

Testosterone Therapy: Increase in Hematocrit is Associated with Decreased Mortality

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Abstract

Objective: Testosterone therapy (TTh) may reduce morbidity/mortality in men with adult-onset testosterone deficiency (TD), though some cardiovascular safety concerns remain. Increased hematocrit (HCT), a recognized effect of therapy, may be associated with cardiovascular disease and mortality. We examined HCT change (Δ) in men prescribed/not prescribed testosterone, and associations with mortality.

Methods: We analyzed data from a prospective registry study with adult-onset TD patients: 353 men given testosterone undecanoate (TU) and 384 opting against TTh. Change in HCT after 12, 48, 72, and 96 months of TU and at final assessment was compared (nonparametric tests). The association between baseline HCT, Δ HCT, and mortality was studied using logistic and Cox regression.

Results: HCT increased significantly (median change at final assessment: +5.0%) in men on TTh. HCT was higher ($p=0.021$, rank-sum test) in those alive than in those who died, although median values were identical (49.0%). Baseline HCT and Δ HCT were inversely associated with mortality after adjustment for age in both logistic and Cox regression models. Men with final HCT >49.0% (median) suffered lower mortality than men with HCT \leq 49.0%.

Conclusions: A median HCT increase of 5.0% was associated with TTh, mostly within 48 months of commencing therapy. An increase in HCT (up to 52.0% at final assessment) was independently associated with reduced mortality, indicating current guidelines using a HCT value of 54.0% as a threshold for management change are appropriate until further study.

Keywords: testosterone therapy; hematocrit; hemoglobin; adult-onset hypogonadism; mortality

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Introduction

Adult-onset testosterone deficiency (TD) (also known as late-onset TD, age-related TD, and functional TD) describes, after exclusion of primary (testicular) and secondary (pituitary/hypothalamic) pathology, a combination of low serum testosterone and associated symptoms that include reduced bone mineral density, muscular strength, cognition, and sexual dysfunction.^{1–3} Prevalence is estimated at 6–12%^{4,5} with levels as high as 40% reported in men with type 2 diabetes (T2DM).^{6,7} The diagnosis is important as adult-onset TD is also associated with increased mortality.⁸ The belief that low serum testosterone is key in the causation of increased morbidity and mortality is supported by the finding that testosterone therapy (TTh) results in significant improvements in associated symptoms including sexual function, depression, physical performance, anemia, and bone mineral density⁹ in men with adult-onset TD as well as reduction in mortality in men with T2DM.^{10–13}

However, concerns remain regarding the safety of TTh. Although most studies demonstrate benefit or no change in cardiovascular disease (CVD), a few have reported higher CVD in men prescribed TTh.^{14–17} An explanation for these discrepant findings is that the population of men with adult-onset TD is heterogeneous¹⁸; thus, subgroups with different lifestyles, genetic, and environmental factors may influence clinical outcomes. Hematocrit (HCT) is a possible candidate in determining outcome as an increase in this variable is the commonest effect of TTh.^{19–21} Different guidelines have set varying HCT percentage thresholds above which they recommend withholding/discontinuing TTh and/or phlebotomy. For example, the British Society of Sexual Medicine,⁴ Endocrine Society,²² American Urological Association,²³ and European Association of Urology²⁴ have all adopted a threshold of 54%. The International Society for the Study of the Aging Male has adopted an HCT threshold of 52%,²⁵ whereas the International Consultation for Sexual Medicine²⁶ has recommended an even more conservative HCT threshold of just 50%.

HCT levels have been associated with changes in morbidity and mortality, although findings vary.¹⁹ A meta-analysis of 16 studies has shown that the highest HCT tertile (>0.463) was associated with increased CVD compared with the lowest tertile (<0.417).²⁷ Similarly, in the Framingham cohort (of >34 years follow-up), the highest HCT quintile was associated with increased CVD as well as all-cause mortality.²⁸

However, the European Prospective Investigation into Cancer and Nutrition-Netherlands study found no difference in CVD between the tertile distributions (>0.47 vs. <0.45) in CVD-free individuals.²⁹ In the Scottish Heart Health Extended Cohort Study, HCT (mean \pm SD: 0.4381 ± 0.0394) was significantly associated with CVD events and mortality, although this association was lost when the analysis was adjusted for the following confounders: lipids, blood pressure (BP), diabetes, smoking status, family history of CVD, and fibrinogen.³⁰

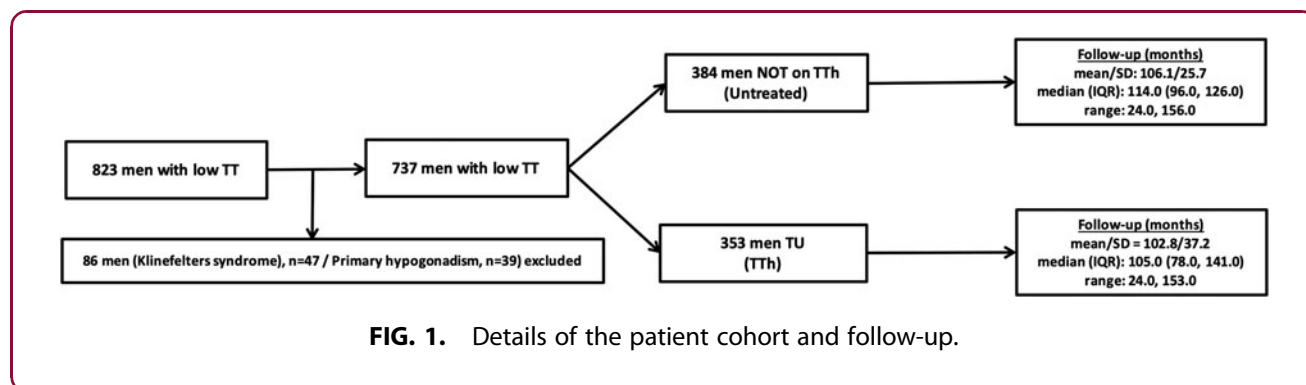
Boffetta et al. suggested that this lack of consensus may result from a nonlinear relationship between HCT, CVD, and mortality.³¹ Thus, a U-shaped relationship between categories of HCT and mortality was found in Iranian adults of both genders, with low and high HCT values associated with increased overall mortality.³¹ Locatelli et al. found, after erythropoietin therapy in patients with end-stage renal disease and low baseline HCT (0.301 ± 0.045), that mortality was inversely proportional to the increase in HCT, also suggesting that the association between morbidity/mortality and HCT is nonlinear.³²

The clinical impact of increased HCT during TTh requires further understanding. In this study, we report baseline characteristics of the men prescribed/not prescribed TTh and compare changes in HCT (intra- and intergroup), though our focus is primarily on men prescribed TTh. This is because of the current uncertainty regarding clinical outcomes associated with change in HCT after TTh. We studied the relationship between HCT and all-cause mortality in men on TTh. HCT is associated with hemoglobin (Hb) level^{33,34} and BP,^{35–37} both of which are predictors of mortality.^{38–42} Hence, these and other established risk factors such as waist circumference (WC), HbA1c, total cholesterol (TC), and triglycerides (TG) at the final assessment were included (if found to be significantly associated with mortality) as confounding variables.

Materials and Methods

We describe analysis of an observational prospective cumulative registry study comprising 737 men diagnosed with adult-onset TD in view of a serum total testosterone (TT) ≤ 12.1 nmol/L and symptoms of TD. In total, 737 men were recruited from 823 men presenting with urological symptoms and diagnosed with TD, after exclusion of primary hypogonadism ($n=39$) and Klinefelter syndrome ($n=47$) (Fig. 1). All the men were offered TTh. Testosterone undecanoate (TU)





1000 mg per 12 weeks after an initial 6-week interval was commenced in 353 men [median age (IQR): 60.0 (55, 64) years, median follow-up (IQR): 105.0 (78, 141) months] whereas the remaining 384 men [median age (IQR): 64.0 (60.0, 67.0) years, median follow-up (IQR): 114.0 (96, 126) months] opted against TTh (untreated) due to financial constraints and/or negative perceptions of TTh (Fig. 1 and Table 1). Data were gathered regularly (at least 6 monthly) during follow-up in all men. The German Medical Association’s ethical guidelines for observational studies were followed and every participant consented to be included and have their data analyzed after being provided study details. Ethics committees (Germany and England) reviewed the study and stated that formal approval was not required. Institutional review board approval was received from University Hospitals Birmingham NHS Foundation Trust.

Study measurements

Serum TT (trough levels) was measured using an immunoassay (Abbott Architect). Hb levels were determined using photometry (CELL DYN Ruby/Abbott) and HCT was calculated using Microhaematocrit (Mindray 3000 Plus). HbA1c was measured using a high-performance liquid chromatography method on a TOSOH G7 (HLC-723-Series), whereas TC and TG concentrations were measured using a colorimetric assay on the Abbott Alinity c-Module (colorimetric analysis). BP was taken with the patient seated with his left arm resting at heart level using a sphygmomanometer according to protocol. Systolic and diastolic Korotkoff sounds were assessed twice to increase precision. Once all the requirement measurements were completed, Nebido[®] was administered intramuscularly and BP was again determined after a few minutes. The two values were usually the same, but if there was a dif-

ference of <5 mmHg, an average was taken, if there was a difference of >5 mmHg, a third measurement was made, and the mean of the closer values was accepted. WC was measured midway between the upper hip bone and the uppermost border of the right iliac crest.

Statistical methods

The baseline HCT in the total cohort was not normally distributed with both skewness ($p < 0.0001$) and kurtosis ($p < 0.0001$) evident, hence nonparametric tests were carried out when comparing HCT distributions. Baseline factors in men on TTh and those untreated were compared using rank-sum and chi square tests. Change during follow-up in the former group was analyzed through sign-rank tests. Risk factor prevalence between survivors/nonsurvivors in TTh-treated men was compared using rank-sum (univariate) and logistic regression (multivariate) analyses. Cox regression analyses were used to additionally study the association between HCT at final assessment (stratified) and survival, with these data presented as a Kaplan–Meier plot.

Results

Table 1 shows baseline data from both groups: men commencing ($n = 353$) and opting against ($n = 384$) TTh. Baseline HCT and Hb were significantly ($p < 0.0001$) lower in men in the TTh group. Metabolic indices also differed significantly with those about to commence TTh having higher baseline HbA1c, BP, TC, and TG levels, but lower WC (Table 1). No difference was observed in the frequency of T2DM or smoking status (Table 1 footnote). Table 1 also shows the differences between data at baseline and final assessment in men prescribed TTh: median change (Δ) in HCT (IQR) was 5.0 (3.0, 7.0)% and median Δ Hb levels (IQR) were 0.6 (0.3, 0.7) g/dL. Apart from the expected increase in trough levels of serum TT, significant



Table 1. Baseline Data of Testosterone Therapy-Treated and Untreated Men, and Changes at Final Assessment in Testosterone Therapy-Treated Men

	Baseline		Final assessment		
	Untreated		TTh (TU)	TTh (TU)	
No. of men	384		353		
	<i>p</i> (intergroup)		Change in values		<i>p</i> (intragroup)
	Median (IQR)		Median (IQR)	Median (IQR)	(Baseline vs. final)
Follow-up (months)	114.0 (96, 126)	0.52	105.0 (78, 141)		
Age (years)	64.0 (60.0, 67.0)	<0.0001	60.0 (55.0, 64.0)		
TT (nmol/l) (trough)	9.7 (9.4, 10.4)	0.079	10.1 (9.4, 10.7)	9.0 (7.6, 10.4)	<0.0001
HCT (%)	46.0 (45.0, 47.0)	<0.0001	44.0 (43.0, 46.0)	5.0 (3.0, 7.0)	<0.0001
Hb (g/dL)	14.7 (14.3, 15.1)	<0.0001	14.5 (14.1, 14.9)	0.5 (0.3, 0.7)	<0.0001
WC (cm)	109.0 (102.5, 116.0)	0.022	108.0 (100.0, 114.0)	-10.0 (-13.0, -6.0)	<0.0001
HbA1c (%)	5.4 (5.1, 7.7)	<0.0001	8.2 (5.8, 8.9), <i>n</i> =270	-2.1 (-3.2, -0.7)	<0.0001
Systolic BP (mmHg)	137.5 (131.5, 154.0)	<0.0001	158.0 (141.0, 167.0)	-25.0 (-37.0, -13.0)	<0.0001
Diastolic BP (mmHg)	78.0 (75.0, 88.0)	<0.0001	94.0 (83.0, 98.0)	-17.0 (-24, -9.0)	<0.0001
TC (mmol/L)	6.5 (5.6, 7.4)	<0.0001	7.7 (7.2, 8.6)	-2.6 (-3.3, -2.1)	<0.0001
TG (mmol/L)	2.9 (2.6, 3.3)	<0.0001	3.2 (2.8, 3.5)	-0.1 (-1.3, -0.6)	<0.0001

Rank-sum and sign-rank nonparametric tests were carried out to determine differences between baseline data (intergroup: untreated vs. TTh) and changes seen at final assessment in men on TTh (intragroup) respectively. No significant differences (chi square) were observed between the two groups regarding T2DM (untreated: 42.7%, TTh: 41.9%, *p*=0.83), smoking status (untreated: 36.8%, TTh: 38.2%, *p*=0.69).

BP, blood pressure; Hb, hemoglobin; HCT, hematocrit; T2DM, type 2 diabetes; TC, total cholesterol; TG, triglyceride; TT, total testosterone; TTh, testosterone therapy; TU, testosterone undecanoate; WC, waist circumference.

improvements in WC, HbA1c, BP (systolic and diastolic), TC, and TG were associated with TTh. In men not given TTh, median Δ HCT (IQR) was 0.0 (-1.0, 2.0) at final assessment (however, sign-rank test suggested a higher HCT at final assessment, *p*=0.0003).

Change in HCT at fixed time points during follow-up

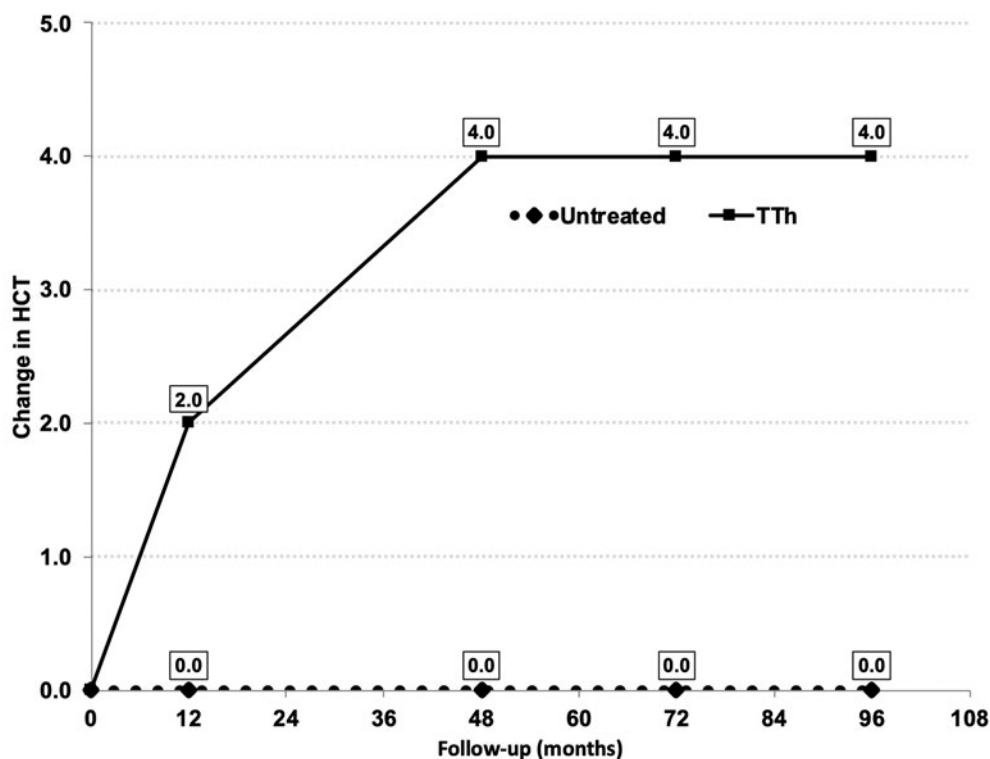
Figure 2 shows median Δ HCT at 12, 48, 72, and 96 months in men prescribed/not prescribed TTh. There was a small but significant increase in HCT distribution (although the median change was 0%) in untreated men (*n*=294) after 96 months compared with baseline, but not at 12, 48, or 72 months (median Δ HCT was 0% at all the time points). In contrast median HCT increased significantly after 12 months in men given TTh with the median Δ HCT subsequently increasing. The median Δ HCT (+4%) was identical at 48, 72, and 96 months of follow-up. At each time point, Δ HCT was greater in the TTh group (rank-sum test) than in untreated men (Fig. 2).

Association between HCT and all-cause mortality

All-cause mortality was significantly higher (*p*<0.0001, Chi Sq) in men not prescribed TTh [74/384 men (19.3%)] than in men on TTh [20/353 men (5.7%)]. Table 2 shows that in men given TTh, HCT was significantly higher (*p*=0.021, rank-sum test) in

men alive [median (IQR): 49.0 (48.0, 50.0)%] than in those who died [median (IQR): 49.0 (48.0, 49.0)%]. Table 2 also shows that age, diastolic BP, and TC at final assessment were significantly higher, whereas TT was lower in the men who died. Accordingly, the association between HCT (baseline and Δ) and mortality was confirmed with logistic regression analyses after adjusting for the mentioned confounding variables (Table 3: Model 1). Importantly, Table 2 shows that Hb was not associated with mortality and was not included as a confounding variable in the logistic regression analyses described in Table 3. Both baseline HCT and Δ HCT were inversely associated with mortality, and age at final assessment (baseline age+follow-up) was positively associated with mortality (Table 3: Model 1). Serum TT, diastolic BP, and TC were not associated with mortality. Interestingly, higher baseline HCT and greater Δ HCT were associated with lower mortality and with similar odds ratios (ORs). Table 3 (Model 2) gives the logistic regression analyses with baseline HCT, Δ HCT, and age at final assessment as independent variables, with all three conferring a significant association with mortality. We then replaced baseline HCT and Δ HCT with its sum (HCT at final assessment), and this, as expected from the previous logistic regression models, remained significantly associated with mortality (Table 3: Model 3). To further characterize the relationship between





Follow-up (months)	Untreated: median Δ HCT (IQR) %, p (sign-rank test)	TTh: median Δ HCT (IQR) %, p (sign-rank test)	p (rank-sum test)
12	0.0 (-1.0, 1.0), p=0.97 (n=384)	2.0 (1.0, 4.0), p<0.0001 (n=353)	p<0.0001
48	0.0 (-1.0, 1.0), p=0.67 (n=367)	4.0 (2.0, 6.0), p<0.0001 (n=313)	p<0.0001
72	0.0 (-2.0, 1.0), p=0.34 (n=343)	4.0 (2.0, 6.0), p<0.0001 (n=279)	p<0.0001
96	0.0 (-1.0, 2.0), p=0.0003 (n=294)	4.0 (2.0, 7.0), p<0.0001 (n=207)	p<0.0001

Sign-rank test: compared to baseline values (within group).

Rank-sum test: between group comparison at that time point.

FIG. 2. Change in HCT at fixed time points (12, 48, 72 and 96 months) in untreated and TTh groups. HCT, hematocrit; TTh, testosterone therapy.

HCT at final assessment and mortality, we stratified the cohort by the median HCT (49%) at final assessment and found that men with HCT (50–52%) at final visit were at lower risk of mortality (Table 3: Model 4) than their counterparts (HCT: 46–49%). It was noted that the median HCT at final assessment of 49% was observed in a large proportion of men ($n=123$), hence a further logistic regression analysis (not shown in Table 3) was carried out, adjusted for age at final assessment and excluding these 123 men. Men with HCT at final assessment of 50–52% ($n=122$) were once again associated with lower mortality (OR:

0.083, 95% CI: 0.010–0.69, $p=0.021$) than their counterparts with HCT at final assessment of 46–48% ($n=108$). Table 3 (footnote) provides the unadjusted mortality rates by HCT at final assessment [46–48% HCT: 8/108 (7.4%), 49% HCT: 11/123 (8.9%), 50–52% HCT: 1/122 (0.8%)].

To graphically demonstrate the difference in survival in men on TTh stratified by the median HCT at final assessment, we plotted a Kaplan–Meier survival curve (Fig. 3) based on a Cox regression analysis (Fig. 3 footnote: Model 2), which, like the previous logistic regression analyses, also demonstrated that men with final



Table 2. Comparison of Variables at Final Assessment in Men Given Testosterone Therapy, Stratified by Mortality

	Men on TTh (n = 353)		p (rank-sum)
	Alive	Dead	
No. of men	333	20	
	Median (IQR)		
Baseline age (years)	59.0 (55.0, 63.0)	66.0 (62.0, 68.0)	0.0001
Follow-up (months)	102.0 (78.0, 141.0)	130.5 (94.5, 135.0)	0.35
	Data at final assessment		
HCT (%)	49.0 (48.0, 50.0)	49.0 (48.0, 49.0)	0.021
Hb (g/dL)	14.9 (14.7, 15.3)	15.0 (14.7, 15.3)	0.89
Age (years)	68.5 (64.0, 71.5)	77.5 (69.3, 78.8)	<0.0001
TT (nmol/L)	19.1 (17.7, 19.8)	17.9 (16.8, 18.7)	0.0050
WC (cm)	97.0 (94.0, 101.0)	98.5 (93.5, 103.0)	0.66
HbA1c (%) (n = 269)	5.4 (5.2, 5.8) n = 255	5.7 (5.4, 6.1) n = 14	0.089
Systolic BP (mmHg) (n = 332)	128.0 (123.0, 133)	130.0 (126.0, 135.0)	0.12
Diastolic BP (mmHg)	75.0 (73.0, 77.0)	77.0 (74.0, 82.0)	0.017
TC (mmol/L)	5.2 (4.9, 5.4)	5.3 (5.1, 5.4)	0.019
TG (mmol/L)	2.2 (2.1, 2.3)	2.2 (2.1, 2.2)	0.99

Intragroup differences were determined using rank-sum nonparametric tests.

Table 3. Logistic Regression Analyses Studying the Association Between Baseline Hematocrit, Δ Hematocrit, Hematocrit at Final Assessment, and Mortality, the Analyses Adjusted for Confounders (Factors Significantly Associated with Mortality in Table 2) in Men on Testosterone Therapy

	OR (95% CI)	p
Model 1		
Baseline HCT	0.50 (0.31–0.79)	0.004
Δ HCT	0.55 (0.35–0.88)	0.012
Age at final assessment (years)	1.26 (1.13–1.41)	<0.001
TT at final assessment (nmol/L)	0.88 (0.74–1.04)	0.13
Diastolic BP at final assessment (mmHg)	1.07 (0.95–1.21)	0.24
Total cholesterol at final assessment (mmol/L)	1.56 (0.36–6.85)	0.55
Model 2		
Baseline HCT	0.49 (0.31–0.79)	0.003
Δ HCT	0.54 (0.34–0.86)	0.009
Age at final assessment (years)	1.26 (1.13–1.40)	<0.001
Model 3		
HCT at final assessment	0.53 (0.33–0.83)	0.006
Age at final assessment (years)	1.27 (1.14–1.41)	<0.001
Model 4 (factorized HCT)		
HCT at final assessment >49 (50–52)%	0.091 (0.012–0.70)	0.006
HCT at final assessment ≤49 (46–49)%	reference	
Age at final assessment (years)	1.27 (1.14–1.41)	<0.001

Adding T2DM into the regression models did not change the association between HCT indices, age, and mortality. Unadjusted mortality rates by HCT at final assessment (median: 49%). HCT (46–48%): mortality = 8/108 (7.4%), HCT (49%): mortality = 11/123 (8.9%), HCT (50–52%): mortality = 1/122 (0.8%).

ORs, odds ratios.

assessment HCT >49% were at lower risk of mortality (Fig. 3 footnote: Model 1), even when adjusted for age at final assessment.

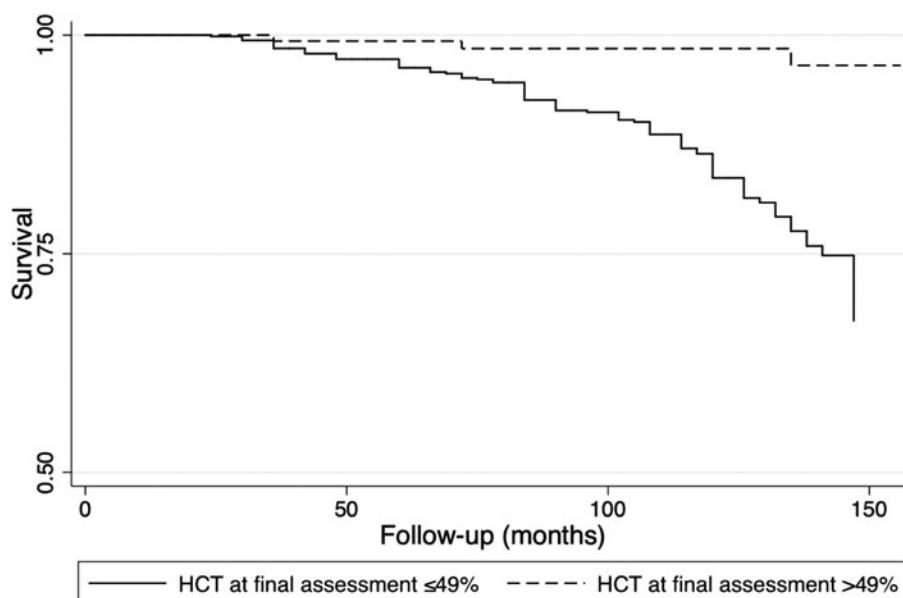
Although this article is mainly focused on men given TTh, we also present data on the association between HCT at final assessment and mortality in 384 men opting against TTh. At final assessment, HCT was significantly higher ($p=0.0001$, rank-sum test) in men alive [median (IQR): 46.0 (45.0, 47.0)%, $n=310$] than in those deceased [median (IQR): 45.0 (44.0, 46.0)%, $n=74$]. However, a logistic regression analysis revealed that HCT at final assessment was not associated with mortality (OR: 0.92, 95% CI: 0.81–1.04, $p=0.20$) when adjusting for the confounding variables (TT, WC, HbA1c, BP, and lipid values) at final assessment. This was the case when baseline HCT (OR: 0.88, 95% CI: 0.68–1.14, $p=0.32$) and Δ HCT (OR: 0.92, 95% CI: 0.81–1.05, $p=0.23$) were substituted for HCT at final assessment as independent variables.

Discussion

Increased HCT is a common consequence of TTh and clinical guidelines set action thresholds for discontinuing treatment that are not based on clear outcome evidence.^{4,22–26} Longitudinal studies suggest that HCT influences CVD morbidity and mortality, although the association may not be linear. We used an ongoing registry database to demonstrate the pattern of Δ HCT associated with TTh, and study putative associations with all-cause mortality. Although HCT was not significantly changed in men not prescribed TTh, it was significantly higher (median: +5.0%) in men on TTh at the end of follow-up. Increased values were observed at 12, 48, 72, and 96 months after TTh compared with baseline, although most of the increase was evident before 48 months (Fig. 2). Down-titrating/discontinuing TU was not required as HCT did not exceed 52% in the 353 men given TTh.

It is tempting to state that the TTh-associated increase in HCT could be a reversal of low HCT values associated with low testosterone in adult-onset TD. However, the distribution of baseline values in both untreated (mean HCT: 45.8%, 95% distribution: 44–48%) and treated men (mean: 43.8%, 95% distribution: 37–47%) was within the reference range (38.3–48.6%) for males quoted by the Mayo Clinic.⁴³ Furthermore, HCT at final assessment in men on TTh (mean: 49.1%, 95% distribution: 47–51%) appears higher than the Mayo Clinic reference range (only 30.6% of





Median HCT at final assessment = 49%
 The above plot is based on model 2 of the Cox regression analysis.

	HR (95% CI)	p
Model 1		
HCT at final assessment >49 (50 - 52)	0.11 (0.015 / 0.84)	0.033
HCT at final assessment ≤49 (46 - 49)	reference	
Age at final assessment (years)	1.15 (1.04 / 1.26)	0.006
Model 2		
HCT at final assessment >49 (50 - 52)	0.095 (0.013 / 0.71)	0.022
HCT at final assessment ≤49 (46 - 49)	reference	

FIG. 3. Kaplan-Meier survival curves of men on TTh, stratified by the median HCT at final assessment.

men having values within this distribution). Thus, it is unlikely to be a return to higher normal levels from a previously low level associated with TD, unless the quoted reference range is subject to a lowering of values due to a high proportion of men with adult-onset TD (prevalence considered to be 6–12%).⁴

Baseline and Δ HCT were inversely associated with mortality in men on TTh with similar ORs, independent of age, serum TT, WC, HbA1c, BP, and lipids. The greater the baseline value and increase in HCT after TTh, the lower the risk of mortality. This association remained evident when HCT at final assessment (as a continuous variable and stratified by median value

and used in a logistic regression model as a factorized variable) was substituted for baseline and Δ HCT. Our data suggest that mortality risk reduction is evident with an upper end of HCT distribution at 52% (50–52%) compared with a lower HCT (46–49%); thus, we recommend the HCT action threshold remains at 54% in well-hydrated men as dehydration can raise HCT.⁴⁴ At this moment, HCT could be considered a marker associated with mortality risk. Oxygen content in the blood is related linearly to HCT and increased HCT could plausibly increase tissue oxygenation.^{45,46} However, increased HCT will exponentially increase blood viscosity, thereby potentially reducing



blood flow.^{47,48} Thus, an ideal HCT should allow optimized tissue oxygenation and blood flow, adding credence to the concept of a U- or J-shaped association between HCT and morbidity/mortality.^{19,31,32} We did not observe a U- or J-shaped association with mortality, with the upper limit of the HCT distribution in our cohort reaching 52%, the inverse association appeared to continue to this point.

HCT at final assessment was not related with mortality in men not given TTh, when adjusted for other confounding variables. Hence, our focus remained with men on TTh. Interestingly, although many of the metabolic risk factors such as WC, HbA1c, BP, and TC were significantly decreased in men on TTh (Table 1), they were not related to intragroup mortality (Table 2).

The clinical impact of TTh-associated elevated HCT is currently in focus after the 24-month T4DM randomized controlled trial, which showed that TU/lifestyle measures (504 obese/overweight men aged 50–74 years with impaired glucose tolerance or newly diagnosed T2DM) were associated with significantly lower glucose values, compared with 503 men on placebo/lifestyle measures.⁴⁹ In contrast to our study where no man was seen to have an HCT >52%, 22% (106 men) of the men on TU had at least a single HCT \geq 54% compared with 1% (6 men) treated with placebo, although it is emphasized that TU was discontinued in only 23 men due to two HCT values \geq 54%.⁴⁹

This longitudinal registry study has strengths and weaknesses. Treatment compliance was not an issue as TU was administered in clinic. Follow-up was long and we had an almost complete data set (except HbA1c). The nature of the study resulted in patients not being randomized into TTh-treated and untreated groups and differences in baseline factors were evident. To counter this, most of the analyses describe intragroup comparisons. Furthermore, our analyses using mortality as the outcome centered on the TTh group as Δ HCT only significantly changed in this cohort (Table 1), hence the disparity of risk factor levels between the two groups was not an issue. The results obtained were not affected when the cohort was stratified by T2DM (Tables 1 and 3).

Conclusions

Our study, characterizing increase in HCT associated with TTh, shows a median increase in HCT of 5.0%, mostly occurring in the initial 48 months of treatment. Our data show that benefit in mortality ex-

tended to HCT values of 52%, the HCT distribution did not allow us to extend this value further. Although it is premature to speculate whether the change in HCT is causative or a surrogate affecting the association between TTh and mortality, the data indicate current guidance suggesting only HCT >54% should trigger changes in TTh treatment, appears reasonable.⁴

Randomized controlled trials are needed to further investigate our findings regarding entry and exit thresholds and also on the association between HCT and mortality to evaluate a possible causative role using the current modified versions of the Bradford Hill criteria.^{50,51}

Authors' Contributions

R.C.S. designed the study and prepared the article. C.S.K. designed the study, analyzed data, and prepared the article. A.A. designed the study and prepared the article. G.H. prepared the article. A.H. and K.S.H. recruited patients, collected data, and prepared the article. P.D. transposed data and maintained the database. F.S. maintained the database, designed the study, and prepared the article. N.L. analyzed data and prepared the article. A.M. analyzed data and prepared the article. S.R. designed the study, analyzed data, and prepared the article.

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S.R. has received research grants, travel grants, and speakers' honoraria from Besins Healthcare. F.S. works as a consultant for and is a stockholder of Bayer AG. G.H. has been an occasional speaker for Bayer AG and Besins Healthcare. A.H. and K.S.H. have received research grants, travel grants, and speakers' honoraria from Bayer AG. R.C.S. has received funding from the North Staffordshire Medical Institute. C.S.K., A.A., N.L., A.M., and P.D. have no disclosures.

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Abbreviations Used

BP = blood pressure
CVD = cardiovascular disease
Hb = hemoglobin
HCT = hematocrit
ORs = odds ratios
T2DM = type 2 diabetes
TC = total cholesterol
TD = testosterone deficiency
TG = triglyceride
TT = total testosterone
TTh = testosterone therapy
TU = testosterone undecanoate
WC = waist circumference



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