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Testosterone Replacement Therapy: Effects on Blood Pressure in Hypogonadal Men

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Purpose: While testosterone therapy can improve the various pathologies associated with adult-onset testosterone deficiency (TD), Summary of Product Characteristics (SPC) of five testosterone preparations caution that treatment may be associated with hypertension. This paper evaluates the impact of testosterone undecanoate (TU) on blood pressure (BP) in men with adult-onset TD.

Materials and Methods: Of 737 men with adult-onset TD in an on-going, observational, prospective, cumulative registry, we studied changes in BP using non-parametric sign-rank tests at final assessment and fixed time points. We used multiple regression analysis to establish factors (baseline BP, age, change/baseline waist circumference [WC] and hematocrit [HCT] and follow-up) potentially associated with BP change in men on TU.

Results: TU was associated with significant reductions in systolic, diastolic BP and pulse pressure, regardless of antihypertensive therapy (at baseline or during follow-up), larger reductions were seen with concurrent antihypertensive therapy. In men never on antihypertensive agents, median changes (interquartile range [IQR]) in systolic BP, diastolic BP and pulse pressure were -12.5 (-19.0, -8.0), -8.0 (-14.0, -3.0), and -6.0 (-10.0, -1.0) mmHg, respectively at final assessment, with only baseline BP values inversely associated with these changes (HCT and WC were not significantly associated). In men not on TU, systolic BP, diastolic BP, and pulse pressure significantly increased. In the TU treated men only 1 of the 152 men (not on antihypertensive agents at baseline) were started on antihypertensives during follow-up. In contrast 33 of the 202 men on antihypertensives (at baseline or follow-up) had the antihypertensive agent discontinued by the end of the follow-up.

Conclusions: TU was associated with lowering of BP during follow-up irrespective of antihypertensive therapy, with greater reductions in men with higher baseline BP. In the context of SPC warnings, our long-term data provide reassurance on the effect of TU on BP.

Keywords: Blood pressure; Hematocrit; Hypogonadism; Testosterone; Waist circumference

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INTRODUCTION

Adult-onset testosterone deficiency (TD) prevalence ranges between 0.6%–12% in men aged over 50 years [1,2]. This syndrome is characterised by low serum testosterone and related symptoms and is associated with hypertension [1,3]. The association between testosterone therapy (TTh) and cardiovascular disease (CVD) is poorly defined. Some studies (despite criticized methodologies) showed positive associations between TTh and CVD [4]. Although Corona et al [5] found increased CVD in randomized controlled trials (RCTs) in frail men and those given higher than usual TTh, reduced CVD was evident following TTh in men with body mass index >30 kg/m^2. A recent systematic review/meta-analysis of RCTs found no evidence that TTh increased short to medium-term CVD in hypogonadal men [6]. Cardiovascular safety following testosterone gel therapy in hypogonadal men was confirmed in the TRAVERSE study, a non-inferiority RCT (mean follow-up±standard deviation=21.7±14.1 months) [7].

No consensus exists on the effect of TTh on blood pressure (BP). White et al [8] found increased systolic and diastolic BP in 138 hypogonadal men aged 18–80 years, the largest increases seen in those with an hematocrit (HCT) increase >6.0% after 4 months treatment following oral testosterone undecanoate (TU). Li et al [9] analyzed 12 (465 men on TTh, 393 controls) and 13 (478 men on TTh, 419 controls) studies and showed neither systolic nor diastolic BP were significantly altered. Carruthers et al [10] studied 2,693 men given various preparations of TTh and showed that most resulted in unchanged systolic BP after 12 months. Traish et al [11] using a registry database of hypogonadal men demonstrated that over 8 years, TU showed a progressive decrease in BP. The recent TRAVERSE RCT did not show a significant rise in mean systolic BP following 6 months treatment with testosterone gel [7]. Currently, the Summary of Product Characteristics (SPC) of many testosterone preparations state that TTh may increase BP and should be used cautiously in men with hypertension [12-15].

Traish et al [11] included men both, on and not on antihypertensive agents. Hence, we examined the effect of TU on BP in the total cohort and subgroups based on antihypertensive agents using an expanded version of this database with longer follow-up, focusing on men never on antihypertensive agents [11]. We adjusted analyses for the possible confounders; age, waist circumference (WC), and HCT [16-18].

MATERIALS AND METHODS

1. Study design

We used an on-going, observational, prospective, cumulative registry database of 823 men with urological (sexual dysfunction, lower urinary tract symptoms) and TD symptoms with serum total testosterone levels ≤12.1 nmol/L. Men with primary hypogonadism (n=39) and Klinefelter's syndrome (n=47) were excluded, with the remaining 737 men, diagnosed with adult-onset TD by the recruiting clinicians using current guidelines [1], studied (Fig. 1A).

These 737 men were assessed at least 6 monthly. They comprised of 353 men prescribed parenteral TU, 1,000 mg/12 weeks (TTh-treated) following a 6-week interval between the first and second administration. At TU initiation, 201 of the 353 men were on antihypertensive agents whilst 152 men were not on antihypertensive agents; 1 man was commenced on antihypertensive agents during follow-up (Fig. 1B). Thus, these men were re-stratified into those ever (at TU initiation or during follow-up) prescribed (202 men) and never prescribed (151 men) antihypertensive agents (Fig. 1B).

The remaining 384 men opted against TU for financial reasons or negative perceptions of TTh such as associations with CVD and carcinoma of the prostate (TTh-untreated). Of these 384 men, 248 men were not on antihypertensive agents when TU was offered, 34 of these men were commenced on antihypertensive agents during follow-up, while the remaining 214 men were never prescribed antihypertensive agents (Fig. 1B). All 136 men on antihypertensive agents when TU was offered remained on them during follow-up (Fig. 1B). Thus, this cohort of 384 men was further stratified into those ever prescribed (170 men) and never prescribed (214 men) antihypertensive agents at any point until final assessment (Fig. 1B). Fig. 1A suggests men who opted for TTh had more features of hypogonadism.

We report all data recommended in the STROBE statement (https://www.equator-network.org/wp-content/uploads/2015/10/STROBE_checklist_v4_cohort.pdf) [19]. The ethical guidelines of the German Medical Association for observational studies were followed. All men consented to be included and have their data ana-

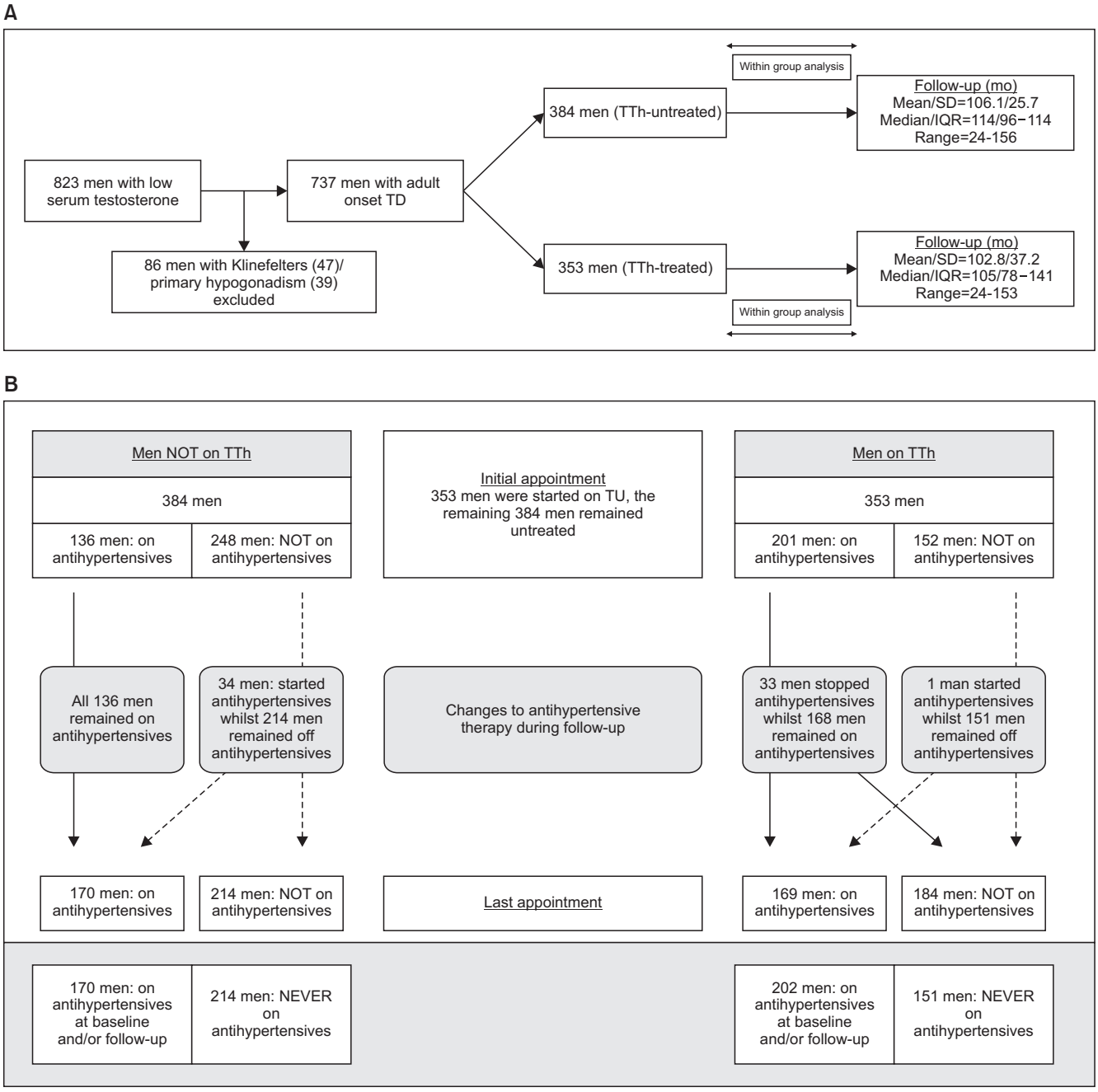

Fig. 1. Baseline characteristics and flow charts demonstrating the cohort stratified into groups used in the statistical analyses. (A) A flow chart of the study groups and their baseline characteristics. All the data are in accordance with the STROBE statement (https://www.equator-network.org/wpcontent/uploads/2015/10/STROBE_checklist_v4_cohort.pdf). Data on patients on/never on antihypertensive agents are provided in Table 1. (B) A flow chart of TTh and antihypertensive treatments at baseline, during follow-up and at the last visit. TD: testosterone deficiency, TTh: testosterone therapy, SD: standard deviation, IQR: interquartile range, TU: testosterone undecanoate.

lyzed after the study was explained. An Institutuional Review Board Statment from University Hospitals Birmingham NHS Foundation Trust was obtained (ref: Department of Laboratory Medicine - 07072023).

2. BP measurements

Each patient was seated with his left arm resting at heart level with their backs supported and legs resting on the floor and BP was measured using a sphygmomanometer according to protocol. The Korotkoff sounds were assessed twice to increase precision. Following the initial BP measurement, TU was injected, and BP determined again. If there was a difference <5 mmHg, an average was taken, if >5 mmHg a third measurement

was obtained. If the difference between the three measurements varied, the outlier was discarded, and the average of the closer values calculated. If BP values differed by >10 mmHg from those made at previous follow up, the patient was requested to undergo a 24-hour BP recording.

3. Laboratory measurements

Serum testosterone was measured via immunoassay (Architect intra-assay, Abbott Diagnostics; Abbott Park); intra-assay variation was 3.4%, inter-assay variation was 5.1%. HCT was determined using Microhematocrit (Mindray 3000 Plus).

4. Statistical analysis

As the men were not randomised into the two TTh groups and significant between-group differences in baseline values were noted the two groups were mostly analyzed separately (Fig. 1) via rank-sum and chi square tests due to skewness/kurtosis in BP distribution. We used sign-rank tests to study within-group differences in BP, WC and HCT, and changes in BP at study end and fixed time points (12, 48, 72, 96 months). Multiple regression analyses were used to establish if baseline BP, age, duration of follow-up, change/baseline WC and HCT were associated with change in BP (outcome).

RESULTS

1. TTh and BP in the total cohort stratified by men prescribed/not prescribed TU

In the total cohort of 737 men, the 353 men given TU (TTh-treated) showed a significant lowering of BP (Table 1). Further, significant changes were seen in WC (decrease) and HCT (increase). Men never given TU (TTh-untreated) showed significant increases in BP (Table 1). In these men WC significantly increased and HCT significantly decreased, although the median and interquartile range (IQR) remained the same.

At baseline, the 353 men on TU, 152 men were not on antihypertensive therapy whilst the remaining 201 men were under treatment for hypertension (Fig. 1B). Significant decreases (median [IQR] in BP and pulse pressure values were observed in both groups (Table 1 footnote).

2. Changes in BP at final assessment in TTh-treated men never prescribed antihypertensive agents

During follow-up, one of the 152 men not on antihypertensive agents at TU initiation, was started on antihypertensive agents (within 3 months of commencing TU); his systolic and diastolic BP decreased following TU prior to the initiation of antihypertensive therapy. Thus, we studied changes in BP in the remaining 151 men not on antihypertensive agents either at baseline or during follow-up to remove the impact of antihypertensive agents on BP change (Table 2, Fig. 1B). In these 151 men (Table 2), TU was associated with significant falls in systolic BP, diastolic BP and pulse pressure at final assessment. Only 2 (1.3%), 14 (9.3%), and 29 (19.2%) of these 151 men demonstrated increases in systolic BP, diastolic BP, and pulse pressure respectively.

3. Change in BP at fixed time points in TTh-treated men never prescribed antihypertensive agents

Table 1 shows data from final assessment with varied follow-up and numbers of men. To negate the impact of TU exposure, we studied change in BP at fixed times during follow-up (12, 48, 72, 96 months) in the TTh-treated men, never prescribed antihypertensive agents (Fig. 2). Systolic BP, diastolic BP and pulse pressure decreased progressively over 96 months follow-up with significantly lower systolic BP and diastolic BP values achieved after 12 months and pulse pressure after 48 months of TU.

4. Factors associated with change in BP in TTh-treated men not on antihypertensive agents

Table 3 shows the results of multiple regression analyses studying the 151 TTh-treated men never receiving antihypertensive agents with the models adjusted for age, follow up, and both baseline and change in WC and HCT, separately and together. Table 3 shows that only the respective baseline BP values were associated with change in systolic BP, diastolic BP and pulse pressure. Age at baseline, WC and HCT were not significantly associated with change in BP. We repeated the analyses at fixed time points (12, 48, 72, 96 months) and baseline BP remained independently associated ($p<0.001$) with change in BP in each analysis. The selected confounding variables (WC and HCT) were not

Table 1. The study cohort stratified by TTh at TTh (TU)

	TTh-treated	TTh-untreated
Patients (n)	353	384
Age (y)	60.0/55.0–64.0/33.0–71.0	64.0/60.0–67.0/45.0–74.0
Follow-up (mo)	105.0/78.0–141.0/24.0–153.0	114.0/96.0–126.0/24.0–156.0
Baseline systolic BP (mmHg)	158.0/141.0–167.0/121.0–189.0	137.5/131.5–154.0/115.0–193.0
Final systolic BP (mmHg)	128.0/123.5–133.5/120.0–154.0 (n=352)	149.0/142.0–159.0/131.0–215.0 (n=382)
Change in systolic BP (mmHg)	-25.0/-59.0 to -13.0/-63.0 to 3.0 (n=352)	10.0/-11.0 to 16.0/-18.0 to 82.0 (n=382)
Final *vs.* baseline systolic BP: p (sign-rank test)	p<0.0001	p<0.0001
Baseline diastolic BP (mmHg)	94.0/83.0–98.0/69.0–126.0	78.0/75.0–88.0/ 66.0–121.0
Final diastolic BP (mmHg)	75.0/73.0–78.0/68.0–94.0 (n=352)	89.0/83.0–96.0/71.0–148.0 (n=381)
Change in diastolic BP (mmHg)	-17.0/-24.0 to -9.0/-45.0 to +7.0 (n=352)	8.0/3.9–13.0/-14.0 to 68.0 (n=381)
Final *vs.* baseline diastolic BP: p (sign-rank test)	p<0.0001	p<0.0001
Baseline pulse pressure (mmHg)	62.0/58.0–68.0/38.0–90.0	59.0/57.0–64.0/37.0–93.0
Final pulse pressure (mmHg)	52.0/49.0–58.0/35.0–97.0 (n=352)	59.0/58.0–67.0/49-0–99.0 (n=381)
Change in pulse pressure (mmHg)	-8.0/-15.0 to -4.0/-34.0 to 44.0(n=352)	1.0/-2.0 to 5.0/-17.0 to 53.0 (n=381)
Final *vs.* baseline pulse pressure: p (sign-rank test)	p<0.0001	p<0.0001
Baseline WC (cm)	108.0/100.0–114.0/86.0–166.0	109.0/102.5–116.0/93.0–155.0
Final WC (cm)	97.0/94.0–101.0/78.0–157.0	113.0/108.0–121.0/95.0–165.0
Final *vs.* baseline WC	p<0.0001	p<0.0001
Baseline HCT	44.0/43.0–46.0/330–50.0	46.0/45.0–47.0/43.0–50.0
Final HCT	49.0/48.0–50.0/46.0–52.0	46.0/45.0–47.0/33.0–53.0
Final *vs.* baseline HCT: p (sign-rank test)	p<0.0001	p=0.014

Values are presented as median/IQR/range.
Details (median [IQR]) of systolic BP, diastolic BP, and pulse pressure in subgroups stratified by antihypertensive treatment at baseline.
a. TTh-treated (1. Not on antihypertensives at baseline, 2. On antihypertensives at baseline)
1. Men not on antihypertensives at baseline (n=152)
Baseline BP values (systolic BP=139 [133.5, 145.5] mmHg, diastolic BP=82 [78, 88] mmHg, pulse pressure=59.0 [54.5–61.0] mmHg).
Change from baseline (systolic BP=-12 [-19, -8] mmHg [p<0.0001], diastolic BP=-8 [-13.5, -3] mmHg [p<0.0001], pulse pressure=-6 [-10, -1] mmHg [p<0.0001]).
2. Men on antihypertensives at baseline (n=201)
Baseline BP values (systolic BP=166 [159, 174] mmHg, diastolic BP=98 [95, 104] mmHg, pulse pressure=67 [62, 70] mmHg).
Change from baseline (systolic BP=-35 [-43, -27] mmHg [p<0.0001], diastolic BP=-22 [-28, -18] mmHg [p<0.0001], pulse pressure=-11 [-17, -6] mmHg [p<0.0001]).
b. TTh-untreated (1. Not on antihypertensives at baseline, 2. On antihypertensives at baseline)
1. Men not on antihypertensives at baseline (n=248)
Baseline BP values (systolic BP=132 [129, 137] mmHg, diastolic BP=76 [73.5, 78.5] mmHg, pulse pressure=58 [54, 60] mmHg).
Change from baseline (systolic BP=11 [7, 18] mmHg [p<0.0001], diastolic BP=9 [5, 15] mmHg [p<0.0001], pulse pressure=2 [-1, 6] mmHg [p<0.0001]).
2. Men on antihypertensives at baseline (n=136)
Baseline BP values (systolic BP=155 [153, 160] mmHg, diastolic BP=91 [86, 95] mmHg, pulse pressure=67 [61, 69] mmHg).
Change from baseline (systolic BP=6 [0, 12] mmHg [p<0.0001], diastolic BP=6 [2, 11] mmHg [p<0.0001], pulse pressure=0 [-2, 4] mmHg [p=0.24]).
TTh: testosterone therapy, TU: testosterone undecanoate, BP: blood pressure, WC: waist circumference, HCT: hematocrit, IQR: interquartile range.

significantly associated with change in the three BP outcomes. Stratifying the cohort by smoking status and T2DM did not alter the results.

To determine if the association between baseline BP values and absolute change in BP was not due to a fixed proportional change (in this case a higher baseline value would result in a greater change), we repeated the analyses shown in Table 3, using percentage change in the three BP indices (100×change in BP/baseline BP) as the dependent variables. Significant associations (p<0.001) with baseline values were evident, in models similarly adjusted for age, WC and HCT, higher baseline BP was associated with a greater % reduction in BP.

To graphically demonstrate that changes in BP in TTh-treated men never given antihypertensive agents

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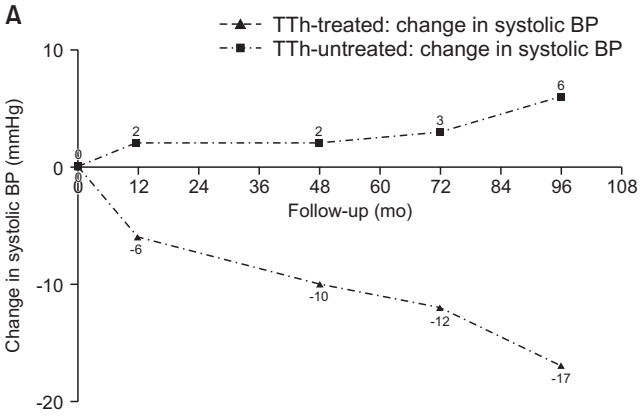
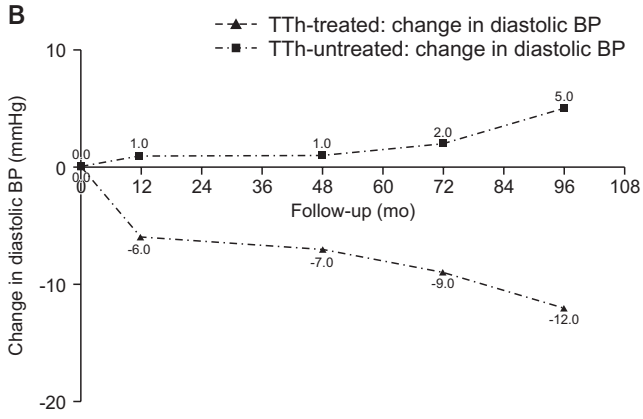
Table 2. The study cohort stratified by concurrent TTh and antihypertensive treatments (the cohort on antihypertensive agent(s) includes men on antihypertensives either at TTh (TU) initiation or during follow-up)

	TTh-treated		TTh-untreated	
	On antihypertensive agents	Not on antihypertensive agents	On antihypertensive agents	Not on antihypertensive agents
Patients (n)	202	151	170	214
Age (y)	61.5/58.0–65.0/44.0–71.0	56.0/53.0–62.0/33.0 –69.0	64.0/60.0–68.8/48.0–73.0	63.5/60.0–67.0/45.0–74.0
Follow-up (mo)	105.0/69.0–138.0/24.0–147.0	102.0 /78.0–141.0/33.0–153.0	108.0/72.0–120.0/24.0 –144.0	120.0/108.0–126.0/36.0–156.0
Baseline systolic BP (mmHg)	166.0/159.0–174.0/125.0–189.0	139.0/133.0–145.0/121.0–183.0	155.0/150.0–159.0/126.0–193.0	132.0/128.0–135.0/115.0–144.0
Final systolic BP (mmHg)	131.0/125.0–137.0/120.0–154.0	125.0/123.0–130.0/121.0–139.0 (n=150)	159.0/155.0–168.0/135.0 –198.0	144.0/139.0–148.0/131.0–215.0 (n=212)
Change in systolic BP (mmHg)	-35.0/-43.0 to -27.0/-63.0 to -1.0	-12.5/-19.0 to -8.0/-59.0 to 3.0 (n=150)	7.0/2.0–12.0/-18.0 to 47.0	11.0/7.0–18.0/-6.0 to 82.0 (n=212)
Final *vs.* baseline systolic BP: p (sign-rank test)	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Baseline diastolic BP (mmHg)	98.0/94.0–104.0/71.0–126.0	82.0/78.0–88.0/69.0–109.0	89.0/84.0–94.0/69.0–121.0	75.0/73.0–78.0/66.0–85.0
Final diastolic BP (mmHg)	76.0/73.0–79.0/70.0–94.0	74.0/72.0–77.0/68.0–90.0 (n=150)	95.5/91.0–99.0/77.0–124.0	85.0/80.5–89.0/71.0–148.0 (n=212)
Change in diastolic BP (mmHg)	-22.0/-28.0 to -18.0/-45.0 to 4.0	-8.0/-14.0 to -3.0/-35.0 to 7.0 (n=150)	7.0/2.0–11.0/-14.0 to 45.0	9.0/5.0–16.0/-5.0 to 68.0 (n=212)
Final *vs.* baseline diastolic BP: p (sign-rank test)	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Baseline pulse pressure (mmHg)	67.0/62.0–70.0/43.0–90.0	59.0/54.0–61.0/38.0–74.0	65.0/60.0–69.0/49.0–93.0	58.0/54.0–59.0/37.0–72.0
Final pulse pressure (mmHg)	54.0/50.0–60.0/43.0–74.0	51.0/49.0–54.0/35.0–97.0 (n=150)	64.5/60.0–69.0/49.0–99.0	59.0/58.0–60.0/51.0–92.0 (n=211)
Change in pulse pressure (mmHg)	-11.0/-17.0 to -6.0/-34.0 to 10.0	-6.0/-10.0 to -1.0/-25.0 to 44.0 (n=150)	0.0/-2.0 to 5.0/-17.0 to 20.0	2.0/-1.0 to 6.0/-13.0 to 53.0 (n=211)
Final *vs.* baseline pulse pressure: p (sign-rank test)	p<0.0001	p<0.0001	p=0.11	p<0.0001
Baseline WC (cm)	112.0/108.0–119.0/89.0–166.0	101.0/97.0–106.0/86.0–124.0	111.5/103.0–122.0/93.0–155.0	106.0/102.0–113.0/93.0–137.0
Final WC (cm)	99.0/96.0–104.0/78.0–157.0	94.0/93.0–97.0/83.0–107.0	116.5/108.0–126.0/97.0–165.0	112.0/107.0–118.0/95.0–145.0
Final *vs.* baseline WC: p (sign-rank test)	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Baseline HCT	45.0/44.0–46.0/33.0–50.0	44.0/42.0–45.0/33.0–48.0	46.0/45.0–47.0/43.0–50.0	46.0/45.0–47.0/43.0–49.0
Final HCT	49.0/48.0–50.0/46.0–52.0	49.0/48.0–50.0/46.0–52.0	46.0/45.0–47.0/33.0–50.0 (n=169)	46.0/45.0–47.0/39.0–53.0
Final *vs.* baseline HCT: p (sign-rank test)	p<0.0001	p<0.0001	p=0.59	p=0.0044

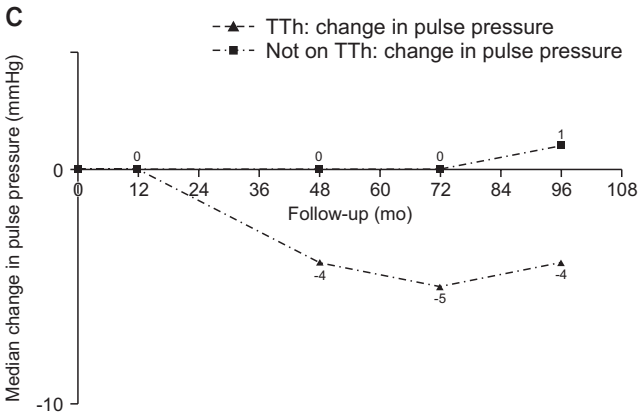
Values are presented as median/IQR/range.
Men started on TTh (n=353)
At TU initiation: 152 men were not on antihypertensive agents, during follow-up 1 man (0.66%) was started on antihypertensive agent(s), 151 men remained off antihypertensive agents. All 201 men on antihypertensive agents remained on them during follow-up.
Men not on TTh (n=384)
At initial visit (when TU was declined): 248 men were not on antihypertensive agents, during follow-up 214 men remained off antihypertensive agents whilst the remaining 34 men (13.71%) were commenced on antihypertensive agents. All 136 men on antihypertensive agents remained on them during follow-up.
TTh: testosterone therapy, TU: testosterone undecanoate, BP: blood pressure, WC: waist circumference, HCT: haematocrit.



Follow-up (mo)	TTh-treated: median change in systolic BP (IQR)	TTh-untreated: median change in systolic BP (IQR)
12	-6.0 (-11.0, -2.0), n=151, p<0.0001	2.0 (-3.0, 4.0), n=214, p=0.0047
48	-10.0 (-15.0, -6.0), n=142, p<0.0001	2.0 (-2.0, 5.0), n=213, p=0.0002
72	-12.0 (-17.0, -8.0), n=129, p<0.0001	3.0 (-1.0, 7.0), n=208, p<0.0001
96	-17.0 (-23.0, -11.0), n=84, p<0.0001	6.0 (2.0, 11.0), n=190, p<0.0001



Follow-up (mo)	TTh-treated: median change in diastolic BP (IQR)	TTh-untreated: median change in diastolic BP (IQR)
12	-6.0 (-10.0, -2.0), n=151, p<0.0001	1.0 (-3.0, 4.0), n=214, p=0.10
48	-7.0 (-13.0, -1.0), n=142, p<0.0001	1.0 (-2.0, 4.0), n=213, p=0.0039
72	-9.0 (-14.0, -4.0), n=129, p<0.0001	2.0 (-1.0, 5.0), n=208, p<0.0001
96	-12.0 (-18.0, -8.0), n=84, p<0.0001	5.0 (0.0, 9.0), n=190, p<0.0001



Follow-up (mo)	TTh-treated: median change in pulse pressure (IQR)	TTh-untreated: median change in pulse pressure (IQR)
12	0.0 (-4.0, 3.0), n=151, p=0.10	0.0 (-2.0, 2.0), n=214, p=0.059
48	-4.0 (-10.0, 1.0), n=142, p<0.0001	0.0 (-2.0, 3.0), n=213, p=0.22
72	-5.0 (-9.0, 1.0), n=129, p<0.0001	0.0 (-2.0, 3.0), n=208, p=0.22
96	-4.0 (-9.0, -1.0), n=84, p<0.0001	1.0 (-1.0, 5.0), n=190, p<0.0001

Fig. 2. Median changes in BP parameters at 12, 48, 72, and 96 months in TTh-treated and TTh-untreated men who were never on antihypertensive agents. (A) Systolic BP. (B) Diastolic BP. (C) Pulse pressure. p (sign-rank test): comparison with baseline values (within group non-parametric analyses). BP: blood pressure, TTh: testosterone therapy, IQR: interquartile range.

(Table 2) were significantly associated with baseline value, we dichotomised men using the median baseline values (systolic BP: 139 mmHg, diastolic BP: 81 mmHg, pulse pressure: 59 mmHg). Fig. 3A shows systolic BP was significantly reduced in men with baseline values both >139 and ≤139 mmHg, this change was significant (p<0.0001, sign-rank test) after 12 months TU. The reduction in systolic BP was significantly greater in the men with baseline systolic BP above the median with significance (p<0.0001, rank-sum test) achieved after 12 months TU. In both groups, systolic BP continued to fall and after 96 months of TU, median changes of -21.0 and -10.0 mmHg were found in men with baseline values >139 and ≤139 mmHg, respectively (Fig. 3A). Corresponding change in diastolic BP in men with baseline values above the median was similar, significant reduction was achieved after 12 months followed by further reduction over the subsequent 84 months (Fig. 3B). However, this pattern was not seen in men with a baseline diastolic BP ≤median. Change in diastolic BP was statistically different (rank-sum test) between the groups stratified by median diastolic BP (Fig. 3B) at all time points. Fig. 3C shows data for pulse pressure. Men with baseline pulse pressure >median (59 mmHg) showed significant falls during 96 months of TU, whilst change in pulse pressure was modest in men with values ≤median.

5. BP change in TU-untreated men

As stratification of men into TTh-treated and -untreated men was based on their choice rather than randomization, there were differences in some variables in TTh-treated and -untreated men (Table 1). Indeed, there was evidence that men given TU suffered

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Table 3. Factors associated with change in systolic, diastolic, and pulse pressure in TTh-treated men never on antihypertensive agents

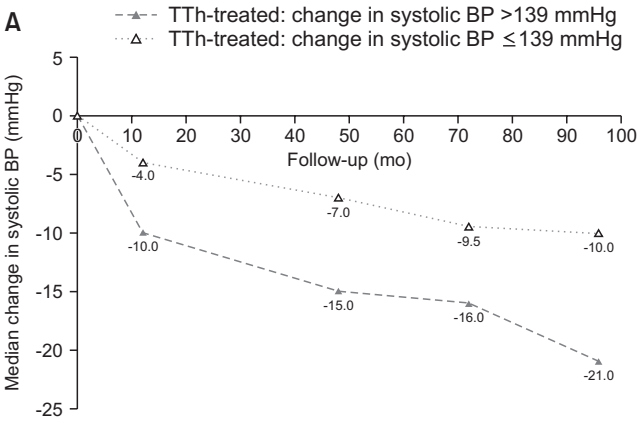
TTh-treated men not on antihypertensive agents	Multiple regression analyses: (95% CI), p-value		
	Association with WC	Association with HCT	Association with WC and HCT
Outcome: Change in systolic BP			
Age (y)	0.092 (-0.020 to 0.20), 0.11	0.098 (-0.0086 to 0.20), 0.071	0.079 (-0.033 to 0.19), 0.16
Baseline systolic BP (mmHg)	-0.93 (-1.01 to -0.85), <0.001	-0.92 (-1.00 to -0.84), <0.001	-0.94 (-1.02 to -0.86), <0.001
Follow-up (mo)	0.019 (-0.0087 to 0.047), 0.18	0.016 (-0.0086 to 0.041), 0.20	0.0053 (-0.025 to 0.035), 0.73
Change in WC (cm)	-0.16 (-0.47 to 0.16), 0.33		-0.18 (-0.49 to 0.14), 0.27
Baseline WC (cm)	-0.067 (-0.27 to 0.13), 0.51		-0.026 (-0.23 to 0.18), 0.80
Change in HCT		0.084 (-0.46 to 0.63), 0.76	0.029 (-0.52 to 0.58), 0.92
Baseline HCT		-0.17 (-0.74 to 0.41), 0.56	-0.30 (-0.90 to 0.31), 0.34
Outcome: Change in diastolic BP			
Age (y)	-0.027 (-0.16 to 0.11), 0.69	-0.0092 (-0.14 to 0.12), 0.87	-0.025 (-0.16 to 0.11), 0.71
Baseline Diastolic BP (mmHg)	-0.92 (-1.06 to -0.77), <0.001	-0.91 (-1.06 to -0.77), <0.001	-0.92 (-1.07 to 0.78), <0.001
Follow-up (mo)	0.015 (-0.022 to 0.052), 0.42	0.021 (-0.011 to 0.054), 0.20	0.017 (-0.023 to 0.056), 0.41
Change in WC (cm)	-0.059 (-0.42 to 0.31), 0.75		-0.060 (-0.42 to 0.30), 0.75
Baseline WC (cm)	0.0091 (-0.23 to 0.25), 0.94		0.021 (-0.22 to 0.26), 0.86
Change in HCT		-0.35 (-1.00 to 0.29), 0.28	-0.39 (-1.05 to 0.27), 0.24
Baseline HCT		-0.29 (-0.97 to 0.40), 0.41	-0.38 (-1.10 to 0.35), 0.30
Outcome: Change in pulse pressure			
Age (y)	0.11 (-0.044 to 0.27), 0.16	0.10 (-0.048 to 0.25), 0.19	0.099 (-0.058 to 0.26), 0.21
Baseline pulse pressure (mmHg)	-0.90 (-1.07 to -0.74), <0.001	-0.90 (-1.05 to -0.74), <0.001	-0.91 (-1.07 to -0.74), <0.001
Follow-up (mo)	0.00024 (-0.038 to 0.038), 0.99	-0.0067 (-0.038 to 0.025), 0.68	-0.014 (-0.056 to 0.028), 0.50
Change in WC (cm)	-0.11 (-0.57 to 0.34), 0.61		-0.13 (-0.59 to 0.32), 0.57
Baseline WC (cm)	-0.10 (-0.39 to 0.19), 0.49		-0.068 (-0.36 to 0.22), 0.64
Change in HCT		0.42 (-0.34 to 1.19), 0.28	0.42 (-0.36 to 1.19), 0.29
Baseline HCT		0.096 (-0.71 to 0.90), 0.81	0.083 (-0.77 to 0.94), 0.85

TTh: testosterone therapy, CI: confidence interval, BP: blood pressure, WC: waist circumference, HCT: haematocrit.

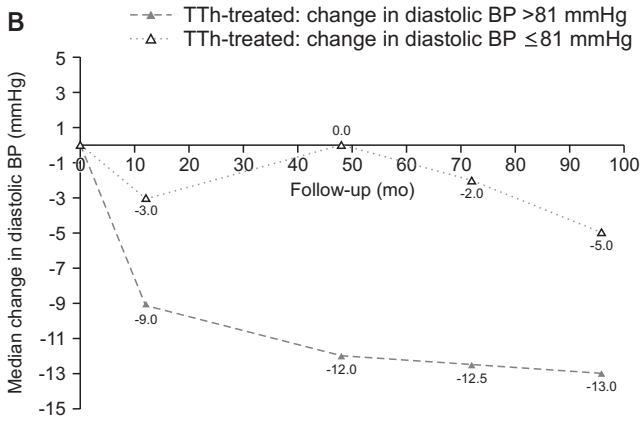
at the start of the study, more severe hypogonadism. The Ageing Male Symptom (AMS) and International Index of Erectile Function-Erectile Function (IIEF-EF) scores were significantly (p<0.001) different in the TU-treated (AMS median score=51, IQR 45–62; IIEF median score=18; IQR 13–23) and TU-untreated (AMS median score=42, IQR 38–44; IIEF median score=21; IQR 18–22) groups (data not presented). Accordingly, no further comparisons were made between TTh-treated and -untreated men. Of the 384 men who declined TU, 136 men were on antihypertensive agents (and remained on them during follow-up) and the remaining 248 men were not on antihypertensive agents when TU was offered (Fig. 1B). Of the latter 248 men, 34 (13.71%) were commenced on antihypertensive agents during follow-up while the remaining 214 men were never prescribed antihypertensives (Fig. 1B).

In TU-untreated men, systolic BP, diastolic BP, and pulse pressure significantly increased during follow-up in both men receiving and not receiving antihypertensives (Table 1). Table 1 (footnote) provides BP details in men who were and were not on antihypertensive agents at baseline. In the 248 men who were not on antihypertensive agents at baseline, systolic, diastolic BP and pulse pressure increased significantly. In the 136 men on hypertensive agents at baseline, significant increases were observed in the systolic and diastolic BP, but change in pulse pressure change was not significant.

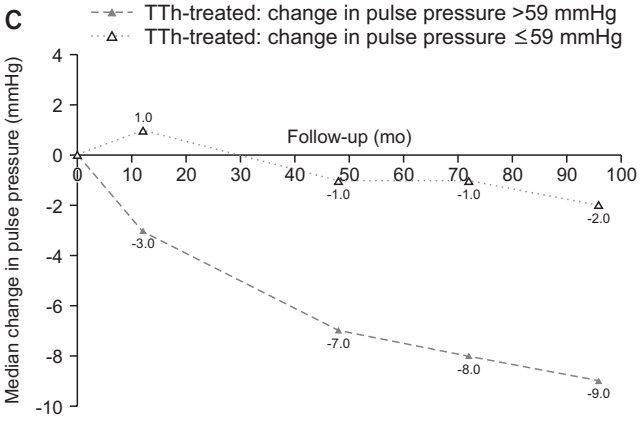
Antihypertensive agents were commenced in 34 of the 248 men who were not on these agents at baseline with the remaining 214 men never being treated (Table 2, Fig. 1B). Thus, 170 men were on antihypertensive agents at the end of follow-up (136 men at baseline and 36 men initiated during the follow-up). In these 170 men given antihypertensive agents changes in systolic BP, diastolic BP and pulse pressure were statistically significant, however, change in pulse pressure did not



Follow-up (mo)	Median (IQR) change in systolic BP >139 mmHg, p (sign-rank)	Median (IQR) change in systolic BP ≤139 mmHg, p (sign-rank)	p (rank-sum)
12	-10.0 (-15.0, -4.0), n=70, p<0.0001	-4.0 (-8.0, 0.0), n=151, p<0.0001	p<0.0001
48	-15.0 (-20.0, -9.0), n=69, p<0.0001	-7.0 (-10.0, -4.0), n=73, p<0.0001	p<0.0001
72	-16.0 (-22.0, -11.0), n=65, p<0.0001	-9.5 (-13.0, -5.5), n=64, p<0.0001	p<0.0001
96	-21.0 (-28.0, -17.0), n=51, p<0.0001	-10.0 (-13.0, -5.0), n=33, p<0.0001	p<0.0001



Follow-up (mo)	Median (IQR) change in diastolic BP >81 mmHg, p (sign-rank)	Median (IQR) change in diastolic BP ≤81 mmHg, p (sign-rank)	p (rank-sum)
12	-9.0 (-12.0, -5.0), n=88, p<0.0001	-3.0 (-6.0, 0.0), n=63, p=0.0001	p<0.0001
48	-12.0 (-15.0, -7.0), n=87, p<0.0001	0.0 (-4.0, 2.0), n=55, p=0.74	p<0.0001
72	-12.5 (-16.0, -9.0), n=84, p<0.0001	-2.0 (-4.0, 2.0), n=45, p=0.18	p<0.0001
96	-13.0 (-18.0, -10.0), n=73, p<0.0001	-5.0 (-7.0, -3.0), n=11, p<0.0001	p=0.0004



Follow-up (mo)	Median (IQR) change in pulse pressure >59 mmHg, p (sign-rank)	Median (IQR) change in pulse pressure ≤59 mmHg, p (sign-rank)	p (rank-sum)
12	-3.0 (-8.0, 0.0), n=63, p<0.0001	1.0 (-1.5, 4.0), n=88, p=0.015	p<0.0001
48	-7.0 (-13.0, -3.0), n=61, p<0.0001	-1.0 (-7.0, 3.0), n=81, p=0.13	p<0.0001
72	-8.0 (-13.0, -3.0), n=55, p<0.0001	-1.0 (-7.0, 3.0), n=74, p=0.062	p<0.0001
96	-9.0 (-13.0, -7.0), n=33, p<0.0001	-2.0 (-4.0, 1.0), n=51, p=0.0029	p<0.0001

Fig. 3. Median changes in BP parameters at 12, 48, 72, and 96 months in TTh-treated men who were never on antihypertensive agents. (A) Systolic BP-stratified by median baseline systolic BP of 139 mmHg. Baseline systolic BP >139 mmHg: median systolic BP=147 mmHg, Baseline systolic BP ≤139 mmHg: median systolic BP=135 mmHg. (B) Diastolic BP-stratified by median baseline diastolic BP of 81 mmHg. Baseline diastolic BP >81 mmHg: median diastolic BP=88.0 mmHg, Baseline diastolic BP ≤81 mmHg: median diastolic BP=77.0 mmHg. (C) Pulse pressure-stratified by median baseline pulse pressure of 59 mmHg. Baseline pulse pressure >59 mmHg: median pulse pressure=62.0 mmHg, Baseline pulse pressure ≤59 mmHg: median pulse pressure=56.0 mmHg. p (sign-rank test): comparison with baseline values (within group non-parametric analyses). p (rank-sum test): comparison between change in BP at fixed time points (between group non-parametric analyses). BP: blood pressure, TTh: testosterone therapy, IQR: interquartile range.

achieve significance (Table 2). In men never given antihypertensive agents changes in systolic BP, diastolic BP and pulse pressure were statistically significant (Table 2). In the 170 TU-untreated men, prescribed antihypertensive agents 132 (77.6%), 137 (80.6%) and 84 (49.4%) men showed increased systolic BP, diastolic BP, and pulse pressure, respectively. In the 214 men neither on TU or antihypertensive agents 196 (91.6%), 192 (89.7%) and 123 (57.5%) men showed increased systolic BP, diastolic BP, and pulse pressure, respectively.

In TTh-untreated men never given antihypertensives, systolic BP increased at each time point being significant after 12 months follow-up (Fig. 2A). The increase in diastolic BP (Fig. 2B) and pulse pressure (Fig. 2C) in these men was significant after 48 and 96 months, respectively.

DISCUSSION

A previous study largely based on the men described here, showed TU was associated with a progressive BP decrease during 8-years follow-up [11]. This cohort included men who had received or never received antihypertensive therapy, making it difficult to differentiate the effects of TU and antihypertensive agents on BP. We used an expanded cohort with longer follow-up, to extend the analysis by describing firstly changes in BP in adult-onset TD patients treated and untreated with TU, secondly by stratifying these above groups into men on/not on antihypertensive agents at baseline and finally in men never receiving antihypertensive medication and thirdly, the association of changes in BP parameters with baseline BP values.

We found TU, irrespective of antihypertensive ther-

apy, was associated with reduced systolic BP, diastolic BP and pulse pressure. In men never prescribed antihypertensive treatment both absolute and relative (%) change in BP was predicted by the baseline level (Table 2). Dichotomising men by the median baseline BP illustrated the extent of fall in BP was greater when baseline BP was above the median (Fig. 3). Thus, patients with the highest baseline BP demonstrated the greatest response (both absolute and relative change in BP) to medication (Wilder's principle), perhaps reducing the likelihood of hypotension post-treatment [20]. The number of men who were hypertensive (BP ≥140/80 mmHg) as defined by the National Institute for Health and Care Excellence [21] guidelines fell with TU (Table 1 footnote) whilst in their counterparts not on TU, the corresponding figures increased. Despite the decrease in median BP in the men on TU, some variation in response was observed; 2 (1.3%), 14 (9.3%), and 29 (19.2%) of these 151 men (not on concurrent anti-hypertensive agents) demonstrated increases in systolic BP, diastolic BP, and pulse pressure respectively. Although we do not have a mechanistic explanation for this, it highlights that heterogeneity exists in men with adult-onset TD.

TU was also associated with significant changes in WC and HCT irrespective of antihypertensive medication (Table 1, 2). Regression analysis showed that only baseline values of systolic and diastolic BP and pulse pressure were significantly associated with extent of change in BP as opposed to baseline/changes in WC and HCT.

The lack of association between HCT and change in BP is reassuring when considering the T4DM study findings [22]. The T4DM study investigated, men with pre- diabetes and basal TT <14 nmol/L showing a 40% reduction in progression to type 2 diabetes over 2 years in men on TTh, compared with placebo. Much has been made of the 22% of the men (106 men) on TTh who had at least a single HCT ≥54% compared to 1% (6 men) treated with placebo, although it must be emphasised that TU was discontinued in only 23 men with two HCT values ≥54% [22]. Further, many studies have shown increased HCT to be associated with hypertension, perhaps mediated by higher viscosity, hence our findings may provide some reassurance [23-25]. Importantly no CVD events were observed in men on TU. Of those not on TU, CVD was documented in 42 of the 214 men (19.6%) (Table 2) never on antihypertensives and 65 of the 170 men (38.2%) on antihypertensives (at baseline or during follow-up).

Our study has strengths and weaknesses. Unlike an RCT population, no exclusion/inclusion factors were used. All men were offered TU, and either accepted or declined therapy rather than being randomised. This perhaps resulted in differences of several phenotypes and perhaps men given TU experienced more severe symptoms of hypogonadism. TU based on patient choice can lead to bias and unfortunately this cannot be easily alleviated. It was the reason that much of our statistical analysis was intra-group and not inter-group. Compliance was absolute TU was injected in clinic. Ambulatory 24-hour BP measurements or home BP measurements in addition to clinic checks were not routinely made, and we recognise that BP determined in the clinic can be imprecise. The trends in BP observed were gradual, consistent, and appeared robust. Studying men never given antihypertensive therapy (either at TU initiation or during follow-up) allowed us to obtain data on BP and pulse pressure free from the possible effects of different classes/doses of antihypertensive agents of varying efficacies. Further, the possibility that antihypertensive agents used to achieve a guideline target which could truncate the post-treatment BP distribution was eliminated. Our unselected cohort perhaps mirrors clinical practice. The follow-up period was longer than most RCTs. Hence, such data should be considered in conjunction with those from RCTs and meta-analyses. Our results are specific for parenteral TU and further research is required to study BP following treatment with different TTh preparations/administration routes. We accept that access to SHBG levels would have allowed study of associations between calculated free testosterone and change in BP. We also acknowledge that despite the long follow-up, our dataset is small and, although the results were reassuring, a large RCT including ambulatory 24-hour BP measurements is required.

Our results apply to injectable TU only. Interestingly White et al [8] found that oral TU was associated with increased BP especially in men also demonstrating an increase in HCT. In our cohort a HCT level of 52% was not breached following TU, which we reported in a prior publication [26]. We also showed that increased HCT levels (up to 52%) was associated with reduced mortality [26]. Thus, it would be interesting whether other studies with non-injectable testosterone preparations

show an association between HCT levels and BP at different time points and data on concurrent initiation of antihypertensive agents.

There are mechanisms such as improvement of endothelial function, decrease in aldosterone levels and reduction in insulin resistance associated with TTh that could perhaps account for the phenomena that we have described above. TTh has been shown to decrease endothelial microparticles (fragments of plasma membrane released from damaged and endothelial progenitor cells and possibly a marker of endothelial dysfunction) and endothelial progenitor cells (cells associated with vasculogenic reparative process and re-endothelisation post-vascular injuries) in the circulation [27]. It has also been seen that normalisation of serum testosterone levels has led to reduced serum asymmetric dimethylarginine which appears to have an inverse association with nitric oxide formation and endothelial health [28]. Goncharov et al [29] demonstrated reductions in aldosterone levels and insulin resistance (both these factors appear associated with hypertension) in 26 men following injectable TU, although no change in BP was observed. Our results show heterogeneity of BP change. Androgen receptor sensitivity could perhaps play a crucial part in the heterogeneous effects observed following TTh via the multiple mechanisms that we have briefly outlined above as well as other unknown mechanistic pathways. The number of CAG repeats in exon 1 of the androgen receptor gene, has been shown to modulate the effect of TTh [30]. Zitzmann and Nieschlag [30] in a single arm observational study showed that injectable TU was associated with decrease in lipids, systolic and diastolic BP and increased HCT, with CAG repeats modifying treatment outcomes. In our view it would be wise for any future RCT assessing TTh efficacy to include measurements of androgen receptor CAG repeats as well as other factors likely to affect outcomes.

CONCLUSIONS

We found that long-term TU is significantly associated with BP lowering in men with adult-onset TD, this important in view of the caution advocated by the SPCs [12-15]. Changes in WC and HCT were not associated with BP change. Concurrent TU and antihypertensive therapy appear to confer greater BP reductions; 16.4% of patients (33/201) on antihypertensive agents had antihypertensive treatment discontinued following TU. Further, absolute, and relative reductions in BP complied with the Wilder's effect [20].

Conflict of Interest

SR has received research grants, travel grants and speakers' honoraria from Basins Healthcare. AH and KSH have received research grants, travel grants and speakers' honoraria from Bayer AG. GH, AM, CSK, PD, and RCS have no disclosures.

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Author Contribution

Conceptualization: SR, CSK, GH, RCS. Data curation: AH, KSH, PD. Formal analysis: SR, CSK, GH, RCS. Funding acquisition: SR, RCS. Investigation: AH, KSH. Methodology: SR, CSK, GH, RCS. Project administration: AH, KSH, SR, CSK, GH, RCS. Resources: SR, RCS. Software: SR, PD. Supervision: SR, CSK, GH, RCS. Validation: AM. Writing - original draft: SR, RCS. Writing - review & editing: all authors.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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