Letter and Reply

Advance Access publication 17 May 2011

Careful re-evaluation of the impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease

Sir,

We read the article by Ahmed et al. [1] with great interest. This clinical research focused on the impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease. Their observational data showed that discontinuation of existing long-term angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptors blockers (ARBs) in advanced chronic kidney disease was beneficial to the estimated glomerular filtration rate (eGFR) for the majority of patients.

Some questions arose:

1. In this study, the urine protein:creatinine ratio (PCR) after stopping ACEi/ARB was increased in absolute value although this increment did not reach statistical significance (before = 77 ± 20 and after = 121.6 ± 33.6 mg/mmol), even though patients were at end stage renal disease stage. Blood pressure was significantly elevated in spite of alternative antihypertensive agents prescribed. Proteinuria reduction, blood pressure control and kidney function preservation have convincingly been shown [2–4]. In this study, proteinuria increment and blood pressure elevation after stopping ACEi/ARB was observed, contrary to the fact that eGFR improved. What is the reasonable explanation?

2. Patients were divided into three groups according to eGFR changes after ACEi/ARB were stopped: with worse eGFRs >25%, improved eGFRs >25–50% and stable eGFRs, respectively. We were interested in the value of PCR, blood pressure in the three groups above, as these data were not shown in the manuscript.

3. The patients included in the study were elderly (mean age 73.3 ± 1.8 years). Loss of lean muscle mass in the elderly will lead to overestimation of eGFR. The article showed examples of the course of selected patients with sustained improvement in eGFR (>25%) up to 54 months after stopping ACEi/ARB. We wonder if muscle mass measurement had been done to rule out influence of muscle mass over this 54-month duration.

4. In chronic kidney disease with existing long-term ACEi/ARB prescription, accelerated decline of eGFR occurred when factors affecting intra-renal hemodynamics were imposed. Commonly seen factors were renal artery stenosis or diffuse arteriosclerosis, water deprivation due to various causes, consumption of non-steroidal anti-inflammatory drugs, hypertension or hypotension and cardiovascular attacks that lowered renal effective blood supply. Yet, messages in the article regarding exclusion of potential factors decreasing eGFR were inadequate.

As had been stated in the article, prominent among interventions aimed at slowing the progression of chronic kidney disease is the inhibition of the renin–angiotensin–aldosterone system. Stopping long-term existing ACEi/ARB therapy resulted in proteinuria aggravation and blood pressure elevation; therefore, we need to be cautious and carefully interpret the results on the eGFR.

Conflict of interest statement. None declared.

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Reply

Sir,

We appreciate the comments made by Meihua et al. to our pilot study on the discontinuation of ACE inhibitors (ACEi) in advanced stages of chronic kidney disease (CKD).

As the authors clearly mention, the rise in proteinuria post stopping ACEi/ARB did not reach statistical significance. The impact of ACEi/ARB on proteinuria in those who reached end stage renal disease would be minimal.
as proteinuria at this stage would, to a large extent, reflect severe glomerular sclerotic changes rather than the early haemodynamic changes of glomerular hypertension that would be amenable to improvement by inhibition of the renin angiotensin aldosterone system (RAAS). Also a tubular component to the proteinuria reflecting extensive tubulointerstitial damage at this stage of CKD would not be affected by ACEi or ARB [1].

We appreciate the effect of loss of lean muscle mass on estimated glomerular filtration rate (eGFR). Patients included in this study had access to dietician advice and none of them had significant weight loss over the period of the study as documented by stable weights at every clinic visit. Moreover, instant muscle mass loss upon discontinuation of RAAS inhibitors has not been previously reported.

Blood pressure (BP) control increased slightly but significantly 12 months after stopping ACEi/ARB. However, 53% of patients had BP levels within the recommended target (<130/80 mmHg). The explanation we proposed for improving of eGFR inspite of the observations on BP is that this may reflect the improved function of the least affected remaining functioning glomeruli through restoration of remnant glomerular hyperfiltration. At this advanced stage of CKD, loss of autoregulation may mean that excessively low BP targets in older patients may cause more harm than good.

We agree with the authors that the change in eGFR is potentially multifactorial including systemic as well as intrarenal haemodynamic changes, intra- and extrarenal arterial and arteriolar sclerosis, which are all common in this age group. We have excluded, to the best of the clinical indications, renal artery stenosis and that was clearly mentioned in our manuscript. Age-related vascular sclerosis is most likely in older patients with CKD, another reason to use RAAS inhibitors with caution in this population.

Conflict of interest statement. None declared.


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CD40/CD40L and cardiovascular risk in patients on haemodialysis: a role for soluble CD40?

Sir,

We read with attention the paper by Desideri et al. (1) recently published in Nephrology Dialysis and Transplantation.

The authors of the RISchio Cardiovascolare nei pazienti afferenti all’ Area Vasta In Dialisi (RISCAVID) study evaluated the involvement of the CD40/CD40L pathway in the increased cardiovascular risk of patients on haemodialysis (HD).

In particular, they demonstrated a strong correlation between combined cardiovascular morbidity and mortality and plasma levels of the soluble form of CD40L (sCD40L). This molecule, mainly produced by platelets, interacts with CD40/CD40L leading to a chronic activation of this pathway and predisposing HD patients to develop a pro-atherothrombotic state.

These results are very interesting but, aiming to better define the role of the co-stimulatory CD40 system in atherosclerosis and different clinical settings, the presence of another important factor should be considered: the soluble form of CD40 (sCD40).

sCD40 is produced by B cells by alternative splicing of CD40 gene and/or by proteolytic cleavage of the membrane form of CD40 and acts as a natural antagonist of the CD40/CD40L interaction (2). As a result of this inhibition, the ability of sCD40 to reduce immunoglobulin production by B lymphocytes and T-cell activation has been demonstrated (3).

HD patients, when compared to healthy subjects, present high sCD40 serum levels which, associated to a reduction of CD40 membrane expression on B cells, set up the presence of a whole imbalance in the CD40 pathway in this clinical setting (4).

In addition, high sCD40 levels in HD have been related to a deficient response to Hepatitis B Virus vaccination, whereas the reduction of sCD40 levels obtained by treatment with a high permeability dialytic membrane has been associated to a significant increase of anti-HBs antibody titre (5).

Therefore, it seems now clear that sCD40 plays a pivotal role in regulating an immune response in HD patients.

However, while several studies have explored the effects of sCD40 on immunity, the involvement of this molecule in the cardiovascular risk in HD has never been investigated so far.

The results of the RISCAVID study show that the CD40/CD40L activation, mediated by sCD40L, could be an important event in the atherosclerotic process in HD. It is presumable that sCD40, which may be considered the counterpart of sCD40L, since it inhibits the CD40/CD40L interaction, has protective effects on the HD-related atherothrombotic risk. This finding could highlight a new aspect of the complex relationship between immune and cardiovascular systems.

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