# Impact of Testosterone Replacement Therapy on Myocardial Infarction, Stroke, and Death in Men With Low Testosterone Concentrations in an Integrated Health Care System

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**The aim of this study was to assess the effect of testosterone replacement therapy (TRT) on cardiovascular outcomes. Men (January 1, 1996, to December 31, 2011) with a low initial total testosterone concentration, a subsequent testosterone level, and >3 years of follow-up were studied. Levels were correlated with testosterone supplement use. The primary outcome was major adverse cardiovascular events (MACE), defined as a composite of death, nonfatal myocardial infarction, and stroke at 3 years. Multivariate adjusted hazard ratios (HRs) comparing groups of persistent low (<212 ng/dl, n = 801), normal (212 to 742 ng/dl, n = 2,241), and high (>742 ng/dl, n = 1,694) achieved testosterone were calculated by Cox hazard regression. A total of 4,736 men were studied. Three-year rates of MACE and death were 6.6% and 4.3%, respectively. Subjects supplemented to normal testosterone had reduced 3-year MACE (HR 0.74; 95% confidence interval [CI] 0.56 to 0.98, p = 0.04) compared to persistently low testosterone, driven primarily by death (HR 0.65, 95% CI 0.47 to 0.90). HRs for MI and stroke were 0.73 (95% CI 0.40 to 1.34), p = 0.32, and 1.11 (95% CI 0.54 to 2.28), p = 0.78, respectively. MACE was noninferior but not superior for high achieved testosterone with no benefit on MI and a trend to greater stroke risk. In conclusion, in a large general health care population, TRT to normal levels was associated with reduced MACE and death over 3 years but a stroke signal with high achieved levels suggests a conservative approach to TRT.**  **(Am J Cardiol 2015;■:■−■)**

Testosterone has been approved in the United States since the 1950s as replacement therapy for male hypogonadism.[1] Beyond relatively uncommon cases of classical hypogonadism, many otherwise healthy men experience a decrease in serum concentrations of testosterone with age. Although the decrease is usually modest, levels may fall below the lower limit of the normal range for younger, healthy men, a condition referred to as "andropause" or "age-related hypogonadism."[2] Furthermore, aging men often experience signs and symptoms associated with hypogonadism, including reduced levels of energy, sexual function, muscle mass and strength, and bone mineral density and increases in fat mass. Epidemiologic studies have identified low testosterone in middle-aged and older men as an independent risk factor for cardiovascular (CV) disease, cancer, and total mortality.[3,4] In response to an aging population, a desire to maintain youthful health and energy, and direct-to-consumer advertising, the use of testosterone replacement therapy (TRT) has increased dramatically in recent years. The US Food and Drug Administration (FDA) has estimated that testosterone supplements sold from 2009 to 2013 increased 65%, and the number of patients receiving TRT prescriptions increased from 1.3 million to 2.3 million, with men 40- to 60-year old accounting for 70% of prescriptions.[1,5] Despite this trend, the extent to which age-related symptoms are a consequence of low testosterone levels and for which TRT is clinically effective is unclear. Furthermore, the impact of TRT on CV outcomes is controversial and largely based on limited, mostly retrospective study data with disparate conclusions.[1,6−13] The incomplete and conflicting data from these studies have led to contrasting international regulatory agency conclusions as to the risk versus benefit of TRT.[1,14,15] Given this lack of clarity in its CV risk impact, we sought to assess the safety of TRT prescribed by licensed physicians for symptomatic patients across a large, integrated health care system.

## Methods

The study prespecified the following primary and secondary hypotheses:

1. Men with documented testosterone deficiency replaced to the normal range with TRT have no greater risk of death, myocardial infarction (MI), or stroke (major adverse CV event [MACE]) at 1 and 3 years (primary outcome) than those who remain at low testosterone.
2. The risk of MACE will be increased for those with (1) persistently low testosterone and (2) an excessively

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See page 6 for disclosure information.

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Table 1
Baseline characteristics of the study population (n = 4,736) stratified by categories of follow-up testosterone level

| Characteristic | Testosterone Levels (ng/dL) | | | p-value |
|---|---|---|---|---|
| | <212 (n=801) | 212-742 (n=2,241) | >742 (n=1,694) | |
| Age (years) | 62.8±9.7 | 61.2±8.3 | 60.4±8.5 | <0.0001 |
| Hypertension | 58.3% | 57.0% | 53.2% | 0.02 |
| Hyperlipidemia | 54.7% | 59.5% | 58.6% | 0.06 |
| Diabetes mellitus | 32.6% | 29.3% | 23.0% | <0.0001 |
| Smoke | 20.3% | 18.2% | 16.5% | 0.06 |
| History of coronary artery disease (stenosis ≥70%) | 25.0% | 20.0% | 19.7% | 0.005 |
| Prior myocardial infarction | 5.7% | 3.9% | 3.5% | 0.03 |
| History of heart failure | 12.1% | 8.2% | 6.8% | <0.0001 |
| Prior stroke | 2.4% | 1.6% | 1.8% | 0.33 |
| Peripheral artery disease | 2.7% | 2.5% | 2.0% | 0.47 |
| Atrial fibrillation | 7.9% | 7.4% | 7.9% | 0.85 |
| Prior pulmonary embolism | 2.6% | 2.7% | 2.4% | 0.77 |
| Chronic obstructive pulmonary disease | 10.1% | 4.9% | 3.2% | <0.0001 |
| Renal failure | 6.3% | 4.8% | 3.7% | 0.02 |
| Body metabolic index (kg/m$^2$), n=1,192 | 33.1±7.1 | 32.4±7.8 | 32.0±6.9 | 0.27 |
| Angiotensin Converting Enzyme Inhibitor* | 12.0% | 12.4% | 10.0% | 0.07 |
| Angiotensin II Receptor Blocker* | 5.5% | 5.0% | 5.8% | 0.59 |
| Calcium Channel Blocker* | 6.2% | 6.2% | 5.7% | 0.75 |
| Diuretic* | 16.0% | 11.9% | 11.3% | 0.003 |
| Statin* | 14.7% | 16.1% | 16.1% | 0.63 |
| Baseline testosterone | 121.7±66.1 (median: 139) | 144.3±60.8 (median: 164) | 141.8±56.8 (median: 158) | <0.0001 |
| Intermountain Mortality Risk Score, n=1,100[17] | 10.0±4.0 | 9.5±3.9 | 9.9±3.6 | 0.21 |
| Charlson Comorbidity Index, n=3,071 | 2.8±2.1 | 2.5±2.0 | 2.4±1.7 | <0.0001 |

* Used within 90 days of index date.

high testosterone compared to those in whom testosterone is normalized.
3. The relative risk of CV outcomes of testosterone-deficient men replaced to normal testosterone is unaffected by age (<65 vs ≥65 years).
4. In men with preexisting coronary artery disease (CAD), MI, or stroke and low testosterone, TRT to normal testosterone is not associated with an increased risk of MACE.

Men who received care at an Intermountain Healthcare facility, were aged ≥50 years of age, had a documented low testosterone level (<212 ng/dl) and a follow-up testosterone, and at least 3 years of follow-up were identified. Those with a baseline diagnosis of malignancy (excluding basal and squamous cell carcinoma) were excluded because of potential confounding interactions with testosterone levels and therapies, resulting in a study cohort of 4,736 subjects. For primary and secondary hypothesis testing: (1) All qualifying men within Intermountain Healthcare with a first documented low testosterone level (<212 ng/dl; with time of test designated as the study entry date) and at least 3 years of electronic medical records follow-up were identified. (2) These men were then verified as receiving (or not) TRT by documentation of a testosterone prescription. (3) Men were categorized by achieved testosterone level (ng/ml) into 3 categories: <212 (low), 212 to 742 (normal), >742 (high). Patients were then followed for study end points at 1 and 3 years, starting from the date of the documentation of initiation of TRT or baseline testosterone in others who did not receive TRT.

Intermountain Healthcare is a large, electronically integrated health care organization that provides most of the health care for the state of Utah and southeastern Idaho. Intermountain's large electronic medical record database warehouse, comprising over 3 million patient records, including laboratory tests, medications, and patient diagnoses and outcomes, was searched from 1996 to 2011 to identify men meeting study inclusion and exclusion criteria. The study was approved by the Intermountain Urban Central Institutional Review Board.

Blood analyte testing was performed by the CLIA-certified (federal regulatory standards that apply to all clinical laboratory testing) Intermountain Healthcare Central Laboratories using standard methods. Serum total testosterone concentration was categorized as low (<212 ng/dl), normal (212 to 742 ng/dl), and high (>742 ng/dl) according to laboratory and manufacturer specifications. Testosterone measurement used a chemiluminescent competitive immune assay. Briefly, a serum sample is mixed with labeled testosterone and a solid-phase antitestosterone antibody. After the mixture achieves equilibrium, bound and free testosterone fractions are separated, and the amount of bound label is measured by the generation of a luminescent signal. Quantitation of testosterone in the sample then is determined by comparison to a standard curve. Because different laboratories may have differing ranges of normal, the laboratory's specified ranges rather than numerical stratification should be used to make comparisons between studies.

The primary independent subgrouping variable was the achieved testosterone level on follow-up, defined as persistently low, normal, or high. The primary end point of the study was the composite of all-cause death or nonfatal MI or stroke (MACE). Secondary end points were the individual

Table 2
Outcomes by achieved low, normal, and high testosterone level: *frequency % (n events)*

| | Testosterone Levels (ng/dL) | | |
|---|---|---|---|
| | <212 (n=801), 18% supplemented | 212-742 (n=2,241), 100% supplemented | >742 (n=1,694), 100% supplemented |
| Major adverse cardiovascular events | | | |
| 1 year[b] | 4.4% (35) | 2.0% (44) | 2.0% (34) |
| 3 years[b] | 11.3% (91) | 5.9% (132) | 5.3% (90) |
| All-cause death | | | |
| 1 year[b] | 2.9% (23) | 1.3% (29) | 0.7% (11) |
| 3 years[b] | 8.9% (71) | 3.8% (86) | 2.8% (47) |
| Myocardial infarction | | | |
| 1 year[a] | 1.4% (11) | 0.3% (7) | 0.6% (10) |
| 3 years | 2.2% (18) | 1.3% (30) | 1.5% (26) |
| Stroke | | | |
| 1 year | 0.6% (5) | 0.5% (11) | 0.9% (15) |
| 3 years | 1.5% (12) | 1.1% (25) | 1.5% (25) |
| Coronary death, n=4,650 | | | |
| 1 year | 0.8% (6/774) | 0.4% (8/2212) | 0.2% (4/1,664) |
| 3 years[a] | 2.2% (17/774) | 0.7% (16/2,212) | 0.9% (15/1,664) |
| Cardiovascular death, n=4,650 | | | |
| 1 year | 1.2% (9/774) | 0.6% (14/2,212) | 0.4% (7/1,664) |
| 3 years[a] | 3.5% (27/774) | 1.6% (35/2,212) | 1.6% (26/1,664) |
| Cardiovascular major adverse cardiovascular events, n=4,650 | | | |
| 1 year[a] | 2.7% (21/774) | 1.3% (28/2,212) | 1.8% (30/1,664) |
| 3 years[a] | 6.1% (47/774) | 3.7% (81/2,212) | 4.1% (69/1,664) |
| Cancer death, n=4,650 | | | |
| 1 year | 0.1% (1/774) | 0.2% (4/2,212) | 0% (0/1,664) |
| 3 years[a] | 1.8% (14/774) | 0.9% (21/2,212) | 0.4% (7/1,664) |

Cardiovascular major adverse cardiovascular events: cardiovascular death, myocardial infarction, and stroke.
[a]p <0.05; [b]p <0.0001.

components of MACE, type of death (CV, coronary, and cancer), and the composite of CV death, nonfatal MI, or stroke (CV-MACE). Death was determined by electronic medical records review, Utah Health Department death certificate records, and the national Social Security Death Index. Cause of death was only available in those who had a Utah State death certificate. CV death was defined as death from MI, stroke, heart failure, presumed arrhythmia (sudden death), or death not known to be due to a non-CV cause. Coronary death included fatal MI, sudden ischemic death, and any other death presumed to be related to coronary atherosclerosis. Nonfatal MI was defined as a hospitalization associated with a troponin I level >0.4 ng/ml or a discharge diagnosis of MI (*International Classification of Diseases* [ICD] 9 code 410; ICD-10 codes: I21, I22, I23). Stroke also was determined by ICD codes (ICD-9 code 433.1 and 434.1; ICD-10 codes: I60 to I64).

The Student *t* test, analysis of variance, and chi-square statistic were used as appropriate to compare baseline characteristics defined by achieved testosterone levels. The chi-square statistic and Fisher's exact test were also used to compare 1- and 3-year outcomes in the groups. Multivariate Cox hazard regression tests were used to determine the adjusted risk of the outcomes by achieved testosterone levels. Variables used in the modeling included age, hypertension, hyperlipidemia, smoking, diabetes, renal failure, previous CAD, previous MI, previous stroke, atrial fibrillation, heart

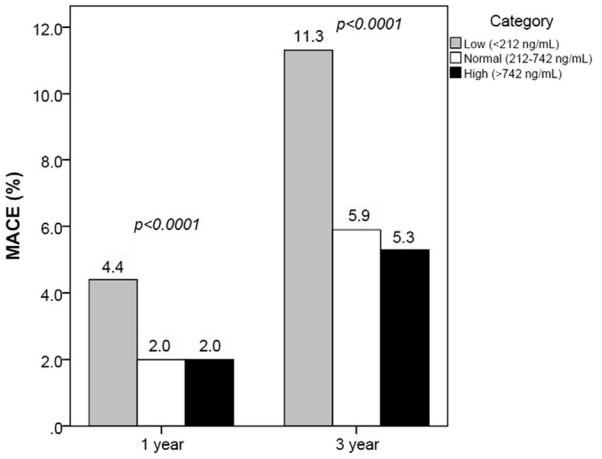


Figure 1. MACE by categories of achieved testosterone level at 1 and 3 years.

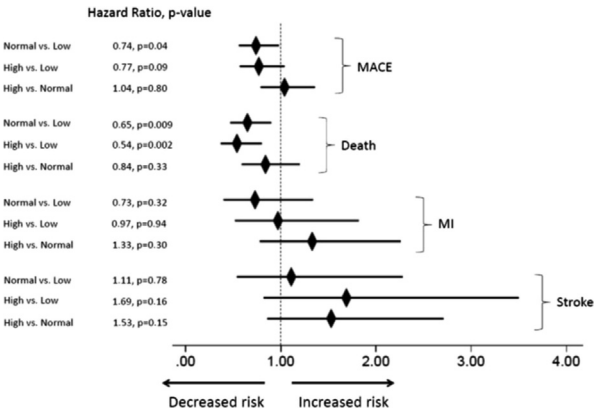


Figure 2. Multivariate adjusted hazard ratio comparisons for death, MI, and stroke in categories of achieved testosterone levels at 3 years.

failure, peripheral vascular disease, previous pulmonary embolism, chronic obstructive pulmonary disease, baseline testosterone level, angiotensin-converting enzyme inhibitors, angiotensin renin blockers, calcium channel blockers, diuretics, and statins. Subanalyses were performed in those who had a Charlson Comorbidity Index (CCI) score,[16] with the CCI used a model covariable. Only significant and confounding variables (i.e., associated with at least a 10% change in the β coefficient) were included in the final models. The noninferiority 95% confidence interval (CI) margin of the 3-year hazard ratio (HR) was designated as a delta of 0.2. When noninferiority was achieved, testing for superiority was performed.

## Results

A total of 4,736 qualifying men with low baseline testosterone were identified and studied. Baseline characteristics are summarized in Table 1. Overall age averaged 61.2 ± 8.7 years, 27.6% were diabetics, and 20.7% had documented CAD. On follow-up testosterone testing (at a median of 742 days after baseline), study patients were categorized as follows: persistently low (<212 ng/dl, n = 801), normal (212 to 742 ng/dl, n = 2,241), and high achieved testosterone

Table 3
Multivariable hazard ratios, 95% confidence intervals, and p-values for the comparisons of differing categories of achieved testosterone level

| | Testosterone Levels (ng/dL) | | |
|---|---|---|---|
| | 212-742 vs. <212 | >742 vs. <212 | >742 vs. 212-742 |
| Major adverse cardiovascular events | | | |
| 1 year | 0.65 (0.41, 1.03) p=0.07 | 0.83 (0.51, 1.36), p=0.47 | 1.28 (0.81, 2.02), p=0.29 |
| 3 years | 0.74 (0.56, 0.98), p=0.04 | 0.77 (0.57, 1.04), p=0.09 | 1.04 (0.79, 1.36), p=0.80 |
| All-cause death | | | |
| 1 year | 0.67 (0.38, 1.20) p=0.18 | 0.45 (0.22, 0.96), p=0.04 | 0.68 (0.33, 1.37), p=0.28 |
| 3 years | 0.65 (0.47, 0.90), p=0.009 | 0.54 (0.37, 0.80), p=0.002 | 0.84 (0.59, 1.20), p=0.33 |
| Myocardial infarction | | | |
| 1 year | 0.31 (0.11, 0.84), p=0.02 | 0.70 (0.27, 1.78), p=0.45 | 2.25 (0.85, 6.00), p=0.10 |
| 3 years | 0.73 (0.40, 1.34), p=0.32 | 0.97 (0.52, 1.82), p=0.94 | 1.33 (0.78, 2.26), p=0.30 |
| Stroke | | | |
| 1 year | 1.42 (0.46, 4.44), p=0.54 | 2.40 (0.81, 7.09), p=0.11 | 1.69 (0.74, 3.83), p=0.21 |
| 3 years | 1.11 (0.54, 2.28), p=0.78 | 1.69 (0.82, 3.50), p=0.16 | 1.53 (0.86, 2.71), p=0.15 |
| Coronary death, n=4,650 | | | |
| 1 year | 0.89 (0.28, 2.79), p=0.84 | 0.76 (0.19, 2.99), p=0.69 | 0.86 (0.25, 3.00), p=0.81 |
| 3 years | 0.58 (0.28, 1.19), p=0.14 | 0.79 (0.38, 1.66), p=0.54 | 1.38 (0.67, 2.81), p=0.38 |
| Cardiovascular death, n=4,650 | | | |
| 1 year | 0.93 (0.38, 2.30), p=0.89 | 0.95 (0.33, 2.74), p=0.92 | 1.01 (0.40, 2.57), p=0.99 |
| 3 years | 0.81 (0.48, 1.38), p=0.44 | 0.96 (0.54, 1.69), p=0.89 | 1.18 (0.71, 1.97), p=0.53 |
| Cardiovascular major adverse cardiovascular events, n=4,650 | | | |
| 1 year | 0.71 (0.39, 1.29), p=0.27 | 1.26 (0.70, 2.28), p=0.30 | 1.78 (1.04, 2.99), p=0.04 |
| 3 years | 0.91 (0.63, 1.32), p=0.62 | 1.20 (0.82, 1.78), p=0.35 | 1.33 (0.96, 1.83), p=0.09 |
| Cancer death | | | |
| 1 year* | – | – | – |
| 3 years | 0.67 (0.34, 1.36), p=0.27 | 0.33 (0.13, 0.84), p=0.02 | 0.49 (0.21, 1.17), p=0.11 |

N's available to assess coronary, cardiovascular, cardiovascular major cardiovascular events, and cancer deaths are noted in Table 2.

* Not enough events for 1 year assessment; major adverse cardiovascular events: all-cause mortality, myocardial infarction, and stroke; cardiovascular major adverse cardiovascular events: cardiovascular death, myocardial infarction, and stroke.

levels (>742 ng/dl, n = 1,694). TRT was provided to only 18% of those who with persistently low testosterone and to all with normal or high achieved testosterone. Of the different modes of testosterone therapy, gel was the primary mode used for supplementation (gel: 90%, injection: 9.0%, oral pill: 1.0%).

MACE event rates at 1 and 3 years by testosterone group are summarized in Table 2 and Figure 1. Overall 3-year rates of MACE and death were 6.6% and 4.3%, respectively. Multivariate adjusted HRs by testosterone group are presented in Figure 2 and Table 3. Noninferiority was achieved for the primary hypothesis test comparing normal attained testosterone to persistently low testosterone. Noninferiority also was achieved individually for all-cause death but not MI or stroke when comparing normal to low. Subsequent superiority testing indicated better outcomes for 3-year MACE (HR 0.74, 95% CI 0.56 to 0.98, p = 0.04), which was driven primarily by superiority for all-cause death (HR 0.65, 95% CI 0.47 to 0.90, p = 0.009).

For high attained testosterone, the adjusted HR for MACE at 3 years was noninferior but not superior to persistently low testosterone (0.77 [0.57 to 1.04], p = 0.09; Figure 2, Table 3). However, CV-MACE did not achieve noninferiority (HR 1.20, 95% CI 0.82 to 1.78) and was not significantly different compared to normal achieved testosterone (HR 1.33, 95% CI 0.96 to 1.83, p = 0.09). Although the risks of MI and stroke were low over 3 years, the adjusted HR trended to a higher stroke rate with high achieved testosterone compared to low (1.69 [0.82, 3.50], p = 0.16) and no benefit on MI rate.

To test for differential safety by age, we stratified by age <65 versus ≥65 years. As expected, event rates were substantially higher in older patients (Supplementary Table 1). However, in both younger and older age strata, higher 3-year rates of MACE (trend in <65-year-olds) and death were noted with persistently low testosterone. When adjusted for baseline characteristics and co-morbidities, 3-year MACE and death rates continued to favor normal and high testosterone levels: for younger subjects, noninferiority was noted for death but not MACE; for older subjects, superiority was noted for MACE and death (Supplementary Table 2). We could not demonstrate noninferiority for either MI or stroke, with power limited by relatively few events.

To test for differential safety by prevalent disease status, we stratified by baseline presence or absence of known CV disease (CAD, MI, or stroke). As expected, event rates were substantially higher in those with prevalent disease at baseline (Supplementary Table 1). However, in both subsets, higher 3-year MACE and death rates were noted with persistently low testosterone. MACE at 3 years and death rates continued to favor TRT to either normal or high testosterone with both absent and prevalent disease (Supplementary Table 2). However, we could not demonstrate noninferiority for either MI or stroke, with power limited by relatively few events.

The impact of TRT on specific causes of death was of prespecified interest, and a determination as to cause of death could be made in most patients (n = 4,650). Paralleling total death, the percentages of coronary death, CV death, and

cancer death all were numerically greater at 3 years in those with persistently low testosterone (Table 2). When adjusted for multiple confounders, the HR for coronary death (0.58 [0.28 to 1.19], p = 0.14) but not CV death (0.81 [0.48 to 1.38], p = 0.44) or cancer death (0.67 [0.34 to 1.36], p = 0.27) achieved noninferiority (Table 3).

In an effort to better account for baseline differences, additional exploratory analyses were performed in subsets of patients in whom the CCI could be calculated (Supplementary Table 3). In these analyses, the CCI was added to models that included adjustment for the other CV risk factors, baseline testosterone levels, and medications. Results demonstrated noninferiority for MACE and death with TRT but not for CV death or CV-MACE (Supplementary Table 3).

## Discussion

Given the controversy relating to the impact of TRT on CV and mortality risk, we studied the association of TRT with clinical outcomes when administered in a real-world scenario in a large general health care population. We found that TRT to normal levels compared to low testosterone was noninferior to no or ineffective TRT for the primary MACE end point. This included a significant reduction in total death but with a neutral or higher risk for stroke. The adjusted HR for MACE also was lower for high achieved testosterone, but numerical signals for higher adjusted stroke and (variably) MI rates were noted, and CV-MACE was not reduced. Findings generally were consistent across age groups and by prevalent CV disease.

The impact of TRT on CV and other health outcomes has been uncertain and controversial based on literature reports to date. A recent study reported that in >80,000 male veterans with documented low testosterone levels without CV disease, patients who received TRT and normalization of testosterone levels had a decreased risk of death, MI, and stroke compared to those who did not receive TRT and also compared to patients who received TRT but did not normalize testosterone levels.[3] However, patients who received TRT but did not normalize testosterone levels had a survival advantage compared to patients who did not receive TRT. These associations persisted after groups were matched by propensity score. The earlier EPIC Norfolk study reported similar findings.[4] However, in contrast, other studies have raised safety concerns. For example, in a small randomized trial in older men with limitations in mobility and a high prevalence of chronic disease, TRT was reported to be associated with an increased risk of adverse CV events.[11] In a retrospective cohort study of men with low testosterone in the VA health care system who underwent coronary angiography, TRT was associated with an increase in the adverse outcomes of death, MI, and stroke.[9] A second observational study reported an increased risk of MI in older men and in younger men with preexisting CV disease prescribed TRT.[10] However, 2 other observational studies in younger men (average age ≈60 years) reported reductions in all-cause mortality with TRT.[6,7]

These differing reports have led to divergent regulatory agency conclusions, with Health Canada raising a concern for harm,[14] the European Medicines Agency finding no consistent evidence for harm,[15] and the FDA finding safety data insufficient to draw firm conclusions.[1] However, a subsequent FDA drug safety communication has announced a labeling change for testosterone products to inform of the possible increased risk of MI and stroke with TRT use for low testosterone due to aging.[18] Adding to this controversy, a current critical literature review raised concerns about the quality of studies reporting adverse CV effects with TRT, found support for absence of increased CV risk in men receiving testosterone (and reduced risk in those with metabolic disease), and concluded that there is no convincing evidence for CV risk with TRT.[11] Overall, our findings are supportive of relative overall health safety of carefully managed TRT, but they fall short of a definitive answer as to the balance of benefit and risk.

The mechanisms contributing to reductions in total mortality while increasing stroke risk are uncertain and require additional investigation. However, TRT leads to favorable changes in CV risk factors, as noted, decreasing fat mass, insulin resistance, and other components of the metabolic syndrome, which may result in lower rates of MI and other coronary- and diabetes-related mechanisms of death.[1−3,19] Furthermore, frailty and depression, to which low testosterone levels may contribute, are potent risk factors for all-cause mortality, and their amelioration with TRT may decrease mortality risk across a spectrum of causes, including low-testosterone−related cancer risk. In contrast, stroke risk may rise with increases in blood pressure and hypercoagulability associated with excessive TRT.[1]

Our study strengths include its large size and its ability to capture TRT prescriptions and relevant clinical outcomes in a large, "real-world" health care system experience. Furthermore, study hypotheses were prespecified, stimulated by the current controversy regarding TRT safety. Disadvantages include, as with all observational studies dependent on retrospective database analyses, the potential for selection bias and uncorrected confounding. We attempted to minimize these differences in the different groups through extensive multivariate adjustment and stratified analyses. However, residual confounding may have still existed. A further limitation is not having information on bioavailable testosterone levels. Another limitation is that nonfatal MI and stroke events may have occurred outside the Intermountain Healthcare system and thus may not have been captured. Past experience has indicated that our population is relatively stable in our system over time and that >80% of these events are documented in the Intermountain electronic medical records. Moreover, using multiple sources, we were most likely able to capture complete information on mortality, and death was the most frequent major adverse event and the principal driver of overall MACE rates. We also are limited by incomplete information on testosterone drug duration and compliance.

Because of the limitations of observational studies, noted previously, and the controversy represented by the body of previous studies of TRT, we suggest a conservative approach to the interpretation and implications of our study. We believe that our data provide reassurance that TRT for low testosterone in populations of primarily younger men (e.g., <70-year-old), managed by appropriately specialized, licensed physicians is relatively safe when TRT to high levels is avoided. We do not view our results as supporting

TRT use in this population for CV prevention, which will require randomized trials. We found no support for recent reports that there is an increased risk soon after initiation of TRT. A novel finding of this study is its ability to evaluate differing levels of testosterone achieved by treatment.

## Disclosures

The authors have no conflicts of interest to disclose.

## Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2015.11.063.


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