

MALE HYPOGONADISM

Risks and benefits of testosterone replacement

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Endorama

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37 yo M who presented to an OSH for evaluation of hypogonadism

- HPI

- Feeling tired
- Sexual dysfunction
- Testes seem smaller
- Difficulty growing facial hair; previously shaving daily, now once every two weeks
- Feels generally weak, unable to work out as vigorously at the gym

- Pubertal development

- Entered puberty at 12-13 yo
- Started shaving at age 18 yo
- Normal libido until
- Married with two children 10 and 14 yo, conceived without difficulty

What else would you like to know?



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MEDICINE

Prior evaluation and treatment at OSH

- Lab evaluation:
 - Testosterone 137, LH 2.1, FSH 3.0 (time of day not reported)
 - Reportedly with multiple low AM testosterone levels
 - Pituitary MRI reportedly normal

- Testosterone therapy initiated

- 5/2015 - Initially transdermal formulation 125 mg daily
- Several months later switched to IM 100 mg weekly for “poor absorption.” Levels 3 days after injection on this dose was 478
- 5/2016 increased to 300 mg IM weekly
- 7/2016 testosterone in 500s (relationship to administration unclear)

Monitoring

IM: Midway between injections for testosterone enanthate or cypionate
Target mid-normal, eg, 500 to 600 ng/dL)

Patch:

Any time

Peak values occur 6-8 hours after application of the patch

Gel:

Variable

Target 400-700 ng/dL

Admission to UCMC

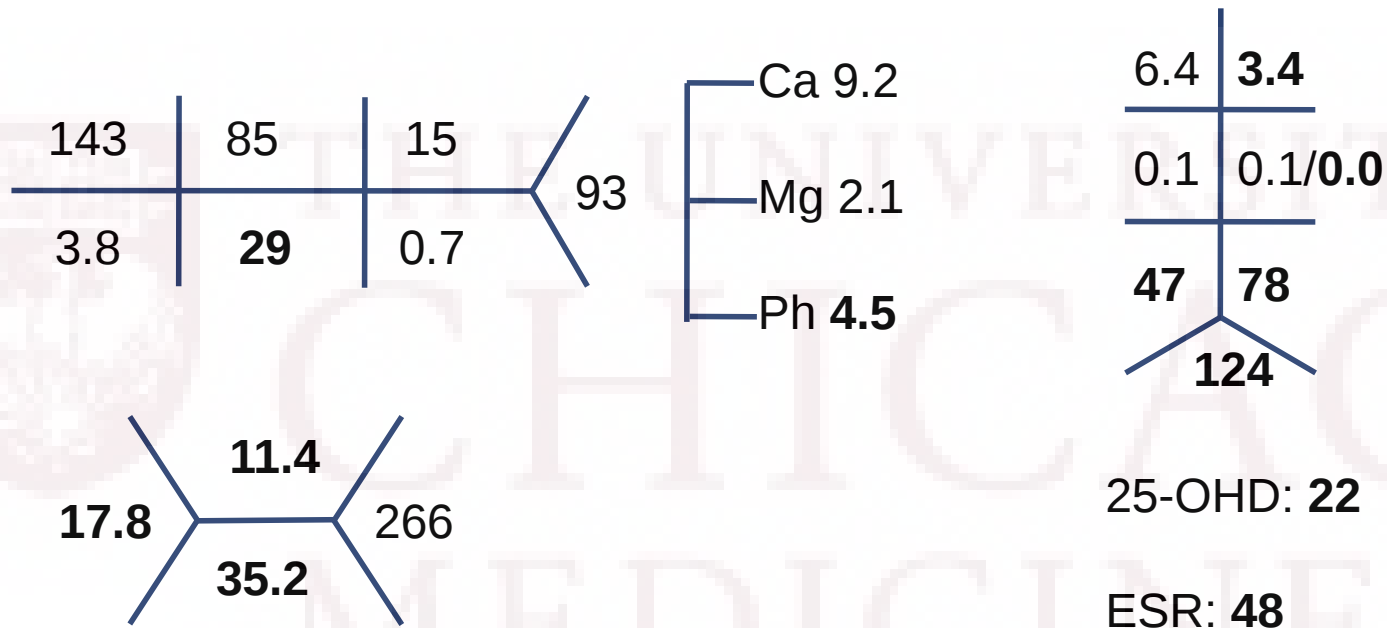
- 1 month later: Presented with progressive worsening pustular rash on chest, back, and face.
- Admitted from Dermatology clinic for severe pain (on opioids) – “I’m unable to get dressed”
- ROS notable for intermittent SOB, fevers, chills.

Additional HPI

- Rash started in early 2016, coinciding with diagnosis of ulcerative colitis (treated with Humira at that time)
- Initially treated with benze foam, followed by topical gentamicin, minocycline
- Admitted in July 2016 with fevers, SOB and treated for PNA with Levaquin and for a ?MRSA and klebsiella skin infection with vancomycin.
- He was discharged by developed worsening rash, leading to readmission and placed on IV linezolid and Levaquin, for possible poor GI absorption, on which he was discharged.
- In total, required 3 hospitalizations
- Rash was stable but did not improve on this regimen and so he was referred to Dermatology at UCMC.



Labs:



Thoughts?

Outpatient pager:

“36 yo M with acne needs urgent appointment for management of testosterone replacement therapy”

Acne Fulminans

- Rare
- Acute onset of painful, friable, ulcerative pustules
- Systemic Symptoms
 - Fever, Leukocytosis, thrombocytosis
 - Hepatomegaly, transaminitis
 - Polyarthralgia
 - Osteolytic lesions (clavicle, sternum)
- Triggers for AF:
 - Isotretinoin
 - Testosterone initiation or interruption
- Dermatology Consult: *“Can occur as a feature of a broader syndrome, called SAPHO Syndrome (Synovitis, acne, pustulosis, hyperostosis, osteitis), which is occasionally associated with enteropathic disease such as ulcerative colitis”*
- Rheumatology Consult: *“SAPHO is not high on the differential given alternate likely cause for his acne as well as development while on tx with humira (which is known to tx SAPHO)”*

Common triggers associated with Acne Fulminans

- Testosterone:
 - hypertrophy of sebaceous glands
 - Increased sebum production
 - Increased *Propionibacterium acnes* population
- Isotretinoin
 - Increases fragility and size of the pilosebaceous duct by disrupting the liposomal membrane,
 - Increased exposure to *P. acnes*
 - May be dose-dependent
- Case reports of association with autoimmune disease
 - SAPHO Syndrome

Patient comes to clinic for an expedited appointment...

- Acne has improved/stabilized
- Hypogonadal symptoms persist and are his **primary health concern** (fatigue, weakness, loss of facial hair, no libido and sexual dysfunction)
- Ulcerative Colitis:
 - 1/2015: Diagnosed with UC following several month illness and 70# weight loss. Initially treated with mesalamine without response, followed by Humira starting in 2/2016 again without response c/b thrombocytopenia.
 - Since 7/2016, has been on vedolizumab (Entyvio – integrin blocker) and prednisone 40 with resolution of GI symptoms (hematochezia and diarrhea) and 30# improvement in weight. 2/2016 – 6/2016 frequent prednisone bursts for recurrent UC flares and possible ITP

ROS

Constitutional: +reduced appetite, 40# weight loss due to UC. No night sweats, fevers

Vision: No photophobia, blurred vision, or other visual changes

ENT: No difficulty swallowing, sinus congestion, hearing deficits

CV: No palpitations, chest pain, lower extremity edema.

Pulm: No dyspnea, wheezing, cough, +snoring.

GI: +Mild diarrhea, hematochezia resolved. No abdominal pain, melena.

GU: +Erectile dysfunction, low libido. No frequency, dysuria, hematuria, discharge

ENDO: No heat or cold intolerance, glucose intolerance.

MSK: +Upper chest pain. No myalgias, joint swelling, abnormal gait.

Neuro: No weakness, tremor, HA, numbness, paresthesias

Skin: +Acne over face, chest, back. +Reduced hair growth. No hyper/hypopigmentation.

Psych: No mood changes, anxiety, depression. +Does not sleep well.

Past Medical History

PMH

- Ulcerative Colitis (4/2015)
- Acne Fulminans
- Hypogonadism

PSH

- Orthopaedic surgery

Social Hx

- Former smoker
- No EtOH
- No other drugs or /supplements

Medications

- Vedolizumab
- Prednisone
- Tramadol (PRN)

Allergies: Clarithromycin, PCN, Sulfa

Family Hx

- Ulcerative Colitis (MGF)
- Ulcerative Colitis, hypogonadism (PU)
- Diabetes (MGF, PGF)
- ALS (MGM)
- Parkinson's disease (Mother)

Physical Exam in clinic

Vita
kg/m
Gen
HE
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GI:
gua
MS
Ne
Ski
bac
Psy



2
air

10

CME : PADSOK

What would you like to do?

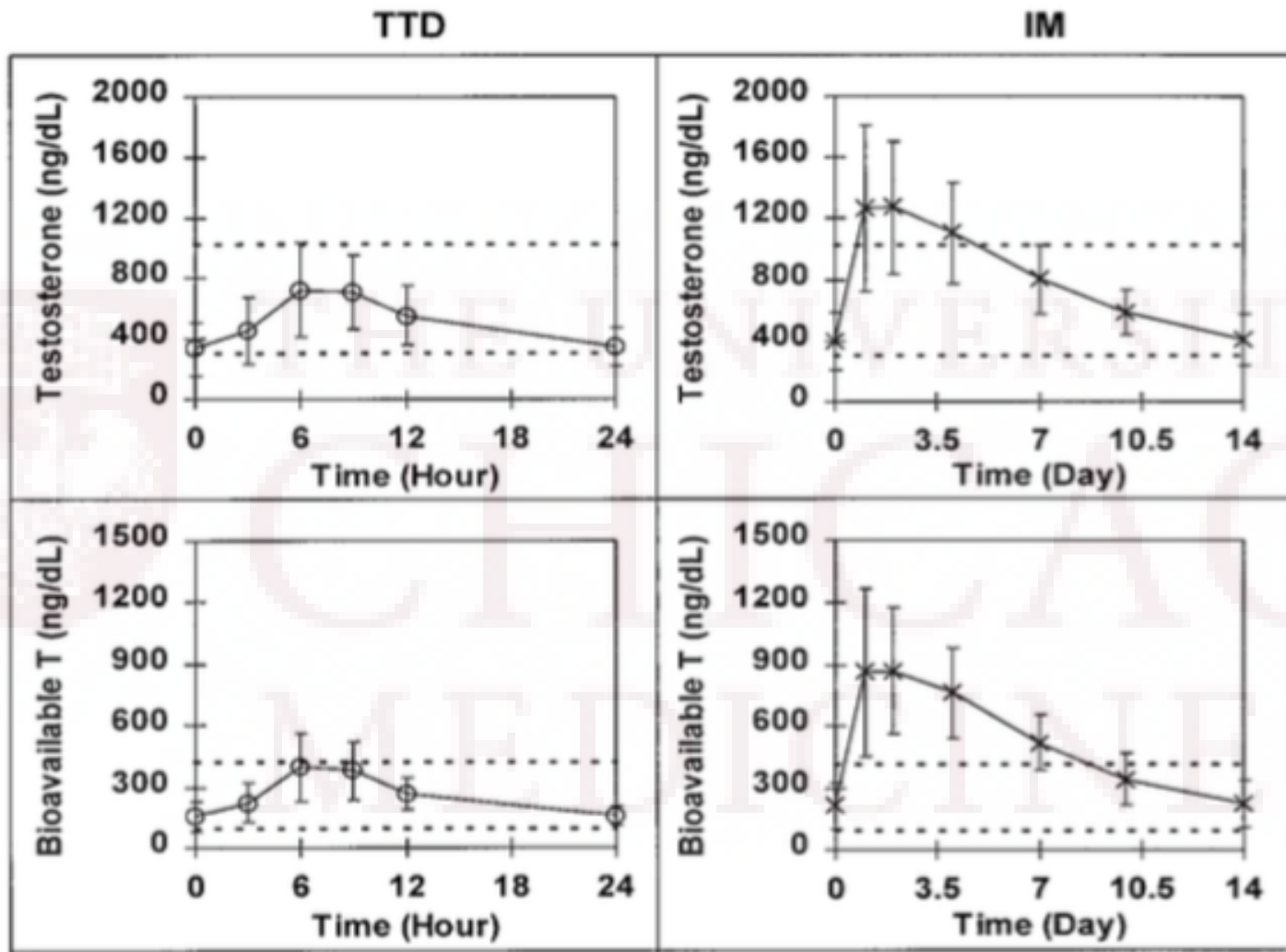
Currently on 40 mg prednisone daily with plan to taper by 5 mg every 5 days (off steroids in about 6 weeks)

Minimal information available – usually seen in adolescent boys.
Treatment is usually with a combination of steroids and isotretinoin

Advised to return for repeat testing after completion of steroid taper.

Does the formulation of testosterone make a difference?

- 24 week multicenter, randomized parallel-group study
- Objective: Compared PK, efficacy, safety of Androderm, IM testosterone entanthate injections
- N = 66 hypogonadal M (22-65 yo)
 - Withdrawn from prior IM testosterone treatment (if taking) for 4-6 weeks followed by randomization to either:
 - Transdermal 2.5 mg x2 patches qHS
 - IM 200 mg injections q2 weeks
 - 58 patients completed the study
 - 26 in the transdermal arm, 32 in the IM arm



Levels measured at week 16

Results and conclusions

- **Transdermal testosterone** produced circadian variations in the levels of total T, bioavailable T, DHT, and estradiol within the normal physiological ranges.
- **IM treatment produced supraphysiologic** levels of T, bioavailable T, and estradiol (but not DHT) for **several days** after each injection.
- Mean morning sex hormone levels were within the normal range in greater proportions of TTD patients (range, 77–100%) than IM patients (range, 19 – 84%). ***High variability with IM treatment***
- Both treatments normalized LH levels in approximately 50% of patients with primary hypogonadism; however, LH levels were suppressed to the subnormal range in 31% of IM patients vs. 0% of TTD patients.
- **Both** treatments maintained sexual function and mood (assessed by validated questionnaire and Rigiscan) and mood (Beck Depression Inventory) at the prior treatment levels.

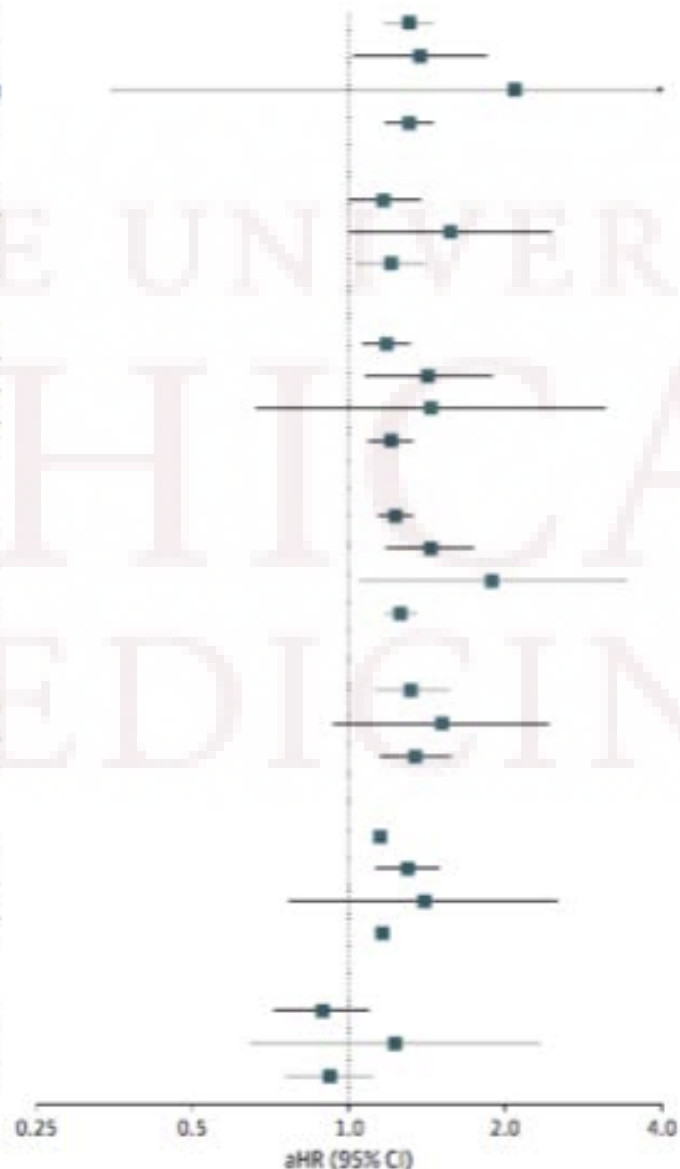
Are different formulations associated with different safety profiles?

Comparative Safety of Testosterone Formulations

- Retrospective cohort study
 - Databases from commercially insured (2000 – 2012) and Medicare (2007 – 2010) in the US and UK
 - Men age ≥ 18 yo initiating testosterone therapy via patch, gel or injection
 - No androgen use in the preceding 180 days; f/u 1 year
- Outcomes:
 - Diagnoses or claims for CV or Cerebrovascular events (MI, unstable angina, stroke or composite of the 3), VTE, mortality all-cause hospitalization
 - N = 544,115
 - 37.4% IM injection
 - 55.8% Transdermal gel
 - 6.9% Transdermal patch

Figure 1. Adjusted Hazard Ratios (aHRs) for the Risk of Outcomes With Injection vs Gel Testosterone

Outcome	Sample Size	aHR (95% CI)
Myocardial infarction		
MarketScan	479 199	1.30 (1.17-1.45)
Medicare	20 934	1.37 (1.02-1.83)
CPRD	5400	2.08 (0.35-12.60)
Pooled		1.30 (1.18-1.45)
Unstable angina		
MarketScan	479 199	1.17 (1.00-1.37)
Medicare	20 934	1.57 (1.01-2.45)
Pooled		1.21 (1.04-1.40)
Stroke		
MarketScan	479 236	1.18 (1.07-1.30)
Medicare	20 972	1.42 (1.08-1.88)
CPRD	5396	1.44 (0.67-3.10)
Pooled		1.21 (1.10-1.32)
Composite acute events		
MarketScan	478 175	1.23 (1.15-1.32)
Medicare	20 843	1.44 (1.19-1.73)
CPRD	5383	1.89 (1.05-3.40)
Pooled		1.26 (1.18-1.35)
Death		
Medicare	21 065	1.32 (1.13-1.55)
CPRD	5414	1.51 (0.94-2.42)
Pooled		1.34 (1.15-1.56)
All-cause hospitalization		
MarketScan	456 636	1.15 (1.13-1.18)
Medicare	20 586	1.30 (1.13-1.49)
CPRD	5361	1.40 (0.77-2.51)
Pooled		1.16 (1.13-1.19)
Venous thromboembolism		
MarketScan	480 029	0.89 (0.72-1.09)
Medicare	21 050	1.23 (0.65-2.32)
Pooled		0.92 (0.76-1.11)



Comparative Safety of Testosterone Formulations

- Compared with men using gels, injection initiators had **higher** hazards of cardiovascular events
 - MI, unstable angina, and stroke (HR: **1.26**; 95% CI: 1.18-1.35),
 - Hospitalization (**1.16**; 1.13-1.19)
 - Death (**1.34**; 1.15-1.56)
 - **but not** VTE (**0.92**; 0.76-1.11).
- Compared with gels, patches did **not** confer increased hazards
 - Cardiovascular events (**1.10**; 0.94-1.29)
 - Hospitalization (**1.04**; 1.00-1.08)
 - Death (**1.02**; 0.77-1.33)
 - VTE (**1.08**; 0.79-1.47).

Absolute risk is small

In the Medicare cohort (oldest, highest risk) the 1-year incidence of the composite MI, angina, and stroke outcome was 23.1 events per 1000 person-years in gels, 36.6 in injections, and 34.9 in patches

Limitations

- Retrospective chart review – missing/misclassified data,
- Not restricted to patients treated based on guideline-directed standard of care
- Behavioral/socioeconomic differences between populations receiving different formulations – Injections cost less, may be administered in clinic

Patient returns to clinic for follow up

- Increased facial hair growth (shaving daily).
- No change in libido or sexual dysfunction
- Reduced muscle strength persistent – unable to work out at the gym as frequently
- PSG: mild OSA, no treatment recommended
- Acne improved s/p 2 months isotretinoin but, stopped due to possible UC flare with increased diarrhea over the past couple of weeks, also being treated for *C. difficile* infection

	12/2/2016 (8am) Off prednisone x6 weeks	12/30/2016 (11am) Prednisone resumed 2 weeks prior
Te Binding Globulin		20 (10-80)
Free Testosterone	62.2 (35-155 pg/mL)	101 (90-300)
Total Testosterone	211 (250-1100 ng/dL)	261 (240-590)

What would you do at this point?

- Recommendations:
 - Avoid testosterone injections due to potential for greater peaks/troughs
 - Androgel 1.62% 1 pump daily (half recommended starting dose) with plan to escalate to 2 pumps daily if tolerates for several weeks
 - Monitor for changes in acne, IBD symptoms
- He asks about blood clots...How do you advise him on the risks and benefits of testosterone replacement therapy?

What is the data on VTE risk?

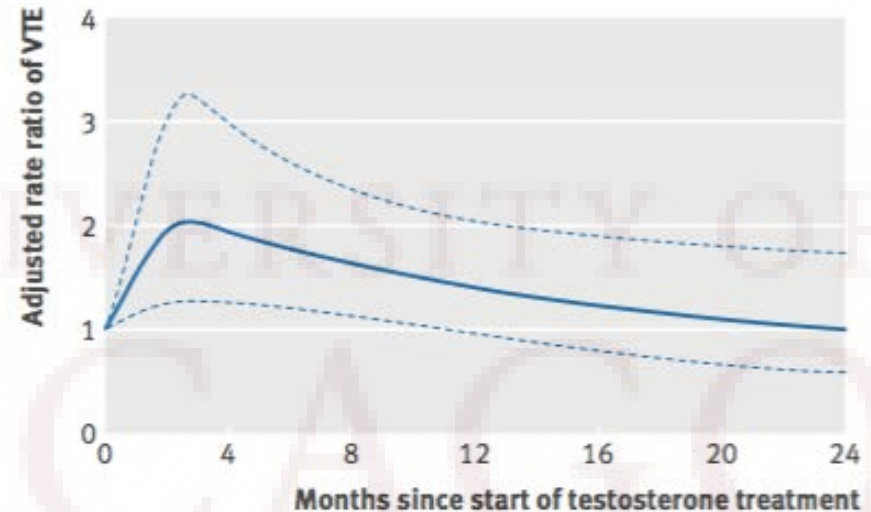
- In 2014 the FDA and Canada Health required manufacturers to add a statement about VTE risk to all testosterone products

Risk of VTE following testosterone therapy

- Database Case-control study
- N = 30,572 men ≥40 years, evaluated 2007-2012.
- Case criteria:
 - Primary diagnosis of VTE
 - Filled a prescription for an anticoagulant drug within 60 days of diagnoses.
- Exclusion Criteria:
 - <40 yo
 - VTE <12 mo prior to event/index date
 - Admission <30 prior to event/index date
 - Dx of cancer
 - Rx for anticoagulant in <90 days prior to event/index date
- For each case, 3 Matched controls for:
 - Age, Timing – event/index month, Geographic region
 - Diagnosis of hypogonadism, Diagnosis of underlying prothrombotic condition
- Results:
 - Exposure to testosterone therapy in the **15 days before the event/index** date was not associated with an increased risk of VTE (**aOR, 0.90**; 95% CI, 0.73-1.12).
 - None of the specific routes of administration examined were associated with an increased risk of VTE
 - topical [aOR, 0.80; 95% CI, 0.61-10.41]
 - transdermal [aOR, 0.91; 95% CI, 0.38-2.16]
 - intramuscular [aOR, 1.15; 95% CI, 0.80-1.64]
 - **Similar findings for exposure windows that extended to 30 and 60 days** before the event/index date

2016 VTE study showed increased risk in first 6 months

- 19,215 patients DVT/PE
- 909,530 age-matched controls
- January 2001 and May 2013.
- Overall VTE rate:
 - Current vs. No Testosterone: **1.25** (95% CI 0.94 to 1.66)
- VTE Rate in first 6 months of tx: **1.63** (1.12 to 2.37)
 - True regardless of hypogonadism diagnosis or hypercoagulability risk factors
 - ~10.0 (1.9 to 21.6) additional VTEs above the base rate of 15.8 /10,000 person-years.
- The rate ratio >6 month on tx: **1.00** (0.68 to 1.47), and after treatment cessation it was **0.68** (0.43 to 1.07).



T(estosterone) Trials

- Originated with 2004 IOM Review that identified a need for the male equivalent to the Women's Health Initiative for HRT in menopause
- Objective: Examine the role of testosterone replacement in the form of gel (AndroGel) versus placebo for older men with hypogonadism
- 7 Endpoints including: Anemia, Bone health, CV health, Sexual function, Physical function, Vitality, Cognition
- Study population
 - 788 men, age ≥ 65 , T < 275 ng/dL on two AM draws, 12 sites across the US, 1 year follow up
- Assignment to treatment groups balanced by:
 - Participation in each of the 3 main trials of the Ttrials
 - Trial site
 - Screening testosterone concentration (≤ 200 ng/dL or > 200 ng/dL)
 - Age (≤ 75 years or > 75 years)
 - Use of antidepressants and phosphodiesterase type 5 (PDE5) inhibitors.
- Exclusion criteria (51,000 men screened out)
 - The main exclusion criterion was high risk of prostate cancer. 14 Men who had a history of myocardial infarction or stroke within the previous 3 months and who had a systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 100 mm Hg were excluded.
- Treatment
 - 1% Testosterone gel via pump, starting at 5 g daily with up-titration to target 500-800 ng/dL
 - Monitoring at: 1, 2, 3, 6, and 9 months

T(estosterone) Trials

- Initial outcomes reported previously in NEJM for:
 - Sexual function/libido (improved 42% compared to baseline but less than PDE5 inhibitors)
 - Mood (mildly improved)
 - Physical activity (no change)
- Updates from the 4 ongoing trial published with this week in JAMA journals
 - Anemia
 - Bone Density
 - CAD – measured by coronary artery plaque accumulation
 - Cognitive function

Cognitive Function Trial

- Verbal memory declines with age, decline is accelerated preceding dementia. Previously correlated with testosterone levels and improved with androgen deprivation therapy. Previous short-term studies have shown improvement with testosterone therapy.
- AAMI (Age-associated Memory Impairment)
 - Subjective complaints of memory decline
 - Objective score of ≤ 1 SD below the mean for young adults on memory testing (MAC-Q)
 - Shown to be at higher risk for developing MCI or dementia
- Primary outcome: decline in verbal memory
- Exclusion: MCI (MMSE < 24), severe depression (PHQ-9 ≥ 20)
- Screening: telephone, 2 clinic visits
- 247 Testosterone, 246 Placebo
- No difference in most demographic and medical characteristics, including sex hormone levels and cognitive performance. However, executive function performance at baseline was slightly better among those assigned to placebo than those assigned to testosterone.
- Memory assessment at 6 mo and 12 mo
- Limitations: duration of only 1 year, may not be generalizable to other hypogonadal populations (e.g. ADT, younger men)

CV disease trial

- Background and Rationale: Data on testosterone effects on CVD are mixed with various studies showing positive, negative or no association with CVD and metabolic outcomes. These studies have been limited by observational design or not being designed to assess CV outcomes.
- Study Design:
 - 170 enrolled, 138 completed study.
 - 82 men assigned to placebo, 88 to testosterone → 73 in the testosterone group and 65 in the placebo group
 - **HIGH risk population
 - 70 of 138 men (50.7%) had a coronary artery calcification score higher than 300 Agatston units.
 - Current and former smokers
 - High rates of DM2, HTN, obesity
 - Study-specific Exclusion Criteria
 - Procedure contraindications (eGFR <60 mL/min/1.73 m² contrast allergy, weight >136 kg, inability to hold the breath for 10 seconds
 - Underling CVD (prior diagnosis of tachycardia or irregular heart rhythm, CABG).
 - CCTA performed at baseline and 12 mo

CV disease trial

- Outcomes:
 - Primary outcome: Noncalcified coronary artery plaque volume, as determined by coronary computed tomographic angiography.
 - Associated with myocardial ischemia, CV events, good inter/intraobserver reproducibility
 - Secondary outcomes included total coronary artery plaque volume and coronary artery calcium score (range of 0 to >400 Agatston units, with higher values indicating more severe atherosclerosis).
- Findings: At 1 year, there was a significant increase in noncalcified coronary artery plaque volume of 41 mm³ more than placebo.
- Limitations and other considerations:
 - Plaque calcification is a surrogate outcome, not powered or designed to study CV outcomes
 - Placebo-controlled RCT of ultrasonic carotid artery intimal media thickness showed no effects of testosterone treatment for 3 years in 308 men.
 - Similar negative trial with High-dose DHT treatment for 2 years in 114 men

Bone trial

Volumetric BMD was chosen as the main method of assessment rather than aBMD by DXA because it is not artifactually influenced by osteophytes and aortic calcification and because it can distinguish between trabecular bone, which testosterone affects primarily, and cortical bone.

- Objective: To determine whether testosterone increases volumetric BMD
- Background and Rationale:
 - Low testosterone is associated with reduced BMD and increased risk of fractures.
 - Testosterone treatment improves BMD in men with hypogonadism
 - Prior studies have been inconclusive
- Study Population:
 - 211 participants (mean [SD] age, 72.3 [5.9] years; 86% white; mean [SD] body mass index, 31.2 [3.4]).
 - Baseline characteristics in the 2 treatment arms were similar, including total and free testosterone levels and aBMD. The mean T scores for the spine and hip were not low (Table 1). Mean body mass index, alcohol consumption, and serum estradiol level were slightly higher in the placebo-treated men.
 - Study-specific Exclusion Criteria
 - Taking a medication known to affect bone, except for calcium and over-the-counter vitamin D
 - If they did not have at least 1 evaluable lumbar vertebra
 - Severe osteoporosis (DEXA T-score at any site of less than -3.0)
- Methods:
 - Spine and hip BMD was determined by quantitative CT at baseline and 12 months.
 - Bone strength was estimated by finite element analysis of quantitative CT data
 - BMD was assessed by DEXA at baseline and 12 months.

Bone trial

- Outcomes:
 - Primary outcome: Percent change from baseline in vBMD of trabecular bone in the lumbar spine, as assessed by means of quantitative computed tomography (QCT).
 - Secondary outcomes:
 - vBMD of peripheral bone and whole bone of the lumbar spine and trabecular, peripheral, and whole bone of the hip
 - Estimated strength of the same sites by finite element analysis (FEA) from CT data; and aBMD of the spine and hip by DXA.
- Findings:
 - Testosterone treatment
 - Increased mean spine trabecular vBMD by 6.8% (95% CI, , 4.8%-8.7%, $P < 0.001$)
 - Increased mean estimated strength of spine trabecular bone by 8.5% (95% CI, 6.0%-10.9%; $P < .001$)
- Limitations and observations
 - Long-term fracture outcomes not available
 - Findings are specific for men with **both** low baseline serum testosterone levels and no osteoporosis, unclear if
 - Similar to response in men with severe hypogonadism due to pituitary or testicular disease
 - Mechanism is thought to be related to conversion to estradiol, which was increased in testosterone recipients
 - Aromatase deficiency in men results in failure of epiphyseal closure and severe osteoporosis. Treatment with estradiol corrects both.

Anemia Trial

- Objective: Determine if testosterone treatment of older men with low testosterone levels and mild anemia improves anemia
- Background and Rationale:
 - In 1/3 of older adults with anemia, there is no identified cause
 - Testosterone treatment in hypogonadal men increases Hb levels
- Study Design:
 - Hypogonadal men with mild anemia (Hb 12.7 – 10.0 g/dL)
 - Study-specific Exclusion Criteria:
 - Hb < 10.0 g/dL
 - Population:
 - 126 M anemic at baseline with a hemoglobin level of ≤ 12.7 g/dL
 - 64 had anemia of known cause (Fe deficiency, chronic inflammation, MDS, B12 deficiency), plasma cell dyscrasia
 - The remaining 62 (49.2%) had unexplained anemia.
- Outcomes:
 - Primary outcome: 1 g/dL change in Hb in men with unexplained anemia
 - Previously used to determine Hb response
 - Associated with positive QOL outcomes
 - Secondary outcomes: Change in Hb in all men with anemia
- Methods:
 - Hb was measured at months 3, 6, 9, and 12

Anemia Trial

- Findings:
 - Increase in Hb by ≥ 1.0 g/dL in men with unexplained anemia
 - Testosterone 54%
 - Placebo 15%
 - No longer anemic:
 - Testosterone 58%
 - Placebo 22%
 - Increase in Hb by ≥ 1.0 g/dL in men with known cause of anemia
 - Testosterone 52%
 - Placebo 19%
 - Testosterone treatment resulted in a hemoglobin concentration of more than 17.5 g/dL in 6 men who had not been anemic at baseline.
- Limitations and comments:
 - Consider measuring testosterone in older men with unexplained anemia
 - Although the increase in hemoglobin levels was significantly associated with improvements in walking distance and vitality, the degree of improvement was below the level needed to be detected by the patient and/or clinically significant.
 - Findings apply only to men with established hypogonadism
 - Small sample size

T(estosterone) Trials Summary

- 7 Endpoints including: Anemia, Bone health, CV health, Sexual function, Physical function, Vitality, Cognition
- Testosterone replacement in the form of gel (AndroGel) versus placebo for men >65 yo **with** hypogonadism
 - Anemia (improved)
 - Bone Density (improved)
 - CAD – measured by coronary artery plaque accumulation (increased)
 - Cognitive function (no change)
- Prior NEJM report:
 - Sexual function/libido (improved 42% compared to baseline but less than PDE5 inhibitors)
 - Mood (mildly improved)
 - Physical activity/Vigor (no change)

Clinical update:

- Update: Jan 2016 – 1 month later
 - Completed C. dif treatment
 - Continuing prednisone taper for IBD flare (improved)
 - Isotretinoin stopped as thought to have contributed to UC flare
 - 3 small pustules since resuming testosterone and stopping isotretinoin
 - Mild improvement in hypogonadal symptoms