Cardiovascular Effect of Testosterone Replacement Therapy

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Endocrine Update 2016
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The Ohio State University
Wexner Medical Center

Late Onset Hypogonadism (LOH)

- Age related decline in Androgen or LOH
- Not universally accepted concept.
- "Pathologizing" the natural aging process?
- Dx criteria for LOH controversial.
- Threshold T level for TRT still debatable
- 2.4 millions of men aged 40-69 in US :LOH [1]

Araujo AB et al. Prevelance and indicene of Androgen deficiency in middle-aged and older me; estimates from Massachusetts Male Aging Study. J Clin Endorinol Metab 2004;89.

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Trend of Testosterone Replacement

- Sale of testosterone double since 2006.
- Expected to triple, reaching $ 5 billions by 2017.

Global industry Analysts. Bloomberg Businessweek. May 10 2013

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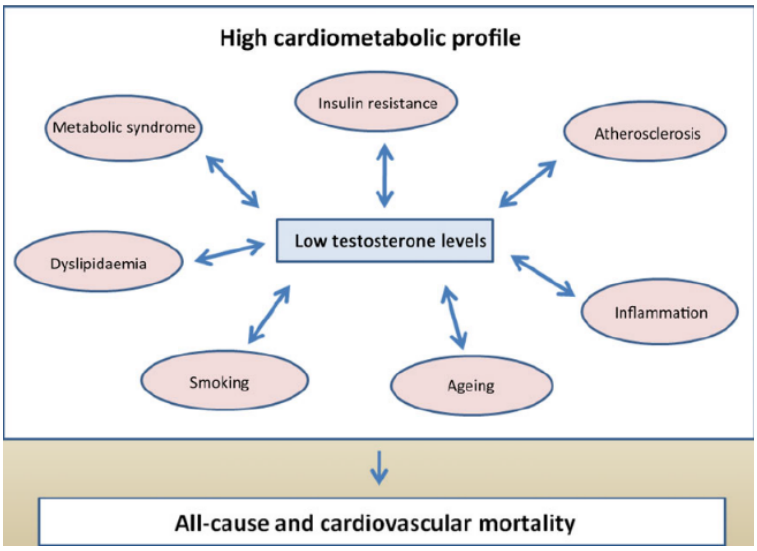

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Men with Low T live shorter!

- Epidemiological link between low T and mortality and CVD.
- **Massachusetts Male Aging Study**: 1886 men, 15 yrs follow-up.[1]
- **Rancho Bernardo Study**: 794 men, 50–91 yrs, 20 years follow-up.[2]
- **Seattle Study**: male veteran, >40 yrs, 5 yrs follow-up.[3]
- **EPIC-Norfolk** (European Prospective Investigation in Cancer in Norfolk Study): nested case-control study,11,606 men, 11 yrs follow-up.[4]

1Araujo AB et al. Arch Intern Med.2007;167:1252-1260.
2.Laughli at al. JCEM.2008;93:68-75.
3.Shores MM et al. Arch Int Med 2006;166:660-1665.
4.Khaw KT et al. *Circulation*. 2007;116(23):2647-2701

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Proven Benefits of Testosterone

- Increases in muscle strength, exercise capacity, bone mineral density (BMD),
- Libido and insulin sensitivity.
- Sense of well being

Adverse Effects

- Polycythemia
- ? HDL cholesterol.
- ? Prostate events.
- ? CV events ?

Adverse Effects

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Effect on muscle strength and exercise

- Massachusetts Male Aging Study (684 men aged 55–85 years)
- InCHIANTI study (Invecchiare in Chianti, aging in the Chianti area) Tuscany Italy.
- TT and FT correlated to muscle mass, strength, and physical performance.
- TOM trial and RCT in Manchester, UK: improvement in physical activity and lower limb strength with TRT.

Schaap LA et al. Clin Endocrinol (Oxf) 2005;63:152– 160.
O' Donnell AB, et al. the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2006;91:425–431.
Maggio M, et al. Aging Male 2011;14:42–47.
Basaria S et al. NEJM July 8 2010.
Srinivas-Shankar et al. JCEM 2010.

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Effect on Angina

- Exercise induced myocardial ischemia during stress test relieved by TRT_1.
- Men with CHD and low T, after 8 wks of oral TRT, ↑myocardial perfusion and ↑LV EF.$_2$
- Improved angina threshold.$_3$
- Vasodilation due to direct stimulation of endothelium-derived NO or vascular smooth muscle K channels$_{4,5}$

1.English at al . Circulation 2000: 102: 1906-11.
2.Webb C. et al.Am J Cardiol 2008; 101:618-24.
3.Malkin CJ et al Heart.2004b.90:871-87
4.Chou et al Circulation 1996;94: 2614-2619.
5.Yue et al Circulation 1995 ;91:1154-1160.

Effect on Lipid

- ↓ Total Chol, LDL-c, TG
- Activation of hepatic lipase and LP lipase.
- ↓ Lpa (TIMES2 study with 2% T gel).
- Effect on HDL-c is variable
- T were supra-physiological→↓HDL-c
- Older version of long acting T ester rather than T patch, gel or T Undecanoate.
- Older T ester produced supra-physiological level for first few days after injection.

Marin et al.Obes Res 1993, 1995.
Swerdloff RS, et al Wang C. Aging Male. 2003;6:207–211.
Heufelder AE et al. J Androl 2009;30:726–733
Zitzmann M, et al . J Clin Endocrinol Metab. 2007;92:3844–3853
Isidori AM, et al. J Endocrinol Invest. 2005;28(suppl 10):73–79.

TIMES 2 study

- Prospective, randomized, double-blind, placebo-controlled
- 220 hypogonadal > 40 yrs men, low T, T2DM and/or MetS.
- 2% testosterone gel (60 mg daily), 12 months.
- Primary outcome: HOMA-IR: improved with TRT Vs placebo at 12 month; 16.4% (95% CI 5-26); p=0.006.
- Secondary outcome: glycemic control, lipid, sexual function.
- ↓Lpa, ↓ HgbA1c (-0.446% P=0.035 at 9 months).
- CVD higher in placebo group (10.7 Vs 4.6 %; P=0.095)
- No difference: adverse events (AEs) or serious AEs.
- Majority of AEs are mild or moderate.

Jones TH et al. The TIMES2 study: Diabetes Care, Vol 34; April 2011

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FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

[03-03-2015]

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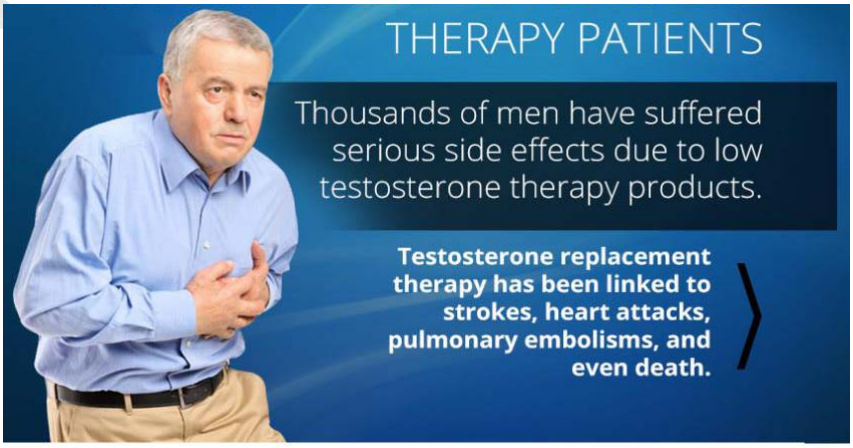
Media attentions !



- How did we reach here?
- From “the fountain of youth” to become a deadly medicine !

TOM (Testosterone in Older Men with Mobility Limitations) Trial

Inclusion

- Men, ≥65 years of age
- Total T level (100 -350 ng/dL) or free T level < 50 pg/dL
- Evidence of limitations in mobility.

Exclusion

- Uncontrolled HTN.
- Unstable angina.
- MI within 3 months.
- NY Heart Association class III/ IV CHF.
- Prostate or other active cancer.
- Severe urinary tract symptoms.
- Untreated severe OSA.
- Gucocorticoid /anabolic steroid Rx.
- HgbA1c > 8.5%.
- Hct > 48%, PSA >4 ng/mL, BMI>40.

TOM Trial - Result

- To evaluate somatic benefit of 6 months of testosterone Rx in frail men over 65 with low T.
- Terminated due to progressive excess of CV related adverse event (23 Vs 5).
- At the time of termination, improvement in muscle strength, particularly in lower limbs.

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TOM

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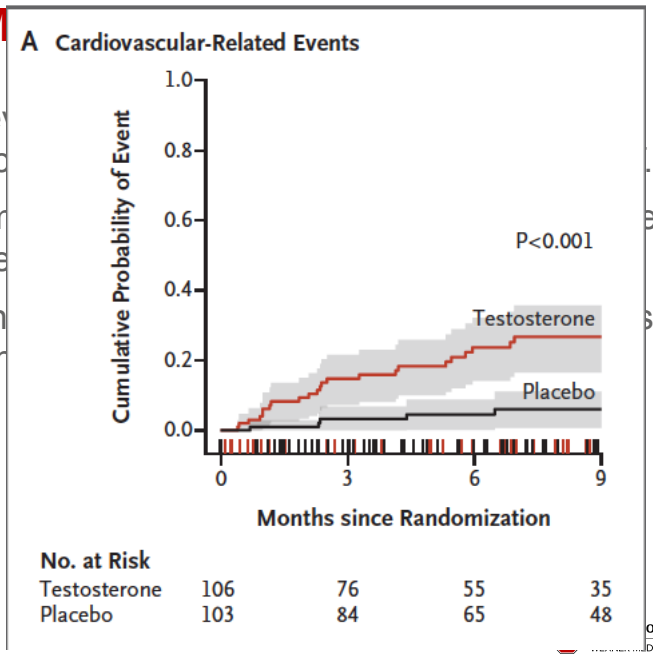

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Pitfalls of TOM Trial

- Use higher dose; up to 150 mg testosterone per day.
- Not enough power for CVE and AEs are not primary endpoints.
- Edema (5 events) , tachycardia (1 event), PVC, syncope (3 events)
- Poorly documented CVD events (self-reported syncope, review of medical records, phone interviews): inadequate validation.
- Studied population are frail old men: result cannot be extrapolated to general population.
- Frail elderly has higher subclinical CVD .

Manchester UK Trial

- Single center RCT : 274 frail elderly men, 65–90 years with low T
- Substantial limitations in mobility and a high prevalence of chronic condition (preexisting heart disease, obesity, diabetes, and HTN)
- T gel 50 mg/day x 6 months→ in somatic benefit but no rise in CVE.

Srinivas-Shankar et al JCEM 2010 and 2011

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Meta-Analysis of CVD Outcomes

- Lin Xu et al : 27 RCT; 2,994 men, 180 CVE. [1]
- TRT increase the risk of CVE (OR -1.54, 95% CI-1.09 to 2.18) [1]
- 3 meta-analyses : No effect or no ↑CVE with TRT. [2-4]

1.Lin Xu et al . BMC medicine 2013 ;11:108
2.Calof OM, et al . J Gerontol A biol Sci Med Sci 2005, 60:1451-1457
3.Haddad RM et al . Mayo Clinic Proc 2007;82:29-39.
4.Fernandex-balsells MM, et al. JCEM 2010;95:2560-2575

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Lin Xu et al . BMC medicine 2013

- CVE (OR 1.54, 95% CI 1.09 to 2.18).
- Effect of TRT varied with source of funding (P <0.03)
- CVE risk due to TRT was greater in trials not funded by the pharmaceutical industry (OR 2.06, 95% CI 1.34 to 3.17) than in pharmaceutical industry funded trials (OR 0.89, 95% CI 0.50 to 1.60).

1.Lin Xu et al . BMC medicine 2013 ;11:108

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Lin Xu et al . BMC medicine 2013

- Selection bias: included only studies in which one or more CV events were reported
- In addition, 2 of the 27 studies contributed 35% of all CV events in the T arm.
- TOM trial : 18 of 23 CV events (incorrectly reported as 25 by Xu et al) would not qualify as CV events.

A Morgentaler et al. Mayo Clinic Proceeding 2015

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Lin Xu et al . BMC medicine 2013

- 1986 Copenhagen study :
- Used non-approved oral T formula. used high dose 600 mg/ day in cirrhosis of liver patients .
- Very high T level 4000 ng/dL (25% of T group) ; as high as 21,000 ng/dL
- Counted any bleeding event as CVE, (variceal bleeding common)
- Out of 21 CVE, only one MI.
- After excluding Copenhagen study and the non-MACE in TOM trial, rate of CVE in T and placebo group similar: *78 events in 1599 (4.88%) vs 60 events in 1174 (5.1%)*

A Morgentaler et al. Mayo Clinic Proceeding 2015

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VA study: JAMA by Vigen et al.

- Retrospective cohort study of all male veteran.
- 76 VA cardiac cath lab.
- Coronary angiography between 2005 -2011.
- 8709 men at VA, total T level <300 ng/dL.
- 1223 men started TRT after coronary angiography.

Vigen R et al. JAMA, Nov 2013

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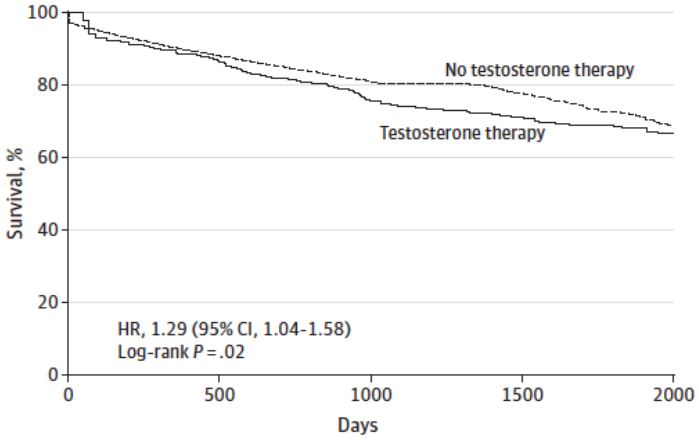
Kaplan Meier Survival Curve



- **3 years after angiography, K-M cumulative % event.**
- **19.9% in the no TRT group Vs 25.7% in TRT.**
- **Absolute risk difference 5.8%.**

Vigen R et al. JAMA, Nov 2013

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Vigen R et al . JAMA study

- once a subject was started on TRT, it was assumed that Rx continued. 17.6% had only one prescription
- No data on the Dx of hypogonadism
- Analyzing raw data showed the % men who suffered a CV event was actually lowered for testosterone-group compared with the no-testosterone group (10.1% vs 21.2%). Statistical analysis using over 50 variables then suggested the opposite result.
- 1132 subjects with MI or stroke, which were given testosterone after these events, were excluded from the analysis. Without that exclusion, the rate of events in the no–treatment group would have been increased by 71%
- 100 women were included in 1,132 individuals by mistake.

A Morgentaler et al. Mayo Clinic Proceeding 2015

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Risk of acute non-fatal MI after TRT

- Compare incidence rate of MI within 90 days after initial TRT with that of MI within one year prior to the initial prescription.
- Post/pre-prescription rate ratio for TRT:
- All subjects: 1.36.
- Men ≥65 yrs : 2.19.
- No data for indication of TRT , Lab, life style etc.

Finkle W et al. Plos one Jan 2014 , vol 9 .

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Finkel et al Plos one; Jan 2014 study

- Insurance data base retrospective study. Limited to Dx code, procedure code and prescription. No info for standard CV risk factors
- 4.75 event per 1000 person-year is less than expected rate by NIH heart attack risk calculator (13 events)
- Absence of control group
- using PDE 5 inhibitor is unfair comparison due to selection bias and vasodilatation benefit of PDE 5 inhibitors.
- Reluctance to prescribe testosterone for patients with recent MI would result in reduced pre-prescription MI rate.
- Short term exposure of testosterone (90 days) does not predict causation rather than underlying CVD. .

A Morgentaler et al. Mayo Clinic Proceeding 2015

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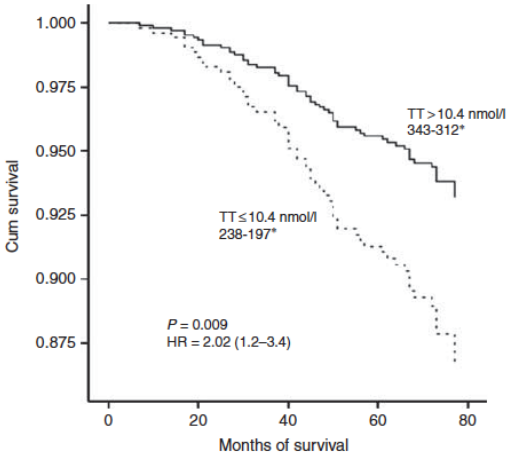
TT level and mortality in T2DM



Muraleedharan V et al . *Eur J Endocrinol* (2013) 169.725-733

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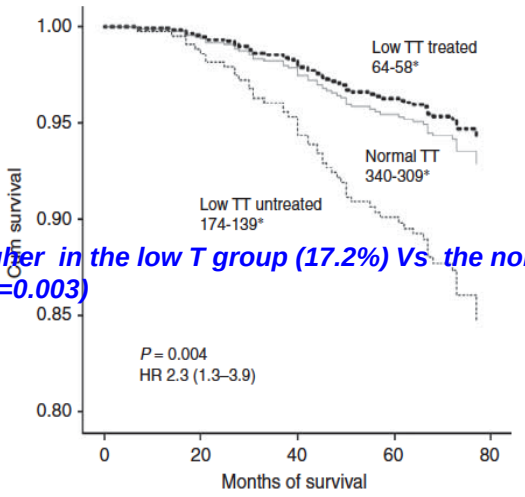
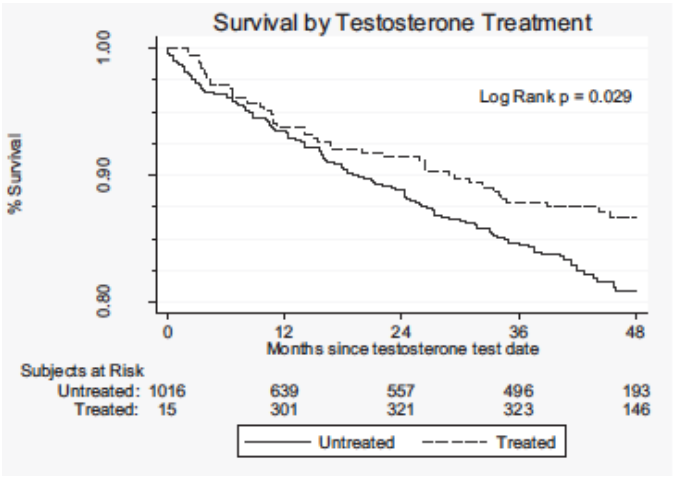
TRT and mortality in T2DM



Mortality: Higher in the low T group (17.2%) Vs the normal T group (9%; P=0.003)

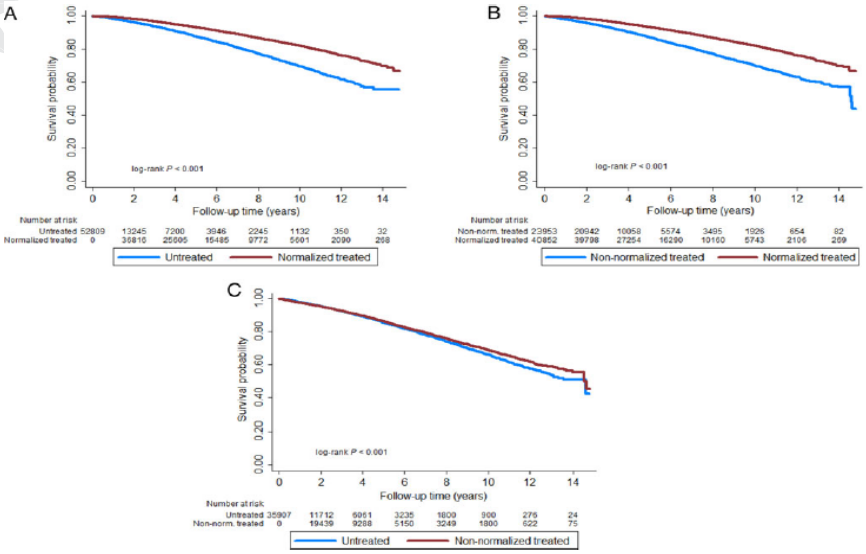
Muraleedharan V et al . *Eur J Endocrinol* (2013) 169.725-733

Testosterone Rx and mortality in men with low T



Shore MM et al; JCEM June 2012

Normalization of T level is associated with reduced incidence of MI and mortality



Sharma R et al. Eur Heart J 2015;36:2706-15.

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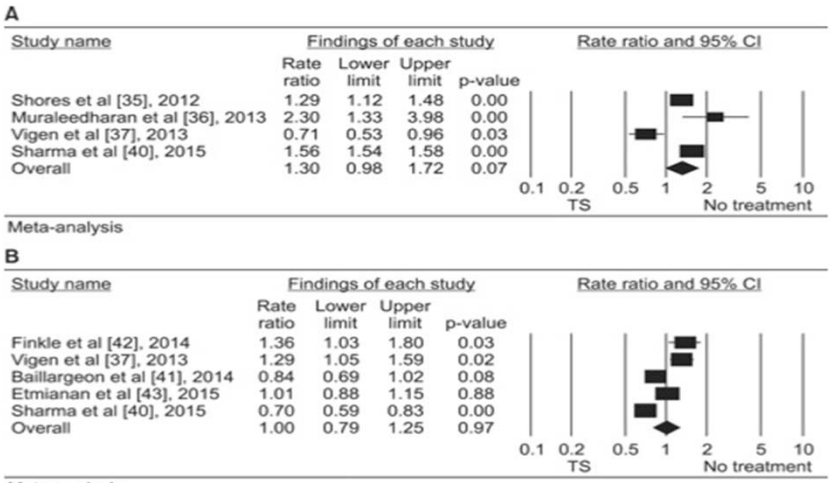
Overall Mortality *(A)* and MI *(B)* among testosterone Vs non-testosterone group



Corona GG et al. World J mens health , Dec 2015

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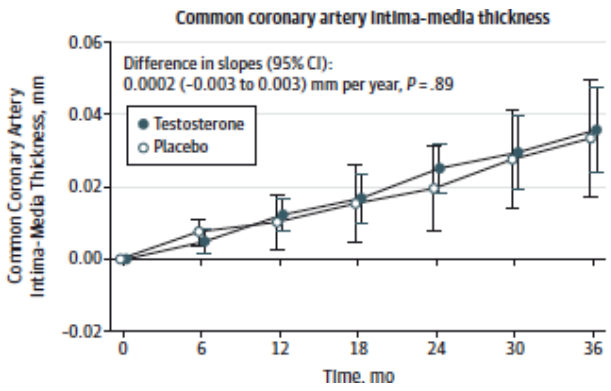
Testosterone effect of atherosclerosis progression in aging male (TEEAM)



mean 67.6 years; n=165
42% HTN; 15%T2DM;
15% CVD; 27% obesity.

S Basaria et al . JAMA Aug 2015

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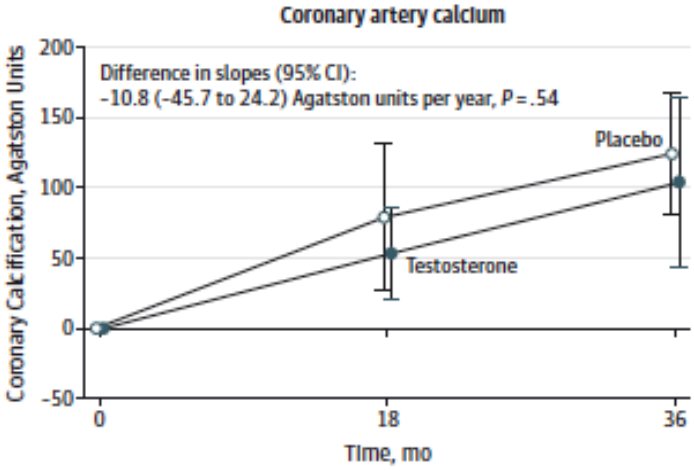
Testosterone effect of atherosclerosis progression in aging male (TEEAM)



S Basaria et al . JAMA Aug 2015

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What safe target testosterone level should we aim for?

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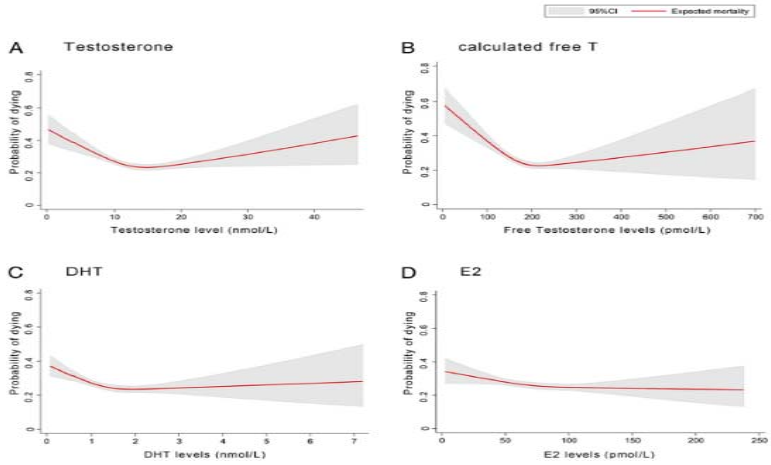
All cause mortality (the HIM Study)



Yeap BB et al. JCEM January 2014, 99(1):E9–E18

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J-shape association

- French three-city prospective cohort study.
- 3650 men >65 yr. 4 years follow-up.
- After adjustment for CVD risk factors;
- J-shaped association total and bioavailable T level and ischemic arterial disease (IAD). ($p<0.01$)
- Total IAD=112 CHD and 34 stroke
- HR: Relative to 2nd quintile; lowest quintile=2.23 (95%CI:1.02;4.88) and highest Total T quintile= 3.61 (95% CI 1.55;8.45) respectively.
- No association of E2 and SHBG with IAD.

Soisson V et all. Maturitus 75 (2013) 282-288

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TOM Trial: CVE Outcome

- Men with T levels in the highest quartile at high risk for CVE (HR: 2.4; P = 0.05).
- CVE: trended up with higher T level.
  - 4 of 14 with T levels >1000 ng/dL.
  - 5 of 21 with levels of 500 -1000 ng/dL.
  - 7 of 46 with levels of < 500 ng/dL.

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Impact of TRT on MI, Stroke, and Death in Men With Low Testosterone

- January 1, 1996, to December 31, 2011
- Men with a low initial total T, a subsequent T level, and > 3 years follow-up
- MACE: composite of death, non-fatal myocardial infarction, and stroke at 3 years.
- Multivariate adjusted HRs were calculated by Cox hazard regression.
- Persistent low (< 212 ng/dl, n =801),
- Normal (212 to 742 ng/dl, n =2,241),
- High (> 742 ng/dl, n = 1,694)

Anderson JL and May HT et al Am J Cardiol Dec 2015

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Impact of TRT on MI, Stroke, and Death in Men With Low Testosterone

- Normal T group had reduced 3-year MACE (HR 0.74; 95% CI 0.56 to 0.98, p <0.04) compared to persistently low testosterone group.
- Primarily driven by death (HR 0.65, 95% CI 0.47 to 0.90).
- HRs for MI and stroke were 0.73 (95% CI 0.40 to 1.34), p =0.32, and 1.11 (95% CI 0.54 to 2.28), p = 0.78, respectively.

Anderson JL and May HT et al Am J Cardiol Dec 2015

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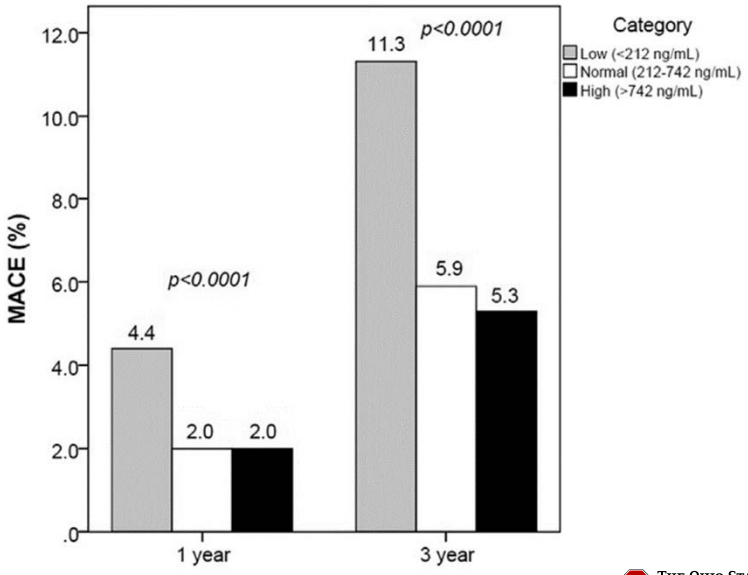
MACE by categories of achieved T level at 1 and 3 years



Anderson JL and May HT et al Am J Cardiol Dec 2015

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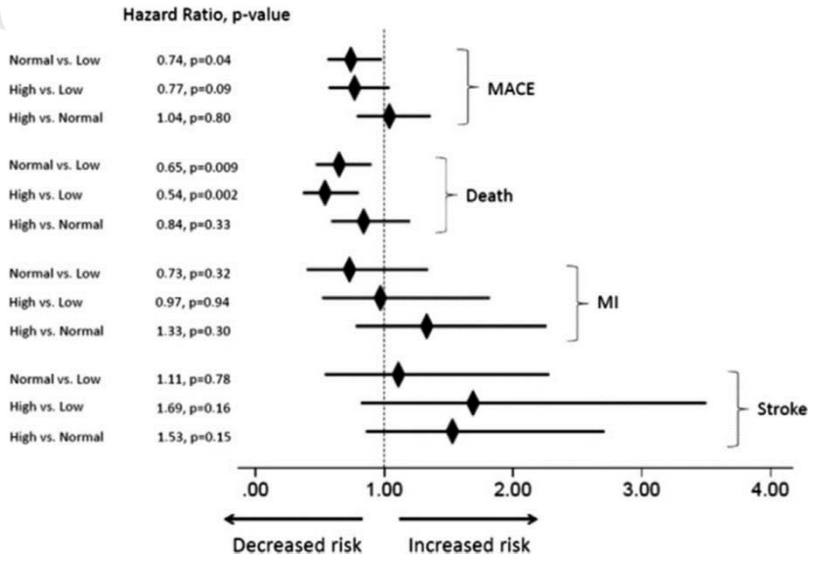
HR for Death, MI and Stroke in the categories of achieved T levels at 3 years



Difference between routes of administration of testosterone

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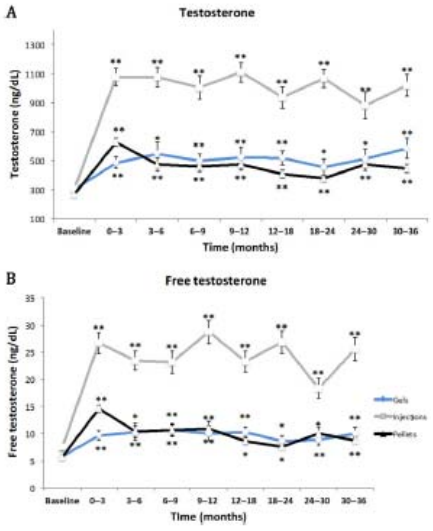
Effect of Testosterone Rx by Different Route



Pastuszak, at et al . Sex Med 2015

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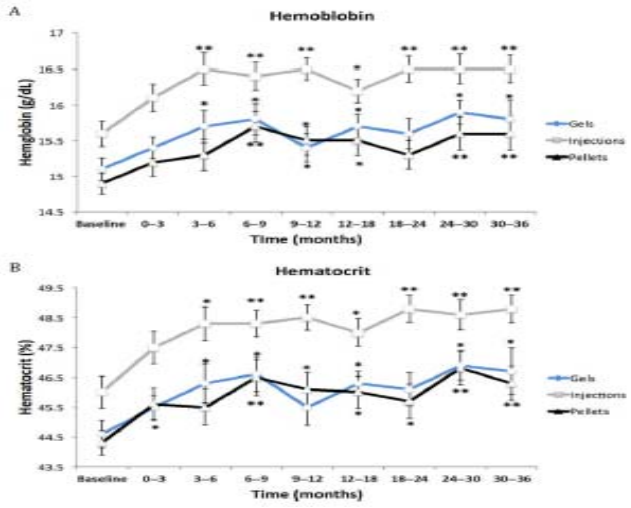
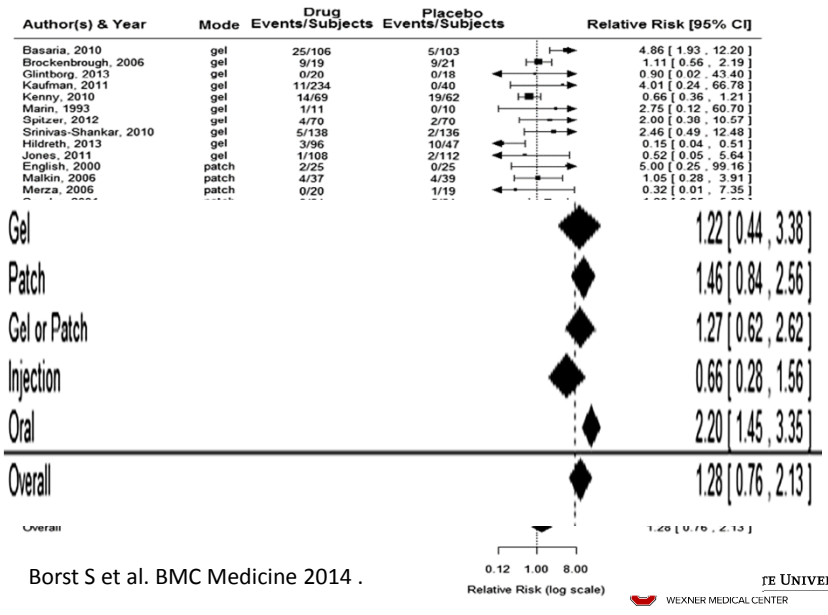
Effect of Testosterone Rx by Different Route



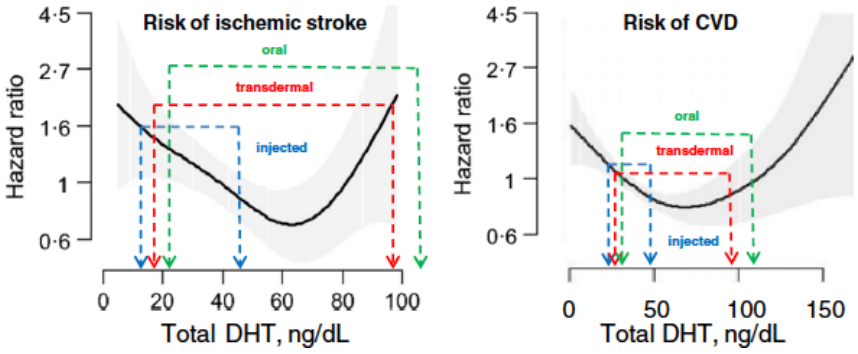
Pastuszak, at et al . Sex Med 2015

CV Risk by Different Routes of Testosterone



Borst S et al. BMC Medicine 2014 .

CV Risk by Different Routes of Testosterone



Borst S et al. BMC Medicine 2014 .

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CV Risk by Different Route of Testosterone Among Testosterone Initiators

- A retrospective cohort study using administrative claims from
- Commercially insured (January 1, 2000, to December 31, 2012)
- Medicare (January 1, 2007, to December 31, 2010) population in the US and
- General practitioner records from the UK (January 1, 2000, to June 30, 2012).
- men >18 years who initiated use of testosterone patches, gels, or injections following 180 days with no testosterone use.

Bradley Layton et al . JAMA Intern Med July 2015

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CV Risk by Different Route of Testosterone Among Testosterone Initiators

Compared to gels-user:

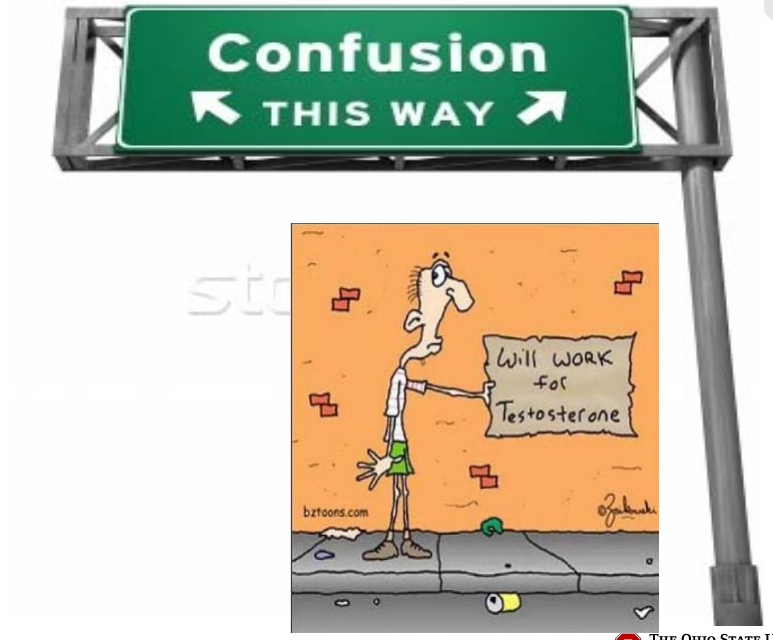
- Injection initiators had higher hazards of CV events (ie, MI, unstable angina, and stroke) hospitalization and death but not VTE
- NO increased in hazards among patches-user
- Did not assess whether patients met criteria for testosterone Rx and did not assess the safety of testosterone among T users Vs non-users .

Bradley Layton et al . JAMA Intern Med July 2015

EMAS (European Male Aging Study) Position Statement

- Testosterone should be given only if a combination of symptoms of testosterone deficiency and low testosterone is present.
- TRT could have positive effects on obesity, Met syndrome, T2DM2, sexual function and osteoporosis, but regular monitoring for adverse events required.
- Potential effects of TRT on CVD, prostate Ca and sleep apnea are yet unclear and remain to be investigated in large-scale prospective studies.
- Individualized evaluation of co-morbidities and careful risk versus benefit estimation.

C Dimopoulou et al. Maturitas 84 (2016)



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