

High Testosterone Levels Protect Against Risk for CV Events CME

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Authors and Disclosures

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Clinical Context

Testosterone and sex hormone-binding globulin (SHBG) levels have important metabolic effects that might contribute to the risk for cardiovascular disease among older men. The authors of the current study note that low serum testosterone levels are associated with increased adiposity, an adverse metabolic risk profile, and atherosclerosis. Low levels of SHBG are associated with insulin resistance and obesity.

Cross-sectional studies suggest that adults with coronary heart disease have lower testosterone levels, but the results of prospective research evaluating the possible link between testosterone levels and cardiovascular risk are more mixed. Moreover, limited data exist regarding the role of SHBG in the development of cardiovascular disease. The current study by Ohlsson and colleagues uses data from a large cohort of older men to address these issues.

Study Synopsis and Perspective

A new Swedish study has shown that elderly men in the highest quartile of serum testosterone levels have around a 30% lower risk of cardiovascular events over five years compared with men in the lower three quartiles [1].

And the association remains even after adjustment for traditional cardiovascular risk factors and excluding those with cardiovascular disease at baseline, say **Dr Claes Ohlsson** (University of Gothenburg, Sweden) and colleagues in their paper in the October 11, 2011 issue of the *Journal of the American College of Cardiology*.

Senior author **Dr Asa Tivesten** (University of Gothenburg) told *heartwire* : "This paper is an important start, because previously data have been inconsistent about whether there is an association between serum testosterone and CVD events or not. We now know there is an association, but we don't know what is causing it."

Study Looked at Community-Dwelling Elderly Men

Ohlsson and colleagues analyzed baseline levels of testosterone in 2416 men aged 69 to 81 years who were participating in the prospective, population-based **Osteoporotic Fractures in Men Study** (MrOS). They also measured SHBG and obtained cardiovascular clinical outcomes from central Swedish registries.

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Over a median of five years of follow-up, there were 485 fatal and nonfatal cardiovascular events, and both total testosterone and SHBG levels were inversely associated with risk of cardiovascular events (trend over quartiles $p=0.009$ and $p=0.012$, respectively).

Tivesten said initially they used quartile 1 (ie, the lowest levels of serum testosterone) as a reference and compared events in this group with those in quartiles 2, 3, and 4. However, they saw no significant difference in the number of cardiovascular events between the first three quartiles.

But men in the highest quartile of testosterone (≥ 550 ng/dL) had a lower risk of cardiovascular events compared with men in the lower three quartiles (hazard ratio 0.70; $p=0.002$). This association remained when the first 2.6 years of follow-up were excluded--in order to rule out any effect of baseline (subacute) disease--and was only slightly attenuated after adjustment for confounding factors (hazard ratio 0.77; $p=0.032$).

In models that included testosterone and SHBG, testosterone, but not SHBG, predicted risk.

More Research to Assess Risk/Benefit of Testosterone Supplements

Tivesten says the research does not suggest that testosterone supplements should be used to try to prevent cardiovascular disease and that more work is required to investigate this, because one trial using high doses of exogenous testosterone in older men has actually shown an increase in cardiovascular events.

However, what is established, she says, is that men with testosterone deficiency should receive testosterone supplementation. But there is currently a debate as to what level of testosterone represents a true deficiency, so this is a gray area, she notes.

And in older men, she adds, the issue is confounded by the fact that testosterone levels decline naturally with age: "So should we regard all elderly men as testosterone deficient? Or just look at subgroups?"

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Åke Wiberg Foundation, and the Novo Nordisk Foundation. Ohlsson and Tivesten report that they have no disclosures. Disclosures for the coauthors are listed in the paper.

References

1. Ohlsson C, Barrett-Connor E, Bhasin S, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men. The MrOS (osteoporotic fractures in men) Study in Sweden. *J Am Coll Cardiol* 2011; 58:[1674-1681](#).

Study Highlights

- Study data were drawn from the MrOS, which enrolled men between the ages of 69 and 81 years. Only Swedish men were evaluated in the current study, and men receiving treatment that might affect serum levels of testosterone or SHBG were excluded from the present analysis.
- Participants underwent a baseline analysis of serum testosterone and SHBG levels as measured by gas chromatography/mass spectrometry. Samples were collected in the morning or at approximately noontime.
- Participants also underwent an assessment of known cardiovascular risk factors at baseline.
- The main study outcome was the relationship between testosterone and SHBG levels and the risk for major cardiovascular events, which were defined as myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, or death from coronary heart disease or cerebrovascular disease. Cardiovascular events were retrieved from central Swedish registers.
- The main study outcome was adjusted to account for traditional cardiovascular risk factors.
- 2416 men provided data for study analysis. The mean age of participants was 75.4 years, and the mean levels of testosterone and SHBG were 454 ng/dL and 44 nmol/L. 26.2% of the study cohort had a history of cardiovascular disease at baseline.
- Increasing testosterone levels were negatively correlated with body mass index, the apolipoprotein B/A1 ratio, and the prevalence of diabetes and hypertension. Smoking and physical activity were more common among men with the highest levels of testosterone.
- A history of cardiovascular disease was nearly twice as common among participants in the lowest 2 quartiles of testosterone concentration vs the top quartile.
- The median follow-up period for cardiovascular events was 5.1 years. 485 men experienced a cardiovascular event during this period.
- The risk for cardiovascular events was similar in comparing the lowest 3 quartiles of testosterone concentration.
- Men in the highest quartile of testosterone concentration (≥ 550 ng/dL) experienced a hazard ratio of 0.70 (95% confidence interval, 0.56 - 0.88; $P = .002$) for cardiovascular events vs men in the lower 3 quartiles. There was limited change in this finding after adjustment for other cardiovascular risk factors.
- Higher levels of SHBG were also associated with a lower risk for cardiovascular disease, with a significant difference noted at levels of 39.5 nmol/L and higher.

- However, after adjustment for testosterone levels, the effect of SHBG on the risk for cardiovascular events was no longer significant.
- Subgroup analysis based on age and a history of cardiovascular disease failed to alter the main study findings regarding the relationship between testosterone levels and the risk for cardiovascular events.
- The protective effect of high testosterone levels appeared slightly greater for cardiovascular vs cerebrovascular disease.
- High levels of free testosterone were associated with nonsignificant reductions in the risk for cardiovascular events, and there was no association between serum estradiol levels and the risk for cardiovascular events.

Clinical Implications

- Low serum testosterone levels are associated with increased adiposity, an adverse metabolic risk profile, and atherosclerosis. Low levels of SHBG are associated with higher rates of insulin resistance and obesity.
- The current study by Ohlsson and colleagues suggests that high serum testosterone levels are significantly protective against the risk for cardiovascular events among older men.