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Reproductive Endocrinology

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Associations Of Testosterone, Dihydrotestosterone, Estradiol And Sex Hormone-binding Globulin With All-cause And Cardiovascular Mortality, And Incident Cardiovascular Events In Men: Individual Participant Data Meta-analyses

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Studies examining associations of circulating sex steroids with mortality risk in men show inconsistent results for testosterone (T), with limited data for dihydrotestosterone (DHT) and estradiol (E2). We aimed to clarify associations of sex steroids, sex hormone-binding globulin (SHBG) and luteinising hormone (LH) with risks of all-cause and cardiovascular disease (CVD) mortality and incident CVD events in men, by conducting individual participant data (IPD) meta-analyses of prospective cohort studies with sex steroids measured using mass spectrometry.

The Androgens In Men Study protocol was registered (PROSPERO: CRD42019139668) and published (BMJ Open 2020;10:e034777). A systematic review (completed Dec 2019) identified relevant studies (BMJ Open 2021;11: e048013). IPD were requested. Cox proportional hazards analyses related total T, SHBG, LH, DHT and E2 concentrations to risk of all-cause mortality and CVD deaths, and risk of incident CVD events. Models were adjusted for age and other sociodemographic factors, lifestyle factors, medical conditions and medications. Summary curves and hazard ratios (HRs) with 95% confidence intervals (CIs) were determined using two-stage random-effects IPD meta-analyses.

Summary estimates were obtained from 11 studies (24,596 men), with median baseline age 49-76 years and 4-20 years follow-up among studies. Associations of T with all-cause and CVD mortality risk were non-linear. Risk of all-cause mortality increased for men with baseline T concentrations <8.7 nmol/L, and risk of CVD death increased for men with baseline T <5.3 nmol/L. Lower SHBG concentrations were associated with lower risk of all-cause mortality (median Quintile [Q]1 vs Q5 [Q1:Q5], 20.6 vs 68.3 nmol/L; HR=0.85, CI=0.77-0.95), and CVD death (HR=0.81, CI 0.65-1.00). Men with LH >10 IU/L or E2 <5.1 pmol/L had higher all-cause mortality, with no association of LH or E2 with CVD deaths. Associations of DHT with all-cause and CVD mortality risk were non-linear. Men with lower baseline DHT concentrations had higher risk of all-cause mortality (median Q1:Q5, 0.69 vs 2.45 nmol/L; HR=1.19, CI=1.08-1.30) and CVD deaths (HR=1.29, CI=1.03-1.61), with risk increasing for DHT >2.45 nmol/L. Men with baseline DHT concentrations <0.59 nmol/L had increased risk of incident CVD events, no other hormones were associated with this outcome.

Our results suggest greater all-cause and CVD mortality risk among men with very low baseline T, higher baseline SHBG, or either lower or very high baseline DHT concentrations. There was greater risk of CVD events among men with very low baseline DHT concentrations. Potential mechanisms by which SHBG and DHT might influence mortality risk in ageing men merit further investigation.

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