

Sex and the risk of acute reduction in kidney function after renin-angiotensin blockade: parallel analyses of a primary care cohort and two randomised trials

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Introduction: Men and women respond differently to renin-angiotensin system blockade. However, it is unknown whether women are more likely to have a reduction in kidney function after initiating angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and if so, how this might affect long-term adverse outcomes. In this study of individuals initiating ACEI/ARBs, we aimed to: 1) examine the relationship between sex and change in kidney function; and 2) examine the sex-specific associations between change in kidney function and long-term adverse cardiovascular, kidney and mortality outcomes.

Methods: We conducted parallel cohort studies using the UK Clinical Practice Research Datalink (CPRD) and combined data from patients randomised to ACEI or ARB in the ONTARGET and TRANSCEND randomised controlled trials (RCTs). We estimated changes in kidney function by calculating the percentage change in estimated glomerular filtration rate (eGFR) using pre- and post- ACEI/ARB initiation serum creatinine measurements. We defined an acute reduction in kidney function as a relative decrease in eGFR $\geq 15\%$ and compared with those with a change in eGFR $< 15\%$. Firstly, we examined the association between sex and the change in eGFR after initiating ACEI/ARB, adjusting for potential confounders using logistic regression. We further stratified the analyses comparing men to women by age, baseline eGFR, baseline proteinuria, retinopathy, peripheral arterial disease, heart failure or decreased blood pressure. Secondly, we used adjusted Cox proportional hazards models to investigate the associations between change in eGFR and adverse cardiovascular, kidney and mortality outcomes; an interaction term was fitted to investigate whether these associations varied by sex. We conducted a number of sensitivity analyses including examining different levels of change in kidney function.

Results: We included 196,596 individuals from CPRD and 9123 individuals from the RCTs. In both CPRD and RCT settings, in strikingly similar findings, we found that female sex was associated with an increased risk of post-ACEI/ARB-initiation eGFR reduction $\geq 15\%$ (Odds ratio, 95% CI: CPRD: 1.19, 1.14-1.24; RCTs: 1.35, 1.19-1.56) (Table 1), after multiple adjustment, including body weight. We observed increased long-term risk of kidney disease, cardiovascular events in CPRD and mortality associated with eGFR decrease $\geq 15\%$ (Figure 1); there was no evidence to suggest that these associations differed by sex. Results were similar in all sensitivity analyses and for different levels of kidney function decline.

Discussion: Women are at greater risk of reductions in kidney function after ACEI/ARB initiation than men, and the association between kidney function and clinical outcomes did not vary by sex. If the association between acute drop in kidney function and adverse outcomes is causal, a greater proportion of women initiating ACEI/ARB would be at risk of adverse outcomes.