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Original Research

Testosterone therapy in females is not associated with increased cardiovascular or breast cancer risk: a claims database analysis

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Abstract

Background: Testosterone therapy (TTh) has been shown to improve libido in women with sexual dysfunction, but its utilization has been limited due to concern for cardiovascular events and past studies reporting highly variable results.
Aim: To assess the association of TTh in women with major adverse cardiac events (MACEs), including heart attack, stroke, or death, using a large database.
Methods: The TriNetX Diamond Network was queried from 2009 to 2022. Our study cohort included adult females with ≥3 systemic testosterone prescriptions within a year. Our control cohort excluded females with any testosterone prescriptions, polycystic ovary syndrome, or androgen excess. Both cohorts excluded females with prior heart failure, unstable angina, intersex surgery (female to male), personal history of sex reassignment, or gender identity disorders. Propensity matching between the cohorts was performed. A subanalysis by age was conducted (18-55 and >55 years).
Outcomes: We evaluated the association of TTh to the following: MACE, upper or lower emboli or deep vein thrombosis (DVT), pulmonary embolism (PE), breast neoplasm, and hirsutism within 3 years of TTh.
Results: When compared with propensity-matched controls, adult females with TTh had a lower risk of MACE (risk ratio [RR], 0.64; 95% CI, 0.51-0.81), DVT (RR, 0.61; 95% CI, 0.42-0.90), PE (RR, 0.48; 95% CI, 0.28-0.82), and malignant breast neoplasm (RR, 0.48; 95% CI, 0.37-0.62). Similarly, females aged 18 to 55 years with TTh had a lower risk of MACE (RR, 0.49; 95% CI, 0.28-0.85) and DVT (RR, 0.48; 95% CI, 0.25-0.93) and a similar risk of malignant breast neoplasm (RR, 0.62; 95% CI, 0.34-1.12). Females aged ≥56 years with TTh had a similar risk of MACE (RR, 0.84; 95% CI, 0.64-1.10), DVT (RR, 0.82; 95% CI, 0.50-1.36), and PE (RR, 0.52; 95% CI, 0.26-1.05) and a significantly lower risk of malignant breast neoplasm (RR, 0.51; 95% CI, 0.38-0.68). Risk of hirsutism was consistently higher in those with TTh as compared with propensity-matched controls.
Clinical Implications: Our results contribute to safety data on TTh, a therapy for sexual dysfunction in women.
Strengths and Limitations: The TriNetX Diamond Network allows for significant generalizability but has insufficient information for some factors.
Conclusions: We found a decreased risk of MACE among women with TTh as compared with matched controls and a similar risk of MACE in postmenopausal women while demonstrating a similar or significantly lower risk of breast cancer on age-based subanalysis.

Keywords: testosterone; myocardial infarction; ischemic stroke; death; female; breast cancer.

Introduction

Androgens, including testosterone, play an important role in sexual health and sexual function in females across the lifetime. With aging, testosterone production from the ovaries and adrenal glands decreases, although there is a small increase in testosterone during menopause due to decreasing sex hormone-binding globulin levels.[1] This decreased testosterone production can contribute to the development of female sexual dysfunction in postmenopausal women.[1,2] Testosterone therapy (TTh) has therefore been proposed and studied as an approach to managing female sexual dysfunction in postmenopausal women, particularly in hypoactive sexual desire disorder (HSDD).[1,3] To date, leading international organizations, such as the International Menopause Society, the Endocrine Society, and the International Society for Sexual Medicine, recommend TTh only for postmenopausal women.[4]

In select populations of postmenopausal women, short-term safety and efficacy data on testosterone use have been reported. A systematic review of androgen therapy in women, which included randomized placebo-controlled clinical trials, showed improvements in sexual function without major safety issues.[5] A recent expert consensus providing clinical practice guidelines for TTh in postmenopausal HSDD noted no serious

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adverse effects but acknowledged a need for more long-term safety data.[3] These concerns are primarily due to the still unknown risks of cardiovascular events and new breast cancer incidence after long-term testosterone use.[5] Of note, there are few studies of TTh in premenopausal women, with the largest including 2103 women, leading to insufficient data to provide recommendations for this population.[6]

Prescribing TTh in females therefore continues to be challenging for providers due to a lack of Food and Drug Administration–approved formulations, largely due to a lack of long-term safety data. In this study, we aimed to investigate the risk of a major adverse cardiac event (MACE) and new breast cancer following TTh in a large cohort of adult women by using a claims database approach. Additionally, we sought to examine the association between TTh and other possible adverse side effects, including new incidence of venous emboli, pulmonary embolism (PE), and hirsutism.

Methods

Study design

We conducted a comprehensive cohort analysis using electronic health records (EHRs) sourced from the real-world data research network TriNetX Diamond. TriNetX offers access to patient EHR data, augmented by linked medical and pharmaceutical claims, as well as information from cancer registries, covering an expansive cohort of approximately 200 million patients across >90 health care organizations worldwide. This extensive data set leverages clinical observations that are indexed by date and patient. For our study, we utilized data—including demographic details, diagnoses coded according to the *ICD-10*, and procedures documented via *CPT* codes—collected and analyzed until December 2022.

TriNetX strictly adheres to the HIPAA guidelines (Health Insurance Portability and Accountability Act), and it obtained a waiver from the Western Institutional Review Board. All patient data undergo deidentification processes in line with the standards defined in §164.514(a) of the HIPAA privacy rule, ensuring the anonymity of patients. Additionally, any patient counts <10 are displayed as 10 to further safeguard patient privacy.

Study participants

The TriNetX database was queried from 2009 to December 2022 with *ICD-10* codes. A patient was considered to have a diagnosis if the corresponding *ICD-10* code was associated with the patient's EHR in the database. Our study and control cohorts exclusively comprised adult females aged ≥18 years. In our study cohort, we included adult females who had received ≥3 injectable or topical testosterone prescriptions (Rx 10379) within a time frame ranging from 1 month to 1 year, as illustrated in Figure 1. To be eligible for inclusion, it was required that the second testosterone prescription occur within 1 month to 1 year from the first prescription and that the first prescription be issued to individuals aged ≥18 years. This criterion aimed to capture patients with consistent prescription adherence. Our control cohort excluded adult females who had ever been prescribed testosterone and those who had received a diagnosis of polycystic ovary syndrome (*ICD-10* E28.2) or androgen excess (E28.1).

Both cohorts excluded adult females with a history of heart failure (I50), unstable angina (I20.0), intersex surgery (female to male; *CPT* 55980), a personal history of sex reassignment (Z87.890), or gender identity disorders (F64). Additionally, we conducted a subanalysis within both cohorts, stratifying individuals into 2 age groups: 18 to 55 years and ≥56 years.

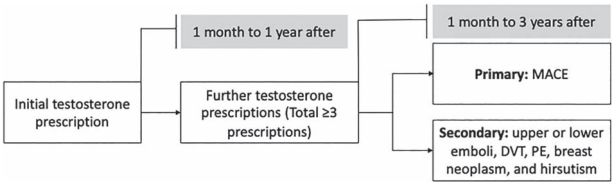

Figure 1. Methodology of creation.

Statistical analyses

The primary study outcome was the risk of MACE following TTh. MACE was defined as heart attack (*ICD-10*: I21, I22), stroke (I60, I61, I62, I63), or death within 1 month to 3 years after initiation of TTh. We also evaluated the risk of developing upper or lower emboli, deep vein thrombosis (DVT; I82.4, I82.6), PE (I26), and malignant breast neoplasm (C50) within 1 month to 3 years after TTh initiation. The odds of developing a diagnosis of hirsutism (L68.0) within 1 month to 3 years after TTh initiation were evaluated as an internal control. The TriNetX platform was utilized to conduct all analyses.

We conducted a 1:1 matching procedure based on propensity scores generated using greedy nearest neighbor algorithms. In this method, pairs are created by iteratively selecting the nearest eligible control unit for each treated unit. To mitigate potential bias introduced by the nearest neighbor algorithms, TriNetX employs row randomization to ensure fairness. We propensity matched for various key variables, such as age at initiation of TTh, current age, ethnicity, race, estrogen usage (HS300), family history of cardiovascular disease (Z82.4), tobacco usage (Z72.0), type 2 diabetes (E11), hyperlipidemia (E78), hypertensive diseases (I10-16), and obesity (E66), as well as the utilization of outpatient (1013626), inpatient (1013659), or emergency department services (1013711). These variables were selected because they are recognized as established risk factors for cardiovascular disease and/or mortality or they exhibited significant differences between the cohorts. For each patient in the smaller cohort, the system identified a 1:1 match from the larger cohort using the greedy nearest neighbor algorithms, with a caliper width of 0.1 pooled SD to ensure precise matching. The balance on covariates was assessed with *P* values, with values <.05 indicating residual imbalance. To compare the matched cohorts, we employed Cox proportional hazards regression analysis, with the proportional hazard assumption tested per the generalized Schoenfeld approach. The TriNetX Platform calculated risk ratios (RRs) and associated 95% CIs with the survival package in R version 3.2-3 (R Group for Statistical Computing).

Results

Our query of the TriNetX database identified 16 783 females with ≥3 topical or injectable testosterone prescriptions, prescribed within 1 month to 1 year of one another. On average, individuals in this cohort received 8 topical or injectable testosterone prescriptions over their lifetimes at a mean ± SD

Table 1. Odds of adverse effects between adult females (≥18 years) receiving testosterone and propensity score–matched controls.

	Female participants, No. (%)	
	Testosterone ($n = 10\,300$)	Controls ($n = 10\,300$)
Major adverse cardiac event	118 (1.15)	184 (1.79)
Odds ratio (95% CI)	0.64 (0.51–0.81)	
Upper or lower emboli and deep vein thrombosis	41 (0.40)	67 (0.65)
Odds ratio (95% CI)	0.61 (0.42–0.90)	
Pulmonary embolism	19 (0.18)	40 (0.39)
Odds ratio (95% CI)	0.48 (0.28–0.82)	
Breast neoplasm	83 (0.81)	174 (1.69)
Odds ratio (95% CI)	0.48 (0.37–0.62)	
Hirsutism	63 (0.61)	25 (0.24)
Odds ratio (95% CI)	2.52 (1.59–4.00)	

age of 41.2 ± 15.7 years at their first testosterone prescription. Of the females receiving testosterone prescriptions, 88% had at least 36 months of follow-up data captured, as required for analysis in this study. For the control population of 3 058 619 women, 95% had at least 36 months of follow-up data captured. After propensity matching, 10 300 females with ≥3 testosterone prescriptions were compared with an equal number of controls (Table 1). The average age of females receiving testosterone was 43.9 ± 15.3 years, and that of our control group was 44.4 ± 16.3 years. When compared with propensity score–matched controls, those with ≥3 testosterone prescriptions had significantly lower risks of MACE (RR, 0.64; 95% CI, 0.51-0.81), upper or lower emboli or DVT (RR, 0.61; 95% CI, 0.42-0.90), PE (RR, 0.48; 95% CI, 0.28-0.82), and malignant breast neoplasm (RR, 0.48; 95% CI, 0.37-0.62) within 1 month to 3 years after receiving ≥3 topical or injectable testosterone prescriptions. When compared with matched controls, those with ≥3 testosterone prescriptions had a significantly higher risk of hirsutism (RR, 2.52; 95% CI, 1.59-4.00).

On subanalysis, we identified 11 098 females aged 18 to 55 years with ≥3 topical or injectable testosterone prescriptions, prescribed within 1 month to 1 year of one another. After propensity matching, 6128 females with ≥3 testosterone prescriptions were compared with an equal number of controls (Table 2). The average age of females receiving testosterone was 33.9 ± 10.6 years, and that of the control group was 33.6 ± 10.6 years. When compared with propensity score–matched controls, those with testosterone prescriptions had significantly lower risks of MACE (RR, 0.49; 95% CI, 0.28-0.85) and upper or lower emboli or DVT (RR, 0.48; 95% CI, 0.25-0.93) and a similar risk of malignant breast neoplasm (RR, 0.62; 95% CI, 0.34-1.12). Odds of PE could not be calculated due to low patient counts ($n \leq 10$ in study, $n = 21$ in control). When compared with matched controls, those with ≥3 testosterone prescriptions had a significantly higher risk of hirsutism (RR, 1.80; 95% CI, 1.04-3.11).

Similarly, we identified 6068 females aged ≥56 years with ≥3 topical or injectable testosterone prescriptions, prescribed within 1 month to 1 year of one another. After propensity matching, 4172 females with ≥3 testosterone prescriptions were compared with an equal number of controls (Table 3). The mean age of females receiving testosterone was 58.7 ± 7.07 years, and that in our control group was 58.7 ± 7.23 years. When compared with propensity score–matched controls, those with testosterone prescriptions had similar risks of MACE (RR, 0.84; 95% CI, 0.64-1.10), upper or lower emboli or DVT (RR, 0.82; 95% CI, 0.50-1.36), and PE (RR, 0.52; 95% CI, 0.26-1.05) and a significantly lower risk of malignant breast neoplasm (RR, 0.51; 95% CI, 0.38-0.68). Risk of hirsutism could not be calculated due to low patient counts ($n = 23$ in study, $n < 10$ in control).

Discussion

Testosterone plays a critical role across a woman's lifetime, including sexual function, cognition, and musculoskeletal health. To date, the benefits of TTh in women have been best described in HSDD. Two recent global consensus statements have endorsed HSDD in postmenopausal women as an evidence-based indication for TTh.[3,4,7-9] However, there remains a need for high-quality studies investigating the effects of TTh on other etiologies of female sexual dysfunction, musculoskeletal health, and cognitive performance.[4,7-9] In addition, insufficient long-term cardiovascular and breast cancer safety data have contributed to the lack of Food and Drug Administration–approved indications for this therapy.[3,10] In this large study, we found a decreased risk of MACE among women with TTh as compared with matched controls and a similar risk of MACE in postmenopausal women. We also demonstrated a similar or significantly lower risk of breast cancer in our cohort, including the pre- and postmenopausal groups.

TTh and MACE

The effects of TTh on the cardiovascular system remain relatively unknown. It has been postulated that TTh causes erythrocytosis in men, increasing the risk for MACE and venous thromboembolism.[11] Recent studies, such as the TRAVERSE trial, have shown no significant increase in MACE with TTh.[12] Meanwhile, the evidence for TTh causing MACE in women has been largely inconclusive. The landmark Women's Health Initiative Study concluded that estrogen with progestin significantly increased the risk for heart disease, stroke, and thromboembolism in postmenopausal women.[13] Since then, there has been a growing interest in understanding hormonal supplementation and its effects on postmenopausal women. Despite this and the increasing use of TTh to effectively treat a variety of conditions in women, there is still a lack of conclusive data on how TTh affects women.

Table 2. Odds of adverse effects between adult females (18-55 years) receiving testosterone and propensity score–matched controls.

	Female participants, No. (%)	
	Testosterone ($n = 6128$)	**Controls ($n = 6128$)**
Major adverse cardiac event	18 (0.29)	37 (0.60)
Odds ratio (95% CI)	0.49 (0.28–0.85)	
Upper or lower emboli and deep vein thrombosis	13 (0.21)	27 (0.44)
Odds ratio (95% CI)	0.48 (0.25–0.93)	
Pulmonary embolism	<10	21 (0.34)
Odds ratio (95% CI)	—	
Breast neoplasm	18 (0.29)	29 (0.47)
Odds ratio (95% CI)	0.62 (0.34–1.12)	
Hirsutism	36 (0.59)	20 (0.33)
Odds ratio (95% CI)	1.80 (1.04–3.11)	

Table 3. Odds of adverse effects between adult females (≥56 years) receiving testosterone and propensity score–matched controls.

	Female participants, No. (%)	
	Testosterone ($n = 4172$)	**Controls ($n = 4172$)**
Major adverse cardiac event	100 (2.40)	119 (2.85)
Odds ratio (95% CI)	0.84 (0.64–1.10)	
Upper or lower emboli and deep vein thrombosis	28 (0.67)	34 (0.82)
Odds ratio (95% CI)	0.82 (0.50–1.36)	
Pulmonary embolism	12 (0.29)	23 (0.55)
Odds ratio (95% CI)	0.52 (0.26–1.05)	
Breast neoplasm	65 (1.56)	128 (3.07)
Odds ratio (95% CI)	0.51 (0.38–0.68)	
Hirsutism	27 (0.65)	<10
Odds ratio (95% CI)	—	

Extremely elevated androgen levels have been shown to increase the risk of ischemic heart disease for pre- and postmenopausal women.[14] The Multi-ethnic Study of Atherosclerosis found that higher endogenous testosterone levels in postmenopausal women were significantly associated with an elevated risk for cardiovascular disease and coronary artery disease (CAD).[15] In this study, women with elevated free testosterone levels showed greater progression of CAD.[16] In contrast, Zhao et al concluded that lower endogenous androgen levels were associated with heart failure progression in postmenopausal women.[17] The Rotterdam Study showed no association between high androgen levels and cardiovascular disease in postmenopausal patients with polycystic ovary syndrome.[18] Similarly, van Staa et al, utilizing 2 UK research databases, concluded that there was no significant increase in risk of cardiovascular events or breast neoplasm among women with TTh.[6] Clearly, highly variable results continue to limit TTh utilization. Hypotheses regarding differential rates of MACE in pre- and postmenopausal women must consider physiologic, social, and environmental factors. Changes to lipid composition following menopause may largely contribute to increased risk of MACE.[19] However, the underlying pathophysiology is unresolved. As such, further research must be undertaken to elucidate not only the risk of MACE based on menopausal status but the contributing mechanisms that influence potential outcomes.

Our findings show that TTh does not result in an increased risk for MACE in postmenopausal women and may be used as a safe treatment option for HSDD in this population. These results support the recommendation from a group of experts through the International Society for the Study of Women's Sexual Health, although the study acknowledged the need for more long-term studies.[3] The study quoted limited data on the risk of myocardial infarction or death in regard to the cardiovascular effects of TTh.

The pathophysiology of the effect of androgens on cardiovascular health in women is not completely understood. A randomized controlled trial found that women with congestive heart failure receiving testosterone experience improved functional effects, such as peak oxygen consumption and muscle strength.[20] Testosterone has also been shown to decrease insulin resistance, which may subsequently protect against MACE.[20,21] In addition, women with higher testosterone levels were found to have increased brachial flow-mediated dilation.[22] Multiple studies have shown that testosterone increases production of anti-inflammatory cytokines while decreasing production of proinflammatory cytokines.[23] While most of these studies were conducted with older men with CAD, one study that included postmenopausal women found that testosterone reduced macrophage expression of multiple proinflammatory cytokines.[24] We therefore postulate a multifactorial mechanism contributing to the protective effect of testosterone on cardiovascular health in postmenopausal women.

TTh and breast cancer

Currently, there is inconclusive and contrasting evidence on the association between TTh and breast cancer. Our results demonstrated TTh to be protective against breast cancer across age groups, especially among postmenopausal women.

In contrast, a study utilizing the UK Biobank showed a significant association between elevated testosterone levels and breast cancer in postmenopausal women.[25] In another study, estrogen and testosterone usage was associated with a modestly increased risk of breast cancer in postmenopausal women.[26] However, many studies have shown the protective effects of TTh on breast cancer, with testosterone and testosterone/estradiol pellet implants significantly decreasing the risk of breast cancer in pre- and postmenopausal women.[27-29] A recent systematic review found no increased risk of breast cancer in postmenopausal women treated with transdermal testosterone for HSDD.[30] Testosterone has also been shown to decrease mammographic breast density in women, recognized as a risk factor for breast cancer.[31]

It is hypothesized that testosterone exerts a protective effect on breast cancer via its antiproliferative and anti-inflammatory characteristics. However, testosterone can be aromatized to estradiol, which is proliferative in hormone receptor–positive breast cancer.[27] While several studies have demonstrated an association with testosterone and breast cancer, the obesity–insulin resistance–testosterone connection must be considered in the pathophysiology of breast cancer. Obesity and insulin resistance are proinflammatory and often lead to elevated testosterone levels while increasing aromatase levels, leading to increased estrogen that can contribute to breast cancer development.[27] Our study propensity matched for obesity and insulin resistance. Moreover, testosterone has been shown to decrease insulin resistance, which may protect against breast cancer by reducing aromatase levels.[21]

The TriNetX database presents inherent limitations to this study, including deidentification for patient anonymity, the lack of available testosterone dosage, the initial indication for testosterone, and whether the medication was taken. Furthermore, our findings pertaining to breast cancer are limited by the lack of information on aromatase inhibitor therapy use and tumor burden. Examining outcomes within the 1-month to 3-year time frame after therapy initiation also introduces a limitation, as we cannot definitively exclude other factors contributing to MACE that may have occurred during this interval. Furthermore, the absence of information on current hypertension treatments, statin regimens, or aspirin therapy for individual patients poses a challenge, given their significant roles in the comprehensive calculation of cardiovascular risk. However, this study has many strengths. The TriNetX Diamond Network allows for significant generalizability on a national level by encompassing >1.8 million providers covering 99% of US health care plans. Furthermore, the database can capture complete health information by linking patient identifiers from participating health care organizations to pharmaceutical data, insurance claims, and EHRs, with >88% of women having >36 months of follow-up data available.

Conclusions

In this large claims-based analysis, we demonstrated that systemic TTh in women is not associated with an increased risk of MACE and may be protective against breast cancer. Our results contribute to safety data on TTh in women, which are needed to enable physicians to provide appropriate therapy to women with sexual dysfunction. It should be noted that the 36-month period used for analysis of clinical outcomes is short, particularly in the context of breast cancer development. However, this analysis provides a robust framework for further translational studies to examine variables with other biologic mechanisms that contribute to clinical outcomes of TTh.

Funding

None declared.

Conflicts of interest

None declared.

Data availability

Data regarding any of the participants in the study has not been previously published. Available data will be made available to the editors of the journal for review or query upon request.

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