

# Cardiovascular benefits and risks of testosterone replacement therapy in hypogonadal men with type 2 diabetes mellitus and/or the metabolic syndrome: a systematic review

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## Abstract

**Background:** Because of the paucity of large randomised controlled trials (RCTs) in men with type 2 diabetes mellitus (T2DM) and/or the metabolic syndrome (MS), the majority of evidence for use of testosterone replacement therapy (TRT) on the cardiovascular (CV) system in such men is derived from observational studies and systematic reviews.

**Methods:** We carried out an extensive retrospective review of the literature, comparing the major comparative trials that involved TRT in hypogonadal men with T2DM and/or MS and focused on CV outcomes.

**Results:** Of 311 studies initially identified, 25 studies (12 RCTs and 13 non-RCTs) with a total number of 729,927 participants were deemed eligible for further review. Three RCTs and one non-RCT were excluded as these had not measured all-cause mortality and CV events as primary outcomes. Benefits of TRT on myocardial infarction were observed in two RCTs which were reviewed, while the rest demonstrated a neutral effect on CV events. In the non-RCTs, seven studies observed reduced all-cause mortality and/or major adverse CV events in the TRT group compared with the placebo group.

**Conclusions:** This retrospective and systematic review of the literature suggests protective effects of TRT against all-cause mortality and major adverse cardiac events in hypogonadal men with T2DM and/or MS, although these results need to be interpreted cautiously.

*Br J Diabetes* 2018;**18**:141-146

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<https://doi.org/10.15277/bjd.2018.192>

**Key words:** testosterone replacement, diabetes, cardiovascular events, men, hypogonadal

## Introduction

Multiple studies have reported the development of hypogonadism in up to 40% of men with type 2 diabetes mellitus (T2DM), with up to 75% of such men presenting with symptoms of sexual dysfunction such as erectile dysfunction, loss of morning erection and low libido.<sup>1,2</sup> There are observational studies which have shown an association between concentrations of testosterone (T) and acute coronary events in men with or without T2DM.<sup>3,4</sup> It is plausible that low T levels contribute to endothelial dysfunction and impair coronary perfusion.<sup>5-7</sup>

There is emerging epidemiological data which suggest that low T levels are linked with an increased risk of cardiovascular disease (CVD).<sup>8,9</sup> Evidence from available observational studies has linked low T concentrations with an increased all-cause mortality as well as CV event rate.<sup>10-13</sup> The severity of coronary artery disease<sup>14,15</sup> and congestive heart failure<sup>16</sup> correlates with the degree of T deficiency.

In contrast with these results, a few observational and meta-analysis studies have reported an increase in CV events such as myocardial infarction, stroke as well as death compared with controls in patients on testosterone replacement therapy (TRT).<sup>17,18</sup>

Based on the contradictory evidence regarding the impact of TRT on CVD, the aim of our review is to examine the available evidence on the pros and cons of TRT on CVD in hypogonadal men with T2DM and/or metabolic syndrome (MS). As there is a paucity of well-designed, randomised, placebo-controlled trials of TRT, we have also included observational studies in our review. As only a small number of studies have been carried out exclusively in hypogonadal men with T2DM and/or MS, we have included all the trials in which the study population comprised a proportion of men with T2DM and/or MS.

## Methods

In this systematic review we have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.<sup>19</sup>

### Data sources and searches

We systematically searched PubMed, Cochrane Library, Google Scholar and Web of Science up to 30 June 2016 using search terms “testosterone” and/or “androgen”, “testosterone replacement therapy” and/or “androgen replacement therapy”, “diabetes mellitus” and “hypogonad\*”.

### Study selection

We included all studies which had at least 15% of participants with T2DM. Studies in which TRT was used for <4 weeks were excluded as the short duration of pharmacotherapy was deemed to be insufficient to have any meaningful impact on CVD outcomes. Men who had used anabolic steroids for indications other than hypogonadism were excluded.

### Outcome

The primary outcomes considered for this systematic review were the incidence of all-cause mortality and major adverse cardiac events (MACEs), which included fatal and non-fatal myocardial infarction (MI), stroke and heart failure.

### Quality assessment of studies and data extraction

We developed a quality assessment table of the selected studies of the effects of TRT on CV events.<sup>20</sup> Of the 25 selected studies, 12 studies were RCTs while 13 trials were non-RCTs. A total of three RCTs and nine non-RCTs had measured all-cause mortality and MACEs as primary outcomes.

To extract the data, the reviewer (LMQ) used the Cochrane data extraction form for reviews of interventions in RCTs and non-randomised studies. Figure 1 shows the search strategy resulting in 25 placebo-controlled and untreated comparative trials.

### Results

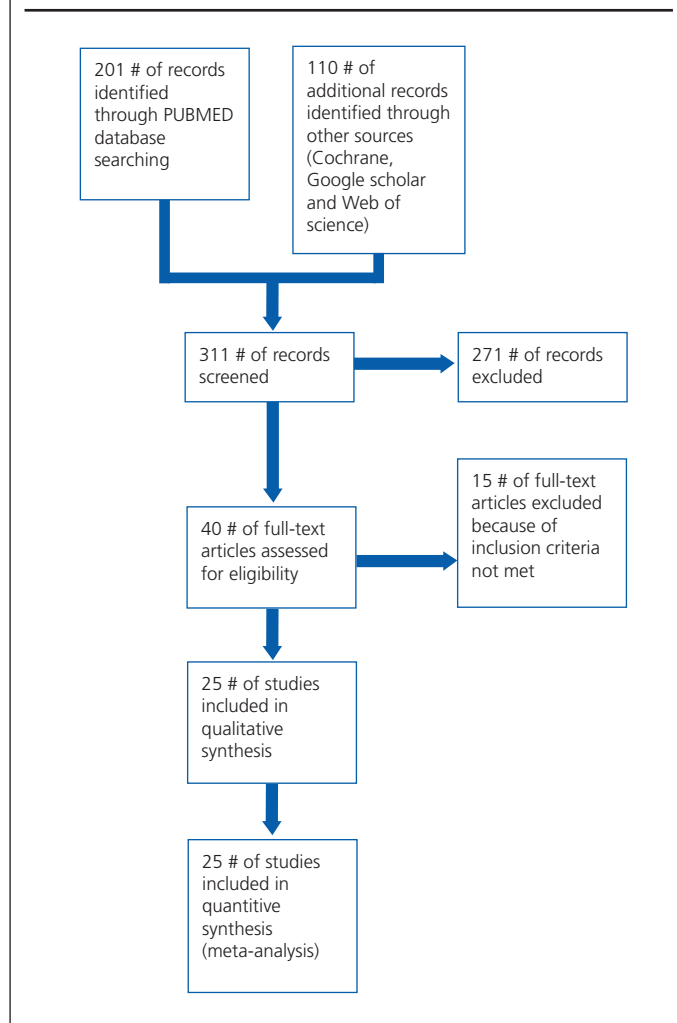
Initially we identified 311 articles related to TRT in men with hypogonadism. Only 40 of these 311 papers were deemed appropriate based on the eligibility criteria mentioned above. After reviewing the full text of these 40 papers, only 25 were found to be relevant comparative trials involving hypogonadal men who had received TRT for at least 4 weeks.

Table 1 shows the 25 selected trials which included 729,927 participants in 12 RCTs and 13 non-RCTs. Three RCTs and nine non-RCTs measured all-cause mortality and MACEs as primary outcomes. Three RCTs and one non-RCT were excluded as they had not measured all-cause mortality and CV events as primary outcomes. In treated groups, participants had received different testosterone formulations.

### Discussion

Epidemiological and observational study-based data consistently support an increased prevalence of hypogonadism in men with T2DM and obesity (diabesity).<sup>46</sup> The aetiopathogenesis of low T levels in men with diabesity is believed to be multifactorial, with reduced insulin and leptin signalling in the central nervous system playing a key role.<sup>46,47</sup> A hypogonadotrophic hypogonadism state induced by an increased aromatase activity in visceral adipose tissue

**Figure 1.** Search strategy resulting in 25 placebo-controlled and untreated comparative trials



along with adipocyte-derived cytokines inhibiting gonadotrophin releasing hormone through an indirect effect on the kisspeptin pathway have also been implicated in the pathogenesis of hypogonadotrophic hypogonadism in men with diabetes and MS.<sup>48</sup> We have carried out this systematic review to seek objective evidence regarding the impact of TRT on atherosclerotic CVD in hypogonadal men with T2DM and MS. We have analysed the available evidence from observational data and RCTs as well as reviewing the results of meta-analyses published during the last 15 years.

### Observational studies

An observational study by Anderson *et al*<sup>21</sup> showed a significant reduction of MACEs in patients with normal T levels (attained with TRT) compared with the rates of MACEs in the low T group. In terms of safety differentiation by age, as expected, the event rates in the older group (>65 years) were higher than the younger age group (<65 years). However, it is worth noting that, in both groups, the rates of 3-year mortality and MACEs were higher in persistently low T subjects. The strengths of this study include its large sample size

**Table 1** Characteristics of included studies

Study authors	Study design	Study duration	Intervention	Comparators	Numbers of participants	Age (years)	% baseline participants with T2D	Pharmaceutical funding
Anderson <i>et al</i> (2015) <sup>21</sup>	Observational	742 days	Different formulations (gel: 90%, injection: 9.0%, oral pill: 1.0%)	Untreated	4,736	61.2	32.6%; 29.3%; 23.0%	No
Aversa <i>et al</i> (2010) <sup>22</sup>	RCT	24 months	IM TU 1000 mg every 12 weeks	PLB	T: 40 PLB: 10	58/57	30%	No
Baillargeon <i>et al</i> (2014) <sup>23</sup>	Retrospective cohort	1495 days	IM different T formulations and dosing (T enanthate or cypionate, up to 1 mL, up to 100 mg and up to 200 mg, T suspension, up to 50 mg), T propionate, up to 100 mg)	Untreated	6,355	>66	Treated: 19.7% Untreated: 15.2%	No
Dhindsa S <i>et al</i> (2016) <sup>24</sup>	RCT	24 weeks	IM 250 mg TU every 2 weeks	PLB	T: 22 PLB: 22	54.6	100%	No
Francomano <i>et al</i> (2013) <sup>25</sup>	RCT	60 months	IM TU 1000 mg every 6 weeks	PLB	T: 20 PLB: 20	58/57	30%	No
Giagulli <i>et al</i> (2015) <sup>26</sup> (26)	Observational	2 years	100 mg T gel once daily	Untreated	30	53.5	100%	No
Hackett <i>et al</i> (2014) <sup>27</sup>	RCT	52 weeks	IM TU 1000 mg at weeks 0, 6 and 18	PLB	T: 92 PLB: 98	61.2/62	100%	No
Hackett <i>et al</i> (2016) <sup>28</sup>	RCT	24 months	IM TU 1000 mg at weeks 0, 6 and 18	PLB	T: 175 PLB: 682	63.5	100%	Yes
Haider <i>et al</i> (2014) <sup>29</sup>	Observational	60 months	IM TU 1000 mg at baseline and 6 weeks and thereafter every 12 weeks	Untreated	181	59.11	40%	No
Haider <i>et al</i> (2016) <sup>30</sup>	Observational	7.3 years	IM TU 1000 mg at 3-monthly intervals	Untreated	77	61	53%	No
Heufelder <i>et al</i> (2009) <sup>31</sup>	RCT	52 weeks	T gel 50 mg once daily	Untreated	T: 16 Untreated: 16	57.3/55.9	100%	No
Jones <i>et al</i> (2011) <sup>32</sup>	RCT	12 months	Transdermal 60 mg T gel once daily	PLB	T: 108 PLB: 112	59.9	62%	Yes
Kalinchenko <i>et al</i> (2010) <sup>33</sup>	RCT	30 weeks	IM TU 1000 mg at weeks 0, 6 and 18	PLB	T: 113 PLB: 71	51.6/52.8	Treated: 28.3% Placebo: 33.8%	Yes
Li <i>et al</i> (2016) <sup>34</sup>	Retrospective cohort	8 years	Different T formulations and dosing (topical/gel, transdermal, injections)	Untreated	533,223	51.5/54.2	20.2–20.8%	Yes
Malkin <i>et al</i> (2004) <sup>35</sup>	RCT	12 weeks	IM 100 mg T every two weeks	PLB	T: 5 PLB: 5	60.8	50%	No
Martinez <i>et al</i> (2016) <sup>36</sup>	Population based case-control	12 years	Different T formulations and dosing (IM, transdermal and oral T)	Untreated	19,215	64.8 (15.2)	14.7%	No
Mathur <i>et al</i> (2009) <sup>37</sup>	RCT	12 months	IM TU 1000 mg at weeks 2, 8, 20, 32 and 44	PLB	T: 7 PLB: 6	65	23%	No
Muraleedharan <i>et al</i> (2013) <sup>38</sup>	Prospective follow-up	41.6 months	Different T formulations and dosing (IM, transdermal and oral T)	Untreated	60	60.3	100%	Yes
Sharma <i>et al</i> (2015) <sup>39</sup>	Observational	3 years	Different T formulations and dosing (injection, gel or patch)	Untreated	83,010	66.5	Treated: 30.3% Untreated: 31.6%	No
Sharma <i>et al</i> (2016) <sup>40</sup>	Observational	15 years	Different T formulations and dosing (injection, gel or patch)	Untreated	71,407	64; 63.9; 66.6	Treated: 30.4% Untreated: 31.9%	No
Shores <i>et al</i> (2012) <sup>3</sup>	Observational	61 months	Different T formulations and dosing (injection, gel or patch)	Untreated	1,031	62.1	Treated: 35.9% Untreated: 39.5%	No
Stanworth <i>et al</i> (2014) <sup>41</sup>	RCT	13 months	Transdermal 60 mg T gel once daily	PLB	T: 73 PLB: 66	59.9	100%	Yes
Tan <i>et al</i> (2013) <sup>42</sup>	RCT	48 weeks	IM TU 1000 mg every 10–14 weeks	PLB	T: 56 PLB: 58	53.8/51.3	Treated: 23.2% Placebo: 15.5%	Yes
Tong <i>et al</i> (2012) <sup>43</sup>	RCT	48 weeks	IM TU 1000 mg at weeks 0, 6, 18, 30 and 42	PLB	T: 56 PLB: 58	53.4/53	Treated: 23.3% Placebo: 15%	Yes
Vigen <i>et al</i> (2013) <sup>44</sup>	Retrospective cohort study	27.5 months	Different T formulations and dosing (injection, gel or patch)	Untreated	8,709	60/63	Treated: 53.2% Untreated: 55.7%	No

CV outcome, cardiovascular outcomes; IM, intramuscular; NR, not recorded; TRT, testosterone replacement therapy; IR, insulin resistance; PLB, placebo; RCT, randomised controlled trial; T, testosterone; TU, testosterone undecanoate

with over 4,700 patients and meticulous follow-up of relevant medical records in a 'real-life' healthcare setting for more than 3 years.

In the retrospective study by Baillargeon *et al*,<sup>23</sup> TRT use was associated with a protective effect in hypogonadal men who were at highest risk of MI. It was suggested that T treatment might improve CV risks by reducing fat mass, improving insulin sensitivity and reducing cholesterol levels. The strength of this study was the analysis of a large cohort of patients with hypogonadism who received TRT (n=6,335) and comparison with a well-matched cohort of T non-users (n=19,065).

In a study by Muraleedharan *et al*,<sup>38</sup> the mortality rate in association with TRT in men with T2DM was compared with a well-matched control group. A significantly increased rate of mortality was observed in the untreated group compared with the men with hypogonadism who received TRT. This study was the first longitudinal cohort study in hypogonadal men with T2DM that reported the value of baseline T level to predict a significantly increased risk of mortality rate during long-term follow-up. Importantly, the increased mortality was independent of other factors such as age, body mass index, smoking habit, glycaemic management, pre-existing CVD and medications. Although no significant increase in CV mortality was reported in the low T group, there was an increased risk of CV death in men with below normal range T levels compared with men with normal T levels. Based on the study results, the authors concluded that the long-term use of TRT was associated with a reduced mortality rate in men with low T and T2DM.

Hackett *et al*,<sup>28</sup> studied the impact of T therapy on clinical and metabolic measures for 24 months in 857 hypogonadal men with T2DM. Reduced mortality was observed in the men with normal T and the low T group who were treated compared with the control group (men with low T who did not receive TRT).

In the observational study by Sharma *et al*,<sup>39</sup> normalised T levels were associated with a significantly increased MI-free survival rate (log-rank,  $p < 0.01$ ), significantly lower stroke events and reduced all-cause mortality. The strength of this study is its large study cohort with an extensive follow-up duration. Shores *et al*,<sup>3</sup> also observed that TRT use was associated with a reduction in mortality in hypogonadal men compared with the control group.

In contrast to the above-mentioned studies, an observational study carried out by Vigen *et al*,<sup>44</sup> reported an increased risk of mortality, MI or ischemic stroke with TRT use. This study was criticised for doubtful statistical techniques, lack of adjustment for baseline T concentrations, inadequacy of T treatment in the study subjects and data corrections. For instance, 17.6% of participants in the treated group received only one prescription of TRT while a significant number of participants did not refill their prescription. Only 60% of patients had T levels tested post-treatment and the average post-treatment T levels were under the therapeutic target.

### Randomised controlled trials

In the TIMES2 study, Jones *et al*,<sup>32</sup> evaluated the efficacy and safety of T therapy on IR and CV risk factors and sexual symptoms in 220 hypogonadal men with T2DM and/or MS over 12 months. This double-blind, randomised, placebo-controlled, multi-centre study

had one of the highest percentages of hypogonadal men with T2DM (62%) included in the study group compared with the other available RCTs. CV events were observed to occur more commonly in the placebo group than in men who received TRT (10.7% vs. 4.6%;  $p = 0.095$ ). This study was criticised for overemphasising the improvement in glycaemic control and insulin sensitivity.

An RCT carried out by Aversa *et al*,<sup>22</sup> and Tan *et al*,<sup>42</sup> reported the beneficial role of TRT in hypogonadal men. There were an increased number of patients in the placebo group who experienced an acute coronary event compared to the patients on TRT.

### Meta-analysis

In a meta-analysis, Xu *et al*,<sup>48</sup> reported an increased risk of CV events with TRT use based on the trials which did not receive pharmaceutical industry funding. It was suggested that reporting of adverse outcomes with TRT may be open to a conflict of interest based on the source of funding. However, the authors did not classify CV events as the incidence of MACE. In a meta-analysis and systematic review of randomised trials, Corona *et al*,<sup>49</sup> compared the effect of TRT against placebo and observed no increased risk of CV events.

In several meta-analyses and systematic reviews there has been no significant reported differences in terms of all-cause mortality and the incidence of MI, cardiac arrhythmias or revascularisation intervention between TRT and control groups.<sup>18,49-51</sup> A recently published (May 2018) meta-analysis by Ponce *et al* analysed four RCTs which included a total of 1,779 patients on TRT therapy compared with placebo treatment. TRT was associated with improved sexual desire and erectile function although there was an increased risk of erythrocytosis.<sup>52</sup>

### Limitations

The limitations of this review include a paucity in the number of large-scale RCTs in hypogonadal men with T2DM and/or MS, with most of the available literature being derived from observational studies. We included the studies in which T2DM patients constituted >15% of total hypogonadal participants as there are only a limited number of studies carried out in men with T2DM. The impact of TRT in hypogonadal men with T2DM and/or MS is contentious with a lack of robust evidence based on RCTs, although epidemiological study-driven data suggest a beneficial effect of TRT as far as CVD mortality is concerned. Most trials only reported serious CV events as a primary outcome, although there was a lack of consistency in methodology to assess severity of CV events among the various trials. In addition, a lack of detailed CV event reporting secondary analysis (by subtype of CV event) was not always available. Such subgroup analysis would undoubtedly have added value in assessing the aetiopathogenesis of the event. The difference observed by source of funding could not just be chance variation, with most pharmaceutical-supported trials reporting positive outcomes.

RCTs in symptomatically hypogonadal participants with T2DM and/or MS need to be at least >1 year duration as shorter trials can potentially underestimate the impact of TRT on vascular endothelium. The mortality and MACEs should be pre-specified as the primary endpoints and should have a consistent definition.





## Key messages

- Type 2 diabetes mellitus and/or metabolic syndrome is associated with an increased prevalence of hypogonadotropic hypogonadism
- Low testosterone levels in men with type 2 diabetes mellitus and/or metabolic syndrome are associated with increased cardiovascular mortality
- Testosterone replacement therapy in men with type 2 diabetes mellitus and/or metabolic syndrome is associated with reduced all-cause mortality and major adverse cardiac events, although testosterone replacement therapy needs to be used cautiously in elderly men with multiple co-morbidities

## Conclusions

Our retrospective and systematic review of the literature suggests an increased risk of all-cause mortality and CV events in men with low endogenous T levels.<sup>53-55</sup> An extensive analysis of published data (available on 30 June 2016) from RCTs and non-RCTs is supportive of the protective effect of TRT on all-cause mortality and MACEs in hypogonadal men with T2DM and/or MS. However, caution needs to be exercised while considering TRT in elderly men with co-morbidities. There is also a need for larger double-blind RCTs to evaluate the long-term outcome of TRT in hypogonadal men.

**Conflict of interest** The authors declare no support from any organisation for the submitted work.

**Authors' contributions** LMQ carried out the systematic search and drafted the manuscript. LMQ and AK did the data extraction and analysis; they also reviewed the manuscript critically. AK helped to carry out the systematic search and draft the manuscript. Both authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Both authors read and approved the final manuscript.

**Acknowledgements** The author would like to thank Atul Kalhan for his strong support in developing and writing this review.

**Funding** None.

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