Testosterone Therapy and Risk of Myocardial Infarction: A Pharmacoepidemiologic Study

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BACKGROUND Recent studies have provided conflicting and controversial results about the risk of cardiovascular events, including myocardial infarction (MI), with testosterone replacement therapy (TRT). The potential adverse effects of different TRT formulations and duration of therapy on MI risk are unknown.

METHODS We performed a case-control study within a cohort of 934,283 men aged 45–80 from the IMS LifeLink Health Plan Claims Database. For each case of MI, four controls were identified using density-based sampling. Rate ratios (RRs) were computed for current and past TRT users. As a sensitivity analysis, the risk of MI before and after the start of a first-time TRT prescription in the same patient was also computed.

RESULTS We identified 30,066 MI cases and 120,264 corresponding controls. Current use of TRT was not associated with an increased risk of MI (RR 1.01, 95% confidence interval [CI] 0.89–1.16); first-time users did show an increased risk (RR 1.41, 95% CI 1.06–1.87; number needed to harm 305). There was no association between MI and past TRT users and no differences among the different formulations. The RRs for current use and first-time use of TRT in men with a previous history of coronary artery disease were 1.05 (95% CI 0.79–1.41) and 1.78 (95% CI 0.93–3.40), respectively.

CONCLUSION In this large observational study, an association between MI and past or current TRT use was not found. However, a statistically significant association was observed between first-time TRT exposure and MI, although the absolute risk was low.

KEY WORDS testosterone therapies, myocardial infarction, case-control study, drug safety.

Testosterone replacement therapy (TRT) has grown increasingly popular over the past decade. From 2001 to 2011, prescriptions for men aged 40 years or older have tripled,1 with sales in the United States reaching $1.6 billion in 2011.2 Part of this growth is attributed to the popularity and direct-to-consumer marketing of new testosterone formulations such as topical gels and solutions.3–5 Moreover, recent evidence suggests that another component of the growth may be expanded and/or inappropriate prescribing, especially in the United States and United Kingdom.1, 6 For example, among men newly prescribed TRT in the United Kingdom, 54% did
not have their testosterone level measured in the preceding 180 days.7

A large body of literature suggests an association between low testosterone levels in men and increased risk of cardiovascular adverse events and mortality.8–13 Although TRT in hypogonadal men would therefore appear to be rational,14 it remains unproved and highly controversial. In 2009, a small randomized trial15 designed to evaluate the effect of TRT on frailty in older men was terminated early because of a higher number of cardiovascular-related adverse events in the testosterone arm compared with placebo. A meta-analysis of 27 randomized placebo-controlled trials over 12 weeks in length found an increased risk of cardiovascular-related events with testosterone therapy.16 Conversely, a widely quoted study14 of 1031 male veterans with low total testosterone (≤ 250 ng/dl) found that TRT was associated with a decreased risk of death. In the past few years, more conflicting studies have been published, including two large database studies suggesting that TRT use was associated with increased cardiovascular risks.17, 18 Unfortunately, concerns about methods used in these studies remain and have not been fully addressed.

Given the increasing use of TRT, possible inappropriate prescribing with uncertain benefit, and conflicting safety signals, additional studies are clearly required. Therefore, we conducted a large pharmacoepidemiologic study designed to address the cardiovascular risk of TRT, particularly as a function of treatment duration and type of drug formulation.

Methods

The IMS LifeLink health plan claims database19, 20 was the main data source. LifeLink data contain physician visits, hospitalizations, procedures, and prescription drug data including dose, quantity of medication dispensed, and number of prescribed days for ~150 million de-identified Americans with fully adjudicated medical claims. The LifeLink data captured a balanced demographic sample from all geographic regions in the United States. LifeLink captured data on 17% of men aged 45–54 years, 13% of men aged 55–64 years, and 8% of men older than 65. Data on men older than 65 years were captured through the Medicare Advantage programs. LifeLink did not capture information on Veterans Affairs beneficiaries. LifeLink captured all inpatient and outpatient diagnoses through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

The database was subject to routine quality checks20 and was used in previous pharmacoepidemiologic studies.19, 21 Cohort entry started with the first prescription drug, physician visit, or hospitalization from 2001 to 2011. Members of the cohort were followed until the occurrence of a study outcome, termination of the insurance claim, or last date of data availability. Men with a previous history of cardiovascular disease were included. We planned a time-matched case-control study, which allowed assessment between time-varying drug exposures and clinical outcomes. This methodology provided similar results as a cohort study using time-dependent Cox regression models.22

Case and Control Selection

The primary outcome was new-onset acute myocardial infarction (MI), defined as a hospitalization occurring after cohort entry with an ICD-9-CM code 410 in the primary or secondary position of the hospital discharge diagnosis. The positive predictive value for this ICD-9 code was between 89% and 97% in similar U.S. administrative claims databases.23, 24 The date of the first MI was deemed the index date. Data on outpatient deaths were not available, which precluded analysis of total cardiovascular mortality.

For each case, a pool of potential controls was identified. To be eligible, controls had to have the same year of birth as the case (± 1 yr), the same calendar year of cohort entry, and the same length of follow-up time. From the eligible pool of controls, four were randomly selected and matched to each case to form a risk set. Each control could have been used more than once for each risk set and could possibly become a future case. This incident density sampling method has been shown to produce incident rate ratios (RRs).22

Exposure Definitions

Testosterone prescriptions were classified by the type of formulation: gels (including solutions), topical patches, injections, or other route of delivery (oral or buccal). Men who filled at least one prescription for TRT within 1 year before the index date were considered testosterone users. The reference nonexposed group was defined as men with no TRT use in the year
before the index date. Current users were defined as men whose last TRT prescription was within 90 days before the index date (0–90 days); otherwise, testosterone users were classified as past users (91–364). We chose the 90-day risk window because it has been used previously in both observational and randomized studies. Because the risk of adverse drug reactions may be higher for first-time users of drug therapies, we prospectively stratified current users to first-time users (men who received their first TRT prescription in the 90-day window) or prevalent users (men who received a prescription before the 90-day window). This new-user design has been shown to reduce potential survivor and adherence bias in other studies.

Statistical Analysis and Covariate Adjustment

Causal diagrams were developed to identify true confounding variables and avoid overadjustment bias that may result from adjustment for intermediate variables or colliders (variables that may introduce selection bias). Variables that were risk factors for the outcome, but not for the exposure, were not included in the model. We used conditional logistic regression to adjust for stroke, diabetes, deep vein thrombosis, peripheral vascular disease, chronic renal failure, cancer, and use of statins or antiplatelet drugs. As a quality measure, we also quantified the risk of MI with finasteride, a drug often prescribed for men that has not been shown to be associated with a risk of MI. Finasteride use was defined similar to TRTs. In order to examine the risk of MI in men with a previous history of coronary artery disease, we performed a subgroup analysis in this group by identifying those who had a history of coronary artery disease (ICD-9 codes 411–414) within 1 year before the index date. In order to estimate absolute risk when appropriate, we computed a number needed to harm (NNH) for both the overall and subgroup analyses. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., SAS 9.1. Cary, NC: SAS Institute Inc., 2002-2004.)

Sensitivity Analysis

Because men with low testosterone levels may inherently have a higher risk of MI, we conducted an additional analysis to control for between-patient confounding. We compared the incident rate of MI among new users of TRT in the 90 days after they filled the first TRT dispensation with the rate of MI in the 90-day period before this dispensation date in the same patient. More specifically, each subject was followed from the date of their first TRT prescription to the first MI or end of the 90-day risk period, whichever came first. Unexposed person-time was computed in the same fashion for the 90-day period before the dispensation date. The RRs were computed for exposed and unexposed incident rates using a stratified Cox regression analysis. Thus, this sensitivity analysis eliminates between-patient confounding that may have incurred due to between-subject variability in testosterone levels or other unmeasured confounders.

Results

We identified 30,066 cases with MI and 120,264 corresponding controls. The mean age for the cases and controls was 70.4 (± 13) years with a mean follow-up of 2.8 (± 2.2) years. Cases were more likely to have been previously diagnosed with stroke, peripheral vascular disease, cancer, or chronic renal failure (Table 1). Among the 515 cases who had used at least one TRT in the year before the index date, testosterone gel was the most common formulation used (n=285), followed by injections (n=133), patch (n=52), and other (n=11). Thirty-four men used more than one type of testosterone product. Current use of TRTs was not associated with an increase in the risk of MI (RR 1.01, 95% CI 0.89–1.16) (Table 2). Current first-time users showed a statistically significant association with MI (RR 1.41, 95% CI 1.06–1.87), whereas prevalent users did not (RR 0.94, 95% CI 0.81–1.04). The RR for past users of any TRT was also not increased (RR 1.04, 95% CI 0.89–1.21). In men with a previous history of coronary artery disease, the TRT RRs for any current use and first-time use were 1.05 (95% CI 0.79–1.41) and 1.78 (95% CI 0.93–3.40), respectively.

Among the different formulations of TRTs, the RRs for first-time users of topical gels was 1.49 (95% CI 1.02–2.18) and reached statistical significance as it contributed to greater than 55% of TRT users. Aside from users of testosterone patches, other formulations also showed a consistent pattern of association between MI and first-time use, although this did not reach statistical significance, possibly due to insufficient power.

The NNH for first-time users based on an annual rate of 8 MIs/1000 person-years among...
nonusers of TRTs in the entire cohort was 305. The results of the sensitivity analysis where the risk of MI was examined before and after first-time TRT use showed similar results to the primary case-control analysis with an incident RR of 1.44 (95% CI 0.99–2.09). Also, in the finasteride control group, no increase in the risk of MI was seen with first-time users (RR 0.97, 95% CI 0.82–1.15).

**Discussion**

In this large retrospective observational study of older men, we observed no association...
between risk of MI and all current or past use of TRTs. However, our study did demonstrate a 41% increase in the risk of MI with current first-time users. These apparently discordant findings between first-time and repeat current users may potentially be explained by a depletion of susceptibles after the initial TRT prescription. Fortunately, in this population, the absolute risk for first-time TRT users was small, resulting in an overall large NNH of 305. Consistent findings were also observed in the population restricted to men with established coronary artery disease, although the increased risk for first-time users in this subcohort did not reach statistical significance, perhaps due to a lack of power due to the smaller sample size (Table 3).

Two recent epidemiologic studies\textsuperscript{17, 18} suggested an increase in the risk of cardiovascular disease with TRT. In the first study,\textsuperscript{17} the risk of a composite end point of all-cause mortality, MI, or ischemic stroke in men with low testosterone (< 300 ng/dl) who underwent coronary angiography after having filled a prescription for TRT was examined. That study found an absolute higher rate of events after 3 years in those not treated with TRT compared with those who were treated (21.2% vs 10.1%). However, after multivariable analysis with stabilized inverse probability weighting, TRT became associated with an increased risk of adverse events (hazard ratio 1.29, 95% CI 1.04–1.58). In the second study,\textsuperscript{18} the rates of MI among new TRT and phosphodiesterase type 5 inhibitor (PDE5i) users were compared. They reported an RR for TRT compared with PDE5i therapy of 1.90 (95% CI 1.04–3.49), with a higher risk among men with a prior history of cardiovascular disease (RR 2.90, 95% CI 1.49–5.62).

These studies have several limitations. The first study\textsuperscript{17} has been challenged due to ambiguous cohort entry criteria and exclusion criteria.\textsuperscript{30} In the second study,\textsuperscript{18} the use of PDE5i as a control group is perhaps problematic as the cardiovascular risk profile may have been different from that of TRT users, although a within-subject analysis did demonstrate an increase in the risk of MI with TRT (RR 1.36, 95% CI 1.03–1.81). However, this study had a short follow-up and contained only a small number of events, so the overall robustness of the results is limited. Finally, both of these studies looked at the risk of TRT in men only after a single prescription and neither examined the risk with different types of TRT formulations.

Our study has several strengths. First, due to the large sample size, it includes the largest number of cases of MI with TRT exposure (n=515). Second, our analyses controlled for the most common potential confounders and examined the time dependency of TRT risk patterns. Third, our before and after sensitivity analyses, which effectively removed between-subject variability, provided consistent results. Fourth, the confirmed neutral findings for our control drug, finasteride, provide some additional quality assurance. Fifth, our study had adequate statistical power to potentially show an increase in the risk of MI, if it existed, with gel formulations, the most common formulations of TRTs used in North America. Finally, the observed trend for increased MI risk in first-time users with previous history of cardiovascular disease is in concordance with two previously published epidemiologic studies.\textsuperscript{17, 18}

As with all pharmacoepidemiologic studies, our study is not without limitations. While our outcome of MI is of sufficient severity that it is probably well measured by a hospitalization, there is not without limitations. While our outcome of MI is of sufficient severity that it is probably well measured by a hospitalization, there is

| Table 3. Crude and Adjusted Rate Ratios for the Risk of Nonfatal Myocardial Infarction with Use of Testosterone Among Subjects with Prior History of Cardiac Events in the Year before the Index Date |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Cases (n=9446)  | Controls (n=14,638) | Crude Rate Ratio (95% CI) |
| No testosterone use\textsuperscript{c} | 9176            | 14,188           | 1 (Reference)           |
| Any testosterone use\textsuperscript{c} | 270             | 450              | 1.03 (0.83–1.28)        |
| Current use                     | 147             | 237              | 0.97 (0.79–1.14)        |
| First-time user                 | 36              | 40               | 1.60 (0.93–3.40)        |
| Prevalent user                  | 111             | 197              | 0.87 (0.67–1.28)        |
| Past use                        | 123             | 213              | 1.09 (0.74–1.37)        |

\textsuperscript{a}Adjusted for age, stroke, diabetes, deep venous thrombosis, peripheral vascular disease, chronic renal failure, cancer, statin use, and antiplatelet agent use.

\textsuperscript{b}During the year before the index date.

\textsuperscript{c}Use of at least 1 prescription at any time before the index date.
uncertainty around the exposure measure and the etiologic risk window. To be consistent with previous studies, we defined a 90-day period from the last prescription as being currently exposed, but it is unknown if this represents the true etiologic window. Moreover, we only have information on drug dispensed and not actual exposure status. This may lead to nondifferential exposure misclassification, which may underestimate the true risk with TRT. There is also the possibility that unmeasured confounding may exist. For example, we did not have access to information on ethnicity, socioeconomic status, or lifestyle factors in our data. However, the within-patient sensitivity analysis would have controlled for the majority of these confounders and provided consistent results with our primary analysis. For both the main analysis and the sensitivity analysis, we did not have mortality data and could not exclude the possibility of an out-of-hospital death. However, such a bias, if present, would underestimate the risk association. Also, we did not have detailed information on the indication or appropriateness of TRT prescriptions, including serum testosterone levels before or during treatment. Therefore, we cannot draw any generalizable conclusions regarding the safety of testosterone therapy in men with properly diagnosed hypogonadism.

While not all the results of our study are concordant with the previous studies, they do raise a potential MI safety signal among first-time TRT-exposed men. Given the higher baseline risk in patients with preestablished cardiovascular disease, this safety signal is potentially most concerning in this group. This was a generally consistent finding, regardless of the type of testosterone formulation. Given this potential safety signal and the absence of established benefit for off-label use, TRT should be reserved only for men with clinically symptomatic and biochemically proven hypogonadism as recommended by current guidelines with appropriate monitoring for adverse events. Until further, more definitive studies are completed and published, it would appear prudent, in the spirit of fully informed consent, to advise all new TRT users to weigh the benefits of therapy against a small potential increase in the risk of MI.

Conflict of Interest

None of the authors have any conflicts of interest to declare. Dr. Brophy receives salary and operating support from the FRQS (Fonds de recherche du Québec-Santé), a nonprofit provincial funding agency. The funding agency had no influence on the choice of study topic, the analyses, or the conclusions. Dr. Carleton’s research is supported by national granting agencies such as the Canadian Institutes of Health Research (CIHR), Canada Foundation for Innovation (CFI), Genome British Columbia, and the Child & Family Research Institute.

References


