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Testosterone treatment is not associated with increased risk of adverse cardiovascular events: results from the Registry of Hypogonadism in Men (RHYME)

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Summary

Aims: The aim of this study was to assess cardiovascular (CV) safety of testosterone replacement therapy (TRT) in a large, diverse cohort of European men with hypogonadism (HG).

Methods: The Registry of Hypogonadism in Men (RHYME) was designed as a multinational, longitudinal disease registry of men diagnosed with hypogonadism (HG) at 25 clinical sites in six European countries. Data collection included a complete medical history, physical examination, blood sampling and patient questionnaires at multiple study visits over 2–3 years. Independent adjudication was performed on all mortalities and CV outcomes.

Results: Of 999 patients enrolled with clinically diagnosed HG, 750 (75%) initiated some form of TRT. Registry participants, including both treated and untreated patients, contributed 23 900 person-months (99.6% of the targeted) follow-up time. A total of 55 reported CV events occurred in 41 patients. Overall, five patients died of CV-related causes (3 on TRT, 2 untreated) and none of the deaths were adjudicated as treatment-related. The overall CV incidence rate was 1522 per 100 000 person-years. CV event rates for men receiving TRT were not statistically different from untreated men (P=.70). Regardless of treatment assignment, CV event rates were higher in older men and in those with increased CV risk factors or a prior history of CV events.

Conclusions: Age and prior CV history, not TRT use, were predictors of new-onset CV events in this multi-national, prospective hypogonadism registry.

1 | INTRODUCTION

Significant controversy exists regarding the cardiovascular (CV) safety and outcomes of testosterone replacement therapy (TRT) in hypogonadal men.[1–5] Citing findings of increased CV adverse events in a single-centre trial of TRT in frail, elderly men,[6] in addition to reports of increased CV event rates in two retrospective studies of medical claims databases in the USA[7,8] the Food and Drug Administration (FDA) issued a special advisory in 2015,[9] cautioning health professionals to pay close attention to potential adverse CV effects of TRT, and recommending proactive education of all patients about these potential risks.[3,9] In contrast to the FDA advisory statement, the European Medicines Agency (EMA) found no consistent evidence of harm associated with TRT administration, regardless of the mode of delivery.[10] Similar conclusions were reached in TRT guidelines from the European Association of Urology,[11] European Menopause Andropause Society (EMAS),[12] and the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE).[13] Nevertheless, these guidelines all recommend comprehensive diagnostic evaluation of hypogonadal patients prior to treatment and further prospective, long-term studies of risks and benefits of TRT.[10–13]

Supporting evidence for CV safety of TRT comes from several sources. These include a recent multi-centre randomised trial (T-Trial) of topical testosterone administration compared to placebo in men over 65,[14] additional retrospective database analyses in large healthcare systems,[15–18] single product registries [19,20] and recent systematic reviews.[21,22] In the T-Trial,[14] rates of CV events and mortalities were nearly identical, although mortalities occurred more frequently on placebo (N=7), than on testosterone therapy (N=3), during the course of 12 months, double-blind, TRT. Cardiometabolic benefits of long-term testosterone administration have also been reported in several studies.[23–25] Despite the accumulating evidence of CV safety of TRT, limitations in prior studies include relatively narrow eligibility criteria,[14] inadequate sample sizes and short duration of clinical trials,[6,14] and well-known shortcomings of retrospective database analyses.[7,8,15,17]

The Registry of Hypogonadism in Men (RHYME) was designed to evaluate both prostate health outcomes and CV safety of TRT in a large, prospective, cohort of hypogonadal men.[26] By design, and in contrast to prior clinical trials, we enrolled patients with a wide range of comorbid illnesses and CV risk factors to evaluate TRT safety in a sufficiently diverse cohort to reflect real-world, clinical experience. Patients were systematically monitored for up to 36 months, a substantially longer period of follow-up compared to recent RCT's.[6,14] To optimise reliability and accuracy of our main outcomes, we included blinded, centralised adjudication of all mortalities and overall CV safety.

What's known

Testosterone replacement therapy is effective in restoring normal testosterone levels and improving quality of life in hypogonadal men. However, conflicting reports have been published regarding cardiovascular (CV) safety of TRT, leading to an FDA advisory statement in 2015 which included specific warnings to physicians and patients about potential CV risks of TRT.

What's new

Cardiovascular safety of TRT was evaluated in a large, multinational registry of hypogonadal men receiving TRT for up to 3 years. In comparison to both untreated men in the same cohort and to age-matched population data, no increase in mortality or CV risk was observed with TRT, regardless of the type of testosterone administered or presence of other comorbidities. These results strongly support the overall CV safety of TRT.

2 | MATERIALS AND METHODS

2.1 | Study design

RHYME is a multi-national, disease registry with longitudinal data collection from a large cohort of hypogonadal men aged 18 years or older. Each patient enrolled was scheduled for at least four and up to five visits over a minimum of 2 years starting at baseline and then 3–6 months, 12 months, 24 and 36 months later. The registry was conducted at 25 sites in six European countries (Germany, Italy, The Netherlands, Spain, Sweden and UK) and included comprehensive and standardised biochemical, quality of life, medical record and questionnaire data. Although not statistically powered to determine differences in CV events between men on TRT compared with untreated men, we aimed to document event rates in TRT and untreated men compared to that in the general population. The Registry protocol was approved by a central IRB and local Ethics Committees (EC) at each clinical site prior to initiation. All patients provided written informed consent with guarantees of confidentiality at enrolment.

2.2 | Data collection and end-points

Data for RHYME were collected primarily through abstraction of medical records. Participants also provided self-reported medical and demographic data and completed a short battery of patient reported outcomes at each visit. Blood samples were obtained for site-specific standard of care measurements of prostate-specific antigen (PSA), sex hormone-binding globulin, luteinizing hormone (LH), total testosterone (TT) and other laboratory values. Secondary outcomes were changes in cardiometabolic parameters, including body mass index (BMI), waist circumference (WC), systolic and diastolic blood pressure (SBP/DBP), haematocrit and cholesterol.

A Clinical Endpoints Committee (CEC)[a] performed blinded adjudication of all mortality reports and CV safety outcomes. Study sites were instructed to record and actively investigate all adverse medical outcomes during the study. Reported CV events included deep vein thrombosis (DVT), myocardial infarction (MI), stroke, pulmonary embolism (PE), stenting, coronary artery bypass graft (CABG), atrial

fibrillation (AF), percutaneous coronary intervention (PCI), transient ischaemic attack (TIA) or death due to ischaemic heart disease or heart failure. Additional details of the study design and methods have been published previously.[26]

2.3 | Study population

2.3.1 | Inclusion criteria

Male patients aged 18 years and older with a confirmed new HG diagnosis were enrolled consecutively at each site. The diagnosis of HG and determination of eligibility was made by the site investigator, based on documented symptoms of androgen deficiency and below normal testosterone levels (using local reference ranges in each centre) on at least two visits. Initiation of TRT and the mode of treatment delivery were determined by the treating physician in consultation with the patient, according to standard of care guidelines.[27,28] The treatment decision was intended to reflect real-world clinical practice and thereby increase generalisability of the study findings.

2.3.2 | Exclusion criteria

Male patients with one or more of the following were excluded: any prior history of TRT, positive history of breast cancer, prostate cancer or high-grade prostatic intraepithelial neoplasia; prior radical prostatectomy; life expectancy shorter than 24 months as judged by the site investigator; current major psychiatric disorders or drug or alcohol abuse; gender dysphoria or sexual reassignment; actively enrolled in any interventional clinical trial or planned relocation outside clinical site region within 24 months.

2.4 | Statistical analyses

Descriptive statistics, including mean or median, standard deviation (SD) and frequency measures were used to characterise the baseline characteristics of our sample, and to evaluate potential pretreatment differences between those receiving TRT and those who did not. Variables that were not normally distributed (e.g. PSA) were log transformed and analysed as geometric means with coefficient of variation (COV). Person-time was calculated as the total time each person was followed until either the CV event or until the final contact (for those without an event). Onset CV event incidence rates for treated and untreated men were calculated as the number of CV events divided by the total person-time and multiplying by 100 000.

Cox proportional hazards models were used for survival analysis for onset CV event reporting hazards ratio (HR) and 95% confidence intervals (CI). Analyses were conducted to evaluate incidence rates in CV events according to treatment status (treated vs. untreated), as well as changes over time and the interaction between time and treatment. This analytic method accounted for repeated observations in the same subject over time, which are expected to be correlated. TRT was treated as time-varying. Subjects were considered untreated up until treatment was initiated. Subjects were considered treated at any visit at or after initiation, even if treatment was discontinued at a later time. Covariates considered in analyses included: age, country, baseline comorbidity, modified Charlson Index score, duration of HG prior to treatment, BMI, prior urologic or prostate diseases, lower urinary tract symptoms, smoking, laboratory measures (cholesterol, TT, SHGB, LH, PSA), and certain medications [for hypertension, diabetes, lipid-lowering, erectile dysfunction (ED), psychiatric disorders, benign prostate hyperplasia (BPH)]. SAS 9.3 (Cary, NC, USA) was used for statistical analyses.

3 | RESULTS

3.1 | Baseline cohort description

The disposition of the RHYME cohort is shown in Fig. 1. Of 1006 patients initially enrolled, seven were found to be ineligible due to lack of biochemical confirmation of hypogonadism (N=4) or a prior history of prostatectomy or prostate cancer (N=3). This resulted in an analytic cohort at baseline of N=999 enrolled participants. A total of 71 patients terminated prematurely resulting in a net retention rate of 92.9% over 3 years of follow-up. Reasons for early termination included death (N=10), loss to follow-up (N=12), patient declined to continue (N=37) and other reasons (N=12). The mean age of the cohort at baseline was 59.1±10.5 years old and mean baseline TT was 9.5 (COV=0.5) nmol/L (Table 1).

Patients who went on to receive TRT were similar in aetiological diagnoses (primary vs secondary hypogonadism) and rates of baseline comorbidities, including late-onset diabetes (26%), hypertension (50%) and hyperlipidaemia (39%). Education levels and socioeconomic statuses were also similar across the two groups (Table 1). Baseline BMI's were slightly higher in men who subsequently received TRT (30.2+5.7 vs 29.4+5.1; $P<.05$), whereas testosterone levels were marginally lower at baseline in treated compared with untreated men (8.3±3.9 nmol/L vs. 9.4±3.7 nmol/L; $P<.01$).

3.2 | Testosterone utilisation

As shown in Fig. 1, of 999 registry participants, 750 (75%) initiated TRT and among these, 70.5% reported continued TRT use at every study visit. We observed a low rate of TRT discontinuation (17.6%), with 15.6% of men discontinuing use after one visit. The majority of testosterone prescriptions were for either topical gels (68%) or injectable testosterone products (31%), with only 2% for orally administered drugs. Effectiveness of TRT in restoring normal testosterone levels was also assessed. Sixty-four per cent of treated men achieved blood levels of testosterone >10 nmol/L at follow-up, and 43% were higher than 14 nmol/L at follow-up, compared with marginally increased T levels over time in untreated men (Fig. 1). Differences of <1% were observed in haematocrit levels at follow-up between untreated men and those who received TRT (treated=45.3% vs untreated=44.6% Hct).

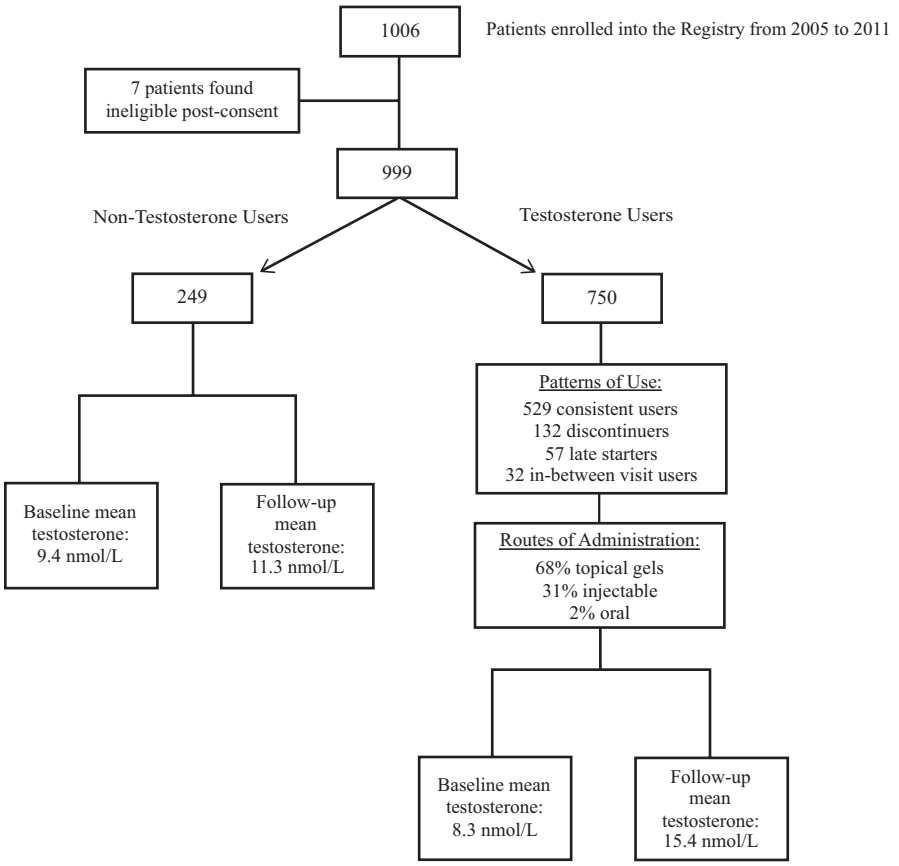

FIGURE 1 Patient disposition and selection process

3.3 | Relationship between TRT, utilisation and new-onset CV events

A total of 55 adverse CV events were reported, which occurred in 41 individual registry participants. As shown in Table 2, most common CV events reported were DVT (n=13), MI (n=14) and stroke (n=9), which occurred in similar proportions of men receiving TRT compared with untreated men. Five deaths were adjudicated as CV-related, two of which occurred in untreated patients and three in the TRT group. Figure 2 shows incidence of CV events by route of TRT administration (topical vs. injectable). No overall associations were observed between new-onset CV events and overall TRT use or duration. The crude risk for onset of CV events among TRT users was 4.3% vs. 3.6% in non-users, and the crude relative risk comparing treated to untreated was 1.18 (95% CI: 0.57–2.44). The overall incidence rates for CV events were not statistically different for men on TRT compared with untreated men (1694.7 vs. 1480.0 per 100 000 person-years, P=.7) (Table 3).

3.4 | Relationship between medical history and new-onset CV events

Registry participants with new-onset or incident CV events were more likely to be older and have more concomitant illnesses, including diabetes and hypertension, a history of smoking and chronic use of blood pressure and cholesterol lowering drugs (Table 1). Rates of new-onset CV events were similar in patients with an original diagnosis of primary (21.4%) compared to secondary hypogonadism (17.8%). Among the 41 hypogonadal men with a new-onset CV event during the study, a prior history of cardiovascular disease (CVD) was significantly more common in those with incident CV events (Table 1).

In adjusted Cox proportional hazard models, we observed significant associations after controlling for multiple potential confounders between new-onset CV events and a prior history of angina [HR=2.6 (95% CI: 1.1–6.1)], older age in units of 1 year [HR=1.1 (95% CI: 1.0–1.1)], and higher BMI [HR=1.1 (95% CI: 1.0–1.1)] (Table 4).

3.5 | Relationship between age and new-onset CV events

Comparing baseline characteristics of those with or without a new-onset CV event, men ≥60 years, as expected, were significantly more likely to have a new-onset CV event (2178.7 vs. 735.0 per 100 000 person-years P<.0001) (Table 3). However, age did not influence the lack of association between TRT and CV events, as a stratified analysis of CV events in younger (<60) vs. older patients (≥60) showed no differences between testosterone treated and untreated men in either of the age categories (Table 1).

TABLE 1 Baseline characteristics overall, by TRT status and new-onset CV event. CV events included DVT, MI, stroke, PE, stenting, CABG, AF, PCI, TIA or death due to ischaemic heart disease or heart failure

	Cohort overall		TRT status			CV event status		
		Overall (n=999)	Untreated (n=249)	Treated (n=750)		Onset CV event (n=41)	No onset CV event (n=958)	
Baseline characteristic	N[a]	n (%) or mean±SD (COV)	n (%) or mean±SD (COV)	n (%) or mean±SD (COV)	*P*-value	n (%) or mean±SD (COV)	n (%) or mean±SD (COV)	*P*-value
Age	999	59.1±10.5	59.7±11.1	58.9±10.3	.30	65.9±7.8	58.8±10.5	<.0001
Age group (years)								
<60	999	516 (51.7)	121 (48.6)	395 (52.7)	0.27	9 (22.0)	507 (52.9)	<.0001
≥60		483 (48.4)	128 (51.4)	355 (47.3)		32 (78.0)	451 (47.1)	
Type of HG								
Primary HG (LH≥7.6)	751	135 (18.0)	39 (20.7)	96 (17.1)	0.26	6 (21.4)	129 (17.8)	.61
Secondary HG (LH<7.6)		616 (82.0)	149 (79.3)	467 (83.0)		22 (78.6)	594 (82.2)	
Testosterone utilisation								
Treated	999	750 (75.1)	0 (0.0)	750 (100)	N/A	32 (78.1)	718 (75.0)	.68
Untreated		249 (24.9)	249 (100)	0 (0.0)		9 (22.0)	240 (25.1)	
CV risk factors								
BMI	989	30.0±5.5	29.4±5.1	30.2±5.7	0.04	31.6±6.1	29.9±5.5	.05
Waist circumference (cm)	853	107.0±13.4	105±12.8	107.6±14.1	0.01	111.2±12.0	106.8±13.9	.05
Systolic blood pressure	979	137.3±18.0	137.5±18.1	137.2±17.9	0.82	144.4±19.1	137.0±17.9	.01
Diastolic blood pressure	979	82.3±10.5	82.2±10.7	82.2±10.4	0.99	81.1±10.8	82.3±10.4	.47
Haematocrit (%)								
<50	493	486 (98.6)	120 (98.4)	366 (98.7)	0.68	21 (100)	465 (98.5)	1.00
>50		7 (1.4)	2 (1.6)	5 (1.4)		0 (0)	7 (1.5)	
Smoking status								
Past	982	531 (54.1)	128 (53.1)	403 (54.4)	0.79	30 (75.0)	501 (53.2)	.03
Current		130 (13.2)	35 (14.5)	95 (12.8)		3 (7.5)	127 (13.5)	
Never		321 (32.7)	78 (32.4)	243 (32.8)		7 (17.5)	314 (33.3)	
Modified Charlson Comorbidity Index[b]								
0	999	545 (54.6)	134 (53.8)	411 (54.8)	0.11	14 (34.2)	531 (55.4)	.01
1–2		330 (33.0)	75 (30.1)	255 (34)		19 (46.3)	311 (32.5)	
3+		124 (12.4)	40 (16.1)	84 (11.2)		8 (19.5)	116 (12.1)	
Cardiovascular disease history								
Any cardiovascular disease	999	515 (51.6)	125 (50.2)	390 (52.01)	0.68	30 (73.2)	485 (50.7)	.01
Angina		74 (7.4)	16 (6.4)	58 (7.7)	0.59	13 (31.7)	61 (6.4)	<.0001
Hypertension		464 (46.4)	112 (45.0)	352 (47)	0.63	25 (61.0)	439 (45.9)	.08
Cerebrovascular disease		23 (2.3)	9 (3.6)	14 (1.9)	0.19	1 (2.4)	22 (2.3)	.62
Stroke		23 (2.3)	9 (3.6)	14 (1.9)	0.19	1 (2.4)	22 (2.3)	.62
Congestive heart failure		16 (1.6)	6 (2.4)	10 (1.3)	0.36	3 (7.3)	13 (1.4)	.02
MI		49 (4.9)	16 (6.4)	33 (4.4)	0.27	6 (14.6)	43 (4.5)	.01
Peripheral vascular disease		41 (4.1)	12 (4.8)	29 (3.9)	0.66	5 (12.2)	36 (3.8)	.02
DVT		12 (1.2)	2 (0.8)	10 (1.3)	0.77	4 (9.8)	8 (0.8)	<.0001
History of diabetes	999	287 (28.7)	74 (29.7)	213 (28.4)	0.76	18 (43.9)	269 (28.1)	.04

Baseline characteristic	N[a]	Cohort overall: Overall (n=999) n (%) or mean±SD (COV)	TRT status: Untreated (n=249) n (%) or mean±SD (COV)	TRT status: Treated (n=750) n (%) or mean±SD (COV)	P-value	CV event status: Onset CV event (n=41) n (%) or mean±SD (COV)	CV event status: No onset CV event (n=958) n (%) or mean±SD (COV)	P-value
Diabetes medications	999	257 (25.7)	65 (26.1)	192 (25.6)	0.94	17 (41.5)	240 (25.1)	.03
Antihypertensive medication	999	495 (49.6)	119 (47.8)	376 (50.1)	0.58	29 (70.7)	466 (48.6)	.01
Lipid-lowering medication	999	391 (39.1)	89 (35.7)	302 (40.3)	0.22	23 (56.1)	368 (38.4)	.03
Statins		362 (36.2)	80 (32.1)	282 (37.6)	0.14	22 (53.7)	340 (35.5)	.03
Other lipid-lowering medications		58 (5.8)	20 (8.0)	38 (5.1)	0.12	2 (4.9)	56 (5.9)	.94

[a]Ns vary for variables with missing data or indeterminate laboratory findings.

[b]Dementia not included.

TABLE 2 New-onset CV events by TRT status

Cardiovascular events (n=55[a])	Overall (n=999)	Untreated (n=249), n (%)	Treated (n=750), n (%)
DVT since last visit	13		
Only once	11	2 (0.8)	9 (1.2)
Twice	1	0 (0)	1 (0.1)
MI since last visit	14		
Only once	12	2 (0.8)	10 (1.3)
Twice	1	0 (0)	1 (0.1)
Stroke since the last visit	9		
Only once	5	1 (0.4)	4 (0.5)
Twice	2	1 (0.4)	1 (0.1)
PE since last visit	4		
Only once	2	0 (0.0)	2 (0.3)
Twice	1	1 (0.4)	0 (0.0)
CV death in RHYME	5		
Ischaemic heart disease	2	0 (0)	2 (0.3)
Cerebrovascular disease[b]	2	1 (0.4)	1 (0.1)
Heart failure	1	1 (0.4)	0 (0)
Events recorded in comments field[c]	14		
New stent	3	0 (0)	3 (0.4)
New CABG	5	1 (0.4)	4 (0.5)
New AF	3	0 (0)	3 (0.4)
New PCI	1	1 (0.4)	0 (0)
New TIA (occurred twice)	1	0 (0)	1 (0.1)

[a]Events occurred among 41 men.

[b]Cerebrovascular disease was determined by the site's principal investigator/clinician; was not officially adjudicated in one of the two cases.

[c]Collected among men with history of angina or myocardial infarction.

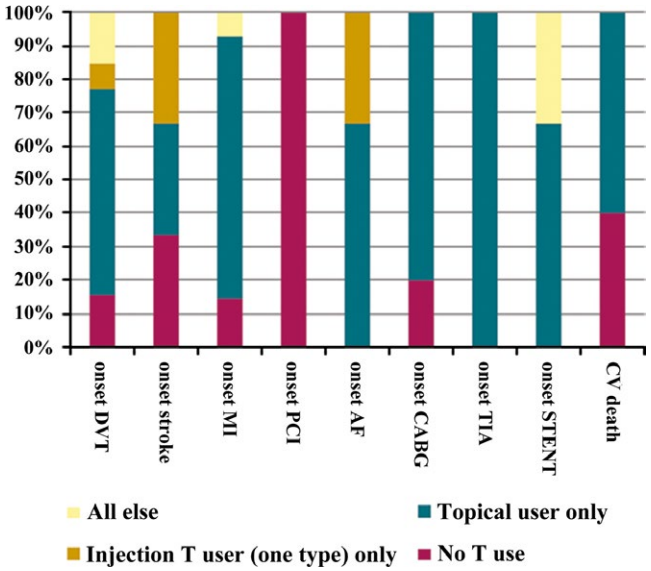

FIGURE 2 CV event classification by route of TRT administration

4 | DISCUSSION

In this large, prospective registry of hypogonadal men, we observed no evidence of increased mortality or more frequent CV events in men receiving TRT compared with untreated men. Adverse CV event rates were significantly related to age, BMI, other comorbidities and risk factors, but not to TRT use in our cohort. Moreover, our CV event rates are roughly comparable to rates for CVD in Europe in 2010 from the WHO European Region's Health with a rate of 2500 per 100 000.[29] This lack of association between TRT use and CV-related adverse events was evident in both younger and older hypogonadal men, regardless of the type of hypogonadism being treated (primary vs. secondary) or mode of TRT administration (injectable vs. topical preparations). None of the CV-related mortalities were judged to be

TABLE 3 Incidence rate of onset CV event by TRT status

	Overall (n=999)	Untreated (n=249)	Treated (n=750)	*P*-value
All RHYME subjects				
Onset CV event (n)	41	9	32	.70
Person-years	2693.2	531.0	2162.2	
Incidence rate (per 100 000 person-years)	1522.3	1694.7	1480.0	
<60 years populations				
Onset CV event (n)	9	2	7	.47
Person-years	1224.4	168.9	1055.6	
Incidence rate (per 100 000 person-years)	735	1184.3	663.1	
≥60 years populations				
Onset CV event (n)	32	7	25	.74
Person-years	1468.8	362.2	1106.6	
Incidence rate (per 100 000 person-years)	2178.7	1932.7	2259.2	
2010 WHO European Region's Health (14)				
Incidence rate (per 100 000 person-years)	2500			

TABLE 4 Multivariable proportional hazards models for onset CV event

Variable	Hazard ratio	95% lower confidence limit for hazard ratio	95% upper confidence limit for hazard ratio	*P*-value
History of hypertension	0.4	0.1	1.1	.08
History of angina	2.6	1.1	6.1	.02
History of DVT	2.1	0.5	9.7	.33
History of peripheral vascular disease	2.4	0.8	7.4	.13
History of congestive heart failure	0.5	0.1	2.9	.45
History of cerebrovascular disease	0.5	0.1	4.4	.57
History of MI	0.5	0.1	2.0	.36
History of PE	5.7	0.6	57.9	.14
History of diabetes	1.1	0.5	2.5	.75
Antihypertensive medications	2.1	0.6	7.2	.23
Statins	1.0	0.5	2.3	.95
Smoking status				
Past	1.9	0.8	4.4	.16
Current	1.5	0.4	5.9	.58
Age at consent	1.1	1	1.1	.0002
Body mass index	1.1	1	1.1	.05
Dyslipidemia	1.4	0.6	3.2	.45

TRT-related, but were significantly associated with prior or current CV conditions.

Our findings are consistent with results from other patient registries in the US[19,20] and Europe,[23,25] showing relative safety of TRT in hypogonadal men with multiple comorbid illnesses and CV risk factors. Moreover, the high retention rate (>90%) reported in these studies was similar to that observed in RHYME (93%), which is attributed to the active role of experienced and committed project staff at each study site, a marked difference to "usual care" management of hypogonadism in large health systems. Other methodologically rigorous retrospective studies[15–18] and a recent, large randomised trial (T-Trial)[14] similarly found no increase in adverse CV events or CV-related mortality in men on active TRT whose testosterone is adequately replaced. The only randomised trial to-date to report increased CV events in elderly, frail men[6] has been criticised for administration of supraphysiological doses of testosterone, inadequate CV assessment prior

to enrolment and inappropriate categorisation of adverse events.[30] Despite FDA's specific labelling caution for potential risks of DVT with TRT,[9] this recommendation is not supported by results from a recent large-scale medical record database review,[18] or the current findings in RHYME or T-Trial.[14]

The large, multi-national sample of men with diagnosed hypogonadism, broad eligibility criteria and large proportion of concomitant CV risk factors and medical illnesses, in addition to regular monitoring of adverse outcomes over a 3 year period of follow-up, contribute to the clinical relevance of our findings. In addition, this is the first large cohort study of hypogonadal men to include sizable samples of men with both primary and secondary hypogonadism, neither of which showed an increase in CV events with TRT. Other strengths of the study included enrolment of consecutive patients at 25 clinical sites throughout Europe, a high retention rate and inclusion of multiple methods of TRT administration. The study was designed and conducted by an independent research organisation (New England Research Institutes) as the first stage in a planned multi-national programme of long-term studies of TRT.[26]

4.1 | Study limitations

Since our primary outcome was prostate cancer incidence, RHYME was not specifically powered to detect changes in mortality or CV risk. At the time the study was initiated (2006–2007), CV risk was not considered a salient risk or likely outcome of TRT. However, the study was designed to obtain comprehensive medical records on all patients during the course of follow-up, and to systematically evaluate CV event rates as a key secondary outcome of the study. Despite limitations regarding the overall number of CV events observed and period of follow-up (2–3 years), no evidence was observed of a trend towards increased mortality or CV events in men receiving TRT in our study. Conversely, we did not find evidence of reduced mortality or improved CV outcomes with TRT, as reported by other investigators.[23–25,30] These benefits may have been observed with a larger patient cohort on TRT or longer period of follow-up. Pending future funding, we plan to obtain 10-year follow-up data on all RHYME patients to investigate further the long-term effects of TRT.

Given the observational design of our study, it is possible that systematic confounding may have influenced our evaluation of outcomes in men on TRT compared with untreated men in the registry. This is unlikely, however, given the large number of variables included in our analyses and control for known covariates in our multivariate analyses. Although lacking the rigorous control of a randomised trial, our study investigated outcomes of TRT in a highly diverse, multi-national sample of hypogonadal men receiving treatment in naturalistic, "real-world" settings. An unfortunate study limitation is the absence of recorded data on the rationale for patient or physician choice of TRT and the type of testosterone formulation selected. Another limitation is the variability in degree of T normalisation achieved, as approximately one third of the RHYME cohort had T levels <10 nmol/L at the last treatment visit. This variability in type of TRT administered and degree of T normalisation achieved are consistent, however, with the non-interventional, observational study design and "real world" applicability of our findings.

Finally, despite the high overall rate of retention and treatment adherence in RHYME, it is possible that selective attrition or treatment discontinuation in patients receiving TRT may have influenced the results. These potential biases were taken into account, however, by assessing incidence rates across treatment conditions in relation to patient years of exposure. Since we observed no evidence of increased CV events in treated men, either in absolute terms or controlling for the duration of exposure, it is unlikely that our findings were due to an imbalance in attrition or treatment discontinuation in either group. Future follow-up may shed further light on this lack of association between TRT and CV events. Regarding the slight increase in plasma testosterone levels observed in untreated men over the course of the study, this may be attributed to systematic monitoring and medical management of all patients in the study, in addition to possible effects of regression to the mean. In contrast to previous reports in the literature,[31–33] we did not observe an increase in CV events in the untreated group, perhaps due to a limited number of untreated men in our cohort and relatively short follow-up period.

4.2 | Conclusions

No evidence was observed of increased CV risk in a large and diverse cohort of hypogonadal men receiving TRT for a period of up to 3 years in a longitudinal, multi-national disease registry. In contrast, and as expected, age and traditional risk factors were significant predictors of CV outcomes in our study.

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Dr Graham Jackson served as consulting cardiologist for RHYME and an active member of the Clinical Endpoints and Adjudication Committee from 2008 until his unfortunate demise earlier in the year. In this pivotal role, Graham made multiple important contributions to the study methods and findings, and contributed actively to the analysis of final data and development of this report. When it became evident in late 2007 that CV risk would be an important outcome of the study, RHYME investigators agreed unanimously that only one cardiologist had sufficient breadth of clinical experience and understanding of men's health and CV disease: Graham Jackson. Despite the pressure of other commitments, including editorship of the journal, Graham agreed willingly and enthusiastically to the assignment. His own research and clinical interests at the time had broadened to include CV aspects of TRT, and it was a natural and inevitable role for him to play. As in our past collaborations on the Princeton Consensus Conferences on Erectile Dysfunction and CV Risk, and various expert panels for the European Sexual Medicine Society and International Society of Men's Health, Graham was always deeply engaged in the scientific and clinical issues, and a "voice of reason" in the face of controversy or dissent. His many contributions to cardiology, men's health and the IJCP have been eloquently expressed in a recent editorial[34] and need no further elaboration. Suffice it to say that he will be sincerely missed by his colleagues in RHYME and all those who had the privilege and pleasure of working with Graham Jackson – a true scholar and gentleman in every sense.

AUTHOR CONTRIBUTIONS

M. Maggi participated in study conception and design, data collection, interpretation of data, critical revision of article and approval of the final version of the manuscript. FCWW participated in study conception and design, data collection, interpretation of data, critical revision of article and approval of the final version of the manuscript. THJ participated in data collection, interpretation of data, critical revision of the article and approval of the final version of the manuscript. GJ participated in study conception and design, collection and interpretation of data, and critical revision of the article. HMB participated in study conception and design, data collection, critical revision of the article and approval of the final version of the manuscript. GH participated in data collection, interpretation of data, critical revision of the article, and approval of the final version of the manuscript. AM-M participated in study conception and design, data collection, interpretation of data, critical revision of article and approval of the final version of the manuscript. GB participated in data collection, critical revision of the article, and approval of the final version of the manuscript. ASD participated in study conception and design, interpretation of data, critical revision of the article, and approval of the final version of the manuscript. STEA participated in study conception and design, data collection, critical revision of the article and approval of the final version of the manuscript. M. Maggio participated in data collection, critical revision of the article and approval of the final version of the manuscript. GRC participated in study conception and design, interpretation of data, critical revision of the article, and approval of the final version of the manuscript. AMI participated in data collection, critical revision of the article and approval of the final version of the manuscript. RQ participated in the critical revision of the article and approval of the final version of the manuscript. OAW participated in data collection, critical revision of the article and approval of the final version of the manuscript. FSS participated in study conception and design, interpretation of data, critical revision of the article, approval of the final version of the manuscript and secured funding. RCR secured funding for the study and participated in study conception and design, interpretation of data, critical revision of the article, approval of the final version of the manuscript.

NOTE

[a] Membership included a cardiologist (G. Jackson), endocrinologist (G. Cunningham) and two urologists (C. Roehrborn, F. Schroder).

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