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Cumbria, Northumberland, Tyne and Wear
NHS Foundation Trust

Outcomes of Testosterone Treatment in Pathological and Functional Male Hypogonadism.

ALM National Audit Meeting, RCPath London
28 November 2025, 11:30–12:10

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Disclosures

Speaker honoraria from Besins and Androlabs

Advisory Boards for Besins and Roche Diagnostics

Basic Definition of Male Hypogonadism

Male hypogonadism is a clinical syndrome defined by deficient testosterone production and impaired spermatogenesis by the testes.

The diagnosis requires a combination of characteristic clinical features and corroborative laboratory evidence.

It's not enough to have had a low serum T level measured.

Make a clear distinction between 1^{o} and 2^{o} (or central) hypogonadism, because the required confirmatory or second-line investigations are very different.

Society for Endocrinology, 2022

Jayasena CN, *Clinical Endocrinology*. 2022

Classification of Male Hypogonadism

- 1º Intrinsic dysfunction of testis = light bulb broken

  - ↑ LH & ↑↑ FSH levels ocal.

  - clinical correlation is us

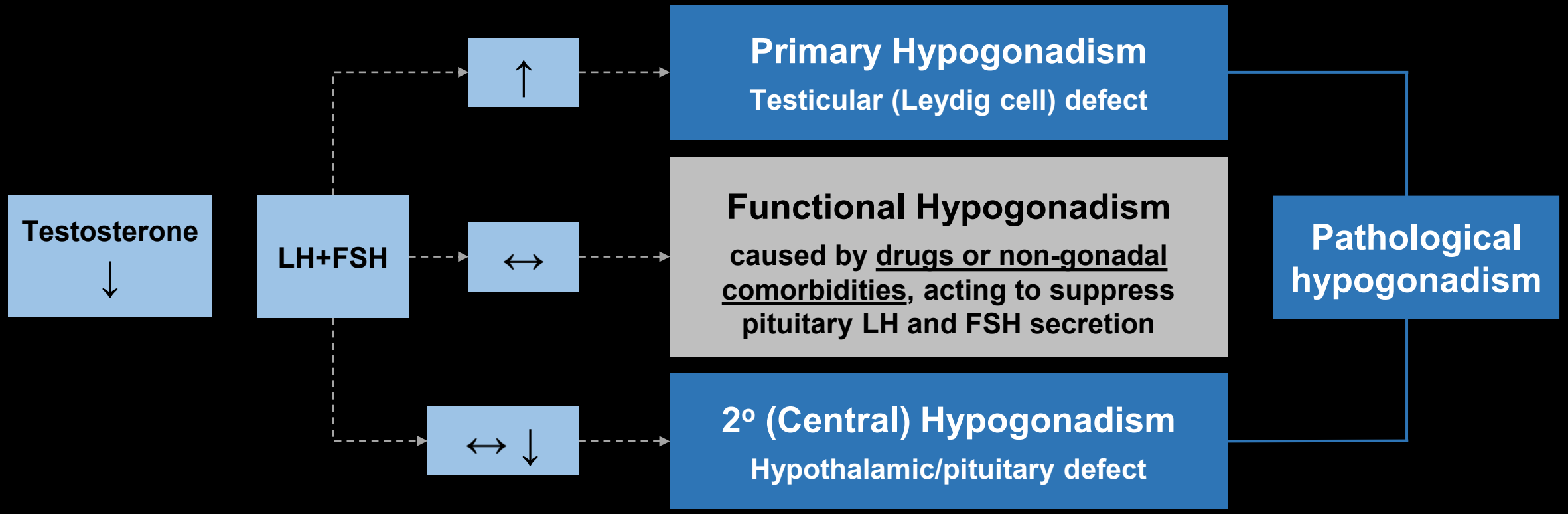
- 2º Lack of LH & FSH st ch off

  - LH & FSH l

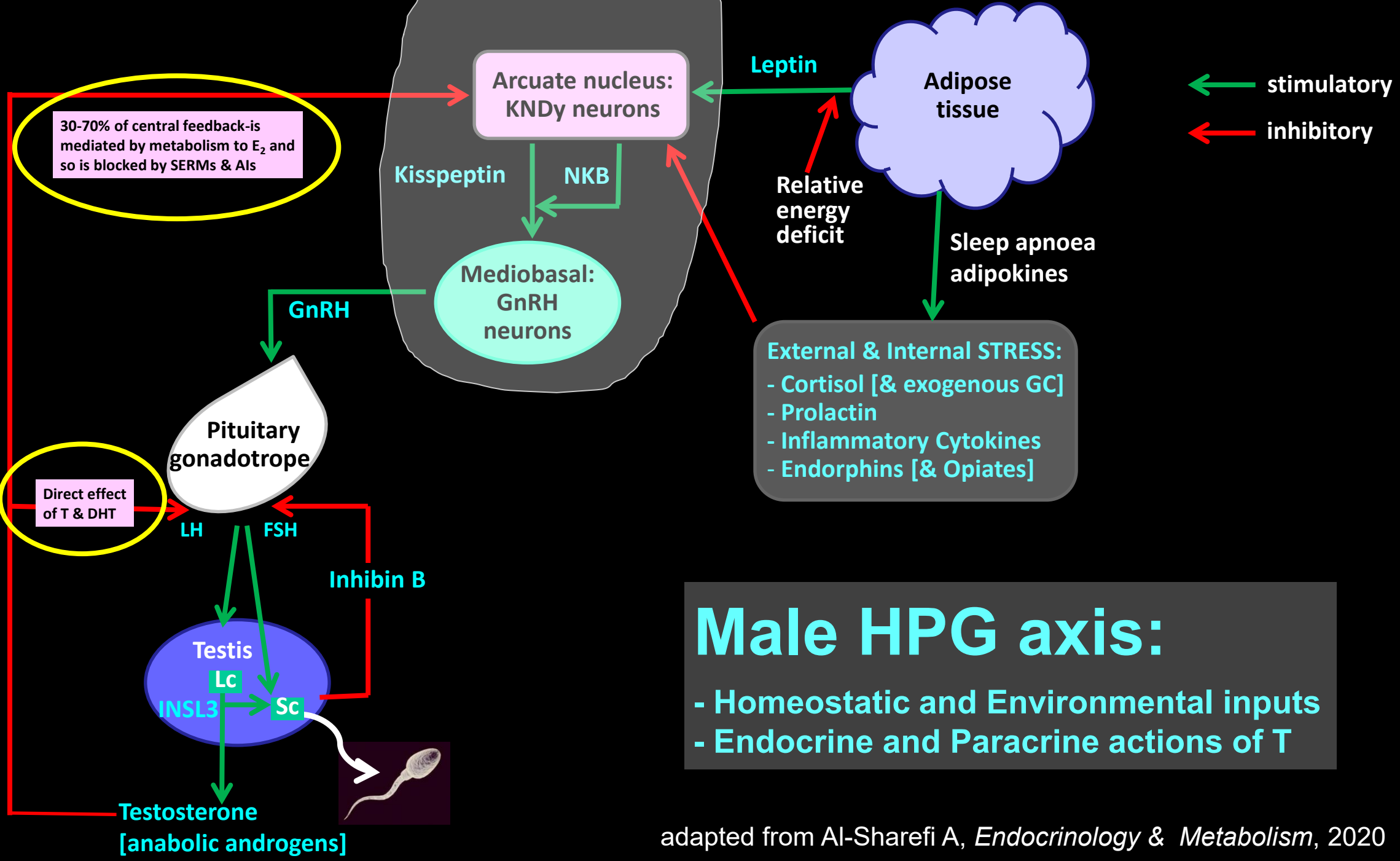
  - biochemica GI), or sampling a re.

  - so clinical c

Basic Classification of Male Hypogonadism



- Functional Hypogonadism or non-gonadal Illness-effect resolves when the proximate cause is cured or remits.
- Physiological phenomenon, but with uncertainty as to whether adaptive or maladaptive in the long-term.
- Biochemical signature overlaps with both central hypogonadism and mis-timed venepuncture-effect.



Male HPG axis:

- Homeostatic and Environmental inputs
- Endocrine and Paracrine actions of T

adapted from Al-Sharefi A, *Endocrinology & Metabolism*, 2020

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Gene

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Think very carefully before prescribing Testosterone to these guys, especially if they are seeking to conceive children

STOPPING T USUALLY RESTORES FERTILITY

Causes of Functional Hypogonadism

Indirect suppression of arcuate nucleus Kisspeptin secretion:

- impaired Leptin signalling due to Relative Energy Deficit or very rare LEP/LEPR gene defect

Direct suppression of arcuate nucleus Kisspeptin secretion:

- hyperprolactinaemia of any cause, including dopamine-antagonist drugs
- opiate use or abuse.
- glucocorticoids or Cushing's syndrome.
- inflammatory cytokines
- acute or chronic non-gonadal illness, including **obesity** and **T2DM**

Multi-level effect with direct suppression of both Kisspeptin and pituitary LH secretion:

- androgens, estrogens and progestins

Direct suppression of pituitary LH+FSH secretion: GnRH analogs and antagonists

Turner H & Wass JAH, *Clin Endocrinol*, 1998 Jayasena CN, *Clin Endocrinol*, 2022

Clinical Features of Male Hypogonadism [1]

Reproductive

- Loss of (or failure to fully develop) 2^{o} sexual characteristics; sexual dysfunction (low libido, ED & loss of spontaneous erections); subfertility, and gynaecomastia.

Non-reproductive

- Physical: fatigue, reduced muscle strength & physical endurance, vasomotor symptoms, anaemia, osteoporosis and fracture
- Psychological *: loss of motivation or concentration, irritability, low or labile mood, body shame & psychosexual issues.

* Least evidence of benefit from testosterone treatment [2]

1. Jayasena CN, et al. Clinical Endocrinology. 2022;96:200-219

2. Hudson J, Lancet Health Longev, 2023

Divergent Features of Functional Hypogonadism in Obesity

Testicular volume and consistency:

- usually preserved and with normal consistency, never hard (as in 1^{o}) or soft (as in 2^{o}).

Bone mineral density and fracture risk:

- BMD is preserved; low fracture risk until the effects of incident T2DM on bone quality kick-in.

Fertility: usually preserved, although sperm numbers and quality may be lower with obesity.

Sexual dysfunction: superimposed effects of T2DM, atherosclerosis and antihypertensive drugs.

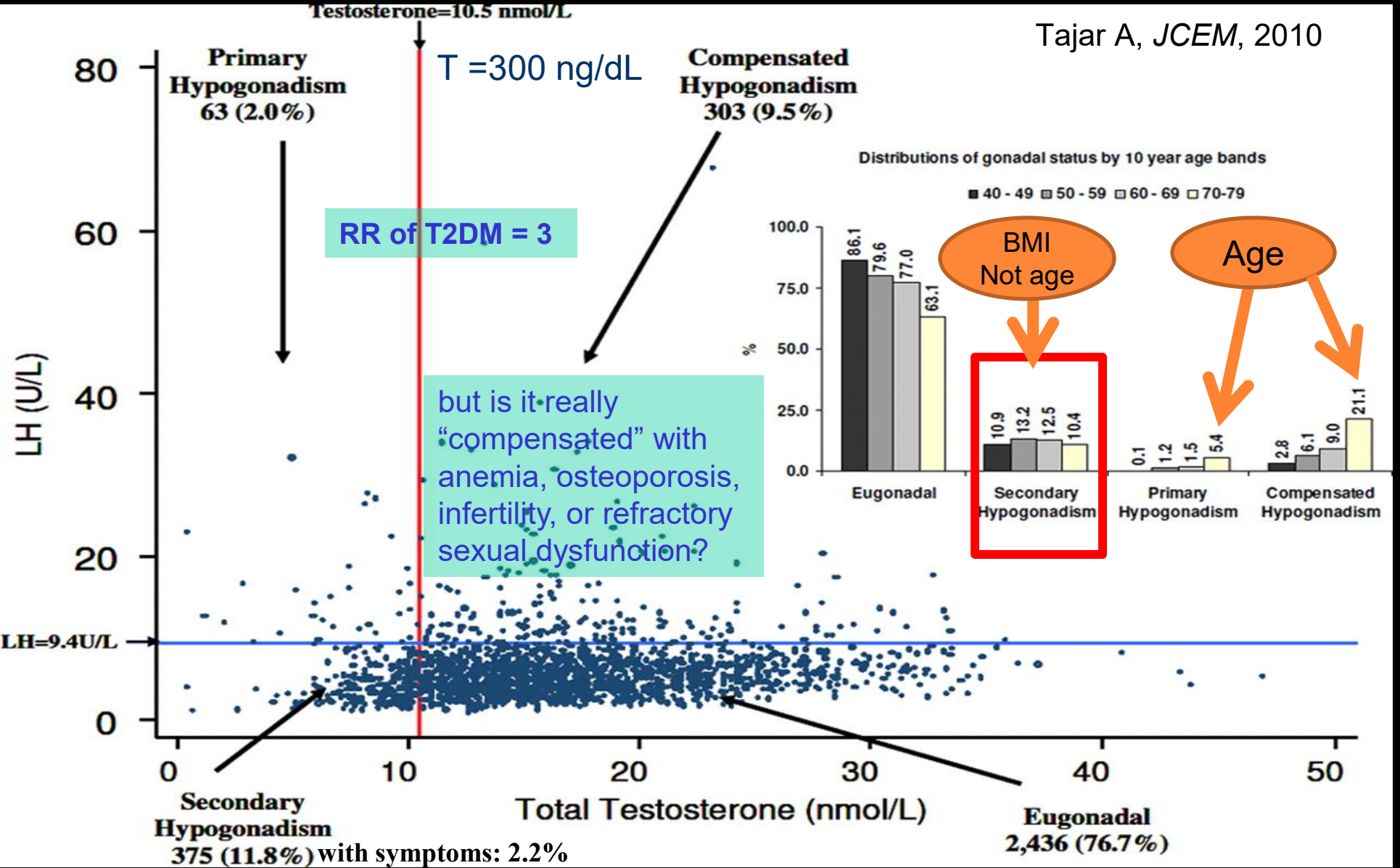
Haematocrit and anaemia:

- overall, anaemia is no more prevalent than background population.
- confounding effects of obesity and incident sleep apnoea or hypertension act to increase Hct.

Biochemistry: LH+FSH are never suppressed and fasted 9am serum T is rarely <8 nmol/L.

Responsive to Estrogen blockade: biochemistry normalises, but clinical benefits are uncertain.

Prevalence of Hypogonadism – EMAS



Tajar A, *JCEM*, 2010

Summary of EMAS

- Although 11% of men aged 40+ had low-LH/low-T biochemistry, only 2.1% fulfill diagnostic criteria for hypogonadism (low total and low free T, and sexual symptoms.
  - EMAS found the decline in LH-driven serum T to reside overwhelmingly in the burden of illness (especially. obesity), with no direct impact of chronological ageing.
  - The prevalence of this functional hypogonadism did not increase in the 40–70+ age range.
- EMAS also identified 2% of men age 40+ (5.4% of 70+) with pathological age-related 1^{o} hypogonadism and raised LH from Leydig cell dysfunction.
  - Although the incidence of new primary hypogonadism is low (0.2%/year after age 40), it increases in tandem with both chronologic age and the burden of illness.
- Age 40+ 2.1% functional + 2.0% pathological = 4.1% prevalence of hypogonadism
  Age 70+ 2.1% functional + 5.4% pathological = 7.5% prevalence of hypogonadism

Tajar A, *NEJM*, 2010

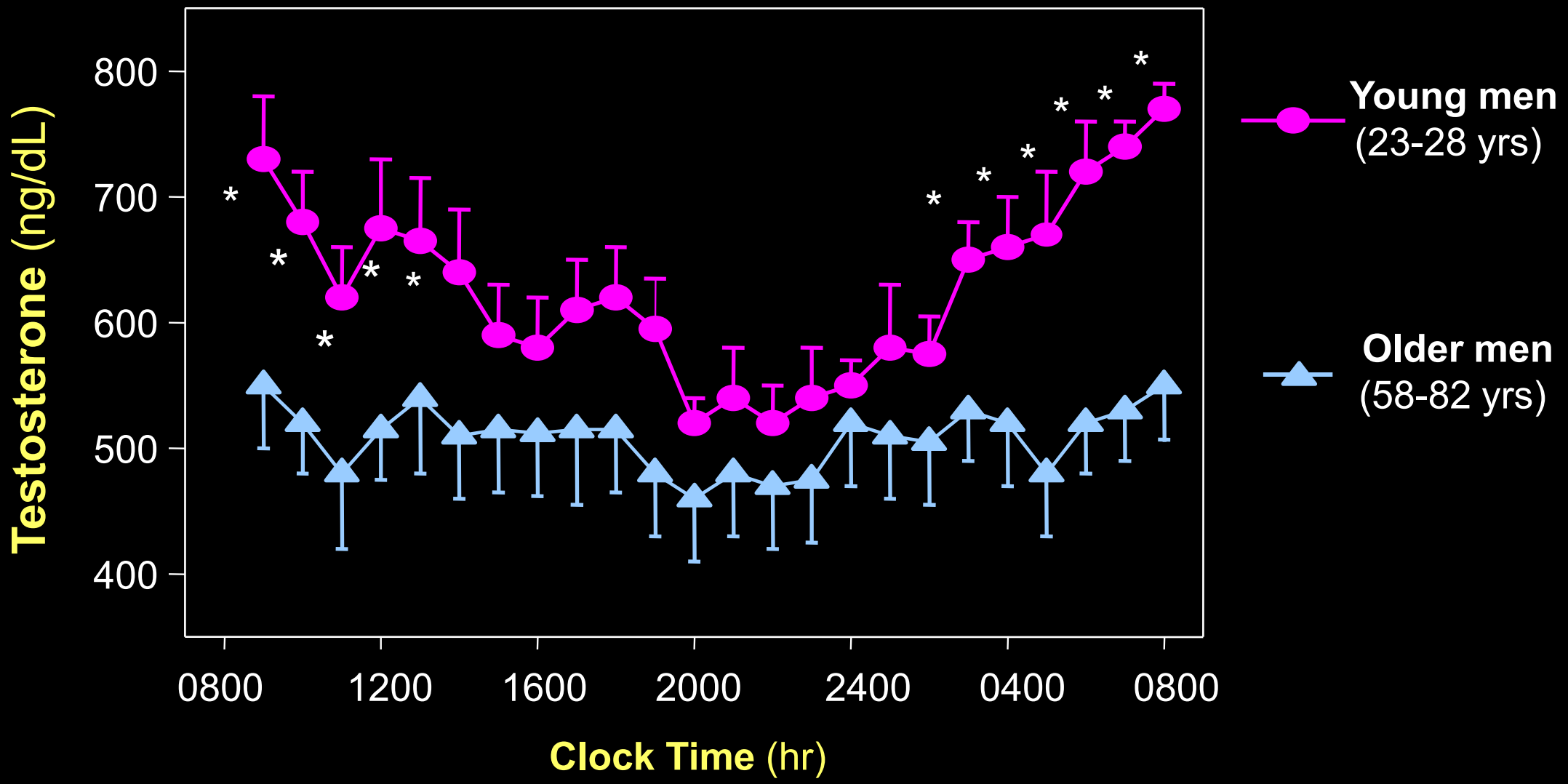
Diagnosing male hypogonadism

What is Required to Diagnose Male Hypogonadism?

- The Society for Endocrinology (SfE) recommends diagnosing hypogonadism in men with:
  - relevant clinical features (a muscular physique would not be among these!) and….
  - unequivocally and consistently low serum total T (and/or when indicated free-T concentrations), when blood was sampled under standard conditions.
  - the highest recent serum T level trumps all other results.
- But 1^{o} hypogonadism can be reliably diagnosed based on a single untimed venepuncture showing low T and raised LH, without need for clinical correlation.
  - also, if apubertal or there's an obvious pituitary cause (mass lesion or HFE), 1 sample will do.
- SfE is working with UK-NEQAS to better standardise T assays and reference ranges.
- Preserved fertility or high-normal Hct: usually incompatible with diagnosing hypogonadism

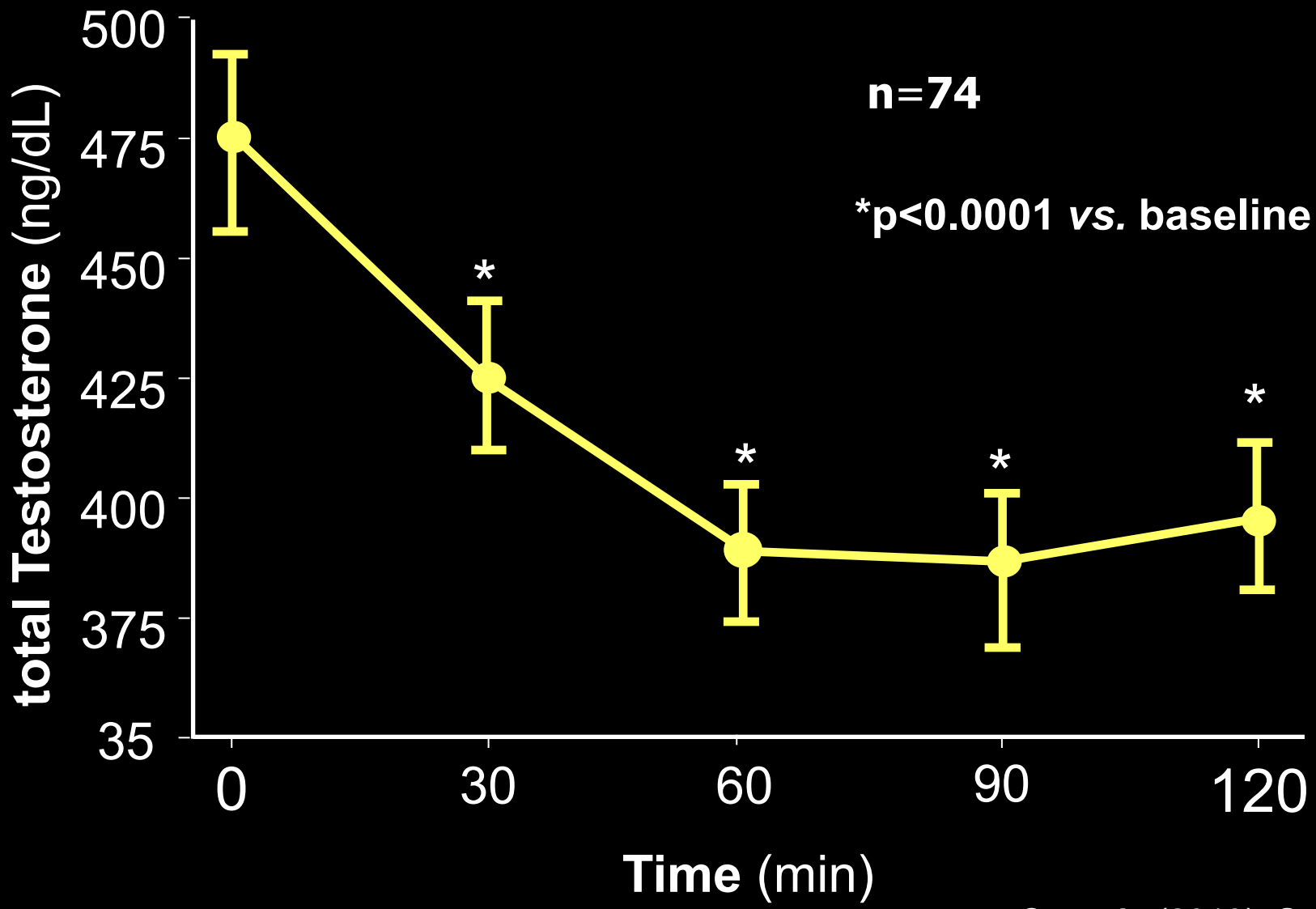
Jayasena CN, *Clin Endocrinol*, 2022 Jayasena CN, *Ann Clin Biochem*, 2024 de Silva NL, *Lancet Diabet Endocrinol*, 2024

Diurnal Rhythm of Testosterone Secretion in Men



Bremner WJ, *JCEM, 1983*

Serum T Falls with 75 g Oral Glucose Load



25% mean fall in LH-mediated total & free T with OGTT

15% <280 mg/dL (9.7 nmol/L) – hypogonadal range

whether normal GT, IGT, or T2DM

similar effect with glucose+protein energy shakes and also pure protein shakes

Caronia (2013); **Schwarz** (2015 & 2019), *Clin Endocrinol*

Investigations for Male Hypogonadism

Testosterone and SHBG:

SHBG normal: no need to calculate FT.[2]

SHBG very low: consider androgen abuse or prediabetes depending on patient physique.

If FT <125 pmol/L, hypogonadism is unlikely.

LH and FSH

Differentiate between primary (testicular) and secondary (pituitary/hypothalamic hypogonadism)

FBC

Hypogonadism unlikely if Hb or Hct are high-normal; more likely if there is anaemia

Pituitary function - especially Prolactin - and iron studies

If low T, LH and FSH, to exclude pituitary lesion and haemochromatosis.

Pituitary MRI

A pituitary MRI is performed to exclude parasellar lesions in men with low LH and significantly low T, especially with increased prolactin level

Genetic Testing

Karyotype for primary hypogonadism.

CHH gene panel for congenital hypogonadotropic hypogonadism, including Kallmann syndrome and Combined Pituitary Hormone Deficiency

Jayasena CN, *Clin Endocrinol*, 2022

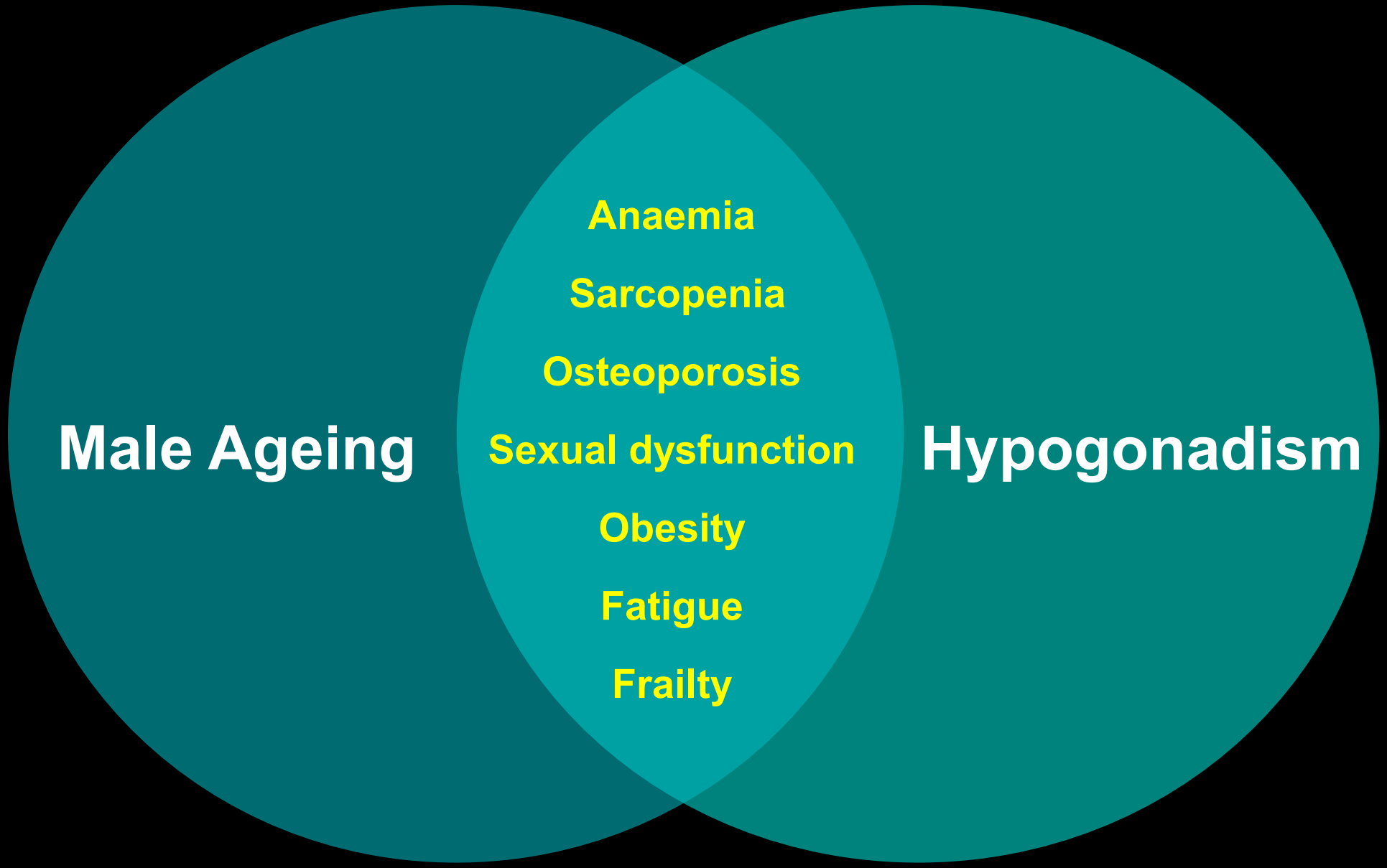
Jayasena CN, *Ann Clin Biochem*, 2024

Clinical Evidence

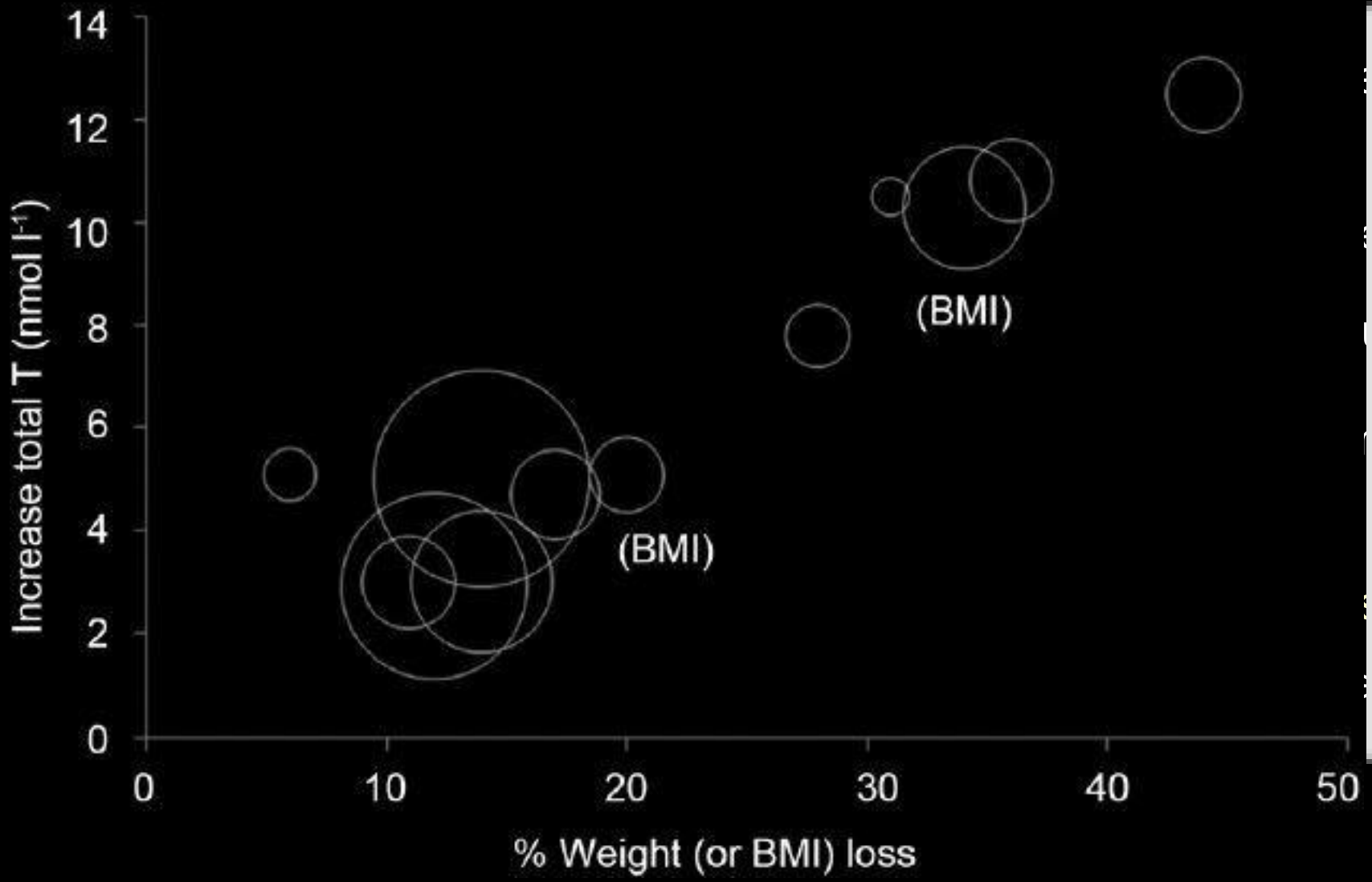
Evidence for Benefit of Testosterone in Pathological Hypogonadism?

- Errrmmm….there isn't any direct high-quality evidence:
  - Testosterone treatment of pathological male hypogonadism is so well established that it would now be considered unethical to conduct an RCT with placebo arm.
  - However, extensive clinical experience indicates its effectiveness at inducing puberty and masculinisation, improving sexual function, correcting anaemia, improving bone density, achieving leaner body composition and having a favourable impact on mood.
  - Androgen deprivation therapy induces negative changes in all these domains.
- All direct RCT evidence arises from studies of men with obesity-related functional hypogonadism and modestly reduced serum T levels, typically 8–11 nmol/L.

Bhasin S & Snyder PJ, *NEJM*, 2025


Male Ageing
Anaemia
Sarcopenia
Osteoporosis
Sexual dysfunction
Obesity
Fatigue
Frailty
Hypogonadism

BMI and Testosterone levels in Obese Males



Fui MNT, *Asian J Androl*, 2017

Grossmann M, *JCEM*, 2024

Al-Sharefi A, *BJGP,* 2020

Bhasin S, *NEJM*, 2023

Wittert G, *Lancet Diabetes Endocrinol*, 2021

Snyder PJ, *NEJM*, 2024

Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM)

Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM)

Design

- **2-year Australian: double-blind RCT of men with serum T <14 nmol/L, without pathological hypogonadism and IGT or recent T2DM.**
- **1,007 men aged 50–74 years were included, 25% of whom already had sleep apnoea.**
- **All participants were enrolled in an active lifestyle program and randomised 1:1 to receive:**
  - Testo undecanoate 1 g every 12 weeks (504 men) – no titration
  - Placebo (503 men)
  - Administered at baseline, 6 weeks, and every 3 months for 2 years.

Inclusion Criteria	Selected Exclusion Criteria
Waist circumference ≥95 cm. Testosterone ≤ 14.0 nmol/L (compared with lower limit of normal 11 nmol/L). IGT (OGTT 2-h glucose 7.8–11.0 mmol/L) or new diagnosis T2DM (OGTT 2-h glucose <15.0 mmol/L). Eligible for a lifestyle program and willing to participate.	High risk of cardiovascular events: • Stroke or TIA in past 3 years • Major CV event in past 6 months • Cardiac failure (NYHA > II), angina, arrhythmia, BP ≥160/100 mmHg • Thrombophilia or haematocrit >50% Type 1 or established Type 2 diabetes. Substance abuse in past 6 months.

Primary Outcomes

1. **Incidence of T2DM at 2 years** (OGTT 2-h glucose >11 mmol/L.
2. **Mean change in OGTT 2-h glucose** at 2 years compared with baseline.

Wittert G, *Lancet Diabet Endocrinol*, 2021

Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): Findings

- In obese men with high prevalence of obstructive sleep apnoea (25%), low or low-normal testosterone levels and prediabetes (at risk of T2DM, or newly diagnosed T2DM), a pharmacological dose of testosterone (**not adjusted as per the usual practice for replacement**) + lifestyle intervention **reduced the prevalence of T2DM after 2 years by 41%** *vs* lifestyle intervention alone (RR 0.59; p<0.001)
- Testosterone + lifestyle intervention for 2 years resulted in **significant improvements in body composition, glucose regulation, bone structure and density** and **physical performance** among these men.
- The proportion who progressed to T2DM was 7.6% (n=355) with pharmacologic Testosterone + lifestyle intervention and 14.9% (n=329) with placebo + lifestyle intervention
- No relationship between basal total or calculated free testosterone concentrations and the testosterone treatment effect, suggesting a pharmacological action of testosterone, rather than a replacement effect.

Wittert G, *Lancet Diabet Endocrinol*, 2021

Fui MNT, *JCEM*, 2021

T4DM: Safety

- Pre-specified SAEs occurred in 37/503 patients on placebo and 55/504 on testosterone [*n.s.*].
- 3% developed new sleep apnoea compared with 0.4% on placebo [p=0.03]
- Haematocrit ≥54%, triggering stop treatment occurred in 22% of 491 men on testosterone, but in many cases that point only occurred after the final study injection, so only 25 actual withdrawals.
  - Unclear whether 54% was upper limit of normal male haematocrit for that laboratory; Hct ranges from 48–54% between centres according to laboratory technique, reagents and local population.
  - Society for Endocrinology recommends maintaining haematocrit <50%.

T4DM: Post-study follow-up – median 5.1 years after final injection [3]

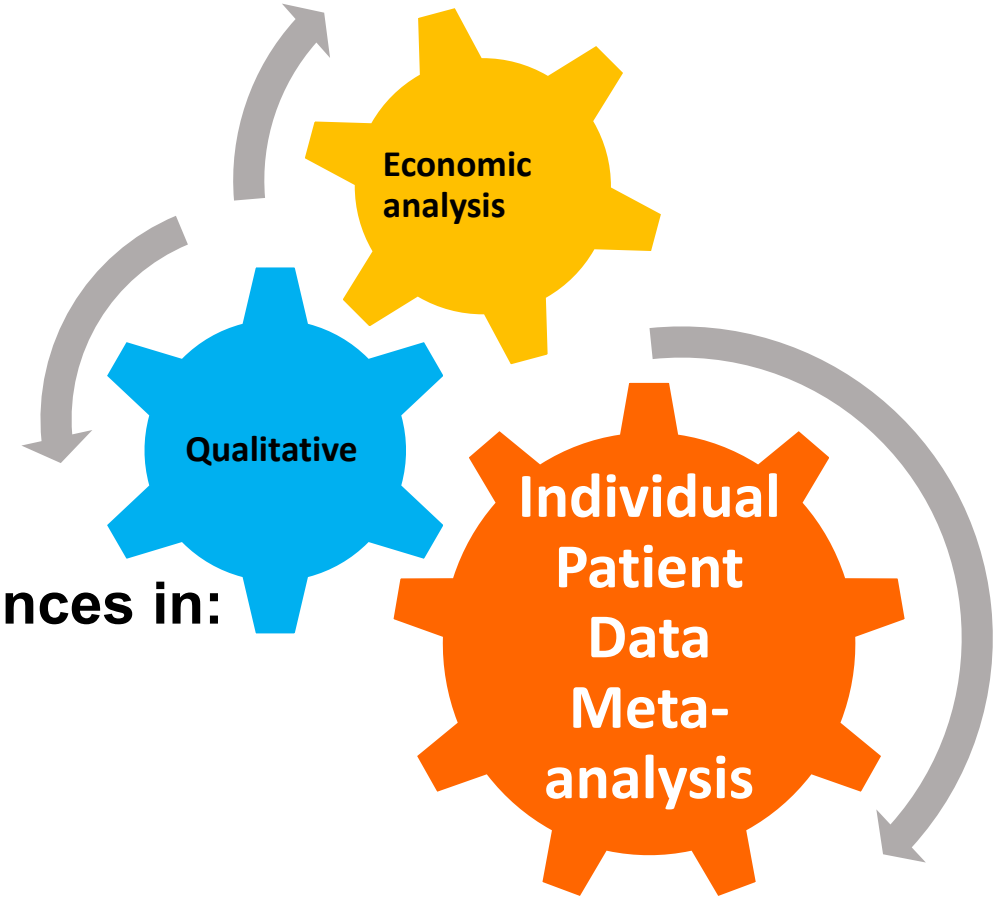
- Full recovery of the HPT axis in the treatment arm took up to 1 year from end of study.
- 8% of men who knew they were in testosterone arm restarted treatment, compared to 3.3% in placebo.

Wittert G. *Lancet Diabet Endocrinol*, 2021

Handelsman DJ, *JCEM*, 2024

Testosterone Efficacy & Safety Consortium (TestES)

NIHR | National Institute for Health Research



3,341/5,601 men
17/35 clinical trials
11 countries

No short-term differences in:

- **deaths**
- **health attacks**
- **stroke**
- **diabetes**
- **prostate cancer**

Prof Channa Jayasena
Imperial College London

Hudson J, *et al.* ***Lancet HL***, 2022

OUTCOMES

Primary

- All-cause mortality
- Cardiovascular and / or cerebrovascular events

Secondary

- Sexual function
- Quality of Life
- Physiological markers (Hb, Hct, T, lipids, glucose, HbA1c, BP)
- Other *e.g.* prostate or diabetes events

- For serial measurements: we used the one closest to 12 months
- All adverse events were categorised by 2 investigators, blinded to intervention

Included trials

- 17 / 35 eligible trials provided IPD
  - Pharma lawyers citing data protection issues
  - Death of CI, corrupted hard drive, *etc*
- n= 3,431 / 5,601 (62%)
- Treatment duration: 9.5 months (3–36)

Participants

- **65 years**
- **BMI 30** kg/m^2
- **Diabetes 28%**
- **Angina 24%**
- **Smokers 11–13%**
- **Previous MI 8%**

No trials had cardio- or cerebrovascular primary endpoints

All-cause mortality

Outcome	No. of studies	Testosterone n/N (%)	Placebo n/N (%)	OR, 95% CI	p-value
All-cause Mortality	**14**	**6 / 1,621 (0.4)**	**12 / 1,537 (0.8)**	**0.46 (0.17, 1.24)**	**0.13**
Myocardial Infarction	3	2 (33.3)	2 (16.7)	*Of 14 studies, 8 reported no deaths and 6 reported deaths.* *For the remaining 3 studies, we were unable to confirm whether any deaths occurred and so they were not included*	
Cancer	1	0 (0)	3 (25.0)		
Ruptured Aortic Aneurysm	1	0 (0)	1 (8.3)		
Constrictive Pericarditis	1	1 (16.7)	0 (0)		
Multiple Organ Failure	1	1 (16.7)	0 (0)		
VTE	1	0 (0)	1 (8.3)		
Unknown	3	2 (33.3)	5 (41.7)		

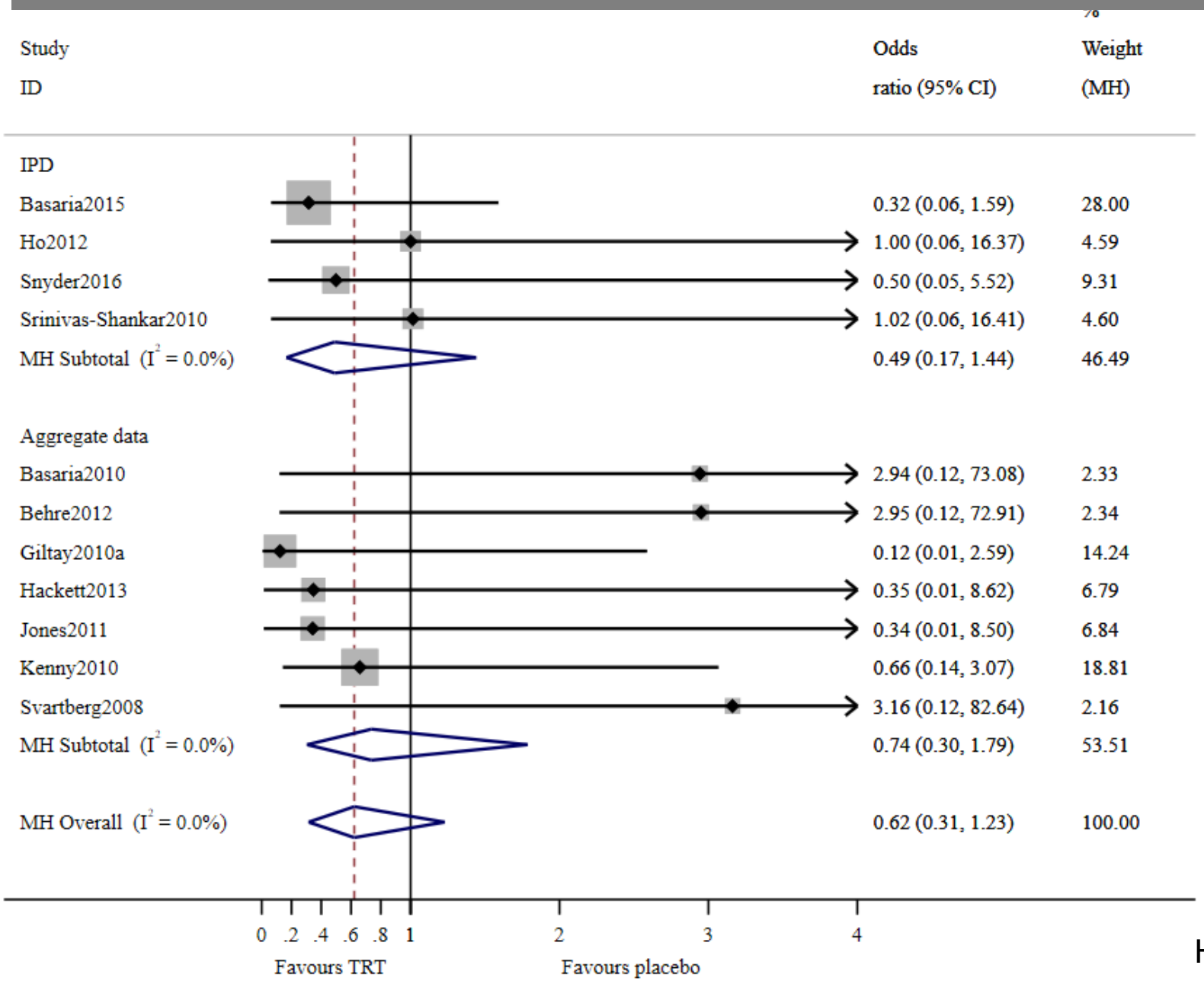
Hudson J, *Lancet Healthy Longevity*, 2022

Cardiovascular and/or cerebrovascular (CV) events

Outcome	Nº. of studies	Testosterone n/N (%)	Placebo n/N (%)	OR 95% CI	p-value
Nº. of participants with CV events	**13**	**120 / 1,601 (7.5)**	**110 / 1,519 (7.2)**	**1.07 (0.81, 1.42)**	**0.62**
Total Nº. of CV events	13	182	183		
Nº. of participants with a cardiovascular event	**11**	**107 / 120 (89.2)**	**105 / 110 (95.5)**		
Total Nº. of cardiovascular events	11	166	176		
Arrhythmia	6	52	47		
Coronary Heart Disease	6	33	33		
Heart Failure	6	22	28		
Myocardial Infarction	7	10	16		
Valvular Heart Disease	2	18	12		
Peripheral Vascular Disease	4	8	14		
Stable Angina	5	7	7		
Aortic Aneurysm[3]	5	6	7		
New Angina	3	5	5		
Unstable Angina	3	2	4		
Aortic Dissection	1	2	0		
Atherosclerosis	1	1	1		
Cardiac Arrest	2	0	2		
Nº. of participants with a cerebrovascular event	**11**	**15 / 120 (12.5)**	**7 / 110 (6.4)**		
Total number of cerebrovascular events[3]	11	16	7		

Hudson J, *Lancet Healthy Longevity*, 2022

Cardiovascular and/or cerebrovascular (CV) events



Hudson J, *Lancet Healthy Longevity*, 2022

Physiological markers

Outcome	Nº. of studies	Testosterone mean (SD); n	Placebo mean (SD); n	MD	95% CI
Testosterone (nmol/L)	16	17.27 (10.34); 1,211	9.87 (3.98); 1,156	7.24	(5.07, 9.41)
free-Testosterone (pmol/L)	12	426.70 (368.42); 1,058	203.57 (86.24); 1,027	186.40	(115.91, 256.90)
Cholesterol (mmol/L)	14	4.51 (1.05); 1,388	4.67 (1.11); 1,314	-0.15	(-0.20, -0.10)
LDL(mmol/L)	14	2.69 (0.98); 1,378	2.70 (0.98); 1,299	-0.03	(-0.08, 0.01)
HDL (mmol/L)	14	1.15 (0.33); 1,384	1.21 (0.39); 1,312	-0.06	(-0.08, -0.04)
Triglyceride (mmol/L)	14	1.73 (1.30); 1,368	1.89 (1.51); 1,297	-0.09	(-0.18, -0.00)
Haemoglobin (g/L)	13	153.53 (14.71); 1,291	143.58 (12.67); 1,206	10.87	(8.19, 13.55)
Haematocrit (%)	15	46.06 (4.37); 1,399	42.94 (3.77); 1,309	3.15	(2.42, 3.88)
fasting Glucose (mmol/L)	12	6.50 (2.09); 1,259	6.75 (2.38); 1,181	-0.16	(-0.24, -0.07)
fasting Glucose: NO DIABETES	11	6.04 (1.69); 946	6.24 (2.04); 897	-0.13	(-0.28, 0.02)
HbA1c (%)	8	6.46 (1.12); 748	6.58 (1.21); 742	-0.09	(-0.25, 0.06)
HbA1c (%): NO DIABETES	7	6.14 (0.94); 519	6.24 (1.08); 523	-0.89	(-2.43, 0.64)
Systolic BP (mmHg)	10	134.11 (17.14); 1,069	133.31 (16.64); 1,041	0.99	(-0.08, 2.06)
Diastolic BP (mmHg)	10	77.20 (11.03); 1,069	76.84 (10.98); 1,041	0.48	(-0.30, 1.26)

Hudson, et al. *Lancet Healthy Longevity*, 2022

Other outcomes

Outcome	Nº. of studies	Testosterone n/N (%)	Placebo n/N (%)
Diabetes / diabetes complications	2	14 / 752 (1.9)	19 / 751 (2.5)
Prostate cancer	8	10 / 1,293 (0.8)	3 / 1,059 (0.3)
Oedema	7	3 4/ 1,301 (2.6)	17 / 1,290 (1.3)
Hypertension	7	28 / 1,195 (2.3)	20 / 1,182 (1.7)
High Haematocrit	7	30 / 1,079 (2.8)	5 / 993 (0.5)
Venous thromboembolism	4	5 / 1,037 (0.5)	7 / 1,034 (0.7)
Non-stroke cerebrovascular pathology	3	4 / 655 (0.6)	11 / 648 (1.7)

Hudson J,. *Lancet Healthy Longevity*, 2022

Limitations of TestES

- IPD data could only be obtained from 62% of global participants, but was still concordant with aggregated analyses including studies from which IPD was unavailable
- Trials did not use a unifying cardiovascular/MACE event classification
- Low number of recorded deaths
- Mean follow-up only 9.5 months

TRAVERSE (**T**he**R**apy for **A**ssessment of long-term **Va**scular **E**vents and **E**fficacy **R**espon**SE** in hypogonadal men)

TRAVERSE – in context

- By far the LARGEST clinical trial of testosterone treatment ever to be carried out.
- Created in response to 2015 FDA guidance that mandated a manufacturer-funded clinical trial designed specifically to investigate whether testosterone treatment was associated with increased major adverse cardiovascular events (MACE) in older men at high risk.
- As with the much smaller T-Trials, which informed the TRAVERSE study design, other endpoints included sexual function and prostate disease.
- Sub-studies evaluated effects on anaemia, fracture risk, vitality, mood and cognition, but not bone mineral density, or serial routine ECGs (*testosterone shortens QTc interval and androgen-deprivation lengthens it*).
- Although high LH was not an exclusion criteria, in practice few if any subjects with pathological (rather than functional) hypogonadism seem to have been recruited.

Lincoff AM, *NEJM*, 2023

TRAVERSE: Inclusion Criteria

- Men, age 45–80 years
- With pre-existing CVD or at high risk
- 68.7% of testosterone group and 70.8% on placebo group had diabetes at baseline
- Symptoms (1 or more) of hypogonadism:
  - Decreased sexual desire or libido
  - Decreased spontaneous erections
  - Decreased energy or fatigue
  - Low or depressed mood
  - Loss of axillary or pubic hair or reduced shaving
  - Hot flashes
- 2 fasting serum testosterone concentrations <10.4 nmol/L (= CDC Atlanta cut-off) from blood obtained between 5–11 AM, collected at least 48 hours apart.
- Excluded HCt >50%, Prostate cancer, high PSA, abnormal DRE or severe LUTS

Lincoff AM, *NEJM*, 2023

TRAVERSE Trial: design

Study drug management

Randomised, double-blind, 1:1 ratio
Stratified by pre-existing CVD *vs* CV risk factors

Testosterone 1.62% gel

Placebo gel

Patients and trial team blinded to post-baseline T levels measured at central lab*
(*Drawn at Weeks 2, 4, 12, 26 and Months 12, 18, 24, 36, 48)

Dose titrations by automated algorithm
to maintain T levels 12.1–26 nmol/L
and haematocrit ≤54%

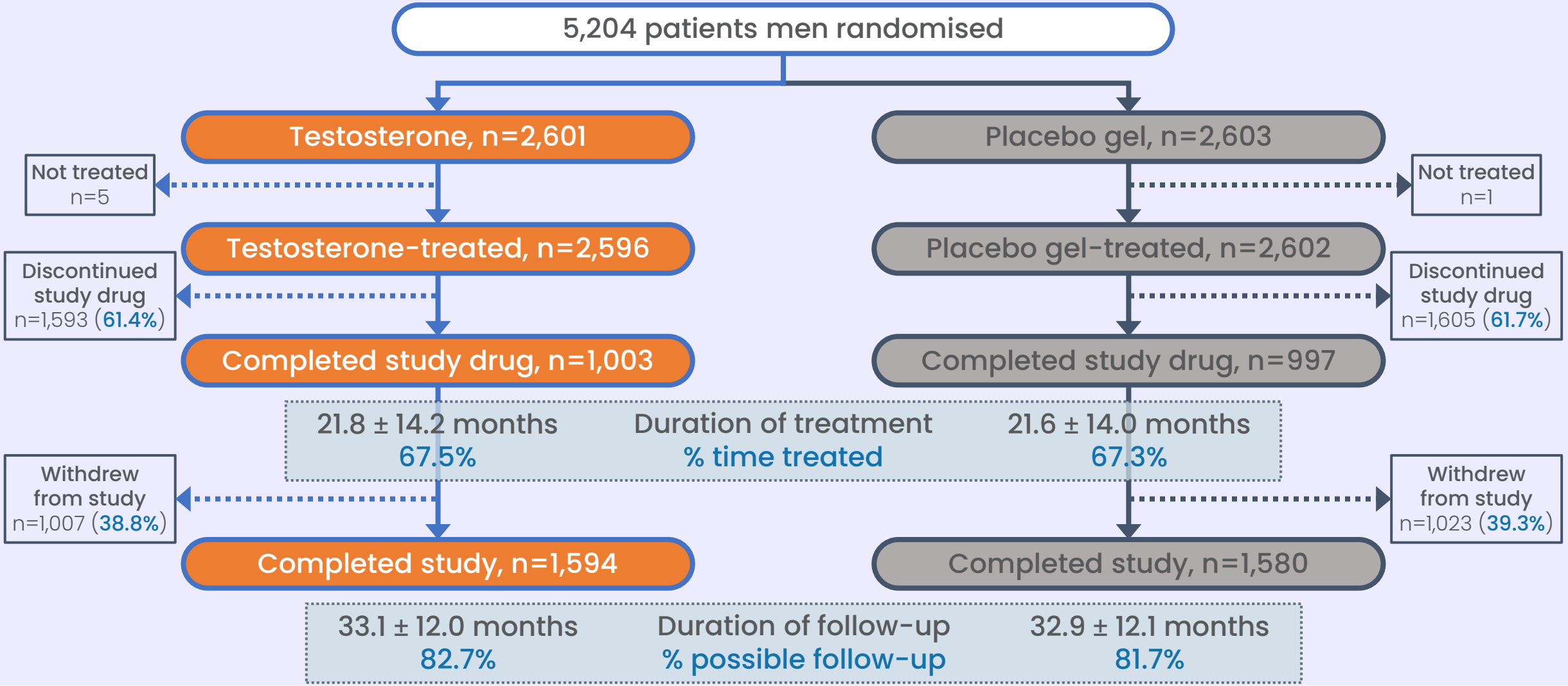
Sham titrations in placebo arm
to facilitate blinding

Study drug discontinued if T level >26 nmol/L or haematocrit >54%,
despite titration to lowest dose

CV, cardiovascular; CVD, cardiovascular disease; T, testosterone.

Lincoff AM, *NEJM*, 2023

TRAVERSE Trial: patient flow through the trial – COVID pandemic



Lincoff AM, *NEJM*, 2023

TRAVERSE: Long term treatment with 1.62% testosterone gel did not increase risk of MACE in men with hypogonadism and previous cardiac disease

Duration of treatment was 21.8±14.2 months in the T group and 21.6±14.0 months in the Placebo group, and follow up was 33.1±12.0 and 32.9±12.1 months, respectively.

Tertiary CV safety endpoints:

% of patients	Testosterone (n=2,596)	Placebo (n=2,602)	HR (95% CI)
All-cause mortality	5.5	5.7	0.98 (0.78–1.23)
Heart failure hospitalisation	2.1	1.9	1.11 (0.76–1.62)
Peripheral arterial revascularisation	1.2	1.3	0.92 (0.56–1.51)
Venous thromboembolic events	1.7	1.2	1.46 (0.92–2.32)
Components of venous thromboembolic events – *Potential influence of Covid pandemic*			
Pulmonary embolism	0.9	0.5	
Deep vein thrombosis	0.6	0.5	
Other peripheral thrombosis	0.4	0.5	

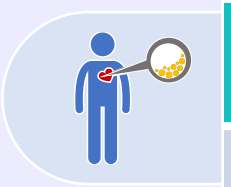
Unexplained: Non-fatal arrhythmias warranting intervention occurred in 134 patients (5.2%) in the testosterone group and in 87 patients (3.3%) in the placebo group (p=0.001); atrial fibrillation occurred in 91 (3.5%) and 63 patients (2.4%), respectively (p=0.02), and acute kidney injury occurred in 60 (2.3%) and 40 patients (1.5%), respectively (p=0.04).

Lincoff AM, *NEJM*, 2023

TRAVERSE: CV trial results

Safety endpoints

Primary and secondary CV safety endpoints



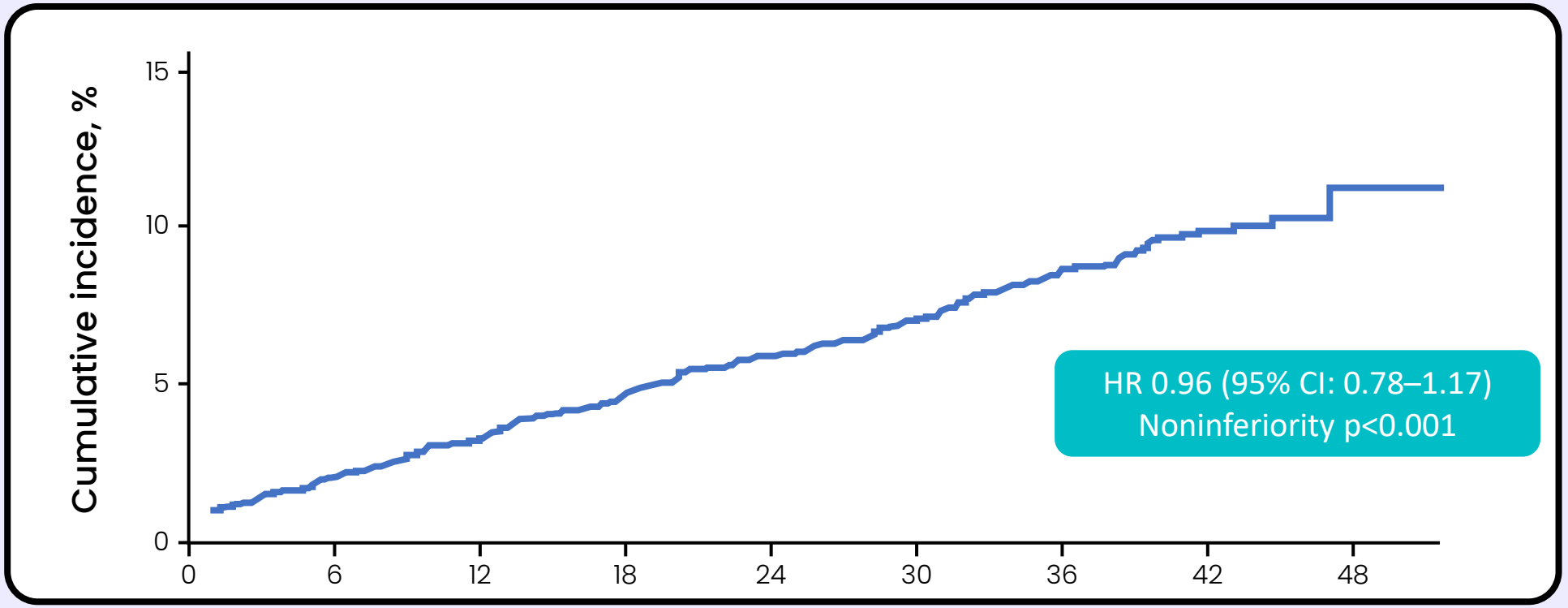
% of patients	Testosterone (n=2596)	Placebo (n=2602)	HR (95% CI)
Primary: CV composite (MACE)* ▪ CV death, non-fatal MI, non-fatal stroke	7.0	7.3	0.96 (0.78–1.17)
Secondary: CV composite ▪ CV death, non-fatal MI, non-fatal stroke, coronary revascularisation	10.4	10.1	1.02 (0.86–1.21)
Components of composite endpoints			
CV death	3.4	4.0	0.84 (0.63–1.12)
Non-fatal MI	2.6	2.4	1.10 (0.78–1.56)
Non-fatal stroke	1.4	1.5	0.94 (0.60–1.49)
Coronary revascularisation	5.5	4.6	1.20 (0.95–1.53)

Lincoff AM, *NEJM*, 2023

TRAVERSE: (Long term?) treatment with 1.62% testosterone gel did not increase risk of MACE in men with hypogonadism and previous cardiac disease compared to Placebo

Duration of treatment was 21.8±14.2 months in the T group and 21.6±14.0 months in the Placebo group and follow up was 33.1±12.0 and 32.9±12.1 months, respectively.

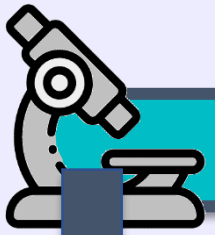
Primary CV safety endpoint (MACE): CV death, non-fatal MI, non-fatal stroke



No at risk									
Placebo	2602	2507	2323	2088	1792	1568	1337	598	33
Testosterone	2596	2504	2339	2120	1829	1605	1380	653	39

Lincoff AM, *NEJM*, 2023

TRAVERSE Prostate Safety sub-study: aims



Because of the TRAVERSE study's size and duration, the TRAVERSE study offered a unique opportunity to evaluate the effects of testosterone on prostate safety events.

Primary

To compare the effects of testosterone versus placebo on the incidence of adjudicated high-grade prostate cancer (Gleason grade 4+3 or higher)

Secondary

To compare the effects of testosterone versus placebo on the incidences of:

- any adjudicated prostate cancer
- acute urinary retention
- invasive prostate surgical procedure for BPH

- Prostate biopsy
- Initiation of new pharmacologic treatment for LUTS

Prostate safety endpoints were adjudicated by a blinded Prostate Adjudication Committee

Bhasin S, *JAMA Netw Open*, 2023

TRAVERSE Prostate Safety sub-study: Conclusions

- During 14,304 person-years of follow-up**, the incidence of high-grade prostate cancer** (5 of 2596 [0.19%] in the TRT group vs 3 of 2602[0.12%] in the placebo group; hazard ratio, 1.62; 95% CI, 0.39-6.77; P =.51) did not differ significantly between groups, nor **did the incidence of prostate cancer of any grade.**

- **Testosterone treatment did not worsen LUTS:**

  The incidences of prostate cancer, acute urinary retention, invasive surgical procedures, prostate biopsy, and new pharmacologic treatment also did not differ significantly. Change in IPSS did not differ between groups. PSA concentrations increased more in testosterone-treated than placebo-treated men, regardless of baseline PSA concentration, but there was no significant between-group difference in PSA levels after month 12.

Bhasin S, *JAMA Netw Open*, 2023

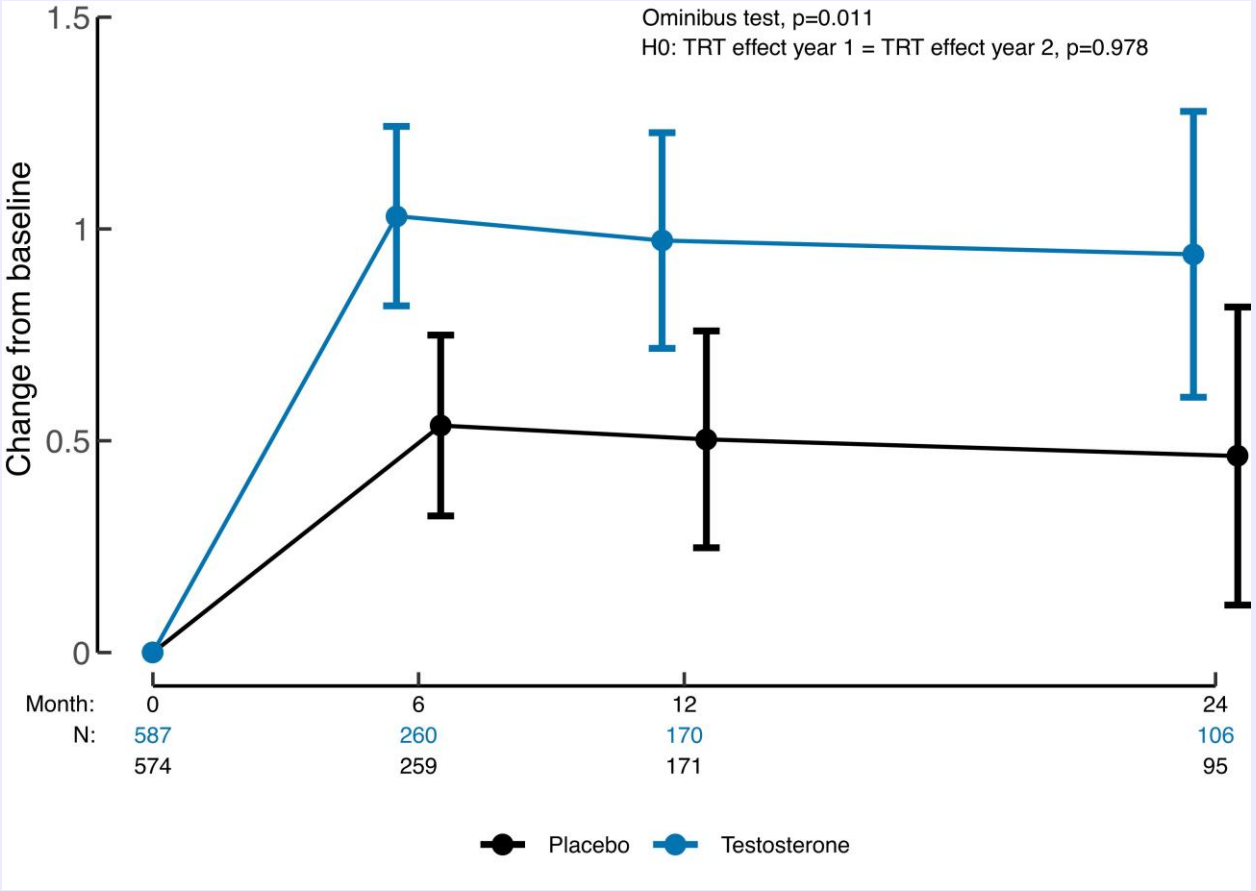
TRAVERSE: Additional safety results

- Prostate cancer occurred in 12 patients (0.5%) on testosterone and 11 patients (0.4%) on placebo (p=0.87)
- Increase PSA level from baseline was greater in patients on testosterone group than placebo (0.20±0.61 vs. 0.08±0.90 ng/mL, respectively; p<0.001);
- Change in mean systolic BP from baseline through 6 months was +0.3 mmHg (95% CI, −0.3 to 0.9) in the testosterone group and −1.5 mmHg (95% CI, −2.0 to −0.9) in the placebo group (p<0.001);
- Nonfatal arrhythmias warranting intervention occurred in 134 patients (5.2%) on testosterone g and in 87 patients (3.3%) on placebo (p=0.001);
- Atrial fibrillation occurred in 91 (3.5%) and 63 patients (2.4%), respectively (p=0.02);
- Acute kidney injury occurred in 60 (2.3%) and 40 patients (1.5%), respectively (p=0.04).
- 3-year cumulative incidence of all clinical fractures: 3.8% for testosterone and 2.8% for placebo (p<0.05).[2]
- No impact on new-onset diabetes [3], although re-analysis by another group claimed a reduction in progression to diabetes in a subgroup of the subgroup. [4]

1. Lincoff AM, *NEJM*, 2023 2. Snyder PJ, *NEJM*, 2024 3. Bhasin S, *JAMA Intern Med*, 2024 4. *Hackett GI, World J Mens Health*, 2024

TRAVERSE: What about sexual function?

- Modest but significant improvement in sexual desire and activity compared to placebo.
  - 1 extra “experience”/day, compared to 0.5 with placebo, at 6 and 12 months (p=0.11)
  - maintained for the duration of the study (up to 24 months).
- No significant improvement in erectile function (IIEF-5).



Pencina KM, *JCEM*,. 2024

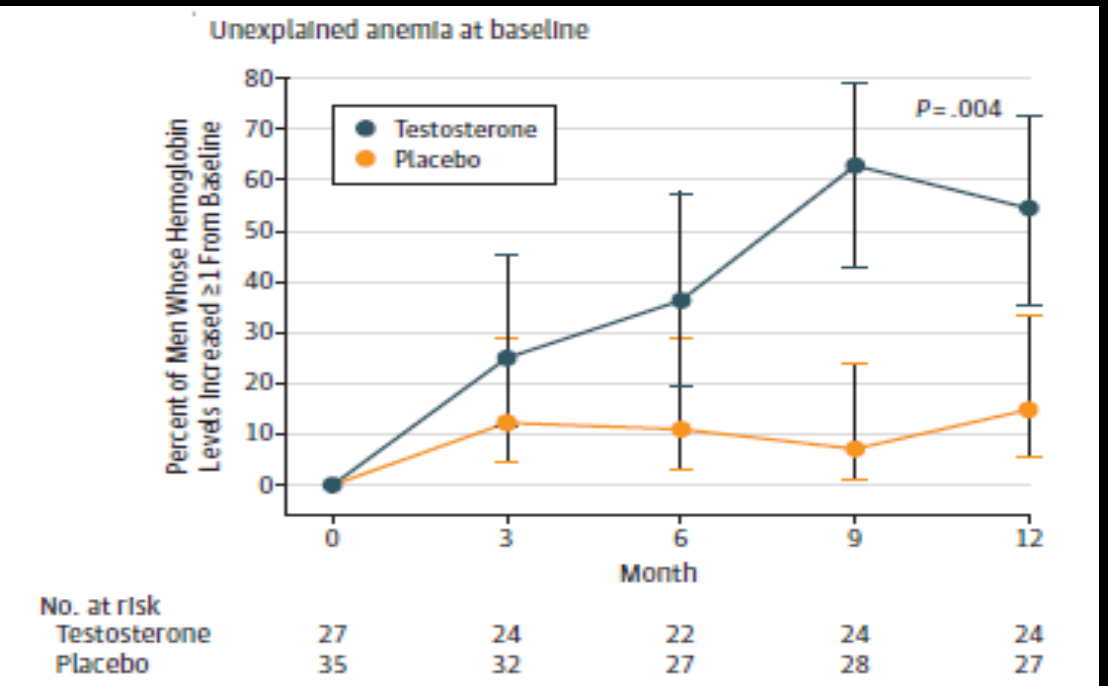
Summary & Conclusions

- Testosterone treatment of men with functional 2^{o} hypogonadism and at high CV risk does not result in an excess of MACE for a period of up to 3–4 years treatment.
- Although ED does not generally improve, benefits to sexual arousal are sustained, albeit modest.
- Small but real excess risks of PE, CKD and cardiac arrhythmias merit further examination.
- Increased in appendicular skeleton fractures likely arise from greater physical activity; but men with functional hypogonadism do not experience reduced fractures on testosterone.
- Men with functional hypogonadism and baseline anaemia experience the greatest benefit, including physical function and vitality.
- Pharmacologic doses of testosterone combined with active lifestyle interventions reduce the risk of T2DM in obese men with- or without- functional hypogonadism.
- Physiological replacement dose testosterone, titrated to achieve mid-range serum T levels and avoid erythrocytosis, does not impact significantly on risk of T2DM in men with functional hypogonadism at high CV risk, …whereas supra-physiological T treatment combined with active lifestyle programme will do so in almost anybody.
- So there's definititely evidence for effectiveness for Testosterone in functional hypogonadism, but it's not necessarily clinically relevant UNLESS there's anaemia.

Osteoporosis, Fractures and Testosterone

- T treatment improves all parameters for assessing bone health: DXA and qCT for areal, volumetric & cortical BMD; bone microarchitecture by DXA and hr-CT. [1,2]
- T should be 1st line treatment of osteoporosis in pathological hypogonadism; no RCTs will ever be available as a placebo arm would be unethical.
- Consider adding a bone-specific agents when the # risk is high, but only IV Zoledronate has (vertebral) # prevention outcomes in males. [3]
- However, T treatment in men with functional 2o hypogonadism due to obesity is associated with increased risk of #, albeit no DXA scans were done: [4]
  - not having pathological hypogonadism, such men are low baseline # risk anyway
  - excess of activity-related #s (fingers, wrists, ribs & ankles), rather than fragility #s
  - # risk lines diverged from 3 months of starting T, suggesting a BMD-independent mechanism.

1. Snyder PJ, *JAMA*, 2017
2. Ng TFM, *JCEM*, 2021
3. Boonen S, *NEJM*, 2012
4. Snyder PJ, *NEJM*, 2024



Testosterone and Anaemia

Anaemia is associated with higher mortality in old age

1/3 of older men have anaemia.

16% had anaemia in both T-trials (#7) and TRAVERSE.

T treatment eliminated anaemia in 45% of cases, whether of known or unknown cause.

Men with increased Hb levels experienced:

- better walking
- greater vitality
- improved global perceptions of health & energy

Did they also experience greater improvement in sexual function than overall subjects on T?

Roy CN. *JAMA Intern Med,* 2017 Pencina KM, *JAMA Netw Open*, 2023

Management

Testosterone and Erythropoiesis

- T stimulates red cell production in bone marrow
  - direct action on bone marrow erythroid precursors?
  - Increased sensitivity of erythroid precursors to EPO?
  - indirectly via increased renal EPO secretion?
  - Inhibition of hepatic Hepcidin secretion?
- SGLT2-inhibitors have similar actions
- T deficiency is associated with lower Hb & Hct.
  - hypogonadism
  - childhood
  - female sex

- Testosterone abuse or overtreatment causes erythrocytosis / polycythaemia.

Why worry about (androgen-induced) erythrocytosis?

Tromso Gene

- 1.5 RR of V ntiles (≥0.46) com ng.

2010

Copenhagen

- Compared
  - top 5% h

stasis, 2019

Priorities in Monitoring Testosterone therapy

1. Hb & Haematocrit – *keep them normal range* (Hct <50% in most labs)
   - if high, the T treatment dose must usually be reduced ± convert to gel
   - T undecanoate depot often needs spacing out beyond the recommended 10–14 weeks
   - also smoking-cessation, weight loss, CPAP and BP-lowering with vasodilators, *etc*
   - routine venesection is not recommended – blood loss activates thrombotic pathways
2. Sexual function and general well-being (but you'll never make "ex-users" happy!)
3. Other things being equal, aim for serum total T ± free-T levels:
   - Gel: mid-range levels 6–12 hrs post-application
   - IM: mid-range levels at mid-point between injections, or low-normal levels at trough
4. Periodic assessment of bone density by DXA.
5. Prostate: follow national advice for general male population, but remember risk factors:
   - Family history of PCa or BRCA, black-African ethnicity, older age.

Al-Sharefi A, *BJGP,* 2020 Jayasena CN, *Clin Endocrinol*, 2022 De Silva NL, *Lancet Diabet Endocrinol*, 2024