Testosterone and the risk of incident atrial fibrillation in older men: further analysis of the ASPREE study

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Summary

Background A cardiovascular safety trial of testosterone in men with cardiovascular risk factors or disease found no difference in rates of major adverse cardiovascular events (MACE) or death but noted more atrial fibrillation (AF) events in testosterone-treated men. We investigated the relationship between endogenous testosterone concentrations with risk of developing AF in healthy older men.

Methods Post-hoc analysis of 4570 male participants in the ASPirin in Reducing Events in the Elderly (ASPREE) study. Men were aged ≥ 70 years, had no history of cardiovascular disease (including AF), thyroid disease, prostate cancer, dementia, or life-threatening illnesses. Risk of AF was modelled using Cox proportional hazards regression.

Findings Median (IQR) age was 73.7 (71.6–77.1) years and median (IQR) follow-up 4.4 (3.3–5.5) years, during which 286 men developed AF (15.3 per 1000 participant-years). Baseline testosterone was higher in men who developed incident AF compared men who did not [17.0 (12.4–21.2) vs 15.7 (12.2–20.0) nmol/L]. There was a non-linear association of baseline testosterone with incident AF. The risk for AF was higher in men with testosterone in quintiles (Q) 4&5 (Q4:Q3, HR = 1.91; 95%CI = 1.29–2.83 and Q5:Q3HR = 1.98; 95%CI = 1.33–2.94). Results were similar after excluding men who experienced MACE or heart failure during follow-up.

Interpretation Circulating testosterone concentrations within the high-normal range are independently associated with an increased risk of incident AF amongst healthy older men. This suggests that AF may be an adverse consequence of high-normal total testosterone concentrations.

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Keywords: Testosterone; Atrial fibrillation; Arrhythmia; Ageing; Gerontology; Epidemiology

Introduction

Circulating testosterone concentrations decline with age, reflecting testicular Leydig cell impairment in older men.[1,2] The decline is often exacerbated by the presence of obesity and other medical comorbidities.[3,4] Testosterone replacement is commonly recommended for men with androgen deficiency resulting from hypothalamic, pituitary or testicular disease.[5,6] However, a belief that testosterone treatment may have rejuvenating or "anti-ageing" effects in older men has contributed to

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Research in context

Evidence before this study

The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) study, a cardiovascular safety trial in older, overweight men with cardiovascular risk factors or disease, showed a signal for excess atrial fibrillation (AF) events in testosterone-treated men. A limited number of epidemiological studies in middle-aged to older men reported inconsistent associations of endogenous testosterone concentrations with incident AF. Whether testosterone is related to risk of AF in older men, who have both lower endogenous testosterone concentrations and higher incidence of AF, was unclear.

Added value of this study

We analysed 4570 healthy, community-dwelling men aged 70 years and older, from the ASPirin in Reducing Events in the Elderly (ASPREE) study, an older population where the risk of developing atrial fibrillation is of most concern. These men were free of cardiovascular disease or AF at baseline, and were not on medications that alter testosterone concentrations. Our results show that healthy older men with higher serum total testosterone concentrations had an increased risk of incident AF. This association was apparent for testosterone concentrations within the reference range. The relationship between testosterone and AF was non-linear, with the highest risk for testosterone concentrations in quintiles 4 and 5 (Q4:Q3, HR = 1.91; 95% CI = 1.29–2.83 and Q5:Q3, HR = 1.98; 95% CI = 1.33–2.94). Exclusion of men who had major cardiovascular events or heart failure during follow-up did not alter the results.

Implications of all the available evidence

Our findings suggest that in healthy older men with 'high-normal' endogenous total testosterone concentrations are at increased risk of AF.

increasing prescriptions for testosterone products which have risen 12-fold internationally between 2000 and 2011.[7,8] This treatment has been directed predominantly towards older men without organic disease and has occurred despite ongoing concerns over the safety of testosterone treatment.[9]

The recently published testosterone replacement therapy for assessment of long-term vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) study randomized more than 5000 overweight/obese middle-aged to older men to testosterone treatment or placebo for an average of 22 months.[10] Participants had established cardiovascular disease and/or increased cardiovascular risk factors, as well as symptoms such as decreased sexual desire, diminished energy, or low mood. Their baseline total testosterone was less than 10.4 nmol/L (<300 ng/dL). The study reported that testosterone treatment did not increase the risk of major adverse cardiovascular events (MACE) or mortality. However there was an increase in reports of atrial fibrillation (AF) amongst those in the treatment group compared with placebo (3.5% vs 2.4%, respectively, p = 0.02). Previous observational studies examining this relationship had reported inconsistent findings.[11–15] Therefore, the influence of endogenous testosterone concentrations on the risk of AF remains unclear.

Male participants in the ASPirin in Reducing Events in the Elderly (ASPREE) trial represent a large cohort of healthy older men without prior cardiovascular disease events or AF at baseline. Measurement of baseline serum total testosterone coupled with prospective follow-up for new AF events in ASPREE men provides an opportunity to clarify the relationship between serum total testosterone and incident AF. We investigated the hypothesis that endogenous testosterone concentrations are associated with an increased risk of developing AF in healthy older men.

Methods

Design and participants

ASPREE was a double-blinded, randomized placebo-controlled clinical trial of low dose aspirin in healthy, community-dwelling older adults.[16] In brief, from March 2010 to December 2014, 19,114 participants (16,703 from Australia and 2411 from the United States) aged ≥ 70 years (≥65 years for U.S minorities) were recruited and randomized to receive 100 mg of aspirin daily or matching placebo. At study entry, participants were free of evident cardiovascular disease (including diagnosed AF), dementia, independence-limiting physical disability or any other chronic illness expected to limit survival to less than 5 years.[16] Only Australian men who had baseline total testosterone measured and were followed up for self-reported AF were included in this analysis. Ethics approval for the principal ASPREE trial was obtained from the Monash University Human Research Ethics committee (2006/745 MC) and for the ASPREE Healthy Ageing Biobank from the Alfred Hospital Ethics Committee (18/08), and written consent was obtained from all participants.

Routine assessments

At baseline, anthropometric and laboratory measurements were collected, and participants completed questionnaires on comorbidities, social and medical history, and physical function and lifestyle.[16,17] Annual in-person visits and 6-monthly phone calls allowed for reassessment and the collection of information

concerning the occurrence of prespecified endpoints and other aspects of general health.

Testosterone & other biochemistry assessment

Blood and urine specimens were collected from consenting Australian participants as part of the ASPREE Healthy Ageing Biobank sub-study. The samples were collected before the commencement of the trial medication (where possible) and serum was processed and stored at –80 °C until analysed for serum total testosterone and thyroid stimulating hormone (TSH) concentrations. Total testosterone was measured using a chemiluminescence microparticle immunoassay (Abbott Alinity ci, Abbott Diagnostics, Australia), which had a reference range of 8.0–3.0 nmol/L. The coefficient of variation (%CV) was 4% at 3.3 nmol/L, 3.8% at 14.4 nmol/L and 3.4% at 29.2 nmol/L. TSH, which was controlled for in our analysis, was assayed using the same analytical platform, with %CV 1.1% at 0.04 mU/L, 1.6% at 0.68 mU/L, 2.0% at 4.9 mU/L and 1.9% at 25.4 mU/L.

Atrial fibrillation ascertainment

An algorithm was used for the ascertainment of AF within ASPREE (Supplementary Fig. S1) and was implemented by study staff blinded to treatment allocation and baseline biochemistry. The algorithm has been described elsewhere.[18] In brief, participants were considered to have incident AF when a new AF diagnosis was identified during the annual review of clinical notes or via a self-report confirmed by evidence from clinical records. Less commonly a diagnosis of AF was assumed if an irregular heart rate or self-report of AF was recorded together with prescription of anticoagulant, cardiac glycoside or another relevant antiarrhythmic medication. Participants with lesser evidence of incident AF were classified as possible or unconfirmed AF and were excluded from the main analysis. For the survival analysis, the time interval for AF started from the trial randomization and ended at the first occurrence of AF or the last follow-up visit, whichever occurred first. The last follow-up was June 2017.

Participant exclusion criteria

Exclusion criteria included the prescription of medications that may interfere with the hypothalamic-pituitary-testicular axis (including androgens, anti-androgens, and spironolactone). Men with a history of thyroid cancer or who were prescribed thyroid-related medications were excluded to avoid confounding both from over-treatment with thyroxine predisposing to AF, and also due to the known association of hyperthyroidism with elevated concentrations of the testosterone binding protein, sex hormone-binding globulin (SHBG).[19,20]

Statistical analysis

A comparison between the baseline characteristics of participants with and without incident AF was evaluated using Pearson's Chi-square or Fisher's exact tests for categorical variables. Normality of continuous variables were assessed using the Q–Q normality plot and as the distributions were skewed, the Mann Whitney U Test was used. To evaluate the relationship between total testosterone and AF, Cox proportional-hazards regression models were constructed to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for incident AF with multivariable adjustment for potential confounders. These included age, smoking (current/former vs never) status, body mass index (BMI), hypertension, alcohol consumption (current/former vs never), diabetes mellitus, dyslipidemia, thyroid stimulating hormone and aspirin allocation. Confounding variables selected for the models adhered to the principles of the modified disjunctive cause criterion where covariates were associated with either testosterone and AF, which were identified through literature searches and clinical relevance, excluding any instrumental variables. The proportional hazards assumptions and non-linearity of quantitative predictors were assessed using the Schoenfeld and martingale residual tests and no violation to the assumptions were observed.

Initially, serum testosterone values were treated as continuous variables. Thereafter, they were analysed according to quintiles (Q) with Q1 being the lowest 20%; and Q5, the highest 20%. The middle quintile (Q3) of total testosterone concentrations was used as the reference. In addition, the linearity of the relationship between testosterone and incident AF was explored using an unadjusted three-knot restricted cubic spline curve, as this had the lowest AIC, using the median value (15.8 nmol/L) as a reference, and knots placed at 0.1, 0.5 and 0.9 as recommended.[21]

Analyses of the relationship were repeated omitting participants who had MACE events (fatal/non-fatal myocardial infarction and fatal/non-fatal ischemic stroke) or hospitalization for heart failure (HHF) during the study duration. A sensitivity analysis was conducted excluding those with a TSH of <0.3 mU/ml to avoid residual confounding from the presence of sub-clinical hyperthyroidism. Additional analyses were conducted restricting the analysis to those who had serum total testosterone within the clinical normal range.

The statistical analyses were performed using Stata software v17.0 (StataCorp LLC, College Station, TX, USA). Analysis was completed from June to September 2023.

Role of funding

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Results

Study population

Of the 16,703 Australian ASPREE participants eligible for clinical biochemistry collection, 7524 were male. After excluding those receiving androgen or thyroid medication or a history of prostate or thyroid cancer and those where the AF status was uncertain, 4357 individuals with baseline measures of serum total testosterone concentrations were included in the analysis (Fig. 1).

The median (IQR) study population age was 73.7 (71.6–77.1) years with a median (IQR) follow-up of 4.4 (3.2–5.5) years (Table 1). A total of 11.8% of the participants reported a diagnosis of diabetes mellitus and 75.9% had a history of hypertension. The median (IQR) BMI was 27.6 (25.3–30.0) kg/m^2 and the overall median (IQR) total testosterone concentration was 15.8

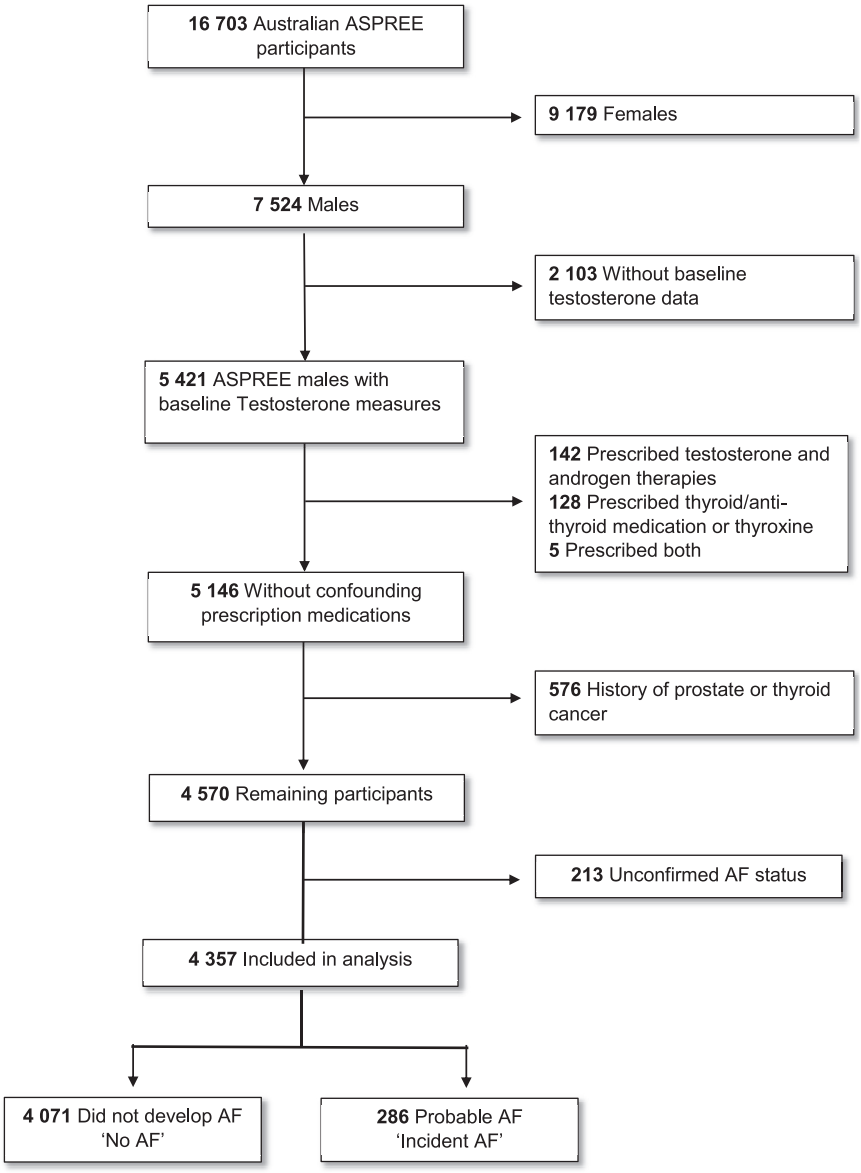


Fig. 1: Strobe flow diagram.

Baseline characteristics	Overall N = 4357	No AF N = 4071	Incident AF N = 286	p value
Age [median (IQR)] years	73.74 (71.59–77.07)	73.65 (71.56–76.95)	74.92 (72.18–79.24)	<0.0001
Smoking status, n(%)				0.0072
Current/former	2425 (55.66)	2244 (55.12)	181 (63.29)	
Never	1932 (44.34)	1827 (44.88)	105 (36.71)	
Alcohol status, n(%)				0.62
Current/former	3956 (90.80)	3694 (90.74)	262 (91.61)	
Never	401 (9.20)	377 (9.26)	24 (8.39)	
BMI [median (IQR)] kg/m^2	27.55 (25.33–30.03)	27.51 (25.31–29.98)	28.00 (25.65–30.86)	0.019
Diabetes, n (%)	515 (11.82)	475 (11.67)	40 (13.99)	0.24
Hypertension, n (%)	3305 (75.85)	3078 (75.61)	227 (79.37)	0.15
Dyslipidemia, n (%)	2453 (56.30)	2298 (56.45)	155 (54.20)	0.46
TSH [median (IQR)] mU/L	1.26 (0.9–1.75)	1.26 (0.9–1.76)	1.23 (0.9–1.75)	0.50
TSH < 0.3 mU/L, n (%)	59 (1.35)	56 (1.38)	3 (1.05)	0.99
Aspirin, n (%)	2191 (50.29)	2058 (50.55)	133 (46.50)	0.19
Testosterone [median (IQR)] nmol/L	15.8 (12.2–20.1)	15.7 (12.2–20.0)	17.0 (12.4–21.2)	0.028

Baseline characteristics are shown, categorised by whether or not incident AF was developed during follow up. To convert testosterone from nmol/L to ng/dL, multiply by 28.82. BMI = body mass index, TSH = thyroid stimulating hormone.

Table 1: **Baseline characteristics of participants.**

(12.2–20.1) nmol/L. Baseline characteristics of the cohort after excluding participants who had a MACE or HHF event during the clinical trial are reported in Supplementary Table S1.

Atrial fibrillation

There were 286 cases of incident AF (Table 1) in the study population. After excluding participants with MACE or HHF during follow-up, there remained 227 cases of AF (Supplementary Table S1). Compared with those who did not develop AF, men with incident AF were older, more likely to report current/former cigarette smoking and had higher BMI at baseline. There was no difference in the prevalence of hypertension, diabetes, dyslipidemia at baseline, TSH concentrations, alcohol consumption or aspirin allocation between the groups.

Testosterone and incident atrial fibrillation

Table 1 shows that the median total testosterone was higher both in the incident AF group compared to the no AF group [median (IQR): 17.0 (12.4–21.2) vs 15.7 (12.2–20.0) nmol/L]. Further details of the association between total testosterone concentrations and incident AF are presented in Table 2. In the unadjusted analyses, men with higher testosterone concentrations, i.e., in the 4th and 5th quintiles, had an increased risk of incident AF when compared to Q3 (hazard ratio, HR 1.84; 95% CI, 1.24–2.71 and HR, 1.77; 95%CI, 1.20–2.63, respectively). In the fully-adjusted model, men in Q4 and Q5 showed a similarly higher risk of incident AF compared to men in Q3 (Q4 HR 1.91; 95% CI, 1.29–2.83 and Q5 HR 1.98; 95% CI, 1.33–2.94, respectively). This translated to an absolute risk of 18.7 per 1000 person years for men in Q4 and 18.2 per 1000 person years for men in Q5. A Kaplan–Meier curve demonstrating survival free of AF over the follow-up time can be found in Fig. 2. The restricted cubic spline confirmed a non-linear relationship between total testosterone and incident AF with a substantial increase at higher total testosterone concentrations (Fig. 3).

In the sensitivity analysis excluding participants with TSH levels < 0.3 mU/L the results were largely unchanged. Restricting the analysis to participants with testosterone measurements inside the clinical normal range also did not alter the results (Supplementary Table S2).

Testosterone and atrial fibrillation in the absence of MACE and HFF

Similar findings were present for total testosterone and the risk of AF in the absence of MACE and HHF (Table 2). In the fully-adjusted model, a 1 nmol/L increase in total testosterone was associated with a 18% higher risk of AF (HR 1.03, 95%CI 1.01–1.05). In the fully-adjusted analyses of total testosterone in quintiles, men with total testosterone in the 4th (HR 2.27; 95%CI, 1.46–3.54) and 5th (HR 2.07; 95%CI, 1.31–3.28) quintiles had higher risk of AF.

Discussion

In this study healthy of older men with no prior documented cardiovascular disease or AF at baseline, higher serum testosterone concentrations within the clinical reference range (Supplementary Fig. S2) were associated with an increased risk of incident AF during follow-up. Compared to men in the middle quintile of total testosterone concentrations, those in the higher two quintiles of testosterone concentrations had a two-fold greater risk of developing AF, independently of

A

	[b]Whole cohort (N = 4357)	Testosterone quintiles [median nmol/L (25th–75th percentile)]				
		Q1 N = 896 [9.6 (7.9–10.6)]	Q2 N = 855 [13.0 (12.3–13.7)]	Q3 N = 866 [15.8 (15.1–16.5)]	Q4 N = 887 [19.0 (18.1–20.2)]	Q5 N = 853 [24.9 (22.7–27.9)]
IR per 1000 PY (95% CI)	15.3 (13.6–17.1)	15.6 (12.1–20.2)	13.5 (10.2–17.9)	10.2 (7.5–14.0)	18.7 (14.8–23.5)	18.2 (14.4–23.1)
Model 1	1.01 (0.99–1.03), p = 0.15	1.57 (1.05–2.36), p = 0.030	1.35 (0.88–2.06), p = 0.16	1.00 (ref)	1.84 (1.24–2.71), p = 0.0022	1.77 (1.20–2.63), p = 0.042
Model 2	1.02 (1.01–1.04), p = 0.0088	1.40 (0.93–2.11), p = 0.11	1.30 (0.85–1.99), p = 0.22	1.00 (ref)	1.92 (1.30–2.83), p = 0.0011	1.95 (1.31–2.89), p = 0.00098
Model 3	1.03 (1.01–1.04), p = 0.0063	1.37 (0.91–2.08), p = 0.13	1.30 (0.85–1.98), p = 0.23	1.00 (ref)	1.91 (1.29–2.83), p = 0.0012	1.98 (1.33–2.94), p = 0.00078

[a]B

	[b]Whole cohort (N = 4185)	Testosterone quintiles [median nmol/L (25th–75th percentile)]				
		Q1 N = 860 [9.6 (7.8–10.6)]	Q2 N = 822 [13.0 (12.3–13.7)]	Q3 N = 831 [15.8 (15.1–16.5)]	Q4 N = 853 [19.0 (18.1–20.2)]	Q5 N = 819 [24.9 (22.7–28.0)]
IR per 1000 PY (95% CI)	12.5 (11.0–14.3)	12.9 (9.6–17.2)	10.7 (7.8–14.8)	7.9 (5.5–11.3)	16.6 (12.9–21.3)	14.4 (11.0–18.9)
Model 1	1.01 (0.99–1.03), p = 0.24	1.69 (1.06–2.69), p = 0.027	1.39 (0.86–2.27), p = 0.18	1.00 (ref)	2.12 (1.36–3.30), p = 0.00084	1.83 (1.16–2.88), p = 0.0088
Model 3	1.03 (1.01–1.05), p = 0.012	1.43 (0.89–2.30), p = 0.14	1.32 (0.81–2.15), p = 0.26	1.00 (ref)	2.27 (1.46–3.54), p = 0.00029	2.07 (1.31–3.28), p = 0.0018

A = Cox proportional hazards regression for testosterone as a continuous variable and in quintiles. B = Cox proportional hazards regression for testosterone as a continuous variable and in quintiles after excluding participants who developed MACE or HF during follow up. Model 1: Unadjusted. Model 2: Adjusted for age, smoking status, BMI. Model 3: Model 2 + hypertension, Alcohol, diabetes, dyslipidemia, thyroid stimulating hormone and aspirin. Quintile upper boundary: Q1 = 11.5 nmol/L; Q2 = 14.4 nmol/L; Q3 = 17.2 nmol/L; Q4 = 21.2 nmol/L. [a]Results for model 2 is not displayed as it did not meet the proportional hazards assumption. [b]Presented as hazard ratio per 1 nmol/L increase in testosterone.

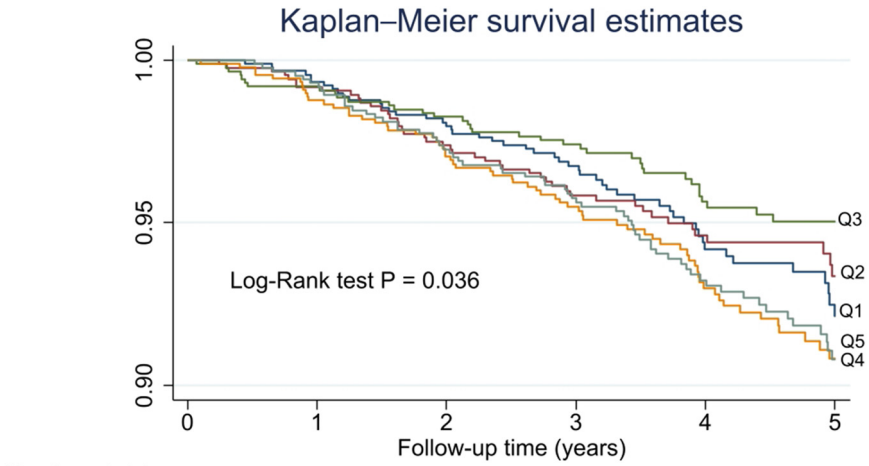
Table 2: **Multivariable analysis of testosterone and risk of incident AF.**

age, smoking status, BMI, hypertension, alcohol consumption, diabetes, dyslipidemia, TSH concentrations or aspirin allocation. After excluding men who experienced a MACE or HHF during the period of follow-up, the association with an increased risk of AF remained unchanged. These findings suggest that higher testosterone concentrations relate to risk of AF distinct from an association with underlying atherosclerotic CVD, or cardiac dysfunction in the setting of heart failure.

In the TRAVERSE trial, testosterone treatment for a mean duration 22 months increased testosterone concentrations from a median (IQR) of 7.8 (6.5–8.9) nmol/L by 5.1 (1.2–10.8) nmol/L. There was no difference reported in the risk of MACE or mortality in testosterone-treated men compared with those receiving placebo. However, men receiving testosterone had a higher frequency of AF (3.5% in the testosterone group vs 2.4% in the placebo group, p = 0.02). The 'Testosterone for Prevention of Type 2 Diabetes Mellitus in Men at High Risk' (T4DM) study in which men with impaired glucose tolerance or newly diagnosed type 2 diabetes mellitus were randomised to testosterone treatment or placebo for two years, on a background of lifestyle intervention, also noted a higher number of arrhythmias (although not specifically AF) in testosterone-treated men compared with placebo.[22] Overall, these findings suggest that in healthy older men, differences in exposure to endogenous testosterone are likely to be associated with a varying risk of AF, supporting the concept that greater testosterone exposure (endogenous or exogenous) potentially predisposes older men to incident AF.

Previous epidemiological studies linking high testosterone concentrations to AF have reported inconsistent results. A summary of these is included in the Supplementary material (Supplementary Table S3). Two of these, the Cardiovascular Health Study (CHS) and the Multi-Ethnic Study of Atherosclerosis (MESA) reported no association, while the Framingham Heart Study (FHS) and FINRISK97 reported inverse association.[11–13,15] However, our findings are consistent with reports from the Atherosclerosis Risk in Communities (ARIC) study of 4224 men although the magnitude of the association was less than in the ASPREE population. Small cohort sizes, generally younger ages, varying proportions with pre-existing cardiovascular disease and differences in ascertainment of AF may have contributed to the variation in findings. However, the ASPREE study is unique in being an exclusively older population whose results are 'validated' by the findings of a randomised clinical trial.

Although the focus of our study was on the impact of high testosterone concentrations, the association between total testosterone and AF appeared to be non-linear, with the lowest incidence of occurring at men with mid-range values of testosterone concentrations. In our study of quintiles, a higher incidence of AF was noted amongst men with lower testosterone concentrations but this did not reach statistical significance. However the non-linear association of testosterone with



Number at risk

Quintile 1	896	883	857	692	468	256
Quintile 2	855	840	802	662	461	251
Quintile 3	866	853	834	727	522	317
Quintile 4	887	869	843	727	529	308
Quintile 5	853	839	805	714	542	332

Fig. 2: Kaplan–Meier survival curve of AF over time. Q = quintile.

incident AF risk is consistent with an observational study of data from the Veterans Administration Corporate Data Warehouse involving 76,693 males with initially low testosterone concentrations.[23] Amongst these men normalisation of testosterone concentrations after testosterone replacement therapy was reported to be associated with a decrease in the incidence of AF. Despite the limitations of this study design, it suggests that testosterone replacement that aims to achieve mid-range concentrations of serum testosterone concentrations will be optimal in terms of AF incidence.

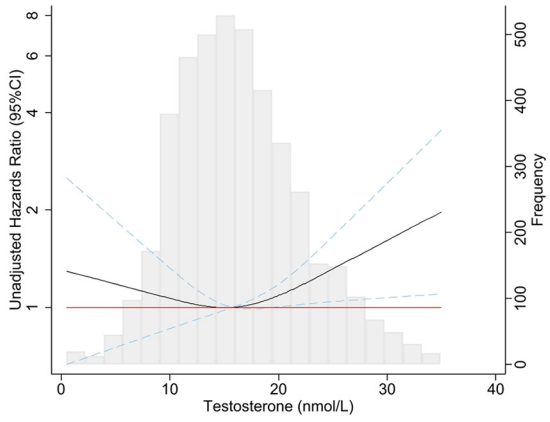


Fig. 3: Relationship between baseline testosterone and risk of incident AF. Restricted cubic splines were used to plot risk of incident AF according to baseline testosterone values. Blue dashed lines = 95% CI. Black line = adjusted hazards ratios.

The mechanisms behind the link between testosterone and AF have not been established. It has been reported that shorter telomeres are associated with higher risk of AF and higher testosterone concentrations have been associated with shorter leukocyte telomere length in middle to older aged men.[24–26] Another study involving animal models has suggested that increased conversion of testosterone to estradiol (by aromatase) results in an increased expression of aromatase within epicardial adipose tissue, which predisposes to arrhythmia.[27] In another in-vitro study, testosterone treatment increased the expression of β1-adrenergic receptor expression and increased the rate of spontaneous action potentials in the pulmonary vein, both of which could predispose to AF.[28–30] Sex hormones may also influence cardiac tissues by modulating the function of ion channels but the data are limited and inconsistent.[29] Therefore, further mechanistic studies are needed to before the mechanism behind this relationship is understood.

The significance of these findings is based on the high incidence of AF amongst older men and the strong association between AF and stroke, heart failure, disability and mortality.[31] Amongst those with high-normal testosterone concentrations the risk of incident AF was doubled compared to men with average testosterone concentrations leading to an absolute risk increase of approximately 8 cases per 1000 person years of follow-up. Previous studies have reported men with low-normal testosterone concentrations have higher all-cause mortality suggesting that lower testosterone concentrations may be a marker of less robust physical

health and are unlikely to be a useful therapeutic goal.[32,33] The findings suggest that treatment regimens might optimally the mid-point of the 'normal range' and avoid the extremes.

Testosterone treatment is routinely prescribed for hypogonadal men with diseases of the hypothalamus, pituitary or testes, alleviating the symptoms and signs of androgen deficiency.[5,6] In men with an intact hypothalamic-pituitary-testicular axis, testosterone is a pharmacological intervention, which improves sexual function, bone density and haemoglobin concentration, and in conjunction with lifestyle intervention, reduces the risk of type 2 diabetes.[22,34] In the latter setting, AF should be considered as part of the risk-benefit evaluation when prescribing testosterone replacement therapy.

The purpose of the study was to confirm or reject the finding of the TRAVERSE trial and in that sense examined a pre-specified hypothesis. The participants comprised healthy older aged men free of prevalent CVD or any other chronic illness expected to limit survival to less than 5 years who were followed by direct personal contact for an average 4.6 years. Each individual was extensively phenotyped allowing for adjustment of key confounders. A high level of follow-up was achieved with over 95% of participants remaining under observation or observation through medical records in the 12 month window prior to study conclusion.[35]

Limitations of the study include its observational nature, precluding a determination of causality. Testosterone measurements show a circadian variation and samples were not taken at a regular time of the day. However, with the large sample size such variation would contribute to 'random error' without influencing the study results. Testosterone concentrations were measured by immunoassay rather than the more accurate mass spectrometry. However, these measures were undertaken by a nationally accredited hospital laboratory participating in a national quality control program. Testosterone concentrations were analysed both as a continuous variable, and in quintiles, avoiding the use of specific thresholds. Sex hormone-binding globulin (SHBG), dihydro-testosterone, oestradiol and free testosterone were not available, thus restricting potential consideration of the mechanism of the finding. We defined incident AF from an algorithm rather than from systematic surveillance with electrocardiograms which would not have been practical in a study of this size. Finally, as is typical with observational studies, we could not exclude the possibility that the results are affected by unknown, unmeasured or inexact measures of known confounders or the effect of selection bias as a result of doing a cox proportional hazards ratio for our analysis.[36]

The relationship between testosterone and other health attributes is complex. Healthy older men who had no prior cardiovascular disease with high-normal total testosterone concentrations had a higher incidence of AF, after adjusting for potential confounders. High-normal circulating testosterone should be recognised as a risk factor for atrial fibrillation in healthy older men. This finding is consistent with results of the TRAVERSE study, suggesting that AF may be an adverse consequence of high-normal total testosterone concentrations whether occurring physiologically or as a result of testosterone supplementation. The risk of AF could be considered when weighing benefits vs risks of testosterone therapy in older men.

Contributors

Ms Tran and Drs Clayton-Chubb and Hussain had full access to and verified the data of the study. Ms Tran and Professor Yeap were joint first authors. Professor McNeil was the senior author.

Drafting and editing of the manuscript: Tran, Yeap, Ball, Clayton-Chubb, Hussain, Brodtmann, Tonkin, Neumann, Schneider, Woods, McNeil.

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Funding acquisition: Schneider, Woods, McNeil.

Data sharing statement

The de-identified dataset used for this analysis can be accessible to researchers and students via a request to http://ams.aspree.org.

Declaration of interests

Professor Yeap reported receiving research support funding from University of Western Australian, and an honoraria for presentations and participation in advisory committee, both of which are outside of the submitted work. Professor Schneider reported receiving a grant from Abbott Diagnostics for consumables and is an unpaid board member of Public Pathology Australia. Dr Woods reported receiving National Institute of Health (NIH) and National Health and Medical Research Council (NHMRC) funding, which is paid to Monash University.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102611.

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