HORMONES & CARDIOMETABOLIC DISEASE
The Safe use of Bioidentical Hormones in Men & Women

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Disclosure

- Dr. Monaco presents educational lectures in seminars sponsored by
  - PCCA
  - ZRT Laboratories
  - Biotics Research
  - Complimentary Prescriptions
  - Metagenics
  - American Academy of Anti-Aging Medicine

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

◦ Explain the effects of hormones on the cardiovascular system.
◦ Discuss clinically important information that can dictate when hormones are appropriate.
◦ Understand the limitations of hormone on cardiovascular disease.
◦ Discuss clinically relevant information to be used in counseling patients for hormone restoration.

HORMONES

Estrogen, Progesterone, Testosterone, DHEA and Thyroid

◦ CVD: #1 non cancer cause of mortality in men and women
◦ More common in men and PMP Women than in pre-menopausal women
◦ Increasing
◦ Rise of CVD related to decline in estrogen levels
◦ Vascular benefits of endogenous estrogen

REFERENCES


Does PMP HRT protect against CVD?

- Literature mixed
- Depends upon type of hormone and route of administration
- Initial experimental evidence seems to indicate that menopausal hormone therapy (MHT) that is, estrogen may protect against CVD

MENOPAUSE

- Not a disease
- Physiologic phase due to changes in hormonal status
- Endogenous estrogens could affect CV function

CARDIOVASCULAR FUNCTION

- Fatty Streaks
  - Early and potentially reversible stage of atherosclerosis
  - Begins during fetal development!!
- Typical coronary manifestations of atherosclerosis:
  - Lag by 10+ years in premenopausal women compared to men
  - Age 60–64: CVD considerably lower in women vs men
  - Natural estrogen protective??

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95% of women with CVD develop after menopause
Endogenous estrogens attenuate progression of CVD
Menopause: a risk factor for atherosclerosis and CVD?


PROTECTIVE CARDIOVASCULAR EFFECTS

Animal studies:
- Protective cardiovascular effects of E2
- Observational studies: MHT in PMP women reduced the risk of M&M of CHD

HERS study: first randomized clinical trial (RCT)
Questioned protective role of MHT

OTHER STUDIES

- 2000–2003: 4 RCT
- Seriously questioned protective role of MHT
- Focus:
  - 2° prevention of ischemic heart disease or CVA
  - Progression of CAD in known CAD

REFERENCES


MENOPAUSE & CARDIOVASCULAR RISK

- CVD: 10–15 years later in women than men
- Major cause of death in women > age 65
- Normal E2 production:
  - Pre-menopause: 70–500µg/day
  - ½ life is 3 hours
  - 20% decline during perimenopause
  - 2% decrease in CVD risk for every year menopause is delayed

Framingham Heart Study & Nurses’ Health Study (NHS):

- Increased CVD risk with BSO
- Risk not seen in oophorectomized women on MHT


Age and estrogen deficiency linked to morbidity in women

MENOPAUSE & CARDIOVASCULAR RISK

- PMP women have higher TC, LDL-c, Tg's and Lp(a) and lower HDL-c.


MENOPAUSE & CARDIOVASCULAR RISK

- Menopause is an independent risk factor for:
  - Metabolic syndrome
  - Hypertension
  - Abdominal adiposity
  - Insulin resistance
  - Dyslipidemia

MENOPAUSE & CARDIOVASCULAR RISK

- The presence of both diabetes mellitus and hypoestrogenemia: higher percentage of angiographic CAD

**MENOPAUSE & CARDIOVASCULAR RISK**

- SWAN (Study of Women’s Health Across the Nation):
  - Transition to menopause/decreased estrogen associated with changes in:
    - CIMT
    - Adventitial Thickness
    - Increased risk of CVD
  

**MENOPAUSE & CARDIOVASCULAR RISK**

- PROTECTIVE EFFECTS OF ENDOGENOUS ESTROGEN
  - Modification of circulating lipoproteins
    - Decreased LDL-c
    - Decreased Lp(a)
    - Increased HDL-c
    - Decreased lipid peroxidation
    - Decreased insulin resistance
    - Inhibition of intravascular accumulation of collagen
    - Decreased VSM growth and proliferation
    - Direct vasodilatation
    - Mediated via estrogen receptors.

**MENOPAUSE & CARDIOVASCULAR RISK**

- VASCULAR ESTROGEN RECEPTORS
  - 2 Receptors: ERα and ERβ
  - Expression may be similar in some organs & different in other tissues where 1 subtype predominates

MENOPAUSE & CARDIOVASCULAR RISK

› VASCULAR ESTROGEN RECEPTORS

› Localized in endothelium and VSM
› Subcellular: localized in cytoplasm, nucleus and endoplasmic reticulum, Golgi apparatus and mitochondria
› Plasma membrane of EC’s, ERs localize to caveolae.

REFERENCES


MENOPAUSE & CARDIOVASCULAR RISK

› VASCULAR ESTROGEN RECEPTORS

› ERα and ERβ Encoded by distinct genes located on chromosomes 6(q24–q27) and 14(q21–q22) respectively
› G protein–coupled 7–transmembrane receptor (GPR30 or GPER)
› Structurally unrelated to ERα and ERβ but binds E2 with high affinity
› May be involved in estrogen signaling
REFERENCES


VASCULAR ESTROGEN RECEPTORS

- ERβ wider tissue distribution than ERα
- ERβ is the predominant subtype in VSM

VASCULAR ESTROGEN RECEPTORS

- ER’s localized in atherosclerotic plaques
- ERβ: predominant ER in human coronary arteries
- Increased ERβ expression may be linked to advanced atherosclerosis and calcification independent of age or hormone status.
REFERENCES


VASCULAR ESTROGEN RECEPTORS

- In coronary arteries of men, ERβ expression in the intima but not in the media positively correlated with plaque area

  - mediated by altered endothelial function


G-protein coupled estrogen receptor (GPER)

- May explain non-genomic effects of estrogen
- GPR-30
  - Localized to the endoplasmic reticulum
  - Specifically binds estrogen
MENOPAUSE & CARDIOVASCULAR RISK

› VASCULAR ESTROGEN RECEPTORS

› 10-fold greater expression of ERβ vs ERα or GPR30 in the internal mammary arteries of men and women with atherosclerosis


› Epigenetic changes in ERβ may contribute to the development of atherosclerosis and vascular ageing in human arteries.


› Abundance of both ERα & ERβ in the media of human aorta not correlated with the degree of atherosclerosis.

VASCULAR ESTROGEN RECEPTORS

Methylation of the ERα in the cardiovascular system is linked to aging and atherogenesis.

In some women, increased methylation of the ERα gene in certain vascular sites may partially negate the benefits of MHT in these women.

REFERENCES


MENOPAUSE & CARDIOVASCULAR RISK

VASCULAR ESTROGEN RECEPTORS

ERα gene methylation is potentially reversible using DNA–methyltransferase enzyme inhibitors

ER gene demethylation: control of VSMC proliferation and restenosis post-angioplasty.
REFERENCES


MENOPAUSE & CARDIOVASCULAR RISK

Genomic & Non–Genomic Effects of Estrogen

- Estrogen increases the gene expression of vasodilatory enzymes such as NOS and prostacyclin synthase.

- ERα & ERβ may have differential and opposing effects at the same promotor sites
- If co-expressed, ERβ may exhibit inhibitory action over ERα mediated gene expression.


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RAPID ACTION ESTROGEN EFFECTS

- Non-Genomic
- Ability to stimulate eNOS
- ER’s in endothelial cells associate with calveolae
- ERα interacts with Calveolin-1 (structural protein which localizes ER to plasma membrane)
- Estrogen then activates eNOS → Nitric Oxide


VASCULAR ESTROGEN RECEPTORS

- EC’s: estrogen modifies the production, release and bioactivity of endothelium derived relaxing factors
  - NO
  - Prostacyclin (PGI₂)
  - Hyperpolarizing factors (EDHF)
  - Endothelin (ET-1)
  - Intracellular calcium kinetics in coronary EC’s
REFERENCES


MENOPAUSE & CARDIOVASCULAR RISK

- VASCULAR ESTROGEN RECEPTORS
  - Small subcutaneous arteries from healthy PMP women NOT receiving PMP HRT:
    - Morphology and function of endothelium are impaired
    - Impairments improved by treating with E2

REFERENCES

In ovariectomized mice, E2 causes rapid, non-genomic arterial dilation of elastic and muscular arteries resulting from ER mediated NO production. ERα but not ERβ mediates effect of E2 on NO.

Darblade B. Estradiol alters nitric oxide production in the mouse aorta through the alpha-, but not beta- estrogen receptor. Circ Res. 2002; 90;413–19

E2 has antioxidant properties
- Reduces ROS
- Increase NO bioactivity


Ovariectomized Rats:
- Increase BP
- Increased lipoperoxides
- Increased vascular free radicals

Estrogen replacement prevents these effects
Superoxide (O$_2$•-) production greater in blood vessels of males than female rats. E2 inhibits NADPH oxidase expression and generation of O$_2$•- peroxynitrite enhancing NO bioactivity.


ESTROGEN AND VSM

E2 inhibits VSM growth and proliferation through inhibition of MAPK


Vasodilation is likely due to long–term effects of estrogen on the expression and permeability of voltage–gated Ca$^{2+}$ channels.

ESTROGEN AND ATHEROSCLEROSIS

Presence or absence of endogenous estrogens affects CV function
May be tied to different stages in progression of atherosclerosis.

ATHEROSCLEROSIS

- Inflammatory process
- EC dysfunction
- Excess deposition of oxidized lipids

EVOLUTION OF ATHEROSCLEROSIS

- Initial accumulation of foam cells in endothelium
- Fatty streak
- Accumulation of fatty deposits (cholesterol)
- True atheroma
- Fibrous cap stabilizes plaque and prevents rupture
- MMP's degrade collagen weaken fibrous cap
- Rupture–release of thrombus
- Vascular occlusion
ESTROGEN & ATHEROSCLEROSIS

- Estrogen reduces development of early atherosclerotic lesions
- Lipid metabolism and reducing fatty deposits

MATURE AThEROMA
- E2 increases MMP expression
- Disruption of fibrous cap and rupture

Thus estrogen, through different mechanisms, inhibits early development of atherosclerosis, but may increase the risk of cardiovascular events once atherosclerosis is established.


MENOPAUSE & CARDIOVASCULAR RISK

- How can you determine a woman’s relative risk of hormone restoration past 10 years?
  - HSCRP: Highly Sensitive CRP
  - MPO: Myeloperoxidase
  - LpPLA2:
  - MMP: Matrix Metallo Proteinase
MENOPAUSE & CARDIOVASCULAR RISK

- HSCRP: Sensitive indicator of vascular inflammation
- LpPLA2: Lipoprotein Associated Phospholipase 2:
  - Determine risk of CVD including coronary heart disease and stroke
  - Platelet activating factor
  - May predict heart disease in people with normal LDL-C
- MMP-9: Matrix Metallo Proteinase
  - Degrades extracellular proteins
  - Activation increases risk of plaque rupture
- MPO: Myeloperoxidase
  - Inflammation releases MPO
  - MPO accumulates in Subendothelial matrix
  - Endothelial dysfunction

ESTROGEN AND ATHEROSCLEROSIS

- Does IV E2 cause vasodilatation in healthy and ASCVD women?
- E2 improves flow-mediated vasodilatation more in women within 5 years since menopause than in women more than 5 years after menopause

REFERENCES

Early observational studies:

- MHT in PMP women reduces the risk of a cardiovascular event in women using unopposed oral estrogens


Meta-analysis

- 1/3 reduction in fatal CVD


Observational study:

- MHT associated with favorable outcomes after coronary angioplasty and CABG surgery.

RESULTS FROM CLINICAL TRIALS

- Early PMP women randomized to E2 showed less progression in Carotid Intimal Media Thickness (CIMT) than PMP women on placebo.


NURSES' HEALTH STUDY

- Prospective observational cohort study
- 2489 women with a previous MI or documented atherosclerosis
- Risk for major coronary events increased among short-term MHT users but decreased among long-term users

RESULTS FROM CLINICAL TRIALS

- Placebo controlled RCT
  - 1017 women age 50–69
  - Experienced first MI

Unopposed estrogen was neither harmful or helpful in terms of frequency or re-infarction or cardiac death after 2 years of treatment

REFERENCES


RESULTS FROM CLINICAL TRIALS

- WHI: Women’s Health Initiative
  - Double blind RCT
  - Healthy PMP women age 50–79
  - Question: Is Menopausal Hormone Therapy (MHT) effective in primary prevention?
  - 2 arms:
    - 16,608 women with intact uterus: CEE (0.625mg/day orally) plus MPA (2.5mg/day orally)
    - 10,739 women w/o uterus: CEE (0.625mg) alone or placebo.
RESULTS FROM CLINICAL TRIALS

- WHI: Women’s Health Initiative
- Results:
  - Neither estrogen nor estrogen plus progestin decreased CVD
  - Stopped prematurely: Data Safety & Monitoring Board (DSMB) concluded that evidence of breast cancer harm and increase in CHD, stroke and PE outweighed benefit seen for bone fractures and possible benefit for colon cancer.

REFERENCES


MENOPAUSE & CARDIOVASCULAR RISK

- VENOUS THROMBOEMBOLISM
  - Uncommon before menopause
  - Increases with age after menopause
  - 1/100 over age 75

MENOPAUSE & CARDIOVASCULAR RISK

ROUTE OF ADMINISTRATION

• RCT’s: 2 fold increased risk of Vascular Thromboembolic Events (VTE) with Menopausal Hormone Therapy (MHT).
• Large cohort case control study:
  • 23,505 PMP women matched with 231,562 controls
  • Risk increased with use of oral estrogen and oral estrogen–progestin combination
• NO SIGNIFICANT INCREASE IN VTE RISK WITH TRANSDERMAL ESTROGEN

REFERENCES


MENOPAUSE & CARDIOVASCULAR RISK

MHT AND AGE

- Menopausal and cardiovascular changes in aging women is partly related to substantial decrease in estrogen levels to <100 pmol/L


ERβ expression exceeded ERα expression in all layers of human coronary arteries

ERβ expression correlated with advanced atherosclerosis

Greater in non–MHT user than in MHT users


REFERENCES
MENOPAUSE & CARDIOVASCULAR RISK

MHT AND AGE

- DNA methylation: age-related disease and decrease in ERα expression related to methylation of ERα gene


Methylation induced inactivation of the ERα gene in vascular tissue may play a role in atherogenesis and aging of the vascular system


PROGESTERONE
There are divergent cardioprotective effects of bioidentical progesterone and synthetic progestins


Classical nuclear estrogen receptors (ERα) and progesterone receptors are expressed in vascular muscle cells (VMC’s)
REFERENCES


PROGESTERONE

- Progesterone inhibits smooth muscle cell proliferation
- Progestins may increase proliferation of coronary artery smooth muscle cells.


- The VCAM–1 protein mediates the adhesion of lymphocytes, monocytes, eosinophils, and basophils to vascular endothelium
- Progesterone inhibits VCAM–1 expression

PROGESTERONE

- Chronic progesterone treatment reduces systemic blood pressure in humans.


PROGESTERONE

- Progesterone may accelerate the process of repolarization and protect the females from drug-induced arrhythmias, thus counteracting the effect of estradiol.


PROGESTERONE

- Progesterone beneficially regulates coronary artery reactivity in monkeys and humans.


REFERENCES


PROGESTERONE

- MPA antagonizes the inhibitory effects of conjugated equine estrogens on coronary atherosclerosis in cynomologus monkeys

PROGESTERONE

- MPA partially inhibited the estrogen associated increase in HDL-c more than micronized progesterone.


PROGESTERONE

- Detrimental effect of MPA on the beneficial effects of CEE with regard to atheroma development and vascular reactivity.

REFERENCES


Estrogen increases the exercise time to myocardial infarction

Natural progesterone enhances this effect


Progesterone but not estrogen inhibits apoptosis in cardiomyocytes.


Low levels of progesterone in men associated with increased carotid IMT independently of age or other risk factors

No association between mean CIMT and progesterone levels in women either before or after adjustment for age and other risk factors.
REFERENCES


PROGESTERONE

• MPA antagonizes the infarct-sparing effects of estradiol, possibly through modulation of the immune response occurring after ischemia and reperfusion.


PROGESTERONE

PROGESTERONE

- Progesterone can decrease arterial thromboxane A₂ receptors
- Progesterone beneficially regulates coronary artery reactivity in monkeys and humans
- May involve regulation (repression) of TxA₂ receptor expression by progesterone

TESTOSTERONE

- Hypogonadism in men is associated with insulin resistance, elevations of pro-inflammatory cytokines, fibrinogen and an atherogenic lipid profile
- Testosterone levels correlate inversely with arterial stiffness, intima-media thickness and aortic diameter


Low testosterone is associated with an increased risk of all-cause mortality.

Serum testosterone levels were inversely related to mortality due to cardiovascular disease and cancer.

TESTOSTERONE

- Associate heart attack with coronary artery occlusion
- 50% caused by sudden cardiac arrest
- Electrical disturbance


SUDDEN CARDIAC ARREST

- 350,000 occurrences
- 75% male
- 5% survival


SUDDEN CARDIAC ARREST

- Deficiency of magnesium and potassium predisposition
- Testosterone important in modulating potassium channels
- Testosterone regulates calcium channels
- Magnesium protects against excess calcium channel influx
REFERENCES


SUDDEN CARDIAC ARREST

- Low testosterone & higher levels of estrogen in men correlated were strongly associated with greater risk of sudden cardiac arrest.

- Men with higher testosterone—25% less likely to suffer SCA

- Men with higher estradiol levels had twice the risk of SCA

- 23% increase in median testosterone levels was associated with a 25% reduction in SCA

- 31% in median estradiol levels doubled the risk SCA
REFERENCES


S UDDEN C A R D I A C A R R E S T

- Low testosterone is associated with abnormal EKG reading that predispose people to SCA

REFERENCES


Low levels of testosterone in men are associated with:
- Greater risk of developing CAD
- More severe atherosclerosis
- Type II diabetes
- Increased visceral adiposity
- Metabolic syndrome

AMERICAN HEART ASSOCIATION REVIEW
- Insulin resistance
- Carotid artery stenosis
- Obesity
- Abnormal EKG
- Angina
- Reduced arterial dilatation (impaired Ca** & K**)
- Increased BMI
- More severe CHF
- Higher rates of all-cause and cardiac mortality
REFERENCES


SUDDEN CARDIAC ARREST

- Potential to identify men at risk for SCA
- Implement preventative treatments
  - Increase testosterone
  - Suppress excess estrogen levels

TESTOSTERONE

- Administration of testosterone to men requires measuring estrogen levels
  - Estradiol
  - Estrone

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TESTOSTERONE

Excess estrogen in men causes:

- Increased platelet aggregation
- Increases probability of abnormal blood clotting forming in jagged coronary arteries


TESTOSTERONE

Estradiol levels measured in 501 men with chronic heart failure:

- Lowest quintile: 317% more likely to die during 3 year follow-up
- Highest quintile: 133% more likely to die
- Balanced quintile with fewest deaths:

  - Estradiol levels between 21.80 and 20.11 pg/mL

REFERENCES

High estradiol in men associated with an increased risk of stroke and acute myocardial infarction


Despite overwhelming evidence to the contrary, the FDA, in March 2015, issued a mandate regarding testosterone. Labels must now carry a warning that testosterone may increase the risk of MI and stroke.

FDA advisory panel admits that there is only a "weak signal of cardiovascular risk".

http://www.fda.gov/downloads
TESTOSTERONE

- Low testosterone levels predictive of hypertension


- Higher LH levels in men are associated with increased ischemic heart disease events.


BENEFITS OF TESTOSTERONE REPLACEMENT

Earlier onset of fatal MI in men 65 years of age or older with prostate cancer who have been on androgen suppression for ≥ 6 months

Men with low testosterone are at increased risk of CAD


TESTOSTERONE

› Low testosterone levels are associated with an increased risk of Type II diabetes and metabolic syndrome.

Laaksonen D, Niskanen L, Punnonen K et al. Testosterone and sex hormone binding globulin predict the metabolic syndrome and diabetes in middle-age men. Diabetes Care 2004;27:1036–1041.

› ...Testosterone, despite lowering HDL cholesterol, intensifies Reverse Cholesterol Transport (RCP) and thereby exerts an anti-atherogenic rather than a pro-atherogenic effect."

Intracoronary artery injection of testosterone at physiologic concentrations in men with established CAD produces coronary artery dilatation and increased coronary blood flow


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**CAN TESTOSTERONE REDUCE THE RISK OF CAD?**

- Epidemiologic studies: low T → ↑ CV mortality
- Androgen Deprivation Therapy (ADT): unfavorable changes in body composition

- TRT:
  - Improves insulin sensitivity & lipid profiles
  - ↓ fat mass  ↑ lean muscle mass
  - Vasodilator  ↓ blood pressure

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Meta analysis (Toma et al.)

- Improved exercise capacity & endurance, FBS, FI, IR and peripheral vasodilatation

- Testosterone appears to be a promising therapy to improve functional capacity in patients with heart failure


In men with heart failure, low serum androgens was associated with an adverse prognosis

**TESTOSTERONE**

- For each 6 ng/dl increase of testosterone per liter an ~ 14% drop in risk of death


**TESTOSTERONE**

- DHT has been shown to enhance early atherosclerosis
- New androgen receptor: NFKB mediated mechanism for VCAM-1 expression
  (? Male predisposition to atherosclerosis)

**REFERENCES**

Mortality, incident CAD and severity of CAD are inversely associated with serum testosterone levels. Largest meta-analysis to date revealed no increase in CV risks in men who received testosterone and reduced CV risk among those with metabolic disease.

No large, long-term placebo controlled randomized clinical trials to provide definitive conclusions about CV risk. There exists abundant literature spanning many decades that provide valuable information in favor of CV protection and other benefits.

2 recent articles contradict the literature and upon careful examination, neither provides credible evidence of increased CV risks. A wealth of modern data accumulated over the past 2 decades has generally revealed that low testosterone is associated with increased risks for atherosclerosis, CV risk factors and mortality and T therapy has a beneficial effect on these risk factors and biomarkers.
DISSECTING THE LITERATURE

- Vigen et al. *JAMA* 2013
- Retrospective analysis of men having coronary angiography in the VA health care system
- Reported overall rate of MI, stroke and death increased in men with serum T levels <300 ng/dl who received testosterone compared to untreated men.
- Actual rate of adverse events on ½ as great in the treated group 123/1223 (10.1%) vs 1587/7486 (21.2%)

DISSECTING THE LITERATURE

- Study flaws and incorrect data analysis/interpretation
- All male study group included nearly 10% women!!

  FDA comment:
  - “Given the described limitations of the study by Vigen et al, it is difficult to attribute the reported findings to testosterone treatment”

DISSECTING THE LITERATURE

- Retrospective study of a health insurance database
- Compared rates of nonfatal MI for a 90 period following T prescription to MI rates in the previous 12 months

- No information regarding standard CV risk factors (diabetes, hypertension, dyslipidemia, smoking or obesity)
- No information regarding blood test results
  - Serum testosterone
  - Lipids
- Used insurance Dx code with verifying that an MI had actually occurred.


- No control group!
- Short exposure time 30–90 days
- Reported MI rates post-T prescription were low 4.75 events/1000 person–years compared to general population of 13 expected MI/1000.
- The observed MI rate was ~1/3 the expected rate.

FDA comment:

“...it is difficult to attribute the increased risk for nonfatal MI seen in the Finkle study to testosterone alone and not consider that the study participants might have remained hypogonadal and thus at higher risk for non-fatal MI.”

Ibid.
DISSECTING THE LITERATURE

- Basaria et al. NEJM 2010
  - Prospective randomized trial
  - T-Gel provided greater muscular/function
  - Positive benefits—stopped early because of increased adverse events categorized as "cardiovascular". 23(treatment) vs 5(placebo)

DISSECTING THE LITERATURE

- PROBLEM
  - Study not designed to investigate CV events
  - Reported events “incidentally” noted
  - Questionable clinical importance
    - Palpitations, pedal edema and PVC’s

DISSECTING THE LITERATURE

- ~200 frail, elderly men
- Pedal edema most common (5 cases in T group)
- Given frail men with multiple comorbidities, unlikely none in placebo had pedal edema
- Violates fundamental concepts in clinical trials
  - Defined end points
  - Systematic data acquisition
DISSECTING THE LITERATURE

- 4 Major Adverse Cardiac Events (MACE)
  - 1 death, 2 MI’s, 1 stroke all in T group
- Similar study in UK: 2 MACE 1 death & 1 MI both in placebo group
- May be due to chance
- ? Using higher than approved doses

Xu et al. BMC Medicine 2013

- Meta-analysis of 27 placebo controlled T studies of 12 weeks duration or longer
- Increase in CV events in T arm
- Excluded studies which reported no CV events!!

SUMMARY

- There exists a broad, rich literature with numerous studies revealing increased CV concerns with testosterone deprivation and improvement in a variety of CV risk factors and some CV outcomes with testosterone therapy

Low levels of TT, free T and bioavailable T are associated with increased mortality from all causes and CV disease.

Incident CAD is associated with lower levels of TT, bioavailable T or free T

Severity of CAD is inversely correlated with concentrations of TT, bioavailable T or free T.

Ibid.

There is insufficient evidence to conclude whether a relationship exists between ischemic stroke and serum androgens

CIMT and/or carotid plaque volume are inversely associated with serum concentrations of TT, bioavailable T or free T

Ibid.

Testosterone therapy is associated with a significant reduction in obesity and fat mass

Testosterone therapy is associated with small decreases in total cholesterol, HDL-c and LDL-c with no clear effect on triglycerides.

Ibid.
SUMMARY

- Testosterone therapy is associated with a decrease in serum glucose, HbA1c and insulin resistance in diabetic and pre-diabetic men.
- Testosterone therapy is associated with an inconsistent reduction in inflammatory markers
  
  Ibid.

SUMMARY

- Testosterone therapy improves time to onset of symptomatic angina with exercise
- Testosterone therapy improves exercise capacity and peak oxygen consumption in men with symptomatic CHF as defined by NY Heart Association functional class II

  Ibid.

SUMMARY

- Hormones can have a significantly positive effect on the cardiovascular system of men & women
- The key is the right hormone, proper physiologic dosing, the correct route of administration and time to initiation of therapy
- Consideration must be given to the interactions of hormones and careful follow-up
THANK YOU

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