New Developments: T & CVD
FDA & The T Trials: Summary

2017 UPDATE FDUS

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Labeling, Guidance and Diagnosis

- Label
  - Intended population for TRT products: hypogonadal men with **specific disease conditions** associated with absent or deficient testosterone (e.g., Klinefelter's disease, pituitary injury, etc)
  - Product use data, however, shows a different real-world population: **middle-aged men with "low T"- "age-related hypogonadism" 40-60 yrs. "AOH" = Adult Onset Hypogonadism**
  - **"Age-Related" often is consistent with "co-morbid related" = AOH**

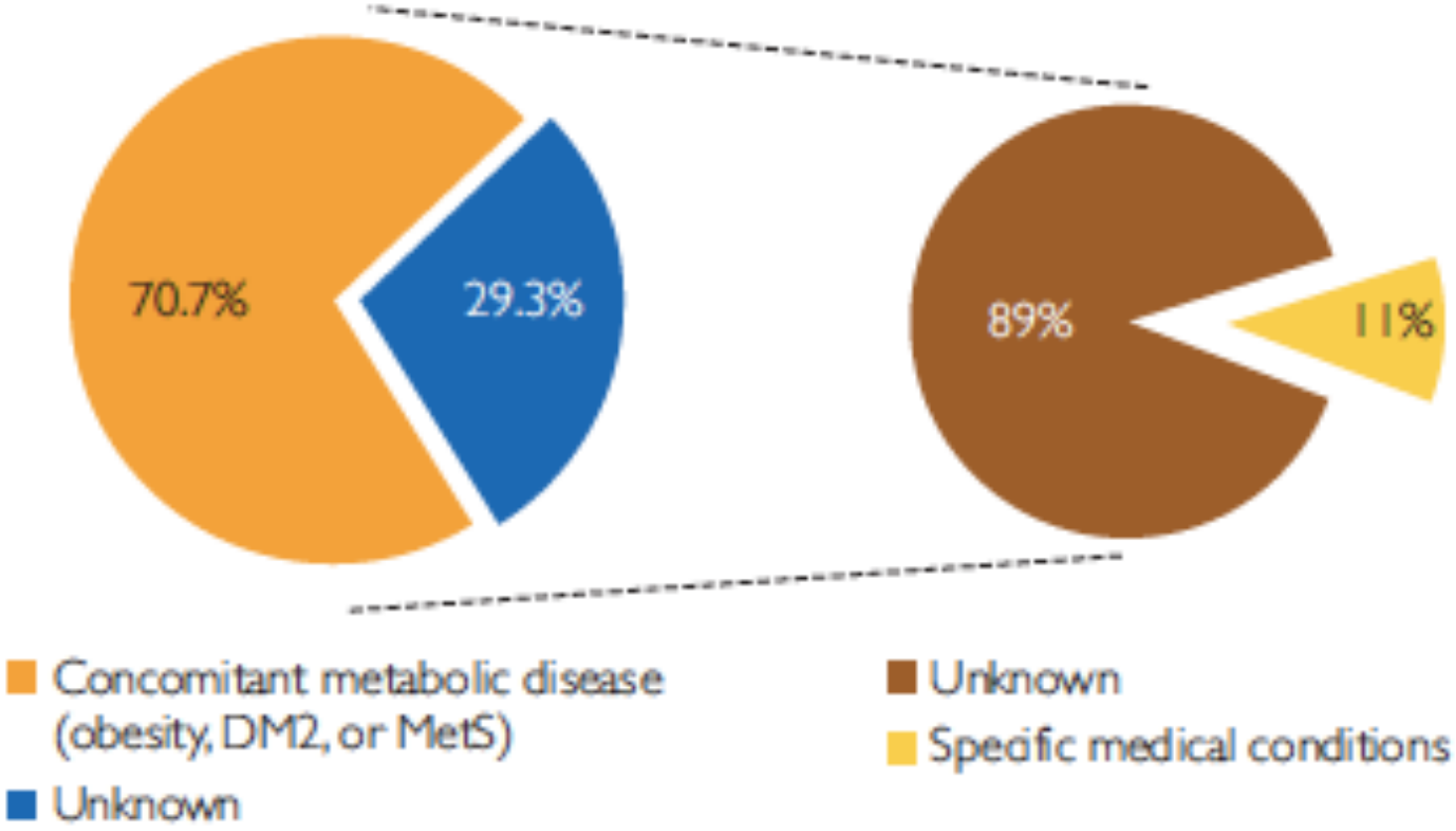

FIGURE 3. Medical conditions associated with secondary hypogonadism in a sample of 4220 men presenting to a sexual dysfunction clinic; 89% of men diagnosed with secondary hypogonadism did not have a diagnosable source for the condition. Most of these patients (70.7%) had a concomitant metabolic disease.[8] DM2 = type 2 diabetes; MetS = metabolic syndrome.

T Def & Men's Health

- Numerous conditions assoc with T Def: Obesity; Met S; DM; Dyslipidemia; HTN; Thyroiditis; COPD; B12 def
- NIH estimates that 75% of men are overweight or obese [Ogden JAMA 2012; Calderon Androl 2016]
- Endogenous T levels inversely related to BMI
- Is T Def simply a marker of declining health?
- Many comorbidities are improved with T Th.
- T improves QOL and sexual function [Ho BJU Int 2012; Hackett J Sex Med 2013; Tong As J Androl 2012]
- T Def assoc with twice mortality risk of men with normal levels [Muraleedharan Eur J Endocrinol 2013; Shores Arch Int Med 2012]

When to Measure T?

TABLE 2. Conditions in Which Serum T Level Measurement Is Suggested[1,11,86]
Infertility
Osteoporosis, low trauma fracture
Type 2 diabetes
Glucocorticoids, ketoconazole, opioid or other medications that affect T metabolism or production
Moderate to severe chronic obstructive pulmonary disease
Sellar mass, radiation to the sellar region, or other diseases of the sellar region
End-stage renal disease, maintenance hemodialysis
Human immunodeficiency virus–associated weight loss

The Patient with ED
The Patient on Chr opioid therapy

Need a screener for specific sx of T Def

TABLE 1. Clinical Signs, Symptoms, and Conditions Consistent With Adult-Onset Hypogonadism and Low Testosterone Levels[1,11,85,86]

Most specific signs/symptoms	More general signs/symptoms	Conditions commonly associated with low testosterone level and adult-onset hypogonadism
Reduced sexual desire & activity	Decreased energy, motivation, initiative	Type 2 diabetes
Decreased spontaneous erections	Delayed ejaculation	Metabolic syndrome
Erectile dysfunction	Reduced muscle bulk & strength	Chronic obstructive lung disease, obstructive sleep apnea syndrome
Hot flushes/sweats	Diminished physical or work performance	End-stage renal disease, hemodialysis
Decreased testicle size	Mild anemia (normocytic, normochromic)	Osteoporosis
Loss of pubic hair, reduced shaving requirement	Depressed mood, irritability	Human immunodeficiency virus–associated weight loss
Increased body mass index, visceral obesity	Poor concentration & memory	History of infertility, cryptorchidism, pituitary disease, delayed puberty
Height loss, low trauma fractures, reduced bone mineral density	Sleep disturbances, sleepiness	Treatment with opioids or glucocorticoids

Mayo Clin Proc. ■ XXX 2016;■■(■):1-19 ■ http://dx.doi.org/10.1016/j.mayocp.2016.04.022

Present Conflicts/Needs

- Current product labeling does not include "age-related hypogonadism" or "aging"
- Need a standardization of levels for diagnosis
- Need a screener: specific and sensitive
- Need a prospective registry of prescribing and RCT for safety and efficacy
- Co-morbid low T ?= AOH = Quagmire= 89% of scrips now prescribed are off Label

T Effects on Atherosclerosis in aging Men (TEAAM) 2015

- AIM: To determine the effect of testosterone administration on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels.
- METHODS:
  - **N = 308 men > 60 yo with low or low normal T levels**
  - TT 100-400 ng/dL; FT < 50 pg/ml
  - Mean Age: 67.6 yo; 42% HTN; 15% DM; 15% CVD; 27% Obese
  - **3-year DBPCT:**
    - 156 men 7.5 gm 1% T
    - 152 placebo gel daily x 3yrs
  - Dose adjusted to achieve levels 500-900 ng/dL
  - **Co Primary Outcomes: CIMT and CAC**
  - Secondary Outcomes: Sexual Function & HR QOL
- RESULTS:
  - Rate of change of CIMT Placebo 0.010mm/yr and in T 0.012 mm/yr p=0.89
  - Rate of change of CAC
  - Placebo 41.4 Agatston units/year
  - T 31.4 Agatston units/year p=0.54
- CONCLUSIONS:
  - **No Changes in intima-media thickness or calcium scores associated with TRx**
  - Sexual desire, erectile function, overall sexual function scores, partner intimacy, health-related quality of life did not differ significantly between groups
  - **Lack of CVD events is most significant & reassuring but again,**
  - **not powered for safety**
  - When T given in appropriate dosages there is no serious morbidity/mortality

Basaria S, Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. JAMA.2015; 314:570-581.

Efficacy of T with Sexual Function, Vitality, & Physical Function of Symptomatic Older Men with Low T at Baseline: "The T Trials"

- AIM: Test hypothesis that baseline TT, FT, E_2 and SHBG are independently associated with sexual functions, vitality, and physical functions in older hypogonadal men (Anemia; Bone Mass; Cognitive Function also studied).
- METHODS:
  - 12 U.S. centers
  - 788 symptomatic men >65 yrs with TT<275 RDBPCT "Highest Quality"
- RESULTS:
  - TT and FT had statistically significant associations with measures of sexual desire, EF, and sexual activity,
  - Not vitality and sexual function.
  - Slightly better mood, less depression in T arm
- CONCLUSIONS:
  - Statistically significant improvements in older men with T in some parameters of sexual function and mood
  - No increase in CVD events with T vs P (Study not powered for safety).
  - Some improvement in strength utilized as walking distance though did not reach target
  - **Sexual Function: 10 of 12 Domains increased PDQ, greatest in libido**

Snyder et al. T Trials JAMA 2016
Validated by Cunningham et al. J Clin Endo Metab 2016

Testosterone Treatment and coronary Artery Plaque Volume: T Trial

- AIM: Test the hypothesis that testosterone treatment of older men with low testosterone slows the progression of noncalcified coronary artery plaque volume in men with low testosterone
- METHODS:
  - Men >65 y/o with only age related decline in T
  - **RDBPCT 9 centers**
  - **170/788 men >65 years**
  - 2 am levels <275 ng/dL (82P, 88T)
  - **Men allocated to treatment by minimization:** computerized technique provides best balance across groups on specific baseline characteristics
- RESULTS:
  - 138 completed study (73T, 65P)
  - Mean age 71.2 years
  - **Rx vs. Pbo showed increase in non-calcified plaque volume from baseline to 12 months**
  - 204mm^3 to 232mm^3 vs 317mm^3 to 321mm^3; (T vs Pbo)
  - Est diff **41mm^3**; 95% CI 14-67mm^3; p=.003 T group

Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER 3rd, Wenger NK, Bhasin S, Barrett-Connor E, Swerdloff RS, Stephens-Shields A, Cauley JA, Crandall JP, Cunningham GR, Ensrud KE, Gill TM, Matsumoto AM, Molitch ME, Nakanishi R, Nezarat N, Matsumoto S, Hou X, Basaria S, Diem SJ, Wang C, Cifelli D, Snyder PJ. JAMA. 2017 Feb 21;317(7):708-716. doi: 10.1001/jama.2016.21043.

Testosterone Treatment and coronary Artery Plaque Volume: T Trial

- OUTCOMES:
  - Primary outcome was Non-calcified Plaque Volume=sum of 4 types of plaque: low attenuation, fibrous-fatty, fibrous and dense calcium
  - Secondary outcomes: Total Plaque Volume = sum of all 4 types and Coronary Artery Calcium Score (CAC)
- RESULTS:
  - Baseline: 61% BMI>30; 31% DM; 67% HTN; 63% Dyslipidemia; 66% Hx Cig abuse; 19% OSA
  - Mean ACC/AHA ASCVD Risk Score: 24% T; 27% P
  - 50.7% had CAC> 300 (severe atherosclerosis)
  - Men in P group had "somewhat greater mean non-calcificed plaque volume" by CCTA and "somewhat greater CAC score"
  - T Treatment associated with a significant increase in fibrous plaque volume (change 25 mm^3) vs placebo (change 1 mm^3)
  - Fibrous Plaque "protective capping" of Vulnerable Plaque= More Stable

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Testosterone Treatment & coronary Artery Plaque Volume: T Trial

- COMMENTS:
  - Among the 170 men in the CVS Trial in TRx group and in Pbo group no reported MACE (NOT POWERED FOR SAFETY)
  - Few studies have examined the effect of T on atherosclerosis in men: TEEAM study in older men showed TRx did not affect the change from baseline CAC or CIMT over 3 years.[1]
  - Increase in non-calcified and total plaque volumes in men on TRx are concerning because any limitation of the vascular lumen could be considered deleterious[2]
  - Fibrous plaque is more stable & protective[3]
  - Single review suggests that total plaque burden may be more important than ind plaque type[2]

1. Basaria S. JAMA 2015; 314(6)570-581 3. Samady H, Circulation 2011;124(7)779-788
2. Arbab-Zadeh A, et al. J Am Coll Cardiol 2015;65(8):846-855

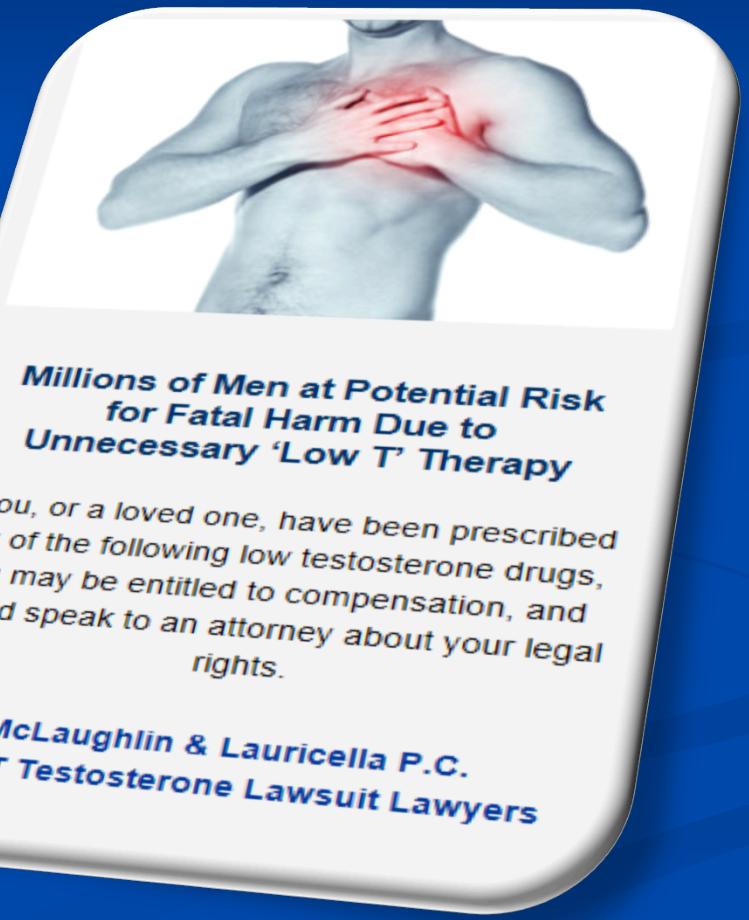
Testosterone Treatment AND coronary Artery Plaque Volume

"The coronary luminal narrowing observed over 12 months in this study is an unprecedented drug effect and appears ominous in signifying accelerated atherosclerosis, and is perhaps a harbinger of increased cardiac ischemic events. Early plaque growth may explain previous reports suggesting an association between testosterone use and cardiovascular harm in older men as well as transient cardiovascular harms confined to the first 6 to 12 months after commencing testosterone treatment. These findings may provide a possible mechanistic basis of an adolescent "head start" in atherogenesis to explain the earlier onset and greater severity of atherosclerosis in men compared with age- matched women despite parallel age-specific risks of men and women."

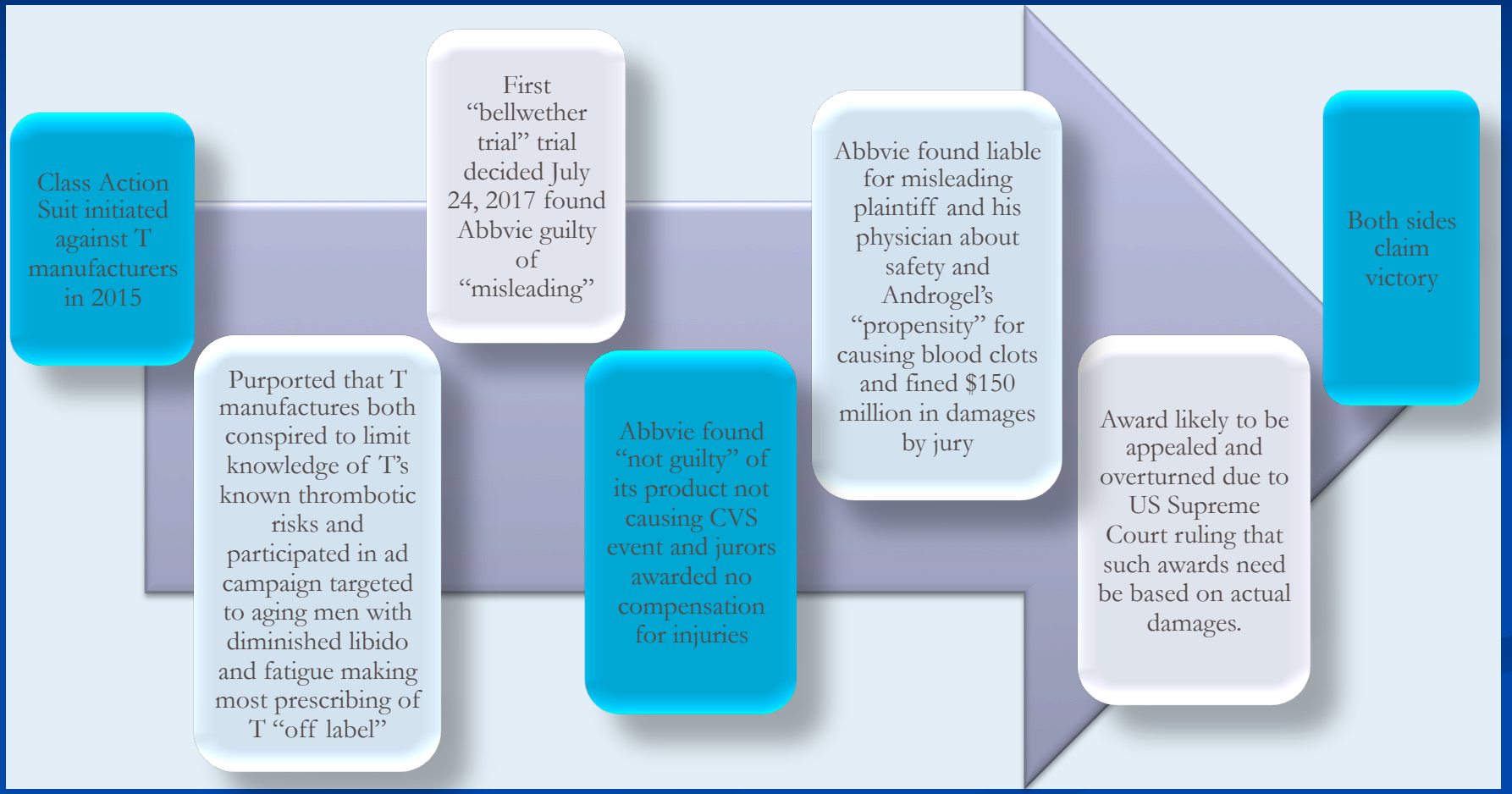
Editorial
Handelsman DJ. Testosterone and Male Aging
Faltering Hope for Rejuvenation. JAMA 2017;317: 699-701

Testosterone and Cardiovascular Disease

Class Action Suits



T Today: A Climate of Litigation



Conclusions

- Low T associated with increased atherosclerosis & MACE
- Meta-analyses show TRT has neutral (or possible beneficial) effect on CV risk factors and cardiac events
- Current evidence about the safety of TRT is hampered by the small n, brief study follow up and soft end points
- The TOM trial suggested possible increased CV risks of T therapy in elderly and very frail individuals
  - Caution is warranted in interpreting & extrapolating findings to other doses and formulations of T or to other populations, particularly men with hypogonadism w/o CVD or mobility limitations.
- Serious limitations of recent JAMA (Vigen), Plos One(Finkel), and BMC (Xu) Retrospective and Meta-analysis studies as pointed out by many investigators and FDA
- No black box warning regarding MI, stroke or death; FDA says weak signal may exist. No association or causal basis.
- T Trials: soft support for T improving sexual function and mood
- No improvement in cognitive function and frailty
- Increase in non-calcified plaque of unknown significance