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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

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Study Need and Importance: There is no direct evidence for what constitutes a safe hematocrit in men using testosterone therapy (TT). Guideline-based cutoffs were extrapolated from data from the general population and not in men who were using TT. This is important, as polycythemia in other clinical scenarios has been shown to increase the risk of major adverse cardiovascular events (MACE) and venous thromboembolism (VTE). Whether or not secondary polycythemia from TT is an independent risk factor for MACE or VTE has never been directly studied.

What We Found: From a database of 74 million people, we identified 2 cohorts of men with a low testosterone who received TT and subsequently either developed polycythemia (hematocrit ≥52%, 5,887 patients) or did not develop polycythemia (42,784). After propensity-score matching for multiple risk factors for MACE and VTE, we were able to compare 5,842 men in each group. Our primary outcome was incidence of MACE and VTE in the first year of TT. We found that men with polycythemia had a higher risk of MACE and VTE (5.15%) versus men who did not develop polycythemia (3.87%). We also showed that hypogonadal men on testosterone versus those off testosterone had similar rates of MACE/VTE in the absence of polycythemia (see figure).

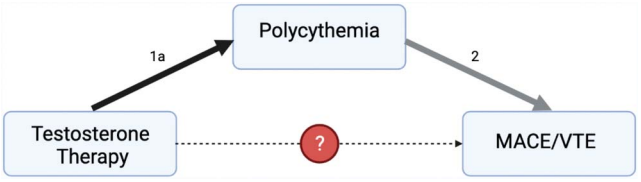

Figure. Association between TT, MACE/VTE and polycythemia. The levels of evidence of the association or lack thereof are indicated.

Limitations: The population of men identified was comorbid and largely Caucasian, limiting the generalizability of our results to minorities and healthy men. Additionally, baseline hematocrit was different in the polycythemia group (47.4%) versus the non-polycythemia group (42.5%).

Interpretations for Patient Care: 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 therapy. Additionally, in the absence of polycythemia, TT does not appear to increase the risk of MACE and VTE.

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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

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Abbreviations and Acronyms

LDL = low-density lipoprotein
MACE = major adverse cardiovascular events
MI = myocardial infarction
RCT = randomized controlled trial
TT = testosterone therapy
VTE = venous thromboembolism

Purpose: An unsafe hematocrit threshold for men receiving testosterone therapy (TT) has never been tested. This study seeks to determine whether secondary polycythemia among men receiving TT confers an increased risk of major adverse cardiovascular events (MACE) and venous thromboembolic events (VTE).

Materials and Methods: Using a multi-institutional database of 74 million patients, we identified 2 cohorts of men with low testosterone (total testosterone <350 ng/dl) who received TT and subsequently either developed polycythemia (5,887) or did not (4,2784). Polycythemia was defined as hematocrit ≥52%. As a secondary objective, we identified 2 cohorts of hypogonadal men without polycythemia, who either did (26,880) or did not (27,430) receive TT. Our primary outcome was the incidence of MACE and VTE in the first year after starting TT. We conducted a Kaplan-Meier survival analysis to assess differences in MACE and VTE survival time, and measured associations following propensity score matching.

Results: A total of 5,842 men who received TT and developed polycythemia were matched and compared to 5,842 men who did not develop polycythemia. Men with polycythemia had a higher risk of MACE/VTE (number of outcomes: 301, 5.15%) than men who had normal hematocrit (226, 3.87%) while on TT (OR 1.35, 95% CI 1.13−1.61, p <0.001). In hypogonadal men who received testosterone, no increased risk of MACE and VTE was identified as compared to hypogonadal men naïve to TT.

Conclusions: Developing polycythemia while on TT is an independent risk factor for MACE and VTE in the first year of therapy. Future research on the safety of TT should include hematocrit as an independent variable.

Key Words: hypogonadism, testosterone, thromboembolism, polycythemia, adverse effects

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Conflict of Interest: RR: consultant and grant recipient for Acerus, Boston Scientific, Endo Pharmaceuticals and Coloplast; grant recipient from Empower Pharmacy and Olympus; consultant for Nestle Health; advisory board of Hims, Inc.; Recipient of NIH funding (1R01DK130991-01). JMH: consultant, shareholder and board member for Longeveron, Vestion and Heart Genomics; grant recipient from NHLBI.

Ethics Statement: In lieu of a formal ethics committee, the principles of the Helsinki Declaration were followed.

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WHETHER testosterone therapy (TT) causes major adverse cardiovascular events (MACE) or venous thromboembolism (VTE) is highly debated and a source of controversy amongst clinicians. Meta-analyses of randomized controlled trials (RCTs) do not support an association between MACE/VTE and TT.[1] Alternatively, some large cohort studies have suggested at an association between TT and VTE.[2] Meanwhile, other large database studies fail to find an association,[3] while some studies support TT in hypogonadal men as cardioprotective.[4] Regardless of the findings, none of these studies investigated the possible role of polycythemia as a causative factor of these adverse events.

It is possible that secondary polycythemia due to TT is a leading factor in causing MACE or VTE because increasing hematocrit can increase blood viscosity, and polycythemia has been shown to cause thrombosis in men with idiopathic erythrocytosis.[5–7] Because of this, multiple professional organizations have established guidelines on safe prescribing of TT and include an upper safe limit for hematocrit during therapy. The upper limit of safe hematocrit varies between 48% to 55% and is based off population data of individuals who were not taking TT.[5,8–10] To date, no studies have tested whether the presence of polycythemia during TT leads to adverse events as a primary outcome.

We hypothesized that TT is a potential risk factor for MACE/VTE due to its ability to increase hematocrit levels. This elevation in hematocrit occurs primarily during initiation of and through the first year of TT,[11] supporting our hypothesis that MACE and VTE risk is highest in the first year of therapy.[2,11,12] Therefore, we evaluated men who developed secondary polycythemia (which we defined as a hematocrit over 52%)[10] while receiving TT using a large national database.

METHODS

We accessed data from the TriNetX Analytics Network, a global federated database that captures anonymized data from electronic medical records amongst 54 health care organizations in the U.S. totaling 74 million patients. Patient data were available from 2002 through 2020. Details of this database have been described previously.[13] The TriNetX data include diagnoses (using ICD-10-CM [International Classification of Diseases, 10th Edition, Clinical Modification] codes), demographics, procedures, medications and measurements. The data from a typical health care organization generally go back around 7 years, with some going back 13 years. The data are continuously updated every 1–4 weeks. The analyses in this manuscript were run July 31, 2021. Additional analyses were run later in the year and are included in the supplementary materials (https://www.jurology.com).

We evaluated 2 separate cohorts for comparison. The first cohort included men over 18 with a testosterone <350 ng/dl who subsequently received 2 prescriptions for TT within 9 months of each other and had at least 1 hematocrit above 52% following initiation of TT. We used 2 prescriptions within 9 months to ensure that men were continuing to use TT throughout the first year of therapy. We used a testosterone of 350 ng/dl in keeping with some national society guidelines, and to be able to include a larger cohort.[14,15] The second cohort was identical to the first, except these men never developed a hematocrit over 52%. Men were excluded if they had ICD-10-CM codes for an acute myocardial infarction (MI; I21), VTE (I26 or I82 or Z86.718), stroke (I63), transient ischemic attack (G45) or polycythemia vera (D45) within a year before their first testosterone prescription. While the definition varies, we defined polycythemia as a hematocrit above 52% in keeping with the American Urological Association guideline definition and that of other publications.[10,16]

Our primary outcome was the odds of MACE and VTE within the first year of receiving TT. Secondary outcomes included the individual components of MACE and VTE. The index event was the first prescription of TT. MACE were defined as a composite of death from any cause, MI (I21–I23) and stroke (I63, G45). VTE included deep vein thrombosis (I82 and Z86.718) and pulmonary embolism (I26).

We used propensity-score matching to control for risk factors of MACE/VTE prior to comparison.[17] The risk factors we used included a series of established risk factors for MACE/VTE: dyslipidemia (E78), diabetes (E08–E13), hypertension (I10), obesity (E66), age, ethnicity, tobacco use (F17), sleep apnea (G47.33), use of statins (CV350), beta-blockers (CV100), aspirin (1191), clopidogrel (32968) and angiotensin-converting enzyme inhibitors (CV800).

We controlled for the effects of TT by creating 2 additional cohorts of hypogonadal men (E29.1 or E23.0) with testosterone <350ng/dl: 1 group that received testosterone and 1 group that did not, restricting both groups to men with hematocrit below 52%. The group that received TT had their first prescription within 3 months of hypogonadism diagnosis.

Finally, we performed a series of sensitivity analyses to test the robustness of our findings. First, we compared our cohorts using an alternate diagnosis of polycythemia (hemoglobin >17.5 gm/dl). Second, we tested 2 alternative definitions of polycythemia: a hematocrit at or above 50% and 54%. Third, we assessed whether the differences in outcomes could be attributable to cardiovascular risk factors that were not accounted for during propensity-score matching. We compared low-density lipoprotein (LDL) and blood pressure levels at 1 year after TT in the propensity-matched cohorts, comparing the high hematocrit and normal hematocrit groups using t-tests. Additionally, we evaluated use of anticoagulants (warfarin, dabigatran, apixaban, rivaroxaban) during the first year of TT as alternative but related outcome to MACE/VTE.

To address potentially confounding variables, we utilized 1:1 greedy nearest-neighbor propensity-score matching through the TriNetX platform, which is powered through Python (Python Software Foundation, Fredericksburg, Virginia) and R software (R Foundation for Statistical Computing, Vienna, Austria).[17] This technique uses logistic regression to develop 2 equally matched cohorts based on demographics, comorbidities and medication use. We determined that the 2 groups had minimal differences

Table 1. *Baseline characteristics of men on testosterone who did and did not develop polycythemia*

	Before Propensity-Score Matching				After Propensity-Score Matching			
	Elevated Hematocrit after Starting TT		Normal Hematocrit after Starting TT		Elevated Hematocrit after Starting TT		Normal Hematocrit after Starting TT	
No. pts	5,887		42,343		5,842		5,842	
Mean±SD yrs age	53.4 ± 12.4		51.6 ± 14.6		53.5±12.4		53.8 ±13.1	
No. race/ethnicity (%):								
Caucasian	4,905	(83)	33,253	(79)	4,870	(83)	4,836	(83)
African American	302	(5.1)	4,194	(10)	302	(5.2)	281	(4.8)
Latino	232	(3.9)	1,713	(4.1)	230	(3.9)	239	(4.1)
Comorbidities:								
Hypogonadism	4,643	(79)	17,425	(41)	4,601	(79)	4,644	(79)
Hypertension	3,216	(55)	18,276	(43)	3,178	(54)	3,154	(54)
Dyslipidemia	3,206	(55)	18,040	(43)	3,172	(54)	3,084	(53)
Obesity	2,031	(35)	9,761	(23)	1,992	(34)	1,967	(34)
Obstructive sleep apnea	1,490	(25)	6,213	(15)	1,462	(25)	1,398	(24)
Diabetes	1,354	(23)	8,947	(21)	1,348	(23)	1,292	(22)
Nicotine use	783	(13)	4,200	(10)	770	(13)	679	(12)
Heart failure	255	(4.3)	1,662	(3.9)	253	(4.3)	225	(3.9)
Medications:								
Statin	2,476	(42)	14,044	(33)	2,447	(42)	2,418	(41)
ACE inhibitor	1,816	(31)	9,673	(23)	1,788	(31)	1,752	(30)
β blocker	1,681	(29)	9,664	(23)	1,661	(28)	1,594	(27)
Aspirin	1,478	(25)	9,157	(22)	1,461	(25)	1,383	(24)
Clopidogrel	199	(3.4)	1,356	(3.2)	196	(3.4)	180	(3.1)

after balancing when standardized differences between propensity scores were less than 0.1.[18]

Statistical associations between index events and outcome variables were determined through the calculation of odds ratios for comparative analysis between the exposure and control cohorts. All confidence intervals for odds ratios were calculated with an alpha of 0.05.

Survival analysis within a 1-year period was performed through the Kaplan-Meier method, with statistically significant differences between survival probabilities of the control and exposure cohorts assessed by the log-rank test. We utilized propensity-score matching to control for confounders for survival analysis as well.

RESULTS

We identified 48,671 men over 18 years of age who received TT: 5,887 of whom had at least 1 recorded hematocrit above 52% after starting TT and 42,784 of whom never had a hematocrit above 52% after starting TT. Matching for the 14 risk factors was achieved resulting in 5,842 men in each group (table 1).

As expected, baseline hematocrit was higher in the men who developed polycythemia vs those who did not (47.4% and 42.5%, respectively). In the first year following TT 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; see figure). Kaplan-Meier survival analysis showed time to survival was significantly different between the 2 groups, and the survival probability (probability of 1 year without MACE/VTE) was significantly lower in the polycythemia group (95% vs 97%, log-rank p

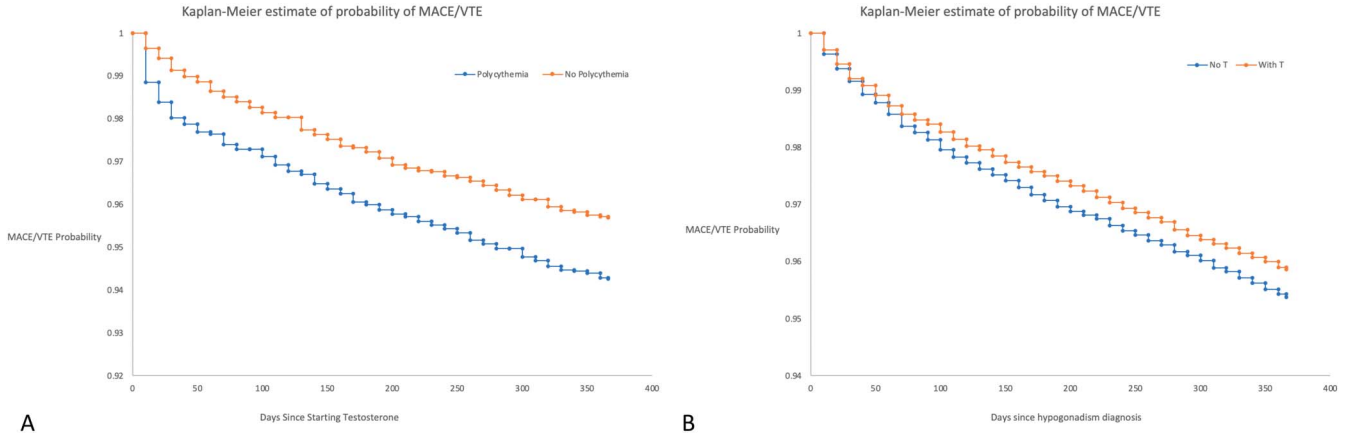

Figure. Kaplan-Meier curves displaying the probability of MACE/VTE in the main (*A*) and secondary (*B*) comparison arms. *A*, men on testosterone who developed secondary polycythemia (hematocrit >52%, blue line) versus men with a normal hematocrit (hematocrit <52%, orange line). *B*, hypogonadal men who did (orange line) and did not (blue line) receive testosterone. Men who developed hematocrit over 52% were excluded in this analysis.

Table 2. *Mean (standard deviation) blood pressure and LDL levels among patients within the first year of testosterone use, after propensity-score matching*

	Normal Hematocrit	Elevated Hematocrit	p Value
Mean mmHg blood pressure (SD):			
Systolic	130 (16.7)	130 (16.8)	0.62
Diastolic	77.9 (10.9)	78.4 (10.5)	0.04
Mean mg/dl LDL (SD)	96 (34.1)	97 (35.3)	0.17

<0.0001, HR 1.22, 95% CI 1.04−1.43; see figure). MACE/VTE subset analysis revealed 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. However, the risk of death (OR 1.14, 95% CI 0.78−1.65) or developing a stroke (OR 0.91, 95% CI 0.64−1.29) was similar.

We then evaluated matched cohorts of hypogonadal men who received TT (26,880) vs those who did not (27,430). Men were excluded from each cohort if they developed a hematocrit over 52%. After matching, 24,983 men were available for comparison in each group. The odds of MACE/VTE in the first year after hypogonadism diagnosis between these groups were similar (OR 1.07, 95% CI 0.98−1.18). Baseline characteristics of these men are available in the supplementary materials (https://www.jurology.com).

A sensitivity analysis using hemoglobin (>17.5 gm/dl) yielded similar results, showing higher incidence of MACE/VTE in men who developed polycythemia compared to those who did not (OR 1.21, 95% CI 1.02−1.36). Additionally, we tested different definitions of polycythemia. Odds of MACE remained higher in the polycythemia group when defined as hematocrit >54% (OR 0.78, 95% CI 0.62−0.98, p=0.03). We were unable to demonstrate a difference between groups when hematocrit >50% was used as the cutoff (OR 0.90, 95% CI 0.78−1.03, p=0.13). A third sensitivity analysis on use of anticoagulants during the first year of therapy as a surrogate for MACE/VTE yielded similar results, as men with polycythemia used more anticoagulants (288) than men with normal hematocrit (230; OR 1.27, 95% CI 1.06−1.51, p <0.01). Finally, LDL and blood pressure were measured at baseline as additional surrogates of comorbidity. We were unable to demonstrate a difference between LDL and systolic blood pressure at 1 year post-TT, while diastolic blood pressure was higher in men with polycythemia (table 2). The majority of men who developed polycythemia while receiving TT were under 65 years of age (72%). Thus, we performed a *post hoc* analysis of our primary objective in younger (18−64 years) and older (65+) men. Men under 65 years receiving TT had a higher rate of MACE/VTE if they developed secondary polycythemia (OR 1.27, 95% CI 1.0−1.6). Interestingly, a difference was not demonstrated in men over 65 years (OR 1.15, 95% CI 0.96−1.38).

DISCUSSION

Whether or not exogenous testosterone causes MACE or VTE is actively debated, with different evidence showing that TT is either protective, neutral or dangerous for cardiovascular or thrombotic outcomes.[19] It is possible that a concurrent, independent risk factor may be driving these adverse events. Whether or not secondary polycythemia may be driving this potential risk has never been evaluated in a population of men using TT. Understanding the factors that may cause MACE or VTE in men on TT is critical to understand, not only for patient and prescribers but for future trial designs investigating this association.

We demonstrated that developing secondary polycythemia while receiving TT, defined as a hematocrit over 52%, was associated with increased risk of developing MACE and VTE during the first year of therapy. TT itself, in the absence of polycythemia, did not appear to increase risk of MACE/VTE in hypogonadal men. To our knowledge, this is the first study to establish secondary polycythemia from TT as an independent risk factor for MACE/VTE using a specific hematocrit-based cutoff.

We used a large national database to answer this question, hypothesizing that real-world data would be best suited to address this issue. Men with high baseline hematocrit are often excluded from randomized trials, and in clinical practice pre-treatment blood work is often not done, and guidelines are frequently not followed.[20,21] This leaves a large population of men using TT who are not represented by RCTs. Our findings are somewhat supported by prior literature. The TOM (Testosterone in Older Men with Sarcopenia) trial, an RCT that was stopped early due to increased risk of cardiovascular adverse events, included older men with a high incidence of comorbid conditions.[22] While this trial only included 209 men, their demographic information is similar in nature to our study, which included a large proportion of men with comorbid conditions. Like most RCTs on testosterone, the TOM trial did not report hematocrit values in those men with cardiovascular events. One systematic review on this topic did not find overall increased cardiovascular risk, however they did find an increased event rate in the first 12 months of therapy, supporting our window of 1 year for evaluation of MACE/VTE.[23] Another review reinforced the value of using large databases in answering this question, highlighting that all published RCTs on this

topic are underpowered to assess any association with treatment and cardiovascular outcomes.[24] This will hopefully be addressed by the TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men) trial (NCT03518034), however polycythemia or hematocrit-based adverse events are not listed as an outcome.

It is well established that TT increases the risk of secondary polycythemia,[25] with higher rates in longer-acting modalities and lower rates in shorter-acting modalities.[16] Multiple national guidelines use elevation in hematocrit as a trigger to stop or change TT in men. TT cessation triggers include 55% from Canadian guidelines,[9] 54% from endocrine society guidelines and European urology guidelines,[5,26] and between 50%–54% from American urological guidelines.[10] While the rationale for these cutoffs is not cited in these guidelines, they appear to come from the Framingham heart study, which found an increase in adverse cardiovascular outcomes with a hematocrit of 49% or higher.[8] These findings were confirmed in a more recent prospective cohort study, which found an increased rate of overall and cardiovascular-related mortality once hematocrit entered the range of 50%–54%.[27] Neither of these studies specifically studied men on testosterone, and thus the currently existing hematocrit cutoffs amongst TT users is arbitrary. For the purposes of our study, we chose a cutoff of 52%, reflecting other published literature, and to ensure a relatively large comparator arm.[10,16]

The strengths of this study include its use of a large multi-institutional database and being a real-world snapshot of the effects of TT in a U.S. cohort. There is increasing evidence that nonrandomized evidence from large databases can accurately emulate a large-scale RCT, lending validity to these results.[28] Detailed propensity-score matching increased the validity of our findings. Lastly, our sensitivity analyses, and analysis of TT-naïve men, support the role of polycythemia as an independent, critical factor in the development of MACE/VTE.

Limitations include the inability to segregate results by type of testosterone prescription. In addition, a large percentage of the men included are Caucasian (86%), and the matched populations have a relatively high comorbidity index, limiting the generalizability of the findings to minorities and healthy individuals. Furthermore, we were not able to match the 2 groups by baseline hematocrit, as the men in the polycythemia group had a higher baseline hematocrit. Therefore, we cannot definitively determine whether the increased risk of MACE/VTE is due to hematocrit reaching 52% or due to men with higher baseline hematocrit starting TT. Regardless, the baseline hematocrit in the polycythemia group was 47.4%, which according to U.S., Canadian and European guidelines does not warrant further investigation before starting TT. Lastly, due to the limitations of the TriNetX database, we were unable to analyze hematocrit as a continuous variable.

Regardless of these limitations, this study lends prescribers a practical approach to informing about risks of TT, and reinforces existing guideline practices of checking hematocrit prior to prescribing.[5] It also provides a hematocrit-based cutoff that comes directly from a population of men using TT, and can hopefully allow future guideline statements to remain consistent across recommendations. Future studies that aim to assess cardiovascular outcomes in men on testosterone (such as the ongoing TRAVERSE study, NCT03518034) should perform detailed analysis on hematocrit change to investigate this as a possible association.

CONCLUSION

Men using TT should be aware that they are at a higher risk for MACE/VTE if their hematocrit reaches or exceeds 52% during the first year of therapy. This is especially relevant in men with cardiovascular comorbidities. Hematocrit-based cutoffs should be incorporated into the outcomes of future RCTs investigating MACE/VTE and TT.

REFERENCES

1. Corona G, Rastrelli G, Di Pasquale G et al: Testosterone and cardiovascular risk: meta-analysis of interventional studies. J Sex Med 2018; **15:** 820.
2. Walker RF, Zakai NA, MacLehose RF et al: Association of testosterone therapy with risk of venous thromboembolism among men with and without hypogonadism. JAMA Intern Med 2020; **180:** 190.
3. Maggi M, Wu FCW, Jones TH et al: Testosterone treatment is not associated with increased risk of adverse cardiovascular events: results from the Registry of Hypogonadism in Men (RHYME). Int J Clin Pract 2016; **70:** 843.
4. Zhang X, Huang K, Saad F et al: Testosterone therapy reduces cardiovascular risk among hypogonadal men: a prospective cohort study in Germany. Androg Clin Res Ther 2021; **2:** 64.
5. Bhasin S, Brito JP, Cunningham GR et al: Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2018; **103:** 1715.
6. Ajayi AA, Mathur R and Halushka PV: Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. Circulation 1995; **91:** 2742.
7. McMullin MF, Bareford D, Campbell P et al: Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol 2005; **130:** 174.
8. Gagnon DR, Zhang T-J, Brand FN et al: Hematocrit and the risk of cardiovascular disease—the Framingham Study: a 34-year follow-up. Am Heart J 1994; **127:** 674.
9. Grober ED, Krakowsky Y, Khera M et al: Canadian Urological Association clinical practice guideline on testosterone deficiency in men: evidence-based Q&A. Can Urol Assoc J 2021; **15:** E234.
10. Mulhall J, Trost L, Brannigan R et al: Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018; **200:** 423.
11. Saad F, Aversa A, Isidori AM et al: Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol 2011; **165:** 675.

12. Jones SD, Dukovac T, Sangkum P et al: Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. Sex Med Rev 2015; **3:** 101.

13. Taquet M, Luciano S, Geddes JR et al: Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021; **8:** 130.

14. Hackett G, Kirby M, Edwards D et al: British Society for Sexual Medicine guidelines on adult testosterone deficiency, with statements for UK practice. J Sex Med 2017; **14:** 1504.

15. Fode M, Salonia A, Minhas S et al: Late-onset hypogonadism and testosterone therapy—a summary of guidelines from the American Urological Association and the European Association of Urology. Eur Urol Focus 2019; **5:** 539.

16. Ohlander SJ, Varghese B and Pastuszak AW: Erythrocytosis following testosterone therapy. Sex Med Rev 2018; **6:** 77.

17. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 2011; **46:** 399.

18. Greenland S: Confounder summary score. In: Wiley StatsRef: Statistics Reference Online. Edited by N Balakrishnan, T. Colton, B. Everitt et al. Hoboken, New Jersey: American Cancer Society 2015; pp 1—3. Available at https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118445112.stat05133.pub2. Accessed June 10, 2021.

19. Gagliano-Jucá T and Basaria S: Trials of testosterone replacement reporting cardiovascular adverse events. Asian J Androl 2018; **20:** 131.

20. Layton JB, Li D, Meier CR et al: Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. J Clin Endocrinol Metab 2014; **99:** 835.

21. Jasuja GK, Bhasin S, Rose AJ et al: Provider and site-level determinants of testosterone prescribing in the veterans healthcare system. J Clin Endocrinol Metab 2017; **102:** 3226.

22. Basaria S, Coviello AD, Travison TG et al: Adverse events associated with testosterone administration. N Engl J Med 2010; **363:** 109.

23. Albert SG and Morley JE: Testosterone therapy, association with age, initiation and mode of therapy with cardiovascular events: a systematic review. Clin Endocrinol (Oxf) 2016; **85:** 436.

24. Onasanya O, Iyer G, Lucas E et al: Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. Lancet Diabetes Endocrinol 2016; **4:** 943.

25. Nackeeran S, Kohn T, Gonzalez D et al: The effect of route of testosterone on changes in hematocrit: a systematic review and bayesian network meta-analysis of randomized trials. J Urol 2022; **207:** 44.

26. Al-Sharefi A and Quinton R: Current national and international guidelines for the management of male hypogonadism: helping clinicians to navigate variation in diagnostic criteria and treatment recommendations. Endocrinol Metab 2020; **35:** 526.

27. Boffetta P, Islami F, Vedanthan R et al: A U-shaped relationship between haematocrit and mortality in a large prospective cohort study. Int J Epidemiol 2013; **42:** 601.

28. Franklin JM, Patorno E, Desai RJ et al: Emulating randomized clinical trials with nonrandomized real-world evidence studies. Circulation 2021; **143:** 1002.

EDITORIAL COMMENT

Testosterone deficiency is a clinical and biochemical diagnosis that may have a significant impact on a patient's quality of life. Testosterone replacement therapy (TRT) has been the mainstay of treatment, however its use may result in clinical consequences. Polycythemia is one such consequence, with the thrombotic risks due to TRT being raised as a concern following U.S. Food and Drug Administration labeling changes in 2014.[1] There is current heterogeneity in what threshold hematocrit levels should trigger intervention, thus creating a potential clinical conundrum, resulting in nonuniform prescribing and management patterns.

Current American Urological Association guidelines use a pre-treatment hematocrit threshold of 50% and a post-treatment level of 54% to define when further investigation or intervention may be necessary.[2] The authors should be commended in their endeavor to clarify this association, as prior investigations have sought to evaluate rates of secondary polycythemia from TRT; however, many such studies have not highlighted cardiovascular events as an endpoint. Notably, other studies have similarly demonstrated increased rates of secondary polycythemia, as defined by a hematocrit threshold of 52%, in patients on TRT when compared to alternative forms of hormone replacement therapy.[3]

The multi-institutional, retrospective cohort study conducted by the authors of this study further investigates this important topic by specifically aiming to highlight major adverse cardiac events and/or venous thromboembolism due to secondary polycythemia associated with TRT in the first year of therapy. Their hematocrit threshold of 52% is in line with prior studies, and their findings indeed highlight a 5.15% increased risk of venous thromboembolism/major adverse cardiac events in hypogonadal men with secondary polycythemia following TRT. While the study was not able to specifically correlate serum levels of testosterone with subsequent development of polycythemia, it is a body of work that may serve to assist clinicians in patient counseling, inform global prescribing patterns and inspire further investigative research.

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REFERENCES

1. U.S. Food and Drug Administration Drug Safety Communication: FDA Cautions about Using Testosterone Products for Low Testosterone Due to Aging; Requires Labeling Change to Inform of Possible Increased Risk of Heart Attack and Stroke with Use. Silver Spring, Maryland: U.S. Food and Drug Administration 2014.

2. Mulhall JP, Trost LW, Brannigan RE et al: Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018; **200:** 423.

3. Wheeler KM, Smith RP, Kumar RA et al: A comparison of secondary polycythemia in hypogonadal men treated with clomiphene citrate versus testosterone replacement: a multi-institutional study. J Urol 2017; **197:** 1127.