

Supplementary Table 1: A detailed summary of the studies

Article	Cohort size	Cohort description	Study years	TRx duration mean (s.d.)	Time at risk	Overall risks	Subgroup risks	MI HR (95% CI)	Stroke HR (95%CI)	Thrombosis HR (95% CI)	Mortality HR(95% CI)	Composite CVD HR (95% CI)
Finkle <i>et al.</i> ¹² 2014 Retrospective cohort	55 593 -All treated with IM T. Compared MI rate. Post-TRx/ Pre-TRx	Insurance Claims Age 54 years; No T levels; No exclusion of MI	2006-2010	na	3 months after TRx and 12 months prior to TRx in the same man	↑ MI 3 months post-TRx compared to 12 months pre-TRx	↑ MI >65, ↑ MI <65 with heart disease	Overall: 1.36(1.02-1.81); ≥65 years: 2.19 (1.27-3.37); <65 with Heart Disease: 2.90 (1.49-5.62)	na	na	na	na
Baillargeon <i>et al.</i> ²⁴ 2014 Matched cohort	Controls: 19 065; TRx: 6365 all with IM T	Medicare, No T levels; No exclusion of MI	1997-2005	4.1 (8) months	No TRx: 3.3 (2.5) years; TRx: 4.1 (2.7) years	No ↑ MI	↓ MI In men with highest risk for MI	All: 0.84 (0.69-1.02); High Risk for MI: 0.69 (0.53-0.92)	na	na	na	na
Etminan <i>et al.</i> ²⁰ 2015 Case control	Controls: 120 264; TRx-1954; T initiators-190; Cases: 30 066; TRx-515; T initiators-68	Insurance claims; Age 70 years; No T levels Excluded MI	2001-2011	na	Current T: T Rx 90 days prior; Past T: TRx 91-364 days prior; No T: TRx >365 days prior to MI	No ↑ MI	↑ MI first 3 months of TRx. NoTRisk with current or past TRx	All: 1.01 (0.89-1.16); T initiator: 1.41 (1.06-1.87)	na	na	na	na
Sharma <i>et al.</i> ²⁷ 2015 Matched cohort	No TRx: 11 957 T treated with low T levels : 23 953 ; T treated with normal T levels : 40 852	VHA: Age 66 years ; Repeated Low T & F/U T: Excluded MI and stroke	1999-2014	T treated with normal T levels after treatment: 6.1 (3.1) years; T treated with low T 3.0 (2.7) years; T treated with low T levels after treatment: 1.5 (1.9) years	T treated with normal T levels after treatment: 6.1 (3.1) years; T treated with low T levels after treatment: 4.5 (2.9) years; No TRx: 4.6 (2.9) years	↓ MI, stroke & mortality; Normal T after TRx vs no TRx	T treated with low T levels after treatment & no TRx had no differences in risk	0.75 (0.63-0.93)	0.64 (0.43-0.96)	na	0.44 (0.42-0.46)	na
Tan <i>et al.</i> ²⁹ 2015 Retrospective cohort	TRx: 19 968; MI registry: 821 725; Stroke registry: 117 000	Low T Centers: Age 46 years; Low T & HG diagnosis prior to TRx	2009-2014	2.1 years	Up to 5 years	↓ MI ↓ stroke in TRx younger men compared to older men in registries	na	0.14 (0.08-0.18)	0.11 (0.02-0.13)	na	na	na
Anderson <i>et al.</i> ³² 2016 Retrospective cohort	Low T: 801, TRx:144; T treated with normal T levels after treatment: 2241; T treated with high T levels after treatment: 1694	Utah: Age 61 years; Base Low T & F/U T; No exclusion of MI or Stroke	1996-2011	Not reported	3 years and 1 year F/U. Results are for 3 years FU	No ↑ MI no ↑ Stroke; ↓ mortality; ↓ T vs low T level	>65 years; Mortality & CVD; Past CVD: ↓CVD	Overall: 0.73 (0.4-1.34) No difference in MI risk related to age or past CVD	Overall: 1.11 (0.54-2.28) No difference in stroke risk related to age or past CVD	na	Overall: 0.65 (0.47-0.90); >65: 0.62 (0.41-0.92); Past CVD: 0.68 (0.43-1.07); No CVD: 0.67 (0.43-0.98); No CVD: 0.74 (0.36-0.89)	CVD: MI, stroke, mortality. Overall: 0.74 >65: 0.67 (0.48-0.93); Past CVD: 0.67 (0.43-0.98); No CVD: 0.74 (0.50-1.09)
Shores <i>et al.</i> ¹⁹ 2012 Retrospective cohort	No TRx: 633; TRx: 398	VHA: Age 62 years ; Base low T	2001-2005	20.2 (16.7) months	40.5 (15.0) months	↓ Mortality	No ↑ risk by DM or CAD	na	na	na	0.61 (0.42-0.88)	na
Wallis <i>et al.</i> ³¹ 2016 Matched cohort	Controls: 28 029; TRx: 10 311	Ontario, Canada; Age >66 years; Excluded MI, Stroke, VTE; No T levels	2007-2012	Tertile 1: 4 months ; Tertile 2: 4 to <17 months; Tertile 3: ≥17 months	No TRx: 5.1 (2.2) years; TRx: 5.3 (2.1) years	↓ mortality ↑ CVD	↑ CVD first 1.4 years; ↑ mortality first 4 months; ↓ CVD & mortality with longer TRx	na	na	na	Overall: 0.88 (0.84-0.93); TRx for 4 months: 1.11 (1.03-1.20); TRx for 4 to 17 months: 0.90 (0.83-0.97); TRx ≥17 months: 0.84 (0.72-0.98)	CVD: MI, stroke, VTE Overall: 1.10 (1.10-1.20) ; TRx for 4 months: 1.26 (1.09-1.46); TRx for 4 to 17 months: 1.16 (1.00-1.35) T Rx ≥17 months: 0.84 (0.72-0.98)

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Vigen <i>et al.</i> ¹³ 2013 Retrospective cohort	No TRx: 7486; TRx: 1223	VHA Base low T	2005-2012	12.5 months after excluding 18% who only filled 1 prescription	27.5 months for all	↑ CVD	No ↑ risk by CAD; No ↑ risk by T formulation	na	na	na	na	CVD: MI, stroke, mortality 1.29 (1.04-1.58)
Layton <i>et al.</i> ²⁸ 2015 Retrospective cohort	Insurance: 515 132; Medicare: 22 376; United Kingdom: 6607; All treated- compared risk by T formulation	Insurance & United Kingdom: Age 50s Medicare: United Kingdom: Age 70s 2000-2012 Excluded CVD	Insurance: 2000-2012 Medicare: 2007-2010 United Kingdom: 2000-2012	IM: 105 (104) days; Gel: 129 (112) days; Patch: 96 (91) days	Up to one year after TRx	IM T compared to T gel; ↑ MI in 1 database; ↑ stroke in 2 databases; ↑ CVD in 3 databases; No ↑ VTE	T-Patch & T-gel had similar risks	Insurance: 1.28 (1.14-1.43); Medicare: 1.25 (0.92-1.71); United Kingdom: 2.14 (0.78-5.89); Pooled: 1.30 (1.18-1.45)	Insurance: 1.24 (1.11-1.37); Medicare: 1.56 (1.17-2.08); United Kingdom: 1.29 (0.58-2.86); Pooled: 1.21 (1.10-1.32)	Insurance: 0.95 (0.77-1.18); Medicare: 1.43 (0.75-2.72); United Kingdom: 1.29 (0.98-1.56); Pooled: 0.92 (0.76-1.11)	Insurance: not available; Medicare: 1.30 (1.09-1.53); United Kingdom: 1.56 (1.19-1.75); Pooled: 1.34 (1.15-1.56)	CVD: MI, stroke, unstable angina. Insurance: 1.24 (1.16-1.33); Medicare: 1.44 (1.19-1.75); United Kingdom: 1.85 (1.05-3.28); Pooled: 1.26 (1.18-1.35)
Baillargeon <i>et al.</i> ³³ 2015 Case control	Controls: 22 929; TRx-505; Cases: 7643; TRx-158	Insurance claims Age >40 No T levels; Excluded VTE & VTE RF	2007-2012	na	TRx 15, 30, or 60 days prior to VTE	No ↑ VTE	No ↑ VTE with prothrombotic disorder	na	na	0.90 (0.73-1.12)	na	na
Martinez <i>et al.</i> ³⁷ 2016 Case control	Controls: 909 530; TRx-1251; Cases: 19 215; TRx-69	United Kingdom: Age 65 years; No T levels ; Excluded VTE; Matched on HG diagnosis & VTE RF	2001-2013	na	Current TRx: TRx when 1 day-2 years prior to VTE; No T exposure: TRx >2 years or no prior TRx	No ↑ VTE	↑ VTE first 6 months of TRx	na	na	Overall: 1.25 (0.94-1.66); 1st 6 months: 1.63 (1.12-2.37)	na	na
Sharma <i>et al.</i> ³⁸ 2016 Retrospective cohort	No TRx: 10 854; T treated with low T levels after treatment : 22 191; T treated with normal T levels after treatment : 38 362	VHA: Age 64-67 years; Repeated low T & F/U T; Excluded VTE RF	1999-2014	na	T treated with normal T : 6.1 (3.1) years; T treated with low T: 4.5 (3.0) years; No TRx: 4.6 (2.9) years	No ↑ VTE	No VTE risk associated with F/U T levels after TRx	na	na	TRx normal T : 1.10 (0.78-1.54); TRx low T : 1.14 (0.78-1.65)	na	na
Li <i>et al.</i> ³⁸ 2016 Matched cohort	No TRx: 102 650; TRx: 102 650	Insurance claims	2004-2012	na	na	No ↑ VTE in Matched Cohort Study or Case control Study	IM T	na	na	Cohort Study 1.08 (0.91-1.27)	na	na
Nested Case Control	Controls: 11 119; Cases: 2785				Case Control: Current Treatment Prescription duration +90 days					Case Control Study 1.02 (0.92-1.13)		

I: decreased; ↑: increased; CAD: coronary artery disease; CI: confidence interval; CVD: cardiovascular disease; DM: diabetes mellitus; F/U: follow-up; HG: hyponatremia; HR-hazard ratio; IM-intramuscular; MI: myocardial infarction; na: not available; Post-TriPre-Trix: after T treatment compared to before T treatment in the same mean; RF: risk factor; SD: standard deviation; T: testosterone; TRx: testosterone treatment; VHA: Veterans Health Administration; VTE: venous thromboembolism