Post Authorization Study (PAS) Report - Study Information

Acronym/Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational ☒ PAS Joint PASS: ☐ YES ☒ NO>
EU PAS register number	EUPAS 23347
Active substance	Testosterone
Medicinal product / Medical Device / Combination Product	Nebido
Product reference	N/A
Procedure number	N/A
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany
Research question and objectives	The objective is to investigate if established cardiovascular risk factors predict the initiation of testosterone use.
Country of study	United Kingdom
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen, Germany
MAH contact person	[redacted]

Confidentiality statement:

Table of contents

Table of contents **3**

1. Abstract **5**

2. List of abbreviations **8**

3. Investigators **9**

4. Other responsible parties **9**

5. Milestones **9**

6. Rationale and background **10**

7. Research question and objectives **10**
7.1 Primary objective 10
7.2 7.2 Secondary objective(s) 11

8. Amendments and updates **11**

9. Research methods **11**
9.1 Study design 11
9.2 Setting 11
9.3 Subjects 11
9.3.1 Inclusion criteria 11
9.3.2 Exclusion criteria 12
9.3.3 Study population 12
9.4 Variables 12
9.4.1 Baseline characteristics 12
9.4.2 Exposure 12
9.4.3 Outcome measures 12
9.5 Data sources and measurement 12
9.6 Bias 13
9.7 Study size 13
9.8 Data transformation 13
9.9 Statistical methods 13
9.9.1 Main summary measures 13
9.9.2 Main statistical methods 13
9.9.3 Missing values 14
9.9.4 Sensitivity analyses 14
9.9.5 Amendments to the statistical analysis plan 14
9.10 Quality control 14

10. Results **14**
10.1 Participants 14
10.2 Descriptive data 14
10.3 Outcome data 15
10.4 Main results 15
10.5 Other analyses 16
10.6 Safety data (Adverse events/adverse reactions) 16

11. Discussion....16
11.1 Key results....16
11.2 Limitations....17
11.3 Interpretation....18
11.4 Generalizability....18
12. Other information....18
13. Conclusion....18
14. References....19
Appendices....21
Annex 1: List of stand-alone documents....21
Annex 2 Additional information....22
Figure 1: Ascertainment of new use of testosterone, Jan 2001 to Jul 2017....22
Table 1: Specification of first testosterone use....23
Table 2: Baseline characteristics of cases and matched controls....26
Table 3: History of cancer in patients with initial testosterone use....29
Table 4: Breakdown of type of pathological hypogonadism....30
Table 5: Predictors for testosterone initiation, entire cohort....31
Table 6: Predictors for testosterone initiation, cohort with pathological hypogonadism 33
Table 7: Predictors for testosterone initiation, cohort with functional hypogonadism....35
Table 8: Predictors for testosterone initiation, entire cohort between 2001 and 2014....37
Table 9: Predictors for testosterone initiation, entire cohort between 2015 and 2017....39
Annex 3 Signature Pages....41

1. Abstract

Acronym/Title	Association between the prevalence of cardiovascular risk factors and new use of testosterone
Report version and date **Author**	1.0, 14 June 2018 [redacted]
Keywords	Testosterone, cardiovascular risk factors, treatment initiation
Rationale and background	Testosterone preparations are indicated for treatment of male testosterone deficiency (hypogonadism). Hypogonadism is highly prevalent (up to 50%) in men with obesity and/or type 2 diabetes, both considered chronic diseases and risk factors for cardiovascular diseases. Hypogonadism can occur at all ages and is not related to advancing age but rather to the presence of comorbidities, in particular chronic conditions as obesity (BMI $\geq$30 kg/m^2) and type 2 diabetes mellitus.
Research question and objectives	Primary: To study the association between the prevalence of cardiovascular risk factors and new use of testosterone Secondary: N/A Safety: N/A
Study design	Matched case-control study.
Setting	The source population was formed from all male patients in the UK Clinical Practice Research Datalink (CPRD) linked to the English Hospital Episodes Statistics (HES) database. All male individuals in the source population with a first testosterone use during the study period (1 Jan 2001 to 31 Jul 2017) were included as cases. The date of the GP consultation

	associated with the first testosterone prescription was designated as the index day. Patients of less than 18 years on the index day, with less than two years contribution to the CPRD/HES subset before the index day, or with use of testosterone before the study period were excluded from the group of cases. For each case, up to five controls were drawn among people in the source population. Controls were matched on exact age, history of hypogonadism and GP consultation ±30 days of the index day of the respective case. The index day of the control was the day of the closest GP visit to the index day (i.e. the calendar day) of the corresponding case. Controls were required to have contributed for at least two years to the CPRD/HES subset before the index day and to have no history of testosterone use on or before the index day.
Subjects and study size, including dropouts	Within the study population of all male patients in the CPRD linked to the HES database, a total of 4631 patients aged 18 years or older were given initial testosterone therapy during the study period and had a minimum of two years contribution to the CPRD/HES subset before the index day. Of those, 1643 had a history of pathological ("true") hypogonadism.
Variables and data sources	The exposure of interest was the presence of the following cardiovascular risk factors: history of stroke/transient ischaemic attack, atrial fibrillation, myocardial infarction, ischaemic heart disease, heart failure, hypertension, diabetes, hypercholesterolemia, high BMI, current- and ex-smoking, lipid-lowering drugs, antihypertensive medication, positive inotropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, drugs affecting the renin-angiotensin system, nitrates, calcium-channel blockers, other antianginal drugs and anticoagulant or antiplatelet drugs. All data were obtained from the United Kingdom CPRD with additional data from HES.
Results	Testosterone was preferentially prescribed in patients with high BMI, hypercholesterinaemia, diabetes, hypertension, ex-smokers, and with use of the following cardiovascular drugs: vasodilator antihypertensive drugs, angiotensin-II receptor antagonists, lipid lowering drugs, loop diuretics, anti-arrhythmic drugs for ventricular arrhythmias, and alpha-adrenoceptor blocking drugs. Predictors associated with a decreased probability of

	testosterone treatment initiation were current smoking, history of use of angiotensin-converting enzyme inhibitors, and of thiazides and related diuretics.
Discussion	Our data indicate that testosterone is preferentially prescribed to patients at an increased baseline risk of acute cardiovascular outcomes and cancer-related mortality. Observational studies on cardiovascular outcomes including mortality may be prone to confounding by indication bias and to selection bias as patients with functional and pathological hypogonadism treated with testosterone have a higher baseline risk for cardiovascular diseases and cancer-related mortality than age matched controls.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany
Names and affiliations of principal investigators	[redacted]

2. List of abbreviations

AIDS/HIV	Acquired immunodeficiency syndrome/Human immunodeficiency virus
BMI	Body mass index
CHF	Congestive heart failure
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
EMA	European Medicine Agency
FDA	Food and Drug Administration
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
GP	General practitioner
HES	Hospital Episodes Statistics
IMD	Index of Multiple Deprivation
LVD	Left ventricular dysfunction
MI	Myocardial infarction
N/A	Not applicable
OR	Odds ratio
OS	Observational Study
PAS	Post-authorization study
PASS	Post-authorization safety study
PI	Principal investigator
PRAC	Pharmacovigilance Risk Assessment Committee
RCT	Randomized controlled trial
SD	Standard deviation
TIA	Transient ischaemic attach
UK	United Kingdom

3. Investigators

[redacted]

4. Other responsible parties

N/A

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection		19 Jan 2018	
End of data collection		1 Mar 2018	
Registration in the EU PAS register	04 Apr 2018	23 Apr 2018	
Interim report 1		0.1, 21 Jan 2018	
Interim report 2		0.2, 11 May 2018	
Final report of study results	31 May 2018	14 June 2018	

6. Rationale and background

Testosterone preparations are indicated for treatment of male testosterone deficiency (pathological or functional hypogonadism). Pathological ("true") hypogonadism occurs in approximately 3% of the male population. In contrast, functional hypogonadism is highly prevalent (up to 50%) in men with obesity and/or type 2 diabetes, both considered chronic diseases and risk factors for cardiovascular diseases.

There are concerns regarding the safety of testosterone therapy, e.g. cardiovascular endpoints and prostate cancer. An ongoing debate about cardiovascular safety was triggered by one RCT,(1) two retrospective epidemiological database analyses,(2, 3) and one meta-analysis (4) leading to safety investigations by FDA and EMA (PRAC procedure). Only three RCTs with a duration of 3 years are published to date on the use of testosterone patch in relatively healthy, slightly overweight men over 65 years with low-normal testosterone; (5) use of short-acting testosterone injections in relatively healthy, overweight men aged 65 years and above with low testosterone (n=46);(6)] and use of testosterone gel in relatively healthy, overweight men aged 60 years and above with low or low-normal testosterone (n=155).(7)

Since 2010, four papers were published suggesting an increased cardiovascular risk in middle-aged to elderly men receiving testosterone therapy.(2-4, 7) These papers triggered safety assessments by EMA and FDA. Both agencies could not detect conclusive evidence for an increased cardiovascular risk, however, the FDA decided to add a warning in the label of testosterone-containing products. In contrast to those 4 papers, numerous publications reported that testosterone therapy reduces all-cause and cardiovascular mortality and morbidity.(8-12)

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) review did not confirm an increase in heart problems with testosterone medicines but decided that "The cardiovascular safety of testosterone medicines will continue to be monitored and the findings of ongoing studies will be reflected in the next regular benefit-risk assessments when available."(13)

Testosterone therapy is considered standard treatment in men with functional hypogonadism and low testosterone levels.(14) Functional hypogonadism can occur at all ages and is not solely related to advancing age but rather to the presence of comorbidities, in particular chronic conditions as obesity (BMI ≥30 kg/m2) and type 2 diabetes mellitus.(15, 16)

We investigated if testosterone was preferentially given to patients at higher risk of cardiovascular events. If this is the case, then observational studies may be prone to selection bias resulting in overestimation of the cardiovascular risk associated with testosterone when compared to a healthier population not taking testosterone.

The objective was to investigate if established cardiovascular risk factors predict the initiation of testosterone use.

7. Research question and objectives

7.1 Primary objective

The objective was to study the association between the prevalence of cardiovascular risk factors and new use of testosterone

7.2 7.2 Secondary objective(s)

N/A

8. Amendments and updates

Table 2: Amendments

Nr.	Date	Section of study protocol	Amendment or Update	Reason
1	27 April 2018	Inclusion criteria	Extension of study period to include data until 31 July 2017	The study population of the original ISAC study protocol covered the period between 1st April 2001 and the latest data available in the CPRD-HES link (SET 14), i.e. 31 March 2016 at the time of the ISAC study protocol approval (29/09/2017). The Bayer study protocol was approved on 18 January 2018. In the meantime CPRD had released Set 15 covering CPRD-HES link data until 31 July 2017. Therefore, it was decided to extend the study period to include the most recent data available at the time of the approval of the Bayer study protocol.

9. Research methods

9.1 Study design

This was a matched case-control study.

9.2 Setting

This study used data from the subset of individuals in the UK Clinical Practice Research Datalink (CPRD) who were eligible for additional data from the English Hospital Episodes Statistics (HES). CPRD is based on primary care and includes demographics, medical history, symptoms, and diagnoses, referrals, laboratory data (tests and results), and prescriptions issued by general practitioners (GPs). HES include ethnic origin, admission and discharge dates, and coded primary and other main discharge diagnoses, and surgical operations and procedures performed during hospital stay.

9.3 Subjects

9.3.1 Inclusion criteria

All male individuals in the study population (see below) with a first testosterone use during the study period (1 Jan 2001 to 31 Jul 2017) were included as cases. The date of the GP consultation associated with the first testosterone prescription was designated as the index day.

9.3.2 Exclusion criteria

Patients of less than 18 years on the index day, with less than two years contribution to the CPRD/HES subset before the index day, or with use of testosterone before the study period were excluded from the group of cases.

9.3.3 Study population

The study population was formed from all male patients in the CPRD linked to the HES database.

Control selection

For each case, up to five controls were drawn among people in the source population. Controls were matched on exact age, history of pathological hypogonadism and GP consultation ±30 days of the index day of the respective case. The index day of the control was the day of the closest GP visit to the index day (i.e. the calendar day) of the corresponding case. Controls were required to have contributed for at least two years to the CPRD/HES subset before the index day and to have no history of testosterone use on or before the index day.

9.4 Variables

9.4.1 Baseline characteristics

Baseline covariates included age, BMI, drinking/smoking status, socioeconomic class, Charlson comorbidity index components, comedications, and comorbidities which sometimes lead to empirical testosterone treatment (i.e. sexual dysfunction, osteoporosis, infertility, hot flushes, loss of appetite and a group of symptoms comprising tiredness, lethargy and depression).

The following clinical characteristics were assessed within the year prior to the index day: hypertension, antiplatelet use, hot flushes, loss of appetite, and the group of symptoms comprising tiredness, lethargy and depression. All other covariates were assessed any time prior to the index day.

9.4.2 Exposure

The exposure of interest was the presence of the following cardiovascular risk factors: history of stroke/transient ischaemic attack, atrial fibrillation, myocardial infarction, ischaemic heart disease, heart failure, hypertension record in last year, diabetes, hypercholesterolemia, high BMI, current- and ex-smoking, lipid-lowering drugs, antihypertensive medication, positive inotropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, drugs affecting the renin-angiotensin system, nitrates, calcium-channel blockers, other antianginal drugs and anticoagulant or antiplatelet drugs.

9.4.3 Outcome measures

The study outcome was initiation with testosterone treatment.

9.5 Data sources and measurement

Initiation with testosterone treatment was identified from respective prescriptions and specific Read medical codes.

The assessment of the comorbidities comprised by the Charlson comorbidity index, history of stroke/transient ischaemic attack, myocardial infarction, heart failure, hypertension, hypercholesterolemia, osteoporosis, infertility and loss of appetite was based on hospital discharge and GP diagnoses. For the definition of atrial fibrillation, in-hospital procedures, hospital discharge diagnoses and GP diagnosis were used. Use of lipid lowering drugs, antihypertensive medication, positive inotropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, drugs affecting the renin-angiotensin system, nitrates, calcium-channel blockers, other antianginal drugs or antiplatelet drugs were identified using GP prescription data. Anticoagulant use, diabetes and sexual dysfunction were defined based on hospital discharge diagnoses, GP diagnoses and GP prescriptions. Hot flushes and the group of symptoms comprising tiredness, lethargy and depression were identified from GP diagnoses, and information on smoking status and BMI were obtained from the CPRD additional data.

9.6 Bias

Data on inpatient drug use and hospital discharge medication and anticoagulation clinic prescriptions are very limited or not available in CPRD. Thus, this information has been missed.

Furthermore, information on the indication for testosterone treatment was not available if not coded as a diagnosis in hospital or by the GP.

9.7 Study size

All available data within the study period were evaluated.

9.8 Data transformation

The study data were collected by CPRD. Data retrieval and preparation of data for online access by the principal investigator (PI) was done by CPRD. The validity of the data and the quality of the data management is the responsibility of CPRD.

9.9 Statistical methods

9.9.1 Main summary measures

Continuous variables were summarized as means and standard deviations (SD), and categorical variables as counts and percentages.

9.9.2 Main statistical methods

Descriptive statistics of the demographic and baseline clinical characteristics on the index day were presented for cases and their matched controls. This included lifestyle factors, proportion with functional and pathological hypogonadism, comorbidities, cardiovascular risk factors and use of comedications including testosterone prescriptions details.

Crude and adjusted odds ratios (OR) with 95% confidence intervals of the association between cardiovascular risk factors and initiation of testosterone therapy were estimated using conditional logistic regression for matched case-control data. Adjusted ORs were derived from the model including the cardiovascular risk factors listed in ‘9.4.2 Exposure’ as potential predictors of testosterone initiation and all variables listed in ‘9.4.1 Baseline characteristics’ as potential confounders. Analyses were stratified by history of pathological hypogonadism.

All statistical procedures were performed using the Stata MP Version 14.2 (StataCorp LP).

The study protocol was approved by the Independent Scientific Advisory Committee for CPRD research (Protocol number 17_210R).

9.9.3 Missing values

Missing data for exposures/covariates occurred when an existing co-morbidity or co-medication was not recorded in the database. Whenever meaningful, missing data was allocated to the category "unknown" (e.g. for BMI and IMD).

9.9.4 Sensitivity analyses

A sensitivity analysis was conducted assessing the relationship between cardiovascular risk factors and initiation of testosterone therapy separately for the two time periods 2001 to 2014 and 2015 to 2017 as the testosterone prescribing behaviour might have been influenced by the publication of the FDA warning letter in 2015.

9.9.5 Amendments to the statistical analysis plan

N/A

9.10 Quality control

See Protocol Section 9.8.

10. Results

10.1 Participants

The source population of all male patients in the CPRD linked to the HES database consisted of 3,257,684 individuals. Of those 1,206,756 were excluded because of age less than 18, less than 2 years of history in the CPRD/HES or use of testosterone before the start of observation. Of the remaining 2,050,928 patients, 4,631 patients with first testosterone use were identified, 1,643 testosterone users with pathological hypogonadism, and 2,988 testosterone users without a recording for pathological hypogonadism and hereby defined as functional hypogonadism. All matching criteria including history of hypogonadism were applied and 8,207 controls were selected at random for those 1,643 testosterone users with pathological hypogonadism and respective 14,940 matches for those 2,988 without pathological hypogonadism, figure 1.

10.2 Descriptive data

Transdermal gel was the most frequently route of administration of all first testosterone prescriptions (55.4%), compared with intramuscular in 25.3% (28.8% in those with pathological hypogonadism and in 23.4% in those with functional hypogonadism, i.e. without a recording for pathological hypogonadism), transdermal patch with 10.4%, and oral with 6.6% (5.2% in pathological and 7.4% in functional hypogonadism), table 1.

As a result of the matching, testosterone users and their matched controls were identical in their age distribution (mean age 55.7±13.5 years) and history of pathological or functional hypogonadism. For patients treated with testosterone in the entire study population, mean BMI was slightly higher (29.9 vs. 28.1) and the proportion of current smokers was lower (14.5% vs. 21.7%) compared with

their matched controls. The prevalence of cardiovascular risk factors was significantly greater in testosterone users with diabetes (22.5% vs. 14.8%), hypercholesterolemia (22.1% vs. 18.7%) and hypertension (12.1% vs. 9.6%), table 2.

The higher prevalence of cardiovascular risk factors in patients initially given testosterone compared with their respective controls was also seen in the strata with and without pathological hypogonadism.

Among patients without pathological hypogonadism, those treated with testosterone had a significantly higher prevalence of symptoms indicative of functional hypogonadism (e.g. sexual dysfunction was 3-fold higher compared to their matched controls), table 2. This pattern was also observed in the respective subgroup of patients with pathological hypogonadism, although with a weaker association.

A history of malignancy was more frequent in testosterone users with 11.5% (531 of 4631) compared with 8.7% (2012 of 23,147) in their respective controls. Of the 531 testosterone users with a malignancy 3.2% (148 of 4631) had a malignancy of the testis or of the pituitary gland. compared with 2.4% (561 of 23,147) among controls, table 3. The 148 patients "Malignancy included in definition of pathological hypogonadism" include 21 testosterone users with a history of a malignancy other than of the testis or pituitary gland. The most frequent malignant cancers other than pathological hypogonadism associated cancers among testosterone users were prostate cancer with 2.6% (119 of 4,631), non-Hodgkin lymphoma with 1.3% (61 of 4,631) and colorectal cancer with 2.6% (42 of 4631), table 3.

Of the 1,643 testosterone users with pathological hypogonadism 1,022 (62.2%) had a pathology associated with primary hypogonadism and 621 (37.8%) with secondary hypogonadism. Controls were matched on pathologies associated with pathological hypogonadism, but not on primary or secondary hypogonadism. As a result, 95.8% of the controls matched on pathological hypogonadism had a pathology associated with primary hypogonadism and only 4.2% with secondary hypogonadism, table 4.

In the entire study population, the following medications investigated were more frequently prescribed among testosterone users compared to patients not treated with testosterone: antiplatelets, antiarrhythmics for ventricular arrhythmias, alpha-adrenoceptor blocking drugs, angiotensin-ii receptor antagonists, lipid lowering drugs, loop diuretics, potassium-sparing diuretics and aldosterone antagonists, and vasodilator antihypertensive drugs, table 5.

10.3 Outcome data

See section 10.1 for number of cases and controls.

10.4 Main results

The following cardiovascular risk factors were associated with a significantly increased probability for initiation of testosterone treatment: high BMI (adjusted odds ratio [OR] 1.39, 95% confidence interval [CI] 1.26-1.53 for BMI 25 to <30; OR 1.73, 95% CI 1.56-1.92 for BMI 30 to <35; OR 2.36,

95% CI 2.09-2.67 for BMI ≥35), diabetes (OR 1.41, 95% CI 1.29-1.55), hypertension in the past year (OR 1.28, 95% CI 1.14-1.43), hypercholesterolemia (OR 1.12, 95% CI 1.02-1.23), ex smoking (OR 1.09, 95% CI 1.01-1.17), history of use of vasodilator antihypertensive drugs (OR 2.65, 95% CI 2.29-3.07), angiotensin-II receptor antagonists (OR 1.26, 95% CI 1.12-1.41), lipid lowering drugs (OR 1.25, 95% CI 1.12-1.38), loop diuretics (OR 1.19, 95% CI 1.04-1.36), anti-arrhythmic drugs for ventricular arrhythmias (OR 1.18, 95% CI 1.06-1.31), and alpha-adrenoceptor blocking drugs (OR 1.13, 95% CI 1.02-1.25). Predictors associated with a decreased probability of testosterone treatment initiation were current smoking (OR 0.68, 95% CI 0.62-0.75), history of use of angiotensin-converting enzyme inhibitors (OR 0.77, 95% CI 0.70-0.85) and thiazides and related diuretics (OR 0.88, 95% CI 0.80-0.98), table 5.

Among patients with a history of pathological hypogonadism, the following factors were associated with an increased probability of initiation of testosterone treatment: high BMI (OR 1.34, 95% CI 1.13-1.60 for BMI 25 to <30; 1.55, 95% CI 1.27-1.90 for BMI 30 to<35; OR 2.18, 95% CI 1.73-2.74 for BMI ≥35), diabetes (OR 1.35, 95% CI 1.13-1.62), ex smoking (OR 1.17, 95% CI 1.01-1.36), history of use of vasodilator antihypertensive drugs (OR 2.38, 95% CI 1.74-3.26), peripheral vasodilators and related drugs (OR 2.24, 95% CI 1.24-4.06), loop diuretics (OR 1.52, 95% CI 1.18-1.95), and angiotensin-II receptor antagonists (OR 1.32, 95% CI 1.05-1.66). In line with the findings for the entire cohort, current smoking was associated with a decreased probability of testosterone use (OR 0.71, 95% CI 0.59-0.84), table 6.

As the group of patients without pathological hypogonadism formed the major part of the entire cohort, the subgroup analysis in these patients yielded similar results as in the entire cohort described above. Furthermore, potassium-sparing diuretics and aldosterone antagonists (OR 1.45, 95% CI 1.05-1.98) was a predictor for testosterone treatment initiation and myocardial infarction was associated with a decreased probability of testosterone use (OR 0.77, 95% CI 0.61-0.96). Hypercholesterolemia and use of loop diuretics were no longer statistically significant predictors for testosterone treatment initiation, table 7.

The stratification by time period (years 2001 to 2014 vs. 2015 to 2017) showed no substantial differences, tables 8 and 9.

10.5 Other analyses

N/A

10.6 Safety data (Adverse events/adverse reactions)

N/A as no clinical outcomes during or after use of testosterone were studied.

11. Discussion

11.1 Key results

High BMI, diabetes, hypertension and use of lipid lowering drugs, vasodilator antihypertensive drugs and angiotensin-II receptor antagonists were associated with an increased probability of testosterone treatment initiation, while current smoking and use of angiotensin-converting enzyme inhibitors were associated with a decreased probability of initiating testosterone treatment.

11.2 Limitations

As in all observational studies unmeasured confounding or hidden bias might exist.

Data on inpatient drug use and hospital discharge medication are very limited or not available in CPRD. Thus, information on in-hospital testosterone use could be missed. If testosterone was given in the in-hospital setting only and not recorded by the GP, then some controls may have a history of testosterone use or be current testosterone users on their index day (day of the testosterone treatment initiation of the respective case) and thus would bias the odds ratio estimate towards the 1.

Diagnosis of an existing cardiovascular risk factor (e.g. asymptomatic AF) may be more likely in patients with a condition leading to initiation of testosterone use than in patients without these conditions. This would lead to an overestimation of the respective odds ratio estimates. To reduce this problem, we have matched on GP visit to assure contact with the GP in matched controls ±30 days to the index day of the respective case.

Information on testosterone levels is hardly available in CPRD. Therefore, adjustment for testosterone levels was not feasible with this database. If low testosterone levels were associated with cardiovascular risk factors (e.g. obesity) as well as with the initiation of testosterone use, then ORs for the association between testosterone initiation and cardiovascular risk factors would be higher compared to what they would be in the presence of adjustment for testosterone levels. To address this issue, we stratified odds ratio estimates by history of pathological hypogonadism.

Furthermore, information on the indication for testosterone treatment was only available if recorded by the GP or as a hospital discharge diagnosis. Study results could be confounded if the recording of the indication for testosterone use (e.g. hypogonadism) was differential among cases and controls.

Patients without pathological hypogonadism who initiated testosterone treatment are likely to have functional hypogonadism. Among patients without pathological hypogonadism, we found a significant association between testosterone initiation and the cardiovascular risk factors (such as diabetes and treated hypertension). Furthermore, patients without pathological hypogonadism and treated with testosterone had a significantly higher prevalence of symptoms indicative of functional hypogonadism (such as infertility, osteoporosis, sexual dysfunction, tiredness/lethargy/depression, hot flushes or loss of appetite) compared to their matched controls without testosterone. This either indicates that there is a direct association between cardiovascular risk factors and testosterone use in this group, or that there is an association between cardiovascular risk factors and functional hypogonadism leading to testosterone treatment. Nevertheless, our study indicates that the prevalence of cardiovascular risk factors among testosterone users is higher than in an age-matched population.

The subgroup of patients with pathological hypogonadism consisted of 1,643 of 4,631 testosterone users (35.5%) and therefore had less study power. In the stratum with pathological hypogonadism, testosterone use was also associated with diabetes, and antihypertensive treatment with loop diuretics and vasodilator antihypertensive drugs. This finding supports the selection of patients with pathological hypogonadism and with increased BMI, diabetes and/or hypertension to be preferentially given testosterone. However, as the proportion of patients with secondary hypogonadism was greater in testosterone users compared with their matched controls (37.8% vs. 4.2%) our findings may question if secondary hypogonadism is associated with diabetes or hypertension.

11.3 Interpretation

Our findings support the hypothesis that testosterone is preferentially given to patients with increased BMI, prevalent diabetes and antihypertensive treatment in patients with and without pathological hypogonadism. This apparent association could be confounded by a strong association between the predictors for testosterone use, i.e. BMI, diabetes and antihypertensive treatment and functional hypogonadism.

The fact that BMI, diabetes and treatment of hypertension with defined antihypertensive drugs were also found to be associated with testosterone among those with pathological hypogonadism supports that testosterone is preferentially given to patients at higher baseline risk of cardiovascular diseases. Patients with a history of cancer were also preferentially prescribed testosterone.

11.4 Generalizability

The study population is representative of male patients aged 18 years or older in the UK. With the limitations noted above, the study results are considered to be generalizable as to the use of testosterone among male patients aged 18 years or older.

12. Other information

Patients with a history of cancer with and without a history of pathological hypogonadism were preferentially prescribed testosterone. However, cancer was a predefined exposure of interest. An exploratory analysis showed an OR (95%-CI) of 1.44 (1.27-1.63) for the association between history of malignant cancer and testosterone use and an OR of 1.34 (0.99-1.82) for the association between history of metastatic cancer and testosterone use. Note, cancer diagnoses were recorded before the initiation of testosterone use. The most frequent cancer was prostate cancer with 22.3% of all cancers in testosterone users.

13. Conclusion

Our data indicate that testosterone is preferentially prescribed to patients at an increased baseline risk of acute cardiovascular outcomes and cancer-related mortality. Observational studies on cardiovascular outcomes including mortality may be prone to confounding by indication bias and to selection bias as patients with functional and pathological hypogonadism treated with testosterone have a higher baseline risk for cardiovascular diseases and cancer-related mortality than age matched controls.

14. References

1. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, et al. Adverse events associated with testosterone administration. The New England journal of medicine. 2010;363(2):109-22.
2. Vigen R, O'Donnell CI, Baron AE, Grunwald GK, Maddox TM, Bradley SM, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. Jama. 2013;310(17):1829-36.
3. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PloS one. 2014;9(1):e85805.
4. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC medicine. 2013;11:108.
5. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. The Journal of clinical endocrinology and metabolism. 1999;84(6):1966-72.
6. Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. The Journal of clinical endocrinology and metabolism. 2004;89(2):503-10.
7. Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, et al. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. Jama. 2015;314(6):570-81.
8. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. The Journal of clinical endocrinology and metabolism. 2012;97(6):2050-8.
9. Sharma R, Oni OA, Gupta K, Chen G, Sharma M, Dawn B, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. European heart journal. 2015;36(40):2706-15.
10. Anderson JL, May HT, Lappe DL, Bair T, Le V, Carlquist JF, et al. Impact of Testosterone Replacement Therapy on Myocardial Infarction, Stroke, and Death in Men With Low Testosterone Concentrations in an Integrated Health Care System. The American journal of cardiology. 2016;117(5):794-9.
11. Tan RS, Cook KR, Reilly WG. Myocardial Infarction and Stroke Risk in Young Healthy Men Treated with Injectable Testosterone. Int J Endocrinol. 2015;2015:970750.
12. Hackett G, Heald AH, Sinclair A, Jones PW, Strange RC, Ramachandran S. Serum testosterone, testosterone replacement therapy and all-cause mortality in men with type 2 diabetes: retrospective consideration of the impact of PDE5 inhibitors and statins. International journal of clinical practice. 2016;70(3):244-53.
13. No consistent evidence of an increased risk of heart problems with testosterone medicines [press release]. European Medicines Agency,21 November 2014.
14. Hackett G, Kirby M, Edwards D, Jones TH, Wylie K, Ossei-Gerning N, et al. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. The journal of sexual medicine. 2017;14(12):1504-23.

15. Grossmann M, Matsumoto AM. A Perspective on Middle-Aged and Older Men With Functional Hypogonadism: Focus on Holistic Management. The Journal of clinical endocrinology and metabolism. 2017;102(3):1067-75.
16. Saboor Aftab SA, Kumar S, Barber TM. The role of obesity and type 2 diabetes mellitus in the development of male obesity-associated secondary hypogonadism. Clinical endocrinology. 2013;78(3):330-7.

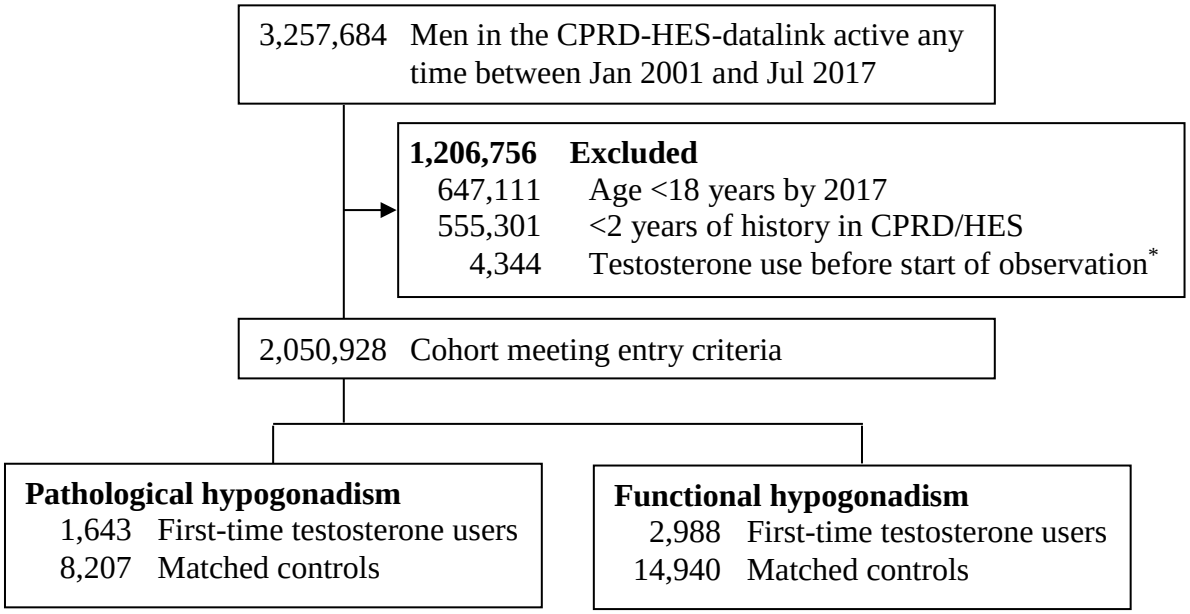
Appendices

Annex 1: List of stand-alone documents

There are no stand-alone documents.

Annex 2 Additional information

Figure 1: Ascertainment of new use of testosterone, Jan 2001 to Jul 2017



*2 years after start date in CPRD/HES, 1 Jan 2001 or age of 18 , whichever occurred last.

Controls were matched on age, type of hypogonadism (i.e. pathological or functional) and GP consultation ±30 days of the index day of the respective case

Table 1: Specification of first testosterone use

Treatment information	Testosterone users		
	All patients n (%)*	**Pathological hypogonadism, n (%)***	**Functional hypogonadism, n (%)***
Total	4631	1643	2988
Route of administration			
Oral	307 (6.6)	85 (5.2)	222 (7.4)
Substance			
Methyltestosterone combinations	5 (1.6)	0 (0.0)	5 (2.3)
Testosterone undecanoate	302 (98.4)	85 (100.0)	217 (97.7)
Strength			
10mg	<5	0 (0.0)	<5
40mg	302 (98.4)	85 (100.0)	217 (97.7)
5mg	<5	0 (0.0)	<5
Quantity [Capsules]			
<30	38 (12.3)	12 (14.0)	26 (11.7)
≥30 to <60	98 (31.8)	24 (27.9)	74 (33.3)
≥60 to <90	85 (27.6)	27 (31.4)	58 (26.1)
≥90	87 (28.2)	23 (26.7)	64 (28.8)
Buccal	18 (0.4)	6 (0.4)	12 (0.4)
Substance			
Testosterone	18 (100.0)	6 (100.0)	12 (100.0)
Strength			
30mg	18 (100.0)	6 (100.0)	12 (100.0)
Quantity [Tablets]			
60	15 (83.3)	6 (100.0)	9 (75.0)
Other	<5	0 (0.0)	<5
Intramuscular	1171 (25.3)	473 (28.8)	698 (23.4)
Substance			
Testosterone decanoate/isocaproate/phenylpropionate/propionate	686 (58.6)	256 (54.1)	430 (61.6)
Testosterone enantate	62 (5.3)	26 (5.5)	36 (5.2)
Testosterone propionate	6 (0.5)	<5	<5

Treatment information	Testosterone users		
	All patients n (%)*	**Pathological hypogonadism, n (%)***	**Functional hypogonadism, n (%)***
Testosterone undecanoate	364 (31.1)	177 (37.4)	187 (26.8)
Unknown	59 (5.0)	14 (3.0)	45 (6.4)
Strength			
100+60+60+30mg/ml	509 (43.5)	185 (39.1)	324 (46.4)
100mg/ml	15 (1.3)	<5	11 (1.6)
250mg/ml	468 (40.0)	216 (45.7)	252 (36.1)
40+40+20mg/ml	122 (10.4)	56 (11.8)	66 (9.5)
50mg/ml	6 (0.5)	<5	<5
Unknown	59 (5.0)	14 (3.0)	45 (6.4)
Quantity [Injections]			
1	576 (49.1)	243 (51.3)	333 (47.7)
2	70 (6.0)	31 (6.5)	39 (5.6)
3	164 (14.0)	58 (12.2)	106 (15.2)
4	57 (4.9)	21 (4.4)	36 (5.2)
5	44 (3.8)	20 (4.2)	24 (3.4)
6	181 (15.4)	76 (16.0)	105 (15.0)
7+	19 (1.6)	10 (2.1)	9 (1.3)
Unknown	61 (5.2)	15 (3.2)	46 (6.6)
Subcutaneous	98 (2.1)	21 (1.3)	77 (2.6)
Substance			
Testosterone	98 (100.0)	21 (100.0)	77 (100.0)
Strength			
100mg	<5	<5	<5
200mg	15 (15.3)	6 (28.6)	9 (11.7)
Unknown	79 (80.6)	13 (61.9)	66 (85.7)
Quantity [Implants]			
3	10 (10.2)	<5	6 (7.8)
Other	9 (9.2)	<5	5 (6.5)
Unknown	79 (80.6)	13 (61.9)	66 (85.7)
Transdermal (Gel)	2566 (55.4)	917 (55.8)	1649 (55.2)

Treatment information	Testosterone users		
	All patients n (%)*	**Pathological hypogonadism, n (%)***	**Functional hypogonadism, n (%)***
Substance			
Testosterone	2566 (100.0)	917 (100.0)	1649 (100.0)
Strength			
20mg/g	511 (19.9)	195 (21.3)	316 (19.2)
50mg/5g	2055 (80.1)	722 (78.7)	1333 (80.8)
Quantity [Sachets/Tubes]			
<30	232 (9.0)	89 (9.7)	143 (8.7)
≥30 to <60	1737 (67.7)	587 (64.0)	1150 (69.7)
≥60 to <90	505 (19.7)	208 (22.7)	297 (18.0)
≥90	92 (3.6)	33 (3.6)	59 (3.6)
Transdermal (Patch)	483 (10.4)	147 (8.9)	336 (11.2)
Substance			
Testosterone	483 (100.0)	147 (100.0)	336 (100.0)
Strength			
0.3mg/24hour	18 (3.7)	5 (3.4)	13 (3.9)
2.5mg/24hour	235 (48.7)	78 (53.1)	157 (46.7)
5mg/24hour	227 (47.0)	63 (42.9)	164 (48.8)
6mg/24hour	<5	<5	<5
Quantity [Patches]			
<30	52 (10.8)	19 (12.9)	33 (9.8)
≥30 to <60	255 (52.8)	67 (45.6)	188 (56.0)
≥60 to <90	171 (35.4)	58 (39.5)	113 (33.6)
≥90	5 (1.0)	<5	<5

*More than one record per patient on index day possible.

Table 2: Baseline characteristics of cases and matched controls

	All patients		Pathological hypogonadism		Functional hypogonadism	
	Testosterone users	**Matched controls**	**Testosterone users**	**Matched controls**	**Testosterone users**	**Matched controls**
Total	4631	23147	1643	8207	2988	14940
Age						
Mean ± SD	55.7 ± 13.5	55.7 ± 13.5	53.9 ± 14.6	53.9 ± 14.6	56.7 ± 12.7	56.7 ± 12.7
<30	168 (3.6)	836 (3.6)	98 (6.0)	486 (6.0)	70 (2.3)	350 (2.3)
30-39	368 (7.9)	1839 (7.9)	174 (10.6)	869 (10.6)	194 (6.5)	970 (6.5)
40-49	904 (19.5)	4520 (19.5)	362 (22.0)	1810 (22.0)	542 (18.1)	2710 (18.1)
50-59	1272 (27.5)	6360 (27.5)	373 (22.7)	1865 (22.7)	899 (30.1)	4495 (30.1)
60-69	1252 (27.0)	6260 (27.0)	399 (24.3)	1995 (24.3)	853 (28.5)	4265 (28.5)
70-79	541 (11.7)	2705 (11.7)	189 (11.5)	945 (11.5)	352 (11.8)	1760 (11.8)
80+	126 (2.7)	627 (2.7)	48 (2.9)	237 (2.9)	78 (2.6)	390 (2.6)
BMI						
Known BMI	4251 (91.8)	20959 (90.5)	1478 (90.0)	7281 (88.7)	2773 (92.8)	13678 (91.6)
Mean BMI	29.9 ± 6.0	28.1 ± 5.3	29.7 ± 6.2	28.0 ± 5.4	29.9 ± 5.8	28.2 ± 5.2
Median (p25,p75)	29 (26,33)	27 (25,31)	29 (26,33)	27 (24,31)	29 (26,33)	28 (25,31)
<18.5	47 (1.1)	283 (1.4)	22 (1.5)	122 (1.7)	25 (0.9)	161 (1.2)
18.5 to <25	739 (17.4)	5566 (26.6)	278 (18.8)	2036 (28.0)	461 (16.6)	3530 (25.8)
25 to <30	1651 (38.8)	8579 (40.9)	572 (38.7)	2921 (40.1)	1079 (38.9)	5658 (41.4)
30 to <35	1105 (26.0)	4450 (21.2)	362 (24.5)	1502 (20.6)	743 (26.8)	2948 (21.6)
35+	709 (16.7)	2081 (9.9)	244 (16.5)	700 (9.6)	465 (16.8)	1381 (10.1)
Unknown BMI	380 (8.2)	2188 (9.5)	165 (10.0)	926 (11.3)	215 (7.2)	1262 (8.4)
Alcohol status						
Known	4106 (88.7)	20648 (89.2)	1434 (87.3)	7226 (88.0)	2672 (89.4)	13422 (89.8)
Never	573 (14.0)	2412 (11.7)	219 (15.3)	871 (12.0)	354 (13.2)	1541 (11.5)
Ex	180 (4.4)	685 (3.3)	64 (4.5)	261 (3.6)	116 (4.3)	424 (3.2)
Current	3353 (81.7)	17551 (85.0)	1151 (80.3)	6094 (84.4)	2202 (82.4)	11457 (85.4)
Smoking status						
Known	4513 (97.5)	22566 (97.5)	1588 (96.7)	7975 (97.1)	2925 (97.9)	14591 (97.7)
Never smoker	2132 (47.2)	10254 (45.4)	776 (48.9)	3564 (44.7)	1356 (46.4)	6690 (45.9)

	All patients		Pathological hypogonadism		Functional hypogonadism	
	Testosterone users	**Matched controls**	**Testosterone users**	**Matched controls**	**Testosterone users**	**Matched controls**
Ex-smoker	1728 (38.3)	7412 (32.8)	567 (35.7)	2502 (31.4)	1161 (39.7)	4910 (33.7)
Current smoker	653 (14.5)	4900 (21.7)	245 (15.4)	1909 (23.9)	408 (13.9)	2991 (20.5)
Socioeconomic status*						
Known	4626 (99.9)	23132 (99.9)	1642 (99.9)	8205 (100.0)	2984 (99.9)	14927 (99.9)
1 (least deprived)	1177 (25.4)	5540 (23.9)	410 (25.0)	1959 (23.9)	767 (25.7)	3581 (24.0)
2	1075 (23.2)	5053 (21.8)	395 (24.1)	1722 (21.0)	680 (22.8)	3331 (22.3)
3	930 (20.1)	4858 (21.0)	309 (18.8)	1727 (21.1)	621 (20.8)	3131 (21.0)
4	811 (17.5)	3970 (17.2)	289 (17.6)	1410 (17.2)	522 (17.5)	2560 (17.2)
5 (most deprived)	633 (13.7)	3711 (16.1)	239 (14.6)	1387 (16.9)	394 (13.2)	2324 (15.6)
Unknown	5 (0.1)	15 (0.1)	1 (0.1)	2 (0.0)	4 (0.1)	13 (0.1)
Charlson comorbidities						
Atrial fibrillation	235 (5.1)	1167 (5.0)	85 (5.2)	468 (5.7)	150 (5.0)	699 (4.7)
CHF/LVD	135 (2.9)	697 (3.0)	50 (3.0)	273 (3.3)	85 (2.8)	424 (2.8)
Diabetes	1042 (22.5)	3429 (14.8)	314 (19.1)	1139 (13.9)	728 (24.4)	2290 (15.3)
Hypercholesterolemia	1022 (22.1)	4325 (18.7)	347 (21.1)	1504 (18.3)	675 (22.6)	2821 (18.9)
Hypertension	561 (12.1)	2220 (9.6)	227 (13.8)	827 (10.0)	334 (11.2)	1393 (9.3)
Ischaemic heart disease	516 (11.1)	2626 (11.3)	170 (10.3)	974 (11.9)	346 (11.6)	1652 (11.0)
Myocardial infarction	251 (5.4)	1419 (6.1)	86 (5.2)	493 (6.0)	165 (5.5)	926 (6.2)
Stroke/TIA	223 (4.8)	1141 (4.9)	86 (5.2)	393 (4.8)	137 (4.6)	748 (5.0)
AIDS/HIV	14 (0.3)	35 (0.2)	4 (0.2)	17 (0.2)	10 (0.3)	18 (0.1)
Cerebrovascular disease	218 (4.7)	1045 (4.5)	83 (5.1)	335 (4.1)	135 (4.5)	710 (4.8)
Chronic pulmonary disease	1004 (21.7)	5178 (22.4)	377 (22.9)	2040 (24.9)	627 (21.0)	3138 (21.0)
Dementia	16 (0.3)	85 (0.4)	5 (0.3)	32 (0.4)	11 (0.4)	53 (0.4)
Hemiplegia/Paraplegia	67 (1.4)	259 (1.1)	25 (1.5)	132 (1.6)	42 (1.4)	127 (0.8)
Malignancies not associated with definition of pathological hypogonadism**	404 (8.7)	1510 (6.5)	145 (8.8)	647 (7.9)	259 (8.7)	863 (5.8)
Malignancies associated with definition of pathological hypogonadism**	148 (3.2)	561 (2.4)	148 (9.0)	561 (6.8)	0 (0.0)	0 (0.0)

	All patients		Pathological hypogonadism		Functional hypogonadism	
	Testosterone users	**Matched controls**	**Testosterone users**	**Matched controls**	**Testosterone users**	**Matched controls**
Metastatic solid tumour**	53 (1.1)	205 (0.9)	31 (1.9)	121 (1.5)	22 (0.7)	84 (0.6)
Mild liver disease	87 (1.9)	395 (1.7)	34 (2.1)	204 (2.5)	53 (1.8)	191 (1.3)
Moderate/severe liver disease	22 (0.5)	83 (0.4)	6 (0.4)	38 (0.5)	16 (0.5)	45 (0.3)
Peptic ulcer disease	276 (6.0)	1235 (5.3)	103 (6.3)	504 (6.1)	173 (5.8)	731 (4.9)
Renal disease	320 (6.9)	1502 (6.5)	125 (7.6)	566 (6.9)	195 (6.5)	936 (6.3)
Rheumatic disease	134 (2.9)	557 (2.4)	53 (3.2)	229 (2.8)	81 (2.7)	328 (2.2)
Indications for testosterone use						
Infertility	177 (3.8)	485 (2.1)	94 (5.7)	260 (3.2)	83 (2.8)	225 (1.5)
Osteoporosis	175 (3.8)	320 (1.4)	89 (5.4)	130 (1.6)	86 (2.9)	190 (1.3)
Sexual dysfunction	2669 (57.6)	4954 (21.4)	704 (42.8)	1814 (22.1)	1965 (65.8)	3140 (21.0)
Tiredness/lethargy/depression	1418 (30.6)	4734 (20.4)	475 (28.9)	1728 (21.1)	943 (31.6)	3006 (20.1)
Hot flushes	103 (2.2)	76 (0.3)	36 (2.2)	28 (0.4)	67 (2.2)	48 (0.3)
Loss of appetite	15 (0.3)	40 (0.2)	7 (0.4)	21 (0.2)	8 (0.3)	19 (0.1)

BMI: body mass index; CHF: congestive heart failure; LVD: left ventricular dysfunction; p25: lower quartile; p75: upper quartile; SD: Standard deviation; TIA: transient ischaemic attack.

* Derived from the UK Index of Multiple Deprivation (IMD).
** See table 3 for further details.

Table 3: History of cancer in patients with initial testosterone use

Cancer type	All patients n (%)*		Pathological hypogonadism n (%)*		Functional hypogonadism n (%)*	
	Testosterone users	Matched controls	Testosterone users	Matched controls	Testosterone users	Matched controls
Total	**4631**	**23147**	**1643**	**8207**	**2988**	**14940**
Malignancy included in definition of pathological hypogonadism	**148 (3.2)**	**561 (2.4)**	**148 (9.0)**	**561 (6.8)**	**0 (0.0)**	**0 (0.0)**
Testis	141 (3.0)	553 (2.4)	141 (8.6)	553 (6.8)	0 (0.0)	0 (0.0)
Pituitary gland and craniopharyngeal duct	7 (0.2)	8 (0.0)	7 (0.4)	8 (0.1)	0 (0.0)	0 (0.0)
Malignancy other	**404 (8.7)**	**1510 (6.5)**	**145 (8.8)**	**647 (7.9)**	**259 (8.7)**	**863 (5.8)**
Prostate	119 (2.6)	507 (2.2)	12 (0.7)	243 (3.0)	107 (3.6)	264 (1.8)
Non-Hodgkin lymphoma	61 (1.3)	94 (0.4)	33 (2.0)	38 (0.5)	28 (0.9)	56 (0.4)
Colorectum	42 (0.9)	207 (0.9)	13 (0.8)	68 (0.9)	29 (1.0)	139 (0.9)
Bladder	31 (0.7)	185 (0.8)	7 (0.4)	88 (1.1)	24 (0.8)	97 (0.6)
Leukaemia	26 (0.6)	60 (0.3)	15 (0.9)	26 (0.3)	11 (0.4)	34 (0.2)
Brain and other parts of CNS	25 (0.5)	45 (0.2)	14 (0.9)	17 (0.2)	11 (0.4)	28 (0.2)
Myeloma	20 (0.4)	23 (0.1)	8 (0.5)	10 (0.1)	12 (0.4)	13 (0.1)
Head and neck	19 (0.4)	106 (0.5)	7 (0.4)	48 (0.6)	12 (0.4)	58 (0.4)
Trachea, bronchus and lung	18 (0.4)	59 (0.3)	7 (0.4)	27 (0.3)	11 (0.4)	32 (0.2)
Malignant melanoma	17 (0.4)	85 (0.4)	8 (0.5)	25 (0.3)	9 (0.3)	60 (0.4)
Hodgkin disease	16 (0.3)	22 (0.1)	<5	7 (0.1)	12 (0.4)	15 (0.1)
Kidney	16 (0.3)	60 (0.3)	5 (0.3)	27 (0.3)	11 (0.4)	33 (0.2)
Other endocrine glands and related structures	14 (0.3)	23 (0.1)	9 (0.5)	11 (0.1)	5 (0.2)	12 (0.1)
Other and unspecific site	50 (1.1)	226 (1.0)	25 (1.5)	113 (1.4)	25 (0.8)	113 (0.8)
Metastatic solid tumour	**53 (1.1)**	**205 (0.9)**	**31 (1.9)**	**121 (1.5)**	**22 (0.7)**	**84 (0.6)**
Secondary and unspecified malignant neoplasm of lymph nodes	34 (0.7)	121 (0.5)	23 (1.4)	67 (0.8)	11 (0.4)	54 (0.4)
Secondary malignant neoplasm of respiratory and digestive organs	19 (0.4)	62 (0.3)	11 (0.7)	38 (0.5)	8 (0.3)	24 (0.2)
Secondary malignant neoplasm of other and unspecified sites	16 (0.3)	32 (0.2)	7 (0.4)	22 (0.3)	9 (0.3)	10 (0.1)
Malignant neoplasm without specification of site	<5	16 (0.1)	<5	11 (0.1)	<5	5 (0.0)

*More than one record per patient with history on index day possible.

Table 4: Breakdown of type of pathological hypogonadism

Type of pathological hypogonadism	Testosterone users n (%)[1]	Matched controls n (%)[1]
Total	**1643**	**8207**
Primary hypogonadism	**1022 (62.2)**	**7864 (95.8)**
Klinefelter's syndrome	70 (4.3)	61 (0.7)
Neoplasm - Testis – Malignant	145 (8.8)	606 (7.4)
Extirpation of scrotum/testes	143 (8.7)	2121 (25.9)
Orchitis and epididymitis	92 (5.6)	4127 (50.3)
Undescended and ectopic testicle	34 (2.1)	337 (4.1)
Placement of testes in scrotum	<5	28 (0.4)
Disorders of iron metabolism	24 (1.5)	327 (4.0)
Atrophy of testis	6 (0.4)	147 (1.8)
Testicular dysfunction	507 (30.9)	110 (1.3)
Secondary	**621 (37.8)**	**343 (4.2)**
Neoplasm - Hypophysis[2] – Benign	285 (17.3)	159 (1.9)
Neoplasm - Hypophysis[2] – Malignant	<5	<5
Neoplasm - Hypophysis[2] - Uncertain behaviour	13 (0.8)	11 (0.1)
Postablative testicular hypofunction	10 (0.6)	<5
Hyperfunction of pituitary gland	10 (0.6)	22 (0.2)
Hypofunction, other disorders and operations on pituitary gland	302 (18.4)	145 (1.8)

[1]: Applying the following hierarchy for patients with multiple recordings for subgroups of pathological hypogonadism: (1) Klinefelter's syndrome, (2) Neoplasm - Hypophysis - Benign, (3) Neoplasm - Hypophysis - Malignant, (4) Neoplasm - Hypophysis - Uncertain behavior, (5) Neoplasm - Testis - Malignant, (6) Extirpation of scrotum/testes, (7) Postablative testicular hypofunction, (8) Hyperfunction of pituitary gland, (9) Hypofunction, other disorders and operations on pituitary gland, (10) Orchitis and epididymitis, (11) Undescended and ectopic testicle, (12) Placement of testes in scrotum, (13) Disorders of iron metabolism, (14) Atrophy of testis, (15) Testicular dysfunction.
[2]: Including pituitary gland and craniopharyngeal duct.

Table 5: Predictors for testosterone initiation, entire cohort

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Total	4631	23147		
BMI				
<18.5	47 (1.01)	283 (1.22)	1.18 (0.86 - 1.63)	1.21 (0.87 - 1.68)
18.5 to <25	739 (15.96)	5566 (24.05)	1	1
25 to <30	1651 (35.65)	8579 (37.06)	1.47 (1.34 - 1.62)	1.39 (1.26 - 1.53)
30 to <35	1105 (23.86)	4450 (19.22)	1.90 (1.72 - 2.11)	1.73 (1.56 - 1.92)
35+	709 (15.31)	2081 (8.99)	2.62 (2.33 - 2.94)	2.36 (2.09 - 2.67)
Missing	380 (8.21)	2188 (9.45)	1.27 (1.11 - 1.46)	1.25 (1.09 - 1.44)
Smoking status				
Never	2132 (46.04)	10254 (44.30)	1	1
Current	653 (14.10)	4900 (21.17)	0.63 (0.58 - 0.70)	0.68 (0.62 - 0.75)
Ex	1728 (37.31)	7412 (32.02)	1.14 (1.06 - 1.23)	1.09 (1.01 - 1.17)
Missing	118 (2.55)	581 (2.51)	0.95 (0.77 - 1.17)	1.01 (0.80 - 1.26)
History of other cardiovascular risk factors				
Stroke/TIA	223 (4.82)	1141 (4.93)	0.97 (0.84 - 1.13)	0.95 (0.81 - 1.11)
Atrial fibrillation	235 (5.07)	1167 (5.04)	1.01 (0.87 - 1.17)	0.97 (0.80 - 1.19)
Ischemic heart disease	516 (11.14)	2626 (11.34)	0.98 (0.88 - 1.09)	0.94 (0.80 - 1.11)
Myocardial infarction	251 (5.42)	1419 (6.13)	0.87 (0.76 - 1.01)	0.85 (0.71 - 1.02)
CHF/LVD	135 (2.92)	697 (3.01)	0.97 (0.80 - 1.17)	0.86 (0.68 - 1.07)
Hypertension	561 (12.11)	2220 (9.59)	1.31 (1.19 - 1.45)	1.28 (1.14 - 1.43)
Diabetes	1042 (22.50)	3429 (14.81)	1.70 (1.57 - 1.85)	1.41 (1.29 - 1.55)
Hypercholesterolemia	1022 (22.07)	4325 (18.68)	1.25 (1.16 - 1.36)	1.12 (1.02 - 1.23)
Lipid lowering drugs	736 (15.89)	2874 (12.42)	1.36 (1.24 - 1.48)	1.25 (1.12 - 1.38)
Anticoagulants	304 (6.56)	1495 (6.46)	1.02 (0.89 - 1.16)	0.95 (0.81 - 1.12)
Antiplatelets	967 (20.88)	4425 (19.12)	1.14 (1.04 - 1.23)	1.01 (0.91 - 1.13)
Medication according to BNF				
2.1 Positive Inotropic Drugs				
2.1.1: Cardiac Glycosides	86 (1.86)	411 (1.78)	1.05 (0.83 - 1.33)	1.08 (0.81 - 1.46)
2.2 Diuretics				

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
2.2.1: Thiazides And Related Diuretics	848 (18.31)	4219 (18.23)	1.01 (0.92 - 1.10)	0.88 (0.80 - 0.98)
2.2.2: Loop Diuretics	460 (9.93)	1813 (7.83)	1.33 (1.19 - 1.49)	1.19 (1.04 - 1.36)
2.2.3: Potassium-sparing Diuretics And Aldosterone Antagonists	109 (2.35)	387 (1.67)	1.42 (1.15 - 1.76)	1.23 (0.95 - 1.58)
2.2.4: Potassium-sparing Diuretics With Other Diuretics	92 (1.99)	426 (1.84)	1.08 (0.86 - 1.36)	0.87 (0.68 - 1.12)
2.2.7: Carbonic Anhydrase Inhibitors	15 (0.32)	65 (0.28)	1.15 (0.66 - 2.02)	1.00 (0.56 - 1.78)
2.2.8: Diuretics With Potassium	0 (0.0)	7 (0.03)	-	-
2.3: Anti-arrhythmic Drugs				
2.3.2.1: Supraventricular & Ventricular Arrhythmias	88 (1.90)	463 (2.00)	0.95 (0.75 - 1.19)	0.92 (0.71 - 1.21)
2.3.2.2: Supraventricular Arrhythmias	<5	15 (0.06)	-	-
2.3.2.3: Ventricular Arrhythmias	500 (10.80)	1984 (8.57)	1.29 (1.17 - 1.44)	1.18 (1.06 - 1.31)
2.4: Beta-adrenoceptor Blocking Drugs	1364 (29.45)	6878 (29.71)	0.99 (0.92 - 1.06)	0.95 (0.87 - 1.03)
2.5: Hypertension And Heart Failure				
2.5.1: Vasodilator Antihypertensive Drugs	324 (7.00)	576 (2.49)	2.99 (2.60 - 3.45)	2.65 (2.29 - 3.07)
2.5.2: Centrally Acting Antihypertensive Drugs	36 (0.78)	131 (0.57)	1.38 (0.95 - 2.00)	1.05 (0.71 - 1.57)
2.5.4: Alpha-adrenoceptor Blocking Drugs	723 (15.61)	3019 (13.04)	1.26 (1.15 - 1.38)	1.13 (1.02 - 1.25)
2.5.5.1: Angiotensin-converting Enzyme Inhibitors	1481 (31.98)	7236 (31.26)	1.04 (0.97 - 1.12)	0.77 (0.70 - 0.85)
2.5.5.2: Angiotensin-ii Receptor Antagonists	565 (12.20)	2140 (9.25)	1.38 (1.25 - 1.53)	1.26 (1.12 - 1.41)
2.5.5.3: Renin Inhibitors	7 (0.15)	20 (0.09)	1.75 (0.74 - 4.14)	1.13 (0.45 - 2.84)
2.5.5.4: Angiotensin-ii Receptor Antagonists With Diuretic	30 (0.65)	133 (0.57)	1.13 (0.76 - 1.69)	0.91 (0.59 - 1.39)
2.6: Nitrates, calcium-channel blockers, and other antianginal drugs				
2.6.1: Nitrates	561 (12.11)	2876 (12.42)	0.97 (0.88 - 1.07)	0.92 (0.80 - 1.05)
2.6.2: Calcium-channel Blockers	1154 (24.92)	5609 (24.23)	1.04 (0.97 - 1.13)	0.92 (0.83 - 1.01)
2.6.3: Other Anti-anginal Drugs	100 (2.16)	440 (1.90)	1.14 (0.92 - 1.42)	1.06 (0.83 - 1.36)
2.6.4: Peripheral Vasodilators And Related Drugs	38 (0.82)	150 (0.65)	1.27 (0.89 - 1.82)	1.35 (0.93 - 1.95)

BMI: body mass index; CI: confidence interval; CHF: congestive heart failure; LVD: left ventricular dysfunction; OR: odds ratio.

*: Additionally adjusted for Charlson components and possible indications for testosterone use

Table 6: Predictors for testosterone initiation, cohort with pathological hypogonadism

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Total	1643	8207		
BMI				
<18.5	22 (1.34)	122 (1.49)	1.25 (0.77 - 2.02)	1.35 (0.80 - 2.31)
18.5 to <25	278 (16.92)	2036 (24.81)	1	1
25 to <30	572 (34.81)	2921 (35.59)	1.46 (1.25 - 1.70)	1.34 (1.13 - 1.60)
30 to <35	362 (22.03)	1502 (18.30)	1.80 (1.51 - 2.13)	1.55 (1.27 - 1.90)
35+	244 (14.85)	700 (8.53)	2.59 (2.14 - 3.15)	2.18 (1.73 - 2.74)
Missing	165 (10.04)	926 (11.28)	1.27 (1.02 - 1.56)	1.13 (0.88 - 1.45)
Smoking status				
Never	776 (47.23)	3564 (43.43)	1	1
Current	245 (14.91)	1909 (23.26)	0.58 (0.50 - 0.68)	0.71 (0.59 - 0.84)
Ex	567 (34.51)	2502 (30.49)	1.06 (0.94 - 1.20)	1.17 (1.01 - 1.36)
Missing	55 (3.35)	232 (2.83)	1.07 (0.77 - 1.48)	1.06 (0.72 - 1.58)
History of other cardiovascular risk factors				
Stroke/TIA	86 (5.23)	393 (4.79)	1.10 (0.86 - 1.40)	1.04 (0.77 - 1.41)
Atrial fibrillation	85 (5.17)	468 (5.70)	0.90 (0.70 - 1.14)	0.81 (0.56 - 1.18)
Ischemic heart disease	170 (10.35)	974 (11.87)	0.84 (0.71 - 1.01)	1.08 (0.79 - 1.47)
Myocardial infarction	86 (5.23)	493 (6.01)	0.86 (0.68 - 1.09)	0.75 (0.53 - 1.06)
CHF/LVD	50 (3.04)	273 (3.33)	0.91 (0.66 - 1.24)	0.92 (0.60 - 1.40)
Hypertension	227 (13.82)	827 (10.08)	1.46 (1.24 - 1.71)	1.14 (0.92 - 1.41)
Diabetes	314 (19.11)	1139 (13.88)	1.49 (1.29 - 1.71)	1.35 (1.13 - 1.62)
Hypercholesterolemia	347 (21.12)	1504 (18.33)	1.22 (1.06 - 1.40)	1.09 (0.91 - 1.32)
Lipid lowering drugs	223 (13.57)	1009 (12.29)	1.13 (0.96 - 1.33)	1.07 (0.86 - 1.32)
Anticoagulants	114 (6.94)	605 (7.37)	0.93 (0.76 - 1.15)	0.90 (0.68 - 1.20)
Antiplatelets	320 (19.48)	1568 (19.11)	1.03 (0.89 - 1.19)	1.08 (0.88 - 1.33)
Medication according to BNF				
2.1 Positive Inotropic Drugs				
2.1.1: Cardiac Glycosides	27 (1.64)	164 (2.00)	0.82 (0.54 - 1.24)	1.33 (0.74 - 2.40)
2.2 Diuretics				

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
2.2.1: Thiazides And Related Diuretics	291 (17.71)	1388 (16.91)	1.06 (0.92 - 1.23)	0.89 (0.72 - 1.09)
2.2.2: Loop Diuretics	176 (10.71)	671 (8.18)	1.38 (1.15 - 1.66)	1.52 (1.18 - 1.95)
2.2.3: Potassium-sparing Diuretics And Aldosterone Antagonists	33 (2.01)	168 (2.05)	0.98 (0.67 - 1.43)	0.73 (0.44 - 1.21)
2.2.4: Potassium-sparing Diuretics With Other Diuretics	31 (1.89)	164 (2.00)	0.94 (0.64 - 1.39)	0.64 (0.40 - 1.04)
2.2.7: Carbonic Anhydrase Inhibitors	7 (0.43)	32 (0.39)	1.09 (0.48 - 2.48)	0.96 (0.38 - 2.44)
2.2.8: Diuretics With Potassium				
2.3: Anti-arrhythmic Drugs				
2.3.2.1: Supraventricular & Ventricular Arrhythmias	27 (1.64)	165 (2.01)	0.81 (0.54 - 1.22)	0.96 (0.56 - 1.63)
2.3.2.2: Supraventricular Arrhythmias	<5	6 (0.07)	-	-
2.3.2.3: Ventricular Arrhythmias	166 (10.10)	744 (9.07)	1.13 (0.95 - 1.35)	1.06 (0.86 - 1.32)
2.4: Beta-adrenoceptor Blocking Drugs	459 (27.94)	2319 (28.26)	0.98 (0.87 - 1.11)	0.97 (0.82 - 1.14)
2.5: Hypertension And Heart Failure				
2.5.1: Vasodilator Antihypertensive Drugs	81 (4.93)	207 (2.52)	2.05 (1.57 - 2.67)	2.38 (1.74 - 3.26)
2.5.2: Centrally Acting Antihypertensive Drugs	9 (0.55)	55 (0.67)	0.82 (0.40 - 1.66)	0.65 (0.28 - 1.52)
2.5.4: Alpha-adrenoceptor Blocking Drugs	245 (14.91)	1148 (13.99)	1.09 (0.93 - 1.27)	1.08 (0.89 - 1.31)
2.5.5.1: Angiotensin-converting Enzyme Inhibitors	476 (28.97)	2334 (28.44)	1.03 (0.91 - 1.17)	0.85 (0.70 - 1.02)
2.5.5.2: Angiotensin-ii Receptor Antagonists	184 (11.20)	708 (8.63)	1.36 (1.14 - 1.63)	1.32 (1.05 - 1.66)
2.5.5.3: Renin Inhibitors	<5	7 (0.09)	-	-
2.5.5.4: Angiotensin-ii Receptor Antagonists With Diuretic	7 (0.43)	40 (0.49)	0.87 (0.39 - 1.97)	0.42 (0.15 - 1.17)
2.6: Nitrates, calcium-channel blockers, and other antianginal drugs				
2.6.1: Nitrates	178 (10.83)	1077 (13.12)	0.79 (0.66 - 0.94)	0.86 (0.66 - 1.12)
2.6.2: Calcium-channel Blockers	382 (23.25)	1846 (22.49)	1.05 (0.92 - 1.20)	0.90 (0.75 - 1.09)
2.6.3: Other Anti-anginal Drugs	39 (2.37)	181 (2.21)	1.08 (0.76 - 1.54)	0.87 (0.55 - 1.39)
2.6.4: Peripheral Vasodilators And Related Drugs	19 (1.16)	70 (0.85)	1.37 (0.82 - 2.28)	2.24 (1.24 - 4.06)

BMI: body mass index; CI: confidence interval; CHF: congestive heart failure; LVD: left ventricular dysfunction; OR: odds ratio.

*: Additionally adjusted for Charlson components and possible indications for testosterone use

Table 7: Predictors for testosterone initiation, cohort with functional hypogonadism

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Total	2988	14940		
BMI				
<18.5	25 (0.84)	161 (1.08)	1.13 (0.73 - 1.75)	1.14 (0.73 - 1.77)
18.5 to <25	461 (15.43)	3530 (23.63)	1	1
25 to <30	1079 (36.11)	5658 (37.87)	1.48 (1.32 - 1.67)	1.38 (1.22 - 1.56)
30 to <35	743 (24.87)	2948 (19.73)	1.96 (1.73 - 2.23)	1.76 (1.54 - 2.02)
35+	465 (15.56)	1381 (9.24)	2.63 (2.28 - 3.04)	2.33 (1.99 - 2.72)
Missing	215 (7.20)	1262 (8.45)	1.28 (1.07 - 1.52)	1.29 (1.07 - 1.55)
Smoking status				
Never	1356 (45.38)	6690 (44.78)	1	1
Current	408 (13.65)	2991 (20.02)	0.67 (0.59 - 0.75)	0.72 (0.64 - 0.82)
Ex	1161 (38.86)	4910 (32.86)	1.18 (1.09 - 1.29)	1.14 (1.04 - 1.25)
Missing	63 (2.11)	349 (2.34)	0.87 (0.66 - 1.15)	0.91 (0.68 - 1.23)
History of other cardiovascular risk factors				
Stroke/TIA	137 (4.59)	748 (5.01)	0.91 (0.75 - 1.10)	0.88 (0.72 - 1.08)
Atrial fibrillation	150 (5.02)	699 (4.68)	1.08 (0.90 - 1.30)	1.02 (0.79 - 1.32)
Ischemic heart disease	346 (11.58)	1652 (11.06)	1.06 (0.93 - 1.20)	0.98 (0.80 - 1.20)
Myocardial infarction	165 (5.52)	926 (6.20)	0.88 (0.74 - 1.05)	0.77 (0.61 - 0.96)
CHF/LVD	85 (2.84)	424 (2.84)	1.00 (0.79 - 1.27)	0.92 (0.69 - 1.22)
Hypertension	334 (11.18)	1393 (9.32)	1.23 (1.08 - 1.40)	1.18 (1.03 - 1.36)
Diabetes	728 (24.36)	2290 (15.33)	1.82 (1.65 - 2.00)	1.49 (1.33 - 1.66)
Hypercholesterolemia	675 (22.59)	2821 (18.88)	1.27 (1.15 - 1.41)	1.10 (0.98 - 1.23)
Lipid lowering drugs	513 (17.17)	1865 (12.48)	1.48 (1.33 - 1.66)	1.35 (1.19 - 1.53)
Anticoagulants	190 (6.36)	890 (5.96)	1.08 (0.91 - 1.27)	0.99 (0.81 - 1.22)
Antiplatelets	647 (21.65)	2857 (19.12)	1.19 (1.08 - 1.32)	1.01 (0.88 - 1.15)
Medication according to BNF				
2.1 Positive Inotropic Drugs				
2.1.1: Cardiac Glycosides	59 (1.97)	247 (1.65)	1.20 (0.90 - 1.60)	1.10 (0.76 - 1.58)
2.2 Diuretics				

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
2.2.1: Thiazides And Related Diuretics	557 (18.64)	2831 (18.95)	0.98 (0.88 - 1.09)	0.85 (0.75 - 0.97)
2.2.2: Loop Diuretics	284 (9.50)	1142 (7.64)	1.30 (1.12 - 1.49)	1.06 (0.89 - 1.26)
2.2.3: Potassium-sparing Diuretics And Aldosterone Antagonists	76 (2.54)	219 (1.47)	1.76 (1.35 - 2.29)	1.45 (1.05 - 1.98)
2.2.4: Potassium-sparing Diuretics With Other Diuretics	61 (2.04)	262 (1.75)	1.17 (0.88 - 1.56)	0.92 (0.68 - 1.26)
2.2.7: Carbonic Anhydrase Inhibitors	8 (0.27)	33 (0.22)	1.21 (0.56 - 2.62)	0.98 (0.44 - 2.20)
2.2.8: Diuretics With Potassium	0 (0.0)	7 (0.05)	-	-
2.3: Anti-arrhythmic Drugs				
2.3.2.1: Supraventricular & Ventricular Arrhythmias	61 (2.04)	298 (1.99)	1.02 (0.77 - 1.35)	0.95 (0.68 - 1.33)
2.3.2.2: Supraventricular Arrhythmias	<5	9 (0.06)	-	-
2.3.2.3: Ventricular Arrhythmias	334 (11.18)	1240 (8.30)	1.39 (1.22 - 1.58)	1.26 (1.10 - 1.44)
2.4: Beta-adrenoceptor Blocking Drugs	905 (30.29)	4559 (30.52)	0.99 (0.91 - 1.08)	0.92 (0.82 - 1.02)
2.5: Hypertension And Heart Failure				
2.5.1: Vasodilator Antihypertensive Drugs	243 (8.13)	369 (2.47)	3.52 (2.98 - 4.17)	2.93 (2.45 - 3.49)
2.5.2: Centrally Acting Antihypertensive Drugs	27 (0.90)	76 (0.51)	1.79 (1.15 - 2.79)	1.32 (0.81 - 2.14)
2.5.4: Alpha-adrenoceptor Blocking Drugs	478 (16.00)	1871 (12.52)	1.37 (1.22 - 1.53)	1.23 (1.09 - 1.39)
2.5.5.1: Angiotensin-converting Enzyme Inhibitors	1005 (33.63)	4902 (32.81)	1.04 (0.95 - 1.14)	0.77 (0.68 - 0.86)
2.5.5.2: Angiotensin-ii Receptor Antagonists	381 (12.75)	1432 (9.59)	1.39 (1.23 - 1.58)	1.27 (1.10 - 1.46)
2.5.5.3: Renin Inhibitors	5 (0.17)	13 (0.09)	1.92 (0.69 - 5.39)	1.12 (0.36 - 3.48)
2.5.5.4: Angiotensin-ii Receptor Antagonists With Diuretic	23 (0.77)	93 (0.62)	1.24 (0.78 - 1.97)	0.96 (0.58 - 1.57)
2.6: Nitrates, calcium-channel blockers, and other antianginal drugs				
2.6.1: Nitrates	383 (12.82)	1799 (12.04)	1.08 (0.96 - 1.22)	1.04 (0.87 - 1.23)
2.6.2: Calcium-channel Blockers	772 (25.84)	3763 (25.19)	1.04 (0.94 - 1.14)	0.91 (0.81 - 1.03)
2.6.3: Other Anti-anginal Drugs	61 (2.04)	259 (1.73)	1.18 (0.89 - 1.57)	1.00 (0.73 - 1.38)
2.6.4: Peripheral Vasodilators And Related Drugs	19 (0.64)	80 (0.54)	1.19 (0.72 - 1.96)	1.17 (0.69 - 1.96)

BMI: body mass index; CI: confidence interval; CHF: congestive heart failure; LVD: left ventricular dysfunction; OR: odds ratio.

*: Additionally adjusted for Charlson components and possible indications for testosterone use

Table 8: Predictors for testosterone initiation, entire cohort between 2001 and 2014

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Total	4149	20738		
BMI				
<18.5	40 (0.96)	246 (1.19)	1.15 (0.81 - 1.64)	1.19 (0.83 - 1.69)
18.5 to <25	659 (15.88)	4954 (23.89)	1	1
25 to <30	1493 (35.98)	7701 (37.13)	1.48 (1.34 - 1.63)	1.39 (1.26 - 1.54)
30 to <35	984 (23.72)	3983 (19.21)	1.89 (1.69 - 2.10)	1.70 (1.52 - 1.90)
35+	613 (14.77)	1827 (8.81)	2.56 (2.26 - 2.90)	2.28 (2.00 - 2.60)
Missing	360 (8.68)	2027 (9.77)	1.30 (1.13 - 1.50)	1.28 (1.11 - 1.49)
Smoking status				
Never	1891 (45.58)	9113 (43.94)	1	1
Current	600 (14.46)	4402 (21.23)	0.65 (0.59 - 0.72)	0.70 (0.63 - 0.78)
Ex	1545 (37.24)	6673 (32.18)	1.14 (1.05 - 1.22)	1.08 (1.00 - 1.17)
Missing	113 (2.72)	550 (2.65)	0.96 (0.77 - 1.20)	1.02 (0.81 - 1.29)
History of other cardiovascular risk factors				
Stroke/TIA	200 (4.82)	1029 (4.96)	0.97 (0.83 - 1.13)	0.95 (0.81 - 1.13)
Atrial fibrillation	205 (4.94)	1054 (5.08)	0.97 (0.83 - 1.13)	0.92 (0.74 - 1.15)
Ischemic heart disease	469 (11.30)	2366 (11.41)	0.99 (0.89 - 1.10)	0.95 (0.81 - 1.13)
Myocardial infarction	227 (5.47)	1268 (6.11)	0.89 (0.76 - 1.03)	0.86 (0.71 - 1.04)
CHF/LVD	115 (2.77)	618 (2.98)	0.93 (0.75 - 1.14)	0.83 (0.65 - 1.05)
Hypertension	499 (12.03)	1986 (9.58)	1.30 (1.17 - 1.45)	1.26 (1.12 - 1.41)
Diabetes	938 (22.61)	3035 (14.63)	1.74 (1.60 - 1.90)	1.44 (1.31 - 1.59)
Hypercholesterolemia	902 (21.74)	3859 (18.61)	1.23 (1.13 - 1.34)	1.09 (0.99 - 1.20)
Lipid lowering drugs	663 (15.98)	2515 (12.13)	1.40 (1.27 - 1.54)	1.29 (1.16 - 1.44)
Anticoagulants	270 (6.51)	1330 (6.41)	1.02 (0.89 - 1.17)	0.98 (0.83 - 1.16)
Antiplatelets	896 (21.60)	4070 (19.63)	1.15 (1.05 - 1.25)	1.00 (0.90 - 1.12)
Medication according to BNF				
2.1 Positive Inotropic Drugs				
2.1.1: Cardiac Glycosides	77 (1.86)	391 (1.89)	0.98 (0.77 - 1.26)	1.02 (0.74 - 1.39)
2.2 Diuretics				

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
2.2.1: Thiazides And Related Diuretics	769 (18.53)	3865 (18.64)	0.99 (0.91 - 1.09)	0.86 (0.77 - 0.95)
2.2.2: Loop Diuretics	413 (9.95)	1644 (7.93)	1.31 (1.17 - 1.48)	1.18 (1.02 - 1.36)
2.2.3: Potassium-sparing Diuretics And Aldosterone Antagonists	95 (2.29)	334 (1.61)	1.43 (1.14 - 1.81)	1.23 (0.94 - 1.61)
2.2.4: Potassium-sparing Diuretics With Other Diuretics	87 (2.10)	404 (1.95)	1.08 (0.85 - 1.37)	0.89 (0.69 - 1.14)
2.2.7: Carbonic Anhydrase Inhibitors	14 (0.34)	58 (0.28)	1.21 (0.67 - 2.17)	1.05 (0.57 - 1.93)
2.2.8: Diuretics With Potassium	0 (0.0)	7 (0.03)	-	-
2.3: Anti-arrhythmic Drugs				
2.3.2.1: Supraventricular & Ventricular Arrhythmias	81 (1.95)	416 (2.01)	0.97 (0.76 - 1.24)	1.00 (0.75 - 1.32)
2.3.2.2: Supraventricular Arrhythmias	<5	13 (0.06)	-	-
2.3.2.3: Ventricular Arrhythmias	462 (11.14)	1832 (8.83)	1.30 (1.16 - 1.45)	1.17 (1.05 - 1.31)
2.4: Beta-adrenoceptor Blocking Drugs	1227 (29.57)	6195 (29.87)	0.99 (0.91 - 1.06)	0.94 (0.86 - 1.03)
2.5: Hypertension And Heart Failure				
2.5.1: Vasodilator Antihypertensive Drugs	294 (7.09)	510 (2.46)	3.08 (2.65 - 3.58)	2.67 (2.29 - 3.13)
2.5.2: Centrally Acting Antihypertensive Drugs	33 (0.80)	120 (0.58)	1.38 (0.94 - 2.04)	1.04 (0.68 - 1.58)
2.5.4: Alpha-adrenoceptor Blocking Drugs	643 (15.50)	2666 (12.86)	1.27 (1.15 - 1.40)	1.13 (1.02 - 1.26)
2.5.5.1: Angiotensin-converting Enzyme Inhibitors	1326 (31.96)	6403 (30.88)	1.06 (0.98 - 1.14)	0.80 (0.72 - 0.88)
2.5.5.2: Angiotensin-ii Receptor Antagonists	500 (12.05)	1885 (9.09)	1.39 (1.25 - 1.55)	1.26 (1.12 - 1.42)
2.5.5.3: Renin Inhibitors	7 (0.17)	16 (0.08)	2.19 (0.90 - 5.32)	1.45 (0.56 - 3.76)
2.5.5.4: Angiotensin-ii Receptor Antagonists With Diuretic	26 (0.63)	112 (0.54)	1.16 (0.76 - 1.79)	0.95 (0.60 - 1.49)
2.6: Nitrates, calcium-channel blockers, and other antianginal drugs				
2.6.1: Nitrates	511 (12.32)	2609 (12.58)	0.97 (0.88 - 1.08)	0.91 (0.79 - 1.06)
2.6.2: Calcium-channel Blockers	1031 (24.85)	4976 (23.99)	1.05 (0.97 - 1.14)	0.94 (0.85 - 1.04)
2.6.3: Other Anti-anginal Drugs	92 (2.22)	388 (1.87)	1.19 (0.95 - 1.50)	1.11 (0.85 - 1.44)
2.6.4: Peripheral Vasodilators And Related Drugs	33 (0.80)	141 (0.68)	1.17 (0.80 - 1.72)	1.26 (0.85 - 1.87)

BMI: body mass index; CI: confidence interval; CHF: congestive heart failure; LVD: left ventricular dysfunction; OR: odds ratio.

*: Additionally adjusted for Charlson components and possible indications for testosterone use

Table 9: Predictors for testosterone initiation, entire cohort between 2015 and 2017

	Testosterone users n (%)	Matched controls n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Total	482	2409		
BMI				
<18.5	7 (1.45)	37 (1.54)	1.37 (0.58 - 3.27)	1.41 (0.58 - 3.43)
18.5 to <25	80 (16.60)	612 (25.40)	1	1
25 to <30	158 (32.78)	878 (36.45)	1.42 (1.06 - 1.90)	1.43 (1.05 - 1.94)
30 to <35	121 (25.10)	467 (19.39)	2.05 (1.51 - 2.80)	2.19 (1.57 - 3.05)
35+	96 (19.92)	254 (10.54)	3.06 (2.18 - 4.30)	3.26 (2.24 - 4.73)
Missing	20 (4.15)	161 (6.68)	0.89 (0.52 - 1.51)	0.89 (0.51 - 1.53)
Smoking status				
Never	241 (50.00)	1141 (47.36)	1	1
Current	53 (11.00)	498 (20.67)	0.48 (0.35 - 0.67)	0.49 (0.35 - 0.69)
Ex	183 (37.97)	739 (30.68)	1.20 (0.97 - 1.49)	1.08 (0.86 - 1.36)
Missing	5 (1.04)	31 (1.29)	0.75 (0.28 - 2.04)	0.71 (0.25 - 1.98)
History of other cardiovascular risk factors				
Stroke/TIA	23 (4.77)	112 (4.65)	1.03 (0.65 - 1.64)	0.86 (0.50 - 1.47)
Atrial fibrillation	30 (6.22)	113 (4.69)	1.38 (0.90 - 2.12)	1.58 (0.83 - 3.00)
Ischemic heart disease	47 (9.75)	260 (10.79)	0.88 (0.63 - 1.25)	0.85 (0.46 - 1.58)
Myocardial infarction	24 (4.98)	151 (6.27)	0.77 (0.49 - 1.22)	0.72 (0.37 - 1.40)
CHF/LVD	20 (4.15)	79 (3.28)	1.29 (0.77 - 2.16)	1.04 (0.50 - 2.17)
Hypertension	62 (12.86)	234 (9.71)	1.39 (1.02 - 1.89)	1.48 (1.04 - 2.11)
Diabetes	104 (21.58)	394 (16.36)	1.42 (1.11 - 1.81)	1.26 (0.95 - 1.67)
Hypercholesterolemia	120 (24.90)	466 (19.34)	1.44 (1.13 - 1.84)	1.44 (1.08 - 1.91)
Lipid lowering drugs	73 (15.15)	359 (14.90)	1.02 (0.77 - 1.36)	0.98 (0.69 - 1.39)
Anticoagulants	34 (7.05)	165 (6.85)	1.03 (0.70 - 1.54)	0.69 (0.39 - 1.19)
Antiplatelets	71 (14.73)	355 (14.74)	1.00 (0.75 - 1.34)	1.17 (0.77 - 1.78)
Medication according to BNF				
2.1 Positive Inotropic Drugs				
2.1.1: Cardiac Glycosides	9 (1.87)	20 (0.83)	2.32 (1.04 - 5.20)	2.80 (0.96 - 8.19)
2.2 Diuretics				

	Testosterone users n (%)	**Matched controls n (%)**	**Crude OR (95% CI)**	**Adjusted* OR (95% CI)**
2.2.1: Thiazides And Related Diuretics	79 (16.39)	354 (14.69)	1.16 (0.87 - 1.53)	1.17 (0.82 - 1.66)
2.2.2: Loop Diuretics	47 (9.75)	169 (7.02)	1.47 (1.03 - 2.08)	1.18 (0.74 - 1.88)
2.2.3: Potassium-sparing Diuretics And Aldosterone Antagonists	14 (2.90)	53 (2.20)	1.34 (0.73 - 2.45)	1.25 (0.57 - 2.75)
2.2.4: Potassium-sparing Diuretics With Other Diuretics	5 (1.04)	22 (0.91)	1.14 (0.43 - 3.03)	0.87 (0.30 - 2.55)
2.2.7: Carbonic Anhydrase Inhibitors	<5	7 (0.29)	-	-
2.2.8: Diuretics With Potassium				
2.3: Anti-arrhythmic Drugs				
2.3.2.1: Supraventricular & Ventricular Arrhythmias	7 (1.45)	47 (1.95)	0.74 (0.33 - 1.65)	0.44 (0.16 - 1.19)
2.3.2.2: Supraventricular Arrhythmias	<5	<5	-	-
2.3.2.3: Ventricular Arrhythmias	38 (7.88)	152 (6.31)	1.28 (0.88 - 1.85)	1.29 (0.87 - 1.91)
2.4: Beta-adrenoceptor Blocking Drugs	137 (28.42)	683 (28.35)	1.00 (0.80 - 1.26)	0.99 (0.74 - 1.31)
2.5: Hypertension And Heart Failure				
2.5.1: Vasodilator Antihypertensive Drugs	30 (6.22)	66 (2.74)	2.36 (1.51 - 3.69)	2.56 (1.57 - 4.18)
2.5.2: Centrally Acting Antihypertensive Drugs	<5	11 (0.46)	-	-
2.5.4: Alpha-adrenoceptor Blocking Drugs	80 (16.60)	353 (14.65)	1.18 (0.89 - 1.57)	1.09 (0.80 - 1.49)
2.5.5.1: Angiotensin-converting Enzyme Inhibitors	155 (32.16)	833 (34.58)	0.88 (0.70 - 1.10)	0.60 (0.44 - 0.80)
2.5.5.2: Angiotensin-ii Receptor Antagonists	65 (13.49)	255 (10.59)	1.35 (0.99 - 1.83)	1.27 (0.89 - 1.83)
2.5.5.3: Renin Inhibitors	0 (0.0)	<5	-	-
2.5.5.4: Angiotensin-ii Receptor Antagonists With Diuretic	<5	21 (0.87)	-	-
2.6: Nitrates, calcium-channel blockers, and other antianginal drugs				
2.6.1: Nitrates	50 (10.37)	267 (11.08)	0.92 (0.66 - 1.29)	0.95 (0.60 - 1.52)
2.6.2: Calcium-channel Blockers	123 (25.52)	633 (26.28)	0.96 (0.75 - 1.21)	0.72 (0.53 - 0.98)
2.6.3: Other Anti-anginal Drugs	8 (1.66)	52 (2.16)	0.76 (0.36 - 1.62)	0.74 (0.30 - 1.80)
2.6.4: Peripheral Vasodilators And Related Drugs	5 (1.04)	9 (0.37)	2.78 (0.93 - 8.29)	2.19 (0.60 - 8.03)

BMI: body mass index; CI: confidence interval; CHF: congestive heart failure; LVD: left ventricular dysfunction; OR: odds ratio.

*: Additionally adjusted for Charlson components and possible indications for testosterone use

Annex 3 Signature Pages

Signature Page – OS – Epidemiologist, Author

Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23347
Medicinal product / Active substance / Medical Device / Combination Product	Testosterone
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – OS - Statistician

Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23347
Medicinal product / Active substance / Medical Device / Combination Product	Testosterone
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – OS - Conduct Responsible

Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23347
Medicinal product / Active substance / Medical Device / Combination Product	Testosterone
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – OS – Medical Expert

Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23347
Medicinal product / Active substance / Medical Device / Combination Product	Testosterone
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – OS – Safety Leader

Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23347
Medicinal product / Active substance / Medical Device / Combination Product	Testosterone
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – OS – Quality Person for Pharmacovigilance

Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23347
Medicinal product / Active substance / Medical Device / Combination Product	Testosterone
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: _____, _____

Signature Page – OS – Country Medical Director (UK)

Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Report version and date	1.0, 14 June 2018
IMPACT study number	19547
Study type / Study phase	Observational PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS23347
Medicinal product / Active substance / Medical Device / Combination Product	Testosterone
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name:

Date, Signature: _____, _____