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Title: Rises in Hematocrit is Associated with An Increased Risk of Major Adverse Cardiac Events in Men Starting Testosterone Therapy - A Retrospective Cohort Claims Database Analysis

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ABSTRACT

Objective: Elevated hematocrit (Hct) can result in increased risk of major adverse cardiac events (MACE) in men receiving testosterone therapy (TTh). However, the impact of the magnitude of the change in Hct from baseline after starting TTh has never been assessed.

Methods: To assess whether an increase in Hct after initiating TTh is associated with an increased risk of MACE within 3 and 24 months of initiating TTh, we queried the TriNetX Research network database for men over the age of 18 with Hct values obtained within six months before starting TTh, and who had follow-up Hct measurements within three and 24 months after beginning TTh from 2010-2021. Men with and without a subsequent increase in Hct after initiating TTh were propensity matched. MACE was defined as myocardial infarction, stroke, or death.

Results: After matching, 10,511 men who experienced an any increase in Hct after initiating TTh and an equal number of controls who did have an increase in Hct were included. Compared to controls who did not have an increase in Hct after starting TTh, the men who had an increase in subsequent Hct had a significantly increased risk of major adverse cardiac events compared with men with no change in Hct.

Conclusions: We demonstrate that increases in Hct from baseline are associated with increased risk of MACE, compared to men whose Hct remains stable while receiving TTh.

Impact Statement: Clinicians should monitor Hct after initiating TTh, as large increase from baseline may be a risk factor for MACE.

INTRODUCTION

Testosterone therapy (TTh) is recommended for men with symptoms of hypogonadism associated with testosterone deficiency.[1] Indications for TTh include delayed puberty, sexual dysfunction, hypopituitarism, and adult men with testosterone levels below an age-specific physiological range exhibiting corresponding symptoms. The primary goal of TTh is to reduce clinical symptoms and restore testosterone levels to age-appropriate ranges.[2]

However, TTh is associated with an increase in hemoglobin (Hb) and hematocrit (Hct) levels. The Endocrine society recommends against starting therapy in patients with elevated baseline Hct due to concerns about an increased risk of major adverse cardiovascular events (MACE) including myocardial infarctions and cerebrovascular accidents potentially due to increase in blood viscosity.[1, 3-5] TTh is postulated to affect Hct by multifactorial mechanisms including decreasing hepcidin production, increasing erythropoietin setpoint and production, and activating peripheral bone marrow estrogen receptors leading to telomere stability.[6] Depending on the different societies, Hct levels of 48% to 55% are regarded as contraindications for TTh given concerns of increased risk of MACE.[1, 2, 5, 7, 8]

While recent studies have shown that TTh-induced secondary polycythemia (Hct > 52%) is an independent risk factor for MACE within the first year of treatment[9], it is not clear whether erythrocytosis – i.e., degree of change in Hct from baseline Hct after starting TTh confers additional risk for MACE. Herein we aimed to determine the incidence of MACE associated with the degree of Hct change from baseline in adult men receiving testosterone therapy for hypogonadism.

METHODS

Data Source and Study Design

The data used in this study was collected and analyzed in June 2022 from the TriNetX, LLC Research Network, which provided access to electronic medical records and insurance claims for approximately 106 million patients from 68 healthcare organizations. Data from TriNetX includes included information on demographics, diagnoses, procedures, prescriptions, and laboratory values. Diagnoses were recorded using International Classification of Disease (ICD) codes, procedures were recorded using Current Procedural Terminology (CPT) codes, and laboratory tests were identified via Logical Observation Identifiers Names and Codes (LOINC). Information on medications was obtained from prescriptions, orders, inpatient medication reconciliations, and charted medications and were identified in the database using Veterans Affairs (VA) Drug classification system. The data used in the study covered the period from January 2010 through December 2021.

The process by which the data was de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. Because studies using TriNetX de-identified patient records do not involve the collection, use, or transmittal of individually identifiable data, the qualified expert has determined these studies are exempted from need of Institutional Review Board. Any patient counts less than 10 are obfuscated to ensure patient anonymity, and only aggregate patient counts and statistical summaries are provided.

Cohorts

To evaluate whether the degree of change in Hct from baseline after initiating TTh is associated with increased risk of MACE, we constructed a cohort of adult men aged 18 or older who did not have a diagnosis of unstable angina (ICD-10: I20.0 & I25.7) or heart failure (ICD-10: I50), had their Hct (LOINC: LAB:9013) tested within 6 months before starting TTh (VA Drug classification system: 10379), and had follow-up Hct laboratory testing within 3 and 24 months after beginning TTh. Men with Hct levels ≤30% at any time while the cohorts were being assessed were excluded from the study as rates of cardiovascular mortality are 3 to 5 times higher in men when Hct levels are less than 30%.[10] The outcomes of interest were MACE, defined as myocardial infarction (ICD-10: I21-22), stroke (I60-63), or death (all causes), within 3 months and 24 months of initiating TTh (Supplemental Figure 1). If men had multiple Hct

laboratory values measured prior to initiating TTh, we used the value closest to the time of TTh initiation. We used the laboratory value that demonstrated the greatest rise in Hct after initiating TTh within the 3-to-24-month period or prior to MACE event if it were to occur as the follow-up Hct value. Men were evaluated as: those with no change in Hct and those who had an increase in Hct after initiating TTh. Men with no change in Hct could not have had a Hct lab drawn within the 3-to-24 month period with a value above or below the specified range. Men with decreasing Hct values after initiating TTh were excluded as men experiencing a decline in Hct after starting testosterone therapy were quite rare. To maintain large enough cohorts that outcomes were not obfuscated by HIPAA privacy measures within the database if outcomes were <10, we binned the pre- and post-TTh Hct values into the following categories: 36-39%, 40-43%, 44-47%, 48-51%, and ≥52%. 36% Hct was used as the lower limit as prior literature suggests that men with Hct less than 35% are at significantly increased risk of all-cause mortality and cardiovascular mortality[10] and >52% was used as this is the threshold at which the AUA guidelines define polycythemia.[8]

To assess the risk of MACE three to 24 months after starting TTh, we compared men with the same baseline Hct who did not experience a change in Hct after starting TTh with men who had an increase in Hct within the same range at baseline. This resulted in 10 separate analyses comparing each increase in Hct category with men who did not experience an increase in Hct. For example, men with baseline Hct of 40-43% who did not experience an increase in after starting TTh were compared with men with a Hct of 40-43% at baseline and a maximum Hct ≥52% within three to 24 months of initiating TTh to assess the differences in rates of resulting major adverse cardiac events three to 24 months after starting TTh.

Statistical Analysis

All analysis was performed on TriNetX platform. Chi square test and T-test were used for univariate analysis. 1:1 propensity score matching was performed with age (continuous variable), race/ethnicity, smoking status (ICD10: Z72.0), baseline pre-testosterone treatment Hct level, history of myocardial infarction (I21), history of cerebral infarction (I63), hyperlipidemia (E78), sleep apnea (G47.3), type 2 diabetes mellitus (E11), current age (continuous variable), and frequency of outpatient services (CPT Concept ID: 1013626), emergency department services (CPT Concept ID: 1013711), and inpatient hospital services (CPT Concept ID: 1013659) as

covariates and a propensity score matched control group of patients starting testosterone but without increase in Hct were identified. These variables were chosen because they are established risk factors for cardiovascular disease and/or mortality or were significantly different between the 2 cohorts. For each patient in the smaller cohort, the system chooses a 1:1 match from the larger cohort based on the propensity scores generated by using greedy nearest neighbor algorithms utilizing a caliper width of 0.1 times pooled standard deviations. Balance on covariates was assessed using standardized mean difference and absolute values > 0.1 were considered positive for residual imbalance. The order of records is randomized to eliminate bias using a fixed seed during matching, allowing for reproducibility. A two-sided alpha of less than 0.05 was defined a priori for statistical significance. The TriNetX Platform calculates risk ratios and associated 95% Cis, using R's Survival package, version 3.2-3 (R Group for Statistical Computing).

Details of propensity score matching:[11] TriNetX platform utilizes input matrices of user-identified covariates and conducts logistic regression analysis to obtain propensity scores for individual subjects. 1:1 matching was performed based on the propensity scores generated by using greedy nearest neighbor algorithms utilizing a caliper width of 0.1 times pooled standard deviations (SD). TriNetX randomizes the order of rows in order to eliminate bias resulting from nearest-neighbor algorithms. This study method has been previously validated.[12, 13]

RESULTS

Before matching, we identified a total of 22,383 men who experienced an increase in Hct after initiating TTh and 6,899 men who did not experience an increase in Hct compared to their baseline Hct (Table 1). After matching, we identified 10,511 men with an increase in Hct and 6,320 men with no increase in Hct after beginning TTh. The matching occurred within each group, resulting in 10 distinct analyses with men not experiencing an increase in Hct serving as the comparison group for multiple analyses (e.g. the cohort of men who had a baseline Hct of 44-47% with no increase in Hct after starting testosterone therapy served as the comparison cohort for men who had a baseline Hct of 44-47% but increased to 48-51% after starting testosterone as well as the cohort with a baseline Hct of 44-47% but increased to ≥52% after starting testosterone, Supplemental Table 1).

Overall, as Hct increased from baseline after the initiation of TTh, the risk ratio of MACE was greater for nearly all groups as seen in Table 2 and Supplemental Table 2. Incidence of MACE were 6.1-6.7% in men with a baseline and follow-up Hct between 36-39% but when compared to cohorts that had increasing Hct after starting testosterone therapy incidence of MACE ranged between 10-14%. A similar trend was seen in those with a baseline Hct of 40-43%, 44-47%, 48-51% where increase in Hct was associated with higher risk of MACE when compared to men who started testosterone therapy but did not see an increase in Hct. Too few men had a baseline Hct of ≥52% and were initiated on testosterone to assess this cohort.

DISCUSSION

The link between TTh and MACE is actively debated, with recent evidence supporting that erythrocytosis may be an important intermediary between these two.[9] While guidelines surrounding erythrocytosis have thus far involved an absolute upper limit cutoff for safety, studies have not investigated whether the magnitude of change in Hct while on TTh is a risk for MACE. We separated Hct into 5 separate quintiles and investigated how risks of MACE changed as Hct increased through these ranges while on TTh compared to men who did not experience an increase. We found that increases in Hct conferred an subsequent risk of MACE, regardless of the final upper limit. The risk of MACE was highest in those men who underwent the largest increases in Hct.

This study has several important implications. Until recently, studies that have informed FDA warnings, or those that have showed TTh to be safe with respect to MACE have not looked at an underlying cause for the association. Recently, Hct over 52% has been found to be an important intermediary linking TTh and MACE.[9] This study looked at a simple cutoff of 52%, and so did not provide any information on whether a large increase in Hct, while still remaining under 52%, was important. Our study suggests that all men, regardless of initial Hct, can potentially be at risk for MACE if their Hct increases. Men can have a Hct below guideline-based cutoffs, but if the overall increase is large enough despite not reaching the upper limit of cutoff for changing dose or therapeutic phlebotomy, they may still experience risk for an adverse event. This may mean more careful tracking of Hct while on TTh instead of simply looking for an upper limit during the first 2 years of therapy.

It is not known why an increase in Hct from any baseline level may increase the risk of MACE. Clinical evidence does support that the change in baseline may be more important than the final upper limit. Walker *et al*. found that men on TTh had a higher risk of VTE during the first 6 months of TTh. On exploratory analysis, they found this risk was highest in the first 3 months of therapy, with no increased risk between month 3 and 6.[14] Upon starting TTh, Hct begins to rise within the first month of therapy, and peaks at month 3.[15] This increased risk of VTE within the first 3 months then may be explained by the rise in Hct. Other research has found that the rate of MACE is higher in the first year of TTh, which may further support that the rise in Hct is more important than final value.[16]

Rates of MACE were greatest in the cohort with a baseline Hct of 36-39% when compared to all other cohorts but this is likely explained by the more unhealthy indiividuals in this cohort. For example in the cohort with baseline Hct of 36-39% that stayed in this range after starting TTh, rates of hypertension were 51.5%, hyperlididemia was 45.1%, type II diabetes 30.7%, prior stroke was 4.1%. Compared to men with a baseline Hct of 44-47% that stayed in this range after starting TTh: hypertension was 38.5%, hyperlididemia was 44.0%, type II diabetes 15.8%, prior stroke was 0.74%. Thus the higher overall frequency of MACE is likely explained by a more unhealthy cohort for those with Hct of 36-39%. This is why each cohort is propensity matched to its own same baseline Hct values to demonstrate the risk associated with each increases in Hct quintile compared to men who saw no increase in Hct after starting TTh.

One of the major strengths of our study is the number of patients we were able to compare. One of the main criticisms of studies linking TTh and MACE is that they are not adequately powered to show causation.[17] With over 16,000 men in our analysis after matching, we were able to have adequate power for our primary outcome. Another strength of our study is separating Hct into quintiles and using this to investigate an exposure-response relationship between Hct and MACE. While a simple cutoff of 52% has been shown to be correlated with increased risk of MACE, finding an exposure-response relationship further strengthens the plausibility that Hct increases are an important factor in MACE risk in men on TTh. One of the major limitations of our study is that due to using an anonymized database, we lose the ability to investigate individual patient factors in the analysis including testosterone preparation used, compliance, or dosages as well as patient diet or exercise routines at baseline. Unfortunately, because the TriNetX database obfuscates any counts where the incidence is 10 or less to protect HIPAA, we are unable to obtain precise counts of the sub-categories of MACE (stroke, MI, and death). Regardless, because we still do show a consistent increase in every starting quintile of Hct, we believe our findings still are intriguing. Because some cohorts that experienced an increase in Hct after starting testosterone had smaller numbers of patients compared to the cohort not experiencing an increase and other times, those experiencing an increase had larger numbers than those not experiencing an increase, we could not consistently keep the target population for propensity score modeling to only those experiencing an increase and this could limit the generalizability of our study. TriNetX database also only allows for propensity score matching rather than regression analysis limiting our analytical approach and requiring categorical

treatment of Hct values rather than as a continuous variable. Additionally, we do not know what interventions were undertaken upon development of erythrocytosis, or if these men were appropriately diagnosed with hypogonadism. More and more clinics are offering TTh without proper guideline-based diagnosis which may increase their risk for adverse effects.[18-20] Lastly, we were not able to determine which testosterone modalities these men were on. Since longer-acting testosterone modalities have a higher risk of erythrocytosis than short-acting modalities, it is theoretically possible that these would also have a higher risk of MACE, but this has not been investigated yet.[21, 22] Finally, assessing whether a decline in Hct after starting testosterone is or is not associated with future MACE would have been intriguing, unfortunately, too few men saw a decrease in Hct upon starting testosterone to allow for analysis of these cohorts.

This study expands the likelihood that increases in Hct account for the incidence of MACE possibly seen in men on TT. A large RCT (TRAVERSE Trial) is currently being undertaken to further elucidate this connection but unfortunately has not included Hct-based increases as a factor in their analysis. While the decision on how or when to act upon a rising Hct once starting testosterone therapy is a conversation that patients and their doctors will have to consider. Certainly, these men who are experiencing a rise in Hct could be encouraged to talk with their primary care physician to determine if any other steps could help to decrease their risk of MACE – such as testing for hyperlipidemia or starting treatment if hypertensive. Further research is needed to determine what amount of Hct increase should raise concerns amongst clinicians to warrant intervention.

CONCLUSIONS

In this study, we find that an increase in Hct from baseline after starting testosterone therapy is associated with an increased risk of MACE even when the increase is below traditional cut-off values, such as 52%. Clinicians should monitor Hct levels after initiating testosterone recognizing and counseling patients that increases in Hct may place patients at higher risk of MACE. Further studies are needed to confirm these findings and to assess when clinicians should intervene when Hct is rising after starting testosterone therapy.

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TABLES AND FIGURES

Table 1 – Unmatched Cohorts of Men Initiating Testosterone Therapy with and without Increase in Hct

Baseline Characteristics		
	Men without Hct Change	**Men with Hct Increase**
Total Patients	6899	22383
Hematocrit Categories, total included men		
Unchanged 36-39%	646	---
Unchanged 40-43%	2027	---
Unchanged 44-47%	3087	---
Unchanged 48-51%	1139	---
36-39% to 40-43%	---	6407
36-39% to 44-47%	---	3869
36-39% to 48-51%	---	1401
36-39% to >52%	---	365
40-43% to 44-47%	---	3162
40-43% to 48-51%	---	1096
40-43% to >52%	---	617
44-47% to 48-51%	---	3100
44-47% to >52%	---	1109
48-51% to >52%	---	1257

Table 2 – Proportion of MACE events by Change in Hematocrit after Starting Testosterone Therapy

Proportion of MACE events by Change in Hematocrit after Starting Testosterone Therapy									
		Hematocrit after starting Testosterone							
		36-39%	***40-43%***	***44-47%***	**48-51%**	**≥52%**	**Relative Risk of MACE**		**Matched Men in Each Group****
Hematocrit Before Testosterone	**36-39%**	6.1-6.7%*	10.7%				**1.62 (1.12-2.34)**		n=631
				10.3%			**1.52 (1.05-2.21)**		n=621
					11.3%		**1.68 (1.14-2.47)**		n=551
						14.3%	**2.29 (1.33-3.95)**		n=274
	40-43%		2.1-2.7%*	3.4%			**1.66 (1.13-2.43)**		n=1985
					4.3%		**2.09 (1.27-3.45)**		n=1059
						5.6%	**2.06 (1.15-3.71)**		n=589
	44-47%			1.0-1.6%*	2.2%		**2.07 (1.34-3.19)**		n=2700
						4.3%	**2.67 (1.56-4.56)**		n=1102
	48-51%				1.4%	3.3%	**2.35 (1.27-4.38)**		n=1004
	≥52%					---	---		Too Infrequent

**Each group with an increase in hematocrit after testosterone was matched to the men with same baseline Hct but with no change after starting testosterone. Range reported for MACE inidence for each matched group without change in Hct. Since Hct before testosterone of 48-51% is only compared to only one group, no range is given.*

***Sample size changes between comparisons due to propensity score matching based on age, race/ethnicity, smoking status, baseline Hct level, history of myocardial infarction, history of cerebral infarction, hyperlipidemia, sleep apnea, type 2 diabetes mellitus, current age, and frequency of outpatient services, emergency department services, and inpatient hospital services*

Bold indicates significance

Supplemental Figure 1 – Sample Criteria and Outcomes

Supplemental Table 1 – Baseline and Matched Demographic of Included Men Assessing MACE after Initiating Testosterone

Supplemental Table 2 – Baseline and Follow-Up Demographic of Matched Men Assessing MACE after Initiating Testosterone