PASS Information

Title	**Testosterone Replacement Therapy (TRT) and Risk of Acute Myocardial Infarction (AMI): An Administrative Healthcare Claims Study**
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Product reference:	DE/H/3320/001; LY900011
Procedure number:	EMEA/H/A-31/1396
Marketing authorisation holder(s)	Eli Lilly and Company (Lilly)
Joint PASS	No
Research question and objectives	The proposed study is to further investigate whether there is an association between TRT and AMI. Specifically the objectives are as following: **Primary objective**: To evaluate the incidence of AMI among patients treated with TRT (any testosterone prescription and major routes of testosterone administration) relative to propensity score matched untreated hypogonal patients. **Secondary objective**: To evaluate the incidence of AMI among patients treated with TRT (any testosterone prescription) relative to propensity score matched PDE5i treated patients.
Country(-ies) of study	United States (US)
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2. List of Abbreviations

Term	Definition
AHA	American Heart Association
AMI	Acute myocardial infarction
CI	Confidence interval
CTPS	Calendar time-specific propensity score
CV	Cardiovascular
CVD	Cardiovascular disease
ED	Erectile dysfunction
EU	European
HIPAA	Health Insurance Portability and Accountability Act
ICD-9	International Classification of Diseases, Ninth Revision (ICD 9) codes
MetS	Metabolic syndrome
PAH	Pulmonary arterial hypertension
PDE5i	Phosphodiesterase type 5 inhibitor
THAM	Truven Health Analytics MarketScan®
TRT	Testosterone replacement therapy
UK	United Kingdom
US	United States

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4. Abstract

Title: Testosterone Replacement Therapy (TRT) and Risk of Acute Myocardial Infarction (AMI): An Administrative Healthcare Claims Study **Version:** 1.0

Author: Hu Li, PhD, M.B.B.S., Eli Lilly and Company

Rationale and background: Low serum testosterone, also called hypogonadism, has previously been associated with cardiovascular risk factors such as hyperglycaemia, abdominal obesity, insulin resistance, adverse lipid profiles, and hypertension. Treatment of hypogonadism with testosterone replacement therapy (TRT) in the United States (US) has increased substantially. The two observational studies that reported a higher risk of acute myocardial infarction (AMI) in patients treated with TRT had limitations due to study design concerns. Thus, the association between TRT and AMI risk is not clearly understood. The proposed study will further investigate the risk of AMI among patients treated with TRT in comparison to patients who are untreated with TRT or treated with a phosphodiesterase type 5 inhibitor (PDE5i).

Research question and objectives: This study proposes to investigate the association between TRT and AMI. The specific objectives are the following:

> **Primary objective:** To evaluate the incidence of AMI among patients treated with TRT (any testosterone prescription and major routes of testosterone prescriptions) relative to propensity score matched untreated hypogonal patients.
>
> **Secondary objectives:** To evaluate the incidence of AMI among patients treated with TRT relative to propensity score matched PDE5i treated patients.

Study design: The proposed retrospective cohort study will utilize medical claims, pharmacy data, and enrollment information from administrative healthcare claims records in the US to compare the crude incidence rate of AMI and adjusted relative risk between the following comparator cohorts:

- One comparison between TRT treated patients versus untreated hypogonadal patients will be assessed on an as-treated basis; and
- The other comparison is between TRT treated patients versus PDE5i treated patients, using an intention-to-treat basis.

Population: The source population will consist of patients with at least 12 months (365 days) of continuous enrollment in the health plan prior to index date. The medical claims will contain at least 12 months of data proceeding cohort entry to characterize baseline variables for study subjects.

Inclusion criteria: Males aged 18 years or older will be eligible for inclusion if they meet any one of the following criteria during the years 2004 to 2013:

- One or more hypogonadal diagnosis;

- One or more prescriptions of TRT; or
- One or more prescription of PDE5i.

Exclusion criteria: Subjects will be excluded from the study if they meet the following criteria:

- Dual gender;
- TRT or PDE5i exposure during baseline (365 days prior to the index date);
- Continuous enrollment in the health plan (medical and prescription) for less than 12 months prior to index date. Continuous enrollment will be defined as no enrollment gap exceeding 31 consecutive days at any given time in the course of the study;
- Received their first prescription of both PDE5i and TRT concomitantly (±3 days); or
- Have a diagnosis of pulmonary arterial hypertension (PAH).

The index date will be defined as the date of the first dispensing of study drug for the TRT- or PDE5i-treated cohorts and as the date of first hypogonadism diagnosis (or a randomly assigned date) for the untreated cohort.

Follow-up will be terminated at the time of the first occurrence of AMI, death from any cause, a gap (≥30 days) in continuous enrollment, end of data availability, or any change in exposure status (including the end of exposure due to discontinuation or a gap ≥90 days in TRT use).

Variables: The exposure variable for this study is exposure to testosterone; any exposure to testosterone for the primary analysis and exposure to different testosterone formulations, for the secondary analysis. The outcome variable for this study is the first AMI occurring during the eligible follow-up time. *A priori* study covariates were selected on the basis of availability in the database and plausibility of association with AMI risk; they include demographics, medical service utilization, comorbidities, concurrent medications, and prior cardiovascular disease.

Data sources: The present study will utilize a US-based administrative healthcare claims database: Truven Health MarketScan ® (THAM) Database.

Study size: Assuming an incidence rate of AMI in the reference (untreated) group of 0.45% and a hazard ratio of 1.5 with 1:1 weighting between treatment groups, and a two-sided α of 0.05, 80% power to detect statistically significant differences will be obtained with 34,908 patients.

Data analysis: AMI risk between propensity score matched TRT patients and both untreated patients (primary analysis) and PDE5i treated patients (secondary analysis) will be assessed using a Cox proportional hazard model. The Cox regression model will include treatment, age at index, index date, risk factors, concomitant medications, and any baseline characteristics that did not reach balance between the 2 cohorts after propensity score matching. Poisson regression, with adjustment for the above variables, will also be utilized. Sensitivity analyses may be performed on a *post hoc* basis.

A secondary analysis will be performed to evaluate the association between AMI and route of testosterone administration for the comparison between treated versus untreated patients. Calendar specific propensity score matching will be used to account for selection bias.

Milestones: Expected timing for major milestones in this study are the following: start of data collection, 06 Apr 15; end of data collection, 03 Jul 15; Registration in the EU PAS register, 06 Apr 15; final report of study results, 18 Dec 15.

5. Amendments and updates

Not applicable

6. Milestones

Milestone	Planned date
Start of data collection	06 Apr 15
End of data collection	03 Jul 15
Registration in the EU PAS register	06 Apr 15
Final report of study results	18 Dec 15

7. Rationale and background

7.1. Rationale

The topic of testosterone and cardiovascular (CV) events has been an area of exploration for many decades. Low endogenous testosterone levels are consistently associated with increased CV risk and mortality (1, 2). To date, there are no published, definitive CV/acute myocardial infarction (AMI) outcome observational studies or clinical trials. Studies to date evaluating TRT have yielded inconclusive results with respect to AMI because they are often not adequately designed or powered to address the question.

Two retrospective observational studies reporting a higher risk of mortality or CV events among groups of men prescribed testosterone therapy were recently published (3, 4). Compared to PDE5i-treatment, Finkle et al. (4) found evidence of a 2-fold increase in AMI risk during the first 90 days of TRT in elderly men and those with pre-existing cardiovascular disease (CVD). Vigen et al. (3) reported a 30% increase of a composite outcome of adverse events including all-cause mortality, AMI, and ischemic stroke in patients who had a coronary angiography procedure and were treated with TRT. Neither Vigen nor Finkle took into account the testosterone formulation, the route of administration or baseline testosterone levels. Two other retrospective observational studies reported no elevated risk of mortality and/or AMI among men prescribed testosterone therapy (5, 6).

The lack of consistent clinical trial data and clinical practice information surrounding this safety topic justifies the need for further investigating the potential risk of AMI in testosterone-treated and untreated hypogonadal populations. The proposed study will further clarify the strength of previous research and add to our understanding of TRT use and AMI by further investigating the risk of AMI among patients treated with TRT in comparison to patients who are untreated with TRT or treated with a PDE5i.

7.2. Background

7.2.1. Hypogonadism

Hypogonadism in men, characterized by a reduced concentration of serum testosterone, causes a constellation of signs and symptoms that may include decreased libido, erectile dysfunction, decreased volume of ejaculate, loss of body and facial hair, weakness, decreased bone density, decreased lean body mass, increased body fat, fatigue, and anemia (7). Studies have shown an increased risk of certain comorbidities among aging hypogonadal men, including a higher prevalence of depression (8), osteoporosis (9), CVD morbidity and mortality (10, 11) as well as diabetes, hypertension, hyperlipidemia, obesity, asthma/chronic obstructive pulmonary disease and prostate disease (1).

The incidence rate of hypogonadism in the US is 12.3 cases per 1,000 person-years (12) and11.7 per 1,000 person-years in Germany (13). Recently, the prevalence of hypogonadism was determined to be 10.4% among US men aged 19-40 and 40.3% among US men aged 65 and older, while the prevalence among European (EU) men aged 40-79 was 23.5% (14).

Low serum testosterone levels have previously been associated with CV risk factors such as hyperglycaemia, abdominal obesity, insulin resistance, adverse lipid profiles, and hypertension (15). There also appears to be a strong association between hypogonadism and metabolic syndrome (MetS), the components of which are also risk factors for CVD. Clinically, low testosterone may contribute to the onset and/or progression of CVD by altering endothelial function, lipid profiles, inflammatory responses, vascular smooth muscle reactivity and other critical cellular signaling pathways in the vascular beds. Conversely, restoring testosterone levels to the eugonadal range positively affects MetS-related risk factors for AMI, stroke and mortality (16). Aversa et al. (17) and Isidori et al. (18) also note the negative consequences of untreated hypogonadism such as increased risks for the development of atherosclerosis, AMI, and chronic heart failure.

Treatment of hypogonadism with testosterone supplementation in the US has increased substantially over the past several years, with a 5-fold increase in prescription sales of testosterone products occurring since 1993 (19). Different forms of testosterone are available for administration including injectable, transdermal, buccal, and oral testosterone formulations for clinical use. According to one study, initiation of testosterone treatment from 2000 to 2011 in the US increased from 20.2 cases to 75.7 cases per 10,000 person-years (20). Initiation in the United Kingdom (UK) was less substantial with rates of 3.4 cases to 4.5 cases per 10,000 person-years (20). In both the US and the UK, transdermal gels were the most popular treatment choice by 2013 at a rate of 69.6% among initiators (20).

7.2.2. Erectile dysfunction

Erectile dysfunction (ED) is a common medical disorder characterized by the inability to achieve and/or maintain an erection. Approximately 52% of males between the ages of 40 and 70 years have some degree of ED with incidence increasing with advanced age (21, 22) . The first line of therapy for ED is phosphodiesterase 5 inhibitors (PDE5i). Treatment with a PDE5i promotes vasodilation and may be cardioprotective (23).

The aforementioned study by Finkle et al. (4) assessed the risk of AMI in patients prescribed a PDE5i and found no increased risk during the first 90 days post-PDE5i prescription versus a 1 year pre-prescription period. A preliminary analysis was performed to assess whether patients receiving a PDE5i prescription represent an appropriate comparator cohort for measuring AMI risk (see Annex 10). This analysis found an increase in AMI rate that was comparable in magnitude among both untreated and TRT-treated patients, but was absent in the PDE5i-treated cohort. These results indicate that PDE5i-treated patients are not an ideal comparator cohort. However, to enable a direct comparison with the results of Finkle et al., the present study proposes to utilize a PDE5i-treated control cohort although PDE5i is not believed to be an ideal comparator group.

7.2.3. Acute myocardial infarction

Acute Myocardial infarction is a major component of CVD that carries significant morbidity and mortality. Specifically, AMI (also known as a heart attack) occurs when a portion of the heart musculature is damaged or dies from lack of oxygen. Risk factors for AMI include

hypertension, diabetes, low levels of physical activity, alcohol use, abdominal obesity, poor diet, abnormal lipids, current smoking and psychosocial stress factors (24, 25). The annual incidence of AMI varies between 90 and 312 cases per 100,000 inhabitants across EU countries (26). In the Framingham Offspring cohort, the incidence of AMI in the US was reported to be 8.7% (27) while the prevalence of AMI in the US was reported as 2.9% among adults 20 years of age or older (28).

Acute Myocardial infarction is a critical medical condition with a relatively high mortality rate. According to one estimate from the American Heart Association (AHA), approximately 15% of patients who experience AMI in a given year will die of it (28). It is estimated that, on average, 16.6 years of life are lost due to an AMI (28). Due to the improvement in initial treatment of AMI and the secondary prevention therapies after AMI, the case fatality rate has decreased over time. From 1990 to 1999, in-hospital AMI mortality declined from 11.2% to 9.4%. Among enrollees of the Kaiser Permanente Northern California healthcare delivery system, the age- and sex adjusted 30-day mortality rate for AMI dropped from 10.5% in 1999 to 7.8% in 2008, and the 30-day mortality rate for non-ST segment elevation myocardial infarction dropped from 10.0% in 1999 to 7.6% in 2008 (29).

8. Research question and objectives

To date, there is no robust evidence to support an association between TRT use and AMI. Given limitations of observational studies, replication studies are warranted to provide further evidence. Therefore, the proposed study is to further investigate whether there is an association between TRT use and AMI. The null hypothesis of the study is that there is no increased risk of AMI among patients receiving a TRT prescription compared to either untreated patients or patients receiving a PDE5i prescription. Specifically the objectives are as follows:

Primary objective: To evaluate the incidence of AMI among patients treated with TRT (any testosterone prescription and major routes of testosterone prescriptions) relative to a propensity score matched untreated cohort of diagnosed hypogonal patients.

Secondary objective: To evaluate the incidence of AMI among patients treated with TRT relative to a propensity score matched PDE5i-treated patients.

9. Research methods

9.1. Study design

The proposed study is a retrospective cohort study, utilizing a new user study design, in a real-world evidence setting. Two comparisons will be conducted to evaluate the AMI risk between the TRT-treated cohort versus the untreated cohort, and the TRT-treated cohort versus the PDE5i-treated cohort. The null hypothesis tested in the present study is that there is no increased incidence of AMI among testosterone-treated males, compared to untreated patients or PDE5i-treated patients with balanced baseline risk factors. It will further explore the difference in the AMI incidence by different routes of testosterone administration. To achieve the study objectives the Truven Health Analytics MarketScan® (THAM) databases of administrative healthcare claims (for details refer to Section 9.4.1) will be assessed.

This retrospective cohort, observational study is proposed to utilize medical claims, pharmacy data, and enrolment information from administrative healthcare claims in the US to compare the crude incidence rate of AMI and adjusted hazard ratio and risk ratio among patients treated with any testosterone products compared to two comparator cohorts: 1) hypogonadal patients without testosterone treatment, and 2) PDE5i-treated patients, who are matched to the TRT-treated cohorts on a propensity score estimated from baseline characteristics. The 4 cohorts are defined in section 9.2.2.

The primary comparison is the incidence rate of AMI and adjusted hazard ratio among hypogonadal patients as-treated with any testosterone relative to those propensity score matched non-treated patients. The secondary comparison is the incidence rate of AMI and adjusted hazard ratio among hypogonadal patients treated with TRT relative to those propensity score matched PDE5i-treated patients. Additionally, the primary comparison between TRT treated and untreated analyses will be conducted to evaluate the association between AMI and testosterone exposure by different routes of administration, including topical gel, transdermal patch, injection, and nonspecific testosterone products.

When utilizing secondary administrative healthcare databases, certain strategies must be used to reduce potential biases. In this protocol, we utilize a new user design to reduce selection bias (e.g. missing early symptoms if using prevalent users), which has been used in previous studies. Additionally, time related bias (e.g. immortal time bias or selection bias) will be addressed using calendar-specific propensity score matching, which allows person-time prior to initiation of TRT (for future patients receiving a TRT prescription) to be assigned to untreated patients if they are matched to a treated patient at given time (30). Immortal time bias can occur when cohort entry is hierarchically based on the index date, which corresponds to the exposure status. In the current study, patients with a hypogonadal diagnosis following TRT prescription will be included in the treated cohorts and are ineligible for the untreated cohort (based on the criteria for forming cohorts). Immortal time bias could occur if the time period between diagnosis and prescription is not accounted for appropriately, resulting in an artificial increase in the rate of AMI in the reference group. Though the solution to control for such bias is still under debate,

the proposed calendar-specific propensity score approach is considered more precise compared to the conventional propensity score approach.

9.2. Setting

9.2.1. Study population

The source population will consist of patients with at least **12 months (365 days)** of continuous enrollment in a health plan prior to the index date. In this way, medical claims will contain at least 12 months of data preceding cohort entry to characterize baseline variables for study subjects.

9.2.1.1. Inclusion criteria

Subjects will be eligible for inclusion if they meet the following criteria during the years 2004 to 2013:

- Males aged 18 years or older; and
- One or more of the following conditions:
    - TRT prescription: at least 1 prescription for testosterone products (prespecified approved testosterone products in the United States are listed in Annex 3). They will be patients receiving a new prescription of testosterone treatment therapy who have not received a prescription of these products during the baseline period.
    - PDE5i prescription: at least 1 prescription for PDE5i (prespecified approved PDE5i products in the United States are listed in Annex 4). They will be patients receiving a new PDE5i prescription who have not received a prescription for these products during the baseline period.
    - Hypogonadism diagnosis: at least 1 diagnosis of hypogonadism condition related International Classification of Diseases, Ninth Revision (ICD 9) codes (see Section 9.2.1.3)

9.2.1.2. Exclusion criteria

Subjects will be excluded from the study if they meet any of the following criteria:

- Dual gender;
- Continuous enrollment in a health plan (medical and prescription) for less than 12 months prior to index date. Continuous enrollment will be defined as no enrollment gap exceeding 31 consecutive days at any given time in the course of the study;
- Patients exposed to TRT or PDE5i during the baseline period (365 days prior to index date);
- Received the first prescription of PDE5i and TRT concomitantly (±3 days); or
- Have a diagnosis of PAH.

9.2.1.3. Diagnosis of hypogonadism

The hypogonadal diagnosis will be defined as either a valid diagnostic code or prescription of a studied testosterone product, which meets at least one of the following criteria:

- Prespecified diagnosis ICD 9 codes

ICD 9 Code	*Descriptions*
257.2	Other testicular hypofunction
257.8	Other testicular dysfunction
257.9	Unspecified testicular dysfunction
758.7	Klinefelter's syndrome

9.2.2. Cohort identification

Four separate cohorts will be created using calendar-time-specific propensity score (CTPS) matching to match TRT-treated patients with untreated or PDE5i-treated patients. These cohorts are the following:

- **Primary TRT-Treated Cohort** will be identified within the database as patients who received at least 1 prescription for a testosterone product, and are matched to an untreated patient during the 6-month calendar time block which includes their first prescription. They are patients receiving a new prescription of TRT who had no TRT prescription during the baseline.
- **Untreated Cohort** will be defined within the database as patients who had a diagnostic code for hypogonadism, did not receive any testosterone prescriptions during the 6-month calendar time block during which they were matched to a TRT-treated patient. Treated and untreated cohorts will be balanced with regard to important baseline characteristics using propensity score matching.
- **TRT-treated cohort** in the secondary comparison is similar to the primary TRT-treated cohort, and will be matched to a PDE-5i treated patient during the 6-month calendar time block which includes their first prescription. Compared to the primary TRT-treated cohort, a patient in this cohort will be censored at the time that he initiated PDE5i prescription during the follow-up period.
- **PDE5i-Treated Cohort** will be identified within the database as patients who received at least 1 prescription for PDE5i, and are propensity score matched to a new TRT patient during the 6-month calendar time block which includes their first PDE5i prescription. They are patients receiving a new prescription of PDE5i treatment who do not have any usage during baseline. Phosphodiesterase type 5 inhibitor-treated and TRT-treated cohorts will be balanced with regard to important baseline characteristics using propensity score matching.

Propensity scores are frequently used in observational studies. Propensity scores are normally estimated over the entire study period without consideration of changing patterns of the included

variables over time. The effects of covariates on the probability of receiving treatment are averaged across years. However, it is possible that the probability of receiving an intervention or treatment may change over the observation period. Therefore, CTPS matching will be adopted to allow the effect of each covariate on the propensity for treatment receipt to be non-univariate over time. This method will also provide insight to prescribing variations and barriers to treatment received across the calendar year (31-33).

Using CTPS matching, cohorts will be formed by matching patients according to the propensity scores calculated for a discrete 6-month period of calendar time (ea. 01-Jan-2005 to 30-June-2005), for a discussion of the calculation see Section 9.2.4. Eligible patients who initiated therapy with TRT between the end of 2004 and the end of 2013 will be matched (using propensity score) to eligible patients who did not initiate TRT. Similarly, eligible patients who initiate TRT between the end of 2004 and the end of 2013 will be matched to eligible patients who initiated PDE5i treatment in a separate propensity score model. Matched cohorts will be assembled within 6-month calendar time blocks (18 blocks), and an index date will be assigned to the patients (see Section 9.2.3.1). Untreated patients with no eligible TRT-treated match, and still meet the inclusion/exclusion criteria, will be eligible for matching to TRT-treated patients in the next 6 month calendar time block; and the propensity score will be recalculated to capture any changes occurring since the previous window.

9.2.2.1. Subgroup study cohort

Among the TRT-treated patient population, subgroups will be identified based on the route of administration which are pre-determined for specific products (for details see Annex 3), including the following:

- Transdermal gel
- Transdermal patch
- Injection
- Nonspecific testosterone products

In order to calculate the baseline rate of AMI, patients who experience AMI at baseline will not be excluded from the study population. Because those patients may be at higher risk of recurrence, a subgroup analysis may be performed.

9.2.3. Study cohort follow-up period

9.2.3.1. Start of Follow-up Period

When a patient enters the cohort by a first diagnosis (i.e. hypogonadism) or a new dispensing (i.e. TRT or PDE5i), follow-up begins on the index date. A second dispensing or diagnosis is not required, because doing so could prevent the capture of acute effects that occurred after a single dispensing. The **index date** is defined as:

- TRT treated cohort (both primary and secondary comparisons): the date of first dispensing of TRT;
- PDE5i treated cohort: the date of first dispensing of PDE5i; and

- Untreated cohort: the date of first diagnosis of hypogonadism or, for non-initiators without a match during their initial accrual block, a randomly chosen physician visit within the subsequent cohort accrual block during which they are matched.

Untreated patients with no matches during the initial 6-month window of their index date will still be eligible for inclusion in the study. These patients will be carried over into the next 6-month eligibility window, a new updated propensity score will be calculated, and that score will be used to search for TRT matches in the new window. If propensity-matched TRT patients are available in this new window, the index date will become a randomly chosen doctor's visit that occurred during the window in which the match was identified. This strategy also allows untreated patients with no match in the previous 6-month calendar period to be evaluated in the next calendar block as TRT-treated patients if they begin TRT during the subsequent eligibility window. Assuming that the incidence of AMI is constant over time in untreated patients, it is appropriate to randomly assign an index date; however if the assumption is invalid, the untreated patients who failed to find a match in the original diagnosed calendar block will be excluded from this analysis.

Testosterone replacement therapy-treated and PDE5i-treated patients with no available propensity-matched controls during their 6-month initiation window will not be carried over and therefore will not be included in this analysis. Given that a patient's status could change (i.e. from untreated to treated) or the possibility of being excluded due to non-matchable controls, the patients' pre-matched status will be evaluated based on their status during the last calendar block when they were eligible for matching.

9.2.3.2. Termination of follow-up period

Follow-up will continue until the first of any of the following events:

- The first occurrence of AMI;
- Death from any cause (Truven Discharge stats codes 20 to 29 and 40 to 42);
- A gap (≥30 days) in continuous enrollment;
- End of exposure due to either of the following:
    - Discontinuation of TRT use for as-treated analysis; or
    - A gap (≥90 days) in use of TRT.
- Any change in exposure status
    - TRT-treated patients discontinuing TRT. For the primary comparison, a change in the route of TRT administration is not considered a change in exposure status. For the subgroup analysis of the primary comparison (TRT-treated patients versus untreated), switching to a different route of TRT administration of TRT will be censored;
    - Untreated patients beginning TRT;

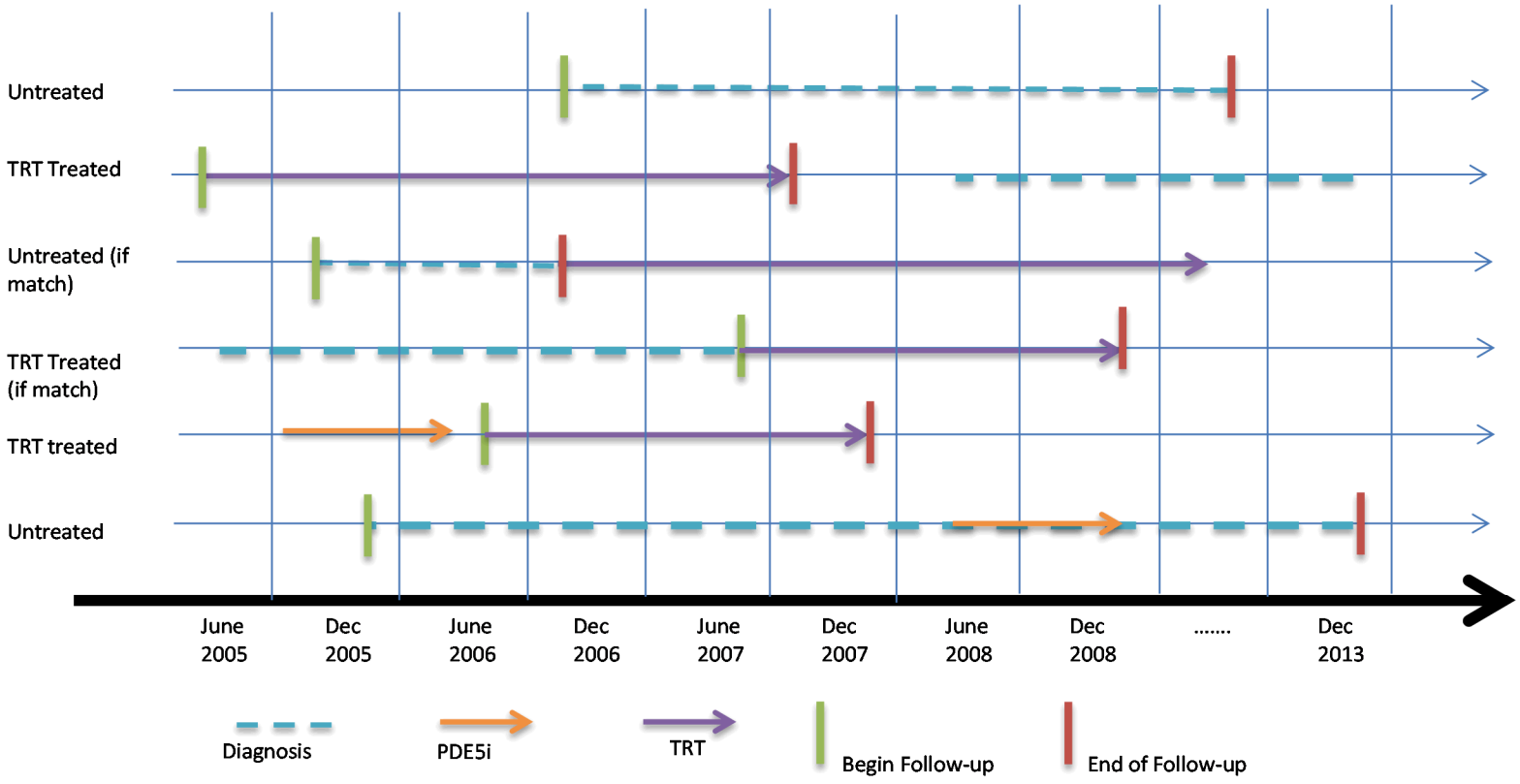
  - PDE5i-treated patients beginning TRT; or
  - TRT-treated patients beginning PDE5i treatment will be censored from the secondary (TRT-treated versus PDE5i-treated) comparison but will remain eligible for the primary TRT-treated versus untreated comparison.
- End of data availability (31 Dec 2013).

Although some patients may have multiple AMI events during observed follow-up, their inclusion would require more complex analytic methods. The predictors of repeat AMI, including drug exposures, may differ from those of an initial AMI. Moreover, treatments are likely to change following an AMI. For all of these reasons, only the first AMI during the study period will be counted and follow-up will be terminated at that point.

9.2.3.2.1. TRT versus untreated comparison

An as-treated analysis will be used for the primary comparison (TRT versus untreated). The follow-up period will last until the end of last prescription plus 90 days, which is to allow the hemoglobin concentration and hematocrit to return to pre-treatment levels (34). Prescriptions for testosterone products classified by the same route of administration that overlap within 90 days will be considered as 1 exposure period. This approach is considered reasonable and was used in a previous study which examined whether testosterone exposure influenced the future risk of developing AMI (35).

Figure 9.1 demonstrates the cohort identification scheme for the TRT-treated versus untreated comparison, for which PDE5i prescription is not evaluated. Patients are enrolled in the study on the date of their first hypogonadism diagnosis or the date they began TRT, assuming an available propensity score match. Untreated patients without an appropriate match in the 6 month window of their diagnosis will be carried over to the next window, their propensity score will be recalculated and they will be available for matching again in the next window. If the patient begins TRT in the new window, that patient becomes eligible for inclusion in the TRT-treatment group only in the window of the original prescription (they are no longer eligible for carryover). Follow-up continues until the patient meets an applicable termination criterion (Section 9.2.3.2) for the untreated comparison.



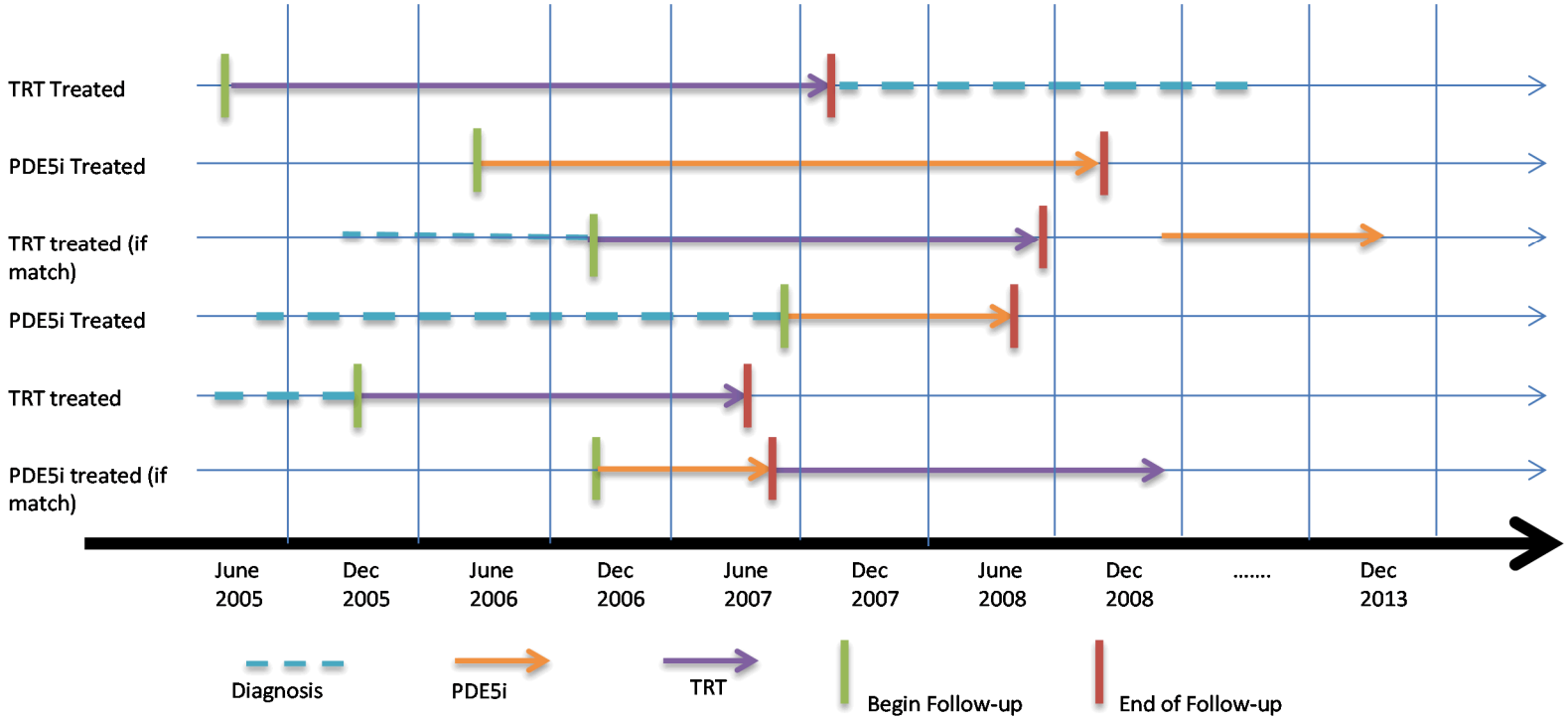
Abbreviations: PDE5i = phosphodiesterase 5 inhibitor; TRT = testosterone replacement therapy

Figure 9.1. Cohort identification for TRT-treated vs untreated comparison – PDE5i prescription is not evaluated.

9.2.3.2.2. TRT versus PDE5i treated comparison

Intent-to-treat analysis will be used for the comparison between TRT and PDE5i because PDE5i exposure can be used on an as-needed basis and it is difficult to estimate the end of the exposure period. These approaches are considered appropriate because PDE5i exposure is used to select a control comparator cohort, rather than to determine the exposure time. No subgroup analyses for route of TRT administration will be performed for this comparison.

Figure 9.2 demonstrates the cohort identification scheme for the TRT-treated versus PDE5i treated comparison, for which a diagnosis of hypogonadism is not evaluated. Patients are enrolled in the study on the date they are first exposed to the appropriate study drug (TRT or PDE5i), assuming an available propensity score match, and follow-up continues to until the patient meets an applicable termination criterion (Section 9.2.3.2) for the untreated comparison.



Abbreviations: PDE5i = phosphodiesterase 5 inhibitor; TRT = testosterone replacement therapy

Figure 9.2. **Cohort identification for TRT-treated versus PDE5i-treated comparison – hypogonadism diagnosis is not evaluated.**

9.2.4. Controlling for confounding factors - propensity score matching

As medication cohorts were not assigned randomly, but were based on usual care, comparisons between cohorts (TRT versus untreated, TRT versus PDE5i) may be confounded by selection bias. To adjust for measured confounders, comparison between cohorts will be performed using propensity score matching. The propensity score for each patient is defined by the predicted probability of testosterone initiation, given his measurable baseline characteristics (36). As described in Section 9.2.4.1.1, CTPS matching will be adapted to allow the effect of each covariate on the propensity for treatment receipt to be nonunivariate over time.

9.2.4.1. Propensity score estimation

The propensity score for each patient is defined by the predicted probability of testosterone initiation, given their measurable baseline characteristics (36). The propensity score will be estimated using logistic regression, with cohort (treated option or untreated) as the outcome variable. The logistic regression propensity model will include the prespecified baseline characteristics provided in Table 9.2. Interaction terms and nonlinear terms for continuous variables will also be considered if needed.

9.2.4.1.1. Propensity score matching

Testosterone replacement therapy initiators will be 1:1 matched to untreated cohort patients on the estimated propensity score and the index date of receiving testosterone treatment, at each 6-month calendar blocks (18- blocks). The exposure or nonexposure will only be determined within the calendar blocks. Testosterone replacement therapy initiators will also be 1:1 matched to PDE5i treated cohort patients on the estimated propensity score and index date, at each 6-month calendar block (18 blocks). One known disadvantage of the propensity score is that a separate propensity score must be calculated for each pairwise comparison of exposures.

Matching will be performed using a standard matching algorithm - a greedy 1:1 matching algorithm (37) will be utilized to match each treated patient with an appropriate control patient in the untreated cohort. The algorithm will utilize ranked-based Mahalanobis distance (or the absolute value of differences in the logit of the propensity score) with a caliper of 0.2 standard deviations of the logit of the propensity score (38, 39). As discussed in Section 9.2.4.1.2, the balance between treated and untreated populations in the matched cohorts will be assessed. If needed, additional variables, interactions, non-linear terms, or a reduction in terms may be considered. However, the propensity score model will be finalized prior to initiating the analysis of the study outcome measure.

9.2.4.1.2. Evaluation of quality of propensity score adjustment

Prior to initiating the outcome analysis, the quality of the propensity score adjustment and associated assumptions will be evaluated. The appropriateness of the propensity score modeling is judged by whether balance on pretreatment characteristics is achieved between the treatment and control groups (40, 41). The balance produced by the propensity scoring will be assessed by

analysis of standardized differences. For Propensity Score Matching: First, t-tests and Chi-square tests will be utilized to assess differences between the cohorts across all measured baseline covariates before and after propensity matching. In addition, the standardized differences, defined as the difference in means between the 2 groups divided by a measure of the standard deviation of the variable, will be computed and displayed. Standardized differences will be computed for both continuous and binary covariates and will be used to identify specific covariates with larger residual imbalances after propensity score adjustment. As a general rule, standardized differences greater than 0.10 indicate an imbalance that may require further investigation (42).

For continuous variables, the standardized difference is:

$$d = \frac{(\overline{X_1} - \overline{X_2})}{\sqrt{\frac{S_1^2 + S_2^2}{2}}}$$

Where $\overline{X_1}$ and $\overline{X_2}$ denote the sample mean of a baseline variable in each group, and S_1^2 and S_2^2 denote the sample variances, respectively. For skewed variables, the equation can be modified using rank statistics.

For binary categorical variables, the standardized difference is:

$$d = \frac{(\widehat{p_1} - \widehat{p_2})}{\sqrt{\frac{\widehat{p_1}(1 - \widehat{p_1}) + \widehat{p_2}(1 - \widehat{p_2})}{2}}}$$

Where $\widehat{p_1}$ and $\widehat{p_2}$ denote the proportion of a binary baseline variable in the treatment and control group, respectively.

9.2.5. Baseline patient characteristics

Baseline patient characteristics, including demographics, hospital utilization, AMI risk factors, comorbidities, and concomitant medications will be compared between cohorts before and after propensity score matching: TRT-treated versus the non-treated cohort, and TRT-treated versus PDE5i – treated cohort. These covariates were selected *a priori* on the basis of their availability in the THAM databases and the plausibility of having an association with risk for AMI. The detailed variables are listed in Section 9.3.3 below.

9.3. Variables

Diagnoses linked to laboratory tests or other non-visit-related utilization will not be included because the validity of these diagnoses is less well established and because they are not available in the THAM databases.

9.3.1. Study exposure

Exposure to testosterone replacement therapy will be categorized by any testosterone use and pre-specified routes of administration: transdermal gel, transdermal patch, injection, and non-specific testosterone use. Due to pharmacokinetic differences between the different routes of

administration (e.g. injectable testosterones are associated with higher peak concentrations of serum testosterone compared to other formulations); such different changes in serum testosterone levels may result in different AMI incidence.

The TRT study drugs and PDE5i study drugs are listed in Annex 3 and Annex 4, respectively.

9.3.2. Study outcome

The primary outcome event is an AMI occurring during eligible follow-up time. Acute Myocardial infarction is identified as a hospital discharge with a discharge International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 410.x0 or 410.x1 or, alternatively, as any record of death occurring within 24 hours of an emergency department visit for ischemic heart disease (ICD-9-CM codes 410.x0, 410.x1, 411.1, 411.8, and 413.x). The positive predictive value for a primary Medicare claims-based definition has been found to be as high as 94.1% (95% confidence interval [CI], 93.0%-95.2%) according to one previous study (43). No length of stay requirement will be applied for otherwise eligible hospitalizations (44). This hospitalization-based definition has been validated within Mini-Sentinel using standardized criteria. The emergency-department-based definition is intended to capture deaths from AMI occurring in an emergency department which may be missed by hospital discharge claims (45).

Table 9.1. Definition of Acute Myocardial Infarction

a) ICD-9-CM hospital discharge codes of 410.x0 and 410.x1.*
b) Deaths occurring within one day of an emergency department encounter for acute ischemic heart disease (ICD-9-CM code: 410.x0, 410.x1, 411.1, 411.8X, 413.x).

Abbreviations: ICD-9-CM=International Classification of Diseases, 9th Edition, Clinical Modification;

*If there are multiple discharge diagnoses associated with a single hospital episode, a single discharge diagnosis of AMI is sufficient.

9.3.3. Study covariates

Table 9.2 presents the baseline covariates that will be used to adjust the analyses for possible confounding. These covariates were selected *a priori* on the basis of their availability in the THAM databases and the plausibility of having an association with risk for AMI.

Table 9.2. Baseline covariates to be used to adjust for possible confounding (risk factors for AMI)

Demographics
Age at first cohort entry (Index date)
Region of residence*
Insurance type
Index year
Duration (in days) of TRT *
Utilization measures during baseline year
Any hospitalization within prior 30 days (Y/N)
Any hospitalization during prior 31–365 days (Y/N)
Any emergency department visit within prior 30 days (Y/N)
Any emergency department visit during prior 31–365 days (Y/N)
Number of outpatient visits in prior year
Number of unique medications in prior year
Health care costs in prior year
Comorbid diagnoses during baseline year
Chronic kidney disease
Hypertension
Hyperlipidemia or lipid disorder
Cigarette smoking—based on diagnostic code
Osteoporosis
Fracture
End-stage renal disease
Diabetes/Hypoglycemia
Dementia
Cancer‡
HIV/AIDS

(Baseline covariates to be used to adjust surveillance analyses for possible confounding)

Asthma or chronic obstructive pulmonary disease
Peripheral neuropathy
Obesity[‖]
Peripheral vascular disease
Alcoholism[‖]
Concurrent medications
Antidiabetic medications (use during the baseline year)
Antihypertensive agents (current at baseline, use during the baseline year) • Alpha agonists (current at baseline, use during the baseline year) • Alpha-2 agonists (current at baseline, use during the baseline year) • Angiotensin converting enzyme inhibitors (current at baseline, use during the baseline year) • Angiotensin receptor blockers (current at baseline, use during the baseline year) • Beta blockers (current at baseline, use during the baseline year) • Calcium channel blockers (current at baseline, use during the baseline year) • Diuretics (current at baseline, use during the baseline year) • Vasodilators (current at baseline, use during the baseline year) • Other/miscellaneous (current at baseline, use during the baseline year)
Lipid-lowering agents (use during the baseline year)
Hematological agents (current at baseline, use during the baseline year) • Antiplatelet (current at baseline, use during the baseline year) • anticoagulant (current at baseline, use during the baseline year)
Opiates (use during the baseline year)
Psychotropics (use during the baseline year)
Sleep medications (use during the baseline year)
PDE5i Medications (for TRT-treated versus untreated comparison only)
Prior cardiovascular disease diagnoses or procedures[§]
Prior acute myocardial infarction:[†] (at baseline)
Other ischemic heart disease diagnosis[†]
Coronary revascularization procedures:[†] coronary artery bypass graft or percutaneous coronary intervention

(Baseline covariates to be used to adjust surveillance analyses for possible confounding)

Other heart disease†
Peripheral artery disease†
Stroke†
Carotid revascularization procedures:† Carotid endarterectomy, stenting, angioplasty, or atherectomy or carotid bypass
Lower extremity amputation†
Lower extremity revascularization:† endarterectomy, lower extremity bypass, or amputation

Abbreviations: AMI = acute myocardial infarction; TRT = testosterone replacement therapy; Y/N = yes/no
* These variables will not be included in the propensity score model but will be included in the baseline characteristics table
‖ These variables will be included in the propensity score model but not in the baseline characteristics table
† These diagnoses will be coded distinctly for inpatient stays within prior 30 days versus any (e.g. inpatient or outpatient) visit earlier.
‡ Cancer (any cancer code other than non-melanoma skin cancer)
§ Presence of any of these diagnoses or procedures during baseline period will serve to place patient in CVD stratum
Note: Only diagnostic codes associated with encounters (inpatient or outpatient) will be used.

9.4. Data sources

The present study will utilize a US-based administrative healthcare claims database: THAM databases.

9.4.1. Truven Health Analytics MarketScan® research databases

Truven Health Analytics MarketScan® Databases contain individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. Since their creation in the early 1990s, the THAM databases have grown into one of the largest collections of de-identified patient-level data in the US. These databases reflect the real world of treatment patterns and costs by tracking millions of patients as they travel through the healthcare system offering detailed information about all aspects of care. Data from individual patients are integrated from all providers of care, maintaining all healthcare utilization and cost record connections at the patient level. Used primarily for research, these databases are fully Health Insurance Portability and Accountability Act (HIPAA) compliant. Research using THAM databases has been widely publicized in peer-reviewed journals. In the most recent full data year, MarketScan claims databases contain data on 50 million covered lives. Its sample size is large enough to allow creation of a nationally representative data sample of Americans with employer-provided health insurance and Medicaid.

9.4.2. Database major limitations

Truven Health Analytics MarketScan® databases provide an opportunity for research purposes. As with any data source, these databases have limitations. Some of the limitations result from

data structure and others are due to the sample population. Key common limitations include the following:

- Lack of clinical details makes it hard to verify the validity of diagnosis codes and to refine statistical analyses. Data on important confounding variables (smoking, alcohol use, body weight, and height) are not available in the claims database;
- Diagnoses, medical procedures, and medicine dispensing will not be captured if no corresponding billing codes were generated. Likewise, the use of the ICD-9-CM codes, current procedural terminology codes, or national drug codes is subject to the incompleteness or inaccuracies of the coding in the database;
- MarketScan claims databases are based on a large convenience sample. The data come mostly from large employers; medium and small firms are not represented. Because the sample is not random, it may contain biases or fail to generalize well to other populations; and
- Only prescribed medicines are recorded in the database. No information about over-the counter drug (e.g., aspirin) use is available.

9.5. Study size

Feasibility assessments to determine the sample size and study power have been conducted (Table 9.3).

Crude analyses suggested that the incidence rate of AMI among patients who did not receive TRT was 0.45%. Additionally, annual reports from the AHA report a range of incidence rates of AMI from 0.3 to 0.6%. The following assumptions have been made in order to derive the sample size estimation for the study:

1. Incidence rate of AMI among reference group (i.e.) is 0.0045
2. The effect size measured by hazard ratio is 1.5
3. Group weight 1:1
4. Two-sided $\alpha = 0.05$
5. Power = 80%

Table 9.3. Power and Sample Size Estimation of the Retrospective Cohort Study (both cohorts)

Number	Incidence rate		
Hazard Ratio	0.003	0.0045	0.006
1.3	133,756	100,326	66,896
1.5	52,350	**34,908**.	26,188
2.0	15,714	10,482	7,866
2.5	8,154	5,440	4,084

Note: assumptions: $\alpha = 0.05$, $\beta=0.80$

Based on a previous study analysis, an initial total of 1,520,704 patients with a hypogonadism diagnosis, a TRT prescription, or both were selected from THAM databases. Therefore, the sample size is considered sufficient for conducting the proposed analyses.

9.6. Data management

SAS (r) Proprietary Software 9.2 will be utilized for data management; the relevant comments such as *proc datasets, proc format, proc sql* etc. will be used to access the raw data, manage the analytical dataset, and process the integrated analytical datasets. Datasets and analytic programs will be kept on a secure server and archived per Lilly record-retention procedures.

9.7. Data analysis

9.7.1. Descriptive analysis

The baseline characteristics for the pre-matched population will be presented. A summary of baseline characteristics will also be presented for those subjects who are not included in the propensity score-matched analysis (Annex 9). An exploratory analysis of lab measurement of total testosterone levels will be assessed to display any difference in baseline testosterone levels between treated and untreated groups during the pre-index date period. Given that the lab measurements in THAM are not representative of the entire cohort, the analysis remains descriptive and will be interpreted in light of the data limitations. The crude prevalence rate of AMI will be calculated during 1-year baseline, in order to compare to the findings of Finkle et al. (2014).

The crude incidence rate of AMI will be calculated at every 30-day window during 1 year post-index date. Additionally, the crude incidence rate will be compared between untreated patients whose index date is based on the original hypogonadism diagnosis versus those whose index date is randomly assigned to a later time (see Section 9.2.3.1). The approach of randomly assigning index date is only appropriate assuming that the incidence of AMI is constant over time in untreated patients; if the assumption is invalid, the untreated patients who failed to find a match in the original diagnosed calendar block will be excluded from this analysis.

9.7.2. Comparative statistical analysis

The primary analysis of this protocol is to compare AMI risk between propensity score matched TRT treated patients versus untreated patients, using a Cox proportional hazard model. The secondary comparison of the AMI risk between propensity score matched TRT-treated patients versus PDE5i-treated patients.

It is recognized that risk differences are important in decision-making, providing a scale on which risks can be weighed against benefits. Further, it should be noted that for rare outcomes (e.g. AMI) the relative risk estimate tends to be unstable, and it can be preferable to model the risk difference directly, rather than derive it from the relative risk estimate. Thus, in addition to reporting relative risks and CIs, we will describe the incidence of AMI in users of testosterone and comparators to provide estimates of risk differences. However, risk differences tend to vary

more across subgroups than the relative risk. Therefore the method used for confounding adjustment will target the relative risk.

Cox regression model will be used for the time-to-event analysis. Only subjects matched on propensity score will be included in the analysis (Annex 9). The start date is the index date. The censored date for the treated subjects is the end of the at-risk period (defined in Section 9.2.3) or the date of last record in the database for the subjects, whichever comes first. The censored date for the untreated subjects is the date of last database record for the subject. The Cox regression model will include treatment and any baseline patient characteristics that did not reach balance between the two arms after propensity score matching as independent variables. The hazard ratio with 95% CI and p-value will be reported. Diagnostics of the proportionality assumption for the Cox model will be conducted primarily through descriptive analyses, if needed an iteration term between treatment and time will be added to the model to further assess the assumption of proportionality. If the proportionality assumption is invalid, a Cox proportional hazard model including an interaction term between treatment and time, in addition to the adjustments in the original model, will be implemented.

Additionally, Poisson regression will be conducted at 90, 180, and 365 days, as well as overall, post-index because it is more intuitive and yields explicit estimates, especially of AMI incidence rate – in subgroups, time periods, and overall. In terms of relative risk, Poisson regression is expected to yield very similar results. If Cox and Poisson yield estimates that differ nontrivially, then the Cox model is less vulnerable to bias because its risk sets are anchored to specific time points, which would presumably make them more homogeneous in the level of risk than the stratified time periods used in Poisson regression.

The following subgroup analyses will be conducted:

1. TRT routes of administration (gel/topical, patch, injectable, non-specified)
2. By prior cardiovascular condition (as listed in Table 9.2)
3. By age group (18-64 years, ≥65 years)

Additional sensitivity analysis may be performed on a post hoc basis.

9.8. Quality control

The study will use an existing database, which has been used primarily for research and is fully HIPAA compliant. The study programs for data management or statistical analyses will be validated by individual(s) outside the study team to ensure data integrity and accuracy. All study programs, log files, and output files will be stored on the secure sever, and archiving any statistical programming performed to generate the results.

9.9. Limitations of the research methods

The current study adopts an existing propensity score methodology and Observational Medical Outcome Partnership-developed macros to identify two comparison groups that are comparable with regard to the elevated risk of AMI in a real-world setting. This approach offers robust control for confounding because it enables tailoring of covariate selection based on pre-treatment characteristics of patients receiving testosterone prescriptions and the event of interest.

However, this study does have limitations. While claims data are extremely valuable for the efficient and effective examination of disease outcome and treatment patterns, claims data are collected for the purpose of payment and not research. Therefore, there are limitations associated with the use of claims data.

I. **First,** the presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed.

II. **Second,** the presence or absence of disease may not be accurate, as the diagnostic code may be incorrectly coded or included as rule-out criteria rather than actual disease. The diagnosis of hypogonadism is solely based on the ICD-9 diagnostic codes without considering clinical symptoms or laboratory measurement, which was infrequently captured in the database.

III. **Third,** several important covariates are missing in the claims database such as body weight, blood pressure, fasting glucose level etc. However, the study does include a number of pre-treatment covariates in the propensity score model to balance and minimize the measured differences between treatment and comparators.

IV. **Fourth,** selection bias could be introduced if the comparator cohorts (PDE5i, untreated) have higher TT levels compared to the treated cohort, which could be potentially related to disease severity. Low endogenous testosterone level is a well-known risk factor for mortality or CV mortality and morbidity. Therefore, a potential concern is that unmeasured confounding factors may exist. However, propensity score matching will employ a number of pre-treatment covariates, which will likely help to minimize the differences in measured confounding factors between the cohorts.

V. **Fifth,** protopathic bias could be introduced in the comparison between TRT versus PDE5is, if the patient are likely to be diagnosed with AMI based on an early symptoms (e.g. fatigue), which is also related to the disease. Additionally, patients receiving a PDE5i prescription may be more likely to have less CV risk factors at the time of prescribing (i.e. a selection bias from prescribers).

9.10. Other aspects

None

10. Protection of human subjects

All information about this observational study and individual medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. This study will be conducted in accordance with applicable laws and regulations of the US, where the study is being conducted, as appropriate.

11. Management and reporting of adverse events/adverse reactions

During the course of retrospective observational research, the proposed study will not involve chart validation to obtain extra information on adverse events. Thus, Lilly is not expecting to report any adverse events or reactions.

12. Plans for disseminating and communicating study results

The study will be registered in the EU EnCepp Registry and the study findings will be submitted to a scientific congress and submitted to a peer-reviewed journal.

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Annex 1. List of Standalone Documents

No.	Document Reference No	Date	Title
1.	Annex 1	20 February 2015	List of standalone documents
2.	Annex 2	3 March 2015	ENCePP Checklist for study protocols
3.	Annex 3	20 February 2015	List of testosterone products by routes of administration
4.	Annex 4	20 February 2015	List of Erectile Dysfunction Medications
5.	Annex 5	20 February 2015	List of Diagnostic Codes for Charlson Comorbidities – for Baseline Demographic Assessment
6.	Annex 6	20 February 2015	List of Diagnostic Codes for Selected Comorbidities to be Included in Propensity Score Model
7.	Annex 7	20 February 2015	Baseline Covariates to be Included in Propensity Score Models
8.	Annex 8	20 February 2015	List of Concomitant Medications
9.	Annex 9	20 February 2015	Statistical outcome analysis mock tables
10.	Annex 10		Methodological Considerations in Conducting Observational Research on Acute Myocardial Infarctions and Testosterone Replacement Therapy

Annex 2. ENCePP Checklist for study protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	#16
1.1.2 The objectives of the study?	☒	☐	☐	
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	#18
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	#16
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	#18
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	#18
2.2.2 Age and sex?	☒	☐	☐	#18
2.2.3 Country of origin?	☒	☐	☐	#17
2.2.4 Disease/indication?	☒	☐	☐	#19

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.5 Co-morbidity?	☒	☐	☐	#28-30
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	#18

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	#18
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	#35-36
3.4 Is sample size considered?	☒	☐	☐	#34
3.5 Is statistical power calculated?	☒	☐	☐	#34

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	#28-29
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	#29
4.1.3 Covariates?	☒	☐	☐	#29-32
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	#32
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD-10)	☒	☐	☐	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)				
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐ ☐	☐ ☐	☒ ☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	#28-29
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	#29
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	#28

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	#27-28
7.1.2 Information biases?	☒	☐	☐	#19
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	#27 #29-32
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	#29-32
7.4 Does the protocol address other limitations?	☒	☐	☐	#35-36

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	#34
8.2 Is the choice of statistical techniques described?	☒	☐	☐	#34-35
8.3 Are descriptive analyses included?	☒	☐	☐	#34
8.4 Are stratified analyses included?	☒	☐	☐	#35
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	#27-28
8.5.2 Effect modifiers?	☐	☐	☒	

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	#27-28
8.6.2 Effect modification?	☐	☐	☒	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	#35
9.2 Are methods of quality assurance described?	☒	☐	☐	#35
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	#32-33
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	#13
9.5.3 Study completion?	☒	☐	☐	#13
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	#13
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	
9.7 Are communication methods to disseminate results described?	☒	☐	☐	#39

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	#35

Comments:

Name of principle investigator: _Kraig S Kinchen_____

Date: 01/04/2015

Signature: Signature on file

Annex 3. List of Testosterone Products by Route of Administration

NDCNUM	*Generic Drug Name*	*Brand Name*	*Route of Administration*
314077270	Testosterone Propionate	TESTOSTERONE PROPIONATE	Injection
364660954	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
364661054	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
574082001	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
574082010	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
574082105	Testosterone Enanthate	TESTOSTERONE ENANTHATE	Injection
591322126	Testosterone Enanthate	TESTOSTERONE ENANTHATE	Injection
591322379	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
703612101	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
703612501	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
781307370	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
781307470	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
781307471	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
35356005810	Testosterone Cypionate	DEPO-TESTOSTERONE	Injection
54396032816	Testosterone Enanthate	DELATESTRYL	Injection
54396032840	Testosterone Enanthate	DELATESTRYL	Injection
54868021600	Testosterone Cypionate	DEPO-TESTOSTERONE	Injection
54868361800	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
54868361801	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Injection
67979050140	Testosterone Enanthate	DELATESTRYL	Injection
10116100102	Testosterone	TESTOPEL PELLETS	Injection
10116100103	Testosterone	TESTOPEL PELLETS	Injection
43773100102	Testosterone	TESTOPEL PELLETS	Injection
43773100103	Testosterone	TESTOPEL PELLETS	Injection

NDCNUM	*Generic Drug Name*	*Brand Name*	*Route of Administration*
43773100104	Testosterone	TESTOPEL PELLETS	Injection
9034702	Testosterone Cypionate	DEPO-TESTOSTERONE	Injection
9041701	Testosterone Cypionate	DEPO-TESTOSTERONE	Injection
9041702	Testosterone Cypionate	DEPO-TESTOSTERONE	Injection
65628002001	Testosterone Propionate	FIRST-TESTOSTERONE	Non-specific
65628002101	Testosterone Propionate	FIRST-TESTOSTERONE MC	Non-specific
364661754	Testosterone Enanthate	TESTOSTERONE ENANTHATE	Injection
574046005	Testosterone	TESTOSTERONE	Non-specific
574046025	Testosterone	TESTOSTERONE	Non-specific
574046105	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
574046125	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
17317056702	Testosterone	TESTOSTERONE	Non-specific
17317056703	Testosterone	TESTOSTERONE	Non-specific
17317056802	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
38779004703	Testosterone	TESTOSTERONE	Non-specific
38779004704	Testosterone	TESTOSTERONE	Non-specific
38779004705	Testosterone	TESTOSTERONE	Non-specific
38779016300	Testosterone	TESTOSTERONE	Non-specific
38779016303	Testosterone	TESTOSTERONE	Non-specific
38779016304	Testosterone	TESTOSTERONE	Non-specific
38779016305	Testosterone	TESTOSTERONE	Non-specific
38779016308	Testosterone	TESTOSTERONE	Non-specific
38779016309	Testosterone	TESTOSTERONE	Non-specific
38779016403	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
38779016404	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
38779016405	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific

NDCNUM	*Generic Drug Name*	*Brand Name*	*Route of Administration*
38779016409	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
38779016503	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
38779016504	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
38779016505	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
38779016508	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
38779253608	Testosterone	TESTOSTERONE	Non-specific
49452001101	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
49452001102	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
49452001103	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
49452765001	Testosterone	TESTOSTERONE	Non-specific
49452765002	Testosterone	TESTOSTERONE	Non-specific
49452765003	Testosterone	TESTOSTERONE	Non-specific
49452765201	Testosterone	TESTOSTERONE	Non-specific
49452765202	Testosterone	TESTOSTERONE	Non-specific
49452765203	Testosterone	TESTOSTERONE	Non-specific
49452765204	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
49452766001	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
49452766002	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
49452766003	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
49452767001	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
49452767002	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
49452767003	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
51552002901	Testosterone	TESTOSTERONE	Non-specific
51552002902	Testosterone	TESTOSTERONE	Non-specific
51552002904	Testosterone	TESTOSTERONE	Non-specific
51552002905	Testosterone	TESTOSTERONE	Non-specific

NDCNUM	*Generic Drug Name*	*Brand Name*	*Route of Administration*
51552002907	Testosterone	TESTOSTERONE	Non-specific
51552002999	Testosterone	TESTOSTERONE	Non-specific
51552003001	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
51552003002	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
51552003004	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
51552003005	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
51552003008	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
51552003099	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
51552010402	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
51552010405	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
51552056404	Testosterone	TESTOSTERONE	Non-specific
51552056405	Testosterone	TESTOSTERONE	Non-specific
51927102600	Testosterone	TESTOSTERONE	Non-specific
51927102700	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
51927102900	Testosterone Propionate, Micronized	TESTOSTERONE PROPIONATE MICRONIZED	Non-specific
51927270600	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
51927432400	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
62991141202	Testosterone Propionate, Micronized	TESTOSTERONE PROPIONATE MICRONIZED	Non-specific
62991141203	Testosterone Propionate, Micronized	TESTOSTERONE PROPIONATE MICRONIZED	Non-specific
62991170701	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
62991170702	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
62991170703	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
62991170705	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
62991215001	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific

NDCNUM	*Generic Drug Name*	*Brand Name*	*Route of Administration*
62991215002	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
62991215003	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
62991215004	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
62991215005	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
62991270001	Testosterone Enanthate	TESTOSTERONE ENANTHATE	Non-specific
63275998209	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
63275998304	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63275998305	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63275998308	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63275998309	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097025	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097035	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097045	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097050	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097125	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097135	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097145	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370097150	Testosterone, Micronized	TESTOSTERONE MICRONIZED	Non-specific
63370098025	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
63370098035	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
63370098050	Testosterone Cypionate	TESTOSTERONE CYPIONATE	Non-specific
63370098315	Testosterone Enanthate	TESTOSTERONE ENANTHATE	Non-specific
63370098525	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
63370098535	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
63370098545	Testosterone Propionate	TESTOSTERONE PROPIONATE	Non-specific
314077170	Testosterone	TESTOSTERONE	Non-specific

NDCNUM	*Generic Drug Name*	*Brand Name*	*Route of Administration*
51842501	Testosterone	ANDROGEL	Topical Gel
51842530	Testosterone	ANDROGEL	Topical Gel
51845001	Testosterone	ANDROGEL	Topical Gel
51845030	Testosterone	ANDROGEL	Topical Gel
51846233	Testosterone	ANDROGEL	Topical Gel
51848833	Testosterone	ANDROGEL	Topical Gel
51848888	Testosterone	ANDROGEL	Topical Gel
54569533900	Testosterone	ANDROGEL	Topical Gel
54569559500	Testosterone	TESTIM	Topical Gel
54868479200	Testosterone	ANDROGEL	Topical Gel
54868481000	Testosterone	ANDROGEL	Topical Gel
54868498900	Testosterone	TESTIM	Topical Gel
54868581400	Testosterone	ANDROGEL	Topical Gel
63481018316	Testosterone	FORTESTA	Topical Gel
66887000105	Testosterone	TESTIM	Topical Gel
68115080930	Testosterone	ANDROGEL	Topical Gel
2197590	Testosterone	AXIRON	Topical Gel
17314460803	Testosterone	TESTODERM	Transdermal Patch
17314460903	Testosterone	TESTODERM	Transdermal Patch
17314471703	Testosterone	TESTODERM TTS	Transdermal Patch
52544046954	Testosterone	ANDRODERM	Transdermal Patch
52544046960	Testosterone	ANDRODERM	Transdermal Patch
52544047030	Testosterone	ANDRODERM	Transdermal Patch
52544047054	Testosterone	ANDRODERM	Transdermal Patch
54868370400	Testosterone	ANDRODERM	Transdermal Patch
55056306001	Testosterone	STRIANT	Transdermal Patch

NDCNUM	*Generic Drug Name*	*Brand Name*	*Route of Administration*
62109913302	Testosterone	ANDRODERM	Transdermal Patch
62109913402	Testosterone	ANDRODERM	Transdermal Patch
115703701	Methyltestosterone	METHITEST	Non-specific
187090101	Methyltestosterone	TESTRED	Non-specific
187090201	Methyltestosterone	ANDROID	Non-specific
52544007730	Testosterone	Androderm	Transdermal Patch
52544007660	Testosterone	Androderm	Transdermal Patch

Annex 4. List of Erectile Dysfunction Medications

- Avanafil
- Sildenafil
- Tadalafil
- Vardenafil

Annex 5. List of Diagnostic Codes for Charlson Comorbidities – for Baseline Demographic Assessment

Variable Names	Comorbidity	ICD-9 Codes	Weight
1	Myocardial Infarction	410, 411	1
2	Congestive Heart Failure	398, 402, 428	1
3	Peripheral Vascular Disease	440-447	1
4	Cerebrovascular Disease	430-433, 435	1
5	Dementia *	290, 291, 294	1
6	Chronic Pulmonary Disease	491-493	1
7	Rheumatologic Disease	710, 714, 725	1
8	Peptic Ulcer Disease	531-534	1
9	Mild Liver Disease	571, 573	1
10	Diabetes (Mild to Moderate)	250.xx	2
11	Diabetes with Chronic Complications	N/A	
12	Hemiplegia or paraplegia	342, 434, 436, 437	2
13	Renal Disease *	403, 404, 580-586	2
14	Leukemia	204, 205, 206, 207	2
15	Lymphoma	200, 202, 203	2
16	Any Tumor	140.xx – 195.xx	2
17	Liver Disease		
18	Moderate or Severe Liver Disease	070, 570, 572	6
19	Metastatic Solid Tumor	196-199	6

Note: Individual condition will be included in the PS model, and the composite score will be listed in baseline table;
* these conditions will be coded as baseline characteristics/risk factors based on coding in Annex 7.
Reference: J Clin Epidemiol Vol. 45, No. 6, pp 613-619, 1992

Annex 6. List of Diagnostic Codes for Selected Comorbidities to be Included in Propensity Score Model

ICD 9 Codes for selected comorbidities	
Sleep Disturbance	
Drug induced sleep disorders	292.85
Specific disorders of sleep of nonorganic origin	307.4
Organic sleep disorders	327
Sleep disturbances	780.5
Malaise or fatigue	780.7
Klinefelter's syndrome	758.7
Pituitary disorders	253
Testicular cancer	
Malignant neoplasm of testis	186
Other and unspecified male genital organs	233.6
Neoplasm of uncertain behavior of Testis	236.4
Secondary malignant neoplasm of Genital organs	198.82
Prostate disease	
Benign neoplasm of male genital organs - prostate	222.2
Hyperplasia of prostate	600
Congestion or hemorrhage of prostate	602.1
Atrophy of prostate	602.2
Dysplasia of prostate	602.3
Unspecified disorder of prostate	602.9
Depression	
Major depressive disorder, single episode	296.2
Major depressive disorder, recurrent episode	296.3
Dysthymic disorder	300.4

ICD 9 Codes for selected comorbidities	
Depressive disorder, not elsewhere classified	311
Sexual dysfunction	
Decreased libido	799.81
Other testicular dysfunction	257.8
Other testicular hypofunction	257.2
Unspecified testicular dysfunction	257.9
Psychosexual dysfunction, unspecified	302.70
Hypoactive sexual desire disorder	302.71
With inhibited sexual excitement	302.72
Male orgasmic disorder	302.74
Premature ejaculation	302.75
Cognitive impairment	
Mild cognitive impairment, so stated	331.83
Late effects of cerebrovascular disease	438.0
Prostate Cancer	
Malignant neoplasm of prostate	185
Carcinoma in situ of prostate	233.4
Neoplasm of uncertain behavior of prostate	236.5

Annex 7. Baseline Covariates to be Included in Propensity Score Models

Both Strata – with or without Prior Cardiovascular Disease	
Demographics	**Codes***
Age at 1st cohort entry Insurance type during prior year Index year	Age in years at the index date
Utilization Measures	
Duration of TRT treatment Any hospitalization within prior 30 days Any hospitalization 31-365 days Any ED visit within prior 30 days Any ED visit 31-365 days before Number of outpatient visits in prior year Number of unique medications dispensed in prior year Total healthcare cost in prior year	"Unique medications" are determined by counting unique 11-digit NDC codes. Combination drugs are not broken into their constituents (The study drugs and covariate drugs are identified in more detail than the 11-digit NDC codes, as specified elsewhere).
Co-morbid conditions related to AMI risk	
Asthma	493
Alcoholism	303.xx, 305.0x, 535.3x, 571.0, 571.1, 571.2, 571.3, V11.3
Cancer (excluding non-melanoma skin cancer)	140-209 (excluding 173 and 209.4-209.6)
Chronic kidney disease (excluding ESRD)	585.1–585.4 HCPCS: G0420, G0421, G8487, G8771
Chronic obstructive pulmonary disease	491, 492, 496
Dementia	290.0–290.4, 291.2, 292.82, 294.0, 294.1, 294.8, 331.0–331.2, 331.7–331.9, 797
Depression	296.2, 296.3, 300.4, 311
End stage renal disease (ESRD)	458.21, 585.5, 585.6, 996.56, 996.68, 996.73, V42.0, V45.1, V56 ICD9P: 38.95, 39.27, 39.42, 39.43, 39.53, 39.93, 39.94, 39.95, 54.98, 55.6 CPT4: 36145, 36800, 36810, 36815, 36825, 36830-36833, 50323, 50325, 50327-50329, 50340, 50341, 50360, 50365, 50366, 90918-90925, 90935, 90937, 90939-90944, 90945, 90947, 90951-90969, 90970, 90976-90979, 90982-90985, 90989, 90993, 90995, 90996, 90997, 90998, 90999, 93990, 99512 HCPCS: A4653, A4656, A4657, A4670-A4674, A4680, A4706- A4709, A4712, A4714, A4719, A4720-A4726, A4728, A4730, A4736, A4737, A4740, A4750, A4755, A4760, A4765, A4766, A4770, A4771, A4773, A4774, A4802, A4860, A4870, A4890, A4911, A4913, A4918, A4928, A4929, C1881, E1500, E1520, E1530, E1540, E1550, E1560, E1570, E1575, E1580, E1600, E1610, E1615, E1620, E1625, E1634-E1639, E1699, G0257, G0308-G0327, G8727, G9013, G9014, J0635, J0636, S2065, S9335, S9339

Fracture	733.1, 733.93-733.98, 805–815 (excluding 807.5 and 807.6), 818-825, 827, 828, V54.13, V54.23 ICD9P: 79.01-79.03, 79.05-79.07, 79.11-79.13, 79.15-79.17, 79.21-79.23, 79.25-79.27, 79.31-79.33, 79.35-79.37, 79.61-79.63, 79.65-79.67, 81.65, 81.66
HIV/AIDS	042, 043, 044, 795.71, V08
Hyperlipidemia	272.0, 272.1, 272.2, 272.4
Hypertension	401–405 (excluding 402.01, 402.11, 402.91)
Hypoglycemia	250.8, 251.0–251.2
Obesity (or weight gain)	278.0, 793.91, V85.3, V85.4 (783.1)
Osteoporosis	733.0, V17.81, V82.81
Peripheral neuropathy	250.6, 337.1, 354, 355, 357.2
Tobacco use	305.1, V15.82
Stratum with Prior Cardiovascular Disuse[§]	
Comorbid Conditions	**Codes**
Prior AMI[†] (i.e., at baseline)	410
Other ischemic heart disease[†]	411–414
Other heart disease[†]	402.01, 402.11, 402.91, 420-429, 440
Stroke (narrow)[‡]	430, 431, 433.x1, 434.x1, 436
Stroke (broad)[‡]	430–434, 436
Peripheral arterial disease[†]	443.9
Coronary revascularization procedures[†]	
Coronary artery bypass graft	ICD9D: 996.03, V45.81 ICD9P: 36.1X, 36.2 CPT4: 33510-33514, 33516-33523, 33525, 33528, 33530, 33533-33536, 33560, 33570, 33572, 33575, 35600 HCPCS: S2205-S2209
Percutaneous coronary intervention	ICD9D: V45.82 ICD9P: 0.66, 36.01-36.09, 37.22, 37.23, 88.5 CPT4: 92973, 92974, 92977, 92980, 92981, 92982, 92984, 92987, 92995, 92996 HCPCS: G0290, G0291
Carotid revascularization procedures[†]	
Carotid endarterectomy, stenting, angioplasty, or atherectomy	ICD9P: 00.61, 00.63, 38.11, 38.12 CPT4: 35301, 35390, 35501, 35601, 35901, 0075T, 0076T, 37215, 37216 HCPCS: S2211
Carotid bypass	ICD9P: 39.28 ***CPT: 33508, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536, 33530, 33572, 35600***
Lower Extremity revascularization[†]	
Lower extremity endarterectomy, stenting, angioplasty, or atherectomy	ICD9P: 38.18, 38.19 CPT4: 35454, 35456, 35459, 35470, 35473, 35474, 35482, 35483, 35492, 35493, 35495, 37207, 37208, 37220-37235
Lower extremity bypass	ICD9P: 39.25, 39.29 CPT4: 35351, 35355, 35361, 35363, 35371, 35372, 35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35582, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647,

	35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681-35683, 35879
Lower extremity amputation	ICD9P: 84.10-84.17 CPT4: 27295, 27590-27592, 27598, 27880-27882, 27888, 27889, 28800, 28805, 28810, 28820, 28825

Abbreviations: ICD9D: ICD-9-CM diagnosis codes; ICD9P: ICD-9 procedure codes; CPT4: Current Procedural Terminology codes; HCPCS: Healthcare Common Procedure Coding System codes.

* Use only codes associated with visits (inpatient or outpatient). All diagnoses and procedures are sought for the 12-month period prior to first dispensing.

† These diagnoses will be coded distinctly for inpatient stays within prior 30 days versus any (e.g. inpatient or outpatient) visit earlier.

‡ The narrowly defined stroke includes the principal discharge diagnoses. The more broadly defined stroke includes diagnoses associated with an inpatient or outpatient encounter.

§ Presence of any of these diagnoses or procedures during baseline period will serve to place patient in stratum with CVD.

Note: Only diagnostic codes associated with encounters (inpatient or outpatient) will be used.

Annex 8. List of Concomitant Medications

- Antihyperlipidemics (Antilipemics)
  - Statins
    - Atorvastatin
    - Cerivastatin
    - Fluvastatin
    - Lovastatin
    - Pitavastatin
    - Pravastatin
    - Rosuvastatin
    - Simvastatin
  - Benzafibrate
  - Cholestyramine
  - Ciprofibrate
  - Clofibrate
  - Colesevelam
  - Colestipol
  - Dextrothyroxine
  - Ezetimibe
  - Fenofibrate
  - Gemfibrozil
  - Neomycin
  - Niacin
  - Omega-3-Acid
  - Probucol
- Antihypertensives
  - Alpha-2 Agonist
    - Clonidine
    - Methyldopa
    - Guanabenz
    - Guanethidine
    - Guanfacine
  - Alpha Antagonist
    - Doxazosin
    - Phenoxybenazmine
    - Phentolamine
    - Prazosin
    - Terazosin
  - Angiotiotensin Converting Enzyme Inhibitor
    - Benazepril
    - Captopril
    - Enalapril

        - Fosinopril
        - Lisinopril
        - Moexipril
        - Quinapril
        - Perindopril
        - Ramipril
        - Trandolapril
    - Angiotensin Receptor Blocker
        - Azilsartan
        - Candesartan
        - Eprosartan
        - Irbesartan
        - Losartan
        - Olmesartan
        - Telmisartan
        - Valsartan
    - Beta Blockers
        - Acebutolol
        - Atenolol
        - Betaxolol
        - Bisoprolol
        - Carvedilol
        - Labetolol
        - Metoprolol
        - Nadolol
        - Nebivolol
        - Pindolol
        - Propranolol
        - Sotalol
        - Timolol
    - Calcium Channel Blockers
        - Amlodipine
        - Clevidipine
        - Diltiazem
        - Felodipine
        - Isradipine
        - Nicardipine
        - Nifedipine
        - Nisoldipine
        - Verapamil
    - Diuretics
        - Amiloride
        - Bendroflumethiazide

        - Bumetanide
        - Chlorothiazide
        - Chlorthalidone
        - Eplerenone
        - Epoprostenol
        - Ethacrynic Acid
        - Furosemide
        - Hydrochlorothiazide
        - Hydroflumethiazide
        - Indapamide
        - Methyclothiazide
        - Metolazone
        - Polythiazide
        - Spironolactone
        - Torsemide
        - Triamterene
        - Trichlormethiazide
    - Vasodilators
        - Ambrisentan
        - Bosentan
        - Cyclandelate
        - Diazoxide
        - Fenoldopam
        - Hydralazine
        - Isoxsuprine
        - Minoxidil
        - Nicotinyl alcohol
        - Nitroprusside
        - Treprostinil
    - Miscellaneous agents to lower blood pressure
        - Aliskiren
        - Alseroxylon
        - Mecamylamine
        - Deserpidine
        - Inamrinone
        - Milrinone
        - Rauwolfia Serpentina
        - Rescinnamine
        - Reserpine
        - Tolazoline
        - Trimethaphan
- Diabetes – agents to lower blood sugar
    - Alpha-glucosidase inhibitors

        - Acarbose
        - Miglitol
    - Amylinomimetic
        - Pramlinitide
    - Biguanides
        - Metformin
    - DPP-4 Inhibitors
        - Linagliptin (Tradjenta)
        - Saxagliptin (Onglyza)
        - Sitagliptin (Januvia)
    - GLP-1 agonist
        - Exenatide
        - Liraglutide
    - Insulins
        - Aspart
        - Beef Isophane – NPH
        - Beef Zinc (Lente)
        - Detemir
        - Glargine
        - Glusine
        - Human Inhaled
        - Human Isophane (NPH)
        - Human Regular
        - Human Zinc – (Lente)
        - Lispro
    - Metglitinides
        - Nateglinide
        - Repaglinide
    - Sulfonylurea
        - Acetohexamide
        - Chlorpropamide
        - Glimepiride
        - Glipizide
        - Glyburide
        - Tolazamide
        - Tolbutamide
    - Thiazolidinediones
        - Pioglitazone
        - Rosiglitazone
        - Troglitazone
- Hematological Agents
    - Platelet Aggregation Inhibitors
        - Aspirin

        - Abciximab
        - Anagrelide
        - Cilostazol
        - Clopidogrel
        - Dipyridamole
        - Eptifibatide
        - Prasugrel
        - Ticagrelor
        - Ticlopidine
        - Tirofiban
    - Anticoagulants
        - Anisindione
        - Antithrombin III
        - Ardeparin
        - Argatroban
        - Bivalirudin
        - Dabigatran
        - Danaparoid
        - Desirudin
        - Dicumarol
        - Elmiron
        - Enoxaparin
        - Fondaparinux
        - Heparin
        - Lepirudin
        - Phenprocoumon
        - Rivaroxaban
        - Tinzaparin
        - Warfarin
- Opiates
    - Alfentanil
    - Belladonna Alaloids/Opium Alkaloids
    - Buprenorphine
    - Butorphanol
    - Codeine
    - Fentanyl (Duragesic)
    - Hydrocodone
    - Hydromorphone
    - Levorphanol
    - Meperidine
    - Methadone
    - Morphine
    - Oxycodone

    - Oxymorphone
    - Propoxyphene
    - Sufentanil
    - Tapentadol
    - Tramadol
- Psychotropics
    - Anticonvulsants used as mood stabilizers
        - Carbamazepine
        - Divalproex
        - Ezogabine
        - Ethosuximide
        - Felbamate
        - Fosphenytoin
        - Gabapentin
        - Lacosamide
        - Lamotrigine
        - Levetiracetam
        - Mephobarbital
        - Methsuximide
        - Oxcarbazepine
        - Pentobarbital
        - Phenobarbital
        - Phenytoin
        - Primidone
        - Rufinamide
        - Tiagabine
        - Topiramate
        - Trimethadione
        - Valproic Acid
        - Vigabatrin
        - Zonisamide
    - Antidepressants
        - Amitriptyline
        - Amoxapine
        - Bupropion
        - Citalopram
        - Clomipramine
        - Desipramine
        - Desvenlafaxine
        - Doxepin
        - Duloxetine
        - Escitalopram
        - Fluoxetine

        - Imipramine
        - Isocarboxazid
        - Fluvoxamine
        - Maprotiline
        - Milnacipran
        - Mirtazapine
        - Nefazodone
        - Nortriptyline
        - Paroxetine
        - Phenelzine
        - Protriptyline
        - Sertraline
        - Tranylcypromine
        - Trazadone
        - Trimipramine
        - Venlafaxine
        - Vilazodone
    - Antipsychotics
        - Atypical
            - Aripiprazole
            - Asenapine
            - Clozapine
            - Iloperidone
            - Lurasidone
            - Olanzapine
            - Paliperidone
            - Quetiapine
            - Risperidone
            - Ziprasidone
        - Typical
            - Acepromazine
            - Chlorpromazine
            - Chlorprothixene
            - Fluphenazine
            - Haloperidol
            - Loxapine
            - Mesoridazine
            - Molindone
            - Perphenazine
            - Pimozide
            - Piperacetazine
            - Prochlorperazine
            - Promazine

        - Thioridazine
        - Thiothixene
        - Trifluoperazine
    - Anxiolytics
        - Alprazolam
        - Buspirone
        - Chlordiazepoxide
        - Clobazam
        - Clonazepam
        - Clorazepate
        - Diazepam
        - Estazolam
        - Flurazepam
        - Lorazepam
        - Meprobamate
        - Midazolam
        - Oxazepam
        - Quazepam
        - Temazepam
        - Triazolam
- Sleep Medications
    - Acetylcarbromal
    - benzodiazepine
    - Chloral Hydrate
    - Eszopiclone
    - Ethchlorvynol
    - Glutethimide
    - Hydroxyzine
    - Mephobarbital
    - Pentobarbital
    - Ramelteon
    - Zaleplon

Zolpidem

Annex 9. Statistical outcome analysis mock tables

Table Annex.1. Mock Table: Baseline Characteristics between Testosterone treated and untreated groups for Before Propensity Match, Propensity Score Matched and Unmatched Subjects

		Before propensity score match (N=xxx)			Propensity Score Matched (N=xxx)			Unmatched Subjects (N=xxx)		
Baseline Characteristics		Treated (N=xx)	Untreated (N=xx)	Standardized Difference	Treated (N=xx)	Untreated (N=xx)	Standardized Difference	Treated (N=xx)	Untreated (N=xx)	Standardized Difference
Demographics										
	Age – Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Region–by category (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Baseline Utilization										
	Any hospitalization within prior 30 days – Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Any hospitalization during prior 31–365 days –Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Any ER visit within prior 30 days – Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Any ER visit during prior 31–365 days – Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

	Number of outpatient visits– Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Number of unique medications – Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Baseline Comorbidities										
	Charson Comobidity Index – Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Hypertension – Count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Hyperlipidemia or lipid disorder – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Smoking – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Osteoporosis – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Fracture – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Renal insufficiency – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	End-stage renal disease – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

	Hypoglycemia – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Dementia – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Cancer – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	HIV/AIDS – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Asthma or COPD – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Depression – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Peripheral neuropathy – Count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Concurrent medications										
	Antidiabetic – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Antihyertensive – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Lipid-lowering – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Hematological	xx.x	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x	xx.x (xx.x)	x.xxx

	agents– count (%)	(xx.x)						(xx.x)		
	Opiates – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Psychotropics – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Sleep medication – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Prior CVD disease										
	Prior AMI – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Other ischemic heart disease – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	CABG/PCI [1] – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Other heart disease – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Stroke – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Carotid revascularization procedures – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Lower extremity amputation – count	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

	(%)									
	Lower extremity revascularization – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

[1] CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention

Table Annex.2. Mock Table: Baseline Characteristics between Testosterone treated and PDE 5i treated groups for Before Propensity Match, Propensity Score Matched and Unmatched Subjects

		Before propensity score match (N=xxx)			Propensity Score Matched (N=xxx)			Unmatched Subjects (N=xxx)		
Baseline Characteristics		Testosterone Treated (N=xx)	PDE 5i Treated (N=xx)	Standardized Difference	Testosterone Treated (N=xx)	PDE 5i Treated (N=xx)	Standardized Difference	Testosterone Treated (N=xx)	PDE 5i Treated (N=xx)	Standardized Difference
Demographics										
	Age – Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Region–by category (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Duration of treatment – Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Baseline Utilization										
	Any hospitalization within prior 30 days – Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Any hospitalization during prior 31–365 days –Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

	Any ER visit within prior 30 days – Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Any ER visit during prior 31–365 days – Y/N (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Number of outpatient visits– Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Number of unique medications – Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Baseline Comorbidities										
	Charson Comobidity Index – Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	x.xxx*	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Hypertension – Count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Hyperlipidemia or lipid disorder – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Smoking – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Osteoporosis – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Fracture – count (%)	xx.x	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x	xx.x (xx.x)	x.xxx

		(xx.x)						(xx.x)		
	Renal insufficiency – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	End-stage renal disease – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Hypoglycemia – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Dementia – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Cancer – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	HIV/AIDS – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Asthma or COPD – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Depression – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Peripheral neuropathy – Count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Concurrent medications										
	Antidiabetic – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

	Antihyertensive – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Lipid-lowering – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Hematological agents– count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Opiates – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Psychotropics – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Sleep medication – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
Prior CVD disease										
	Prior AMI – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Other ischemic heart disease – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	CABG/PCI [1] – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Other heart disease – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Stroke – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

	Carotid revascularization procedures – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Lower extremity amputation – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx
	Lower extremity revascularization – count (%)	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx	xx.x (xx.x)	xx.x (xx.x)	x.xxx

[1] CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention

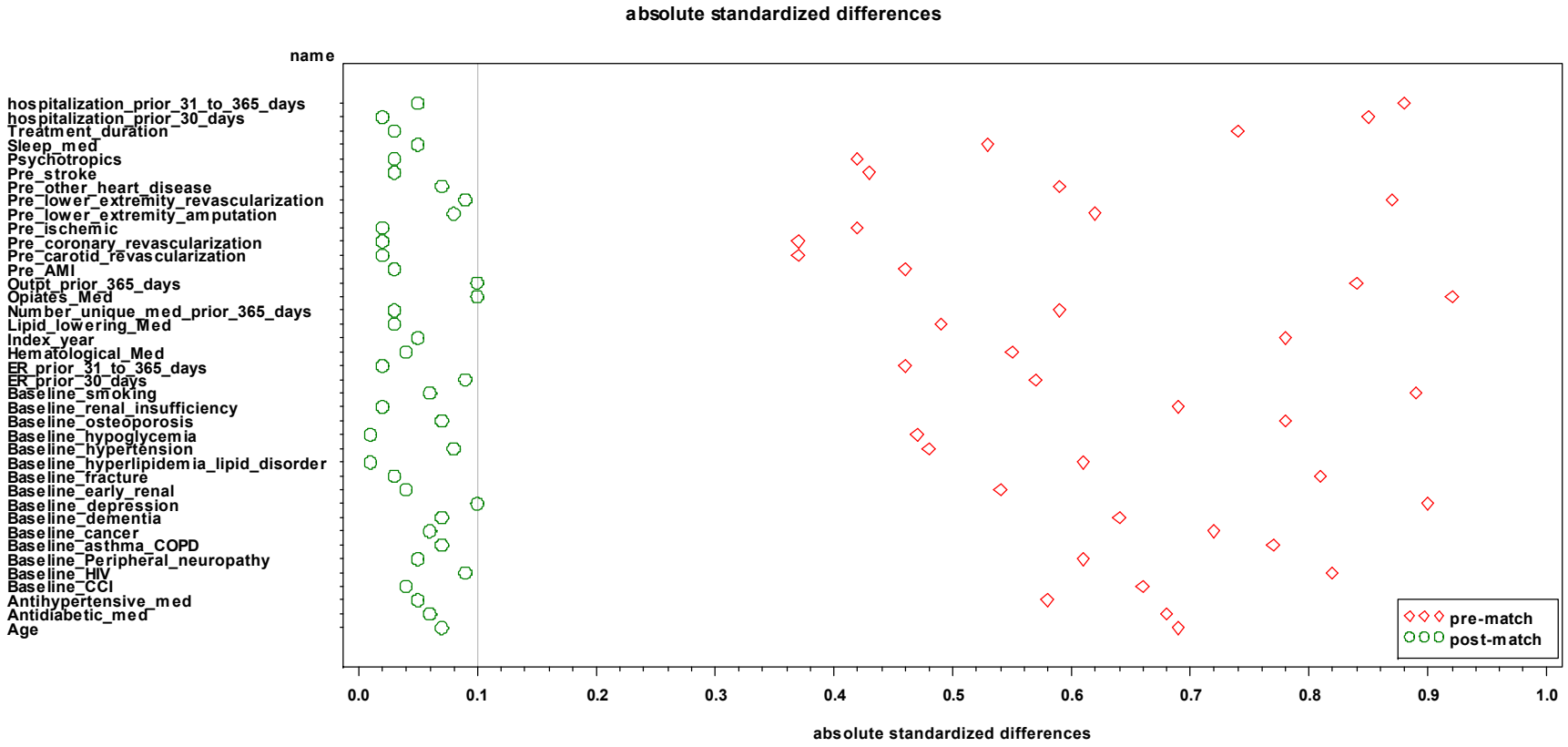

Figure Annex.1. **Mock Figure: Balance of Baseline Characteristics between cohorts before and after propensity score matching.**

Table Annex.3. Mock Table: Treatment Difference in the Time to AMI for Propensity Matched Population between Testosterone treated and untreated group using Cox Regression

MI Incidence				Unadjusted			Adjusted		
Treated N=xxx		Untreated N=xxx		HR	95% CI	P value	HR	95% CI	P value
n	%	n	%						
xx	x.xx	xx	x.xx	xx.xx	xx.xx-xx.xx	.xxxx	xx.xx	xx.xx-xx.xx	.xxxx

N=number of subjects in the propensity score matched sample; HR= hazard ratio (treated vs. untreated); CI=confidence interval for the HR; HR, 95% CI and p value are from the proportion hazard model with covariate adjustment and without covariate adjustment. Unadjusted model: TimeToEvent * Censor(1)=Exposure; Adjusted model: TimeToEvent*Censor(1)=Exposure Group + Age+ index year + baseline risk factors + concomitant medication + any baseline characteristics not balanced after propensity score matching

Table Annex.4. Mock Table: Treatment Difference in the Time to AMI for Propensity Matched Population between Testosterone treated and PDE 5i treated group using Cox Regression

MI Incidence				Unadjusted			Adjusted		
Testosterone Treated N=xxx		PDE 5i treated N=xxx		HR	95% CI	P value	HR	95% CI	P value
n	%	n	%						
xx	x.xx	xx	x.xx	xx.xx	xx.xx-xx.xx	.xxxx	xx.xx	xx.xx-xx.xx	.xxxx

N=number of subjects in the propensity score matched sample; HR= hazard ratio (Testosterone treated vs. PDE 5i treated); CI=confidence interval for the HR; HR, 95% CI and p value are from the proportion hazard model with covariate adjustment and without covariate adjustment. Unadjusted model: TimeToEvent * Censor(1)=Exposure; Adjusted model: TimeToEvent*Censor(1)=Exposure Group + Age+ index year + baseline risk factors + concomitant medication + any baseline characteristics not balanced after propensity score matching

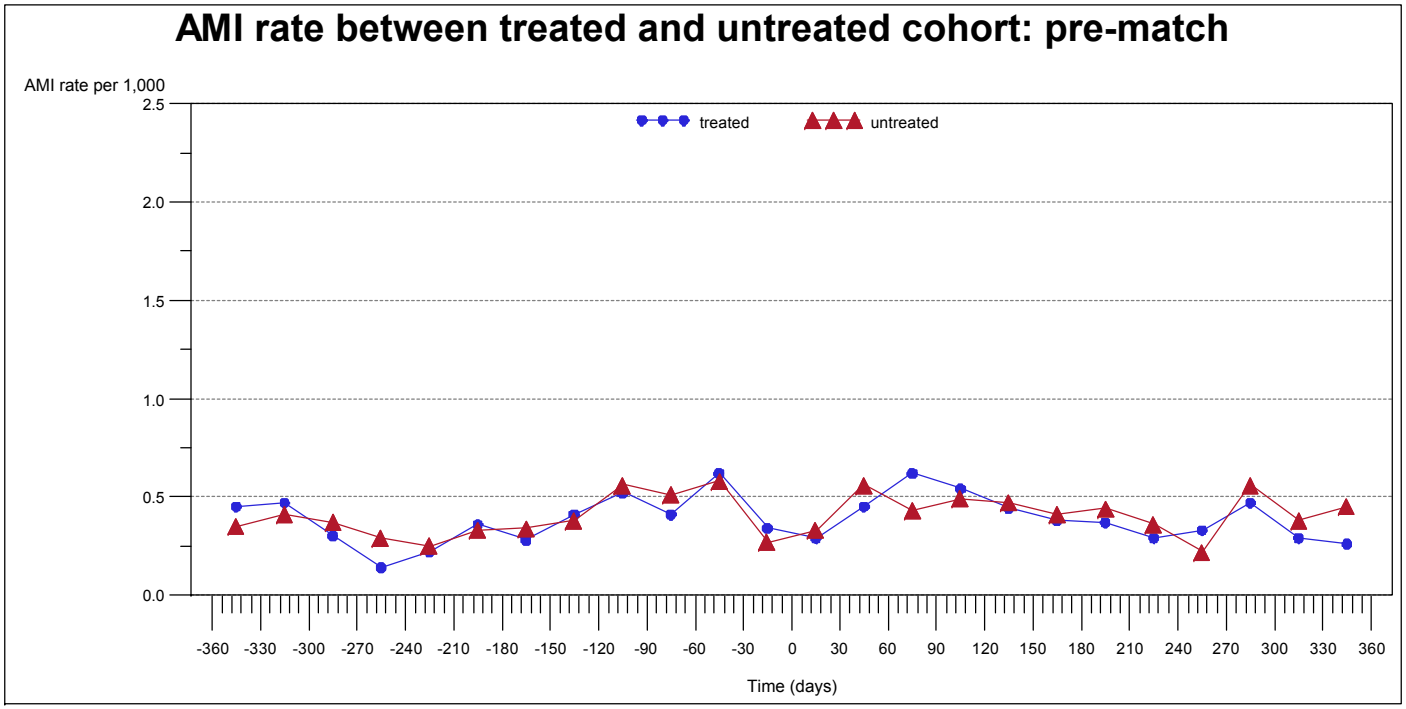

Figure Annex.2. **Mock Figure: AMI rate in every 30 days window during baseline and 1 year post-index period between TRT treated and untreated cohort.**

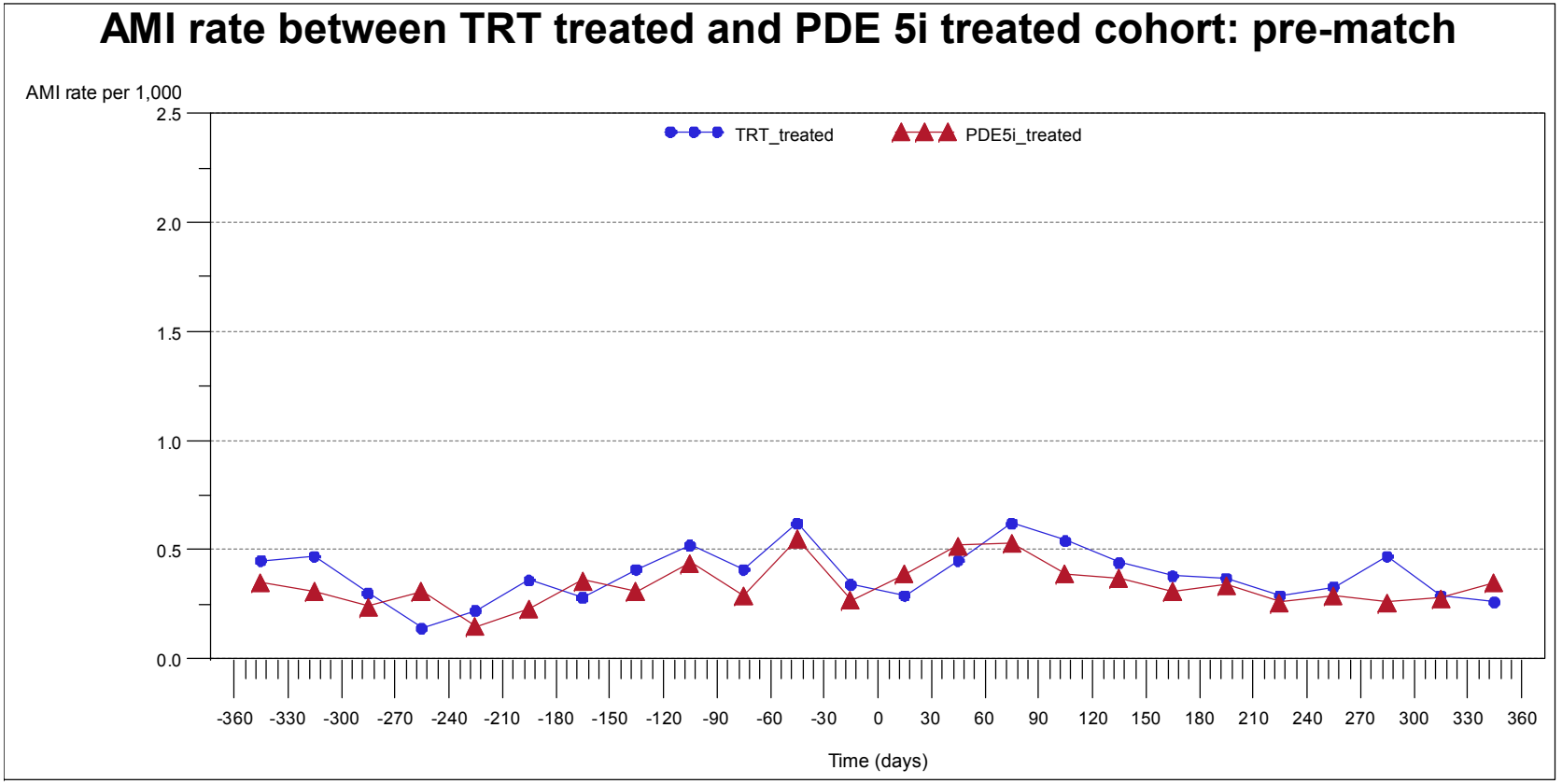

Figure Annex.3. **Mock Figure: AMI rate in every 30 days window during baseline and 1 year post-index period between TRT treated and PDE 5i treated cohort.**

Table Annex.5. Mock Table: Treatment Difference in the AMI rate during X days follow-up period for Propensity Matched Population between Testosterone treated and untreated group using Poisson Regression

MI Incidence rate				Unadjusted			Adjusted		
Treated N=xxx		Untreated N=xxx		RR	95% CI	P value	RR	95% CI	P value
n	%	n	%						
xx	x.xx	xx	x.xx	xx.xx	xx.xx-xx.xx	.xxxx	xx.xx	xx.xx-xx.xx	.xxxx

N=number of subjects in the propensity score matched sample; RR=risk ratio (treated vs. untreated); CI=confidence interval for the RR; RR, 95% CI and p value are from the poisson model with covariate adjustment and without covariate adjustment. Unadjusted model: AMI rate = Exposure; Adjusted model: AMI rate =Exposure Group + Age+ index year + baseline risk factors + concomitant medication + any baseline characteristics not balanced after propensity score matching

Table Annex.6. Mock Table: Treatment Difference in the AMI rate during X days follow-up period for Propensity Matched Population between Testosterone treated and PDE 5i treated group using Poisson Regression

MI Incidence rate				Unadjusted			Adjusted		
Testosterone Treated N=xxx		PDE 5i Treated N=xxx		RR	95% CI	P value	RR	95% CI	P value
n	%	n	%						
xx	x.xx	xx	x.xx	xx.xx	xx.xx-xx.xx	.xxxx	xx.xx	xx.xx-xx.xx	.xxxx

N=number of subjects in the propensity score matched sample; RR=risk ratio (testosterone treated vs. PDE 5i treated); CI=confidence interval for the RR; RR, 95% CI and p value are from the poisson model with covariate adjustment and without covariate adjustment. Unadjusted model: AMI rate = Exposure; Adjusted model: AMI rate =Exposure Group + Age+ index year + baseline risk factors + concomitant medication + any baseline characteristics not balanced after propensity score matching

Annex 10. Methodological Considerations in Conducting Observational Research on Acute Myocardial Infarctions and Testosterone Replacement Therapy

Methodological considerations in conducting observational research on myocardial infarction and testosterone replacement therapy

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Short title: Myocardial infarction and testosterone therapy

Abstract

Background: The potential link between testosterone replacement therapy (TRT) and increased risk of myocardial infarction (MI) is controversial. Finkle et al, using the 2006 to 2010 US-based Truven Health MarketScan Database, concluded that MI risk increased in men prescribed TRT but not in a control group prescribed a phosphodiesterase type 5 inhibitor (PDE5i). The analysis herein assessed the impact of the choice of comparator group on potential association of TRT and MI risk.

Methods: Using the MarketScan Database and the same post/pre-analysis as Finkle et al., MI risk was assessed in males prescribed: 1) TRT only vs PDE5i only and 2) TRT vs untreated hypogonadal men. Index date was first TRT or PDE5i prescription or randomly assigned first hypogonadal diagnosis date. MI event rate was calculated during 12-month pre- and post-index periods (30 days and 1 year) stratified by age.

Results: 142,358 TRT-treated men (105,815 excluding PDE5i users), 86,643 untreated hypogonadal men, and 359,321 PDE5i-treated men were identified. Compared to untreated men (aged 51.5±13.0), men in the TRT cohort (aged 53.0±11.5) and PDE5i cohort (aged 54.9±10.8) were slightly older. Among TRT-treated men, a numerical increase in observed MI incidence rate was found during 90-day post-index period (5.61; 95% CI, 4.76–6.45 per 1,000 person years) vs pre-index period (4.59; 95% CI, 4.24–4.95), especially among elderly men (>65 years). Among untreated hypogonadal men, a similar increase was observed during 90-day post-index (6.57; 95% CI, 5.40–7.73) vs pre-index periods (4.48; 95% CI, 4.03–4.92). An increased observed MI incidence rate in post-index period was not found for the PDE5i-treated cohort.

Conclusion: This descriptive analysis demonstrated a similar increase in observed MI risk between TRT-treated men and hypogonadal men not receiving TRT. These results raise methodological concerns regarding the impact of the chosen control group on conclusions of the previous observational study.

Introduction

Prescriptions for testosterone supplementation are typically written for men desiring to overcome the signs and symptoms of hypogonadism [1]. A total of 3% of men in the United States (US) are current users of testosterone replacement therapy (TRT) [2]. Deciding who should receive TRT is challenging because of the difficulty in diagnosing hypogonadism in older men, as the condition is often associated with multiple co-morbid conditions [3].

Although TRT has been used for decades, there are limited long-term safety data [4]. Notably, recent epidemiological/clinical studies, meta-analyses, and commentaries have stimulated debates on whether or not TRT may increase the risk of adverse cardiovascular outcomes [5-19]. Specifically, 3 prospective studies have shown an association of cardiovascular-related risk with TRT [6,9,10], whereas other reports, including a recent meta-analysis, have refuted or not confirmed claims that TRT is associated with increased risk of cardiovascular-related events [12-19].

Finkle and colleagues performed a retrospective cohort analysis in more than 55,000 men using a real-world claims database [6]. They compared rates of non-fatal myocardial infarction (MI) in men in the 12 months prior to being prescribed TRT vs the immediate 3 months following the prescription. As a control group, they also evaluated rates of non-fatal MI in a group of men before and after receiving a phosphodiesterase type 5 inhibitor (PDE5i) prescription. The authors concluded that the risk of non-fatal MI was increased in older men (≥65 years), as well as in younger men (<65 years) with pre-existing heart disease, who had received TRT [6]. By contrast, a significant increase in

MI risk was not seen among men prescribed a PDE5i. Questions have been raised about the analysis performed by Finkle et al regarding whether the choice of the control group may have led to erroneous conclusions [20]. Specifically, given that their analysis sought to determine the cardiovascular impact of the use of TRT, it is worthwhile to understand whether men with a diagnosis of hypogonadism (the condition that TRT may treat), but who were not prescribed testosterone therapy may have been a more appropriate comparator than men prescribed PDE5i. It is well appreciated that men with low total or free serum testosterone levels are at increased risk for potentially fatal cardiovascular events [21,22]. It is possible that the increased risk of MI in men treated with TRT was a reflection of their increased cardiovascular risk due to hypogonadism rather than treatment with testosterone. In addition, previous publications have raised the possibility that PDE5i medications may have cardioprotective properties to reduce mortality/morbidity (eg, anti-cardiac remodeling effects, inotropism, cardiac performance, and endothelial function), especially when the patients take a PDE5i medication long term [23-25].

In an effort to better assess the impact of a different study design on the association between testosterone treatment and the risk of MI, we used the MarketScan database to understand if the choice of the comparator group might have had an impact on the study outcome. Our analysis included an evaluation of the appropriateness of the comparator cohort (ie, PDE5i) and the study design (ie, post- vs. pre-treatment period). The present study was not intended to evaluate if the risk of MI did or did not increase among patients treated with TRT using statistical modeling, but rather the purpose was to evaluate the appropriateness of the validity of the study design used by Finkle et al.

Methods

This retrospective, cohort study used the 2006 to 2010 US-based Truven Health MarketScan® Research Database in the analysis, which includes individual-level, de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. The primary outcome of MI (fatal, non-fatal, or both) was defined by inpatient ICD-9 diagnosis code 410.

The study population consisted of men at least 18 years of age treated with TRT or PDE5i for underlying disease or men with relevant hypogonadal diagnoses without a testosterone prescription. All men had at least 12 months (365 days) of continuous enrollment in the health plan prior to the index date, which was defined as no enrollment gap exceeding 31 consecutive days. The index date was identified as the first prescription of TRT, first prescription of PDE5i, or first randomly assigned hypogonadism diagnosis date [26]. Unlike Finkle et al, we did not include a 6-month pre-baseline period in this preliminary analysis. Subjects were excluded from the study if they were female or of dual gender. The identify of each subject was protected prior to the data analysis (eg, all data was anonymized and de-identified prior to analysis).

Two descriptive and comparative post-index vs pre-index analyses were conducted in the current study among 4 cohorts of men: 1) TRT only treated men vs PDE5i-treated men [analysis 1], and 2) TRT-treated men vs untreated hypogonadal men [analysis 2]. The cohorts were defined as follows: The **TRT-treated** cohort included men within the database who received at least 1 new prescription for a testosterone product after the baseline period. The **untreated cohort** included men who had at least 1

diagnostic code for a hypogonadal condition in the claims database (ICD-9 codes: 257.2, 257.8, 257.9, and 758.7), but who had not received TRT. Men in these 2 cohorts were not excluded on the basis of having a prescription for a PDE5i. The **TRT only** cohort included men in the TRT-treated cohort, but excluded those also prescribed PDE5i. The **PDE5i cohort** included men who received at least 1 new PDE5i prescription after the baseline period and did not have a record of a TRT prescription. This study adopted an incident-user design, which included incident users of TRT and incident users of PDE5i who had not received relevant prescriptions during the baseline period.

The first post-index vs pre-index analysis was performed to reflect the comparison in Finkle et al, between the TRT only vs PDE5i cohort; the second post-index vs pre-index analysis was added to assess the impact on their findings by using a different comparator group (ie, untreated hypogonadal cohort). For untreated hypogonadal men, the index date was derived from the distribution of the number of days between the initial hypogonadal diagnosis and prescription date of initial testosterone among the treated men. To address timing-related bias (accounting for the lag between hypogonadism diagnosis and TRT), the index date was selected at random and assigned to the untreated men. Therefore, the overall distribution of the index date of the untreated men matched that of the treated time for men receiving their first testosterone prescription. The pre-index period was defined as 12 months prior to the index date. The incidence rate was defined as the number of new cases of MI during the post-index time periods divided by the person-time-at-risk throughout the observation period; 95% confidence intervals (CI) for the rates were also calculated. The observation period was based on 1) the entire follow-up time before the index date, 2) the 90-day follow up time

after the index date, and 3) the 1-year post index follow-up time divided by 30-day time windows (sensitivity analysis). All analyses were descriptive without covariate adjustment, stratifying by age (any age, ≤65 years, and >65 years). All analyses were performed using SAS® 9.2 version (Copyright (c) 2002-2008 by SAS Institute Inc., Cary, NC, US).

Results

In the current study, 142,358 TRT-treated men, 105,815 TRT only treated men, 86,643 untreated hypogonadal men, and 359,321 men treated with PDE5i only were identified from the database. Compared to untreated men (aged 51.5 ± 13.0 years), men treated with TRT (aged 53.0 ± 11.5 years), TRT only (aged 52.3±11.8), or PDE5i only (aged 54.9 ± 10.8 years) were, on average, slightly older (**Table 1**). Furthermore, a higher prevalence of baseline cardiovascular comorbidities (eg, hypertension, diabetes mellitus, and dyslipidemia) [27] and associated medications were found among men initiating TRT compared to those who did not receive treatment (untreated hypogonadal cohort) (**Table 1**). Slightly higher rates of cardiovascular comorbidities, risk factors, and associated medications were also observed in the cohort receiving TRT only vs PDE5i only (**Table 1**).

The first descriptive analysis demonstrated a numerical increase in the observed MI incidence rate among men receiving TRT only vs. PDE5i only during the post-index period compared to the pre-index period (**Table 2**). Specifically, the unadjusted analysis showed an increase in the observed MI incidence rate for the TRT only cohort during the 90-day post-index period (5.64; 95% CI, 4.65–6.63 per 1000 person years [PY]) vs the

365-day pre-index period (4.80; 95% CI, 4.38–5.22 per 1000 PY), especially among elderly patients (>65 years). By contrast, an increase trend in the MI incidence rate was not clearly found during the 90-day post-index period among men administered PDE5i.

In the second descriptive analysis, a similar numerical increase in the observed MI incidence rate was demonstrated in the TRT-treated cohort during the first 90 days after they obtained prescriptions for TRT and in the cohort of untreated hypogonadal men during the first 90 days after a randomly assigned hypogonadism diagnosis date. For the treated cohort, the increase in the observed MI incidence rate during the 90-day post-index period (5.61 [95% CI, 4.76–6.45] per 1000 PY) vs the 365-day pre-index period (4.59 [95% CI, 4.24–4.95] per 1000 PY) was similar to the increase observed among untreated hypogonadal men in the 90-day post-index period (6.57 [95% CI, 5.40–7.73] per 1000 PY) vs the 365-day pre-index period (4.48 [95% CI, 4.03–4.92] per 1000 PY) (**Table 3**).

Further sensitivity analyses showed that the MI event rate in 30-day time windows during the 1-year pre-index period was similar in TRT-treated men compared with untreated hypogonadal men (**Figure 1A-1C**). The lack of apparent differences in the observed incidence of MI between TRT-treated men and untreated hypogonadal men was also upheld in the post-index period, especially among men ≤65 years. Although similar results were also observed for men >65 years, there was greater variability in the MI incidence rates in this age group.

Discussion

Although this analysis and the Finkle et al study [6] demonstrated a numerical increase of MI risk in TRT-treated patients, it does not imply a causal relationship or a positive association. The current descriptive analyses reported herein are methodologically and potentially clinically relevant, as they raise concerns that study findings can vary greatly when a different comparison cohort is chosen. It has also been recognized by others that PDE5i-treated patients may not be an appropriate comparator to study CV risk [20] due to a selection bias because patients who are eligible for a PDE5i prescription and maintain sexual activities may have better cardiovascular function [24,25]. Furthermore, a protopathic bias may exist among patients who took TRT or who were diagnosed with hypogonadism. Specifically, fatigue is a common symptom that leads clinicians to prescribe TRT or make a hypogonadism diagnosis, yet it is also a possible prodromal symptom of a pending acute MI [28]. Such biases have to be carefully considered before conducting any epidemiological study.

The first analysis described herein supports the findings of Finkle et al [6] that demonstrated a numerical increase in observed MI risk from the 12-month pre-index to the 90-day post-index period among men receiving TRT, but not among men receiving a PDE5i. The second analysis confirmed a numerical rise in the observed 90-day post-index MI rate following TRT, in the context of similar findings within an untreated hypogonadal population. As recently stated by Morgentaler, the absence of a correct comparator group (ie, men with low testosterone levels who did not receive TRT) in the study by Finkle et al makes it impossible to ascertain whether the observed increase in MI rates was due to increased testosterone levels or the subject's underlying condition (hypogonadism) [20]. In contrast, a very recent study published by Baillargeon et al that

utilized a cohort from the general population based on prognostic index score and matched non-users as a comparison group did not find an increased risk of MI among intramuscular testosterone users [29].

Moreover, men receiving PDE5i cannot be assumed to have underlying hypogonadism (ie, low testosterone levels) and may in fact be healthier and have less underlying cardiovascular comorbidity and concomitant associated medications, possibly due to warnings and precautions in the PDE5i product labels, than men receiving TRT (as shown in Table 1). However, as 1 limitation of this observational study, the diagnosis of hypogonadism was solely based on the ICD-9 diagnostic codes without considering clinical symptoms or laboratory measurement, which was infrequently captured in the database. In order to address this potential concern, we conducted a preliminary assessment of the laboratory data in the Truven MarketScan database. Although not representative of the study cohorts, patients with reported baseline testosterone levels showed a numerically higher endogenous testosterone level among patients treated with a PDE5i, followed by the untreated patients with a hypogonadism diagnosis; TRT-treated patients had the numerically lowest testosterone levels among all groups (data not shown). In any event, because this analysis used a secondary data source, we do not have the ability to check the correctness of the diagnosis. Therefore, future studies are warranted to evaluate a more accurate ascertainment of hypogonadism by taking into account the differences in baseline endogenous testosterone level, other appropriate measures, and symptomatology.

The second descriptive post-index vs pre-index analysis among men treated with TRT and untreated hypogonadal men provides evidence that the underlying disease of

hypogonadism, and not a short course of TRT, may be correlated with the observed increased rates of MI during the 90 days after the index date. This supposition is not unexpected given the plethora of literature that has linked testosterone deficiency with increased cardiovascular adverse events and increased mortality [21, 22, 30-37]. It is possible that low testosterone in some men may be a marker of poorer overall health status, which may be reflected in an increased risk of MI. The reason for the observed increased risk of MI among men with a hypogonadal diagnosis deserves further evaluation. It is also possible that the observation of increased MI risk in newly diagnosed hypogonadal men might be attributable to other factors such as imperfections in the study design (eg, pre-index MI events were non-fatal, vs post-index MI events that were a mix of fatal and non-fatal).

Furthermore, the difference in findings reported in our analyses vs. Finkle et al may have resulted from the impact of different eligibility criteria on the study outcome. For example, the patients included in the Finkle et al study [6] were required to have different months of data records for the pre- and post-index periods (18 month pre-index and 3 or 6 month post index), and the MIs that occurred during the pre-index period were likely to be non-fatal given that men had to survive to receive the TRT prescription or diagnosis (index date). In contrast, MIs that occurred post index did not have the same eligibility criteria, as these events could be a mix of fatal and non-fatal episodes. A similar approach was used in the present analysis to replicate the Finkle et al findings, but the pre/post-index approach used by Finkle et al was not endorsed by our group. Additionally, because a similar trend was also observed among untreated hypogonadal patients, those not exposed to TRT, this finding raises concerns with the conclusions

drawn from the Finkle et al study [6]. Future studies are warranted to better understand if the post/pre-analysis approach is applicable to pharmacoepidemiological studies involving fatal outcomes such as acute MI.

It is important to reemphasize that the current analyses aimed to raise methodology concerns with the study design used by Finkle et al [6], but did not intend to evaluate the association of MI between TRT-treated vs untreated cohorts using any statistically adjusted approach; however, another adjusted comparative safety study is underway to evaluate this question. In the current descriptive study, the incidence rate of MI was constant during the 1-year post-index period, which did not replicate observations by Finkle et al that the rate declined in the 91- to 180-day post-index period among older men (>65 years) who did not have their TRT prescription refilled [6].

The new descriptive data presented above should not be compared directly with that reported by Finkle et al [6], in part, because of the distinct differences in study objectives and some potential study design features, including data source and definition of MI. For example, it is unknown whether the study by Finkle and colleagues included all data sources from the MarketScan Database in their analyses (Commercial, Medicare, and Multi-State Medicaid data) and which definition of MI was applied in their analyses (eg, inpatient only or inpatient and outpatient codes).

The current analysis has a number of limitations in addition to those mentioned above. The analyses are descriptive in nature; therefore, the results were not adjusted for confounding factors (eg, risk factors of MI) and no formal statistical tests were conducted to compare rates between cohorts (eg, relative risk [RR], hazard ratio [HR]). Assessment of such factors is critical as previously published analyses in the same data source

showed that there were differences in the demographic profile and cardiovascular risk factors among men treated with TRT vs untreated (of note, in this study men treated with TRT had a worse cardiovascular profile at pre-treatment baseline compared to untreated men) [38,39]. Future comparative safety analyses with an aim to evaluate the drug event association will need to adjust the pre-treatment (baseline) comorbidities and this refinement will allow more robust estimation of quantitative estimates of MI association in the treatment cohort. In addition, the current descriptive analyses reported herein did not exclude men who had an acute MI prior to the 365-day baseline period (as done in the study by Finkle et al [6]) because we did not include a 6-month evaluation prior to the baseline period. Therefore, the MI events included in the baseline period may be a combination of incident and recurrent MI events. This combination is considered conservative because only the incident MI rate was used during the post-index period. Therefore, due to fewer cases/events that were captured in the post-index period, there may be a larger variation observed for the post index period. Further adjusted analyses are currently underway to address these limitations. Finally, there are a number of limitations inherent to observational studies such as diagnoses, medical procedures, and medicine dispensing that will not be captured if corresponding billing codes were not generated; therefore, the use of the ICD-9-CM codes, current procedural terminology codes, or national drug codes is subject to the incompleteness or inaccuracies of the coding in the database. Additionally, Truven MarketScan claims databases are based on a large convenience sample with the data captured mostly from large employers including Medicare and Medicaid (medium and small firms are not represented); thus, the sample is not random and may contain biases or fail to generalize well to other populations. Finally,

only prescribed medicines are recorded in the MarketScan database; therefore, no information about adherence or over-the-counter drug (eg, aspirin) use is available.

In summary, our descriptive analyses raise several methodological concerns and the possibility that the recent findings of Finkle and colleagues should be questioned. If rates of MI rise similarly in men treated with TRT and in hypogonadal men not receiving TRT, it is difficult to assign causality to TRT using observational data. Rather, consistent with the epidemiologic literature, hypogonadism itself may increase the risk of MI or the observed increased MI risk shortly following TRT may simply be a reflection of the limitations of the study design. It is important that when future analytical studies to evaluate MI risk among TRT-treated patients are performed that these considerations in study design, including the appropriate choice of comparators, are factored in.

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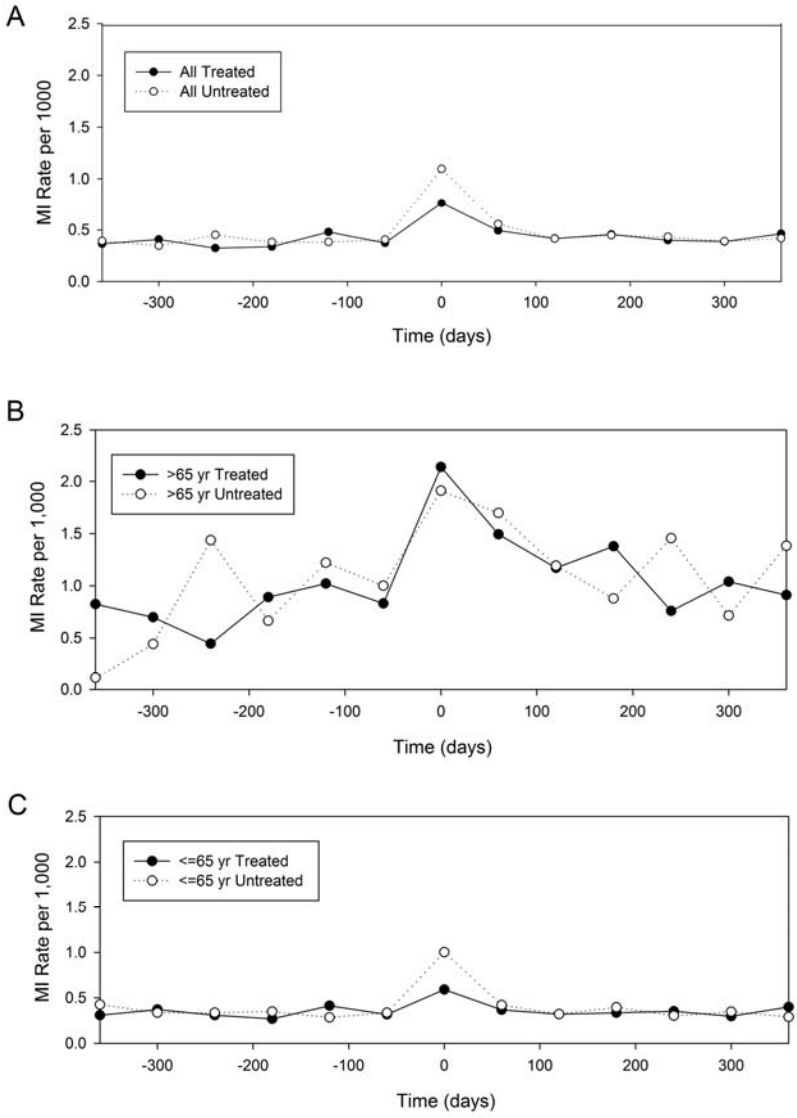
Figure Legend

Figure 1A-1C. Myocardial risk rate 1 year prior to and 1 year post index date

Full legend: Conditional probability of a myocardial event rate in TRT-treated men and untreated hypogonadal men (men taking a phosphodiesterase type 5 inhibitor [PDE5i] were not excluded from either cohort) 1 year prior to and 1 year post index date using 30-day window intervals: 1A) all ages combined, 1B) >65 years, 1C) ≤65 years. Index date defined as the first prescription of testosterone replacement therapy, first prescription of PDE5i, or first randomly assigned hypogonadism diagnosis date.
0 = index date.


A
All Treated
All Untreated
MI Rate per 1000
Time (days)
B
>65 yr Treated
>65 yr Untreated
MI Rate per 1,000
Time (days)
C
<=65 yr Treated
<=65 yr Untreated
MI Rate per 1,000
Time (days)

462

463

Table 1. Baseline demographics and risk factors for acute myocardial infarction in men with a testosterone replacement therapy (TRT) prescription, men diagnosed with hypogonadism without a TRT prescription, and men with a phosphodiesterase type 5 inhibitor (PDE5i) only prescription

Characteristic	TRT vs Hypogonadism analysis		TRT vs PDE5i analysis	
	Men with TRT prescription* (N=142,358)	Men with no TRT prescription† (N=86,643)	Men with TRT only prescription‡ (N=105,815)	Men with PDE5i only prescription‡ (N=359,321)
Demographics and healthcare utilization				
Mean age at index date, years ± SD	53.0 ± 11.5	51.5 ± 13.0	52.3 ± 11.8	54.9 ± 10.8
Number of hospitalizations, n ± SD	0.1 ± 0.5	0.1 ± 0.4	0.1 ± 0.5	0.1 ± 0.4
Total days in hospital, n ± SD	0.7 ± 5.1	0.5 ± 4.1	0.7 ± 5.4	0.5 ± 3.0
Risk factor for acute myocardial infarction and other comorbid conditions (Based on diagnosis codes), n (%)				
Charlson comorbidity index, mean ± SD	1.1 ± 1.7	1.0 ± 1.7	1.1 ± 1.7	1.0 ± 1.6)
Hypertension	64,780 (45.5)	34,327 (39.6)	47,016 (44.4)	151,755 (42.2)
Hypercholesterolemia	67,324 (47.3)	38,148 (44.0)	49,688 (47.0)	144,584 (40.2)
Diabetes mellitus	32,519 (22.8)	16,305 (18.8)	23,412 (22.1)	66,120 (18.4)

Congestive heart failure	6,898 (4.9)	3,692 (4.3)	5,163 (4.9)	13,379 (3.7)
Ischemic stroke	4,108 (2.9)	2,347 (2.7)	3,039 (2.9)	8,116 (2.3)
Cerebrovascular disease	4,471 (3.1)	2,587 (3.0)	3,290 (3.1)	9,010 (2.5)
Peripheral vascular disease	6,299 (4.4)	3,661 (4.2)	4,629 (4.4)	12,522 (3.5)
Hypogonadism	57,249 (40.2)	50,696 (58.5)	42,819 (40.5)	7,268 (2.0)
Infection	13,082 (9.2)	8,123 (9.4)	9.799 (9.3)	25,879 (7.2)
Cancer	13,334 (9.4)	8,906 (10.3)	9.671 (9.1)	43,966 (12.2)
Renal disease	4,618 (3.2)	2,732 (3.2)	3.466 (3.3)	8,667 (2.4)
Klinefelter syndrome	124 (0.1)	107 (0.1)	123 (0.1)	2 (<0.1)
Sleep disturbance	25,775 (18.1)	11,328 (13.1)	19,482 (18.4)	31,730 (8.8)
Malaise	41,409 (29.1)	17,293 (20.0)	33,106 (31.3)	29,419 (8.2)
Pituitary disorders	5,251 (3.7)	1,449 (1.7)	4,200 (4.0)	634 (0.2)
Testicular cancer	615 (0.4)	450 (0.5)	513 (0.5)	508 (0.1)
Prostate disease	19,236 (13.5)	12,838 (14.8)	13,087 (12.4)	44,733 (12.5)
Prostate cancer	2,647 (1.9)	3,125 (3.6)	1,730 (1.6)	22,586 (6.3)
Thyroid disease	14,954 (10.5)	8,560 (9.9)	11,607 (11.0)	17,294 (4.8)

Osteoporosis	2,745 (1.9)	1,492 (1.7)	2,180 (2.1)	1,931 (0.5)
Depression	14,392 (10.1)	6,830 (7.9)	10,989 (10.4)	20,922 (5.8)
Cognitive impairment	180 (0.1)	123 (0.1)	132 (0.1)	289 (0.1)
Chronic obstructive pulmonary disease	6,805 (4.8)	3,701 (4.3)	5,145 (4.9)	13,403 (3.7)
Asthma	6,346 (4.5)	3,563 (4.1)	4,802 (4.5)	11,114 (3.1)
Concomitant medications, n (%)				
Antihyperlipidemic agents	64,360 (45.2)	30,304 (35.0)	46,180 (43.6)	147,480 (41.0)
Antihypertensive agents	75,260 (52.9)	35,893 (41.4)	54,101 (51.1)	182,326 (50.7)
Antidiabetic agents	27,229 (19.1)	12,245 (14.1)	19,538 (18.5)	55,296 (15.4)
Hematologic agents	12,521 (8.8)	6,072 (7.0)	9,303 (8.8)	27,442 (7.6)
Opiates	62,766 (44.1)	31,044 (35.8)	45,966 (43.4)	128,243 (35.7)
Psychotropic agents	54,015 (37.9)	24,211 (27.9)	40,271 (38.1)	88,402 (24.6)
Sleep medications	18,982 (13.3)	8,281 (9.6)	13,629 (12.9)	30,543 (8.5)

*Includes men who received any testosterone product with or without a phosphodiesterase type 5 inhibitor (PDE5i)
†Includes men who may have received a PDE5i
‡Excludes men who received any testosterone product and PDE5i concomitantly

Table 2. Rates of myocardial infarction per 1000 person years (PY) in all men, men aged ≤65 years, and men aged >65 years in pre- and post-prescription interval for initial testosterone replacement therapy (TRT) vs phosphodiesterase type 5 inhibitor (PDE5i)

Unadjusted analysis						
	Men with TRT only prescription*			Men with PDE5i only prescription*		
	All ages	Age ≤65 years	Age >65 years	All ages	Age ≤65 years	Age >65 years
Subjects (N)	105,815	94,570	11,245	359,321	310,243	49,078
Pre-prescription (pre-index): 365 days						
Cases, n	508	402	106	1656	1354	302
Rate per 1,000 PY	4.80	4.25	9.43	4.61	4.36	6.15
95% CI	4.38, 5.22	3.84, 4.67	7.63, 11.22	4.39, 4.83	4.13, 4.60	5.46, 6.85
Post-prescription (post-index): 90 days						
Cases, n	125	91	34	379	298	81
Rate per 1,000 PY	5.64	4.61	14.17	4.82	4.42	7.27

95% CI	4.65, 6.63	3.66, 5.56	9.41, 18.94	4.34, 5.31	3.92, 4.92	5.69, 8.86

*Men taking a concomitant testosterone product and phosphodiesterase type 5 inhibitor (PDE5i) were excluded

Table 3. Rates of myocardial infarction per 1000 person years (PY) pre- and post-index intervals for initial testosterone replacement therapy (TRT) prescription or first randomly assigned date of diagnosis with hypogonadism without a TRT prescription

Unadjusted analysis						
	Men with TRT prescription*			Men with no TRT prescription*		
	All ages	Age ≤65 years	Age >65 years	All ages	Age ≤65 years	Age >65 years
Subjects (N)	142,358	126,575	15,783	86,643	77,579	9,064
Pre-prescription (pre-index): 365 days						
Cases, n	654	511	143	388	305	83
Rate per 1,000 PY	4.59	4.04	9.06	4.48	3.93	9.16
95% CI	4.24, 4.95	3.69, 4.39	7.58, 10.55	4.03, 4.92	3.49, 4.37	7.19, 11.13
Post-prescription (post-index): 90 days						
Cases, n	169	124	45	122	93	29
Rate per 1,000 PY	5.61	4.64	13.29	6.57	5.61	14.55
95% CI	4.76, 6.45	3.82, 5.45	9.41, 17.17	5.40, 7.73	4.47, 6.75	9.26, 19.85

*Men taking a phosphodiesterase type 5 inhibitor (PDE5i) were not excluded

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