Update on Men's Health

George Everett MD MS FACP

Objectives

- 1. Update use and abuse of testosterone products
- 2. Update controversies on screening for prostate cancer

Use and Abuse of Testosterone Products

- -Healthy males have declining testosterone with age.

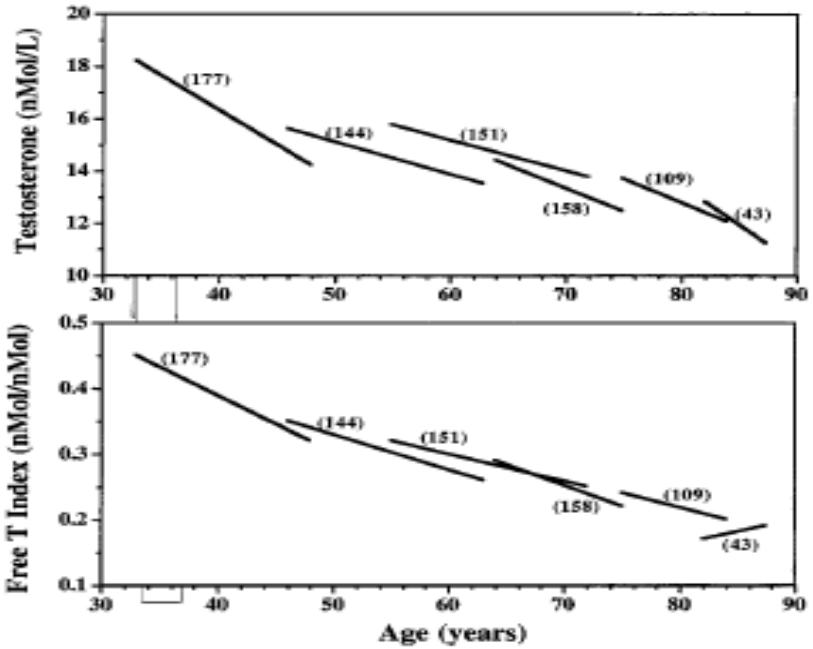


FIG. 2. Longitudinal effects of aging on date-adjusted T and free T index. Linear segment plots for total T and free T index *vs.* age are shown for men with T and SHBG values on at least two visits. Each linear segment has a slope equal to the mean of the individual longitudinal slopes in each decade, and is centered on the median age, for each cohort of men from the second to the ninth decade. *Numbers in parentheses* represent the number of men in each cohort. With the exception of free T index in the ninth decade, segments show significant downward progression at every age, with no significant change in slopes for T or free T index over the entire age range.

Testosterone cont.

- Testosterone declines at about 1-2% per year

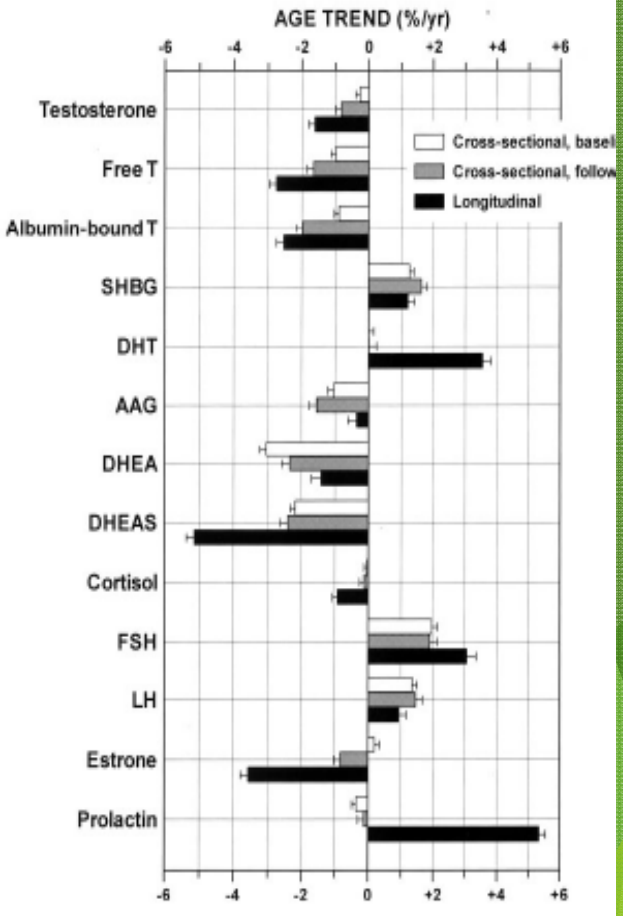


FIG. 2. Cross-sectional and longitudinal trends of T, other androgens and metabolites, and related hormones in middle-aged men, participants in MMAS, 1987–97.

Testosterone cont.

- -By age 80, 50-90% of males are at “hypogonadal” levels.

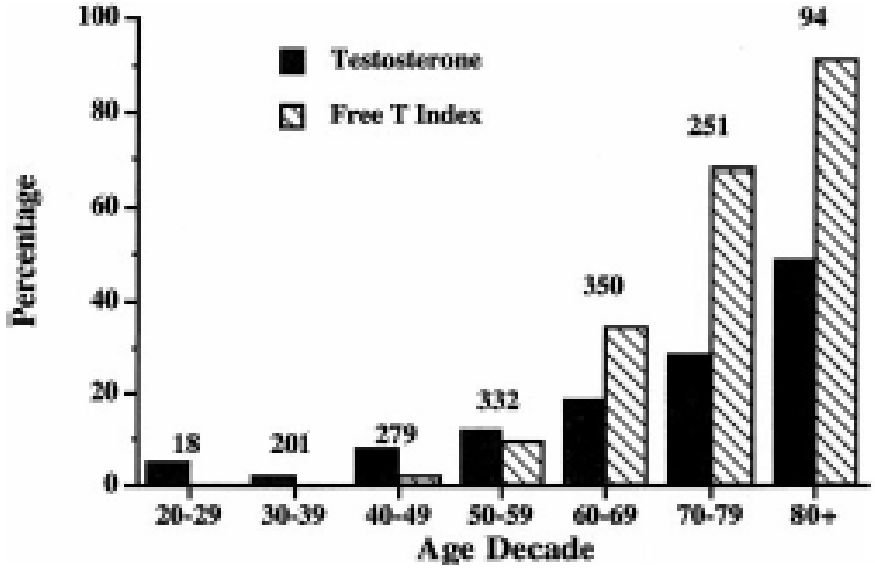


FIG. 3. Hypogonadism in aging men. *Bar height* indicates the percent of men in each 10-yr interval, from the third to the ninth decades, with at least one T value in the hypogonadal range, by the criteria of total T < 11.3 nmol/L (325 ng/dL) (*shaded bars*), or T/SHBG (free T index) < 0.153 nmol/nmol (*striped bars*). *Numbers above each pair of bars* indicate the number of men studied in the corresponding decade. The fraction of men who are hypogonadal increases progressively after age 50 by either criterion. More men are hypogonadal by free T index than by total T after age 50, and there seems to be a progressively greater difference, with increasing age, between the two criteria.

Testosterone cont.

- -Reductions in testosterone levels are not primarily due to health problems, medications and chronic diseases. The longitudinal studies were of healthy men in cohort studies.
- -TTrials are 7 randomized trials to determine effects of testosterone replacement in men with low levels.
- -Cognitive function, Unexplained anemia, CAD, Bone density, Physical functioning, Sexual functioning, Vitality.

Testosterone cont.

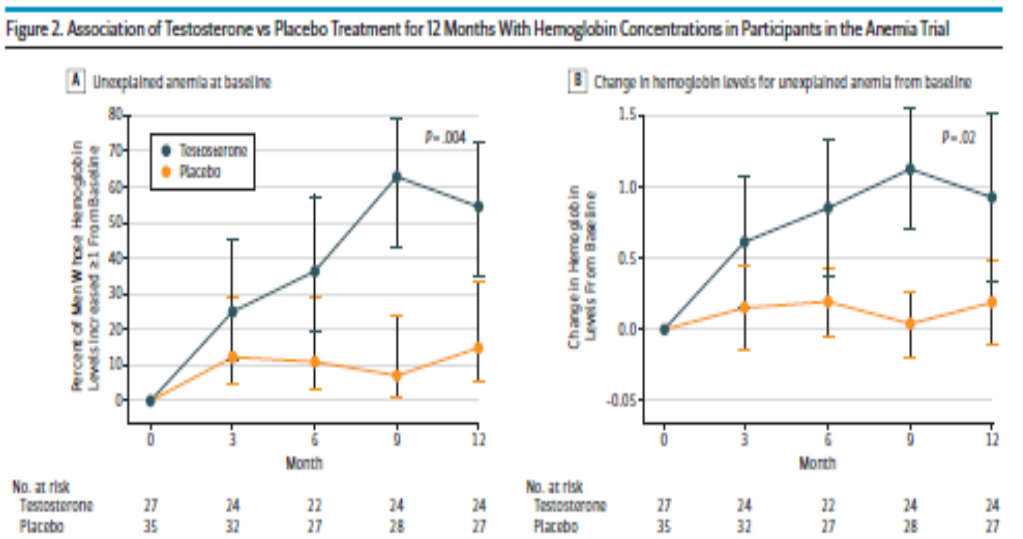
Table 1. Common inclusion and exclusion criteria for The Testosterone Trials[a]

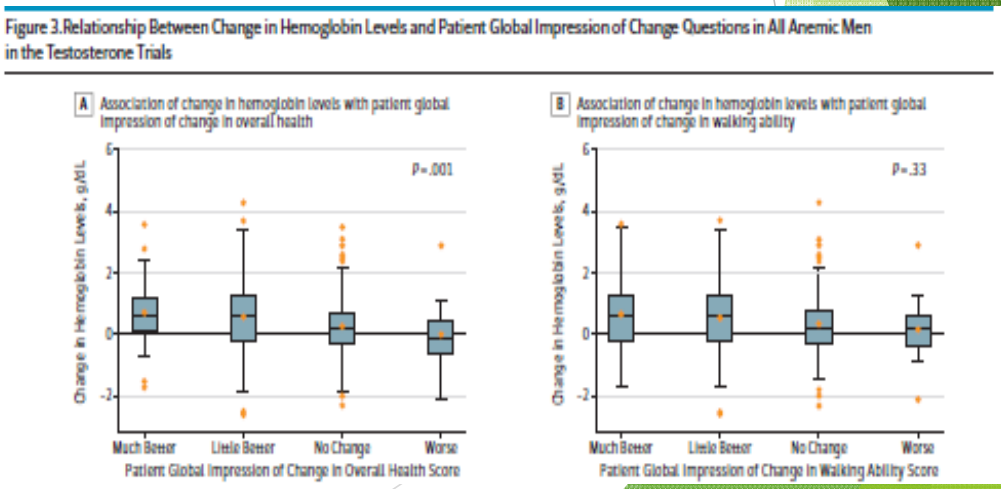
Inclusion criteria
Men ≥ 65 years old
Total serum testosterone concentration at screening visit 1 < 275 ng/dL, at screening visit 2 < 300 ng/dL, and an average of both values < 275 ng/dL
Exclusion criteria
Diagnosed prostate cancer or prostatic intraepithelial neoplasia
Risk of prostate cancer by the Prostate Cancer Risk Calculator: >35% of overall prostate cancer or >7% risk of high-grade prostate cancer
Severe lower urinary tract symptoms (score of >19) by the International Prostate Symptom Score questionnaire
Sleep apnea, diagnosed but untreated
Illnesses or medications that would interfere with interpretation of the results
Medications that affect serum testosterone concentration

[a]Abbreviated list. The complete list of the common inclusion and exclusion criteria is in the supplemental data section.

Testosterone cont.

- Effect on Anemia:
- Significant improvement in hemoglobin
- No significant benefit to overall health
- No significant benefit to walking

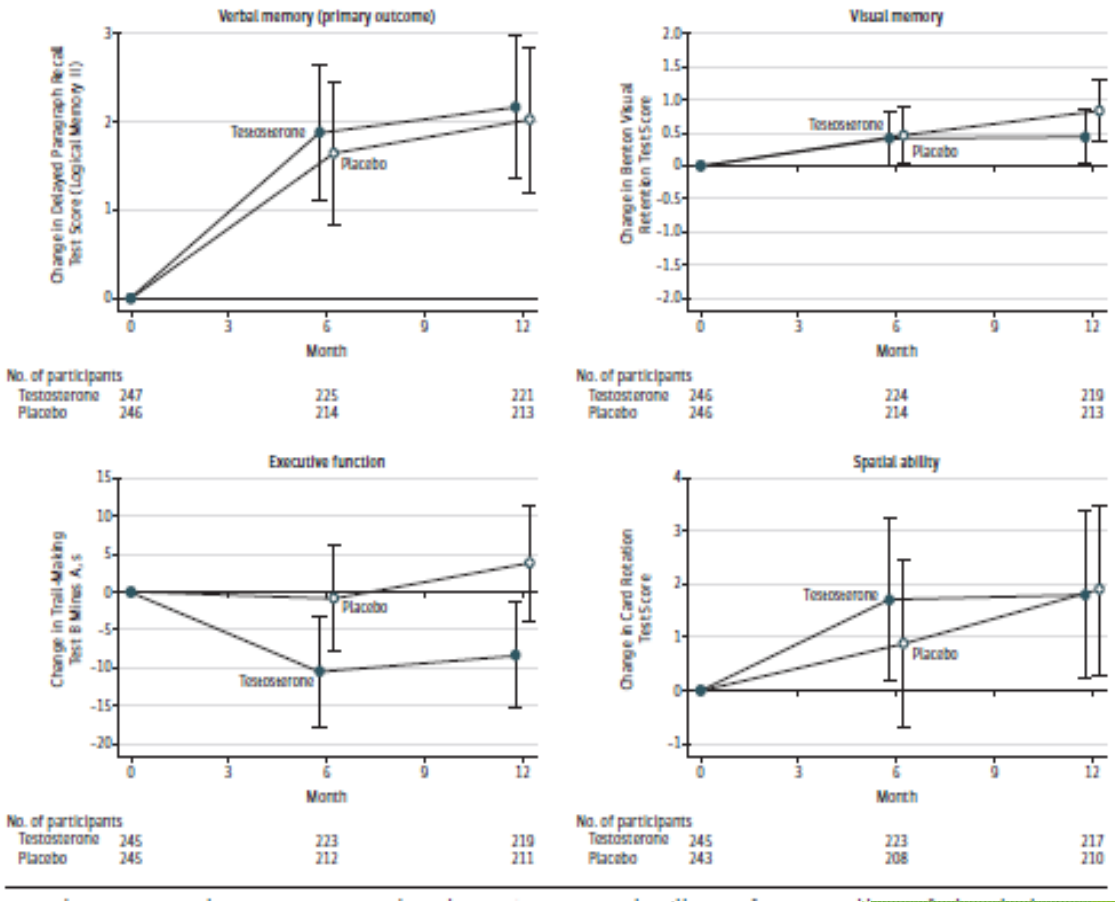




Testosterone cont.

- Effect on Cognition
- No benefit

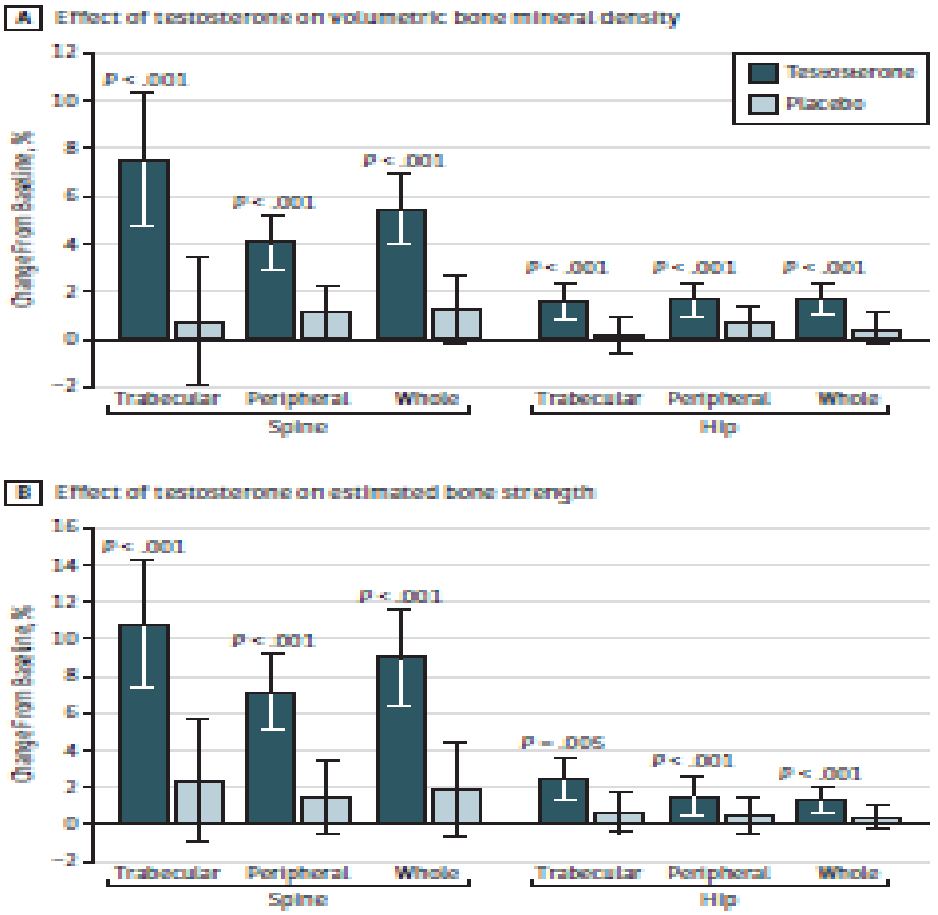
Figure 2. Adjusted Mean Change From Baseline to 6 Months and 12 Months for Men With AAMI by Treatment Group (Testosterone vs Placebo) for Verbal Memory (Delayed Paragraph Recall), Visual Memory, Executive Function, and Spatial Ability



Testosterone cont.

- Effect on Bone Density
- Significant benefit at all bone sites

Figure 3. Effects of Testosterone or Placebo Treatment for 12 Months on Volumetric Bone Mineral Density and Estimated Bone Strength of Trabecular, Peripheral, and Whole Bone of the Spine and Hip, as Assessed by Quantitative Computed Tomography



Testosterone cont.

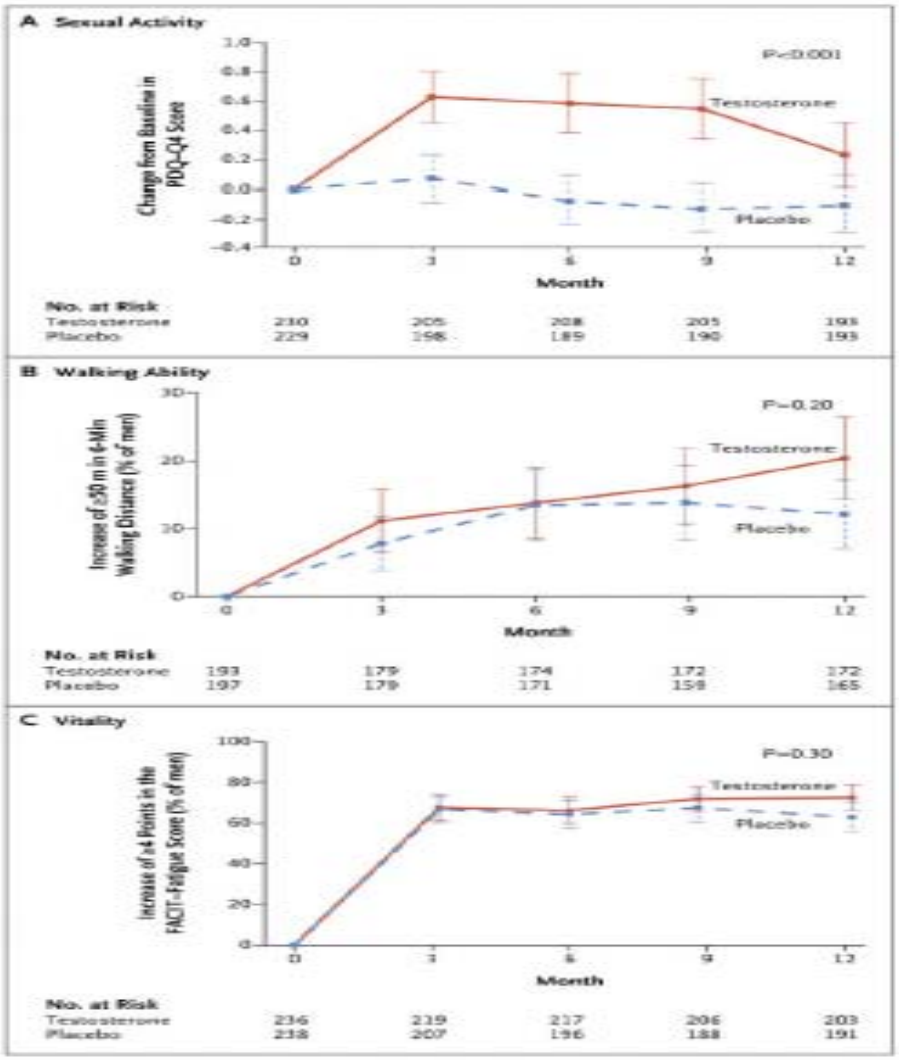
- Effect on Coronary CT:
- Significant increase in non-calcified
- plaque volume

Table 2. Change From Baseline and Estimated Differences for Primary, Secondary, and Exploratory Outcomes in the Cardiovascular Trial

Outcome	Treatment Group: Testosterone (n = 73)	Treatment Group: Placebo (n = 65)	Estimated Difference (95% CI)[a]	*P* Value[b]
Primary				
Noncalcified plaque volume, mm³				
Baseline, median (IQR)	204 (60 to 420)	317 (168 to 589)		
Month 12, median (IQR)	232 (103 to 473)	325 (172 to 560)		
Change from baseline value, unadjusted mean (95% CI)	40 (23 to 56)	4 (−14 to 22)		
LS mean (95% CI)[c]	54 (12 to 97)	14 (−29 to 56)	41 (14 to 67)	.003
Secondary				
Total plaque volume, mm³				
Baseline, median (IQR)	272 (84 to 600)	499 (246 to 925)		
Month 12, median (IQR)	318 (133 to 693)	541 (248 to 950)		
Change from baseline value, unadjusted mean (95% CI)	57 (35 to 78)	21 (0 to 42)		
LS mean (95% CI)[c]	75 (22 to 128)	28 (−24 to 81)	47 (13 to 80)	.006
Coronary artery calcium score, Agatston units[d]				
Baseline, median (IQR)	255 (43 to 963)	494 (146 to 1892)		
Month 12, median (IQR)	244 (52 to 1013)	503 (146 to 2108)		
Change from baseline value, unadjusted mean (95% CI)	53 (25 to 82)	118 (73 to 164)		
LS mean (95% CI)[c]	64 (−19 to 146)	91 (7 to 174)	−27 (−80 to 26)	.31
Exploratory				
Low-attenuation plaque volume, mm³				
Baseline, median (IQR)	7.1 (1.5 to 32.4)	15.3 (2.6 to 31.1)		
Month 12, median (IQR)	9.5 (2.1 to 24.2)	11.0 (3.2 to 30.8)		
Change from baseline value, unadjusted mean (95% CI)	6 (0 to 12)	2 (−2 to 6)		
LS mean (95% CI)[c]	8 (−4 to 20)	3 (−9 to 14)	5 (−2 to 13)	.14
Fibrous–fatty plaque volume, mm³				
Baseline, median (IQR)	40.0 (11.5 to 72.6)	43.7 (18.9 to 107)		
Month 12, median (IQR)	46.3 (14.0 to 100)	54.5 (14.7 to 107)		
Change from baseline value, unadjusted mean (95% CI)	9 (1 to 17)	1 (−6 to 9)		
LS mean (95% CI)[c]	12 (−7 to 30)	2 (−17 to 21)	10 (−2 to 21)	.11
Fibrous plaque volume, mm³				
Baseline, median (IQR)	160 (51.5 to 305)	254 (122 to 426)		
Month 12, median (IQR)	177 (64.1 to 320)	253 (138 to 471)		
Change from baseline value, unadjusted mean (95% CI)	25 (14 to 35)	1 (−13 to 15)		
LS mean (95% CI)[c]	31 (0 to 62)	7 (−24 to 37)	24 (5 to 43)	.01
Dense calcium plaque volume, mm³				
Baseline, median (IQR)	69.5 (13.6 to 211)	173 (35.2 to 351)		
Month 12, median (IQR)	74.8 (13.9 to 245)	177 (47.2 to 323)		
Change from baseline value, unadjusted mean (95% CI)	17 (7 to 27)	17 (6 to 28)		
LS mean (95% CI)[c]	17 (−8 to 42)	11 (−14 to 36)	5 (−11 to 21)	.51

Testosterone cont.

Effect on sexual function, walking ability and vitality. Sexual function improved.



Testosterone cont.

- Conclusions:
- 1. Modest beneficial effect on sexual function but not on vitality or walking
- 2. No benefit on cognitive function
- 3. Increase in hemoglobin but limited symptom improvement
- 4. Modest benefit in bone density
- 5. Increase in coronary artery plaque volume

Prostate Cancer Screening Controversy

- Valid screening tests must meet all of the following 5 criteria
  - 1. Burden of suffering from disease must be substantial
  - 2. Early detection of disease must improve outcome over later stage
  - 3. Screening test must be accurate and valid
  - 4. Acceptable: test must be simple, inexpensive and safe
  - 5. Outcome: outcome of screening test and subsequent treatment must be improved compared to natural history or treatment at later stage

Prostate Cancer Screening Controversy, cont.

- Current screening meets criteria 1 and 4 but perhaps not 2,3,5.
- Let's examine the evidence and look at the USPTF previous and current recommendations

Prostate Cancer Screening Controversy, cont.

- Prostate cancer facts
  - 1. 2.5 million US men are diagnosed and alive with prostate cancer
  - 2. ~25,000 US men died of prostate cancer in 2016
  - 3. Median age at death from prostate cancer is 80
  - 4. More than 2/3 of deaths are after age 75
  - 5. Prostate cancer increases with age with 20% prevalence in men age 50-59 and more than 1/3 age 70-79.
  - 6. Overwhelming majority of men with prostate cancer die **with** but not **from** prostate cancer.

Prostate Cancer Screening Controversy, cont

- 2009: First report of Prostate, Lung, Colorectal, Ovarian cancer screening trial (PLCO) in NEJM 2009;360:1310.
- -Screened with yearly PSA for 6 yrs and DRE
- -~50% of controls had off-study PSA
- -PSA cutoff level was 4.
- -78,693 US men in Trial
- -ages 55-75
- No difference in mortality or prostate specific mortality at 10 years

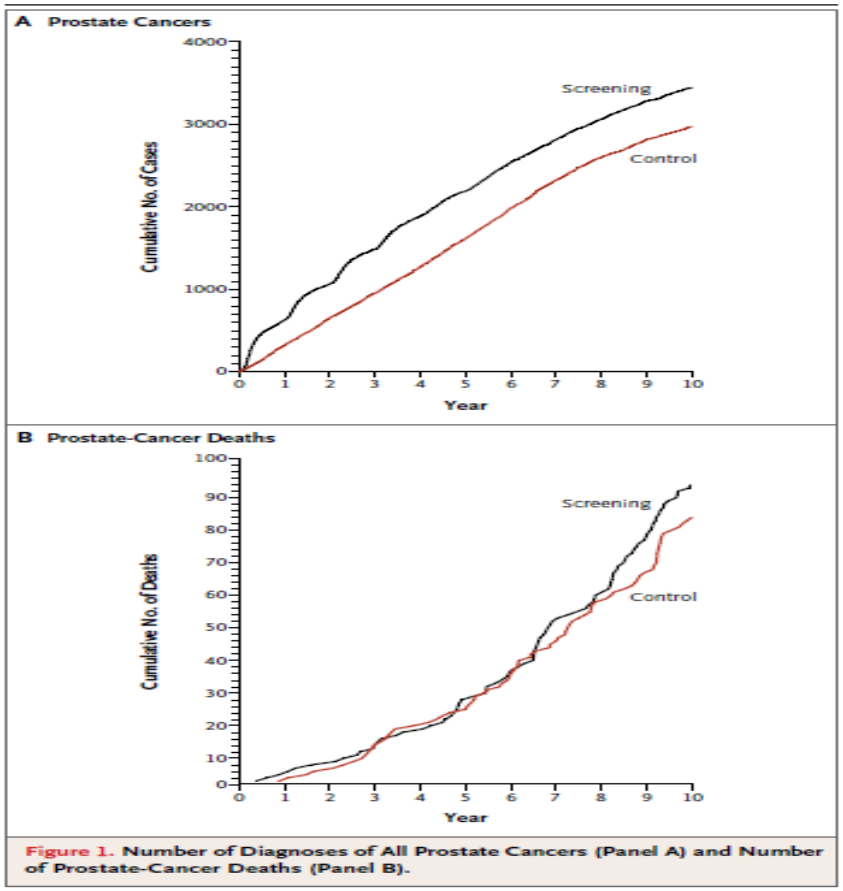


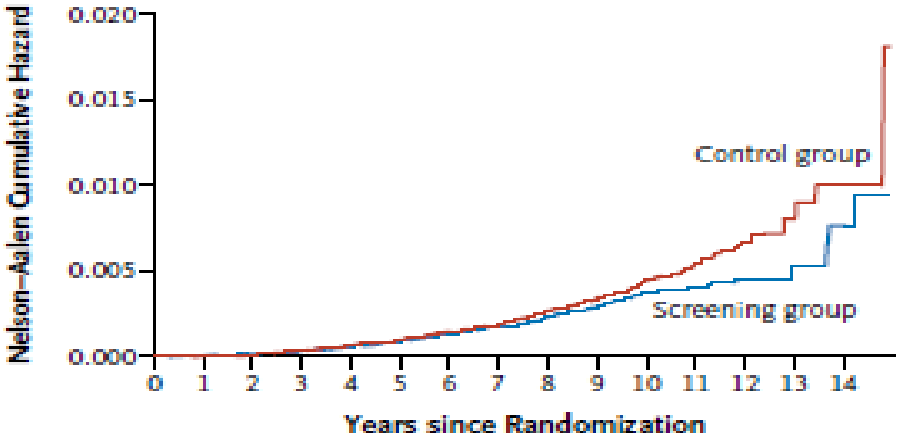
Figure 1. Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B).

Prostate Cancer Screening Controversy, cont

- European Randomized Study of Screening for Prostate Cancer (ERSPC)
- -NEJM 2009;360:1320.
- -182,000 European men in trial
- -ages 55-69
- -2-4 year screening interval
- -PSA cutoff 3-4, mostly 3

Prostate Cancer Screening Controversy, cont

- ERSPC results



No. at Risk

Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Figure 2. Cumulative Risk of Death from Prostate Cancer.

As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The adjusted rate ratio for death from prostate cancer in the screening group was 0.80 (95% CI, 0.65 to 0.98; P=0.04). The Nelsen–Aalen method was used for the calculation of cumulative hazard.

Prostate Cancer Screening Controversy, cont

- ERSPC results, cont.

- No diff in overall mortality
- 20% relative risk reduction in death from prostate cancer

Table 3. Rate Ratios for Death from Any Cause and Death from Prostate Cancer, with Exclusions According to Location of Study Center.*

Variable	Rate Ratio (95% CI)	P Value†
All deaths from any cause	0.99 (0.97–1.02)	0.50
All deaths from prostate cancer	0.80 (0.67–0.95)	0.01
Excluding the Netherlands	0.81 (0.67–0.99)	0.04
Excluding Finland	0.74 (0.58–0.94)	0.01
Excluding Sweden	0.84 (0.70–1.01)	0.06
Excluding Belgium	0.79 (0.66–0.94)	0.01
Excluding Spain	0.79 (0.67–0.94)	0.01
Excluding Italy	0.79 (0.66–0.94)	0.01
Excluding Switzerland	0.80 (0.68–0.96)	0.02

* Rate ratios, which were calculated with the use of Poisson regression, compare the rate of death from prostate cancer in the screening group with the rate in the control group. The calculations were restricted to men in the core age group (55 to 69 years).

† P values have not been corrected for multiple testing.

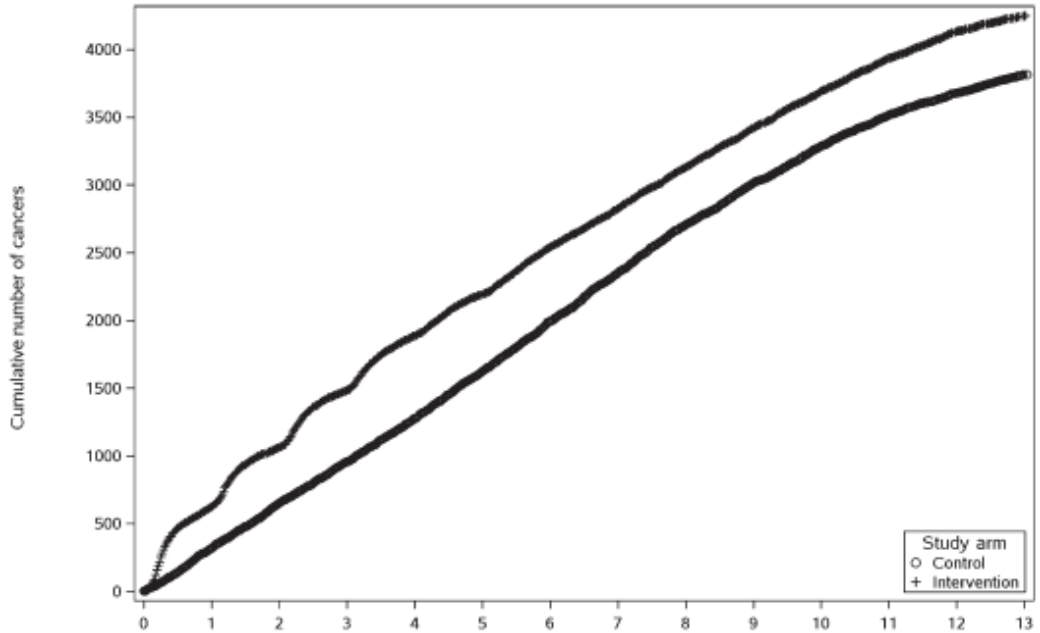
Prostate Cancer Screening Controversy, cont

- 2011: USPSTF recommended against PSA or DRE screening based upon the results of these 2 trials
- -Grade of D (harm exceeds benefit)
- - Controversy was related to methodological differences between trials, the “contamination” of PLCO control group with many getting PSA tests, and differing views of the value of delayed benefits vs early risks

Prostate Cancer Screening Controversy, cont

- PLCO follow-up

- -Higher incidence in intervention group

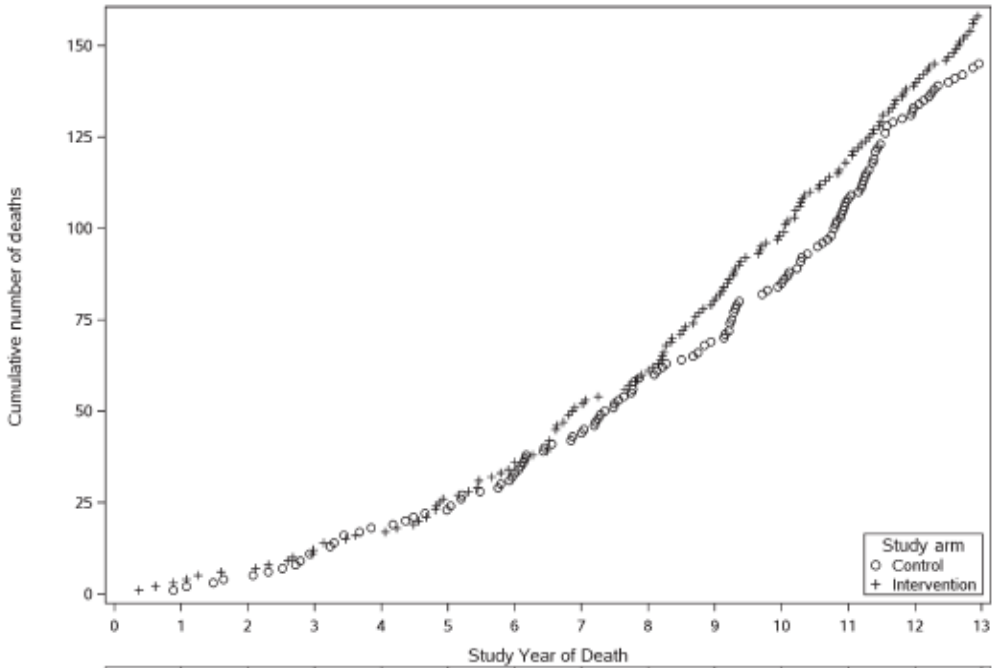


Cumulative cancers - I	622	1060	1485	1886	2190	2541	2830	3132	3426	3698	3939	4138	4250
Cumulative PY - I	37560	74193	109937	144808	178854	212064	244376	275790	306070	334050	357928	377196	392022
Cumulative cancers - C	313	648	953	1274	1624	1997	2351	2710	3021	3288	3521	3681	3815
Cumulative PY - C	37674	74605	110719	145980	180338	213709	246077	277429	307582	335355	359107	378262	392977

Figure 2. Cumulative number of prostate cancers in the intervention and control arms from year 1 to year 13. C = control arm; I = intervention arm;

Prostate Cancer Screening Controversy, cont

- PLCO follow-up:
- -no difference in prostate cancer mortality



Cumulative deaths - I	3	6	12	16	26	36	51	61	80	98	118	140	158
Cumulative PY - I	38217	76112	113629	150725	187382	223541	259118	294052	328048	359768	387164	409535	426977
Cumulative deaths - C	1	4	11	18	23	33	44	59	69	85	108	133	145
Cumulative PY - C	38223	76132	113635	150689	187278	223329	258811	293631	327455	358904	386109	408262	425439

Figure 3. Cumulative deaths from prostate cancer in the intervention and control arms from year 1 to year 13. C = control arm; I = intervention arm; PY = person-years

Prostate Cancer Screening Controversy, cont

- ERSPC follow-up: Lancet 2014;384:2017
- 17% relative reduction in prostate cancer mortality but no diff in overall mortality

	Intervention group			Control group			Rate ratio (95% CI)	p value
	Deaths (n)	Person-years	Rate per 1000 person-years	Deaths (n)	Person-years	Rate per 1000 person-years		
All-cause mortality								
Core age group	15 369	825 018	18·6	19 108	1 011 192	18·9	1·00 (0·98–1·02)	0·82
All ages	18 251	935 185	19·5	21 992	1 120 432	19·6	1·00 (0·98–1·02)	0·98
Prostate cancer mortality								
Age groups (years)								
≤54	6	64 265	0·09	7	62 312	0·11	0·84 (0·28–2·49)	0·75
55–59	114	411 834	0·28	174	524 314	0·33	0·81 (0·93–1·03)	0·09
60–64	121	240 895	0·50	159	280 404	0·57	0·90 (0·71–1·15)	0·41
65–69	120	172 289	0·70	212	206 474	1·03	0·69 (0·55–0·87)	0·002
70≥	66	45 903	1·44	58	46 928	1·24	1·17 (0·82–1·66)	0·40
Core age group	355	825 018	0·43	545	1 011 192	0·54	0·79 (0·69–0·91)	0·001
All ages	427	935 185	0·46	610	1 120 432	0·54	0·83 (0·73–0·94)	0·004

Test for heterogeneity for prostate cancer mortality: all ages χ^2_4=6·26 p=0·18; core age group: χ^2_2=2·31 p=0·32.

Table 4: **All cause and prostate cancer mortality by age at randomisation (France excluded)**

Prostate Cancer Screening Controversy, cont

- What treatment is best if treatment is given?
- PIVOT trial: 731 men randomized to radical prostatectomy vs observation in localized prostate cancer. NEJM 2012;367:203
- No diff in overall mortality or prostate cancer mortality

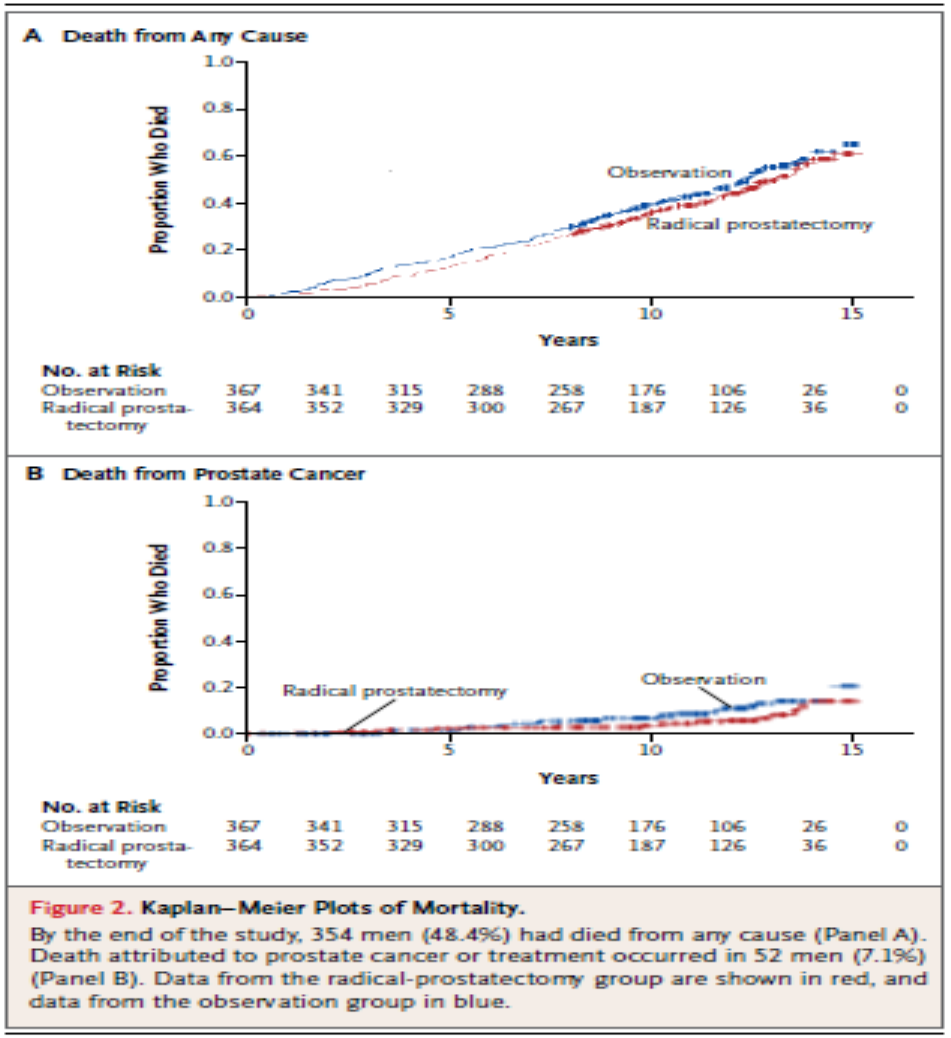


Figure 2. Kaplan–Meier Plots of Mortality.
By the end of the study, 354 men (48.4%) had died from any cause (Panel A). Death attributed to prostate cancer or treatment occurred in 52 men (7.1%) (Panel B). Data from the radical-prostatectomy group are shown in red, and data from the observation group in blue.

Prostate Cancer Screening Controversy, cont

ProtecT trial: Randomized trial of 1600 subjects into surgery, radiotherapy and observation for localized prostate cancer.

NEJM 2016;375:1415

No diff in cancer survival but observation shows increased risk of progression.

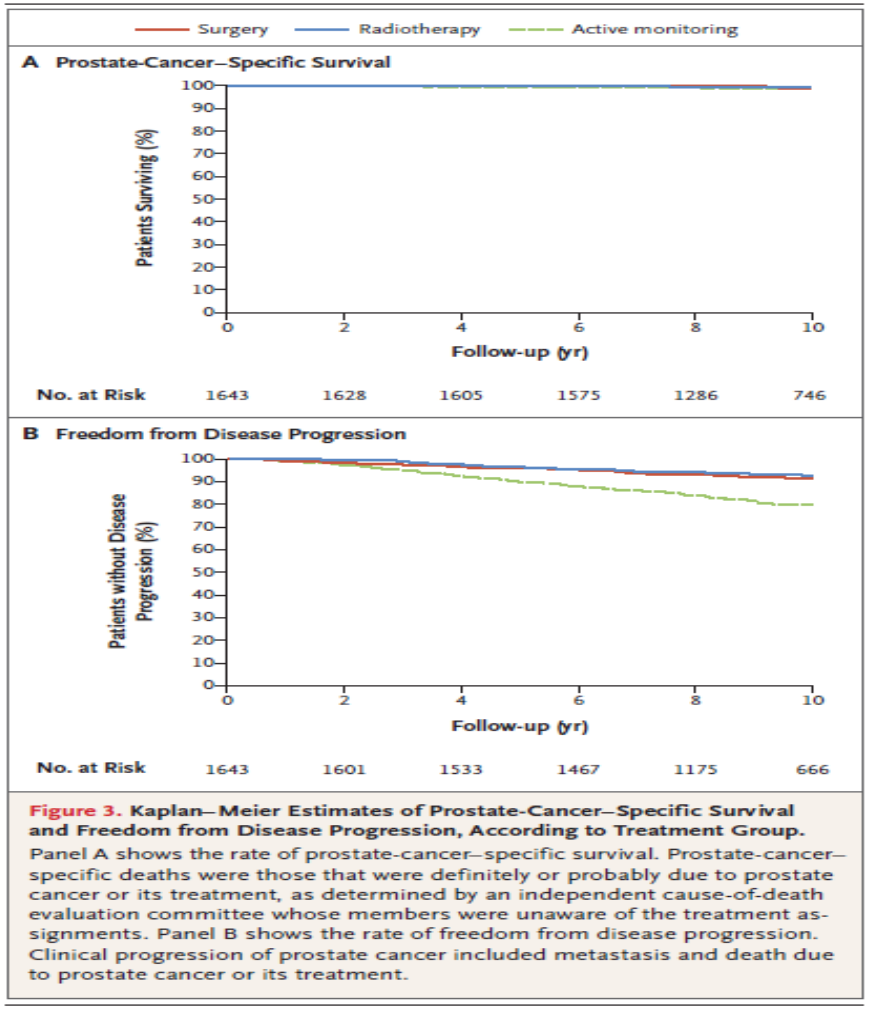


Figure 3. Kaplan–Meier Estimates of Prostate-Cancer–Specific Survival and Freedom from Disease Progression, According to Treatment Group.
Panel A shows the rate of prostate-cancer–specific survival. Prostate-cancer–specific deaths were those that were definitely or probably due to prostate cancer or its treatment, as determined by an independent cause-of-death evaluation committee whose members were unaware of the treatment assignments. Panel B shows the rate of freedom from disease progression. Clinical progression of prostate cancer included metastasis and death due to prostate cancer or its treatment.

Prostate Cancer Screening Controversy, cont

- Latest USPSTF recommendations:

Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men ages 55 to 69 years	The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA) –based screening for prostate cancer. The decision about whether to be screened for prostate cancer should be an individual one. Screening offers a small potential benefit of reducing the chance of dying of prostate cancer. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and impotence. The USPSTF recommends individualized decisionmaking about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision. Please refer to the Clinical Considerations sections on screening in African American men and men with a family history of prostate cancer for more information on these higher-risk populations.	C
Men age 70 years and older	The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older.	D

Prostate Cancer Screening Conclusions

- 1. No difference in overall mortality in any study
- 2. Minimal difference in prostate specific mortality in European study and no significant difference in US study
- 3. Observation vs treatment may result in modest disease progression risk in observation group
- 4. The latest USPSTF recommendation will likely prove unworkable in practice
- 5. Canadian Preventive Task Force recommends not screening.

References-Testosterone

- 1. Feldman HA, Longcope C et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endo Metab 2002;87:589
- 2. Harman SM, Metter EJ et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. J Clin Endo Metab 2001;86:724
- 3. Snyder PJ, Bhasin S et al. Effects of testosterone treatment in older men. NEJM 2016;374:611.
- 4. Budoff MJ, Ellenberg SS et al. Testosterone treatment and coronary artery plaque volume in oldr men with low testosterone. JAMA 2017;317:708
- 5. Snyder PJ, Kopperhahl DL et al. Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone. JAMA Intern Med 2017;177:471
- 6. Roy CN, Snyder PJ, et al. Association of testosterone levels with anemia in older men. A controlled trial. JAMA Intern Med 2017;177:480.
- 7. Resnick SM, Matsumoto AM et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017;317:717

References: Prostate Cancer Screening

- 1. Andriole GL, Crawford ED et al. Mortality results from a randomized prostate cancer screening trial. NEJM 2009;360:1310.
- 2. Schroder FH, Hugosson J et al. Screening and prostate cancer mortality in a randomized European study. JAMA 2009;360:1320.
- 3. Andriole GL, Crawford ED et al. Prostate cancer screening in the randomized prostate, lung, colorectal and ovarian cancer screening trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012;104:125
- 4. Wilt TJ, Brawer MK et al. Radical prostatectomy versus observation for localized prostate cancer. NEJM 2012;367:203
- 5. Schroder FH, Hugosson J et al. The European randomized study of screening for prostate cancer-prostate cancer mortality at 13 years of follow-up. Lancet 2014;384:2027
- 6. Donovan JL, Hamdy FC et al. Patient reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. NEJM 2016;375:1425
- 7. Hamdy FC, Donovan JL et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. NEJM 2016;375:1415