Renin–angiotensin inhibitors in stage 4 chronic kidney disease


To the Editor: In their commentary on the Hemmelgarn et al.
study of kidney dysfunction in the elderly, Locatelli and Pozzoni note that patients with the most progressive disease were the most likely to have been treated with renin–angiotensin system inhibitors (RASIs). They suggest that ‘...this association can be explained by selection bias’. An alternative explanation may be that the RASIs (and the increased use of diuretics in this group) led to hemodynamic-mediated declines in glomerular filtration rate.

It is well known that RASIs lead to immediate declines in glomerular filtration rate based largely on reduction of intraglomerular pressure. These declines are tolerated because the reduction in intraglomerular pressure is believed to contribute toward long-term deceleration of kidney disease progression, and because the hemodynamic changes are reversible; for example, Bakris and Weir substituted clonidine for angiotensin-converting enzyme inhibitors in patients with chronic kidney disease (CKD) and documented a mean increase in glomerular filtration rate of ~10 ml/min.

The improvement in glomerular filtration rate that follows discontinuation of RASIs, and the long-term beneficial effect of (nevertheless) continuing RASIs, are both well known. However, nephrologists have not yet synthesized a unified strategy for treating CKD that applies all of this information in a complementary manner. That strategy might be applicable in late stage 4 CKD, as initiation of dialysis appears imminent. In other words, a comprehensive strategy might emphasize aggressive RAS inhibition to stabilize CKD throughout most of its course, but would also recognize that for patients who eventually do progress to end-stage renal disease, RASIs will have outlived their usefulness in preventing end-stage renal disease. At that very late stage, instead of starting dialysis, discontinuation of RASIs may lead to increases in glomerular filtration rate of ~3–10 ml/min, which, in some patients, may delay dialysis initiation for several additional years.

Treatment of CKD with RASIs has been studied (and exhaled) throughout the course of CKD up to early stage 4. We have not formally studied the use of RASIs at late stage 4. Such a study appears warranted to evaluate the approach described. It will need to address appropriate patient selection, with sensitivity towards patients who require RASIs for heart disease. It will also need to address other nuances including timing, substitute medicines and levels of blood pressure control, and measure not only dialysis-free intervals but also overall outcomes.

In the absence of data in late stage 4 CKD, physicians should remain aware of the reversible hemodynamic effects of RASI inhibitors and diuretics, and may consider a short trial of manipulation of these medicines, in selected patients, in lieu of immediate initiation of dialysis.


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Response to ‘Renin–angiotensin inhibitors in stage 4 chronic kidney disease’


We are grateful to Dr Hirsch for his comment.

We are of course aware that the use of renin–angiotensin system inhibitors (RASIs) may cause hemodynamic-mediated declines in glomerular filtration rate. This was clearly seen in the Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) study: the patients in the benazepril arm experienced significantly higher serum creatinine levels than those randomized to placebo during the first 6 months of treatment, although their renal survival during follow-up was statistically much better. It is for this reason that the use of these drugs should be carefully weighed, particularly in elderly patients with diffuse atherosclerotic lesions, and above all if they are being administered diuretics. It should also be borne in mind that, as was documented in the study by Himmelgarn et al., such patients frequently make use of non-steroidal anti-inflammatory drugs (often without even informing their physician) and this may further contribute to renal impairment.

We consequently also agree that, in the case of a major deterioration in renal function, an attempt to discontinue RASIs should be encouraged before deciding to start dialysis in the later stages of chronic kidney disease. However, the hypothetical deterioration in renal function in the patients taking part in the study by Himmelgarn et al. with the most advanced degree of renal impairment was too great to be attributable to the effect of RASIs; we also have no information about the duration of RASI treatment or the deterioration in renal function during the treatment itself.

The main message we wanted to send through our commentary was that we cannot expect the positive renoprotective effects of RASIs seen in younger patients with overt proteinuria (mainly secondary to glomerulo-
nephritis or diabetic nephropathy) participating in controlled, randomized clinical trials to be automatically transferred to everyday clinical practice. The general population is getting increasingly older every year, and the majority of treated patients are elderly subjects with nephroangiosclerosis and little or no proteinuria, with no actual possibility for checking for renal artery stenosis. We should remember, for example, what the RALES study taught us about the risk of hyperkalemia when its results were translated into everyday clinical practice.\(^4\)

Another aspect we wanted to underline was that we should not only look at deteriorating renal function but also (and above all) cardiovascular prevention, because many more chronic kidney disease patients in the general population die before needing dialysis than actually start chronic dialysis even in the most advanced stages of the disease.\(^5,6\) This is a rather different scenario from what is observed in randomized, controlled clinical trials, and further underlines the need for randomized controlled studies of older patients with more comorbidities and a greater likelihood of vascular disease as the cause of their chronic kidney disease. Such studies should consider cardiovascular as well as renal end points in order to evaluate the cost-effectiveness of RASI administration in such a non-selected patient population.


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**Is inflammation the missing link between low fat mass and low survival in hemodialysis patients?**


To the Editor: In their interesting study, Kakiya et al.\(^1\) found that a higher fat mass index was associated with lower mortality rate in hemodialysis patients. Moreover, fat mass index was positively correlated with total cholesterol in the studied group. As the authors mention, malnutrition in dialysis population often coexists with inflammation. Furthermore, it is well known that ‘reverse epidemiology’ found for fat mass index is also observed for serum cholesterol level and is also associated with inflammation in this population.\(^2\)

Recently, we tried to investigate cholesterol-inflammation relationship in hemodialysis patients. We found that the production of soluble components of interleukin-6 (interleukin-6, soluble interleukin-6 receptor, and soluble gp130) from activated peripheral blood mononuclear cells isolated from hypocholesterolemic hemodialysis patients is higher than the production of the same molecules from monocytes isolated from hyper-cholesterolemic patients.\(^3\) In case our data are confirmed in similar studies, it seems that hypo-cholesterolemia – and potentially low fat mass – is not simply associated but may also be causally related to the production of soluble components of a crucial proinflammatory and potentially atherogenic cytokine, as interleukin-6, by an also crucial for atherosclerotic process cell type, namely the circulating monocyte. Cellular cholesterol depletion may be the link connecting hypo-cholesterolemia and increased interleukin-6 components’ production.\(^4\)

Thus, as the study of Kakiya et al. showed, ‘reverse epidemiology’ regarding low fat mass – and potentially hypo-cholesterolemia – is a reality that may also be causally linked to the high inflammatory activity observed in this population; this later hyper-reactivity may be implicated in the evolution of processes like atherosclerosis,\(^5\) which explain lower survival of hemodialysis patients with low fat mass.


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