THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH

ENDOCRINE

Testosterone Therapy and Risk of Acute Myocardial Infarction in Hypogonadal Men: An Administrative Health Care Claims Study

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ABSTRACT

Background: There are some ongoing debates on the potential link between testosterone therapy (TT) and risk of acute myocardial infarction (MI).

Aim: To investigate the association between acute MI and TT use compared with non-use in men having documented hypogonadism (diagnostic *International Classification of Diseases, Ninth Revision* codes 257.2, 257.8, 257.9, 758.7) in patient claims records.

Methods: This retrospective cohort study used a real-world US-based administrative health care claims database (MarketScan 2004–2013; Truven Health Analytics, Ann Arbor, MI, USA) to compare MI rates between TT-treated men and a cohort of untreated hypogonadal men matched by a calendar time-specific propensity score. Subgroup analyses were performed by route of administration, age, and prior cardiovascular disease (CVD).

Outcomes: Incidence rates of MI (per 1,000 person-years) and hazard ratio.

Results: After 1:1 calendar time-specific propensity score matching, 207,176 TT-treated men and 207,176 untreated hypogonadal men were included in the analysis (mean age = 51.8 years). Incidence rates of MI were 4.20 (95% CI = 3.87–4.52) in the TT-treated cohort and 4.67 (95% CI = 4.43–4.90) in the untreated hypogonadal cohort. Cox regression model showed no significant association between TT use and MI when comparing TT-treated with untreated hypogonadal men overall (hazard ratio = 0.99, 95% CI = 0.89–1.09), by age, or by prior CVD. A significant association was observed when comparing a subgroup of injectable (short- and long-acting combined) TT users with untreated hypogonadal men (hazard ratio = 1.55, 95% CI = 1.24–1.93).

Clinical Implication: In this study, there was no association between TT (overall) and risk of acute MI.

Strengths and Limitations: Strengths included the use of a comprehensive real-world database, sophisticated matching based on calendar blocks of 6 months to decrease potential bias in this observational study, carefully chosen index dates for the untreated cohort to avoid immortal time bias, and implemented sensitivity analysis to further investigate the findings (stratification by administration route, age, and prior CVD). Key limitations included no information about adherence, hypogonadism condition based solely on diagnosis (no information on clinical symptoms or testosterone levels), lack of information on disease severity, inability to capture diagnoses, medical procedures, and medicine dispensing if corresponding billing codes were not generated and findings could contain biases or fail to generalize well to other populations.

Conclusion: This large, retrospective, real-world observational study showed no significant association between TT use and acute MI when comparing TT-treated with untreated hypogonadal men overall, by age, or by prior CVD; the suggested association between injectable TT and acute MI deserves further investigation. **Li H, Mitchell L, Zhang X, et al. Testosterone Therapy and Risk of Acute Myocardial Infarction in Hypogonadal Men: An Administrative Health Care Claims Study. J Sex Med 2017;14:1307–1317.**

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Key Words: Myocardial Infarction; Testosterone Therapy; Hypogonadism

Received March 3, 2017. Accepted September 16, 2017.

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Trial Registration: EU PAS, number ENCEPP/SDPP/9151.

The findings of this study were presented in part at the 32nd International Society of Pharmacoepidemiology; Dublin, Ireland; August 25–28, 2016.

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https://doi.org/10.1016/j.jsxm.2017.09.010

INTRODUCTION

The incidence of low serum testosterone in men increases with age and is associated with cardiovascular (CV) risk factors such as hyperglycemia, abdominal obesity, insulin resistance, adverse lipid profiles, and hypertension.[1] Studies have shown that men with low total or free serum testosterone levels are at increased risk for coronary artery disease, more severe coronary artery disease, and potentially fatal CV events.[2–5]

Recent observational studies, systematic reviews and meta-analyses, and commentaries have cited conflicting findings on whether exogenous testosterone therapy (TT) use provides CV disease (CVD) protection including decreased CV-related mortality,[6–10] shows neutral net findings of TT on CVD risk,[11–19] or increases the risk of acute myocardial infarction (MI), mortality, or risk factors associated with CVD.[20–26] For example, studies have shown a decrease in risk or no increased risk when TT users with normalized serum testosterone levels are compared with TT-treated men without normalized testosterone levels.[6,7,11] Other studies have shown an increased risk of CV-related adverse events in patients treated with TT vs placebo or phosphodiesterase type 5 inhibitors (PDE5is).[22,24,25] However, the article by Vigen et al[24] has been widely criticized by Traish et al[27] for multiple reasons including their misreporting of the absolute rate of CV events after TT and data errors. The inappropriateness of comparing MI risk between TT and PDE5i users[22] is another concern because PDE5is were used mostly by patients with healthy heart conditions.[28]

The aim of the study was to assess the association between TT use and acute MI in a real-world clinical setting.

METHODS

Study Design

This retrospective cohort analysis used the 2004 to 2013 Truven Health Analytics (Ann Arbor, MI, USA) MarketScan database, which includes individual-level, de-identified, health care claims information (diagnoses, procedures, and prescriptions) from health plans and Medicare Part D and Medicaid programs. Specifically, the database includes information for employees, dependents, and retirees with commercial or Medicare insurance whose employers license health care data to Truven Health Analytics. A new-user design (ie, men newly exposed to TT) was used.[29] This study was designed to provide information to address a public health concern regarding TT use in the real-world setting. Hypogonadism is the only indication for TT; a diagnosis of hypogonadism was not an inclusion criterion for the TT-treated cohort because real-world TT users at the population level are treated for hypogonadism. Because previous literature has indicated that a low baseline testosterone level is associated with an increased risk of CV outcomes,[1–5] to adjust for confounding by indication, this study used men with hypogonadism who did not receive TT treatment as a comparator group, and statistical methods were applied to balance the baseline characteristics and CV risk factors of the 2 cohorts.

Study Population

The study population included men at least 18 years old who received a new prescription for TT or had a diagnosis of hypogonadism based only on claims codes (ie, *International Classification of Diseases, Ninth Revision* [ICD-9] codes 257.2, 257.8, 257.9, 758.7). During the baseline period (the year before the index date), TT-treated and untreated men had not received TT. All men had at least 365 days of continuous enrollment in a health plan before the index date, with continuous enrollment defined as no enrollment gap longer than 31 consecutive days. Subjects were excluded if they were women or of dual sex, received their first prescriptions of TT and a PDE5i concomitantly (±3 days), or had a diagnosis of pulmonary arterial hypertension.

Cohort Identification and Calendar Time-Specific Propensity Score Matching

Calendar time-specific propensity score (CTPS) matching was used to adjust for potential changes in patterns of standard care of hypogonadism over time and to avoid immortal time bias.[30] Briefly, the CTPS for each patient was defined by the predicted probability of TT initiation given the patient's measurable baseline characteristics.[31] The CTPS was constructed at discrete 6-month periods of calendar time, and TT-treated men were matched 1:1 with untreated hypogonadal men using the estimated CTPS. The TT-treated cohort included men who received at least 1 new prescription for a testosterone product after the baseline period. The untreated cohort included men who had a diagnostic code for hypogonadism but did not receive a TT prescription before the calendar block. By design, untreated patients who initiated TT later would have been included in the analysis but censored at the prescription date.

TT-treated and untreated cohorts were balanced for relevant baseline characteristics, including demographic characteristics, comorbid diagnoses, prior CVD diagnoses or procedures, concomitant medications, and health care use, which were assessed by standardized differences.[32,33] These covariates were selected a priori based on the plausibility of having an association with risk for acute MI and their availability in the MarketScan databases. Any imbalanced baseline characteristics were included in the statistical model to be adjusted further.

Baseline, Index Date, and Follow-Up

The index date for TT-treated patients was identified as first prescription dispensing of TT. The index date for untreated patients was based on the equal probability of them receiving a TT prescription, which was the date of hypogonadism diagnosis during the first 6-month calendar block (if they were matched initially) or the randomly assigned date of any clinical or hospital visit within the subsequent 6-month calendar block (ie, if the patient was not matched initially and rolled over to the subsequent 6-month calendar block and remained untreated).[34]

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