

Letters

Low Serum Free Testosterone Association With Cardiovascular Mortality in Men With Stable CAD



Low serum testosterone (T) levels in men are associated with increased all-cause mortality in community-based studies, whereas the association with cardiovascular (CV) mortality is less robust (1-3). Most studies have measured total T (i.e., the sum of

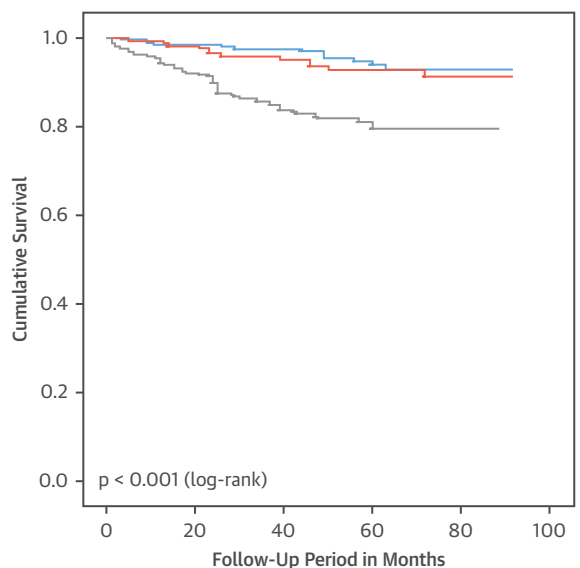
free testosterone [FT] and T bound either tightly to sex-hormone binding globulin, which is biologically inactive, or loosely to albumin). Thus far, no study has investigated the prognostic role of FT, presumed to be the most biologically potent form of T, in patients with coronary artery disease (CAD). Thus, we examined whether serum FT is associated with CV mortality in men with stable CAD.

Serum FT, lipids, high-sensitivity C-reactive protein (hsCRP), and interleukin (IL)-6 levels were measured from venous fasting blood samples collected between 08:00 and 09:00 in 612 consecutive men with stable CAD. Serum FT was measured by competitive radioimmunoassay (Beckman Coulter DLS 4900, Prague, Czech Republic) and the intra-assay and interassay coefficients of variation were 4.8% and 6.6%, respectively, with a sensitivity of 0.18 pg/ml.

All patients were participants of an ongoing prospective, hospital-based registry investigating risk factors and prognosis in patients with stable CAD, as previously described (4). The primary endpoint was CV mortality, and the secondary endpoint was readmission for acute coronary syndrome, arrhythmic event (life-threatening ventricular arrhythmia), or ischemic stroke.

During a median follow-up of 5 years, 243 CV events (39.7%) occurred. Of these, 68 were CV deaths (11%), 140 acute coronary syndromes (22.9%), 7 strokes (1.1%), and 28 arrhythmic events (4.6%). FT was inversely associated with CV death after adjustment for CV risk factors, that is, age, diabetes mellitus (DM), cholesterol, hypertension, smoking, and family history for CAD (hazard ratio [HR]: 0.853; 95% confidence interval [CI]: 0.782 to 0.930; $p < 0.001$). Further adjustment for both ejection fraction of the left ventricle and hsCRP did not change the association (HR: 0.873; 95% CI: 0.793 to 0.961; $p = 0.006$). Patients in the lower tertile of FT (≤ 7 pg/ml) had 2.8 times higher risk of CV death compared with patients with higher FT levels (> 7 pg/ml), that is, in the middle and higher tertiles after adjustment for CV risk factors (HR: 2.815; 95% CI: 1.428 to 5.550; $p = 0.003$). **Figure 1** presents unadjusted Kaplan-Meier survival curves stratified according to tertiles of FT levels. FT levels did not predict secondary endpoints (HR: 0.965; 95% CI: 0.920 to 1.013; $p = 0.151$).

FIGURE 1 Survival Curves for CV Death by Tertiles of FT Levels



	Higher Tertile	Middle Tertile	Lower Tertile
Patients at Risk			
Upper Tertile	202	196	166
Middle Tertile	167	163	141
Lower Tertile	243	221	172

Unadjusted Kaplan-Meier curves of event-free survival for cardiovascular (CV) death classified by tertiles of serum free testosterone (FT) levels. Higher CV mortality is observed in the lower tertile of FT levels. Higher tertile: FT levels ≥ 10 pg/ml (blue line); middle tertile: FT levels > 7 and < 10 pg/ml (orange line); and lower tertile: FT levels ≤ 7 pg/ml (gray line).

FT levels were inversely and significantly correlated with age ($r = -0.241$), waist circumference ($r = -0.138$), hsCRP ($r = -0.101$), IL-6 ($r = -0.219$), and DM ($\beta = -0.686$, $SE = 0.292$).

Our results demonstrated for the first time that FT levels are inversely associated with 5-year CV mortality in men with stable CAD, independently of CV risk factors, hsCRP, and ejection fraction. The exact mechanism by which low T levels increase CV mortality is largely unknown. It has been suggested that endogenous T affects atherosclerosis by modifying CV risk factors. Consistent with this, we found that FT was inversely correlated with waist circumference, DM, hsCRP, and IL-6.

Most previous studies measured mainly total T or a few of them FT, and found inconsistent results regarding its prognostic value on CV endpoints (1-3). This is the first study to our knowledge to examine the prognostic impact of FT in patients with stable CAD. It is plausible to speculate that FT, the most biologically active form of T, is more likely to identify the impact of T on future CV events. In addition, we measured FT by competitive radioimmunoassay, which shows a good correlation with equilibrium dialysis, considered the gold standard for FT measurements (5).

A limitation of this study, considering the high diurnal and seasonal variation of T, was its measurement from a single blood sample.

In conclusion, low FT levels are associated with high 5-year CV mortality in men with stable CAD. Large prospective studies are needed to confirm our results and support the hypothesis that FT is the most active and predictive fraction of T.

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Switching, Discontinuation, and Reinitiation of Statins Among Older Adults



In clinical settings, poor compliance is a major obstacle in achieving the full benefits of statin therapy. We examined switching, discontinuation, and reinitiation of statins among older adults.

Pharmaceutical Benefits Scheme (PBS) data for a 10% random sample of the Australian population were analyzed (1). Adults ≥ 65 years of age newly dispensed (without dispensation in the previous 12 months) atorvastatin, simvastatin, rosuvastatin, pravastatin, or fluvastatin between January 1, 2007 and December 31, 2015 were followed until death or December 31, 2016, whichever occurred first. Statins were stratified into low, moderate, or high intensity according to their low-density lipoprotein cholesterol-lowering capacity. Analysis was restricted to individuals for whom complete dispensing records were available (1).

Switching was defined as the first change in statin or intensity. For each person, we calculated the number of days on statin assuming a dosage of 1 tablet daily. Discontinuation was defined as the first ≥ 90 days without statin coverage and reinitiation as statin dispensation between discontinuation and end of follow-up.

We characterized users who switched, discontinued, or restarted statins by demographics, prescriber-type, statin type and intensity, comorbidities, other cardiovascular medication use, lifestyle factors, and polypharmacy. Comorbidities were identified using medication records for the 12 months preceding statin initiation via the validated Rx-Risk-V tool (2). The association between covariates and