

Supplemental Material

Data S1. Case-crossover design comparing current and former testosterone treatment among those with a composite cardiovascular outcome.

In this study design, subjects with a composite cardiovascular outcome serve as their own control at the selected times prior to the cardiovascular outcome. Testosterone treatment status (current or former) was determined at the time of the cardiovascular outcome and at 1, 3, and 6 months prior to the outcome. This design controls for non-time dependent factors including unmeasured in-person confounders. In this exploratory analysis, we did not consider further adjustments and our investigation was limited to those who had treatment during follow-up (to reduce the possibility of treatment bias) and who were either on current treatment or former treatment at the time prior to and at the time of the outcome. In addition, both modalities of treatment (intramuscular and transdermal) were combined into a single testosterone exposure.

The three tables below present the windows of testosterone treatment 1, 3, and 6 months prior to the composite cardiovascular outcome as the control. The table diagonals (former & former treatment and current & current treatment) contain the majority of the subjects, indicating that treatment status is relatively stable across the follow-up periods. These cells do not inform the analysis, as the subject is on the same treatment prior to the event and at the event. The subjects with *discordant* treatment status inform the case-crossover analysis: the case-crossover odds ratio is estimated by the ratio of the counts in the cells with discordant treatment status. For each control time period (1, 3, and 6 months), the estimated odds ratio (OR) was consistent with an association towards protection by current treatment rather than harm. The proportion of those on current treatment is lower at the time of the composite outcome than at control time prior to the composite outcome. McNemar’s test was used to test the null hypothesis of no association.

Table 1. Testosterone treatment one month prior to composite outcome vs testosterone treatment at time of the composite outcome

		Testosterone treatment 1 month prior to outcome		
		Current	Former	Total
Testosterone treatment at outcome	Current	1023	293	1316
	Former	309	3203	3512
	Total	1332	3469	4828

Proportion of subjects on current treatment at time of composite outcome: 0.273

Proportion of subjects on Current treatment one month prior to composite outcome: 0.276

OR = 0.95 (95% CI: 0.81-1.12); p-value=0.51

Table 2. Testosterone treatment three months prior to composite outcome vs testosterone treatment at time of the composite outcome

		Testosterone treatment 3 months prior to outcome		
		Current	Former	Total
Testosterone treatment at outcome	Current	935	351	1286
	Former	475	3010	3485
	Total	1410	3361	4771

Proportion of subjects on current treatment at time of composite outcome: 0.270

Proportion of subjects on current treatment three months prior to composite outcome: 0.296

OR = 0.74 (95% CI: 0.64-0.85); p-value <0.01

Table 3. Testosterone treatment six months prior to composite outcome vs testosterone treatment at composite outcome

		Testosterone treatment 6 months prior to outcome		
		Current	Former	Total
Testosterone treatment at outcome	Current	836	371	1207
	Former	562	2839	3401
	Total	1398	3210	4608

Proportion of subjects on current treatment at time of composite outcome: 0.262

Proportion of subjects on current treatment six months prior to composite outcome: 0.303

OR = 0.66 (95% CI: 0.58-0.75); p-value <0.01

Table S1. Criteria for Cardiovascular Outcomes

Cardiovascular Events	ICD-9 Diagnostic Codes	ICD-9 Procedure Code	CPT4#	Internal Entry Number (IEN)*
Myocardial infarction	410.0, 410.00-410.02, 410.1, 410.10-410.12, 410.2, 410.20-410.22, 410.3, 410.30-410.32, 410.4, 410.40-410.42, 410.5, 410.50-410.52, 410.6, 410.60-410.62, 410.7, 410.70-410.72, 410.8, 410.80-410.82, 410.9, 410.90-410.92			
Pulmonary embolism	415.1, 415.11, 415.13, 415.19			
Deep vein thrombosis (DVT)^	451.1, 451.11, 451.19, 451.2, 451.8, 451.81-451.84, 451.89, 451.9, 453.0, 453.1, 453.2, 453.40-453.42, 453.8, 453.81-453.87, 453.89, 453.9	38.7	75940, 75941	11785, 12935, 12938, 13678, 15894, 17111, 18874, 18877, 21208, 21213, 21214, 21215, 22021, 22022, 22575, 22765, 4653, 4654, 4658, 4660, 12362, 12932, 13675, 13676, 15440, 15895, 15896, 17183, 18878, 21207, 21209, 21210, 21212, 22573, 22764, 22766, 4652, 4656, 11784, 11787, 12936, 13624, 13625, 13674, 13677, 13679, 15439, 17110, 17112, 18876, 19109, 21211, 22019, 22020, 4650, 4651, 4657, 4659, 11783, 11786, 12360, 12361, 12933, 12934, 14609, 15480, 22763, 4655, 5592, 5593
Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436			

#CPT: Current procedural terminology procedure code

*IEN (internal entry number) for VHA pharmacy data for anticoagulants.

^ Criteria for DVT required both an ICD-9 diagnostic code and either inferior vena cava filter placement or anticoagulation treatment

Table S2. Covariate Codes

Characteristic	Based on	Codes
Cardiac Arrhythmia	ICD-9 codes	ICD-9 codes: 426.xx, 427.xx
Cardiomyopathy	ICD-9 codes	ICD-9 codes: 425.xx
Cerebrovascular Disease	ICD-9 codes	ICD-9 codes: 38.11, 430.x, 431.x, 434.x, 435.x, 436; 437, 437.0, 437.1, 437.8, 437.9, V12.54
Chronic Heart Failure	ICD-9 codes	ICD-9 codes: 428.xx, 398.91
Chronic Kidney Disease	ICD-9 codes or LOINC [#] for GFR* \leq 45	ICD-9 codes: 585, 585.3x, 585.4x, 585.5x, 585.6x, 585.9x LOINC: 62238-1, 33914-3, 48642-3, 48643-1, 70969-1, 50384-7
Chronic Liver Failure	ICD-9 codes	ICD-9 codes: 456.0, 456.1, 456.2x, 571.2, 571.3, 571.40, 571.41, 571.42, 571.49, 571.5, 571.6, 571.8, 571.9, 572.2, 572.3, 572.4, 572.8
COPD ⁻	ICD-9 codes	ICD-9 codes: 491.2x, 492.xx, 493.xx, 496.xx
Coronary artery disease and angina	ICD-9 codes or CPT [§] codes	ICD-9 codes: 411.1, 411.8, 411.81, 411.89, 412.xx, 414.4, 414.8, 414.9; 413.0, 413.1, 413.9 ICD-9 procedure codes: 36.0-36.17, 36.19, 36.2 CPT codes: 33510-14, 33516- 33523, 33525, 33528, 92980- 92982, 92984
Diabetes	ICD-9 codes or IEN ^{&} for insulin and oral hypoglycemics or LOINC for HbA _{1c} > 6	ICD-9 codes: 250.xx, 362.0x IEN: 22955, 17238, 17239, 14371, 14913, 16264, 16280, 17587, 18029, 19354, 20717, 822, 826, 829, 831, 834, 838, 841, 845, 846, 850, 852, 858, 862, 863, 868, 873, 874, 879, 880, 886, 888, 889, 891, 13113, 13485, 16265, 16466, 16467, 16746, 17588, 18242, 18243, 18690, 823, 824, 828, 836, 837, 842, 844, 853, 856, 867, 869, 871, 875, 882, 885, 890, 13351, 13484, 14591, 14592, 16199, 16200, 16437, 16665, 17851, 18590, 19355, 825, 827, 839, 840, 851, 854, 855, 857, 859, 860, 864, 866, 870, 877, 881, 883, 884, 887, 13352, 13353, 13486, 14476, 14477, 16263, 16370, 17849, 17850, 17894, 19356, 20714, 821, 830, 832, 833, 835, 843, 847, 848, 849, 861, 865, 872, 876, 878, 892, 12469, 12485, 13579, 14537, 15347, 15983, 16137, 17220, 1780, 18086, 18282, 1836, 19238, 2079, 21861, 22043, 22947, 23321, 23629, 23631, 23632, 23638, 23797, 4519, 12369, 12470, 12472, 12483, 12484, 12594, 12766, 13507, 13508, 13580, 13581, 13712, 13713, 13714, 14538, 14620, 15981, 15982, 16125, 16139, 17926, 18281, 1837, 19239, 2078, 20859, 22946, 22948, 22959, 23796, 2877, 576, 12468, 12471, 12592, 12593, 12768, 12901, 12976, 13875, 14539, 14941, 16635, 16711, 1779, 1781, 1782, 17912, 18006, 18009, 20177, 21862, 22042, 22389, 22732, 22733, 22958, 22960, 23333, 23623, 23624, 23630, 23637, 2876, 2879, 2880, 4518, 4520, 4521, 12370, 12767, 12899, 12900, 13509, 14319, 14940, 16124, 16126, 16138, 17191, 17542, 17543, 17925, 17927, 18007, 18008, 18010, 18011, 18085, 19240, 20559, 20561, 20858, 22041, 22731, 23332, 23622, 23628, 23633, 2878, 2881, 577, 21531, 17188, 19123, 19375, 19124, 19125 LOINC: 41995-2, 55454-3, 4548-4, 4549-2, 17855-8, 17856-6, 59261-8, 71875-9, 62388-4
Sexual Dysfunction	ICD-9 codes or	ICD-9 codes: 302.70, 302.71, 302.72, 302.74, 302.75, 302.76, 607.84, 799.81

Sexual Dysfunction (con)	IENs for medications for erectile dysfunction	IENs: 16380, 16384, 12823, 16381, 16385, 16522, 20312, 22644, 12822, 12824, 16520, 16521, 16379, 16382, 16383, 16146, 2956, IENs: 2957, 2962, 2963, 2954, 2961, 2964, 16147, 16509, 2955, 2965, 16148, 16508, 2958, 2959, 2960, 2966
Hyperlipidemia	ICD-9 codes or IENs for lipid-lowering medications	ICD-9 codes: 272.0x, 272.1x, 272.2x IENs: 13591, 18377, 22009, 5850, 5851, 5854, 5856, 5859, 5861, 5862, 5864, 6227, 13589, 18376, 18378, 21539, 22008, 22010, 5846, 5853, 5860, 6223, 13592, 17507, 21541, 5847, 5855, 5857, 5858, 6226, 13588, 13590, 21540, 5848, 5849, 5852, 5863, 6224, 6225, 11937, 12860, 12861, 13578, 14096, 14585, 14760, 15318, 15470, 15866, 16386, 16389, 16400, 16403, 16531, 16775, 16776, 16880, 17012, 17338, 17552, 18969, 19385, 21013, 23564, 2907, 5098, 5238, 6115, 6116, 6118, 7994, 12596, 14759, 15317, 15865, 16004, 16390, 16392, 16405, 16442, 16532, 16877, 16879, 16882, 16883, 16885, 17013, 17335, 17336, 19374, 19386, 19387, 19510, 19636, 20339, 21312, 21729, 23572, 23859, 23860, 2906, 2908, 2909, 6114, 6119, 8519, 9680, 9741, 12595, 12597, 13788, 14321, 14618, 16135, 16244, 16387, 16391, 16404, 16881, 16884, 18040, 19527, 20340, 21014, 21310, 21311, 21867, 23735, 23858, 2910, 5239, 6117, 8520, 9743, 9744, 11938, 12831, 12914, 13725, 14527, 14594, 14960, 15864, 16003, 16388, 16401, 16402, 16530, 16777, 16878, 17334, 17337, 18970, 19366, 19526, 19637, 21509, 21866, 23563, 23565, 23864, 4436, 5097, 6113, 8521, 9681, 9682, 9742
Hypertension	ICD-9 codes	ICD-9 codes: 401.xx, 402.xx, 403.xx, 404.xx, 405.xx
Major Depression	ICD-9 codes	ICD-9 codes: 296.2x-296.3x
Malignancy	ICD-9 codes	ICD-9 codes: 140.xx-239.xx (except excluded basal cell cancer: 173.xx)
Morbid Obesity	ICD-9 codes	ICD-9 codes: V85.4x, 278.01
Peripheral Vascular Disease	ICD-9 codes or CPT codes	ICD-9 codes: 38.18, 38.19, 38.38, 38.39, 38.48, 38.49, 38.88, 38.89, 39.25, 39.26, 39.28, 39.29, 39.50, 39.90, 433, 433.9, 440.2x, 440.3x, 440.4x, 442.x, 443.x, 445.0x CPT codes: 34800, 34802, 34803, 34804, 34805, 35226, 35256, 35286, 35351, 35355, 35371, 35372, 35381, 35454, 35456, 35459, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35646, 35656, 35661, 35663, 35665, 35666, 35671
Polycythemia	ICD-9 codes or LOINC codes for Hematocrit ≥ 52	ICD-9 codes: 289.0x LOINC codes: 24360-0, 4544-3, 71833-8, 4545-0, 48703-3, 20570-8, 41655-2, 71830-4, 31100-1
PSA ⁺	LOINC laboratory codes	LOINC codes: 19195-7, 19197-3, 2857-1, 35741-8, 10886-0, 19201-3, 19203-9, 12841-3, 14120-0, 33667-7, 15323-9, 15324-7, 15325-4
Sleep Apnea	ICD-9 codes or CPT codes for CPAP ⁺	ICD-9 codes: 780.51, 780.53, 780.57 CPT codes: E0452, E0601, 94660
Smoking	ICD-9 codes or IEN codes for smoking cessation medications	ICD-9 codes: V15.82, 305.1x, 989.84 IENs: 17847, 23100, 9697, 9703, 16376, 18746, 18749, 22944, 5095, 9700, 9701, 16375, 17845, 18747, 5096, 9696, 13203, 16685, 17846, 17848, 18748, 22943, 9694, 9695, 9698, 9699, 9702

Testosterone Formulations	IEN for testosterone medications	IENs: 513, 514, 515, 516, 518, 524, 525, 526, 527, 530, 531, 532, 533, 534, 14379, 14380, 14775, 15507, 15508, 16064, 16544, 17475, 17503, 17901, 21468, 21470, 21471, 22219, 22384, 22523, 22526, 22791, 168, 169, 170, 171, 172, 173, 174, 512, 517, 519, 520, 521, 522, 523, 528, 529, 1301, 1302, 1303, 3055, 3637, 3638, 3639, 3795, 4220, 4550, 4551, 4552, 4553, 4554, 4555, 4556, 6577, 6578, 6976, 16141
Testosterone Level	LOINC for serum testosterone measures	LOINC: 14913-8, 1639-4, 21555-8, 2986-8, 49041-7, 49042-7, 55519-3, 58835-0, 70239-9, 51005-7, 58716-2, 49042-5, 49043-3, 70240-7, 58952-3, 2990-0, 30123-4, 14914-6, 25987-9, 2991-8, 35225-2, 24125-7, 15432-8, 16286-7, 17686-7

~COPD: Chronic obstructive pulmonary disease

^CPAP: Continuous positive airway pressure

§CPT: Current procedural terminology procedure code

*GFR: Glomerular filtration rate

&IEN: Internal Entry Numbers for medications,

#LOINC: Logical observation identifiers names and codes for laboratory data

+PSA: Prostate specific antigen

Table S3. Results using different definitions for current testosterone treatment

		Adjusted HR (No Prevalent CVD at cohort entry)						
TD Treatment		No overrun	10%	20%*	25%	30%	35%	40%
Composite	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Cardiovascular Endpoint#	Current	0.89 (0.74-1.05)	0.87 (0.74-1.03)	0.89 (0.76-1.05)	0.88 (0.75-1.04)	0.88 (0.75-1.04)	0.89 (0.76-1.05)	0.90 (0.77-1.05)
	No use	1.02 (0.94-1.11)	1.01 (0.93-1.1)	1.02 (0.94-1.11)	1.02 (0.93-1.10)	1.02 (0.93-1.10)	1.02 (0.93-1.11)	1.02 (0.94-1.11)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.91 (0.72-1.16)	0.88 (0.7-1.11)	0.92 (0.73-1.15)	0.90 (0.72-1.13)	0.90 (0.72-1.12)	0.90 (0.72-1.13)	0.88 (0.70-1.10)
	No use	1.07 (0.95-1.19)	1.06 (0.94-1.18)	1.06 (0.95-1.19)	1.06 (0.95-1.19)	1.06 (0.94-1.19)	1.06 (0.94-1.19)	1.05 (0.94-1.18)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	1 (0.71-1.41)	0.98 (0.7-1.37)	0.96 (0.69-1.34)	0.93 (0.67-1.29)	0.91 (0.65-1.27)	0.89 (0.64-1.24)	0.91 (0.66-1.26)
	No use	1.07 (0.91-1.26)	1.06 (0.9-1.26)	1.06 (0.90-1.25)	1.05 (0.89-1.24)	1.05 (0.89-1.24)	1.04 (0.88-1.23)	1.05 (0.88-1.24)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.7 (0.49-1.01)	0.73 (0.52-1.04)	0.75 (0.53-1.05)	0.77 (0.55-1.07)	0.80 (0.57-1.11)	0.82 (0.60-1.14)	0.89 (0.65-1.21)
	No use	0.86 (0.72-1.01)	0.86 (0.73-1.01)	0.86 (0.73-1.02)	0.87 (0.73-1.03)	0.87 (0.73-1.03)	0.88 (0.74-1.04)	0.89 (0.75-1.06)
IM Treatment								
Composite	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Cardiovascular Endpoint#	Current	0.91 (0.8-1.04)	0.91 (0.8-1.04)	0.91 (0.80-1.04)	0.89 (0.79-1.01)	0.89 (0.79-1.01)	0.90 (0.79-1.02)	0.90 (0.80-1.02)
	No use	0.82 (0.76-0.89)	0.82 (0.76-0.89)	0.82 (0.75-0.89)	0.81 (0.75-0.89)	0.81 (0.75-0.89)	0.81 (0.75-0.89)	0.81 (0.75-0.89)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.93 (0.78-1.1)	0.95 (0.8-1.13)	0.95 (0.80-1.13)	0.93 (0.78-1.10)	0.93 (0.79-1.11)	0.95 (0.80-1.12)	0.95 (0.81-1.13)
	No use	0.83 (0.74-0.93)	0.84 (0.75-0.94)	0.84 (0.75-0.94)	0.83 (0.74-0.93)	0.83 (0.74-0.93)	0.83 (0.74-0.94)	0.84 (0.74-0.94)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.97 (0.75-1.27)	0.95 (0.73-1.23)	0.95 (0.73-1.23)	0.92 (0.71-1.19)	0.94 (0.73-1.22)	0.95 (0.74-1.23)	0.93 (0.72-1.20)
	No use	0.87 (0.73-1.03)	0.86 (0.73-1.02)	0.86 (0.72-1.02)	0.85 (0.72-1.01)	0.86 (0.72-1.02)	0.86 (0.72-1.03)	0.85 (0.72-1.02)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.8 (0.61-1.05)	0.78 (0.59-1.02)	0.77 (0.59-1.00)	0.76 (0.58-1.00)	0.74 (0.57-0.97)	0.74 (0.56-0.96)	0.75 (0.57-0.98)
	No use	0.73 (0.61-0.87)	0.72 (0.6-0.86)	0.71 (0.60-0.85)	0.71 (0.60-0.85)	0.70 (0.59-0.84)	0.70 (0.59-0.84)	0.70 (0.59-0.84)

TD Treatment		Adjusted HR (Prevalent CVD at cohort entry)						
		No overrun	10%	20%*	25%	30%	35%	40%
Composite Cardiovascular Endpoint#	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.81 (0.7-0.93)	0.81 (0.7-0.92)	0.80 (0.70-0.91)	0.83 (0.73-0.95)	0.84 (0.73-0.95)	0.85 (0.75-0.96)	0.87 (0.77-0.99)
	No use	1.04 (0.98-1.1)	1.03 (0.97-1.09)	1.03 (0.97-1.09)	1.03 (0.97-1.1)	1.04 (0.98-1.1)	1.04 (0.98-1.1)	1.04 (0.98-1.11)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.81 (0.67-0.97)	0.83 (0.69-0.99)	0.80 (0.67-0.95)	0.8 (0.68-0.96)	0.81 (0.69-0.96)	0.82 (0.69-0.97)	0.84 (0.71-0.99)
	No use	1.07 (1-1.16)	1.07 (1-1.16)	1.07 (0.99-1.15)	1.07 (0.99-1.15)	1.07 (0.99-1.15)	1.07 (0.99-1.16)	1.07 (1-1.16)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.92 (0.72-1.17)	0.9 (0.71-1.14)	0.90 (0.72-1.14)	0.94 (0.75-1.18)	0.94 (0.75-1.18)	0.97 (0.78-1.21)	0.99 (0.8-1.23)
	No use	1.05 (0.95-1.17)	1.05 (0.95-1.16)	1.05 (0.94-1.16)	1.06 (0.95-1.17)	1.05 (0.95-1.17)	1.06 (0.95-1.18)	1.07 (0.96-1.18)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.73 (0.55-0.96)	0.7 (0.53-0.92)	0.72 (0.55-0.94)	0.75 (0.58-0.98)	0.78 (0.6-1)	0.78 (0.6-1)	0.82 (0.64-1.05)
	No use	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0.94 (0.83-1.05)	0.93 (0.83-1.05)	0.94 (0.84-1.06)
IM Treatment								
Composite Cardiovascular Endpoint#	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.99 (0.9-1.1)	0.99 (0.9-1.09)	0.98 (0.89-1.09)	0.97 (0.88-1.07)	0.97 (0.88-1.07)	0.97 (0.88-1.06)	0.97 (0.88-1.06)
	No use	0.96 (0.9-1.02)	0.96 (0.9-1.02)	0.96 (0.90-1.02)	0.95 (0.89-1.01)	0.95 (0.89-1.01)	0.95 (0.89-1.01)	0.95 (0.89-1.01)
MI	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.99 (0.87-1.13)	1 (0.88-1.13)	0.99 (0.87-1.12)	0.97 (0.86-1.1)	0.97 (0.85-1.09)	0.97 (0.85-1.09)	0.97 (0.86-1.1)
	No use	0.96 (0.89-1.04)	0.97 (0.89-1.05)	0.97 (0.89-1.04)	0.96 (0.88-1.04)	0.96 (0.88-1.04)	0.96 (0.88-1.04)	0.96 (0.88-1.04)
Stroke	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.89 (0.74-1.08)	0.89 (0.74-1.07)	0.87 (0.73-1.05)	0.86 (0.72-1.04)	0.9 (0.75-1.07)	0.91 (0.76-1.08)	0.9 (0.75-1.07)
	No use	0.95 (0.85-1.05)	0.94 (0.85-1.05)	0.94 (0.84-1.04)	0.93 (0.83-1.04)	0.94 (0.84-1.05)	0.94 (0.84-1.05)	0.94 (0.84-1.05)
VTE	Former	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	Current	0.96 (0.78-1.18)	0.96 (0.78-1.17)	0.97 (0.79-1.18)	0.96 (0.79-1.17)	0.96 (0.79-1.17)	0.94 (0.78-1.15)	0.97 (0.8-1.18)
	No use	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.94 (0.83-1.07)	0.93 (0.82-1.06)	0.94 (0.83-1.07)

Results using different definitions for current testosterone treatment with an overrun ranging from none to 40% of prescription duration. Current testosterone is defined as prescription duration plus a 20% overrun. An overrun was included to account for refill times, noncompliance or residual effects. This sensitivity analysis varies the overrun from 0-40%.

* 20% overrun is the definition for current testosterone treatment that is used in the paper.

#The composite cardiovascular endpoint was comprised of MI, stroke and VTE.

Table S4. Incidence rates (IR) associated with testosterone initiation during continuous treatment with testosterone[#]

MI	Continuous treatment time	PY/1000	Events	IR (95% CI)
TD*	-All continuous treatment time	8.5	64	7.51 (5.87-9.59)
	-1 st Year continuous treatment	8.4	64	7.65 (5.99-9.78)
	- 6 Months continuous treatment	7.8	63	8.03 (6.28-10.29)
	- 3 Months continuous treatment	6.6	52	7.92 (6.03-10.40)
IM⁺	- All continuous treatment time	13.1	113	8.62 (7.17-10.37)
	-1 st Year continuous treatment	12.0	101	8.41 (6.92-10.22)
	- 6 Months continuous treatment	10.0	87	8.71 (7.06-10.75)
	- 3 Months	7.0	61	8.69 (6.76-11.17)
* IR = 6.49 for current-use of TD in the primary analysis; + IR = 8.16 for current-use of IM in the primary analysis				
STROKE	Continuous treatment time	PY/1000	Events	IR (95% CI)
TD[§]	- All continuous treatment time	8.6	34	3.93 (2.81-5.50)
	-1 Year continuous treatment	8.5	34	4.01 (2.86-5.61)
	- 6 Months continuous treatment	8.0	31	3.90 (2.74-5.54)
	-3 Months continuous treatment	6.7	26	3.90 (2.66-5.73)
IM^{&}	-All continuous treatment time	13.3	34	2.55 (1.82-3.57)
	-1 Year continuous treatment	12.2	34	2.78 (1.99-3.89)
	- 6 Months continuous treatment	10.2	26	2.56 (1.74-3.76)
	-3 Months continuous treatment	7.1	19	2.66 (1.70-4.17)
§ IR = 3.41 for current-use of TD in the primary analysis, & IR = 3.50 for current-use of IM in the primary analysis				
VTE	Continuous treatment time	PY/1000	Events	IR (95% CI)
TD[~]	-All continuous treatment time	8.6	28	3.24 (2.24-4.69)
	-1 Year continuous treatment	8.5	28	3.30 (2.28-4.78)
	- 6 Months continuous treatment	8.0	28	3.52 (2.43-5.10)
	-3 Months continuous treatment	6.7	26	3.90 (2.66-5.73)
IM[^]	All Continuous treatment time	13.3	39	2.92 (2.14-4.00)
	-1 Year continuous treatment	12.2	37	3.03 (2.19-4.18)
	- 6 Months continuous treatment	10.2	35	3.44 (2.47-4.80)
	-3 Months continuous treatment	7.1	20	2.80 (1.81-4.34)
~ IR = 2.76 for current-use of TD in the primary analysis ^IR = 3.17 for current-use of IM in the primary analysis				

[#]Incidence rates were those associated with testosterone initiation during continuous monotherapy treatment with testosterone. Subjects were censored at the end of the initial period of continuous testosterone treatment or if they switched to a different testosterone formulation.

Table S5. Criteria for Composite Cardiovascular Endpoint in Different Studies

	MI ^{&}	VTE ⁺	Stroke	TIA [^]	Unstable angina	Re- Vascularization Procedures	SCD [#]	Total mortality
Vigen ⁴	x		Ischemic					x
Anderson ¹⁸	x		Ischemic & hemorrhagic					x
Wallis ¹²	x	x	Ischemic					
Layton ⁹	x		Ischemic	x	x			
Cheetham ¹⁹	x		Ischemic	x	x	x	x	
Argalious ²⁵	x	x	Ischemic & hemorrhagic					x*
Loo ¹⁴	x		Ischemic	x				

&MI: myocardial infarction

*Mortality defined as post-operative, in-hospital mortality

#SCD: sudden cardiac death

[^]TIA: transient ischemic attack

⁺VTE: venous thromboembolism consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE)