TESTOSTERONE AND THE PROSTATE IN ADULT MEN: WHAT ARE THE DATA

Culley C. Carson M.D.
...a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis...
Importance of Testosterone in Adult Males: Physiologic Effects

- Maintains reproductive tissues
- Stimulates spermatogenesis
- Stimulates, maintains sexual function
- Increases body weight, nitrogen retention
- Increases lean body mass
- Maintains bone density
- Promotes sebum production, axillary and body hair growth
- Stimulates erythropoiesis

Controversies in the Diagnosis and Treatment of Male Hypogonadism

- No consensus on definition of TD
- Clinicians lack knowledge about TD-associated morbidity, mortality
- Clinicians fear TRT may promote BPH, aggravate LUTS, lead to PCa, contribute to cardiovascular disease

BPH, benign prostatic hypertrophy; LUTS, lower urinary tract symptoms; PCa, prostate cancer; TD, testosterone deficiency; TRT, testosterone replacement therapy
Peak testosterone levels in late teens and early 20s
Peak prostate cancer rates in 60s and 70s
Prostate cancer prevalence increases as testosterone levels decline
BACH Study Results

- ≈24% of men had TT < 300 ng/dL (biochemical prevalence)
- 9.3% had both low TT, FT levels
- 5.6% had symptomatic hypogonadism
  - Prevalence of symptoms:
    - ED, 16%
    - Low libido, 12%
    - Osteoporosis/fracture, 1%
    - ≥2 nonspecific symptoms, 20%

BACH, Boston Area Community Health Survey; TT, total testosterone; FT, free testosterone; ED, erectile dysfunction

Prevalence of Low Testosterone

High-Risk Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Opioid Use</td>
<td>74%</td>
</tr>
<tr>
<td>Obesity</td>
<td>52%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50%</td>
</tr>
<tr>
<td>AIDS</td>
<td>50%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>40%</td>
</tr>
<tr>
<td>Erectile Dysfunction</td>
<td>19%</td>
</tr>
</tbody>
</table>

8-year study of 858 men
Low T = <250 ng/dL or FT <0.75 ng/dL

T, testosterone; FT, free testosterone

Mortality in Treated vs Untreated Testosterone-Deficient Men in VA Population

1031 men aged >40 years, T<250 ng/dL
Mortality: 10.3% treated vs 20.7% untreated (P<.0001)

Concerns increased despite more education about testosterone therapy

Although more men were treated with testosterone in 2010, 11% of eligible candidates did not receive therapy
Established androgen dependence of prostate cancer

Asserted that testosterone administration “enhanced” growth of prostate cancer

Conclusion based on a single patient

3886 men with prostate cancer
6448 age-matched control participants
No significant relationship between androgens and prostate cancer

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Fifth</th>
<th>Case Patients (n)/Control Participants (n)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>1</td>
<td>784/1302</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>761/1309</td>
<td>0.97 (0.85 to 1.11)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>837/1287</td>
<td>1.08 (0.95 to 1.23)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>792/1281</td>
<td>1.03 (0.90 to 1.17)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>712/1259</td>
<td>0.94 (0.82 to 1.07)</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>1</td>
<td>691/1181</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>684/1165</td>
<td>1.01 (0.88 to 1.16)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>750/1155</td>
<td>1.13 (0.98 to 1.29)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>707/1162</td>
<td>1.09 (0.95 to 1.25)</td>
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<tr>
<td></td>
<td>5</td>
<td>718/1152</td>
<td>1.11 (0.96 to 1.27)</td>
</tr>
<tr>
<td>DHT</td>
<td>1</td>
<td>240/298</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>192/284</td>
<td>0.83 (0.65 to 1.07)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>188/282</td>
<td>0.82 (0.63 to 1.06)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>194/295</td>
<td>0.83 (0.64 to 1.08)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>196/286</td>
<td>0.86 (0.66 to 1.11)</td>
</tr>
</tbody>
</table>

CI, confidence interval; DHT, dihydrotestosterone; RR, relative risk.
In men with hypogonadism, normalization of serum testosterone for 6 months caused no changes in prostatic...

- Androgen concentrations
- Histology or biomarkers
- Gene expression
- Cancer incidence

Effects of Testosterone Therapy on Prostate Tissue of Aging Hypogonadal Men

Randomized, double-blind, placebo-controlled trial of 44 men (aged 44-78 y)

Inclusion criteria
- T<300 ng/dL
- Hypogonadism symptoms

Treatment groups receive T enanthate 150 mg or placebo every 2 weeks for 6 mo

12-core TRUS prostate biopsies, at baseline, 6 mo

Primary outcome: 6-month change in prostatic T, DHT

T, testosterone; TRUS, transrectal ultrasound; DHT, dihydrotestosterone

Effects of Testosterone Therapy on Prostate Tissue of Aging Men With Low Serum Testosterone

DHT, dihydrotestosterone.
Intraprostatic concentrations of testosterone and DHT did not differ after treatment despite substantial changes in serum concentrations.

DHT, dihydrotestosterone.
Intraprostatic concentrations of testosterone and DHT did not differ after treatment despite substantial changes in serum concentrations.

These data suggest that, although 6 months of testosterone therapy normalizes serum androgen levels, it has little effect on prostatic androgen levels.

DHT, dihydrotestosterone.
Articles Showing Testosterone Therapy Causes Prostate Cancer in PSA Era

None!
a/b: The traditional belief; higher concentrations increase prostate cancer rates
c: The saturation model; testosterone has a powerful effect on prostate cancer growth at low concentrations but little or no effect beyond the near-castrate range

, Morgentaler A, Testosterone Replacement Therapy and Prostate Cancer, 555-563, vii, 2007,
Testosterone 600 mg or placebo weekly for 10 weeks

PSA did not change significantly from baseline despite supraphysiologic testosterone levels (>2500 ng/dL)

PSA, prostate-specific antigen.

31 men randomized to weekly injections of testosterone 100, 250, and 500 mg
No significant changes in prostate volume even at supraphysiologic testosterone levels (1138-1994 ng/dL) at 6 months
Serum PSA and Testosterone Flare

PSA, prostate-specific antigen.
451 hypogonadal men started on testosterone therapy

Divided by baseline total testosterone level: <250 ng/dL versus >250 ng/dL

**Only** in men with testosterone <250 ng/dL...

- PSA correlated with testosterone and free testosterone
- Significant rise in PSA after 12 months of testosterone therapy

PSA, prostate-specific antigen.
Morgentaler and Rhoden\textsuperscript{1}
- 345 consecutive hypogonadal men with PSA <4.0 ng/mL
- Prostate biopsy before testosterone therapy initiated
- **Low testosterone** (<250 ng/dL): 21% had prostate cancer
- **High testosterone** (>250 ng/dL): 12% had prostate cancer

Hoffman et al\textsuperscript{2}
- 117 men with prostate cancer
- **Low testosterone** (<300 ng/dL): 47% chance of prostate cancer on TRUS biopsy
- **Normal testosterone** (>300 ng/dL): 28% chance of prostate cancer on TRUS biopsy ($P=.018$)
Relationship Between Serum Testosterone and Grade and Extent of Prostate Cancer at Biopsy

N=117.
272 patients with localized prostate cancer treated with radical prostatectomy

Preoperative testosterone levels
- <300 ng/dL, n=49
- >300 ng/dL, n=223

Independent and significant predictors of PSA recurrence
- Gleason grade ($P=.006$)
- Surgical margin status ($P=.0001$)
- PSA ($P=.0001$)
- Preoperative testosterone level ($P=.021$)

5-year PSA failure-free survival rates
- <300 ng/dL, 67.8%
- >300 ng/dL, 84.9% ($P=.035$)

PSA, prostate-specific antigen.
Low Testosterone Increases Risks in Men With Prostate Cancer

- **Isom-Batz et al**
  - Pathological stage
  - Clinical stage
  - Higher Gleason grade

- **Teloken et al**
  - Increased positive surgical margins
    - 39% in group with low total testosterone versus 14.6% with normal total testosterone

- **Schatzl et al**
  - Higher tumor density
  - Higher Gleason grade

Incidence of Prostate Cancer in Men Receiving Testosterone Therapy

- Prostate cancer rate in >7 published testosterone therapy trials was similar to screening trials in general population\(^1\)
- Meta-analysis of 19 placebo-controlled testosterone therapy studies in men with low or low-normal testosterone\(^2\)
  - Comparison of men treated with testosterone versus placebo revealed no differences in...
    - Prostate cancer incidence
    - Change in PSA
    - Urinary symptom scores

PSA, prostate-specific antigen.
75 hypogonadal men treated with testosterone therapy for 12 months

Prostate biopsy prior to testosterone therapy
- Benign biopsies (PIN-), n=55
- PIN found (PIN+), n=20

Results
- No significant change in PSA in either group
- 1 patient in PIN+ group found to have prostate cancer on biopsy after abnormal DRE

Conclusion
- After 1 year of testosterone therapy, PIN+ men did not have greater increase in PSA or significantly higher risk of prostate cancer than PIN- men

DRE, digital rectal examination; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen.
Retrospective study of 14 men elected prostate cancer surveillance & received testosterone therapy for >6 months

13 men had Gleason 6 at initial biopsy, and 1 had Gleason 7 (3+4)

Mean duration of testosterone therapy after diagnosis of prostate cancer 23.5 months (range, 9-43 mo)
No significant change in PSA
- Initial: 5.5±6.4 ng/mL (range, 0.6-24.1 ng/mL)
- Most recent: 3.7±2.6 ng/mL ($P=.29$)

No change in prostate volume
- Initial: 45.6±14.5 mL
- Most recent: 52.4±19.8 mL ($P=.11$)
PSA Values During Testosterone Therapy in Men With Untreated Prostate Cancer

PSA, prostate-specific antigen.
Follow-up biopsy in 13 men

11 patients had no evidence of progression
- Including 8 with ≥1 follow-up biopsy that revealed no cancer

Other 2 patients
- Patient 1
  - Initial biopsy revealed low-volume Gleason 6 disease
  - Gleason grade 7 (3+4) in 5% of 1 core
  - Two subsequent annual biopsies revealed only low-volume Gleason 6 disease
- Patient 2
  - Elected radical prostatectomy after biopsy showed Gleason 7 (4+3) cancer in 1 of 12 cores, with 75% involvement
  - Final pathology: Gleason 6 disease involving 5% of gland, with negative margins and nodes
Testosterone therapy was started a median 2 years after brachytherapy (N=31).

Testosterone therapy continued for a median 4.5 years.

Follow-up ranged from 1.5 to 9.0 years (median, 5 y).

Testosterone rose from 188 to 498 ng/dL.

No patient stopped testosterone therapy because of cancer recurrence or demonstrated cancer progression.

5 hypogonadal men after EBRT

Testosterone therapy initiated after PSA nadir

Follow-up of 14.5 months

Results

- Testosterone values rose from 5.2 to 17.6 nmol/L
- 1 patient had transient increase in PSA, but none had levels >1.5 ng/mL
- All patients experienced improvement in hypogonadal symptoms

EBRT, external beam radiotherapy; PSA, prostate-specific antigen.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, N</th>
<th>Follow-up, mo</th>
<th>PSA, ng/mL Before Therapy</th>
<th>PSA, ng/mL After Therapy</th>
<th>Serum Total Testosterone, ng/dL Before Therapy</th>
<th>Serum Total Testosterone, ng/dL After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal¹</td>
<td>10</td>
<td>19</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>197</td>
<td>591</td>
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<tr>
<td>Kaufman²</td>
<td>7</td>
<td>24</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>97</td>
<td>434</td>
</tr>
<tr>
<td>Khera³</td>
<td>57</td>
<td>13</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>254</td>
<td>459</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>74</strong></td>
<td></td>
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</tr>
</tbody>
</table>

PSA, prostate-specific antigen.

8 studies (abstracts and manuscripts) to date provide information about testosterone therapy after prostate cancer treatment (radical prostatectomy, brachytherapy, EBRT)\(^1\)

- 283 men received testosterone therapy
- Only 2 men (1.4%) had biochemical recurrence

Recurrence rate less than that of published series in favorable groups\(^2\)

Is testosterone therapy protective?

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EBRT, external beam radiotherapy.
- FDA-approved, randomized, placebo-controlled trial in hypogonadal men
- Testosterone therapy started 3 months after radical prostatectomy
- Inclusion criteria
  - Bilateral nerve-sparing radical prostatectomy
  - 2 consecutive nadir PSA values <0.01 ng/mL 4 weeks apart at start of treatment
- Exclusion criteria
  - Testosterone >300 ng/dL
  - Preoperative SHIM score <17
  - Positive surgical margins or evidence of residual prostate cancer
  - Clinically suspected advanced disease or evidence of metastatic prostate cancer
  - Primary Gleason grade >3 and secondary Gleason >4 in final pathologic specimen

Although testosterone therapy significantly affects PSA concentrations at low levels of serum testosterone, it does not appear to affect prostate size or prostatic testosterone levels. Perhaps due to early saturation of androgen receptors within prostate.

No evidence that testosterone therapy causes new prostate cancer in hypogonadal men.

To date, 283 men reported in literature have received testosterone therapy after prostate cancer treatment, with low recurrence rates of 1.4%.
Androgen replacement therapy contributes to improving lower urinary tract symptoms in patients with hypogonadism and benign prostate hypertrophy: a randomized controlled study

- Fifty-two hypogonadal men with BPH randomized
  - Testosterone enanthate 250 mg every 4 weeks
  - Untreated control group
- IPSS, uroflowmetry, PVR, systemic body muscle volume at baseline, 12 months evaluated

BPH, benign prostatic hypertrophy; IPSS, international prostate symptom score; PVR, post-void residual volume
<table>
<thead>
<tr>
<th></th>
<th>Testosterone Therapy Group, Mean Change (SD)</th>
<th>Control Group, Mean Change (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA value, ng/mL</td>
<td>0.322 (0.516)</td>
<td>0.305 (0.707)</td>
<td>.399</td>
</tr>
<tr>
<td>AMS score</td>
<td>0.2 (8.8)</td>
<td>−0.5 (7.7)</td>
<td>.289</td>
</tr>
<tr>
<td>IPSS</td>
<td>−4.1 (6.6)</td>
<td>−0.5 (6.7)</td>
<td>.042</td>
</tr>
<tr>
<td>UFM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFR, mL</td>
<td>4.2 (9.1)</td>
<td>−0.19 (4.27)</td>
<td>.031</td>
</tr>
<tr>
<td>VV, mL</td>
<td>44 (112)</td>
<td>−24 (80)</td>
<td>.008</td>
</tr>
<tr>
<td>PVR, mL</td>
<td>4.9 (44.2)</td>
<td>−0.8 (31.1)</td>
<td>.723</td>
</tr>
<tr>
<td>Systemic body muscle</td>
<td>0.61 (1.33)</td>
<td>−0.30 (0.66)</td>
<td>.035</td>
</tr>
</tbody>
</table>

### Effect of Testosterone Therapy on Bladder Function Parameters and AMS Score

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total testosterone, ng/mL</strong></td>
<td>2.14 (0.53)</td>
<td>5.09 (2.13)</td>
<td>.001</td>
</tr>
<tr>
<td><strong>IPSS</strong></td>
<td>9.72 (7.52)</td>
<td>8.16 (6.19)</td>
<td>.029</td>
</tr>
<tr>
<td><strong>Maximal bladder capacity, mL</strong></td>
<td>564 (175.9)</td>
<td>628.6 (139.6)</td>
<td>.007</td>
</tr>
<tr>
<td><strong>Bladder compliance, mL/cm H$_2$O</strong></td>
<td>46.02 (45.89)</td>
<td>76.4 (72.78)</td>
<td>.032</td>
</tr>
<tr>
<td><strong>AMS score</strong></td>
<td>40.4 (7.3)</td>
<td>28.8 (5.31)</td>
<td>.001</td>
</tr>
</tbody>
</table>

- Study not placebo-controlled

Data are mean (SD).
AMS, Aging Males Symptoms; IPSS, International Prostate Symptom Score.
312 men (mean age, 62.8 y)

Estradiol (but not testosterone) correlated with prostate volume ($r=0.17; P=.01$)

Peak flow rate and PSA did not correlate with any endocrinologic parameter

Hypogonadism (serum testosterone <3.0 ng/mL) detected in 22.1%

- Did not affect clinical (IPSS, peak flow rate, prostate volume, PSA level) or endocrine (LH, FSH, estradiol, prolactin, and DHEA) parameters
Baseline serum sex hormone concentrations measured in mid 1980s & correlated with results of AUA-SI mailed 20 years later

Men (N=158) with no prostate cancer history (mean age, 58 y)

Age-adjusted analysis showed significant inverse association between LUTS and T:DHT ratio ($P=.05$)

Men in highest T:DHT quartile had 66% lower risk of LUTS compared to those in lowest quartile

No significant association between LUTS & total testosterone, DHT, estradiol, T:E$_2$ ratio, or DHEA

Men with higher bioavailable testosterone levels at lower risk for LUTS, but non-statistically significant association not found evenly across quartiles

AUA-SI, American Urological Society Symptom Index; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; E$_2$, estradiol; LUTS, lower urinary tract symptoms; T, testosterone.

Testosterone therapy increases prostate volume to same extent as in age-matched controls\textsuperscript{1,2}

Some long-term testosterone therapy studies have shown that PSA levels increase but remain within normal range\textsuperscript{3}

Patients with hypogonadism & LUTS treated with daily testosterone for 3 months (N=41)
- Serum free testosterone levels rose significantly ($P=.0047$)
  - Total AMS scores decreased
    - Psychological, physiologic, and sexual disturbance domains significantly reduced
  - 6 of 8 SF-36 domains improved significantly
  - Erectile function improved significantly
- Total IPSS & all domain scores improved significantly, with marked improvement in voiding function
- Study not placebo-controlled (Japanese governmental restrictions)

AMS, Aging Males Symptoms; SF-36, 36-Item Short-Form Health Survey; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms.
Open-label, randomized pilot study

Effect of testosterone therapy in older men with symptomatic LUTS & low testosterone

Patients randomized to receive testosterone gel 50 mg/d for 3 months (n=10) or testosterone undecanoate 1000 mg for 26 weeks (n=20)

- Both groups attained eugonadal plasma testosterone levels
- AMS and IIEF-5 scores and IPSS improved significantly
- No increase in prostate volume
- Notably, PSA levels decreased

AMS, Aging Males Symptoms; IIEF-5, 5-item International Index of Erectile Function; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen.

Effect of Testosterone on BPH/LUTS & PCa: SUMMARY

- While TRT significantly affects PSA levels at low levels of serum T, it does not appear to affect prostate size or intraprostatic T levels. Perhaps due to early saturation of androgen receptors in the prostate.
- No evidence that TRT promotes initiation of PCa in hypogonadal men.
- To date, 386 men reported in literature receiving TRT after PCa treatment, with recurrence rates <1.5%.
- Larger randomized, placebo-controlled trials needed to assess safety, efficacy of TRT following PCa.

TRT, testosterone replacement therapy; PSA, prostate-specific antigen; T, testosterone; PCa, prostate cancer.
Recent Concerns Raised About Testosterone Replacement Therapy

New Concern About Testosterone and Heart Risks
By ANAHAD O'CONNOR
Vigen et al:¹
- Medical records of 1223 men with T levels <300 ng/dL taking T vs 7486 men with similar T levels, not using TRT
- TRT associated with increased risk of heart attack, stroke, death

Finkle et al:²
- Cohort study of risk of acute non-fatal MI following initial T prescription (N=55,593) in a large health-care database
- In men aged ≥65 y, TRT associated with 2-fold increase in risk of heart attack in first 90 days of treatment, 2- to 3-fold increase in younger men with a history of cardiovascular disease

Flawed Studies

- Retrospective, nonrandomized, observational studies of unhealthy, already at-risk population\(^1\)
- Neither study evaluated T levels (ie, initial, follow-up check) per Endocrine Society recommendations.\(^1\) In Vigen, only 60% of participants had follow-up T level checks\(^2\)
- In Vigen study, average T levels rose from 175.5 ng/dL to 332.2 ng/dL, a level where therapy is usually initiated\(^2\)
- Neither study assessed RBC count, estrogen level prior to or during therapy per Endocrine Society recommendations\(^1\)
- Other studies show low T increases adverse CV event risk\(^1\)
- Hypogonadal men treated with TRT live longer than untreated hypogonadal men\(^1\)

T, testosterone; TRT, testosterone replacement therapy; RBC, red blood cell; CV, cardiovascular

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al, 2011¹ CCS, N=87; Examined TT</td>
<td>CAD</td>
<td>Patients with CAD have lower TT</td>
</tr>
<tr>
<td>Akishita et al, 2010² CS, N=171; Examined TT</td>
<td>CV events* (H&amp;P, physician, hospital records)</td>
<td>Patients with lower TT more likely to experience CV events</td>
</tr>
<tr>
<td>Rosano et al, 2007³ CCS, N=120; Examined TT, FT, BT</td>
<td>CAD</td>
<td>Patients with CAD have lower TT, BT</td>
</tr>
<tr>
<td>Dobrzycki et al, 2003⁴ CCS, N=96; Examined TT, FT, FAI</td>
<td>CAD</td>
<td>Patients with CAD have lower TT, FT, FAI</td>
</tr>
<tr>
<td>English et al, 2000⁵ CCS, N=90; Examined TT, FT, BT, FAI</td>
<td>CAD</td>
<td>Patients with CAD have lower TT, FT, FAI</td>
</tr>
</tbody>
</table>

*CV events include stroke, CAD, sudden cardiac death, peripheral vascular disease
CCS, case control study; TT, total testosterone; CAD, coronary artery disease (shown by cardiac catheterization); CS, cohort study; CV, cardiovascular; H&P, history and physical; FT, free testosterone; BT, bioavailable testosterone; FAI, free androgen index