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Breaking News

Men's Health Medical & Marketing Network

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PDF

TestES - Safety

Issue No. 3

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.

TestES news coverage

- https://www.thecardiologyadvisor.com/general-cardiology/testosterone-for-hypogonadism-not-associated-with-short-to-medium-term-cardiovascular-cv-risk/
- https://www.physiciansweekly.com/conference-endo2022-highlights
- https://www.physiciansweekly.com/testosterone-therapy-for-hypogonadism-not-tied-to-increased-cv-risk/
- https://www.tctmd.com/news/short-term-testosterone-use-doesnt-spur-cv-events-meta-analysis
- https://indianexpress.com/article/explained/explained-testosterone-deficiency-safety-replacement-therapy-7961353/
- https://consumer.healthday.com/b-6-9-no-sign-1-year-of-testosterone-supplements-cause-heart-trouble-study-2657463235.html
- https://www.medscape.com/viewarticle/975273
- https://medicalxpress.com/news/2022-06-evidence-testosterone-treatment-cardiovascular-events.html
- https://www.eurekalert.org/news-releases/954980
- https://www.eurekalert.org/news-releases/954872
- https://www.webmd.com/men/news/20220610/new-study-shows-short-term-testosterone-may-be-safe
- https://www.wfmz.com/lifestyles/health-med-fit/no-sign-1-year-of-testosterone-supplements-cause-heart-trouble-study/article_a0c65ad4-3032-5ff7-944e-06e495a662f2.html
- https://www.imperial.ac.uk/news/237318/testosterone-treatment-does-increase-risk-heart/
- https://www.techexplorist.com/men-taking-testosterone-therapy-no-greater-risk-heart-attack/48128/
- https://medicaldialogues.in/urology/news/little-evidence-of-heart-problems-in-men-undergoing-testosterone-treatment-finds-analysis-94865

TestES Consortium:

"Our study is likely to supersede the previous evidence and suggests that, within the first year of treatment at least, testosterone treatment is not associated with heart problems. While our study does not look at the longer-term safety of the treatment, these findings will enable doctors to be more confident prescribing testosterone to men who need it."

**** Please note - Baseline HCT in the TestES analysis was 43% in the T group. Mean HCT in the T group rose to 46%**

"Testosterone significantly elevated haematocrit and haemoglobin. Furthermore, testosterone treatment was associated with a five-times higher risk of polycythemia."

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Relevant Publications in TD

Men's Health Medical & Marketing Network

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Ory, J et al 2022

Issue No. 3

Secondary Polycythemia in Men Receiving Testosterone Therapy Increases Risk of MACE and VTE in the First Year of Therapy. Ory, J et al. Journal of Urology. Vol. 207, 1295-1301, June 2022

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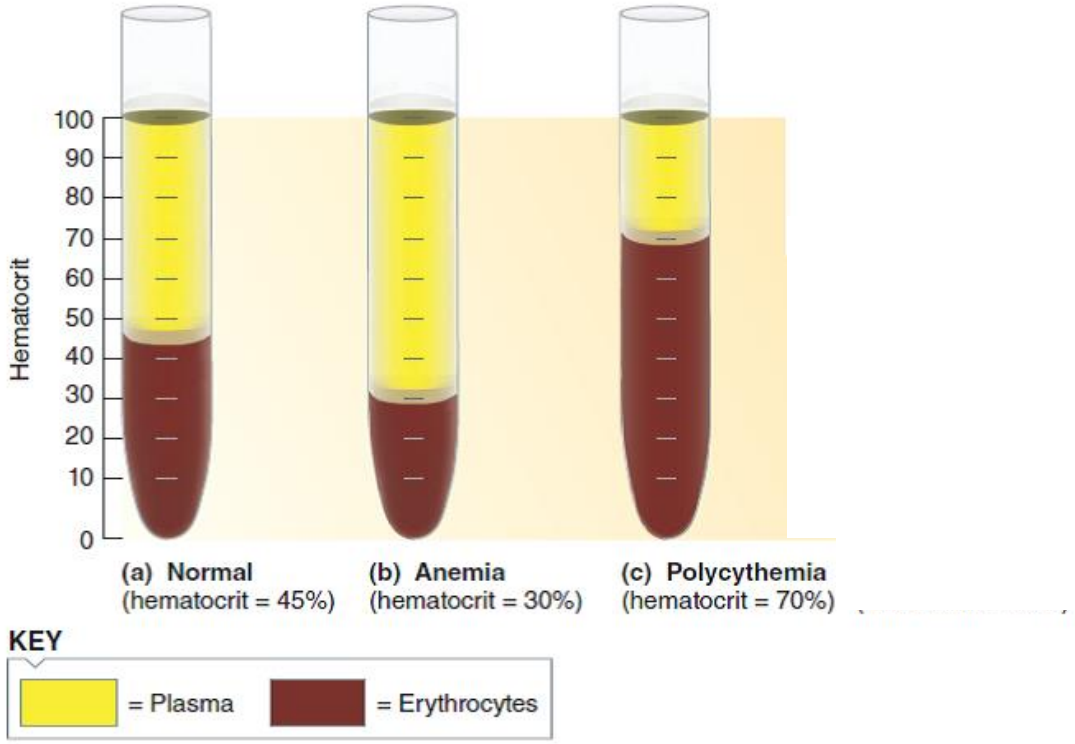
An elevated hematocrit is the most common adverse effect of testosterone therapy (TTh)

- Any elevation above the normal range for hematocrit (HCT) usually becomes evident between 3 and 12 months after TTh initiation.
- Higher HCT is more common with parenteral rather than topical formulations.
- HCT > 54% should require testosterone therapy withdrawal, reduction in dose, change of formulation and venesection depending on the clinical situation to avoid any potential CV complications.



› **Figure 11-5 Hematocrit under various circumstances.** (a) Normal hematocrit. (b) The hematocrit is lower than normal in anemia because of too few circulating erythrocytes. (c) The hematocrit is above normal in polycythemia because of excess circulating erythrocytes. (d) The hematocrit can also be elevated in dehydration when the normal number of circulating erythrocytes is concentrated in a reduced plasma volume.

https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Sexual-and-Reproductive-Health-2021-V3.pdf

Much of the concern surrounding elevations in blood viscosity centers on the increased risk for venous thromboembolism (VTE), myocardial infarction (MI), and stroke[1].

Supraphysiologic/high pick serum T levels have been associated with **polycythemia** with an incidence that varies from 13% for transdermal gels to **67% for short-acting IM TTh[2].**

Whether or not exogenous testosterone causes MACE or VTE is actively debated, but the relationship between TTh-induced polycythemia and subsequent risk for VTE and other CV complications has never been directly studied[3].

1. Ohlander S. et al. Erythrocytosis Following Testosterone Therapy. Sex Med Rev. 2018; 6(1): 77–85. doi:10.1016/j.sxmr.2017.04.001
2. Pastuszak AW, Gomez LP, Scovell JM, et al. Comparison of the effects of testosterone gels, injections, and pellets on serum hormones, erythrocytosis, lipids, and prostate-specific antigen. Sex Med 2015;3:165-173.
3. Ory J et al. Secondary Polycythemia in Men Receiving Testosterone Therapy Increases Risk of Major Adverse Cardiovascular Events and Venous Thromboembolism in the First Year of Therapy. J Urol. 2022 Jun;207(6):1295-1301.

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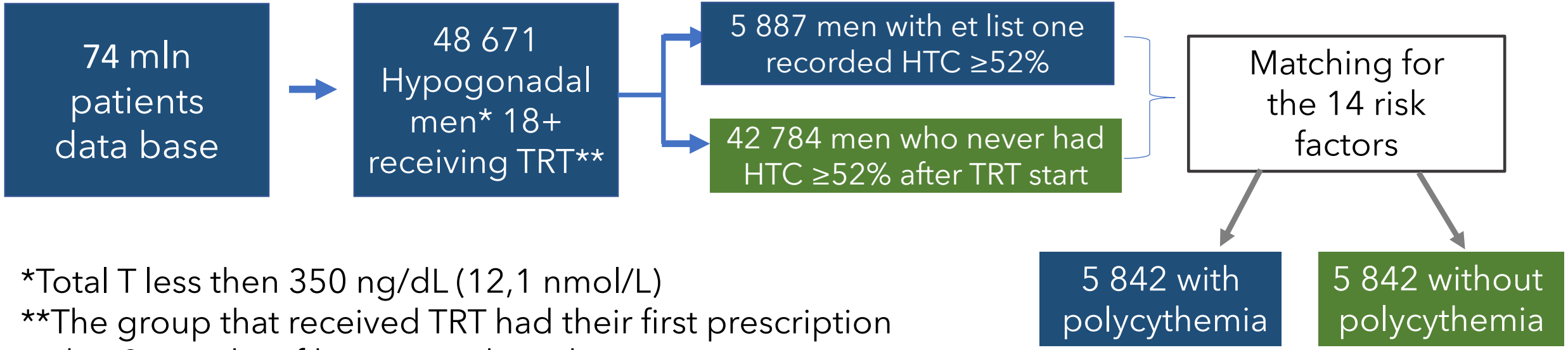
Secondary Polycythemia in Men Receiving Testosterone Therapy Increases Risk of Major Adverse Cardiovascular Events and Venous Thromboembolism in the First Year of Therapy

Jesse Ory, Sirpi Nackeeran, Navin C. Balaji et al.

The objective of the study was to determine if the presence of polycythemia during TTh leads to adverse events (MACE and VTE) as a primary outcome

J Urol. 2022 Jun;207(6):1295-1301. doi: 10.1097/JU.0000000000002437.

Study design

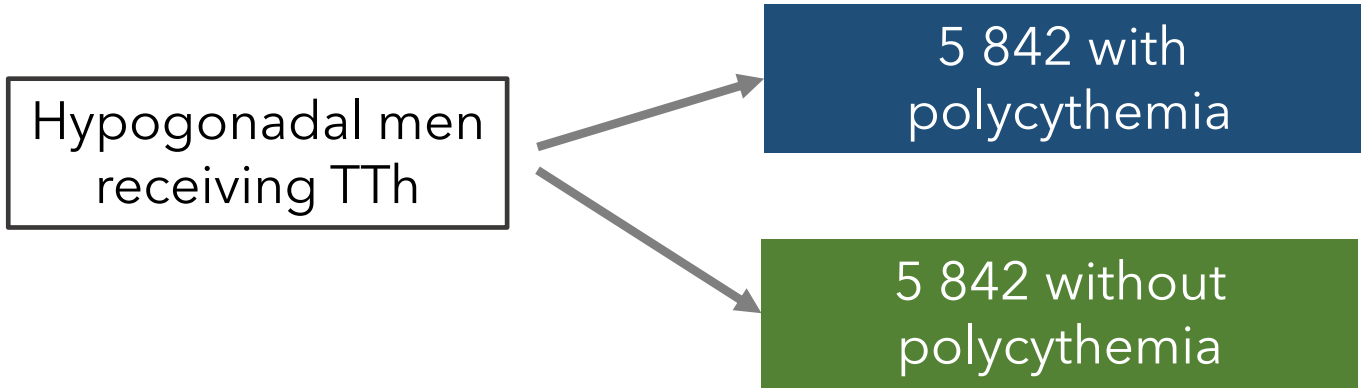


*Total T less then 350 ng/dL (12,1 nmol/L)
**The group that received TRT had their first prescription within 3 months of hypogonadism diagnosis.

The primary outcome was the odds of MACE and VTE within the first year of TRT

MACE were defined as a composite of death from any cause, MI and stroke. VTE included deep vein thrombosis and pulmonary embolism.

Secondary Polycythemia in Men Receiving Testosterone Therapy Increases Risk of Major Adverse Cardiovascular Events and Venous Thromboembolism in the First Year of Therapy



In the first year following TRT and after propensity-score matching, **the risk of MACE/VTE** was 5.2% in men who developed polycythemia vs 3.9% in those men who did not (**OR 1.35**; 95% CI 1.13-1.61).

- **the survival probability** (probability of 1 year without MACE/VTE) was significantly lower in the polycythemia group (95% vs 97%, p<0.0001, HR 1.22, 95% CI 1.04-1.43);
- **an increased risk of developing acute MI** (OR 1.81, 95% CI 1.2-2.7) **and VTE** (OR 1.51, 95% CI 1.17-1.94) in the men with polycythemia.

Men using testosterone should be aware that they are at a higher risk of MACE and VTE if their hematocrit reaches or exceeds 52% during the first year of TRT.

Ory J. et al. J Urol. 2022 Jun;207(6):1295-1301. doi: 10.1097/JU.0000000000002437.

Important considerations (1):

- Guidelines recommendations on HCT cut-offs were extrapolated from data from the general population, while the results obtained by Ory et al, 2022 are based on the data from men who are using TRT.
- This is the first study to establish secondary polycythemia from TTh as an independent risk factor for MACE/VTE using a specific hematocrit-based cut-off (≥52%).

1. **Doctors prescribing TRT should be aware about increased risk of MACE and VTE related with polycythemia during the first year of TRT.** TTh itself, in the absence of polycythemia, did not appear to increase risk of MACE/ VTE in hypogonadal men.

2. This new data provides ample reason for new iterations of guidelines to align on **a level of 52% and that is where the difference between T Gel and Nebido can be highlighted to HCPs (The HEAT-registry).**

Important considerations (2):

We can inform HCPs about this new study alongside the only head-to-head study of AndroGel and Nebido (The HEAT- Registry)

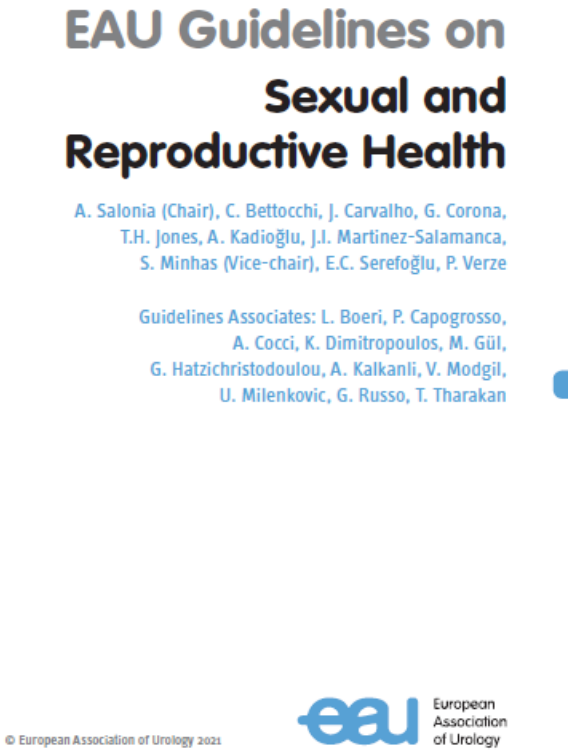
	AndroGel	Nebido	Chi-Square-Test
Haematocrit >50%	25 / 498 (5 %)	69 / 304 (23 %)	<0.001
Haematocrit >52%	9 / 498 (2 %)	25 / 304 (9 %)	<0.001
Haematocrit >54%	2 / 498 (<1 %)	8 / 304 (3 %)	0.03
Haematocrit >56%	0 / 498 (0%)	2 / 304 (~<1%)	0.14

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

Testosterone substitution by either AndroGel or Nebido increases HCT, but

- **The effect is significantly more pronounced in men receiving Nebido (p<0.001)**



«**Use testosterone gels rather than long-acting depot administration when starting initial treatment,** so that therapy can be adjusted or stopped in the case of treatment-related adverse effects».

EAU recommendation to start TRT with T Gels in order to reduce possible risks should be applied and followed for at least first 12 months after the therapy initiation.

https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Sexual-and-Reproductive-Health-2021-V3.pdf