Testosterone preparations for men with hypogonadism

A cohort study of US and UK data found that men who used testosterone injections were at higher risk of cardiovascular events, death and hospitalisation than men who used testosterone gels, although the absolute risks were small.

**Overview:**

- Compared with men who used testosterone gels, men who used testosterone injections were at higher risk of acute cardiovascular events, death and hospitalisation.
- No significant difference was seen in the risk of adverse events between men using testosterone patches and those using gels.

**Background:** Hypogonadism is the term given to low testosterone levels, low sperm levels or both (Basaria 2014). Low testosterone levels can cause loss of muscle mass and body hair, low libido, erectile dysfunction, hot flushes and other less specific signs and symptoms, such as fatigue and depression (Bhasin et al. 2010).

Low testosterone levels can be remedied with testosterone treatment, which can be delivered in many forms such as intramuscular injections, skin patches or gels. Testosterone therapy may be associated with an increased risk of cardiovascular events (Basaria et al. 2010). Given the differences in pharmacokinetics (Dobs et al. 1999), the different approaches to delivering testosterone therapy may be associated with differing risks.

**Current advice:** Guidance on male hypogonadism from the European Association of Urology recommends that the diagnosis of male hypogonadism should be based on signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.

The following testosterone preparations are recommended for replacement therapy:

- Testosterone undecanoate: oral (2–6 capsules every 6 hours) or injection (1 intramuscular injection every 10–14 weeks).
- Testosterone enantate: 1 intramuscular injection every 2–3 weeks.
• Transdermal testosterone: daily application of a gel or of skin patches.
• Buccal testosterone: buccal tablets twice a day.
• Subdermal depots: subdermal implant every 5–7 months.

Selection of testosterone preparation should be a joint decision by the patient and their healthcare professional. The patient should be fully informed about expected benefits and side effects of the treatment option.

Haematological, cardiovascular, breast and prostatic assessment should be performed before the start of treatment. Men with hypogonadism and pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require testosterone replacement therapy should be treated with caution and monitored carefully with clinical assessment.

**New evidence:** A retrospective cohort study by Layton et al. (2015) assessed the adverse cardiovascular effects of 3 different approaches to delivering testosterone.

Data were collected from 3 sources: a database of commercially insured men in the USA; a sample of US Medicare records; and a UK database of general practitioner records. Men who were starting testosterone therapy for the first time by injection, gel or patch were included in the study. These men were followed up for 1 year to observe for incidence of acute cardiovascular events (myocardial infarction, unstable angina and stroke), hospitalisation, mortality and venous thromboembolism.

A total of 544,115 men were included in this study, 55.8% of whom had used testosterone gel, 37.4% had used injections and 6.9% had used patches. Less than half of participants (43.4%) had a recorded diagnosis of hypogonadism or low testosterone (only 12.0% of men in the UK cohort).

Compared with men using testosterone gel, men using testosterone injections were at higher risk of all outcomes except venous thromboembolism over 1 year of follow-up. Among men using injections, the risk of cardiovascular events was 26% higher than in men using testosterone gel (adjusted hazard ratio [aHR]=1.26, 95% confidence interval [CI] 1.18 to 1.35). The risks of death (aHR=1.34, 95% CI 1.15 to 1.56) and hospitalisation (aHR=1.16, 95% CI 1.13 to 1.19) were also higher.

When men using testosterone patches were compared with those using gels, no significant difference was seen in the risk of any adverse event, bar a marginally significant increase in the risk of myocardial infarction in men using testosterone patches (aHR=1.21, 95% CI 1.01 to 1.43).

The authors cautioned that despite the raised risk of adverse events in men using testosterone injections, the absolute event rates were low. For example, among UK men using testosterone injections, the event rates were 16.9 acute cardiovascular events per 1000 person–years and 21.3 deaths per 1000 person–years.

Strengths of this study include that the sample was large and diverse, comprising men from a range of age groups, populations and healthcare systems. This study was limited by its use of secondary data, which meant that important patient characteristics were unavailable, such as BMI and smoking status. In addition, data may have been missing and outcomes misclassified.

**Commentary by Dr Paul Carroll, Consultant Endocrinologist, Guy’s and St Thomas’ NHS Foundation Trust:**

“In this well-conducted study using information from large retrospective database, Layton et al. (2015) have compared the short-term cardiovascular and mortality risks associated with different testosterone formulations: intramuscular injections and transdermal patches and gels. The authors concluded that transdermal preparations were associated with fewer cardiovascular adverse events and a lower mortality risk than injectable testosterone preparations over a 1 year period of use.

“The large study cohort and robust statistical analysis strategy form the strengths of this paper. However, there are a number of key weaknesses, most importantly the absence of a control group.
not using testosterone to clarify the absolute risks associated with initiation of testosterone treatment.

“This study does not report indications for testosterone treatment, biochemical evidence of hypogonadism, confounding risk factors for cardiovascular disease and data on monitoring of testosterone levels. These deficiencies and the short duration of follow-up (1 year) limit the usefulness of the results and mean that this study, although thought provoking, is unlikely to influence UK prescribing practice.

“In the UK, men who choose intramuscular depot therapy increasingly use the long-acting preparation testosterone undecanoate. The safety of intramuscular testosterone undecanoate was not addressed in the paper by Layton et al. (2015). Whether testosterone undecanoate is associated with the same increase in cardiovascular events this paper reports for other injections is unknown.

“This study highlights the need to comply with current guidance on initiating treatment based on signs, symptoms and biochemical confirmation of testosterone deficiency. Existing guidance also recommends that the method of replacement is discussed with the patient and appropriate safety monitoring is used. The results highlight that appropriate selection of men who may benefit from testosterone supplementation is important and that there may be risks associated with testosterone treatment.

“Replacement of testosterone to physiological levels, irrespective of the formulations used, forms the cornerstone of current treatment strategies for hypogonadism. It is unlikely that this study will lead to change in UK practice. Testosterone prescribing is increasing in the UK, and mostly in the form of transdermal gel preparations. Although long-term safety concerns related to testosterone use remain unanswered, it is likely that use of testosterone treatment will continue to increase in the UK in line with the USA and other developed countries.”

Study sponsorship: US National Institute on Aging.

About this article: This article appeared in the April 2016 issue of Eyes on Evidence.

Eyes on Evidence is a monthly email service that summarises and provides expert commentary on important new evidence in health, public health and social care, to help busy professionals stay up to date. The service outlines how the new evidence fits in with current guidance and provides expert views on how the evidence might influence practice. It does not constitute formal NICE guidance. The commentaries included are the opinions of contributors and do not necessarily reflect the views of NICE.

Subscribe on the NICE website to receive Eyes on Evidence each month.

Visit NICE Evidence search

Copyright © 2016 National Institute for Health and Care Excellence. All Rights Reserved.