Preclinical studies found that rats exposed to pioglitazone had an increased risk of bladder cancer.

In 2005, the ProActive trial, (a large European randomised controlled trial evaluating the effects of pioglitazone on cardiovascular outcomes), showed a non-significant increase in the incidence of bladder cancer in the pioglitazone treatment arm.

The US Food and Drug Administration commissioned the manufacturer to carry out a ten-year observational cohort study to evaluate the effect of pioglitazone on bladder cancer, and both this and another French cohort study showed an increase in incidence of bladder cancer with exposure to pioglitazone.

Following this the drug was withdrawn in France and Germany. Restrictions were placed on it in the USA, to be avoided in patients with existing bladder cancer and prescribed with caution in those who had previously had the disease. The European Medicines Agency added a further restriction category of uninvestigated macroscopic haematuria.

The authors of the current analysis point out that previous studies were too small to have power to be certain of detecting a causative effect, and were all subject to potential selection bias. The authors assimilated a large sample size by pooling data and analysed for cumulative effects, adjusting for ever usage in a time-dependent approach.

When rosiglitazone was withdrawn, and questions were raised about pioglitazone, I reviewed all the patients in our practice who were taking it. There remain a small number of patients who are on it because they felt happy to continue rather than destabilise their control, and some who take it with insulin because they are particularly insulin resistant.

I have not been initiating pioglitazone routinely since the concerns were raised. It is interesting to learn that pioglitazone may not carry an increased risk of causing bladder cancer, because as GPs we may have to counsel those with bladder malignancies who have been exposed to the drug, and because there is still a group of patients who may need to start it.

DR MATTHEW LOCKYER

● **Levin D, Bell S, Sund R. Pioglitazone and bladder cancer risk: a multipopulation pooled, cumulative exposure analysis. *Diabetologia* 2015;58:493-504**

Cardiovascular disease

Sex differences revealed in cardiovascular outcomes in aortic stenosis

Women with aortic stenosis had a lower rate of all cause mortality and fewer ischaemic cardiovascular events then men, in a randomised controlled trial. However, rate of disease progression was similar for both genders.

Data were used from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study, a randomised, double-blind, placebo-controlled trial which assessed the effect of combined treatment with simvastatin and ezetimibe on the progression of mild to moderate aortic stenosis and cardiovascular morbidity and mortality.

The sub-study was a prospectively planned analysis of those patients in whom left ventricular (LV) geometry could be assessed. Echocardiography and cardiovascular events were recorded during a median of 4.0 years in 979 men and 632 women aged 28-86 years. LV systolic function was assessed by ejection fraction and midwall shortening.

The outcomes were aortic stenosis-related events, ischaemic cardiovascular events and total mortality.

Aortic stenosis-related events included aortic valve replacement, hospitalisation for congestive heart failure caused by aortic stenosis or death from cardiovascular causes.

Ischaemic cardiovascular events included non-fatal myocardial infarction, hospitalisation for unstable angina, coronary revascularisation at the time of aortic valve replacement, non-haemorrhagic stroke and cardiovascular death.

Women and men had a similar rate of progression of aortic stenosis irrespective of the echo parameter used to assess severity (peak jet velocity, mean gradient or valve area). The authors performed multivariate analyses which showed that female gender independently predicted less reduction in LV function either by midwall score or ejection fraction during follow-up.

Compared with men women had:

- A 40% lower rate of ischaemic events: hazard ratio (HR) 0.60 (95% CI:0.46-0.79, P < 0.001) with
- More than a 50% lower rate of stroke: HR 0.47 (95% CI:0.26-0.85, P = 0.01) and coronary artery bypass grafting: HR 0.49 (95% CI:0.34-0.71, P < 0.001).
- A 31% lower all-cause mortality: HR 0.69 (95% CI:0.49-0.99, P = 0.04).

This was independent of study treatment, age and hypertension.

However, the rate of events directly attributable to aortic stenosis did not differ by gender.

As the population ages aortic stenosis will become increasingly prevalent. The authors conclude that although both men and women had a similar rate of progression of aortic stenosis and similar stenosis-related events, women had a lower rate of death from all causes and fewer ischaemic cardiovascular events compared with men.

DR PETER SAVILL

● **Cramariuc D, Rogge BP, Lønnebakken MT et al. Sex differences in cardiovascular outcome during progression of aortic valve stenosis. *Heart* 2015;101:209-214 doi:10.1136/heartjnl-2014-306078**