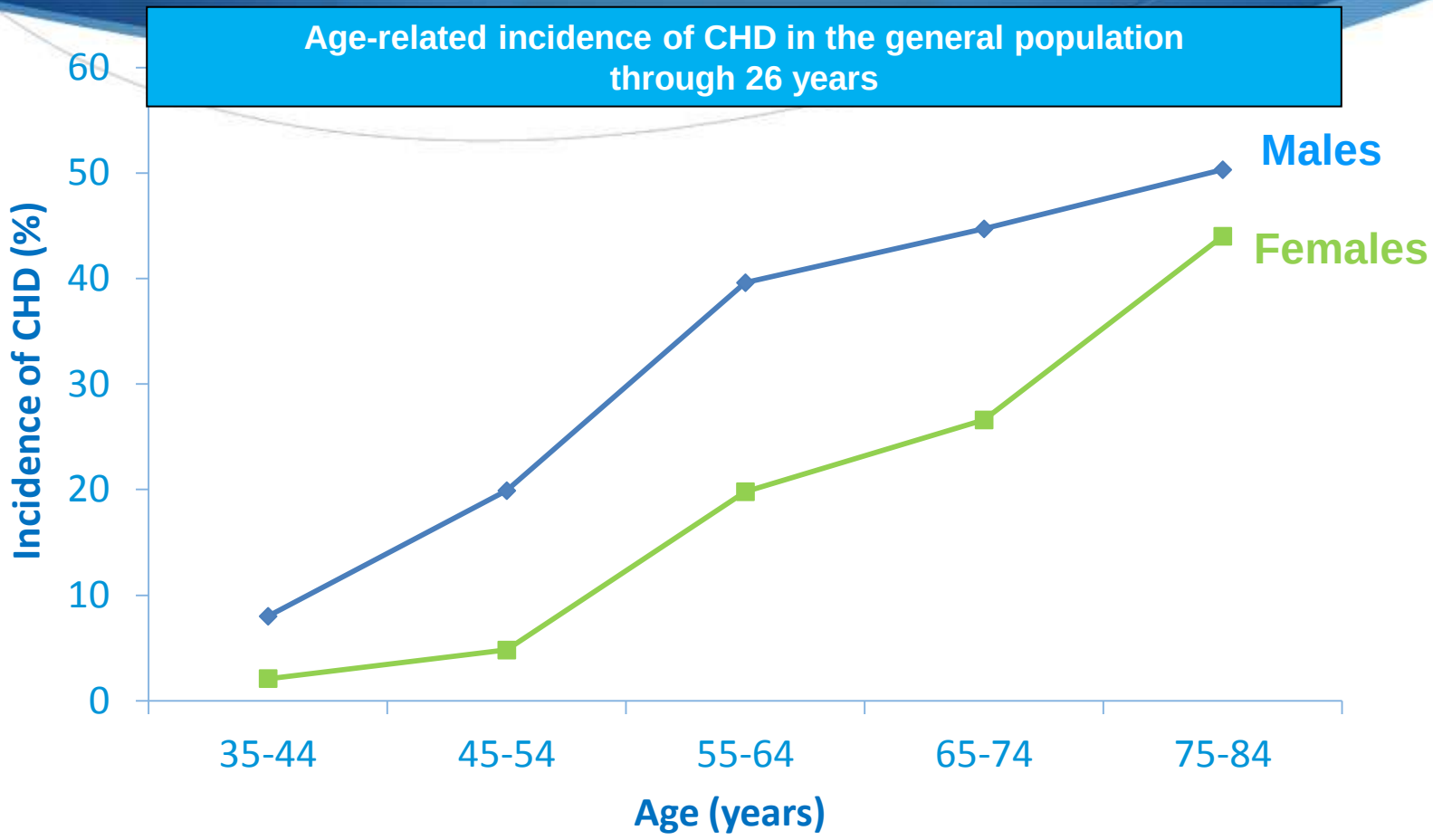
RECENT TRENDS : DO TESTOSTERON ARE NEEDED ?

Safety concerns over testosterone replacement therapy (TRT)

- Concerns over the safety of testosterone may have contributed to underuse of TRT
  - Cardiovascular (CV) risk
  - Prostate cancer and other prostate disorders (e.g. BPH)

- Extensive evidence shows that neither of these safety issues now warrants the concerns raised

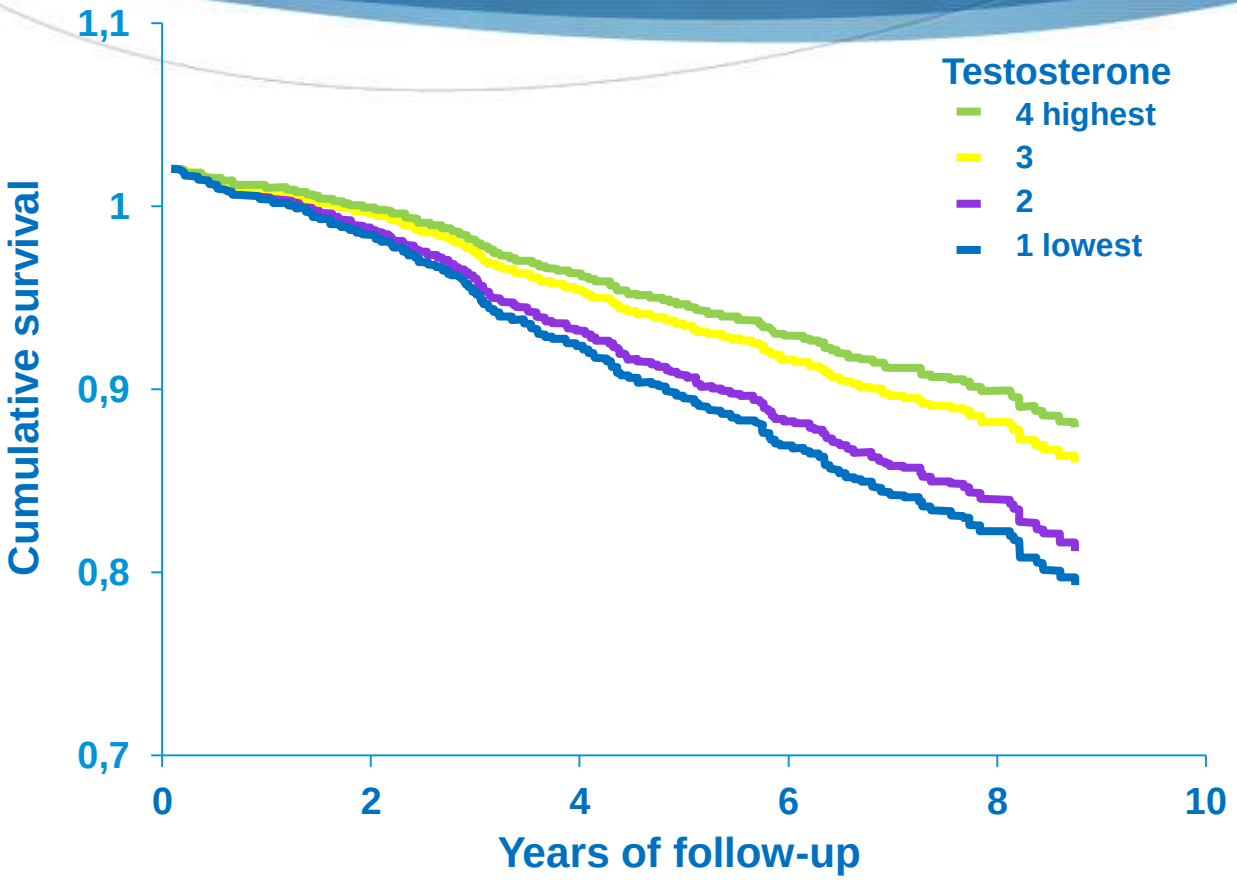
Testosterone and cardiac risk – incidence of coronary heart disease (CHD) higher in men



N=5,127

Lerner DJ & Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1986;111:383–390.

CV mortality: adjusted survival by quartile of total testosterone in men aged 42–78 yrs in the EPIC-Norfolk Study 1993–2003



N=2,314

Khaw KT *et al*. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study*Circulation* 2007;116:2694–2701.

The Norway Tromsø-Study: androgens and the prospective mortality risk

Number of deaths from all causes by decentiles of free testosterone

N=1,687

Vikan T *et al*. Endogenous testosterone and the prospective association with carotid atherosclerosis in men: the Tromsø study. *Eur J Endocrinol* 2009;161:435–44.2

Testosterone and coronary artery disease (CAD)

- Bioavailable testosterone (BT) levels are significantly reduced in males with CAD:
  - Approximately 1 in 4 men (23.4%) with CAD have serum T levels within the clinically hypogonadal range (93.5% positive ADAM questionnaire)
- TRT improves anginal symptoms and cardiac ischaemia.
- TRT improves functional capacity and NYHA class compared with placebo:
  - Malkin *et al* showed a significant correlation between the increase in BT with treatment and the increase in walking distance, with results sustained over 12 months

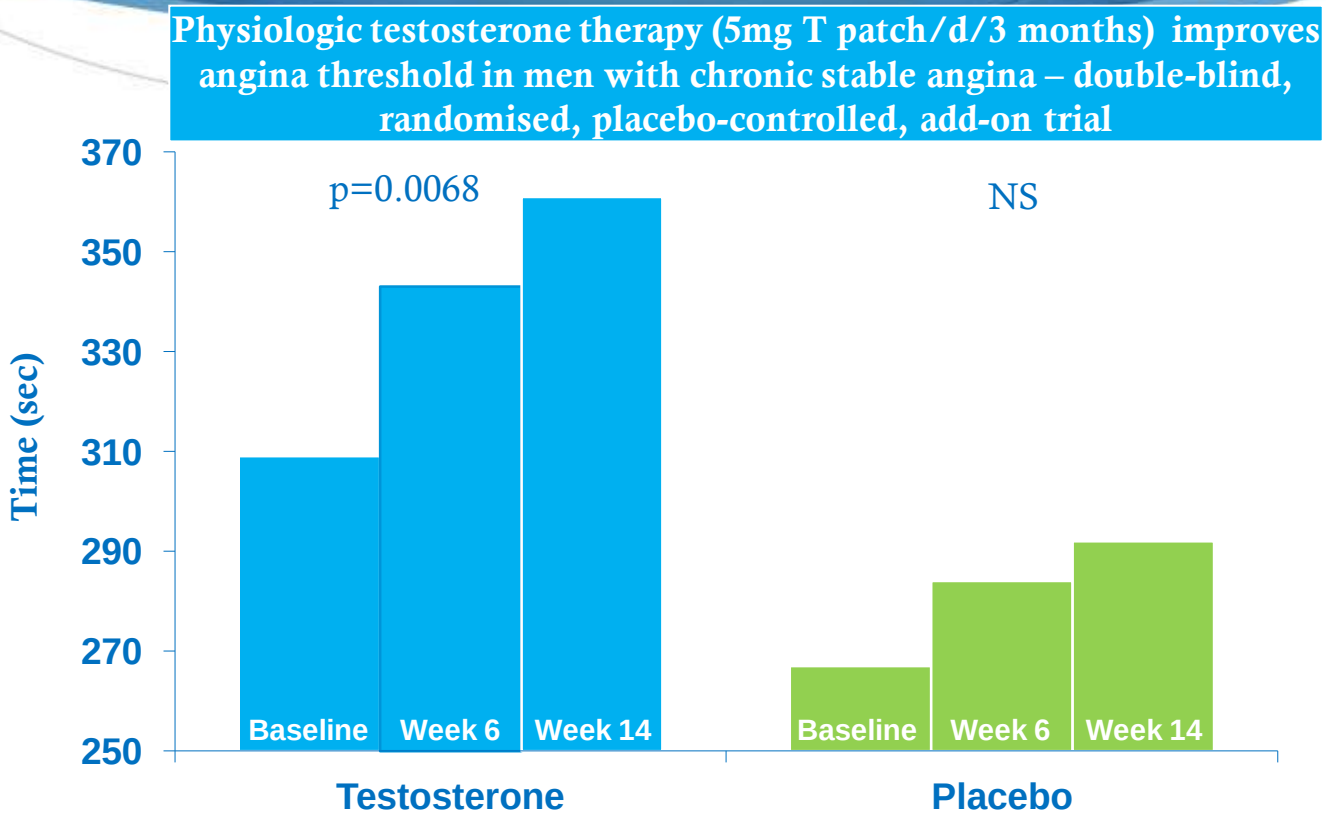
English *et al*. *Eur Heart J* 2000;21:890–894

English *et al*. *Circulation* 2000;102:1906–1911

Pugh PJ *et al*. *Heart*. 2004 Apr;90(4):446-7

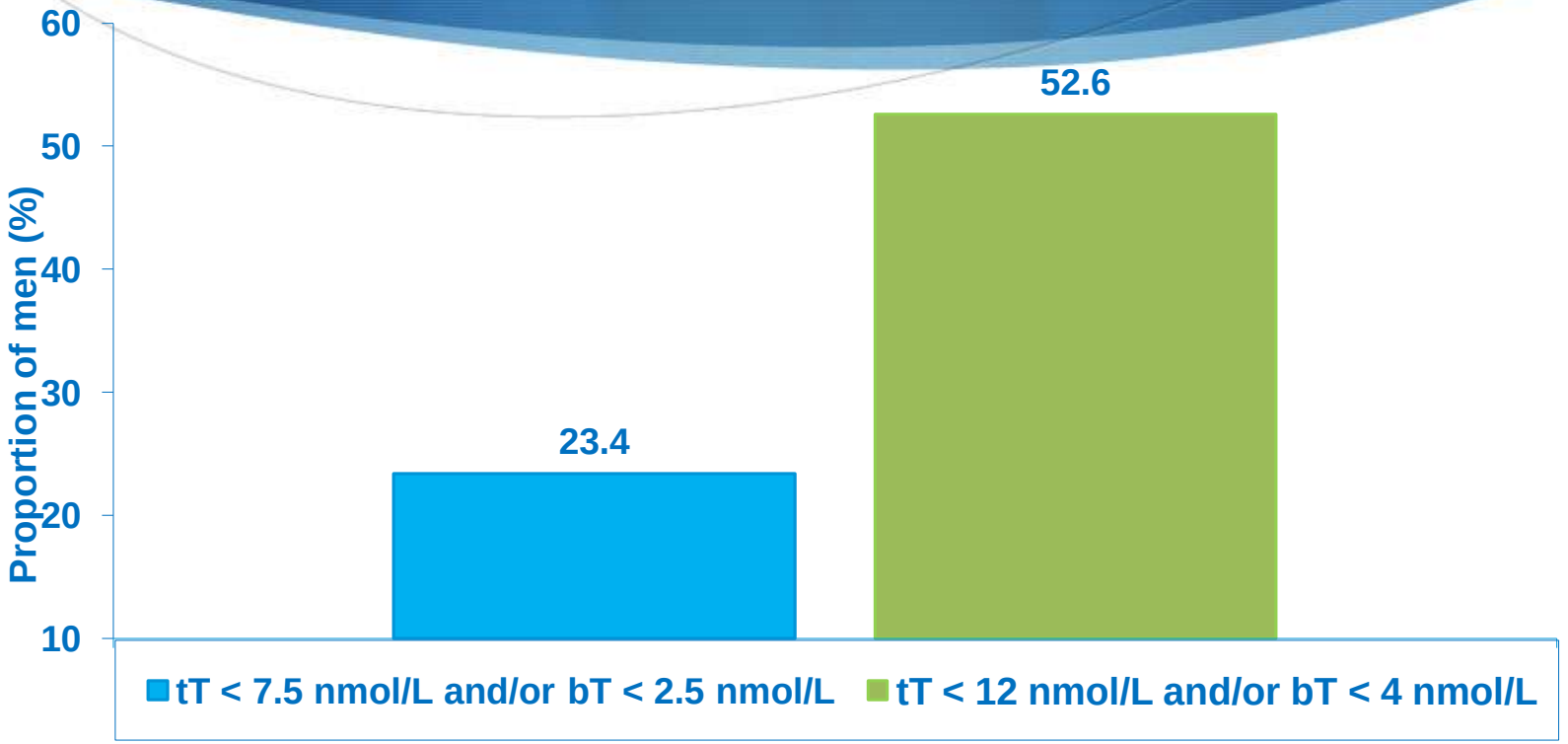
Malkin *et al*. *Eur Heart J* 2006;27:57–64

Studies in men with cardiovascular disease



English KM *et al*. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study*Circulation* 2000;102:1906–1911

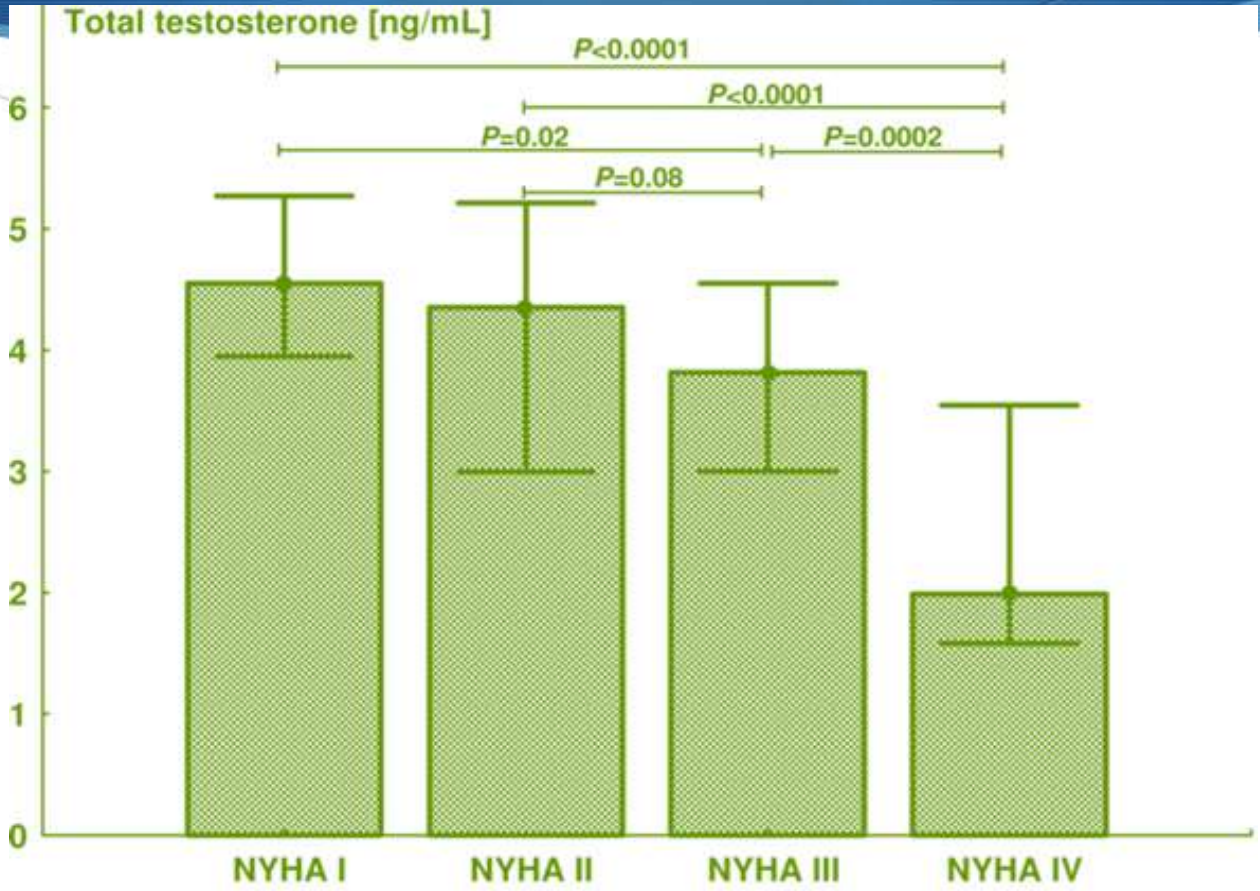
Hypogonadism is present in a high proportion of men with CAD



N=891

South Yorkshire Study, Pugh *et al*. Unpublished.

Serum levels of total testosterone in men with cardiac heart failure (CHF) by NYHA Class



Jankowska EA *et al*. Anabolic deficiency in men with chronic heart failure: prevalence and detrimental impact on survival. *Circulation* 2006;114:1829–1837.

J Clin Endocrin Metab. First published ahead of print December 11, 2013 as doi:10.1210/jc.2013-2052

Late-Onset Hypogonadism and Mortality in Aging Men

S. R. Pye, I. T. Huhtaniemi, J. D. Finn, D. M. Lee, T. W. O'Neill, A. Tajar, G. Bartfai, S. Boonen, F. F. Casanueva, G. Forti, A. Giwercman, T. S. Han, K. Kula, M. E. Lean, N. Pendleton, M. Punab, M. K. Rutter, D. Vanderschueren, F. C. W. Wu,* and the EMAS Study Group

Context: Late-onset hypogonadism (LOH) has recently been defined as a syndrome in middle-aged and elderly men reporting sexual symptoms in the presence of low T. The natural history of LOH, especially its relationship to mortality, is currently unknown.

Objective: The aim of this study was to clarify the associations between LOH, low T, and sexual symptoms with mortality in men.

Design, Setting, and Participants: Prospective data from the European Male Aging Study (EMAS) on 2599 community-dwelling men aged 40–79 years in eight European countries was used for this study.

Main Outcome Measure(s): All-cause, cardiovascular, and cancer-related mortality was measured.

Results: One hundred forty-seven men died during a median follow-up of 4.3 years. Fifty-five men (2.1%) were identified as having LOH (31 moderate and 24 severe). After adjusting for age, center, body mass index (BMI), current smoking, and poor general health, compared with men without LOH, those with severe LOH had a 5-fold [hazard ratio (HR) 5.5; 95% confidence interval (CI) 2.7, 11.4] higher risk of all-cause mortality. Compared with eugonadal men, the multivariable-adjusted risk of mortality was 2-fold higher in those with T less than 8 nmol/L (irrespective of symptoms; HR 2.3; 95% CI 1.2, 4.2) and 3-fold higher in those with three sexual symptoms (irrespective of serum T; compared with asymptomatic men; HR 3.2; 95% CI 1.8, 5.8). Similar risks were observed for cardiovascular mortality.

Conclusions: Severe LOH is associated with substantially higher risks of all-cause and cardiovascular mortality, to which both the level of T and the presence of sexual symptoms contribute independently. Detecting low T in men presenting with sexual symptoms offers an opportunity to identify a small subgroup of aging men at particularly high risk of dying. ***J Clin Endocrinol Metab* 99: 0000–0000, 2014)**

Low Testosterone predicts T2D

1 **MMAS** (Stellato) 1709 men (40- 70) Follow Up 9 yrs (table)

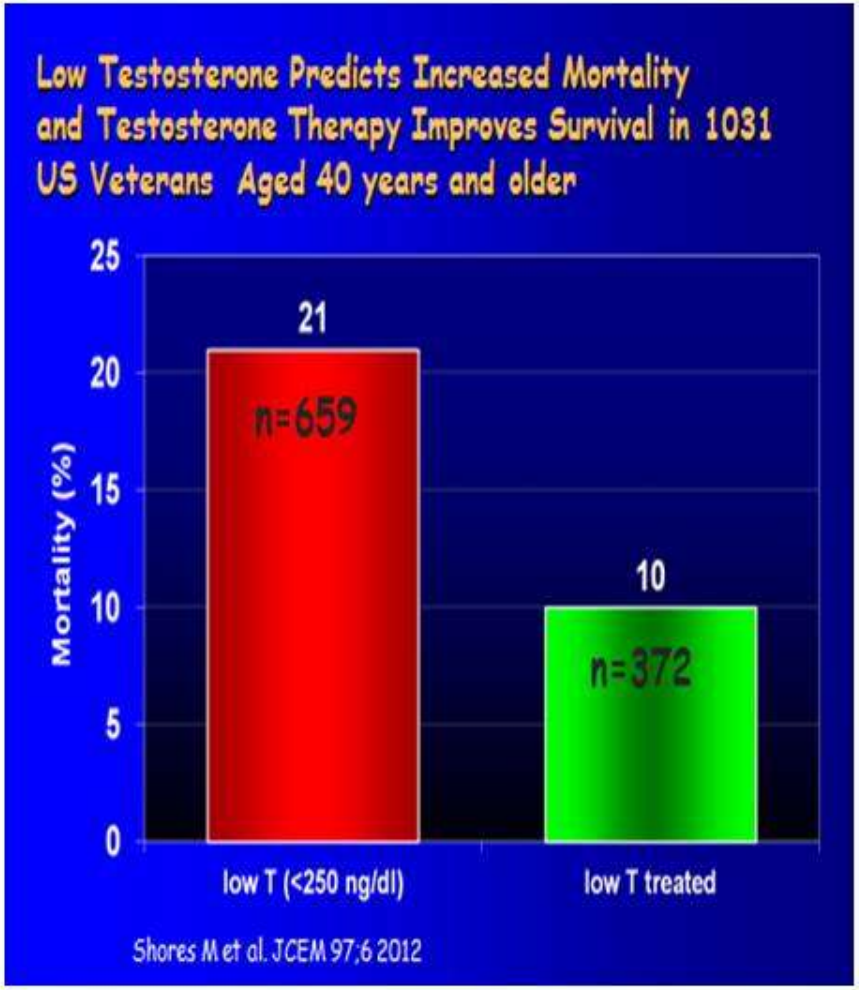
2 **Rancho Bernardo (Oh et al)** 294 M 233 women (55-89) FU 8yrs

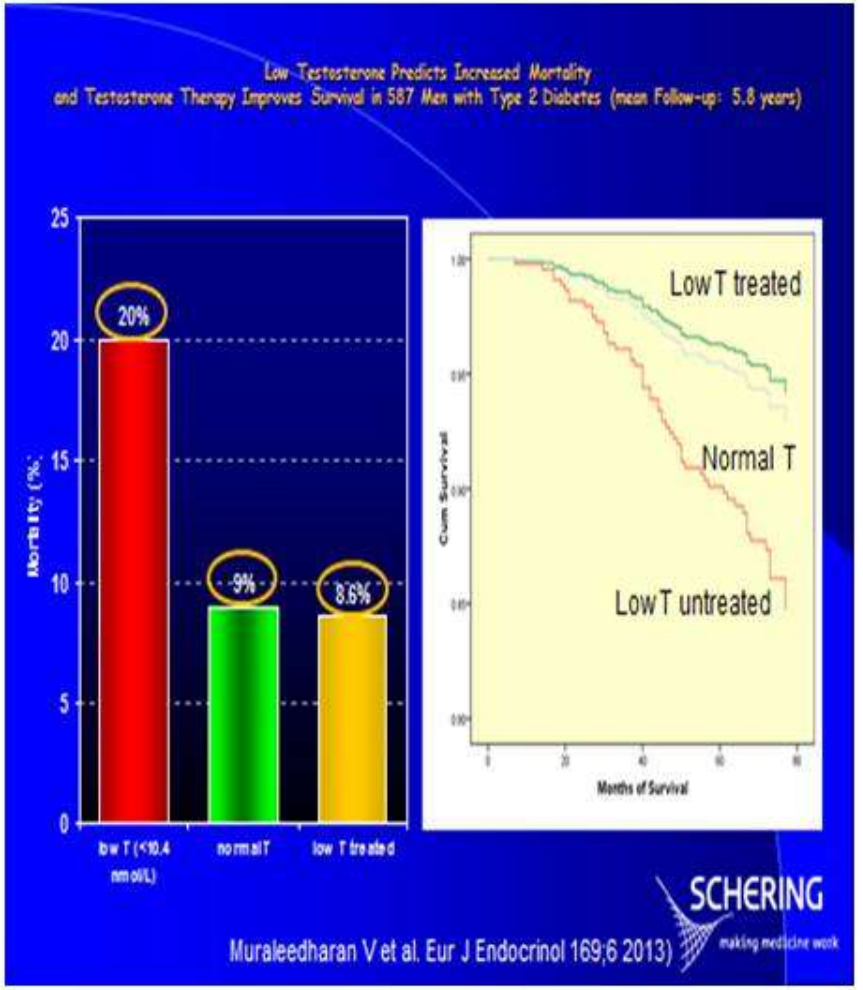
3 **NHANES-III (Selvam et al)** 1413 men (>20) 10 yr follow up Men in towest tertile of TT and FT -4 times more likely to develop T2D independent of obesity and ethnicity

FACTOR	T2D	No-T2D	p
TT	15.2	18.2	<0.001
FT	0.28	0.34	0.004
SHBG	24.4	32.3	<0.001
Hypogon <10.4 nmol/l	**15.1%**	**3.3%**	**<0.001**
HTN	48.1%	23.8%	<0.001
Moderate Exercise	64.8	68	0.24
Depress	18.9%	8.5%	0.02
BMI	31.0	26.9	<0.001

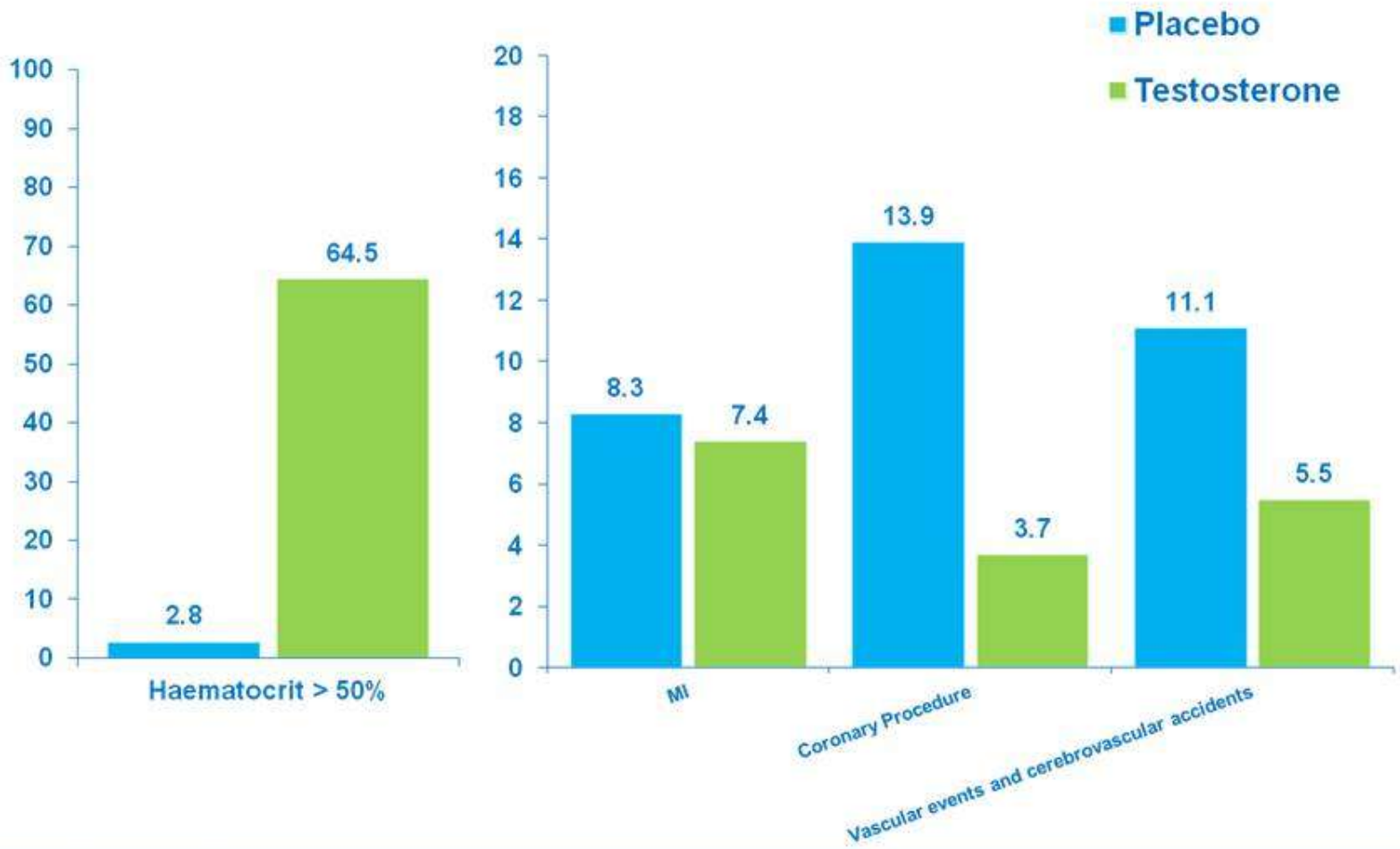
- 1 Diabetes Care 2000 Apr; 23(4):490-4. 2 Diabetes Care 2002 Jan;25(1):55-60 3 *Diabetes Care* 30:23-84, 2007

Long term mortality studies on TRT





Meta-analysis of placebo-controlled testosterone trials in middle-aged and older men: cardiovascular adverse event rates per 1,000 patient-years



Calof OM *et al. J Gerontol* 2005;60A(11):4051–4057.

Research

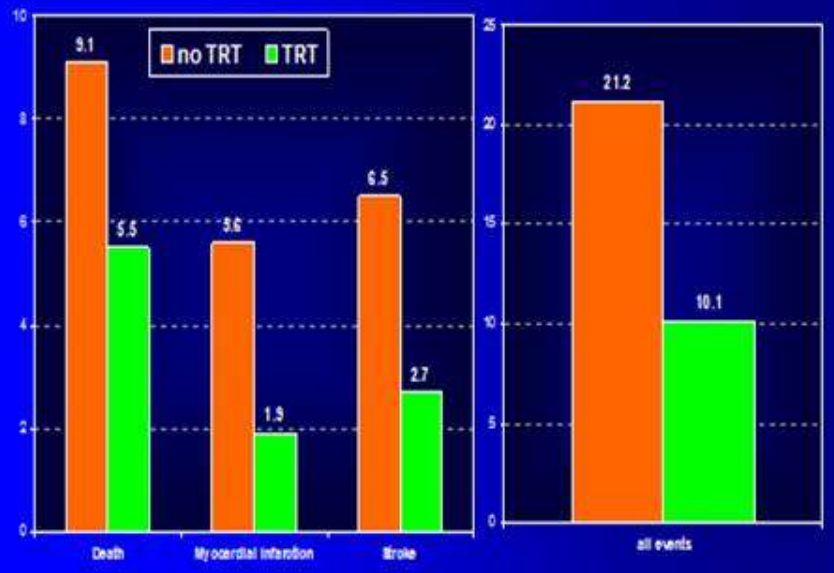
Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

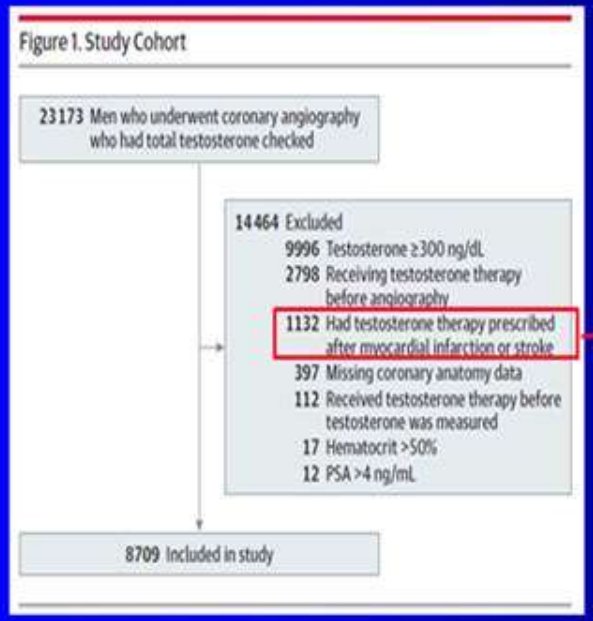
Vigen R et al. J Am Med Assoc 310(17): 1829–1836 (2013)

Proportion of All Events (Composite of All-cause Mortality, Myocardial Infarction and Stroke) in Hypogonadal Patients (%) with or without Testosterone Replacement Therapy (TRT)



Data from: Vigen R et al. J Am Med Assoc 310(17): 1829-1836 (2013)

Selection Bias?

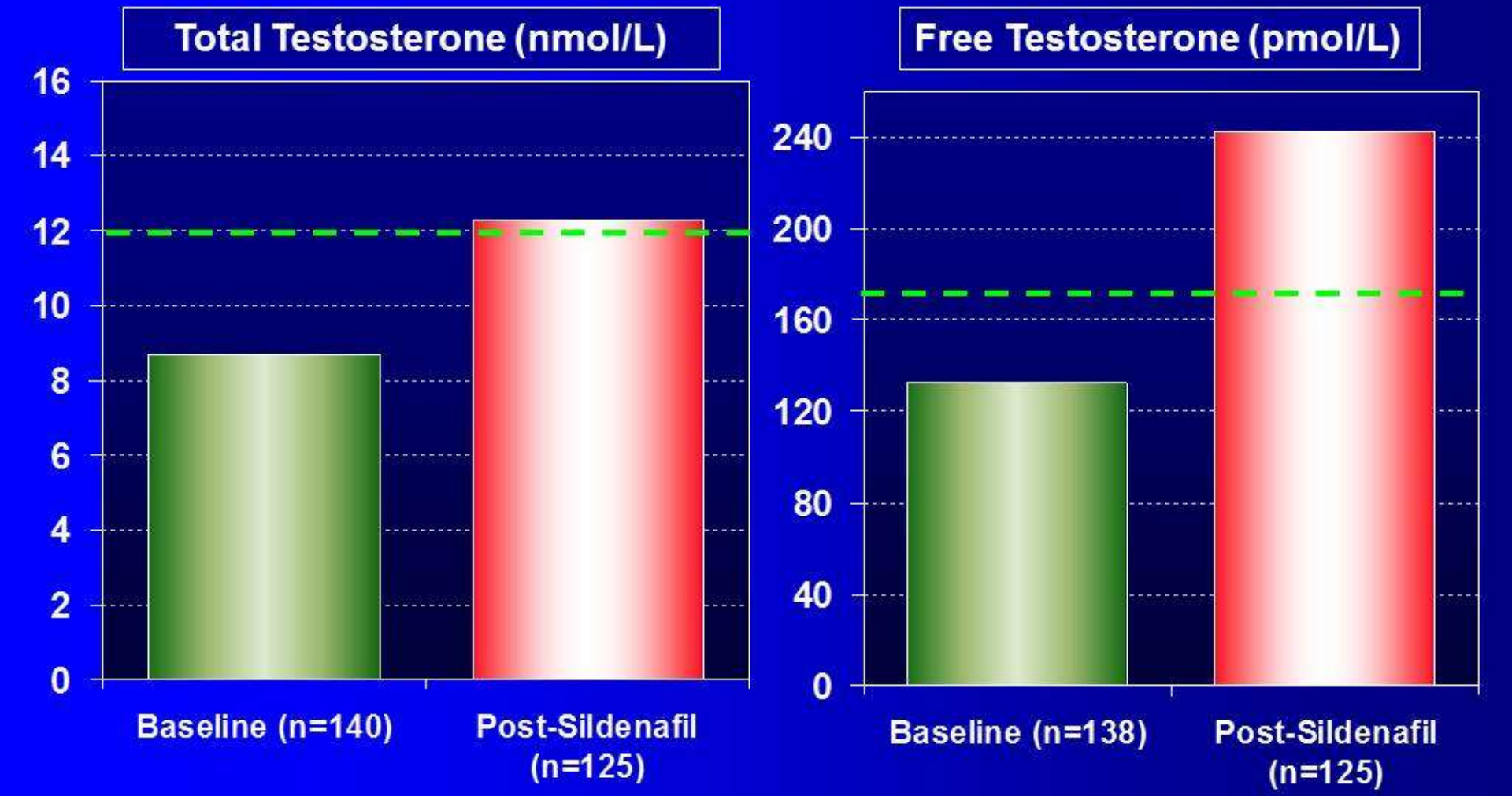


Patients who had received testosterone therapy after MCI or CVA had been excluded from the study. The number of men excluded due to this aspect is 1132. It would have been expected that these events should be attributed to the untreated group. Number of events in untreated group would have increased by 71%. Authors later confirmed this number should have been 128 and that over 104 women had been included by error!

Vigen R et al. J Am Med Assoc 310(17): 1829-1836 (2013)

Users of PDE5 Inhibitors as Control Group?

Increase of Total and Free Testosterone after Use of Sildenafil in 140 Hypogonadal Men with Erectile Dysfunction



Spitzer M et al. Androl 1: 913-918 (2013)

Studies following publication of Vigen and Finkle

Author	Year	Journal / Congress	Study type	# of patients on TRT	Results
TESTOSTERONE REPLACEMENT THRAPY (TRT)					
Baillargeon et al.	2014	Ann Pharmacother	Retrospective Medicare database review	6,355	No increased risk of MI, moderately protective effect of TRT in high risk patients.
Anderson JL et al.	2014	Circulation/AHA	Retrospective medical records review	4,713	Reduced incidence of MACE.
Eisenberg ML et al.	2015	Int J Impot Res	Retrospective medical records review	284	No increased mortality risk.
Janmohamed S et al.	2015	Endocrin Rev /Endo	Retrospective	217	Reduced incidence of MACE.
Li H et al.	2015	Endocrin Rev /Endo	Truven database review	102,650	No increased risk of VTE.
Saad F et al.	2015	Endocrin Rev /Endo	Prospective registry	68	No MACE in patient with CVD history.

MACE; Major Adverse Cardiovascular Event, VTE; Venous Thromboembolism

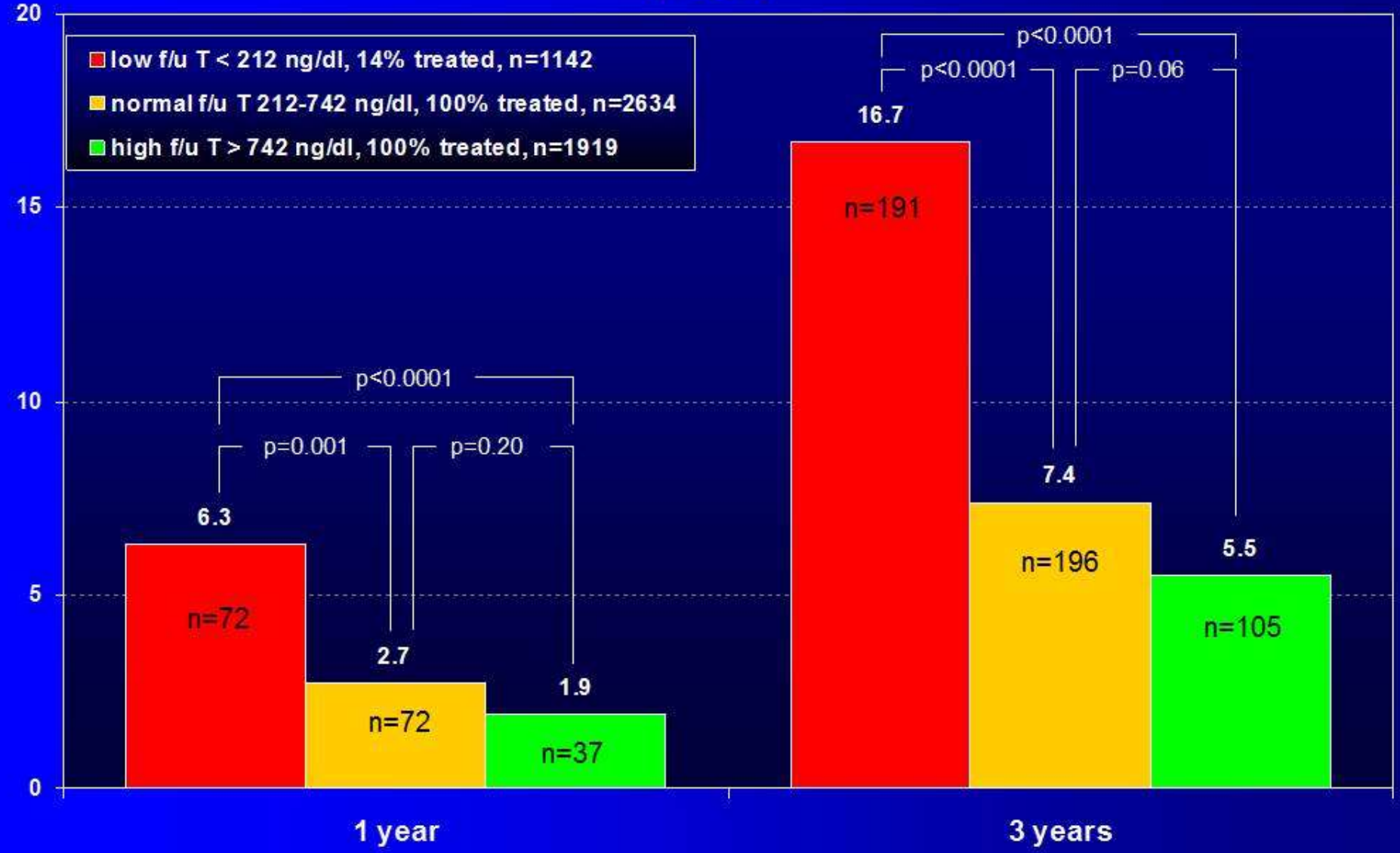
Studies following publication of Vigen and Finkle

Author	Year	Journal / Congress	Study type	# of patients on TRT	Results
Ali Z et al.	2015	JACC / ACC	Retrospective community-based healthcare system	3,115	No increased risk of CV events.
Patel P et al.	2015	JACC / ACC	Meta-analysis	122,899	No increase in CV events.
Tan RS et al.	2015	Int J Endocrinol	Retrospective medical chart review	19,968	Reduced incidence of MI and stroke.
Sharma R et al.	2015	Eur Heart J	Retrospective	43,931 achieving normal T 25,701 not achieving normal T	Reduced incidence of MI and stroke, reduced mortality. No increase in CV events.
Baillargeon J et al.	2015	Mayo Clin Proc	Retrospective	663	No increased risk of VTE.

Studies following publication of Vigen and Finkle

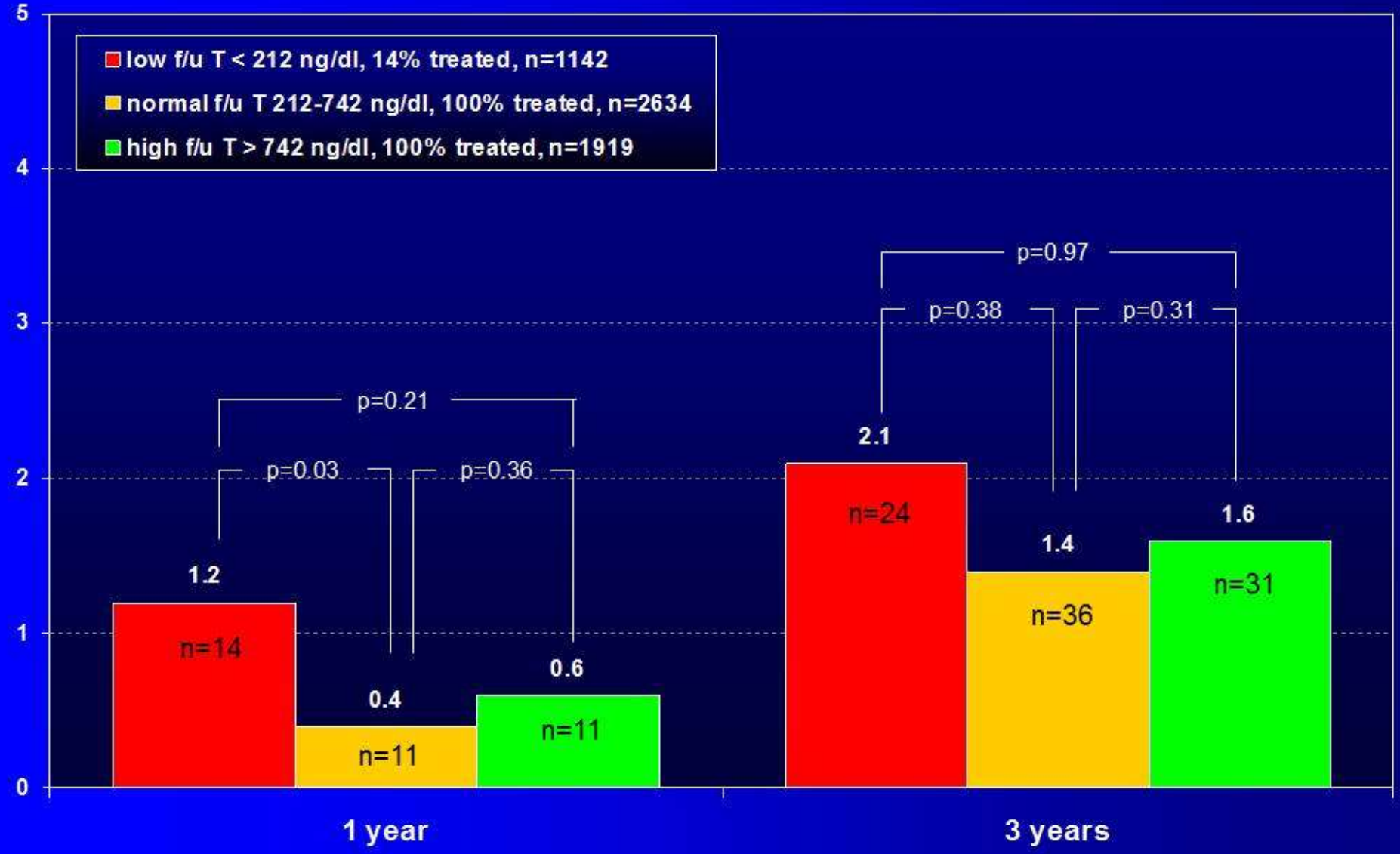
Author	Year	Journal / Congress	Study type	# of patients on TRT	Results
Etminam M et al.	2015	Pharmacotherapy	Retrospective	2469 720	No increased risk of MI. No increased risk of MI in men with prior cardiac event. Small increased risk of MI in first-time users.
Ramasamy R et al.	2015	Urology	Retrospective	153	Increased all-cause mortality in hypogonadal men not on TRT, compared to men on TRT. No difference in prevalence of MI, TIA/CVA, or PE between men on TRT on men not on TRT.
Anderson JL et al.	2015	Am J Cardiol	Retrospective	4,736 >3 years of follow-up	Reduced MACE and death.

Cardiovascular Impact of Testosterone Therapy in 5,695 Men with Low Testosterone Levels – Event Rates (%) of Major Adverse Cardiovascular Events (MACE)



Anderson JL et al. Circulation 130 (Suppl. 2): A13220 (2014)

Cardiovascular Impact of Testosterone Therapy in 5,695 Men with Low Testosterone Levels – Event Rates (%) of Myocardial Infarction (MI)



Anderson JL et al. Circulation 130 (Suppl. 2): A13220 (2014)

The most convincing study.

European Heart Journal Advance Access published August 6, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv346

FASTTRACK CLINICAL RESEARCH
Coronary artery disease

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

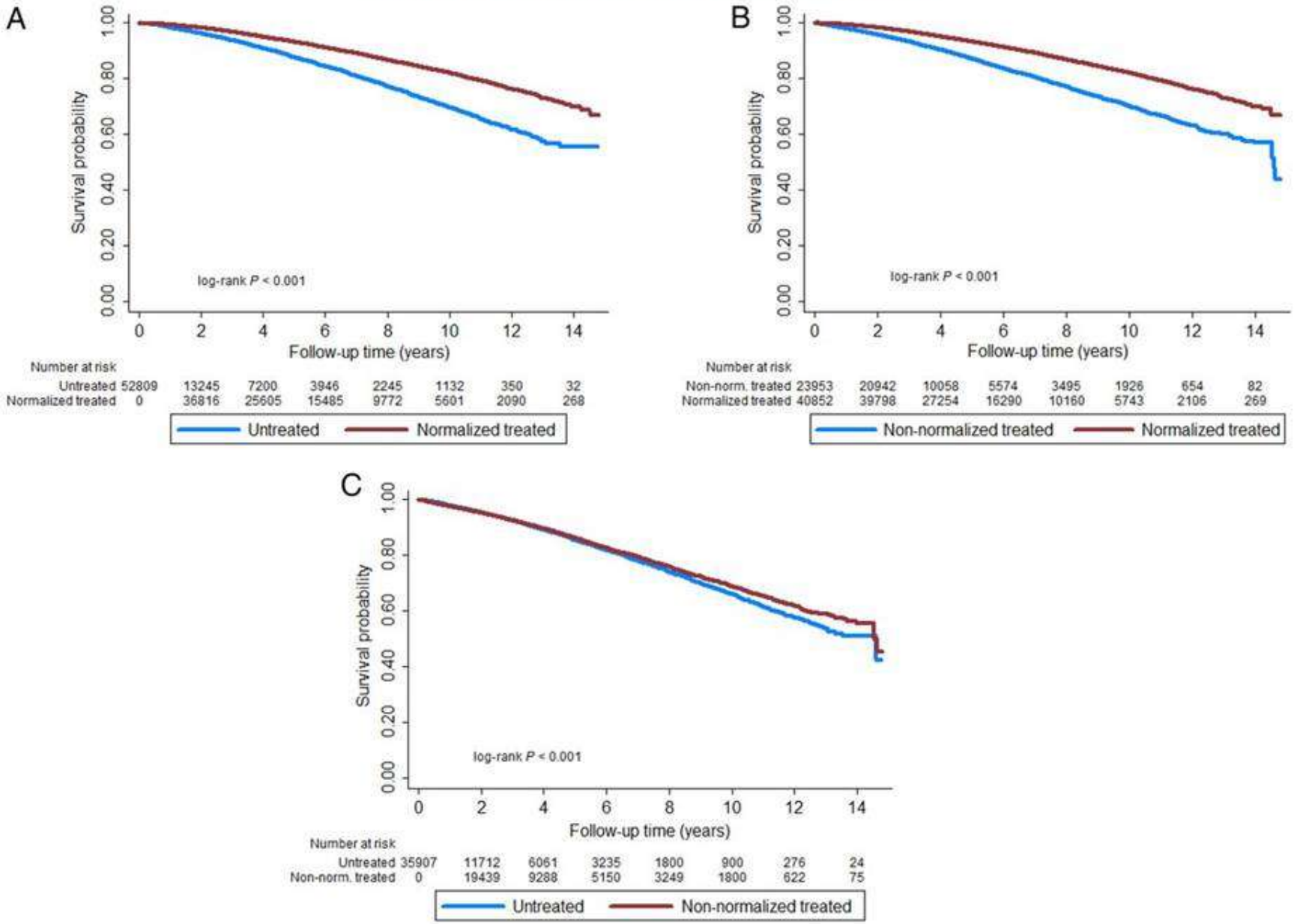
Rishi Sharma[1], Olurinde A. Oni[1], Kamal Gupta[2], Guoqing Chen[3], Mukut Sharma[1], Buddhadeb Dawn[2], Ram Sharma[1], Deepak Parashara[2,4], Virginia J. Savin[5], John A. Ambrose[6], and Rajat S. Barua[1,2,4]*

[1]Division of Cardiovascular Research, Kansas City VA Medical Center, Kansas City, MO, USA; [2]Division of Cardiovascular Diseases, University of Kansas Medical Center, Kansas City, KS, USA; [3]Division of Health Services Research, University of Kansas Medical Center, Kansas City, KS, USA; [4]Division of Cardiovascular Medicine, Kansas City VA Medical Center, 4801 E. Linwood Boulevard, Kansas City, MO 64128, USA; [5]Division of Nephrology, Kansas City VA Medical Center, Kansas City, MO, USA; and [6]Division of Cardiovascular Medicine, University of California San Francisco, Fresno, CA, USA

Received 2 June 2015; revised 1 July 2015; accepted 6 July 2015

Sharma R et al. Eur Heart J, published online August 06, 2015; doi: 10.1093/eurheartj/ehv346

Only men achieving *normal* T levels had a significantly reduced mortality, compared to untreated and treated men who did *not* achieve normal T.



Sharma R et al. Eur Heart J, published online August 06, 2015; doi: 10.1093/eurheartj/ehv346

Abstract

Aims There is a significant uncertainty regarding the effect of testosterone replacement therapy (TRT) on cardiovascular (CV) outcomes including myocardial infarction (MI) and stroke. The aim of this study was to examine the relationship between normalization of total testosterone (TT) after TRT and CV events as well as all-cause mortality in patients without previous history of MI and stroke.

Methods and results We retrospectively examined 83 010 male veterans with documented low TT levels. The subjects were categorized into (Gp1: TRT with resulting normalization of TT levels), (Gp2: TRT without normalization of TT levels) and (Gp3: Did not receive TRT). By utilizing propensity score-weighted Cox proportional hazard models, the association of TRT with all-cause mortality, MI, stroke, and a composite endpoint was compared between these groups. The all-cause mortality [hazard ratio (HR): 0.44, confidence interval (CI) 0.42–0.46], risk of MI (HR: 0.76, CI 0.63–0.93), and stroke (HR: 0.64, CI 0.43–0.96) were significantly lower in Gp1 ($n = 43\,931$, median age = 66 years, mean follow-up = 6.2 years) vs. Gp3 ($n = 13\,378$, median age = 66 years, mean follow-up = 4.7 years) in propensity-matched cohort. Similarly, the all-cause mortality (HR: 0.53, CI 0.50–0.55), risk of MI (HR: 0.82, CI 0.71–0.95), and stroke (HR: 0.70, CI 0.51–0.96) were significantly lower in Gp1 vs. Gp2 ($n = 25\,701$, median age = 66 years, mean follow-up = 4.6 years). There was no difference in MI or stroke risk between Gp2 and Gp3.

Conclusion In this large observational cohort with extended follow-up, normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke.

Sharma R et al. Eur Heart J, published online August 06, 2015; doi: 10.1093/eurheartj/ehv346

Association Between Testosterone Supplementation Therapy and Thrombotic Events in Elderly Men

Ranjith Ramasamy, Jason Scovell, Michael Mederos, Renzhong Ren, Lakshay Jain, and Larry Lipshultz

OBJECTIVE To determine the prevalence of thrombotic events and all-cause mortality in men older than 65 years with hypogonadism treated with testosterone therapy (TST).

PATIENTS AND METHODS We retrospectively reviewed the charts of 217 hypogonadal men >65 years. We compared men who received TST (n = 153) to hypogonadal men (n = 64) who did not receive TST. We evaluated all-cause mortality, prevalence of myocardial infarction (MI), transient ischemic attack (TIA), cerebrovascular accident (CVA or "stroke"), and deep vein thrombosis/pulmonary embolism (DVT/PE). All events were verified by contacting patients. We excluded men with previous thrombotic events, men previously on androgen deprivation therapy, and men who had used TST before age of 65 years.

RESULTS Median age and Charlson Comorbidity Index of men on TST (74y; 5.1) was similar to hypogonadal men not on TST (73y, $P = .48$; 5.3, $P = .36$). Median follow-up was 3.8 vs 3.5 years (TST vs no TST). No man on TST died, whereas 5 hypogonadal men who did not receive TST died ($P = .007$). There were 4 thrombotic events (1 MI, 2 CVA/TIA, and 1 PE) in men who received TST and 1 event (CVA/TIA) among men who did not receive TST ($P = .8$). All events (1 death, 6-month follow-up) occurred at least after 2 years of follow-up.

CONCLUSION There was increased all-cause mortality in hypogonadal men not treated with testosterone compared to men who received TST. There was no difference in prevalence of MI, TIA/CVA, or PE between patients treated with testosterone and hypogonadal men not treated with testosterone. UROLOGY 86: 283–286, 2015.

The most recent and largest meta-analysis.

EXPERT OPINION

1. Introduction
2. Androgen boosting increases cardiovascular risk
3. T and CVD: the evidence
4. Epidemiological studies
5. Intervention studies

Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis

Giovanni Corona, Elisa Maseroli, Giulia Rastrelli, Andrea M Isidori, Alessandra Sforza, Edoardo Mannucci & Mario Maggi†

†*University of Florence, Department of Experimental, Clinical and Biomedical Sciences, Sexual Medicine and Andrology Unit, Florence, Italy*

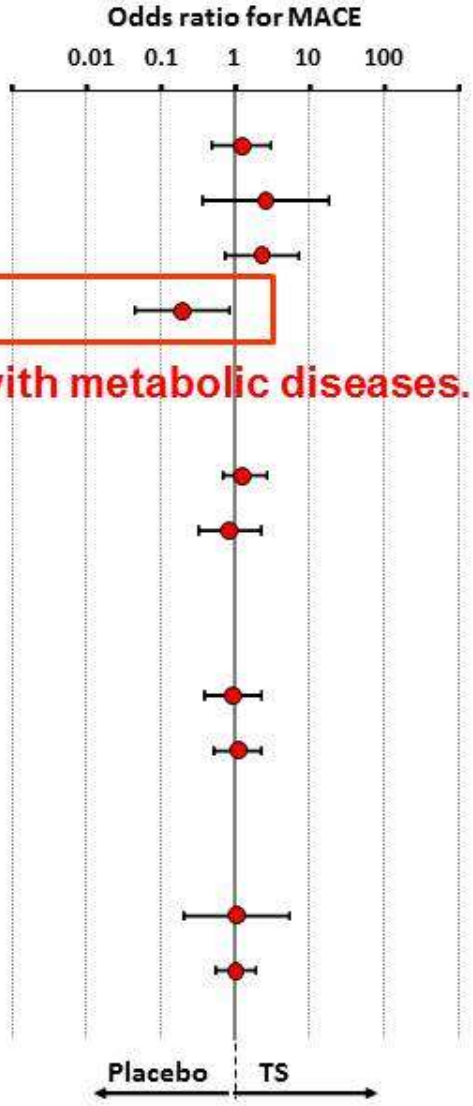
Expert opinion: The present systematic review and meta-analysis does not support a causal role between TS and adverse CV events. Our results are in agreement with a large body of literature from the last 20 years supporting TS of hypogonadal men as a valuable strategy in improving a patient's metabolic profile, reducing body fat and increasing lean muscle mass, which would ultimately reduce the risk of heart disease.

Corona G et al. Expert Opin Drug Saf 13(10): 1327-1351 (2014)

Odds Ratio for Major Adverse Cardiovascular Events (MACE) According to Baseline Characteristics in Subjects Treated with Testosterone or Placebo

MACE: cardiovascular death, non-fatal myocardial infarction, stroke, acute coronary syndromes, and/or heart failure

Source	# Trials	MH-OR	LL	UL	p	TRT #Events	TRT # Patients	Placebo #Events	Placebo # Patients
Associated diseases									
Elderly men	10	1,22	0,49	3,03	0,67	13	954	6	549
Men with CVD	2	2,48	0,35	17,45	0,36	3	62	1	64
Frail men	5	2,25	0,72	7,08	0,17	13	401	4	355
Men with metabolic diseases	4	0,19	0,04	0,85	0,03	1	303	5	203
Hypogonadism status									
Mixed population	14	1,26	0,58	2,73	0,56	15	1066	11	865
TT < 12 nM	12	0,84	0,32	2,23	0,73	16	829	9	476
Type of support									
Drug company not supported	12	0,94	0,39	2,24	0,88	10	437	8	332
Drug company supported	14	1,07	0,51	2,24	0,86	21	1458	12	1009
Trial duration									
≤ 12 weeks	4	1,02	0,20	5,29	0,98	2	147	2	145
>12 weeks	22	1,01	0,55	1,84	0,98	29	1746	18	1196



Protective effect of testosterone in men with metabolic diseases.

CVD: Cardiovascular diseases; LL: Lower limit; UL: Upper limit;
MH-OR: Mantel-Haenszel odds ratio; TT: Total testosterone

Corona G et al. Expert Opin Drug Saf 13(10): 1327-1351 (2014)

SUMMARY

- **Who to screen and who to consider for TRT**

1. **Men with type 2 diabetes and Metabolic Syndrome**
2. **Men with comorbid obesity**
3. **Men with chronic disease : COPD, HIV , HF**
4. **Men with erectile disfunction**

THANKS YOU