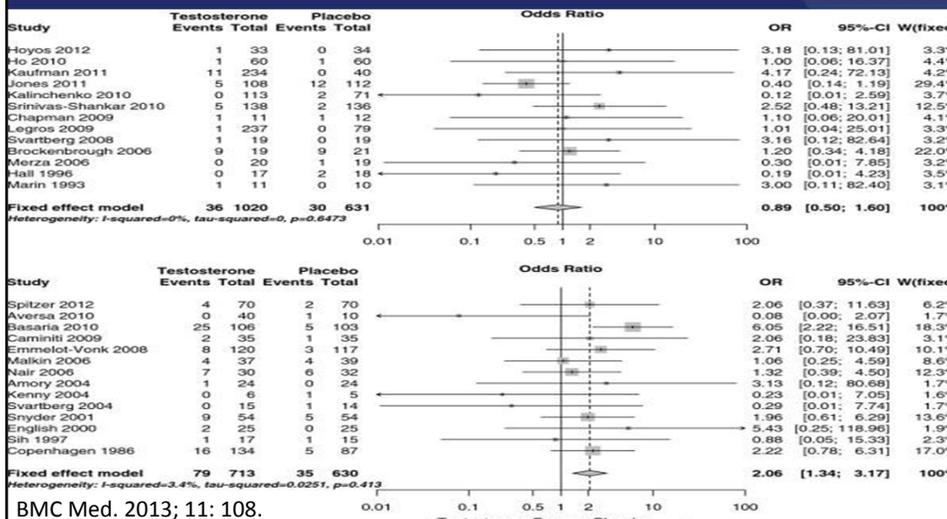


No. at Risk				
Testosterone	106	76	55	35
Placebo	103	84	65	48

CV Events in All Randomized Trials of Testosterone Therapy



Does Industry Sponsorship Make a Difference?



Increased Risk of Non-Fatal MI in Men Taking Testosterone Therapy

- Published in Jan 2014
- 55,593 patients looked at retrospectively for MI rates 90 days post prescription of testosterone vs. rates for one year pre prescription.
- Risk of MI increased with testosterone use vs pre use 36% overall.
- Risk of MI was doubled in patients taking testosterone at age >65 and tripled at age >75.

Risk of MI with Testosterone Therapy in Men: The FDA Steps In

- In 2015, the FDA released a warning of the possible increased risk of MI in patients taking testosterone therapy. This risk increased with age and also with prior cardiovascular events.
 - “Testosterone is an FDA-approved replacement therapy only for men with disorders of the testicles, pituitary gland or brain that cause hypogonadism and it should not be used to relieve symptoms in men who have low testosterone for no reasons other than aging.”
- Other side effects were noted with testosterone therapy:
 - contributing to sleep apnea
 - stimulating noncancerous growth of the prostate
 - enlarging breasts
 - limiting sperm production
 - stimulating growth of existing prostate cancer
 - contributing to the formation of blood clots in the veins.

American College of Endocrinology Position Statement on TRT

- We recommend that symptomatic men, who have unequivocally low total and/or free testosterone levels that are assayed on at least 2 samples drawn before 10 am should be considered for TRT.
- The decision to replace testosterone therapy should be guided by the signs/symptoms and testosterone concentrations rather than the underlying cause.
- Men should be told that we do not have definitive studies demonstrating efficacy or risk for treating men with these conditions. Since the risk/benefit ratio of TRT is not well established in aging-associated hypogonadism, we advise the practicing clinician to be extra cautious in the symptomatic elderly with demonstrably low testosterone levels prior to embarking on replacement therapy and to avoid treatment of the frail elderly altogether.

American College of Endocrinology Position Statement on TRT

- The benefits of TRT are more consistent in men with very low testosterone concentrations than in those with concentrations just below the normal range. Health care professionals should make patients aware of the possible increased cardiovascular risk when deciding whether to start or continue a patient on testosterone therapy.
- TRT should not be provided to men who have untreated or metastatic prostate cancer or breast cancer.
- Relative contra-indications include:
 - Untreated severe sleep apnea
 - A Hematocrit >50%
 - Severe lower urinary tract symptoms with an International Prostate Symptom Score above 19
 - Uncontrolled or poorly controlled heart failure, a MI or cerebrovascular accident within the past 6 months
 - A personal or family history of a procoagulant state, or a personal history of thromboembolism

The “T Trials”

- A 7 part trial of testosterone therapy looking at major endpoints of sexual function, exercise tolerance, and vitality
- 51,085 men screened but only 790 enrolled.
 - Few had low enough T levels to qualify
- Eligibility criteria:
 - Age of 65 years or older
 - Testosterone levels that averaged less than 275 ng per deciliter.

N Engl J Med 2016; 374:611-624 February 18, 2016

The “T Trials”

- Exclusion criteria:
 - History of prostate cancer
 - A risk of all prostate cancer of more than 35% or of high-grade prostate cancer of more than 7% as determined according to the Prostate Cancer Risk Calculator
 - Conditions known to cause hypogonadism
 - Receipt of medications that alter the testosterone concentration
 - High cardiovascular risk (myocardial infarction or stroke within the previous 3 months, unstable angina, New York Heart Association class III or IV congestive heart failure, a systolic blood pressure >160 mm Hg, or a diastolic blood pressure >100 mm Hg)
 - Severe depression (defined by a score of ≥ 20 on the Patient Health Questionnaire)

N Engl J Med 2016; 374:611-624 February 18, 2016

The “T Trials”: Results

- Men who received testosterone reported better sexual function, including activity, desire, and erectile function, than those who received placebo. (P<0.001)
- The percentage of men whose 6-minute walking distance increased by at least 50 m did not differ significantly between the two study groups in the Physical Function Trial. However, men who received testosterone were more likely than those who received placebo to perceive that their walking ability had improved since the beginning of the trial (P=0.002)
- Testosterone had no significant benefit with respect to vitality, as assessed by the FACIT–Fatigue scale, except as a continuous outcome when men in all three trials were included. However, testosterone was associated with small but significant benefits with respect to mood and depressive symptoms. Men in the testosterone group were also more likely than those in the placebo group to report that their energy was better
- The study was not powered to identify safety issues but no significant difference in cardiovascular risk was noted.

N Engl J Med 2016; 374:611-624 February 18, 2016

Male Hormone Replacement Therapy: Conclusions

- The initial rationale would seem to suggest a benefit in cardiovascular health treating low testosterone levels in aging men.
- Benefit:
 - Sexual function, both objectively and subjectively
 - A perception of improved exercise tolerance and vitality without objective supportive data.
- Risk:
 - Prostate cancer
 - Prostatic hypertrophy
 - DVT
 - ?CV Risk

Male Hormone Replacement Therapy: Cardiovascular Risk

- Inconclusive, based on randomized, placebo controlled trials
- Retrospective meta-analysis suggests increased risk but there is debate:
 - Non-traditional definitions of cardiac symptoms (syncope) in some trials in the metaanalysis
 - Questions of industry influence
- We need a large Men's Health Initiative Study to answer the CV safety issues

Male Hormone Replacement Therapy: My Recommendations

- TRT is not for every man older than 40.
 - Test testosterone levels before 10am on at least two occasions to prove "Low T". Not just a random level.
 - Men should be symptomatic
- Exclude any man with known prostate or breast cancer
- Exclude any man with known cardiovascular disease within the previous 6 months
- Have a frank discussion of the potential risks vs. benefit for men with:
 - History of cardiovascular disease
 - Sleep apnea
 - Prostatic hypertrophy
 - Hematocrit 50% or greater
 - History of DVT or PE

Thank You