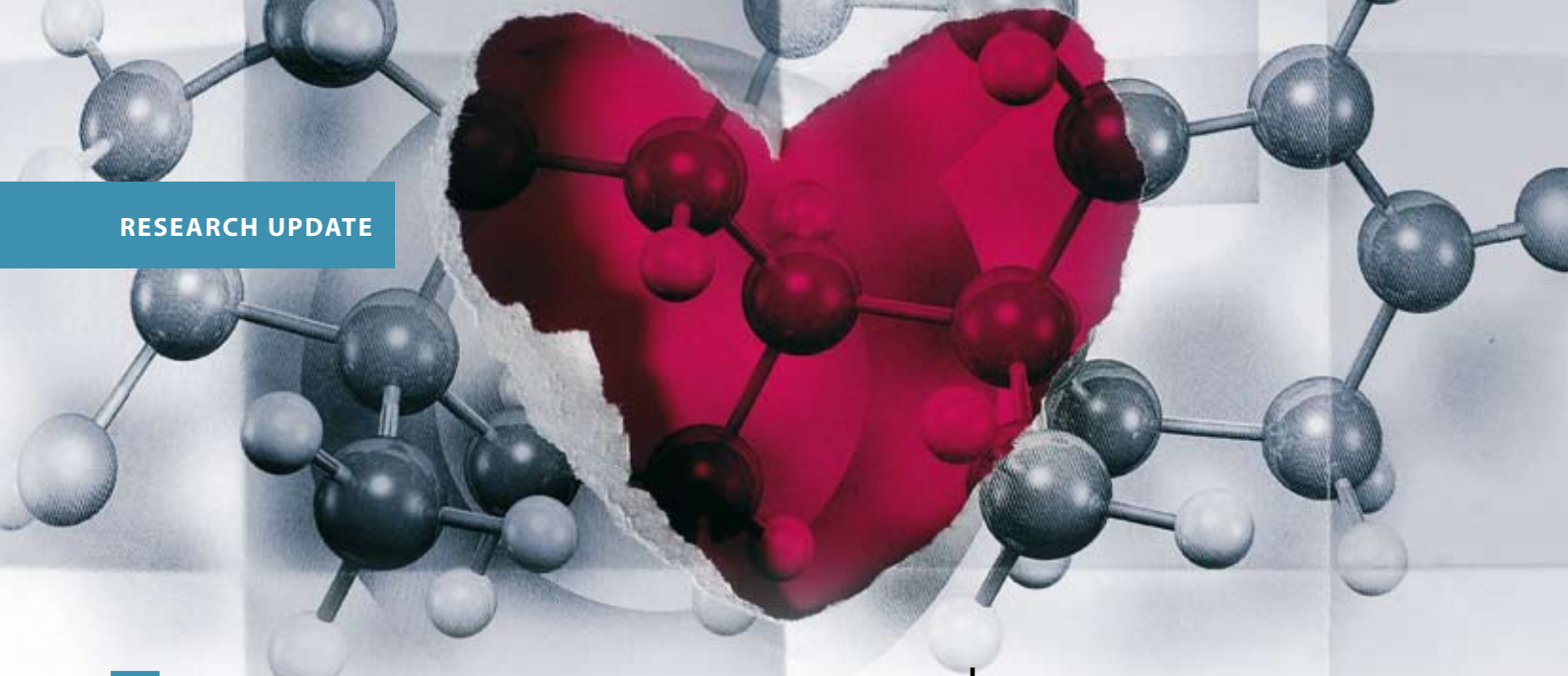
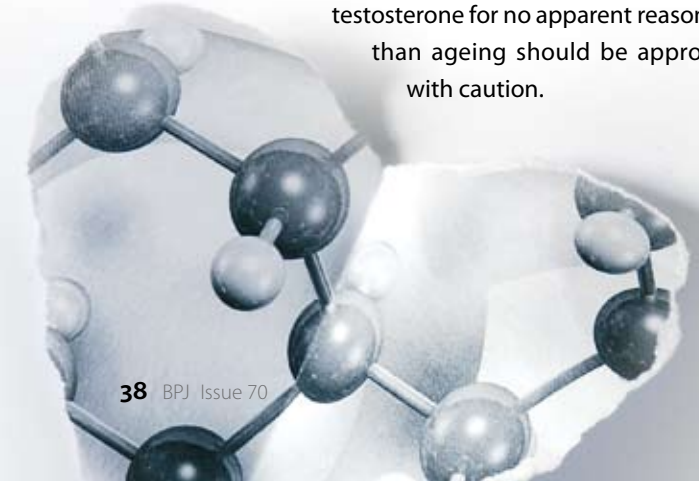


Testosterone use and cardiovascular risk in older males

In the previous edition of Best Practice Journal, we covered the appropriate use of testosterone in older male patients (see: "Prescribing testosterone in ageing males: why you shouldn't read this article", BPJ 69, Aug, 2015). One area of concern discussed in the article is whether testosterone use in this patient group affects cardiovascular risk. Three studies that suggested an increase in cardiovascular risk in older males taking testosterone drew the attention of the United States Food and Drug Administration (FDA), American Urological Association, and New Zealand Medicines Adverse Reaction Committee. As the previous Journal went to print, two additional studies regarding the cardiovascular safety of testosterone in older males, and an editorial from the FDA regarding the use of testosterone in older males, were published.

Although we are drawing attention to these new studies and concerns from the FDA to keep readers informed, the conclusions of our previous article remain the same: at present there is no data from randomised controlled trials in older males regarding the effect of testosterone use on cardiovascular events. Therefore, the use of testosterone in older males who have low testosterone for no apparent reason other than ageing should be approached with caution.



The TEAAM trial[1]

The Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) trial investigated whether testosterone use (in the form of a transdermal gel) altered the progression of atherosclerosis in males aged 60 years and over. The study recruited 308 participants who were community-dwelling males; 15% had prior coronary artery disease and approximately 44% were using statins. Participants applied 7.5 g of testosterone gel daily, which could be adjusted to 5 g or 10 g depending on achieved testosterone levels, or a placebo gel daily, for three years. The progression of atherosclerosis was assessed by measuring carotid artery intima-media thickness and coronary artery calcium.

The rate of change of coronary artery intima-media thickness or coronary artery calcium scores did not differ between participants taking testosterone or placebo; both groups showed the same rate of progression. Among participants using testosterone, changes in measures of atherosclerosis did not correlate with changes in total or free testosterone levels. The findings suggest testosterone use does not affect the progression of atherosclerosis in older males. The strengths of this study include a double-blind randomised controlled trial design, the use of doses of testosterone adjusted to match what would normally occur in clinical practice, and that patients were followed for three years of testosterone use. While these results are reassuring, the study only examined atherosclerosis; testosterone could potentially affect other factors which influence risk of a cardiovascular event, such as plaque stability, clot formation or physiological processes involved in cardiovascular disease which are not yet well understood.

Retrospective review of testosterone treatment in older males[2]

Sharma *et al*. conducted a retrospective assessment of older males in the Veteran's Affairs network of clinical centres in the United States. The study identified males who had biochemical evidence of hypogonadism. Patients were then divided into three groups depending on whether they were untreated (13,378 patients), were prescribed testosterone and subsequently achieved normal total testosterone levels (normalised treated; 43,931 patients), or were prescribed testosterone but continued to have low testosterone levels, suggesting lack of compliance or inappropriate dosing (non-normalised treated; 25,701 patients). The median age of participants was 66 years, and the duration of testosterone use was on average three years for males who achieved normalisation of testosterone levels and one and a half years for non-normalised treated males.

This study found that males who achieved normal testosterone levels had a lower risk of all-cause mortality (hazard ratio, HR: 0.44, 95% confidence interval, CI: 0.42–0.46), myocardial infarction (HR: 0.76, CI 0.63–0.93) and ischaemic stroke (HR: 0.64, CI 0.43–0.96) than males who were not prescribed testosterone*. Males who were prescribed testosterone but continued to have low testosterone levels had significantly lower mortality rates (HR: 0.84, CI 0.80–0.89), but not lower rates of myocardial infarction or stroke, than untreated males.

This is not the first study to conduct a retrospective review of testosterone use. Previous research has, however, been limited by lack of assessment of patient compliance or whether the dose prescribed was appropriate. By classifying patients according to achieved testosterone levels, this study design largely overcomes this limitation. The results suggest that older males with hypogonadism who achieve normalisation of serum testosterone levels have a reduced risk of overall mortality, myocardial infarction and stroke.

However, the study has the limitations of any retrospective observational study: it is not a randomised controlled trial and unrecognised confounding factors may be present which influence the study's results. For example, it is possible that patients who were not prescribed testosterone had contraindications or other clinical factors which led their treating clinician to decide not to initiate testosterone use in spite of biochemical evidence of hypogonadism. Although the authors of the study conducted statistical adjustments for recorded differences in cardiovascular risk between groups, unknown factors may have caused spurious associations of cardiovascular events, mortality and testosterone use.

* The hazard ratio is a measure of the chance of an event occurring at any point during follow-up, so that these results mean, for example, that males taking testosterone were 44% as likely to die as males not using testosterone at any point during the follow-up period included in the study.[3]

What is a prescriber to make of this?

Both of these studies provide further data on an area of clinical controversy, although their results are not sufficient to direct a change in clinical practice. The TEAAM trial provides reassuring data that testosterone use does not appear to influence progression of atherosclerosis, and Sharma et al. found an association between testosterone use and reduced all cause mortality and cardiovascular disease. However, these results are insufficient by themselves to offer a clean bill of cardiovascular safety for testosterone use in older males.

In an editorial published in August, 2015 in the New England Journal of Medicine, authors from the FDA summarised various areas of concern for the agency.[4] In particular, testosterone products have previously only been required to show that they are able to raise testosterone levels for FDA approval. The intention was that these products would be used for males with conditions falling under what the agency called "classic hypogonadism", such as Klinefelter's syndrome, pituitary disease or testicular damage; patients for whom supplementation was clearly clinically indicated. The FDA holds concerns over the use of these products to treat males with age-related declines in testosterone, since this appears to be a common feature of ageing and the risks and benefits of testosterone use in this patient group are uncertain. The agency has now signalled that it is encouraging companies that manufacture testosterone products to work together on a single trial which will assess cardiovascular safety.[4]

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