ANDROLOGY

ISSN: 2047-2919

ANDROLOGY

ORIGINAL ARTICLE

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Keywords:
cardiovascular risk, erectile dysfunction, testosterone

Received: 24-Jan-2014
Revised: 7-Apr-2014
Accepted: 21-May-2014

doi: 10.1111/j.2047-2927.2014.00241.x

Low testosterone syndrome protects subjects with high cardiovascular risk burden from major adverse cardiovascular events

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SUMMARY

The role of testosterone (T) in the cardiovascular (CV) health of men is controversial. Some data suggest that hypogonadism is associated with CV mortality but not morbidity, however, recent evidence shows that hypogonadal subjects treated with T replacement therapy have a higher incidence of new CV events. The aim of this study is to analyse whether gonadal status might predict new CV event incidence according to a patient's previous history of CV events, in a cohort of subjects complaining of sexual dysfunction. A consecutive series of 1687 patients was followed-up for a mean time of 4.3 ± 2.6 years for new occurrence of CV events, detecting 139 events. Hypogonadism (total T < 12 nmol/L) was not associated with an increased incidence of new CV events in the entire cohort. However, when considering patients with a previous history of CV events, hypogonadism was associated with a reduced risk of new CV events, even after adjusting for confounders (hazard ratios – HR = 0.498 [0.240; 0.996]; $p = 0.049$), whereas no relationship was observed in subjects free of previous CV events. Similar results were observed when reduced testis volume (TV) was considered as a predictor of new CV events in subjects with previous CV events (HR = 0.486 [0.257; 0.920]; $p = 0.027$). In patients with a history of previous CV events, but not in those without previous CV events, having both low T and low TV was associated with a lower incidence of new CV events as compared with subjects with only one or none of these conditions, even after adjusting for confounders (HR = 0.514 [0.306; 0.864]; p for trend < 0.02). Notably, CV risk estimated with risk engines based on traditional risk factors was not different between hypogonadal and eugonadal subjects. In conclusion, hypogonadism could be interpreted as a protective mechanism in unhealthy conditions, such as previous CV events, to avoid fatherhood and spare energy.

INTRODUCTION

Several observational studies clearly showed a significant relationship between low testosterone (T) and a higher cardiovascular risk profile (Corona *et al.*, 2011a). It is not completely known whether reduced T levels in elderly males might play a direct pathogenetic role in the stratification of cardiovascular risk, or if cardiovascular diseases (CVD) and low T are concomitant conditions, both associated with the aging process. In fact, at least three different interpretations of such a relationship are plausible: (i) CVD and hypogonadism are concomitant conditions that seniors often face as they age; (ii) low T favours CVD; (iii) CVD induces a hypogonadal state. Much evidence supports all of these possibilities (see for review Araujo *et al.*, 2011; Corona *et al.*, 2013a; Huhtaniemi & Forti, 2011; Ruige *et al.*, 2011; Buvat *et al.*, 2013).

Interventional studies might help in shedding light on this controversy, however, only few clinical trials have investigated the effect of T supplementation (TS) in subjects with known CV diseases (see for review Corona *et al.*, 2013a; Huhtaniemi & Forti, 2011; Buvat *et al.*, 2013). Three meta-analyses on placebo-controlled RCTs with various primary end-points, other than CVD, did not find any significant difference between the TS and placebo groups for all CV events, or for each type of event, except an increase in haematocrit over 50%, which was significantly more prevalent in the active-treated arm (Calof *et al.*, 2005; Haddad *et al.*, 2007; Fernández-Balsells *et al.*, 2010). However, a more recent meta-analysis including 27 RCTs with 2994 eligible elderly men for the first time stated the possibility that TS might *increase* the risk of CV-related events, in particular if non-pharmaceutical industry supported studies were taken into

consideration (Xu *et al.*, 2013). The latter meta-analysis included a larger number of studies evaluating the effect of testosterone replacement therapy (TRT) in older frail and sick men, when compared to the previous ones. As recognized by the Authors, older persons may be affected to a greater extent by any further noxa, because of their greater frailty. It is possible that hypogonadism, even when caused by a pre-existing disease, might contribute to disease progression or induce other conditions, finally resulting in an increased risk of events. Accordingly, the Testosterone in Older Men with Mobility Limitations (TOM) trial, involving older frail men with co-morbidities and testing the effect of a high dose of T on frailty, was stopped prematurely due to an *increased* number of CV events in the treatment arm (Basaria *et al.*, 2010). In a more recent pharmaco-epidemiological study, retrospectively evaluating 8709 male veterans who had undergone coronary angiography between 2005 and 2011, 25.7% of men who were receiving any TS had new CV events, or died from any cause, vs. 19.9% of those who did not receive T therapy (Vigen *et al.*, 2013). More recently, another retrospective study funded by the National Institutes of Health investigated, in a large health care database from Truven Health Analytics, the rate of non-fatal myocardial infarction (MI) in 56 000 middle-aged and older men, who were prescribed TS (Finkle *et al.*, 2014). The authors compared the rate of heart events in the 90 days after starting TS with the rate in the prior year. The study reported a doubling in the risk of heart attack among men aged 65 years and older and a two- to threefold increased risk in younger men with a pre-existing history of heart disease, but not in those without CV events. However, the latter association was not confirmed in individuals prescribed a phosphodiesterase type 5 inhibitor or when the follow-up was extended for other 90 days. In addition, although the authors found an association between TS and increased risk of heart attack, this study, as well as the previous one (Vigen *et al.*, 2013), did not prove a cause- and effect-relationship.

The possibility that low T does not play a causal role in CVD but represents only an indicator of some unidentified, underlying illness and/or of some associated morbidities is growing (Corona *et al.*, 2011b,d). Alternatively, it can be speculated that CVD-associated hypogonadism represents a restraint to male fertility, thus limiting fatherhood in unhealthy conditions such as malnutrition, obesity or chronic illnesses. In fact, increased testis volume (TV) was a positive predictor of unfavourable CV profile and incident CV events (Rastrelli *et al.*, 2013).

Erectile dysfunction (ED), along with other sexual complaints, is now considered a chief symptom of late-onset hypogonadism (LOH) (Wu *et al.*, 2010). A growing amount of evidence has shown that ED is not only associated with LOH, but also an early marker of CVD (Corona *et al.*, 2010a; Dong *et al.*, 2011). In addition, considering that T has a crucial role in the erectile process, the prevalence of hypogonadism is five times higher among patients consulting a medical care unit for ED than in the geographically corresponding general population (Corona *et al.*, 2009a, 2013a). Hence, subjects with ED are a population enriched in both CV risk factors and hypogonadism, therefore, representing the optimal experimental sample to study interactions between the two conditions. We previously reported that in ED populations, hypogonadism was not a risk factor for incident CV events, but it was an independent determinant for their lethality (Corona *et al.*, 2010b).

The aim of this study is to investigate the association between a previous history of CVD and LOH in subjects complaining of sexual dysfunction and to analyse whether the hypogonadal condition might predict new CV events in subjects with and without a previous history of CVD.

MATERIALS AND METHODS

A non-selected series of 4358 male patients attending our Unit seeking medical care, up to July 2013, for ED was retrospectively analysed. The baseline characteristics of the subjects included in the study are reported in Table 1. All patients enroled underwent the usual diagnostic protocol applied to newly referred subjects at our Unit, in agreement with current guidelines (Hatzichristou *et al.*, 2010) as previously reported (Petrone *et al.*, 2003; Corona *et al.*, 2008; Boddi *et al.*, 2012; Corona *et al.*, 2012a). An informed consent to the study was obtained from all subjects enroled. ANDROTEST, a 12-item structured interview previously validated for the screening of hypogonadism in patients with ED, was applied to all subjects as previously reported (Corona *et al.*, 2006a,b).

Chronic Diseases Score (CDS) was calculated and applied to quantify the relevance of concomitant morbidities as previously described (McGregor *et al.*, 2005).

Main outcome measures

A complete physical examination was performed in all patients including the evaluation of blood pressure, height, weight and body mass index (BMI). TV was assessed using

Table 1 Characteristics of the cross-sectional sample. Data are expressed as mean ± SD when normally distributed, median [quartiles] when not normally distributed, and as percentages when categorical

Characteristics	*N* = 4358
Age	51.6 ± 13.1
Education (%)	
None/primary school	13.2
Secondary school	31.8
Secondary higher	35.4
University	19.6
Marital status (%)	
Stable relationship	87.9
Non-stable relationship	12.1
Alcohol consumption (%)	
<4 drinks daily	81.1
4–6 drinks daily	15.4
6–8 drinks daily	2.6
≥8 drinks daily	0.9
Morbidities (%)	
Current smoker	30.0
Hypertension	26.3
Diabetes mellitus	21.2
Previous CV event	12.1
Clinical and laboratory parameters	
Body mass index (kg/m^2)	26.6 ± 4.2
Testis volume (mL)	18.9 ± 4.6
Systolic blood pressure (mmHg)	135 [120–140]
Diastolic blood pressure (mmHg)	80 [80–90]
Glycaemia (mg/dL)	105.4 ± 37.8
Total cholesterol (mg/dL)	201.8 ± 40.6
HDL cholesterol (mg/dL)	48.3 ± 12.4
Triglycerides (mg/dL)	116 [83–164]
Total testosterone (nmol/L)	15.7 ± 6.4
Calculated free testosterone (pmol/L)	306.3 ± 138.2
Prolactin (mU/L)	154 [110–224]
ANDROTEST score	7.6 ± 3.6
Progetto Cuore risk (%)	9.7 ± 10.1

CV, cardiovascular; HDL, high density lipoprotein.

Prader orchidometer as previously reported (Rastrelli *et al.*, 2013). Biochemical analyses were drawn in a fasting condition and included the determination of glycaemia, total cholesterol, HDL cholesterol and triglycerides, total testosterone and prolactin (PRL) as previously reported (Corona *et al.*, 2012b, 2013b). Total T and sex hormone binding globulin (SHBG) were evaluated by electrochemiluminescent method (Modular Roche, Milan, Italy), whereas free T was calculated according to the formula of Vermeulen *et al.* (1999). SHBG, and therefore calculated free T (cFT) were available only for a subset of subjects enroled after September 2006 (2158 and 408 subjects in the cross sectional study and in the longitudinal survey respectively; see below). The characteristics of this sub-set were not significantly different from those of the whole sample (data not shown). Prior CV events were collected as reported by patients.

Longitudinal study

All patients attending the Clinic between 2000 and 2007 (N = 1687) were enroled in a longitudinal study, the characteristics of which have been previously described (Corona *et al.*, 2010a,b). New CV events were classified according to the International Classification of Diseases. In particular, fatal and non-fatal major adverse cardiovascular events (MACE) were coded as 410–414 (ischaemic heart disease), 420–429 (other heart diseases), or 798–799 (sudden death) from cardiac diseases, as 430–434 or 436–438 for cerebrovascular disease and 440 for peripheral arterial disease. Information on mortality and hospitalization up to 31 December 2007, including causes of death, was obtained from the City of Florence Registry Office, which maintains complete and updated records of all persons living within city boundaries. For those individuals who had moved out of the city, queries were sent to the Registry Office of the new city of residence. The assessment of CV predicted risk was evaluated using the algorithm derived from the Progetto Cuore study (Palmieri *et al.*, 2004).

Statistical analysis

Mean ± SD was used to express data when normally distributed, whereas parameters with non-normal distribution were reported as median [quartiles]. One-way ANOVA or Kruskal–Wallis tests were applied to detect differences, according to normal or non-normal distribution. Spearman's or Pearson's methods were used to estimate correlations in not normally or normally distributed parameters respectively. Unpaired two-sided Student's *t*- and Mann–Whitney *U*-tests were applied for comparisons between groups of normally or non-normally distributed variables respectively. Multivariate analyses were performed using stepwise multiple linear or logistic regression models whenever appropriate. Kaplan–Meier analysis of survival was performed with definition of hazard ratios (HR) and 95% confidence intervals, and a stepwise Cox regression was carried out for multivariate analysis adjusting all data for age and CDS (McGregor *et al.*, 2005). All statistical analyses were performed on SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) for Windows 20.1

RESULTS

Cross-sectional study

Among the population studied, 527 (12.1%) subjects reported previous CV events at enrolment. Subjects with a positive history of previous CV events were older and had lower total and cFT when compared to the rest of the sample (Table 2). In addition, higher gonadotropin and SHBG levels along with ANDROTEST score (an index of hypogonadism-related symptoms and signs), as well as lower PRL values, were observed in patients with a history of previous CV events (Table 2). Conversely, no differences between patients with and without previous CV events were observed for TV (Table 2). Based on ROC curve analysis, thresholds of 12 nM, 225 pM and 8.5 were considered for total T, cFT and ANDROTEST score as indicators of previous CV events. A sensitivity and specificity of 71 and 40% were detected when a threshold of 12 nM for total testosterone was considered. Similar results were observed when a cut-off of 225 pM for cFT was chosen (sensitivity and specificity of 74 and 39% respectively). Interestingly, when the validated ANDROTEST pathological score of 8.5 was considered, the sensitivity and specificity for previous CV events were 67 and 65% respectively. The association between history of previous CV events and both total testosterone <12 nM or pathological ANDROTEST score were confirmed even after adjusting for confounding factors, including, age, smoking and drinking habits as well as all important CVD risk factors including diabetes, hypertension, dyslipidemia and pathological BMI (>25 kg/m^2) (OR = 1.275 [1.006; 1.616] and 1.770 [1.245; 2.516] respectively; both $p < 0.05$).

Longitudinal study

In the whole longitudinal sample (n = 1687), during a mean follow-up of 4.3 ± 2.6 years (median 4 years, range 0–8 years), 139 new CV events were observed, as previously reported (Corona *et al.*, 2010a; see also Table S1).

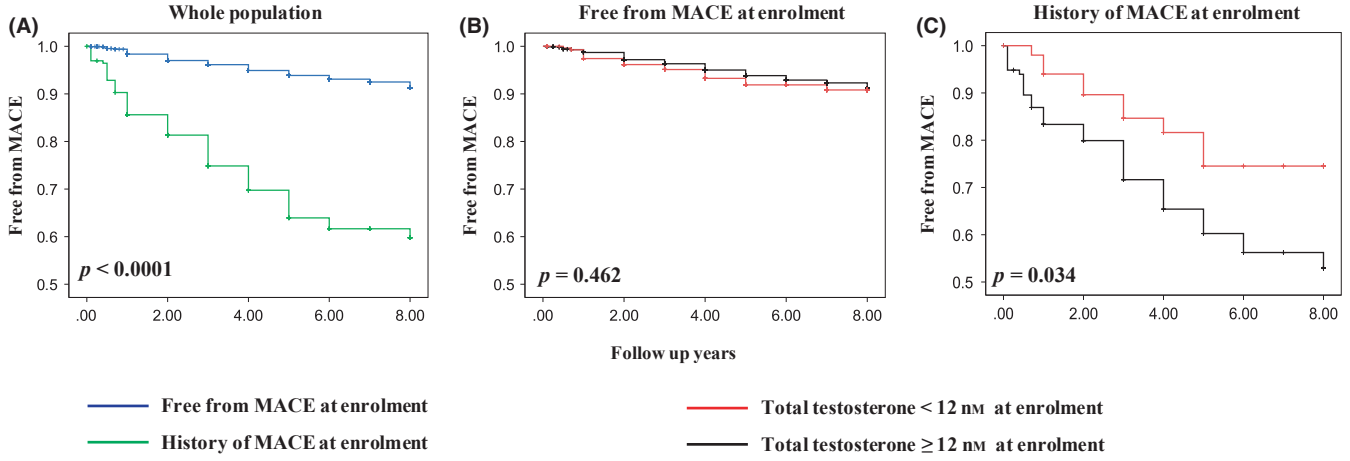
As expected, subjects with a history of previous CV events at enrolment had an increased risk of new CV events at follow-up (Fig. 1A). The association was confirmed in a multivariate Cox regression model, after adjusting for possible confounders such as age, smoking and drinking habits, as well as the presence of co-morbidities, as detected by CDS (HR = 3.751 [2.555; 2.507], $p < 0.0001$). No association between new CV events and hypogonadism (total T < 12 nM) was observed in the entire cohort (χ^2 0.021; p = 0.889). Similarly, no difference in baseline total T, SHBG and cFT levels were observed between subjects with or without a new CV event at follow-up (16.6 ± 6.2 nM vs. 15.9 ± 5.6 nM, 324 ± 127 pM vs. 281 ± 89 pM and 36.6 ± 18.8

Table 2 Difference in clinical and biochemical parameters between subjects with (W) and without (W/O) a history of previous cardiovascular (CV) events

	W/O a history of previous CV events (n = 3831)	W a history of previous CV events (n = 527)	p
Age	49.9 ± 13.1	61.8 ± 8.9	0.0001
Prolactin	156 [112; 229]	141 [105; 200]	0.0001
LH	3.7 [2.6; 5.4]	4.2 [2.9; 6.3]	0.0001
FSH	4.5 [2.9; 7.4]	5.8 [3.8; 10.1]	0.0001
Total testosterone	15.8 ± 6.4	14.6 ± 6.6	0.0001
SHBG[a]	35.4 ± 18.4	39.3 ± 21.8	0.003
Calculated free testosterone[a]	312.2 ± 268.6	135.5 ± 148.9	0.0001
Mean testis volume	19.1 ± 4.5	18.9 ± 4.4	0.531
ANDROTEST score	9.9 ± 2.9	7.3 ± 3.6	0.0001

LH, luteinizing hormone; FSH, follicle stimulating hormone; SHBG, sex hormone binding globulin. [a]Available in a subset of 2158 subjects.

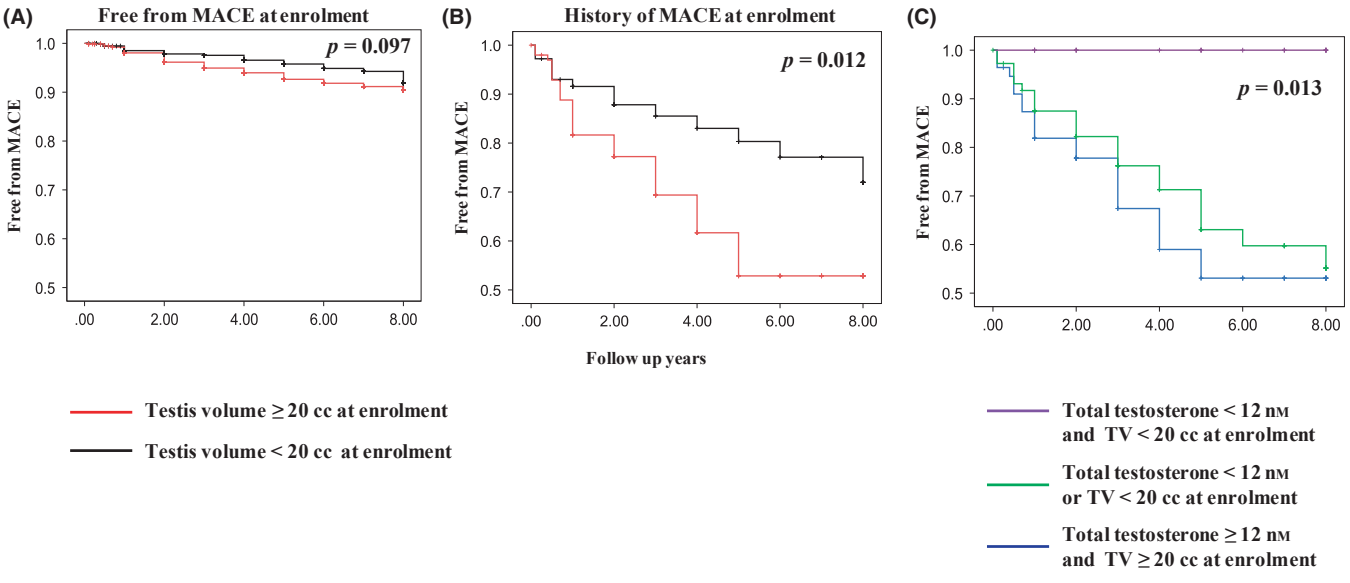
Figure 1 Kaplan–Mayer curves for incident major adverse cardiovascular events (MACE) in the whole population (A) as a function of history of MACE at baseline. (B) and (C) respectively show Kaplan–Mayer curves for incident MACE in the population with and without a history of MACE at enrolment as a function of baseline testosterone.



vs. 41.7 ± 17.2 nM for total T cFT and SHBG respectively; all p = NS). However, when the same analysis was performed according to the history of previous CV events at enrolment, the presence of hypogonadism was significantly associated with a reduced risk of new CV events in patients with a history of previous CV events (Fig. 1C), whereas no relationship was observed in subjects free of previous CV events at baseline (Fig. 1B). The association between new CV events and hypogonadism was confirmed in a Cox regression model after adjusting for the aforementioned confounders (HR = 0.498 [0.240; 0.996]; p = 0.049). Similar results were observed when clinical signs of hypogonadism, such as the presence of reduced TV, were considered (Fig. 2A, B). In particular, the detection of a reduced TV at baseline was associated with a lower incidence of new CV events in subjects with a positive history of CVD (HR = 0.486 [0.257; 0.920]; p = 0.027], but not in the rest of the sample (data not shown).

Finally, in patients with a history of previous CV events at baseline, but not in those free of previous CV events (data not shown), no event was observed in those fulfilling the criteria of low T (total T < 12 nM) and low TV (p < 0.01 vs. those positive for only one factor or eugonadal, Fig. 2C). The protection conferred by hypogonadism was confirmed after adjusting for the aforementioned confounders (HR = 0.514 [0.306; 0.864]; p for trend <0.02). Interestingly, no difference in the predicted CV risk as assessed by Progetto Cuore risk engine score at baseline was detected among the three different groups (10.7 ± 9.9, 12.3 ± 10.9, 12.7 ± 9.6 respectively for eugonadism and one or two factors for hypogonadism; p for trend = 0.144).

Figure 2 Kaplan–Mayer curves for incident major adverse cardiovascular events (MACE) in subjects without (A) and with (B) a history of MACE as a function of testis volume (TV) at baseline. (C) shows the Kaplan–Mayer curves for incident MACE in the population with a history of MACE at enrolment as a function of baseline testosterone and baseline TV.



DISCUSSION

In this study, we confirmed the view (Corona *et al.*, 2011a) that low total and SHBG-unbound T, along with hypogonadism-related symptoms and signs (ANDROTEST score), are all increased in subjects with a previous history of CVD, even in a population at high CV risk, such as those consulting for ED. Hence, hypogonadism is more frequent in ED subjects with previous CVD. However, when a subset of the same cohort was followed longitudinally and categorized according to their baseline history of previous CV events, hypogonadism (total T < 12 nM or 350 ng/dL) was associated, in subjects at high CV risk, with a lower (and not higher) incidence of new CV events. Similar results were obtained when reduced TV was considered: subjects with a history of CVD and lower TV have a lower incidence of CV events, even after adjusting for life-style factors and chronic disease score. When the two factors were combined (low T + low TV), those with a history of CVD and fulfilling the two criteria (low T + low TV) were entirely free of further incident CV events. Present results suggest a protective effect of hypogonadism in subjects with a high CV risk burden.

It has been extensively reported that hypogonadism has a deleterious effect on several metabolic parameters related to CV risk. The underlying mechanisms have been reviewed elsewhere (Huhtaniemi & Forti, 2011; Buvat *et al.*, 2013; Corona *et al.*, 2013a). Therefore, it is conceivable that low T is associated with accelerated atherogenesis. It has also been reported, even by our group (Corona *et al.*, 2010b), and reviewed in three distinct meta-analyses (Araujo *et al.*, 2011; Corona *et al.*, 2011a; Ruige *et al.*, 2011), that hypogonadism is associated with an increased CV mortality, but not morbidity. Two recent retrospective studies in Veterans Administration (Shores *et al.*, 2012) and diabetes (Muraleedharan *et al.*, 2013) subjects with hypogonadism, and their meta-analysis (Corona *et al.*, 2013c), indicate that TS is associated with a decreased overall mortality. However, as there is the non-random assignment of TS, these results should be interpreted cautiously because of the substantial risk of a primary selection bias. Hence, physicians may have selected healthier men for T treatment or not considered treatment in men who were less healthy (Wu *et al.*, 2008). Recent retrospective studies (Vigen *et al.*, 2013; Finkle *et al.*, 2014) and a placebo-controlled (Basaria *et al.*, 2010) trial in unhealthy hypogonadal individuals indicate that TS might increase CV events. We hypothesized the existence of a *low T syndrome*: low T characterizes subjects that are less healthy and frailer, because they are affected by overt or silent chronic diseases, and therefore more prone to fatal CV events. Hence, higher T represents a useful biomarker of general and CV health, as demonstrated also by the present report. On the other hand, the reduction in T in unfavourable situations might represent a protective mechanism, turning off T-dependent functions (such as reproduction and/or physical and sexual activity) that are not desirable when the physical condition, including CV function, is ailing. Similar adaptive mechanisms have been previously described for other hormonal axes. A typical pattern of altered thyroid hormone metabolism, characterized by low T3 circulating levels (*low T3 syndrome*), has been reported in patients with different chronic illnesses, including CVD (Bartalena *et al.*, 1998; Iervasi *et al.*, 2003). In fact, in subjects at high CV burden, but not in those without apparent CV risk factors, low T and lower TV were associated with a significant decrease in incident CV events, which resulted impressive when both factors were simultaneously present. The protective association retained significance even after adjusting for age and known chronic diseases, as measured by Chronic Disease Score.

The finding that *low T syndrome* could protect against forthcoming CV events might be of importance when considering replacement treatment in LOH, a condition where low T is often associated with co-morbidities related to CV burden such as metabolic syndrome (Buvat *et al.*, 2013), type 2 diabetes (Corona *et al.*, 2011c,e,f; Schipf *et al.*, 2011), hypertension (Corona *et al.*, 2009b) and dyslipidaemia (Corona *et al.*, 2011c). In the case that *low T syndrome* is a naturally occurring protective mechanism, its treatment might be deleterious for overall and CV health. In line with this view, a recent meta-analysis of 27 placebo-controlled T intervention studies demonstrated that TRT increased the risk of incident CV events (Xu *et al.*, 2013). Although previous meta-analyses failed to demonstrate any adverse effects of TRT on forthcoming CV events (Calof *et al.*, 2005; Haddad *et al.*, 2007; Fernández-Balsells *et al.*, 2010), they also did not show any advantage of T substitution in CV health, while erythrocytosis was universally demonstrated. In addition, although Haddad *et al.* (2007) in their meta-analysis did not reach statistical significance for CV events, the overall pooled OR was 1.82 and the OR for MI was 2.24 suggesting a trend towards an increased risk related to TS. In addition, men typically die earlier than women in Westernized societies (Lindau & Gavrilova, 2010), often interpreted, even by us (Corona *et al.*, 2010a), because of the typical risky behaviours associated with maleness. On the other hand, Nieschlag *et al.* (1993) compared the lifespan of castrated and intact males and did not reveal any differences in total or CV mortality. Supporting this view, castration prolonged lifespan in eunuchs (Min *et al.*, 2012) and in mentally ill, institutionalized men (Hamilton & Mestler, 1969).

We believe that the observation of an epidemiological association between a clinical condition (low T) and CV events may prompt clinicians to treat the supposed risk factor aggressively. Our data show, however, that careful consideration of the mechanisms involved is always necessary prior to translating observational data into therapeutic decisions. In fact, many epidemiological associations are determined by adaptive mechanisms and not by pathogenetic factors; the treatment of a compensatory alteration can easily produce a detrimental effect.

Several limitations of this study should be recognized. These results are derived from patients consulting an Italian Andrology Clinic for ED, which could have different characteristics from those consulting general practitioners or not seeking medical care. Furthermore, it should be recognized that the results obtained in specific clinical settings cannot be easily generalized to wider populations. Conversely, phenomena observed in samples from the general population cannot always be extended to patients seeking treatment for a specific condition. The values of the testosterone levels reported reflect the first measurement. Regardless of whether the first measurement resulted as being pathological (total testosterone < 12 nM) or not, T levels were then systematically reassessed, at least a second time, before decision making. However, only the first T determination is available in our database. It should be recognized that we were unable to determine whether some of the hypogonadal patients

received replacement therapy during follow-up, however, we hypothesized that TS would bias the results towards the null, because it would minimize the differences between men with low and normal T levels. In addition, the retrospective nature of this study does not allow us to capture systematic determinations of T levels during follow-up. No data on physical function were available; in fact, an accurate assessment of physical activity levels is difficult per se, and even more so in a retrospective study. A further limitation is represented by the fact that CV events were identified using administrative sources, without access to clinical documentation. This procedure, which allows the collection of a full dataset without any loss at follow-up, has the disadvantage of possible misclassification of some cases. In our Unit, all the physicians have been systematically trained to estimate TV using Prader orchidometer, as a part of their andrology training, however, we cannot deny that, during the study, variability in TV estimation during clinical evaluation by different investigators could have occurred. Nonetheless, our results – obtained in a large series of patients seeking medical care for sexual dysfunction – showed that this procedure might be an important source of clinical information for cardiovascular stratification.

In conclusion, our data suggest that hypogonadism could be interpreted as a resilient strategy in unhealthy situations, such as previous CV events, to protect the species from inefficient fathers and the subjects from spending excessive energy. In our opinion, the *low T syndrome* denotes a protective condition, characterizing frail men; because they are frail men, they die more often from CV diseases. This hypothesis needs to be corroborated by further studies.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Type and age distribution of the 139 new cardiovascular (CV) events occurring during the longitudinal study**.**