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Adverse Cardiovascular Events and Cause Mortality in Men During Testosterone Treatment: Individual Patient and Aggregate Data Meta-Analyses

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Background: The cardiovascular safety of testosterone treatment in low testosterone is widely acknowledged to be unclear. Testosterone increases haematocrit, thereby potentially increasing venous thromboembolism risk. The FDA lists cardiovascular risk and stroke as adverse effects of testosterone. Systematic reviews and meta-analyses of published data have limited ability to confirm source data quality and categorisation. Some published meta-analyses have included participants with distinct risk profiles (e.g. cancer, HIV), with serum testosterone atypical for hypogonadism (>12nmol/L), short durations of testosterone treatment, and studies without placebo treatment. Furthermore, subtypes of cardiovascular or cerebrovascular events (e.g. stable angina) during testosterone treatment are seldom published, so have not been analysed previously. **Objective:** Evaluate frequencies of all-cause mortality, and all cardiovascular or cerebrovascular event subtypes, and analyse efficacy of testosterone monotherapy compared to placebo for men with low testosterone, using individual patient data (IPD) and aggregate data meta-analyses. **Methods:** MEDLINE, EMBASE, Science Citation Index, CENTRAL and clinical trial registries (PROSPERO CRD42018111005) were searched for placebo-controlled RCTs including men with serum testosterone <12nmol/L. One-stage meta-analyses were performed for studies providing IPD and two-stage meta-analyses were performed to integrate IPD and aggregated data. Primary outcomes were all-cause mortality and cardiovascular and/or cerebrovascular events at 12 months or nearest time point. **Results:** IPD were obtained from 17 of 35 eligible RCTs (3431/5601 participants) in men with low testosterone. Most participants had functional hypogonadism. Risks of cardiovascular and/or cerebrovascular events were similar between the testosterone and placebo arms (testosterone 120/1601, 7.5%; placebo, 110/1519, 7.2% OR 1.07, 95% CI 0.81-1.42 p=0.62). Frequencies of all cardiovascular or cerebrovascular event subtypes were also similar between testosterone and placebo arms, but testosterone increased risks of oedema and erythrocytosis. No subgroups at higher cardiovascular and/or cerebrovascular event risk were identified. Fewer deaths were recorded in the testosterone arm, but this difference was non-significant (testosterone, 6/1621, 0.4%; placebo, 12/1537, 0.8% OR 0.46, 95% CI 0.17-1.24 p=0.13). Testosterone significantly reduced serum total cholesterol, high-density lipoprotein (HDL), and triglycerides versus placebo. No significant differences in serum low-density lipoprotein (LDL), blood pressure, glycaemic parameters, diabetes incidence or prostate outcomes were observed between groups. Testosterone had positive, albeit varied, effects on quality of life and sexual function. **Conclusions:** This is the most comprehensive study to date interrogating the safety of testosterone treatment in men with low testosterone. We were unable to find evidence from our IPD meta-analyses that testosterone increases risks of mortality or cardiovascular and/or cerebrovascular events in the short- to medium-term in men with low testosterone, most of whom have various forms of functional hypogonadism. These data provide some reassurance to men with low testosterone and their clinicians about the safety of testosterone in the short-to-medium term although more long-term data are required.Acknowledgement: NIHR TestES Consortium.

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