Association of Testosterone Replacement Therapy and the Incidence of a Composite of Postoperative In-hospital Mortality and Cardiovascular Events in Men Undergoing Noncardiac Surgery

Maged Y. Argalious, M.D., M.Sc., M.B.A., M.Ed., F.A.S.E., Jing You, M.S., Guangmei Mao, Ph.D., M.P.H., Daniel Ramos, M.D., Sandeep Khanna, M.D., Kamal Maheshwari, M.D., M.P.H., Carlos Trombetta, M.D.

ABSTRACT

Background: Whether patients on testosterone replacement therapy undergoing noncardiac surgery have an increased risk of postoperative in-hospital mortality and cardiovascular events remains unknown. We therefore sought to identify the impact of testosterone replacement on the incidence of a composite of postoperative in-hospital mortality and cardiovascular events in men undergoing noncardiac surgery.

Methods: Data from male American Society of Anesthesiologists I through IV patients 40 yr or older who underwent noncardiac surgery between May 2005 and December 2015 at the Cleveland Clinic (Cleveland, Ohio) main campus were included. The primary exposure was preoperative testosterone use. The primary outcome was a composite of postoperative in-hospital mortality and cardiovascular events. We compared patients who received testosterone and those who did not using propensity score matching within surgical procedure matches.

Results: Among 49,273 patients who met inclusion and exclusion criteria, 947 patients on testosterone were matched to 4,598 nontestosterone patients. The incidence of in-hospital mortality was 1.3% in the testosterone group and 1.1% in the nontestosterone group, giving an odds ratio of 1.17 (99% CI, 0.51 to 2.68; $P = 0.63$). The incidence of myocardial infarction was 0.2% in the testosterone group and 0.6% in the nontestosterone group (odds ratio = 0.34; 99% CI, 0.05 to 2.28; $P = 0.15$). Similarly, no significant difference was found in stroke (testosterone *vs.* nontestosterone: 2.0% *vs.* 2.1%), pulmonary embolism (0.5% *vs.* 0.7%), or deep venous thrombosis (2.0% *vs.* 1.7%).

Conclusions: Preoperative testosterone is not associated with an increased incidence of a composite of postoperative in-hospital mortality and cardiovascular events. **(Anesthesiology 2017; 127:457-65)**

THE use of testosterone replacement therapy to treat modest age-related decline in serum testosterone, also known as *andropause*,[1] has dramatically increased in recent years.[2] Testosterone replacement therapy has also been used to treat reduced physical function and decreased extremity strength in healthy older men with reduced serum testosterone[3] and in some cases has been used in younger men and in those without documented low serum testosterone levels.[4]

This expansion in the use of testosterone therapy beyond its classical indication of treating classical hypogonadism has resulted in a 65% increase in the sale of testosterone supplements in the 4-yr time period between 2009 and 2013.[2,5] The number of prescriptions increased in the same period from 1.3 to 2.3 million, with men between 40 and 60 yr of age accounting for 70% of prescriptions.[2]

Data on the effect of testosterone on cardiovascular outcomes are conflicting; several observational trials[4,6] and a meta-analysis[7] have identified an increased cardiovascular risk in patients taking testosterone replacement therapy, prompting the U.S. Food and Drug Administration to require labeling changes for all prescription testosterone products to reflect the possible increased risk of myocardial infarction (MI), strokes, and thrombotic complications associated with testosterone use.[8]

In addition, a randomized trial of testosterone therapy in older men with mobility limitation and a high prevalence of

What We Already Know about This Topic

- Testosterone replacement therapy is increasingly being prescribed to men to improve physical function and strength
- Although there are conflicting data regarding the impact of testosterone therapy on cardiovascular events in the general medical literature, there are no data regarding the short-term impact of the therapy in men undergoing noncardiac surgery

What This Article Tells Us That Is New

- In a single-center observational analysis, testosterone replacement therapy was not associated with a measurable increase or decrease in cardiovascular events or mortality within 30 days of surgery

This article is featured in "This Month in Anesthesiology," page 1A.

Submitted for publication January 9, 2017. Accepted for publication May 26, 2017. From the Department of General Anesthesiology (M.A., S.K., K.M.), Department of Quantitative Health Sciences (J.Y., G.M.), Department of Cardiothoracic Anesthesiology (C.T.), and Center for Anesthesiology Education (M.A, D.R., C.T.), Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio.

 Anesthesiology 2017; 127:457-65

<zdoi;10.1097/ALN.0000000000001757>

chronic disease was stopped early due to a higher frequency of self-reported cardiovascular-related adverse events in men assigned to the testosterone arm compared with the placebo arm.[9] In contrast, a randomized trial in a similar patient population reported no increase in cardiovascular events.[10] Furthermore, several observational trials[11,12] and meta-analyses[13,14] also reported no increase in cardiovascular risk.

Whether patients on testosterone replacement therapy undergoing noncardiac surgery have an increased risk of postoperative in-hospital mortality and cardiovascular events remains unknown. We therefore sought to identify the impact of testosterone replacement therapy on the incidence of a composite of postoperative in-hospital mortality and cardiovascular events in men undergoing noncardiac surgery.

Materials and Methods

The research protocol submitted and approved by the Anesthesiology Institute Research Advisory Committee and the institutional review board (Cleveland Clinic, Cleveland, Ohio) prospectively (*a priori*) identified the study population, the analysis plan, and the variables of interest including the primary outcome, the exposure variable, and the confounding variables. Following institutional review board approval, data from patients undergoing noncardiac surgery at the Cleveland Clinic main campus between May 2005 and December 2015 were obtained from the Anesthesia Institute's Perioperative Health Documentation System database and Epic, healthcare software for secure housing of patient medical records. We included male American Society of Anesthesiologists physical status I to IV patients who were at least 40 yr old. Patients who underwent outpatient procedures, those who underwent emergency surgery, and patients missing any of the prespecified potential confounding factors and/or outcomes were excluded.

The primary exposure of interest was preoperative testosterone replacement therapy, defined as a preoperative prescription for testosterone replacement agents. This was determined by querying the active medication list of patients in Epic (medications within 1 month before the date of surgery) for the presence of any commercially available testosterone replacement therapy. These include the following pharmacologic names: testosterone, testosterone cypionate, testosterone enanthate, and testosterone propionate, as well as the following trade names: Androderm (Allergan, Ireland), AndroGel (Abbvie, USA), Aveed, Natesto, Fortesta, Testim, Testopel, Delatestryl (Endo Pharmaceuticals, USA), Striant (Columbia Labs, USA), Axiron (Lilly, USA), Android, Methyl Testosterone, Testred (Valeant, USA), Depotestadiol, Depot-testosterone (Pfizer, USA), Ditate-ds (Fougera, USA), Metandren (Ciba, USA), Oreton methyl (Schering, USA), Testoderm, TestodermTTS (Alza, USA), Virilon (Star, USA), Vogelxo (Upsher-Smith, USA), Testogel (Bayer, Australia). Specifically, we searched all of the testosterone medications indicating therapy within one month before surgery from Cleveland Clinic prescriptions using the Unified Medical Language System. Each prescription has an order date and an end date. The end date is either accompanied by a statement specifying that the medication was discontinued due to medication review or a new order is placed for the same medication. If the end date was missing, the period of active medication prescription was based on order date plus 90 days. We defined a patient as receiving testosterone treatment if the prescription period from the order date to the end date occurred within one month before surgery.

The primary outcome was a composite of postoperative in-hospital mortality and cardiovascular events, including MI, stroke, pulmonary embolism (PE), and deep vein thrombosis. In-hospital mortality was defined based on the Epic discharge summary, whereas all of the postoperative in-hospital cardiovascular events were identified based on discharge diagnosis codes (appendix). We did not use the present-on-admission indicator to additionally exclude cardiovascular events that occurred before hospital admission because the present-on-admission indicator was not available from 2005 to 2010.

Statistical Analysis

We compared patients who were prescribed testosterone replacement therapy (testosterone group) and those who were not (nontestosterone group). To control for the observed confounding, we matched the testosterone group with the nontestosterone group using propensity score matching within surgical procedure matches. Specifically, each patient in the testosterone group was matched to a maximum of five patients in the nontestosterone group. First, we estimated the probability of receiving testosterone within one month before surgery (propensity score) for each patient using a multivariable logistic regression; the propensity score was based on the values of the baseline variables listed in table 1. Then we matched testosterone patients with nontestosterone patients using a greedy distance matching algorithm,[15] restricting successful matches to those with the same type of surgery (as characterized using the Agency for Healthcare Research and Quality's Clinical Classifications Clinical Classifications Software categories) and those whose estimated propensity score logits (*i.e.*, $\log\left(\frac{\hat{p}}{1-\hat{p}}\right), \hat{p}$ where $\hat{p}$ is the estimated propensity score) are within 0.2 propensity score logit SDs of each other.

Assessment of covariable balances between the testosterone and nontestosterone patients before and after matching was performed using absolute standardized difference (ASD; as the absolute difference in means or proportions divided by the pooled SD). Imbalance was defined as an ASD greater than 0.10. After matching, any imbalanced covariates were included in the models so as to reduce potential confounding when comparing testosterone and nontestosterone patients on outcomes.

The propensity score–matched testosterone and nontestosterone patients were compared on the composite of postoperative in-hospital mortality and cardiovascular events. We did not analyze the outcome as a collapsed composite of any

Table 1. Demographics and Baseline Characteristics for Patients with and without Preoperative Testosterone Supplementation before and after Propensity Score Matching

	Before Matching			After Matching		
Variable	TRT (N = 955)	Non-TRT (N = 48,318)	ASD*	TRT (N = 947)	Non-TRT (N = 4,598)	ASD*
Age, mean ± SD	62 ± 10	63 ± 12	0.15	62 ± 10	62 ± 11	0.01
Race, %			0.26			0.03
White	95	87		95	94	
Black	4	11		4	5	
Others	1	2		1	1	
Body mass index, median (IQR), kg/m^2	30 (27–35)	28 (25–32)	0.42	30 (27–35)	30 (27–35)	0.04
ASA physical status, %			0.20			0.02
I	0	1		0	0	
II	21	27		21	21	
III	66	59		66	65	
IV	13	13		13	13	
Medical history, yes, %						
Atrial fibrillation	10	8	0.07	10	10	0.00
Diabetes mellitus	32	24	0.18	32	32	0.00
Hypertension	74	66	0.18	74	75	0.02
Hyperlipidemia	58	46	0.24	58	57	0.02
Coronary artery disease	30	28	0.05	30	30	0.02
Congestive heart failure	13	11	0.06	13	13	0.00
Chronic obstructive pulmonary disease	12	11	0.02	12	11	0.02
Peripheral vascular disease	22	20	0.05	22	21	0.03
Stroke	9	9	0.00	8	9	0.03
Preoperative anemia	30	30	0.00	30	28	0.04
Chronic kidney disease	13	13	0.02	13	13	0.00
Venous thromboembolism	4.3	4.8	0.03	4.3	4.6	0.01
Preoperative creatinine, median (IQR), mg/dl	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.11	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.12
Preoperative hemoglobin, median (IQR), mg/dl	14 (13–16)	14 (12–15)	0.24	14 (13–16)	14 (13–15)	0.02
Preoperative medications, %						
Statins	50	41	0.17	50	49	0.02
ACEIs/ARBs	47	38	0.18	47	48	0.03
β-Blockers	49	45	0.07	49	49	0.00
Calcium-channel blockers	23	21	0.04	23	23	0.00
Diuretics	38	33	0.12	38	39	0.02
Antiplatelet agents	9	8	0.03	9	9	0.00
Year of surgery, %			0.38			0.07
2005	2	3		2	2	
2006	5	9		5	6	
2007	5	9		5	5	
2008	5	9		5	5	
2009	8	10		8	8	
2010	10	10		10	10	
2011	10	10		10	9	
2012	14	10		14	14	
2013	16	11		16	16	
2014	16	11		16	16	
2015	10	9		10	10	
Duration of surgery, median (IQR), h	3.5 (2.7–4.8)	3.6 (2.5–5.1)	0.03	3.5 (2.7–4.8)	3.5 (2.7–4.7)	0.02
Most frequent type of surgery, %†			–			–
Laminectomy, excision intervertebral disc	9	16		7	7	
Other therapeutic endocrine procedures	6	5		10	9	
Arthroplasty knee	6	14		12	12	
Other OR therapeutic procedures, male genital	5	5		12	12	
Hip replacement, total and partial	5	13		10	10	
Gastric bypass and volume reduction	4	4		8	8	
Spinal fusion	4	9		8	9	
Colorectal resection	4	13		18	18	
Nephrectomy, partial or complete	4	16		8	8	
Other hernia repair	3	6		7	6	

*Absolute standardized difference is the absolute difference in means or proportions divided by the pooled SD; any covariables with ASD ≥ 0.10 after the propensity score matching were adjusted for in the analyses.

†Surgery type was classified based on 244 mutually exclusive, clinically appropriate categories using the Agency for Healthcare Research and Quality's single-level Clinical Classifications Software for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), procedure codes. The 10 most frequent categories are reported due to the limited space.

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; ASA = American Society of Anesthesiologists; OR = operating room; TRT = testosterone replacement therapy.

versus none. Rather, we used a multivariate (*i.e.*, multiple outcomes) analysis to simultaneously capture information on each individual component of the composite outcome for a patient and the correlations among the components while still allowing for the outcome-specific odds ratio. Specifically, we compared the propensity score–matched patients on the composite of postoperative in-hospital mortality and cardiovascular events, using a distinct-effects generalized estimating equation model with unstructured covariance matrix, in which we estimated the average log-odds ratio treatment (testosterone replacement therapy) effect across the components of the primary outcome composite.[16] In an analogous model we also assessed the heterogeneity of the treatment effect across the components with an exposure-by-component interaction test. For information purposes, the treatment effects for each component of the composite outcome were reported separately regardless of the significance of the exposure-by-component interaction. Moreover, we did a sensitivity analysis adjusting for propensity score but not unbalanced covariates in an analogous generalized estimating equation model. The significance criterion was $P < 0.05$ for the average relative effect across all the components of the composite, $P < 0.10$ for the interaction, and $P < 0.01$ for each of the five individual components (*i.e.*, 0.05/5, Bonferroni correction). All of the statistical tests were two tailed.

Sample Size Consideration

We planned to use all of the available patients on testosterone replacement therapy who met the inclusion/exclusion criteria (approximate of 1,000 based on a query of Epic conducted to assess feasibility before the start of the study). We expected to have 6,000 propensity score–matched patients total. Available power for the study was assessed by comparing the matched testosterone and nontestosterone patients on the composite of postoperative in-hospital mortality and cardiovascular events using an SAS macro (SAS Institute Inc., USA) developed for designs with multiple binary correlated endpoints ("multibinpow")[17] based on 1,000 simulations. With 6,000 patients, we would have approximately 90% power at the 0.05 significance level to detect an average relative effect odds ratio of 0.7 or stronger for testosterone patients *versus* nontestosterone patients, assuming incidences of 1.0% for MI, 2.5% for stroke, 1.0% for PE, 1.5% for deep venous thrombosis, and 1.0% for mortality, as well as a compound symmetric correlation structure with a between-outcome correlation of less than 0.1. SAS software version 9.4 for Windows (SAS Institute, USA) was used for all of the statistical analyses.

Results

We identified 49,273 patients who met inclusion and exclusion criteria, including 955 patients who had an active prescription for testosterone within one month before the surgery and 48,318 patients who did not use testosterone (fig. 1). Based on demographics, baseline characteristics, and surgical factors, we successfully matched 947 testosterone replacement

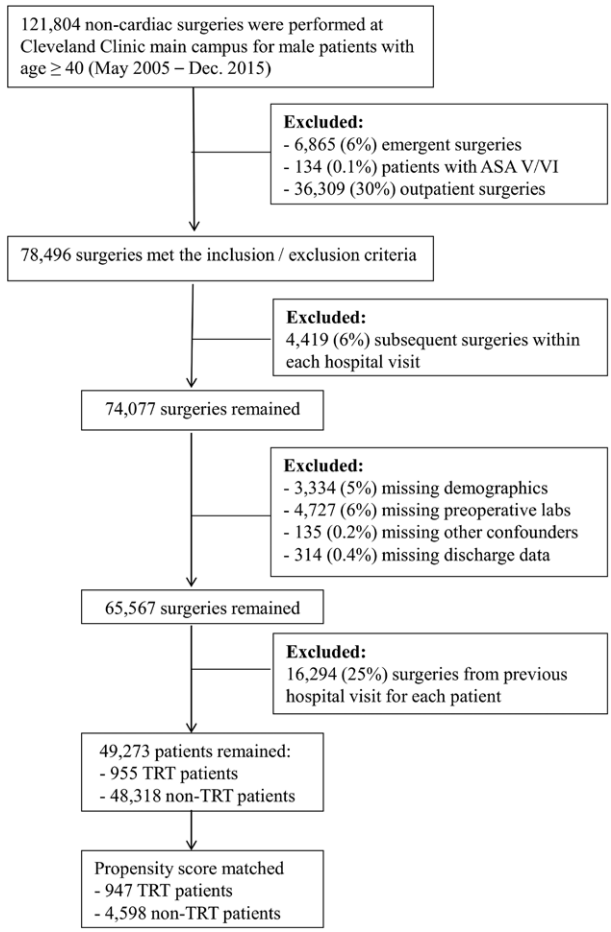

Fig. 1. Dataset inclusion/exclusion flow chart. ASA = American Society of Anesthesiologists; TRT = testosterone replacement therapy.

therapy patients (99% of 955 testosterone patients) with 4,598 nontestosterone patients. Among 947 testosterone patients, 886 (94%) matched with 5 nontestosterone patients and 61 (6%) matched with 4 or fewer nontestosterone patients. Specifically, the testosterone and nontestosterone patients were exactly matched on type of surgery and were much better balanced on other covariates as a result of propensity score matching (table 1 and fig. 2). Only preoperative creatinine level was slightly imbalanced (ASD > 0.1) after the propensity score matching, which was adjusted for in all of the analyses comparing testosterone and nontestosterone patients.

Within the matched subset of patients, patients taking testosterone before surgery was not significantly different from those not taking testosterone on the composite of postoperative in-hospital mortality and cardiovascular events, including MI, stroke, PE, and deep venous thrombosis. The incidence of in-hospital mortality was 1.3% in the testosterone group and 1.1% in the nontestosterone group, giving an odds ratio of 1.17 (99% CI, 0.51 to 2.68; testosterone replacement therapy *vs.* nontestosterone replacement therapy; $P = 0.63$). The incidence of MI was 0.2% in the testosterone group and 0.6% in the nontestosterone group, again giving a nonsignificant odds ratio of

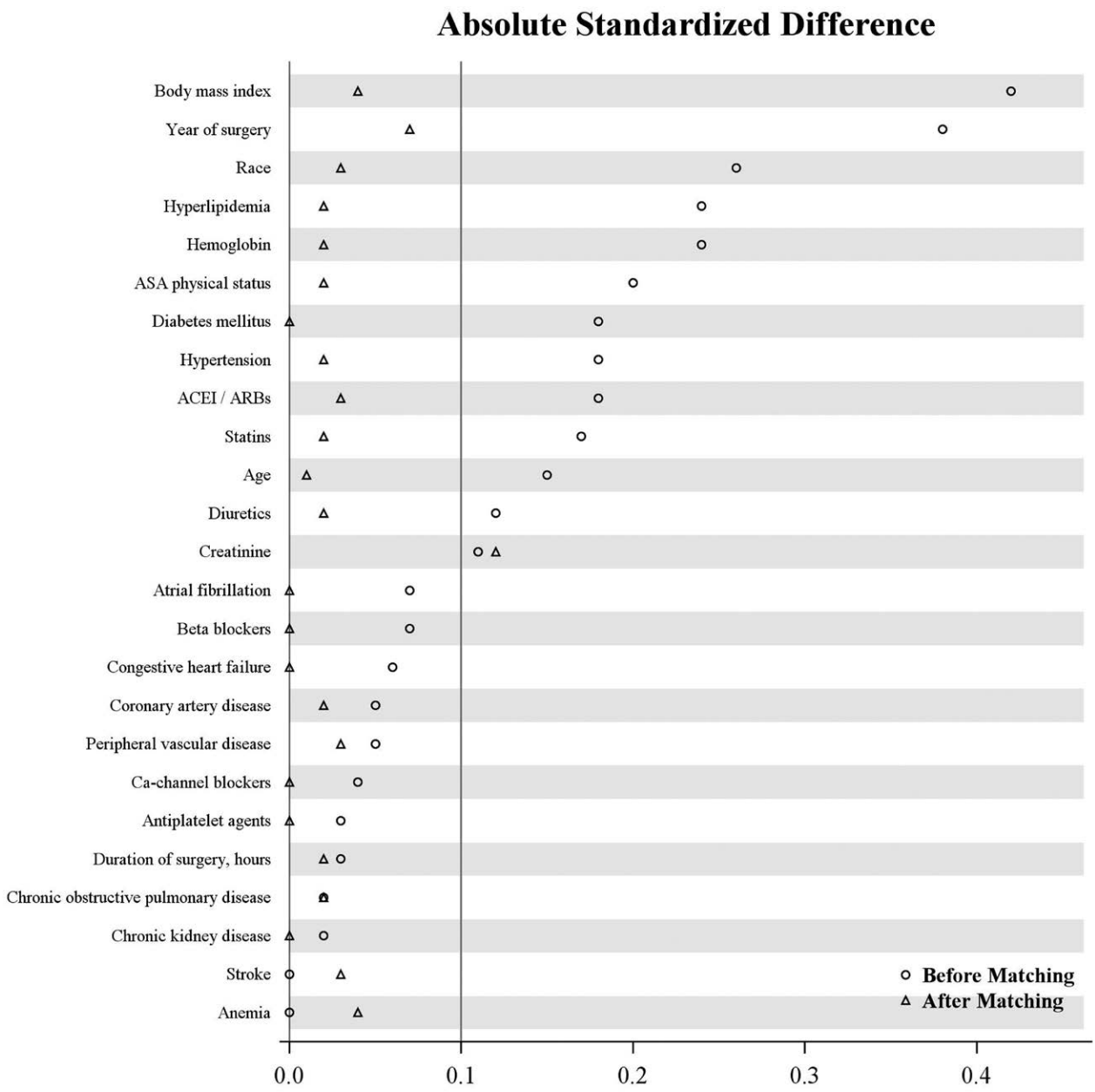

Fig. 2. Plot of absolute standardized difference of covariables used to estimate the propensity score before (*circles*) and after (*triangles*) the propensity score matching. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists.

0.34 (99% CI, 0.05 to 2.28; $P = 0.15$). Similarly, no significant difference was found in stroke (testosterone *vs.* nontestosterone: 2.0% *vs.* 2.1%), PE (0.5% *vs.* 0.7%), or deep venous thrombosis (2.0% *vs.* 1.7%; table 2 and fig. 3). Although the association was not in the same direction across all of the individual components of the composite, the group-by-outcome interaction was not significant ($P = 0.21$). The average relative effect across the five components of the composite was 0.81 (95% CI, 0.53 to 1.25) for testosterone *versus* nontestosterone ($P = 0.33$), adjusting for preoperative creatinine. Our sensitivity analyses adjusting for the estimated propensity score provided the same conclusions and very similar effect estimates (odds ratio = 0.82; 95% CI, 0.53 to 1.26; $P = 0.37$).

Moreover, we summarized the parameters of intraoperative management, which are not included in propensity score matching. The matched testosterone and nontestosterone patients were descriptively similar on intraoperative managements, including crystalloids, colloids, erythrocyte, fresh frozen plasma, platelets transfusion, estimated blood loss, urine output, use of vasopressor, and hypotension (table 3). Although testosterone patients tended to have higher urine output (ASD > 0.10), the difference was not clinically important (table 3).

Table 2. Comparison between Propensity Score–matched TRT and Non-TRT Patients on the Composite of Postoperative In-hospital Mortality and Cardiovascular Events

Outcome	TRT (N = 947), %	Non-TRT (N = 4,598), %	OR* (95% CI)†	*P* Value†
In-hospital mortality	1.3	1.1	1.17 (0.51–2.68)	0.63
Myocardial infarction	0.2	0.6	0.34 (0.05–2.28)	0.15
Stroke	2.0	2.1	0.96 (0.50–1.84)	0.87
Pulmonary embolism	0.5	0.7	0.76 (0.22–2.62)	0.56
Deep vein thrombosis	2.0	1.7	1.20 (0.62–2.34)	0.48
Average relative effect			0.81 (0.53–1.25)	0.33

*The unadjusted odds ratio (OR) of the outcome occurring in the TRT patients *versus* non-TRT patients.

†CIs were adjusted for multiple testing by Bonferroni correction. Correspondingly, $P < 0.05$ was considered significant for the average relative effect across all of the components of the composite. $P < 0.01$ was considered significant for the individual component.

TRT = testosterone replacement therapy.

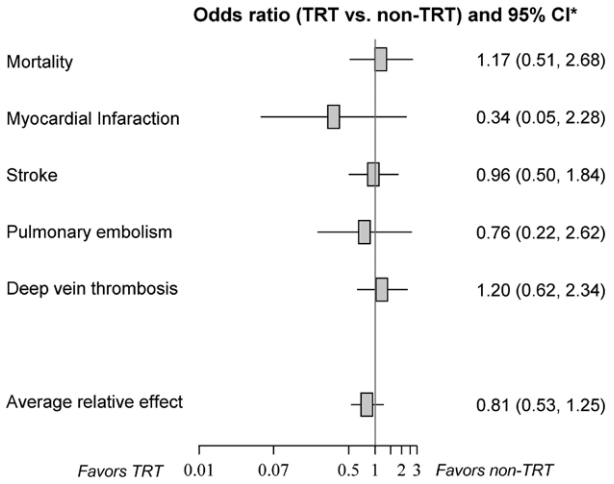

Fig. 3. Odds ratio of a composite of postoperative in-hospital mortality and cardiovascular events in patients with and without preoperative testosterone replacement therapy (TRT and non-TRT, respectively) *CIs were Bonferroni adjusted. The significance criterion was $P < 0.05$ for the average relative effect across all of the components of the composite and $P < 0.01$ for each of the five individual components (*i.e.*, 0.05/5). We refer to them as *95% CI* to indicate that the overall significance level was controlled at 5%.

Discussion

In this propensity score–matched, retrospective, single-center cohort trial, preoperative testosterone therapy was not associated with an increased incidence of a composite outcome of in-hospital mortality and cardiovascular events. To our knowledge, this is the first study investigating the association of preoperative testosterone therapy and the incidence of postoperative in-hospital mortality and cardiovascular events. Although this study was not designed to study the impact of testosterone replacement therapy on long-term adverse outcomes, our study results are in line with several recently published trials identifying similar or reduced long-term mortality and cardiovascular event rates in patients receiving testosterone replacement therapy.[11,12,18,19] A recent study by Anderson *et al.*[2] showed that testosterone replacement to normal levels was associated with a reduced death and cardiovascular event rate but also showed a higher stroke signal when testosterone levels were replaced to higher-than-normal levels.

Differences in the results of testosterone replacement therapy studies can generally be explained by the varying ages of the studied population, the varying prevalence of coronary artery disease across studied populations, the varying testosterone formulations used, the expansion in indications for the use of testosterone replacement therapy, and the lack of treatment endpoint across studies. This lack of treatment endpoint across studies may explain why some studies identified an increased cardiovascular and mortality risk with testosterone replacement therapy. For example, the increased cardiovascular events reported by Basaria *et al.*[9] in their testosterone replacement therapy arm were found to be associated with a higher serum testosterone concentration, achieved with treatment using higher-than-approved doses of testosterone replacement therapy, contrary to the recommendations of the Endocrine Society (Washington, D.C.) guidelines.[20,21] This is in addition to the fact that their study was not designed to investigate cardiovascular events.

In addition to studies associating higher-than-recommended serum testosterone levels with increased cardiovascular events, several studies also report a significant association of low testosterone levels and increased cardiovascular mortality.[12,18,22,23] This inverse bell-shaped curve (or J curve) relationship is in line with a recent study by Yeap *et al.*[24] documenting an optimum testosterone level that is associated with reduced cardiovascular mortality.

Mechanistically, testosterone replacement therapy can reduce cardiovascular events and mortality by decreasing fat mass, reducing insulin resistance, and modifying other components of the metabolic syndrome.[25] Another reported protective effect of testosterone replacement therapy is its ability to reverse low testosterone–associated all-cause mortality in several studies.[12,18,22,23] Conversely, several mechanisms have been proposed to explain the increased cardiovascular risk of testosterone therapy, including increased thromboxane A2 receptor density, which promotes platelet aggregation and vascular smooth muscle contraction.[26] Testosterone has also been shown to contribute to atherosclerotic plaque development by expressing vascular cell adhesion molecule 1.[27] Testosterone

Table 3. Summary of Intraoperative Fluid Management for Propensity Score–matched Patients (N = 5,545)

Variables	TRT (N = 947)	Non-TRT (N = 4,598)	ASD*
Amount of crystalloids, median (IQR), L	2.2 (1.5–3.2)	2.2 (1.5–3.1)	0.03
Amount of colloids, median (IQR), L	0 (0–0.5)	0 (0–0.5)	0.04
Transfusion of erythrocytes, %	6	6	0.03
Transfusion of fresh frozen plasma, %	2	2	0.01
Transfusion of platelets, %	1	2	0.05
Estimated blood loss, median (IQR), ml	100 (25–250)	100 (25–250)	0.00
Urine output, median (IQR), ml	235 (0–540)	200 (0–465)	0.12
Hypotension (30% drop from baseline for 5 consecutive minutes), %	50	49	0.02
Use of vasopressor, %	73	75	0.04

*The absolute difference in means or proportions divided by the pooled SD.

ASD = absolute standardized difference; IQR = interquartile range; TRT = testosterone replacement therapy.

replacement therapy also stimulates erythropoiesis, and the resultant polycythemia can predispose to thrombosis.[28]

Another possible explanation for the lack of association of preoperative testosterone replacement therapy and postoperative in-hospital mortality and cardiovascular events in our study population, albeit speculative, is the possible presence of a healthy user bias, explained by the fact that patients receiving testosterone replacement therapy may also be embracing a healthier lifestyle and may be receiving other cardioprotective medications (*e.g.*, statins or antiplatelet drugs).[29] Conversely, the unmatched testosterone replacement therapy group had a higher percentage of patients with American Society of Anesthesiologists physical status III or IV, as well as a higher prevalence of patients with diabetes mellitus, hypertension, and hyperlipidemia, pointing to the fact that the testosterone replacement therapy group may actually be sicker. Although propensity score matching and other statistical methodologies aim to reduce these biases, the possibility of uncorrected confounding may have existed.

According to the Revised Cardiac Risk Index, type of surgery is one of six factors associated with an elevated risk (1% or higher) of major adverse cardiac events.[30] Our studied patient population underwent a variety of noncardiac surgeries (the most frequent types of surgeries are listed in table 1). Although most listed surgeries are not associated with an elevated cardiac risk, our patient population had a high incidence of comorbid medical conditions/risk factors associated with an elevated risk of major adverse cardiac events. These include coronary artery disease and diabetes mellitus (requiring insulin) and, to a lesser extent, heart failure, cerebrovascular accident, and chronic kidney disease (with a creatinine of more than 2 mg/dl).[31]

To adjudicate our electronic medical chart–reported outcomes, the records of 50 patients with in-hospital mortality/morbidity were manually reviewed (10 for each component of the composite outcome). In 47 patients, the reported outcomes were confirmed (positive predictive value of 94%). In two patients, the timing of reported outcomes were erroneous (most likely due to miscoding in Epic), and in the third patient the timing could not be accurately identified. Validation of electronic medical chart–based data based on International Classification of Diseases, Ninth Revision, codes using the same source of data was reported previously and showed good sensitivity and specificity.[32]

Given the retrospective observational nature of this trial, unmeasured confounding may exist. To minimize any potential confounding, the testosterone and nontestosterone groups were exactly matched on type of surgery and the covariates were well balanced on other covariates as a result of propensity score matching. In addition, sensitivity analyses for the estimated propensity score provided similar effect size estimates. Another limitation of our study is that the exact dosing, equivalency, and duration of therapy of the multiple testosterone preparations were not collected. In addition, we queried patients' Epic medication lists for active prescriptions of testosterone formulation but cannot confirm whether patients actually took their prescribed medications. We also note that we did not collect data on other anabolic steroid use in the study cohort nor data on the use of testosterone antagonists in the nontestosterone patient population. Finally, data on the time of resumption of postoperative testosterone use are lacking. We note that our preoperative guidelines recommend continuation of testosterone preparations as scheduled up until the time of surgery. Patient medications, including testosterone preparations, are typically resumed as soon as postoperatively feasible.

In this single tertiary center, retrospective, propensity score–matched study, preoperative testosterone replacement therapy was not associated with an increased incidence of a composite of postoperative in-hospital mortality and cardiovascular events, including MI, stroke, deep venous thrombosis, and PE.

Acknowledgments

The authors thank Altia Douglas, M.A., Administrative Program Coordinator, Department of General Anesthesiology, Cleveland Clinic, Cleveland, Ohio.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Argalious: Center for Anesthesiology Education, Anesthesiology Institute, 9500 Euclid Avenue, E3-041, Cleveland, Ohio 44195. argalim@ccf.org. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Appendix. Definition of Postoperative Cardiovascular Event

Postoperative Adverse Events	ICD-9 (Before September 30, 2015)	ICD–10 (After September 30, 2015)
Myocardial infarction	410 Acute myocardial infarction	I21 ST elevation and non-ST elevation myocardial infarction
		I22 Subsequent ST elevation and non-ST elevation myocardial infarction
		I23 Certain current complications after ST elevation and non-ST elevation myocardial infarction
Stroke	430 Subarachnoid hemorrhage	I60 Nontraumatic hemorrhage
	431 Intracerebral hemorrhage	I61 Nontraumatic intracerebral hemorrhage
	432 Other and unspecified intracranial hemorrhage	I62 Other and unspecified nontraumatic intracranial hemorrhage
	433 Occlusion and stenosis of precerebral arteries	I63 Cerebral infarction
	434 Occlusion of cerebral arteries	I65 Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
	435 Transient cerebral ischemia	I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
Pulmonary embolism	415.1 Pulmonary embolism and infarction	I26 Pulmonary embolism
Deep vein thrombosis	453.4 Venous embolism and thrombosis of deep vessels of lower extremity	I82.4 Acute embolism and thrombosis of deep veins of lower extremity

ICD = International Classification of Diseases.

References

1. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging: Longitudinal effects of aging on serum total and free testosterone levels in healthy men: Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001; 86:724–31
2. Anderson JL, May HT, Lappé DL, Bair T, Le V, Carlquist JF, Muhlestein JB: Impact of testosterone replacement therapy on myocardial infarction, stroke, and death in men with low testosterone concentrations in an integrated health care system. Am J Cardiol 2016; 117:794–9
3. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, Tenover JL: Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005; 90:1502–10
4. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF Jr, Hoover RN: Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014; 9:e85805
5. Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS: Trends in androgen prescribing in the United States, 2001 to 2011. JAMA Intern Med 2013; 173:1465–6
6. Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM: Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013; 310:1829–36
7. Xu L, Freeman G, Cowling BJ, Schooling CM: Testosterone therapy and cardiovascular events among men: A systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013; 11:108
8. Seftel AD: Re: testosterone products: Drug safety communication–FDA Cautions about using testosterone products for low testosterone due to aging; Requires labeling change to inform of possible increased risk of heart attack and stroke. J Urol 2015; 194: 759–60
9. Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S: Adverse events associated with testosterone administration. N Engl J Med 2010; 363:109–22
10. Srinivas-Shankar U, Roberts SA, Connolly MJ, O'Connell MD, Adams JE, Oldham JA, Wu FC: Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: A randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab 2010; 95:639–50
11. Baillargeon J, Urban RJ, Kuo YF, Ottenbacher KJ, Raji MA, Du F, Lin YL, Goodwin JS: Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014; 48:1138–44
12. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM: Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012; 97:2050–8
13. Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E, Maggi M: Cardiovascular risk associated with testosterone-boosting medications: A systematic review and meta-analysis. Expert Opin Drug Saf 2014; 13:1327–51
14. Fernández-Balsells MM, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM: Clinical review 1: Adverse effects of testosterone therapy in adult men–A systematic review and meta-analysis. J Clin Endocrinol Metab 2010; 95:2560–75
15. Bergstrahl E, Kosanke J: Computerized matching of cases to controls using the greedy matching algorithm with a fixed

number of controls per case (gmatch) [SAS macro]. Mayo Clinic Division of Biostatistics 2003. Available at: http://www.mayo.edu/research/documents/gmatchsas/doc-10027248. Accessed June 12, 2017

16. Mascha EJ, Imrey PB: Factors affecting power of tests for multiple binary outcomes. Stat Med 2010; 29:2890–904
17. Mascha EJ: Calculations for tests on a vector of binary outcomes, 2011: Power calculations for tests on a vector of binary outcomes (MULTBINPOW), Cleveland Clinic Statistical Software Series, 1.0 edition. Available at: http://www.lerner.ccf.org/qhs/software/multbinpow.php. Accessed June 12, 2017.
18. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH: Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013; 169:725–33
19. Sharma R, Oni OA, Gupta K, Chen G, Sharma M, Dawn B, Sharma R, Parashara D, Savin VJ, Ambrose JA, Barua RS: Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015; 36:2706–15
20. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Task Force, Endocrine Society: Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010; 95:2536–59
21. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM: Testosterone therapy and cardiovascular risk: Advances and controversies. Mayo Clin Proc 2015; 90:224–51
22. Akishita M, Hashimoto M, Ohike Y, Ogawa S, Iijima K, Eto M, Ouchi Y: Low testosterone level as a predictor of cardiovascular events in Japanese men with coronary risk factors. Atherosclerosis 2010; 210:232–6
23. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA: Clinical review: Endogenous testosterone and mortality in men–A systematic review and meta-analysis. J Clin Endocrinol Metab 2011; 96:3007–19
24. Yeap BB, Alfonso H, Chubb SA, Handelsman DJ, Hankey GJ, Almeida OP, Golledge J, Norman PE, Flicker L: In older men an optimal plasma testosterone is associated with reduced all-cause mortality and higher dihydrotestosterone with reduced ischemic heart disease mortality, while estradiol levels do not predict mortality. J Clin Endocrinol Metab 2014; 99:E9–18
25. Srinath R, Hill Golden S, Carson KA, Dobs A: Endogenous testosterone and its relationship to preclinical and clinical measures of cardiovascular disease in the atherosclerosis risk in communities study. J Clin Endocrinol Metab 2015; 100:1602–8
26. Ajayi AA, Mathur R, Halushka PV: Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses. Circulation 1995; 91:2742–7
27. McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS: Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. Circulation 1999; 99:2317–22
28. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, De Stefano V, Elli E, Iurlo A, Latagliata R, Lunghi F, Lunghi M, Marfisi RM, Musto P, Masciulli A, Musolino C, Cascavilla N, Quarta G, Randi ML, Rapezzi D, Ruggeri M, Rumi E, Scortechini AR, Santini S, Scarano M, Siragusa S, Spadea A, Tieghi A, Angelucci E, Visani G, Vannucchi AM, Barbui T; CYTO-PV Collaborative Group: Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med 2013; 368:22–33
29. Beattie WS, Wijeysundera DN: Statins and the "healthy user bias" in cardiac surgery. Anesth Analg 2010; 111:261–3
30. Ford MK, Beattie WS, Wijeysundera DN: Systematic review: Prediction of perioperative cardiac complications and mortality by the revised cardiac risk index. Ann Intern Med 2010; 152:26–35
31. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2014; 130:e278–333
32. Navaneethan SD, Jolly SE, Schold JD, Arrigain S, Saupe W, Sharp J, Lyons J, Simon JF, Schreiber MJ Jr, Jain A, Nally JV Jr: Development and validation of an electronic health record-based chronic kidney disease registry. Clin J Am Soc Nephrol 2011; 6:40–9