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Testosterone replacement therapy is not associated with increased prostate cancer incidence, prostate cancer-specific, or cardiovascular disease-specific mortality in Finnish men

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ABSTRACT

Background: Concerns have been expressed over the safety of testosterone replacement therapy (TRT) in men with late-onset hypogonadism (LOH). Previous studies have shown controversial results regarding the association of TRT with the risk of cardiovascular events or prostate cancer (PCa) incidence, aggressiveness, and mortality. This study explores the overall risk of PCa and risk by tumor grade and stage, as well as mortality from PCa and cardiovascular disease (CVD), among men treated with TRT compared to men without LOH and TRT use.

Materials and methods: The study included 78,615 men of age 55–67 years at baseline from the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC). Follow-up started at randomization and ended at death, emigration, or a common closing date January 1st, 2017. Cox proportional hazards regression model with time-dependent variables and adjustment for age, trial arm, use of other medications, and Charlson comorbidity index was used. Comprehensive information on TRT purchases during 1995–2015 was obtained from the Finnish National Prescription Database. PCa cases were identified from the Finnish Cancer Registry and causes of death obtained from Statistics Finland.

Results: Over the course of 18 years of follow-up, 2919 men were on TRT, and 285 PCa cases were diagnosed among them. TRT users did not exhibit a higher incidence or mortality rate of PCa compared to non-users. On the contrary, men using TRT had lower PCa mortality than non-users (HR = 0.52; 95% CI 0.3–0.91). Additionally, TRT users had slightly lower CVD and all-cause mortality compared to non-users (HR = 0.87; 95% CI 0.75–1.01 and HR = 0.93; 95% CI 0.87–1.0, respectively). No time- or dose-dependency of TRT use was evident in any of the analyses.

Conclusion: Men using TRT were not associated to increased risk for PCa and did not experience increased PCa- or CVD-specific mortality compared to non-users. Further studies considering blood testosterone levels are warranted.

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Introduction

Testosterone deficiency (TD) due to late-onset hypogonadism (LOH) results in a variety of unfavorable physiological outcomes. General symptoms caused by TD include fatigue, sexual dysfunction, and low libido, decreased muscle mass and strength, as well as decreased bone mineral density. In addition, TD has been associated with metabolic conditions, including increased fat mass and elevated risk of metabolic syndrome (MetS) and type 2 diabetes mellitus (DMII). This has increased interest in treating symptomatic hypogonadism in elderly men [1]. Men with hypogonadism may benefit from testosterone replacement therapy (TRT) which can reduce all the aforementioned adverse outcomes [2–4].

However, controversy persists regarding the cardiovascular (CV) safety of testosterone (T) administration to elderly men with comorbid conditions [5–7]. Widely noted and debated studies have raised concerns on whether treating TD with TRT is associated with an increased risk of CV events [7–10]. A recently published randomized placebo-controlled clinical trial evaluating cardiovascular safety of TRT in hypogonadal men did not find any increased risk on cardiovascular events among TRT users [11]. Furthermore, some studies have shown an association of endogenously low blood T levels with an increased risk of CV outcomes and progression of atherosclerosis. Thus, men with TD may, in fact, benefit from TRT [2,12,13].

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Another concern regarding the administration of TRT relates to prostate cancer (PCa) [3]. Benign prostate hyperplasia (BPH) and PCa development are dependent on serum T availability [14,15]. However, the current paradigm is a threshold theory assuming that the androgen receptors (AR) in the prostate become saturated already at low T levels. Consequently, increasing T levels do not impact saturated AR receptors and do not further increase the risk of PCa [16–18]. Thus, the role of T in the progression of PCa remains unclear; PCa is a hormone-dependent disease, and androgen deprivation is a standard treatment in advanced PCa [19]. Therefore, TRT in PCa patients is considered contraindicated [16,20,21].

Altogether, the effect of T levels on PCa and CVD risk is unclear. This study addressed PCa risk as well as all-cause, PCa-specific, and CVD mortality in men with LOH using TRT in the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC).

Materials and methods

Study cohort

FinRSPC included a total of 80,144 men aged 55–67 years at baseline. Information of drug purchases was available for 78,615 men [22]. The cohort was recruited and randomized during 1996–1999; the screening arm was invited to prostate cancer screening with prostate-specific antigen (PSA) test at four-year intervals. Men with a previous diagnosis of PCa were excluded. The follow-up started at randomization and ended at death, emigration, or the common closing date of 1st January 2017, whichever came first.

FinRSPC registered all new PCa cases during the follow-up. Information on PCa incidence was obtained from the population-based, nationwide Finnish Cancer Registry (with 96% coverage of solid cancers diagnosed in Finland) [23]. Clinical data including PSA, TNM stage, and Gleason grade was abstracted from medical records [22]. Causes of death were obtained from Statistics Finland (permission Dnro THL/1182/14.06.00/2021), where all deaths in Finland are registered. The information includes the immediate, underlying (primary), and contributing causes of death [22]. The accuracy of prostate cancer as an official cause of death was evaluated by an adjudication committee by comparing the assigned cause of death with medical records. Agreement between the registry and the committee was 95–98%, confirming the accuracy of cause of the official cause of death [24,25]. In this study, deaths with ICD-10 code C61 as the primary cause of death were considered prostate cancer deaths, deaths with ICD-10 codes I20 to I25 as primary cause were regarded as due to ischemic heart disease. Additionally, we performed separate analysis of deaths with prostate cancer as either primary or contributory cause of death and for deaths with cardiovascular disease recorded as immediate, primary, or contributory cause. PCa cases with Gleason grade 8 or higher were considered high-grade PCa, Gleason grade 7 as intermediate, and 6 as low-grade.

Information on use of medication

In Finland, all medication purchases reimbursed by the Finnish Social Security Institution (SII) are recorded in a prescription database [26]. The reimbursement is granted on medication to treat illness and it is usually deducted from the price of the medicine at the pharmacy at the time of the purchase. The reimbursement applies, after annual deductible (50 €) to all people living in Finland covered by the Finnish social security system and public universal health insurance.

TRT is available only through physician's prescription and reimbursable for treatment of hypogonadism. Therefore, all purchases are recorded in the prescription database, where the information on the use of medication in the cohort was obtained from. Purchases were identified from database based on drug-specific Anatomic Therapeutic Chemical (ATC) codes [27]. All different androgen products used for treatment of TRT, including oral, injectable, and transdermal administered, were collected. Recorded information covers the purchase date, drug dose, number of doses in the package, and number of drug packages for each purchase. Information on the use of aspirin, statins, antihypertensive drugs, antidiabetic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), 5-alpha reductase inhibitors, and anticoagulants was acquired similarly and used to adjust our model.

Standardized cumulative doses of TRT use were calculated based on Defined Daily Doses (DDD) [27]. Annual cumulative doses were calculated by summing up all DDD doses per year. Cumulative years of TRT use were calculated based on the number of years with drug purchases. Annual intensities of the TRT use was calculated by dividing cumulative doses by cumulative years of use. Risk trends by intensity, cumulative DDD amount, and duration of drug use were analyzed by stratifying the study population into tertiles indicating low, medium, and high TRT exposures.

Statistical analysis

Overall PCa risk, disease grade (Gleason 6, 7, and high-grade), and stage (localized (N0 or N1 and M0), metastasized (M1), and T-stage 2 or less, 3, and 4 PCa) were compared between never-users and active, or ever-users of TRT. Analyses on risk of death were also conducted comparing never-users to ever-users of TRT, as well as comparing never-users to active users.

Cox proportional hazards regression was used to estimate hazard ratios (HR) and their 95% confidence intervals (95% CI) using time-dependent TRT use; the usage status was updated separately for each year of follow-up. Analysis of PCa incidence was adjusted for age only (age-adjusted model) and additionally for screening trial arm, use of other medication (statins, aspirin, NSAIDs, anticoagulants, antihypertensive drugs, 5-alpha reductase inhibitors, and antidiabetics), and Charlson comorbidity index (multivariable-adjusted model). A subgroup analysis was further adjusted with marital and socioeconomical status. In analysis of PCa mortality, multivariate-adjusted model was the same as

Table 1. Population characteristics of cohort of the Finnish randomized study for screening of prostate cancer -trial (FinRSPC).

	TRT ever-users ($n = 2919$)	Non-users ($n = 75,696$)	*p*-value	TRT users among PCa cases ($N = 285$)	Non-users ($N = 8980$)	*p*-value
Follow-up time, years:	Median, IQR	Median, IQR		Median, IQR	Median, IQR	
From randomization to study end point	18 (17–19)	17 (13.8–19)	n.s.	18 (17–19)	18 (16.6–19)	n.s.
From randomization to PCa diagnosis	18 (15.1–19)	17 (10.9–19)	n.s.	10.3 (7–14.7)	8.8 (4.8–13.3)	n.s.
From PCa diagnosis to study end point	6.7 (3–10.4)	7.2 (3.1–11.5)	n.s.	6.7 (3–10.4)	7.2 (3.1–11.5)	n.s.
From start of TRT to PCa diagnosis	8 (4–12)			8 (4–12)		
From start of TRT to study end point	14 (8–19)			8 (4–12)		
Age at entry (median, IQR)	59 (55–63)	59 (55–63)	n.s.	59 (55–63)	59 (55–63)	n.s.
Age at time of diagnosis (median, IQR)	67 (64–71)	67 (63–71)	n.s.	67 (64–71)	67 (63–71)	n.s.
Age at time of start of TRT (median, IQR)	65 (61–69)			65 (61–69)		
BMI (median, IQR)	26.8 (24.6–29.4)	26.3 (24.3–29)	<0.05	26.8 (24.1–28.7)	26.2 (24.2–28.7)	n.s.
Charlson comorbidity index (median, IQR)	1 (0–2)	1 (0–2)	n.s.	2 (2–4)	2 (2–4)	n.s.
Study arm:	*N (%)*	*N (%)*		*N (%)*	*N (%)*	
Screening arm	1090 (37)	29104 (38)	n.s.	124 (44)	3673 (41)	n.s
Control arm	1829 (63)	46592 (62)		161 (56)	5307 (59)	
Medication use:	*N (%)*	*N (%)*		*N (%)*	*N (%)*	
Aspirin	677 (23)	13271 (18)	<0.05	66 (23)	1426 (16)	<0.05
NSAID	2778 (95)	64548 (85)	<0.05	275 (96)	8256 (92)	<0.05
Anticoagulants	1562 (54)	32532 (43)	<0.05	168 (59)	4605 (51)	<0.05
Statins	1914 (66)	38089 (50)	<0.05	184 (65)	5046 (56)	<0.05
Antihypertensive drugs	2499 (86)	57703 (76)	<0.05	239 (84)	7292 (81)	n.s.
Antidiabetic drugs	738 (25)	14003 (18)	<0.05	73 (26)	1742 (19)	<0.05
Prostate cancer:	*N (%)*	*N (%)*		*N (%)*	*N (%)*	
PCa diagnosis	285 (10)	8980 (12)	<0.05	285 (10)	8980 (12)	
Incidence per 1000 subjects	97.6	118.6		97.6	118.6	
Gleason grade ≤6	124 (4)	4228 (6)	n.s.	124 (44)	4228 (47)	n.s.
Gleason grade 7	85 (3)	2607 (3)		85 (30)	2607 (29)	
Gleason grade 8–10	29 (1)	1492 (2)		49 (17)	1492 (17)	
Metastatic	11 (0.4)	631 (1)	n.s.	11 (4)	631 (7)	n.s.
Deaths:	*N (%)*	*N (%)*		*N (%)*	*N (%)*	
All	781 (27)	28155 (37)	<0.05	67 (24)	2881 (32)	<0.05
PCa	12 (0.4)	910 (1)	<0.05	12 (4)	910 (10)	<0.05
CVD	190 (7)	6805 (9)	<0.05	11 (4)	496 (6)	n.s.

TRT = testosterone replacement therapy, n.s.= non-significant.

before. A subgroup analysis was further adjusted with PCa risk groups. Risk groups are defined as low risk (Gleason grade 6, T1 or T2, or PSA less than 10 ng/ml), intermediate risk (Gleason grade 7, T-stage 3, or PSA 10–20 ng/ml), and high risk (Gleason grade 8–10, T4, metastatic cases, or PSA over 20 ng/ml). Analysis of PCa mortality was limited to PCa cases. Socioeconomic status, marital status, and body mass index (BMI) were not available for all subjects (data available for 81.5, 76.2, and 14.9% of subjects, respectively).

In all analysis, men who were not users at baseline were classified as non-users until the first purchase, when the status was changed to a current user. The user status remained for each year with recorded purchases. If purchases were discontinued, the status was changed to a previous user. We also formed own variable for ever-users, then men remained user status after the first purchased of T until the end of follow-up. Statistical analyses were carried out using IBM SPSS program (version 24).

Results

Population characteristics

The total number of men included in our study was 78,615, of whom 2919 (3.7%) had any TRT use during the median follow-up of 18 years (Table 1). Follow-up time from TRT use to PCa diagnosis and end of follow-up were 8 and 14 years, respectively (Table 1). The median age upon study entry was 59 years in both TRT users and non-users. Median age of starting TRT treatments was 65 years. Information on BMI

Table 2. Role of testosterone replacement therapy (TRT) on prostate cancer (PCa) risk, cancer grade, and stage.

	Overall PCa risk		Gleason ≤6 PCa risk	Gleason 7 PCa risk	Gleason 8-10 PCa risk	Risk of localized PCa	Risk of metastasized PCa	Risk of T-stage 2 or less Pca	Risk of T-stage 3 PCa	Risk of T-stage 4 Pca
	Age adjusted	Multivariate adjusted model	Multivariate adjusted model	Multivariate adjusted model	Multivariate adjusted model	Multivariate adjusted model	Multivariate adjusted model	Multivariate adjusted model	Multivariate adjusted model	Multivariate adjusted model
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Non-users	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Ever user	0.89 (0.78–1.01)	0.87 (0.77–0.99)	0.93 (0.77–1.13)	1.05 (0.83–1.32)	0.99 (0.74–1.34)	0.94 (0.73–1.23)	1.27 (0.68–2.39)	0.91 (0.8–1.06)	1.19 (0.81–1.73)	1.24 (0.51–3.04)
Current users	0.58 (0.44–0.77)	0.59 (0.44–0.78)	0.81 (0.56–1.17)	0.69 (0.38–1.25)	0.43 (0.16–1.15)	0.81 (0.62–1.05)	0.53 (0.07–3.83)	0.76 (0.55–1.03)	0.59 (0.24–1.42)	*
Previous users	1.03 (0.92–1.15)	1.0 (0.89–1.12)	1.1 (0.92–1.32)	1.2 (0.98–1.46)	1.1 (0.83–1.44)	1.06 (0.92–1.22)	1.76 (1.04–3.12)	1.06 (0.93–1.2)	1.22 (0.89–1.68)	1.79 (0.78–4.08)
					Annual DDD values (calculated for ever-users)					
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
0–40	0.92 (0.75–1.12)	0.92 (0.75–1.1)	0.95 (0.69–1.32)	1.17 (0.79–1.73)	0.86 (0.55–1.34)	0.89 (0.69–1.16)	1.73 (0.64–4.7)	0.87 (0.69–1.09)	1.5 (0.82–2.72)	1.44 (0.2–10.5)
40–160	0.89 (0.71–1.1)	0.88 (0.71–1.1)	0.89 (0.63–1.24)	0.74 (0.5–1.09)	1.14 (0.66–1.97)	0.81 (0.62–1.06)	0.95 (0.42–2.18)	0.84 (0.65–1.07)	1.09 (0.58–2.03)	2.22 (0.31–16.17)
>160	0.86 (0.68–1.08)	0.86 (0.68–1.08)	0.95 (0.67–1.35)	1.59 (1.06–2.37)	0.99 (0.56–1.75)	1.06 (0.8–1.41)	1.11 (0.15–8.03)	1.1 (0.85–1.42)	1.06 (0.5–2.24)	1.02 (0.32–3.23)
					Years of use (calculated for ever-users)					
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≤1	0.87 (0.72–1.04)	0.86 (0.72–1.03)	0.84 (0.64–1.11)	0.88 (0.62–1.24)	0.79 (0.53–1.19)	0.78 (0.62–0.98)	1.76 (0.77–4.01)	0.78 (0.64–0.96)	0.91 (0.49–1.69)	2.48 (0.6–10.22)
1–3 y	1.04 (0.83–1.3)	0.99 (0.79–1.24)	0.99 (0.7–1.41)	1.16 (0.79–1.7)	1.97 (1.11–3.49)	1.16 (0.87–1.53)	0.83 (0.31–2.27)	1.1 (0.84–1.42)	2.11 (1.19–3.74)	0.91 (0.22–3.69)
>3	0.77 (0.59–1.01)	0.73 (0.56–0.96)	1.1 (0.73–1.68)	1.35 (0.82–2.21)	0.85 (0.44–1.64)	1.04 (0.74–1.47)	0.76 (0.11–5.47)	1,09 (0.8–1.48)	0.94 (0.42–2.1)	0.94 (1.13–6.9)
					Intensity of use (DDD/year) (calculated for ever-users)					
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≤25.0011	0.87 (0.7–1.09)	0.94 (0.76–1.18)	1.18 (0.81–1.71)	1.29 (0.87–1.9)	1.29 (0.79–2.12)	1.14 (0.85–1.53)	1.19 (0.44–3.25)	1.06 (0.81–1.37)	1.53 (0.88–2.66)	*
25.0011–60.0000	0.91 (0.74–1.12)	0.83 (0.67–1.01)	0.78 (0.56–1.06)	0.82 (0.57–1.19)	0.78 (0.48–1.25)	0.76 (0.59–0.98)	1.1 (0.48–2.52)	0.75 (0.6–0.94)	1.48 (0.77–2.86)	2.91 (0.9–9.38)
>60.0000	0.88 (0.71–1.07)	0.85 (0.68–1.05)	0.98 (0.71–1.35)	1.22 (0.79–1.87)	0.96 (0.54–1.7)	1 (0.76–1.3)	1.45 (0.2–10.41)	1.05 (0.82–1.34)	0.7 (0.31–1.56)	0.9 (0.22–3.7)

Sub-group analyses were made to investigate possibly dose- and time-dependency of TRT use. Multivariate adjusted model was adjusted with age, trial study arm, additional drug use, and Charlson comorbidity index.

was limited; however, among the men with information available ($n = 11,698$ (14.9%)), the median BMI upon entry was similar (26.8 vs. 26.3). Use of additional medication, such as statins, NSAIDs, and antidiabetics, was more common among TRT users than non-users (Table 1).

PCa was diagnosed in 9265 patients, of whom 285 (3.1%) used TRT during the follow-up. PCa incidence per 1000 subjects was slightly lower among TRT users compared to non-users (97.6 vs. 118.6, respectively, $p < 0.05$). Among the PCa cases, Gleason grade was 6 or less in 4352 (47%), 7 in 2692 (29%), 1514 had 8 or more (17%). Furthermore, 642 (7%) had metastatic (M1) cancer (Table 1). There were 12 (4%) PCa death among TRT users and 910 (10%) in never-users ($p < 0.05$). In total, 781 deaths (27%) were recorded in TRT users and 28,155 (37%) among never-users ($p < 0.05$). There were 190 (7%) deaths due to CVD in the TRT users and 6805 (9%) in the never-user group ($p < 0.05$) (Table 1).

Prostate cancer risk

TRT ever or previous users did not have a higher PCa incidence than non-users in any investigated groups or sub-analyses (Table 2). Current TRT users had a decreased risk of PCa in age-adjusted (HR = 0.58, 95% CI 0.44–0.77) and multivariable-adjusted model (HR = 0.59, 95% CI 0.44–0.78) analysis (Table 2). Further adjustment with marital, socioeconomical status, and BMI did not markedly modify the risk rates (Supplementary table 1). Risk rate trends stayed similar in the subgroup analysis by PCa grade or stage in all other analysis, but previous TRT users had slightly increased risk for metastatic disease (HR = 1.76, 95% CI 1.04–3.12) (Table 2). No clear risk trends in PCa risk were found by dose, duration of intensity of TRT use (Table 2).

Risk of death

TRT users did not have higher mortality from any analyzed cause of death except previous TRT users had slightly increased risk for all-cause mortality compared to non-users (HR = 1.13, 95% CI 1.06–1.12) (Table 3). Active as well as ever-users of TRT was associated with significantly decreased overall mortality compared to non-users (HR = 0.56, 95% CI 0.46–0.68 for active and HR = 0.93, 95% CI 0.87–1 for ever-users) (Table 3). No dose-, duration-, or intensity-dependency of the TRT use was observed (Table 3).

Ever-users of TRT was associated with a lower PCa mortality compared to non-users (HR = 0.52, 95% CI 0.3–0.91) (Table 3). However, this was not observed among previous TRT users (Table 3). PCa mortality showed no gradient by dose, duration, or intensity of TRT use (Table 3).

Cardiovascular mortality was decreased in active and ever-users of TRT (HR = 0.7, 95% CI 0.5–0.99, HR = 0.87, 95% CI 0.75–1.01, respectively), while previous use was not associated with CVD mortality (Table 3). No dose-, duration-, or intensity-dependency of the TRT use was observed (Table 3).

Further adjustment with marital, socioeconomic status, and BMI did not markedly modify the risk rates of cause of death in any analysis (Supplementary table 1).

Table 3. Association of testosterone replacement therapy (TRT) on all-cause, prostate cancer (PCa), and cardiovascular disease (CVD) deaths.

	Death due to any cause		PCa death		CVD death	
	Age adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Age adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)	Age adjusted HR (95% CI)	Multivariate adjusted HR (95% CI)
Non-users	Ref	Ref	Ref	Ref	Ref	Ref
Ever users	0.81 (0.75–0.87)	0.93 (0.87–1)	0.49 (0.29–0.85)	0.52 (0.3–0.91)	0.79 (0.68–0.92)	0.87 (0.75–1.01)
Active users	0.47 (0.4–0.57)	0.56 (0.46–0.68)	*	*	0.64 (0.46–0.9)	0.7 (0.5–0.99)
Previous users	1 (0.93–1.06)	1.13 (1.06–1.21)	0.84 (0.58–1.22)	0.92 (0.63–1.35)	0.97 (0.85–1.11)	1.07 (0.94–1.2)
Total use (DDD) (calculated for ever-users)						
None	Ref	Ref	Ref	Ref	Ref	Ref
<40	0.82 (0.72–0.92)	0.94 (0.84–1.06)	0.39 (0.15–1.05)	0.35 (0.13–0.92)	0.83 (0.65–1.06)	0.93 (0.73–1.19)
40–160	0.86 (0.76–0.97)	0.99 (0.87–1.1)	0.56 (0.23–1.36)	0.74 (0.31–1.79)	0.77 (0.59–1.01)	0.84 (0.64–1.09)
>160	0.74 (0.65–0.85)	0.87 (0.76–0.99)	0.55 (0.21–1.48)	0.61 (0.23–1.79)	0.77 (0.59–1.01)	0.85 (0.64–1.09)
Years of use (calculated for ever-users)						
None	Ref	Ref	Ref	Ref	Ref	Ref
≤1	0.8 (0.72–0.89)	0.9 (0.81–0.99)	0.15 (0.04–0.59)	0.14 (0.03–0.55)	0.8 (0.64–0.99)	0.87 (0.7–1.08)
1–3 years	0.81 (0.7–0.93)	0.94 (0.82–1.08)	1.38 (0.74–2.57)	1.62 (0.86–3.05)	0.76 (0.56–1.02)	0.87 (0.64–1.17)
>3	0.82 (0.71–0.94)	0.94 (0.82–1.08)	0.18 (0.03–1.27)	0.25 (0.04–1.81)	0.82 (0.61–1.11)	0.89 (0.67–1.2)
Intensity of use (DDD/year) (calculated for ever-users)						
None	Ref	Ref	Ref	Ref	Ref	Ref
<25.0011	0.9 (0.79–1.01)	0.92 (0.83–1.02)	0.6 (0.25–1.44)	0.53 (0.22–1.27)	0.89 (0.69–1.14)	0.99 (0.77–1.28)
25.0011–60.0000	0.82 (0.73–0.92)	0.96 (0.84–1.1)	0.31 (0.1–0.97)	0.39 (0.13–1.21)	0.8 (0.62–1.02)	0.87 (0.68–1.1)
>60.0000	0.71 (0.62–0.81)	0.94 (0.82–1.08)	0.6 (0.25–1.44)	0.65 (0.27–1.58)	0.69 (0.52–0.92)	0.76 (0.57–1.01)

Sub-group analyses were made to investigate possibly dose- and time-dependency of TRT use. Multivariate model was adjusted with age, trial study arm, additional drug use, PCa risk group, and Charlson comorbidity index. Analysis with PCa specific deaths were limited to PCa cases.
*Due to low number of annual active TRT users with diagnosed PCa, a fair amount of HR were non-attainable or 95% CI were of excessively wide range.

Discussion

In our study, TRT users did not have increased PCa incidence or mortality from PCa, CVD, or all causes. On the contrary, men using TRT for hypogonadism had decreased risks compared to non-users. A limitation of our study was the inability to use a comparison group of men with hypogonadism, but not using TRT. Hence, it is difficult to distinguish whether the finding reflects an effect of the medication or its indication (confounding by indication). Furthermore, we did not find any dose- or time-dependency of TRT use in any analysis, which further supports the lack of TRT impact on PCa incidence or PCa mortality.

Our results contradict the idea that TRT in hypogonal men promote the growth of PCa [19], as no increased association for PCa incidence, PCa-specific death, or metastatic disease was found among TRT users. Furthermore, our results are in concordance with several recent studies that have challenged the association of T and PCa [16–18,28–31]. However, in most of these studies, including ours, it is not possible to distinguish between the effects of low endogenous and administration of exogenous T.

Current American Urological Association guidelines for TRT underline that there is absence of evidence that TRT use has impact on PCa development and quantification of risk-benefit ration for TRT use in subjects with history of PCa is impossible with current research evidence [32]. Furthermore, guidelines conclude that more research of long-term T use in PCa patient is needed, even though, in guidelines of European Association of Urology TRT is absolute contraindicated in locally advanced or metastatic PCa patients [21]. The impact of TRT on low-grade PCa is investigated during active surveillance in small trials [33,34]. Hashimoto et al. evaluated the multiparametric prostate magnetic resonance imaging findings in twelve active surveillance patients who receive TRT [33]. Two patients had Gleason score upgrade during the follow-up. Another study investigated TRT compared to non-TRT during active surveillance patients and concluded that TRT was not associated with treatment conversions [34]. Based on these studies, TRT seems to be safe in low-grade PCa patients; however, larger studies are needed before any final conclusions.

In Finland, TRT is contraindicated in men with PCa [21] and TRT medication is only available through prescription to men with diagnosed TD. Therefore, we assumed that all TRT users had TD before initiation of TRT. Amount of TRT use is a surrogate for the degree of hypogonadism, as patients with more severe TD would receive TRT at higher doses. We did not have information the severity of TD or the serum T levels of our subjects, however, we did not observe any effect modification by dose or duration of TRT use.

Use of other medications (aspirin, NSAIDs, anticoagulants, statins, antihypertensive drugs, and antidiabetic drugs) was significantly higher among TRT users during the follow-up. This may be due to the fact that TD associates with comorbid conditions, such as type 2 diabetes and metabolic syndrome [2,3]. Around one third of men were users of additional drugs already before TRT use. Also, it is likely that men with metabolic disorders attend physicians more often and, therefore, may be more prone to be diagnosed with even subclinical TD.

Active and ever-users of TRT showed a decreased CVD and overall mortality. Previous studies suggest that hypogonadal men on TRT benefit also by improvements in the TD-associated metabolic conditions, which may lead to lowered overall mortality [2,3,35–37]. We did not evaluate impact of TRT use on hypogonadal men compared to men without TRT but with TD. However, a recent randomized placebo-controlled clinical trial concluded that TRT use in hypogonadal men did not impact on subjects' cardiovascular safety compared to placebo [11]. In general, our overall

results challenge the concerns regarding TRT safety in men with CVD [8–10], even though we cannot estimate the impact of TRT limited to men with TD. However, we cannot draw conclusions on the dosage of TRT or ideal T levels regarding the safe administration of TRT.

As a strength of our study, data collected from Finnish registries are accurate and comprehensive, maximizing comparability and minimizing differential error. For instance, all reimbursements for TRT purchases are recorded in the prescription database. However, as a limitation, we had only information of purchases of the drugs, thus, it is impossible to know whether patients used them. Also, we lacked information of patients' serum T levels and men with TD but without TRT use. Causes of deaths were obtained from the cause of death registry, which is shown to be accurate for PCa-specific deaths [24] which has been a problem in some countries [38].

In conclusion, our findings do not support concerns regarding the oncological and cardiovascular safety of TRT in hypogonadal men and suggest that the use of TRT with the indication of treating LOH does not increase the risk of these outcomes to the level in the general population. Further analysis should conduct comparing TRT use and non-use in men with TD.

Authors' contributions

Study concept and design: Original FinRSPC-cohort: Tammela and Auvinen. Current study: Murtola, Auvinen, Tammela. Acquisition of data: Taari, Tammela, Auvinen, Talala and Murtola. Analysis and interpretation of data: Kausz, Siltari and Murtola. Drafting of the manuscript: Kausz, Siltari and Murtola. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Siltari and Murtola. Obtaining funding: Siltari and Murtola. Administrative, technical, or material support: Talala. Supervision: Murtola and AuvinenNew paragraph: use this style when you need to begin a new paragraph.

Disclosure statement

TJ Murtola: consultation fees from Astellas and Janssen Cilag, speaker's honorarium from Astellas and Janssen Cilag, participation in scientific meetings at expense of Astellas and Sanofi.

A Siltari: Nothing to declare.

J Kausz: Nothing to declare.

K Talala: Nothing to declare.

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TLJ Tammela: Investigator in clinical trials sponsored by Pfizer, Astellas, Janssen, Myovant and Lidds Ab.

A Auvinen: Lecture fee by Amgen/Janssen.

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Data availability statement

Sharing individual-level data, even in pseudonymized form is not possible according to the current Finnish regulation regarding privacy, data protection, and EU-level GDPR. Full anonymization of the data is not feasible, because at individual level, there would be numerous unique records if all variables used in the analyses were to be retained (even if collapsing discrete variables and categorizing continuous variables). Permission for data access was applied from Finnish institute of health and welfare and data access can be applied from there (kirjaamo@thl.fi).

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