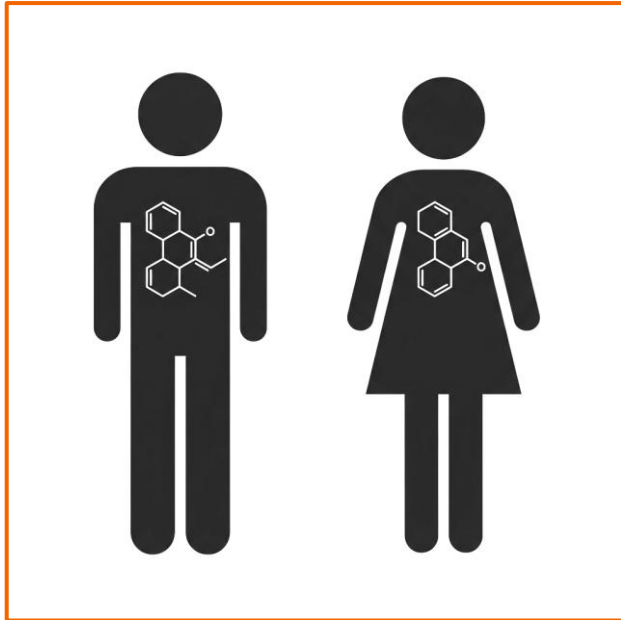




MEDICINE



Hormone Therapy for Men and Women

Hanna Fogg, DO

Disclosures

- Clinical consultant for Amgen
- Speaker bureau for Sanofi

Learning Objectives

- Identify patients who would benefit from hormone therapy
- Differentiate between the various types of hormone therapies available for men and women
- Apply current guidelines in managing hormone therapy
- Be able to define contraindications for hormone therapy
- Be familiar with monitoring of patients on hormone therapy

The FDA Is Set To Remove Black Box Warning On **Hormone Therapy** For Menopause—Here's What That Means For You

Women'sHealth

NEWS
20 YEAR OLD MEN TODAY HAVE TESTOSTERONE LEVELS SIMILAR TO WHAT 70 YEAR OLD MEN HAD IN THE 1970S



FDA Reverses **BLACK BOX WARNING** On **HORMONE** Replacement Therapy




male **excel** 1/2

TEENAGERS TODAY HAVE LOWER TESTOSTERONE LEVELS THAN 68-YEAR-OLDS



DOES HORMONE REPLACEMENT THERAPY CAUSE DEMENTIA?



LADIES, BIG PHARMA DOESN'T WANT YOU TO KNOW THIS.

Hormone therapy could actually prolong your life.

DR. VASS
CORNELL M.D. & LONGEVITY EXPERT

IS MY ESTROGEN *too high?*

There are some telltale signs that your estrogen level is too high.

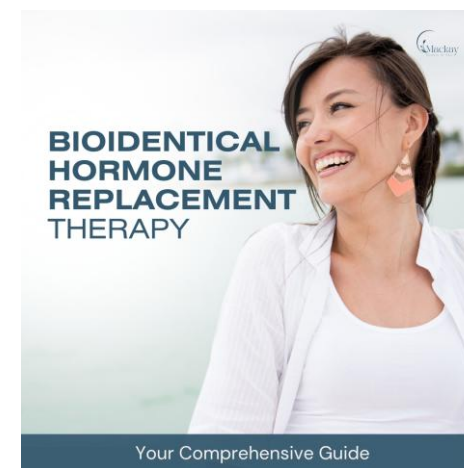
DHEA
The Fountain of Youth Hormone

KathleenBarnes.com



BIOIDENTICAL HORMONE REPLACEMENT THERAPY

Your Comprehensive Guide



Menopause



85%

Women will experience menopausal symptoms

169,000,000

Number of Women in the US

20%

US Family Medicine, Internal Medicine and OB/GYN Residents had not had a single lecture on Menopause in a 2017 study

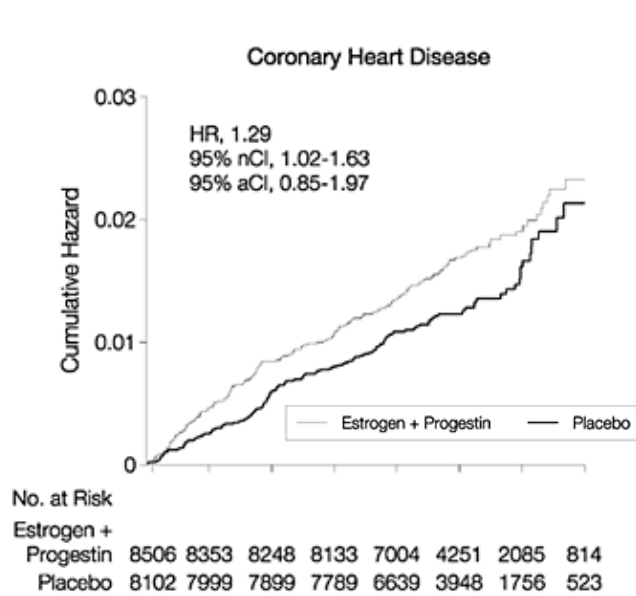


The Women's Health Initiative

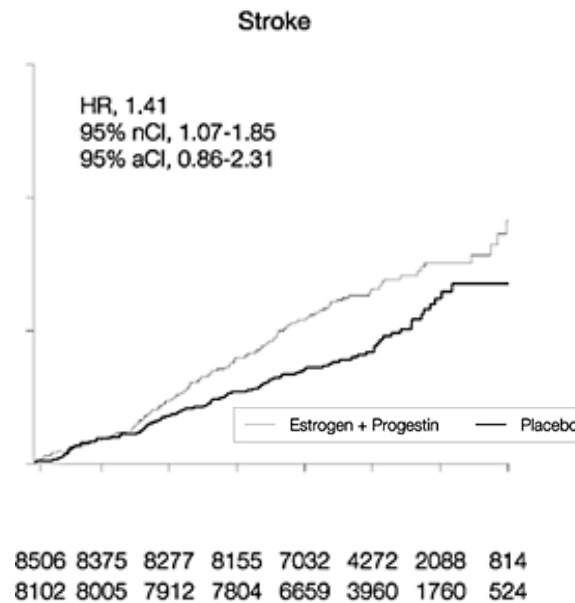


SO WE'RE NOT GOING TO DISCUSS IT?

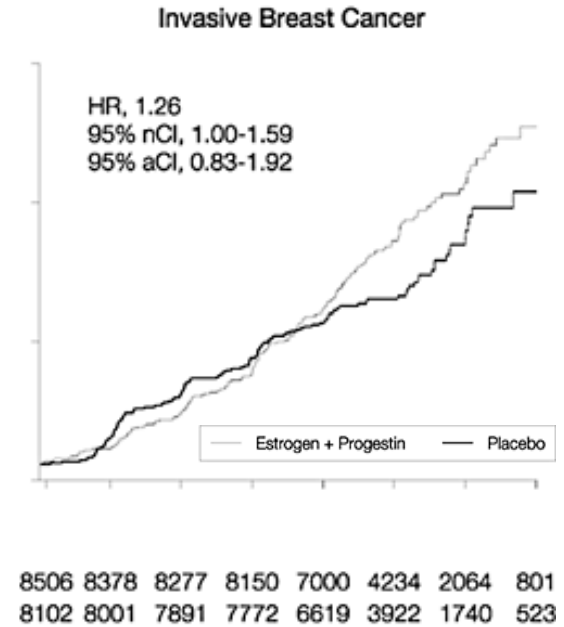
WHI- Study Results



29% ↑*
Coronary Disease



41% ↑*
Stroke



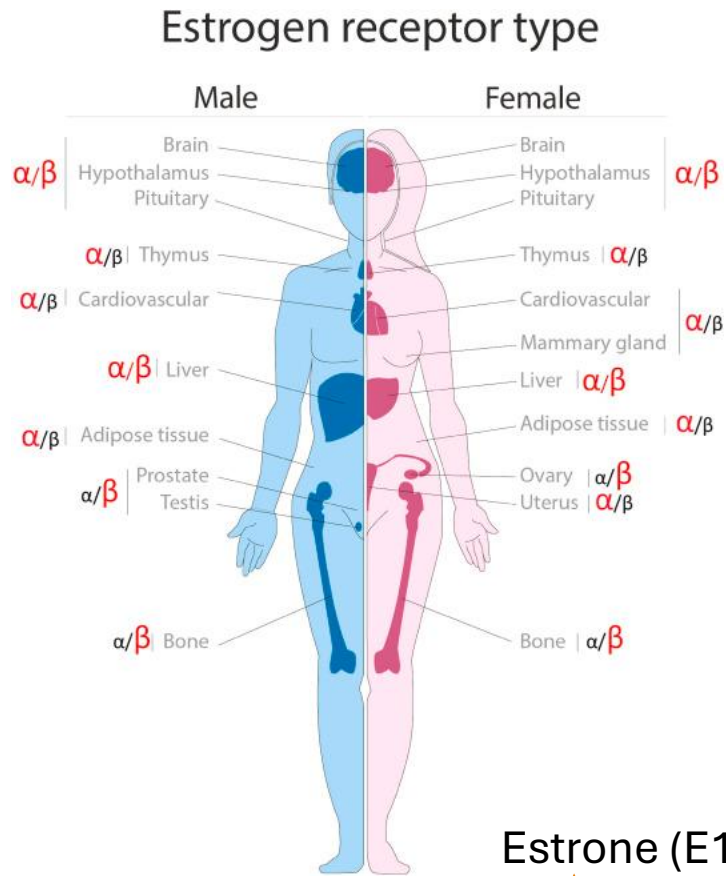
26% ↑*
Breast Cancer

WHI Study – who was studied & what was used?

- **Estrogen Alone** – conjugated equine estrogen (CEE)
 - 10,739 women
 - mean age of 63.6 years
 - 3,313 women (31%) were aged 50-59 years
- **Estrogen + Progesterone** - CEE + medroxyprogesterone acetate
 - Synthetic progestin
 - 16,608 women
 - mean age of 63.3 years
 - 5,520 women (33%) were aged 50-59 years

This is the only study we have looking at long term effects of MHT

Estrogen preparations

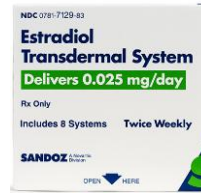


Estrone (E1)



Estradiol (E2) → Estriol (E3)

Potency ↑



Estradiol (E2)

1st line

Primary Premenopausal Estrogen Patches, oral, and OCPs

ER α = ER β



Estrone (E1)

The Postmenopausal Estrogen

Predominant Estrogen in CEE (used in WHI)

ER β > ER α



Estriol (E3)

Mostly Pregnancy Estrogen

Efficacy in genitourinary symptoms and safety profile

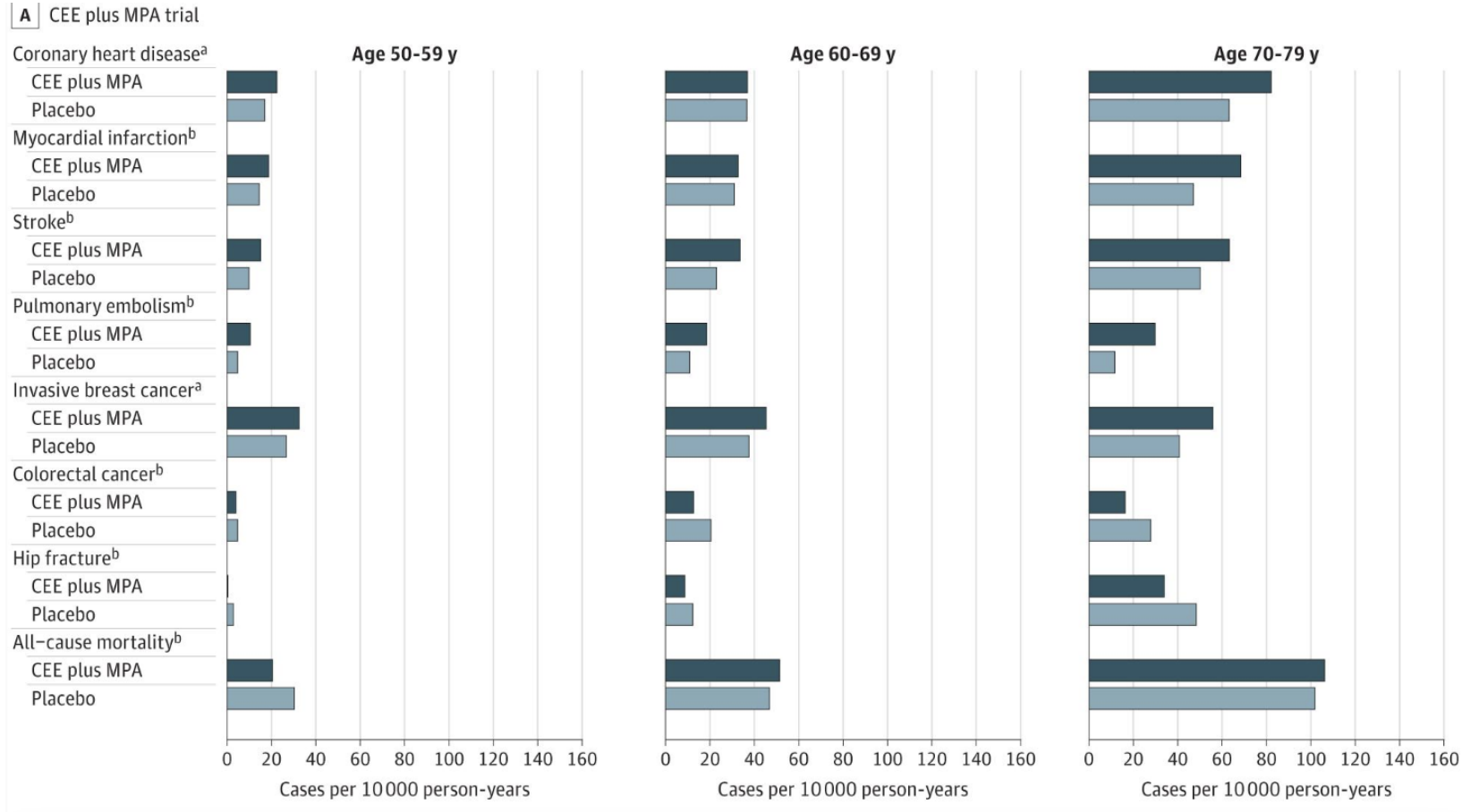
Not FDA-approved for systemic use in US

ER β > ER α

WHI Study Results – Relative & Absolute Risk or Benefit Combined CEE+MPA

Relative and Absolute Risk or Benefit Combined E+P			
Outcome	RR vs. Placebo at 5.2 years (95% CI)	Increased Absolute Risk per 10,000 Women/year	Increased Absolute Benefit per 10,000 Women/year
Heart Attack	1.29 (1.02-1.63)	7	
Stroke	1.41 (1.07-1.85)	8	
Breast Cancer	1.26 (1.00-1.59)	8	
VTE	2.11(1.39-3.25)	18	
Colorectal Cancer	0.63 (0.43-0.92)		6
Hip Fracture	0.66 (0.45-0.98)		5

Combined CEE+MPA – Breakdown by Age

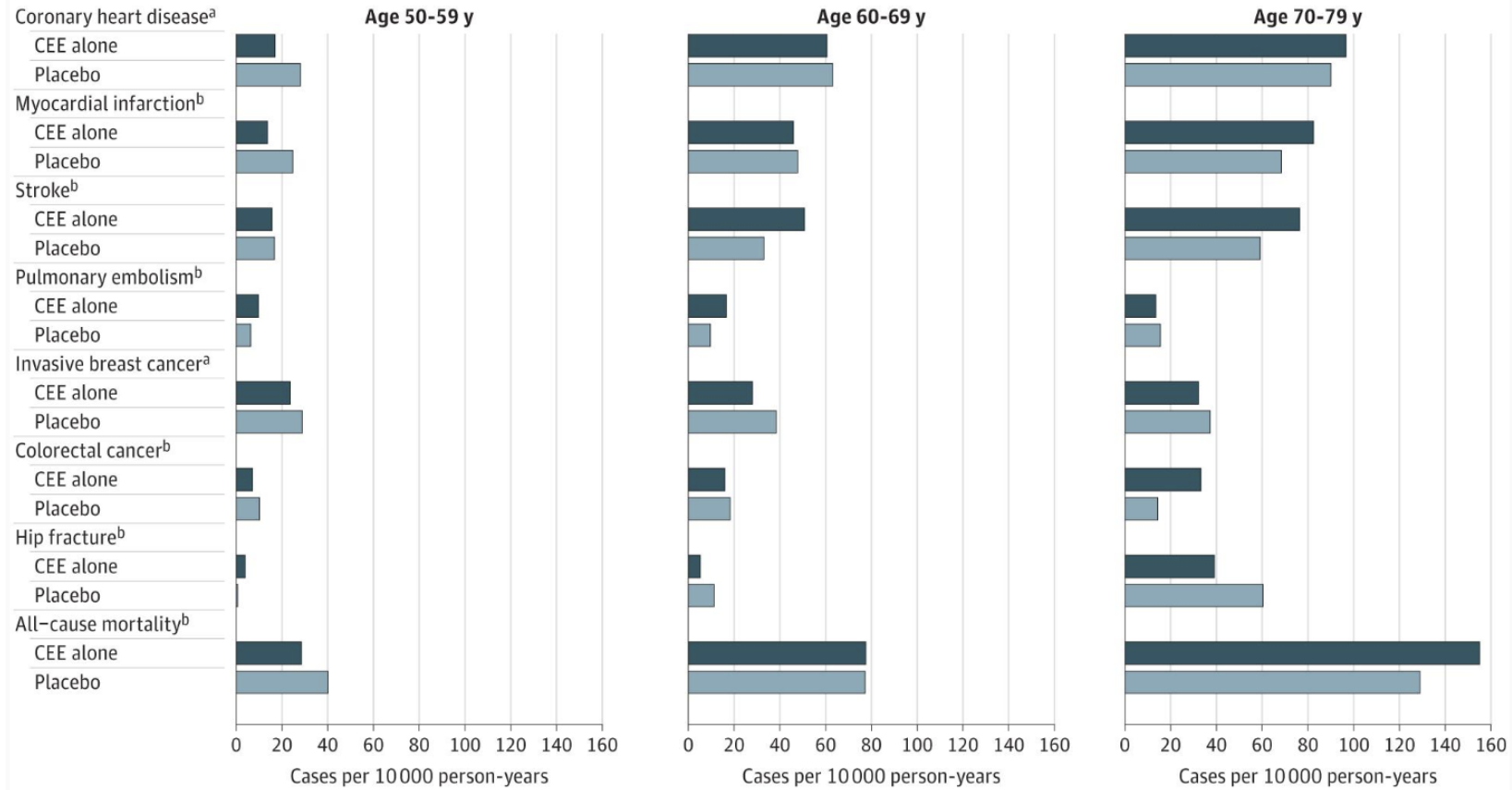


WHI Study Results – Relative & Absolute Risk or Benefit CEE only

Relative and Absolute Risk or Benefit CEE-only			
Outcome	RR vs. Placebo at 5.2 years (95% CI)	Increased Absolute Risk per 10,000 Women/year	Increased Absolute Benefit per 10,000 Women/year
Heart Attack	0.91 (0.75-1.12)		2
Stroke	1.39 (1.10-1.77)	11	
Breast Cancer	0.77 (0.59-1.01)		7
VTE	1.39 (1.10-1.77)	8	
Colorectal Cancer	1.08 (0.75-1.55)	1	
Hip Fracture	0.61(0.41-0.91)		6

CEE-only– Breakdown by Age

B CEE-alone trial



WHI 18 years later...

CEE + MPA 5.6 years

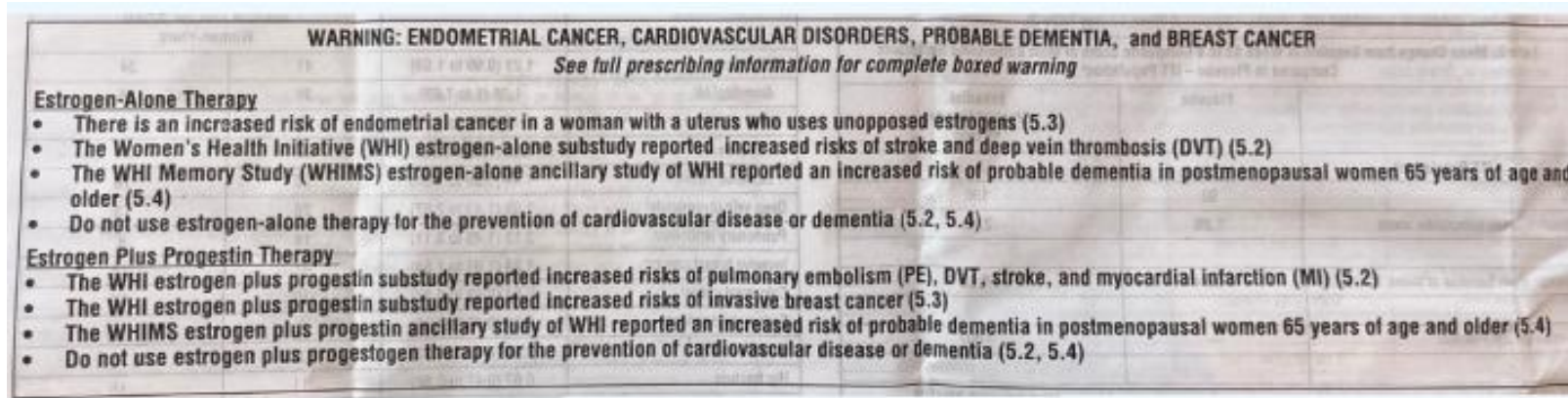
CEE-only 7 years

- NO INCREASE in overall cancer deaths (including breast cancer)
- NO INCREASE in deaths from CVD
- Statistically significant reduction of all-cause mortality when started at 50-59 years

WHI Study Results – Subgroup Analysis Takeaways

Women aged 50-59	Women aged 60-69	Women aged 70-79
<p>Favorable outcomes Both regimens</p> <p>No absolute excess risk for cardiovascular disease stroke</p> <p>Reduction in all-cause mortality</p>	<p>Effects were generally neutral</p>	<p>Risk is increased</p> <p>Increased risk for cardiovascular disease</p> <p>Increase in all-cause mortality</p>

FDA removes black box warning November 2025



Warnings that were removed:

- Increased risk of cardiovascular disease
- Increased risk of breast cancer
- Probable dementia risk
- * Risk of endometrial cancer remains

Additional label updates –post Nov 2025



Removal of the recommendation:

Using the lowest dose
for the shortest duration



Labels will include:

Guidance on initiating treatment
in women younger than 60 years
or within 10 years of menopause
onset to optimize risk-benefit
balance



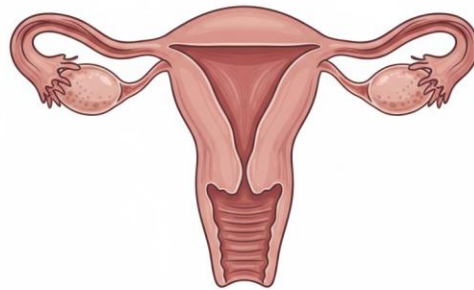
For vaginal estrogen:

broader warnings
associated with systemic
exposure will be removed

Hormone Therapy is Approved for FOUR Indications



Vasomotor Symptoms



Genitourinary Syndrome



Prevention of bone loss in high-risk women



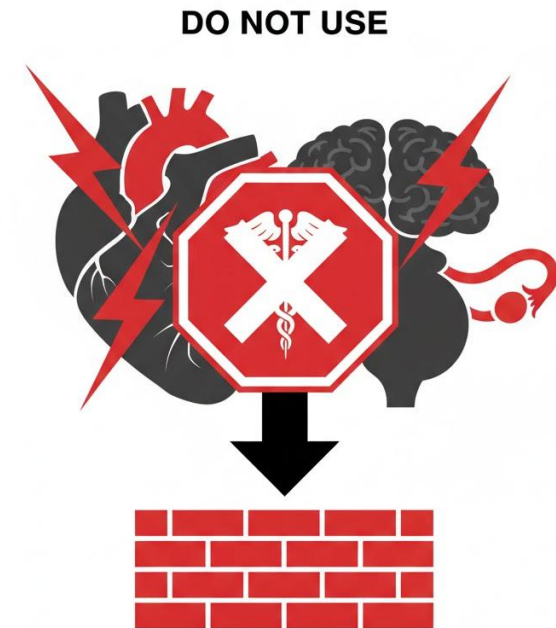
Premature menopause
*need secondary evaluation and physiologic dosing

Absolute Contraindications to MHT

- Cardiovascular disease
- Stroke
- DVT or PE
- Personal History of Breast Cancer
- Personal History of Endometrial Cancer
- Undiagnosed vaginal bleeding

Relative Contraindications to MHT

- Risk factors for absolute contraindications
 - Always a discussion of risk/benefit balance



Patient Factors that Modify Risk of MHT

Age



Age 50-59 years

Age >60 years

Time



Years since last menstrual period

Over 10 years
Under 10 years

Metabolic syndrome



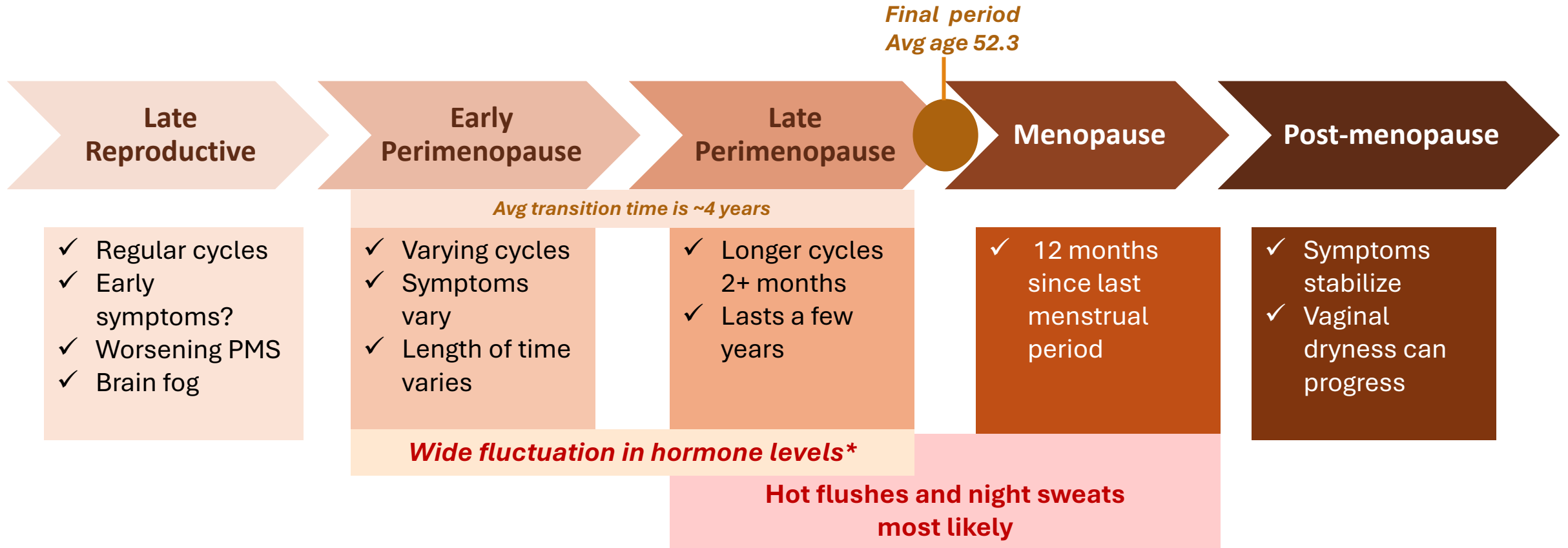
Uncontrolled HTN
Triglyceridemia
Hyperlipidemia

High ASCVD



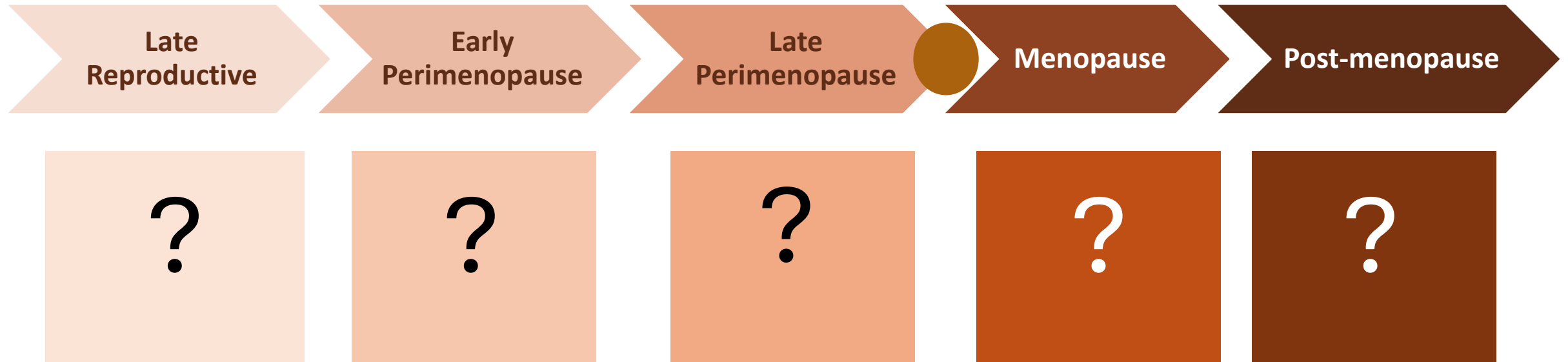
ASCVD risk >10%

Menopause Transition Timeline



* Estradiol levels may be as high as 2,000+ pg/mL

When Should MHT Be Initiated?



Considerations when selecting a MHT regimen

- Does the patient have any absolute contraindications to MHT?
- Is there a need for contraception?
- Type of menopausal symptoms for which treatment is desired
- Presence of a uterus?
- How long since onset of Menopause?
- Comorbid medical conditions that may influence management options

Early
Perimenopause

Late
Perimenopause

MARY: perimenopause



45-year-old stay at home mom

Healthy, no medications

Cycles lengthening

Skipped one period in the last year

Frequent hot flashes both day and night causing
sleep disturbance

Feels “off” and is experiencing brain fog

Natural History of Hot Flashes

Transition Stage	% Affected	Age
Pre-menopause	20-45%	< 45
Pre-to-early perimenopause	25-55%	45-47
Early-to-late perimenopause	50- 80%	47-49
Late perimenopause to post-menopause	35- 75%	49-55
Late post-menopause	16- 44%	56+

Barnabei V et al. *Obstet Gynecol*, 2002
Gold EB, et al. *Am J Pub Health*, 2006
Politi MC et al. *J Gen Intern Med*, 2008

- ✓ 30-50% spontaneous improve in 4-5 years
- ✓ 85-90% experience resolution in 7-10 years
- ✓ 10-15% "Super Flusher" into late 60s/70s

Early
Perimenopause

Late
Perimenopause

MARY: perimenopause



Needs BOTH:

CYCLE CONTROL - and - CONTRACEPTION

MHT is about 1/4th the amount of the lowest oral contraceptive so it will not be enough to control abnormal bleeding

OPTIONS for Treatment:

Monophasic oral contraceptive pill

Levonorgestrel IUD + estradiol patch

Menopause

Post-menopause

Sherry: post-menopause



54-year-old Teacher

Last menstrual period: 24 months ago

Has symptoms of frequent hot flashes, night sweats, sleep disturbance, fatigue and irritability

Has tried Ashwagandha, Black Cohosh, and soy without improvement

History of hypothyroidism, fibrocystic breasts, benign breast biopsy at age 50

Medications: levothyroxine

She is interested in bioidentical hormone therapy

What is a “bioidentical” hormone

Chemical structure that is identical to reproductive age hormones

Estradiol, progesterone, testosterone are all bioidentical

Does not mean COMPOUNDED

34% compounded HT failed quality standards

Purity, bioavailability, dose-to dose consistency is questionable

Transdermal progesterone is ineffective for endometrial protection

And if on topical estrogen, they need IUD, oral progesterone

Estrogen preparations

These are ALL "Bioidentical"

Estrone (E1)



Estradiol (E2) → Estriol (E3)

Potency ↑



Estradiol (E2)

1st line

Primary Premenopausal Estrogen
Patches, oral, and OCPs



Estrone (E1)

The Postmenopausal Estrogen
Predominant Estrogen in CEE (used in WHI)



Estriol (E3)

Mostly Pregnancy Estrogen
Efficacy in genitourinary symptoms and safety profile
Not FDA-approved for systemic use in US

Menopause

Post-menopause

Sherry: post-menopause



54-year-old Teacher

Fully menopausal and symptomatic

No absolute contraindications to MHT

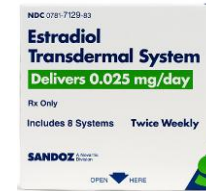
You recommend:

Estradiol 0.05 mg/day patch

Micronized progesterone 100 mcg nightly or IUD

Return to clinic in 2-3 months to reassess

Transdermal Estradiol



Estradiol (E2)

1st line

Primary Premenopausal Estrogen
Patches, oral, and OCPs

ORAL v. Transdermal Estrogen Therapy and Thromboembolic Complications

Study	Oral	Transdermal
	Odds Ratios (95% CI)	
Scarabin et al. <i>Lancet</i> , 2003	3.5 (1.8-6.8)	0.9 (0.5-1.6)
Canonico et al. <i>Circulation</i> , 2007	4.2 (1.5-11.6)	0.9 (0.4-2.1)

The prothrombotic effect of oral estrogen is attributed to hepatic first-pass metabolism –
Induces prothrombotic substances including factor VII, factor VIIIc, and factor IX.

No RCTs in this area, but observational data shows transdermal preparation takes down to baseline risk

Menopause

Post-menopause

Sherry: post-menopause



What if she had a personal history of breast cancer?

BIG NO

Doesn't matter the type –
triple negative, etc

*Fibrocystic breasts, dense breasts, prior benign biopsy or family history of breast cancer would not absolutely exclude her from MHT

*Strong family history – risk assess
- BRISK calculator

Menopause

Post-menopause

Sherry: post-menopause



What if she had a history of DVT?

Depends –provoked?

Consider progestin-only

Consider non-hormonal option

Progestin-only is the best alternative to estrogen
to control VMS (off-label)

Hot flash frequency and severity reduction by
80-90%

Micronized progesterone 300 mg QHS

Menopause

Post-menopause

Sherry: post-menopause



**What if she had presented at Age 65?
11 years after menopause onset**

**Review cardiovascular risk
Weigh Risk v Benefit
Consider non-hormonal option**

Menopause

Post-menopause

Sherry: post-menopause



54-year-old Teacher

Fully menopausal and symptomatic

No absolute contraindications to MHT

Current regimen:

Estradiol 0.05 mg/day patch

Progesterone 100 mcg nightly or IUD

Returns to clinic and is experiencing breakthrough bleeding and symptoms are not controlled

Increase estradiol dose

Ensure no missed progesterone – breakthrough

Monitoring & When to stop MHT

- No need to check levels – treat to symptoms
- “Use the lowest dose” no longer applies – use the most appropriate dose
 - Usually, a mid-range dose to start for someone with significant symptoms is the most appropriate dose
- No recommendation to automatically stop at Age 65
- Reassess risk factors regularly
- Stop if risk factors increase
- Stop if heavy bleeding/unexplained bleeding occurs

Is Testosterone or DHEA indicated for MHT?

- **Testosterone**

- Only indicated for low libido in menopause – HSDD
- No effect on VMS, general well being, mood, cognition, BMD
- No FDA formulation exists – off label testosterone gel or compound
- Must monitor testosterone levels

- **DHEA**

- FDA-approved as an alternative to vaginal estrogen for treatment of genitourinary syndrome or painful intercourse
 - Intravaginal prasterone (Intrarosa[®])

Nonhormonal options

SSRIs			
Paroxetine	10-25 mg	Start with 10 mg	FDA-approved
Citalopram	10-20 mg	Start with 10 mg	
Escitalopram	10-20 mg	Start with 10 mg	Start 5 mg older women
SNRIs			
Desvenlafaxine	100-150 mg	Start 25-50 mg	
Venlafaxine	37.5-150 mg	Start 37.5 mg	
Gabapentin			
	900-2400 mg	Start 100-300 mg QHS	Can increase or add AM

Supplements

Very little to NO Benefit

Black cohosh

Soy

Pollen extract

Rhubarb

Dong quai

Evening primrose

Ammonium succinate

Milk thistle

Ginseng

Cannabinoids

Chasteberry

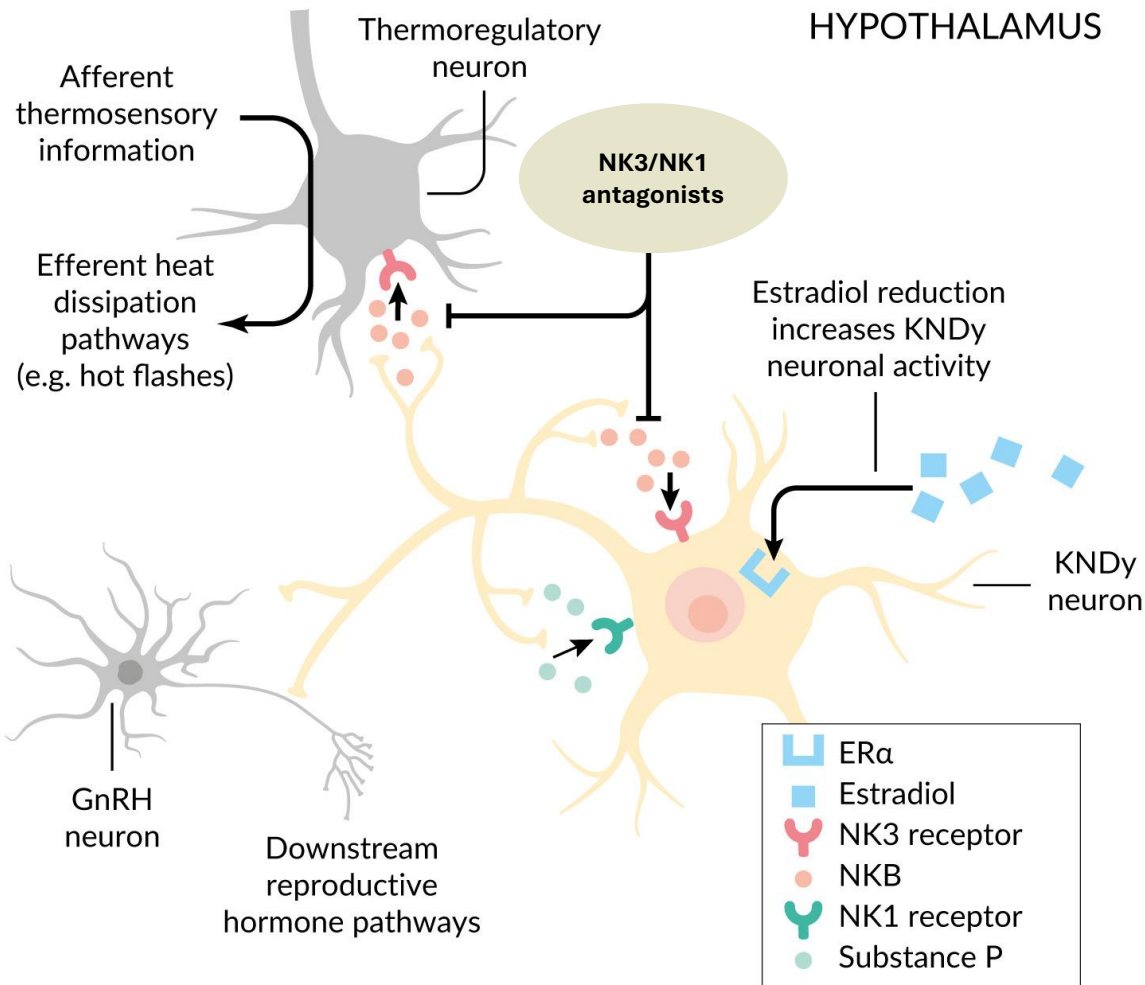
Wild yam

Lactobacillus

Maca



New kids on the block



Elinzanetant Lynkuet[®]



Blocks NK1 and NK3 receptors which blocks the binding of SP and NKB on KNDy neurons.

Fezolinetant Veozah[®]



Blocks neurokinin 3 (NK3) receptor antagonist that blocks NKB from binding on KNDy neurons

Summary on MHT

- MHT is indicated to control symptoms of menopause
- Everything on the formulary is “bioidentical”
- May have benefit in women within 10 years of menopause onset, age 50-59
- Caution in women with onset of menopause >10 years of presentation or older women
 - Alternative therapy may be more appropriate
- Use the most appropriate dose, not the lowest dose
- Oral progesterone or IUD is needed if uterus is intact, transdermal progesterone is not sufficient

MALE HYPOGONADISM



Testosterone Declines Steadily with Age

Starting in mid-30s

Total testosterone declines 1.6% per year

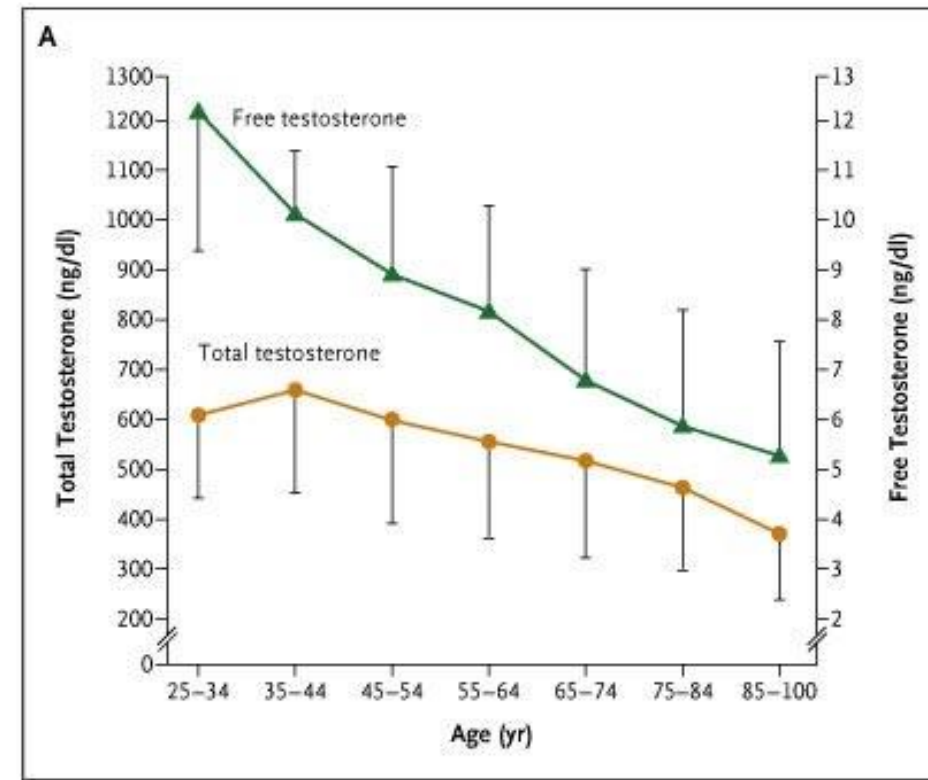
Affects

20% over 60 years

30% over 70 years

50% over 80 years

No “andropause”



Real Case

A 23-year-old collegiate athlete is referred for evaluation of hypogonadism

He is otherwise healthy and has complaints of fatigue

The patient's father is on testosterone and recommended his son be tested

Patient recalls having total testosterone levels that were in the low 300s.

He took testosterone injections over the summer that was prescribed by an online men's clinic

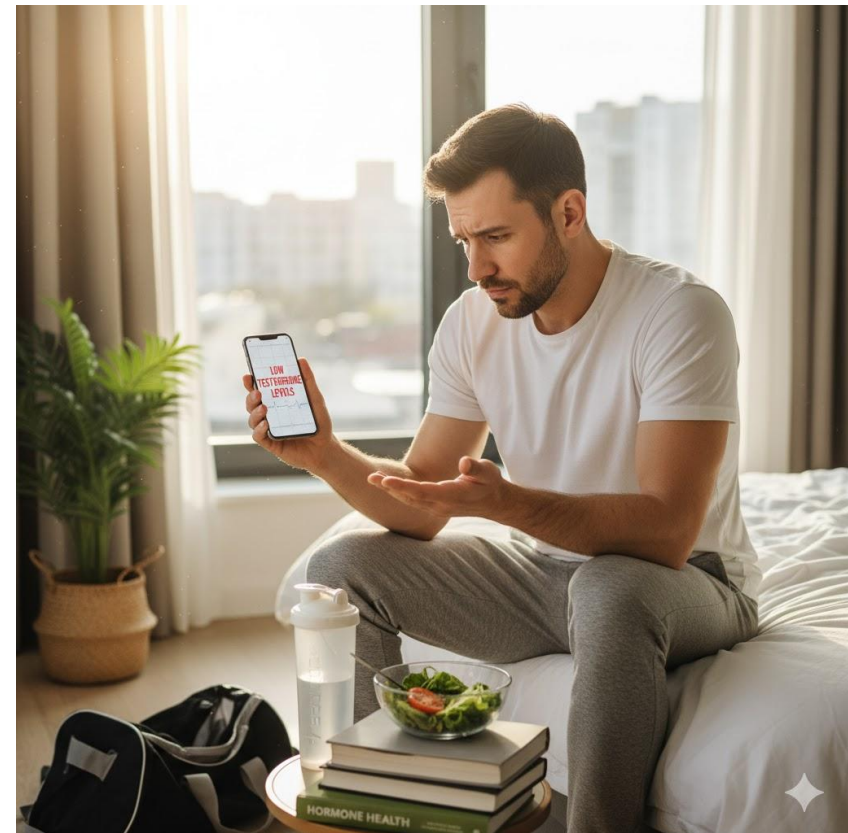
Vitals and exam are normal, muscular build

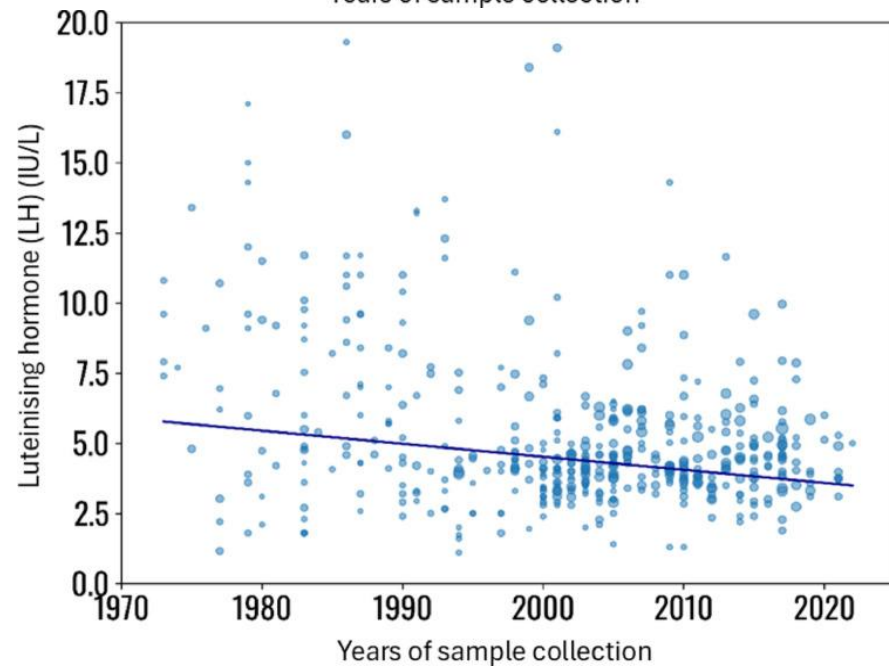
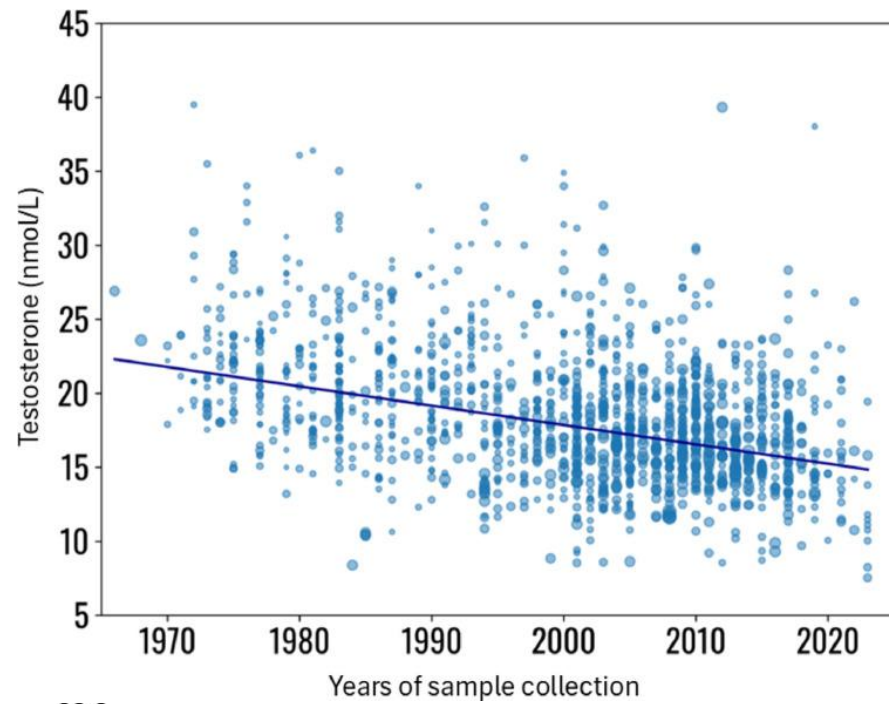
OTHER CHEM		10/24/24 09:28
Alkaline Phosphatase		
Creatinine		
Free T4	1.5	📄
FSH	2.3	📄
Total Testosterone	326	📄
Free Testosterone	9.5	📄
Triiodothyronine, Free (Free T3)	3.8	📄
TSH	3.160	📄

Are levels lower in younger men compared to previous decades?

Is a total testosterone level of 326 ng/dL normal for a 23-year-old athlete?

What about a free testosterone of 9.5 ng/dL?





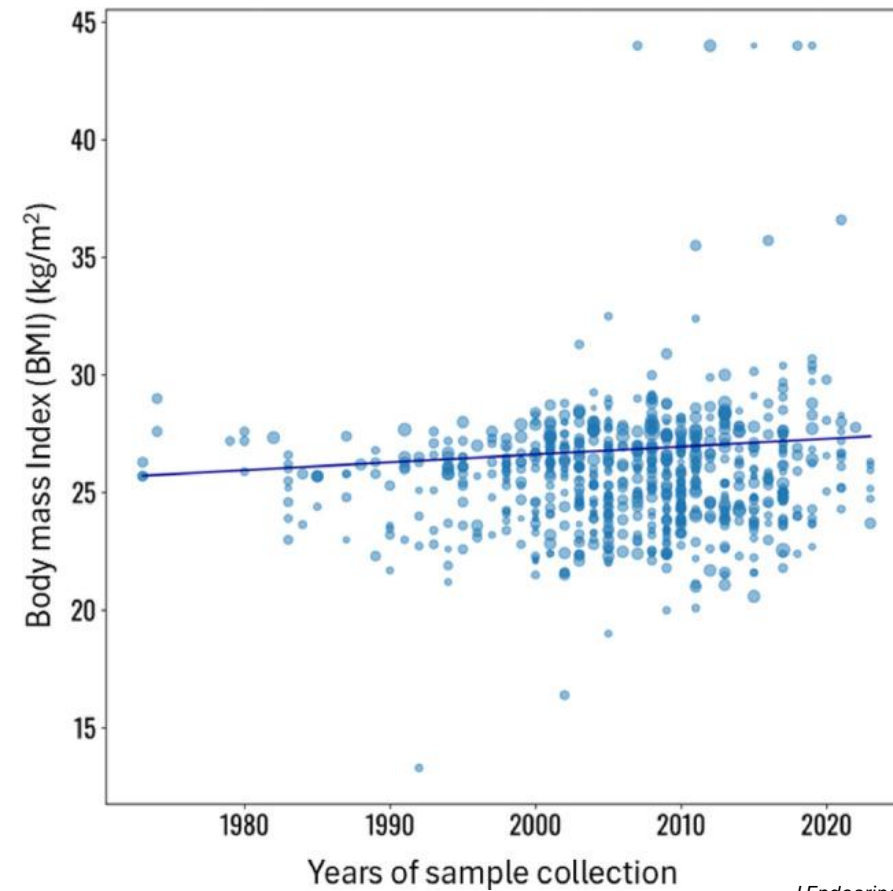
Meta-analysis

1,504 study groups

Testosterone was measured for any reason

1,064,891 healthy subjects, mean age 42 +/- 7 years

Testosterone, LH, BMI



Are levels lower in younger men compared to previous decades?

Maybe?

Several observational studies with similar findings

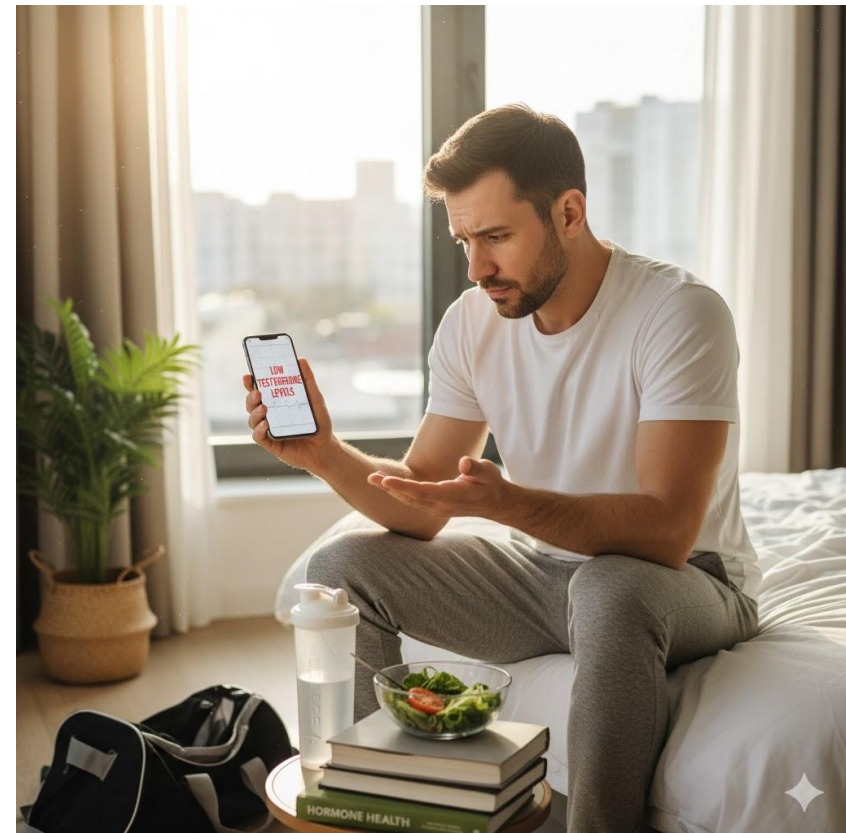
Lack of sleep

Diet

Sedentary lifestyle

Environmental factors

We aren't sure



Optimal levels



**There is no single universally accepted consensus
on normal testosterone levels
by age**

Total testosterone **264-916 ng/dL**

Free testosterone **5-15 ng/dL**

2.5th and 97.5th percentiles of CDC-standardized measurements

Diagnosis of Male Hypogonadism

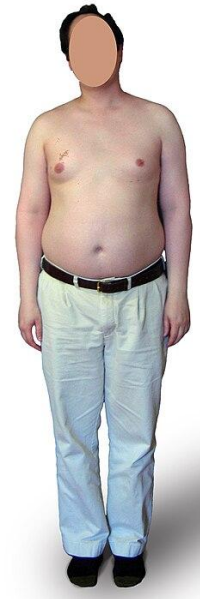
Symptoms & signs

Delayed sexual development
Absence of body hair
Infertility
Small testes
Lack of morning erections
Anemia
Fragility fracture
Erectile dysfunction
Decreased libido
Gynecomastia

Sleep disturbance
Fatigue
Depressed mood
"Feeling off"

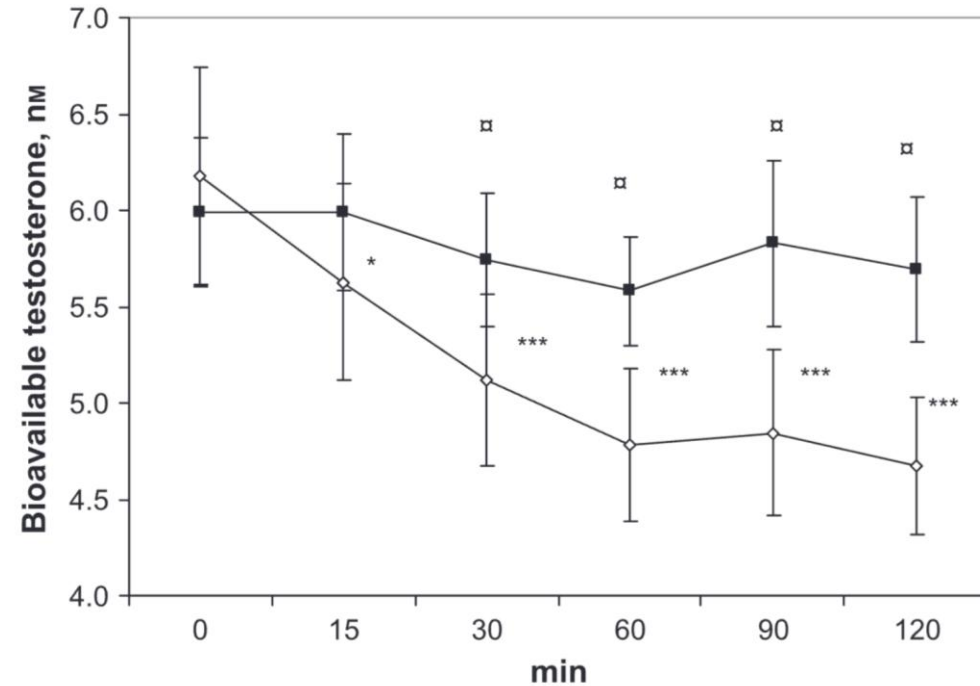
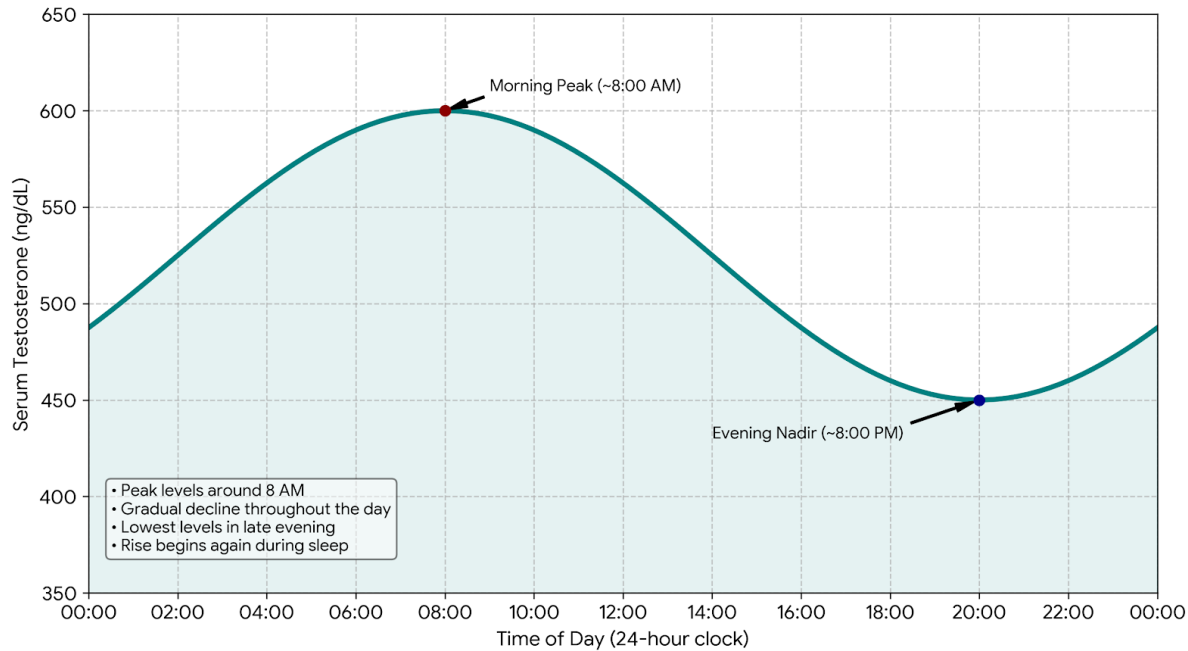
Laboratory values

Unequivocally low 8AM levels
Confirmed at least 2 values



Yes, it has to be fasting and around 0800

Typical Diurnal Rhythm of Testosterone in Men



Which level should be checked?

- To start, just check an 8AM fasting level
- Diagnosis of hypogonadism should be based on free or bioavailable testosterone (not total)
- %free is not relevant
- On 2nd check
 - LH
 - Prolactin
 - Iron studies
 - PSA, CBC

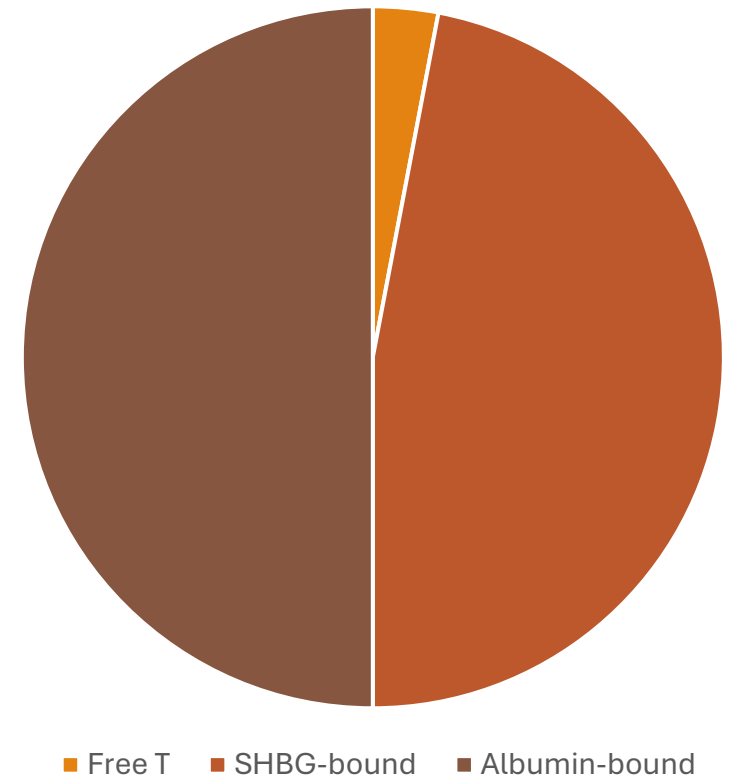


Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

Primary Hypogonadism	Secondary Hypogonadism
ORGANIC	
<ul style="list-style-type: none"> KS Cryptorchidism, myotonic dystrophy, anorchia Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy Orchitis Testicular trauma, torsion Advanced age 	<ul style="list-style-type: none"> Hypothalamic/pituitary tumor Iron overload syndromes Infiltrative/destructive disease of hypothalamus/pituitary Idiopathic hypogonadotropic hypogonadism
FUNCTIONAL	
<ul style="list-style-type: none"> Medications (androgen synthesis inhibitors) End-stage renal disease^a 	<ul style="list-style-type: none"> Hyperprolactinemia Opioids, anabolic steroid use, glucocorticoids Alcohol and marijuana abuse^a Systemic illness^a Nutritional deficiency/excessive exercise Severe obesity, some sleep disorders Organ failure (liver, heart, and lung)^a Comorbid illness associated with aging^a

**LH/FSH
HIGH**



**LH/FSH
LOW**

When should I be worried that something else is going on?

- Primary hypogonadism (high LH/FSH) in young male
 - Absence of virilization – small testes, absence of body hair
- Secondary hypogonadism (low LH/FSH) with concerning features
 - Absence of virilization – small testes, absence of body hair
 - Very low Total Testosterone <150 ng/dl
 - Visual field deficit
 - Any degree of prolactin elevation
 - Anosmia
 - Polydactyly
 - Short stature

Absolute Contraindications

- Male breast cancer
- Any cardiovascular event within the last 6 months
- Uncontrolled heart failure
- Active prostate cancer
 - *use does not increase risk of prostate cancer
- Desires fertility
- Uncontrolled obstructive sleep apnea



Proceed with caution

- Previously treated prostate cancer
 - Risk v benefit discussion
- Hct > 48
- Lower urinary symptoms
- BPH/ PSA over 4 ng/dL
- Can worsen sleep apnea
- Hepatic or renal disease

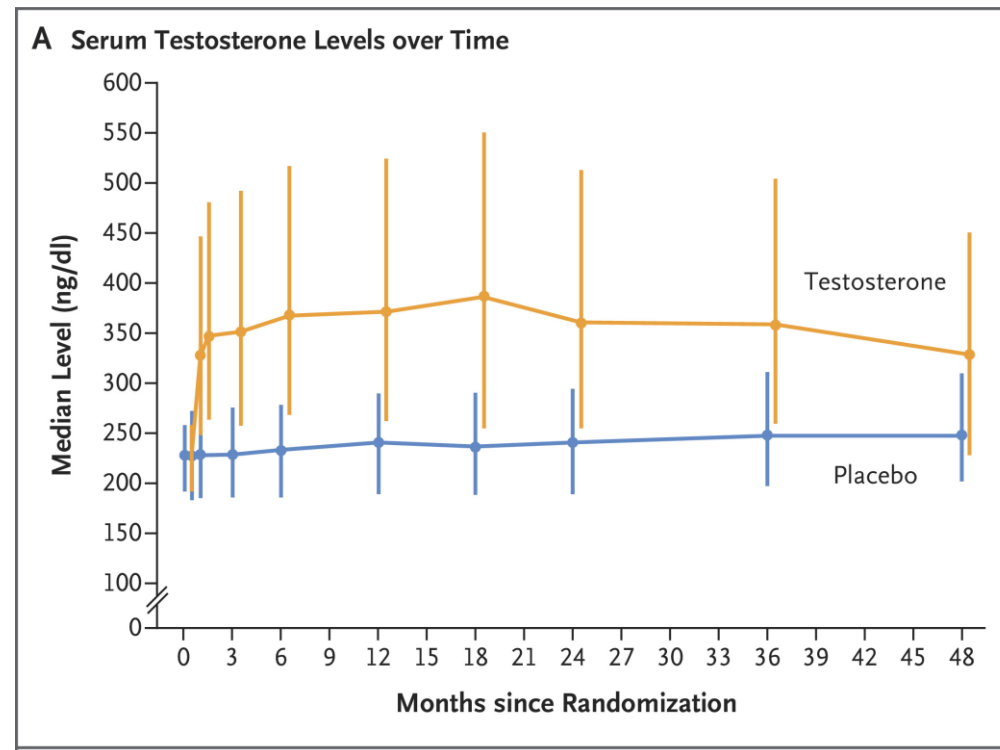




**TESTOSTERONE THERAPY:
INCREASED
CARDIOVASCULAR
RISK?**

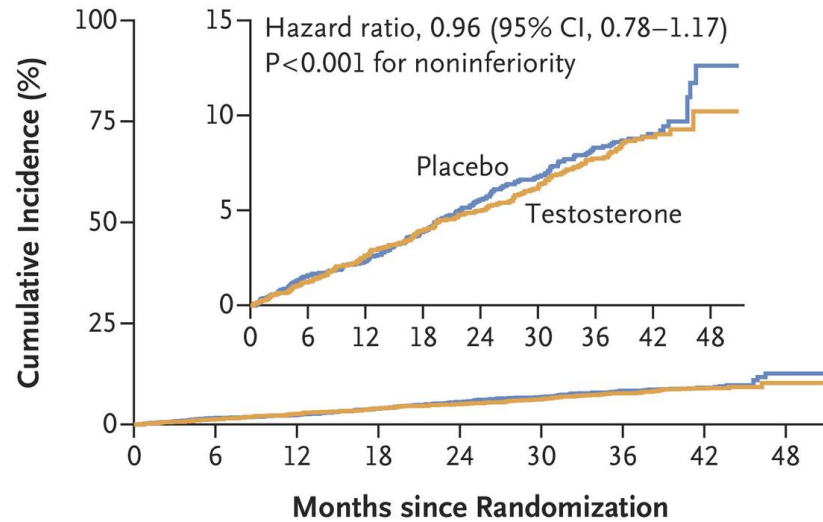
TRAVERSE STUDY: Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men

- Multicenter, randomized, double-blind, placebo-controlled, noninferiority trial
- 5246 men
- Age 45 – 80
- Had preexisting or high risk of cardiovascular disease
 - HTN, DLD, smoke, CKD-III, DM, ↑CRP, CAC >75th percentile for age/race
- Had symptoms + two fasting testosterone levels of 300 ng/dL or less
- Patients were randomly assigned to receive daily transdermal 1.62% testosterone gel (dose adjusted to maintain levels between 350-750 ng/dL) or placebo gel



TRAVERSE STUDY

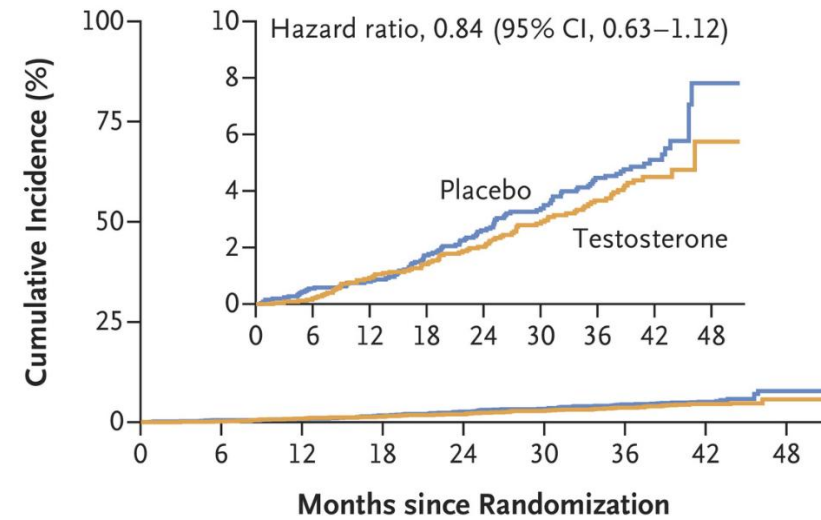
A Primary Cardiovascular Composite Safety End Point: Safety Population



No. at Risk

Placebo	2602	2507	2323	2088	1792	1568	1337	598	33
Testosterone	2596	2504	2339	2120	1829	1605	1380	653	39

D Death from Cardiovascular Causes: Safety Population



No. at Risk

Placebo	2602	2533	2360	2130	1845	1624	1390	619	34
Testosterone	2596	2529	2375	2167	1875	1647	1423	672	40

Testosterone therapy was noninferior to placebo for MACE, with no increased risk of cardiovascular events or venous thromboembolism

TRT has positive effects on

- Insulin resistance/Type 2 diabetes
- Sexual desire
- Lean body mass
- Bone density
 - ? Effects on fracture risk

- Placebo effect: Fatigue

Testosterone Preparations



Transdermal Gel

Daily

No peak/trough

Risk of transference



Testosterone cypionate

Twice monthly

Peak/trough

SubQ or IM



Testosterone enanthate

Weekly

Less peak/trough

SubQ or IM
Cough



Testosterone undecanoate

Twice daily

No peak/trough

IM/Oral \$\$\$

Monitoring

CBC

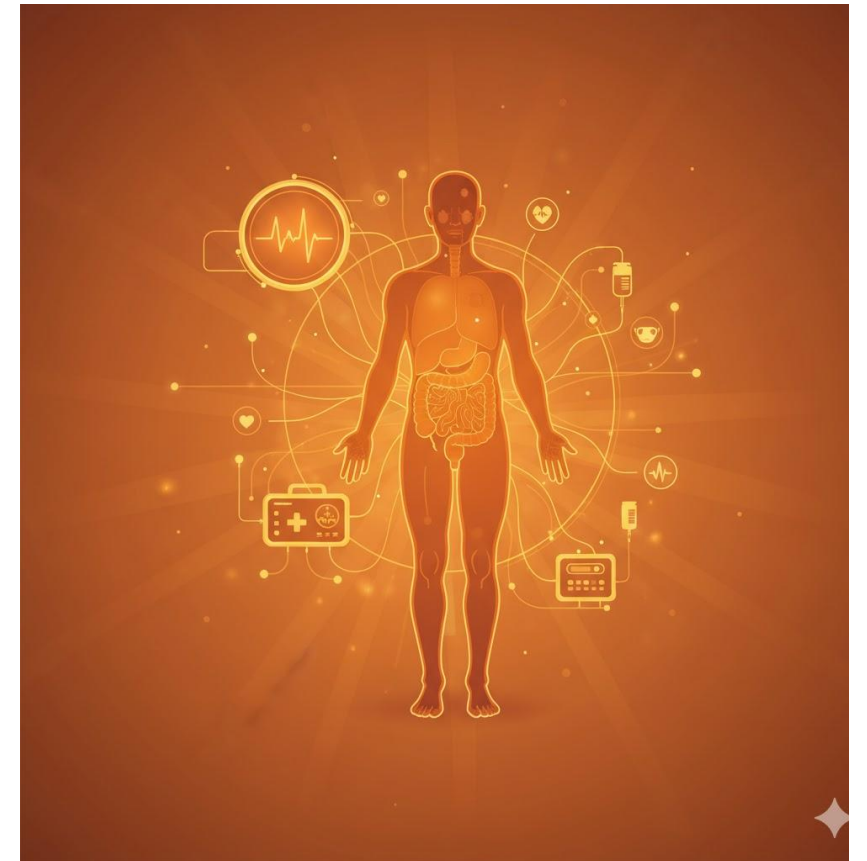
- 3 months for a year then annually
- If Hct > 54
 - Stop
 - Send for therapeutic phlebotomy twice monthly – OBI
 - More likely to happen with injections – cypionate > enanthate
 - re-initiate lower dose

PSA

- 3 months for a year then annually
- If PSA > 4 ng/mL or rises more than 1.4 ng/mL over 12 months
 - Discontinue
 - Repeat
 - Consider urology referral

Total or free testosterone every 3-6 months

- Fasting
- Reassess symptoms
- Increase/decrease depending on levels and symptom
- If on gel – afternoon check if applying in the AM



Indications that someone is abusing testosterone

- Low HDL
- Tendon rupture
- Gynecomastia
- Small testes
- Acne
- High hemoglobin
- Balding



Stopping TRT

- Duration of use and dose determines recovery time
 - Longer and higher the dose = longer the recovery period
- Duration of therapy for 2 years took a slow 15 months for recovery
 - Testosterone undecanoate 1000 mg q3 months
 - Comparable to 200 mg testosterone cypionate q2 weeks
- Withdrawal symptoms
- A small minority of men may never recover

Summary on TRT

- Indicated for symptoms and 2 confirmed low levels, 8AM fasting
- No consensus on “low for age”
- If testosterone is very low, a secondary evaluation, imaging is warranted
- Does not increase cardiovascular risk or increase risk of prostate cancer
- Monitor every 3-6 months
- Consider tapering off rather than “cold turkey”

What I generally use for HT

Uterus intact - perimenopause (need symptom, cycle control and birth control)

Monophasic OCPs– delivers same dose daily
Levonorgestrel 0.09-0.1 mg/ethinyl estradiol 20-30 mg

OCP

Ethinyl estradiol 0.05 bi-weekly or weekly patch +
Levonorgestrel IUD

Patch + IUD

Uterus intact - post-menopause (need for symptom control only)

Ethinyl estradiol 0.05 bi-weekly or weekly patch +
continuous micronized progesterone 100 mg QHS

Patch + pill

Ethinyl estradiol 0.05 bi-weekly or weekly patch +
Levonorgestrel IUD

Patch + IUD

Uterus intact - hormone alt to E+P - post-menopause (need for symptom control only)

Micronized progesterone 200-300 QHS

Pill

What I generally use for HT

Uterus absent – menopausal age	
Ethinyl estradiol 0.05 bi-weekly or weekly patch to start	Patch only

Testosterone for HSDD in post-menopause	
12 mg compounded testosterone daily for one month then decrease to once or twice a week thereafter *titrate levels and symptom control *discontinue if no benefit	Cream
Pea sized amount of 1.62% testosterone gel once weekly	Gel

Testosterone – concerns of elevated Hgb/Hct	
Testosterone gel 1.62% Packet delivers 40.5 mg daily – 1 packet to start Pump bottle delivers 20.25 mg per pump – 2 pumps to start	Packets or bottle
Testosterone enanthate Autoinjector: 50, 75, 100 mg weekly	Auto-injector or vials

Resources for Physician:

Menopause Society, Menopause.org (Formerly North American Menopause Society NAMS)

- 2022 Position Statement on MHT

- 2024 Position Statement on non-hormonal options

Endocrine Society guidelines for Male Hypogonadism – 2018

Resources for Patients:

Menopause Manifesto – Jen Gunter, MD

Menopause Society, Menopause.org

Let’s Talk Menopause, letstalkmenopause.org