

Statins and the risk of acute kidney injury: **keep calm – carry on**

THERE HAVE BEEN RECENT REPORTS in the literature associating the use of statins with acute kidney injury (AKI). A study by Hippisley-Cox and Coupland of over 225 000 patients starting statin treatment for the first time in England and Wales found a dose-response association between statin treatment and acute kidney injury (AKI).¹ Over 70% of these patients were taking simvastatin.¹ The increased risk of AKI was observed within one year of initiation and remained for the first five years of treatment, returning to normal within one to three years of treatment ceasing.¹

In their analysis, Hippisley-Cox and Coupland calculated numbers needed to harm (NNH) and numbers needed to treat (NNT) for statin treatment in patients without cardiovascular disease, with a cardiovascular risk $\geq 15\%$. The NNT with any statin to prevent one case of cardiovascular disease over five years was 44 for females and 38 for males.¹ For females the NNH for an additional case of AKI over five years was 593, and for males the NNH was 447.¹ Potential harms and benefits both increased in patients with cardiovascular risks $\geq 20\%$.¹ For patients with elevated cardiovascular risk, the benefits of statin initiation therefore clearly outweigh any increased risk of AKI.

A larger, and more recent study by Dormuth *et al* investigated the use of high and low-dose statins in more than two million

people in Canada, Great Britain and the United States. High-dose statin use was defined as ≥ 40 mg simvastatin, ≥ 20 mg atorvastatin or ≥ 10 mg rosuvastatin daily.² A 34% increase in the relative risk of hospitalisation for AKI within 120 days of initiation of high-dose statins, compared to low-dose statins, was reported in people without chronic kidney disease (CKD).² This risk remained elevated for at least two years of treatment, which was the maximum follow-up period for each patient.² Interestingly, the rate of hospitalisation for AKI did not increase significantly in patients with existing CKD.²

Dormuth *et al* also calculated a NNH for high-dose statin use. They estimated that 1700 patients without CKD need to receive high-dose statin treatment for 120 days (rather than low-dose statins), for one additional hospital admission due to AKI to occur.²

Rhabdomyolysis is proposed as a mechanism linking statin treatment to AKI, although there was no evidence of this among patients who had experienced an episode of AKI following statin treatment in the Dormuth study.² Another possible explanation is statin blockage of co-enzyme Q10, a fat soluble enzyme with antioxidant properties.² Human and animal studies have reported co-enzyme Q10 to be linked to improved kidney function in subjects with kidney disease.²

What do these studies mean for primary care?

The benefits of statins in reducing cardiovascular risk are well known. Given that the increased risk of AKI in patients taking statins is modest and the mechanism for this association is unknown, there is currently insufficient evidence to alter the prescribing of statins in primary care. However, in older patients with reduced kidney function there may be a need for increased vigilance when initiating high-dose statin treatment.

References

1. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010;340:c2197.
2. Dormuth CR, Hemmelgarn BR, Paterson JM, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ* 2013;346:f880.

An alternative explanation for the association between statins and acute kidney injury

The finding by Dormuth *et al* that patients with existing CKD who were on high-dose statin treatment were not at significantly increased risk of AKI is unexpected. This may signal the need for caution when interpreting the results of this study.

Patients are prescribed statins because they have elevated vascular risk factors. These patients may therefore also be at increased risk of renal atherosclerosis. Statin treatment could therefore be a confounding factor in both studies that study design and analysis strategies may be unable to completely compensate for. High-dose statins are likely to be prescribed for patients with higher vascular risk, and this could account for the increased rate of AKI associated with high-dose statin use as reported by Dormuth *et al*. Furthermore, atherosclerosis is an ongoing process which may explain why Hippisley-Cox and Coupland observed an increased risk of AKI for patients who used statins six months after the medicine was stopped. The relative incidence rate ratio of AKI during use of simvastatin for males and females combined was 1.57, compared to 2.21 during the six-month washout period.¹

