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Breaking News

Men's Health Medical & Marketing Network

Committed to the Science of Improving Men's Health

Issue No. 2

Adverse Cardiovascular Events and Cause Mortality in Men During Testosterone Treatment: Individual Patient and Aggregate Data Meta-Analyses. Jayasena, C et al. Lancet Healthy Longevity June 2022 (TestES Safety)

Beneficial for BH

Stoplight system:

- Green light means it is supportive/aligned to BH product use in clinical practice.
- Yellow light means it is neutral or informational on the therapeutic area or BH related products.
- Red means it is not supportive/aligned to BH product use in clinical practice or may have negative impact to BH products.

What is the Testosterone Efficacy & Safety (TestES) Consortium?

- https://www.imperial.ac.uk/metabolism-digestion-reproduction/research/diabetes-endocrinology-metabolism/endocrinology-and-investigative-medicine/nihr-testosterone/

- **Background:** Several high quality trials have investigated the clinical benefits and risks of testosterone replacement therapy (TRT) in men with symptomatic low testosterone. Nevertheless, there remains uncertainty among clinicians regarding the clinical benefits and harm associated with.

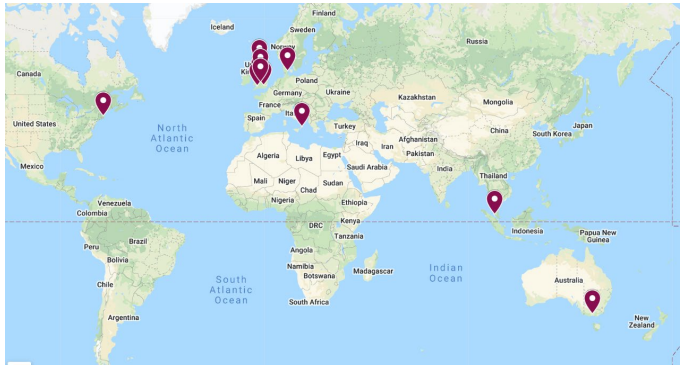
- **The TestES Consortium:** The UK National Institute of Health Research Health Technology Assessment (NIHR HTA) has commissioned and funded this study (500,000 GBP) to systematically review the literature on the use of TRT in symptomatic men with testosterone deficiency.

- **Methods:** TestES uses a rigorous evidence synthesis that includes an individual participant data meta-analysis (IPD MA). This approach impartially selects and combines clinical trials data from around the world to estimate the clinical effectiveness and safety of TRT in men with TD and to inform key parameters for the development of a decision model.

- **Expected Outcomes:** Results of this evidence synthesis and economic evaluation will provide clinicians with up-to-date, relevant information on which to form their evidence-based decisions and, therefore, are likely to impact on current clinical practice, both at national and international level.

TestES Consortium - Investigators

- The NIHR TestES consortium is led by Dr Channa Jayasena, Clinical Senior Lecturer in Reproductive Endocrinology & Andrology at Imperial College London
- Collaborators include:
  - **USA:** ***Shalender Bhasin*** - Brigham and Women's Hospital, Boston. ***Peter J. Snyder*** - University of Pennsylvania, Philadelphia. ***Kerry Hildreth***, University of Colorado, Aurora, Colorado. ***Leonard Marks***, UCLA, California. ***Lisa Tenover***, Stanford University, California.
  - **UK:** ***Geoffrey Hackett*** - Good Hope Hospital, Birmingham. ***Richard Ross*** - University of Sheffield. ***Fred Wu*** - University of Manchester. ***Richard Quinton*** – University of Newcastle
  - **Netherlands:** ***Marielle Emmelot-Vonk*** - UMC Utrecht. ***Erik Giltay*** - Leiden University Medical Centre, Leiden. ***Emily Gianatti*** – UMC Utrecht.
  - **Denmark:** ***Marianne Skovsager Andersen*** - Odense University Hospital, Odense.
  - **Italy:** ***Antonio Aversa*** - University of Catanzaro, Magna Graecia.
  - **Australia:** ***Mathis Grossmann*** - University of Melbourne.
  - **Malaysia:** ***Hui Meng Tan*** - University of Malaya.
  - **Slovenia:** ***Kristina Antonic*** - Ljubljana University Medical Centre, Ljubljana.
  - **Norway:** ***Johan Svartberg*** - University of Tromso, Tromso.



TestES Consortium: Aims

- The TestES consortium aims to answer three specific questions:

1. What are the benefits and risks to men with hypogonadism taking TRT? (**Safety paper published today (8/6/22), being presented at ENDO on 13th June https://www.thelancet.com/journals/lanhl/home .** Efficacy paper to follow soon)

2. What is the experience and acceptability of TRT in men with hypogonadism? (Published Feb 2022 – Andrology)

TestES - Andrology 2022

3. What is the cost-effectiveness of giving TRT to men with hypogonadism? (likely published end of 2022)

Adverse cardiovascular events and mortality in men during testosterone treatment: an individual patient and aggregate data meta-analysis

Jemma Hudson, Moira Cruickshank, Richard Quinton, Lorna Aucott, Magaly Aceves-Martins, Katie Gillies, Shalender Bhasin, Peter J Snyder, Susan S Ellenberg, Mathis Grossmann, Thomas G Travison, Emily J Gianatti, Yvonne T van der Schouw, Marielle H Emmelot-Vonk, Erik J Giltay, Geoff Hackett, Sudarshan Ramachandran, Johan Svartberg, Kerry L Hildreth, Kristina Groti Antonic, Gerald B Brock, J Lisa Tenover, Hui Meng Tan, Christopher Ho Chee Kong, Wei Shen Tan, Leonard S Marks, Richard J Ross, Robert S Schwartz, Paul Manson, Stephen Roberts, Marianne Skovsager Andersen, Line Velling Magnussen, Rodolfo Hernández, Nick Oliver, Frederick Wu, Waljit S Dhillo, Siladitya Bhattacharya, Miriam Brazzelli, Channa N Jayasena**

PDF

TestES - Safety

What is already known?

Testosterone treatment is most often given to men aged 40–65 years. Testosterone has potentially favourable effects on cardiovascular risk such as increased lean-to-fat body mass and improved insulin sensitivity and glycaemia. Conversely, testosterone treatment increases haematocrit, might lower high-density lipoprotein (HDL) cholesterol, and some studies have observed increased cardiovascular event risk. Uncertainty regarding the safety of testosterone might unduly influence decision making regarding the management of men with hypogonadism who could otherwise derive substantial benefits from treatment.

Why is this study important?

The investigators designed highly sensitive search strategies to identify reports of published, ongoing, and unpublished randomised controlled trials assessing the clinical effectiveness of testosterone treatment in men with hypogonadism. Searches were restricted to reports published in English from 1992. We searched major electronic databases, clinical trial registries, and contacted clinical experts. We focused on trials with 3-month to 3 years treatment duration and mean baseline total testosterone of 12 nmol/L or less (or equivalent) before treatment. 35 trials were included and they collected individual patient data (IPD) from 17 trials (3431 participants in total). In general, the risk of bias of IPD trials was low.

Conclusion

This individual IPD meta-analysis allowed a reliable assessment of the frequency of mortality and cardiovascular events (including subtypes) during testosterone treatment in men with hypogonadism. Few deaths have occurred during trials of testosterone in men. Furthermore, testosterone treatment is not associated with an increased risk of any recorded cardiovascular event subtype in the short to medium term. **Men with hypogonadism should be counselled that there is no current evidence that testosterone treatment increases cardiovascular risk in the short to medium term.**

Lancet Healthy Longev 2022; 3: e381–93
https://www.thelancet.com/journals/lanhl/article/PIIS2666-7568(22)00096-4/fulltext

	Number of studies	Testosterone treatment group	Placebo group	OR (95% CI)	p value
Mortality from any cause					
Number of participants*	14	6/1621 (0·4%)	12/1537 (0·8%)	0·46 (0·17–1·24)	0·13
Myocardial Infarction	3	2/6 (33·3%)	2/12 (16·7%)	..	..
Cancer	1	0	3/12 (25·0%)	..	..
Ruptured aortic aneurysm	1	0	1/12 (8·3%)	..	..
Constrictive pericarditis	1	1/6 (16·7%)	0	..	..
Multiple organ failure	1	1/6 (16·7%)	0	..	..
Venous thromboembolism	1	0	1/12 (8·3%)	..	..
Unknown	3	2/6 (33·3%)	5/12 (41·7%)	..	..

Individual participants dataset meta-analysis for all-cause mortality

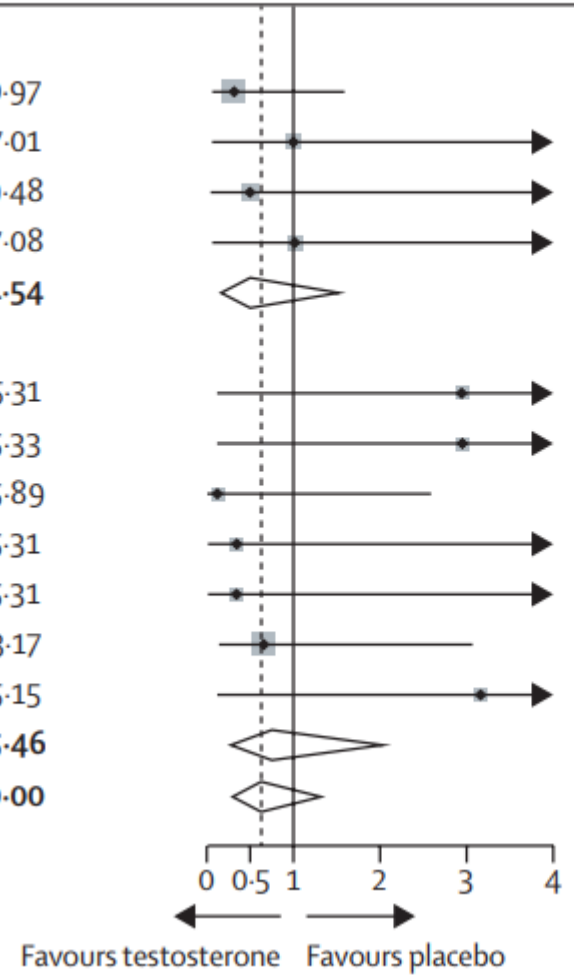
Cardiovascular or cerebrovascular events					
Number of participants†	13	120/1601 (7·5)	110/1519 (7·2)	1·07 (0·81, 1·42)	0.62
Total number of events	13	182	183	..	..
Number of participants with a cardiovascular event	11	107/120 (89·2%)	105/110 (95·5%)	..	..
Total number of cardiovascular events‡	11	166	176	..	..
Arrhythmia	6	52/166 (31·3%)	47/176 (26·7%)	..	..
Coronary heart disease	6	33/166 (19·9%)	33/176 (18·8%)	..	..
Heart failure	6	22/166 (13·3%)	28/176 (15·9%)	..	..
Myocardial infarction	7	10/166 (6·0%)	16/176 (9·1%)	..	..
Valvular heart disease	2	18/166 (10·8%)	12/176 (6·8%)	..	..
Peripheral vascular disease	4	8/166 (4·8%)	14/176 (8·0%)	..	..
Stable angina	5	7/166 (4·2%)	7/176 (4·0%)	..	..
Aortic aneurysm§	5	6/166 (3·6%)	7/176 (4·0%)	..	..
New angina	3	5/166 (3·0%)	5/176 (2·8%)	..	..
Unstable angina	3	2/166 (1·2%)	4/176 (2·3%)	..	..
Aortic dissection	1	2/166 (1·2%)	0	..	..
Atherosclerosis	1	1/166 (0·6%)	1/176 (0·6%)	..	..
Cardiac arrest	2	0	2/176 (1·1%)	..	..
Number of participants with a cerebrovascular event	11	15/120 (12·5%)	7/110 (6·4%)	..	..
Total number of cerebrovascular events‡	11	16	7	..	..

Individual participants dataset meta-analysis for cardiovascular or cerebrovascular events

None of the cardiovascular event subtypes were significantly more common in patients assigned to testosterone treatment than in patients assigned to placebo. Neither patient age nor the previous diagnosis of cardiovascular events were associated with an increased risk of cardiovascular events.

A

	Testosterone group (n/N)	Placebo group (n/N)	Weight (%)	OR (95% CI)
IPD				
Basaria et al (2015)[38]	2/155	6/151	20·97	0·32 (0·06–1·59)
Ho et al (2012)[46]	1/60	1/60	7·01	1·00 (0·06–16·37)
Snyder et al (2016)[17]	1/394	2/394	9·48	0·50 (0·05–5·52)
Srinivas-Shankar et al (2010)[47]	1/130	1/132	7·08	1·02 (0·06–16·41)
REML subtotal I^2=0%	**5/739**	**10/737**	**44·54**	**0·50 (0·17–1·52)**
Aggregate data				
Basaria et al (2010)[15]	1/106	0/103	5·31	2·94 (0·12–73·08)
Behre et al (2012)[51]	1/183	0/179	5·33	2·95 (0·12–72·91)
Giltay et al (2010)[45]	0/113	2/71	5·89	0·12 (0·01–2·59)
Hackett et al (2013)[50]	0/97	1/102	5·31	0·35 (0·01–8·62)
Jones et al (2011)[52]	0/108	1/112	5·31	0·34 (0·01–8·50)
Kenny et al (2010)[53]	3/69	4/62	23·17	0·66 (0·14–3·07)
Svartberg et al (2008)[49]	1/19	0/19	5·15	3·16 (0·12–82·64)
REML subtotal I^2=0%	**6/695**	**8/648**	**55·46**	**0·75 (0·28–2·03)**
REML overall I^2=0%	**11/1434**	**18/1385**	**100·00**	**0·63 (0·30–1·32)**



Two-stage IPD meta-analysis for all-cause mortality

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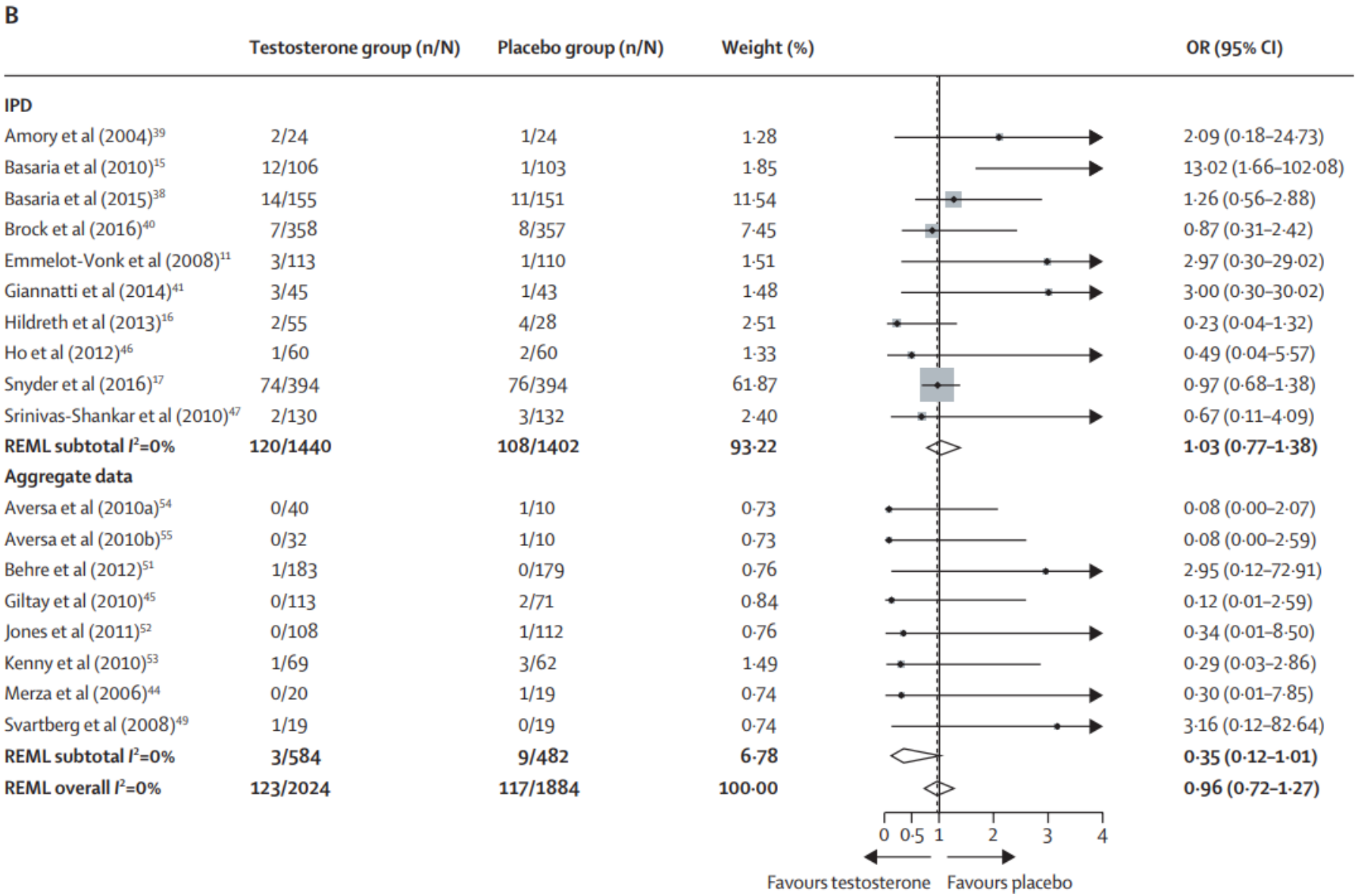

	Testosterone group (n/N)	Placebo group (n/N)	Weight (%)	OR (95% CI)
IPD				
Amory et al (2004)[39]	2/24	1/24	1·28	2·09 (0·18–24·73)
Basaria et al (2010)[15]	12/106	1/103	1·85	13·02 (1·66–102·08)
Basaria et al (2015)[38]	14/155	11/151	11·54	1·26 (0·56–2·88)
Brock et al (2016)[40]	7/358	8/357	7·45	0·87 (0·31–2·42)
Emmelot-Vonk et al (2008)[11]	3/113	1/110	1·51	2·97 (0·30–29·02)
Giannatti et al (2014)[41]	3/45	1/43	1·48	3·00 (0·30–30·02)
Hildreth et al (2013)[16]	2/55	4/28	2·51	0·23 (0·04–1·32)
Ho et al (2012)[46]	1/60	2/60	1·33	0·49 (0·04–5·57)
Snyder et al (2016)[17]	74/394	76/394	61·87	0·97 (0·68–1·38)
Srinivas-Shankar et al (2010)[47]	2/130	3/132	2·40	0·67 (0·11–4·09)
REML subtotal I^2=0%	**120/1440**	**108/1402**	**93·22**	**1·03 (0·77–1·38)**
Aggregate data				
Aversa et al (2010a)[54]	0/40	1/10	0·73	0·08 (0·00–2·07)
Aversa et al (2010b)[55]	0/32	1/10	0·73	0·08 (0·00–2·59)
Behre et al (2012)[51]	1/183	0/179	0·76	2·95 (0·12–72·91)
Giltay et al (2010)[45]	0/113	2/71	0·84	0·12 (0·01–2·59)
Jones et al (2011)[52]	0/108	1/112	0·76	0·34 (0·01–8·50)
Kenny et al (2010)[53]	1/69	3/62	1·49	0·29 (0·03–2·86)
Merza et al (2006)[44]	0/20	1/19	0·74	0·30 (0·01–7·85)
Svartberg et al (2008)[49]	1/19	0/19	0·74	3·16 (0·12–82·64)
REML subtotal I^2=0%	**3/584**	**9/482**	**6·78**	**0·35 (0·12–1·01)**
REML overall I^2=0%	**123/2024**	**117/1884**	**100·00**	**0·96 (0·72–1·27)**

Two-stage IPD meta-analysis for cardiovascular or cerebrovascular events

	Number of studies	Testosterone treatment group	Placebo group	Mean difference (95% CI)	τ^2
Testosterone, nmol/L	16	17·27 (10·34); 1211	9·87 (3·98); 1156	7·24 (5·07 to 9·41)	17·01
Free testosterone, pmol/L	12	426·70 (368·42); 1058	203·57 (86·24); 1027	186·40 (115·91 to 256·90)	13741·90
Fasting glucose, mmol/L	12	6·50 (2·09); 1259	6·75 (2·38); 1181	−0·16 (−0·24 to −0·07)	0·00
Fasting glucose sensitivity*, mmol/L	11	6·04 (1·69); 946	6·24 (2·04); 897	−0·13 (−0·28 to 0·02)	0·04
Cholesterol, mmol/L	14	4·51 (1·05); 1388	4·67 (1·11); 1314	−0·15 (−0·20 to −0·10)	0·00
Low-density lipoproteins cholesterol, mmol/L	14	2·69 (0·98); 1378	2·70 (0·98); 1299	−0·03 (−0·08 to 0·01)	0·00
High-density lipoproteins cholesterol, mmol/L	14	1·15 (0·33); 1384	1·21 (0·39); 1312	−0·06 (−0·08 to −0·04)	0·00
Triglycerides, mmol/L	14	1·73 (1·30); 1368	1·89 (1·51); 1297	−0·09 (−0·18 to −0·00)	0·01
Haemoglobin, g/L	13	153·53 (14·71); 1291	143·58 (12·67); 1206	10·87 (8·19 to 13·55)	20·80
Haematocrit (%)	15	46·06 (4·37); 1399	42·94 (3·77); 1309	3·15 (2·42 to 3·88)	1·77
HbA_{1c} (%)	8	6·46 (1·12); 748	6·58 (1·21); 742	−0·09 (−0·25 to 0·06)	0·03
HbA_{1c} (%) sensitivity*	7	6·14 (0·94); 519	6·24 (1·08); 523	−0·89 (−2·43 to 0·64)	4·29
Systolic blood pressure, mmHg	10	134·11 (17·14); 1069	133·31 (16·64); 1041	0·99 (−0·08 to 2·06)	0·00
Diastolic blood pressure, mmHg	10	77·20 (11·03); 1069	76·84 (10·98); 1041	0·48 (−0·30 to 1·26)	0·15

Data are mean (SD), unless otherwise specified. Outcomes were analysed using a random-effects model. *Participants with diabetes at baseline were excluded.

Table 3: **One-stage analysis for secondary outcome of physiological markers**

	Number of studies	Testosterone treatment group	Placebo group
Diabetes or diabetes complications	2	14/752 (1·9%)	19/751 (2·5%)
Prostate cancer	8	10/1293 (0·8%)	3/1059 (0·3%)
Oedema	7	34/1301 (2·6%)	17/1290 (1·3%)
Hypertension	7	28/1195 (2·3%)	20/1182 (1·7%)
High haematocrit	7	30/1079 (2·8%)	5/993 (0·5%)
Venous thromboembolism	4	5/1037 (0·5%)	7/1034 (0·7%)
Non-stroke cerebrovascular pathology*	3	4/655 (0·6%)	11/648 (1·7%)

Data are n/N (%). *Examples include carotid occlusion and carotid stenosis.

Table 4: **Summary of additional outcomes**

TestES Consortium: Safety Conclusions

- Results of this meta-analysis have potentially important implications for the management of men with hypogonadism.
- Worldwide prescribing of testosterone for hypogonadism is increasing; however, conflicting messages on testosterone safety might have caused variations in treatment among patients.
- The TestES consortium have conducted the most comprehensive study to date investigating the safety of testosterone treatment of hypogonadism. Testosterone treatment did not increase cardiovascular event risk in the short term to medium term.
- Furthermore, they did not identify subgroups with high cardiovascular risk.
- An ongoing trial (NCT03518034 - TRAVERSE) is investigating the longer-term safety of testosterone, and future studies are needed to analyse the risk–benefit and cost-effectiveness of testosterone therapy.
- However, the current results provide some reassurance about the short-term to medium-term safety of testosterone to treat male hypogonadism.

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Relevant Publications in TD

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Issue No. 2

Recovery of male reproductive endocrine function after ceasing prolonged testosterone undecanoate injections. European Journal of Endocrinology (2022) 186, 307–318. Handelsman, DJ et al (T4DM Run-off Study)

Neutral for BH

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PDF

T4DM Run Off Study

Recovery of male reproductive endocrine function after ceasing prolonged testosterone undecanoate injections

What is already known?	Product labels of testosterone therapies indicate that testosterone therapy may reversibly reduce spermatogenesis. This is due to suppression of reproductive hormones (LH, FSH) by exogenous TTh. FSH is required for spermatogenesis. Therefore, if fertility is desired, many hypogonadal patients will be treated with alternative therapies in order to preserve levels of reproductive hormones thus avoiding any potential impact on spermatogenesis.
Why is this study important?	The time course of male reproductive hormone recovery after stopping long-acting injectable testosterone undecanoate (TU) treatment is not known. This is a run-off study from the highly important T4DM study. The aim of this study was to investigate the rate, extent, and determinants of reproductive hormone recovery over 12 months after stopping TU injections.
Conclusion	303 men who had glucose intolerance but without pathologic hypogonadism completed a 2-year placebo-controlled randomized clinical trial of TU treatment (T4DM) and were recruited for a further 12 months while remaining blinded to treatment. After stopping 2 years of 1000 mg injectable TU treatment, full reproductive hormone recovery is slow and progressive over 15 months since the last testosterone injection and may take longer than 12 months to be complete.

Please note - Sperm production was not measured as part of this study

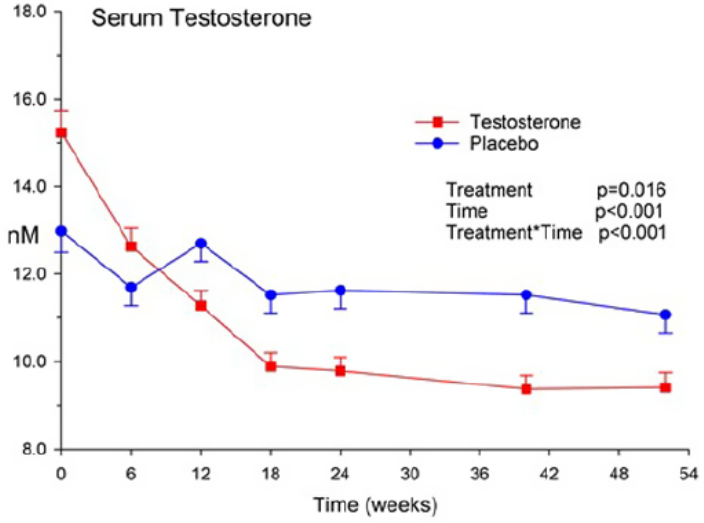
Recovery of male reproductive endocrine function after ceasing prolonged testosterone undecanoate injections. European Journal of Endocrinology (2022) 186, 307–318. Handelsman, DJ et al (T4DM Run-off Study)

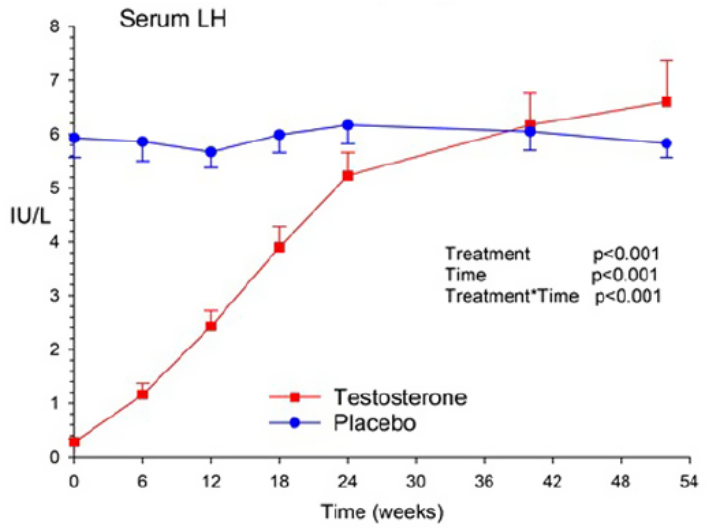
T4DM Run-off Study (n = 303)

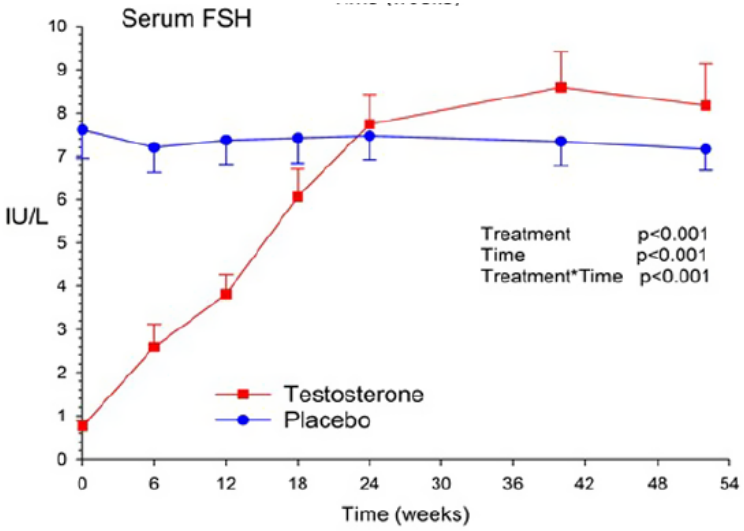
Table 2 Matching of participants after 2 years in T4DM study prior to entry into runoff study.

	Placebo treated				Testosterone treated			
	Enter runoff study		Not in runoff study		Enter runoff study		Not in runoff study	
	n	Values	*n*	Values	*n*	Values	*n*	Values
Randomized patients	148		355		155		349	
2 h glucose on OGTT (mmol/L)	145	8.7 (3.4)	268	8.8 (3.1)	152	7.6 (2.7)	291	8.2 (2.7)
Testosterone (nmol/L)	142	14.7 (5.7)	237	14.4 (5.2)	148	17.8 (6.3)	271	16.0 (6.4)
Waist circumference (cm)	148	111.7 (12.4)	262	113.0 (11.5)	154	109.2 (12.2)	287	111.7 (13.0)
Weight (kg)	148	103.7 (16.8)	262	103.5 (16.6)	154	101.4 (16.6)	286	103.4 (17.8)
BMI (kg/m^2)	148	33.2 (5.1)	262	33.2 (5.0)	154	32.9 (5.2)	286	33.3 (5.3)

Time course of serum testosterone, LH and FSH plotted as mean and s.e.m. on the y-axis over time in weeks on the x-axis

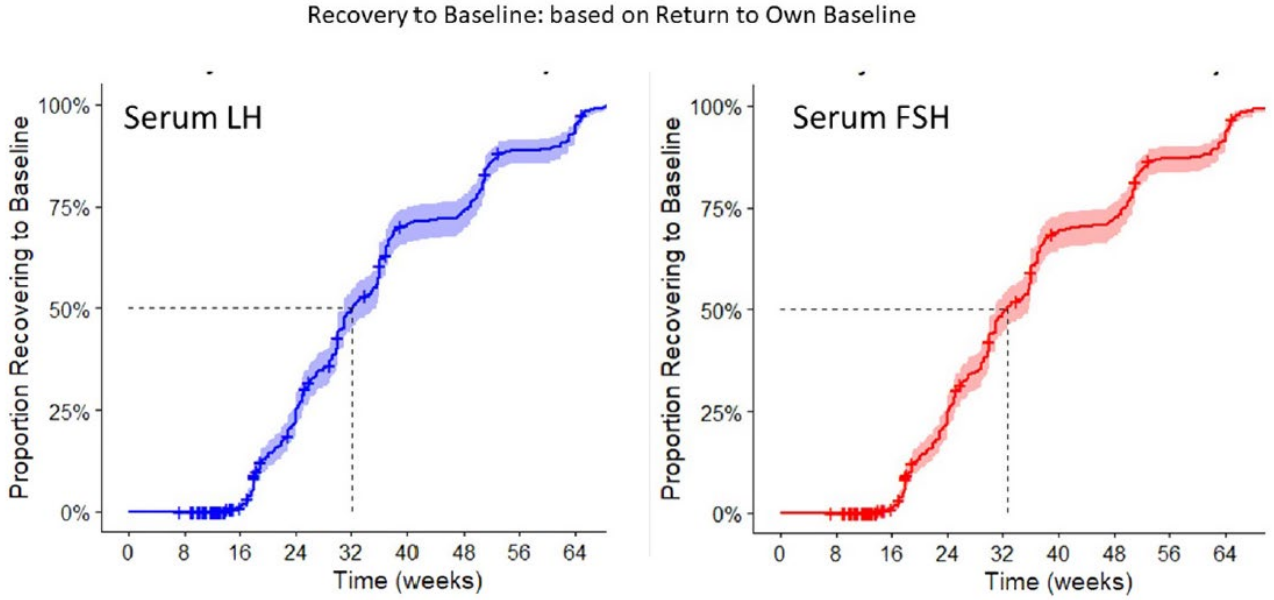






****Time in these figures is the time in weeks since entry to the runoff study – this entry occurs 12 weeks after the last T4DM study injection**

T4DM Run-off Study



Kaplan–Meier survival analysis of the time to recovery of serum LH (left) and FSH (right) to the participants' own pre-treatment baseline. Time in this analysis is from the time of the last injection – which is 12 weeks earlier than entry to the runoff study

- Recovery of serum LH and FSH was based on the return to the participant's own pre-treatment baseline serum LH and FSH.
  - It took approx. 34 weeks for 50% of subjects to recover to their own pre-treatment baseline level for serum FSH and serum LH.
  - It took 63 weeks for 90% of subjects to reach their own pre-treatment baseline level for serum FSH and LH

T4DM Run-off Study

Take home messages:

When long-acting testosterone undecanoate treatment is ceased after 2 years, patients aged 50-74 with metabolic disturbances but without pathological hypogonadism risk androgen withdrawal symptoms, and the time to recovery of their reproductive hormones (LH, FSH) is slow and may take longer than 12 months to return to pre-treatment levels.

While recovery from suppression by exogenous T is expected, the delayed recovery signifies a prolonged depot effect of injectable TU.

The HEAT-Registry

The HEAT-Registry (HEmatopoietic Affection by Testosterone): comparison of a transdermal gel vs long-acting intramuscular testosterone undecanoate in hypogonadal men

Zitzmann, M. et al. THE AGING MALE 2022, VOL. 25, NO. 1, 134–144

- **The study is open-access and free for commercial use**
- **You don´t have to contact Taylor & Francis for reprints.**
- **Copies can be printed in a normal printing shop without copyright issues (print without "The Aging Male" title page)**
- **Alternatively the link to the PDF can be shared with interested doctors**
  - **https://www.tandfonline.com/doi/full/10.1080/13685538.2022.2063830**

HEAT Registry