Higher statin doses linked to acute kidney injury: South African experts comment on clinical implications

A meta-analysis published this week in the British Medical Journal has linked higher doses of statins (resulting in at least a 45% reduction in low-density lipoprotein cholesterol) to a higher risk of acute kidney injury (AKI) in the first four months of therapy compared to lower-dose statins.

The study was based on data from Canadian, UK and USA databases of some two million patients, where each index case of AKI was matched with 10 controls from the same database and also matched in terms of time of initiation of therapy. Patients were judged to be treated with higher statin doses if they were given ≥ 10 mg rosvastatin, ≥ 20 mg atorvastatin and ≥ 40 mg simvastatin.

The rate ratio of hospitalisation for AKI for users of high-potency versus low-potency statins was 1.34 (95% CI: 1.25–1.43) for those without a chronic kidney disease (CKD) history and a non-significant 1.10 (95% CI: 0.99–1.23) for those with a CKD history.

CVJAfrica asked two South African experts for their comments on the study:

Prof Brian Rayner, hypertension and renal expert, University of Cape Town, and Dr Dirk Blom, lipid expert, University of Cape Town

Prof Brian Rayner

The risks of acute kidney injury were shown to be raised by 34% over the first four months. This sounds large, but translates to only one extra acute kidney injury event per 1 700 patients treated with the higher dose.

The difficulties of interpreting meta-analyses of this kind are well known as they group together patients with different co-morbidities and perhaps different predispositions to AKI, although this study did try to match index cases to appropriate controls.

There were important differences in demographics in the high-dose statin group, with more heart failure and more use of ARBs and ACE inhibitors, factors well known to predispose to AKI. Additionally there are no data in the use of contrast between the groups, which is a major omission from the article. This could account for the higher incidence in the first 120 days, especially in patients treated for secondary prevention requiring coronary angiograms.

For the clinician there are also no data on the causes and severity of AKI, which would be useful in determining causation in the high-dose group. Additionally AKI can range from a 25% increase in creatinine level to life-threatening renal failure requiring dialysis.

Dr Dirk Blom

Observational database studies rely on the accuracy and completeness of diagnostic coding; in this case the coding for acute kidney injury. Because this is a database study, we do not know the context in which higher statin doses were prescribed, e.g. were statin doses increased following an intervention (contrast administration) or cardiovascular event. We also do not know much about the severity of the kidney injuries observed.

Observational studies are prone to confounding (e.g. sicker patients are prescribed more therapy) and although the authors adjusted their data by using propensity scoring, a residual risk of confounding remains. Patients on high-dose statins had higher rates of congestive cardiac failure (not sufficiently different to account for the observed effect on AKI) and were more likely to use ACE inhibitors, ARBs, loop diuretics and beta-blockers.

This study showed no statistically significant harm with the higher dose of statins given to patients with CKD. This is certainly at odds with expectations, as CKD patients would be more vulnerable to any potential renal effects of the ‘more-potent statins’.

Our clinical recommendations for daily practice are:

- We would not change therapy at the moment, i.e. continue patients who are on high doses on their current therapy if indicated.
- Be alert that there may be a small excess risk of AKI in those on high-dose statin therapy and avoid nephrotoxic medications or interventions.
- Clinical judgement is required when choosing a statin; the clinician needs to balance cardiovascular risk, lipid profile and potential statin side effects.
- Statin therapy has known benefits and should not be withheld because of fears of AKI. The absolute risk of AKI remains very low
- Clinicians should not lose sight of the fact that admission rates for AKI are markedly higher in those with CKD than those with no CKD (the difference varies by database but the rate is at least tenfold and often greater). The risk of AKI in those with CKD is therefore, a major concern and statins do not pose a specific threat here. Focus on good management of those with CKD to avoid precipitating acute kidney injury. This will likely be the intervention that has the largest benefit. The absolute risk increase for AKI from high-dose statins is very small in those without CKD when compared to the very high baseline risk of AKI in those with CKD.
- There have been reports of proteinuria with high-dose statins (especially with very high doses, such as rosvastatin 80 mg/day, which was subsequently not marketed).
- Other observational studies have also shown an increased risk of AKI with statin therapy, but
observational data are not well suited to causality analyses.

Reference